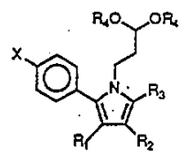
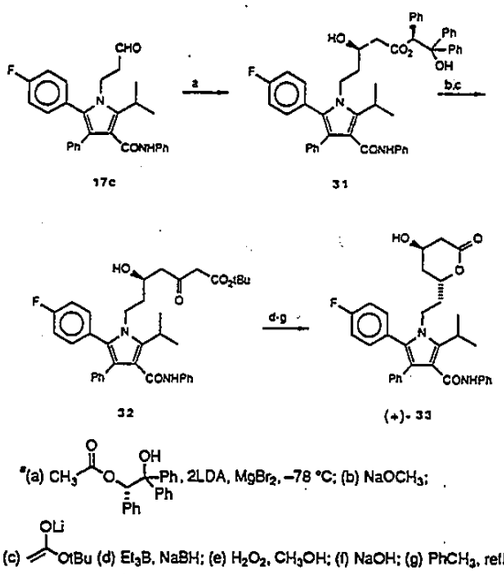
Table I



no.	X	R_1	R_2	R_3	R_4	% yield (method)	mp,[a,b] °C
6a	H	Ph	CO_2Et	CH_3	$-CH_2CH_2-$	75 (A)	oil[c]
6b	H	Ph	CO_2Et	Et	$-CH_2CH_2-$	36 (A)	oil[c]
6c	H	Ph	CO_2Et	*i*-Pr	$-CH_2CH_2-$	4 (A)	oil[c]
11a	F	CO_2CH_3	CO_2CH_3	*i*-Pr	$-CH_2CH_2-$	65 (B)	143–6
11b	F	CO_2Et	CO_2Et	*i*-Pr	$-CH_2CH_2-$	70 (B)	oil[c]
11c	F	CO_2Et	Ph	*i*-Pr	$-CH_2CH_2-$	30 (B)	146–8
16a	F	Ph	CO_2Et	*i*-Pr	$-CH_2CH_2-$	45 (C)	158–9
16b	F	Ph	CO_2CH_2Ph	*i*-Pr	$-CH_2CH_2-$	51 (C)	oil[c]
16c	F	Ph	CONHPh	*i*-Pr	$-CH_2CH_2-$	43 (C)	161–3
16d	F	4-CNPh	CO_2Et	*i*-Pr	$-CH_2CH_2-$	88 (C)	oil[c]
18	F	CH_3	CH_3	*i*-Pr	$-CH_2CH_2-$	64 (D)	oil[c]
23a	F	Ph	H	*i*-Pr	Et	71 (E)	84–7
23b	F	2-pyridyl	H	*i*-Pr	Et	76 (E)	84–6
23c	F	3-pyridyl	H	*i*-Pr	Et	64 (E)	96–8
23d	F	4-pyridyl	H	*i*-Pr	Et	46 (E)	123–5

[a] All compounds possess ^1H NMR spectra consistent with assigned structure. [b] Combustion analyses within ±0.4% of theoretical unless otherwise noted. [c] This compound was purified, but not analyzed before use in the next step.

Scheme VIII[a]

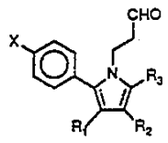


[a] (a) CH_3 O O OH Ph, 2LDA, $MgBr_2$, −78 °C; (b) $NaOCH_3$; (c) OLi OtBu (d) Et_3B, $NaBH_4$; (e) H_2O_2, CH_3OH; (f) NaOH; (g) $PhCH_3$, reflux.

propane[14] and deprotection (Scheme VI, method E). Finally, the 3,4-dichloro, 3,4-dibromo, and 3-trifluoroacetyl analogues (**30a–c**) were prepared from **1** by protection of the 4′-hydroxyl as the *tert*-butyldimethylsilyl ether, followed by electrophilic substitution on the pyrrole ring[15] and deprotection with *n*-Bu_4NF buffered with acetic acid (Scheme VII). The assignment of the regiochemistry of **30c** was made in a manner analogous to **11c** and **11d**.

Chiral lactone (+)-**33** was prepared by application of the asymmetric aldol procedure developed by Braun (Scheme VIII).[16] Thus, reaction of aldehyde **17c** with the magnesium enolate of (*S*)-(+)-2-acetoxy-1,1,2-triphenylethanol afforded alcohol **31** in 60% yield and 97% ee. Transesterification ($NaOCH_3$, CH_3OH) followed by Claisen condensation with excess lithio *tert*-butylacetate produced δ-hydroxy-β-keto ester **32** in 75% yield. After reduction with Et_3B and $NaBH_4$, base hydrolysis, and lactonization, (+)-**33** was isolated as a 98:2 mixture of stereoisomers. Fortuitously, the *d,l* pair selectively crystallized from ethyl acetate–hexanes and pure (+)-**33** ($[\alpha]^{23}_D = +24.53°$, 0.53% in $CHCl_3$) could then be isolated from the mother liquors as a foamy solid.[17]

Table II

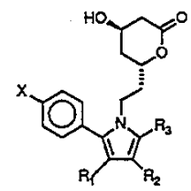


no.	X	R_1	R_2	R_3	% yield	mp,[a,b] °C
7a	H	Ph	CO_2Et	CH_3	77	100–1
7b	H	Ph	CO_2Et	Et	88	oil[c]
7c	H	Ph	CO_2Et	*i*-Pr	100	oil[c]
12a	F	CO_2CH_3	CO_2CH_3	*i*-Pr	90	oil[c]
12b	F	CO_2Et	CO_2Et	*i*-Pr	95	oil[c]
12c	F	CO_2Et	Ph	*i*-Pr	90	oil[c]
17a	F	Ph	CO_2Et	*i*-Pr	81	127–8
17b	F	Ph	CO_2CH_2Ph	*i*-Pr	60	oil[c]
17c	F	Ph	CONHPh	*i*-Pr	86	164–5
17d	F	4-CNPh	CO_2Et	*i*-Pr	75	oil[c]
19	F	CH_3	CH_3	*i*-Pr	66	oil[c]
24a	F	Ph	H	*i*-Pr	85	oil[c]
24b	F	2-pyridyl	H	*i*-Pr	70	120–2
24c	F	3-pyridyl	H	*i*-Pr	93	oil[c]
24d	F	4-pyridyl	H	*i*-Pr	95	oil[c]
28	F	H	Ph	*i*-Pr	90	oil[c]

[a] All compounds possessed ^1H NMR and IR spectra consistent with assigned structure. [b] Combustion analyes within ±0.4% of theoretical unless otherwise noted. [c] This compound was purified by chromatography, but not analyzed before use in the next step.

(13) Broadbent, H. S.; Burnham, W. S.; Olsen, R. K.; Sheeley, R. M. *J. Heterocycl. Chem.* 1968, *5*, 757–67.
(14) Suzuki, E.; Inone, S.; Goto, T. *Chem. Pharm. Bull.* 1968, *16*, 933–8.
(15) Aiello, E.; Dattolo, G.; Cirrincione, G.; Almerico, A. M.; D'Asdia, I. *J. Heterocycl. Chem.* 1982, *19*, 977–9.
(16) Braun, M.; Devant, R. *Tetrahedron Lett.* 1984, 5031–4.

Table III



no.	X	R_1	R_2	R_3	mp, °C	formula[a]	IC_{50},[b] μM	relative potency[c]
1	F	H	H	*i*-Pr	105–6	$C_{20}H_{24}FNO_3$	0.23	10.9
3a	H	Ph	CO_2Et	CH_3	oil	$C_{27}H_{29}NO_5$	4.0	0.6
3b	H	Ph	CO_2Et	Et	65–8	$C_{28}H_{31}NO_5$	0.89	6.3
3c	H	Ph	CO_2Et	*i*-Pr	157–9	$C_{29}H_{33}NO_5$	0.17	23.5
3d	F	CO_2CH_3	CO_2CH_3	*i*-Pr	169–170	$C_{24}H_{28}FNO_7$	0.180	14.3
3e	F	CO_2Et	CO_2Et	*i*-Pr	121–3	$C_{26}H_{32}FNO_7$	0.35	2.8
3f	F	CO_2Et	Ph	*i*-Pr	158–9	$C_{29}H_{32}FNO_5$	0.050	100
3g	F	Ph	CO_2Et	*i*-Pr	159–160	$C_{29}H_{32}FNO_5$	0.20	35.5
3h	F	Ph	CO_2CH_2Ph	*i*-Pr	174–5	$C_{34}H_{34}FNO_5$	0.040	24.0
(±)-3i	F	Ph	CONHPh	*i*-Pr	104–110	$C_{33}H_{33}FN_2O_4$	0.025	81.4
3j	F	4-CN-Ph	CO_2Et	*i*-Pr	oil	$C_{30}H_{31}FN_2O_5$	0.280	16.2
3k	F	CH_3	CH_3	*i*-Pr	oil	$C_{24}H_{28}FNO_3$	0.140	16.0
3l	F	Ph	H	*i*-Pr	oil	$C_{26}H_{28}FNO_3$	0.347	12.5
3m	F	2-pyridyl	H	*i*-Pr	186–7	$C_{25}H_{27}FN_2O_3$	0.046	76
3n	F	3-pyridyl	H	*i*-Pr	70–4	$C_{25}H_{27}FN_2O_3$	0.071	9.4
3o	F	4-pyridyl	H	*i*-Pr	174–6	$C_{25}H_{27}FN_2O_3$	0.310	2.1
3p	F	H	Ph	*i*-Pr	135–6	$C_{26}H_{28}FNO_3$	0.120	36.3
30a	F	Cl	Cl	*i*-Pr	129–131	$C_{20}H_{22}Cl_2FNO_3$	0.028	78.6
30b	F	Br	Br	*i*-Pr	141.2	$C_{20}H_{22}Br_2FNO_3$	0.028	78.6
30c	F	$COCF_3$	H	*i*-Pr	oil	$C_{22}H_{23}F_4NO_4$	0.800	8.8
(+)-33	F	Ph	CONHPh	*i*-Pr	foam	$C_{33}H_{33}FN_2O_4$	0.007	500
(−)-33	F	Ph	CONHPh	*i*-Pr	foam	$C_{33}H_{33}FN_2O_4$	0.440	13.9
		compactin					0.030	100

[a] Analytical results are within ±0.4% of theoretical values except where otherwise noted. [b] CoA reductase inhibition (COR) screen; a measure of the direct conversion of D,L-[^{14}C]HMG-CoA to mevalonic acid. Assays of each inhibitor were performed at four concentrations in triplicate. The precision for compactin was 37%. See ref 7 for experimental details. [c] Calculated as follows: (IC_{50} of compactin/IC_{50} of test compound determined simultaneously) × 100. Compactin arbitrarily assigned a value of 100.

Alternatively, relatively pure (+)- and (−)-33 could be obtained by preparation of the corresponding diastereomeric (*R*)-α-methylbenzylamides, separation by preparative HPLC, hydrolysis, and relactonization.[6b] This process afforded 94.6% pure (+)-33 ($[\alpha]^{23}_D$ = +25.5°, 0.51% in $CHCl_3$) and 97.8% pure (−)-33 ($[\alpha]^{23}_D$ = −24.8°, 0.51% in $CHCl_3$).

Biological Results and Discussion

The compounds listed in Table III were all hydrolyzed to the corresponding dihydroxy acid sodium salts and evaluated for their ability to inhibit a partially purified preparation of rat liver HMG-CoA reductase.[3] Two conclusions were readily apparent. The first was the confirmation of the 5-isopropyl as the preferred substituent (compare 3c with 3a and 3b). The second was the significant increase in in vitro potency found with the introduction of certain lipophilic electron-withdrawing groups into the 3 and 4 positions of the pyrrole ring (e.g., Cl or Br, compare 1 with 30a and 30b), such that, these compounds displayed potency equivalent to compactin. This effect did not hold for the esters or ketones (CO_2Me, CO_2Et, $COCF_3$, compounds 3d, 3e, 30c), except when combined with a phenyl (compounds 3f, 3h, and 3i). There also appeared to be a positional effect, since the 3-carbethoxy-4-phenyl analogue (3f) was 4 times more potent than the 3-phenyl-4-carbethoxy analogue (3g). In vitro activity for the 3-phenyl analogues were improved significantly by increasing the size of the 4-substituent (compare 3h, 3i, and 3g with 3l). Potency was also increased when the 3-phenyl was replaced with a 3-(2-pyridyl) moiety (compound 3m). The 3-(3- and 4-pyridyl) isomers (3n and 3o) were equipotent to phenyl (3l). Introduction of the electron-withdrawing cyano group into the 4-position of the 3-phenyl (3j) led to a slight reduction in potency. Finally, as others have reported, in the case of 3i essentially all of the biological activity was contained in the dextrorotatory stereoisomer ((+)-33 vs 3i).[6b] We speculate that the activity found in (−)-33 (97.8% pure) is derived from the 2% contamination with (+)-33.

An attempt was made to confirm these observations with a quantitative structure–reactivity relationship (QSAR) analysis. In the early stages of the development of the series, there was an indication that size, as parameterized by MR of the combined 3- and 4-substituents, as well as electronic-withdrawing character might be possible contributors to activity and this preliminary analysis partially guided further synthesis. Synthetic constraints precluded the preparation of an optimally designed set, however, and the set of compounds described in this paper did not ultimately support the derivation of a significant Hansch equation including these parameters. Furthermore, available parameters for electronic and lipophilic effects of these highly hindered functional groups are likely to be seriously inaccurate. Nevertheless, the trends observed from plots and single parameter correlations supported the observation that a size benefit exists, but derives mainly from the 4-substituent, as opposed to the 3-substituent. Polar functionality can be tolerated in this region, although there is a suggestion that lipophilicity may ultimately play

(17) A similar sequence was employed by Lynch et al.: Lynch, J. E.; Volante, R. P.; Wattley, R. V.; Shinkai, I. *Tetrahedron Lett.* 1987, 1385–8.

the dominant role among the simple parameterized effects, since $Pi_{3,4}$ has one of the best single parameter correlations with activity ($r = 0.46$). Clearly, other factors not readily parameterized have equal or larger influence on relative activity in this series. The activity of polar-substituted analogues is enhanced when the polar group is "insulated" from the enzyme as in **3m** vs **3n** and **3o**. Similarly, the better activity of **3f** over **3g** may derive from the better shielding of the polar ester group in the former compound by the flanking phenyl groups as opposed to a phenyl and isopropyl group in the latter. The activity of the halogenated analogues **30a** and **30b** is better accommodated by a lipophilicity effect, rather that a size or dispersion effect reflected in MR. Other QSAR analyses of synthetic HMG-CoA reductase inhibitors have reached similar conclusions about structural variations in this region of related molecules.[18,19]

In conclusion, although it is still most critical in this type to have the optimal substituents flanking the dihydroxyglutarate side chain, i.e., 4-fluorophenyl and isopropyl,[7] this work shows that further modulation and improvement in potency at inhibiting HMG-CoA reductase may be obtained with a variety of additional substituents capable of interacting with an apparently fairly spacious hydrophobic region distal from the side-chain location. The importance of this interaction is further supported by the potent inhibition evidenced by other inhibitors which possess substituents in this region.[1] Preparation of the optically pure *R,R*-isomer ((+)-33) of the most potent compound in this series (**3i**) resulted in a compound which was 5 times more potent than the fungal metabolite compactin in vitro. Further in vivo studies with (+)-33 will be described in subsequent papers from this laboratory.

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 when 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 spectrometer, or a Varian XL-200 or Bruker 250 MHz 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. Optical rotations were determined with use of a Perkin-Elmer 241 polarimeter. Routine HPLC analyses were performed with use of a Varian 5500 unit equipped with a Reodyne 7126 loop injector, a Dupont variable wavelength detector, and an octadecylsilane (Alltech C18 600RP, CH_3CN-H_2O eluant, 60:40, v/v) or silica gel column (Beckman Altex Ultrasphere 5 μm) interfaced to Varian 402 data system for computation of peak areas. Chiral HPLC analyses were performed with use of a Cbiracel of 10-μm column (Diacel Chem. Ind., LTD).

Method A. Ethyl 3-[2-(1,3-Dioxolan-2-yl)ethyl]amino-2-pentenoate (4b). A solution of methyl propionylacetate (12.55 mL, 100 mmol), 2-(2-aminoethyl)-1,3-dioxolane[8] (12.3 g, 105 mmol) and one drop of glacial acetic acid was stirred and heated in refluxing toluene (200 mL) for 2 h with azeotropic removal of water. The cooled solution was concentrated to provide 24 g of pure **4b**, which was used without further purification.

Ethyl 2-Ethyl-1-[2-(1,3-dioxolan-2-yl)ethyl]-4,5-diphenyl-1*H*-pyrrole-3-carboxylate (6b). A mixture of benzoin (4.25 g, 20 mmol), **4b** (5.44 g, 22 mmol), and $ZnCl_2$ (6 g, 44 mmol) in 50 mL of absolute ethanol was stirred and heated at reflux for 48 h. The cooled solution was diluted with ether (500 mL), washed with water (50 mL), 2 *M* HCl (2 × 50 mL), saturated aqueous bicarbonate (50 mL), and brine (50 mL), and dried. Flash chromatography (silica gel, 10:1 v/v hexane–ethyl acetate) provided 3 g (36%) of **6b**: 90-MHz NMR ($CDCl_3$) δ 0.98 (t, 3 H, *J* = 7 Hz), 1.34 (t, 3 H, *J* = 7 Hz), 1.85 (m, 2 H), 3.08 (q, 2 H, *J* = 7 Hz), 3.7–4.1 (m, 8 H), 4.60 (t, 1 H, J = 4 Hz), 7.1 (s, 5 H), 7.22 (s, 5 H) ppm.

Ethyl 2-Ethyl-1-[1-(3-oxopropyl)]-4,5-diphenyl-1*H*-pyrrole-3-carboxylate (7b). A solution of **6b** (2.4 g, 5.7 mmol) in 100 mL of absolute ethanol containing 1 drop of concentrated HCl was stirred and heated at reflux for 24 h. The cooled solution was concentrated and dissolved in 125 mL of 4:1 acetone–water, and 1 g of *p*-TSA–H_2O was added. The resulting solution was stirred and heated at reflux for 24 h. The cooled solution was concentrated and partitioned between ether and water. The ether layer was then washed with saturated aqueous bicarbonate and brine and dried. Filtration and concentration afforded 1.9 g of **7b** (88%): 90-MHz NMR ($CDCl_3$) δ 1.0 (t, 3 H, *J* = 7 Hz), 1.28 (t, 3 H, *J* = 7 Hz), 2.58 (m, 2 H), 3.10 (q 2 H, *J* = 7 Hz), 4.05 (q, 2 H, *J* = 7 Hz), 4.2 (m, 2 H), 7.05 (s, 5 H), 7.1–7.4 (m, 5 H), 9.50 (s, 1 H) ppm.

Ethyl 3-[[2-(1,3-Dioxolan-2-yl)ethyl]amino]-4-methyl-2-pentanoate (4c). A solution of ethyl isobutyrylacetate (6 g, 42 mmol) and 2-(2-aminoethyl)-1,3-dioxolane (5.4 g, 46.7 mmol) in toluene (50 mL) containing 2 drops of glacial acetic acid was stirred and heated at reflux with azeotropic removal of water for 2 h. Concentration provided crude **4c** which was used without further purification.

Ethyl 1-[2-(1,3-Dioxolan-2-yl)ethyl]-2-(1-methylethyl)-4,5-diphenyl-1*H*-pyrrole-3-carboxylate (6c). A mixture of **4c** (17 g, 80 mmol), benzoin acetate (75 mmol, 19 g), and $ZnCl_2$ (20 g, 147 mmol) in 100 mL of ethanol was stirred and heated at reflux for 2 days. The mixture was cooled to room temperature, poured into ether (1 L), washed with water (200 mL), 2 M HCl (100 mL), H_2O (100 mL), and brine, and dried. Flash chromatography (silica gel, 10:1 v/v hexane–ethyl acetate) provided 1.2 g of **6c**: 90-MHz NMR ($CDCl_3$) δ 0.90 (t, 3 H, *J* = 7 Hz), 1.45 (d, 6 H, *J* = 7 Hz), 1.90 (m, 2 H), 3.45 (septet, 1 H, *J* = 7 Hz), 3.8–4.1 (m, 8 H), 4.60 (t, 1 H, *J* = 4 Hz), 7.0 (s, 5 H), 7.0–7.3 (m, 5 H) ppm.

Ethyl 1-(3-Oxopropyl)-5-(1-methylethyl)-4,5-diphenyl-1*H*-pyrrole-3-carboxylate (7c). A solution of **6c** (1.3 g, 3 mmol) and *p*-TSA–H_2O (0.6 g, 3 mmol) in 50 mL of 4:1 acetone–water was stirred and heated at reflux overnight. The cooled mixture was poured into ether (200 mL), washed with saturated aqueous bicarbonate (2 × 50 mL), water (50 mL), and brine (50 mL), and dried. Filtration and concentration provided 1.0 g (100%) of pure **7c** which was used without further purification: 90-MHz NMR ($CDCl_3$) δ 0.90 (t, 3 H, *J* = 7 Hz), 1.40 (d, 6 H, *J* = 7 Hz), 2.55 (m, 2 H), 3.44 (septet, 1 H, *J* = 7 Hz), 3.95 (q, 2 H, *J* = 7 Hz), 4.15 (m, 2 H), 7.0 (s, 5 H), 7–7.3 (m, 5 H), 9.43 (s, 1 H) ppm.

Method B. *N*-[2-(1,3-Dioxolan-2-yl)ethyl]-DL-valine, Methyl Ester (9). A solution of the methyl 2-hromo-3-methylbutyrate (4.6 g, 23.6 mmol), 2-(2-aminoethyl)-1,3-dioxolane (2.9 g, 25 mmol), and triethylamine (3.5 mL, 25 mmol) in 25 mL of acetonitrile was stirred and heated at reflux for 20 h. The cooled solution was poured into ether (500 mL) and extracted with 2 M HCl (2 × 50 mL). The aqueous layer was made alkaline with 25% aqueous NaOH and extracted with ethyl acetate (2 × 100 mL). The combined ethyl acetate extracts were washed with brine and dried. Filtration and concentration provided 3 g (55%) of **9** as a yellow oil: 90-MHz NMR ($CDCl_3$) δ 0.93 (d, *J* = 7 Hz, 6H), 1.70 (br s, 1 H, 4NH), 1.86 (m, 2 H), 2.60 (m, 3 H), 2.94 (d, *J* = 6 Hz, 1 H), 3.68 (s, 3 H), 3.85 (m, 4 H), 4.89 (t, *J* = 4 Hz, 1 H) ppm.

***N*-[2-(1,3-Dioxolan-2-yl)ethyl]-*N*-(4-fluorobenzoyl)-DL-valine (10).** To a stirred solution of **9** (3 g, 13 mmol) and triethylamine (3.6 mL, 26 mmol) in 20 mL of CH_2Cl_2, cooled to 0 °C, was added a solution of 4-fluorobenzoyl chloride (1.65 mL, 14 mmol) in 10 mL of CH_2Cl_2. The solution was stirred 50 min at 0 °C and 60 min at room temperature. It was then poured into ether (200 mL), washed with water (2 × 50 mL), saturated aqueous bicarbonate (50 mL), and brine (50 mL), and dried. Flash chromatography (silica gel, 1:1 v/v hexane–ethyl acetate) provided 3 g (65%) of crude (±)-methyl *N*-(4-fluorobenzoyl)-*N*-[2-(2-ethyl)-1,3-dioxolanyl]valine: 90-MHz NMR ($CDCl_3$) δ 0.92 (or

(18) Aggarwal, D.; Saha, R. N.; Gupta, J. K.; Gupta, S. P. *J. Pharmacobio-Dyn.* **1988**, *11*, 591.
(19) Prabhakar, Y. S.; Saxena, A. K.; Doss, M. J. *Drug Des. Deliv.* **1989**, *4*, 97.

d, J = 7 Hz, 6 H), 1.8–2.5 (m, 3 H), 3.45 (br dd, J = 6, 8 Hz, 1 H), 3.72 (s, 3 H), 3.80 (m, 6 H), 4.80 (m, 1 H), 6.9–7.5 (m, 4 H) ppm.

A solution of this methyl ester (1 g, 2.83 mmol) and NaOH (0.4 g, 10 mmol) in 10 mL of 4:1 methanol–water was stirred and heated at reflux for 3 h. The cooled solution was diluted with water and extracted with ether. The aqueous layer was acidified with 6 M HCl and extracted with ethyl acetate (2×). The combined ethyl acetate extracts were washed with brine and dried. Filtration and concentration provided 0.96 g (2.8 mmol) of 10 as a gum: 90-MHz NMR ($CDCl_3$) δ 0.85 (m, 6 H), 1.8 (m, 2 H), 2.5 (m, 1 H), 3.3–3.9 (m, 7 H), 4.6 (m, 1 H), 6.8–7.4 (m, 4 H) ppm.

Dimethyl 1-[2-(1,3-Dioxolan-2-yl)ethyl]-2-(4-fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrole-3,4-dicarboxylate (11a). Dimethyl acetylenedicarboxylate (1.3 mL, 10.6 mmol) was added to a solution of 10 (1.8 g, 5.28 mmol) in 10 mL of acetic anhydride at room temperature. Carbon dioxide evolution began immediately. The solution was stirred a further 2 h, concentrated to remove excess dimethyl acetylenedicarboxylate and solvent, and then filtered through silica gel. This provided 2 g (89%) of 11a as a colorless solid. Recrystallization from isopropyl ether–hexane afforded colorless crystals: mp 143–146 °C; IR (KBr) 1719, 1449, 1241, 1209, 1178, 945 cm^{-1}; 200-MHz NMR ($CDCl_3$) δ 1.35 (d, J = 7 Hz, 6 H), 1.80 (m, 2 H), 3.18 (septet, J = 7 Hz, 1 H), 3.56 (s, 3 H), 3.7 to 4.0 (m, 6 H), 3.83 (s, 3 H), 4.64 (t, J = 4 Hz, 1 H), 7–7.3 (m, 4 H) ppm. Anal. C, H, N.

Dimethyl 2-(4-Fluorophenyl)-5-(1-methylethyl)-1-(3-oxopropyl)-1*H*-pyrrole-3,4-dicarboxylate (12a). A solution of 11a (0.5 g, 1.18 mmol) and *p*-TSA–H_2O (0.23 g, 1.2 mmol) in 12 mL of 5:1 acetone–water was stirred and heated at reflux for 48 h. The cooled solution was concentrated, diluted with ether (200 mL), washed with saturated aqueous bicarbonate (2 × 50 mL) and brine (50 mL), and dried. Flash chromatography on silica gel (4:1 v/v hexane–ethyl acetate) provided 0.4 g (90%) of pure 12a: 90-MHz NMR ($CDCl_3$) δ 1.35 (d, J = 7 Hz, 6 H), 2.61 (t, J = 7 Hz, 2 H), 3.18 (septet, J = 7 Hz, 1 H), 3.53 (s, 3 H), 3.81 (s, 3 H), 4.03 (t, J = 7 Hz, 2 H), 6.9–7.3 (m, 4 H), 9.45 (s, 1 H) ppm.

Ethyl 1-[2-(1,3-Dioxolan-2-yl)ethyl]-2-(4-fluorophenyl)-5-(1-methylethyl)-4-phenyl-1*H*-pyrrole-3-carboxylate (11c). A mixture of 10 (3.0 g, 8.8 mmol), acetic anhydride (15 mL), and ethyl phenylpropiolate (3.0 g, 17.6 mmol) was stirred at 110 °C for 5 h. The solution was then cooled and the excess acetic anhydride removed under vacuum. The residual dark oil was purified by flash chromatography on silica gel (4:1 v/v ethyl acetate–hexane). The product solidified on standing and was recrystallized from ether–hexane. The first crop gave 2.2 g (30%) of pure 11c: 90-MHz NMR ($CDCl_3$) δ 0.65 (t, 3 H, J = 7 Hz), 1.10 (d, 6 H, J = 7 Hz), 1.7–2.0 (m, 2 H), 3.00 (septet, 1 H, J = 7 Hz), 3.6–4.0 (m, 8 H), 4.60 (t, 1 H, J = 4 Hz), 6.9–7.4 (m, 9 H) ppm.

Method C. Ethyl α-[[2-(1,3-Dioxolan-2-yl)ethyl]amino]-4-fluorobenzeneacetate (14). A solution of 26 g (220 mmol) of 2-(2-aminoethyl)-1,3-dioxolane in 50 mL of acetonitrile was added at room temperature with stirring to a solution of 52 g (200 mmol) of ethyl α-bromo-4-fluorobenzeneacetate[20] and 42 mL (300 mmol) of triethylamine in 350 mL of acetonitrile. The resulting mixture was stirred at room temperature overnight and then poured into ether (500 mL). The suspension which resulted was washed with water (300 mL) and 2 M HCl (2 × 300 mL). The combined acidic extracts were made alkaline with 25% aqueous NaOH and extracted with ethyl acetate (2 × 500 mL). The ethyl acetate extracts were combined, washed successively with water and brine, and dried. Filtration and concentration yielded 49.5 g (82.5%) of 14 as an oil: 90-MHz NMR ($CDCl_3$) δ 1.18 (t, 3 H, J = 7 Hz), 1.85 (m, 2 H), 2.20 (br s, 1 H), 2.6 (m, 2 H), 3.85 (m, 4 H), 4.1 (q, 2 H, J = 7 Hz), 4.22 (s, 1 H), 4.83 (t, 1 H, J = 4.5 Hz), 6.8–7.3 (m, 4 H) ppm.

α-[[2-(1,3-Dioxolan-2-yl)ethyl](2-methyl-1-oxopropyl)-amino]-4-fluorobenzeneacetic Acid (15). 14 (30 g, 100 mmol) was dissolved in 200 mL of CH_2Cl_2 with 28.6 mL (205 mmol) of triethylamine. The resulting mixture was cooled to 0 °C under dry nitrogen. A solution of 11 mL (105 mmol) of isobutyryl chloride in 50 mL of CH_2Cl_2 was slowly added with stirring. After addition was complete, the mixture was stirred for an additional 1 h and then poured into 100 mL of ether. The ether solution was washed successively with water (25 mL), 2 M HCl (25 mL), saturated aqueous bicarbonate (25 mL), and brine (25 mL), and dried. Filtration and evaporation of the solvents yielded 35 g of α-[[2-(1,3-dioxolan-2-yl)ethyl](2-methyl-1-oxopropyl)amino]-4-fluorobenzeneacetic acid, ethyl ester: 90-MHz NMR ($CDCl_3$) δ 1.2 (m, 9 H), 1.7 (m, 2 H), 2.85 (m, 1 H), 3.35 (m, 2 H), 3.80 (m, 4 H), 4.20 (q, 2 H, J = 7 Hz), 4.60 (t, 1 H, J = 4.5 Hz), 5.81 (s, 1 H), 6.8–7.3 (m, 4 H) ppm.

A solution of this ester (35 g) and 12 g (300 mmol) of NaOH in 480 mL of 5:1 methanol–water was stirred and heated at reflux for 2 h. The solution was cooled to room temperature, concentrated, and diluted with 500 mL of water. The resulting solution was extracted with ether. The aqueous layer was then acidified with ice-cold 6 M HCl and extracted with ethyl acetate (2 × 300 mL).

The combined ethyl acetate extracts were washed with brine, dried, filtered, and evaporated to yield 30 g of crude 15 as a gum which was used without further purification: 90-MHz NMR ($CDCl_3$) δ 1.11 (d, 6 H, J = 7 Hz), 1.4–1.9 (m, 2 H), 2.85 (m, 1 H), 3.32 (m, 2 H), 3.75 (m, 4 H), 4.52 (t, 1 H, J = 4.5 Hz), 5.73 (s, 1 H), 6.8–7.3 (m, 4 H) ppm.

1-[2-(1,3-Dioxolan-2-yl)ethyl]-5-(4-fluorophenyl)-2-(1-methylethyl)-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (16b). A solution of 95 g (280 mmol) of 15 and 98 g (439 mmol) of *N*,3-diphenylpropynamide[21] in acetic anhydride (200 mL) was heated at 90 °C with stirring for 4 h (vigorous gas evolution). The mixture was then cooled to room temperature, concentrated, and chromatographed twice on silica gel (4:1 v/v hexane–ethyl acetate) to separate the product (R_f = 0.35, 4:1 hexane–ethyl acetate) from the *N*,3-diphenylpropynamide (R_f = 0.5). Recrystallization of the product from isopropyl ether provided 59.5 g (119 mmol) of 16b as colorless crystals: mp 159–162 °C; 200-MHz NMR ($CDCl_3$) δ 1.54 (d, 6 H, J = 7 Hz), 1.91 (m, 2 H), 3.60 (septet, 1 H, J = 7 Hz), 3.7–4.1 (m, 6 H), 4.74 (t, 1 H, J = 4.3 Hz), 7.0–7.3 (m, 15 H); IR (KBr) 3400, 1658, 1596, 1530 cm^{-1}. Anal. C, H, N.

5-(4-Fluorophenyl)-2-(1-methylethyl)-1-(3-oxopropyl)-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (17c). A solution of 59 g (118 mmol) of 16c and 0.4 mL of concentrated HCl in 1200 mL of absolute ethanol was heated under reflux with stirring for 24 h. The mixture was cooled to room temperature and concentrated and the residue taken up in 3:1 acetone–water (1200 mL). *p*-TSA–H_2O (5 g) was added. This mixture was heated under reflux with stirring for 2 days, cooled to room temperature, and partitioned between ether (1000 mL) and brine (200 mL). The organic layer was separated, washed successively with saturated aqueous bicarbonate (2 × 200 mL) and brine (100 mL), dried, filtered, and concentrated. The resulting oil was dissolved in the minimum amount of hot isopropyl ether, and the crystals which formed upon cooling were collected by filtration to yield 36.8 g (81 mmol) of 17c, mp 164–5 °C. A further crop of 9.8 g was obtained from the mother liquor: 200-MHz NMR ($CDCl_3$) δ 1.52 (d, 6 H, J = 7 Hz), 2.68 (br t, 2 H, J = 4 Hz), 3.63 (septet, 1 H, J = 7 Hz), 4.27 (br t, 2 H, J = 4 Hz), 6.86 (br s, 1 H), 7.0–7.2 (m, 14 H), 9.60 (s, 1 H); IR (KBr) 3400, 2966, 1720, 1673, 1596, 1511 cm^{-1}. Anal. C, H, N.

Methyl 7-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrol-1-yl]-3-hydroxy-5-oxo-1-heptanoate. A solution of methyl acetoacetate (26.4 mL, 243 mmol) in 250 mL of anhydrous THF was added dropwise to a stirred suspension of hexane-washed sodium hydride (6.4 g, 267 mmol) in 200 mL of THF at 0 °C. When gas evolution was complete, 97.2 mL of a 2.5 M solution of *n*-butyllithium in hexanes was added dropwise over 1 h.

The resulting solution was stirred for 30 min at 0 °C and cooled to −78 °C, and a solution of 36.8 g (81 mmol) of 17c in 100 mL of THF was added over a period of 30 min. The resulting solution was stirred for 30 min at −78 °C, then warmed to 0 °C, and held for an additional 1 h.

(20) Epstein, J. W.; Brabander, H. J.; Fanshawe, W. J.; Hofmann, C. M.; McKenzie, T. C.; Safir, S. R.; Osterberg, A. C.; Cosulich, D. B.; Lovell, F. M. *J. Med. Chem.* 1981, *24*, 481–90.

(21) Cabre, J.; Palomo, A. L. *Synthesis* 1984, 413–7.

The mixture was then acidified by the dropwise addition of 300 mL of ice-cold 3 M HCl, diluted with ether, washed with water and brine, dried, filtered, and evaporated. Flash chromatography on silica gel (3:1 v/v hexane–ethyl acetate) yielded 37.9 g of methyl 7-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrol-1-yl]-5-hydroxy-3-oxo-1-heptanoate: 90-MHz NMR ($CDCl_3$) δ 1.50 (d, 6 H, J = 7 Hz), 1.8 (m, 2 H), 2.45 (d, 2 H, J = 7 Hz), 2.8 (br s, 1 H), 3.33 (s, 2 H), 3.5 (m, 1 H), 3.67 (s, 3 H), 3.8–4.0 (m, 2 H), 6.8–7.3 (m, 14 H) ppm.

(±)-*trans*-5-(4-Fluorophenyl)-2-(1-methylethyl)-*N*,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-6-yl)ethyl]-1*H*-pyrrole-3-carboxamide (3i). Air (60 mL) was bubbled via a syringe through a solution of methyl 7-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrol-1-yl]-5-hydroxy-3-oxo-1-heptanoate (48 g, 84 mmol) and 92.5 mL of a 1 M THF solution of tributylborane in 100 mL of anhydrous THF. The mixture was stirred overnight at room temperature and then cooled to −78 °C. Sodium borohydride (3.85 g, 102 mmol) was added to the cooled mixture in one portion. The vigorously stirred suspension was allowed to warm slowly to 0 °C over 3 h (vigorous gas evolution ensued).

The dry ice–acetone bath cooling the reaction vessel was replaced by an ice bath and 18.3 mL of glacial acetic acid was added dropwise, followed by 204 mL of 3 N NaOH and 30.5 mL of 30% aqueous H_2O_2.

The mixture was vigorously stirred and allowed to warm to room temperature overnight. The mixture was partitioned between ether and water. The aqueous layer was separated, acidified, and extracted with ethyl acetate (2×).

The ethyl acetate extracts were washed with brine, dried, and evaporated to yield crude (*R**,*R**)-3,5-dihydroxy-7-[(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1*H*-pyrrol-1-yl]-1-heptanoic acid which was used without further purification.

The crude acid was taken up in toluene and heated at reflux for 6 h with azeotropic removal of water. Chromatography (silica gel, 1:1 v/v hexane–ethyl acetate) provided 30 g of 3i as a foamy solid, mp 90–97 °C.

This material was found by HPLC analysis to be a 9:1 mixture cis and trans isomers. Recrystallization from toluene–ethyl acetate yielded essentially pure trans 3i: mp 148–9 °C; 200-MHz NMR ($CDCl_3$) δ 1.52 (m, 6 H), 1.6–2.0 (m, 4 H), 2.48 (br s, 1 H), 2.51 (m, 2 H), 3.55 (septet, 1 H, J = 7 Hz), 4.0–4.2 (m, 2 H), 4.29 (m, 1 H), 4.52 (m, 1 H), 6.90 (br s, 1 H), 7.0–7.3 (m, 14 H) ppm; IR (KBr) 3400, 1734, 1654, 1597, 1511 cm^{-1}. Anal. C, H, N.

Phenylmethyl 1-[2-(1,3-Dioxolan-2-yl)ethyl]-5-(4-fluorophenyl)-2-(1-methylethyl)-4-phenyl-1*H*-pyrrole-3-carboxylate (16a). A solution of 15 (10 g, 29 mmol) and benzyl phenylpropiolate (7.7 g, 44 mmol) was stirred and heated in 30 mL of acetic anhydride at 90 °C for 6 h. After cooling to room temperature, the solution was concentrated, diluted with ether, washed with water, saturated aqueous bicarbonate, and brine, and dried. Flash chromatography on silica gel (10:1 v/v hexane–ethyl acetate) provided 5.9 g (45%) of crude 16a. Recrystallization from isopropyl ether provided 4.8 g of colorless 16a: mp 158–9 °C; IR (KBr) 1683 cm^{-1}; 200-MHz NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 7 Hz), 1.48 (d, 6 H, J = 7 Hz), 1.93 (m, 2 H), 3.50 (septet, 1 H, J = 7 Hz), 3.7–4.1 (m, 8 H), 4.71 (t, 1 H, J = 4.4 Hz), 6.95–7.2 (m, 9 H) ppm. Anal. C, H, N.

Method D. 1-[2-(1,3-Dioxolan-2-yl)ethyl]-2-(4-fluorophenyl)-3,4-dimethyl-5-(1-methylethyl)-1*H*-pyrrole (18). A solution of 11a (1.0 g, 2.37 mmol) in 5 mL of CH_2Cl_2 was added dropwise to a stirred suspension of lithium aluminum hydride (0.3 g, 7.4 mmol) in 20 mL of ether at room temperature. When addition was complete, the mixture was heated to reflux for 30 min, cooled to room temperature, and quenched by dropwise addition of water (0.3 mL), 25% aqueous NaOH (0.2 mL), and water (0.9 mL). After stirring vigorously for 30 min, the mixture was filtered and washed well with CH_2Cl_2. The filtrated was dried, filtered, and concentrated, providing 0.78 g (90%) of pure diol.

Trifluoroacetic acid (5.2 mL, 67 mmol) was added to a stirred solution of the diol (1.23 g, 3.4 mmol) and triethylsilane (1.2 mL, 7.5 mmol) in 10 mL of CH_2Cl_2 cooled to 0 °C under dry nitrogen. The solution was stirred for 2 h at 0 °C before warming to room temperature for 1 h. It was then poured into 300 mL of 50:50 ether–hexane and washed with saturated aqueous bicarbonate (3 × 50 mL) and brine (50 mL), and dried. Flash chromatography on silica gel (10:1 v/v hexane–ethyl acetate) provided 0.80 g (71%) of 18 as an oil: 90-MHz NMR ($CDCl_3$) δ 1.32 (d, 6 H, J = 7 Hz), 1.7–1.9 (m, 2 H), 1.86 (s, 3 H), 2.07 (s, 3 H), 3.10 (septet, 1 H, J = 7 Hz), 3.7–4.0 (m, 6 H), 4.58 (t, 1 H, J = 4 Hz), 6.9–7.3 (m, 4 H) ppm.

Method E. Methyl 4-Methyl-3-oxo-2-(phenylmethylene)pentanoate (21a). A mixture of methyl isobutyrylacetate (144 g, 1 mol), benzaldehyde (116 g, 1.1 mol), piperidine (4 mL), and HOAc (12 mL) in 200 mL of toluene was stirred and heated at reflux with azeotropic removal of water for 3 h. The solution was cooled, poured into ether (1 L), washed with 1 M HCl (200 mL), saturated aqueous bicarbonate (200 mL), and brine, and dried. Concentration and distillation (bp 127–130 °C/1 mmHg) provided 186.6 g (80%) of 21a as a mixture of diastereomers (isomer 1, major ~70%): 90-MHz NMR ($CDCl_3$) δ 0.98 (d, 6 H, J = 7 Hz), 2.58 (septet, 1 H, J = 7 Hz), 3.70 (s, 3 H), 7.28 (s, 5 H), 7.68 (s, 1 H) ppm. Isomer 2: 90-MHz NMR ($CDCl_3$) δ 1.14 (d, 6 H, J = 7 Hz), 3.14 (septet, 1 H, J = 7 Hz), 3.70 (s, 3 H), 7.80 (s, 5 H), 7.48 (s, 1 H) ppm.

1-(4-Fluorophenyl)-5-methyl-2-phenyl-1,4-hexanedione (22a). To a solution of 21a (376 g, 1.62 mol), 4-fluorobenzaldehyde (201 g, 1.62 mol), and Et_3N (158 mL) in a 3-L three-neck round-bottom flask with an air-driven stirrer was added 2-(2-hydroxyethyl)-3-methyl-4-benzylthiazolium chloride (65.5 g, 243 mmol). The mixture was stirred and heated at 70 °C for 24 h. After cooling to room temperature, the mixture was diluted with ether (3 L), washed with water, dilute HCl, saturated aqueous bicarbonate, and brine, and dried. The crude oil which remained after filtration and concentration was dissolved in THF (1500 mL) and added to a solution of NaOH (130 g) in 750 mL of water. The mixture was vigorously stirred overnight, acidified (pH 5) with 6 N HCl, and extracted with ether. The ether layer was washed several times with 3 N NaOH and water (to remove a low R_f, base soluble material) and brine and dried. The crude material was filtered through silica gel (100 g) and concentrated. It was then Kugelrohr distilled in two portions to afford 314 g (66%) of 22a: bp 145 °C (0.3 mmHg) IR (film) 1711, 1684, 1600 cm^{-1}; 200-MHz NMR ($CDCl_3$) δ 1.08 (d, 3 H, J = 7 Hz), 1.13 (d, 3 H, J = 7 Hz), 2.65 (septet, 1 H, J = 7 Hz), 2.77 (dd, 1 H, J = 18, 4 Hz), 3.63 (dd, 1 H, J = 18, 10 Hz), 5.07 (dd, 1 H, J = 10, 4 Hz), 7.10 (m, 2 H), 7.27 (m, 5 H), 7.98 (m, 2 H) ppm.

1-(3,3-Diethoxypropyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-1*H*-pyrrole (23a). To a solution of 22a (230 g, 0.77 mol) in 1 L of toluene was added 3,3-diethoxy-1-aminopropane[19] (176 g, 1.2 mol) at room temperature. The mixture solidified, but dissolution occurred on adding *p*-TSA–H_2O and heating to reflux (Dean–Stark) for 24 h. To the cooled solution was added 100 mL of absolute ethanol and the mixture concentrated and filtered through silica gel. The residue on concentration was dissolved in the minimum amount of isopropyl ether and allowed to crystallize. A first crop of 89 g (mp 84–7 °C) was isolated. A further 145 g were isolated as an oil: IR (KBr) 2973, 1603, 1511 cm^{-1}; 200-MHz NMR ($CDCl_3$) δ 1.11 (t, 3 H, J = 7 Hz), 1.35 (d, 6 H, J = 7 Hz), 1.75 (m, 2 H), 3.04 (septet, 1 H, J = 7 Hz), 3.2–3.6 (m, 4 H), 3.91 (m, 2 H), 4.27 (t, 1 H, J = 4.4 Hz), 6.20 (s, 1 H), 7.0–7.4 (m, 9 H) ppm. Anal. C, H, N.

Methyl 3-(4-Fluorophenyl)-3-oxopropanoate. To a suspension of dimethyl carbonate (195 g, 2.17 mmol) and hexane-washed NaH (72g, 3.0 mol) in dry THF (600 mL) at 60 °C was added 164 g (1.2 mol) of *p*-fluoroacetophenone dropwise. The reaction was maintained at gentle reflux by adjusting the temperature and addition rate (exothermic). After the addition was complete, the reaction was heated at reflux for 4 h, then cooled to room temperature.

The reaction was poured carefully into ice cold acetic acid (183 mL, 3.2 mol) and water (400 mL). The product was extracted with ether (2×), and the combined ether layers were washed with saturated aqueous bicarbonate, brine and dried. Distillation provided 204 g (96%) of desired product (bp 91 °C/0.5 mmHg): 90-MHz NMR ($CDCl_3$) δ 3.65 (s, 3 H), 3.92 (s, 2 H), 6.82–7.20 (m, 2 H), 7.57–8.01 (m, 2 H), 12.45 (singlet, 1 H) ppm.

Methyl 3-(4-Fluorophenyl)-3-oxo-2-(phenylmethylene)-propanoate (26). A mixture of methyl, 3-(4-fluorophenyl)-3-oxopropionate (100 g, 510 mmol), benzaldehyde (59.5 g, 561 mmol), piperidine (2 mL), and acetic acid (6 mL) in toluene (100 mL)

was stirred and heated at reflux with azeotropic removal of water for 4 h. The solution was cooled and filtered through silica gel (600 g) with toluene as eluant. Concentration afforded 127.2 g (88%) of **26** as a mixture of *E*- and *Z*-isomers: 90-MHz NMR ($CDCl_3$) δ 2.22 (s, 3 H, isomer 1), 3.62 (s, 3 H, isomer 2), 6.80–8.11 (m, 10 H) ppm.

1-(4-Fluorophenyl)-3-phenyl-5-methylhexane-1,4-dione (27). A mixture of **26** (130 g, 454 mmol), isobutyraldehyde (41 mL, 454 mmol), Et_3N (33 mL), and 2-(2-hydroxyethyl)-3-methyl-4-benzylthiazolium chloride (24 g, 91 mmol) was stirred and heated at 70 °C for 18 h. Additional isobutyraldehyde (6 g) was added and stirring continued for a further 6 h. After cooling to room temperature, the mixture was diluted with ether, washed with 2 M HCl (2×), saturated aqueous bicarbonate, and brine, and dried. The crude product was used without further purification.

To a solution of the crude diketo ester (31 g, 86.9 mmol) in 5:1 THF–H_2O (500 mL) was added NaOH (8 g, 200 mmol) in one portion. A small amount of methanol was added to ensure homogeneity. The reaction was stirred overnight at room temperature. The solvent was removed on the rotary evaporator, and the residue was dissolved in ether. This was then washed with 2 M HCl and brine and dried. Purification by flash chromatography (9:1 v/v ethyl acetate–hexane) gave 9.0 g (35%) of **27** as an oil: 90-MHz NMR ($CDCl_3$) δ 0.8 (d, 3 H, J = 7 Hz), 1.2 (d, 3 H, J = 7 Hz), 2.4–3.0 (m, 1 H), 3.6–4.0 (m, 1 H), 4.4–4.55 (m, 1 H), 6.8–7.3 (m, 7 H), 7.7–7.9 (m, 2 H) ppm.

5-(4-Fluorophenyl)-2-(1-methylethyl)-3-phenyl-1*H*-pyrrole-1-propanal (28). To a solution of **17** (9.0 g, 30.2 mmol) and 3,3-diethoxy-1-aminopropane (6.6 g, 45.3 mmol) in toluene (150 mL) was added a catalytic amount of *p*-TSA–H_2O. The resulting mixture was heated to reflux with azeotropic removal of water (Dean–Stark) overnight.

The solution was cooled and concentrated, and the residue was purified by flash chromatography on silica gel (10:1 v/v ethyl acetate–hexane). This provided 2.4 g (19%) of the pyrrole acetal as an oil and 7.1 g of recovered **27**. The pyrrole acetal was taken up in 5:1 acetone–water. Camphorsulfonic acid (0.2 g) was added and the solution refluxed for 18 h. The cooled solution was concentrated, diluted with ether, washed with water, bicarbonate, and brine, and dried. Flash chromatography on silica gel (9:1 v/v hexane–ethyl acetate) afforded 1.9 g of **28** as an oil: 90-MHz NMR ($CDCl_3$) δ 1.3 (d, 6 H, J = 7 Hz), 2.56 (m, 2 H), 3.22 (septet, 1 H, J = 7 Hz), 4.37 (m, 2 H), 6.1 (s, 1 H), 6.9–7.5 (m, 9 H), 9.5 (s, 1 H) ppm.

(2*R*)-*trans*-4-[[(1,1-Dimethylethyl)silyl]oxy]-6-[2-[2-(4-fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrol-1-yl]ethyl]-tetrahydro-2*H*-pyran-2-one (29). To a solution of **1** (0.52 g, 1.5 mmol) and *tert*-butyldimethylchlorosilane (0.27 g, 1.8 mmol) in 5 mL of dry DMF was added imidazole (0.31 g, 4.5 mmol) in one portion. The solution was stirred overnight at room temperature before partitioning between hexane (100 mL) and water (50 mL). The aqueous layer was extracted with two 50-mL portions of hexane. The combined hexane extracts were washed with water (2 × 25 mL) and brine (25 mL) and dried. Filtration through silica gel and concentration provided 0.7 g (100%) of **29** as a colorless oil: 90-MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.90 (s, 9 H), 1.30 (d, J = Hz, 6 H), 1.4–1.8 (m, 4 H), 2.48 (m, 2 H), 2.95 (m, 1 H), 3.9–4.3 (m, 3 H), 5.85 (d, J = 2 Hz, 1 H), 6.02 (d, J = 2 Hz, 1 H), 6.8–7.3 (m, 4 H).

(2*R*)-*trans*-6-[2-[3,4-Dichloro-2-(4-fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (30a). *N*-Chlorosuccinimide (6.48 mmol, 0.87 g) was added in one portion to a stirred solution of **29** (1.49 g, 3.24 mmol) in dry DMF (10 mL) cooled to 0 °C under dry nitrogen. The solution was stirred for 1 h at 0 °C then warmed to room temperature over 3 h. This was then diluted with water (50 mL) and extracted with ether (2 × 100 mL). The ether extracts were diluted with 100 mL of hexane, washed with water (50 mL), saturated aqueous bicarbonate (50 mL), 10% aqueous $NaHSO_3$ (50 mL), and brine (50 mL), and dried. After filtration and concentration, the crude product was dissolved in THF (15 mL) and treated with glacial acetic acid (0.75 mL, 13 mmol) and *n*-Bu_4F (9.72 mL of 1 M THF solution). The solution was stirred for 5 h, diluted with ethyl acetate (100 mL), washed with saturated aqueous bicarbonate (2 × 50 mL) and brine (25 mL), and dried. The residue which remained after filtration and concentration was flash chromatographed on silica gel (2:1 v/v hexane–ethyl acetate). This provided 0.50 g (35%) of **30a** as a colorless solid. Recrystallization from ether–hexane provided colorless crystals: mp 129–131 °C; IR (KBr) ν 3550, 2990, 1711, 1518, 1225, 1160, 1055, 851, 816 cm^{-1}; 200-MHz NMR ($CDCl_3$) δ 1.44 (d, J = 7 Hz, 6 H), 1.8 (m, 4 H), 2.12 (d, J = 3 Hz, 1 H, OH), 2.55 (m, 2 H), 3.10 (m, 1 H), 4.0 (m, 2 H), 4.30 (m, 1 H), 4.45 (m, 1 H), 7.0–7.4 (m, 4 H) ppm. Anal. C, H, N.

(2*R*)-*trans*-6-[2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3-(trifluoroacetyl)-1*H*-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (30c). Trifluoroacetic anhydride (0.17 mL, 1.2 mmol) was added dropwise to a stirred solution of **29** (0.50 g, 1.09 mmol) in 2 mL of DMF cooled to 0 °C under nitrogen. The light yellow solution was stirred for 1 h at 0 °C, diluted with 150 mL of 50:50 ether–hexane, washed with saturated aqueous bicarbonate (3 × 50 mL), and brine, and dried. Filtration and concentration provided a single product which was dissolved in 5 mL of anhydrous THF and stirred overnight at room temperature with 4 equiv of glacial acetic acid and 3 equiv of *n*-Bu_4NF. The mixture was then diluted with ether, washed with 2 M HCl and brine, and dried. Flash chromatography on silica gel (2:1 v/v hexane–ethyl acetate) provided 0.25 g of **30c** as an oil: IR (KBr) 3450, 1687, 1609 cm^{-1}; 200-MHz NMR ($CDCl_3$) δ 1.31 (d, 6 H, J = 7 Hz), 1.4–2.0 (m, 5 H), 2.6 (m, 2 H), 3.00 (septet, 1 H, J = 7 Hz), 3.9–4.1 (m, 2 H), 4.33 (m, 1 H), 4.49 (m, 1 H), 6.48 (q, 1 H, J = 2.1 Hz), 7.0–7.4 (m, 4 H) ppm. Anal. C, H, N.

[*S*-(*R,*S**)]-5-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrol-1-yl]-3-hydroxy-1-pentanoic Acid, 2-Hydroxy-1,2,2-triphenylethyl Ester (31).** *n*-Butyllithium in hexane (285 mL, 2.2 M) was added dropwise with stirring to diisopropylamine (92 mL) in THF (300 mL) at −50 to −60 °C in a 1000-mL one-neck flask via a dropping funnel under nitrogen. The yellow solution was allowed to warm to approximately −20 °C, then cannulated into a suspension of 99 g of (*S*)-(+)-2-acetoxy-1,1,2-triphenylethanol[16] in 500 mL of anhydrous THF at −70 °C. When addition was complete, the reaction mixture was allowed to warm to −10 °C over a period of 2 h. Meanwhile, a suspension of 0.63 mol of $MgBr_2$ was prepared by addition of 564 mL (0.63 mol) of bromine dropwise into a suspension of 15.3 g of magnesium (0.63 mol) in 500 mL of THF in a 3-L flask equipped with reflux condenser and mechanical stirrer. The $MgBr_2$ suspension was cooled to −78 °C and the enolate solution cannulated into the suspension over 30 min. Stirring was continued for 1 h at −78 °C. **17c** (150 g) in 800 mL of THF was then added dropwise over 30 min. The solution was stirred for 1.5 at −78 °C and then quenched with 200 mL of glacial acetic acid at −78 °C. After warming to 0 °C, 500 mL of water were added and the mixture concentrated in vacuo at 40–50 °C. 1:1 ethyl acetate–heptane (500 mL) was added to the yellow slurry, which was then filtered. The filtrate was washed extensively with 0.5 N HCl, then several times with water, and finally with cold (−20 °C) ethyl acetate–heptane (3:1). The light brown crystalline product was dried in vacuo at 40 °C, affording 194 g of crude aldol product. Recrystallization from ethyl acetate at −10 °C yielded 100 g of **31** (mp 229–230 °C) which analyzed as a 97.4:2.2 mixture of the *R,S*-:*S,S*-isomers by HPLC: IR (KBr) 3400, 2961, 1716, 1663, 1595, 1511, 701 cm^{-1}; 200-MHz NMR ($CDCl_3$) δ 1.44 (d, 6 H, J = 7 Hz), 1.5 (m, 2 H), 2.12 (m, 2 H), 2.39 (br s, 1 H) 3.40 (septet, 1 H, J = 7 Hz), 3.62 (m, 1 H), 3.81 (m, 1 H), 4.07 (m, 1 H), 6.63 (s, 1 H), 6.8–7.5 (m, 29 H) ppm. Anal. C, H, N.

Methyl (*R*)-(+)-5-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrol-1-yl]-3-hydroxy-1-pentanoate. To a suspension of 162 g (0.206 M) of the triphenylethanediol ester prepared above in 800 mL methanol–THF (5:3) cooled to 0 °C was added 11.7 g of sodium methoxide. The mixture was stirred until dissolution occurred and then put in the freezer overnight. The reaction mixture was then allowed to warm to room temperature, quenched with 15 mL of glacial acetic acid and concentrated in vacuo at 40 °C to obtain an oil, which was partitioned between water (500 mL) and ethyl acetate (2 × 300 mL). The combined organic extracts were washed with saturated aqueous bicarbonate and brine, dried, and filtered and the solvent evaporated. The residue was chromatographed on silica gel (1:4 v/v, ethyl acetate–heptane) to yield 109 g of the methyl ester as a colorless oil which solidified on

standing. Recrystallization from ether–heptane yielded 73.9 g of colorless crystals: mp 125–6 °C; $[\alpha]^{20}_D$ = 4.23° (1.17 M, CH_3OH); IR (KBr) 3400, 2960, 1720, 1646, 1511, 1160, 755 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 1.53 (d, 6 H, J = 7 Hz) 1.6–1.7 (m, 2 H), 2.30 (d, 2 H, J = 6 Hz), 2.88 (br s, 1 H), 3.57 (septet, 1 H, J = 7 Hz), 3.67 (s, 3 H), 3.85 (m, 1 H), 3.97 (m, 1 H), 4.15 (m, 1 H), 6.85 (s, 1 H), 6.95–7.25 (m, 14 H) ppm. Anal. C, H, N.

1,1-Dimethylethyl (*R*)-7-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrol-1-yl]-5-hydroxy-3-oxo-1-heptanoate (32). Diisopropylamine (75 mL, 550 mmol) was dissolved in THF (250 mL) in a 2000-mL three-neck flask equipped with thermometer and dropping funnel under nitrogen. The mixture was cooled to −42 °C and then 200 mL of 2.2 M *n*-butyllithium in hexane was added dropwise over 20 min. After stirring for 20 min, 62 mL (460 mmol) of *tert*-butyl acetate dissolved in THF (200 mL) was added over 30 min. This mixture was stirred for 30 min at −40 °C, then a further 140 mL of 2.2 M *n*-butyllithium was added over 20 min. When addition was complete, 81 g (153 mmol) of methyl (*R*)-(+)-5-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrol-1-yl]-3-hydroxy-1-pentanoate in anhydrous THF (500 mL) was added as quickly as possible without allowing the temperature to rise above −40 °C. Stirring was continued for 4 h at −70 °C. The reaction mixture was quenched with glacial acetic acid (69 mL) and allowed to warm to room temperature. It was then concentrated in vacuo and the residue taken up in ethyl acetate, washed extensively with water, saturated aqueous NH_4Cl, saturated aqueous bicarbonate, and brine. The organic layer was dried and filtered and the solvent evaporated to produce 73 g of 32: IR (KBr) 3400, 2933, 1700, 1665, 1511, 1151 cm^{-1}; 200-MHz NMR ($CDCl_3$) δ 1.45 (s, 9 H), 1.53 (dd, 6 H, J = 7.1 Hz), 1.6 (m, 2 H), 2.51 (s, 1 H), 2.53 (d, 1 H, J = 2 Hz), 2.80 (d, 1 H, J = 2 Hz, O*H*), 3.31 (s, 2 H), 3.60 (septet, 1 H, J = 7 Hz), 3.9–4.0 (m, 2 H), 4.09–4.22 (m, 1 H), 6.85 (s, 1 H), 6.95–7.2 (m, 14 H) ppm. Anal. C, H, N.

(+)-(4*R*)-*trans*-2-(4-Fluorophenyl)-5-(1-methylethyl)-*N*,3-diphenyl-1-[(tetrahydro-4-hydroxy-2-oxo-2*H*-pyran-6-yl)ethyl]-1*H*-pyrrole-4-carboxamide ((+)-33). To a solution of 73 g (119 mmol) of 32 in THF (500 mL) was added triethylborane (120 mL of a 1 M THF solution) and pivalic acid (0.7 g). The mixture was stirred for 10 min and cooled to −78 °C and methanol (70 mL) was added, followed by $NaBH_4$ (4.5 g, 119 mmol). The mixture was stirred at −78 °C for 6 h, then poured slowly into a 4:1:1 mixture of ice–30% aqueous H_2O_2–water. This mixture was stirred overnight and then allowed to warm to room temperature. Chloroform (400 mL) was added and the mixture partitioned between chloroform and water. The aqueous layer was further extracted with chloroform. The organic extracts were combined and washed extensively with water until a test for peroxide was negative. The organic layer was dried, filtered, and evaporated. The residue was flash chromatographed on silica gel (1:3 v/v ethyl acetate–hexane) to yield 51 g of crude dihydroxy ester which was dissolved in THF–methanol and 1 N NaOH (100 mL) was added with stirring at room temperature. After 4 h, the solution was concentrated, water (100 mL) was added, and it was extracted with ether (2 × 100 mL). The aqueous layer was acidified with 1 N HCl and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with water. The organic layer was dried, filtered and evaporated. The residue was taken up in toluene (2 L) and heated to reflux (Dean–Stark) for 20 min. After cooling, the procedure above was repeated. The reaction was left at room temperature for 10 days and then concentrated to yield 51 g of crude (+)-33 as a colorless foam. This was dissolved in the minimum amount of chloroform and chromatographed on silica gel (1:1 v/v ethyl acetate–heptane) to yield 23 g of impure (+)-33. Further chromatography on silica gel (98.5:1.5 v/v chloroform–propanol) yielded 13.2 g of (+)-33 as a crude solid.

Recrystallization from ethyl acetate–hexane produced 8.2 g of crystals shown to be a mixture of isomers by HPLC. Concentration of the mother liquors yielded 4.6 g of an oil which was shown to be 100% of pure (+)-33 by HPLC. Chromatography (silica gel, 98:2 v/v chloroform–2-propanol) afforded 4.18 g of (+)-33 as colorless foam, $[\alpha]^{23}_D$ = +24.53° (0.53% in $CHCl_3$).

α-Methylbenzeneacetamides. A solution of 3i (30 g, 55.5 mmoL) in (*R*)-(+)-α-methylbenzylamine (575 mL, 4.45 mol, 98% Aldrich) was stirred overnight at room temperature. The resulting solution was diluted with ether (2 L) and washed exhaustively with 2 M HCl (4 × 500 mL), water (2 × 500 mL), and brine (2 × 500 mL). The organic extract was dried, filtered, and concentrated in vacuo to yield 28.2 g of the diastereomeric α-methylbenzylamides as a white solid, mp 174–7 °C. The α-methylbenzylamides were separated by dissolving 1.5 g of the mixture in 1.5 mL of 98:1.9:0.1 chloroform–methanol–NH_4OH and injecting onto a preparative HPLC column (silica gel, 300 mm × 41.4 mm i.d.) by a gas-tight syringe and eluting with the above solvent mixture. Diastereomer 1 eluted at 41 min. Diastereomer 2 eluted at 49 min. Center cut fractions were collected. This procedure was repeated 3 times and the like fractions combined and concentrated. Examination of each by analytical HPLC indicated that diastereomer 1 was 99.84% pure and diastereomer 2 was 96.53% pure. Each isomer was taken on separately.

(+)-(4*R*)-*trans*-2-(4-Fluorophenyl)-5-(1-methylethyl)-*N*,3-diphenyl-1-[(tetrahydro-4-hydroxy-2-oxo-2*H*-pyran-6-yl)ethyl]-1*H*-pyrrole-4-carboxamide ((+)-33). To an ethanolic solution (50 mL) of diastereomer 1, [3*R*-[3*R**,5*R**]]-7-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1*H*-pyrrol-1-yl]-3,5-dihydroxy-*N*-[(*R*)-1-phenylethyl]-1-heptanamide, (1 g, 1.5 mmol) was added 1 N NaOH (3.0 mL, 3 mmol). The resulting solution was heated to reflux for 48 h.

The solution was cooled to room temperature and concentrated in vacuo. The residue was resuspended in water and carefully acidified with 6 N HCl. The resulting acidic solution was extracted with ethyl acetate. The organic extract was washed with water and brine, dried, filtered, and concentrated in vacuo. This residue was redissolved in toluene (100 mL) and heated to reflux with azeotropic removal of water for 3 h. This was cooled to room temperature and concentrated in vacuo to yield 1.2 g of a yellow semisolid. Flash chromatography on silica gel (2:3 v/v ethyl acetate–hexane) afforded 0.42 g of a white solid which still contained some impurities. This was rechromatographed (same system) to produce 0.1 g of essentially pure (+)-33, as a white foam. HPLC showed this material to be 94.6% chemically pure ($[\alpha]^{23}_D$ = +25.5° (0.51% in $CHCl_3$). The peak with a retention time of 53.46 min was tentatively assigned to an unknown diastereomer resulting from the 2% (*S*)-(−)-α-methylbenzylamine present in the Aldrich α-methylbenzylamine.

Preparation of (−)-(4*S*)-*trans*-2-(4-Fluorophenyl)-5-(1-methylethyl)-*N*,3-diphenyl-1-[(tetrahydro-4-hydroxy-2-oxo-2*H*-pyran-6-yl)ethyl]-1*H*-pyrrole-4-carboxamide ((−)-33). Carrying out the procedure described above on diastereomer 2 afforded 0.6 g of a foamy solid which was flash chromatographed on silica gel (1:1 v/v ethyl acetate–hexane) to afford 0.46 g of essentially pure (−)-33, as a white foam. HPLC showed this material to be 97.83% chemically pure, $[\alpha]^{23}_D$ = −24.8% (0.51% in $CHCl_3$).

Acknowledgment. We are indebted to Dr. S. Brennan, Mr. T. Hurley, and Mr. D. Sherwood for HPLC analyses and the separation of the α-methylbenzylamides derived from 3i, Dr. G. McClusky, Ms. S. Uhlendorf, and staff for spectral and analytical data, and Ms. P. Elka for manuscript preparation.

Inhibitors of Cholesterol Biosynthesis. 4. *trans*-6-[2-(Substituted-quinolinyl)ethenyl/ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-ones, a Novel Series of HMG-CoA Reductase Inhibitors[1]

D. R. Sliskovic,* J. A. Picard, W. H. Roark, B. D. Roth, E. Ferguson, B. R. Krause, R. S. Newton, C. Sekerke, and M. K. Shaw

Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, Michigan 48105.
Received June 8, 1990

A series of substituted quinoline mevalonolactones were prepared and evaluated for their ability to inhibit the enzyme HMG-CoA reductase both in vitro and (cholesterol biosynthesis) in vivo. Since previous studies suggested that the 4-(4-fluorophenyl) and 2-(1-methylethyl) substituents afforded optimum potency, attention was focused on variations at position 6 of the quinoline ring. Biological evaluation of a small number of analogues bearing a variety of 6-substituents showed that modification at this position had little effect on potency. Several compounds (8b, 8e, and 11) were identified that showed comparable potency to compactin and mevinolin in both the in vitro and in vivo assays.

We have previously described two series of novel HMG-CoA reductase inhibitors. In each series the structurally complex hexahydronaphthalene ring system common to the naturally occurring fungal metabolites compactin and mevinolin was replaced by a five-membered monocyclic heteroaromatic system, such as the nonbasic pyrrole[2] and pyrazole[3] ring systems. Inhibitors containing basic six-membered monocyclic heteroaromatic[4] and nonbasic[5,6] heteroaromatic ring systems have been reported.

This report describes the synthesis and biological activity of a series of quinoline mevalonolactones, the first HMG-CoA reductase inhibitors to contain a basic bicyclic heteroaromatic ring system.

In addition, many of the compounds described herein exhibit improved in vitro potency when compared to both the pyrrole and pyrazole mevalonolactones previously reported.

Chemistry

Most potent inhibitors of HMG-CoA reductase have the 4-hydroxy-2*H*-pyran-2-one moiety flanked by a bulky lipophilic group and an alkyl group, where both of these groups are anchored in the correct spatial arrangement by various carbocyclic and heterocyclic structures.[7]

We initially investigated the synthesis of quinoline-containing mevalonolactones in which the lactone moiety was connected to position 3 of the quinoline nucleus via a two-carbon spacer and was flanked at positions 2 and 4 by an alkyl group and a 4-fluorophenyl group, respectively.[2,3] By attaching the lactone moiety at position 4 of the quinoline nucleus and employing an alkyl flanking group at position 3 we were able to investigate whether the "benzenoid" ring of the quinoline nucleus could replace the 4-fluorophenyl flanking group and give a compound which retained biological activity. Our general synthetic strategy to the quinolin-3-ylmevalonolactones employed the Friedlander reaction between a suitably substituted benzophenone derivative and an active methylene compound to construct the target quinoline nucleus (Scheme I).

Acid-catalyzed condensation of the requisite 2-aminobenzophenones[8] with various β-keto esters produced esters 1a–e. Reduction to alcohols 2a–e followed by Swern oxidation afforded the corresponding aldehydes 3a–e, which were converted, with >95% *E* selectivity, to α,β-unsaturated esters 4a–e by reaction with carbomethoxymethylenetriphenylphosphorane. DIBAL-H reduction afforded alcohols 5a–e, which were oxidized to aldehydes 6a–e by employing either MnO_2 or the Swern procedure. Condensation with the dianion of ethyl acetoacetate[9] then gave δ-hydroxy-β-keto esters 7a–e. Stereoselective reduction employing the boron-chelation method of Narasaka and Pai[10] gave, after hydrolysis, a mixture of *erythro*- and *threo*-1,3-dihydroxy acids (>12:1) which were lactonized by refluxing in toluene with azeotropic removal of water. Generally, the lactones were crystalline, such that the small amount of the cis stereoisomer present was easily removed by recrystallization, providing almost exclusively the racemic trans stereoisomers 8a–e.

Compounds containing a saturated bridging unit were readily available from 4 via catalytic hydrogenation to give 9. The same sequence of steps utilized for the synthesis of lactones 8a–e was then employed to convert 9 to lactone 10.

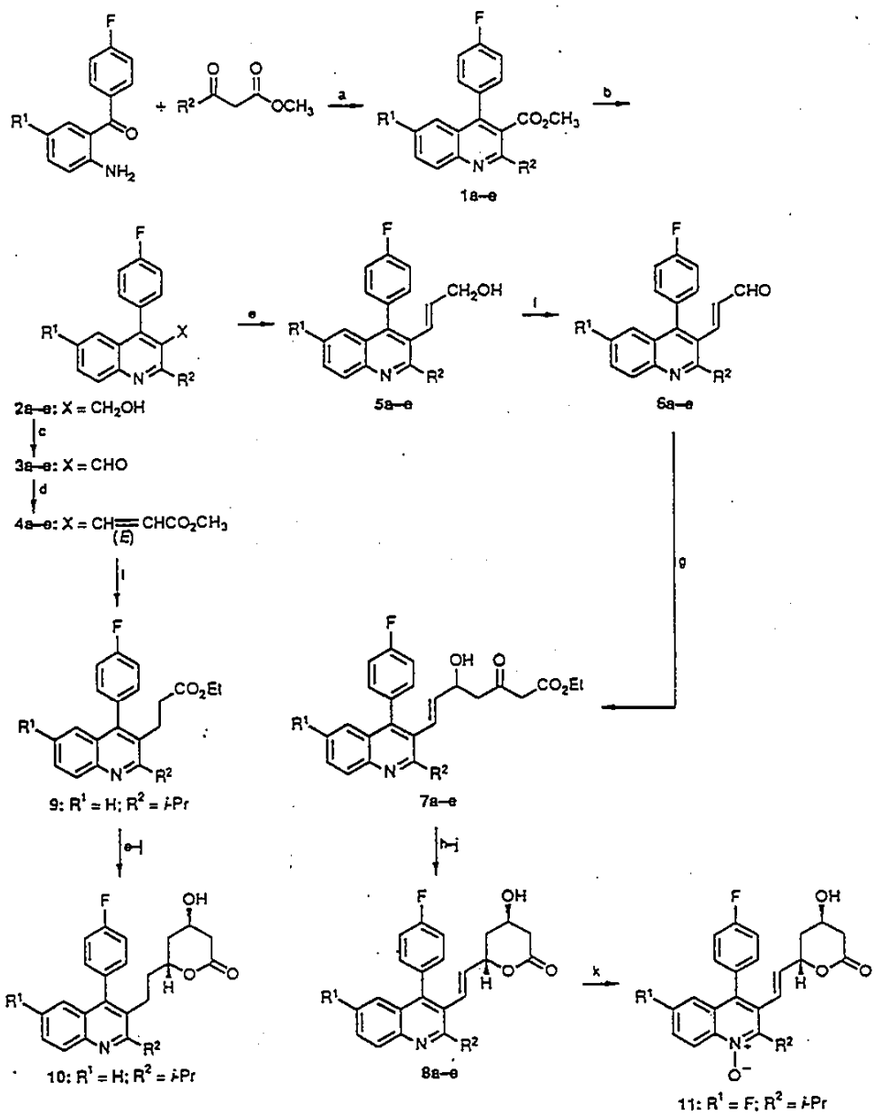
Treatment of lactone 8d with *m*-chloroperbenzoic acid in refluxing dichloromethane produced *N*-oxide 11, which was expected to exhibit very different physicochemical properties than the parent quinoline (vide supra).

Lactone 8d was also synthesized as the pure, biologically active 3*R*,5*S* stereoisomer employing Heathcock's β-ketophosphonate lactone synthon[11] (Scheme II). Thus, β-ketophosphonates 12 and 13 (prepared as an 8:1 mixture of diastereomers employing the literature procedure[12]) were

(1) A preliminary report of this work was presented at the 198th Meeting of the ACS, Miami, FL, September 10–15, 1989, MEDI 73. Following this report workers at Bayer AG presented data on a similar series of compounds at the 10th International Symposium on Drugs Affecting Lipid Metabolism, Houston, TX, November 8–11, 1989, Abstracts 510, 511.
(2) Roth, B. D.; Ortwine, D. F.; Stratton, C. D.; Sliskovic, D. R.; Wilson, M. W.; Newton, R. S. *J. Med. Chem.* 1990, *33*, 21 and references contained therein.
(3) Sliskovic, D. R.; Roth, B. D.; Wilson, M. W.; Hoefle, M. L.; Newton, R. S. *J. Med. Chem.* 1990, *33*, 31.
(4) Beck, G.; Kesseler, K.; Baader, E.; Bartmann, W.; Bergmann, E.; Granzer, H.; Jendralla, B.; v. Kerekjarto, B.; Krause, R.; Paulus, E.; Schubert, W.; Wess, G. *J. Med. Chem.* 1990, *33*, 52.
(5) Coppola, G. M.; Scallen, T. J.; DelPrete, A.; Montano, R. *Heterocycles* 1989, *29*, 1497.
(6) Kathawala, F. G.; Scallen, T. J.; Engstom, R. G.; Weinstein, D. B.; Schuster, H.; Stabler, R. *Abstracts of Papers*, 194th National Meeting of the American Chemical Society, New Orleans, August 30–September 4, 1987; American Chemical Society: Washington, DC, 1987; MEDI 79.
(7) Roth, B. D.; Sliskovic, D. R.; Trivedi, B. K. *Annu. Rep. Med. Chem.* 1989, *24*, 147.
(8) Walsh, D. A. *Synthesis* 1980, 677 and references contained therein.
(9) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* 1981, *96*, 1082.
(10) (a) Narasaka, K.; Pai, H. C. *Chem. Lett.* 1980, 1415. (b) Ibid. *Tetrahedron* 1984, *40*, 2233.
(11) Heathcock, C. H.; Hadley, C. R.; Rosen, T.; Theisen, P. D.; Hecker, S. J. *J. Med. Chem.* 1987, *30*, 1858.

0022-2623/91/1834-0367$02.50/0

Scheme I[a]



[a] (a) pTSA, toluene, Δ; (b) DIBAL-H, CH_2Cl_2, −78 °C; (c) $(COCl)_2$, DMSO, TEA, −78 °C; (d) $Ph_3P{=}CHCO_2CH_3$; (e) DIBAL-H, CH_2Cl_2, −78 °C; (f) Swern or MnO_2, toluene, Δ; (g) $^-CH_2CO^-CHCO_2Et$; (h) $B(Et)_3$, $NaBH_4$, $(CH_3)_3CCO_2H$ then H_2O_2; (i) NaOH then HCl; (j) toluene, Δ; (k) *m*CPBA, CH_2Cl_2, Δ; (l) 10% Pd/C, H_2, MeOH.

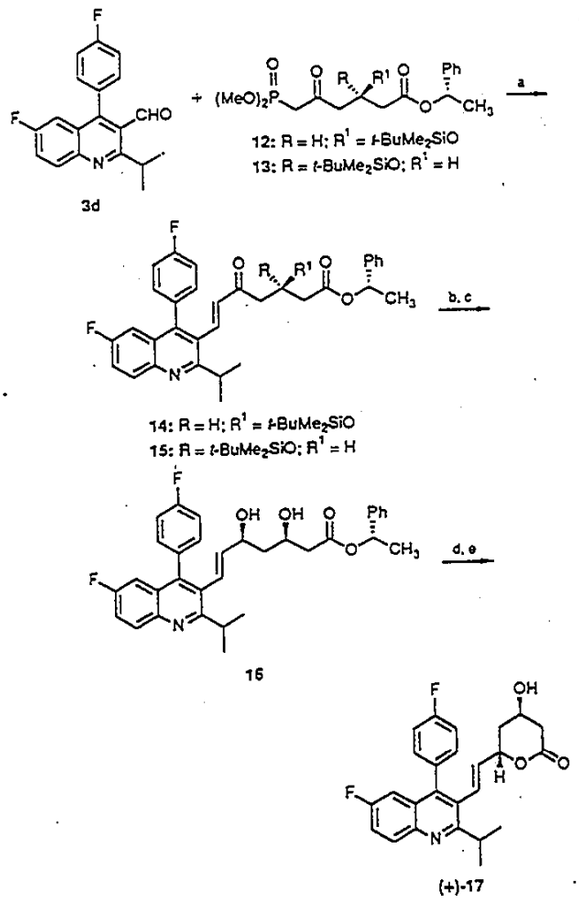
coupled with aldehyde 3, employing the conditions developed by Roush and Masamune[13] (LiCl, DBU, CH_2Cl_2), in 64% yield. This yield represents the best achieved.[14] The resulting enones (14 and 15) were deprotected and stereoselectively reduced (Et_3B, $NaBH_4$) to give a mixture of *erythro*- (16) and *threo*-1,3-dihydroxy esters. Saponification followed by lactonization and chromatography gave predominantly *trans*-lactone (+)-17 (trans:cis = 26:1). HPLC analysis of the corresponding (*R*)-(+)-α-methylbenzamide derivatives indicated an enantiomeric purity of 89% ee.

In an attempt to increase the aqueous solubility of these compounds (and thereby improve absorption in vivo), a dimethylamino group was incorporated into position 2 of the quinoline ring in place of the isopropyl group (Scheme III).

Treatment of benzophenone 18 with ethyl malonyl chloride and silica gel gave 1,2-dihydroquinoline 19 in 88% yield. Chlorination using phosphoryl chloride gave ester 20, which was then reduced and reoxidized to aldehyde 21. Nucleophilic substitution of the chloride with dimethylamine gas in toluene at 130 °C (autoclave) gave dimethylamino aldehyde 22. Aldehyde 22 was then con-

(12) This ratio of diastereomers may be improved to 22:1 by employing (*R*)-1-(1′-naphthyl)ethanol as chiral auxilliary; see: Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* 1988, *53*, 2374.
(13) Blanchette, M. A.; Choy, C. O.; Davis, J. T.; Essenfield, A. P.; Masamune, S.; Roush, W. R. *Tetrahedron Lett.* 1984, *25*, 2183.
(14) A variety of other conditions were examined, e.g., K_2CO_3/18-crown-6/toluene, $(NH_4)_2CO_3$/toluene, and NaH/THF, however, all of these led to β-elimination products derived from both the starting materials (12 and 13) and products (14 and 15). See: Rosen, T.; Heathcock, C. H. *J. Am. Chem. Soc.* 1985, *107*, 3731.

Scheme II[a]



[a] (a) LiCl, DBU, CH_2Cl_2, −10 °C; (b) HF, CH_3CN; (c) $B(Et)_3$, $NaBH_4$, $(CH_3)_3CCO_2H$ then H_2O_2; (d) NaOH then HCl; (e) toluene, Δ.

verted to the desired lactone 26 by employing the chemistry described previously.

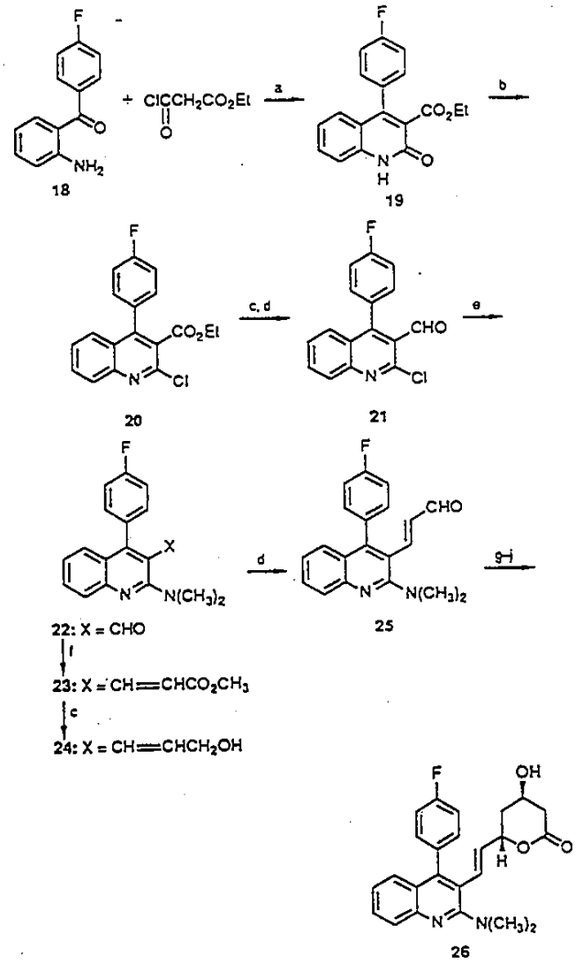
Quinolin-4-ylmevalonolactone 34 was synthesized as shown in Scheme IV. Methyl 3-methyl-4-quinolinecarboxylate[15] (27) was reduced to alcohol 28 and then oxidized under Swern conditions to aldehyde 29. α,β-Unsaturated aldehyde 32 was constructed in an entirely analogous manner to that depicted in Scheme I and was subsequently treated with the dianion of ethyl acetoacetate to yield 33, which was converted to the target lactone 34 (trans:cis = 23:1).

Biological Results

The lactones listed in Table I were saponified to the 3,5-dihydroxy acids and tested for their ability to inhibit the enzyme HMG-CoA reductase, employing two protocols.[2] Method I (cholesterol synthesis inhibition screen or CSI) measured the rate of conversion of [^{14}C]acetate to cholesterol by employing a crude liver homogenate derived from rats fed a chow diet containing 5% cholestyramine. Method II (HMG-CoA reductase inhibition screen or COR) was a more specific screen employing a partially purified microsomal enzyme preparation to measure the direct conversion of [^{14}C]HMG-CoA to mevalonic acid. The

(15) Lindberg, U. H.; Ulff, B.; Yeoman, G. *Acta. Pharm. Suec.* 1968, 5, 441.

Scheme III[a]



[a] (a) CH_2Cl_2 then SiO_2; (b) $POCl_3$, Δ; (c) DIBAL-H, CH_2Cl_2, −78 °C; (d) $(COCl)_2$, DMSO, TEA, −78 °C; (e) $HN(CH_3)_2$, toluene, autoclave, 130 °C; (f) $Ph_3P{=}CHCO_2CH_3$, CH_2Cl_2; (g) $^-CH_2CO^-CHCO_2Et$; (h) $B(Et)_3$, $NaBH_4$, $(CH_3)_3CCO_2H$ then H_2O_2; (i) NaOH then HCl; (j) toluene, Δ.

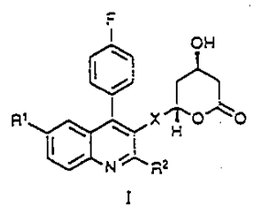
biological activities are displayed in Table I as an IC_{50} (i.e., the concentration needed to inhibit enzyme activity by 50%). Compactin was employed as the internal standard in each testing protocol. The compounds were also evaluated for their ability to inhibit cholesterol biosynthesis in male rats, as determined by the inhibition of the incorporation of sodium [1-^{14}C]acetate into plasma [^{14}C]-cholesterol after po administration of the test substance.[16] This screen was designated the AICS (acute inhibition of cholesterol synthesis) screen.

Most of the compounds tested were more potent than compactin in the in vivo screen and 8b–e exhibited both in vitro and in vivo potencies comparable to those of mevinolin.

As expected, an isopropyl group at position 2 of the quinolinyl-3-mevalonolactones produced a compound, 8b,

(16) Alberts, A. W.; Chen, J.; Kuron, J.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hoogsteen, K.; Liesch, J.; Springer, J. *Proc. Natl. Acad. Sci. U.S.A.* 1980, 77, 3997.

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

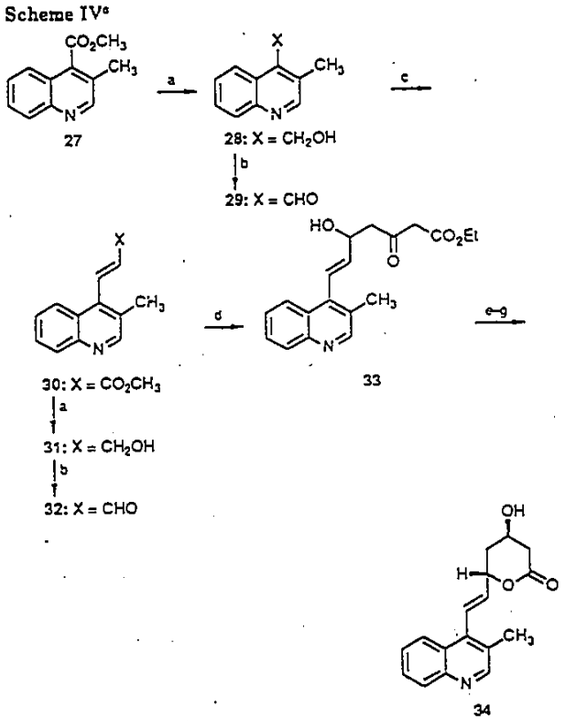


I

no.	R^1	R^2	X	mp, °C	formula[a]	CSI[b,c] IC_{50}, μM	rel (CSI)[c] potency	COR[c,h] IC_{50}, μM	AICS[c] (% inhibn)
compactin						0.030		0.025	36
mevinolin						0.025	118	0.028	72
8a	Cl	CH_3	-CH=CH-	188–190	$C_{23}H_{19}ClFNO_3$	0.4	6.3	0.72	18 (1.5)
8b	Cl	$CH(CH_3)_2$	-CH=CH-	173–175	$C_{25}H_{23}ClFNO_3$	0.032	100	0.025	61 (1.5)
8c	H	$CH(CH_3)_2$	-CH=CH-	168–170	$C_{25}H_{24}FNO_3$	0.042	75.8	0.032	70
10	H	$CH(CH_3)_2$	$-CH_2CH_2-$	199–202	$C_{25}H_{26}FNO_3$	>1.0	<1	-	-
8d	F	$CH(CH_3)_2$	-CH=CH-	174–176	$C_{25}H_{23}F_2NO_3$	0.05	77.6	0.20	68
17	F	$CH(CH_3)_2$	-CH=CH-	foam	$C_{25}H_{23}F_2NO_3 \cdot 0.25C_4H_8O_2$	ND[d]	ND[d]	-	69
11 (*N*-oxide)	F	$CH(CH_3)_2$	-CH=CH-	235–238	$C_{25}H_{23}F_2NO_4$	0.018	112	0.079	47
8e	OCH_3	$CH(CH_3)_2$	-CH=CH-	foam	$C_{26}H_{25}FNO_4$[f]	0.013	100	0.053	60
26	H	$N(CH_3)_2$	-CH=CH-	150–152	$C_{24}H_{23}FN_2O_3 \cdot 0.5C_4H_8O_2$	0.047	13.2	0.35	52
34				198–200	$C_{17}H_{17}NO_3 \cdot 0.25C_4H_8O_2$	>1.0	<1	-	42

[a] Analytical results are within ±0.4% of the theoretical values unless otherwise noted. [b] Cholesterol synthesis inhibition (CSI). Assays of each inhibitor concentration were performed in triplicate, and the precision for compactin was 37%. [c] All compounds tested had a diastereomeric purity of >95% of the trans diastereomer as determined by HPLC and/or 200-MHz NMR. [d] Potency of compactin arbitrarily assigned a value of 100 and the IC_{50} value of the test compound was compared with that of compactin determined simultaneously. [e] All compounds were dosed in DMA/PEG solution of 1.0 mg/kg unless otherwise indicated in parentheses. [f] Anal. Calcd: C, 71.70. Found: C, 70.67. >98% pure by HPLC. [g] Not determined. [h] HMG-CoA reductase inhibition (COR). Assays of each inhibitor concentration were performed in triplicate, and the precision for compactin was 37%.

Scheme IV[a]



[a] (a) DIBAL-H, CH_2Cl_2, -78 °C; (b) $(COCl)_2$, DMSO, TEA, -78 °C; (c) $Ph_3P{=}CHCO_2CH_3$, CH_2Cl_2; (d) $^-CH_2CO^-CHCO_2Et$; (e) B-$(Et)_3$, $NaBH_4$, $(CH_3)_3CCO_2H$ then H_2O_2; (f) $NaOH^-$ then HCl; (g) toluene, Δ.

significantly more potent both in vitro and in vivo than the corresponding 2-methyl compound 8a. Compound 10, which has a saturated two-carbon bridging unit between the quinoline moiety and the mevalonolactone, was considerably less potent than the corresponding unsaturated bridge containing compound 8c.

As previous studies suggested that the 4-(4-fluorophenyl) and 2-(1-methylethyl) substitution afforded optimum potency, attention was focused on variations at position 6 of the quinoline ring. From the limited number of compounds prepared (i.e., 8b–e), it can be seen that varying the substitution at position 6 did not significantly effect either in vivo or in vitro potencies. The dimethylamino containing compound 26 retained in vivo potency when compared to the corresponding isopropyl-containing compound 8c, but was somewhat less potent in vitro.

N-Oxide 11 was as potent in vitro as compactin and mevinolin and more potent than the corresponding free base but was slightly less potent in vivo.

Quinolin-4-ylmevalonolactone 34 was considerably less potent than either compactin or mevinolin in vitro, however it was comparable to compactin when tested in vivo. The source of the in vivo activity for 34, despite its lack of in vitro activity, is unclear.

Conclusion

A series of quinoline mevalonolactones was prepared and evaluated for their ability to inhibit the enzyme HMG-CoA reductase in vitro and cholesterol biosynthesis in vivo. By focusing on compounds possessing the 4-(4-fluorophenyl) and 2-(1-methylethyl) substituents found to be optimum in previous studies, several compounds, i.e., 8b, 8e, and 11, were identified that were of comparable potency to compactin and mevinolin both in vitro and in vivo. Modifications at position 6 of the quinoline ring had little effect on potency.

In conclusion it has been shown that the quinoline nucleus can be used as a suitable replacement for the hexahydronaphthalene ring present in the fungal metabolites compactin and mevinolin. Compounds have been described which are equipotent to both naturally occurring HMG-CoA reductase inhibitors under the conditions studied.

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 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 spectrometer. Nuclear magnetic resonance spectra were determined on either a Varian EM-390 or a Varian XL-200 spectrometer. Chemical shifts are expressed as parts per million downfield from internal tetramethylsilane. Elemental analyses were determined on a Perkin-Elmer 240C elemental analyzer. HPLC analyses were performed on a Varian 5500 HPLC with a UV 200 detector (wavelength was 251 nm) and an octadecylsilane column [Alltech Econisil C18; mobile phase, 50:50 0.05 M citric acid (pH = 4.0)–CH_3CN]. Optical rotations were performed on a Perkin-Elmer 241 polarimeter. The detailed protocols of the in vitro biological assays are described in ref 2.

Methyl 4-(4-Fluorophenyl)-2-(1-methylethyl)-3-quinolinecarboxylate (1c). A solution of methyl 4-methyl-3-oxopentanoate (14.7 g, 0.102 mol), (2-aminophenyl)-4-(fluorophenyl)methanone[15] (18.34 g, 0.085 mol), and a small amount of *p*-TSA in toluene (400 mL) was heated under reflux with azeotropic removal of water for 5 h. The solution was then cooled and concentrated in vacuo. Flash chromatography of the residue, eluting with 10% ethyl acetate–hexane, gave 1c (7.66 g, 28%): ^{1}H NMR ($CDCl_3$) δ 3.05 (d, 1 H), 7.72–6.95 (m, 7 H), 3.52 (s, 3 H), 3.16 (heptet, 1 H), 1.40 (d, 6 H) ppm. Anal. ($C_{20}H_{18}FNO_2$) C, H, N.

4-(4-Fluorophenyl)-2-(1-methylethyl)-3-quinolinemethanol (2c). To a solution of 1c (7.66 g, 0.024 mol) in dichloromethane (100 mL) at −78 °C under an atmosphere of nitrogen was added 55 mL of a 1.0 M solution of DIBAL-H. The resulting solution was stirred for 3 h before quenching with saturated aqueous sodium sulfate (20 mL). After warming to room temperature, the solution was filtered through Celite and the resulting filtrate dried and concentrated in vacuo to yield 6.61 g (94%) of 2c: ^{1}H NMR ($CDCl_3$) δ 7.97 (d, 1 H), 7.57–6.93 (m, 7 H), 4.52 (bs, 2 H), 3.62 (heptet, 1 H), 1.9 (bs, 1 H), 1.43 (d, 6 H) ppm. Anal. ($C_{19}H_{18}FN_2O$) C, H, N.

4-(4-Fluorophenyl)-2-(1-methylethyl)-3-quinolinecarboxaldehyde (3c). To a solution of oxalyl chloride (2.3 mL, 0.027 mol) in anhydrous dichloromethane (50 mL), at −78 °C under an atmosphere of nitrogen, was added dimethyl sulfoxide (3.8 mL, 0.053 mol). After complete addition the resulting solution was stirred for 15 min at −78 °C and then a solution of 2c (6.05 g, 0.02 mol) in dichloromethane (50 mL) was added dropwise. This was stirred for a further 1 h at −78 °C and then quenched by the addition of triethylamine (14.3 mL, 0.103 mol) and saturated aqueous ammonium chloride solution (15 mL). The organic layer was separated and the aqueous layer was extracted with additional dichloromethane. The combined organic layers were dried, filtered, and concentrated in vacuo to yield 3c (6.38 g, quant.) as a pale yellow solid: mp 119–121 °C; ^{1}H NMR ($CDCl_3$) δ 9.92 (s, 1 H), 8.02 (d, 1 H), 7.72–7.52 (m, 1 H), 7.37–6.98 (m, 6 H), 3.94 (heptet, 1 H), 1.38 (d, 6 H) ppm. Anal. ($C_{19}H_{16}FNO$) C, H, N.

Methyl (*E*)-3-[4-(4-Fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]-2-propenoate (4c). Methyl (triphenylphosphoranylidene)acetate (7.5 g, 0.024 mol) and 3c (6.38 g, 0.021 mol) in dichloromethane (100 mL) were stirred at room temperature under nitrogen for 72 h. The solution was then concentrated in vacuo. Flash chromatography on silica gel, eluting with hexanes–ethyl acetate, gave 4c (5.62 g, 74%) as a pale orange solid: mp 147–149 °C; ^{1}H NMR ($CDCl_3$) δ 7.96 (d, 1 H), 7.72–7.04 (m, 8 H), 5.58 (d, 1 H), 3.63 (s, 3 H), 3.38 (heptet, 1 H), 1.35 (d, 6 H) ppm. Anal. ($C_{22}H_{20}FNO_2$) C, H, N.

(*E*)-3-[4-(4-Fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]-2-propen-1-ol (5c). To a solution of 4c (5.62 g, 0.016 mol) in dichloromethane (100 mL) at −78 °C under an atmosphere of nitrogen was added 37.7 mL of a 1.0 M solution of DIBAL-H. The resulting solution was stirred for 2 h at −78 °C and then quenched by addition of saturated aqueous sodium sulfate (15 mL). After warming to room temperature, the solution was filtered through Celite. The resulting filtrate was dried and concentrated in vacuo. The residue was flash chromatographed, eluting with 10% ethyl acetate–hexanes, to yield 5c (4.7 g, 91%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.99 (d, 1 H), 7.60–6.97 (m, 7 H), 6.48 (d, 1 H), 5.45 (dt, 1 H), 4.00 (bs, 2 H), 3.48 (heptet, 1 H), 2.05 (bs, 1 H), 1.38 (d, 6 H) ppm.

(*E*)-3-[4-(4-Fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]-2-propenal (6c). To a solution of oxalyl chloride (1.66 mL, 0.019 mol) in anhydrous dichloromethane (25 mL), at −78 °C under an atmosphere of nitrogen, was added dimethyl sulfoxide (2.75 mL, 0.038 mol) in dichloromethane (25 mL). The resulting solution was stirred for 15 min at −78 °C and then a solution of 5c (4.7 g, 0.015 mol) in dichloromethane (50 mL) was added dropwise. This was stirred for 1 h and then quenched by the addition of triethylamine (10.2 mL, 0.073 mol) and saturated aqueous ammonium chloride solution (15 mL). The organic layer was separated and the aqueous layer was extracted with additional dichloromethane. The combined organic layers were dried, filtered, and concentrated in vacuo to yield 6c (4.37 g, 94%): ^{1}H NMR ($CDCl_3$) δ 9.36 (d, 1 H), 7.96 (d, 1 H), 7.63–7.00 (m, 8 H), 5.90 (dd, 1 H), 3.4 (heptet, 1 H), 1.4 (d, 6 H) ppm.

Ethyl (*E*)-7-[4-(4-Fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]-5-hydroxy-3-oxo-6-heptenoate (7c). Ethyl acetoacetate (2.25 g, 0.017 mol) in anhydrous THF (25 mL) was added dropwise to a stirred suspension of sodium hydride (60% oil suspension, 0.74 g, 0.018 mol) in anhydrous THF (25 mL) at 0 °C under a nitrogen atmosphere. When gas evolution was complete, a 2.4 M solution (7.2 mL, 0.017 mol) of *n*-butyllithium in hexanes was added over 30 min. This was then treated with a solution of 6c (3.68 g, 0.011 mol) in anhydrous THF added dropwise over 30 min. The resulting solution was stirred for 1 h at −78 °C and then quenched by the addition of glacial acetic acid (15 mL) with vigorous stirring. The resulting mixture was then partitioned between diethyl ether and water. After separation of the phases, the aqueous layer was reextracted with diethyl ether, and the combined organic extracts were washed with saturated aqueous sodium bicarbonate and dried. The solvents were removed in vacuo, and the residue was flash chromatographed with hexanes–ethyl acetate as eluant to yield 5.1 g (95%) of the title compound 7c as an orange oil: ^{1}H NMR ($CDCl_3$) δ 8.07 (d, 1 H), 7.64–7.17 (m, 7 H), 6.62 (d, 1 H), 5.34 (dd, 1 H), 4.59 (m, 1 H), 4.21 (q, 2 H), 3.48 (heptet, 1 H), 3.41 (s, 2 H), 2.44 (d, 2 H), 1.38 (d, 6 H), 1.29 (t, 3 H) ppm.

[4α,6β(*E*)]-6-[2-[4-(4-Fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (8c). To a room temperature solution of triethylborane (7.2 mL of a 1 M THF solution; 0.007 mol) under a dry-air atmosphere was added, with stirring, a catalytic amount of pivalic acid (0.7 g, 0.0007 mol). The resulting solution was stirred at room temperature for 10 min before a THF (25 mL) solution of 7c (3.0 g, 0.007 mol) was added dropwise. The resulting solution was stirred at room temperature for a further 15 min before cooling to −78 °C. Methanol (5 mL) was added followed by the addition of sodium borohydride (0.28 g, 0.007 mol) in one portion. Vigorous effervescence ensued. This mixture was stirred at −78 °C for 6 h. It was then quenched by pouring into ice-cold 30% hydrogen peroxide (10 mL). The mixture was allowed to warm slowly to room temperature and then was partitioned between chloroform and water. The organic layer was washed extensively with water, dried, and concentrated in vacuo to yield 3.07 g of the corresponding 1,3-diols as a mixture of erythro and threo diastereomers which were used without any further purification.

This residue was then redissolved in THF (50 mL) and methanol (5 mL) and treated with 1 N aqueous sodium hydroxide (6.7 mL). The resulting solution was stirred at room temperature for 2 h and then concentrated to dryness. The residue was then partitioned between water and ether. The ether layer was extracted with 1 N aqueous NaOH. The aqueous layers were combined, acidified with concentrated HCl, and extracted with ethyl acetate. The ethyl acetate extracts were combined, washed with water, and dried. Removal of the solvents in vacuo yielded a yellow foam which was dissolved in toluene (100 mL) and heated for 3 h at reflux with azeotropic removal of water. The cooled solution was concentrated and the residue flash chromatographed on silica gel, eluting with 50% hexanes–ethyl acetate to yield 8c (1.26 g, 56%) as a white solid, which was shown to be a 97:3 mixture of trans and cis diastereomers by HPLC: mp 168–170

°C; ^{1}H NMR ($CDCl_3$) δ 8.02 (d, 1 H), 7.71 (dt, 1 H), 7.51–7.28 (m, 6 H), 6.69 (d, 1 H), 5.48 (dd, 1 H), 5.24 (bs, 1 H), 5.10–5.00 (m, 1 H), 4.0 (bs, 1 H), 3.48 (heptet, 1 H), 2.67–2.31 (m, 2 H), 1.57–1.42 (m, 2 H), 1.33 (d, 6 H) ppm; IR (KBr) 3430, 2967, 1715, 1514, 1256, 1224, 1160, 1067, 974 cm^{-1}. Anal. ($C_{25}H_{24}FNO_3$) C, H, N.

Compounds 8a–e were synthesized by the general method outlined in Scheme I and exemplified for compound 8c; their physical and biological properties are listed in Table I.

[4α,6β(*E*)]-6-[2-[6-Fluoro-4-(4-fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one, *N*-Oxide (11). A dichloromethane solution (100 mL) of 8d and *m*-CPBA was heated under reflux for 6 h under an atmosphere of nitrogen. The solution was then cooled and washed with saturated aqueous sodium bicarbonate solution. The organic layer was then dried, filtered, and concentrated in vacuo to yield an orange foam (1.24 g), which was flash chromatographed (eluant, 30% ethyl acetate–hexanes) to yield 11 (0.77 g, 74%) as a white solid: mp 235–238 °C; ^{1}H NMR ($CDCl_3$) δ 8.81 (dd, 1 H), 7.49–7.41 (m, 1 H), 7.20 (d, 4 H), 7.01 (dd, 1 H), 6.53 (d, 1 H), 5.44 (dd, 1 H), 5.18–5.13 (m, 1 H), 5.02 (bs, 1 H), 4.15–4.09 (m, 1 H), 3.74 (m, 1 H), 2.79 (bs, 2 H), 2.60 (d, 2 H), 1.55 (d, 6 H) ppm; IR (KBr) 3430, 3260, 1730, 1624, 1513, 1303, 1248, 1218, 1049, 831 cm^{-1}. Anal. ($C_{25}H_{23}F_2NO_4$) C, H, N.

The compounds bearing a saturated two-carbon spacer between the quinoline nucleus and the lactone moiety can be synthesized in an entirely similar manner to that of lactones 8a–e. The experimental details for the key reduction of the α,β-unsaturated esters 4 is exemplified below for the preparation of compound 9.

Methyl 3-[4-(4-Fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]propanoate (9). Compound 4c (10.0 g, 0.029 mol) and 10% Pd/C (0.75 g) were stirred in methanol (250 mL) at room temperature under 50 psi of hydrogen gas. After 5 h, the suspension was filtered and the filtrate concentrated in vacuo to yield 10.14 g of an orange oil. Trituration with hexanes afforded 6.06 g (60%) of 9 as an off-white solid: mp 117–119 °C; ^{1}H NMR ($CDCl_3$) δ 8.06 (d, 1 H), 7.62 (t, 1 H), 7.33 (t, 1 H), 7.29–7.16 (m, 5 H), 3.64 (s, 3 H), 3.44 (heptet, 1 H), 2.96 (t, 2 H), 2.39 (t, 2 H), 1.44 (d, 6 H) ppm. Anal. ($C_{22}H_{22}FNO_2$) C, H, N.

[*R*-(*R,*R**)]-1-Phenylethyl 3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-7-[6-fluoro-4-(4-fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]-5-oxo-6-heptenoate (14).** To a solution of 3d (0.6 g, 0.002 mol) and β-ketophosphonates (12–13, 8:1 mixture of diastereomers) (1.35 g, 0.003 mol) in dichloromethane (10 mL) at −10 °C under a nitrogen atmosphere was added a small amount of LiCl and DBU (2.85 mL, 0.019 mol). The resulting orange solution was stirred at −10 °C for 1.5 h and then quenched by addition of ice-cold phosphoric acid (0.5 M). The organic layer was separated, washed with water, dried, filtered, and concentrated in vacuo to yield a yellow oil (1.65 g). Flash chromatography on silica gel, eluting with 10% ethyl acetate–hexanes gave recovered aldehyde 3d (0.29 g, 0.0009 mol, 48%), 14–15 (0.42 g, 0.0006 mol, 33%), and recovered β-ketophosphonate 12–13: ^{1}H NMR ($CDCl_3$) δ 7.98 (dd, 1 H), 7.51 (d, 1 H), 7.33–6.84 (m, 11 H), 5.89 (d, 1 H), 5.77 (q, 1 H), 4.45 (m, 1 H), 3.34 (heptet, 1 H), 2.59 (d, 2 H), 2.40 (d, 2 H), 1.48 (d, 3 H), 1.33 (d, 6 H), 0.78 (s, 9 H), 0.01 (s, 6 H) ppm.

[4*R*-[4α,6β(*E*)]]-6-[2-[6-Fluoro-4-(4-fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (17). A solution of 48% aqueous HF (0.36 mL, 0.0007 mol) in acetonitrile (3 mL) was added to a solution of 14–15 (0.42 g, 0.0006 mol) in acetonitrile (3 mL). The resulting solution was stirred at room temperature for 1.5 h. It was then diluted with diethyl ether (20 mL) and washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the desilylated compound (0.31 g, 0.0006 mol, 89%) as a colorless oil, which was used in the next step without any further purification: ^{1}H NMR ($CDCl_3$) δ 8.02 (dd, 1 H), 7.58 (d, 1 H), 7.39–6.83 (m, 11 H), 5.93 (d, 1 H), 5.85 (q, 1 H), 4.34 (m, 1 H), 3.34 (heptet, 1 H), 2.59 (d, 2 H), 2.48 (d, 2 H), 1.52 (d, 3 H), 1.37 (d, 6 H) ppm.

The alcohols were then dissolved in anhydrous THF (5 mL) containing pivalic acid (0.006 g, 0.00006 mol) under a dry-air atmosphere at room temperature. To this solution was added triethylborane (0.63 mL of a 1 M THF solution; 0.0006 mol). The resulting solution was stirred at room temperature for 10 min before cooling to −78 °C. Methanol (1 mL) was added, followed by sodium borohydride (0.024 g, 0.0006 mol) in one portion. Vigorous effervescence ensued. This mixture was stirred at −78 °C for 6 h and then quenched by pouring into ice-cold 30% hydrogen peroxide (1 mL). The mixture was allowed to warm slowly to room temperature and then partitioned between chloroform and water. The organic layer was washed extensively with water, dried, and concentrated in vacuo to yield a foam (0.25 g) which contained compound 16 as its major component.

The crude product was then dissolved in THF (5 mL) and methanol (0.5 mL) and treated with 1 N aqueous sodium hydroxide (0.46 mL). This solution was stirred at room temperature for 3 h, and then all solvents were removed in vacuo. The residue was partitioned between diethyl ether and water. The aqueous layer was acidified with 1 N hydrochloric acid, extracted with ethyl acetate, dried, filtered, and concentrated in vacuo to yield a yellow foam, which was redissolved in toluene (60 mL) and heated for 6 h at reflux with azeotropic removal of water. The cooled solution was concentrated and the residue flash chromatographed on silica gel, eluting with 30% ethyl acetate–hexanes, to give 17 (0.035 g, 18%) as a white foam: $[\alpha]_D = +3.4°$ (c = 0.235, $CHCl_3$); HPLC analysis of the corresponding (*R*)-(+)-α-methylbenzylamide derivative indicated an enantiomeric purity of 89% ee; ^{1}H NMR ($CDCl_3$) δ 8.09 (dd, 1 H), 7.47–7.37 (m, 1 H), 7.27–7.18 (m, 4 H), 6.99 (dd, 1 H), 6.68 (d, 1 H), 5.38 (dd, 1 H), 5.20–5.10 (m, 1 H), 4.25–4.19 (m, 1 H), 3.46 (heptet, 1 H), 2.77–2.52 (m, 2 H), 1.83–1.26 (m, 9 H) ppm. Anal. ($C_{25}H_{23}F_2NO_3 \cdot 0.25C_4H_8O_2$) C, H, N.

Ethyl 4-(4-Fluorophenyl)-1,2-dihydro-2-oxo-3-quinolinecarboxylate (19). Ethyl malonyl chloride (125 g, 0.84 mol) was added in portions to a solution of 18[17] in dichloromethane (1 L) at 0 °C under an atmosphere of nitrogen. The reaction mixture was warmed slowly (~1 h) to room temperature, dried, and concentrated to an approximate volume of 600 mL. Silica gel (50 g) was then added. The resulting suspension was stirred overnight at room temperature, and filtered, and the silica gel was washed extensively with ethyl acetate. The filtrate was then concentrated and the residue triturated with hexanes to yield 19 (192 g, 88%) as a white solid: mp 204–206 °C; ^{1}H NMR ($CDCl_3$) δ 12.60 (bs, 1 H), 7.60–7.10 (m, 8 H), 4.17 (q, 2 H), 1.04 (t, 3 H) ppm. Anal. ($C_{18}H_{14}FNO_3$) C, H, N.

Ethyl 2-Chloro-4-(4-fluorophenyl)-3-quinolinecarboxylate (20). A solution of 19 (12.8 g, 0.041 mol) in phosphorus oxychloride (40 mL) was heated to reflux under an atmosphere of nitrogen for 1 h. It was then cooled and concentrated in vacuo and the resulting residue neutralized by the careful addition of cold 1 N sodium hydroxide solution. This was then extracted with ethyl acetate; the organic solution was filtered through a small bed of silica gel to yield 20 (13.2 g, 98%) as a white solid: mp 113–114 °C; ^{1}H NMR ($CDCl_3$) δ 8.02 (d, 1 H), 7.75–7.70 (m, 1 H), 7.52–7.43 (m, 2 H), 7.34–7.28 (m, 2 H), 7.20–7.12 (m, 2 H), 4.14–4.07 (q, 2 H), 1.02 (t, 3 H) ppm. Anal. ($C_{18}H_{13}ClFNO_2$) H, N, Cl, F; C: calcd, 65.56; found, 66.17.

2-Chloro-4-(4-fluorophenyl)-3-quinolinecarboxaldehyde (21). Compound 20 was reduced to the corresponding alcohol, 2-chloro-4-(4-fluorophenyl)-3-quinolinemethanol, in 83% yield in a manner analogous to the reduction of compounds 1a–e to compounds 2a–e in Scheme I: mp 159–160 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 (d, 1 H), 7.79–7.70 (m, 1 H), 7.53–7.22 (m, 6 H), 4.67 (d, 2 H), 2.24 (t, 1 H) ppm. Anal. ($C_{16}H_{11}ClFNO$) C, H, N.

This compound was then oxidized to 21 in a manner analogous to the oxidation of compounds 2a–e to compounds 3a–e in Scheme I: mp 168–169.5 °C; yield 90%; ^{1}H NMR ($CDCl_3$) δ 10.25 (s, 1 H), 8.12 (d, 1 H), 7.91–7.83 (m, 1 H), 7.57–7.53 (m, 2 H), 7.36–7.22 (m, 4 H) ppm. Anal. ($C_{16}H_9ClFNO$) C, H, N.

2-(Dimethylamino)-4-(4-fluorophenyl)-3-quinolinecarboxaldehyde (22). A solution of 21 (5.28 g, 0.019 mol) and dimethylamine (15 mL) in toluene (75 mL) was heated in an autoclave at 123–126 °C for 14 h. It was then cooled and concentrated in vacuo. The residue was partitioned between ethyl acetate and saturated aqueous potassium carbonate solution. The organic layer was dried, filtered, and concentrated in vacuo. The residue was flash chromatographed on silica gel, eluting with 10%

(17) Suzuki, K.; Weisburger, E. K.; Weisburger, J. H. *J. Org. Chem.* 1961, *26*, 2239.

ethyl acetate–hexanes, to yield 22 (4.2 g, 77%) as an orange solid: ^{1}H NMR ($CDCl_3$) δ 9.73 (s, 1 H), 7.78–6.96 (m, 8 H), 3.10 (s, 6 H) ppm. Anal. ($C_{18}H_{15}FN_2O$) C, H, N.

Methyl (*E*)-3-[2-(dimethylamino)-4-(4-fluorophenyl)-3-quinolinyl]-2-propenoate (23) was prepared analogously to compounds 4a–e in Scheme I: yield 92%; ^{1}H NMR ($CDCl_3$) δ 7.78–6.87 (m, 9 H), 5.98 (d, 1 H), 3.60 (s, 3 H), 2.95 (s, 6 H) ppm. Anal. ($C_{21}H_{19}FN_2O_2$) C, H, N.

(*E*)-3-[2-(Dimethylamino)-4-(4-fluorophenyl)-3-quinolinyl]-2-propen-1-ol (24) was prepared analogously to compounds 5a–e in Scheme I: yield 98%; ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 1 H), 7.50–7.30 (m, 1 H), 7.20–6.98 (m, 6 H), 6.31 (d, 1 H), 5.72 (dt, 1 H), 3.99 (bd, 2 H), 2.96 (s, 6 H), 1.54 (bs, 1 H) ppm. Anal. ($C_{20}H_{19}FN_2O$) H; C: calcd, 74.51; found, 72.52; N: calcd, 8.69; found, 7.84.

(*E*)-3-[2-(Dimethylamino)-4-(4-fluorophenyl)-3-quinolinyl]-2-propenal (25) was prepared analogously to compounds 6a–e in Scheme I: yield 92%; ^{1}H NMR ($CDCl_3$) δ 9.35 (d, 1 H), 7.75 (d, 1 H), 7.58–6.98 (m, 8 H), 6.32 (dd, 1 H), 2.99 (s, 6 H) ppm. Anal. ($C_{20}H_{17}FN_2O$) H, N; C: calcd, 74.98; found, 72.85.

[4α,6β(*E*)]-6-[2-[2-(Dimethylamino)-4-(4-fluorophenyl)-3-quinolinyl]ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (26) was prepared in 29% overall yield from compound 25 in an analogous manner to the preparation of lactones 8a–e from aldehydes 6a–e: mp 150–152 °C; ^{1}H NMR ($CDCl_3$) δ 7.83 (d, 1 H), 7.57–7.50 (m, 1 H), 7.26–7.16 (m, 6 H), 6.49 (d, 1 H), 5.66 (dd, 1 H), 5.16–5.06 (m, 1 H), 4.28–4.25 (m, 1 H), 3.01 (s, 6 H), 2.75–2.60 (q, 2 H), 2.07 (bs, 1 H), 1.82–1.51 (m, 1 H) ppm. Anal. ($C_{24}H_{23}FN_2O_3 \cdot 0.5C_4H_8O_2$) C, H, N.

3-Methyl-4-quinolinemethanol (28) was prepared in 73% yield via a DIBAL-H reduction of 27:[15] ^{1}H NMR ($CDCl_3$) δ 8.55 (s, 1 H), 8.17–7.90 (m, 2 H), 7.68–7.42 (m, 2 H), 5.05 (s, 2 H), 2.46 (s, 3 H), 2.20 (bs, 1 H) ppm.

3-Methyl-4-quinolinecarboxaldehyde (29) was prepared in 70% yield from 28 via a Swern oxidation: ^{1}H NMR ($CDCl_3$) δ 10.77 (s, 1 H), 8.68 (s, 1 H), 8.52–8.41 (m, 1 H), 8.03–7.87 (m, 1 H), 7.67–7.34 (m, 2 H), 2.67 (s, 3 H) ppm.

Methyl (*E*)-3-(3-methyl-4-quinolinyl)-2-propenoate (30) was prepared in 76% yield via treatment of 29 with methyl (triphenyiphosphoranylidene)acetate in an analogous manner to the preparation of compounds 4a–e in Scheme I: ^{1}H NMR ($CDCl_3$) δ 8.70 (s, 1 H), 8.10–7.34 (m, 5 H), 6.21 (d, 1 H), 3.80 (s, 3 H), 2.42 (s, 3 H) ppm. Anal. ($C_{14}H_{13}NO_2$) C, H, N.

(*E*)-3-(3-Methyl-4-quinolinyl)-2-propen-1-ol (31) was prepared in 71% yield from 30 via DIBAL-H reduction: ^{1}H NMR ($CDCl_3$) δ 8.65 (s, 1 H), 8.10–7.85 (m, 2 H), 7.66–7.33 (m, 2 H), 6.92 (d, 1 H), 6.11 (dt, 1 H), 4.35 (bs, 3 H), 2.46 (s, 3 H) ppm.

(*E*)-3-(3-Methyl-4-quinolinyl)-2-propenal (32) was prepared in 71% yield from 31 via a Swern oxidation. ^{1}H NMR ($CDCl_3$) δ 9.75 (d, 1 H), 8.63 (s, 1 H), 8.02–7.14 (m, 5 H), 6.38 (dd, 1 H), 2.41 (s, 3 H) ppm.

[4α,6β(*E*)]-6-[2-(3-Methyl-4-quinolinyl)ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (34) was prepared in 10% overall yield from aldehyde 32. The low yield is due to inefficient extraction of the dihydroxy acid from the aqueous phase during the acidification procedure: mp 198–200 °C; ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1 H), 7.94–7.87 (m, 2 H), 7.55–7.34 (m, 2 H), 6.87 (d, 1 H), 5.92 (dd, 1 H), 5.46–5.37 (m, 1 H), 4.90 (bs, 1 H), 4.26 (bs, 1 H), 2.62 (d, 2 H), 2.33 (s, 3 H), 2.15–2.03 (m, 1 H), 1.89–1.76 (m, 1 H) ppm.

In Vivo Acute Inhibition of Cholesterol Synthesis Assay (AICS). Male Sprague–Dawley rats (250 g body weight), previously fed 2.5% cholestyramine for 3 days, were randomly divided into groups (N = 5/group) and given a single dose of vehicle (controls) or compound by an oral gavage at the indicated doses. One hour after drug dosing, all rats were injected intraperitoneally with sodium [1-^{14}C]acetate (20.0 μCi/rat in 0.3 mL of saline). After 50 min, blood samples were taken, plasma was obtained by centrifugation, and plasma [^{14}C]cholesterol was measured after saponification and extraction.

Acknowledgment. We thank Dr. F. A. MacKellar and staff for analytical and spectral determinations, and last but not least Ms. Patty Elka for manuscript preparation.

Disubstituted Tetrahydrofurans and Dioxolanes as PAF Antagonists

Javier Bartroli, Elena Carceller, Manuel Merlos, Julián García-Rafanell, and Javier Forn*

Chemistry Laboratories and Pharmacology Laboratories, Research Center, J. Uriach & Cía.S.A., Degà Bahí 59–67, 08026 Barcelona, Spain. *Received August 4, 1989*

A new series of disubstituted tetrahydrofuran and dioxolane derivatives were prepared and evaluated for their PAF antagonist activity in the PAF-induced in vitro platelet-aggregation and in vivo hypotension tests. Several of these compounds exhibited more potent activity than the structurally related 2-[*N*-acetyl-*N*-[[[[2-methoxy-3-[(octadecylcarbamoyl)oxy]propoxy]carbonyl]amino]methyl]-1-ethylpyridinium chloride (CV-6209, 3) in the in vitro assay, whereas all showed less potency in the in vivo test. The role of both the substituent nature and the placement and number of oxygen atoms in the ring are discussed. A qualitative SAR study was carried out on these nuclei.

Platelet activating factor (PAF, 1) is a naturally occurring phospholipid first described in 1972.[1] It is produced by stimulated basophils, neutrophils, platelets, macrophages, endothelial cells, and IgE-sensitized bone marrow cells.[2] PAF is involved in a wide range of biological actions such as stimulation of platelets and leukocytes, bronchoconstriction, hypotension, negative inotropic cardiac effects, and increase in vascular permeability.[3–5] In vivo experiments have demonstrated PAF's role in several pathological conditions,[6] such as asthma,[7] inflammation,[8] anaphylactic shock,[9] gastric ulceration,[10] and

(1) Benveniste, J.; Henson, P. M.; Cochrane, C. G. *J. Exp. Med.* 1972, *136*, 1356.
(2) Vargaftig, B. B.; Benveniste, J. *Trends Pharmacol. Sci.* 1983, *4*, 341.
(3) Braquet, P.; Vargaftig, B. B. *Transplant. Proc.* 1986, *18* (*Suppl. 4*), 10.
(4) Morley, J. *Agents Actions* 1986, *5*, 107.
(5) (a) Snyder, F. *Med. Res. Rev.* 1985, *5*, 107. (b) Venuti, M. C. *Annu. Rep. Med. Chem.* 1985, *20*, 193.
(6) (a) *New Horizons in Platelet Activating Factor Research*; Winslow, C. M., Lee, M. L., Eds.; Wiley: New York, 1987. (b) Braquet, P.; Touqui, L.; Shen, T. Y.; Vargaftig, B. B. *Pharmacol. Rev.* 1987, *39*, 97.
(7) (a) Page, C. P. *Developments in Asthma. A View of Current Research*; PJB Publications: Richmond, Surrey, England, 1987. (b) Mencia Huerta, J. M.; Benhamou, M. In *Asthma. Clinical Pharmacology and Therapeutic Progress*; Kay, A. B., Ed.; Blackwell Scientific: Oxford, 1986; pp 237–250. (c) Patterson, R.; Bernstein, P. R.; Harris, K. E.; Krell, R. D. *J. Lab. Clin. Med.* 1984, *104*, 340. (d) Morley, J.; Page, C. P.; Sanjar, S. *Int. Arch. Allergy Appl. Immunol.* 1985, *77*, 73. (e) Page, C. P.; Archer, C. B.; Paul, W.; Morley, J. *Trends Pharmacol. Sci.* 1984, *5*, 239.

0022-2623/91/1834-0373$02.50/0

mol) of 6 and 10 mL of HCOOH was heated at reflux for 14 h. Then, 200 mL of water was added and the solution was made basic (pH 9) by addition of sodium carbonate. The resulting solution was extracted with benzene (2 × 150 mL); the organic extracts were dried (Na_2SO_4) and evaporated to give a residue, which crystallized as yellow needles from acetone–hexane. 11: ^{1}H NMR (DMSO) 9.22 (1 H, s, C1-H), 8.97 (1 H, ex, t, $NHCH_2$), 8.40 (2 H, t, C10-H and C7-H), 8.00 (1 H, d, J = 8.6, C3-H), 7.92 (1 H, t, C9-H), 7.59 (1 H, t, C8-H), 6.83 (1 H, d, J = 9.0, C4-H), 3.46 (2 H, qu*, $-NHCH_2CH_2-$), 2.62 (2 H, t, $CH_2CH_2NMe_2$), 2.28 (6 H, s, $N(CH_3)_2$).

Compounds 12, 13, and 16–22 were obtained in an analogous manner. Compound 14 required a refluxing time of 28 h.

(b) 5-[[2-(Dimethylamino)ethyl]amino]-1-octylimidazo-[4,5,1-*de*]acridin-6-one (15). A mixture of 1.48 g (0.004 mol) of hydrochloride 6, 8 mL (0.045 mol) of nonanoic acid, and 10 mL of bromobenzene was heated at reflux for 12 h. After cooling, the solution was diluted with $CHCl_3$ (100 mL) and extracted with 5% aqueous HCl. The aqueous extracts were made basic with NaOH and extracted with benzene. The organic extracts, dried with $CaCl_2$, were evaporated to dryness, and the crude product was crystallized from benzene–heptane. 15: ^{1}H NMR (CD_3OD) 8.56 (1 H, d, C7-H), 8.20 (1 H, d, C10-H), 7.92 (1 H, t, C9-H), 7.88 (1 H, d, J = 8.8, C3-H), 7.59 (1 H, t, C8-H), 6.84 (1 H, d, J = 8.9, C4-H), 3.66–0.88 (27 H, m, series of overlapping signals relative to the aliphatic moieties).

Acknowledgment. This work was supported by Polish Project CPBR 11.5 and by Italian Ministero della Pubblica Instruzione (Fondi 60%). We thank E. Augustin for the determination of cytotoxic activity against $HeLaS_3$ cells in tissue culture, K. Maturska for skillful technical assistance in animal experiments, and F. Lupidi for NMR spectra.

Registry No. 3, 99139-99-8; 3-HCl, 123381-64-6; 3-$MeSO_3H$, 99140-00-8; 4, 99140-23-5; 4-HCl, 123381-65-7; 4-$MeSO_3H$, 99140-24-6; 5, 123381-83-9; 5-HCl, 123381-66-8; 6, 123381-84-0; 6-2HCl, 123381-67-9; 7, 123381-85-1; 7-2HCl, 123381-68-0; 8, 123381-86-2; 8-2HCl, 123381-69-1; 9, 123381-87-3; 9-2HCl, 123381-70-4; 10, 123381-88-4; 10-2HCl, 123381-71-5; 11, 123381-89-5; 11-2HCl, 123381-72-6; 12, 123381-90-8; 12-2HCl, 123381-73-7; 13, 123381-91-9; 13-2HCl, 123381-74-8; 14, 123381-92-0; 14-2HCl, 123381-75-9; 15, 123381-93-1; 15-2HCl, 123381-76-0; 16, 123381-94-2; 16-2HCl, 123381-77-1; 17, 123381-95-3; 17-2HCl, 123381-78-2; 18, 123381-96-4; 18-2HCl, 123411-29-0; 19, 123381-97-5; 19-2HCl, 123381-79-3; 20, 123381-98-6; 20-2HCl, 123381-80-6; 21, 123381-99-7; 21-2HCl, 123381-81-7; 22, 123382-00-3; 22-2HCl, 123381-82-8; $Me_2N(CH_2)_2NH_2$, 108-00-9; $Me_2N(CH_2)_3NH_2$, 109-55-7; $Me_2N(CH_2)_5NH_2$, 3209-46-9; $EtCO_2H$, 79-09-4; $PrCO_2H$, 107-92-6; Me_2CHCO_2H, 79-31-2; $PhCO_2H$, 65-85-0; 1-chloro-4-nitroacridin-9(10*H*)-one, 20621-51-6; nonanoic acid, 112-05-0.

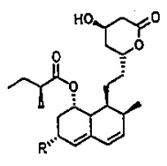
Synthesis and Biological Activity of New HMG-CoA Reductase Inhibitors. 1. Lactones of Pyridine- and Pyrimidine-Substituted 3,5-Dihydroxy-6-heptenoic (-heptanoic) Acids

G. Beck, K. Kesseler, E. Baader, W. Bartmann,* A. Bergmann, E. Granzer, H. Jendralla, B. v. Kerekjarto, R. Krause, E. Paulus, W. Schubert, and G. Wess

Hoechst AG, Postfach 80 03 20, 6230 Frankfurt/M. 80, West Germany. *Received October 24, 1988*

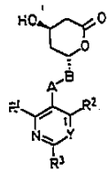
Lactones of pyridine- and pyrimidine-substituted 3,5-dihydroxy-6-heptenoic (-heptanoic) acids 2–4 have been synthesized. Extensive exploration of structure-activity relationships led to several compounds exceeding the inhibitory activity of mevinolin (1b) on HMG-CoA reductase, both in vitro and in vivo. First clinical trials with 2i (HR 780) are in preparation.

Only a few years after the discovery of the LDL receptor by Brown and Goldstein in 1973,[1] the fungal metabolites compactin (1a)[2,3] and mevinolin (1b)[4,5] have been isolated. Both compounds are potent inhibitors of cholesterol biosynthesis at the level of the major rate-limiting enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase). Through a feedback mechanism, inhibition of HMG-CoA reductase results in an increase of LDL-receptor synthesis with subsequent removal of LDL from the bloodstream.[6]



1a: R = H

1b: R = CH_3



2: A–B = (E)–CH=CH; Y = CH, N

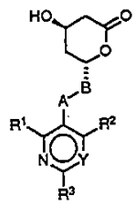
3: A–B = (Z)–CH=CH; Y = CH, N

4: A–B = CH_2–CH_2 ; Y = CH, N

(1) Goldstein, J. L.; Brown, M. S. *Proc. Natl. Acad. Sci. U.S.A.* 1973, *70*, 2804.
(2) (a) Endo, A.; Kuroda, M.; Tsujita, Y. J. *Antibiotics* 1976, *29*, 1346. (b) Endo, A.; Kuroda, M.; Tanzawa, K. *FEBS Lett.* 1976, *72*, 323. (c) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc. Perkin Trans. 1* 1976, 1165.
(3) Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffmann, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, 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*, 3957.
(4) (a) Hoffmann, W. F.; Alberts, A. W.; Anderson, P. S.; Chen, J. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* 1986, *29*, 849. (b) Mol, M. J. T. M.; Erkelens, D. W.; Gevers Leuven, J. A.; Schouten, J. A. *Lancet* 1986, 936.
(5) (a) Serizawa, N.; Nakagawa, K.; Hamano, K.; Tsujita, Y.; Terahara, A.; Kuwano, H. *J. Antibiotics* 1983, *36*, 5. (b) *Drugs Future* 1987, *12*, 437.
(6) Brown, M. S.; Goldstein, J. L. *Sci. Am.* 1984, 52.

0022-2623/90/1833-0052$02.50/0

Table I. Physical Properties and Inhibitory Activities of Lactones 2–4



2: A–B = (*E*)-CH=CH
3: A–B = (*Z*)-CH=CH
4: A–B = CH_2CH_2

no.	Y	R^1	R^2	R^3	purifn[a]	% yield[b]	formula	mp, °C	anal.[c]	IC_{50},[d] nM
1b	–	–	–	–	–	–	–	–	–	8
2a	CH	CH_3	4-FC_6H_4	CH_3	A	16	$C_{20}H_{20}FNO_3$	205	C, H, F, N	260
2b	CH	CH_3	4-ClC_6H_4	CH_3	A	15	$C_{20}H_{20}ClNO_3$	oil	C, H, Cl, N	94
2c	CH	CH_3	4-FC_6H_4	C_6H_5	B	13	$C_{25}H_{22}FNO_3$	149	C, H, F, N	38
2d	CH	C_2H_5	4-FC_6H_4	C_6H_5	C	13	$C_{26}H_{24}FNO_3$	oil	C, H, F, N	40
2e	CH	*i*-C_3H_7	4-FC_6H_4	CH_3	C	23	$C_{22}H_{24}FNO_3$	oil	C, H, F, N	9
2f	CH	*i*-C_3H_7	4-FC_6H_4	*i*-C_3H_7	C	28	$C_{24}H_{28}FNO_3$	137–140	C, H, F, N	3
2g	CH	*i*-C_3H_7	4-FC_6H_4	*t*-C_4H_9	C	16	$C_{25}H_{30}FNO_3$	158–160[e]	C, H, F, N	1
2h	CH	*i*-C_3H_7	4-FC_6H_4	c-C_6H_{11}	C	13	$C_{27}H_{32}FNO_3$	135–138	C, H, F, N	4
2i	CH	*i*-C_3H_7	4-FC_6H_4	C_6H_5	C	24	$C_{27}H_{26}FNO_3$	141[f,g]	C, H, F, N	3
2j	CH	*i*-C_3H_7	4-FC_6H_4	4-FC_6H_4	C	22	$C_{27}H_{25}F_2NO_3$	oil	C, H, F, N	2
2k	CH	*i*-C_3H_7	4-FC_6H_4	2,5-$(CH_3)_2C_6H_3$	C	28	$C_{29}H_{30}FNO_3$	oil	C, H, F, N	5
2l	CH	*i*-C_3H_7	4-FC_6H_4	3,5-$(CH_3)_2C_6H_3$	C	26	$C_{29}H_{30}FNO_3$	80	C, H, F, N	8
2m	CH	*i*-C_3H_7	4-$CH_3OC_6H_4$	C_6H_5	C	30	$C_{28}H_{29}NO_4$	oil	C, H, N	13
2n	CH	*i*-C_3H_7	4-$CF_3C_6H_4$	C_6H_5	C	21	$C_{28}H_{26}F_3NO_3$	oil	C, H, F, N	36
2o	CH	*t*-C_4H_9	4-FC_6H_4	C_6H_5	C	19	$C_{28}H_{28}FNO_3$	oil	C, H, F, N	18
2p	CH	c-C_6H_{11}	4-FC_6H_4	C_6H_5	C	11	$C_{30}H_{30}FNO_3$	196–198	C, H, F, N	30
2q	CH	4-FC_6H_4	*i*-C_3H_7	C_6H_5	C	25	$C_{27}H_{26}FNO_3$	oil	C, H, F, N	4
2r	N	CH_3	4-FC_6H_4	CH_3	D	18	$C_{19}H_{19}FN_2O_3$	174–176[h]	C, H, F, N	500
2s	N	CH_3	4-ClC_6H_4	CH_3	D	20	$C_{19}H_{19}ClN_2O_3$	oil	C, H, Cl, N	600
2t	N	*i*-C_3H_7	4-FC_6H_4	*i*-C_3H_7	E	13	$C_{23}H_{27}FN_2O_3$	oil	C, H, F, N	3
2u	N	*i*-C_3H_7	4-FC_6H_4	c-C_6H_{11}	C	19	$C_{26}H_{31}FN_2O_3$	128	C, H, F, N	1
2v	N	*i*-C_3H_7	4-FC_6H_4	C_6H_5	D	18	$C_{26}H_{25}FN_2O_3$	164–166[i]	C, H, F, N	3
2w	N	*i*-C_3H_7	4-FC_6H_4	4-FC_6H_4	C	22	$C_{26}H_{24}F_2N_2O_3$	138–140	C, H, F, N	1
3a	CH	CH_3	4-FC_6H_4	CH_3	A	8	$C_{20}H_{20}FNO_3$	188	C, H, F, N	>1000
3c	CH	CH_3	4-FC_6H_4	C_6H_5	B	8	$C_{25}H_{22}FNO_3$	216	C, H, F, N	100
3s	N	CH_3	4-ClC_6H_4	CH_3	D	18	$C_{19}H_{19}ClN_2O_3$	165–166	C, H, Cl, N	>1000
4d	CH	C_2H_5	4-FC_6H_4	C_6H_5	–	17	$C_{26}H_{26}FNO_3$	53–55	C, H, F, N	3
4i	CH	*i*-C_3H_7	4-FC_6H_4	C_6H_5	–	22	$C_{27}H_{28}FNO_3$	oil	C, H, F, N	19
4r	N	CH_3	4-FC_6H_4	CH_3	–	18	$C_{19}H_{21}FN_2O_3$	170–172	C, H, F, N	1000

[a] Purified by flash chromatography on silica using the following eluents: A ethyl acetate/methanol 10:1, B cyclohexane/ethyl acetate 1:4, C cyclohexane/ethyl acetate 2:1, D ethyl acetate, E cyclohexane/ethyl acetate 1:1. [b] Represents overall yield for purified material from Wittig reaction of 6. [c] Analytical results for purified material were within ±0.4% of the theoretical values. [d] Tested in the ring-opened potassium dihydroxycarboxylate form, for assay protocol see the Experimental Section. [e] $[\alpha]^{20}_D = +26°$ ($c = 1$, methanol). [f] $[\alpha]^{20}_D = +25°$ ($c = 1$, methanol). [g] Obtained as an oil, which crystallized on standing for several weeks; melting point determined after recrystallization from diisopropyl ether/ethyl acetate 2:1. [h] $[\alpha]^{20}_D = +21°$ ($c = 1$, methanol). [i] $[\alpha]^{20}_D = +14°$ ($c = 1$, methanol).

Recent reports by Merck Sharp & Dohme,[7] Sandoz,[8] and Warner-Lambert[9] have described natural products and synthetic analogues related to mevinolin (1b). In our laboratories structurally simplified HMG-CoA reductase inhibitors have been synthesized as well.[10,11] Structure–activity relationships (SAR) in previous series[7,10,11] revealed that the chiral lactone moiety in mevinolin (1b) is essential for strong biological activity, whereas the hexahydronaphthalene moiety allows more structural variations. In the present paper we describe the synthesis and biological activity of new HMG-CoA reductase inhibitors 2–4, which contain for the first time monocyclic,[12] six-membered

(7) (a) Stokker, G. E.; Hoffmann, W. F.; Alberts, A. W.; Cragoe, E. J., Jr.; Deana, A. A.; Gilfillan, J. L.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* 1985, *28*, 347. (b) Hoffmann, W. F.; Alberts, A. W.; Cragoe, E. J., Jr.; Deana, A. A.; Evans, B. E.; Gilfillan, J. L.; Gould, N. P.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Rittle, K. E.; Smith, R. L.; Stokker, G. E.; Willard, A. K. *J. Med. Chem.* 1986, *29*, 159. (c) Stokker, G. E.; Alberts, A. W.; Anderson, P. S.; Cragoe, E. J., Jr.; Deana, A. A.; Gilfillan, J. L.; Hirshfield, J.; Holtz, W. F.; Hoffmann, 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. (d) Hoffmann, W. F.; Alberts, A. W.; Anderson, P. S.; Chen, J. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* 1986, *29*, 849. (e) Stokker, G. E.; Alberts, A. W.; Gilfillan, J. L.; Huff, J. W.; Smith, R. L. *J. Med. Chem.* 1986, *29*, 852.

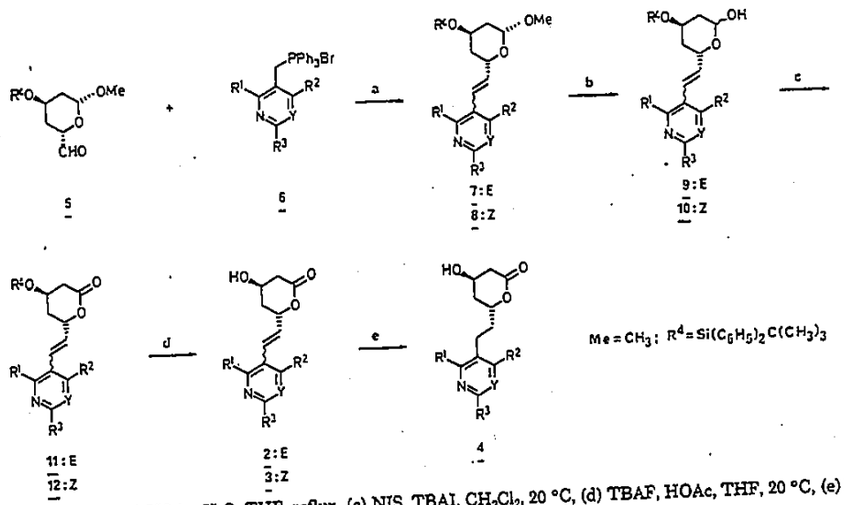
(8) (a) Sandoz, patent WO 84/02131, 1984. (b) Sandoz, patent WO 86/00307, 1986. (c) Sandoz, patent WO 86/07054, 1986. (d) Sandoz, European Application EP-A-0221025, 1987.

(9) Warner-Lambert, European Application EP-A-0179559, 1986.

(10) Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Granzer, E.; Jendralla, H.; v. Kerekjarto, B.; Kesseler, K.; Krause, R.; Paulus, E. F.; Schubert, W.; Wess, G.; 4th. International Conference of Chemistry and Biotechnology of Biologically Active Natural Products, Budapest, August 10–14, 1987, submitted for publication (Raven Press, New York).

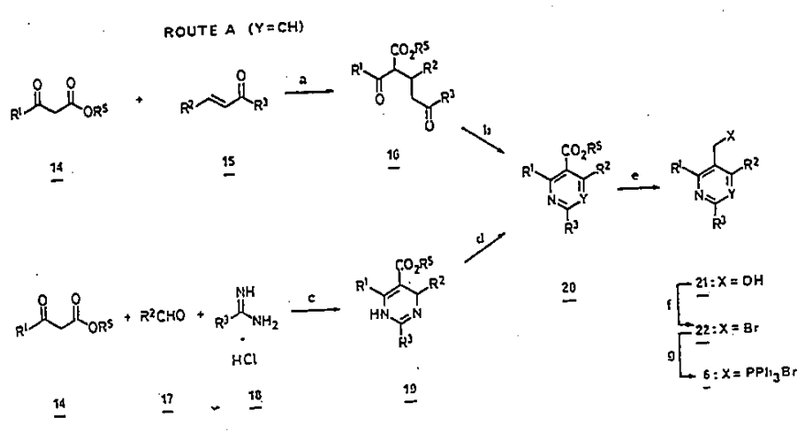
(11) (a) Bartmann, W.; Beck, G.; Granzer, E.; Jendralla, H.; v. Kerekjarto, B.; Wess, G. *Tetrahedron Lett.* 1986, *27*, 4709. (b) Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Jendralla, H.; Kesseler, K.; Wess, G.; Schubert, W.; Granzer, E.; v. Kerekjarto, B.; Krause, R. *Tetrahedron Lett.* 1988, *29*, 933

Scheme I[a]



a (a) *n*-BuLi, THF, 0–20 °C, (b) HOAc, H_2O, THF, reflux, (c) NIS, TBAI, CH_2Cl_2, 20 °C, (d) TBAF, HOAc, THF, 20 °C, (e) H_2, Pd/C cat., MeOH, EtOAc, 20 °C.

Scheme II[a]



a (a) KO-*t*-Bu cat., *i*-Pr_2O, 20 °C, (b) NH_4OAc, $FeCl_3 \cdot 6H_2O$, HOAc, reflux, (c) KOAc, PhMe, reflux, (d) DDQ, PhMe, reflux, (e) $LiAlH_4$, THF, 20 °C, (f) PBr_3, CH_2Cl_2, 20 °C, (g) PPh_3, PhMe, reflux.

heteroaromatic groups with basic properties.

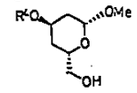
Chemistry

The new compounds 2–4 were synthesized in optically pure form by the general method shown in Scheme I and are listed in Table I. Compounds 2 were obtained through Wittig reaction with the chiral aldehyde 5 and ylides generated from the phosphonium salts 6, followed by cleavage of the lactol ether moiety of 7, oxidation of 9 to lactones 11, and desilylation. *Z*-configurated analogues 3 were prepared through the general sequence 8 → 10 → 12 → 3.

The Wittig reaction proceeded with high stereoselectivity, leading predominantly to the biologically more potent *E* isomers. Double-bond geometry was assigned on the basis of the ^1H NMR coupling constants of the olefinic protons (*E* isomers, J = 16 Hz; *Z* isomers, J = 11 Hz).

The saturated analogues 4 were synthesized by catalytic hydrogenation of compounds 2 or 3.

In all cases, the configuration of the lactone moiety results from synthesis via the optically pure 4*R*,6*S* aldehyde 5.[13] Compound 5 was easily prepared through Swern oxidation[14] of the corresponding alcohol 13,[13] obtained stereoselectively from glucose.



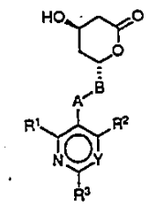
13

For compound 2i the assigned relative configuration has been additionally confirmed by X-ray crystallographic analysis.

(12) Quinoline-containing HMG-CoA reductase inhibitors have recently been produced by Warner-Lambert, U.S. Patent 4761419 A, 1988.

(13) Yang, Y. L.; Falck, J. R. *Tetrahedron Lett.* 1982, *23*, 4305.
(14) Swern, D.; Manusco, A.; Huany, S. *J. Org. Chem.* 1978, *43*, 2480.

Table II. Inhibitory Effect of Compounds 2–4 on the de Novo Cholesterol Biosynthesis of HEP-G2 Cell Cultures[a]



2: A–B = (*E*)-CH=CH
3: A–B = (*Z*)-CH=CH
4: A–B = CH_2CH_2

no.	Y	R^1	R^2	R^3	IC_{50}, nM	rel potency[b]
1b	–	–	–	–	50	1.00
2a	CH	CH_3	$4\text{-}FC_6H_4$	CH_3	2000	0.03
2c	CH	CH_3	$4\text{-}FC_6H_4$	C_6H_5	90	0.56
2e	CH	$i\text{-}C_3H_7$	$4\text{-}FC_6H_4$	CH_3	50	1.00
2g	CH	$i\text{-}C_3H_7$	$4\text{-}FC_6H_4$	$t\text{-}C_4H_9$	20	2.50
2h	CH	$i\text{-}C_3H_7$	$4\text{-}FC_6H_4$	$c\text{-}C_6H_{11}$	9.5	5.26
2i	CH	$i\text{-}C_3H_7$	$4\text{-}FC_6H_4$	C_6H_5	5.0	10.00
2j	CH	$i\text{-}C_3H_7$	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	7.5	6.67
2k	CH	$i\text{-}C_3H_7$	$4\text{-}FC_6H_4$	$2,5\text{-}(CH_3)_2\text{-}C_6H_3$	20	2.50
2m	CH	$i\text{-}C_3H_7$	$4\text{-}CH_3OC_6H_4$	C_6H_5	150	0.33
2p	CH	$c\text{-}C_6H_{11}$	$4\text{-}FC_6H_4$	C_6H_5	>5000	>0.01
2q	CH	$4\text{-}FC_6H_4$	$i\text{-}C_3H_7$	C_6H_5	10	5.00
2t	N	$i\text{-}C_3H_7$	$4\text{-}FC_6H_4$	$i\text{-}C_3H_7$	4.8	10.42
2u	N	$i\text{-}C_3H_7$	$4\text{-}FC_6H_4$	$c\text{-}C_6H_{11}$	26	1.92
2y	N	$i\text{-}C_3H_7$	$4\text{-}FC_6H_4$	C_6H_5	5	10.00
2w	N	$i\text{-}C_3H_7$	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	18	2.78
3c	CH	CH_3	$4\text{-}FC_6H_4$	C_6H_5	5000	0.08
4i	CH	$i\text{-}C_3H_7$	$4\text{-}FC_6H_4$	C_6H_5	370	0.14

[a] For assay protocol, see the Experimental Section. [b] Potency of mevinolin (1b) was arbitrarily assigned a value of 1.00.

The synthesis of phosphonium salts 6, via esters 20, is outlined in Scheme II. Pyridine esters 20 (Y = CH) were obtained through Michael addition[15] of keto esters 14[16] and enones 15,[17] followed by oxidative cyclization[18] of the intermediate 1,5-diketones 16 (route A, see Table III). Pyrimidine esters 20 (Y = N) were synthesized through condensation of 14 with aldehydes 17 and amidinium salts 18,[19] followed by oxidation of the resulting 1,4-dihydropyrimidines 19 by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; route B, see Table III). In all cases, esters 20 were transformed to phosphonium salts 6 in three steps via reduction, halogenation of the resulting alcohols 21, and finally reaction of bromides 22 with triphenyl phosphine (see Table IV).

Biological Results and Discussion

The new pyridine and pyrimidine analogues 2–4 (Table I) were evaluated for their ability to inhibit solubilized, partially purified rat liver HMG-CoA reductase in vitro. Compounds 2–4 were also investigated for inhibition of cellular HMG-CoA reductase in cultures of hepatic cells (HEP G2, a human hepatoma cell line), determined by decreased incorporation of sodium [^{14}C]acetate into cholesterol (Table II). Selected compounds were further evaluated for their ability to inhibit hepatic cholesterol synthesis and to decrease cholesterol levels in several animal species upon po administration.[20]

All biological experiments were performed with optically pure 1b as reference for direct comparison.

In general, the structure–activity relationships of pyrimidines (2r–w) are comparable to those of the corresponding pyridines (2a–q) (e.g. 2i vs 2v, 2a vs 2r, 2j vs 2w; Table I). The inhibitory potency strongly depends on the substitution pattern of the heteroaromatic ring. We[10–12] and others[7] have recently shown that substitution in 2-, 4-, and 6-position of the central aromatic ring leads to strong biological activity.

However, through appropriate choice of substituents, the inhibitory potency of the compounds can be further increased by 3 orders of magnitude.

The biological activity of compounds 2 reaches a maximum if an isopropyl group is introduced in position 2 of the central heteroaromatic ring (e.g. 2i vs 2o, 2p, 2d, and 2a). Polar substituents in position 4, which seem to mimic the polar ester moiety of mevinolin, have previously been shown to result in compounds with high activity.[7]

In our series 4-(chlorophenyl)- and 4-(fluorophenyl)-substituted analogues are equally potent inhibitors (e.g. 2a vs 2b, 2r vs 2s). 4-(Methoxyphenyl) or 4-[(trifluoromethyl)phenyl] substitution leads to significant loss of activity (2m, 2n, vs 2i).

Substitution in position 6 turns out to be the most critical for optimal biological activity. Marked increase of potency is obtained not only by introduction of bulky alkyl groups (e.g. 2f, 2g, 2h, 2t vs 2e, 2s) but also by the use of phenyl moieties (e.g. 2i, 2j, 2k, 2v, 2w).

In order to further understand the structure–activity relationships, inhibitor 2i was compared with mevinolin (1b) by using computer-assisted methods.

For both compounds a conformational analysis was carried out in order to determine their low-energy conformations. Structure 2i was fitted to 1b by reorienting it as a whole and allowing groups to move independently (for details, see the Experimental Section).

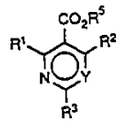
A graphical representation of the fit of 2i against 1b is shown in Figure 1. If the lactone moieties are oriented the same way in both conformers, the isopropyl group of 2i occupies partly the region of the hexahydronaphthalene system of 1b. At the same time the 4-fluorophenyl group of 2i occupies most of the space of the ester group of 1b. The phenyl ring of 2i, however, completely extends beyond the volume of 1b.

Since 2i and all other compounds bearing bulky substituents as R^3 (e.g. 2f, 2h, 2j, 2n, 2t, 2w) are more potent than mevinolin, one might speculate that R^3 serves as an additional anchor, interacting with a second hydrophobic region of the enzyme and thus increases binding. A final explanation might be expected by the elucidation of the tertiary structure of the HMG-CoA reductase. All *Z* double bond isomers 3 showed only weak in vitro activity (e.g. 3a, 3c, 3r). Also hydrogenation of *E* isomers 2 in most cases significantly decreased inhibitory potency (e.g. 2i vs 4i, 2r vs 4r). However, rather unexpectedly, 4d was 10 times more active in vitro than 2d. This points to a delicate balance[21] between the length of the carbon bridge and the steric bulk of R^1 with regard to adaptation of the inhibitor to the active site of the enzyme.

(15) Connor, R.; Andrews, D. B. *J. Am. Chem. Soc.* 1934, *56*, 2713.
(16) Jackman, M.; Klenk, M.; Fishburn, B.; Tullar, B. F.; Archer, S. *J. Am. Chem. Soc.* 1948, *70*, 2884.
(17) (a) Drake, N. L.; Allen, P. In *Organic Synthesis*; John Wiley & Sons, Inc. New York, 1932; Collect. Vol. I, p 77. (b) Kohler, E. L.; Chadwell, H. M. *Ibid.* p 78.
(18) Rehberg, R.; Kroehnke, F. *Justus Liebigs Ann. Chem.* 1968, *717*, 91.
(19) (a) Dox, A. W. In *Organic Synthesis*; Wiley and Sons Inc., New York, 1932; Collect. Vol. I, p 5. (b) Brown, D. J.; Lan, S.; Mori, K. *Aust. J. Chem.* 1984, *37*, 2093. (c) Hagemeyer, J. H.; Gammans, W. J. U.S. 3, 402, 193 (Eastman Kodak Co.); *Chem. Abstr.* 1960, *70*, 3316.

(20) Results will be published separately.

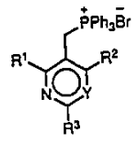
Table III. Physical Properties of Esters 20



no.	Y	R^1	R^2	R^3	R^5	purifn[a]	% yield[b]	formula	mp, °C	anal.[c]
20a	CH	CH_3	4-FC_6H_4	CH_3	CH_3	A	66	$C_{15}H_{14}FNO_2$	oil	C, H, F, N
20b	CH	CH_3	4-ClC_6H_4	CH_3	CH_3	B	73	$C_{15}H_{14}ClNO_2$	oil	C, H, Cl, N
20c	CH	CH_3	4-FC_6H_4	C_6H_5	C_2H_5	B	69	$C_{21}H_{18}FNO_2$	oil	C, H, F, N
20d	CH	C_2H_5	4-FC_6H_4	C_6H_5	C_2H_5	C	28	$C_{22}H_{20}FNO_2$	oil	C, H, F, N
20e	CH	i-C_3H_7	4-FC_6H_4	CH_3	C_2H_5	D	58	$C_{16}H_{20}FNO_2$	oil	C, H, F, N
20f	CH	i-C_3H_7	4-FC_6H_4	i-C_3H_7	C_2H_5	C	68	$C_{20}H_{24}FNO_2$	oil	C, H, F, N
20g	CH	i-C_3H_7	4-FC_6H_4	t-C_4H_9	C_2H_5	E	46	$C_{21}H_{26}FNO_2$	oil	C, H, F, N
20h	CH	i-C_3H_7	4-FC_6H_4	c-C_6H_{11}	C_2H_5	E	45	$C_{23}H_{28}FNO_2$	oil	C, H, F, N
20i	CH	i-C_3H_7	4-FC_6H_4	C_6H_5	C_2H_5	D	66	$C_{23}H_{22}FNO_2$	oil	C, H, F, N
20j	CH	i-C_3H_7	4-FC_6H_4	4-FC_6H_4	C_2H_5	E	55	$C_{23}H_{21}F_2NO_2$	109–111	C, H, F, N
20k	CH	i-C_3H_7	4-FC_6H_4	2,5-$(CH_3)_2C_6H_3$	C_2H_5	E	79	$C_{25}H_{26}FNO_2$	oil	C, H, F, N
20l	CH	i-C_3H_7	4-FC_6H_4	3,5-$(CH_3)_2C_6H_3$	C_2H_5	E	61	$C_{25}H_{26}FNO_2$	oil	C, H, F, N
20m	CH	i-C_3H_7	4-$CH_3OC_6H_4$	C_6H_5	C_2H_5	E	66	$C_{24}H_{23}NO_3$	70–74	C, H, N
20n	CH	i-C_3H_7	4-$CF_3C_6H_4$	C_6H_5	C_2H_5	E	71	$C_{24}H_{22}F_3NO_2$	oil	C, H, F, N
20o	CH	t-C_4H_9	4-FC_6H_4	C_6H_5	C_2H_5	C	22	$C_{24}H_{24}FNO_2$	oil	C, H, F, N
20p	CH	c-C_6H_{11}	4-FC_6H_4	C_6H_5	C_2H_5	C	55	$C_{26}H_{26}FNO_2$	oil	C, H, F, N
20q	CH	4-FC_6H_4	i-C_3H_7	C_6H_5	CH_3	D	52	$C_{22}H_{20}FNO_2$	114	C, H, F, N
20r	N	CH_3	4-FC_6H_4	CH_3	C_2H_5	F	43	$C_{15}H_{15}FN_2O_2$	oil	C, H, F, N
20s	N	CH_3	4-ClC_6H_4	CH_3	C_2H_5	F	47	$C_{15}H_{15}ClN_2O_2$	oil	C, H, Cl, N
20t	N	i-C_3H_7	4-FC_6H_4	i-C_3H_7	C_2H_5	A	33	$C_{19}H_{23}FN_2O_2$	141	C, H, F, N
20u	N	i-C_3H_7	4-FC_6H_4	c-C_6H_{11}	C_2H_5	B	47	$C_{22}H_{27}FN_2O_2$	oil	C, H, F, N
20v	N	i-C_3H_7	4-FC_6H_4	C_6H_5	C_2H_5	C	51	$C_{22}H_{21}FN_2O_2$	105	C, H, F, N
20w	N	i-C_3H_7	4-FC_6H_4	4-FC_6H_4	C_2H_5	C	73	$C_{22}H_{20}F_2N_2O_2$	105–108	C, H, F, N

[a] Purified by flash chromatography on silica using the following eluents: A cyclohexane/ethyl acetate 2:1, B cyclohexane/ethyl acetate 1:1, C cyclohexane/ethyl acetate 4:1, D cyclohexane/ethyl acetate 3:1, E cyclohexane/ethyl acetate 8:1, F cyclohexane/methanol 9:1. [b] Represents overall yield from Michael reaction of keto esters 14. [c] Analytical results were within ±0.4% of the theoretical values.

Table IV. Physical Properties of Phosphonium Salts 6



no.	Y	R^1	R^2	R^3	% yield[a]	formula	mp, °C	anal.[b]
6a	CH	CH_3	4-FC_6H_4	CH_3	65	$C_{32}H_{28}BrFNP$	218–220	C, H, Br, F, N, P
6b	CH	CH_3	4-ClC_6H_4	CH_3	32	$C_{32}H_{28}BrClNP$	oil	C, H, Br, Cl, N, P
6c	CH	CH_3	4-FC_6H_4	C_6H_5	64	$C_{37}H_{30}BrFNP$	230–232	C, H, Br, F, N, P
6d	CH	C_2H_5	4-FC_6H_4	C_6H_5	91	$C_{38}H_{32}BrFNP$	218–220	C, H, Br, F, N, P
6e	CH	i-C_3H_7	4-FC_6H_4	CH_3	29	$C_{34}H_{32}BrFNP$	209	C, H, Br, F, N, P
6f	CH	i-C_3H_7	4-FC_6H_4	i-C_3H_7	60	$C_{36}H_{36}BrFNP$	100[c]	C, H, Br, F, N, P
6g	CH	i-C_3H_7	4-FC_6H_4	t-C_4H_9	63	$C_{37}H_{38}BrFNP$	100[c]	C, H, Br, F, N, P
6h	CH	i-C_3H_7	4-FC_6H_4	c-C_6H_{11}	64	$C_{39}H_{40}BrFNP$	223–226	C, H, Br, F, N, P
6i	CH	i-C_3H_7	4-FC_6H_4	C_6H_5	34	$C_{39}H_{34}BrFNP$	268–274	C, H, Br, F, N, P
6j	CH	i-C_3H_7	4-FC_6H_4	4-FC_6H_4	42	$C_{39}H_{33}BrF_2NP$	235–239	C, H, Br, F, N, P
6k	CH	i-C_3H_7	4-FC_6H_4	2,5-$(CH_3)_2C_6H_3$	54	$C_{41}H_{38}BrFNP$	250	C, H, Br, F, N, P
6l	CH	i-C_3H_7	4-FC_6H_4	3,5-$(CH_3)_2C_6H_3$	58	$C_{41}H_{38}BrFNP$	250	C, H, Br, F, N, P
6m	CH	i-C_3H_7	4-$CH_3OC_6H_4$	C_6H_5	67	$C_{40}H_{37}BrNOP$	270–275	C, H, Br, N, P
6n	CH	i-C_3H_7	4-$CF_3C_6H_4$	C_6H_5	82	$C_{40}H_{34}BrF_3NP$	250	C, H, Br, F, N, P
6o	CH	t-C_4H_9	4-FC_6H_4	C_6H_5	55	$C_{40}H_{36}BrFNP$	250	C, H, Br, F, N, P
6p	CH	c-C_6H_{11}	4-FC_6H_4	C_6H_5	70	$C_{42}H_{38}BrFNP$	270[c]	C, H, Br, F, N, P
6q	CH	4-FC_6H_4	i-C_3H_7	C_6H_5	41	$C_{33}H_{34}BrFNP$	254	C, H, Br, F, N, P
6r	N	CH_3	4-FC_6H_4	CH_3	45	$C_{31}H_{27}BrFN_2P$	232–236	C, H, Br, F, N, P
6s	N	CH_3	4-ClC_6H_4	CH_3	56	$C_{31}H_{27}BrClN_2P$	217–219	C, H, Br, Cl, N, P
6t	N	i-C_3H_7	4-FC_6H_4	i-C_3H_7	40	$C_{35}H_{33}BrFN_2P$	166–169	C, H, Br, F, N, P
6u	N	i-C_3H_7	4-FC_6H_4	c-C_6H_{11}	42	$C_{38}H_{39}BrFN_2P$	oil	C, H, Br, F, N, P
6v	N	i-C_3H_7	4-FC_6H_4	C_6H_5	69	$C_{38}H_{33}BrFN_2P$	272–274	C, H, Br, F, N, P
6w	N	i-C_3H_7	4-FC_6H_4	4-FC_6H_4	70	$C_{38}H_{32}BrF_2N_2P$	210–214	C, H, Br, F, N, P

[a] Represents overall yield from reduction of esters 20. [b] Analytical results were within ±0.4% of the theoretical values. [c] Decomposition.

In HEP G2 cells, lactones 2–4 show comparable structure–activity relationships (SAR) as indicated above for their sodium salts in the enzyme test (Table II). A series of compounds (e.g. 2g–k, 2v, 2w) are more potent in HEP G2 cells than mevinolin.

Inhibition of hepatic cholesterol "de novo" synthesis in vivo after oral administration to rats for selected compounds 2 also exceeds that of mevinolin.[20] Several compounds (e.g. 2i and 2t) were also investigated in normolipemic rabbits. Analogue 2i (10 mg/kg) after oral ad-

(21) Although these results are somewhat conflicting, they are in line with observations made in a series of HMG-CoA reductase inhibitors containing a central phenyl moiety.[7] Depending on the substitution pattern of the aromatic ring, saturation of the ethylenic bridge in some cases decreased activity,[7c] whereas in other cases it increased activity.[7a,b]

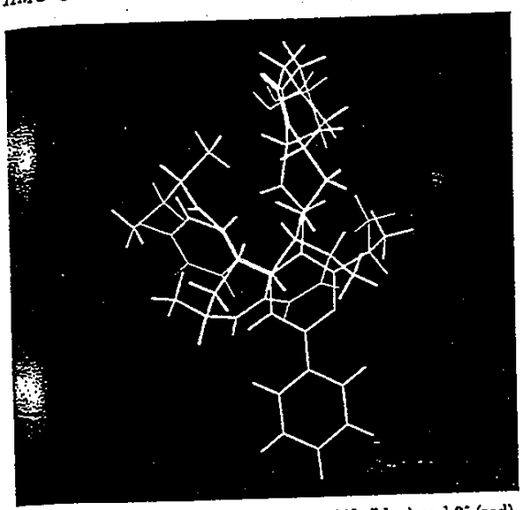


Figure 1. Superposition of structures of 1b (blue) and 2i (red). Except for the phenyl ring, 2i occupies the same regions of space as 1b.

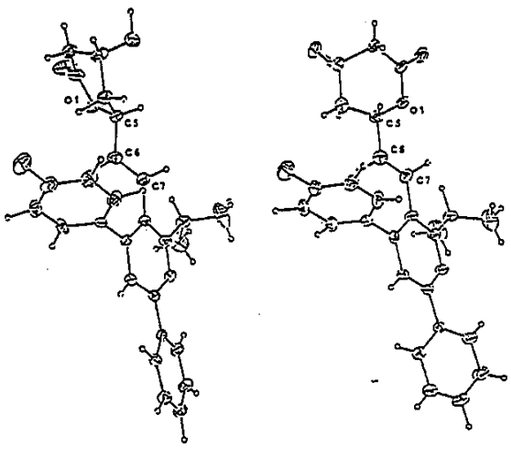


Figure 2. Computer-generated ORTEP drawings of conformers A (left) and B (right) of compound 2i forming an asymmetrical unit within the unit cell.

ministration for 19 days decreased serum total and LDL-cholesterol levels by 35% and 53%, respectively (mevinolin at 10 mg/kg for 19 days: total cholesterol −17%, LDL-cholesterol −30%). Oral treatment with 2t (5 mg/kg) for 10 days resulted in a 30% decrease of total cholesterol.

X-ray Crystallography for 2i

The X-ray structure analysis of 2i resulted in two distinct molecules forming an asymmetric unit, which show quite different conformations (Figure 2). The lactone ring of molecule A adopts a boat conformation; that of molecule B is in the chair conformation. Further, large differences in the torsion angles O1–C5–C6–C7 (43.4° and 130.4°, respectively) were detected. There are no substantial differences in bond lengths or bond angles; all the different planar groups of atoms are not coplanar, because otherwise the steric hindrance would be too large. The dihedral angles between the central pyridine ring and the ethylene bridge, the fluorophenyl, and the phenyl group are 50.8°, 83.2°, and 18.3° (conformer A) and 51.4°, 71.5°, and 17.6° (conformer B). The congruency of the parameters of the two molecules was not optimal, because of the unsatisfactory crystal quality usually obtained when two molecules of different conformation are crystallizing together.

Conclusion

The pyridine and pyrimidine analogues 2–4 synthesized for this study are potent inhibitors toward HMG-CoA reductase. SAR studies showed that a similar 2,4,6-substitution pattern of the pyridine and pyrimidine ring was necessary for optimal biological activity. Different from SAR studies in other series,[7] we showed that bulky lipophilic substituents in position 6 of the central aromatic ring add significantly to the biological activity of synthetic HMG-CoA reductase inhibitors. A series of compounds 2 and 4 exceeded the activity of mevinolin in HEP G2 cells, as well as in the reduction of plasma cholesterol levels in normolipemic rabbits. Some of these compounds are currently being evaluated for development as antiarteriosclerotic drugs. With the pyridine analogue 2i (HR 780) toxicological studies in rats and monkeys have already been performed.[20] The first clinical trials with this compound are in preparation.

Experimental Section

Reaction with materials sensitive to air or moisture were run in dry-glass apparatus under an argon atmosphere with absolute solvents. All reactions were monitored by TLC. Unless noted otherwise, reaction mixtures were worked up by quenching with water, separation of the organic layer, and extraction of the aqueous phase with ether. The combined organic extracts were washed with water or brine, dried over $MgSO_4$, and evaporated on a rotary evaporator. Melting points were determined on a Büchi capillary melting point apparatus (according to Dr. Tottoli) and are uncorrected. ^1H NMR spectra were recorded on a Bruker WP60 or WM270 spectrometer using $CDCl_3$ as solvent. Chemical shifts are given in ppm relative to tetramethylsilane as an internal standard. Mass spectra were recorded on a Kratos MS 9 (FAB) or MS 80 (CI) mass spectrometer. Optical rotations were determined on a Perkin-Elmer 141 polarimeter.

β-Keto Esters 14. These compounds were synthesized according to the method of Jackman.[16]

Enones 15. These compounds were prepared according to literature methods.[17]

Amidinium Hydrochlorides 18. These compounds were prepared according to literature,[19] if not commercially available.

General Procedure for the Synthesis of Pyridine- and Pyrimidine-3-carboxylic Acid Esters 20a–w (Table III). 3-(4-Fluorophenyl)-2-(1-oxoethyl)-5-oxohexanoic Acid Methyl Ester (16a). A solution of 4-(4-fluorophenyl)but-3-en-2-one (15a; 41.0 g, 0.25 mol) in ether (600 mL) was added dropwise to a mixture of methyl acetoacetate (14a; 58.1 g, 0.50 mol), potassium hydroxide (1.2 g), and ethanol (12 mL). During the addition, the reaction temperature was kept below 30 °C. The resulting solution was allowed to stand for 3 h, was acidified (pH 5) by addition of acetic acid, and successively shaken with water and saturated $NaHCO_3$ solution. Usual workup gave 50.6 g (72%) of 16a as a yellow oil, which was used in the next step without purification: ^1H NMR δ 0.8–1.0 (6 H, m), 1.9 (3 H, s), 2.2–2.9 (2 H, m), 3.1–4.1 (7 H, m), 7.0–7.8 (4 H, m).

1,4-Dihydro-4-(4-fluorophenyl)-2-isopropyl-6-phenylpyrimidine-3-carboxylic Acid Ethyl Ester (19v). To a suspension of benzamidine hydrochloride (18b; 102.2 g, 0.85 mol) and potassium acetate (90.7 g, 0.94 mol) in 1.5 L of toluene were added 4-methyl-3-oxopentanoic acid ethyl ester (98.6 g, 0.62 mol) and 4-fluorobenzaldehyde (17a; 77.0 g, 0.62 mol); the mixture was stirred for 24 h under reflux, with a Dean–Stark trap, until no more water separated. The reaction mixture was cooled and worked up in the usual manner. The residual oil was chr[illegible]

tographed on silica gel. Elution with cyclohexane/ethyl acetate 4:1 provided 19v (110 g, 50%) as a viscous, yellow oil: ^{1}H NMR δ 1.2 (3 H, t, J = 7 Hz), 1.3 (6 H, d, J = 7 Hz), 4.0–4.5 (3 H, m), 5.8 (1 H, s), 7.0–7.9 (10 H, m). Anal. ($C_{22}H_{23}FN_2O_2$) C, H, F, N.

2,6-Dimethyl-4-(4-fluorophenyl)pyridine-3-carboxylic Acid Methyl Ester (20a). A suspension of 16a (28.0 g, 100 mmol), ammonium acetate (120 g), and iron(III) chloride hexahydrate (120 g) in acetic acid (1000 mL) was refluxed for 4 h with continuous stirring. The resulting deep red mixture was cooled and filtered. After washing of the remaining solid with toluene and ethanol, the filtrates were combined and evaporated. The residue was suspended in water, neutralized by addition of solid $NaHCO_3$, and worked up as usual. Chromatography gave 20a (23.6 g, 91%) as a white solid: mp 89–90 °C; ^{1}H NMR δ 2.6 (6 H, s), 3.7 (3 H, s), 7.0–7.5 (5 H, m); MS $C_{15}H_{14}FNO_2$ m/e = 259 (M^+). Anal. ($C_{15}H_{14}FNO_2$) C, H, F, N.

4-(4-Fluorophenyl)-2-isopropyl-6-phenylpyrimidine-3-carboxylic Acid Ethyl Ester (20v). To a solution of 19v (24.2 g, 66 mmol) in toluene (300 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 18.0 g, 79 mmol), and the mixture was stirred for 3 h at 50 °C. The reaction mixture was cooled, the solvent was evaporated, and the dark residual oil was extracted five times with cyclohexane/ethyl acetate 4:1 (100 mL). The organic extracts were evaporated and the brown, residual oil was chromatographed on silica gel. Elution with cyclohexane/ethyl acetate 4:1 provided 20v (19.9 g, 82%): mp 105–107 °C; ^{1}H NMR δ 1.1 (3 H, t, J = 7 Hz), 1.4 (6 H, d, J = 7 Hz), 3.2 (1 H, h, J = 7 Hz), 4.2 (2 H, q, J = 7 Hz), 7.0–8.0 (7 H, m), 8.5–8.8 (2 H, m). Anal. ($C_{22}H_{21}FN_2O_2$) C, H, F, N.

General Procedure for the Synthesis of Pyridine and Pyrimidine Phosphonium Salts 6a–w (Table IV). [2,6-Dimethyl-4-(4-fluorophenyl)pyridin-3-yl]methanol (21a). A 1.0 M solution of $LiAlH_4$ in THF (30 mL, 30 mmol) was added to a solution of 20a (7.80 g, 30.1 mmol) in THF (40 mL). The resulting reaction mixture was stirred at room temperature for 1.5 h and poured onto water. After usual workup, the crystalline residue was washed with a 1:1 mixture of cyclohexane and ethyl acetate, which gave 21a (6.5 g, 93%) as a white solid: mp 124 °C; ^{1}H NMR δ 2.0 (1 H, s), 2.5 (3 H, s), 2.7 (3 H, s), 4.6 (2 H, s), 6.9 (1 H, s), 7.0–7.5 (4 H, m); MS $C_{14}H_{14}FNO$ m/e = 231 (M^+). Anal. ($C_{14}H_{14}FNO$) C, H, F, N.

Bromo[2,6-dimethyl-4-(4-fluorophenyl)pyridin-3-yl]-methane (22a). A solution of 21a (6.4 g, 27.7 mmol) and phosphorous tribromide (5.3 mL, 54.4 mmol) in a mixture of toluene (50 mL) and dichloromethane (25 mL) was stirred at room temperature for 1 h. The resulting mixture was poured onto saturated $NaHCO_3$ solution and worked up as usual to yield essentially pure 22a (6.4 g, 79%) as a pale yellow solid, mp 86–87 °C, which was used in the next step without purification: ^{1}H NMR δ 2.5 (3 H, s), 2.7 (3 H, s), 4.4 (2 H, s), 6.9 (1 H, s), 7.0–7.5 (4 H, m); MS $C_{14}H_{13}BrFN$ m/e = 295, 293 (M^+). Anal. ($C_{14}H_{13}BrFN$) C, H, F, N.

[2,6-Dimethyl-4-(4-fluorophenyl)pyridin-3-yl]methyltriphenylphosphonium Bromide (6a). A solution of 22a (6.4 g, 22.5 mmol) and triphenylphosphine (6.2 g, 23 mmol) in toluene (200 mL) was refluxed for 5 h. Upon cooling, a white precipitate formed, which was collected on a Büchner funnel, washed with ether, and dried in vacuo to yield analytically pure 6a (6.4 g, 89%): mp 218–220 °C; ^{1}H NMR δ 2.3 (3 H, d, J = 2 Hz), 2.5 (3 H, d, J = 3 Hz), 6.5 (2 H; d, J = 16 Hz); 6.8–7.9 (20 H, m); MS $C_{32}H_{28}BrFNP$ m/e = 476 (M^+). Anal. ($C_{32}H_{28}BrFNP$) C, H, Br, F, N, P.

General Procedure for the Synthesis of Lactones 2–4 (Table I). (*E*)- and (*Z*)-4(*R*)-[(*tert*-Butyldiphenylsilyl)-oxy]-6(*S*)-[2-[2,6-dimethyl-4-(4-fluorophenyl)pyridin-3-yl]-ethenyl]-2(*R*)-methoxy-3,4,5,6-tetrahydro-2*H*-pyrans (7a and 8a). A 1.6 M solution of *n*-butyllithium in hexane (12 mL, 19.2 mmol) was added dropwise to a solution of 6a (9.70 g, 17.5 mmol) in THF (100 mL) at 0 °C. The resulting reaction mixture was stirred for 0.5 h, then a solution of 5 (7.29 g, 18.4 mmol) in THF (40 mL) was added, and the stirring was continued for 1 h. The solution was poured onto water, acidified (pH 5–6) by addition of acetic acid, and extracted several times with ether. The combined organic layers were shaken with saturated $NaHCO_3$ solution and further worked up as usual. The remaining oil was chromatographed to provide 7a (4.99 g, 48%) as an oil and the corresponding *Z* isomer 8a (2.36 g, 22%) as a white solid. 7a: ^{1}H NMR δ 1.1 (9 H, s), 1.1–1.9 (4 H, m), 2.5 (3 H, s), 2.6 (3 H, s), 3.5 (3 H, s), 4.2 (1 H, mc), 4.5 (1 H, mc), 4.9 (1 H, mc), 5.5 (1 H, dd, J = 16 Hz, 6 Hz), 6.4 (1 H, d, J = 16 Hz), 6.9–7.7 (15 H, m); MS $C_{37}H_{42}FNO_3Si$ m/e = 596 (M + 1)$^+$. Anal. ($C_{37}H_{42}FNO_3Si$) C, H, F, N. 8a: mp 111–113 °C; ^{1}H NMR δ 0.9 (9 H, s), 1.0–1.8 (4 H, m), 2.6 (6 H, s), 3.3 (3 H, s), 4.2 (1 H, mc), 4.3 (1 H, mc), 4.5 (1 H, m), 5.5 (1 H, mc), 6.3 (1 H, d, J = 10 Hz), 6.9–7.8 (15 H, m); MS $C_{37}H_{42}FNO_3Si$ m/e = 596 (M + 1)$^+$. Anal. ($C_{37}H_{42}FNO_3Si$) C, H, F, N.

(*E*)- and (*Z*)-4(*R*)-[(*tert*-Butyldiphenylsilyl)oxy]-6(*S*)-[2-[2,6-dimethyl-4-(4-fluorophenyl)pyridin-3-yl]ethenyl]-2-hydroxy-3,4,5,6-tetrahydro-2*H*-pyrans (9a and 10a). A solution of 7a (4.93 g, 8.4 mmol) in THF (60 mL), water (60 mL), and acetic acid (100 mL) was refluxed for 48 h. Toluene (150 mL) was added and the resulting mixture was evaporated. The residue was shaken with saturated $NaHCO_3$ solution and worked up as usual. Chromatography (silica gel, cyclohexane/ethyl acetate 1:1) gave 9a (3.14 g, 63%): mp 119 °C; ^{1}H NMR δ 1.1 (9 H, s), 1.2–2.0 (4 H, m), 2.5 (3 H, s), 2.6 (3 H, s), 3.9–5.0 (3 H, m), 5.1–5.6 (2 H, m), 6.4 (1 H, d, J = 16 Hz), 6.9–7.8 (15 H, m); MS $C_{36}H_{40}FNO_3Si$ m/e = 581 (M^+). Anal. ($C_{36}H_{40}FNO_3Si$) C, H, F, N.

The corresponding *Z* isomer 10a was prepared by the same procedure in 60% yield: mp 147–149 °C; ^{1}H NMR δ 0.9 (9 H, s), 1.0–1.9 (4 H, m), 2.5 (6 H, s), 4.0–4.4 (2 H, m), 4.8–6.5 (3 H, m), 6.9–7.6 (15 H, m); MS $C_{36}H_{40}FNO_3Si$ m/e = 581 (M^+). Anal. ($C_{36}H_{40}FNO_3Si$) C, H, F, N.

(*E*)- and (*Z*)-4(*R*)-[(*tert*-Butyldiphenylsilyl)oxy]-6(*S*)-[2-[2,6-dimethyl-4-(4-fluorophenyl)pyridin-3-yl]ethenyl]-3,4,5,6-tetrahydro-2*H*-pyran-2-ones (11a and 12a). A solution of 9a (3.00 g, 5.18 mmol), *N*-iodosuccinimide (5.82 g, 25.9 mmol), and tetra-*n*-butylammonium iodide (1.91 g, 5.18 mmol) in dichloromethane (70 mL) was stirred for 2 h at room temperature, poured into a saturated $Na_2S_2O_3$ solution, and worked up in the usual manner. The remaining oil was treated with diisopropyl ether and filtered. After evaporation, the oily residue was chromatographed (silica gel, deactivated with 10% water; cyclohexane/ethyl acetate 1:1) to yield pure 11a (2.45 g, 76%) as an oil: ^{1}H NMR δ 1.1 (9 H, s), 1.3–1.7 (2 H, m), 2.4–2.6 (8 H, m), 4.2 (1 H, mc), 5.2 (1 H, mc), 5.4 (1 H, mc), 6.5 (1 H, d, J = 16 Hz), 6.9–7.7 (15 H, m); MS $C_{36}H_{38}FNO_3Si$ m/e = 580 (M + 1)$^+$. Anal. ($C_{36}H_{38}FNO_3Si$) C, H, F, N.

In a similar run, the corresponding *Z* isomer 12a was obtained from 10a in 76% yield: mp 188 °C; ^{1}H NMR δ 0.9 (9 H, s), 1.3–1.7 (2 H, m), 2.4 (2 H, mc), 2.6 (6 H, s), 4.2 (1 H, mc), 5.0 (1 H, mc), 5.6 (1 H, mc), 6.5 (1 H, d, J = 11 Hz), 6.9–7.5 (15 H, m); MS $C_{36}H_{38}FNO_3Si$ m/e = 580 (M + 1)$^+$. Anal. ($C_{36}H_{38}FNO_3Si$) C, H, F, N.

(*E*)- and (*Z*)-6(*S*)-[2-[2,6-Dimethyl-4-(4-fluorophenyl)-pyridin-3-yl]ethenyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-ones (2a and 3a). Tetra-*n*-butylammonium fluoride trihydrate (3.42 g, 10.8 mmol) was added to a solution of 11a (2.10 g, 3.64 mmol) and acetic acid (8.3 mL, 14.5 mmol) in THF (35 mL). The resulting solution was stirred at room temperature for 15 h and then quenched with saturated $NaHCO_3$ solution. After usual workup, the crude product was purified by chromatography (silica gel, desactivated with 10% water; ethyl acetate/methanol 10:1) to give 2a (0.97 g, 78%) as a white solid: mp 205 °C; ^{1}H NMR δ 1.6–1.9 (3 H, m), 2.5 (3 H, s), 2.6 (3 H, s), 2.6–2.8 (2 H, m), 4.3 (1 H, mc), 5.3 (1 H, mc), 5.5 (1 H, mc), 6.6 (1 H, d, J = 16 Hz), 6.9 (1 H, s), 7.0–7.3 (4 H, m); MS $C_{20}H_{20}FNO_3$ m/e = 341 (M^+). Anal. ($C_{20}H_{20}FNO_3$) C, H, F, N.

The corresponding *Z* isomer 3a was prepared from 12a analogously in 75% yield: mp 188 °C; ^{1}H NMR δ 1.5 (1 H, mc), 1.8–2.2 (2 H, m), 2.4–2.6 (8 H, m), 4.2 (1 H, mc), 4.8 (1 H, mc), 5.6 (1 H, mc), 6.5 (1 H, mc), 6.9 (1 H, s), 7.0–7.4 (4 H, m); MS $C_{20}H_{20}FNO_3$ m/e = 341 (M^+). Anal. ($C_{20}H_{20}FNO_3$) C, H, F, N.

6(*R*)-[2-[4-(4-Fluorophenyl)-2-(1-methylethyl)-6-phenylpyridin-3-yl]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (4i). A mixture of 2i (1.00 g, 2.3 mmol), triethyl amine (50 μL), methanol (10 mL), and ethyl acetate (10 mL) was shaken under an hydrogen atmosphere, until no more hydrogen was consumed. This mixture was filtered through a pad of Celite and evaporated to give 4i (0.91 g, 91%) as an oil: ^{1}H NMR δ 1.3–1.8 (11 H, m), 2.3–2.8 (4 H, m), 3.4 (1 H, h, J = 7 Hz), 4.2 (1 H, mc), 4.5 (1 H, mc), 7.1 (2 H, mc), 7.3–7.5 (6 H, m), 8.1 (2

H, mc); MS $C_{27}H_{28}FNO_3$ m/e = 433 (M^+). Anal. ($C_{27}H_{28}FNO_3$) C, H, F, N.

Biological Assays. HMG-CoA Reductase Inhibition Assay. The inhibitory activity of compounds 2–4 on rat liver HMG-CoA reductase was estimated with soluble-enzyme preparations obtained from the microsomal fraction.[22] The test was performed according to the method described by Avigan.[23] The complete assay medium contained the following in a total volume of 0.2 mL: Tris, 6mM; EDTA, 2.5 mM; DTT 2.5, mM; NADP, 50 mM; glucose 6-phosphate, 50 mM; glucose 6-phosphate dehydrogenase, 2.8 units; HMG-CoA, 0.91 mM containing 100 nCi (3.7 kBq) of [^{14}C] HMG-CoA (New England Nuclear); partially purified enzyme stock solution, 50 μL. Test compounds 2–4 as well as 1b (after conversion to their corresponding potassium 3(*R*),5(*S*)-dihydroxy carboxylates through reaction with 1 equiv of potassium hydroxide in ethanol) were added to the assay system in 10-μL volumes at multiconcentration levels. The complete assay was incubated at 37 °C with shaking during 20 min and the reaction was stopped by addition of 75 μL of 2 N $HClO_4$. After 1 h at room temperature and 10 min in an ice bath, 75 μL of 3 N potassium acetate and 150 μL of water were added, and the precipitate was centrifuged. The supernatant (250 μL) was applicated to an 0.6 × 8.0 cm column containing 100–200-mesh AG 1×8, Cl form (Bio-Rad). Mevalonolactone was eluted with 3.5 mL of Milli-Q water and 0.5-mL portions of the eluate were mixed with 10 mL of Quickscint 212 (Zinsser) for measurement in a Beckman scintillation counter. The assay was carried out in triplicate; the average of six values was calculated for the percentage inhibition. IC_{50} values were obtained by plotting the percentage inhibition against test compound concentration.

Inhibition of Acetate Incorporation in Cholesterol in Cultures of HEP G2 Cells. Monolayers of HEP G2 cells in RPMI 1640 medium (Flow) with 10% delipidated fetal calf serum were preincubated for 1 h with suitable concentrations of the test compounds 2, 3, or 4. After addition of ^{14}C-labeled sodium acetate, the incubation was continued for 3 h. [^{3}H] Cholesterol was added as an internal standard and an aliquot of the cells was saponified with alkali. The lipids were extracted with chloroform/methanol 2:1. After addition of carrier cholesterol, the lipid mixture was separated preparatively on TLC plates using chloroform/acetone 9:1. The cholesterol zone was visualized with iodine vapor and a TLC radioscanner and scraped out. The amount of [^{14}C] cholesterol was determined scintigraphically. With another aliquot of cell monolayers, cell proteins were determined for calculation of [^{14}C] cholesterol biosynthesis per milligram of cell protein. The same procedure was done at three different inhibitor concentrations, using cells of the same culture, and additionally without preincubation with a test compound (solvent control).

For each compound, IC_{50} values were calculated by plotting the ratio between the relative amount of [^{14}C] cholesterol synthesized in inhibitor-treated cells and in solvent controls against inhibitor concentrations. Relative potencies were calculated on the basis of 1b as external standard.

Hypocholesterolemic Activity in Rabbits. Normolipemic male white New Zealand rabbits (3–5.5 kg) in groups of four to six animals received the compounds, suspended in 1% aqueous (carboxymethyl)cellulose (Tylose) daily in the morning by stomach tube; the control groups were given only Tylose. In samples of venous blood, taken every 3–4 days 20 h after the oral administration, serum total cholesterol was enzymatically determined by test combination of Boehringer-Mannheim (CHOD-PAP high-performance method). The serum cholesterol level of drug-treated groups was compared with that of control groups. After the time of "administration" a time of "withdrawal" followed.

Conformational Analysis and Structural Comparison of Compounds 1b and 2i. A computer-assisted conformational analysis of 1b and 2i was carried out using a commercially available program[24] in order to determine their low-energy conformations.

An initial conformation of 1b was modeled from the conformation of compactin (1a) as determined by X-ray crystallography.[25,26] A systematic conformational search with rotatable bonds

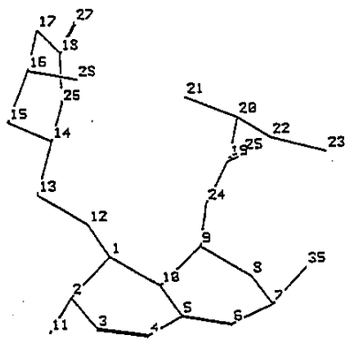


Figure 3. Low-energy conformation of 1b as determined by computer-assisted analysis (hydrogen atoms omitted).

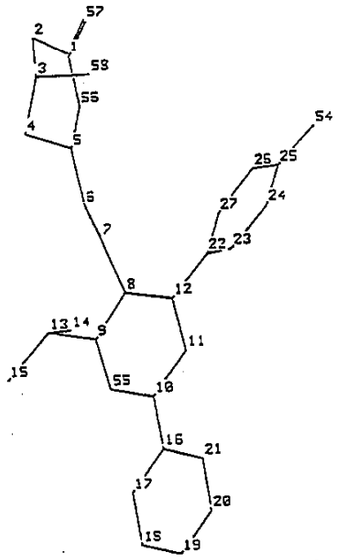


Figure 4. Low-energy conformation of 2i as determined by computer-assisted analysis (hydrogen atoms omitted).

13–14, 12–13, 1–12, 9–24, 19–24, 19–20, and 20–22 (see Figure 3) being varied in 30° steps over a range of 360° led to 13 669 conformations. Atom number 14 was the anchor atom. Scale factors for the van der Waals radii of 0.85 for 1,5 and greater interactions, 0.75 for 1,4 interactions, and 0.55 for H-bond interactions were specified in order to make sure that the initial conformation was contained in the set of generated conformations. A set of 1605 conformations were within 5.0 kcal/mol of the energy minimum. The minimum was located at the starting conformation with an energy of −9.8 kcal/mol (Figure 3). All energy values did not include Coulombic interactions.

A systematic conformational search was carried out in order to also determine the low-energy conformations of 2i. The initial conformation was taken from the crystal structure (see Figure 2). Since there are two conformations present in the crystal, the one which has the lactone in almost the same conformation as 1b (conformer B) was chosen. The energy of this conformation could be minimized[24] from 262.7 to 5.0 kcal/mol. Althougb the

(22) Phillippi, B. W.; Shapiro, D. J. *J. Lipid Res.* 1979, *20*, 588.
(23) Avigan, J.; Bathena, S. J.; Schreiner, M. E. *J. Lipid Res.* 1975, *16*, 151.
(24) SYBYL 3.3, Tripos Associates, St. Louis, MI 63117.
(25) Brown, A. G.; Smale, T. C. *J. Chem. Soc. Perkin Trans. 1* 1976, 1165.
(26) Since the crystal structure of 1b is not known, 1a was used for analysis. Compactin differs from 1b by just one methyl group, suggesting that the conformational energies of both compounds should be similar.

energy decreased substantially, the original and minimized structure showed a standard deviation of only 0.15 Å. The high energy of the crystal structure is due to terminal hydrogens being slightly displaced. The systematic conformational search[24] yielded 1056 conformations. The rotatable bonds 5–6, 6–7, 7–8, 12–22, 10–16, and 9–13 (see Figure 4) were varied in steps of 30°, 180°, 30°, 30°, and 30° over ranges of 360°, 360°, 360°, 180°, 180°, and 360°, respectively. Atom number 5 was chosen to be the anchor atom. The van der Waals radii were scaled by 0.9 for 1,5 and greater interactions, 0.8 for 1,4 interactions, and 0.6 for H-bond interactions. With these scale factors the initial conformation was contained in the set of generated conformations.

From the 1056 conformations generated, 348 were within 5.0 kcal/mol of the minimum of 3.5 kcal/mol found. The energies did not contain Coulombic interactions. With use of computer graphics, these conformations were oriented in space such that the lactone moiety approximately fitted the lactone of 1b and the fluorophenyl group qualitatively matched the ester group of 1b. The structure of 2i thus selected was then subjected to a flexible fit[24] against 1b.

The conformation of 2i chosen graphically differs from its crystal structure. However, with an energy value of 4.0 kcal/mol, it still is one of the low-energy conformations. For the flexible fit a force constant of 100.0 kcal/mol Å^2 was specified among the oxygen atoms 56, 57, and 58 of 2i and 26, 27, and 28 of 1b. A force constant of 20.0 kcal/mol Å^2 was given for atom pairs 8 and 27 of 2i and 1 and 24 of 1b. The fit energy of 16.0 kcal/mol was counterbalanced by an energy of 17.4 kcal/mol of 2i. The standard deviation of the specified atoms was calculated to be 0.217 Å. When the fitted structure was relaxed, its energy is lowered to 8.1 kcal/mol, which appeared to be mainly due to releasing angle strain. The structure underwent only slight changes as indicated by standard deviation of atoms of 0.066 Å.

X-ray Structural Analysis of 2i. Compound 2i (60 mg) was recrystallized from a mixture of 1 mL of diisopropyl ether and 0.5 mL of ethyl acetate. The crystal used for X-ray analysis was 0.55 × 0.35 × 0.13 mm, sealed in a Lindeman glass capillary: 25 reflections for cell refinement, Mo-Kα radiation, Nicolet R3 computer-controlled diffractometer, monoclinic, $C2$, $Z = 8$, $a = 34.99$ (2) Å, $b = 8.201$ (4) Å, $c = 16.66$ (1) Å, $\beta = 104.98$ (3)°, $V = 4618.2$ Å^3, $D = 1.241$ g/cm^3, $\mu = 0.8$ mm^{-1}, Ω scan, $2\vartheta_{max} = 56°$, 3° ϑ/min, 1 standard reflection (8 0 0), variation 2.8%; 6421 reflections measured, 4616 of the 5942 unique reflections had $I > \sigma(I)$ and were used for the structure analysis, $-46 < h < 2$, $0 < k < 10$, $-21 < l < 21$, no corrections for absorption or extinction. The phase problem could not be solved by the usual direct methods, but it was solved by the random-start multisolution program SHELXS-86;[27] in the final refinement all hydrogens were also refined, partly found in a difference electron density synthesis and partly calculated by using a model with idealized geometry (C–H 0.96 Å); other atoms were refined anisotropically; least-squares refinement on F with 4609 data, 720 parameters: $w = 1/\sigma(F)$, $R(1) = 0.108$, $R(2) = R(w) = 0.045$, $S = 1.7$ max $\Delta/\sigma = 0.1$; 10 largest peaks in final difference electron density synthesis between 0.27 and 0.31 e Å^{-3}; calculations were performed with a Nova 3/12 computer and SHELXTL scattering factors and f', f'' from *International Tables for X-ray Crystallography* (1974).

Supplementary Material Available: Analytical and spectral data for compounds 2a–w, 3a,c,r, and 4d,i,r and analysis data for 6a–w and 20a–w (10 pages). Ordering information is given on any current masthead page.

(27) Sheldrick, G. M. In *Crystallographic Computing 3*, Sheldrick, G. M., Krueger, C., Goddard, R., Eds.; Oxford University Press, 1985; p 175.

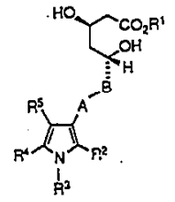
Synthesis and Biological Activity of New HMG-CoA Reductase Inhibitors. 2. Derivatives of 7-(1*H*-Pyrrol-3-yl)-substituted-3,5-dihydroxyhept-6(*E*)-enoic (-heptanoic) Acids

H. Jendralla, E. Baader, W. Bartmann,* G. Beck, A. Bergmann, E. Granzer, B. v. Kerekjarto, K. Kesseler, R. Krause, W. Schubert, and G. Wess

Hoechst AG, Postfach 800320, 6230 Frankfurt (Main) 80, West Germany. *Received October 24, 1988*

A series of 7-(1*H*-pyrrol-3-yl)-substituted-3,5-dihydroxyhept-6(*E*)-enoates (-heptanoates) 1 and 2 have been prepared and tested for inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. The most potent compounds exceeded mevinolin's activity in vitro and in vivo.

In continuation of our work on HMG-CoA reductase inhibitors with a central heterocyclic ring containing nitrogen atoms,[1] we report here on analogues 1 and 2 with a 1*H*-pyrrol-3-yl central moiety.



1 and 2: R^1 = CH_3, H, Na; A–B = (*E*)—CH=CH (1), CH_2CH_2 (2); R^2–R^5 = see Table I

Chemistry

Compounds 1 cannot be obtained in reasonable yield by utilizing the glucose-derived "compactin aldehyde" 3. This difference in behavior compared with pyridine and pyrimidine analogues[1] stems from the instability of pyrroles against acid-catalyzed hydrolysis. Instead, compounds 1 and 2, respectively, were prepared from the appropriate aldehydes 4 (Scheme I). Compounds 4 were converted with >95% *E* selectivity to the corresponding α,β-unsaturated aldehydes 6, by utilizing *cis*-(2-ethoxyvinyl)lithium according to Wollenberg.[2] Alternatively, some aldehydes 4 were converted by Emmons–Horner coupling with diisopropyl (cyanomethyl)phosphonate to the α,β-unsaturated nitriles 5. Compounds 5 were reduced and then hydrolyzed to aldehydes 6. Addition of the dianion of methyl acetoacetate gave the racemic β-keto-δ-hydroxy esters 7. Highly stereoselective reduction of the keto group[3,4] was conducted with triethylborane and sodium horohydride to give methyl β,δ-dihydroxy carhoxylates 1, R^1 = CH_3.

Catalytic hydrogenation of 1 led to 2. Saponification of the methyl esters 1 and 2 gave the corresponding sodium salts 1 and 2 (R^1 = Na), respectively.

Selected examples of these racemic sodium salts 2 were also synthesized in optically active form 13, having the biologically active configuration 3*R*,5*R* (Scheme II). It should he emphasized that 2 and 13 are structurally identical, except for the ratio of the two enantiomers. They have been assigned different numbers for the sake of unambiguous differentiation in tables with biological results.

Aldehydes 6 were subjected to a highly stereoselective aldol reaction,[5,6] using the dianion 8 (generated from (*S*)-(–)-phenyl 2-hydroxy-2,2-diphenylacetate[7] and 2 equiv of LDA) to give 9. In all cases, the indicated 3(*S*)-hydroxy isomer 9 exceeded its undesired 3*R* diastereomer by more than 96:4 (HPLC). Compound 9 was transformed into the corresponding methyl ester 10 with sodium in methanol. Reaction of 10 with 4 equiv of the enolate of *tert*-butyl acetate yielded the *tert*-butyl β-keto-δ-(*S*)-hydroxy carboxylate 11, which was transformed to 3(*R*),5(*R*)-dihydroxyheptanoate 13 (R^1 = *t*-Bu) in analogy to the racemic ester 7 described above.

As shown by the HPLC analysis, 13 exceeded its undesired 3*S*,5*R* diastereomer by more than 96:4. Additionally according to ^{1}H NMR (Eu(hfc)$_3$) analyses, 13 had an optical purity of more than 92% ee. Saponification of the *tert*-butyl ester 13 gave the corresponding sodium salt (13, R^1 = Na).

The sodium salts of the olefins 1 (A–B = (*E*)-HC=CH) are acid sensitive while the hydrogenated analogues 2 (A–B = CH_2CH_2) are perfectly stable. When the olefinic methyl esters 1 (R^1 = CH_3) or their precursors 7 were dissolved in $CDCl_3$ that had not been filtered through basic alumina immediately before use, they decomposed very quickly, while 2 was stable. Likewise, the olefinic compounds 1 and 7 decomposed when chromatographed through silica gel in the absence of triethylamine, while the saturated analogue 2 was stable. Protolytic removal of the 5-hydroxy group of 1 leads to a cation that has a highly stabilizing resonance structure with a positively charged tetravalent nitrogen when A–B = HC=CH, but not when A–B = CH_2CH_2.

Aldehydes 4 were prepared following several synthetic routes as outlined in Schemes III–VI.

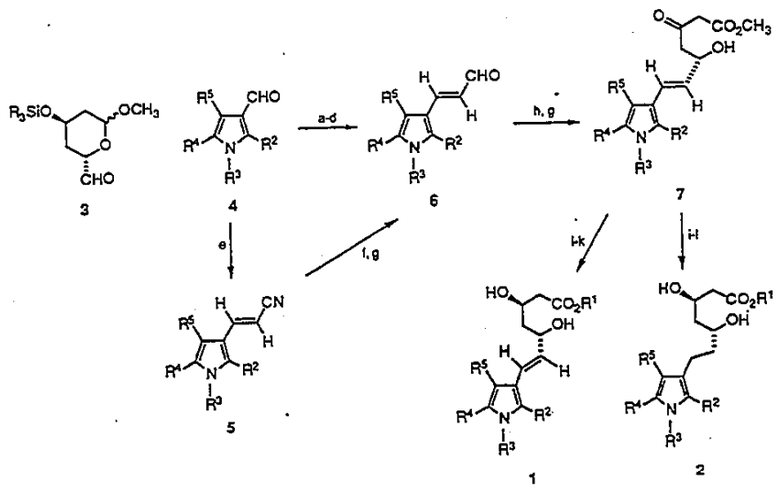
On the basis of the work of Gômez-Sanchez et al.,[8] substituted nitroethenes 15 were reacted with 2 equiv of β-keto esters 16[9] to give the hydroxylamines 17. Upon heating 17 with primary amines, especially anilines, the pyrrolecarboxylic acid esters 18 were obtained; they gave aldehydes 4 after reduction/oxidation (Scheme III).

According to H. Meyer[10] pyrrole esters 18 or 21 could also he prepared by cyclocondensation of nitroethenes 15

(1) Beck, G.; Kesseler, K.; Baader, E.; Bartmann, W.; Bergmann, A.; Granzer, E.; Jendralla, H.; von Kerekjarto, B.; Krause, R.; Paulus, E.; Schubert, W.; Wess, G. *J. Med. Chem.* Preceding paper in this issue.
(2) Wollenberg, R. H.; Albizati, K. F.; Peries, R. *J. Am. Chem. Soc.* 1977, *99*, 7365.
(3) Kathawala, F. G.; Prager, B.; Prasad, K.; Repic, O.; Shapiro, M. J.; Stabler, R. S.; Widler, L. *Helv. Chim. Acta* 1986, *69*, 803.
(4) Narasaka, K.; Pai, F.-C. *Tetrahedron* 1984, *40*, 2233.
(5) Braun, M.; Devant, R. *Tetrahedron Lett.* 1984, *25*, 5031.
(6) Devant, R.; Mahler, U.; Braun, M. *Chem. Ber.* 1988, *121*, 397.
(7) Commercially available as (*S*)-(–)-HYTRA from Merck-Schuchhardt, West-Germany.
(8) Gômez-Sanchez, A.; Stiefel, B. M.; Fernández, R.; Pascual, C.; Bellanato, J. *J. Chem. Soc., Perkin Trans. 1* 1982, 441.
(9) Jackman, M.; Klenk, M.; Fishburn, B.; Tullar, B. F.; Archer, S. *J. Am. Chem. Soc.* 1948, *70*, 2884.
(10) Meyer, H. *Liebigs Ann. Chem.* 1981, 1534.

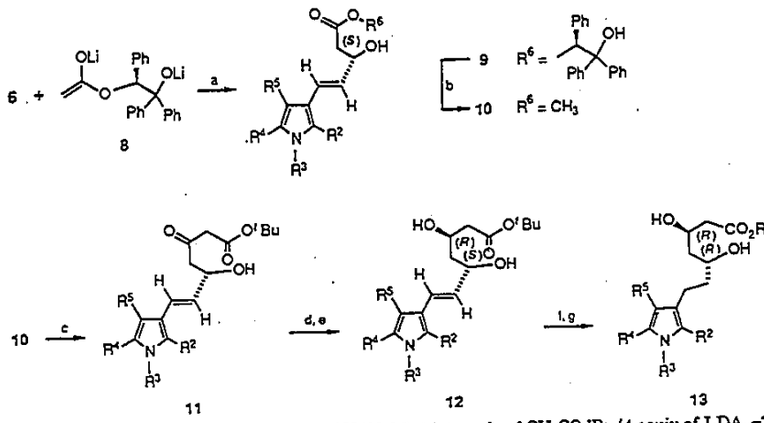
0022-2623/90/1833-0061$02.50/0

Scheme I[c]



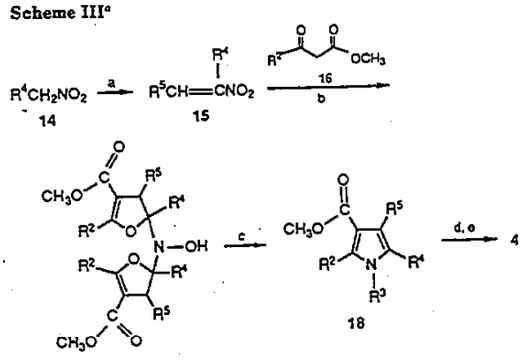
[c] (a) EtOCH=CHSn(*n*-Bu)$_3$;[2] (b) *n*-BuLi/−70 °C; (c) NH_4Cl/H_2O; (d) $TsOH/H_2O$; (e) $NCCH_2PO(O\text{-}i\text{-}Pr)_2/NaH/0$ °C; (f) $(i\text{-}Bu)_2AlH$; (g) NaH_2PO_4/H_2O; (h) $CH_3COCH_2CO_2CH_3/NaH/n\text{-}BuLi/-15$ °C; (i) Et_3B; (j) $NaBH_4/-75$ °C; (k) $NaOH/H_2O/CH_3OH$; (l) $Pd/C/H_2$.

Scheme II[a]



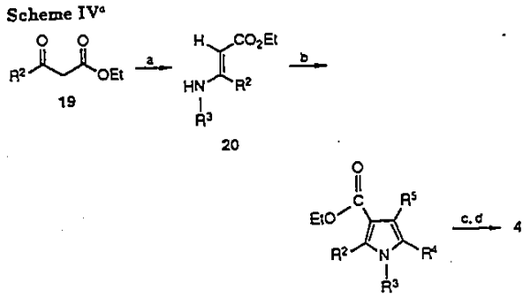
[a] (a) THF/−80 to −90 °C, 2 h; (b) 0.5 equiv of $NaOCH_3/CH_3OH/23$ °C; (c) 4 equiv of $CH_3CO_2{}^tBu/4$ equiv of LDA, −30 °C; (d) 1.05 equiv of $Et_3B/24$ equiv of CH_3OH in THF/−70 °C; (e) (1) 1.3 equiv of $NaBH_4/-70$ °C, (2) $CH_3OH/25$ °C; (f) $Pd/C/H_2$; (g) $NaOH/H_2O/CH_3OH/12$ h.

Scheme III[a]



[a] (a) R^3CHO; (b) $NaOCH_3$; (c) R^3NH_2/Δ; (d) $LiAlH_4$; (e) MnO_2.

Scheme IV[a]

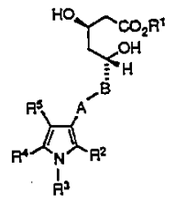


[a] (a) $R^3NH_2/AcOH/-H_2O$; (b) 15/Δ; (c) $LiAlH_4$; (d) MnO_2.

with enamino esters 20 (Scheme IV). When substituent R^2 was not sterically demanding (e.g. $R^2 = CH_3$), 20 were easily obtained by addition of 1 equiv of amine to the β-keto ester 19 under acid catalysis.

However, when R^2 was bulky (e.g. R^2 = isopropyl), amines R^3NH_2 (especially anilines) attacked the ester

Table I. Inhibition of Solubilized Rat Liver HMG-CoA Reductase in Vitro[a] for Compounds of the General Structure 1,[c] 2,[c] and 13[d]

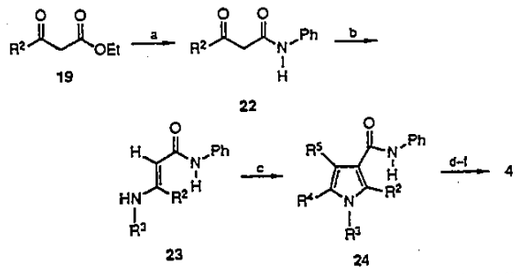


1[c], 2[c], and 13[d]

no.	R^1	R^2	R^3	R^4	R^5	A–B	formula	anal.[e]	IC_{50},[f] nM	rel[g] pot.
1a	Na	CH_3	Ph	H	*p*-C_6H_4F	CH=CH	$C_{24}H_{23}FNO_4Na$	C, H, N	65	12
1b	Na	*i*-Pr	Ph	H	*p*-C_6H_4F	CH=CH	$C_{26}H_{27}FNO_4Na$	C, H, N	7	110
2b	Na	*i*-Pr	Ph	H	*p*-C_6H_4F	CH_2CH_2	$C_{26}H_{29}FNO_4Na$	C, H, N	6	128
13b	Na	*i*-Pr	Ph	H	*p*-C_6H_4F	CH_2CH_2	$C_{26}H_{29}FNO_4Na$	C, H, N	3	257
1c	Na	CH_3	Ph	CH_3	*p*-C_6H_4F	CH=CH	$C_{25}H_{25}FNO_4Na$	C, H, N	250	3
2c	Na	CH_3	Ph	CH_3	*p*-C_6H_4F	CH_2CH_2	$C_{25}H_{27}FNO_4Na$	C, H, N	70	11
1d	Na	CH_3	*i*-Pr	H	*p*-C_6H_4F	CH=CH	$C_{21}H_{25}FNO_4Na$	C, H, N	330	2
2d	Na	CH_3	*i*-Pr	H	*p*-C_6H_4F	CH_2CH_2	$C_{21}H_{27}FNO_4Na$	C, H, N	100	9
1e	Na	*i*-Pr	*i*-Pr	H	*p*-C_6H_4F	CH=CH	$C_{23}H_{29}FNO_4Na$	C, H, N	117	6
2e	Na	*i*-Pr	*i*-Pr	H	*p*-C_6H_4F	CH_2CH_2	$C_{23}H_{31}FNO_4Na$	C, H, N	18	42
13e	Na	*i*-Pr	*i*-Pr	H	*p*-C_6H_4F	CH_2CH_2	$C_{23}H_{31}FNO_4Na$	C, H, N	9	85
1f	Na	*i*-Pr		H	*p*-C_6H_4F	CH=CH	$C_{25}H_{33}FNO_4Na$	C, H, N	69	12
2f	Na	*i*-Pr		H	*p*-C_6H_4F	CH_2CH_2	$C_{25}H_{35}FNO_4Na$	C, H, N	9	92
1g	Na	*i*-Pr	Ph	CH_3	*p*-C_6H_4F	CH=CH	$C_{27}H_{29}FNO_4Na$	C, H, N	6	125
2g	Na	*i*-Pr	Ph	CH_3	*p*-C_6H_4F	CH_2CH_2	$C_{27}H_{31}FNO_4Na$	C, H, N	5	149
13g	Na	*i*-Pr	Ph	CH_3	*p*-C_6H_4F	CH_2CH_2	$C_{27}H_{31}FNO_4Na$	C, H, N	2.5	300
mevinolin							$C_{24}H_{37}O_6Na$		8	100

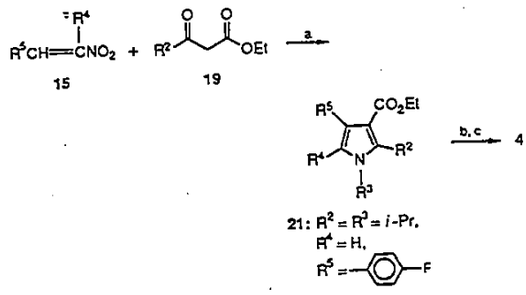
[a] The assay system described in ref 1 was used. [b] Ring-opened sodium dihydroxy carboxylate form, optically pure. [c] Racemic. [d] Optically active 3*R*,5*R* configuration. [e] Analytical results were within ±0.4% of the theoretical value. [f] IC_{50} values were determined by using four or five concentrations of each inhibitor. [g] For estimation of relative inhibitory potencies, mevinolin was assigned a value of 100. The IC_{50} value of test compound was compared with that of mevinolin, corrected for the somewhat different molecular weight.

Scheme V[a]



[a] (a) $PhNH_2$/AcOH; (b) R^3NH_2/AcOH/$-H_2O$; (c) 15/Δ; (d) NaH/CH_3I/toluene/Δ; (e) $LiAlH_4$/Δ; (f) CrO_3/pyridine.

Scheme VI[a]



[a] (a) R^3NH_2/CH_3OH/25 °C/1 day; (b) $LiAlH_4$; (c) 4 equiv of  /0.02 equiv of $(Ph_3P)_3RuCl_2$.

functionality much faster than the keto group of 19. In this case, it was necessary to preform the anilides 22 (Scheme V). Addition of aliphatic or aromatic primary amines R^3NH_2 to 22 under acid catalysis gave 23, which were cyclocondensed with nitroethenes 15 to give 3-pyrrolecarbanilides 24. While amides on LAH reduction usually lead to the corresponding amines, carbanilides 24 could be reduced to the corresponding aldehydes 4 via N-methylation, LAH treatment, and subsequent oxidation.

A new three-component coupling reaction allowed a one-pot synthesis of ethyl 1,2-diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxylate (21, Scheme VI).

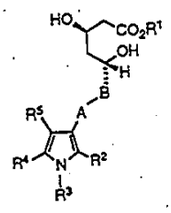
When a methanolic solution of β-nitro-*p*-fluorostyrene (15: R^4 = H, R^5 = *p*-C_6H_4F), β-keto ester 19 (R^2 = *i*-Pr), and isopropylamine was stirred at ambient temperature, the pyrrole ester 21 was obtained in 50% yield. LAH reduction followed by ruthenium(II)-catalyzed oxidation of the alcohol with *N*-methylmorpholine-*N*-oxide[11] gave the corresponding aldehyde 4. This convenient three-component coupling may also be applicable for the syntheses of pyrrole esters 21 with other substitution patterns for R^2–R^5.

Biological Results and Discussion

The racemic sodium salts (1 and 2, R^1 = Na) as well as the optically active sodium salts 13 (R^1 = Na) were evaluated for their ability to inhibit solubilized, partially purified rat liver HMG-CoA reductase in vitro (Table I) and

(11) Sharpless, K. B.; Akashi, K.; Oshima, K. *Tetrahedron Lett.* 1976, 29, 2503.

Table II. Inhibition of Cellular HMG-CoA Reductase in Cultures of HEP G2 Cells[a] for Sodium Salts of the General Formula 1[c] and 2[c]



1[c] and 2[c]

	IC_{50},[d] μM	relative[e] potency
mevinolin[b]	0.05	100
1a	0.83	6
1b	0.014	350
2b	<0.01	>500
1c	5.0	1
2c	0.57	9
1d	6.0	1
2d	0.27	19
1e	0.05	100
2e	0.002	2500
1f	0.106	47
2f	0.018	275

[a] Assay described in the preceding paper.[1] [b] Ring-opened sodium dihydroxy carboxylate form, optically pure. [c] Racemic. For definition of R^1–R^5 and A–B see Table I. [d] IC_{50} values varied somewhat for different batches of cells. Mevinolin sodium salt averaged $IC_{50} = 5 \times 10^{-8}$ M and was used in every run as an internal standard. The measured IC's for test compounds 1 and 2 were corrected for deviations of mevinolin's IC from its average value. [e] Mevinolin was assigned a value of 100. Potencies were obtained by comparison of racemic test compounds 1 or 2 with the internal standard mevinolin.

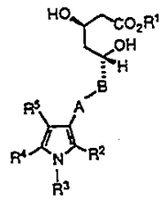
to inhibit *cellular* HMG-CoA reductase in cultures of hepatic cells (HEP G2, a human hepatoma cell line), as determined by the inhibition of the incorporation of sodium [^{14}C]acetate into cholesterol (Table II).

Selected compounds were evaluated for their ability to inhibit hepatic cholesterol "de novo" synthesis in male rats after po administration, as determined by the inhibition of the incorporation of sodium [^{14}C]octanoate[12] into hepatic cholesterol (Table III).

Selected compounds were further evaluated for their ability to decrease plasma cholesterol levels in normolipemic rabbits and dogs after po administration.

All tests were also conducted under the same experimental conditions with optically pure mevinolin. The respective results are included in Tables I–III. For substitution patterns "b", "e", and "g", we prepared and tested the racemic 2 as well as the optically active 3*R*, 5*R* sodium salt 13. Optically active compounds 13 proved to have twice the potency in HMG-CoA reductase inhibition than the structurally identical but racemic 2 (Table I). This result was expected, since the antipode of the configuration drawn for 1, 2, and 13, is biologically inactive.[13]

Table III. Inhibition of Hepatic Cholesterol "De Novo" Synthesis in Vivo (Rat, Orally)[a]



1 and 2

	% cholesterol "de novo" synthesis	relative potency
no drug	100	
mevinolin[b]	14	100
1b[c]	5.5	255
2b[c]	5.6	250
2e[c]	9	156
2f[c]	6.0	233

[a] Assay described in ref 16. [b] Lactone form, optically pure, 5 mg/kg bw. [c] Racemic sodium salts, 10 mg/kg bw. For definition of R^1–R^5 and A–B see Table I.

For better comparison of structure–activity relationships in 1 and 2 as well as with extensive work on analogues of the phenolic type (isocyclic central aromatic, A = oxygen, B = CH_2),[14,15] R^5 was kept constant as *p*-fluorophenyl.

The work on analogues of the phenolic type[14,15] has shown that alkyl substitution of the second ortho position is essential and leads to optimal biological activity for an isopropyl substituent.

We concentrated on R^2 = methyl or isopropyl, since ortho substituents smaller (methyl, ethyl, longer *n*-alkyl) or larger (cyclopentyl, *tert*-butyl) than the isopropyl group decreased activity in analogues of the phenolic type[14,15] and since halogen substituents (Cl, Br) led to good activity but increased toxicity.

Table I shows that the isopropyl derivatives were more potent than the methyl derivatives by a factor of 10–40 (e.g. 1b vs 1a, 1g vs 1c, 2g vs 2c).

There is much tolerance concerning R^3. Variation of R^3 (Ph, *i*-Pr, cyclohexyl) led to only small activity changes (e.g. 2b vs 2e vs 2f, 1b vs 1e vs 1f, 1a vs 1d).

Substitution of R^4 = hydrogen for a methyl group either slightly decreased (e.g. 1a vs 1c) or slightly increased (2b vs 2g and 1b vs 1g) activity, depending on the nature of the other substituents. Hydrogenation of the trans olefinic bridge (A–B = (*E*)-HC=CH) had little influence on the biological activity of 1 in vitro (e.g. 1b vs 2b, 1c vs 2c; 1d vs 2d, 1e vs 2e, 1f vs 2f, 1g vs 2g); however, the hydrogenated derivatives 2 were much less acid sensitive (vide supra) and much more active in vivo.

In the HEP G2 cell-test (Table II) the racemic compounds 1b, 2b, and 2e are 3.5, 5.0, and 25 times, respectively, more active than optically pure mevinolin sodium salt of the same concentration. General trends in Tables I and II are comparable. The superiority of 1b, 2b, and

(12) Dietschy, J. M.; McGarry, J. D. *J. Biol. Chem.* 1974, *249*, 52. Andersen, J. M.; Dietschy, J. M. *J. Lipid Res.* 1979, *20*, 740. Stange, E. F.; Dietschy, J. M. *J. Lipid Res.* 1983, *24*, 72.

(13) 3-epi, 5-epi, and 3,5-bis epi isomers of compactin and mevinolin have been reported to be biologically inactive: Heathcock, C. H.; Hadley, C. R.; Rosen, T.; Theisen, P. D.; Hecker, S. J. *J. Med. Chem.* 1987, *30*, 1858. Stokker, G. E.; Rooney, C. S.; Wiggins, J. M.; Hirshfield, J. J. *J. Org. Chem.* 1986, *51*, 4931. The biological inactivity of synthetic compactin analogues with 3*S* configuration has also been reported: Lee, T.-J. *Trends Pharmacol. Sci.* 1987, *8*, 442 and references cited therein.

(14) Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Granzer, E.; Jendralla, H.; von Kerekjarto, B.; Kesseler, K.; Krause, R.; Wess, G. International Symposium on Cholesterol Control And Cardiovascular Diseases: Prevention And Therapy, Milan (Italy) July 7–9, 1987; Abstract book page 133.

(15) European Application 0216 127, 1987.

(16) Dietschy, J. M.; Spady, D. K. *J. Lipid Res.* 1984, *25*, 1469. Alfin-Slater, R. B.; Deuel, H. J., Jr.; Scholtz, M. C.; Shimoda, F. K. Group Report No. N3, 1950; University of Southern California, Consolidated Eng. Corp.

especially 2e compared with mevinolin is more pronounced in the cell test. Inhibition of hepatic cholesterol "de novo" synthesis in vivo by oral 1b or 2b is about 2.5 times stronger than that for mevinolin (Table III). In normally fed rabbits ($n = 6$), 20 mg/kg racemic 2b decreased total plasma cholesterol levels by 34% after oral administration for 10 days (optically pure mevinolin at 10 mg/kg for 10 days, 25%), while 1b was totally inactive under the same conditions. The reason for the lack of activity of 1b in the rabbit experiment is currently not known.[22] The chemically demonstrated acid sensitivity of 1b (vide supra) would suggest that, contrary to 2b, 1b may not survive the stomach passage. However this view is not consistent with the comparable activity of 1b and 2b to inhibit hepatic cholesterol "de novo" synthesis in rats after po administration (Table III). In normally fed rabbits ($n = 4$), 10 mg/kg racemic 2e decreased total plasma cholesterol levels by 42% after oral administration for 6 days (optically pure mevinolin at 10 mg/kg for 6 days, 25%).[17,18]

In normally fed male beagle dogs ($n = 4$), 20 mg/kg racemic 2b decreased LDL-cholesterol levels by 48% and increased HDL-cholesterol levels by 14% after oral administration for 14 days (optically pure mevinolin at 10 mg/kg for 19 days: LDL-cholesterol −18%, HDL-cholesterol +2%).[18]

In conclusion, some compounds of general formula 2 exceeded mevinolin in their ability to inhibit HMG-CoA reductase in vitro and to inhibit cholesterol biosynthesis in vivo. They are promising candidates for development as antiarterosclerotic agents.

Experimental Section

For general remarks see the preceding paper in this issue.[1] ^{1}H NMR spectra were recorded in $CDCl_3$, unless noted otherwise. All starting materials were commercially available unless indicated otherwise.

1-(*p*-Fluorophenyl)-2-nitropropene (15). A solution of *p*-fluorobenzaldehyde (84 g), nitroethene (69.4 g), and *n*-butylamine (4 mL) in xylol (110 mL) was refluxed for 20 h under a Dean–Stark trap. On cooling to 0 °C, 21.7 g of the product crystallized (mp 64–65 °C). To the filtrate were added nitroethene (41.4 g) and *n*-butylamine (3 mL), and the solution was refluxed for 14 h under a Dean–Stark trap. The solution was evaporated in vacuo and the residue was digerated with methanol at 0 °C, until crystallization occurred. The crystals were collected and washed with cold methanol (53.8 g, mp 65–66 °C). Anal. ($C_9H_8FNO_2$) C, H, F, N.

Ethyl 3-(Phenylamino)-but-2(*E*)-enoate (20). A solution of aniline (45.5 mL, 0.5 mol), ethyl acetoacetate (63.5 mL, 0.5 mol), and glacial acetic acid (1 mL) in toluene (100 mL) was refluxed for 4 h under a Dean–Stark trap. The solvent was evaporated and the residue was distilled to give 57.9 g of colorless oil: bp 118–120 °C (1.5 mm); MS $C_{12}H_{15}NO_2$ $m/e = 205$ (M^+). Anal. ($C_{12}H_{15}NO_2$) C, H, N.

***N*,*N*-Bis[3-(4-fluorophenyl)-4-(methoxycarbonyl)-5-methyl-2,3-dihydrofuran-2-yl]hydroxylamine (17).** To a stirred solution of sodium methanolate (2.92 g, 54 mmol) in methanol (54 ml) was added methyl acetoacetate (20.9 g, 180 mmol) dropwise at 0 °C followed by 4-fluoro-β-nitrostyrene[19] (30.1 g, 180 mmol). After 15 min, a thick mash formed that was allowed to stand for 2 h at 0 °C. The solid was collected by suction, washed with ice-cold methanol, and dried over P_4O_{10} in vacuo to give 22.0 g of colorless solid: mp 139–141 °C; 7.0 g of product were obtained from the mother liquor; NMR δ 2.25 (6 H, s), 3.32 (3 H, s), 3.50 (3 H, s), 4.30 (2 H, dd), 5.40 (2 H, d), 7.16 (8 H, d), 8.72 (1 H, s); MS $C_{26}H_{25}F_2NO_7$ FAB $m/e = 502$ ($M + H^+$), 458, 235. Anal. ($C_{26}H_{25}F_2NO_7$) C, H, F, N.

1-Phenyl-2-methyl-3-(methoxycarbonyl)-4-(4-fluorophenyl)-1*H*-pyrrole (18a). Aniline (5.59 g, 60 mmol) was added to a solution of hydroxylamino compound 17 (15 g, 30 mmol) in ethanol (600 mL). The mixture was refluxed for 24 h. Aniline (1.1 g) was added and the mixture was refluxed for 16 h. The solvent was removed in vacuo and the residue was distributed between dichloromethane and 1 N hydrochloric acid. The organic layer was washed with saturated sodium bicarbonate solution and then with brine, dried, and concentrated. The residue was chromatographed with *n*-hexane/ether/dichloromethane (16:3.5:0.5) over silica, giving 4.0 g of reddish, thick oil: NMR δ 2.43 (3 H, s), 3.70 (3 H, s), 6.70 (1 H, s), 6.87–7.66 (9 H, m); MS $C_{18}H_{16}FNO_2$ $m/e = 309$ (M^+), 278, 248. Anal. ($C_{18}H_{16}FNO_2$) C, H, F, N.

1-Isopropyl-2-methyl-3-(methoxycarbonyl)-4-(4-fluorophenyl)-1*H*-pyrrole (18d). Isopropylamine (3.6 g, 60 mmol) was added to a suspension of hydroxylamino compound 17 (15 g, 30 mmol) in methanol (500 mL). The suspension was heated for 2 h at 40 °C and for 5 h at 50 °C, changing to a clear solution. The solvent was removed in vacuo and the residue was chromatographed with *n*-hexane/ether (4:1) over silica to yield 7.3 g of pale reddish crystals: mp 97–99 °C; NMR δ 1.42 (6 H, d), 2.53 (3 H, s), 3.65 (3 H, s), 4.37 (1 H, sept.), 6.60 (1 H, s), 6.80–7.46 (4 H, m); MS $C_{16}H_{18}FNO_2$ $m/e = 275$ (M^+), 244, 202, 201. Anal. ($C_{16}H_{18}FNO_2$) C, H, F, N.

Ethyl 1-Phenyl-2,5-dimethyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxylate (21c). A solution of 20 (23.1 g, 113 mmol) and 15 (20.5 g, 113 mmol) in ethanol (250 mL) was refluxed for 30 h. The solvent was evaporated in vacuo and the residue was chromatographed over silica (1 kg) with cyclohexane/ethyl acetate (95:5) to give 26.0 of a colorless oil: NMR δ 1.05 (3 H, t), 1.85 (3 H, s), 2.3 (3 H, s), 4.1 (2 H, q), 6.9–7.6 (9 H, m); MS $C_{21}H_{20}FNO_2$ $m/e = 337$ (M^+), 308, 292. Anal. ($C_{21}H_{20}FNO_2$) C, H, F, N.

Preparation of Substituted 1*H*-Pyrrole-3-carboxaldehydes 4 from Substituted 3-(Alkoxycarbonyl)-1*H*-pyrroles 18 or 21. General Procedure. A solution of ester 18 or 21 (82 mmol) in ether (150 mL) was added dropwise at 0–5 °C to the stirred suspension of lithium aluminum hydride (7.8 g, 200 mmol) in ether (300 mL). The suspension was stirred for 1 h at 0 °C and then for 2 h at room temperature. At 0 °C, 35 mL of ethyl acetate and then 16 mL of water followed by 24 mL of 2 N aqueous sodium hydroxide were added dropwise. The suspension was stirred for 30 min at room temperature and filtered. The filtrate was concentrated in vacuo and the residue was chromatographed over 1 kg of silica with cyclohexane/ethyl acetate (2:1) containing 0.2% triethylamine (yield 85–95%).

To a solution of the substituted 3-(hydroxymethyl)pyrrole (70 mmol) in ether (1.2 L) and triethylamine (12 mL) was added activated manganese dioxide (182.5 g). The suspension was stirred at room temperature under nitrogen. After 24 h, the same amount of manganese dioxide was added. After 24 h the solid was removed and washed with ether. The filtrates were concentrated in vacuo; the residue was chromatographed over silica with cyclohexane/ethyl acetate (6:1) containing 0.1% triethylamine (yield 65–85%).

1-Phenyl-2,5-dimethyl-3-(hydroxymethyl)-4-(4-fluorophenyl)-1*H*-pyrrole: colorless oil, crystallizing on standing; NMR δ 1.3 (1 H, br s), 2.0 (3 H, s), 2.1 (3 H, s), 4.55 (2 H, s), 6.9–7.65 (9 H, m); MS $C_{19}H_{18}FNO$ $m/e = 295$ (M^+), 278 ($M^+ -$ OH). Anal. ($C_{19}H_{18}FNO$) C, H, F, N.

1-Phenyl-2-methyl-3-(hydroxymethyl)-4-(4-fluorophenyl)-1*H*-pyrrole: pale yellow, resinous solid; NMR δ 1.5 (1 H, br s), 2.26 (3 H, s), 4.63 (2 H, s), 6.87 (1 H, s), 6.93–7.70 (9 H, m); MS $C_{18}H_{16}FNO$ $m/e = 281$ (M^+), 264 ($M^+ -$ OH). Anal. ($C_{18}H_{16}FNO$) C, H, F, N.

1-Isopropyl-2-methyl-3-(hydroxymethyl)-4-(fluorophenyl)-1*H*-pyrrole: colorless oil; MS $C_{15}H_{18}FNO$ $m/e = 247$ ($M^+ -$ OH), 188. Anal. ($C_{15}H_{18}FNO$) C, H, F, N.

1-Phenyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxaldehyde (4a): yellow, resinous solid; NMR δ 2.50 (3 H, s), 6.80 (1 H, s), 6.85–7.70 (9 H, m), 10.03 (1 H, s); MS $C_{18}H_{14}FNO$ $m/e = 279$ (M^+), 278 ($M^+ -$ H). Anal. ($C_{18}H_{14}FNO$) C, H, F, N.

1-Phenyl-2,5-dimethyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxaldehyde (4c): yellow solid; NMR δ 1.94 (3 H, s), 2.35 (3 H, s), 6.95–7.7 (9 H, m), 9.85 (1 H, s); MS $C_{19}H_{16}FNO$ *m*/

(17) Hypocholesterolemic activity in rabbits was tested following the protocol described in ref 1.
(18) Hypocholesterolemic activity in animal studies will be described in detail in a future publication.
(19) Gattermann-Wieland *Die Praxis des Organischen Chemikers*, 43rd ed.; W. de Gruyter: Berlin, 1982; p 361.

293 (M^+). Anal. ($C_{18}H_{16}FNO$) C, H, F, N.

1-Isopropyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxaldehyde (4d): colorless oil; NMR δ 1.43 (6 H, d), 2.60 (3 H, s), 4.30 (1 H, sept), 6.68 (1 H, s), 6.9–7.56 (4 H, m), 9.92 (1 H, s); MS $C_{15}H_{16}FNO$ m/e = 245 (M^+), 202. Anal. ($C_{15}H_{16}FNO$) C, H, F, N.

3-Oxo-4-methylpentanoic Acid Anilide (22). A solution of ethyl 3-oxo-4-methylpentanoate[9] (47.4 g, 0.3 mol), aniline (27.93 g, 27.3 mL, 0.3 mol), and acetic acid (0.6 mL) in toluene (360 mL) was refluxed for 4 h with a Dean–Stark trap. The cold mixture was washed twice with 0.5 N hydrochloric acid, twice with saturated sodium bicarbonate solution, once with brine, dried, concentrated, and chromatographed with toluene/ethyl acetate (10:1) over 1 kg of silica, giving 40.5 g (66% yield) of a pale pink oil: NMR δ 1.2 (6 H, d), 2.8 (1 H, sept), 3.65 (2 H, s), 7.0–7.75 (5 H, m), 9.1–9.4 (1 H, br s); MS $C_{21}H_{15}NO_2$ m/e = 205 (M^+), 93. Anal. ($C_{21}H_{15}NO_2$) C, H, F, N.

3-(Phenylamino)-4-methylpent-2(*E*)-enoic Acid Anilide (23b). A solution of ethyl 3-oxo-4-methylpentanoate[9] (31 mL, 0.2 mol), aniline (37 mL, 0.41 mol), and acetic acid (1.0 mL) in toluene (50 mL) was refluxed for 6 h with a Dean–Stark trap. The solvent was removed in vacuo. On cooling the residue crystallized. It was recrystallized from toluene/petroleum ether (80–110 °C) (2:1) to yield 38.7 g of colorless solid: mp 147–148 °C; a second crop of crystals can be obtained from the mother liquor; NMR δ 1.1 (7 H, d + m), 2.9 (1 H, sept), 4.75 (1 H, s), 6.8–7.6 (10 H, m), 11.1 (1 H, br s). Anal. ($C_{18}H_{20}N_2O$) C, H, N.

3-(Isopropylamino)-4-methylpent-2(*E*)-enoic Acid Anilide (23e). To a solution of anilide 22 (35.7 g, 174 mmol) and acetic acid (0.6 mmol) in toluene (600 ml), refluxing under a Dean–Stark trap, was added isopropylamine (20.6 g, 348 mmol) dropwise over 3 h. The mixture was refluxed for 16 h, concentrated in vacuo, and cooled, leading to crystallization. The solid was digerated with diisopropyl ether/petroleum ether (1:1), collected with suction filtration, and washed with petroleum ether, giving 28.9 g of colorless solid: mp 152–153 °C; NMR δ 1.1 (6 H, d), 1.25 (6 H, d), 2.73 (1 H, sept), 3.8 (1 H, m), 4.43 (1 H, s), 6.7 (1 H, s), 6.9–7.6 (5 H, m), 9.1–9.6 (1 H, br s); MS $C_{15}H_{22}N_2O$ CI m/e = 247 (M + H^+), 154. Anal. ($C_{15}H_{22}N_2O$) C, H, N.

3-(Cyclohexylamino)-4-methylpent-2(*E*)-enoic Acid Anilide (23f). A solution of anilide 22 (31.6 g, 154 mmol), acetic acid (1.5 mL), and cyclohexylamine (30.55 g, 308 mmol) in toluene (750 mL) was refluxed for 20 h under a Dean–Stark trap. The solvent was removed in vacuo, the residue was swirled with 150 mL of diisopropyl ether, collected with suction filtration, and washed with petroleum ether to give 27.1 g of a colorless solid (an addition 8.9 g came from the mother liquor): yield 82%; mp 123–132 °C; NMR δ 1.15 (6 H, d), 1.0–2.1 (10 H, m), 2.7 (1 H, sept), 3.45 (1 H, m), 4.4 (1 H, s), 6.55 (1 H, m), 6.9–7.6 (5 H, m), 9.5 (1 H, br s) MS $C_{18}H_{26}N_2O$ m/e = 286 (M^+), 194, 93. Anal. ($C_{18}H_{26}N_2O$) C, H, N.

Preparation of Substituted 1*H*-Pyrrole-3-carboxanilides 24 from Enamino Anilides 23. General Procedure. A solution of the nitro olefin 15 (95 mmol) and enamino carboxanilide 23 (100 mmol) in ethanol (300 mL) was refluxed for 12 h under nitrogen. Most of the solvent was removed in vacuo. Cooling of the residue in an ice bath gave crystals that were swirled in cyclohexane/ethyl acetate (200 mL), collected, and recrystallized.

1-Phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxanilide (24b): yield 78%; mp 192–194 °C (from methanol); NMR δ 1.30 (6 H, d), 3.14 (1 H, sept), 6.73 (1 H, s), 7.00–7.70 (10 H, m). Anal. ($C_{26}H_{23}FN_2O$) C, H, F, N.

1,2-Diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxanilide (24e): yield 50%; mp 131–133 °C (not recryst); NMR δ 1.45 (6 H, d), 1.55 (6 H, d), 3.75 (1 H, sept), 4.6 (1 H, sept), 6.7 (1 H, s), 6.7–7.6 (10 H, m); MS $C_{23}H_{25}FN_2O$ m/e = 364 (M^+), 272, 230. Anal. ($C_{23}H_{25}FN_2O$) C, H, F, N.

1-Cyclohexyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxanilide (24f): yield 52%; mp 215–216 °C (not recryst); NMR δ 0.9–2.2 (16 H, d + m), 3.5–4.3 (2 H, m), 6.65 (1 H, s), 6.8–7.6 (10 H, m) MS $C_{26}H_{29}FN_2O$ CI m/e = 405 (M + H^+), 312, 230. Anal. ($C_{26}H_{29}FN_2O$) C, H, F, N.

1-Phenyl-2-isopropyl-4-(4-fluorophenyl)-5-methyl-1*H*-pyrrole-3-carboxanilide (24g): yield 80%; mp 190–192 °C (from cyclohexane/ethyl acetate); NMR δ 1.3 (6 H, d), 1.83 (3 H, s), 3.2 (1 H, sept), 6.8–7.6 (15 H, m); MS $C_{27}H_{25}FN_2O$ m/e = 412 (M^+), 320 (M^+ – PhNH). Anal. ($C_{27}H_{25}FN_2O$) C, H, F, N.

Preparation of Substituted 1*H*-Pyrrole-3-carboxaldehydes 4 from Substituted 1*H*-Pyrrole-3-carboxanilides 24. General Procedure. (a) **N-Methylation.** To a mechanically stirred solution of anilide 24 (55 mmol) in toluene (300 mL) was added a 50% dispersion of NaH in mineral oil (5.5 g, 115 mmol) at 25 °C under a nitrogen atmosphere. The suspension was warmed for 30 min at 60 °C and for 10 min at 100 °C. The suspension was cooled to 20 °C and methyl iodide (62.5 g, 440 mmol) was added. It was refluxed (bath at 75 °C) for 4–16 h, depending on steric hindrance (TLC control). With external cooling with dry ice/methanol, first water (80 mL) was added dropwise, followed by ether (400 mL). The organic phase was separated, washed with brine, dried, and concentrated in vacuo. The residues often crystallized when swirled with *n*-hexane or diisopropyl ether to a colorless to pale yellow solid. Oily products were purified by chromatography with cyclohexane/ethyl acetate/triethylamine (8:2:0.01) over silica.

1-Phenyl-2-isopropyl-4-(4-fluorophenyl)-*N*-methyl-1*H*-pyrrole-3-carboxanilide: yield 94%; mp 126–127 °C (not recryst); MS $C_{27}H_{25}FN_2O$ m/e = 412 (M^+), 306, 262. Anal. ($C_{27}H_{25}FN_2O$) C, H, F, N.

1,2-Diisopropyl-4-(4-fluorophenyl)-*N*-methyl-1*H*-pyrrole-3-carboxanilide: yield 73%; oil; NMR δ 1.40 (12 H, d), 3.23 (4 H, s + sept), 4.40 (1 H, sept), 6.50 (1 H, s), 6.5–7.5 (9 H, m); MS $C_{24}H_{27}FN_2O$ m/e = 378 (M^+), 272, 91. Anal. ($C_{24}H_{27}FN_2O$) C, H, F, N.

1-Cyclohexyl-2-isopropyl-4-(4-fluorophenyl)-*N*-methyl-1*H*-pyrrole-3-carboxanilide: yield 98%; mp 102–105 °C (not recryst); NMR δ 1.35 (3 H, d), 1.50 (3 H, d), 1.1–2.2 (11 H, m), 3.25 (3 H, br s) 3.95 (1 H, m), 6.4–7.4 (10 H, m); MS $C_{27}H_{31}FN_2O$ CI m/e = 419 (M + H^+), 312. Anal. ($C_{27}H_{31}FN_2O$) C, H, F, N.

1-Phenyl-2-isopropyl-4-(4-fluorophenyl)-5-methyl-*N*-methyl-1*H*-pyrrole-3-carboxanilide: yield 84%; mp 62–63 °C (not recryst); NMR δ 1.2 (3 H, d), 1.3 (3 H, d), 1.8 (3 H, s), 2.8 (1 H, sept), 3.17 (3 H, s), 6.5–7.5 (14 H, m); MS $C_{28}H_{27}FN_2O$ m/e = 426 (M^+), 320 (M^+ – $PhNCH_3$). Anal. ($C_{28}H_{27}FN_2O$) C, H, F, N.

(b) **Reduction.** To a suspension of lithium aluminum hydride (60 mmol) in dry THF (120 mL) under nitrogen was added dropwise a solution of *N*-methylanilides (29 mmol) in THF (120 mL). The mixture was refluxed for 20 h and then cooled to 0 °C. Ethyl acetate (15 mL) and then water (5 mL) followed by 2 N sodium hydroxide solution (10 mL) were added dropwise. The mixture was stirred for 30 min at 25 °C. The solids were removed and washed with ether.

The filtrate was concentrated in vacuo. The residues often crystallized when swirled with *n*-pentane. Oily products were purified by chromatography with toluene/ethyl acetate/triethylamine (20:1:0.01) over silica.

1-Phenyl-2-isopropyl-3-(hydroxymethyl)-4-(4-fluorophenyl)-1*H*-pyrrole: yield 92%; oil; NMR δ 1.28 (7 H, d + m), 3.03 (1 H, sept), 4.70 (2 H, s), 6.73 (1 H, s), 6.90–7.70 (9 H, m); MS $C_{20}H_{20}FNO$ m/e = 309 (M^+), 294, 276. Anal. ($C_{20}H_{20}FNO$) C, H, F, N.

1,2-Diisopropyl-3-(hydroxymethyl)-4-(4-fluorophenyl)-1*H*-pyrrole: yield 75%; pale yellow oil that slowly crystallized; NMR δ 1.2–1.6 (12 H, m), 2.35 (1 H, br s), 3.33 (1 H, sept), 4.40 (2 H, s), 4.50 (1 H, sept), 6.70 (1 H, s), 6.8–7.65 (4 H, m); MS $C_{17}H_{22}FNO$ CI m/e = 275 (M^+), 258, 242, 200. Anal. ($C_{17}H_{22}FNO$) C, H, F, N.

1-Cyclohexyl-2-isopropyl-3-(hydroxymethyl)-4-(4-fluorophenyl)-1*H*-pyrrole: yield 67%; mp 114–116 °C (not recryst); NMR δ 1.37 (6 H, d), 1.2–2.1 (10 H, m), 3.30 (1 H, sept), 3.96 (1 H, m), 4.38 (2 H, s), 6.70 (1 H, s), 6.95 (2 H, m), 7.47 (2 H, m); MS $C_{20}H_{26}FNO$ m/e = 315 (M^+), 300, 282, 200. Anal. ($C_{20}H_{26}FNO$) C, H, F, N.

1-Phenyl-2-isopropyl-3-(hydroxymethyl)-4-(4-fluorophenyl)-5-methyl-1*H*-pyrrole: yield 63%; colorless solid; NMR δ 1.25 (6 H, d), 1.9 (3 H, s), 2.8 (1 H, m), 4.35 (1 H, s), 4.55 (2 H, s), 6.85–7.75 (9 H, m); MS $C_{21}H_{22}FNO$ m/e = 323 (M^+), 308 (M^+ – CH_3), 290 (M^+ – CH_3 – H_2O). Anal. ($C_{21}H_{22}FNO$) C, H, F, N.

(c) **Oxidation. Variant A.** To a mechanically stirred suspension of Celite (50 g) and finely powdered CrO_3 (25 g, 250 mmol) in dry dichloromethane (250 mL) at 15 °C was added dropwise a solution of dry pyridine (39.5 g, 500 mmol) in CH_2Cl_2 (40 mL).

After stirring at room temperature (20 min), a solution of the substituted (hydroxymethyl)pyrrole (25 mmol) in CH_2Cl_2 (250 mL) was added dropwise but quickly. The reaction temperature was kept between 20 and 24 °C. After 15 min cyclohexane (500 mL) was added. The solid was suction filtered and washed with dichloromethane/cyclohexane (3:7). The filtrate was concentrated and chromatographed with cyclohexane/ethyl acetate/triethylamine (4:1:0.01) over 500 g of silica.

Variant B.[11] To a solution of *N*-methylmorpholine *N*-oxide (46.8 g, 400 mmol) in acetone (400 mL, dried over K_2CO_3) was added tris(triphenylphosphine)ruthenium(II) dichloride (3.8 g, 4.0 mmol). The mixture was stirred 20 min at 20 °C. A solution of the substituted (hydroxymethyl)pyrrole (100 mmol) in dry acetone (600 mL) was added dropwise. The mixture was stirred for 10–20 h at room temperature. After complete reaction (TLC, cyclohexane/ethyl acetate/triethylamine 4:1:0.1), the mixture was filtered through a short, thick silica pad. The pad was washed with ether (3 L); the filtrate was concentrated in vacuo. The residue, pure 4, usually crystallized, when digerated with *n*-pentane at 0 °C.

1-Phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxaldehyde (4b): yield (variant A) 35%, (variant B) 87%; pale yellow solid; mp 119–120 °C; NMR δ 1.36 (6 H, d), 3.16 (1 H, sept), 6.65 (1 H, s), 7.0–7.7 (9 H, m), 10.1 (1 H, s); MS $C_{20}H_{18}FNO$ m/e = 307 (M^+), 292. Anal. ($C_{20}H_{18}FNO$) C, H, F, N.

1,2-Diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxaldehyde (4e): yield (variant B) 87%; yellow oil; NMR δ 1.43 (6 H, d), 1.47 (6 H, d), 3.80 (1 H, sept), 4.57 (1 H, sept), 6.62 (1 H, s), 7.06 (2 H, m), 7.37 (2 H, m), 9.89 (1 H, s); MS $C_{17}H_{20}FNO$ m/e = 273 (M^+), 258, 244. Anal. ($C_{17}H_{20}FNO$) C, H, F, N.

1-Cyclohexyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxaldehyde (4f): yield (variant B) 98%; colorless crystals; mp 134–135 °C; NMR δ 1.45 (6 H, d), 1.1–2.2 (10 H, m), 3.55–4.35 (2 H, m + sept), 6.65 (1 H, s), 6.9–7.6 (4 H, m), 9.95 (1 H, s); MS $C_{20}H_{24}FNO$ m/e = 313 (M^+), 298, 231, 216. Anal. ($C_{20}H_{24}FNO$) C, H, F, N.

1-Phenyl-2-isopropyl-4-(4-fluorophenyl)-5-methyl-1*H*-pyrrole-3-carboxaldehyde (4g): yield (variant A) 45%; pale yellow solid; NMR δ 1.3 (6 H, d), 2.1 (3 H, s), 3.1 (1 H, sept), 6.9–7.6 (9 H, m), 10.0 (1 H, s); MS $C_{21}H_{20}FNO$ m/e = 321 (M^+). Anal. ($C_{21}H_{20}FNO$) C, H, F, N.

Synthesis of 1,2-Diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxaldehyde (4e) via Three-Component Coupling Reaction According to Scheme VI. (a) Three-Component Coupling. Ethyl 1,2-Diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxylate (21e). To a suspension of 4-fluoro-β-nitrostyrene[19] (209 g, 1.25 mol) in absolute methanol (500 mL) was added ethyl 3-oxo-4-methylpentanoate[9] (214 g, 1.35 mol) under ice cooling followed by isopropylamine (128 mL, 1.50 mol), both in one portion. Absolute methanol (1 L) was added, the ice bath was removed, and the reaction mixture was stirred for 48 h in a tightly stoppered flask. Volatile components were removed in vacuo. The brown, viscous oil was filtered with toluene/0.1% triethylamine through 5 kg of silica gel (70–200 μm) to give 197 g (49.7% yield) of a yellow solid: mp 72–74 °C; NMR (CD_2Cl_2) δ 1.07 (3 H, t), 1.36 (6 H, d), 1.42 (6 H, d), 3.73 (1 H, sept), 4.06 (2 H, q), 4.50 (1 H, sept), 6.60 (1 H, s), 6.80–7.40 (4 H, m); MS (DCI, posit, isobutane) $C_{19}H_{24}FNO_2$ m/e = 318 ($M + H^+$), 317, 302. Anal. ($C_{19}H_{24}FNO_2$) C, H, F, N.

(b) Reduction. 1,2-Diisopropyl-3-(hydroxymethyl)-4-(4-fluorophenyl)-1*H*-pyrrole. A solution of the ethyl ester (197 g, 0.62 mol) in ether (750 mL) was added dropwise at 0 °C to a suspension of lithium aluminum hydride (47.2 g, 1.24 mol) in ether (1.5 L). The reaction mixture was stirred for 1 h at 0 °C and for 1 h at 20 °C. At 0–10 °C ethyl acetate (150 mL) was added dropwise, and then water (38 mL) followed by 2 N sodium hydroxide solution (75 mL) was added. The mixture was stirred for 15 min at room temperature. The inorganic solids were removed by suction filtration and washed thoroughly with ether.

Triethylamine (1 mL) was added to the combined filtrate and washings and the solvent was removed in vacuo to give a yellow solid (131 g, 77% yield) that had spectra identical with those of the authentic material described above.

(c) Oxidation was performed as described above to give 4e as a yellow solid in 92% yield.

Pyrrole-Substituted Acrylonitriles 5. General Procedure. At 0 °C a solution of diisopropyl (cyanomethyl)phosphonate (13.5 g, 66.0 mmol) in dry THF (200 mL) was added dropwise to a suspension of sodium hydride (3.78 g of a 50% dispersion in mineral oil, 78.7 mmol) in dry THF (700 mL). After 40 min at 0 °C, a solution of aldehyde 4 (44.0 mmol) in THF (100 mL) was added dropwise. The mixture was stirred for 2 h at room temperature. The reaction mixture was poured into 1 L of brine. The organic phase was separated and the aqueous phase was extracted with ether. The combined organic phases were dried and concentrated in vacuo. The residue was chromatographed over silica with cyclohexane/ethyl acetate (6:1), containing 0.1% triethylamine.

β-[1-Phenyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-(*E*)-acrylonitrile (5a): yield 78%; pale yellow solid; NMR δ 2.30 (3 H, s), 5.23 (1 H, d), 6.73 (1 H, s), 7.0–7.6 (10 H, m); MS $C_{20}H_{15}FN_2$ m/e = 302 (M^+). Anal. ($C_{20}H_{15}FN_2$) C, H, F, N.

β-[1,2-Diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-(*E*)-acrylonitrile (5e): yield 91%; crystals; mp 121–123 °C (not recryst); NMR δ 1.43 (12 H, 2 × d), 3.30 (1 H, sept), 4.50 (1 H, sept), 4.93 (1 H, d), 6.60 (1 H, s), 6.9–7.4 (4 H, m), 7.53 (1 H, d); MS $C_{19}H_{21}FN_2$ m/e = 296 (M^+), 281, 256, 239. Anal. ($C_{19}H_{21}FN_2$) C, H, F, N.

β-[1-Cyclohexyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-(*E*)-acrylonitrile (5f): yield 96%; pale yellow solid; mp 130–132 °C (not recryst); NMR δ 1.40 (6 H, d), 1.2–2.1 (10 H, m), 3.30 (1 H, sept), 4.00 (1 H, m), 4.95 (1 H, d), 6.60 (1 H, s), 6.9–7.4 (4 H, m), 7.55 (1 H, d); MS $C_{22}H_{25}FN_2$ m/e = 336 (M^+), 321, 239. Anal. ($C_{22}H_{25}FN_2$) C, H, F, N.

Preparation of Pyrrole-Substituted Acroleins 6 from Acrylonitriles 5. General Procedure. To a solution of nitrile 5 (24 mmol) in dry THF (200 mL) was added dropwise 60 mL (72 mmol) of a 1.2 M solution of diisobutylaluminum hydride in toluene at 0 °C. The mixture was stirred for 1 h at 0 °C and then for 1.5 h at room temperature. At 0 °C, saturated aqueous sodium dihydrogen phosphate solution (100 mL) and then water (200 mL) were added dropwise. The mixture was stirred for 1 h at room temperature and then saturated with sodium chloride and extracted with ether. The combined organic phases were washed with saturated aqueous sodium bicarbonate and then dried and concentrated in vacuo. The residue was chromatographed over silica with cyclohexane/ethyl acetate (5:1), containing 0.1% triethylamine.

3-[1-Phenyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-(*E*)-propenal (6a): yield 70%; pale yellow solid; NMR δ 2.36 (3 H, s), 6.26 (1 H, dd), 6.97 (1 H, d), 7.15–7.70 (10 H, m), 9.54 (d, 1 H); MS $C_{20}H_{16}FNO$ m/e = 305 (M^+), 290, 276, 264. Anal. ($C_{20}H_{16}FNO$) C, H, F, N.

3-[1,2-Diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-(*E*)-propenal (6e): yield 70%; crystals; mp 119–121 °C; NMR δ 1.45 (12 H, 2 × d), 3.45 (1 H, sept), 4.53 (1 H, sept), 6.00 (1 H, d), 6.65 (1 H, s), 6.9–7.5 (4 H, m), 7.63 (1 H, d), 9.45 (1 H, d); MS $C_{19}H_{22}FNO$ m/e = 299 (M^+), 256, 214. Anal. ($C_{19}H_{22}FNO$) C, H, F, N.

3-[1-Cyclohexyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-(*E*)-propenal (6f): yield 81%; pale yellow crystals; mp 124 °C (not recryst); NMR δ 1.46 (6 H, d), 1.3–2.2 (10 H, m), 3.50 (1 H, sept), 4.00 (1 H, m), 6.05 (1 H, dd), 6.65 (1 H, s), 6.9–7.5 (4 H, m), 7.65 (1 H, d), 9.50 (1 H, d); MS $C_{22}H_{26}FNO$ m/e = 339 (M^+), 296, 214. Anal. ($C_{22}H_{26}FNO$) C, H, F, N.

Synthesis of Pyrrole-Substituted Acroleins 6 from Aldehydes 4 with the Wollenberg Reagent. General Procedure. To a solution of 1-ethoxy-2-(tri-*n*-butylstannyl)ethylene[20] (3.46 g, 9.6 mmol) in dry THF (110 mL) was added a solution of *n*-butyllithium in *n*-hexane (6.25 mL of a 1.6 M solution, 10 mmol) at −70 °C under nitrogen. After 2 h at −73 °C, a solution of the aldehyde 4 (8 mmol) in THF (12 mL) was added dropwise. During this operation, the reaction temperature rose to −66 °C. After 2 h at −73 °C and 10 min at −50 °C, a saturated aqueous ammonium chloride solution (18.6 mL) was added dropwise at −40 °C. The mixture was allowed to warm to room temperature. The organic layer was separated; the aqueous layer was extracted twice

(20) Leusink, A. J.; Budding, H. A.; Drenth, W. *J. Organomet. Chem.* 1967, *9*, 285.

with ether. The combined organic layers were washed with brine and then dried and concentrated in vacuo. The residue was taken up in THF (93 mL) and water containing *p*-toluenesulfonic acid (18 mL) and stirred for 1 h at room temperature. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine and then dried and concentrated. The residue was chromatographed with cyclohexane/ethyl acetate/triethylamine (3:1:0.1) over 450 g of silica.

3-[1-Phenyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-(*E*)-propenal (6a): yield 98%; spectra, see above.

3-[1-Phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-(*E*)-propenal (6b): yield 50% (46% recovered starting material); NMR δ 1.35 (6 H, d), 3.16 (1 H, sept), 6.05 (1 H, dd), 6.63 (1 H, s), 7.0–7.5 (9 H, m), 7.75 (1 H, d), 9.50 (1 H, d); MS $C_{22}H_{20}FNO$ DCI m/e = 334 ($M + H^+$), 290. Anal. ($C_{22}H_{20}FNO$) C, H, F, N.

3-[1-Phenyl-2,5-dimethyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-(*E*)-propenal (6c): yield 88%; amorphous solid; NMR δ 1.9 (3 H, s), 2.2 (3 H, s), 6.07 (1 H, dd), 6.9–7.7 (10 H, m), 9.45 (1 H, d); MS $C_{21}H_{18}FNO$ m/e = 319 (M^+), 290 ($M^+ - CHO$). Anal. ($C_{21}H_{18}FNO$) C, H, F, N.

3-[1-Isopropyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-(*E*)-propenal (6d): yield 94%; colorless solid; NMR δ 1.47 (6 H, d), 2.43 (3 H, s), 4.42 (1 H, sept), 6.20 (1 H, dd), 6.72 (1 H, s), 6.9–7.5 (4 H, m), 7.50 (1 H, d), 9.48 (1 H, d); MS $C_{17}H_{18}FNO$ m/e = 271 (M^+), 256, 242, 200. Anal. ($C_{17}H_{18}FNO$) C, H, F, N.

3-[1-Phenyl-2-isopropyl-4-(4-fluorophenyl)-5-methyl-1*H*-pyrrol-3-yl]-(*E*)-propenal (6g): yield 91%; yellow solid; NMR δ 1.3 (6 H, d), 2.0 (3 H, s), 3.1 (1 H, sept), 6.1 (1 H, dd), 7.0–7.8 (10 H, m), 9.5 (1 H, d); MS $C_{23}H_{22}FNO$ DCI m/e = 348 ($M + H^+$). Anal. ($C_{23}H_{22}FNO$) C, H, F, N.

β-Keto-δ-hydroxy Esters 7. General Procedure. To a suspension of sodium hydride (12.7 mmol) in THF (86 mL) was added dropwise a solution of methyl acetoacetate (1.43 g, 12.33 mmol) in THF (10 mL) at −15 °C during 5 min. The solution was stirred for 50 min at −15 °C. A solution of *n*-butyllithium in hexane (7.68 mL of a 1.6 M solution, 12.26 mmol) was added during 10 min. The reaction mixture was stirred for 20 min at −15 °C. A solution of aldehyde 6 (7.0 mmol) in THF (25 mL) was added during 10 min. The reaction mixture was stirred for 45 min at −15 °C. At −10 °C, a saturated sodium dihydrogen phosphate solution (13 mL) was added dropwise. After 5 min at 0 °C, the mixture was distributed between ether and brine. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried, concentrated, and chromatographed with cyclohexane/ethyl acetate/triethylamine (2:1:0.1) over silica, giving a pale yellow oil (76–85% yield).

Methyl 5(*RS*)-hydroxy-3-oxo-7-[1-phenyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (7a): NMR δ 2.27 (3 H, s), 2.55 (1 H, br), 2.80 (2 H, m), 3.50 (2 H, s), 3.74 (3 H, s), 4.69 (1 H, q), 5.65 (1 H, dd), 6.60 (1 H, d), 6.76 (1 H, s), 7.00–7.12 (4 H, m), 7.30–7.52 (5 H, m); MS $C_{25}H_{24}FNO_4$ m/e = 421 (M^+), 403, 345, 302. Anal. ($C_{25}H_{24}FNO_4$) C, H, F, N.

Methyl 5(*RS*)-hydroxy-3-oxo-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (7b): MS $C_{27}H_{28}FNO_4$ m/e = 449 (M^+), 432, 373, 334, 290. Anal. ($C_{27}H_{28}FNO_4$) C, H, F, N.

Methyl 5(*RS*)-hydroxy-3-oxo-7-[1-phenyl-2,5-dimethyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (7c): NMR δ 1.6 (1 H, s), 1.9 (3 H, s), 2.13 (3 H, s), 2.36 (2 H, s), 3.57 (2 H, AB), 3.73 (3 H, s), 5.99 (1 H, d), 6.16 (1 H, dd), 6.94 (1 H, d), 7.08–7.33 (5 H, m), 7.44–7.58 (4 H, m); MS $C_{26}H_{26}FNO_4$ m/e = 435 (M^+), 417, 320, 319, 316, 290. Anal. ($C_{26}H_{26}FNO_4$) C, H, F, N.

Methyl 5(*RS*)-hydroxy-3-oxo-7-[1-isopropyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (7d): NMR δ 1.44 (8 H, d + m), 1.58 (1 H, br s), 2.37 (3 H, s), 3.58 (2 H, s), 3.75 (3 H, s), 4.35 (1 H, sept), 6.02 (1 H, d), 6.27 (1 H, dd), 6.67 (1 H, s), 7.06 (2 H, m), 7.28 (2 H, m); MS $C_{22}H_{25}FNO_4$ m/e = 387 (M^+), 369, 272. Anal. ($C_{22}H_{26}FNO_4$) C, H, F, N.

Methyl 5(*RS*)-hydroxy-3-oxo-7-[1,2-diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (7e): NMR (CD_2Cl_2) δ 1.36 (6 H, d), 1.42 (6 H, d), 2.37 (1 H, d), 2.68 (2 H, m), 3.30 (1 H, sept), 3.48 (2 H, s), 3.70 (3 H, s), 4.44 (1 H, sept), 4.59 (1 H, m), 5.32 (1 H, dd), 6.62 (1 H, d), 7.00 (2 H, m), 7.30 (2 H, m); MS $C_{24}H_{30}FNO_4$ m/e = 415 (M^+), 397, 300, 256. Anal. ($C_{24}H_{30}FNO_4$) C, H, F, N.

Methyl 5(*RS*)-hydroxy-3-oxo-7-[1-cyclohexyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (7f): NMR (CD_2Cl_2) δ 1.35 (6 H, d), 1.3–2.3 (10 H, m), 2.35 (1 H, d), 2.65 (2 H, d), 3.30 (1 H, sept), 3.50 (2 H, s), 3.70 (3 H, s), 4.00 (1 H, m), 4.60 (1 H, m), 5.35 (1 H, dd), 6.65 (1 H, s), 6.65 (1 H, d), 6.85–7.50 (4 H, m); MS $C_{27}H_{34}FNO_4$ m/e = 455 (M^+), 437, 340, 296, 214. Anal. ($C_{27}H_{34}FNO_4$) C, H, F, N.

Methyl 5(*RS*)-hydroxy-3-oxo-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-5-methyl-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (7g): MS $C_{28}H_{30}FNO_4$ m/e = 463 (M^+), 446. Anal. ($C_{28}H_{30}FNO_4$) C, H, F, N.

β,δ-Dihydroxy Esters 1 ($R^1 = CH_3$). General Procedure. To a solution of β-keto-δ-hydroxy ester 7 (5 mmol) in dry THF (70 mL) was added dropwise a solution of triethylborane in THF (6 mL of a 1 M solution, 6 mmol) during 5 min. After 20 min at 20 °C, 14 mL of dry air was bubbled through the solution with a syringe. After 2 h at 20 °C, the reaction mixture was cooled to −75 °C. Sodium borohydride (246 mg, 6.5 mmol) was added at once. After 12 h at −75 °C under nitrogen, the mixture was allowed to warm to −10 °C and saturated sodium dihydrogen phosphate solution (35 mL) was added dropwise. The reaction mixture was partitioned between ether and brine. The organic layer was washed with brine, dried, and concentrated. The residue was stirred for 3 h with dry methanol (300 mL). The solvent was evaporated and the residue was chromatographed with cyclohexane/ethyl acetate/triethylamine (1:1:0.1) through silica to yield 60–85% of a thick, pale yellow oil.

Methyl 3(*RS*),5(*SR*)-dihydroxy-7-[1-phenyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (1a): NMR δ 2.12 (2 H, m), 2.24 (3 H, s), 2.37 (2 H, s), 2.54 (1 H, dd), 2.75 (1 H, dd), 3.72 (3 H, s), 4.26 (1 H, m), 5.32 (1 H, m), 5.75–5.85 (2 H, m), 6.78 (1 H, s), 7.00–7.10 (2 H, m), 7.28–7.50 (7 H, m); MS $C_{25}H_{26}FNO_4$ m/e = 423 (M^+), 306, 264. Anal. ($C_{25}H_{26}FNO_4$) C, H, F, N.

Methyl 3(*RS*),5(*SR*)-dihydroxy-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (1b): NMR (C_6D_6) δ 1.30 (7 H, d + m), 1.57 (1 H, dt), 2.03 (1 H, dd), 2.18 (1 H, dd), 2.70 (1 H, br s), 3.09 (1 H, sept), 3.27 (3 H, s), 3.45 (1 H, br s), 4.03 (1 H, m), 4.34 (1 H, m), 5.67 (1 H, dd), 6.50 (1 H, s), 6.87–7.15 (8 H, m), 7.45 (2 H, dd); MS $C_{27}H_{30}FNO_4$ m/e = 451 (M^+), 433, 334, 292, 290, 276. Anal. ($C_{27}H_{30}FNO_4$) C, H, F, N.

Methyl 3(*RS*),5(*SR*)-dihydroxy-7-[1-phenyl-2,5-dimethyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (1c): NMR (C_6D_6) δ 1.37 (1 H, dt), 1.67 (1 H, dt), 1.90 (3 H, s), 2.08 (3 H, s), 2.05–2.12 (1 H, dd), 2.26 (1 H, dd), 2.40 (1 H, d), 3.26 (3 H, s), 3.48 (1 H, d), 4.11 (1 H, m), 4.30 (1 H, m), 5.72 (1 H, dd), 6.72 (1 H, d), 6.85–6.91 (2 H, m), 6.95–7.17 (5 H, m), 7.32–7.40 (2 H, m); MS $C_{26}H_{28}FNO_4$ m/e = 437 (M^+), 419, 320, 302, 278. Anal. ($C_{26}H_{28}FNO_4$) C, H, F, N.

Methyl 3(*RS*),5(*SR*)-dihydroxy-7-[1-isopropyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (1d): NMR (C_6D_6) δ 0.98 (6 H, d), 1.40 (1 H, dt), 1.68 (1 H, dt), 2.05 (3 H, s), 2.09 (1 H, dd), 2.27 (1 H, dd), 3.27 (3 H, s), 3.73 (1 H, sept), 4.14 (1 H, m), 4.34 (1 H, m), 5.72 (1 H, dd), 6.50 (1 H, s), 6.73 (1 H, d), 6.98 (2 H, m), 7.43 (2 H, m); MS $C_{22}H_{28}FNO_4$ m/e = 389 (M^+), 272, 230. Anal. ($C_{22}H_{28}FNO_4$) C, H, F, N.

Methyl 3(*RS*),5(*SR*)-dihydroxy-7-[1,2-diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (1e): NMR (CD_2Cl_2) δ 1.35 (6 H, d), 1.42 (6 H, d), 1.50–1.70 (2 H, m), 2.45 (2 H, d), 2.62 (1 H, br s), 3.31 (1 H, sept), 3.54 (1 H, d), 3.68 (3 H, s), 4.22 (1 H, m), 4.33–4.52 (2 H, sept + m), 5.32 (1 H, d), 6.58 (1 H, d), 6.62 (1 H, s), 7.00 (2 H, m), 7.31 (2 H, m); MS $C_{24}H_{32}FNO_4$ m/e = 417 (M^+), 399 ($M^+ - H_2O$), 300, 258, 212. Anal. ($C_{24}H_{32}FNO_4$) C, H, F, N.

Methyl 3(*RS*),5(*SR*)-dihydroxy-7-[1-cyclohexyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (1f): NMR (CD_2Cl_2) δ 1.25–2.05 (12 H, m), 1.34 (6 H, d), 2.45 (2 H, d), 2.62 (1 H, d), 3.30 (1 H, sept), 3.55 (1 H, d), 3.69 (3 H, s), 3.95 (1 H, tt), 4.20 (1 H, m), 4.38 (1 H, m), 5.33 (1 H, dd), 6.58 (1 H, d), 6.62 (1 H, s), 7.00 (2 H, m), 7.30 (2 H, m); MS $C_{27}H_{36}FNO_4$ m/e = 457 (M^+), 439 ($M^+ - H_2O$), 421 ($M^+ - 2H_2O$), 366, 340, 298, 212. Anal. ($C_{27}H_{36}FNO_4$) C, H, F, N.

Methyl 3(*RS*),5(*SR*)-dihydroxy-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-5-methyl-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (1g): NMR (C_6D_6) δ 1.3 (7 H, d + m), 1.6 (1 H, m), 1.95 (3 H, s), 2.0–2.3 (2 H, m), 2.5 (1 H, br s), 3.1 (1 H, sept), 3.3 (3 H, s), 3.5 (1 H, s), 4.1 (1 H, m), 4.3 (1 H, m), 5.7 (1 H, dd), 6.8–7.5 (10 H, m); MS $C_{28}H_{32}FNO_4$ *m/e* = 465 (M^+), 447 ($M^+ - H_2O$). Anal. ($C_{28}H_{32}FNO_4$) C, H, F, N.

Hydrogenated β,δ-Dihydroxy Esters 2 ($R^1 = CH_3$). General Procedure. Ten percent palladium on charcoal (2.2 g) was added under nitrogen to a solution of the olefinic β,δ-dihydroxy ester 1 ($R^1 = CH_3$) (70 mmol) in methanol (1.3 L) and triethylamine (13 mL). The mixture was shaken for 20 min in a hydrogen atmosphere at atmospheric pressure and room temperature. H_2 (1240 mL) was taken up (theoretical 1570 mL). The catalyst was filtered off and washed with methanol. The filtrate was concentrated in vacuo. The residue was chromatographed with cyclohexane/ethyl acetate (5:3), containing 0.1% triethylamine, through 1.3 kg of silica. The first compound eluted was the pure product 2 (yield 75–80%, pale yellow thick oil). Shortly thereafter a diastereomer of 2 (yield 8%) was eluted that stemmed either from incomplete stereoselectivity during the borane-catalyzed reduction of keto ester 6 (steps i, j) or from some isomerization during the catalytic hydrogenation. As a last fraction, the lactonized form of 2 (yield 4–5%) was obtained, containing some diastereomers. TLC (cyclohexane/ethyl acetate 1:1, silica) R_f values: 1 (starting material), 0.26; 2, 0.29; diastereomer of 2, 0.25; δ-lactone of 2, 0.19.

Methyl 3(*RS*),5(*RS*)-dihydroxy-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]heptanoate (2h): NMR (C_6D_6) δ 1.03 (1 H, dt), 1.28–1.43 (1 H, m), 1.32 (3 H, d), 1.33 (3 H, d), 1.60–1.85 (2 H, m), 1.94 (1 H, dd), 2.12 (1 H, dd), 2.90–3.02 (1 H, m), 3.03–3.22 (3 H, m), 3.24 (3 H, s), 3.43 (1 H, br s), 3.75 (1 H, m), 3.88 (1 H, m), 6.58 (1 H, s), 6.94 (2 H, m), 7.03–7.15 (5 H, m), 7.42 (2 H, m); MS $C_{27}H_{32}FNO_4$ *m/e* = 454 (M + H^+), 292. Anal. ($C_{27}H_{32}FNO_4$) C, H, F, N.

Methyl 3(*RS*),5(*RS*)-dihydroxy-7-[1-phenyl-2,5-dimethyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]heptanoate (2c): NMR (C_6D_6) δ 1.10 (1 H, dt), 1.38 (1 H, dt), 1.50–1.76 (2 H, m), 1.97 (3 H, s), 2.01 (1 H, dd), 2.08 (3 H, s), 2.17 (1 H, dd), 2.77 (2 H, m), 2.86 (1 H, d), 3.27 (3 H, s), 3.50 (1 H, d), 3.72 (1 H, m), 3.95 (1 H, m), 6.90–7.13 (7 H, m), 7.28–7.36 (2 H, m); MS $C_{25}H_{30}FNO_4$ *m/e* = 439 (M^+), 407, 279. Anal. ($C_{25}H_{30}FN$) C, H, F, N.

Methyl 3(*RS*),5(*RS*)-dihydroxy-7-[1-isopropyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]heptanoate (2d): NMR (C_6D_6) δ 1.02 (6 H, 2 × d), 1.38 (2 H, dt), 1.50–1.75 (2 H, m), 1.97 (1 H, dd), 2.10 (3 H, s), 2.15 (1 H, dd), 2.82 (2 H, m), 3.27 (3 H, s), 3.70 (1 H, m), 3.78 (1 H, sept), 3.93 (1 H, m), 6.58 (1 H, s), 6.98 (2 H, m), 7.39 (2 H, m); MS $C_{22}H_{30}FNO_4$ DCI *m/e* = 392 (M + H^+), 391, 360, 331, 230. Anal. ($C_{22}H_{30}FNO_4$) C, H, F, N.

Methyl 3(*RS*),5(*RS*)-dihydroxy-7-[1,2-diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]heptanoate (2e): NMR (CD_2Cl_2) δ 1.36 (6 H, d), 1.42 (6 H, d), 1.4–1.55 (4 H, m), 2.40 (2 H, d), 2.50–2.76 (2 H, m), 2.87 (1 H, br s), 3.22 (1 H, sept), 3.60 (1 H, br d), 3.68 (3 H, s), 3.76 (1 H, qui), 4.12 (1 H, qui), 4.43 (1 H, sept), 6.62 (1 H, s), 7.03 (2 H, m), 7.32 (2 H, m); MS $C_{24}H_{34}FNO_4$ DCI *m/e* = 420 (M + H^+), 419 (M^+), 259. Anal. ($C_{24}H_{34}FNO_4$) C, H, F, N.

Methyl 3(*RS*),5(*RS*)-dihydroxy-7-[1-cyclohexyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]heptanoate (2f): NMR (CD_2Cl_2) δ 1.36 (6 H, d), 1.3–1.8 (10 H, m), 1.32–2.05 (4 H, m), 2.39 (2 H, d), 2.50–2.72 (2 H, m), 2.88 (1 H, br s), 3.22 (1 H, sept), 3.61 (1 H, br d), 3.67 (3 H, s), 3.76 (1 H, qui), 3.94 (1 H, tt), 4.12 (1 H, qui), 6.61 (1 H, s), 7.02 (2 H, m), 7.31 (2 H, m); MS $C_{27}H_{38}FNO_4$ *m/e* = 459 (M^+), 427 ($M^+ - CH_3OH$), 299, 298, 256. Anal. ($C_{27}H_{38}FNO_4$) C, H, F, N.

Methyl 3(*RS*),5(*RS*)-dihydroxy-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-5-methyl-1*H*-pyrrol-3-yl]heptanoate (2g): NMR (C_6D_6) δ 1.1–1.5 (2 H, m), 1.3 (6 H, d), 1.6–2.2 (7 H, m + s), 2.9–3.2 (4 H, m), 3.3 (3 H, s), 3.45 (1 H, br s), 3.8–4.1 (2 H, m), 6.8–7.5 (9 H, m); MS $C_{28}H_{34}FNO_4$ FAB *m/e* = 468 (M + H^+). Anal. ($C_{28}H_{34}FNO_4$) C, H, F, N.

Optically Active HMG-CoA Reductase Inhibitors of General Formula 13 via Asymmetric Synthesis According to Scheme II. (a) Diastereoselective Aldol Reaction of Enolate 8 with Aldehydes 6. General Procedure. To a solution of diisopropylamine (97 mL, 70.0 g, 692 mmol) in dry THF (500 mL), cooled with dry ice, was added a 1.6 M solution of *n*-butyllithium in hexane (430 mL, 688 mmol) via a Flex-needle.[21] The mixture was stirred for 30 min at 0 °C under nitrogen. Another 4-L-four-necked flask, equipped with a mechanical stirrer, low-temperature thermometer, dropping funnel with cooling finger, and nitrogen inlet/mercury bubbler, was charged with (*S*)-(−)-phenyl 2-hydroxy-2,2-diphenylacetate[7] (104.7 g, 315 mmol) and dry THF (1 L). The suspension was cooled with dry ice.

A LDA-solution (vide supra) was transferred via a Flex-needle through a septum into the dropping funnel and added to the stirred suspension at such a rate that the reaction temperature stayed below −20 °C. The mixture was stirred for 30 min at 0 °C and became a reddish-brown, clear solution. A precooled solution of aldehyde 6 (300 mmol) in dry THF (300 mL) was added to this solution of dianion 8 at −90 °C. The reaction mixture was stirred for 1–2 h (TLC control) at this temperature. The cold mixture was poured into the mechanically stirred saturated aqueous solution of ammonium chloride (2 L) and stirred for 20 min (pH 8, 0 °C). The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried, and filtered, and the solvent was evaporated in vacuo to give a pale yellow solid that according to TLC consisted mostly of aldol product 9 with small amounts of unreacted chiral acetate and traces of unreacted aldehyde 6. For purification, the crude solid was shaken with hot toluene/ethyl acetate (2 L, 6:4 + 0.1% triethylamine). After the suspension had come to room temperature it was filtered, and the solid after washing with toluene was discarded. Combined filtrate and washings were evaporated in vacuo, and the remaining solid residue was stirred with *n*-pentane (2 × 1 L). The resulting suspension was suction filtered. Colorless solid 9, obtained in 95–98% yield, was pure by TLC. The pentane solution contained unreacted aldehyde 6.

The diastereomeric excess (de) of the desired 3*S* isomer of 9 was 95–96% according to HPLC analysis (LiChrosorb SI 60 Merck 506487, 40 °C, 1.2 mL/min *n*-hexane/methyl *tert*-butyl ether 3:1).

(*S*)-(−)-2-Hydroxy-1,2,2-triphenylethyl (3*S*)-hydroxy-5-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-pent-4(*E*)-enoate (9b): mp 188–190 °C; NMR (CD_2Cl_2) δ 1.22 (6 H, 2 × d), 1.53 (1 H, s), 1.57 (1 H, d), 2.38 (2 H, d), 3.00 (1 H, hept), 4.37 (1 H, m), 5.26 (1 H, dd, *J* = 16 and 7 Hz), 6.59 (1 H, s), 6.67 (1 H, dd, *J* = 16 and 1.5 Hz), 6.69 (1 H, s), 6.93–7.58 (24 H, m); MS (DCI, posit, isobutane) $C_{44}H_{40}FNO_4$ *m/e* = 665 (M^+), 648 (M^+ − OH), 376, 334. Anal. ($C_{44}H_{40}FNO_4$) C, H, F, N.

(*S*)-(−)-2-Hydroxy-1,2,2-triphenylethyl (3*S*)-hydroxy-5-[1,2-diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]pent-4-(*E*)-enoate (9e): mp 194 °C; NMR (CD_2Cl_2) δ 1.32 (6 H, d), 1.43 (6 H, d), 2.10 (1 H, d), 2.38 (2 H, d), 2.98 (1 H, s), 3.27 (1 H, sept), 4.37 (1 H, m), 4.43 (1 H, sept), 5.23 (1 H, dd, *J* = 16 and 7 Hz), 6.53 (1 H, dd, *J* = 16 and 1.5 Hz), 6.62 (1 H, s), 6.68 (1 H, s), 6.93–7.01 (2 H, m), 7.05–7.37 (15 H, m), 7.50–7.60 (2 H, m); MS (FAB, NBA/LiI) $C_{41}H_{42}FNO_4$ *m/e* = 638 (M + Li^+), 631 (M^+), 614 (M^+ − OH), 358, 342, 300. Anal. ($C_{41}H_{42}FNO_4$) C, H, F, N.

(b) Transesterification of 9 to Optically Active Methyl Esters 10. General Procedure. To a suspension of ester 9 (178 mmol) in absolute methanol (1.4 L) was added dropwise a solution of sodium (2.0 g, 89 mmol) in absolute methanol (200 mL) at 20 °C. The mixture was stirred for 3 h at room temperature. At <10 °C, the mixture was neutralized by dropwise addition of the solution of acetic acid (5.1 mL, 89 mmol) in methanol (15 mL). Triethylamine (0.5 mL) was added, and the solvent was evaporated

(21) Commercially available from Aldrich Chemical Co., Milwaukee, WI.

(22) The oral activity in the rat is an *acute* experiment, in which the hepatic cholesterol biosynthesis inhibition is measured within 3 h after po administration. Oral activities in the rabbit and dog are *chronic* experiments, in which decrease of serum cholesterol is measured. The decrease of serum cholesterol should be coupled to the hepatic cholesterol biosynthesis inhibition, but only via a long, complex chain of biochemical reactions. It seems possible that pronounced differences of the two compounds in metabolic stability and pharmacokinetics are responsible for the lack of oral activity of the unsaturated compound 1b in the rabbit model.

at <20 °C in vacuo. The solid residue was taken up in ether and half-concentrated brine. The ether phase was washed with sodium bicarbonate and then with brine. The solvent was removed in vacuo. The liberated diol was removed from methyl ester 10 by filtration with diisopropyl ether/cyclohexane (1:1) through 2 kg of silica: yield 94–100% 10; pale-yellow oil.

Methyl esters 10 decomposed quickly in solution at room temperature, especially on air contact.

Methyl (3*S*)-hydroxy-5-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]pent-4(*E*)-enoate (10b): NMR (CD_2Cl_2) δ 1.26 (6 H, d), 2.48 (2 H, AB of AB X), 3.03 (1 H, hept), 3.60–3.71 (1 H, m), 3.67 (3 H, s), 4.53 (1 H, br s), 5.37 (1 H, dd), 6.58 (1 H, s), 6.72 (1 H, dd), 7.00 (2 H, m), 7.27–7.49 (7 H, m). Anal. ($C_{25}H_{26}FNO_3$) C, H, F, N.

Methyl (3*S*)-hydroxy-5-[1,2-diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]pent-4(*E*)-enoate (10e): MS (DCI, posit, isobutane) $C_{22}H_{28}FNO_3$ m/e = 373 (M^+), 356 (M^+ – OH). Anal. ($C_{22}H_{28}FNO_3$) C, H, F, N.

(c) Transformation of δ-Hydroxy Methyl Esters 10 to β-Keto-δ-hydroxy *tert*-Butyl Esters 11. General Procedure. *tert*-Butyl acetate (81.3 g, 94 mL, 700 mmol) was added dropwise at –75 °C under N_2 to a solution of LDA (730 mmol) in THF/hexane (1:1, 1 L). After 40 min at –70 °C, the solution of methyl ester 10 (178 mmol) in THF (100 mL) was added dropwise. The mixture was stirred for 10 min at –70 °C and then for 1 h at –30 °C. The cold solution was poured into mechanically stirred, half-saturated ammonium chloride solution (2 L). After 10 min, the organic phases were washed twice with sodium bicarbonate solution and then with brine, dried, filtered, and evaporated. Toluene (100 mL) was added and then evaporated at 20 °C (to remove the excess *tert*-butyl acetate). Residual volatile components were removed in high vacuo (24 h). *tert*-Butyl esters 11 were obtained as yellow, very viscous oils in 95–100% yield.

***tert*-Butyl (5*S*)-hydroxy-3-oxo-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (11b)**: NMR (CD_2Cl_2) δ 1.25 (6 H, d), 1.46 (9 H, s), 2.68 (2 H, d), 3.03 (1 H, hept), 3.37 (2 H, s), 3.68 (1 H, m), 4.60 (1 H, m), 5.37 (1 H, dd), 6.60 (1 H, s), 6.74 (1 H, dd), 7.03 (2 H, m), 7.30–7.52 (7 H, m); MS (DCI, posit, isobutane) $C_{30}H_{34}FNO_4$ m/e = 491 (M^+), 474 (M^+ – OH), 418 (M^+ – isobutene), 390 (M^+ – CO_2tBu), 334. Anal. ($C_{30}H_{34}FNO_4$) C, H, F, N.

***tert*-Butyl (5*S*)-hydroxy-3-oxo-7-[1,2-diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (11e)**: NMR (CD_2Cl_2) δ 1.36 (6 H, d), 1.40–1.48 (15 H, s + 2 × d), 1.57 (1 H, d), 2.67 (2 H, d), 3.32 (1 H, hept), 3.36 (2 H, s), 4.45 (1 H, hept), 4.57 (1 H, m), 5.32 (1 H, dd, J = 16 and 7 Hz), 6.62 (1 H, dd, J = 16 and 1.5 Hz), 6.63 (1 H, s), 7.00 (2 H, m), 7.30 (2 H, m); MS (DCI, posit, isobutane) $C_{27}H_{36}FNO_4$ m/e = 457 (M^+), 440 (M^+ – OH), 397. Anal. ($C_{27}H_{36}FNO_4$) C, H, F, N.

(d) Diastereoselective Reduction of β-Keto-δ-hydroxy *tert*-Butyl Esters 11 to β,δ-Dihydroxy *tert*-Butyl Esters 12. General Procedure. Triethylborane (185 mL of a 1 M solution in THF) was added dropwise at 20 °C to a solution of 130 mL of absolute methanol in 510 mL of dry THF. A solution of crude *tert*-butyl ester 11 (177 mmol) in THF (150 mL) was added dropwise. The mixture was stirred for 1 h at –70 °C. Sodium borohydride (8.73 g, 231 mmol) was added at once. The mixture was stirred for 1.5 h at –70 °C and then poured into half-concentrated ammonium chloride solution (2 L). The mixture was stirred for 15 min and the organic phase was separated. The aqueous phase was extracted twice with ether. The combined organic layers were washed with brine, and the solvent was evaporated in vacuo. The residue was taken up several times in wet methanol and this solvent was evaporated in vacuo at <20 °C. TLC (100% diisopropyl ether) indicated the successful conversion of the unpolar boron ester of the diol (R_f ~0.57) to free diol 12 (R_f ~0.19). Pure 12 was obtained after chromatography through silica (2 kg, 70–200 μm) with diisopropyl ether as a colorless solid (yield 70–80%).

***tert*-Butyl 3(*R*),5(*S*)-dihydroxy-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (12b)**: mp 107–110 °C; NMR (CD_2Cl_2) δ 1.26 (6 H, d), 1.48 (9 H, s), 1.55 (2 H, m), 2.38 (2 H, d), 2.87 (1 H, t), 3.03 (1 H, hept), 3.63 (1 H, br s), 4.16 (1 H, m), 4.39 (1 H, m), 5.37 (1 H, dd), 6.60 (1 H, s), 6.71 (1 H, dd), 7.03 (2 H, m), 7.30–7.52 (7 H, m); MS (DCI, posit, isobutane) $C_{30}H_{36}FNO_4$ m/e = 493 (M^+), 476 (M^+ – OH), 458 (M^+ – OH – H_2O). Anal. ($C_{30}H_{36}FNO_4$) C, H, F, N.

***tert*-Butyl 3(*R*),5(*S*)-dihydroxy-7-[1,2-diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (12e)**: MS (DCI, posit, isobutane) $C_{27}H_{38}FNO_4$ m/e = 459 (M^+). Anal. ($C_{27}H_{38}FNO_4$) C, H, F, N.

(e) Catalytic hydrogenations of *tert*-butyl esters 12 were performed in analogy to that of the corresponding methyl esters 2 (vide supra), yield 75–82%.

***tert*-Butyl 3(*R*),5(*R*)-dihydroxy-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]heptanoate**: mp 108–110 °C; NMR (CD_2Cl_2) δ 1.25 (6 H, d), 1.46 (9 H, s), 1.40–1.57 (4 H, m), 2.33 (2 H, m), 2.63–2.91 (2 H, m), 3.02 (1 H, hept), 3.13 (1 H, br s), 3.67 (1 H, br s), 3.79 (1 H, qui), 4.11 (1 H, br qui), 6.62 (1 H, s), 7.05 (2 H, m), 7.30–7.50 (7 H, m); MS (DCI, posit, isobutane) $C_{30}H_{38}FNO_4$ 496 (M + H^+), 495 (M^+), 440 (M + H^+ – isobutene), 293. Anal. ($C_{30}H_{38}FNO_4$) C, H, F, N.

***tert*-Butyl 3(*R*),5(*R*)-dihydroxy-7-[1,2-diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]heptanoate**: mp 128–130 °C; MS (DCI, posit, isobutane) $C_{27}H_{40}FNO_4$ m/e = 462 (M + H^+), 461 (M^+), 406 (M + H^+ – isobutene), 259. Anal. ($C_{27}H_{40}FNO_4$) C, H, F, N.

β,δ-Dihydroxy Sodium Carboxylates 1 or 2 (R^1 = Na). General Procedure. To a solution of methyl ester 1 or 2 (R^1 = CH_3, 48 mmol) in methanol (500 mL) was added dropwise 1 N aqueous sodium hydroxide solution (50 mL, 50 mmol) during 1 h at 0–10 °C. The mixture was stirred for 1 h at 0 °C and for 1 h at room temperature. The mixture was filtered and the filtrate was evaporated in vacuo. The residue was taken up in ethanol (100 mL), evaporated in vacuo, and dried in high vacuo. The residue was stirred with ether (300 mL). The solid was collected by suction filtration, washed with pentane, and dried for 4 h in vacuo in a desiccator over phosphorous pentoxide and potassium hydroxide; pale yellow solid, yield 64%. The ethereal mother liquor was evaporated in vacuo and treated as described above to give a solid with the same melting point and ^1H NMR; yield 31%, combined yield 95%.

Sodium 3(*RS*),5(*SR*)-dihydroxy-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (1b): mp 232–234 °C dec; NMR (DMSO-d_6) δ 1.20 (6 H, d), 1.25–1.62 (2 H, m), 1.80–2.11 (2 H, m), 2.98 (1 H, sept), 3.72 (1 H, m), 4.20 (1 H, m), 4.83 (1 H, br s), 5.37 (1 H, dd), 6.52 (1 H, d), 6.80 (1 H, s), 7.14 (2 H, t), 7.30 (1 H, br s), 7.40–7.60 (8 H, m). Anal. ($C_{25}H_{27}FNO_4Na$) C, H, N.

Sodium 3(*RS*),5(*RS*)-dihydroxy-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]heptanoate (2b): mp 231–233 °C dec. Anal. ($C_{25}H_{29}FNO_4Na$) C, H, N.

Sodium 3(*R*),5(*R*)-Dihydroxy-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]heptanoate (13b). The corresponding *tert*-butyl ester (48 g, 97 mmol) was suspended in ethanol (250 mL) at 5 °C. Sodium hydroxide (1 N, 98.8 mL) was added dropwise. The suspension was stirred for 20 h at room temperature, becoming a clear solution. Solvents were removed in vacuo. The residue was washed with ether and then with pentane to give 44.6 g (yield 99.8%) of a colorless solid: mp 252–254 °C dec; NMR (DMSO-d_6) δ 1.22 (6 H, d), 1.20–1.50 (4 H, m), 1.83 (1 H, dd, J = 15 and 8 Hz), 2.04 (1 H, dd, J = 15 and 4 Hz), 2.50–2.67 (1 H, m), 2.71–2.87 (1 H, m), 2.96 (1 H, hept), 3.61 (1 H, br s), 3.74 (1 H, m), 4.70 (1 H, br s), 6.77 (1 H, s), 7.10–7.21 (2 H, m), 7.32–7.57 (7 H, m). Anal. ($C_{26}H_{29}FNO_4Na$) C, H, N.

Sodium 3(*R*),5(*R*)-dihydroxy-7-[1,2-diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]heptanoate (13e) was obtained from the corresponding *tert*-butyl ester in analogy to the method for 13b (vide supra) to give a colorless solid: mp 255 °C dec; NMR (DMSO-d_6) δ 1.30 (6 H, d), 1.37 (6 H, d), 1.82 (1 H, dd, J = 15 and 8 Hz), 2.03 (1 H, dd, J = 15 and 4 Hz), 2.32–2.48 (1 H, m), 2.52–2.67 (1 H, m), 3.18 (1 H, hept), 3.57 (1 H, br s), 3.76 (1 H, hept), 4.41 (1 H, hept), 4.57 (1 H, br s), 6.80 (1 H, s), 7.12 (2 H, m), 7.33 (2 H, m). Anal. ($C_{23}H_{31}FNO_4Na$) C, H, N.

Biological assays: see the preceding paper in this issue.

Phosphorus-Containing Inhibitors of HMG-CoA Reductase. 2.[1] Synthesis and Biological Activities of a Series of Substituted Pyridines Containing a Hydroxyphosphinyl Moiety[2]

Jeffrey A. Robl,* Laurelee A. Duncan, Jelka Pluscec, Donald S. Karanewsky, Eric M. Gordon, Carl P. Ciosek, Jr., Lois C. Rich, Viviane C. Dehmel, Dorothy A. Slusarchyk, Thomas W. Harrity, and Kelly A. Obrien

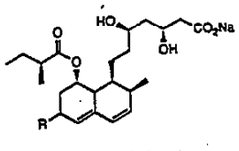
The Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, New Jersey 08543-4000.

Received February 22, 1991

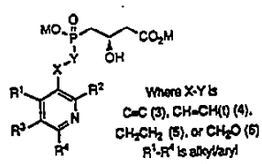
A series of 2,3,4,(5),6-substituted pyridines containing a hydroxyphosphinyl functionality have been prepared and were evaluated for their ability to inhibit the enzyme HMG-CoA reductase. Systematic substitution of both R^1–R^4 and X–Y led to compounds of type 3–6 with in vitro potency greater than that of mevinolin (Na salt).

Introduction

High serum cholesterol levels have been linked to the development of atherosclerosis and coronary heart disease (CHD).[3] A major constituent of serum cholesterol, low density lipoprotein (LDL), is widely believed to be atherogenic upon oxidative modification in vivo,[4] and therefore methods to reduce circulating levels of LDL are highly desirable. Mevinolin (1) and pravastatin (2), two closely



1, R = α-Me (Mevinolin Na)
2, R = β-OH (Pravastatin)

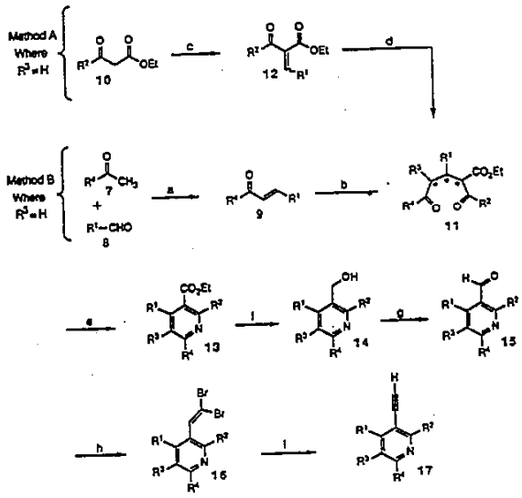


Where X-Y is C=C (3), CH=CH(t) (4), CH_2CH_2 (5), or CH_2O (6). R^1-R^4 is alkyl/aryl and M is Na or Li

related natural products, are currently finding use as therapeutic agents in the treatment of hypercholesterolemia.[5] These compounds act as HMG-CoA reductase (HMGR) inhibitors. Through a complex sequence of regulatory mechanisms, they serve to increase hepatic LDL receptor levels, thereby lowering LDL concentration in the plasma.[6] Inhibition of HMGR, the rate-limiting enzyme in the biosynthesis of cholesterol, is therefore a proven approach to the treatment of hypercholesterolemia.

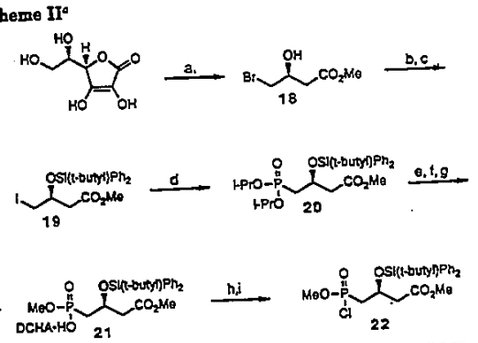
In an attempt to design better, more potent reductase inhibitors, much effort has been expended on replacing the complex decalin portion of the mevinic acids (i.e. 1 or 2) with structurally simpler, achiral aromatic surrogates.[7] In most cases, the 3,5-dihydroxyheptanoic acid portion of the molecule, the pharmacophore that interacts with Se13-

Scheme I[a]



[a] (a) EtONa, EtOH, room temperature; (b) **10**, EtONa, EtOH, room temperature; (c) **8**, piperidine, HOAc, PhH, reflux, $-H_2O$; (d) $R^4COCH_2R^3$, $LiN(TMS)_2$, THF, −78 °C; (e) NH_4OAc, $Cu(OAc)_2$, HOAc, reflux; (f) $LiAlH_4$, THF; (g) Dess–Martin periodinane, *tert*-butyl alcohol, CH_2Cl_2, room temperature, *or* $(CO)_2Cl_2$, DMSO, CH_2Cl_2, −78 °C then TEA *or* TPAP, 4-methylmorpholine *N*-oxide, 4A molecular sieves, CH_2Cl_2, room temperature; (h) CBr_4, PPh_3, $CH_2Cl_2(CH_3CN)$; (i) *n*-BuLi (2.2 equiv), THF, −78 °C, then saturated NH_4Cl quench.

Scheme II[a]



[a] (a) See ref 12; (b) (*t*-Bu)Ph_2SiCl, DMAP, imidazole, DMF; (c) NaI, MEK, reflux; (d) $(i\text{-PrO})_3P$, 160 °C; (e) TMSBr, BSTFA, Et_2O; CH_2Cl_2; (f) MeOH, DCC, pyridine; (g) dicyclohexylamine, Et_2O; (h) 5% $KHSO_4$, then TMSDEA, CH_2Cl_2; (i) $(CO)_2Cl_2$, catalytic DMF, CH_2Cl_2.

(1) For part 1 in this series, see: Karanewsky, D. S.; Badia, M. C.; Ciosek, C. P., Jr.; Robl, J. A.; Sofia, M. J.; Simpkins, L. M.; DeLange, B.; Harrity, T. W.; Biller, S. A.; Gordon, E. M. Phosphorus-Containing Inhibitors of HMG-CoA Reductase. 1. 4-[(2-Arylethyl)hydroxyphosphinyl]-3-hydroxybutanoic Acids: A New Class of Cell Selective Inhibitors of Cholesterol Biosynthesis. *J. Med. Chem.* **1990**, *33*, 2952–2956.

(2) Presented in part at the 199th Meeting of the American Chemical Society, Boston, MA, April 1990, Abstract MEDI 128.

(3) Endo, A. Compactin (ML-236B) and Related Compounds as Potential Cholesterol-Lowering Agents That Inhibit HMG-CoA Reductase. *J. Med. Chem.* **1985**, *28*, 401–405 and references therein.

(4) Steinberg, D.; Parthasarathy, S.; Carew, T. E.; Khoo, J. C.; Witztum, J. L. Modifications of Low-Density Lipoprotein That Increase Its Atherogenicity. *N. Eng. J. Med.* **1989**, *320*, 915–924.

(5) (a) Hoeg, J. M.; Brewer, H. B., Jr. 3-Hydroxy-3-Methylglutaryl-CoEnzyme A Reductase Inhibitors in the Treatment of Hypercholesterolemia. *J. Am. Med. Assoc.* **1987**, *258*(24), 3532–3536. (b) Grundy, S. M. HMG-CoA Reductase Inhibitors for Treatment of Hypercholesterolemia. *N. Eng. J. Med.* **1988**, *319*, 24–31.

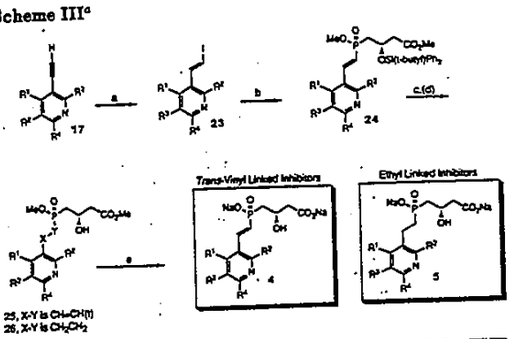
(6) Brown, M. S.; Goldstein, J. L. A Receptor-Mediated Pathway for Cholesterol Homeostasis. *Science* **1986**, *232*, 34–47.

0022-2623/91/1834-2804$02.50/0

hydroxy-3-methylglutaryl (HMG) binding domain of the enzyme,[8] has been retained. In our previous communication,[1] we described a rationale for the design of a new class of HMGR inhibitors that utilizes a hydroxyphosphinyl functionality in place of the commonly exploited C-5 hydroxy functionality present in the 3,5-dihydroxyheptanoic acid pharmacophore. The hydroxyphosphinyl group was designed to bind to the protonated form of the catalytic group, which serves to activate substrate carbonyl groups toward delivery of a hydride ion in the enzymatic reduction of HMG-CoA to mevalonic acid.

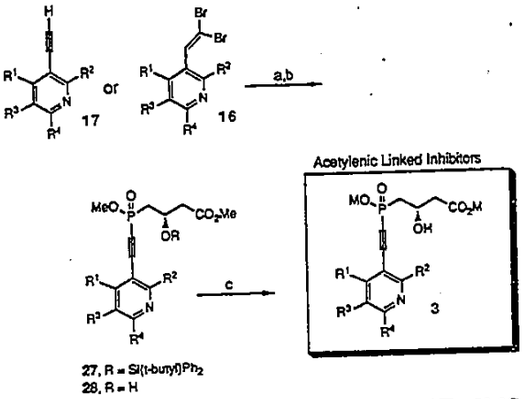
We have prepared hydroxyphosphinyl-containing HMGR inhibitors utilizing a wide variety of aromatic hydrophobic binding domain surrogates. In this paper, we

Scheme III[a]



[a] (a) Bu_3SnH, cat. AIBN, 140 °C, then I_2, Et_2O; (b) *t*-BuLi, THF, −78 °C, then 22, THF, −100 °C; (c) TBAF, HOAc, THF; (d) H_2, Pd/C, MeOH; (e) NaOH, H_2O, dioxane, Δ.

Scheme IV[a]



[a] (a) *n*-BuLi (1.1 equiv for 17, 2.2 equiv for 16), THF, −78 °C, then 22, THF, −78 °C; (b) TBAF, HOAc, THF, then CH_2N_2, Et_2O; (c) NaOH or LiOH, H_2O, dioxane, 50 °C.

describe the utilization of substituted pyridines[2,9] in the synthesis of hydroxyphosphinyl containing inhibitors **3–6**, in which both the "linker" portion (X–Y) of the molecule and the substituents on the pyridine "anchor" have been widely varied.

Chemistry

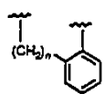
Methods for the synthesis of the requisite pyridine nuclei are depicted in Scheme I. Claisen–Schmidt condensation of methyl ketone **7** with aldehyde **8** provided *trans*-enone **9**. Ethoxide-catalyzed Michael addition of β-keto ester **10** to **9** gave the desired adducts **11**, usually as a 1:1 mixture of diastereomers. Method B provides **11**

(7) (a) Stokker, G. E.; Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J.; Deana, A. A.; Gilfillan, J. L.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Smith, R. L.; Willard, A. K. 3-Hydroxy-3-methylglutaryl-coenzyme A Reductase Inhibitors. 1. Structural Modification of 5-Substituted 3,5-dihydroxypentanoic Acids and Their Lactone Derivatives. *J. Med. Chem.* 1985, *28*, 347. (b) Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J.; Deana, A. A.; Evans, B. E.; Gilfillan, J. L.; Gould, N. P.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Rittle, K. E.; Smith, R. L.; Stokker, G. E.; Willard, A. K. 3-Hydroxy-3-methylglutaryl-coenzyme A Reductase Inhibitors. 2. Structural Modification of 7-(substituted aryl)-3,5-dihydroxy-6-heptenoic Acids and Their Lactone Derivatives. *J. Med. Chem.* 1986, *29*, 159–169. (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. 3-Hydroxy-3-methylglutaryl-coenzyme A Reductase Inhibitors. 3. 7-(3,5-Disubstituted [1,1′-biphenyl]-2-yl)-3,5-dihydroxy-6-heptenoic Acids and Their Lactone Derivatives. *J. Med. Chem.* 1986, *29*, 170–181. (d) Stokker, G. E.; Alberts, A. W.; Gilfillan, J. L.; Huff, J. W.; Smith, R. L. 3-Hydroxy-3-methylglutaryl-coenzyme A Reductase Inhibitors. 5. 6-(Fluoren-9-yl)- and 6-(Fluoren-9-ylidenyl)-3,5-dihydroxyheptanoic Acids and Their Lactone Derivatives. *J. Med. Chem.* 1986, *29*, 852–855. (e) Balasubramanian, N.; Brown, P. L.; Catt, J. D.; Han, W. T.; Parker, R. A.; Sit, S. Y.; Wright, J. J. A Potent, Tissue-Selective, Synthetic Inhibitor of HMG-CoA Reductase. *J. Med. Chem.* 1989, *32*, 2038–2041. (f) Roth, B. D.; Ortwine, D. F.; Hoefle, M. L.; Stratton, C. D.; Sliskovic, D. R.; Wilson, M. W.; Newton, R. S. 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. (g) Sliskovic, D. R.; Roth, B. D.; Hoefle, M. L.; Wilson, M. W.; Newton, R. S. Inhibitors of Cholesterol Biosynthesis. 2. 1,3,5-Trisubstituted [2-(Tetrahydro-4-hydroxy-2-oxopyran-6-yl)ethyl]pyrazoles. *J. Med. Chem.* 1990, *33*, 31–38. (h) Jendralla, H.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Granzer, E.; Kerekjarto, B. v.; Kesseler, K.; Krause, R.; Schubert, W.; Wess, G. Synthesis and Biological Activity of New HMG-CoA Reductase Inhibitors. 2. Derivatives of 7-(1*H*-Pyrrol-3-yl)-substituted-3,5-dihydroxyhept-6(*E*)-enoic(-heptanoic) Acids. *J. Med. Chem.* 1990, *33*, 61–70. (i) Roth, B. D.; Blankley, C. J.; Chucholowski, A. W.; Ferguson, E.; Hoefle, M. L.; Ortwine, D. F.; Newton, R. S.; Sekerke, C. S.; Sliskovic, D. R.; Stratton, C. D.; Wilson, M. W. Inhibitors of Cholesterol Biosynthesis. 3. Tetrahydro-4-hydroxy-6-[2-(1*H*-pyrrol-1-yl)ethyl]-2*H*-pyran-2-one Inhibitors of HMG-CoA Reductase. 2. Effects of Introducing Substituents at Positions Three and Four of the Pyrrole Nucleus. *J. Med. Chem.* 1991, *34*, 357–366. (j) Sliskovic, D. R.; Picard, J. A.; Roark, W. H.; Roth, B. D.; Ferguson, E.; Krause, B. R.; Newton, R. S.; Sekerke, C. S.; Shaw, M. K. Inhibitors of Cholesterol Biosynthesis. 4. *trans*-6-[2-(Substituted quinolinyl)ethenyl/ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-ones, a Novel Series of HMG-CoA Reductase Inhibitors. *J. Med. Chem.* 1991, *34*, 367–373.

(8) Abeles, R. H.; Nakamura, C. E. Mode of Interaction of β-Hydroxy-β-methylglutaryl CoEnzyme A Reductase with Strong Binding Inhibitors: Compactin and Related Compounds. *Biochemistry* 1985, *24*, 1364–1376.

(9) During the course of this work, others have disclosed their efforts on pyridine based 3,5-dihydroxyheptanoic acid containing HMGR inhibitors; see (a) Beck, G.; Kesseler, K.; Baader, E.; Bartmann, W.; Bergmann, A.; Granzer, E.; Jendralla, H.; Kerekjarto, B. v.; Krause, R.; Paulus, E.; Schubert, W.; Wess, G. Synthesis and Biological Activity of New HMG-CoA Reductase Inhibitors. 1. Lactones of Pyridine- and Pyrimidine-Substituted 3,5-Dihydroxy-6-heptenoic(-heptanoic) Acids. *J. Med. Chem.* 1990, *33*, 52–60. (b) Angerbauer, R.; Fey, P.; Hubsch, W.; Phillips, T.; Bischoff, H.; Petzinna, D.; Schmidt, D.; Thomas, G. European Patent Application EP-A-0325130. (c) Chucholowski, A. W.; Roth, B. D.; Creswell, M. W.; Sliskovic, D. R. European Patent Application EP-A-0306929.

Table I. Pyridyl Alcohols 14

no.	R^1	R^2	R^3	R^4	mp, °C	% yield[a] (method)	formula	anal.[b]
14a	4-FC_6H_4	i-C_3H_7	H	C_6H_5	167–169	82 (B)	$C_{21}H_{20}FNO$	C, H, N
14b	4-FC_6H_4	i-C_3H_7	H	2-MeC_6H_4	114–115	65 (B)	$C_{22}H_{22}FNO$	C, H, F, N
14c	4-FC_6H_4	i-C_3H_7	H	2-($C_6H_5CH_2$)C_6H_4	122–124	40 (B)	$C_{28}H_{28}FNO$	C, H, F, N
14d	4-FC_6H_4	i-C_3H_7	H	1-naphthyl	73–75	30 (B)	$C_{25}H_{22}FNO$	C, H, F, N
14e	4-FC_6H_4	i-C_3H_7	H	2,3,5,6-(F)$_4C_6H_1$	130–132	60 (B)	$C_{21}H_{16}F_4NO$	c
14f	4-FC_6H_4	i-C_3H_7	H	2-thienyl	151–153	37 (B)	$C_{19}H_{18}FNOS$	C, H, F, N, S
14g	4-FC_6H_4	i-C_3H_7	H	CH_3	154–155	22 (B)	$C_{16}H_{18}FNO$	C, H, F, N
14h	4-FC_6H_4	i-C_3H_7	H	i-C_3H_7	88–90	57 (B)	$C_{18}H_{22}FNO$	C, H, F, N
14i	4-FC_6H_4	i-C_3H_7	H	c-C_3H_5	94–95	24 (B)	$C_{18}H_{20}FNO$	C, H, F, N
14j	4-FC_6H_4	i-C_3H_7	H	$(C_6H_5)_2CH$	139–140	13 (B)	$C_{28}H_{26}FNO$	C, H, F, N
14k	4-FC_6H_4	i-C_3H_7	H	t-C_4H_9	112–113	49 (B)	$C_{19}H_{24}FNO$	C, H, F, N
14l	4-FC_6H_4	i-C_3H_7	H	c-C_6H_{11}	101–104	40 (B)	$C_{21}H_{26}FNO$	C, H, F, N
14m	4-FC_6H_4	i-C_3H_7	H	1-adamantyl	143–145	56 (B)	$C_{25}H_{30}FNO$	C, H, F, N
14n	4-FC_6H_4	i-C_3H_7	H		114–115	42 (B)	$C_{22}H_{20}FNO_3$	C, H, F, N
14o	4-FC_6H_4	i-C_3H_7	CH_3	C_6H_5	182–184	68 (A)	$C_{22}H_{22}FNO$	C, H, F, N
14p	4-FC_6H_4	i-C_3H_7	CH_2CH_3	C_6H_5	228–230	53 (A)	$C_{23}H_{24}FNO$	C, H, F, N
14q	4-FC_6H_4	i-C_3H_7	i-C_3H_7	C_6H_5	244–246	21 (A)	$C_{24}H_{26}FNO$	C, H, F, N
14r	4-FC_6H_4	i-C_3H_7	C_6H_5	C_6H_5	169–171	52 (A)	$C_{27}H_{24}FNO$	C, H, F, N
14s	4-FC_6H_4	i-C_3H_7	F	C_6H_5	163–165	8 (A)	$C_{21}H_{19}F_2NO$	c
14t	4-FC_6H_4	i-C_3H_7	$n = 1$		166–167	13 (A)	$C_{22}H_{20}FNO$[d]	C, H, F, N
14u	4-FC_6H_4	i-C_3H_7	$n = 2$		138–139	41 (A)	$C_{22}H_{22}FNO$	C, H, F, N
14v	4-FC_6H_4	i-C_3H_7	$n = 3$		161–162	68 (A)	$C_{24}H_{24}FNO$	C, H, F, N
14w	4-FC_6H_4	t-C_4H_9	H	C_6H_5	oil	20 (B)	$C_{23}H_{24}FNO$	c
14x	4-FC_6H_4	c-C_3H_5	H	C_6H_5	176–177	62 (B)	$C_{21}H_{18}FNO$	C, H, F, N
14y	4-FC_6H_4	c-C_3H_5	CH_3	C_6H_5	140–142	71 (A)	$C_{22}H_{20}FNO$	C, H, F, N
14z	4-FC_6H_4	C_2H_5	CH_3	C_6H_5	180–181	61 (A)	$C_{21}H_{20}FNO$	c
14aa	4-FC_6H_4	CH_3	CH_3	C_6H_5	178–180	72 (A)	$C_{20}H_{18}FNO$	C, H, F, N
14bb	i-C_3H_7	4-FC_6H_4	H	C_6H_5	172–173	31 (B)	$C_{21}H_{20}FNO$	C, H, F, N
14cc	4-F-3-MeC_6H_3	i-C_3H_7	H	C_6H_5	159–160	60 (B)	$C_{22}H_{22}FNO$	C, H, F, N
14dd	4-F-2-MeC_6H_3	i-C_3H_7	H	C_6H_5	134–135	66 (B)	$C_{22}H_{22}FNO$	C, H, F, N

[a] Represents overall yield from 12 (method A) or from 9 (method B). [b] Analytical results were within ±0.4% of the theoretical value. [c] Microanalysis was not performed. Compound possessed ^1H NMR and MS in accord with assigned structure. [d] Anal. Calcd: C, 79.25. Found: C, 78.74.

in generally good yields in the cases where R^3 = H but was unsatisfactory in cases where R^3 was alkyl or aryl. In these cases, introduction of the R^3 substituent was best carried out utilizing method A. β-Keto α,β-unsaturated ester 12, generated by Knoevenagel condensation of β-keto ester 10 with aldehyde 8, readily underwent Michael addition with lithium enolate $R^4C(OLi)=CHR^3$ to give 11 as a complex mixture of diastereomers. Treatment of 1,5-diketone 11 with NH_4OAc in hot HOAc afforded the intermediate dihydropyridine, which underwent $Cu(OAc)_2$ oxidation[10] in situ, affording pyridyl ester 13. Utilization of either method A or method B allowed for the rapid and convenient generation of tetra- and pentasubstituted pyridines 13, in which the substituents R^1–R^4 could be independently selected from a variety of alkyl or aryl groups. Simple $LiAlH_4$ reduction of 13 gave pyridyl alcohols 14 (Table I). Alcohols 14 provided an entry to phosphonic acid based inhibitors 6 (see Scheme V), but a one-carbon homologation was necessary for generation of the phosphinic acid class of compounds (see Schemes III and IV). Oxidation of 14 could be effected under a variety of conditions to give the corresponding aldehydes 15. Reaction of 15 with CBr_4/PPh_3 provided the vinyl dibromides[11] (Table II) in generally excellent yields. Treatment of 15 with *n*-BuLi in THF at −78 °C generated the corresponding acetylenic anions in situ. The anions could be utilized in carbon–phosphorus bond formation directly or quenched with a proton source to give acetylenes 17.

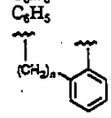
The routes we have developed[1] for the synthesis of both the phosphinic and phosphonic acid based inhibitors utilize phosphonochloridate 22 as a synthon for the introduction of the 3-hydroxy-4-(hydroxyphosphinyl)butanoic side chain. The *S* enantiomer of compound 22 was prepared by a multistep route (outlined in Scheme II) from isoascorbic acid via known[12] bromohydrin ester 18. Silylation of 18 followed by Finkelstein reaction on the silylated bromide provided 19 in 74% overall yield. Arbuzov reaction of 19 was best effected with triisopropyl phosphite to give 20 in 75% yield. Phosphorus deesterification with TMSBr followed by reesterification with MeOH/DCC in pyridine gave the corresponding phosphonic acid monomethyl ester, which was conveniently isolated and stored in stable form as its dicyclohexylamine salt 21. Regeneration of the free acid followed by subsequent treatment with TMSDEA and oxalyl chloride thus provided phos-

(10) Bell, T. W.; Rothenberger, S. D. Synthesis of Annelated Pyridines from 1,5-Diketone Equivalents using Cupric Acetate and Ammonium Acetate. *Tetrahedron Lett.* 1987, 4817–4820.

(11) Corey, E. J.; Fuchs, P. L. A Synthetic Method for Formyl–Ethynyl Conversion (RCHO – RC≡CH or RC≡CR'). *Tetrahedron Lett.* 1972, 3769–3772.

(12) (a) Bock, K.; Lundt, L; Pedersen, C. Synthesis of (*S*)- and (*R*)-4-Amino-3-hydroxybutyric Acid (GABOB) and (*S*)- and (*R*)-Carnitine from Arabinose or *Ascorbic Acid. *Acta Chem. Scand., B* 1983, *37*, 341–344. (b) Isbell, H. S.; Frush, H. L. Oxidation of L-ascorbic acid by hydrogen peroxide; preparation of L-threonic acid. *Carbohydr. Res.* 1979, 72, 301–304.

Table II. Pyridyl Vinyl Dibromides 16

no.[a]	R^1	R^2	R^3	R^4	mp, °C	% yield[b] (method)[c]
16a	4-FC_6H_4	i-C_3H_7	H	C_6H_5	oil	88 (C)
16b	4-FC_6H_4	i-C_3H_7	H	2-MeC_6H_4	108–110	68 (D)
16c	4-FC_6H_4	i-C_3H_7	H	2-($C_6H_5CH_2$)C_6H_4	foam	62 (D)
16d	4-FC_6H_4	i-C_3H_7	H	1-naphthyl	foam	74 (D)
16e	4-FC_6H_4	i-C_3H_7	H	2,3,5,6-$(F)_4C_6H_1$	77	62 (D)
16f	4-FC_6H_4	i-C_3H_7	H	2-thienyl	107–108	86 (D)
16g	4-FC_6H_4	i-C_3H_7	H	CH_3	oil	94 (D)
16h	4-FC_6H_4	i-C_3H_7	H	i-C_3H_7	52–53	71 (D)
16i	4-FC_6H_4	i-C_3H_7	H	c-C_3H_5	oil	71 (D)
16j	4-FC_6H_4	i-C_3H_7	H	$(C_6H_5)_2CH$	141–142	86 (D)
16k	4-FC_6H_4	i-C_3H_7	H	t-C_4H_9	98–100	68 (D)
16l	4-FC_6H_4	i-C_3H_7	H	c-C_6H_{11}	98–100	72 (D)
16m	4-FC_6H_4	i-C_3H_7	H	1-adamantyl	176–177	69 (D)
16n	4-FC_6H_4	i-C_3H_7	H		129–131	74 (D)
16o	4-FC_6H_4	i-C_3H_7	CH_3	C_6H_5	169–170	85 (D)
16p	4-FC_6H_4	i-C_3H_7	CH_2CH_3	C_6H_5	155–157	82 (D)
16q	4-FC_6H_4	i-C_3H_7	i-C_3H_7	C_6H_5	foam	83 (D)
16r	4-FC_6H_4	i-C_3H_7	C_6H_5	C_6H_5	155–158	88 (D)
16s	4-FC_6H_4	i-C_3H_7	F	C_6H_5	105–107	76 (D)
16t	4-FC_6H_4	i-C_3H_7	$n = 1$		foam	58 (D)[d]
16u	4-FC_6H_4	i-C_3H_7	$n = 2$		121–122	76 (E)
16v	4-FC_6H_4	i-C_3H_7	$n = 3$		173–175	83 (D)
16w	4-FC_6H_4	t-C_4H_9	H	C_6H_5	oil	58 (D)
16x	4-FC_6H_4	c-C_3H_5	H	C_6H_5	170–172	69 (E)
16y	4-FC_6H_4	c-C_3H_5	CH_3	C_6H_5	155–157	77 (E)
16z	4-FC_6H_4	C_2H_5	CH_3	C_6H_5	137–138	72 (E)
16aa	4-FC_6H_4	CH_3	CH_3	C_6H_5	141–143	73 (E)
16bb	i-C_3H_7	4-FC_6H_4	H	C_6H_5	124–126	84 (C)
16cc	4-F-3-MeC_6H_3	i-C_3H_7	H	C_6H_5	102–104	89 (D)
16dd	4-F-2-MeC_6H_3	i-C_3H_7	H	C_6H_5	128–129	75 (D)

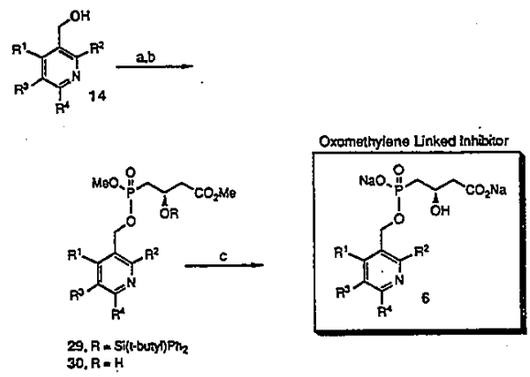
[a] All spectral data were consistent with assigned structures. [b] Represents overall yield from 14. [c] Represents method of oxidation. Method C: Dess–Martin periodinane, *tert*-butyl alcohol, CH_2Cl_2, room temperature. Method D: $(CO)_2Cl_2$, DMSO, CH_2Cl_2, −78 °C, then TEA. Method E: TPAP, 4-methylmorpholine *N*-oxide, 4A molecular sieves, CH_2Cl_2, room temperature. [d] CH_3CN used as solvent in the formation of 16w from 15w.

phonochloridate 22. Silylation of the free acid of 21 prior to treatment with oxalyl chloride generates TMSCl rather than HCl as a byproduct of the reaction, allowing the *tert*-butyldiphenylsilyl protecting group to remain intact.

Scheme III outlines the route developed for the synthesis of *trans*-vinyl (X–Y = CH=CH(t)) and ethyl (X–Y = CH_2CH_2) linked inhibitors 4 and 5. Hydrostannylation of acetylene 17 with tributyltin hydride under free-radical conditions[13] followed by treatment of the intermediate *trans*-vinylstannane with iodine stereospecifically provided the *trans*-vinyl iodides 23 in good yields. Metallation of 23 with *tert*-butyllithium generated the corresponding vinyl anion, which was subsequently coupled with phosphonochloridate 22 at −100 °C to give 24 in yields averaging 55%. Higher reaction temperatures led to a substantial diminution in product yield. Desilylation with buffered fluoride provided 25, which was saponified to give *trans*-vinyl-linked inhibitors 4, or, was subjected to catalytic hydrogenation followed by saponification to give ethyl linked inhibitors 5.

Synthesis of ethynyl (X–Y = C≡C) linked inhibitors 3 was, in general, more straight forward (Scheme IV). The

Scheme V[a]



[a] (a) 22, pyridine, 4 °C; (b) TBAF, HOAc, THF; (c) NaOH, H_2O, dioxane, 55 °C.

lithium anion of 17, generated by the reaction of either 16 or 17 with *n*-butyllithium, smoothly underwent coupling with phosphonochloridate 22 at −78 °C to give 27, usually in 65–80% yields. Desilylation followed by saponification thus provided diacids 3. In the case of the ethynyl-linked compounds, cleavage of the silyl ether of 27 with fluoride ion also led to partial deesterification at the methyl phosphinate ester. Reesterification with diazomethane was

(13) Tolstikov, G. A.; Miftakhov, M. S.; Danilova, N. A.; Vel'der, Y. L. Regio- and Stereoselective Hydrostannylation of 3-Hydroxy-4-phenoxy-1-butyne: Effective Approach to Intermediates in the Total Synthesis of ω-Aryloxyprostaglandins. *Synthesis* 1986, 496–499.

necessary in order to obtain the desired products, 28, in consistently good yields.

Phosphonic acid based inhibitors 6 were generated as shown in Scheme V. Reaction of pyridyl alcohols 14 with phosphonochloridate 22 in pyridine gave 29, which were subsequently desilylated and saponified to give inhibitors of type 6. Treatment of diesters 30 with base led to a mixture of both 6 and 14, resulting from competing hydrolysis of the methyl and pyridylmethyl phosphonic esters.

Biological Results

Compounds 3–6 were tested for inhibition of the conversion of ^{14}C-HMG-CoA to [^{14}C]mevalonic acid by partially purified HMG-CoA reductase (Table III). Activities are expressed as concentration of drug producing 50% inhibition of the enzyme (I_{50} value). The I_{50}'s of the sodium salts of mevinolin (1) and pravastatin (2) are shown for comparison. Structure–activity relationships were studied by (i) varying the nature of the substituents ortho to the binding domain pharmacophore, (ii) varying the substituents at carbons C-5 and C-6 (R^3 and R^4) on the pyridine ring, (iii) varying the nature of the "linking" group X–Y, and (iv) fusing the C-5 and C-6 positions of the pyridine ring with cycloalkylbenzo substituents.

Workers at Merck had previously shown[7b] in a dihydroxyheptanoic acid based inhibitor series that, for optimal inhibitory potency, an aryl and an alkyl group must flank the HMGR binding domain pharmacophore. Early in our studies, we found that placement of the alkyl substituent (preferably isopropyl) at R^2 and the aryl substituent (preferably 4-fluorophenyl) at R^1 lead to compounds of higher potency relative to their regioisomers (compare 3a and 4a with 3bb and 4bb). Subsequent studies were carried out utilizing this substitution pattern. It is apparent that the enzyme is able to accommodate a wide variety of substituents at C-6 (R^4) of the pyridine nucleus. Very large groups such as naphthyl (3d), 2-benzylphenyl (3c), and adamantyl (3m) are well tolerated. In general, the presence of sterically demanding groups such as diphenylmethyl (3j) and *tert*-butyl (3k) is preferred over smaller substituents such as methyl and isopropyl. A notable exception is seen in the case where R^4 is cyclopropyl (3i). This compound was found to be 20-fold more active than its isopropyl counterpart (3h).

Substitution at C-5 (R^3) of the pyridine nucleus with an alkyl or aryl group dramatically increases intrinsic potency (compare compounds 3o–r with 3a). The effect is greatest with methyl and decreases with increasing steric bulk (i.e. for R^3, methyl > ethyl > isopropyl > phenyl) with R^4 as phenyl. It is believed that this effect is due to a favorable skewing of the R^4 phenyl group out of the plane of the pyridine ring. In order to test this hypothesis, a series of conformationally restricted cycloalkylbenzo-fused pyridines were evaluated (compounds 3t–v). Cyclopentyl- and cyclohexylbenzo-fused pyridines 3t and 3u were essentially equipotent to their nonfused counterpart 3a, whereas cycloheptylbenzo-fused pyridine 3v was 4–5-fold more active. The propylene bridge in 3v necessarily holds the fused phenyl group out of the plane with the pyridine ring.[14] The converse is true with methylene or ethylene bridging units. As proposed above, deviation of planarity of the R^4 phenyl substituent leads to optimal inhibitory potency.

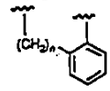
In order to study the relationship between activity, the linker group X–Y, and the alkyl substituent at R^2, a variety of inhibitors were synthesized in which the R^2 group (R^2 = methyl, ethyl, cyclopropyl, and isopropyl) as well as the linker X–Y (C≡C, CH=CH(t), CH_2CH_2, and CH_2O) were varied. These studies show there is a strong interdependence between R^2 and X–Y. Where R^2 is isopropyl or cyclopropyl (e.g 3–6a,k,o,p,v,y), the general order of activity with respect to X–Y is CH=CH(t) > CH_2O ≥ C≡C > CH_2CH_2. In general, compounds possessing the *trans*-vinyl group are 2–32-fold more active than their acetylenic or methylene ether counterparts and 5–95-fold more potent than their ethyl-linked counterparts. A reversal in activity occurs when R^2 is methyl. In this case (e.g. 3aa, 5aa, and 6aa), the order of activity is CH_2CH_2 ≫ C≡C ≈ CH_2O. As expected, ethyl substitution at R^2 (e.g. 3–6z) exhibits activity that is intermediate between that of isopropyl and methyl substitution (i.e. CH_2CH_2 ≈ C≡C for X–Y). In essentially all cases studied, the *trans*-vinyl group was found to be the superior linking functionality, regardless of the substitution pattern at R^1 and R^2. The SAR of the phosphonic acid based inhibitors 6 (X–Y is CH_2O) more closely parallels that of the inhibitors possessing the acetylenic or *trans*-vinyl linkers, rather than the isosteric ethylene linkers. These data indicate that the alkyl R^2 group must be tailored to the appropriate linker X–Y in order to optimize inhibitory potency. On the basis of these SAR, the most potent compounds possess either an isopropyl or a cyclopropyl group at R^2, a *trans*-vinyl or oxomethylene linker for X–Y, a 4-fluorophenyl group at R^1, and substitution at both R^3 and R^4. Indeed, most of the compounds that possess low to subnanomolar activity against HMGR (i.e. 4o, 4p, 4v, 6v, and 6y) fulfill these criteria.

Since the main site of both LDL synthesis and expression of LDL receptors is in the liver, inhibition of cholesterol biosynthesis in extrahepatic tissue may lead to undesirable side effects. We therefore felt it would be advantageous to develop HMGR inhibitors that would be selective for hepatic cells over extrahepatic cells.[15] Consequently, the phosphorus-based inhibitors were evaluated for their ability to inhibit cholesterol synthesis from [^{14}C]acetate in both hepatic and nonhepatic cells (Table IV). For comparison, mevinolin (1) and pravastatin (2) were also evaluated. One striking difference between pravastatin and mevinolin is exhibited in their ability to inhibit cholesterol synthesis in whole cells. Pravastatin shows inhibition in freshly isolated rat hepatocytes com-

(14) For a study on the conformational analysis of bridged biphenyls and 2,2'-bipyridines, see: Jaime, C.; Font, J. Conformational Analysis of Bridged Biphenyls and 2,2'-Bipyridines Empirical Force Field Calculations (MM2-V4). *J. Org. Chem.* 1990, *55*, 2637–2644.

(15) For papers concerning cell and tissue selectivity of HMGR inhibitors, see: (a) Tsujita, Y.; Kuroda, M.; Shimada, Y.; Tanzawa, K.; Arai, M.; Kaneko, I.; Tanaka, M.; Masuda, H.; Tarumi, C.; Watanabe, Y.; Fiji, S. 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. (b) Reference 7e. (c) Germershausen, J. I.; Hunt, V. M.; Bostedor, R. G.; Bailey, P. J.; Karkas, J. D.; Alberts, A. W. Tissue Selectivity of the Cholesterol-Lowering Agents Lovastatin, Simvastatin, and Pravastatin in Rats in Vivo. *Biochem. Biophys. Res. Commun.* 1989, *158*, 667–675. (d) Roth, B. D.; Bocan, T. M. A.; Blankley, C. J.; Chucholowski, A. W.; Creger, P. L.; Creswell, M. W.; Ferguson, E.; Newton, R. S.; O'Brien, P.; Picard, J. A.; Roark, W. H.; Sekerke, C. S.; Sliskovic, D. R.; Wilson, M. W. Relationship between Tissue Selectivity and Lipophilicity for Inhibitors of HMG-CoA Reductase. *J. Med. Chem.* 1991, *34*, 463–466. (e) Shaw, M. K.; Newton, R. S.; Sliskovic, D. R.; Roth, B. D.; Ferguson, E.; Krause, B. R. HEP-G2 Cells and Primary Rat Hepatocytes Differ In Their Response To Inhibitors Of HMG-CoA Reductase. *Biochem. Biophys. Res. Commun.* 1990, *170*, 728–734.

Table III. Inhibition of HMG-CoA Reductase in Vitro for Compounds 1–6

no.	R^1	R^2	R^3	R^4	X–Y	M	$[\alpha]_D$, deg (c, MeOH)	% yield[a] (method)[b]	formula[c]	I_{50},[d] nM
1[e]	–	–	–	–	–	–	–	–	–	4.0
2	–	–	–	–	–	–	–	–	–	,24.0
3a	4-FC_6H_4	i-C_3H_7	H	C_6H_5	C≡C	Li	+4.8 (0.72)	59 (I)	[illegible]	62.0
4a	4-FC_6H_4	i-C_3H_7	H	C_6H_5	CH=CH(t)	Li	+6.2 (0.56)	36 (F)	[illegible]	1.9
5a	4-FC_6H_4	i-C_3H_7	H	C_6H_5	CH_2CH_2	Li	–3.3 (0.45)	10[f]	[illegible]	181
6a	4-FC_6H_4	i-C_3H_7	H	C_6H_5	CH_2O	Na	–2.4 (0.47)	34 (J)	[illegible]	12.7
3b	4-FC_6H_4	i-C_3H_7	H	2-MeC_6H_4	C≡C	Li	+4.0 (0.59)	15 (H)	[illegible]	32.6
3c	4-FC_6H_4	i-C_3H_7	H	2-$(C_6H_5CH_2)C_6H_4$	C≡C	Na	+3.4 (0.53)	55 (H)	[illegible]	62.6
3d	4-FC_6H_4	i-C_3H_7	H	1-naphthyl	C≡C	Na	+4.9 (0.80)	33 (H)	[illegible]	28.7
3e	4-FC_6H_4	i-C_3H_7	H	2,3,4,5-$F_4C_6H_1$	C≡C	Na	+2.7 (0.48)	28 (H)	[illegible]	8.9
3f	4-FC_6H_4	i-C_3H_7	H	2-thienyl	C≡C	Na	+7.6 (0.95)	33 (H)	[illegible]	14.6
3g	4-FC_6H_4	i-C_3H_7	H	CH_3	C≡C	Na	+4.7 (0.62)	22 (H)	[illegible]	231
3h	4-FC_6H_4	i-C_3H_7	H	i-C_3H_7	C≡C	Na	+5.6 (0.78)	16 (H)	[illegible]	80.9
3i	4-FC_6H_4	i-C_3H_7	H	c-C_3H_5	C≡C	Na	+5.1 (0.74)	28 (H)	[illegible]	4.2
3j	4-FC_6H_4	i-C_3H_7	H	$(C_6H_5)_2CH$	C≡C	Na	+4.2 (0.38)	17 (I)	[illegible]	14.9
3k	4-FC_6H_4	i-C_3H_7	H	t-C_4H_9	C≡C	Na	+6.5 (0.77)	33 (H)	[illegible]	6.1
4k	4-FC_6H_4	i-C_3H_7	H	t-C_4H_9	CH=CH(t)	Na	+3.3 (0.60)	16 (F)	[illegible]	3.2
5k	4-FC_6H_4	i-C_3H_7	H	t-C_4H_9	CH_2CH_2	Na	+0.9 (0.68)	28 (G)	[illegible]	17.2
6k	4-FC_6H_4	i-C_3H_7	H	t-C_4H_9	CH_2O	Na	–1.6 (0.43)	32 (J)	[illegible]	1.4
3l	4-FC_6H_4	i-C_3H_7	H	c-C_6H_{11}	C≡C	Na	+4.4 (0.45)	34 (H)	[illegible]	48.4
3m	4-FC_6H_4	i-C_3H_7	H	1-adamantyl	C≡C	Na	+5.8 (0.72)	15 (H)	[illegible]	43.8
3n	4-FC_6H_4	i-C_3H_7	H		C≡C	Li	+6.9 (0.72)	13 (H)	$C_{27}H_{23}FNO_7PLi_2 \cdot 1.40H_2O$	84.6
3o	4-FC_6H_4	i-C_3H_7	CH_3	C_6H_5	C≡C	Li	+9.4 (0.36)	46 (H)	[illegible]	4.5
4o	4-FC_6H_4	i-C_3H_7	CH_3	C_6H_5	CH=CH(t)	Na	+10.0 (0.50)	47 (F)	[illegible]	1.2
5o	4-FC_6H_4	i-C_3H_7	CH_3	C_6H_5	CH_2CH_2	Na	+0.8 (0.49)	65 (G)	[illegible]	9.2
6o	4-FC_6H_4	i-C_3H_7	CH_3	C_6H_5	CH_2O	Na	–2.0 (0.50)	34 (J)	[illegible]	5.1
3p	4-FC_6H_4	i-C_3H_7	CH_2CH_3	C_6H_5	C≡C	Na	+11.1 (0.45)	53 (H)	[illegible]	5.6
4p	4-FC_6H_4	i-C_3H_7	CH_2CH_3	C_6H_5	CH=CH(t)	Na	+10.9 (0.52)	36 (F)	[illegible]	0.55
5p	4-FC_6H_4	i-C_3H_7	CH_2CH_3	C_6H_5	CH_2CH_2	Na	+1.0 (0.48)	68 (G)	[illegible]	19.1
6p	4-FC_6H_4	i-C_3H_7	CH_2CH_3	C_6H_5	CH_2O	Na	–0.1 (0.82)	33 (J)	[illegible]	2.5
3q	4-FC_6H_4	i-C_3H_7	i-C_3H_7	C_6H_5	C≡C	Na	+11.0 (0.39)	40 (H)	[illegible]	9.8
3r	4-FC_6H_4	i-C_3H_7	C_6H_5	C_6H_5	C≡C	Na	+12.1 (0.52)	49 (H)	[illegible]	15.6
3s	4-FC_6H_4	i-C_3H_7	F	C_6H_5	C≡C	Na	+5.8 (0.48)	40 (H)	[illegible]	44.9
3t	4-FC_6H_4	i-C_3H_7	$n = 1$		C≡C	Li	+14.1 (0.46)	18 (H)	$C_{27}H_{23}FNO_6PLi_2 \cdot 1.31H_2O$	75.6
3u	4-FC_6H_4	i-C_3H_7	$n = 2$		C≡C	Na	+11.4 (0.40)	18 (H)	$C_{28}H_{25}FNO_6PNa_2 \cdot 2.25H_2O$	52.5
3v	4-FC_6H_4	i-C_3H_7	$n = 3$		C≡C	Na	+11.2 (0.60)	66 (H)	$C_{29}H_{27}FNO_6PNa_2 \cdot 0.60H_2O$	14.4
4v	4-FC_6H_4	i-C_3H_7	$n = 3$		CH=CH(t)	Na	+12.2 (0.45)	21 (F)	$C_{29}H_{29}FNO_6PNa_2 \cdot 2.50H_2O$	1.3
5v	4-FC_6H_4	i-C_3H_7	$n = 3$		CH_2CH_2	Na	+1.3 (0.38)	80 (G)	$C_{29}H_{31}FNO_6PNa_2 \cdot 2.04H_2O$	18.6
6v	4-FC_6H_4	i-C_3H_7	$n = 3$		CH_2O	Na	–0.3 (0.34)	28 (J)	$C_{29}H_{29}FNO_6PNa_2 \cdot 2.0H_2O$	1.2
3w	4-FC_6H_4	t-C_4H_9	H	C_6H_5	C≡C	Li	+13.1 (0.42)	17 (H)	$C_{27}H_{25}FNO_6PLi_2 \cdot 1.01H_2O$	68.4
3x	4-FC_6H_4	c-C_3H_5	H	C_6H_5	C≡C	Na	+5.6 (0.81)	59 (H)	$C_{26}H_{21}FNO_6PNa_2 \cdot 2.0H_2O$	90.9
6x	4-FC_6H_4	c-C_3H_5	H	C_6H_5	CH_2O	Na	–1.2 (0.50)	35 (J)	$C_{25}H_{23}FNO_6PNa_2 \cdot 2.50H_2O$	29
3y	4-FC_6H_4	c-C_3H_5	CH_3	C_6H_5	C≡C	Na	+8.8 (0.62)	57 (H)	$C_{27}H_{25}FNO_6PNa_2 \cdot 1.25H_2O$	4.6
4y	4-FC_6H_4	c-C_3H_5	CH_3	C_6H_5	CH=CH(t)	Na	+6.7 (0.50)	30 (F)	$C_{27}H_{25}FNO_6PNa_2 \cdot 1.33H_2O$	2.5
5y	4-FC_6H_4	c-C_3H_5	CH_3	C_6H_5	CH_2CH_2	Na	–0.3 (0.32)	76 (G)	$C_{27}H_{27}FNO_6PNa_2 \cdot 1.25H_2O$	9.2
6y	4-FC_6H_4	c-C_3H_5	CH_3	C_6H_5	CH_2O	Na	–2.4 (0.41)	32 (J)	$C_{26}H_{25}FNO_6PNa_2 \cdot 1.75H_2O$	1.3
3z	4-FC_6H_4	C_2H_5	CH_3	C_6H_5	C≡C	Na	+8.1 (0.35)	21 (H)	$C_{26}H_{23}FNO_6PNa_2 \cdot 2.0H_2O$	109.9
4z	4-FC_6H_4	C_2H_5	CH_3	C_6H_5	CH=CH(t)	Na	+11.8 (0.48)	13 (F)	$C_{26}H_{25}FNO_6PNa_2 \cdot 1.75H_2O$	4.7
5z	4-FC_6H_4	C_2H_5	CH_3	C_6H_5	CH_2CH_2	Na	0 (0.33)	46 (G)	$C_{26}H_{27}FNO_6PNa_2 \cdot 1.25H_2O$	79.8
6z	4-FC_6H_4	C_2H_5	CH_3	C_6H_5	CH_2O	Na	–0.7 (0.45)	22 (J)	$C_{25}H_{25}FNO_6PNa_2 \cdot 3.13H_2O$	19.4
3aa	4-FC_6H_4	CH_3	CH_3	C_6H_5	C≡C	Na	+7.5 (0.4)	19 (H)	$C_{25}H_{21}FNO_6PNa_2 \cdot 2.75H_2O$	1300
5aa	4-FC_6H_4	CH_3	CH_3	C_6H_5	CH_2CH_2	Na	0 (0.44)[j]	44[f]	$C_{25}H_{25}FNO_6PNa_2 \cdot 2.05H_2O$	235
6aa	4-FC_6H_4	CH_3	CH_3	C_6H_5	CH_2O	Na	–0.7 (0.58)	29 (J)	$C_{24}H_{23}FNO_6PNa_2 \cdot 1.84H_2O$	1300
3bb	i-C_3H_7	4-FC_6H_4	H	C_6H_5	C≡C	Li	+7.5 (0.85)	41 (I)	$C_{26}H_{23}FNO_6PLi_2 \cdot H_2O$	420
4bb	i-C_3H_7	4-FC_6H_4	H	C_6H_5	CH=CH(t)	Li	+1.8 (0.45)	12 (F)	$C_{26}H_{25}FNO_6PLi_2 \cdot 2.25H_2O$	45.3
3cc	4-F-3-MeC_6H_3	i-C_3H_7	H	C_6H_5	C≡C	Li	+9.5 (0.78)	53 (H)	$C_{27}H_{25}FNO_6PLi_2 \cdot 1.11H_2O$	22.0
3dd	4-F-2-MeC_6H_3	i-C_3H_7	H	C_6H_5	C≡C	Na	+8.8 (0.38)	33 (I)	$C_{27}H_{25}FNO_6PNa_2 \cdot 3.0H_2O$	156
4dd	4-F-2-MeC_6H_3	i-C_3H_7	H	C_6H_5	CH=CH(t)	Na	+1.6 (0.41)	12 (F)	$C_{27}H_{27}FNO_6PNa_2 \cdot 2.2H_2O$	3.9
5dd	4-F-2-MeC_6H_3	i-C_3H_7	H	C_6H_5	CH_2CH_2	Na	–1.9 (0.43)	63 (G)	$C_{27}H_{29}FNO_6PNa_2 \cdot 1.75H_2O$	115

[a] Represents overall yield from vinyl dibromide 16 or acetylene 17. [b] Method F (Scheme III, steps a–c, e). Method G (Scheme III, steps d, e from 25). Method H (Scheme IV, steps a–c from 16). Method I (Scheme IV, steps a–c from 17). Method J (Scheme V, steps a–c). [c] Analyzed for C, H, N, F, and P. Results were within ±0.4% of theory unless otherwise noted. [d] Compounds were assayed against rat microsomal reductase using 100 μM R,S-HMG-CoA and 2.7 mM NADPH. See the Experimental Section for a description of this assay. Reductase enzyme I_{50} values and 95% confidence intervals were calculated from the linear segments of composite log dose versus percent inhibition regressions from 2–5 experiments. The average 95% confidence interval for I_{50} values reported was ±18.4% with a range of 8–40%. [e] Dihydroxy acid form, sodium salt. [f] Anal. Calcd: H, 5.36. Found: H, 5.82. [g] Obtained via hydrogenation of 27 rather than 25. [h] Not analyzed for phosphorus. [i] Anal. Calcd: H, 4.18. Found: H, 3.68. [j] $[\alpha]^{Hg}_{365} = -3.9°$ (MeOH, $c = 0.44$).

parable to mevinolin but is a much weaker inhibitor in human skin fibroblasts (31-fold). In fact, mevinolin is 7.7-fold more potent in fibroblasts than in hepatocytes. In contrast, our phosphorus-containing inhibitors exhibit a 4–140-fold selectivity for inhibition in hepatocytes versus fibroblasts, with 3o being the most selective. This selectivity is directly related to the presence of the phosphinic acid functionality. The corresponding dihydroxyheptanoic

Table IV. Inhibition of Cholesterol Synthesis from [^{14}C]Acetate in Hepatocytes and Fibroblasts and Inhibition of Cholesterol Biosynthesis from [^{14}C]Acetate in Rats on Intravenous (iv) and Oral (po) Administration[a]

no.	reductase (I_{50}, nM)	hepatocytes (I_{50}, nM)	fibroblasts[b] (I_{50}, nM)	selectivity[c]	in vivo testing (ED_{50}, mpk) iv	po
1[d]	4.0	146	18.8	0.13	0.033	0.40[e]
2	24.0	100	3080	31	0.053	0.75
3a	59	197	9300	47	0.47	3.9
4a	1.9	77	2000	26	0.22	21.4
3o	4.5	81	11300	140	0.13	3.1
3k	6.1	556	2400	4.3	0.7	3.5
4o	1.2	260	2000	7.7	0.1	0.46
3p	5.6	519	6750	13	ND[f]	4.5
4p	0.55	241	4700	19.5	0.2[e]	>10

[a] The average 95% confidence intervals for the reported reductase, hepatocyte, and fibroblast I_{50} values were ±18.4, 40.9, and 56.9%, respectively. The average 95% confidence intervals for the iv and po ED_{50} values were 33.8 and 37.6%, respectively. All compounds were tested in 2–5 experiments. [b] Human skin fibroblasts. [c] Selectivity is measured as a ratio of I_{50} fibroblasts/I_{50} hepatocytes. [d] Tested as the dihydroxy acid form, sodium salt. [e] Tested po as the corresponding δ-lactone form. [f] Not determined.

acid[16] of 4a (where the P(O)OH group in 4a is replaced by (*S*)-OH) is 69-fold more potent in fibroblast (I_{50} = 2.6 nM) than in hepatocytes (I_{50} = 180 nM). These and other examples[1] indicate that hepatocyte selectivity is a general phenomenon in the phosphinic and phosphonic acid class of reductase inhibitors.

Also listed in Table IV are data obtained for the inhibition of cholesterol biosynthesis from [^{14}C]acetate in rats for a selected number of inhibitors. In general, these phosphinic acids are not as effective as the mevinic acids 1 and 2 upon intravenous (iv) or oral (po) administration. An exception is compound **4o**, which shows in vivo activity comparable to that of both 1 and 2. The oral activity of these phosphorus-containing HMGR inhibitors shows no direct correlation with either in vivo reductase inhibitory potency or with in vivo activity after intravenous administration. However, there does appear to be a correlation between iv in vivo activity and activity in isolated rat hepatocytes. For example, despite the fact that 3o and 3k are nearly equipotent against HMGR, 3k is a 7-fold weaker inhibitor of cholesterol biosynthesis in hepatocytes. This is mirrored in a 5-fold loss in potency relative to 3o upon iv administration. However, 3o is still 4-fold less active than mevinolin (1) on iv administration despite equivalent intrinsic potency against reductase. This suggests that the poor in vivo activity of these compounds may be due in part to poor bioavailability to the liver, the target organ. Differences in oral activity (e.g., compare 3o and 4o) are probably due to poor oral absorption. The reasons for the lack of correlation between the in vitro and in vivo potencies of these compounds are currently under investigation.

Conclusion

A potent series of phosphorus-containing reductase inhibitors has been synthesized based on the utilization of highly substituted pyridine nuclei as hydrophobic anchor groups. By proper selection of both the pyridine anchor group and linker X–Y, compounds with enzyme inhibitory activities comparable to or greater than mevinolin (Na salt) have been attained. As determined with rat hepatocytes and human skin fibroblasts, these compounds also show a degree of hepatocyte selectivity not generally exhibited in the dihydroxyheptanoic acid class of inhibitors. In these studies, compound 4o exhibited acute in vivo activity in rats comparable to the clinically proven agents 1 and 2. Inhibitor 4o has been studied for cholesterol-lowering activity in other animal species such as rabbits, dogs, and monkeys. The results of these studies will be presented separately. In addition, an extension of this work to other aromatic and heteroaromatic hydrophobic anchor systems will also be the subject of future disclosures.

Experimental Section

All reactions were carried out under a static atmosphere of argon and stirred magnetically unless otherwise noted. All reagents used were of commercial quality and were obtained from Aldrich Chemical Co. Dry THF and Et_2O were obtained by distillation from the sodium ketyl of benzophenone under nitrogen. Dry CH_2Cl_2 was obtained by distillation from CaH_2 under nitrogen. Pyridine and dioxane were obtained from American Burdick and Jackson and were stored over 4A molecular sieves. Boiling points are uncorrected. Melting points were obtained on a Hoover Uni-melt melting point apparatus and are uncorrected. Infrared spectra were recorded on a Mattson Sirius 100-FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL JNM-GX270 spectrometer using Me_4Si as an internal standard. Optical rotations were measured in a 1-dm cell on a Perkin-Elmer 241 polarimeter and *c* is expressed in g/100 mL. All flash chromatographic separations were performed using E. Merck silica gel (60, particle size, 0.040–0.063 mm). MCI Gel CHP-20P is a highly porous polystyrene–divinylbenzene copolymer resin (75–150 μM) supplied by Mitsubishi Chemical Industries Ltd. Reactions were monitored by TLC using 0.25 mm E. Merck silica gel plates (60 F_{254}) and were visualized with UV light, 5% phosphomolybdic acid in 95% EtOH, or *p*-anisaldehyde in EtOH/H_2SO_4/HOAc.

General Procedure for the Synthesis of 1,5-Diketones 11. Method A. 2-[(4-Fluorophenyl)methylene]-4-methyl-3-oxopentanoic Acid, Ethyl Ester (12, R^1 = 4-FC_6H_4, R^2 = i-C_3H_7). A mixture of 4-fluorobenzaldehyde (3.00 g, 24 mmol), ethyl isobutyrylacetate (3.82 g, 24 mmol), piperidine (240 μL), and HOAc (42 μL) was refluxed in benzene (15 mL) with removal of water (Dean–Stark trap) for 22 h. The cooled mixture was diluted with Et_2O, washed successively with 2% HCl, saturated $NaHCO_3$, H_2O, and brine, dried (Na_2SO_4), filtered, and stripped to yield an oil. Distillation of the oil (bp 110–113 °C (0.25 mmHg)) afforded 12 (R^1 = 4-FC_6H_4, R^2 = i-C_3H_7, 5.32 g, 83%) as a pale yellow liquid. The compound was obtained as a 1:1 mixture of *E* and *Z* isomers (**a** and **b**): TLC R_f 0.35 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ 1.07 (d, *J* = 7.2 Hz, 6 H_a), 1.18 (d, *J* = 7.2 Hz, 6 H_b), 1.25–1.35 (m, 6 $H_{a\&b}$), 2.70 (m, 1 H_a), 3.14 (m, 1 H_b), 4.25–4.37 (m, 4 $H_{a\&b}$), 7.01–7.09 (m, 4 $H_{a\&b}$), 7.34–7.49 (m, 4 $H_{a\&b}$), 7.53 (s, 1 H_b), 7.72 (s, 1 H_a); IR (neat) 1722, 1699, 1605, 1510, 1239 cm^{-1}. Anal. ($C_{15}H_{17}FO_3$) C, H, F. In the same manner, ethyl 3-cyclopropyl-3-oxopropionate[17] (R^2 = c-C_3H_5), methyl propionylacetate (R^2 = CH_2CH_3), and ethyl acetoacetate (R^2 = CH_3) were reacted with 4-fluorobenzaldehyde to give the corresponding Knoevenagel condensation products 12 in 82%, 70%, and 68% yields, respectively.

(16) The corresponding dihydroxyheptanoic acid (Li salt) of 4a was prepared in racemic form from 15a utilizing methods similar to that described in ref 7c.

(17) Jackman, M.; Bergman, A. J.; Archer, S. The Preparation of Some 6-Substituted-2-thiouracils. *J. Am. Chem. Soc.* 1949, *70*, 497–500.

β-(4-Fluorophenyl)-α-(2-methyl-1-oxopropyl)-δ-oxobenzenepentanoic Acid, Ethyl Ester (11o). A −78 °C solution of $LiN(TMS)_2$ (1.0 M in THF, 14.1 mL, 14.1 mmol) in dry THF (15 mL) was treated with a solution of propiophenone (1.900 g, 14.2 mmol) in THF (1.5 mL) over a 5-min period. After 1 h, a solution of compound 12 (R^1 = 4-FC_6H_4, R^2 = i-C_3H_7, 3.717 g, 14.1 mmol) in THF (3 mL) was added dropwise to the above solution. After 1.5 h, the mixture was quenched with saturated NH_4Cl and warmed to room temperature. The mixture was diluted with H_2O and subsequently extracted twice with Et_2O. The combined Et_2O extracts were washed with brine, dried (Na_2SO_4), filtered, and stripped to give an oil. Flash chromatography (15% EtOAc in hexane as eluant) afforded Michael adduct 11o (4.755 g, 85%) as a complex mixture of three diastereomers. The mixture was used directly in the next reaction: TLC R_f 0.34–0.31 (20% EtOAc in hexanes); IR ($CHCl_3$) 2974, 1740, 1713, 1682, 1510, 1224 cm^{-1}. In most cases, an excess of ketone $R^4COCH_2R^3$ (1.2 equiv) and $LiN(TMS)_2$ (1.2 equiv) relative to 12 were used for the formation of compound 11. The crude adducts were used directly in the next reaction prior to removal of the volatiles by vacuum distillation (0.2 mmHg at 80 °C).

Method B. 3-(4-Fluoro-3-methylphenyl)-1-phenyl-2-propen-1-one (9, R^1 = 4-F, 3-MeC_6H_3, R^4 = C_6H_5). A mixture of 4-fluoro-3-methylbenzaldehyde 8 (16.000 g, 115.8 mmol) and acetophenone (13.920 g, 115.8 mmol) in absolute EtOH (120 mL) was treated with a solution of EtONa in EtOH (21% wt solution, 4.3 mL, 11.6 mmol). A precipitate soon fell out of solution. After stirring at room temperature for 16 h, the mixture was cooled to −10 °C and the precipitate was collected by filtration. The solid was washed with cold EtOH and dried in vacuo to yield enone 9 (R^1 = 4-F, 3-MeC_6H_3, R^4 = C_6H_5, 23.560 g, 85%) as a pale yellow solid: mp 100–101 °C; TLC R_f 0.42 (20% EtOAc in hexane); ^1H NMR ($CDCl_3$) δ 2.32 (s, 3 H), 7.04 (t, J = 8.8 Hz, 1 H), 7.40–7.62 (m, 6 H), 7.75 (d, J = 15.8 Hz, 1 H), 7.97–8.06 (m, 2 H); IR (KBr) 1659, 1600, 1587, 1501, 1247 cm^{-1}. Anal. ($C_{16}H_{13}FO$) C, H, F.

β-(4-Fluoro-3-methylphenyl)-α-(2-methyl-1-oxopropyl)-δ-oxo-δ-phenylpentanoic Acid, Ethyl Ester (11cc). A slurry of enone 9 (R^1 = 4-F, 3-MeC_6H_3, R^4 = C_6H_5, 23.165 g, 96.5 mmol) and ethyl isobutyrylacetate (22.88 g, 144.6 mmol) in absolute EtOH (400 mL) was treated with a solution of EtONa in EtOH (21% wt solution, 5.4 mL, 14.5 mmol). After being stirred at room temperature for 4.5 h, the solution was concentrated to 200 mL and partitioned between 50% saturated NH_4Cl and EtOAc. The layers were separated, and the EtOAc layer was washed with H_2O (2×) and brine (2×), dried (Na_2SO_4), filtered, and stripped to yield an oil. The oil was taken up in warm hexane and cooled to produce a solid. The solid was boiled in hexanes and cooled to give Michael adduct 11cc (30.815 g, 80%), a 1:1 mixture of diastereomers, as a white amorphous solid: TLC R_f 0.34 and 0.30 (20% EtOAc in hexanes); ^1H NMR ($CDCl_3$, 270 MHz, integration values are relative) δ 0.70 (d, J = 6.6 Hz, 3 H), 0.94–1.05 (m, 6 H), 1.07–1.13 (m, 6 H), 1.24 (t, J = 7.2 Hz, 3 H), 2.18 (s, 6 H), 2.39 (m, 1 H), 2.76 (m, 1 H), 3.20–3.52 (m, 4 H), 3.93 (q, J = 7.2 Hz, 2 H), 4.06–4.23 (m, 6 H), 6.83 (pseudo t, 2 H), 7.01 (m, 4 H), 7.38–7.57 (m, 6 H), 7.87 (m, 4 H); IR (KBr) 1738, 1711, 1683, 1503, 1245 cm^{-1}. Anal. ($C_{24}H_{27}FO_4$) C, H, F.

General Procedure for the Synthesis of Pyridyl Alcohols 14 (Table I). 4-(4-Fluorophenyl)-5-methyl-2-(1-methylethyl)-6-phenyl-3-pyridinecarboxylic Acid, Ethyl Ester (13o). A mixture of 11o (4.730 g, 11.87 mmol), NH_4OAc (2.745 g, 35.6 mmol), and $Cu(OAc)_2$ (5.935 g, 29.7 mmol) in glacial HOAc (30 mL) was gently refluxed for 24 h. The solution was cooled to room temperature and subsequently poured into an ice-cold mixture of concentrated NH_4OH (50 mL) in H_2O (100 mL). The mixture was extracted twice with Et_2O, and the pooled Et_2O extracts were washed with H_2O and brine, dried (Na_2SO_4), filtered, and stripped to yield an oil. The oil was flash chromatographed (20% EtOAc in hexanes as eluant) to give pyridyl ester 13o as an oil (3.916 g, 87%), which slowly solidified on standing: mp 84–88 °C; TLC R_f 0.47 (20% EtOAc in hexanes); ^1H NMR ($CDCl_3$) δ 1.00 (t, J = 7.0 Hz, 3 H), 1.33 (d, J = 6.5 Hz, 6 H), 2.04 (s, 3 H), 3.12 (m, 1 H), 4.01 (q, J = 7.0 Hz, 2 H), 7.05–7.59 (m, 9 H); IR (KBr) 1718, 1510, 1270 cm^{-1}. Anal. ($C_{24}H_{24}FNO_2$) C, H, F, N.

4-(4-Fluorophenyl)-5-methyl-2-(1-methylethyl)-6-phenyl-3-pyridinemethanol (14o). An ice-cold slurry of $LiAlH_4$ (1.49 g, 39.3 mmol) in dry THF (50 mL) was treated with a solution of ester 13o (4.571 g, 12.11 mmol) in dry THF (20 mL). Ten minutes after the addition, the cooling bath was removed and the mixture was stirred at room temperature for 4 h. Additional $LiAlH_4$ (500 mg) was added, and stirring was continued for 2 more h. The solution was recooled to 0 °C and quenched in succession with H_2O (2 mL), 10% NaOH (2.5 mL), and H_2O (6 mL). The solution was filtered, and the salts were washed with EtOAc. The filtrate was washed with H_2O and brine and then dried (Na_2SO_4). Filtration and removal of the solvent afforded a solid. The solid was recrystallized from EtOAc/hexane to provide compound 14o (3.729 g, 92%) as white crystals: mp 182–184 °C; TLC R_f 0.20 (20% EtOAc in hexanes); ^1H NMR ($CDCl_3$) δ 1.29 (t, J = 5.3 Hz, 1 H, OH), 1.36 (d, J = 7.0 Hz, 6 H), 1.96 (s, 3 H), 3.50 (m, 1 H), 4.44 (d, J = 5.3 Hz, 2 H), 7.12–7.26 (m, 4 H), 7.33–7.47 (m, 3 H), 7.54–7.60 (m, 2 H); IR (KBr) 3420, 1509, 1218 cm^{-1}. Anal. ($C_{22}H_{22}FNO$) C, H, N, F.

General Procedure for the Synthesis of Pyridyl Vinyl Dibromides 16 (Table II). Oxidation with Dess–Martin Periodinane.[18] 4-(4-Fluorophenyl)-2-(1-methylethyl)-6-phenyl-3-pyridinecarboxaldehyde (15a). A slurry of Dess–Martin periodinane (8.60 g, 20.3 mmol) in CH_2Cl_2 (100 mL) was treated with *tert*-butyl alcohol (1.9 mL, 1.49 g, 20.2 mmol), and the mixture was stirred at room temperature for 15 min. A solution of alcohol 14a (5.011 g, 15.6 mmol) in CH_2Cl_2 (85 mL) was then added over a 5-min period. After 30 min, the mixture was diluted with Et_2O and 1 N NaOH and stirred rapidly for 10 min. The organic layer was separated and washed in succession with 1 N NaOH, H_2O, and brine, dried (Na_2SO_4), filtered, and stripped. The solid residue was flash chromatographed (10% EtOAc in hexanes as eluant) to give aldehyde 15a (4.314 g, 87%) as a white solid: mp 105–107 °C (hexane); TLC R_f (0.50 (20% EtOAc in hexanes); ^1H NMR ($CDCl_3$) δ 1.41 (d, J = 6.6 Hz, 6 H), 3.98 (m, 1 H), 7.16 (m, 2 H), 7.33–7.53 (m, 5 H), 7.57 (s, 1 H), 8.17 (m, 2 H), 10.07 (s, 1 H); IR (KBr) 1688, 1573, 1508, 1233 cm^{-1}. Anal. ($C_{21}H_{18}FNO$) C, H, F, N.

Oxidation with TPAP/NMO.[19] 6-(Cyclopropyl)-4-(4-fluorophenyl)-5-methyl-2-(1-methylethyl)-3-pyridinecarboxaldehyde (15y). A solution of 4-methylmorpholine *N*-oxide (4.002 g, 34.2 mmol) in CH_2Cl_2 (130 mL) was dried over $MgSO_4$ for 15 min. The solution was filtered directly into a 500-mL flask, using approximately 30 mL of CH_2Cl_2 to effect the transfer. The flask was then charged with dry 4A molecular sieves (16 g), alcohol 14y (5.686 g, 17.05 mmol), and tetrapropylammonium perruthenate (TPAP, 301 mg, 0.86 mmol). After being stirred at room temperature for 30 min, the black solution was diluted with Et_2O (200 mL), stirred for 5 min, and then filtered through a plug of silica gel (65 × 30 mm), washing with Et_2O. The filtrate was stripped to give a pale yellow solid. The solid was recrystallized from EtOAc/hexane to give aldehyde 15y (3.982 g) as white crystals. Flash chromatography of the mother liquor (20% EtOAc in hexane as eluant) gave additional product, which was recrystallized from hexane (499 mg). Total pooled solids, 4.481 g (79%): mp 137–139 °C; TLC R_f 0.50 (20% EtOAc in hexane); ^1H NMR ($CDCl_3$, 270 MHz) δ 1.00 (m, 2 H), 1.24 (m, 2 H), 2.00 (s, 3 H), 3.16 (m, 1 H), 7.14–7.26 (m, 4 H), 7.39–7.58 (m, 5 H), 9.88 (s, 1 H); IR (KBr) 1686, 1545, 1508, 1223 cm^{-1}. Anal. ($C_{22}H_{18}FNO$) C, H, F, N.

Oxidation with Oxalyl Chloride/DMSO.[20] 4-(4-Fluorophenyl)-6,7-dihydro-2-(1-methylethyl)benzo[6,7]cyclohepta[1,2-*b*]pyridine-3-carboxaldehyde (15v). A −78 °C solution of oxalyl chloride (630 μL, 917 mg, 7.2 mmol) in CH_2Cl_2 (40 mL) was treated dropwise with a solution of dry DMSO (1.10 mL, 1.21 g, 15.5 mmol) in CH_2Cl_2 (1 mL). After 10 min, a solution

(18) Dess, D. B.; Martin, J. C. Readily Accessible 12-I-5′ Oxidant for the Conversion of Primary and Secondary Alcohols to Aldehydes and Ketones. *J. Org. Chem.* 1983, *48*, 4155–4156.
(19) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. Preparation and Use of Tetra-*n*-butylammonium Perruthenate (TBAP reagent) and Tetra-*n*-propylammonium Perruthenate (TPAP reagent) as New Catalytic Oxidants for Alcohols. *J. Chem. Soc., Chem. Commun.* 1987, 1625–1627.
(20) Mancuso, A. J.; Huang, S.-L.; Swern, D. Oxidation of Long-Chain and Related Alcohols to Carbonyls by Dimethyl Sulfoxide "Activated" by Oxalyl Chloride. *J. Org. Chem.* 1978, *43*, 2480–2482.

of alcohol 14v (2.000 g, 5.5 mmol) in THF (5 mL) was added dropwise to the above mixture. Fifteen minutes after the addition, TEA (4.6 mL) was added and the mixture was stirred at −78 °C for 5 min and then warmed to room temperature. The mixture was diluted with Et_2O and washed twice with H_2O and once with brine. The organic layer was dried (Na_2SO_4), filtered, and stripped to give a yellow oil, which produced a solid upon cooling to −78 °C in hexane. The mixture was crystallized from hexane to give aldehyde 15v (1.775 g, 89%) as white needles: mp 132–134 °C; TLC R_f 0.54 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.37 (d, J = 7.0 Hz, 6 H), 2.06 (m, 2 H), 2.18 (m, 2 H), 2.62 (m, 2 H), 3.96 (m, 1 H), 7.11–7.48 (m, 7 H), 7.89 (d, J = 8.0 Hz, 1 H), 9.90 (s, 1 H); IR (KBr) 1693, 1546, 1507, 1223 cm^{-1}. Anal. ($C_{24}H_{22}FNO$) H, F, N; C: calcd 80.20, found 79.58.

3-(2,2-Dibromoethenyl)-4-(4-fluorophenyl)-6,7-dihydro-2-(1-methylethyl)benzo[6,7]cyclohepta[1,2-*b*]pyridine (16v). A solution of carbon tetrabromide (2.336 g, 7.0 mmol) in CH_2Cl_2 (6 mL) was added over a 7-min period to a cold (0 °C) solution of aldehyde 15v (1.688 g, 4.7 mmol) and triphenylphosphine (3.698 g, 14.1 mmol) in CH_2Cl_2 (20 mL). After the addition was complete, the cooling bath was removed and the mixture was stirred at room temperature for 25 min. The solution was quenched with saturated $NaHCO_3$ and extracted twice with CH_2Cl_2. The organic layers were dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed (40% CH_2Cl_2 in hexane as eluant) to give vinyl dibromide 16v as a solid. Recrystallization of the material from EtOAc/hexane provided pure 16v (2.257 g, 93%) as a white solid: mp 173–175 °C; TLC R_f 0.44 (10% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.33 (broad, 6 H), 2.06 (m, 2 H), 2.18 (m, 2 H), 2.61 (m, 2 H), 3.19 (m, 1 H), 7.03–7.43 (m, 8 H), 7.84 (d, J = 8.4 Hz, 1 H); IR (KBr) 2950, 2920, 1603, 1508, 1222 cm^{-1}. Anal. ($C_{25}H_{22}Br_2FN$) C, H, Br, F, N.

(*S*)-4-Iodo-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]butanoic Acid, Methyl Ester (19). A solution of bromohydrin 18 (4.00 g, 20.4 mmol), imidazole (6.94 g, 102 mmol), and DMAP (12 mg) in dry DMF (40 mL) was treated with *tert*-butylchlorodiphenylsilane (5.84 mL, 6.17 g, 22.5 mmol), and the homogeneous mixture was stirred at room temperature overnight. The mixture was partitioned between 5% $KHSO_4$ and EtOAc, and the organic phase was washed with H_2O and brine, dried (Na_2SO_4), filtered, and stripped to give 9.32 g (100%) of the crude silyl ether (TLC R_f 0.75 (25% EtOAc in hexanes)). A solution of the silyl ether (9.32 g, 20.1 mmol) in dry methyl ethyl ketone (MEK, 60 mL) was treated with sodium iodide (15.06 g, 100.5 mmol), and the yellow suspension was refluxed for 5 h. The mixture was cooled, diluted with EtOAc, and filtered, and the filtrate was washed with dilute $NaHSO_3$ and brine. The organic layer was dried (Na_2SO_4), filtered, and stripped to give a yellow oil. Flash chromatography (25% CH_2Cl_2 in hexanes as eluant) afforded iodide 19 (7.69 g, 74% from 18) as a colorless oil: TLC R_f 0.75 (25% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.05 (s, 9 H), 2.67 (m, 2 H), 3.20 (m, 2 H), 3.58 (s, 3 H), 3.95 (m, 1 H), 7.28–7.72 (m, 10 H).

(*S*)-4-[Bis(isopropyloxy)phosphinyl]-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]butanoic Acid, Methyl Ester (20). Freshly distilled triisopropyl phosphite (113.4 mL, 93.92 gm, 451 mmol) was added in one portion to iodide 19 (21.70 g, 45.1 mmol), and the mixture was heated at 155 °C for 16.5 h. The mixture was cooled to room temperature, and the excess triisopropyl phosphite and volatile reaction products were removed by short path distillation (10 mmHg) followed by Kugelrohr distillation (100 °C, 8 h at 0.5 mmHg). The product was further purified by flash chromatography (6:3:1 hexanes–acetone–toluene as eluant) to afford 20 (17.68 g, 75%) as a clear viscous oil: TLC R_f 0.32 (6:3:1 hexanes–acetone–toluene); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.01 (s, 9 H), 1.12 and 1.19 (2 d, J = 6.3 Hz each, 12 H), 1.87–2.24 (m, 2 H), 2.60 and 2.65 (2 d, J = 7.4 Hz each, 1 H), 2.88 and 2.94 (2 d, J = 3.7 Hz each, 1 H), 3.59 (s, 3 H), 4.44–4.57 (m, 3 H), 7.35–7.45 (m, 6 H), 7.65–7.70 (m, 4 H).

(*S*)-4-(Hydroxymethoxyphosphinyl)-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]butanoic Acid, Methyl Ester, Dicyclohexylamine (1:1) Salt (21). A solution of compound 20 (10.66 g, 30.5 mmol) in dry CH_2Cl_2 (80 mL) was treated dropwise (5 minutes) with bis(trimethylsilyl)trifluoroacetamide (BSTFA, 8.71 mL, 8.44 g, 32.8 mmol), followed by dropwise addition (10 min) of trimethylsilyl bromide (TMSBr, 6.75 mL, 7.84 g, 51.3 mmol). After stirring at room temperature for 20 h, the reaction mixture was quenched with 200 mL of 5% $KHSO_4$ and stirred vigorously for 15 min. The aqueous layer was extract with EtOAc (3×), and the pooled organic layers were washed with brine, dried (Na_2SO_4), filtered, and stripped. The residue was azeotroped twice with 50 mL of toluene. The precipitate that formed was suspended in toluene and removed by filtration. The filtrate was concentrated, and the azeotrope/filter process was repeated to give a viscous, clear oil. The oil was dissolved in pyridine (50 mL) and subsequently treated with dicyclohexylcarbodiimide (DCC, 4.65 g, 22.6 mmol) followed by methanol (1.67 mL, 1.31 g, 41 mmol). After being stirred at room temperature for 20 h, the mixture was filtered through a pad of Celite, which was subsequently washed with EtOAc. The filtrate was stripped, redissolved in EtOAc, and washed with 5% $KHSO_4$ (2×) and brine. The EtOAc solution was dried (Na_2SO_4), filtered, and stripped, and the residue was azeotroped twice with toluene. The residue was suspended in toluene and filtered. The filtrate was again concentrated, taken up in toluene, filtered, stripped, and placed under high vacuum to give the corresponding phosphonate monoester (10.2 g, >100%, TLC R_f 0.50 (7:2:1 *n*-PrOH–NH_4OH–H_2O)) as a clear, viscous oil. The monoester (1.16 g, 2.57 mmol) was dissolved in dry Et_2O (10 mL) and treated with dicyclohexylamine (0.528 mL, 0.481 g, 2.65 mmol). The resulting homogeneous solution was stored at room temperature for 7 h and at −20 °C for 16 h. The solid/liquid suspension was warmed to room temperature and filtered, and the solid was washed with cold Et_2O and dried in vacuo to give 21 (1.25 g, 77% yield) as a white powdery solid: mp 155–156 °C; TLC R_f 0.57 (20% MeOH in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.00 (s, 9 H), 1.08–1.92 (m, 22 H), 2.56–2.62 (m, 1 H), 2.64–2.77 (m, 2 H), 3.11 (d, J = 11.0 Hz, 3 H), 3.22 and 3.28 (2 m, 1 H), 3.52 (s, 3 H), 4.02 (m, 1 H), 7.32–7.40 (m, 6 H), 7.65–7.71 (m, 4 H); IR (KBr) 1736 cm^{-1}; $[\alpha]_D$ = −16.0° (MeOH, c = 3.57). Anal. ($C_{22}H_{31}O_6PSi \cdot C_{12}H_{23}N$) C, H, N.

General Procedure for the Synthesis of Acetylenic Linked Phosphinic Acids 3. **(*S*)-4-[[[4-(4-Fluorophenyl)-2-(1-methylethyl)benzo[6,7]cyclohepta[1,2-*b*]pyridin-3-yl]-ethynyl]methoxyphosphinyl]-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]butanoic Acid, Methyl Ester (27v).** DCHA salt 21 (3.682 g, 5.83 mmol) was partitioned between EtOAc and 5% $KHSO_4$. The EtOAc layer was washed three times with 5% $KHSO_4$ and then with brine, dried (Na_2SO_4), filtered, and stripped to give a colorless oil (phosphonic acid monomethyl ester). The oil was dissolved in dry CH_2Cl_2 (10 mL) and treated with diethyl(trimethylsilyl)amine (2.10 mL, 1.61 g, 11.1 mmol). After the mixture was stirred at room temperature for 1 h, the solvent was removed in vacuo and the residue was azeotroped with dry toluene (15 mL). The residue was redissolved in dry CH_2Cl_2 (15 mL), cooled to 0 °C, and treated with 2 drops of DMF and oxalyl chloride (620 μL, 902 mg, 7.1 mmol). After 15 min, the solution was warmed to room temperature and stirred for an additional 45 min. The solvent was stripped, and the yellow residue (phosphonochloridate 22) was azeotroped with toluene (15 mL) and dried in vacuo (oil pump) for 1 h.

Meanwhile, a solution of vinyl dibromide 16v (2.000 g, 3.88 mmol) in THF (10 mL) at −78 °C was treated with *n*-BuLi (2.5 M in hexane, 3.3 mL, 8.2 mmol) over a 1-min period, and the resulting clear green solution was stirred at −78 °C for 50 min. The acetylenic anion solution was added dropwise via canula over a 10-min period to a −78 °C solution of the above prepared phosphonochloridate 22 in THF (12 mL). The resulting mixture was stirred at −78 °C for 30 min and then quenched with 50% saturated NH_4Cl. The solution was warmed to 0 °C and poured into saturated $NaHCO_3$. The aqueous phase was extracted once with Et_2O. The Et_2O layer was washed with brine, dried (Na_2SO_4), filtered, and stripped to give an oil. The residue was flash chromatographed (40% EtOAc in hexanes as eluant) to afford compound 27v, a mixture of diastereomers, as a colorless foam (2.517 g, 82%): TLC R_f 0.31 (40% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.02 (s, 9 H), 1.31 and 1.35 (2 d, J = 6.6 Hz each, 6 H), 2.00–2.38 (m, 6 H), 2.47–2.81 (m, 4 H), 3.30 and 3.37 (2 d, $J_{H,P}$ = 12.6 Hz each, 3 H), 3.54 (m, 1 H), 3.58 (s, 3 H), 4.51 (m, 1 H), 6.99–7.46 (m, 13 H), 7.58–7.72 (m, 4 H), 7.83 (d, J = 7.2 Hz, 1 H); IR (KBr) 2168, 1740, 1508, 1224, 1036 cm^{-1}. In the case where acetylene 17 is used in the coupling reaction, 1.5

of *n*-BuLi is added to a solution of the acetylene in 17 in THF at −78 °C. After 20 min, the acetylenic anion solution is then coupled to 22 as described above.

(*S*)-4-[[[4-(4-Fluorophenyl)-2-(1-methylethyl)benzo[6,7]cyclohepta[1,2-*b*]pyridin-3-yl]ethynyl]methoxyphosphinyl]-3-hydroxybutanoic Acid, Methyl Ester (28v). A mixture of compound 27v (2.487 g, 3.15 mmol) and HOAc (810 μL, 850 mg, 14.1 mmol) in THF (40 mL) was treated with tetra-*n*-butylammonium fluoride (1.0 M in THF, 11.0 mL, 11.0 mmol). After stirring at room temperature for 18 h, the solution was diluted with EtOAc and washed with 5% $KHSO_4$ (3×) and once with brine. The EtOAc layer was dried (Na_2SO_4), filtered, and stripped to afford a yellow oil. The oil was dissolved in Et_2O, cooled to 0 °C, and treated with excess diazomethane for 10 min. The excess diazomethane was destroyed by the addition of HOAc, and the solvent was removed in vacuo. The residue was flash chromatographed (40% acetone in hexanes as eluant) to afford compound 28v (1.534 g, 89%) as a colorless foam: TLC R_f 0.38 (1:1 acetone–hexanes); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.40 (d, J = 6.6 Hz, 6 H), 1.94–2.15 (m, 4 H), 2.15–2.28 (m, 2 H), 3.53–3.67 (m, 4 H), 3.59 (d, $J_{H,P}$ = 12.6 Hz, 3 H), 3.57–3.70 (m, 2 H, C*H*-$(CH_3)_2$ and O*H*), 3.73 (s, 3 H), 4.36 (m, 1 H), 7.12–7.48 (m, 7 H), 7.85 (d, J = 6.6 Hz, 1 H); IR (KBr) 2170, 1737, 1508, 1223, 1035 cm^{-1}.

(*S*)-4-[[[4-(4-Fluorophenyl)-2-(1-methylethyl)benzo[6,7]cyclohepta[1,2-*b*]pyridin-3-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic Acid, Disodium Salt (3v). A solution of compound 27v (780 mg, 1.42 mmol) in dioxane (7 mL) was treated with 1 N NaOH (5.0 mL, 5.0 mmol), and the mixture was stirred at room temperature for 18 h. The solvent was evaporated, and the residue was chromatographed on CHP-20P (25 mm × 90 mm), eluting in succession with H_2O (200 mL), 50% MeOH in H_2O (200 mL), and MeOH (100 mL). The desired fractions were pooled and evaporated, and the residue was taken up in H_2O and lyophilized to give 3v (744 mg, 90%) as a white solid: TLC R_f 0.17 (8:1:1 CH_2Cl_2–HOAc–MeOH); ^{1}H NMR (CD_3OD, 270 MHz) δ 1.36 (d, J = 7.0 Hz, 6 H), 1.55–1.72 (m, 2 H), 2.01–2.20 (m, 4 H), 2.26 (dd, J = 7.8, 15.0 Hz, 1 H), 2.40 (dd, J = 4.2, 15.0 Hz, 1 H), 2.59 (m, 2 H), 3.83 (m, 1 H), 4.19 (m, 1 H), 7.16–7.42 (m, 7 H), 7.72 (m, 1 H); IR (KBr) 2164, 1634, 1508, 1213, 1184, 1058 cm^{-1}. Anal. ($C_{29}H_{27}FNNa_2O_5P$·0.80H_2O) C, H, F, N, P.

General Procedure for the Synthesis of *trans*-Vinyl- and Ethyl-Linked Phosphinic Acids 4 and 5. 3-(1-Ethynyl)-4-(4-fluorophenyl)-5-methyl-2-(1-methylethyl)-6-phenylpyridine (17o). To a solution of *n*-BuLi (2.5 M in hexanes, 4.00 mL, 10.0 mmol) in dry THF (8 mL) at −78 °C was added a solution of vinyl dibromide 16o (2.267 g, 4.63 mmol) in dry THF (8 mL) over a 5-min period. After being stirred at −78 °C for 1 h, the pale green solution was quenched with saturated NH_4Cl and warmed to room temperature. The mixture was diluted with H_2O and extracted with Et_2O, and the Et_2O extract was washed with brine, dried (Na_2SO_4), filtered, and stripped to yield a solid. The residue was recrystallized from EtOAc/hexane to afford acetylene 17o (1.420 g, 93%, 2 crops) as a white solid: mp 178.0–178.5 °C; TLC R_f 0.43 (10% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.34 (d, J = 7.0 Hz, 6 H), 2.04 (s, 3 H), 3.18 (s, 1 H), 3.69 (m, 1 H), 7.15 (m, 2 H), 7.27 (m, 2 H), 7.36–7.48 (m, 3 H), 7.60 (m, 2 H); IR (KBr) 3165, 2099, 1509, 1213 cm^{-1}. Anal. ($C_{23}H_{20}FN$) C, H, F, N.

(*E*)-4-(4-Fluorophenyl)-3-(2-iodoethenyl)-5-methyl-2-(1-methylethyl)-6-phenylpyridine (23o). A mixture of acetylene 17o (1.355 g, 4.1 mmol) and AIBN (20 mg) in tri-*n*-butyltin hydride (2.0 mL) was rapidly heated to 120 °C. After 4 min of heating, the mixture was treated with additional Bu_3SnH (0.6 mL) and the temperature of the reaction was raised to 140 °C. Approximately 20 mg of AIBN was added to the reaction mixture 1 and 2 h after heating was initiated. After 3 h, the mixture was cooled to room temperature, diluted with Et_2O (50 mL), and treated with solid I_2 (3.50 g, 13.8 mmol). The dark reaction mixture was stirred for 45 min and then poured into a 50% saturated $NaHCO_3$ solution containing 6.7 g of $Na_2S_2O_3$. The layers were shaken and separated. The ethereal layer was washed successively with H_2O, 1.7 M NH_4OH, and brine, dried (Na_2SO_4), filtered, and stripped to yield a wet solid. The solid was taken up in Et_2O, filtered through Celite, and stripped. The residue was recrystallized from hexane to give compound 23o (1.335 g) as white crystals. The mother liquor was flash chromatographed (5% EtOAc in hexanes as eluant), and the desired fractions were pooled, stripped, recrystallized, and pooled with the above solid to give a total of 1.637 g (87%) of *trans*-vinyl iodide 23o: mp 148.5–150.0 °C; TLC R_f 0.13 (2% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.29 (d, J = 7.0 Hz, 6 H), 2.00 (s, 3 H); 3.31 (m, 1 H), 6.03 (d, J = 15.2 Hz, 1 H), 7.05–7.22 (m, 5 H), 7.34–7.49 (m, 3 H), 7.59 (m, 2 H); IR (KBr) 2961, 1508, 1221, 841 cm^{-1}. Anal. ($C_{23}H_{21}FIN$) C, H, F, I, N.

(*E*),(*S*)-4-[[2-[4-(4-Fluorophenyl)-5-methyl-2-(1-methylethyl)-6-phenyl-3-pyridinyl]ethenyl]methoxyphosphinyl]-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]butanoic Acid, Methyl Ester (24o). A solution of *trans*-vinyl iodide 23o (1.400 g, 3.06 mmol) in THF (6 mL) was added over a 5-min period to a −100 °C solution of fresh *tert*-butyllithium (1.7 M in pentane, 3.70 mL, 6.3 mmol) in THF (8 mL). The resulting deep red solution was stirred at −100 °C for 25 min and then added via canula over an 8-min period to a −100 °C solution of phosphonochloridate 22 (prepared as in the example for compound 27v from 3.288 g 21) in THF (15 mL). The resulting yellow mixture was stirred at −100 °C for 5 min and at −78 °C for 25 min and then quenched with 50% saturated NH_4Cl. The solution was warmed to room temperature, diluted with H_2O, and poured into saturated $NaHCO_3$. The aqueous phase was extracted twice with Et_2O. The combined Et_2O layers were washed with brine, dried (Na_2SO_4), filtered, and stripped. The resulting yellow oil was flash chromatographed (50% EtOAc in hexanes as eluant) to afford adduct 24o, a 1:1 mixture of diastereomers, as an off-white foam (1.541 g, 66%): TLC R_f 0.22 (40% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.01 and 1.03 (2 s, 9 H), 1.20–1.31 (m, 7 H), 1.78 (m, 1 H), 1.98 and 2.00 (2 s, 3 H), 2.56 (m, 1 H), 2.81 (m, 1 H), 3.19 (pseudo t, $J_{H,P}$ = 11.5 Hz, 3 H), 3.21 (m, 1 H), 3.59 and 3.61 (2 s, 3 H), 4.38 and 4.52 (2 m, 1 H), 5.01 (dd, J = 17.9, 24.8 Hz, 0.5 H), 5.26 (dd, J = 17.9, 24.3 Hz, 0.5 H), 6.89–7.72 (m, 20 H); IR ($CHCl_3$) 2959, 1740, 1605, 1508, 1223, 1036 cm^{-1}.

(*E*),(*S*)-4-[[2-[4-(4-Fluorophenyl)-5-methyl-2-(1-methylethyl)-6-phenyl-3-pyridinyl]ethenyl]methoxyphosphinyl]-3-hydroxybutanoic Acid, Methyl Ester (25o). A solution of compound 24o (1.519 g, 1.98 mmol) in THF (15 mL) was treated with HOAc (640 μL, 671 mg, 11.2 mmol) followed by tetra-*n*-butylammonium fluoride (1.0 M in THF, 10.0 mL, 10.0 mmol). After being stirred at room temperature for 19 h, the solution was poured into saturated $NaHCO_3$ and extracted with EtOAc. The EtOAc extract was washed with brine, dried (Na_2SO_4), filtered, and stripped to give an oil that was subsequently flash chromatographed (40–60% acetone in hexanes as eluant). Compound 25o (978 mg, 94%) was obtained as a white foam: TLC R_f 0.34 (1:1 acetone–hexanes); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.30 (d, J = 7.0 Hz, 6 H), 1.68–1.93 (m, 2 H), 2.00 (s, 3 H), 2.57 (m, 2 H), 3.30 (m, 1 H), 3.43 and 3.47 (2 d, $J_{H,P}$ = 4.7 and 4.1 Hz, 3 H), 3.66 and 3.79 (2 d, J = 2.4 Hz each, 1 H, O*H*), 3.72 (s, 3 H), 4.19 and 4.31 (2 m, 1 H), 5.51 (dd, J = 17.6, 24.6 Hz, 0.5 H), 5.52 (dd, J = 17.6, 24.3 Hz, 0.5 H), 7.10–7.65 (m, 10 H); IR ($CHCl_3$) 2961, 1736, 1605, 1510, 1221, 1034 cm^{-1}.

(*S*)-4-[[2-[4-(4-Fluorophenyl)-5-methyl-2-(1-methylethyl)-6-phenyl-3-pyridinyl]ethyl]methoxyphosphinyl]-3-hydroxybutanoic Acid, Methyl Ester (26o). A mixture of compound 25o (494 mg, 0.94 mmol) and 10% Pd on carbon (110 mg) in MeOH (20 mL) was shaken under 50 psi of H_2 for 3 days. The solution was filtered through Celite, stripped, and flash chromatographed (50% acetone in hexanes) to give compound 26o (419 mg, 85%) as a colorless oil: TLC R_f 0.36 (1:1 acetone–hexanes); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.33 (d, J = 6.6 Hz, 6 H), 1.57–1.91 (m, 4 H), 1.92 (s, 3 H), 2.42–2.59 (m, 2 H), 2.60–2.74 (m, 2 H), 3.25 (m, 1 H), 3.55 and 3.57 (2 d, $J_{H,P}$ = 10.8 Hz each, 3 H), 3.72 (s, 3 H), 3.78 and 3.87 (2 d, J = 3.0 Hz each, 1 H, O*H*), 4.25 and 4.40 (2 m, 1 H), 7.11–7.25 (m, 4 H), 7.33–7.47 (m, 3 H), 7.56 (m, 2 H); IR ($CHCl_3$) 1734, 1509, 1221, 1179, 1040 cm^{-1}.

(*S*)-4-[[2-[4-(4-Fluorophenyl)-5-methyl-2-(1-methylethyl)-6-phenyl-3-pyridinyl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic Acid, Disodium Salt (4o). A solution of compound 25o (461 mg, 0.88 mmol) in dioxane (5 mL) was treated with 1 N NaOH (3.2 mL, 3.2 mmol), and the mixture was stirred at 60 °C for 1.5 h. The solvent was evaporated, and the residue was dissolved in H_2O and chromatographed on CHP-20P (25 mm

× 80 mm), eluting in succession with H_2O (150 mL) and 50% MeOH in H_2O (200 mL). The desired fractions were pooled and evaporated, and the residue was taken up in H_2O and lyophilized to give **4o** (430 mg, 87%) as a white solid: TLC R_f 0.10 (8:1:1 CH_2Cl_2–HOAc–MeOH); ^1H NMR (CD_3OD, 400 MHz) δ 1.27 (d, J = 7.0 Hz, 6 H), 1.54 (dd, J = 7.2, 14.5 Hz, 2 H), 1.93 (s, 3 H), 2.33 (m, 2 H), 3.57 (m, 1 H), 4.10 (m, 1 H), 5.85 (dd, J = 18.0, 19.8 Hz, 1 H), 7.07 (pseudo t, J = 18.0 Hz, 1 H), 7.19 (d, J = 7.0 Hz, 4 H), 7.37–7.54 (m, 5 H); MS (FAB) $[M - 2\,Na + 3\,H]^+$ 498. Anal. ($C_{27}H_{27}FNNa_2O_5P$·1.2H_2O) C, H, F, N, P.

(*S*)-4-[[2-[4-(4-Fluorophenyl)-5-methyl-2-(1-methylethyl)-6-phenyl-3-pyridinyl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic Acid, Disodium Salt (5o). Saponification of ethyl linked phosphinate **26o** was similar to that of *trans*-vinyl-linked phosphinate **25o** to give **5o** in 77% yield: TLC R_f 0.10 (8:1:1 CH_2Cl_2–HOAc–MeOH); ^1H NMR (CD_3OD, 270 MHz) δ 1.41 (d, J = 7.0 Hz, 6 H), 1.49 (dd, J = 6.0, 12.6 Hz, 2 H), 1.71 (m, 2 H), 1.93 (s, 3 H), 2.35 (m, 2 H), 2.78 (m, 2 H), 3.58 (m, 1 H), 4.25 (m, 1 H), 7.20–7.60 (m, 9 H); IR (KBr) 2961, 1579, 1509, 1405, 1157 cm^{-1}. Anal. ($C_{27}H_{29}FNNa_2O_5P$·3.69H_2O) C, H, F, N, P.

General Procedure for the Synthesis of Phosphonic Monoesters 6. (*S*)-4-[[[5-Ethyl-4-(4-fluorophenyl)-2-(1-methylethyl)-6-phenyl-3-pyridinyl]methoxy]methoxyphosphinyl]-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]butanoic Acid, Methyl Ester (29p). A 0 °C solution of phosphonochloridate **22** (from 2.89 g, 4.57 mmol DCHA salt **21**) in pyridine (20 mL) was treated with a solution of alcohol **14p** (888 mg, 2.54 mmol) in dry pyridine (7.0 mL). The resulting mixture was stirred at 0 °C for 16 h, diluted with EtOAc, and washed with 50% saturated NH_4Cl. The organic layer was then washed with H_2O followed by brine, dried (Na_2SO_4), filtered, and stripped. The amber residue was subject to flash chromatography (30% EtOAc in hexane) to give adduct **29p** (1.104 gm, 56%) as a yellow oil: TLC R_f 0.53 (45% EtOAc in hexanes); ^1H NMR ($CDCl_3$, 270 MHz) δ 0.70 (m, 3 H), 1.00 (s, 9 H), 1.22–1.38 (m, 8 H), 1.90 and 2.12 (2 m, 1 H), 2.37 (m, 2 H), 2.55 and 2.81 (2 m, 1 H), 3.29–3.39 (m, 4 H), 3.58 (s, 3 H), 4.43 (m, 1 H), 4.59 and 4.71 (2 m, 2 H), 7.02–7.70 (m, 9 H); IR (CH_2Cl_2) 2954, 1740, 1511, 1223, 1015 cm^{-1}.

(*S*)-4-[[[5-Ethyl-4-(4-fluorophenyl)-2-(1-methylethyl)-6-phenyl-3-pyridinyl]methoxy]methoxyphosphinyl]-3-hydroxybutanoic Acid, Methyl Ester (30p). The silyl protecting group on **29p** was removed via the same procedure as that described for compound **24o** to give **30p** in 90% yield: TLC R_f 0.59 (1:1 acetone–hexanes); ^1H NMR ($CDCl_3$, 270 MHz) δ 0.70 (t, J = 6.8 Hz, 3 H), 1.34 (d, J = 7.0 Hz, 6 H), 1.92 (m, 2 H), 2.39 (q, J = 6.8 Hz, 2 H), 2.57 (d, J = 7.2 Hz, 2 H), 3.43 (m, 1 H), 3.63 (d, $J_{H,P}$ = 10.8 Hz, 3 H), 3.72 (s, 3 H), 4.31 (m, 1 H), 4.85 (m, 2 H), 7.12–7.28 (m, 5 H), 7.39–7.56 (m, 4 H); IR (CH_2Cl_2) 1734, 1636, 1510, 1221 cm^{-1}.

(*S*)-4-[[[5-Ethyl-4-(4-fluorophenyl)-2-(1-methylethyl)-6-phenyl-3-pyridinyl]methoxy]hydroxyphosphinyl]-3-hydroxybutanoic Acid, Disodium Salt (6p). A solution of compound **30p** (650 mg, 1.20 mmol) in dioxane (10 mL) was treated with 1 N NaOH (3.7 mL, 3.7 mmol), and the mixture was stirred at 55 °C for 3 h. The solvent was evaporated to give a white solid. The residue was slurried in warm H_2O and chromatographed on CHP-20P (25 mm × 100 mm) eluting in succession with H_2O (200 mL) and 50% MeOH in H_2O (400 mL). The desired fractions were pooled and evaporated, and the residue was taken up in H_2O and lyophilized to give **6p** (435 mg, 65%) as a white solid: TLC R_f 0.31 (8:1:1 CH_2Cl_2–HOAc–MeOH); ^1H NMR (CD_3OD, 270 MHz) δ 0.65 (t, J = 6.8 Hz, 3 H), 1.30 (d, J = 7.0 Hz, 6 H), 1.48 (dd, J = 7.6, 16.0 Hz, 2 H), 2.28 (q, J = 6.8 Hz, 2 H), 2.37 (m, 2 H), 3.66 (m, 1 H), 4.19 (m, 1 H), 4.64 (m, 2 H), 7.18–7.50 (m, 9 H); IR (KBr) 2935, 1581, 1510, 1404, 1222, 1020 cm^{-1}. Anal. ($C_{27}H_{29}FNNa_2O_5P$·H_2O) C, H, F, N, P.

Biological Assays. Rat Hepatic HMG-CoA Reductase Inhibition. Rat hepatic HMG-CoA reductase activity is measured using a modification of the method described by Edwards.[21] Rat hepatic microsomes are used as a source of enzyme, and the enzyme activity is determined by measuring the conversion of the ^{14}C-HMG-CoA substrate to [^{14}C]mevalonic acid. Livers are removed from 2–4 cholestyramine-fed, decapitated, Sprague–Dawley rats, and homogenized in phosphate buffer A (potassium phosphate, 0.04 M, pH 7.2; KCl, 0.05 M; sucrose, 0.1 M; EDTA, 0.03 M, aprotinin, 500 KI units/mL). The homogenate is spun at 16000*g* for 15 min at 4 °C. The supernatant is removed and recentrifuged under the same conditions a second time. The second 16000*g* supernatant is spun at 100000*g* for 70 min at 4 °C. Pelleted microsomes are resuspended in a minimum volume of buffer A (3–5 mL per liver) and homogenized in a glass homogenizer. Dithiothreitol is added (10 mM), and the preparation is aliquoted, quick frozen in acetone/dry ice, and stored at −80 °C. The specific activity of a typical microsomal preparation is 0.68 nmol of mevalonic acid/mg of protein per minute. The reductase is assayed in 0.25 mL, which contains the following components at the indicated final concentrations: 0.04 M potassium phosphate, pH 7.2; 0.05 M KCl; 0.10 M sucrose; 0.03 M EDTA; 0.01 M dithiothreitol; 3.5 mM NaCl; 1% dimethyl sulfoxide; 50–200 μg of microsomal protein; 100 μM of ^{14}C-[D,L]-HMG-CoA (0.05 μCi, 30–60 mCi/mmol); 2.7 mM NADPH. Reaction mixtures are incubated at 37 °C. Under conditions described, enzyme activity increases linearly up to 300 μg of microsomal protein per reaction mixture and is linear with respect to incubation time up to 30 min. The standard incubation time chosen for drug studies is 20 min, which results in 12–15% conversion of HMG-CoA substrate to the mevalonic acid product. [D,L]HMG-CoA substrate is used as 100 μM, twice the concentration needed to saturate the enzyme under the conditions described. NADPH is used in excess at a level 2.7 times the concentration required to achieve maximum enzyme velocity. Standardized assays for the evaluation of inhibitors are conducted according to the following procedure. Microsomal enzyme is incubated in the presence of NADPH at 37 °C for 15 min. DMSO vehicle with or without test compound is added, and the mixture further incubated for 15 min at 37 °C. The enzyme assay is initiated by adding ^{14}C-HMG-CoA substrate. After 20 min of incubation at 37 °C, the reaction is stopped by the addition of 25 μL of 33% KOH. [^3H]Mevalonic acid (0.05 μCi) is added, and the reaction mixture allowed to stand at room temperature for 30 min. Fifty microliters of 5 N HCl is added to lactonize the mevalonic acid. Bromophenol blue is added as a pH indicator to monitor an adequate drop in pH. Lactonization is allowed to proceed for 30 minutes at room temperature. Reaction mixtures are layered onto 2 g of AG 1-X8 anion exchange resin (Biorad, formate form), poured in 0.7 cm (i.d.) glass columns, and eluted with 2.5 mL of H_2O. The first 0.5 mL is discarded, and the next 2.0 mL is collected and counted for both tritium and carbon-14 in 10.0 mL of Opti-fluor (Packard) scintillation fluid. Results are calculated as nanomoles mevalonic acid produced per 20 min and are corrected to 100% recovery of tritium. Drug effects are expressed as I_{50} values (concentration of drug producing 50% inhibition of enzyme activity) derived from composite dose response data from 2–5 experiments.

Inhibition of Cholesterol Synthesis in Freshly Isolated Rat Hepatocytes. Inhibitors of HMG-CoA reductase are evaluated for their ability to inhibit [^{14}C]acetate incorporation into cholesterol in freshly isolated rat hepatocyte suspensions using a modification of the methods originally described by Capuzzi.[22] Sprague–Dawley rats (180–220 g) are anesthetized with Nembutal (50 mg/kg). The abdomen is opened, and the first branch of the portal vein is tied closed. Two closing sutures are placed on the distal section of the portal vein, and the portal vein is canulated between the sutures and the first branching vein. The liver is perfused at a rate of 20 mL/min with prewarmed (37 °C) oxygenated buffer A ((HBSS, Hanks' Balanced Salt Solution) without calcium or magnesium containing 0.05% EDTA) after severing the vena cava to allow drainage of the effluent. The liver is additionally perfused with 200 mL of prewarmed oxygenated buffer B (HBSS containing 0.05% bacterial collagenase). Following perfusion with buffer B, the liver is excised and decapsulated in 50 mL of Waymouth's medium, allowing free cells to

(21) Edwards, P. A.; Lemongello, D.; Fogelmann, A. M. Improved Methods for the Solubilization and Assay of Hepatic 3-Hydroxy-3-methylglutaryl Coenzyme A Reductase. *J. Lipid Res.* 1979, *20*, 40–46.

(22) Capuzzi, D. M.; Margolis, S. Metabolic Studies in Isolated Rat Liver Cells: 1. Lipid Synthesis. *Lipids* 1971, *6*, 600–607.

disperse into the medium. Hepatocytes are isolated either by low-speed centrifugation for 3 min at 50g at room temperature or by unit gravity sedimentation at 4 °C for 30–45 min. Pelleted hepatocytes are washed once in Waymouth's medium, counted, and assayed for viability by trypan blue exclusion. These hepatocyte enriched cell suspensions routinely show 70–90% viability. Hepatocytes are resuspended at 5×10^6 cells per 2.0 mL in incubation medium (IM) [0.02 M Tris-HCl (pH 7.4), 0.1 M KCl, 0.33 mM $MgCl_2$, 0.01 mM $MnCl_2$, 0.001 mM sodium succinate, 0.003 mM Coenzyme A, 0.33 mM sodium citrate, 0.67 mM nicotinamide, 0.23 mM NADP, 1.7 mM glucose-6-phosphate]. Test compounds are routinely dissolved in H_2O, DMSO, or DMSO–H_2O (1:3) and added to the IM. Final DMSO concentration in the IM is ≤1.0% and has no significant effect on cholesterol synthesis. Incubation is initiated by adding [^{14}C]acetate (58 mCi/mmol, 2 μCi/mL) and placing the cell suspensions (2.0 mL) in 35-mm tissue culture dishes at 37 °C for 2.0 h. Following incubation, cell suspensions are transferred to glass centrifuge tubes and spun at 50g for 3 min at room temperature. Cell pellets are resuspended and lysed in 1.0 mL of H_2O. Lipids are extracted essentially as described by Bligh and Dyer.[23] Following extraction, the lower organic phase is removed and dried under a stream of nitrogen and the residue resuspended in 100 μL $CHCl_3$–MeOH (2:1). The total sample is spotted on silica gel (LK6D) thin-layer plates and developed in CH_2Cl_2–acetone (60:1). Plates are scanned and counted using a BioScan automated scanning system. Radiolabel in the cholesterol peak (R_f 0.28) is determined and expressed as total counts per peak and as a percent of the label in the total lipid extract. Cholesterol peaks in control cultures routinely contain 5000–20000 dpm, and are approximately 30% of the label present in the total lipid extract. Drug effects (percent inhibition of cholesterol synthesis) are determined by comparing the percent of label in the cholesterol peak for control and drug treated cultures. Dose response curves are constructed from composite data from two or more studies and results are expressed as I_{50} values (concentration of drug which inhibits cholesterol synthesis 50%).

Inhibition of Cholesterol Synthesis in Human Skin Fibroblasts. Human skin fibroblasts (passage 7-27) are grown in minimal essential medium (MEM, Gibco) containing 10% fetal calf serum. For each experiment, stock cultures are trypsinized to disperse the cell monolayer, counted, and plated in 35-mm tissue culture wells (5×10^5 cells/2.0 mL). Cultures are incubated for 18 h at 37 °C in 5% CO_2/95% humidified room air. Cholesterol biosynthetic enzymes are induced by removing the serum containing medium, washing the cell monolayers with MEM, adding 1.0 mL of MEM containing 1.0% fatty acid free bovine serum albumin, and incubating the cultures an additional 24 h. Test compounds are dissolved in H_2O, DMSO, or DMSO–EM (1:3) (final DMSO concentration in cell cultures ≤1.0%) and added to the cultures, and the cultures are preincubated for 30 min at 37 °C in 5% CO_2/95% humidified room air. Following preincubation with drugs, sodium [1-^{14}C]acetate (2.0 μCi/mL, 58 mCi/mmol) is added, and the cultures are reincubated for 4 h. After incubation, the culture medium is removed and the cell monolayer is scraped into 1.0 mL of H_2O. Lipids in the lysed cell suspension are extracted as described for hepatocyte suspensions. The organic phase is dried under nitrogen, and the residue is resuspended and analyzed as described for hepatocytes. Cholesterol peaks in control cultures routinely contain 8000–12000 dpm and are approximately 15% of the label present in the total lipid extract.

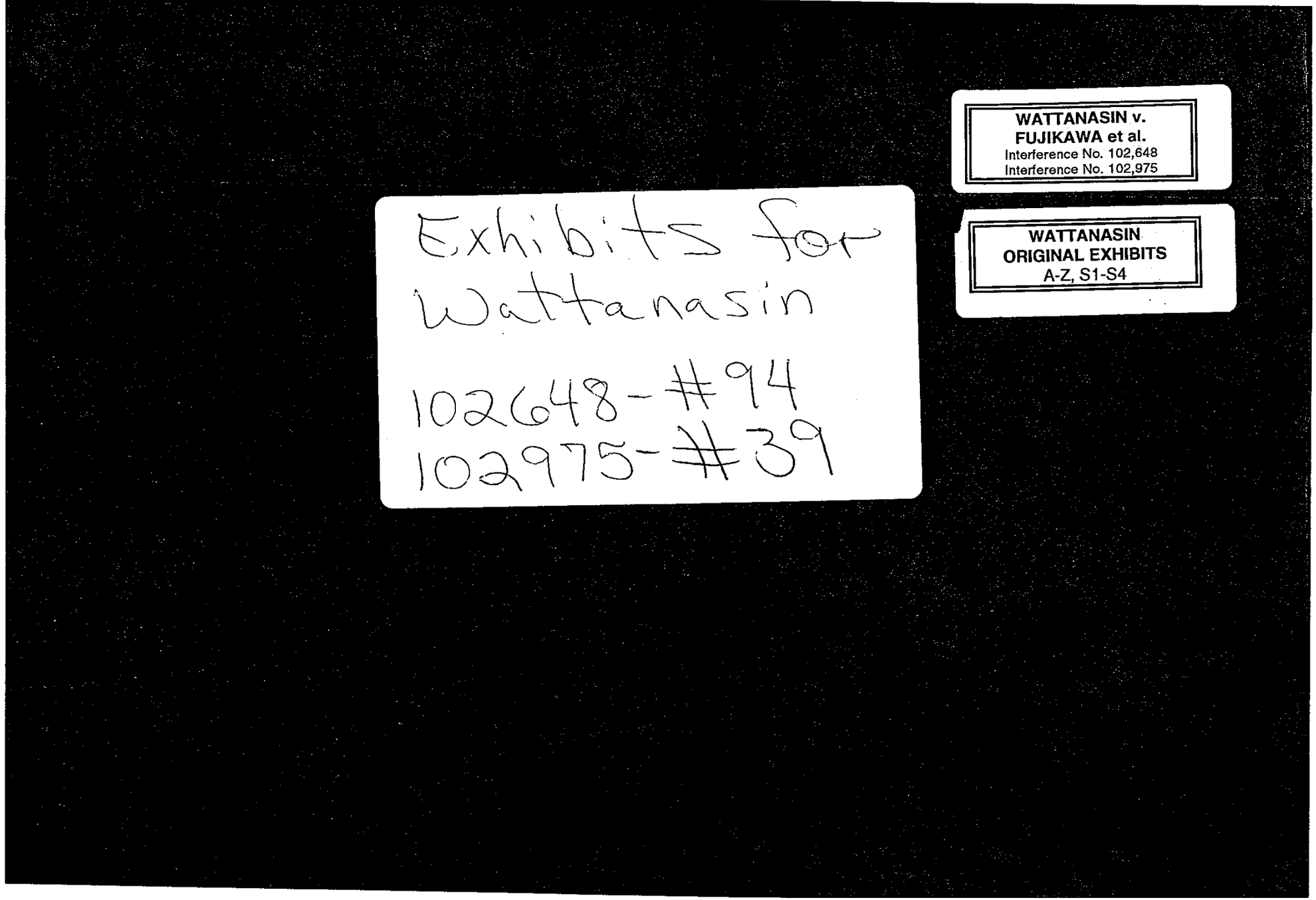
Inhibition of cholesterol synthesis is determined as described for hepatocytes. Results are expressed as I_{50} values and are derived from composite dose response curves from two or more experiments.

In Vivo Cholesterol Biosynthesis Inhibition in Rats. The methods used for intravenous (iv) and oral (po) drug testing were adapted from a procedure originally described by Sandoz.[24] Male Sprague–Dawley rats (200–300 g) were adapted to a reverse light cycle for 7–10 days and fed Purina rat chow (no. 5001) ad libitum. In order to measure cholesterol synthesis, sodium [1-^{14}C]acetate (1–3 mCi/mmol) (25 μCi/100 g of body weight) was injected intraperitoneally (ip) 2 h before the mid-dark point in the diurnal cycle. Two hours after the mid-dark point animals were anesthetized ip with ketamine/xylazine and bled into EDTA-treated centrifuge tubes from the abdominal aorta. Plasma was obtained by centrifugation at 1100g for 10 min. One-milliliter plasma samples were aliquoted and either processed directly or frozen at −20 °C. For iv testing, the salt forms of test compounds were routinely dissolved in saline and injected iv into the tail vein 5 min before [^{14}C]acetate injection. For po testing, drugs were dissolved in saline and given by gavage 30 min before [^{14}C]acetate injection. Cholesterol synthesis was measured by determining the level of ^{14}C-labeled nonsaponifiable lipid present in 1 mL of plasma; the method used is a modification of the method described by Dugan.[25] One milliliter physiological saline was added to 1 mL of plasma, followed by the addition of 5.0 mL of 10% KOH in absolute ethanol. Samples were mixed and saponified at 75 °C for 1 h. After cooling, approximately 0.02 μCi (44,000 dpm) [1,2-^{3}H]cholesterol (40–60 Ci/mmol) was added to each sample. Samples were extracted once with 5 mL of petroleum ether, and the organic phase was backwashed with 5 mL of saline. This extraction procedure resulted in 50–90% recovery of the added [^{3}H]cholesterol internal standard. The extracts were dried in glass vials, and the residue resuspended in 0.5 mL of $CHCl_3$–MeOH (2:1). Samples were counted for both ^{3}H and ^{14}C in 10 mL of Optifluor scintillation fluid. The [^{3}H]cholesterol internal standard recovery value from each sample was used to correct each sample to 100% recovery of [^{14}C]cholesterol. In early experiments, sample extract residues were redissolved in 100 mL of $CHCl_3$–MeOH (2:1) and chromatographed on silica gel (Whatman LK6D) thin-layer plates using either hexanes–Et_2O–HOAc (75:25:1) or CH_2Cl_2–acetone (60:1). Using either chromatographic system, greater than 90% of the ^{14}C-label cochromatographed with authentic cholesterol. Thus, to simplify the method, the TLC step was omitted in subsequent experiments and results were calculated as ^{14}C-labeled nonsaponifiable plasma lipid values, of which, greater than 90% of the ^{14}C-label is authentic cholesterol. The percent inhibition of cholesterol synthesis was derived by comparing ^{14}C-labeled nonsaponifiable plasma lipid values per milliliter of plasma from control and drug-treated animal groups (4–5 rats/group). Percent inhibition is plotted relative to the log drug dose and a linear best fit regression line is determined for each experiment. Mean ED_{50} values (level of drug required to suppress cholesterol synthesis in vivo by 50%) were calculated from two or more experiments.

(23) Bligh, E. G.; Dyer, W. J. A Rapid Method of Total Lipid Extraction and Purification. *Can. J. Biochem. Physiol.* 1959, *37*, 911–917.

(24) Wareing, J., U.S. Patent 4,613,610 and PCT Int. Appl., WO 86/00367.

(25) Dugan, R. E.; Slakey, L. L.; Briedis, A. V.; Porter, J. W. Factors affecting the Diurnal Variation in the Level of β-Hydroxy-β-methylglutaryl Coenzyme A Reductase and Cholesterol Synthesizing Activity in Rat Liver. *Arch. Biochem. Biophys.* 1972, *152*, 21–27.


WATTANASIN v.
FUJIKAWA et al.
Interference No. 102,648
Interference No. 102,975
WATTANASIN
ORIGINAL EXHIBITS
A-Z, S1-S4
Exhibits for
Wattanasin
102648 - #94
102975 - #39

(3) copy to Dr. Kathawala 1/5

1984 Proposal

Sompong Wattanasin
November 28, 1983

Our plan for 1984 was organized into four general areas of increasing difficulty.

We will conduct the work in the approximate order present below. All of our work will be guided by results of biological assays and we will use biological information as it becomes available to modify our synthetic objectives.

The four areas are:

① Synthesis of Indenes

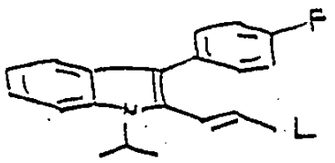
② Synthesis of "restricted rotation" Indole analogues,

× ③ Synthesis of complex analogues based on SAH 62-528 - Aza analogue of Compactin

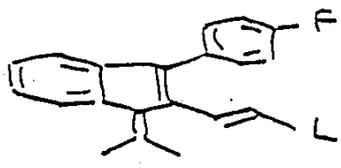
④ Synthesis of new analogues based on ① → ③.

① Synthesis of Indenes

Based on the indole 1, we intend to prepared and testing compounds 2 - 4

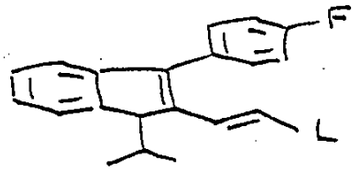


1

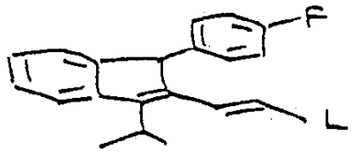


2

L = Lactone



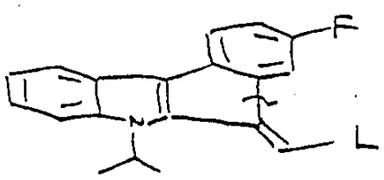
3



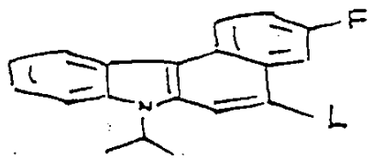
4

Compound 2 will be prepared to examine the effect of replacement of the nitrogen by carbon. Compound 3 and/or 4 will next be prepared to test whether or not the free rotation of the isopropyl group necessary for activity.

(2) Synthesis of "restricted rotation" Indoles



5

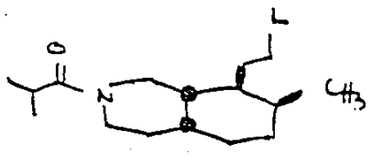


6

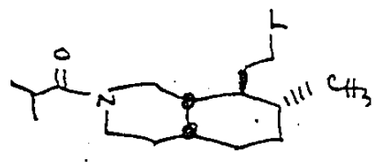
Analogues 5 and/or 6 are proposed as probes of the rotation requirements of the para-fluorophenyl group and the double bond side chain of the lactone. Nothing is currently known in this regard.

(3) Synthesis of complex analogues based on SAH 62-528 – Aza analogue of compactin.

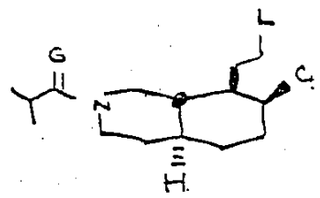
A) Asymmetric synthesis of an aza analogue of compactin



7



8

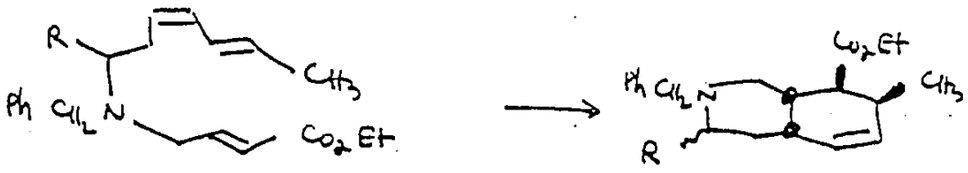


9

The racemic compounds 4 - 9, aza analogue of compactin, have already prepared and submitted for testing. If any of these compounds showed significant activity, we intend to prepare one of them in optically active form.

B) Diels-Alder reaction of 2 aza trienes

We have found that the Diels-Alder reaction of the 2 aza triene is highly stereospecific to yield the cis isoquinoline compound 10, as the only product.

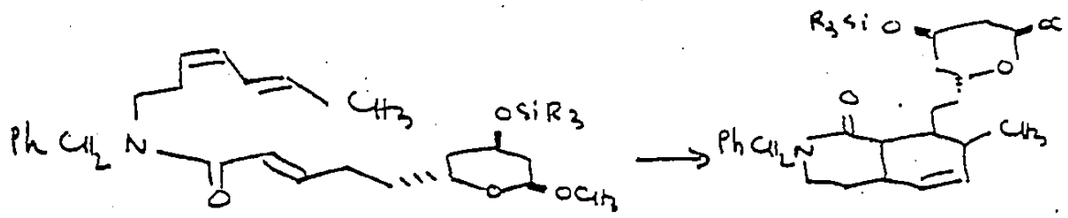


10

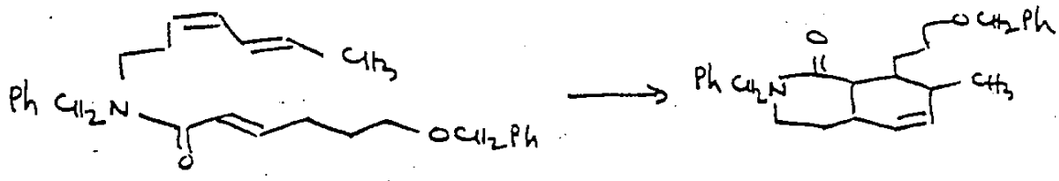
The highly stereospecific and the usefulness of the method in the synthesis of this type of compounds makes us feel necessary to demonstrate the followings:

(a) Effect of the R group (R = CH_3 rather than H) in the cyclisation.

(b) Identity of the products from the following Diels-Alder reactions.

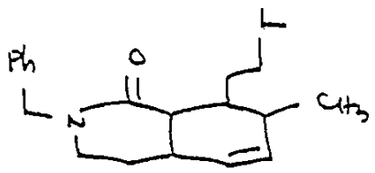


stereochemistry



C). Synthesis of the analogue II.

Compound II is a close relative of the aza analogues of compactin 7 – 9, but might be more readily obtainable by the route shown above.

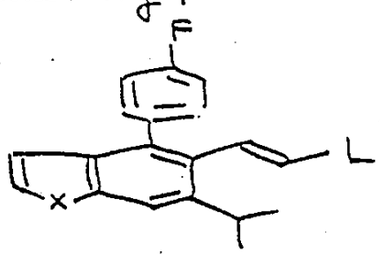


II

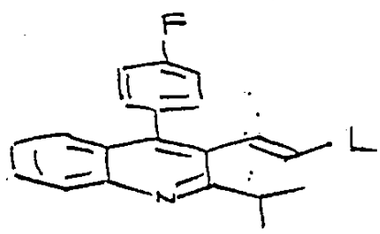
In addition, computer modellings show a better overlapping between compactin and II than those of 7 – 9

④ Synthesis of new analogues based on ① – ③

If any of the analogues thus far proposed show interesting activity, it may be necessary to prepare a variety of compounds with various modifications. In addition, several more analogues such as 12 – 14 are of interesting.



12 X = NR
13 X = S



14

It is unrealistic to expect all of these goals to be accomplished during the next year period, but we certainly expect to complete the indene analogue, the restricted rotation indole analogue, the optical synthesis of an aza analogue of compactin, to complete general study of Diels-Alder reaction of 2 aza trienes, and to make a substantial progress into the synthesis of other analogues.

Copy to Dr. F. K. Kawasaki

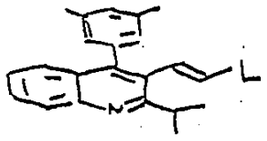
(3)

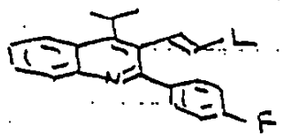
Sompong Wattanasin
Nov. 19, 1984.

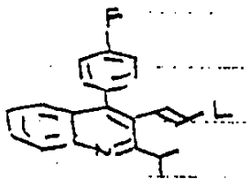
1985 Proposal

The followings are my objectives in 1985

(1) Complete the project on QUINOLINE system. If one of the quinoline proved to be very active, all of these three quinolines and

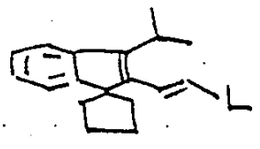


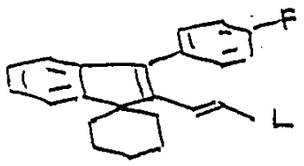


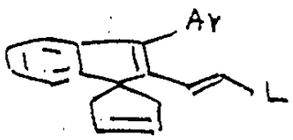


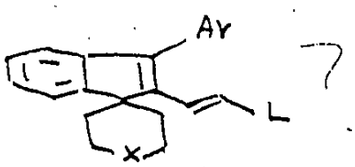
a few modifications might need to be prepared, because of their apparent ease of synthesis.

(2) Complete the project on INDENE systems. Some of these closely related analogs may be necessary to prepare, to find out the optimum structure.



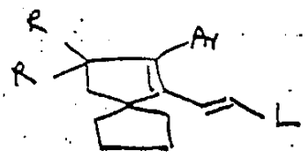




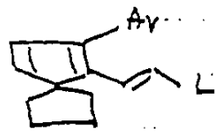


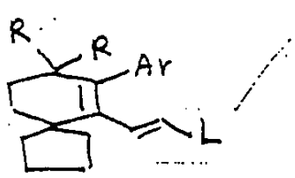
X = O, NR, S

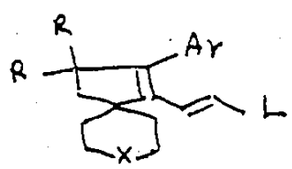
(3) New Analogs of Indenes.



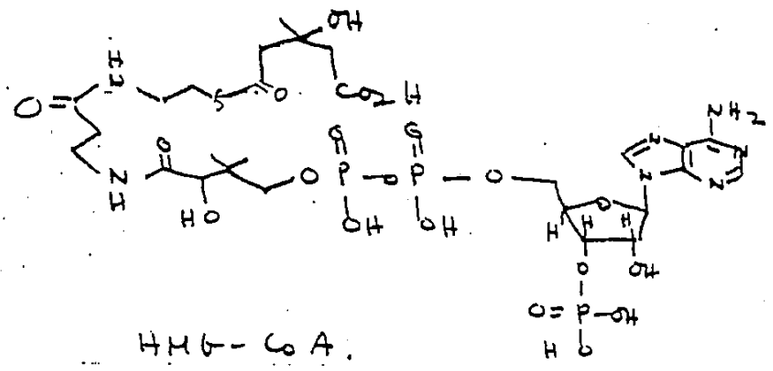
R = Aryl, alkyl groups
X = O, NR, S





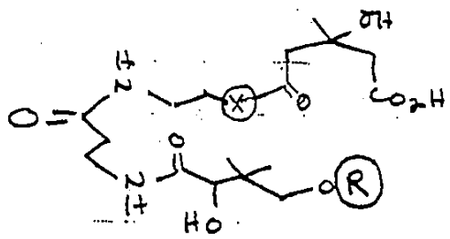


(4) X-ray structure of crystalline HMG-CoA derivatives.

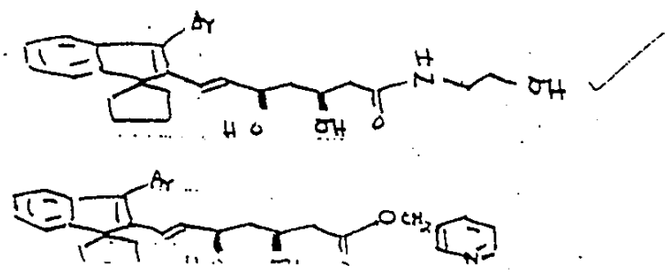


HMG-CoA.

Derivatives vary R ← X



(5) New modifications based on (1 – 3), and modifications on ester R groups eg.



B-July 87 X-11/87 Y-11/87

DISCLOSURE OF INVENTION

124

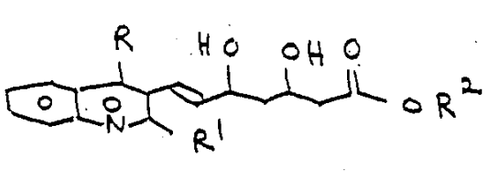
General Subject Matter: QUINOLINES	Invention pertains to: (check all applications) ☒ NEW PRODUCT ☐ NEW PROCESS ☐ NEW FORMULATION ☐ NEW USE	FOR PATENT DEPARTMENT USE: Pat. Comm. Rating; Disclosure No. 299/84; Assigned to; Case No.

Proposed Utility: Cholesterol Biosynthesis Inhibitors, HMG-CoA Reductase Inhibitors

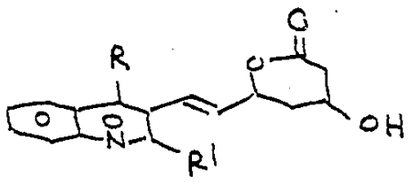
Conception and Reduction to practice of Invention	Date	To whom disclosed	Where recorded
(a) First drawing or written description of invention	11/28/83	Dr. F. G. Kathawala	PATENT AND TRADEMARK DEPT.
(b) First disclosure of invention to another person	11/28/83	Dr. F. G. Kathawala	MAR 1 8 1987
(c) First act(s) establishing conception of Invention	11/28/83	Dr. F. G. Kathawala	
(d) First actual reduction to practice of Invention	5/29/84	Dr. F. G. Kathawala	1049 - 237

All other pertinent Notebook Pages				All other pertinent Memos and Reports		
Notebook	Page(s)	Notebook	Page(s)	Date	From	To
1049	237, 239, 241, 243, 244, 245, 248, 251	1079	22, 24, 27, 30, 33, 34, 39, 41, 87, 91, 101, 111	11/28/83	S. WATTANASIN	F. G. KATHAWALA
		1127	11, 13	11/15/85	S. WATTANASIN	F. G. KATHAWALA

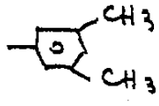
Description of Invention: (include flow sheet where applicable, applicable conditions, critical features, if any, advantages of invention, contemplated scope, products prepared)



I



II

R =  , (i-Pr)

R^1 = CH_3, i-Pr,

R^2 = Et

Compound Numbers: 63-366 ;63-548 ;63-549 ;6 ;6 ;6 6 ;6 ;6 ;6 ;6 ;6 ;6 ;6 ;6

List Closest Prior Art

WATTANASIN EXHIBIT A-3 Wattanasin v. Fujikawa et al. Interference No. 102,648 Interference No. 102,975

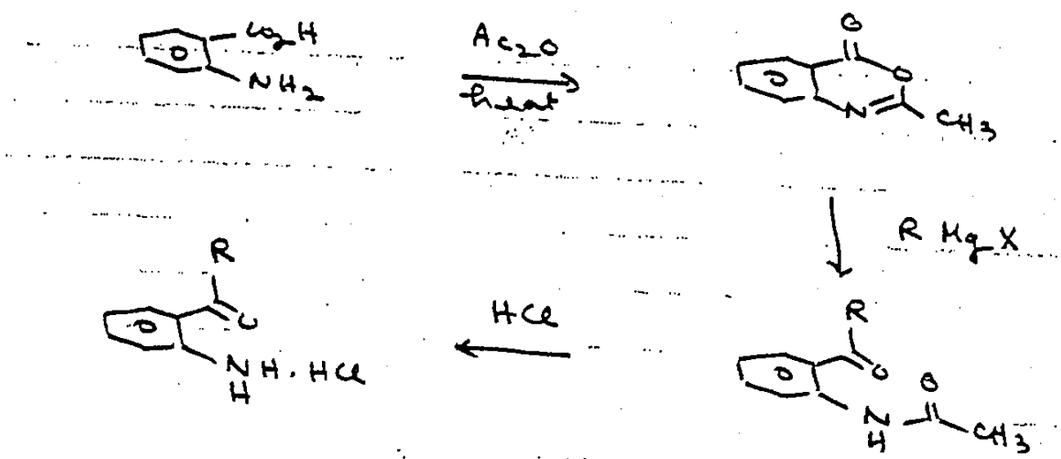
B1520/63 Rev. 3

L & D Report No.

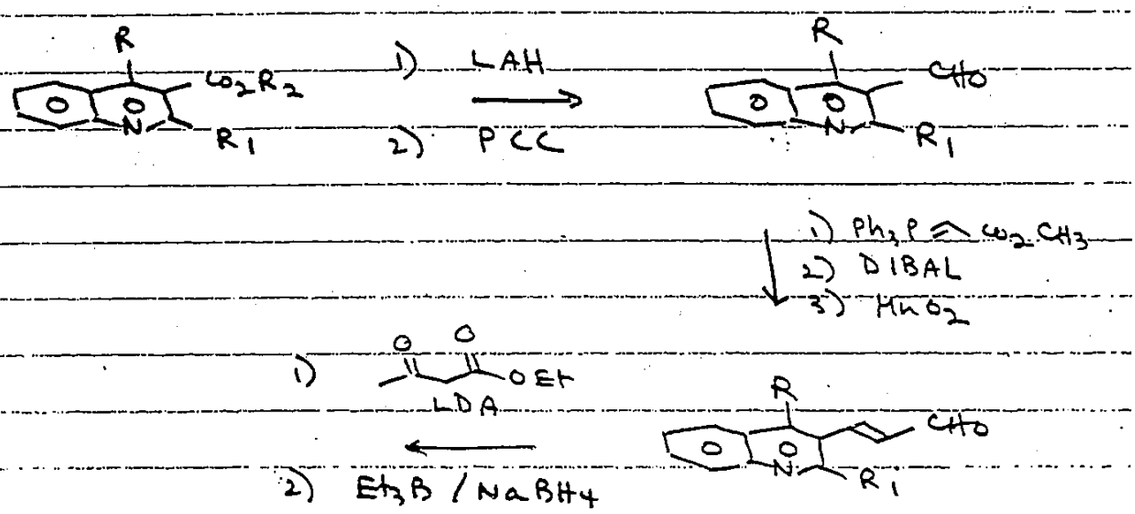
Inventor Signatures: (a) S. Wattanasin (SOMPONG WATTANASIN) Date: 3/16/87; (b) Date:; (c) Date:

Witnessed by: Date: 3/16/87

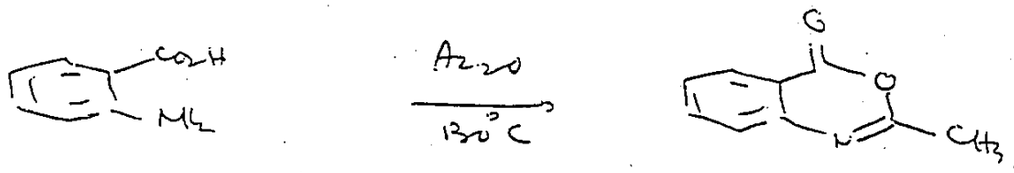
Route I


Ac2O
heat
R MgX
HCl
EtOH
reflux
1) LAH
2) SOCl2
P(OEt)3
1) LDA
I + II
2)
OHC
CO2R3
3) nBu4NF

Route II


R
CO_2R_2
R_1
1) LAH
2) PCC
CHO
1) $Ph_3P=CO_2CH_3$
2) DIBAL
3) MnO_2
I
1)
OEt
LDA
2) Et_3B / $NaBH_4$
3) CH_3OH

See JCS 2702 (1978)



anthranilic acid = 10 g
acetic anhydride = 54 ml.

A mixture of anthranilic acid and acetic anhydride was heated at 130°C. 12.00 pm. for 30 min. Then ~ 30 ml of Ac2O was removed, the residue was cooled to give a yellow solid. Recrystallization from Ac2O gave a pale yellow solid = 8.9 g (1049-237-19)

hmr

(1049-237-19) was dissolved in ether and filtered through a short pad of silica gel. Evap gave a colorless solid = 7.0 g (1049-237-27) mp. 76-77°C

hmr IR micro

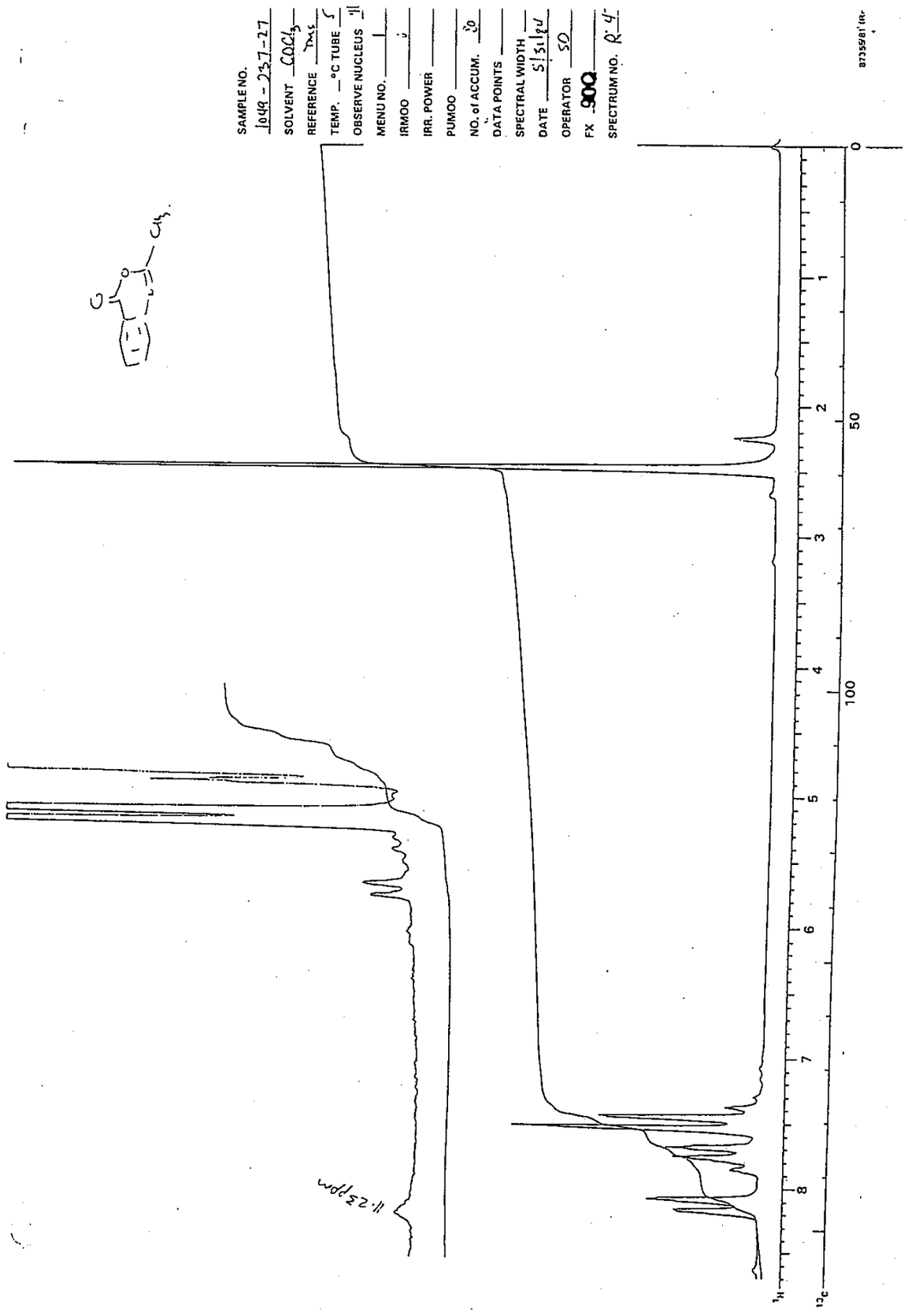
$C_9H_7O_2N$ 161.161

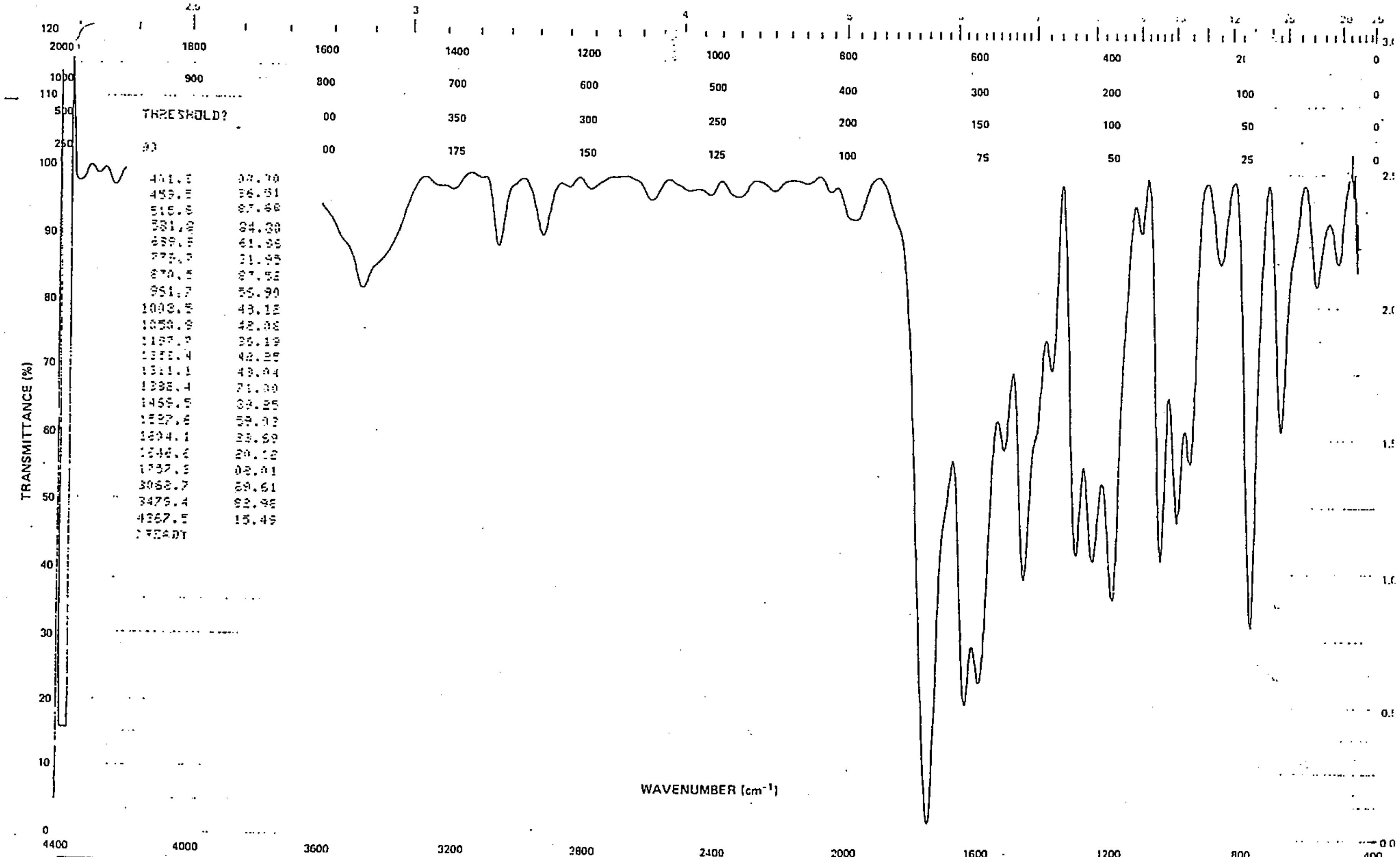
	C	H	N	O		
Calc.	67.08	4.38	8.69			
Found						
	66.80	4.46	8.75			

Performed by- S. Wattanasin.

Witness- [signature]

WATTANASIN EXHIBIT
B-1
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

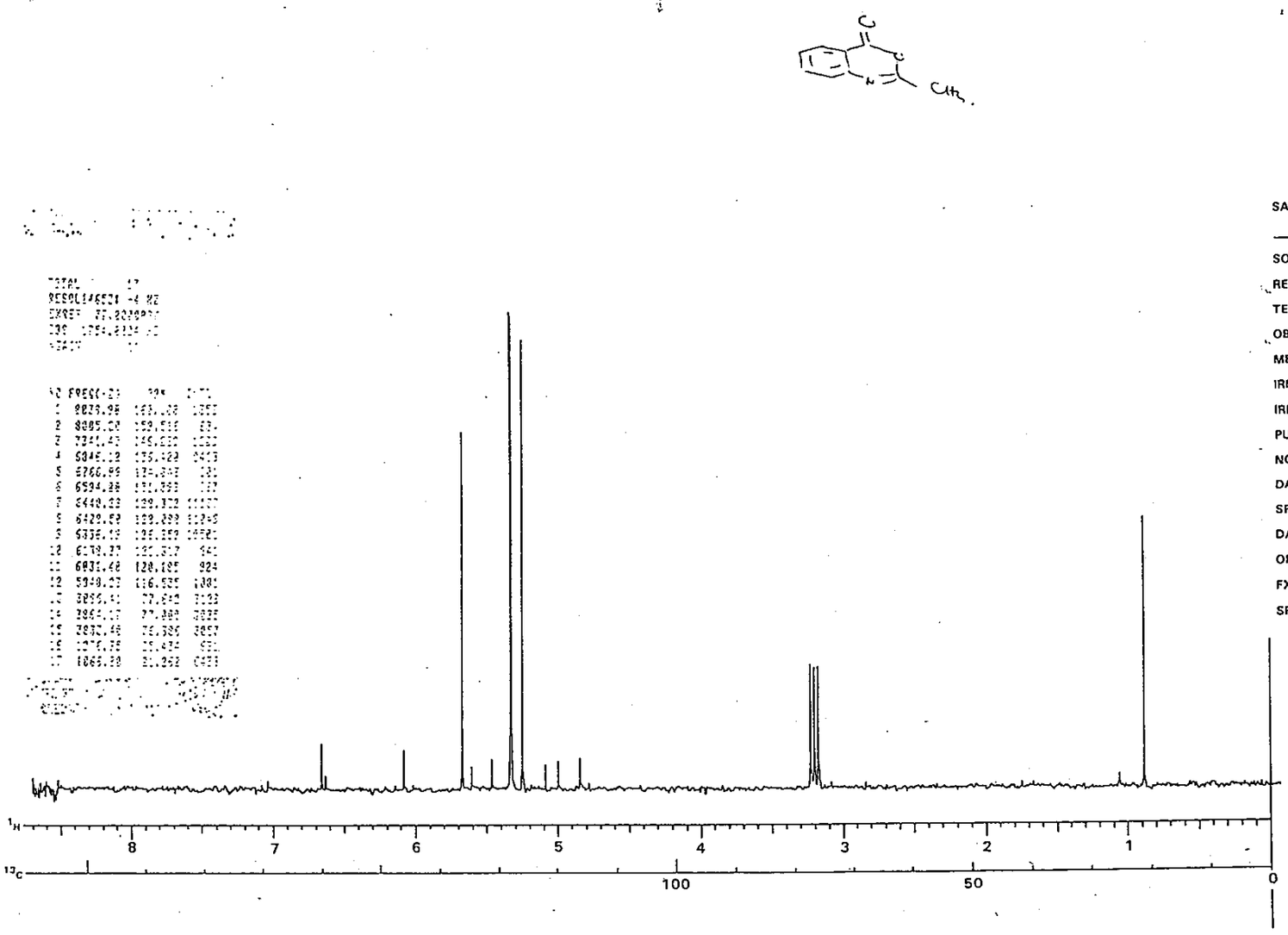

SAMPLE NO. 1049 - 237-27
SOLVENT CDCl3
REFERENCE TMS
TEMP. °C TUBE 5
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOO
IRR. POWER
PUMOO
NO. of ACCUM. 20
DATA POINTS
SPECTRAL WIDTH
DATE 5/31/84
OPERATOR SO
FX 90Q
SPECTRUM NO. R-4
11.25ppm
0
1
2
50
3
4
100
5
6
7
8
1H
13C



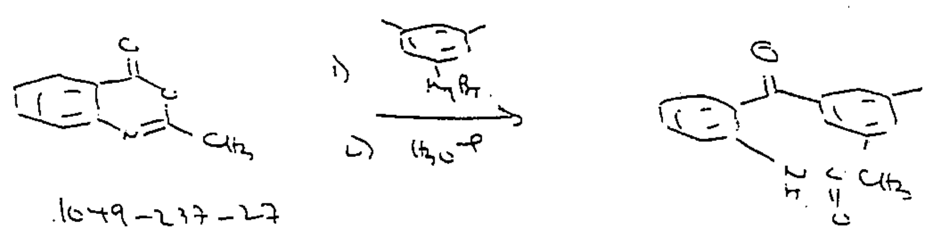
DATE 5-31-84	SAMPLE 1049-237-27	NOTES: Quntitate B: 049-237-27	STORED (✓) INTERLEAVED (✓) BKG	TRANS. (✓) ABSORBANCE ( )
SPECTRUM NO. 1377	PHASE KBr	Smooth N	NO. SCAN PAIRS (SAM/BKG) (32/64)	VERT. ORIGIN 0 SPAN 120
OPERATOR J.M.	THICKNESS	BS/4	AUXILIARY DISPLAY	HOR. ORIGIN 400 SPAN 4000
	Dr. Waltenspühl			

SANDOZ

129



cf. P. 182.



1049-237-27

161	1049-237-27	=	2 g (0.0124 mol)
(185)	5-bromo-m-xylene	=	3.44 g (0.0186 mol)
(24)	Mg	=	446 mg (0.0186 mol)
	ether	=	10 ml.
	benzene	=	

To a suspension of Mg in ether 2 ml a a few drop of I_2 at r.t. was added a few drops of 1,2 dibromoethane, followed by a sol'n of 5-bromo-m-xylene in ether (8 ml) dropwise (at a rate that the reaction mixture reflux gently). 9.05 am. → ~~9.??~~ 9.45 am. The reaction mixture was then heated at reflux for 3 h. Then the grignard reagent (~8 ml) was withdrawn by a syringe and added to a sol'n of 1049-237-27 in THF (10 ml) + ether (2 ml) dropwise (via a funnel)

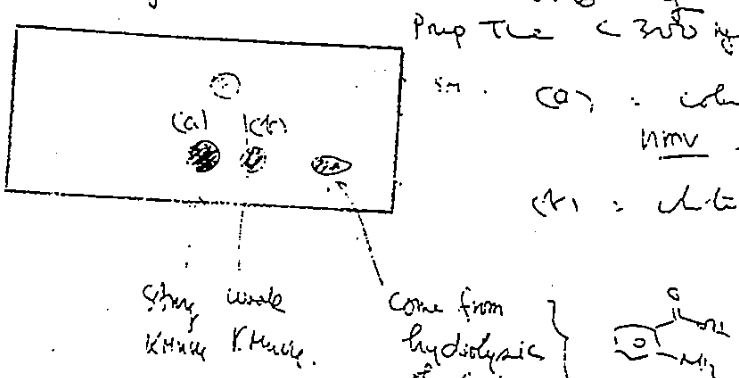
6/1/84: 8.30 am: The reaction was decomposed with 3N HCl & extracted with EtOAc to give a yellow oil = 3.6 g (1049-241-31)

Prep TLC (300 mg) (1:1 ether - pet.) gave

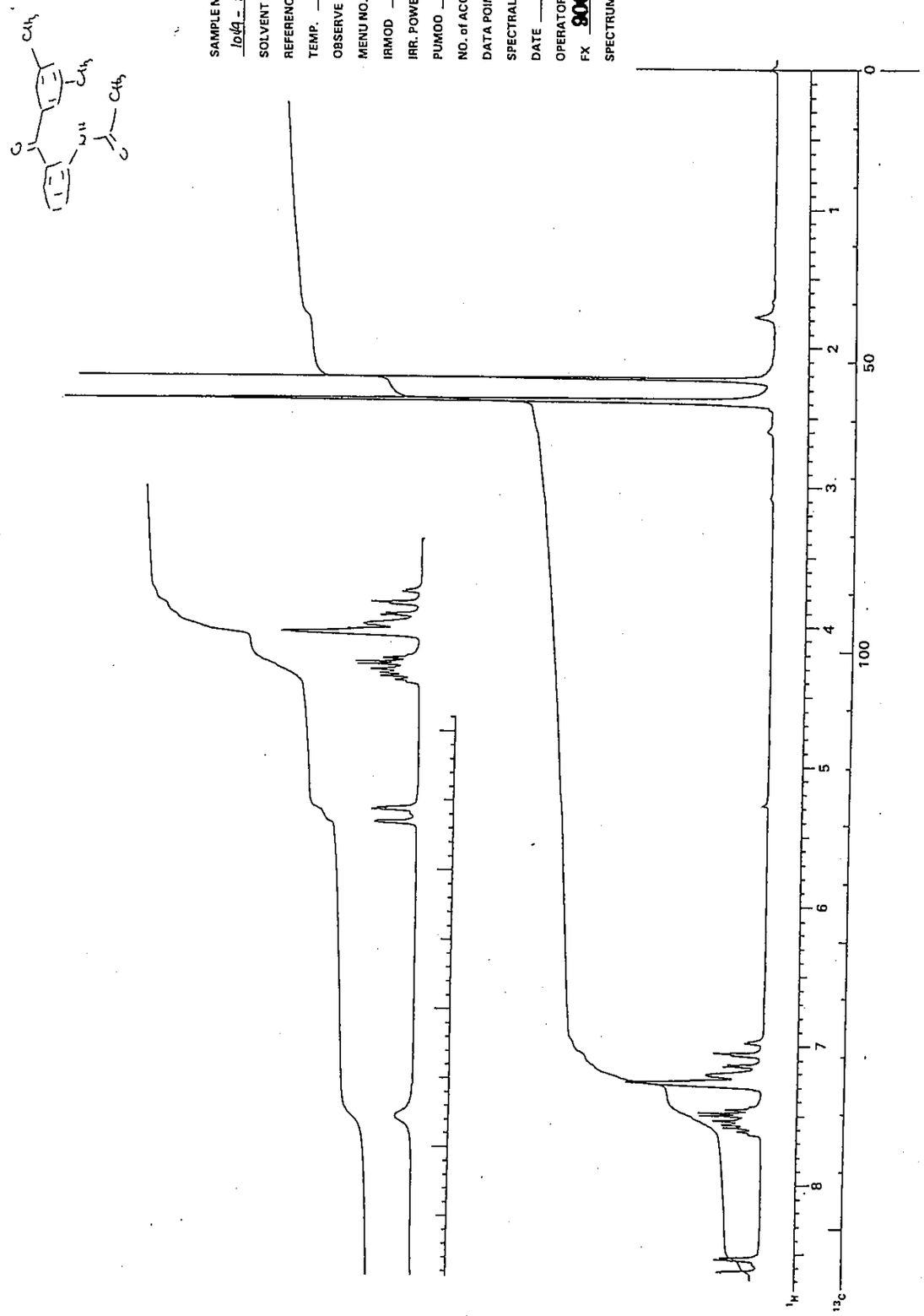
S.M. (a): colorless oil = 128 mg (1049-241-34)

NMR ✓

(b): white solid = 24 mg (1049-241-35)



HPLC of the rest gave the product = 1.6 g (1049-241-43)

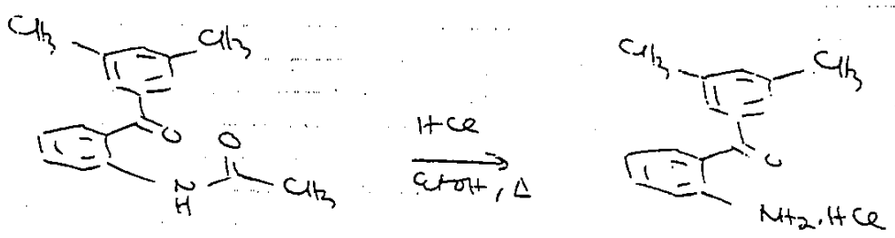

SAMPLE NO. 1049-241-34
SOLVENT CDCl3
REFERENCE TMS
TEMP. °C TUBE 5 m
OBSERVE NUCLEUS 1H
MENU NO. 5
IRMOD 0
IRR. POWER
PUMOD
NO. of ACCUM. 48
DATA POINTS
SPECTRAL WIDTH
DATE 6/4/84
OPERATOR SO
FX 300
SPECTRUM NO. 47511
87359/81 (Rev. 1
1H
13C

Title- 1049

133

Date 6/6/89, Proj.

Cont'd From-



1049-241-43 = 1.6 g
EtOH = 20 ml
Conc HCl = 0.5 ml.

The solution was heated at 90°C

start 8.50 am.

stop 4.00 pm TLC showed very small amt of the starting material.

The solvs was concentrated and the residue was taken up in ether and filtered to give a pale yellow solid = 1.15 g (1049-248-24)

Performed by S Wattanasin

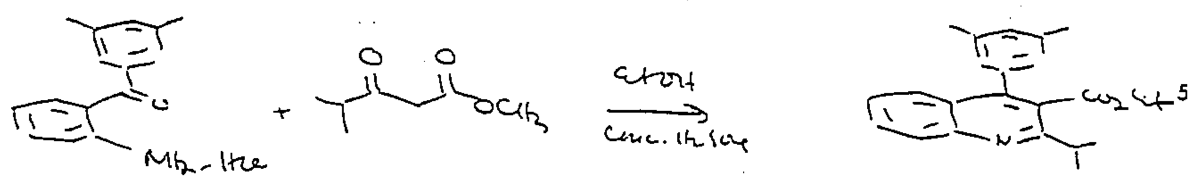
Witnessed N. Rodella

Cont'd to-

Date 6/8/84. Proj.

Cont'd From-

Title- ACS Meeting at Cincinnati. June 10 – 14



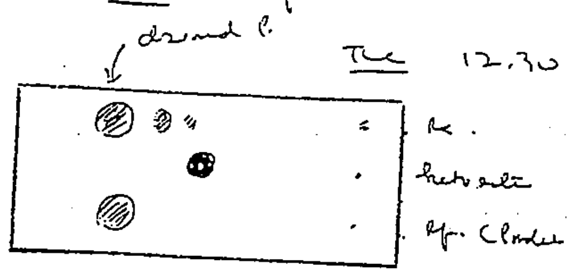
(261.5) 1049 - 248 - 24 : 500 mg (0.001912 mol)
(144) [structure] OCH3 : 412 mg (0.002864 mol)
EtOH : 20 ml.
conc H_2SO_4 : 0.1 ml.

Procedure Same as 1049-245 Rx.

Start reflux. 8.50 am:

TLC 12.30 pm. Stop 12.30 pm.

20% ether-pet



Concentrated, basified with NH_4OH, diluted with water & extracted with ether to give an oil = 420 mg. Prep TLC (20% ether-petrol) gave one main band,

= 565 mg which on standing in the fridge solidified : pale yellow solid.
(1049-251-29)

m.p. 82-83°C

$C_{23}H_{25}NO_2$ micro

	C	H	N
Calc.	79.51	7.25	4.03
Found			
	80.38	6.83	4.30
	80.3	7.01	4.32

Performed by- S. Waltzman

Witness- N. Paolella

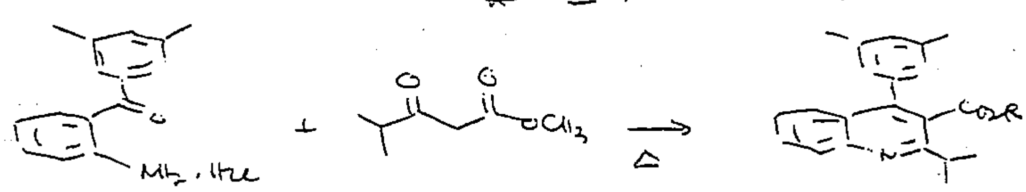
Cont'd to-

Date 6/5/84 Proj.

Title- 1049

Cont'd From-

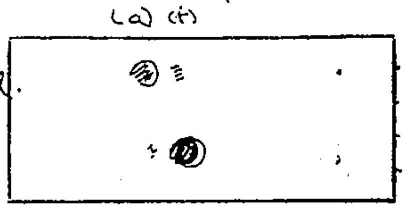
cf. J. Het. Chem. 7 565 (1970)
J. Prakt. Chem. [4] 34, 298 (1966)



(261.5) 1049-244-24 = 20 mg (0.0000766 mol)
(144) [structure] OCH3 = 11 mg (0.000011 mol)
EtOH = 2 ml. → 0.02 ml.
conc. H2SO4 = 1 drop.

The solution was heated at reflux
9.30 am. → ~~12.30 pm.~~ 5.00 pm.

Concentrated, ~~extract~~ basified with NH4OH + extracted with ether. The crude oil was purified by prep TLC (1:1 ether - petrol) to give

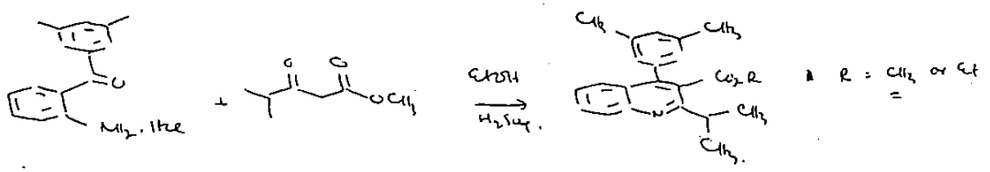


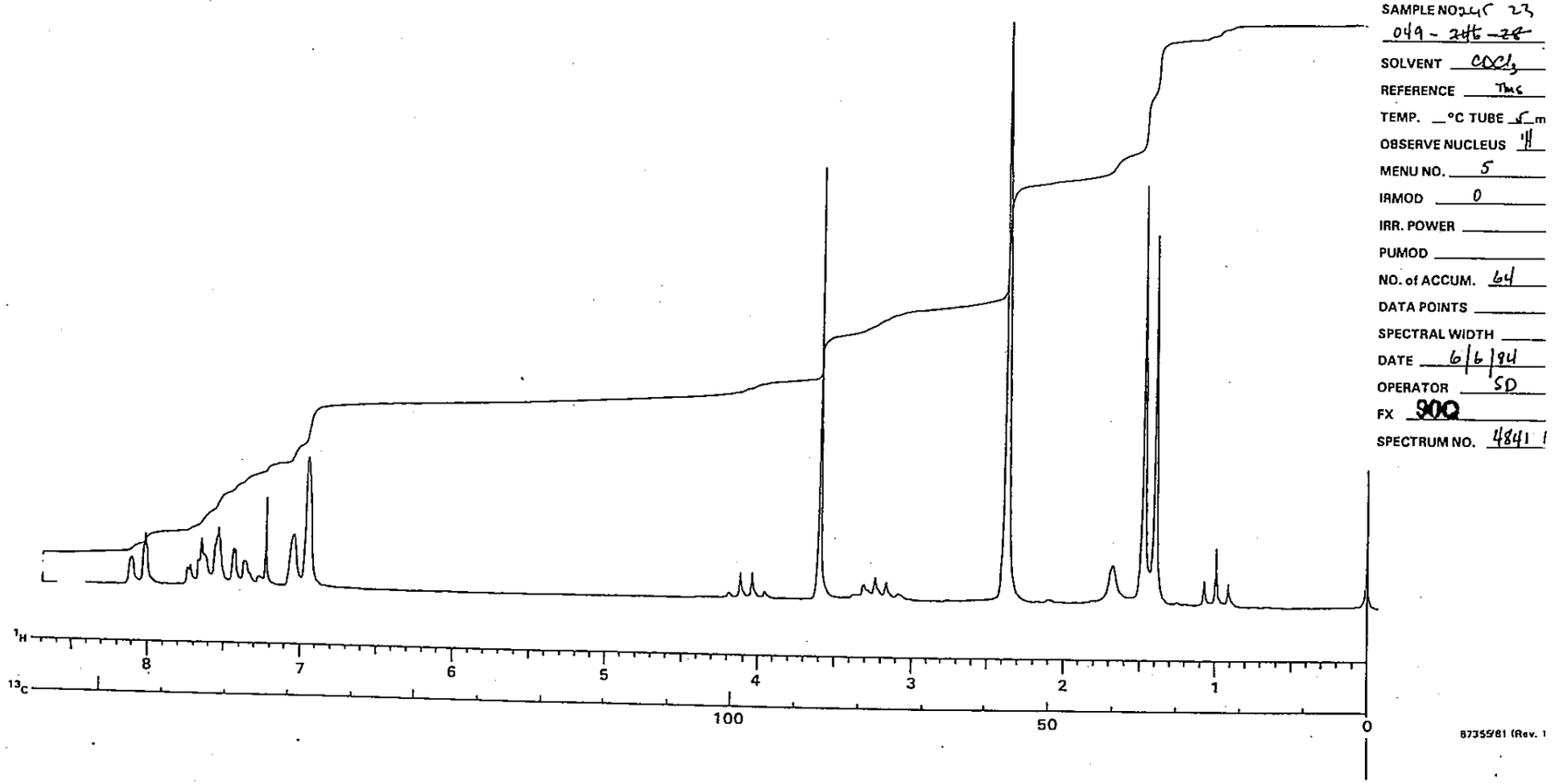
colorless oil
(a) = 17 mg (1049-245-23)
nmr ✓ ⇒ perfect.

Performed by- S. Watterson

Witness- N. Barlella

Cont'd to-


R = CH3 or Et

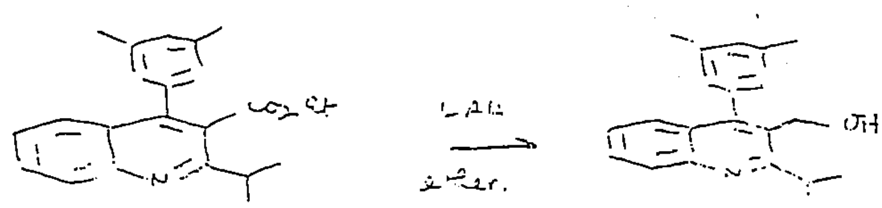

SAMPLE NO 24C 23
049 - 246 - 2B
SOLVENT CDCl3
REFERENCE TMS
TEMP. °C TUBE 5 m
OBSERVE NUCLEUS 1H
MENU NO. 5
IRMOD 0
IRR. POWER
PUMOD
NO. of ACCUM. 64
DATA POINTS
SPECTRAL WIDTH
DATE 6/6/94
OPERATOR SD
FX 90Q
SPECTRUM NO. 4841 1
1H
13C
8
7
6
5
4
3
2
1
100
50
0
87355/81 (Rev. 1

Title- # 1079 (1)

Date 5/11/94 Proj.

Cont'd From-

137



$C_{23}H_{25}O_2N$

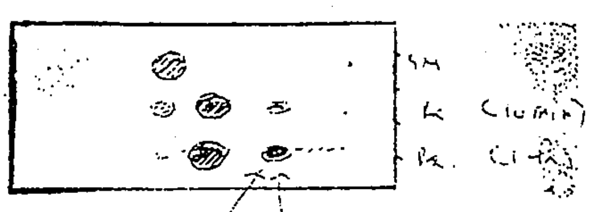
(347) 1049-271-29	=	535 mg	(0.00154 mol)
(38) LAH	=	117 mg	(0.00311 mol)
ether	=	8 ml	

To a solution of (1049-271-29) in dry ether at r.t. was added LAH portionwise. The mixture was then stirred at r.t. and followed by TLC.

9.15 am:

TLC after 10 min ⇒ 2 spots mainly the product.

STOP 10.15 am, the reaction was poured into cold then extracted with ether to give a colorless foam = 427 mg (1049-22-23)



50% EtOAc-pet.

SM

R (10 min)

R (1 h)

this spot increase.

This spot disappear after workup.

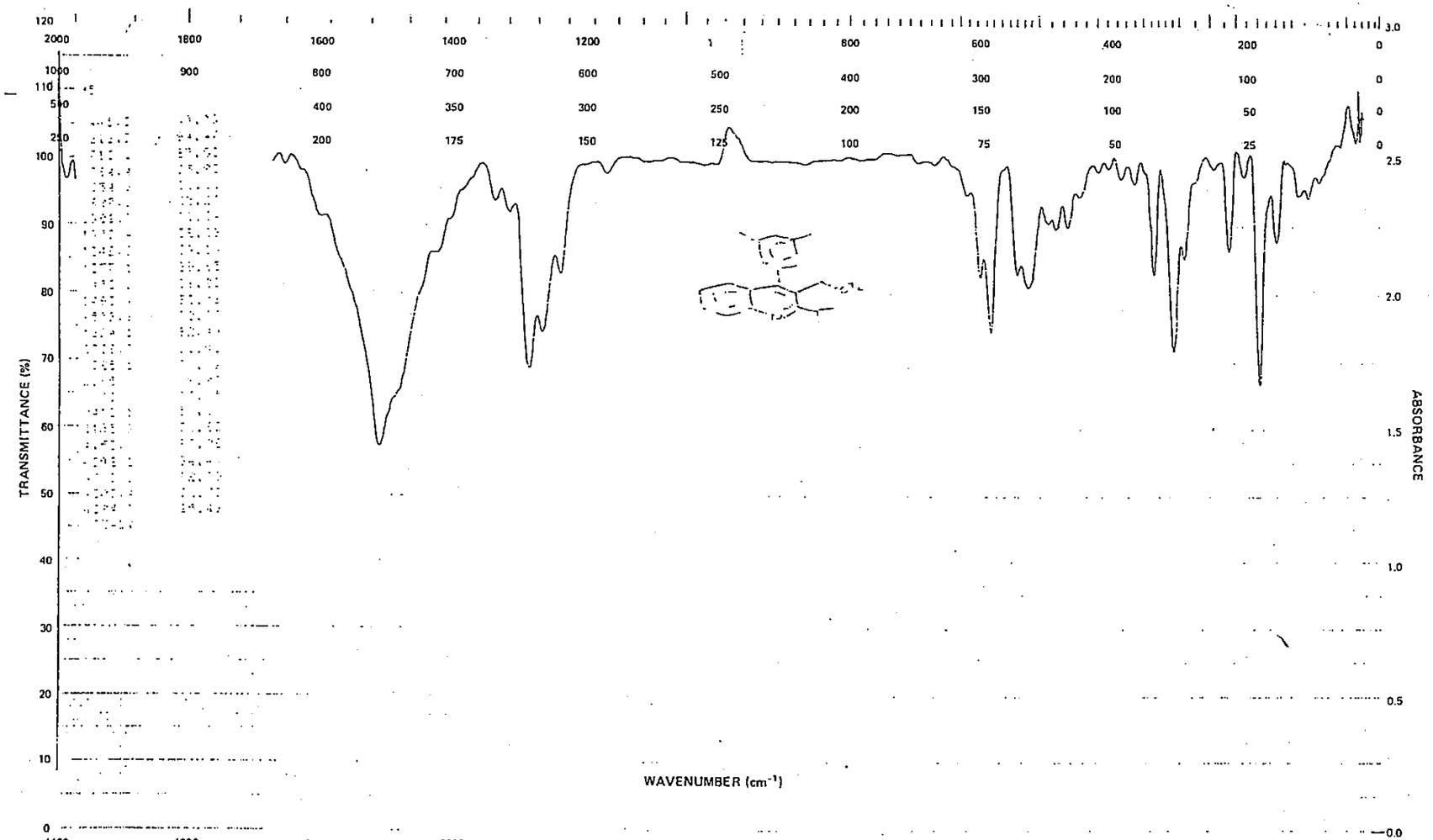
mp 115-118°C solidifies on standing

1H ⇒ pure (at solid not ester)

Performed by- S. Watanabe

Witness- N. Pisolella

Cont'd to-



DATE 8-10-84	SAMPLE 1079-22-28	NOTES: p.t.= Fr. B: 1079-22-28	STORED ( ) INTERLEAVED ( ) BKG	TRANS. (✓) ABSORBANCE ( )	
SPECTRUM NO. 2009	PHASE KBr	Smooth 15	NO. SCAN PAIRS (SAM/BKG) 32/64	VERT. ORIGIN 0 SPAN 120	
OPERATOR J.J.	THICKNESS P.P. Williamson	BS/11	AUXILIARY DISPLAY	HOR. ORIGIN 4400 SPAN 4400	

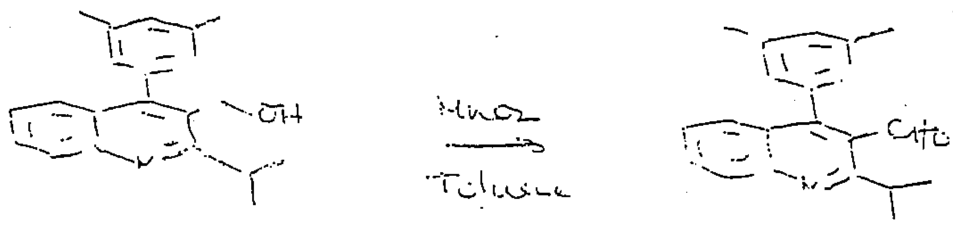
SANDOZ

138

24 Title- # 1079

Date 5/10/84 Proj.

Cont'd From-



1079-22-24 = 430 mg
MnO2 = 5070 mg
Toluene = 6 ml

A mixt. of (1079-22-24) and MnO2 in Toluene was stirred at R.T / [illegible] [illegible] [illegible] [illegible] min.

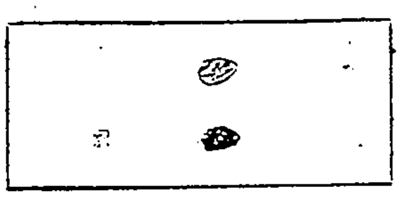
TLC after 2 days still S.M.

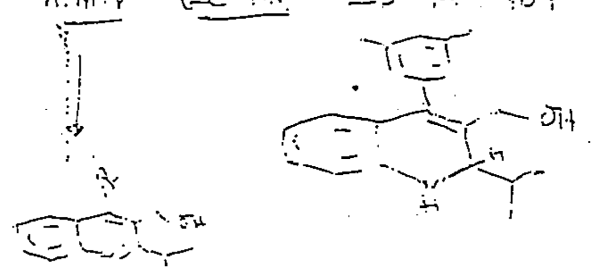
The reaction was diluted with ether and filtered through a pad of silica gel (...) Evap. gave a pale yellow solid = [illegible] mg (1079-24-24).

92.9 % pure

n.m.r GC-MS ⇒ M+ 307 ?

20 % Eth-pet.





Performed by- S. Watanabe

Witness- M. Paolella

Cont'd to-

SAMPLE NO.
1079-24-24 *
SOLVENT CDCl3
REFERENCE TMS
TEMP. RT°C TUBE 5mm
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOD MN
IRR. POWER -
PUMOD -
NO. of ACCUM.
DATA POINTS
SPECTRAL WIDTH
DATE
OPERATOR
FX 200
SPECTRUM NO.
* This is vial number. Number on report sheet = 22-24
87355/81 (Rev. 11
1H
13C
0
50
100
150
200
1
2
3
4
5
6
7
8

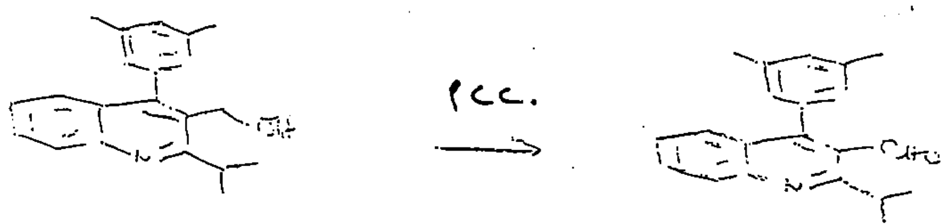
140

Date 8/4/89 Proj. | Title # 1079

Cont'd From-

27

141

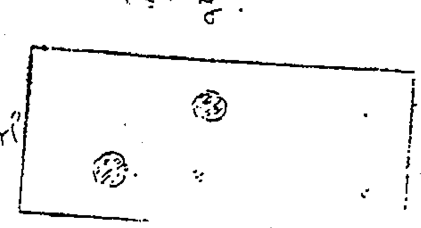


1079-24-14 = 350 mg.
DDQ = 400 mg.
Toluene = 4 ml.

→ The mixt. was stirred at r.t. overnight. TLC no rx.

The reaction mixt. (dark red color) was diluted with ether and filtered through a pad of silica gel. Evap'n gave a dark red film. TLC ⇒ no change. X

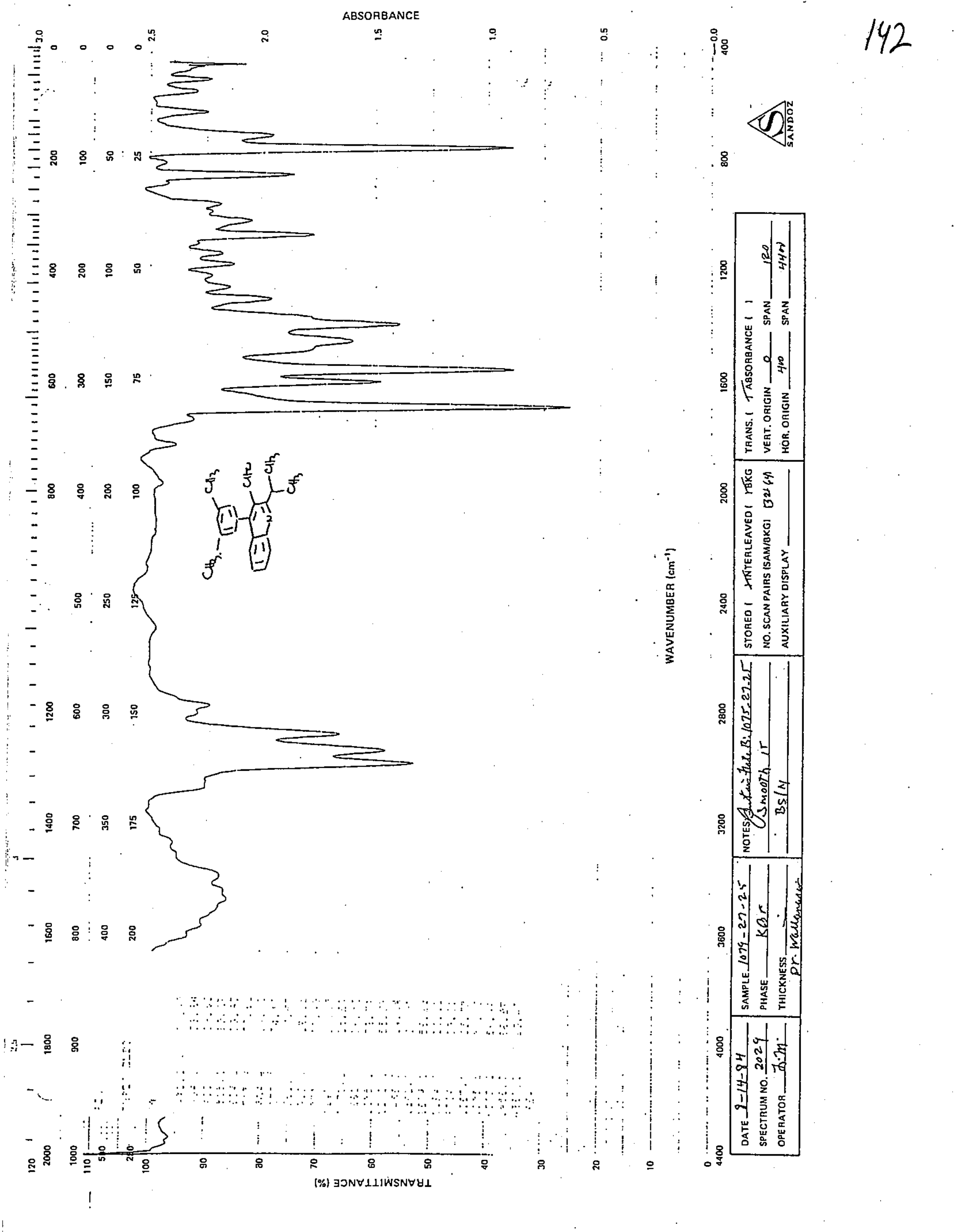
→ The crude film was dissolved in 10 ml CH_2Cl_2, PCC (400 mg), and neutral alumina (2 g) was added. The mixt. was stirred for 1 hr at r.t. ⇒ TLC ⇒ complete rx? Diluted with ether, filtered through silica gel. Evap'n gave a pale yellow oil = 132 mg (1079-27-15). Solidified on standing. NMR ✓ IR ✓ 151 mg.

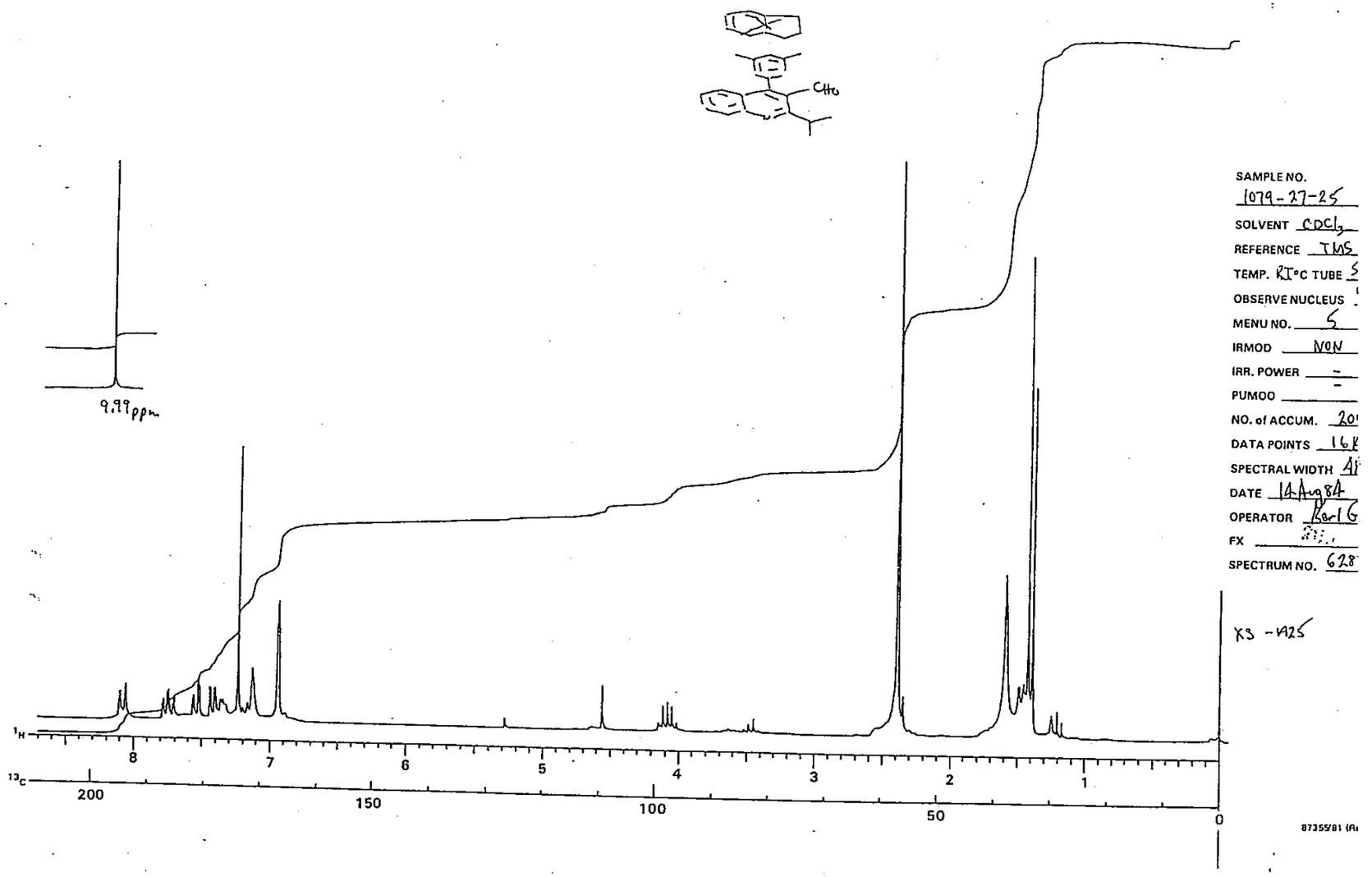


Performed by- S. Watanabe

Witness- M. Pavlella

Con'd to-

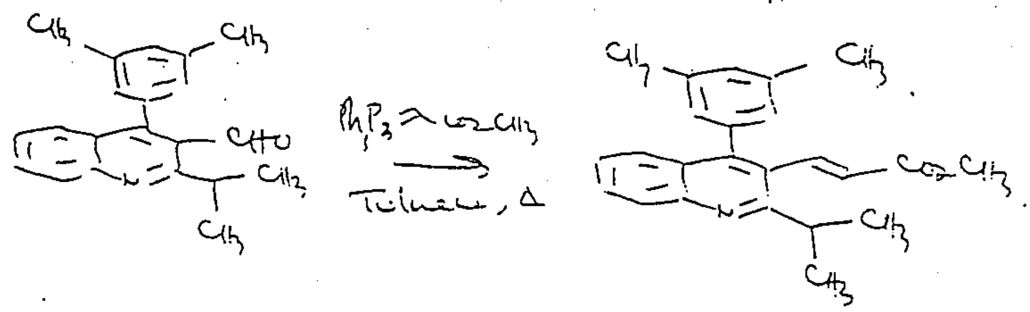

ABSORBANCE
TRANSMITTANCE (%)
WAVENUMBER (cm⁻¹)
SANDOZ
DATE 9-14-84
SPECTRUM NO. 2029
OPERATOR
SAMPLE 1079-27-25
PHASE KBr
THICKNESS
NOTES
STORED ( ) INTERLEAVED ( ) BKG
NO. SCAN PAIRS (SAM/BKG)
AUXILIARY DISPLAY
TRANS. ( ) ABSORBANCE ( )
VERT. ORIGIN 0 SPAN 120
HOR. ORIGIN 400 SPAN 4400



Title # 1079

Date 8/17/89 Proj.

Cont'd From-



1079-27-25 = 140 mg
the ylide = 200 mg
toluene = 5 ml.

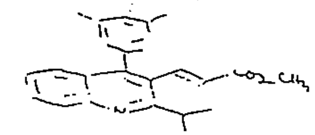
The mixt. was heated at reflux for 3 h. After cooling, the reaction mixt. was diluted with ether and filtered through a pad of silica gel. Concentration gave a semisolid, which was purified by prep. TLC to give a colorless solid = 140 mg (1079-30-23) IR nmr ✓ mp 110-112°C

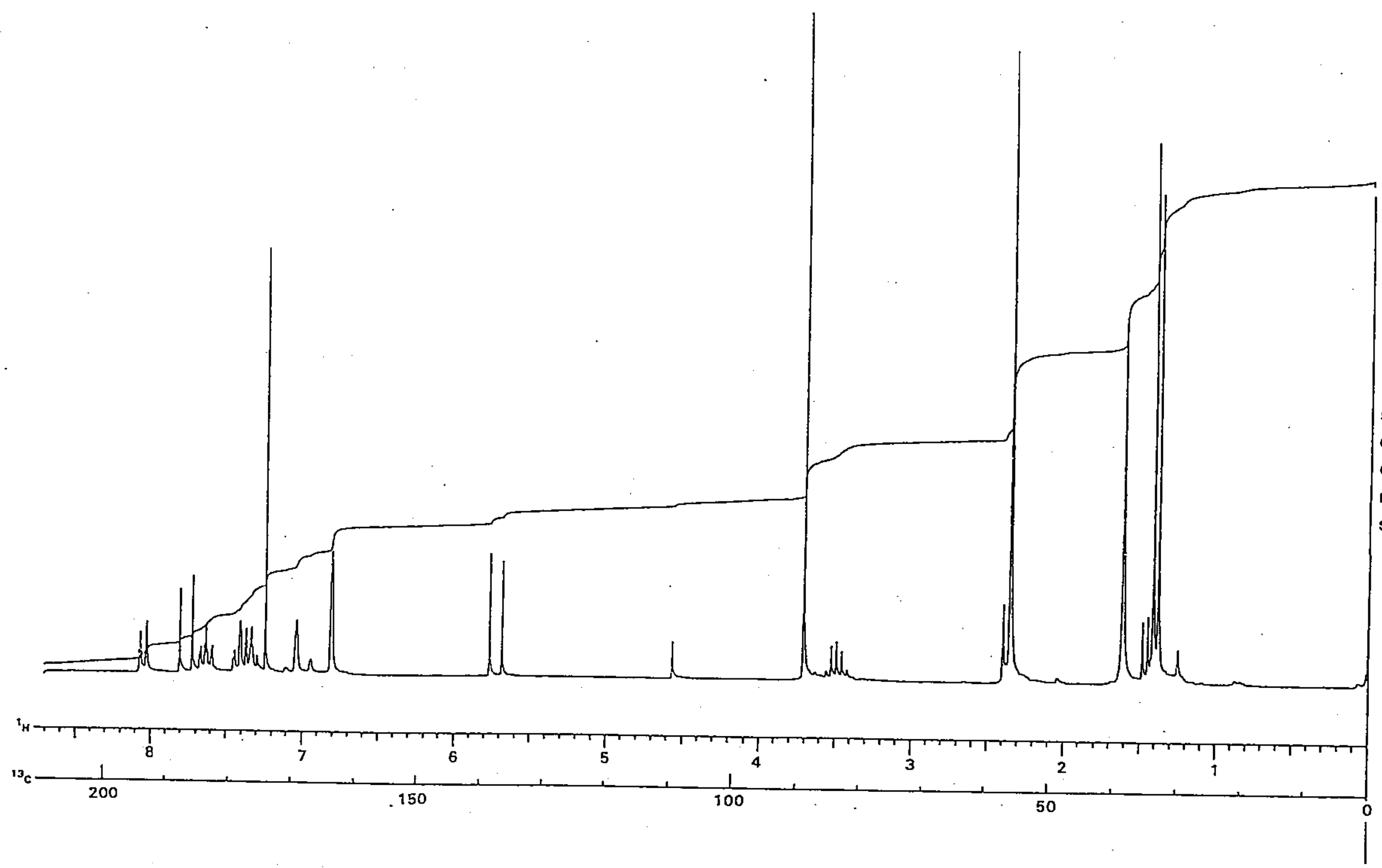
TLC ⇒ only one main band of product

Performed by- S. Watanabe

Witness- M. Biolella

Con'd to-

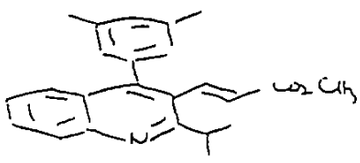




SAMPLE NO. 1079-30-23
SOLVENT CDCl$_3$
REFERENCE TMS
TEMP. RT °C TUBE 5 mm
OBSERVE NUCLEUS ¹H
MENU NO. 1
IRMOD NON
IRR. POWER
PUMOD
NO. of ACCUM. 88
DATA POINTS 16K
SPECTRAL WIDTH 2K
DATE 8/23/84
OPERATOR MB
FX 200
SPECTRUM NO. 640F-G

8735981 (Rev. 1)

145



1079-30-23 = 130 mg (0.000378 mol)
DIBAL-H = 0.5 ml. (0.0007 BL ml).
CH_2Cl_2 = 5 ml.

To a Solution of (1079-30-23) in dry CH_2Cl_2 at -78°C was added DIBAL-H, The mixt. was then stirred at -78°C
11.30 am:
12.00 pm ⇒ complete reaction
The reaction was diluted with ether and filtered through a pad of silica gel. Evpn gave a crude oil = 135 mg which was used directly in the next step The ⇒ one spot

(1079-33-19)

1:1 Eth-petrol.

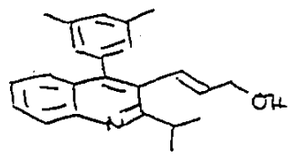
Performed by-
Witness- M. Pavelle
Cont'd to-

Title- # 1079

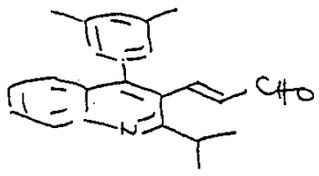
Date 8/23/84 Proj.

Cont'd From-

147



$\xrightarrow[r.t.]{MnO_2}$



1079-33-19 = 135 mg

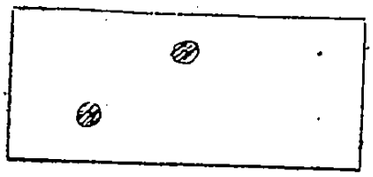
MnO_2 = 300 mg

Toluene = 5 ml.

A mixture of (1079-33-(9) and MnO_2 in toluene was stirred at r.t. overnight

pale yellow oil ⇒ 104 mg (1079-34-17)

hmv



Performed by- S Wattamwar

Witness- N. Paolella

Cont'd to-

148

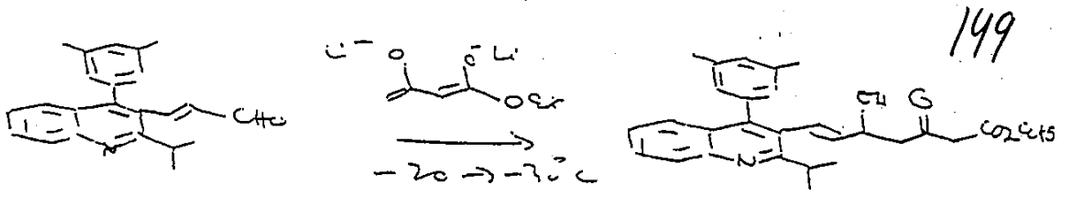
SAMPLE NO. 1079-34-17
SOLVENT CDCl3
REFERENCE TMS
TEMP. °C TUBE 5 mm
OBSERVE NUCLEUS H
MENU NO. 5
IRMOD NOJ
IRR. POWER
PUMOD
NO. of ACCUM.
DATA POINTS 16K
SPECTRAL WIDTH 4K
DATE 9/5/84
OPERATOR MCS
FX 200
SPECTRUM NO. 6592-2
8705/81 (Rev. 1)
0
1
2
50
3
4
100
5
6
150
7
8
200
^1H
^{13}C

Date 9/5/84. Proj.

Cont'd From-

Title- # 1079

149



(3.9) 1079-34-17 = 100 mg (0.0003039 mol).
the diamine from
1079-38-2A = 5 ml (~ 0.004 mol) 10
THF = 4 ml.

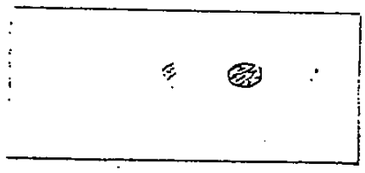
10.20 am - 10.52 am:
The ⇒ complete reaction
The reaction was quenched with sat. NH4Cl & extracted with EtOAc. 15

to give an yellow oil = 177 mg (1079-39-1)

The crude p. was reduced directly without 20
further purification
see P. ~~40~~, 41

The ⇒ one main spot. 25

1:1 grey-pink.



30

35

40

Performed by- S. Wattanasin.

Witness- M. Padelli

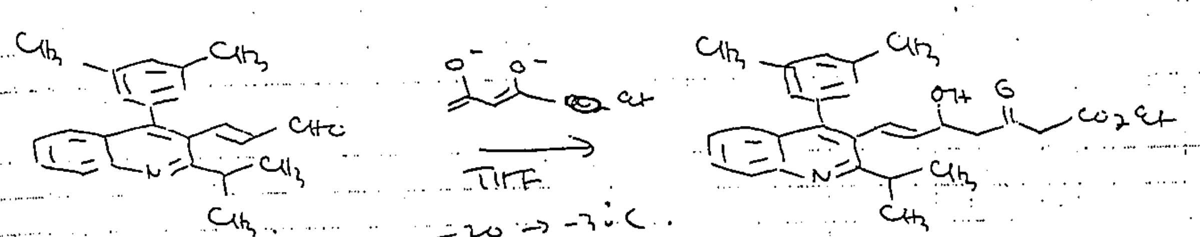
Cont'd to-

Date 11/8/89. Proj.

Title- 23.57 wt = 1.8 M ... = ... ~2 ml.

Cont'd From-

150



(329)	1079-101-28	=	110 mg	(0.0003343 mol)
101.19, .722	Diisopropylamine	=	0.5 ml	(0.00334 mol)
	1.6 M nBuLi	=	2 ml.	(0.00334 mol).
130.14, 1.021	ethyl acetoacetate	=	0.22 ml	(0.0200 (1.7 ml)
	THF	=	5 ml.	

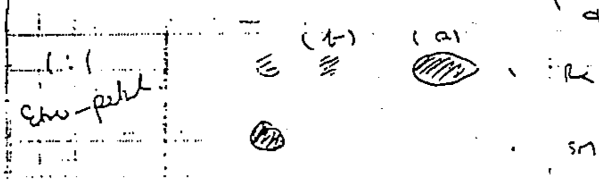
commercially available

To a soln of diisopropylamide (1.8 M in cyclohexane (1.8 ml) in THF (4 ml) at −20°C, was added ethylacetoacetate (0.22 ml). The resulting yellow soln was stirred at −20° → −30°C for 30 min.

4.00 pm: 4 ml. of the diisopropylamide soln was added to a soln of (1079-101-28) in THF (2 ml) at −30°C. → −10°C

4.20 pm.

TLC after 20 min ⇒ only trace of S.M. One main spot of product. The reaction was quenched with 2 ml of sat. NH4Cl & extracted with EtOAc



gave a yellow oil = 290 mg

Prep TLC (1:1 ether − petrol)

(a) : yellow oil = 112 mg (1079-105-35)

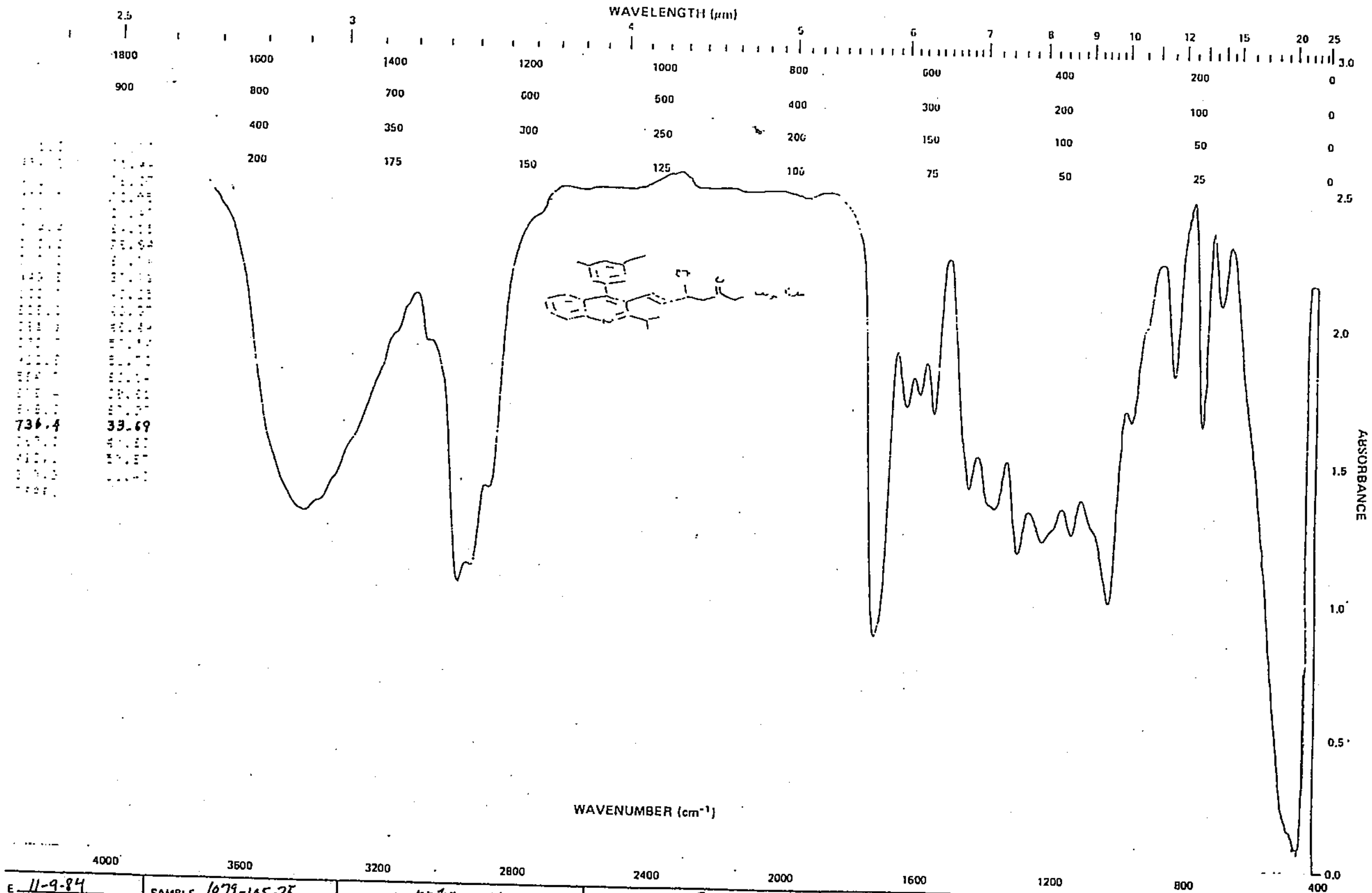
n.mr ✓ IR ✓

Performed by- S. W...

Witness- M. Bolla...

Cont'd to-

151



E. 11-9-84
SPECTRUM NO. 2514
OPERATOR FM.

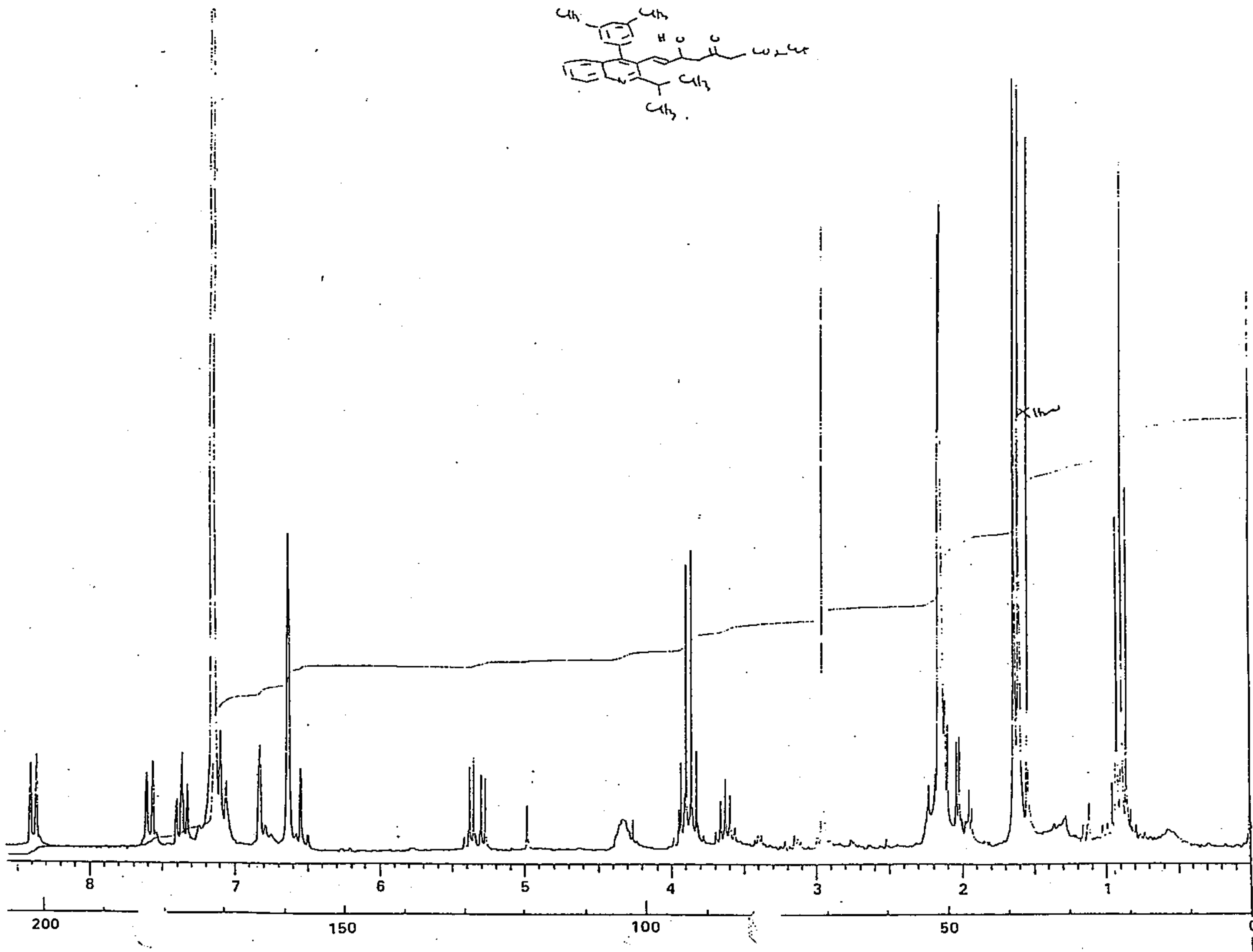
SAMPLE 1079-105-35
PHASE film
THICKNESS
Dr. Wattanasin

NOTES: Jantra Files: 079-105-35
Smooth 15
3514

STORED (✓) INTERLEAVED (✓) BKG
NO. SCAN PAIRS (SAM/BKG) 44:44
AUXILIARY DISPLAY

TRANS. (✓) ABSORBANCE ( )
VERT. ORIGIN 0 SPAN 120
HOR. ORIGIN 40 SPAN 440

SANDOZ



SAMPLE NO. 1079- 105-35

SOLVENT C_6D_6

REFERENCE TMS

TEMP. 25°C TUBE 5 mm

OBSERVE NUCLEUS ^1H

MENU NO. 1

IRMOD NON

IRR. POWER

PUMOD

NO. of ACCUM. 160

DATA POINTS 16K

SPECTRAL WIDTH 2KHz

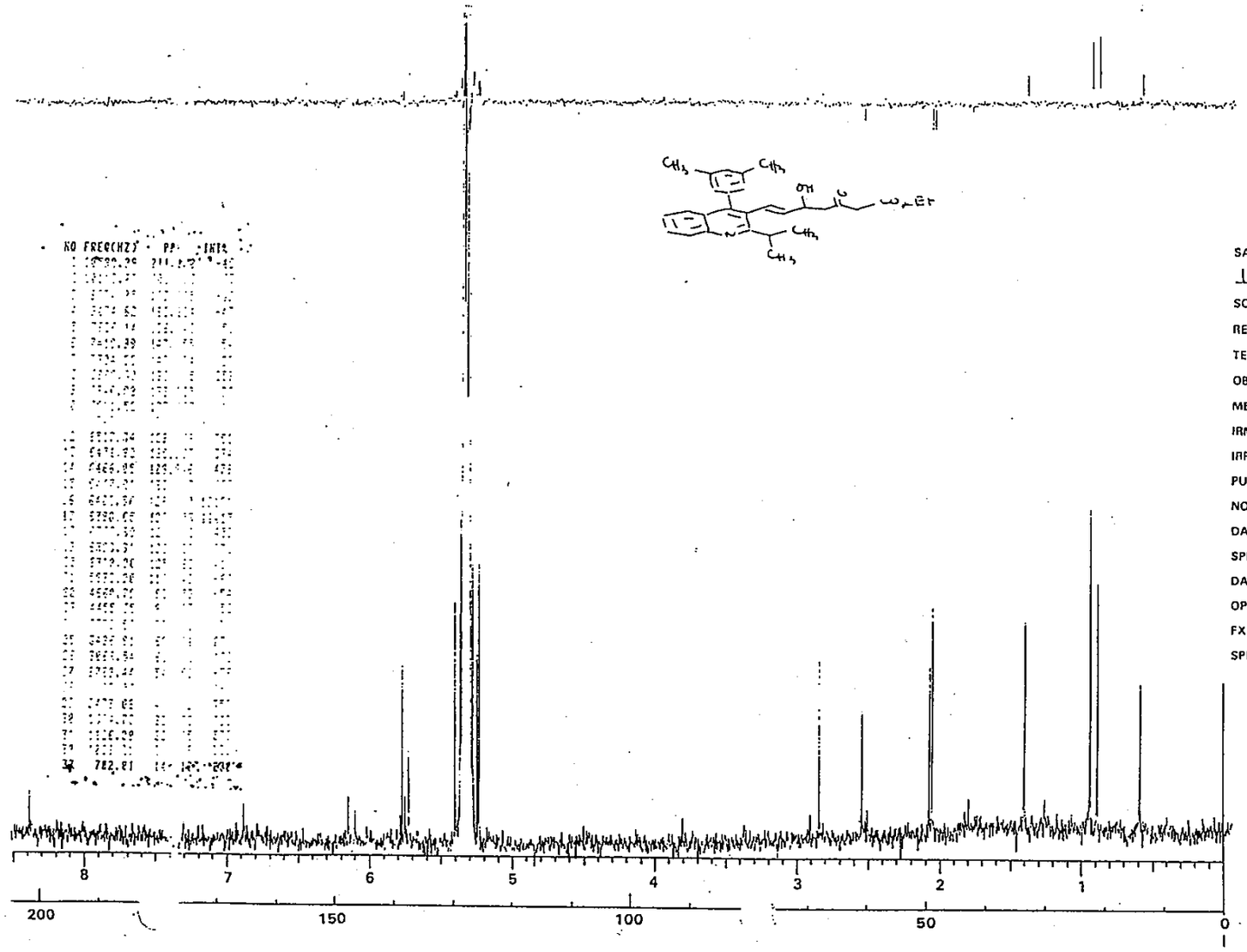
DATE 12 Nov 84

OPERATOR Karl G.

FX 200

SPECTRUM NO. 7784-K

152



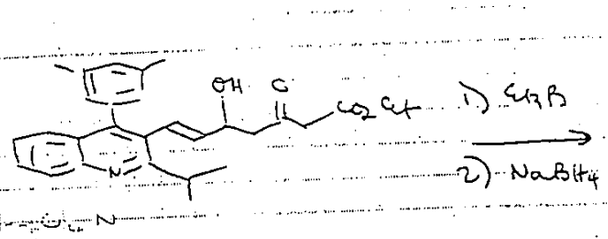
153

Title-

106

Date 11/12/94. Proj.

Cont'd From- 154

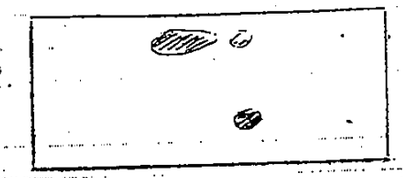


(479) 1079-105-35 = 15 mg (0.0001198 mol)
1 M Et_2B in THF = 0.15 (0.0001437 mol)
THF = 2 ml.

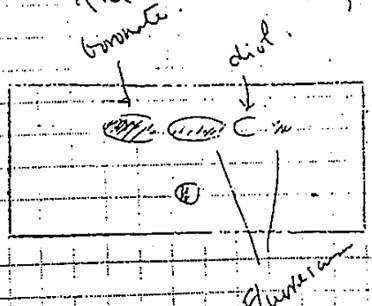
To a soln of (1079-105-35) in THF (2 ml) at r.t. was added 1 M Et_2B & (1 ml) of air by syringe. The soln was stirred for 15h.
9.00 am.
10.30 am. At -78°, $NaBH_4$ (10 mg) was added.

11/13/94. 8.30 am ⇒ TLC ⇒ still showed spot of S.M. 15 mg more of $NaBH_4$ was added & continued stirring.

TLC 3.00 pm ⇒ Spot of the product increased, but still some S.M.



The reaction was worked from dry in into acidified 3N HCl was added until acidic (pH ~ check), diluted with H2O (during this period reaction mix. turned to fluorescence?, dehydration ??).



The crude product (150 mg) was used directly in the next step (1079-106-36).

Performed by- S. Wattanasin

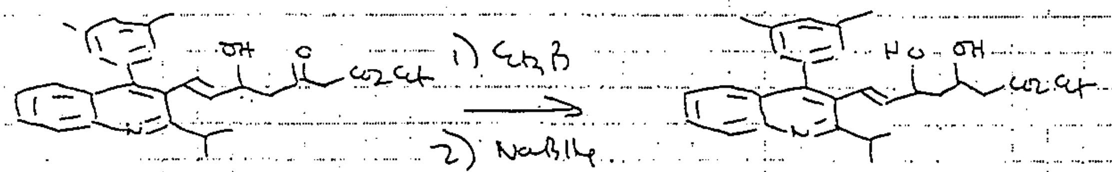
Witness- M. Radcliffe

Cont'd to-

Title-

Date 11/14/84 Proj.

Cont'd From- 155



avoid HCl treatment!

1079-105-35 = 52 mg
1M Et3B = 0.2 ml.
THF = 2 ml.
NaBH4 = 20 mg.

1) 2:30 pm:

2) 3:30, -78 C

11/15/84: The reaction mixt, almost colorless, was diluted with 4 ml CH3OH, after the cool bath was removed. After 10 min.* 1 ml H2O + a few drops of H2O2, was added. After the evolution of H2 subsided. The reaction mixt. was concentrated H2O was added & extracted with ether.
* slightly fluorescent color occurred.

see TLC p. 109 ⇒ mixture of boronate + diol ?

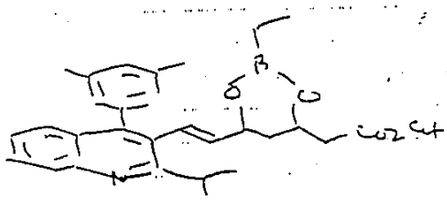
⇒ pale yellow & some fluorescent oil = 40 mg (1079-110-33) which was used directly in the next step.

Performed by- S. Watanabe

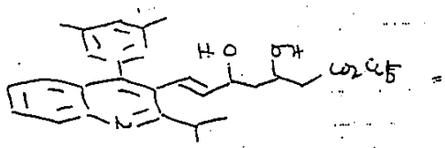
Witness- N. Paolella

Cont'd to-

156



CH_3OH ⟶



$C_{29}H_{35}O_4N$ FW

1079-110-33 = 40 mg

CH_3OH = 4 ml.

The soln was stirred at r.t. for 2 days.

~~9.30 am~~

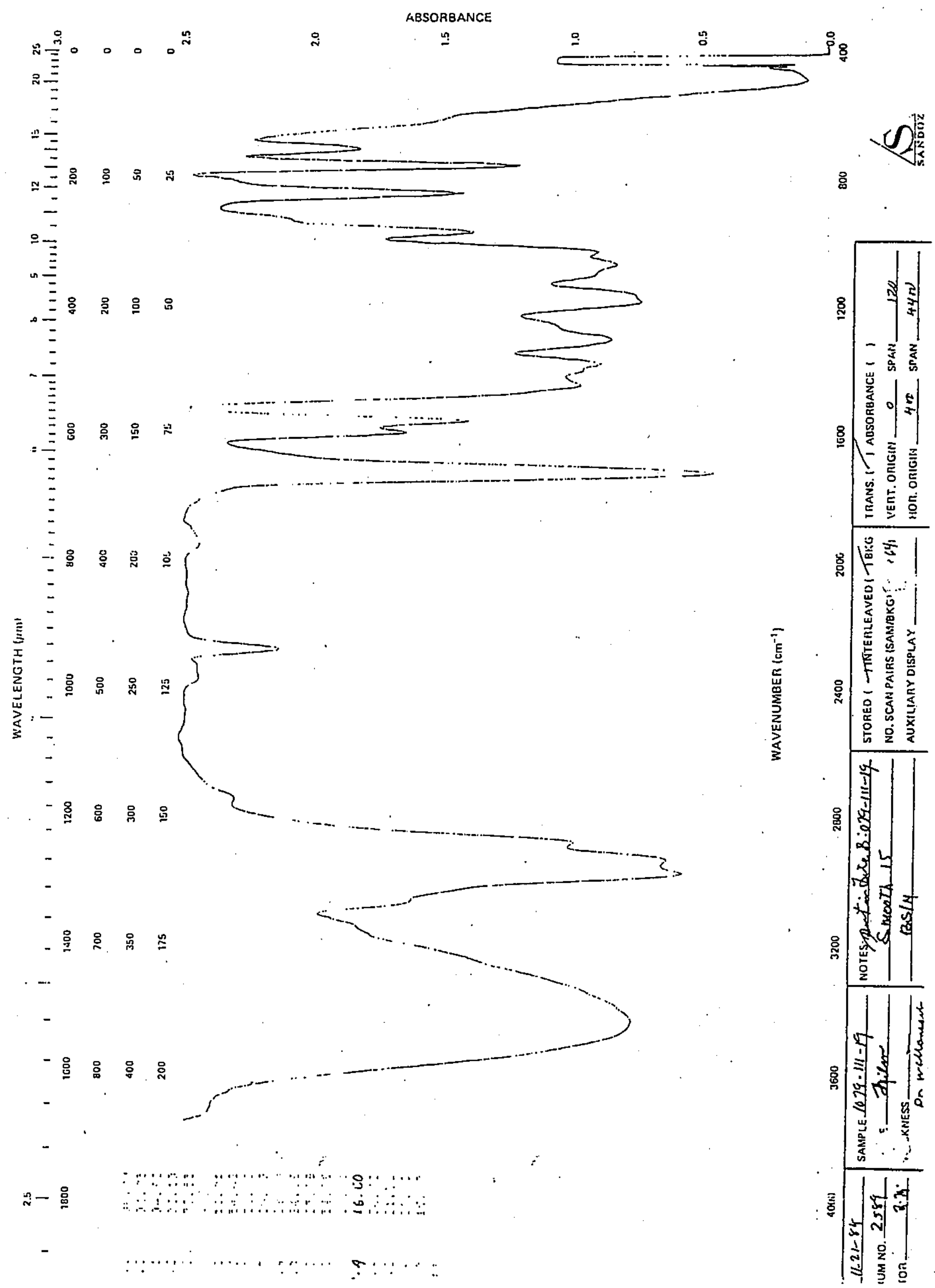
TLC ⇒ showed one main spt (1:1 ether-petrol).

Prep TLC ⇒ (1079-111-19) pale yellow oil = 25.6 mg

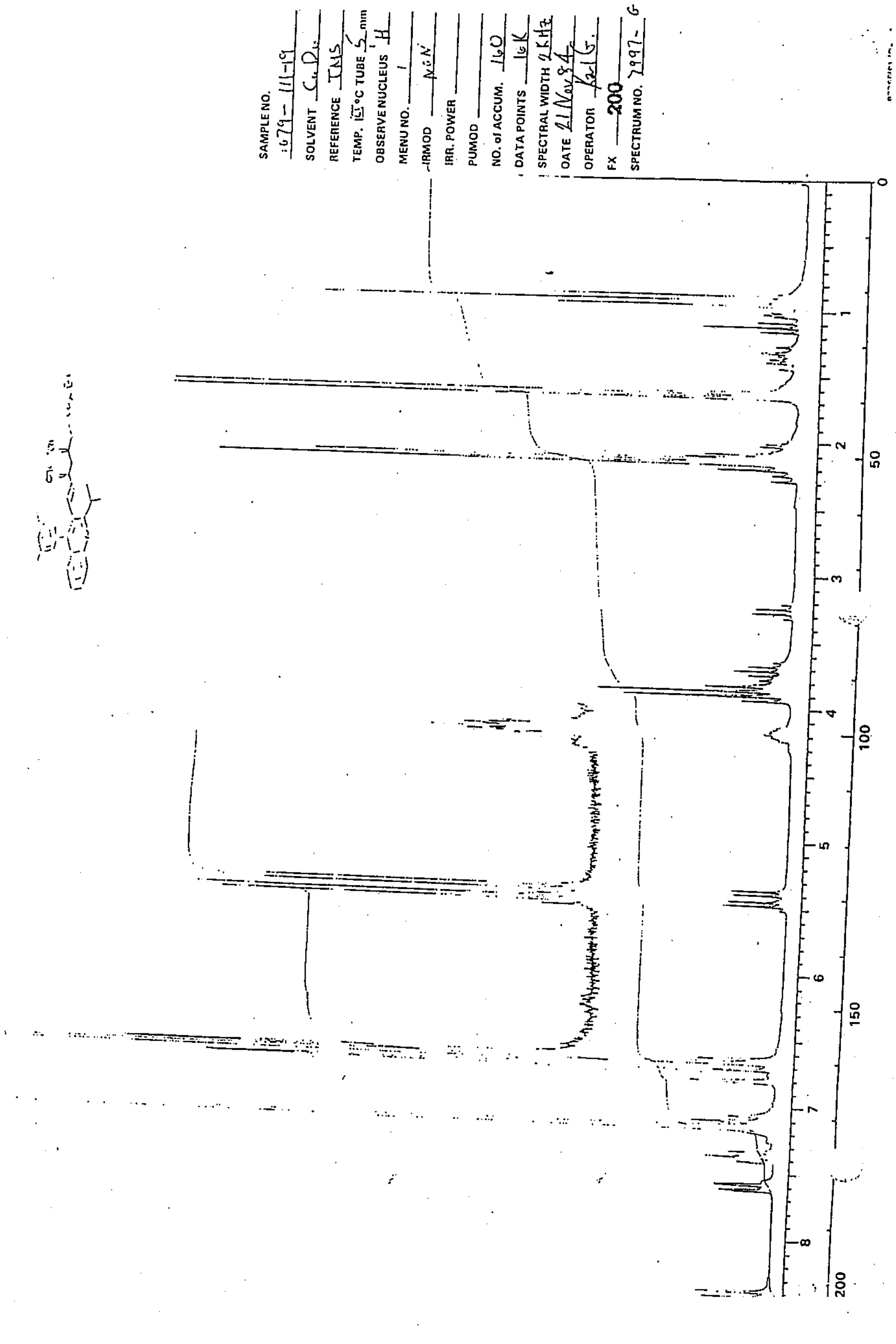
nmr 10 mg.

11/16/84. T. Scallen 14.5 mg.

157


ABSORBANCE
WAVELENGTH (μm)
WAVENUMBER (cm⁻¹)
SANDOZ
SAMPLE
NOTES
STORED
INTERLEAVED
BKG
NO. SCAN PAIRS (SAM/BKG)
AUXILIARY DISPLAY
TRANS.
ABSORBANCE
VERT. ORIGIN
HOR. ORIGIN
SPAN

158



SAMPLE NO.
SOLVENT
REFERENCE
TEMP. °C TUBE mm
OBSERVE NUCLEUS
MENU NO.
IRMOD
IRR. POWER
PUMOD
NO. of ACCUM.
DATA POINTS
SPECTRAL WIDTH
DATE
OPERATOR
FX 200
SPECTRUM NO.
0
1
2
50
3
4
100
5
6
150
7
8
200

Date 5/2/98 Proj.

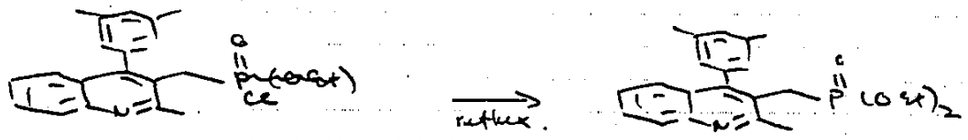
Cont'd From-

Title

5

159 -

cf. P. 1079-86.



397.458
$C_{23}H_{28}NO_3P$.

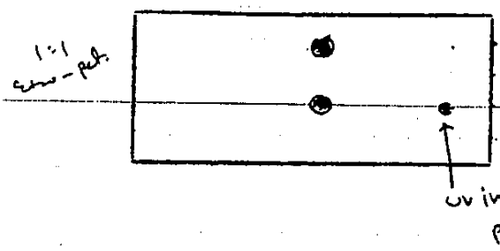
(295) 1079-296-35 = 150 mg
$P(OEt)_3$ = 0.3 ml.
Toluene = 2 ml.

9.10 am:

TLC 11.20 am: => SM.

0.5 ml of $P(OEt)_3$ was added

prolonged heating refluxing at 110° for 20h
=> complete reaction



Concentration by distill & in vacuo gave an oil which solidified on standing 160 mg (127-1-23)
mp 105-107 (almost colorless solid)

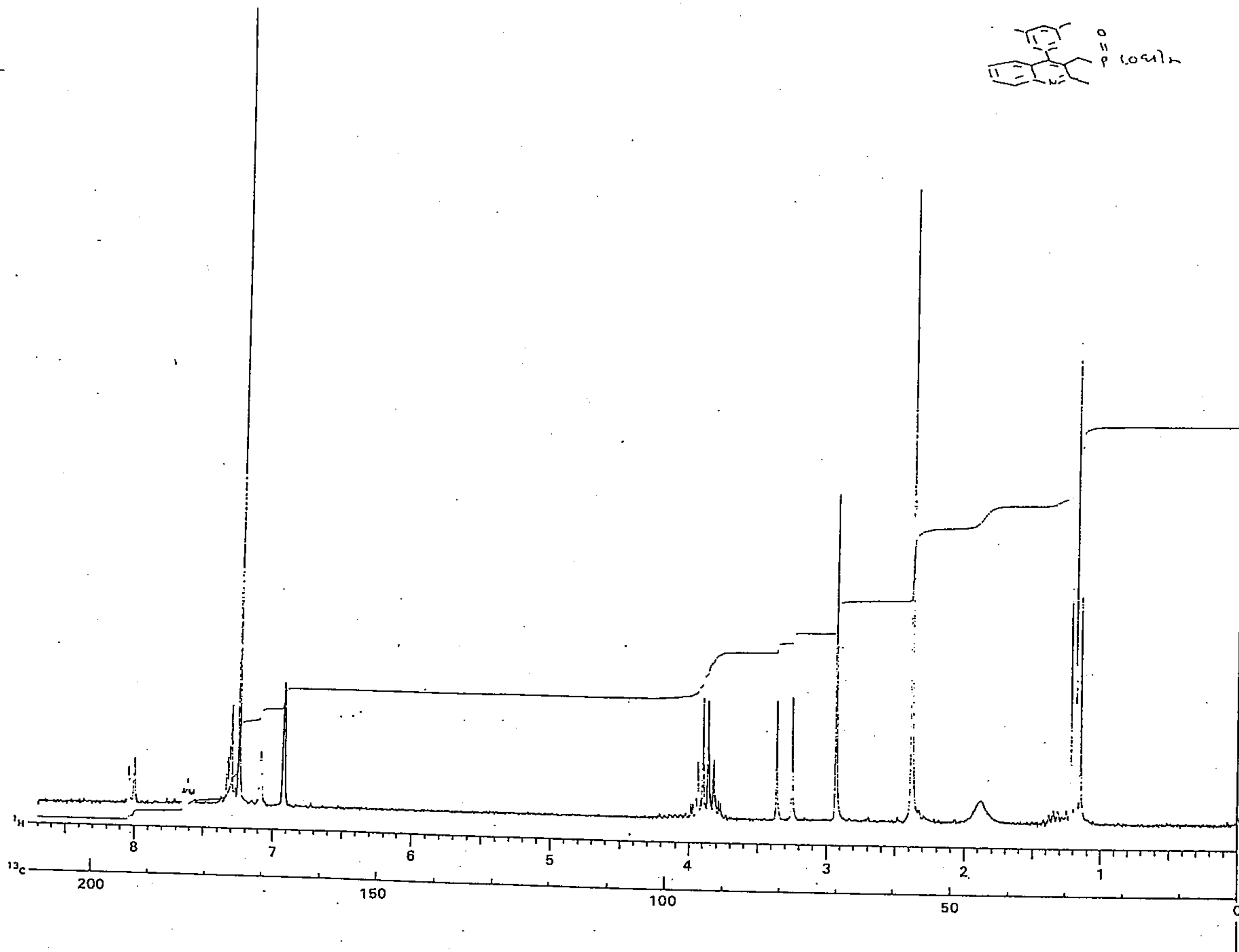
micro ✓ OH · HMR ✓ : desired p.
MS MP 397 ✓

WATTANASIN EXHIBIT
B-2
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

Performed by- S. Wattanasin

Witness- Robert W. Rickards 12/12/89

Con'd to-

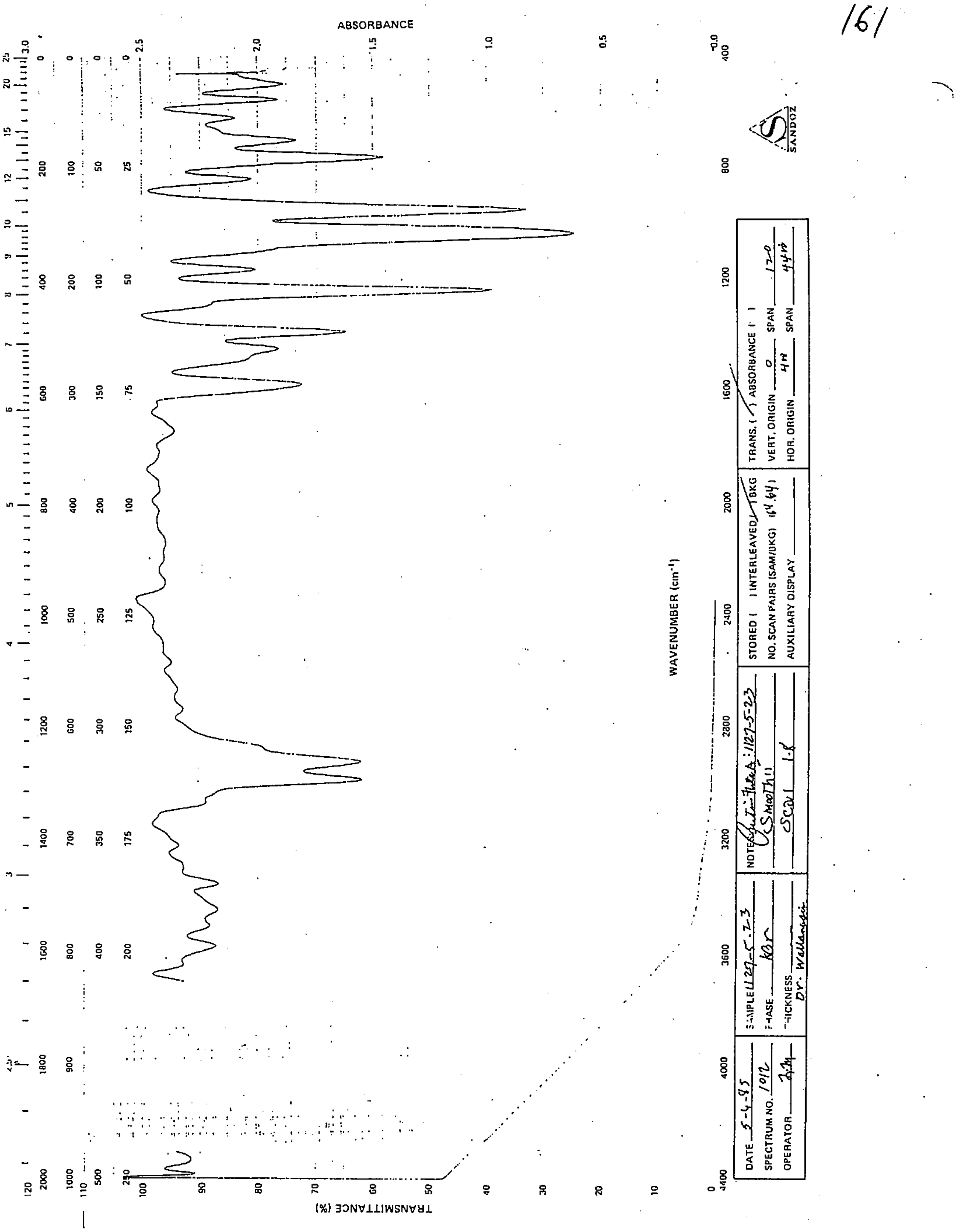


SAMPLE NO. 1127-5-23
SOLVENT CDCl3
REFERENCE TMS
TEMP. RT °C TUBE 5 mm
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOD NON
IRR. POWER
PUMOD
NO. of ACCUM. 120
DATA POINTS 16K
SPECTRAL WIDTH 2KHz
DATE 7 May 85
OPERATOR
FX 200
SPECTRUM NO. 2517-B

87356/81 (Rev. 1)

160

161

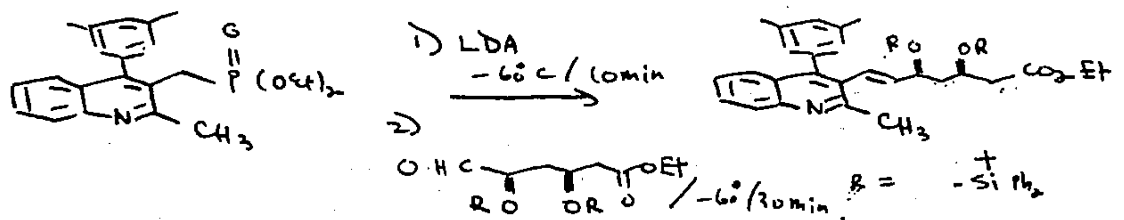

ABSORBANCE
TRANSMITTANCE (%)
WAVENUMBER (cm⁻¹)
SANDOZ
DATE 5-4-95
SPECTRUM NO. 1012
OPERATOR
SAMPLE 1127-5-23
PHASE KBr
THICKNESS
NOTES
STORED ( ) INTERLEAVED ( ) BKG
NO. SCAN PAIRS (SAM/BKG)
AUXILIARY DISPLAY
TRANS. ( ) ABSORBANCE ( )
VERT. ORIGIN
HOR. ORIGIN
SPAN

[redacted]

Date 5/6/88 Proj.

Title-

Cont'd From-

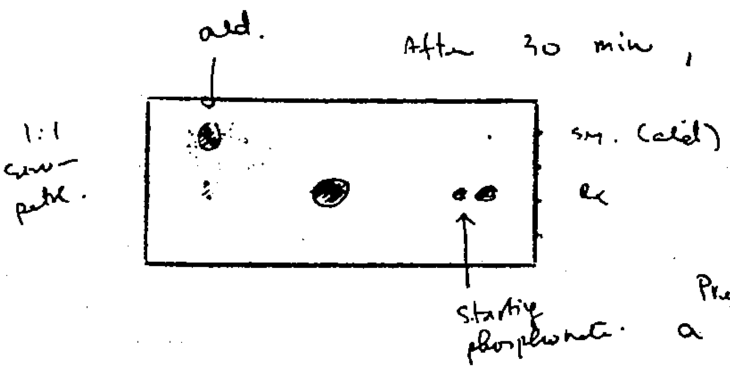


(397)	1127-5-23	=	150 mg	(0.0003778 mol)
647	Pracad ald.	=	293 mg	(0.0004534 mol)
1.7 M	LDA	=	0.27 ml.	1.2 eq.
	THF	=	3 ml.	

To a solution of 1127-5-23 in THF (3 ml) at -55°C was added LDA. The resulting dark orange sol^n was then stirred at -55° → -60°C for 10 min.
9.50 am - 10.00 am.

Then a sol^n of aldehyde in THF (2 ml) was added.
TLC after 20 min. ⟹ mainly one product

After 30 min, the reaction was quenched at -60°C with 0.5 ml HOAc. Then dil. HCl & then was added and extracted with EtOAc. to give a yellow oil = 500 mg (1127-9-30)



Prep TLC (1:1 ether-petrol) gave a yellow oil = 100 mg (1127-9-33)

nmr ✓

Performed by- S. Watanabe.

Witness- [signature] 12/12/89

Cont'd to-

SAMPLE NO. 1127-33
SOLVENT CDCl3
REFERENCE TMS
TEMP. RT °C TUBE 5
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOD NON
IRR. POWER
PUMOD
NO. of ACCUM. 160
DATA POINTS 16K
SPECTRAL WIDTH 2511
DATE 7 May 85
OPERATOR
FX
SPECTRUM NO. 2538
163
0
1
2
3
4
5
6
7
8
50
100
150
200
1H
13C

Title- Book # 1127

Date 5/7/85 Proj.

Cont'd From-

cf. 1079-97

SiR₃ : Si(Ph)(Ph)+

433 ✓
$C_{27}H_{31}O_4N$

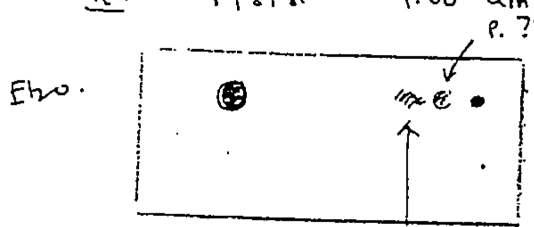
(559)

	1127-9-33	=	90 mg	(0.0001012 mol)
1M	Bu_4NF	=	0.61 ml.	(0.000607 mol) 10
60.04 ; 1.09	HOAc	=	0.03 ml.	(0.0005 mol) 5
	THF	=	2 ml.	

The mixt. was stirred at r.t.

9.00 am: | - Bu_4NF 0.6 | - " - 0.6 | - HOAc 0.05 ml |

TLC 5/8/85 9.00 am.



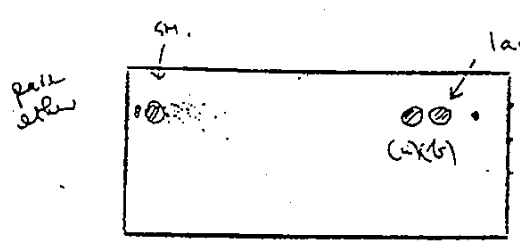
TLC 5/13/85 : 8.30 am ⇒ a mixt of SM + P(s)

The soln was heated at 50°

9.00 am:

TLC 11.00 pm : mixt. of 2 spots.

stop 5.30 pm



Concentrated & the crude oil was purified by prep TLC (ether & EtOAc)

(a) : colorless oil = 10 mg (1127-11-34)

nmr MS ✓ M⁺ 433 ✓

(b) : oil = 10 mg (1127-11-37)

nmr MS ✓ M⁺ 387 ✓
$C_{25}H_{25}O_3N$

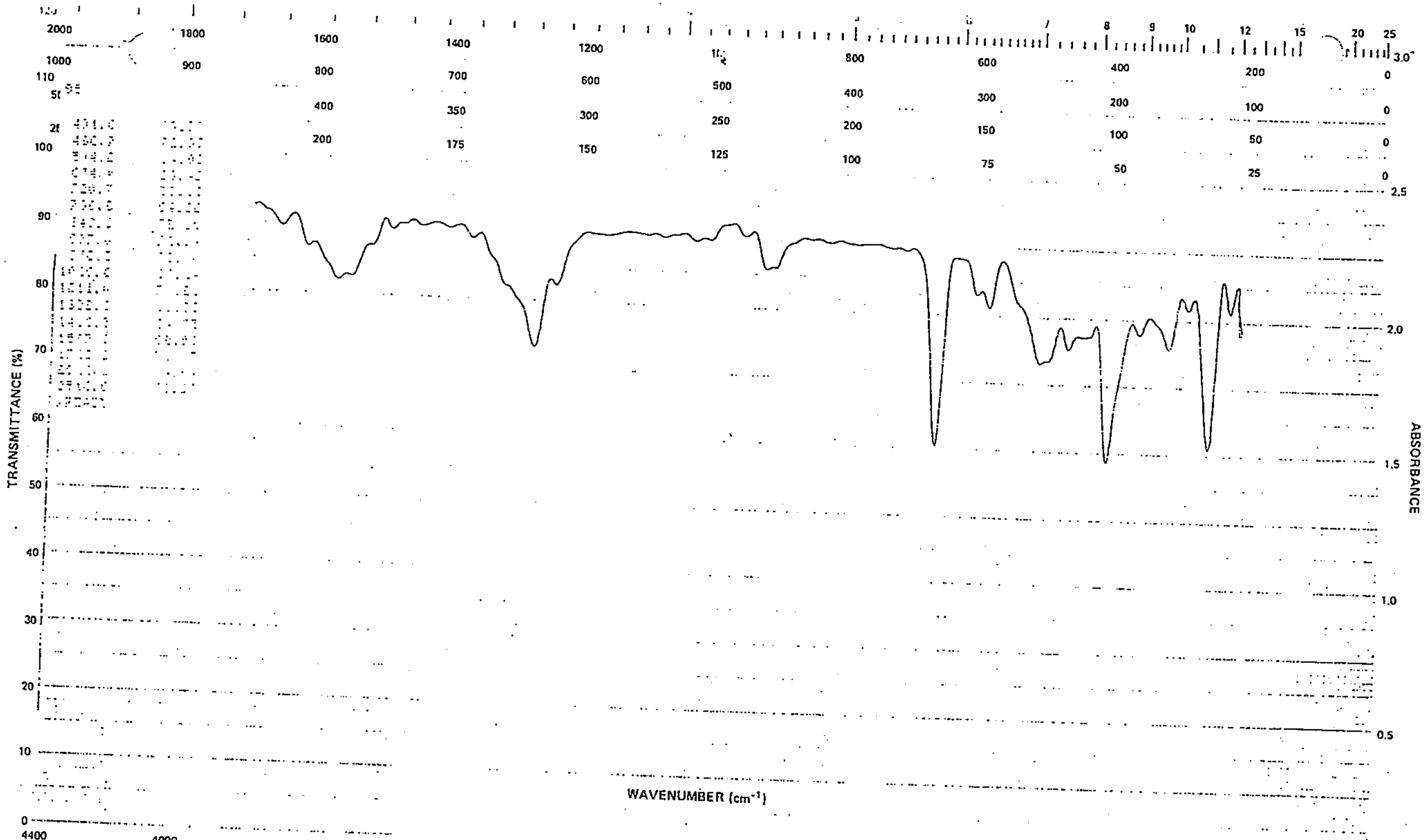
5/17/85. 1127-11-34 { 2 mg CSI / 4.8 mg CSTU, CSTC

1127-11-37 { 2 mg CSI

Performed by- S. Watanabe

Witness-

Cont'd to-



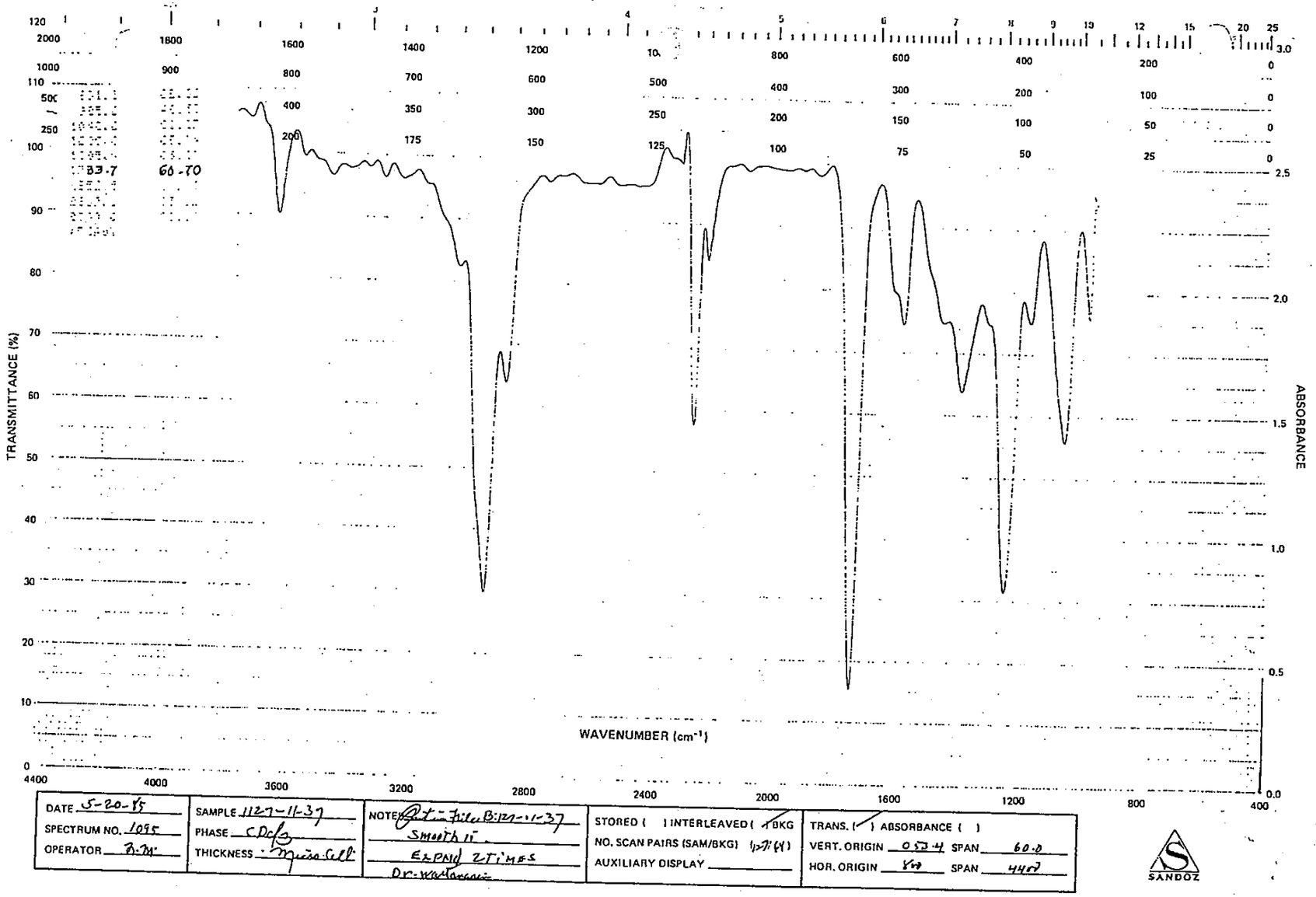
DATE 5-17-85	SAMPLE 1127-11-34	NOTE Pt. file B: 127-11-34	STORED ( ) INTERLEAVED (BKG)	TRANS. (✓) ABSORBANCE ( )
SPECTRUM NO. 1094	PHASE CDcl3	Scal 1.8	NO. SCAN PAIRS (SAM/BKG)	VERT. ORIGIN 0 SPAN
OPERATOR	THICKNESS Micro cell Dr. Wallenius	Evaporated Sample down	AUXILIARY DISPLAY	HOR. ORIGIN SPAN

SANDOZ

165

SAMPLE NO. 127-11-34
SOLVENT CDCl3
REFERENCE TMS
TEMP. RT °C TUBE 5 mm
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOD NOM
IRR. POWER
PUMOD
NO. of ACCUM. 640
DATA POINTS 16K
SPECTRAL WIDTH 2KHz
DATE 15 Mar 85
OPERATOR Karl G
FX
SPECTRUM NO. 2683-G
8735/81 (Rev. 11)
H2O
OEt
1H
13C

166



167

SAMPLE NO. -1127-11-37
SOLVENT CDCl3
REFERENCE TMS
TEMP. RT °C TUBE 5 mm
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOD NON
IRR. POWER
PUMOD 296
NO. of ACCUM. 16
DATA POINTS 16K
SPECTRAL WIDTH 2KHz
DATE 15 May 85
OPERATOR RAC
FX 300
SPECTRUM NO. 26866
8735/81 (Rev. 1)
Bn
O
O
N
1H
13C
0
1
2
3
4
5
6
7
8
50
100
150
200

168

circle 169

IR UV-Vis OR NMR90 200 500 Micro Misc Request Sheet

solvent or medium | empirical formula | mp. ____ °C bp

do not fill in

sample # book page line

IW-AW-KP ☐ pure ☐ crude

unit head requestor

bldg. lab. ext.

date submitted

sensitivities: hazards:

☐ routine ☐ ^{1}H ☐ ^{13}C ☐ ^{31}P

☐ expand spectral region from to

☐ assign for ☐ ^{1}H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level) %

SAMPLE WEIGHT

Required for 200 or 500 mHz

synthetic pathway:
reagents solvents
esp. last solvent:

suspected structures in order of prob:

models available

data available	IR	UV	H nmr	micro	MS			count

fill in # & circle requested elements

formula	C	H	N	O				
calc.								
found								

mol. wt. req. ____ ____

drying done ____ °C ____ hrs.

90	^{1}H		
200	^{13}C		
500	^{31}P		
COM DEC	NON		
DEPT	HOM DEC		
SEL DEC	DIF NOE		
NOE	D_2O EX		
COSY	SOLV SUPP		
CH	LSR		
RELA	T_1		
	VT		
MQ	SPIN SIM		
NOSY			
	STRUCT		

87147/81 (Rev. 3)

IR UV-Vis OR NMR60 90 200 Micro Misc Request Sheet (circle) 170

KBr | | | | $CDCl_3$ | empirical formula | mp. °C

solvent or medium | bp

sample # book page line: 1049-237-22 | W-AW-KP ☐ pure ☒ crude | unit head | requestor

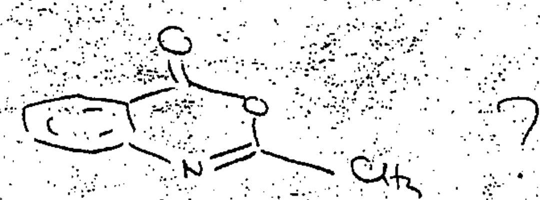
bldg. | lab | ext.

date submitted

sensitivities: | hazards: H, 13C, 13C, CH3 | do not fill in: 1377

nature of request: problem statement or specific instructions:

synthetic pathway: reagents, solvents esp. last solvent:



suspected structures in order of prob.:

models available

T1	13C
VT	1H
NON	other
COM	LSR
OFR	DT
NOE	DP
NNE	60
SEL	90
HOM	200
HMG	D_2O

count

other measurements	IR	UV	H nmr	micro	MS		

fill in # & circle requested elements

formula C H N O

mol. wt.

drying req. done °C hrs.

calc.								
found								

misc. & comments:

samp

87147/81

WATTANASIN EXHIBIT
C-2
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

IR UV-Vis OR NMR60 90 200 Micro Misc Request Sheet 171

Film KBr					empirical formula	mp °C
solvent or medium						bp

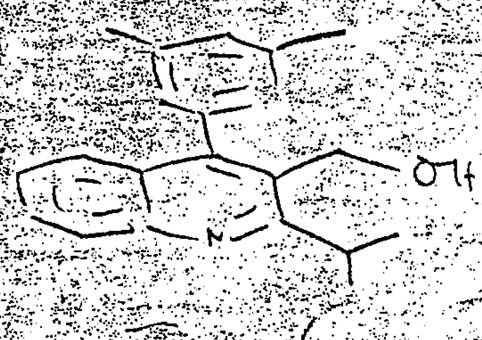
sample # book page line	IW-AW-KP ☐ pure ☐ crude	unit head	requestor
1079-22-28		bldg. 404 date submitted	lab. 36 ext.

sensitivities: hazards:

do not fill in

2009

nature of request:
problem statement or
specific instructions:



synthetic pathway:
reagents, solvents
esp. last solvent:

suspected structures
in order of prob.:

models available

T1	13C
VT	1H
NON	other
COM	LSR
OFR	DT
NOE	DP
NNE	60
SEL	90
HOM	200
HMG	D_2O

other measurements	IR	UV	H nmr	micro	MS	count

fill in # & circle requested elements

formula C H N O

mol. wt.

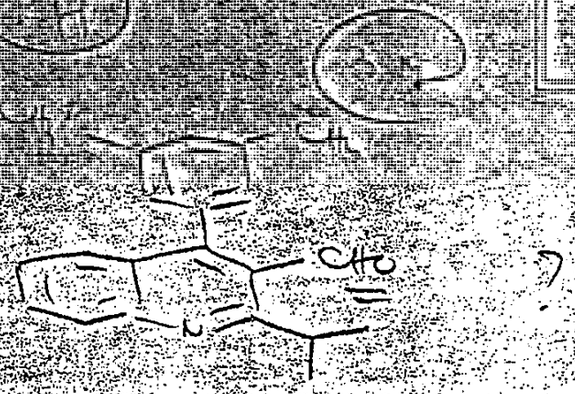
drying req. done °C hrs.

calc.

misc. & comments:

Sawai Ex 1005
Page 3114 of 4322

IR UV-Vis OR NMR60 90 200 Micro Misc Request Sheet 12



synthetic pathway:
reagents, solvents
esp. last solvent

suspected structures
in order of prob.

models available

NON other
COM LSR
OFR DT
NOE DP
NNE 60
SEL 90
HOM 200
HMG D_2O

other measurements IR UV H nmr micro MS

count

fill in # & circle requested elements

mol. wt.

formula C H N O

drying req. °C hrs
done

calc.

misc. & comments:

IR UV-Vis OR NMR60 90 200 Micro Misc Request Sheet 173

empirical formula

m.p. °C

b.p.

solvent or medium C_6D_6

notebook page line 10797-105-35

requestor S Watanabe

pure crude

lab. 365

ext. 8404

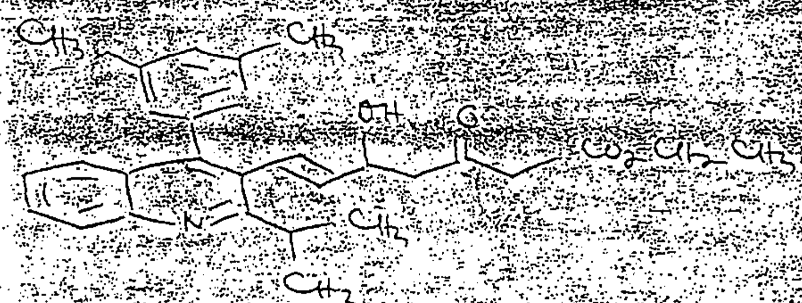
date submitted

do not fill in

2374

problem statement or specific instructions:

synthetic pathway: reagents, solvents esp. last solvent:



suspected structures in order of prob.

— Sample in the fridge

models available

T_1	^{13}C
VT	^1H
NON	^{31}P
COM	LSR
OFR	DEPT
NOE	COSY
NNE	60
SEL	90
HOM	200
HMG	D_2O
DIF. NOE	CH

other measurements | IR | UV | H nmr | micro | MS

count

fill in # & circle requested elements

formula C H N O

calc.

mol. wt.

drying req. done °C hrs.

misc. & comments

circle requests

IR | UV-Vis | OR | NMR60 | 90 | 200 | Micro | Misc | Request Sheet

mp. 174

F. lm — solvent or medium: C_6D_6

empirical formula

bp

sample # book page line: 1079-111-19

IW-AW-KP ☑ pure ☐ crude

unit head

requestor: S. Wadham

bldg. lab. ext. 8406

date submitted

do not fill in

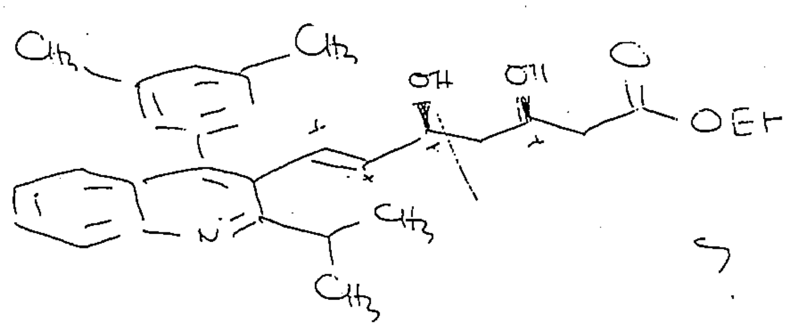
2589 2.74

sensitivities:

hazards:

nature of request: problem statement or specific instructions: (H) (8 mg)

synthetic pathway: reagents, solvents esp. last solvent:



suspected structures in order of prob.:

— Sample in the fridge.

models available

— expand vinylic protons & methide protons.

T1	13C
VT	1H
NON	31P
COM	LSR
OFR	DEPT
NOE	COSY
NNE	60
SEL	90
HOM	200
HMG	D_2O
DIF NOE	CH

other measurements	IR	UV	H nmr	micro	MS		count

fill in # & circle requested elements

formula C H N O

calc.							
found							

mol. wt.

drying req. ___ °C ___ hrs. done ___

misc. & comments:

sample # book #

87147/81 (Rev. 1)

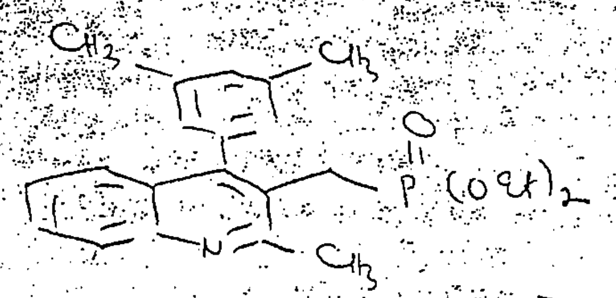
IR / UV-Vis OR NMR60 90 200 Micro Misc **Request Sheet** circle requests

CH (IR, circled) … $CDCl_3$ (200, circled) — solvent or medium	empirical formula	mp. 175 °C; bp
sample # book page line: 1127-5-23 — IW-AW-KP ☐ pure ☐ crude	unit head; bldg.; lab. 365; date submitted	requestor: S. Watanabe; ext. 8406

sensitivities: hazards: H (circled)

do not fill in: 1012 3.3

nature of request: problem statement or specific instructions: 3 mg (circled)



77

synthetic pathway: reagents, solvents esp. last solvent:

suspected structures in order of prob.:

models available

T_1	^{13}C
VT	^1H
NON	^{31}P
COM	LSR
OFR	DEPT
NOE	COSY
NNE	60
SEL	90
HOM	200
HMG	D_2O
DIF. NOE	CH

other measurements | IR | UV | H nmr | micro | MS | count

fill in # & circle requested elements

formula C H N O

mol. wt.

drying req. done °C hrs

calc.

misc. & comments:

IR UV-Vis OR NMR60 90 200 Micro Misc — Request Shee 176

~~Film~~ $CDCl_3$ — solvent or medium

empirical formula

mp. °C

bp

sample # book page line: 1127-11-34,

IW-AW-KP ☒ pure ☐ crude

unit head

requestor S. Wattanasin

bldg. lab. 365 ext. 8404

date submitted

sensitivities:

hazards:

do not fill in 1094

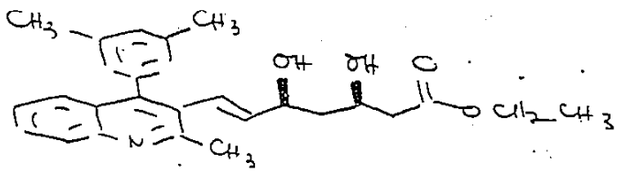
nature of request: problem statement or specific instructions:

^1H

1 mg

sample from NMR in $CDCl_3$

synthetic pathway: reagents, solvents esp. last solvent:



suspected structures in order of prob.:

- Sample in the fridge.
- Sample for testing
- please get a good S/N

models available

T_1	^{13}C						
VT	^1H						
NON	^{31}P						
COM	LSR						
OFR	DEPT						
NOE	COSY						
NNE	60						
SEL	90						
HOM	200						
HMG	D_2O						
DIF NOE	CH						

other measurements	IR	UV	H nmr	micro	MS			count

fill in # & circle requested elements

formula C H N O

calc.								
found								

mol. wt.

drying req. °C hrs. done

misc. & comments:

sample # book #

87147/81 (Rev. 1)

IR UV-Vis OR NMR60 90 200 Micro Misc **Request Sheet** circle requests

						empirical formula	mp. 177 °C
CDCl3					CDCl3 - filtered		bp

solvent or medium

sample # book page line	IW-AW-KP ☐ pure ☐ crude	unit head	requestor S. Watanasin
1127-11-37		bldg. lab. 361	ext. 8404
		date submitted	

sensitivities: 1127-11-37

hazards:

do not fill in

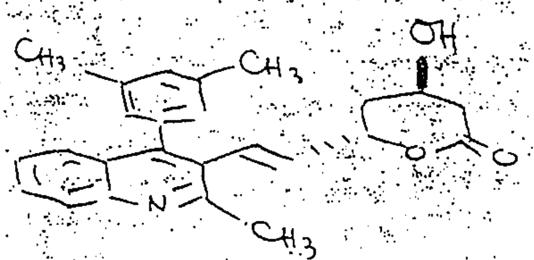
1095 J.M.

nature of request: problem statement or specific instructions:

H → 1 mg

Sample from NMR

synthetic pathway: reagents, solvents esp. last solvent:



7.7

suspected structures in order of prob.:

- Sample in the fridge
- Testing sample, please get a good S/N

models available

T1	13C
VT	1H
NON	31P
COM	LSR
OFR	DEPT
NOE	COSY
NNE	60
SEL	90
HOM	200
HMG	D_2O
DIF NOE	CH

other measurements | IR | UV | H nmr | micro | MS | count

fill in # & circle requested elements

formula C H N O

calc.								
found								

mol. wt.

drying req. done °C hrs.

misc. & comments:

sample # book #

87147/81 (Rev. 1)

IR UV-Vis OR NMR90 200 500 Micro Misc **Request Sheet** circle 178

thin film | CDCl3 | solvent or medium

empirical formula

mp. °C

bp

sample # book page line 206-130-27

IW-AW-KP

☐ pure ☒ crude

unit head S. Watt requestor R. Patel

bldg. lab. ext. 8578

date submitted 6-5-87

sensitivities: hazards:

SAMPLE WEIGHT

Required for 200 or 500 mHz

do not fill in

899 d.M.

☒ routine ☒ ^1H ☐ ^{13}C ☐ ^{31}P

☐ expand spectral region from to

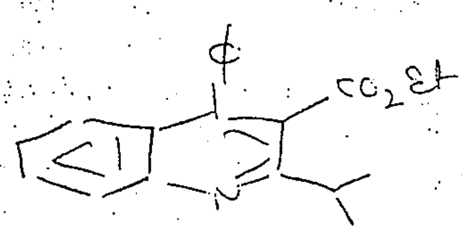
☐ assign for ☐ ^1H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level) %

90	^1H
200	^{13}C
500	^{31}P
COM DEC	NON
DEPT	HOM DEC
SEL DEC	DIF NOE
NOE	D_2O EX
COSY	SOLV SUPP
CH	LSR
RELA	T_1
	VT
MQ	SPIN SIM
NOSY	
	STRUCT
count	

synthetic pathway: reagents, solvents esp. last solvent:



suspected structures in order of prob.:

models available

data available	IR	UV	H nmr	micro	MS		

fill in # & circle requested elements

formula C H N O

calc.								
found								

mol. wt.

drying req. done °C hrs.

misc. & comments:

sample # book #

87147/81 (Rev. 2)

Put in file B 206-137-31

IR UV-Vis OR NMR90 200 500 Micro Misc **Request Sheet** 179

circle requests

film / film | CDCl3 | solvent or medium

empirical formula | mp. °C | bp

sample # book page line: 1206-137-31

IW-AW-KP ☐ pure ☒ crude

unit head S. Watts requestor R. Patel

bldg. lab. 358 ext.

date submitted 6-11-87

sensitivities: hazards:

SAMPLE WEIGHT

Required for 200 or 500 mHz

do not fill in

922

☐ routine ☒ ^{1}H ☐ ^{13}C ☐ ^{31}P

☐ expand spectral region from to

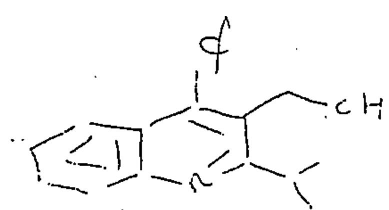
☐ assign for ☐ ^{1}H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level) %

90	^{1}H
200	^{13}C
500	^{31}P
COM DEC	NON
DEPT	HOM DEC
SEL DEC	DIF NOE
NOE	D_2O EX
COSY	SOLV SUPP
CH	LSR
RELA	T_1
	VT
MQ	SPIN SIM
NOSY	
	STRUCT
	count

synthetic pathway: reagents, solvents esp. last solvent:



suspected structures in order of prob.:

models available

data available	IR	UV	H nmr	micro	MS		

fill in # & circle requested elements

formula C H N O

mol. wt.

drying req. done °C hrs.

calc.								
found								

misc. & comments:

sample # book #

87.147/81 (Rev. 2)

...requests

IR UV-Vis OR NMR90 200 500 Micro Misc Request SI - 180

pellet / $CDCl_3$ solvent or medium	empirical formula	mp. °C bp
sample # book page line 1-CC-168-34 1206	IW-AW-KP ☒ pure ☐ crude	unit head ... requestor ... bldg. lab. 3 3 2 ext. date submitted 7-2?-87
sensitivities:	hazards:	SAMPLE WEIGHT 5mg Required for 200 or 500 mHz

do not fill in

-1007 ...

☒ routine ☒ ^{1}H ☐ ^{13}C ☐ ^{31}P

☐ expand spectral region from to

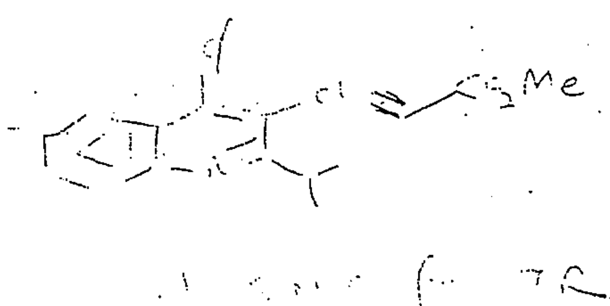
☐ assign for ☐ ^{1}H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level) %

90	^{1}H
200	^{13}C
500	^{31}P
COM DEC	NON
DEPT	HOM DEC
SEL DEC	DIF NOE
NOE	D_2O EX
COSY	SOLV SUPP
CH	LSR
RELA	T_1
	VT
MQ	SPIN SIM
NOSY	
	STRUCT
	count

synthetic pathway:
reagents, solvents
esp. last solvent:



suspected structures
in order of prob.:

models available

0615331

Save - d, a: 0615331

data available	IR	UV	H nmr	micro	MS		

fill in # & circle requested elements

formula C H N O

calc.								
found								

mol. wt.

drying req. done °C hrs.

misc. & comments:

sample # book #

7/47/81 (Rev. 2)

IR UV-Vis OR NMR90 200 500 Micro Misc **Request Sheet** 181

CDCl3 thin film — solvent or medium

empirical formula

mp. °C

bp

sample # book page line 1206-158-41

IW-AW-KP ☐ pure ☑ crude

unit head S. Watt requestor R. Patel

bldg. 464 lab. 358 ext.

date submitted 7.09.87

sensitivities: hazards:

SAMPLE WEIGHT

Required for 200 or 500 mHz

do not fill in

1037 poo

☐ routine ☐ ^{1}H ☐ ^{13}C ☐ ^{31}P

☐ expand spectral region from to

☐ assign for ☐ ^{1}H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level)

%

synthetic pathway:
reagents, solvents
esp. last solvent:

suspected structures in order of prob.:

models available

Save_d,a: 61541

90	^{1}H							
200	^{13}C							
500	^{31}P							
COM DEC	NON							
DEPT	HOM DEC							
SEL DEC	DIF NOE							
NOE	D_2O EX							
COSY	SOLV SUPP							
CH	LSR							
RELA	T_1							
	VT							
MQ	SPIN SIM							
NOSY								
	STRUCT							

data available	IR	UV	H nmr	micro	MS			count

fill in # & circle requested elements

formula C H N O

calc.								
found								

mol. wt.

drying req. °C hrs. done

misc. & comments:

sample # book #

87147/81 (Rev. 2)

IR UV-Vis OR NMR90 200 500 Micro Misc Request Sheet 182

thin film | CD2Cl2 | CDCl3 — solvent or medium

empirical formula

mp. °C

bp

sample # book page line: N206186-30

IW-AW-KP

☒ pure ☐ crude

unit head S. L. Hansen requestor R. Patel

bldg. 404 lab. 35 ext.

date submitted 7-28-89

sensitivities: hazards:

SAMPLE WEIGHT

Required for 200 or 500 mHz

do not fill in

1084 2Hz

☐ routine ☐ ^{1}H ☐ ^{13}C ☐ ^{31}P

☐ expand spectral region from to

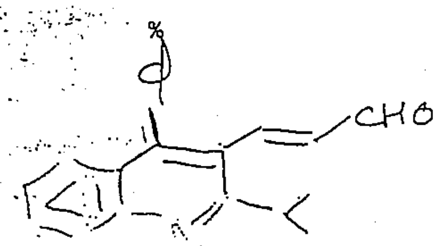
☐ assign for ☐ ^{1}H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level) %

90	^{1}H
200	^{13}C
500	^{31}P
COM DEC	NON
DEPT	HOM DEC
SEL DEC	DIF NOE
NOE	D_2O EX
COSY	SOLV SUPP
CH	LSR
RELA	T_1
	VT
MQ	SPIN SIM
NOSY	
	STRUCT
	count

synthetic pathway:
reagents, solvents
esp. last solvent:



suspected structures
in order of prob.:

models available

Save - d, a; 616630

data available	IR	UV	H nmr	micro	MS		

fill in # & circle requested elements

formula C H N O

calc.								
found								

mol. wt.

drying req. done °C hrs.

misc. & comments:

sample # book #

87147/81 (Rev. 2)

IR UV-Vis OR NMR90 200 500 Micro Misc Request Shee 183 sts

thin film

solvent or medium

empirical formula

mp. °C

bp

sample # book page line 1205 175-85

IW-AW-KP ☒ pure ☐ crude

unit head

requestor R Rabbat

bldg. lab. ext.

date submitted 3/22/89

sensitivities:

hazards:

SAMPLE WEIGHT Required for 200 or 500 mHz

do not fill in 1052 poc

☐ routine ☐ ^{1}H ☐ ^{13}C ☐ ^{31}P

☐ expand spectral region from to

☐ assign for ☐ ^{1}H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level)

synthetic pathway: reagents, solvents esp. last solvent:

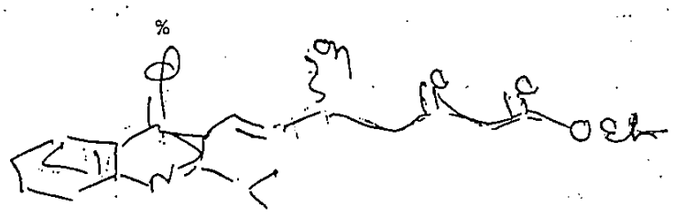


Fig.

suspected structures in order of prob.:

models available

save_d, a; 061754

data available	IR	UV	H nmr	micro	MS			count

fill in # & circle requested elements

formula C H N O

calc.								
found								

mol. wt.

drying req. °C hrs. done

misc. & comments:

sample # book #

90	^{1}H
200	^{13}C
500	^{31}P
COM DEC	NON
DEPT	HOM DEC
SEL DEC	DIF NOE
NOE	D_2O EX
COSY	SOLV SUPP
CH	LSR
RELA	T_1
	VT
MQ	SPIN SIM
NOSY	
	STRUCT

787147/81 (Rev. 2)

circle requests

IR UV-Vis OR NMR90 200 500 Micro Misc Request Sh 184

Thin film

solvent or medium

empirical formula

mp. °C

bp

sample #
book page line
1206-176-41

IW-AW-KP
☒ pure ☐ crude

unit head

requestor R Patel

bldg. lab. ext.

date submitted 7-29-87

sensitivities: hazards:

SAMPLE WEIGHT

Required for 200 or 500 mHz

do not fill in

1087

☐ routine ☐ ^{1}H ☐ ^{13}C ☐ ^{31}P

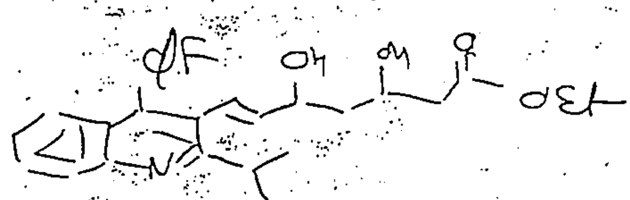
☐ expand spectral region from to

☐ assign for ☐ ^{1}H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level) %

synthetic pathway:
reagents, solvents
esp. last solvent:



suspected structures
in order of prob.:

Save - d,a: 6176-41

models available

90	^{1}H
200	^{13}C
500	^{31}P
COM DEC	NON
DEPT	HOM DEC
SEL DEC	DIF NOE
NOE	D_2O EX
COSY	SOLV SUPP
CH	LSR
RELA	T_1
	VT
MQ	SPIN SIM
NOSY	
	STRUCT
count	

data available	IR	UV	H nmr	micro	MS		

fill in # & circle requested elements

formula C H N O

calc.								
found								

mol. wt.

drying req. _____ °C _____ hrs.
done _____

misc. & comments:

sample # book #

87.147/81 (Rev. 2)

IR UV-Vis OR NMR90 200 500 Micro Misc — circle requests

Request Sheet

thin film on KBr

solvent or medium

empirical formula $C_{25}H_{26}N_2O_4Na$

mp. 185 °C

bp

sample # book page line 120677-30

IW-AW-KP ☑ pure ☐ crude

unit head

requestor K. Dale

bldg. lab. ext.

date submitted 7-25-97

sensitivities:

hazards:

SAMPLE WEIGHT

Required for 200 or 500 mHz

do not fill in

1085 g-m

☐ routine ☐ ^1H ☐ ^{13}C ☐ ^{31}P

☐ expand spectral region from to

☐ assign for ☐ ^1H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level) %

synthetic pathway: reagents, solvents esp. last solvent:

suspected structures in order of prob.:

617930

models available

90	^1H
200	^{13}C
500	^{31}P
COM DEC	NON
DEPT	HOM DEC
SEL DEC	DIF NOE
NOE	D_2O EX
COSY	SOLV SUPP
CH_3	LSR
REL A	T1
	VT
MQ	SPIN SIM
NOSY	
	STRUCT

data available	IR	UV	H nmr	micro	MS			ACOUNT

fill in # & circle requested elements

mol. wt.

formula	C	H	N	O				
calc.								

drying req. °C hrs.

done

misc. & comments:

IR UV-Vis OR NMR90 200 500 Micro Misc **Request Sheet** circle requests 186

thin film

solvent or medium

empirical formula

mp. °C

bp

sample # book page line 1206-179-30

IW-AW-KP ☒ pure ☐ crude

unit head requestor R. Patel

bldg. lab. ext.

date submitted 7-30-97

sensitivities: hazards:

SAMPLE WEIGHT

Required for 200 or 500 mHz

do not fill in

9

1093 9.2

☐ routine ☐ ^{1}H ☐ ^{13}C ☐ ^{31}P

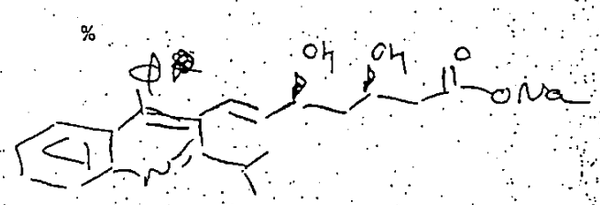
☐ expand spectral region from to

☐ assign for ☐ ^{1}H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level)

%



synthetic pathway: reagents, solvents esp. last solvent:

suspected structures in order of prob.:

line_d, a: 617930

models available

90	^{1}H								
200	^{13}C								
500	^{31}P								
COM DEC	NON								
DEPT	HOM DEC								
SEL DEC	DIF NOE								
NOE	D_2O EX								
COSY	SOLV SUPP								
CH	LSR								
RELA	T_1								
	VT								
MQ	SPIN SIM								
NOSY									
	STRUCT								

data available	IR	UV	H nmr	micro	MS			count

fill in # & circle requested elements

formula C H N O

calc.								
found								

mol. wt.

drying req. °C hrs. done

misc. & comments:

sample # book #

87147/81 (Rev. 2)

IR UV-Vis OR NMR 60 90 200 Micro Misc Request Sheet 187

KBr | | | | $CDCl_3$ | solvent or medium

empirical formula

mp. °C

bp

sample # book page line: 1049-237-27

IW-AW-KP: ☒ pure ☐ crude

unit head

requestor: S. Wattanasin

bldg. 404 lab. 365 ext. 8444

date submitted

RECEIVED
4716 MAY 30 84
INSTRUMENTAL ANALYSIS

sensitivities:

hazards:

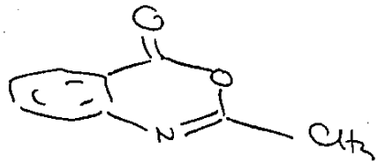
nature of request:
problem statement or
specific instructions:

^1H ^{13}C

15 mg

T_1	^{13}C
VT	^1H
NON	other
COM	LSR
OFR	DT
NOE	DP
NNE	60
SEL	90
HOM	200
HMG	D_2O

synthetic pathway:
reagents, solvents
esp. last solvent:



?

suspected structures
in order of prob.:

models available

other measurements	IR	UV	H nmr	micro	MS			count 2

fill in # & circle requested elements

mol. wt.

drying req. °C hrs.
done

formula	C	H	N	O				
calc.								
found								

misc. & comments:

sam

WATTANASIN EXHIBIT
C-3
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

87147/81

IR UV-Vis OR NMR 60 90 200 Micro Misc Request Sheet 188

CDCl3

solvent or medium

empirical formula

mp. °C

bp

sample # book page line 1049-241-34

IW-AW-KP ☒ pure ☐ crude

unit head

requestor S Wattanasin

bldg. 404 lab. 365 ext. 8404

date submitted

sensitivities:

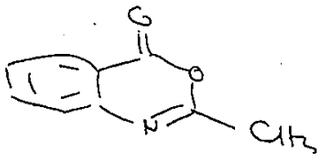
hazards:

1H

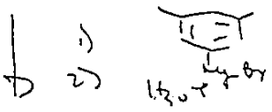
IR mg

nature of request:
problem statement or
specific instructions:

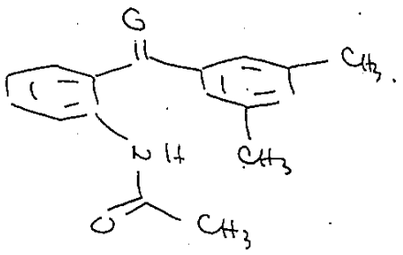
do not fill in
RECEIVED
1751 JUN. - 1. 84
INSTRUMENTAL ANALYSIS



synthetic pathway:
reagents, solvents
esp. last solvent:



suspected structures
in order of prob.:



?

models available

T1	13C
VT	1H
NON	other
COM	LSR
OFR	DT
NOE	DP
NNE	60
SEL	90
HOM	200
HMG	D2O

count

other measurements	IR	UV	H nmr	micro	MS		

fill in # & circle requested elements

formula	C	H	N	O				
calc.								
found								

mol. wt.

drying req. °C hrs.
done

misc. & comments:

sample # book #

87147/81

IR | UV-Vis | OR | NMR60 | 90 | 200 | Micro | Misc | Request Sheet cir 189

Film. | | | | CDCl3 | empirical formula | mp. °C

solvent or medium | | bp

sample # book page line: 1079-22-28

IW-AW-KP ☐ pure ☐ crude

unit head | requestor S. Watanabe

bldg. 404 | lab. 365 | ext. 8404

date submitted

do not fill in

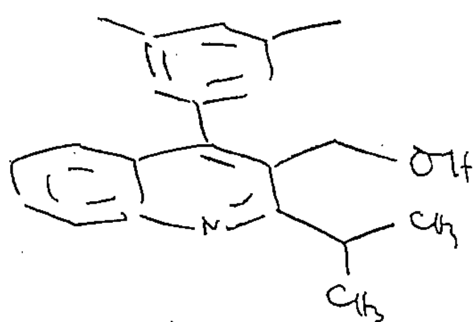
RECEIVED
6255 AUG.13.84
INSTRUMENTAL ANALYSIS

sensitivities: # ouvrial = 1079-24-24 hazards:

1H

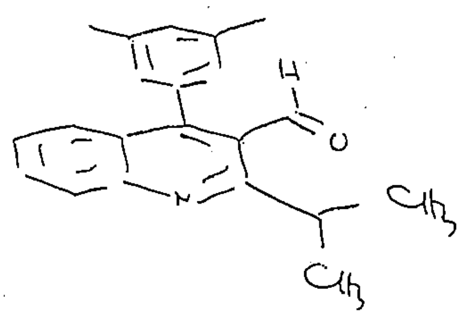
4 mg

nature of request:
problem statement or
specific instructions:



synthetic pathway:
reagents, solvents
esp. last solvent:

or.



suspected structures
in order of prob.:

models available

T1	13C
VT	1H
NON	other
COM	LSR
OFR	DT
NOE	DP
NNE	60
SEL	90
HOM	200
HMG	D_2O

other measurements	IR	UV	H nmr	micro	MS			count

fill in # & circle requested elements

formula C H N O

calc.								
found								

mol. wt.

drying req. ______ °C ______ hrs. done ______

misc. & comments:

sample # book #

87147/81

IR UV-Vis OR NMR 60 90 200 Micro Misc Request Sheet 190 s

IR Br. CDCl3

solvent or medium

empirical formula

mp. °C

bp

sample # book page line: 1079-27-35

IW-AW-KP ☐ pure ☐ crude

unit head

requestor S. Wattanasin

bldg. 400 lab. 365 ext. 5400

date submitted

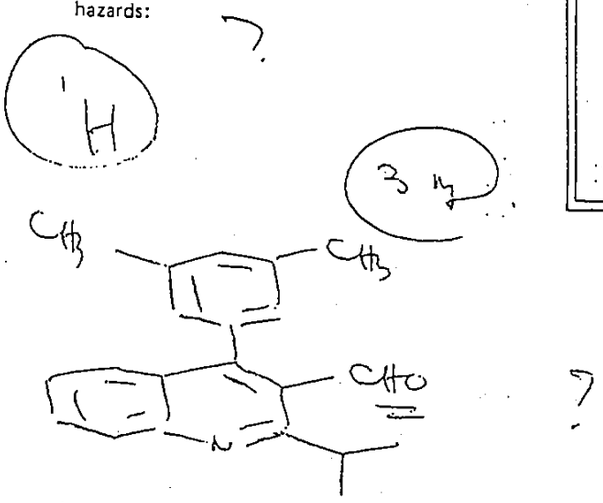
sensitivities:

hazards:

do not fill in

RECEIVED
C288 AUG. 14 84
INSTRUMENTAL ANALYSIS

nature of request:
problem statement or
specific instructions:



T_1	^{13}C
VT	^1H
NON	other
COM	LSR
OFR	DT
NOE	DP
NNE	60
SEL	90
HOM	200
HMG	D_2O

synthetic pathway:
reagents, solvents
esp. last solvent:

suspected structures
in order of prob.:

models available

other measurements	IR	UV	H nmr	micro	MS			count

fill in # & circle requested elements

mol. wt.

drying req. °C hrs. done

formula	C	H	N	O					
calc.									
found									

misc. & comments:

sample # book #

87147/81

IR | UV-Vis | OR | NMR60 | 90 | 200 | Micro | Misc — Request Sheet (circle r) 191

IR	UV-Vis	OR	NMR60	90	200
KBr					$CDCl_3$

solvent or medium

empirical formula

mp. ______ °C

bp

sample # — book page line: 1079-30-23

IW-AW-KP — ☒ pure ☐ crude

unit head

requestor: S. Wattanasin

bldg.: 404 lab.: 365 ext.: 8404

date submitted

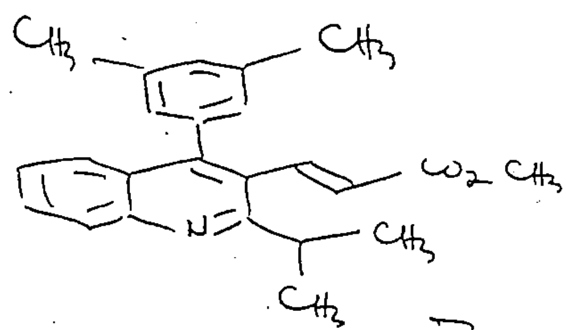
sensitivities: ?

hazards: (H) ?

do not fill in

RECEIVED 0404 AUG. 22. 84 INSTRUMENTAL ANALYSIS

nature of request: problem statement or specific instructions: 4 mg



?

synthetic pathway: reagents, solvents esp. last solvent:

suspected structures in order of prob.:

models available

T1	13C
VT	1H
NON	other
COM	LSR
OFR	DT
NOE	DP
NNE	60
SEL	90
HOM	200
HMG	D_2O

other measurements	IR	UV	H nmr	micro	MS			count

fill in # & circle requested elements

formula C H N O

calc.								
found								

mol. wt.

drying req. ______ °C ______ hrs. done ______

misc. & comments:

sample # book #

87147/81

circ' ... requests

IR UV-Vis OR NMR60 90 200 Micro Misc Request Sheet 192

solvent or medium	empirical formula	mp. °C / bp
200: $CDCl_3$		

sample # book page line	IW-AW-KP	unit head	requestor
1079-34-17	☒ pure ☐ crude	bldg. 404 / lab. 365 / date submitted	S. Wattanasin / ext. 8204

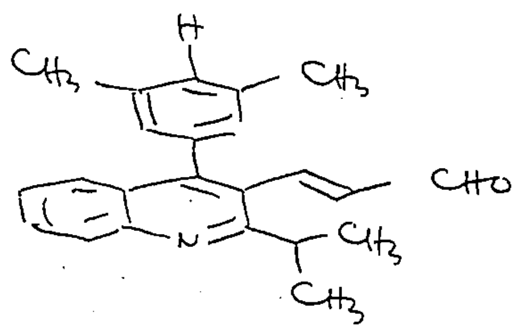
do not fill in

RECEIVED 0501 SEP.-5.84 ELEMENTAL ANALYSIS

sensitivities:

hazards: H

nature of request: problem statement or specific instructions: ~ 3 mg



synthetic pathway: reagents, solvents esp. last solvent:

suspected structures in order of prob.:

models available

T_1	^{13}C
VT	1H
NON	other
COM	LSR
OFR	DT
NOE	DP
NNE	60
SEL	90
HOM	200
HMG	D_2O

other measurements	IR	UV	H nmr	micro	MS			count

fill in # & circle requested elements

formula C H N O

mol. wt.

drying req. ______ °C ______ hrs. done ______

calc.								
found								

misc. & comments:

sample # book #

87147/81.

IR UV-Vis OR NMR60 90 200 Micro Misc Request Sheet cir 193

KBr.					CDCl3.	empirical formula	mp. °C bp
solvent or medium							

sample #
book page line
1127-5-23

IW-AW-KP
☐ pure ☐ crude

unit head
requestor
bldg. lab. 365 ext. 8404
date submitted

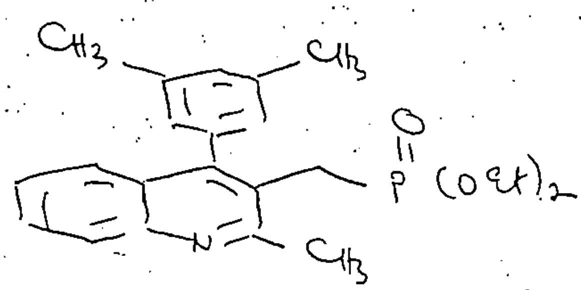
do not fill in
RECEIVED
2517 MAY -6 85
INSTRUMENTAL ANALYSIS

sensitivities:

hazards: H.

nature of request:
problem statement or
specific instructions:

3 mg



77

synthetic pathway:
reagents, solvents
esp. last solvent:

suspected structures
in order of prob.:

models available

T1	13C
VT	1H
NON	31P
COM	LSR
OFR	DEPT
NOE	COSY
NNE	60
SEL	90
HOM	200
HMG	D_2O
DIF NOE	CH

other measurements	IR	UV	H nmr	micro	MS			count

fill in # & circle requested elements

mol. wt.

drying req. °C hrs. done

formula C H N O

calc.								
found								

misc. & comments:

sample # book #

87147/81 (Rev. 1)

IR | UV-Vis | OR | NMR60 | 90 | (200) | Micro | Misc — **Request Sheet** 194

solvent or medium: $CDCl_3$

empirical formula:

mp. ____ °C

bp

sample # — book page line: 1127-9-33

IW-AW-KP: ☑ pure ☐ crude

unit head:

requestor: S. Wattanasin

bldg.: lab.: 365 ext.: 8404

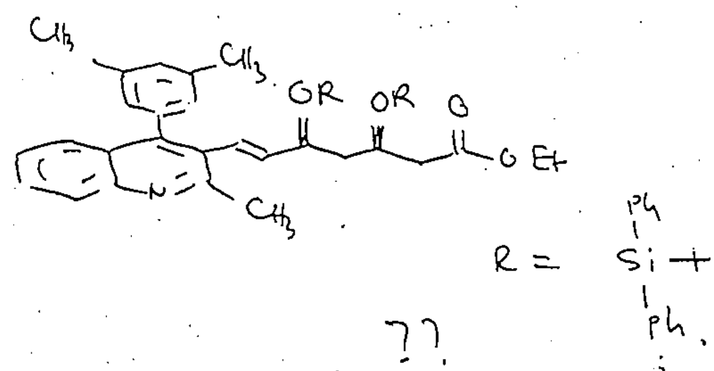
date submitted:

do not fill in

sensitivities: hazards:

nature of request: problem statement or specific instructions: (H) 3 (mg)

synthetic pathway: reagents, solvents esp. last solvent:



suspected structures in order of prob.:

models available

- Sample in the fridge.
- please keep sample in

T_1	^{13}C
VT	(^{1}H)
NON	^{31}P
COM	LSR
OFR	DEPT
NOE	COSY
NNE	60
SEL	90
HOM	(200)
HMG	D_2O
DIF NOE	CH

other measurements | IR | UV | H nmr | micro | MS — count

fill in # & circle requested elements

formula C H N O

mol. wt.

drying req. ____ °C ____ hrs. done ____

	C	H	N	O				
calc.								
found								

misc. & comments:

sample # book #

87147/81 (Rev. 1)

circle requests

IR UV-Vis OR NMR60 90 200 Micro Misc **Request Sheet**

Film | | | | | $CDCl_3$ — solvent or medium

empirical formula

mp. 195

bp

sample # book page line: 1127-11-34,

IW-AW-KP ☒ pure ☐ crude

unit head

requestor S. Wattanasin

bldg. lab. 365 ext. 8404

date submitted

sensitivities:

hazards:

do not fill in
RECEIVED
2683 MAY 14 85
INSTRUMENTAL ANALYSIS

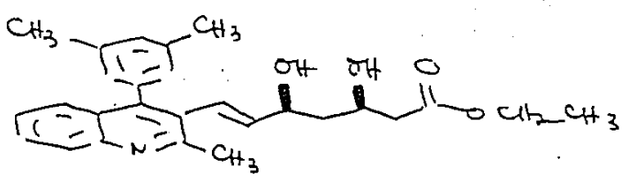
nature of request:
problem statement or
specific instructions:

^1H

1 mg

T_1	^{13}C
VT	^1H
NON	^{31}P
COM	LSR
OFR	DEPT
NOE	COSY
NNE	60
SEL	90
HOM	200
HMG	D_2O
DIF NOE	CH

synthetic pathway:
reagents, solvents
esp. last solvent:



suspected structures
in order of prob.:

- Sample in the fridge.
- sample for testing
- please get a good S/N

models available

other measurements	IR	UV	H nmr	micro	MS			count

fill in # & circle requested elements

formula C H N O

calc.								
found								

mol. wt.

drying req. ____ °C ____ done ____ hrs.

misc. & comments:

sample # book #

87147/81 (Rev. 1)

IR UV-Vis OR NMR60 90 200 Micro Misc Request Sheet circle 195a

Film				CDCl3	empirical formula — filtered.

solvent or medium

mp. °C

bp

unit head

requestor S. Wattanasin

sample # book page line 1127-11-37

IW-AW-KP ☐ pure ☐ crude

bldg. lab. 365 ext. 8404.

date submitted

do not fill in

RECEIVED 2686 MAY 14 85 INSTRUMENTAL ANALYSIS

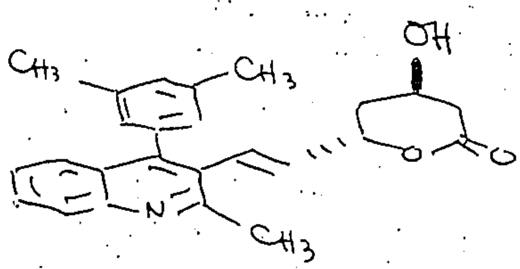
sensitivities: 1127-11-37

hazards: H

1 mg.

nature of request: problem statement or specific instructions:

synthetic pathway: reagents, solvents esp. last solvent:



77

suspected structures in order of prob.:

models available

– Sample in the fridge
– Testing sample, please get a good S/N

T1	13C
VT	1H
NON	31P
COM	LSR
OFR	DEPT
NOE	COSY
NNE	60
SEL	90
HOM	200
HMG	D_2O
DIF NOE	CH

other measurements	IR	UV	H nmr	micro	MS			count

fill in # & circle requested elements

formula	C	H	N	O				
calc.								
found								

mol. wt.

drying req. °C hrs. done

misc. & comments:

sample # book #

87147/81 (Rev. 1)

IR UV-Vis OR NMR90 200 500 Micro Misc Request Sheet ci 196

thin film		CDCl3		empirical formula	mp. °C bp

solvent or medium

sample # book page line: 1206 130-27

IW-AW-KP ☐ pure ☒ crude

unit head S. Watt requestor R Patel

bldg. lab. ext. 5578

date submitted 6-5-87

sensitivities: hazards:

SAMPLE WEIGHT

Required for 200 or 500 mHz

do not fill in

RECEIVED 3256 JUN -5 87 INSTRUMENTAL ANALYSIS

☒ routine ☒ ^1H ☐ ^{13}C ☐ ^{31}P

☐ expand spectral region from to

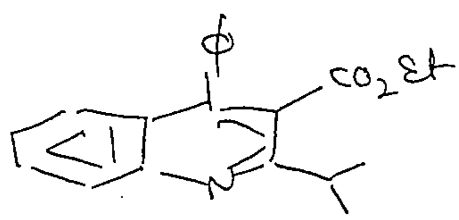
☐ assign for ☐ ^1H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level) %

90	^1H
200	^{13}C
500	^{31}P
COM DEC	NON
DEPT	HOM DEC
SEL DEC	DIF NOE
NOE	D_2O EX
COSY	SOLV SUPP
CH	LSR
RELA	T_1
	VT
MQ	SPIN SIM
NOSY	
	STRUCT
count	

synthetic pathway:
reagents, solvents
esp. last solvent:



suspected structures
in order of prob.:

models available

data available	IR	UV	H nmr	micro	MS		

fill in # & circle requested elements

formula C H N O

calc.							
found							

mol. wt.

drying req. ____ °C ____ hrs. done ____

misc. & comments:

sample # book #

87147/81 (Rev. 2)

circle requests

IR UV-Vis OR NMR 90 200 500 Micro Misc Request Sheet 197

thin film | $CDCl_3$ | solvent or medium

empirical formula

mp. ____ °C

bp

sample # book page line: 1206-137-31

IW-AW-KP ☐ pure ☒ crude

unit head S. Watta requestor R Patel

bldg. lab. 358 ext.

date submitted 6-11-87

sensitivities: hazards:

SAMPLE WEIGHT

Required for 200 or 500 mHz

do not fill in

RECEIVED
3326 JUN. 12. 87
SUPPLEMENTAL ANALYSIS

☒ routine ☑ ^1H ☐ ^{13}C ☐ ^{31}P

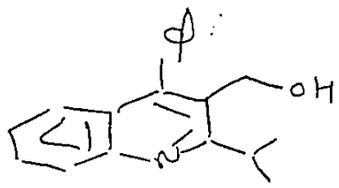
☐ expand spectral region from to

☐ assign for ☐ ^1H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level) %

synthetic pathway:
reagents, solvents
esp. last solvent:



suspected structures in order of prob.:

models available

90	^1H						
200	^{13}C						
500	^{31}P						
COM DEC	NON						
DEPT	HOM OEC						
SEL DEC	DIF NOE						
NOE	D_2O EX						
COSY	SOLV SUPP						
CH	LSR						
RELA	T_1						
	VT						
MQ	SPIN SIM						
NOSY							
	STRUCT						

data available	IR	UV	H nmr	micro	MS			count

fill in # & circle requested elements

mol. wt.

formula C H N O

drying req. ____ °C ____ done ____ °C ____ hrs.

calc.								
found								

misc. & comments:

sample # book #

87147/81 (Rev. 2)

IR UV-Vis OR NMR90 200 500 Micro Misc Request Sheet circle 198

solvent or medium

empirical formula

mp. °C

bp

sample # book page line 206-145-25

IW-AW-KP ☐ pure ☒ crude

unit head requestor

bldg. lab. ext.

date submitted 6-19-87

sensitivities: hazards:

SAMPLE WEIGHT Required for 200 or 500 mHz

do not fill in

RECEIVED 9450 JUN 19 87 ENVIRONMENTAL ANALYSIS

☐ routine ☐ ^{1}H ☐ ^{13}C ☐ ^{31}P

☐ expand spectral region from to

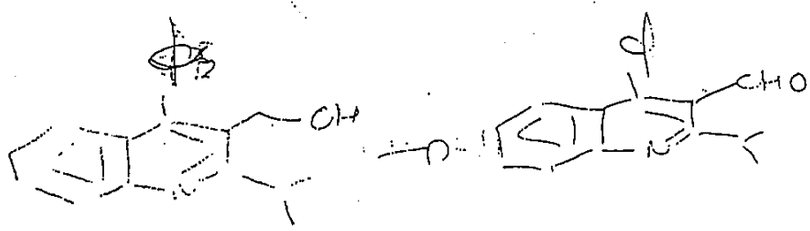
☐ assign for ☐ ^{1}H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level) %

90	^{1}H
200	^{13}C
500	^{31}P
COM DEC	NON
DEPT	HOM DEC
SEL DEC	DIF NOE
NOE	D_2O EX
COSY	SOLV SUPP
CH	LSR
RELA	T_1
	VT
MQ	SPIN SIM
NOSY	
	STRUCT

synthetic pathway: reagents, solvents esp. last solvent:



suspected structures in order of prob.:

models available

data available	IR	UV	H nmr	micro	MS			count

fill in # & circle requested elements

formula C H N O

mol. wt.

drying req. °C hrs. done

calc.								
found								

misc. & comments:

sample # book #

87147/81 (Rev. 2)

IR | UV-Vis | OR | NMR90 | 200 | 500 | Micro | Misc | Request Sheet | circ 199

			$CDCl_3$			empirical formula

solvent or medium

mp. _______ °C

bp

sample #
book page line
- 145-26

IW-AW-KP
☐ pure ☒ crude

unit head

requestor

bldg. lab. ext.

date submitted 6-19-87

sensitivities: hazards:

SAMPLE WEIGHT

Required for 200 or 500 mHz

do not fill in

RECEIVED
3451 JUN. 19. 87
INSTRUMENTAL ANALYSIS

☒ routine ☐ ^1H ☐ ^{13}C ☐ ^{31}P

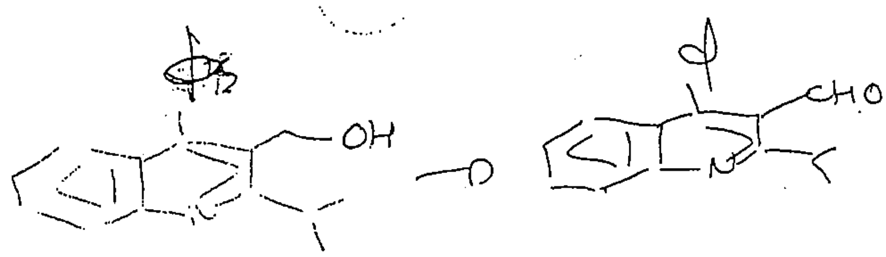
☐ expand spectral region from to

☐ assign for ☐ ^1H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level) %

synthetic pathway:
reagents, solvents
esp. last solvent:



suspected structures
in order of prob.:

models available

90	^1H
200	^{13}C
500	^{31}P
COM DEC	NON
DEPT	HOM DEC
SEL DEC	DIF NOE
NOE	D_2O EX
COSY	SOLV SUPP
CH	LSR
RELA	T_1
	VT
MQ	SPIN SIM
NOSY	
	STRUCT
	count

data available	IR	UV	H nmr	micro	MS		

fill in # & circle requested elements

formula C H N O

calc.							
found							

mol. wt.

drying req. _______ °C _______ hrs.
done _______

misc. & comments:

sample # book #

87147/81 (Rev. 2)

IR UV-Vis OR NMR 90 200 500 Micro Misc — Request Sheet — circle requests — 200

Pellet

solvent or medium

empirical formula

mp. °C

bp

sample # book page line: 1-153-31

IW-AW-KP ☒ pure ☐ crude

unit head requestor

bldg. lab. 358 ext.

date submitted 7-2-87

sensitivities: hazards:

SAMPLE WEIGHT 5mg Required for 200 or 500 mHz

do not fill in
RECEIVED
3596 JUL.-2 87
INSTRUMENTAL ANALYSIS

☐ routine ☒ ^1H ☐ ^{13}C ☐ ^{31}P

☐ expand spectral region from to

☐ assign for ☐ ^1H (500) ☐ ^{13}C

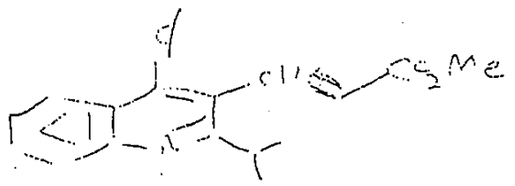
☐ save on tape if pure

☐ check for impurities (state level) %

SAVE

90	H J
200	^{13}C
500	^{31}P
COM DEC	NON
DEPT	HOM DEC
SEL DEC	DIF NOE
NOE	D_2O EX
COSY	SOLV SUPP
CH	LSR
RELA	T_1
	VT
MQ	SPIN SIM
NOSY	
	STRUCT
	count

synthetic pathway: reagents, solvents esp. last solvent:



1st soln for TR

suspected structures in order of prob.:

models available

data available	IR	UV	H nmr	micro	MS		

fill in # & circle requested elements

mol. wt.

formula	C	H	N	O					
calc.									
found									

drying req. °C hrs. done

misc. & comments:

sample # book #

87147/81 (Rev. 2)

circle requests

IR UV-Vis OR NMR90 200 500 Micro Misc **Request Sheet**

CD_3

solvent or medium

empirical formula

mp. 201 C

bp

sample # book page line: 120G 153-39

IW-AW-KP ☒ pure ☐ crude

unit head S. Watthan requestor R Patel

bldg. lab. ext.

date submitted 7-6-87

sensitivities: hazards:

SAMPLE WEIGHT

Required for 200 or 500 mHz

do not fill in

RECEIVED

3615 JUL.-7.87

INSTRUMENTAL ANALYSIS

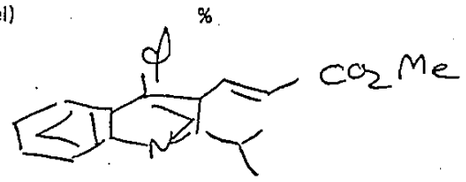
☒ routine ☒ ^1H ☐ ^{13}C ☐ ^{31}P

☐ expand spectral region from to

☐ assign for ☐ ^1H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level) %



synthetic pathway:
reagents, solvents
esp. last solvent:

suspected structures in order of prob.:

models available

(90)	^1H							
200	^{13}C							
500	^{31}P							
COM DEC	NON							
DEPT	HOM DEC							
SEL DEC	DIF NOE							
NOE	D_2O EX							
COSY	SOLV SUPP							
CH	LSR							
RELA	T_1							
	VT							
MQ	SPIN SIM							
NOSY								
	STRUCT							

data available	IR	UV	H nmr	micro	MS			count

fill in # & circle requested elements

mol. wt.

drying req. ____ °C ____ done ____ hrs.

formula	C	H	N	O				
calc.								
found								

misc. & comments:

sample # book #

87147/81 (Rev. 2)

IR UV-Vis OR NMR 90 200 500 Micro Misc Request Shee 202 sts

solvent or medium CDCl3

empirical formula

mp. °C

bp

sample # book page line 1206 158-41

IW-AW-KP ☐ pure ☒ crude

unit head S. Watt requestor R Patel

bldg. 404 lab. 358 ext.

date submitted 7-9-87

sensitivities: hazards:

SAMPLE WEIGHT

Required for 200 or 500 mHz

do not fill in

RECEIVED
3677 JUL. 10. 87
INSTRUMENTAL ANALYSIS

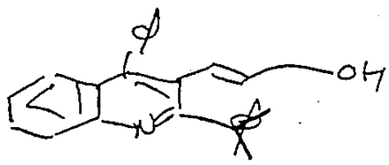
☐ routine ☐ ^{1}H ☐ ^{13}C ☐ ^{31}P

☐ expand spectral region from to

☐ assign for ☐ ^{1}H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level) %



synthetic pathway:
reagents, solvents
esp. last solvent:

suspected structures in order of prob.:

models available

90	^{1}H
200	^{13}C
500	^{31}P
COM DEC	NON
DEPT	HOM DEC
SEL DEC	DIF NOE
NOE	D_2O EX
COSY	SOLV SUPP
CH	LSR
RELA	T_1
	VT
MQ	SPIN SIM
NOSY	
	STRUCT

data available	IR	UV	H nmr	micro	MS			count

fill in # & circle requested elements

mol. wt.

drying req. °C hrs. done

formula	C	H	N	O				
calc.								
found								

misc. & comments:

sample # book #

87147/81 (Rev. 2)

IR UV-Vis OR NMR 90 200 500 Micro Misc Request Sheet 203

solvent or medium CD_3OD

empirical formula

mp. °C

bp

sample # book page line 1206 16630

IW-AW-KP ☒ pure ☐ crude

unit head requestor

bldg. lab. ext.

date submitted 7-16-87

sensitivities: hazards:

SAMPLE WEIGHT

Required for 200 or 500 mHz

do not fill in

RECEIVED
3793 JUL 16 87
INSTRUMENTAL ANALYSIS

☐ routine ☐ ^1H ☐ ^{13}C ☐ ^{31}P

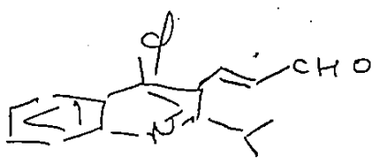
☐ expand spectral region from to

☐ assign for ☐ ^1H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level)

%



synthetic pathway:
reagents, solvents
esp. last solvent:

suspected structures in order of prob.:

models available

90	^1H							
200	^{13}C							
500	^{31}P							
COM DEC	NON							
DEPT	HOM DEC							
SEL DEC	DIF NOE							
NOE	D_2O EX							
COSY	SOLV SUPP							
CH	LSR							
RELA	T_1							
	VT							
MQ	SPIN SIM							
NOSY								
	STRUCT							

data available	IR	UV	H nmr	micro	MS			count

fill in # & circle requested elements

mol. wt.

drying req. °C hrs. done

formula C H N O

calc.								
found								

misc. & comments:

sample # book #

87147/81 (Rev. 2)

IR UV-Vis OR NMR 90 200 500 Micro Misc Request Sheet 204

CDCl3

solvent or medium

empirical formula $C_{27}H_{29}NO_4$

mp. °C

bp

sample # book page line 12875-4

IW-AW-KP ☐ pure ☐ crude

unit head requestor R Patel

bldg. lab. ext.

date submitted 7-22-87

sensitivities: hazards:

SAMPLE WEIGHT Required for 200 or 500 mHz

do not fill in

RECEIVED
3874 JUL.22.87
INSTRUMENTAL ANALYSIS

☐ routine ☑ ^1H ☐ ^{13}C ☐ ^{31}P

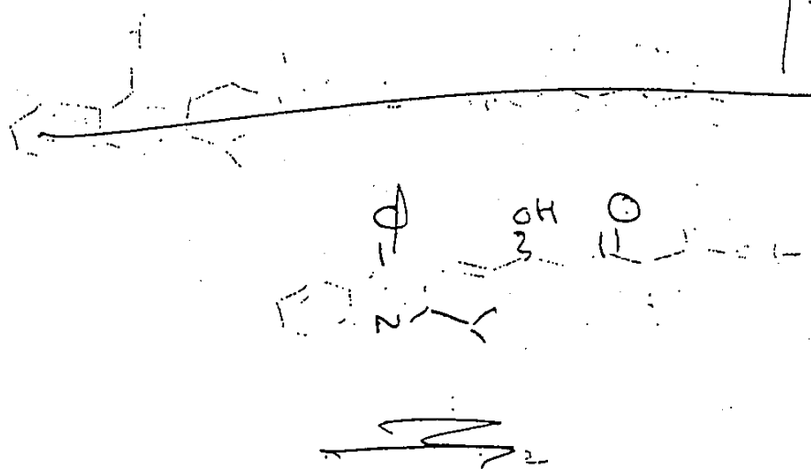
☐ expand spectral region from to

☐ assign for ☐ ^1H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level) %

synthetic pathway: reagents, solvents esp. last solvent:



suspected structures in order of prob.:

models available

90	^1H						
200	^{13}C						
500	^{31}P						
COM DEC	NON						
DEPT	HOM DEC						
SEL DEC	DIF NOE						
NOE	D_2O EX						
COSY	SOLV SUPP						
CH	LSR						
RELA	T_1						
	VT						
MQ	SPIN SIM						
NOSY							
	STRUCT						

data available	IR	UV	H nmr	micro	MS			count

fill in # & circle requested elements

mol. wt.

formula	C	H	N	O				
calc.								
found								

drying req. °C hrs. done

misc. & comments:

sample # book #

87147/81 (Rev. 2)

circle 205

IR UV-Vis OR NMR 90 200 500 Micro Misc **Request Sheet**

thin film — $CDCl_3$ — solvent or medium

empirical formula

mp. ____ °C

bp

sample # book page line: 120G 176 41

IW-AW-KP ☒ pure ☐ crude

unit head

requestor R Patel

bldg. 404 lab. ext.

date submitted 7-27-87

sensitivities:

hazards:

SAMPLE WEIGHT

Required for 200 or 500 mHz

do not fill in

RECEIVED
3934 JUL. 27. 87
INSTRUMENTAL ANALYSIS

☐ routine ☐ ^1H ☒ ^{13}C ☐ ^{31}P

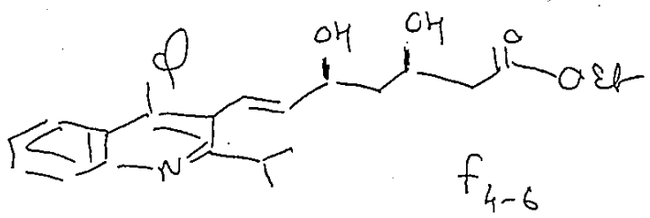
☐ expand spectral region from to

☐ assign for ☐ ^1H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level) %

synthetic pathway: reagents, solvents esp. last solvent:



f_{4-6}

Pl. save for ~~name~~ IR

extended date region δ 5-7

Rush

suspected structures in order of prob.:

models available

90	^1H
200	^{13}C
500	^{31}P
COM DEC	NON
DEPT	HOM DEC
SEL DEC	DIF NOE
NOE	D_2O EX
COSY	SOLV SUPP
CH	LSR
RELA	T_1
	VT
MQ	SPIN SIM
NOSY	
	STRUCT

count

data available	IR	UV	H nmr	micro	MS		

fill in # & circle requested elements

formula C H N O

calc.								
found								

mol. wt.

drying req. ____ °C ____ hrs. done ____

misc. & comments:

sample # book #

87147/81 (Rev. 2)

IR UV-Vis OR NMR 90 200 500 Micro Misc **Request Sheet** circ 206

solvent or medium

empirical formula

mp. °C

bp

sample # book page line 200 124-43

IW-AW-KP ☐ pure ☐ crude

unit head requestor

bldg. 416 lab. ext.

date submitted 7-27-87

sensitivities: hazards:

SAMPLE WEIGHT

Required for 200 or 500 mHz

do not fill in

RECEIVED
3933 JUL.27.87
INSTRUMENTAL ANALYSIS

☐ routine ☐ ^{1}H ☒ ^{13}C ☐ ^{31}P

☐ expand spectral region from to

☐ assign for ☐ ^{1}H (500) ☐ ^{13}C

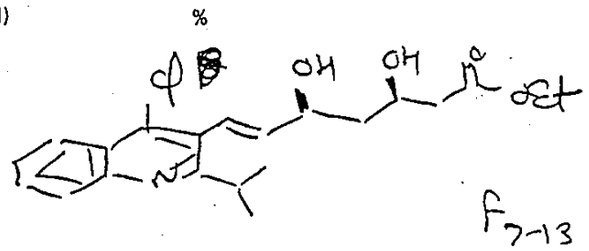
☐ save on tape if pure

☐ check for impurities (state level)

90	^{1}H
200	^{13}C
500	^{31}P
COM DEC	NON
DEPT	HOM DEC
SEL DEC	DIF NOE
NOE	D_2O EX
COSY	SOLV SUPP
CH	LSR
RELA	T_1
	VT
MQ	SPIN SIM
NOSY	
	STRUCT
	ACCOUNT

synthetic pathway: reagents, solvents esp. last solvent:

%



f_{7-13}

Pl. save for I.R.:

Pl. extrapolate region δ5-7

Resh

suspected structures in order of prob.:

models available

data available	IR	UV	H nmr	micro	MS		

fill in # & circle requested elements

formula C H N O

calc.								
found								

mol. wt.

drying req. °C hrs.
done

misc. & comments:

sample # book #

87147/81 (Rev. 2)

207

SANDOZ RESEARCH INSTITUTE
EAST HANOVER, NEW JERSEY
CHEMICAL INFORMATION

Date:

Compound No.:

Structure:

Emp. Form :
Mol. Wt. :
m.p. :
b.p. :
*Others :

Hanover :
AM/AV :
Tr :
Agro :

Name:

Screen:	✓	Screen:	✓
AO			
GHI			
GLUC			
HG			
HL			
PL		AM/AV	
TC		Tr	
		Agro	

Compare With:

Pat. Disclosure No.
L & D No.
Known ____ Unknown ____

Remarks:

Preparation of Physiol. Solution:

Synthesis:

Chemist:

Chem. No.:

RESEARCH DEPARTMENT

SANDOZ HANOVER

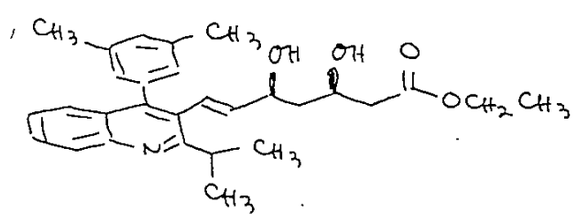
208

Date:

CHEMICAL INFORMATION

Compound No.: 63-366

Structure:



6

25496

Emp. Form: $C_{29}H_{35}O_4N$.

Mol. Wt. : 461.606

m.p. :

b.p. :

*Others : oil.

Hanover : —

AM/AV :

Tr :

Agro :

Name:

Screen:	✓	Screen:	✓
AO		CSI	✓
GHI			
GLUC			
HG			
HL			
PL		AM/AV	
TC		Tr	
		Agro	

Compare With: 58-512

Pat. Disclosure No. 299/84

L & D No. —

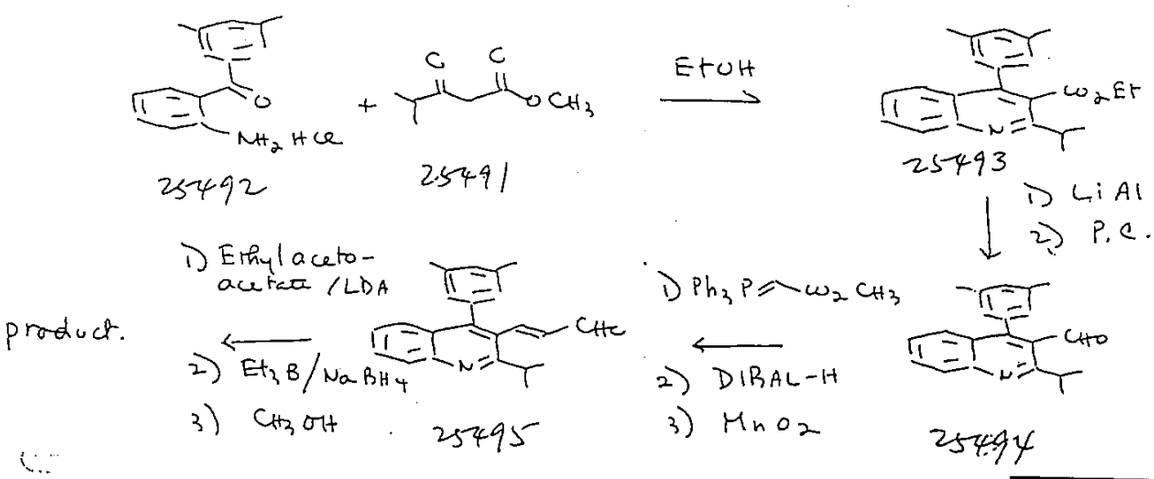
Known ___ Unknown X

Remarks: Dr. Scallen 14.5 mg
— Keep refrigerate
— erythro : threo ≈ 95 : 5

Preparation of Physiol. Solution:

DMA D
or
EtOH E
or
CMC suspension C

Synthesis:



Chemist: S. WATTANASIN / F.G. KATHAWALA.

Chem. No.: 1079-111-19

WATTANASIN EXHIBIT
D-2
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

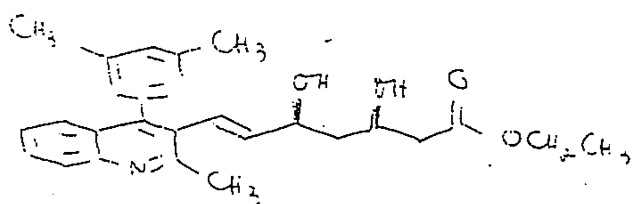
RESEARCH DEPARTMENT — SANDOZ HANOVER

CHEMICAL INFORMATION

Date:	9/16/85
Compound No.:	63-548

209

Structure:



26080

Emp. Form:	$C_{27}H_{31}O_4N$
Mol. Wt.:	433
m.p.:	
b.p.:	
*Others:	oil
Hanover:	4.8 mg
AM/AV:	
Tr:	
Agro:	

Name:

Screen:	✓	Screen:	✓
AO		CSI	✓
GHI		CITC	✓
GLUC		CETU.	✓
HG			
HL			
PL		AM/AV	
TC		Tr	
		Agro	

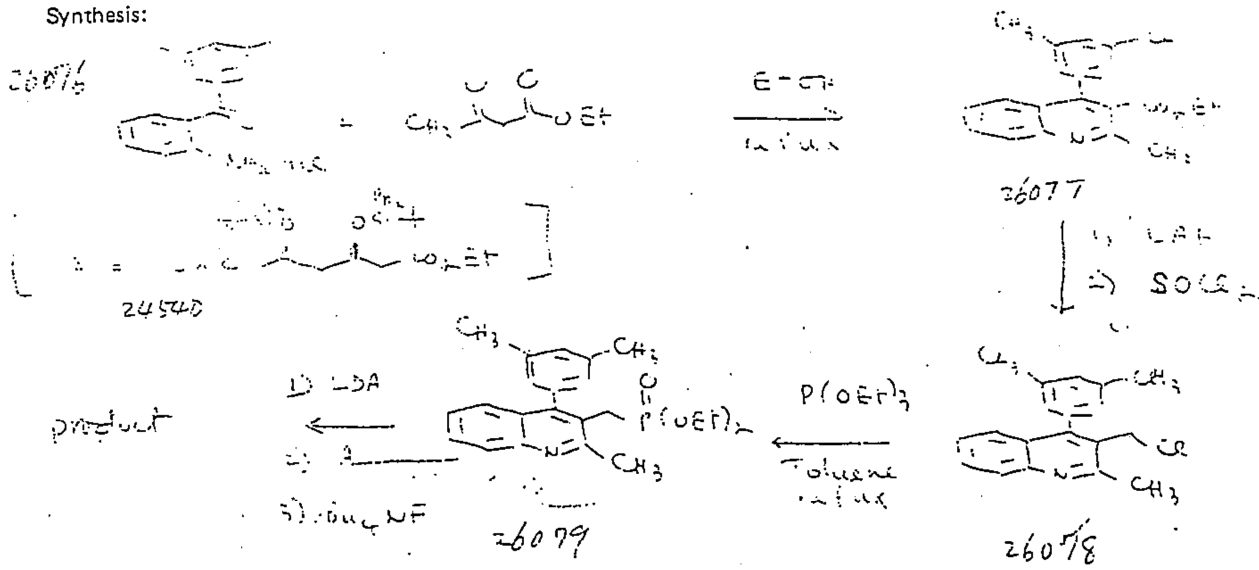
Compare With: [illegible]

Pat. Disclosure No. 299/84
L & D No. 17329
Known____ Unknown ✓

Remarks: Dr Scallen 5.0 mg — [illegible] compound — Keep in frigidaire.

Preparation of Physiol. Solution:
DMA D
or
EtOH E
or
CMC suspension C

Synthesis:



26076 — 26077 — 24540 — 26078 — 26079

Chemist: S. WATTANASIN & F. G. KATHAWALA

Chem. No.: 123-11-34

83520/74 Rev. 6

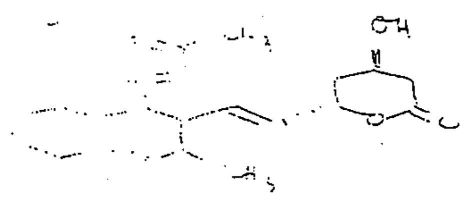
RESEARCH DEPARTMENT — SANDOZ HANOVER

CHEMICAL INFORMATION

Date: [illegible] 210

Compound No.: 63-549

Structure:



7082

Emp. Form: $C_{25}H_{25}O_3N$
Mol. Wt.: 3[illegible]
m.p.:
b.p.:
*Others: [illegible]

Hanover: —
AM/AV:
Tr:
Agro:

Name:

Screen:	✓	Screen:	✓
AO			
GHI			✓
GLUC			
HG			
HL			
PL		AM/AV	
TC		Tr	
		Agro	

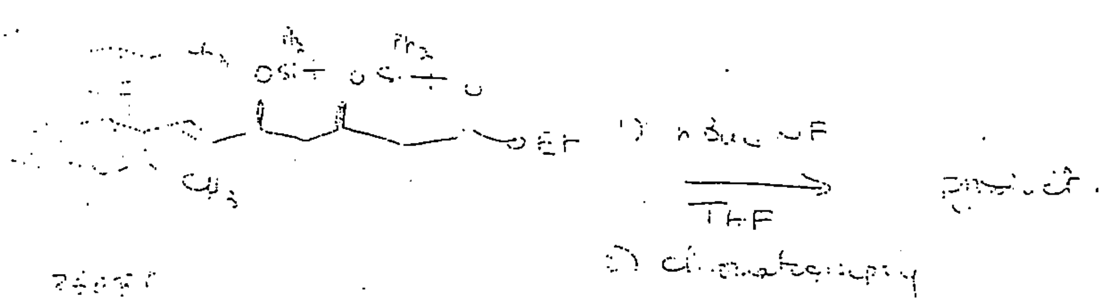
Pat. Disclosure No. 299/84
L & D No. 13329
Known____ Unknown ✓

Remarks: [illegible]
— pure [illegible] lactone
— contains [illegible]
— [illegible]

Compare With:

Preparation of Physiol. Solution:
[illegible]
EtOH [illegible]
[illegible] suspension [illegible]

Synthesis:



Chemist: [illegible]

Chem. No.: [illegible] - 11 - 37

83520/74 Rev. 6

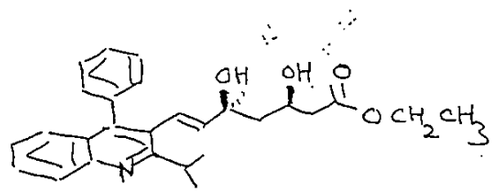
211

SANDOZ RESEARCH INSTITUTE
EAST HANOVER, NEW JERSEY
CHEMICAL INFORMATION

Date:

Compound No.: 67-933

Structure:



30441

Emp. Form: $C_{27}H_{31}NO_4$
Mol. Wt. : 433.527
m.p. :
b.p. :
*Others :

Hanover : 50 mg
AM/AV :
Tr :
Agro :

Name:

Screen:	✓	Screen:	✓
AO		CSI	V
GHI		CSTc	V
GLUC		CSTv	V
HG			
HL			
PL		AM/AV	
TC		Tr	
		Agro	

Compare With: 62-320

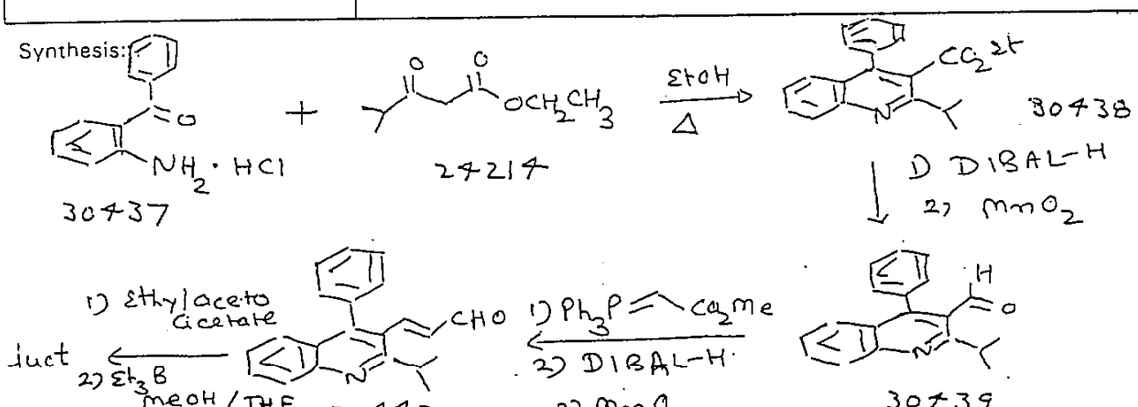
Pat. Disclosure No. 299/84
L & D No.
Known ___ Unknown X

Remarks: Dv. Scallen 50mg erythro : threo > 95 : 5
Keep refrigerate.

Preparation of Physiol. Solution:

DMA D
CV
EtOH E
CV
CMC suspension C

Synthesis:



Chemist: S. Wattanasin / R. Patel

Chem. No.: 1206-176-43

83520/74 Rev. 7

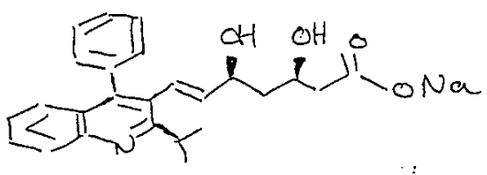
212

SANDOZ RESEARCH INSTITUTE
EAST HANOVER, NEW JERSEY
CHEMICAL INFORMATION

Date:

Compound No.: 64-934/Na

Structure:



30472

Emp. Form: $C_{25}H_{26}NO_4Na$
Mol. Wt. : 427.467
m.p. : > 210°C
b.p. :
*Others :

Hanover : 50 mg
AM/AV :
Tr :
Agro :

Name:

Screen:	✓	Screen:	✓
AO		CSI	V
GHI		CSIC	V
GLUC		CSIV	V
HG			
HL			
PL		AM/AV	
TC		Tr	
		Agro	

Compare With: 62-320

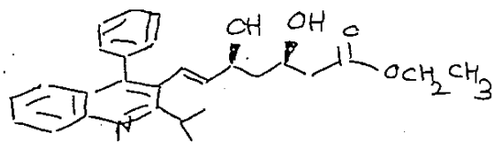
Pat. Disclosure No. 299 184
L & D No.
Known ___ Unknown X

Remarks: Dr. Scallen 50mg
erythro: threo > 95:5
Keep refrigerate

Preparation of Physiol. Solution:

DMA D
or
EtOH E
or
CMC suspension C

Synthesis:



30441

NaOH
0°C

Product

Chemist: S. Wattanasin / R. Patel

Chem. No.: 1206-179-30

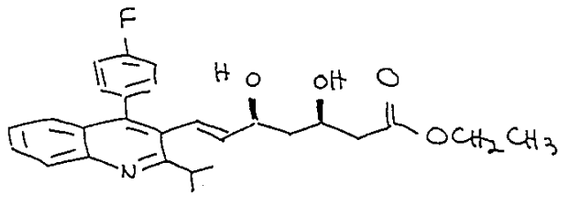
83520/74 Rev. 7

SANDOZ RESEARCH INSTITUTE
EAST HANOVER, NEW JERSEY
CHEMICAL INFORMATION

Date: 213

Compound No.: 64-935

Structure:



30447

Emp. Form: $C_{27}H_{30}NO_4F$
Mol. Wt. : 451
m.p. :
b.p. :
*Others :

Hanover : 20.0 mg
AM/AV :
Tr :
Agro :

Name:

Screen:	✓	Screen:	✓
AO		CS1	✓
GHI		CSTC	✓
GLUC		CSTV	✓
HG			
HL			
PL		AM/AV	
TC		Tr	
		Agro	

Compare With: 62-320

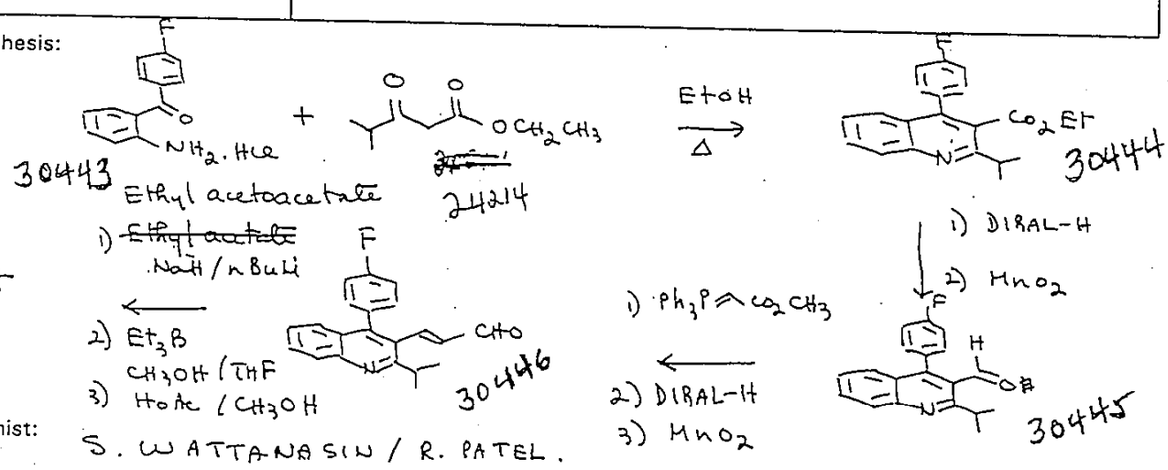
Pat. Disclosure No. 299184
L & D No. —
Known ____ Unknown X

Remarks: Dr. Scallen 20.0 mg erythro : threo > 95:5 Keep refrigerate

Preparation of Physiol. Solution:

DMA D
or
EtOH E
or
CMC suspension C

Synthesis:



Chemist: S. WATTANASIN / R. PATEL.

Chem. No.: 1206-190-41

83520/74 Rev. 7

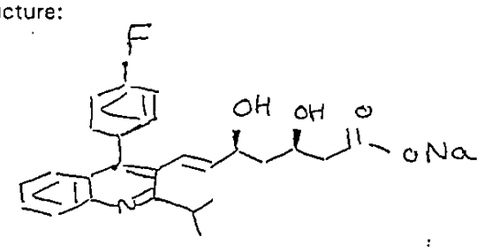
214

SANDOZ RESEARCH INSTITUTE
EAST HANOVER, NEW JERSEY
CHEMICAL INFORMATION

Date:

Compound No.: 64-936 / Na

Structure:



30448

Emp. Form: $C_{25}H_{25}FNO_4Na$
Mol. Wt. : 445.5
m.p. :
b.p. : > 225°C
*Others :

Hanover : 20mg
AM/AV :
Tr :
Agro :

Name:

Screen:	✓	Screen:	✓
AO		CSI	✓
GHI		CSIC	✓
GLUC		CSIV	✓
HG			
HL			
PL		AM/AV	
TC		Tr	
		Agro	

Compare With: 62-320

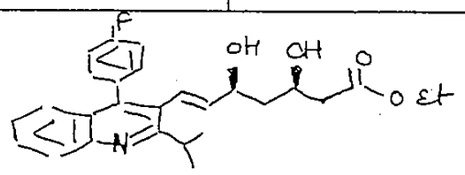
Pat. Disclosure No. 299 / 84
L & D No.
Known ____ Unknown X

Remarks: Dr. Scallen 20 mg
~~erythro~~ threo : threo > 95 : 5
Keep refrigerate

Preparation of Physiol. Solution:

DMA D
or
EtOH E
or
Cme Suspension C

Synthesis:

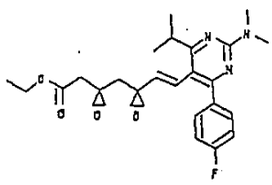
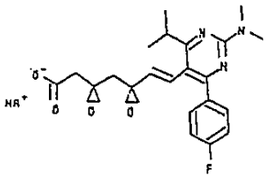
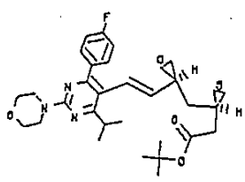
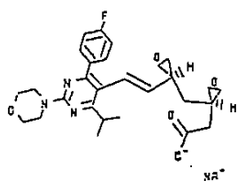
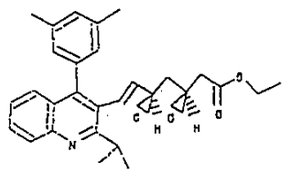
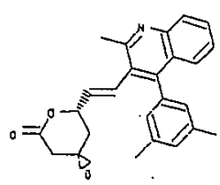


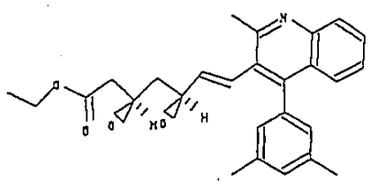
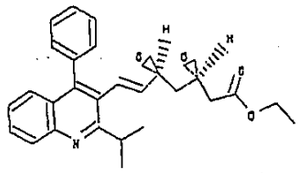
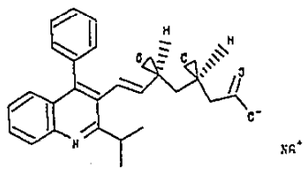
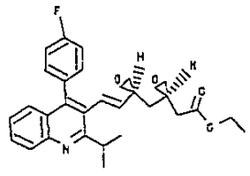
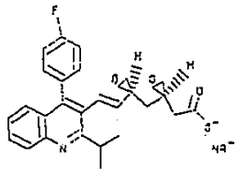
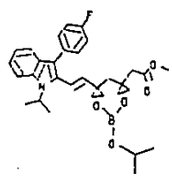
$\xrightarrow[0^\circ C]{NaOH}$ Product.

30447

Chemist: S. Wattanasin / R. Patel
Chem. No.: 1206-201-30

83520/74 Rev. 7

SAH-064747 30067 1190-248-32 298-84		ICSO (UM) - MICROSOMAL ASSAY 0.0820 DATE TESTED 05-03-87 REFERENCE 1149-295 COMMENTS
SAH-064748 30068 1190-257-26 298-84		ICSO (UM) - MICROSOMAL ASSAY 0.0600 DATE TESTED 05-01-87 REFERENCE 1149-296 COMMENTS
SAH-064998 30622 1245-108-35 298-84	CHIRAL 	ICSO (UM) - MICROSOMAL ASSAY 3.0400 DATE TESTED 11-17-87 REFERENCE 1238-020 COMMENTS
SAH-064999 30623 1245-120-30 298-84	CHIRAL 	ICSO (UM) - MICROSOMAL ASSAY 0.0800 DATE TESTED 11-17-87 REFERENCE 1238-021 COMMENTS BUFFER A
SAH-063366 25496 1079-111-19 299-84		ICSO (UM) - MICROSOMAL ASSAY 1.5800 DATE TESTED 12-13-84 REFERENCE 1069-113 COMMENTS
SAH-063549 26082 1127-011-37 299-84		ICSO (UM) - MICROSOMAL ASSAY 7.3100 DATE TESTED 06-13-84 REFERENCE 1069-197 COMMENTS

SAH-063548 26080 1127-011-34 299-84		ICSO (UM) - MICROSOMAL ASSAY 3.7750 DATE TESTED 06-13-84 REFERENCE 1069-198 COMMENTS
SAH-064933 30441 1206-176-43 299-84		ICSO (UM) - MICROSOMAL ASSAY 2.3700 DATE TESTED 10-08-87 REFERENCE 1238-013 COMMENTS
SAH-064934 30442 1206-179-30 299-84		ICSO (UM) - MICROSOMAL ASSAY 2.6100 DATE TESTED 10-08-87 REFERENCE 1238-014 COMMENTS
SAH-064935 30447 1206-190-41 299-84		ICSO (UM) - MICROSOMAL ASSAY 0.4130 DATE TESTED 10-08-87 REFERENCE 1238-015 COMMENTS
SAH-064936 30448 1206-201-30 299-84		ICSO (UM) - MICROSOMAL ASSAY 0.5300 DATE TESTED 10-13-87 REFERENCE 1238-016 COMMENTS
SAH-063224 25041 1036-087-41 431-84		ICSO (UM) - MICROSOMAL ASSAY 0.0019 DATE TESTED 07-26-84 REFERENCE 1069-033 COMM

250

Sandoz HMG-Co-A Reductase
Screening Book VI
page 56-57

12-13-84

217

Sandoz Compounds Tested for HMG-CoA Reductase

1) Following compounds weighed out to make 10mM dilution:

63-364 (25489)	1.30 mg	in 13.015 ml	DMA
63-365 (25490)	1.60 mg	in 18.836 ml	DMA
63-366 (25496)	1.50 mg	in 15.473 ml	DMA
63-369 (25512)	.5 mg	in 5.338 ml	DMA
63-162/3 (25500)	1.80 mg	in 19.284 ml	DMA
63-270/2 (25501)	.70 mg	in 15.411 ml	DMA

Following compounds saponified in 50° waterbath for 2 hrs:

2) Microsomes were made on 12-10-84 and kept frozen at -80° until thawed and rehomogenized for this experiment. Protein concentration of microsomes .180 X 10 X .68 = 1.18 mg/ml

3) Samples were pre-incubated 20 minutes in 37° waterbath.

4) 20µl 2mM NADPH added to each sample with repeating Eppendorf.

   20µl [^{14}C]HMG-CoA added to each sample with repeating Eppendorf.

5) Samples incubated 20 min in 37° waterbath.

6) Reaction stopped with addition of 50µl conc. HCL (12M).

7) 100µl [^{3}H]MVA added to each sample with pipetman.

8) Samples on benchtop 60 minutes before putting samples on columns.

9) Factor for calculations 48.44.

RESULTS OF EXPERIMENT:

218

12-13-84

PROGRAM #: 10
REGION A: LL-UL= 0- 6 LCR= 0 BKG= .11 +/- 2 sigma
REGION B: LL-UL= 24- 156 LCR= 0 BKG= 17 +/- 3 sigma
NUCLIDE 1 = 0 NUCLIDE 2 = 0
TIME= 10.00 DIP= SIE/AEC SCR= B/A K= 1.000

P#	S#	TIME	CPMA/K DPM1/K	%DEV	CPMB/K DPM2/K	%DEV	DIP	FLAGS	ECA	MIN		
									93572 / 96209 x 50 = 48.44			
					³H Recounted							
10	1	10.00	20582.7	.44	93.20	6.02	456.		.041	11		1.18 mg
			87534.5		43.27				.000			
10	2	10.00	7170.70	.75	55512.3	.27	501.		7.742	33		
			0.00		96209.0				.000			
10	3	10.00	12318.5	.57	194.60	4.35	436.		.014	33		
			52667.1		267.29				.054			
10	4	10.00	10848.5	.61	200.40	4.29	425.	Blank	.018	44		
			53428.8		289.65				.007			
10	5	10.00	11003.1	.60	3214.70	1.11	427.		.273	57		
			57072.2		5961.65				.103			
10	6	10.00	11823.8	.58	3211.50	1.11	424.	Buffer A .102	.272	44	1.00	
			61181.7		5968.35				.099			
10	7	10.00	12406.9	.57	3391.40	1.08	422.		.273	76		
			64623.8		6315.88				.091			
10	8	10.00	12170.4	.57	3456.30	1.12	421.	DMA .096	.283	57	.94	
			63621.3		5956.84				.075			
10	9	10.00	11314.1	.59	161.50	4.73	437.		.014	51	.00	100 I
			57798.3		213.54				.004			
10	10	10.00	12186.1	.57	256.70	3.82	424.	1mM 10^{-1}	.021	109	.02	98 I
			63777.3		384.87				.009			
10	11	10.00	12123.3	.57	519.80	2.73	427.	-2	.043	139	.10	90 I
			64522.7		880.36				.019			
10	12	10.00	11927.2	.58	1557.40	1.59	430.	-3	.131	174	.43	55 I
			61719.5		2823.10				.044			
10	13	10.00	11836.3	.58	2375.40	1.24	425.	-4	.200	244	.75	20 I
			60625.0		4737.92				.078			
10	14	10.00	11727.5	.58	2674.40	1.18	427.	-5	.230	191	.86	9 I
			60152.4		5310.16				.055			
10	15	10.00	12721.4	.56	3280.00	1.10	426.	-6	.245	197	.91	3 I
			64564.0		6060.68				.063			
10	16	10.00	12886.7	.56	3258.00	1.11	427.	-7	.243	274	.89	5 I
			66065.7		6023.92				.051			
10	17	10.00	12062.2	.58	3107.30	1.13	430. (24291)	-8	.255	167	.92	2 I
			61956.6		5725.33			Compactin	.038			
10	18	10.00	11753.4	.58	218.60	4.12	426.		.014	153		
			63082.9		316.24				.007		.01	99 I
10	19	10.00	11535.3	.59	318.10	3.45	427.	-3	.021	204	.04	96 I
			60526.9		504.78				.005			
10	20	10.00	11261.1	.60	603.00	2.54	425.	-4	.037	317	.13	86 I
			60350.9		1045.52				.011			
10	21	10.00	11621.5	.59	1007.80	1.98	426.	-5	.037	224	.25	73 I
			61450.8		1803.82				.025			
10	22	10.00	10983.5	.60	2628.40	1.23	429.	-6	.099	274	.84	10 I
			56002.5		4842.56				.024			
10	23	10.00	11265.4	.60	2946.80	1.16	425.	-7 (24291)	.073	256	.92	2 I
			58143.0		5466.68				.021			
10	24	10.00	10858.7	.61	2737.20	1.21	432.	-8	.071	341	.90	4 I
			54797.2		5028.53			62-320/Na-4	.013			

219

S#	TIME	CPMA/K DPM1/K	%DEV	CPMB/K DPM2/K	%DEV	GIP	FLAGS	SCR	MIN			
25	10.00	11571.1 58603.4	.56	2465.80 4511.85	1.27	432.	10^{-2}	.2[illegible] .07[illegible]	[illegible]	.71	24 I	
[illegible]	10.00	12009.1 61065.6	.58	2902.20 5344.66	1.17	429.	-3	.242 .06[illegible]	[illegible]	.86	9 I	
27	10.00	11570.3 61453.[illegible]	.58	3012.20 5572.15	1.15	426.	-7	.2[illegible] .0[illegible]	[illegible]	.89	5 I	
28	10.00	11459.2 56676.7	.57	2898.90 5340.51	1.17	430.	-5	[illegible] .0[illegible]	[illegible]	.90	4 I	
29	10.00	11745.5 59333.1	.58	2775.20 5164.85	1.20	431.	-4	.2[illegible] .0[illegible]	[illegible]	.84	10 I	
30	10.00	11443.1 56562.5	.59	2803.50 5186.67	1.19	426.	-7	.24[illegible] .0[illegible]	[illegible]	.86	9 I	
31	10.00	13386.9 68366.4	.55	3153.90 5838.62	1.12	425.	(25489) -8 63-364	.2[illegible] [illegible]	[illegible]	.82	13 I	19
32	10.00	11644.3 62787.8	.58	246.70 367.48	3.59	430.		[illegible]	[illegible]	.02	98 I	
33	10.00	10624.9 55337.4	.61	412.56 687.23	3.05	431.		[illegible]	[illegible]	.08	92 I	
34	10.00	12111.1 63257.6	.57	716.00 1248.47	2.33	430.		[illegible]	[illegible]	.16	83 I	
35	10.00	11355.5 58355.1	.59	1952.70 3563.63	1.43	431.		.171 .061	380	58	38 I	
36	10.00	12313.9 62437.3	.57	2925.50 5379.74	1.17	430.		.2[illegible] .08[illegible]	[illegible]	.84	11 I	
37	10.00	11429.9 56369.1	.59	2682.70 4888.43	1.22	437.		.2[illegible] .087	[illegible]	.85 ~~.85~~	10 I	
38	10.00	12475.8 62911.6	.57	3041.80 5588.37	1.14	431.	(25490) 63-365	.244 .08[illegible]	[illegible]	.87	8 I	20
[illegible]	10.00	11757.3 60468.4	.58	855.00 1502.14	2.14	433.		[illegible] .02[illegible]	[illegible]	.21	78 I	
40	10.00	11450.2 57757.9	.59	1903.50 3454.64	1.44	434.		.1[illegible] .0[illegible]	[illegible]	.57	39 I	
41	10.00	12775.5 63608.8	.56	2880.70 5258.52	1.17	435.		.225 .083	[illegible]	.81	14 I	
42	10.00	12769.3 63746.6	.56	3125.20 5733.39	1.13	432.		[illegible]	[illegible]	.80	6 I	
43	10.00	12097.7 60665.8	.57	3059.30 5623.40	1.14	431.		[illegible]	[illegible]	.90	4 I	
44	10.00	11673.6 59158.1	.55	3083.80 5705.71	1.17	430.		[illegible]	[illegible]	.88	6 I	
45	10.00	12125.7 61616.9	.57	2971.50 5473.37	1.15	429.	(25496) 63-366	[illegible]	[illegible]	.87	8 I	21
46	10.00	10567.4 53555.1	.60	235.10 352.63	3.55	430.		[illegible]	[illegible]	.02	98 I	
47	10.00	12710.0 63775.6	.57	673.10 1160.11	2.41	432.		[illegible]	[illegible]	.14	85 I	
48	10.00	11275.[illegible] 57120.2	.60	1478.90 2664.33	1.64	435.		[illegible]	[illegible]	.44	54 I	
49	10.00	10505.7 55[illegible]5.2	.61	1955.70 3632.51	1.41	430.		[illegible]	[illegible]	.62	34 I	
50	10.00	[illegible].4 [illegible]	.57	2562.30 4673.53	1.25	434.		[illegible]	[illegible]	.72	23 I	
	10.00	11105.9 55740.7	.60	2723.40 4980.73	1.21	435.		[illegible] .0[illegible]	[illegible]	.67	8 I	

8/20/85

ASSAY FOR HMG-CoA REDUCTASE

1) Thaw frozen microsomes in ice water for approximately 30-45 minutes, and rehomogenize microsomes with a tight-fitting pestle 10X.

2) Check the protein concentration of the sample by the method of Bradford, using a 1:10 dilution of microsomes. If needed dilute microsomes with Buffer A + 10mM DTT (pH 7.2). Microsomes should have a protein concentration of 1.0 mg/ml to 1.5 mg/ml.

3) 200 µl Buffer A + DTT is used for blank, run parallel with the enzyme samples.

4) 200 µl of the microsomal suspension is used to assay each sample.

5) Pre-incubate samples at 37° C in shaking waterbath for 20 minutes.

6) With Eppendorf repeating pipette, add 20 µl 2mM Nadph to each sample at timed intervals.

7) With Eppendorf repeating pipette, add 20µl [^{14}C]HMG-CoA (30,000 dpm, 2.5 mM final concentration).

8) Incubate samples 30 minutes in shaking 37° waterbath.

9) Stop reaction with 30µl 12M HCL at the same timed intervals as before.

10) Add 100 µl [^{3}H]mevalonate in distilled water (90,000 dpm) to each sample with pipetman.

11) Incubate samples at room temperature for at least 60 minutes. (Samples may be left at room temperature overnight.)

12) After room temperature incubation, each entire assaying volumn is applied to, and allowed to drain into the top of the resin column. The sample is eluted with 2 ml of distilled water, and counted in a dual channel detector with 5 mls of Merit Radioassay Medium (Isolab, Inc.)

13) Activity is calculated using the internal standard method of Goldfarb and Pitot.

PREPARATION OF COLUMNS USED FOR
HMG-CoA REDUCTASE ASSAY

1) Dowex 1-X8 200-400 mesh was obtained from Polysciences, Inc. The chloride salts of these resins were converted to the hydroxide form with 20 volumns of 1N sodium hydroxide followed by 5 volumns of distilled water. The subsequent conversion to the formate salt with 3-4 volumns of 1N formic acid is indicated by a distinct return of the resin to a lighter golden color. Excess salt is removed by rinsing extensively with distilled water. The well drained but damp resin is stored in the dark at 4° C.

2) Columns are prepared by pouring a slurry of resin, consisting of one part formate resin and three parts water into a polystyrene column (QS-J from Isolab, Inc.). Dimensions of the settled resin are 0.7 by 4 cm (1.5 ml if 5 mls of slurry are applied).

222

6-13-85.
1.07 mg/ml

PROGRAM #: 4
REGION A: LL-UL= 0- 8 LCR= 0 BKG= 11 % 2 SIGMA= .2
REGION B: LL-UL= 24- 156 LCR= 0 BKG= 17 % 2 SIGMA= .2
NUCLIDE 1 = 0 NUCLIDE 2 = 0
TIME= 10.00 QIP= SIE/AEC SCR= B/A K= 1.000

81731 / 31376 x 46.2 = 120.35

	S#	TIME	CPMA/K DPM1/K	%DEV	CPMB/K DPM2/K	%DEV	QIP	FLAGS	SCR	MIN	
4	1	10.00	19925.7 81731.8	.45	74.00 21.71	6.63	502.		.004 .000	11	
4	2	10.00	2275.30 0.00	1.32	18306.4 31376.4	.47	515.		8.046 .000	23	
4	3	10.00	12008.9 63316.8	.58	187.40 255.96	4.42	430.		.016 .004	33	
4	4	10.00	11819.5 62654.8	.58	183.40 249.90	4.47	429.	B1	.016 .004	44	
4	5	10.00	12376.4 65114.9	.57	987.30 1755.36	2.00	428.	Buffer .020	.080 .027	55	
4	6	10.00	6022.80 29724.8	.81	495.30 866.74	2.79	443.		.082 .029	66	.49
4	7	10.00	12240. [illegible]	[illegible]	0 4	1.95	428.		.085 .029	77	
4	8				3 3	2.01	425.	DMA .029	.085 .029	11.47	
4	9		11642.3 62636.8	.58	187.90 258.19	4.42	429.		.016 .004	22	.00 100 I
4	10	10.00	12091.9 64859.9	.57	217.50 311.77	4.13	426.	10^{-1}	.018 .005	33	.02 96 I
4	11	10.00	11725.2 61948.2	.58	282.20 435.93	3.66	429.	-2	.024 .007	44	.06 88 I
4	12	10.00	12117.6 63918.1	.57	616.90 1061.13	2.51	428.	-3	.051 .017	55	.24 48 I
4	13	10.00	12445.1 64654.8	.57	954.10 1686.41	2.03	431.	-4	.077 .026	66	.41 12 I
4	14	10.00	12006.8 62627.3	.58	1028.60 1831.99	1.96	430.	-5	.086 .029	76	.47 100 C
4	15	10.00	11767.0 60883.9	.58	1003.20 1782.27	1.98	431.	-6	.085 .029	87	.47 100 C
4	16	10.00	884.10 4239.44	2.11	67.20 116.16	6.89	451.	-7	.076 .027	98	.43 8 I
4	17	10.00	11813.5 60665.0	.58	1010.70 1792.17	1.97	433.	-8 Compactin	.086 .030	109	.49 104 C
4	18	10.00	5972.70 29944.0	.82	64.00 73.74	7.03	442.	10^{-2}	.011 .002	120	.00 100 I
4	19	10.00	11719.0 61510.3	.58	215.10 310.10	4.15	431.	-3	.018 .005	130	.02 96 I
	20	10.00	10876.4 56671.8	.61	331.00 533.04	3.39	432.	-4	.030 .009	141	.09 80 I
4	21	10.00	12112.8 64688.1	.57	470.40 787.87	2.86	426.	-5	.039 .012	199	.15 68 I
4	22	10.00	11203.1 57384.7	.60	701.80 1219.14	2.36	435.	-4	.063 .021	210	.32 32 I
4	23	10.00	12137.9 [illegible]	.57	995.80 [illegible]	1.99	430.	DMA -1	.082 .028	220	.45 4 I

4	31	10.00	12309.5 63810.8	...	-- 1890.28			63-210[illegible]					
4	32	10.00	12229.2 62777.4	.57	223.30 321.20	4.08	436.		10^{-2}	.016 .003	--	.02	96 I
4 (4)	33	10.00	12060.9 62360.8	.58	346.00 551.10	3.32	434.		-3	.029 .009	55	.09	80 I 223
	34	10.00	12161.0 63889.7	.57	754.10 1317.56	2.28	429.		-4	.062 .021	66	.32	32 I
4	35	10.00	12069.8 62939.3	.58	895.00 1580.24	2.09	430.		-5	.074 .025	77	.39	16 I
4	36	10.00	12133.6 63042.8	.57	987.90 1752.51	2.00	431.		-6	.081 .028	88	.45	4 I
4	37	10.00	12321.3 63352.7	.57	1036.30 1836.46	1.95	433.	(RN 26039)	-7	.084 .029	98	.47	100 C
4	38	10.00	12464.4 63999.6	.57	1038.50 1838.68	1.95	433.	63-537/Wa	-8	.083 .029	109	.47	100 C
4	39	10.00	12399.5 64833.9	.57	202.40 281.02	4.27	432.		10^{-2}	.016 .024	120	.00	100 I
4 (5)	40	10.00	12278.9 62975.6	.57	260.70 390.25	3.80	436.		-3	.021 .006	131	.04	92 I
4	41	10.00	11232.7 [illegible]	.60	406.30 671.54	3.07	431.		-4	.036	142	.13	72 I
4	[illegible]			.58	598.00 1020.12				-5			.22	52 I
4	43	10.00	[illegible] 63806.6	.57	929.20 1637.39	2.06	433.		-6	.075 .026	23	.41	12 I
4	44	10.00	12288.0 64072.1	.57	1040.60 1851.99	1.94	430.	(RN 26075)	-7	.085 .029	34	.47	100 C
4	45	10.00	12189.6 64092.5	.57	1042.40 1860.53	1.94	428.	63-547	-8	.086 .029	44	.47	100 C
4 (6)	46	10.00	12119.8 63770.7	.57	432.00 713.38	2.98	429.		10^{-2}	.036 .011	55	.13	72 I
4	47	10.00	12026.4 62744.7	.58	858.70 1512.64	2.14	430.		-3	.071 .024	66	.37	20 I
4	48	10.00	12099.0 63125.5	.57	1016.70 1808.97	1.97	430.		-4	.084 .029	77	.47	100 C
4	49	10.00	12212.9 62712.4	.57	1038.30 1840.44	1.95	433.		-5	.085 .029	88	.47	100 C
4	50	10.00	12166.8 62337.9	.57	1002.90 1773.52	1.98	434.		-6	.082 .028	98	.45	4 I
4	51	10.00	11720.1 60751.7	.58	988.90 1756.73	1.99	431.	(RN 26080)	-7	.084 .029	109	.47	100 C
4	52	10.00	11999.0 62691.6	.58	999.90 1778.92	1.98	429.	63-548	-8	.083 .028	[illegible]	.45	4 I
4	53	10.00	12032.0 62970.3	.58	556.20 946.02	2.64	430.		10^{-2}	[illegible]		.21	56 I
4 (7)	54	10.00	11866.9 63061.2	.58	933.20 1662.26	2.05	426.		-3	[illegible]	[illegible]	.41	12 I
4	55	10.00	11647.4 60781.4	.59	988.90 1760.63	1.99	429.		-4	[illegible]	[illegible]	.47	100 C
4	56	10.00	12011.1 64054.0	.58	1021.80 1830.37	1.96	424.		-5	[illegible] .029	164	.47	100 C
4	57	10.00	12067.7 63119.5	.58	1019.10 1815.00	1.96	429.		-6	.084 .029	174	.47	100 C
4	58	10.00	12212.6 62328.7	.57	985.50 1738.75	2.00	435.	(RW 26081)	-7	[illegible]	185	.45	4 I
4	59	10.00	11400.9 59940.9	.59	958.40 1708.90	2.03	428.	63-549	-8	[illegible]	[illegible]	.47	100 C
4	60	10.00	11300.5 59446.6	.59	304.50 480.86	3.53	430.		10^{-2}	[illegible]		.07	84 I
4	61	10.00	11780.8 61152.5	.58	674.40 1167.36	2.41	432.		-3	[illegible]	[illegible]	.28	40 I
			[illegible]	.58	909.30 [illegible]	2.08	426.		-4	[illegible]	[illegible]	.41	12 I
											[illegible]	.47	100 C

224

10	50	10.00	12404.4 62141.9	.57	2562.30 4673.53	1.25	434.	[illegible]		.72 23 I
10	51	10.00	11205.5 55740.7	.60	2723.40 4980.75	1.21	435.	[illegible] .065	[illegible]	.87 8 I

P#	S#	TIME	CPMA/K DPM1/K	%DEV	CPMB/K DPM2/K	%DEV	QIP FLAGS	SCP	MIN	Handwritten notes
10	52	10.00	11753.4 60586.7	.58	2944.10 5444.86	1.16	427.	.158 .059	[illegible]	(25512) 63-369 .88 6I 22
10	53	10.00	11765.0 62249.7	.58	214.10 307.89	4.16	429.	.016 .005	[illegible]	.01 99 I
10	54	10.00	10748.4 55439.6	.61	226.20 338.05	4.06	435.	.021 .006	[illegible]	.62 98 I
10	55	10.00	12134.1 63682.0	.57	552.20 938.29	2.65	430.	.046 .015	[illegible]	.11 89 I
10	56	10.00	10750.4 55637.9	.61	721.60 1261.87	2.33	433.	.067 .023	[illegible]	.19 80 I
10	57	10.00	11988.4 61226.1	.58	2270.30 4154.19	1.32	430.	[illegible] .068	[illegible]	.65 31 I
10	58	10.00	12140.5 61534.3	.57	2764.90 [illegible]	1.20	431.	[illegible] .082	[illegible]	.81 14 I
10	59	10.00	12035.4 60645.6	.58	2669.10 4893.27	1.22	431.	[illegible]	[illegible]	(25500) 63-162/3 .78 17I 23.
10	60	10.00	12245.9 64692.3	.57	227.60 329.78	4.04	425.	[illegible] .005	[illegible]	162 .01 99 I
10	61	10.00	10555.8 58713.3	.60	324.60 522.15	3.42	426.	.030 .009	[illegible]	-3 .05 95 I
10	62	10.00	11783.4 62219.8	.58	466.60 781.54	2.88	429.	.040 .013	[illegible]	-4 [illegible] 91 I
10	63	10.00	11538.9 61266.4	.58	1117.40 1996.45	1.88	433.	.054 .032	[illegible]	-5 .28 70 I
10	64	10.00	12183.0 63370.6	.57	2545.80 4700.04	1.25	425.	[illegible] .074	[illegible]	-6 .71 24 I
10	65	10.00	11091.6 57125.0	.60	2441.30 4500.65	1.28	427.	[illegible] .077	[illegible]	(25501) -7 .77 18 I
10	66	10.00	11976.4 62224.6	.58	2728.90 5050.30	1.21	425.	[illegible] .081	[illegible]	63-270/2 -8 .79 16 I

P#	S#	TIME	CPMA/K DPM1/K	%DEV	CPMB/K DPM2/K	%DEV	QIP FLAGS	SCP	MIN
4	1	5.00	6663.06 0.00	1.09	52764.0 59501.8	.39	508.	7.605 .000	6
PIN JAM									
4	2	5.00	7371.60 0.00	1.04	55378.8 55646.8	.38	505.	7.512 .000	12
PIN JAM									

avg
BH
93273.5

93273.5

OCTOBER 8, 1987

DRUG INHIBITION STUDY FOR SANDOZ CONTRACT

Sandoz unknowns were dissolved in DMA (Dimethylacetamide from Sigma), and Buffer A
Dilution of each compound gave the concentrations indicated in the results.

Microsomes were prepared from male Sprague-Dawley rats (150 g) in Buffer A with 10 mM DTT and frozen at -80°C until thawed and used for experiment. 200 µl Aliquots of microsomal suspension (0.91 mg/ml) plus 10 µl of drug dilution were assayed for HMG-CoA reductase activity.

Compactin in DMA at various concentrations was assayed for inhibition also and is indicated in the results. Buffer A, and DMA were also assayed by adding 10 µl of each to 200 µl of microsomal suspension and they showed no significant inhibition of HMG-CoA reductase.

COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL	% OF INHIBITION	REMARKS
) Compactin (29299)	10/8/87	DMA				
1mM			.01	1	99	
10^{-1}			.04	3	97	
10^{-2}			.18	17	83	
10^{-3}			.62	61	39	
10^{-4}			.88	86	14	
10^{-5}			1.04	102	-	
10^{-6}			1.04	102	-	
10^{-7}			1.02	100	-	
10^{-8}			1.04	102	-	
) 62-320 (24135)	10/8/87	DMA				
10^{-2}			.01	1	99	
10^{-3}			.06	6	94	
10^{-4}			.20	20	80	
10^{-5}			.36	36	64	
10^{-6}			.83	82	18	
10^{-7}			1.02	100	-	
10^{-8}			1.02	100	-	
:) 64-906 (RN 30393)	10-8-87	DMA				
10^{-2}			.01	1	99	
10^{-3}			.01	1	99	
10^{-4}			.11	10	90	
10^{-5}			.27	26	74	
10^{-6}			.55	54	46	
10^{-7}			1.02	100	-	
10^{-8}			1.02	100	-	
1) 64-933 (RN 30441)	10-8-87	DMA				
10^{-2}			.20	20	80	
10^{-3}			.69	68	32	
10^{-4}			.99	98	2	
10^{-5}			1.04	102	-	
10^{-6}			.99	98	2	
10^{-7}			1.04	102	-	
10^{-8}			.99	98	2	

COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL	% OF INHIBITION	REMARKS
5) 64-934/Na(RN 30442)	10/8/87	DMA				
10^{-2}			.22	22	78	
10^{-3}			.71	70	30	
10^{-4}			.99	98	2	
10^{-5}			1.04	102	-	
10^{-6}			1.04	102	-	
10^{-7}			1.02	100	-	
10^{-8}			1.23	121	-	
6) 64-935 (RN 30447)	10/8/87	DMA				
10^{-2}			.13	13	87	
10^{-3}			.32	31	69	
10^{-4}			.74	72	28	
10^{-5}			.92	91	9	
10^{-6}			.95	93	7	
10^{-7}			.97	95	5	
10^{-8}			1.02	100	-	
7) 64-942/Na(RN 30461)	10/8/87	DMA				
10^{-2}			.71	70	30	Unable to weigh out
10^{-3}			.99	98	2	compound-assuming
10^{-4}			.99	98	2	exactly 0.6mg in vial
10^{-5}			.97	95	5	sent from Sandoz,
10^{-6}			1.02	100	-	dilution calculated
10^{-7}			1.02	100	-	and made directly in
10^{-8}			1.02	100	-	vial.
8) 64-727/Na(RN 30024)	10/8/87	DMA				
1 mM			.06	6	94	
10^{-1}			.39	38	62	
10^{-2}			.90	89	11	
10^{-3}			1.02	100	-	
10^{-4}			1.06	105	-	
10^{-5}			.99	98	2	
10^{-6}			.99	98	2	

227

228

PROGRAM #: 10
REGION A: LL-UL= 0- 8 LCR= 0 BKG= 15 % 2 SIGMA= .2
REGION B: LL-UL= 24- 156 LCR= 0 BKG= 10 % 2 SIGMA= .2
NUCLIDE 1 = 0 NUCLIDE 2 = 0
TIME= 10.00 QIP= SIE/REC SCR= B/A K= 1.000

10-8-87

0.91 mg/ml

81965.9 / 32519.6 x 50.6 = 127.54

P#	S#	TIME	CPM A/K / DPM1/K	%DEV	CPM B/K / DPM2/K	%DEV	QIP	FLAGS	SCR	MIN		
10	1	10.00	3091.60 / 235.65	1.13	20162.1 / 32519.6	.45	623.		6.522 / 138.00	11		
10	2	10.00	25818.6 / 81965.9	.39	25.60 / 0.00	10.6	614.	1	.001 / .000	23		
10	3	10.00	15376.8 / 57803.8	.51	118.30 / 152.01	5.58	536.	1	.008 / .003	34		
10	4	10.00	14913.9 / 55504.1	.52	98.70 / 120.38	6.07	540.	Blank	.007 / .002	45	S.A.	% I
10	5	10.00	15943.8 / 58737.5	.50	1667.70 / 2783.28	1.54	537.	1	.105	55		
10	6	10.00	14562.0 / 53578.4	.52	1500.00 / 2501.69	1.63	538.	1	DNA control .047 / .103 / .047	Avg. .046 66	1.02	
10	7	10.00	15625.1 / 59001.1	.51	147.00 / 199.82	5.05	534.		.009	77		
10	8	10.00	14951.6 / 56705.7	.52	146.30 / 200.61	5.06	532.	1	1mM .002 / .010	88	.01	99 I
10	9	10.00	16065.6 / 59499.6	.50	373.50 / 582.69	3.23	540.	1	10^{-1} .004 / .023	99	.04	97 I
10	10	10.00	16091.8 / 58934.3	.50	1038.90 / 1708.91	1.95	542.	1	-2 .010 / .063	110	.18	83 I
10	11	10.00	15994.6 / 58487.0	.50	1410.50 / 2339.90	1.68	541.	1	-3 .029 / .088	121	.62	39 I
10	12	10.00	14930.8 / 54627.5	.52	1525.80 / 2540.53	1.61	540.		-4 .040 / .102	132	.88	14 I
10	13	10.00	16937.4 / 63125.5	.49	1780.10 / 2979.86	1.49	533.	1	-5 .047 / .105	143	1.04	10
10	14	10.00	15441.7 / 57114.5	.51	1579.60 / 2637.63	1.59	536.		-6 .047 / .102	153	1.04	10
10	15	10.00	15874.9 / 58835.7	.50	1648.60 / 2755.17	1.55	535.	(29299)	-7 .046 / .104	164	1.02	10
10	16	10.00	16273.6 / 62289.0	.50	150.40 / 202.79	4.99	529.	Competit 1 10μM	-8 .047 / 10^{-2} .009	175	1.04	10
10	17	10.00	15753.3 / 59820.1	.50	208.90 / 304.73	4.27	531.	1	.003		.01	99 I
10	18	10.00	15849.2 / 58981.0	.50	418.40 / 660.18	3.06	538.	1	-3 .013 / .035	186	.06	94 I
10	19	10.00	15451.8 / 57686.1	.51	645.60 / 1048.57	2.47	536.	1	-4 .026 / .011	197	.20	80 I
10	20	10.00	15316.0 / 56089.6	.51	1287.10 / 2133.36	1.76	541.	1	-5 .043 / .018	208	.36	64 I
10	21	10.00	16492.1 / 60323.7	.49	1669.40 / 2778.83	1.54	540.	1	-6 .034 / .038	219	.83	18 I
10	22	10.00	15743.7 / 57748.1	.50	1581.50 / 2633.97	1.59	539.	(24135) 62-320	-7 .101 / .046	230	1.02	10
10	23	10.00	15611.7 / 58828.3	.51	132.80 / 175.79	5.29	535.		-8 .100 / .046	240	1.02	10
10	24	10.00	15512.4 / 58038.1	.51	137.60 / 184.46	5.21	537.	1	.009 / -2 .003	251	.01	99 I
									.009 / -3 .003	262	.01	99 I

P#	S#	TIME	CPMA/K DPM1/K	%DEV	CPMB/K DPM2/K	%DEV	QIP	FLAGS	SCR	MIN		
10	25	10.00	16190.3 59961.2	.50	261.30 392.02	3.84	541.		.016 -4 .007	273	.11	90I
10	26	10.00	16559.8 62307.7	.49	537.30 861.72	2.70	534.	1	.032 -5 .014	284	.27	74I
10	27	10.00	16551.0 61974.6	.49	984.30 1623.19	2.01	534.	1	.059 -6 .026	295	.55	46I
10	28	10.00	16260.6 60033.6	.50	1649.80 2753.02	1.55	536.	1	-7 .101 .046	306	1.02	100C
10	29	10.00	16764.8 61837.3	.49	1705.70 2845.79	1.53	537.	1	-8 .102 .046	317	1.02	100C
10	30	10.00	16189.0 60617.9	.50	435.30 688.63	3.00	536.	1	-2 .027 .011	328	.20	80I
10	31	10.00	16090.9 60145.2	.50	1156.80 1818.69	1.85	534.	1	.072 -3 .032	339	.69	32I
10	32	10.00	16286.0 60445.6	.50	1159.40 1821.69	1.56	535.	1	.100 -4 .045	350	.99	2 I
10	33	10.00	16217.7 58786.2	.50	1665.60 2766.93	1.55	544.	1	.103 -5 .047	360	1.04	102C
10	34	10.00	16174.1 59576.6	.50	1621.90 2704.09	1.57	537.		.100 -6 .045	371	.99	2 I
10	35	10.00	16642.2 61808.1	.49	1733.70 2899.09	1.51	534.	1	-7 .104 .047	382	1.04	102C
10	36	10.00	15984.6 58807.1	.50	1604.50 2674.30	1.57	538.	1	-8 .100 .045	393	.99	2 I
10	37	10.00	16010.2 60104.5	.50	457.90 727.94	2.92	535.		-2 .029 .012	404	.22	78I
10	38	10.00	15910.1 59043.1	.50	1188.50 1970.18	1.83	536.	1	-3 .075 .033	415	.71	30I
10	39	10.00	15210.9 56444.4	.51	1511.00 2523.37	1.62	535.	1	-4 .099 .045	426	.99	2I
10	40	10.00	15940.7 58354.9	.50	1630.10 2714.63	1.56	540.	1	-5 .102 .047	437	1.04	102C
10	41	10.00	15797.7 58542.5	.50	1640.90 2742.23	1.56	535.	1	-6 .104 .047	448	1.04	102C
10	42	10.00	15693.3 57754.7	.50	1605.20 2676.87	1.57	538.	1	-7 .102 .046	458	1.02	100C
10	43	10.00	17034.4 62837.8	.48	2050.90 3434.60	1.39	536.	1	-8 .120 .055	469	1.25	121C
10	44	10.00	15281.6 57387.8	.51	310.10 478.64	3.53	535.	1	-2 .020 .008	480	.13	87I
10	45	10.00	16345.3 61027.6	.49	588.20 947.92	2.59	536.	1	-3 .036 .016	491	.32	69I
10	46	10.00	16369.7 60434.1	.49	1226.10 2030.00	1.80	538.	1	-4 .075 .034	502	.74	28I
10	47	10.00	16280.1 59712.9	.50	1515.40 2519.27	1.62	540.	1	-5 .093 .042	513	.92	9I
10	48	10.00	16271.8 60108.7	.50	1562.10 2603.64	1.60	537.	1	-6 .096 .043	524	.95	7I
10	49	10.00	15953.0 59171.0	.50	1567.10 2616.87	1.59	535.	1	-7 .098 .044	535	.97	5I
10	50	10.00	15663.0 57617.7	.51	1599.00 2653.15	1.58	537.	1	-8 .102 .045	547	1.02	100C
10	51	10.00	16211.6 60604.2	.50	184.40 262.19	4.54	533.	1	-2 .011 .004		.04	97I

(RN 30393) 64-906/Na

(RN 30441) 64-933

(RN 30442) 64-934/Na

(RN 30447) 64-935

P#	S#	TIME	CPMA/K DPM1/K	%DEV	CPMB/K DPM2/K	%DEV	QIP	FLAGS	SCR	MIN		
10	52	10.00	15089.3 56615.4	.51	545.90 880.81	2.68	534.		-3 .036	567		69I

P#	S#	TIME	CPMA/K CPM1/K	%DEV	CPMB/K CPM2/K	%DEV	DIP	FLAG				
10	42	10.00	15693.3 57754.7	.50	1605.20 2676.87	1.57	538.	1	-7	.102 .046	458	1.02	1 230
10	43	10.00	17034.4 62837.8	.48	2050.90 3434.60	1.39	536.	1	-8	.120 .055	469	1.28	121C
10	44	10.00	15281.6 57367.8	.51	310.10 478.64	3.53	535.	1	-2	.020 .008	480	.13	87 I
10	45	10.00	16345.3 61027.6	.49	588.20 947.92	2.59	536.	1	-3	.036 .016	491	.32	69 I
10	46	10.00	16369.7 60434.1	.49	1226.10 2030.00	1.80	538.	1	-4	.075 .034	502	.74	28I
10	47	10.00	16200.1 59712.9	.50	1515.40 2519.27	1.62	540.	1	-5	.093 .042	313	.92	9 I
	48	10.00	16271.8 60108.7	.50	1562.10 2603.64	1.60	537.	1	-6	.096 .043	324	.95	7I
10	49	10.00	15953.0 59171.0	.50	1567.10 2616.07	1.59	535.	1	-7	.098 .044	335	.97	5I
10	50	10.00	15663.0 57817.7	.51	1590.00 2653.15	1.58	537.	1	-8	.100 .045	347	1.02	100C
10	51	10.00	16011.6 60604.2	.50	184.40 262.19	4.54	533.	1	-2	.011 .004		.04	97I
10	52	10.00	15089.3 56615.4	.51	545.90 880.81	2.68	534.		-3	.036 .016	567	.32	69I
10	53	10.00	16394.2	.49	1082.90	1.91	533.	1	-4	.065 .029	578	.62	39 I
10	54	10.00	61438.0 15760.3 59017.1	.50	1792.44 16.80 0.00	12.2	539.	1	-5	.091 .040	589	—	—
10	55	10.00	15147.5 56761.0	.51	14.10 0.00	12.8	537.	1	-6	.091 .040	600	—	—
	56	10.00	15504.2 57376.3	.51	1645.90 2751.02	1.55	535.	1	-7	.104 .046	611	1.06	105C
10	57	10.00	15646.4 58003.1	.51	1633.90 2731.11	1.56	535.	1	-8	.104 .047	623	1.04	102C
10	58	10.00	16494.4 60623.6	.49	1675.70 2795.44	1.54	537.	1		.105 .047			
10	59	10.00	16837.0 62238.5	.49	1673.10 2791.43	1.54	536.	1		.105 .047			
10	60	10.00	16031.2 58941.1	.50	1638.80 2732.18	1.56	538.	1	10xM	.104 .046		1.02	100C

Dark current

OCTOBER 15, 1987

DRUG INHIBITION STUDY FOR SANDOZ CONTRACT

Sandoz unknowns were dissolved in DMA (Dimethylacetamide from Sigma), and Buffer A
Dilution of each compound gave the concentrations indicated in the results.

Microsomes were prepared from male Sprague-Dawley rats (150 g) in Buffer A with 10 mM DTT and frozen at -80°C until thawed and used for experiment. 200 µl Aliquots of microsomal suspension (0.96 mg/ml) plus 10 µl of drug dilution were assayed for HMG-CoA reductase activity.

Compactin in DMA at various concentrations was assayed for inhibition also and is indicated in the results. Buffer A, and DMA were also assayed by adding 10 µl of each to 200 µl of microsomal suspension and they showed no significant inhibition of HMG-CoA reductase.

COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL	% OF INHIBITION
1) Compactin (29299)	10-13-87	DMA			
1mM			.02	2	98
10^{-1}			.02	2	98
10^{-2}			.18	20	80
10^{-3}			.64	69	31
10^{-4}			.84	91	9
10^{-5}			.95	103	–
10^{-6}			1.02	110	–
10^{-7}			.98	106	–
10^{-8}			.98	106	–
2) 62-320 (24135)	10-13-87	DMA			
10^{-2}			.02	2	98
10^{-3}			.05	5	95
10^{-4}			.18	20	80
10^{-5}			.30	32	68
10^{-6}			.86	93	7
10^{-7}			.98	106	–
10^{-8}			.95	103	–
3) 64-942/Na (30461)	10-13-87	DMA			
10^{-2}			.73	79	21
10^{-3}			.95	103	–
10^{-4}			1.05	113	–
10^{-5}			.91	98	2
10^{-6}			.93	101	–
10^{-7}			1.00	108	–
10^{-8}			.98	106	–
4) 62-526/Na (29724)	10-13-87	DMA			
10^{-2}			.02	2	98
10^{-3}			.11	12	88
10^{-4}			.46	50	50
10^{-5}			.80	86	14
10^{-6}			.93	101	–
10^{-7}			.98	106	–
10^{-8}			.98	106	–

COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL	% OF INHIBITION	REMARK
5) 64-727 (RN 30024)	10-13-87	DMA				
1mM			.05	5	95	
10^{-1}			.34	37	63	
10^{-2}			.82	88	12	
10^{-3}			.93	101	-	
10^{-4}			.95	103	-	
10^{-5}			.98	106	-	
10^{-6}			.93	101	-	
10^{-7}			.93	101	-	
10^{-8}			.95	103	-	
6) 64-948/Na(RA 30485)	10-13-87	DMA				
10^{-2}			.95	103	-	
10^{-3}			1.00	108	-	
10^{-4}			.95	103	-	
10^{-5}			.98	106	-	
10^{-6}			.95	103	-	
10^{-7}			.98	106	-	
7) 64-936/Na (RN 30448)	10-13-87	DMA				
10^{-2}			.07	7	93	
10^{-3}			.32	34	66	
10^{-4}			.73	79	21	
10^{-5}			.89	96	4	
10^{-6}			.93	101	-	
10^{-7}			.95	103	-	
10^{-8}			.95	103	-	

233

234

PROGRAM #: 10
REGION A: LL-UL= 0- 8 LCR= 0 BKG= 15 % 2 SIGMA= .0
REGION B: LL-UL= 24- 156 LCR= 0 BKG= 10 % 2 SIGMA= .2
NUCLIDE 1 = 0 NUCLIDE 2 = 0
TIME= 10.00 QIP= SIE/AEC SCR= B/A K= 1.000

10-13-87

P#	S#	TIME	CPMA/K DPM1/K	%DEV	CPMB/K DPM2/K	%DEV	QIP	FLAGS	SCR	MIN		
									87022.6/33633.3 × 50.6-130.9			
.0	1	10.00	3063.30 0.00	1.14	20864.8 33633.3	.44	624.		6.811 .000	11		
.0	2	10.00	27939.4 87022.6	.38	22.40 0.00	11.1	624.	1	.001 .000	23		
.0	3	10.00	14743.0 53935.1	.52	89.10 105.03	6.35	546.	1	.006 .002	33		
.0	4	10.00	15103.6 55527.8	.51	91.20 107.35	6.29	544.	1	Blank .006 .002	44	S.A.	
.0	5	10.00	16545.8 59952.0	.49	1543.10 2557.41	1.60	545.	1	.093 .043	55	.043	
.0	6	10.00	15478.0 56015.2	.51	1569.50 2605.45	1.59	544.		Dmin control .101 .047	66	0.93	
.0	7	10.00	15921.3 58454.7	.50	130.10 170.59	5.34	545.	1	.008 1mM .003	77	.02	98 I
.0	8	10.00	16044.9 58913.1	.50	145.70 196.57	5.07	545.	1	.009 10⁻¹ .003	88	.02	98 I
.0	9	10.00	14929.8 54113.5	.52	340.10 527.59	3.38	549.	1	.023 -2 .010	99	.18	80 I
.0	10	10.00	15351.1 55587.1	.51	1024.60 1682.45	1.97	547.	1	.067 -3 .030	110	.64	31 I
.0	11	10.00	15655.7 56431.5	.51	1331.40 2198.60	1.73	547.	1	.085 -4 .039	120	.84	9 I
.0	12	10.00	16111.9 57735.5	.50	1542.40 2530.58	1.61	549.	1	.096 -5 .044	131	.95	103C
.0	13	10.00	15710.6 56752.8	.50	1606.60 2666.29	1.57	545.	1	.102 -4 .047	142	1.02	110C
.0	14	10.00	15175.0 55220.6	.51	1491.70 2478.03	1.63	542.	1	(29299) -7 .098 .045	153	.98	106C
.0	15	10.00	15977.0 57579.1	.50	1580.20 2618.88	1.59	546.	1	-8 .099 Compactin .045	164	.98	106C
.0	16	10.00	16098.9 58807.5	.50	135.80 179.70	5.24	547.	1	.008 -2 .003	175	.02	98 I
.0	17	10.00	14956.1 54842.4	.52	159.80 223.76	4.85	545.	1	.011 -3 .004	186	.05	95 I
.0	18	10.00	15643.9 57352.4	.51	383.20 599.35	3.19	544.	1	.024 -4 .010	197	.18	80I
.0	19	10.00	16031.6 58424.5	.50	554.50 886.95	2.66	546.	1	.035 -5 .015	207	.30	68 I
.0	20	10.00	15638.5 56659.5	.51	1368.20 2283.93	1.70	545.	1	.087 -6 .040	218	.86	7 I
.0	21	10.00	16301.4 58292.5	.50	1602.40 2650.00	1.58	550.	1	(24135) -7 .098 .045	229	.98	106C
.0	22	10.00	15996.2 58[illegible]	.50	1543.10 2[illegible]	1.60	547.	1	-8 .096 .044	240	.95	103C
.0	23	10.00	16477.1 59531.6	.49	1226.40 2019.18	1.80	547.		1e2-320 .074 .034	251	.73	21 I
.0	24	10.00	15445.1 55659.6	.51	1483.40 2456.75	1.64	547.	1	.096 .044	262	.95	103C

#	S#	TIME	CPMA/K DPM1/K	%DEV	CPMB/K DPM2/K	%DEV	QIP	FLAGS	SCR	MIN		
0	25	10.00	16087.8 58014.3	.50	1679.80 2787.82	1.54	546.	1	.104 .048	293	1.05	113C
0	26	10.00	16237.2 59020.8	.50	1487.80 2466.71	1.63	543.		.092 .042	284	.91	2I
0	27	10.00	15786.5 57087.1	.50	1481.70 2454.77	1.64	545.	1	.094 .043	295	.93	101C
0	28	10.00	16477.1 59148.7	.49	1640.10 2715.81	1.56	548.	1	.100 .046	306	1.00	108C
0	29	10.00	16689.9 59692.7	.49	1641.20 2714.32	1.56	550.	1	.098 .045	317	.98	106C
10	30	10.00	15803.5 54349.8	.51	110.10 139.60	5.77	553.	1	10^{-2} .007 .003	327	.02	98I
10	31	10.00	15986.5 57774.5	.50	281.30 425.04	3.71	551.	1	-3 .018 .007	338	.11	88I
10	32	10.00	15810.4 54035.6	.52	795.50 1294.24	2.23	550.		-4 .053 .024	349	.46	50I
10	33	10.00	15729.1 56993.4	.50	1289.60 2130.37	1.75	545.	1	-5 .082 .037	360	.80	14I
10	34	10.00	16357.9 59860.3	.49	1533.10 2538.81	1.61	546.	1	-4 .094 .043	371	.93	101C
10	35	10.00	15098.9 54628.8	.51	1476.00 2448.00	1.64	545.	1	-7 .098 .045	382	.98	106C
10	36	10.00	14843.9 52996.7	.52	1442.70 2384.31	1.66	550.	1	-8 .097 .045	393	.98	106C
10	37	10.00	15203.0 55123.7	.51	174.20 247.13	4.66	550.		10^{-1} .011 .004	404	.05	95I
1	38	10.00	15340.4 55110.1	.51	578.00 925.95	2.61	552.	1	10^{-1} .038 .017	415	.34	63I
10	39	10.00	15278.8 54718.9	.51	1274.30 2099.84	1.76	550.	1	-2 .083 .038	425	.82	12I
10	40	10.00	15634.7 55800.0	.51	1463.40 2416.17	1.65	551.	1	-3 .094 .043	436	.93	101C
10	41	10.00	15570.0 55720.7	.51	1495.90 2473.86	1.63	549.	1	-4 .096 .044	447	.95	103C
10	42	10.00	16599.6 59379.4	.49	1614.90 2670.27	1.57	550.	1	-5 .097 .045	457	.98	106C
10	43	10.00	15425.8 55637.3	.51	1460.60 2418.70	1.65	546.		-6 .096 .043	468	.93	101C
10	44	10.00	15553.8 56231.7	.51	1508.10 2500.05	1.62	545.	1	10^{-2} .011 .004	479	.95	103C
10	45	10.00	16699.3 60849.5	.49	1660.60 2750.91	1.55	547.	1	-1 .044 .019	489	1.00	108C
10	46	10.00	16603.4 59991.7	.49	1597.90 2648.30	1.58	545.	1	-4 .044 .019	500	.95	103C
10	47	10.00	16750.7 60361.5	.49	1621.10 2686.67	1.57	547.	1	-5 .045 .020	511	.98	106C
10	48	10.00	15341.0 55700.3	.51	1471.10 2435.34	1.64	547.	1	-6 .044 .019	521	.95	103C
10	49	10.00	16059.6 58218.2	.50	1577.80 2618.46	1.59	544.	1	-7 .045 .020	532	.98	106C
10	50	10.00	15048.4 54760.6	.51	1213.30 2000.23	1.81	548.	1	-8 .037 .017	543	.80	14I ?
10	51	10.00	15549.0 56878.9	.51	199.80 289.47	4.37	546.	1	10^{-2} .013 .005	554	.07	93I

#	S#	TIME	CPMA/K	%DEV	CPMB/K	%DEV	QIP	FLAGS	SCR	MIN

(30461) 64-942/Na

(29724) 62-526/Na

64-727

(RN 30485 64-948/Na

			60849.5		2750.91								
10	46	10.00	16602.4	.49	1597.90	1.58	545.	1		-4 .044		.95	103C
			59991.7		2646.70								
10	47	10.00	16750.7	.49	1622.10	1.57	547.	1		-5 .045		.98	101C
			60761.5		2686.67								
10	48	10.00	15341.0	.51	1471.10	1.64	547.	1		-6 .044		.95	103C
			55700.3		2435.34								
10	49	10.00	16059.6	.50	1577.80	1.59	547.	1		-7 .045		.98	101C
			58213.2		2618.46								
10	50	10.00	15968.4	.51	1213.30	1.61	548.	1		-8 .037		.80	14I ?
			54760.6		2000.23								

(RN 30485)

64-948 / Na

10	51	10.00	15549.0	.51	199.60	4.37	546.	1		-2 .013		.07	93I
			56878.9		289.47					.005			

P#	S#	TIME	CPMA/K DPM1/K	%DEV	CPMB/K DPM2/K	%DEV	QIP	FLAGS	SCR	MIN		
10	52	10.00	15816.7	.50	574.60	2.62	545.	1	.036	567		
			57837.6		922.29				-3 .016		.32	66I
10	53	10.00	15180.4	.51	1145.30	1.86	547.	1	.075	578		
			54882.5		1886.68				-4 .034		.73	21I
10	54	10.00	15774.1	.50	1401.00	1.68	545.	1	.089	589		
			57123.9		2318.80				-5 .041		.89	4I
10	55	10.00	15900.1	.50	1509.00	1.62	545.	1	.095	600		
			57567.7		2501.44				-4 .043		.93	101C
10	56	10.00	16502.8	.49	1574.50	1.59	543.	1	-7 .095	611		
			59946.6		2612.55				.044		.95	103C
10	57	10.00	16387.2	.49	1575.30	1.59	545.	1	-8 .096	622		
			59239.5		2611.10				.044		.95	103C

(RN 30448)

64-936 / Na

10	58	10.00	16200.5	.50	1510.50	1.62	548.	1	.093	633			
			58151.9		2497.36				-7 .043		.93	101C	
10	59	10.00	15843.5	.50	1512.80	1.62	545.	1	-8 .095	643			
			57283.5		2507.21				.044		.95	103C	
10	60	10.00	16033.5	.50	1514.70	1.62	547.	1	.094	654			
			57707.8		2506.81				.043				
10	61	10.00	16912.0	.49	1388.70	1.69	547.	1	.082	665			
			61089.5		2292.19				.038				

64-727

Dmk Crushed

237

DRUG INHIBITION STUDY FOR SANDOZ CONTRACT

Sandoz unknowns were dissolved in DMA (Dimethylacetamide from Sigma), and Buffer A and DMSO: 0.1 M NaOH.
Dilution of each compound gave the concentrations indicated in the results.

Microsomes were prepared from male Sprague-Dawley rats (~180g) in Buffer A with 10 mM DTT and frozen at -80°C until thawed and used for experiment. 200 µl Aliquots of microsomal suspension (1.12-1.30 mg/ml) plus 10 µl of drug dilution were assayed for HMG-CoA reductase activity.

Compactin in DMA at various concentrations was assayed for inhibition also and results indicated in the results. Buffer A, and DMA : DMSO:0.1M NaOH were also assayed by adding 10 µl of each to 200 µl of microsomal suspension and they showed no significant inhibition of HMG-CoA reductase.

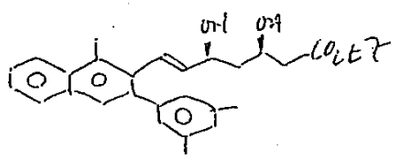
NOTE: That compound marked (SAP) was saponified in a 50° waterbath for 2 hr.

RECEIVED
DEC 20 1984

WATTANASIN EXHIBIT
E-5
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

RESULTS

COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL	IC_{50}	% OF INHIBITION	REMARK
1) Compactin (24291)	12/4/84	DMA					
1mM			.02	4		96	
10^{-1}			.02	4		96	
10^{-2}			.09	18		82	
10^{-3}			.33	64	1.78	36	
10^{-4}			.51	98		2	
10^{-5}			.58	112		-	
10^{-6}			.61	118		-	
10^{-7}			--	--		-	
10^{-8}			.53	102		-	
2) 62-320/Na-4 (~~24291~~ 23531)	12/4/84	DMA					
10^{-2}			.02	4		96	
10^{-3}			.04	8		92	
10^{-4}			.10	20		80	
10^{-5}			.18	34		66	
10^{-6}			.54	104	0.006	-	
10^{-7}			.59	114		-	
10^{-8}			.57	110		-	
3) 63-346(25467)(SAP)	12-4-84	DMSO:0.1M NaOH					
10^{-2}			.61	69		31	
10^{-3}			.85	96		4	
10^{-4}			.94	106	>10	-	
10^{-5}			.92	104		-	
10^{-6}			.95	108		-	
10^{-7}			.98	111		-	
10^{-8}			.97	110		-	
4) 63-346 (25467)	12/4/84	DMA					
10^{-2}			.50	96		4	
10^{-3}			.63	122		-	
10^{-4}			.65	126	>10	-	
10^{-5}			.59	114		-	
10^{-6}			.53	102		-	
10^{-7}			.60	116		-	
10^{-8}			.58	112		-	

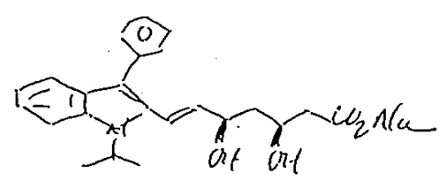


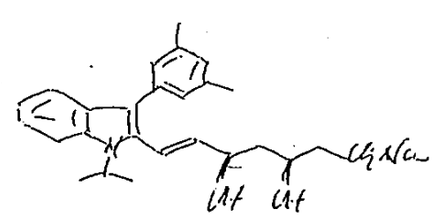
238

COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL		% OF INHIBITION	REMARK
5) 63-347/Na(25468)	12/4/84	Buffer A					
10^{-2}			.84	83		17	
10^{-3}			1.02	101		-	
10^{-4}			1.02	101	>10	-	
10^{-5}			.98	97		3	
10^{-6}			1.07	106		-	
10^{-7}			1.00	99		1	
10^{-8}			1.02	101		-	
6) 63-352/Na(25475)	12/4/84	DMA					
10^{-2}			.05	10		90	
10^{-3}			.25	48		52	
10^{-4}			.51	98	1.11	2	
10^{-5}			.56	108		-	
10^{-6}			.57	110		-	
10^{-7}			.60	116		-	
10^{-8}			.65	126		-	
7) 63-353 (25476)	12/4/84	DMA					
10^{-2}			.04	8		92	
10^{-3}			.20	38		62	
10^{-4}			.46	90	0.77	10	
10^{-5}			.56	108		-	
10^{-6}			.59	114		-	
10^{-7}			.57	110		-	
10^{-8}			.58	112		-	
8) ~~63~~ 265/3 (25488)	12/4/84	DMA					
10^{-2}			.01	2		98	
10^{-3}			.03	6		94	
10^{-4}			.06	12	0.004	88	
10^{-5}			.13	26		74	
10^{-6}			.39	76		24	
10^{-7}			.55	106		-	
10^{-8}			.58	112		-	

239

COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL		% OF INHIBITION	REMARKS
9) Compactin (24291)	12/12/84	DMA					
1mM			.00	-		100	
10^{-1}			.01	1		99	
10^{-2}			.10	9		91	
10^{-3}			.55	50	0.85	50	
10^{-4}			.90	83		17	
10^{-5}			1.01	93		7	
10^{-6}			1.12	103		-	
10^{-7}			1.06	97		3	
10^{-8}			1.04	96		4	
10) 62-320/Na-4 (24531)	12/12/84	DMA					
10^{-2}			.00	-		100	
10^{-3}			.04	3		97	
10^{-4}			.16	15	0.004	85	
10^{-5}			.37	34		66	
10^{-6}			. -	-		-	
10^{-7}			1.03	95		5	
10^{-8}			1.03	95		5	
11) 63-361/Na (25481)	12/12/84	DMA					
10^{-2}			.00	-		100	
10^{-3}			.07	7		93	
10^{-4}			.31	28	0.016	72	
10^{-5}			.54	50		50	
10^{-6}			.98	91		9	
10^{-7}			1.01	93		7	
10^{-8}			1.02	94		6	
12) 62-562/Na(24908)	12/12/84	DMA					
10^{-2}			.00	-		100	
10^{-3}			.01	1		99	
10^{-4}			.08	8		92	
10^{-5}			.26	24	0.005	76	
10^{-6}			.94	86		14	
10^{-7}			.97	90		10	
10^{-8}			.99	91		9	

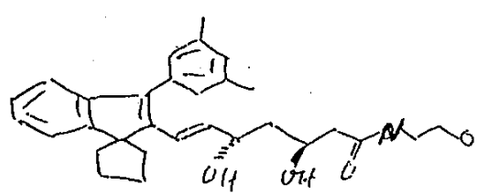


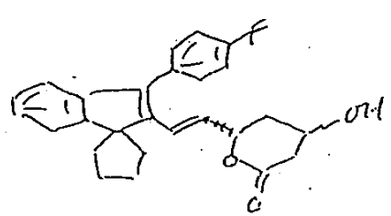


240

COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL		% OF INHIBITION	REMARK:
13) 63-354 (25477)	12/12/84	DMA					
10^{-2}			.09	9		91	
10^{-3}			.48	44		56	
10^{-4}			.89	82	0.73	18	
10^{-5}			1.01	93		7	
10^{-6}			1.03	95		5	
10^{-7}			1.03	95		5	
10^{-8}			.93	85		15	
14) 63-355 (25474)	12/12/84	DMA					
10^{-2}			.26	24		76	
10^{-3}			.57	52		48	
10^{-4}			.94	86	1.35	14	
10^{-5}			.97	90		10	
10^{-6}			1.01	93		7	
10^{-7}			1.02	94		6	
10^{-8}			.99	91		9	
15) 63-356 (25480)	12/12/84	DMA					
10^{-2}			.00	-		100	
10^{-3}			.06	5		95	
10^{-4}			.26	24		76	
10^{-5}			.44	40	0.009	60	
10^{-6}			.92	85		15	
10^{-7}			.96	89		11	
10^{-8}			.98	91		9	
16) 62-265/3 (25488)	12/12/84	DMA					
10^{-2}			.00	-		100	
10^{-3}			.02	2		98	
10^{-4}			.11	10		90	
10^{-5}			.22	21	0.004	79	
10^{-6}			.84	78		22	
10^{-7}			.96	89		11	
10^{-8}			.96	89		11	

COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL		% OF INHIBITION	REMARKS
17) Compactin (24291)	12/13/84	DMA					
1mM			.00	-		100	
10^{-2}			.02	2		98	
10^{-3}			.10	10		90	
10^{-4}			.43	45	0.72	55	
10^{-5}			.75	80		20	
c 10^{-6}			.86	91		9	
10^{-7}			.91	97		3	
10^{-8}			.89	95		5	
			.92	98		2	
18) 62-320/Na-4(~~24291~~ 23531)	12/13/84	DMA					
10^{-2}			.01	1		99	
10^{-3}			.04	4		96	
x 10^{-4}			.13	14	0.007	86	
10^{-5}			.25	27		73	
10^{-6}			.84	90		10	
10^{-7}			.92	98		2	
10^{-8}			.90	96		4	
19) 63-364 (24489)	12/13/84	DMA					
10^{-2}			.71	76		24	
10^{-3}			.86	91		9	
10^{-4}			.89	95	>10	5	
10^{-5}			.90	96		4	
10^{-6}			.84	89		11	
10^{-7}			.86	91		9	
10^{-8}			.82	87		13	
20) 63-365 (25490)	12/13/84	DMA					
10^{-2}			.02	2		98	
10^{-3}			.08	8		92	
10^{-4}			.16	17	0.017	83	
10^{-5}			.58	62		38	
b 10^{-6}			.84	89		11	
10^{-7}			.85	90		10	
10^{-8}			.87	92		8	





242

RESULTS

COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL		% OF INHIBITION	REMARK
21) 63-366 (25496)	12/13/84	DMA					
10^{-2}			.21	22		78	
10^{-3}			.57	61	1.58	39	
10^{-4}			.81	86		14	
10^{-5}			.80	94		6	
10^{-6}			.90	96		4	
10^{-7}			.88	94		6	
10^{-8}			.87	92		8	
22) 63-369 (25512)	12/12/84	DMA					
10^{-2}			.02	2		98	
10^{-3}			.14	15		85	
10^{-4}			.44	46	0.035	54	
10^{-5}			.62	66		34	
10^{-6}			.72	77		23	
10^{-7}			.87	92		8	
10^{-8}			.88	94		6	
23) 63-162/3 (25500)	12/13/84	DMA					
10^{-2}			.01	1		99	
10^{-3}			.02	2		98	
10^{-4}			.11	11	0.007	89	
10^{-5}			.19	20		80	
10^{-6}			.65	97		3	
10^{-7}			.81	86		14	
10^{-8}			.78	83		17	
24) 63-270/2	12/13/84	DMA					
10^{-2}			.01	1		99	
10^{-3}			.05	5		95	
10^{-4}			.09	9	0.004	91	
10^{-5}			.28	30		70	
10^{-6}			.71	76		24	
10^{-7}			.77	82		18	
10^{-8}			.79	84		16	

243

RESULTS

COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL		% OF INHIBITION	REMARKS
25) Compactin (24291)	12/14/84	DMA					
1mM			.00	-		100	
10^{-1}			.00	-		100	
10^{-2}			.02	3		97	
10^{-3}			.38	46	0.87	54	
10^{-4}			.78	93		7	
10^{-5}			.85	101		-	
10^{-6}			.93	111		-	
10^{-7}			.89	107		-	
10^{-8}			.89	107		-	
26) 62-320/Na-4	12/14/84	DMA					
10^{-2}			.00	-		100	
10^{-3}			.00	-		100	
10^{-4}			.08	10	0.007	90	
10^{-5}			.21	25		75	
10^{-6}			.78	93		7	
10^{-7}			.88	106		-	
10^{-8}			.80	96		4	
27) 63-346 (25467)	12/14/84	DMSO:0.1M NaOH					
10^{-2}			.59	89		31	
10^{-3}			.89	104		-	
10^{-4}			.85	99	>10	1	
10^{-5}			.81	95		5	
10^{-6}			.85	99		1	
10^{-7}			.80	93		7	
10^{-8}			.83	97		3	
28) 63-347 (25468)	12/14/84	DMA					
10^{-2}			.76	82		18	
10^{-3}			.97	105		-	
10^{-4}			.97	105	>10	-	
10^{-5}			1.02	109		-	
10^{-6}			.97	105		-	
10^{-7}			.94	100		-	
10^{-8}			.96	103		-	

PSSILIS

COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL		% OF INHIBITION	REMAI
29) 63-352 (25475)	12/14/84	DMA					
10^{-2}			.08	10		90	
10^{-3}			.29	35		65	
10^{-4}			.73	88	0.72	12	
10^{-5}			.83	100		-	
10^{-6}			.79	94		6	
10^{-7}			.80	96		4	
10^{-8}			.89	107		-	
30) Compactin (24291)	12/17/84	DMA					
1mM			.01	1		99	
10^{-1}			.03	3		97	
10^{-2}			.14	13		87	
10^{-3}			.61	55		45	
10^{-4}			1.00	90		10	
10^{-5}			1.09	98	1.17	2	
10^{-6}			1.22	109		-	
10^{-7}			1.18	105		-	
10^{-8}			1.23	110		-	
31) 62-320/Na-4(~~25488~~ 23531)	12/~~12~~17/84	DMA					
10^{-2}			.01	1		99	
10^{-3}			.05	5		95	
10^{-4}			.18	17	0.012	83	
10^{-5}			.47	42		58	
10^{-6}			1.13	102		-	
10^{-7}			1.12	104		-	
10^{-8}			1.18	106		-	
32) 62-~~562~~265/Na-2(25488)	12/17/84	DMA					
10^{-2}			.01	1		99	
10^{-3}			.04	4		96	
10^{-4}			.09	8	0.005	92	
10^{-5}			.25	22		78	
10^{-6}			.98	88		12	
10^{-7}			1.06	95		5	
10^{-8}			1.06	95		5	

MPOUND	DATE	SOLVENT	S.I	CONTROL	INHIBITION	REMARK
33) 63-361 (25485)	12/17/84	DMA				
10^{-2}			.01	1	99	
10^{-3}			.08	7	93	
10^{-4}			.31	28	72	0.017
10^{-5}			.50	45	55	
10^{-6}			1.01	91	9	
10^{-7}			1.10	99	1	
10^{-8}			1.11	100	-	
34) 63-162/3 (25500)	12/17/84	DMA				
10^{-2}			.01	1	99	
10^{-3}			.04	4	96	
10^{-4}			.14	13	87	0.005
10^{-5}			.25	22	78	
10^{-6}			.96	86	14	
10^{-7}			1.02	92	8	
10^{-8}			1.01	91	9	
35) 63-270/2 (25501)	12/17/84	DMA				
10^{-2}			.02	2	98	
10^{-3}			.07	6	94	
10^{-4}			.12	11	89	0.008
10^{-5}			.47	42	58	
10^{-6}			.97	87	13	
10^{-7}			1.04	94	6	
10^{-8}			1.05	94	6	
36) 62-265/3 (25488)	12/17/84	DMA				
10^{-2}			.01	1	99	
10^{-3}			.01	1	99	
10^{-4}			.07	6	94	0.001
10^{-5}			.18	17	83	
10^{-6}			.55	50	50	
10^{-7}			.99	89	11	
10^{-8}			1.01	91	9	

June 27, 1985

DRUG INHIBITION STUDY FOR SANDOZ CONTRACT

Sandoz unknowns were dissolved in DMA (Dimethylacetamide from Sigma), and Buffer A and DMSO: 0.1 M NaOH. Dilution of each compound gave the concentrations indicated in the results.

Microsomes were prepared from male Sprague-Dawley rats (163 g) in Buffer A with 10 mM DTT and frozen at -80°C until thawed and used for experiment. 200 µl Aliquots of microsomal suspension (.97 - 1.11 mg/ml) plus 10 µl of drug dilution were assayed for HMG-CoA reductase activity.

Compactin in DMA at various concentrations was assayed for inhibition also and is indicated in the results. Buffer A, and DMA were also assayed by adding 10 µl of each to 200 µl of microsomal suspension and they showed no significant inhibition of HMG-CoA reductase.

247

COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL	IC50 (mM)	% OF INHIBITION	REMARKS
1) Compactin (24291)	6/13/85	DMA					
1mM			.00	-		100	
10^{-1}			.02	4		96	
10^{-2}			.06	12	1.041	88	
10^{-3}			.24	52		48	
10^{-4}			.41	88		12	
10^{-5}			.47	100		-	
10^{-6}			.47	100		-	
10^{-7}			.43	92		8	
10^{-8}			.49	104		-	
2) 62-320/Na-4(23531)	6/13/85	DMA					
10^{-2}			.00	-		100	
10^{-3}			.02	4		96	
10^{-4}			.09	20		80	
10^{-5}			.15	32	0.0038	68	
10^{-6}			.32	68		32	
10^{-7}			.45	96		4	
10^{-8}			.47	100		-	
3) 63-518/2(RN 26020)	6/13/85	DMA					
10^{-2}			.37	80		20	
10^{-3}			.45	96		4	
10^{-4}			.49	104	>10	-	
10^{-5}			.45	96		4	
10^{-6}			.51	108		-	
10^{-7}			.49	104		-	
10^{-8}			.49	104		-	
4) 63-537/Na(RN 26039)	6/13/85	DMA					
10^{-2}			.02	4		96	
10^{-3}			.09	20		80	
10^{-4}			.32	68	0.169	32	
10^{-5}			.39	84		16	
10^{-6}			.45	96		4	
10^{-7}			.47	100		-	
10^{-8}			.47	100		-	

COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL		% OF INHIBITION	REMARKS
5) 63-547(RN 26075)	6/13/85	DMA					
10^{-2}			.00	-		100	
10^{-3}			.04	8	0.017	92	
10^{-4}			.13	28		72	
10^{-5}			.22	48		52	
10^{-6}			.41	88		12	
10^{-7}			.47	100		-	
10^{-8}			.47	100		-	
6) 63-548(RN 26080)	6/13/85	DMA					
10^{-2}			.13	28		72	
10^{-3}			.37	80		20	
10^{-4}			.47	100	3.775	-	
10^{-5}			.47	100		-	
10^{-6}			.45	96		4	
10^{-7}			.47	100		-	
10^{-8}			.45	96		4	
7) 63-549(RN 26082)	6/13/85	DMA					
10^{-2}			.21	44		56	
10^{-3}			.41	88		12	
10^{-4}			.47	100	7.31	-	
10^{-5}			.47	100		-	
10^{-6}			.47	100		-	
10^{-7}			.45	96		4	
10^{-8}			.47	100		-	
8) 63-550(RN 26083)	6/13/85	DMA					
10^{-2}			.07	16		84	
10^{-3}			.28	60		40	
10^{-4}			.41	88	1.348	12	
10^{-5}			.47	100		-	
10^{-6}			.47	100		-	
10^{-7}			.47	100		-	
10^{-8}			.47	100		-	

x2582A

242

			RESULTS			
COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL	% OF INHIBITION	REMARKS
9) Compactin (24291)	6/18/85	DMA				
1mM			.02	2	98	
10^{-1}			.02	2	98	
10^{-2}			.14	14	86	
10^{-3}			.54	52	48	0.978
10^{-4}			.86	83	17	
10^{-5}			.94	91	9	
10^{-6}			.98	95	5	
10^{-7}			1.04	101	-	
10^{-8}			1.10	107	-	
10) 62-320/Na-4(23531)	6/18/85	DMA				
10^{-2}			.02	2	98	
10^{-3}			.04	4	96	
10^{-4}			.16	16	84	
10^{-5}			.38	37	63	0.0081
10^{-6}			.90	87	13	
10^{-7}			1.00	97	3	
10^{-8}			.98	95	5	
11) 63-551(RN 26084)	6/18/85	DMA				
10^{-2}			.78	76	24	
10^{-3}			.96	93	7	
10^{-4}			1.00	97	3	
10^{-5}			1.04	101	-	>10
10^{-6}			1.02	99	1	
10^{-7}			.98	95	5	
10^{-8}			1.00	97	3	
12) 63-552/Na(RN 26085)	6/18/85	DMA				
10^{-2}			.82	80	20	
10^{-3}			1.04	101	-	
10^{-4}			1.00	97	3	>10
10^{-5}			1.00	97	3	
10^{-6}			.98	95	5	
10^{-7}			1.02	99	1	
10^{-8}			.98	95	5	

250

COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL		% OF INHIBITION	REMARKS
13) 63-553(RN26086)	6/18/85	DMA					
10^{-2}			.36	35		65	
10^{-3}			.80	78		22	
10^{-4}			.94	91	4.479	9	
10^{-5}			1.02	99		1	
10^{-6}			1.00	97		3	
10^{-7}			1.04	101		-	
10^{-8}			1.00	97		3	
14) 63-554/Na(RN 26087)	6/18/85	DMA					
10^{-2}			.18	17		83	
10^{-3}			.64	62		38	
10^{-4}			.92	89	1.468	11	
10^{-5}			1.00	97		3	
10^{-6}			1.02	99		1	
10^{-7}			1.02	99		1	
10^{-8}			.98	95		5	
15) Compactin (24291)	6/19/85	DMA					
1mM			.04	4		96	
10^{-1}			.04	4		96	
10^{-2}			.14	15	1.247	85	
10^{-3}			.51	53		47	
10^{-4}			.90	93		7	
10^{-5}			.98	101		-	
10^{-6}			1.00	103		-	
10^{-7}			1.06	109		-	
10^{-8}			1.00	103		-	
16) 62-320/Na-4(23531)	6/19/85	DMA					
10^{-2}			.04	4		96	
10^{-3}			.08	8		92	
10^{-4}			.20	21	.0059	79	
10^{-5}			.45	46		54	
10^{-6}			.65	67		33	
10^{-7}			1.02	105		-	
10^{-8}			1.04	107		-	

251

COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL		% OF INHIBITION	REMARKS
17) 63-558/Na(RN 26098)	6/19/85	DMA					
10^{-2}			.06	6		94	
10^{-3}			.31	32		68	
10^{-4}			.73	76	0.454	24	
10^{-5}			.96	99		1	
10^{-6}			1.02	105		-	
10^{-7}			.96	99		1	
10^{-8}			.98	101		-	
18) 63-559(RN 26106)	6/19/85	DMA					
10^{-2}			.12	13		87	
10^{-3}			.49	51		49	
10^{-4}			.90	93	1.144	7	
10^{-5}			.98	101		-	
10^{-6}			1.00	103		-	
10^{-7}			1.00	103		-	
10^{-8}			.92	95		5	
19) 63-550/2 Na(RN 26108)	6/19/85	DMA					
10^{-2}			.12	13		87	
10^{-3}			.53	55		45	
10^{-4}			.94	97	1.315	3	
10^{-5}			1.00	103		-	
10^{-6}			1.00	105		-	
10^{-7}			1.02	105		-	
10^{-8}			1.04	107		-	
20) 63-563(RN 26127)	6/19/85	DMA					
10^{-2}			.31	32		68	
10^{-3}			.80	82	4.365	18	
10^{-4}			.96	99		1	
10^{-5}			1.00	103		-	
10^{-6}			1.00	103		-	
10^{-7}			1.02	105		-	

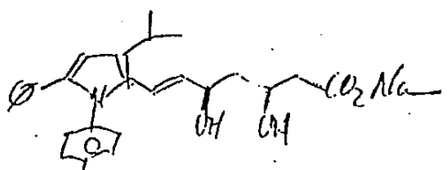
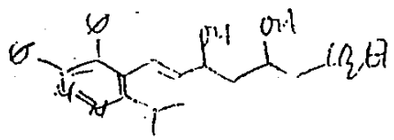
252

COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL		% OF INHIBITION	REMARK:
21) 63-564/Na(26129)	6/19/85	DMA					
10^{-2}			.20	21		79	
10^{-3}			.67	69	2.488	31	
10^{-4}			.96	99		1	
10^{-5}			1.02	105		-	
10^{-6}			1.00	103		-	
10^{-7}			1.04	107		-	
10^{-8}			1.04	107		-	
22) 63-565(RN 26128)	6/19/85	DMA					
10^{-2}			.10	11		89	
10^{-3}			.33	34		66	
10^{-4}			.78	80	0.573	20	
10^{-5}			.96	99		1	
10^{-6}			1.00	103		-	
10^{-7}			.96	99		1	
10^{-8}			.98	101		-	
23) Compactin (24291)	6/24/85	DMA					
1mM			.03	3		97	
10^{-1}			.03	3		97	
10^{-2}			.13	15	1.538	85	
10^{-3}			.50	61		39	
10^{-4}			.81	97		3	
10^{-5}			.91	109		-	
10^{-6}			.96	115		-	
10^{-7}			.91	109		-	
10^{-8}			.88	106		-	
24) 62-320/Na-4(23531)	6/24/85	DMA					
10^{-2}			.00	-		100	
10^{-3}			.05	6		94	
10^{-4}			.15	18	0.01	82	
10^{-5}			.33	39		61	
10^{-6}			.78	94		6	
10^{-7}			.86	103		-	
10^{-8}			.88	106		-	

253

COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL		% OF INHIBITION	REMARKS
25) 63-566(RN 26148)	6/24/85	DMA					
10^{-2}			.73	88		12	
10^{-3}			.86	103	>10	–	
10^{-4}			.91	109		–	
10^{-5}			.91	109		–	
10^{-6}			.83	100		–	
10^{-7}			.86	103		–	
10^{-8}			.91	109		–	
26) 63-567(RN 26149)	6/24/85	DMA					
10^{-2}			.23	27		73	
10^{-3}			.63	76		24	
10^{-4}			.70	85	2.734	15	
10^{-5}			.76	91		9	
10^{-6}			.78	94		6	
10^{-7}			.78	94		6	
10^{-8}			.76	91		9	
27) 63-568(RN 26152)	6/24/85	DMA					
10^{-2}			.03	3		97	
10^{-3}			.13	15		85	
10^{-4}			.28	33	0.086	67	
10^{-5}			.78	94		6	
10^{-6}			.81	97		3	
10^{-7}			.78	94		6	
10^{-8}			.78	94		6	
28) 63-560(RN 26107)	6/24/85	Buffer A					
10^{-2}			.08	9		91	
10^{-3}			.43	52		48	
10^{-4}			.73	88	0.981	12	
10^{-5}			.81	97		3	
10^{-6}			.81	97		3	
10^{-7}			.88	106		–	
10^{-8}			.86	103		–	

254

COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL		% OF INHIBITION	REMARKS
29) 63-555(RN 26088)	6/24/85	DMA					
10^{-2}			.00	-		100	
10^{-3}			.05	6		94	
10^{-4}			.20	24	0.014	76	
10^{-5}			.40	48		52	
10^{-6}			.70	85		15	
10^{-7}			.78	94		6	
10^{-8}			.78	94		6	
30) Compactin (24291)	6/26/85	DMA					
1mM			.00	-		100	
10^{-1}			.02	2		98	
10^{-2}			.11	12		88	
10^{-3}			.44	49	0.899	51	
10^{-4}			.74	84		16	
10^{-5}			.87	99		1	
10^{-6}			.90	101		-	
10^{-7}			.83	94		6	
10^{-8}			.87	99		1	
31) 62-320/Na-4(23531)	6/26/85	DMA					
10^{-2}			.00	-		100	
10^{-3}			.04	5		95	
10^{-4}			.13	15	0.008	85	
10^{-5}			.28	32		68	
10^{-6}			.81	91		9	
10^{-7}			.85	96		4	
10^{-8}			.90	101		-	
32) 63-556 (RN 26093)	6/26/85	DMA					
10^{-2}			.11	12		88	
10^{-3}			.44	49		51	
10^{-4}			.68	77	0.753	23	
10^{-5}			.83	94		6	
10^{-6}			.87	99		1	
10^{-7}			.90	101		-	
10^{-8}			.85	96		4	

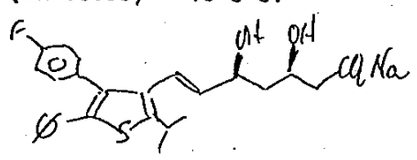
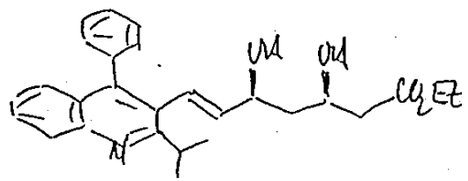
OCTOBER 8, 1987

DRUG INHIBITION STUDY FOR SANDOZ CONTRACT

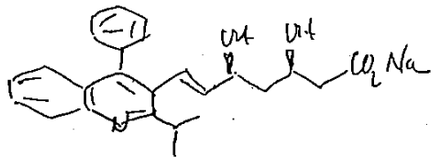
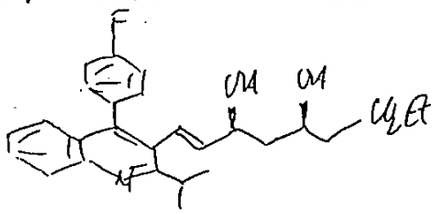
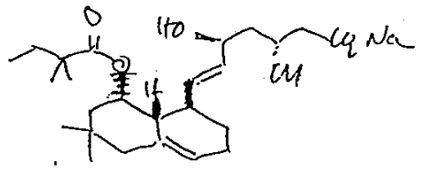
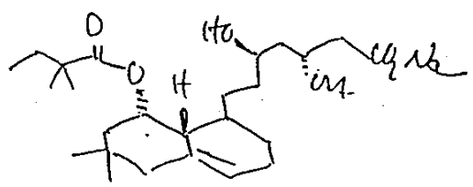
Sandoz unknowns were dissolved in DMA (Dimethylacetamide from Sigma), and Buffer A
Dilution of each compound gave the concentrations indicated in the results.

Microsomes were prepared from male Sprague-Dawley rats (150 g) in Buffer A with 10 mM DTT and frozen at -80°C until thawed and used for experiment. 200 µl Aliquots of microsomal suspension (0.91 mg/ml) plus 10 µl of drug dilution were assayed for HMG-CoA reductase activity.

Compactin in DMA at various concentrations was assayed for inhibition also and is indicated in the results. Buffer A, and DMA were also assayed by adding 10 µl of each to 200 µl of microsomal suspension and they showed no significant inhibition of HMG-CoA reductase.

	COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL		% OF INHIBITION	REMARKS
)	Compactin (29299)	10/8/87	DMA					
	1mM			.01	1		99	
	10^{-1}			.04	3	1.37	97	
	10^{-2}			.18	17		83	
	10^{-3}			.62	61		39	
	10^{-4}			.88	86		14	
	10^{-5}			1.04	102		-	
	10^{-6}			1.04	102		-	
	10^{-7}			1.02	100		-	
	10^{-8}			1.04	102		-	
)	62-320 (24135)	10/8/87	DMA					
	10^{-2}			.01	1		99	
	10^{-3}			.06	6	0.007	94	
	10^{-4}			.20	20		80	
	10^{-5}			.36	36		64	
	10^{-6}			.83	82		18	
	10^{-7}			1.02	100		-	
	10^{-8}			1.02	100		-	
)	64-906 (RN 30393)	10-8-87	DMA					
	10^{-2}		CHIRAL	.01	1		99	
	10^{-3}			.01	1		99	
	10^{-4}			.11	10	0.0012	90	
	10^{-5}			.27	26		74	
	10^{-6}			.55	54		46	
	10^{-7}			1.02	100		-	
	10^{-8}			1.02	100		-	
)	64-933 (RN 30441)	10-8-87	DMA					
	10^{-2}			.20	20		80	
	10^{-3}			.69	68	2.37	32	
	10^{-4}			.99	98		2	
	10^{-5}			1.04	102		-	
	10^{-6}			.99	98		2	
	10^{-7}			1.04	102		-	
	10^{-8}			.99	98		2	

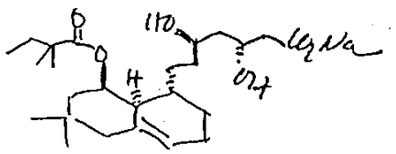
257

COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL		% OF INHIBITION	REMARKS
5) 64-934/Na(RN 30442)	10/8/87	DMA					
10^{-2}			.22	22		78	
10^{-3}			.71	70	2.61	29	
10^{-4}			.99	98		2	
10^{-5}			1.04	102		-	
10^{-6}			1.04	102		-	
10^{-7}			1.02	100		-	
10^{-8}			1.23	121		-	
6) 64-935 (RN 30447)	10/8/87	DMA					
10^{-2}			.13	13		87	
10^{-3}			.32	31		69	
10^{-4}			.74	72	0.413	28	
10^{-5}			.92	91		9	
10^{-6}			.95	93		7	
10^{-7}			.97	95		5	
10^{-8}			1.02	100		-	
7) 64-942/Na(RN 30461)	10/8/87	DMA					
10^{-2}			.71	70		30	Unable to weigh out
10^{-3}			.99	98		2	compound-assuming
10^{-4}			.99	98	>10	2	exactly 0.6mg in via
10^{-5}			.97	95		5	sent from Sandoz,
10^{-6}			1.02	100		-	dilution calculated
10^{-7}			1.02	100		-	and made directly in
10^{-8}			1.02	100		-	vial.
8) 64-727/Na(RN 30024)	10/8/87	DMA					
1 mM			.06	6		94	
10^{-1}			.39	38		62	
10^{-2}			.90	89	0.73	11	
10^{-3}			1.02	100		-	
10^{-4}			1.06	105		-	
10^{-5}			.99	98		2	
10^{-6}			.99	98		2	

258

RESULTS

COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL		% OF INHIBITION	REMARKS
) 64-948/Na(RN 30485)	10/8/87	DMA					
10^{-2}			.99	98		2	
10^{-3}			.99	98	>10	2	
10^{-4}			1.02	100		-	
10^{-5}			.97	95		5	
10^{-6}			.99	98		2	
10^{-7}			.99	98		2	
10^{-8}			.95	93		7	



259

OCTOBER 15, 1987

DRUG INHIBITION STUDY FOR SANDOZ CONTRACT

Sandoz unknowns were dissolved in DMA (Dimethylacetamide from Sigma), and Buffer A
Dilution of each compound gave the concentrations indicated in the results.

Microsomes were prepared from male Sprague-Dawley rats (150 g) in Buffer A with 10 mM DTT and frozen at -80°C until thawed and used for experiment. 200 µl Aliquots of microsomal suspension (0.96 mg/ml) plus 10 µl of drug dilution were assayed for HMG-CoA reductase activity.

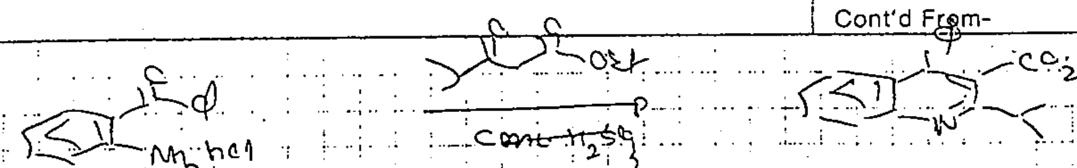
Compactin in DMA at various concentrations was assayed for inhibition also and is indicated in the results. Buffer A, and DMA were also assayed by adding 10 µl of each to 200 µl of microsomal suspension and they showed no significant inhibition of HMG-CoA reductase.

COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL	% OF INHIBITION
1) Compactin (29299)	10-13-87	DMA			
1mM			.02	2	98
10^{-1}			.02	2	98
10^{-2}			.18	20	80
10^{-3}			.64	69	31
10^{-4}			.84	91	9
10^{-5}			.95	103	–
10^{-6}			1.02	110	–
10^{-7}			.98	106	–
10^{-8}			.98	106	–
2) 62-320 (24135)	10-13-87	DMA			
10^{-2}			.02	2	98
10^{-3}			.05	5	95
10^{-4}			.18	20	80
10^{-5}			.30	32	68
10^{-6}			.86	93	7
10^{-7}			.98	106	–
10^{-8}			.95	103	–
3) 64-942/Na (30461)	10-13-87	DMA			
10^{-2}			.73	79	21
10^{-3}			.95	103	–
10^{-4}			1.05	113	–
10^{-5}			.91	98	2
10^{-6}			.93	101	–
10^{-7}			1.00	108	–
10^{-8}			.98	106	–
4) 62-526/Na (29724)	10-13-87	DMA			
10^{-2}			.02	2	98
10^{-3}			.11	12	88
10^{-4}			.46	50	50
10^{-5}			.80	86	14
10^{-6}			.93	101	–
10^{-7}			.98	106	–
10^{-8}			.98	106	–

COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL	% OF INHIBITION	REMARK
5) 64-727 (RN 30024)	10-13-87	DMA				
1mM			.05	5	95	
10^{-1}			.34	37	63	
10^{-2}			.82	88	12	
10^{-3}			.93	101	-	
10^{-4}			.95	103	-	
10^{-5}			.98	106	-	
10^{-6}			.93	101	-	
10^{-7}			.93	101	-	
10^{-8}			.95	103	-	
6) 64-948/Na(RA 30485)	10-13-87	DMA				
10^{-2}			.95	103	-	
10^{-3}			1.00	108	-	
10^{-4}			.95	103	-	
10^{-5}			.98	106	-	
10^{-6}			.95	103	-	
10^{-7}			.98	106	-	
7) 64-936/Na (RN 30448)	10-13-87	DMA				
10^{-2}			.07	7	93	
10^{-3}			.32	34	66	
10^{-4}			.73	79	21	
10^{-5}			.89	96	4	
10^{-6}			.93	101	-	
10^{-7}			.95	103	-	
10^{-8}			.95	103	-	

Title- Date 6-1-? Proj.

Cont'd From-



263

233.23 1206-129-18

319.44 $C_{21}H_{21}NO_2$

233.24 (1206-129-18) = 11.5 g (0.04930 mole)

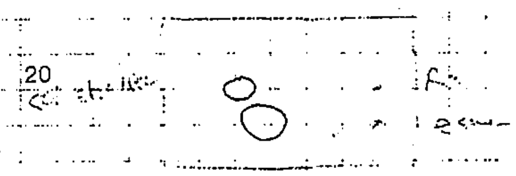
(0.989) 158.2 OEt = 11.93 ml (0.07395 mol) 1.5 equiv.

EtOH = 10 ml + 5 ml

~~Conc H_2SO_4 = 2.5 ml~~

Ref: 1206-92

Above mix was heated to reflux (107 - 4 hrs) stirred at r.t. overnight



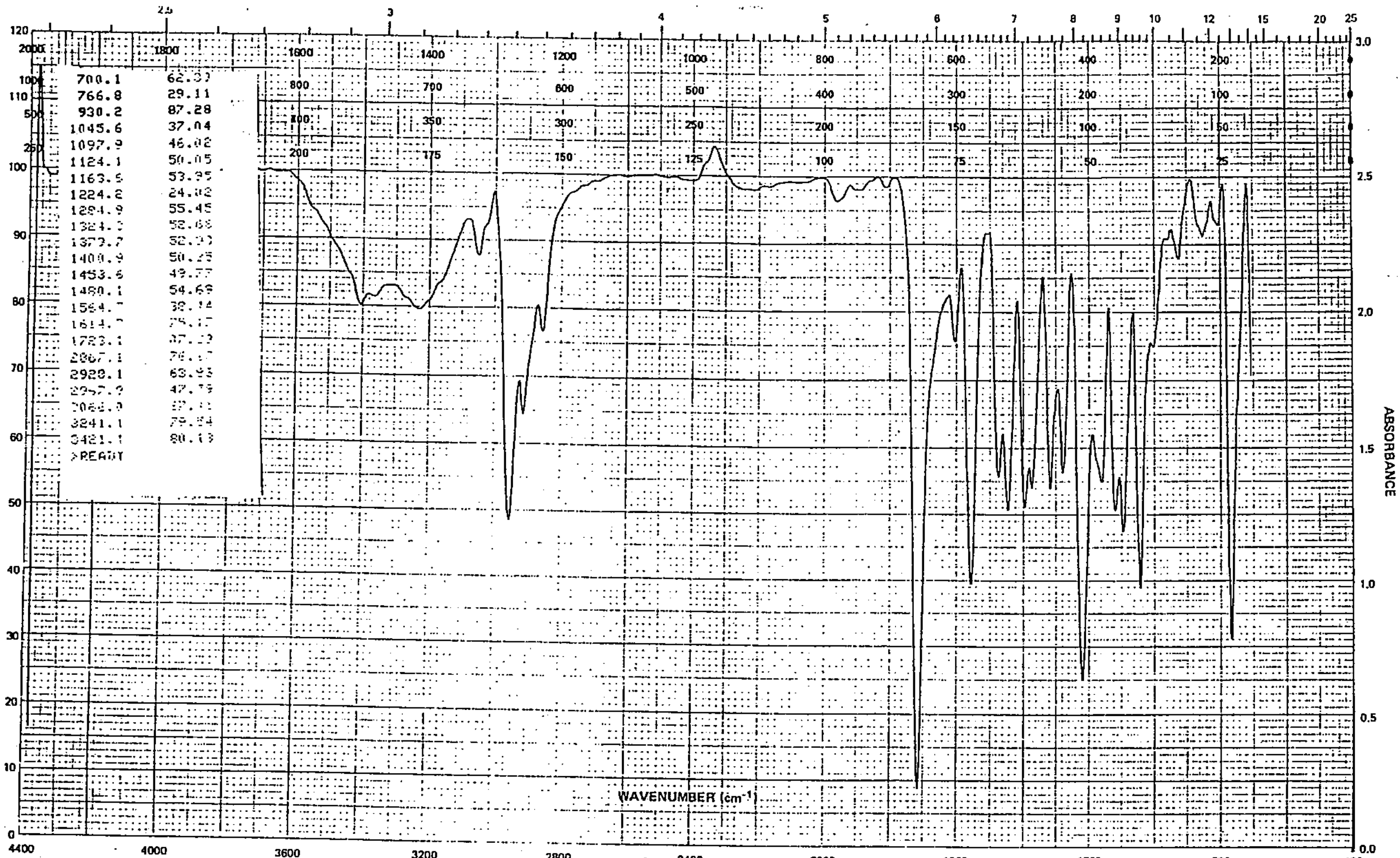
Rotavap to dryness to yellow oil basified with NH_4OH, extracted with Et_2O washed with H_2O, brine, dried filtered washed, rotavap gave 10.21g orange yellow solids (1206-130-27)

nmr, ir, ms → m+1 = 320

Theory: 15.748 g, % = 64.86

Performed by- Raj Patel 6-5-?

Witness- S. Wattanasin



700.1	62.[illegible]
766.8	29.11
930.2	87.28
1045.6	37.04
1097.9	46.02
1124.1	50.05
1163.5	53.95
1224.2	24.02
1284.9	55.45
1324.[illegible]	52.68
1373.7	52.[illegible]
1400.9	50.25
1453.6	49.77
1480.1	54.69
1564.[illegible]	38.14
1614.[illegible]	75.[illegible]
1723.1	87.[illegible]
2867.1	76.[illegible]
2920.1	63.93
29[illegible].9	47.79
[illegible]	[illegible]
3241.1	79.84
3421.1	80.13

>READY

DATE 6-5-87
SPECTRUM NO. 999
OPERATOR 3.Tly.

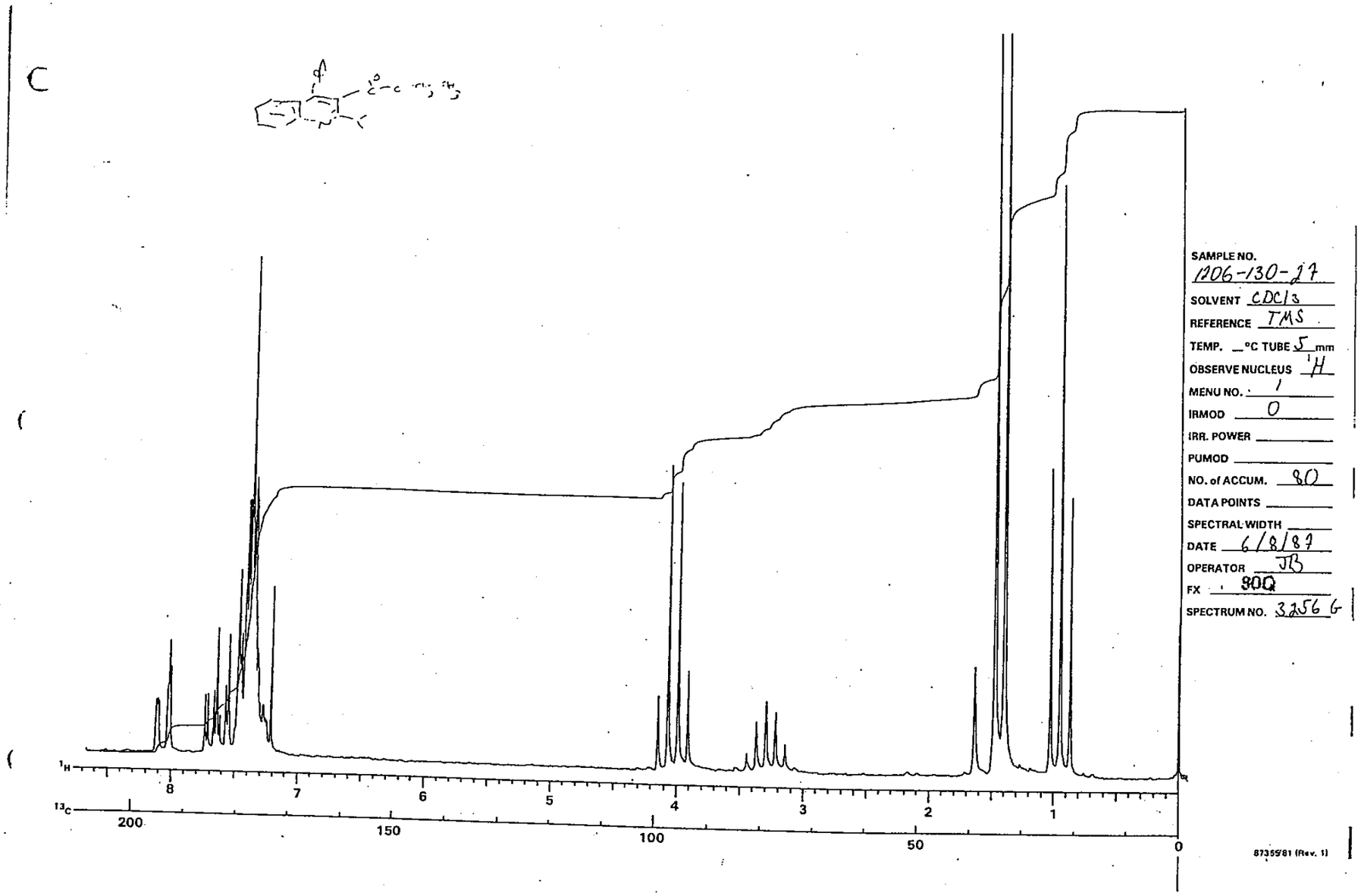
SAMPLE 1206-130-27
PHASE KBr
THICKNESS 1mg
pr. [illegible] / K. Patel

NOTES [illegible] 1206-130-27
Smooth 15
Cos/4

STORED ( ) INTERLEAVED (✓) BKG
NO. SCAN PAIRS (SAM/BKG) (4/4)
AUXILIARY DISPLAY

TRANS. (✓) ABSORBANCE ( )
VERT. ORIGIN 0 SPAN 120
HOR. ORIGIN 7[illegible] SPAN 4400

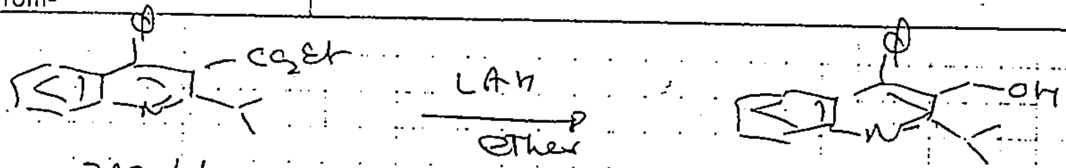
264



Date 6-9-87 Proj. | Title-

Cont'd From-

266



(319.44) 1206 130-27 = 10.21 g (0.0319621 mole)
(38) LAH = 2.43 g (0.063942 mole)
dry ether = 100 ml
Ref: 1206-96

To 1206-130-27 in dry ether with cooling was added LAH portionwise, exothermic, foaming, stirred at r.t. for 3 hr

Rx mix. poured in ice H_2O (exothermic, strong Rx), extracted with ether, washed with H_2O, brine, dried, filtered, washed, rotavap gave yellow solids at = 8.5 g (1206-137-B1) nmr, ir, ms

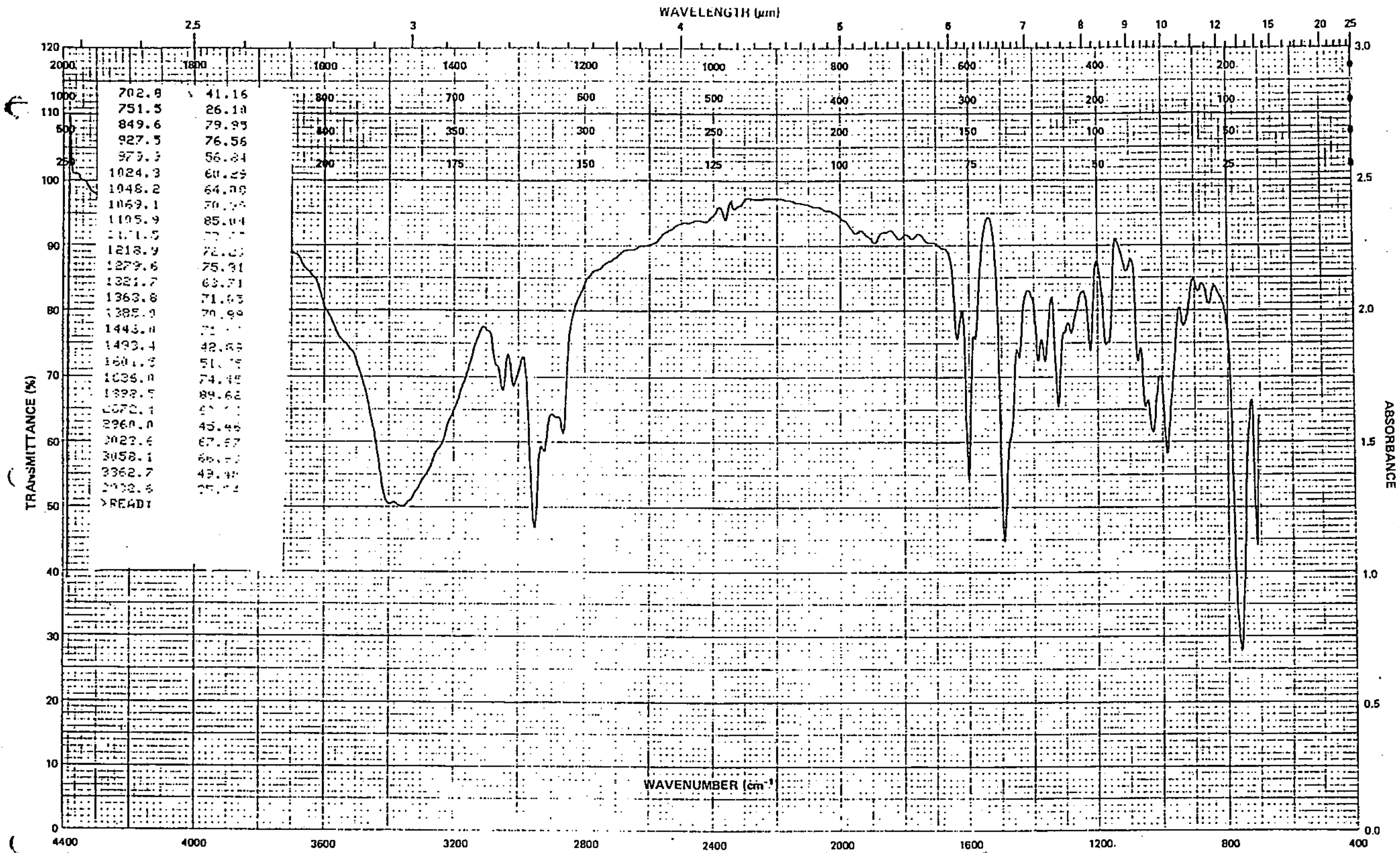
Theory: 8.86 g (95.8%)

Performed by- Raj Patel 9-2-87

Witness- S. [illegible]

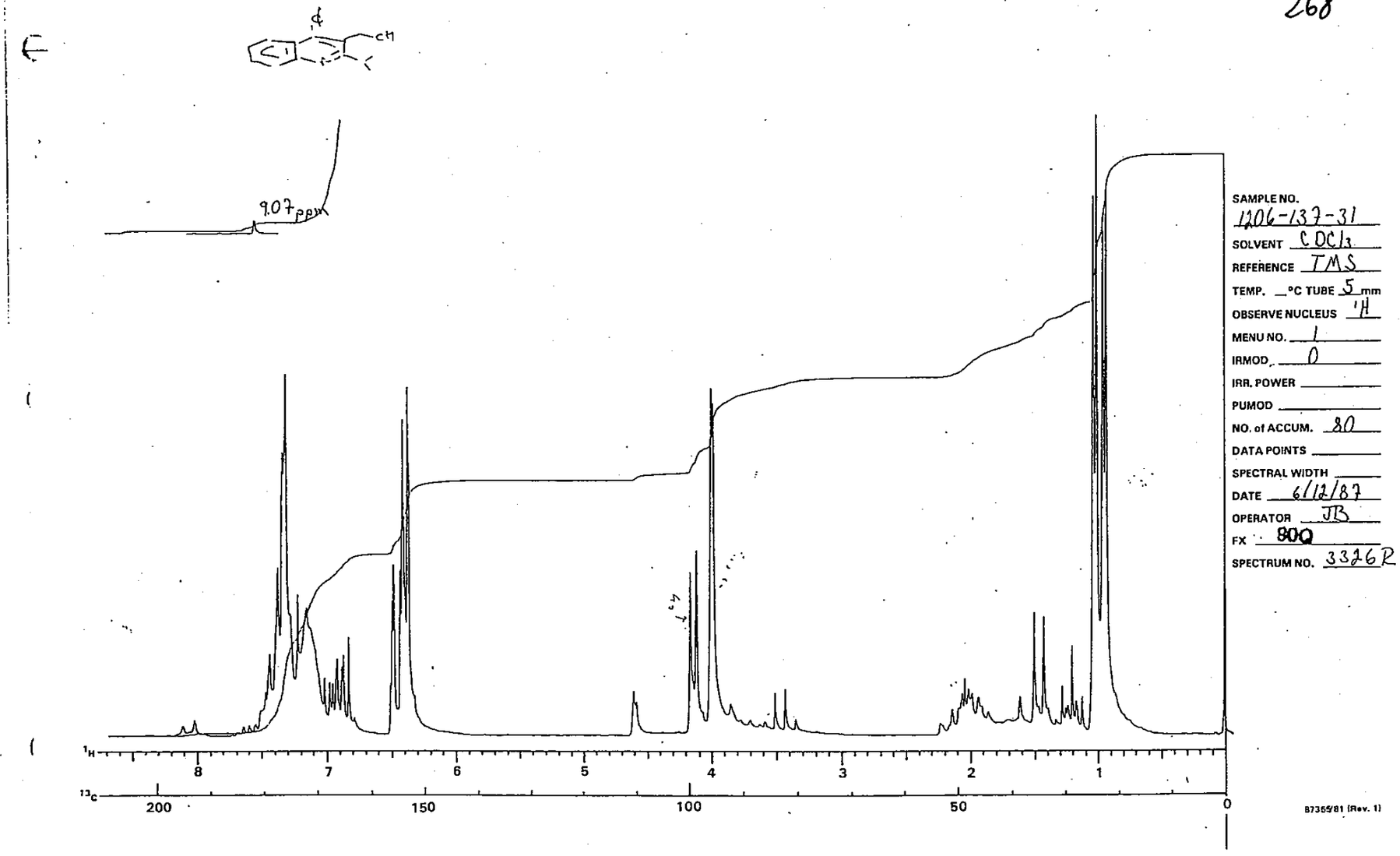
Cont'd to-

267



DATE 6-12-87	SAMPLE 1206-137-31	NOTES: Cut-Nsol B: 206-137-31	STORED ( ) INTERLEAVED (+BKG	TRANS. (✓) ABSORBANCE ( )
SPECTRUM NO. 922	PHASE Film	Smooth/15	NO. SCAN PAIRS (SAM/BKG) (3-14)	VERT. ORIGIN 0 SPAN 120
OPERATOR RM	THICKNESS Dr. Wellman / E. Pact	Scale 1:1	AUXILIARY DISPLAY	HOR. ORIGIN 70 SPAN 44.0

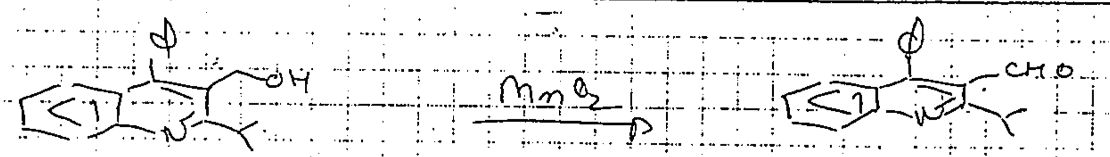
SANDOZ



Date 6-17-97 Proj. | Title-

Cont'd From-

269

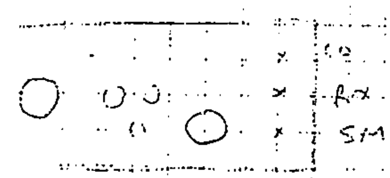


1206-137-31
277.4

275.0
$C_{19}H_{17}NO$

277.4 1206-137-31 = ~~8.0 g~~ 8.0 g (0.02883 92 mole)
MnO_2 = 16.0 g
toluene = 150.0 ml

To 1206-137-31 in toluene was added MnO_2 → heated to reflux (11^45 - 2P.)



filtered thru' pad of *silica gel, washed with toluene, rotovap to dryness, gave yellow solids = 2.6518 g (1206-145-25) nmr, ir, ms MH^+ = 276 desired pr.
orange solids = ~~4~~ 4.6463 g (1206-145-26) nmr, ir, ms MH^+ = 278 S.M.

- During filtration, separated two bands, which was filtered separately & rotovap

Theory : 7.91 g (74.52%)

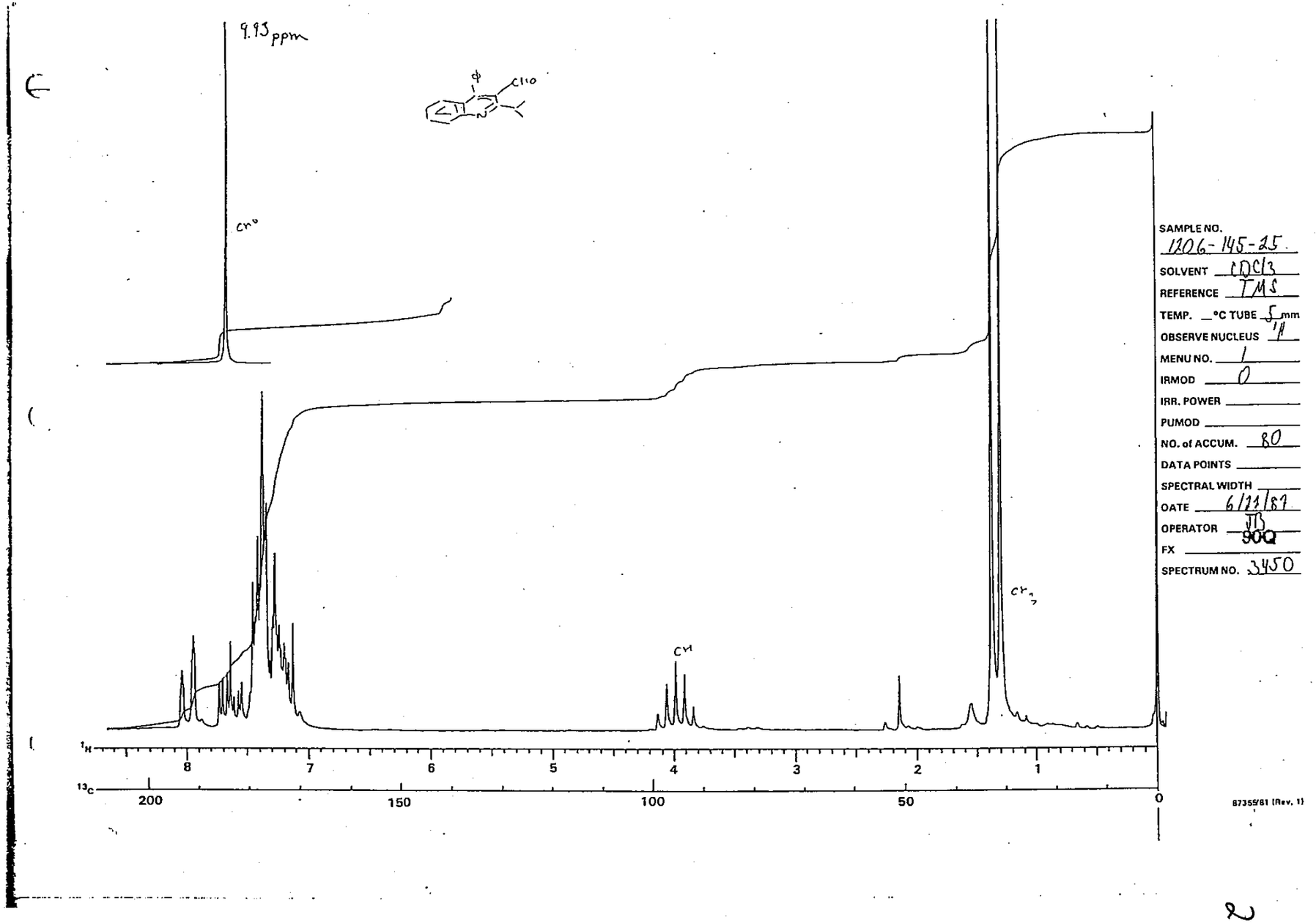
Total yield = 2.6518 g (1206-145-25) + 3.26 g (1206-148-33) = 5.91 g

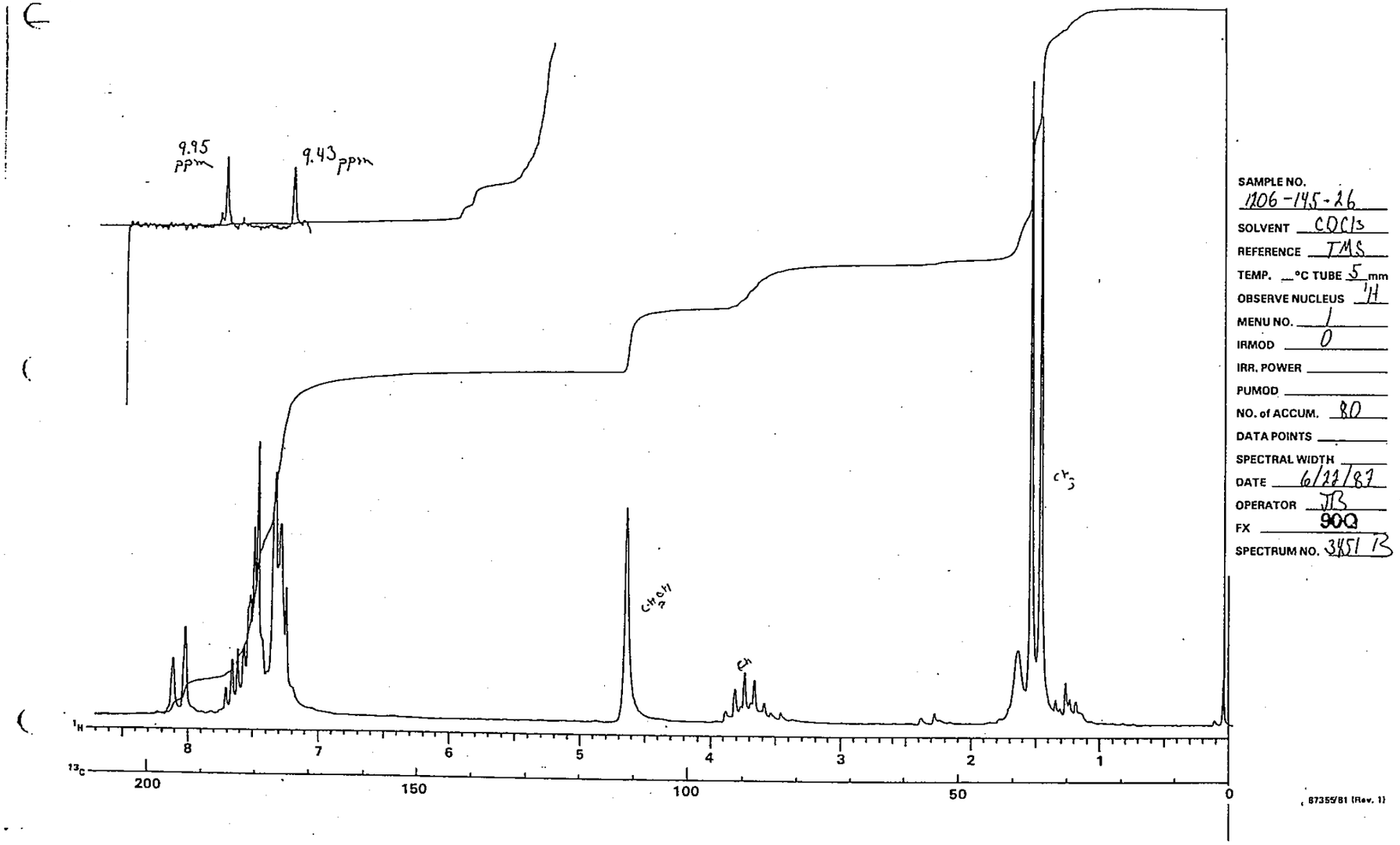
*

Performed by-

Witness- S. [signature]

Cont'd to- 148





SAMPLE NO. 1106-145-26
SOLVENT CDCl3
REFERENCE TMS
TEMP. °C TUBE 5 mm
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOD 0
IRR. POWER
PUMOD
NO. of ACCUM. 80
DATA POINTS
SPECTRAL WIDTH
DATE 6/17/87
OPERATOR JB
FX 90Q
SPECTRUM NO. 3451 B

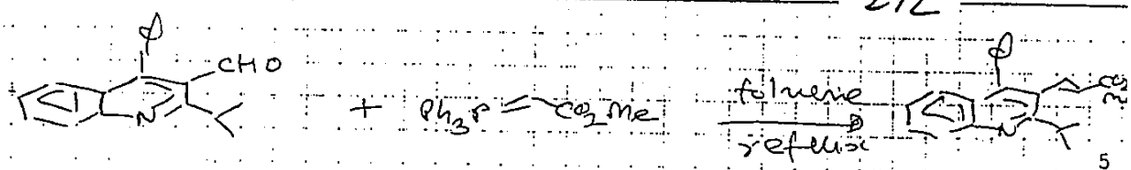
87355/81 (Rev. 1)

27

Date 6 Jan 87 Proj. Title-

Cont'd From-

272



275 331

(275) {1206-145-25, 1206-148-33} = 2-65+ 326 = 5.915 (0.02149 mole)

~~MeOH~~ = ~~11.8 g~~

toluene = 85 ml + 20 ml

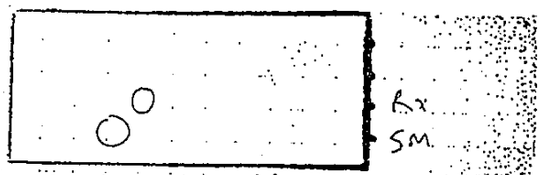
(334) $Ph_3P=CO_2Me$ = 8.6135 g (0.025789 mole) 1.2 eq

2 eq

Ref: 1206-146

Above mix. was heated to reflux (yellow heterogenous before heating) for 1½ hrs. stirred at r.t. overnight

7-1-87



7-2-87 Diluted with 50% Et_2O/Pet ether filtered thru' pad of silicagel washed Rotavap to dryness to give yellow crystalline solid 8.68 g : Triturate with MeOH gave off white solids (Theory: 7.113 g) wt = 5.5198 g (1206-153-31) 77.6%

nmr, ir, ms mp = 332

Rotavap mother liquor to dryness to yellow oil wt = 2.7593 g (1206-153-34)

7-6-87 Trituration with MeOH gave 761.6 mg light yellow solids (1206-153-37) nmr ms mp 332

Rotavap mother liquor to dryness to yellow solid (1206-153-35) ms

Total yield = 5.5198 + 0.7616 (1206-153-)

7-9-87 m.p = 128°-130°C

	C	H	N
~~77~~	~~69.84~~	~~7.37~~	
	74.65	4.65	
	75.26	5.42	3.75

Performed by- Ray Patel 7-6-87

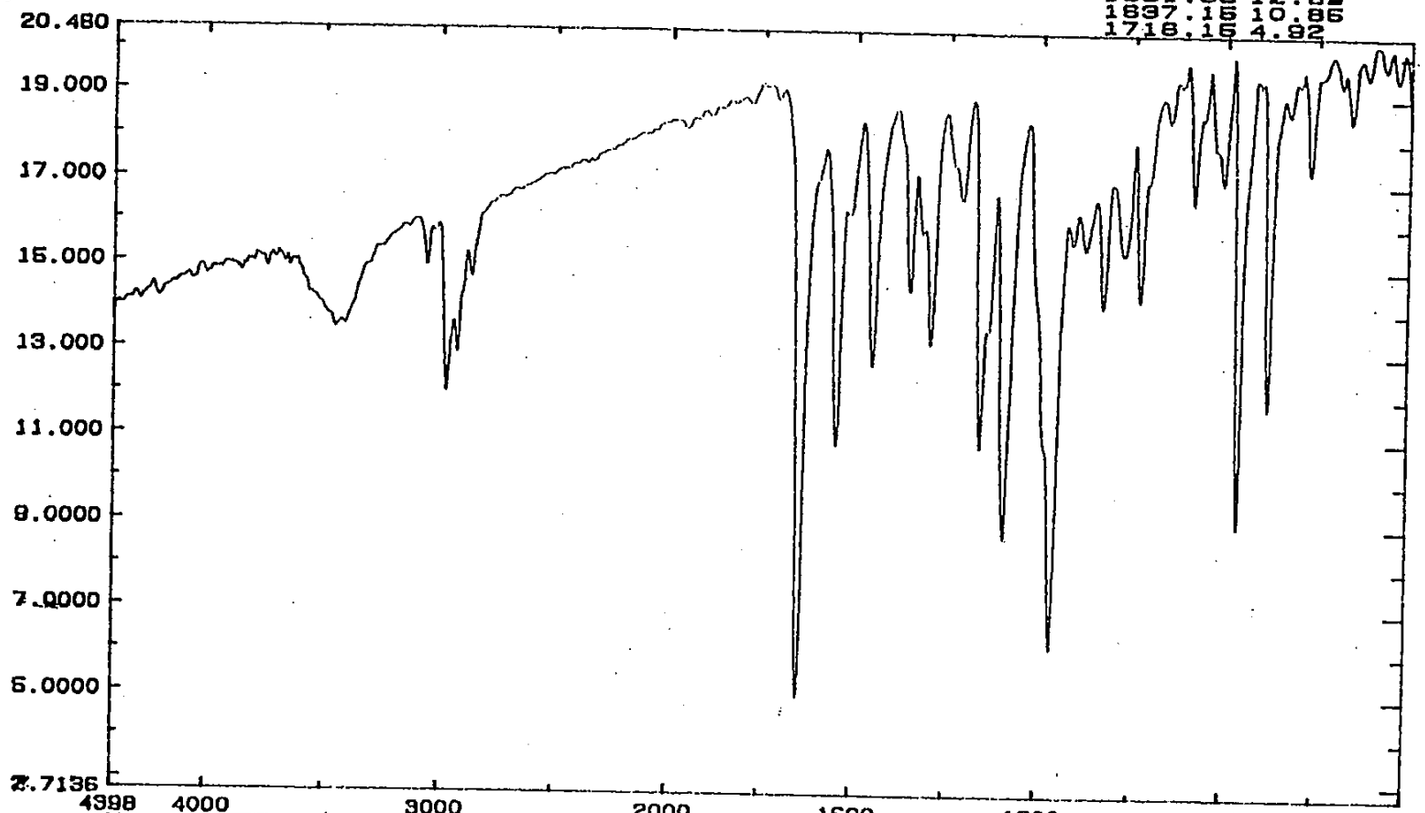
Witness- S Wattanasin

Cont'd to-

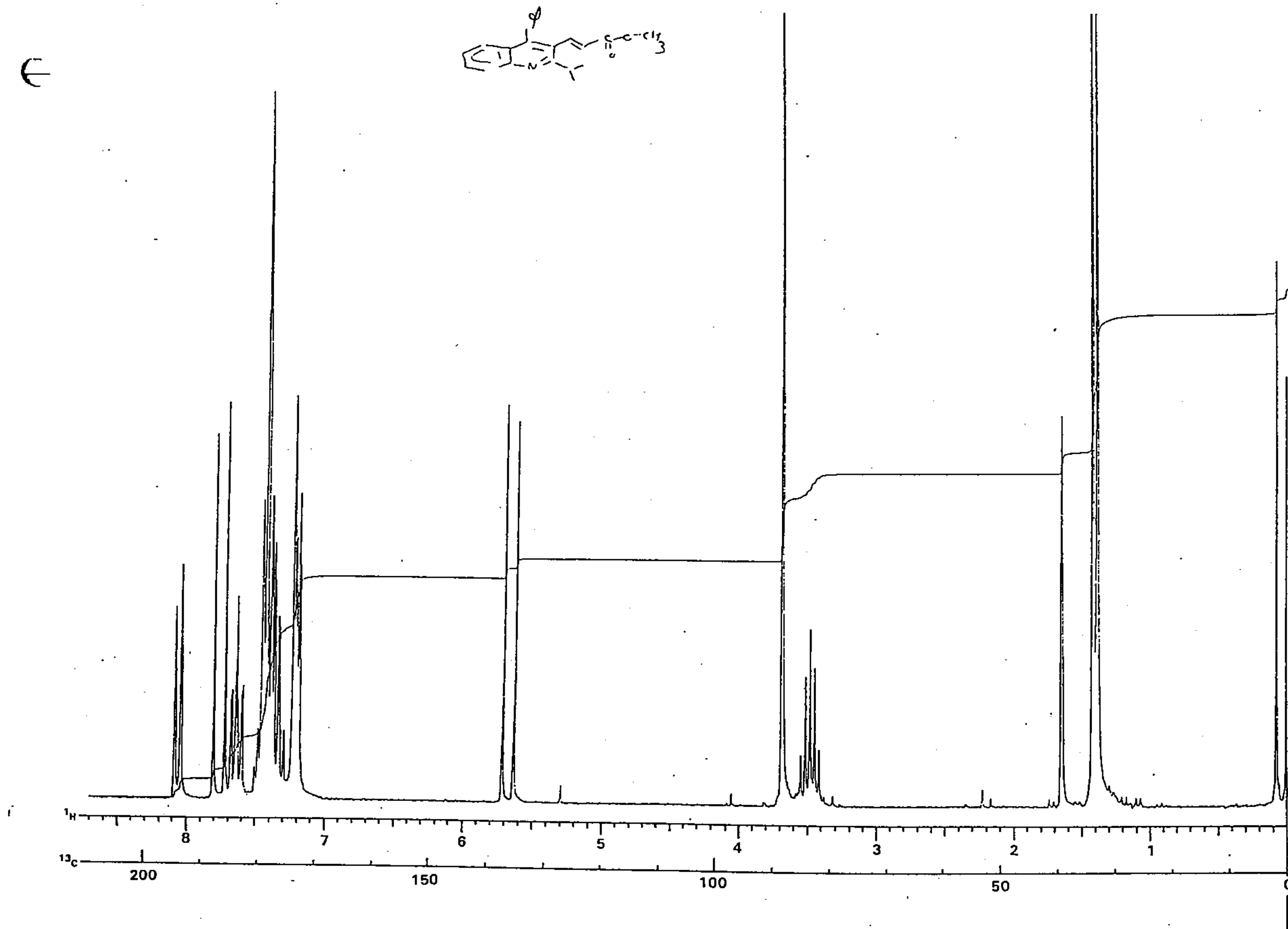
L

23

CM-1	%T	CM-1	%T
2927.38	12.93	704.39	11.79
2979.07	12.02	769.73	9.00
3413.38	13.58	1065.82	14.10
3452.89	13.49	1172.68	6.14
4207.46	14.18	1278.44	6.70
4289.61	14.08	1328.08	10.79
		1438.60	13.20
		1581.36	12.89
		1697.15	10.86
		1718.16	4.92



FILE NAME : 1206-153-34 #1007		GAIN : 2	ANALECT FX-6160
#SCANS : 64		DET : TGS	ORD : %T
#BKG : 64		RES : 4 CM-1	ABSC: WAVENUMBER
APOD : HAPP-GENZEL		DATE : 07/15/87	TIME: 11:46:59
COMMENT : kbr wattasin/r.p.lab358 pcc			



SAMPLE NO. 1206 – 153-31

SOLVENT CDCl3

REFERENCE TMS

TEMP. RT °C TUBE 5 mm

OBSERVE NUCLEUS 13C

MENU NO. 1

IRMOD MN

IRR. POWER

PUMOD

NO. of ACCUM. 8D

DATA POINTS 16K

SPECTRAL WIDTH 2KHz

DATE 6 July 87

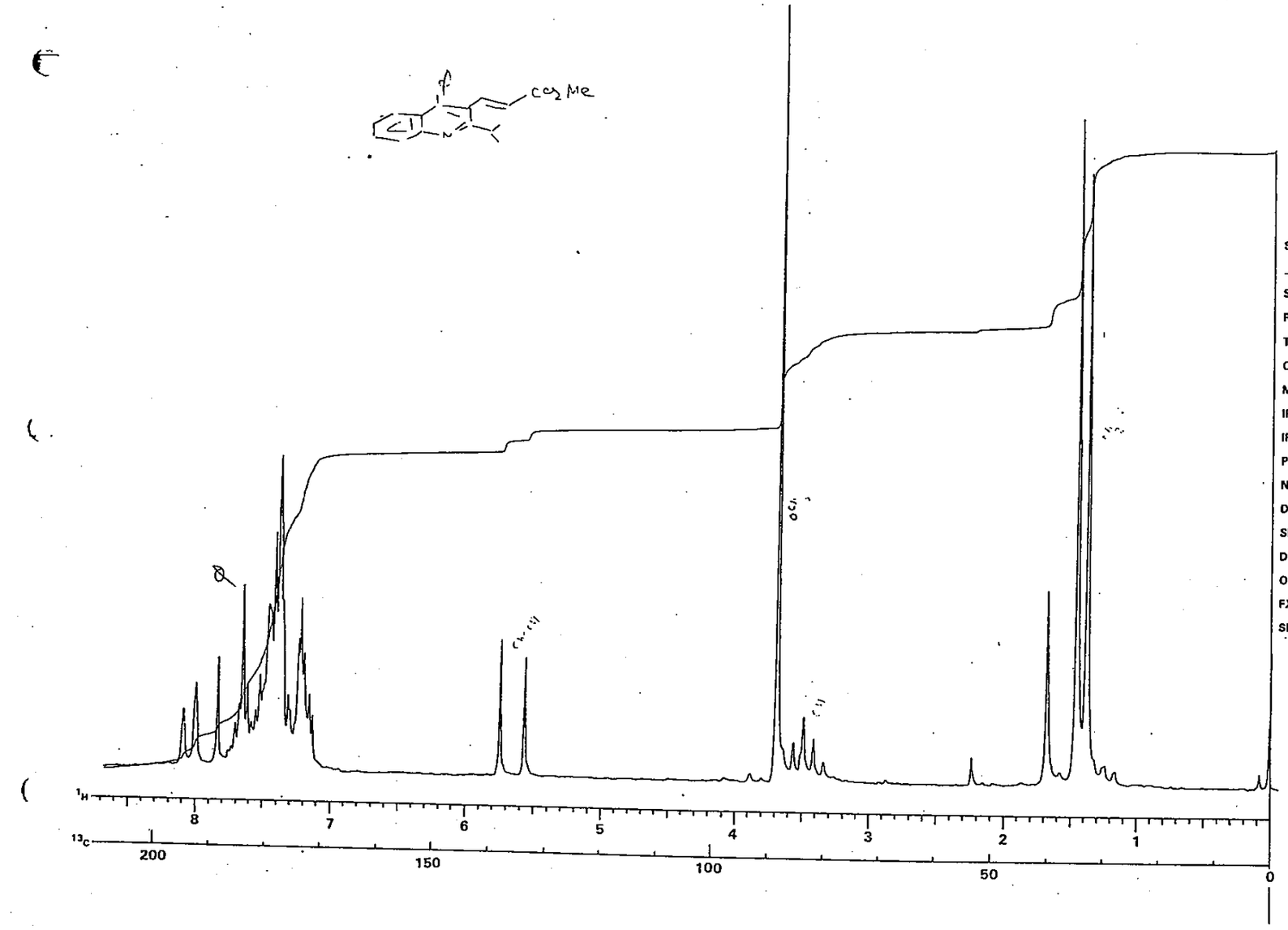
OPERATOR K.I.G.

FX 200

SPECTRUM NO. 3596-G

8735981 (Rev. 1)

274

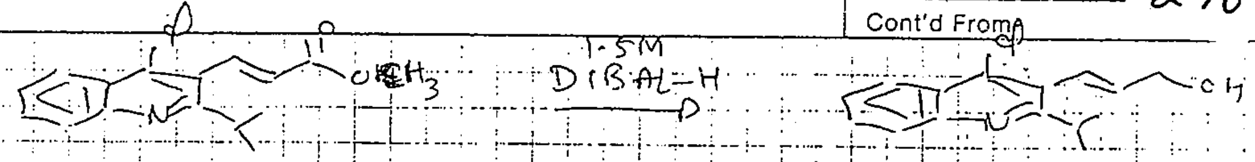


225

Title-

Date 7-7-87 F 276

Cont'd From



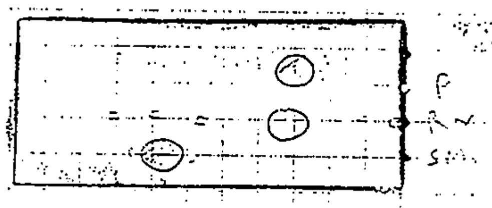
331 | 303 ($C_{21}H_{21}NO$)

1206-153-40 = 6.25g (0.018821 mole)
1.5M DIBAL-H/toluene = 25.18 ml (0.037642 mole) 2eq.
CH_2Cl_2 = 75 ml

Ref: 1206-155, 87

To soln of 1206-153-40 in CH_2Cl_2 was added at −78°C 1.5M DIBAL-H/toluene, stirred at −78°C for 3 hrs (12^15 − 3^10)

Si/Et... [illegible]



C	H	N	O
83.13	6.98	4.62	5.27
82.65	6.86	3.9	
82.68	6.89	3.89	

quenched with 12.55 ml 2N NaOH, diluted with EtOAc stirred at r.t. overnight → lots of white (gel) solids came out. 7-8-87

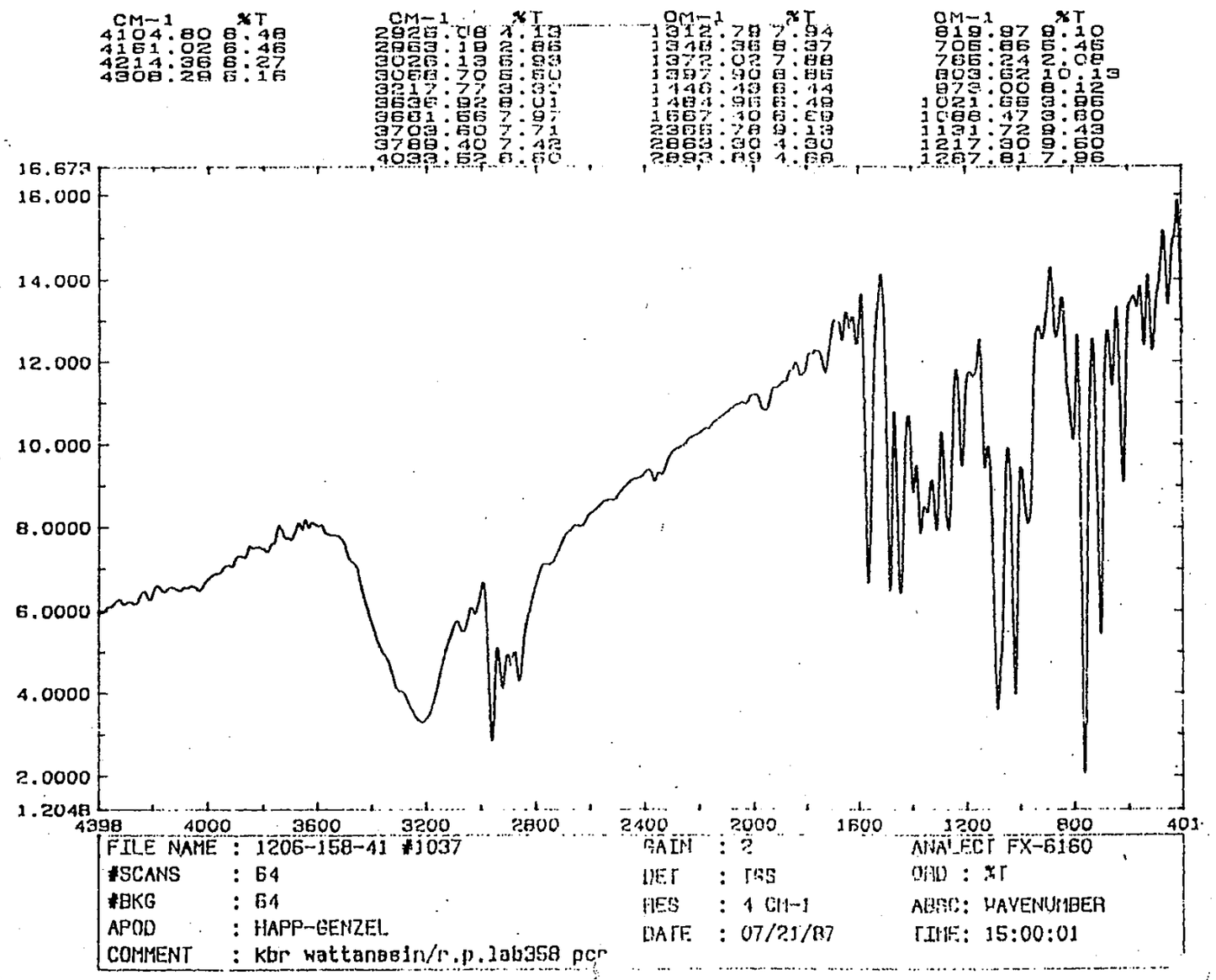
filtered thru' pad of silica gel, washed with EtOAc, washed org. layer with H_2O, brine dried rotevap to dryness gave off white solid = 5.42g (1206-158-35) Dissolved solids in Et_2O insolubles (white) (aluminium oxide) was filtered thru' sintered glass funnel rotavap to dryness gave white-yellow solids = 5.22g (1206-158-3..)
Theory: 5.79g 73.7%
Dissolved solids in Et_2O, insoluble (aluminium oxide) was filtered rotavap to dryness gave yellowish solids = 4.2117g (1206-158-41) nmr, ir, ms, ~~[illegible]~~ M+ = 304 micro

m.p. = 119°−121°C

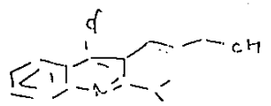
Performed by- Raj Patel 7-17-87

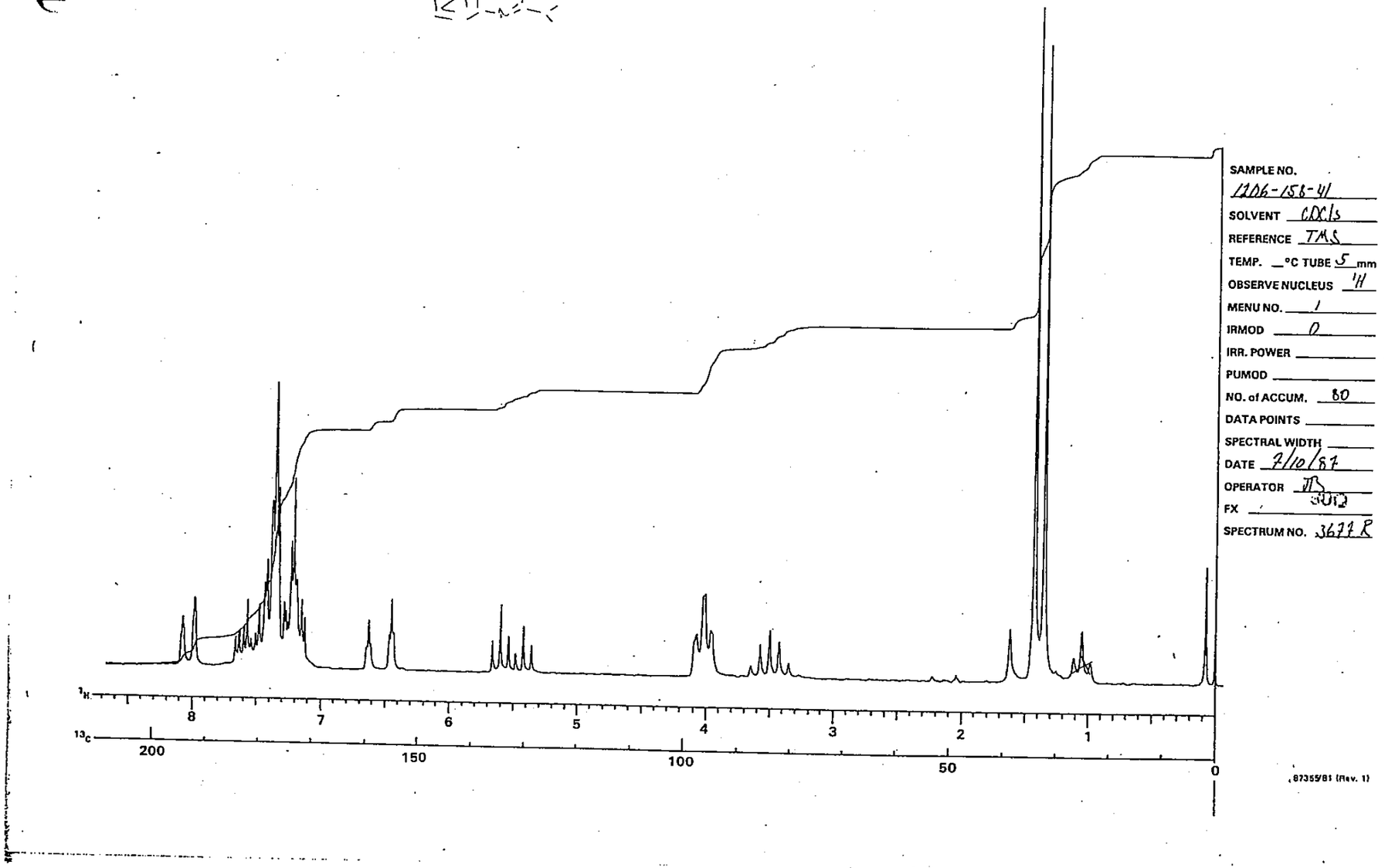
Witness- S. Wattanasin

Cont'd to-


CM-1 %T
4104.80 6.46
4161.02 6.46
4214.36 6.27
4308.29 6.16
CM-1 %T
2925.08 4.13
2853.19 2.86
2026.13 6.93
1956.70 6.50
1217.77 3.30
1536.92 8.01
1461.66 7.97
1703.60 7.71
1788.40 7.42
1033.52 6.50
CM-1 %T
1312.75 7.94
1348.36 8.37
1372.02 7.88
1397.90 8.86
1446.43 8.44
1484.96 6.49
1567.40 6.69
2365.78 9.13
2869.90 4.90
2893.89 4.68
CM-1 %T
819.97 9.10
705.86 5.45
765.24 2.08
803.66 10.13
973.00 8.12
1021.66 3.96
1088.47 3.80
1131.72 9.43
1217.90 9.60
1267.81 7.96
16.673
16.000
14.000
12.000
10.000
8.0000
6.0000
4.0000
2.0000
1.2048
4398 4000 3600 3200 2800 2400 2000 1600 1200 800 401
FILE NAME : 1206-158-41 #1037
#SCANS : 64
#BKG : 64
APOD : HAPP-GENZEL
COMMENT : kbr wattanasin/r.p.lab358 pcr
GAIN : 2
DET : TGS
RES : 4 CM-1
DATE : 07/21/87
ANALECT FX-6160
ORD : %T
ABSC: WAVENUMBER
TIME: 15:00:01

278



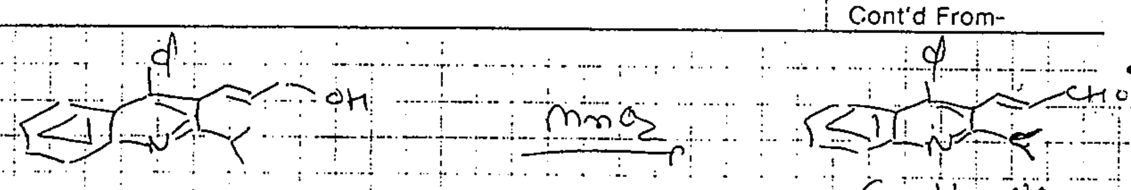


Title-

Date 7-15-87 Proj. —

Cont'd From-

279



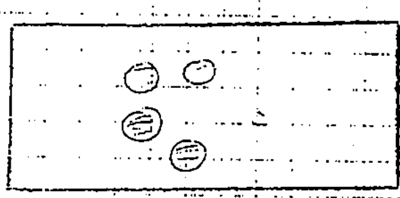
303 → $C_{21}H_{19}NO$ 304

1206-158-41 = 4.0g (0.0132013 mole)
MnO_2 = 8.0g
toluene = 50 ml

Ref: 1206-164

To 1206-158-41 in toluene added MnO_2 & heated to reflux (2 hr - 3 hr), stirred at r.t. overnight

silica gel



co
Rx
SM

7-16-87

filtered thru pad of silica gel, washed pad with ether, rotavap to dryness gave 3.4946g yellow crystaline material (1206-166-30)
✓ ir ✓ nmr ✓ ms $m^+ = 302$
Theory: 3.9736g (88%)

7-28-87 micro

	C	H				
[illegible]	[illegible]	[illegible]	[illegible]			
[illegible]	[illegible]	[illegible]				
	[illegible]	[illegible]	[illegible]			

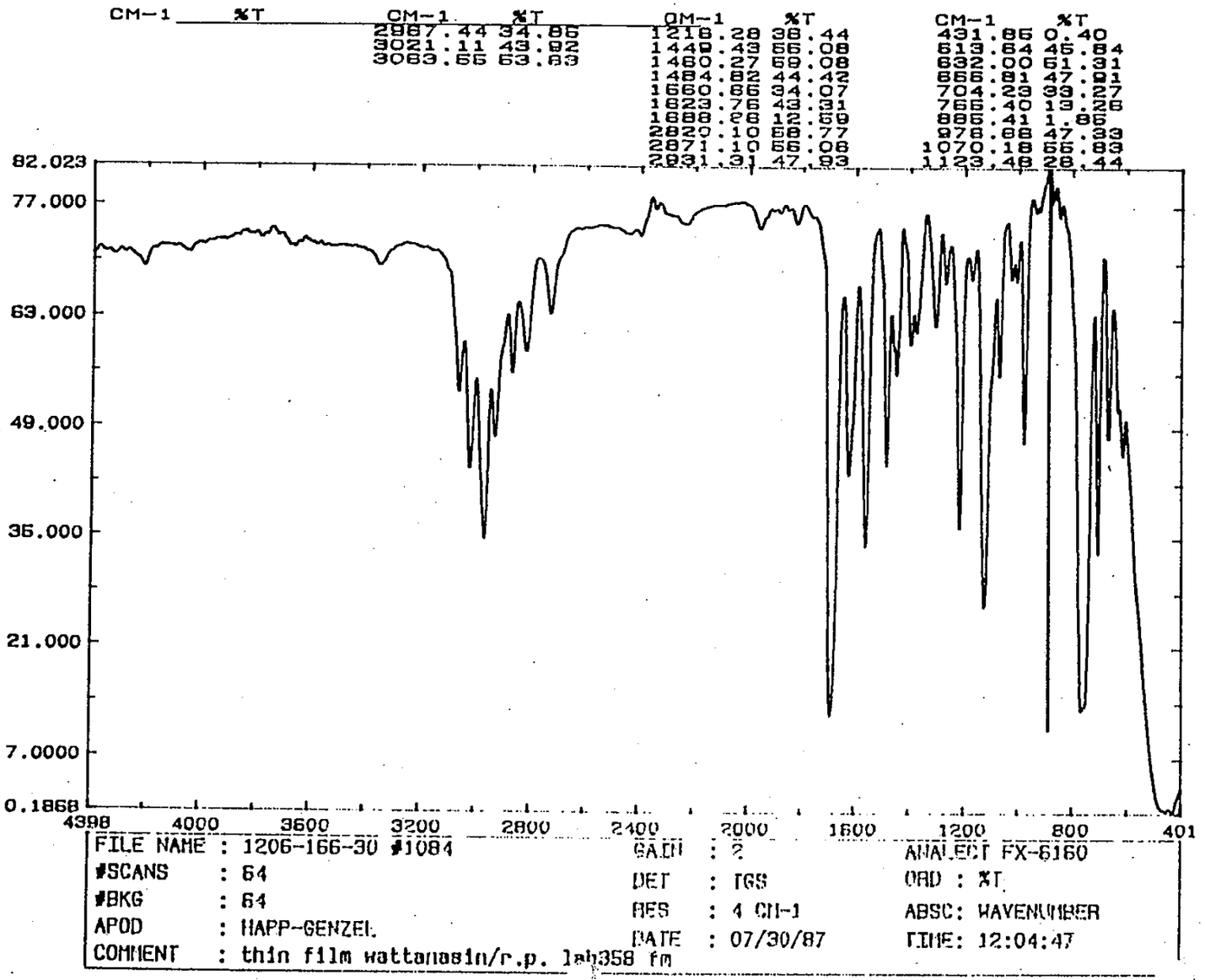
7-30-87

exact mass obs. mass = 302.15404 m.p. = 98-101°C
Calc. mass = 302.15448

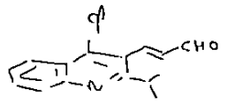
Performed by- Raj Patel 7-20-87

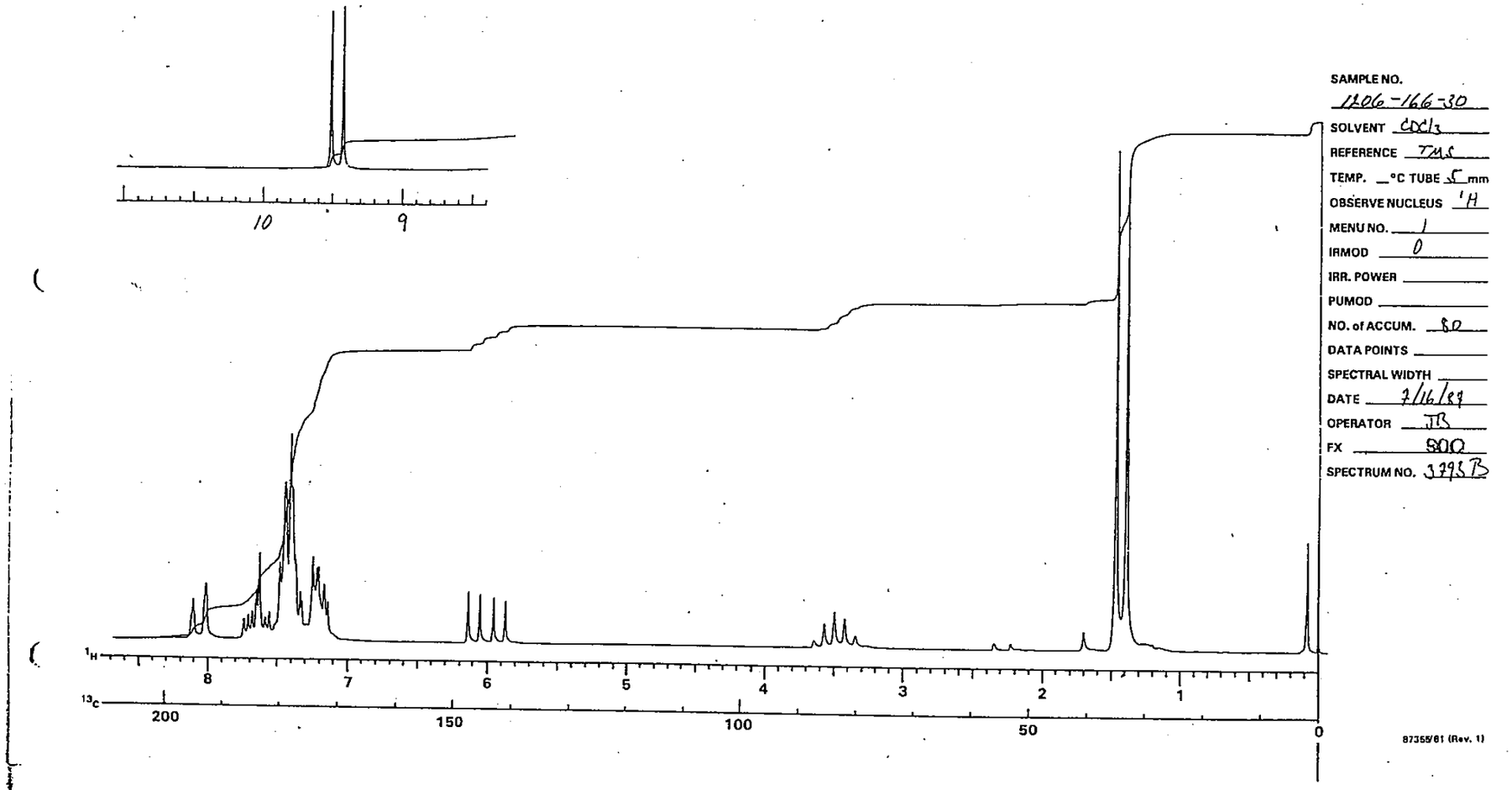
Witness- S. Wattanasin

Cont'd to-


CM-1 %T
2987.44 34.85
3021.11 43.92
3063.55 63.69
1218.28 38.44
1449.49 66.08
1480.27 69.08
1484.82 44.42
1660.85 34.07
1623.76 43.31
1688.28 12.69
2820.10 58.77
2871.10 56.08
2931.31 47.93
431.85 0.40
613.64 45.84
632.00 51.31
666.81 47.91
704.29 33.27
765.40 13.26
885.41 1.85
978.68 47.33
1070.18 65.89
1123.48 28.44
82.023
77.000
63.000
49.000
35.000
21.000
7.0000
0.1868
4398
4000
3600
3200
2800
2400
2000
1600
1200
800
401
FILE NAME : 1206-166-30 #1084
#SCANS : 64
#BKG : 64
APOD : HAPP-GENZEL
COMMENT : thin film wattanasin/r.p. lab358 fm
GAIN : 2
DET : TGS
RES : 4 CM-1
DATE : 07/30/87
ANALECT FX-6160
ORD : %T
ABSC: WAVENUMBER
TIME: 12:04:47

280

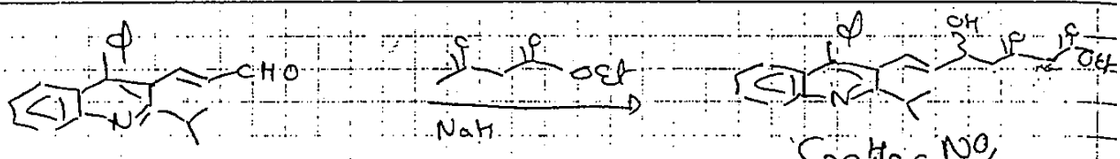




Title-

Date 7-20-87 Prc 282

Cont'd From-



301

$C_{27}H_{29}NO_4$
431.6

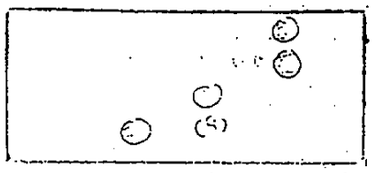
301	1206-166-30	= 3.5g	(0.011629 mole)
130.14, 1.021	Ethyl acetoacetate	= 5ml	(0.04 mole)
24	60% NaH	=	
	1.6M n-Buli/Hex	= 27ml	
	THF	= 60ml + 40ml	

To a sol^n of 1206-166-30 in dry THF (40ml) at -5° to -10°C was added a sol^n of dianion (11ml + 27ml) (38 ml), prepared as described previously.

Dianion (got from Dr. Som)

To sol^n of 5 ml Ethyl acetoacetate in 60ml dry THF was added 1.9 g 50% NaH at -5° to 0°C, stirred for 15 min (foaming H_2 evolved). At -10° - -15°C was added 27 ml 1.6 M n-Buli/Hex, stirred for 20 min at -10°C → yellow homogeneous sol^n. Total vol = 92 ml (0.04 mole used 48 38 ml dianion = 0.01652 mole (1.4 equiv.) → color changed from yellow to orange to dark red

TLC (50% Et_2O/Pet) after 15 min, → complete rxn



Rx was stirred for 30 min, quenched with NH_4Cl, extracted with EtOAc, washed with H_2O brine, dried, filtered, rotavap'd gave yellow oil 5.9188 g (1206-172-41)
Theory: 5.01 g (67.8%)

Performed by- Raj Patel 7-21-87

Witness-

Cont'd on p. 286-175

Date 7-22-87 Proj.
Cont'd From- 120G-172
Title-

283

Flash chromatography (25% EtOAc/Pet) gave
(a) Yellow solids = 3.4004 g (120G-175-4) nmr, ir, ms
m.p. = 84-87°C   68% yield   micro   mp=4

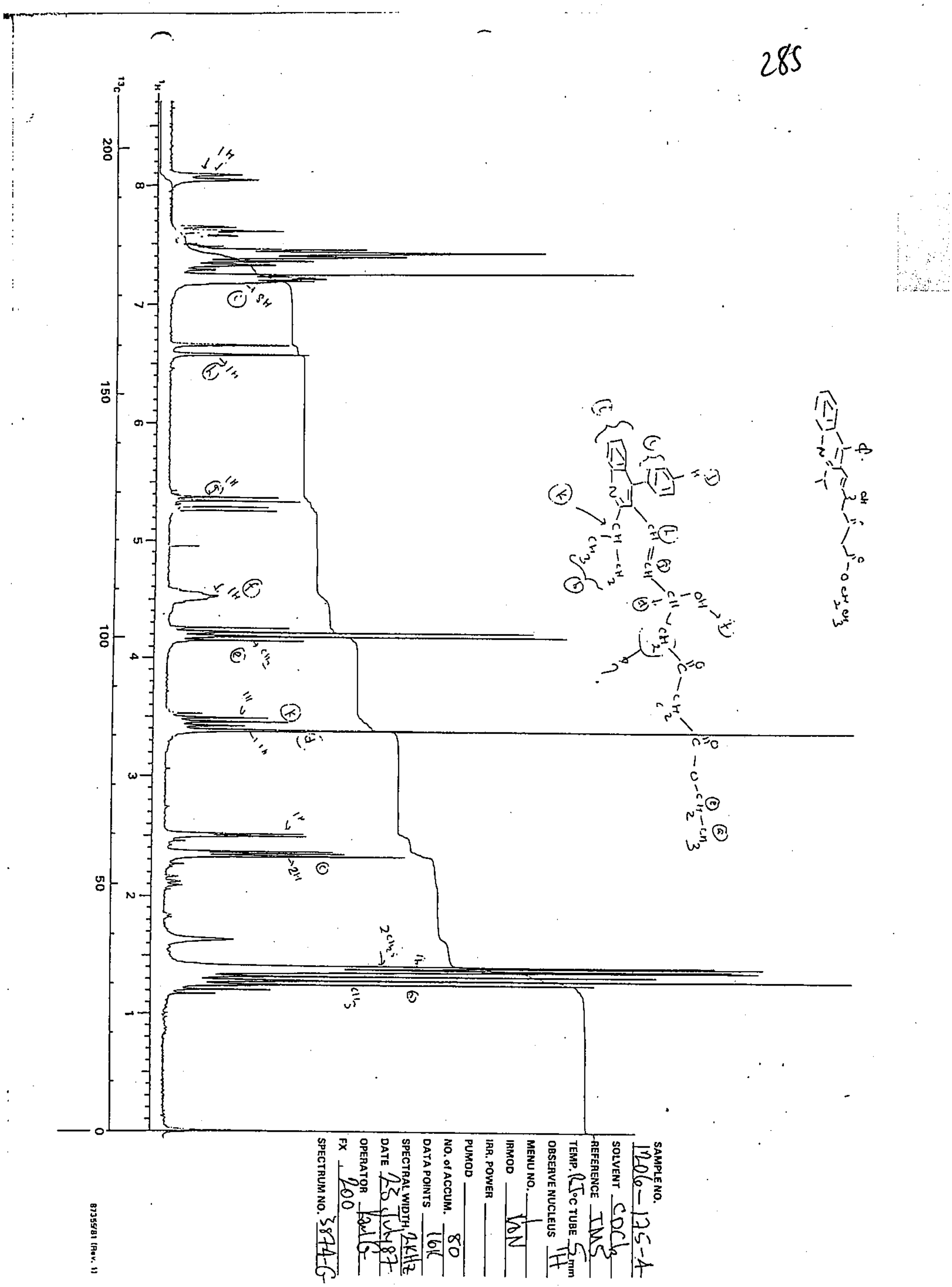
	C	H	N	O		
Calc.	[illegible]	[illegible]	[illegible]	14.[illegible]		
Found	[illegible]		[illegible]			
	[illegible]					

Performed by- Raj Patel 8-5-87

Witness- S. [illegible]

Cont'd to-

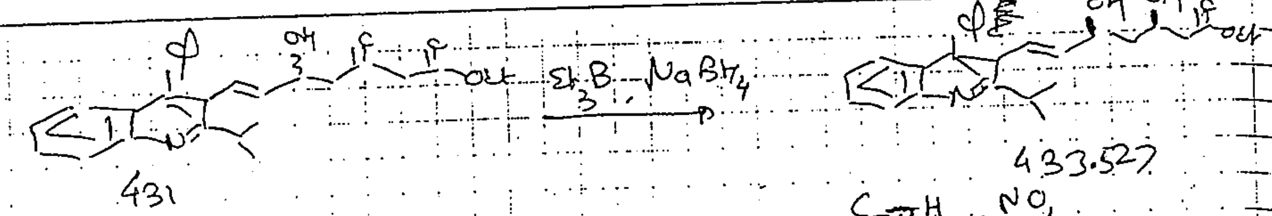
CM-1 %T
73.667
66.000
54.000
42.000
30.000
18.000
6.0000
0.2820
4398
4000
3600
3200
2800
2400
2000
1600
1200
800
401
FILE NAME : 12061-176-4 #1052
#SCANS : 64
#BKG : 64
APOD : HAPP-GENZEL
COMMENT : thin film wattanasin/r.p. lab358 pcc
GAIN : 2
DET : TGS
RES : 4 CM-1
DATE : 07/23/87
ANALECT FX-6160
ORD : %T
ABSC: WAVENUMBER
TIME: 08:56:47


285
SAMPLE NO.
SOLVENT CDCl3
REFERENCE TMS
TEMP. °C TUBE mm
OBSERVE NUCLEUS
MENU NO.
IRMOD
IRR. POWER
PUMOD
NO. of ACCUM.
DATA POINTS
SPECTRAL WIDTH
DATE
OPERATOR
FX
SPECTRUM NO.

Title-

Date 7-23-87 Proj. 286

Cont'd From-

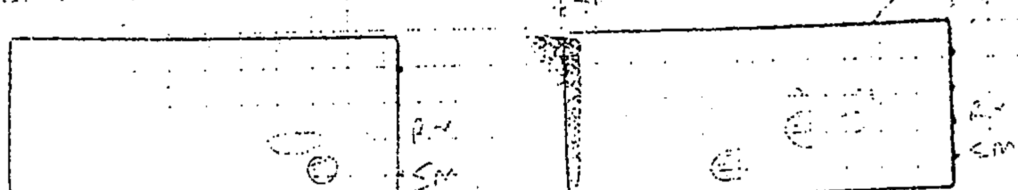


(431) 1206-175-4 = 1.0 g (0.002320 mole)
1 m Et_3B / THF = 3.5 ml (0.003480 mole) 1.5 eq.
dry THF = 10 ml
CH_3OH = 2.5 ml
37.8 $NaBH_4$ = 0.1315 g (0.003480 mole) 1.5

Ref: 1206-140

(homogeneous)

To 1206-175-4 in THF / MeOH & added 1 m Et_3B / THF at r.t. stirred for 1 hr (9:45 - 10:45). The solution was cooled to -78°C, $NaBH_4$ was added portionwise. The rxn was stirred at -78°C for (11:00 - 3:00) 4 hrs.



The rxn was quenched with AcOH (5 ml) at -78°C. Ethyl acetoacetate was added & let it warm up to r.t. Org. layer was washed with satd. $NaHCO_3$, H_2O, brine, dried, filtered. Residue was redissolved in MeOH, evaporated to dryness. This evaporation process (in MeOH) was repeated until TLC showed desired product.

wt. of orange oil = 1.0914 g (1206-176-39)

Flash column (EtOAc / Pet) gave ✓ m.p. = 104-106° exact mass

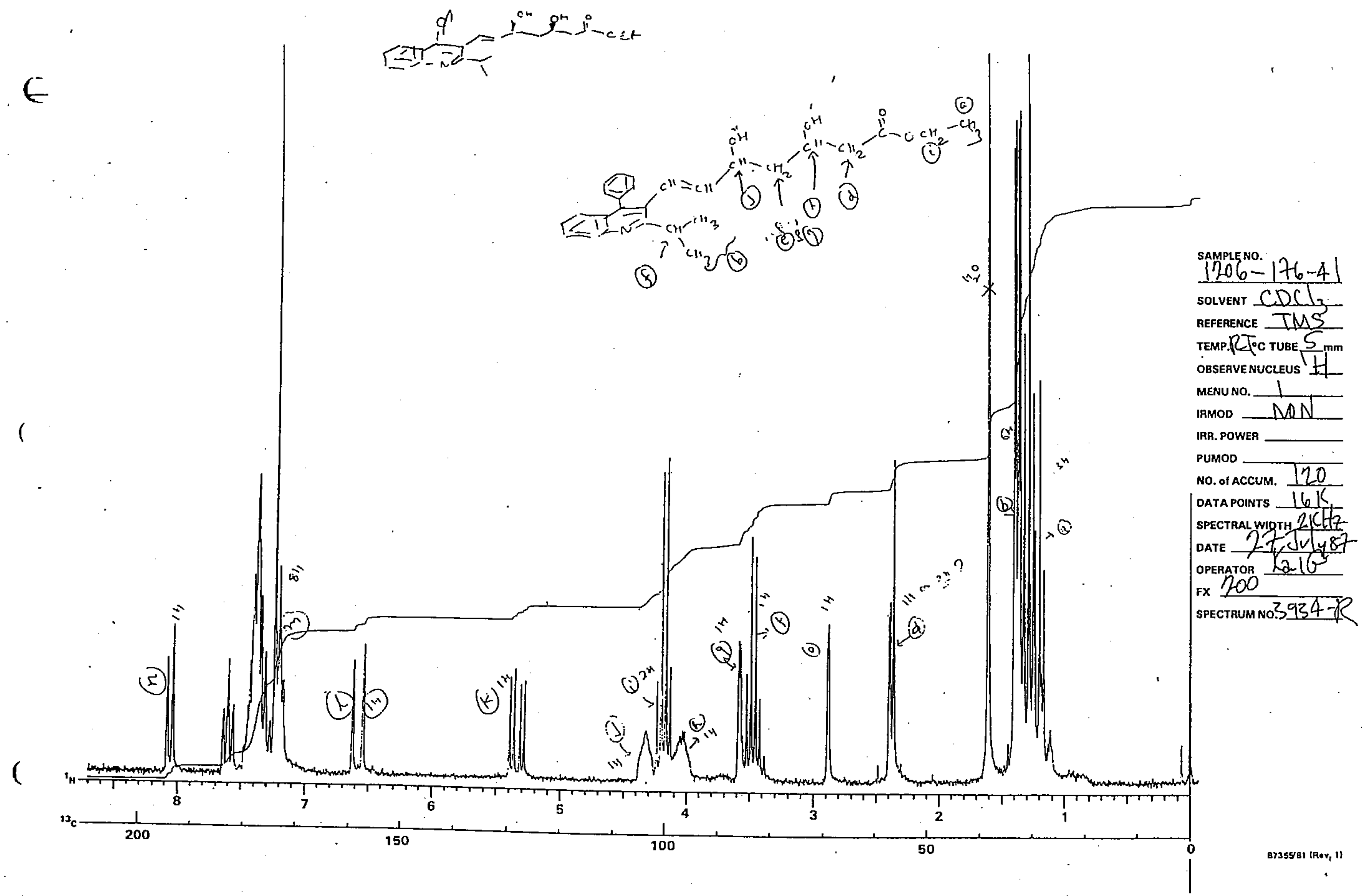
yellow oil + solid- (a) F_{4-6} = 0.4043 g (1206-176-41) ir nmr, ms mh^+ = 434 ✓ ^{13}C HPLC (98.3%)

F_{7-13} = 0.510 g (1206-176-43) ir nmr, ms mh^+ = 434 ✓ ^{13}C HPLC (93.2%)

Performed by- Raj Patel 8-5-87

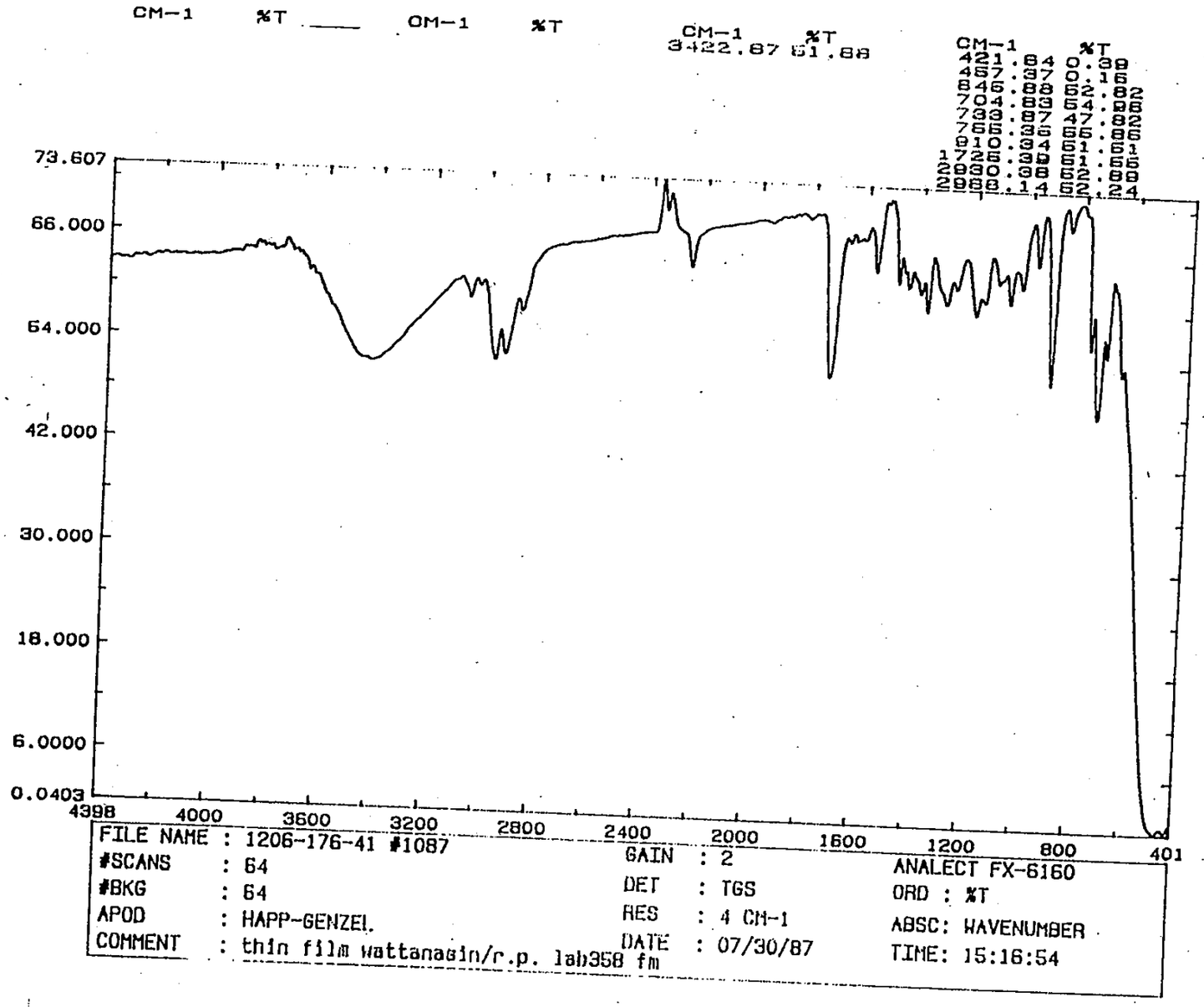
Witness- [signature]

Cont'd to-


SAMPLE NO. 1206-176-41
SOLVENT CDCl3
REFERENCE TMS
TEMP. RT °C TUBE 5 mm
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOD NON
IRR. POWER
PUMOD
NO. of ACCUM. 120
DATA POINTS 16K
SPECTRAL WIDTH 2KHz
DATE 27 July 87
OPERATOR
FX 200
SPECTRUM NO. 3934-R
1H
13C
8
7
6
5
4
3
2
1
0
200
150
100
50
0
87355/81 (Rev. 1)

287

288

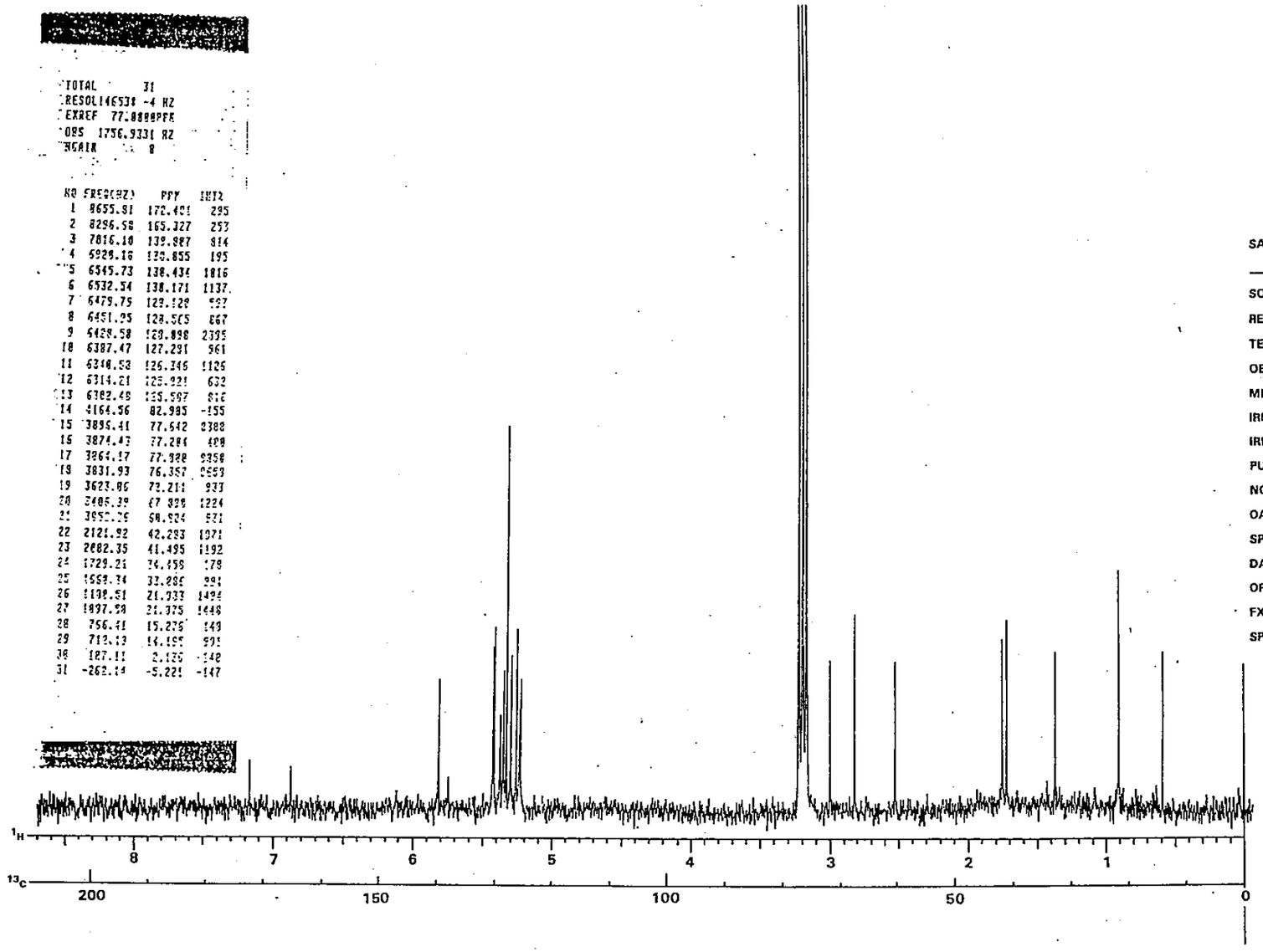

CM-1 %T
CM-1 %T
CM-1 %T
3422.87 51.88
CM-1 %T
421.84 0.39
457.37 0.16
846.88 52.82
704.83 54.98
733.87 47.82
755.36 55.86
910.34 51.61
1725.35 51.65
2930.38 52.89
2988.14 52.24
73.607
66.000
54.000
42.000
30.000
18.000
6.0000
0.0403
4398 4000 3600 3200 2800 2400 2000 1600 1200 800 401
FILE NAME : 1206-176-41 #1087
#SCANS : 64
#BKG : 64
APOD : HAPP-GENZEL
COMMENT : thin film wattanasin/r.p. lab358 fm
GAIN : 2
DET : TGS
RES : 4 CM-1
DATE : 07/30/87
ANALECT FX-6160
ORD : %T
ABSC: WAVENUMBER
TIME: 15:16:54

[redacted]

TOTAL 31
RESOL146538 -4 HZ
EXREF 77.0000PPE
OBS 1756.9331 HZ
NGAIN 0

NO	FREQ(HZ)	PPF	INTZ
1	9655.81	172.401	295
2	9296.58	165.327	253
3	7816.10	139.587	814
4	6928.16	123.655	195
5	6545.73	138.434	1816
6	6532.54	138.171	1137
7	6479.75	129.128	927
8	6451.25	128.505	867
9	6428.58	128.098	2395
10	6387.47	127.291	961
11	6348.58	126.346	1126
12	6314.21	125.921	632
13	6302.48	125.597	816
14	4164.56	82.985	-155
15	3895.41	77.642	8388
16	3874.43	77.284	488
17	3864.17	77.988	9358
18	3831.93	76.352	9559
19	3623.86	72.211	933
20	3485.39	67.326	1224
21	3052.26	58.824	571
22	2121.92	42.283	1071
23	2082.35	41.495	1192
24	1729.21	34.458	178
25	1658.74	33.086	991
26	1138.51	21.933	1494
27	1097.58	21.375	1648
28	756.41	15.276	149
29	713.13	14.195	991
30	187.11	3.125	-148
31	-262.14	-5.221	-147

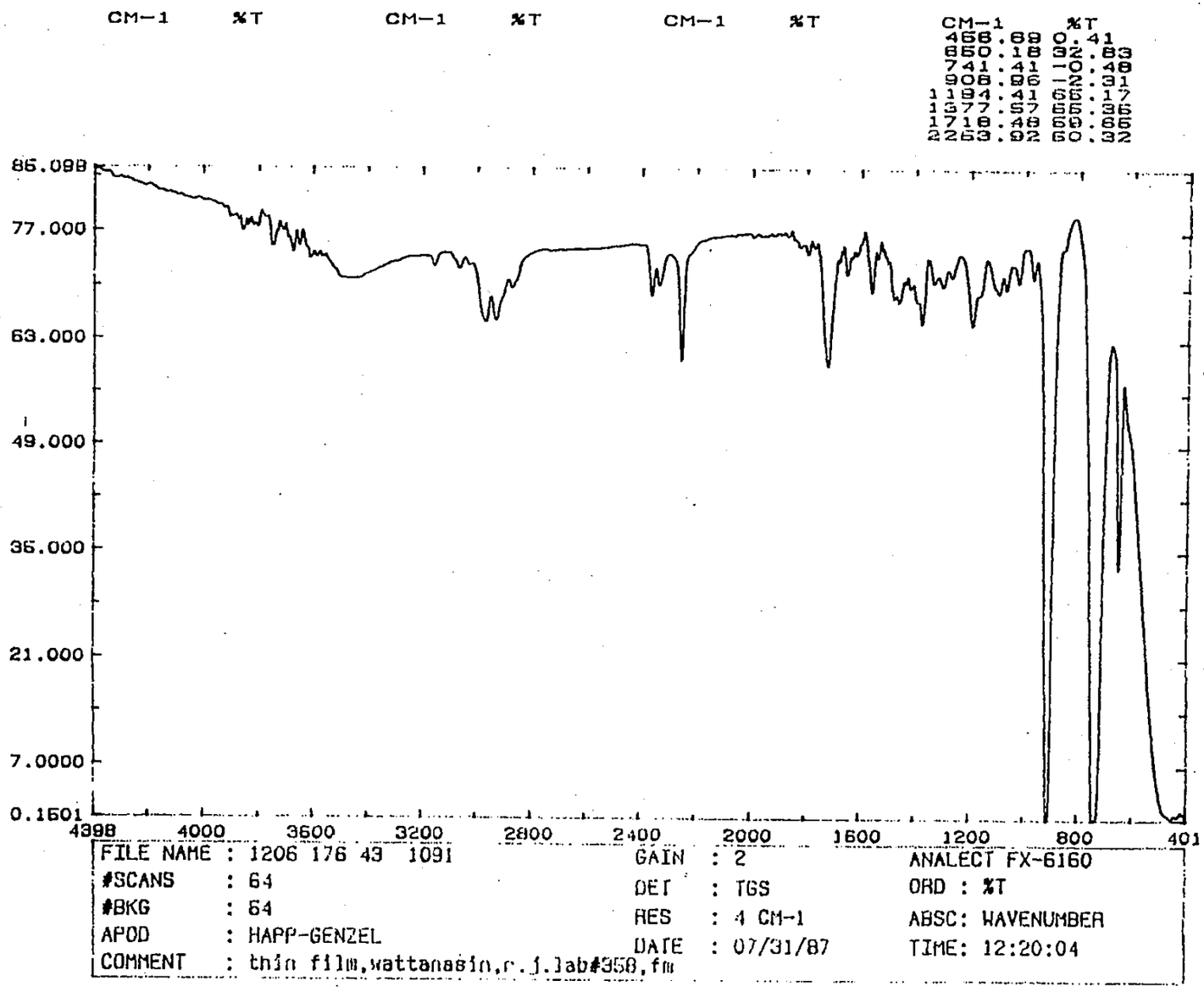
[redacted]

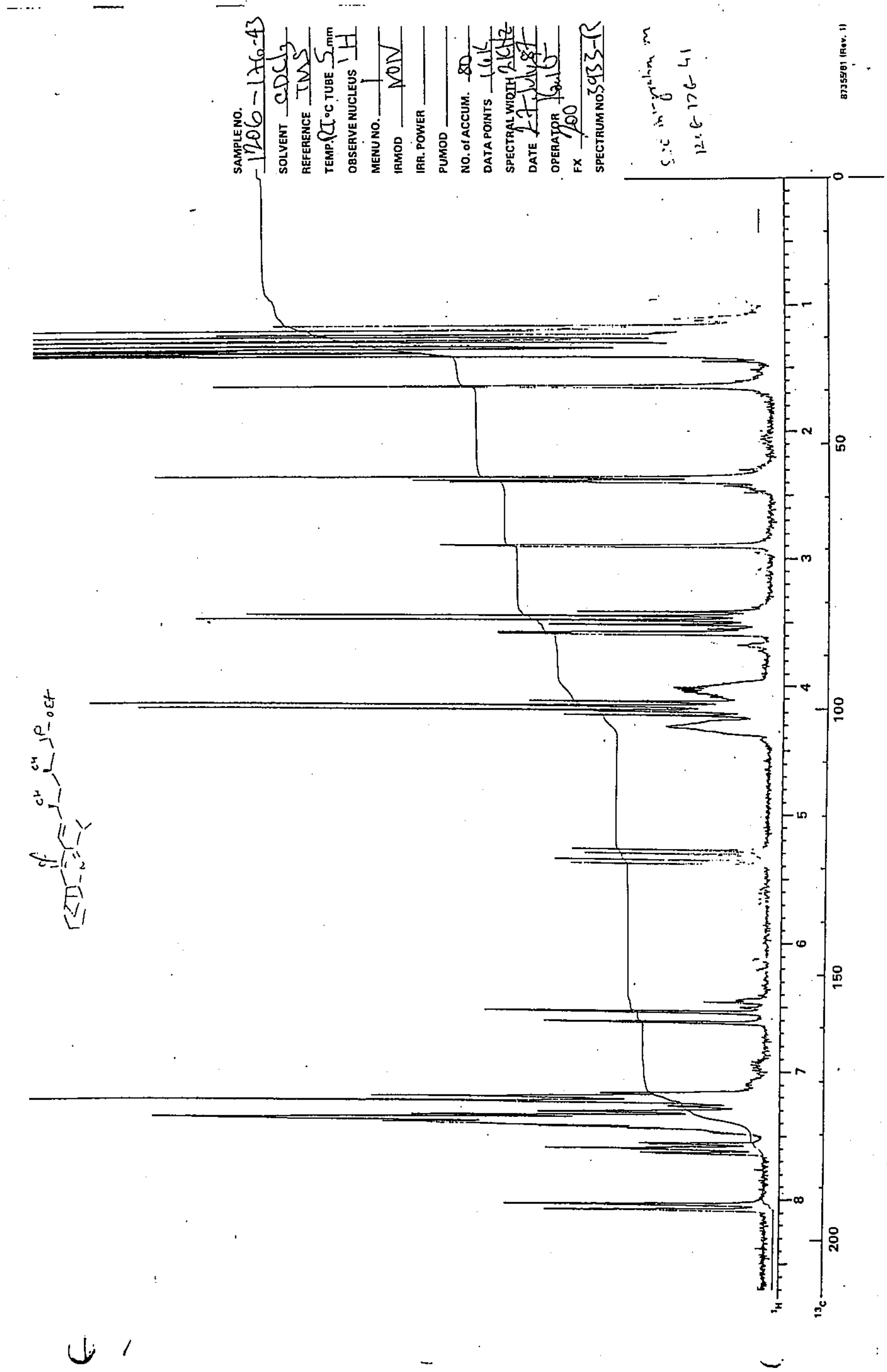


SAMPLE NO. 1706-176-41
SOLVENT $CDCl_3$
REFERENCE $CDCl_3$
TEMP. RT °C TUBE 5 mm
OBSERVE NUCLEUS ^{13}C
MENU NO. #-22
IRMOD COM
IRR. POWER
PUMOD
NO. of ACCUM. 30667
DATA POINTS #16K
SPECTRAL WIDTH 12KHz
DATE 29 July 87
OPERATOR Randy
FX 200
SPECTRUM NO. 03934-1

87355/81 (Rev. 1)

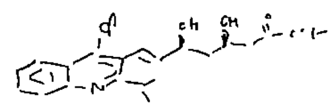
289

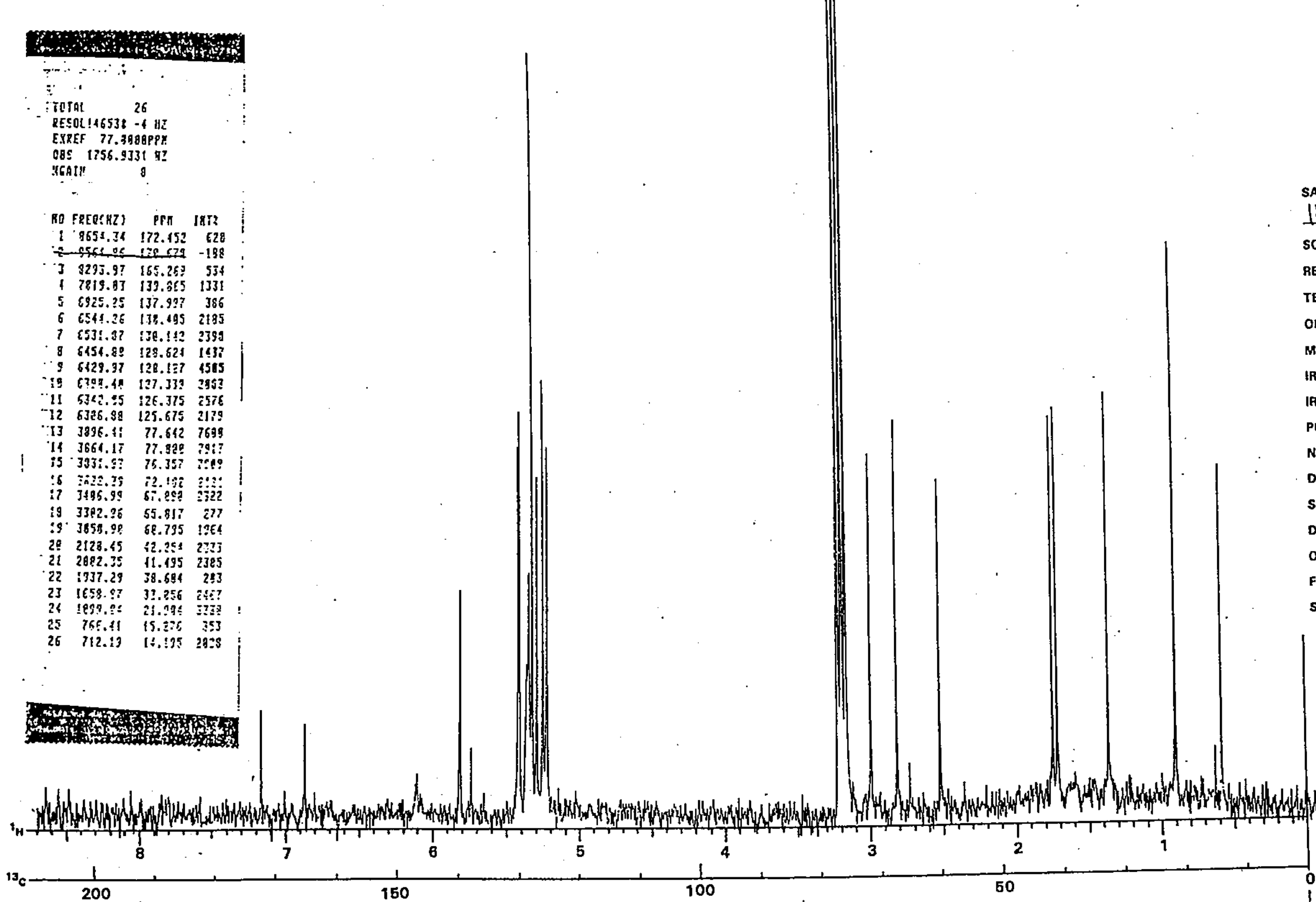

CM-1 %T
CM-1 %T
CM-1 %T
CM-1 %T
466.89 0.41
650.18 32.83
741.41 10.48
908.96 12.31
1184.41 66.17
1377.57 55.36
1718.48 69.66
2263.92 60.32
85.098
77.000
63.000
49.000
36.000
21.000
7.0000
0.1501
4398 4000 3600 3200 2800 2400 2000 1600 1200 800 401
FILE NAME : 1206 176 43 1091
#SCANS : 64
#BKG : 64
APOD : HAPP-GENZEL
COMMENT : thin film,wattanasin,r.j.lab#358,fm
GAIN : 2
DET : TGS
RES : 4 CM-1
DATE : 07/31/87
ANALECT FX-6160
ORD : %T
ABSC: WAVENUMBER
TIME: 12:20:04



SAMPLE NO. 1206-176-43
SOLVENT CDCl3
REFERENCE TMS
TEMP. RT °C TUBE 5 mm
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOD NON
IRR. POWER
PUMOD
NO. of ACCUM. 80
DATA POINTS 16K
SPECTRAL WIDTH 2KHz
DATE 27 July 87
OPERATOR
FX 200
SPECTRUM NO. 3933-R
8735/81 (Rev. 1)
0
1
2
3
4
5
6
7
8
50
100
150
200
1H
13C

291





TOTAL 26
RESOL 146538 -4 HZ
EXREF 77.0000PPM
OBS 1756.9331 HZ
NGAIN 8

NO	FREQ(HZ)	PPM	INT2
1	9654.34	172.452	628
~~2~~	~~9564.96~~	~~170.679~~	-198
3	9293.97	165.269	534
4	7819.87	139.865	1331
5	6925.25	137.997	366
6	6544.26	130.495	2185
7	6531.87	130.142	2399
8	6454.89	129.624	1437
9	6429.97	128.127	4585
10	6398.40	127.339	2963
11	6342.95	126.375	2576
12	6326.98	125.675	2179
13	3896.41	77.642	7699
14	3664.17	77.000	7917
15	3831.97	76.357	7909
16	3622.39	72.192	2121
17	3496.99	67.898	2322
18	3382.96	65.817	277
19	3858.90	60.795	1964
20	2128.45	42.354	2333
21	2082.35	41.495	2385
22	1937.29	38.604	283
23	1658.97	33.056	2467
24	1099.94	21.994	3339
25	765.41	15.276	353
26	712.13	14.195	2828

SAMPLE NO. 1206-176-43
SOLVENT CDCl3
REFERENCE CDCl3
TEMP. RT °C TUBE 5 mm
OBSERVE NUCLEUS 13C
MENU NO. #22
IRMOD COM
IRR. POWER
PUMOD
NO. of ACCUM. 23596
DATA POINTS #16K
SPECTRAL WIDTH 12 KHZ
DATE 30 July 87
OPERATOR KaiG
FX 200
SPECTRUM NO. 03933-6

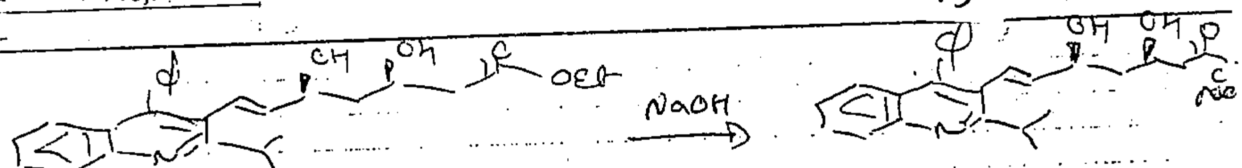
87355/81 (Rev. 1)

292

293

Date 7-28-87 Proj.   Title-

Cont'd From-

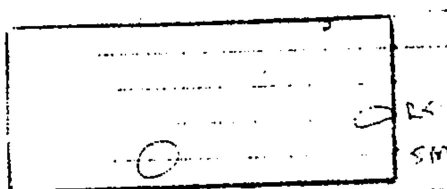


433   427.467

$C_{25}H_{26}NO_4Na$

(433)	1206-126-41	=	200.0 mg (0.4618937 mmol)
	0.5N NaOH	=	439.4 ml (0.438799 mmole) 95%
	abs EtOH	=	5 ml + 439 ml

To 1206-176-43 in abs. EtOH, was added at 0°c 0.5N NaOH stirred at 0°c for 1hr. (12:30 - 1:30) → yellow oil



Diluted with ether. Rotavap to dryness to yellow oil diluted with ether. Lots of solids came out of sol^n washed with ether, decant out ether dried yellow solids under vac.

wt: 128.8 mg (1206-179-30)

nmr ✓, ir ✓, uv, micro, m.p.: Shrinked at 187°c, does not melt up to 210°c

ms^+ = 428

Rotavap ether layer to dryness to yellow solids (1206-179-34)

Theory: 197.2 mg (90.6%)

10-6-87 submitted for (20mg) solubility test

10-7-87 Solubility = 0.0809 mg/ml

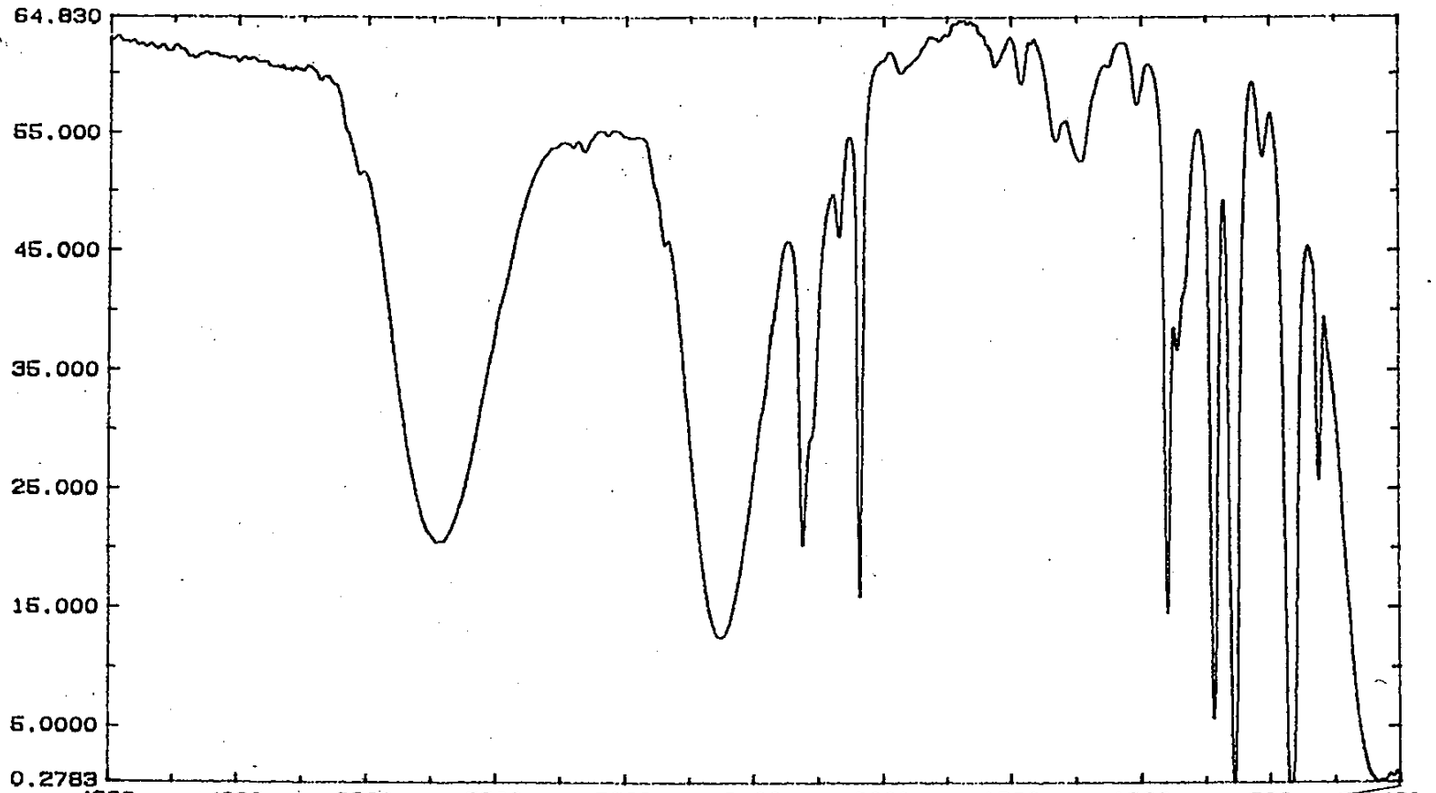
	C	H	N	O		
Calc.						
Found						

Performed by- Roy Patel 8-5-87

Witness- L Perez

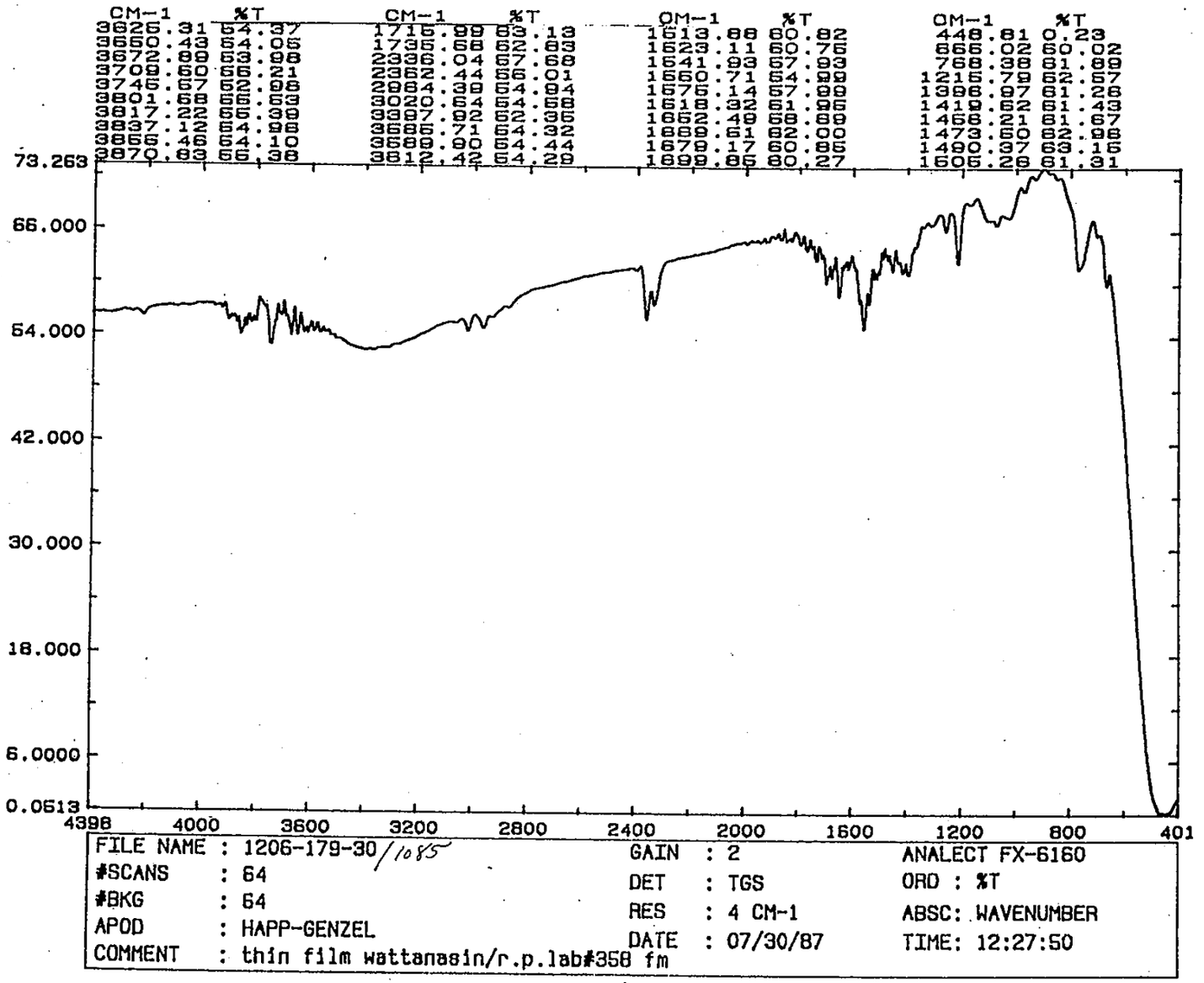
Cont'd to-

CM-1	%T	CM-1	%T	CM-1	%T
488.45	0.45				
739.00	-0.38				
810.64	-0.24				
976.43	5.67				
2601.90	12.69				



FILE NAME : 1206-179-30 1093	GAIN : 2	ANALECT FX-6160
#SCANS : 64	DET : IGS	ORD : %T
#BKG : 64	RES : 4 CM-1	ABSC: WAVENUMBER
APOD : HAPP-GENZEL	DATE : 07/31/87	TIME: 14:09:38
COMMENT : thin film,wattanasin,r.j. lab#358 fm		

294



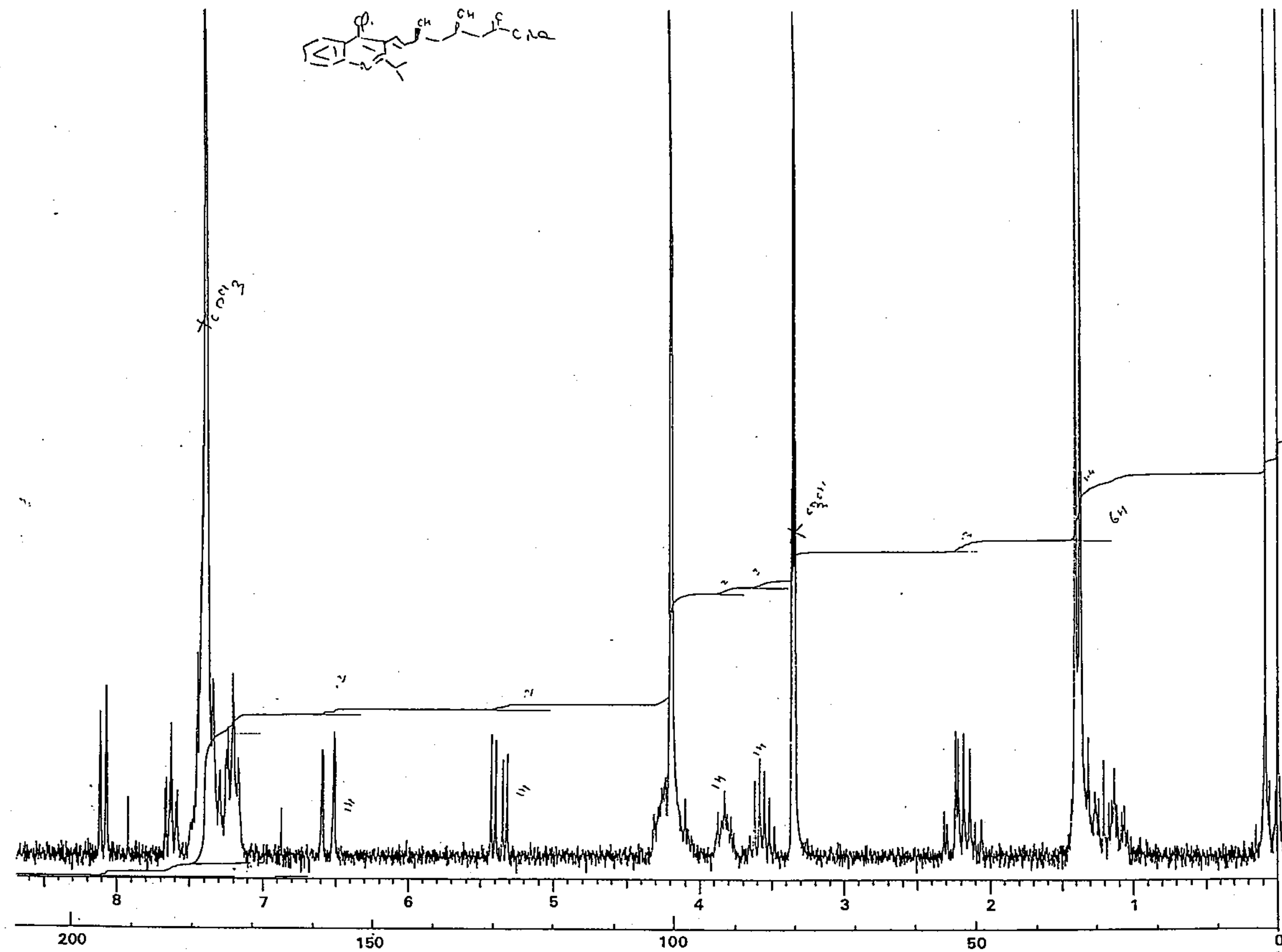
CM-1	%T	CM-1	%T	CM-1	%T	CM-1	%T
3626.31	54.37	1715.99	63.13	1513.88	60.82	448.81	0.23
3650.43	54.05	1735.68	62.83	1523.11	60.75	665.02	60.02
3672.89	53.98	2336.04	57.68	1541.93	57.93	768.38	61.89
3709.60	56.21	2362.44	56.01	1560.71	54.99	1215.79	62.57
3746.57	62.98	2984.39	54.94	1575.14	57.99	1396.97	61.26
3801.68	65.53	3020.64	54.58	1618.32	61.96	1419.62	61.43
3817.22	65.39	3387.92	62.35	1652.49	58.89	1458.21	61.67
3837.12	64.98	3585.71	64.32	1888.61	62.00	1473.60	62.98
3866.46	64.10	3589.90	64.44	1679.17	60.85	1490.37	63.15
3870.83	66.38	3812.42	64.29	1699.85	60.27	1606.26	61.31

73.263
66.000
54.000
42.000
30.000
18.000
6.0000
0.0513
4398 4000 3600 3200 2800 2400 2000 1600 1200 800 401

FILE NAME : 1206-179-30/1085	GAIN : 2	ANALECT FX-6160
#SCANS : 64	DET : TGS	ORD : %T
#BKG : 64	RES : 4 CM-1	ABSC: WAVENUMBER
APOD : HAPP-GENZEL	DATE : 07/30/87	TIME: 12:27:50
COMMENT : thin film wattanasin/r.p.lab#358 fm		

Small Sample

295



SAMPLE NO. 1206-179-30
SOLVENT CDCl3/CD3OD
REFERENCE TMS
TEMP. 24 °C TUBE 5 mm
OBSERVE NUCLEUS 1H
MENU NO. 4
IRMOD NON
IRR. POWER
PUMOD
NO. of ACCUM. 120
DATA POINTS 16K
SPECTRAL WIDTH 2KHz
DATE 29 July 87
OPERATOR
FX 200
SPECTRUM NO. 3967-R

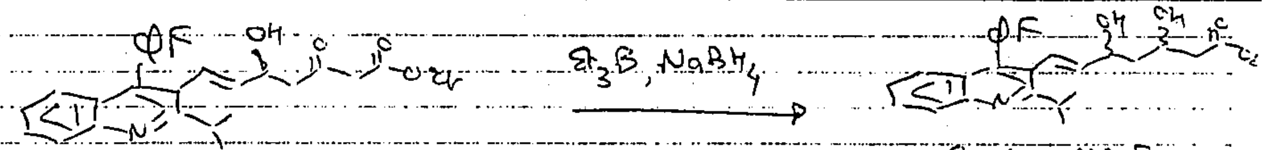
87355/81 (Rev. 1)

296

 Title-

Date 8-10-87 Proj.

Cont'd From-



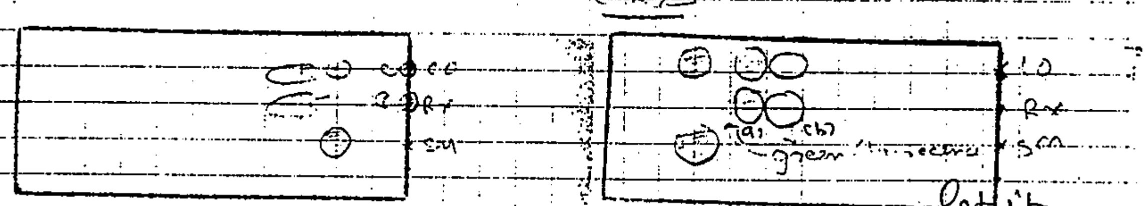
$C_{27}H_{30}NO_4F$

449 → 451

449 1206-187-18 = 400 mg (0.8908685 mmole)
1M Et_3B / THF = 133.64 ml (1.336302 mmole) 1.5eqm
dry THF = 5 ml
HPLC grade CH_3OH = 1.25 ml
37.8 $NaBH_4$ = 50.5 mg (1.336302 mmole) 1.5eqm.

Ref: 1206-176

To 1206-187-18 in THF & MeOH was added 1M Et_3B/THF, stirred at r.t. for 1hr (yellow homogeneous) Cooled to -78°C, added 51 mg $NaBH_4$ stirred at -78°C for (12 PM - 3 PM)



quenched with 2.5 ml AcOH added EtoAc / warmed up to r.t., extracted with EtoAc washed with Satd $NaHCO_3$, H₂O, brine, dried, filtered washed, added MeOH evap. to dryness to give yellow oil washed with 5X MeOH gave yellow oil = 414 mg (1206-190-35) ms MH^+:452

8-11-87

8-12-87 Flash column (80% Et_2O / Pet) gave mix of (a) & (b) again seperated on flash (20% acetone / pet ether) gave
yellow-orange oil (a) = 228 mg (1206-190-38) nmr, ms, exact mass MH^+=452
green fluorescence (b) = 139.2 mg (1206-190-39) nmr, ms

Dried (a) over high vac gave 206.6 mg solid + oil (1206-190- nmr ^{13}C

obs. Mass = 452.223566
Calc " = 452.22371

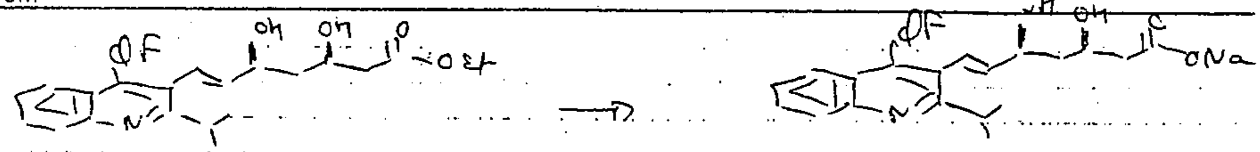
Theory: 401.78 mg (51.4%)

Performed by- Rajeshwari D. Patel 9-1-87

Witness- L Perez

Cont'd to-

CM-1 %T
CM-1 %T
CM-1 %T
CM-1 %T
106.86
103.00
91.000
79.000
67.000
55.000
43.000
30.933
4000 3600 3300 3000 2700 2400 2100 1800 1500 1200 900 600
FILE NAME : 1206-190-38 1176
#SCANS : 16
#BKG : 64
APOD : HAPP-GENZEL
COMMENT : CAST FILM (CDCL3) WATTANASIN/R.P.LAB#358
GAIN : 2
DET : TGS
RES : 4 CM-1
DATE : 08/20/87
ANALECT FX-6260
ORD : %T
ABSC: WAVENUMBER
TIME: 08:37:25

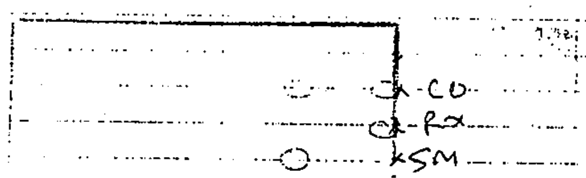


451 → 445.5

451 1206-190-41 = 100 mg (0.2217294 mmole)
1N NaOH = 217.3 μl ml (0.2172948 mmole) 98%
abs. EtOH = 3 ml +2 ml

Ref: 1206-179

To 1206-190-41 in abs. EtOH, at 0°c with stirring was added dropwise 1N NaOH. The mixt was stirred at 0°c (11 3c/4 – 2 30/4 ?) → yellow oil

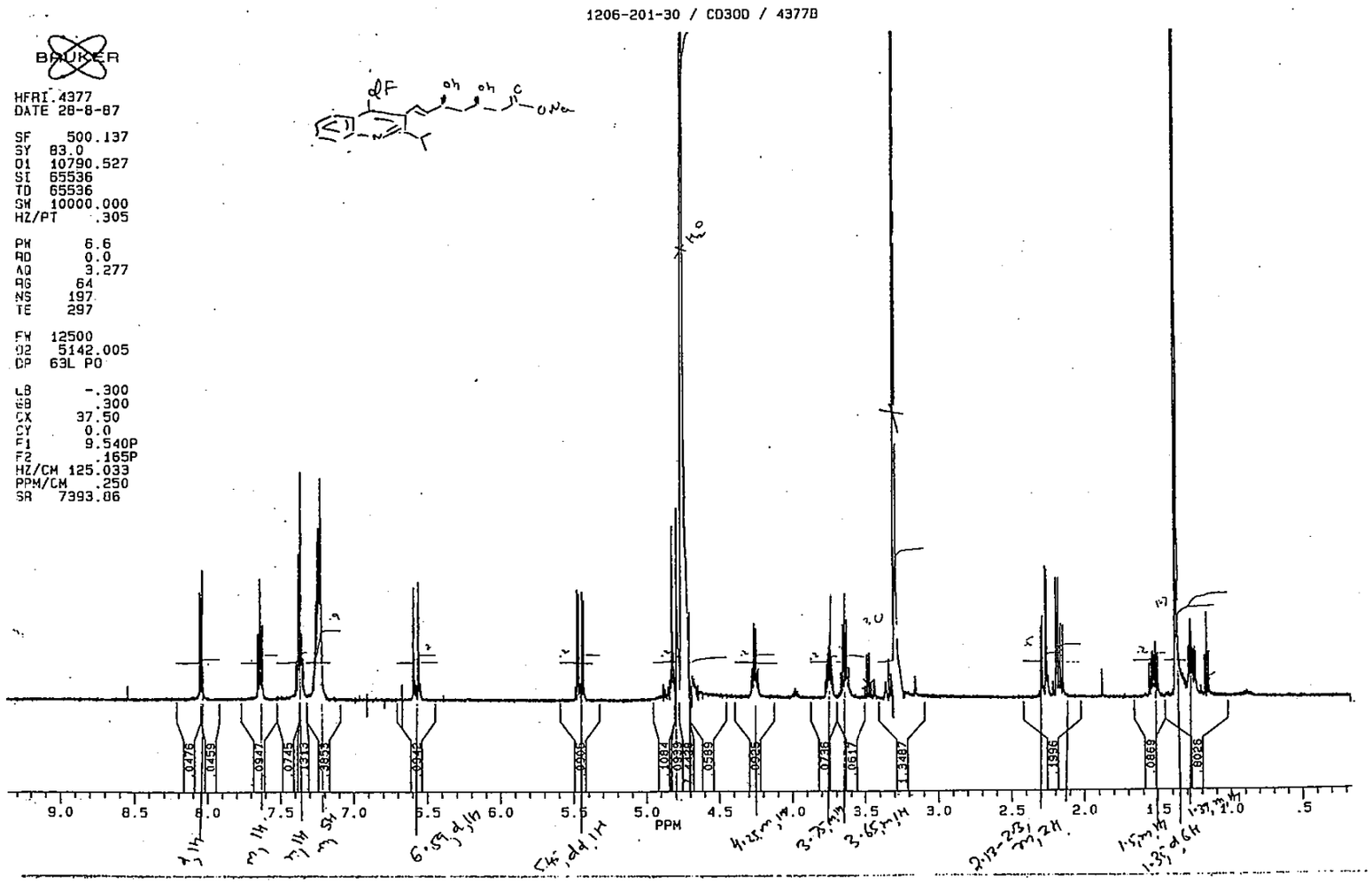


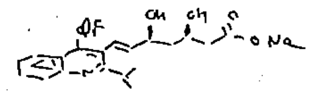
Diluted with ether, rotavap to dryness to yellow oil added ether. ppts (yellow) came out. filtered, washed, dried gave 86.4 mg yellow solid (1206-201-30)
– nmr, MS, micro → not too good
MH+=446
Theory: 98.7 mg (87.5%)

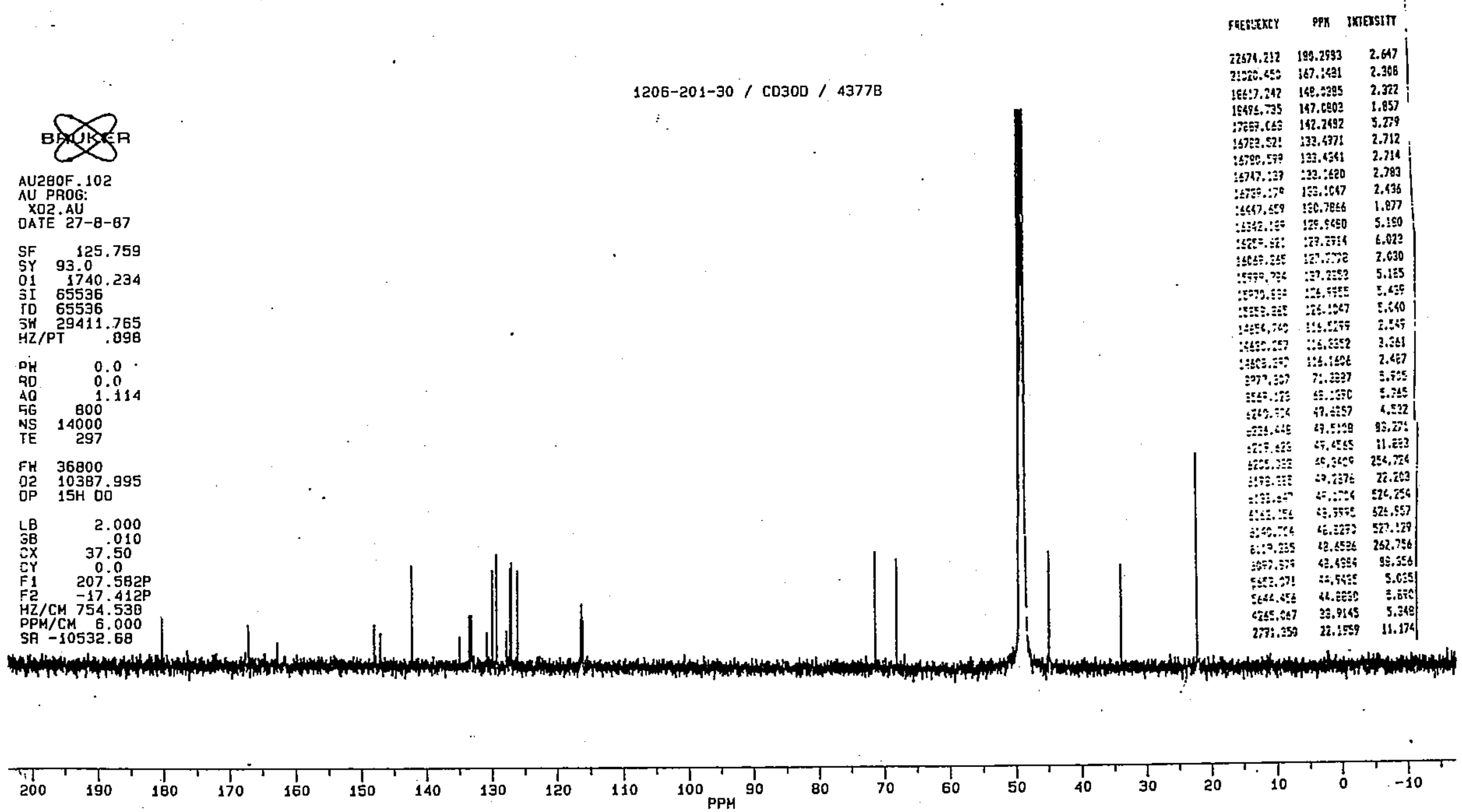
Doesn't melt up to 225°C
10-6-87 Submitted for solubility study (20 mg) to micro lab.
10-7-87 Solubility: 0.0958 mg/ml

Performed by- Ray Patel 9-1-87
Witness- L Perez
Cont'd to-

[redacted]


1206-201-30 / CD3OD / 4377B
BRUKER
HFRI.4377
DATE 28-8-87
SF 500.137
SY 83.0
O1 10790.527
SI 65536
TD 65536
SW 10000.000
HZ/PT .305
PW 6.6
RD 0.0
AQ 3.277
RG 64
NS 197
TE 297
FW 12500
O2 5142.005
DP 63L PO
LB -.300
GB .300
CX 37.50
CY 0.0
F1 9.540P
F2 .165P
HZ/CM 125.033
PPM/CM .250
SR 7393.86
PPM





1206-201-30 / CD3OD / 4377B
BRUKER
AU280F.102
AU PROG:
XO2.AU
DATE 27-8-87
SF 125.759
SY 93.0
O1 1740.234
SI 65536
TD 65536
SW 29411.765
HZ/PT .898
PW 0.0
RD 0.0
AQ 1.114
RG 800
NS 14000
TE 297
FW 36800
O2 10387.995
DP 15H DO
LB 2.000
GB .010
CX 37.50
CY 0.0
F1 207.582P
F2 -17.412P
HZ/CM 754.538
PPM/CM 6.000
SR -10532.68
FREQUENCY PPM INTENSITY
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
PPM

301

SAMPLE #	BOOK #	DATE
1351	1040-237-23	MAY 25 1984
1352	977-228-17	MAY 25 1984
1353	1040-238-24	MAY 25 1984
OR 1354	1054-246-24	MAY 25 1984
1355	1065-12-32	MAY 25 1984
1356	1066-45-5	MAY 29 1984
1357	1060-143-26	MAY 29 1984
1358	1064-89-21	MAY 29 1984
1359	1049-232-37	MAY 29 1984
1360	978-171-37	MAY 29 1984
1361	1023-292-36	MAY 29 1984
1362	1040-239-36	MAY 29 1984
1363	1067-40-31	MAY 29 1984
1364	1017-244-37	MAY 29 1984
1365	1061-77-12	MAY 29 1984
UV-VIS 1366	1039-246-26	MAY 30 1984
OR 1367	1054-229-38	MAY 30 1984
1368	972-248-44	MAY 30 1984
UV-VIS 1369	1061-77-12	MAY 30 1984
1370	1049-237-19	MAY 30 1984
1371	1061-77-12	MAY 30 1984
1372	1065-13-27	MAY 30 1984
1373	1033-129-24	MAY 30 1984
1374	1023-291-18	MAY 30 1984
1375	1060-146-24	MAY 31 1984

SAMPLE #	BOOK #	DATE
1376	1060-147-25	MAY 31 1984
1377	1049-237-27	MAY 31 1984
1378	1049-240-36	MAY 31 1984
OR 1379	1054-252-43	MAY 31 1984
OR 1380	1054-259-24	MAY 31 1984
OR 1381	1054-256-11	MAY 31 1984
1382	981-258-35	MAY 31 1984
1383	1013-228-14	MAY 31 1984
1384	1024-233-5	MAY 31 1984
1385	1024-231-22	MAY 31 1984
1386	1024-231-21	MAY 31 1984
1387	1024-231-19	MAY 31 1984
1388	1070-19-37	MAY 31 1984
1389	1013-226-42	MAY 31 1984
1390	1013-226-31	MAY 31 1984
1391	000-185-19	MAY 31 1984
1392	1040-240-27	JUN. 1 1984
1393	1068-014-39	JUN. 1 1984
1394	1066-48-18	JUN. 1 1984
1395	1048-42-27	JUN. 1 1984
1396	1066-46-19	JUN. 1 1984
1397	1064-92-29	JUN. 1 1984
1398	1070-21-40	JUN. 1 1984
-5		JUN. 1 1984
25		JUN. 4 1984

	2001	1060-220-25	AUG. 9 . 1984	OR 2026	1057-56-303 AUG. 1 4 1984
	2002	1080-8-32	AUG. 9 . 1984	2027	1079-13-42 AUG. 1 4 1984
	2003	1060-221-25	AUG. 9 . 1984	2028	977-27712 AUG. 1 4 1984
	2004	1021-212-27	AUG. 9 . 1984	2029	1079-27-25 AUG. 1 4 1984
	2005	1024-271-22	AUG. 1 0 1984	OR 2030	000-132-29 AUG. 1 5 1984
	2006	1040-299-28	AUG. 1 0 1984	2031	1075-42-35 AUG. 1 5 1984
	2007	1064-170-22	AUG. 1 0 1984	OR 2032	1055-204-35 AUG. 1 5 1984
	2008	1049-257-29	AUG. 1 0 1984	OR 2033	1057-61-24 AUG. 1 5 1984
	2009	1079-22-28	AUG. 1 0 1984	2034	1024-275-34 AUG. 1 5 1984
	2010	1033-229-35	AUG. 1 0 1984	2035	1057-23-27 AUG. 1 5 1984
	2011	1084.5-33	AUG. 1 3 1984	2036	1063-132-28 AUG. 1 5 1984
	2012	1061-136-36	AUG. 1 3 1984	2037	1063-119-28 AUG. 1 5 1984
	2013	1084-3-33	AUG. 1 3 1984	2038	1084-2-39 AUG. 1 5 1984
	2014	1061-133-29	AUG. 1 3 1984	2039	1017-292-14 AUG. 1 5 1984
OR	2015	1061-136-36	AUG. 1 3 1984	OR 2040	1052-16-28 AUG. 1 6 1984
OR	2016	1057-53-4	AUG. 1 3 1984	2041	1080-18-32 AUG. 1 6 1984
OR	2017	1057-45-38	AUG. 1 3 1984	2042	1038-221-6 AUG. 1 6 1984
OR	2018	1057-55-31	AUG. 1 3 1984	2043	1038-223-39 AUG. 1 6 1984
	2019	1021-215-26	AUG. 1 3 1984	2044	1061-138-23 AUG. 1 6 1984
	2020	1080-13-34	AUG. 1 3 1984	OR 2045	998-90-18 AUG. 1 6 1984
	2021	1063-130-26	AUG. 1 3 1984	OR 2046	998-90-24 AUG. 1 6 1984
	2022	1021-215-39	AUG. 1 3 1984	OR 2047	998-90-21 AUG. 1 6 1984
NV	2023	1030-138-2	AUG. 1 4 1984	2048	977-277-24 AUG. 1 6 1984
NV	2024	1030-138-5	AUG. 1 4 1984	2049	1080-21-22 AUG. 1 6 1984
	2025	1084-6-35	AUG. 1 4 1984	OR 2050	1033-229-35 AUG. 1 7 1984

SAMPLE #	BOOK #	DATE
2501	1062-221-24	NOV. 8 1984
OR 2502	1838-132-13	NOV. 8 1984
OR 2503	1038-130-9	NOV. 8 1984
2504	1085-53-44	NOV. 8 1984
OR 2505	1078-18-4	NOV. 8 1984
OR 2506	1078-20.09	NOV. 8 1984
2507	1079-101-28	NOV. 8 1984
2508	1085-49-30	NOV. 8 1984
2509	1079-101-28	NOV. 8 1984
2510	972-296-31	NOV. 8 1984
2511	1077-85-39	NOV. 8 1984
2512	1060-289-39	NOV. 9 1984
2513	1060-289-36	NOV. 9 1984
2514	1079-105-35	NOV. 9 1984
2515	1063-182-29	NOV. 9 1984
2516	1075-107-5	NOV. 9 1984
2517	1075-106-43	NOV. 9 1984
2518	1080-89-32	NOV. 12 1984
2519	1063-183-27	NOV. 12 1984
2520	1063-184-32	NOV. 12 1984
2521	1080-86-28	NOV. 12 1984
2522	972-295-40	NOV. 12 1984
2523	1062-222-35	NOV. 12 1984
2524	1090-7-30	NOV. 12 1984
2525	1090-9-24	NOV. 12 1984

SAMPLE #	BOOK #	DATE
OR 2526	993-83-12	NOV. 13 1984
2527	1075-163-24	NOV. 13 1984
2528	1037-300-35	NOV. 13 1984
2529	1063-184-32	NOV. 13 1984
2530	1075-109-36	NOV. 13 1984
2531	1060-291-23	NOV. 13 1984
2532	1057-205-14	NOV. 13 1984
2533	1060-285-30	NOV. 13 1984
2534	1063-185-29	NOV. 13 1984
2535	1080-94-22	NOV. 13 1984
2536	1063-187-31	NOV. 14 1984
2537	1079-99-29	NOV. 14 1984
2538	1079-107-29	NOV. 14 1984
2539	1065-69-35	NOV. 14 1984
2540	1058-42-36	NOV. 14 1984
2541	1057-213-28	NOV. 14 1984
2542	1080-80-31	NOV. 14 1984
2543	1063-189-18	NOV. 14 1984
2544	1080-92-22	NOV. 15 1984
2545	1063-189-25	NOV. 15 1984
2546	1063-188-25	NOV. 15 1984
CDcl3 Sol 2547	1059-221-8	NOV. 15 1984
2548	1100-13-40	NOV. 15 1984
2549	1084-71-39	NOV. 15 1984
2550	1064-221-30	NOV. 15 1984

SAMPLE #	BOOK #	DATE
2551	1060-29[illegible]3	NOV. 1 5 1984
2552	1060-296-42	NOV. 1 6 1984
2553	1063-190	NOV. 1 6 1984
2554	1058-50-33	NOV. 1 6 1984
2555	1058-50-20	NOV. 1 [illegible]
2556	1059-221-21	NOV. 1 6 1984
2557	1059-221-27	NOV. 1 6 1984
2558	1060-297-39	NOV. 1 6 1984
2559	1024-263-16	NOV. 1 6 1984
2560	1084-63-33	NOV. 1 6 1984
2561	1060-297-31	NOV. 1 6 1984
2562	1058-51-23	NOV. 1 6 1984
2563	1058-43-32	NOV. 1 6 1984
OR 2564	1037-296-30	NOV. 1 6 1984 1986 SESSION
2565	1080-96-28	NOV. 1 9 1984
2566	1061-243-3	NOV. 1 9 1984
2567	1062-224-38	NOV. 1 9 1984
2568	1080-90-FH,S	NOV. 1 6 1984
2569	1063-192-29	NOV. 2 0 1984
2570	1063-188-30	NOV. 2 0 1984
2571	1063-188-32	NOV. 2 0 1984
2572	1075-113-31	NOV. 2 0 1984
2573	1060-295-36	NOV. 2 0 1984
2574	1084-65-33	NOV. 2 0 1984
2575	1034-173-27	NOV. 2 0 1984

JK

SAMPLE #	BOOK #
2576	1058-58-21
2577	1061-212-20
2578	1060-299-9
2579	1063-193-27
2580	1063-194-28
2581	1080-95-FS-8
2582	1040-286-32
2583	1079-112-23
2584	1004-207-30
2585	972-294-37
2586	997-247-36
2587	1080-100-26
2588	1080-98-32
2589	1079-111-19
2590	1063-198-25
2591	1063-198-23
2592	1063-199-25
2593	1063-197-23
2594	1063-196-28
2595	1063-175-18
2596	1062-229-32
2597	1058-62-10
2598	1079-113-25
2599	1064-225-33
2600	1075-119-23

305

SAMPLE #	BOOK #	DATE
UV 1001	978-189-44	
1002	1123-3-17	MAY 3 1985
1003	1116-58-41	MAY 3 1985
1004	1126-29-34	MAY 3 1985
1005	1108-44-30	May 3-1985
1006	1108-43-44	May 3, 1985
1007	1126-30-15	MAY 6 1985
1008	1116-76-14	MAY 6 1985
1009	1092-204-34	MAY 6 1985
1010	1127-8-26	MAY 6 1985
1011	1127-7-28	MAY 6 1985
1012	1127-5-23	MAY 6 1985
1013	1053-86-31	MAY 6 1985
1014	1053-88-31	MAY 6 1985
1015	1053-83-35	MAY 6 1985
1016	1053-86-33	MAY 6 1985
UV 1017	555-146-22	MAY 6 1985
1018	1100-103-20	MAY 7 1985
UV 1019	555-146-22	MAY 1985
1020	1114-42-10	MAY 7 1985
1021	1119-59-31	MAY 8 1985
1022	1119-56-32	MAY 8 1985
1023	1119-61-31	MAY 8 1985
1024	1092-209-27	MAY 8 1985
1025	1080-285-24	MAY 8 1985

SAMPLE #	BOOK #	DATE
UV 1026	993-170-42	306
1027	1053-90-35	MAY 8 198
1028	1053-89-30	MAY 8 198
1029	1108-47-44	MAY 8 198
OR 1030	1068-138-35	MAY 8 198
1031	1092-210-35	MAY 9 198
1032	1092-213-7	MAY 9 198
1033	SC-3-30	MAY 9 198
1034	1080-281-41	MAY 9 198
1035	998-154-36	MAY 9 198
1036	62-562 Step 2 By-Prod	MAY 9 198
1037	1080-283-22	MAY 9 198
OR 1038	1068-138-35	MAY 9 198
1039	1126-35-35	MAY 10 198
1040	SC-4-25	MAY 10 198
1041	1126-37-33	MAY 10 198
1042	1095-43-16	MAY 10 198
1043	1100-107-21	MAY 10 198
1044	1092-214-30	MAY 13 198
1045	1123-41-21	MAY 13 198
1046	1079-264-28	MAY 13 198
1047	1075-271-41	MAY 13 198
1048	1123-42-38	[illegible]
1049	1127-17-30	MAY 13 198
P Acetal 1050	1125-58-42	MAY [illegible]

SAMPLE #	BOOK #	DATE
1051	602-320 NA	MAY 13 1985
OR 1052	1085-142-29	MAY 14 1985
OR 1053	1080-301	MAY 14 1985
1054	1127-17-32	MAY 14 1985
1055	1080-290-26	MAY 14 1985
1056	1080-289-22	MAY 14 1985
1057	1080-301	MAY 14 1985
1058	1092-215-33	MAY 14 1985
1059	1123-43-48	MAY 14 1985
1060	1116-105-14	MAY 14 1985
1061	969-264-24	MAY 14 1985
1062	1092-216-37	MAY 14 1985
1063	1112-38-27	MAY 14 1985
1064	1119-65-36	MAY 15 1985
OR 1065	969-266-19	MAY 15 1985
1066	969-266-19	MAY 15 1985
1067	1110-134-19	MAY 15 1985
1068	1108-48-40	MAY 15 1985
1069	1119-70-29	MAY 15 1985
1070	1110-130-32	MAY 15 1985
UV 1071	1128-4-12	MAY 15 1985
UV 1072	1128-4-10	MAY 15 1985
UV 1073	1128-4-9	MAY 15 1985
1074	1092-223-30	MAY 15 1985
1075	SC-7-25	MAY 15 1985

SAMPLE #	BOOK # 307	DATE
1076	SC-7-28	MAY 15 1985
1077	1092-217-35	MAY 15 1985
1078	1080-291-F6	MAY 16 1985
1079	1119-68-30	MAY 16 1985
1080	1127-24-27	MAY 16 1985
1081	998-155-40	MAY 16 1985
1082	1058-215-44	MAY 16 1985
1083	1080-292-32	MAY 16 1985
1084	1080-287-22	MAY 16 1985
1085	1085-144-21	MAY 16 1985
1086	1085-144-24	MAY 16 1985
UV 1087	1045-295-14	MAY 16 1985
1088	1080-294-22	MAY 17 1985
1089	1092-227-31	MAY 17 1985
1090	1092-218-24	MAY 17 1985
1091	1100-109-14	MAY 17 1985
1092	1100-109-16	MAY 17 1985
1093	1119-71-28	MAY 17 1985
1094	1127-11-34	MAY 17 1985
1095	1127-11-37	MAY 17 1985
1096	1095-48-24	MAY 17 1985
1097	1058-215-31	MAY 17 1985
1098	1056-111-19	MAY 17 1985
UV 1099	1045-201-14	MAY 17 1985
1100	1110-141-25	MAY 17 1985

SAMPLE #	BOOK #	DATE
851	1190-266-39	MAY 26 1987
852	1205-28-35	MAY 26 1987
853	1201-253-18	MAY 26 1987
854	000-122-25	MAY 27 1987
855	000-124-29	MAY 27 1987
856	000-104-27	MAY 27 1987
857	60-104-29	MAY 27 1987
858	1224-29-40	MAY 27 1987
859	121-114-30	MAY 27 1987
860	1230-115-31	MAY 27 1987
OP 861	1230-111-24	MAY 27 1987
862	121-[illegible]	MAY 28 1987
863	123-[illegible]	MAY 28 1987
864	1230-115-[illegible]	MAY 28 1987
865	121-100-[illegible]	MAY 28 1987
866	1205-36-[illegible]	MAY 28 1987
867	121-[illegible]	MAY 28 1987
868	121-120-21	MAY 28 1987
OP 869	1138-193-06	MAY 29 1987
870	205-397 KPI-51-B1	MAY 29 1987
871	1230-120-21	MAY 29 1987
872	1230-121-28	MAY 29 1987
873	1191-119-19	MAY 29 1987
OR 874	1230-117-34	MAY 29 1987
875	000-126-28	JUN 1 1987
876	000-126-24	JUN. 1 1987
877	000-126-26	JUN. 1 1987
878	1161-334-[illegible]	JUN. 1 1987
879	1190-273-37	JUN. 1 1987
880	1205-33-20	JUN. 1 1987
881	1206-128-39	JUN. 2 1987
882	1206-129-18	JUN. 2 1987
883	1216-37-39	JUN. 2 1987
884	1190-272-41	JUN. 2 1987
885	000-119-20	JUN. 2 1987
886	000-111-10	JUN. 2 1987
887	1206-132-42	JUN. 2 1987
888	1211-122-28	JUN. 2 1987
889	JS-650	JUN. 3 1987
890	1211-124-23	JUN. 3 1987
891	1234-54-1[illegible]	JUN. 3 1987
892	1190-272-41	JUN. 4 1987
893	1208-118-22	JUN. 5 1987
894	000-127-28	JUN. 5 1987
895	1205-43-29	JUN. 5 1987
896	1138-192-28	JUN. 5 1987
897	1133-193-35	JUN. 5 1987
898	1190-270-33	JUN. 5 1987
899	1206-150-27	JUN. 5 1987
900	1206-124-21	JUN. 6 1987

SAMPLE #	BOOK #	DATE
901	1206-133-38	JUN. 6 1987
902	1216-53	JUN. 8 1987
903	1216-44	JUN. 8 1987
904	1215-109-27	JUN. 8 1987
905	1239-2-21	JUN. 8 1987
906	1208-132-16	JUN. 8 1987
907	1230-129-26	JUN. 9 1987
908	1215-115-25	JUN. 9 1987
909	1190-278-29	JUN. 10 1987
910	1206-131-43	JUN. 10 1987
911	JS-6833	JUN. 10 1987
912	JS-682B	JUN. 10 1987
913	JS-684A	JUN. 10 1987
914	1225-5-6	JUN. 10 1987
915	1230-122-30	JUN. 11 1987
916	1197-92-37	JUN. 11 1987
917	1200-130-25	JUN. 11 1987
918	1200-130-27	JUN. 11 1987
919	1208-133-13	JUN. 11 1987
920	1208-134-19	JUN. 11 1987
921	1216-57-28	JUN. 11 1987
922	1206-137-31	JUN. 12 1987
923	1208-135-15	JUN. 12 1987
924	1230-131-28	JUN. 15 1987
RA 925	1172-299-26	JUN. 16 1987

SAMPLE #	BOOK #	DATE
STd 926	1172-299-26	JUN. 16 1987
927	1208-137-17	JUN. 15 1987
928	1216-59-27	JUN. 16 1987
929	1216-59-31	JUN. 15 1987
930	1183-234-13	JUN. 15 1987
931	1206-141-31	JUN. 17 1987
932	1216-55	JUN. 17 1987
933	1216-63-31	JUN. 17 1987
934	1225-15-29	JUN. 17 1987
935	1225-13-11	JUN. 17 1987
936	1215-127-30	JUN. 17 1987
937	1216-58-27	JUN. 18 1987
938	1190-289-32	JUN. 18 1987
939	1211-130-28	JUN. 18 1987
940	1216-62-30	JUN. 19 1987
941	1195-115-35	JUN. 22 1987
942	1224-38-35	JUN. 22 1987
OR 943	1230-135-f14-13	JUN. 24 1987
OR 944	1230-135-f.3	JUN. 24 1987
945	1224-36-40	JUN. 25 1987
OR 946	1206-135-38	JUN. 25 1987
OR 947	1230-148-26	JUN. 29 1987
OR 948	1206-149-39	JUN. 30 1987
949	1215-130-21	JUL. 1 3 1987
950	1142-106-15	JUL. 1 3 1987

SAMPLE #	BOOK #	DATE
1001	1190-297-27	JUL 15 1987
1002	1216-73-33	JUL 15 1987
1003	1216-72-35	JUL 15 1987
1004	000-134-29	JUL 15 1987
1005	000-134-27	JUL 15 1987
1006	1230-157-22	JUL 15 1987
1007	1206-153-34	JUL 15 1987
OR 1008	1230-158①	JUL 15 1987
1009	000-137-29	JUL 16 1987
1010	000-135-21	JUL 16 1987
1011	1224-48-15	JUL 16 1987
1012	1224-51-35	JUL 16 1987
KBR 1013	HG-61-26	JUL 17 1987
CHCl2 1014	HG-61-26	JUL 17 1987
KBr2 1015	HG-61-29	JUL 17 1987
CHCl2 1016	HG-61-29	JUL 17 1987
1017	1225-35-29	JUL 20 1987
OR 1018	1197-132-38	JUL 20 1987
OR 1019	1197-141-24	JUL 20 1987
1020	1225-34-37	JUL 20 1987
1021	1205-55-30	JUL 20 1987
1022	1225-31-9	JUL 20 1987
RA 1023	1204-127-28R	JUL 20 1987
STD 1024	Lot # To 23 1204-127-36	JUL 20 1987
OR 1025	1197-143-10	JUL 20 1987

SAMPLE #	BOOK #	DATE
1026	1230-158-①	JUL 21 1987
1027	1230-163-30	JUL 21 1987
1028	1230-159-37	JUL 21 1987
1029	1230-168-30	JUL 21 1987
1030	1230-165-26	JUL 21 1987
1031	1230-159-28	JUL 21 1987
1032	1206-160-39	JUL 21 1987
1033	1206-157-39	JUL 21 1987
1034	1206-154-40	JUL 21 1987
1035	1206-158-41	JUL 21 1987
1036	1206-154-40	JUL 21 1987
1037	1206-158-41	JUL 21 1987
1038	1225-38-17	JUL 22 1987
CL 1039	1215-157-28	JUL 22 1987
1040	1216-783/	JUL 22 1987
1041	1216-77-76	JUL 22 1987
1042	000-136-35	JUL 22 1987
1043	000-140-28	JUL 22 1987
1044	000-140-26	JUL 22 1987
1045	000-141-27	JUL 22 1987
1046	1205-59-17	JUL 22 1987
1047	1205-59-15	JUL 22 1987
1048	1205-59-13	JUL 22 1987
1049	1205-59-11	JUL 22 1987
1050	1230-172-20	JUL 23 1987

SAMPLE #	BOOK #	DATE
1051	1230-171 (2)	JUL 23 1987
1052	1206-175-4	JUL 23 1987
1053	1215-158-36	JUL 23 1987
1054	HG-62-19	JUL 23 1987
1055	HG-62-21	JUL 23 1987
1056	000-142-23	JUL 23 1987
1057	HG-63-24	JUL 23 1987
1058	1211-163-25	JUL 23 1987
1059	1206-173-39	JUL 24 1987
OR 1060	1138-229-15	JUL 24 1987
1061	HG-64-28	JUL 24 1987
1062	1215-159-38	JUL 24 1987
OR 1063	1138-229-15	JUL 24 1987
1064	1245-6-39	JUL 24 1987
1065	1230-174-34	JUL 24 1987
1066	1230-175-25	JUL 24 1987
OR 1067	1230-176-22	JUL 27 1987
1068	1152-43-27	JUL 27 1987
1069	1216-80	JUL 27 1987
1070	1237-101-20	JUL 27 1987
1071	1237-100-24	JUL 27 1987
1072	1211-166-20	JUL 27 1987
OR 1073	1138-232-21	JUL 27 1987
1074	1224-55-39	JUL 28 1987
1075	1215-166-27	JUL 28 1987

SAMPLE #	BOOK #	DATE
OR 1076	1138-234-34	JUL 28 1987
1077	1138-232-21	JUL 28 1987
1078	1224-53-20	JUL 28 1987
1079	1205-63-36	JUL 28 1987
1080	HG-65-28	JUL 28 1987
OR 1081	1138-234-34	JUL 29 1987
1082	1205-63-38	JUL 29 1987
1083	1245-8-35	JUL 28 1987
1084	1206-166-30	JUL 30 1987
1085	1206-179-30	JUL 30 1987
1086	1206-177-33	JUL 30 1987
1087	1206-176-41	JUL 30 1987
1088	1197-149-8	JUL 30 1987
1089	1225-40-41	JUL 30 1987
1090	1208-178-19	JUL 31 1987
1091	1206-176-43	JUL 31 1987
1092	1206-180-39	JUL 31 1987
1093	1206-179-30	JUL 31 1987
1094	1215-159-38	JUL 31 1987
OR 1095	1181-232-38	AUG 3 1987
OR 1096	1181-228-38	AUG 3 1987
1097	1215-168-28	AUG 3 1987
1098	1215-163-21	AUG 3 1987
1099	1224-63-34	AUG 3 1987
OR 1100	1225-45-34	AUG 3 1987

E #	BOOK #	DATE	SAMPLE #	BOOK #	
501	1195-122-38	JUL. 01 1987	526	GCC 10523	JUL. 16 1987
502	1219-63-20	JUL. 06 1987	527	1213-123-30	JUL. 17 1987
503	1219-61-27	JUL. 06 1987	528	1169-263-31	JUL. 17 1987
504	1203-101-35	[illegible]	529	1169-265-34	[illegible]
505	1170-275-29	JUL. 06 1987	UV 530	1225-34-37	[illegible]
506	1142-163-6	JUL. 06 1987	UV 531	1225-25-29	JUL. 17 1987
507	1224-45-38	JUL. 06 1987	532	1204-165-10	JUL. 22 1987
508	1206-146-37	JUL. 07 1987	533	1219-72-30	JUL. 22 1987
509	1169-258-30	JUL. 07 1987	534	1219-68-24	JUL. 22 1987
510	1214-41-42	JUL. 07 1987	535	1219-67-32	JUL. 22 1987
511	1214-41-22	JUL. 07 1987	536	1213-146-26	JUL. 22 1987
12	1203-104-39	JUL. 07 1987	537	1213-131-25	JUL. 22 1987
513	1169-259-26	[illegible]	UV 538	1204-130-2	JUL. 22 1987
514	1190-297-27	JUL. 08 1987	UV 539	1120-192-12	JUL. 22 1987
515	1224-48-15	JUL. 08 1987	540	1245-1-22	JUL. 22 1987
516	1183-251-32	JUL. 08 1987	541	1203-115-35	JUL. 23 1987
517	1216-73-34	JUL. 08 1987	542	H6-62-19	JUL. 23 1987
518	1206-153-31	JUL. 09 1987	543	H6-62-21	JUL. 23 1987
519	1230-159-28	JUL. 09 1987	544	1230-171-(2)	JUL. 23 1987
520	000-135-21	JUL. 10 1987	545	1206-175-4	JUL. 23 1987
521	1230-159-37	JUL. 13 1987	546	1230-172-20	JUL. 23 1987
522	1223-46-29	JUL. 14 1987	UV 547	1228-111-11	JUL. 23 1987
523	1230-158-(1)	JUL. 14 1987	548	[illegible]	JUL. 24 1987
524	1206-158-41	JUL. 15 1987			JUL. 24 1987
525	1224-51-35	[illegible] 1987			[illegible] 1987

LE #	BOOK #	DATE	SAMPLE #	BOOK #	DAT
551	H6-64-28	JUL. 24 1987	576	1169-275-5	AUG. 03 1987
552	1206-173-39	JUL. 2 1987	577	1213-153-29	AUG. 03 1987
553	1230-175-25	JUL. 2 1987	578	1204-176-7	AUG. 03 1987
554	1010-63-2	JUL. 27 1987	579	1204-182-9	AUG. 03 1987
555	1219-77-20	JUL. 27 1987	UV 580	1157-290-12	AUG. 04 1987
556	1213-153-23	JUL. 28 1987	581	1224-63-34	AUG. 05 1987
557	H6-65-28	JUL. 28 1987	582	1181-234-38	AUG. 05 1987
558	1206.77.33	JUL. 28 1987	583	1181-233-38	AUG. 05 1987
559	1207.1222	JUL. 28 1987	584	1213-121-34	AUG. 05 1987
560	1216-166-30	JUL. 28 1987	585	1213-153-32	AUG. 05 1987
561	1224.55.39	JUL. 28 1987	586	1206-185-31	AUG. 05 1987
62	1213.1492.7	JUL. 28 1987	587	1152-55-22	AUG. 05 1987
563	1206.179.30	JUL. 28 1987	588	1169-276-22	AUG. 06 1987
564	1219.79.24	JUL. 29 1987	589	1247-27-35	AUG. 06 1987
565	1206.180.39	JUL. 29 1987	590	1158-254-34	AUG. 07 1987
566	63-370	JUL. 29 1987	591	1206-187-15	AUG. 10 1987
567	1239-40-12	JUL. 30 1987	592	1224-62-40	AUG. 10 1987
568	1239-40-20	JUL. 30 1987	593	000-147-27	AUG. 10 1987
569	1239-40-26	JUL. 30 1987	594	1215-166-27	AUG. 11 1987
570	1169-268-41	JUL. 31 1987	595	1211-172-26	AUG. 11 1987
571	000-144-22	JUL. 31 1987	596	1245-15-35	AUG. 11 1987
572	1224-59-16	JUL. 31 1987	597	1213-153-39	AUG. 11 1987
573	1245-11-31	JUL. 31 1987	598	1181-242-36	AUG. 11 1987
574	1181-228-38	AUG. 03 1987	599	1245-16-40	AUG. 12 1987
575	1181-232-38	AUG. 03 1987	600	1205-68-22	AUG. 12 1987

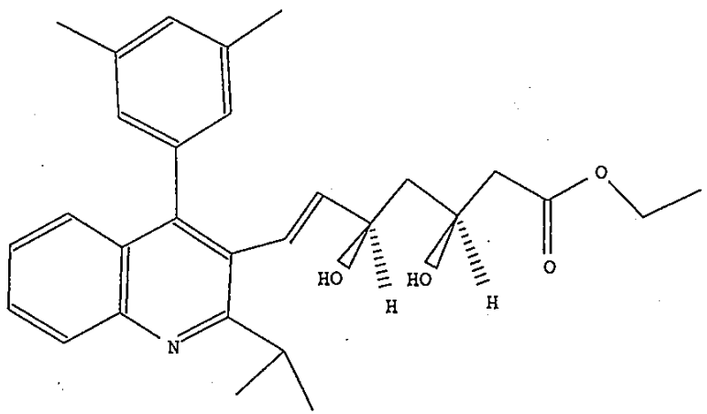
1111020

BOOK #	DATE
1245-21-37	AUG. 12 1987
UDO-149-21	AUG. 12 1987
Povidone RTA 378	AUG. 13 1987
1213-171-27	AUG. 13 1987
000-150-20	AUG. 13 1987
1205-25-37	AUG. 13 1987
1158-256-29	AUG. 13 1987
624-64-35	AUG. 14 1987
1158-259-15	AUG. 14 1987
1237-117-9	AUG. 14 1987
1237-116-7	AUG. 17 1987
719-94-25	AUG. 17 1987
945-299-35	AUG. 18 1987
996-94-18	AUG. 18 1987
1141-295-39	AUG. 18 1987
1152-65-38	AUG. 18 1987
000-151-23	AUG. 18 1987
000-151-24	AUG. 18 1987
1169-279-30	AUG. 19 1987
1152-69-8	AUG. 19 1987
1219-100-24	AUG. 20 1987
1219-100-3	AUG. 20 1987
1211-68-35	AUG. 21 1987
1213-127-23	AUG. [illegible]
1203-122-34	AUG. [illegible]

SAMPLE #	BOOK #	DATE
626	1245-21-42	AUG. 21 1987
627	1245-40-39	AUG. 21 1987
628	1245-21-42	AUG. 21 1987
629	1220-76-41	AUG. 24 1987
630	1219-102-19	AUG. 24 1987
631	Povidone RTA 378	AUG. 25 1987
632	Crospovidone RA #1	AUG. 25 1987
633	1152-72-140	AUG. 25 1987
634	1206-201-30	AUG. 26 1987
635	000-152-9	AUG. 27 1987
636	000-144-29	AUG. 27 1987
pKa 637	1158-173-10	AUG. 27 1987
638	1169-287-38	AUG. 28 1987
639	000-151-29	AUG. 28 1987
640	1211-177-31	AUG. 28 1987
641	1211-189-23	AUG. 28 1987
642	1169-290-22	AUG. 28 1987
643	010-6-25	AUG. 31 1987
644	1237-134-25	AUG. 31 1987
UV 645	1228-84-32	AUG. 31 1987
646	1245-57-40	SEP. 01 1987
647	1213-193-22	SEP. 02 1987
648	62-320 Lot 5	SEP. 03 1987
649	62-320 Lot 11	SEP. 03 1987
	1219-112-16	SEP. 03 1987

801	844-17	MAY 29 1984	826	1060-152-38	MAY 31 1984
802	844-19	MAY 29 1984	827	1013-230-38	JUN. 4 1984
803	1040-221-24	MAY 29 1984	828	1064-96-21	JUN. 4 1984
804	972-248-44	MAY 30 1984	829	1067-51-2	JUN. 6 1984
805	1013-228-4	MAY 30 1984	830	990-286-39	JUN. 6 1984
806	1017-24934	MAY 30 1984	831	981-261-25	JUN. 6 1984
807	1017-254-6	MAY 30 1984	832	981-259-21	JUN. 6 1984
808	1033-179-24	MAY 30 1984	833	1049-246-28	JUN. 6 1984
809	1036-124-39	MAY 30 1984	834	921-270-42	JUN. 7 1984
810	1036-124-38	MAY 30 1984	835	945-239-28	JUN. 7 1984
811	1036-124-37	MAY 30 1984	836	1070-24-35	JUN. 7 1984
812	070-123-27	MAY 31 1984	837	1040-244-38	JUN. 7 1984
813	1049-237-27	MAY 31 1984	838	978-176-40	JUN. 7 1984
814	981-255-20	MAY 31 1984	839	1013-231-04	JUN. 8 1984
815	1024-231-22	MAY 31 1984	840	1024-239-84	JUN. 8 1984
816	981-258-35	MAY 31 1984	841	604-59-15	JUN. 8 1984
817	1060-141-30	MAY 31 1984	842	1064-97-24	JUN. 8 1984
818	1070-19-37	MAY 31 1984	843	978-175-41	JUN. 8 1984
819	1040-240-27	MAY 31 1984	844	1013-231-24	JUN. 8 1984
820	1033-178-37	MAY 31 1984	845	1062-100-15	JUN. 8 1984
821	1013-228-16	MAY 31 1984	846	1067-54-15	JUN. 8 1984
822	844-19	MAY 31 1984	847	1040-251-29	JUN. 8 1984
823	844-14	MAY 31 1984	848	1040-250-31	JUN. 11 1984
824	1040-192-37	MAY 31 1984	849	1070-26-35	JUN. 11 1984
825	1060-146-24	MAY 31 1984	850	1060-160-7	JUN. 11 1984

INT.REG.NO	SAH.NO	SALTCODE	CHEM.NO	SUBMITTED	UNIT	CHEMISTS	DISCL
25496	SAH-063366		1079-111-19	11-26-84	KATH	KATHAWALA WATTANASIN	299-84



KNOWN? N | L&D. NO

MP

BP

PRESSURE

OTHER.PHYS.DATA

OIL

SOL. CODE D OR E OR C

DETAILS DMA OR EtOH OR CMC SUSPENSION

SCREENS

CSI

NOTES SEE LONGNOTE

KEEP REFRIGERATE
ERYTHRO:THREO=95:5

FORM DESIGNED BY DARCEA

	MW	
H35 N O4	461.606	SAH

COMPARE WITH 58-512

25495.0 A)ETHYLACETOACETATE/LDA B)Et3B/NaBH4 C)CH3OH

AMOUNTS,mg

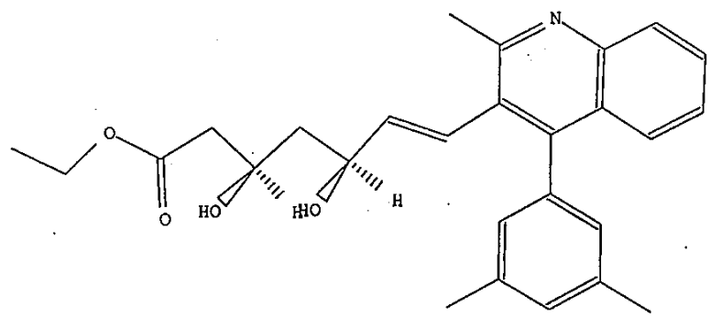
0.0
14.5 - 0.0 SCALLEN

25491+25492--->25493--->25494--->25495--->25496

WATTANASIN EXHIBIT
H-1
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

5/16

INT.REG.NO	SAH.NO	SALTCODE	CHEM.NO	SUBMITTED	UNIT	CHEMISTS	DISCL
26080	SAH-063548		1127-011-34	05-17-85	KATH	KATHAWALA WATTANASIN	299-84



FORM DESIGNED BY BARCZA

KNOWN? N

L&D. NO 13329.0

MP

BP

PRESSURE

OTHER.PHYS.DATA

OIL

SOL. CODE C OR D OR E

DETAILS CMC OR DMA OR EtOH

SCREENS

CSI, CSTC, CSTV

NOTES SEE LONGNOTE

PURE ERYTHRO COMPOUND
KEEP REFRIGERATE

C27 H31 N O4	MW 433.552	SAH

COMPARE WITH 58-512

MADE. FROM. REGNO 26079.0 - 24540.0 A) LDA B) 24540 C) n-Bu4NF

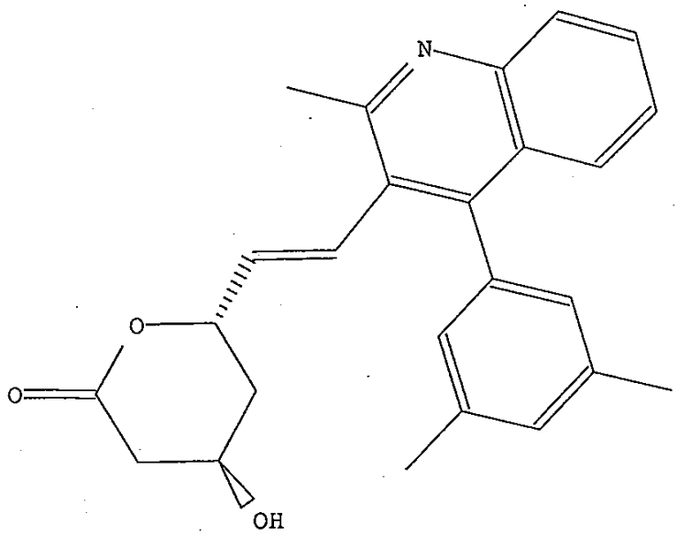
AMOUNTS, mg

4.8
2.0 - 4.8 SCALLEN

SUM. SYNTH 26076--->26077--->26078--->26079+24540--->26080

317

INT.REG.NO	SAH.NO	SALTCODE	CHEM.NO	SUBMITTED	UNIT	CHEMISTS	DISCL
26082	SAH-063549		1127-011-37	05-17-85	KATH	KATHAWALA WATTANASIN	299-84



FORM DESIGNED BY BARCZA

KNOWN? N

L&D. NO 13329.0

MP

BP

PRESSURE

OTHER.PHYS.DATA

OIL

SOL. CODE C OR D OR E

DETAILS CMC SUSPENSION OR DMA OR EtOH

SCREENS

CSI

NOTES SEE LONGNOTE

PURE TRANS LACTONE
CONTAINS SOME IMPURITIES
KEEP REFRIGERATE

	MW	
C25 H25 N O3	387.483	SAH

COMPARE WITH 58-512

MADE. FROM. REGNO 26081.0 A)Bu4NF,THF B)CHROMATOGRAPHY

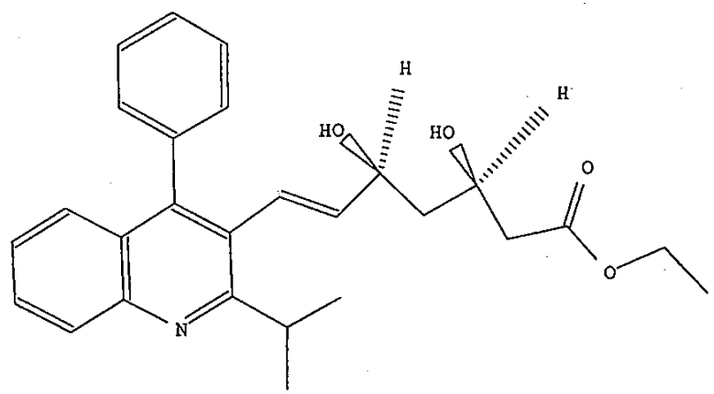
AMOUNTS,mg

2.0 - 0.0 SCALLEN

SUM. SYNTH 26081--->26082

318

INT.REG.NO	SAH.NO	SALTCODE	CHEM.NO	SUBMITTED	UNIT	CHEMISTS	DISCL
30441	SAH-064933		1206-176-43	09-21-87	WATT	PATEL WATTANASIN	299-84



FORM DESIGNED BY BARCIA

KNOWN? N

L&D. NO

MP

BP

PRESSURE

OTHER.PHYS.DATA

SOL. CODE D OR E OR C

DETAILS DMA,EtOH,CMC SUSPENSION

SCREENS

CSI CSIC CSIV

NOTES SEE LONGNOTE

ERYTHRO:THREO > 95:5
REFRIGERATE

C27 H31 N O4	MW 433.552	SAH

COMPARE WITH 62-320

MADE. FROM. REGNO 30440.0 A) ETHYLACETOACETATE B) Et3B,MeOH/THF C) HOAc/MeOH

AMOUNTS,mg

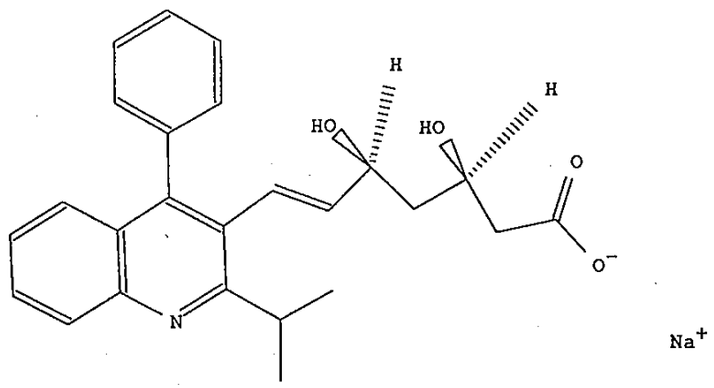
50.0
50.0 SCALLEN

SUM. SYNTH 30437+24214---> 30438---> 30439---> 30440---> 30441

319

INT.REG.NO	SAH.NO	SALTCODE	CHEM.NO	SUBMITTED	UNIT
30442	SAH-064934	NA	1206-179-30	09-21-87	WATT

CHEMISTS	DISCL
PATEL WATTANASIN	299-84



FORM DESIGNED BY BARCZA

KNOWN? N

L&D. NO

MP 210.0 PLUS

BP

PRESSURE

OTHER.PHYS.DATA

SOL. CODE D OR E OR C

DETAILS DMA,EtOH,CMC SUSPENSION

SCREENS
CSI CSIC CSIV

NOTES SEE LONGNOTE

ERYTHRO: THREO > 95:5
REFRIGERATE

	MW	
C25 H26 N Na O4	427.48	SAH

COMPARE WITH 62-320

MADE. FROM. REGNO 30441.0 NaOH, 0 DEG.

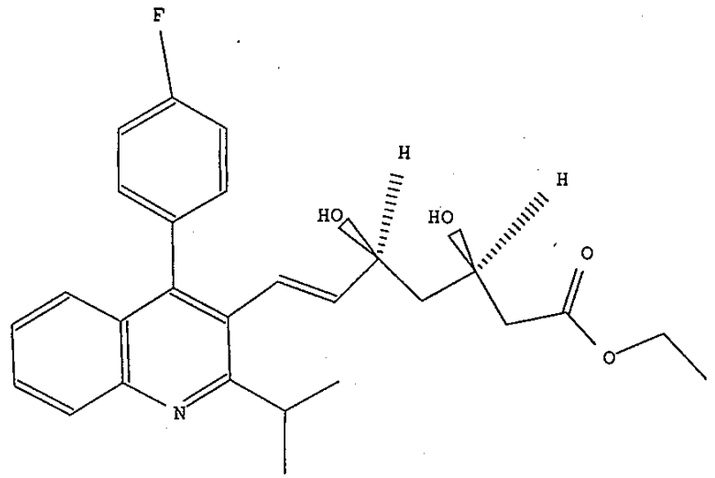
SUM. SYNTH 30441---> 30442

AMOUNTS,mg

50.0
50.0 SCALLEN

320

INT.REG.NO	SAH.NO	SALTCODE	CHEM.NO	SUBMITTED	UNIT	CHEMISTS	DISCL
30447	SAH-064935		1206-190-41	09-21-87	WATT	PATEL WATTANASIN	299-84



FORM DESIGNED BY BARCZA

KNOWN?	L&D. NO
N	

MP

BP

PRESSURE

OTHER.PHYS.DATA

SOL. CODE D OR E OR C

DETAILS DMA,EtOH,CMC SUSPENSION

SCREENS

CSI CSIC CSIV

NOTES SEE LONGNOTE

ERTHRO: THREO > 95:5
REFRIGERATE

	MW	
C27 H30 F N O4	451.543	SAH

COMPARE WITH 62-320

MADE. FROM. REGNO 30446.0 A) ETHYLACETOACETATE,NaH/BuLi B) Et3B,CH3OH/THF C)HOAc/CH3OH

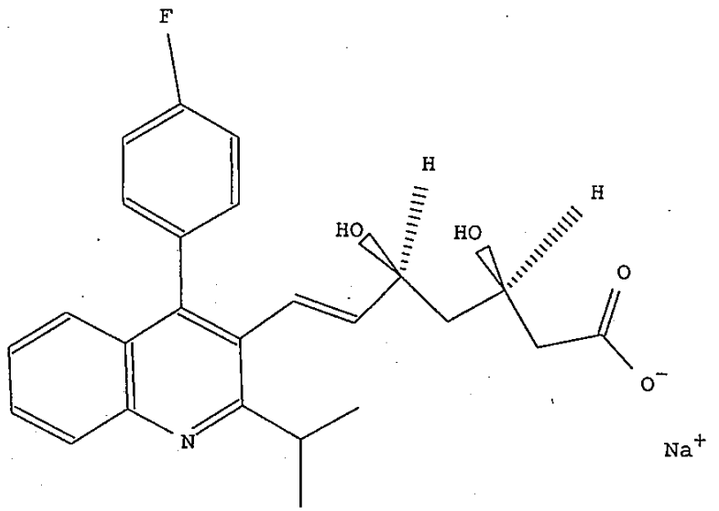
SUM. SYNTH 30443+24214---> 30444---> 30445---> 30446---> 30447

AMOUNTS,mg

20.0
20.0 SCALLEN

321

INT.REG.NO	SAH.NO	SALTCODE	CHEM.NO	SUBMITTED	UNIT	CHEMISTS	DISCL
30448	SAH-064936	NA	1206-201-30	09-22-87	WATT	PATEL WATTANASIN	299-84



FORM DESIGNED BY BARCZA

KNOWN? N

L&D. NO

MP

BP 225.0 PLUS

PRESSURE

OTHER.PHYS.DATA

SOL. CODE D OR E OR C

DETAILS DMA, EtOH, CMC SUSPENSION

SCREENS
CSI CSIC CSIV

NOTES SEE LONGNOTE

ERYTHRO: THREO > 95:5
REFRIGERATE

C25 H25 F N Na O4	MW 445.47	SAH

COMPARE WITH 62-320

MADE. FROM. REGNO 30447.0 NaOH, 0 DEG.

SUM. SYNTH 30447---> 30448

AMOUNTS, mg

20.0
20.0 SCALLEN

322

SANDOZ, INC.
E. HANOVER, N.J.

323

FROM: Dr. R. Damon DATE: Dec. 3, 1984

TO: Prof. T. Scallen

PURPOSE: HMG CoA REDUCTASE SCREENING

COMPOUND No.	QUANTITY	PRECAUTIONS &/OR SPECIAL INSTRUCTIONS & SOLVENTS
#63-364(25489)	6mg	CMC, DMA, EtOH (Refrigerate)
63-365(25490)	10mg	CMC, DMA, EtOH (Refrigerate)
63-366(25496)	14.5mg	CMC, DMA, EtOH (Refrigerate)
63-369(25512)	3.9mg	DMA
#63-162/3(25500)	10mg	DMA, Ethanol (Refrigerate)
63-270/2(25501)	10mg	CMC (Refrigerate)

FOR LABORATORY USE ONLY

82374/80 (Rev. 1)

WATTANASIN EXHIBIT
I-1
Wattanasin v. Fujikawa et al.
Interference No. 102,646
Interference No. 102,975

SANDOZ, INC.
E. HANOVER, N.J.

324

FROM: Dr. R. Damon

DATE: June 3, 1985

TO: Prof. T. Scallen

PURPOSE: HMG CoA REDUCTASE SCREENING

COMPOUND No.	QUANTITY	PRECAUTIONS &/OR SPECIAL INSTRUCTIONS & SOLVENTS
#63-518/2(RN 26020)	7.5mg	CMC, DMA, EtOH (Refrigerate)
63-537/Na(RN 26039)	19mg	50/D
63-547(RN 26075)	6.0mg	DMA
✓ 63-548(RN 26080)	2.0mg	CMC, DMA, EtOH (Refrigerate)
✓ 63-549(RN 26082)	2.0mg	CMC, DMA, EtOH (Refrigerate)
63-550/Na(RN 26083)	5.2mg	DMA
63-551(RN 26084)	20mg	CMC, DMA, EtOH (Refrigerate)
63-552/Na(RN 26085)	22mg	" " " "
63-553(RN 26086)	20mg	" " " "
63-554/Na(RN 26087)	24mg	" " " "
63-555/Na(RN 26088)	5.0mg	DMA (Refrigerate)
63-556(RN 26093)	14mg	CMC, DMA, EtOH (Refrigerate)
63-558/Na(RN 26098)	5.2mg	DMA
63-559 (RN 26106)	5mg	DMA
63-550/2-Na(RN 26-108)	0.6mg	DMA
63-563 (RN 26127)	10mg	DMA
63-564/Na(RN 26129)	10mg	DMA
63-565 (RN 26128)	10mg	DMA
63-566(RN 26148)	10mg	DMA
63-567 (RN 26149)	2.7mg	DMA
63-568 (RN 26157)	25mg	DMA
63-560 (RN 26107)	5mg	Water

FOR LABORATORY USE ONLY

H. Lukas

82374/80 (Rev. 1)

SANDOZ, INC.
E. HANOVER, N.J.

325

FROM: Dr. R. Damon

DATE: Oct. 2, 1987

TO: Prof. T. Scallen

PURPOSE: HMG CoA REDUCTASE SCREEN

COMPOUND No.		QUANTITY	PRECAUTIONS &/OR SPECIAL INSTRUCTIONS & SOLVENTS
#64-906/Na	(RN 30393)	80.0 mg	50/W
64-933	(RN 30441)	50.0 mg	CMC, DMA, EtOH (Refrigerate)
64-934/Na	(RN 30442)	50.0 mg	" " " "
64-935	(RN 30447)	20.0 mg	" " " "
64-936/Na	(RN 30448)	20.0 mg	" " " "
64-942/Na	(RN 30461)	0.6 mg	CMC, DMA (Compare with #62-526 & #64-727)
64-948/Na	(RN 30485)	1.5 mg	" " (Refrigerate) Compare with 62-526 Or 58-512 and 64-727

FOR LABORATORY USE ONLY

82374/80 (Rev 1)

H. Lukas

SANDOZ PHARMACEUTICALS CORP. | MAIL SERVICES REQUEST | ADMINISTR. SERVICES

326

FROM: HONORA LUKAS | DEPT: PRECLIN RES. | BLDG. # 403 | DATE: 10/2/87 | EXT: 7994

IDENTIFICATION (JOB) NUMBER (5): 61529

COST UNIT (6 7 8 9): 8 | 4 | 0 | 2

TYPE OF MAIL (CHECK DESIRED BLOCKS): MAILING DATE REQUESTED: _____ ◀ STATE REALISTIC DATE NOT RUSH, ASAP, ETC.

- ☐ APPROXIMATE ARRIVAL DATE SHOULD BE _____
- ☐ MOST ECONOMICAL WAY
- ☐ FIRST CLASS MAIL
- ☐ AIR MAIL
- ☐ REGISTERED MAIL
- ☐ CERTIFIED MAIL
- ☐ RETURN RECEIPT
- ☒ OVERNIGHT SERVICE
- ☐ UNITED PARCEL

INSURANCE NEEDED ☐ YES ☒ NO | VALUE:

ADDRESSEE:

Prof. T. Scallen
Dept. Of Biochemistry
School of Medicine
University of New Mexico
Albuquerque, New Mexico
87131

ITEM DESCRIPTION & QUANTITY OF EACH: (SPECIAL INSTRUCTIONS)

7 --- Hanover samples

FOR LABORATORY USE ONLY!

ITEMS FOR MAILING WILL BE RECD. FROM: | DATE: 10/2/87

SANDOZ		DORSEY
_____	SALES REPRESENTATIVES	_____
_____	REGIONAL MANAGERS	_____
_____	AREA SALES MANAGERS	_____
	TECHNICAL REPRESENTATIVES	_____
_____	MANAGERS, GOVERNMENT AFFAIRS	
_____	MEDICAL SCIENCES LIAISON MANAGERS	
_____	MEDICAL SCIENCES LIAISON	
_____	HOSPITAL REPRESENTATIVES	
_____	AREA HOSPITAL SALES MANAGERS	
	IN-HOUSE DISTRIBUTION	_____

MISCELLANEOUS INFORMATION

DATE RECEIVED WORK ORDER 10/7/87
DATE RECEIVED MATERIAL 11/
DATE DISPATCHED 11/
SUPPLY COST 25
WEIGHT 1
TOTAL PIECES 1
PREPARATION TIME 5
TOTAL POSTAGE 1.75

82100/83-1 (Rev. 7)

White — Mailroom; Canary — Returned to Originator when job is completed.

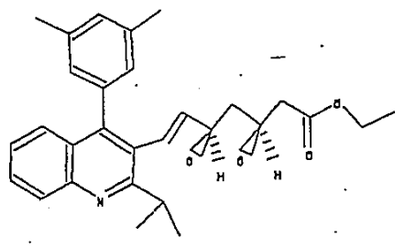
Date Proj.

Cont'd From-

Title- 63366 1069-113 327

PATENT AND TRADEMARK DEPT.
FEB 27 1990
JMG

SAH-063366 | 25496



CHEM.NO. 1079-111-19 | TESTS2

DATE 11-26-84 | MOL.WEIGHT 461.606

BIOCL.NO. 299-84 | CHEMISTS KATHAWALA WATTANASIN

TESTS1 CSI | AMOUNTS 0.0 14.5 - 0.0 SCALLEN

MICROSOMAL ASSAY (SCALLEN)

CONC. (UM)	% INHIBITION DATE 12/13/84 SOLVENT DMA	DATE SOLVENT	DATE SOLVENT	DATE SOLVENT
1000	>			
100	>			
10	78			
1	39			
0.1	14			
0.01	6			
0.001	4			
0.0001	6			
IC50	1.58			

17

Performed by-

Witness-

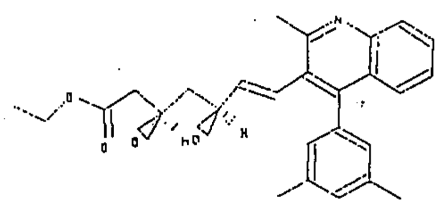
WATTANASIN EXHIBIT
J-1
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

198 Title-

Date 328

Cont'd From-

SAH-363548	26080



CHEM.NO. 1127-011-34	TESTS2
DATE 05-17-85	MOL.WEIGHT 433.552
DISCL.NO. 299-84	CHEMISTS KATHAWALA WATTANASIN
TESTS1 CSI, CSTC, CSTV	AMOUNTS 4.8 2.0 - 4.8 SCALLEN

MICROSOMAL ASSAY (SCALLEN)

CONC. (UM)	% INHIBITION			
	DATE 6/13/85	DATE	DATE	DATE
	SOLVENT DMA	SOLVENT	SOLVENT	SOLVENT
1000	[illegible]			
100	[illegible]			
10	72 R			
1	20 R			
0.1	0 R			
0.01	0			
0.001				
0.0001				
IC50	3.775			

Performed by- [signature]

Witness- S. Watanasin

Cont'd to-

Date Proj.

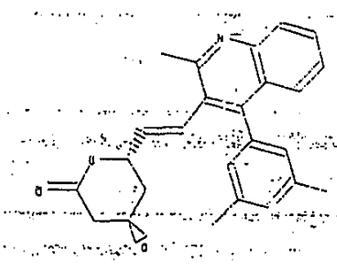
Cont'd From-

Title-

197

329

SAH-063549 | 26082



CHEM. NO. 1127-011-37

TESTS2

DATE 05-17-85

MOL. WEIGHT 387.483

DISCL. NO. 299-84

CHEMISTS KATHAWALA WATTANASIN

TESTS1 CSI

AMOUNTS 2.0 - 0.0 SCALLEN

MICROSOMAL ASSAY (SCALLEN)

CONC. (UM)	% INHIBITION			
	DATE 6/13/85	DATE	DATE	DATE
	SOLVENT DMA	SOLVENT	SOLVENT	SOLVENT
1000	X			
100	X			
10	56 R			
1	12 R			
0.1	0			
0.01	0			
0.001	0			
0.0001				
IC50	7.31			

Performed by- R. Dawson

Witness- S. Wattanasin

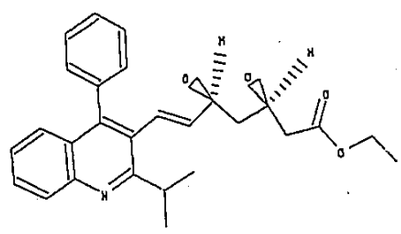
Cont'd to-

Date Proj. Title-

Cont'd From-

330

SAH-064933 | 30441



CHEM.NO. 1206-176-43	TESTS2
DATE 09-21-87	MOL.WEIGHT 433.552
DISCL.NO. 299-84	CHEMISTS PATEL WATTANASIN
TESTS1 CSI CSIC CSIV	AMOUNTS 50.0 50.0 SCALLEN

MICROSOMAL ASSAY (SCALLEN)

CONC. (UM)	% INHIBITION DATE 10/8/87 SOLVENT DMSO	DATE SOLVENT	DATE SOLVENT	DATE SOLVENT
1000	x			
100	x			
10	80			
1	32			
0.1	2			
0.01	(-2)			
0.001				
0.0001				
IC50	2.37			

Performed by- R. Patel

Witness- S. C. Wattanasin

Cont'd to-

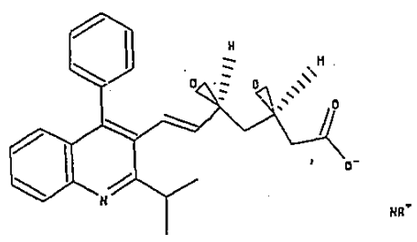
14

Title-

Date 331

Cont'd From-

SAH-064934	30442



CHEM.NO.	TESTS2
1206-179-30	
DATE	MOL.WEIGHT
09-21-87	427.48
DISCL.NO.	CHEMISTS
299-84	PATEL WATTANASIN
TESTS1	AMOUNTS
CSI CSIC CSIV	50.0 50.0 SCALLEN

MICROSOMAL ASSAY (SCALLEN)

CONC. (UM)	% INHIBITION			
	DATE 10/8/87	DATE	DATE	DATE
	SOLVENT DMSO	SOLVENT	SOLVENT	SOLVENT
1000	b			
100	b			
10	78			
1	30			
0.1	2			
0.01	(-2)			
0.001				
0.0001				
IC50	2.61			

Performed by-

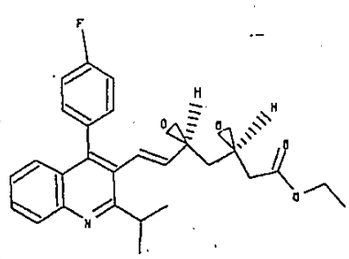
Witness-

Cont'd to-

Date Proj. Title- 332 15

Cont'd From-

SAH-064935 | 30447



CHEM.NO. 1206-190-41

TESTS2

DATE 09-21-87

MOL.WEIGHT 451.543

DISCL.NO. 299-84

CHEMISTS PATEL WATTANASIN

TESTS1 CSI CSIC CSIV

AMOUNTS 20.0 20.0 SCALLEN

MICROSOMAL ASSAY (SCALLEN)

CONC. (UM)	% INHIBITION DATE 10/8/87 SOLVENT DMA	DATE SOLVENT	DATE SOLVENT	DATE SOLVENT
1000	X			
100	X			
10	87			
1	69			
0.1	28			
0.01	9			
0.001	7			
0.0001	5			
IC50	0.413			

Performed by- R. Patel

Witness- S. Wattanasin

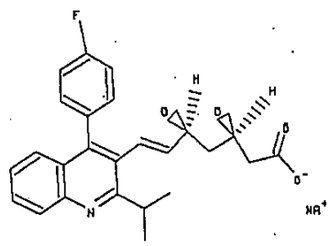
Cont'd to-

16 Title-

Date 333

Cont'd From-

SAH-064936 | 30448



CHEM.NO. 1206-201-30	TEST52
DATE 09-22-87	MOL.WEIGHT 445.47
DISCL.NO. 299-84	CHEMISTS PATEL WATTANASIN
TEST51 CSI CSIC CSIV	AMOUNTS 20.0 20.0 SCALLEN

MICROSOMAL ASSAY (SCALLEN)

CONC. (UM)	% INHIBITION DATE 10/13/87 SOLVENT DMA	DATE SOLVENT	DATE SOLVENT	DATE SOLVENT
1000	8			
100	6			
10	93			
1	66			
0.1	21			
0.01	4			
0.001				
0.0001				
IC50	0.53			

Performed by- R. Patel

Witness- S. Wattanasin

Cont'd to-

Date: 10/22/87 Proj. H318

Cont'd From- 134

Title Cholesterol Synthesis Inhibition Screen

133

334

CHOLESTEROL BIOSYNTHESIS INHIBITION

LIPID METABOLISM DEPARTMENT
HMGR SCREENING UNIT
Sandoz Research Institute
To: Dr. D. Weinstein, Departmenthead
Mr. R. Slaughter, Responsible Technician
From: Mr. R. Engstrom, Responsible Investigator
CC: D.N., M.L.R., ARC

STUDY #: H318
STUDY ON 10/22/87
BK.REF. 917-33
APPROVAL
DATE 10/21/87
GEN. ARC#86-006

Title: In vivo single dose assay to test for inhibition of biosynthesis by compounds: 63-748, 64-844, 64-936

Purpose: Determine the invivo effects of test compounds in rats on cholesterol biosynthesis.

Experimental design: IN VIVO CHOLESTEROL BIOSYNTHESIS INHIBITION DT0065 Invivo single dose assay or inhibition of Reference method: 740/001. Stock solutions and dilutions prepared in 0.5% CMC, administered p.o. at 1ml/100gm weight. Rats bled via carotid incision using hexobarbital anesthesia. Animal use will be in compliance with ARC regulations. Duration = 1 hr. No/group = 6. No of groups = 14. WCR rats.

RATs	COMPOUND	REGNO	DOSE mg/kg	STOCK mg/20ml	WORKING SOLUTION ml stock q.s. to 15ml
1-6	Control	------	------	------	----------
7-12	63-748	26628	1	2	UNDILUTED
13-18	"	"	0.3	-	4.5
19-24	"	"	0.1	-	1.5
25-30	64-844	30280	0.3	2	4.5
31-36	"	"	0.1	-	1.5
37-42	"	"	0.03	-	0.45
43-48	64-936	30456	1	2	UNDILUTED
49-54	"	"	0.3	-	4.5
55-60	"	"	0.1	-	1.5
61-66	62-510	30359	0.3	2	4.5
67-72	"	"	0.1	-	1.5
73-78	"	"	0.03	-	0.45
79-84	Control	------	------	------	----------

WATTANASIN EXHIBIT
K-1
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

Performed by- Robert A. Slaughter

Witness- R Engstrom

Cont'd to- 135

134 Title- Cholesterol Synthesis Inhibition Screen

Date 10/22/88 Proj 183

Cont'd From- 133

335

IN VIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN H318

RAT	COMPOUND	REGNO	DOSE mg/kg	uCi/dpm	STATISTICS	
BLANK				STD		
14C-STANDARD				20178	% EFFIC=	99
1	CONTROL			493		
2	CONTROL			677	MEAN =	537.7
3	CONTROL			590	STD =	128.6
4	CONTROL			455	SE =	37.1
5	CONTROL			490		
6	CONTROL			365		
79	CONTROL			462		
80	CONTROL			316		
81	CONTROL			599		
82	CONTROL			650		
83	CONTROL			610		
84	CONTROL			745		
8	63-748	26688	1.00	170	MEAN =	155.9
9	63-748	26688	1.00	278	STD =	73.1
10	63-748	26688	1.00	113	SE =	32.7
11	63-748	26688	1.00	113	t =	7.7
12	63-748	26688	1.00	106	p	<.01
7	63-748	26688	1.00	528*	%CHG =	-71
13	63-748	26688	.300	396	MEAN =	319.3
14	63-748	26688	.300	356	STD =	68.3
15	63-748	26688	.300	391	SE =	39.5
17	63-748	26688	.300	199	t =	4.0
18	63-748	26688	.300	253	p	<.01
15	63-748	26688	.300	794*	%CHG =	-40.6
19	63-748	26688	.100	348	MEAN =	458.7
20	63-748	26688	.100	728	STD =	213.5
21	63-748	26688	.100	310	SE =	87.2
22	63-748	26688	.100	650	t =	0.6
23	63-748	26688	.100	538	p	N.S.
24	63-748	26688	.100	178	%CHG =	-14.7
25	64-844	30280	.300	286	MEAN =	185.8
26	64-844	30280	.300	170	STD =	57.3
27	64-844	30280	.300	155	SE =	23.4
28	64-844	30280	.300	126	t =	8.5
29	64-844	30280	.300	174	p	<.01
30	64-844	30280	.300	101	%CHG =	-65.2
31	64-844	30280	.100	308	MEAN =	219.8
32	64-844	30280	.100	273	STD =	65.9
33	64-844	30280	.100	195	SE =	29.9
35	64-844	30280	.100	157	t =	6.7
36	64-844	30280	.100	165	p	<.01
34	64-844	30280	.100	696*	%CHG =	-59.1

Performed by- Todd A. Slaughter

Witness- R Boyton

Cont'd to- 135

Date 10/22/87 Proj# 3,8

Cont'd From- 134

Title- Cholesterol Synthesis Inhibition Screen

135

336

INVIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN HS18

RAT	COMPOUND	REGNO	DOSE mg/kg	nCi/dl	STATISTICS	
37	64-844	30280	.030	354	MEAN =	419.7
38	64-844	30280	.030	518	STD =	138.6
39	64-844	30280	.030	639	SE =	56.6
40	64-844	30280	.030	248	t =	1.7
41	64-844	30280	.030	358	p	N.S.
42	64-844	30280	.030	402	%CHG =	-21.9
43	64-936	30486	1.00	580	MEAN =	489.4
44	64-936	30486	1.00	642	STD =	132.8
45	64-936	30488	1.00	280	SE =	54.2
46	64-936	30486	1.00	388	t =	0.7
47	64-936	30488	1.00	532	p	N.S.
48	64-936	30488	1.00	513	%CHG =	-9.0
49	64-936	30488	.300	167	MEAN =	326.7
50	64-936	30486	.300	232	STD =	165.0
51	64-936	30488	.300	586	SE =	67.4
52	64-936	30488	.300	278	t =	2.7
53	64-936	30488	.300	223	p	<.02
54	64-936	30488	.300	473	%CHG =	-38.2
55	64-936	30486	.100	485	MEAN =	416.5
56	64-936	30486	.100	181	STD =	166.8
57	64-936	30488	.100	339	SE =	68.9
58	64-936	30488	.100	696	t =	1.8
59	64-936	30488	.100	367	p	N.S.
60	64-936	30486	.100	439	%CHG =	-22.5
61	62-320	30559	.300	72	MEAN =	67.5
62	62-320	30559	.300	89	STD =	12.1
63	62-320	30559	.300	72	SE =	5.4
64	62-320	30559	.300	53	t =	12.5
65	62-320	30559	.300	64	p	<.01
66	62-320	30559	.300	55	%CHG =	-87.5
67	62-320	30559	.100	135	MEAN =	165.3
68	62-320	30559	.100	236	STD =	51.1
70	62-320	30559	.100	198	SE =	32.8
71	62-320	30559	.100	109	t =	8.5
69	62-320	30559	.100	149	p	<.01
72	62-320	30559	.100	138	%CHG =	-69.3
73	62-320	30559	.030	323	MEAN =	351.2
74	62-320	30559	.030	380	STD =	173.6
75	62-320	30559	.030	77	SE =	70.8
76	62-320	30559	.030	579	t =	2.8
77	62-320	30559	.030	463	p	<.05
78	62-320	30559	.030	277	%CHG =	-34.7

* = rejected by "Q" test Computed 12-09-87
\- =LACK OF SAMPLE

Performed by- Rod K. Slaughter

Witness- D Engelhardt

Cont'd to-

136 Title- Cholesterol Synthesis Inhibition Screen

Date 10/29/87 Proj: 319

Cont'd From-

337

CHOLESTEROL BIOSYNTHESIS INHIBITION SCREEN

LIPID METABOLISM DEPARTMENT
HNGR SCREENING UNIT
Sandoz Research Institute
To: Dr. D. Weinstein, Departmenthead
Mr. R. Slaughter, Responsible Technician
From: Mr. R. Engstrom, Responsible Investigator
CC: D.N., M.L.R., ARC

STUDY # H319
STUDY ON 10/29/87
BK.REF. 917-135
APPROVAL
DATE 10/28/87
GEN. ARC#86-006

Title: In vivo single dose assay to test for inhibition of biosynthesis by compounds: 84-295, 84-938, 83-935

Purpose: Determine the invivo effects of test compounds in rats on cholesterol biosynthesis.

Experimental design: IN VIVO CHOLESTEROL BIOSYNTHESIS INHIBITION OT0065 Invivo single dose assay of inhibition of Reference method: 730/001. Stock solutions and dilutions prepared in 0.5% CMC, administered p.o. at 1ml/100gm weight. Rats bled via carotid incision using hexobarbital anesthesia. Animal use will be in compliance with ARC regulations. Duration = 1 hr. No/group = 6. No of groups = 14, WCR rats.

RATS	COMPOUND	REGNO	DOSE mg/kg	STOCK mg/20ml	WORKING SOLUTION ml stock q.s. to 15ml
1-6	Control	------	------	------	------
7-12	84-295	29277	1	2	UNDILUTED
13-18	"	"	0.3	-	4.5
19-24	"	"	0.1	-	1.5
25-30	84-938	30447	1	2	UNDILUTED
31-36	"	"	0.3	-	4.5
37-42	"	"	0.1	-	1.5
43-48	84-935	20441	1	2	UNDILUTED
49-54	"	"	0.3	-	4.5
55-60	"	"	0.1	-	1.5
61-66	82-320	30556	0.3	2	4.5
67-72	"	"	0.1	-	1.5
73-78	"	"	0.03	-	0.45
79-84	Control	------	------	------	------

Performed by-

Witness- R Engstrom

Cont'd to- 337

Date | Proj. | Title- |

Cont'd From-

338

INVIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN H319

RAT	COMPOUND	REGNO	DOSE mg/kg	nCi/dl	STATISTICS		
	BLANK			7			
	14C-STANDARD			20176	% EFFIC	=	99
1	CONTROL			983			
2	CONTROL			515	MEAN	=	671.8
3	CONTROL			646	STD	=	211.0
4	CONTROL			578	SE	=	60.9
5	CONTROL			934			
6	CONTROL			354			
79	CONTROL			756			
80	CONTROL			347			
81	CONTROL			814			
82	CONTROL			549			
83	CONTROL			872			
84	CONTROL			714			
7	64-298	28277	1.00	203	MEAN	=	151.7
8	64-298	28277	1.00	361	STD	=	113.6
9	64-298	28277	1.00	82	SE	=	46.4
10	64-298	28277	1.00	78	t	=	6.8
11	64-298	28277	1.00	71	p		<.01
12	64-298	28277	1.00	115	%CHG	=	-77
13	64-298	28277	.300	311	MEAN	=	235.1
14	64-298	28277	.300	284	STD	=	81.4
15	64-298	28277	.300	257	SE	=	33.2
16	64-298	28277	.300	307	t	=	6.3
17	64-298	28277	.300	114	p		<.01
18	64-298	28277	.300	157	%CHG	=	-65.0
19	64-298	28277	.100	381	MEAN	=	388.7
20	64-298	28277	.100	387	STD	=	81.5
21	64-298	28277	.100	248	SE	=	33.3
22	64-298	28277	.100	392	t	=	4.1
23	64-298	28277	.100	499	p		<.01
24	64-298	28277	.100	425	%CHG	=	-42.1
25	64-933	30447	1.00	838	MEAN	=	428.1
26	64-933	30447	1.00	275	STD	=	253.4
27	64-933	30447	1.00	136	SE	=	103.5
28	64-933	30447	1.00	584	t	=	2.0
29	64-933	30447	1.00	288	p		N.S.
30	64-933	30447	1.00	447	%CHG	=	-36.3
31	64-933	30447	.300	530	MEAN	=	557.4
32	64-933	30447	.300	646	STD	=	100.5
33	64-933	30447	.300	525	SE	=	41.0
34	64-933	30447	.300	596	t	=	1.6
35	64-933	30447	.300	368	p		N.S.
36	64-933	30447	.300	618	%CHG	=	-17.0

Performed by-

Title-

Date [illegible] Proj

Cont'd From- 137

INVIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN H319

RAT	COMPOUND	REGNO	DOSE mg/kg	nCi/dl	STATISTICS	
37	64-933	30447	.100	556		
38	64-933	30447	.100	735	MEAN =	547.0
39	64-933	30447	.100	370	STD =	147.2
40	64-933	30447	.100	378	SE =	60.1
41	64-933	30447	.100	591	t =	1.5
42	64-933	30447	.100	652	p	N.S.
					%CHG =	-18.6
43	64-935	30441	1.00	182	MEAN =	230.0
44	64-935	30441	1.00	307	STD =	78.2
45	64-935	30441	1.00	186	SE =	31.9
46	64-935	30441	1.00	321	t =	6.4
47	64-935	30441	1.00	124	p	<.01
48	64-935	30441	1.00	261	%CHG =	-65.8
49	64-935	30441	.300	776	MEAN =	472.2
50	64-935	30441	.300	282	STD =	179.5
51	64-935	30441	.300	520	SE =	73.3
52	64-935	30441	.300	413	t =	2.1
53	64-935	30441	.300	344	p	N.S.
54	64-935	30441	.300	438	%CHG =	-29.7
55	64-935	30441	.100	411	MEAN =	428.2
56	64-935	30441	.100	320	STD =	119.1
57	64-935	30441	.100	296	SE =	48.6
58	64-935	30441	.100	425	t =	3.1
59	64-935	30441	.100	521	p	<.02
60	64-935	30441	.100	495	%CHG =	-36.3
61	62-320	30559	.300	90	MEAN =	165.6
62	62-320	30559	.300	107	STD =	107.1
63	62-320	30559	.300	222	SE =	43.7
64	62-320	30559	.300	60	t =	5.8
65	62-320	30559	.300	217	p	<.01
66	62-320	30559	.300	327	%CHG =	-75.3
67	62-320	30559	.100	262	MEAN =	331.7
68	62-320	30559	.100	434	STD =	165.7
70	62-320	30559	.100	569	SE =	74.1
71	62-320	30559	.100	168	t =	3.5
69	62-320	30559	.100	228	p	<.01
72	62-320	30559	.100	604	%CHG =	-50.6
73	62-320	30559	.030	421	MEAN =	445.1
74	62-320	30559	.030	472	STD =	94.1
75	62-320	30559	.030	571	SE =	38.4
76	62-320	30559	.030	374	t =	3.1
77	62-320	30559	.030	517	p	<.01
78	62-320	30559	.030	315	%CHG =	-33.8

Computed 12-09-87

Performed by-

Witness- [illegible]

Cont'd to-

64566	29851	280-85	>	1	09-JUN-87	917-065
64569	29852	280-85	=	.16	15-JUN-87	917-081
64602	29743	101-85	>	.3	05-MAY-87	917-050
64602	29743	101-85	>	.3	05-MAY-87	917-050
64604	29744	101-85	>	.3	05-MAY-87	917-051
64604	29744	101-85	>	.3	05-MAY-87	917-051
64604	29745	101-85	=	.48	14-JUL-87	917-086
64608	29756	298-85	>	7.5	15-MAY-87	917-055
64638	29835	570-83		.34	09-DEC-87	917-140
64639	29836	570-83	>	1	09-JUN-87	917-066
64640	29839	367-86	>	1	09-JUN-87	917-068
64641	29840	367-86	>	1	09-JUN-87	917-068
64642	29841	367-86	>	1	09-JUN-87	917-089
64673	29904	280-85	=	2.6	18-SEP-87	917-111
64686	29927	387-85	>	10	18-SEP-87	917-113
64691	29942	366-86		.58	16-DEC-87	917-141
64722	30004	280-85	=	.2	23-OCT-87	917-126
64723	30627	100-85	=	.16	19-FEB-88	917-159
64723	30877	100-85	=	.09	19-FEB-88	917-159

SAHNUM	REGNO	PATENT	R	ED50	EDATE	REF
64723	30766	100-85	=	.22	19-FEB-88	917-159
64723	30009	100-85	=	.36	18-SEP-87	917-107
64744	30059	295-84	>	.1	14-JUL-87	917-090
64745	30765	295-84	=	.016	19-FEB-88	917-154
64745	30060	295-84	=	.016	20-OCT-87	917-127
64747	30067	298-84	=	.11	01-JUL-87	917-087
64748	30068	298-84	=	.04	19-FEB-88	917-165
64792	30146	260-85	=	.74	13-OCT-87	917-123
64816	30199	295-84	=	.1	12-OCT-87	917-119
64844	30280	384-85	=	.07	09-DEC-87	917-135
64844	30769	384-85	=	.08	19-FEB-88	917-167
64896	30378	366-87	>	.3	06-OCT-87	917-119
64897	30379	366-87	>	.3	06-OCT-87	917-120
64906	30393	280-85	=	.045	05-JAN-88	917-150
64906	30772	280-85	=	.1	15-JAN-88	917-155
64933	30441	299-84	>	1	09-DEC-87	917-138
64935	30447	299-84	=	.49	09-DEC-87	917-138
64936	30488	299-84	>	1	09-DEC-87	917-135
64999	30623	298-84	=	.1	19-FEB-88	917-168
65002	30629	101-85	=	.76	05-JAN-88	917-144
65003	30630	101-85	=	.09	19-FEB-88	917-159

SAHNUM	REGNO	PATENT	R	ED50	EDATE	REF
65003	30902	101-85	=	.06	19-FEB-88	917-170
86665	25887	102-82	>	10	06-MAY-87	917-056
87469	26362	101-82	>	10	06-MAY-87	917-056
89826	29587	101-82	>	10	06-MAY-87	917-057
317223	24022		>	16	20-MAR-84	812-183
880349	29591	102-82	>	10	18-AUG-87	917-098
880586	29588	102-82	>	10	18-AUG-87	917-098
880820	29589	102-82	>	10	18-AUG-87	917-099

140 records selected.

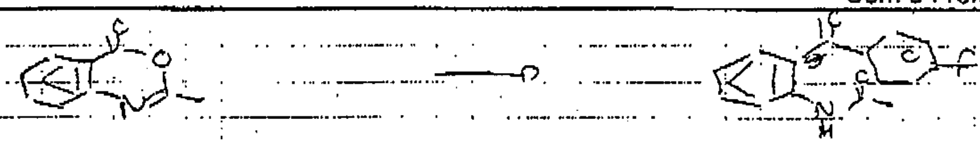
SQL>

Title-

Date 4-13-87 Proj.

Cont'd From-

341



$C_9H_7O_2N$ (161) — Benzoxazine — 1206-66-14

252 — $C_{15}H_{12}O_2NF$

Ref: K. Suzuki et al JOC 1961, 2239, 2247

(161.61) 1206-66-14 = 9.4 g ~~1206~~ (0.0581683 mole)

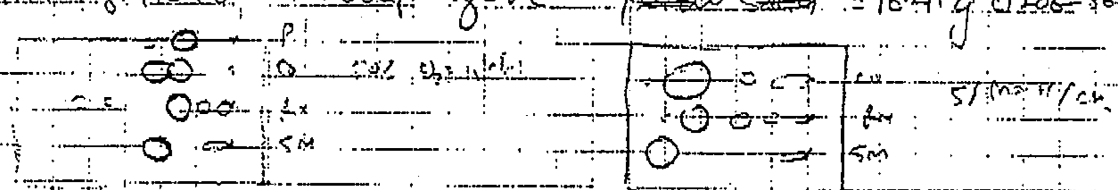
~~Et_2O~~

dry Benzene = 216 ml

(199.2) 2.0 M F-⟨O⟩-MgBr = 29.28 ml (0.0585585) in ether

Benzoxazine in 216 ml benzene + 10 ml Et_2O was cooled to 0°C (brown solution) slowly via addition funnel added F-⟨O⟩-MgBr 2.0 M dropwise over min. at 0°-10°C → yellow heterogeneous mix. Stirred for 1 hr at this temp then ~~warmed~~ warmed up to r.t., stirred at r.t. overnight (1:45 pm – overnight)

4-14-87 3:30 PM → yellow orange heterogeneous mix ~~stirred~~ quenched in 2N HCl extracted with Et_2O, washed with brine dried filtered, rotevap gave ~~yellow solid~~ brown oil = 16.41 g (1206-86-27)



Sent for Prep LC Theory: 14.94 g

4-21-87 F8-9 = 9.63 g (1206-86-38) nmr, IR, ms, mnt = 258

Sample

5-4-87 micro 5-8-87

	C	H	N	O
Cal	70.03	4.70	5.44	12.43
Found	70.1	4.46	5.40	

% = 64.45%

m.p. = 95°-97°C

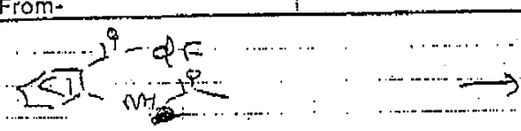
Performed by- Roy Patel 4-14-87

Witness- A Perez

WATTANASIN EXHIBIT
L-1
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

Date 4-28-87 Proj. Title-

Cont'd From- 342



(257) (251)

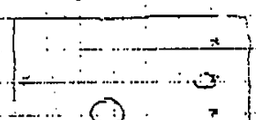
1206-99-26 $C_{13}H_{11}NOFCl$

257 (1206-86-36) = 9.5g (CO 0369649 made)

dry HCl = 200ml

EtOH

To 1206-86-36 in 200ml EtOH (homogeneous light yellow) passed HCl gas for 15 min, He → dark yellow sol^n (homogeneous) Heated to reflux (11A - 2PM) → brownish homogeneous sol^n



Concentrated to dryness to give pinkish solids; diluted with ether filtered, washed with ether gives 8.5g pinkish solids (1206-99-26)

5-4-87 nmr, ir micro

m.p. = 172-175°C

	C	H	N	Cl
calc	62.03	4.40	5.56	14.08
f	61.91	4.24	5.50	14.32

Theory: 9.2g

%: 92.4%

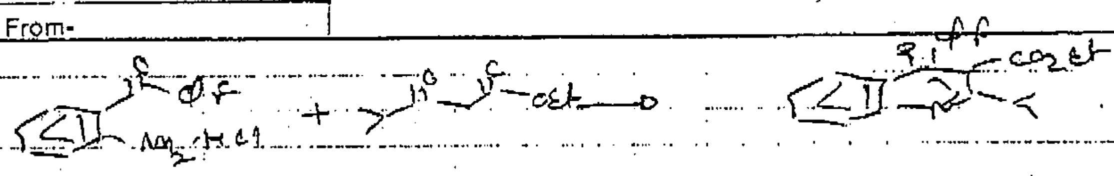
Performed by- Ray Patel 5-5-87

Witness- L Perez

Cont'd to-

Date 5-4-87 Proj. Title-

Cont'd From-



1206-99-26 ... 332.2

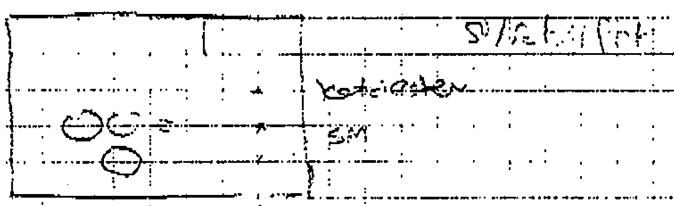
(251)

(251) 1206-99-28 : 7.5 g (0.02958)

158.2, d=0.981 : 7.25 ml (0.0448206) 1.5 equiv

abs. EtOH : 75 ml

Above mix was heated to reflux (9^45 A - 11^00 Pm)



5-5-87 Showed out v.t.

5-5-87 Concentrated basified with NH_4OH, extracted with ether, washed with H_2O, brine, dried, filtered

5-11-87 Rotavap to dryness to give 8.00 g yellow oil (1206-153-28) nmr, ms mh+=338 solidified on standing

% yield : 79.5%

Theory = 10.07

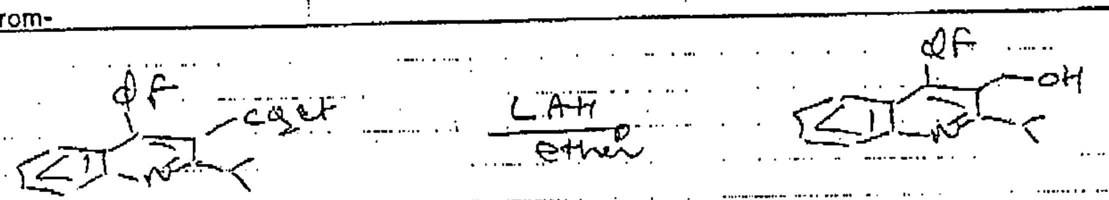
Performed by- Roy Patel 5-5-87

Witness- L Perez

Cont'd to-

Date 5-20-87 Proj. Title-

Cont'd From- 344

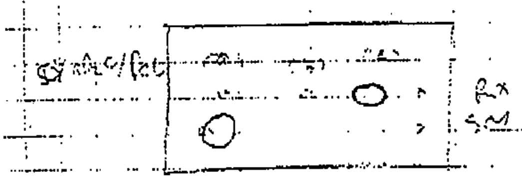


337.2 — 295.359

1206 103-28 — C19H18NOF

337.2 1206 103-28 = 8.0 g (0.0237247 mole)
38 LAH = 1.8 g (0.04 74494 mole) 2 eqn
ether = 90 ml

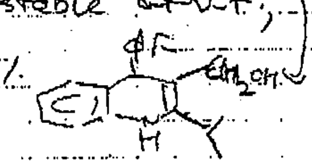
To 1206-103-28 in ether (yellow homogeneous) with cooling was added 1.8 g LAH portionwise at 15-20°C (exothermic!) stirred at r.t. (9A - 12 P)



Added in acid H2O extracted with ether washed with H2O, brine, dried filtered washed rotavap gave 8.0 g Yellow solid (1206-119-26)

yellow solid (a) = 180.2 mg (1206-119-28)
orange yellow solid (b) = 294.8 mg (1206-119-29)
beige solid (c) = 5.0883 g (1206-119-30) nmr, ir, ms, mp
mp 129.8
turned to orange on standing (may be unstable at r.t., next time store in refrigerator)

Theory: 7.0 g % = 72.5%



	C	H	N	O
Calc	77.26	6.14	4.74	
Found	75.77	7.41	4.51	

Performed by- Ray Patel 5-20-87

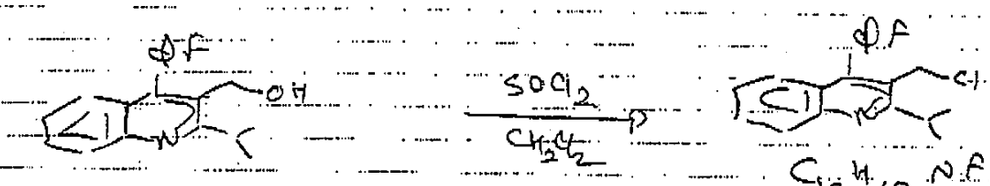
Witness- L Perez

Cont'd to-

Title-

Date 5-26-87 Proj.

Cont'd From- 345



1206-119-30
(R95)

$C_{19}H_{17}NFCl$
313

295 1206-119-30 = 5.0 g (0.016949 mole)
$SOCl_2$ = 5.0 mL
anhy CH_2Cl_2 = 50 ml

Ref: 1206-110

1206-119-30 in anhy CH_2Cl_2 was cooled in ice bath (orange homogeneous sol'n) to 15°C. $SOCl_2$ at 15°-20°C with cooling → dark room temp homogeneous sol'n was stirred at r.t. overnight.

5.22.87 Rotovap to dryness to give yellow foam (1206-124-2) basified with satd NaHCO3 extracted into CH_2Cl_2 was washed with H_2O, brine dried filtered washed, rotovap gave yellow solids wt: 4.25g (1206-124-26)

Theory: 5.3g

% = 80.2%

Performed by- Ray Patel 5-27-87

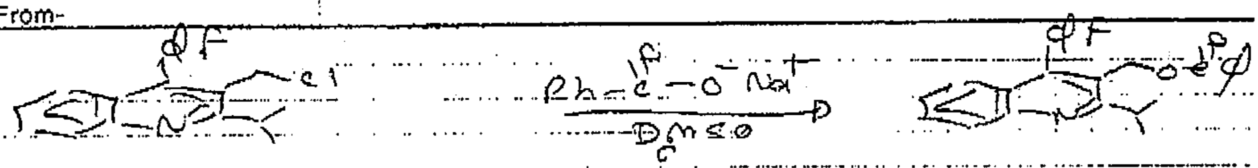
Witness- L Perez

Cont'd to-

[redacted]

Date 8-15-87 Proj. Title-

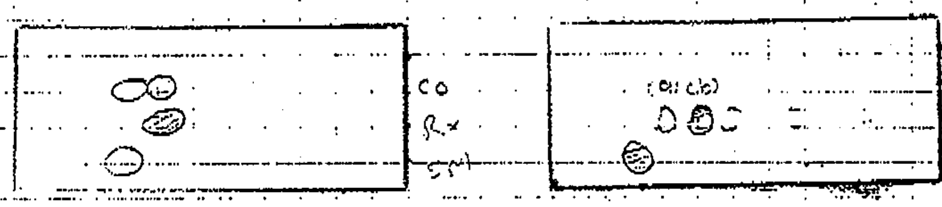
Cont'd From-



313 399

1206-124-26 = 3.7g (0.01182 mol)
Ph-C-O⁻Na⁺ = 3.2g
DMSO = 75 ml
Ref: 1206-162

Above mix was heated to 100°C (1 hr) for 1 hr.



quenched with H_2O, extracted with Et_2O washed org. layer with H_2O, brine dried, filtered washed
7-17-87 rotavap gave yellow foam wt: 6.0206 g (1206-167-2)
on drying at: 5.7503 g nmr, ms
Theory: 4.7165 g (98.6%) mH⁺

7-20-87

flash column (10% EtOAc/hex) gave

Mix of (9a+b) { F_{3-11} yellow foam = 3.48g (1206-167-35) mH^+=400
{ F_{12-31} yellow oil/foam = 630.4 mg (1206-167-37) ms mH⁺
only (b) F_{32-76} yellow foam = 541.2 mg (1206-167-39) ms mH⁺
Total: 4.65g (1206-167-41)

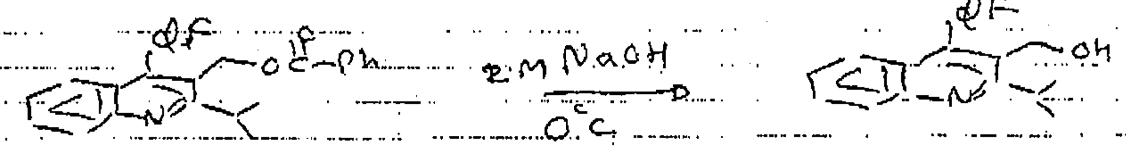
Performed by- Raj Patel 7-20-87

Witness- K. Perez

Cont'd to-

Date 7-22-87 Proj. Title-

Cont'd From-



399 295

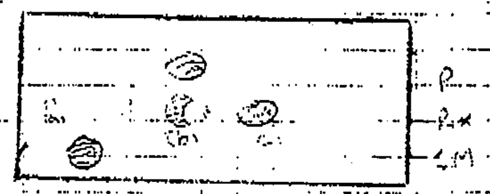
$C_{19}H_{18}NOF$

1206-167-48 = ~~5.75~~ 4.05g (0.011654mole)
2M NaOH = 5.8ml (0.011654mole)
abs EtOH = 60 ml + 110ml

Ref: 1206-165

To 1206-167-48 in abs. EtOH at 0°C was added 5.8ml 2M NaOH, stirred at 0°C for 3 hrs (9 AM - 12) → (yellow heterogeneous mix, lots of white solids came out on addn of NaOH, most of which on stirring went in to soln)

~~Rotav~~



	C	H	N	O		
Calc.	77.[illegible]	6.1[illegible]	5.12	6.[illegible]		
Found	75.[illegible]	[illegible]	4.5[illegible]			
	75.57	6.57	4.7[illegible]			

Concentrated to yellow solids, extracted with ether, washed with H_2O, brine, dried, filtered, rotavap gave yellow foam: 3.12g

3-23-87 Flash chromatography (25% Et₂O/Pet) gave

Theory: 3.49 (45%)
(a) = 510.4 mg (1206-173-38) nmr, ms 328 = mH⁺
(b) Yellow solid = 1.5186g (1206-173-39) micro, nmr, ir, ms mH⁺=296
(c) yellow foam = 2.1391g (1206-173-41) + oil (red) nmr, ir, ms mH⁺=328

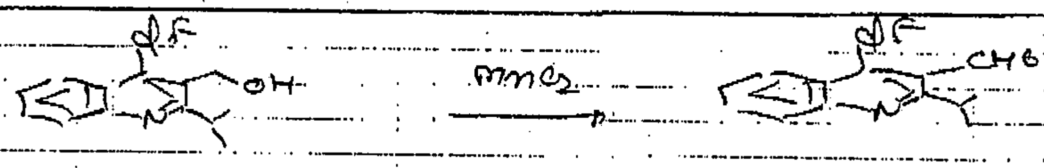
m.p.: 114°-116°C

Performed by- Key Patel 8-5-87

Witness- L Perez Cont'd to-

Date 7-24-87 Proj. Title-

Cont'd From-



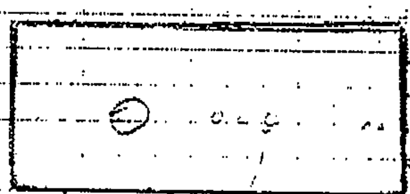
295 → 293

$C_{19}H_{17}NOF$

295 1206-173-39 = 100 mg (0.338983 mmole)
MnO_2 = 200 mg
toluene = 2 ml

Ref: 1206-148.

To 1206-173-39 in toluene was added MnO_2 & heated to reflux (11 A - 5 P). Stirred at r.t. over weekend



Rx
SM

	C	H	N	O
[illegible]	77.2[illegible]	[illegible]	[illegible]	5.[illegible]
[illegible]	77.[illegible]7	6.[illegible]	3.[illegible]	
	[illegible]2.6	[illegible]	[illegible]	

Filtered thru' pad of silica gel, washed with toluene, ether. rotevap gave yellow crystalline solids
wt = 88mg (1206-177-33) ms mr=293 nmr
Theory: 99 mg (89.6%) IR micro
m.p. = 117-119°

Performed by- Ray Patel 8-5-87

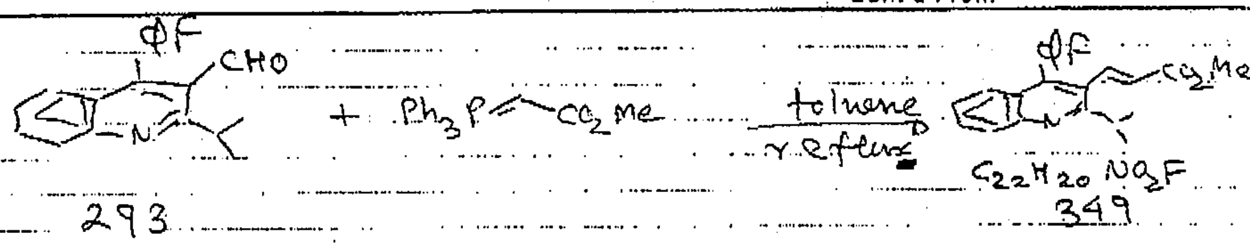
Witness- L Perue

Cont'd to

180 Title-

Date 7-28-87 Proj.

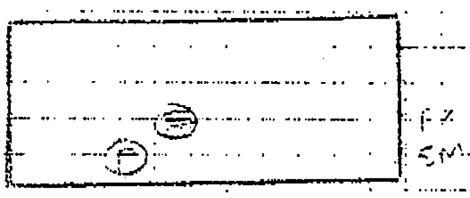
Cont'd From-



(293)	1206-177-33	= 75 mg	(0.2559726 mmole)
(334)	Ph_3P=CO_2Me	= 102.6 mg	(0.3071671 mmole) 1.2eq.
	toluene	= 2 ml	

Ref: 1206-153

Above mix was heated to reflux (117°) for 1 hr.



	C	H	N	O	F
Calc.	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Found	[illegible]	[illegible]	[illegible]		

Diluted with ~25 ml 50% Et_2O/Pet ether, filtered thru pad of silica gel (to remove phosphine oxide), washed with 50% Et_2O/Pet ether, Rotevap to dryness gave yellow solids which on trituration with MeOH gave 58.2 mg white solids (1206-180-34) nmr ✓, ms M^+ = 350

Theory: 89.3 mg (65%)

Rotevap MeOH layer triturate again with MeOH gave 12.7 mg yellow solids (1206-180-39) ms ✓ M^+ = 350
m.p.: 145-147°C, nmr ✓

3rd crop: 6.0 mg (1206-180-41) ms M^+ = 350

total: 58.2+12.7 = 70.9 mg (79.4%) (1206-180-42)

Performed by- Raj Patel 8-5-87

Witness- J Perez

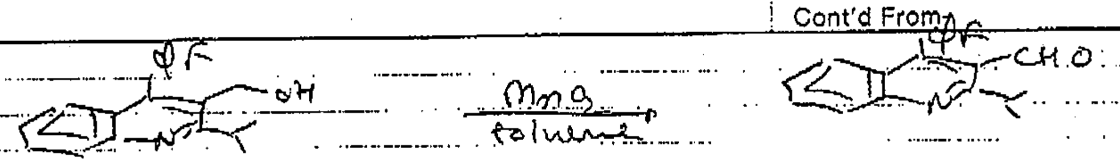
Cont'd to-

Title-

Date 7-27-87 Proj.

Cont'd From

350



295 293

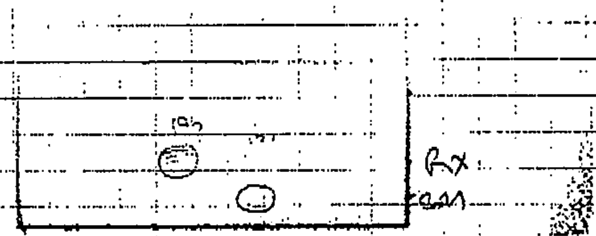
$C_{19}H_{16}NOF$

(295) 1206-123-39 = 1.41 g (0.004779 mole)

MnO2 = 2.82 g

toluene = 25 ml

CH_2Cl_2 - 4 Above mix was heated to reflux



Stirred at r.t. overnight

7-28-87

Filtered thr' pad of silica gel washed with toluene & ether collected washings in two portions, Rotavap to dryness to give

(97 yellow crystalline solids = 930.8 mg (1206-178-31) nmr, MS

mixture of yellow oil = 230 mg exact mass. mH^+=293

obs. mass = 294.13008

theory: 1.4 g (66.4%) cal. mass = 294.12941

Seperated 210 mg oil on flash (25% Et2O/Pet) chrom gave

(9) yellow oil = 60.05 mg (1206-178-39) ms mH^+=294

(9) white foam = 170 mg (1206-178-40) ms mH^+=296 s.m.

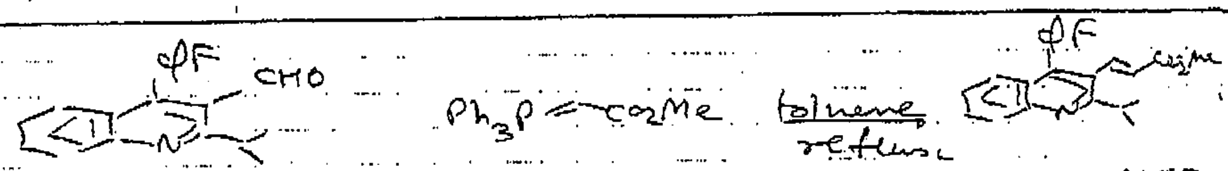
Performed by- Ray Patel 8.5.87

Witness- R Perez

Cont'd to-

e 7-29-87 Proj.   Title-

't'd From-



293    $C_{25}H_{20}NO_2F$ 349

293 { 1206-178-31 = 910.8 mg } 3.3135836 mmole
{ 1206-178-39 = 60-08 }
334 Ph3P=CO2Me = 1.328 g (3.9763003 mmole)
toluene = 15 ml

Ref: 1206-153, 180

Above mix was heated to reflux
(16 hr = 127°)
TLC ⇒ No S.M. only P

Diluted with 50% Et2O/Pet, filtered thr' pad of silica gel, washed with 50% Et2O/Pet, Rotavap to dryness, gave yellow solid which on trituration with MeOH gave light yellow solid. wt = 1.1608 g (1206 181-26) nmr ✓ MS m^+ = 350

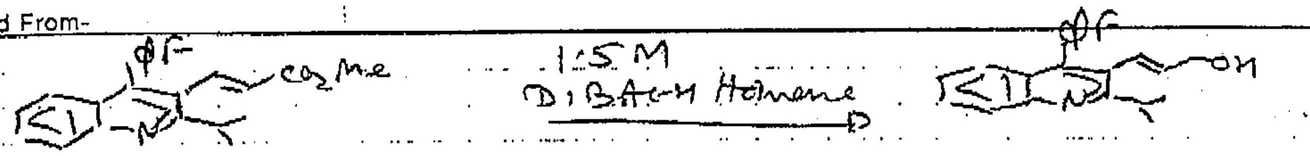
Theory: 1.1564 g

Performed by- Raj Patel 8-5-87

Witness- A Perez   Cont'd to-

Date 8-3-87 Proj. Title-

Cont'd From-

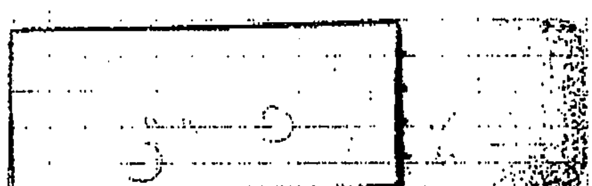


349 321

349 1206-181-26 = 1.1608 (0.003326 mole)
1.5 M DIBAL-H /toluene = 4.4 ml (0.006652 mole)
CH_2Cl_2 = 20 ml

Ref: 1206-182

To 1206-182-26 in CH_2Cl_2 at -78°C was added 4.4 ml 1.5 M DIBAL-H (9:15 - 10:7)



Added 2.5 ml 2M NaOH warmed up to r.t., added EtOAc, dried over $MgSO_4$, filtered, washed, Rotavap to dryness gave white foam wt: 1.1651g. Flash chromatography (50 25% EtOAc; Pet) gave 1.0417g yellow oil (1206-183-31) in NMR, MS MH+ = 322 exact mass.

Theory: 1.0676 g m.p. = 79-84°C

8-6-87 exact mass: obsd. mass: 321.15303
calcd mass: 321.15289

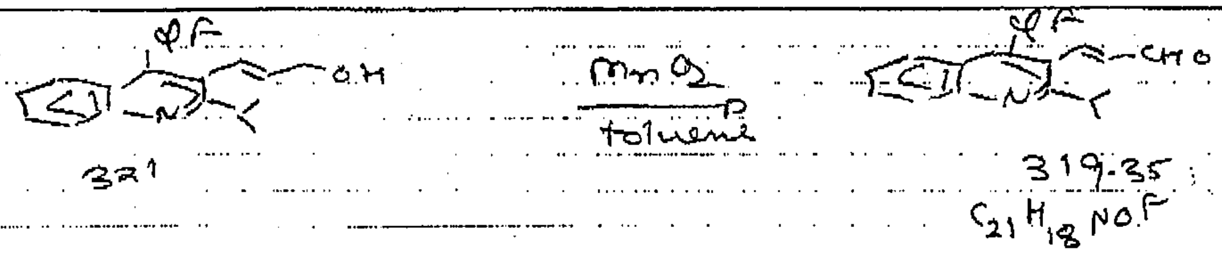
Performed by- Raj Patel 8-8-87

Witness- L Perez

Cont'd to-

Date 8-4-87 Proj. Title-

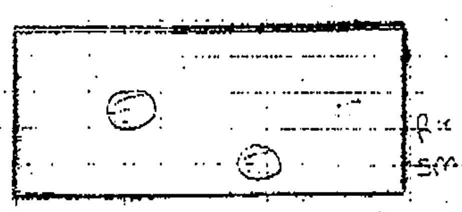
Cont'd From-



(321) 1206-183-31 = 1.01 g (0.003146[illegible] mole)
MnO2 = 2.02 g
toluene = 15 ml

Above mix. was heated to reflux for ½ hr. T.L.C. (50% Et2O/Pet) ⇒ only desired P

50% Et2O/Pet



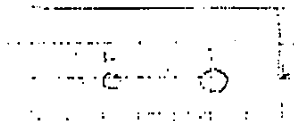
	C	H	N	O	F
Calc.	78.[illegible]	5.69	4.[illegible]	5.01	[illegible]
Found	78.[illegible]	[illegible]	[illegible]		
	[illegible]	[illegible]	[illegible]		

Combined 1206-184, Cooled to r.t. filtered thru' pad of silica gel, washed with toluene, rotavap to dryness to give yellow solids

8-5-87 wt = 536 mg (1206-185-31) nmr, ms, micro, ir
m/z^+ 320.

Theory: 1.00 g (53.6%) m.p. = 123-126°C

* By mistake combine 100 mg 1206-185-31 with 1206-174-40
∴ Seperated on Prep TLC (50% Et2O/Pet)



(a) yellow oil : 45.5 mg (1206-185-40) ms m/z^+ 315
(b) white solids : 43 mg 1206-185-41) ms m/z 320
(c) : 1206-174-40

Performed by-

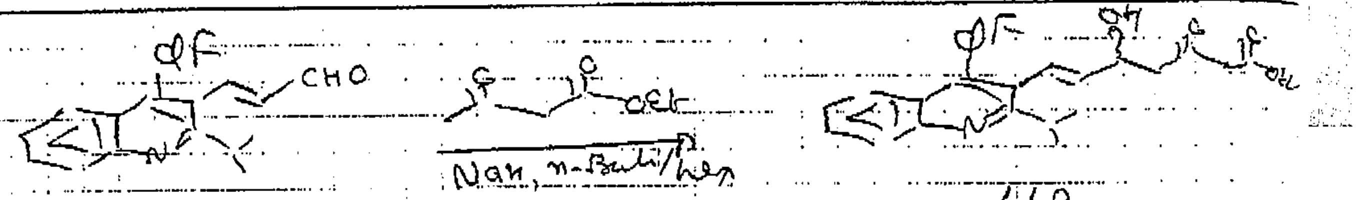
Witness- Z Perez

Cont'd to-

Title-

Date 8-5-87 Proj.

Cont'd From-



319

449

$C_{27}H_{28}NO_4F$

319 1206-185-31 = 450 mg (1.4106583 mmole)

(1.021, 130.14 Ethyl acetoacetate = 799 µml (6.2695924 mmole)

24 50% NaH = 301 mg (" ")

1.6M n-BuLi/hex = 4.18 ml (" " ")

THF = 10 ml + 30 ml

Ref: 1206-172

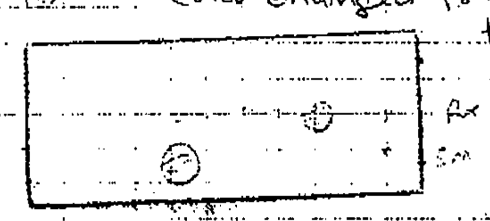
To a solⁿ of 1206-185-31 in 30 ml THF was added at -20° to -15°C a solⁿ of dianion total = 9.8 ml (*2.5 equiv) prepared as below:

Dianion (* Need to use only ~~2 equiv. to~~ 2 equiv. by TLC.)

To solⁿ of 799 µml Ethyl acetoacetate in 10 ml dry THF was added 301 mg 50% NaH at once at -15° to -10°C (foaming, H_2 gas evolved) → clear homogeneous solⁿ stirred for 15 min. At -10° → -15°C was added 4.18 ml 1.5M n-BuLi/Hex dropwise solⁿ changed color to yellow homogeneous solⁿ total vol. = 15.2 ml

Used in portions to get complete rxn by TLC

color changed from light yellow to dark yellow to orange to dark yellow



Stirred at -20° to -15°C for 30 min. quenched with satd NH_4Cl & warmed up to r.t. extracted with Et_2O, washed with H_2O, brine, dried over $MgSO_4$, filtered, washed

Performed by- Ray Patel 8-5-87

Witness- R Perez

Cont'd to- 1206-187

Date 8-5-87 Proj. Title-

Cont'd From- (206-186

rotavap to dryness gave yellow oil = 918 mg (1206-187-2)

(Theory: 633.38 mg) (~~78~~ (74%)

Added ether to oil for flash chromatography (25% Et2O/Pet) → some solids crystallized out. Filtered solids washed with ether gave yellow crystals = 90.7 mg (1206-187-11) ms m+ 450, nmr. ~~Res~~ Rotavap mother liquor to dryness to yellow oil. Flash chromatography of mother liquor (~~50%~~ (25% Et2O/Pet) gave yellow solids = 378 mg (1206-187-15) ms, ir, nmr, m+ 450, micro, m.p. = 101-103°C

~~total~~ yield: 90.7 + 378 = 468.7 mg (1206-187-18)

	C	H	N	O	F	
Calc.	72.41	6.13	3.12	14.24	4.22	
Found	71.4	6.46	2.58			
	[illegible]	[illegible]	[illegible]			

obs. mass = 450.20831
Calc. " = 450.20806

Performed by- Rajeshvari D. Patel 9-1-87

Witness- [illegible]

382

DR. D. CORNISH	DR. J. NADELSON	MR. J. BOROVIAN	MR. T. MC GOVERN
DR. J. FOLEY	DR. L. SALANS	MR. T. DOYLE	MRS. L. ROTHWELL
DR. G. HARDTMANN	DR. R. SAUNDERS	MR. R. HONOR	MR. G. SHARKIN
DR. W. HOULIHAN	DR. D. WEINSTEIN(2)	MR. W. JEWELL	MR. R. VILA
DR. F. KATHAWALA	DR. D. WINTER	MR. M. KASSENOFF	MR. F. WEINFELDT
BASLE (2)			

MINUTES

PATENT COMMITTEE MEETING

HELD WEDNESDAY, APRIL 29, 1987

* *

3. NOTICES OF ALLOWANCE:

3.1 Th
a

13

in-part;

3.2 Th
th

65

respecting

4. FINAL REJECTIONS:

4.1 T

5. DISCLOSURES:

5.1 The following disclosure has been rated "A":

5.2

"A" and a
matter from a
U.S. patent
considering
tent
a separate
ter in due

5.3 The following disclosures have been rated "X":

5.4 The following disclosures have been rated "B":

299/84 WATTANASIN FHW

5.5

384

DR. D. CORNISH	DR. L. OSTBERG	MR. J. BOROVIAN	MR. T. MC GOVERN
DR. J. FOLEY	DR. L. SALANS	MR. T. DOYLE	MRS. L. ROTHWELL
DR. G. HARDTMANN	DR. R. SAUNDERS	MR. R. HONOR	MR. G. SHARKIN
DR. W. HOULIHAN	DR. D. WEINSTEIN(2)	MR. W. JEWELL	MR. R. VILA
DR. F. KATHAWALA	DR. D. WINTER	MR. M. KASSENOFF	MR. F. WEINFELDT
DR. J. NADELSON	BASLE (2)		

MINUTES

PATENT COMMITTEE MEETING

HELD WEDNESDAY, JULY 29, 1987

* *

5. DISCLOSURES:

5.1 The following disclosures are rated "X":

5.2 The following disclosures are rated "B":

299/84 WARRANASIN FHW

386

DR. D. CORNISH	DR. L. OSTBERG	MR. J. BOROVIAN	MR. T. MCGOVERN
DR. J. FOLEY	DR. L. SALANS	MR. T. DOYLE	MRS. L. ROTHWELL
DR. G. HARDTMANN	DR. R. SAUNDERS	MRS. J. GIESSER	MR. G. SHARKIN
DR. W. HOULIHAN	DR. D. WEINSTEIN(2)	MR. R. HONOR	MR. R. VILA
DR. F. KATHAWALA	DR. D. WINTER	MR. W. JEWELL	MR. F. WEINFELDT
DR. J. NADELSON	BASLE (2)	MR. M. KASSENOFF	

MINUTES OF THE

PATENT COMMITTEE MEETING

HELD WEDNESDAY, OCTOBER 28, 1987

* *

5.3 The following disclosures are rated X.

299/84 WATTANASIN FHW

5.4 The following disclosures are rated B.

REV:lmc
11/6/87

DR. D. CORNISH	DR. L. OSTBERG	MR. J. BOROVIAN	MR. M. KASSENOFF
DR. J. FOLEY	DR. L. SALANS	MR. T. DOYLE	MR. T. MC GOVERN
DR. G. HARDTMANN	DR. R. SAUNDERS	MRS.J. GIESSER	MRS.L. ROTHWELL
DR. W. HOULIHAN	DR. D. WEINSTEIN(2)	MR. R. HONOR	MR. G. SHARKIN
DR. F. KATHAWALA	DR. D. WINTER	MR. W. JEWELL	MR. R. VILA
DR. J. NADELSON	BASLE (2)		

MINUTES

PATENT COMMITTEE MEETING

HELD WEDNESDAY, NOVEMBER 25, 1987

* *

1A. FOREIGN FILINGS:

5. DISCLOSURES:

5.1 The following disclosures are rated "X":

299/84	WATTANASIN	FHW
6		
1		
8		
9		

DR. D. CORNISH	DR. L. OSTBERG	MR. J. BOROVIAN	MR. T. MCGOVERN
DR. J. FOLEY	DR. L. SALANS	MR. T. DOYLE	MRS. L. ROTHWELL
DR. G. HARDTMANN	DR. R. SAUNDERS	MRS. J. GIESSER	MR. G. SHARKIN
DR. W. HOULIHAN	DR. D. WEINSTEIN(2)	MR. R. HONOR	MR. R. VILA
DR. F. KATHAWALA	DR. D. WINTER	MR. W. JEWELL	
DR. J. NADELSON	BASLE (2)	MR. M. KASSENOFF	

MINUTES OF THE

PATENT COMMITTEE MEETING

HELD WEDNESDAY, JANUARY 27, 1988

* *

1.A. FOREIGN FILINGS:

5. DISCLOSURES:

5.1 The following disclosures are rated A.

.lity search
formed).

.ction
only).

299/84 WATTANASIN JMG

REV:lmc

want:

1) Typical example or lab notebook pages
2) Scope
   a) R_1, R_1, R_2
   b) (E)-CH=CH- replacement
   c) other substitu on quinoline ring
3) Which compds are known
4) Process condns for ~~AA-AD~~
5) Unusual condns for std rxns
6) Anything unusual - lab, Standard rxns that didn't work
7) Complete list of end products + NMR (tabulated) spectrum, mp. and isomeric compn of each

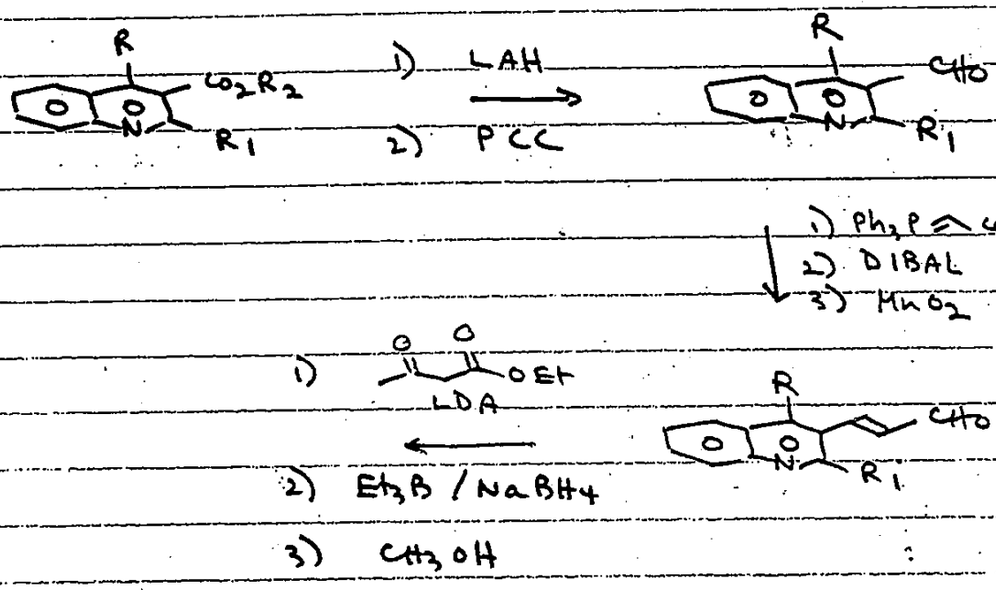
Scope same as naphthalene

X = (Z) or (E)-CH=CH $-CH_2CH_2-$, $-CH-$, $-(CH_2)_3-$

Substituents on
- alkyl
- alkoxy
- OH
- OCH$_2$O
- CF_3
- halo

Spoke with S.W. 2-12-88; Requested info will be sent

Route II


R
CO_2R_2
R_1
1) LAH
2) PCC
CHO
1) $Ph_3P=CHCO_2CH_3$
2) DIBAL
3) MnO_2
I
1)
OEt
LDA
2) Et_3B / $NaBH_4$
3) CH_3OH

sent to

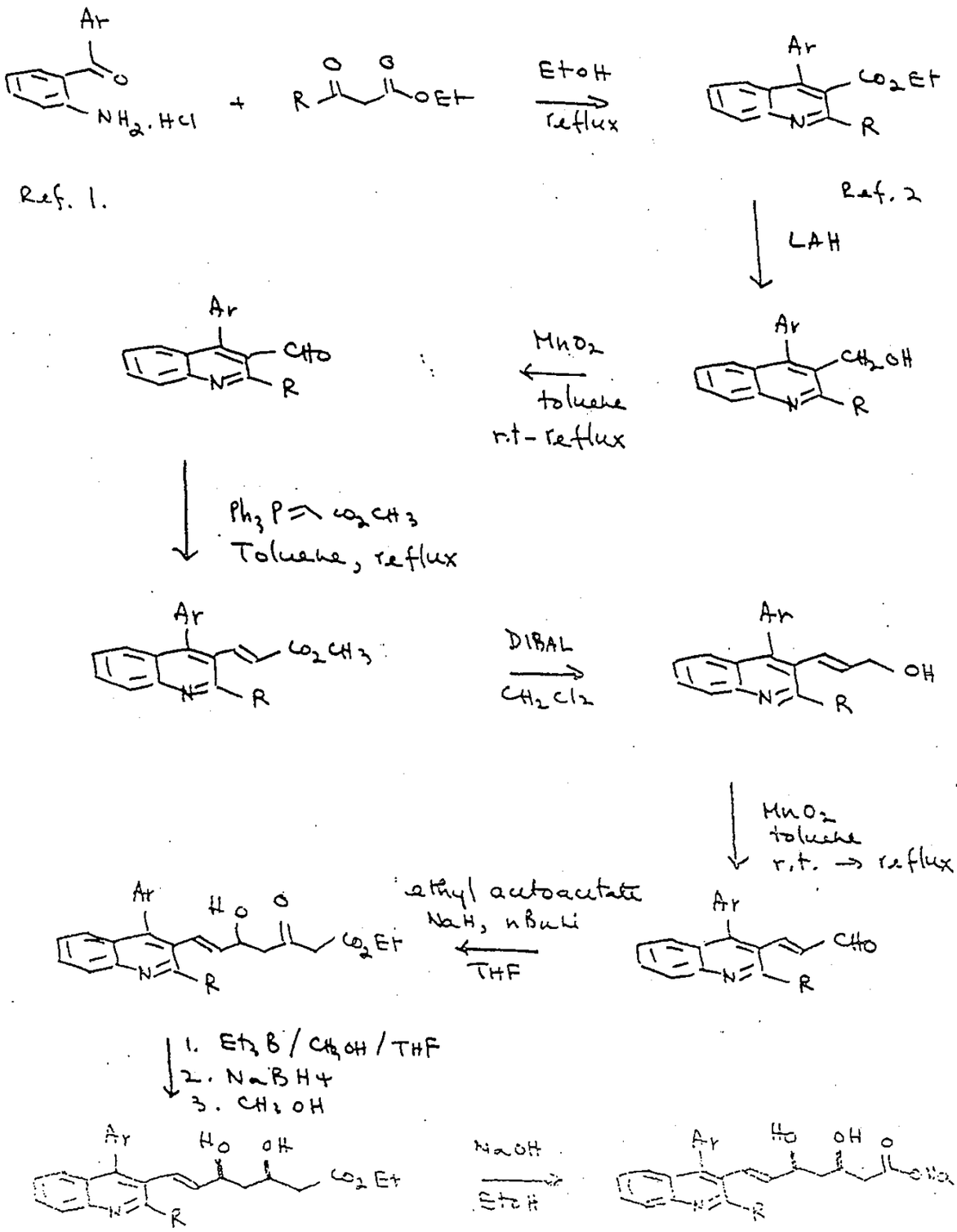
M. Kasuga.

2/29/88.

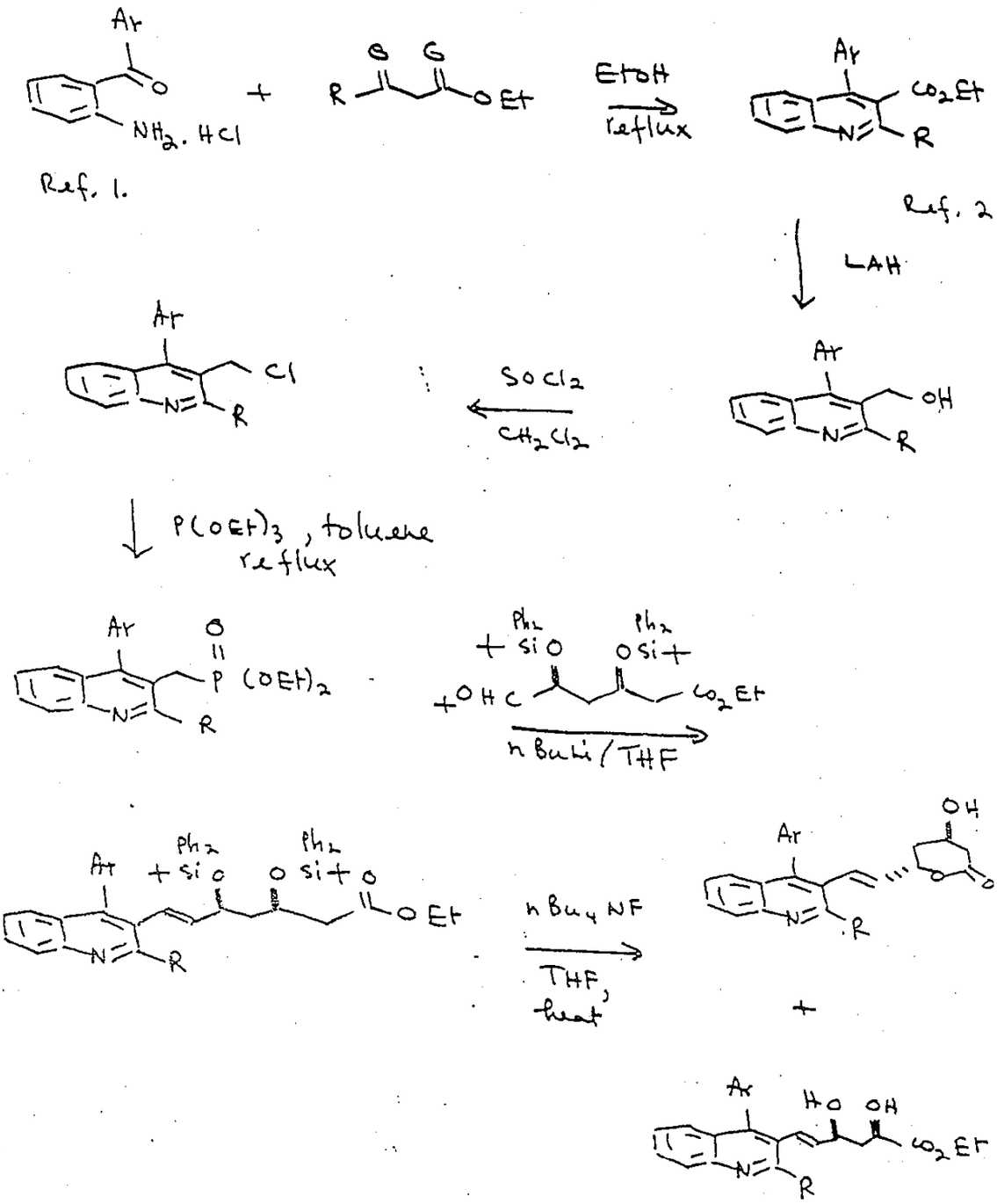
S. Wattanasin.
2/29/88

394

SCHEME I



SCHEME 2

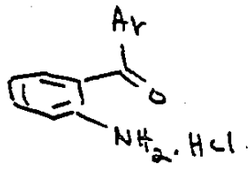

Ar
NH2. HCl
R
OEt
EtOH
reflux
CO2Et
Ref. 1.
Ref. 2
LAH
OH
SOCl2
CH2Cl2
Cl
P(OEt)3, toluene
reflux
P (OEt)2
Ph2 Si O
O Si Ph2
OHC
CO2Et
n BuLi / THF
nBu4NF
THF,
heat

References + Notes

1. A. Morrison and T.P. C. Mulholland, J. Chem. Soc. 2702 (1958)

2. E.A. Fehnel J. Heterocyclic Chem. 4, 565 (1968).

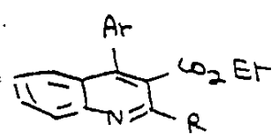
3. The starting aminoketones 1 are known compounds and prepared according to



1 Ar = Phenyl
= 3,5-dimethylphenyl
= p-Fluorophenyl

a procedure described in ref. 1.

4. The quinolines 2 were prepared by a modified procedure of ref. 2.



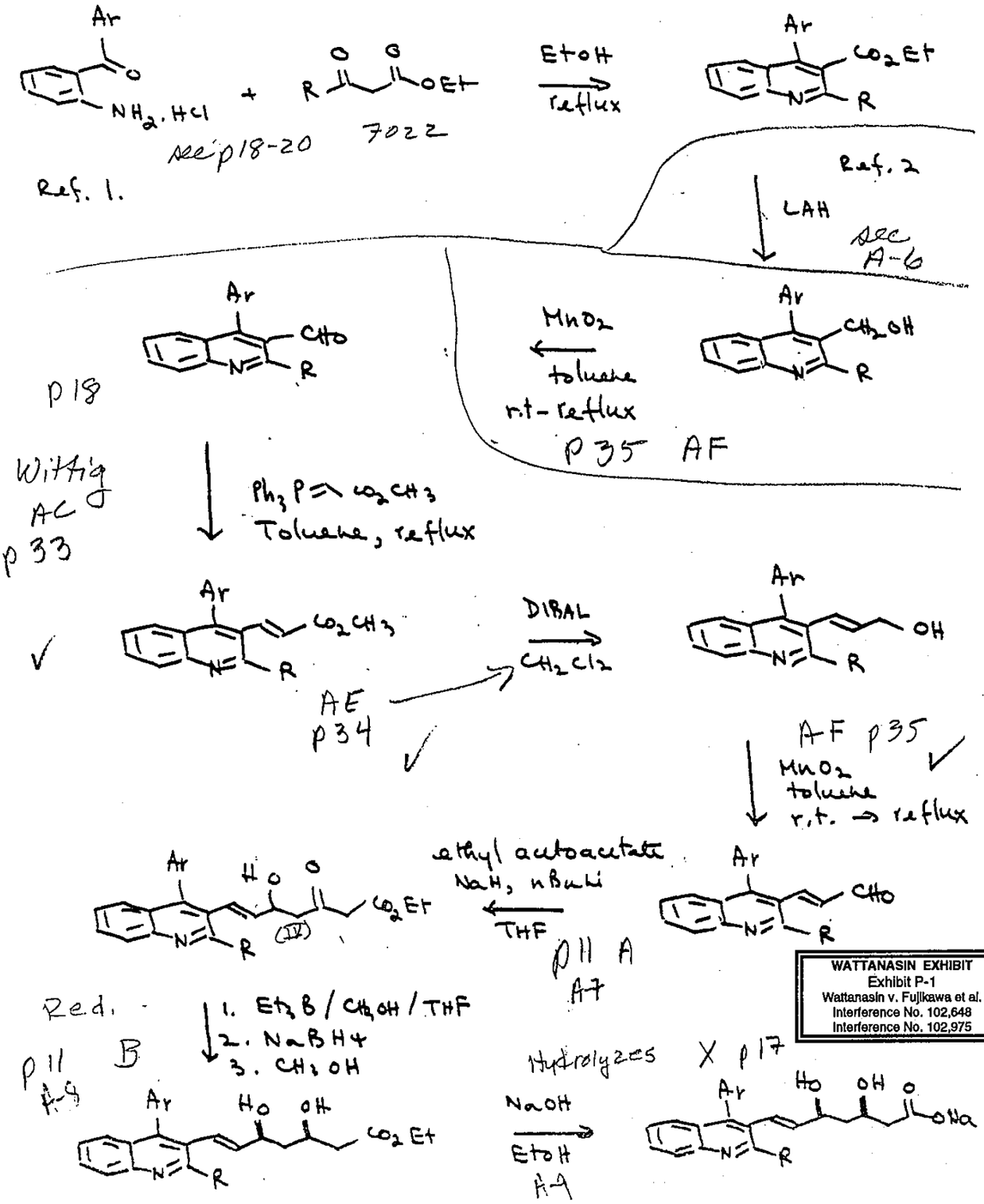
2

5. According to a search, only quinoline 2 where Ar = Ph and R = CH_3 is known

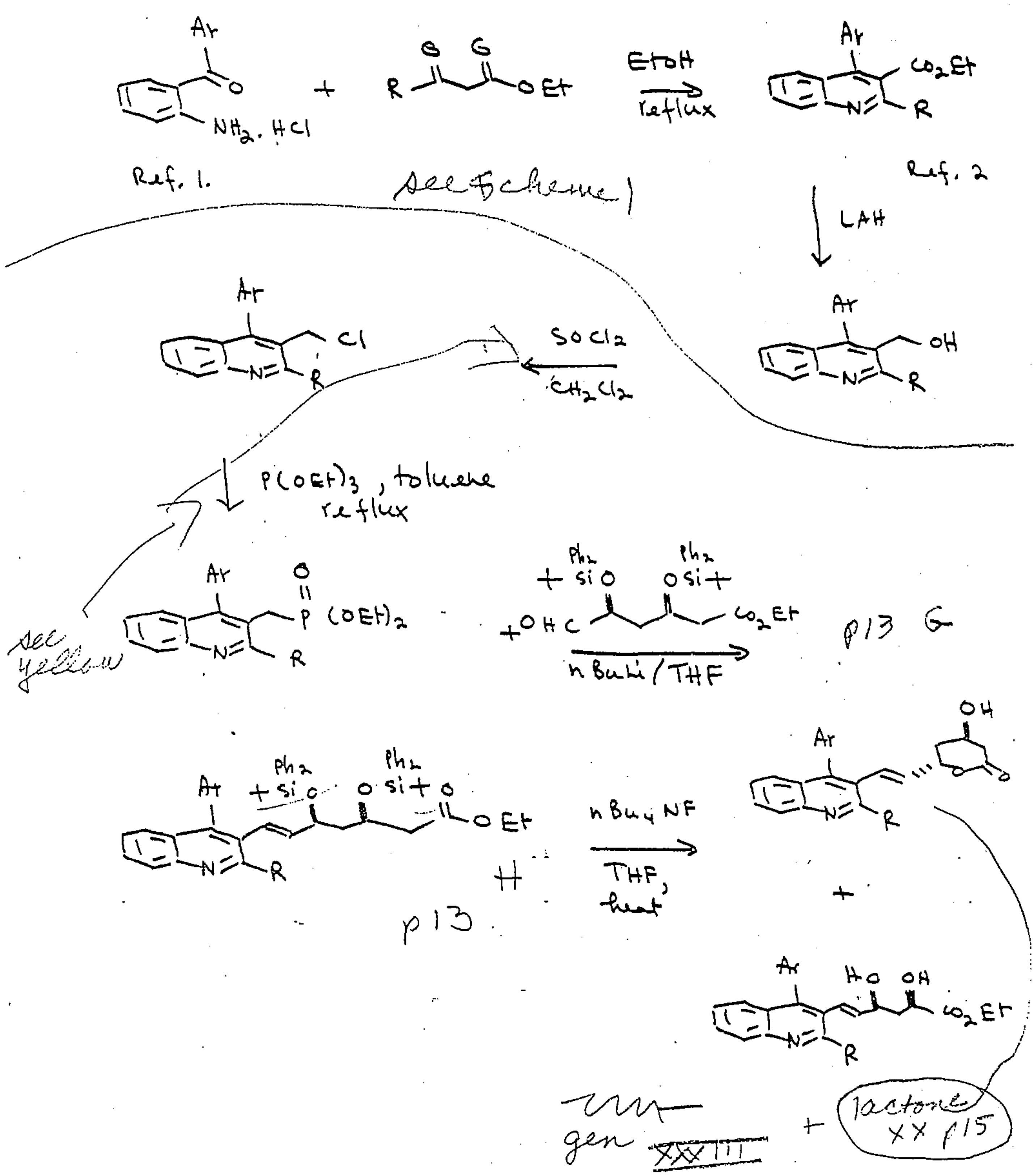
see 7022 C

S. Wattanasin, 2/24/88. 398

SCHEME I



SCHEME 2

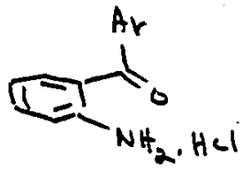

Ar
NH2 . HCl
Ref. 1.
+
R
OEt
EtOH
reflux
CO2Et
R
Ref. 2
see Scheme 1
LAH
OH
Cl
SOCl2
CH2Cl2
P(OEt)3 , toluene
reflux
see yellow
P (OEt)2
Ph2
OHC
CO2Et
nBuLi / THF
p13
nBu4NF
THF,
heat
p13
HO OH
lactone
XX p15
gen XXIII

References + Notes

1. A. Morrison and T.P. C. Mulholland, J. Chem. Soc. 2702 C(1958)

2. E.A. Fehnel J. Heterocyclic Chem. 4, 565 C(1968).

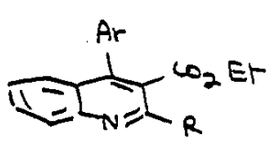
3. The starting aminoketones 1 are known compounds and prepared according to



1 Ar = Phenyl
= 3,5-dimethylphenyl
= p-Fluorophenyl

a procedure described in ref. 1.

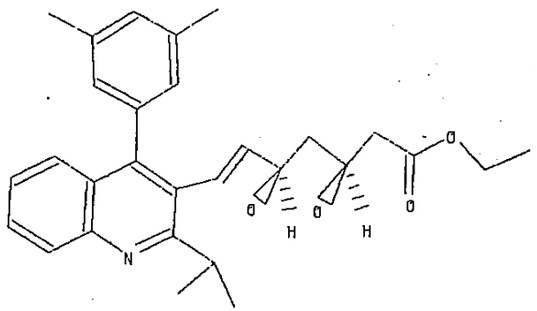
4. The quinolines 2 were prepared by a modified procedure of ref. 2.



3

5. According to a search, only quinoline 2 where Ar = Ph and R = CH_3 is known.

STRUCTURE



DATA

- Notebook # 1079-111-19
- oil
- erythro : threo ≈ 95 : 5
- nmr

0.9 (t, 3H)
1.6 (d , 6H)
2.1 (m , 2H)
3.7 (m, 1H)
3.7 - 4.0 (m, 3H)
4.2 (m, 1H)
5.4 (q , 1H)
6.6 - 7.7 (m, 8H)
8.4 (d, 1H)

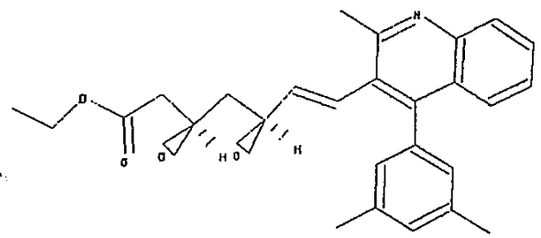
- prepared according to SCHEME 1.

SAH. NO	REG. NO	MW	CHEMIST	DATE
SAH-063366	25496	461.606	KATHAWALA WATTANASIN	11-26-84

Ex 3A

402

STRUCTURE



DATA

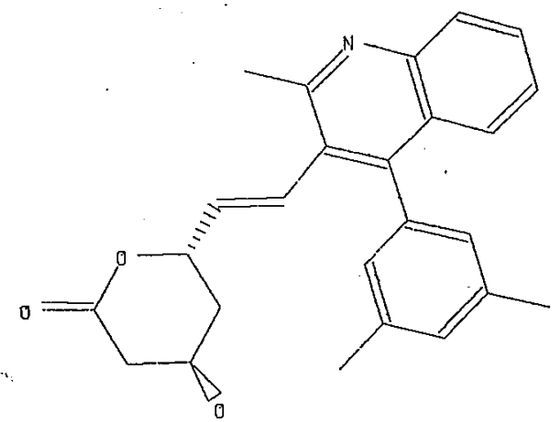
- Notebook # 1127-11-34
- oil
- erythro: threo ~ 95 : 5
- nmr
  - 1.3 (t, 3H)
  - 2.4 (m, 5H)
  - 4.1 (m, 1H)
  - 4.2 (q, 2H)
  - 4.4 (m, 1H)
  - 5.5 (q, 1H)
  - 6.5 (d, 1H)
  - 6.7-8 (m, 7H)
- prepared according to SCHEME2

SAH.NO	REG.NO	MW	CHEMIST	DATE
SAH-063548	26080	433.552	KATHAWALA WATTANASIN	05-17-85

Ex 3E

403

STRUCTURE



DATA

- Notebook # 1127-11-37
- oil
- cis : trans lactone ~ 5 : 95
- nmr

2.3 (s, 1H)
2.5-2.9 (m, 4H)
4.1 (m, 1H)
5.1 (m, 1H)
5.5 (q, 1H)
6.6 (d, 1H)
6.8-8.0 (m, 7H)

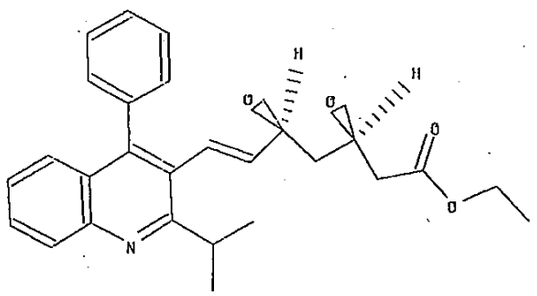
- prepared according to SCHEME 2.

SAH.NO	REG.NO	MW	CHEMIST	DATE
SAH-063549	26082	387.483	KATHAWALA WATTANASIN	05-17-85

Ex 2

404

STRUCTURE



DATA

- Notebook # 1206-176-43
- m.p. 104-106°C
- erythro : threo ≥ 95:5
- nmr
  1.3 (t, 3H)
  1.35 (d, 6H)
  2.35 (m, 1H)
  2.9 (d, 1H)
  3.6 (d, 1H)
  3.5 (m, 1H)
  4.6 (m, 1H)
  4.12 (q, 2H)
  4.35 (m, 1H)
  5.35 (q, 1H)
  6.6 (d, 1H)
  7.1 -7.7 (m, 8H)
  8.1 * (d, 1H)
- prepared according to SCHEME 1. *

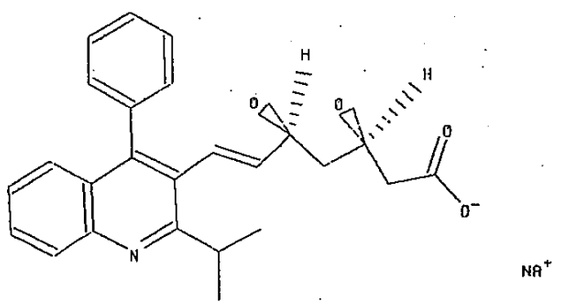
SAH.NO	REG.NO	MW	CHEMIST	DATE
SAH-064933	30441	433.552	PATEL WATTANASIN	09-21-87

* A copy of the notebook of all steps is attached.

Ex 1

405

STRUCTURE



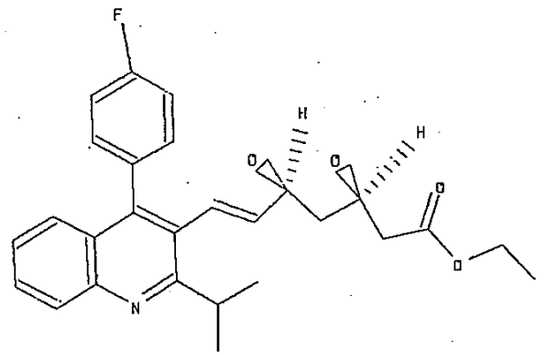
DATA

- Note book # 1206-179-30
- m.p. > 216°C
- erythro : threo ≥ 95:5
- nmr
  - 1.4 (d, 6H)
  - 2.2 (m, 2H)
  - 3.6 (m, 1H)
  - 3.8 (m, 1H)
  - 4.2 (m, 1H)
  - 5.4 (q, 1H)
  - 6.6 (d, 1H)
  - 7.1-7.7 (m, 8H)
  - 8.1 (d, 1H)
- prepared according to SCHEME I.

SAH.NO	REG.NO	MW	CHEMIST	DATE
SAH-064934	30442	427.48	PATEL WATTANASIN	09-21-87

Ex 3B

STRUCTURE



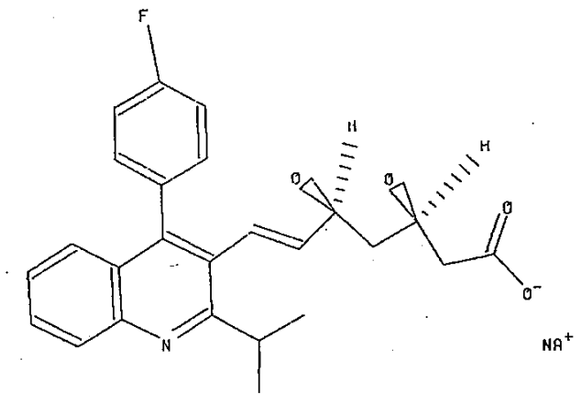
DATA

- Notebook # 1206 - 190- 41
- oil
- erythro : threo ~ 95 : 5
- nmr
  1.3 (t, 3H)
  1.4 (dd, 6H)
  2.4 (m, 2H)
  3.1 (d, 1H)
  3.5 (m, 1H)
  3.6 (m, 1H)
  4.1 (m, 1H)
  4.2 (q, 2H)
  4.4 (m, 1H)
  5.4 (q, 1H)
  6.6 (d, 1H)
  7.0 - 7.4 (m, 7H)
  7.6 (m, 1H), 8.1 (d, 1H)
- prepared according to SCHEME I.

SAH.NO	REG.NO	MW	CHEMIST	DATE
SAH-064935	30447	451.543	PATEL WATTANASIN	09-21-87

Ex 3C

STRUCTURE



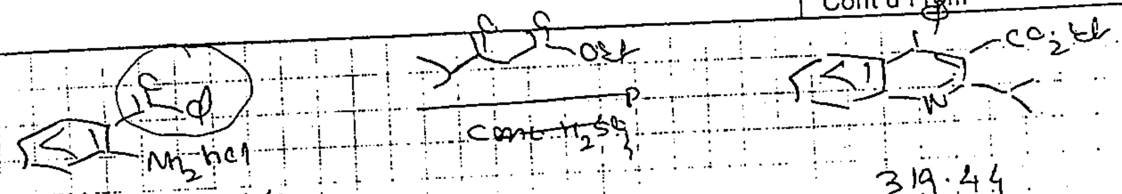
DATA

- Notebook # 1206-201-30
- mp > 225°C
- erythro : threo ≥ 95 : 5
- nmr
  - 1.3 (d, 6H)
  - 2.2 (m, 2H)
  - 3.6 (m, 1H)
  - 3.8 (m, 1H)
  - 4.25 (m, 1H)
  - 5.5 (q, 1H)
  - 6.6 (d, 1H)
  - 7.3-7.4 (m, 7H)
  - 7.6 (m, 1H)
  - 8.1 (d, 1H)
- prepared according to SCHEME 1.

SAH.NO	REG.NO	MW	CHEMIST	DATE
SAH-064936	30448	445.47	PATEL WATTANASIN	09-22-87

Ex 3D

804



5233-24 1206-129-18

23324 (1206-129-18) = 11.5 g (0.04930 mole)

(0.989) 158.2 [structure] OEt = 11.93 ml (0.07395 81 mol) 1.5 equiv.

EtOH = 10 ml + 5 ml

~~Conc H_2SO_4 = 2.3 ml~~

Ref : 1206-92

Above mixt. was heated to reflux (107 - 4 hrs) stirred at r.t. overnight

TLC 20% EtOAc/Hex — Rx, ester

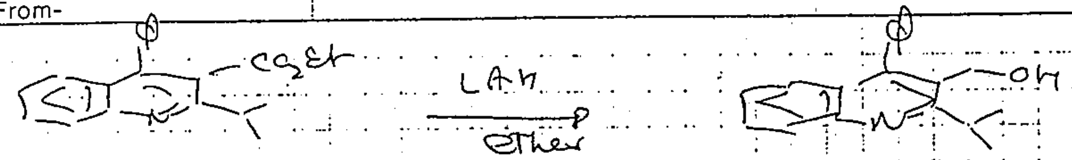
Rotavap to dryness to yellow oil, basified with NH_4OH, extracted with Et_2O, washed with ~~20% HCl~~ H_2O, brine, dried, filtered, washed, rotavap gave 10.21 g orange yellow solids (1206-130-27)

nmr, ir, ms → ~~no 319 (m+)~~ m+ = 320

Theory: 15.748 g, % = 64.86

Date 6-9-87 Proj. Title-

Cont'd From-



319.44 1206-130-27 277.44 $C_{21}H_{21}NO$

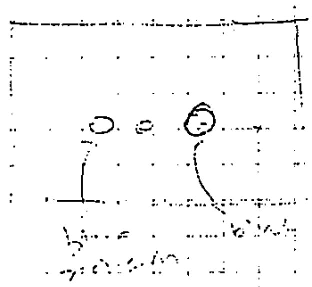
(319.44) 1206-130-27 = (0.21 g (0.0319621 mole)

(38) LAH = 2.43 g (0.0632421 mole)

dry ether = 100 ml

Ref: 1206-96

To 1206-130-27 in dry ether with cooling was added LAH portionwise, exothermic, foaming, stirred at r.t. for 3 hr. C9 3C-12 3C-



Rx mix poured in ice H_2O (exothermic, strong Rx) extracted with ether, washed with H_2O, brine, dried, filtered, washed, rotavap gave yellow solids wt = 8.5 g (1206-137-31) nmr, ir, ms

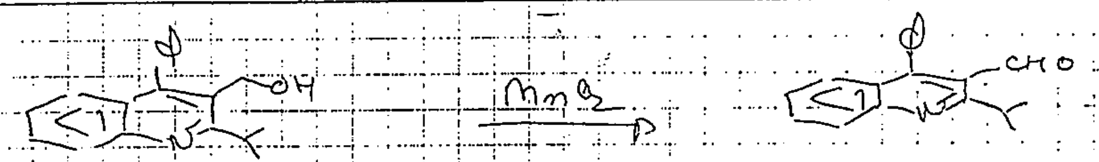
Theory: 8.86 g (95.8%)

Performed by- Raj Patel 7-2-87

Witness- [illegible] Cont'd to-

Date 6-17-87 Proj. Title-

Cont'd From-

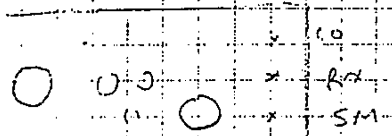


1206-137-31
277.4

275.0
$C_{19}H_{17}NO$

277.4 1206-137-31 = ~~8.0g~~ 8.0g (0.028839 2mole)
MnO2 = 16.0g
toluene = 150 ml

To 1206-137-31 in toluene was added MnO2 → heated to reflux (11:45 - 2P)



filtered thr' pad of silica gel* washed with toluene rotovap to dryness, gave yellow solids: 2.6518g (1206-145-25) nmr, ir, ms MH+ = 276 desired pd.
orange solids: 4.6463g (1206-145-26) nmr, ir, ms MH+ = 278 S.M.

* During filtration, separated two bands, which was filtered separately & rotovap

Theory: 7.91g (74.52%)

Total yield = 2.6518g (1206-145-25) + 3.26g (1206-148-33) = 5.91g

Performed by-

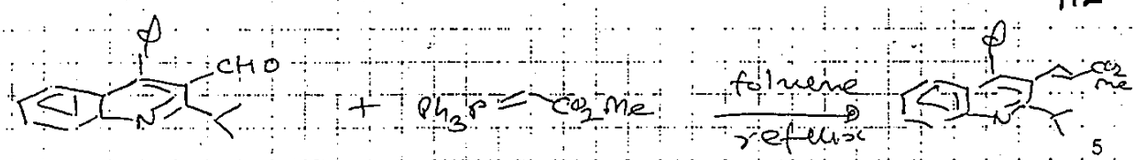
Witness- S. [signature]

Cont'd to- 145

Date 6-30-87 Proj. Title-

Cont'd From-

412



275 331

(275) { 1206-145-25 / 1206-148-33 } = 2.65+3.26 = 5.915 (0.02149 mole)

~~MeOH~~ = ~~11.8 g~~

toluene = 85 ml + 20 ml

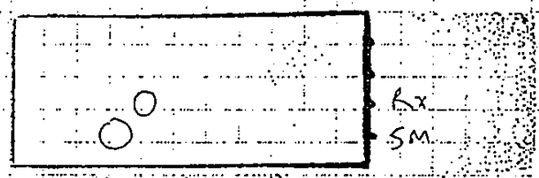
(334) $Ph_3P{=}CO_2Me$ = 8.6135 g (0.025789 mole) 1.2 eq.

2 eq.

Ref: 1206-146

Above mix. was heated to reflux (yellow heterogeneous before heating) for 1½ hrs. stirred at r.t. overnight

7-1-87



Diluted with 50% Et_2O/Pet ether filtered thru pad of silica gel washed Rotavap to dryness to give yellow crystalline solid 8.6 g : Triturate with MeOH gave off white solids (Theory: 7.113 g) wt = 5.5198 g (1206-153-31) 77.6%

nmr ir ms $mn^+ = 332$

7-2-87

Rotavap mother liquor to dryness to yellow oil wt = 2.7593 g (1206-153-34)

7-6-87

Trituration with MeOH gave 761.6 mg light yellow solids (1206-153-37) nmr ms mn^+ 332

Rotavap mother liquor to dryness to yellow solid (1206-153-38) ms

Total yield = 5.5198 + 0.7616 (1206-153-40)

7-9-87

m.p = 128-130°C

	C	H	N
Calc	72	6.32	4.37
Found	71.65	6.03	
	72.52	6.42	3.75

Performed by- Raj Patel 7-6-87

Witness- S. Wattamwar

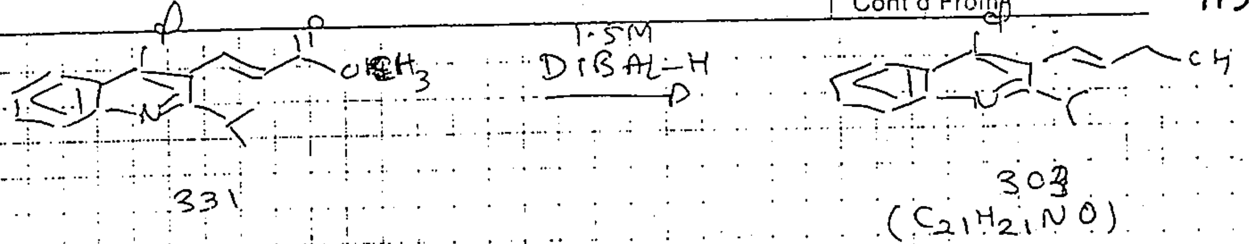
Cont'd to-

Title-

Date 7-7-87 Proj

Cont'd From

413

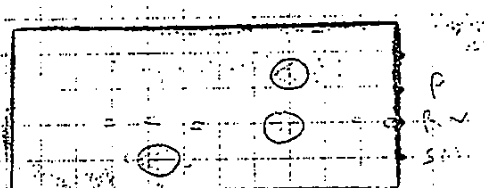


1206-153-40 = 6.25g (0.0188821 mole)
1.5M DIBAL-H/toluene = 25.18 ml (0.0377642 mole) 2 eqm
CH_2Cl_2 = 75 ml

Ref: 1206-155, 87

To soln of 1206-153-40 in CH_2Cl_2 was added at -78°C 1.5M DIBAL-H/toluene, stirred at -78°C for 3 hrs (12^{15} - 3^{15})

SW/ shel ...



	C	H	N	O
	83.13	6.98	4.62	5.27
	82.65	6.56	3.9	
	82.68	6.89	3.89	

quenched with 12.55 ml 2N NaOH, diluted with EtOAc stirred at r.t. overnight → lots of white (gel) solids came out.
7-8-87

Filtered thru' pad of silica gel, washed with EtOAc, washed org. layer with H_2O (brine) dried rotevap to dryness gave off white solid: 5.42g (1206-158-35) Dissolved solids in Et_2O insolubles (white) (aluminium oxide) was filtered thru' cintered glass funnel rotavap to dryness gave white-yellow solids 5.22g (1206-158-37)
Theory: 5.72g 73.7%
Dissolved solids in Et_2O, insoluble (aluminium oxide) was filtered rotavap to dryness gave yellowish solids = 4.2117g (1206-158-41) nmr, ir, ms, ( ) mw = 304 micro

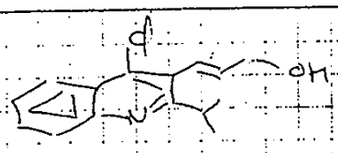
m.p. = 119°-121°C

Performed by- Raj Patel 7-17-87

Witness- S. Wattanasin

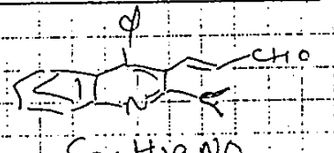
Cont'd to-

166 Title- Date 8-15-87 Proj 414
Cont'd From-



303

MnO2

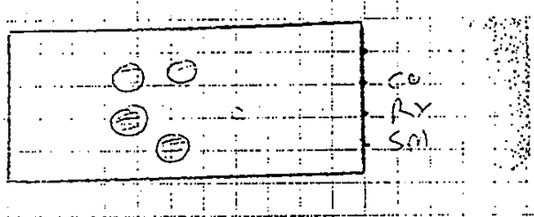


$C_{21}H_{19}NO$
301

1206-158-41 = 4.0g (0.0132013 mole
MnO2 = 8.0g
toluene = 50 ml

Ref: 1206-164

To 1206-158-41 in toluene added MnO2 & heated to reflux (2hr - 3hr), stirred at r.t. overnight



7-16-87

filtered thru' pad of silica gel, washed pad with ether, rotavap to dryness, gave 3.4946g yellow crystaline material (1206-166-30)
IR NMR MS mwt=302
Theory: 3.9736g (88%)

7-28-87 micro

	C	H

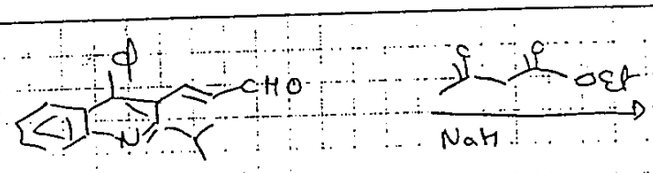
7-30-87 Exact mass obs. mass = 302.15404 m.p. = 98-101°
calc. mass = 302.15448

Performed by- Ray Patel 7-20-87
Witness- Cont'd to-

Title-

Date 7-20-87 Proj. 415

Cont'd From-



$C_{27}H_{29}NO_4$
431.0

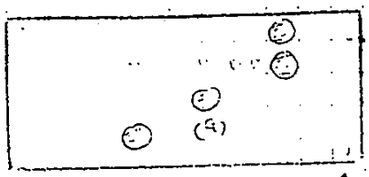
301

301 1206-166-30 = 3.5g (0.0116279 mole)
130.14, 1.02 ml Ethyl acetoacetate = 5 ml (0.04 mole)
24 60% NaH +
1.6M n-Buli/Hex = 27 ml
THF = 60 ml + 40 ml

To a soln of 1206-166-30 in dry THF (40 ml) at -5° to -10°C was added a soln of dianion (11 ml + 27 ml) (38 ml), prepared as described previously

Dianion (got from Dr. Som)

To soln of 5 ml Ethyl acetoacetate in 60 ml dry THF was added 1.9 g 50% NaH at -5° to 0°C, stirred for 15 min (foaming - H_2 evolved). At -10° - -15°C was added 27 ml 1.6M n-Buli/Hex, stirred for 20 min at -10°C → yellow homogeneous soln
Total vol = 92 ml (0.04 mole used up 38 ml dianion
= 0.01652 mole (1.4 equiv.) → color changed from yellow to orange to dark red
TLC (50% Et_2O/Pet) after 15 min ⇒ complete rxn



Rx was stirred for 30 min. quenched with NH_4Cl Extracted with Et acetate, washed with H_2O brine, dried, filtered, rotavap gave yellow oil 5.9188 g (1206-172-41)
Theory: 5.01 g (67.87%)

Performed by- Raj Patel 7-21-87

Witness- S. Wattamwar

Cont'd to- 1206-175

Date 7-22-87 Proj. Title-

Cont'd From- 1206-172

416

Flash chromatography (25% EtOAc/Pet) gave

(a) Yellow solids = 3.4004 g CR06-175-4 7 mixture, in ms micro mp =

m.p. = 84-87°C 68% yield.

	C	H	N	O		
Calc.	75.9[illegible]	[illegible]	[illegible]	14.13		
Found	75.9[illegible]	[illegible]	[illegible]			
	75.20	[illegible]	[illegible]			

Performed by- Raj Patel 8-5-87

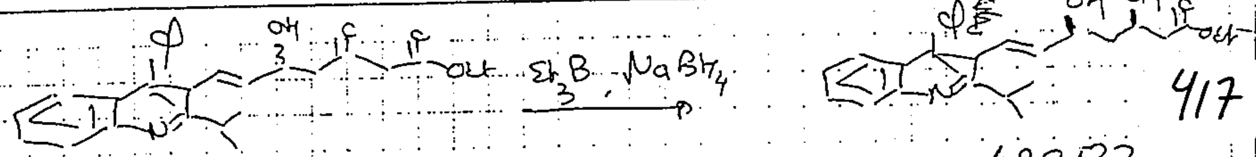
Witness- S. Wattanasin

Cont'd to-

Title-

Date 7-23-87 Proj.

Cont'd From-



431

417

433.527

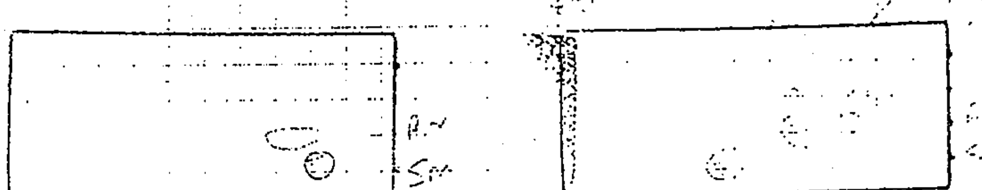
$C_{27}H_{31}NO_4$

(431)	1206-175-4	= 1.0 g	(0.0023201 mole)
	1m Et3B / THF	= 3.5 ml	(0.0034801 mole) 1.5 eq.
	dry THF	= 10 ml	
	CH3OH	= 2.5 ml	
37.8	NaBH4	= 0.1315 g	(0.003480 mole) 1.5

Ref: 1206-140

(homogeneous)

To 1206-175-4 in THF / MeOH, added 1m Et3B / THF at r.t., stirred for 1 hr (9:45 - 10:45). The solution was cooled to -78°C, NaBH4 were added portionwise. The rxn was stirred at -78°C for (11:00 - 3:00) 4 hrs.



The rxn was quenched with AcOH (5 ml) at -78°C. Ethyl acetoacetate was added & let it warm up to r.t. Org. layer was washed with satd. NaHCO3, H2O, brine, dried, filtered. Residue was redissolved in MeOH, evaporated to dryness. This evaporation process (in MeOH) was repeated until TLC showed desired product.

wt. of orange oil = 1.0914 g (1206-176-39)

Flash column (EtOAc/Pet) gave

yellow oil + solid - (a) F_{4-6} = 0.4043 g (1206-176-41) ir, nmr, ms, m.p. = 104-106°, exact mass MH^+ = 434, 13C, HPLC (93.3%)

F_{7-13} = 0.510 g (1206-176-43) ir, nmr, ms, MH^+ = 434, 13C, HPLC (93.2%)

Performed by- Raj Patel 8-5-87

Witness- [signature]

Cont'd to-

BIOLOGICAL ACTIVITY DATA REPORT (FOR PATENT DEPT.)

INVENTOR: S. Wattanasin DISCL. NO.: 299-84 418

ATTORNEY: M. Kassenoff DATE: May 24, 1988

1. ACTIVITY TO BE DISCLOSED:
Inhibition of cholesterol biosynthesis, antihypercholesteremic, antiatherosclerotic

2. IF ANY COMPOUNDS COVERED BY ABOVE-NOTED DISCLOSURE HAVE MORE THAN ONE ACTIVITY, INDICATE TOTAL NUMBER OF ACTIVITIES AND PREPARE A SEPARATE B.A.D.R. SHEET FOR EACH. TOTAL NO. OF ACTIVITIES: 1

3.a) TEST METHODS USED TO ESTABLISH ACTIVITY:
HMG-CoA reductase inhibition in rat liver microsomes (DT 64)
Cholesterol synthesis inhibition invivo in rats (DT 65)

b) DOSAGE RANGES BASED ON ACTUAL DOSES USED IN TEST PROCEDURE:
0.050 - 1.5 mg/kg

4. COMPOUNDS TESTED WITHIN DISCLOSURE WHICH EXHIBIT WEAK OR GREATER ACTIVITY:
64-935, 64-933

5. DOSAGE SCHEDULE - Broad Ranges:

a) Large / small animals:	.10	to	1.0	mg/kg.
b) Large animals:	20	to	200	mg/day.

6. MOST PREFERED COMPOUND FOR ACTIVITY DESIGNATED:

64-935

7. OTHER PREFERRED OR POTENTIALLY PREFERRED COMPOUNDS FOR DESIGNATED ACTIVITY:
64-936, 63-366, 64-933, 64-934

8. ED50 FOR THE PREFERRED COMPOUND IN EACH OF THE TEST METHODS INDICATED IN 3a) FOR THE DESIGNATED ACTIVITY:

COMPOUND	IC50 uM DT64	ED50 mg.kg DT65	Potency x Mevinolin*
Compactin	1.01	3.5	0.11
Mevinolin	0.14	0.41	1 (standard)
64-935	0.41	0.49	0.3
64-936	0.53	>1.0	
64-933	2.37	2.40	

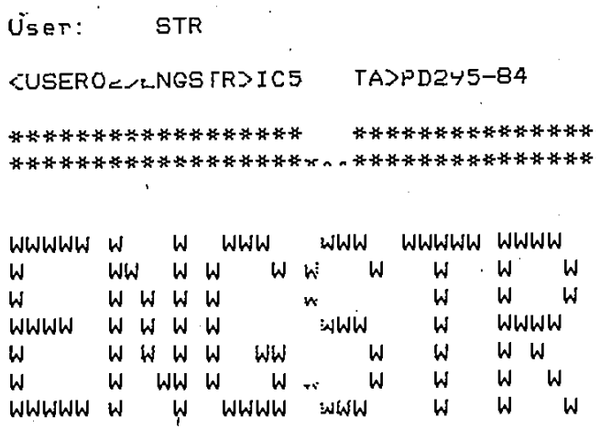
* Clinical dose of mevinolin (Lovasatin) = 20-80 mg/day

User: STR -at pr0

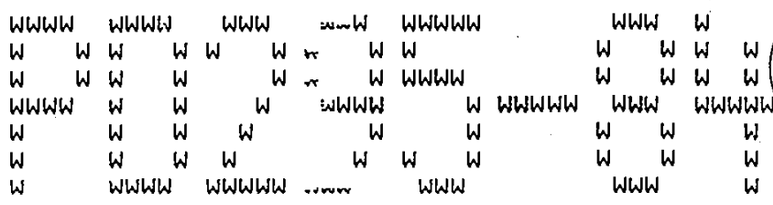
<USER02>ENGSTR>IC5 TA>PD295-84

419

299/84



295-84 &
299-84



Label: PRT002 -form

Pathname: <USER02>ENGSTR>IC50DATA>PD295-84
File last modified: 88-05-23.08:25:36.Mon

Spooled: 88-05-23 08:50:36.Mon [Spooler rev 19.4.6]
Started: 88-05-23 08:50:40.Mon on: PR0 by: PR0

IC50 TABLE RAT MICROSOMAL ASSAY (CSI-DT64)

THIS FILE IS A CALCULATED ESTIMATE OF THE IC50 (CONCENTRATION WHICH REDUCES THE CONVERSION OF HMG-CoA TO MEVALONATE BY 50%) USING ALL THE STUDIES ON THE RELEVANT COMPOUNDS UP TO THE SORT DATE.

LAST UPDATE: 02-04-88 SORT BY: DISCLNO

COMPOUND	REGNO	DISCL	IC50 uM	DATE	REF	COMMENTS
SAH-062977	24162	295-84	25.0000	02-07-84	1014-248	
SAH-062978	24163	295-84	0.0180	02-07-84	1014-249	
SAH-063033	24315	295-84	0.0450	04-18-84	1014-257	SAPONIFIED
SAH-063033	24315	295-84	0.5250	02-29-84	1014-257	
SAH-063034	24316	295-84	0.3630	02-22-84	1014-258	
SAH-063035	24317	295-84	0.0400	02-22-84	1014-259	
SAH-063074	24446	295-84	0.4000	05-23-84	1014-277	
SAH-063074	24446	295-84	0.6900	03-26-84	1014-277	
SAH-063075	24448	295-84	0.5300	04-18-84	1014-278	SAPONIFIED
SAH-063075	24448	295-84	0.9040	03-26-84	1014-278	
SAH-063076	24449	295-84	0.5800	06-12-84	1014-279	
SAH-063076	24449	295-84	0.6400	05-23-84	1014-279	
SAH-063076	24449	295-84	0.9000	03-26-84	1014-279	
SAH-063083	24511	295-84	1.9100	03-28-84	1014-281	
SAH-063083	24511	295-84	2.3200	03-28-84	1014-281	
SAH-063084	24512	295-84	3.1600	06-12-84	1014-282	
SAH-063084	24512	295-84	6.3200	03-28-84	1014-282	
SAH-063144	24750	295-84	1.1600	05-10-84	1014-294	SAPONIFIED
SAH-063144	24750	295-84	2.0200	05-10-84	1014-294	
SAH-063145	24755	295-84	>10.0000	05-07-84	1014-295	SAPONIFIED
SAH-063145	24755	295-84	>10.0000	05-10-84	1014-295	
SAH-063146	24756	295-84	>10.0000	05-07-84	1014-296	
SAH-063158	24809	295-84	0.1000	06-04-84	1069-002	SAPONIFIED
SAH-063158	24809	295-84	0.3430	06-04-84	1069-002	
SAH-063159	24810	295-84	0.2250	06-12-84	1069-003	
SAH-063159	24810	295-84	0.2630	06-04-84	1069-003	
SAH-063160	24811	295-84	0.1110	06-04-84	1069-004	SAPONIFIED
SAH-063160	24811	295-84	1.5600	06-04-84	1069-004	
SAH-063161	24821	295-84	0.0020	06-04-84	1069-005	
SAH-063161	24821	295-84	0.0020	06-12-84	1069-005	
SAH-063162	24822	295-84	0.0030	06-04-84	1069-006	
SAH-063162	24822	295-84	0.0035	06-12-84	1069-006	
SAH-063174	24865	295-84	0.0140	06-06-84	1069-013	SAPONIFIED
SAH-063174	24865	295-84	0.0190	06-06-84	1069-013	
SAH-063175	24866	295-84	0.0260	06-06-84	1069-014	
SAH-063229	25075	295-84	>10.0000	08-04-84	1069-036	
SAH-063230	25078	295-84	0.0042	08-01-84	1069-037	
SAH-063231	25079	295-84	0.0058	08-04-84	1069-038	
SAH-063269	25205	295-84	0.0030	09-10-84	1069-053	SAPONIFIED
SAH-063269	25205	295-84	0.0440	09-12-84	1069-053	
SAH-063270	25206	295-84	0.0080	09-05-84	1069-054	
SAH-063271	25208	295-84	0.0320	09-10-84	1069-055	SAPONIFIED
SAH-063271	25208	295-84	0.1450	09-12-84	1069-055	

SAH-064484	F	29413	I95-84	0.0320	11-24-86	1149-227
SAH-064744	E	30059	I95-84	0.0320	05-01-87	1149-293
SAH-064745	S	30060	I95-84	0.0030	05-01-87	1149-294
SAH-064745	S	30060	I95-84	0.0030	07-07-87	1149-297
SAH-064815	E	30198	I95-84	0.0220	07-07-87	1238-001
SAH-064816	S	30199	I95-84	0.0450	07-07-87	1238-002
SAH-063162	S	30203	I95-84	0.0080	07-07-87	1238-003
SAH-064745		30765	I95-84	0.0020	01-12-88	1238-030
SAH-063366		25496	I99-84	1.5800	12-13-84	1069-113
SAH-063549		26082	I99-84	7.3100	06-13-84	1069-197
SAH-063548		26080	I99-84	3.7750	06-13-84	1069-198 —
SAH-064933	E	30441	I99-84	2.3700	10-08-87	1238-013
SAH-064934	S	30442	I99-84	2.6100	10-08-87	1238-014
SAH-064935	E	30447	I99-84	0.4130	10-08-87	1238-015 —
SAH-064936	S	30448	I99-84	0.5300	10-13-87	1238-016 —

ED50 TABLE RAT INVIVO ACETATE INCORPORATION (CSIV-DT65)

THIS FILE IS A CALCULATED ESTIMATE OF THE ED50 (DOSE WHICH REDUCES THE INCORPORATION OF 14C-ACETATE INTO CHOLESTEROL BY 50%) USING ALL THE STUDIES ON THE RELEVANT COMPOUNDS UP TO THE SORT DATE.

LAST UPDATE: 1-06-88 SORT BY: REGNO

COMPOUND	REGNO	CISCL		ED50 mg/kg	DATE mm-dd-yy	REF bk-pg	COMMENTS
SAH-064745	30060	I95-84	=	0.016	10-20-87	917-127	N=9
SAH-064745	30765	I95-84	=	0.016	02-19-88	917-154	N=3 BS BATCH
SAH-064745	ALL	I95-84	=	0.016	02-19-88	917-154	N=12 2BATCHES
SAH-063162	25500	I95-84	=	0.019	09-18-87	917-101	N=10
SAH-063162	ALL	I95-84	=	0.040	09-18-87		N=19 3BATCHES
SAH-063162	25085	I95-84	=	0.079	10-11-84	812-266	N=8
SAH-064119	27563	I95-84	=	0.08	05-16-86	869-228	N=6
SAH-064744	30059	I95-84	>	0.10	07-14-87	917-090	N=3 -21% @.10
SAH-064816	30199	I95-84	=	0.10	10-12-87	917-119	N=6
SAH-064483	29412	I95-84	=	0.13	02-06-87	917-024	N=3
SAH-064063	27424	I95-84	=	0.19	04-17-86	869-211	N=3
SAH-064309	28718	I95-84	=	0.19	11-03-86	869-283	N=3
SAH-063231	25079	I95-84	>	0.25	08-30-84	812-250	
SAH-064393	29163	I95-84	=	0.25	02-25-87	917-031	N=6
SAH-063161	24821	I95-84	>	0.250	11-29-84	812-293	-12@0.25
SAH-063989	27237	I95-84	=	0.28	04-04-86	869-195	N=6
SAH-063425	25687	I95-84	>	0.3	03-20-85	869-046	N=3
SAH-064305	28701	I95-84	>	0.3	11-03-86	869-280	N=3 -34% @.3
SAH-064480	29404	I95-84	>	0.3	02-06-87	917-023	N=3 +3% @.3
SAH-063270	ALL	I95-84	=	0.308	02-07-85		N=11 2BATCHES
SAH-063270	25206	I95-84	=	0.33	10-11-84	812-267	
SAH-063270	25501	I95-84	=	0.362	01-21-85	869-018	
SAH-064307	28705	I95-84	=	0.47	02-06-87	917-020	N=6
SAH-063159	24810	I95-84	>	0.5	06-19-84	812-219	

422

SAH-063162	24822	E95-84	<	0.5	06-19-84	812-219	N=1 -87@0.5
SAH-063175	24866	E95-84	<	0.5	06-19-84	812-220	
SAH-063230	25078	E95-84	>	0.500	11-29-84	812-294	
SAH-064391	29161	E95-84	=	0.51	10-30-86	917-011	N=3
SAH-063035	24317	E95-84	>	0.6	05-07-84	812-201	
SAH-063145	24755	E95-84	>	0.6	05-18-84	812-208	
SAH-063146	24756	E95-84	>	0.6	05-18-84	812-208	
SAH-063174	24865	E95-84	=	0.706	06-19-84	812-220	
SAH-064481	29406	E95-84	>	1.0	02-06-87	917-024	N=3 -28% @1.0
SAH-064482	29411	E95-84	>	1.0	03-18-87	917-041	N=3 -41% @1.0
SAH-064064	27433	E95-84	=	1.05	07-17-86	869-263	N=6
SAH-064204	27793	E95-84	=	1.21	10-02-86	869-298	N=6
SAH-064141	27630	E95-84	>	1.25	02-24-87	917-029	N=6 -24% @1.25
SAH-064308	28717	E95-84	>	1.5	11-03-86	869-283	N=3 -16% @1.5
SAH-064193	27760	E95-84	>	2.4	07-24-86	869-269	N=3 -24% @2.4
SAH-063076	24449	E95-84	<	2.5	05-14-84	812-204	
SAH-063084	24512	E95-84	>	2.5	05-07-84	812-201	
→ SAH-064933	30441	E99-84	=	~~0.49~~ 1	12-09-87	917-138	N=3 -36 %@1.0
→ SAH-064935	30447	E99-84	≈	~~1.0~~ .79	12-09-87	917-138	N=3

423

600-7022/C

United States Patent [19]

Kathawala et al.

[11] Patent Number: 5,001,255

[45] Date of Patent: Mar. 19, 1991

[54] IDENE ANALOGS OF MEVALONOLACTONE AND DERIVATIVES THEREOF

[75] Inventors: Faizulla G. Kathawala, Mountain Lakes; Sompong Wattanasin, Hopatcong, both of N.J.

[73] Assignee: Sandoz Pharm. Corp., E. Hanover, N.J.

[21] Appl. No.: 214,560

[22] Filed: Jul. 1, 1988

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 837,479, Mar. 7, 1986, abandoned, which is a continuation-in-part of Ser. No. 677,917, Dec. 4, 1984, abandoned.

[51] Int. Cl.[5] C07C 69/76

[52] U.S. Cl. 560/56; 560/53; 556/441; 549/264; 549/291; 562/462; 562/466

[58] Field of Search 560/56, 53; 549/264, 549/291; 562/462, 466; 514/530, 569

[56] References Cited

U.S. PATENT DOCUMENTS

3,207,779	9/1965	Cutler	560/56
3,532,752	10/1970	Shen	560/56
3,668,241	6/1972	Cragoe et al.	560/56
3,983,140	9/1976	Endo et al.	260/343.5
4,006,180	2/1977	Cragoe et al.	560/56
4,012,524	3/1977	Cragoe et al.	560/56
4,057,573	11/1977	Haas et al.	560/56
4,070,539	1/1978	Cragoe et al.	560/56
4,125,731	11/1978	Sugie et al.	560/56
4,137,322	1/1979	Endo et al.	424/273
4,198,425	4/1980	Mitsui et al.	424/279
4,248,889	2/1981	Oka et al.	424/308
4,255,444	3/1981	Oka et al.	424/279
4,308,378	12/1981	Stokker	542/441
4,361,515	11/1982	Terahara et al.	549/292
4,375,475	3/1983	Willard et al.	424/279
4,474,971	10/1984	Wareing	549/214
4,588,715	5/1986	Damon	514/63
4,613,610	9/1986	Wareing	514/406
4,647,576	3/1987	Hoefle	514/422
4,654,363	3/1987	Prugh	560/56

FOREIGN PATENT DOCUMENTS

142146	5/1985	European Pat. Off. .
84/02131	6/1984	PCT Int'l Appl. .
84/02903	8/1984	PCT Int'l Appl. .
86/03488	6/1986	PCT Int'l Appl. .

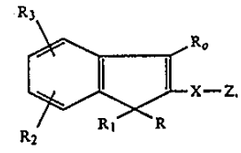
OTHER PUBLICATIONS

Hulcher, Arch. Biochem. Biophys. 146, 422–427 (1971).
Sato et al., Chem. Pharm. Bull. 28, 1509–1525 (1980).
Singer et al., Proc. Soc. Exp. Biol. Med. 102, 370–373 (1959).

Primary Examiner—Paul J. Killos
Attorney, Agent, or Firm—Gerald D. Sharkin; Richard E. Vila; Melvyn M. Kassenoff

[57] ABSTRACT

Compounds of the formula



the use thereof for inhibiting cholesterol biosynthesis and lowering the blood cholesterol level and, therefore, in the treatment of hyperlipoproteinemia and atherosclerosis, pharmaceutical compositions comprising such compounds and processes for and intermediates in the synthesis of such compounds.

27 Claims, No Drawings

12/86

NAME: Joanne M. Giesser

BASE CITY: E. Hanover

CAR NO.: _____ REGION NO.

EMPLOYEE NUMBER 05854

PERIOD COVERED

	MO.	DAY	YEAR
FROM	2	21	88
TO	2	26	88

COMMENTS:

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS MEALS (6)	BUSINESS ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1		Airplane tickets										visited Northrop King (Minneapolis), Rogers Brothers (Boise) and Zoecon (Palo Alto)
2		Newark - Minneapolis - Boise -										
3		San Francisco - Newark	939 00									
4												
5	2/21	Hotel - Minneapolis					116 60			19 99		
6	2/23	Shuttle bus to airport				15 00						
7	2/23							14	22			
8	2/23	Hotel - Boise					122 10			14 25		
9												
10	2/25	Hotel - Palo Alto					115 56					
11		Rental Car				49 67						
12												
13	2/26	Airport parking			2 00							
14												
15												
16												
17												
18												
19												
20												
21												
22												
		TOTAL EXPENSES	939 00		2 00	64 67	354 20	14 07		34 24		TOTAL EXPENSES (COLUMNS 1-9) $ 1409 13
		OFFICE USE ONLY Adj ded 1.00 cols 5					354.20					TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ 939 00
												DUE EMPLOYEE → $ 470 13

RECEIVED
Finance Division
MAR 4 1988
Travel Expense Section

XPENSES ANAGER (E) C.U.

Joanne M. Giesser

Richard C. Hile

OFFICE USE	ODOMETER READING	COMPANY FLEET CARS – MILEAGE
AUDITED BY: MM	END.	PERSONAL →
	BEG.	BUSINESS →
	DIFF.	EXPENSE DAYS

FOR OFFICE USE

WATTANASIN EXHIBIT
Exhibit S
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

Sawai Ex 1005
Page 3343 of 4322

90222/86

NAME: Joanne M. Giesser

BASE CITY: E. Hanover

CAR NO.: _____ REGION NO. _____

EMPLOYEE NUMBER 05854

PERIOD COVERED

FROM MO. 3 DAY 1 YEAR 88

TO 3 1 88

COMMENTS:

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS MEALS (6)	BUSINESS ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	3/1	Airplane tickets	158 00									Washington D.C., attended NASA patent committee meeting
2												
3		Subway tickets				3 60						
4												
5		Lunch + Dinner						19 50				
6												
7		Airport parking			4 00 ✓							
8												
9												
10												
11												
12												
13												
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	158 00 ✓		4 00 ✓	3 60 ✓		19 50 ✓				

RECEIVED
Finance Division
MAR 4 1988
Travel Expense Section

TOTAL EXPENSES (COLUMNS 1-9) $ 195 10

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ ✓ 158 00

DUE EMPLOYEE → $ 27 10

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) C.U.

OFFICE USE 60

EMPLOYEE'S FULL SIGNATURE: Joanne M. Giesser

APPROVED BY: FULL SIGNATURE Richard F Vida

OFFICE USE — AUDITED BY: MM

ODOMETER READING: END. ____ BEG. ____ DIFF. ____

COMPANY FLEET CARS – MILEAGE: PERSONAL → ____ BUSINESS → ____ EXPENSE DAYS ____

FOR OFFICE USE: 60 2/21/88 425

90222/86

NAME: Joanne M. Giesser

BASE CITY: E. Hanover

CAR NO.: — REGION NO.

EMPLOYEE NUMBER: 05854

PERIOD COVERED

	MO.	DAY	YEAR
FROM	3	15	88
TO	4	15	88

Sandoz Pharmaceuticals Corporation

TEAMSPIRIT

SANDOZ PHARMACEUTICALS

TRAVEL ~~& ENTER~~TAINMENT EXPENSE REPORT

COMMENTS:

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS MEALS (6)	BUSINESS ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	3/15	Plane tickets	~~165.75~~									
2		Taxi	179.00			10.00						Boston- visit Repligen-Sandoz Res. Corp.
3	3/16	Hotel					148.09	17.85		7.35		
4												
5												
6	3/28	Plane tickets EMP	690.00									Palo Alto, CA. visit
7		Rental car				122.99						Sandoz Crop Protection
8		Hotel (3 nights)					365.00	16.59		23.99		
9								10.03				
10								14.74				
11	3/31	Airport parking			2.00							
12												
13												
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	~~860.75~~		2.00	132.99	644.08	59.21		31.34		TOTAL EXPENSES (COLUMNS 1-9) $ ~~1743.62~~
		OFFICE USE	869.00									

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) C.U.

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ ~~869~~

DUE EMPLOYEE → $ ~~874~~ [illegible]

EMPLOYEE'S FULL SIGNATURE: Joanne M. Giesser

APPROVED BY: FULL SIGNATURE: [signature]

OFFICE USE AUDITED BY:

ODOMETER READING	
END.	
BEG.	
DIFF.	

COMPANY FLEET CARS – MILEAGE	
PERSONAL →	APR 20 1988
BUSINESS →	GG
EXPENSE DAYS	

FOR OFFICE USE

1738.62

~~869.00~~ 17...

~~869.62~~ 1559.62

426

90222/86

NAME: Joanne M. Giesser

BASE CITY: E. Hanover

CAR NO.: _____ REGION NO.

EMPLOYEE NUMBER: 05854

PERIOD COVERED

	MO.	DAY	YEAR
FROM	4	20	88
TO	4	22	88

COMMENTS:

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS MEALS (6)	BUSINESS ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	4/20	Plane tickets	325 00									Des Plaines Ill
2	4/22											Visit with Seed
3												Committee &
4							88 80					Crop Protection
5	4/20-	Hotel (2 nights)					~~177 60~~			22 11		
6	4/22						88 80					
7												
8		Taxi (Newark-Morristown)				40 00						
9												
10		Parking			10							
11												
12												
13												
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	325 00		10 00	41 00	177 60			22 11		TOTAL EXPENSES (COLUMNS 1-9) $ 575 71

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) C.U.

OFFICE USE

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ 325 00

DUE EMPLOYEE → $ 250 71

EMPLOYEE'S FULL SIGNATURE: Joanne M. Giesser

APPROVED BY: FULL SIGNATURE Richard E. Vila 4/28/88

OFFICE USE — AUDITED BY:

ODOMETER READING: END. ____ BEG. ____ DIFF. ____

COMPANY FLEET CARS – MILEAGE: PERSONAL → ____ BUSINESS → ____ EXPENSE DAYS ____

FOR OFFICE USE

MAY 13 1988

427

90222/86

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

TEAMSPIRIT

NAME: Joanne M. Giesser

BASE CITY: E. Hanover

CAR NO.: ______ REGION NO.

EMPLOYEE NUMBER: 05854

PERIOD COVERED: FROM MO. 5 DAY 2 YEAR 88 — TO 6 27 88

COMMENTS:

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS MEALS (6)	BUSINESS ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	5/2/88	Plane Tickets	178.00									Wash, DC
2		Taxi			3.00	3.25						IBA meeting
3												
4	6/15	Plane Tickets	690.00									Palo Alto - Visit
5		Hotel					242.00	25.05		32.67*		* Phone Sandoz Crop Protech
6	6/16							18.25				
7		Airport parking			5.00							
8		Rental Car				95.27						
9												
10	6/24	Plane Tickets	178.00		3.00							Wash, DC
11		Metro Ticket				1.00						IBA Meeting
12												
13												
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												TOTAL EXPENSES (COLUMNS 1-9)
		TOTAL EXPENSES	1,046.00		11.00	99.52	242.00	43.30		32.67		$ 1,474.49

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) C.U.

OFFICE USE

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ 1,046.00

DUE EMPLOYEE → $ 428.49

EMPLOYEE'S FULL SIGNATURE: Joanne M. Giesser

APPROVED BY: FULL SIGNATURE: [signature]

OFFICE USE — AUDITED BY:

ODOMETER READING — END. / BEG. / DIFF.

COMPANY FLEET CARS – MILEAGE — PERSONAL → / BUSINESS → / EXPENSE DAYS

FOR OFFICE USE: 11/21 428

90222/86

NAME: Joanne M. Giesser

BASE CITY:

CAR NO.: REGION NO.

EMPLOYEE NUMBER: 05854

PERIOD COVERED

FROM: MO. 07 DAY 12 YEAR 88

TO: 07 14 88

COMMENTS:

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS MEALS (6)	BUSINESS ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	7/12	Airline tickets	253 00									Des Plaines, Ill.
2		Cab (E. Hanover- Newark)				38						Sandoz Crop Protection
3		Cab to hotel				11 00						Patent Committee Meeting
4		Hotel					75 60	11 72		5 60		
5								2 50				(no receipt)
6		Cab (Newark- Morristown)				35 00						
7												
8												
9												
10												
11												
12												
13												
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	253 00			84 00	75 60	14 22		5 60		TOTAL EXPENSES (COLUMNS 1-9) $ 432 42

RECEIVED
Finance Division
JUL 19 1988
Travel Expense Section

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) C.U.

OFFICE USE

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ 253

DUE EMPLOYEE → $ 179

EMPLOYEE'S FULL SIGNATURE: Joanne M. Giesser

APPROVED BY: FULL SIGNATURE Richard E. Vela

OFFICE USE	ODOMETER READING		COMPANY FLEET CARS – MILEAGE	
AUDITED BY:	END.		PERSONAL →	
	BEG.		BUSINESS →	
	DIFF.		EXPENSE DAYS	

FOR OFFICE US

JL 22 1988

429

90222/86

NAME: Joanne M. Giesser

BASE CITY: E. Hanover

CAR NO.: _____ REGION NO. _____

EMPLOYEE NUMBER: 05854

PERIOD COVERED: FROM MO. 08 DAY 20 YEAR 88 — TO 09 20 88

TEAMSPIRIT

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

COMMENTS: Swiss franc exchange rate - 1 Fr = $0.66.

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS MEALS (6)	BUSINESS ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	8/29	Plane tickets	690 00									Palo Alto - Patent
2	8/29-9/1	hotel room					115 50	12 34		23 15		Policy meeting w/
3							115 50					Oesterup King + Sandoz
4		Airport parking			15 00		115 50					crop Protection
5												
6												
7	9/6	Passport								67 00		Basle - Patent policy
8		Passport photo (no receipt)								5 00		(seeds) meeting
9	9/10	Plane tickets	209 00									(Authorization attached
10		Limo (Morristown - JFK)				91 20						
11	9/11-14	Hotel					6 60	6 60				
12		Limo (JFK - Morristown-shared)				54 50	59 40					
13							59 40					
14							59 40					
15							59 40					
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	2789 00		15 00	145 70	584 10	18 94		95 15		TOTAL EXPENSES (COLUMNS 1-9) $

RECEIVED
Finance Division
SEP 20 1988
Travel Expense Section

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) _____ C.U. _____

OFFICE USE

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ [illegible]

DUE EMPLOYEE → $ [illegible]

EMPLOYEE'S FULL SIGNATURE: Joanne M. Giesser

APPROVED BY: FULL SIGNATURE [signature]

OFFICE USE — AUDITED BY: KH

ODOMETER READING: END. _____ BEG. _____ DIFF. _____

COMPANY FLEET CARS – MILEAGE: PERSONAL → _____ BUSINESS → SEP 23 1988 EXPENSE DAYS KH

FOR OFFICE USE: 3647. 2789. 858.8

430

Sawai Ex 1005
Page 3349 of 4322

90222/86

NAME: Joanne M. Giesser

BASE CITY: E. Hanover

CAR NO.: _____ REGION NO.

EMPLOYEE NUMBER: 05854

PERIOD COVERED

	MO.	DAY	YEAR
FROM	9	20	88
TO	10	20	88

COMMENTS:

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS MEALS (6)	BUSINESS ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	10/9	Plane tickets	690 00									Palo Alto - Sandoz
2	10/7	Car rental				56 80						Crop Protection Patent
3	10/9-11	Hotel					121 00			21 80		Committee Meeting
4		Phone										
5		Food						6 72				
6	10/11	Taxi (Newark-Morristown)				35 00						
7												
8												
9	10/16	Plane Tickets	549 00									Madison, WI - visit
10	10/16-17	Hotel					70 56			4 77		Agrigenetics, return
11		Phone										via Wash. D.C.
12		Food						27 07				
13		Parking			18 00							
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	1239 00		18 00	91 80	383 12	33 79		26 57		

RECEIVED
Finance Division
OCT 21 1988
Travel Expense Section

TOTAL EXPENSES (COLUMNS 1-9): $ 1792 28

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ 1239 ✓ 00

DUE EMPLOYEE → $ 553 28

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) C.U.

OFFICE USE

EMPLOYEE'S FULL SIGNATURE: Joanne M. Giesser

APPROVED BY: FULL SIGNATURE Richard E. Vida

OFFICE USE — AUDITED BY:

ODOMETER READING: END. / BEG. / DIFF.

COMPANY FLEET CARS – MILEAGE: PERSONAL → / BUSINESS → / EXPENSE DAYS

FOR OFFICE USE

EH

OCT 24 1988

431

NAME: Joanne M. Giesser | 05854

BASE CITY: E. Hanover | PERIOD COVERED

CAR NO.: | REGION NO. | FROM MO. 10 DAY 20 YEAR 88 | TO 11 20 88

COMMENTS:

TEAMSPIRIT

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS: MEALS (6)	BUSINESS: ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	10/27	Plane tickets	218 00									Boulder, CO - inspect patent files of Agrigenetics
2	10/27	Morristown - Newark				45 54						
3	10/27	Hotel					49 19					
4		Phone								2 11		
5	10/28	Rental car				51 07						
6	10/28	Newark - Morristown				57 54						
7												
8												
9												
10												
11												
12												
13												
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	218 00	+	+	154 15	49 19	+	+	2 11		

RECEIVED
Finance Division
NOV 02 1988
Travel Expense Section

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) | C.U.

OFFICE USE

TOTAL EXPENSES (COLUMNS 1-9): $ 423 45

TOTAL PAID BY CO. AIR & RAIL (Col. 1) →: $ 218 00

DUE EMPLOYEE →: $ 205 45

EMPLOYEE'S FULL SIGNATURE: Joanne M. Giesser

APPROVED BY: FULL SIGNATURE Richard E. Wilson

OFFICE USE — AUDITED BY:

ODOMETER READING: END. | BEG. | DIFF.

COMPANY FLEET CARS — MILEAGE: PERSONAL → | BUSINESS → | EXPENSE DAYS

FOR OFFICE USE

NOV 14 1988

432

90222/86

NAME: Joanne M. Giesser

BASE CITY: E. Hanover

CAR NO.: _____ REGION NO. _____

EMPLOYEE NUMBER: 05854

PERIOD COVERED

	MO.	DAY	YEAR
FROM	12	1	88
TO	12	31	88

COMMENTS:

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS MEALS (6)	BUSINESS ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	12/02	Airline tickets	595 00									*Chicago- delivered
2	12/03											patent lecture to
3	12/6	Hotel					157 36	7 44				Northrup King group
4	12/5									24 80		phone charges
5	12/6	cab to hotel				12 50						
6	12/8	van service to airport				9 75						no receipt available
7								4 80				
8	12/8	airport parking			15 00							
9												
10												
11												
12												
13												
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	595 00		15 00	22 25	157 36	12 24		24 80		

DEC 20

TOTAL EXPENSES (COLUMNS 1-9): $ 826 65

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ 595 00

DUE EMPLOYEE → $ 231 65

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) _____ C.U. _____

OFFICE USE

EMPLOYEE'S FULL SIGNATURE: Joanne M. Giesser

APPROVED BY: FULL SIGNATURE Richard E. Uhle

OFFICE USE — AUDITED BY:

ODOMETER READING: END. _____ BEG. _____ DIFF. _____

COMPANY FLEET CARS – MILEAGE: PERSONAL → _____ BUSINESS → _____ EXPENSE DAYS _____

FOR OFFICE USE: JAN 18 433

90222/86

NAME: Joanne M. Giesser

BASE CITY: E. Hanover

CAR NO.: _____ REGION NO. _____

EMPLOYEE NUMBER: 05854

PERIOD COVERED: FROM MO. 1 DAY 1 YEAR 89 — TO 1 20 89

COMMENTS:

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS MEALS (6)	BUSINESS ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	1/4	Plane tickets	1078 00									Minneapolis (Northrup King Patent Committee)
2												Palo Alto (Zoecon Patent Committee)
3												
4												
5												
6	1/8	Taxi (Airport - Hotel)				30 00						
7	1/9	Taxi (Hotel - Northrup King)				6 00						
8	1/9	Hotel					160 42			8 52		(phone)
9	1/11	Rental Car				92 69						
10	1/11	Hotel					242 00	7 06		24 27		(phone)
11	1/12	Parking at Airport			2 00	✓	121 00					no receipt
12						✓	121 00					
13												
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	1078 00		2 00	128 69	302 42	7 06		32 79		TOTAL EXPENSES (COLUMNS 1-9) $ 1550

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) _____ C.U. _____

OFFICE USE

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ 1078

DUE EMPLOYEE → $ 472

EMPLOYEE'S FULL SIGNATURE: Joanne M. Giesser

APPROVED BY: FULL SIGNATURE Richard E. Vila

OFFICE USE — AUDITED BY: _____

ODOMETER READING: END. _____ BEG. _____ DIFF. _____

COMPANY FLEET CARS – MILEAGE: PERSONAL → _____ BUSINESS → _____ EXPENSE DAYS _____

FOR OFFICE USE: JAN 24 1989

434

90222/86

NAME: Joanne M. Giesser

BASE CITY: E. Hanover

CAR NO.: REGION NO.

EMPLOYEE NUMBER 05854

PERIOD COVERED

	MO.	DAY	YEAR
FROM	2	1	89
TO	2	28	89

COMMENTS:

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS MEALS (6)	BUSINESS ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	2/21	Plane tickets	844 00 ✓									Boise, Id. Patent
2												Lecture to Rogers Bros.
3	2/28-	Hotel					~~84~~ 40	~~35 87~~ ✓		6 39		phone
4	3/2						44 40	6 67 ✓				
5		Airport parking			2 00							No receipt available
6												
7												
8												
9												
10												
11												
12												
13												
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	$44 00 ✓		2 00		88 80	42 49 ✓		6 39		

Finance Division

MAR 09 1989

Travel Expense

TOTAL EXPENSES (COLUMNS 1-9) $ ~~1,12~~ 983

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) C.U.

OFFICE USE

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ 844

DUE EMPLOYEE → $ 139

435 ✓

EMPLOYEE'S FULL SIGNATURE: Joanne M. Giesser

APPROVED BY: FULL SIGNATURE

OFFICE USE — AUDITED BY:

ODOMETER READING	
END.	
BEG.	
DIFF.	

COMPANY FLEET CARS – MILEAGE	
PERSONAL →	
BUSINESS →	
EXPENSE DAYS	

FOR OFFICE USE

MAR 20 1989 89

90222/86

NAME: Joanne M. Giesser

BASE CITY: E. Hanover

CAR NO.: — REGION NO.

EMPLOYEE NUMBER 05854

PERIOD COVERED

	MO.	DAY	YEAR
FROM	03	2	89
TO	03	31	89

COMMENTS:

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS MEALS (6)	BUSINESS ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	3/20	Plane tickets	422 00									Stanton, MN Northrup King Research Mgmt Comm. Meeting
2												
3	3/20	Car rental				94 45						
4												
5	3/20	Hotel					61 04	2 70		7 90		Phone
6								2 50				no receipt
7												
8	3/31	Parking			15 45							NYC - Judges Dinner
9		Tolls			4 00							
10												
11												
12												
13												
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	422 00		19 45	94 45	61 04	5 20		7 90		TOTAL EXPENSES (COLUMNS 1-9)
												$ 610 04
												TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ 422 00
												DUE EMPLOYEE → $ 188 04

RECEIVED

APR 4 19

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) C.U.

OFFICE USE

EMPLOYEE'S FULL SIGNATURE: Joanne M. Giesser

APPROVED BY: FULL SIGNATURE Richard S. Vila MS

OFFICE USE — AUDITED BY:

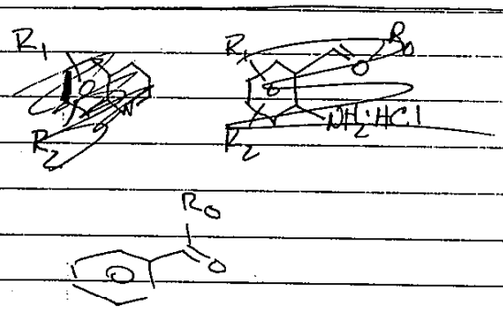
ODOMETER READING: END. / BEG. / DIFF.

COMPANY FLEET CARS — MILEAGE: PERSONAL → / BUSINESS → / EXPENSE DAYS

FOR OFFICE USE: APR 13 1989 RS

436

Add before pg 4



A_1 ~~reflux~~ – condensation

X_1 = any alkyl group

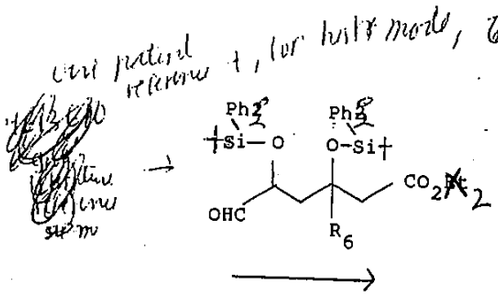
X_2 = R_{13} of indene

X_3 = any alkyl

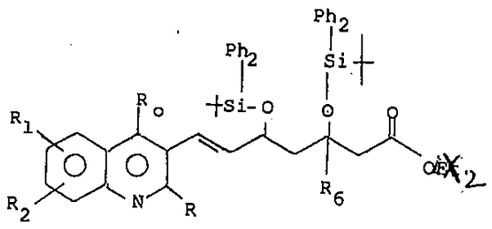
$X_{3'}$ = any ethyl or methyl

R_6 as defined

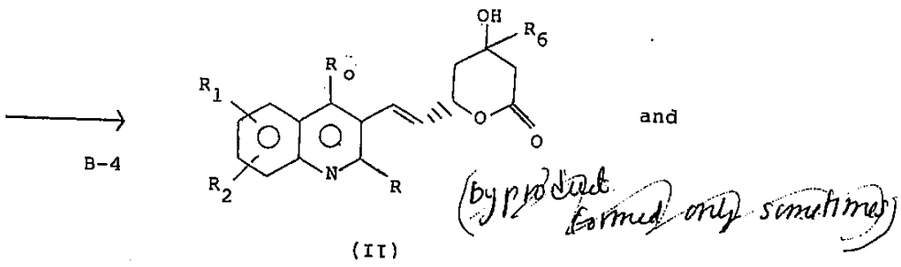
List of all var before table p11
incorp Rx scheme into example



B-3



(XVI)

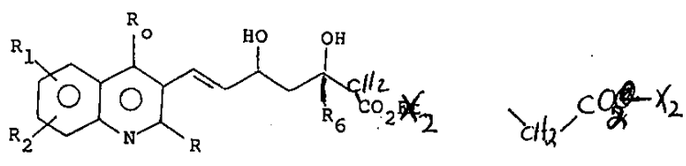


B-4

and

(by product formed only sometimes)

(II)



(I)

Need 1) Statement that when any compound of Formula A contains an hydroxy group as R_1-R_5, said hydroxy group is protected by a diphenyl t-butylsilyl group in the compounds of formula VII - XI and XIV - XVI which group is cleaved at the end of the synthesis by Reaction B-4.

2) Hydrogenation reaction to get compounds wherein X is $-CH_2CH_2-$ or

(3) Process for obtaining compounds wherein X is (4-CH=CH-(CH)). Add phosphonium Wittig equivalent to Reaction B-2

(4) Process for Q = $-\overset{O}{\overset{\|}{C}}-$ compound

(5) Process for lactonization, hydrolysis of lactone intraconversion of esters, salts, free acid, etc.

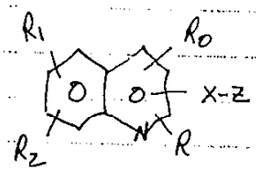
7064

2-composition
3- method

Insert

but are not limited to the following

1) 1) ~~those~~ Compounds which are included in ~~the~~ formula of ~~the~~ Proposed Count 1 including ~~such as~~ (referring to the formula of Proposed Count 1)



i) Compound 63-366, where $R_1 = H$; $R_2 = H$; R_D = 3,5-dimethylphenyl; R = isopropyl; X = -CH=CH-; ~~and~~ Z = (a); Q = $-\underset{OH}{C}-$; and R_g = ethyl

ii) Compound 63-548, where $R_1 = H$; $R_2 = H$; R_D = 3,5-dimethylphenyl; R = CH_3, X = -CH=CH-; Z = (a); Q = $-\underset{OH}{C}-$; and R_7 = ethyl.

iii) Compound 63-549, where $R_1 = H$; $R_2 = H$; R_D = 3,5-dimethylphenyl; R = CH_3, X = -CH=CH-; and Z = (b).

iv) Compound 64-933, where $R_1 = H$; [redacted]; R_D = phenyl; R = isopropyl; X = -CH=CH-; Z = (a); Q = $-\underset{OH}{C}-$ and R_g = ethyl

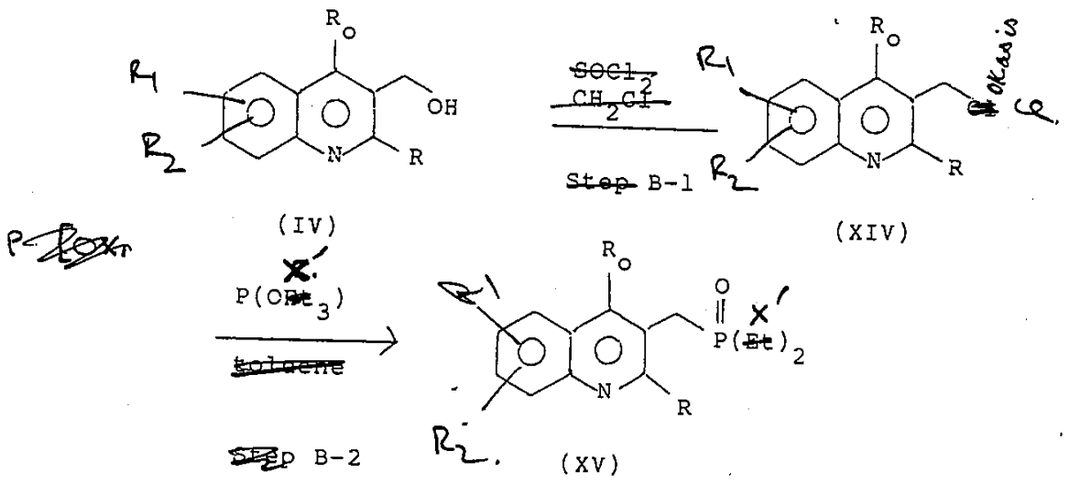
v) Compound 64-934, where $R_1 = H$; $R_2 = H$; R_D = phenyl; R = isopropyl; X = -CH=CH; Z = (a); Q = $-\underset{OH}{C}-$; $R_7 = M$; $M = Na^+$

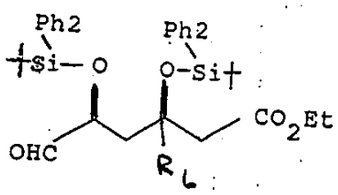
vi) Compound 64-935, where $R_1 = H$; $R_2 = H$; R_D = 4-fluorophenyl, R = isopropyl; Z = (a); Q = $-\underset{OH}{C}-$; R_g = ethyl

Starting material III is known and can be obtained by methods described by Morrison and Mulholland, 1958, J. Chem. Soc. p. 2702, which is hereby incorporated by reference. Next, V is reduced with lithium aluminum hydride, (LAH) to give VI. This reaction has also been described by Fehnel, 1968. J. Heterocyclic Chem 4:565, which is also hereby incorporated by reference. In Step A-3, VI is oxidized to VII. Step A-4 is a Wittig reaction producing VIII. Compound VIII is then reduced using diisobutylaluminum hydride (DIBAL) to IX. In Step A-6, IX is oxidized to X. The aldehyde X is then reacted with ethyl acetoacetate in Step A-7 to give XI. Compound XI is reduced to give XII. Next, in Step A-9, XII is hydrolyzed to the salt form XIII.

Compounds of both Formula I and II may be made according to Reaction Scheme B. Starting material for Reaction Scheme B is Compound VI from Reaction Scheme A.

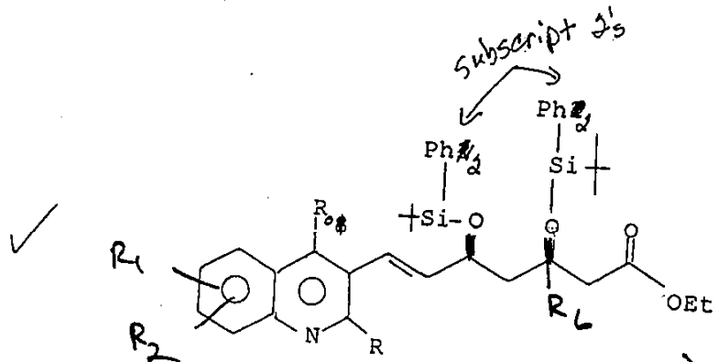
REACTION SCHEME B





~~nBuLi / THF~~

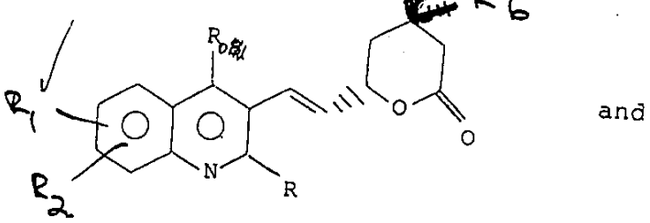
~~Step~~ B-3



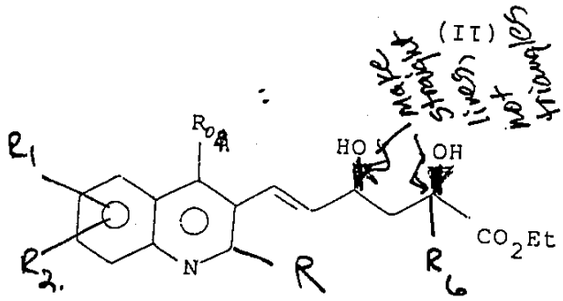
(XVI)

~~nBu4NF~~

~~Step~~ B-4



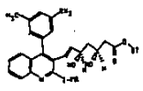
and



(I)

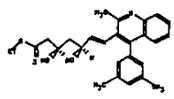
3A

11-26-84
MW 461.606
LD
SAH-063366
25496 D OR E OR C
1079-111-19
KATH 299-84
CSI



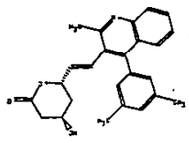
2

05-17-85
MW 433.552
LD 13329.0
SAH-063548
26080 C OR D OR E
1127-011-34
KATH 299-84
CSI, CSTC, CSTV



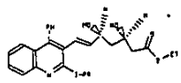
2

05-17-85
MW 387.483
LD 13329.0
SAH-063549
26082 C OR D OR E
1127-011-37
KATH 299-84
CSI



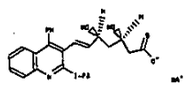
1

09-21-87
MW 433.552
LD
SAH-064933
30441 D OR E OR C
1206-176-43
WATT 299-84
CSI CSIC CSIV



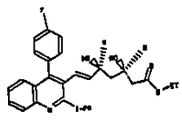
3B

09-21-87
MW 427.48
LD
SAH-064934 NA
30442 D OR E OR C
1206-179-30
WATT 299-84
CSI CSIC CSIV

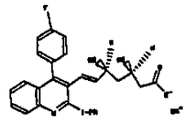


3C

09-21-87
MW 451.543
LD
SAH-064935
30447 D OR E OR C
1206-190-41
WATT 299-84
CSI CSIC CSIV



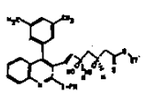
09-22-87
MW 445.47
LD
SAH-064936 NA
30448 D OR E OR C
1206-201-30
WATT 299-84
CSI CSIC CSIV



4

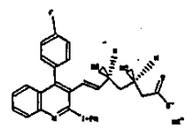
Ex 4

11-26-84
MW 461.606
LD
SAH-063366
25496 D OR E OR C
1079-111-19
KATH 299-84
CSI

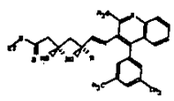


Ex 3A

09-22-87
MW 445.47
LD
SAH-064936 NA
30448 D OR E OR C
1206-201-30
WATT 299-84
CSI CSIC CSIV

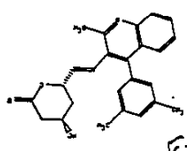


05-17-85
MW 433.552
LD 13329.0
SAH-063548
26080 C OR D OR E
1127-011-34
KATH 299-84
CSI. CSTC. CSTV



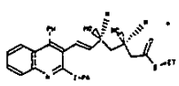
Ex 2

05-17-85
MW 387.483
LD 13329.0
SAH-063549
26082 C OR D OR E
1127-011-37
KATH 299-84
CSI



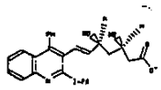
Ex 2

09-21-87
MW 433.552
LD
SAH-064933
30441 D OR E OR C
1206-176-43
WATT 299-84
CSI CSIC CSIV



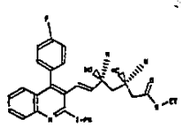
Ex 1

09-21-87
MW 427.48
LD
SAH-064934 NA
30442 D OR E OR C
1206-179-30
WATT 299-84
CSI CSIC CSIV



Ex 3B

09-21-87
MW 451.543
LD
SAH-064935
30447 D OR E OR C
1206-190-41
WATT 299-84
CSI CSIC CSIV



Ex 3C

DISCLOSURE
299-84

Back mail 5/4/89

LIST FOR PUBLICATION CLEARANCES

1) Running number of publication: 4751 (Will be attributed by ST)

2) Names of all the authors:

S. WATTANASIN/F. G. KATHAWALA/R. PATEL/T. SCALLEN/
R. G. ENGSTROM/D. B. WEINSTEIN

3) Full title of the publication:

QUINOLINES AS HMG-CoA REDUCTASE INHIBITORS

4) Date of the receipt of the publication:

APRIL 4, 1989

5) Type of publication (lecture/article, poster/abstract or full publication) and proposed date of publication (if known):

POSTER - 5TH SCI-RSC MEDICINAL CHEMISTRY SYMPOSIUM CHURCHILL COLLEGE, CAMBRIDGE, SEPTEMBER 10-13, 1989

6) Bereiche: HANOVER,

7) SB Patent Department: MRS. J. M. GIESSER Joanne M. Giesser

8) Subject matter ("Stichwort"), e.g. "Zaditen", "20-511", "Allylamines", "HPLC-apparatus" etc. and/or Case-No. if possible:
The compounds are covered in Case 600-7101
63-366 63-549 64-934 64-936
63-548 64-933 64-935

9) Date of return of the publication to source:

10) PA comments to source:

☐ No Objection

☐ Objection

WATTANASIN EXHIBIT
Exhibit S-2
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

Exhibit No. S2 ID
Date 4-9-93
DiAsio Reporting

Scientific Publication Release Request

SANDOZ

Name of Requestor	Date
Dr. S. Wattanasin	3/30/89

I. STATEMENT OF REQUEST

I request release of the attached ☐ *manuscript,* ☐ *abstract,* ☐ *lecture* ☐ *other* Poster

By (names of all authors)

S. Wattanasin, F. G. Kathawala, R. Patel, T. Scallen

R. G. Engstrom, D. B. Weinstein

Entitled

Quinolines as HMG-CoA Reductase Inhibitors

For Disclosure in (periodical, symposium, meeting, correspondence, etc.) on (date, if known).

5th SCI-RSC Medicinal Chemistry Symposium

Churchill College, Cambridge September 10-13, 1989

Listed below in numerical order are SANDOZ compounds:

63-366	64-933	64-936
63-548	64-934	
63-549	64-935	

PATENT AND TRADEMARK DEPT.

APR 4 - 1989

JMG

II. CIRCULATION ORDER, RECOMMENDATIONS, AND ACTION

CO-AUTHOR APPROVAL (Initials)

1. Supervisor Dr. F. G. Kathawala FGK	☒ Approve	☐ Withhold	Date 4/3/89
2. Department Director Dr. F. G. Kathawala FGK	☒ Approve	☐ Withhold	Date 4/3/89
3. Patent Department Joanne M. Giesser	☒ Approve	☐ Withhold	Date 4/19/89
4. V.P. Clinical or Preclinical Research	☐ Approve	☐ Withhold	Date

COMMENTS:

The material in this abstract is covered under Case No. 600-7101-U.S., Quinoline Analogs of Mevalonolactone and Derivatives Thereof, which was filed with the Patent Office on March 3, 1989.
SIMILAR WORK HAS APPEARED AFTER THE START OF OUR WORK & COMPLETION IN A PATENT FILED BY WARNER LAMBERT FGK.

5. President *SANDOZ RESEARCH INSTITUTE*	☐ Released	☐ Withheld	Date

86704/84

QUINOLINES AS HMG-CoA REDUCTASE INHIBITORS.

S. Wattanasin[1], F.G. Kathawala[1], R. Patel[1], T. Scallen[2], R.G. Engstrom[1], and D.B. Weinstein[1]

[1]Sandoz Research Institute, E. Hanover, New Jersey 07936

[2]Department of Biochemistry, School of Medicine, University of New Mexico, Albuquerque, New Mexico 87131

Inhibition of HMG-CoA reductase, the rate limiting enzyme in cholesterol biosynthesis, has proved to be an effective method of lowering serum low density lipoprotein(LDL-C) levels in both animals and man. Efforts at Sandoz Research Institute in the design and synthesis of new HMG-CoA reductase inhibitors have led to the discoverry of a number of classes of compounds which inhibit the enzyme HMG-CoA reductase. We present here the synthesis of quinolines as potent inhibitors of this enzyme *in vitro* and cholesterol biosynthesis *in vivo*.

April 19, 1989

Dr. S. Wattanasin/
Dr. F. Kathawala

Joanne M. Giesser

Abstract entitled:
"Quinolines as HMG-CoA Reductase Inhibitors"

The above abstract to be presented at the 5th SCI-RSC Medicinal Chemistry Symposium Churchill College, Cambridge, September 10-13 is approved by the Patent Department. However, the full text will still have to be reviewed and cleared by this department before presentation.

Joanne M. Giesser

JMG:lmc
Enc.

SANDOZ

Patent and Trademark Department
59 Route 10
E. Hanover, New Jersey 07936

Telex 240867
Telefax (201) 503-8807

May 4, 1989

SANDOZ LTD.
Patents and Trademarks Division
CH-4002
Basle, Switzerland

Re: Clearance for Abstract Entitled
"QUINOLINES AS HMG-CoA REDUCTASE
INHIBITORS"
Ref: 3700/RA

Dear Sirs:

Enclosed please find the Publication Clearance regarding the above-identified abstract.

We look forward to receiving the corresponding number in due course.

Very truly yours,

Linda C. Rothwell

Linda C. Rothwell

LCR
Enc. Publication Clearance

Basle Mail 6/15/89

LIST FOR PUBLICATION CLEARANCES

1) Running number of publication: 4878 (Will be attributed by ST)

2) Names of all the authors:

S. WATTANASIN/F.G. KATHAWALA/R. PATEL/T. SCALLEN/
R.G. ENGSTROM/D.B. WEINSTEIN

3) Full title of the publication:

QUINOLINES AS HMG-CoA REDUCTASE INHIBITORS

4) Date of the receipt of the publication:

MAY 23, 1989

5) Type of publication (lecture/article, poster/abstract or full publication) and proposed date of publication (if known):

Poster for 5th SCI-RSC Medicinal Chemistry Symposium
Churchill College, Cambridge
September 10-13, 1989

6) Bereiche: HANOVER

7) SB Patent Department: MRS. GIESSER Joanne M. Giesser

8) Subject matter ("Stichwort"), e.g. "Zaditen", "20-511", "Allylamines", "HPLC-apparatus" etc. and/or Case-No. if possible:
The compounds are covered in case 600-7101
63-366 64-933 64-936
63-548 64-934
63-549 64-935

9) Date of return of the publication to source:

10) PA comments to source:

☒ No Objection

☐ Objection

Scientific Publication Release Request

SANDOZ

Name of Requestor: Dr. S. Wattanasin

Date: 5/12/89 ~~3/30/89~~

I. STATEMENT OF REQUEST

I request release of the attached ☐ *manuscript,* ☐ *abstract,* ☐ *lecture* ☐ *other* Poster

By (names of all authors)

S. Wattanasin, F. G. Kathawala, R. Patel, T. Scallen

R. G. Engstrom, D. B. Weinstein

Entitled

Quinolines as HMG-CoA Reductase Inhibitors

For Disclosure in (periodical, symposium, meeting, correspondence, etc.) on (date, if known).

5th SCI-RSC Medicinal Chemistry Symposium

Churchill College, Cambridge September 10-13, 1989

Listed below in numerical order are SANDOZ compounds:

63-366
63-548
63-549
64-933
64-934
64-935
64-936

PATENT AND TRADEMARK DEPT.
MAY 23 1989
JMG

II. CIRCULATION ORDER, RECOMMENDATIONS, AND ACTION

CO-AUTHOR APPROVAL (Initials)

1. Supervisor Dr. F. G. Kathawala FGKathawala	☒ Approve	☐ Withhold	Date 5/19/89
2. Department Director Dr. F. G. Kathawala FGKathawala	☒ Approve	☐ Withhold	Date 5/19/89
3. Patent Department	☐ Approve	☐ Withhold	Date
4. V.P. Clinical or Preclinical Research	☐ Approve	☐ Withhold	Date

COMMENTS:

The material in this abstract is covered under Case No. 600-7101-U.S., Quinoline Analogs of Mevalonolactone and Derivatives Thereof, which was filed with the Patent Office on March 3, 1989.

The abstract of this poster had been approved.

5. President *SANDOZ RESEARCH INSTITUTE*	☐ Released	☐ Withheld	Date

86704/01

QUINOLINES AS HMG-CoA REDUCTASE INHIBITORS.

S. Wattanasin[1], F.G. Kathawala[1], R. Patel[1], T. Scallen[2], R.G. Engstrom[1], and D.B. Weinstein[1]

[1]Sandoz Research Institute, E. Hanover, New Jersey 07936

[2]Department of Biochemistry, School of Medicine, University of New Mexico, Albuquerque, New Mexico 87131

Inhibition of HMG-CoA reductase, the rate limiting enzyme in cholesterol biosynthesis, has proved to be an effective method of lowering serum low density lipoprotein(LDL-C) levels in both animals and man. Efforts at Sandoz Research Institute in the design and synthesis of new HMG-CoA reductase inhibitors have led to the discovery of a number of classes of compounds which inhibit the enzyme HMG-CoA reductase. We present here the synthesis of quinolines as potent inhibitors of this enzyme *in vitro* and cholesterol biosynthesis *in vivo*.

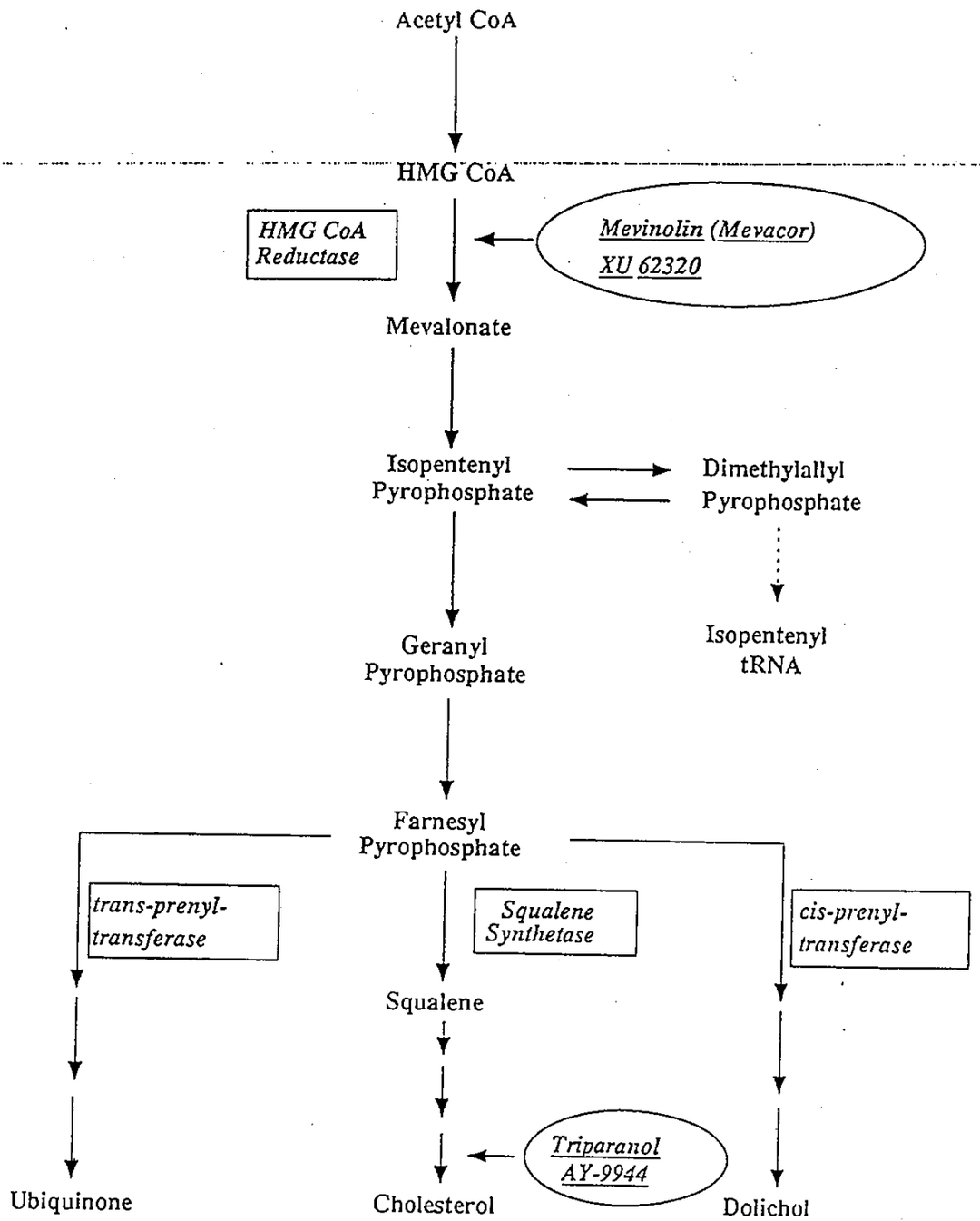
INTRODUCTION

Inhibition of 3-hydroxy-3-methylglutaryl-coenzymeA, the rate-limiting enzyme in cholesterol biosynthesis, has proved to be an effective method of lowering serum low density lipoprotein (LDL-C) levels in both animals and man. Epidemiological evidence implicating elevated LDL-C as a major risk factor for the development of coronary heart disease, have stimulated intensive efforts directed towards the development of agents affecting serum LDL-C levels.

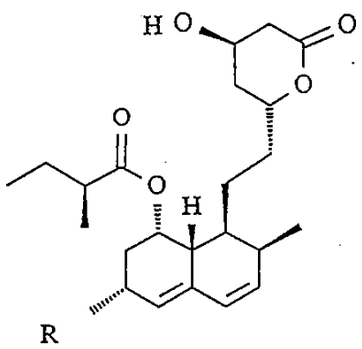
Recent reports have described XU 62-320, an indole analog of compactin and mevinolin, as one of the most potent HMG-CoA reductase inhibitors both in vitro and in vivo studies.

Discovery of XU 62-320 has prompted a search of a variety of new structural prototypes as potential inhibitors of HMG-CoA reductase. Described in this paper are the results of our initial study with a series of quinoline derivatives as HMG-CoA reductase inhibitors.

q-intro

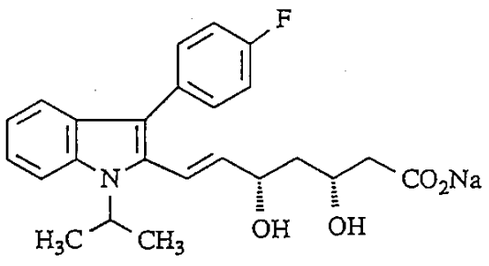

Acetyl CoA
HMG CoA
HMG CoA Reductase
Mevinolin (Mevacor)
XU 62320
Mevalonate
Isopentenyl Pyrophosphate
Dimethylallyl Pyrophosphate
Isopentenyl tRNA
Geranyl Pyrophosphate
Farnesyl Pyrophosphate
trans-prenyl-transferase
Squalene Synthetase
cis-prenyl-transferase
Squalene
Triparanol
AY-9944
Ubiquinone
Cholesterol
Dolichol

HMG-CoA REDUCTASE INHIBITORS



R = H; COMPACTIN

R = Me ; MEVINOLIN (LOVASTATIN)

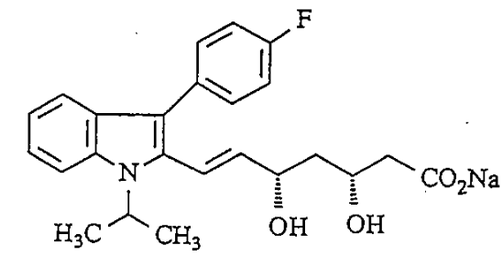


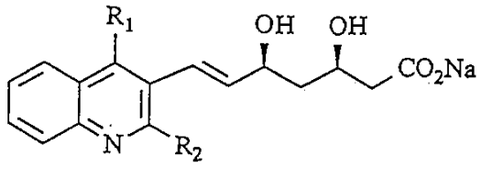
XU 62-320

q2
slide1

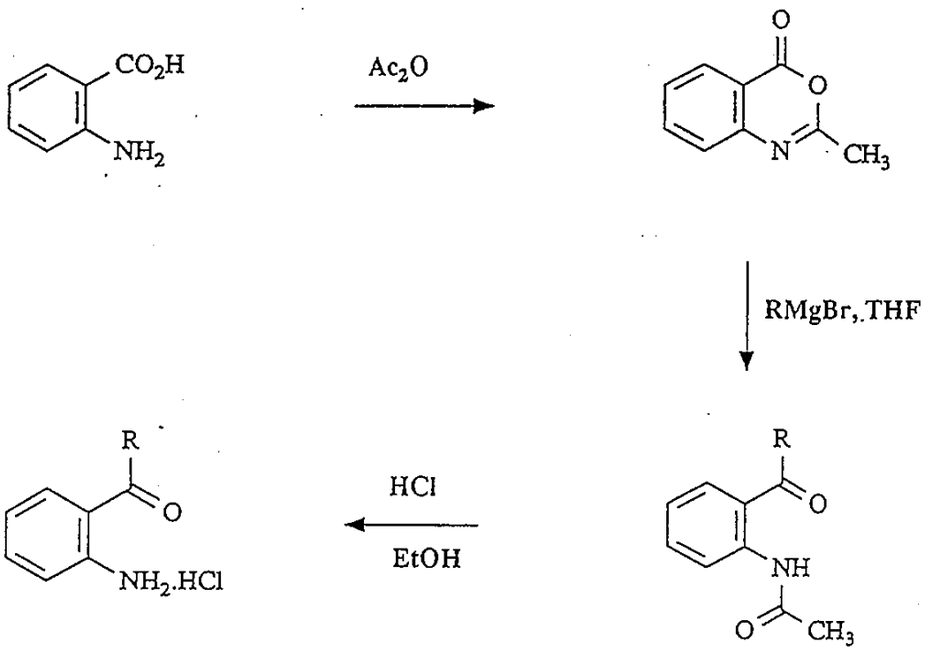
GENERATION OF NEW LEADS

INDOLE XU 62-320



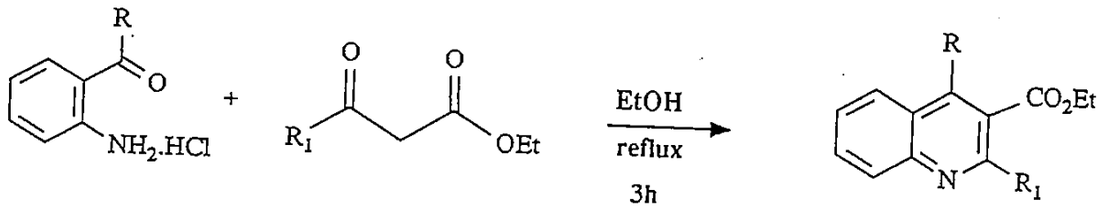


SYNTHESIS OF ortho-AMINO KETONES



R = 3,5-Dimethylphenyl
= isoPropyl
= 4-Fluorophenyl

SYNTHESIS OF 2,3,4-SUBSTITUTED QUINOLINES

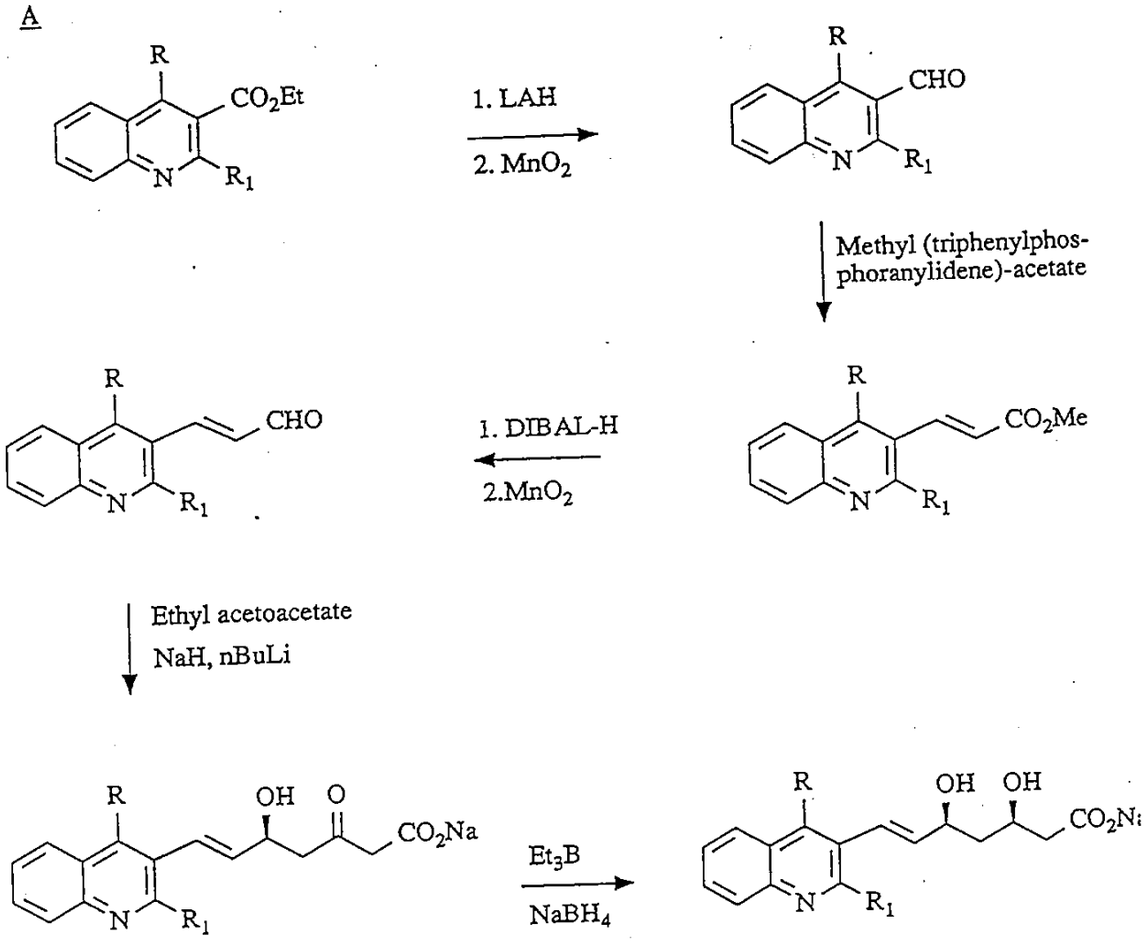


65-85%

R	R_1
i-Propyl	Me
Ph	i-Propyl
3,5-Dimethyl	4-Fluorophenyl
4-Fluorophenyl	

INTRODUCTION OF THE DIHYDROXY SIDECHAIN

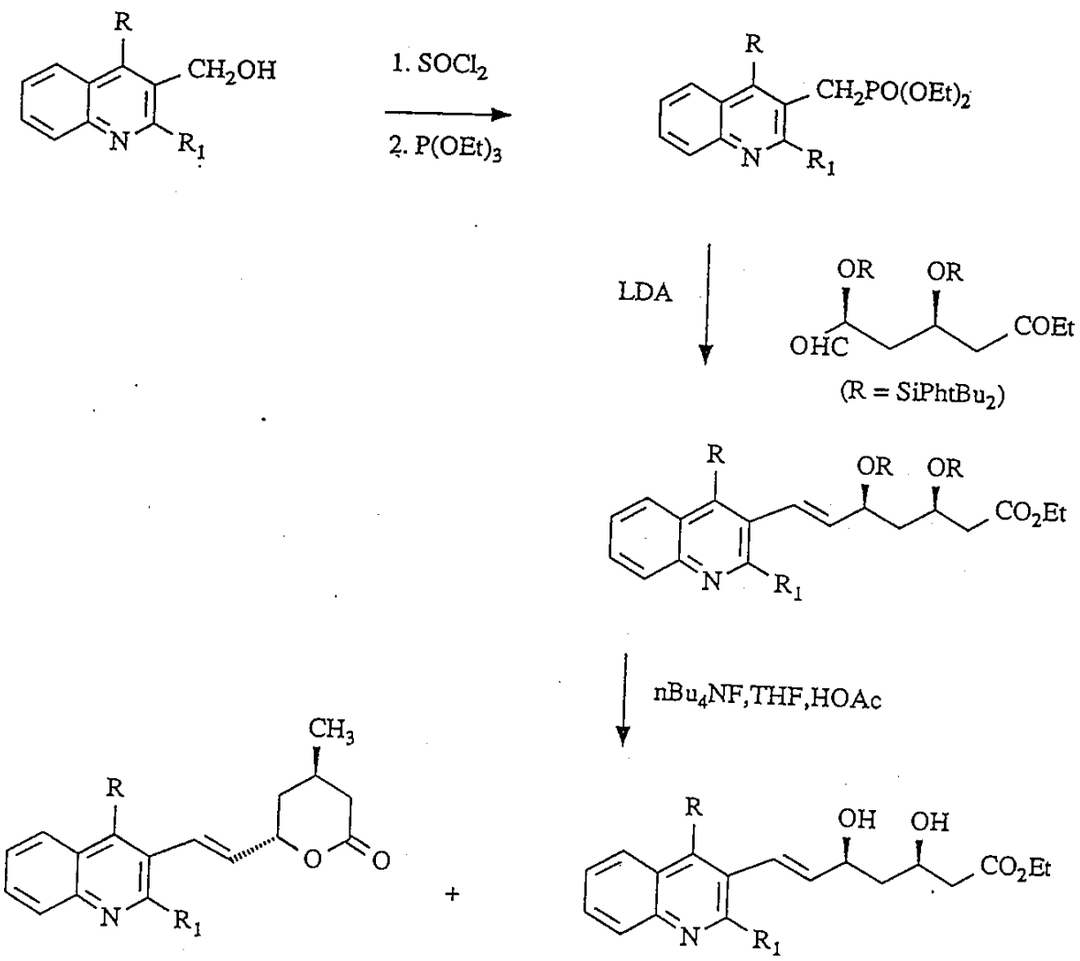
A



q6

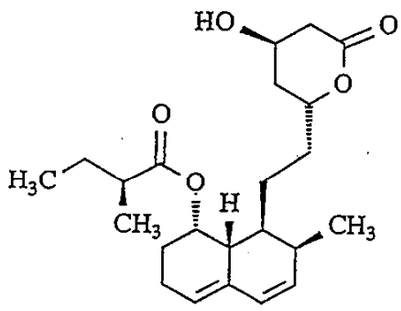
INTRODUCTION OF THE DIHYDROXY SIDECHAIN

B

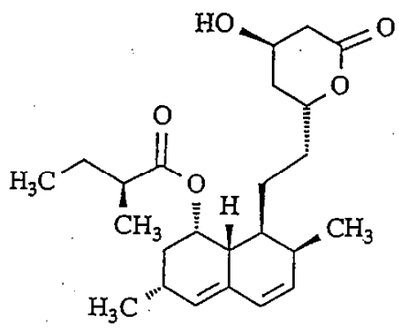


INHIBITORY EFFECT ON HMG-C0A REDUCTASE (Rat Liver Microsome)

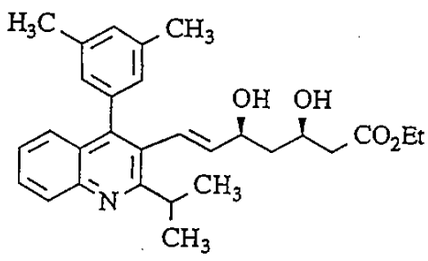
RELATIVE POTENCY*



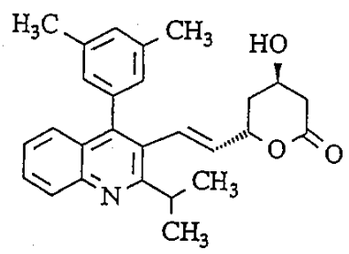
Compactin
1



Mevinoline
7.2



SDZ 63-366
0.64

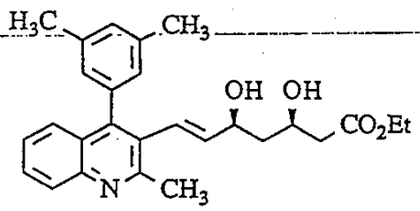


SDZ 63-549
0.14

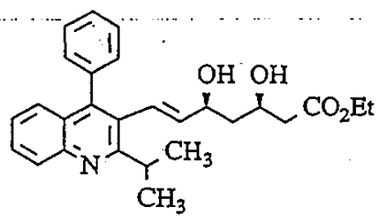
* The relative potency of the test compound was determined by comparing its IC_{50} value** with that of compactin, which was tested simultaneously and arbitrarily assigned a relative potency value of 1

** Method according to : Ackerman et.al. J. Lipid Res., 18 , 408-413 (1977)

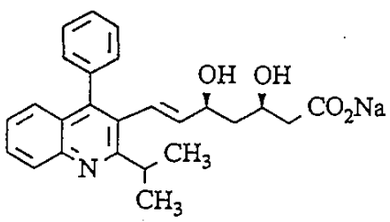
RELATIVE POTENCY*



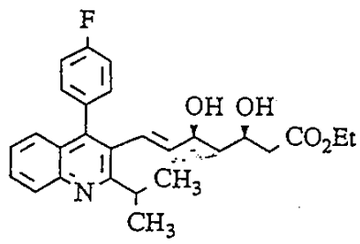
SDZ 63-548
0.27



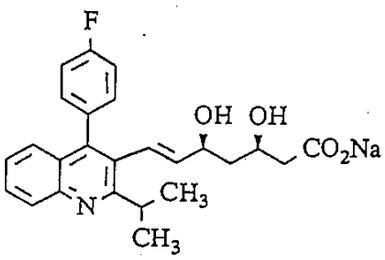
SDZ 64-933
0.43



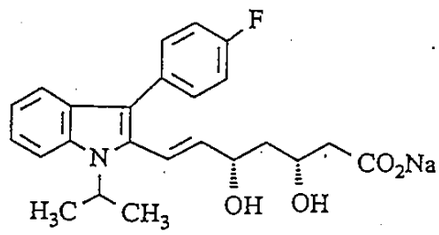
SDZ 64-934
0.39



SDZ 64-935
2.46

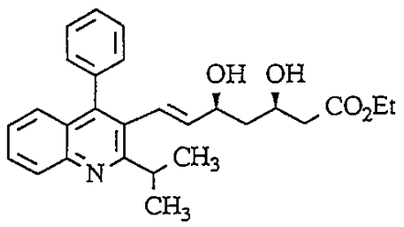


SDZ 64-936
1.9



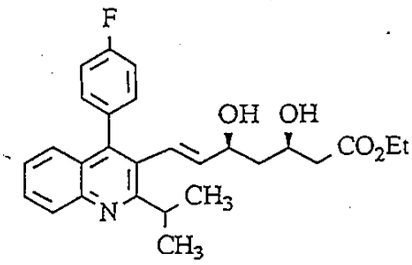
XU 62-620
146

INHIBITORY EFFECT ON CHOLESTEROL SYNTHESIS (RATS) ED_{50} (mg/Kg)



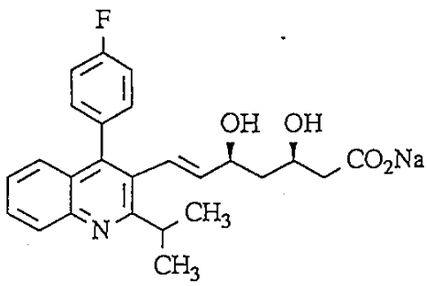
SDZ 64-933

>1.0



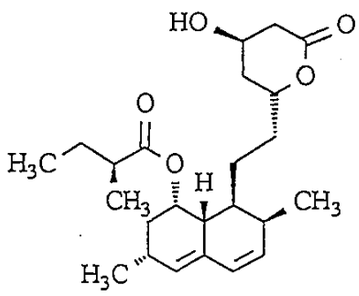
SDZ 64-935

0.49



SDZ 64936

>1.0



Mevinolin

0.38

CONCLUSION

1. QUINOLINE ANALOGS HAVE BEEN SYNTHESIZED AS NOVEL HMG-COA REDUCTASE INHIBITORS, BASED ON THE STRUCTURE AND SAR DATA OF XU 62-320

2. THESE ANALOGS ARE POTENT INHIBITORS OF HMG-COA REDUCTASE IN RAT MICROSOMAL ASSAYS AS WELL AS CHOLESTEROL BIOSYNTHESIS FROM C^{14}-ACETATE IN VIVO.

3. THE MOST ACTIVE COMPOUND (SDZ 64935) IS AS ACTIVE AS MEVINOLIN BUT IS FIVE FOLD LESS ACTIVE THAN XU 62-320 IN IN VIVO ASSAYS.

SANDOZ PATENT AND TRADEMARK DEPARTMENT

To: Dr. S. Wattanasin
Dr. F. Kathawala

From: Joanne M. Giesser

Date: June 13, 1989

Subject: Proposed publication "Quinolines as HMG-CoA Reductase Inhibitors" 5th SCI-RSC Medicinal Chemistry Symposium, Churchill College, Cambridge Sept. 10-13, 1989

The above-identified publication has been reviewed from a patent standpoint and is approved by the Patent and Trademark Department for publication.

Joanne M. Giesser

SANDOZ

Patent and Trademark Department
59 Route 10
E. Hanover, New Jersey 07936

Telex 240867
Telefax (201) 503-8807

June 15, 1989

SANDOZ LTD.
Patents and Trademarks Division
CH-4002
Basle, Switzerland

Re: Clearance for Poster Entitled
"QUINOLINES AS HMG-CoA REDUCTASE INHIBITORS"

Ref: 3700/RA

Dear Sirs:

Enclosed please find the Publication Clearance regarding the above-identified poster.

We look forward to receiving the corresponding number in due course.

Very truly yours,

Linda C. Rothwell

LCR
Enc. Publication Clearance

BASLE

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/047,358	5/5/87	KATHAWALA	600-7025/CIP

PATENT AND
TRADEMARK DEPT.
JAN 6 - 1989
JMG

EXAMINER	
ART UNIT	PAPER NUMBER
121	6

DATE MAILED: 1/3/89

NOTICE OF ABANDONMENT

This application is abandoned in view of:

1. ☒ Applicant's failure to respond to the Office letter, mailed Mar. 11, 1988.
2. ☐ Applicant's letter of express abandonment which is in compliance with 37 C.F.R. 1.138.
3. ☐ Applicant's failure to timely file the response received _____ within the period set in the Office letter.
4. ☐ Applicant's failure to pay the required issue fee within the statutory period of 3 months from the mailing date of _____ of the Notice of Allowance.
   - ☐ The issue fee was received on _____.
   - ☐ The issue fee has not been received in Allowed Files Branch as of _____.

   In accordance with 35 U.S.C. 151, and under the provisions of 37 C.F.R. 1.316(b), applicant(s) may petition the Commissioner to accept the delayed payment of the issue fee if the delay in payment was unavoidable. The petition must be accompanied by the issue fee, unless it has been previously submitted, in the amount specified by 37 C.F.R. 1.17 (l), and a verified showing as to the causes of the delay.

   If applicant(s) never received the Notice of Allowance, a petition for a new Notice of Allowance and withdrawal of the holding of abandonment may be appropriate in view of Delgar Inc. v. Schuyler, 172 U.S.P.Q. 513.
5. ☐ Applicant's failure to timely correct the drawings and/or submit new or substitute formal drawings by _____ as required in the last Office action.
   - ☐ The corrected and/or substitute drawings were received on _____.
6. ☐ The reason(s) below.

MARY C. LEE
SUPERVISORY PRIMARY EXM.
ART UNIT 121

PTO-1432 (REV. 5-83)

WATTANASIN EXHIBIT
Exhibit S-3
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

Exhibit No. 53 ID
Date 4-9-93
DiAsio Reporting

The impressed Mail Room date stamp acknowledges receipt on the date indicated of

PATENT AND TRADEMARK DEPT.
OCT 21 1988

- ☐ Communication
- ☐ Claim of Priority
- ☐ Mot. of Appeal
- ☐ Appeal Brief
- ☐ Prel. Amendment
- ☐ Amendment
- XX Ext. of Time in duplicate
- ☐ Req. for Recon.
- XX Postcard: COM Stamp

MAIL ROOM OCT 20 1988 PTO TRADEMARK OFF.

for Case No. 600-7025/CIP
Application of FAIZULLA G. KATHAWALA

Serial No. 07/047,358
Filed May 5, 1987

REV:lmc 10/11/88

BASLE

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/047,358	05/05/87	KATHAWALA	~~600-7025/CIP~~ 600-7025/CIP

07/047,358 5/5/87 KATHAWALA

GERALD D. SHARKIN
SANDOZ CORP.
59 ROUTE 10
EAST HANOVER, NJ 07936

PATENT AND TRADEMARK DEPT.
MAY 13 1988
JMG

EXAMINER	
BRISCOE,R	
BRISCOE,K	
ART UNIT	PAPER NUMBER
~~121~~ 121	4

DATE MAILED: ~~05/11/88~~ 5/11/88

This is a communication from the examiner in charge of your application.

COMMISSIONER OF PATENTS AND TRADEMARKS

August 11, 1988

☑ This application has been examined ☑ Responsive to communication filed on Jan. 19, 1988 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-23 and 26-32 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☑ Claims 1-23 and 26-29 are allowed.
4. ☑ Claims 30-32 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings which are acceptable for examination purposes until such time as allowable subject matter is indicated.
8. ☐ Allowable subject matter having been indicated, formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. These drawings are ☐ acceptable; ☐ not acceptable (see explanation).
10. ☐ The ☐ proposed drawing correction and/or the ☐ proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved. ☐ disapproved (see explanation). However, the Patent and Trademark Office no longer makes drawing changes. It is now applicant's responsibility to ensure that the drawings are corrected. Corrections MUST be effected in accordance with the instructions set forth on the attached letter "INFORMATION ON HOW TO EFFECT DRAWING CHANGES", PTO-1474.
12. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Case No. 600-7025/CIP
Serial No. 07/047,358

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :

FAIZULLA G. KATHAWALA : Art Unit: 121

Serial No. 07/047,358 : Examiner: K. BRISCOE

Filed: May 5, 1987 :

For: PYRIMIDINE DERIVATIVES :

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on October 11, 1988
(Date of Deposit)
Richard E. Vila
Name of applicant, assignee, or Registered Representative
/s/
Signature
October 11, 1988
Date of Signature

REQUEST FOR EXTENSION OF TIME

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Dear Sir:

It is respectfully requested that the period for responding to the Office Action of May 11, 1988 or taking an appeal or further action in connection with the above-identified application, originally set to expire on August 11, 1988 , be extended for two (2) month(s) to October 11, 1988.

☐ A check in the amount of $ to cover the fee for this extension is enclosed.

☒ Please charge the extension fee of $170.00 required by 37 CFR 1.17(c) to Deposit Account No. 19-0134 in the name of Sandoz Corporation.

Respectfully submitted,

/s/
Richard E. Vila
Attorney for FAIZULLA G. KATHAWALA
(201) 503- 7852

JMG:lmc

SANDOZ CORP.
59 Route 10
E. Hanover, N.J. 07936

Enclosures: Postcard; COM Stamp

SUBMITTED IN DUPLICATE

BASLE

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/165,656	03/08/88	ANDERSON	P 500-7049-7(CON

GERALD D. SHARKEN
SANDOZ CORP.
59 ROUTE 10
E. HANOVER, NJ 07936

PATENT AND TRADEMARK DEPT.
JUN 15 1989
JMG

EXAMINER	
DIETZ, B	
ART UNIT	PAPER NUMBER
121	17

DATE MAILED: 06/12/89

NOTICE OF ABANDONMENT

This application is abandoned in view of:

1. ☐ Applicant's failure to respond to the Office letter, mailed _____.
2. ☐ Applicant's letter of express abandonment which is in compliance with 37 C.F.R. 1.138.
3. ☐ Applicant's failure to timely file the response received _____ within the period set in the Office letter.
4. ☒ Applicant's failure to pay the required issue fee within the statutory period of 3 months from the mailing date of 1-3-89 of the Notice of Allowance.
   - ☐ The issue fee was received on _____.
   - ☐ The issue fee has not been received in Allowed Files Branch as of _____.

   In accordance with 35 U.S.C. 151, and under the provisions of 37 C.F.R. 1.316(b), applicant(s) may petition the Commissioner to accept the delayed payment of the issue fee if the delay in payment was unavoidable. The petition must be accompanied by the issue fee, unless it has been previously submitted, in the amount specified by 37 C.F.R. 1.17 (l), and a verified showing as to the causes of the delay.

   If applicant(s) never received the Notice of Allowance, a petition for a new Notice of Allowance and withdrawal of the holding of abandonment may be appropriate in view of Delgar Inc. v. Schuyler, 172 U.S.P.Q. 513.
5. ☐ Applicant's failure to timely correct the drawings and/or submit new or substitute formal drawings by _____ as required in the last Office action.
   - ☐ The corrected and/or substitute drawings were received on _____.
6. ☐ The reason(s) below.

DIRECT ANY INQUIRIES TO :
[redacted]
OR
MARCIA CAMPBELL
PUBLISHING DIVISION
(703) 557-[redacted]
8190

PTO-1432 (REV. 5-83)

WATTANASIN EXHIBIT
Exhibit S-4
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

Exhibit No. 54 ID
Date 4-9-93
DiAsio Reporting

PTOL-85 (REV. 4 86)

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

GERALD D. SHARKIN
SANDOZ CORP.
59 ROUTE 10
E. HANOVER, NJ 07936

PATENT AND TRADEMARK DEPT.
JAN 5 - 1989
JMG

April 3, 1989

All communications regarding this application should give the serial number, date of filing, name of applicant, and batch number.

Please direct all communications to the Attention of "OFFICE OF PUBLICATIONS" unless advised to the contrary.

The application identified below has been examined and found allowable for issuance of Letters Patent. PROSECUTION ON THE MERITS IS CLOSED.

SC/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT		DATE MAILED
07/165,656	03/08/88	017	DENTZ, B	121	01/03/89

First Named Applicant: ANDERSON, PAUL L.

TITLE OF INVENTION: AZAINDOLE DERIVATIVES USEFUL AS CHOLESTEROL BIOSYNTHESIS INHIBITORS (AS AMENDED)

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
600-7044/CONT	514-300.000	P15	UTILITY	NO	$560.00	04/03/89

The amount of the issue fee is specified in 37 C.F.R. 1.18. If the applicant qualified for and has filed a verified statement of small entity status in accordance with 37 C.F.R. 1.27, the issue fee is one-half the amount for non-small entities. The issue fee due printed above reflects applicant's status as of the time of mailing this notice. A verified statement of small entity status may be filed prior to or with payment of the issue fee. However, in accordance with 37 C.F.R. 1.28, failure to establish status as a small entity prior to or with payment of the issue fee precludes payment of the issue fee in the amount so established for small entities and precludes a refund of any portion thereof paid prior to establishing status as a small entity.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE as indicated above. The application shall otherwise be regarded as ABANDONED. The issue fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office. Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of the notice of allowance, the issue fee is charged to the deposit account at the time of mailing of this notice in accordance with 37 C.F.R. 1.311. If the issue fee has been so charged, it is indicated above.

In order to minimize delays in the issuance of a patent based on this application, **this Notice may have been mailed prior to completion of final processing.** The nature and/or extent of the remaining revision or processing requirements may cause slight delays of the patent. In addition, **if prosecution is to be reopened, this Notice of Allowance will be vacated and the appropriate Office action will follow in due course.** If the issue fee has already been paid and prosecution is reopened, the applicant may request a refund or request that the fee be credited to a deposit account. However, applicant may request that the previously submitted issue fee be applied. If abandoned, applicant may request refund or credit to a deposit account.

In the case of each patent issuing without an assignment, the complete post office address of the inventor(s) will be printed in the patent heading and in the Official Gazette. If the inventor's address is now different from the address which appears in the application, please fill in the information in the spaces provided on PTOL-85b enclosed. If there are address changes for more than two inventors, enter the additional addresses on the reverse side of the PTOL-85b.

The appropriate spaces in the ASSIGNMENT DATA section of PTOL-85b must be completed in all cases. If it is desired to have the patent issue to an assignee, an assignment must have been previously submitted to the Patent and Trademark Office or must be submitted not later than the date of payment of the issue fee as required by 37 C.F.R. 1.334. Where there is an assignment, the assignee's name and address must be provided on the PTOL-85b to ensure its inclusion in the printed patent.

Advance orders for 10 or more printed copies of the prospective patent can be made by completing the information in Section 4 of PTOL-85b and submitting payment therewith. If use of a deposit account is being authorized for payment, PTOL-85c should also be forwarded. The order must be for at least 10 copies and must accompany the issue fee. The copies ordered will be sent only to the address specified in section 1 or 1A of PTOL-85b.

[✓] Note attached communication from the Examiner.

[ ] This notice is issued in view of applicant's communication filed _____

IMPORTANT REMINDER

Patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. See 37 CFR 1.20 (e)—(j).

PTOL 85b (REV. 4 Sc)

U.S. Department of Commerc
Patent and Trademark Offi

ISSUE FEE TRANSMITTAL

This form is provided in lieu of a formal transmittal and should be used for transmitting the Issue Fee. Sections 1A through 4 must be completed as appropriate.

INVENTOR(S) ADDRESS CHANGE | SC. SERIAL NO

INVENTOR S NAME

Street Address

City, State and ZIP Code

CO INVENTOR'S NAME

Street Address

City, State and ZIP Code

☐ Check if additional changes are on reverse side

MAILING INSTRUCTIONS

All further correspondence including the Issue Fee Receipt the Patent, and advanced orders will be mailed to the addressee entered in section 1 on PTOL-85c, unless you direct otherwise by specifying the appropriate name and address in 1A below. (Note: See box 5 below for correspondence concerning maintenance fee payments.)

2A. The COMMISSIONER OF PATENTS AND TRADEMARKS is requested to apply the Issue Fee to the application identified below.

(Signature of party in interest of record) | (Date)

Note: The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

	SC/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT		DATE MAILED
	[illegible]	09/08/88	01/	DENTZ, B	121	01/03/89

First Named Applicant: ANDERSON, PAUL L.

TITLE OF INVENTION: AZAINDOLE DERIVATIVES USEFUL AS CHOLESTEROL BIOSYNTHESIS INHIBITORS (AS AMENDED)

	ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
	600-7044/CON	514-300.000	P15	UTILITY	NO	$560.00	04/03/89

1A. Further correspondence to be mailed to the following:

2B. For printing on the patent front page, list the names of not more than 3 registered patent attorneys or agents OR, alternatively, the name of a firm having as a member a registered attorney or agent. If no name is listed, no name will printed.

1 _____

2 _____

3 _____

DO NOT USE THIS SPACE

3. ASSIGNMENT DATA (print or type)

A. (1) ☐ This application is NOT assigned.
(2) ☐ Assignment previously submitted to the Patent and Trademark Office.
(3) ☐ Assignment submitted herewith.

B. For Printing On The Patent: (Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data below is only appropriate when an assignment has been previously submitted to the PTO or is submitted herewith. Completion of this form is NOT a substitute for filing of an assignment as required by 37 C.F.R. 1.334).

(1) NAME OF ASSIGNEE:

(2) ADDRESS: (City & State or Country)

(3) STATE OF INCORPORATION, IF ASSIGNEE IS A CORPORATION.

4. The following fees are enclosed:

☐ Issue fee ☐ Advanced order ☐ Assignment recording

The following fees should be charged to deposit acc. no. _____

(PTOL-85c or additional copy of PTOL-85b must be enclosed)

☐ Issue fee ☐ Assignment recording

☐ Advanced order ☐ Any additional fees due

Number of advanced order copies requested. _____

(must be for 10 or more copies

5. All correspondence relating to maintenance fees will be addressed to the correspondence address unless a separate "Fee Address" is provided to the Patent and Trademark Office (37 C.F.R. 1.363). A "Fee Address" may be submitted by the owner of record with the payment of the issue fee or thereafter by using form PTO-1537.

TRANSMIT THIS FORM WITH FEE

PTOL 85c (REV 4 86)

ISSUE FEE TRANSMITTAL

U.S. Department of Commerc
Patent and Trademark Offic

1.

GERALD D. SHARKIN
SANDOZ CORP.
59 ROUTE 10
E. HANOVER, NJ 07936

2A. The COMMISSIONER OF PATENTS AND TRADEMARKS is requested to apply the Issue Fee to the application identified below.

(Signature of party in interest of record) | (Date)

Note: The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

SC/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT		DATE MAILED
07/165,856	03/08/88	017	DENTZ, B	121	01/03/89

First Named Applicant: ANDERSON, PAUL L.

TITLE OF INVENTION: AZAINDOLE DERIVATIVES USEFUL AS CHOLESTEROL BIOSYNTHESIS INHIBITORS (AS AMENDED)

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
600-1044/CON	514-300,000	F15	UTILITY	NO	$560.00	04/03/89

1A. Further correspondence to be mailed to the following:

2B. For printing on the patent front page, list the names of not more than 3 registered patent attorneys or agents OR, alternatively, the name of a firm having as a member a registered attorney or agent. If no name is listed, no name will printed.

1 _____
2 _____
3 _____

DO NOT USE THIS SPACE

3. ASSIGNMENT DATA (print or type)

A. (1) ☐ This application is NOT assigned.
(2) ☐ Assignment previously submitted to the Patent and Trademark Office.
(3) ☐ Assignment submitted herewith.

B. For Printing On The Patent: (Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data below is only appropriate when an assignment has been previously submitted to the PTO or is submitted herewith. Completion of this form is NOT a substitute for filing of an assignment as required by 37 C.F.R. 1.334).

(1) NAME OF ASSIGNEE:

(2) ADDRESS: (City & State or Country)

(3) STATE OF INCORPORATION, IF ASSIGNEE IS A CORPORATION:

4. The following fees are enclosed:
☐ Issue fee ☐ Advanced order ☐ Assignment recording

The following fees should be charged to deposit acc. no. _____
(PTOL-85c or additional copy of PTOL-85b must be enclosed)

☐ Issue fee
☐ Advanced order
☐ Assignment recording
☐ Any additional fees due

Number of advanced order copies requested. _____
(must be for 10 or more copies

TRANSMIT THIS FORM WITH PTOL-85b WHEN AUTHORIZING USE OF A DEPOSIT ACCOUNT

An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the Issue Fee.

Authorization for this Examiner's Amendment was given in a telephone interview with Ms. Giesser on December 21, 1988.

Non-elected claims 18 and 19 have been canceled without prejudice to the filing of one or more divisional applications drawn thereto.

Claim 16, line 3, after "compound" --according to claim 1-- has been inserted.

Claim 16, last line "; said compound of claim 1" has been canceled.

Any inquiry concerning this communication should be directed to Examiner Dentz at telephone number 703-557-3572.

12/22/88;df

JOHN M. FORD
EXAMINER
GROUP ART UNIT 121

PTO-103X
(Rev. 11-86)

FILING RECEIPT

CORRECTED

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

437

SERIAL NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTORNEY DOCKET NO.	DRWGS	TOT CL	IND CL
07/254,514	10/06/88	121	$ 450.00	600-7025/CIP/KIP	0	14	1

GERALD D. SHARKIN
SANDOZ CORPORATION
59 ROUTE 10
EAST HANOVER, NJ 07936

PATENT AND
TRADEMARK DEPT.
MAY 7 - 1990

Receipt is acknowledged of the patent application identified herein. It will be considered in its order and you will be notified as to the examination thereof. Be sure to give the U.S. SERIAL NUMBER, DATE OF FILING, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this transmittal.

Applicant(s)
FAIZULLA G. KATHAWALA, MOUNTAIN LAKES, NJ.

CONTINUING DATA AS CLAIMED BY APPLICANT-
THIS APPLN IS A CIP OF. 07/047,358 05/11/88
WHICH IS A CIP OF 06/722,829 04/12/85 ABAN

FOREIGN FILING LICENSE GRANTED 12/29/88
TITLE
PYRIMIDINE DERIVATIVES

PRELIMINARY CLASS: 514

(see reverse)

WATTANASIN EXHIBIT
Exhibit T
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

438

JMG application started 11/3/88
mailed 3/3/89

QUINOLINE ANALOGS OF MEVALONOLACTONE AND DERIVATIVES THEREOF

CASE NO. 600-7101-US

WATTANASIN EXHIBIT
Exhibit U-1
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

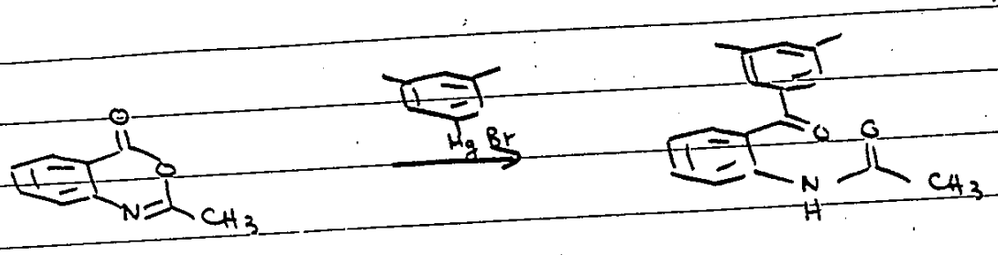
f 439

To: J. Giesser

Fwm: S. Wattanasin

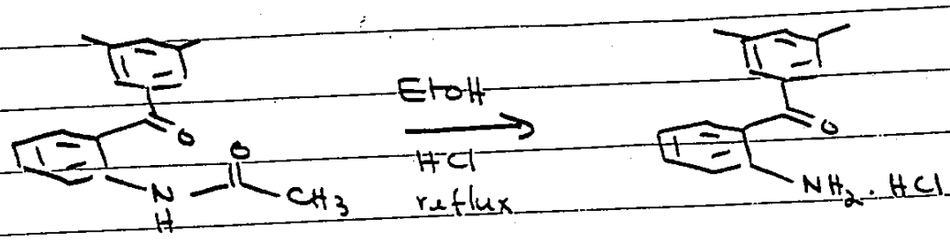
Attached is the written procedures for the synthesis of quinolin analogs according to Route I in the disclosure of invention # 299/84.

Som
11/7/88

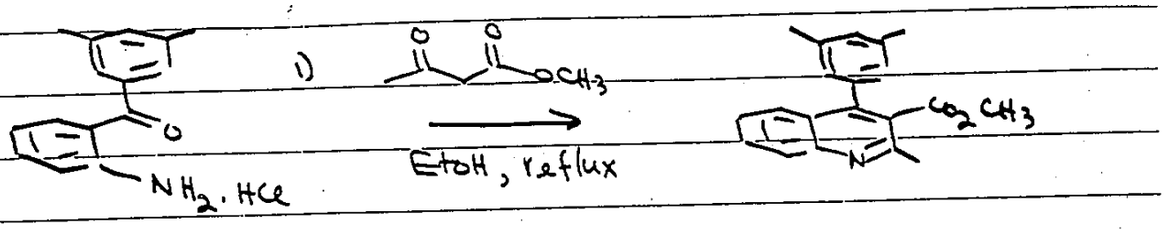


A solution of the benzoxazine* (10 g, 0.062 mol) in THF (50 ml) was added dropwise over a 30 min period to a solution of 3,5-dimethylphenyl-magnesium bromide [prepared from 5-bromo-m-xylene (17.2 g, 0.093 l), magnesium (2.33 g, 0.093 l mol) and a trace of iodine in THF and 1,2-dibromo-ethane in diethyl ether (40 ml)] stirred at room temperature under nitrogen. The reaction mixture was stirred at room temperature for 1 h, and quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The extracts were dried (Na_2SO_4) and evaporated at reduced pressure, and the residual oil (10 g) was chromatographed on a silica gel column to obtain the product as an oil (6 g).

* prepared according for a literature procedure. Morrison and Mullholland JCS 2700 (1958)



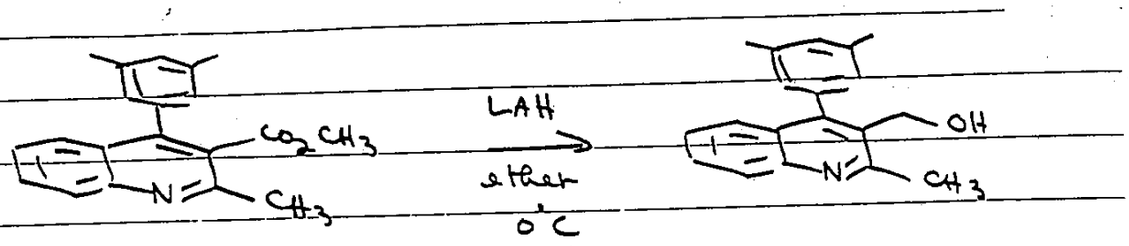
A mixture of the keto amide (3.8 g, 0.01428 mol) and 12 N hydrochloric acid (1.19 ml, 0.01428 mol) in absolute ethanol (20 ml) was stirred and heated at reflux for 3 h. The mixture was cooled and diluted with diethyl ether. The resulting solid was collected by filtration, washed with diethyl ether and vacuum dried to afford the product as a pale yellow solid (2.85 g), m.p. 193–195°C.



2) diisopropylamine
diethyl ether

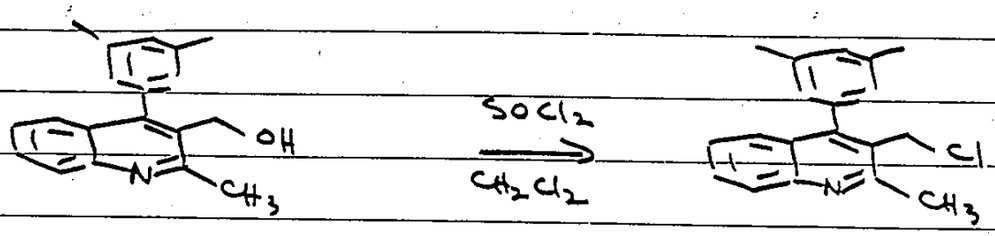
A mixture of the ketone hydrochloride (0.8 g, 0.003059 mol), methyl acetoacetate (0.33 ml, 0.00306 mol) in absolute ethanol (20 ml) was stirred at reflux for 3h. The mixture was slowly cooled to 10° C and diluted with diethyl ether. The precipitating white solid is collected by filtration and dried to obtain the quinoline hydrochloride (930 mg), m.p 209 – 211° C.

A mixture of the above hydrochloride salt (620 mg) and diisopropylamine (2 ml) in dry diethylether (10 ml) was stirred at room temperature for 1h. The mixture was diluted with diethyl ether and diisopropylamine hydrochloride was removed by filtration. The filtrate was evaporated at reduced pressure and the obtained colorless oil was crystallized from petrol to give the product as a colorless solid (600 mg), mp 88–90° C.

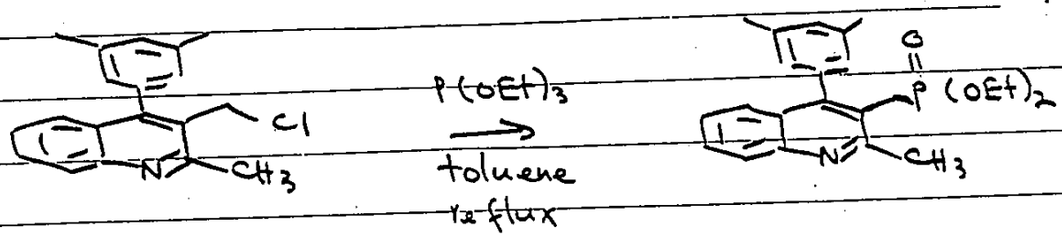


To a solution of the ester (486 mg, 0.00189 mol) in dry diethyl ether (9 ml) was added lithium aluminium hydride (~~74~~ 148 mg) at 0°C. The reaction mixture was stirred at 0°C for 3.5 h. The reaction mixture was cautiously poured into cold water and extracted with ethyl acetate. The extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated at reduced pressure to give a ~~colorless~~ solide ~~(243 mg)~~. Recrystallization (ether–petrol) gave the product as a colorless ~~solids~~ solid (213 mg), m.p. 194–195°C.

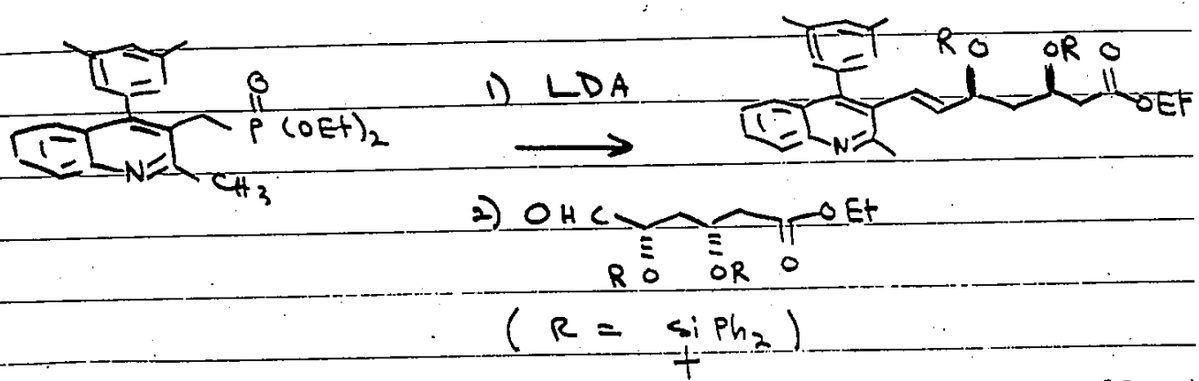
444



To a solution of the quinoline alcohol (190 mg , 0.0006859 mol) in CH_2Cl_2 (5 ml) at room temperature was added thionyl chloride (0.1 ml , 0.00137 mol). The reaction solution was stirred at room temperature for 4 h. The ~~sol~~ solvent was removed at reduced pressure. The crude oil was purified by Prep TLC (ether – petrol, 1:1) to give the product as a white solid (160 mg).



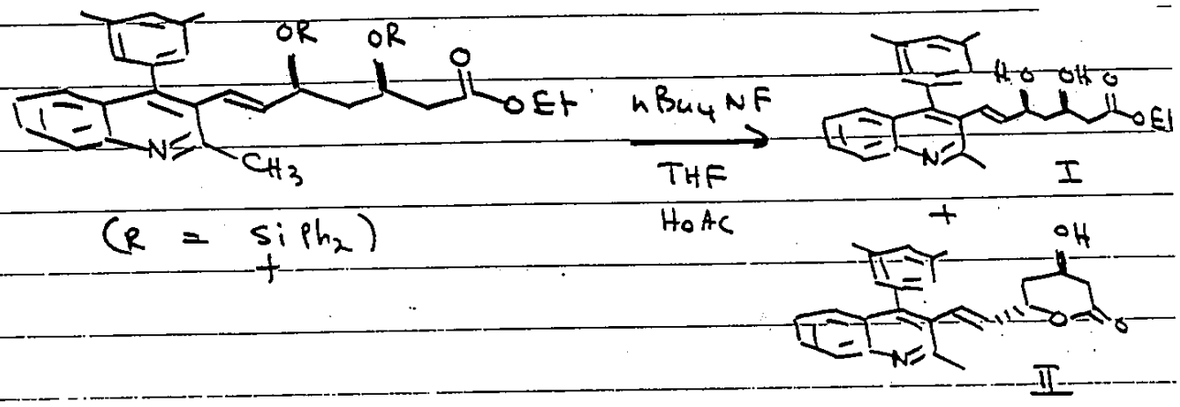
A mixture of the chloride (150 mg, 0.000508 mol) and triethyl phosphite (0.8 ml) in toluene (2ml) was stirred at reflux under nitrogen for 20 h. Evaporation at ~~ref~~ reduced pressure gave an oily product which solidified on standing (160 mg), m.p. 105-107°



(150 mg, 0.000337 mol)

To a solution of the diethyl phosphonate (in THF (3 ml) at −55°C was added a solution of lithium diisopropylamide monotetrahydrofuran / cyclohexane (1.7 M, 0.27 ml). The reaction mixture was stirred at −55 → −60°C for 10 min., a solution of the aldehyde (293 mg, 0.0004534 mol) in THF (2 ml) was added dropwise with stirring at −55°C. The reaction mixture was stirred at −55°C for 20 min. Acetic acid (0.5 ml) and 10% HCl solution were added, and the mixture was extracted with ethyl acetate. The extracts were combined, washed with water, saturated sodium bicarbonate, water and brine. Dried (Na_2SO_4), filtered and evaporated at reduced pressure gave the crude product as a yellow oil. Preparative TLC (ether-petrol, 1:1) gave the product as a pale yellow oil (100 mg).

447



To a solution of the silyl ether (90 mg, 0.000 1012 mol) and glacial acetic acid (0.03 ml, 0.0005 mol) in THF (2 ml) at room temperature was added a solution of tetra-n-butylammonium fluoride (tetrahydrofuran (1M, 0.61 ml, 0.000 607 mol). The reaction mixture was stirred at 50°c 50-60°c for 40 h. The mixture was evaporated at reduced pressure to give the crude product as a brown oil. The crude product was purified by preparative chromatography (ether : ethyl acetate, 1:1) to obtain the product I as an oil (10 mg) and product II as an oil (10 mg).

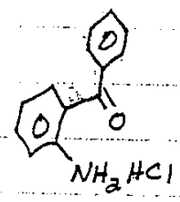
448

LDH 15994

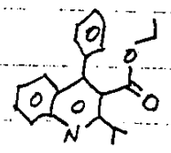
To: Ziggy Wahrman
From: Jody Giesser

Please provide the names for the following compounds. Thanks.

(1)

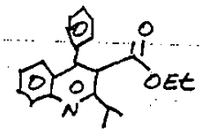


(2)

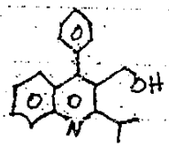


same?

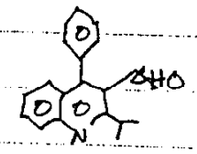
(3)



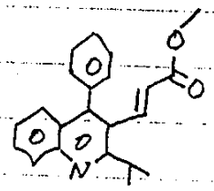
(4)



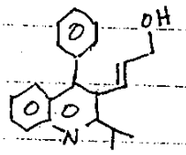
(5)



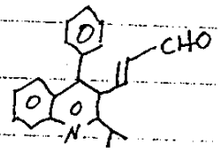
(6)



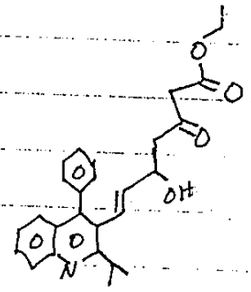
(7)



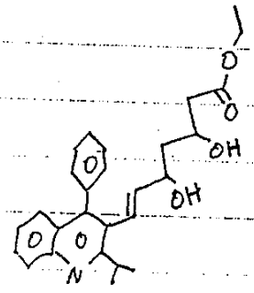
(8)



(9)



(10)



SANDOZ RESEARCH INSTITUTE

East Hanover, New Jersey

To: Jody Giesser

From: Henry Mah

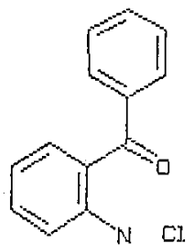
Date: November 8, 1988

Subject: Nomenclature on the following

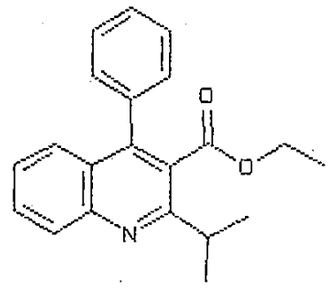
L&D # 15994

PLEASE NOTE THE CHANGE IN THE NUMBERING OF THE COMPOUNDS. COMPOUNDS (2) AND (3) ON THE ORIGINAL SHEET ARE IDENTICAL.

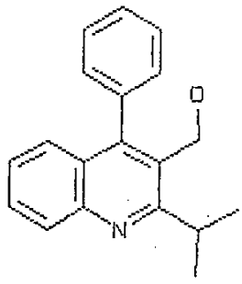
(1)



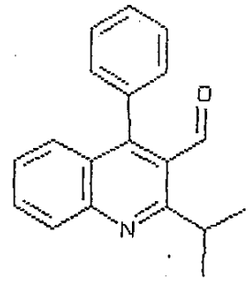
(2)



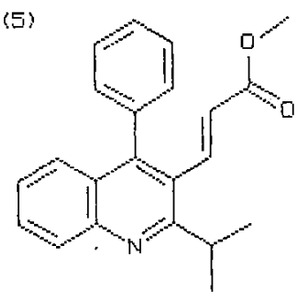
(3)



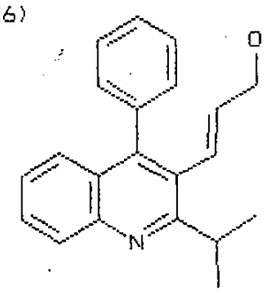
(4)



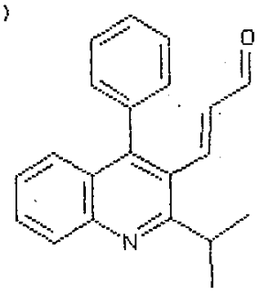
(5)



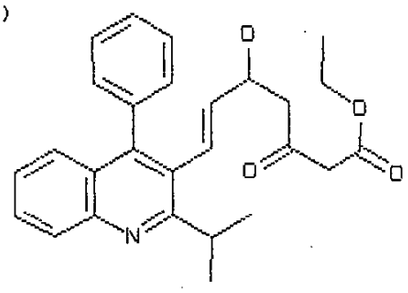
(6)



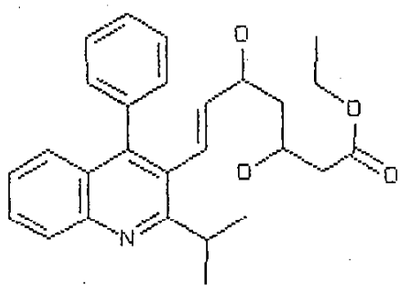
(7)



(8)



(9)



(1) Methanone, (2-aminophenyl)phenyl-
hydrochloride

(2) 3-Quinolinecarboxylic acid, 2-(1-methylethyl)-4-phenyl-
ethyl ester

(3) 3-Quinolinemethanol, 2-(1-methylethyl)-4-phenyl-

(4) 3-Quinolinecarboxaldehyde, 2-(1-methylethyl)-4-phenyl-

(5) 2-Propenoic acid, 3-[2-(1-methylethyl)-4-phenylquinolin-3-yl]-
methyl ester, (E)-

(6) 2-Propenol, 3-[2-(1-methylethyl)-4-phenylquinolin-3-yl]-
(E)-

(7) 2-Propenal, 3-[2-(1-methylethyl)-4-phenylquinolin-3-yl]-
(E)-

(8) 6-Heptenoic acid, 5-hydroxy-7-[2-(1-methylethyl)-4-phenylquinolin-
3-yl]-3-oxo-
ethyl ester, (E)-

(9)6-Heptenoic acid, 3,5-dihydroxy-7-[2-(1-methylethyl)-4-
phenylquinolin-3-yl]-
ethyl ester, (E)-

451

SANDOZ RESEARCH INSTITUTE

East Hanover, New Jersey

To: Ms. Jody Giesser

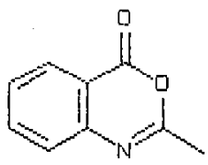
From: Henry Mah

Date: November 14, 1988

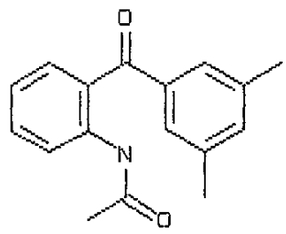
Subject: Nomenclature on the following

L&D # 16008

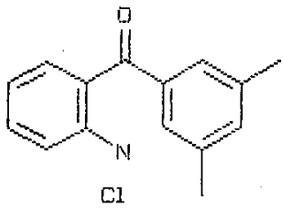
(1)



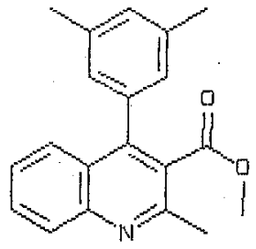
(2)



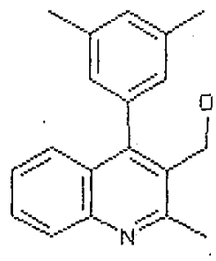
(3)



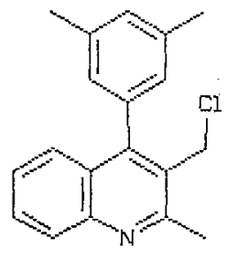
(4)



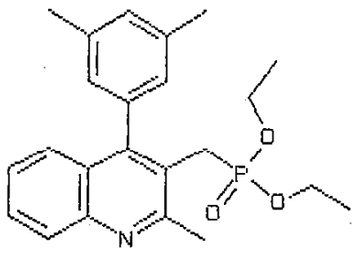
(5)



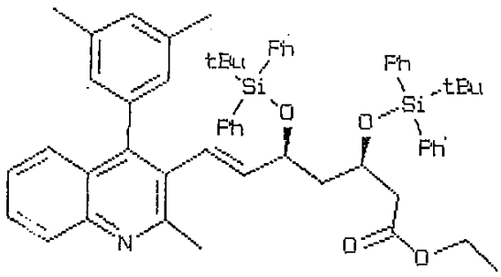
(6)



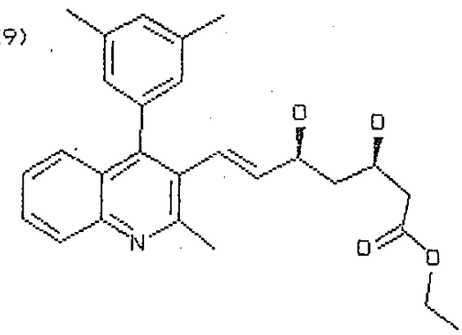
(7)



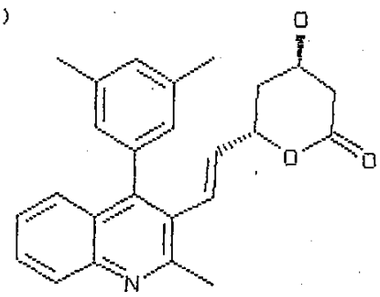
(8)



(9)



(10)



(1) 4H-3,1-Benzoxazine-4-one, 2-methyl-

(2) Acetamide, N-[2-(3,5-dimethylbenzoyl)phenyl]-

(3) Methanone, (2-aminophenyl)(3,5-dimethylphenyl)-
hydrochloride

(4) 3-Quinolinecarboxylic acid, 4-(3,5-dimethylphenyl)-2-methyl-
methyl ester

(5) 3-Quinolinemethanol, 4-(3,5-dimethylphenyl)-2-methyl-

(6) Quinoline, 3-chloromethyl-4-(3,5-dimethylphenyl)-2-methyl-

(7) Phosphonic acid, [[4-(3,5-dimethylphenyl)-2-methylquinolin-3-yl]methyl]-, diethyl ester

(8) 6-Heptenoic acid, 3,5-bis[[(1,1-dimethylethyl)diphenylsilyl]oxy]-7-[4-(3,5-dimethylphenyl)-2-methylquinolin-3-yl]-, ethyl ester, [(R*,S*)-(E)]-, (+,-)-

(9) 6-Heptenoic acid, 7-[4-(3,5-dimethylphenyl)-2-methylquinolin-3-yl]-3,5-dihydroxy-, ethyl ester, [(R*,S*)-(E)]-, (+,-)-

(10) 2H-Pyran-2-one, 6-[2-[4-(3,5-dimethylphenyl)-2-methylquinolin-3-yl]ethenyl]tetrahydro-, [trans-(E)]-, (+,-)-

Henry Mehta
9/5

454 V.

SANDOZ

PATENT AND TRADEMARK DEPARTMENT
Telex 240867
Telefax (201) 503-8807

DATE: December 14, 1988

TO: Dr. Sompong Wattanasin

FROM: Joanne M. Giesser

SUBJECT: Quinoline Analogs of Mevalonolactone and Derivatives Thereof

Enclosed is the first draft of the patent application entitled "Quinoline Analogs of Mevalonolactone and Derivatives Thereof". Please feel free to make any changes you think are appropriate and call me at X8420 so we can discuss the next draft.

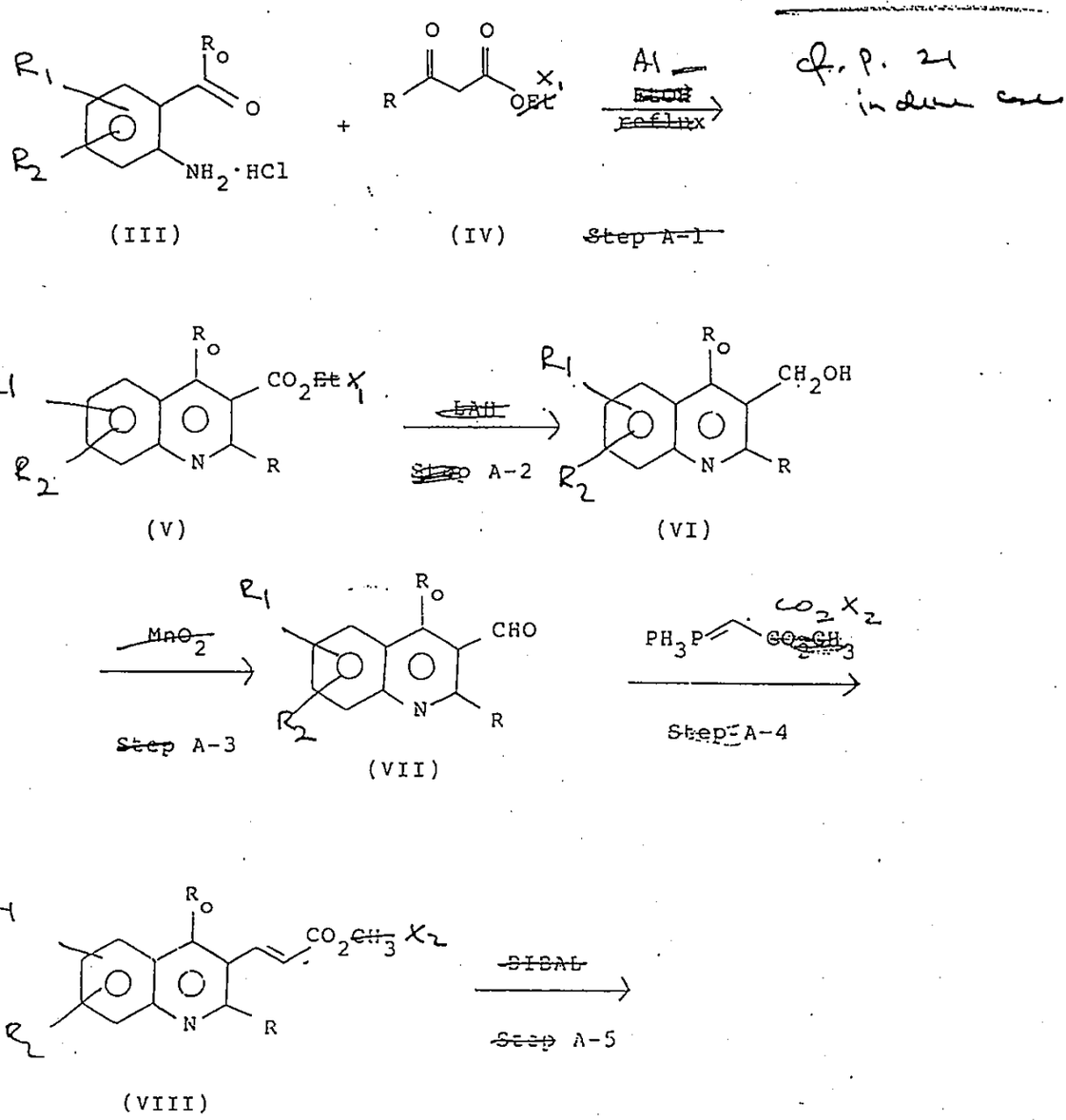
Regards,

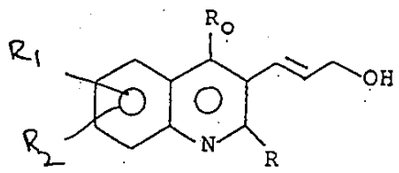
JMG:lmc
Enc.

85330/81A (Rev. 2)

The compounds of both Formula I may be prepared according to the following Reaction Scheme A.

GENERAL REACTION SCHEME A

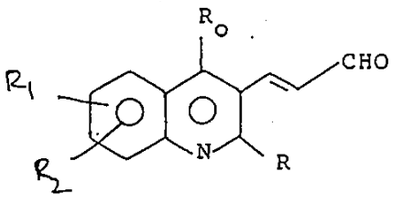




(IX)

MnO_2

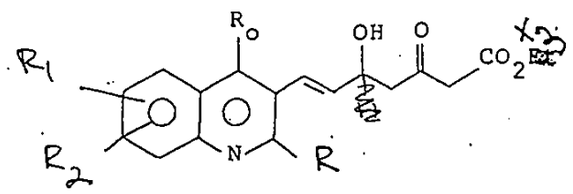
Step A-6



(X)

~~ethyl aceto-~~ ~~acetate (Xa)~~ ~~base~~ ?

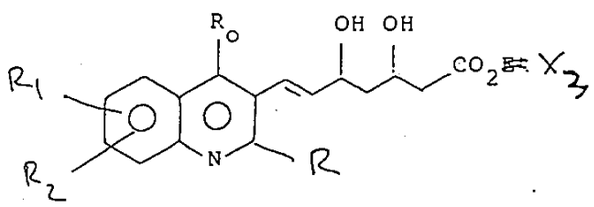
Step A-7



(XI)

~~reducing agent~~

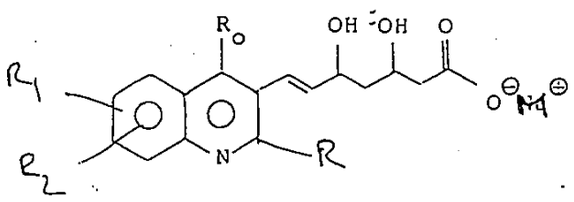
Step A-8



(XII)

NaBH

Step A-9

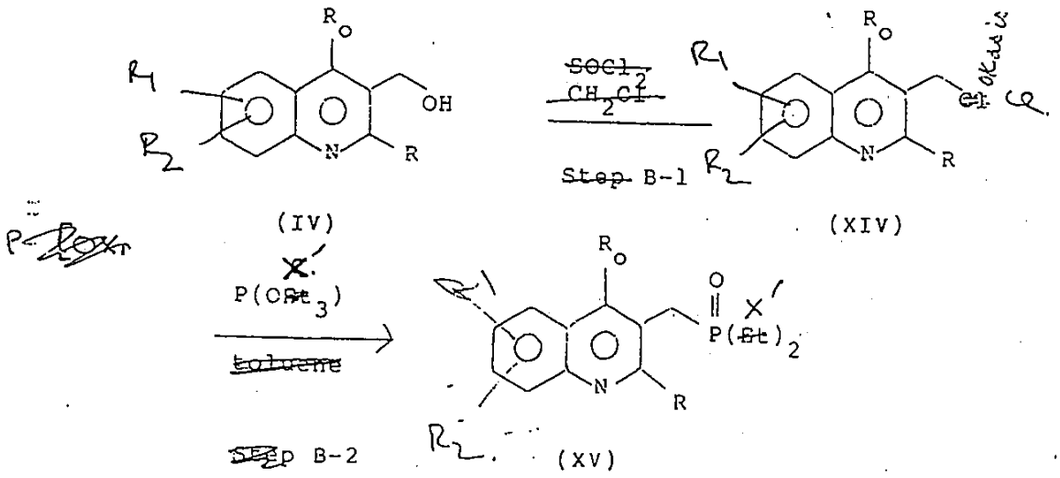


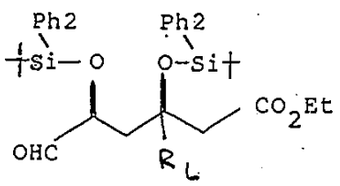
(XIII)

Starting material III is known and can be obtained by methods described by Morrison and Mulholland, 1958, J. Chem. Soc. p. 2702, which is hereby incorporated by reference. Next, V is reduced with lithium aluminum hydride, (LAH) to give VI. This reaction has also been described by Fehnel, 1968. J. Heterocyclic Chem 4:565, which is also hereby incorporated by reference. In Step A-3, VI is oxidized to VII. Step A-4 is a Wittig reaction producing VIII. Compound VIII is then reduced using diisobutylaluminum hydride (DIBAL) to IX. In Step A-6, IX is oxidized to X. The aldehyde X is then reacted with ethyl acetoacetate in Step A-7 to give XI. Compound XI is reduced to give XII. Next, in Step A-9, XII is hydrolyzed to the salt form XIII.

Compounds of both Formula I and II may be made according to Reaction Scheme B. Starting material for Reaction Scheme B is Compound VI from Reaction Scheme A.

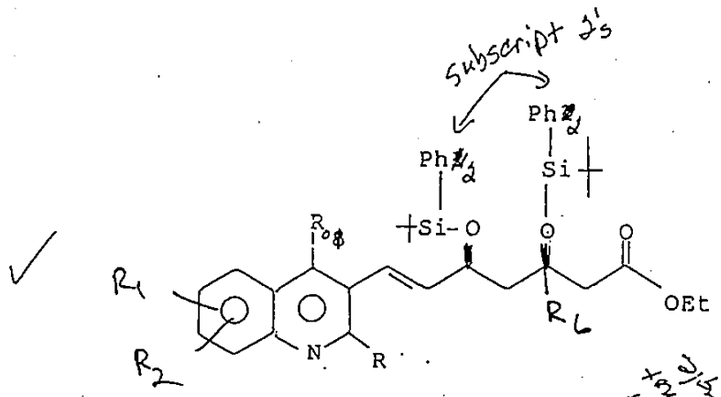
REACTION SCHEME B





~~nBu4NF/THF~~

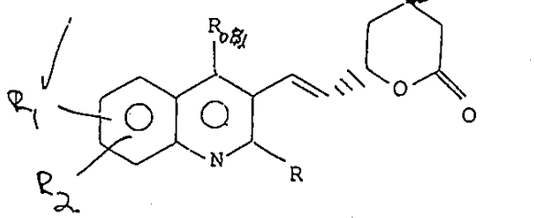
~~Step~~ B-3



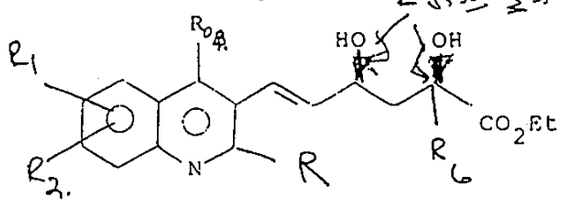
(XVI)

~~nBu4NF~~

~~Step~~ B-4



and



(I)

To: J. Giesser
From: S. Wattanasin
CASE 299/84

XW.
1/4/89.

459

The following changes are suggested:

1) On page 2, structure (6), change H (on C-3) to R6

2) On page 3,

- change H to R6 (as above)
- ~~R~~ line 19 and 20, R and Ro should be ~~independ~~ independently a C_{1-6} alkyl, and more preferably isopropyl and methyl or ring A
- Ring A preferably 3,4-dimethyl phenyl or 4-fluoro phenyl

- ~~Preferably~~ Preferred definition for
  R_1 & R_2
  R_7
  H

- Page 4-7, reaction scheme A and B should change to general schemes with general structures for starting materials, reagents and ~~conc~~ conditions (cf. P. [illegible] 10 [illegible] case; CN # 600-7028 reaction schemes can be shown

WATTANASIN EXHIBIT
Exhibit Y-1
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

later, preferably before the experimental procedures.

3) Page 8
- line 1 : delete "reduction and"
- line 3 : change "with to coupling"

4) Page 6
- line 1 : delete "is known and"
- line 4 : add "a reducing agent such as" after with
- line 9 : delete using diisobutylaluminum hydride (DIBAL)
- line 11 : change ethyl to alkyl
- change structure IV to VI

5) Page 7
- add R to structure I

6) Page 11 a ~~et~~.
- A-~~3~~1 :
- A-~~3~~2 :
- A-~~3~~3 :
- A-5 :
- ~~A-4~~ :

} See attached.

7) Page 14

- A-9
- B-2
- B-3
- add B-4

} see attached.

8) Page 15

- should show IC_{50} of ~~Sa~~ Sah - 64935 and 64936 with proper numbering referring numbers. (see attached list of IC_{50} - ED_{50}).

9) Page 16

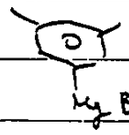
- should show ED_{50} of Sah - 63548 and 64935 with proper referring numbers.

10) Page 17

- The preferred compounds of the invention are 63548 and 64935 (see structures in the above list)

11) Page 24

- structure of the reagent in step A should be



- Add the hydrolysis procedure (see attached)

before example 2.

12. Page 29

— add CH_3 gmp to the 2-position of the structure of product.

13. Page 33

— No. 4 should be deleted or changed to cover ~~salt 63548~~ our key structures such as salt - 63548, 64935, 63366 and their sodium salts.

i.e.

R + R_0 is independently CH_3 and i-Pr or 3,5-dimethylphenyl and 4-fluorophenyl

14. Page 35

— in the lactone structure change H to R_6.

B-3 (Coupling Reaction).

1) 1 – 1.2 moles strong base, pref. n-butyl lithium or lithium diisopropylamide per mole XV

-78 – 0° C

10 – 90 min

THF

2) 1 – 1.2 moles aldehyde per mole XV

-78 – 0° C

10 – 90 min

solvent same as step 1

3) Quenched with, eg. acetic acid

-78 – 25° C

1 – 5 min

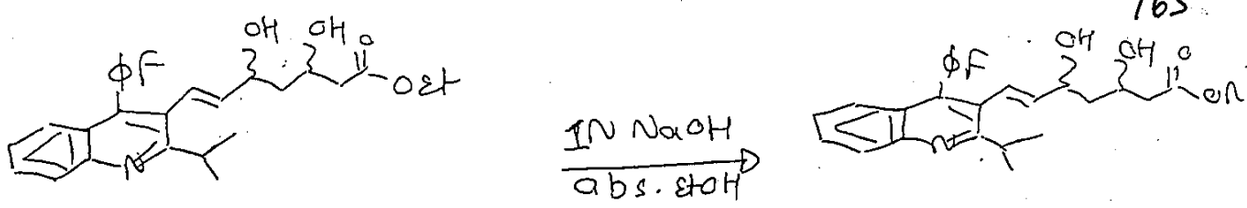
B-4 (Deprotection)

2 - 15 moles, pref. 4-10 moles, fluoride reagent, esp. tetra-n-butylammonium fluoride per mole XXII and 0.5 - 2 mole, pref. ~~1.2~~ 1.0 - 1.5 moles, glacial acetic acid per mole fluoride reagent

20 - 60° C

2 - 120 hrs

Ale, eg. ES, pref. THF, or mixture of ES, pref. THF, and acetonitrile.



To the sol^{n} of 100mg (0.0002172 mole) diol ester in 3 ml abs. EtOH was added 0.2173 ml (0.0002172 94 mole) 1 N NaOH dropwise at 0°C. After stirring at 0°C for 3 hrs, the reaction mixture was diluted with ether and evaporated in vacuo leaving yellow oil. On addition of ether, yellow solids came out which was then filtered, washed with ether and on drying gave 86.4 mg (87.5%) yellow solids M.P. > 225°C. NMR (CD_3OD, 500 MH_z) : 1.39, m, 1H; 1.35, d, 6H; 1.5, m, 1H; 2.13–2.3, m, 1H; 3.65, q, 1H; 3.75, m, 1H; 4.25, m, 1H; 5.45, dd, 1H; 6.59, d, 1H; 7.21, m, 5H, 7.36, m, 1H; 7.62, m, 1H; 8.05, d, 1H

EDso from Bob Engstrom
11/4/89.

WATTANASIN_S

MET002

SPOOLED: 11/01/88 11:53 AM

WATTANASIN EXHIBIT
Exhibit Y-2
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

466

26082 (SAH-063549) SAH

26080 (SAH-063548) SAH

25496 (SAH-063366) SAH

30447 (SAH-064935) SAH

30442 (SAH-064934) SAH

30441 (SAH-064933) SAH

IC50 0.53.

>10.0

% 1.0

30448 (SAH-064936) SAH

469

600 - 7013 -C

United States Patent [19]

Damon, II

[11] Patent Number: 4,588,715

[45] Date of Patent: May 13, 1986

[54] HEPTENOIC ACID DERIVATIVES

[75] Inventor: Robert E. Damon, II, Wharton, N.J.

[73] Assignee: Sandoz, Inc., E. Hanover, N.J.

[21] Appl. No.: 616,720

[22] Filed: Jun. 4, 1984

[51] Int. Cl.[4] C07F 7/08; A61K 31/695

[52] U.S. Cl. 514/63; 549/214; 549/292; 556/441

[58] Field of Search 549/214, 292; 556/441; 424/184; 560/56; 514/63

[56] References Cited

U.S. PATENT DOCUMENTS

4,000,265	12/1976	Quilichini	424/184
4,255,444	3/1981	Oka et al.	549/292
4,262,013	4/1981	Mistui et al.	549/292
4,293,496	10/1981	Willard	549/292
4,361,515	11/1982	Terahara et al.	549/292
4,375,475	3/1983	Willard et al.	549/292
4,420,475	12/1983	Damon, II	424/184
4,472,426	9/1984	Hoffman et al.	549/292

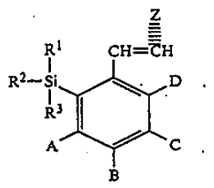
FOREIGN PATENT DOCUMENTS

7713317	5/1979	France	424/184

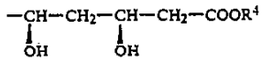
Primary Examiner—Alton D. Rollins
Assistant Examiner—D. L. Dinner
Attorney, Agent, or Firm—Gerald D. Sharkin; Richard E. Vila; Frederick H. Weinfeldt

[57] ABSTRACT

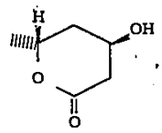
Compounds of the formula



wherein R^1, R^2 and R^3 are alkyl or aryl groups, A, B, C and D are non-reactive substituents or two are joined to form an additional ring, and Z is either of the formula Z':



wherein R^4 is H, lower alkyl or a cation; or a -6-oxotetrahydropyran-2-yl ring of the formula Z":



e.g. 4-hydroxy-6-{2-[2-(methyldiphenylsilyl)phenyl]ethenyl]ethyenyl}-tetrahydro-2H-pyran-2-one, (trans, trans). The compounds inhibit cholesterol biosynthesis and are useful as anti-atherosclerotic agents.

22 Claims, No Drawings

600-1015. 470

United States Patent [19]

Wareing

[11] Patent Number: 4,613,610

[45] Date of Patent: Sep. 23, 1986

[54] CHOLESTEROL BIOSYNTHESIS INHIBITING PYRAZOLE ANALOGS OF MEVALONOLACTONE AND ITS DERIVATIVES

[75] Inventor: James R. Wareing, Randolph, N.J.

[73] Assignee: Sandoz Pharmaceuticals Corp., E. Hanover, N.J.

[21] Appl. No.: 741,903

[22] Filed: Jun. 6, 1985

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 623,393, Jun. 22, 1984, abandoned.

[51] Int. Cl.[4] A61K 31/415; C07D 231/12; C07D 405/06

[52] U.S. Cl. 514/406; 548/374; 548/378

[58] Field of Search 548/374, 378; 514/406

[56] References Cited

U.S. PATENT DOCUMENTS

3,983,140	9/1976	Endo et al.	549/292
4,198,425	4/1980	Mitsui et al.	549/292
4,248,889	2/1981	Oka et al.	560/56
4,255,444	3/1981	Oka et al.	549/292
4,308,378	12/1981	Stokker	549/292
4,351,844	9/1982	Patchett et al.	549/292
4,361,515	11/1982	Terahara et al.	549/292
4,375,475	3/1983	Willard et al.	549/292
4,376,863	3/1983	Lam	549/292
4,387,242	6/1983	Lam	560/119
4,440,927	4/1984	Prugh	549/292
4,474,971	10/1984	Wareing	549/214
4,503,072	3/1985	Hoffman et al.	514/529

FOREIGN PATENT DOCUMENTS

895445	4/1983	Belgium	549/292
38061	10/1981	European Pat. Off.	549/292
68038	1/1983	European Pat. Off.	549/292
56-7775	1/1981	Japan	549/292
WO84/02131	6/1984	PCT Int'l Appl.	548/467
WO84/02903	8/1984	PCT Int'l Appl.	549/292

OTHER PUBLICATIONS

Hulcher, Arch. Biochem. Biophys. 146, 422–427 (1971).

Sato et al., Chem. Pharm. Bull. 28, 1509–1525 (1980).

Singer et al., Proc. Soc. Exp. Biol. Med. 102, 370–373 (1959).

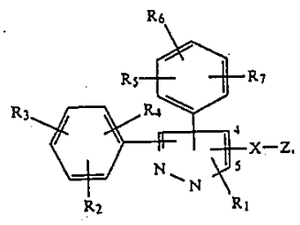
Primary Examiner—Richard A. Schwartz

Assistant Examiner—Kurt G. Briscoe

Attorney, Agent, or Firm—Gerald D. Sharkin; Richard E. Vila; Melvyn M. Kassenoff

[57] ABSTRACT

Compounds of the formula



wherein

R_1 is C_{1-6}alkyl not containing an asymmetric carbon atom,

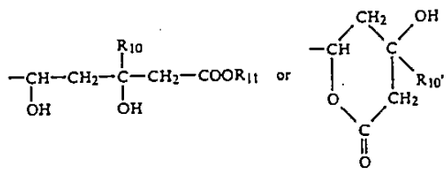
each of R_2 and R_5 is independently hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenyl, phenoxy or benzyloxy,

each of R_3 and R_6 is independently hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

each of R_4 and R_7 is independently hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro, with the provisos that not more than one of R_2 and R_3 is trifluoromethyl, not more than one of R_2 and R_3 is phenoxy, not more than one of R_2 and R_3 is benzyloxy, not more than one of R_5 and R_6 is trifluoromethyl, not more than one of R_5 and R_6 is phenoxy, and not more than one of R_5 and R_6 is benzyloxy,

X is $-(CH_2)_m-$, $-CH=CH-$, $-CH=CH-CH_2-$ or $-CH_2-CH=CH-$, wherein m is 0, 1, 2 or 3, and

Z is



wherein R_{10} is hydrogen or C_{1-3}alkyl, wherein R_{12} is a physiologically acceptable and hydrolyzable ester group, and

M is a pharmaceutically acceptable cation,

with the provisos that (i) the—X—Z group is in the 4- or 5-position of the pyrazole ring, and (ii) the R_1 group and the —X—Z group are ortho to each other,

the use thereof for inhibiting cholesterol biosynthesis and lowering the blood cholesterol level and, therefore, in the treatment of hyperlipoproteinemia and atherosclerosis, pharmaceutical compositions comprising such compounds and processes for and intermediates in the synthesis of such compounds.

27 Claims, No Drawings

471

600-6951/B/cont-US

United States Patent [19]

Kathawala

[11] Patent Number: 4,739,073

[45] Date of Patent: Apr. 19, 1988

[54] INTERMEDIATES IN THE SYNTHESIS OF INDOLE ANALOGS OF MEVALONOLACTONE AND DERIVATIVES THEREOF

[75] Inventor: Faizulla G. Kathawala, Mountain Lakes, N.J.

[73] Assignee: Sandoz Pharmaceuticals Corp., E. Hanover, N.J.

[21] Appl. No.: 707,854

[22] Filed: Mar. 4, 1985

Related U.S. Application Data

[63] Continuation of Ser. No. 548,850, Nov. 4, 1983, which is a continuation-in-part of Ser. No. 443,668, Nov. 22, 1982.

[51] Int. Cl.[4] C07D 405/06; C07D 209/12

[52] U.S. Cl. 548/406; 548/414; 548/494

[58] Field of Search 548/465, 467, 494, 468, 548/414, 406

[56] References Cited

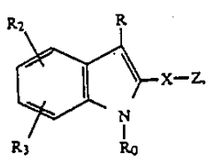
U.S. PATENT DOCUMENTS

3,259,633	7/1966	Metlesics et al.	548/493
4,248,889	2/1981	Oka et al.	514/532
4,255,444	3/1981	Oka et al.	514/460
4,272,533	6/1981	Gradient et al.	514/212
4,375,475	3/1983	Willard et al.	514/460
4,474,971	10/1984	Wareing	549/214

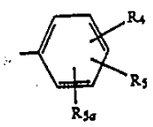
Primary Examiner—Donald G. Daus
Assistant Examiner—William A. Teoli, Jr.
Attorney, Agent, or Firm—Gerald D. Sharkin; Richard E. Vila; Melvyn M. Kassenoff

[57] ABSTRACT

Compounds of the formula



wherein one of R and R_o is



and the other is primary or secondary C_{1-6}alkyl not containing an asymmetric carbon atom, C_{3-6}cycloalkyl or phenyl$(CH_2)_m$—, wherein

R_4 is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_5 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_{5a} is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro, and

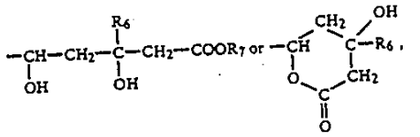
m is 1, 2 or 3, with the provisos that both R_5 and R_{5a} must be hydrogen when R_4 is hydrogen, R_{5a} must be hydrogen when R_5 is hydrogen, not more than one of R_4 and R_5 is trifluoromethyl, not more than one of R_4 and R_5 is phenoxy, and not more than one of R_4 and R_5 is benzyloxy,

R_2 is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{3-6}cycloalkyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_3 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, with the provisos that R_3 must be hydrogen when R_2 is hydrogen, not more than one of R_2 and R_3 is trifluoromethyl, not more than one of R_2 and R_3 is phenoxy, and not more than one of R_2 and R_3 is benzyloxy,

X is $—(CH_2)_n—$ or —CH=CH—, wherein n is 0, 1, 2 or 3, and

Z is



wherein

R_6 is hydrogen or C_{1-3}alkyl, and

R_7 is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, benzyl or M, wherein M is a pharmaceutically acceptable cation,

the use thereof for inhibiting cholesterol biosynthesis and lowering the blood cholesterol level, and, therefore, in the treatment of hyperlipoproteinemia and atherosclerosis, pharmaceutical compositions comprising such compounds and processes for and intermediates in the synthesis of such compounds.

20 Claims, No Drawings

600-7050-US
472

United States Patent [19]

Anderson

[11] **Patent Number: 4,751,235**

[45] **Date of Patent: Jun. 14, 1988**

[54] **ANTI-ATHEROSCLEROTIC INDOLIZINE DERIVATIVES**

[75] Inventor: **Paul L. Anderson, Randolph, N.J.**

[73] Assignee: **Sandoz Pharm. Corp., East Hanover, N.J.**

[21] Appl. No.: **945,750**

[22] Filed: **Dec. 23, 1986**

[51] **Int. Cl.**[4] **A61K 31/435; C07D 471/04**

[52] **U.S. Cl.** **514/299; 546/112**

[58] **Field of Search** **546/112; 514/299**

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,248,889	2/1981	Oka et al.	424/308
4,255,444	3/1981	Oka et al.	424/279
4,375,475	3/1983	Willard et al.	549/292
4,474,971	10/1984	Wareing	549/214
4,520,026	5/1985	Rosseels et al.	546/112

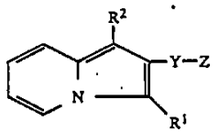
FOREIGN PATENT DOCUMENTS

8402131	6/1984	PCT Int'l Appl. .
8402903	8/1984	PCT Int'l Appl. .
8600307	1/1986	PCT Int'l Appl. .
8603488	6/1986	PCT Int'l Appl. .

Primary Examiner—Richard A. Schwartz
Assistant Examiner—Bernard I. Dentz
Attorney, Agent, or Firm—Gerald D. Sharkin; Richard E. Vila; Melvyn M. Kassenoff

[57] **ABSTRACT**

7-(indolizin-2-yl)hept-6-enoic acids of the formula I:



I

wherein each of R^1 and R^2 is, independently, H, alkyl, cycloalkyl, aralkyl or aryl,

Y is $-CH=CH-$, or $-CH_2-CH_2-$; and

Z is $CH(OH)-CH_2-CH(OH)-CH_2COOR^8$

in which R^8 is H, an ester residue or cation; or the lactone thereof. The compounds are useful as hypocholesteremic agents.

20 Claims, No Drawings

473

600-7028/B/CONT

United States Patent [19]

Wareing

[11] Patent Number: 4,755,606

[45] Date of Patent: Jul. 5, 1988

[54] IMIDAZOLYL-3,5-DI-(DIPHENYL-BUTYL-SILYLOXY) CARBOXYLIC ACID ESTER INTERMEDIATES

[75] Inventor: James R. Wareing, Randolph, N.J.

[73] Assignee: Sandoz Pharm. Corp., E. Hanover, N.J.

[21] Appl. No.: 79,194

[22] Filed: Jul. 29, 1987

Related U.S. Application Data

[60] Division of Ser. No. 863,267, May 14, 1986, abandoned, which is a continuation-in-part of Ser. No. 736,679, May 22, 1985, Pat. No. 4,668,794.

[51] Int. Cl.[4] C07D 7/18

[52] U.S. Cl. 548/110

[58] Field of Search 548/110

[56] References Cited

U.S. PATENT DOCUMENTS

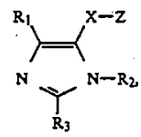
4,028,343	6/1977	Amort et al.	548/110 X
4,530,922	7/1985	Moberg	548/110 X
4,650,890	3/1987	Jewell et al.	556/446
4,677,211	6/1987	Jewell et al.	548/491

Primary Examiner—Richard A. Schwartz

Attorney, Agent, or Firm—Gerald D. Sharkin; Richard E. Vila; Melvyn M. Kassenoff

[57] ABSTRACT

Compounds of the formula



and the pharmaceutically acceptable acid addition salts thereof, wherein the various substituents are defined herein below,

the use thereof for inhibiting cholesterol biosynthesis and lowering the blood cholesterol level and, therefore, in the treatment of hyperlipoproteinemia and atherosclerosis, pharmaceutical compositions comprising such compounds and processes for and intermediates in the synthesis of such compounds.

12 Claims, No Drawings

474

600-7064-45

United States Patent [19]

Kathawala

[11] Patent Number: 4,822,799

[45] Date of Patent: Apr. 18, 1989

[54] PYRAZOLOPYRIDINE ANALOGS OF MEVALONOLACTONE AND DERIVATIVES THEREOF USEFUL FOR INHIBITING CHOLESTEROL BIOSYNTHESIS IN MAMMALS

[75] Inventor: Faizulla G. Kathawala, Mountain Lakes, N.J.

[73] Assignee: Sandoz Pharm. Corp., E. Honover, N.J.

[21] Appl. No.: 149,232

[22] Filed: Jan. 27, 1988

[51] Int. Cl.[4] C07D 471/04; A61K 31/395

[52] U.S. Cl. 514/303; 546/119

[58] Field of Search 546/119; 514/303

[56] References Cited

U.S. PATENT DOCUMENTS

4,248,889	2/1981	Oka et al.	424/308
4,255,444	3/1981	Oka et al.	424/279
4,293,496	10/1981	Willard	260/343.5
4,459,422	7/1984	Willard et al.	560/59
4,479,965	10/1984	Terahara et al.	424/279
4,571,428	2/1986	Kapa	556/437
4,588,715	5/1986	Damon	514/63
4,613,610	9/1986	Wareing	514/406
4,647,576	3/1987	Hoefle et al.	514/422
4,751,235	6/1988	Anderson	514/299
4,755,606	7/1988	Wareing	548/110

FOREIGN PATENT DOCUMENTS

84/02131 6/1984 World Int. Prop. O. .

87/02662 5/1987 World Int. Prop. O. .

OTHER PUBLICATIONS

Hulcher, Arch. Biochem. Biophys. 146, 422–427 (1971).

Sato et al., Chem. Pharm. Bull. (Tokyo) 28, 1509–1525 (1980).

Singer et al., Proc. Soc. Exp. Biol. Med. 102, 370–373 (1959).

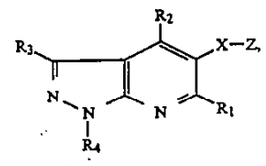
Primary Examiner—Mary C. Lee

Assistant Examiner—John A. H. Russell

Attorney, Agent, or Firm—Gerald D. Sharkin; Richard E. Vila; Melvyn M. Kassenoff

[57] ABSTRACT

Compounds of the formula



and processes for and intermediates in the synthesis thereof, pharmaceutical compositions comprising such a compound and the use of such compounds for inhibiting cholesterol biosynthesis and lowering the blood cholesterol level and, therefore, in the treatment of hyperlipoproteinemia and atherosclerosis.

20 Claims, No Drawings

475

600-7035/B

United States Patent [19]

Wareing

[11] Patent Number: 4,851,427

[45] Date of Patent: Jul. 25, 1989

[54] PYRROLE ANALOGS OF MEVALONOLACTONE, DERIVATIVES THEREOF AND PHARMACEUTICAL USE

[75] Inventor: James R. Wareing, Randolph, N.J.

[73] Assignee: Sandoz Pharm. Corp., E. Hanover, N.J.

[21] Appl. No.: 919,275

[22] Filed: Oct. 15, 1986

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 791,198, Oct. 25, 1985, abandoned.

[51] Int. Cl.[4] A61K 31/40; C07D 707/337; C07D 405/04; C07D 405/05

[52] U.S. Cl. 514/422; 514/427; 548/517; 548/562

[58] Field of Search 548/517, 562; 514/422, 514/427

[56] References Cited

U.S. PATENT DOCUMENTS

4,198,425	4/1980	Mitsui et al.	424/279
4,255,444	3/1981	Oka et al.	424/279
4,459,422	7/1984	Willard et al.	560/59
4,472,426	9/1984	Hoffman et al.	424/279
4,474,971	10/1984	Wareing	549/214
4,588,715	5/1986	Damon	514/63
4,613,610	9/1986	Wareing	514/406
4,647,576	3/1987	Hoefle et al.	514/422
4,681,893	7/1987	Roth	514/422

FOREIGN PATENT DOCUMENTS

11928	6/1980	European Pat. Off. .
179559	4/1986	European Pat. Off. .
2261965	6/1973	Fed. Rep. of Germany .
84/02131	6/1984	PCT Int'l Appl. .
84/02903	8/1984	PCT Int'l Appl. .

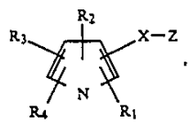
OTHER PUBLICATIONS

Hoffman et al., J. Med. Chem., 29, 159–169, (1986).
Hulcher, Arch. Biochem. Biophys., 146, 422–427, (1971).
Sato et al., Chem. Pharm. Bull., (Tokyo), 28, 1509–1525, (1980).
Singer et al., Proc. Soc. Exper. Biol. Med., 102, 370–373, (1959).
Stokker et al., J. Med. Chem., 28, 347–358, (1985).
Stokker et al., J. Med. Chem., 29, 170–181, (1986).

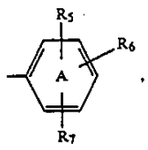
Primary Examiner—Richard L. Raymond
Attorney, Agent, or Firm—Gerald D. Sharkin; Richard E. Vila; Melvyn M. Kassenoff

[57] ABSTRACT

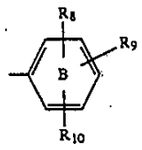
Compounds of the formula



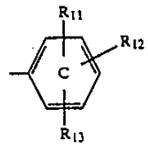
wherein R_1 is C_{1-6}alkyl not containing an asymmetric carbon atom, C_{3-7}cycloalkyl or



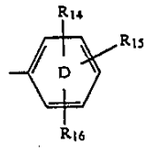
wherein R_5, R_6 and R_7 are as defined below,
R_2 is C_{1-6}alkyl not containing an asymmetric carbon atom, C_{3-7}cycloalkyl or



wherein R_8, R_9 and R_{10} are as defined below,
R_3 is hydrogen, C_{1-6}alkyl not containing an asymmetric carbon atom, C_{3-7}cycloalkyl or



wherein R_{11}, R_{12} and R_{13} are as defined below,
R_4 is hydrogen, C_{1-6}alkyl not containing an asymmetric carbon atom, C_{7-7}cycloalkyl or



wherein R_{14}, R_{15} and R_{16} are as defined below,
X is $-(CH_2)_m-$, $-CH=CH-$, $-CH=CH-CH_2-$ or $-CH_2-CH=CH-$, wherein m is 0, 1, 2 or 3, and
Z is

(Abstract continued on next page.)

476

600-6955/XN/B/cont X

United States Patent [19]

Damon, II

[11] Patent Number: 4,876,280

[45] Date of Patent: Oct. 24, 1989

[54] ARYLCYCLOHEXANE AND ARYLCYCLOHEXENE ANALOGS OF MEVALONOLACTONE DERIVATIVES AND THEIR USE

[75] Inventor: Robert E. Damon, II, Wharton, N.J.

[73] Assignee: Sandoz Pharm. Corp., E. Hanover, N.J.

[21] Appl. No.: 166,356

[22] Filed: Mar. 10, 1988

[51] Int. Cl.[4] A61K 31/19; A61K 31/215

[52] U.S. Cl. 514/510; 549/292; 514/460; 514/532; 562/469

[58] Field of Search 549/292; 562/469

[56] References Cited

U.S. PATENT DOCUMENTS

3,983,140	9/1976	Endo et al.	260/343.5
4,248,889	2/1981	Oka et al.	424/308
4,375,475	3/1983	Willard et al.	424/279
4,474,971	10/1984	Wareing	549/214
4,499,289	2/1985	Baran et al.	549/292
4,650,890	3/1987	Jewell et al.	556/446
4,772,626	9/1988	Smith et al.	549/292

FOREIGN PATENT DOCUMENTS

86/03488	6/1986	PCT Int'l Appl. .	
1325056	8/1973	United Kingdom	562/469

OTHER PUBLICATIONS

Hulcher, Arch. Biochem. Biophys. 146, 422–427 (1971).

Singer et al., Proc. Soc. Exp. Biol. Med. 102, 370–373 (1959).

Stokker et al., J. Med. Chem. 28, 347–358 (1985).

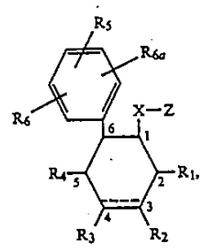
Primary Examiner—Robert T. Bond

Assistant Examiner—B. A. Trinh

Attorney, Agent, or Firm—Gerald D. Sharkin; Richard E. Vila; Melvyn M. Kassenoff

[57] ABSTRACT

Compounds of the formula



wherein R_1 is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl or t-butyl,

R_2 is hydrogen or C_{1-3}alkyl,

R_3 is hydrogen or C_{1-3}alkyl,

R_4 is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl or t-butyl,

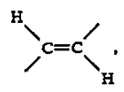
R_5 is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, fluoro, chloro, trifluoromethyl, phenoxy or benzyloxy,

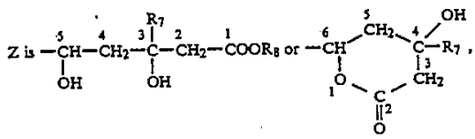
R_6 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, fluoro, chloro, trifluoromethyl, phenoxy or benzyloxy, with the provisos that not more than one of R_5 and R_6 is trifluoromethyl, not more than one of R_5 and R_6 is phenoxy, and not more than one of R_5 and R_6 is benzyloxy, or

R_5 and R_6 are attached to adjacent carbon atoms and taken together form a radical of the formula $-CH=CH-CH=CH-$,

R_{6a} is hydrogen, C_{1-2}alkyl, fluoro or chloro,

X is $-CH_2CH_2-$ or





wherein R_7 is hydrogen or C_{1-3}alkyl, and

R_8 is hydrogen, R_9 or M, wherein R_9 is a physiologically acceptable ester group, and M is a pharmaceutically acceptable cation, and the broken line represents a double (π) bond or two hydrogen atoms (one on each carbon atom), the use thereof for inhibiting cholesterol biosynthesis and lowering the blood cholesterol level and, therefore, in the treatment of hyperlipoproteinemia and atherosclerosis, pharmaceutical compositions comprising such compounds and processes for and intermediates in the synthesis of such compounds.

13 Claims, No Drawings

600-7022/C

477

United States Patent [19]

Kathawala et al.

[11] Patent Number: 5,001,255

[45] Date of Patent: Mar. 19, 1991

[54] IDENE ANALOGS OF MEVALONOLACTONE AND DERIVATIVES THEREOF

[75] Inventors: Faizulla G. Kathawala, Mountain Lakes; Sompong Wattanasin, Hopatcong, both of N.J.

[73] Assignee: Sandoz Pharm. Corp., E. Hanover, N.J.

[21] Appl. No.: 214,560

[22] Filed: Jul. 1, 1988

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 837,479, Mar. 7, 1986, abandoned, which is a continuation-in-part of Ser. No. 677,917, Dec. 4, 1984, abandoned.

[51] Int. Cl.[5] C07C 69/76

[52] U.S. Cl. 560/56; 560/53; 556/441; 549/264; 549/291; 562/462; 562/466

[58] Field of Search 560/56, 53; 549/264, 549/291; 562/462, 466; 514/530, 569

[56] References Cited

U.S. PATENT DOCUMENTS

3,207,779	9/1965	Cutler	560/56
3,532,752	10/1970	Shen	560/56
3,668,241	6/1972	Cragoe et al.	560/56
3,983,140	9/1976	Endo et al.	260/343.5
4,006,180	2/1977	Cragoe et al.	560/56
4,012,524	3/1977	Cragoe et al.	560/56
4,057,573	11/1977	Haas et al.	560/56
4,070,539	1/1978	Cragoe et al.	560/56
4,125,731	11/1978	Sugie et al.	560/56
4,137,322	1/1979	Endo et al.	424/273
4,198,425	4/1980	Mitsui et al.	424/279
4,248,889	2/1981	Oka et al.	424/308
4,255,444	3/1981	Oka et al.	424/279
4,308,378	12/1981	Stokker	542/441
4,361,515	11/1982	Terahara et al.	549/292
4,375,475	3/1983	Willard et al.	424/279
4,474,971	10/1984	Wareing	549/214
4,588,715	5/1986	Damon	514/63
4,613,610	9/1986	Wareing	514/406
4,647,576	3/1987	Hoefle	514/422
4,654,363	3/1987	Prugh	560/56

FOREIGN PATENT DOCUMENTS

142146	5/1985	European Pat. Off. .
84/02131	6/1984	PCT Int'l Appl. .
84/02903	8/1984	PCT Int'l Appl. .
86/03488	6/1986	PCT Int'l Appl. .

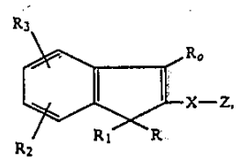
OTHER PUBLICATIONS

Hulcher, Arch. Biochem. Biophys. 146, 422–427 (1971).
Sato et al., Chem. Pharm. Bull. 28, 1509–1525 (1980).
Singer et al., Proc. Soc. Exp. Biol. Med. 102, 370–373 (1959).

Primary Examiner—Paul J. Killos
Attorney, Agent, or Firm—Gerald D. Sharkin; Richard E. Vila; Melvyn M. Kassenoff

[57] ABSTRACT

Compounds of the formula



the use thereof for inhibiting cholesterol biosynthesis and lowering the blood cholesterol level and, therefore, in the treatment of hyperlipoproteinemia and atherosclerosis, pharmaceutical compositions comprising such compounds and processes for and intermediates in the synthesis of such compounds.

27 Claims, No Drawings

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
	:	INTERFERENCE NO.: 102,648
V.	:	EXAMINER-IN-CHIEF:
FUJIKAWA ET AL	:	MICHAEL SOFOCLEOUS

**FUJIKAWA ET AL MOTION FOR SANCTIONS,
37 CFR §1.616**

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231
BOX INTERFERENCE

SIR:

Pursuant to the provisions of Rule 616, and in accordance with the provisions of 37 CFR §1.635, Fujikawa et al hereby request an order entering sanctions against the party Wattanasin for deliberate and knowing of violation of 37 CFR §10.62(b) and §10.63(a). Specifically, Fujikawa seeks sanctions for Wattanasin's introduction of, and reliance on, the testimony of one Melvyn Kassenoff, a crucial witness of the party Wattanasin with respect to the issues of abandonment, suppression and concealment, while at

the same time listing the same Melvyn Kassenoff as "Of Counsel" on the Record filed by Wattanasin in the above Interference, and refusing to exclude Melvyn Kassenoff from participation in the preparation of Wattanasin's Brief and Reply Brief, and in participation and preparation for Final Hearing. Further, to the extent Melvyn Kassenoff has acted as Counsel, in an advisory capacity, for the party Wattanasin throughout the Interference, such action further aggravates the violates of 37 CFR §10.62.

For the convenience of the Examiner, Fujikawa requests three different sanctions of varying severity, in the alternative. As a final matter Fujikawa requests a conference call be initiated on this matter at the earliest convenience of the EIC.

I. STATEMENT OF FACTS

1. In Wattanasin's Designation of Lead Attorney, filed March 23, 1992, Diane E. Furman was designated as Lead Attorney. Melvyn Kassenoff was designated as "Deputy Lead Attorney with full power and authority to act in the absence, for any reason, of the Lead Attorney."

2. At no time during this Interference has there been any need for action on the party Wattanasin in the absence of Lead Counsel Furman. A review of the Record reflects that only Lead Counsel Furman has appeared on behalf of Wattanasin, with supplemental questioning during certain depositions conducted by Mr. Richard Vila. No action has been taken, directly, by Melvyn Kassenoff in this Interference.

3. The Declaration of Melvyn Kassenoff was submitted by Wattanasin as evidence with respect to the issue of abandonment, suppression or concealment. The Declaration can be found at Wattanasin Record (herein after WR) pages 227-232. The Declaration is replete with statements of subjective intent that can be verified only by Melvyn Kassenoff's memory. See, e.g., paragraph 4, WR-228, "I was aware that patent disclosure 229/84 of Sampong Wattanasin had received an "A" rating. It was my intention that the case would be filed...". Similarly, paragraph 6 of the Declaration refers to Melvyn Kassenoff's "best recollection that in February of 1988, I was in communication with Dr. Wattanasin concerning information...". Finally, see paragraph 11, which refers to Melvyn Kassenoff's assertion that at no time "did I or, insofar as I aware, any other member of the patent and trademark

department of Sandoz Corporation, ever have any intention not to file a United States patent application...".

4. Due to the conclusory nature of some of the assertions in Melvyn Kassenoff's Declaration, and the lack of clarity of certain terms used, such as "backlog", Melvyn Kassenoff's cross-examination was taken, that cross-examination appearing at WR-234-317.

5. On May 15, 1993, Wattanasin filed and served its Record, which lists, as "Of Counsel" Melvyn M. Kassenoff, as well as Richard E. Vila. While Richard E. Vila has appeared in the proceedings, as a questioner in certain depositions, Melvyn M. Kassenoff had not previously appeared in the proceedings in any faculty. Thus, receipt of the Record filed by Wattanasin, which occurred on May 19, 1993, was the first opportunity undersigned Counsel had to be apprised of the fact that witness Melvyn Kassenoff would be undertaking an active, advocacy role in this proceeding.

On the following day, undersigned Counsel forwarded a letter via facsimile to Lead Counsel Furman objecting to reliance on witness Melvyn Kassenoff as Counsel, and specifically requesting, in writing, reassurance:

> That Mr. Kassenoff will have no participation in the preparation of the Brief, advice to yourself or other Counsel acting in this matter, appearance at, or suggestions with regard to Final Hearing, or any other participation in this matter.

It was further indicated that a Motion for Disqualification would be promptly filed if such written confirmation was not received. Relevant case citation was included in the letter.

On May 24, 1993, undersigned Counsel received a letter via facsimile from Lead Counsel Furman, refusing to provide the reassurances requested, and indicating reliance on 37 CFR §10.62(b)(2)-(4). A copy of that letter is enclosed herewith as Exhibit A.

6. On May 25, 1993, undersigned Counsel verified, by teleconference, that Wattanasin would oppose this Motion.

II. ARGUMENT

A. MELVYN KASSENOFF'S APPEARANCE AND PARTICIPATION AS COUNSEL VIOLATES 37 CFR §10.62(b) AND §10.63(a) AS WELL AS 37 CFR §10.110

The provisions of 37 CFR §10.62(b) are specific and unequivocal.

> A practitioner shall accept employment in a proceeding before the Office if the practitioner knows or it is obvious that the practitioner or another practitioner in the practitioner's firm ought to sign an affidavit to be filed in the Office or be called as a witness....

The Rule provides for exceptions to this provision. Proof that the exceptions applies rests on the party trying to rely on those exceptions. Universal Athletic Sales Company v. American Gym, Recreational and Athletic Equipment Corporation, Inc., 192 USPQ 193, 198-199 (3rd Cir. 1976), cert. denied, 193 USPQ 570 (1977). It is unquestioned that Melvyn Kassenoff appeared as a witness. In view of his listing as "Of Counsel", and Counsel for Wattanasin's refusal to provide written assurances that he would not act in

support of Wattanasin in the Brief or at Final Hearing, Fujikawa is forced to conclude that he is also acting, actively, as Counsel for Wattanasin in this matter.

A brief inspection of the four possible exceptions clearly demonstrates that they do not apply in this case. The first exception provides that simultaneous employment and testimony may proceed

> If the testimony will relate solely to an uncontested matter.

This is clearly not applicable herein. Melvyn Kassenoff's testimony goes solely to the issue of abandonment, suppression or concealment. This is clearly a contested issue in the case. Moreover, the specifics of Melvyn Kassenoff's testimony, including the clauses quoted above, are highly contested, particularly with respect to the issue of "backlog" and the "intentions of Sandoz".

Simultaneous employment and testimony may also go forward

> If the testimony will relate solely to a matter of formality and there is no reason to

> believe that substantial evidence will be offered in opposition to the testimony.

Similarly, the testimony relates not to a matter of formality, but to a crucial issue in the case, abandonment, suppression or concealment. Moreover, Melvyn Kassenoff himself offered testimony in contradiction to his Declaration, on cross-examination, see, e.g., WR-253-257 with regard to the issue of "backlog". See also, WR-266-267 with regard to the issue of who was to be assigned responsibility for the application in question. See also the testimony of Giesser, WR-319-463. Clearly, exception 2 to Rule 10.62(b) is not applicable.

The third exception to the prohibition on simultaneous representation and testimony on behalf of a client applies only

> If the testimony will relate solely to the nature and value of legal serves rendered in the case by the practitioner or the practitioner's firm to the client.

This clearly does not characterize Melvyn Kassenoff's testimony in this matter. His testimony goes not only to value of his own

services, or the practitioner's firm, but to the practice of the firm in general, to the firm's activity with regard to other cases (and inventors other than Wattanasin) and the methods by which the real party-in-interest for Sandoz arrives at a decision to file a case. Clearly, exception 3 is not applicable.

Finally, the fourth exception is an omnibus exception, which provides that if the practitioner has distinctive value as Counsel in the particular case, simultaneous representation and testimony may be permitted. Quite clearly, that is not applicable herein. Counsel for Wattanasin has gotten along quite well without reliance on the activities of Melvyn Kassenoff. One can scan the over 140 filings in this case without ever seeing the name Melvyn Kassenoff as the attorney acting on behalf of Wattanasin. Quite simply, until receipt of the Record, attorney Melvyn Kassenoff's activity on behalf of Wattanasin was unknown to Fujikawa. This fact was made painfully clear by Fujikawa during cross-examination of Wattanasin, at which Melvyn Kassenoff was present, for undisclosed reasons. Specifically, at WR-97, Melvyn Kassenoff broke into the exchange to say

> Let me ask one question on redirect. Page 97, lines 9-10.

In response, as no question had been asked, no objection was advanced, but undersigned Counsel made it clear that activity by the witness on behalf of the party was improper. WR-97, lines 11-12. In response, Mr. Vila, appearing for Wattanasin, indicated that the question would be taken up later, WR-97, lines 13-14, and in fact, it was never taken up. If Melvyn Kassenoff's unique attributes were really so critical to the representation of Wattanasin that he be permitted to participate both as Counsel and as witness, it is absolutely clear that he would have appeared, in some capacity, in this proceeding, prior to filing of the Record. In point of fact, Melvyn Kassenoff was an emergency contact person, in Furman's absence, and as Lead Counsel Furman has never been absent from the proceedings, Melvyn Kassenoff's role was never triggered.

It should be noted that Melvyn Kassenoff may have acted, without notice or visible presence, by providing advice as Counsel to Wattanasin to Lead Counsel Furman. This is regrettable, but undersigned Counsel could not have earlier brought this Motion, as Melvyn Kassenoff's involvement was made overt only upon the filing of the Record by Wattanasin.

Even in the event Sandoz should argue that its actions do not constitute a violation of §10.62(b) and §10.63(a), it is absolutely

clear that the practice engaged in by Sandoz on behalf of Wattanasin, employing, as an attorney, a critical and contested witness in the case raises at least the appearance of professional impropriety. Such is precluded by 37 CFR §10.110. Clearly, if Sandoz determined at some point in the course of conduct of the Interference that it was necessary to have Melvyn Kassenoff testify, and Sandoz believed it could not secure other Counsel to represent Wattanasin's interests, it was incumbent on Sandoz to draw the attention of the EIC and Fujikawa to the fact that its witness was simultaneously engaging in the representation of Wattanasin, and establishing the grounds for exception to §10.62 and §10.63, in an open and fair manner, which would have permitted sufficient time to review the entire matter, rather than just prior to filing of the Brief. By failing to fully disclose and discuss this matter in a fashion that would avoid the appearance of professional impropriety, Sandoz has violated the restrictions of 37 CFR §10.110, and should appropriately be sanctioned.

B. DISQUALIFICATION IS AN APPROPRIATE REMEDY

37 CFR §10.62(b) and §10.63(a) parallels disciplinary rules of

the Code of Professional Responsibility, including DR5-101 and 102. The Code specifically provides that disqualification of Counsel acting as a witness, and the members of the witness' firm, in the case the patent and trademark department of Sandoz, is an appropriate remedy when the party elects to present the testimony of its Counsel without satisfying the exceptions to Rule 10.62(b). Accordingly, as an appropriate sanction, Fujikawa hereby requests disqualification of all members of the Sandoz patent department from further participation in this Interference. Specifically, Fujikawa requests that the EIC issue an order directing Sandoz not to further participate in this Interference, to secure outside representation, and act only to provide a complete copy of the file and Record, already conveniently prepared, to outside Counsel who will act further in this case without contact with or participation by Sandoz Counsel. Clearly, the Rule does not contemplate the simultaneous representation and testimony by Counsel for a party.

It is noted that Wattanasin's opening Brief is currently due June 15, 1993. Fujikawa appreciates the imposition on outside Counsel to grow familiar with the case solely from the Record and file an adequate Brief by the June 15, 1993 deadline. Nonetheless, this problem was of Wattanasin's own making, Wattanasin ought to pay the price. However, if this sanction is applied, Fujikawa

would be agreeable to an extension of time of up to two weeks in which to provide outside Counsel opportunity to grow familiar with the file.

Disqualification of all members of the Sandoz patent department from further representation on behalf of Wattanasin is accordingly requested.

C. IN THE ABSENCE OF DISQUALIFICATION, AN APPROPRIATE SANCTION WOULD BE TO PRECLUDE SANDOZ FROM RELYING ON THE TESTIMONY OF MELVYN KASSENOFF

Fujikawa notes that Wattanasin has provided abundant testimony from a plurality of witnesses in this case. Fujikawa also notes that as to the facts allegedly testified to by Melvyn Kassenoff, similar facts are established by reference to the Declaration of Giesser and Rothwell, and therefor, Melvyn Kassenoff's testimony as to those facts are redundant. Testimony as to opinion, thought processes and the like, should not be permitted. In the event the EIC finds the sanction of disqualification too severe under the circumstances, it is respectfully requested that Wattanasin be denied opportunity to rely on the testimony of Melvyn Kassenoff. This would permit Melvyn Kassenoff to fully act as Counsel on behalf of Wattanasin, without unduly prejudicing Wattanasin due to

the largely duplicative nature of the factual testimony provided, and at the same time avoid the impropriety and improper practice prohibited by the rules.

In the absence of disqualification, Wattanasin should be precluded from relying on the testimony of Melvyn Kassenoff to support its position in this Interference.

D. TO THE EXTENT WATTANASIN IS PERMITTED TO RELY ON THE TESTIMONY OF MELVYN KASSENOFF, IT SHOULD BE SEVERELY DISCOUNTED

It is recognized that there is precedent that suggests that notwithstanding the impropriety of an attorney acting on behalf of a client also offering testimony on that client's behalf, the testimony is not thereby rendered incompetent, and admission, per se, does not constitute reversible error. Universal Athletic Sales, Supra at 199. It is to be noted that this finding is largely due to the fact that the Code of Professional Responsibility does not have the force or effect of a statute, Universal at 198, FN 19. In contrast, Counsel for Wattanasin has violated the specific wording of a regulation, which in this case does have the force and impact of statute. Accordingly, it is believed that disqualification, or in the alternative, preclusion of reliance on the testimony of Melvyn Kassenoff by party

Wattanasin is required. Nonetheless, even if not required, it is believed that the case law clearly establishes that where not required by law, such tainted testimony should be severely discounted. Quoting from the Universal opinion at page 199:

> The Court noted that the relationship of such a witness to his client detrimentally effected the weight to be accorded his testimony and therefor "discounted" its value. Such an approach, which would appear to be equally applicable to attorneys who serve as experts for their clients, also reflects our view. We believe that, while a District Court may in limited circumstances receive the testimony of a lawyer-witness, the value of that testimony must be discounted because of the interest of the lawyer or his firm in the outcome of the litigation.

It should be noted that this discounting referred to in the decision may be so severe as to be cause to vacate a decision based on the testimony adduced. Universal at page 203.

There is abundant precedent for severely discounting the testimony of a witness who acts as Counsel for the client on whose behalf the testimony is introduced, largely acknowledging the fact that such discounting is the only remedy, as the disciplinary rules have no statutory effect. This was clearly expressed by the Court in Lau Ah Tew v. Dulles, 257 F.2d 744 (9th Cir. 1958), the Court observing:

> It is usually inappropriate for an attorney connected with the trial of a case to testify on behalf of his client. He should ordinarily withdraw before becoming a witness. (Cites omitted). It is true that the professional relationship of such a witness does not effect his competency. (Cite omitted). However, an attorney who assumes the burden of a witness while representing his client in a lawsuit does so at the very great detriment to the credibility of his testimony. (Numerous cites omitted). 257 F.2d at 747.

The Board of Patent Interferences, in Wilder v. Snyder, 201 USPQ 927 (POBI 1977) took cognizance of this rule of law in citing 97

CJS Witnesses Section 71, page 467. The Court's discussion appears at page 934 of the decision, wherein it is noted that the law directs that

> The professional relationship of the witness effects his credibility....

Disqualification was considered in the decision Little Caesar Enterprises, Inc. v. Dominos Pizza, Inc., 11 USPQ 2d 1233 (Comm. of Pats. 1989). Therein it was noted that the rules preclude conduct that would be prohibited by the disciplinary rules of the ABA Model Code of Professional Responsibility. Clearly, the conduct engaged in by Wattanasin is precluded, see the decision, at page 1235. This includes the situation where an attorney is or ought to be called to testify on behalf of his client. Thus, the Commissioner of Patents and Trademarks, having established that Wattanasin's practices here specifically violates the rules, sanction of the type requested and recognized by prior precedent is appropriate.

In the absence of disqualification or preclusion of reliance on Melvyn Kassenoff's testimony, Fujikawa submits that an appropriate sanction would be to severely discount Melvyn Kassenoff's testimony, as is required by prior precedent.

E. SUMMARY

It is beyond question that Wattanasin's offering of Melvyn Kassenoff's testimony, while simultaneously employing Melvyn Kassenoff as Counsel in this Interference, violates the explicit provisions of 37 CFR §10.62 and §10.63. The appropriate measure for such a violation would be disqualification. Time pressures may preclude the appropriate remedy from being applied herein. Accordingly, in the alternative, it would be appropriate simply to preclude Wattanasin from relying, in any fashion, on the testimony of Melvyn Kassenoff. Should the EIC find this sanction too severe, at a minimum, it is believed that the Rules, and prior case law, clearly directs that the testimony of Melvyn Kassenoff be strongly discounted, that testimony having been prejudiced and tainted by Melvyn Kassenoff's involvement and complicity in the preparation of Wattanasin's case.

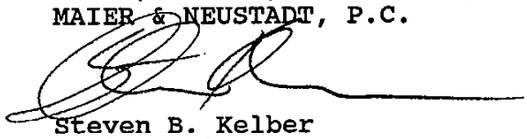
Due to the impending date for filing the Brief, and the nature of the violation, it is respectfully requested that a conference call on this issue be conducted, to expedite matters. EIC Sofocleous is not in the office through May 28, 1993. Accordingly, on his return to the office, a conference call is respectfully

requested.

As noted above, Counsel for Wattanasin was contacted, and indicated that this Motion would be opposed.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

ENCLOSURE: COPY OF MAY 24, 1993 LETTER
TO STEVEN B. KELBER FROM
DIANE FURMAN (EXHIBIT A)

CERTIFICATE OF SERVICE

I hereby certify that true copies of:

1. **FUJIKAWA ET AL MOTION FOR SANCTIONS, 37 CFR §1.616 and MAY 24, 1993 LETTER TO STEVEN B. KELBER FROM DIANE FURMAN (EXHIBIT A)**

2. **CERTIFICATE OF SERVICE**

were served upon Counsel for Wattanasin as follows:

Diane E. Furman
SANDOZ CORP.
59 Route 10
E. Hanover, New Jersey 07936

via FACSIMILE and FEDERAL EXPRESS, this 25TH day of MAY, 1993.

STEVEN B. KELBER

Interference 102,648

SANDOZ CORPORATION
59 ROUTE 10, EAST HANOVER NJ 07936

SANDOZ

PATENT AND TRADEMARK DEPARTMENT

TELEFAX 201 503 8807

May 24, 1993

VIA TELEFAX
(703) 413-2220

Steven B. Kelber, Esq.
Oblon, Spivak, McClelland, Maier and Neustadt, P.C.
1755 S. Jefferson Davis Highway
Crystal Square 5, Ste. 400
Arlington, VA 22202

Re: WATTANASIN v. FUJIKAWA et al.
Interference Nos. 102,648 and 102,975

Dear Steve:

I am in receipt of your telefax letter of May 20, 1993.

I. With regard to attorney Melvyn Kassenoff's of counsel status in these interferences, we believe his involvement falls squarely within the ambit of 37 CFR §10.62(b)(2)-(4), cf. 1045 OG 36.

First, as you have recognized, Mr. Kassenoff is a fact witness in these interferences, not an opinion witness. His testimony goes to the nature of his legal services rendered in connection with the involved Wattanasin application.

Second, given the distinctive nature of Mr. Kassenoff's expertise in the relevant technical area of HMG-CoA reductase inhibitors, as well as his status as a former Patent Examiner having extensive knowledge of Patent and Trademark Office procedures, it would work a substantial hardship on the Wattanasin real party of interest, i.e. Sandoz Corporation, if Mr. Kassenoff were to be prevented from providing technical or legal advice in this matter.

Indeed, practically speaking, the standard which you now evidently seek to impose on the party Wattanasin, would effectively deprive any corporation which is a party of interest in an interference, of the unique legal and technical skill of its own in-house patent staff simply because one or more of those same attorneys may almost necessarily be called as a fact witness concerning activities within the scope of their employment in connection with an involved application.

The fact is, since virtually "day one" of these interferences, you were on notice that Mr. Kassenoff is a designated deputy lead attorney for the party Wattanasin, with full power and authority to act in my absence (Int. No. 102,648, Wattanasin paper dated March 23, 1992).

Yet, for whatever reason, you failed to raise any issue in this regard when the Kassenoff Declaration of February 19, 1993 was served, and you even went ahead and took complete cross-examination by deposition from Mr. Kassenoff.

We will assume that you do not mean to impugn Mr. Kassenoff's probity, his conduct as an officer of the court, or his testimony under oath as a fact witness concerning his activities in connection with the involved Wattanasin application.

Accordingly, we simply find no inconsistency in Mr. Kassenoff's status as a fact witness and as an attorney of counsel for the party Wattanasin.

Since your position finds no support either in your own legal citations or in the Patent and Trademark Office Code of Ethics, or any legal authority of which we are aware, we must inform you that we cannot accede to your request that Mr. Kassenoff refrain from providing advice in respect of the above interferences.

II. With reference to the pentultimate paragraph of your letter, your attention is directed to pages 10-11 of the Wattanasin record, which comprise a "Cross-Reference Index of: Parties' Exhibits Marked for Identification at Cross-Examination Depositions with Documents of Record".

More specifically, Wattanasin Deposition Exhibit W-3 is cross-referenced to Wattanasin Exhibit B-2. As the Wattanasin deposition transcript, p. 69, makes clear, the deposition testimony refers to pages 164, 165 and 166 of Exhibit B-2, the pages of which are clearly marked at the upper right hand corner.

If you still insist upon copies of all of the exhibits of the relevant depositions, please let me know, and I will have them out to you as soon as possible.

III. A second copy of the Wattanasin record was mailed to you by first-class mail on Friday, May 21, 1993.

Very truly yours,

Diane Furman

Diane E. Furman

DEF:rmf

Received Time May. 24. 3:31PM

Paper No. 96

All communications respecting this case should identify it by number and names of parties.

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: BOX INTERFERENCE
Commissioner of Patents and Trademarks
Washington, D.C. 20231

Telephone: (703)557-4007
Facsimile: (703)557-8642

Interference No. 102,648

Wattanasin et al.

v.

Fujikawa et al.

Receipt is acknowledged of the following papers, filed on May 26, 1993 by Fujikawa:

1. Motion to consolidate the record (Paper No. 90).
2. Motion for sanctions under 37 CFR 1.616 (Paper No. 95).

For the reasons stated therein, the unopposed motion to consolidate the record is granted subject to (1) Wattanasin et al. and Fujikawa et al. clearly identifying the party and interference to which the testimony is directed, (2) dividing the record, where possible, into separate volumes that will related to a single interference, (3) providing a separate index as required in 37 CFR 1.653(c) and (4) maintaining the testimony of the witnesses relating to the two interferences separate and distinct insofar as possible.

The motion (item 2) for sanctions will be considered after the expiration of the time for filing an opposition and reply thereto to the motion.

Michael Sofocleous
Examiner-in-Chief
(703) 557-4066

FORM PTO-78B
(Rev. 11-92)

#97

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN

v. Interference Nos. [redacted] 102,975

FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

COMMUNICATION

FYI

MAY 28 1993

RECEIVED IN
BOX INTERFERENCE

VIA EXPRESS MAIL

Honorable Commissioner of Patents and Trademarks
Washington, DC 20231

Attention: Mrs. Hall

I appreciated your telephoning me on Tuesday, May 25, 1993 concerning the Consolidated Record of the party Wattanasin in the above interferences.

I. In response to your telephone call, I am enclosing the following documents with this letter:

---

(1) Page 162 of the Wattanasin record: you indicated that this page was missing from bound Volume II; and

(2) Exhibit S-4: you indicated that while our extra two spiral-bound courtesy copies of the Wattanasin Exhibits did contain Exhibit S-4, a loose copy of Exhibit S-4 was missing.

(continued)

II. Other corrections which you have called my attention to are as follows:

-TABLE OF CONTENTS:

Index (3) (i.e. the Cross-reference Index) begins at page 10 (not page 9 as indicated);

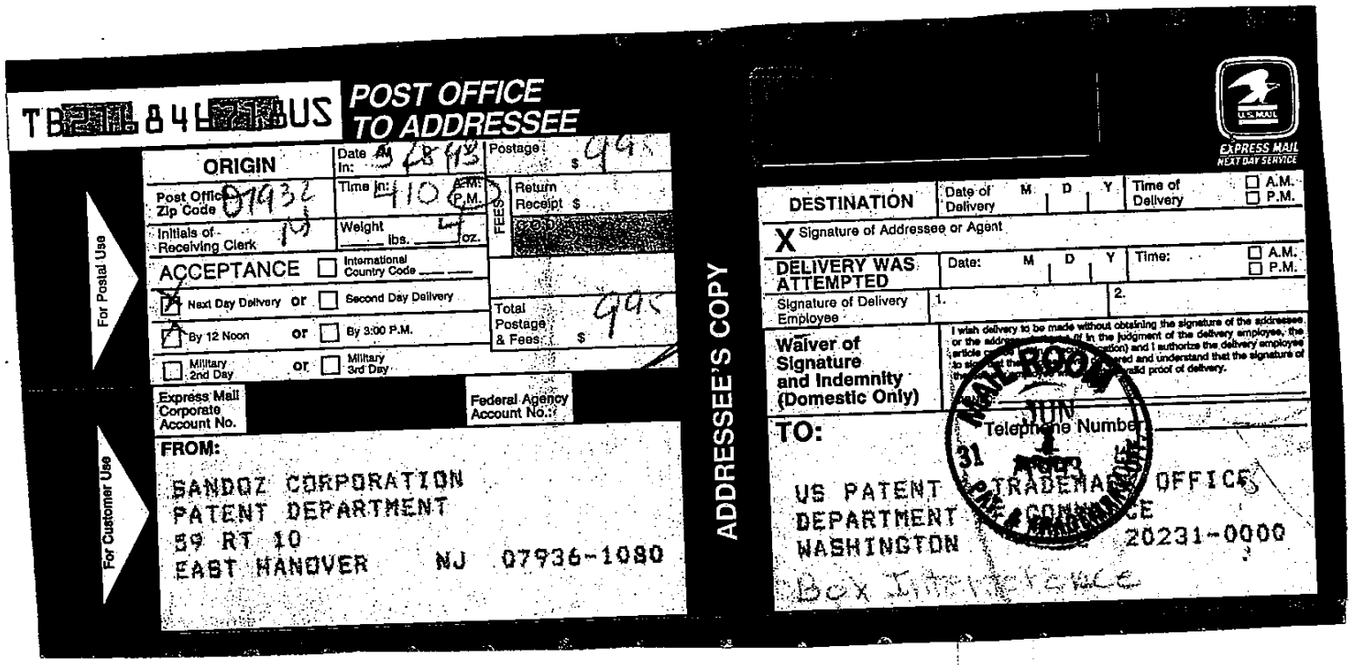
-CROSS-REFERENCE INDEX, p. 10:

Exhibit W-1 is marked for identification at page 283 of the record (not page 83 as indicated);

Exhibit W-3 is marked for identification at page 104 of the record (not page 372 as indicated).

III. You have also requested a second set of the Wattanasin record (i.e. 15 volumes comprising 3 copies each of Vols. I-V) and exhibits.

It was not clear to me that Examiner-in-Chief Sofocleous had requested duplicate sets of the Wattanasin consolidated record and exhibits for the above interferences. Since I have limited remaining bound copies in my posession, I will



TB [illegible] 84 [illegible] US

POST OFFICE TO ADDRESSEE

ORIGIN

Post Office Zip Code 01932

Initials of Receiving Clerk

Date In: 5/28/93

Time In: 410 A.M. P.M.

Weight ___ lbs. 4 oz.

ACCEPTANCE

Next Day Delivery or Second Day Delivery

By 12 Noon or By 3:00 P.M.

Military 2nd Day or Military 3rd Day

International Country Code

FEES

Postage $ 9.95

Return Receipt $

COD

Total Postage & Fees $ 9.95

For Postal Use

Express Mail Corporate Account No.

Federal Agency Account No.

For Customer Use

FROM:

SANDOZ CORPORATION
PATENT DEPARTMENT
59 RT 10
EAST HANOVER NJ 07936-1080

ADDRESSEE'S COPY

EXPRESS MAIL NEXT DAY SERVICE

DESTINATION

Date of Delivery M D Y

Time of Delivery A.M. P.M.

X Signature of Addressee or Agent

DELIVERY WAS ATTEMPTED

Date: M D Y

Time: A.M. P.M.

Signature of Delivery Employee 1. 2.

Waiver of Signature and Indemnity (Domestic Only)

I wish delivery to be made without obtaining the signature of the addressee or the addressee's agent if, in the judgment of the delivery employee, the article can be left [illegible] and I authorize the delivery employee to sign [illegible] delivered and understand that the signature of the [illegible] valid proof of delivery.

TO:

Telephone Number

US PATENT AND TRADEMARK OFFICE
DEPARTMENT OF COMMERCE
WASHINGTON 20231-0000

Box Interference

MAIL ROOM JUN 1 1993 PM

31

wait until I can speak with the EIC on his return to the office next week to confirm that he does want the additional copies.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
East Hanover, NJ 07936

DEF:rmf

May 28, 1993

Encls.: As noted
cc: S. Kelber (w. Record, p. 162, Exhibit S-4)

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on May 28, 1993
(Date of Deposit)

Diane E. Furman
Name of applicant, assignee, or Registered Representative

Diane Furman
Signature

5/28/93
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

COMMUNICATION

and enclosures were served on counsel for the party Fujikawa et al., this 28th day of May 1993, by postage pre-paid first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
Attn: Steven B. Kelber, Esq.
1755 South Jefferson Davis Highway
Crystal Square 5, Ste. 400
Arlington, VA 22202

Diane Furman

Diane E. Furman

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#98

WATTANASIN

v.

FUJIKAWA et al.

Interference Nos. 102,648, 102,975
Examiner-in-Chief: M. Sofocleous

WATTANASIN REQUEST FOR EXTENSION OF TIME

The party Wattanasin hereby respectfully petitions for an extension of time of one month, from June 15, 1993 to July 15, 1993, for filing the two Wattanasin opening briefs in the above-numbered interferences, as well as a corresponding extension of the dates for taking subsequent action.

Steven Kelber, Esq., counsel for Fujikawa et al., who was consulted prior to the filing of this motion, has indicated that he will oppose any extension of time to Wattanasin, except on the following condition:

that the EIC agree to rule on Fujikawa's Motion for Sanctions of May 25, 1993 prior to the due date of the opening briefs, in which case Mr. Kelber would not oppose a 10-day extension beyond the date of the EIC's decision.

However, the party Wattanasin is simply herein requesting grant of a one-month extension of time to file the two opening briefs in the above interferences, and corresponding extensions of the subsequent due dates.

DISCUSSION

On May 25, 1993, undersigned counsel for Wattanasin was served with Fujikawa's motion for sanctions in the above interferences.

Given the severity of the sanctions demanded by counsel for Fujikawa -- including complete disqualification of the entire Sandoz in-house patent staff and retention of outside counsel on short notice and at significant expense, and, in particular, the discrediting of the testimony of Melvyn Kassenoff, Esq. -- this matter requires immediate and complete attention of the undersigned, who is also carrying a full workload otherwise.

The Wattanasin opposition paper is due June 14, 1993. The Wattanasin opening briefs are currently due June 15, 1993.

Clearly, one effect of the Fujikawa motion at this point in the interferences is to distract Wattanasin at a critical period during which the opening briefs are being prepared.

In point of fact, the apparent basis for the Fujikawa motion would seem to have existed for some months, ever since Mr. Kassenoff's affidavit was caused to be filed in February of 1993 in response to the Fujikawa notice concerning an issue of abandonment. Fujikawa have been on notice since the very beginning of these interferences that Mr. Kassenoff is a deputy lead counsel of record. Fujikawa even took cross-examination of Mr. Kassenoff in March of 1993 without raising the issue of his status as deputy lead counsel.

Now, evidently timed in a fashion to conflict with the preparation of the Wattanasin main briefs, Fujikawa have come forward with their motion for sanctions.

Wattanasin does not believe that the Fujikawa motion has any merit whatsoever, and will be filing an opposition in due course.

Prior extensions in this interference have been reasonably limited and generally confined to the logistics of testimony. At least one motion, unopposed by Wattanasin, was granted mainly for the convenience of Mr. Kelber, who now chooses, as counsel for Wattanasin sees it, to belatedly complicate the important period leading to the filing of the two main briefs.

It is submitted that the requested extension of time is justified, and its granting is respectfully requested.

Finally, it is suggested that a conference of the parties and the EIC on this matter may be worthwhile.

Accordingly, Wattanasin now moves to re-set the relevant dates of the above interferences as follows:

Wattanasin opening briefs due ..... July 15, 1993.
Fujikawa brief due ..... August 15, 1993.
Wattanasin reply brief due.....September 4, 1993.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
East Hanover, NJ 07936

DEF:rmf

June 4, 1993

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below:

DIANE E. FURMAN
Type or print name of person signing certification

Diane Furman
Signature

6/4/93
Date

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN REQUEST FOR EXTENSION OF TIME

was served on counsel for the party Fujikawa et al., this 4th day of June 1993, by telefax addressed to the following:

(703) 413-2220
Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
Attn: Steven B. Kelber, Esq.
1755 South Jefferson Davis Highway
Crystal Square 5, Ste. 400
Arlington, VA 22202

Diane Furman
Diane E. Furman

ACTIVITY REPORT

RECEPTION OK

TN #	6273
CONNECTION TEL	9
CONNECTION ID	G3
START TIME	06/04 17:00
USAGE TIME	02'59
PAGES	5

[redacted]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#99

WATTANASIN

v.

FUJIKAWA et al.

Interference Nos. 102,648, 102,975
Examiner-in-Chief: M. Sofocleous

WATTANASIN REQUEST FOR EXTENSION OF TIME

The party Wattanasin hereby respectfully petitions for an extension of time of one month, from June 15, 1993 to July 15, 1993, for filing the two Wattanasin opening briefs in the above-numbered interferences, as well as a corresponding extension of the dates for taking subsequent action.

Steven Kelber, Esq., counsel for Fujikawa et al., who was consulted prior to the filing of this motion, has indicated that he will oppose any extension of time to Wattanasin, except on the following condition:

that the EIC agree to rule on Fujikawa's Motion for Sanctions of May 25, 1993 prior to the due date of the opening briefs, in which case Mr. Kelber would not oppose a 10-day extension beyond the date of the EIC's decision.

However, the party Wattanasin is simply herein requesting grant of a one-month extension of time to file the two opening briefs in the above interferences, and corresponding extensions of the subsequent due dates.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#100

WATTANASIN

v.

FUJIKAWA et al.

Interference Nos. 102,648, 102,975

Examiner-in-Chief: M. Sofocleous

FYI

JUN 17 1993

RECEIVED IN
BOX INTERFERENCE

WATTANASIN OPPOSITION
TO FUJIKAWA MOTION FOR SANCTIONS

STATUS

By motion of May 25, 1993 in the above-identified interferences, the party Fujikawa et al. have requested sanctions against the party Wattanasin for alleged violation of Sections 10.62(b) and 10.63(a) of 37 CFR.

The purported violation concerns Wattanasin's introduction of and reliance on testimony of Melvyn M. Kassenoff, Esq., a patent attorney on the staff of the Sandoz Corporation Patent and Trademark Department[1], going to the issue of abandonment, suppression or concealment, while he is at least apparently participating in the interferences as "deputy lead counsel".

The sanctions demanded by Fujikawa are as follows (in the alternative):

1. Disqualification of all members of the Sandoz Patent and Trademark Department from further participation in the interferences;

2. Striking the testimony of Kassenoff;

3. "Severely discounting" the testimony of Kassenoff.

---

1. Melvyn M. Kassenoff has been employed in the Sandoz Patent and Trademark Department for about 20 years.

Wattanasin now opposes the Fujikawa motion. It is respectfully submitted that the Fujikawa motion is completely devoid of support in fact or law; and that furthermore, that it is belated, having been raised over three months after the Kassenoff testimony was made of record, and over one year after Mr. Kassenoff's designation as a counsel in these interferences.

Accordingly, Wattanasin requests that the Fujikawa motion, and each and every sanction requested therein, be denied.

STATEMENT OF FACTS

1. When these interferences first went forward, management at Sandoz Pharmaceuticals Corporaton, the assignee of interest of the party Wattanasin, made a decision to rely for representation on the Sandoz in-house patent staff (consistent with the usual practice of Sandoz in patent interferences).

2. Effective March 23, 1992, the undersigned, Diane E. Furman, an attorney in the Sandoz Corporation Patent and Trademark Department, was designated the lead attorney of record for the interferences. Melvyn M. Kassenoff, Esq., also with Sandoz, was designated deputy lead counsel, with full power and authority to

act in the absence of the lead attorney.[1] (see Exhibit A)

3. The designation of Kassenoff was made in recognition of the fact that he has substantial experience, unique to the Sandoz Patent and Trademark Department, in the subject matter area of these interferences, i.e. HMG-CoA reductase inhibitor compounds. Melvyn Kassenoff is also regarded as the Sandoz Patent and Trademark Department's foremost expert on PTO rules and regulations, and had more experience in interference procedure under the new rules than any other member of the department.[2]

4. Kassenoff's role as an attorney in these interferences has been primarily as a consultant or "sounding board," providing occasional advice on procedural and scientific issues.

5. Kassenoff did not provide any testimony in these interferences as to priority.

6. It was only when Fujikawa raised the issue of abandonment, supression or concealment, that it became apparent that Mr.

---

1. Melvyn M. Kassenoff is also listed as an attorney of record on the involved Wattanasin application. Another Sandoz patent attorney of record on the application, Richard E. Vila, Esq., became active in the interference at the deposition stage.

2. It is noted that Mr. Kassenoff is the only member of the Sandoz staff who is a former patent examiner, and also is distinguished by having an advanced degree (M.S.) in chemistry.

Kassenoff had relevant testimony which needed to be taken in order for Wattanasin to present a complete defense. More specifically, Kassenoff's testimony goes to the period between the last documented laboratory work in connection with the Wattanasin invention and the filing of the involved Wattanasin application. Although Mr. Kassenoff himself did not draft the Wattanasin involved application, his testimony of record shows that he participated in information gathering for the application, and that he was familiar with Sandoz patent policies and procedures as they applied to filing the Wattanasin case[3].

7. Wattanasin filed the Kassenoff declaration in February of 1993 (Exhibit B). At that time, not one word was heard from Mr. Kelber as to any impropriety in Mr. Kassenoff's concurrent designation as deputy lead counsel or in his continuation in such capacity.

8. In fact, in March of 1993, virtually one year to the day from Mr. Kassenoff's designation as deputy lead counsel of record, Steven B. Kelber, counsel for Fujikawa, came to the Sandoz Patent

3. Until January 1, 1993, when Mr. Kassenoff became supervisor of Patents Group II, one of two patent groups comprising the Sandoz Patent and Trademark Department, he reported to Mr. Vila, (who is supervisor of Patents Group I), and had no formal supervisory responsibilities. However, since about 1982, Mr. Kassenoff had certain de facto responsibilities in relation to HMG-CoA reductase matters, including assisting of junior department members working in the area, i.e. Joanne M. Giesser, Esq. (now departed from Sandoz), who drafted the involved Wattanasin application, and the undersigned lead counsel.

and Trademark Department in East Hanover, New Jersey, and subjected Mr. Kassenoff to rigorous cross-examination by deposition (see Kassenoff cross-examination transcript at pages 233-318 of the Wattanasin Record), without ever raising the question of impropriety as to Mr. Kassenoff's continuing status as deputy lead counsel.[4]

9. Subsequently, the Wattanasin Record was filed and served. The Record cover pages (Exhibit C) bear a designation of Mr. Kassenoff and Richard E. Vila, Esq. as being "of counsel".[5] No change was made in the status of Mr. Kassenoff as deputy lead counsel.

10. Thereafter, a letter was received by the undersigned from Mr. Kelber (Exhibit D) identifying Mr. Kassenoff as a "critical fact witness" for Wattanasin and objecting to his participation as an attorney for Wattanasin.

---

4. During the cross-examination session at Sandoz, Mr. Kassenoff refrained from taking any testimony since he was a witness at the session, but the subject of his continued participation as deputy lead counsel was never questioned or discussed, let alone protested, by Mr. Kelber.

5. It should be noted that it has been the practice in the Sandoz Patent and Trademark Department, at least in cases before the Court of Appeals for the Federal Circuit, that the briefs and record would designate as of counsel, one or more of the immediate supervisors of the principal attorney of record, and/or to indicate that the named individuals had background or consultant status in connection with the case. This practice was followed in the current interferences.

11. On May 25, 1993, Fujikawa filed their motion for sanctions, which Wattanasin now opposes.

STATEMENT OF THE ISSUES

The critical issue is whether Melvyn M. Kassenoff's testimony for Wattanasin violates any known legal requirement, or even presents an appearance of impropriety, or needs to be discounted, in view of his status as deputy lead counsel (or "of counsel") in this matter.

APPLICABLE LAW AND ARGUMENTS

As a first matter, there is nothing in the Federal Rules of Evidence, which govern these interferences, which prevents an attorney from testifying on behalf of his client.

The most pertinent regulations bearing on the circumstances under which an attorney may serve as a witness for his client are located at 37 CFR §§10.62(b) and 10.63(a) (both effective 1985) (Exhibit E). These sections essentially track the language of the American Bar Association Code of Professional Responsibility, Disciplinary Rules (DR) 5-101(B) and 5-102(A), respectively.

1. 37 CFR §10.62, 10.63

(i) **37 CFR §10.62(b)** indicates that prospective employment should be refused by a practitioner or another practitioner in his firm when the practitioner or his associate "ought to be" called as a witness for the client in the matter.

(ii) **37 CFR §10.63(a)** likewise indicates that a practitioner who has already undertaken employment should withdraw if it becomes apparent that the practitioner or another in his firm "ought to" testify on behalf of the client.[6]

Of course, by their strict wording, both rules are directed to situations involving "firms," a term which is left undefined in the definitions section of Part 10 of 37 CFR. In conventional usage, however, the term "firm," would not even apply to an in-house corporate patent department.

However, assuming arguendo that Rules 10.62(b) and 10.63(a) would apply to in-house counsel, both rules are subject to four defined areas where an attorney's testimony for his client need not require him to withdraw from representation:

(1) If the testimony will relate solely to an uncontested matter.

6. 37 CFR §10.63(b) is directed to a case where the testimony is "other than" on behalf of the client, and is therefore inapplicable to the present situation.,

(2) If the testimony will relate solely to a matter of formality and there is no reason to believe that substantial evidence will be offered in opposition to the testimony.

(3) If the testimony will relate solely to the nature and value of legal services rendered in the case by the practitioner or the practitioner's firm to the client.

(4) As to any matter, if refusal would work a substantial hardship on the client because of the distinctive value of the practitioner or the practitioner's firm as counsel in the particular case.

Sub-paragraph (1)

Sub-paragraph (1) above may or may not apply to the present situation. However, it is respectfully submitted that the Kassenoff testimony certainly falls within any one or more of sub-paragraphs (2), (3) and (4).

Sub-paragraph (2)

Concerning sub-paragraph (2), Mr. Kassenoff's testimony in part clearly relates essential to formalities, e.g., the existence of his handwriting in certain documents of record [e.g., see pages 4-5 of the Kassenoff Declaration (WR at 230-231)].

Sub-paragraph (3)

Furthermore, Mr. Kassenoff's testimony should be entirely permitted under sub-paragraph (3), which goes to the nature and value of legal services. For example, he provided testimony concerning his involvement as a member of the Sandoz Patent and

Trademark Department in the activities leading to filing of the Wattanasin application, and policy and practices applied to the filing of the Wattanasin application, as well as examples of cases which he drafted in the HMG-CoA reductase area [e.g., see pages 1-5 of the Kassenoff Declaration (WR at 227-231)].

Indeed, if there were any doubt that the Kassenoff testimony falls squarely within the purview of at least sub-paragraph (3), the underlying PTO commentary makes this crystal clear:

> "One comment suggested that proposed §10.62 should specifically authorize a registered patent practitioner to testify concerning attorney diligence in patent cases. This suggestion is not to be adopted. However, it should be clear that in most cases, the exception of proposed §10.62 (b)(3) would apply.***[citation to Wilder v. Snyder, 201 USPQ 927 (Bd. Pat. Inter. 1977]
>
> [emphasis supplied] 1045 OG 36[7] (see Exhibit F)

Thus, while the PTO drafters did not incorporate into Rule 10.62(b) the above proposed language relating to admissible attorney testimony as to diligence -- probably in the desire to adhere strictly to language paralleling the sister ABA disciplinary rules, DR 5-101(B) and 5-102(A) -- the commentary

---

7. Conspicuously absent from the Fujikawa motion is any reference to this PTO commentary, to which Fujikawa were expressly directed by Wattanasin in the undersigned's letter included as Exhibit A to the Fujikawa motion.

does clarify that the present circumstances should fall within the sub-paragraph (3) exception.

The commentary goes on to state that "the weight to be given testimony by a practitioner on behalf of his or her client would be determined on a case-by-case basis" -- which, of course, the Board is free to do with respect to any testimony.

In short, there is nothing in Mr. Kassenoff's testimony, required by Fujikawa's raising of the abandonment issue, which does not legitimately come within exception (3), above.

Sub-paragraph (4)

With respect to sub-paragraph (4), the "hardship exception," it is a given that disqualification of Mr. Kassenoff from this matter would work a substantial hardship on the party Wattanasin. As indicated above, Mr. Kassenoff not only has distinctive knowledge of the HMG-CoA reductase inhibitor area, but also considerable and valued expertise concerning PTO interference procedure. In particular, Mr. Kassenoff has been engaged in the drafting and prosecution of HMG-CoA cases, and building of a patent estate in this subject matter area, since about 1982. Mr. Kassenoff has been a primary liaison with Sandoz management concerning both Sandoz and third-party coverage in the HMG-CoA reductase area. Disqualification of Mr. Kassenoff as a counsel in these interferences would unfairly deprive Sandoz of Mr. Kassenoff's wide technical and patent knowledge gained from substantial experience in the HMG-CoA area. Furthermore, Mr. Kassenoff, as a member of the Sandoz Patent Committee, also has

intimate knowledge of the procedure and practices of the Committee in the rating of patent disclosures.

Accordingly, it is believed that the present facts amply justify application of subparagraph (4) permitting attorney testimony in hardship cases.

2. Caselaw

There appears to be no decisional law under the 1985-enacted 37 CFR 10.62 or 10.63, save for the Domino[8] case referred to by Fujikawa, where, in fact, the Commissioner was concerned with Rule 10.63(b) which is not at issue here, and in any event, denied a motion for disqualification.

This points up a fundamental problem with the legal authority relied on by Fujikawa in their brief: in the context of a highly fact-dependent inquiry such as one directed to attorney impropriety and sanctions, Fujikawa are casting about for support in various judicial dicta and broad-brush restatements of the law -- in complete disregard, however, of the underlying facts which distinguish their cited caselaw from the instant situation.[9]

8. Little Caesar Enterprises Inc. v. Domino's Pizza Inc., 11 USPQ2d 1233 (Comm. 1989).

9. Fujikawa certainly cast wide for the broad dicta appearing in Lau Ah Tew v. Dulles, 257 F.2d 744 (9th. Cir. 1958), a naturalization case where the attorney's testimony in question concerned his ability to recognize the identity of his client, a petitioner for naturalization.

For example, the 1977 Wilder case (Exhibit G) mentioned in the PTO commentary on Rule 10.62(b) and also cited by Fujikawa, involved an interference situation where the Board, in fact, found "no reason not to accord weight" to testimony given by an attorney for the senior party.

Universal Athletic Sales Co. v. American Gym, Rec. & Ath. Equip. Corp., 192 USPQ 193 (3d Cir. 1976), cert. den. 193 USPQ 570 (1977) (Exhibit H), relied on extensively by Fujikawa, is concerned with a situation where an attorney in the law firm representing the infringement defendant testified as a purported expert as to the invalidity of plaintiff's patent at issue. The Third Circuit vacated the district judge's finding of patent invalidity on the ground that the arguable deficiency of the witness as an expert and his role as an attorney should have prevented his testimony from being given controlling weight to rebut the presumption of validity of an issued patent.

Therefore, the Universal case, notwithstanding its broad-brush restatements of the law amounting to dicta, is limited on its facts to a situation involving expert testimony by a law firm attorney -- which is recognized to be severely deficient to begin with -- being given controlling weight in overcoming the presumption of validity attaching to an issued U.S. patent. The Third Circuit ruling overturning the trial judge's unpatentability finding had to be colored by the obvious deficiencies of the witness's purported expert testimony.

By contrast, Mr. Kassenoff is an in-house counsel being relied on as a fact witness, as even Fujikawa acknowledge. Mr. Kassenoff is not being offered as an expert witness. Nor is Mr. Kassenoff testifying as to the validity of an issued patent. In sum, it is difficult to find any substantive influence that the Universal case on its facts could have as to these interferences.

In very illustration of this point, the court in the succeeding interference case of Wilder, while paying "lip service" to the broad pronouncements in Universal and similar language in 97 C.J.S. Witnesses §71, in fact, chose to admit into evidence the attorney testimony at issue in Wilder.

Even more instructive in an interference setting is a case overlooked by Fujikawa: Wick v. Zindler, 230 USDPQ 241 (Bd. Pat. Inter. 1984) (Exhibit I). In that case, the attorney, Holtz, who prepared the involved application of the senior party, also served as a designated co-counsel in the interference. Holtz's testimony was needed to corroborate the senior party's date of conception.

The junior party moved to exclude the Holtz testimony. In deciding the motion, the Board first referred to the Wilder case for authority that an attorney is competent to serve as a witness for or against his client. In dictum, the Board also recited that this testimony could be discounted. However, in fact, the Board went on to consider the testimony:

> Nevertheless, under the circumstances of this case where Holtz has identified certain documents that the inventor used to explain the invention during conferences with him, we believe that his testimony as to when the conferences occurred and that the invention was then explained and understood by him is entitled to sufficient weight to corroborate conception. We note that Holtz supported his tesitimony with documentary evidence in the form of calendar entries... and entries in his law firm's log of invention disclosures ... [emphasis supplied]

230 USPQ at 246

Finally, reference is made to the case of SMI Industries Canada Ltd. v. Caelter Industries, Inc., 223 USPQ 742 (NDNY 1984) (Exhibit J), which involved an action for patent and trademark infringement, and unfair competition. Denying plaintiff's motion to disqualify defendant's law firm under DR 5-102(A) of the ABA Code of Professional Responsibility, the parallel section to 37 CFR 10.63(a), the court stated that the resulting loss of services would create precisely the kind of hardship which is protected against by sub-paragraph (4) of DR 5-101(B) [analogous to 37 CFR 10.62(b)(4)]:

> Even assuming, arguendo, that members of the Limbach firm ought to be called as witnesses at trial, the court concludes that disqualification is not appropriate in this case. As noted previously, DR 5-101(B)(4) provides that an attorney may continue representation of his client in a proceeding in which the attorney is called upon to testify if disqualification would work a special and unwarranted hardship on the client by virtue of the distinctive value of the lawyer or his firm as counsel in the case.

> In the present case, George Limbach has represented the related predecessor coporation of defendant in patent and trademark matters since 1967, and the Limbach firm has represented defendant and its related companies since early in 1968. The attorney-client relationship has become intimate, and the firm has acquired specialized knowledge of defendant, defendant's related companies, and their operations. The Limbach firm's representation of defendant in the present action involves a complex set of legal and factual issues which the firm has been familiar with for many years. At this late juncture it would work a substantial hardship upon the defendant to require it to retain new counsel. Moreover, there is no basis for concluding that the continued representation by the Limbach firm will prejudice the plaintiff in this proceeding in any way or taint the underlying trial. Accordingly, plaintiff's motion to disqualify pursuant to Canon 5 is denied. [emphasis supplied]

223 USPQ at 748.

It is believed that the disqualification of Kassenoff or any other in-house Sandoz attorney would present no less hardship on the party Wattanasin than is described in the above SMI decision concerning the Limbach disqualification.

Counsel for Wattanasin can understand that there would be legitimate concern to separate the role of an attorney as a witness from the role of an advocate at trial before a jury. Avoiding prejudice before the jury is a guiding consideration in many disqualification cases. However, even in these cases, the courts have often simply prevented the attorney giving testimony from appearing in court before the jury as trial counsel for his client.

Of course, the present case does not involve a jury trial, but a proceeding conducted before a panel of Examiners-in-Chief. Surely the concern to avoid prejudice that informs the ABA's restraints against attorney testimony in jury trials, would not obtain in a patent interference proceeding.

Particularly in a case where an attorney is testifying on behalf of his client, there is a harsh injustice to the client to force him to choose between the attorney's legal knowledge and the attorney's often critical knowledge as fact witness. The hardship is even greater when an attorney is forced to abandon his legal role in mid-stream in order to have his testimony received into the record.

In particular, the policy which Fujikawa now seeks to apply against Wattanasin is manifestly unfair: If the EIC were to approve the Fujikawa motion, this would mean that any corporation which is a party of interest in an interference, would effectively be deprived of the unique legal and technical skill of its own in-house patent staff simply because one or more of those same attorneys may almost necessarily be called as a fact witness concerning activities within the scope of their employment in connection with an involved application.

In summary, the express terms of 37 CFR §10.62(b) and §10.63(a), and the weight of decisional authority as well as

policy considerations, are squarely against disqualification of the Sandoz Patent and Trademark Department, or Mr. Kassenoff individually, from the present interferences. Similarly, it is submitted that under the present circumstances, there is absolutely no reason or justification for discrediting the Kassenoff testimony.

Given the improbability under all relevant legal authorities of his obtaining disqualification of the Sandoz Patent and Trademark Department or of Mr. Kassenoff alone, what Mr. Kelber is transparently really after is "discounting" or "discrediting" of the Kassenoff testimony.

Why Mr. Kassenoff's testimony should be "discounted" as opposed to that of any other witness is not entirely clear. Like the other deposed Wattanasin witnesses, Mr. Kassenoff was subjected to rigorous cross-examination by Mr. Kelber. Even more so than the other, non-attorney witnesses, Mr. Kassenoff would have been conscious of his obligation, as member of the bar and an officer of the court, to uphold his oath. Likewise, Mr. Kassenoff would have been aware of the severe toll on his professional status that could attend violation of his oath. Mr. Kassenoff furthermore being an acknowledged fact witness, there is no good reason to discredit his testimony, and none is really offered by Fujikawa.

FUJIKAWA BELATEDNESS

For whatever reason, Fujikawa have until now -- over three months after the Kassenoff testimony was presented and over a year after Mr. Kassenoff's designation as a deputy counsel of record -- failed to raise any issue of disqualification or "discounting" of testimony, and even have taken cross-examination from Mr. Kassenoff without raising the issue.

In short, Fujikawa are raising an issue long after it should have been raised. To all appearances, Fujikawa saved their motion for a time when opposition to it would have been due one day before Wattanasin's main briefs.

It has to be concluded that the probable cause for the Fujikawa motion for sanctions is that counsel for Fujikawa happened to elicit from Mr. Kassenoff on cross-examination, information going to Sandoz Patent and Trademark Department procedure and the like, which could not be favorable to Fujikawa. Grasping for a rationale to eliminate or discredit this testimony, Fujikawa counsel have fabricated a strategy based on allegations of attorney impropriety. Such belated action and conduct should not be permitted.

CONCLUSION

Accordingly, the Fujikawa motion for sanctions should be denied on the basis of any one or more of the following reasons:

1. The testimony of Melvyn M. Kasssenoff for the party Wattanasin falls within the protected activity of 37 § 10.62(b)(2) and (3), because it constitutes testimony going to formalities and the factual circumstances of his activities in relation to the Wattanasin invention;

2. The testimony of Melvyn M. Kassenoff also falls within 37 CFR 10.62(b)(4), because otherwise the party Wattanasin would be deprived of Kassenoff's in-house technical and patent law expertise, which would work a serious hardhip;

3. The Fujikawa motion is belated, as it could have been filed much earlier. The suggestion by Mr. Kelber that he only became aware of the situation upon filing of the Wattanasin Record is without merit. Mr. Kassenoff has been listed as deputy lead attorney from the beginning of this matter.

4. None of the sanctions sought by Fujikawa is justified, and in fact would only serve to give Fujikawa undeserved advantage to the extent the Kassenoff testimony was discounted. Counsel for Fujikawa caused this testimony to be taken, and subjected Mr. Kassenoff to cross-examination under oath. Counsel for Fujikawa

should face the testimony rather than have the PTO discount it in advance for no justifiable reason.

Finally, Mr. Kassenoff has not been an active participant in these interferences (particularly following his changed responsibilities as of January 1993, referred to above); rather, he has served as a consultant on an intermittent basis concerning technical or PTO procedural matters. Wattanasin would be willing to remove Mr. Kassenoff as deputy lead counsel, but cannot without hardship meet Fujikawa's demands, which would deny the undersigned any right to consult with Melvyn Kassenoff concerning these interferences.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
East Hanover, NJ 07936

June 14, 1993

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on June 14, 1993
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
June 14, 1993
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN OPPOSITION
TO FUJIKAWA MOTION FOR SANCTIONS

was served on counsel for the party Fujikawa et al., this 14th day of June 1993, by first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
Attn: Steven B. Kelber, Esq.
1755 South Jefferson Davis Highway
Crystal Square 5, Ste. 400
Arlington, VA 22202

Diane Furman
Diane E. Furman

Exhibit A

Case No. 600-7101/CONT
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
v.	:	Interference No. 102,648
PICARD et al.	:	Examiner-in-Chief:
v.	:	M. Sofocleous
FUJIKAWA et al.	:	

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231
BOX INTERFERENCE

37 CFR 1.613 DESIGNATION OF LEAD ATTORNEY
FOR THE PARTY WATTANASIN

In accordance with 37 CFR 1.613, the undersigned, Diane E. Furman, is hereby designated as the lead attorney for the party Wattanasin in the above-identified interference.

Melvyn M. Kassenoff, Registration No. 26,389, attorney of record at phone no. (201) 503-8477, is hereby designated deputy lead attorney with full power and authority to act in the absence, for any reason, of the lead attorney.

As per the power of record, the address for both of the foregoing is: Patent and Trademark Department, Sandoz Corporation, 59 Route 10, East Hanover, New Jersey 07936.

Respectfully submitted,

Diane Furman 3/23/92
Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332 (phone)
201-503-8807 (facsimile)

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on March 23, 1992
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
March 23, 1992
Date of Signature

SANDOZ CORP.
59 Route 10
E. Hanover, NJ 07936
RMF:def
March 23, 1992

Exhibit B

Case No. 600-7101/CONT/INT.(2)
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v.
FUJIKAWA et al.

Interference Nos. 102,648, 102,975
Examiner-in-Chief: M. Sofocleous

DECLARATION OF MELVYN M. KASSENOFF PURSUANT TO 37 CFR §1.672

I, Melvyn M. Kassenoff, do hereby declare as follows:

1. All of the below-indicated activities took place in the United States.

2. I have been employed by Sandoz Corporation in the Patent and Trademark Department since 1972. My current position is Director, Patent and Trademark Affairs. I am an associate counsel of record in these interferences.

3. I have had responsibility for the filing and prosecution of Sandoz patent applications in the HMG-CoA reductase inhibitor area since 1982. However, this area was only a very small portion of my total workload, the bulk of which comprised prosecuting applications in the azo dye area originating from research done by Sandoz AG in Basle, Switzerland.

Since about 1981, Sandoz Research Institute has been engaged in a research effort to develop compounds having utility as HMG-CoA reductase inhibitors for use in the treatment of hypercholesterolemia. This project resulted in numerous patent disclosures being submitted to the Patent Department, including Patent Disclosure 299/84 of Dr. Wattanasin.

Prior to approximately April 1987, when he took permanent leave for health reasons, Mr. Fred Weinfeldt, a senior patent attorney in the Sandoz Patent Department, shared the responsibility of filing of patent applications in the HMG-CoA reductase inhibitor area. In August 1987, Mrs. Joanne M. Giesser joined the Department as a patent attorney and took over a portion of Mr. Weinfeldt's docket of patent disclosures to be filed.

4. Within a week or two following the January 27, 1988 Patent Committee meeting, I was aware that Patent Disclosure 299/84 of Sompong Wattanasin had received an "A" rating. It was my intention that the case would be filed by Mrs. Giesser or myself depending on who was available after existing filing priorities had been completed, inasmuch as following Mr. Weinfeldt's departure, a backlog in unfiled HMG-CoA reductase disclosures had been developing.

5. It is noted that the Sandoz U.S. filings in the HMG-CoA reductase area commenced in about 1982 and continued into 1991. For example, a representative list of Sandoz original (including CIP) U.S. patent application filings in the HMG-CoA reductase inhibitor area comprises the following:

Case 600-6951 filed Nov. 22, 1982 (abandoned)
Case 600-6951/B filed Nov. 4, 1983 (R60 of which) issued as U.S. 4,739,073 (1988)
Case 600-6951/C filed Nov. 22, 1982 (pending)
Case 600-7013 filed June 4, 1984 now U.S. 4,588,715 (1986)
Case 600-7015 filed June 22, 1984 (abandoned)
Case 600-7022 filed Dec. 4, 1984 (abandoned)
Case 600-7025 filed Apr. 12, 1985 (abandoned)
Case 600-7028 filed May 22, 1985 now U.S. 4,668,794 (1988)

Case 600-7015/B	filed	June 6, 1985	now U.S. 4,613,610 (1986)
Case 600-7035	filed	Oct. 25, 1985	(abandoned)
Case 600-7022/B	filed	Mar. 7, 1986	(abandoned)
Case 600-7041	filed	Apr. 30, 1986	(abandoned)
Case 600-7028/B	filed	May 14, 1986	(R60 of which) issued as U.S. 4,755,606 (1988)
Case 600-7035/B	filed	Oct. 15, 1986	now U.S. 4,851,427 (1989)
Case 600-7050	filed	Dec. 23, 1986	now U.S. 4,751,235 (1988)
Case 600-7025/ CIP	filed	May 5, 1987	(abandoned)
Case 600-7022/C	filed	Jul. 1, 1988	now U.S. 5,001,255 (1991)
Case 600-7025/ CIP/CIP/CIP	filed	Oct. 6, 1988	(abandoned)
Case 600-7025/ CIP/CIP/CIP/ CIP	filed	Jan. 16, 1990	(pending)
Case 600-7041/ CIP	filed	Mar. 6, 1987	(abandoned for R60)
Case 600-7064	filed	Jan. 27, 1988	now U.S. 4,822,799 (1989)
Case 600-7041/ CIP/CIP	filed	Mar. 10, 1988	(abandoned)
Case 600-6955/ XN//B/CONT/X	filed	Mar. 10, 1988	now U.S. 4,876,1989 (1989)
Case 600-7087	filed	Oct. 13, 1988	(abandoned)
Case 600-7101	filed	Mar. 3, 1989	(abandoned for R60 cont.)
Case 600-7087/B	filed	May 8, 1989	(abandoned)
Case 600-7104	filed	May 22, 1989	(abandoned)
Case 600-7041/ CIP/CIP/II	filed	Jul. 13, 1989	now U.S. 4,870,199
Case 600-7104/ CIP	filed	Feb. 20, 1990	(pending)
CAse 600-7087/C	filed	Sept. 5, 1990	(abandoned)
Case 600-7087/D	filed	Feb. 26, 1991	(pending)

Appendix Z hereto contains copies of the cover sheets of some of the above-indicated U.S. patents which issued on the above cases.

6. It is my best recollection that in February of 1988, I was in communication with Dr. Wattanasin concerning information

which was needed by the Patent Department in order to prepare an application based PD 299/84. (The application that was subsequently filed was designated as, and is referred to herein as, "Case 600-7101".)

Exhibit N hereto comprises a true copy of a page containing my handwritten notations concerning Case 600-7101 and a handwritten date of February 12, 1988.

These notes comprise a checklist of information items which needed to be developed or confirmed in order to draft Case 600-7101. The fact that these notes were made on the reverse side of the second attachment page to PD 299/84; and furthermore, that paragraph 2 discusses the scope of the disclosure and in sub-paragraph (c), refers to "other substitu [sic] on the quinoline ring," indicates their pertinence to the involved Wattanasin application.

These notes further indicate that I spoke with Sompong Wattanasin ("S.W.") on February 12, 1988 concerning his quinoline compounds and requested that he provide me with certain information.

7. On or about March 1, 1988, I received from Dr. Wattanasin certain reaction schemes which were to be included in case 600-7101.

Exhibit O comprises a copy of material which I received from Dr. Wattanasin for the preparation of Case 600-7101. This shows two different reaction routes to preparing quinoline compounds of the case.

8. It was my practice to request the Sandoz Biology Department to send me IC_{50} and ED_{50} values for compounds I was planning to cover in a patent application, as well as other biological information necessary to properly draft a patent application directed to a pharmaceutical.

Exhibit Q hereto comprises a Biological Data Report and computer printout which I received from the Sandoz Biology Department. The Wattanasin disclosure number, i.e. "299/84" is written in my handwriting on the front page, and the compounds of Patent Disclosure 295/84 as well as PD 299/84 are included in the printout.

The printout bears a date of May 23, 1988.

9. On July 1, 1988 I filed Case 600-7022/C based on PD 295/84, which was indicated for filing ahead of PD 299/84.

Exhibit R hereto comprises a copy of the front page of U.S. Patent No. 5,001,255, which issued on Case 600-7022/C, and indicates a filing date of July 1, 1988.

10. With reference to **Exhibit Y-2:** page 2 of this computer printout bears a date of January 11, 1989 written in my handwriting.

11. At no time subsequent to the "A" rating of Patent Disclosure 299/84 did I or, insofar as I am aware, any other member of the Patent and Trademark Department of Sandoz Corporation, ever have any intention not to file a United States patent application on the quinoline compounds of said patent disclosure in due course.

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

I hereby subscribe my name to the foregoing Declaration this 19th day of February, 1993.

Melvyn M. Kassenoff

MELVYN M. KASSENOFF

Exhibit C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN v. FUJIKAWA ET AL.

INTERFERENCE NO. 102,648
INTERFERENCE NO. 102,975

WATTANASIN CONSOLIDATED RECORD

VOLUME I

[PAGES 1 - 135]

Diane E. Furman
Sandoz Corporation
Patent and Trademark Department
Building 418
59 Route 10
E. Hanover, NJ 07936-1080
(201) 503-7332
Attorney for the party WATTANASIN

Of Counsel
Richard E. Vila
Melvyn M. Kassenoff
Sandoz Corporation
Patent and Trademark Department
Building 418
59 Route 10
E. Hanover, NJ 07936-1080
(201) 503-7852

May 15, 1993

Exhibit D

OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C.
ATTORNEYS AT LAW
FOURTH FLOOR
1755 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202 U.S.A.

TELEPHONE
(703) 413-3000
FACSIMILE
(703) 413-2220
TELEX
248855 OPAT UR

NORMAN F. OBLON
MARVIN J. SPIVAK
C. IRVIN McCLELLAND
GREGORY J. MAIER
ARTHUR I. NEUSTADT
ROBERT C. MILLER
RICHARD D. KELLY
JAMES D. HAMILTON
EckHARD H. KUESTERS
ROBERT T. POUS
DAVID J. KERA
CHARLES L. GHOLZ
VINCENT J. SUNDERDICK*
WILLIAM C. BEAUMONT
STEVEN B. KELBER*
STUART D. DWORK
ROBERT F. GNUSE
JEAN-PAUL LAVALLEYE, PH.D.
JEFFREY M. KAUFMAN
BRIAN D. ANDERSON*
ROBERTA S. BREN
WILLIAM B. WALKER*
TIMOTHY R. SCHWARTZ, PH.D.
RICHARD N. STERN*
JOHN H. WEGER
STEPHEN G. BAXTER, PH.D.

DAVID A. NOVAIS
MARTIN M. ZOLTICK
CARL E. SCHLIER
DENNIS R. DALEY
STEVEN P. WEIHROUCH
P. JAY HINES
JOSEPH T. LEONE
BARRY P. MILLER
SURINDER SACHAR
JAMES J. KULBASKI
FREDERICK D. VASTINE, PH.D.*
MURRAY TILLMAN*
ROBERT W. HAHL, PH.D.*
RICHARD L. CHINN, PH.D.*
ANDREW D. FORTNEY, PH.D.*
MARC R. LABGOLD, PH.D.*
RICHARD A. NEIFELD, PH.D.*
J. DEREK MASON, PH.D.*
KENNETH B. WELLS*
ANDREW B. GRIFFIS*
RICHARD L. TREANOR, PH.D.*
KAREN L. SHANNON, PH.D.*

MILTON STERMAN*
SAMUEL H. BLECH*
JOHN G. TRESANSKY*
ALTON D. ROLLINS
JOHN H.O. CLARKE*

PATENT, TRADEMARK AND COPYRIGHT LAW AND RELATED FEDERAL AND ITC LITIGATION

WEST COAST OFFICE
9081 THE ALAMEDA, SUITE 110
SAN JOSE, CALIFORNIA 95126
TELEPHONE
(408) 345-3600
FACSIMILE
(408) 345-3899

*BAR MEMBERSHIP OTHER THAN VIRGINIA
*REGISTERED PATENT AGENT

May 20, 1993
VIA FACSIMILE
1-201-503-8807
TWO PAGES

Diane Furman, Esquire
SANDOZ CORPORATION
Patent and Trademark Department
59 Route 10
E. Hanover, NJ 07936

Re: Interference No. 102,648
Interference No. 102,976
Wattanasin v. Fujikawa et al
Our Ref.: 49-111-0 and 49-125-0 DIV

Dear Diane:

I noted two items with some concern on receipt of your Consolidated Record in the above Interferences. First and foremost, I am particularly concerned that you have listed as "Of Counsel" Melvyn M. Kassenoff. As you are aware, Mr. Kassenoff was a critical fact witness for you in this case, providing an extensive Declaration, and an even longer and more contested cross-examination. It is wholly and completely inappropriate to have a fact witness participating as an attorney on behalf of the same party. Universal Athletic Sales Company v. American Gym Recreational and Athletic Equipment Corporation, 546 F.2d 530, 539, FN 21 (3rd Cir. 1976), Cert. denied, 430 US 984 (1977). See also, SMI Industries Canada, Ltd. v. Caelter Industries, 223 USPQ 742 (ND NY 1984). It is particularly offensive to me to have listed Melvyn M. Kassenoff as "Of Counsel" when I indicated, during the Wattanasin cross-examination, that I had discomfort with a witness taking the examination of another witness. Your Record, page 97.

In any event, it is demonstrably improper to have a fact witness acting as an attorney on behalf of the party for whom he

Diane Furman, Esquire
SANDOZ CORPORATION
Patent and Trademark Department

appeared as a witness. We require that you immediately reassure us, in writing, that Mr. Kassenoff will have no participation in the preparation of the Brief, advice to yourself or other Counsel acting in this matter, appearance at or suggestions with regard to Final Hearing, or any other participation in this matter. Mr. Kassenoff's participation should have ended with the statement "No further questions".

Because we must move for disqualification promptly if we do not receive your written confirmation that Mr. Kassenoff will not participate, please forward it via facsimile. We would also expect you in due course to file a paper with the Patent Office indicating that Mr. Kassenoff was improperly designated as "Of Counsel", and will not participate in the matter beyond his appearance as a fact witness. On this matter, we require your urgent cooperation.

I am also surprised that you failed to include as exhibits, or provide a cross-reference, with respect to the exhibits submitted during cross-examination depositions. I appreciate that these exhibits appear elsewhere, but a review of your record, and the cross-examination transcripts provided therein, makes no sense, because it is not apparent to anyone that exhibit W-3, for instance, corresponds to anything of record. As these were your depositions, they were your responsibility to submit. We will be filing a cross-reference table next week, to at least simplify matters. I would appreciate it if you could provide us with copies of all the exhibits, since you received the original depositions. This, of course, would not pertain to the exhibits submitted in the Holmlund deposition.

I look forward to hearing from you in the near future.

Very truly yours,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Steven B. Kelber

SBK/bb

P.S. I note further we received only one record copy. We should have received two under the Rules. Please forward another as soon as possible.

Exhibit E

(4) Confidences or secrets necessary to establish or collect the practitioner's fee or to defend the practitioner or the practitioner's employees or associates against an accusation of wrongful conduct.

(d) A practitioner shall exercise reasonable care to prevent the practitioner's employees, associates, and others whose services are utilized by the practitioner from disclosing or using confidences or secrets of a client, except that a practitioner may reveal the information allowed by paragraph (c) of this section through an employee.

§10.58-10.60 [RESERVED]

§10.61 CANON 5.

A practitioner should exercise independent professional judgment on behalf of a client.

§10.62 REFUSING EMPLOYMENT WHEN THE INTEREST OF THE PRACTITIONER MAY IMPAIR THE PRACTITIONER'S INDEPENDENT PROFESSIONAL JUDGMENT.

(a) Except with the consent of a client after full disclosure, a practitioner shall not accept employment if the exercise of the practitioner's professional judgment on behalf of the client will be or reasonably may be affected by the practitioner's own financial, business, property, or personal interests.

(b) A practitioner shall not accept employment in a proceeding before the Office if the practitioner knows or it is obvious that the practitioner or another practitioner in the practitioner's firm ought to sign an affidavit to be filed in the Office or be called as a witness, except that the practitioner may undertake the employment and the practitioner or another practitioner in the practitioner's firm may testify:

(1) If the testimony will relate solely to an uncontested matter.

(2) If the testimony will relate solely to a matter of formality and there is no reason to believe that substantial evidence will be offered in opposition to the testimony.

(3) If the testimony will relate solely to the nature and value of legal services rendered in the case by the practitioner or the practitioner's firm to the client.

(4) As to any matter, if refusal would work a substantial hardship on the client because of the distinctive value of the practitioner or the practitioner's firm as counsel in the particular case.

§10.63 WITHDRAWAL WHEN THE PRACTITIONER BECOMES A WITNESS.

(a) If, after undertaking employment in a proceeding in the Office, a practitioner learns or it is obvious that the practitioner or another practitioner in the practitioner's firm ought to sign an affidavit to be filed in the Office or be called as a witness on behalf of a practitioner's client, the practitioner shall withdraw from the conduct of the proceeding and the practitioner's firm, if any, shall not continue representation in the proceeding, except that the practitioner may continue the representation and the practitioner or another practitioner in the practitioner's firm may testify in the circumstances enumerated in paragraphs (1) through (4) of § 10.62(b).

(b) If, after undertaking employment in a proceeding before the Office, a practitioner learns or it is obvious that the practitioner or another practitioner in the practitioner's firm may be asked to sign an affidavit to be filed in the Office or be called as a witness other than on behalf of the practitioner's client, the practitioner may continue the representation until it is apparent that the practitioner's affidavit or testimony is or may be prejudicial to the practitioner's client.

Exhibit F

draw. A fifth comment suggested that there is no need for a petition to withdraw "when there is already a substitute attorney." The comment did not define a "substitute attorney." If a power of attorney is revoked (37 CFR §1.36) when a "substitute attorney" is appointed, a petition to withdraw is not necessary. If a revocation is not filed, any attorney of record continues to be an attorney of record until the power is revoked or the attorney withdraws. The suggestion made in the fifth comment is not being adopted.

One comment was concerned with timing of a decision on a petition to withdraw and suggested that a time be given for the PTO to act. It was further suggested that if the PTO fails to act within a specified time, that failure to act is to be construed as approval of the petition. This suggestion is not being adopted. In patent cases, it is presently contemplated that action will be taken by the Director in the Examining Group in which the patent application is pending or by the Chairman of the Board of Patent Inteferences, if the application is involved in an interference. In trademark cases, it is presently contemplated that a decision on a petition to withdraw would be made by the Director, if an application is pending before a trademark attorney (examiner), or by the Chairman of the Trademark Trial and Appeal Board in those cases where the application is before the board on an ex parte appeal or for *inter partes* proceedings.

One comment suggested that proposed §10.40 does not address the situation where an attorney resigns as member of a corporate legal department. Under current practice (37 CFR §1.36) and proposed §10.40, leave to withdraw would ordinarily be granted to any practitioner who resigns as a member of a corporate patent and/or trademark legal department.

One comment suggested that proposed §10.48 would not permit a registered patent attorney and a general lawyer to share legal fees even when the patent attorney and general lawyer are members of the same firm. Two comments suggested that proposed §10.49 would not permit formation of partnership between a patent attorney and a general attorney. It was not the intent of the rules published in the advance notice to prevent such sharing of legal fees or to preclude formation of such partnerships. In view of the changed definition of "practitioner" in proposed §10.1(r), the concerns expressed in the three comments should no longer exist. See also the change made to the preamble of proposed §10.1. Another comment suggested that proposed §10.49 would make it impossible for a patent attorney and a suspended or excluded practitioner to remain partners. This would be true if the suspended or excluded practitioner continues to practice law before the Office. If the suspended or excluded practitioner does not practice law before the PTO, then no problem is foreseen. As pointed out in discussing the comments concerning proposed §10.158, however, when a partner is suspended or excluded from practice before the PTO, business may not be able to continue as usual.

One comment suggested that the reporting requirements of proposed §10.57 may be different than those imposed by the Code of Professional Responsibility of a given State. This may be true. However, the reporting requirements of the States are not uniform. It follows that the PTO cannot propose a rule which will be consistent with rules in all States.

One comment suggested that proposed §10.62 should specifically authorize a registered patent practitioner to testify concerning attorney diligence in patent cases. This suggestion is not to be adoped. However, it should be clear that in most cases, the exception of proposed §10.62 (b)(3) would apply. As pointed out in the advance notice, however, the weight to be given testimony by a practitioner on behalf of his or her client would be determined on a case-by-case basis. *Wilder* v. *Snyder,* 201 USPQ 927, 934 (Bd.Pat.Int. 1979). The same comment suggested that permission by a client should be made the basis for permitting a practitioner to testify. This suggestion is not being adopted. Virtually all clients would give permission and such permission would not obviate the rationale behind the rule.

Three comments were received which suggested that a patent attorney or agent should be able to acquire a proprietary interest in the subject matter of a patent proceeding before the PTO. There are inventors who would not be able to apply for a patent and secure the assistance of a registered practitioner unless the practitioner may take an interest in the patent as part or all of his or her fee. The text of proposed §10.64(a) is being changed to permit a practitioner to acquire an interest in a patent case. Acquiring an interest in trademark and other non-patent cases would continue to be prohibited. Proposed §10.64(a) is now consistent with Informal Opinion No. 280 of the American Bar Association which states: "A lawyer may acquire an interest in a patent for his [or her] fee." Newly proposed §10.64(a)(3) would not change PTO policy which prohibits a practitioner from obtaining a proprietary interest for the sole purpose of obtaining a filing date under 37 CFR §1.47(b). See *Manual of Patent Examining Procedure* §409.03(f)(5th Ed. Aug. 1983).

Two comments questioned the need for proposed §10.65(b) as it appeared in the advance notice. In response to these comments, it has been decided to delete paragraph (b) from proposed §10.65.

One comment suggested that Rules 5.1 and 5.2 of the Model Rules of Professional Conduct of the American Bar Association (1983) "are more in tune [than proposed §10.66(a)] with the present day practice of law." It is said that the ABA rules "account for supervisory relationships found in law firms and in corporate legal departments." Proposed §10.66(d) permits the Director or the Commissioner to authorize the creation of "Chinese Walls." In determining whether a "Chinese Wall" can or should, be erected, the Commissioner should be free to take into account all factors. Compare *Plus Products* v. *Con-Stan Industries, Inc.,* 221 USPQ 1071 (Comm'r.Pat. 1984) and *Sunkist Growers, Inc.* v. *The Benjamin Ansehl Co.,* 221 USPQ 1077 (Comm'r.Pat. 1984).

Two comments were received which indicated, in the words of one comment, that "[u]nder many local jurisdictions, it is permissible for a non-lawyer to own stock in a professional corporation or to be a director or officer thereof." Accordingly, subparagraphs (1) and (2) of proposed §10.68(c) as they appeared in the advance notice have been deleted. Paragraph (c) of proposed §10.68(c) has been revised to limit its application to those situations where the non-practitioner has the right to direct or control the professional judgment of the practitioner. The ownership of professional corporations or associations and the directors and officers thereof are matters which are deemed better left to state law.

One comment was received with respect to proposed §10.85(a)(7) as it appeared in the advance notice. Section 10.85(a)(7) as it appeared in the advance notice has been deleted as being unnecessary. See Fedders, 56 Notre Dame Law. 5, 59-60 (1980).

Several comments were received discussing proposed §10.85(b)(1). Some comments suggested the entire subparagraph should be deleted. Others suggested it should be strengthened. It has been decided to delete from the text of §10.85(b)(1) as it appeared in the advance notice the language "except when the information is protected as a privileged communication." This amendment was suggested by the Statewide Grievance Committee of Connecticut and the Patent, Trademark, and Copyright Section of the Indiana State Bar Association.

Three comments relative to proposed §10.87 were received. All three pointed out a mispelling of the word "advice." One comment questioned whether a practitioner could tell a party who refuses to retain counsel that "I don't think you have a leg to stand on." Proposed §10.87 covers those cases in which the party is represented by counsel. If a party refuses to retain counsel, then a practitioner may deal with that party as he would with a lawyer for that party. In response to another

Exhibit G

an output readily discernible from the other (MR-26). The evidence also tends to show that there are devices functioning as frequency translators which are not considered to involve modulation (MR-33, 60, 61). Further, the evidence indicates there are devices functioning as temporal modulators which are not considered to perform strict frequency translation (MR-64). However, when asked on direct examination what ways were known to obtain frequency translation, the expert witness Mezrich volunteered:

(MR-33,34)

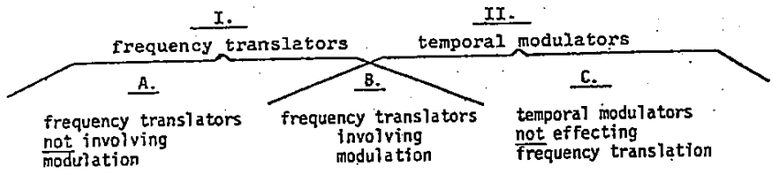
> You could amplitude modulate a signal and by using filters to suppress some components you don't want or select a particular component, generate a frequency to translate a signal. This is a particular case where you can modulate something to produce a frequency translation.

Mezrich repeated this view in response to Question 78 on direct examination: (MR-36)

> As I think I said before, by taking particular pains you can temporally modulate a wave and then by removing or filtering out the effects of this modulation you can result with a replica of the input signal at a new channel, but you have to have gone to some pains to do that.

The Lee brief does not call attention to this testimony. We are raising this point on our own.

This indicates that there are sub-systems which function as frequency translators and which *do involve temporal modulation*. We will employ the following diagram to illustrate the situation we see indicated by this evidence.



[5] We find that the Lee claims corresponding to the counts, as they preclude no particular types of frequency translators, clearly encompass category "B", above. We further find that the Mezrich claims corresponding to the counts, as they do not preclude further operations on one of the beams, such as the filtering of an amplitude modulated beam (of the type described at MR-33, 34, 36 by Mezrich), also encompass category "B", above. On this basis it is our view that the respective claims of the parties corresponding to the counts call for the same invention in that they embrace overlapping subject matter (category "B") and, thus, there is an interference-in-fact. Mezrich has failed to sustain his burden of proof and we see no reason to exercise our discretionary authority under 37 CFR 1.259.

As we find an interference-in-fact to exist and Mezrich raises no other issues which would preclude judgement against him, priority of invention as to both counts 1 and 2 is hereby awarded to Tzuo-Chang Lee, the senior party.

Patent and Trademark Office Board of Patent Interferences

Wilder, Reick, and Picut v. Snyder

Opinion dated Oct. 21, 1977
Patent No. 4,141,361 issued Feb. 27, 1979

PATENTS

1. Interference — Burden of proof — In general (§41.051)

Junior party whose application is copending with that of senior party bears burden of proof by preponderance of evidence.

2. Interference — Evidence — In general (§41.351)

Interference — Practice (§41.60)

Pleading and practice in Patent Office — Rules effect (§54.9)

Party's sketches made during taking of his testimony and introduced into evidence, but not noticed in its service under Patent Rule 287(a), nor included in its motion under Patent Rule 287(d)(1), since they did not come into existence until time testimony was taken, are properly in evidence.

3. Interference — Evidence — In general (§41.351)

Interference — Practice (§41.60)

Pleading and practice in Patent Office — Rules effect (§54.9)

Exhibits of party who did not file motion under Patent Rule 287(d)(1) that he be permitted to rely on those exhibits, which were introduced during testimony of his witnesses, but were not noticed in service under Patent Rule 287(a), are given no consideration.

4. Interference — Burden of proof — In general (§41.051)

Interference — Evidence — Corroboration (§41.355)

Party having burden of proof must establish his case by corroborated testimony; proof of alleged inventor's conception and reduction to practice requires full corroboration by other than inventor's own self serving testimony or records.

5. Interference — Evidence — Corroboration (§41.355)

Interference — Practice (§41.60)

Co-applicant's testimony regarding substantially all of his work in constructing and testing invention that stands uncorroborated is given no weight.

6. Interference — Evidence — Conception (§41.353)

Interference — Evidence — Corroboration (§41.355)

Interference — Evidence — Reduction to practice (§41.361)

Alleged corroborator's testimony from which it is not evident that he knew construction of invention or that he saw completed invention model provides proof of neither conception nor reduction to practice of invention.

7. Interference — Conception (§41.10)

Conception must include all essential elements defined in counts.

8. Interference — Diligence — Excuses (§41.253)

Interference — Diligence — Period of diligence (§41.257)

Attorney's time consumed in rendering infringement opinion on invention does not constitute excuse for lack of diligence; 35 U.S.C. 102(a) requires party's diligence from time just prior to opponent's conception date until party's reduction of his invention to practice.

9. Interference — Reduction to practice — Tests (§41.758)

Some inventions are of such simple nature that they require no testing to establish actual reduction to practice; evacuator for extracting body fluids would require testing on human or animal body.

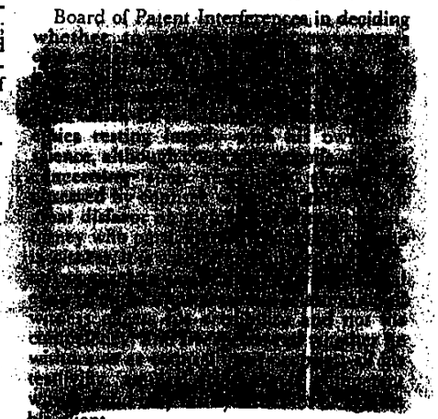
10. Attorneys — Propriety of conduct (§17.7)

Evidence — Weight and credibility (§36.40)

Interference — Evidence — In general (§41.351)

Interference — Practice (§41.60)

Board of Patent Interferences in deciding



his client.

11. Interference — Issues determined (§41.45)

Question of third party inventorship is not ancillary to priority and therefore not entitled to consideration at final hearing.

12. Interference — Priority (§41.70)

Party who was first to conceive and first to reduce invention to practice is entitled to prevail in interference.

Particular patents — Surgical Evacuator

Snyder, application, Surgical Evacuator, awarded priority against Wilder, Reick, and Picut, application.

Patent interference No. 98,632, between Joseph R. Wilder, Franklin G. Reick, and Frederick R. Picut, application, Serial No.

238,177, filed Mar. 27, 1972, accorded benefit of application, Serial No. 57,288, filed July 22, 1970, and Harold I. Snyder, application, Serial No. 254,080, filed May 17, 1972, accorded benefit of application, Serial No. 9,610, filed Feb. 9, 1970. Priority awarded to party Snyder.

Michael Ebert, New York, N.Y., and John L. White, Arlington, Va., for party Wilder.

Olson, Trexler, Wolters, Bushnell & Fosse, Ltd., Richard A. Giangiorgi, Caliste J. Alster, and Richard B. Trexler, all of Chicago, Ill., and Charles L. Sturtevant, Arlington, Va., for party Snyder.

Before Champion, Forrer, and Calvert, Examiners of Interferences.

Champion, Examiner of Interferences.

This interference is between an application of Snyder having an effective filing date of February 9, 1970, and an application of Wilder et al. having an effective filing date of July 22, 1970. Snyder is the senior party on the basis of his earlier effective filing date; Wilder et al. are the junior party.

Assignees of the Wilder et al. application are Michael Ebert, Frederick R. Picut, Franklin G. Reick and Joseph R. Wilder. The Snyder application is unassigned, insofar as the record shows.

[1] Both parties took testimony for the purpose of establishing priority dates earlier than their respective effective filing dates. Also, both parties filed briefs for our consideration and appeared and presented oral argument through counsel at final hearing. Wilder et al. bear the burden of proof by a preponderance of the evidence since they are the junior party and their application is copending with that of Snyder.

The Subject Matter

The invention is a diaphragm-type, manually-operable surgical evacuator for drawing body fluids from closed wounds. Counts 2 and 3, corresponding respectively to claims 1 and 27 of Snyder and to claims 9 and 19 of Wilder et al., are in issue. They adequately describe the invention and are reproduced below:

Count 2

A self-contained, independently operable, evacuator for the extraction of body fluids, for ambulatory human use, said evacuator comprising in combination, a container, a resilient diaphragm formed as a movable end wall of said container with its outer face open to atmosphere, said diaphragm having a normal position which it tends to assume by reason of its resiliency across one end of the container and being operable upon the manual actuation thereof to a stretched negative pressure applying position within the container confines and toward the opposite end thereof with the outer face of the diaphragm remaining open to atmosphere during this movement, said container being provided with an opening into which a conduit of flexing tubing may be connected, the other end of said tubing being of a material compatible with human tissue and being arranged for insertion into a body wound, whereby as said diaphragm returns to normal position across the said one end of the container the negative pressure applied by the diaphragm within the container will effect the extraction of body fluids from the wound by continuous suction, said fluids being thereby expressed into the container for storage therein.

Count 3

A self-contained, independently-operable surgical evacuator unit adapted to drain fluid from a body site and to transfer fluid to the unit, said unit comprising:

a. a cup formed of rigid material and having a continuous side wall and an unbroken end wall;

b. an elastic membrane covering the cup and sealed to the lip thereof to define a sump chamber to hold liquid, said membrane in its unstretched state being substantially planar;

c. an inlet-exhaust fixture mounted on said side wall and communicating with said chamber, said fixture when functioning in an inlet mode being adapted for connection to a drain tube leading to a body site to be drained; said fixture also being arranged to function in an exhaust mode; and

d. an actuator member associated with said membrane and manually-operable by an inwardly-directed force to effect inward stretching of said membrane to displace the atmosphere of said chamber through said fixture in the exhaust mode and to create in the inlet mode of said fixture a negative pressure acting to draw fluid into said chamber when the member is released, said membrane then being capable of returning to its original unstretched state without the use of an external force whereby fluid withdrawn from the body site proceeds to fill said chamber.

Issues

Wilder et al. have asserted that they conceived the invention on either November 17, 1969 or January 9, 1970, and that they actually reduced the invention to practice on February 13, 1970. They further assert that they were diligent during a period beginning prior to Snyder's conception date and ending with their actual reduction to practice on February 13, 1970. Wilder et al. make no assertion of diligence continuing until their constructive reduction to practice as of their July 22, 1970 effective filing date.

Snyder asserts a date of conception as early as December 5, 1969, but no later than December 30, 1969. He asserts that he was diligent from the date of his conception until a constructive reduction to practice as of his February 9, 1970 effective filing date.

Snyder Objections to Wilder et al. Exhibits

On July 9, 1976, prior to the beginning of the Wilder et al. period for taking testimony, Wilder et al. filed a motion under 37 C.F.R. 1.287(d)(1) to be permitted to rely on further documents and things (Paper No. 43) not noticed in the service under 37 C.F.R. 1.287(a), which documents and things were later introduced into evidence as Wilder et al. Documentary Exhibits 6 to 9 and Physical Exhibits B, C and E. Snyder opposed the motion (Paper No. 44) on the ground that he did not receive it until the beginning of the Wilder et al. testimony period. Decision on the motion was deferred to final hearing (Paper No. 47). In view of the reasons on which Wilder et al. based the motion, and in view of the fact that Snyder has failed to show that he was prejudiced by the belated notification of the additional documents and things, the motion is *granted*.

[2] Snyder has objected to sketches made by Reick during the taking of Reick's testimony. The sketches were introduced into evidence as Wilder et al. Exhibits 11, 13, 21, 28, 29 and 30, but were not noticed in the Wilder et al. service under 37 C.F.R. 1.287(a). Obviously the exhibits could not have been noticed, nor included in the Wilder et al. motion under 37 C.F.R. 1.287(d)(1), since they did not come into existence until the time the testimony was taken. Hence, the sketches are properly in evidence.

[3] Snyder has objected to Wilder et al. Documentary Exhibits 1 to 4, 10, 14, 22 to 27, and Physical Exhibits A and D. The exhibits were introduced into evidence during the taking of the testimony of the Wilder et al. witnesses, but were not noticed in the service under 37 C.F.R. 1.287(a). Nor did Wilder et al. file a motion under 37 C.F.R. 1.287(d)(1) that he be permitted to rely on the exhibits. Accordingly, we will give them no consideration.

Findings of Fact

Wilder's Priority Case

1. Three inventors are named on the Wilder et al. application: Joseph R. Wilder, a medical doctor; Franklin G. Reick, a "free lance" inventor; and Frederick R. Picut, President of Picut Manufacturing Co., Inc.

2. Of the three named inventors, Reick was the only one to testify. Two other witnesses testified on behalf of Wilder et al.: Paul McMahon, an employee of Picut, and Michael Ebert, the patent attorney who filed the Wilder et al. application.

3. According to Reick's testimony, he is a prolific inventor, having been granted patents in numerous and varied fields. He works out of a "home laboratory."

4. Reick first met Dr. Wilder in May of 1969, and he, Dr. Wilder and Picut had their first meeting during the same month. During the period immediately thereafter, the three met two or three times a week to discuss various projects on which they were associated.

5. The subject of surgical evacuators was first discussed during this period when it was suggested by Dr. Wilder that Reick improve the "Snyder HEMOVAC," a surgical evacuator disclosed in McElvenny et al. Patent No. 3,115,138. Although structurally different, the HEMOVAC functions as a vacuum to draw fluids from closed wounds in a manner analogous to the involved invention.

6. Reick testified that during the period August-October, 1969, he constructed a rough prototype of an evacuator for use in feasibility studies, a recently constructed replica of which was introduced into evidence as Wilder et al. Physical Exhibit B, the original having been discarded in 1969. The prototype consists of a tin can having one open end, a stretchable member made of polyurethane secured in sealed relationship across the open end, and a flexible tube having one end inserted through and secured with glue to the cylindrical side wall of the can. Depressing the membrane into the can and then releasing it causes air to exhaust and then intake through the flexible tube. Reick stated that the prototype proved the feasibility of using an open-ended container and diaphragm combination as a means for creating a vacuum in a surgical evacuator.

7. No witness corroborated the construction of the tin can prototype, or that it was even in existence in 1969.

8. Reick stated that during the period of about October 17, 1969 to about December 17, 1969, he constructed at least two other models of a diaphragm-type surgical evacuator. None of the models were introduced into evidence since, according to Reick, they were thrown away; however, during the taking of his testimony, Reick sketched the evacuators on sheets of paper. The sketches, introduced into evidence as Wilder et al. Exhibits 11 and 13, show the structure defined by the counts in issue, with the exception that they omit the flexible drain tube. Reick stated that in addition to constructing the models he also tested them to the extent of manually operating the parts.

9. The only witness to corroborate any of Reick's work on the model evacuators constructed in October-December, 1969 was McMahon, and he testified only that he made cups for the evacuators; he did not testify that he ever saw the completed evacuators, or that he knew the exact construction of the evacuators in which the cups were to be used.

10. In support of their asserted November 17, 1969 conception, Wilder et al. rely on the testimony of the inventor Reick and the corroborating witness Ebert, and Wilder et al. Exhibits 8 and 12.

11. Exhibit 8 is a letter, dated November 15, 1969, sent by Reick to his patent attorney Ebert. Attached to the letter when sent was a copy of the above-noted McElvenny et al. patent. Pertinent parts of the letter state:

> Attached patent for "HEMOVAC".
> I can design a superior evacuator from blow molded thermoplastic rubber. The springs will be designed into the walls of the container as an integral part of it.
> Very cheap to manufacture.
> If you think such an approach would not infringe McElvenny perhaps we should make a prototype.

12. Exhibit 12 is a letter dated November 17, 1969, and was written by Ebert in answer to Reick's letter of November 15th. It reads as follows (original emphasis):

> I refer to your letter of November 15 regarding the Snyder HEMOVAC which is covered by McElvenny patent *3,115,138.*
>
> On the folder you sent me describing the HEMOVAC produced by Snyder Mfg. Co., at the very end there is printed *Zimmer U.S.A.* Apparently Snyder sells through Zimmer. I mention this only because I believe Joe is scheduled to see Zimmer on another item.
>
> The fact that you can design a superior evacuator in which the springs are an integral part may avoid some but not all of the claims. One need infringe only a single claim to infringe a patent. *Claim 4* in the McElvenny patent appears to be of broadest scope. Would you, therefore, with your proposed evacuator in mind, study claim 4 and tell me to what extent, if any, you deviate in the slightest respect from what is set forth in claim 4.
>
> If, in fact, your new design infringes the patent, however superior it may be, you will not be in a particularly good bargaining position with Snyder or anyone else, for Snyder then has the power to stop you dead in your tracks.

13. With regard to the meaning of the statements he made in the second paragraph of his November 15th letter to Ebert, Reick testified as follows at WR 210:

> XQ203. In the letter of November 15th you were talking about blow-molding the KRATON rubber into a convoluted sidewall to give you sidewall flexibility?
> A. That's right.
> XQ204. Like an accordion?
> A. This was an exploratory, very flexible thing which we didn't pursue as far as development is concerned.

14. With respect to Reick's November 15th letter and his own letter of November 17th, Ebert testified as follows at WR 274, 275:

> However, you must remember that I was in constant touch with Frank [Reick] and *shortly after I wrote this letter* which acknowledged the November 15, 1969 letter I had telephone conversations with Frank, and there any doubts as to what he meant were resolved in my mind.
>
> What he had in mind was a rigid can with a membrane on top so that the — by "membrane" I mean something which could be depressed and when released would create a partial vacuum, and which made it possible to do away with the connecting tube on the top wall, which was the principal objection to this HEMOVAC. (Emphasis added)

15. In his testimony, Ebert does not give any exact dates of his telephone conversations with Reick; nor does he explain how much time was involved when he stated "shortly after I wrote this letter [of November 17, 1969]."

16. Wilder et al. Exhibit 15 is a drawing of a surgical evacuator conforming to all of the essential elements of counts 2 and 3 with the exception that the inlet-exhaust fixture is mounted in the base of the cup rather than on the side wall as set forth in count 3. The drawing was prepared by Reick and sent to Ebert with an accompanying letter (WX 16) dated January 6, 1970.

17. Ebert acknowledged receipt of the Exhibit 15 drawing in a letter dated January 9, 1970 (WX 17), and in the letter inquired of Reick if he intended to make a "working model." Reick, in a letter of reply dated January 15, 1970 (WX 18), stated in effect that he would not make any further "samples" until the invention "cleared" Ebert's desk (i.e. when, and if, Ebert decided the invention did not infringe the McElvenny patent).

18. In a letter to Reick dated January 30, 1970 (WX 20), Ebert advised that the device disclosed in Exhibit 15 did not infringe the McElvenny patent, and further that "there appears to be some possibility of obtaining patent protection on your device."

19. Reick testified that he did no work on the invention at least from January 6, 1970 until he received Ebert's letter of January 30th, but that he thereafter made several "elegant models" which were completed on February 13, 1970 and sent to Ebert.

20. No witness testified as to having seen Reick construct the "elegant models," nor did any witness testify as to having seen any of the models tested.

21. Ebert corroborates the correspondence between himself and Reick, and testified that he received the "elegant models" sometime in February of 1970. Ebert in his testimony describes the models in detail, stating that they conformed to the drawings of the Wilder et al. application since the drawings were made from the models. However, Ebert's testimony is silent as to whether or not any tests were performed on the models while they were in his possession.

Snyder's Priority Case

22. Mr. Trexler, attorney for Snyder, was the first fact witness deposed during the Snyder testimony period. His deposition was taken by Mr. Alster. Thereafter, Mr. Trexler took the depositions of the remaining Snyder witnesses.

23. In addition to Mr. Trexler and the inventor Snyder, witnesses testifying on behalf of Snyder were Norman R. Kinggard, the patent draftsman who prepared the Snyder patent application drawings, and Helen Schrampfer, who was the Chief Docket Clerk and Accountant for Mr. Trexler and paid Kinggard's drafting bill.

24. Snyder Exhibit 3 is a sheet of paper containing sketches and handwritten matter. Mr. Trexler testified that he prepared the exhibit on December 5, 1969 as the result of previous discussions with Snyder, and that he used the exhibit in giving the case to Kinggard to prepare patent drawings.

25. Kinggard testified that Exhibit 3 was given to him on December 5, 1969 by Mr. Trexler, and that he prepared the Snyder patent drawings from the subject matter disclosed thereon. Copies of the drawings prepared by Kinggard were introduced into evidence as Snyder Exhibits 12a and 12b. Kinggard stated that the drawings were completed on December 30, 1969, and that he was paid for their preparation on that date. Schrampfer corroborated the payment.

26. After Kinggard had completed the patent drawings Mr. Trexler prepared a draft of the Snyder application and forwarded it to Snyder on January 9, 1970 (SX 4).

27. The draft was returned to Mr. Trexler who then made additions to the application, and on January 23, 1970 again forwarded the draft to Snyder (SX 5) (SX 6).

28. Snyder executed the application papers and returned them to Mr. Trexler who received them on February 3, 1970 (SX 7).

29. A letter of transmittal was prepared by Mr. Trexler and the application sent to the Patent Office on February 5, 1970 where it was given a filing date of February 9, 1970.

Conclusions of Law

[4] 1. A party having the burden of proof must establish his case by corroborated testimony. Rodin v. Spalding, 49 CCPA 870, 297 F.2d 256, 132 USPQ 285 (1962). Proof of an alleged inventor's conception and reduction to practice requires full corroboration by other than the inventor's own self serving testimony or records. Eastman Kodak Company v. E. I. Du Pont de Nemours & Company, Inc., 161 USPQ 150, 157 (D.C. E.D. Tenn 1969).

2. To carry their burden of proof, Wilder et al. depend for the most part on the activity of Reick. However, Reick is an inventor named in the Wilder et al. application, and his testimony regarding substantially all of his work in constructing and testing the invention stands uncorroborated.

[5] 3. None of Reick's testimony respecting his alleged activity during the August-

October, 1969 period, including the alleged building of the "tin can" prototype, will be given weight since it is without corroboration (See Findings of Fact 6 and 7). Moreover, the activity is unsupported by contemporaneous documents or models.

[6] 4. Reick's testimony that he built and tested models of the invention during the period October-December, 1969 (See Finding of Fact 8) is of little value. Except for the testimony of McMahon, who stated that he built cups for the suction device during this period, Reick's testimony is uncorroborated. With respect to McMahon's testimony, it is not evident that he knew the construction of the surgical evacuator in which the cups were to be used, or that he ever saw a completed evacuator. McMahon's testimony thus provides proof of neither a conception or a reduction to practice of the invention.

[7] 5. We do not find that Wilder et al. Exhibits 8 and 12 and the testimony of Reick and Ebert (Findings of Fact 10-15) are sufficient proof to establish a conception of the invention by Wilder et al. on the November 17, 1969 date alleged by Wilder et al. Reick's Exhibit 8 letter to Ebert, dated November 15, 1969, fails to disclose a resilient diaphragm or membrane across one end of a container as a means of creating a vacuum in a surgical evacuator. A conception must include all essential elements defined in the counts, Interference Law and Practice, Rivise and Caesar, Vol. 1, Sec. 123; Cislak v. Wagner, 42 CCPA 701, 215 F.2d 275, 103 USPQ 39 (1954), and the resilient diaphragm or membrane is clearly an essential element of counts 2 and 3 here in issue. Nor does Ebert's answering letter of November 17, 1969 reflect that he understood Reick to have had knowledge of a surgical evacuator having a resilient diaphragm or membrane as a means to create vacuum. Moreover, Ebert's testimony that "shortly after" November 17, 1969 "any doubts as to what he [Reick] meant were resolved in my mind" does not provide proof of conception on the November 17th date inasmuch as Ebert did not provide an explanation of the time involved in his use of the term "shortly after." His testimony was taken seven years after the events took place, and in that context "shortly after" could mean as much as several months, possibly not until just prior to the time he received the Wilder et al. Exhibit 15 drawing accompanying Reick's letter dated January 6, 1970.

6. We conclude that Reick's letter to Ebert dated January 6, 1970 (WX 16), the Wilder et al. Exhibit 15 drawing, Ebert's letter to Reick dated January 9, 1970 (WX 17), and the testimony of Reick and Ebert (Findings of Fact 16 and 17) are sufficient to establish proof of conception of the invention defined by count 2, but not count 3, on the date of January 9, 1970. When the Reick drawing (WX 15) showing all of the essential elements of count 2 was received and understood by Ebert, the Wilder et al. conception of count 2 was complete. Ebert's letter of January 9, 1970 acknowledging receipt of the Exhibit 15 drawing establishes the date of conception of count 2. As to count 3, the drawing fails to include all of the essential features recited; it does not disclose the inlet-exhaust as being located in the side wall of the cup, but rather in the base thereof.

[8] 7. The preliminary statement of Wilder et al. alleges reasonable diligence toward an actual reduction to practice of the invention commencing November 18, 1969 and ending with an actual reduction to practice on February 13, 1970. Wilder et al. admit that they were inactive from January 6, 1970 until the end of the month, but assert that their lack of diligence during this period is excused due to the fact that they were waiting for their attorney, Mr. Ebert, to render an infringement opinion on their invention (See Findings of Fact 17-19). We consider this position untenable. We do not decide whether an attorney's time consumed in rendering an infringement opinion constitutes "commercial exploitation" as Snyder has urged, but we do find that such activity does not constitute an excuse for lack of diligence. On this exact point, Wilder et al. have cited no decisions, and we know of none. Accordingly, assuming that Snyder conceived the invention as late as January 23, 1970, as admitted on page 6 of the Wilder et al. main brief, Wilder et al. were not diligent from a time just prior to that date until they reduced the invention to practice, as required by 35 USC 102(g). D'Amico v. Koike, 347 F.2d 867, 146 USPQ 132 (CCPA 1963).

[9] 8. Moreover, we conclude that the evidence fails to establish that Wilder et al. reduced the invention to practice on the February 13, 1970 date they have alleged. While no witness corroborates the testimony of Reick that he built and tested the invention on that date, the evidence does establish that a model conforming to the terms of the counts was received by Ebert immediately thereafter. However, even assuming that construction of the invention was complete on the February 13th date, the record is devoid of any corroborated proof that it was tested. While some inventions are of such a simple nature that they require no testing, Mason v. Hepburn, 13 App. D.C. 86, 1898 CD 510, 84 OG 147, such is not the case

with respect to the present invention. Without detailing all the tests we consider necessary for an actual reduction to practice, we are of the opinion that the surgical evacuator defined by the involved counts would at least require operation of the suction element to determine whether it would hold a vacuum for a reasonable length of time. Moreover, particularly since the counts specify that the evacuator is for the extraction of body fluids, we think the evacuator would require testing on a human or animal body, or a simulation thereof, in order to determine whether it would perform its intended function successfully under conditions of actual use. Successful testing would require the vacuum to be strong enough to evacuate fluids from a wound and yet be sufficiently weak to avoid flesh being sucked into the openings in the tube. Lack of such testing by Wilder et al. precludes the finding of an actual reduction to practice.

9. On the basis of the above conclusions Wilder et al. have failed to overcome the February 9, 1970 effective filing date of Snyder and are not entitled to prevail in this interference.

[10] 10. Nevertheless, for the sake of completeness, we will decide the issues raised by the priority case for Snyder. Initially, Wilder et al. have objected to counsel for Snyder testifying as a fact witness (Finding of Fact 22). They contend that Mr. Trexler's appearance as the first witness for Snyder provided him with the opportunity to fill any "gaps" left in his own testimony with the testimony of subsequent witnesses. With respect to this contention, it is pointed out that Mr. Alster could have also filled in the "gaps" had he continued taking the testimony of the subsequent Snyder witnesses. On pages 19 and 20 of the Snyder record, Mr. Trexler has explained his reasons for appearing as a Snyder witness, and under the circumstances of this case we find no reason not to accord weight to his testimony, although we are guided by the principles set forth as follows at 97 C.J.S. Witnesses §71, p. 467 (footnotes omitted):

> In the final analysis the question of whether counsel should testify in a case with which he is professionally connected is one of legal ethics resting largely with his own conscience, although a court rule or code of ethics concerning such testimony should be observed by counsel. While a court looks with great disfavor on the giving of testimony by an attorney who participates in the trial in which he is a witness, it is clearly within the discretion of the trial court to permit counsel to testify, and not prejudicial error to allow it. The professional relationship of the witness affects his credibility and not his competency, and irrespective of whether he withdraws as counsel or of the propriety of his testifying, counsel in a cause is a competent witness, and may testify either for or against his client.

See also Universal Athletic Sales Co. v. American Gym, Rec. & Ath. Equip. Corp., 546 F.2d. 530, 192 USPQ 193 (3d. Cir. 1976), cert. den. 193 USPQ 570 (1977).

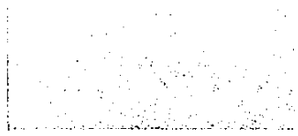
[11] 11. Upon considering the Snyder record as a whole, we conclude that Snyder has established a conception of the invention in issue on December 5, 1969. The Snyder Exhibit 3 sketches made by Mr. Trexler on that date disclose all of the count limitations, as appears clear from the exhibit, and also as evidenced by the testimony of Kinggard who stated that he prepared the Snyder patent drawings from the sketches on instructions from Mr. Trexler. Mr. Trexler testified that he prepared the sketches as the result of previous discussions with Snyder, and he further testified that he dictated the specification of the Snyder application from the drawings prepared by Kinggard. Realistically, the only reasonable conclusion to be drawn from these facts is that Mr. Trexler possessed full knowledge of the invention at the time he made the Exhibit 3 sketches, and that he gained his knowledge from Snyder. The argument by Wilder et al. to the effect that Mr. Trexler is the inventor of the subject matter of the counts involves the question of third party inventorship, which is not ancillary to priority and therefore not entitled to consideration at final hearing. Mortsell v. Laurila, 49 CCPA 1028, 301 F.2d 947, 133 USPQ 380 (1962).

[12] 12. Accordingly, we find that Snyder is entitled to prevail in this interference on the additional ground that he was the first to conceive and the first to reduce the invention to practice (i.e., his constructive reduction to practice).

Award of Priority

Priority of invention of the subject matter of the counts here in issue is hereby awarded to Harold I. Snyder, the senior party.

Exhibit H



Court of Appeals, Third Circuit

Universal Athletic Sales Co.
v. American Gym, Recreational & Athletic Equipment Corporation, Inc., et al.

No. 76-1023 Decided Nov. 19, 1976
As amended Dec. 30, 1976

PATENTS

1. Courts of Appeals — Orders appealable (§29.20)

28 U.S.C. 1292(a)(4) authorizes appeal from federal district court judgment in patent infringement action that is final except for accounting; court of appeals has jurisdiction under 28 U.S.C. 1292(a)(1) over appeal from federal district court that, in effect, denied injunction against further infringement.

2. Evidence — Expert testimony (§36.10)

Evidence — Weight and credibility (§36.40)

Federal district court erred in according great weight to opinions of witness whose qualifications as expert are questionable insofar as instant litigation is concerned; federal district court erred in failing to discount testimony given by associate in law firm representing accused infringers.

3. Evidence — Expert testimony (§36.10)

Patentability — New use or function — Analogous art (§51.553)

Which art is pertinent one must be determined when considering whether witness should be recognized as expert; engineer would have to have at least some familiarity with body building machines to assist trial judge in action involving patented "Body Exercising Apparatus," and weight lifter would probably be of marginal assistance, so that germane art is design of body-training devices.

4. Evidence — Expert testimony (§36.10)

It is doubtful whether witness that had little familiarity with design of weight lifting machines prior to litigation, did not undertake extensive study of technical references with respect to body-exercising apparatus in connection with lawsuit, and confined examination to elements of prior art selected by accused infringers' counsel, was suited to serve as expert in case in which germane art was design of body-training devices.

5. Evidence — Expert testimony (§36.10)

Federal district court did not clearly abuse its discretion in recognizing witness, who had no expertise in weight training, held bachelor's degree in electrical engineering, worked as examiner for seven years and patent attorney for thirty-five, and handled patent work primarily pertaining to electrical engineering and had limited background in mechanical engineering although he had handled patent matters relating to turbines, motors, and generators, as expert in action involving "Body Exercising Apparatus" patent, but his limited experience with class of devices present in litigation should have substantially circumscribed weight accorded his testimony.

6. Attorneys — Propriety of conduct (§17.7)

Evidence — Expert testimony (§36.10)

Pleading and practice in courts — Trial (§53.80)

Accused infringers' law firm should have withdrawn once it decided that its associate would testify, or else firm should have found another expert; infringement action tried without jury could have been adjourned, without prejudice to parties or waste of court's resources, until accused infringers selected another expert or law firm.

7. Attorneys — In general (§17.1)

Evidence — In general (§36.01)

Testimony of associate in accused infringers' law firm is not incompetent in case in which attorney-client privilege was not claimed; court of appeals does not approve of attorney's testifying as expert for his law firm's client, especially absent some necessity for testimony, but federal district court in infringement action did not err solely by not extirpating testimony.

8. Attorneys — In general (§17.1)

Evidence — Weight and credibility (§36.40)

Presumption from patent grant — Weight of (§55.9)

It is one thing for trial court to give testimony of interested witness some weight in reaching decision, but quite another to permit presumption of patent validity to be rebutted by primary reliance on it; federal district court erred when it placed controlling weight, as to patent validity, on opinions of lawyer associated with defense counsel; there is considerable doubt that heavy presumption of patent validity can be overcome by testimony of attorney on behalf of his client.

9. Presumption from patent grant — Patent Office consideration of prior art (§55.5)

Presumption from patent grant — Weight of (§55.9)

Fundamental canon governing judicial consideration of patent validity is that presumption of validity attaches to patents; presumption of validity often is further reinforced where Patent and Trademark Office specifically considered references of prior art invoked by accused infringer to invalidate patent; precision exhibited by Patent and Trademark Office reinforces presumption of validity in case in which examiner specifically considered prior art patent relied on by accused infringers and their expert stated that examiner made "good search"; patent invalidity must be demonstrated by clear and convincing proof.

10. Patentability — Invention — In general (§51.501)

Patent may be deemed invalid if it is "obvious."

11. Patentability — Invention — In general (§51.501)

Most authoritative construction of 35 U.S.C. 103 appears in Graham v. John Deere Co., 148 USPQ 459, which has enduring vitality.

12. Patentability — Evidence of — State of art (§51.467)

Patentability — Invention — In general (§51.501)

It was proper to disregard devices designed subsequent to patent when analyzing prior art's scope and content.

13. Evidence — Expert testimony (§36.10)

There may be some instances where trial court can review prior art references without expert assistance; trial judge ordinarily decides whether he needs expert assistance to understand or evaluate reference relied on as prior art; experts are not absolutely required, and court may disregard their testimony if it appears unreasonable, but judge should rely on expert testimony in cases involving complex inventions.

14. Patentability — Invention — In general (§51.501)

It would be difficult to evaluate differences between challenged claims and prior art whose content was not convincingly demonstrated.

15. Patentability — Invention — In general (§51.501)

Patentability — Tests of — Skill of art (§51.707)

Pleading and practice in courts — Issues determined — Validity or infringement only (§53.507)

Level of ordinary skill in pertinent art is mandatory criterion under Graham v. John Deere Co., 148 USPQ 459; trial judge who indicated record was deficient as to level of ordinary skill in pertinent art should have refused to invalidate claims as obvious.

16. Courts of Appeals — Issues determined (§29.10)

Court of Appeals — Weight given findings of District Court — Validity and infringement (§29.359)

Patentability — Evidence of — In general (§51.451)

Patentability — Evidence of — Commercial success — In general (§51.4551)

Patentability — Evidence of — Delay and failure of others to produce invention (§51.459)

Secondary criteria for obviousness need not be considered in case in which evidence adequate to justify invalidating claims under 35 U.S.C. 103 was not presented; device's commercial success and failure of others to obviate hazards and requirements of traditional method would reinforce conclusion that claims are not obvious; requisite findings as to Graham v. John Deere, 148 USPQ 459, criteria that are not supported by sufficient evidence are clearly erroneous, so that conclusion as to invalidity cannot stand.

17. Courts of Appeals — Weight given findings of District Court — Validity and infringement (§29.359)

Presumption from patent grant — Weight of (§55.9)

Court of appeals does not sustain federal district court's conclusion that claims were anticipated, absent sufficient evidence to rebut heavy presumption of patent validity.

18. Patentability — Anticipation — Publications — What is publication (§51.2277)

Photograph may qualify as "printed publication" for purposes of 35 U.S.C. 102; photograph may disclose invention as well as or better than drawing and is "printed

publication" for purposes of statute; restricting interpretation of section's "printed" publication requirement solely to traditional printing press would ignore realities of modern scientific and technological period; photograph may so anticipate patent as to render it invalid.

19. Patentability — Anticipation — Publications — In general (§51.2271)

Magazine photograph that is not full, clear, and exact representation of device, it being questionable whether one skilled in germane art could produce patented device based on photograph's examination, does not render patent invalid on ground of anticipation.

20. Patentability — Anticipation — Patents — In general (§51.2211)

Fact that it is unclear whether prior art patent encompasses all or substantially all of patented invention's elements, and evidence does not reveal whether one skilled in germane art or mechanical engineer could develop patented invention based on prior art patent or his own skills, warrants conclusion that accused infringers failed to demonstrate invalidity under 35 U.S.C. 102.

Particular patents — Exercising Apparatus

2,932,509, Zinkin, Body Exercising Apparatus, judgment invalidating claims 3 and 4 vacated.

Appeal from District Court for Western District of Pennsylvania, Knox, J.; 187 USPQ 104.

Action by Universal Athletic Sales Co., against American Gym, Recreational & Athletic Equipment Corporation, Inc., Grayson Industries Corp., American Super Gym Corp., Super Athletics Corporation, Ronald Arbasek, and Larry Salkeld, Donald E. Pinchock, and S. David Brodsky, doing business as Super Athletics Corporation, for patent infringement and unfair competition. From judgment for defendants in part, plaintiff appeals. Vacated.

Robert D. Yeager and Robert DeMajistre, both of Pittsburgh, Pa., and Lewis M. Dalgarn, Los Angeles, Calif. (Nilsson, Robbins, Dalgarn & Berliner, Los Angeles, Calif., of counsel) for appellant.

Thomas H. Murray, Pittsburgh, Pa., and Hymen Diamond, Monroeville, Pa., for appellees.

Floyd B. Carothers, Pittsburgh, Pa., for Donald E. Pinchock.

Before Adams, Rosenn, and Garth, Circuit Judges.

Adams, Circuit Judge.

At issue in this case is the validity of a United States patent[1] that pertains to a weight-lifting apparatus. Originally granted to Harold Zinkin, the patent was owned by Universal Athletic Sales Co. at the time of suit. The patent consists of eight claims, and the district court struck down two of them on grounds of anticipation and obviousness.[2] We must decide whether these rulings were warranted.

Two issues underlie the basic question of patent validity which is before the Court. The first concerns the controlling weight accorded by the trial judge to the testimony of defendants' principal expert witness, an associate in the law firm representing two of the defendants. Assuming that such testimony deserved little or no weight, as plaintiff maintains, we must then decide the second issue, whether there was nonetheless evidence sufficient to support the district court's decision.

I.

Modern technology has, of course, pervaded almost every province of human endeavor. The Zinkin patent demonstrates the verity of this postulate, for it deals with a somewhat unusual activity — weight-lifting. Specifically, the patent relates to the chest-press exercise, one of the cornerstones of the bodily arts. As athletes and physical fitness enthusiasts well know, the chest press enables the zealous practitioner to develop the musculature of his upper torso. Like many modern advances, the Zinkin patent attempts to retain the advantages of old methods, while conferring added benefits with the new.

In the traditional chest press, the exerciser lies on a bench and raises a free barbell from his chest to a position in which his arms are fully extended. He raises and lowers the barbell for as long as he desires or

---

[1] United States Letters Patent No. 2,932,509 for "Body Exercising Apparatus," issued on April 12, 1960.

[2] The original opinion of the district court is reported at 397 F.Supp. 1063, 187 USPQ 104 (W.D. Pa. 1975). That opinion subsequently was amended, and the amended judgment is set forth at 397 F. Supp. at 1074. For the amended opinion, see Appendix at 61-63. (Note that the appendix was filed jointly by the parties.)

is able. The exercise requires the continuing assistance of another person, the "spotter." Not only must the spotter hand the barbell to the exerciser at the inception of the routine, but he must also attempt to retrieve the bar should it begin to totter. Occasionally, the spotter is unable to catch the barbell so that it falls upon the exerciser, causing injury that can be quite serious.

The patent in this appeal discloses an apparatus which permits an exerciser to simulate, safely and effectively, the chest press exercise.[3] To use the patented apparatus, the exerciser lies upon a table in a supine position and pushes against handles in an upward movement. These handles shift in an arcuate fashion, analogous to the movement of the bar in the chest press exercise. They extend from a box-like structure which supports and contains the lifting mechanism. The design of the apparatus is such that the handles, the attached bar and the weights cannot strike the exerciser even should he falter. In addition, the Zinkin machine may be utilized without the assistance of a spotter. The patented apparatus thus eliminates the safety hazards posed by the conventional chest press and obviates its manpower requirements as well.[4]

This action was initiated by Universal against the defendants as part of a complex litigation involving, *inter alia*, questions of patent infringement, unfair competition, copyright infringement and antitrust violations. When Universal alleged patent infringement in its complaint, the defendants pleaded invalidity of the patent itself. The district court severed the patent infringement and unfair competition issues for trial,[5] and the patent issue, alone, is before us on appeal. After a nonjury trial, the district court initially adjudged the Zinkin patent entirely invalid. However, an amended order vacated the earlier judgment, leaving as invalid patent claims numbered 3 and 4.

Defendants had developed a body-exercising apparatus very similar to that covered by the Zinkin patent. Indeed, the district court found that "the defendants' chest press apparatus would infringe the Zinkin patent if the Zinkin patent were not * * *" invalid.[6] In their briefs, defendants list several differences between their own device and that of Zinkin. Nevertheless, the defendants do not vigorously contest the determination of infringement by the trial judge. Instead, they rely solely upon his ruling of

[3] The claims of the Zinkin patent that are contested by the defendants contain the following descriptions:

"3. A body exercising apparatus comprising an elongated substantially horizontal table having a predetermined head end and a foot end, an elongated bar extended from the head end of the table in substantial alignment therewith and having an end adjacent to the table and an opposite end, means pivotally mounting the extended end of the bar for pivotal movement about a substantially horizontal axis transversely of the table and in spaced relation to the head end thereof whereby elevational movement of the bar causes the end thereof adjacent to the table to describe an arc with its concave side disposed toward the table, a pair of handles aligned transversely of the table, means rigidly mounting the handles on the bar for integral pivotal movement therewith, stop means engageable with the bar limiting downward travel of the handles to positions in upwardly spaced relation to the table, and means connected to the bar resistive to upward pivotal movement thereof."

"4. A body exercising apparatus comprising an elongated substantially horizontal table adapted to support a person in supine position thereon having a predetermined head end and foot end, a framework adjacent to the head end of the table, an elongated bar pivotally mounted in the framework in substantial alignment with the table for movement about a substantially horizontal axis transversely of the table in spaced relation to the head end thereof and said bar being extended toward the table, a pair of handles rigidly mounted on the bar and disposed on opposite sides of the head end of the table, said bar terminating short of the table and leaving the area above the head end thereof free from obstruction, adjustable weight means borne by the bar, and a stop mounted in the framework engageable with the bar limiting downward pivotal movement thereof to a position with the handles disposed at an elevation above the table."

[4] The problems inherent in the simple chest press exercise had spurred several previous attempts at improvement. See Brief of Appellants, at 10-14. The "cradle" device, for example, utilized a rack which held the barbell at the beginning and end of the exercise. This primitive apparatus, however, did not eliminate the need for a spotter during the course of the exercise. Moreover, the cradle device was unstable and often flipped over, injuring the exerciser, his spotter or others. Subsequent improvements included the "power rack" and the "verti-slide." While these advances remedied the dangers posed by the chest press, their protective features often proved disruptive to the exercise routine. Consequently, prior to the Zinkin patent, many devotees of the chest press continued to use the free barbell in spite of its perils, inconvenience and added expense. The district court did not consider these primitive improvements as "prior art" with respect to the Zinkin apparatus, nor do any of the defendants.

[5] For a report on the related proceedings, see the original district court opinion, 397 F.Supp. at 1065, 187 USPQ at 106 and n.1.

[6] 397 F.Supp. at 1070-71, 187 USPQ at 109-111.

invalidity, and attempt to buttress his analysis in this respect. At trial, as in the appeal now before us, the primary focus was on whether the Zinkin patent was "anticipated" or made "obvious" by the prior art.

Two references were relied upon by the district court in holding the Zinkin claims invalid: a patent issued to C. A. Simmons in 1871[7] and a magazine photograph, dated 1950, of a lifting machine designed by Sam Loprinzi.[8] Disclosing a lifting machine for "developing the muscular system," the Simmons device consists of weighted levers which the exerciser apparently lifts and lowers as part of the exercise. The Loprinzi machine is described in the photograph caption as a "super-duper pressing apparatus," but the magazine caption itself provides no information as to the features of the device or how it was to be used. Defendants' principal expert witness attempted to explain its features based solely on his examination of the photograph.

That expert was Firman Lyle, an associate lawyer in the law firm that represented several of the defendents.[9] Controlling weight was given by the district court to his testimony as to obviousness and anticipation: "The court chooses to adopt the view of defendant's expert Firman Lyle."[10] Relying on the Simmons patent, the Loprinzi photograph, and Mr. Lyle's testimony as to these references, the trial court concluded that the two central claims of the Zinkin patent are void, since they were anticipated and made obvious by prior art.

[1] For reasons to be discussed in this opinion, we have decided that the judgment of the district court must be vacated.[11]

II.

[2] For the district court to grant controlling weight to the testimony of Mr. Lyle constitutes error for two reasons. First, because Mr. Lyle's qualifications as an expert are questionable, at least insofar as this litigation is concerned, the trial judge erred in according great weight to his opinions. Second, the district court committed error in failing to discount the value of the testimony, given the interest in the litigation of the law firm with which Mr. Lyle was associated.

A.

Universal first contends that Mr. Lyle's testimony should have been excluded because he was not an expert with respect to the patent claims at issue here.

This Court previously has delineated the standard which governs the competency of an expert witness in a particular case. As we noted in United States v. 60.14 Acres of Land,[12] an expert witness " 'must have such skill, knowledge and experience in [the] field or calling as to make it appear that his opinion or inference will probably aid the trier in his search for truth.' "[13] Ordinarily, the determination of competency of an expert witness rests within the discretion of the trial court.[14] The Supreme Court has posited that "the trial judge has broad discretion in the matter of the admission or exclusion of expert evidence, and his action is to be sustained unless manifestly erroneous."[15] It follows that this Court will not interfere with the decision of the trial judge as to an expert, absent an abuse of discretion.

[3] In considering whether the trial judge should have recognized Mr. Lyle as an expert in this litigation, we must first determine which art is the pertinent one. Universal asserts that the relevant art is weight-training, whereas the defendants and the district court selected mechanical engineering. We doubt whether any mechanical engineer could provide meaningful opinions regarding the devices at issue here. For an engineer to assist the trial judge in his

---

[7] Patent No. 117,339, dated July 25, 1871, for a "Lifting Machine."

[8] The photograph appeared in Strength and Health Magazine, May-June 1950, at 50.

[9] See Appendix at 280 (Trial Transcript at 383).

[10] 397 F.Supp. at 1070, 187 USPQ at 109-110.

[11] This Court has jurisdiction pursuant to 28 U.S.C. §1292(a)(1), for the district court below, in effect, denied an injunction against further infringement. It may be that we also possess jurisdiction pursuant to 28 U.S.C. §1292(a)(4), which authorizes an appeal from a district court judgment in a patent infringement action that is final except for an accounting. But see 9 J. Moore's Federal Practice ¶110.19[4] (1975). Because we believe that these provisions constitute sufficient grounds for jurisdiction, we did not certify this case for appeal under 28 U.S.C. §1292(b), as desired by the district court. See 397 F. Supp. at 1074. Absent these sources of jurisdiction, however, we would have issued the requisite §1292(b) certificate because this case raises substantial issues, the resolution of which should materially enhance resolution of this protracted litigation.

[12] 362 F.2d 660 (3d Cir. 1966).

[13] Id. at 667 quoting Jenkins v. United States, 307 F.2d 637, 643 (U.S. App. D.C. 1962), in turn quoting McCormick, Evidence §13 (1954).

[14] See, e.g., Salem v. United States Lines Co., 370 U.S. 31, 35, reh. denied 370 U.S. 965 (1962); United States v. 60.14 Acres of Land, 362 F.2d 660, 663 (3d Cir. 1966); Arnold v. Loose, 352 F.2d 959 (3d Cir. 1965).

[15] Salem v. United States Lines Co., 370 U.S. 31, 35 (1962).

search for truth would require that he have at least some familiarity with body-building machines. At the same time, a mere weight lifter probably would be of marginal assistance to a court in evaluating the design facets of exercise apparatus. Consequently, the art germane to the present case is the design of body-training devices.

[4] Having selected the relevant art, we may consider whether Mr. Lyle possessed the qualifications to be an expert in this case. It is apparent that he had little familiarity with the design of weight-lifting machines prior to the present litigation. The record reveals that Mr. Lyle did not undertake, even in connection with this law suit, any extensive study of technical references with respect to body-exercising apparatus. His examination was confined to the elements of prior art selected by defendants' counsel, i.e., the Simmons patent and the Loprinzi photograph. As a result, it is doubtful whether he was suited to serve as an expert here.

[5] Even assuming that the disciplines designated by the parties were the apposite ones, Mr. Lyle's standing as an expert in this litigation still may be called into question. He had no expertise whatsoever in weight training, as he repeatedly conceded during the course of his testimony.[16] It is also questionable whether Mr. Lyle possessed any skill or knowledge in the field of mechanical engineering. A recipient of a bachelor's degree in *electrical* engineering, he had served for seven years as an examiner in the United States Patent Office and for thirty-five years as a patent attorney for Westinghouse. Although he did handle patent matters relating to turbines, motors and generators, which have mechanical facets, his patent work primarily pertained to electrical engineering. Experience may vest one with the qualifications of an expert,[17] but Mr. Lyle had only a limited background even in the province of mechanical engineering.

However, since Mr. Lyle may possess skill and knowledge greater than the average layman with respect to mechanical apparatus, we cannot find that the district court clearly abused its discretion in recognizing him as an expert. Nevertheless, coupled with the arguable deficiencies in his qualifications as an expert witness, Mr. Lyle's limited experience with the class of devices present in this litigation should have substantially circumscribed the weight accorded his testimony. The trial court thus erred in attaching controlling weight to the opinions of defendants' expert.

B.

Universal also challenges the expert testimony of Mr. Lyle, citing the conflict between his association with defense counsel and his role as an expert witness. Over the objection of Universal, the district court permitted Mr. Lyle to testify as an expert.[18]

[6] Ordinarily it is inappropriate for an attorney, or a lawyer in his firm, to testify on behalf of a client. Rules DR5-101 and 102 of the Code of Professional Responsibility[19] provide that a lawyer shall refuse employment or withdraw as counsel if the "lawyer learns or it is obvious that he or a lawyer in his firm ought to be called as a witness on behalf of his client * * *." Under such circumstances, the attorney, or his firm, must decide whether to serve either as an advocate or as a witness in a particular case. Recognizing that "the role of an advocate and of a witness are inconsistent * * *,"[20] the Code would appear to preclude the testimony of Mr. Lyle here. As the disciplinary rules logically apply to expert as well as lay witnesses, the law firm should have withdrawn once it decided that its associate would testify, or else the firm should have found another expert.[21]

---

[16] See, e.g., Appendix at 327, 394-95 (Trial Transcript at 458, 211, 632).

[17] See, e.g., United States v. 60.14 Acres of Land, 362 F.2d 660, 667 (3d Cir. 1966).

[18] See Appendix at 273-79 (Trial Transcript at 376-382).

[19] The Code of Professional Responsibility was promulgated by the American Bar Association in 1969, and it became effective in 1970. The Pennsylvania Supreme Court explicitly adopted the Code in 1974 for members of the Pennsylvania bar, among whose ranks are Mr. Lyle and defendants' attorneys. *See* Pennsylvania Rules of Court 1975 at 175-241. However, it is apparent that the Code was applicable in Pennsylvania prior to 1974. *See In re* Estate of Lohm, 440 Pa. 268, 278-79, 269 A.2d 451, 457 (1970); Rules of Court, 331 Pa. xxxvi (1938). By contrast, seither the District Court for the Western District of Pennsylvania, which tried the present case, nor this Court has expressly adopted the Code.

Although the Code does not have the force or effect of a statute, it delineates the basic norms of professional conduct, and courts generally have considered the Code as highly persuasive in disciplinary matters. See, e.g., Handelman v. Weiss, 368 F.Supp. 258, 261 n.4 (S.D. N.Y. 1973); Estates Theatres, Inc. v. Columbia Pictures Indus., Inc., 345 F.Supp. 93, 95 n.1 (S.D. N.Y. 1972); E. F. Hutton & Company v. Brown, 305 F.Supp. 371, 377 n.7 (S.D. Tex. 1969).

[20] EC 5-9.

[21] The defendants contend that DR5-101 and 102 do not reach the testimony of Mr. Lyle. An exception to these rules allows a lawyer-witness to continue the representation of his client: "As to any matter, if [withdrawal] would work a sub-

[7] Even though the Code inveighs against the participation of Mr. Lyle as a witness, it does not necessarily follow that any alleged professional misconduct on his part would in itself render his testimony, once it was adduced, a nullity. This is so because the Code does not delineate rules of evidence but only strictures on attorney conduct. Moreover, it is well settled that a lawyer is competent to testify on behalf of his client.[22] Of course, such testimony may subject the attorney to separate disciplinary action. Thus, while we do not approve of the practice of an attorney testifying as an expert witness for a client of his law firm, and certainly in the absence of some necessity for such testimony, we cannot say that the district court committed error solely by not extirpating that testimony. In so concluding, we are in accord with the courts of appeals in several other circuits.[23]

In the case at hand, however, the district court did err when it relied so heavily on the testimony of Mr. Lyle. In Lau Ah Yew v. Dulles,[24] the Ninth Circuit, after criticizing the practice of an attorney testifying as a lay witness for his client, declared that testimony competent. But the court noted that the relationship of such a witness to his client detrimentally affected the weight to be accorded his testimony and therefore "discounted" its value.[25] Such an approach, which would appear to be equally applicable to attorneys who serve as experts for their clients, also reflects our view. We believe that, while a district court may in limited circumstances receive the testimony of a lawyer-witness, the value of that testimony must be discounted because of the interest of the lawyer or his firm in the outcome of the litigation.

[8] Here, there is little indication that the district judge, as the sole trier of fact, scrutinized the expert testimony of Mr. Lyle

---

stantial hardship on the client because of the distinctive value of the lawyer or his firm as counsel in a particular case." DR5-101 (B)(4). Defense counsel asserted at trial that this exception permitted the firm to continue its representation of the defendants, even if Mr. Lyle testified as an expert. The law firm contended, and the district court agreed, that withdrawal would cause "substantial hardship" for their clients, as the firm had spent great time and resources in preparing for the case.

Because the action was tried below without a jury, the trial judge could have adjourned the proceedings, without prejudice to the parties or a waste of court resources, until defendants selected another expert or, if they still desired the testimony of Mr. Lyle, another law firm. There is nothing in the record which indicates that the law firm with which Mr. Lyle was associated had such distinctive value in this litigation as to call DR5-101(b)(4) into play.

Nevertheless, we do recognize that DR5-101 and 102 are somewhat ambiguous as to whether these disciplinary rules apply literally to Mr. Lyle and his law firm. DR5-101 and 102 require the withdrawal of an attorney from the conduct of a trial if he or another lawyer in the firm "*ought*" to be called as a witness on behalf of his client. Such language suggests that these sections of the Code were concerned only with the lawyer-witness who has crucial information in his possession which must be divulged. Under this test, Mr. Lyle hardly may be characterized as a witness who "ought" to testify on behalf of his firm's client. Defense counsel could have called any number of other experts to the stand. There is no suggestion in the record, nor could there be, that Mr. Lyle alone possessed the expertise necessary to assist the trier of fact. Because the defendants' expert was not an indispensable witness, arguably his testimony at trial did not breach the mandate of the Code.

[22] See, e.g., City Bank of Honolulu v. Rivera Davila, 438 F.2d 1367, 1369 (1st Cir. 1971); United States v. Harry Barfield Company, 359 F.2d 120, 124 (5th Cir. 1966); United Parts Mfg. Co. v. Lee Motor Products, Inc., 266 F.2d 20, 24, 121 USPQ 206, 208 (6th Cir. 1959); Lau Ah Yew v. Dulles, 257 F.2d 744, 746 (9th Cir. 1958). While three of these cases were decided before the promulgation of the Code of Professional Responsibility, Canon 19 of the predecessor Canons of Ethics was roughly identical to DR5-101 and 102. Consequently, the principles enunciated in the pre-Code cases would appear to retain vitality.

Naturally, the statement in the text does not apply where the client invokes the attorney-client privilege, a long-standing rule of evidence. A client may refuse to disclose, and prevent his lawyer from disclosing, confidential communications between the attorney and his client. See 8 Wigmore on Evidence, §§2290-2329. (McNaughton rev.-1961). Generally, invocation of the privilege results in the exclusion of the attorney's testimony. The attorney-client privilege even embraces a lawyer not presently in the employ of the client, so long as he was the client's lawyer at the time of the privileged communication. See Wigmore, supra, §2323. In the case at bar, the attorney-client privilege obviously was not claimed, and so Mr. Lyle's testimony is not incompetent.

[23] See cases cited in note 22 supra.

It would be appropriate to consider incorporating within the body of evidentiary rules the current disciplinary norm proscribing the testimony of a lawyer for his client. The recently promulgated Federal Rules of Evidence, however, do not render such testimony incompetent. Nor is there any judicial precedent, insofar as we are aware, to support a nouncement of such a rule at this time.

[24] 257 F.2d 744 (9th Cir. 1958).

[25] See id. at 746-47.

with the proper circumspection.[26] It is one thing for a trial court to give the testimony of an interested witness some weight in reaching a decision. But it is quite another to permit the presumption of patent validity to be rebutted by primary reliance on the testimony of that witness. Even if, in the context of this case, it was not error to permit Mr. Lyle to testify, we conclude that the district court erred when it placed controlling weight, as to patent validity, on the opinions of a lawyer associated with defense counsel.[27]

III.

Because the district court gave undue weight to the testimony of Mr. Lyle, we must consider whether the remaining evidence in the record is sufficient to sustain the ruling that the patent claims are invalid.

[9] It is a fundamental canon governing judicial consideration of patent validity that a presumption of validity attaches to patents issued by the United States Patent Office.[28] Not only has a unanimous Supreme Court noted that "patentees are heavily favored as a class of litigants by the patent statute,"[29] but we have stated on several occasions that the burden of proving patent invalidity is a heavy one.[30] Moreover, such invalidity must be demonstrated by "clear and convincing proof."[31] In the case at bar, the evidence as to invalidity, once the testimony of Mr. Lyle is discounted, consists of only two items — the Simmons patent and the magazine photograph of Loprinzi's "super-duper pressing apparatus." This evidence in itself is not adequate to rebut the presumptive validity of the Zinkin patent, or to sustain the lower court's rulings as to obviousness and anticipation.

A.

We now turn to the ruling of the district court on the issue of obviousness. Although the trial judge invoked the proper authorities and standards in his consideration of this question, we believe that he erred in applying them to the Zinkin claims.

[10] Inasmuch as this Court has adumbrated the precepts of obviousness on previous occasions,[32] we need not do so here. Instead, we enunciate only the analytical framework necessary for this case. Simply stated, a patent may be deemed invalid if it is "obvious." 35 U.S.C. §103 provides, in part: "A patent may not be obtained * * * if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole

---

[26] When he refused to disqualify Mr. Lyle as an expert witness, the trial judge did state: "We will permit the witness to testify, but as to what effect this has upon his credibility, that will be up to the court * * *." Appendix at 278-79 (Trial Transcript at 381-82). Nevertheless, there is no subsequent suggestion in the record that the district court evaluated Mr. Lyle's testimony with the requisite special care.

[27] In so holding, we express considerable doubt that the heavy presumption of patent validity can be overcome by the testimony of an attorney on behalf of his client. For a discussion of the presumption, see Part III infra.

[28] 35 U.S.C. §282 provides, in pertinent part: "A patent shall be presumed valid * * *. The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting it."

Where the Patent Office specifically has considered references of prior art invoked by a defendant to invalidate a patent, the presumption of validity often is further reinforced. See, e.g., Ellipse Corp. v. Ford Motor Co., 452 F.2d 163, 170, 171 USPQ 513, 517 n.6 (7th Cir. 1971), cert. denied, 406 U.S. 948, 173 USPQ 705 (1972); Woodstream Corporation v. Herter's, Inc., 446 F.2d 1143, 1156 (8th Cir. 1971); Tapco Products Co. v. Van Mark Products Corp., 446 F.2d 420, 426, 170 USPQ 550, 554 (6th Cir.), cert. denied 404 U.S. 986, 172 USPQ 1 (1971); cf. Philips Electronic and Pharmaceutical Industries Corp. v. Thermal and Electronics Industries, Inc., 450 F.2d 1164, 171 USPQ 641 (3d Cir. 1971). In the case at hand, the Patent Office specifically considered the Simmons patent, as Mr. Lyle noted in his testimony. See Appendix at 368 (Trial Transcript at 564). The defendants' expert also stated that the examiner had made a "good search." The precision exhibited by the Patent Office reinforces the presumption of validity accorded the Zinkin claims.

[29] Blonder-Tongue Laboratories v. University of Illinois Foundation, 402 U.S. 313, 335, 169 USPQ 513, 522 (1971).

[30] E.g., Trio Process Corporation v. L. Goldstein's Sons, Inc., 461 F.2d 66, 70, 174 USPQ 129, 131-132 (3d Cir.), cert. denied 409 U.S. 997, 175 USPQ 577 (1972); Eagle Iron Works v. McLanahan Corporation, 429 F.2d 1375, 1382, 166 USPQ 225, 230 (3d Cir. 1970); Schmidinger v. Welsh, 383 F.2d 455, 462, 155 USPQ 289, 295 n.10 (3d Cir. 1967), cert. denied, 390 U.S. 946, 156 USPQ 720 (1968).

[31] Trio Process Corporation v. L. Goldstein's Sons, Inc., 461 F.2d 66, 70, 174 USPQ 129, 130-131 (3d Cir. 1972). Cf. Woodstream Corporation v. Herter's, Inc., 446 F.2d 1143, 1149, 170 USPQ 380, 384 n.4 (1971).

[32] See, e.g., Trio Process Corporation v. L. Goldstein's Sons, Inc., 461 F.2d 66, 70-73, 174 USPQ 131-134 (3d Cir. 1972); Philips Electronic and Pharmaceutical Industries Corp. v. Thermal and Electronics Industries, Inc., 450 F.2d 1164, 1172-75, 171 USPQ 641, 646-649 (3d Cir. 1971); Eagle Iron Works v. McLanahan Corporation, 429 F.2d 1375, 1377-79, 166 USPQ 225, 226-228 (3d Cir. 1970).

would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains."

[11] As observed in Trio Process Corporation v. L. Goldstein's Sons, Inc.,[31] the most authoritative construction of section 103 appears in Graham v. John Deere Co.[34] There the Supreme Court established three mandatory criteria with which to frame judicial determinations as to obviousness: "The scope and content of the prior art * * *; differences between prior art and the claims at issue * * *; and the level of ordinary skill in the pertinent art * * *."[35] The Supreme Court also set forth several permissive, or "secondary," considerations: "commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented."[36] This past term the Supreme Court continued to apply these criteria, thereby indicating the enduring vitality of Graham.[37] While the district court, in the present case, specifically considered the three mandatory tests, it erred in its evaluations under these tests, largely because of the dearth of evidence submitted by the defendants.

[12] In analyzing the "scope and content" of the prior art, the trial judge indicated that the only relevant references offered by the defendants were the Simmons patent and the Loprinzi photograph. He properly disregarded exercising machines designed subsequent to the Zinkin patent. Although his opinion does not explicitly discuss the scope of the prior art, the fact that there were only two references suggests that the scope of the prior art is quite limited.

[13] The trial judge did attempt to examine the content of the Simmons patent and the Loprinzi photograph. It is evident that he relied considerably upon the testimony of Mr. Lyle in analyzing the latter. As Mr. Lyle's testimony must be discounted, the district court would be hard pressed to evaluate the photograph. Even with Mr. Lyle's assistance, the trial judge appeared to be troubled about the features of the Loprinzi device. Indeed, his opinion reflects uncertainty concerning that apparatus.[38] While the Simmons patent may have been more easily examined, since the defendants did produce detailed patent specifications, there were unanswered questions regarding its content as well. For example, it is unclear whether the described apparatus could be used for the chest-press exercise. In the absence of expert testimony, other than that of Mr. Lyle, the trial judge could not properly appraise the prior art, narrow in scope as it was. Although there may be instances where a trial court may be able to review prior art references without expert assistance, the devices in this litigation do not lend themselves to such evaluation."[39]

[14] The district court also found that the differences between the prior art and the claims at issue were such that the invention is obvious. Nevertheless, because the defendants did not convincingly demonstrate the content of the prior art, we believe that it

---

[33] 461 F.2d at 70, 174 USPQ at 131-132.

[34] 383 U.S. 1, 148 USPQ 459 (1966). See also United States v. Adams, 383 U.S. 39, 148 USPQ 479 (1966).

[35] 383 U.S. at 17, 148 USPQ at 466. Subsequently, the Supreme Court, in referring to these tests, "admonished that 'strict observance' of those requirements is necessary." Anderson's Black Rock, Inc. v. Pavement Salvage Co., 396 U.S. 57, 62, 163 USPQ 673, 675 (1969).

[36] 383 U.S. at 17-18, 148 USPQ at 466-467.

[37] See Sakraida v. Ag Pro, Inc., U.S. , 47 L.Ed.2d 784, 189 USPQ 449 (1976); Dann v. Johnston, U.S. , 47 L.Ed.2d 692, 189 USPQ 257 (1976).

[38] See 397 F.Supp. at 1069, 187 USPQ at 109. The trial judge, in discussing the Loprinzi apparatus, stated: "From looking at the picture, it is not clear in what direction the levers can be moved, but the caption 'super-duper pressing apparatus' would clearly indicate to one familiar with weight-training that the movement is vertical. It also appears that each level is moved independently of the other, but that, too, is not certain from the picture and caption."

[39] Ordinarily, the trial judge decides whether he needs expert assistance to understand or evaluate a reference relied on as prior art. Experts are not absolutely required, and a district court may disregard the testimony of experts if that testimony appears unreasonable. See Deller's Walker on Patents §231 (2d ed. 1965) and cases cited therein. Nevertheless, in cases involving complicated inventions, the better rule is that the judge should rely on expert testimony. In Nyssonen v. Bendix, 342 F.2d 531, 144 USPQ 555 (1st Cir. 1965), for example, the First Circuit stated: "a patent speaks to its art and what it says can be told in complicated cases like this only by one skilled in the art." Id. at 537, 144 USPQ at 559-560. Not only are the devices in this litigation somewhat intricate, but the evidence pertaining to them is unclear. We believe that the trial judge should have required the testimony of one skilled in the design of weight-lifting machines before invalidating the Zinkin claims. Even if defendants had produced such an expert, it still is questionable whether the factual proof submitted in this case was sufficient to void the patent.

would be difficult for any court to evaluate differences between that prior art and the challenged claims. Even if it would be possible to do so, there is little evidence to support the conclusion that any variances between defendants' references and the Zinkin claims are "insignificant."

We recognize that there *may* be some important differences between the prior art and the Zinkin claims. It is questionable, for example, whether either the Simmons patent or the Loprinzi apparatus obviates the spotter requirement of the chest-press exercise, as does the Zinkin device. The caption of the Loprinzi photograph depicts Sam Loprinzi "coaching a pupil in the use of [the] super-duper pressing apparatus." Arguably, Mr. Loprinzi is acting as a spotter as well as a coach in the picture, just as Harold Zinkin performed both roles in his gymnasium before designing his machine. Moreover, it is unclear whether the Simmons and Loprinzi devices circumvent, as does the Zinkin apparatus, the safety hazards posed by the chest press. Technically, there are various differences in design between the prior art and the challenged claims, involving, inter alia, the types of handles, the "stops," the requirement of a single bar and the positioning of numerous elements. While there is some doubt whether the differences between the references and the Zinkin claims are so substantial as to defeat the allegation of obviousness, we conclude that the evidence is insufficient to sustain the conclusion of the trial judge that all differences were such as to render the patented device obvious.

[15] With respect to the third mandatory criteria under Graham, that is, the level of ordinary skill in the pertinent art, the district court acknowledged that "The record on this point is somewhat deficient."[40] Even so, the trial judge declared that "any competent mechanical engineer * * * could readily create a machine substantially the same as that of plaintiffs."[41] As discussed above, we believe that the pertinent art is neither weight-lifting nor mechanical engineering, but rather the design of body-exercising apparatus. Not only did the district court fail to select the proper art, but it is questionable whether the evidence submitted by the defendants speaks to the level of ordinary skill in the design of weight-lifting devices. Assuming that mechanical engineering is the relevant art, we are skeptical whether Mr. Lyle, upon whose testimony the district court substantially relied, could provide meaningful opinions thereon, given his inexperience in mechanical engineering. The trial judge suggested that the record as to the level of ordinary skill in the pertinent art was "deficient." Having so indicated, he should have refused to invalidate the challenged patent claims as obvious.

[16] This Court need not consider the permissive, or secondary, criteria mandated in Graham for determinations of obviousness. For we are convinced that the defendants failed to provide adequate evidence to justify invalidation of the Zinkin claims under section 103. Even if the permissive tests were applied, the commercial success of the Zinkin machine[42] would reinforce our conclusion, as would the "failure of others" to obviate the safety hazards and manpower requirements of the traditional chest press exercise.[43] Thus, we cannot say that the Zinkin claims are so obvious as to render them invalid.[44]

B.

[17] Besides holding the Zinkin claims void for obviousness, the district court concluded that they were anticipated by prior art. 35 U.S.C. §102 provides, in pertinent part: "A person shall be entitled to a patent unless — (a) the invention was * * * patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent * * *." The defendants had contended, and the trial judge agreed, that both the Simmons patent and the Loprinzi photograph anticipated the Zinkin claims so as to render them nugatory under the statute. Since there is insufficient evidence to rebut the heavy presumption of patent validity, we do not sustain this conclusion of the district court.

---

[40] 397 F.Supp. at 1070, 187 USPQ at 109.

[41] Id.

[42] 397 F.Supp. at 1066, 187 USPQ at 106-107. While the district court expressly recognized the commercial success of the Zinkin chest press machine, it did not utilize this fact in its analysis of obviousness.

[43] See note 4 supra.

[44] Such a holding is not at all inconsistent with Philips Electronic and Pharmaceutical Industries Corp. v. Thermal and Electronics Industries, Inc., 450 F.2d 1164, 171 USPQ 641 (1971). There this Court declared that a trial judge's findings as to the Graham criteria are to be evaluated under the "clearly erroneous" standard of Fed. R. Civ. Pro. 52(a). In the case at bar, the requisite findings would appear to be clearly erroneous, as there is insufficient evidence to support them. Thus the district court's conclusion as to invalidity cannot stand.