No. 102040

Vol. I
Pps. 1 - 31

(A)
B-702975

Sofocleous
EXAMINER IN CHIEF

U.S. PATENT AND TRADEMARK OFFICE
RETURN TO PTO-1058
Interference Service Branch
This case is involved in an
Interference Proceeding.

1.
2.
3.

INTERFERENCE

C4fC

Wattanasin S.N. 07/498,301

v.

Picard et al. P.N. 4,761,449

v.

Fujikawa et al. S.N. 07/233,752

Quinoline Type Mevalonolactones

Group 1201

PTO-257

Oct. 2
PP. 1 – 31

102648

ATTORNEY

Interference Instruction Label
1. Enter correct PALM trans. No. and any further required info. - i.e LOC -
2. Scan Interference No. Label
3. Scan Send No. Label

SEND

Sompong Wattanasin
attys: Gerald D. Sharkin
address: Sandoz Corp.
59 Route 10
E. Hanover, NJ 07936

Joseph A. Picard et al.
attys: Jerry F. Janssen et al.
address: Warner-Lambert Co.
2800 Plymouth Road
Ann Arbor, MI 48105

Yoshihiro Fujikawa et al.
attys: Norman F. Oblon et al.
address: Oblon, Fisher, Spivak,
McClelland & Maier
1755 S. Jeff. Davis Hwy.
Crystal Square 5, Ste. 400
Arlington, VA 22202

MS of Sofocleous 2/15 102648

FORM PTO-850
(REV 3-86)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

INTERFERENCE—INITIAL MEMORANDUM

BOARD OF PATENT APPEALS & INTERFERENCES

EXAMINERS INSTRUCTIONS—This form need not be typewritten. Complete the items below and forward to the Group Clerk with all files including those benefit of which has been accorded. The parties need not be listed in any specific order. Use a separate form for each count.
(See MPEP 2309.02)

SEP 26 1991

BOARD OF PATENT APPEALS AND INTERFERENCES: An Interference is found to exist between the following cases:

This is count 1 of 2 count(s).

2. NAME	SERIAL NO.	FILING DATE	PATENT NO., IF ANY
PICARD et al.	07/129,516	12-7-87	4,761,419

The claims of this party which correspond to this count are:	The claims of this party which do not correspond to this count are:
(1), 2-13, 14 (allowable)	15 (allowable)

* Accorded benefit of: COUNTRY	SERIAL NO.	FILING DATE	PATENT NO., IF ANY

3. NAME	SERIAL NO.	FILING DATE	PATENT NO., IF ANY
FUJIKAWA et al	07/233,752	8-19-88	

The claims of this party which correspond to this count are:	The claims of this party which do not correspond to this count are:
1-9, 11-34, 36, 39, 40 (allowable)	35, 37, 38 (allowable)

BOARD OF PATENT APPEALS & INTERFERENCES OCT -9 1991

* Accorded benefit of: COUNTRY	SERIAL NO.	FILING DATE	PATENT NO., IF ANY
JAPAN	207224	8-20-87	
JAPAN	15585	1-26-88	

1. NAME	SERIAL NO.	FILING DATE	PATENT NO., IF ANY
WATTANASIN	07/498,301	3-23-90	

The claims of this party which correspond to this count are:	The claims of this party which do not correspond to this count are:
1-7 and 10 (allowable)	8, 9

BOARD OF PATENT APPEALS & INTERFERENCES FEB - 1992

* Accorded benefit of: COUNTRY	SERIAL NO.	FILING DATE	PATENT NO., IF ANY
US	07/318,773	3-3-89	

If a claim of any party is **exactly** the same as this count, it should be circled above. If not, type the count in this space (attach additional sheet if necessary):

BOARD OF PATENT APPEALS & INTERFERENCES SEP 26 1991

* The serial number and filing date of each application the benefit of which is intended to be accorded must be listed. It is not sufficient to merely list the earliest application if there are intervening applications necessary for continuity.

DATE	PRIMARY EXAMINER	TELEPHONE NO.	ART UNIT
8-20-91	JOHANN RICHTER	308-4532	121

Clerk's instructions:	GROUP DIRECTOR SIGNATURE (if required)
1. Obtain a title report for all cases and include a copy. 2. Forward all files including those benefit of which is being accorded.	

10264/8(A)

FORM PTO-850
(REV. 3-86)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

INTERFERENCE—INITIAL MEMORANDUM

BOARD OF PATENT APPEALS & INTERFERENCES
SEP 26 1991

EXAMINERS INSTRUCTIONS—This form need not be typewritten. Complete the items below and forward to the Group Clerk with all files **including those benefit of which has been accorded.** The parties need not be listed in any specific order. Use a separate form for each count.
(See MPEP 2309.02)

BOARD OF PATENT APPEALS AND INTERFERENCES: An interference is found to exist between the following cases:

This is count 2 of 2 count(s).

1. NAME	SERIAL NO.	FILING DATE	PATENT NO., IF ANY
PICARD et al	07/129,516	12-7-87	4,761,419

The claims of this party which correspond to this count are:
(15), (allowable)

The claims of this party which do not correspond to this count are:
1-14 (allowable)

* Accorded benefit of: COUNTRY	SERIAL NO.	FILING DATE	PATENT NO., IF ANY

2. NAME	SERIAL NO.	FILING DATE	PATENT NO., IF ANY
FUJIKAWA et al	07/233,752	8-19-88	

The claims of this party which correspond to this count are:
35, 37, 38 (allowable)

The claims of this party which do not correspond to this count are:
1-9, 11-34, 36, 39, 40 (allowable)

BOARD OF PATENT APPEALS & INTERFERENCES
OCT 9 1991

* Accorded benefit of: COUNTRY	SERIAL NO.	FILING DATE	PATENT NO., IF ANY
JAPAN	207224	8-20-87	
JAPAN	15585	1-26-88	

3. NAME	SERIAL NO.	FILING DATE	PATENT NO., IF ANY
WATTANASIN	07/498301	3-23-90	

The claims of this party which correspond to this count are:
8, 9 allowable

The claims of this party which do not correspond to this count are:
1-7, 10

* Accorded benefit of: COUNTRY	SERIAL NO.	FILING DATE	PATENT NO., IF ANY
US	07/318,773	3-3-89	

If a claim of any party is **exactly** the same as this count, it should be circled above. If not, type the count in this space (attach additional sheet if necessary):

BOARD OF PATENT APPEALS & INTERFERENCES
SEP 26 1991

BOARD OF PATENT APPEALS & INTERFERENCES
DEC -3 1991

* The serial number and filing date of each application the benefit of which is intended to be accorded must be listed. It is not sufficient to merely list the earliest application if there are intervening applications necessary for continuity.

DATE	PRIMARY EXAMINER	TELEPHONE NO.	ART UNIT
8-20-91	JOHANN RICHTER	308-4532	121

Clerk's instructions:
1. Obtain a title report for all cases and include a copy.
2. Forward all files **including those benefit of which is being accorded.**

GROUP DIRECTOR SIGNATURE (if required)

1.608(b) Sofocleous

FORM PTO-850
(REV. 3-86)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

INTERFERENCE—INITIAL MEMORANDUM

EXAMINERS INSTRUCTIONS—This form need not be typewritten. Complete the items below and forward to the Group Clerk with all files including those benefit of which has been accorded. The parties need not be listed in any specific order. Use a separate form for each count.

(See MPEP 2309.02)

BOARD OF PATENT APPEALS AND INTERFERENCES: An Interference is found to exist between the following cases:

This is count 1 of 2 count(s).

1. NAME	SERIAL NO.	FILING DATE	PATENT NO., IF ANY
PICARD et al	129,516	12-7-87	4,761,419

The claims of this party which correspond to this count are:	The claims of this party which do not correspond to this count are:
1, 2-14 (allowed)	15

* Accorded benefit of: COUNTRY	SERIAL NO.	FILING DATE	PATENT NO., IF ANY

2. NAME	SERIAL NO.	FILING DATE	PATENT NO., IF ANY
WATTANASIN	07/498,301	3-23-90	

The claims of this party which correspond to this count are:	The claims of this party which do not correspond to this count are:
1-7 and 10 (allowable)	8, 9

* Accorded benefit of: COUNTRY	SERIAL NO.	FILING DATE	PATENT NO., IF ANY
U.S.	07/318,773	3-3-89	

3. NAME	SERIAL NO.	FILING DATE	PATENT NO., IF ANY

The claims of this party which correspond to this count are:	The claims of this party which do not correspond to this count are:

* Accorded benefit of: COUNTRY	SERIAL NO.	FILING DATE	PATENT NO., IF ANY

If a claim of any party is exactly the same as this count, it should be circled above. If not, type the count in this space (attach additional sheet if necessary):

* The serial number and filing date of each application the benefit of which is intended to be accorded must be listed. It is not sufficient to merely list the earliest application if there are intervening applications necessary for continuity.

DATE	PRIMARY EXAMINER	TELEPHONE NO.	ART UNIT
1-27-92	JOHANN RICHTER	308-4572	1201

Clerk's instructions:
1. Obtain a title report for all cases and include a copy.
2. Forward all files including those benefit of which is being accorded.

GROUP DIRECTOR SIGNATURE (if required)

BOARD OF PATENT APPEALS AND INTERFERENCES JUN 30 1992

~~102808~~

FORM PTO-850
(REV. 3-86)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

INTERFERENCE—INITIAL MEMORANDUM

EXAMINERS INSTRUCTIONS—This form need not be typewritten. Complete the items below and forward to the Group Clerk with all files including those benefit of which has been accorded. The parties need not be listed in any specific order. Use a separate form for each count.
(See MPEP 2309.02)

BOARD OF PATENT APPEALS AND INTERFERENCES: An interference is found to exist between the following cases:

This is count 2 of 2 count(s).

2

2. NAME	SERIAL NO.	FILING DATE	PATENT NO., IF ANY
PICARD et al	129,516	12-7-87	4,761,419

The claims of this party which correspond to this count are:	The claims of this party which do not correspond to this count are:
(15) (allowed)	1-14

* Accorded benefit of: COUNTRY	SERIAL NO.	FILING DATE	PATENT NO., IF ANY

1

NAME	SERIAL NO.	FILING DATE	PATENT NO., IF ANY
WATTANASIN	07/498,301	3-23-90	

The claims of this party which correspond to this count are:	The claims of this party which do not correspond to this count are:
8,9 (allowable)	1-7,10

* Accorded benefit of: COUNTRY	SERIAL NO.	FILING DATE	PATENT NO., IF ANY
U.S.	07/318,773	3-3-89	

BOARD OF PATENT APPEALS & INTERFERENCES
JAN 30 1992

3. NAME	SERIAL NO.	FILING DATE	PATENT NO., IF ANY

The claims of this party which correspond to this count are:	The claims of this party which do not correspond to this count are:

* Accorded benefit of: COUNTRY	SERIAL NO.	FILING DATE	PATENT NO., IF ANY

If a claim of any party is exactly the same as this count, it should be circled above. If not, type the count in this space (attach additional sheet if necessary):

* The serial number and filing date of each application the benefit of which is intended to be accorded must be listed. It is not sufficient to merely list the earliest application if there are intervening applications necessary for continuity.

DATE	PRIMARY EXAMINER	TELEPHONE NO.	ART UNIT
1-27-92	JOHANN RICHTER	308-4532	1201

Clerk's instructions:	GROUP DIRECTOR SIGNATURE (if required)
1. Obtain a title report for all cases and include a copy. 2. Forward all files including those benefit of which is being accorded.	

The cases involved in this interference are:

Junior Party

Applicant: Sompong Wattanasin

Address: 11 Divito Trail Hopatcong, New Jersey 07843

Serial No.: 07/498,301 filed 03/23/90

For: Quinoline Analogs Of Mevalonolactone And Derivatives Thereof

Assignees: None

Attorneys of Record: Gerald D. Sharkin, Robert S. Honor, Richard E. Villa, Walter F. Jewell, Thomas O. McGovern, Thomas C. Doyle, Melvyn M. Kassenoff, Joseph J. Borovian, Joanne M. Giesser and Diane E. Furman

Associate Attorney: None

Accorded Benefit of: U.S. Serial No. 07/318,773 filed 03/03/89

Address: Gerald D. Sharkin
Sandoz Corp.
59 Route 10
E. Hanover, NJ 07936

Junior Party

Patentees: Joseph A. Picard, Bruce D. Roth and Drago R. Sliskovic

Addresses: 3545 Greenbrier Apt. 65C, Ann Arbor, Michigan 48105
1440 King George Blvd., Ann Arbor, Michigan 48104
4860 Cole Blvd., Ypsilanti, Michigan 48197

Serial No.: 07/129,516 filed 12/07/87, Patent No. 4,761,419 issued 08/02/88

For: 6-(((Substituted)Quinolinyl)Ethyl)-And Ethenyl)Tetrahydeo-4-Hydroxypyran-2-One Inhibitors Of Cholesterol Biosynthesis

Assignees: Warner-Lambert Company, A Corp. of DE

Attorneys of Record: Elizabeth M. Anderson, Ronald A. Daignault, Charles Gaglia, Jerry F. Janssen, Henry Jeanette, Anne M. Kelly, Gary M. Nath, Howard Olevsky, Stephen Raines, Daniel A. Scola and Joan Thierstein

Associate Attorney: None

Accorded Benefit of: None

Address: Jerry F. Janssen
Warner-Lambert Co.
2800 Plymouth Road
Ann Arbor, MI 48105 lle # 19

Senior Party

Applicants: Yoshihiro Fujikawa, Mikio Suzuki, Hiroshi Iwasaki, Mitsuaki Sakashita and Masaki Kitahara

Addresses: Nissan Chemical Industries, Ltd, Chuo Kenkyusho, 722-1, Tsuboi-cho, Funabashi-shi, Chiba-ken, Japan

Serial No.: 07/233,752 filed 08/19/88

For: Quinoline Type Mevalonolactones

Assignees: Nissan Chemical Industries Ltd., Tokyo, Japan

Attorneys of Record: Norman F. Oblon, Stanley P. Fisher, 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, Charles L. Gholz, Vincent J. Sunderdick, William E. Beaumont and Steven B. Kelber

Associate Attorney: None

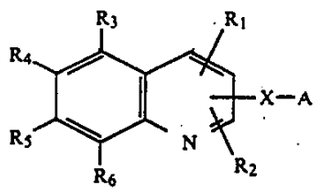
Accorded Benefit of: Japan Serial Nos. 207224 filed 08/20/87 and 15585 filed 01/26/88
Japan Serial No. 193606, filed August 3, 1988

H 59

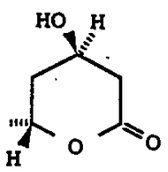
Address: Oblon, Fisher, Spivak,
McClelland & Maier
1755 S. Jeff. Davis Hwy.
Crystal Square 5, Ste. 400
Arlington, VA 22202

Count 1

A compound of structural Formula I

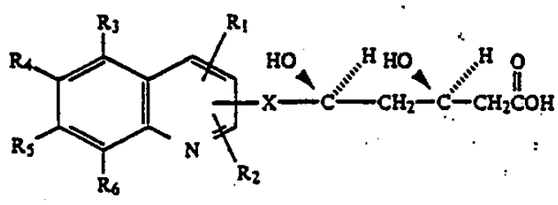


wherein A is



X is —CH2CH2— or —CH=CH—;
R_1 and R_2 are independently
hydrogen;
alkyl of from one to six carbons;
trifluoromethyl;
cyclopropyl;
cyclohexyl;
cyclohexylmethyl;
phenyl;
phenyl substituted with
fluorine,
chlorine,
bromine,
hydroxy,
trifluoromethyl,
alkyl of from one to four carbon atoms, or
alkoxy of from one to four carbon atoms;
phenylmethyl;
phenylmethyl substituted with
fluorine,
chlorine,
bromine,
hydroxy,
trifluoromethyl,
alkyl of from one to four carbon atoms, or
alkoxy of from one to four carbon atoms;
2-, 3-, or 4-pyridinyl; or
2-, 4-, or 5-pyrimidinyl;

R_3, R_4, R_5, R_6 are independently selected from
hydrogen;
alkyl of from one to six carbon atoms;
trifluoromethyl;
cyclopropyl;
fluorine;
chlorine;
bromine;
hydroxy;
alkoxy of from one to four carbon atoms;
cyano;
nitro;
amino;
acetylamino;
aminomethyl;
phenyl;
phenyl substituted with
fluorine,
chlorine,
bromine,
hydroxy,
trifluoromethyl,
alkyl of from one to four carbon atoms, or
alkoxy of from one to four carbon atoms;
phenylmethyl; or
phenylmethyl substituted with
fluorine,
chlorine,
bromine,
hydroxy,
trifluoromethyl, or
alkyl of from one to four carbon atoms;
provided that when X is in the 2-position, Rl is hydrogen and is attached in the 4-position;
or a corresponding 3,5-dihydroxyacid of Formula II



II

wherein A, X, R_1, R_2, R_3, R_4, and R_5 are as defined above, or a pharmaceutically acceptable salt thereof.

The claims of the parties which correspond to Count 1 are:

Wattanasin : Claims 1-7 and 10

Picard et al. : Claims 1-14

Fujikawa et al.: Claims 1-9, 11-34, 36, 39 and 40

Count 2

A method of inhibiting cholesterol biosynthesis in a patient in need of said treatment comprising administering a cholesterol synthesis inhibiting amount of a compound as defined by count 1 in combination with pharmaceutically acceptable carrier.

The claims of the parties which correspond to Count 2 are:

Wattanasin : Claims 8 and 9

Picard et al. : Claim 15

Fujikawa et al.: Claims 35, 37 and 38

Counts 1 & 2 are stricken & Ct 3 is added per #45
gjh

Michael Sofocleous
Examiner-in-Chief
(703) 557-4066

Paper No. 2

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

MAILED

MAR 1 1 1992

PAT. & T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

Interference No. 102,648

Wattanasin

v.

Picard et al.

v.

Fujikawa et al.

This interference has been assigned to the undersigned in accordance with 37 CFR 1.610. All future papers filed in this interference should be captioned to include this information.

Any questions regarding procedure in this interference should be directed to the undersigned. However, any such contact must include the participation of both parties, e.g., via a conference call.

Each party is required to file a paper in accordance with 37 CFR 1.613 identifying its lead attorney or agent (see 37 CFR 1.601(k)) by no later than 25 MAR 1992. Future changes in the lead attorney or agent must likewise be called to the attention of this board as soon as reasonably possible. No contact should be made with the undersigned by anyone other than the lead attorneys or agents.

The time for filing and serving notice of filing (but not serving) preliminary statements (37 CFR 1.621 - 1.628) and for filing preliminary motions (37 CFR 1.633, et. seq., note in particular, 1.637) is set to expire 11 JUN 1992.

The parties are strongly encouraged to make contact with each other at the time that its lead attorney or agent are identified in an attempt to settle this interference. The examiner-in-chief can be expected to cooperate in allowing reasonable time for a bona fide attempt at settlement negotiations, which will obviate the necessity for filing preliminary motions and will result in the filing of an appropriate termination paper under 37 CFR 1.662.

There has been confusion regarding the use of the "BOX INTERFERENCE" requirement of 37 CFR 1.1(e) in the filing of papers. Unless the paper itself is hand carried to the Service Branch of the Board of Patent Appeals and Interferences, located in Room 10C01 of Crystal Gateway 2 (1225 Jefferson Davis Highway, Arlington, VA), the designation "BOX INTERFERENCE" must be on the outside of the envelope containing the paper as well as on the paper itself. Merely hand carrying a paper to the PTO Mail Room does not suffice.

Summary of Times Running

1. Statements and Motions due 11 JUN 1992.

2. Identity of lead attorney or agent due 25 MAR 1992.

Michael Sofocleous
Examiner-in-Chief
(703) 557-4066

gjh

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	INTERFERENCE 102,648
	:	EXAMINER-IN-CHIEF:
V.	:	MICHAEL SOFOCLEOUS
	:	
PICARD ET AL	:	
	:	
V.	:	
	:	
FUJIKAWA ET AL	:	

DESIGNATION OF LEAD COUNSEL, 37 CFR §1.601(k)

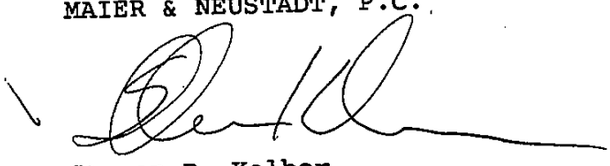
HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231
BOX INTERFERENCE

SIR:

Pursuant to 37 CFR §1.601(k), the Senior Party Fujikawa et al hereby designates as lead attorney Steven B. Kelber, Reg. No. 30,0731.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Steven B. Kelber
Registration No.: 30,073
Attorney of Record

Fourth Floor
1755 South Jefferson Davis Highway
Arlington, Virginia 22202
703-521-5940

CERTIFICATE OF SERVICE

I hereby certify that true copies of:

DESIGNATION OF LEAD COUNSEL, 37 CFR §1.601(k)

were served upon Counsel for the Wattanasin and Picard et al as follows:

Gerald D. Sharkin, Esq.
Sandoz Corp.
59 Route 10
E. Hanover, NJ 07936

and

Jerry F. Janssen, Esq.
Warner-Lambert Co.
2800 Plymouth Road
Ann Arbor, MI 48105

via first-class mail, postage prepaid, this 17th day of March, 1992.

STEVEN B. KELBER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#4

WATTANASIN

V.

PICARD ET AL

V.

FUJIKAWA ET AL

INTERFERENCE 102,648
EXAMINER-IN-CHIEF:
MICHAEL SOFOCLEOUS

POWER TO INSPECT AND MAKE COPIES

BOX INTERFERENCE
HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

SIR:

The undersigned, being an Attorney of Record for the above-identified Interference, hereby grants to MURALIDHAR PAI/SAM BROWN, the power to inspect and make copies of the above-identified Interference files.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Steven B. Kelber
Registration No.: 30,073
Attorney of Record

#5

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
	:	INTERFERENCE 102,648
V.	:	EXAMINER-IN-CHIEF:
	:	MICHAEL SOFOCLEOUS
PICARD ET AL	:	
	:	
V.	:	
	:	
FUJIKAWA ET AL	:	

SUPPLEMENTAL
DESIGNATION OF LEAD COUNSEL, 37 CFR §1.601(k)

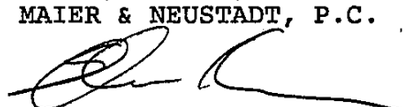
HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231
BOX INTERFERENCE

SIR:

Superseding Senior Party Fujikawa's earlier filed Designation of Lead Counsel, 37 CFR §1.601(k) is a Supplemental Designation of Lead Counsel, 37 CFR §1.601(k) correctly identifying Lead Counsel's Registration Number as 30,073. The Senior Party Fujikawa regrets this inadvertent error and any inconvenience it may have caused.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Steven B. Kelber
Registration No.: 30,073
Attorney of Record

Fourth Floor
1755 South Jefferson Davis Highway
Arlington, Virginia 22202
703-521-5940

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
	:	INTERFERENCE 102,648
V.	:	EXAMINER-IN-CHIEF:
	:	MICHAEL SOFOCLEOUS
PICARD ET AL	:	
	:	
V.	:	
	:	
FUJIKAWA ET AL	:	

SUPPLEMENTAL
DESIGNATION OF LEAD COUNSEL, 37 CFR §1.601(k)

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231
BOX INTERFERENCE

SIR:

Pursuant to 37 CFR §1.601(k), the Senior Party Fujikawa et al hereby designates as lead attorney Steven B. Kelber, Reg. No. 30,073.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Steven B. Kelber
Registration No.: 30,073
Attorney of Record

Fourth Floor
1755 South Jefferson Davis Highway
Arlington, Virginia 22202
703-521-5940

CERTIFICATE OF SERVICE

I hereby certify that true copies of:

SUPPLEMENTAL DESIGNATION OF LEAD COUNSEL, 37 CFR §1.601(k)

were served upon Counsel for the Wattanasin and Picard et al as follows:

Gerald D. Sharkin, Esq.
Sandoz Corp.
59 Route 10
E. Hanover, NJ 07936

and

Jerry F. Janssen, Esq.
Warner-Lambert Co.
2800 Plymouth Road
Ann Arbor, MI 48105

via first-class mail, postage prepaid, this 26th day of March, 1992.

STEVEN B. KELBER

FYI

Case No. 600-7101/CONT
Patent

MAR 25 1992

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

RECEIVED IN BOX INTERFERENCE

#6

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 1.602 NOTIFICATION OF INTEREST
FOR THE PARTY WATTANASIN

In accordance with 37 CFR 1.602, the Board of Patent Appeals and Interferences is hereby advised that the involved application of the party Wattanasin is assigned to, and the real party in interest is, Sandoz Pharmaceuticals Corporation, a corporation of Delaware, having its principal place of business at 59 Route 10, East Hanover, New Jersey 07936.

Respectfully submitted,

Diane Furman 3/24/92

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332 (phone)
201-503-8807 (facsimile)

SANDOZ CORP.
59 Route 10
E. Hanover, NJ 07936
RMF:def
March 24, 1992

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 24, 1992
(Date of Deposit)
Diane E. Furman
(Name of applicant, assignee, or Registered Representative)
Diane Furman
(Signature)
March 24, 1992
(Date of Signature)

CERTIFICATE OF SERVICE

It is hereby certified that true copies of the paper entitled:

37 CFR 1.602 NOTIFICATION OF INTEREST
FOR THE PARTY WATTANASIN

were served on counsel for the parties Fujikawa et al. and Picard et al., this 24th day of March, 1992, by postage pre-paid first-class mail addressed to the following:

Warner-Lambert Co.
Patent Department
Attn: Jerry F. Janssen, Esq.
2800 Plymouth Road
Ann Arbor, MI 48105

for the party Picard et al.

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

for the party Fujikawa et al.

Diane Furman 3/24/92
Diane E. Furman

Case No. 600-7101/CONT
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#7

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

CERTIFICATE OF SERVICE

It is hereby certified that true copies of the paper entitled:

37 CFR 1.613 DESIGNATION OF LEAD ATTORNEY
FOR THE PARTY WATTANASIN

were served on counsel for the parties Fujikawa et al. and Picard et al., this 23rd day of March, 1992, by postage pre-paid first-class mail addressed to the following:

Warner-Lambert Co.
Patent Department
Attn: Jerry F. Janssen, Esq.
2800 Plymouth Road
Ann Arbor, MI 48105

for the party Picard et al.

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

for the party Fujikawa et al.

Diane Furman 3/23/92
Diane E. Furman

PATENT
CASE NO. 600-7101/CONT.

#8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: SOMPONG WATTANASIN
Serial No.: 07/498,301
Filed: March 23, 1990
For: QUINOLINE ANALOGS OF MEVALONOLACTONE AND DERIVATIVES THEREOF

POWER TO INSPECT AND MAKE COPIES

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

Kindly permit Marian Schwartz, Ann Rutledge, Rosalie Jared, Somchay Chinyavong, Judy Valusek, James Jackson, Bobbie Judy, or Nancy Perry of Specialized Patent Services to inspect and make copies in the above noted matter, including recently declared Interference No. 102,648 in which said patent is involved.

Respectfully submitted,

SANDOZ CORP.
59 Route 10
E. Hanover, N.J. 07936

By Diane Furman 4/1/92
Diane E. Furman
Registration No. 31,104
(201) 503-7332

DEF:lcr

April 1, 1992

Encl.: postcard

IN THE UNITED STATES PATENT & TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#9

Wattanasin v. Picard, et al. v. Fujikawa, et al.

Interference No. 102,648

Examiner-In-Chief:
Michael Sofocleous

FYI

APR 8 1992

RECEIVED IN
BOX INTERFERENCE

DESIGNATION OF LEAD ATTORNEY
FOR THE PARTY PICARD, ET AL.

BOX INTERFERENCE
Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

The party Picard, et al. hereby designates RONALD A. DAIGNAULT, Registration Number 25,968, as lead attorney for the above-identified interference. The lead attorney's address and direct dial telephone are:

WARNER-LAMBERT COMPANY
2800 Plymouth Road
Ann Arbor, MI 48105
(313) 996-7530

Respectfully submitted,

Dated: April 6, 1992

Ronald A. Daignault
Registration No. 25,968
Attorney for the party
Picard, et al.

RAD:cm/184/3

PROOF OF SERVICE UNDER 37 C.F.R. §1.646 AND
CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

I hereby state that true and complete copies of the DESIGNATION OF LEAD ATTORNEY FOR THE PARTY PICARD, ET AL. was served upon the parties Wattanasin and Fujikawa, et al. this 6th day of April, 1992, by mailing same with sufficient first class postage affixed and prepaid as follows:

For the Party Wattanasin

Diane E. Furman, Esq.
SANDOZ CORP.
59 Route 10
East Hanover, NJ 07936

and

For the Party Fujikawa, et al.

Steven B. Kelber, Esq.
OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Fourth Floor
1755 S. Jefferson Davis Hwy.
Arlington, VA 22202

Furthermore, I hereby certify that this correspondence is being deposited today with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, BOX INTERFERENCE, Washington, D.C. 20231.

Dated: April 6, 1992

Ronald A. Daignault
(Reg. No. 25,968)

IN THE UNITED STATES PATENT & TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#10

Wattanasin v. Picard, et al. v. Fujikawa, et al.	Interference No. 102,648 Examiner-In-Chief: Michael Sofocleous

FYI

APR 8 1992

RECEIVED IN
BOX INTERFERENCE

**REQUEST BY THE PARTY PICARD, ET AL.
UNDER 37 CFR 1.662(a) FOR
ENTRY OF ADVERSE JUDGMENT AS TO
COUNTS 1 AND 2 OF THE INTERFERENCE**

BOX INTERFERENCE
Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

The party Picard, et al. hereby requests entry of Adverse Judgment as to the subject matter of Counts 1 and 2 of the Interference which corresponds to Picard, et al.'s Claims 1 and 2-14.

Respectfully submitted,

Ronald A. Daignault

Dated: April 6, 1992

Ronald A. Daignault
Registration No. 25,968
Attorney for the party
Picard, et al.

Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

RAD:cm/183/3

PROOF OF SERVICE UNDER 37 C.F.R. §1.646 AND
CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

I hereby state that true and complete copies of the REQUEST BY THE PARTY PICARD, ET AL. UNDER 37 CFR 1.662(a) FOR ENTRY OF ADVERSE JUDGMENT AS TO COUNTS 1 AND 2 OF THE INTERFERENCE was served upon the parties Wattanasin and Fujikawa, et al. this 6th day of April, 1992, by mailing same with sufficient first class postage affixed and prepaid as follows:

For the Party Wattanasin

Diane E. Furman, Esq.
SANDOZ CORP.
59 Route 10
East Hanover, NJ 07936

and

For the Party Fujikawa, et al.

Steven B. Kelber, Esq.
OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Fourth Floor
1755 S. Jefferson Davis Hwy.
Arlington, VA 22202

Furthermore, I hereby certify that this correspondence is being deposited today with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, BOX INTERFERENCE, Washington, D.C. 20231.

Dated: April 6, 1992

Ronald A. Daignault
(Reg. No. 25,968)

MAILED

APR 1 1992

PAT. & T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

Judgment

Paper No. 11
MS\gjh

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Patent Interference No. 102,648

Wattanasin v. Picard et al. v. Fujikawa et al.

Whereas Picard et al., a junior party, have filed a request for entry of an adverse judgment, pursuant to 37 CFR 1.662(a) judgment as to the subject matter of the counts in issue is hereby entered against Joseph A. Picard, Bruce D. Roth and Drago R. Sliskovic, a junior party. Accordingly, Picard et al. are not entitled to a patent containing claims 1 to 15 corresponding to the count.

The foregoing judgment is deemed to terminate the proceeding as to Picard et al.

Stanley M. Urynowicz
Examiner-in-Chief

Examiner-in-Chief

Mary F. Downey
Examiner-in-Chief

BOARD OF PATENT APPEALS AND INTERFERENCES

CERTIFICATE OF SERVICE

I hereby certify that true copies of:

1. **FUJIKAWA NOTICE OF FILING PRELIMINARY STATEMENT**
2. **AMENDMENT--37 CFR 1.633(C)**
3. **FUJIKAWA ET AL STATEMENT OF RELATED APPLICATIONS**
4. **FUJIKAWA MOTION FOR BENEFIT, 37 CFR 1.633(f)**
5. **FUJIKAWA ET AL MOTION TO ADD COUNTS, 37 CFR 1.633(c)**
6. **DECLARATION--PATENTABLY DISTINCT SUBJECT MATTER OF MASAKI KITAHARA (EXECUTED)**
7. **FUJIKAWA ET AL MOTION FOR BENEFIT, 37 CFR 1.633(f)**
8. **ENGLISH TRANSLATION (CERTIFIED COPY) OF JAPANESE PATENT APPLICATION 193606/1988**

were served upon Counsel for Wattanasin as follows:

Diane E. Furman
SANDOZ CORP.
59 Route 10
E. Hanover, New Jersey 07936

via first-class mail, postage prepaid, this 11th day of June, 1992.

STEVEN B. KELBER

#13

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
	:	**INTERFERENCE 102,648**
V.	:	**EXAMINER-IN-CHIEF:**
	:	**MICHAEL SOFOCLEOUS**
PICARD ET AL	:	
	:	
V.	:	
	:	
FUJIKAWA ET AL	:	

FUJIKAWA ET AL NOTICE OF FILING
PRELIMINARY STATEMENT, 37 CFR §1.626

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231
BOX INTERFERENCE

SIR:

Pursuant to the above-captioned Rule, Fujikawa et al hereby gives notice of the filing of a Preliminary Statement.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
	:	INTERFERENCE 102,648
V.	:	EXAMINER-IN-CHIEF:
	:	MICHAEL SOFOCLEOUS
PICARD ET AL	:	
	:	
V.	:	
	:	
FUJIKAWA ET AL	:	

FUJIKAWA ET AL
PRELIMINARY STATEMENT, 37 CFR §1.626

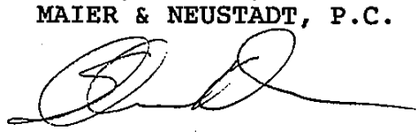
HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231
BOX INTERFERENCE

SIR:

Fujikawa et al intends to rely solely on the filing date of Japanese Patent Applications 207224/1987, 15585/1988 and 193606/1988, filed August 20, 1987, January 26, 1988 and August 3, 1988, respectively to prove a constructive reduction to practice of the Counts of the Interference.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
	:	INTERFERENCE 102,648
V.	:	EXAMINER-IN-CHIEF:
	:	MICHAEL SOFOCLEOUS
PICARD ET AL	:	
	:	
V.	:	
	:	
FUJIKAWA ET AL	:	

FUJIKAWA MOTION FOR BENEFIT, 37 CFR §1.633(f)

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231
BOX INTERFERENCE

SIR:

Pursuant to the provision of Rule 637(c)(1)(vi) and the above-captioned Rule, Fujikawa hereby request benefit of Japanese patent application Serial numbers 207224 and 15585, filed August 20, 1987 and January 26, 1988, respectively, as to Counts 3 and 4 proposed in Fujikawa's Motion to Redefine the Interference, and Claims 41-44 submitted by Amendment herein.

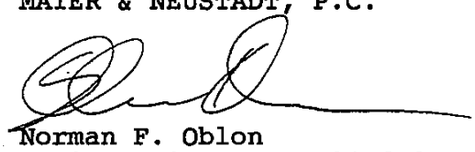
As grounds for this motion, Fujikawa notes that it has been granted benefit of the identified priority applications on the grounds that the priority documents represent constructive

reduction to practice of Counts 1 and 2 of the Interference. These same cases constitute constructive reduction to practice of the narrowed Counts 3 and 4, see the certified translations of record, and the detailed descriptions at pages 2-6. Note also the specific examples falling within the scope of the Count.

Accordingly, benefit as to Counts 3 and 4, and the Claims 41-44 added by Amendment is respectfully requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Norman F. Oblon
Registration No.: 24,618

Steven B. Kelber
Registration No.: 30,073
Attorneys of Record

Fourth Floor
1755 South Jefferson Davis Highway
Arlington, Virginia 22202
703-521-5940

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
	:	**INTERFERENCE 102,648**
V.	:	**EXAMINER-IN-CHIEF:**
	:	**MICHAEL SOFOCLEOUS**
PICARD ET AL	:	
	:	
V.	:	
	:	
FUJIKAWA ET AL	:	

FUJIKAWA ET AL MOTION TO ADD COUNTS,
37 CFR §1.633(c)

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231
BOX INTERFERENCE

SIR:

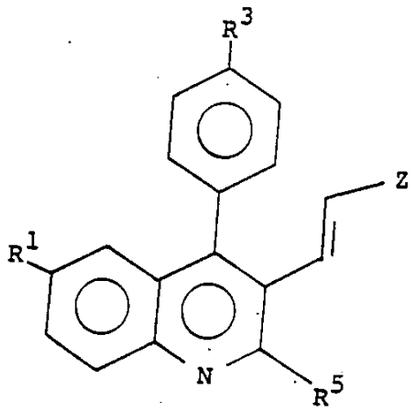
Pursuant to the provisions of the above Motion, the Senior Party hereby moves that the subject matter of this Interference be redefined by the addition of Counts 3 and 4, set forth below. As required by 37 CFR §1.637(c)(1)(ii) and (vi), this Motion is accompanied by an Amendment in Fujikawa's application involved herein, and a Request for Benefit as to the proposed Counts, and claims added by Amendment.

Fujikawa moves the following Counts be added to redefine the

Interference.

Count 3

A compound of the formula:



wherein R^1 = H

R^3 = F

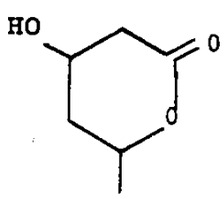
R^5 = cyclopropyl (c-Pr) and Z is selected from the group consisting of

$-CH(OH)-CH_2-CH(OH)-CH_2-COOH$

$-CH(OH)-CH_2-CH(OH)-CH_2-COONa$

$-CH(OH)-CH_2-CH(OH)-CH_2COO1/2Ca$

$-CH(OH)-CH_2-CH(OH)-CH_2-COOR$, Wherein R is C_{1-3}, alkyl and



lactone.

Count 4

A method of inhibiting cholesterol biosynthesis in a patient in need of said treatment comprising administering thereto a cholesterol synthesis inhibiting amount of a compound as defined by Count 3 in combination with a pharmaceutically acceptable carrier.

STATEMENT OF MATERIAL FACTS

1. The compounds embraced by Count 1 of the current Interference and the claims of the Senior and Junior Party thereto (Judgment against Picard et al having been rendered based on request for the same) designated as corresponding to the Count have utilities as inhibitors of biosynthesis of cholesterol (the synthesis, in vivo by animals, of cholesterol).

2. The method of inhibiting cholesterol biosynthesis in an animal in need of same by administration of the compounds of Count has been judged to be patentably distinct from Count 1, and constitutes separate Count 2 of this Interference.

3. The compounds of proposed Count 3, characterized by a cyclopropyl substituent at R^5, exhibit unusually high activity in the inhibition of cholesterol biosynthesis. Page 3 of the Declaration of Kitahara.

4. In side-by-side comparisons with structural isomers of the proposed Count 3, varying only with respect to the identity of the R^5 substituent, the n-propyl and isopropyl isomers exhibited dramatically reduced activity, whether measured in vivo or in vitro. The Declaration of Kitahara, see the tables attached thereto.

5. The unusually high activity exhibited by compounds of proposed Count 3 is not a function of the molecular weight of the substituent at R^5. Analogous substituents, both lower and greater molecular weight, show lower activity, when the remainder of the molecule is the same. See the Kitahara Declaration, tables attached thereto.

6. There is nothing in the art that would suggest the enhanced activity conferred on the compounds of Count 1 when R^5 is cyclopropyl and the remaining identities of Count 3 are observed.

One of ordinary skill in the art could not have predicted the differences between compounds of Count 3, and isomers thereof with respect to R^5, on the basis of structure only. Kitahara Declaration, paragraph 5.

7. The Fujikawa application describes, and enablingly discloses, compounds within the scope of proposed Count 3, as well as providing a generic description of that Count.

8. The application of Wattanasin involved herein does not specifically identify cyclopropyl as a substituent at the R^5 position (R in the claims of Wattanasin). This substituent is suitably identified as cycloalkyl C_{3-7}, however, and the application elsewhere identifies isopropyl and methyl as suitable substituents for this position. Thus, the identity of this substituent as cyclopropyl is reasonably conveyed to those of ordinary skill in the art by the application of Wattanasin.

REASONS IN SUPPORT OF THE DESIRED RELIEF

As set forth in MPP 2309.01, each Count must be drawn to a separate patentable invention. Separate counts to a species or

sub-genus may be presented, if the specie or sub-genus is unobvious over the genus, even though the genus may not be patentable, given the specie. Thus, in this Interference, adoption of Counts 3 and 4 is appropriate if the sub-genus of Count 3 is patentable over the genus of Count 1, and the sub-genus of Count 4 is patentable over the genus of Count 2. Fujikawa respectfully submits that the declaration of Kitahara clearly indicates that such is the situation here.

There is no question that the sub-genus of Counts 3 and 4 are herein embraced by Counts 1 and 2. Demonstration of the unobvious nature, and patentability, of a sub-genus or a species over an embracing genus can be achieved by proof tending to show activity in the sub-genus or species that is unpredictably higher than that exhibited in the genus as a whole. Ex parte Ebata, 19 USPQ2d 1952 (POBAI 1991). The Declaration of Kitahara submitted herewith clearly demonstrates such unpredicted superior bioactivity.

As noted above, Count 1 embraces a wide number of compounds whose utility is identified by both parties as the inhibition of the biosynthesis of cholesterol. In other words, administration of these compounds to individuals can result in the reduction of

biosynthesis of cholesterol by the individual so treated. This second invention is addressed by Count 2. As set forth in the Declaration of Kitahara submitted herewith, compounds within the limited sub-genus of Count 3, when R^5 is cyclopropyl, exhibit unexpectedly superior cholesterol biosynthesis inhibition activity, when compare with isomeric forms of the compounds of Count 1. Not only the isomers, but analogous compounds, wherein R^5 is an alkyl group of lower or higher carbon number, branched or unbranched, have also been demonstrated to be patentably distinct from the compounds of Count 3, in terms of bioactivity.

Similar to the relation between Counts 1 and 3, administration of the compounds of Count 3 to an animal in need of inhibition of biosynthesis of cholesterol as called for in Count 4 is equally patentable over the broad genus of Count 2. This can be most clearly seen by reference to the Declaration of Kitahara, and the Tables attached thereto. The unobviously superior bioactivity of Kitahara is evidenced in the dramatically reduced IC_{50} values of the compounds of Count 3. Thus, administration will require dramatically reduced dosages, or reduced administration periods, to achieve the same results. Such is the stuff of unobviousness.

Structural similarity would predict similar bioactivity. Certainly, there is nothing of record which would predict the unusual bioactivity keyed by the R^5 substituent as cyclopropyl. See the Declaration of Kitahara. Indeed, it is respectfully submitted that one of ordinary skill in the art would not immediately recognize the substitution as a point on the molecule determining activity. Nonetheless, the same has been demonstrated to be true, by competent comparative experiment.

Counts 3 and 4 having been demonstrated, by comparative experiment commensurate in scope with the Counts themselves, to be unobvious over the genus over Counts 1 and 2, addition of Counts 3 and 4 to this Interference is respectfully requested.

FUJIKAWA'S CLAIMS TO CORRESPOND TO THE COUNTER INTERFERENCE

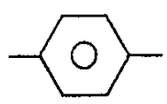
The original claim 10 of the Fujikawa application was cancelled, and pursued in a copending application which is the subject of a separate paper in this Interference, during ex parte prosecution, see the Amendment of December 19, 1990. Claim 10 would have corresponded to proposed Count 3. In a separate Amendment pursuant to 37 CFR 1.637(c)(1)(ii), Fujikawa submits an

Amendment presenting claims 41-44, claims 41-43 corresponding to Count 3 and claim 44 corresponding to Count 4.

PROPOSED CLAIM FOR WATTANASIN

Pursuant to the provisions of Rule 637(c)(1)(iii), Fujikawa notes that no claim currently presented by Wattanasin appears to correspond to either Count 3 or Count 4. Such claims can be presented by Wattanasin, and the same are suggested below.

As a claim corresponding to Count 3 of the Interference, Fujikawa suggests Wattanasin adapt the following claim 11.

Claim 11. The compound of claim 1, wherein R_1 and R_2 are hydrogen, R_o is  F, X is -CH=CH-, R is cyclopropyl, Q is  R_6 is H, R_8 is an alkyl of 1-3 carbon atoms and M is sodium.

As a claim corresponding to Count 4, Fujikawa proposes Wattanasin adopt the following claim 12.

Claim 12. A method of inhibiting cholesterol biosynthesis in a patient in need of said treatment comprising administering a cholesterol biosynthesis inhibiting amount of the compound of Claim 11 in combination with a pharmaceutically acceptable carrier.

Save for the issue of a priority, these claims appear to be patentable to Wattanasin. Note in particular that in Claim 11, the identity of all substituents is selected from a disclosure appearing in Claim 2, save for the identification of M and R. With regard to the identity of M, Wattanasin identifies sodium as a pharmaceutically acceptable cation at page 5 of the specification. Indeed, this is the preferred cation. With regard to cyclopropyl, as the identity for R, note that Claim 1 specifies that this group may be cycloalkyl of 3-7 carbon atoms. Although cyclopropyl is not specified, the corresponding non-cyclocpropyl isomer, isopropyl is particularly identified. See, e.g. Claim 4 and with more particularity, the disclosure at page 4 of the specifications. Accordingly, substituent R as cyclocpropyl in the Application and Claim 1 of Wattanasin appears to be reasonably conveyed to those of ordinary skill in the art, and the claim appears to be patentable to Wattanasin, save for the issue of priority in this Interference. With regard to Claim 12, this appears to correspond exactly to Claim 8 of Wattanasin, substituting Claim 11 for Claim 1.

Accordingly, as Wattanasin appears able to contest this Interference with claims patentable thereto, entry of an appropriate Order is respectfully requested.

Fujikawa, having demonstrated proposed Counts 3 and 4 to be directed to subject matter patentable over the current Counts of the Interference and directed to an invention separately patentable from every Count in the Interference, having added claims to its own Application that correspond to the Count and suggested Claims for Wattanasin that correspond to the Count, redefinition of the subject matter of the Interference by addition of Counts 3 and 4 is respectfully requested. A Motion for Benefit accompanies this Motion.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Registration No.: 24,618

Steven B. Kelber
Registration No.: 30,073
Attorneys of Record

Fourth Floor
1755 South Jefferson Davis Highway
Arlington, Virginia 22202
703-521-5940

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
	:	INTERFERENCE 102,648
V.	:	EXAMINER-IN-CHIEF:
	:	MICHAEL SOFOCLEOUS
PICARD ET AL	:	
	:	
V.	:	
	:	
FUJIKAWA ET AL	:	

DECLARATION--PATENTABLY DISTINCT
SUBJECT MATTER

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231
BOX INTERFERENCE

SIR:

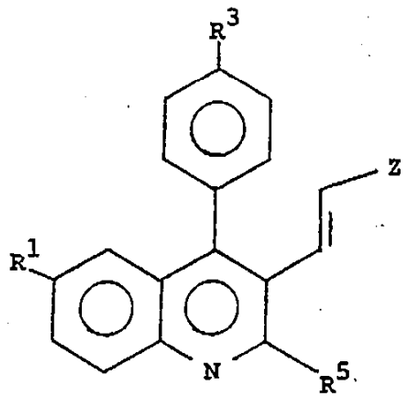
I, MASAKI KITAHARA, do hereby declare and state that:

1. I am a citizen and resident of Japan, and a named co-inventor in U.S. Patent Application 07/233,752, involved in the above-captioned patent Interference.

2. To demonstrate the unpredicted improvement in inhibition of cholesterol biosynthesis obtained when making specific election

for the substituents of the subject matter of the Count of the above Interference, the tests described below were conducted by me, or under my direct supervision.

3. Tests were conducted to determine the impact of specific substituents on compounds of the following formula:



wherein R^1 = H

R^3 = F

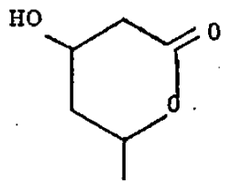
R^5 = cyclopropyl (c-Pr) and Z is selected from the group consisting of

$-CH(OH)-CH_2-CH(OH)-CH_2-COOH$ (carboxylic acid),

$-CH(OH)-CH_2-CH(OH)-CH_2-COONa$ (sodium salt),

$-CH(OH)-CH_2-CH(OH)-CH_2COO\frac{1}{2}Ca$ (calcium salt),

$-CH(OH)-CH_2-CH(OH)-CH_2COOR$, wherein R is C_{1-3} alkyl and



(lactone)

In compounds of the above formula, where R^5 is cyclopropyl, unpredictably enhanced inhibition of cholesterol biosynthesis, as tested both <u>in vitro</u> and <u>in vivo</u> (culture cell) is obtained. This unexpected improvement is maintained even when contrasted with identical compounds save for the identity of R^5, wherein R^5 is isopropyl or n-propyl. This is true even if the identity of R^5 is of larger size, such as a C_6 substituent.

4. In the test described above, inhibition of cholesterol

biosynthesis was determined according to two tests, A and B, as set forth in the specification of U.S. Patent Application 07/233,752, involved in the above-captioned Interference. These tests are set forth and identified as tests A and B on pages 28-30 of the specification. The results of the tests are set forth in the Tables attached to this Declaration. In the tables presented, the IC_{50} values are given, thus indicating higher activity in compounds giving lower IC_{50} values.

5. The superior activity of compounds bearing a R^5 cyclopropyl substituent could not, on the basis of my personal knowledge and experience, be predicted on the basis of chemical structure alone. There is nothing in the art that would lead one of skill, having the approximate level of a graduate chemist with several years of experience in the field, to conclude, on the basis of structural comparison alone, that the cyclopropyl substituent at R^5 would confer superior activity in the inhibition of cholesterol biosynthesis.

I hereby declare that all statements made herein of my own knowledge are true, and all statements made on information and belief are believed true. Further, I am aware that willful false

statements and the like are punishable by fine, imprisonment or both, 18 U.S.C. §1001, and that such willful false statements may jeopardize the validity of U.S. Patent Application 07/233,752, any patent issued thereon, as well the rights of the party Fujikawa et al in the above-captioned Interference.

DATE: June 1, 1992

Masaki Kitahara
MASAKI KITAHARA

(1) Test A: Inhibition of cholesterol biosynthesis from acetate in vitro

This test was carried out as described on pages 28-29 of the specification. The numerical values indicate IC_{50} (nanomolar concentration i.e. mol x 10^{-9}).

(a) Sodium salt

R^5	carbon number		1	2	3	6
	structure	normal	71.0	15.0	93.1(n-Pr)	>1000
		iso	X	X	10.0(i-Pr)	-
		cyclic	X	X	4.2(c-Pr)	51

(b) Calcium salt

R^5	carbon number		1	2	3	6
	structure	normal	-	-	-	-
		iso	X	X	23.0(i-Pr)	-
		cyclic	X	X	4.4(c-Pr)	-

(c) Ethyl ester

R^5	carbon number		1	2	3	6
	structure	normal	-	24.3	39.9(n-Pr)	>1000
		iso	X	X	-	-
		cyclic	X	X	2.8(c-Pr)	96

(d) Lactone

R^5	carbon number		1	2	3	6
	structure	normal	-	-	-	-
		iso	X	X	25.9(i-Pr)	-
		cyclic	X	X	6.8(c-Pr)	-

X: Not existing

-: Not tested

(2) Test B: Inhibition of cholesterol biosynthesis in culture cells

This test was carried out as described on pages 29 to 30 of the specification. The numerical values indicate IC_{50} (nanomolar concentration i.e. mol x 10^{-9}).

(a) Sodium salt

R^5	carbon number		1	2	3	6
	structure	normal	-	1050	733(n-Pr)	>10000
		iso	X	X	100(i-Pr)	-
		cyclic	X	X	17.5(c-Pr)	394

(b) Calcium salt

R^5	carbon number		1	2	3	6
	structure	normal	-	-	-	-
		iso	X	X	105(i-Pr)	-
		cyclic	X	X	35.0(c-Pr)	-

(c) Ethyl ester

R^5	carbon number		1	2	3	6
	structure	normal	-	797	501(n-Pr)	>10000
		iso	X	X	-	-
		cyclic	X	X	39.1(c-Pr)	4000

X: Not existing

-: Not tested

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
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PICARD ET AL	:	
	:	
V.	:	
	:	
FUJIKAWA ET AL	:	

FUJIKAWA ET AL
MOTION FOR BENEFIT, 37 CFR §1.633(f)

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231
BOX INTERFERENCE

SIR:

Fujikawa hereby moves for benefit of its foreign priority application, Japanese Patent Application 193606, filed August 3, 1988. Fujikawa moves for benefit of this priority case not only as to current Counts 1 and 2, but Counts 3 and 4 as proposed in the Fujikawa Motion to Redefine the Interference, and Claims 41-44 added by Amendment in support of Fujikawa's Motion to Redefine the Interference.

I. STATEMENT OF MATERIAL FACTS

1. Japanese Patent Application 193606/1988 was filed August 3, 1988 by the assignee of the entire right, title and interest in and to the Fujikawa et al application involved herein, Nissan Chemical.

2. A certified translation of the priority document, as well as the document itself, is of record in the file history of U.S Application Serial No. 07/233,752, involved in the above-captioned Interference.

3. The certified translation of the priority document reflects disclosure and description of compounds within the scope of Interference Count 1, and a method of administering those compounds to individuals in need of inhibition cholesterol biosynthesis in an amount sufficient to inhibit such synthesis, as set forth in current Count 2 of the Interference. Moreover, the reference discloses and describes compounds within proposed Count 3 of the Interference, and methods of administering those compounds to individuals in need of cholesterol biosynthesis inhibition, in an inhibiting amount, as set forth in proposed Count 4 of the Interference.

II. ARGUMENTS IN SUPPORT OF RELIEF REQUESTED

Pursuant to the provisions of 37 CFR §1.637(f), Fujikawa has identified Japanese Patent Application 193606/1988 as an earlier-filed Japanese Patent Application, benefit of the filing date of which, August 3, 1988, Fujikawa seeks herein. A copy of the application, together with the certified translation of the application, is of record in Fujikawa's U.S. Application Serial 07/233,752 file history. Accordingly, it is incumbent on Fujikawa to demonstrate that this reference is a constructive reduction to practice of each Count of the Interference. Fujikawa requests benefit not only as to current Counts 1 and 2, but as to Counts 3 and 4 proposed by Fujikawa, and Claims 41-44 added by Fujikawa. A discussion of the nature of this constructive reduction to practice follows.

III. CURRENT COUNTS 1 AND 2

Current Count 1 broadly embraces any of a variety of compounds characterized by the chemical structure set forth. In point of fact, complete description of such compounds appears in the

Fujikawa priority document, as can be confirmed by the certified translation (reference herein to page numbers constitutes reference to the pages of the certified translation). Claim 1, pages 1-2 of the translation, describes a wide variety of compounds each fitting within the Count of the Interference. Beginning on page 5, with Claim 6, claims are presented directed to a common family of compounds having the identical structure, but including the carboxylic acid, condensation lactone or salt of the identified compound. The compounds identified in these claims, which continue on to page 10 of the translation, all fall within the Count of the Interference. Moreover, see the examples beginning on page 39, which again fall within the Count of the Interference.

A full and complete disclosure of how to make the compounds set forth in the translation, and embraced by the Count of the Interference, appears at pages 23-31 of the translation. The translation discloses that the compounds have utility as cholesterol biosynthesis inhibitors. See pages 11-12 of the translation. Accordingly, it is respectfully submitted that the compounds of Count 1 of the Interference are fully disclosed, in terms of the manner of making and using the compounds of Count 1, and full benefit of Japanese Patent Application 193606/1988 is respectfully requested as to this Count.

Count 2 embraces a method of administration of the compounds of Count 1, calling for administration of those compounds to individuals in need of cholesterol biosynthesis inhibition in an amount effective to inhibit the cholesterol biosynthesis. The same is disclosed in the translation of Japanese Patent Application 193606/1988, see in particular pages 36-38, followed by examples demonstrating the cholesterol biosynthesis inhibition activity of the compounds identified. Accordingly, it is respectfully submitted that full constructive reduction to practice of Count 2 is also made out by the certified translation.

Benefit as to Counts 1 and 2 is respectfully requested.

IV. COUNTS 3 AND 4, AND CLAIMS 41-44

Elsewhere, Fujikawa has moved to redefine the Interference by adding limited Counts 3 and 4, which parallel the broader Counts, but limit the identities of R^1, R^2, R^6 and R^4 to hydrogen, require R^3 to be fluorine, and identify R^5 as cyclopropyl. Moreover, Y is limited to an ethylene bridge, and Z is narrowly limited to a dihydroxy carboxylic acid, sodium or calcium salt thereof or a lactone corresponding thereto. These compounds have all been

demonstrated to yield unobviously superior cholesterol biosynthesis inhibition activity, when compared with isomeric forms not bearing the cyclopropyl substituent at R^5. Contingent on the grant of Fujikawa's Motion to Redefine the Interference, benefit of Japanese Patent Application 193606 is also respectfully requested as to Counts 3 and 4 and Claims 41-44 added by Fujikawa, which correspond to proposed Counts 3 and 4.

With regard to narrowed Count 3, attention is directed to the broad disclosure, pages 1-2, and Claim 10, page 5 of the benefit application. Note, moreover, the identification of preferred forms in Claims 4 and 5, page 4 of the translation. With respect to the necessary choices in substituents to arrive at the claimed invention, see pages 14-15, which identify preferred embodiments.

Again, with regard to the compounds identified herein, a full disclosure of how to make these compounds appears at pages 23-31. Note, moreover, the final example set forth on page 35, with regard to choice of substituents.

Accordingly, a constructive reduction to practice of Count 3 is believed clearly made out by the priority case.

Count 4 corresponds to Count 2 discussed above, but recites the compounds of Count 3. Again, these compounds, discussed above, are described and enabled with regard to their method of use at

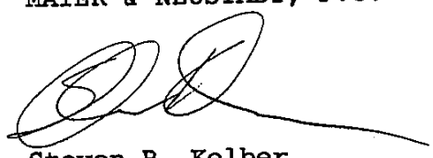
pages 36-38 of the translation. Full benefit as to these Counts is respectfully requested.

Claims 41-44 were added as corresponding to Counts 3 and 4 of the Interference. They claim essentially identical subject matter, and identical support, demonstrating a constructive reduction to practice, can be found in the translation. Benefit as to these claims is respectfully requested as well.

Fujikawa having shown the certified translation of Japanese Patent Application 193606 filed August 3, 1988, to be a constructive reduction to practice of Counts 1-4 and Fujikawa Claims 41-44, benefit is respectfully requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

Fourth Floor
1755 South Jefferson Davis Highway
Arlington, Virginia 22202
703-521-5940

#17

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
	:	**INTERFERENCE 102,648**
V.	:	**EXAMINER-IN-CHIEF:**
	:	**MICHAEL SOFOCLEOUS**
PICARD ET AL	:	
	:	
V.	:	
	:	
FUJIKAWA ET AL	:	

FUJIKAWA ET AL STATEMENT OF RELATED APPLICATIONS

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231
BOX INTERFERENCE

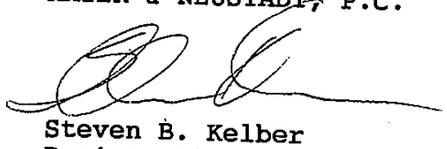
SIR:

By reason of a plurality of restriction and election requirements issued in the prosecution of the application of the Senior Party involved herein, and its progeny, Fujikawa et al and the assignee of the entire right, title and interest, Nissan Chemical, have secured patent protection, and currently have pending U.S. Patent Applications on subject matter patentably distinct from the claims of Fujikawa involved herein, but related as divisional or continuation applications.

Thus, U.S. Patent 5,011,930, now the subject of Reissue Patent Application 07/799,058, as well as U.S. Patent 5,102,888 have issued. Additionally, U.S. Patent Application Serial Nos. 07/631,092, 07/483,829 and 07/883,398, related to the application involved herein under 35 U.S.C. §120, are also pending. As the Patent Office has previously held the claims presented in each application to be patentably distinct from the claims of Fujikawa et al designated as corresponding to Counts 1 and 2 of the Interference, no action with respect thereto is believed necessary.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



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Case No. 60' '101/CONT
Patent

FYI

JUN 15 1992

#18 RECEIVED IN BOX INTERFERENCE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN

v.

PICARD et al.

v.

FUJIKAWA et al.

Interference No. 102,648

Examiner-in-Chief: M. Sofocleous

NOTICE OF THE FILING OF THE PRELIMINARY STATEMENT OF THE PARTY WATTANASIN

Appended is the Preliminary Statement of the party Wattanasin for the subject interference.

Respectfully submitted,

Diane Furman 6/11/92

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

DEF:rmf

June 11, 1992

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

NOTICE OF THE FILING OF THE PRELIMINARY STATEMENT OF THE PARTY WATTANASIN

was served on counsel for the party Fujikawa et al., this 11th day of June, 1992, 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

Case No. 600-/101/CONT/Int.
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN

v.

PICARD et al.

v.

FUJIKAWA et al.

Interference No. 102,648

Examiner-in-Chief: M. Sofocleous

PRELIMINARY STATEMENT OF THE PARTY WATTANASIN

In accordance with 37 CFR 1.622 and 1.623, the party Wattanasin hereby states as follows:

(1) That the invention of each of Counts 1 and 2 was made in the United States by Sompong Wattanasin.

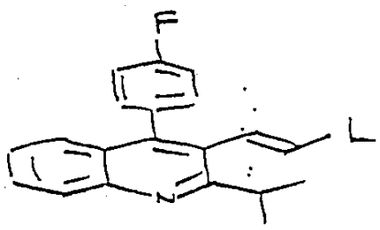
(2) That the invention of each of Counts 1 and 2 was first disclosed by Dr. Sompong Wattanasin, to Dr. Faizulla Kathawala of Sandoz Pharmaceuticals Corporation, by November 28, 1983.

(3) That the invention was first conceived no later than November 28, 1983.

(4) That the first drawing or written description of the invention of each of Counts 1 and 2 also occurred by November 28, 1983, when Dr. Wattanasin proposed to Dr. Kathawala to synthesize compounds of the invention of Counts 1 and 2 from previously synthesized intermediates and commercially available compounds for formulation into compositions for use as HMG-CoA reductase inhibitors.

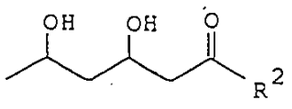
Exhibits A-C[1] document the first drawing or written description of the invention.

Exhibit A comprises a true copy of a research proposal of Sompong Wattanasin, the last page of which lists a compound designated 14, as follows:

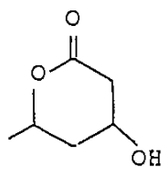


14

and "L" indicates either of the following side chains:



and

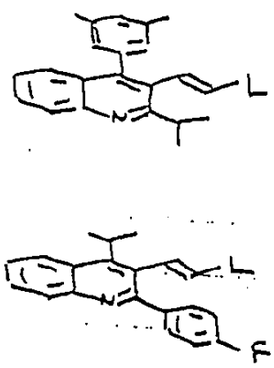


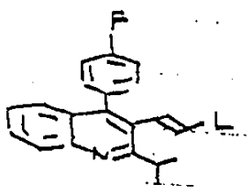
where R^2 is an acid, a salt or an ester.

---

1. The documents appended as exhibits hereto correspond to certain of the exhibits already provided with Wattansin's Request for Interference of May 25, 1990, with the exception that the dates are left unmasked. A detailed explanation of the exhibits is provided in the Request.

Exhibit B comprises a true copy of another research proposal submitted by Dr. Wattanasin to Dr. Kathawala which further indicates a drawing or written description of the invention on November 19, 1984. Page 1 thereof contains the following compounds:





wherein L and R_2 have the significances mentioned above.

(5) That the date after conception when active exercise of reasonable diligence began was no later than May 31, 1984.

(6) That the first synthesis of a compound within the scope of Count 1, and an active agent of a method of Count 2, was performed by Sompong Wattanasin and was completed on November 15, 1984, when Compound 1079-111-19 (subsequently redesignated Compound **63-366**), comprising an erythro racemate, was prepared, and recorded in his laboratory notebook.

Exhibits C-D comprise true copies of laboratory pages from the notebook of Sompong Wattanasin followed by copies of NMR spectra for the final product synthesized[2]:

Exhibit C comprises a true copy of Laboratory Notebook No. 1049, pages 237, 241, 248, 251, and Laboratory Notebook No. 1079, pages 22, 24, 27, 30, 33, 34, 39, 105, 106, 110 and 111, corresponding to the synthesis of Compound 63-366 and its non-commercially available intermediates. The NMR spectrum of Compound 63-366 was taken on November 21, 1984.

Exhibit D comprises copies of Laboratory Notebook No. 1127, pages 5, 9, and 11 (together with copies of spectra) corresponding to Compound 1127-11-34 of the invention (later redesignated Compound 63-548) and Compound 1127-11-37 (later redesignated Compound 63-549) of the invention and their non-commercially available intermediates. Both compounds also comprise erythro racemates.

(7) That the date of first actual reduction to practice was no later than December 31, 1984, when Compound 63-366 was known to have in vitro activity as an HMG-CoA reductase inhibitor.

---

2. On some of the notebook pages, microanalysis data were affixed subsequent to the date the actual synthesis was performe

Exhibits E-F comprise true copies of portions of bioassay data sheets which were prepared by Dr. Terence J. Scallen, an outside consultant for Sandoz. The bioassay data sheets were prepared concurrently with the tests, and then sent to Dr. Robert E. Damon of Sandoz. (The sheets bear the handwritten notations of Dr. Damon after he received them from Dr. Scallen.)

The bioassay data show that a composition containing Compound 63-366, i.e., a dimethylacetamide solution of Compound 63-366, was tested for HMG-CoA reductase inhibition activity on December 13, 1984. The test demonstrated that Compound 63-366 achieved a 50% inhibition of HMG-CoA reductase at a concentration of $< 1x10^{-6}$ µ/l.

Additionally, dimethylacetamide solutions of, respectively, Compounds 63-548 and 63-549, were each tested for HMG-CoA reductase inhibition activity on June 13, 1985.

Exhibit E comprises a true copy, of the protocol which was followed, and Scallen's Laboratory Notebook pages which recorded the data for **63-366**.

Exhibit F comprises a true copy, of the description of the procedure and the printout showing the data for **63-548** and **63-549**.

Respectfully submitted,

Diane Furman 6/11/92

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

DEF:rmf

June 11, 1992

Exhibits A,B,C,D,E,F

EXHIBIT A

(3) copy + Dr. Kathawala

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

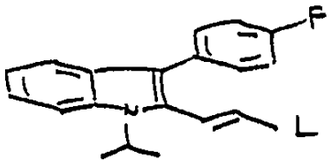
② Synthesis of "restricted rotation" Indole analogues,

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

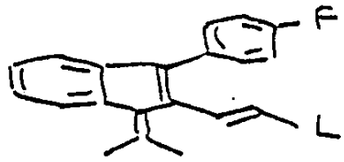
④ Synthesis of new analogues based on ① → ③.

① Synthesis of Indenes

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

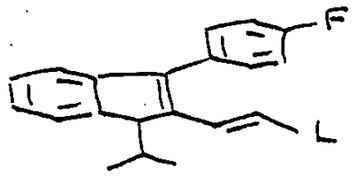


1

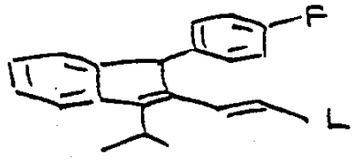


2

L = Lactone



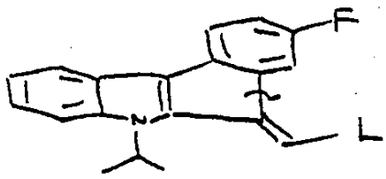
3



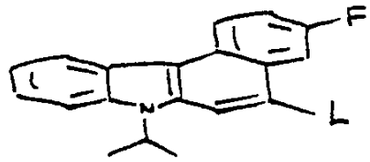
4

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

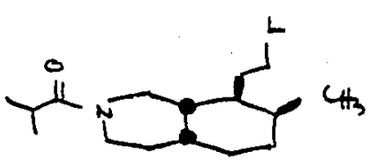


6

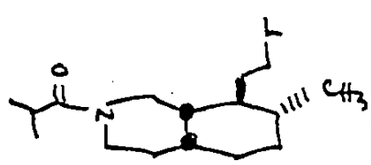
Analogues 5 and/or 6 are proposed as probes of the rotation requirements of the para-fluorophenyl group and the double bond side chain of the lactone. Nothing is currently known in this regard.

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

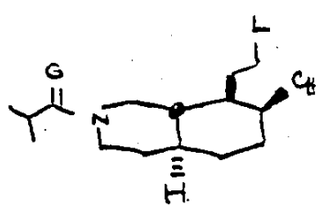
A) Asymmetric synthesis of an aza analogue of compactin



7



8

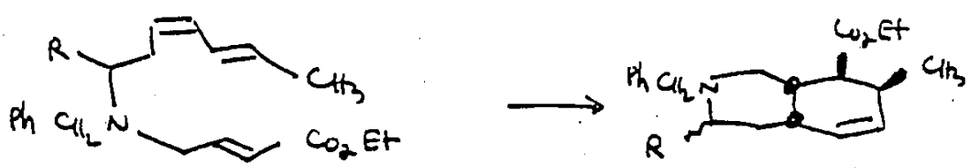


9

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.

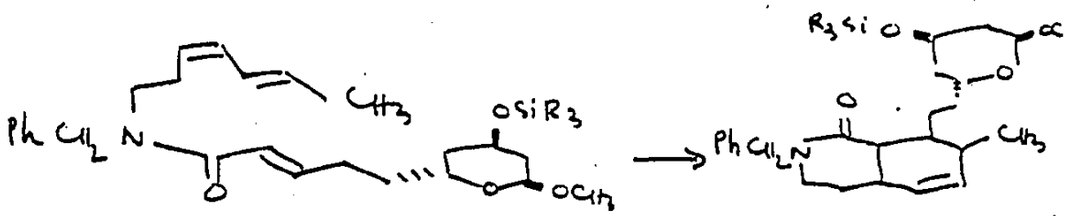


10

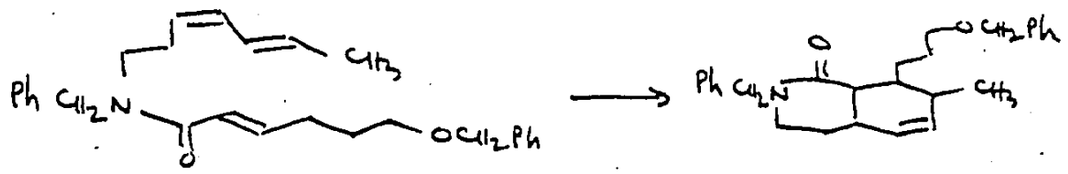
The highly stereospecific and the usefulness of the method in the synthesis of this type of compounds makes us feel necessary to demonstrate the followings:

(a) Effect of the R group (R = CH3 rather than H) in the cyclisation.

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

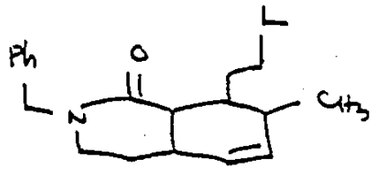


stereochemistry



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.

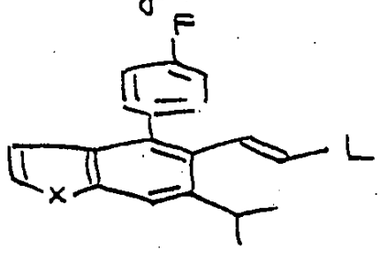


II

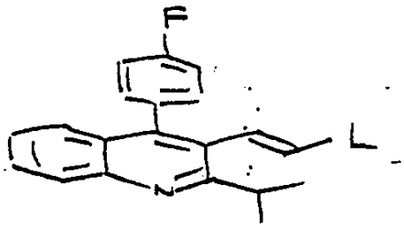
In addition, computer modellings show a better overlapping between compactin and II than those of 7 – 9

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 triene, and to make a substantial progress into the synthesis of other analogues.

EXHIBIT B

copy to Dr. P.K. Kadaba

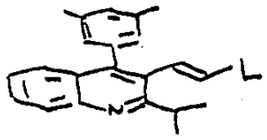
(3)

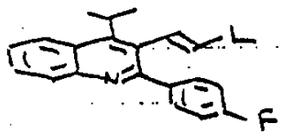
Sompong Watthanasin
Nov. 19, 1984.

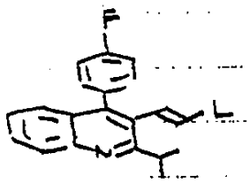
1985 Proposal

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

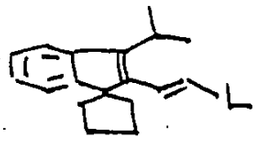


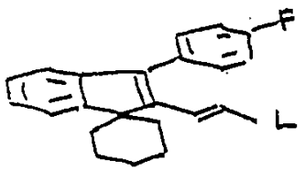


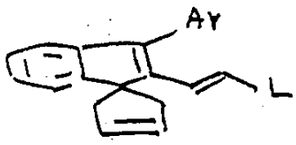


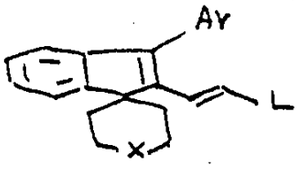
a few modifications might need to be prepared, because of their appearent ease of synthesis.

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



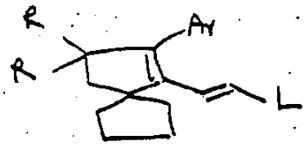




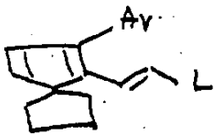


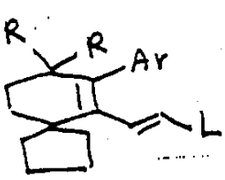
X = O, NR, S

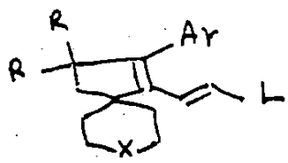
(3) New Analogs of Indenes.



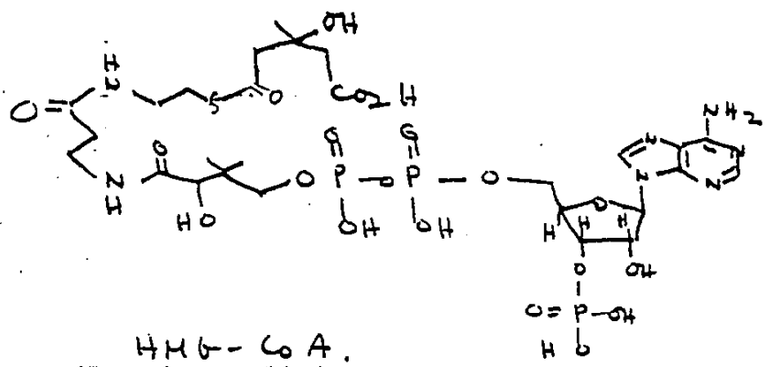
R = Aryl, alkyl groups
X = O, NR, S





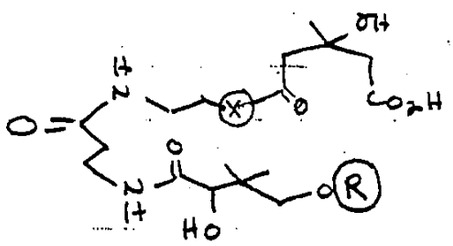


(4) X-ray structure of crystalline HMG-CoA derivatives.



HMG-CoA.

Derivatives vary R & X



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

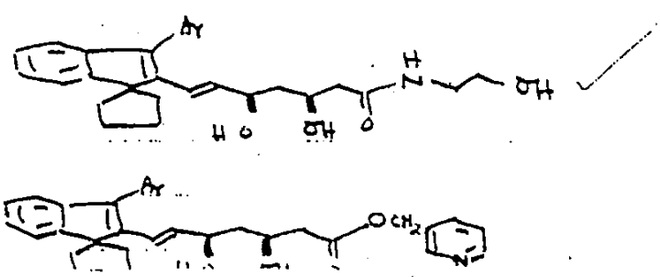
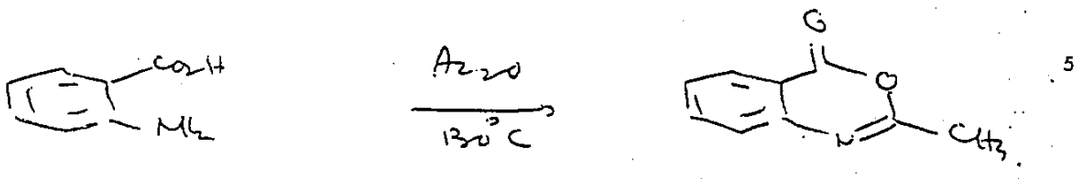


EXHIBIT C

Acc. JCS 2702 (1978)



anthranilic acid = 10 g
acetic anhydride = 54 ml.

A mixture of anthranilic acid and acetic anhydride was heated at 130°C. 12.000 rpm. 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)

nmr

(1049-237-19) was dissolved in ether and filtered through a short pad of silica gel. Evap n gave a crystalline solid = 7.0 g (1049-237-27) mp. 76-78°C

nmr IR micro

$C_9H_7O_2N$ 161.161

	C	H	N	O		
Calc.	67.08	4.38	8.69			
Found						
	66.90	4.45	8.57			

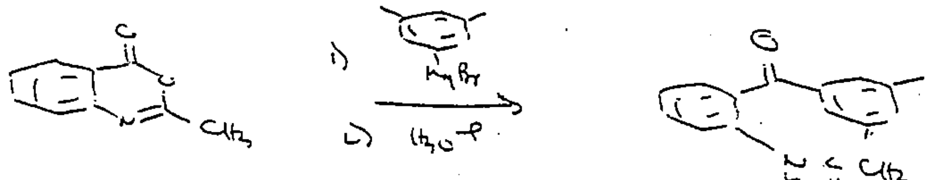
Performed by- S. Wattanasin

Witness- M. Rockelle

Cont'd to-

[redacted]

cf. P. 182.



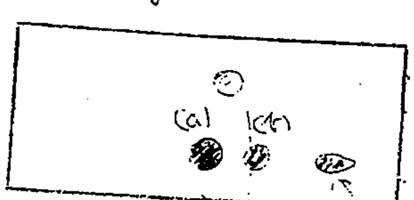
1049-237-27

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 few drop of I_2 at r.t., was added a few drops of 1,2 dibromoethane, followed by a soln of 5-bromo-m-xylene in ether (8 ml) dropwise (at a rate that the reaction mixture reflux gently). 9.05 am. → ~~9.27~~ 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 soln of 1049-237-27 in PhH (10 ml) + ether (2 ml) dropwise (via a funnel).

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

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



SM (a): white oil = 128 mg (1049-241-34)
NMR ✓
(b): white solid: 24 mg (1049-241-32)

Strong KMnO4 — weak KMnO4. — Come from hydrolysis of S.M.

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

Performed by- S. Wattanasin

Witness- N. Barbella

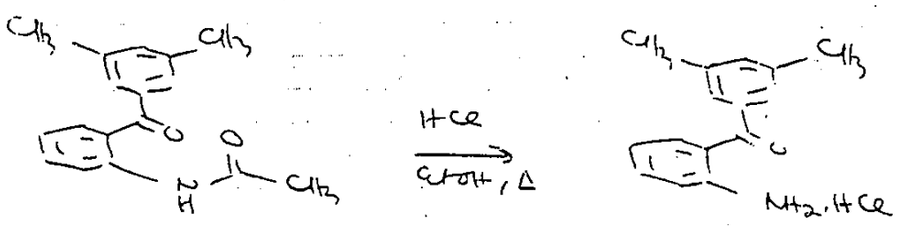
Cont'd to-

[redacted]

Title- 1049

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.

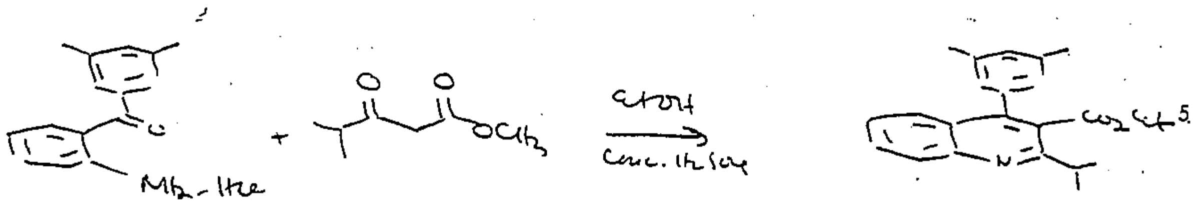
stop 4.00 pm TLC showed very small amt of the starting material.

The soln was concentrated and the residue was taken up in ether and filtered to give a pale yellow solid = 1.15 g (1049-148-24)

Performed by S Wattanasin

Witnessed N. Rotella

Cont'd to-

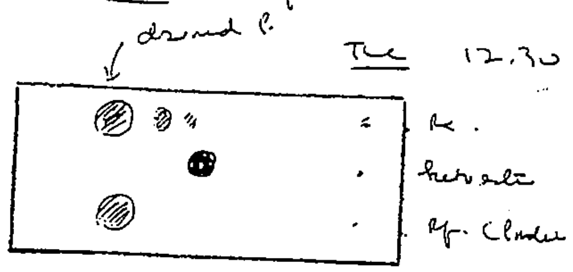


(261.5)	1049 - 248 - 24	=	500 mg	(0.001912 mol)
(144)	OCH3	:	412 mg	(0.002868 mol)
	EtOH	:	20 ml.	
	conc H_2SO_4	:	0.1 ml.	

Procedure same as 1049-245 Rx.

Start reflux. 8.50 am.

TLC 12.30 pm. Stop 12.30 pm.



Concentrated, basified with NH_4OH, diluted with H_2O & 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

$C_{22}H_{23}NO_2$ micro

	C	H	N	
Calc.	[illegible]	7.15	4.03	
Found	80.78	6.83	4.30	
	80.3	7.01	4.32	

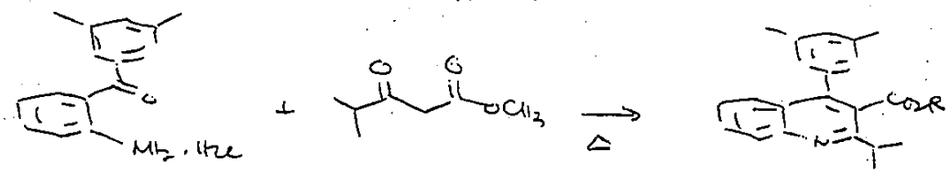
Performed by- S. Waltsman

Witness- N. Paolella

Cont'd to-

[redacted]

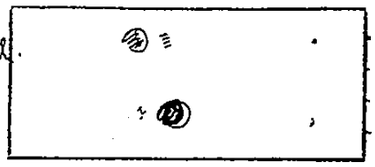
cf. J. Het. Chem. 7 (5) (1970)
J. Prakt. Chem. [4] 34, 298 (1966)



(261.5) 1049-244-24 = 20 mg (0.0000766 mol)
(144) = 11 mg (0.0000211 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 MeOH + extracted with ether. The crude oil was purified by prep TLC (1:1 eth – petrol) to give



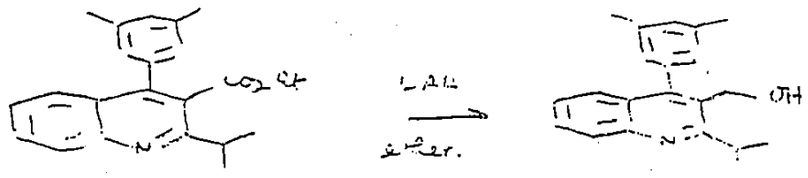
calculated oil
ca 1.2 17 mg (1049-244-23).

nmr ✓ => perfect.

Title- # 1079

Date 8/10/84 Proj. D.

Cont'd From- C



$C_{23}H_{27}O_2N$

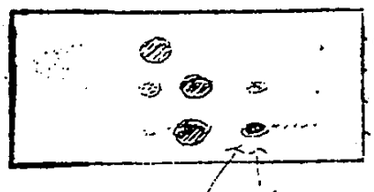
(347) . 1049-271-29 : 535 mg (0.00154 mol)
(38) LAH : 117 mg. (0.0031 mol)
ether : 8 ml.

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 T.L.C.

9.15 am:

T.L.C. after 10 min ⇒ 2 spots mainly the product.

then 10.15 am the reaction was poured into cold H2O and extracted with ether, to give on evaporation 427 mg (1049-271-29) as mp 111-113°C (solidified on standing)



50% cyclo-pinol.

this spot (pdt) increases

This spot disappears after wind-up.

1R ⇒ pure (oil which set solid)

Performed by- S. Wattanasin

Witness- M. Perelli

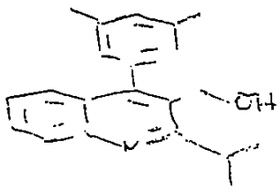
Cont'd to-

24

Title- # 1079

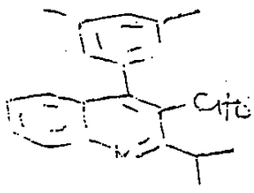
Date 5/10/94 Proj.

Cont'd From-



MnO_2

Toluene



10 mg - 22 - 24 = 420 mg

Max = 500 mg

Should = 600 mg.

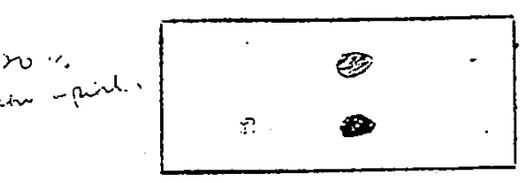
A melt of (10 mg - 22 - 24) and MnO_2 in toluene was stirred at R.T / overnight. Still future. 1.5T a.m.

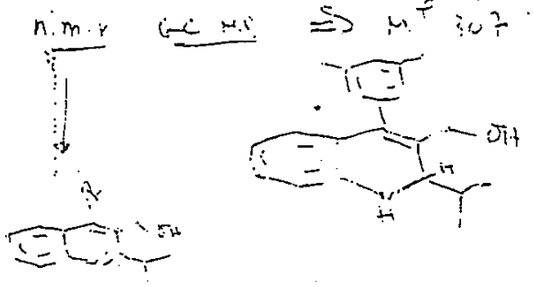
TLC ethyl acetate : hexane 3:4.

The reaction was filtered with ether and filtrate was washed with pH 4 citric buffer (pH 7) + 5% sodium bicarbonate solution + water (10 mg - 22 - 24).

92.9 % pure

N.M.R (CDCl3) ⇒ MF 307 ?

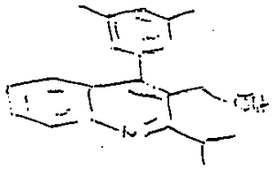




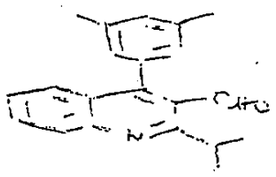
Performed by- S. Wattanasin

Witness- M. Padilla

Cont'd to-



PCC.

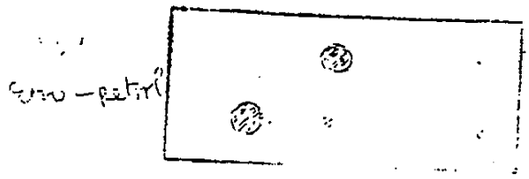


1079 - 2y - LF = 3[illegible] mg.
DDQ = 400 mg.
Toluene = 4 ml.

⇒ The mixt. was stirred at r.t. overnight. TLC no r.a.

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

⇒ The ether gum was dissolved in 10 ml CH2Cl2, PCC (400 mg) added, and mixt. stirred for 1½ hr at r.t. ⇒ TLC ⇒ complete rx. Diluted with ether, filtered through silica gel (10 g). Evap. gave a pale yellow oil = 132 mg (1079 - 2y - LF). Solidified on standing + 14 mg of m.m.y. IR. 151 mg.

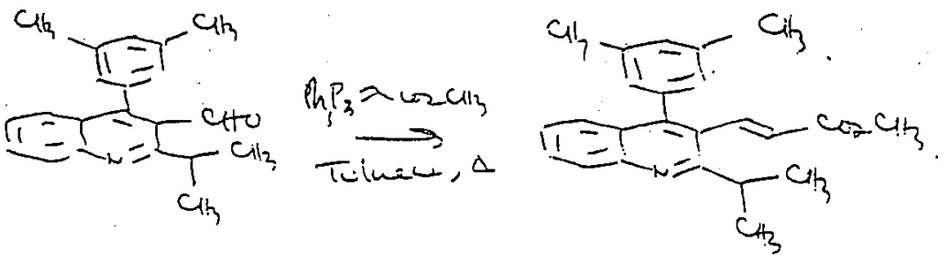


Semi-petrol

30 Title # 1079

Date 8/17/94 Proj.

Cont'd From-



1079-27-2 = 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 p.tlc. The 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. Waldman

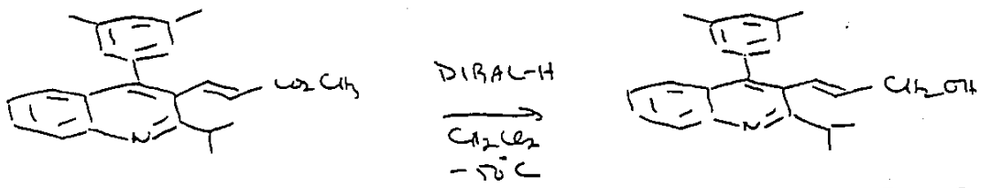
Witness- M. Molella

Con'd to-

Date 8/21/84. Proj.

'd From-

Title- # 1079



1079-30-23 = 130 mg (0.0003768 mol)
DIBAL-H = 0.5 ml. (0.0007536 ml).
CH_2Cl_2 = 5 ml.

To a solution of (1079-30-23) in dry CH_2Cl_2 at $-70^\circ C$ was added DIBAL-H. The mixt. was then stirred at $-70^\circ C$

11.30 am:
12.00 pm ⇒ complete reaction

The reaction was diluted with ether and filtered through a pad of silica gel. Evapn gave a crude oil = 135 mg which was used directly in the next step. TLC ⇒ one spot

(1079-33-19)

1:1 Etro-petrol

Performed by-

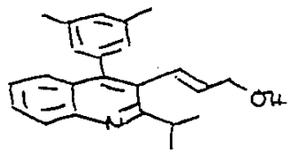
Witness- M. Pandelle

Cont'd to-

Title- # 1079

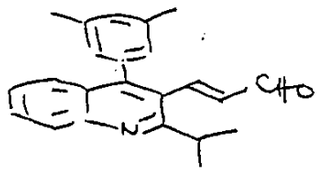
Date 8/23/84 Proj.

Cont'd From-



MnO_2.

r.t.



1079-33-19 = 135 mg

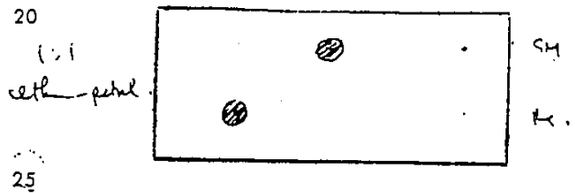
MnO_2 = 300 mg

Toluene = 5 ml.

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

pale yellow oil ⇒ 107 mg (1079-34-17)

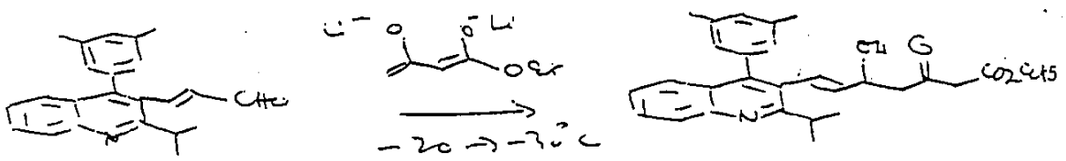
hmv



Performed by- S Wattanasin

Witness- N. Isabella

Cont'd to-



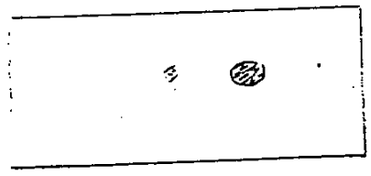
(3.9) 1079-74-17 = 100 mg (0.0003039 mol).
the diamion from
1079-38-21 = 5 ml (~ 0.0014 mol).
THF = 4 ml.

10.20 am - 10.50 am:
The => complete reaction
The reaction was quenched with sat. Nitrea
& extracted with Etoac.

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

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

The => one major spot.

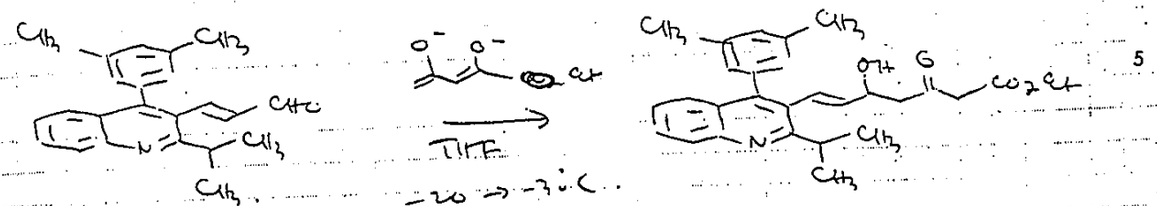


1:1
ether
pet.

Date 11/8/84. Proj.

Cont'd From-

Title- LDA (cyclohexane 23.57 wt % : 1.8 M. ⇒ 1.8 ml. reqd. 2 ml.



THF

−20 → −30°C.

(329)	1079-101-28 =	110 mg	(0.000 3343 mol)
101.19, .322	Diisopropylamine =	0.5 ml.	(0.00334 mol)
	1.6 M nBuLi =	2 ml.	(0.00336 mol).
130.14, 1.021	Ethyl acetoacetate =	0.22 ml.	(0.000 1667 ml)
	THF =	6 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 (1079-101-29) in THF (2 ml) at −30°C. ⇒ −10°C

4.40 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 ether

1:1 Ether-petrol

(1) (a) (b) (c) (d) (e) (f) (g) (h) (i) (j) (k) (l) (m) (n) gave a yellow oil = 290 mg

Prep TLC. (1:1 ether – petrol)

(a) : yellow oil = 112 mg (1079-101-35)

n.mr ✓ IR ✓

Performed by- S. Wattanasin

Witness- M. Bolella

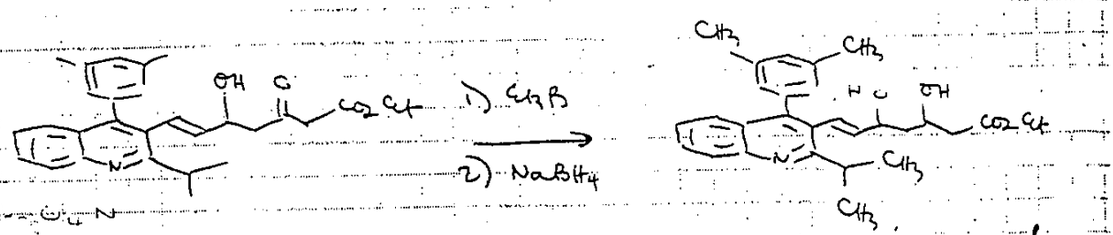
Cont'd to-

106

Title-

Date 11/12/94 Proj.

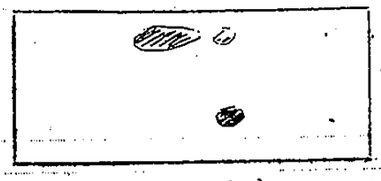
Cont'd From-



(479) 1079-105-35 = 55 mg (0.0001198 mol)
1 M Et_3B in THF = 0.15 (0.0001437 mol)
THF = 2 ml.

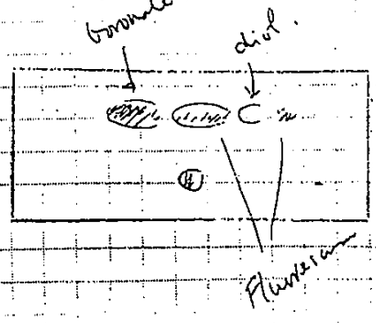
To a soln of (1079-105-35) in THF (2ml) at r.t. was added 1M Et_3B & (1ml) of air by syringe. The soln was stirred for 1½h.
9.00 am.
10.30 am. At -78°, $NaBH_4$ (10 mg) was added.

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 removed from dry ice bath, acidified 3N HCl was added until acidic (pH-check), diluted with H_2O (during this period reaction mixt. turned to fluorescence ?, dehydration ??).



The crude product (50 mg) was used directly in the next step (1079-106-36)

Performed by- S. Wattanasin

Witness- M. Radcliffe

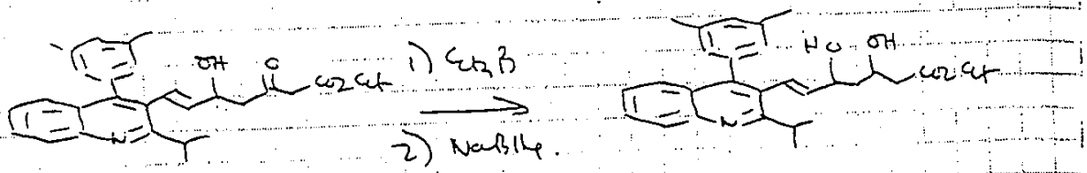
Cont'd to-

110

Title-

Date : 11/14/84 Proj.

Cont'd From-



acid free treatment

107a – 105 – 15 =	50	mg
1M Et2B	=	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 mps of Hoke, was added. After the evolution of H2 subsided. The reaction mixt. was concentrated H2O was added & extracted with ether

* slightly fluorescent color occured.

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

⇒ pale yellow + som fluorescent oil = 40 mg (109g-110-33) which was used directly in the next step.

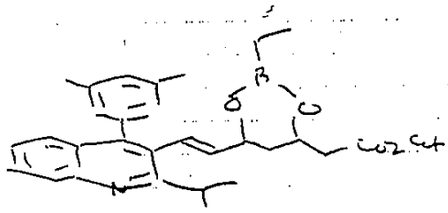
Performed by- G. Wuitz

Witness- N. Rodella

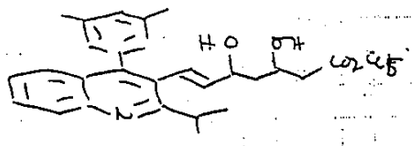
Cont'd to-

Date 11/15/Sne Proj. | Title- | 111

Cont'd From-



CH_3OH →



$C_{29}H_{37}O_4N$

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

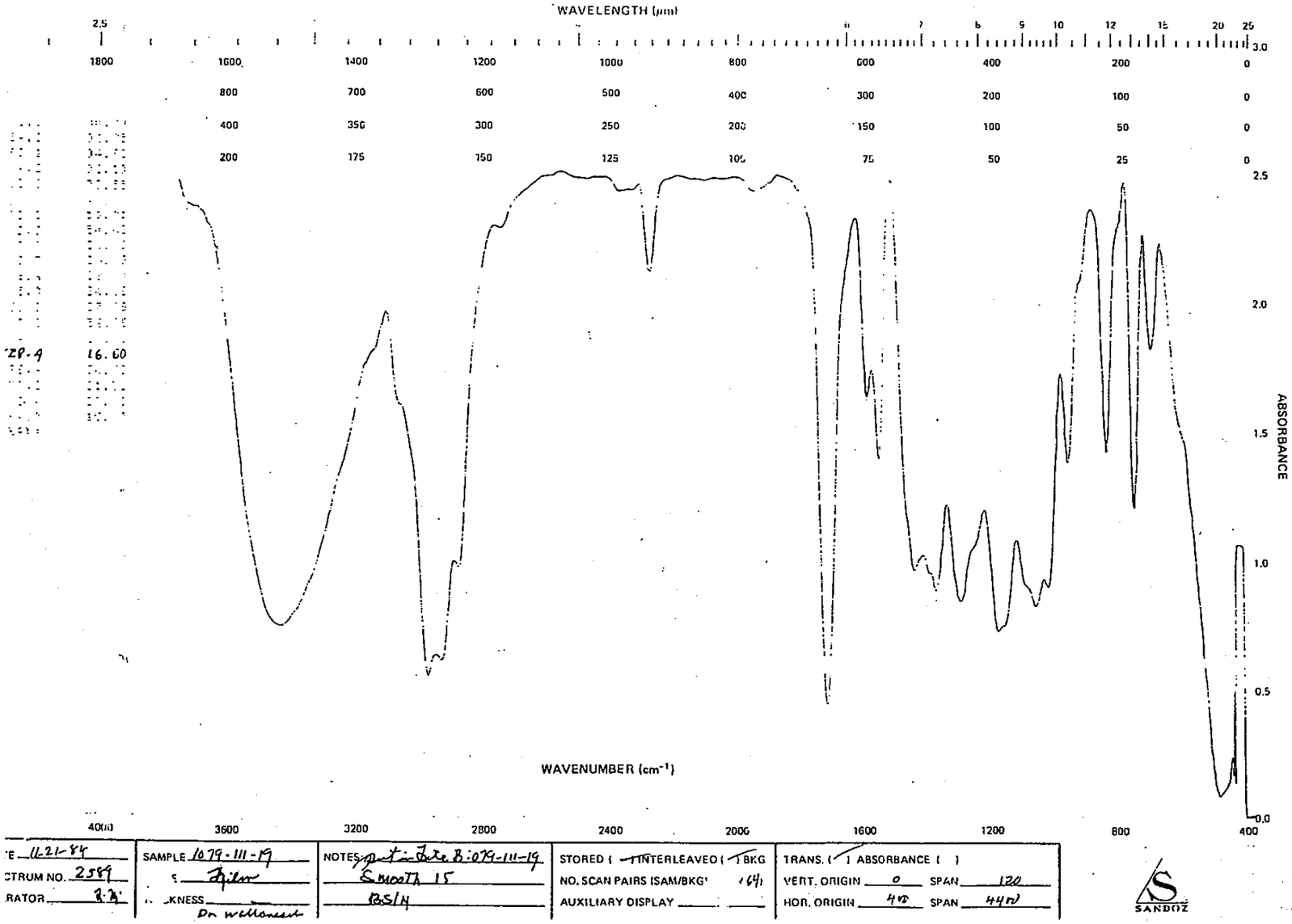
nmr 10 mg.

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

Performed by- S. Wattanasin

Witness- M. Paolella

Cont'd to-


WAVELENGTH (μm)
2.5
1800
1600
1400
1200
1000
800
600
400
200
0
800
700
600
500
400
300
200
100
0
400
350
300
250
200
150
100
50
0
200
175
150
125
100
75
50
25
0
ZP-4
16.60
2.5
2.0
1.5
1.0
0.5
0.0
ABSORBANCE
WAVENUMBER (cm⁻¹)
4000
3600
3200
2800
2400
2000
1600
1200
800
400
E 11-21-84
CTRUM NO. 2589
RATOR B.A.
SAMPLE 1079-111-19
Film
KNESS Dr wallowen
NOTES: put in file B:079-111-19
SMOOTH 15
BS/4
STORED ( ) INTERLEAVED ( ) BKG
NO. SCAN PAIRS (SAM/BKG) 64
AUXILIARY DISPLAY
TRANS. ( ) ABSORBANCE ( )
VERT. ORIGIN 0 SPAN 120
HOR. ORIGIN 4000 SPAN 4400
SANDOZ

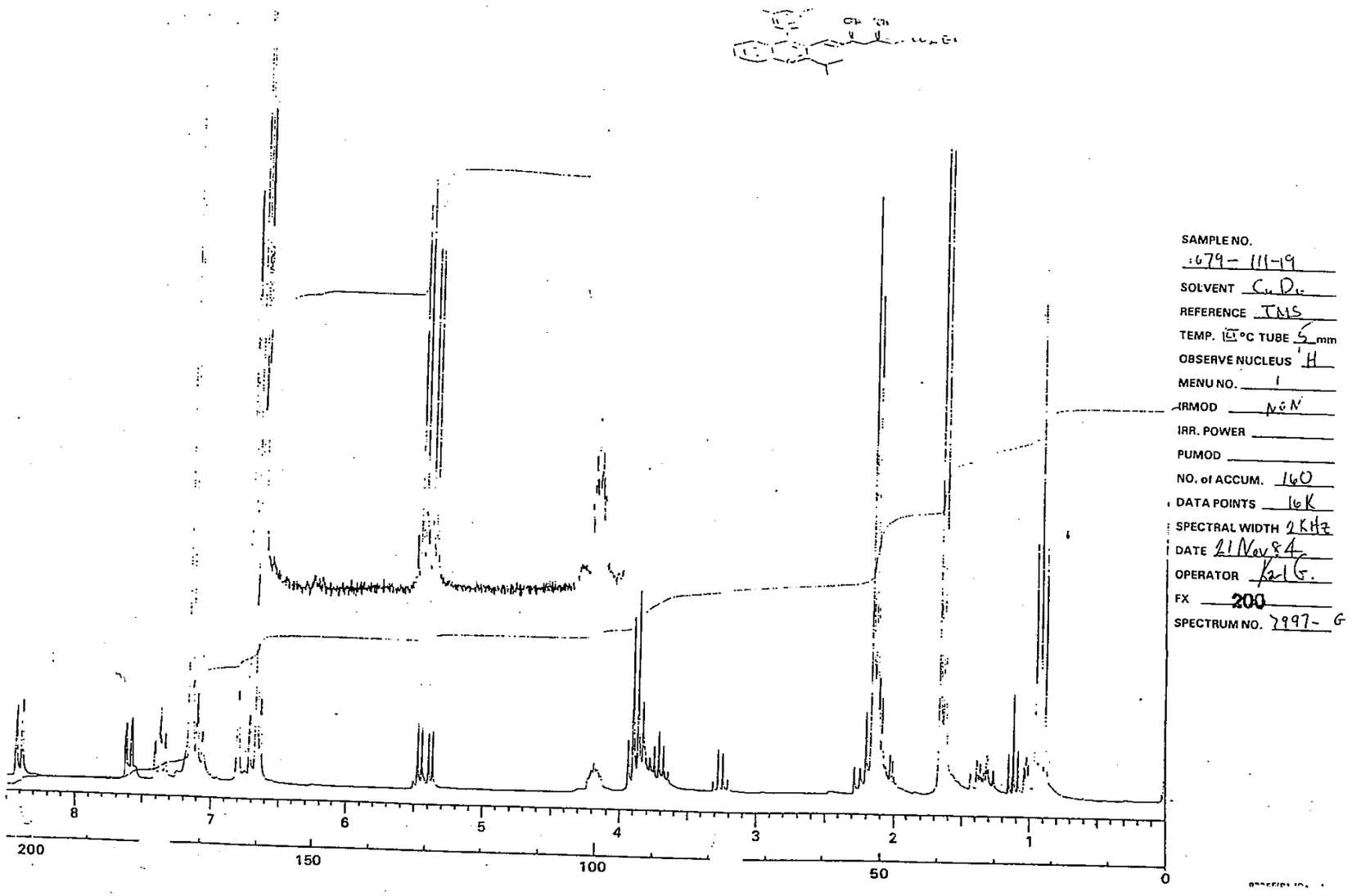
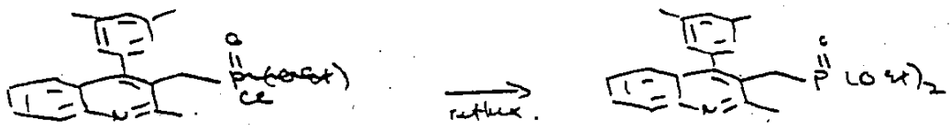

SAMPLE NO.
679-111-19
SOLVENT C6D6
REFERENCE TMS
TEMP. 25 °C TUBE 5 mm
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOD NON
IRR. POWER
PUMOD
NO. of ACCUM. 160
DATA POINTS 16K
SPECTRAL WIDTH 2KHz
DATE 21Nov84
OPERATOR KaiG.
FX 200
SPECTRUM NO. 7997-G
8
7
6
5
4
3
2
1
0
200
150
100
50

EXHIBIT D

cf. P. 1079-46.



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

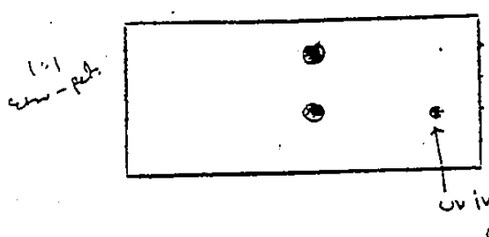
(295) 1079-296-3S = 150 mg
P(OEt)$_3$ = 0.3 ml.
Toluene = 2 ml.

9.10 am:

TLC 11.20 am: ⇒ SM.

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

prolonged heating at 110° for 20h ⇒ complete reaction



Concentration by distiln in vacuum - gave an oil which solidified on standing 160 mg (127-5-23). mp 105-107 (almost colorless solid)

micro ✓ OH

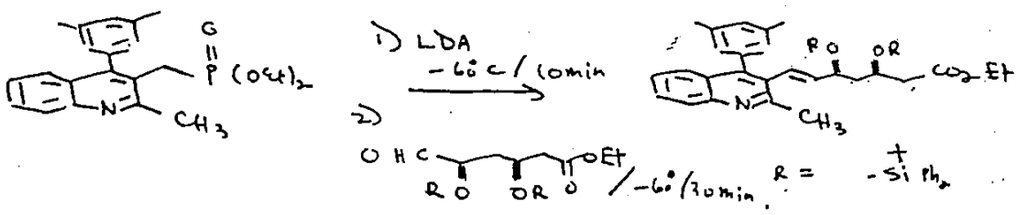
hmr ✓ : desired P.

MS MP 397 ✓

Performed by- S. Wattanasin

Witness- Stuart W. Mc

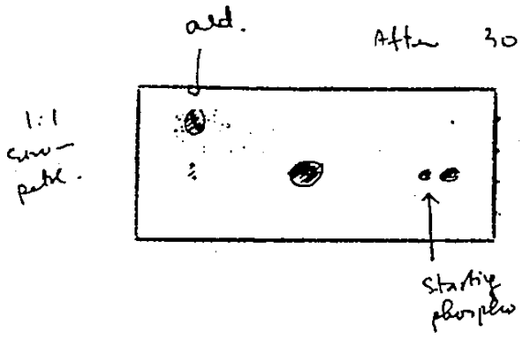
Cont'd From- | #1127



(397) 1127-5-23 = 150 mg (0.0003728 mol)
647 Pracad ald. = 293 mg (0.0004534 mol)
1.7M 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 soln was then stirred at -11° → -6°C for 10 min.
9.50 am - 10.00 am.

Then a soln 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 EtOAc. Then dil. Hex + Et was added and extracted with EtOAc. to give a yellow oil = 500 mg (to 1127-9-

Prep TLC (1:1 cmp-petrol) gave a yellow oil = 100 mg (to 1127-9-3

Nmr ✓

Performed by- S. Wattanasin

Witness- [redacted]

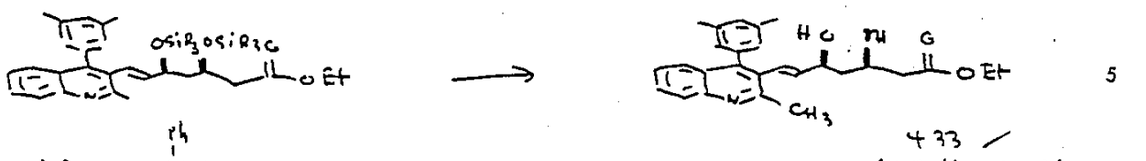
Date 5/7/85 Proj.

Title- Book # 1127

11

Cont'd From-

cf. 1079-97



SiR_3 : $Si(Ph)_2$

(F89)

1127-9-33	=	90 mg	(0.0001012 mol)
1M Bu$_4$NF	=	0.61 ml.	(0.00061 07 mol)
H_2O_2	=	0.03 ml.	(0.0005 mol)
THF	=	2 ml.	

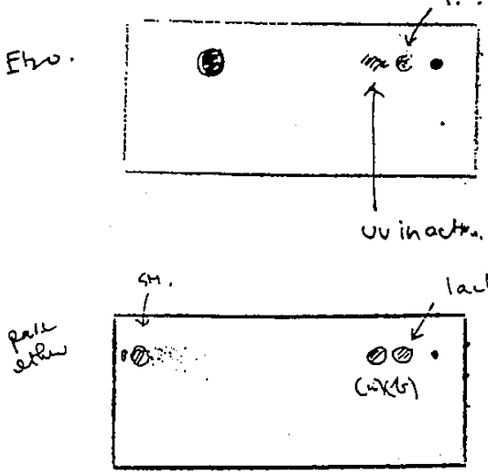
433 / $C_{27}H_{31}O_4N$

60.04 ; 1.09

The mixt. was stirred at r.t.

9.00 am:
- Bu$_4$NF 0.6
- " " 0.6
- H_2O_2 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°C

9.00 am:

TLC 11.00 pm : mixt. of 2 spots.

stop 5.50 pm

concentrated on the crude ⇒ was purified by prep TLC (ether & CH$_2$Cl$_2$/AcOEt)

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

nmr MS ✓ M^+ 433 ✓

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

nmr ms ✓ M^+ 387 ✓ $C_{24}H_{29}O_3N$

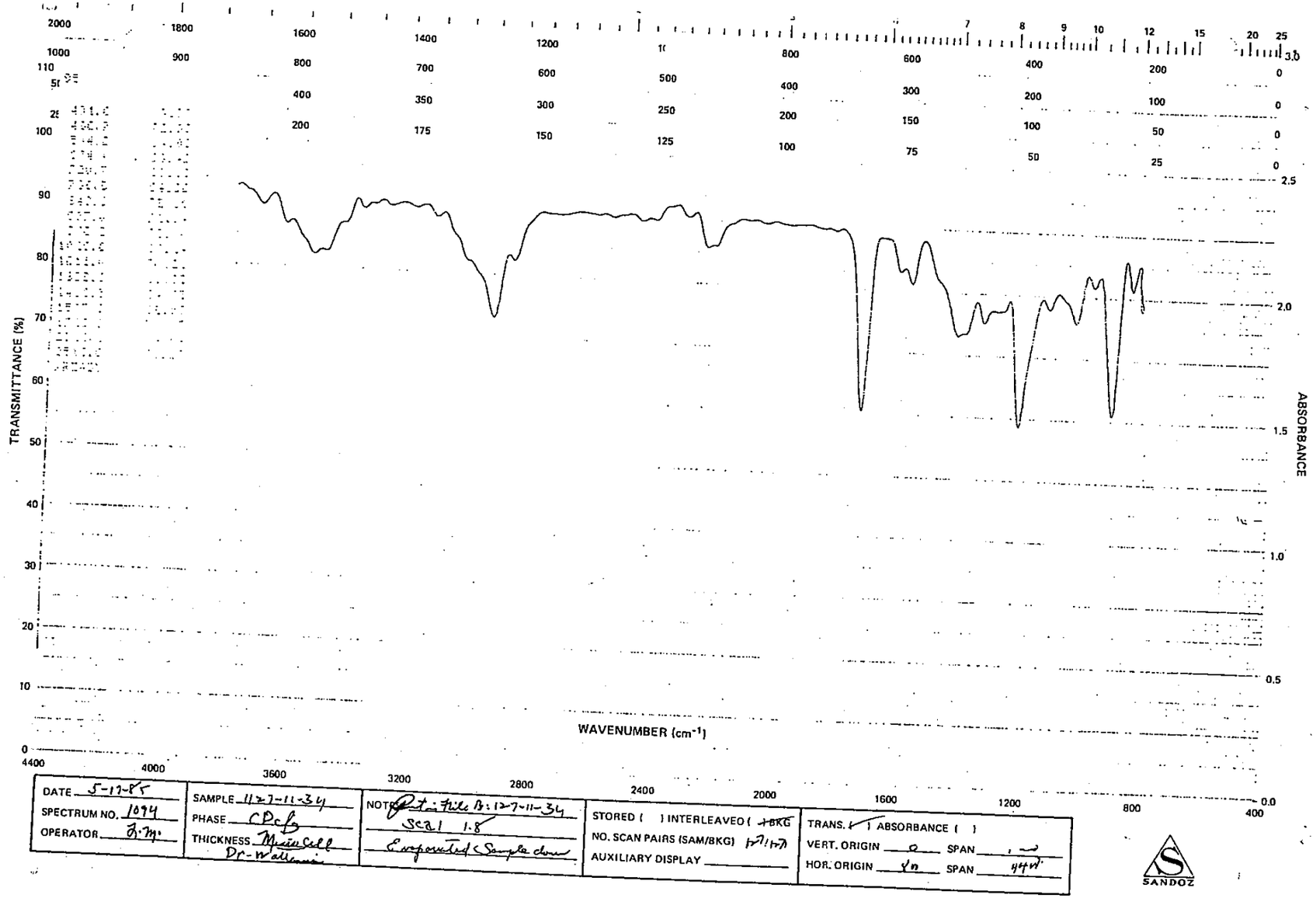
5/17/85. 1127-11-34 { 2 mg CSI, 4 mg CSTU, CSTC

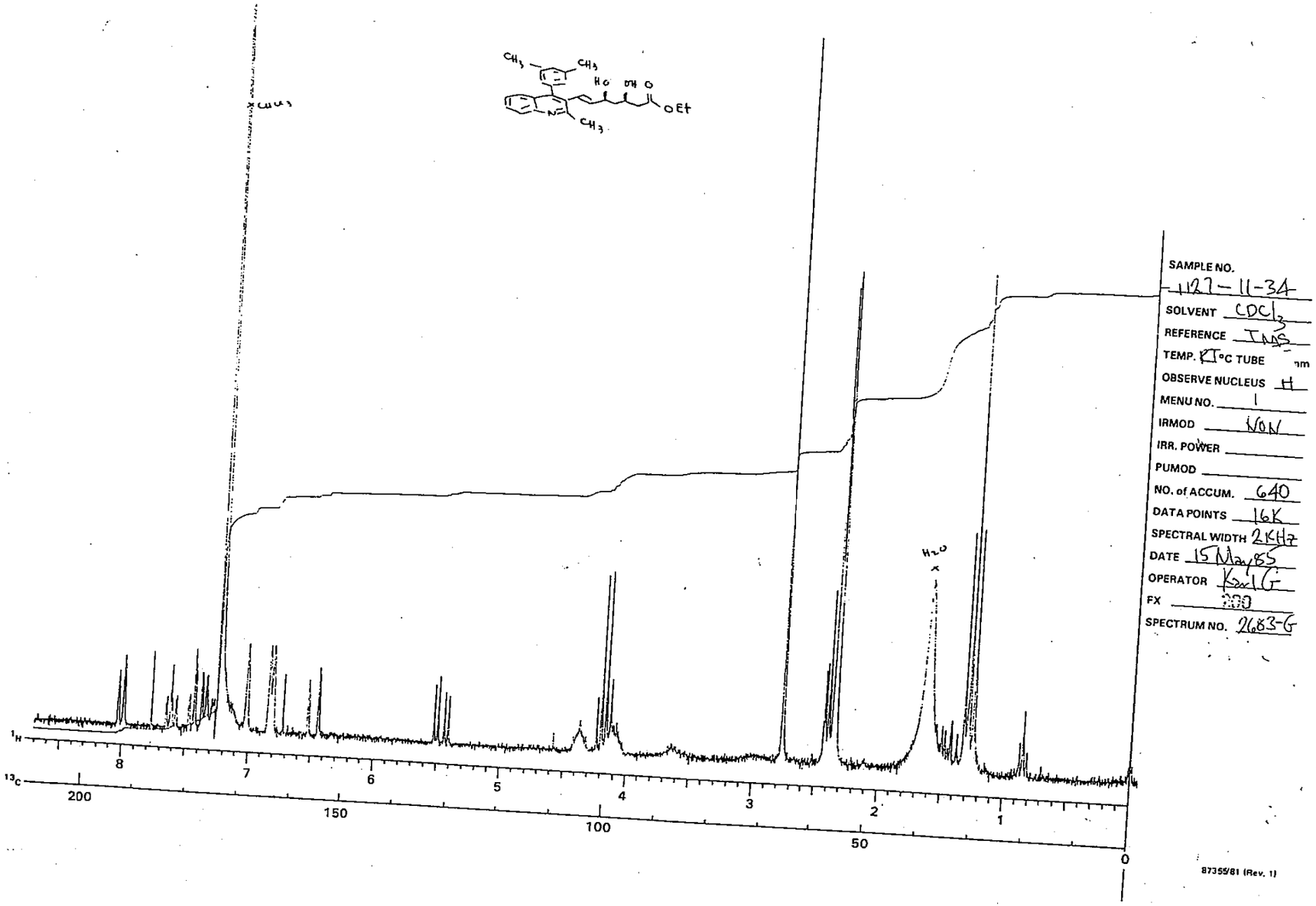
1127-11-37 { 2 mg CSI

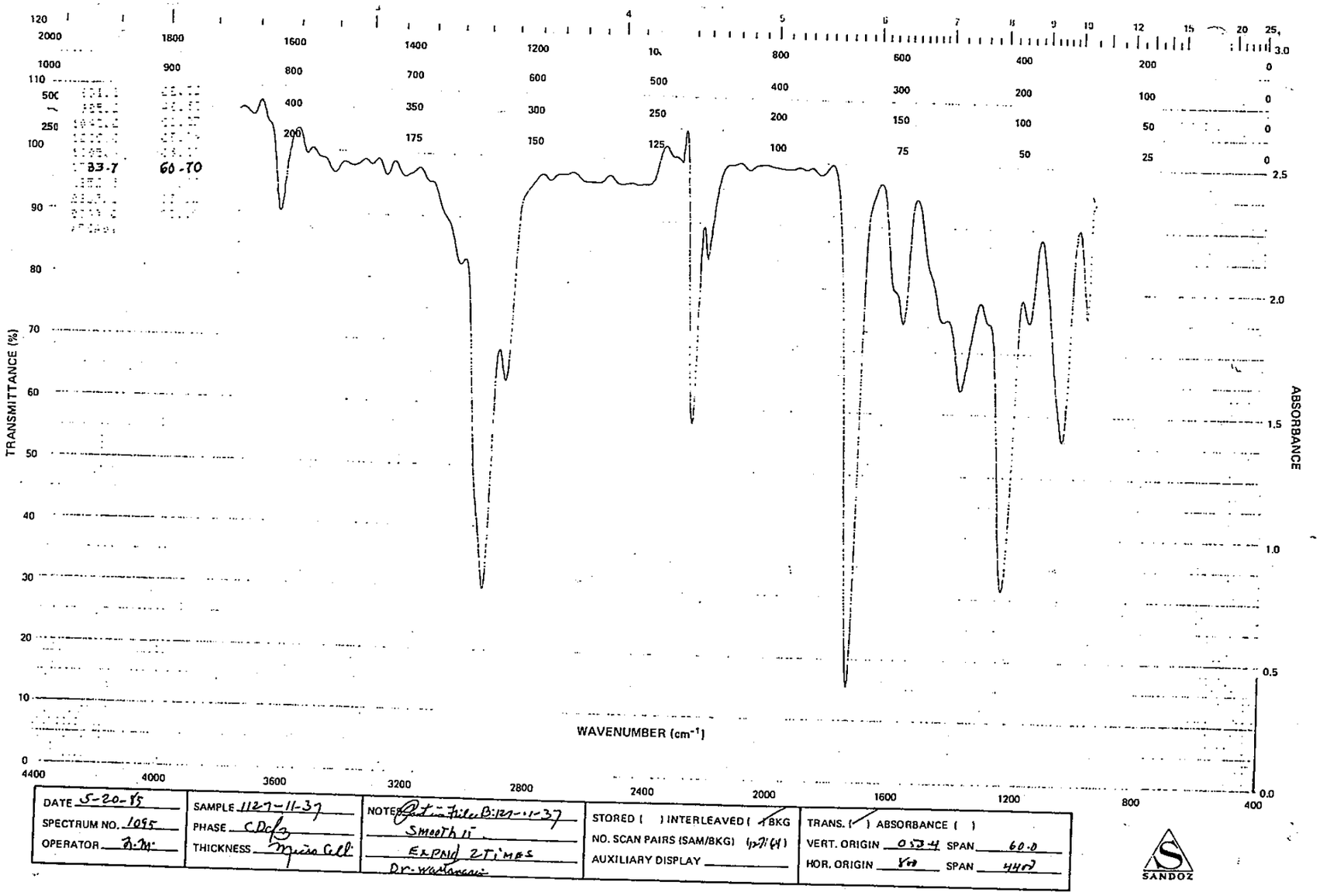
Performed by- S. Wattanasin

Witness-

Cont'd to-


TRANSMITTANCE (%)
ABSORBANCE
WAVENUMBER (cm⁻¹)
4400
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
900
800
700
600
500
400
350
300
250
200
175
150
125
100
7
8
9
10
12
15
20
25
30
3.0
2.5
2.0
1.5
1.0
0.5
0.0
DATE 5-17-85
SPECTRUM NO. 1094
OPERATOR J.M.
SAMPLE 1127-11-34
PHASE CDCl3
THICKNESS Micro Cell
Dr-Wallmac
NOTE Put in file B:127-11-34
Scal 1.8
Evaporated Sample down
STORED ( ) INTERLEAVED (+BKG
NO. SCAN PAIRS (SAM/BKG) 17/17
AUXILIARY DISPLAY
TRANS. ✓) ABSORBANCE ( )
VERT. ORIGIN 0 SPAN 1
HOR. ORIGIN 4m SPAN 4cm
SANDOZ


SAMPLE NO. H27-11-34
SOLVENT CDCl3
REFERENCE TMS
TEMP. RT °C TUBE mm
OBSERVE NUCLEUS H
MENU NO. 1
IRMOD NON
IRR. POWER
PUMOD
NO. of ACCUM. 640
DATA POINTS 16K
SPECTRAL WIDTH 2KHz
DATE 15 May 85
OPERATOR KaiG
FX 200
SPECTRUM NO. 2683-G
H2O
1H
13C
8
7
6
5
4
3
2
1
200
150
100
50
0
87355/81 (Rev. 1)


TRANSMITTANCE (%)
WAVENUMBER (cm⁻¹)
ABSORBANCE
33-7
60-70
DATE 5-20-85
SPECTRUM NO. 1095
OPERATOR T.M.
SAMPLE 1127-11-37
PHASE CDCl3
THICKNESS Micro Cell
NOTE Put in file B:127-11-37
Smooth 11
EXPND 2 TIMES
Dr. Wasfaoui
STORED ( ) INTERLEAVED ( ) BKG
NO. SCAN PAIRS (SAM/BKG) (1x7)(4)
AUXILIARY DISPLAY
TRANS. ( ) ABSORBANCE ( )
VERT. ORIGIN 0534 SPAN 60.0
HOR. ORIGIN 4400 SPAN 4402
SANDOZ

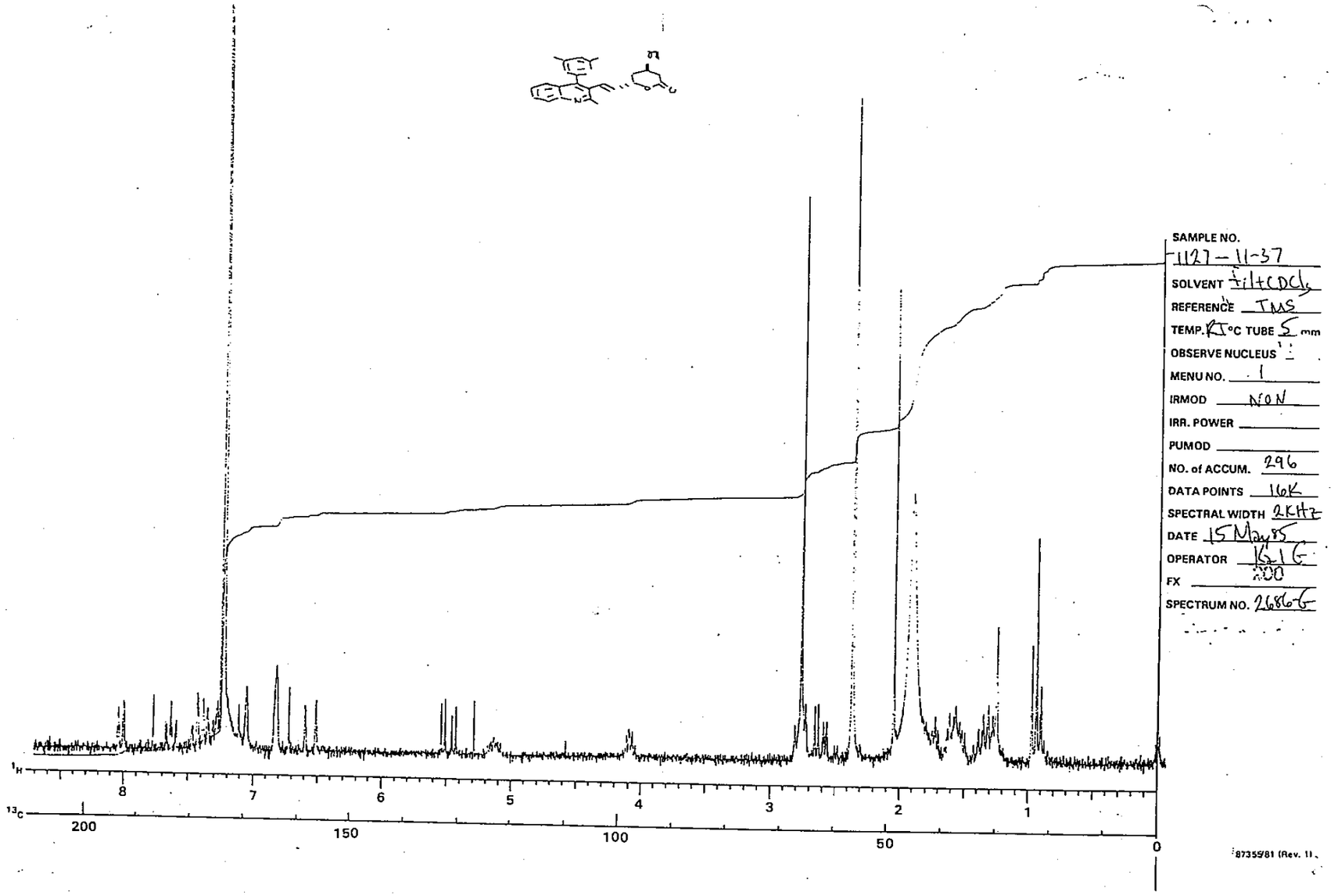
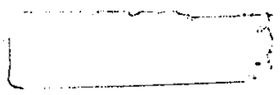

SAMPLE NO.
1127-11-37
SOLVENT 7:1 + CDCl3
REFERENCE TMS
TEMP. RT °C TUBE 5 mm
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOD NON
IRR. POWER
PUMOD
NO. of ACCUM. 296
DATA POINTS 16K
SPECTRAL WIDTH 2KHz
DATE 15 May 85
OPERATOR KJG
FX 200
SPECTRUM NO. 2686-G
1H
13C
8
7
6
5
4
3
2
1
200
150
100
50
0
8735/81 (Rev. 11)

EXHIBIT E



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 is 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.

COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL		% OF INHIBITION	RE
21) 63-366 (25496)	12/13/84	DMA					
10^{-2}			.21	22		78	
10^{-3}			.57	61		39	
10^{-4}			.81	86	1.58	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}							
10^{-3}							
10^{-4}							
10^{-5}							
10^{-6}							
10^{-7}							
10^{-8}							
23) 63-162/3							
10^{-2}							
10^{-3}							
10^{-4}							
10^{-5}							
10^{-6}							
10^{-7}							
10^{-8}							
24) 63-270/2							
10^{-2}							
10^{-3}							
10^{-4}							
10^{-5}							
10^{-6}							
10^{-7}							
10^{-8}							

EXHIBIT F

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.

COMPOUND				% OF CONTROL		% OF INHIBITION	REMARK
5) 63-547(RN							
	10^{-2}			–		100	
	10^{-3}			8		92	
	10^{-4}			28	0.017	72	
	10^{-5}			48		52	
	10^{-6}			88		12	
	10^{-7}			100		–	
	10^{-8}			100		–	
6) 63-548(RN 26080)		6/13/85	DMA				
	10^{-2}			.13		28	72
	10^{-3}			.37		80	20
	10^{-4}			.47	3.775	100	–
	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	–
	10^{-5}			.47	7.31	100	–
	10^{-6}			.47		100	–
	10^{-7}			.45		96	4
	10^{-8}			.47		100	–
8) 63-550(RN							
	10^{-2}						
	10^{-3}						
	10^{-4}						
	10^{-5}						
	10^{-6}						
	10^{-7}						
	10^{-8}						

x2582A

Case No. 600-7101/CONT/Int.(1)
Patent

FYI
#19
JUN 15 1992

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

RECEIVED IN
BOX INTERFERENCE

WATTANASIN

v.

PICARD et al.

v.

FUJIKAWA et al.

Interference No. 102,648

Examiner-in-Chief: M. Sofocleous

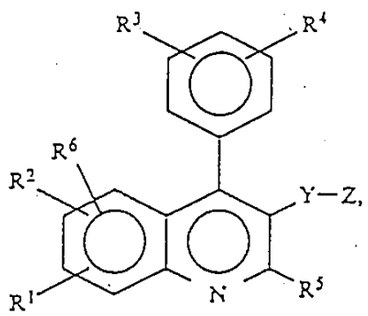
PRELIMINARY MOTION UNDER 37 CFR §1.633(c)(1)
BY THE PARTY WATTANASIN

The party Watanasin moves to substitute a count for the present Count 1 of the subject interference:

In compliance with 37 CFR 1.637(c)(1)(i), said Proposed Substitute Count I comprises the following:

Proposed Substitute Count I

A compound of the formula:



wherein R^1, R^2, R^3, R^4 and R^6 are independently
hydrogen,
C_{1-6} alkyl,
C_{1-6} cycloalkyl,

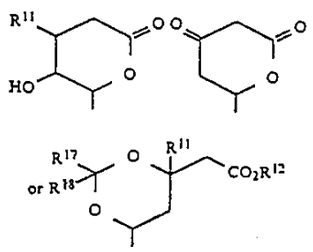
C_{1-3} alkoxy,
n-butoxy,
i-butoxy,
sec-butoxy,
R^7R^8N- (wherein R^7 and R^8 are independently hydrogen or C_{1-3} alkyl),
trifluoromethyl,
trifluoromethoxy,
difluoromethoxy,
fluoro,
chloro,
bromo,
phenyl,
phenoxy,
benzyloxy,
hydroxy,
hydroxymethyl,
$-O(CH_2)_\alpha OR^{19}$ (wherein R^{19} is hydrogen or C_{1-3}alkyl and α is 1, 2 or 3),
or when located at the ortho position to each other, R^3 and R^4 together optionally form -CH=CH-CH=CH-;

R^5 is hydrogen,
C_{1-6} alkyl,
C_{2-3} alkenyl,
C_{3-6} cycloalkyl,
phenyl substituted by R^9 (wherein R^9 is hydrogen, C_{1-4}alkyl, C_{1-3}alkoxy, fluoro, chloro, bromo or trifluoromethyl),
phenyl-$(CH_2)_m$- (wherein m is 1, 2 or 3), $-(CH_2)_nCH(CH_3)$-phenyl or phenyl-$(CH_2)_nCH(CH_3)$- (wherein n is 0, 1 or 2).

Y is

$-CH_2-$,
$-CH_2CH_2-$,
$-CH=CH-$,
$-CH_2-CH=CH-$, or
$-CH=CH-CH_2-$;

Z is



or $-Q-CH_2WCH_2-CO_2R^{12}$ (where R^{12} is hydrogen or R^{14});

Q is $-CH(OH)-$.
$-C(O)-$, or
$-C(OR^{13})_2-$;

W is $-C(R^{11})(OH)-$ (where R^{11} is hydrogen or C_{1-3} alkyl),
$-C(O)-$, or
$-C(OR^{13})_2-$;

the two R^{13} are independently primary or secondary C_{1-6} alkyl; or two R^{13} together form $-(CH_2)_2-$ or $-(CH_2)_3-$;

R^{14} is physiologically hydrolyzable alkyl or M (wherein M is NH_4, sodium, potassium, 1/2 calcium or a hydrate of lower alkylamine, di-lower alkylamine or tri-lower alkylamine); and

R^{17} and R^{18} are independently hydrogen or C_{1-3} alkyl;

REMARKS

The present Count 1 of the interference was drawn to cover subject matter in the involved patent applications in common with U.S. Patent No. 4,761,419 of the party Picard et al., with whom each of the parties Wattanasin and Fujikawa et al. had respectively requested interference.

In view of the termination of this proceeding as to Picard et al., it is respectfully suggested that the present count is deficient in not covering subject matter common to both of the involved applications. For example:

(1) The proviso of the present Count 1 is irrelevant since the claims of both Wattanasin and Fujikawa et al. require that the "X-Z" chain (equivalent to Fujikawa et al.'s Y-Z chain) be bonded to the quinoline ring at the 3-position;

(2) The scope of the present Count 1 is deficient in that it is limited to erythro (or trans lactone) compounds. However, neither Fujikawa's claim 1 or Wattanasin's claim 1 is similarly limited;

(3) The scope of the present Count 1 is deficient in that it excludes esters of the open ring compound, which are claimed by both Wattanasin and Fujikawa et al.;

(4) The scope of the present Count 1 is deficient in that it excludes open ring compounds wherein a carbonyl group is at the 5-position of the side chain, which are claimed by both parties; and

(5) The scope of the present Count 1 is ambiguous insofar as the definition of R_1 or $_{R2}$ is concerned when either substituent is phenyl substituted by C_{1-4}alkyl, because it is unclear whether the phenyl can be di-substituted.

Accordingly, the party Wattanasin moves to substitute the above Proposed Substitute Count 1 for the present Count 1.

It will be noted that this Proposed Substitute Count 1 duplicates the party Fujikawa's claim 1 as amended during prosecution.

The proposed count is suupported by Wattanasin at e.g., . Example 1, page 42 of the specification and original claims 1-7.

Claims 1-7 and 10 of the involved application of the party Wattanasin correspond to Proposed Substitute Count 1.

In compliance with 37 CFR 1.637(c)(1)(ii), claims 1-7 and 10 are believed patentable in view of the Communication from the Examiner dated March 13, 1991 in Wattanasin's involved application.

In compliance with 37 CFR 1.637(c)(1)(iii), claims 1-34, 36 and 39-40 of the involved application of the party Fujikawa et al. are believed to correspond to Proposed Substitute Count 1.

Respectfully submitted,

Diane Furman 6/11/92

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

DEF:rmf
June 11, 1992

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

PRELIMINARY MOTION UNDER 37 CFR §§1.633(c)(1)
BY THE PARTY WATTANASIN

was served on counsel for the party Fujikawa et al., this 11th day of June, 1992, 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

Case No. 600-7101/CONT/Int.(2)
Patent

FYI

#20

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

JUN 15 1992

RECEIVED IN
BOX INTERFERENCE

WATTANASIN

v.

PICARD et al.

v.

FUJIKAWA et al.

Interference No. 102,648

Examiner-in-Chief: M. Sofocleous

PRELIMINARY MOTION UNDER 37 CFR §1.635
BY THE PARTY WATTANASIN

The party Wattanasin moves that U.S. Patent No. 5,011,930 on the basis of claim 1 thereof be included in the present interference.

Remarks

U.S. Patent No. 5,011,930 (the "'930" patent) issued on April 30, 1991 on a divisional application from the involved application of the party Fujikawa et al (hereinafter "Fujikawa"). A copy of the patent is appended hereto.

On information and belief, the '930 patent is also assigned to Nissan Chemical Industries Ltd.

It is respectfully submitted that claim 1 of the '930 patent contains interfering subject matter with the involved application of Wattanasin. Said claim 1 is essentially encompassed by Count 1 of this interference.

It is also submitted that Claim 1 of the '930 patent and the involved claims of the party Fujikawa are not drawn to separate and distinct inventions.

BACKGROUND

Reference is made to the prosecution history of the party Fujikawa's involved application wherein the Examiner issued a restriction requirement to one of four groups of claims respectively directed to: (1) quinolinoyl substituted heptenoic acids ; (2) silyloxy-containing quinoline compounds; (3) quinoline compounds containing a fused heterooxygen-containing ring; and (4) carbocyclic ring-containing quinoline compounds and use (see Fujikawa Serial No. 07/233,752, office action of June 6, 1989).

In response to the restriction requirement, Fujikawa elected with traverse the invention defined by group (1), i.e. quinolinoyl substituted heptenoic acids (Restriction Response of July 13, 1989); elected a lactone species within the scope (compound "I-31" wherein R^5 is isopropyl; and amended the claims to delete the canceled subject matter.

Then Fujikawa requested interference with the Picard et al. patent (Fujikawa Paper of August 21, 1989).

Fujikawa's application Serial No. 483,720 was then filed on February 23, 1990, in which the subject matter of group (4) above (i.e. the carbocyclic-containing compounds) was pursued (maturing into claims 2-7), but which also contained claim 1 of the parent application encompassing subject matter within group (1) above.

This original claim 1 was eventually dropped and replaced by newly presented claim 38 (Fujikawa Amendment of July 3, 1990) directed to a subgenus of compounds wherein R^5 of structural formula I of Fujikawa is defined to be cyclopropyl or isopropyl. The subject matter of claim 38 is clearly within the scope of Group (1) which was elected for prosecution in the involved Fujikawa application, and essentially involves the invention of Count 1 of this interference.

In late October 1990, the issue fee was paid on the '720 divisional application.

It will be noted that shortly thereafter, in the ongoing prosecution of the involved parent application, Fujikawa canceled original claim 10 directed to a species within group (1) wherein R^5 of Fujikawa's structural formula I was cyclopropyl[1]. Fujikawa indicated that the subject matter of claim 10 would be pursued in a divisional application filed concurrently with the cancellation of claim 10, because:

> "Applicants have discovered that the subject matter of Claim 10, and related subject matter, exhibits unobvious and distinguishing properties, with respect to the genus

(cont'd)

---

1. Claim 10 covered the compound (E)-3,5-dihydroxy-7-[4'-(4"-(fluorophenyl)-2'-cyclopropyl-quinolin-3'-yl]- hept-6-enoic acid, a lactone formed by condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3}alkyl ester of the carboxylic acid.

> circumscribed by the remaining claims of the above-captioned application, as well as the claims of the patent with which an Interference is to be declared. Accordingly, that claim will be pursued in a separate application."

(Serial No. 07/233,752, Amendment of December 19, 1990)

The party Wattanasin is not aware of a divisional application of the party Fujikawa which may have been filed concurrently with Fujikawa's December 19, 1990 amendment.

However, the '720 divisional application did issue on April 30, 1991 (as the '930 patent) containing the mentioned claim 1, which reads on canceled claim 10.

Unlike claims 2-7 of the '930 patent, which are limited to compounds having a carbocyclic fused ring, claim 1 of Fujikawa's '930 patent is not so limited; it does not even embrace the carbocyclic compounds, but rather is directed to compounds of the present Count 1.

Insofar as can be determined from the copy of the '930 prosecution history obtained from the Patent and Trademark Office, no evidence of "unobvious and distinguishing properties" was proffered during prosecution in support of compounds within the scope of claim 1 of the '930 patent.[2]

---

2. A few pages were missing from Wattanasin's copies of the prosecution histories of Fujikawa's involved application and the '930 patent.

The Fujikawa specification is not considered to provide evidence of superiority over the claimed range of compounds of claim 1.

The inventorship on the '930 patent is the same as the inventorship on the involved application of the party Fujikawa.

Accordingly, the party Wattanasin submits that the subject matter of claim 1 of Fujikawa's '930 patent does not constitute a separate and distinct invention from the involved subject matter, and that this issued claim 1, which falls squarely within the ambit of subject matter common to both involved applications, should not remain sequestered from this interference.

It will be noted that the '930 patent issued nearly a year after the party Wattanasin filed its Request for Interference. By Information Disclosure mailed June 3, 1991, the party Wattanasin did advise the Examiner of the '930 patent and indicated its suitability for inclusion in the requested interference. However, no further action appears to have been taken by the Examiner in this regard.

CONCLUSION

This motion is being filed under Rule 635 because Rule 633 does not appear to expressly provide for a motion to include an additional patent of an involved party in an interference.

It is respectfully urged that the Examiner-In-Chief bring the '930 patent into the present interference to the extent of claim 1 thereof.

In the event of denial of this motion, a contingent motion under Rule 633(e) is being filed concurrently herewith.

It will be noted for purposes of 35 USC §135(b), that the claims of Wattanasin were made prior to one year from the date on which the '930 patent of Fujikawa was granted.

Respectfully submitted,

Diane Furman 6/11/92

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

DEF:rmf
June 11, 1992

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

PRELIMINARY MOTION UNDER 37 CFR §1.635
BY THE PARTY WATTANASIN

was served on counsel for the party Fujikawa, this 11th day of June, 1992, 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

United States Patent [19]

Fujikawa et al.

[11] Patent Number: 5,011,930

[45] Date of Patent: Apr. 30, 1991

[54] QUINOLINE TYPE MEVALONOLACTONES

[75] Inventors: Yoshihiro Fujikawa; Mikio Suzuki; Hiroshi Iwasaki, all of Funabashi; Mitsuaki Sakashita; Masaki Kitahara, both of Shitaoka, all of Japan

[73] Assignee: Nissan Chemical Industries Ltd., Tokyo, Japan

[21] Appl. No.: 483,720

[22] Filed: Feb. 23, 1990

Related U.S. Application Data

[62] Division of Ser. No. 233,752, Aug. 19, 1988.

[30] Foreign Application Priority Data

Aug. 20, 1987 [JP] Japan 62-207224
Jan. 26, 1988 [JP] Japan 63-15585

[51] Int. Cl.[5] C07D 215/00; C07D 221/06

[52] U.S. Cl. 546/101; 546/173; 546/174; 546/175; 546/178

[58] Field of Search 546/101, 174, 173, 175, 546/178; 514/290

[56] References Cited

U.S. PATENT DOCUMENTS

4,761,419 8/1988 Picard et al. 546/174

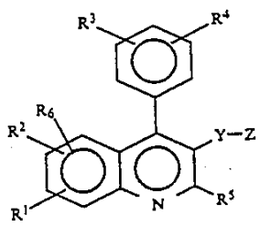
FOREIGN PATENT DOCUMENTS

114027 7/1985 European Pat. Off. .
179559 4/1986 European Pat. Off. .
WO860307 1/1986 World Int. Prop. O. .

Primary Examiner—David B. Springer
Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt

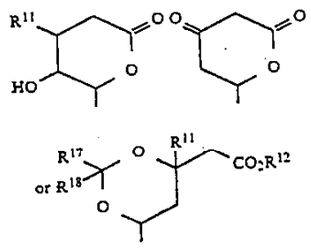
[57] ABSTRACT

A compound of the formula:

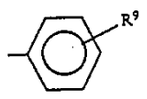


(I)

wherein R^1, R^2, R^3, R^4 and R^6 are independently hydrogen, C_{1-6} alkyl, C_{1-6}cycloalkyl, C_{1-3} alkoxy, n-botoxy, i-botoxy, sec-butoxy, R^7R^8N— (wherein R^7 and R^8 are independently hydrogen or C_{1-3} alkyl), trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoro, chloro, bromo, phenyl, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-t-butylsilyloxy, hydroxymethyl or $—O(CH_2)_lOR^{19}$ (wherein R^{19} is hydrogen or C_{1-3} alkyl, and l is 1,2 or 3); or when located at the ortho position to each other, R^1 and R^2, and R^3 and R^4 together form —CH=CH—CH=CH—; or when located at the ortho position to each other, R^1 and R^2 together form $—OC(R^{15})(R^{16})O—$ (wherein R^{15} and R^{16} are independently hydrogen or C_{1-3} alkyl); Y is $—CH_2—$, $—CH_2CH_2—$, —CH=CH—, $—CH_2CH=CH—$ or $—CH=CH—CH_2—$; and Z is $—Q—CH_2WCH_2—CO_2R^{12}$,



(wherein Q is —C(O)—, $—C(OR^{13})_2—$ or $—CH(OH)—$; W is —C(O)—, $—C(OR^{13})_2—$ or $—C(R^{11})(OH)—$; R^{11} is hydrogen atom or C_{1-3} alkyl; R^{12} is hydrogen or R^{14} (wherein R^{14} is physiologically hydrolyzable alkyl or M (wherein M is NH_4, sodium, potassium, ½ calcium or a hydrate of lower alkyl amine, di-lower alkyl amine or tri-lower alkyl amine)); two R^{13} are independently primary or secondary C_{1-6} alkyl; or two R^{13} together form $—(CH_2)_2—$ or $—(CH_2)_3$; R^{17} and R^{18} are independently hydrogen or C_{1-3} alkyl; and R^5 is hydrogen, C_{1-6} alkyl, C_{2-3} alkenyl, C_{3-6} cycloalkyl,



(wherein R^9 is a hydrogen atom, C_{1-4} alkyl, C_{1-3} alkoxy, fluoro, chloro, bromo or trifluoromethyl), phenyl-$(CH_2)_m$— (wherein m is 1,2 or 3), $—(CH_2)_nCH(CH_3)$-phenyl or phenyl-$(CH_2)_nCH(CH_3)$— (wherein n is 0,1 or 2).

7 Claims, No Drawings

QUINOLINE TYPE MEVALONOLACTONES

This is a division, of application Ser. No. 07/233/752, filed on Aug. 19, 1988.

The present invention relates to novel mevalonolactones having a quinoline ring, processes for their production, pharmaceutical compositions containing them and their pharmaceutical uses particularly as anti-hyperlipidemic, hypolipoproteinemic and anti-atherosclerotic agents, and intermediates useful for their production and processes for the production of such intermediates.

Some fermentation metabolic products such as compactine, CS-514, Mevinolin or semi-synthetic derivatives or fully synthetic derivatives thereof are known to be inhibitors against HMG-CoA reductase which is a rate limiting enzyme for cholesterol biosynthesis. (A. Endo J. Med Chem., 28(4) 401 (1985))

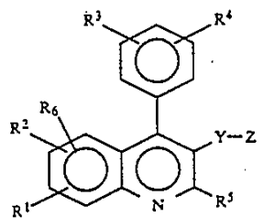
CS-514 and Mevinolin have been clinically proved to be potentially useful anti-hyperlipoproteinemic agents, and they are considered to be effective for curing or preventing diseases of coronary artery sclerosis or atherosclerosis. (IXth Int. Symp. Drugs Affect. Lipid Metab., 1986, p30, p31, p66)

However, with respect to fully synthetic derivatives, particularly hetero aromatic derivatives of inhibitors against HMG-CoA reductase, limited information is disclosed in the following literatures:

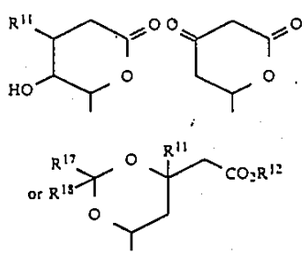
WPI ACC NO. 84-158675, 86-028274, 86-098816, 86-332070, 87-124519, 87-220987, 88-07781, 88-008460, 88-091798 and 88-112505.

The present inventors have found that mevalonolactone derivatives having a quinoline ring, the corresponding dihydroxy carboxylic acids and salts and esters thereof have high inhibitory activities against cholesterol biosynthesis wherein HMG-CoA reductase acts as a rate limiting enzyme. The present invention has been accomplished on the basis of this discovery.

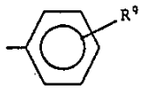
The novel mevalonolactone derivatives of the present invention are represented by the following formula I:


(I)

wherein R^1, R^2, R^3, R^4 and R^6 are independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-3} alkoxy, n-butoxy, i-butoxy, sec-butoxy, R^7R^8N— (wherein R^7 and R^8 are independently hydrogen or C_{1-3} alkyl), trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoro, chloro, bromo, phenyl, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-t-butylsilyloxy, hydroxymethyl or $—O(CH_2)_lOR^{19}$ (wherein R^{19} is hydrogen or C_{1-3} alkyl, and l is 1, 2 or 3); or when located at the ortho position to each other, R^1 and R^2, or R^3 and R^4 together optionally form —CH=CH—CH=CH—; or when located at the ortho position to each other, R^1 and R^2 together optionally form $—OC(R^{15})(R^{16})O—$ (wherein R^{15} and R^{16} are independently hydrogen or C_{1-3} alkyl); Y is $—CH_2—$, $—CH_2CH_2—$, —CH=CH—, —CH
$_2$—CH=CH— or —CH=CH—CH_2—; and Z is $—Q—CH_2WCH_2—CO_2R^{12}$,



(wherein Q is —C(O)—, $—C(OR^{13})_2—$ or —CH(OH)—; W is —C(O)—, $—C(OR^{13})_2—$ or $—C(R^{11})(OH)—$; R^{11} is hydrogen or C_{1-3} alkyl; R^{12} is hydrogen or R^{14} (wherein R^{14} is physiologically hydrolyzable alkyl or M (wherein M is NH_4, sodium, potassium, ½ calcium or a hydrate of lower alkylamine, di-lower alkylamine or tri-lower alkylamine)); two R^{13} are independently primary or secondary C_{1-6} alkyl; or two R^{13} together form $—(CH_2)_2—$ or $—(CH_2)_3—$; R^{17} and R^{18} are independently hydrogen or C_{1-3} alkyl; and R^5 is hydrogen, C_{1-6} alkyl, C_{2-3} alkenyl, C_{3-6} cycloalkyl,



(wherein R^9 is hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, fluoro, chloro, bromo or trifluoromethyl), phenyl$—(CH_2)_m—$ (wherein m is 1, 2 or 3), $—(CH_2)_nCH(CH_3)$-phenyl or phenyl$—(CH_2)_nCH(CH_3)—$ (wherein n is 0, 1 or 2).

Various substituents in the formula I will be described in detail with reference to specific examples. However, it should be understood that the present invention is by no means restricted by such specific examples.

C_{1-6} alkyl for R^1, R^2, R^3, R^4, R^6 and R^9 includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. C_{1-3} alkoxy for R^1, R^2, R^3, R^4 and R^6 includes, for example, methoxy, ethoxy, n-propoxy and i-propoxy.

C_{1-3} alkyl for R^{11} includes, for example, methyl, ethyl, n-propyl and i-propyl.

C_{1-3} alkyl for R^{13} includes, for example, methyl, ethyl, n-propyl and i-propyl.

Alkyl for R^{14} includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl and i-butyl.

M is a metal capable of forming a pharmaceutically acceptable salt, and it includes, for example, sodium and potassium.

CO_2M includes, for example, $—CO_2NH_4$ and $—CO_2H$. (primary to tertiary lower alkylamine such as trimethylamine).

C_{1-6} alkyl for R^5 includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

C_{3-6} cycloalkyl for R^5 includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

C_{2-3} alkenyl for R^5 includes, for example, vinyl and i-propenyl.

Phenyl$—(CH_2)_m—$ for R^5 includes, for example, benzyl, β-phenylethyl and γ-phenylpropyl.

Phenyl—$(CH_2)_nCH(CH_3)$— for R^5 includes, for example, α-phenylethyl and α-benzylethyl.

C_{1-3} alkyl for R^7 and R^8 includes, for example, methyl, ethyl, n-propyl and i-propyl.

Further, these compounds may have at least one or two asymmetric carbon atoms and may have at least two to four optical isomers. The compounds of the formula I include all of these optical isomers and all of the mixtures thereof.

Among compounds having carboxylic acid moieties falling outside the definition of $—CO_2R^{12}$ of the carboxylic acid moiety of substituent Z of the compounds of the present invention, those which undergo physiological hydrolysis, after intake, to produce the corresponding carboxylic acids (compounds wherein the $—CO_2R^{12}$ moiety is $—CO_2H$) are equivalent to the compounds of the present invention.

Now, preferred substituents of the compounds of the present invention will be described.

In the following preferred, more preferred still further perferred and most preferred examples, the numerals for the positions of the substituents indicate the positions on the quinoline ring. For example, N' shown by e.g. 1' or 2' indicates the position of the substituent on the phenyl substituted at the 4-position of the quinoline ring (the carbon connected to the quinoline ring is designated as 1'). The meanings of the respective substituents are the same as the above-mentioned meanings.

Preferred substituents for R^1, R^2 and R^6 are hydrogen, fluoro, chloro, bromo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{3-6} cycloalkyl, dimethylamino, hydroxy, hydroxymethyl, hydroxyethyl, trifluoromethyl, trifluoromethoxy, difluoromethoxy, phenoxy and benzyloxy.

Further, when R^6 is hydrogen, it is preferred that R^1 and R^2 together form methylenedioxy.

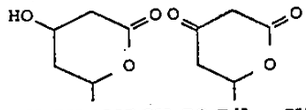
As preferred examples for R^3 and R^4, when R^4 is hydrogen, R^3 is hydrogen, 3'-fluoro, 3'-chloro, 3'-methyl, 4'-methyl, 4'-chloro and 4'-fluoro.

Other preferred combinations of R^3 and R^4 include 3'-methyl-4'-chloro, 3',5'-dichloro, 3',5'-difluoro, 3',5'-dimethyl and 3'-methyl-4'-fluoro.

Preferred examples for R^5 include primary and secondary C_{1-6} alkyl and C_{3-6} cycloalkyl.

Preferred examples for Y include $—CH_2—CH_2—$ and —CH=CH—.

Preferred examples for Z include



$—CH(OH)CH_2CH_2(OH)CH_2CO_2R^{12}$, $—CH(OH)CH_2C(O)CH_2CO_2R^{12}$ and $—CH(OH)CH_2C(OR^{13})_2CH_2CO_2R^{12}$.

Now, more preferred substituents of the compounds of the present invention will be described.

As more preferred examples for R^1, R^2 and R^6, when both R^2 and R^6 are hydrogen, R^1 is hydrogen, 5-fluoro, 6-fluoro, 7-fluoro, 8-fluoro, 5-chloro, 6-chloro, 7-chloro, 8-chloro, 5-bromo, 6-bromo, 7-bromo, 8-bromo, 5-methyl, 6-methyl, 7-methyl, 8-methyl, 5-methoxy, 6-methoxy, 7-methoxy, 8-methoxy, 5-trifluoromethyl, 6-trifluoromethyl, 7-trifluoromethyl, 8-trifluoromethyl, 6-trifluoromethoxy, 6-difluoromethoxy, 8-hydroxyethyl, 5-hydroxy, 6-hydroxy, 7-hydroxy, 8-hydroxy, 6-ethyl, 6-n-butyl and 7-dimethylamino.

When R^6 is hydrogen, R^1 and R^2 together represent 6-chloro-8-methyl, 6-bromo-7-methoxy, 6-methyl-7-chloro, 6-chloro-8-hydroxy, 5-methyl-2-hydroxy, 6-methoxy-7-chloro, 6-chloro-7-methoxy, 6-hydroxy-7-chloro, 6-chloro-7-hydroxy, 6-chloro-8-bromo, 5-chloro-6-hydroxy, 6-bromo-8-chloro, 6-bromo-8-hydroxy, 5-methyl-8-chloro, 7-hydroxy-8-chloro, 6-bromo-8-hydroxy, 6-methoxy-7-methyl, 6-chloro-8-bromo, 6-methyl-8-bromo, 6,7-difluoro, 6,8-difluoro, 6,7-methylenedioxy, 6,8-dichloro, 5,8-dimethyl, 6,8-dimethyl, 6,7-dimethoxy, 6,7-diethoxy, 6,7-dibromo or 6,8-dibromo.

When R^1, R^2 and R^6 are not hydrogen, they together represent 5,7-dimethoxy-8-hydroxy, 5,8-dichloro-6-hydroxy, 6,7,8-trimethoxy, 6,7,8-trimethyl, 6,7,8-trichloro, 5-fluoro-6,8-dibromo or 5-chloro-6,8-dibromo.

As more preferred examples for R^3 and R^4, when R^3 is hydrogen, R^4 is hydrogen, 4'-methyl, 4'-chloro or 4'-fluoro. When both R^3 and R^4 are not hydrogen, they together represent 3',5'-dimethyl or 3'-methyl-4'-fluoro.

As more preferred examples for R^5, the above-mentioned preferred examples of R^5 may be mentioned.

As preferred examples for Y, $—CH_2—CH_2—$ and (E)—CH=CH— may be mentioned. As more preferred examples for Z, the above preferred examples for Z may be mentioned.

Now, still further preferred substituents of the compounds of the present invention will be described. As examples for R^1, R^2 and R6, when both R^2 and R^6 are hydrogen, R^1 is hydrogen, 6-methyl, 6-ethyl, 6-trifluoromethyl, 6-hydroxy, 6-methoxy, 6-chloro, 6-bromo, 6-n-butyl and 7-dimethylamino.

When only R^6 is hydrogen, R^1 and R^2 represent 6,8-dichloro, 5,8-dimethyl, 6,8-dimethyl, 6,7-dimethoxy, 6,7-diethoxy, 6,7-dibromo, 6,8-dibromo, 6,7-difluoro and 6,8-difluoro.

As still further preferred examples for R^3 and R^4, when R^3 is hydrogen, R^4 is hydrogen, 4'-chloro or 4'-fluoro, or R^3 and R^4 together represent 3'-methyl-4'-fluoro.

Still further preferred examples for R^5 include ethyl, n-propyl, i-propyl and cyclopropyl.

Still further preferred examples for Y include (E)—CH=CH—.

As still further preferred examples for Z, the above-mentioned preferred example for Z may be mentioned.

Now, the most preferred substituents for the compounds of the present invention will be described.

As the most preferred examples for R^1, R^2 and R^6, when both R^2 and R^6 are hydrogen, R^1 is hydrogen, 6-methyl or 6-chloro.

When only R^6 is hydrogen, R^1 and R^2 together represent, for example, 6,7-dimethoxy.

As the most preferred examples for R^3 and R^4, R^3 is hydrogen and R^4 is hydrogen, 4'-chloro or 4'-fluoro.

The most preferred examples for R^5 include i-propyl and cyclopropyl. The most preferred example for Y may be (E)—CH=CH—.

As the most preferred examples for Z, the above-mentioned preferred examples for Z may be mentioned.

Now, particularly preferred specific compounds of the present invention will be presented. The following compounds (a) to (z) are shown in the form of carboxylic acids. However, the present invention include not only the compounds in the form of carboxylic acids but also the corresponding lactones formed by the condensation of the carboxylic acids with hydroxy at the 5-position, and sodium salts and lower alkyl esters (such

as methyl, ethyl, i-propyl and n-propyl esters) of the carboxylic acids, which can be physiologically hydrolyzed to the carboxylic acids.

(a) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid

(b) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

(c) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(d) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

(e) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropyl-quinolin-3'-yl]-hept-6-enoic acid

(f) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropyl-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

(g) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropyl-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(h) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropyl-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

(i) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-(1"-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid

(j) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-(1"-methylethyl)-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

(k) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-(1"-methylethyl)-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(l) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-(1"-methylethyl)-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

(m) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-cyclopropyl-quinolin-3'-yl]-hept-6-enoic acid

(n) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-cyclopropyl-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

(o) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-cyclopropyl-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(p) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-cyclopropyl-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

(q) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-(1"-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid

(r) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-(1"-methylethyl)-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

(s) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-(1"-methylethyl)-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(t) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-(1" -methylethyl)-6',7'-dimethoxy-quinolin-3,-yl]-hept-6-enoic acid

(u) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-quinolin-3'-yl]-hept-6-enoic acid

(v) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

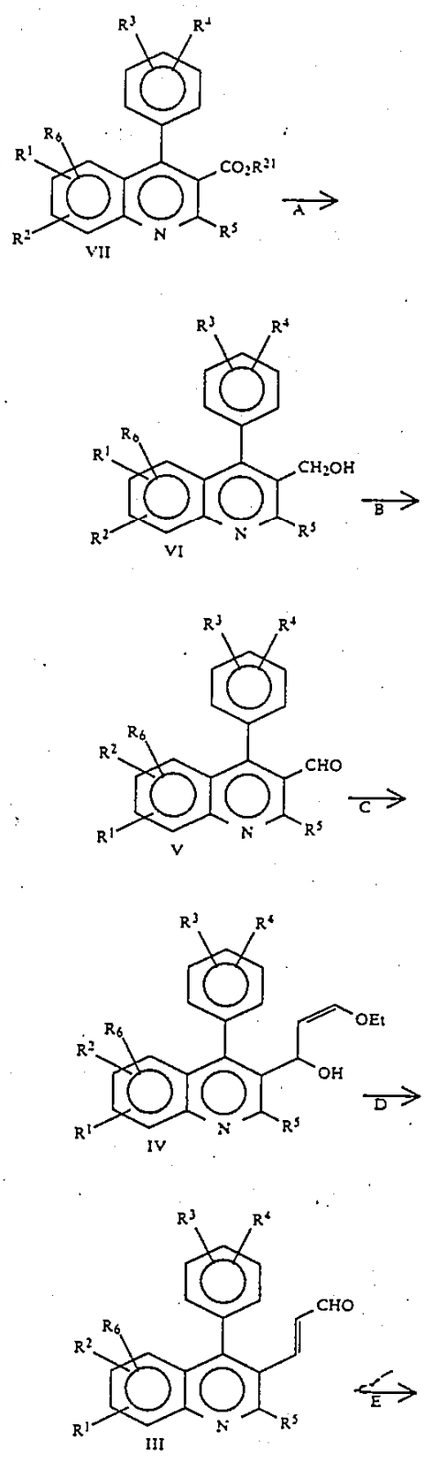
(w) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(x) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

(y) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1" -methylethyl)-6'-methoxy-quinolin-3'-yl]-hept-6-enoic acid

(z) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropyl-6'-methoxy-quinolin-3'-yl]-hept-6-enoic acid

The mevalonolactones of the formula I can be prepared by the following reaction scheme. The enal III can also be prepared by processes K, L and M.



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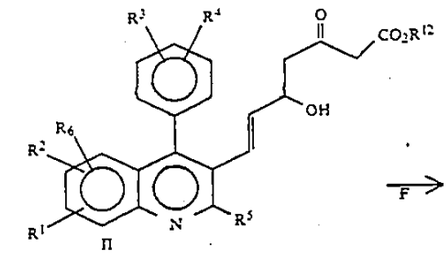
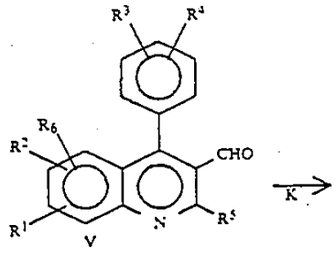


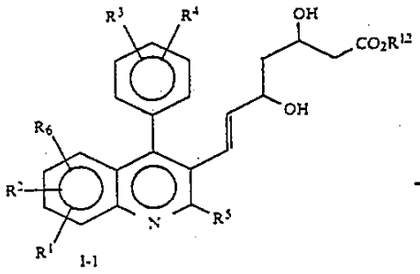
II

F



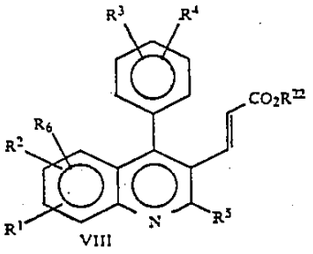
V

K



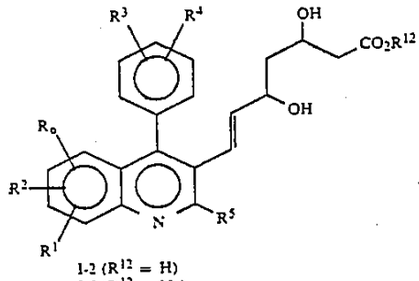
I-1

G



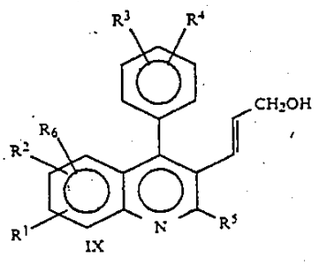
VIII

L



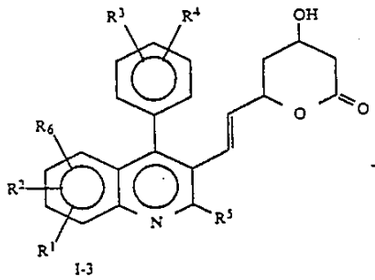
I-2 (R^{12} = H)
I-5 (R^{12} = Na)

H



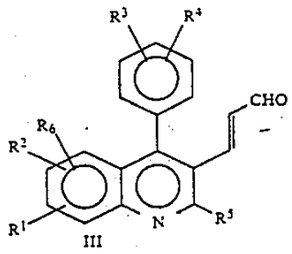
IX

M

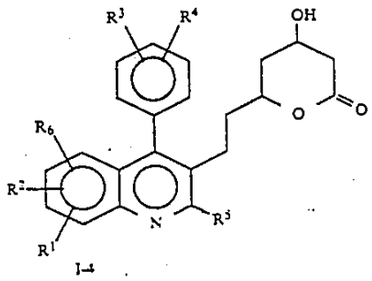


I-3

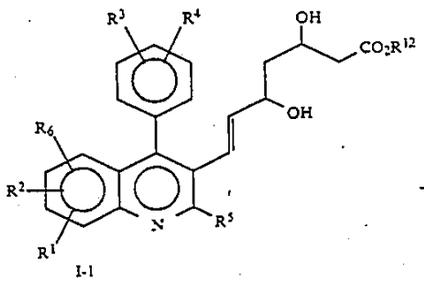
J



III



I-4



I-1

N

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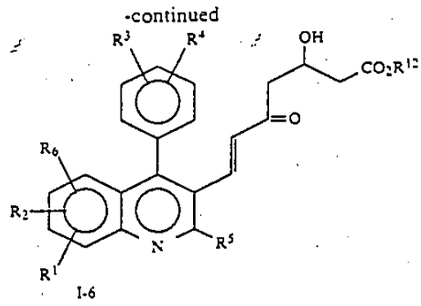


I-6

In the above reaction scheme, R^1, R^2, R^3, R^4, R^5, R^6 and R^{12} are as defined above with respect to the formula I, and R^{21} and R^{22} independently represent C_{1-4} lower alkyl such as methyl, ethyl, n-propyl, i-propyl or n-butyl.

Step A represents a reduction reaction of the ester to a primary alcohol. Such reduction reaction can be conducted by using various metal hydrides, preferably diisobutylaluminium hydride, in a solvent such as tetrahydrofuran or toluene at a temperature of from −20° to 20° C., preferably from −10° to 10° C.

Step B represents an oxidation reaction of the primary alcohol to an aldehyde, which can be conducted by using various oxidizing agents. Preferably, the reaction can be conducted by using pyridinium chlorochromate in methylene chloride at a temperature of from 0° to 25° C., or by using oxalyl chloride, dimethyl sulfoxide and a tertiary amine such as triethylamine (Swern oxidation), or by using a sulfur trioxide pyridine complex.

Step C represents a synthesis of a 3-ethoxy-1-hydroxy-2-propene derivative, which can be prepared by reacting a compound V to lithium compound which has been preliminarily formed by treating cis-1-ethoxy-2-(tri-n-butylstannyl)ethylene with butyl lithium in tetrahydrofuran.

As the reaction temperature, it is preferred to employ a low temperature at a level of from −60° to −78° C.

Step D represents a synthesis of an enal by acidic hydrolysis. As the acid catalyst, it is preferred to employ p-toluene sulfonic acid, hydrochloric acid or sulfuric acid, and the reaction may be conducted in a solvent mixture of water and tetrahydrofuran or ethanol at a temperature of from 10° to 25° C. The 3-ethoxy-1-hydroxy-2-propene derivative obtained in Step C can be used in Step D without purification i.e. by simply removing tetra-n-butyl tin formed simultaneously.

Step E represents a double anion condensation reaction between the enal III and an acetoacetate. Such condensation reaction is preferably conducted by using sodium hydride and n-butyl lithium as the base in tetrahydrofuran at a temperature of from −80° to 0° C., preferably from −30° to −10° C.

Step F represents a reduction reaction of the carbonyl group, which can be conudcted by using a metal hydride, preferably sodium borohydride in ethanol at a temperature of from −10° to 25° C., preferably from −10° to 5° C.

Further, the reduction reaction may be conducted by using zinc borohydride in dry ethyl ether or dry tetrahydrofuran at a temperature of −100° to 25° C., preferably from −80° to −50° C.

Step G is a step for hydrolyzing the ester. The hydrolysis can be conducted by using an equimolar amount of a base, preferably potassium hydroxide or sodium hydroxide, in a solvent mixture of water and methanol or ethanol at a temperature of from 10° to 25° C. The free acid hereby obtained may be converted to a salt with a suitable base.

Step H is a step for forming a mevalonolactone by the dehydration reaction of the free hydroxy acid I-2. The dehydration reaction can be conducted in benzene or toluene under reflux while removing the resulting water or by adding a suitable dehydrating agent such as molecular sieve.

Further, the dehydration reaction may be conducted in dry methylene chloride by using a lactone-forming agent such as carbodiimide, preferably a water soluble carbodiimide such as N-cyclohexyl-N'-[2'-(methylmorpholinium)ethyl]carbodiimide p-toluene sulfonate at a temperature of from 10° to 35° C., preferably from 20° to 25° C.

Step J represents a reaction for hydrogenating the double bond connecting the mevalonolactone moiety and the quinoline ring. This hydrogenation reaction can be conducted by using a catalytic amount of palladium-carbon or rhodium-carbon in a solvent such as methanol, ethanol, tetrahydrofuran or acetonitrile at a temperature of from 0° to 50° C., preferably from 10° to 25° C.

Step K represents a reaction for the synthesis of an α,β-unsaturated carboxylic acid ester, whereby a transform α,β-unsaturated carboxylic acid ester can be obtained by a so-called Horner-Wittig reaction by using an alkoxycarbonylmethyl phosphonate. The reaction is conducted by using sodium hydride or potassium t-butoxide as the base in dry tetrahydrofuran at a temperature of from −30° to 0° C., preferably from −20° to −15° C.

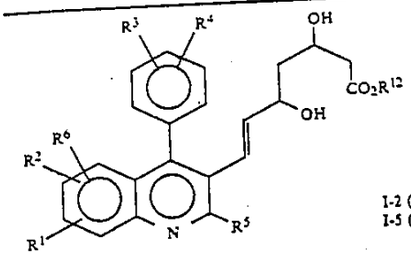
Step L represents a reduction reaction of the α,β-unsaturated carboxylic acid ester to an allyl alcohol. This reduction reaction can be conducted by using various metal hydrides, preferably diisobutylaluminiumhydride, in a solvent such as dry tetrahydrofuran or toluene at a temperature of from −10° to 10° C., preferably from −10° to 0° C.

Step M represents an oxidation reaction of the allyl alcohol to an enal. This oxidation reaction can be conducted by using various oxidizing agents, particularly active manganese dioxide, in a solvent such as tetrahydrofuran, acetone, ethyl ether or ethyl acetate at a temperature of from 0° to 100° C., preferably from 15° to 50° C.

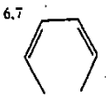
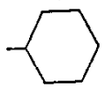
Step N represents a reaction for the synthesis of an α,β-unsaturated ketone by the selective oxidation of the dihydroxy carboxylic acid ester. This reaction can be conducted by using activated manganese dioxide in a solvent such as ethyl ether, tetrahydrofuran, benzene or toluene at a temperature of from 20° to 80° C., preferably from 40° to 80° C.

In addition to the compounds disclosed in Examples given hereinafter, compounds of the formulas I-2 and I-5 given in Table 1 can be prepared by the process of the present invention. In Table 1, i- means iso, sec- means secondary and c- means cyclo. Likewise, Me means methyl, Et means ethyl, Pr means propyl, Bu means butyl, Pent means pentyl, Hex means hexyl and Ph means phenyl.

TABLE 1



I-2 (R^{12} = H)
I-5 (R^{12} = Na)

R^1	R^2	R^3	R^4	R^5	R^6
6-OMe	H	H	H	i-Pr	H
6-OMe	H	4-F	H	i-Pr	H
6-Br	H	4-F	H	i-Pr	H
6-Me	8-Me	4-F	H	i-Pr	H
7-OMe	8-OMe	4-F	H	i-Pr	H
6-Br	H	2-F	H	i-Pr	H
6,7 		4-F	H	i-Pr	H
H	H	4-F	H		H
H	H	4-Ph	H	i-Pr	H
H	H	4-PhCH$_2$	H	i-Pr	H
6-Cl	H	4-F	H	c-Pr	H
6-Cl	H	4-F	H	sec-Bu	H
6-OCH$_2$Ph	H	4-F	H	i-Pr	H
H	H	4-F	H	i-Bu	H
H	H	4-F	H	c-Pent	H
6-Cl	H	4-F	H	c-Pent	H
6-Me$_2$N	H	4-F	H	i-Pr	H
6-Me	H	4-F	H	c-Pr	H
6-i-Pr	H	4-F	H	i-Pr	H
7-Me	H	4-F	H	c-Pr	H
6-OMe	H	4-F	H	c-Pr	H
6-Br	H	4-F	H	c-Pr	H
6-i-Pr	H	4-F	H	c-Pr	H
6-Cl	8-Cl	4-F	H	c-Pr	8-Br
5-F	6-Br	4-F	H	i-Pr	8-OMe
6-OMe	7-OMe	4-F	H	i-Pr	8-Me
6-Me	7-Me	4-F	H	i-Pr	8-Cl
6-Cl	7-Cl	4-F	H	i-Pr	H
H	H	4-F	H	c-Bu	H
H	H	4-F	H	c-Hex	H
6-OMe	7-OMe	H	H	i-Pr	H
6-OMe	7-OMe	4-Cl	H	i-Pr	H
6-OMe	7-OMe	H	H	c-Pr	H
6-OMe	7-OMe	4-Cl	H	c-Pr	H
6-OMe	7-OMe	4-F	H	c-Pr	H
6-Me	H	H	H	i-Pr	H
6-Me	H	4-Cl	H	i-Pr	H
6-Me	H	H	H	c-Pr	H
6-Me	H	4-Cl	H	c-Pr	H
6-Me	H	4-F	H	c-Pr	H
6-Cl	H	H	H	i-Pr	H
6-Cl	H	4-Cl	H	i-Pr	H
6-Cl	H	H	H	c-Pr	H
6-Cl	H	4-Cl	H	c-Pr	H
6-Cl	H	4-F	H	c-Pr	H
H	H	H	H	i-Pr	H
H	H	4-Cl	H	i-Pr	H
H	H	H	H	c-Pr	H
H	H	4-Cl	H	c-Pr	H
H	H	4-F	H	c-Pr	H

Further, pharmaceutically acceptable salts such as potassium salts or esters such as ethyl esters or methyl esters of these compounds can be prepared in the same manner.

The compounds of the present invention exhibit high inhibitory activities against the cholesterol biosynthesis wherein HMG-CoA reductase acts as a rate limiting enzyme, as shown by the test results given hereinafter, and thus are capable of suppressing or reducing the amount of cholesterol in blood as lipoprotein. Thus, the compounds of the present invention are useful as curing agents against hyperlipidemia, hyperlipoproteinemia and atheroscleosis.

They may be formulated into various suitable formulations depending upon the manner of the administration. The compounds of the present invention may be administered in the form of free acids or in the form of physiologically hydrolyzable and acceptable esters or lactones, or pharmaceutically acceptable salts.

The pharmaceutical composition of the present invention is preferably administered orally in the form of the compound of the present invention per se or in the form of powders, granules, tablets or capsules formulated by mixing the compound of the present invention with a suitable pharmaceutically acceptable carrier including a binder such as hydroxypropyl cellulose, syrup, gum arabic, gelatin, sorbitol, tragacanth gum, polyvinyl pyrrolidone or CMC-Ca, an excipient such as lactose, sugar, corn starch, calcium phosphate, sorbitol, glycine or crystal cellulose powder, a lubricant such as magnesium stearate, talk, polyethylene glycol or silica, and a disintegrator such as potato starch.

However, the pharmaceutical composition of the present invention is not limited to such oral administration and it is applicable for parenteral administration. For example, it may be administered in the form of e.g. a suppository formulated by using oily base material such as cacao butter, polyethylene glycol, lanolin or fatty acid triglyceride, a transdermal therapeutic base formulated by using liquid paraffin, white vaseline, a higher alcohol, Macrogol ointment, hydrophilic ointment or hydro-gel base material, an injection formulation formulated by using one or more materials selected from the group consisting of polyethylene glycol, hydro-gel base material, distilled water, distilled water for injection and excipient such as lactose or corn starch, or a formulation for administration through mucous membranes such as an ocular mucous membrane, a nasal mucous membrane and an oral mucous membrane.

Further, the compounds of the present invention may be combined with basic ion-exchange resins which are capable of binding bile acids and yet not being absorbed in gastraintestinal tract.

The daily dose of the compound of the formula I is from 0.05 to 500 mg, preferably from 0.5 to 50 mg for an adult. It is administered from once to three times per day. The dose may of course be varied depending upon the age, the weight or the condition of illness of the patient.

The compounds of the formulas II to VII are novel, and they are important intermediates for the preparation of the compounds of the formula I. Accordingly, the present invention relates also to the compounds of the formulas II to VII and the processes for their production.

Now, the present invention will be described in further detail with reference to Test Examples for the pharmacological activities of the compounds of the present invention, their Preparation Examples and Formulation Examples. However, it should be understood

that the present invention is by no means restricted by such specific Examples.

PHARMACOLOGICAL TEST EXAMPLES

Test A: Inhibition of cholesterol biosynthesis from acetate in vitro

Enzyme solution was prepared from liver of male Wistar rat billialy cannulated and discharged bile for over 24 hours. Liver was cut out at mid-dark and microsome and supernatant fraction which was precipitable with 40–80% of saturation of ammonium sulfate (sup fraction) were prepared from liver homogenate according to the modified method of Knauss et. al.; Kuroda, M., et. al., Biochim. Biophys. Acta, 489, 119 (1977). For assay of cholesterol biosynthesis, microsome (0.1 mg protein) and sup fraction (1.0 mg protein) were incubated for 2 hours at 37° C. in 200 μl of the reaction mixture containing ATP; 1 mM, Glutathione; 6 mM, Glucose-1-phosphate; 10 mM, NAD; 0.25 mM, NADP; 0.25 mM, CoA; 0.04 mM and 0.2 mM [2-^{14}C]sodium acetate (0.2 μCi) with 4 μl of test compound solution dissolved in water or dimethyl sulfoxide. To stop reaction and saponify, 1 ml of 15% EtOH-KOH was added to the reactions and heated at 75° C. for 1 hour. Nonsaponifiable lipids were extracted with petroleum ether and incorporated ^{14}C radioactivity was counted. Inhibitory activity of compounds was indicated with IC50.

Test B: Inhibition of cholesterol biosynthesis in culture cells

Hep G2 cells at over 5th passage were seeded to 12 well plates and incubated with Dulbecco's modified Eagle (DME) medium containing 10% of fetal bovine serum (FBS) at 37° C., 5% CO_2 until cells were confluent for about 7 days. Cells were exposed to the DME medium containing 5% of lipoprotein deficient serum (LpDS) prepared by ultracentrifugation method for over 24 hours. Medium was changed to 0.5 ml of fresh 5% LpDS containing DME before assay and 10 μl of test compound solution dissolved in water or DMSO were added. 0.2 μCi of [2-^{14}C]sodium acetate (20 μl) was added at 0 hr(B-1) or 4 hrs(B-2) after addition of compounds. After 4 hrs further incubation with [2-^{14}C]sodium acetate, medium was removed and cells were washed with phosphate buffered saline(PBS) chilled at 4° C. Cells were scraped with rubber policeman and collected to tubes with PBS and digested with 0.2 ml of 0.5 N KOH at 37° C. Aliquot of digestion was used for protein analysis and remaining was saponified with 1 ml of 15% EtOH—KOH at 75° C. for 1 hour. Nonsaponifiable lipids were extracted with petroleum ether and ^{14}C radioactivity was counted. Counts were revised by cell protein and indicated with DPM/mg protein. Inhibitory activity of compounds was indicated with IC50.

Test C: Inhibition of cholesterol biosynthesis in vivo

Male Sprague-Dawley rats weighing about 150 g were fed normal Purina chow diet and water ad libitum, and exposed to 12 hours light/12 hours dark lighting pattern (2:00 PM–2:00 AM dark) prior to use for in vivo inhibition test of cholesterol biosynthesis. Animals were separated groups consisting of five rats as to be average mean body weight in each groups. Test compounds at dosage of 0.02–0.2 mg/kg body weight (0.4 ml/100 g body weight), were dissolved in water or suspended or in 0.5% methyl cellulose and orally administered at 2–3 hours before mid-dark (8:00 PM), while cholesterol biosynthesis reaches to maximum in rats. As control, rats were orally administered only water or vehicle. At 90 minutes after sample administration, rats were injected intraperitoneally with 10 μCi of [2-^{14}C]sodium acetate at volume of 0.2 ml per one. 2 Hours later, blood samples were obtained and serum were separated immediately. Total lipids were extracted according to the method of Folch et al. and saponified with EtOH-KOH. Nonsaponifiable lipids were extracted with petroleum ether and radio activity incorporated into nonsaponifiable lipids was counted.

Inhibitory activity was indicated as percent decrease of counts in testing groups (DPM/2 ml serum/2 hours) from that in control group.

With respect to the compounds of the present invention, the inhibitory activities against the cholesterol biosynthesis in which HMG-CoA reductase serves as a rate limiting enzyme, were measured by the above Test A and B. The results are shown in Tables, 2, 2-2, 3 and 3-2. Further, the results of the measurements by Test C are also presented.

TABLE 2

Inhibitory activities by Test A	
Compound	I_{50} (molar concentration)
(Compounds of the present invention)	
I-13	1.25×10^{-7}
I-51	1.0×10^{-8}
I-52	7.1×10^{-8}
I-53	1.9×10^{-7}
(Reference compounds)	
Mevinolin	1.4×10^{-8}
CS-514	9.0×10^{-9}

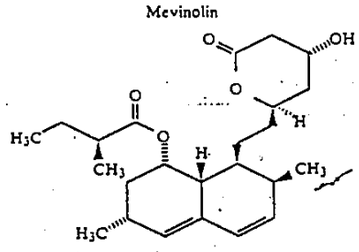
In Table 2-2, the relative activities are shown based on the activities of CS-514 being evaluated to be 1.

TABLE 2-2

Relative activities by Test A	
Compound	Relative activities
(Compounds of the present invention)	
I-16	1.75
I-116	2.25
I-117	0.37
I-120	3.21
I-522	0.76

Structures of reference compounds:

Mevinolin (I)



CS-514

-continued

(2)

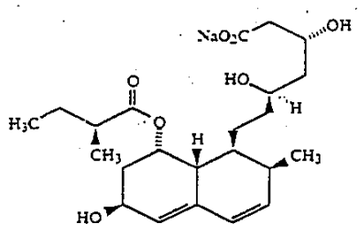


TABLE 3

Inhibitory activities by Test B-1

Compound	I_{50} (molar concentration)
(Compound of the present invention)	
I-51	1×10^{-7}
(Reference compound)	
CS-514	3.5×10^{-7}

In Table 3-2, the relative activities are shown based on the activities of CS-514 being evaluated to be 1.

TABLE 3-2

Relative activities by Test B-1

Compound	Relative activities
I-116	19.4
I-520	20.0
II-20	20.8

Results of the measurement of the inhibitory activities by Test C

The percent decrease of counts after the oral administration of 0.05 mg/kg of compound I-520 was 55% relative to the measured value of the control group. The percent decrease of counts after the oral administration of 10 mg/kg of CS-514 was 55% under the same condition. The compounds of the present invention exhibited activities superior to the reference compound such as CS-514 or Mevinolin in Test A, and exhibited activities superior to CS-514 in Tests B and C.

Test D: Acute toxicity

A 0.5% CMC suspension of a test compound was orally administered to ICR male mice (group of three mice). The acute toxicity was determined based on the mortality after seven days. With compound I-57, I-58, I-59, I-511, I-512, I-513, I-514, I-515, I-517 and I-523 of the present invention, the mortality was 0% even when they were orally administered in an amount of 1000 mg/kg.

EXAMPLE 1

Ethyl (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-quinolin-3'-yl]-hept-6-enoate (compound I-11) (prepared by steps of Example 1-a through Example I-q)

EXAMPLE 1-a

Ethyl 4-(4'-fluorophenyl)-2-(1'-methylethyl)-quinolin-3-yl-carboxylate (compound VII-1)

The synthesis was conducted in accordance with the method disclosed in J. Org. Chem., 2899 (1966).

6.45 g (0.03 mol) of 2-amino-4'-fluorobenzophenone, 5.53 g (0.035 mol) of ethyl isobutyrylacetate and 0.1 ml of conc. sulfuric acid were dissolved in 30 ml of glacial acetic acid, and the mixture was heated at 100° C. for about 10 hours. After confirming the substantial disappearance of 2-amino-4'-fluorobenzophenone by thin layer chromatography, the reaction solution was cooled to room temperature, and a mixture of 45 ml of conc. aqueous ammonia and 120 ml of water cooled with ice, was gradually added thereto. A separated oily substance was solidified when left to stand overnight in a refrigerator. This solid was recrystallized from a small amount of ethanol to obtain 6.47 g (55%) of white powder. Melting point: 68°–70.5° C.

EXAMPLE 1-b

4-(4'-fluorophenyl)-3-hydroxymethyl-2-(1'-methylethyl)-quinoline (compound VI-1)

5.4 g (0.016 mol) of compound VII-1 was dissolved in dry toluene under a nitrogen atmosphere and cooled in ice bath to 0° C. To this solution, 40 ml of a 16 wt % diisobutylaluminium hydride-toluene solution was dropwise added, and the mixture was stirred at 0° C. for two hours. After confirming the complete disappearance of compound VII-1 by thin layer chromatography, a saturated ammonium chloride solution was added thereto at 0° C. to terminate the reaction. Ethyl ether was added to the reaction mixture, and the organic layer was separated. A gelled product was dissolved by an addition of an aqueous sodium hydroxide solution and extracted anew with ethyl ether. The ethyl ether extracts were put together, dried over anhydrous magnesium sulfate and filtered. The solvent was distilled off. The residual oil underwent crystallization when left to stand. It was recrystallized from ethyl acetate-n-hexane to obtain 3.3 g of white crystals. Yield: 70%. Melting point: 136°–137° C.

EXAMPLE 1-c

4-(4'-fluorophenyl)-2-(1'-methylethyl)quinolin-3-yl-carboxyaldehyde (compound V-1)

2.0 g (9.3 mmol) of pyridinium chlorochromate and 0.4 g of anhydrous sodium acetate was suspended in 10 ml of dry dichloromethane. To this suspension, a solution obtained by dissolving 1 g (3.4 mmol) of compound VI-1 in 10 ml of dry dichloromethane, was immediately added at room temperature. The mixture was stirred for one hour. Then, 100 ml of ethyl ether was added thereto, and the mixture was throughly mixed. The reaction mixture was filtered under suction through a silica gel layer. The filtrate was dried under reduced pressure. The residue was dissolved in the isopropyl ether, and insoluble substances were filtered off. The

filtrate was again dried under reduced pressure, and the residue was recrystallized from diisopropyl ether to obtain 0.7 g (Yield: 70%) of slightly yellow prism crystals. Melting point: 124°–126° C.

EXAMPLE 1-d

3-(3'-ethoxy-1'-hydroxy-2'-propenyl)-4-(4'-fluorophenyl)-2-(1'-methylethyl)-quinoline (compound IV-1)

1.13g (3.13 mmol) of cis-1-ethoxy-2-(tri-n-butylstannyl)ethylene was dissolved in 8 ml of dry tetrahydrofuran, and the solution was cooled to −78° C. in a nitrogen stream. To this solution, 2 ml (3.2 mmol) of a 15 wt % n-butyllithium-n-hexane solution was dropwise added. The mixture was stirred for 45 minutes. Then, a solution prepared by dissolving 0.76 g (2.6 mmol) of compound V-1 in 10 ml of dry tetrahydrofuran was dropwise added thereto. The reaction mixture was stirred at −78° C. for two hours. Then, 2 ml of a saturated ammonium chloride solution was added thereto to terminate the reaction. The organic layer was extracted with diethyl ether, and the diethyl ether extract was washed with a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was separated with n-hexane and acetonitrile. The solvent was distilled off under reduced pressure from the acetonitrile layer, and an oily substance thereby obtained was purified by silica gel column chromatography (eluent: 2.5% methanol-chloroform) to obtain 0.91 g of the desired compound in a purified oily form.

H-MNR ($CDCl_3$) δ ppm: 1.1(t,3H,7 Hz) 1.37(d,6H,J=7 Hz) 3.7(m,1H) 3.7(q,2H,J=7 Hz) 4.75(t,1H,7 Hz) 5.7(m,1H) 5.95(m,1H) 7.05-8.2(m,8H).

EXAMPLE 1-e

(E)-3-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-quinolin-3'-yl]propenaldehyde (compound III-1)

0.91 g of compound IV-1 was dissolved in 20 ml of tetrahydrofuran, and 5 ml of water and 100 mg of p-toluenesulfonic acid were added thereto. The mixture was stirred at room temperature for 24 hours. The reaction solution was extracted with diethyl ether a few times. The extracts were washed with a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. Then, the solvent was distilled off. The residue was purified by silica gel column chromatography (eluent: chloroform) to obtain the desired product as white prism crystals. 0.4 g (50%). Melting point: 127°–128° C.

EXAMPLE 1-f

Ethyl (E)-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-quinolin-3'-yl]-5-hydroxy-3-oxohepto-6-enoate (compound II-1)

50 mg of 60% sodium hydride was washed with dry petroleum ether and dried under a nitrogen stream, and then suspended in 5 ml of dry tetrahydrofuran. The suspension was cooled to −15° C. in a nitrogen atmosphere. Then, 120 mg (0.92 mmol) of ethyl acetoacetate was dropwise added thereto, and the mixture was stirred for 15 minutes. Then, 0.6 ml (0.92 mmol) of a 15 wt % n-butyllithium-n-hexane solution was dropwise added thereto, and the mixture was stirred for 30 minutes. Then, a solution prepared by dissolving 160 mg (0.5 mmol) of compound III-1 in dry tetrahydrofuran, was dropwise added thereto, and the mixture was stirred for one hour. To the reaction mixture, 1 ml of a saturated ammonium chloride aqueous solution was added at −15° C. Then, the mixture was extracted three times with diethyl ether. The diethyl ether solution was washed with a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. The solution was evaporated to dryness under reduced pressure. The residue was recrystallized from diisopropyl ether to obtain 130 mg (yield: 59%) of white crystals. Melting point: 99°–101° C.

EXAMPLE 1-g

Ethyl (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-quinolin-3'-yl]-hept-6-enoate (compound I-11)

110 mg (0.245 mmol) of compound II-1 was dissolved in 5 ml of ethanol in a nitrogen atmosphere, and the solution was cooled 0° C. Then, 10 mg (0.263 mmol) of sodium borohydride was added, and the mixturer was stirred for one hour. Then, 1 ml of a 10% hydrochloric acid aqueous solution was added thereto, and the mixture was extracted three times with ethyl ether. The ethyl ether solution was washed with a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. Then, the solution was evaporated to dryness under reduced pressure. The residual oil was purified by silica gel column chromatography (eluent: 5% methanol-chloroform) to obtain the desired product as a pure colorless oily substance. 70 mg (Yield: 64%)

H-NMR ($CDCl_3$) δ ppm: 1.30(t,3H,J=8 Hz) 1.39(d,6H,J=8 Hz) 1.4–1.8(m,2H) 2.42(d,2H,J=7 Hz) 3.0–3.8 (m,2H) 3.50(m,1H) 3.9–4.6(m,2H) 4.20(q,2H,J=8 Hz) 5.35(m,1H) 6.59(m,1H) 7.10–8.18(m,8H).

EXAMPLE 2

Sodium salt of (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid (compound I-51)

60 mg (0.133 mmol) of compound I-11 was dissolved in 3 ml of ethanol. Then, 0.26 ml of a 0.5 N sodium hydroxide aqueous solution was dropwise added thereto. The mixture was stirred at room-temperature for further one hour, and ethanol was distilled off under reduced pressure. Then, 5 ml of water was added thereto, and the mixture was extracted with ethyl ether. The aqueous layer was freeze-dried to obtain 40 mg (67%) of hygroscopic white powder. Melting point: 207°–209° C. (decomposed).

EXAMPLE 3

(E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid (compound I-21)

110 mg (0.244 mmol) of compound I-11 was dissolved in 10 ml of ethanol. Then, 0.79 ml of a 0.5 N sodium hydroxide aqueous solution was dropwise added thereto. The mixture was stirred at room temperature for further one hour, and ethanol was distilled off under reduced pressure. Then, 10 ml of water was added thereto, and the mixture was extracted with ethyl ether. The aqueous layer was weakly acidified (pH 4) with a

dilute hydrochloric aqueous solution and extracted three times with ethyl ether. The ethyl ether layers were put together and dried over anhydrous magnesium sulfate. Then, the solvent was distilled off under reduced pressure to obtain 90 mg of slightly yellow oily substance.

H-NMR ($CDCl_3$) δ ppm: 1.36(d,6H,J=7 Hz) 2.4(m,2H) 3.5(m,1 H) 3.45(m,1H) 3.8–4.6(m,2H) 5.40(dd,1H,J_1=19 Hz,J_2=8 Hz) 6.55 (d,1H,J=19 Hz) 7.0–8.3(m,8H)

EXAMPLE 4

(E)-6-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)quinolin-3'-ylethenyl]-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (compound I-31)

90 mg of compound I-21 was dissolved in 10 ml of dry toluene, and the solution was refluxed under heating for 3 hours by means of a Dean Stark apparatus.

Toluene was distilled off under reduced pressure, and the residual solid was recrystallized from diisopropyl ether to obtain 40 mg of colorless prism crystals. Melting point: 182°–184° C.

By silica gel thin chromatography, the product gave two absorption spots close to each other attributable to the diastereomers. (Developping solvent: 3% methanol-chloroform)

These diasteromers were separated and isolated by silica gel thin layer chromatography. [Developping solvent: t-BuOMe/hexane/acetone=7/2/1 (v/v), Rf=0.6 and 0.7 (obtained weight ratio: 1/2)]

Rf=0.7: trans lactone

H-NMR ($CDCl_3$) δ ppm: 1.40(d,6H,J=7 Hz) 1.6(m,2H) 2.65(m,2H) 3.48(m,1H) 4.20(m,1H) 5.15(m,1H) 5.37(dd,1H,J_1=18 Hz,J_2=7 Hz) 6.68(d,1H,J=19 Hz) 7.1–8.2(m,8H).

Rf=0.6: cis lactone

H-NMR ($CDCl_3$) δ ppm: 1.40(d,6H,J=7 Hz) 1.6(m,2H) 2.65(m,2H) 3.48(m,1H) 4.20(m,1H) 4.65(m,1H) 5.40(dd,1H,J_1=18 Hz,J_2=7 Hz) 6.66(m,1H) 7.0–8.2(m,8H).

EXAMPLE 5

6-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)quinolin-3'-ylethynyl]-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (compound I-41)

20 mg of a mixture of diastereomers of compound I-31 was dissolved in 5 ml of ethanol, and 10 mg of 5% palladium-carbon was added thereto. The mixture was stirred under a hydrogen atmosphere. After confirming the disappearance of the starting substance and the appearance of a new spot by thin layer chromatography, the palladium-carbon was filtered off, and ethanol was distilled off to obtain colorless oil.

This oil was purified by preparative thin layer chromatography to obtain 16 mg of the desired product as pure colorless oil.

MS(m/e): 408(M^++H), 407(M^+), 366, 292, 278

In the same manner as in Example 1-a, compounds VII-2 to VII-27 were prepared. The physical properties of these compounds are shown in Table 4. (In the Table, R^1, R^2, R^3, R^4, R^5 and R^{21} correspond to the substitients of compound VII.)

TABLE 4

(Compounds in this Table are compounds of the formula VII wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	R^{21}	m. p. (°C.)
VII-2	H	H	4-F	H	CH_3	C_2H_5	121–122
VII-3	H	H	H	H	CH_3	C_2H_5	102–102.5
VII-4	H	H	H	H	i-Pr	C_2H_5	85–85.5
VII-5	6-Cl	H	H	H	CH_3	C_2H_5	100.5–101.5
VII-6	6-Cl	H	H	H	i-Pr	C_2H_5	105.5–106.5
VII-7	H	H	2-F	H	i-Pr	C_2H_5	101.0–102.0
VII-8	7-Me	H	H	H	i-Pr	C_2H_5	oil
VII-9	H	H	4-Cl	H	i-Pr	C_2H_5	134.0–136.5
VII-10	H	H	4-OMe	H	i-Pr	C_2H_5	88.0–89.0
VII-11	H	H	4-Me	H	i-Pr	C_2H_5	108.5–109.5
VII-12	6-Cl	H	2-Cl	H	i-Pr	C_2H_5	101.0–103.0
VII-13	H	H	4-CF_3	H	i-Pr	C_2H_5	117.5–119.0
VII-14	H	H	3-Me	4-F	i-Pr	C_2H_5	oil
VII-15	H	H	3-Me	5-Me	i-Pr	C_2H_5	oil
VII-16	6-OMe	7-OMe	4-F	H	i-Pr	C_2H_5	96.0–98.0
VII-17	H	H	4-F	H	C_2H_5	CH_3	139.0–139.5
VII-18	H	H	4-F	H	n-Pr	C_2H_5	oil
VII-19	6-Cl	H	4-F	H	i-Pr	C_2H_5	94.5–95.5
VII-20	H	H	4-F	H	c-Pr	CH_3	113.5–116.5
VII-21	H	H	4-OPh	H	i-Pr	C_2H_5	oil
VII-22	6-Cl	8-Cl	4-F	H	i-Pr	C_2H_5	96.0–98.0
VII-23	6-Cl	H	H	H	Ph	C_2H_5	118.8–119.5
VII-24	6-Cl	H	H	H	c-Pr	CH_3	97.0–98.5
VII-25	H	H	4-F	H	sec-Bu	CH_3	oil
VII-26	6-Me	H	4-F	H	i-Pr	C_2H_5	109.0–111.0
VII-27	6-OMe	7-OMe	4-F	H	c-Pr	CH_3	153.0–153.5

VII-8
H-NMR (in $CDCl_3$) δ ppm: 0.92 (t, 3H, J=7Hz), 1.41 (d, 6H, J=6Hz) 2.47 (s, 3H), 3.27 (Heptaplet, 1H, J=6Hz) 3.96 (q, 2H, J=7Hz), 7.0–7.8 (m, 8H)

VII-14
H-NMR (in $CDCl_3$) δ ppm: 1.01 (t, 3H, J=7Hz), 1.42 (d, 6H, J=6Hz) 2.38 (s, 3H, J=3Hz), 3.25 (Heptaplet, 1H, J=6Hz) 4.04 (q, 2H, J=7Hz), 6.9–8.1 (m, 7Hz)

VII-15
H-NMR (in $CDCl_3$) δ ppm: 0.97 (t, 3H, J=7Hz), 1.43 (d, 6H, J=6Hz) 2.29 (s, 6H), 3.25 (Heptaplet, 1H, J=6Hz) 4.00 (q, 2H, J=7Hz), 6.8–8.0 (m, 7H)

VII-18
H-NMR (in $CDCl_3$) δ ppm: 0.98 (t, 3H, J=7Hz), 1.02 (t, 3H, J=7Hz) 1.6–2.3 (m, 2H), 2.8–3.1 (m, 2H) 4.03 (q, 2H, J=7Hz), 6.9–8.1 (m, 8H)

VII-21
H-NMR (in $CDCl_3$) δ ppm: 1.03 (t, 3H, J=7Hz), 1.41 (d, 6H, J=6Hz) 3.25 (Heptaplet, 1H, J=6Hz), 4.05 (q, 2H, J=7Hz), 6.8–8.1 (m, 13H)

VII-25
H-NMR (in $CDCl_3$) δ ppm: 0.97 (d, 6H, J=6Hz), 2.0–2.6 (m, 1H) 2.85 (d, 2H, J=7Hz), 3.51 (s, 3H), 6.8–8.1 (m, 8H)

In the same manner as in Example 1-b, compounds VI-2 to VI-27 were prepared. (In Table 5, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents in compound VI.)

TABLE 5

(Compounds in this Table are compounds of the formula VI wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	m. p. (°C.)
VI-2	H	H	p-F	H	CH_3	—
VI-3	H	H	H	H	CH_3	149–151

TABLE 5-continued

(Compounds in this Table are compounds of the formula VI wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	m. p. (°C.)
VI-4	H	H	H	H	i-Pr	130–130.5
VI-5	6-Cl	H	H	H	CH_3	139–141
VI-6	6-Cl	H	H	H	i-Pr	168–169
VI-7	H	H	2-F	H	i-Pr	140.5–142.0
VI-8	7-Me	H	H	H	i-Pr	155.0–157.0
VI-9	H	H	4-Cl	H	i-Pr	192.0–195.0
VI-10	H	H	4-OMe	H	i-Pr	186.0–188.5
VI-11	H	H	4-Me	H	i-Pr	161.0–164.0
VI-12	6-Cl	H	2-Cl	H	i-Pr	122.0–124.0
VI-13	H	H	4-CF_3	H	i-Pr	183.0–186.0
VI-14	H	H	3-Me	4-F	i-Pr	161.0–162.5
VI-15	H	H	3-Me	5-Me	i-Pr	137.0–138.0
VI-16	6-Me	7-OMe	4-F	H	i-Pr	164.0–165.0
VI-17	H	H	4-F	H	C_2H_5	141.5–143.5
VI-18	H	H	4-F	H	n-Pr	146.5–148.5
VI-19	6-Cl	H	4-F	H	i-Pr	171.0–172.0
VI-20	H	H	4-F	H	c-Pr	120–126
VI-21	H	H	4-OPh	H	i-Pr	153.0–154.0
VI-22	6-Cl	8-Cl	4-F	H	i-Pr	98.5–103
VI-23	6-Cl	H	H	H	Ph	171.5–172.5
VI-24	6-Cl	H	H	H	c-Pr	84.0–86.0
VI-25	H	H	4-F	H	sec-Bu	119.0–121.0
VI-26	6-Me	H	4-F	H	i-Pr	160.0–161.5
VI-27	6-OMe	7-OMe	4-F	H	c-Pr	162.0–163.0

In the same manner as in Example 1-c, compounds V-2 to V-27 were prepared. (In Table 6, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents of compound of V.)

TABLE 6

(Compounds in this Table are compounds of the formula V wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	m. p. (°C.)
V-2	H	H	p-F	H	CH_3	125—128
V-3	H	H	H	H	CH_3	143–146
V-4	H	H	H	H	i-Pr	92–93
V-5	6-Cl	H	H	H	CH_3	220–222
V-6	6-Cl	H	H	H	i-Pr	140–140.5
V-7	H	H	2-F	H	i-Pr	121.5–124.0
V-8	7-Me	H	H	H	i-Pr	105.1–109.2
V-9	H	H	4-Cl	H	i-Pr	147.0–147.8
V-10	H	H	4-OMe	H	i-Pr	135.6–136.8
V-11	H	H	4-Me	H	i-Pr	119.4–120.4
V-12	6-Cl	H	2-Cl	H	i-Pr	105.8–106.9
V-13	H	H	4-CF_3	H	i-Pr	163.7–164.2
V-14	H	H	3-Me	4-F	i-Pr	161.1–108.1
V-15	H	H	3-Me	5-Me	i-Pr	120.8–122.3
V-16	6-OMe	7-OMe	4-F	H	i-Pr	164.4–165.2
V-17	H	H	4-F	H	C_2H_5	143.1–144.2
V-18	H	H	4-F	H	n-Pr	150.2–155.3
V-19	6-Cl	H	4-F	H	i-Pr	164.5–165.3
V-20	H	H	4-F	H	c-Pr	150.1–151.6
V-21	H	H	4-OPh	H	i-Pr	106.9–107.7
V-22	6-Cl	8-Cl	4-F	H	i-Pr	135.0–135.7
V-23	6-Cl	H	H	H	Ph	174.8–175.3
V-24	6-Cl	H	H	H	c-Pr	157.5–158.0
V-25	H	H	4-F	H	sec-Bu	125.0–126.5
V-26	6-Me	H	4-F	H	i-Pr	155.0–157.0
V-27	6-OMe	7-OMe	4-F	H	c-Pr	200.0–200.5

In the same manner as in Example 1-d, compounds IV-2 to IV-6 were prepared. (In Table 7, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents of compound IV.)

TABLE 7

(Compounds in this Table are compounds of the formula IV wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	m. p. (°C.)
IV-2	H	H	4-F	H	CH_3	177–179
IV-3	H	H	H	H	CH_3	—
IV-4	H	H	H	H	i-Pr	—
IV-5	6-Cl	H	H	H	CH_3	—
IV-6	6-Cl	H	H	H	i-Pr	—

In the same manner as in Example 1-e, compounds III-2 to III-27 were prepared. (In Table 8, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents of compound III.)

TABLE 8

(Compounds in this Table are compounds of the formula III wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	m. p. (°C.)
III-2	H	H	4-F	H	CH_3	194–196
III-3	H	H	H	H	CH_3	170–171.5
III-4	H	H	H	H	i-Pr	107–108.5
III-5	6-Cl	H	H	H	CH_3	192–194
III-6	6-Cl	H	H	H	i-Pr	125.5–127
III-7	H	H	2-F	H	i-Pr	80.1–80.2
III-8	7-Me	H	H	H	i-Pr	121.1–122.3
III-9	H	H	4-Cl	H	i-Pr	148.0–149.1
III-10	H	H	4-OMe	H	i-Pr	137.4–140.1
III-11	H	H	4-Me	H	i-Pr	111.6–113.1
III-12	6-Cl	H	2-Cl	H	i-Pr	83.8–

TABLE 8-continued

(Compounds in this Table are compounds of the formula III wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	m. p. (°C.)
III-13	H	H	4-CF_3	H	i-Pr	84.5 126.2–128.8
III-14	H	H	3-Me	4-F	i-Pr	124.8–126.4
III-15	H	H	3-Me	5-Me	i-Pr	117.6–120.3
III-16	6-OMe	7-OMe	4-F	H	i-Pr	147.8–150.9
III-17	H	H	4-F	H	C_2H_5	124.3–128.5
III-18	H	H	4-F	H	n-Pr	117.8–121.5
III-19	6-Cl	H	4-F	H	i-Pr	135.2–135.9
III-20	H	H	4-F	H	c-Pr	141.3–144.1
III-21	H	H	4-OPh	H	i-Pr	oil
III-22	6-Cl	8-Cl	4-F	H	i-Pr	117–122
III-23	6-Cl	H	H	H	Ph	142.8–144.3
III-24	6-Cl	H	H	H	c-Pr	161.0–161.5
III-25	H	H	4-F	H	sec-Bu	78.0–81.0
III-26	6-Me	H	4-F	H	i-Pr	137.0–137.5
III-27	6-OMe	7-OMe	4-F	H	c-Pr	189.5–191.0

III-22
H-NMR (in $CDCl_3$) δ ppm: 1.40 (d, 6H, J=7Hz), 3.44 (Heptaplet, 1H, J=7Hz) 5.93 (dd, 1H, J=8Hz, J=16Hz), 6.8–8.1 (m, 14H) 9.34 (d, 1H, J=8Hz)

In the same manner as in Example 1-f, compounds II-2 to II-27 were prepared. (In Table 9, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents of compound II.)

TABLE 9

(Compounds in this Table are compounds of the formula II wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	R^{12}	m. p. (°C.)
II-2	H	H	p-F	H	CH_3	C_2H_5	oil
II-3	H	H	H	H	CH_3	C_2H_5	105–106
II-4	H	H	H	H	i-Pr	C_2H_5	88.5–90.5
II-5	6-Cl	H	H	H	CH_3	C_2H_5	77–82
II-6	6-Cl	H	H	H	i-Pr	C_2H_5	96–98
II-7	H	H	2-F	H	i-Pr	C_2H_5	oil
II-8	7-Me	H	H	H	i-Pr	C_2H_5	68.5–74.0
II-9	H	H	4-Cl	H	i-Pr	C_2H_5	91.0–94.0
II-10	H	H	4-OMe	H	i-Pr	C_2H_5	78.0–78.5
II-11	H	H	4-OMe	H	i-Pr	C_2H_5	75.0–78.0
II-12	6-Cl	H	2-Cl	H	i-Pr	C_2H_5	oil
II-13	H	H	4-CF_3	H	i-Pr	C_2H_5	78.0–83.0
II-14	H	H	3-Me	4-F	i-Pr	C_2H_5	66.0–71.0
II-15	H	H	3-Me	5-Me	i-Pr	C_2H_5	oil
II-16	6-OMe	7-OMe	4-F	H	i-Pr	C_2H_5	83.0–90.0
II-17	H	H	4-F	H	C_2H_5	C_2H_5	94.0–97.0
II-18	H	H	4-F	H	n-Pr	C_2H_5	oil
II-19	6-Cl	H	4-F	H	i-Pr	C_2H_5	111.0–113.5
II-20	H	H	4-F	H	c-Pr	C_2H_5	91.0–93.0

TABLE 9-continued

(Compounds in this Table are compounds of the formula II wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	R^{12}	m. p. (°C.)
II-21	H	H	4-OPh	H	i-Pr	C_2H_5	121.0–125.0
II-22	6-Cl	8-Cl	4-F	H	i-Pr	C_2H_5	oil
II-23	6-Cl	H	H	H	Ph	C_2H_5	oil
II-24	6-Cl	H	H	H	c-Pr	C_2H_5	69.0–71.0
II-25	H	H	4-F	H	sec-Bu	C_2H_5	oil
II-26	6-Me	H	4-F	H	i-Pr	C_2H_5	oil
II-27	6-OMe	7-OMe	4-F	H	c-Pr	C_2H_5	oil

II-7
H-NMR (in $CDCl_3$) δ ppm: 1.21 (t, 3H, J=7Hz), 1.32 (d, 6H, J=6Hz) 2.2–2.4 (m, 2H), 2.5–2.7 (m, 1H) 3.28 (s, 1H), 3.34 (Heptaplet, 1H, J=6Hz) 4.08 (q, 2H, J=7Hz), 4.3–4.6 (m, 1H) 5.28 (dd, 1H, J=6Hz, J=15Hz), 6.53 (dd, 1H, J=1.5Hz, J=15Hz), 6.9–8.0 (m, 8H)

II-12
H-NMR (in $CDCl_3$) δ ppm: 1.25 (t, 3H, J=7Hz), 1.33 (d, 6H, J=6Hz) 2.2–2.4 (m, 2H), 2.5–2.8 (m, 1H) 3.32 (s, 2H), 3.35 (Heptaplet, 1H, J=6Hz) 4.13 (q, 2H, J=7Hz), 4.2–4.6 (m, 1H) 5.34 (dd, 1H, J=6Hz, J=15Hz), 6.53 (dd, 1H, J=1.5Hz, J=15Hz), 7.0–8.0 (m, 7H)

II-15
H-NMR (in $CDCl_3$) δ ppm: 1.23 (t, 3H, J=7Hz), 1.35 (d, 6H, J=6Hz) 2.2–2.4 (m, 2H), 2.31 (s, 6H) 2.6–2.8 (m, 1H), 3.32 (s, 2H) 3.35 (Heptaplet, 1H, J=6Hz), 4.12 (q, 2H, J=7Hz) 4.3–4.7 (m, 1H), 5.30 (dd, 1H, J=6Hz, J=16Hz) 6.51 (dd, 1H, J=1Hz, J=16Hz), 6.7–8.0 (m, 7H)

II-18
H-NMR (in $CDCl_3$) δ ppm: 1.00 (t, 3H, J=7Hz), 1.26 (t, 3H, J=7Hz) 1.6–2.3 (m, 2H), 2.42 (d, 2H, J=6Hz) 2.6–3.2 (m, 3H), 3.35 (s, 2H) 4.11 (q, 2H, J=7Hz), 4.3–4.7 (m, 1H) 5.27 (dd, 1H, J=6Hz, J=16Hz) 6.46 (dd, 1H, J=1.5Hz, J=16Hz), 6.9–8.0 (m, 8H)

II-22
H-NMR (in $CDCl_3$) δ ppm: 1.26 (t, 3H, J=7Hz), 1.33 (d, 6H, J=6Hz) 2.43 (d, 2H, J=6Hz), 2.6–2.9 (m, 1H) 3.36 (s, 2H), 3.44 (Heptaplet, 1H, J=6Hz) 4.13 (q, 2H, J=7Hz), 4.3–4.7 (m, 1H) 5.30 (dd, 1H, J=6Hz, J=16Hz), 6.53 (dd, 1H, J=1.5Hz, J=16Hz, 7.0–7.6 (m, 6H)

II-23
H-NMR (in $CDCl_3$) δ ppm: 1.23 (t, 3H, J=7Hz), 2.21 (d, 2H, J=6Hz) 2.4–2.6 (m, 1H), 3.25 (s, 2H) 4.09 (q, 2H J=7Hz), 4.1–4.4 (m, 1H) 5.08 (dd, 1H, J=6Hz, J=16Hz), 6.26 (dd, 1H, J=1.5Hz, J=16Hz), 7.0–8.0 (m, 13H)

II-25
H-NMR (in $CDCl_3$) δ ppm: 0.96 (d, 6H, J=6Hz), 1.26 (t, 3H, J=7Hz), 1.8–2.4 (m, 1H), 2.43 (d, 2H, J=6Hz), 2.6–2.9 (m, 1H), 2.88 (d, 2H, J=7Hz), 3.36 (s, 2H), 4.14 (q, 2H, J=7Hz), 4.3–4.7 (m, 1H), 5.0–5.5 (m, 1H), 6.3–6.7 (m, 1H), 6.9–8.1 (m, 8H)

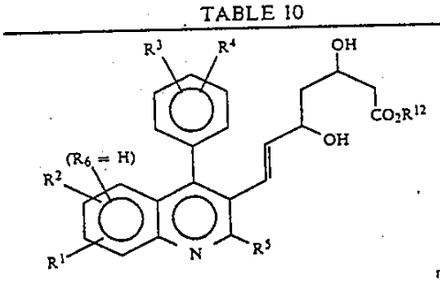
II-26
H-NMR (in $CDCl_3$) δ ppm: 1.25 (t, 3H, J=7Hz), 1.32 (d, 6H, J=6Hz), 2.32 (s, 3H), 2.39 (d, 2H, J=7Hz), 2.6–3.1 (m, 1H), 3.36 (s, 2H), 3.41 (Heptaplet, 1H, J=6Hz), 4.11 (q, 2H, J=7Hz), 4.3–4.7 (m, 1H), 5.0–5.5 (m, 1H), 6.3–6.7 (m,1H), 6.8–7.9 (m, 7H)

II-27
H-NMR (in $CDCl_3$) δ ppm: 0.8–1.5 (m, 4H), 1.26 (t, 3H, J=7Hz), 2.0–2.9 (m, 4H), 3.42 (s, 2H), 3.71 (s, 3H), 4.00 (s, 3H), 4.20 (q, 2H, J=7Hz), 4.4–4.8 (m, 1H), 5.3–5.8 (m, 1H), 6.4–6.9 (m, 1H), 6.58 (s, 1H), 7.0–7.5 (m, 5H)

In the same manner as in Example 1-g, compounds I-12 to I-127 were prepared.

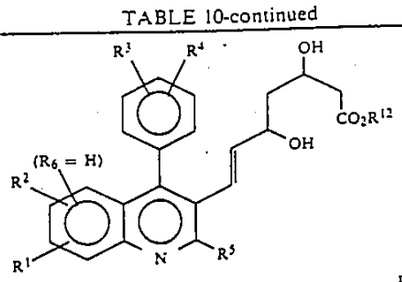
TABLE 10

I-1



Compound	R^1	R^2	R^3	R^4	R^5	R^{12}	m.p.(°C.) Mass spectrum
I-12	H	H	4-F	H	CH_3	C_2H_5 M/e	oil 423.292 264.249
I-13	H	H	H	H	CH_3	C_2H_5	92–105
I-14	H	H	H	H	i-Pr	C_2H_5	97–100
I-15	6-Cl	H	H	H	CH_3	C_2H_5	oil
I-16	6-Cl	H	H	H	i-Pr	C_2H_5	oil

TABLE 10-continued



I-1

Compound	R^1	R^2	R^3	R^4	R^5	R^{12}	m.p.(°C.) Mass spectrum
I-17	H	H	2-F	H	i-Pr	C_2H_5	oil
I-18	7-Me	H	H	H	i-Pr	C_2H_5	oil
I-19	H	H	4-Cl	H	i-Pr	C_2H_5	98–104
I-110	H	H	4-OMe	H	i-Pr	C_2H_5	94–98
I-111	H	H	4-Me	H	i-Pr	C_2H_5	79–85
I-112	6-Cl	H	2-Cl	H	i-Pr	C_2H_5	oil
I-113	H	H	4-CF_3	H	i-Pr	C_2H_5	117–128
I-114	H	H	3-Me	4-F	i-Pr	C_2H_5	85–92
I-115	H	H	3-Me	5-Me	i-Pr	C_2H_5	oil
I-116	6-OMe	7-OMe	4-F	H	i-Pr	C_2H_5	gum
I-117	H	H	4-F	H	C_2H_5	C_2H_5	oil
I-118	H	H	4-F	H	n-Pr	C_2H_5	oil
I-119	6-Cl	H	4-F	H	i-Pr	C_2H_5	79–82
I-120	H	H	4-F	H	c-Pr	C_2H_5	100–104
I-121	H	H	4-OPh	H	i-Pr	C_2H_5	oil
I-122	6-Cl	8-Cl	4-F	H	i-Pr	C_2H_5	133–143
I-123	6-Cl	H	H	H	Ph	C_2H_5	gum
I-124	6-Cl	H	H	H	c-Pr	C_2H_5	oil
I-125	H	H	4-F	H	sec-Bu	C_2H_5	oil
I-126	6-Me	H	4-F	H	i-Pr	C_2H_5	oil
I-127	6-OMe	7-OMe	4-F	H	c-Pr	C_2H_5	gum

I-17 H-NMR (in $CDCl_3$) δ ppm:
1.29(t,3H,J=7Hz), 1.40(d,6H,J=6Hz)
1.4–1.7(m,2H), 2.3–2.5(m,2H)
2.9–3.2(m,1H), 3.49(Heptaplet,1H,J=6Hz)
3.5–3.8(m,1H), 3.9–4.5(m,2H)
4.20(q,2H,J=7Hz), 5.2–5.7(m,1H)
6.5–6.9(m,1H), 7.0–8.2(m,8H)

I-18 H-NMR (in $CDCl_3$) δ ppm:
1.0–1.4(m,2H), 1.31(t,3H,J=7Hz)
1.39(d,6H,J=6Hz), 2.3–2.5(m,2H)
2.52(s,3H), 3.1–3.4(m,1H)
3.48(Heptaplet,1H,J=6Hz), 3.5–3.8(m,1H)
3.8–4.1(m,1H), 4.20(q,2H,J=7Hz)
4.2–4.5(m,1H), 5.2–5.6(m,1H)
6.4–6.8(m,1H), 7.0–8.0(m,8H)

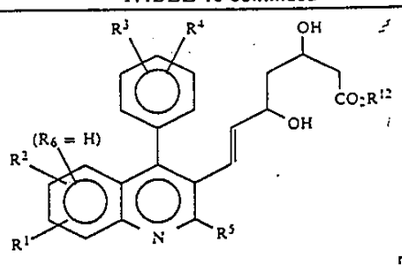
I-19 H-NMR (in $CDCl_3$) δ ppm:
1.29(t,3H,J=7Hz), 1.38(d,6H,J=6Hz)
1.4–1.8(m,2H), 2.3–2.5(m,2H)
3.2–3.4(m,1H), 3.49(Heptaplet,1H,J=6Hz)
3.6–3.8(m,1H), 3.9–4.2(m,1H)
4.20(q,2H,J=7Hz), 4.3–4.5(m,1H)
5.2–5.5(m,1H), 6.5–6.8(m,1H)
7.0–8.2(m,8H)

I-110 H-NMR (in $CDCl_3$) δ ppm:
1.29(t,3H,J=7Hz), 1.40(d,6H,J=6Hz)
1.5–1.6(m,2H), 2.3–2.5(m,2H)
2.8–3.0(m,1H), 3.4–3.6(m,1H)
3.52(Heptaplet,1H,J=6Hz), 3.88(s,3H)
3.9–4.1(m,1H), 4.20(q,2H,J=7Hz)
4.3–4.5(m,1H), 5.3–5.5(m,1H)
6.5–6.7(m,1H), 6.9–8.1(m,8H)

I-111 H-NMR (in $CDCl_3$) δ ppm:
1.30(t,3H,J=7Hz), 1.3–1.5(m,2H)
1.39(d,6H,J=6Hz), 2.3–2.5(m,2H)
2.43(s,3H), 2.8–3.0(m,1H)
3.50(Heptaplet,1H,J=6Hz), 3.5–3.7(m,1H)
3.9–4.2(m,1H), 4.19(q,2H,J=7Hz)
4.2–4.5(m,1H), 5.2–5.6(m,1H)
6.4–6.8(m,1H), 6.9–8.2(m,8H)

I-112 H-NMR (in $CDCl_3$) δ ppm:
1.30(t,3H,J=7Hz), 1.3–1.6(m,2H)
1.37(d,6H,J=6Hz), 2.3–2.5(m,2H)
2.9–3.2(m,1H), 3.47(Heptaplet,1H,J=6Hz)
3.5–3.8(m,1H), 3.9–4.1(m,1H)

TABLE 10-continued



I-1

Compound	R^1	R^2	R^3	R^4	R^5	R^{12}	m.p.(°C.) Mass spectrum

4.19(q,2H,J=7Hz), 4.2–4.5(m,1H)
5.3–5.7(m,1H), 6.5–6.8(m,1H)
7.1–8.1(m,7H)

I-113 H-NMR (in $CDCl_3$) δ ppm:
1.0–1.3(m,2H), 1.30(t,3H,J=7Hz)
1.40(d,6H,J=6Hz), 2.3–2.4(m,2H)
3.3–3.5(m,1H), 3.49(Heptaplet,1H,J=6Hz)
3.6–3.7(m,1H), 3.9–4.1(m,1H)
4.18(q,2H,J=7Hz), 4.2–4.5(m,1H)
5.1–5.5(m,1H), 6.5–6.8(m,1H)
7.2–8.2(m,8H)

I-114 H-NMR (in $CDCl_3$) δ ppm:
1.2–1.4(m,2H), 1.30(t,3H,J=7Hz)
1.39(d,6H,J=6Hz), 2.32(bs,3H)
2.3–2.5(m,2H), 3.0–3.3(m,1H)
3.50(Heptaplet,1H,J=6Hz), 3.6–3.8(m,1H)
3.8–4.1(m,1H), 4.20(q,2H,J=7Hz)
4.3–4.6(m,1H), 5.2–5.6(m,1H)
6.5–6.8(m,1H), 7.0–8.2(m,7H)

I-115 H-NMR(in $CDCl_3$) δ ppm:
1.1–1.4(m,2H), 1.30(t,3H,J=7Hz)
1.40(d,6H,J=6Hz), 2.2–2.5(m,2H)
2.35(s,6H), 2.7–3.1(m,1H)
3.51(Heptaplet,1H,J=6Hz), 3.6–3.7(m,1H)
3.8–4.1(m,1H), 4.20(q,2H,J=7Hz)
4.2–4.6(m,1H), 5.2–5.6(m,1H)
6.4–6.8(m,1H), 6.8–8.2(m,7H)

I-116 H-NMR (in $CDCl_3$) δ ppm:
1.30(t,3H,J=7Hz), 1.37(d,6H,J=6Hz)
1.5–1.8(m,2H), 2.3–2.5(m,2H)
2.9–3.2(m,1H), 3.46(Heptaplet,1H,J=6Hz)
3.6–3.8(m,1H), 3.75(s,3H)
3.9–4.1(m,1H), 4.07(s,3H)
4.20(q,2H,J=7Hz), 4.2–4.5(m,1H)
5.1–5.5(m,1H), 6.4–6.8(m,2H)
7.1–7.5(m,5H)

I-117 H-NMR (in $CDCl_3$) δ ppm:
1.30(t,3H,J=7Hz), 1.37(t,3H,J=7Hz)
1.4–1.7(m,2H), 2.2–2.6(m,2H)
2.8–3.2(m,3H), 3.6–3.9(m,1H)
3.9–4.7(m,4H), 5.2–5.7(m,1H)
6.3–6.7(m,1H) 7.0–8.2(m,8H)

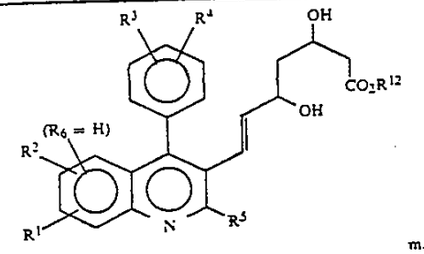
I-118 H-NMR (in $CDCl_3$) δ ppm:
1.01(t,3H,J=7Hz), 1.27(t,3H,J=7Hz)
1.4–2.1(m,4H), 2.3–2.6(m,2H)
2.8–3.3(m,3H), 3.6–3.8(m,1H)
3.9–4.1(m,1H), 4.18(q,2H,J=7Hz)
4.2–4.5(m,1H) 5.2–5.6(m,1H)
6.4–6.7(m,1H), 7.0–8.1(m,8H)

I-119 H-NMR (in $CDCl_3$) δ ppm:
1.2–1.5(m,2H), 1.31(t,3H,J=7Hz)
1.37(d,6H,J=7Hz), 2.3–2.6(m,2H)
3.0–3.4(m,1H), 3.49(Heptaplet,1H,J=6Hz)
3.6–3.8(m,1H), 3.8–4.2(m,1H)
4.20(q,2H,J=7Hz), 4.3–4.5(m,1H)
5.2–5.6(m,1H), 6.4–6.8(m,1H)
7.0–8.1(m,7H)

I-120 H-NMR (in $CDCl_3$) δ ppm:
0.8–1.8(m,6H), 1.30(t,3H,J=7Hz)
2.1–2.6(m,3H), 2.9–3.3(m,1H)
3.4–3.7(m,1H), 3.8–4.6(m,2H)
4.20(q,2H,J=7Hz), 5.4–5.8(m,1H)
6.4–6.8(m,1H), 6.8–8.0(m,8H)

I-121 H-NMR (in $CDCl_3$) δ ppm:
1.29(t,3H,J=7Hz), 1.39(d,6H,J=6Hz)
1.4–1.9(m,2H), 2.3–2.5(m,2H)

TABLE 10-continued

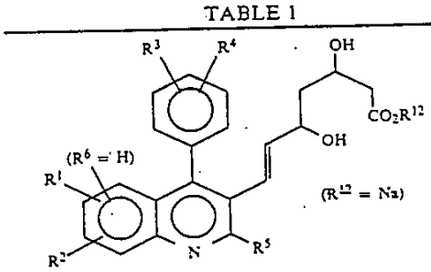


I-1

Compound	R^1	R^2	R^3	R^4	R^5	R^{12}	m.p.(°C.) Mass spectrum
		2.7–3.2(m,1H), 3.51(Heptaplet,1H,J=6Hz) 3.6–3.8(m,1H), 3.9–4.2(m,1H) 4.19(q,2H,J=7Hz), 4.3–4.6(m,1H) 5.2–5.6(m,1H), 6.4–6.8(m,1H) 6.9–8.2(m,13H)					
I-122		H-NMR (in $CDCl_3$) δ ppm: 1.1–1.8(m,2H), 1.31(t,3H,J=7Hz) 1.41(d,6H,J=6Hz), 2.3–2.5(m,2H) 2.9–3.4(m,1H), 3.50(Heptaplet,1H,J=6Hz) 3.6–3.8(m,1H), 3.9–4.5(m,2H) 4.20(q,2H,J=7Hz), 5.2–5.6(m,1H) 6.4–6.8(m,1H), 7.1–7.3(m,5H) 7.72(d,1H,J=6Hz)					
I-123		H-NMR (in $CDCl_3$) δ ppm: 0.8–1.5(m,2H), 1.29(t,3H,J=7Hz) 2.2–2.4(m,2H), 2.6–2.9(m,1H) 3.2–3.6(m,1H), 3.7–4.3(m,2H) 4.17(q,2H,J=7Hz), 5.0–5.4(m,1H) 6.1–6.5(m,1H), 7.0–8.2(m,13H)					
I-124		H-NMR (in $CDCl_3$) δ ppm: 0.8–1.8(m,6H), 1.29(t,3H,J=7Hz), 2.2–2.6(m,3H), 2.8–3.2(m,1H), 3.3–3.7(m,1H), 3.9–4.5(m,2H), 4.19(q,2H,J=7Hz), 5.4–5.8(m,1H), 6.5–6.8(m,1H), 7.1–8.0(m,8H),					
I-125		H-NMR (in $CDCl_3$) δ ppm: 0.94(d,6H,J=6Hz), 1.0–1.7(m,3H), 1.27(t,3H,J=7Hz), 1.9–2.5(m,3H), 2.90(d,2H,J=7Hz), 3.3–4.4(m,3H), 4.12(q,2H,J=7Hz), 5.0–5.5(m,1H), 6.2–6.7(m,1H), 6.9–8.0(m,8H),					
I-126		H-NMR (in $CDCl_3$) δ ppm: 1.0–1.6(m,3H), 1.21(t,3H,J=7Hz), 1.34(d,6H,J=6Hz), 2.34(s,3H), 2.37(d,2H,J=7Hz), 2.9–3.7(m,2H), 3.8–4.5(m,2H), 4.15(q,2H,J=7Hz), 5.0–5.5(m,1H), 6.3–6.7(m,1H), 6.9–8.0(m,7H),					
I-127		H-NMR (in $CDCl_3$) δ ppm: 0.8–1.9(m,8H), 1.29(t,3H,J=7Hz), 2.1–2.6(m,3H), 2.8–3.2(m,1H), 3.72(s,3H), 4.02(s,3H), 4.19(q,2H,J=7Hz), 4.3–4.6(m,1H), 5.4–5.8(m,1H), 6.4–6.8(m,1H), 6.56(s,1H), 7.0–7.4(m,5H)					

In the same manner as in Example 2, compounds I-52 to I-527 were prepared.

TABLE 1



I-5

Compound	R^1	R^2	R^3	R^4	R^5	R^{12}	m.p. (°C.)
I-52	H	H	4-F	H	CH_3	Na	135–142 (decomposed)
I-53	H	H	H	H	CH_3	Na	130–132 (decomposed)
I-54	H	H	H	H	i-Pr	Na	196–197 (decomposed)
I-55	6-Cl	H	H	H	CH_3	Na	211–215 (decomposed)
I-56	6-Cl	H	H	H	i-Pr	Na	195–198 (decomposed)
I-57	H	H	2-F	H	i-Pr	Na	193–201 (decomposed)
I-58	7-Me	H	H	H	i-Pr	Na	170–175 (decomposed)
I-59	H	H	4-Cl	H	i-Pr	Na	193–202 (decomposed)
I-510	H	H	4-OMe	H	i-Pr	Na	178–193 (decomposed)
I-511	H	H	4-Me	H	i-Pr	Na	187–200 (decomposed)
I-512	6-Cl	H	2-Cl	H	i-Pr	Na	203–209 (decomposed)
I-513	H	H	4-CF_3	H	i-Pr	Na	200–212 (decomposed)
I-514	H	H	3-Me	4-F	i-Pr	Na	195–200 (decomposed)
I-515	H	H	3-Me	5-Me	i-Pr	Na	192–197 (decomposed)
I-516	6-OMe	7-OMe	4-F	H	i-Pr	Na	239–245 (decomposed)
I-517	H	H	4-F	H	C_2H_5	Na	230–237 (decomposed)
I-518	H	H	4-F	H	n-Pr	Na	193–200 (decomposed)
I-519	6-Cl	H	4-F	H	i-Pr	Na	193–198 (decomposed)
I-520	H	H	4-F	H	c-Pr	Na	197–199 (decomposed)
I-521	H	H	4-OPh	H	i-Pr	Na	180–189 (decomposed)
I-522	6-Cl	8-Cl	4-F	H	i-Pr	Na	183–187 (decomposed)
I-523	6-Cl	H	H	H	Ph	Na	190–196 (decomposed)
I-524	6-Cl	H	H	H	c-Pr	Na	204–210 (decomposed)
I-525	H	H	4-F	H	sec-Bu	Na	—
I-526	6-Me	H	4-F	H	i-Pr	Na	204–208 (decomposed)
I-527	6-OMe	7-OMe	4-F	H	c-Pr	Na	234–238 (decomposed)

I-57 H-NMR(in DMSO-d^6) δ ppm:
0.9–1.2(m, 2H), 1.37(d, 6H, J=7Hz)
1.6–2.1(m, 2H), 3.48(Heptaplet, 1H, J=6Hz)

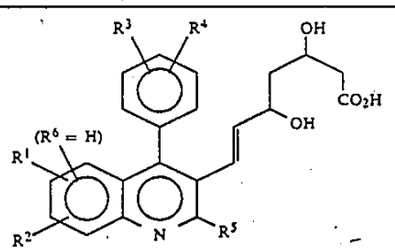
TABLE 1-continued

	3.7–4.3(m, 4H), 5.3–5.6(m, 1H)
	6.4–6.7(m, 1H), 7.1–8.1(m, 8H)
I-58	H-NMR(in DMSO-d^6) δ ppm:
	0.9–1.2(m, 2H), 1.31(d, 6H, J=7Hz)
	1.7–2.2(m, 2H), 2.50(s, 3H)
	3.3–4.5(m, 5H), 5.2–5.6(m, 1H)
	6.3–6.6(m, 1H), 7.1–7.9(m, 8H)
I-59	H-NMR(in DMSO-d^6) δ ppm :
	0.9–1.3(m, 2H), 1.33(d, 6H, J=7Hz)
	1.6–2.2(m, 2H), 3.48(Heptaplet, 1H, J=7Hz)
	3.5–4.6(m, 4H), 5.2–5.6(m, 2H)
	6.3–6.6(m, 1H), 7.1–8.1(m, 8H)
I-510	H-NMR(in DMSO-d^6) δ ppm:
	1.0–1.3(m, 2H), 1.32(d, 6H, J=7Hz)
	1.6–2.2(m, 2H), 3.0–3.8(m, 4H)
	3.86(s, 3H), 4.0–4.3(m, 1H)
	5.3–5.6(m, 1H), 6.3–6.6(m, 1H)
	6.9–8.1(m, 8H)
I-511	H-NMR(in DMSO-d^6) δ ppm:
	0.9–1.3(m, 2H), 1.33(d, 6H, J=7Hz)
	1.7–2.1(m, 2H), 2.41(s, 3H)
	3.2–4.3(m, 5H), 5.3–5.6(m, 1H)
	6.3–6.6(m, 1H), 7.0–8.3(m, 8H)
I-512	H-NMR(in DMSO-d^6) δ ppm:
	0.9–1.3(m, 2H), 1.33(d, 6H, J=7Hz)
	1.6–2.2(m, 2H), 3.1–3.8(m, 3H)
	3.48(heptaplet, 1H, J=7Hz), 3.9–4.2(m, 1H)
	5.3–5.7(m, 1H), 6.3–6.7(m, 1H)
	7.0–8.1(m, 7H)
I-513	H-NMR(in DMSO-d^6) δ ppm:
	0.8–1.3(m, 2H), 1.34(d, 6H, J=7Hz)
	1.6–2.2(m, 2H), 2.7–3.9(m, 3H)
	3.49(Heptaplet, 1H, J=7Hz), 3.9–4.3(m, 1H)
	5.2–5.6(m, 1H), 6.3–6.7(m, 1H)
	7.1–8.1(m, 8H)
I-514	H-NMR(in DMSO-d^6) δ ppm:
	0.9–1.3(m, 2H), 1.35(d, 6H, J=7Hz)
	1.7–2.1(m, 2H), 2.30(d, 3H, J=2Hz)
	3.0–3.8(m, 3H), 3.51(Heptaplet, 1H, J=7Hz)
	3.9–4.3(m, 1H), 5.3–5.6(m, 1H)
	6.3–6.6(m, 1H), 6.9–8.1(m, 7H)
II-515	H-NMR(in DMSO-d^6) δ ppm:
	1.0–1.2(m, 2H), 1.35(d, 6H, J=7Hz)
	1.6–2.2(m, 2H), 2.35(s, 6H)
	3.0–3.8(m, 3H), 3.51(Heptaplet, 1H, J=7Hz)
	4.0–4.3(m, 1H), 5.3–5.6(m, 1H)
	6.3–6.6(m, 1H), 6.8–8.0(m, 7H)
I-516	H-NMR(in DMSO-d^6) δ ppm:
	0.9–1.3(m, 2H), 1.31(d, 6H, J=7Hz)
	1.7–2.0(m, 2H), 3.2–3.7(m, 4H)
	3.62(s, 3H), 3.9–4.2(m, 1H)
	3.94(s, 3H), 5.1–5.5(m, 1H)
	6.2–6.6(m, 1H), 7.0–7.5(m, 6H)
I-517	H-NMR(in DMSO-d^6) δ ppm:
	0.9–1.5(m, 2H), 1.34(t, 3H, J=7Hz)
	1.6–2.2(m, 2H), 2.7–3.4(m, 4H)
	3.6–4.3(m, 2H), 5.2–5.7(m, 1H)
	6.1–6.6(m, 1H), 6.9–8.1(m, 8H)
I-518	H-NMR(in DMSO-d^6) δ ppm:
	0.8–1.3(m, 2H), 1.01(t, 3H, J=7Hz)
	1.6–2.1(m, 4H), 2.7–3.8(m, 5H)
	3.9–4.3(m, 1H), 5.2–5.7(m, 1H)
	6.3–6.6(m, 1H), 7.1–8.1(m, 8H)
I-519	H-NMR(in DMSO-d^6) δ ppm:
	0.9–1.3(m, 2H), 1.33(d, 6H, J=7Hz)
	1.6–2.2(m, 2H), 2.9–3.9(m, 3H)
	3.49(Heptaplet, 1H, J=7Hz), 4.0–4.3(m, 1H)
	5.3–5.6(m, 1H), 6.3–6.6(m, 1H)
	7.2–8.1(m, 7H)
I-520	H-NMR(in DMSO-d^6) δ ppm:
	0.8–1.5(m, 6H), 1.7–2.2(m, 2H)
	2.3–2.7(m, 1H), 3.0–3.9(m, 3H)
	4.0–4.3(m, 1H), 5.5–5.8(m, 1H)
	6.4–6.7(m, 1H), 7.2–8.0(m, 8H)
I-521	H-NMR(in DMSO-d^6) δ ppm:
	0.9–1.5(m, 2H), 1.36(d, 6H, J=7Hz)
	1.7–2.3(m, 2H), 3.0–3.9(m, 3H)
	3.50(Heptaplet, 1H, J=6Hz), 4.0–4.3(m, 1H)
	5.2–5.6(m, 1H), 6.4–6.7(m, 1H)
	7.0–8.1(m, 13H)
I-522	H-NMR(in DMSO-d^6) δ ppm:
	0.8–1.3(m, 2H), 1.37(d, 6H, J=7Hz)
	1.6–2.2(m, 2H), 3.1–3.9(m, 3H)
	3.51(Heptaplet, 1H, J=7Hz), 4.0–4.3(m, 1H)
	5.3–5.7(m, 1H), 6.3–6.7(m, 1H)
	7.1–8.0(m, 6H)
I-523	H-NMR(in DMSO-d^6) δ ppm:
	0.8–1.4(m, 2H), 1.6–2.1(m, 2H)
	2.9–3.7(m, 3H), 3.7–4.1(m, 1H)
	5.1–5.4(m, 1H), 6.1–6.4(m, 1H)
	7.1–8.2(m, 13H)
I-524	H-NMR(in DMSO-d^6) δ ppm:
	0.8–1.5(m, 5H), 1.6–2.2(m, 2H)
	2.3–2.7(m, 2H), 3.0–3.8(m, 3H)
	3.9–4.3(m, 1H), 5.4–5.8(m, 1H)
	6.3–6.6(m, 1H), 7.0–8.0(m, 8H)
I-525	H-NMR(in DMSO-d^6) δ ppm:
	0.9–1.6(m, 2H), 0.96(d, 6H, J=6Hz)
	1.7–2.6(m, 3H), 2.89(d, 2H, J=7Hz)
	3.0–3.8(m, 3H), 3.9–4.2(m, 1H)
	5.2–5.6(m, 1H), 6.2–6.6(m, 1H)
	7.1–8.1(m, 8H)
I-526	H-NMR(in DMSO-d^6) δ ppm:
	1.30(d, 6H, J=7Hz), 1.7–2.0(m, 2H),
	2.34(s, 3H), 2.4–2.6(m, 1H),
	3.0–3.3(m, 2H), 3.3–3.8(m, 3H)
	3.9–4.2(m, 1H), 5.2–5.6(m, 1H)
	6.3–6.6(m, 1H), 7.0–8.0(m, 7H)
I-527	H-NMR(in DMSO-d^6) δ ppm:
	0.7–1.5(m, 5H), 1.8–2.2(m, 2H),
	2.2–2.6(m, 2H), 3.1–3.3(m, 2H),
	3.59(s, 3H), 3.9–4.2(m, 2H),
	3.91(s, 3H), 5.4–5.7(m, 1H)
	6.3–6.6(m, 1H), 6.52(s, 1H),
	7.0–7.4(m, 5H)

In the same manner as in Example 3, compounds I-22 to I-26 can be prepared.

TABLE 12

I-2

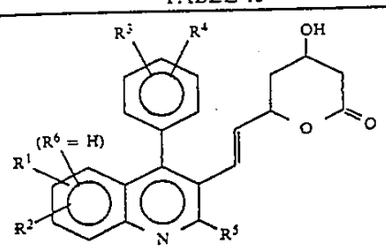


Compound	R^1	R^2	R^3	R^4	R^5
I-22	H	H	4-F	H	CH_3
I-23	H	H	H	H	CH_3
I-24	H	H	H	H	i-Pr
I-25	6-Cl	H	H	H	CH_3
I-26	6-Cl	H	H	H	i-Pr

In the same manner as in Example 4, compounds I-32 to I-36 can be prepared.

TABLE 13

I-3



Compound	R^1	R^2	R^3	R^4	R^5
I-32	H	H	4-F	H	CH_3
I-33	H	H	H	H	CH_3
I-34	H	H	H	H	i-Pr
I-35	6-Cl	H	H	H	CH_3
I-36	6-Cl	H	H	H	i-Pr

FORMULATION EXAMPLE 1

Tablets	
Compound I-51	1.0 g
Lactose	5.0 g
Crystal cellulose powder	8.0 g
Corn starch	3.0 g
Hydroxypropyl cellulose	1.0 g
CMC-Ca	1.5 g
Magnesium stearate	0.5 g
Total	20.0 g

The above components were mixed by a usual method and then tabletted to produce 100 tablets each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 2

Capsules	
Compound I-51	1.0 g
Lactose	3.5 g
Crystal cellulose powder	10.0 g
Magnesium stearate	0.5
Total	15.0 g

The above components were mixed by a usual method and then packed in No. 4 gelatin capsules to obtain 100 capsules each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 3

Soft capsules	
Compound I-51	1.00 g
PEG (polyethylene glycol) 400	3.89 g
Saturated fatty acid triglyceride	15.00 g
Peppermint oil	0.01 g
Polysorbate 80	0.10 g
Total	20.00 g

The above components were mixed and packed in No. 3 soft gelatin capsules by a usual method to obtain 100 soft capsules each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 4

Ointment	
Compound I-51	1.0 g (10.0 g)
Liquid paraffin	10.0 g (10.0 g)
Cetanol	20.0 g (20.0 g)
White vaseline	68.4 g (59.4 g)
Ethylparaben	0.1 g (0.1 g)
L-menthol	0.5 g (0.5 g)
Total	100.0 g

The above components were mixed by a usual method to obtain a 1% (10%) ointment.

FORMULATION EXAMPLE 5

Suppository	
Compound I-51	1.0 g
Witepsol H15*	46.9 g
Witepsol W35*	52.0 g
Polysorbate 80	0.1 g
Total	100.0 g

*Trademark for triglyceride compound

The above components were melt-mixed by a usual method and poured into suppository containers, followed by cooling for solidification to obtain 100 suppositories of 1 g each containing 10 mg of the active component.

FORMULATION EXAMPLE 6

Injection formulation	
Compound I-51	1 mg
Distilled water for injection formulation	5 ml

The formulation is prepared by dissolving the compound in the distilled water whenever it is required.

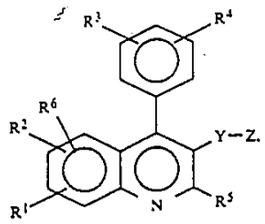
FORMULATION EXAMPLE 7

Granules	
Compound I-51	1.0 g
Lactose	6.0 g
Crystal cellulose powder	6.5 g
Corn starch	5.0 g
Hydroxypropyl cellulose	1.0 g
Magnesium stearate	0.5 g
Total	20.0 g

The above components were granulated by a usual method and packaged to obtain 100 packages each containing 200 mg of the granules so that each package contains 10 mg of the active ingredient.

We claim:

1. A compound of the formula



wherein R^1 is hydrogen, 5-fluoro, 6-fluoro, 7-fluoro, 8-fluoro, 5-chloro, 6-chloro, 7-chloro, 8-chloro, 5-bromo, 6-bromo, 7-bromo, 8-bromo, 5-methyl, 6-methyl, 7-methyl, 8-methyl, 5-methoxy, 6-methoxy, 7-methoxy, 8-methoxy, 5-trifluoromethyl, 6-trifluoromethyl, 7-trifluoromethyl, 8-trifluoromethyl, 6-trifluoromethoxy, 6-difluoromethoxy, 8-hydroxyethyl, 5-hydroxy, 6-hydroxy, 7-hydroxy, 8-hydroxy, 6-ethyl, 6-n-butyl or 7-dimethylamino;

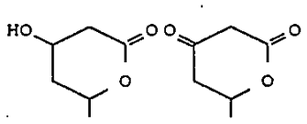
R^2, R^3 and R^6 are hydrogen,

R^4 is hydrogen, 4'-chloro or 4'-fluoro,

R^5 is i-propyl or cyclopropyl,

Y is (E) —CH=CH—, and

Z is



—$CH(OH)CH_2CH(OH)CH_2CO_2R^{12}$, —$CH(OH)CH_2C(O)CH_2CO_2R^{12}$ or —$CH(OH)CH_2C(OR^{13})_2CH_2CO_2R^{12}$, wherein R^{12} is hydrogen, physiologically hydrolyzable alkyl, NH_4, sodium, potassium ½ calcium, or a hydrate of lower alkylamine, di-lower alkylamine or tri-lower alkylamine; two R^{13} are independently primary or secondary C_{1-6} alkyl; or two R^{13} together form —$(CH_2)_2$— or —$CH_2)_3$—.

2. The compound (E)-3,5-dihydroxy-7[5',6'-(1'',3''-butadienyl)-4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

3. The compound (E)-3,5-dihydroxy-7-[6',7'-(1'',3''-butadienyl)-4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-6'-chloro-quinolin-3,-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

4. The compound (E)-3,5-dihydroxy-7-[7',8'-(1'',3''-butadienyl)-4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

5. The compound (E)-3,5-dihydroxy-7-[5',6'-(1'',3''-butadienyl)-2'-cyclopropyl-4'-(4''-fluorophenyl)-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

6. The compound (E)-3,5-dihydroxy-7-[5',6'-(1'',3''-butadienyl)-2'-cyclopropyl-4'-(4''-fluorophenyl)quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt of C_{1-3} alkyl ester of the carboxylic acid.

7. The compound (E)-3,5-dihydroxy-7-[7',8'-(1'',3''-butadienyl)-2'-cyclopropyl-4'-(4''-fluorophenyl)-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

* * * * *

Case No. 600-[illegible]01/CONT/Int.(3)
Patent

FYI

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE #21
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES JUN 15 1992

RECEIVED IN
BOX INTERFERENCE

WATTANASIN
v.
PICARD et al.
v.
FUJIKAWA et al.

Interference No. 102,648
Examiner-in-Chief: M. Sofocleous

CONTINGENT PRELIMINARY MOTION UNDER 37 CFR 1.633(e)
BY THE PARTY WATTANASIN

Contingent on the denial of the party Wattanasin's Preliminary Motion under 37 CFR §1.635 being filed concurrently herewith, the party Wattanasin moves for declaration of an additional interference between the party Wattanasin's involved application in the present interference and U.S. Patent No. 5,011,930, for the reasons stated in the aforementioned Rule 635 motion.

Count 1 of the present interference is proposed for the additional interference.

Alternatively, contingent on the granting of the party Wattanasin's Rule 633(c)(1) Motion being filed concurrently herewith, Proposed Substitute Count 1 is proposed for the additional interference.

Claim 1-7 and 10 of Wattanasin are designated to correspond to Count 1 (or Proposed Substitute Count 1).

Claim 1 of Fujikawa et al. '930 should be designated to correspond to Count 1 (or Proposed Substitute Count 1).

Remarks

Rule 633(e) does not specifically provide for a motion to institute the granting of an additional interference with another patent of an involved party.

However, in the event Wattanasin's concurrently filed Rule 635 Motion is denied, Rule 633 is being relied on to provide an alternative remedy to the party Wattanasin to fully adjudicate the subject matter in conflict with Fujikawa et al.

With respect to the present motion under Rule 633(e), notwithstanding Rule 637(e)((1)(vii), on the available evidence it is not believed possible to propose a count for the additional interference which defines a separate patentable invention from all counts of the present interference; and therefore the present count 1 of the present interference (or alternatively, the party Wattanasin's Proposed Substitute Count 1) is proposed to comprise the count in the requested interference.

The Remarks of the party Wattanasin in his Rule 635 Motion are otherwise hereby incorporated by reference.

Respectfully submitted,

Diane Furman 6/11/92

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

DEF:rmf
June 11, 1992

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

PRELIMINARY MOTION UNDER 37 CFR 1.633(e)
BY THE PARTY WATTANASIN

was served on counsel for the party Fujikawa et al., this 11th day of June, 1992, 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

Case No. 600-.101/CONT/Int.(4)
Patent

FYI

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

JUN 15 1992

#22 RECEIVED IN BOX INTERFERENCE

WATTANASIN
v.
PICARD et al.
v.
FUJIKAWA et al.

Interference No. 102,648
Examiner-in-Chief: M. Sofocleous

CONTINGENT PRELIMINARY MOTION FOR BENEFIT UNDER 37 CFR §1.633(f) BY THE PARTY WATTANASIN

Contingent on the granting of one or more of the party Wattanasin's preliminary motions being filed concurrently herewith, the party Wattanasin also moves to be accorded the benefit of parent application Serial No. 07/318,773 filed March 3, 1989, from which the involved application is a Rule 60 continuation.

This will certify that a complete copy of the file of Serial No. 07/318,773, except for documents filed under 37 CFR 1.131 or 1.608, is being concurrently served on the party Fujikawa et al. [37 CFR 1.637(f)(2)]

The parent application fulfills the four requirements of 35 USC §112 for at least one species of the involved application, and constitutes a constructive reduction to practice of Counts 1 and 2 (see, e.g., pages 33-35, 51-53 of the specification).

Respectfully submitted,

Diane Furman 6/11/92

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07986

DEF:rmf
June 11, 1992

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

CONTINGENT PRELIMINARY MOTION FOR BENEFIT UNDER 37 CFR §1.633(f) BY THE PARTY WATTANASIN

was served on counsel for the party Fujikawa et al., this 11th day of June, 1992, 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

PATENT
CASE NO. 600-7101/CONT.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

102648

In Re: WATTANASIN
Serial No.: 07/498,301
Filed: March 23, 1990
For: QUINOLINE ANALOGS OF MEVALONOLACTONE AND DERIVATIVES THEREOF

POWER TO INSPECT AND MAKE COPIES

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

Kindly permit Marian Schwartz, Ann Rutledge, Rosalie Jared, Somchay Chinyavong, Judy Valusek, James Jackson, Bobbie Judy, or Nancy Perry of Specialized Patent Services to inspect and make copies in the above noted matter, including recently declared Interference No. 102,648 in which said patent is involved.

Respectfully submitted,

June 19, 1992

SANDOZ CORP.
59 Route 10
E. Hanover, N.J. 07936

By Diane Furman 6/19/92
Diane E. Furman
Registration No. 31,104
(201) 503-7332

DEF:lcr

Encl.: postcard

#24

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
	:	**INTERFERENCE 102,648**
V.	:	**EXAMINER-IN-CHIEF:**
	:	**MICHAEL SOFOCLEOUS**
PICARD ET AL	:	
	:	
V.	:	
	:	
FUJIKAWA ET AL	:	

FUJIKAWA ET AL
OPPOSITION TO CONTINGENT
PRELIMINARY MOTION, 37 CFR §1.633(e)
AND PRELIMINARY MOTION UNDER 37 CFR §1.635

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231
BOX INTERFERENCE

SIR:

By Motion under 37 CFR §1.635 and by Contingent Preliminary Motion under 37 CFR §1.633(e), Wattanasin seeks designation of Claim 1 of Fujikawa et al U.S. Patent 5,011,930, as being in Interference with Claims 1-7 and 10 of Wattanasin, and corresponding to Wattanasin's proposed substitute Count, or the current Count, of the Interference. It appears, from the joint Motions, that Wattanasin does not care whether a separate

Interference is declared, or Claim 1 of the '930 Patent is designated as corresponding to the broad Count of the current Interference, just so long as it is designated in some fashion.

Wattanasin's Motion pursuant to 37 CFR §1.633(e) appears to run clearly against the holding in Gerk v. Cottringer, 17 USPQ 2d 1615 (POBAI 1990). Note in particular the holding therein that Rule 633(c)(3) is confined to patent claims of patent applications already involved in the Interference, and that Motions seeking relief not specifically provided for under Rule 633 are improper as Preliminary Motions, and the same relief cannot be obtained pursuant to Rule 635. By analogy, 37 CFR §1.633(e) which is expressly confined to patents involved in the Interference cannot be relied on by Wattanasin. Note, not even 37 CFR §1.633(c)(3) permits the Motion relied on.

Wattanasin specifically acknowledges that the relief sought is not provided for under Rule 633(e). The relief sought by Wattanasin under Rule 635 is not substantially different from the relief sought, and denied, in Gerk v. Cottringer, and accordingly, save for the stipulation, the Motion ought to be denied as well.

Specifically, Wattanasin acknowledges its Motion (either under Rule 633(e) or 635) is not provided for under Rule 633 at al. Motions which are in the nature of Preliminary Motions that are not

provided for under Rule 633(a)-(j) may not be brought, and must be dismissed.

> §1.633 would be rendered a nullity if every preliminary motion which did not comply with its requirements could avoid dismissal by being characterized as a motion under §1.635.

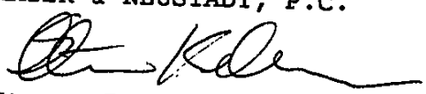
Theeuwes v. Bogentoft, 2 USPQ 2d 1378, 1379 (Comm. of Pats. 1987). See also, Gerk, 17 USPQ 2d at 1616. Clearly, a Preliminary Motion (or 2!) the movant acknowledges is not authorized by 37 CFR §1.633 must be dismissed.

Wattanasin's Motion under Rule 635 ought to be denied as well. Specifically, one cannot achieve, via Rule 635, relief governed by Rule 633. If that relief is not provided for, seeking the same via Rule 635 would render Rule 633, and its limitations a nullity. It is further noted that the Rule 635 Motion should be dismissed for failure to comply with 37 CFR §1.637(b). The Rule 635 Motion is devoid of any certification that agreement of opposing Counsel was sought. This is grounds for dismissal. M v. V, 6 USPQ 2d 1039

(POBAI 1987). For failure to comply with the requirements of the Rules, these Motions should be dismissed, and if not dismissed, denied.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

CERTIFICATE OF SERVICE

I hereby certify that true copies of:

1. **FUJIKAWA ET AL OPPOSITION TO CONTINGENT PRELIMINARY MOTION, 37 CFR §1.633(e) AND PRELIMINARY MOTION UNDER 37 CFR §1.635**

2. **FUJIKAWA ET AL OPPOSITION TO THE CONTINGENT PRELIMINARY MOTION FOR BENEFIT, 37 CFR §1.633(f)**

3. **FUJIKAWA ET AL MOTION FOR BENEFIT, 37 CFR §1.633(j)**

4. **FUJIKAWA ET AL OPPOSITION TO PRELIMINARY MOTION TO SUBSTITUTE A COUNT**

5. **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 first-class mail, postage prepaid, this 1st day of July, 1992.

STEVEN B. KELBER

#25

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
	:	INTERFERENCE 102,648
V.	:	EXAMINER-IN-CHIEF:
	:	MICHAEL SOFOCLEOUS
PICARD ET AL	:	
	:	
V.	:	
	:	
FUJIKAWA ET AL	:	

FUJIKAWA ET AL OPPOSITION TO THE
CONTINGENT PRELIMINARY MOTION FOR BENEFIT,
37 CFR §1.633(f)

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231
BOX INTERFERENCE

SIR:

In a one-page Motion, Wattanasin requests benefit of its parent application, U.S. Application Serial No. 07/318,773. It is unclear as to what Wattanasin seeks benefit for, as no specific Rule is identified, nor are the provisions of 37 CFR §1.637 complied with. In particular, 37 CFR §1.637(a) requires a statement of the precise relief requested, and a full statement of the reasons why the relief should be granted. Further, 37 CFR

§1.633(f) requires that the movant show that the earlier application constitutes a constructive reduction to practice of each Count. Neither of these Rules has been complied with by Wattanasin.

Initially, it is noted that Wattanasin has been granted benefit of its parent application. Accordingly, what further benefit is required? The Wattanasin Motion is apparently contingent upon the grant of certain other Motions filed concurrently. Wattanasin declines to identify which Motions those are. It is noted that Wattanasin has sought designation of Claim 1 of Fujikawa et al's U.S. Patent 5,011,930, which would not, if granted, be a basis for a grant of benefit already accorded. Accordingly, the premise of the Wattanasin Motion is confusing and unclear, and in violation of Rule 637(a). It should be dismissed.

Similarly, Wattanasin refers to the "four requirements of 35 U.S.C. §112, for at least one species of the involved application". Compliance with 35 U.S.C. §112, as to species (claimed? or of the Count?) of the involved application is irrelevant. Demonstration of the requirements of 35 U.S.C. §112, first paragraph, as to the Count of the Interference is required. Further, Wattanasin urges that the parent application constitutes a constructive reduction to practice of Counts I and II of the Interference. Again, as

Fujikawa et al have not moved to deny benefit of that parent application as to Counts I and II, this is not seen to be relevant.

Wattanasin has not requested benefit as to Wattanasin's proposed substitute Count I, and accordingly, cannot be granted benefit of the parent application as to that proposed substitute Count, if the Motion to substitute is granted. It would be highly inappropriate for Wattanasin to seek benefit in a Reply, and Fujikawa et al will move to strike any Reply that so requests benefit, in untimely fashion.

Dismissal or denial of the Contingent Preliminary Motion, to the extent benefit of the parent application is sought therein for anything other than current Counts I and II of the Interference is respectfully requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

CERTIFICATE OF SERVICE

I hereby certify that true copies of:

1. FUJIKAWA ET AL OPPOSITION TO CONTINGENT PRELIMINARY MOTION, 37 CFR §1.633(e) AND PRELIMINARY MOTION UNDER 37 CFR §1.635

2. FUJIKAWA ET AL OPPOSITION TO THE CONTINGENT PRELIMINARY MOTION FOR BENEFIT, 37 CFR §1.633(f)

3. FUJIKAWA ET AL MOTION FOR BENEFIT, 37 CFR §1.633(j)

4. FUJIKAWA ET AL OPPOSITION TO PRELIMINARY MOTION TO SUBSTITUTE A COUNT

5. 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 first-class mail, postage prepaid, this 1st day of July, 1992.

STEVEN B. KELBER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	INTERFERENCE 102,648
	:	EXAMINER-IN-CHIEF:
V.	:	MICHAEL SOFOCLEOUS
	:	
PICARD ET AL	:	
	:	
V.	:	
	:	
FUJIKAWA ET AL	:	

FUJIKAWA ET AL MOTION FOR BENEFIT,
37 CFR §1.633(j)

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231
BOX INTERFERENCE

SIR:

Pursuant to the provisions of the above-captioned Rule, and responsive to the Wattanasin Motions under Rule 633(e), Rule 635 and Rule 633(c)(1), Fujikawa et al hereby requests benefit of its priority applications, Japanese Patent Application Serial No. 207224, filed August 20, 1987; Japanese Patent Application Serial

No. 15585, filed January 26, 1988 and Japanese Patent Application Serial No. 193606, filed August 3, 1988, as to proposed substitute Count I of Wattanasin's Motion under 37 CFR §1.633(c)(1), and as to Claim 1 of U.S. Patent 5,011,930, if designated as corresponding to the Count of the Interference.

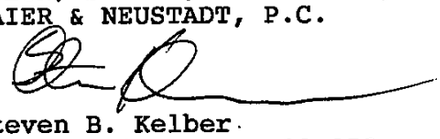
With respect to the proposed substitute Count, it should be noted that each of the Japanese Patent Applications, certified translations of which are of record, has ipsis verbis support, as well as a plurality of examples falling therewithin. Indeed, Wattanasin's Motion recognizes that proposed substitute Count I is identical to Fujikawa et al's Claim 1, as to which Fujikawa has already received the benefit of Japanese Patent Application 207224, filed August 20, 1987, and 15585, filed January 26, 1988. Further, on the grounds set forth with respect to Japanese Patent Application 193606, filed August 3, 1988, benefit as to current Counts I and II has already been requested, see Fujikawa et al Motion for Benefit, and benefit as to proposed substitute Counts is requested on the same grounds.

Clearly, in addition to literal support, each of the three Japanese Patent Applications identified has a plurality of examples

which constitute constructive reduction to practice of proposed substitute Count I. Benefit, should proposed substitute Count I be adopted, is respectfully requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



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Attorney for Fujikawa et al

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STEVEN B. KELBER

#27

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

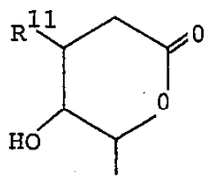
WATTANASIN	:	
	:	INTERFERENCE 102,648
V.	:	EXAMINER-IN-CHIEF:
	:	MICHAEL SOFOCLEOUS
PICARD ET AL	:	
	:	
V.	:	
	:	
FUJIKAWA ET AL	:	

FUJIKAWA ET AL
OPPOSITION TO PRELIMINARY MOTION
TO SUBSTITUTE A COUNT

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231
BOX INTERFERENCE

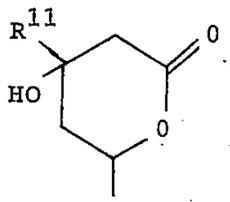
SIR:

Fujikawa et al oppose the Motion by Junior Party Wattanasin to substitute proposed substitute Count I for the current Count of the Interference, on the grounds that the identity set forth for moiety Z, the first structural formula thereof, is incorrect. On page 3 of the Motion, moiety Z is defined as being one of three ring structures, or a fourth linear structure, the first ring structure being:



a moiety not found in the claims of the parties. Further, Wattanasin advances, as grounds for its Preliminary Motion, the argument that the proposed substitute Count I is intended to

correspond to Claim 1 of the involved Fujikawa et al application. Claim 1 of the involved Fujikawa et al application does not present a cyclic structure of the type set forth above for moiety Z, or any other substituent. The closest corresponding ring structure, which does not appear in proposed Count I, is



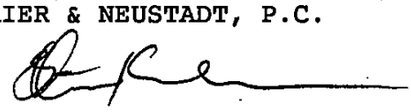
wherein the hydroxy substituent and the R^{11} substituent are on the same ring carbon atom. On this ground, Fujikawa et al opposes the Motion to substitute Count I.

Further, it is noted that Wattanasin's Motion does not address Count II. If substitute Count I is adopted, Count II will call for

the administration of a compound of current Count I, while those compounds may not be the subject of this Interference, if Wattanasin's Motion is granted. Accordingly, if the Motion is granted, it would be necessary to modify Count II to call for the administration of a compound from proposed substitute Count I, rather than current Count I of the Interference. On this ground as well, the Motion to substitute is opposed.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

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via first-class mail, postage prepaid, this 1st day of July, 1992.

STEVEN B. KELBER

Case No. 600-/101/CONT FYI
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE JUL 6 1992
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

RECEIVED IN
BOX INTERFERENCE

WATTANASIN

v.

PICARD et al.

v.

FUJIKAWA et al.

Interference No. 102,648

Examiner-in-Chief: M. Sofocleous

#28

OPPOSITION OF WATTANASIN TO FUJIKAWA ET AL. MOTION TO ADD COUNTS AND TO ADD CLAIMS TO WATTANASIN APPLICATION

SUMMARY

The party Wattanasin hereby opposes the party Fujikawa et al.'s motion to redefine the interference by adding proposed Counts 3 and 4.

The opposition is on the ground that the party Fujikawa et al. (hereinafter "Fujikawa") are not in compliance with 37 CFR 1.637(c).

More particularly, Fujikawa have not met the requirements of either or both of, sub-sections (c)(1)(iii) and c(1)(v) of Rule 637.

First, with respect to 37 CFR (c)(1)(iii), there is no written description in the involved application of Wattanasin, of the subject matter of species claims 11 and 12 which Fujikawa have proposed to Wattanasin to correspond to proposed Counts 3 and 4. Since the Fujikawa proposed claims 11 and 12 do not comply with 35 USC 112, written description requirement, Fujikawa have failed to meet the requirement of 37 CFR 1.637(c)(1)(iii) that proposed claims be patentable to the other party. Accordingly, given that

Fujikawa are unable to propose claims to Wattanasin corresponding to their proposed narrow counts, which also meet the written description requirement of 35 USC 112, the Fujikawa motion to redefine the interference should be denied.

Second, the Fujikawa proposed Counts 3 and 4 do not define a separately patentable invention from the subject matter of Counts 1 and 2 of this interference, as required by 37 CFR 1.637(c)(1)(v).

The proposed counts 3 and 4 cover a cyclopropyl (4-fluorophenyl)-substituted quinoline species within the generic scope of Counts 1 and 2 of the present interference.

As the basis for separate patentability of the counts, Fujikawa allege that the cyclopropyl (4-fluorophenyl) species exhibits "unexpected improvement" in HMG-CoA reductase inhibition activity compared to that of its closest structural isomer, i.e. the corresponding isopropyl spcies.

It is the position of Wattanasin, however, that: (1) the state of the art even prior to the earliest Fujikawa priority date included a recognition that improved HMG-CoA reductase inhibition activity was exhibited by both isopropyl- and cyclopropyl-bearing nitrogen-containing (4-fluorophenyl bearing) heterocycles; (2) that the Fujikawa comparative data submitted into the record do

not indicate an improvement in activity of cyclopropyl (4-fluorophenyl) over isopropyl (4-fluorophenyl) that rises to the level of "unexpectedness," particularly given the clear direction in the art to prepare the cyclopropyl (4-fluorophenyl); and (3) that the Fujikawa comparative data of record are deficient in not presenting a comparison of the cyclopropyl species of the Fujikawa proposed counts 3 and 4 at issue with other cyclopropyl species within counts 1 and 2 of this interference which are excluded from the scope of the Fujikawa proposed counts.

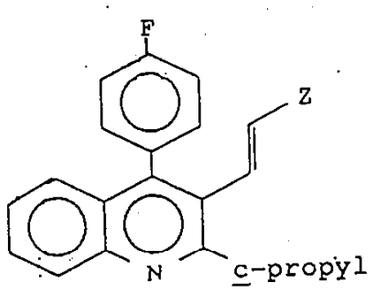
For the above reasons, which are more fully described below, Wattanasin requests that Fujikawa's motion be denied.

BACKGROUND

Fujikawa moved to redefine the present interference by adding proposed Counts 3 and 4.

Fujikawa's proposed Count 3 is directed in essence to a single species embraced by Count 1 (as well as Wattanasin's proposed Substitute Count 1). This species has the following structural formula:

(A)



(where Z is selected from the group consisting of 3,5-dihydroxy- substituted carboxylic acids, sodium and calcium salts, and C_{1-3}alkyl esters thereof, and the lactone formed by condensation of the carboxylic acid with the hydroxy at the 5-position)

Fujikawa's Proposed Count 4 is directed in essence to a method of using a compound of proposed Count 3.

It will be noted that in the above structural formula (A), the quinoline ring is substituted at the 2-position, i.e. between the nitrogen atom and the "Z" substituent, by cyclopropyl. Also, the quinoline ring is substituted at the 4-position by 4-fluorophenyl.

Compounds having structural formula (A) are hereinafter referred to collectively as the "cyclopropyl (4-fluorophenyl) species" (or alternately, the "cyclopropyl species").

It will be further noted that compounds disclosed by Fujikawa in their involved application which are similar in structure to the cyclopropyl species but which fall outside the scope of proposed Counts 3 and 4 comprise:

(i) compounds of structure (A), with the sole exception that cyclopropyl is replaced by isopropyl (see compound of claim 6 of Fujikawa application) [referred to herein as the "isopropyl" or "isopropyl (4-fluorophenyl)" species].

(ii) compounds of structure (A), with the sole exception that fluorine is replaced by chlorine (see compound of claim 18 of Fujikawa application).

The cyclopropyl species which is the subject of proposed Counts 3 and 4 is embraced by Counts 1 and 2 of this interference. Additionally, the cyclopropyl species falls within the scope of claims 1-5, and 32-34, and newly presented claims 41-44, of the Fujikawa involved application, as well as claim 1 of Fujikawa U.S. Patent No. 5,011,930, which Fujikawa have indicated is being taken into reissue. The cyclopropyl species also falls within the generic scope of claims 1-3 and 8-10 of Wattanasin's involved application.

To correspond to proposed Count 3, Fujikawa have proposed to Wattanasin added claim 11, which is directed to the cylopropyl (4-fluorophenyl) species.

As corresponding to proposed Count 4, Fujikawa also propose a claim 12 to Wattanasin which is directed to the use of a compound of claim 11.

In support of proposed Counts 3 and 4, Fujikawa represent that the cyclopropyl (4-fluorophenyl) species of the proposed counts has "unusually high" activity as an inhibitor of cholesterol biosynthesis relative to the genus covered by Count 1, and that "nothing of record" would predict the increased activity associated with the cyclopropyl substituent. A Declaration of one

of the named co-inventors, Masaki Kitihara, is presented for the purpose of demonstrating the "unexpectedly superior" activity of the cyclopropyl species relative to its structural isomer, i.e. the corresponding isopropyl species, as well as homologs of isopropyl.

ARGUMENT

Fujikawa's motion to add proposed claims 11 and 12 to the involved application of Wattanasin should be denied.

Wattanasin discloses quinoline compounds substituted at the 2-position by (1) isopropyl or (2) C_{3-7}cycloalkyl. However, while the involved application of Wattanasin certainly covers within its generic scope compounds which are substituted by cyclopropyl, there is no description by Wattanasin of a cyclopropyl species, as acknowledged by Fujikawa.

Neither the term "isopropyl" nor the term "C_{3-7}cycloalkyl" provides a written description of "cyclopropyl" for purposes of 35 USC 112.

Since Wattanasin does not provide a written description in its involved application of the species proposed by Fujikawa, Fujikawa has failed to comply with 35 USC 112.

Fujikawa, in proposing claims to Wattanasin, are required to show the patentability of the claims to Wattanasin, 37 CFR 1.637(c)(1)(5), MPEP 2338.

Since Fujikawa are unable to establish the patentability of their proposed claims to Wattanasin, the Fujikawa motion to redefine should be denied.

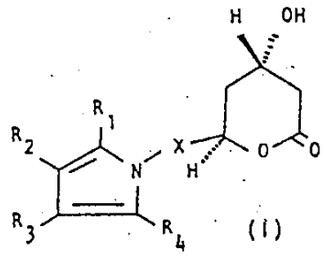
Even assuming arguendo that Fujikawa had fully complied with 37 CFR 1.637(c)(1)(iii) by proposing a claim to Wattanasin which fulfilled the requirements of 35 USC 112, the Fujikawa motion should still be denied because the proposed Counts 3 and 4 do not define a separately patentable invention.

It is self-evident that the question of separate patentability of the cyclopropyl (4-fluorophenyl) species, independent of the genus in which it is contained, involves the principle of selection. That is, the patentability of Fujikawa's proposed counts hinges on whether the cyclopropyl species possesses properties which are truly "surprising" or "unexpected," or which otherwise make it distinct from the generic invention. Fujikawa appear to rely on mere activity differences between the cyclopropyl species and certain other members of the genus. However, these differences are not beyond normal variations to be expected in a generic invention, and moreover, could even be expected based on the prior art.

First of all, the state of the art well prior to Fujikawa's earliest priority date, as reflected in actual prior art of record in Fujikawa's U.S. Patent No. 5,011,930, reflects a clear direction to prepare a species of an HMG-CoA inhibitor compound which contains either an isopropyl or a cyclopropyl substituent.

In particular, reference is made to Warner-Lambert European Patent Application 179,559 (published on April 30, 1986) which discloses a pyrrole series of HMG-CoA reductase inhibition compounds having the formula:

(B)



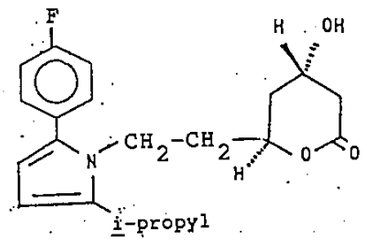
(I)

(or a ring-opened dihydroxyacid derived therefrom, or a pharmaceutically acceptable salt thereof).

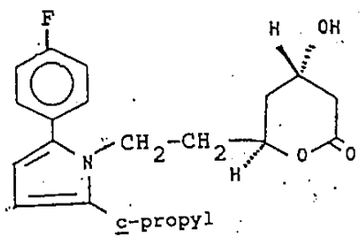
Most pertinent for present purposes is that in the above compounds of Warner-Lambert, R_4 is selected from the limited Markush group comprising: C_{1-4}alkyl, cyclopropyl, cyclobutyl or trifluoromethyl.

Furthermore, at pp. 13-14 of the publication Warner-Lambert express a "particular" preference for the following two compounds:

trans-6-[2-[2-(4-fluorophenyl)-5-(1-methylethyl)-1H-pyrrol-1-yl]-ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one:



trans-6-[2-[2-cyclopropyl]-5-(4-fluorophenyl)-1H-pyrrol-1-yl]-ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one:



Based on the Warner-Lambert disclosure alone, it is fair to say that by April 1986, i.e. well prior to the earliest Fujikawa filing date of August 20, 1987, there was a recognition in the art that: an isopropyl (4-fluorophenyl) species could provide enhanced HMG-CoA reductase activity; and further, that the isopropyl could be cyclized to form cyclopropyl; and finally that the resulting cyclopropyl (4-fluorophenyl) itself exhibited particular improvements in activity relative to a genus of compounds within the same series. Note that in both Warner-Lambert species, above, the isopropyl or cyclopropyl occupies a position on the pyrrole ring adjacent to the nitrogen, as in the case of the cyclopropyl species at issue.

Therefore, it is submitted that certain improved activity levels were already noted in the art in connection with a cyclopropyl-bearing compound well prior to Fujikawa's filing date, such that by August 1987 if not earlier, one of ordinary skill, guided by the Warner-Lambert publication and others, would have considered the activity levels of Fujikawa's cyclopropyl species, as being at best merely consistent with the preferences expressed in the prior art in connection with other nitrogen-containing heterocycles, and certainly well removed from the realm of surprise or unexpectedness.

Further noted in connection with the state of the art is U.S. patent No. 4,952,852 of Hoechst, the foreign counterpart of which would have published in December 1988. The Hoechst disclosure is directed to pyridinyl compounds such as, e.g., the compound of Examples 13ac and 13e, col. 62.

Note particularly in the Hoechst reference the activity level of various compounds which is indicated on Table 1, col. 13-14. Compare especially Example 13e on Table 1 (isopropyl) to Example 13ac (cyclopropyl), which indicates a higher activity level for cyclopropyl than for isopropyl.

It is noted that while the Hoechst publication was available only after Fujikawa's priority filings, it was in the art prior both to Fujikawa's assertion during prosecution of its involved application that the cyclopropyl species had "unobvious"

properties (Amendment of December 19, 1990), and also prior to the February 23, 1990 filing date of the divisional application which issued as the '330 patent.

Copies of relevant portions of the Warner-Lambert and Hoechst publications are enclosed.

The clear direction in the art surrounding Fujikawa's involved application virtually deprive Fujikawa of the argument that increased activity of its cyclopropyl (4-fluorophenyl) species over the other species within its scope would be "unexpected" or "surprising".

Put differently, given the preferences expressed in the art, Fujikawa is necessarily held to a very high threshold of improvement in activity of its cyclopropyl (4-fluorophenyl) species over, e.g., the isopropyl (4-fluorophenyl), in order to justify a conclusion of "unexpectedness" such as would give rise to separate patentability; and this threshold is simply not overcome by the comparative evidence of record.

Turning now to the Kitihara Declaration proffered in support of Fujikawa's motion to redefine, it is submitted that this data simply does not provide a basis for according separate patentability to the cyclopropyl species.

Kitihara provides Test A and Test B IC_{50} data for the sodium and calcium salts, ethyl ester and lactone forms of the cyclopropyl species of structure (A), above, which is covered by proposed Counts 3 and 4. Comparative data is provided with respect to quinoline compounds also having structure (A), with the sole exception that the cyclopropyl group is substituted by methyl, ethyl, isopropyl or C_6.

The data may be summarized as follows:

A. Test A:

Table (a), containing data for the sodium salts of cyclopropyl and the comparative compounds, demonstrates that:
i - cyclopropyl is more active than isopropyl by a factor of about 2.4, and
ii - isopropyl is more active than n-propyl by a factor of about 9.

Table (b) has only two data points for the calcium salts, which indicate that cyclopropyl is more active than isopropyl by a factor of about 5. However, it is difficult to determine how meaningful this activity difference is given the absence of additional comparative data.

Table (c), listing data on the ethyl esters, indicates that the cyclopropyl is more active than n-propyl by a factor of about 14, but no data is given for isopropyl.

Table (d), listing data on the lactones, indicates that the cyclopropyl is more active than the isopropyl by a factor of about 3.8. Again, given that no other compounds were tested, it is difficult to determine how meaningful this data is.

B. Test B

Table (a), listing data on the sodium salts, indicates that

i. cyclopropyl is about 5.7 times more active than isopropyl;

ii. isopropyl is about 7 times more active than n-propyl.

Table (b): the calcium salt of the cyclopropyl is about 3 times more active than the i-propyl; no other data is given.

Table (c), ethyl ester -- No data is given for the isopropyl. The cycopropyl is about 13 times more active than the n-propyl.

It is noted, first, that the above-summarized Kitihara data give no indication that toxicity does not also increase with actvitiy.

Second, given that the difference in activity level between isopropyl and its homologous species is typically substantially greater than the difference in activity betweeen cyclopropyl and isopropyl, Fujikawa is in the untenable position of claiming that

cyclopropyl is a separate and distinct invention from a genus of compounds which includes both the isopropyl and the other species tested above.

Third, the Kitihara Declaration is deficient in failing to make a complete comparison with compounds supported in its case which fall outside the scope of proposed Count 2.

Reference is made, for example, to claim 18 of Fujikawa's involved application, for example, which is directed to a compound having structural formula (A), above, with the sole exception that the quinoline ring is substituted at the "4" position not by 4-fluorophenyl, but by 4-chlorophenyl. This species falls outside the scope of proposed Counts 3 and 4 solely by virtue of the substitution of fluorine with another halogen, chlorine. No comparative data is offered by Fujikawa in respect of this chlorine species.

CONCLUSION

Fujikawa have failed to establish two requisites for entering a separate cyclopropyl (4-fluorophenyl) species count in this interference:

(1) The claims proposed to be added by Wattanasin do not comply with 35 USC 112 in the Wattanasin application, and therefore do not meet the requirement of 37 CFR 1.637(c)(1)(iii).

(2) Fujikawa have failed to demonstrate the separate patentability of the cyclopropyl species over the genus of Counts 1 and 2.

It is concluded that the comparative data presented by Fujikawa, to the extent meaningful, merely indicate activity of the cylopropyl species as an HMG-CoA reductase inhibitor which is well within the range of normal expectancy across the genus of quinoline compounds corrres- ponding to Counts 1 and 2, particularly given the teachings and expectations of the prior art which point to ispropyl, cyclopropyl and 4-fluorophenyl as clearly preferred features (it also being noted that cyclopropyl is a mere ring homolog of isopropyl).

Accordingly, it is repectfully requested that Fujikawa's motion to redefine the interference be denied.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
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E. Hanover, NJ 07936

DEF:rmf

July 1, 1992

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**OPPOSITION OF WATTANASIN
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AND TO ADD CLAIMS TO WATTANASIN APPLICATION**

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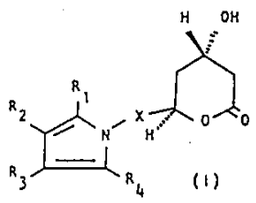
(54) **Trans-6-]2-(substitutedpyrrol-1-yl)alkyl[-pyran-2-one inhibitors of cholesterol synthesis.**

(57) 6-[2-(Substituted-pyrrol-1-yl)alkyl]pyran-2-ones of formula I



(I)

and the corresponding ring-opened hydroxy-acids derived therefrom are potent inhibitors of the enzyme 3-hydroxy-3-methylglutarylcoenzyme A reductase (HMG-CoA reductase), and are thus useful hypolipidemic and hypocholesterolemic agents. Pharmaceutical compositions containing such compounds, and a method of prepering the compounds are also disclosed.

EP 0 179 559 A2

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TRANS-6-[2-(SUBSTITUTEDPYRROL-1-YL)ALKYL]-PYRAN-2-ONE INHIBITORS OF CHOLESTEROL SYNTHESIS

The present invention is related to compounds and pharmaceutical compositions useful as hypocholesterolemic and hypolipidemic agents. More particularly, this invention concerns certain trans-6-[2-(substitutedpyrrol-1-yl)alkyl]-2-ones and the corresponding ring-opened acids derived therefrom which are potent inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), pharmaceutical composition containing such compounds, and a method of lowering blood serum cholesterol levels employing such pharmaceutical compositions.

High levels of blood cholesterol and blood lipids are conditions which are involved in the onset of arteriosclerosis. It is well known that inhibitors of HMG-CoA reductase are effective in lowering the level of blood plasma cholesterol, especially low density lipoprotein cholesterol (LDL-C), in man (cf. M. S. Brown and J. L. Goldstein, New England Journal of Medicine (1981), 305, No. 9, 515-517). It has now been established that lowering LDL-C levels affords protection from coronary heart disease (cf. Journal of the American Medical Association (1984) 251, No. 3, 351-374).

Moreover, it is known that certain derivatives of mevalonic acid (3,5-dihydroxy-3-methylpentanoic acid) and the corresponding ring-closed lactone form, mevalonolactone, inhibit the biosynthesis of cholesterol (cf. F. M. Singer et al., Proc. Soc. Exper. Biol. Med. (1959), 102, 270) and F. H. Hulcher, Arch. Biochem. Biophys. (1971), 146, 422.

United States Patents 3,983,140; 4,049,495 and 4,137,322 disclose the fermentative production of a natural product, now called compactin, having an inhibitory effect on cholesterol biosynthesis. Compactin has been shown to have a complex structure which includes a mevalonolactone moiety (Brown et al., J. Chem. Soc. Perkin I, (1976), 1165.

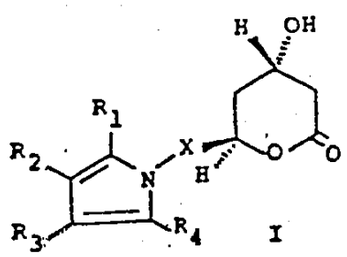
United States Patent 4,255,444 to Oka et al. discloses several synthetic derivatives of mevalonolactone having antilipidemic activity.

United States Patents 4,198,425 and 4,262,013 to Mitsue et al. disclose aralkyl derivatives of mevalonolactone which are useful in the treatment of hyperlipidemia.

United States Patent 4,375,475 to Willard et al. discloses certain substituted 4-hydroxytetrahydropyran-2-ones which, in the 4(R)-trans stereoisomeric form, are inhibitors of cholesterol biosynthesis.

In accordance with the present invention, there are provided certain trans-6-[2-(substitutedpyrrol-1-yl)-alkyl]pyran-2-ones and the corresponding ring-opened hydroxy-acids derived therefrom which are potent inhibitors of cholesterol biosynthesis by virtue of their ability to inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase).

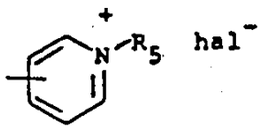
In particular, in its broadest chemical compound aspect, the present invention provides compounds of structural formula I



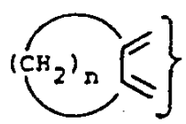
I

wherein X is $-CH_2-$, $-CH_2CH_2-$, or $-CH(CH_3)CH_2-$. R_1 is 1-naphthyl; 2-naphthyl; cyclohexyl; norbornenyl; phenyl; phenyl substituted by fluorine, chlorine, hydroxy, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon

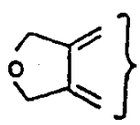
atoms, or alkanoyloxy of from two to eight carbon atoms; 2-, 3-, or 4-pyridinyl; 2-, 3-, or 4-pyridinyl-N-oxide; or



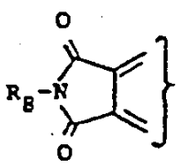
where R_5 is alkyl of from one to four carbon atoms and hal^- is chloride, bromide, or iodide. R_2 and R_3 are independently hydrogen; chlorine; bromine; cyano; trifluoromethyl; phenyl; alkyl of from one to four carbon atoms; carboalkoxy of from two to eight carbon atoms; $-CH_2OR_6$ where R_6 is hydrogen, alkanoyl of from one to six carbon atoms, or where R_2 and R_3 are $-CH_2OCONHR_7$ where R_7 is alkyl of from one to six carbon atoms, phenyl, or phenyl substituted with chlorine, bromine, or alkyl of from one to four carbon atoms. R_2 and R_3 may also, when taken together with the carbon atoms to which they are attached, form a ring denoted by



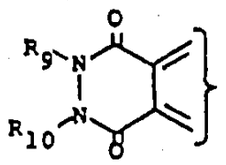
where n is three or four; a ring denoted by



a ring denoted by



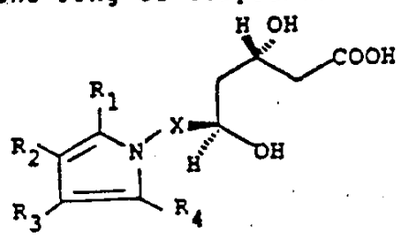
where R_8 is hydrogen, alkyl of from one to six carbon atoms, phenyl, or benzyl; or a ring denoted by



where R_9 and R_{10} are hydrogen, alkyl of from one to four carbon atoms, or benzyl.

R_4 is alkyl of from one to four carbon atoms, cyclopropyl, cyclobutyl, or trifluoromethyl.

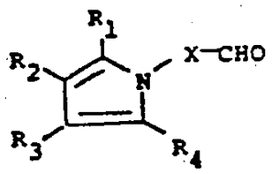
Also contemplated as falling within this aspect of the invention are the corresponding dihydroxy-acid compounds of formula II corresponding to the opened form of the lactone ring of compounds of formula I



II

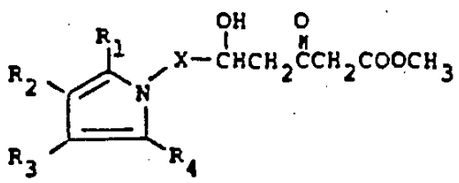
where X, R_1, R_2, R_3, and R_4 are as defined above, and the pharmaceutically acceptable salts thereof, all of the compounds being in the trans racemate of the tetrahydropyran moiety.

In another aspect of the present invention, there is provided a method of preparing compounds of formula I above by (a) first reacting a substituted [(pyrrol-1-yl)-alkyl]aldehyde compound of formula III



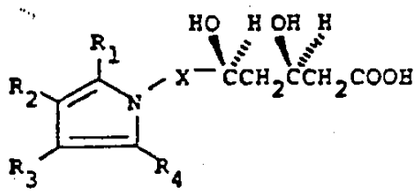
III

where X, R_1, R_2, R_3, and R_4 are as defined above, with the alkali metal salt of the dianion of methyl acetoacetate to form a compound of structural formula IV



IV

where X, R_1, R_2, R_3, and R_4 are as defined above, then successivly (b) reducing compound IV with a trialkylborane and sodium borohydride and (c) oxidizing with alkaline hydrogen peroxide to produce an acid compound of formula V



V

and finally (d) cyclizing, if desired, the acid compound of formula V to a lactone compound of formula I by heating in an inert solvent or, alternatively converting, if desired, the acid compound of formula V to a pharmaceutically acceptable salt.

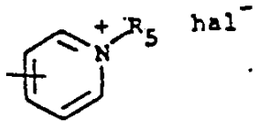
In another aspect, the present invention provides pharmaceutical compositions, useful as hypolipidemic or hypocholesterolemic agents, comprising a hypolipidemic or hypocholesterolemic affective amount of a compound in accordance with this invention as set forth above, in combination with a pharmaceutically acceptable carrier.

In another aspect, the present invention provides a method of inhibiting cholesterol biosynthesis in a patient in need of such treatment by administering a pharmaceutical composition in accordance with the present invention as defined above.

In a first preferred subgeneric chemical compound aspect, the present invention provides compounds of formula I above wherein X is $-CH_2CH_2-$, R_1 is

as defined above, R_2 and R_3 are independently hydrogen, chlorine, or bromine, and R_4 is as defined above.

In a second preferred subgeneric chemical compound aspect, the present invention provides compounds of formula I above where X is $-CH_2CH_2-$, R_1 is phenyl or phenyl substituted by fluorine, chlorine, hydroxy, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms, or where R_1 is 2-, 3-, or 4-pyridinyl; 2-, 3-, or 4-pyridinyl-N-oxide, or

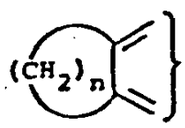


where R_5 is alkyl of from one to four carbon atoms and hal^- is chloride, bromide, or iodide. In this aspect of the invention, R_2 and R_3 are preferably independently hydrogen, chlorine, or bromine, and R_4 is alkyl of from one to four carbon atoms or trifluoromethyl.

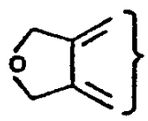
In a third preferred subgeneric chemical compound aspect, the present invention provides compounds of formula I above where X is $-CH_2CH_2-$, R_1 is phenyl or phenyl substituted by fluorine, chlorine, hydroxy, trifluoromethyl, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms, R_2 and R_3 are independently hydrogen, chlorine, or bromine, and R_4 is isopropyl or trifluoromethyl.

In a fourth preferred subgeneric chemical compound aspect, the present invention provides compounds of formula I above where X is $-CH_2CH_2-$, and R_1 is phenyl or phenyl substituted by fluorine, chlorine, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms, or where R_1 is 1-naphthyl, or 2-naphthyl. In this preferred aspect of the invention, R_2 and R_3 are independently

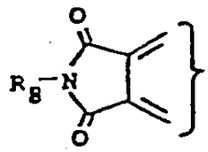
hydrogen, chlorine, bromine, cyano, trifluoromethyl, phenyl, alkyl of from one to four carbon atoms, carboalkoxy of from two to eight carbon atoms, $-CH_2OR_6$ where R_6 is hydrogen or alkanoyl of from one to six carbon atoms, $-CH_2OCONHR_7$ where R_7 is alkyl of from one to six carbon atoms, phenyl, or phenyl substituted with chlorine, bromine, or alkyl of from one to four carbon atoms. In this aspect of the invention, R_2 and R_3 may also, when taken together with the carbon atoms to which they are attached, form a ring denoted by



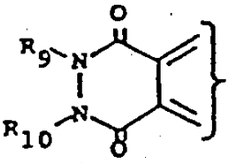
where n is three or four; a ring denoted by



a ring denoted by



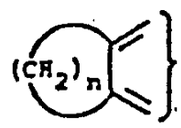
where R_8 is hydrogen, alkyl of from one to four carbon atoms, phenyl, or benzyl; or a ring denoted by



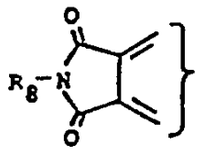
where R_9 and R_{10} are hydrogen, alkyl of from one to four carbon atoms, or benzyl. In this aspect of the invention, R_4 is preferably alkyl of from one to four carbon atoms, cyclopropyl, cyclobutyl, or trifluoromethyl.

In a fifth preferred subgeneric chemical compound aspect, the present invention provides compounds of formula I above where X is $-CH_2CH_2-$, and R1

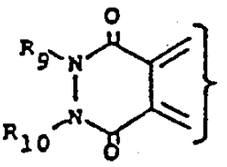
is phenyl or phenyl substituted by fluorine, chlorine, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms. R_2 and R_3 are preferably independently hydrogen, chlorine, bromine, phenyl, or carboalkoxy of from two to eight carbon atoms. In this aspect of the invention R_2 and R_3 may also, when taken together with the carbon atoms to which they are attached, form a ring denoted by



where n is three or four; a ring denoted by



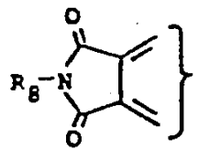
where R_8 is hydrogen, or alkyl of from one to four carbon atoms; or a ring denoted by



where R_9 and R_{10} are hydrogen or alkyl of from one to four carbon atoms. In this aspect of the invention, R_4 is preferably alkyl of from one to four carbon atoms, or trifluoromethyl.

In a sixth preferred subgeneric chemical compound aspect, the present invention provides compounds of formula I above where X is $-CH_2CH_2-$, R_1 is is phenyl or phenyl substituted by fluorine, chlorine, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms. R_2 and R_3 are

preferably independently carboalkoxy of from two to eight carbon atoms or, when taken together with the carbon atoms to which they are attached form a ring denoted by



where R_8 is hydrogen or alkyl of from one to four carbon atoms. In this aspect of the invention, R_4 is preferably isopropyl or trifluoromethyl.

As used throughout this specification and the appended claims, the term "alkyl" denotes a branched or unbranched saturated hydrocarbon group derived by the removal of one hydrogen atom from an alkane.

The term "alkoxy" denotes an alkyl group, as just defined, attached to the parent molecular residue through an oxygen atom.

The term "alkanoyloxy" is meant to denote an alkyl group, as defined above, attached to a carbonyl group and thence, through an oxygen atom, to the parent molecular residue.

The term "carboalkoxy" is meant to denote an alkyl group, as defined above, attached to an oxygen atom and thence, through a carbonyl group, to the parent molecular residue.

The term "norbornenyl" denotes a group derived by the removal of a hydrogen atom (other than at a bridgehead carbon atom) from bicyclo[2.2.1]hept-2-ene.

Specific examples of compounds contemplated as falling within the scope of the present invention include the following:

trans-6-[2-[2-Cyclobutyl-5-(4-fluorophenyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-6-[2-[2-Cyclohexyl-5-(4-fluorophenyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-pyran-2-one.

trans-Tetrahydro-4-hydroxy-6-[2-(2-methyl-5-phenyl-1H-pyrrol-1-yl)ethyl]-2H-pyran-2-one.

trans-6-[2-[2-(4-Chlorophenyl)-5-methyl-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-Tetrahydro-4-hydroxy-6-[2-[2-(4-methoxyphenyl)-5-methyl-1H-pyrrol-1-yl]ethyl]-2H-pyran-2-one.

trans-6-[2-[2-([1,1'-Biphenyl]-4-yl)-5-methyl-1H-pyrrol-1-yl)ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-Tetrahydro-4-hydroxy-6-[2-[2-methyl-5-[3-(trifluoromethyl)phenyl]-1H-pyrrol-1-yl]ethyl]-2H-pyran-2-one.

trans-6-[2-[2-(2,5-Dimethylphenyl)-5-(1-methylethyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-6-[2-[2-(2,6-Dimethoxyphenyl)-5-(1-methylethyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-Tetrahydro-4-hydroxy-6-[2-[2-methyl-5-(2-naphthalenyl)-1H-pyrrol-1-yl]ethyl]-2H-pyran-2-one.

trans-6-[2-(2-(Cyclohexyl-5-trifluoromethyl-1H-pyrrol-1-yl)ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-6-[2-[2-(4-Fluorophenyl)-3,4-dimethyl-5-(1-methylethyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-2-(4-Fluorophenyl)-5-(1-methylethyl)-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3,5-dicarboxylic acid.

trans-2-(4-Fluorophenyl)-N^3,N^3,N^4,N^4-tetramethyl-5-(1-methylethyl)-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3,4-dicarboxamide.

trans-6-[2-[3,4-Dichloro-2-(3-fluorophenyl)-5-(1-methylethyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-2-(4-Fluorophenyl)-5-(1-methylethyl)-1-[2-(tetrahydro)-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3,4-dicarbonitrile.

trans-6-[2-[3,4-Diacetyl-2-(4-fluorophenyl)-5-(1-methylethyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-Diethyl 2-(4-Fluorophenyl)-1-[2-(tetrahydro)-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-(trifluoromethyl)-1H-pyrrole-3,4-dicarboxylate.

trans-Bis(1-methylethyl) 2-(4-Fluorophenyl)-5-(1-methylethyl)-1-[2-(tetrahydro)-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3,4-dicarboxylate.

trans-6-[2-[3,4-Diethyl-2-(4-fluorophenyl)-5-(1-methylethyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-6-[2-[2-(4-Fluorophenyl)-3,4-bis(hydroxymethyl)-5-(1-methylethyl)-1H-pyrrol-1-yl]-ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-1-Methylethyl 4-Chloro-2-(4-fluorophenyl)-5-(1-methylethyl)-1-[2-(tetrahydro)-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxylate.

trans-6-[2-[4-(4-Fluorophenyl)-6-(1-methylethyl)-1H-furo[3,4-c]pyrrol-5(3H)-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-6-[2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3,4-bis[[[(phenylamino)carbonyl]oxy]methyl]-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-1-Methylethyl 4-Chloro-5-(4-fluorophenyl)-2-(1-methylethyl)-1-[2-(tetrahydro)-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxylate.

trans-Ethyl 5-(4-Fluorophenyl)-1-[2-(tetrahydro)-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)-1H-pyrrole-3-carboxylate.

trans-Ethyl 5-(4-Fluorophenyl)-2-(1-methylethyl)-4-phenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxylate.

trans-6-[2-[1-(4-Fluorophenyl)-4,5,6,7-tetrahydro-3-methyl-2H-isoindol-2-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-4-(4-Fluorophenyl)-2-methyl-6-(1-methylethyl)-5-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-pyrrolo[3,4-c]pyrrole-1,3(2H,5H)-dione.

trans-6-[2-[1-(4-Fluorophenyl)-5,6-dihydro-3-(1-methylethyl)pyrrolo[3,4-c]pyrrol-2(4H)-yl]ethyl]-tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-6-[2-[1-(4-Fluorophenyl)-5,6-dihydro-5-methyl-3-(1-methylethyl)pyrrolo[3,4-c]pyrrol-2(4H)-yl]-ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-6-[2-[3-Chloro-5-(4-fluorophenyl)-2-(1-methylethyl)-4-phenyl-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-6-[2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3,4-diphenyl-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

Particularly preferred compounds in accordance with the present invention are:

trans-6-[2-[3,4-Dichloro-2-(4-fluorophenyl)-5-(1-methylethyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-6-[2-[3,4-Dibromo-2-(4-fluorophenyl)-5-(1-methylethyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-6-[2-[2-(4-Fluorophenyl)-5-(trifluoromethyl)-1H-pyrrol-1-yl)ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-Dimethyl 2-(4-Fluorophenyl)-5-(1-methylethyl)-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3,4-dicarboxylate.

trans-6-[2-[2-(4-Fluorophenyl-5-methyl-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-6-[2-[2-(4-Fluorophenyl-5-(1-methylethyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-6-[2-[2-Cyclopropyl-5-(4-fluorophenyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-6-[2-[2-(1,1-Dimethylethyl)-5-(4-fluorophenyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-Tetrahydro-4-hydroxy-6-[2-[2-(2-methoxyphenyl)-5-trifluoromethyl-1H-pyrrol-1-yl]ethyl]-2H-2-one.

trans-Tetrahydro-4-hydroxy-6-[2-[2-(2-methoxyphenyl)-5-(1-methylethyl)-1H-pyrrol-1-yl]ethyl]-2H-pyran-2-one.

trans-Tetrahydro-4-hydroxy-6-[2-[2-methyl-5-(1-naphthalenyl)-1H-pyrrol-1-yl]ethyl]-2H-pyran-2-one.

trans-6-[2-(2-Bicyclo[2.2.1]hep-5-en-2-yl-5-methyl-1H-pyrrol-1-yl)ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-6-[2-[2-(4-Fluorophenyl)-5-(1-methylphenyl)-1H-pyrrol-1-yl]propyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

Compounds of the present invention where R_2 and R_3 are hydrogen are prepared by the methods outlined in Reaction Sequence 1 or Reaction Sequence 2.

As shown in Reaction Sequence 1, the aldehydes, VI, are reacted with the appropriately substituted vinylketones, VII, in the presence of the thiazolium salt, VIII, and a base such as triethylamine, to produce the diketones, IX. (See Ang. Chem. Int. Ed., 15: 639-712 (1976)).

The diketones, IX, are reacted with an omega-aminoalkylnitrile (compound Roman numeral ten where the value of X is methylene, ethylene, or 1-methylethylene) in acetic acid to produce the disubstituted pyrrole nitriles, XI.

Treatment of the pyrrole nitriles, XI, with diisobutylaluminum hydride in an inert solvent such as dichloromethane produces the corresponding pyrrole aldehydes, XII.

United States Patent [19]

Kesseler et al.

[11] Patent Number: 4,925,852

[45] Date of Patent: May 15, 1990

[54] **3-DEMETHYLMEVALONIC ACID DERIVATIVES, AND PHARMACEUTICAL PRODUCTS BASED ON THESE COMPOUNDS**

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[21] Appl. No.: **216,458**

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[52] U.S. Cl. **514/333**; 514/277; 514/334; 514/336; 514/357; 514/269; 544/333; 544/335; 546/256; 546/257; 546/258; 546/283; 546/284; 546/335; 546/341; 546/342; 546/268

[58] Field of Search 546/256, 268, 283, 284, 546/257, 258, 335, 341, 342, 268; 514/277, 333, 334, 336, 357

[56] **References Cited**

FOREIGN PATENT DOCUMENTS

0306929	3/1989	European Pat. Off.	546/256
0308736	3/1989	European Pat. Off.	546/256
0325130	7/1989	European Pat. Off.	546/256
0330057	8/1989	European Pat. Off.	546/256

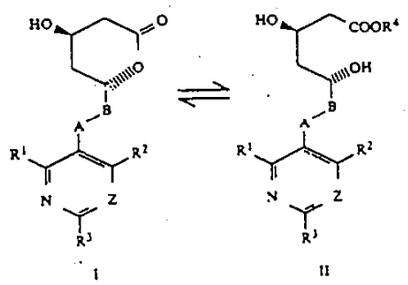
OTHER PUBLICATIONS

Stokker et al., "Journal of Medicinal Chemistry", vol. 28, No. 3, 1985, pp. 347–358.

Primary Examiner—Mary C. Lee
Assistant Examiner—J. Richter
Attorney, Agent, or Firm—Finnegan, Henderson, Farabow, Garrett and Dunner

[57] **ABSTRACT**

3-Demethylmevalonic acid derivatives of the formula I (δ-lactone) and II (corresponding dihydroxy carboxylic acid derivative)



I ⇌ II

in which A—B, Z, R^1, R^2, R^3 and R^4 have the indicated meanings, a process for the preparation of these compounds, their use as medicaments, and pharmaceutical products, are described. In addition, new intermediates for the preparation of the compounds of the formula I and formula II are described.

9 Claims, No Drawings

3-DEMETHYLMEVALONIC ACID DERIVATIVES, AND PHARMACEUTICAL PRODUCTS BASED ON THESE COMPOUNDS

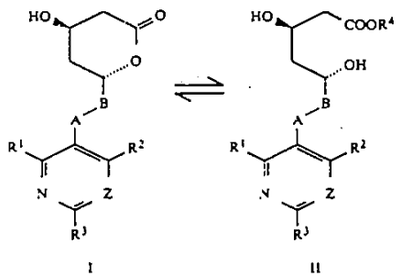
Derivatives of 3-hydroxy-3-methylglutaric acid (HMG) and of mevalonic acid have been described as inhibitors of cholesterol biosynthesis (M. T. Boots et al., J. Pharm. Sci. 69, 306 (1980), F. M. Singer et al., Proc. Soc. Exper. Biol. Med. 102, 270 (1959), H. Feres, Tetrahedron Lett. 24, 3769 (1983)). 3-Hydroxy-3-methylglutaric acid itself shows a significant cholesterol-lowering action in the rat and in human experiments (Z. Beg, Experimentia 23, 380 (1967), ibid 24, 15 (1968), P. J. Lupien et al., Lancet 1978, 1, 283).

Endo et al. (FEBS Letters 72, 323 (1976), J. Biol. Chem. 253, 1121 (1978)) reported the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), the rate-determining enzyme of cholesterol biosynthesis, by the fermentation product "compactin".

Brown et al. (J. Chem. Soc. 1165 (1976) determined the chemical structure and the absolute configuration of "compactin" by a combination of chemical, spectroscopic and X-ray crystallographic methods and were able to show that "compactin" is a derivative of the lactone of 3-demethylmevalonic acid.

Compactin derivatives which inhibit the activity of HMG-CoA reductase have already been described (G. E. Stokker et al., J. Med. Chem. 28, 347-358 (1985)).

The present invention relates to new synthetic analogs of "compactin" in the form of the δ-lactone of the formula I or in the form of the dihydroxy acid derivative II



I II

In the formulae

A—B denotes a radical of the formula —CH=CH— or —CH_2—CH_2—,

Z denotes a radical of the formula —CH or a nitrogen atom,

R^1, R^2 and R^3, independently of one another, denote hydrogen, a saturated or unsaturated, straight-chain or branched hydrocarbon radical which has up to 6 carbon atoms and can optionally be substituted on the terminal carbon by a saturated or unsaturated, cyclic hydrocarbon radical having 3–6 carbon atoms, a cyclic hydrocarbon radical which has 3–7 carbon atoms and is saturated or is unsaturated once or twice, an aromatic radical selected from the group comprising phenyl, furyl, thienyl or pyridinyl, which can optionally carry in the nucleus 1–3 identical or different substituents from the following groups: halogen, trifluoromethyl, alkyl or alkenyl, each having up to 6 carbon atoms, hydroxyl, alkoxy having 1–6 carbon atoms, carboxyl, or carbalkoxy having 1–6 carbon atoms in the alkoxy moiety,

R^4 denotes hydrogen, a straight-chain or branched, saturated or unsaturated hydrocarbon radical having up to 5 carbon atoms, a benzyl radical whose nucleus can be substituted 1–2 times by halogen or an alkyl radical having 1–4 carbon atoms, an alkali metal or an ammonium ion $NR^5R^6R^7R^8$, where R^{R5}, R^6, R^7 and R^8 are identical or different and denote hydrogen, alkyl having 1–4 carbon atoms or hydroxyalkyl having 1–4 carbon atoms.

The invention relates to the pure enantiomers having the absolute configuration 4R,6S indicated in the general formula I or the absolute configuration 3R,5S depicted in formula II.

Preferred substituents R^1 and R^2 are a straight-chain or branched alkyl radical having 1–4 carbon atoms, a cycloalkyl radical having 3–6 carbon atoms, a cycloalkylmethyl or cycloalkenylmethyl radical having a ring size of 5–6 carbon atoms, a phenyl radical which can optionally carry 1–3 identical or different substituents from the following groups halogen, trifluoromethyl, alkyl having 1–4 carbon atoms, hydroxyl, alkoxy having 1–4 carbon atoms or carbalkoxy having 1–4 carbon atoms in the alkoxy moiety.

The preferred meanings for R^3 are hydrogen, a straight-chain or branched alkyl or alkenyl radical having up to 6 carbon atoms, a cycloalkyl or cycloalkenyl radical, each having 3–6 carbon atoms, a phenyl or pyridinyl radical, it being possible for the aromatic radicals optionally to carry 1–3 identical or different substituents from the following groups: halogen, alkyl having 1–4 carbon atoms, hydroxyl, alkoxy having 1–4 carbon atoms or carbalkoxy having 1–4 carbon atoms in the alkoxy moiety.

The preferred radicals R^4 are hydrogen, methyl, ethyl, isopropyl, isobutyl, benzyl, sodium, potassium, ammonium (NH_4) or methyltris(hydroxymethyl)ammonium.

Particularly preferred substituents R^1 are: methyl, ethyl, isopropyl, sec.-butyl, tert.-butyl, cyclopropyl, cyclohexyl, phenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-fluoro-3-methylphenyl, 3,5-dimethylphenyl, cyclohexylmethyl and 4-trifluoromethylphenyl.

Particularly preferred substituents R^2 are methyl, ethyl, isopropyl, sec.-butyl, tert.-butyl, cyclopropyl, cyclohexyl, phenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-fluoro-3-methylphenyl, 3,5-dimethylphenyl, cyclohexylmethyl and 4-trifluoromethylphenyl.

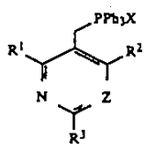
Particularly preferred substituents R^3 are hydrogen, methyl, isopropyl, tert.-butyl, cyclohexyl, phenyl, 4-fluorophenyl, 4-hydroxyphenyl, 2,5-dimethylphenyl, 3,5-dimethylphenyl and 4-trifluoromethylphenyl.

Particularly preferred substituents R^4 are hydrogen, methyl, ethyl, sodium and potassium.

Very particular preference is given to compounds of the formula I in which Z denotes a radical of the formula —CH or N, R^1 denotes ethyl, isopropyl, cyclopropyl, R^2 denotes 4-fluorophenyl, 4-hydroxyphenyl and R^3 denotes isopropyl, tert.-butyl, cyclohexyl, phenyl, 4-hydroxyphenyl or 4-fluorophenyl, and to the sodium and potassium salts of the corresponding dihydroxy carboxylic acids of the formula II.

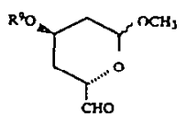
The invention also relates to a process for the preparation of compounds of the formulae I and II, which comprises

(a) reaction of the phosphonium salts of the formula III



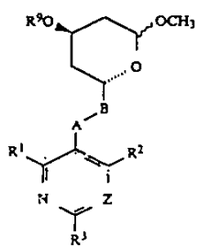
III

in which R^1, R^2, R^3 and Z have the meaning indicated for formula I, and X is Cl, Br or I, with the chiral aldehyde of the formula IV



IV

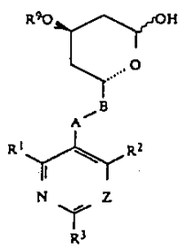
in which R^9 is a protective group which is stable to bases and weak acids, for example the t-$C_4H_9(C_6H_5)_2Si$ group, to give a compound of the formula V



V

in which R^1, R^2, R^3 and Z have the meaning given for formula I, R^9 has the meaning given for formula IV, and A-B represents the (—CH=CH—) group,

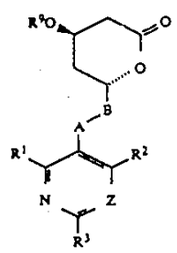
(b) acid hydrolysis of the methyl acetal group in a compound of the general formula V to give a lactol of the formula VI



VI

in which R^1, R^2, R^3 and Z have the meaning given for formula I, R^9 has the meaning given for formula IV, and A-B represents the (—CH=CH—) group,

(c) oxidation of the compound of the formula VI to give a lactone of the general formula VII



VII

in which R^1, R^2, R^3 and Z have the meaning given for formula I, R^9 has the meaning given for formula IV, and A-B represents the (—CH=CH—) group,

(d) elimination of the protective group R^9 in a compound of the general formula VII to give a compound of the formula I in which R^1, R^2, R^3 and Z have the meaning indicated for formula I, and A-B represents the (—CH=CH—) group,

(e) where appropriate hydrogenation of a resulting compound of the general formula I in which A-B represents a (—CH=CH—) group to give a compound of the general formula I in which A-B represents a (—CH_2—CH_2—) group, it also being possible for the hydrogenation to be carried out on the compounds of the formula V, VI or VII to give compounds in which A-B represents the (—CH_2—CH_2—) group,

(f) where appropriate conversion of a hydroxylactone of the general formula I into the corresponding dihydroxy acid of the formula II, or its salts, or, where appropriate, preparation from the hydroxylactone I or the free hydroxy acid II of the corresponding esters.

The phosphonium salts which are used as starting material in the process according to the invention and have the general formula III, in which R^1, R^2 and R^3 have the meaning given for the general formula I, are obtained as depicted in scheme 1.

Ketones of the general formula VIII, where R^2 and R^3 have the indicated meaning, are known from the literature or can be prepared by processes known from the literature (cf., for example, D. Vorländer and F. Kalkow, Berichte d. Dtsch. Chem. Ges. 30, 2268 (1897) or H. Stetter in Houben-Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry) Vol. VII/26, 1449–1507, Thieme, Stuttgart 1976). Likewise known from the literature or amenable to preparation by processes known from the literature (for example in analogy to M. Jackman, M. Klenk, B. Fishburn, B. F. Tullar and S. Archer, J. Am. Chem. Soc. 70, 2884 (1948)) are the β-keto esters of the general formula IX, where R^1 has the abovementioned meaning, and R^{10} denotes a straight-chain or branched alkyl radical having up to 6 carbon atoms, preferably a methyl or ethyl radical.

Compounds of the formula X in which R^1, R^2, R^3 and R^{10} have the indicated meaning are prepared in analogy to literature processes, for example according to R. Connor, D. B. Andrews, J. Am. Chem. Soc. 56 2713 (1943) and literature cited therein. An example of a process used to convert compounds of the type X into pyridines of the general formula XV (in this, R^1, R^2 and R^3 have the abovementioned meaning, and Z denotes a CH group) is that described by F. Rehberg and F. Kröhnke, Liebigs Ann. Chem. 717, 91 (1968).

Dihydropyrimidines of the general formula XIV can be prepared, for example, in analogy to a literature process (E. F. Silversmith, J. Org. Chem. 27, 4090 (1962)) or, for example, also by a synthesis shown in scheme 1, route A, by reacting a β-keto ester of the general formula IX with an aldehyde of the type XI to give a compound of the general formula XII, and reacting the latter, without further purification, with an amidinium compound of the type XIII to give a dihydropyrimidinecarboxylic ester of the general formula XIV. The preparation of compounds of the type XIV from components of the general formulae IX, XI and XIII can likewise be carried out as a one-pot reaction (scheme 1, route B).

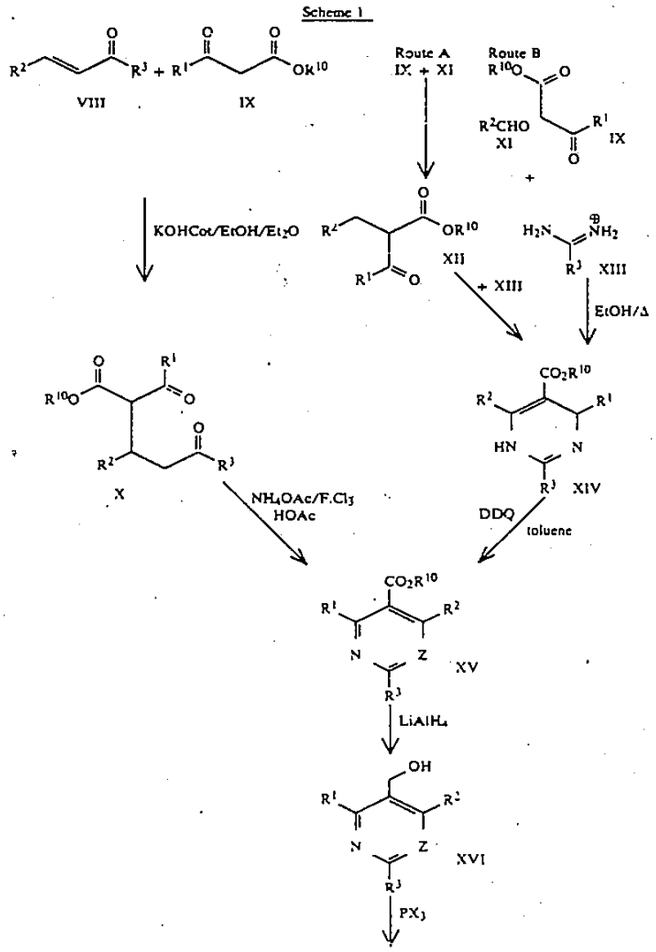
The oxidation of compounds of the formula XIV to give pyrimidinecarboxylic esters of the general formula XV in which R^1, R^2, R^3 and R^{10} have the abovementioned meaning, and Z denotes a nitrogen atom, is carried out in analogy to processes known from the literature, for example by dehydrogenation using chloroanil or 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) as described by E. A. Braude, J. Hannah, R. Linstead, J. Chem. Soc. 1960, 3257.

Compounds of the general formula XV are reduced by reaction with complex metal hydrides such as, for example, lithium aluminum hydride or diisobutylaluminum hydride, in aprotic solvents, for example diethyl ether or tetrahydrofuran, at temperatures between −30° C. and +50° C.

Alkyl halides of the general formula XVII, where R^1, R^2, R^3 and X have the abovementioned meaning, can be prepared from alcohols of the type XVI, for example by reaction with phosphorus halides in inert solvents such as, for example, dichloromethane or toluene, at temperatures between 0° and 100° C., or by reaction with hydrohalic acids.

Phosphonium salts of the general formula III are obtained by, for example, reaction of the alkyl halides XVII with triphenylphosphine in inert solvents such as toluene, at temperatures between 20° C. and 120° C. (cf. scheme 1).

Scheme 1



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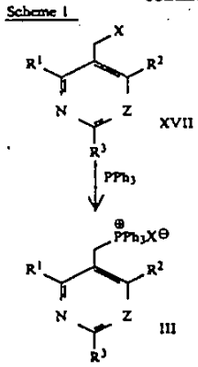
Scheme 1



The chiral aldehyde of the formula IV which is used as starting material in the process according to the invention is obtained by a process known from the literature (Yuh Lin, J. R. Falck, Tetrahedron Letters 23, 4305–4308 (1982)) from the corresponding alcohol by oxidation with, for example, CrO_3 or oxalyl chloride/-dimethyl sulfoxide in the presence of triethylamine.

Reaction of the chiral aldehyde of the formula IV with a phosphonium salt of the formula III by the Wittig method (for example Wittig, Haag, Chem. Ber. 88, 1654 (1955)) results in compounds of the formula V, a preferred embodiment comprising dissolution or suspension of phosphonium salts of the formula III in a solvent such as tetrahydrofuran, dimethyl sulfoxide or DME, liberation of the corresponding phosphoranes using a suitable strong base such as, for example, sodium hydride, potassium tert.-butylate, Li ethylate or butyllithium, and then addition of the aldehyde of the formula IV and allowing reaction to take place at −10° C. to +50° C. for 1–6 h.

In this, the compounds of the formula V are mainly obtained in the form of mixtures of the E/Z olefins. Mixtures of E/Z olefins can, where appropriate, be fractionated by chromatography. The pure Z-olefins can also be obtained, as described by G. Drefahl Chem. Ber. 94, 907 (1961), by irradiation of the E/Z mixture in solutions, such as, for example, toluene or nitrobenzene.

The corresponding pure E-olefins can be obtained, as described by De Tar et al. in J. Amer. Chem. Soc. 78, 474 (1955), by heating the E/Z mixtures in solution in the presence of iodine.

The methyl acetal protective group in the compounds of the formula V can be selectively eliminated by acid hydrolysis in the generally customary manner, preferably using a mixture of glacial acetic acid, tetrahydrofuran and water in the ratio 3:2:2, at +20° to +90° C., within 6–24 hours.

Oxidation of the compounds of the formula VI to give a lactone of the formula VII can be carried out by oxidizing agents such $CrO_3 \times 2Pyr$, or pyridinium chlorochromate in inert solvents such as, for example, methylene chloride or chloroform. Further possibilities for the oxidation comprise reaction with thioanisole/Cl_2-/NEt_3 in carbon tetrachloride, reaction with DMSO-/oxalyl chloride/NEt_3 at −20° C., or reaction with N-iodosuccinimide/tetrabutylammonium iodide in dichloromethane.

To prepare the compounds of the formula I, the protective group R^9 in the compounds of the formula VII is eliminated. This can take place with strong acids, such as 5-normal hydrochloric acid or sulfuric acid, at −10° C. to +30° C., or with fluoride ions, preferably by dissolving the compounds of the formula VII in tetrahydrofuran or diethyl ether, and adding a mixture of tetrabutylammonium fluoride and glacial acetic acid, followed by stirring at 0° C. to 40° C. for between 1 and 12 hours.

Compounds of the formula I in which A-B represents a (CH=CH) group are hydrogenated by a generally customary method, expediently at a temperature between 20° C. and 40° C. using hydrogen in the presence of a metal catalyst, preferably palladium, platinum, PtO_2 or PdO_2, to give compounds of the formula I, in which A-B denotes a $-CH_2-CH_2-$ group. This hydrogenation can be carried out under atmospheric pressure in customary solvents such as tetrahydrofuran, ethyl acetate, methanol, low molecular weight alcohols, glacial acetic acid or chloroform, or in autoclaves under elevated pressure (2–50 atm). The hydrogenation of the —CH=CH— group can also be carried out on the compounds of the formulae V, VI or VII.

The resulting compounds of the formula I can be isolated in a straightforward manner by evaporation of the solvent, where appropriate after purification by chromatography.

The compounds of the formula I are obtained in optically pure form. Concerning the configuration of the double bond (A-B=—CH=CH—), E/Z mixtures are obtained, and these can, at all stages of the synthesis, be fractionated by chromatography or isomerized to give the E form (cf. in this context, De Tar et al., J. Amer. Chem. Soc. 78 475 (1955)).

Compounds of the formula I in the form of the δ-lactone can be hydrolyzed in alkaline medium to give the corresponding salts of the dihydroxy acids, for example using NaOH or KOH in a low molecular weight alcohol such as methanol, or in ethers such as dimethoxyethane or THF, where appropriate in the presence of water. The alkali metal cation in the resulting salts of the dihydroxy acids can, after acidification, be exchanged by any desired cations in ion exchangers in the customary manner. For this purpose, for example, the dihydroxy acids are allowed to run through a column packed with a cation exchanger, such as, for example, based on polystyrene/divinylbenzene (®AMBERLITE CG-150 or ®DOWEX CCR-2). The cation

exchanger is loaded with the desired cation, for example with ammonium ions derived from a primary, secondary or tertiary amine. The desired salt is obtained by evaporation of the eluate.

Ammonium salts of the dihydroxy acids, which are derived from a primary, secondary or tertiary amine, can also be prepared by mixing the free dihydroxy acids in an alcohol solution with an equimolar amount of the appropriate amine, and evaporating the solvent.

The free dihydroxy acids II of the δ-lactones I can be esterified by customary methods, for example using a diazoalkane. Thus, for example, compounds of the formula I can be esterified with a diazoalkane at temperatures between −40° C. and +20° C., it being possible to use the customary solvents such as, for example, diethyl ether, tetrahydrofuran, chloroform or low molecular weight alcohols such as methanol. The resulting esters can be isolated in a straightforward manner by evaporation of the solvent and, where appropriate, purified by chromatography. Another esterification method comprises reaction of salts of the dihydroxy acids II with an alkylating agent in the presence of a base such as, for example, a metal alcoholate or metal carbonate in a suitable solvent. An example of a suitable metal alcoholate is sodium ethylate or potassium tertiarybutylate. Suitable solvents are alcohols such as, for example, methanol or tert.-butanol, ethers such as tetrahydrofuran or 1,2-dimethoxyethane and, in particular, dipolar aprotic solvents such as dimethylformamide, dimethylsulfoxide, acetonitrile or N-methylpyrrolidone. Another suitable method for the preparation of esters of the dihydroxy acids is transesterification with an excess of alcohols, such as, for example, methanol, ethanol or isopropanol.

Where the individual reaction products do not result in a form which is sufficiently pure for them to be used in the subsequent reaction step, it is advisable to purify by crystallization, or column, thin-layer or high-pressure liquid chromatography.

If the aldehyde of the formula IV is not in the form of the pure enantiomer, it is also possible for mixtures of the enantiomeric final products to be produced, and these can be fractionated by generally customary processes.

It is expedient in the synthesis of compounds of the general formulae I and II in which R^1, R^2 and R^3, independently of one another, contain hydroxyl groups to use starting compounds of the general formulae VIII-XII in which the hydroxyl groups are protected in a suitable manner, for example as alkyl or silyl ethers. The compounds then obtained in the process according to the invention are of the general formulae I or II in which R^1, R^2 or R^3 contain the correspondingly protected hydroxyl groups. The latter can be converted, by elimination of the protective groups by processes known from the literature, into compounds of the general formula I with hydroxyl-substituted radicals R^1, R^2 or R^3. Suitable protective groups, as well as methods for the introduction and removal thereof, are known from the literature (cf. for example T. W. Greene, Protective Groups in Organic Synthesis, Wiley and Sons, N.Y., 1981).

In more cases, where the intention is to prepare compounds of the general formulae I and II with acid-sensitive radicals R^1, R^2 or R^3, this can also take place by the process described in patent application No. P37 22 807.2.

Apart from the compounds described in the examples, the process according to the invention can be used to prepare the following compounds:

E-6S-(2-(2-Cyclohexyl-4-(4-fluorophenyl)-6-phenylpyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(4-Cyclohexyl-2-(4-fluorophenyl)-6-phenylpyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(4-Cyclohexylmethyl)-2-(1-methylethyl)-6-phenylpyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2-Cyclohexylmethyl)-2-(1-methylethyl)-6-phenylpyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(4-(3,5-Dimethylphenyl)-2-(1-methylethyl-6-phenylpyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2-(3,5-Dimethylphenyl)-2-(1-methylethyl-6-phenylpyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(4,6-Diphenyl-2-(1-methylethyl)pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2,6-Diphenyl-2-(1-methylethyl)pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2-(1-Methylethyl)-6-phenyl-4-(4-trifluoromethylphenyl)pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(4-(1-Methylethyl)-6-phenyl-4-(4-trifluoromethylphenyl)pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(4-(4-Fluoro-3-methylphenyl)-2-(1-methylethyl)-6-phenylpyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2-(4-Fluoro-3-methylphenyl)-2-(1-methylethyl)-6-phenylpyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(6-(4-Fluorophenyl)-2-(1-methylethyl)-4-phenylpyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(6-(4-Fluorophenyl)-4-(1-methylethyl)-2-phenylpyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(6-(3,5-Dimethylphenyl)-4-(4-fluorophenyl)-2-(1-methylethyl)pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(6-(3,5-Dimethylphenyl)-2-(4-fluorophenyl)-4-(1-methylethyl)pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(4,6-Bis-(1-methylethyl)-2-(4-fluorophenyl)-pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2,6-Bis-(1-methylethyl)-4-(4-fluorophenyl)-pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(4-(4-Fluorophenyl)-2-(1-methylethyl)-6-(4-trifluoromethylphenyl)pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2-(4-Fluorophenyl)-4-(1-methylethyl)-6-(4-trifluoromethylphenyl)pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(6-(4-Fluorophenyl)-4-(4-methoxyphenyl)-2-(1-methylethyl)pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(6-(4-Fluorophenyl)-2-(4-methoxyphenyl)-2-(1-methylethyl)pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2,6-Bis(1,1-dimethylethyl)-4-(4-fluorophenyl)-pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(4,6-Bis(1,1-dimethylethyl)-2-(4-fluorophenyl)-pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(4,6-Dimethyl-2-(4-fluorophenyl)pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2-Chlorophenyl)-4,6-dimethylpyridin-3-yl)-ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2-(4-Fluorophenyl)-4-methyl-6-phenylpyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2-(4-Fluorophenyl)-6-methyl-4-(1-methylethyl)pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(4-(1,1-Dimethylethyl)-2-(4-fluorophenyl)-6-phenylpyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2,6-Dimethyl-4-(4-methoxyphenyl)pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(4,6-Dimethyl-2-(4-methoxyphenyl)pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(4-(4-Methoxypbenyl)-6-methyl-2-(1-methylethyl)pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2-(4-Methoxyphenyl)-6-methyl-4-(1-methylethyl)pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5.6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2-(4-Methoxyphenyl)-4-(1-methylethyl)-6-phenylpyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(6-(2,5-Dimethylphenyl)-2-(4-fluorophenyl)-4-(1-methylethyl)pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2,4-Bis-(4-fluoropbenyl)-4-(1-methylethyl)-pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(6-Cyclohexyl-4-(4-fluorophenyl)-2-(1-methylethyl)pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(6-Cyclohexyl-2-(4-fluo· ·henyl)-4-(1-methylethyl)pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(4-(4-Fluorophenyl)-2-(1R-methylpropyl)-6-phenylpyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(4-(4-Fluorophenyl)-2-(1S-methylpropyl)-6-phenylpyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2-(4-Fluorophenyl)-4-(1R-methylpropyl)-6-phenylpyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2-(4-Fluorophenyl)-4-(1S-methylypropyl)-6-phenylpyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2,6-Dimethyl-4-(4-fluorophenyl)pyridin-3-yl)ethyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(4-(4-Fluorophenyl)-2-(1-methylethyl)-6-phenylpyridin-3-yl)ethyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2-(4-Fluorophenyl)-4-(1-methylethyl)-6-phenylpyridin-3-yl)ethyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2-Cyclohexyl-4-(4-fluorophenyl)-6-phenylpyridin-3-yl)ethyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(4-(4-Methoxyphenyl)-2-(1-methylethyl)-6-phenyl)ethyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(6-(2,5-Dimethylphenyl)-4-(4-fluorophenyl)-2-(1-methylethyl)pyridin-3-yl)ethyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(6-(3,5-Dimethylphenyl)-4-(4-fluorophenyl)-2-(1-methylethyl)pyridin-3-yl)ethyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2-Phenyl-4-(4-fluorophenyl)-6-isopropyl)-pyrimidinyl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2-(2-Methylphenyl)-4-(4-chlorophenyl)-6-isopropyl)pyrimidinyl)ethenyl)-4R-hydroxy-3,4,5,6-t·trahydro-2H-pyran-2-one

E-6S-(2-(5-(2-(2,6-Dimethylphenyl)-4-(4-fluorophenyl)-6-isopropyl)pyrimidinyl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2-(2,6-Dichlorophenyl)-4-(4-fluorophenyl)-6-isopropyl)pyrimidinyl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2-Phenyl-4-(4-chlorophenyl)-6-t-butyl)-pyrimidinyl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2-Phenyl-4-(4-fluorophenyl)-6-t-butyl)-pyrimidinyl)ethyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2-Phenyl-4-(4-fluoro-3-methylphenyl)-6-isopropylpyrimidinyl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2-Phenyl-4-(4-fluoro-3-methylphenyi)-6-isopropylpyrimidinyl)ethyl)-4R-hydroxy-3,4,5,6-tet·ahydro-2H-pyran-2-one

E-6S-(2-(5-(2,6-Diisopropyl-4-(4-chlorophenyl)-pyrimidinyl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2,6-Diisopropyl-4-(4-methoxyphenyl)-pyrimidinyl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2,6-Dimethyl-4-cyclohexyl)pyrimidinyl)e-thenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2,6-Diisopropyl-4-cyclohexyl)pyrimidinyl-)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2-Phenyl-4-cyclohexyl-6-isopropyl)-pyrimidinyl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2,6-Ditert.-butyl-4-(4-chlorophenyl)-pyrimidinyl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2,6-Ditert.-butyl-4-(4-fluorophenyl)-pyrimidinyl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2-Methyl-4(4-fluoro-3-methylphenyl)-6-isopropyl)pyrimidinyl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2-Methyl-4(4-fluorophenyl)-6-isopropyl)-pyrimidinyl)ethyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2-(2,6-Dichlorophenyl)-4-(4-fluorophenyl)-6-isopropyl)pyrimidinyl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2-(2-Chloro-4-methylphenyl)-4-(4-chlorophenyl)-6-isopropyl)pyrimidinyl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2-(2,4-Dichlorophenyl)-4-(4-fluorophenyl)-6-methyl)pyrimidinyl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2-(2,4-Dimethyl-phenyl)-4-(4-methoxyphenyl)-6-isopropyl)pyrimidinyl)ethyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2-(2-Chloro-4-methyl-phenyl)-4-(4-fluoro-3-phenyl)-6-isopropyl)pyrimidinyl)ethyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2-Methyl-4-phenyl-6-tert.butyl)-pyrimidinyl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2-Methyl-4-phenyl-6-tert.butyl)-pyrimidinyl)ethyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2-Phenyl-4-(4-fluorophenyl)-6-isopropyl)-pyrimidinyl)ethyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(5-(2-Phenyl-4-(4-fluoro-3-methyl-phenyl)-6-tert.butyl)pyrimidinyl)ethyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2-(4-Fluorophenyl)-6-(4-hydroxyphenyl)-4-(1-methylethyl)pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(2-(4-Hydroxyphenyl)-4-(1-methylethyl)-6-phenylpyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

E-6S-(2-(4-Cyclopropyl-2-(4-fluorphenyl)-6-phenyl-pyridin-3-yl)ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

BIOLOGICAL ASSAY SYSTEMS

1. HMG-CoA reductase activity in enzyme preparations

The HMG-CoA reductase activity was measured on solubilized enzyme preparations from rat liver microsomes induced, after a changeover in the day/night rhythm, with cholestyramine (® CUEMID). The substrate used was (S,R)-^{14}C-HMG-CoA, and the NADPH concentration was maintained during the incubation by a regenerating system. ^{14}C-Mevalonate was separated from the substrate and other products (for example ^{14}C-HMG) by column elution, the elution profile of each individual sample being determined. ^{3}H-Mevalonate was not always included in the determination because relative data on the inhibitory effects were required. In each series of tests, the enzyme-free control, the enzyme-containing normal mixture (=100%) and those with additions of product, final concentration 10^{-5} to 10^{-9} M, were treated together. Each individual value was the mean formed from 3 parallel samples. The significance of the mean differences between product-free and product-containing samples was assessed using the t test.

Using the method described above, the following values for the inhibition of HMG-CoA reductase was determined for the compounds according to the invention, for example [IC_{50}/mol/liter denotes the molar concentration of the compound required for 50% inhibition]:

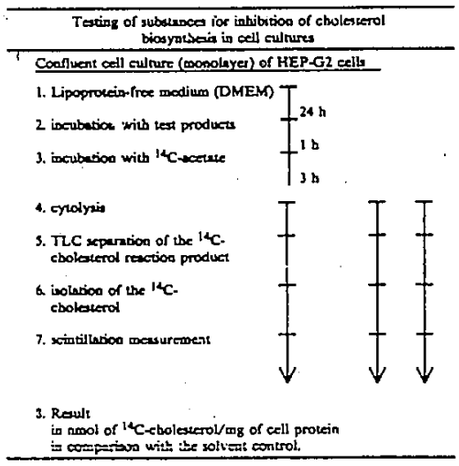
TABLE 1

Compound of Example	Z	R^1	R^2	R^3	A-B	IC_{50}/mol/Liter
13a	CH	CH_3	4-FC_6H_4	CH_3	(E)—CH=CH	$2.6 \cdot 10^{-7}$
13b	CH	CH_3	4-ClC_6H_4	CH_3	(E)—CH=CH	$9.4 \cdot 10^{-8}$
13c	CH	CH_3	4-FC_6H_4	C_6H_5	(E)—CH=CH	$3.8 \cdot 10^{-8}$
13d	CH	iC_3H_7	4-FC_6H_4	CH_3	(E)—CH=CH	$9.1 \cdot 10^{-9}$
13e	CH	iC_3H_7	4-FC_6H_4	C_6H_5	(E)—CH=CH	$2.9 \cdot 10^{-9}$
13f	CH	4-FC_6H_4	iC_3H_7	C_6H_5	(E)—CH=CH	$4.0 \cdot 10^{-9}$
13g	CH	tC_4H_9	4-FC_6H_4	C_6H_5	(E)—CH=CH	$1.8 \cdot 10^{-8}$
13i	CH	iC_3H_7	4-FC_6H_4	2,5-$(CH_3)_2C_6H_4$	(E)—CH=CH	$5.0 \cdot 10^{-9}$
13j	CH	iC_3H_7	4-FC_6H_4	4-FC_6H_4	(E)—CH=CH	$2.3 \cdot 10^{-9}$
13k	N	CH_3	4-FC_6H_4	CH_3	(E)—CH=CH	$5.0 \cdot 10^{-7}$
13l	N	CH_3	4-ClC_6H_4	CH_3	(E)—CH=CH	$6.0 \cdot 10^{-7}$
13o	N	iC_3H_7	4-FC_6H_4	C_6H_5	(E)—CH=CH	$3.0 \cdot 10^{-9}$
13q	CH	iC_3H_7	4-FC_6H_4	iC_3H_7	(E)—CH=CH	$2.5 \cdot 10^{-9}$
13r	CH	$1C_3H_7$	4-FC_6H_4	tC_4H_9	(E)—CH=CH	$1.2 \cdot 10^{-9}$
13s	CH	iC_3H_7	4-FC_6H_4	cC_6H_{11}	(E)—CH=CH	$3.7 \cdot 10^{-9}$
missing						
missing						
13v	N	iC_3H_7	4-FC_6H_4	iC_3H_7	(E)—CH=CH	$2.5 \cdot 10^{-9}$
13w	N	iC_3H_7	4-FC_6H_4	4-FC_6H_4	(E)—CH=CH	$0.9 \cdot 10^{-9}$
13z	N	iC_3H_7	4-FC_6H_4	C_6H_5	$—CH_2—CH—$	$3.3 \cdot 10^{-9}$
13ab	CH	iC_3H_7	4-FC_6H_4	4-HOC_6H_4	(E)—CH=CH	$1.5 \cdot 10^{-9}$
13ac	CH	cC_3H_5	4-FC_6H_4	C_6H_5	(E)—CH=CH	$1.0 \cdot 10^{-9}$

2. Suppression or inhibition of HMG-CoA reductase in cell cultures of HEP-G2 cells

Monolayers of HEP-G2 cells in lipoprotein-free nutrient medium were preincubated with appropriate concentrations of the test substances for a defined time (for example 1 hour), the labeled precursor, for example sodium ^{14}C-acetate was added and then the incubation was continued (for example for 3 hours). Addition of an internal standard (^{3}H-cholesterol) was followed by alkaline hydrolysis of some of the cells. The lipids were extracted from the hydrolyzed cells using chloroform/methanol. Carrier cholesterol was added to this lipid mixture which was then subjected to preparative thin-layer chromatography, the cholesterol band was visualized with iodine vapor and then isolated, and the amount of ^{14}C-cholesterol formed from the ^{14}C-precursor was determined by scintigraphy. Cellular protein was determined in an aliquot of the cells, so that it is possible to calculate the amount of ^{14}C-cholesterol formed per mg of cellular protein in unit time. Comparison of this figure with the amount of ^{14}C-cholesterol

formed per mg of cellular protein and unit time in a culture treated in the same way but containing no test substance revealed the inhibitory effect of the particular test product on the cholesterol biosynthesis of HEP-G2 cell cultures.



Using the method described above, the following values for the inhibition of cholesterol biosynthesis (in HEP-G2 cells) were determined for the compounds according to the invention, for example (the IC_{50}/mol/-liter is the concentration of the compound which brings about 50% inhibition of cholesterol biosynthesis) (Tab. 2):

TABLE 2

Compound of Example	Z	R^1	R^2	R^3	A-B	IC_{50}/mol/liter
11c	CH	CH_3	4-F-C_6H_4	C_6H_5	(E)—CH=CH	$9 \cdot 10^{-8}$
11d	CH	i-C_3H_7	4-F-C_6H_4	CH_3	(E)—CH=CH	$5 \cdot 10^{-8}$
11e	CH	i-C_3H_7	4-F-C_6H_4	C_6H_5	(E)—CH=CH	$5 \cdot 10^{-9}$
11o	N	i-C_3H_7	4-F-C_6H_4	C_6H_5	(E)—CH=CH	$5 \cdot 10^{-9}$

The compounds of the general formula I or II are distinguished by strong inhibition of HMG-CoA reductase, the rate-determining enzyme of cholesterol biosynthesis.

The extent of inhibition which is characterized by IC_{50} values in the range 10^{-7}–10^{-9} mol per liter for compounds of the general formula I or II is distinctly higher than that for fully synthetic HMG-CoA reductase inhibitors known from the literature, such as, for example, those described by G. E. Stokker et al., J. Med. Chem. 29, 170 (1986).

The enzyme HMG-CoA reductase is widespread in nature. It catalyzes the formation of mevalonic acid from HMG-CoA. This reaction is a central step in cholesterol biosynthesis (cf. J. R. Sabine in CRC Series in Enzyme Biology: 3-hydroxy-3-methylglutaryl Coenzyme A Reductase, CRS Press Inc. Boca Raten, Fla. 1983 (ISBN 0-8493-6551-1)).

A connection is drawn between high cholesterol levels and a number of disorders such as, for example, coronary heart disease or arteriosclerosis. Hence the lowering of elevated cholesterol levels is an aim of therapy for the prevention and treatment of disorders of these types. One starting point for this is the inhibition or reduction of endogenous cholesterol biosynthesis. Inhibitors of HMG-CoA reductase block cholesterol biosynthesis at an early stage.

Hence the compounds of the general formula I or II are suitable as hypolipidemics and for the treatment or prophylaxis of arteriosclerotic changes.

Hence the invention also relates to pharmaceutical products based on these compounds and to their use as medicaments, in particular as hypolipodemics and for the prophylaxis of arteriosclerotic changes.

The compounds of the formula I or II are used as hypolipidemics or anti-arteriosclerotics in oral doses of 3 to 2500 mg, but preferably in the dose range 10–500 mg. These daily doses can, where required, also be divided into two to four single doses or administered in sustained release form. The dosage regimen may depend on the type, age, weight, sex and medical condition of the patient.

An additional cholesterol-lowering effect can be achieved by concurrent administration of the compounds according to the invention with substances which bind bile acids, such as, for example, anion exchanger resins. Excretion of bile acids results in an increase in neosynthesis and thus in an increase in cholesterol breakdown (cf. M. S. Brown, P. T. Koranen and J. C. Goldstein, Science 212, 628 (1981); M. S. Brown, J. C. Goldstein, Spektrum der Wissenschaft 1985, 1, 96).

The compounds of the formula I or II, according to the invention, can be used in the form of the δ-lactones, as the free acids or in the form of their physiologically acceptable inorganic or organic salts or as esters. Acids and salts or esters can be used in the form of their aqueous solutions or suspensions, or dissolved or suspended in pharmacologically acceptable organic solvents such as monohydric or polyhydric alcohols such as, for example, ethanol, ethylene glycol or glycerol, in triacetin, in alcohol/acetaldehyde diacetal mixtures, oils such as, for example, sunflower oil or fish liver oil, ethers such as, for example, diethylene glycol dimethyl ether, or polyethers such as, for example, polyethylene glycol, or in the presence of other pharmacologically acceptable polymeric vehicles such as, for example, polyvinylpyrrolidone, or in solid formulations.

The preferred pharmaceutical forms for the compounds of the formula I or II are solid, can be administered orally and may contain the customary auxiliaries. They are produced by customary methods.

Particularly suitable formulations for oral use are tablets, coated tablets or capsules. One dosage unit preferably contains 10 to 500 mg of active substance.

The compounds of the formula III, V, VI and VII are new and represent valuable intermediates for the preparation of compounds of the formula I. Hence the invention also relates to these compounds and to processes for their preparation.

Preliminary note: Unless otherwise specified, NMR spectra were measured in $CDCl_3$ with TMS as internal

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FROM THE U.S. PATENT OFFICE

OFFICIAL FILE WRAPPER

Columns 17 - 60

tered through kieselguhr and evaporated. Ix remained in the form of white crystals.

Yield: 3.93 g (98%).

Melting point: 170°–172° C.

$[\alpha]_D^{25}$(CH_3OH): +13°.

^{1}H-NMR: δ/ppm = 1.5–1.9 (m,2H), 1.9 (brs,1H), 2.6 (s,3H), 2.7 (s,3H), 2.6–3.0 (m,2H), 4.3 (m,1H), 4.5–4.6 (m,1H), 7.1–7.2 (m,2H), 7.4–7.5 (m,2H).

EXAMPLE 12b

1.0 g of the compound E-Ie (Example 11e) was reacted under the conditions indicated in Example 12a to give the hydrogenation product Iy. (R^1 = iC_3H_7, R^2 = 4-FC_6H_4, R^3 = C_6H_5, Z=CH, A—B=—CH_2—CH_2).

Yield: 0.91 g (91%).

Melting point: oil.

$[\alpha]_D^{25}$(CH_3OH): +26°.

^{1}H-NMR: δ/ppm = 1.3–1.8 (m,11H), 2.3–2.8 (m,7H), 3 4 (h,J=7 Hz,1H), 4.2 (mc,1H), 4.5 (mc,1H), 7.1 (mc,2H), 7.3–7.5 (m,6H), 8.1 (mc,2H)

MS: m/e=433 (M^+).

EXAMPLE 12c

1.0 g of the compound E-It (Example 11t) was reacted under the conditions indicated in Example 12a to give the hydrogenation product Iz. (R^1 = C_2H_5, R^2 = 4-FC_6H_4, R^3 = C_6H_5, Z=CH, A—B=—CH_2—CH_2).

Yield: 0.93 g (91%).

Melting point: 53°–55° C.

^{1}H-NMR: δ/ppm = 1.4 (mc,6H), 1.5–1.9 (m,4H), 2.5–2.9 (m,4H), 4.3 (mc,1H), 4.5 (mc,1H), 7.1 (mc,2H), 7.3–7.5 (m, 6H), 8.0 (mc,2H)

MS: m/e=429 (M^+).

It is possible in a manner analogous to that described in Example 12 to hydrogenate the compounds of the general formula I with A—B=—CH=CH— to give compounds of the general formula I with A—B=—CH_2—CH_2—.

EXAMPLE 13

Preparation of the salts of the free dihydroxy acids of the general formula II

Example 13a (R^1=CH_3, R^2=4-FC_6H_4, R^3=CH_3, R^4=K, Z=CH, A—B=(E)—CH=CH—)

(E)- and (Z)-(3R,5S)-3,5-Dihydroxy-7-(2,6-dimethyl-4-(4-fluorophenyl)pyridin-3-yl)-6-heptenoic acid potassium salts E-IIa and Z-IIa (as 30:70 mixture of Z and E isomers)

0.10 g (0.29 mmol) of the compound Ia was dissolved in 5 ml of ethanol. 2.9 ml (0.29 mmol) of a 0.1-molar solution of potassium hydroxide in ethanol was added to this solution at room temperature. The progress of the reaction was followed by thin-layer chromatography (mobile phase ethyl acetate/methanol 10:1). Precursor was no longer present after 3 h. The reaction solution was concentrated in vacuo. The potassium salt IIa remained in the form of white crystals.

Yield: 0.11 g (96%) (30:70 mixture of Z-IIa and E-IIa)

The isomers were then separated by medium pressure liquid chromatography.

Z-IIa: Rf (ethyl acetate/methanol 2:1): 0.23.

IR: 1605/1575 cm^{-1} (C=O band).

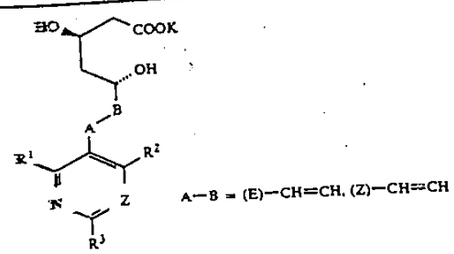
E-IIa: Rf (ethyl acetate/methanol 2:1) 0.19.

IR: 1610/1580 cm^{-1} (C=O band).

EXAMPLES 13b–13z

The compounds IIb–IIz were prepared in a manner analogous to that described in Example 13a (cf. Table 14).

TABLE 14



A—B = (E)—CH=CH, (Z)—CH=CH

Example	Compound	Z	R^1	R^2	R^3	Yield %	R_f(Z; E)
b	IIb	CH	CH_3	4-ClC_6H_4	CH_3	95	0.25; 0.23
c	IIc	CH	CH_3	4-FC_6H_4	CH_3	97	0.30; 0.26
d	IId	CH	iC_3H_7	4-FC_6H_4	CH_3	92	—; 0.29
e	IIe	CH	iC_3H_7	4-FC_6H_4	C_6H_5	99	—; 0.44
f	IIf	CH	4-FC_6H_4	iC_3H_7	C_6H_5	91	—; 0.38
g	IIg	CH	tC_4H_9	4-FC_6H_4	C_6H_5	97	—; 0.59
h	IIh	CH	iC_3H_7	4-$CH_3OC_6H_4$	C_6H_5	96	—; 0.47
i	IIi	CH	iC_3H_7	4-FC_6H_4	2,5-$(CH_3)_2C_6H_3$	100	—; 0.56
j	IIj	CH	iC_3H_7	4-FC_6H_4	4-FC_6H_4	94	—; 0.46
k	IIk	N	CH_3	4-FC_6H_4	CH_3	94	0.20; 0.14
l	IIl	N	CH_3	4-ClC_6H_4	CH_3	97	0.17; 0.13
m	IIm	N	CH_3	cC_6H_{11}	CH_3	96	0.32; 0.27
n	IIn	N	CH_3	4-ClC_6H_4	H	93	0.20; 0.15
o	IIo	N	iC_3H_7	4-FC_6H_4	C_6H_5	97	—; 0.35
p	IIp	N	iC_3H_7	4-FC_6H_4	CH_3	93	—; 0.31
q	IIq	CH	iC_3H_7	4-FC_6H_4	iC_3H_7	95	—; 0.46
r	IIr	CH	iC_3H_7	4-FC_6H_4	tC_4H_9	98	—; 0.53
s	IIs	CH	iC_3H_7	4-FC_6H_4	cC_6H_{11}	96	—; 0.55
t	IIt	CH	C_2H_5	4-FC_6H_4	C_6H_5	98	0.40; 0.34
u	IIu	CH	cC_6H_{11}	4-FC_6H_4	C_6H_5	100	—; 0.44
v	IIv	N	iC_3H_7	4-FC_6H_4	iC_3H_7	100	—; 0.34
w	IIw	N	iC_3H_7	4-FC_6H_4	4-FC_6H_4	100	—; 0.33

PATENT
CASE NO. 600-710

#29

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

102,648

In Re: WATTANASIN
Serial No.: 07/498,301
Filed: March 23, 1990
For: QUINOLINE ANALOGS OF MEVALONOLACTONE AND DERIVATIVES THEREOF

POWER TO INSPECT AND MAKE COPIES

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

Kindly permit Marian Schwartz, Ann Rutledge, Rosalie Jared, Somchay Chinyavong, Judy Valusek, James Jackson, Bobbie Judy, or Nancy Perry of Specialized Patent Services to inspect and make copies in the above noted matter, including recently declared Interference No. 102,648 in which said patent is involved.

Respectfully submitted,

June 19, 1992

By Diane Furman 6/19/92
Diane E. Furman
Registration No. 31,104
(201) 503-7332

SANDOZ CORP.
59 Route 10
E. Hanover, N.J. 07936

DEF:lcr

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE JUL 16 1992 #30

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN

v.

PICARD et al

v.

FUJIKAWA et al

INTERFERENCE 102,648
EXAMINER-IN-CHIEF:
MICHAEL SOFOCLEOUS

APPROVED

JUL 16 1992

By ..... Examiner-in-Chief

MOTION FOR EXTENSION OF TIME TO FILE
REPLIES, 37 C.F.R. 1.645, 1.635

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

BOX INTERFERENCE

SIR:

Pursuant to the provisions of the above rule, Fujikawa et al hereby requests a five-day extension of time to reply to Oppositions to Preliminary Motions in the above-captioned interference. Replies are currently due July 16, 1992. If granted, this Motion would make the Replies due July 21, 1992.

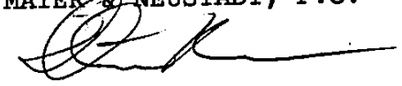
As grounds for the Request, undersigned counsel submits that the Opposition of the Junior Party to Fujikawa's Motion to Add Counts and Claims to the Application was not received until July 6, 1992, at which time undersigned counsel had left on vacation, intending to return July 13, 1992. Unfortunately, while on vacation, undersigned counsel injured his left hand, occasioning

surgery, which surgery is due to be completed July 16, 1992. An extension until July 21, 1992 would permit completion of the Replies.

Counsel for Wattanasin was contacted, and graciously indicated the Motion for Extension of Time would not be opposed. In the absence of Examiner-in-Chief Sofocleous, Examiner-in-Chief Smith indicated that on the grounds set forth above, the Motion for an Extension of five days would be granted. The cooperation and assistance of the Examiner-in-Chief is deeply appreciated.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

Crystal Square Five
Fourth Floor
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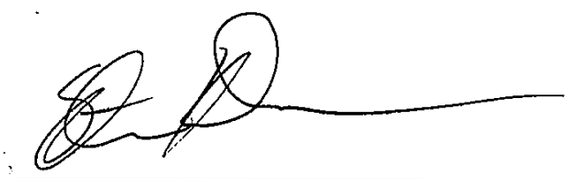
Arlington, Virginia 22202
(703) 521-5940

CERTIFICATE OF SERVICE

I hereby certify that a true copy of the foregoing MOTION FOR EXTENSION OF TIME TO FILE REPLIES, 37 C.F.R. 1.645, 1.635 was served by first class mail, postage prepaid, on counsel for the Party Wattanasin, as follows:

Diane E. Furman
SANDOZ CORP.
59 Route 10
E. Hanover, New Jersey 07936

this 16th day of July, 1992.



Steven B. Kelber

[redacted]

[redacted]

BOARD OF PATENT APPEALS & INTERFERENCES

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE JUL 16 1992 #30 31

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN

v.

PICARD et al

v.

FUJIKAWA et al

INTERFERENCE 102,648
EXAMINER-IN-CHIEF:
MICHAEL SOFOCLEOUS

MAILED

JUL 20 1992

PAT & T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

APPROVED

JUL 16 1992

By ..... Examiner-in-Chief

BOARD OF PATENT APPEALS & INTERFERENCES JUL 16 1992

MOTION FOR EXTENSION OF TIME TO FILE REPLIES, 37 C.F.R. 1.645, 1.635

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

BOX INTERFERENCE

SIR:

Pursuant to the provisions of the above rule, Fujikawa et al hereby requests a five-day extension of time to reply to Oppositions to Preliminary Motions in the above-captioned interference. Replies are currently due July 16, 1992. If granted, this Motion would make the Replies due July 21, 1992.

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Apps. 32—10

No. 102,648

Sofocleous
EXAMINER IN CHIEF

INTERFERENCE

Wattanasin S.N. 07/498,301

v

Picard et al P.N. 4,761,419

v

Fujikawa et al S.N. 07/233,752

Quinoline Type Mevalonolactones

Group 1201

PTO-257

102648
Vol. II
pgs. 32-70

102648

ATTORNEYS

Wattanasin v. Picardet et al. vs. Fujikawa et al.
(Patentee)

DECLARATION, MOTIONS DUE

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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.	:	MICHAEL SOFOCLEOUS
FUJIKAWA et al	:	

FUJIKAWA ET AL REPLY TO THE OPPOSITION
TO FUJIKAWA ET AL'S MOTION TO ADD COUNTS 3 AND 4

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

BOX INTERFERENCE

SIR:

In opposition to Fujikawa's Motion to Add Counts 3 and 4, and add claims to the Wattanasin application, Wattanasin essentially urges three different grounds of opposition. First, Wattanasin insists that the claims proposed by Fujikawa for the Wattanasin application, that correspond to Counts 3 and 4, are not patentable to Wattanasin, Wattanasin lacking a written description the same, 35 U.S.C. 112, first paragraph. Second, Wattanasin urges that the

evidence submitted with the Fujikawa Motion is inadequate to demonstrate that the subject matter of Counts 3 and 4 is directed to subject matter patentably distinct from Counts 1 and 2 in the interference. Third, Wattanasin objects to the Motion on the grounds that Fujikawa's Claim 18 is directed to subject matter closely related to the subject matter of Counts 3 and 4, and not shown to be patentably distinct therefrom. Each of the arguments is replied to, below.

I. Written Description in Wattanasin's Application

Wattanasin urges that Fujikawa's proposed Claims 11 and 12 for the Wattanasin application are unsupported by the Wattanasin disclosure, in that they lack a written description. It is to be particularly noted that the contentions of Wattanasin are unsupported by proof of any kind, and that in fact the evidence of record, including admissions by Wattanasin, supports the opposite conclusion.

In exploring any question of written description, attention is focused on whether or not the specification, as originally filed,

conveys to those of skill in the art that the inventors had possession of the invention at the time the application was filed. Quite conspicuously, any testimony from the inventors, regarding their possession of this invention, is absent from the Wattanasin opposition. Note that the standard for determining compliance with written description, whether or not those of skill in the art would conclude that applicants had possession of the invention at the time of filing, has been long established. In re Smith, 178 U.S.P.Q. 620 (C.C.P.A. 1973). Thus, the sole inquiry presented to the Board on this issue is whether or not one of ordinary skill in the art, reading the Wattanasin disclosure, would conclude that Wattanasin had possession of the invention addressed in Claims 11 and 12 at the time the Wattanasin application was filed.

The sole limitation of proposed Claims 11 and 12 Wattanasin urges is not described in the Wattanasin application is the identity of substituent R as cyclopropyl. Wattanasin urges that there is no specific recitation or exemplification of this species. Fujikawa agrees, but notes that the same is not required for written description. In re Kaslow, 217 U.S.P.Q. 1089, 1996 (Fed. Cir. 1983) and cases cited therein. Specifically, Wattanasin discloses that the substituent at the 2-position may be cycloalkyl

of 3-7 carbon atoms. This identifies a class of five possible substituents. The class is not all that large, and Fujikawa submits that, without more, one of ordinary skill in the art would clearly conclude that the compound of Claim 11, and process of Claim 12, was clearly within the scope of the invention discovered by Wattanasin at the time of filing. Indeed, Wattanasin urges the same. See page 6 of the Opposition. Under similar circumstances, courts of competent jurisdiction have repeatedly held that selection of one among five is clearly supported, for the purposes of written description. In re Driscoll, 195 U.S.P.Q. 434 (C.C.P.A. 1978) (one of 14); and In re Johnson, 194 U.S.P.Q. 187, 195-96 (C.C.P.A. 1977) (a reduction of from 12 to 10 members clearly supported).

While prior cases may be of limited value in determining compliance with the written description provision of 35 U.S.C. 112, first paragraph, it is respectfully submitted that, without more, prior cases have held that the selection of one member of a class of five, when that member is encompassed by the generic disclosure, is supported by that generic disclosure, in the absence of countervailing evidence. Clearly, one of ordinary skill in the art taught that the substituent at the 2-position may be any one of cyclo-

propyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl would clearly conclude that cyclopropyl is within the province of the invention of Wattanasin. Indeed, it is the likely starting point, having the lowest molecular weight. More is not required.

Beyond that, however, Wattanasin acknowledges that the Wattanasin application repeatedly exemplifies isopropyl. Indeed, isopropyl is mentioned by name as an alternate substituent at the 2-position. Having been taught that isopropyl is an acceptable substituent and within the scope of Wattanasin's invention, those of skill in the art would readily arrive at the selection of cyclopropyl, out of the disclosure of cycloalkyl of 3-7 carbon atoms, as the next logical, and analogous compound, isomerically related to exemplified species. Clearly, in the given case, there is more than simple narrowing of the Wattanasin claims from a genus of five to a sub-genus of one. Here there is additional supportive teaching that the isomer of that sub-genus is also suitable. It is well established that isomeric species are expected to behave in similar fashion, in the absence of evidence to the contrary. Those of skill in the art would certainly consider cyclopropyl to be within the scope of the compound and processes taught and claimed by Wattanasin.

The Wattanasin argument that there is no written description of the claims in question, Claims 11 and 12, must be rejected. The "selection", urged by Wattanasin to be totally beyond those of ordinary skill in the art, is simple, straightforward, and additionally supported by the selection of isopropyl as an alternate substituent in the disclosure of Wattanasin.

If further evidence were required, it is provided by Wattanasin. Wattanasin urges, pages 8-9 of its Opposition, that those of skill in the art were well aware that both isopropyl and cyclopropyl substituents could be employed in a similar position on related compounds. Specifically, Wattanasin relies on European Patent Publication 179,559. Regardless of what that publication actually teaches, there is a clear admission, on the part of Wattanasin, pages 8-9, that those of skill in the art, reading the Wattanasin application, would be aware that wherever isopropyl is taught for substitution next to the nitrogen atom on the ring, cyclopropyl may be similarly employed (note, as discussed below, Fujikawa does not agree that the art teaches that one would expect particular improvements in going from isopropyl to cyclopropyl in the subject matter of the claims of Wattanasin and Fujikawa). It is sufficient, for the issue of written description, to note that

those of ordinary skill in the art would be aware that given a teaching of isopropyl as an appropriate substituent for the position in question, one of skill in the art, taught that cycloalkyl of 3 carbon atoms was acceptable, would move to cyclopropyl. Again, Wattanasin's argument undercuts its position, and grant of the Fujikawa Motion is respectfully solicited.

II. The Evidence Offered in Support is Inadequate to Make Out Patentable Distinction

Fujikawa agrees with Wattanasin that it is incumbent on Fujikawa to demonstrate that the subject matter of Counts 3 and 4 is patentably distinct from the subject matter of Counts 1 and 2. Evidence of that patentable distinction is made out in the Declaration of Kitahara submitted with the Fujikawa Motion. Fujikawa submits herewith the Supplemental Declaration of Kitahara, providing similar evidence for the lactone species, Test B. As made out in paragraph 2 of the Declaration, this data simply was not available at the time of filing of the Fujikawa Motion. It is submitted herewith, in completion of the evidential burden placed on Fujikawa to demonstrate patentable distinction.

Wattanasin urges that the type of evidence presented does not make out an unexpected difference between the isopropyl and cyclopropyl classes (in the language adopted in the Wattanasin Opposition, the cyclopropyl class is the class of proposed Counts 3 and 4, while the isopropyl class is the class of current Counts 1 and 2). The Wattanasin position, unsupported by any evidence of record, is that the type of differences set forth, uniform superiority for the cyclopropyl class independent of substituent Z identity and test type, would be expected by those of ordinary skill in the art. Quite simply, the position adopted by Wattanasin is contrary to the expectations of those of ordinary skill in the art.

As made out in the Kitahara Declaration and Supplemental Declaration, regardless of the identity of moiety Z, the cyclopropyl class is always more than twice as active as the closely related isomeric species isopropyl and n-propyl. Indeed, for the sodium salt, the IC_{50} value for isopropyl is about 2.5 times greater than that for cyclopropyl, and the IC_{50} value for n-propyl is 22 times greater than that of cyclopropyl. Where other values for Z are considered, the comparison is even more drastic, the calcium salt cyclopropyl species having a five-fold greater activity, the

ethyl ester species having a fourteen-fold greater activity, and the lactone activity, again as measured by Test A, being nearly four times higher.

When the alternative test, Test B, is given, the relative values are similar. Further, Kitahara, one of particular skill in this art, concludes in both the Supplemental Declaration and original Declaration that such increased activity could not have been predicted on the basis of structure alone. While Wattanasin urges to the contrary, the Wattanasin position is unsupported by any evidence of any type. Attorney argument, alone, is not an adequate substitute for proof. The Wattanasin position must be rejected.

Wattanasin also urges that the level of skill in the art, as reflected by European Patent Publication 179,559 and U.S. Patent 4,925,852, would have predicted the differences obtained and reported in the Kitahara Declarations. Initially, it must be noted that U.S. Patent 4,925,852 is not part of the prior art, and not appropriate for consideration as to the level of skill brought to the question by artisans prior to the Fujikawa filing date. Specifically, Wattanasin urges that this patent was in the art prior to Fujikawa's assertion herein of patentable distinction and,

accordingly, must be considered. No legal support is provided, and Wattanasin's position is contrary to specific holdings on this issue. It is well established that facts, determined at a date after filing, are permissible to support a finding of non-obviousness as to compounds and processes, at the time of filing. Kansas Jack, Inc. v. Kuhn, 219 U.S.P.Q. 857 (Fed. Cir. 1983). Thus, the U.S. patent relied on by Wattanasin must be ignored, and attention focused only on the European patent publication.

European Patent Publication 179,559 is confined to compounds and processes patentably distinct from the compounds claimed herein. The formulas are substantially unrelated. Note that the European patent publication is confined to trans-6-[2-substituted-pyrrol-1-yl)alkyl]-pyran-2-ones, thus, compounds quite unrelated to the phenyl-substituted, lactone-substituted quinolines of the claimed invention. It is respectfully submitted that Wattanasin

has failed to make out any art-recognized equivalency between phenyl-substituted quinolines and the pyrroles of the reference. Indeed, review of the file history of U.S. Patent 5,011,930 reflects the conclusion of Fujikawa and the Patent Office that, without evidence of any type, the subject matter of Counts 3 and 4 and the disclosure of the European patent publication are patentably distinct, one from the other. In the absence of such an art-recognized equivalence, Wattanasin's argument is fatally defective.

Moreover, Fujikawa respectfully submits that Wattanasin deliberately, and without support, misrepresents the teaching of the European patent publication. Specifically, Wattanasin urges, in the last paragraph on page 9 and first paragraph of page 10 of its Opposition, that this European patent publication teaches that one of skill in the art would expect "particular improvements in activity relative to a genus of compounds with the same series." Further, Wattanasin urges that one of ordinary skill in the art would have expected the cyclopropyl species to be better than the isopropyl species. No such teaching appears in the European patent publication. Indeed, at best, the European patent publication identifies isopropyl and cyclopropyl as equivalent. See, e.g.,

page 8, lines 30-35, wherein these two species are identified as equivalent. Many other preferences in the European patent publication identify isopropyl as preferred to the cyclic species. See the sixth preferred genus, page 9, line 31 - page 10, line 12; the fifth preferred genus, particularly, page 9, lines 28-30; the fourth, page 7, line 29; and the second, page 7, line 20. Indeed, only the first and third preferences equate isopropyl and cyclopropyl. Accordingly, it is respectfully submitted that the only reference Wattanasin submits that may be looked to, the European patent publication, at best establishes isopropyl and cyclopropyl to be equivalent, and may indicate isopropyl to be superior.

Further, it is respectfully submitted that in fact, the compounds of the European Patent Publication relied upon by Wattanasin have a much higher activity when isopropyl, rather than cyclopropyl is used as a substituent at the identified position. Submitted herewith please find Roth et al, Journal of Medicinal Chemistry, 1990, 33, pages 21-31, which, authored by the inventors identified in the European Patent Publication relied upon by Wattanasin in its Opposition, reflects the activities of certain of the compounds embraced by the European Patent Publication, EP 179-559.

Particular attention is directed to page 25 of the reference, which shows, Table III, that the IC_{50} value for compound 8x (trans-6-[2[2-(4-fluorophenyl)-5-(1-methylethyl)-1-H-pyrrol-1-yl]-ethyl] tetrahydro-4-hydroxy-2-H-pyran-2-one is 0.40, while the IC_{50} value for the cyclopropyl isomeric counterpart (compound 8aa) is 2.2. Thus, the isopropyl species is 5.5 times more active, by Warner-Lambert's own reckoning, than the corresponding cyclopropyl species. To the extent the Warner Lambert European Publication is relevant to the issue at all, it again suggests those of ordinary skill in the art would look to the isopropyl species to have higher activity than the cyclopropyl species. Rather than supporting the Wattanasin position, the Warner Lambert publication serves to only more clearly highlight the fact that the art would <u>not</u> expect higher activities in the cyclopropyl species designated for the Count of the Interference, clearly drawing attention to the unexpected and unobvious nature of the proposed Counts 3 and 4.

Certainly, at best, there is no teaching in the art anywhere that one of ordinary skill in the art would expect the cyclopropyl class to be superior, consistently so by better than a factor of two, regardless of the identity of the Z substituent. This, it has been sworn to, could not have been predicted on the basis of

structure alone. Wattanasin offers no proof to the contrary, and, accordingly, the Wattanasin Opposition cannot succeed. Grant of the Motion is respectfully requested.

III. Fujikawa's Claim 18

On page 14 of the Opposition, in the final paragraph, prior to the Conclusion, Wattanasin makes reference to Fujikawa's Claim 18, which is a 4-chlorophenyl-substituted species. The Wattanasin reference to this claim is not clearly understood. Fujikawa has no data to indicate that the chlorine-substituted species is equivalent to the fluorine-substituted species, and, indeed, the record lacks disclosure of the same. The burden would be on Wattanasin to demonstrate to the contrary. Notwithstanding the above, should the Examiner find it appropriate, it would be acceptable to designate Claim 18 of the Fujikawa patent application as corresponding to Counts 3 and 4 of the interference.

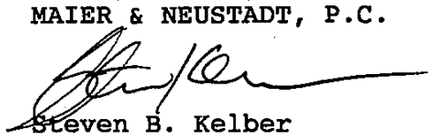
IV. Conclusion

The Wattanasin position is totally unsupported by evidence confirming the arguments offered by Wattanasin's counsel. Wattanasin, having urged that those of ordinary skill would recognize both isopropyl and cyclopropyl as suitable substituents at the 2-position in the compounds of the claimed invention, and having disclosed the suitability of both isopropyl and cycloalkyl of 3 carbon atoms as suitable substituents at that position, cannot successfully argue that Claims 11 and 12 proposed by Fujikawa are not supported by the written description of the Wattanasin application. Similarly, there is absolutely no evidence of record that suggests that the differences between the compounds of Counts 3 and 4, proposed by Fujikawa, and Counts 1 and 2, respectively, would be anywhere predicted by those of skill in the art. Indeed, the prediction would be quite to the contrary, that those of skill would expect similar performance, given the isomeric relationship of the compounds tested. Having successfully demonstrated patentable distinction between Counts 3 and 4 and Counts 1 and 2, and having an appropriate claim for Wattanasin to contest priority with respect thereto, the Fujikawa Motion should be granted. Should the

Examiner-in-Chief find it necessary, Claim 18 may be designated as corresponding to Counts 3 and 4, and benefit with respect thereto, on the grounds previously urged in Fujikawa's Motion for Benefit as to those counts, is respectfully requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



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

(±)-*cis*-[4-(5,7-Diamino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-2-cyclopentenyl]carbinol (11a). Compound 9a (267 mg, 1 mmol) was processed as described for compound 6a with a reaction time of 20 h at 50 °C. The residual mixture was absorbed onto silica gel (2 g); it was packed into a column (2.0 × 10 cm) and eluted by $CHCl_3$–MeOH (15:1) to yield 11a as white crystals, 204 mg (83%). The crude product was recrystallized from ethanol–water (2:1) to yield 11a: mp 240–242 °C dec; MS (30 eV, 240 °C) *m/e* 247 (M^+), 229 ($M^+ - 18$), 217 ($M^+ - 30$), 151 (B^+); IR (KBr) 3600–3100 (NH_2, OH), 1700, 1650, 1600 cm^{-1} (C=O, C=C, C=N); UV λ_{max} 253, 283 nm in 0.1 N HCl; NMR (dimethyl-d_6 sulfoxide) δ 7.80–7.20 (br, 2 H, NH_2, D_2O exchangeable), 6.50–6.30 (s, 2 H, NH_2, D_2O exchangeable), 6.15–6.10 and 5.95–5.90 (dd, 2 H, CH=CH vinyl, J = 5.0 Hz), 5.65–5.55 (m, 1 H, H-1'), 4.75–4.65 (t, 1 H, CH_2OH, D_2O exchangeable), 3.65–3.40 (m, 2 H, CH_2OH), 2.95–2.85 (m, 1 H, H-4'), 2.65–2.55 (m, 1 H, CHH'), 1.90–1.80 (m, 1 H, CHH'). Anal. ($C_{10}H_{13}N_7O \cdot H_2O$) C, H, N.

(±)-*cis*-[2-(5,7-Diamino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)cyclopentyl]carbinol (11b). Compound 9b (268 mg, 1 mmol) was processed as described for 9a to yield 220 mg of 11b (88%), which was recrystallized from ethanol–water (1:2) to afford pink-white crystals: mp 223–225 °C; MS (30 eV, 250 °C) *m/e* 249 (M^+), 218 ($M^+ - 31$), 151 (B^+); IR (KBr) 3600–3100 (NH_2, OH), 1700, 1600 cm^{-1} (C=C, C=N); UV λ_{max} 253, 283 nm in 0.1 N HCl; NMR (dimethyl-d_6 sulfoxide) δ 7.85–7.25 (br, 2 H, NH_2, D_2O exchangeable), 6.50–6.30 (s, 2 H, NH_2, D_2O exchangeable), 4.95–4.85 (m, 1 H, H-1'), 4.65–4.60 (t, 1 H, CH_2OH, D_2O exchangeable), 3.50–3.40 (d, 2 H, CH_2OH), 2.35–1.60 (m, 7 H, H-4', CH_2CH_2, CHH'). Anal. ($C_{10}H_{13}N_7O$) C, H, N.

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

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

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

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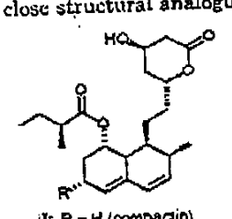
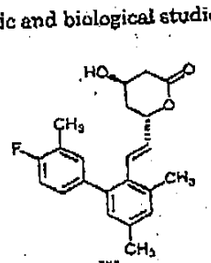
A novel series of *trans*-6-(2-pyrrol-1-ylethyl)-4-hydroxypyran-2-ones and their dihydroxy acid derivatives were prepared and evaluated for their ability to inhibit the enzyme HMG-CoA reductase in vitro. A systematic study of substitution at the 2- and 5-positions of the pyrrole ring revealed that optimum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

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



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



III

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

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

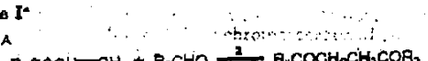
(2) (a) Endo, A. *J. Antibiot.* 1979, *32*, 852. (b) Alberts, A.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Pachett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hirshfield, J.; Hoogsteen, K.; Liesch, J.; Springer,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

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

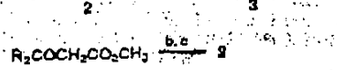
(4) For a review, see: Rosen, T.; Heathcock, C. *Tetrahedron* 1986, *42* (18), 4909–51.

Scheme I[a]

Method A



Method B



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

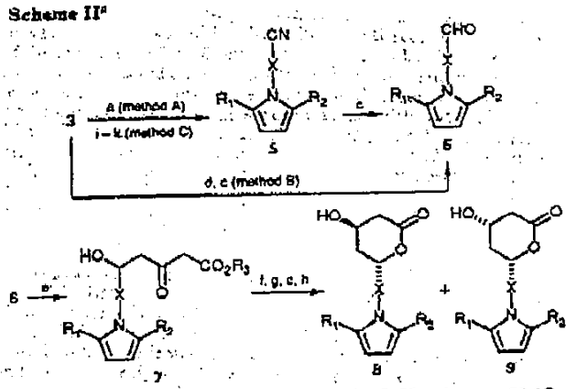
feature possessed by all of these agents was a large lipophilic group held in a particular spatial relationship with respect to the 4-hydroxypyran-2-one moiety. Indeed, examination of CPK models of these inhibitors suggested that the ortho phenyl ring might occupy the same space as the isobutyric ester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

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

Chemistry

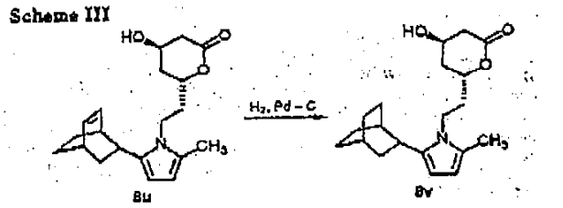
Our general synthetic strategy entailed the preparation of a suitable 1,4-diketone (3, Table I), either by the thiazolium salt chemistry developed by Stetter (Scheme I, method A)[8] or by alkylation of a β-keto ester with an α-halo ketone followed by hydrolysis and decarboxylation (method B). The Stetter reaction proved to be the more versatile and generally higher yielding of the two. Paal–Knorr cyclization with 3-aminopropionitrile or an ω-amino acetal provided the pyrroles in good yield (Scheme II). The one exception was 1-(4-fluorophenyl)-5,5-dimethylhexane-1,4-dione (3q), which was extremely resistant to cyclization. After considerable experimentation, it was found that treatment with ethanolamine in acetic acid resulted in an exothermic reaction from which the pyrrole was isolated in 84% yield. Mesylation and displacement with potassium cyanide in DMF/H_2O afforded the requisite nitrile. Reduction of the nitriles 5 with DIBAL-H produced the desired aldehydes 6 in good yields (Table II). Condensation of 6 with the dianion of methyl or ethyl acetoacetate under the conditions of Weiler[9] afforded the corresponding alcohols 7. Sih et al.[10] reported the reduction of a related δ-hydroxy-β-keto ester in their synthesis of compactin in which little stereoselectivity (2:1 erythro:threo) was found employing either sodium or zinc borohydride. We, and others,[5b] have found excellent selectivity (>10:1 erythro:threo) employing the procedure of Narasaka and Pai,[11] in which 7 was complexed with a trialkylborane prior to treatment with borohydride at low temperature. The resultant boronate was hydrolyzed with

Scheme II[a]

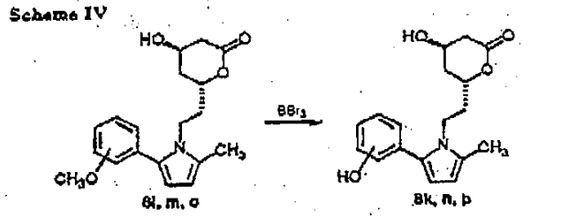


[a] (a) H_2N–X–CN, HOAc, reflux. (b) DIBAL-H, toluene, −78 °C. (c) aqueous HCl. (d) H_2N–X–$CH(OEt)_2$, toluene, cat. *p*-TSA, reflux. (e) $^-CH_2CO^-CHCH_2CH_3$, THF, −78 °C. (f) *n*-Bu_2B, $NaBH_4$, −78 °C. (g) H_2O_2, OH^-. (h) Toluene, reflux. (i) H_2N–X–OH, HOAc. (j) CH_3SO_2Cl, pyr. (k) KCN, DMF–H_2O, 100 °C.

Scheme III



Scheme IV



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

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

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

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

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

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

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

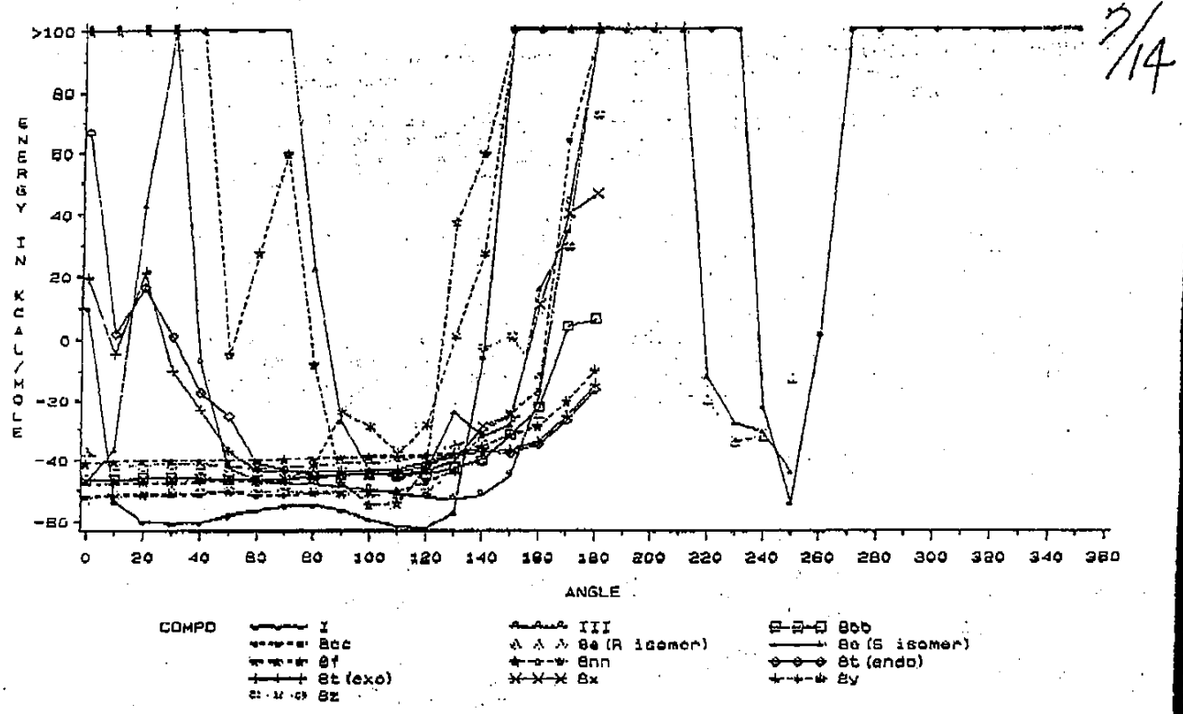


Figure 2. CAMSEQ-II energies calculated for comparable orientations of the lactone side chain. Dashed lines represent less potent analogues (8j, 8z, 8bb, 8cc, and 8nn; CSI $IC_{50} > 5$ μM).

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

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

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

Structure–Activity Relationships

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

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

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

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

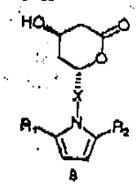
(15) Kita, T.; Brown, M.; Goldstein, J. J. Clin. Invest. 1980, 66, 1094–1100.

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

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

8/14

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



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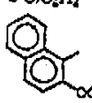
no.	X	R_1	R_2	mp, °C	% yield	formula[a]	IC_{50},[b] μM, CSI	log IC_{50}, CSI	relative potency,[d] CSI	IC_{50},[e,f] μM, COR	log IC_{50}, COR
8a		4-FC_6H_4	CH_3	155–7	32	$C_{25}H_{30}FNO_3$	26	−4.7	0.10	–	–
8b		4-FC_6H_4	CH_3	84–7	29	$C_{22}H_{28}FNO_3$	24	−4.6	0.01	63	−4.2
8c		4-FC_6H_4	CH_3	142–5	21	$C_{22}H_{28}FNO_3$	>100	−4.0	<0.01	>100	−4.0
8d	$-CH_2CH_2CH_2-$	4-FC_6H_4	CH_3	oil	41	$C_{19}H_{22}FNO_3$	53	−4.3	0.02	–	–
8e	$-CH(CH_3)CH_2-$	4-FC_6H_4	$CH(CH_3)_2$	167–9	30	$C_{21}H_{26}FNO_3$	5.0	−5.3	0.50	40	−4.4
8f	$-CH_2CH_2-$	4-FC_6H_4	CH_3	oil	32	$C_{18}H_{20}FNO_3$	0.51	−6.3	0.90	2.8	−5.6
8g	$-CH_2CH_2-$	Ph	CH_3	89–91	29	$C_{18}H_{21}NO_3$	1.4	−5.9	0.40	13	−4.9
8h	$-CH_2CH_2-$	4-PhC_6H_4	CH_3	104–7	35	$C_{24}H_{25}NO_3$	23	−4.6	0.10	23	−4.6
8i	$-CH_2CH_2-$	4-$MeOC_6H_4$	CH_3	95–96	50	$C_{19}H_{23}NO_4$	13	−4.9	0.10	28	−4.6
8j	$-CH_2CH_2-$	4-ClC_6H_4	CH_3	118–121	28	$C_{18}H_{20}ClNO_3$	10	−5.0	0.20	8.2	−5.5
8k	$-CH_2CH_2-$	4-HOC_6H_4	CH_3	161–2	–	$C_{18}H_{21}NO_4$	2.6	−5.6	1.0	6.3	−5.2
8l	$-CH_2CH_2-$	3-$F_3CC_6H_4$	CH_3	oil	65	$C_{19}H_{20}F_3NO_3$	1.5	−5.8	0.30	5.4	−5.3
8m	$-CH_2CH_2-$	3-$MeOC_6H_4$	CH_3	106–9	21	$C_{19}H_{23}NO_4$	2.5	−5.6	0.80	11	−5.0
8n	$-CH_2CH_2-$	3-HOC_6H_4	CH_3	144–5	–	$C_{18}H_{21}NO_4$	1.9	−5.7	1.40	12	−5.0
8o	$-CH_2CH_2-$	2-$MeOC_6H_4$	CH_3	112–3	38	$C_{19}H_{23}NO_4$	2.1	−5.7	0.90	25	−4.6
8p	$-CH_2CH_2-$	2-HOC_6H_4	CH_3	140–2	–	$C_{18}H_{21}NO_4$	2.5	−5.6	1.10	30	−4.5
8q	$-CH_2CH_2-$	2-naphthyl	CH_3	foam	30	$C_{22}H_{23}NO_3$[f]	16	−4.8	0.10	3.6	−5.4
8r	$-CH_2CH_2-$	1-naphthyl	CH_3	137–8	21	$C_{22}H_{23}NO_3$	1.8	−5.8	0.70	4.0	−5.4
8s	$-CH_2CH_2-$	cyclohexyl	CH_3	129–130	25	$C_{18}H_{27}NO_3$	0.69	−6.2	0.50	2.2	−5.6
8t	$-CH_2CH_2-$		CH_3	125–6	20	$C_{19}H_{23}NO_3$	1.4	−5.8	1.10	5.8	−5.2
8u	$-CH_2CH_2-$		CH_3	135–8	13	$C_{20}H_{27}NO_3$[g]	1.3	−5.9	1.60	8.2	−5.5
8v	$-CH_2CH_2-$		CH_3	135–9	68	$C_{20}H_{29}NO_3$	2.3	−5.6	1.10	2.3	−5.6
8w	$-CH_2CH_2-$	Ph_2CH	CH_3	129–132	33	$C_{25}H_{27}NO_3$	13	−4.9	0.10	8.9	−5.4
8x	$-CH_2CH_2-$	4-FC_6H_4	$CH(CH_3)_2$	105–6	34	$C_{20}H_{24}FNO_3$	0.40	−6.4	30.3	0.23	−6.6
8y	$-CH_2CH_2-$	4-FC_6H_4	$C(CH_3)_3$	117–8	24	$C_{21}H_{26}FNO_3$	1.8	−5.8	1.70	1.8	−5.7
8z	$-CH_2CH_2-$	4-FC_6H_4	$CH(C_2H_5)_2$	107–8	36	$C_{22}H_{28}FNO_3$	20	−4.7	0.10	32	−4.5
8aa	$-CH_2CH_2-$	4-FC_6H_4	cyclopropyl	foam	22	$C_{20}H_{22}FNO_3$	2.2	−5.7	1.30	2.6	−5.6
8bb	$-CH_2CH_2-$	4-FC_6H_4	cyclobutyl	88–9	5	$C_{21}H_{24}FNO_3$	17	−4.8	0.20	–	–
8cc	$-CH_2CH_2-$	4-FC_6H_4	cyclohexyl	64–6	30	$C_{23}H_{28}FNO_3$	>100	−4.0	<0.01	>100	−4.0
8dd	$-CH_2CH_2-$	4-FC_6H_4	CF_3	oil	58	$C_{18}H_{17}F_4NO_3$	0.25	−6.6	8.0	0.63	−6.2
8ee	$-CH_2CH_2-$	3-FC_6H_4	$CH(CH_3)_2$	87–9	40	$C_{20}H_{24}FNO_3$	1.3	−5.9	1.8	2.6	−5.6
8ff	$-CH_2CH_2-$	2-FC_6H_4	$CH(CH_3)_2$	oil	9	$C_{20}H_{24}FNO_3$[h]	3.2	−5.5	0.9	1.8	−5.8
8gg	$-CH_2CH_2-$	2,4-$F_2C_6H_3$	$CH(CH_3)_2$	75–7	8	$C_{20}H_{23}F_2NO_3$	1.6	−5.8	1.5	2.6	−5.6
8hh	$-CH_2CH_2-$	2-$MeOC_6H_4$	$CH(CH_3)_2$	oil	16	$C_{21}H_{27}NO_4$	2.2	−5.6	1.0	5.6	−5.2
8ii	$-CH_2CH_2-$	2,6-$(MeO)_2C_6H_3$	$CH(CH_3)_2$	foam	36	$C_{22}H_{29}NO_5$	19	−4.7	0.2	87	−4.1
8jj	$-CH_2CH_2-$	2,6-$Me_2C_6H_3$	$CH(CH_3)_2$	oil	25	$C_{22}H_{29}NO_3$[i]	12	−4.9	0.2	16	−4.8
8kk	$-CH_2CH_2-$	3-$iPrOC_6H_4$	$CH(CH_3)_2$	oil	12	$C_{23}H_{31}NO_3$[j]	3.2	−5.5	0.9	–	–
8ll	$-CH_2CH_2-$	2-ClC_6H_4	$CH(CH_3)_2$	foam	25	$C_{20}H_{24}ClNO_3$	3.2	−5.5	0.5	9.1	−5.0
8mm	$-CH_2CH_2-$		$CH(CH_3)_2$	oil	34	$C_{23}H_{29}NO_4$[k]	9.6	−5.0	0.2	25	−4.6
8nn (I)	$-CH_2CH_2-$ compactin	$CH(C_2H_5)_2$	$CH(C_2H_5)_2$	oil	20	$C_{21}H_{33}NO_3$	>100 0.026	−4.0 −7.6	<0.01 100	– 0.025	– −7.6

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

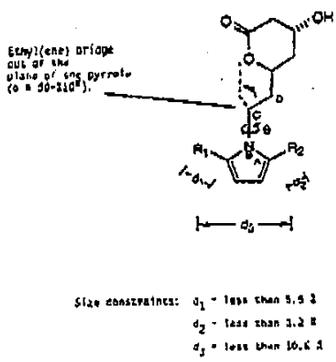


Figure 3. Summary of conclusions from the molecular modeling study.

Molecular Modeling

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

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

Thus, it is concluded that a conformation of the ethyl(ene) bridge to the 4-hydroxypyran-2-one ring out of the plane (90–120°) of the parent ring systems is consistent with increased potency as a HMGR inhibitor. Interestingly, this corresponds to the calculated minimum energy and not the X-ray conformation[1b] of compactin. The X-ray conformation represents a secondary minimum at θ = 24.5°, 1.2 kcal/mol higher in energy, probably due to packing interactions.

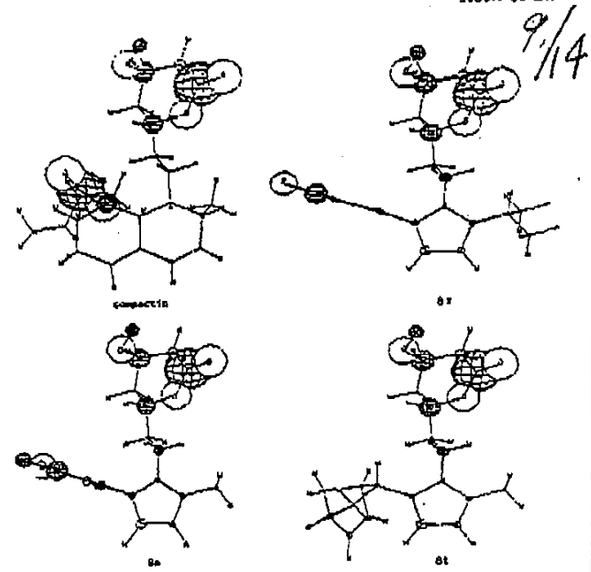


Figure 4. Charge distribution of compactin and selected analogues. Hatched and open spheres represent positive and negative charges, respectively. Sphere size is proportional to the magnitude of the atomic charge.

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

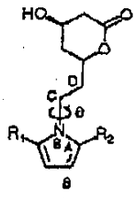
The maximum lengths of R_1 and R_2 and the overall width of the molecule across the parent ring system from R_1 to R_2 are given in Table IV. The calculations show a clear dependence of CSI potency on all three distances summarized in Figure 3. High potency (IC_{50} < 1.6 μM) is observed only for those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

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

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

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

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



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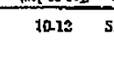
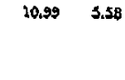
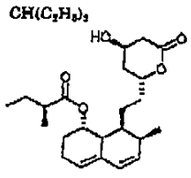
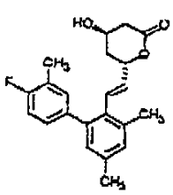
no.	R_1	R_2	IC_{50},[a] μM	lactone side chain rotations, CAMSEQ energies[b] 0°	90°	180°	min en conf	maximum overall width, Å (R_1 to R_2)	maximum lengths, Å R_1	R_2	other rotations[c]
8e	4-FC_6H_4 (α-Me)[d]	$CH(CH_3)_2$	5.0	−37.10[e]	−41.43[e]	100[e]	60°, −42.92[e]	10.12	5.58	2.48	 also bond from α-Me to lactone side chain from 0° to 60° by 20°
8o	4-FC_6H_4 (α-Me)[f]	$CH(CH_3)_2$	5.0	−46.93[e]	−27.09[e,g]	100[e]	0°, −46.93[f]	10.12	5.58	2.48	as above
8f	4-FC_6H_4	CH_3	0.51	−40.92	−39.27	−10.08	0°, −40.92	7.66	5.58	1.50	methyl group (R_2) from 0° to 60° by 10°
8j	4-ClC_6H_4	CH_3	10					9.33	5.69	1.50	as above
8t[h]		CH_3	1.4	67.11	−44.98	−16.40	80°, −44.98	7.22	3.64	1.50	bond from R_1 to pyrrole from 0° to 360° by 20°
8t[i]		CH_3	1.4	19.63	−43.55	−15.01	70°, −44.65	7.97	4.27	1.50	as above
8x	4-FC_6H_4	$CH(CH_3)_2$	0.40	−46.64	−45.06	46.29	0°, −46.64	10.12	5.58	2.48	
8y	4-FC_6H_4	$C(CH_3)_3$	1.6	−47.77	−24.10[j]	100	0°, −47.77	10.20	5.58	2.48	all bonds from 0° to 60° by 20°
8z	4-FC_6H_4	$CH(C_2H_5)_2$	20	−52.35	−50.97	100	0°, −52.35	10.99	5.58	3.74	 terminal methyls set to a staggered conformation
8bb	4-FC_6H_4	cyclobutyl	17	−46.46	−44.82	6.01	60°, −46.64	10.62	5.58	3.35	bond from R_2 to pyrrole from 0° to 360° by 20°
8cc	4-FC_6H_4	cyclohexyl	100	−51.76	−50.31	100	0°, −51.76	11.92	5.58	4.33	bond from R_2 to pyrrole from 0° to 360° by 20°
8nn	$CH(C_2H_5)_2$	$CH(C_2H_5)_2$	100	100	−47.28	100	100°, −54.31	9.41	3.74	3.74	see compound 8z above
I			0.025	10.17[j]	−56.04[j]	100[j]	120°, −61.74[j]	8.81	5.66	1.50	terminal alkyl groups set to a staggered conformation
III			0.01	100	−48.89	100	130°, −52.92	8.74	5.52	1.50	bond from R_2 (Me) to phenyl from 0° to 60° by 20°; bond from R1 (4-F,3-MeC_6H_3) to phenyl from 0° (biphenyl coplanar) to 90° by 15°

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

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

Conclusions

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

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

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

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

Experimental Section

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

Preparation of 1-(4-Fluorophenyl)-5-methyl-1,4-hexanedione (3p). Method A. 1-(4-Fluorophenyl)-2-propen-1-one (43.0 g, 287 mmol) was mixed with 31.2 mL (344 mmol) of isobutyraldehyde, 28 mL (200 mmol) of triethylamine, and 14.5 g (58 mmol) of 2-(2-hydroxyethyl)-3-methyl-4-benzylthiazolium chloride. The mixture was stirred at 70 °C under nitrogen for 12 h, cooled to room temperature, and partitioned between ether (500 mL) and water (100 mL). The aqueous layer was further extracted with ether (300 mL). The combined ether extracts were washed successively with water (200 mL), 2 M HCl (2 × 100 mL), and brine (100 mL) and dried. Filtration and concentration to dryness in vacuo provided an oil which was distilled (bp 115–120 °C, 0.2 mmHg) to provide 36.7 g (58%) of the title compound which [illegible] $CDCl_3$) δ 1.11 (d, 6 H, J = 7 Hz), 2.27 (septet, 1 H, J = 7 Hz), 2.8 (m, 2 H), 3.05 (m, 2 H), 7.12 (t, 3 H), 7.98 (m, 2 H). An analytical sample could be obtained by recrystallization from hexane, mp 51–3 °C. Anal. ($C_{12}H_{15}FO_2$) C, H, N.

Alternate Synthesis of 3p. A mixture of 2-methyl-4-penten-4-one[38] (2.0 g, 20 mmol), 4-fluorobenzaldehyde (2.4 g, 20 mmol), 2 mL (14 mmol) of triethylamine, and 1.0 g (4 mmol) of 2-(2-hydroxyethyl)-3-methyl-4-benzylthiazolium chloride was stirred under nitrogen for 5 h at 70 °C, cooled to room temperature, and partitioned between ether (200 mL) and water (50 mL). The water layer was extracted with ether (200 mL). The ether extracts were combined, washed successively with water (50 mL), 2 M HCl (50 mL), and brine (50 mL), and dried. After concentration to dryness in vacuo, the residue was flash chromatographed on silica gel with hexane–ethyl acetate (20:1 v/v) as eluant, affording 2.6 g of 3p, mp 47–49 °C.

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

Preparation of 2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrol-1-yl]-1-cyanoethane (5, R_1 = 4-FPh, R_2 = $CH(CH_3)_2$, X = $-CH_2CH_2-$). A mixture of 3p (365 g, 1.65 mol), 3-aminopropionitrile $^1/_2$-fumarate (234 g, 1.88 mol), and 1 g of p-TSA in glacial acetic acid (1800 mL) was stirred and heated at reflux for 8 h. After cooling to room temperature, the solution was poured into ice water (3 L). The solid that formed was isolated by suction filtration and recrystallized from isopropyl ether and hexane (212 g, mp 75–78 °C). The filtrate was extracted with ether (2 × 1 L). The combined ether extracts were washed with water (1 L), saturated aqueous sodium bicarbonate (until gas evolution ceased), and brine (500 mL) and dried. Filtration and concentration to dryness in vacuo afforded a solid which was recrystallized from isopropyl ether to provide a further 98 g of the title compound (310 g total, 73%): IR (KBr) 2990, 2249, 1566, 1522, 1484, 1219, 1162, 847, 782 cm^{-1}; 200-MHz NMR ($CDCl_3$) δ 1.30 (d, 6 H, J = 7 Hz), 2.32 (t, 2 H, J = 7 Hz), 2.92 (septet, 1 H, J = 7 Hz), 4.22 (t, 2 H, J = 7 Hz), 6.00 (d, 1 H, J = 3.5 Hz), 6.10 (d, 1 H, J = 3.5 Hz), 7.0–7.4 (m, 4 H). Anal. ($C_{16}H_{17}FN_2$) C, H, N.

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

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

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

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

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

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

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

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

A solution of KCN (1.54 g, 23.6 mmol) and KI (1.16 g, 10 mmol) in water (12 mL) was added dropwise to a stirred, 70 °C solution of the mesylate (4.0 g, 18 mmol) in DMF (35 mL). The resulting solution was heated under reflux for 24 h, cooled, and poured into ice water. The mixture was extracted with ether (2 × 200 mL). The combined ether extracts were washed with water (50 mL), 2 M HCl (25 mL), bicarbonate (2 × 50 mL), and brine (25 mL), dried, and concentrated to dryness in vacuo. Flash chromatography of the residue on silica gel, eluting with hexane–ethyl acetate (20:1, v/v), provided 2.8 g (83%) of the title compound: 90-MHz NMR ($CDCl_3$) δ 1.42 (s, 9 H), 2.20 (t, 2 H), J = 2 Hz), 4.30 (t, 2 H, J = 7 Hz), 5.90 (d, 1 H, J = 4 Hz), 6.00 (d, 2 H, J = 4 Hz), 6.9–7.4 (m, 4 H).

Prepartion of 6-[2-(2-Bicyclo[2.2.2]oct-2-yl-5-methyl-1*H*-pyrrol-1-yl)ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (8v). To a solution of 8u (0.3 g, 0.91 mmol) in ethyl acetate (10 mL) was added 0.03 g of 10% Pd–C. The mixture was evacuated, placed under a balloon of hydrogen (1 atm) at room temperature, and stirred overnight. The suspension was filtered through Celite and concentrated to dryness in vacuo, and the solid residue was recrystallized from isopropyl ether to afford 0.21 g of 8v (68%), mp 135–139 °C. Anal. ($C_{19}H_{29}NO_3$) C, H, N.

General Demethylation Procedure (Preparation of 8n). BBr_3 (11 mmol) was dissolved in 8 mL of CH_2Cl_2 and added dropwise to a solution of 8m (1.2 g, 3.64 mmol) in 100 mL of CH_2Cl_2 at −20 °C under dry nitrogen. The mixture was stirred for 2 h, and then a further 2 mmol of BBr_3 was added. The solution was allowed to warm slowly to 0 °C, poured into saturated aqueous bicarbonate (500 mL), and extracted with ethyl acetate (2 × 200 mL). The combined organic extracts were washed with 10% aqueous bisulfite (50 mL), saturated aqueous bicarbonate (30 mL), and brine (30 mL), dried, and concentrated to dryness in vacuo. Flash chromatography of the residue provided 450 mg of impure phenol. Two recrystallizations from isopropyl ether provided pure 8n, mp 110–111.5 °C. Anal. ($C_{18}H_{27}NO_4$) C, H, N.

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

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

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

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

Assay Conditions. The assay was carried out in duplicate in 16 × 125 mm screw-capped tubes. The reaction mixture contained the following, on ice (initial concentrations): 0.1 mL of 20 mM NAD, 0.1 mL of 20 mM NADP, 0.1 mL of 200 mM glucose 6-phosphate, 0.5 mL of 0.12 mM niacinamide, and 0.2 mL of the 10 × drug stocks. Controls were also run with 0.2 mL of a mixture of 1 mL of 0.1 N KOH, plus 11 mL of homogenizing buffer in place of drug. One milliliter of the crude microsomal preparation was added immediately after the drugs, to give a total volume of 2 mL. Final drug concentrations were 10^{-4} to 10^{-7} M, or in the case of compactin, 10^{-6} to 10^{-9} M. The samples were warmed at 37 °C for 5 min before adding the radioactive precursor. [1-^{14}C]Acetate was used in the amount of 2.88 μCi per sample, plus 96 μmol of sodium acetate as cold carrier. When [^{3}H]-mevalonate was used, the amount of 0.5 μCi per sample with cold carrier was added to make a total of 0.2 μmol per sample. Volume of radiolabel per sample was 100 μL. After receiving radiolabel, samples were incubated at 37 °C for 1 h and treated with 2.5 mL of 10% KOH in ethanol, and the saponification was carried out at 70 °C for 2 h in a water bath. After cooling to room temperature, the nonsaponifiable lipids (cholesterol accounts for approximately 80% of nonsaponifiable lipids; the remainder are methyl sterols) were extracted by shaking the samples with 4.2 mL of hexane for 10 min. After phase separation, 2 mL of the hexane layer was diluted with 8 mL of Handifluor and counted.

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

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

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

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

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

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

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

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

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

Molecular Modeling. Selected analogues were modeled by using an in-house modified version[17] of CAMSEQ-II[18] operating on an IBM 3083 machine. The structure of compactin was obtained from published[19] X-ray data; the structure of pyrrole came from a compendium[20] of minimized structures. Coordinates for other groups were extracted from the library of fragments within CAMSEQ-II. Structures III and 8 were built to attaching the side chain containing the 4-hydroxypyran-2-one ring (coordinates for which were copied from the X-ray structure of compactin) to the benzene and pyrrole rings, respectively, and adding the other substituents. Side chains were rotated to remove steric contacts.

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

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

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

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Registry No. 1 (R_1 = Ph), 768-08-6; 1 (R_1 = 4-F-C_6H_4), 51694-59-3; 1 (R_1 = 4-Ph-C_6H_4), 42575-11-1; 1 (R_1 = 4-Cl-C_6H_4), 7448-87-5; 1 (R_1 = 4-CH_3O-C_6H_4), 7448-86-4; 1 (R_1 = 3-F_3C-C_6H_4), 123184-14-5; 1 (R_1 = 3-CH_3O-C_6H_4), 51694-60-6; 1 (R_1 = 2-CH_3O-C_6H_4), 77942-10-0; 1 (R_1 = 2-naphthyl), 4452-06-6; 1 (R_1 = 1-naphthyl), 22422-69-1; 1 (R_1 = bicyclo[2.2.1]-hept-5-en-2-yl), 100234-78-4; 1 (R_1 = bicyclo[2.2.2]-oct-5-en-2-yl), 123184-15-6; 1 (R_1 = cyclohexyl), 2177-34-6; 1 (R_1 = Ph_2CH), 93021-71-7; 1 (R_1 = $CH(C_2H_5)_2$), 123184-16-7; 1 (R_1 = 2-F-C_6H_4), 89638-21-1; 1 (R_1 = 2,4-F_2-C_6H_3), 123184-17-8; 1 (R_1 = $CH(CH_3)_2$), 1606-47-9; 2 (R_2 = CH_3), 75-07-0; 2 (R_2 = $CH(CH_3)_2$), 78-84-2; 2 (R_2 = $CH(C_2H_5)_2$), 97-96-1; 2 (R_2 = cyclopropyl), 1489-69-6; 2 (R_2 = cyclobutyl), 2987-17-9; 2 (R_2 = cyclohexyl), 2043-61-0; 2 (R_2 = $C(CH_3)_3$), 630-19-3; 2 (R_2 = 4-F-C_6H_4), 459-57-4; 2 (R_2 = C_2H_5), 123-38-6; 3a, 583-05-1; 3b, 123183-95-9; 3c, 63472-37-7; 3d, 53842-12-9; 3e, 2108-54-5; 3f, 123183-96-0; 3g, 123183-97-1; 3h, 104562-48-3; 3i, 123183-98-2; 3j, 123263-79-6; 3k, 70353-45-6; 3l, 123183-99-3; 3m, 61771-79-7; 3n, 123184-00-9; 3o, 123184-01-0; 3p, 104568-88-5; 3q, 123184-02-1; 3r, 123184-03-2; 3s, 123184-04-3; 3t, 123184-05-4; 3u, 123184-06-5; 3v, 123184-07-6; 3w, 123184-08-7; 3x, 123184-09-8; 3y, 123184-10-1; 3z, 123184-11-2; 3aa, 123184-12-3; 3bb, 123184-13-4; 5a, 123184-20-3; 5b, 123184-21-4; 5c, 123184-22-5; 5d, 123184-23-6; 5e, 123184-89-4; 5f, 123184-24-7; 5g, 123184-25-8; 5h, 123184-26-9; 5i, 123184-27-0; 5j, 123184-28-1; 5k, 123184-29-2; 5l, 123184-30-5; 5m, 123184-31-6; 5n, 123184-32-7; 5o, 123184-33-8; 5p, 123184-34-9; 5q, 123184-35-0; 5r, 123184-36-1; 5s, 123184-37-2; 5t, 104568-69-6; 5u, 123184-88-3; 5v, 123184-38-3; 5w, 123184-39-4; 5x, 123184-40-7; 5y, 123184-41-8; 5z, 104568-91-4; 5aa, 104568-69-6; 5bb, 123184-42-9; 5cc, 123184-43-0; 5dd, 123184-44-1; 5ee, 123184-45-2; 5ff, 123184-46-3; 5gg, 123184-47-4; 5hh, 123184-48-5; 5ii, 123184-49-6; 5jj, 123184-50-9; 6a, 123184-51-0; 6b, 123184-52-1; 6c, 123184-53-2; 6d, 123184-54-3; 6e, 123184-55-4; 6f, 123184-56-5; 6g, 123184-57-6; 6h, 123184-58-7; 6i, 123184-59-8; 6j, 123184-60-1; 6k, 123184-61-2; 6l, 123184-62-3; 6m, 123184-63-4; 6n, 123184-64-5; 6o, 123184-65-6; 6p, 123184-66-7; 6q, 123184-67-8; 6r, 123184-68-9; 6s, 123184-69-0; 6t, 104568-70-9; 6u, 123184-70-3; 6v, 123184-71-4; 6w, 123184-72-5; 6x, 123184-73-6; 6y, 123184-74-7; 6z, 123184-75-8; 6aa, 123184-76-9; 6bb, 123184-77-0; 6cc, 123184-78-1; 6dd, 123184-79-2; 6ee, 123184-80-5; 6ff, 123184-81-6; 6gg, 123184-82-7; 6hh, 123184-83-8; 6ii, 123184-84-9; 6jj, 123184-85-0; 7a, 123184-90-7; 7b, 123184-91-8; 7c, 123184-92-9; 7d, 123184-93-0; 7e, 123184-94-1; 7f, 123184-95-2; 7g, 123184-96-3; 7h, 123184-97-4; 7i, 123184-98-5; 7j, 123184-99-6; 7k, 123185-00-2; 7m, 123185-01-3; 7o, 123186-02-4; 7q, 123185-03-5; 7r, 123185-04-6; 7s, 123185-05-7; 7t, 123185-06-8; 7u, 123185-07-9; 7w, 123185-08-0; 7x, 104568-71-0; 7y, 123185-09-1; 7z, 123185-10-4; 7aa, 123185-11-5; 7bb, 123185-12-6; 7cc, 123185-13-7; 7dd, 123185-14-8; 7ee, 123185-15-9; 7ff, 123185-16-0; 7gg, 123185-17-1; 7hh, 123185-18-2; 7ii, 123185-19-3; 7jj, 123185-20-6; 7kk, 123185-21-7; 7ll, 123185-22-8; 7mm, 123185-23-9; 7nn, 123185-24-0; 8a, 123185-25-1; 8b, 123185-26-2; 8c, 123185-27-3; 8d, 123185-28-4; 8e (stereoisomer 1), 123185-29-5; 8e (stereoisomer 2), 123185-49-9; 8f, 104568-74-3; 8g, 105356-37-4; 8h, 104568-81-2; 8i, 104568-78-7; 8j, 123185-30-8; 8k, 123185-31-9; 8l, 104568-80-1; 8m, 123185-32-0; 8n, 123185-33-1; 8o, 104568-77-6; 8p, 123185-34-2; 8q, 104568-83-4; 8r, 104568-82-3; 8s, 104568-79-8; 8t (stereoisomer 1), 123355-04-4; 8t (stereoisomer 2), 123283-97-6; 8u, 123185-35-3; 8v, 123185-36-4; 8w, 104568-85-6; 8x, 104568-73-2; 8y, 104568-76-5; 8z, 123185-37-5; 8aa, 104568-75-4; 8bb, 123185-38-6; 8cc, 123185-39-7; 8dd, 104568-92-5; 8ee, 123185-40-0; 8ff, 123185-41-1; 8gg, 123185-42-2; 8hh, 105356-38-5; 8ii, 123185-43-3; 8jj, 123185-44-4; 8kk, 123185-45-5; 8ll, 123185-46-6; 8mm, 123185-47-7; 8nn, 123185-48-8, $EtCOCH_2CO_2Me$, 30414-53-0; $CF_3COCH_2CO_2Me$, 83643-84-9; m-$FC_6H_4COCH_2Br$, 53631-18-8; $(CH_3)_2CHCH_2CO_2Me$, 42558-54-3; p-$FC_6H_4COCH_2Br$, 403-29-2; 2,6-$(MeO)_2C_6H_3COCH_2Br$, 123184-19-0; 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride, 4568-71-2; 2-(2-hydroxyethyl)-3-methyl-4-benzylthiazolium chloride, 123184-18-9; 3-aminopropionitrile $^1/_2$-fumarate, 2079-89-2; 2-[2-(4-fluorophenyl)-5-(1,1-dimethylethyl)-1*H*-pyrrol-1-yl]-2-ethanol, 123184-86-1; 2-[2-(4-fluorophenyl)-5-(1,1-dimethylethyl)-1*H*-pyrrol-1-yl]-2-ethyl methanesulfonate, 123184-87-2; methyl acetoacetate, 105-45-3; cholesterol, 57-88-5.

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

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

D. R. Sliskovic,* B. D. Roth, M. W. Wilson, M. L. Hoefle, and R. S. Newton

Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, Michigan 48105. *Received March 16, 1989*

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

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

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

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

0022-2623/90/1833-0031$02.50/0

CERTIFICATE OF SERVICE

I hereby certify that a true copy of the foregoing

1. **FUJIKAWA ET AL REPLY TO THE OPPOSITION TO FUJIKAWA ET AL'S MOTION TO ADD COUNTS 3 AND 4**

2. **J. Med. Chem, 1990,33, 21-31**

3. **EXECUTED JOINT STIPULATION TO DESIGNATE CLAIM 1 OF U.S. PATENT 5,011,930 AS CORRESPONDING TO THE COUNT OF THE INTERFERENCE, 37 CFR §1.642**

was served by first class mail, postage prepaid, on counsel for the Party Wattanasin, as follows:

Diane E. Furman
SANDOZ CORP.
59 Route 10
E. Hanover, New Jersey 07936

this 21st day of JULY, 1992.

Steven B. Kelber

#33

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
	:	INTERFERENCE 102,648
V.	:	EXAMINER-IN-CHIEF:
	:	MICHAEL SOFOCLEOUS
PICARD ET AL	:	
	:	
V.	:	
	:	
FUJIKAWA ET AL	:	

JOINT STIPULATION TO
DESIGNATE CLAIM 1 OF U.S. PATENT 5,011,930
AS CORRESPONDING TO THE COUNT OF THE INTERFERENCE,
37 CFR §1.642

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231
BOX INTERFERENCE

SIR:

The parties against whom Judgment has not been entered in the above-captioned Interference, Wattanasin and Fujikawa et al, hereby jointly stipulate that Claim 1 of U.S. Patent 5,011,930 should be designated as corresponding to Count 1 (or substituted Count 1) of the above-captioned Interference. The parties agree that Claim 1 of U.S. Patent 5,011,930 embraces subject matter that may not be patentably distinct from either the current or proposed Count of

the above-captioned Interference.

The parties further agree that Claims 2-7 of U.S. Patent 5,011,930 do not correspond to the Count of the Interference or any of the proposed Counts of the Interference.

Accordingly, pursuant to the provisions Rule 642, the parties jointly request the Examiner-in-Chief designate Claim 1 of U.S. Patent 5,011,930, and Claim 1 only of that patent, as corresponding to Count 1 or substitute Count 1 of the Interference.

BY: _____
STEVEN B. KELBER
REG. NO. 30,073
ATTORNEY FOR FUJIKAWA ET AL
Date: July 10, 1992

BY: Diane Furman
DIANE E. FURMAN
REG. NO. 31,104
ATTORNEY FOR WATTANASIN
Date: July 1, 1992

CERTIFICATE OF SERVICE

I hereby certify that a true copy of the foregoing

1. **FUJIKAWA ET AL REPLY TO THE OPPOSITION TO FUJIKAWA ET AL'S MOTION TO ADD COUNTS 3 AND 4**
2. J. Med. Chem, 1990,33, 21-31
3. **EXECUTED JOINT STIPULATION TO DESIGNATE CLAIM 1 OF U.S. PATENT 5,011,930 AS CORRESPONDING TO THE COUNT OF THE INTERFERENCE, 37 CFR §1.642**

was served by first class mail, postage prepaid, on counsel for the Party Wattanasin, as follows:

Diane E. Furman
SANDOZ CORP.
59 Route 10
E. Hanover, New Jersey 07936

this 21st day of JULY, 1992.

Steven B. Kelber

#34

Case No. 600-7101/CONT/INT.(1)
Patent

FYI

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

JUL 27 1992

RECEIVED IN
BOX INTERFERENCE

WATTANASIN

v.

PICARD et al.

v.

FUJIKAWA et al.

Interference No. 102,648

Examiner-in-Chief: M. Sofocleous

REPLY OF WATTANASIN TO FUJIKAWA ET AL. OPPOSITION TO WATTANASIN MOTION TO SUBSTITUTE A COUNT

BACKGROUND

The opposition of the party Fujikawa et al. to the party Wattanasin's Preliminary Motion under 37 CFR 1.633(c)(1) to substitute a count is on two limited and hypertechnical grounds:

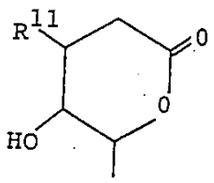
(1) There is an apparent error in the depiction of one of the three lactone structures representing the substituent "Z" of Wattanasin's proposed Substitute Count I; and

(2) Wattanasin has not specifically requested via contingent motion, that Count 2 of this interference also be modified to call for administration of a compound of Wattanasin's proposed Substitute Count I rather than the present Count 1 of the interference.

REMARKS

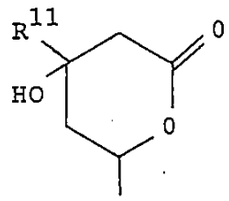
(1) Wattanasin agrees with Fujikawa et al. that in Wattanasin's proposed Substitute Count I, the following structure representing the substituent "Z":

"a"



should be changed to:

"b"



Structure "a" is incorrect because the -OH group should be a substituent on the same carbon atom of the lactone ring on which R^{11} is a substituent, rather than a substituent on the adjacent carbon atom. The correct structure "b", above, is consistent with definition (b) of substituent "Z" of claim 1 of the Wattanasin involved application, and is identical to the first lactone structure for the "Z" substituent of Fujikawa et al. in claim 1 of their involved application.

Wattanasin regrets the inadvertent error and notes that it resulted from photocopying an incorrect printed structure depicted in the Abstract of Fujikawa's U.S. Patent No. 5,011,930 (which issued on a divisional application of the Fujikawa et al. involved application).

Accordingly, Wattanasin respectfully requests in the accompanying "Wattanasin Motion to Correct Typographical Error..." that proposed Substitute Count I be corrected by replacing structure "a" therein with the correct structure "b".

(2) With respect to the second ground of the Fujikawa et al. Opposition to Wattanasin's Rule 633(c)(1) Motion, Wattanasin acknowledges that the Motion to substitute was not accompanied by a motion to modify Count 2 contingent on the granting of the motion to substitute.

However, it is Wattanasin's position that the presence or absence of such a contingent motion with respect to Count 2 has no effect on Wattanasin's motion to substitute a count.

Moreover, if the Wattanasin motion to substitute is granted and proposed Count I becomes Count 1 of this interference, then there is no need to amend existing Count 2 because Count 2 is automatically dependent on Count 1. It is self-evident that Count 2 is dependent on Count 1 irrespective of whether Count 1 comprises the original Count 1 of the interference as declared or Substitute Count 1.

Accordingly, for the reasons set forth herein and in Wattanasin's Rule 633(c)(1) Motion to substitute a count, it is respectfully requested that the Wattanasin motion be granted.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORP.
59 Route 10
E. Hanover, NJ 07936

DEF:rmf
Enc.: Wattanasin Motion to Correct Typographical Error

July 21, 1992

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 July 21, 1992
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
July 21, 1992
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

REPLY OF WATTANASIN TO FUJIKAWA ET AL. OPPOSITION TO WATTANASIN MOTION TO SUBSTITUTE A COUNT

was served on counsel for the party Fujikawa et al., this 21st day of July 1992, by postage pre-paid first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
Attn: Steven B. Kelber, Esq.
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Arlington, VA 22202

Diane Furman 7/21/92
Diane E. Furman

#35

Case No. 600-7101/CONT/INT.(2) FYI
Patent

JUL 27 1992

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

RECEIVED IN
BOX INTERFERENCE

WATTANASIN

v.

PICARD et al.

v.

FUJIKAWA et al.

Interference No. 102,648

Examiner-in-Chief: M. Sofocleous

WATTANASIN MOTION TO CORRECT TYPOGRAPHICAL ERROR IN PROPOSED SUBSTITUTE COUNT I

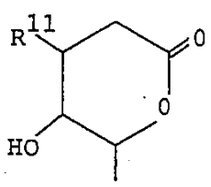
Wattanasin hereby moves to correct proposed Substitute Count I to correct an inadvertent typographical error in one of the structures representing the substituent "Z" of the structural formula therein. This motion is necessitated by one of the grounds raised by Fujikawa et al. in their opposition to the Wattanasin Rule 633(c)(1) motion to substitute a count.

REMARKS

The party Fujikawa et al. in their Opposition have identified a typographical error in the Wattanasin Substitute Count I. Wattanasin acknowledges the error, which was inadvertent.

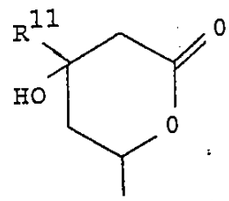
Accordingly, Wattanasin herein moves to correct Substitute Count I by replacing the following incorrect structure appearing on page 3 of its Rule 633(c)(1) Motion:

"a"



with the following correct structure:

"b"



Structure "a" is incorrect because the -OH group should be a substituent on the same carbon atom of the lactone ring on which R^{11} is a substituent, rather than a substituent on the adjacent carbon atom. The correct structure "b", above, is consistent with definition (b) of substituent "Z" of claim 1 of applicant's involved application, and is identical to the first lactone structure for the "Z" substituent of Fujikawa et al. in claim 1 of their involved application.

Wattanasin notes that the error inadvertently resulted from photocopying an incorrect printed structure depicted in the Abstract of Fujikawa's U.S. Patent No. 5,011,930.

Accordingly, Wattanasin respectfully requests that the Wattanasin proposed Substitute Count I be corrected by substituting the above structure "b" for structure "a" therein, of the "Z" substituent.

The error is regretted, and entry of this motion would be gratefully appreciated.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORP.
59 Route 10
E. Hanover, NJ 07936
DEF:rmf

July 21, 1992

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 July 21, 1992
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
July 21, 1992
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN MOTION TO CORRECT TYPOGRAPHICAL ERROR IN PROPOSED SUBSTITUTE COUNT I

was served on counsel for the party Fujikawa et al., this 21st day of July 1992, by postage pre-paid first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
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Arlington, VA 22202

Diane Furman 7/21/92
Diane E. Furman

#36

Case No. 600-7101/CONT/INT.(3) FYI
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN

v.

PICARD et al.

v.

FUJIKAWA et al.

Interference No. 102,648

Examiner-in-Chief: M. Sofocleous

REPLY OF WATTANASIN TO FUJIKAWA ET AL. OPPOSITION TO WATTANASIN 37 CFR §§1.635 AND 1.633(e) MOTIONS

BACKGROUND

The party Wattanasin by Rule 635 Motion has moved to include claim 1 of the Fujikawa et al. related patent, U.S. 5,011,930 (hereinafter the "'930 patent") in this interference; or alternatively by Contingent Preliminary Motion under Rule 633(e), Wattanasin has sought to declare an additional interference between the involved application of Wattanasin and the '930 patent of Fujikawa et al. [Fujikawa et al. in their Statement of Related Applications have indicated that they have now taken the '930 patent into reissue as application Serial No. 07/799,058.]

The party Fujikawa et al. have opposed the Wattanasin Rule 635 and 633(e) motions, principally on the ground that the motions are not specifically authorized by the Rules.

Wattanasin herein responds to the Opposition of Fujikawa et al.

REMARKS

In implementing the new rules of interference effective February 11, 1985, the Patent and Trademark Office stated that "The object of the interference will be to resolve all controversies as to all interfering subject matter defined by one or more counts. A final decision in the interference will determine who, if anyone, is entitled to claims which correspond to a count." [emphasis supplied] 1050 OG 385.

Consistent with the above statement of administrative purpose to resolve all interfering subject matter defined by one or more counts, the interference rules do specifically provide that if during the pendency of an interference, the EIC becomes aware of an application or a patent not involved in the interference which claims the same patentable invention as a count in the interference, the EIC may add the application or patent to the interference on such terms as may be fair to all parties, 37 CFR 1.642. (See also 37 CFR 1.610(e), which gives the EIC discretion "to determine a proper course of conduct in an interference for any situation not specifically covered by this part.")

It is therefore believed in conformity with the overall purpose of the interference rules to include an additional patent or application of a party which contains claims directed to interfering subject matter.

Wattanasin submits that the factual context of the present interference particularly justifies the granting of Wattanasin's Rule 635 or 633(e) Motions, and give the EIC substantial reason to exercise his discretion to involve claim 1 of the Fujikawa et al. '930 patent (or any corresponding claim of the reissue application). That is, claim 1 of the Fujikawa et al. '930 patent clearly corresponds to, and is substantially embraced by, counts 1 and 2 of this interference (as well as to Wattanasin's proposed substitute count I), and therefore would not require that an additional count be added to the interference.

Furthermore, in view of this specific factual setting, the prior opinions cited by Fujikawa et al. in their Opposition are not considered squarely on point.

In Theeuwes v. Bogentoft, 2 USPQ2d 1378 (Comm. of Pats. 1987), patentee Theeuwes unsuccessfully moved to add or substitute a pending Theeuwes application to the interference. However, in denying the motion, the opinion of the Commissioner was careful to clarify that it was not apparent why the requested addition of the copending application would be necessary, since the stated purpose of Theeuwes' motion was to permit broadening of the count to include his best proofs, which Theeuwes in any case would be permitted to do without addition of the copending application, 2 USPQ2d at 1379.

In Gerk v. Cottringer, 17 USPQ2d 1615 (POBAI 1990), Gerk unsuccessfully moved under Rule 633(c)(2) or 633(c)(3) to involve an additional application of Cottringer et al. in the interference. However, there is no indication of the relationship, if any, of the involved patent or application of Cottringer and the application which Gerk sought to be included.

In the instant case, Wattanasin is seeking to involve a claim of another patent (or corresponding reissue application) of Fujikawa et al. which issued on a divisional application of the involved application of Fujikawa et al. and which is already substantially covered by Counts 1 and 2 (and the Wattanasin proposed Substitute Count I) of the present interference.

In the interest of administrative economy and fairness to Wattanasin, there should be a full and final resolution of the matters at issue in this interference. Assuming arguendo that Wattanasin's 635 or 633(e) motions are denied, then the possibility will exist that Fujikawa will emerge from reissue with a claim still within the scope of Count 1 of this interference, and Wattanasin could bear the burden of reinstituting interference on the very same issues that are now before the EIC.

As a final matter, Fujikawa et al. have advanced a technical ground for opposition to Wattanasin's Motion under Rule 635, with regard to a need for certification of opposing counsel [Rule 637(b)]. Wattanasin acknowledges this inadvertent omission.

However, the EIC is advised that counsel for Fujikawa et al. and the undersigned have been conferring in an attempt to resolve by agreement the issues raised by Wattanasin's Rule 635 [or 633(e)] Motion. More particularly, counsel for the parties have reached agreement on a joint stipulation to be filed in this proceeding which states that claim 1 of the Fujikawa et al. '930 patent should be designated as corresponding to Count 1 (or proposed Substitute Count I) of the present interference, and that said claim 1 embraces subject matter that may not be patentably distinct from either the current or proposed count of this interference. (A reference is made to this stipulation by Fujikawa et al. in their Opposition on page 2, fourth line from bottom.) These activities indicate good faith efforts by the parties to resolve the issues raised by the Wattanasin Rule 635 Motion, notwithstanding the lack of formal certification therein.

Furthermore, Fujikawa's citation to M. v. V., 6 USPQ2d 1039 (Bd. Pat. App. Interfer. 1987) is not considered to support its request for dismissal or denial of the Wattanasin 635 Motion on the ground of technical insufficiency. In that case, notwithstanding that movant's 635 Motion lacked a certification pursuant to 637(b), the Board nevertheless did not deny or dismiss the motion on that ground but instead went on to consider the motion on the merits, 6 USPQ2d at 1040.

Accordingly, for the reasons indicated above and as outlined in the Wattanasin Motion under Rule 635 and Contingent Motion under Rule 633(e), the EIC is respectfully requested to act favorably on the subject motions of Wattanasin.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

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July 21, 1992

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 July 21, 1992
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
July 21, 1992
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

REPLY OF WATTANASIN TO FUJIKAWA ET AL. OPPOSITION TO WATTANASIN 37 CFR §§1.635 AND 1.633(e) MOTIONS

was served on counsel for the party Fujikawa et al., this 21st day of July 1992, 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 7/21/92
Diane E. Furman

#37

Case No. 600-7101/CONT/INT.(4)
Patent

FYI

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

JUL 27 1992

RECEIVED IN
BOX INTERFERENCE

WATTANASIN
v.
PICARD et al.
v.
FUJIKAWA et al.

Interference No. 102,648
Examiner-in-Chief: M. Sofocleous

REPLY OF WATTANASIN TO FUJIKAWA ET AL. OPPOSITION TO WATTANASIN MOTION FOR BENEFIT

BACKGROUND

Fujikawa et al. have opposed the Wattanasin Contingent Motion for Benefit (37 CFR 1.633(f)) primarily on the ground that Wattanasin has not shown how the parent U.S. application constitutes a constructive reduction to practice of the Wattanasin proposed Substitute Count I.

Wattanasin submits that the Fujikawa et al. opposition is without basis, for the reasons set forth below.

REMARKS

It is a matter of record that:

(1) Wattanasin's involved application is a R60 continuation application of a now-abandoned parent application; and

(2) The parent application is the only application of record on which Wattanasin can base a request for benefit; and

(3) The EIC has already independently granted Wattanasin the benefit of the parent filing date in connection with Counts 1 and 2 when this interference was declared; and

(4) Fujikawa et al. have not contested Wattanasin's right to the benefit of the parent filing date in connection with Counts 1 and 2.

Wattanasin's Contingent Motion for Benefit (Rule 633(f)) was filed concurrently with three Preliminary Motions: Motion under 633(c)(1); Motion under Rule 635; and Contingent Motion under Rule 633(e). Rule 637(c)(1)(vi) requires a request for benefit in connection with a 633(c) Motion. Rule 637(e)(1)(viii) requires such a motion to accompany a Rule 633(e) Motion. No specific requirement in this regard exists with reference to Rule 635.

It is obvious that Wattanasin's Contingent Motion for Benefit was filed in connection with the abovementioned motions under Rules 633(c)(1), 635 and 633(e), since the Motion for Benefit expressly states that it is contingent on the granting of any one or more of the motions being filed concurrently therewith.

It is further evident that the granting of the Rule 633(c)(1) Motion would have resulted in the substitution of Wattanasin's Substitute Count I for the present Count 1 of the interference.

It is still further apparent that Wattanasin has effectively fulfilled the requirements of Rule 633(f) with respect to proposed Substitute Count I.

Wattanasin fulfills these requirements by: (1) identifying the earlier Wattanasin application and certifying that a copy was served on Fujikawa et al.; and (2) showing that the earlier application constitutes a constructive reduction of the Substitute Count I by identifying relevant specific pages of the parent application (namely, pages 33-35 and pages 51-53) which contain everything necessitated by the first paragraph of 35 USC §112 for constructive reduction to practice of at least one compound embraced by said proposed Substitute Count I. More particularly, the disclosure at pages 51-53 (i.e. Examples 3A-E and 4) satisfies the written description, how-to-make, and best mode requirements for at least one compound within the scope of proposed Substitute Count I; and the utility statement at pages 33-35 of the parent specification satisfies the how-to-use requirement of 35 USC § 112 for at least one compound within the scope of Substitute Count I.

Therefore, given that the EIC has already held that the Wattanasin parent application fulfills the requirement for priority of 35 USC §112 with respect to Counts 1 and 2, and that on the present facts the Motion for Benefit is a virtual "formality" to reaffirm that which the EIC has already granted with respect to proposed Substitute Count I, Wattanasin hereby traverses the Fujikawa et al. Opposition to the Wattansin Motion for Benefit and submits that it is without foundation.

Respectfully submitted,

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July 21, 1992

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Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
July 21, 1992
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

REPLY OF WATTANASIN TO FUJIKAWA ET AL. OPPOSITION TO WATTANASIN MOTION FOR BENEFIT

was served on counsel for the party Fujikawa et al., this 21st day of July 1992, by postage pre-paid first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
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Diane Furman 7/21/92
Diane E. Furman

Case No. 600-7101/CONT/Int.(5) #38
Patent
FYI

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

JUL 27 1992
RECEIVED IN BOX INTERFERENCE

WATTANASIN
v.
PICARD et al.
v.
FUJIKAWA et al.

Interference No. 102,648
Examiner-in-Chief: M. Sofocleous

WATTANASIN SECOND CONTINGENT MOTION FOR BENEFIT 37 CFR §1.633(f)

Contingent on the granting of Wattanasin's concurrently filed "Motion to Correct Typographical Error in Proposed Substitute Count I," the party Wattanasin hereby moves to be accorded the benefit of parent application Serial No. 07/318,773 filed March 3, 1989, from which the involved application is a Rule 60 continuation, with respect to said corrected Substitute Count I.

This will certify that a complete copy of the file of Serial No. 07/318,773, except for documents filed under 37 CFR 1.131 or 1.608, has previously been served on the party Fujikawa et al. [37 CFR 1.637(f)(2)]

The parent application satisfies all four requirements of 35 USC §112 for at least one species of proposed Substitute Count I.

More particularly, the written description and enablement requirements of 35 USC §112 for species of the count are satisfied by the parent disclosure at, e.g., pages 36-53 directed to the preparation of various species within the scope of the Count (for example, see the compounds of Examples 3A-E and 4, pp. 51-53); the how-to-make requirement is satisfied at pages 5-32 as well as in the Examples at pages 36-53; and the how-to-use requirement is fulfilled at pages 33-35 (utility statement).

Therefore, since the parent application satisfies all four requirements of 35 USC §112 for at least one species of proposed Substitute Count I, it is respectfully submitted that the parent application of Wattanasin's involved application constitutes a constructive reduction to practice of proposed Substitute Count I as corrected.

Respectfully submitted,

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July 21, 1992

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Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
July 21, 1992
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN SECOND CONTINGENT MOTION FOR BENEFIT
37 CFR §1.633(f)

was served on counsel for the party Fujikawa et al., this 21st day of July 1992, by postage pre-paid first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
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Arlington, VA 22202

Diane Furman 7/21/92
Diane E. Furman

Case No. 600-7101/CONT/Int.(6)
Patent

FV1 #39

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

JUL 27 1992

RECEIVED IN
BOX INTERFERENCE

WATTANASIN

v.

PICARD et al.

v.

FUJIKAWA et al.

Interference No. 102,648

Examiner-in-Chief: M. Sofocleous

WATTANASIN CONTINGENT OPPOSITION TO FUJIKAWA ET AL. MOTION FOR BENEFIT, 37 CFR §1.633(J)

Fujikawa et al. have requested benefit of their three Japanese priority applications[1], for Wattanasin's proposed Substitute Count I.

In their motion, Fujikawa et al. have stated that the Japanese applications contain "ipsis verbis support" for Substitute Count I and also contain a "plurality of examples" embraced thereby.

However, Fujikawa et al. did not show how any of the three Japanese applications, let alone each of them, constitutes a constructive reduction to practice of Substitute Count I. In particular, Fujikawa et al. have failed to identify the specific portions of the Japanese applications that purportedly satisfy the "how to make" and "how to use" requirements of the first paragraph of 35 USC §112.[2]

---

1. Japanese Patent Application Serial No. 207,224 (August 20, 1987), Serial No. 15,585 (January 26, 1988) and Serial No. 193,606 (August 3, 1988).

2. Fujikawa et al. have alleged that they have already received the benefit of two of their Japanese applications for claim 1. That is not seen to be the case; they have been accorded benefit for existing Counts 1 and 2, but not for any particular claim corresponding thereto.

Fujikawa et al. have now also opposed the Wattanasin Contingent Motion for Benefit on the ground that Wattanasin has not shown how his U.S. parent application constitutes a constructive reduction to practice of Proposed Substitute Count I. For the reasons set forth in Wattanasin's Reply (being filed concurrently herewith) to the Fujikawa et al. Opposition to the Wattanasin Motion for Benefit, Wattanasin disagrees with the grounds of the Fujikawa Opposition.

However, if the Wattanasin Motion for Benefit is deemed to be defective, then the Fujikawa et al. Motion must also be defective for the reasons set forth above.

Therefore, contingent on the denial of the "Wattanasin Contingent Preliminary Motion for Benefit Under 37 CFR §1.633(f)" or the "Wattanasin Second Contingent Motion for Benefit" being filed concurrently herewith, Wattanasin opposes the granting of the Fujikawa et al. Opposition to the Wattanasin Contingent Preliminary Motion for Benefit.

Respectfully submitted,

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July 21, 1992

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Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
July 21, 1992
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN CONTINGENT OPPOSITION TO FUJIKAWA ET AL. MOTION FOR BENEFIT, 37 CFR §1.633(J)

was served on counsel for the party Fujikawa et al., this 21st day of July 1992, by postage pre-paid first-class mail addressed to the following:

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Arlington, VA 22202

Diane Furman 7/21/92
Diane E. Furman

Paper No. 40

All communications respecting this case should identify it by number and names of parties.

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Interference No. 102,648

Wattanasin et al.

v.

Fujikawa et al.

The following preliminary motions were filed on June 21, 1991 by Wattanasin et al. (Wattanasin) and are before the Examiner-in-Chief (EIC) for decision:

1. Preliminary motion under 37 CFR 1.633(c)(1) to redefine by substituting proposed count 1 (Paper No. 19).

2. Motion under 37 CFR 1.635 to add U.S. Patent No. 5,011,930 to this interference (Paper No. 20).

3. Contingent preliminary motion under 37 CFR 1.633(e) to declare an additional interference (Paper No. 21).

4. Contingent preliminary motion under 37 CFR 1.633(f) to be accorded benefit (Paper No. 22).

The following motions and notices were filed by Fujikawa et al. (Fujikawa):

1. Preliminary motion under 37 CFR 1.633(c)(1) to redefine by adding proposed counts 3 and 4 (Paper No. 15).

2. Preliminary motion under 37 CFR 1.633(f) to be accorded benefit with respect to proposed counts 3 and 4 (Paper No. 14).

3. Preliminary motion under 37 CFR 1.633(f) to be accorded benefit with respect to counts 1 and 2, proposed counts 3 and 4 and claims 41 to 44 (Paper No. 16).

4. Notice of related application (Paper No. 17).
5. Preliminary motion under 37 CFR 1.633(j) to be accorded benefit (Paper No. 26).

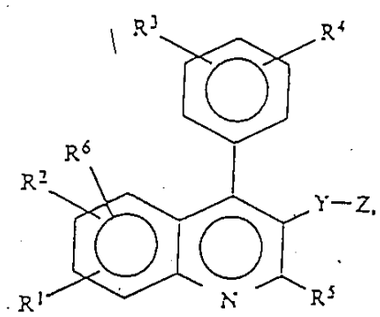
Various oppositions and replies thereto have been filed. In addition, the parties filed a joint stipulation (Paper No. 33) to add claim 1 of U.S. Patent No. 5,011,930 to this interference.

Sua Sponte Action

The EIC proposes to declare an additional interference with Fujikawa's uninvolved patent No. 5,011,930 on the basis of a new count similar in scope to that proposed by Wattanasin's motion (1) by modifying Wattanasin's proposed count in the manner suggested by Fujikawa's opposition (Paper No. 27). See the parties' stipulation (Paper No. 33). The proposed count is as follows:

Count 1

A compound of the formula:

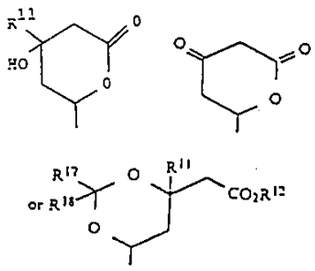


wherein R^1, R^2, R^3, R^4 and R^6 are independently
hydrogen,
C_{1-6} alkyl,
C_{1-6} cycloalkyl,
C_{1-3} alkoxy,
n-butoxy,
i-butoxy,
sec-butoxy,
R^7R^8N- (wherein R^7 and R^8 are independently hydrogen or C_{1-3} alkyl),
trifluoromethyl,
trifluoromethoxy,
difluoromethoxy,
fluoro,
chloro,
bromo,
phenyl,
phenoxy,
benzyloxy,
hydroxy,
hydroxymethyl,
$-O(CH_2)_\alpha OR^{19}$ (wherein R^{19} is hydrogen or C_{1-3}alkyl and α is 1, 2 or 3),
or when located at the ortho position to each other, R^3 and R^4 together optionally form -CH=CH-CH=CH-;

R^5 is hydrogen,
C_{1-6} alkyl,
C_{2-3} alkenyl,
C_{3-6} cycloalkyl,
phenyl substituted by R^9 (wherein R^9 is hydrogen, C_{1-4}alkyl, C_{1-3}alkoxy, fluoro, chloro, bromo or trifluoromethyl),
phenyl-$(CH_2)_m$- (wherein m is 1, 2 or 3),
-$(CH_2)_n$CH(CH_3)-phenyl or phenyl-$(CH_2)_n$CH(CH_3)- (wherein n is 0, 1 or 2).

Y is
-CH_2-,
-CH_2CH_2-,
-CH=CH-,
-CH_2-CH=CH-, or
-CH=CH-CH_2-;

Z is



or -Q-CH_2WCH_2-CO_2R^{12} (where R^{12} is hydrogen or R^{14});

Q is $-CH(OH)-$.
$-C(O)-$, or
$-C(OR^{13})_2-$;

W is $-C(R^{11})(OH)-$ (where R^{11} is hydrogen or C_{1-3} alkyl),
$-C(O)-$, or
$-C(OR^{13})_2-$;

the two R^{13} are independently primary or secondary C_{1-6} alkyl; or two R^{13} together form $-(CH_2)_2-$ or $-(CH_2)_3-$;

R^{14} is physiologically hydrolyzable alkyl or M (wherein M is NH_4, sodium, potassium, 1/2 calcium or a hydrate of lower alkylamine, di-lower alkylamine or tri-lower alkylamine); and

R^{17} and R^{18} are independently hydrogen or C_{1-3} alkyl;

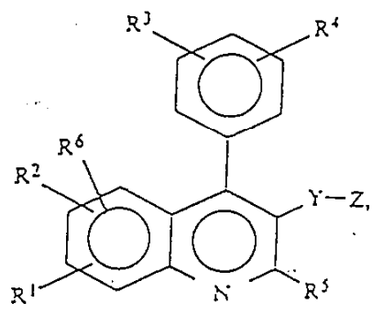
The claims of the parties which correspond to the count are as follows:

Wattanasin et al.:	Claims 1 to 7 and 10.
Fujikawa et al.:	Claims 1 to 9, 11 to 34, 36, 39 and 40.
Fujikawa et al. '930:	Claim 1.

The EIC also proposes to substitute a new count 3 for count 2. Count 2 is as follows:

Count 3

A method of inhibiting cholesterol biosynthesis in a patient in need of said treatment comprising administering a cholesterol synthesis inhibiting amount of a compound of the formula:



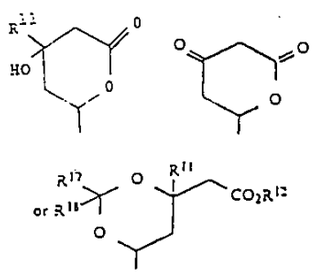
wherein R^1, R^2, R^3, R^4 and R^6 are independently
hydrogen,
C_{1-6} alkyl,
C_{1-6} cycloalkyl,
C_{1-3} alkoxy,
n-butoxy,
i-butoxy,
sec-butoxy,
R^7R^8N- (wherein R^7 and R^8 are independently hydrogen or C_{1-3} alkyl),
trifluoromethyl,
trifluoromethoxy,
difluoromethoxy,

fluoro,
chloro,
bromo,
phenyl,
phenoxy,
benzyloxy,
hydroxy,
hydroxymethyl,
$-O(CH_2)_\alpha OR^{19}$ (wherein R^{19} is hydrogen or C_{1-3}alkyl and α is 1, 2 or 3),
or when located at the ortho position to each other, R^3 and R^4 together optionally form $-CH=CH-CH=CH-$;

R^5 is hydrogen,
C_{1-6} alkyl,
C_{2-3} alkenyl,
C_{3-6} cycloalkyl,
phenyl substituted by R^9 (wherein R^9 is hydrogen, C_{1-4}alkyl, C_{1-3}alkoxy, fluoro, chloro, bromo or trifluoromethyl),
phenyl-$(CH_2)_m$- (wherein m is 1, 2 or 3),
$-(CH_2)_nCH(CH_3)$-phenyl or phenyl-$(CH_2)_nCH(CH_3)$- (wherein n is 0, 1 or 2).

Y is
$-CH_2-$,
$-CH_2CH_2-$,
$-CH=CH-$,
$-CH_2-CH=CH-$, or
$-CH=CH-CH_2-$;

Z is



or $-Q-CH_2WCH_2-CO_2R^{12}$ (where R^{12} is hydrogen or R^{14});

Q is $-CH(OH)-$.
$-C(O)-$, or
$-C(OR^{13})_2-$;

W is $-C(R^{11})(OH)-$ (where R^{11} is hydrogen or C_{1-3} alkyl),
$-C(O)-$, or
$-C(OR^{13})_2-$;

the two R^{13} are independently primary or secondary C_{1-6} alkyl; or two R^{13} together form $-(CH_2)_2-$ or $-(CH_2)_3-$;

R^{14} is physiologically hydrolyzable alkyl or M (wherein M is NH_4, sodium, potassium, 1/2 calcium or a hydrate of lower alkylamine, di-lower alkylamine or tri-lower alkylamine); and

R^{17} and R^{18} are independently hydrogen or C_{1-3} alkyl;

as defined in combination with pharmaceutically acceptable carrier.

The claims of the parties which correspond to Count 3 are:

Wattanasin : Claims 8 and 9

Fujikawa et al.: Claims 35, 37 and 38

Since the parties have had the opportunity to argue the merits of Wattanasin's substituted count, the EIC is not setting a time for either party to file its views as to the substitute count.

Each party is accorded the benefit of the applications listed in the notice declaring this interference with respect to the count of the additional interference and count 3.

Wattanasin's motions (1 to 4)

These motions are dismissed as moot in view of the EIC's sua sponte action.

Fujikawa's motion (1)

The motion requests that proposed counts 3 and 4 be added to the proceeding. The motion is denied. The EIC agrees with Wattanasin's opposition (Paper No. 28) that his application disclosure does not contain a written description within the meaning of 35 U.S.C. 112, first paragraph, for proposed claims 11 and 12 to be added to the application to correspond to counts 3 and 4.

Fujikawa's motion (2)

The motion is dismissed as moot in view of the denial of Fujikawa's motion (1), supra.

Fujikawa's motion (3)

The motion is dismissed as unnecessary. Fujikawa has been accorded the benefit of the prior Japanese applications with respect to the present counts.

Fujikawa's motion (5)

The motion is dismissed as moot in view of the EIC's accordation of benefit to Fujikawa in the sua sponte action, supra.

Serving of Preliminary Statements

Preliminary statements have been opened. In light of the EIC's sua sponte action, supra, each party may file a supplemental preliminary statement with respect to count 3. Both the original and supplement statements must be served within 10 days after the date of mailing of this order. 37 CFR 1.631(a). With respect to the count of the additional interference, each party must file with 10 days after the date of mailing of this order a preliminary statement and serve a copy upon its opponent.

Suggestion for Negotiations

After the redeclaration of this interference, the EIC will set times for the parties to present testimony. The parties are strongly encouraged to make contact with each other, before the times are set, and attempt to settle this interference or, failing that, to

narrow down, as much as possible, the issues for final hearing. The EIC can be expected to cooperate in allowing reasonable time for a bona fide attempt at such negotiations.

Michael Sofocleous
Examiner-in-Chief
(703) 557-4066

gjh

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.	:	MICHAEL SOFOCLEOUS
FUJIKAWA et al	:	

FUJIKAWA REPLY TO BELATED
OPPOSITION TO FUJIKAWA'S MOTION FOR BENEFIT

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

BOX INTERFERENCE

SIR:

In papers filed July 21, 1992, Wattanasin contingently opposes Fujikawa's Motion for Benefit. Fujikawa's Motion for Benefit was filed June 11, 1992. Any Opposition thereto was clearly due July 1, 1992. 37 CFR §1.638. Wattanasin was aware of this date, as it filed Opposition to another Fujikawa Motion filed on the same date

in timely fashion on July 1, 1992. Clearly, the Wattanasin Opposition to Fujikawa's Motion for Benefit is belated.

The provisions of Rule 645 are quite clear. Any belated Motion must be accompanied by a Motion Rule under 635 explaining why the Motion could not be earlier filed. Here, quite clearly, there is no explanation, Wattanasin now adopts an argument it did not present earlier. The fact that it did not occur Wattanasin until Fujikawa made a similar argument against Wattanasin's Motion is hardly acceptable. A failure of original thinking does not excuse delay.

Further, had a Motion been properly brought pursuant to Rule 635, compliance with that Rule would have required contact with undersigned Counsel to resolve the issue. No such contact was attempted, itself grounds for dismissal. M v. V, 6 USPQ 2d 1039 (PTOBAI 1987). The Opposition should clearly be dismissed.

Fujikawa would like to take further issue with footnote 2 in the Wattanasin contingent Opposition, to the extent it is not dismissed. Specifically, Wattanasin urges that Fujikawa have not been granted benefit for their existing Claim 1, as to their priority cases, Wattanasin urging that they have only been accorded

benefit as to existing Counts 1 and 2. The Wattanasin argument is wrong, and misperceives the case.

Wattanasin moved to substitute Fujikawa's Claim 1 as the Count of the Interference. In prosecution, Fujikawa was in fact granted benefit as to this Claim 1, in order to overcome a rejection under 35 U.S.C. §102(e). It is in fact true that Fujikawa has been accorded benefit as to existing Counts 1 and 2, but that is less relevant than the fact that the Primary Examiner specifically found support in the Japanese priority cases for Fujikawa's Claim 1, which Wattanasin urges as substitute Count 1 of the Interference. While the Primary Examiner's decision is not binding, it is strong evidence, coupled with the remainder of the discussion in the Fujikawa Motion for Benefit, that Fujikawa is entitled to that benefit. Grant of the same is respectfully requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

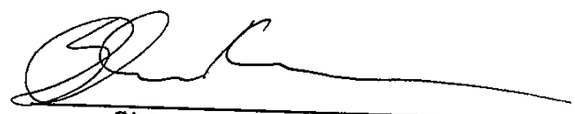
Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

CERTIFICATE OF SERVICE

I hereby certify that a true copy of the foregoing **FUJIKAWA REPLY TO BELATED OPPOSITION TO FUJIKAWA'S MOTION FOR BENEFIT** was served by first class mail, postage prepaid, on counsel for the Party Wattanasin, as follows:

Diane E. Furman
SANDOZ CORP.
59 Route 10
E. Hanover, New Jersey 07936

this 3rd day of AUGUST, 1992.



Steven B. Kelber

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.	:	MICHAEL SOFOCLEOUS
FUJIKAWA et al	:	

**FUJIKAWA OPPOSITION TO
WATTANASIN'S MOTION TO CORRECT
TYPOGRAPHICAL ERROR AND WATTANASIN'S
SECOND CONTINGENT MOTION FOR BENEFIT**

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

BOX INTERFERENCE

SIR:

On July 21, 1992, Wattanasin filed papers replying to Fujikawa's Opposition to various Preliminary Motions filed by Wattanasin. In addition to those Replies, Wattanasin filed three additional papers that are clearly untimely, a second contingent

Motion for Benefit, a Motion to Correct Typographical Error and a contingent Opposition to Fujikawa's Motion. Fujikawa herein opposes Wattanasin's Motions belatedly filed, that is, the second contingent Motion and the Motion to correct a typographical error. The belatedly Opposition is replied to elsewhere.

I. THE PAPERS ARE LATE WITHOUT EXPLANATION

The time for filing Preliminary Motions in this Interference is long past. Motions were filed June 11, 1992. This is the absolute final due date for such Preliminary Motions, and no further extension of that time was sought by either party. Accordingly, as Motions pursuant to Rule 633, the Motions are clearly belated. 37 CFR §1.645 provides explicit instruction on how such filing may be effected. Specifically, Rule 645(b) provides:

> Any paper belatedly filed, will not be considered except upon Motion

(§1.635) which shows sufficient cause why the paper was not timely filed.

Wattanasin did not file a Motion under Rule 635. Rule 645 is not discretionary, neither paper filed by Wattanasin may be considered.

Moreover, Rule 635 clearly provides that if entry of a belated Motion is sought, the issue must be discussed by Counsel for the parties, in an effort to arrive at resolution in good faith. 37 CFR §1.637(b). Wattanasin did not contact undersigned Counsel for Fujikawa, nor does Wattanasin make any representation of such effort. Clearly, Wattanasin was aware of the penalty for failure to comply with this requirement as the case of M v. V, 6 USPQ 2d 1039 (PTOBAI 1987) was cited in Fujikawa's Opposition, and discussed in Wattanasin's Reply. Having elected to flaunt prior case holding, and the clear requirements of the Rule, the Wattanasin belated Motions, the Motion to correct a typographical error, and the second contingent Motion for Benefit must be dismissed. This was the holding of the Board in M v. V.

II. THE MOTION TO CORRECT IS NOT AUTHORIZED UNDER RULE 633

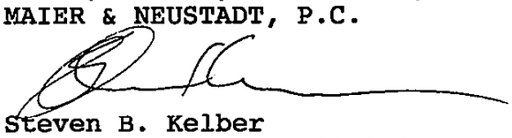
A review of Wattanasin's Motion "to correct typographical error" reflects that no where in that Motion is there a substitute Count proposed. Rather, Wattanasin discusses alterations of an earlier substitute Count. The Rules require that any Motion seeking to propose a substitute Count set forth that Count. Rule 637(c)(1)(i). There is no authority under the Rules to provide a Motion to correct a Count in an earlier Motion not reflected in the "correcting" Motion, and accordingly, the Motion to correct must clearly be dismissed. If this Motion is acceptable at all, it is acceptable only pursuant to Rule 635, although that itself is doubtful. Unauthorized Motions, even where the provisions of Rule 635 are complied with, are generally not acceptable. Gerk v. Cottringer, 17 USPQ 2d 1615 (PTOBAI 1990).

In any event, the "Motion to correct" is clearly not provided for under Rule 633, and if brought at all, should have been brought under Rule 635. The requirements of Rule 635, including Rule

637(b) were not complied with. The Motion should be dismissed.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

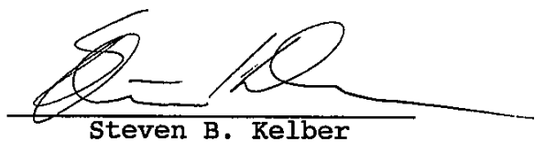
Crystal Square Five
Fourth Floor
1755 Jefferson Davis Highway
Arlington, Virginia 22202
(703) 521-5940

CERTIFICATE OF SERVICE

I hereby certify that a true copy of the foregoing **FUJIKAWA OPPOSITION TO WATTANASIN'S MOTION TO CORRECT TYPOGRAPHICAL ERROR AND WATTANASIN'S SECOND CONTINGENT MOTION FOR BENEFIT** was served by first class mail, postage prepaid, on counsel for the Party Wattanasin, as follows:

Diane E. Furman
SANDOZ CORP.
59 Route 10
E. Hanover, New Jersey 07936

this 3rd day of AUGUST, 1992.



Steven B. Kelber

#43

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.	:	MICHAEL SOFOCLEOUS
FUJIKAWA et al	:	

REFILING OF SUPPLEMENTAL DECLARATION

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

BOX INTERFERENCE

SIR:

On August 5, 1992, Wattanasin caused to be filed and served an unauthorized paper entitled "Wattanasin Response to Fujikawa et al Reply...". The paper is clearly unauthorized, surrebuttals or surreplies of the type presented by Wattanasin not being permitted by the Rules. Accordingly, Fujikawa will not respond to the assertions therein.

Nonetheless, Wattanasin does assert that it did not receive a copy of the Supplemental Declaration of Kitahara. While it is unclear as to why this was not received, Fujikawa refiles and reserves copies of the Declaration herewith.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

Fourth Floor
1775 Jefferson Davis Highway
Arlington, Virginia 22202
(703) 521-5940

CERTIFICATE OF SERVICE

I hereby certify that true copies of each of the foregoing **REFILING OF SUPPLEMENTAL DECLARATION** and **SUPPLEMENTAL DECLARATION - PATENTABLY DISTINCT SUBJECT MATTER** were served by first class mail, postage prepaid, on counsel for the Party Wattanasin, as follows:

Diane E. Furman
SANDOZ CORP.
59 Route 10
E. Hanover, New Jersey 07936

this 11th day of AUGUST, 1992.

Steven B. Kelber

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	INTERFERENCE 102,648
V.	:	EXAMINER-IN-CHIEF:
PICARD ET AL	:	MICHAEL SOFOCLEOUS
V.	:	
FUJIKAWA ET AL	:	

COPY

SUPPLEMENTAL DECLARATION - PATENTABLY DISTINCT SUBJECT MATTER

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231
BOX INTERFERENCE

SIR:

I, MASAKI KITAHARA, do hereby declare and state that:

1. I am a citizen and resident of Japan, and a named co-inventor in U.S. Patent Application Serial No. 07/233,752, involved in the above-captioned Interference. Further, I am the same Masaki Kitahara executing the Declaration dated June 1, 1992 entitled "Patentably Distinct Subject Matter" in the above-captioned

Interference.

2. In my prior Declaration dated June 1, 1992, data for the lactone species identified, as determined by test B, the inhibition of cholesterol biosynthesis in culture cells, carried out pursuant to the description on pages 29-30 of U.S. Patent Application Serial No. 07/233,752, was not included, as it was not available at that time. I have now obtained such data, and the same is reproduced in the table attached to this Declaration.

3. As can be readily confirmed by the comparison between the IC_{50} value reported for the isopropyl and cyclopropyl isomers, that subject matter wherein Z is of the lactone structure and R^5 is cyclopropyl exhibits unobvious superiority, when compared with the closely related isopropyl isomer of the same compound. Thus, all compounds within the scope of the formula set forth in paragraph 3 of my Declaration dated June 1, 1992, uniformly demonstrate unobvious superiority when R^5 is cyclopropyl, as opposed to closely related isomeric structures.

The observations in paragraphs 4 and 5 of my Declaration of June 1, 1992 remain accurate.

I hereby declare that all statements made herein of my own knowledge are true, and all statements made on information and belief are believed true. Further, I am aware that willful false statements and the like are punishable by fine, imprisonment or both, 18 U.S.C. §1001, and that such willful false statements may jeopardize the validity of U.S. Patent Application 07/233,752, any patents issued thereon, as well as the rights of the party Fujikawa et al in the above-captioned Interference.

DATE: July 6, 1992 Masaki Kitahara

MASAKI KITAHARA

Test B: Inhibition of cholesterol biosynthesis in culture cells

This test was carried out as described on pages 29 to 30 of the specification. The numerial values indicate IC_{50} (nanomolar concentration i.e. mol x 10^{-9}).

R^5	carbon number		1	2	3	6
	structure	normal	-	-		-
		iso	x	x	123.8(i-pr)	-
		cyclic	x	x	47.5(c-pr)	-

Case No. 600-..01/CONT/INT. FYI
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v.
PICARD et al.
v.
FUJIKAWA et al.

Interference No. 102,648 #44
Examiner-in-Chief: M. Sofocleous

WATTANASIN RESPONSE TO FUJIKAWA ET AL. REPLY TO WATTANASIN "OPPOSITION TO FUJIKAWA ET AL. MOTION TO ADD COUNTS AND TO ADD CLAIMS TO WATTANASIN APPLICATION"

Wattanasin hereby responds to particular allegations or statements made by Fujikawa et al. (hereinafter "Fujikawa") in their Reply to Wattanasin's Opposition to Fujikawa's motion to add counts directed to a cyclopropyl-substituted species within the scope of current Counts 1 and 2 (and proposed substitute Count 1):

1. First, on information and belief the "Supplemental Declaration of Kitahara" which Fujikawa in their Reply (p. 7) indicate to have been filed concurrently with the Reply "in completion of the evidential burden placed on Fujikawa to demonstrate patentable dis Declaration has apparently been received; nor is it listed on Fujikawa's Certificate of Service; nor can Wattanasin find any indication by Fujikawa that the Declaration was being provided as an attachment to their Reply.

Accordingly, Wattanasin is left to conclude that the Supplemental Declaration of Kitahara was not proferred, and that Fujikawa's evidential burden remains uncompleted.

2. Second, Fujikawa in their Reply (pp. 6-7) argue that Wattanasin's citation and discussion of the prior art Warner-Lambert publication, EP 179,559, showing isopropyl- and cyclopropyl-substituted pyrrole compounds having HMG-CoA reductase activity, amounts to some sort of an "admission" as to the level of skill in the art as it bears on the Wattanasin disclosure, which serves to "undercut" Wattanasin's position that the Wattanasin application does not provide 35 USC 112 written description support for a cyclopropyl species.

However, the prior art teachings are irrelevant to whether the Wattanasin disclosure itself, within its four corners, complies with the written description requirement of Section 112 with respect to a cyclopropyl species. The Wattanasin disclosure, in itself, simply does not provide a written description of a cyclopropyl species, and therefore does not reasonably convey cyclopropyl as being an aspect of the Wattanasin invention.

Additionally, it is difficult to reconcile Fujikawa's allegations, on the one hand, that Wattanasin's characterizations of the Warner-Lambert teaching constitute an "admission" against interest bearing on the sufficiency of the Wattanasin application under Section 112 with respect to the cyclopropyl species at issue, with the arguments of Fujikawa elsewhere in their Reply (pp. 10-11) that the Warner-Lambert pyrrole formulas are "substantially unrelated" to the quinoline compounds at issue in this interference, and that Wattanasin has "failed to make out any art-recognized equivalency" between the two.

Furthermore, the case law cited by Fujikawa concerning Section 112, first paragraph, is inapposite. In re Driscoll, 195 USPQ 434 (CCPA 1978) concerns selection of an individually described member of a Markush group. In In re Johnson, 194 USPQ 187 at 195-196, the CCPA expressly stated that "Appellants...are narrowing their claims, and the full scope of the limited genus now claimed is supported in appellant's earlier application, generically and by specific examples." (emphasis supplied) Compare Fields v. Conover, 170 USPQ 276, 280 (CCPA 1971).

The fact is, Fujikawa find themselves in a position rather analogous to that of the Godtfredsen party in Bigham v. Godtfredsen, 8 USPQ2d 1266 (CAFC 1988). Like Godtfredsen, Fujikawa in essence want to 'have their cake and eat it too'.

Godtfredson urged the patentable distinction of bromo and iodo over chloro, and obtained a bifurcation of the count on that theory; and at the same time urged a contrary theory (i.e. that halogen exemplified by chloro was a disclosure of bromo and iodo) in order to obtain priority as to those species. The CAFC rejected this contrary position as follows:

> "When the [PTO] board held that there was a patentable distinction between chloro, on the one hand, and bromo and iodo on the other, Godtfredsen's disclosure of halogen and chloro lost the possibility of serving as a "full, clear, concise and exact", in the words of §112, written description of the separate invention of the unnamed bromo and iodo compounds." (emphasis supplied), 8 USPQ2d at 1268 (bot.)-1269.

In the present circumstances, Fujikawa in order to propose their counts 3 and 4, need to comply with Rule 637(c) by proposing corresponding claims to Wattanasin. Therefore Fujikawa, likewise, find themselves in an inherently contradictory position of urging, on the one hand, that cyclopropyl is separately patentable (over the four remaining members of Wattanasin's sub-genus comprising C_{3-7}cycloalkyl, as well as over the other species within the scope of count 1 (or proposed substitute count 1), while at the same time urging that Wattanasin by virtue of his C_{3-7}cycloalkyl disclosure, provides §112, written description support for a cyclopropyl species.

The CAFC rejected this kind of argument when presented by Godtfredsen; and the EIC should also reject it in relation to Fujikawa.

3. Third, Watanasin would prefer not to let stand without rebuttal, the assertion by Fujikawa (p. 11) that the Wattanasin Opposition "deliberately, and without support, misrepresents" the teaching of Warner-Lambert European Patent Application 179,559 (1986).

According to Fujikawa et al., what apparently constitutes this purported "misrepresentation" is the statement of Wattanasin

in connection with the Warner-Lambert reference, that prior to Fujikawa,

> "there was a recognition in the art that: an isopropyl (4-fluorophenyl) species could provide enhanced HMG-CoA reductase activity; and further that the isopropyl could be cyclized to form cyclopropyl; and finally that the resulting cyclopropyl (4-fluorophenyl) itself exhibited particular improvements in activity relative to a genus of compounds within the same series." (Opposition at p. 9)

Fujikawa attempt to insinuate into the above statement of Wattanasin, an implication by Wattanasin that Warner-Lambert are teaching that "one of ordinary skill in the art would have expected the cylopropyl species to be better than the isopropyl species." Nowhere is this statement actually made by Wattanasin in connection with the Warner-Lambert application.

The fact is, the Warner-Lambert disclosure to the full extent of its breadth covers scores of compounds. However, at pages 11-13, Warner-Lambert choose to exemplify some 33 species of compounds falling within their scope. Still further, at page 13, they specifically recite only 13 compounds which are said to be "particularly preferred compounds." Two of these compounds are the cyclopropyl and isopropyl species depicted on page 9 of the Wattanasin Opposition. In face of the clear teaching of the prior art that these are "particularly preferred" compounds, Wattanasin believes there is ample justification for the simple statement of Wattanasin's, duplicated above, that the prior art showed that "cyclopropyl (4-fluorophenyl) itself exhibited particular improvements in activity relative to a genus of compounds within the same series."

It is Wattanasin's position that there is no misrepresentation, and certainly no deliberate misrepresentation, in this

characterization of the Warner-Lambert disclosure, and any suggestion otherwise by Fujikawa is vigorously denied.

4. Also, Fujikawa at page 9 of their Reply indicate that Hoechst U.S. Patent No. 4,925,852 is inappropriate for consideration, given that it would have been available as prior art only after Fujikawa's priority filings. On the other hand, Fujikawa at pages 12-13 urge that the teachings of the prior art Warner-Lambert European patent application be interpreted in light of a related 1990 article which is also not prior art to Fujikawa. It is respectfully submitted that Fujikawa, again, cannot have it both ways; if the 1990 article is suitable for consideration; then the Hoechst reference should be considered as well.

5. Finally, Wattanasin hereby opposes the designation of Fujikawa claim 18 (covering a 4-chlorophenyl substituted species) as corresponding to counts 3 and 4 of the interference, since the counts exclude this species from their scope.

For the reasons set forth above and in Wattanasin's Opposition, the Motion of to Fujikawa to Add Counts and to Add Claims to the Wattanasin Application, should be denied.

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 August 5, 1992
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
8/5/92
Date of Signature

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORP.
59 Route 10
E. Hanover, NJ 07936
DEF:rmf
August 5, 1992

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN RESPONSE TO FUJIKAWA ET AL. REPLY TO WATTANASIN "OPPOSITION TO FUJIKAWA ET AL. MOTION TO ADD COUNTS AND TO ADD CLAIMS TO WATTANASIN APPLICATION"

was served on counsel for the party Fujikawa et al., this 5th day of August 1992, 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 8/5/92
Diane E. Furman

AUG 2 1 1992

Paper No. 45

Wattanasin

v.

Fujikawa et al.

REDECLARATION

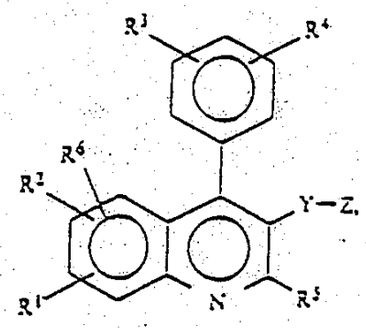
Interference No. 102,648

The above identified interference is hereby redeclared as follows:

Counts 1 and 2 are stricken, and count 3 is added.

Count 3

A method of inhibiting cholesterol biosynthesis in a patient in need of said treatment comprising administering a cholesterol synthesis inhibiting amount of a compound of the formula:



wherein R^1, R^2, R^3, R^4 and R^6 are independently

hydrogen,

C_{1-6} alkyl,

C_{1-6} cycloalkyl,

C_{1-3} alkoxy,

n-butoxy,

i-butoxy,

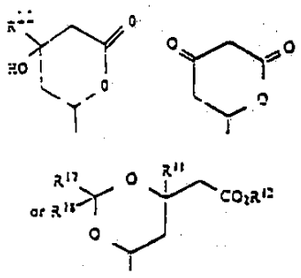
sec-butoxy,

R^7R^8N- (wherein R^7 and R^8 are independently hydrogen or C_{1-3} alkyl),
trifluoromethyl,
trifluoromethoxy,
difluoromethoxy,
fluoro,
chloro,
bromo,
phenyl,
phenoxy,
benzyloxy,
hydroxy,
hydroxymethyl,
$-O(CH_2)_\alpha OR^{19}$ (wherein R^{19} is hydrogen or C_{1-3}alkyl and α is 1, 2 or 3),
or when located at the ortho position to each other, R^3 and R^4 together optionally form $-CH=CH-CH=CH-$;

R^5 is hydrogen,
C_{1-6} alkyl,
C_{2-3} alkenyl,
C_{3-6} cycloalkyl,
phenyl substituted by R^9 (wherein R^9 is hydrogen, C_{1-4}alkyl, C_{1-3}alkoxy, fluoro, chloro, bromo or trifluoromethyl),
phenyl-$(CH_2)_m$- (wherein m is 1, 2 or 3), $-(CH_2)_nCH(CH_3)$-phenyl or phenyl-$(CH_2)_nCH(CH_3)$- (wherein n is 0, 1 or 2).

Y is
$-CH_2-$,
$-CH_2CH_2-$,
$-CH=CH-$,
$-CH_2-CH=CH-$, or
$-CH=CH-CH_2-$;

Z is



or $-Q-CH_2WCH_2-CO_2R^{12}$ (where R^{12} is hydrogen or R^{14});

Q is $-CH(OH)-$.
$-C(O)-$, or
$-C(OR^{13})_2-$;

W is $-C(R^{11})(OH)-$ (where R^{11} is hydrogen or C_{1-3} alkyl),
$-C(O)-$, or
$-C(OR^{13})_2-$;

the two R^{13} are independently primary or secondary C_{1-6} alkyl; or two R^{13} together form $-(CH_2)_2-$ or $-(CH_2)_3-$;

R^{14} is physiologically hydrolyzable alkyl or M (wherein M is NH_4, sodium, potassium, 1/2 calcium or a hydrate of lower alkylamine, di-lower alkylamine or tri-lower alkylamine); and

R^{17} and R^{18} are independently hydrogen or C_{1-3} alkyl;

as defined in combination with pharmaceutically acceptable carrier.

The claims of the parties which correspond to count 3 are:

Wattanasin : Claims 8 and 9

Fujikawa et al.: Claims 35, 37 and 38

Michael Sofocleous
Examiner-in-Chief
(703) 557-4066

gjh

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#46

WATTANASIN	:	
	:	INTERFERENCE 102,648
V.	:	EXAMINER-IN-CHIEF:
	:	MICHAEL SOFOCLEOUS
PICARD ET AL	:	
	:	
V.	:	
	:	
FUJIKAWA ET AL	:	

POWER TO INSPECT AND MAKE COPIES

BOX INTERFERENCE
HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

SIR:

The undersigned, being an Attorney of Record for the above-identified Interference, hereby grants to MURALIDHAR PAI/SAM BROWN, the power to inspect and make copies of the above-identified Interference files.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Steven B. Kelber
Registration No.: 30,073
Attorney of Record

Fourth Floor
1755 South Jefferson Davis Highway
Arlington, Virginia 22202
703-521-5940

Case No. 60' 7101/CONT/Int.
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#47

WATTANASIN

v. Interference No. 102,648

FUJIKAWA et al. Examiner-in-Chief:

APPROVED
AUG 21 1992
By ..... Examiner-in-Chief

WATTANASIN
REQUEST FOR EXTENSION OF TIME,
37 CFR §§1.635, 645

The party Wattanasin hereby requests a ten-day extension of time for the parties to file and/or serve Preliminary Statements and/or Supplemental Preliminary Statements which are currently due August 17, 1992 in the above-captioned interference. If granted, this Motion would make the Preliminary Statements and/or Supplemental Preliminary Statements due August 27, 1992.

As grounds for the Request, undersigned counsel submits that the decision of the Examiner-in-Chief mailed August 7, 1992 (Paper No. 40) was not received by the undersigned until Friday, August 14, 1992; and certain critical issues addressed in said decision concerning an additional interference and the counts of said interference and the present interference desirably ought to be clarified by the EIC in consultation with the parties, before Wattanasin can adequately respond by filing a Preliminary Statement and/or Supplemental Preliminary Statement.

In a telephone conversation today with the undersigned, Examiner-In-Chief Sofocleous indicated that he would act favorably on this request. Opposing counsel, Steven B. Kelber, has also agreed to a reciprocal extension of time.

Accordingly, Wattananasin hereby moves that the time period for response by the parties to the decision of the EIC mailed August 7, 1992 (Paper No. 40), by filing and/or serving a Preliminary Statement and/or Supplemental Preliminary Statement, be extended to August 27, 1992.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936
DEF:rmf
August 17, 1992

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 August 17, 1992
(Date of Deposit)
Diane E. Furman
Name of Applicant, Assignee, or Registered Representative
Diane Furman
Signature
August 17, 1992
Date of Signature

CERTIFICATION OF FACSIMILE TRANSMISSION
ATTENTION BOX INTERFERENCE

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below:

Diane Furman
Diane E. Furman

Aug 17, 1992
Date

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN
REQUEST FOR EXTENSION OF TIME,
37 CFR §§1.635, 645

was served on counsel for the party Fujikawa et al., this 17th day of August 1992, 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

Case No. 60(101/CONT/Int.
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN

v. Interference No. 102,648

FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

WATTANASIN
REQUEST FOR EXTENSION OF TIME,
37 CFR §§1.635, 645

The party Wattanasin hereby requests a ten-day extension of time for the parties to file and/or serve Preliminary Statements and/or Supplemental Preliminary Statements which are currently due August 17, 1992 in the above-captioned interference. If granted, this Motion would make the Preliminary Statements and/or Supplemental Preliminary Statements due August 27, 1992.

As grounds for the Request, undersigned counsel submits that the decision of the Examiner-in-Chief mailed August 7, 1992 (Paper No. 40) was not received by the undersigned until Friday, August 14, 1992; and certain critical issues addressed in said decision concerning an additional interference and the counts of said interference and the present interference desirably ought to be clarified by the EIC in consultation with the parties, before Wattanasin can adequately respond by filing a Preliminary Statement and/or Supplemental Preliminary Statement.

In a telephone conversation today with the undersigned, Examiner-In-Chief Sofocleous indicated that he would act favorably on this request. Opposing counsel, Steven B. Kelber, has also agreed to a reciprocal extension of time.

Accordingly, Wattananasin hereby moves that the time period for response by the parties to the decision of the EIC mailed August 7, 1992 (Paper No. 40), by filing and/or serving a Preliminary Statement and/or Supplemental Preliminary Statement, be extended to August 27, 1992.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936
DEF:rmf
August 17, 1992

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 August 17, 1992
(Date of Deposit)
Diane E. Furman
Name of Applicant, Assignee, or Registered Representative
Diane Furman
Signature
August 17, 1992
Date of Signature

.....

CERTIFICATION OF FACSIMILE TRANSMISSION
ATTENTION BOX INTERFERENCE

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Diane Furman
Diane E. Furman

Aug 17, 1992
Date

.....

CERTIFICATE OF SERVICE

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Arlington, VA 22202

Diane Furman

Diane E. Furman

[redacted] Case No. 6[redacted] Int.
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#48

WATTANASIN

MAILED

AUG 21 1992

v.

Interference No. 102,648

FUJIKAWA et al.

PAT. & T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

Examiner-in-Chief: APPROVED

AUG 21 1992

By [signature] Examiner-in-Chief

WATTANASIN
REQUEST FOR EXTENSION OF TIME,
37 CFR §§1.635, 645

The party Wattanasin hereby requests a ten-day extension of time for the parties to file and/or serve Preliminary Statements and/or Supplemental Preliminary Statements which are currently due August 17, 1992 in the above-captioned interference. If granted, this Motion would make the Preliminary Statements and/or Supplemental Preliminary Statements due August 27, 1992.

As grounds for the Request, undersigned counsel submits that the decision of the Examiner-in-Chief mailed August 7, 1992 (Paper No. 40) was not received by the undersigned until Friday, August 14, 1992; and certain critical issues addressed in said decision concerning an additional interference and the counts of said interference and the present interference desirably ought to be clarified by the EIC in consultation with the parties, before Wattanasin can adequately respond by filing a Preliminary Statement and/or Supplemental Preliminary Statement.

In a telephone conversation today with the undersigned, Examiner-In-Chief Sofocleous indicated that he would act favorably on this request. Opposing counsel, Steven B. Kelber, has also agreed to a reciprocal extension of time.

#49

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 COMMENT ON
WATTANASIN'S MOTION FOR EXTENSION OF TIME

BOX INTERFERENCE
HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

SIR:

In a paper filed, through the mail, and dated August 17, 1992, Wattanasin seeks an extension of time in which to file its Preliminary Statement and Supplemental Preliminary Statement. Fujikawa, through undersigned counsel, had earlier agreed not to oppose that Motion for Extension of Time, and does not expressly oppose it at this time. Fujikawa notes, however, that the Motion was not filed in accordance with the provisions of 37 C.F.R. §1.645, which directs the movant to file the Motion in a fashion designed to ensure that it will reach the EIC in advance of the

expiration of the period in question. Quite simply, that was not done herein.

Fujikawa notes that the Motion for Extension of Time was evidently sent via facsimile to the Patent Office. It was not served via facsimile on undersigned counsel. Moreover, the files of the Board of Patent Appeals and Interferences did not have either the facsimile version, or the signed version, of the Motion for Extension of Time present at 2:45 p.m. on August 17, 1992, at which time the file was inspected by counsel for Fujikawa. As a result, Fujikawa, not having sought an extension on its own, was obliged to file its Preliminary Statement and Supplemental Preliminary Statement as required by the Decision of the EIC.

Ordinarily, this would not result in any specific prejudice to Fujikawa. Wattanasin, having earlier filed its Preliminary Statement, can only serve that Preliminary Statement it earlier filed. However, the Decision of the EIC requires the parties to serve two additional Preliminary Statements not previously prepared, a Supplemental Preliminary Statement with respect to Count 3, and, potentially, a Preliminary Statement with respect to the Interference to be declared. It would be extreme prejudice if Wattanasin were allowed to craft its Preliminary Statement in light of

Fujikawa's own Supplemental Preliminary Statement, alleging a date earlier than, or different from, the date alleged in Wattanasin's Preliminary Statement previously filed in the above-captioned Interference.

Accordingly, Fujikawa submits that the Wattanasin Motion for Extension of Time should be granted, notwithstanding its violation of Rule 645, only on the condition that any Supplemental Preliminary Statement of Wattanasin, or additional Preliminary Statement to be filed by Wattanasin, alleges facts identical to the Wattanasin Preliminary Statement already filed. As Wattanasin has urged that Count 3 of the above-captioned Interference and the Count of the Interference to be declared by the EIC are not patentably distinct from original Counts 1 and 2 of this Interference, this should not work a hardship to Wattanasin.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

Fourth Floor
1755 Jefferson Davis Highway
Arlington, Virginia 22202
(703) 521-5940

CERTIFICATE OF SERVICE

I hereby certify that true copies of:

1. **REQUEST FOR RECONSIDERATION**

2. **FUJIKAWA COMMENT ON WATTANASIN'S MOTION FOR EXTENSION OF TIME**

3. **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 first-class mail, postage prepaid, this 21st day of August, 1992.

STEVEN B. KELBER

#50

BOARD OF PATENT APPEALS & INTERFERENCES
AUG 21 1992

49-111-0

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

REQUEST FOR RECONSIDERATION

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

BOX INTERFERENCE

SIR:

Responsive to the Decision on Preliminary Motions, Paper No. 40 in the above-captioned patent Interference, Fujikawa respectfully requests reconsideration of aspects of that Decision, pursuant to the provisions of 37 CFR §1.640(c). As points and issues Fujikawa submits the Examiner-in-Chief may have misapprehended or overlooked, Fujikawa identifies the following:

1. The nature and character of the literal and generic description in the Wattanasin application of Claims 11 and 12 proposed by Fujikawa, for the purposes of contesting additional Counts 3 and 4.

2. The duplicative nature of the Interference declared sua sponte, by the Examiner, and the increased burden on the Patent Office and parties for contesting this second Interference, when alternatives exist under the law.

3. The Examiner's rejection of Fujikawa's Motion for Benefit, Paper No. 16, on the grounds that it was unnecessary, when benefit of the application requested had not been previously granted.

4. Failure to indicate the status of Fujikawa's Motion to redefine the interfering subject matter by addition of Claims 41-44.

Each of these issues is considered, in turn, below.

I. WRITTEN DESCRIPTION ISSUE

Fujikawa moved that the Interference be redefined by adding proposed Counts 3 and 4, confined to a sub-genus, on the grounds that the sub-genus defined subject matter patentably unobvious over the current Counts of the Interference, due to unusual and unpredicted activity exhibited by the members of that sub-genus. As one element of that Motion, Fujikawa proposed a claim, Claim 11, to be adopted by Wattanasin, corresponding to Count 3, and a corresponding administration Claim 12, to correspond to proposed Count 4. In the Decision on Motions, the Motion to redefine the Interference was denied on the grounds that the EIC agreed with the

opposition that the application of Wattanasin "does not contain a written description within the meaning of 35 U.S.C. §112, first paragraph, for proposed Claims 11 and 12 to be added to the application to correspond to Counts 3 and 4."

As the Decision of the EIC did not make independent findings, either factual or legal, to support the legal conclusion, it must be presumed that the Examiner has adopted the arguments set forth in the Wattanasin opposition agreed with. The sole argument presented with regard to written description in that opposition (Paper No. 28) is that Wattanasin lacks a written description of a cyclopropyl substituent for R, that is, the substituent at the 2 position being cyclopropyl. This argument appears on page 6 of the Opposition, and can be summed in the third full paragraph set forth therein, which consists solely of the recitation

> Neither the term "isopropyl" nor the term "C_{3-7} cycloalkyl" provides a written description of "cyclopropyl" for purposes of 35 U.S.C. §112. (Quotes in original).

The statement is neither sufficient as a matter of law, nor accurate as a matter of fact. As the EIC has not provided

independent findings, it must be assumed that the EIC has relied on this statement, and accordingly, Fujikawa respectfully submits that the EIC has misapprehended or overlooked the descriptive nature of the Wattanasin application, with regard to the substitution, at the 2 position, of a cyclopropyl group.

A. The Test for Written Description

As discussed below, Fujikawa submits that the Wattanasin application includes literal support for the identity of cyclopropyl as the substituent at the 2 position, or moiety R of the Wattanasin application claims. But surely, it is well established that the test for determining written description is broader than the presence of literal support, or indeed, exemplary support. Fujikawa submits that it is established beyond peradventure that the test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed would reasonably convey to those of skill in the art that the inventors had possession of the subject matter claimed in the claims at issue, at the time the application

was originally filed. This test, rather than the presence or absence of literal or exemplary support in the specification has been repeatedly expressed by the Court of Appeals for the Federal Circuit. Vas-Cath, Inc. v. Mahurkar, 19 USPQ 2d 1111,1116 (Fed. Cir. 1991), In re Kaslow, 217 USPQ 1089,1096 (Fed. Cir. 1983). It is, at least, quite clear that the claim need not be described, either in identical or literal correspondence in the specification, to satisfy the written description requirement, Kennecott Corporation v. Kyocera International, Inc., 5 USPQ 2d 1194,1197 (Fed. Cir. 1987), cert. denied, 108 Supreme Ct 1735 (1988). Additional cases to the same effect are legion, and need not be cited herein.

Fujikawa respectfully submits that it is inarguably clear that the Wattanasin disclosure conveys to those of skill in the art possession of the compounds of proposed Claim 11 and method of proposed Claim 12, with respect to the cyclopropyl substituent. Wattanasin acknowledges that the proposed claim is entirely embraced within the Wattanasin disclosure, and the broad Wattanasin claims. From Wattanasin's Opposition, page 6:

> The involved application of Wattanasin certainly covers within its generic scope compounds which are substituted by cyclopropyl...(emphasis added).

Similar discussion of the scope of Wattanasin's broad claims appears at page 5 of the Opposition.

> The cyclopropyl species also falls within the generic scope of Claims 1-3 and 8-10 of Wattanasin's involved application.

It is thus clear that the proposed claim falls within Wattanasin's broad claims, and the test becomes whether the claim is so narrow, directed to a species or sub-genus so limited, that those of skill in the art would not ordinarily appreciate it, on reading the Wattanasin disclosure.

Wattanasin discloses, as possible substituents for the 2 position (moiety R of the Wattanasin application claims) three different narrow sub-genera:

C_{1-6}alkyl,

C_{3-7}cycloalkyl,

Ring A.

See, e.g., page 1, lines 3-4 of the Wattanasin application. Thus, those of skill in the art are clearly taught that one group of substituents within the invention in possession of Wattanasin at the time of filing are those compounds wherein R is C_{3-7}cycloalkyl. This is a genus of five species, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. It is a narrow and closed group. Regardless of the presence or absence of literal support, discussed below, it is respectfully submitted that the selection of one out of five is not beyond the level of skill of those in the art. Clearly, even if they would not form Claim 11 in their minds, those of skill in the art would recognize the possession by the Wattanasin inventors of the cyclopropyl substituted species. This is more the case for C_3 than any of the other members of the group, because it is the starting point for the group, and the most likely substituent. This is particularly in light of the fact that Wattanasin teaches, as a preferred, and repeatedly exemplified species, isopropyl. If one were to select a cycloalkyl substituent, as directed by Wattanasin, one would almost certainly

select that most closely related to the preferred embodiment, one would select the cyclopropyl moiety. Clearly, those of skill in the art would recognize possession, by Wattanasin, of Claim 11 at the time of filing.

The selection of one out of five, where no other selection need be made, is hardly beyond the level of skill of those in the art, or something not clearly taught by the application. This is supported by evidence beyond the written description itself, Wattanasin having in fact argued that those of skill in the art, given the disclosure of compounds of the type exemplified by Wattanasin, would have recognized the suitability of a cyclopropyl group at the 2 position. Specifically, Wattanasin argued, page 9 of its Opposition (Paper No. 28) and admitted against interest,

> There was a recognition in the art that: an isopropyl (4-fluorophenyl) species could provide enhanced HMG-CoA reductase activity; and further that the isopropyl could be cyclized to form cyclopropyl; and finally that the resulting cyclopropyl (4-fluorophenyl) itself exhibited particular improvements in activity relative to a genus of compounds

> within the same series. Note that in both Warner-Lambert species, above, the isopropyl or cyclopropyl occupies a position on the pyrole ring adjacent to the nitrogen, as in the case of the cyclopropyl species at issue.

The reliability and truth of the statements advanced by Wattanasin, together with their relevance to the current Interference, have been discussed in Fujikawa's reply. For the purposes of this Request for Reconsideration, it suffices to note that Wattanasin has admitted against interest that those of skill in the art, given compounds of the type embraced by the Wattanasin disclosure, which admits of the insertion of a cyclopropyl species, and exemplifies isopropyl, would recognize that the isopropyl substituent could be cyclized to form cyclopropyl substituents, without loss of activity. Clearly, given the Wattanasin disclosure of the suitability of cycloalkyl species, having three carbon atoms, and the identification of isopropyl as a suitable substituent, those of skill in the art would have recognized the cyclopropyl substituent as within the scope of Wattanasin's invention. On that grounds, Fujikawa seeks reconsideration of the Decision of the EIC.

B. Literal Support

Fujikawa agrees that there is no exemplary support of a compound within the scope of Claim 11 bearing a cyclopropyl substituent in Wattanasin's application. Exemplary support, however, is not the only means of meeting the written description test. Literal description is an equal means of satisfying the requirements of 35 U.S.C. §112, first paragraph, with regard to written description. Snitzer v. Etzel, 175 USPQ 108 (CCPA 1972). Fujikawa respectfully submits that literal support for the identity of moiety R, the substituent at the 2 position, as cyclopropyl, exists in the Wattanasin disclosure. The Wattanasin disclosure advances, as possible identities for R, C_{3-7}cycloalkyl. Regardless of the number of members of the group encompassed by that generic recitation (there are five), it is clear that those of skill in the art are certainly taught two cyclic substituents, specifically, C_3cycloalkyl and C_7cycloalkyl. It might well be argued that a C_5 alkyl, if singled out, is not literally supported by the Wattanasin disclosure, however, the term "C_3cycloalkyl" appears repeatedly in the Wattanasin disclosure, page 1, line 4, page 54, line 4, and in the Abstract, line 4. The uncyclized corresponding alkyl,

isopropyl, is repeatedly identified as a preferred example throughout the application. See, e.g., pages 51 and 53.

C_3cycloalkyl IS cyclopropyl. There are no other moieties that meet the description. Note that the Wattanasin disclosure is confined to cycloalkyls, and accordingly, a potential, though sterically strained, cycloalkene is not available for consideration. Having specifically identified, by accepted chemical nomenclature, cyclopropyl as a substituent, Wattanasin can hardly be heard to argue, as it does now, that it does not provide a written description of the same.

It should be noted that as the proponent of this argument, the burden rests on Wattanasin to demonstrate lack of compliance with 35 U.S.C. §112, written description requirement. While Fujikawa bears the burden of proof with respect to the Motion, per se, that burden has been supported. Fujikawa has pointed to those part of the specification which provide support for Claim 11, as well as meeting the other requirements of the Rules which the EIC does not quarrel with. Accordingly, Wattanasin must advance an explanation of why the disclosure of C_3 does not support the identification of cyclopropyl as the potential substituent.

In this regard, it should be noted that although the standards for establishing anticipatory disclosure are different from those

required to meet 35 U.S.C. §112, first paragraph, 35 U.S.C. §102 and 35 U.S.C. §112 share a common denominator, the reference or patent application in question must contain a description of the subject matter at issue. There is abundant case law which clearly directs that the Wattanasin disclosure is a description of cyclopropyl at the substitution point in question. The Court in In re Petering, 133 USPQ 275 (CCPA 1962) considered a similar question, whether or not the generic disclosure of a U.S. Patent described the invention to those of skill in the art, or that application provided a generic disclosure, and one of skill in the art would have to fashion, upon reading the disclosure, a more limited class, to meet the claims. At page 280, the Court observed:

> We think the Karrer patent, as a printed publication describes to one skilled in this art not only the broad class but also this much more limited class within that broad class, and we think it is immaterial that Karrer did not expressly spell out the limited class as we have done here. It is our opinion that one skilled in this art would, on reading

> the Karrer patent, at once envisage each member of this limited class, even though the skilled person might not at once define in his mind the formal boundaries of the class as we have done here....For these reasons, we hold that each compound within the limited class in Karrer, as defined supra, has been described in a printed publication, within the meaning of 35 U.S.C. §102(b), and that it is of no moment that each compound is not specifically named or shown by structural formula in that publication. (Emphasis in the original) at page 280.

Like the reference in Petering, in the current case, Wattanasin provides a limited genus, five compounds, out of which one could and would, on the basis of the Wattanasin teaching, certainly envisage each member separately, including the cyclopropyl species. More is unnecessary to meet the written description requirement. See to the same effect, In re Sivaramakirshna, 213 USPQ 441,442 (CCPA 1982) where the Court found that prior art disclosure of the species claimed, among seventy different members of a disclosed

genus, was a description of that species. Where there is no requirement to make multiple simultaneous choices from different genuses, a limited genus amounts to a description of each member of the genus.

That in fact the Wattanasin disclosure necessarily includes a description of each member of the class C_{3-7}cycloalkyl is brought home by the Decision in Snitzer v. Etzel, supra, where the Court found that the identification of trivalent ytterbium, out of a list of fourteen possible ions, was a literal description of a claim reciting trivalent ytterbium, specifically. The Court expressly found that even within a class of fourteen, nearly triple the size of the class considered herein, each member of the class was described, within the meaning of 35 U.S.C. §112, first paragraph. Similar application of the law is requested herein.

It should be noted that this is not a case like Bigham v. Godtfredsen, 8 USPQ 2d 1266 (Fed. Cir. 1988), which found a lack of disclosure of a constructive reduction to practice of specific halogens iodo and bromo, based on a disclosure of chloro and halogen, where patentable distinction had been drawn between the two. Here, Wattanasin has specifically named C_3cycloalkyl, that is cyclopropyl. More is unnecessary for 35 U.S.C. §112 support for Claims 11 and 12.

In summary, Fujikawa respectfully submit that whether measured by literal description, or by the impression conveyed to those of skill in the art that Wattanasin had possession of the invention at the time the application was filed, the Wattanasin application clearly supports proposed Claims 11 and 12, 35 U.S.C. §112, first paragraph. Should the Decision not be reconsidered, it is respectfully requested that the EIC make, of record, specific findings as to why the identification of C_3cycloalkyl is not a description of cyclopropyl, and why the recitation of C_3-C_7cycloalkyl does not constitute a description of a limited genus whose each member is described, for purposes of preparation of the Brief at Final Hearing.

II. THE EXAMINER'S SUA SPONTE ACTION

In Paper No. 40, the Examiner, sua sponte, declared an additional Interference, designating that the claims of Wattanasin and Fujikawa corresponding to the current Interference, as well as Claim 1 of U.S. Patent 5,011,930. Although the Examiner proposed to declare an additional Interference, no additional Interference

was actually declared, and yet, on page 10 of Paper No. 40, the EIC directed the filing and service of a Preliminary Statement with respect thereto. Fujikawa respectfully submits that the requirement of the filing of a Preliminary Statement in an Interference not yet declared, independent of the question of whether a Preliminary Motions period would be granted, merely serves to highlight the difficulties presented by the Examiner's sua sponte action. Fujikawa respectfully submits that there are easier ways of achieving the same goal.

Specifically, there can be no question that the Count of the Interference the Examiner proposed to declare is not patentably distinct from current Count 1 of the Interference. There is substantial overlap between the Counts, and no evidence or reason to believe that this overlap is entirely contained within patentably distinct sub-genera. The Rules of Interference proceeding would seem to require that Counts of separate Interferences, between the same parties, be directed to patentably distinct subject matter. In particular, it is not seen that contesting two Interferences between the same parties, on the same applications, to patentably indistinct Counts serves the interests of justice in any fashion, given Rule 658(c), Interference Estoppel. The creation of a second Interference file, together

with the necessary briefing papers and the like, on patentably indistinct subject matter, creates an administrative and paper burden on both applicants and the Patent Office, without substantially deciding any additional questions that could not be decided in the current Interference. In particular, it is noted that although a second Interference could not be requested by the parties, Gerk v. Cottringer, 17 USPQ 2d 1615 (BPAI 1990), Gerk does specifically provide that the EIC can exercise his discretion and jurisdiction to do that which is considered a proper course of conduct for any situation not specifically covered by the Rules of Interference practice. 37 CFR §1.610(e). Among those acts that are specifically provided for is the addition of a patent to an Interference, on terms fair to all parties. 37 CFR §1.642. The parties requested just that in a Stipulation. The Stipulation would have designated as corresponding to current Count 1 of the Interference, Claim 1 of U.S. Patent 5,011,930. It is believed that this is the intended substantive effect of the Examiner's sua sponte action. The Stipulation proposed by the parties would achieve the same goal, be consistent with the Rules of Practice and particularly Rule 610, 642 and 658, and yet not increase the paper trail, administrative and filing burden, and complications created by the Examiner's sua sponte action.

It is further pointed out that due to errors which can occur in the shouldering of administrative and paper responsibilities discussed above, the situation could well occur where one party receives a favorable award of priority in the above-captioned Interference, while the other party received the award of priority in the Interference to be declared under the Examiner's sua sponte action. Were this to occur, who would be entitled to a patent on what? Quite simply, Fujikawa submits the Examiner's sua sponte action unnecessarily burdens the parties, and the Patent Office, and creates a possibility of mass confusion that would serve neither the parties nor the public.

It is uncertain, from the Decision on Motions, why the EIC did not adopt the stipulated proposal of the parties. Fujikawa recognizes that the Fujikawa '930 patent does not present a claim directed to administration of the subject matter of Claim 1. Thus, it is quite true that the '930 patent does not present a claim that can be designated as corresponding to current Count 3 of the above-captioned Interference. There is nothing in the Rules, however, which would seem to require that a patent or application involved in an Interference have at least one claim designated as corresponding to each Count of the Interference, when there are more than two patents or applications involved in an Interference.

Indeed, the combination of Rules 610 and 642 seem to imply that this situation may occur.

Fujikawa is unaware of any precedent with respect to the sua sponte action taken by the Examiner. It is true that there is case law which holds that the initial Declaration of more than one Interference with Counts not patentably distinct therebetween is not objectionable by the parties. That is not the case, herein. Here, the Examiner seeks to add an Interference in order to resolve a question that would otherwise be left to resolution by Rule 658(c). It is believed simpler to resolve the issue by adding the patent claim in question to this Interference, than creating a whole new Interference.

Fujikawa further requests reconsideration of the Examiner's Order to submit a Preliminary Statement with respect to the proposed Count. It is respectfully submitted that the Rules make it clear that a Preliminary Statement cannot be filed until an Interference is declared. See, e.g., 37 CFR §1.614, and 37 CFR §1.621. In order to secure benefits that otherwise might be denied, Fujikawa hereby serves notice that were the Interference proposed by the Examiner declared, Fujikawa would rely, with respect to the proposed Count of the proposed Interference, solely on the filing date of Japanese Patent Applications 207224/1987,

15585/1988 and 193606/1988, filed August 20, 1987, January 26, 1988 and August 3, 1988, respectively, to prove a constructive reduction to practice of the Counts of the Interference. Fujikawa cannot do so at this time, as no such Interference has been declared. Should it be necessary, the Examiner is respectfully requested to consider this Request for Reconsideration to include a request for extension of time nunc pro tunc, for the purpose of filing a Preliminary Statement in the Interference to be declared.

In view of the foregoing, it is respectfully submitted that the Examiner's sua sponte action should be reconsidered, with an eye towards simplifying the procedure proposed. In this respect, Fujikawa would be open to a conference call, as set forth in 37 CFR §1.610(d)(1), for simplification of the issue presented.

Appropriate relief is respectfully requested.

III. FUJIKAWA'S MOTION FOR BENEFIT

The EIC dismissed Fujikawa's Motion for Benefit, Paper No. 16, on the grounds that it was unnecessary, benefit having been previously accorded Fujikawa as to the priority application

identified. The Examiner's action is respectfully submitted to have overlooked the specific priority document whose benefit was requested in the Motion, and nature of the priority documents as to which benefit was granted in the original Declaration of Interference.

In the Interference, as originally declared, Fujikawa was accorded benefit of Japanese Patent Applications Serial Numbers 207224 and 15585, filed August 20, 1987 and January 26, 1988, respectively. The Motion identified in the Decision on Motions as Paper No. 16, i.e., Fujikawa Motion 3, seeking benefit with respect to Counts 1, 2, proposed Counts 3 and 4, and Claims 41-44, sought benefit not of these priority applications, but a third priority application, Japanese Patent Application 193606, filed August 3, 1988. While it is recognized that this priority date is later than the dates of the priority applications whose benefit has previously been accorded, Fujikawa is nonetheless entitled to seek that benefit, and furthermore, the Motion should be considered, not dismissed, as it is possible that for reasons that Fujikawa cannot currently imagine, Fujikawa benefit as to the earlier applications might be denied or removed. Further, Rule 658(c) commands that this issue be raised now, or forever be denied Fujikawa in subsequent ex parte practice. Since Fujikawa intends to seek

benefit of the priority application in question in ex parte practice in the involved application, and other applications, subsequent to the termination of this Interference, were Fujikawa to lose, it would denied the opportunity explore this issue.

In short, the benefit sought in Motion 16, the benefit of Japanese Patent Application 193606 has not previously been accorded Fujikawa, and was not accorded Fujikawa with respect to the Interference proposed in the Examiner's sua sponte action. Grant of that benefit, since the Motion was not opposed, is respectfully requested, on reconsideration.

IV. FUJIKAWA'S MOTION TO AMEND, 37 CFR §1.633(c)

The Decision of the EIC neither refers to, nor decides, the status of Fujikawa's paper filed pursuant 37 CFR §1.633(c), the Amendment adding Claims 41-44 to the Fujikawa application. Consideration of this Amendment, and entry, pursuant to the provisions of Rule 615(a) is respectfully requested. Specifically, the Amendment introduced claims confined to the subject matter of Fujikawa's proposed Counts 3 and 4. As discussed above, it is

believed that on reconsideration, Fujikawa's Motion to add Counts 3 and 4 will be granted. Even if that Motion is denied, however, the issue of Fujikawa's Amendment is not mooted. No one has questioned that Fujikawa has support for Claims 41-44. As such, Fujikawa is entitled to present claims directed to that subject matter. If Fujikawa's Motion to add the Counts is granted, presentation of Claims 41-44 is essential. If the Motion is denied, Fujikawa may nonetheless add Claims 41-44, which clearly, because of the unobvious superiority exhibited thereby, and the alleged failure on the part of Wattanasin to be able to contest priority as to that subject matter, would not correspond to any of the Counts of the current Interference, or the proposed Interference. Thus, entry of the Fujikawa Amendment will not require disturbing the Decision on Motions, or the designation of claims corresponding to any of the identified Counts of any Interference involving the two parties, if Fujikawa's Motion to redefine is not granted. Nonetheless, presentation of these claims is essential to Fujikawa's subsequent ex parte prosecution of those claims, something to which Fujikawa is entitled to, and neither Wattanasin nor the EIC has indicated otherwise. If the claims are not entered into the application at this time, were Fujikawa to lose the Interference, with respect to all Counts, the application

would be considered abandoned. Accordingly, consideration and entry of the Amendment submitted pursuant to Rule 633(c) is respectfully requested.

It is noted that items I-IV set forth above are independent, and each can be decided separately of the other. Reconsideration, as set forth above, is respectfully requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

Fourth Floor
1755 South Jefferson Davis Highway
Arlington, Virginia 22202
703-521-5940

CERTIFICATE OF SERVICE

I hereby certify that true copies of:

1. **REQUEST FOR RECONSIDERATION**
2. **FUJIKAWA COMMENT ON WATTANASIN'S MOTION FOR EXTENSION OF TIME**
3. **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 first-class mail, postage prepaid, this 21st day of August, 1992.

STEVEN B. KELBER

Interference

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#51

WATTANASIN	:	
v.	:	INTERFERENCE NO.: 102,648
PICARD et al	:	EXAMINER-IN-CHIEF:
v.	:	MICHAEL SOFOCLEOUS
FUJIKAWA et al	:	

NOTICE OF SERVICE

BOX INTERFERENCE
HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

SIR:

Pursuant to Paper No. 40, page 10 thereof, Fujikawa hereby certifies that it has served on the Party Wattanasin its Preliminary Statement, together with its Supplemental Preliminary Statement.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

Fourth Floor
1755 Jefferson Davis Highway
Arlington, Virginia 22202
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN ET AL	:	INTERFERENCE NO. 102,648
	:	
v.	:	EXAMINER-IN-CHIEF:
	:	
FUJIKAWA ET AL	:	MICHAEL SOFOCLEOUS

SUPPLEMENTAL PRELIMINARY STATEMENT

BOX INTERFERENCE
HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

SIR:

Responsive to Paper No. 40, Fujikawa et al intends to rely, with respect to Count 3, solely on the filing date of Japanese Patent Applications 207224/1987, 15585/1988 and 193606/1988, filed August 20, 1987, January 26, 1988 and August 3, 1988, respectively, to prove a constructive reduction to practice of the Counts of the Interference.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

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Arlington, Virginia 22202
(703) 521-5940

CERTIFICATE OF SERVICE

I hereby certify that true copies of:

--PRELIMINARY STATEMENT
--SUPPLEMENTAL PRELIMINARY STATEMENT

were served upon counsel for the Party Wattanasin et al as follows:

Diane E. Furman, Esquire
SANDOZ CORP.
59 Route 10
East Hanover, New Jersey 07936

via first-class mail, postage prepaid, this 17th day of August, 1992.

Steven B. Kelber

#51

FYI

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN

v. Interference No. 102,975

FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

JUNIOR PARTY WATTANASIN
PROPOSED FINDINGS OF FACT

Fujikawa took no direct testimony, and is therefore restricted to its uncontested benefit date under 35 USC §119, based on its earliest Japanese priority application filed on August 20, 1987.

1. The junior party Wattanasin has established by a preponderance of the evidence conception and reduction to practice prior to the Fujikawa effective date.

a. Wattanasin has demonstrated conception and synthesis of at least one species of the count in an initial activity phase by May 17, 1985, and did not abandon, suppress or conceal his invention in the period prior to the second activity phase in early 1987, or otherwise.

b. In the second activity phase commencing in early 1987, Wattanasin synthesized at least one species of the count prior to the Fujikawa filing date, but testing was not completed until after August 20, 1987. However, testing of the compounds prior to August 20, 1987 was not necessary for reduction to practice since their practical utility was clear and certain. Hence the invention was reduced to practice on July 28, 1987 and July 29, 1987, the respective dates of completion of preparation of 64-933 and 64-934/NA.

2. If the Board finds that testing is required for the compounds made in 1987, Wattanasin has clearly demonstrated diligence from a time prior to the Fujikawa filing date of August 20, 1987 until such testing and reductions to practice were completed by and on behalf of Wattanasin. The in vitro testing was completed by October 20, 1987 for all 1987 compounds. The in vivo testing was completed by October 29, 1987.

3. No abandonment of the invention by Wattanasin is indicated or proved because of apparent or alleged delay in filing the Wattanasin application after the 1987 reductions to practice.

4. The Wattanasin biological testing satisfies the utility requirement of the count.

a. The Wattanasin in vitro assays meet the utility requirement of the count;

b. The Wattanasin in vivo testing also satisfies the requirement of practical utility of the count.

c. The Wattanasin in vivo testing is competent to show the efficacy of the Wattanasin compounds of the count in inhibiting cholesterol biosynthesis in a patient in need of said treatment when administered in combination with a pharmaceutically acceptable carrier.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

July 16, 1993

DEF:rmf

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 July 16, 1993
(Date of Deposit)

Diane E. Furman
Name of applicant, assignee, or Registered Representative

Diane Furman
Signature

July 16, 1993
Date of Signature

Wattanasin
Int. No. 102,975
Prop. Findings Fact

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

JUNIOR PARTY WATTANASIN
PROPOSED FINDINGS OF FACT

was served on counsel for the party Fujikawa et al., this 16th day of July 1993, by postage prepaid first-class mail addressed to the following:

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Neustadt P.C.
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1755 South Jefferson Davis Highway
Crystal Square 5, Ste. 400
Arlington, VA 22202

Diane Furman
Diane E. Furman

Case No. 60 7101/CONT/Int.(5)
Patent

FYI

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

AUG 31 1992

RECEIVED IN BOX INTERFERENCE #52

WATTANASIN

v.

FUJIKAWA et al.

Interference No. 102,848

Examiner-in-Chief: M. Sofocleous

WATTANASIN
ACKNOWLEDGEMENT OF CLARIFICATION

The party Wattanasin hereby acknowledges that the "request for clarification" which undersigned counsel for Wattanasin had indicated to the EIC would be filed by Wattanasin in this interference[1] , has now been mooted in view of the EIC's decision mailed August 21, 1992 (Paper No. 14), redeclaring the above-identified interference, cancelling counts 1 and 2, and adding count 3.

---

1. In decisions mailed August 7 and 19, 1992 the EIC had (1) initially redeclared the present interference, and (2) declared additional Interference No. 102,975 between the Wattanasin involved application, the Fujikawa U.S. Patent No. 5,011,930, and the Fujikawa involved application. A due date of August 17, 1992 was set for the parties to file and/or serve Preliminary Statements and/or Supplemental Preliminary Statements.

On Monday, August 17, 1992, undersigned counsel for Wattanasin telephoned the EIC for the purpose of obtaining clarification of the status and counts of the two interferences. The EIC indicated that he would act favorably on a request to extend the due date of the parties' Preliminary Statements and/or Supplemental Preliminary statements, for ten (10) days, to August 27, 1992, to permit Wattanasin to file a Request for Clarification of the order of August 7. (Wattanasin filed a written Request for Extension on August 17, 1992, which was granted on August 21, 1992.)

However, the action taken by the EIC in the paper of August 21, 1992, has rendered a request for clarification moot.

However, the courtesy of the EIC in responding to Wattanasin's phone inquiry and in orally approving a request for extension of time are gratefully acknowledged.

Since Interference No. 102,975 contains solely (compound) count 1 as set out in Paper No. 2 therein, and since the present interference contains solely (method) count 3, the EIC has now clarified the status of the counts in the two interferences, and the Wattanasin request has been mooted.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936
DEF:rmf
August 27, 1992

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 August 27, 1992
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
8/27/92
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN
ACKNOWLEDGEMENT OF CLARIFICATION

was served on counsel for the party Fujikawa et al., this 27th day of August 1992, by postage pre-paid first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
Attn: Steven B. Kelber, Esq.
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Crystal Square 5, Ste. 400
Arlington, VA 22202

Diane Furman

Diane E. Furman

Case No. 600-7101/CONT/Int.(2)
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

FYI #53

AUG 31 1992

RECEIVED IN BOX INTERFERENCE

WATTANASIN

v.

Interference No. 102,648

FUJIKAWA et al.

Examiner-in-Chief: M. Sofocleous

WATTANASIN
NOTIFICATION OF SERVICE OF PRELIMINARY STATEMENT

The party Wattanasin hereby notifies the Examiner-in-Chief that counsel for Wattanasin is serving on counsel for the party Fujikawa et al., this 27th day of August 1992, a true copy of the Wattanasin Preliminary Statement filed June 11, 1992 in the subject interference.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

DEF:rmf
August 27, 1992

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 August 27, 1992
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
8/27/92
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN
NOTIFICATION OF SERVICE OF PRELIMINARY STATEMENT

was served on counsel for the party Fujikawa et al., this 27th day of August 1992, by postage pre-paid first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
Attn: Steven B. Kelber, Esq.
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Arlington, VA 22202

Diane Furman
Diane E. Furman

Case No. 60 7101/CONT/Int.(6)
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

FYI

WATTANASIN

v.

FUJIKAWA et al.

Interference No. 102,648

Examiner-in-Chief: M. Sofocleous

#54

WATTANASIN RESPONSE TO
FUJIKAWA REQUEST FOR RECONSIDERATION

In response to the Fujikawa Request for Reconsideration of the EIC's decision on Preliminary Motions, Paper No. 40, in the above-referenced interference, the party Wattansin offers the following limited remarks:

(1) **WRITTEN DESCRIPTION ISSUE**

Aside from urging the truly questionable proposition that a (4-fluorophenyl)cyclopropylquinoline species within count 1 has an activity level as an HMG-CoA reductase inhibitor which is so far removed from what would be normally expected over the series of compounds contained within the counts, and in view of the prior art, as to render it separately patentable, Fujikawa also cling to the tenuous argument that the Wattanasin disclosure fulfills the written description requirement of 35 USC §112, first paragraph, with respect to that same (4-fluorophenyl)cyclopropyl species (see Fujikawa Paper No. 15).

The following points are noted with respect to the inability of Wattanasin to satisfy the 35 USC §112, written description requirement for the count proposed by Fujikawa.

As pointed out previously by Wattanasin, a close analogy to the present factual circumstances exists in the inter partes case of Bigham v. Godtfredsen, 8 USPQ2d 1266 (Fed. Cir. 1988).

In the Godtfredsen case, the issue turned on whether the term "halogen" provided written description support of bromo or iodo.

It can hardly be denied that the term "halogen" is transparently self-evident to any worker in the art and would immediately signify, for practical purposes, at least the species: fluoro, chloro, bromo and iodo.

This the Federal Circuit did recognize when it stated in Godtfredsen that under ordinary circumstances, a generic disclosure of "halogen" would be sufficient to constitute a written description of the various common halogen species.

However, the Court went on to say that "this simple rule does not apply when the count is based on and requires patentable distinction among specific halogens," 8 USPQ2d at 1268.

Most pertinently, the Federal Circuit stated that a party in an interference may not, on the one hand, invoke one theory of law based on chemistry (i.e. that bromo and iodo are patentably distinct from chloro) to obtain, in Godtfredsen, a bifurcation of a count on that theory, and on the other hand, urge a contrary theory (i.e. that halogen exemplified by chloro comprises 35 USC §112 written description support for bromo and iodo) for priority purposes.

Like Godtfredsen, Fujikawa want it both ways: They argue on the one hand, that cyclopropyl is patentably distinct from the genus C_{3-7}cycloalkyl and, on the other hand, that the genus C_{3-7}cycloalkyl amounts to a specific disclosure of cyclopropyl (and presumably every other member of the C3-7cycloalkyl group.)

Fujikawa acknolwedge that Wattanasin certainly contains no exemplification of a cyclopropyl species and only discloses "C_{3-7}cycloalkyl"; however, they point out that "C_3cycloalkyl" constitutes an endpoint of the C_{3-7}cycloalkyl group, and is therefore specifically named.

As in Godtfredsen, it will be no revelation to the worker in the art that the group of substituents embraced by C_{3-7}cycloalkyl consists of: C_3cycloalkyl (cyclopropyl), C_4cycloalkyl (cyclobutyl), C_5cycloalkyl (cyclopentyl), C_6cycloalkyl (cyclohexyl), and C_7cycloalkyl (cycloheptyl).

However, the fact that C_3cycloalkyl constitutes the lower endpoint of this group makes it no more or less described than the other individual species, i.e. C_4-, C_5-, C_6- and C_7- cycloalkyl.

Yet if, for example, Wattanasin in ex parte prosecution were to propose a claim directed to, say, C_6cycloalkyl, the claim would surely would draw a 35 USC §112, written description, rejection. This may also be the case with cyclopropyl. See Fields v. Conover, 170 USPQ 276, 280 (CCPA 1971).

Written Description Support: 35 USC 102/103 v. 35 USC 112

Fujikawa acknowledge that "the standards for establishing anticipatory disclosure are different from those required to meet 35 U.S.C. §112, first paragraph" (pages 12-13).

Nevertheless, they continue to muddle this distinction both in their argument and their citation of case law.

For example, they rely on the opinion in Petering which, however, was decided under 35 USC 102(b). [Held, that preferences set out in the prior art patent to Karrer were effective to limit Karrer's practical teachings to 20 compounds (not otherwise specifically mentioned) within the broad generic scope which, therefore, conssitute 102(b) prior art, In re Petering, 133 USPQ 275 (CCPA 1962)].

In re Sivaramakrishnan, 213 USPQ 441 (Fed. Cir. 1982), is also a 35 USC 102(b) decision, wherein the Federal Circuit concluded that a prior art disclosure of polycarbonate comprising a metal salt, of which cadmium laurate was exemplified as one of up to 70 such salts, anticipated applicant's claims to polycarbonate resins containing that same cadmium laurate.

The other cases cited by Fujikawa do turn on 35 USC 112 issues but are only marginally, or not at all, relevant on their facts.

For example, in Snitzer v. Etzel, 175 USPQ 108 (CCPA 1972), the verbatim naming of "trivalent ytterbium" as an individual member of a 14-member Markush-type group of laser materials was held in compliance with the 35 USC §112, written description requirement to support a claim to the same trivalent ytterbium. Compare in In re Kaslow, 217 USPQ 1089, 1096 (Fed. Cir. 1983) (no written description sufficiency).

Kennecott Corp. v. Kyocera Int'l., Inc., 5 USPQ2d 1194, 1198 (Fed. Cir. 1987), cert. denied, 108 Sup. Ct. 1735 (1988) is of remote relevance (disclosure in a subsequent patent application of an inherent property of a product does not deprive that product of the benefit of an earlier filing date). Nor is the Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991) particularly helpful to Fujikawa (whether drawings alone may fulfill the written description requirement).

Fujikawa derive little actual support from the legal and factual bases of their cited case law.

It is notable that what is pertinent about the cited Vas-Cath decision is the observation of Judge Rich, as follows:

> The CCPA also recognized a subtle distinction between a written description adequate to support a claim under §112 and a written description sufficient to anticipate its subject matter under 102(b). The difference between "claim-anticipating disclosures" was dispositive in In re Lukach [citation omitted] where the court held that a U.S. "grandparent" application did not sufficiently describe the later-claimed invention, but the appellant's intervening British application, a counterpart to the U.S. application, anticipated the claimed subject matter.***

19 USPQ2d at 1115

Given that Fujikawa initially at least acknowledge this distinction, it is particularly eggregious that Fujikawa go on to mischaracterize certain of Wattanasin's prior remarks (see Wattanasin's Opposition to the Fujikawa Motion to Add Counts) which were clearly directed to the 35 USC 102/103 patentability issue, as "admissions against interest" purportedly with respect to the 35 USC 112, written description issue. This mischaracterization is unwarranted.

Specifically, at page 9 of their Request paper, Fujikawa excerpt a passage from Wattanasin's Opposition in which Wattanasin stated why the proposed count of Fujikawa directed to a (4-fluorophenyl)cyclopropyl species could not be considered separately patentable over the (4-fluorophenyl)isopropyl species, given specific prior art teachings of cyclopropyl-substituted compounds having improved HMG-CoA reductase activity.

Clearly, the excerpted Wattanasin remarks went to the issue of patentable distinctness of the separate cyclopropyl species in view of the prior art teachings, rather than the written description requirement.

Fujikawa may attempt to obfuscate the issue, but the fact remains that for purposes of complying with the 35 USC 112, written description requirement, support for the cyclopropyl species has to be found within the four corners of the Wattanasin specification, and here it does not.

Accordingly, the EIC should maintain the rejection of the Fujikawa motion to redefine by adding counts (Paper No. 15).

(2) **FUJIKAWA MOTION TO AMEND**

(see Fujikawa Request paper at page 23)

Fujikawa have previously proposed species claims 41-44 (directed to the (4-fluorophenyl)cyclopropyl species), be added by amendment to their involved application in Int. No. 102,975 (see Fujikawa Amendment --37 CFR 1.633(c)) in order to correspond to their proposed counts 3 and 4.

The EIC apparently did not enter this amendment.

Fujikawa now request, even in the event the denial of their motion to add species counts 3 and 4 is maintained, that their proposed claims 41-44 be entered.

What is confusing to Wattanasin is that Fujikawa go on to state that these claims 41-44, "because of the unobvious superiority exhibited thereby, and the alleged failure on the part of Wattanasin to be able to contest priority as to that subject matter, would not correspond to any of the Counts of the current Interference, or the proposed Interference."

Whatever Fujikawa presume to suggest here, Wattanasin submits that the subject matter of these added claims 41-44 does fall squarely within the scope of count 1 of Interference No. 102,975 (claims 41-43) or count 3 of Interference No. 102,648 (claim 44).

In fact, if Fujikawa's claims 41-44 are added to their involved application, the EIC should designate said claims 41-44 to either of counts 1 and 3, since they are clearly encompassed by these counts, and moreover have not been shown to be patentably distinct from the genera thereof.[1]

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
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August 27, 1992

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 August 27, 1992
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
8/27/92
Date of Signature

1. Wattanasin notes that the belatedly received Fujikawa Supplemental Declaration by Kitihara does not convincingly establish separate patentability of the lactone (4-fluorophenyl)-cyclopropyl species.

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN RESPONSE TO FUJIKAWA REQUEST FOR RECONSIDERATION

was served on counsel for the party Fujikawa et al., this 27th day of August 1992, by postage pre-paid first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
Attn: Steven B. Kelber, Esq.
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Crystal Square 5, Ste. 400
Arlington, VA 22202

Diane Furman
Diane E. Furman

Case No. 60 7101/CONT/Int.
Patent

FYI

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

Examiner-in-Chief: M. Sofocleous

#55

WATTANASIN RESPONSE TO
FUJIKAWA COMMENT ON WATTANASIN MOTION FOR EXTENSION OF TIME

Wattanasin's Motion for Extension of Time has been granted by the Examiner-in-Chief, and therefore the Fujikawa Comment and is moot.

However, it is noted that Fujikawa has challenged the Wattanasin motion on the sole basis that Wattanasin copied Fujikawa on the Wattanasin motion by first-class mail on August 17, 1992, instead of telefaxing a copy.

Wattanasin acknowledges that regrettably, through inadvertent oversight, a copy of the Wattanasin Request for Extension was not telefaxed to counsel for Fujikawa.

However, Wattanasin further notes for the record that counsel for Wattanasin did orally inform counsel for Fujikawa on August 17, 1992 that the EIC had orally granted an extension of ten (10) days to August 27, 1992.

With respect to the Fujikawa request that the EIC deny entry of a Wattanasin Supplemental Preliminary Statement or modified Preliminary Statement in the related interference, it is submitted that this request was mooted by the EIC's grant of the extension.

Moreover, there is absolutely no prejudice to Fujikawa whether or not Wattanasin files such a Supplemental Preliminary Statement in this interference, or a modified Preliminary Statement in Interference No. 102,975, since Fujikawa are relying solely on their Japanese priority applications as evidence of a constructive reduction to practice.

Therefore the Fujikawa request is simply punitive in nature, and without rational basis.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

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August 27, 1992

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 August 27, 1992
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
8/27/92
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN RESPONSE TO
FUJIKAWA COMMENT ON WATTANASIN MOTION FOR EXTENSION OF TIME

was served on counsel for the party Fujikawa et al., this 27th day of August 1992, by postage pre-paid first-class mail addressed to the following:

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Telefax: (703) 486-2347

Diane Furman

Diane E. Furman

Case No. 600-[illegible]01/CONT/Int.(10)
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES FYI

WATTANASIN

v. Interference No. 102[illegible]

FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

WATTANASIN
NOTICE OF THE FILING OF SUPPLEMENTAL PRELIMINARY STATEMENT

Appended is the Supplemental Preliminary Statement of the party Wattanasin for the subject interference.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

DEF:rmf
August 27, 1992

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 August 27, 1992
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
Aug. 27, 1992
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the papers entitled:

WATTANASIN
NOTICE OF THE FILING OF SUPPLEMENTAL PRELIMINARY STATEMENT

and

WATTANASIN
SUPPLEMENTAL PRELIMINARY STATEMENT

were served on counsel for the party Fujikawa et al., this 27th day of August 1992, 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

Case No. 600-/101/CONT/Int.(9)
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN

v. Interference No. 102,648

FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

WATTANASIN
SUPPLEMENTAL PRELIMINARY STATEMENT

The above interference has been redeclared by a decision of the Examiner-in-Chief mailed August 21, 1992 (Paper No. 14).

For purposes of a Supplemental Preliminary Statement with respect to the sole count of the redeclared interference, i.e. (method) count 3, the party Wattanasin hereby relies on his Preliminary Statement filed on June 11, 1992, which is hereby incorporated by reference and is being concurrently served on opposing counsel, and on the following additional information:

Compound 64-933, the compound of Example 1 (step H) of the Wattanasin application, was synthesized on or before July 23, 1987, and characterized no later than July 27, 1987 (**Exhibit G**), and was tested in vivo (i.e. administered to a patient) on or before December 9, 1987 according to the procedure described in the Wattanasin application at pages 33-34, as substantiated by the accompanying computer printout (**Exhibit H**). Diligence is alleged between June 8, 1987 and December 9, 1987.

For purposes of this interference as redeclared by the EIC (paper mailed August 21, 1992), it shall be understood as follows:

(1) Count "1" wherever it appears in the Wattanasin Preliminary Statement refers to count 1 of related Interference No. 102,975; and

(2) Count "2" wherever it appears in the Wattanasin Preliminary Statement refers to count 3 of the present Interference No. 102,648.

Respectfully submitted,

Diane Furman 8/27/92

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

DEF:rmf
August 27, 1992

Enclosures: **Exhibits G and H**

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of papers entitled:

WATTANASIN
SUPPLEMENTAL PRELIMINARY STATEMENT

were served on counsel for the party Fujikawa et al., this 27th day of August 1992, by postage pre-paid first-class mail addressed to the following:

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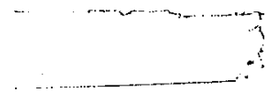
Attn: Steven B. Kelber, Esq.
1755 South Jefferson Davis Highway
Crystal Square 5, Ste. 400
Arlington, VA 22202

Diane Furman

Diane E. Furman


G



Title-

Date 6-1-15 Proj.

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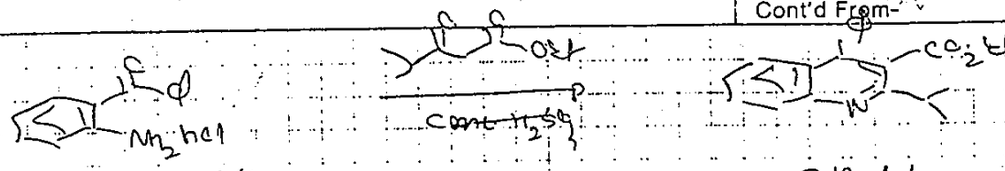


5233-24 120G-129-18

319.44
$C_{21}H_{21}NO_2$

23324 (120G-129-18) = 11.5 g (0.04930 mole)

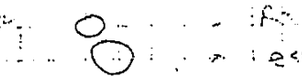
(a0980) 1582 = 11.93 ml (0.07395 81mM) - 5 equiv.

Etoh = 10 ml + 5 ml

~~Conc H_2SO_4~~ = ~~2.5 ml~~

Ref : 120G-92

Above misc. was heated to reflux (10.7 = 4 hrs) stirred at r.t. overnight



Roavap to dryness to yellow oil 25 g basified with NH_4OH, extracted with Et_2O, washed with H_2O, brine, dried, filtered, washed, rotavap gave 1.21 g orange/yellow solids (120G-130-27)

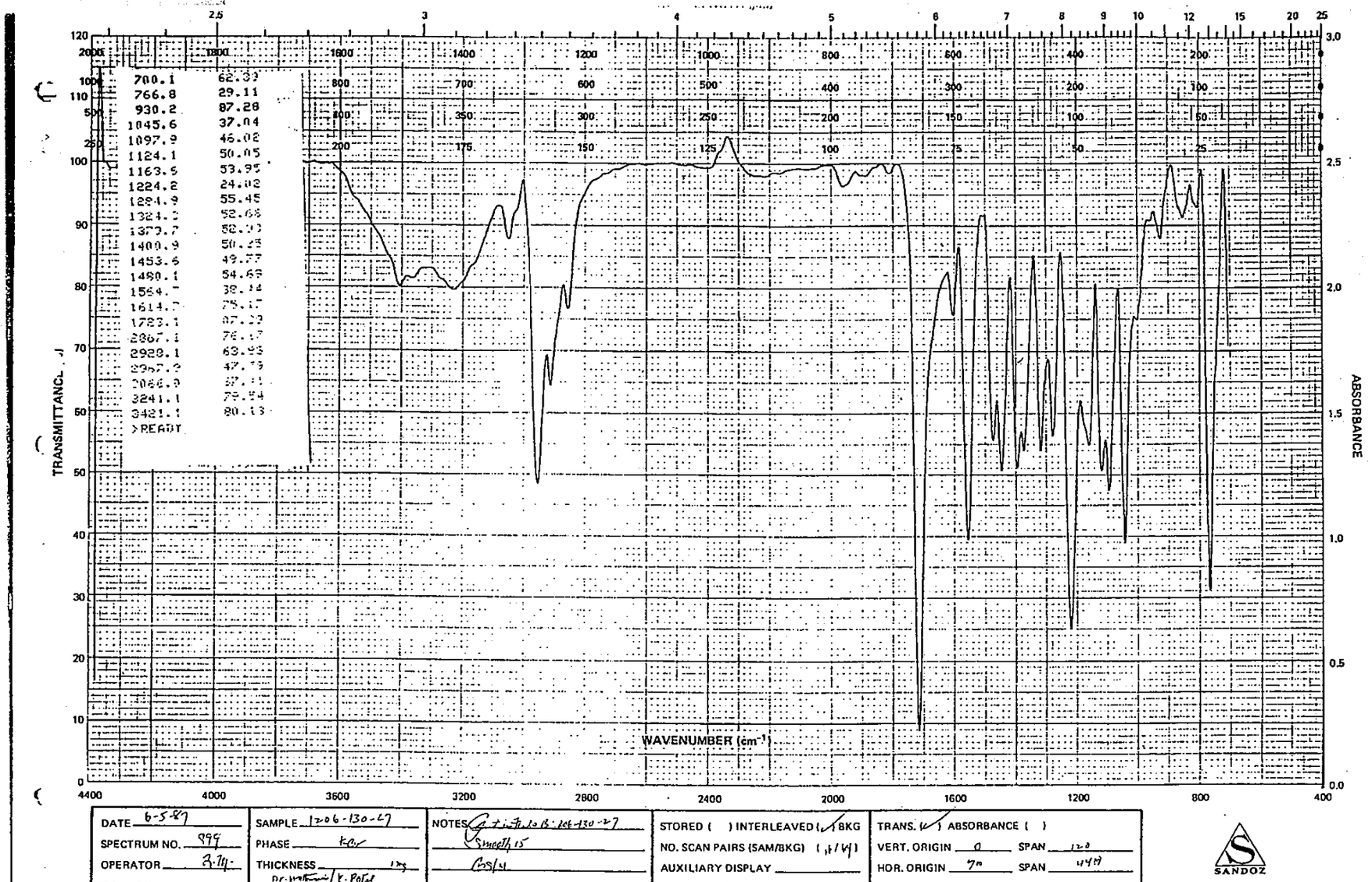
nmr, tlc, ms → ~~no mwt~~ mwt = 320

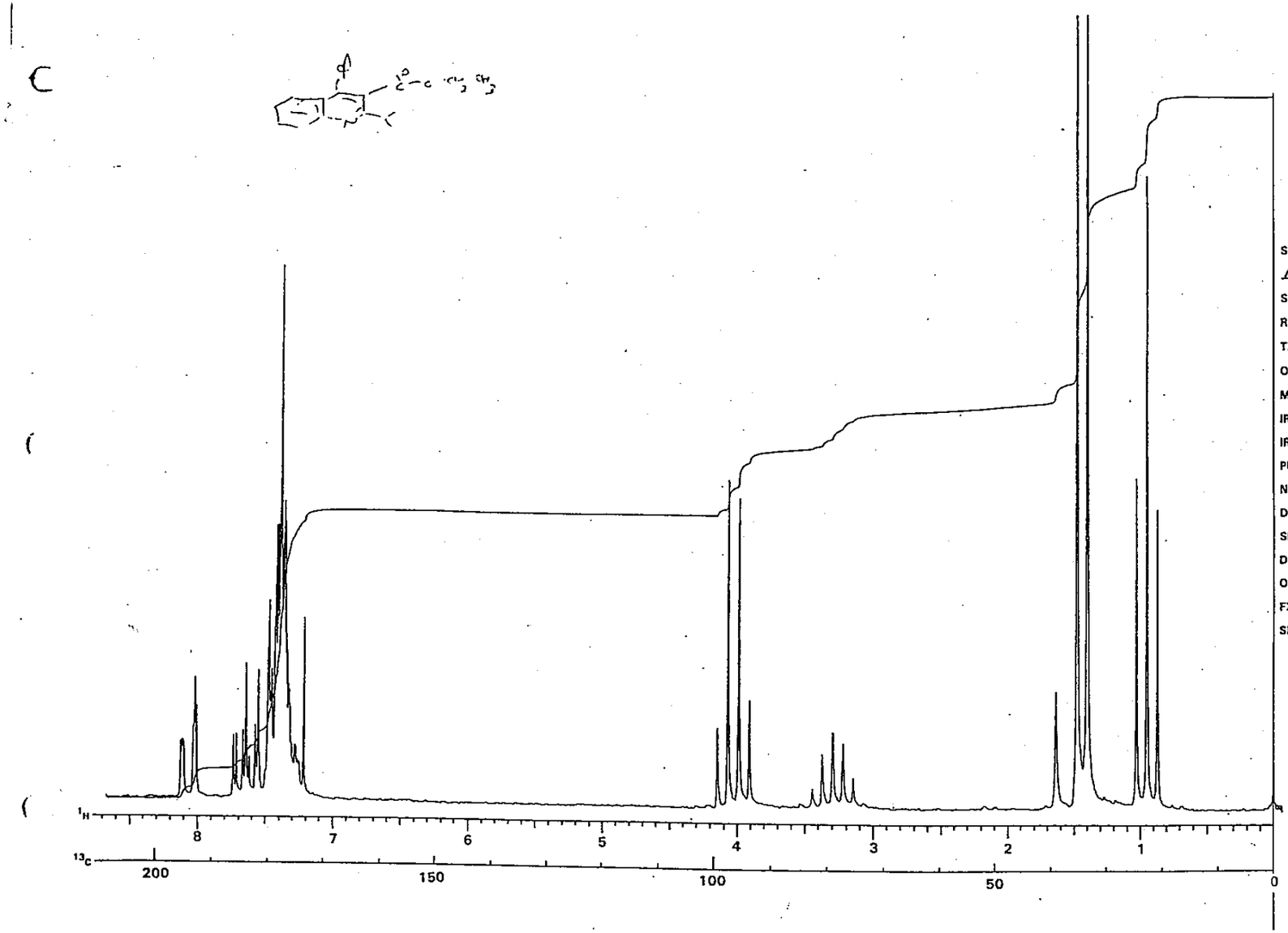
Theory: 1.5748 g, % = 64.86

Performed by- Raj Patel 6-1-15

Witness- Siwattanan

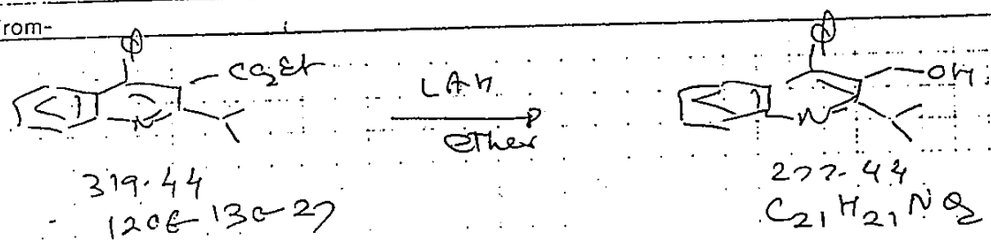
Cont'd to-


700.1 62.33
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
1324.3 52.68
1379.7 52.03
1400.9 50.28
1453.6 49.77
1480.1 54.69
1564.7 38.14
1614.5 75.17
1723.1 87.29
2867.1 76.17
2928.1 63.93
2957.9 47.79
3066.9 87.41
3241.1 79.54
3421.1 80.13
>READY
TRANSMITTANCE, %
ABSORBANCE
WAVENUMBER (cm⁻¹)
DATE 6-5-87
SPECTRUM NO. 995
OPERATOR A.M.
SAMPLE 1206-130-C7
PHASE KBr
THICKNESS 1mg pr. mat'l / K. Pot'l
NOTES C7 in 1206-130-C7
Smooth 15
CDCl3
STORED ( ) INTERLEAVED (✓) BKG
NO. SCAN PAIRS (SAM/BKG) (4/4)
AUXILIARY DISPLAY
TRANS. (✓) ABSORBANCE ( )
VERT. ORIGIN 0 SPAN 120
HOR. ORIGIN 7m SPAN 44H
SANDOZ


SAMPLE NO. 1206-130-27
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 6/8/87
OPERATOR JB
FX 80Q
SPECTRUM NO. 3256 G
1H
8
7
6
5
4
3
2
1
13C
200
150
100
50
0
87355/81 (Rev. 1)

ate 9-8) Proj. Title-

ont'd From-

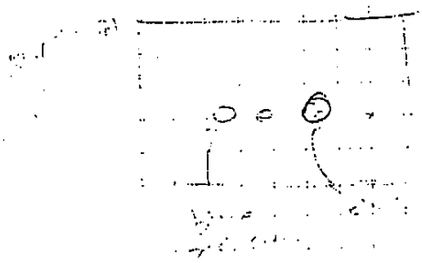


319.44
120G-130-27

277.44
$C_{21}H_{21}NO_2$

(319.44) 120G-130-27 = 10.21g (0.0319621 mole)
(38) LAH = 2.43g (0.0639242 mole)
dry ether = 100ml
Ref: 120G-96

To 120G-130-27 in dry ether with cooling was added LAH portionwise, exothermic, foaming, stirred at r.t. for 3hr. C9 32 12 35



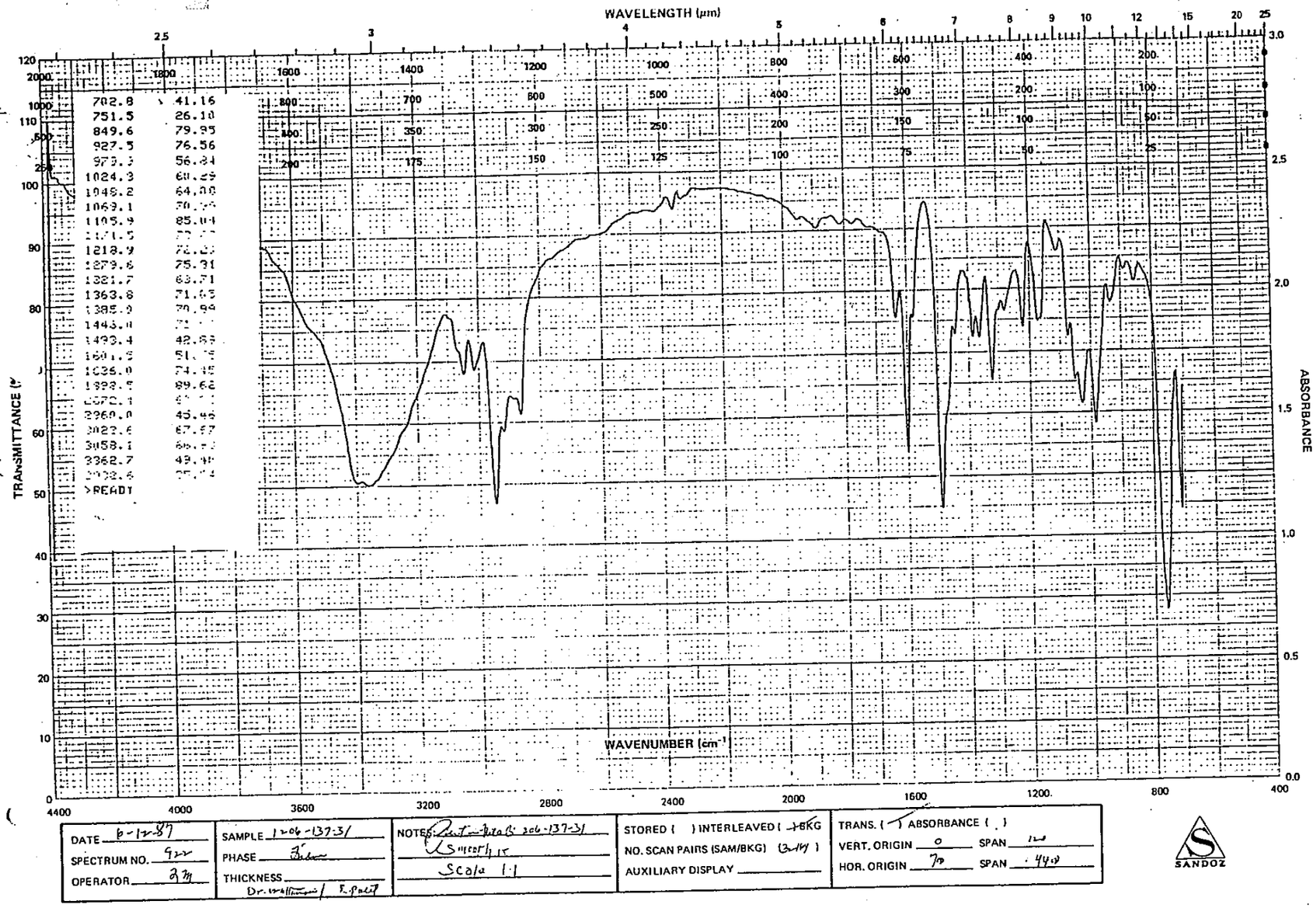
Rx mix. poured in ice H_2O (exothermic, strong Rx) extracted with ether, washed with H_2O brine, dried, filtered, washed, rotavap. to give yellow solids at 8.5g
C120G-137-B1) nmr, ir, ms

Theory: 8.86g (95.8%)

Performed by- Raj Patel 9-2-87

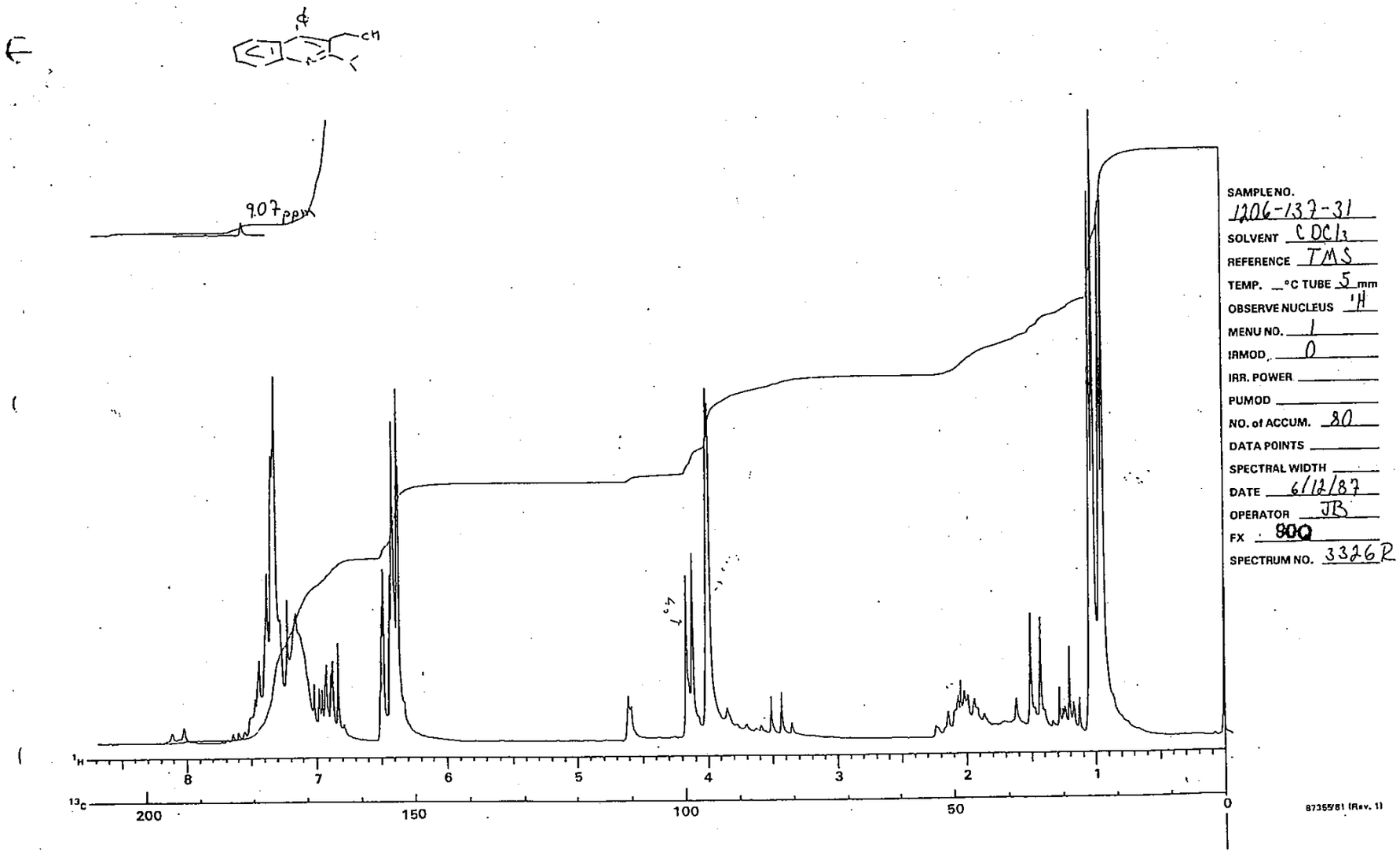
Witness- S. Wattanasin

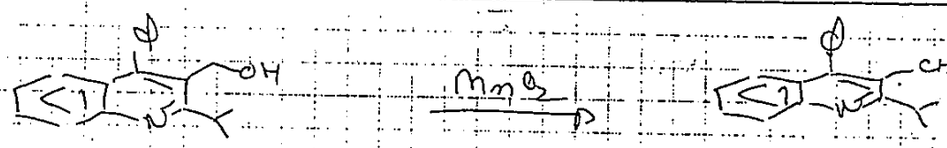
Cont'd to-



DATE 6-17-87	SAMPLE 1206-137-31	NOTES: Rust-Stabi 206-137-31	STORED ( ) INTERLEAVED (+BKG	TRANS. (✓) ABSORBANCE ( )
SPECTRUM NO. 9xx	PHASE Film	Support IR	NO. SCAN PAIRS (SAM/BKG) (32/64)	VERT. ORIGIN 0 SPAN 120
OPERATOR JM	THICKNESS Dr. Williams / E. Pretsch	Scale 1:1	AUXILIARY DISPLAY	HOR. ORIGIN 70 SPAN 4000

SANDOZ


9.07 ppm
4.1
SAMPLE NO. 1206-137-31
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 6/12/87
OPERATOR JB
FX 90Q
SPECTRUM NO. 3326R
1H
13C
8
7
6
5
4
3
2
1
0
200
150
100
50
87365/81 (Rev. 11)



1206-137-31
277.4

275.0
$C_{19}H_{17}NO$

277.4 1206-137-31 = ~~8.0~~ 8.0 g (Co-C2883-92mk)
MnO_2 = 16.0 g
toluene = 150 mL

To 1206-137-31 in toluene was added MnO_2
→ heated to reflux (111 – 115°C)

○	0.5	Rx
1	○	SM

filtered thru pad of* silica gel washed with toluene, rotovap to dryness, gave yellow solids: 2.6518 g (1206-145-25) nmr, tlc, ms MH+ = 276 desired pdt
orange solids: 3.6483 g (1206-145-26) nmr, tlc, ms MH+ = 278 S.M.

- During filtration, separated two bands, which was filtered separately & rotovap

Theory: 7.91 g (74.52%)

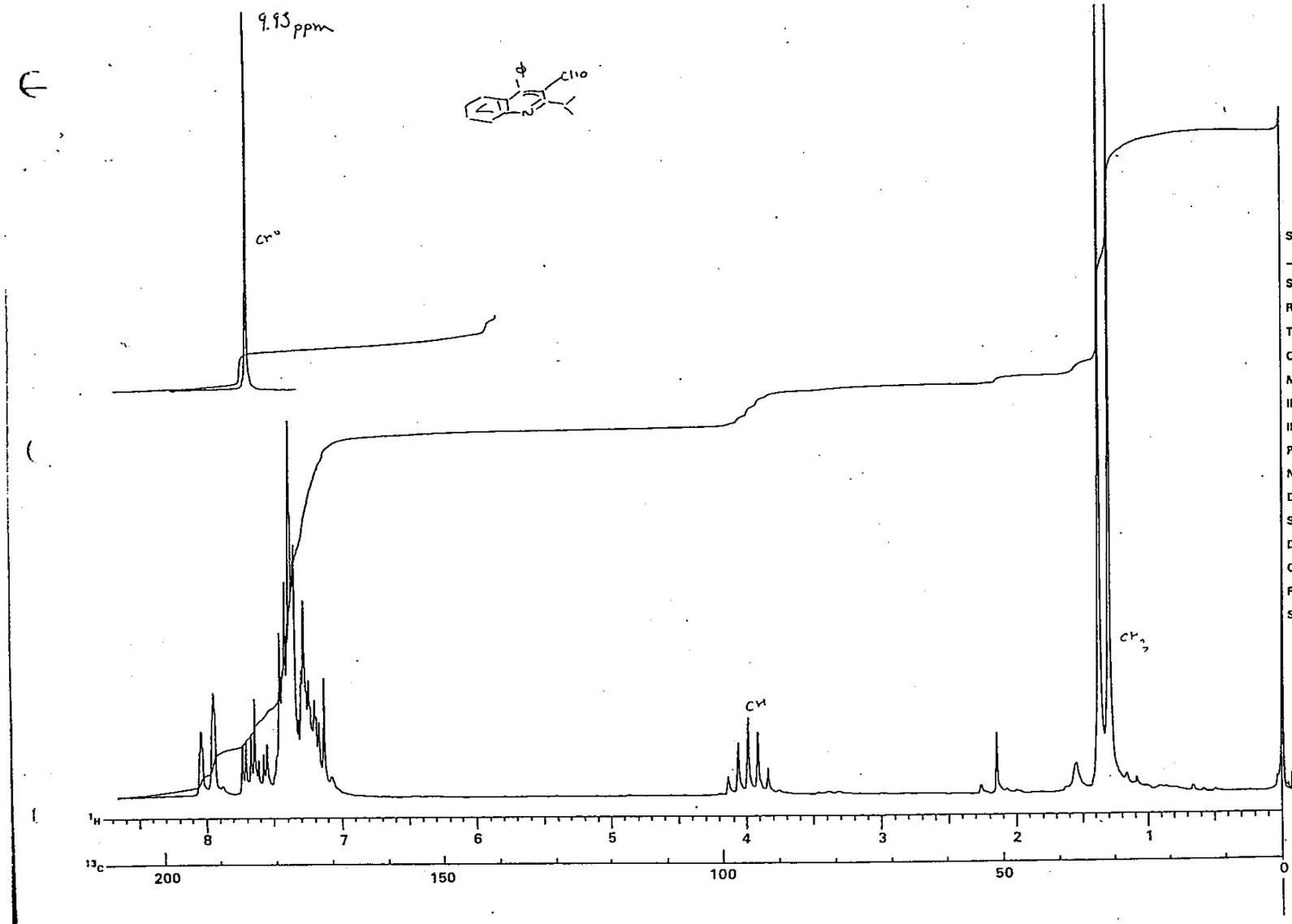
Total yield: 2.6518 g + 3.26 g = 5.91 g
(1206-145-25) (1206-148-33)

*

Performed by-

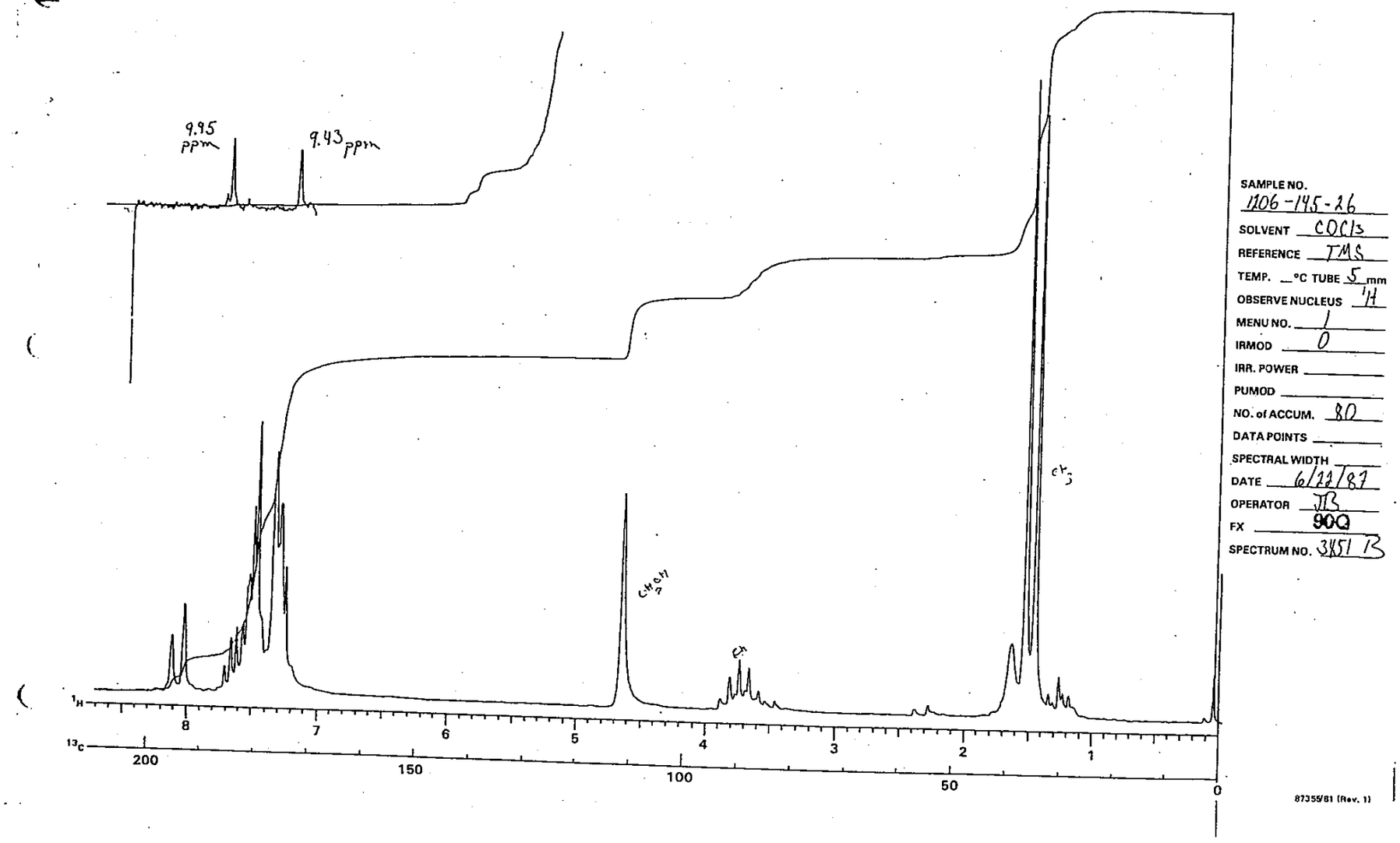
Witness- S. Wattanasin

Cont'd to- 148



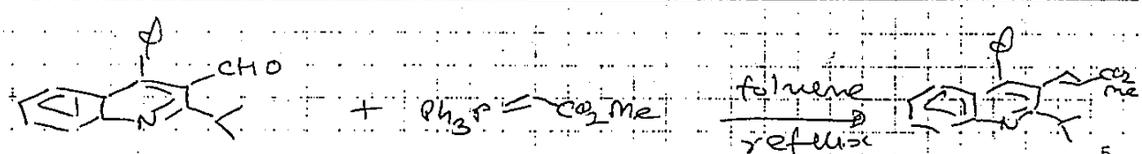
SAMPLE NO. 1206-145-25
SOLVENT CDCl3
REFERENCE TMS
TEMP. °C TUBE 5 mm
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOD 0
IRR. POWER
PUMOD
NO. of ACCUM. 80
DATA POINTS
SPECTRAL WIDTH
DATE 6/11/87
OPERATOR JD
FX ~~90Q~~
SPECTRUM NO. 3450

87355/81 (Rev. 1)


9.95 ppm
9.43 ppm
CH3OH
CH3
1H
13C
8
7
6
5
4
3
2
1
0
200
150
100
50
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 6/22/87
OPERATOR JB
FX 90Q
SPECTRUM NO. 3451 B
87359/81 (Rev. 1)

Date 6 Jan 87 Proj. Title-

Cont'd From-



275 331

(275) { 1206-145-25 / 1206-148-33 } = 2.65 + 3.26 = 5.91 g (0.021490 mole)

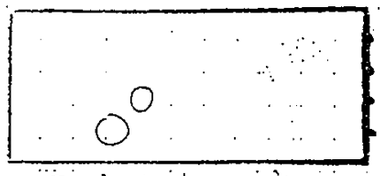
toluene = ~~11.82 g~~ 85 ml + 20 ml

(334) $Ph_3P=CO_2Me$ = 8.6135 g (0.025789 mole) (1.2 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% Et2O/Pet ether filtered thru pad of silicagel washed Rotavap to dryness to give yellow crystalline solid 8.6 g : Trituate with MeOH gave offwhite solids (Theory: 7.113 g) wt = 5.5198 g (1206-153-31) 77.6%

nmr ir ms mnt = 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 mnt 332

Rotavap mother liquor to dryness to yellow solid (1206-153-38) ms

Total yield = 5.5198 + 0.7616 (1206-153-)

7-9-87

m.p = 128°-130°c

	C	H	N	O
	77.3	6.98	4.37	
	74.65	4.65		
	75.26	4.23	3.75	

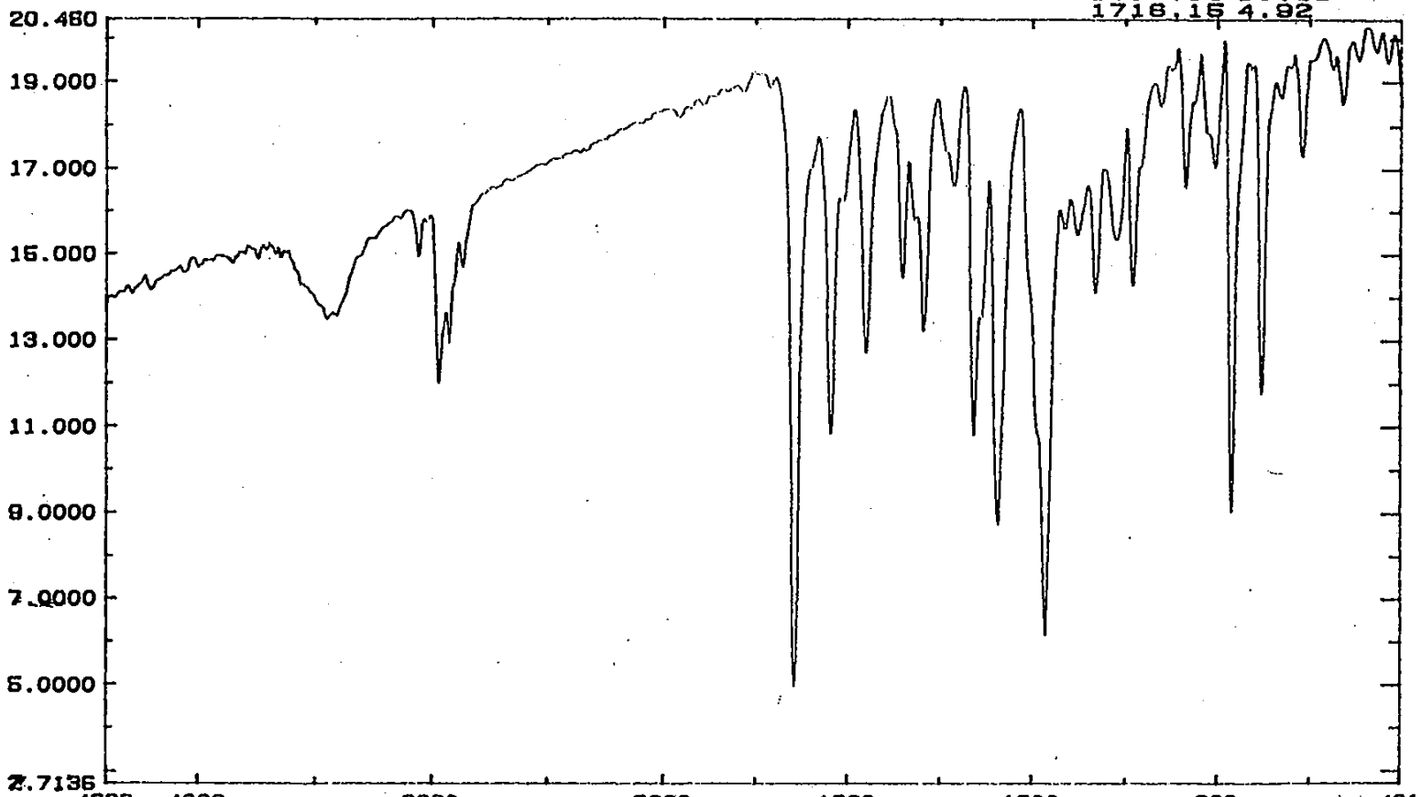
Performed by- Ray Patel 7-6-87

Witness- S Wattanasin

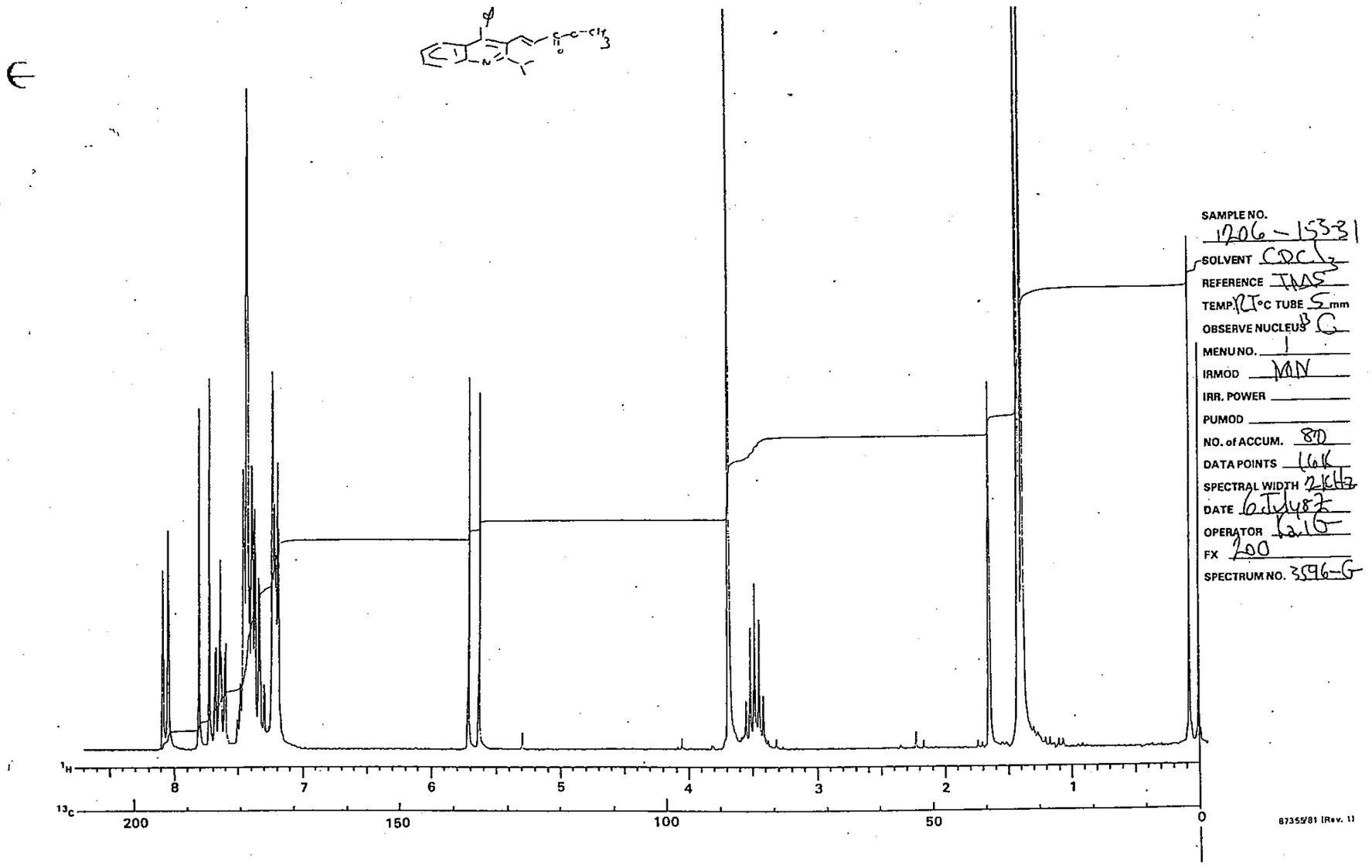
Cont'd to-

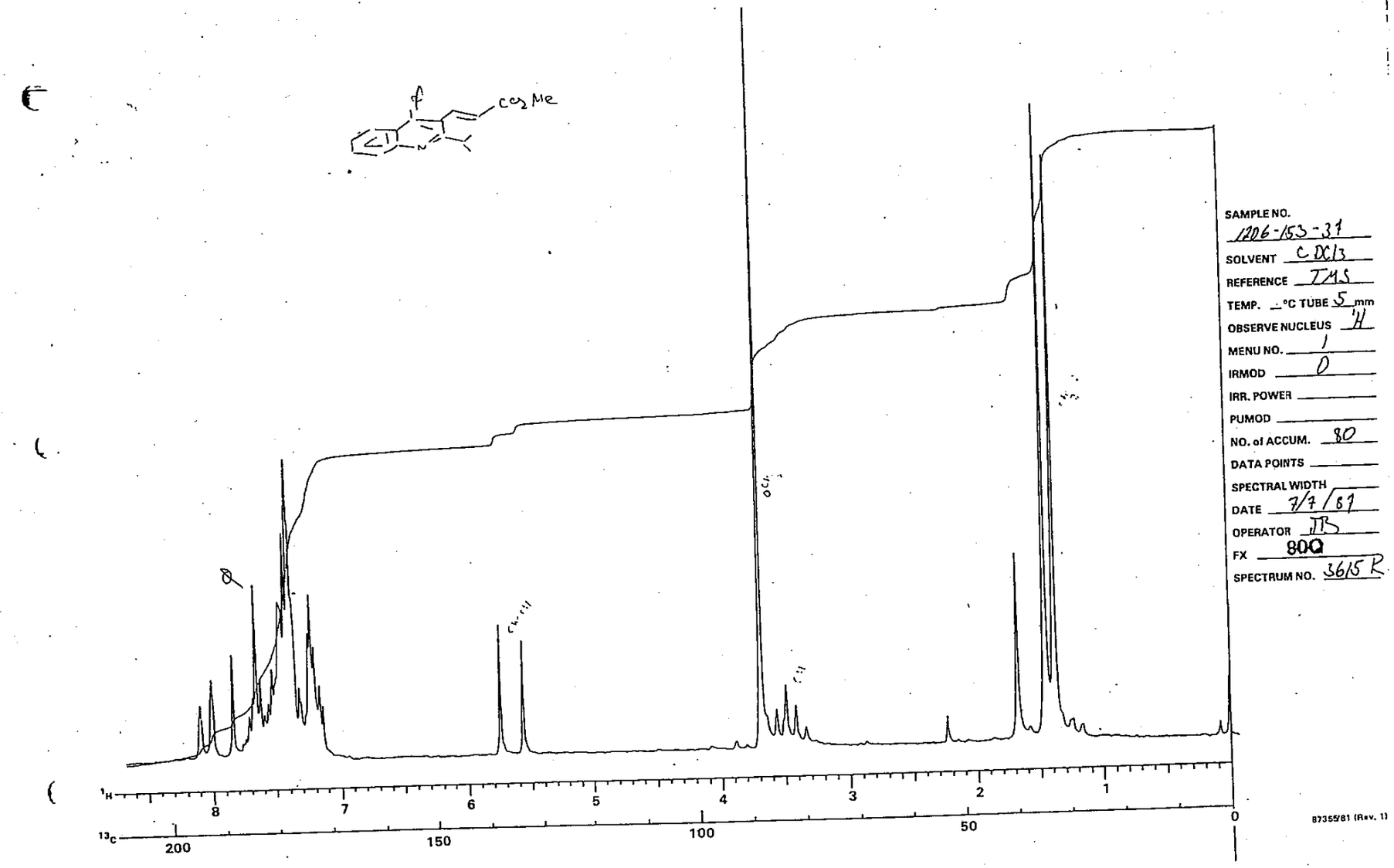
L

CM-1	%T	CM-1	%T
2927.38	12.83	704.38	11.78
2973.07	12.02	759.73	9.00
3413.38	13.56	1065.82	14.10
3462.89	13.49	1172.68	6.14
4207.45	14.18	1278.44	8.70
4289.51	14.08	1328.08	10.79
		1438.60	13.20
		1581.35	12.89
		1637.15	10.85
		1716.15	4.92



FILE NAME : 1206-163-34 #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 wattsin/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 NON
IRR. POWER
PUMOD
NO. of ACCUM. 800
DATA POINTS 16K
SPECTRAL WIDTH 2KHz
DATE 6 JUL 82
OPERATOR kalo
FX 200
SPECTRUM NO. 3596-G
1H
8
7
6
5
4
3
2
1
0
13C
200
150
100
50
87355/81 (Rev. 11)


CO2Me
SAMPLE NO. 1206-153-31
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 7/7/87
OPERATOR JB
FX 80Q
SPECTRUM NO. 3615R
1H
13C
8
7
6
5
4
3
2
1
0
200
150
100
50
87355/81 (Rev. 1)

158

Title-

Date 7-7-87 Proj.

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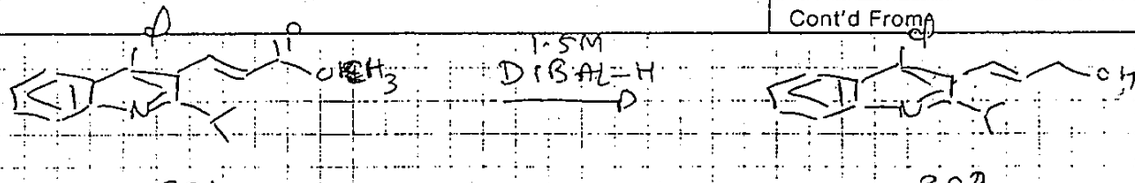


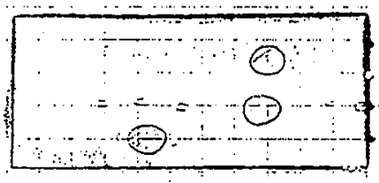
331

302
($C_{21}H_{21}NO$)

1206-153-40 = 6.259 g (0.0188821 mole)
1.5M DIBAL-H/toluene = 25.18 ml (0.0377642 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 (TLC 15% EtOAc/Hex - 3 spots)



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, rotavap to dryness gave off white solid = 5.429 (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 = 5.229 (1206-158-37) Theory = 5.729 g 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, mts, ~~tlc~~ mw = 304 micro

m.p. = 119°−121°C

Performed by- Ray Patel 7.17.87

Witness- S. Wattanasin

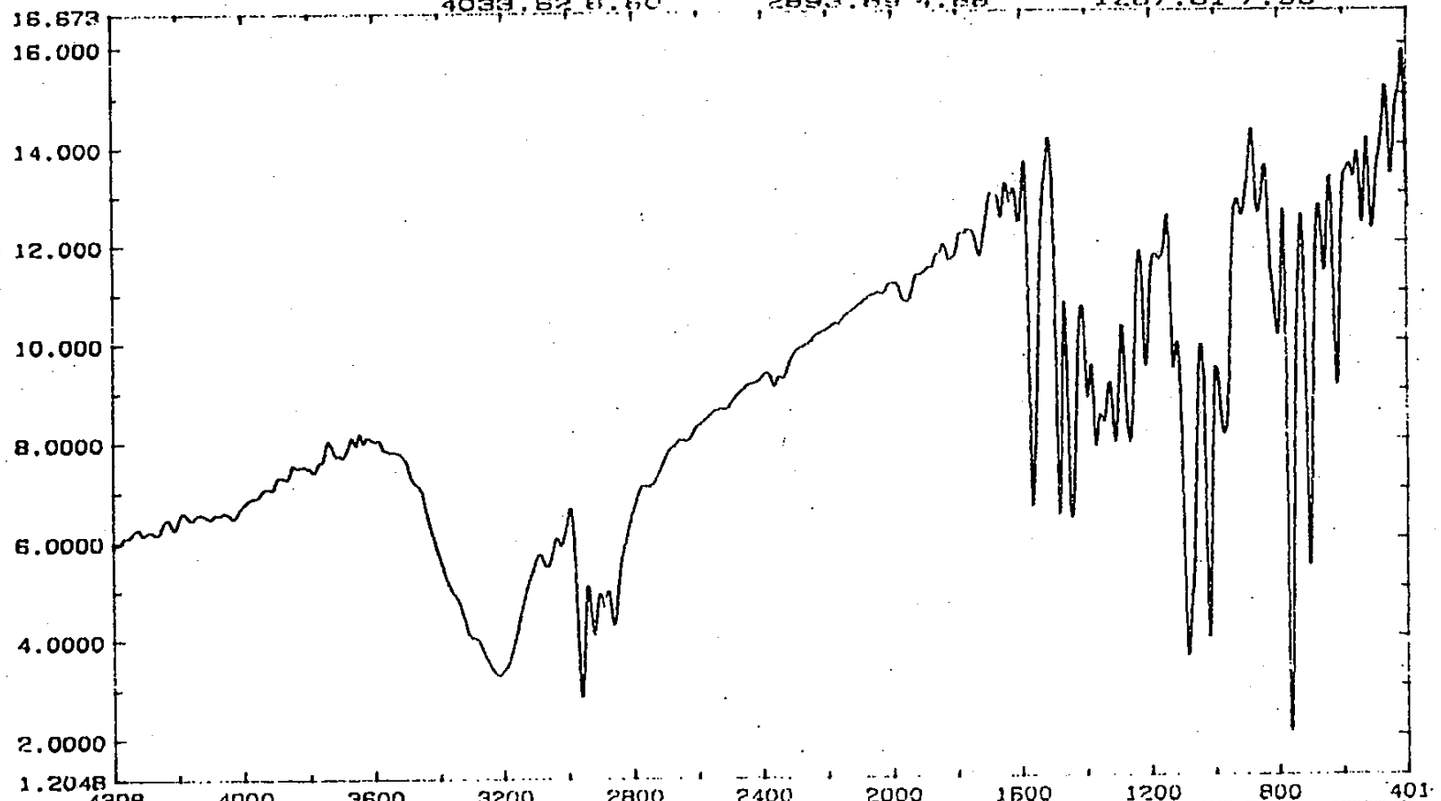
Cont'd to-

CM-1	%T
4104.80	8.48
4161.02	8.46
4214.36	8.27
4308.29	8.16

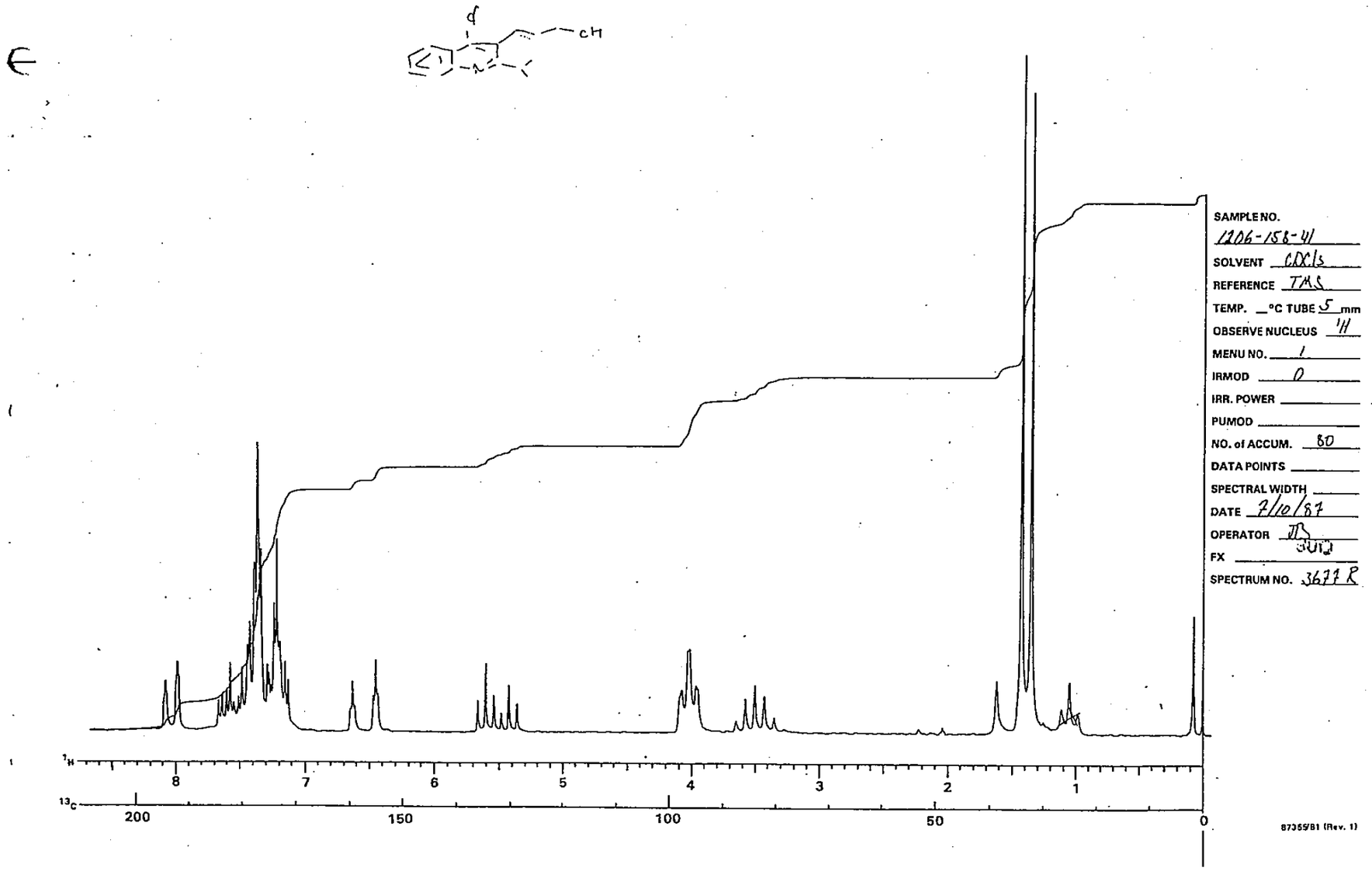
CM-1	%T
2925.08	4.13
2869.18	2.86
2026.13	3.93
3056.70	5.50
3217.77	3.30
3635.92	8.01
3681.66	7.97
3709.50	7.71
3789.40	7.42
4033.62	8.60

CM-1	%T
1312.78	7.94
1348.36	8.37
1372.02	7.88
1397.90	8.85
1446.43	8.44
1484.95	8.49
1567.40	8.69
2356.78	9.13
2863.30	4.30
2893.89	4.66

CM-1	%T
819.97	9.10
705.86	5.45
765.24	2.08
803.66	10.13
979.00	8.12
1021.66	8.96
1068.47	9.60
1131.72	9.43
1217.90	9.60
1287.81	7.96



FILE NAME : 1206-158-41 #1037		GAIN : 2	ANALECT FX-6160
#SCANS : 64		DET : TGS	ORD : %T
#BKG : 64		RES : 4 CM-1	ABSC: WAVENUMBER
APOD : HAPP-GENZEL		DATE : 07/21/87	TIME: 15:00:01
COMMENT : Kbr wattanasin/r.p.lab358 pcr			

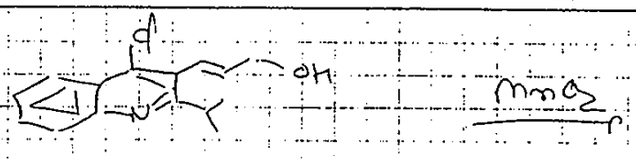

SAMPLE NO.
1206-158-41
SOLVENT CDCl3
REFERENCE TMS
TEMP. °C TUBE 5 mm
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOD 0
IRR. POWER
PUMOD
NO. of ACCUM. 80
DATA POINTS
SPECTRAL WIDTH
DATE 2/10/87
OPERATOR JT
FX
SPECTRUM NO. 3677 R
1H
8
7
6
5
4
3
2
1
13C
200
150
100
50
0
87359/B1 (Rev. 1)

166

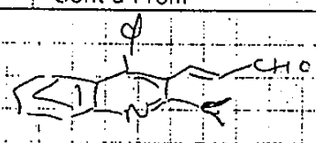
Title-

Date 7-15-87 Proj.

Cont'd From-



303

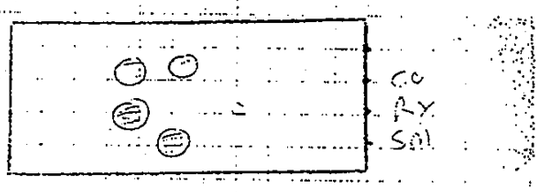


$C_{21}H_{19}NO$
301

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



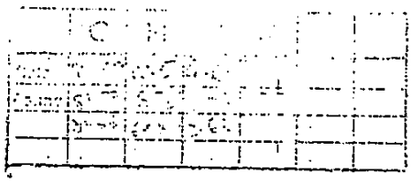
7-16-87

filtered thru pad of silica gel washed pad with ether, rotavac to dryness gave 3.4946g yellow crystaline material (1206-166-30)

IR NMR GC/MS mwt = 302

Theory: 3.9736g (88%)

7-28-87 micro



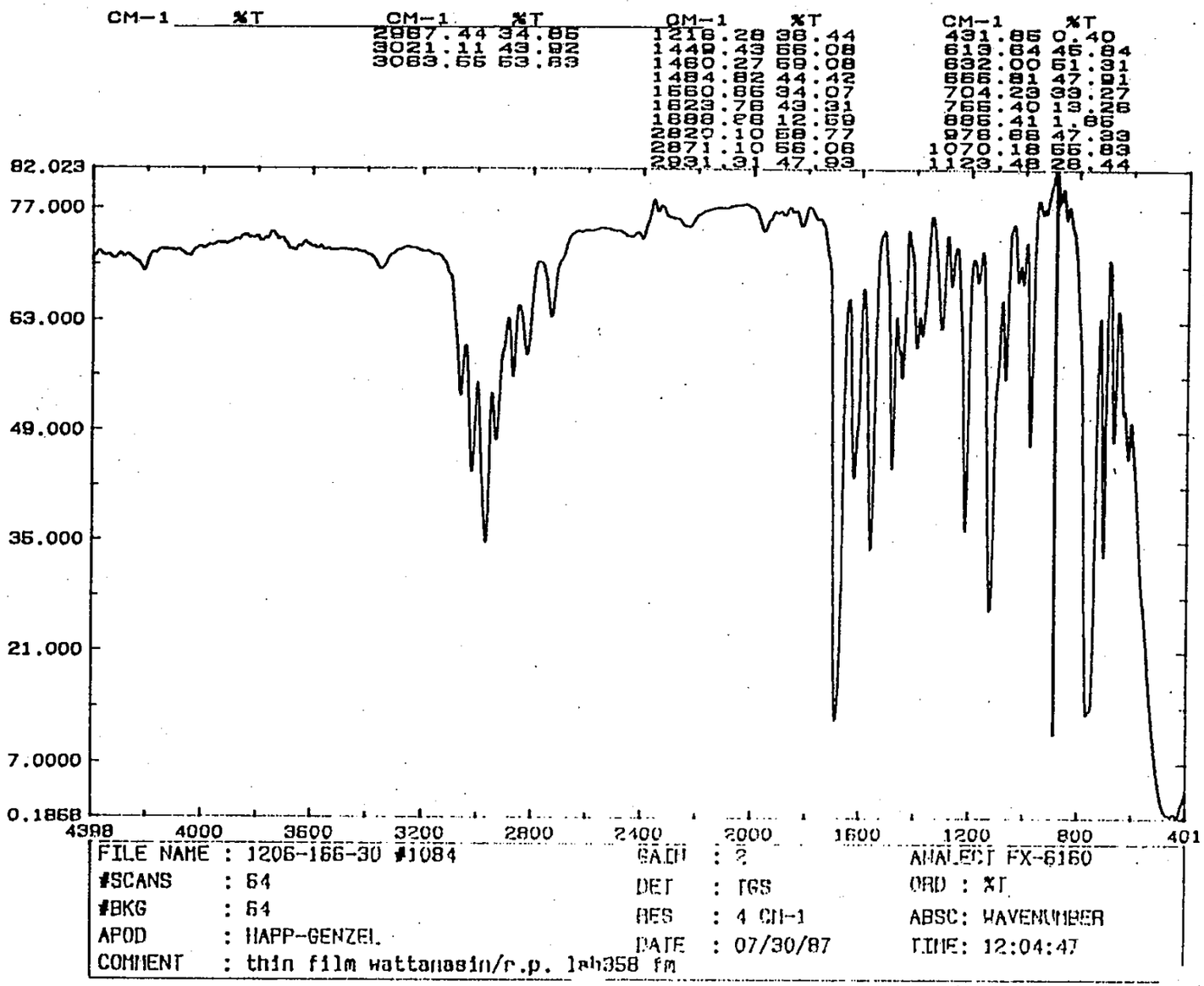
7-30-87

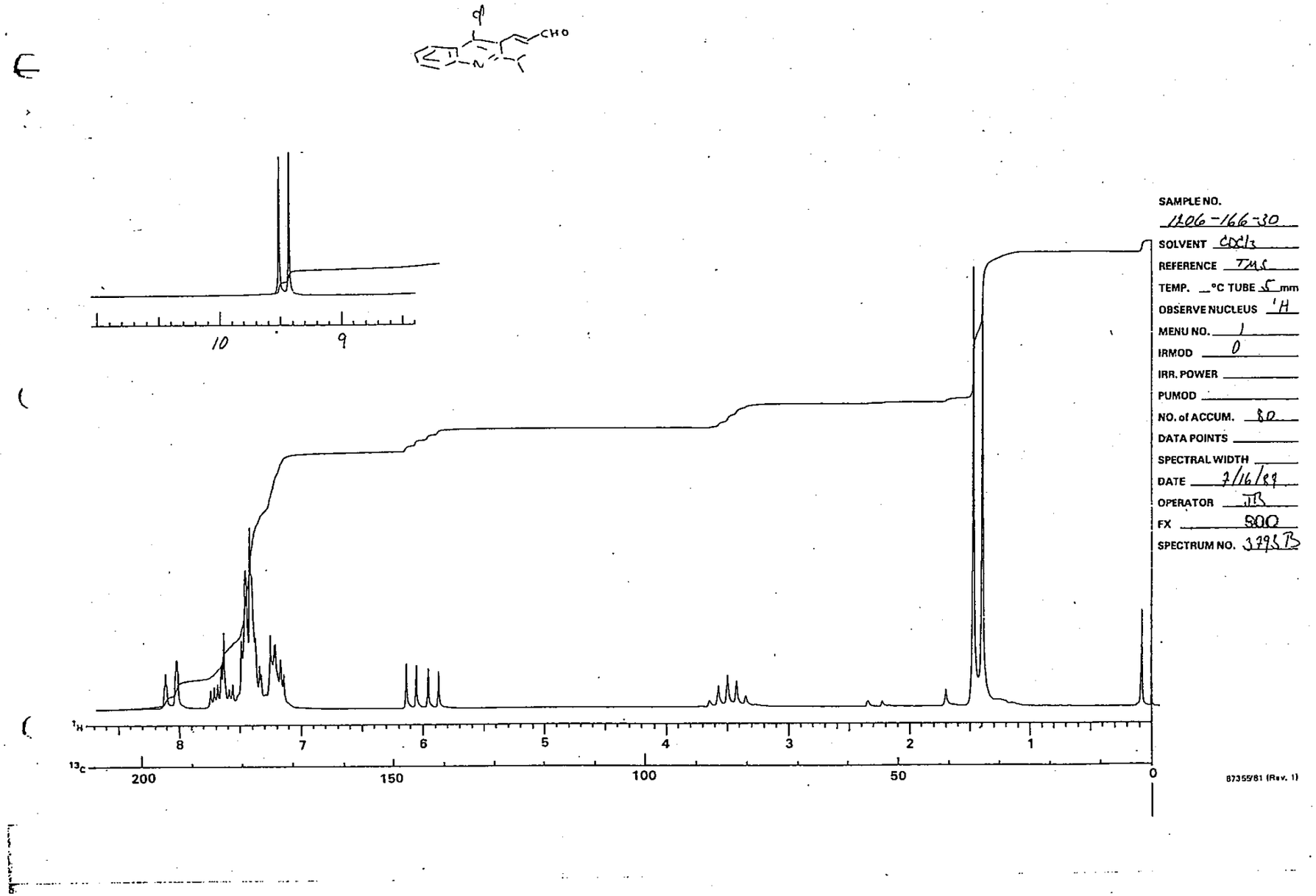
Exact mass obs. mass = 302.15464 m.p. = 98-101°
Calc. mass = 302.15448

Performed by- [illegible] Patel 7-20-87

Witness- S. Wattanasin

Cont'd to-

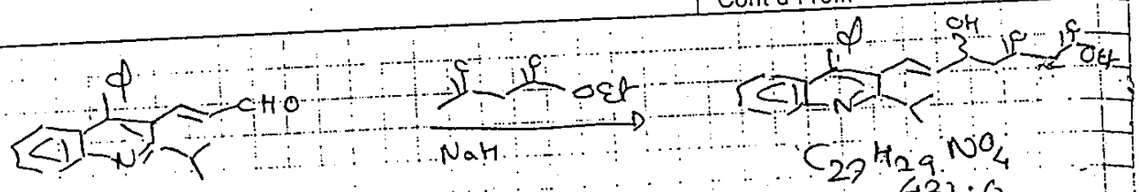

CM-1 %T CM-1 %T CM-1 %T CM-1 %T
2987.44 34.85 1216.28 38.44 431.85 0.40
3021.11 43.92 1449.43 56.08 613.64 46.84
3063.56 53.63 1460.27 59.08 632.00 51.31
1484.82 44.42 565.81 47.91
1560.85 34.07 704.23 33.27
1623.76 43.31 765.40 13.26
1688.68 12.59 885.41 1.85
2820.10 58.77 978.68 47.33
2871.10 56.08 1070.18 56.83
2931.31 47.93 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


CHO
10
9
SAMPLE NO. 1206-166-30
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 7/16/89
OPERATOR JTB
FX 500
SPECTRUM NO. 3795 B
1H
8
7
6
5
4
3
2
1
13C
200
150
100
50
0
87355/81 (Rev. 1)

Title-

Date 7-20-87 Proj.

Cont'd From-



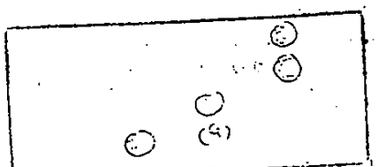
301

301 1206-166-30 = 3.5g (0.0116279 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 soln of 1206-166-30 in dry THF (40ml) at -5° to -10°C was added a soln of dianion (11ml + 27ml)(38ml), prepared as described previously

Dianion (got from Dr. Som)

To soln 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 1.6M 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 darkened
TLC (50% Et_2O/Pet) after 15 min → complete rxn



P
Rx
ethyl acetoacetate
SM (Aldehyde)

Rx was stirred for 30 min. quenched with sat NH_4Cl & extracted with Et$_2$O, washed with H_2O brine, dried, filtered, rotavaped gave yellow oil 5.9188 g (1206-172-41)
Theory: 5.01g (67.87%)

Performed by- Raj Patel 7-21-87

Cont'd to- 72 & 6-175

Witness-

Date 7-22-87 Proj. Title-

Cont'd From- 120G-172

Flash chromatography (5% EtOAc/Hex) gave (9) yellow solids = 3.4004 g CR0G-175-43 micro mp 42-43

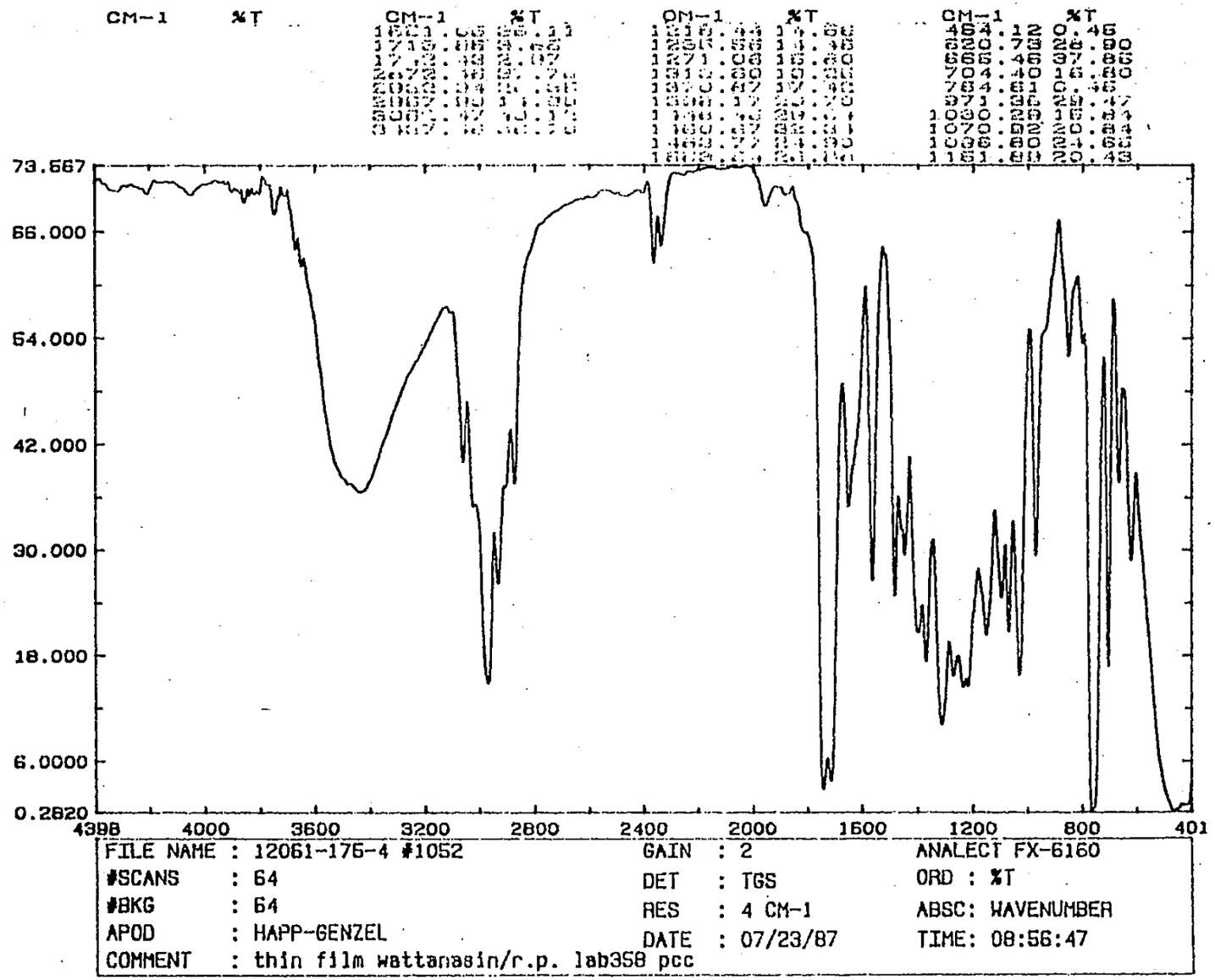
m.p. = 84-87°C 68% yield

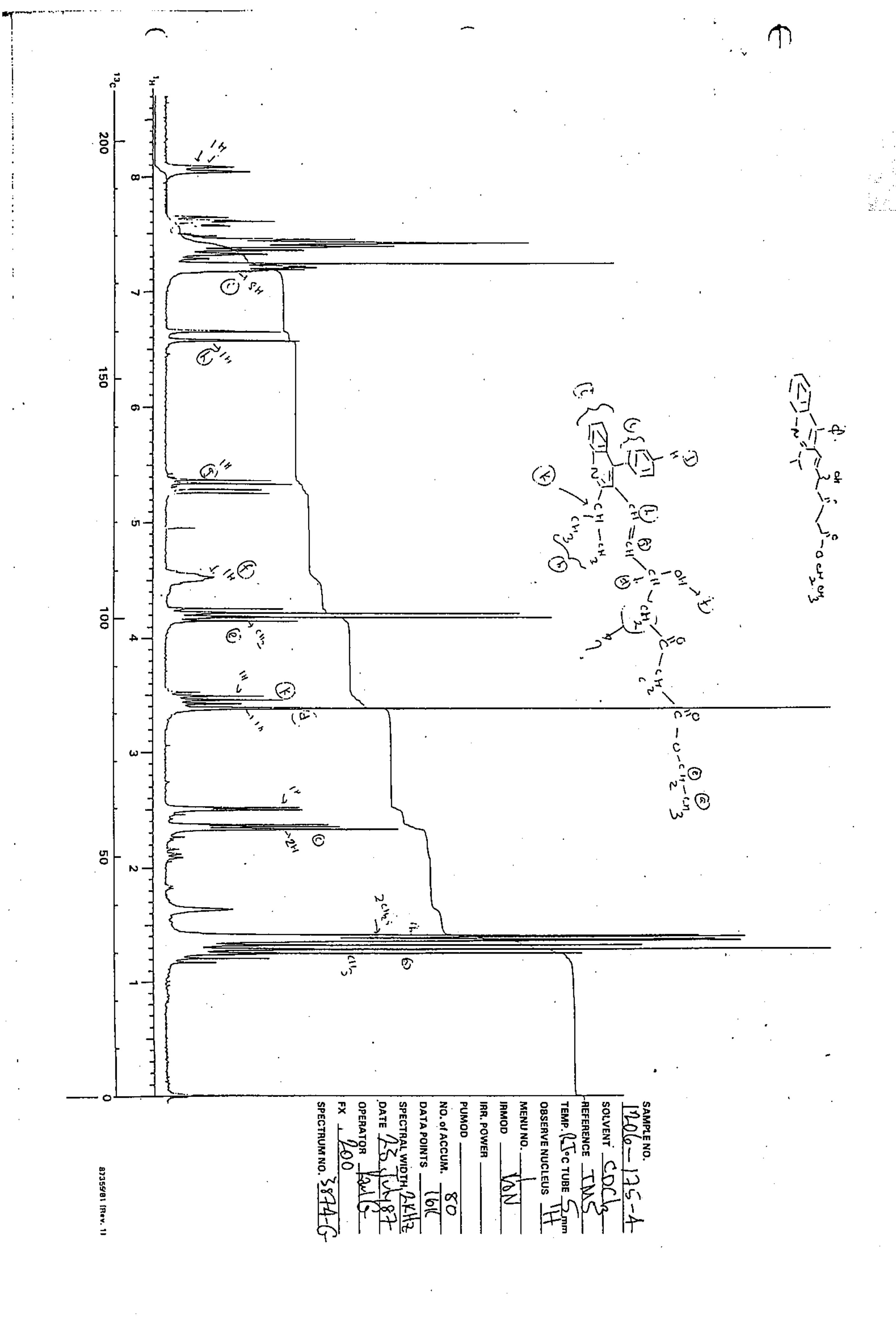
	C	H	N	O		
Calc.						
Found						

Performed by- Raj Patel 8-5-87

Witness- S. Wattanasin

Cont'd to-

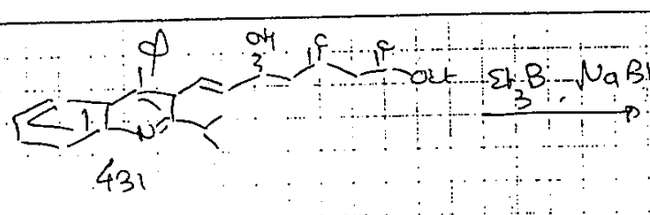

CM-1 %T
73.667
66.000
54.000
42.000
30.000
18.000
6.0000
0.2820
4398 4000 3600 3200 2800 2400 2000 1600 1200 800 401
FILE NAME : 12061-175-4 #1052
#SCANS : 64
#BKG : 64
APOD : HAPP-GENZEL
COMMENT : thin film wattanasin/r.p. lab358 pcc
GAIN : 2
DET : TGS
RES : 4 CM-1
DATE : 07/23/87
ANALECT FX-6160
ORD : %T
ABSC: WAVENUMBER
TIME: 08:56:47


SAMPLE NO. 1206-175-4
SOLVENT CDCl3
REFERENCE TMS
TEMP. RT °C TUBE 5 mm
OBSERVE NUCLEUS 1H
MENU NO.
IRMOD NON
IRR. POWER
PUMOD
NO. of ACCUM. 80
DATA POINTS 16K
SPECTRAL WIDTH 2KHz
DATE 23 JUL 87
OPERATOR
FX 200
SPECTRUM NO.

Title-

Date 7-23-87 Proj.

Cont'd From-



431

433.527

$C_{29}H_{31}NO_4$

(431) 1206-175-4 = 1.0 g (0.0023201 mole)

1m Et_3B / THF = 3.5 ml (0.0034801 mole) 1.5eq.

dry THF = 10 ml

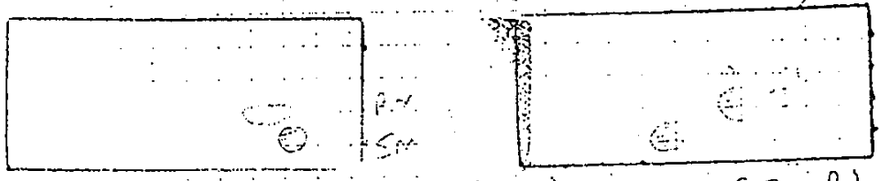
CH_3OH = 2.5 ml

32.8 $NaBH_4$ = 0.1315 g (0.0034801 mole) 1.5

Ref: 1206-140

(homogeneous)

To 1206-175-4 in THF / MeOH added 1m Et_3B / THF at r.t. stirred for 1 hr (9 A.M. - 10 A.M.) The solution was cooled to -78°C, $NaBH_4$ was added portionwise. The rxn was stirred at -78°C for (11 A.M. - 3 P.M.) 4 hrs.



The rxn was quenched with MeOH (5 ml) at -78°C. Ethyl acetoacetate was added & let it warm upto r.t. Org. layer was washed with sat. $NaHCO_3$, 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 (packed / pet) gave ✓ m.p. = 104-106° ✓ exact mass 15

yellow oil (a) F_{4-6} = 0.4043 g (1206-176-41) ir nmr, ms mh^+ = 434 c

(solid) HPLC (98.3%) 13

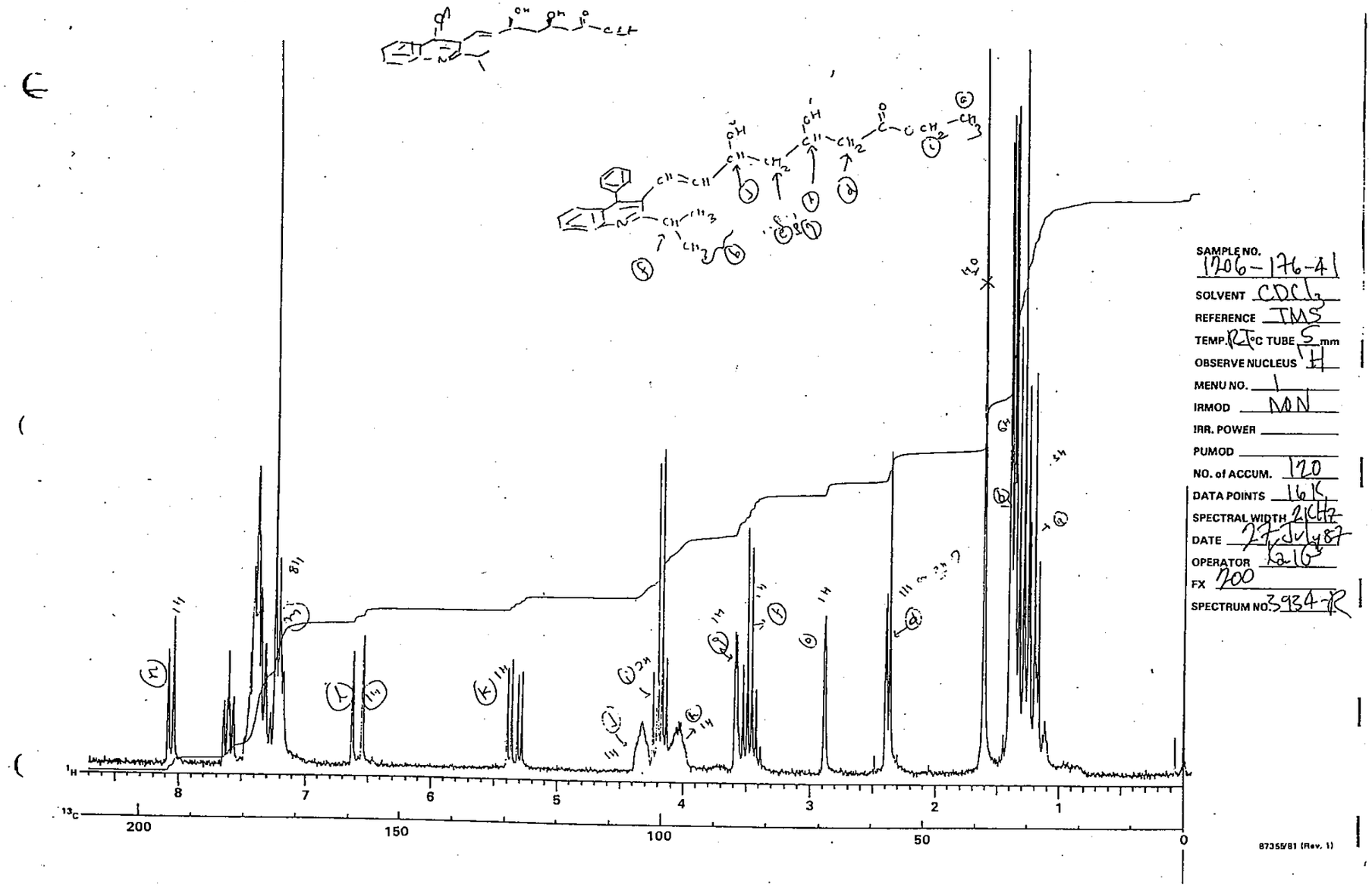
F_{7-13} = 0.510 g (1206-176-43) ir nmr, ms mh^+ = 434 a

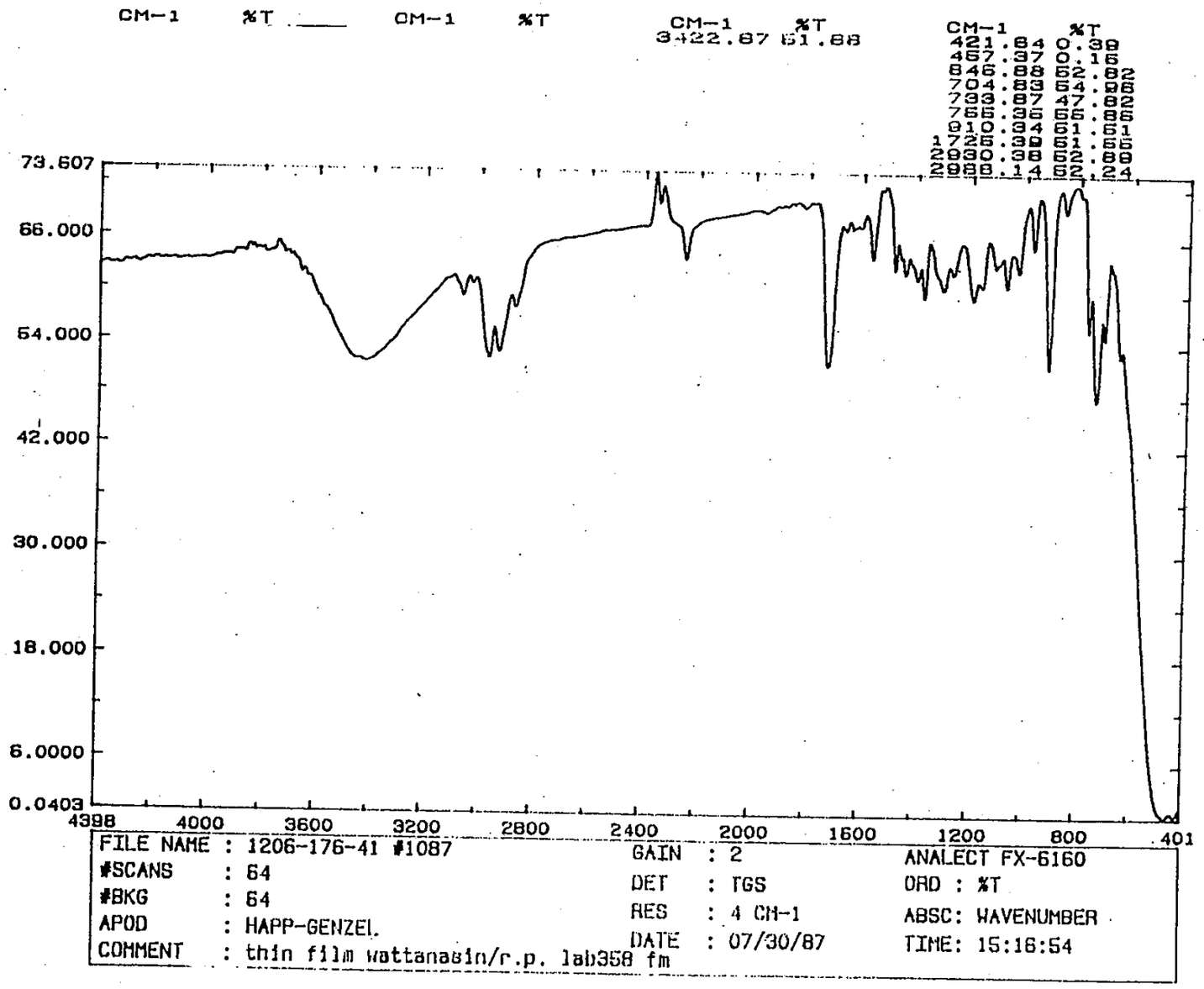
HPLC (93.2%)

Performed by- Ray Patel 8-5-87

Witness- S. Wadhwa

Cont'd to-


SAMPLE NO. 1706-176-41
SOLVENT CDCl3
REFERENCE TMS
TEMP. RT °C TUBE 5 mm
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOD MN
IRR. POWER
PUMOD
NO. of ACCUM. 120
DATA POINTS 16K
SPECTRAL WIDTH 2.1KHz
DATE 27 Jul 87
OPERATOR RAG
FX 200
SPECTRUM NO. 3934-PR
1H
13C
8
7
6
5
4
3
2
1
200
150
100
50
0
87355/81 (Rev. 1)


CM-1 %T
CM-1 %T
CM-1 %T
3422.87 51.88
CM-1 %T
421.64 0.38
467.37 0.15
846.88 52.82
704.83 54.96
793.87 47.82
755.35 56.86
910.34 61.51
1725.39 61.55
2930.38 52.88
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

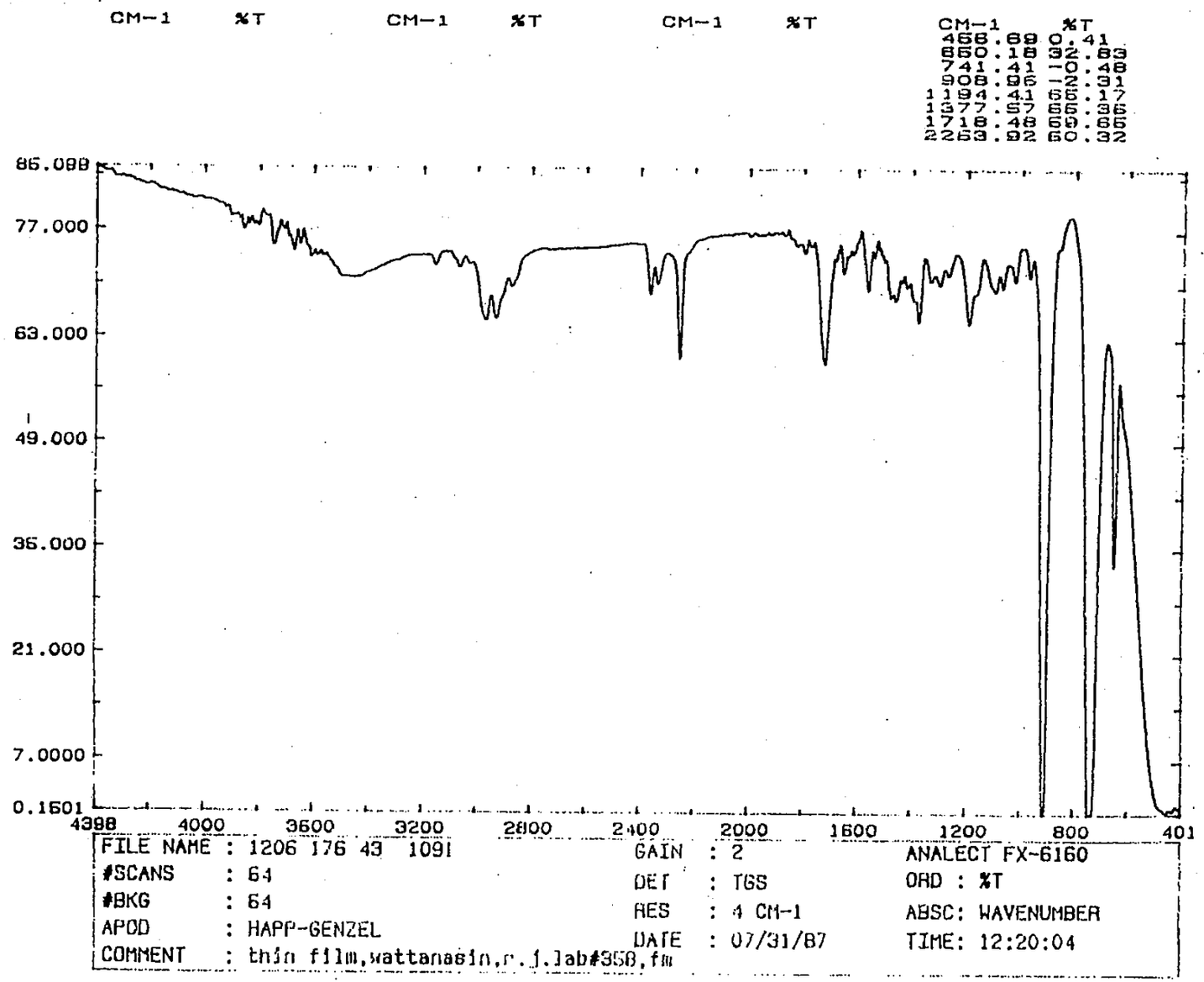
TOTAL 31
RESOL146538 -4 HZ
EXREF 77.0000PPM
OBS 1756.9331 HZ
AGAIN 8

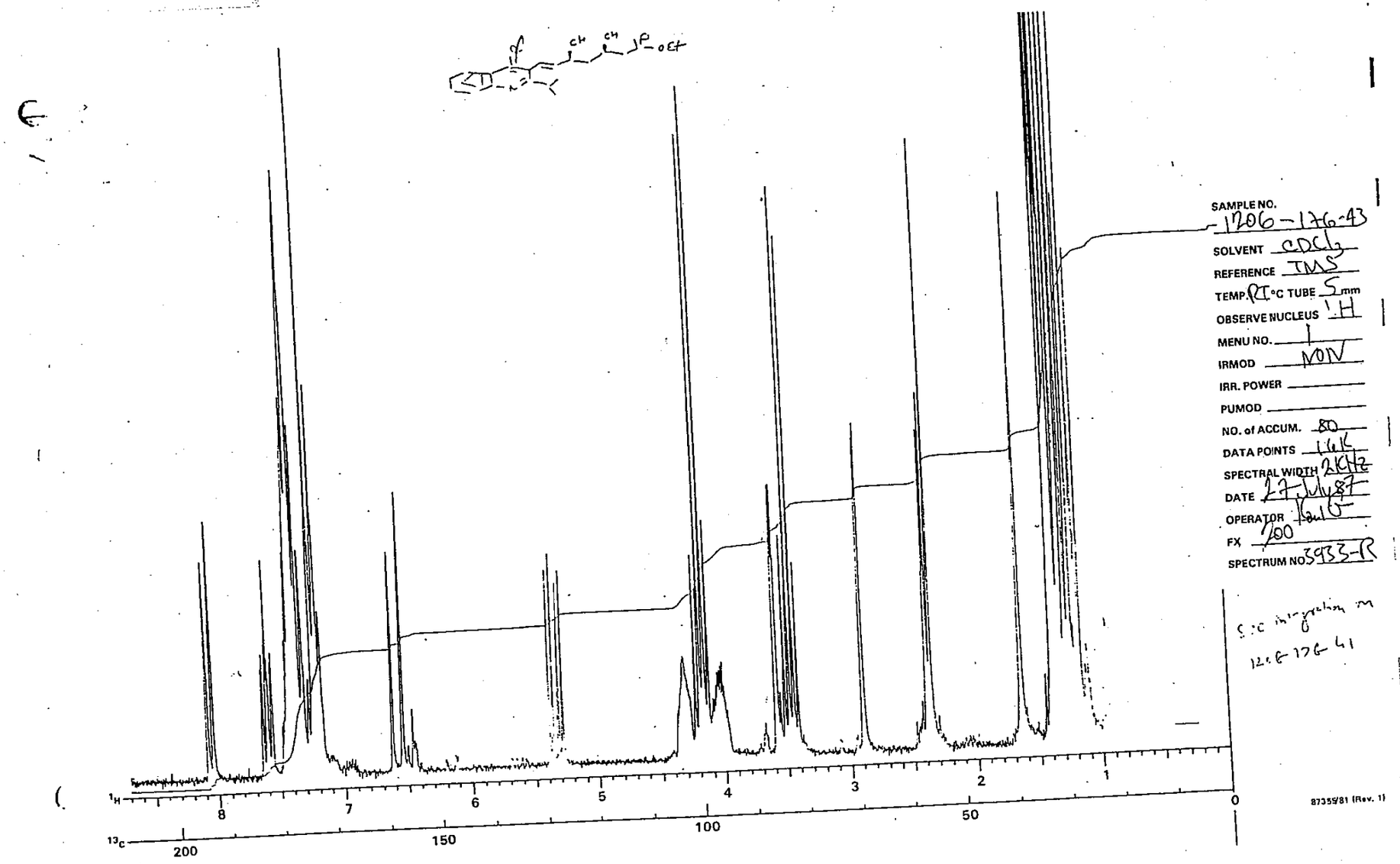
NO	FREQ(HZ)	PPM	HERZ
1	9655.91	172.491	295
2	8296.58	165.327	257
3	7816.18	139.887	814
4	6929.16	130.855	195
5	6545.73	138.434	1016
6	6532.54	138.171	1137
7	6479.75	129.120	597
8	6451.25	128.565	867
9	6428.58	128.098	2395
10	6387.47	127.291	961
11	6340.53	126.346	1126
12	6314.21	125.921	632
13	6282.46	125.587	816
14	4164.56	82.995	-155
15	3895.41	77.642	8388
16	3874.43	77.284	688
17	3864.17	77.988	9358
18	3831.93	76.357	9559
19	3623.86	72.211	937
20	3485.39	67.899	1224
21	3952.75	58.924	921
22	2121.92	42.293	1971
23	2082.35	41.495	2192
24	1729.21	34.459	178
25	1559.74	32.886	991
26	1178.51	21.933	1434
27	1097.58	21.975	1448
28	756.41	15.275	549
29	712.19	14.199	591
30	187.11	2.126	-148
31	-262.14	-5.221	-147

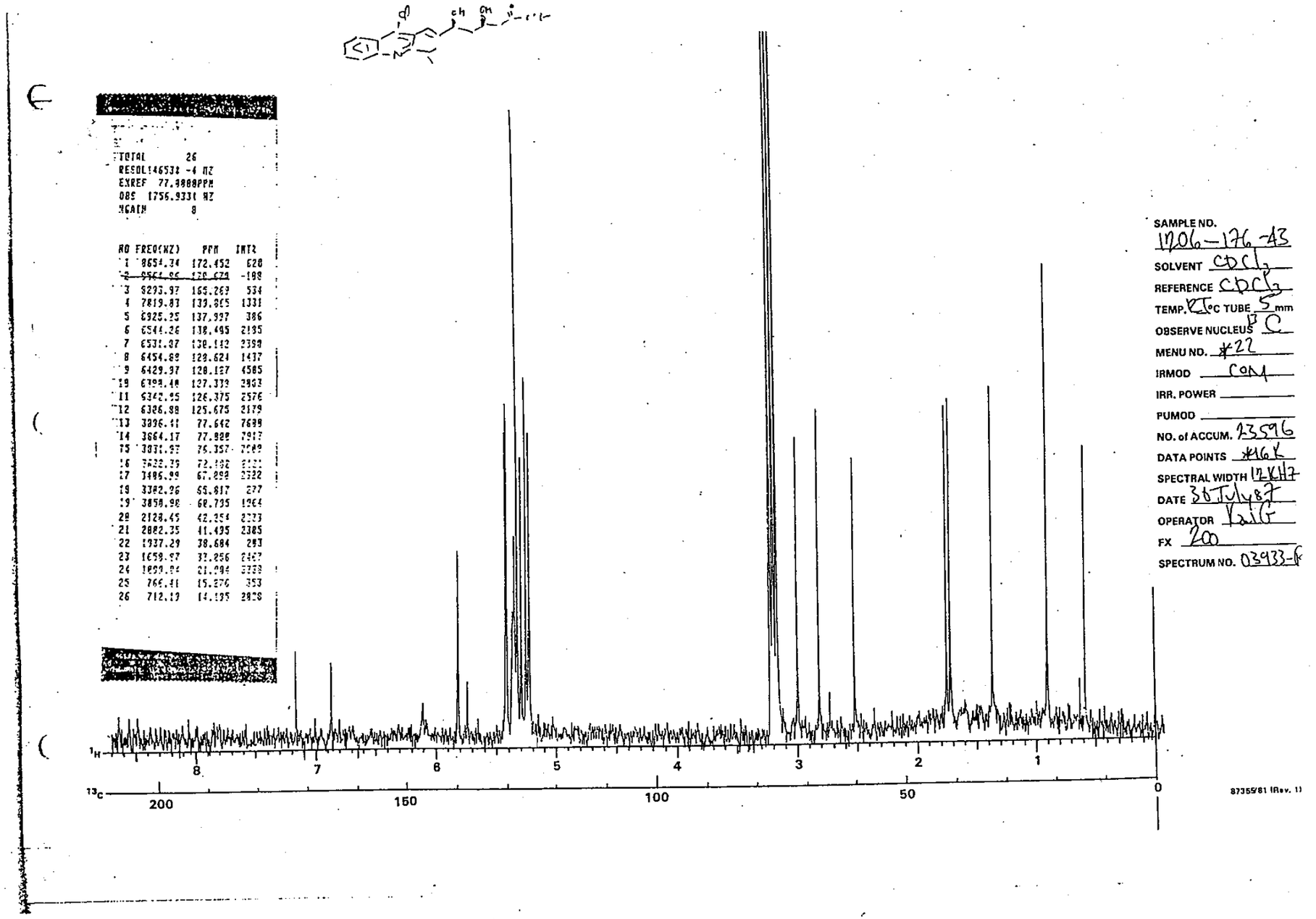
SAMPLE NO. 1106-176-41
SOLVENT $CDCl_3$
REFERENCE $CDCl_3$
TEMP. RT °C TUBE 5 mm
OBSERVE NUCLEUS ^{13}C
MENU NO. #-22
IRMOD COM
IRR. POWER
PUMOD
NO. of ACCUM. 30667
DATA POINTS #16K
SPECTRAL WIDTH 12KHz
DATE 29/July/87
OPERATOR Randy
FX 200
SPECTRUM NO. 03934-1

^1H 8 7 6 5 4 3 2 1
^{13}C 200 150 100 50 0

87355/81 (Rev. 1)


CM-1 %T
CM-1 %T
CM-1 %T
CM-1 %T
466.69 0.41
650.18 32.83
741.41 10.48
908.96 2.31
1194.41 55.17
1377.57 56.36
1718.48 59.65
2253.92 60.32
86.088
77.000
63.000
49.000
36.000
21.000
7.0000
0.1601
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 5mm
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOD NOV
IRR. POWER
PUMOD
NO. of ACCUM. 80
DATA POINTS 16K
SPECTRAL WIDTH 2KHz
DATE 27 July 87
OPERATOR
FX 200
SPECTRUM NO 3933-PR
1H
13C
8
7
6
5
4
3
2
1
0
200
150
100
50
87359/81 (Rev. 1)



TOTAL 26
RESOL146538 -4 HZ
EXREF 77.0000PPM
OBS 1756.9331 HZ
MGAIN 8

NO	FREQ(HZ)	PPM	INTS
1	8654.34	172.452	620
2	9564.96	170.639	-198
3	9293.97	165.269	534
4	7819.83	139.005	1331
5	6925.25	137.997	386
6	6544.26	130.495	2135
7	6531.87	130.112	2398
8	6454.89	128.624	1437
9	6429.97	128.127	4585
10	6398.48	127.339	2963
11	6342.95	126.375	2576
12	6306.88	125.675	2179
13	3896.41	77.642	7698
14	3864.17	77.000	7917
15	3831.97	76.357	7269
16	3622.25	72.182	2121
17	3486.99	67.898	2522
18	3382.96	65.817	277
19	3858.98	60.735	1964
20	2128.45	42.354	2223
21	2082.35	41.495	2385
22	1937.29	38.604	293
23	1658.97	33.056	2467
24	1059.84	21.094	2238
25	766.41	15.270	353
26	712.19	14.195	2828

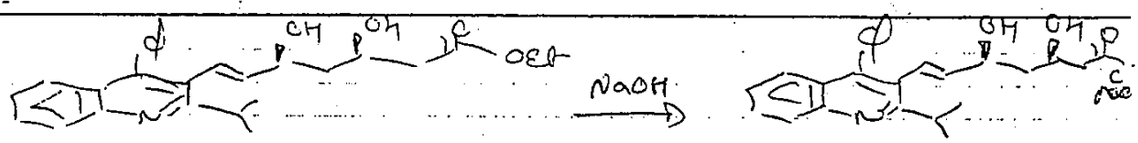
SAMPLE NO. 17206-176-43
SOLVENT $CDCl_3$
REFERENCE $CDCl_3$
TEMP. RT °C TUBE 5 mm
OBSERVE NUCLEUS ^{13}C
MENU NO. #22
IRMOD COM
IRR. POWER
PUMOD
NO. of ACCUM. 23596
DATA POINTS #16K
SPECTRAL WIDTH 12KHZ
DATE 30JUL87
OPERATOR Vail
FX 200
SPECTRUM NO. 03933-F

^1H 8 7 6 5 4 3 2 1 0
^{13}C 200 150 100 50 0

87355/81 (Rev. 11)

Date 7-28-87 Proj. Title-

Cont'd From-

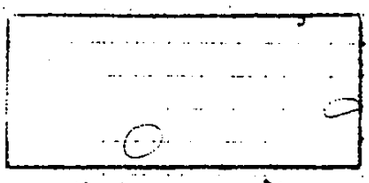


433 427-467

$C_{25}H_{26}NO_4Na$

(433) 1206-176-41 = 200.0mg (0.461893 mmole)
0.5N NaOH = 439 ml (0.438799 mmole)
abs EtOH = 5 ml + 439 ml 95%

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

Rotavap ether layer to dryness to yellow solids (1206-179-34)

Theory: 197.2 mg (90.6%)

	C	H	N	O		
Calc.						
Found						

10-6-87 submitted for (2mg) solubility test

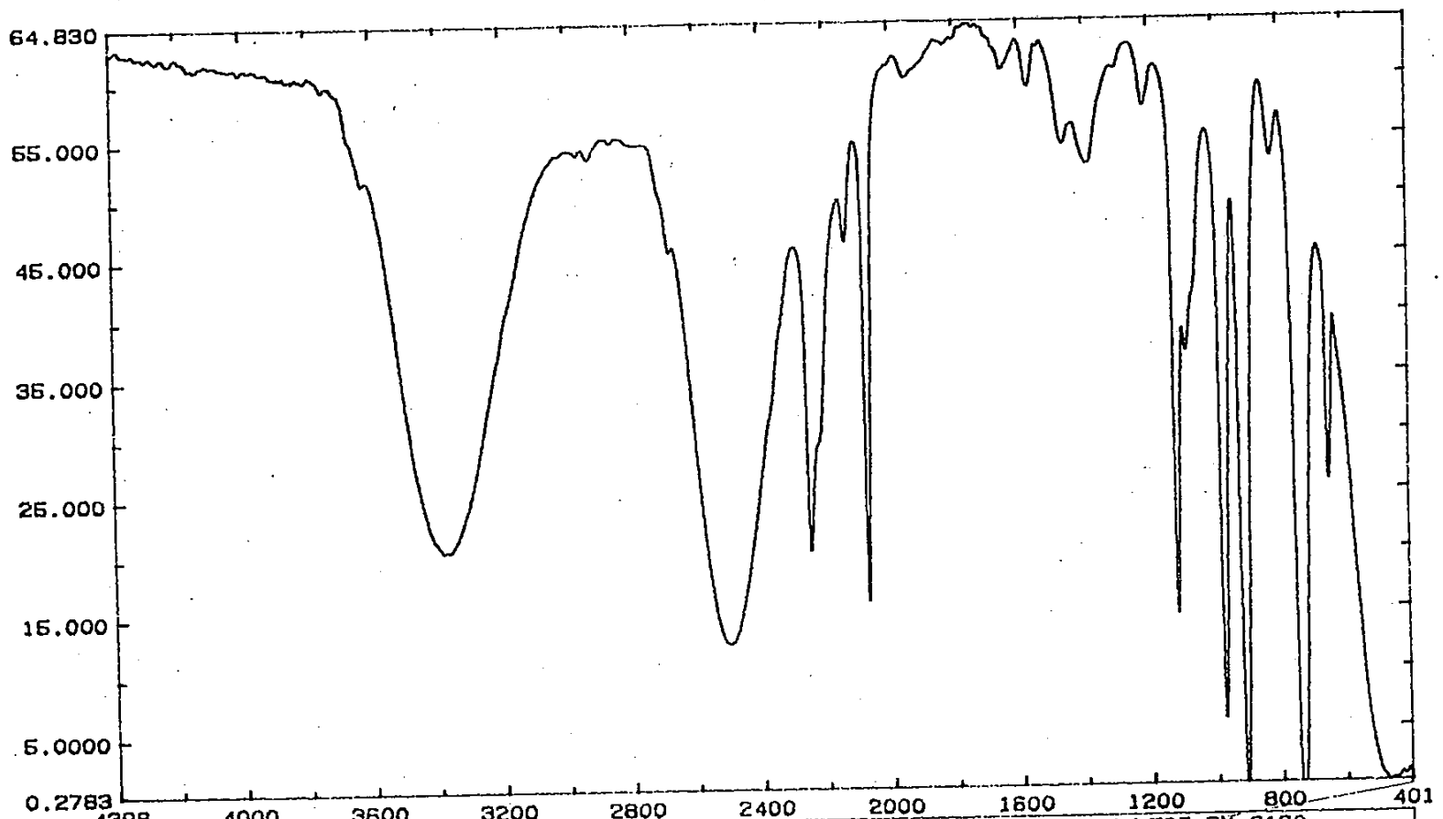
(6-7-87) Solubility = 0.0809 mg/ml

Performed by- Roy Patel 8-5-87

Witness- L Perez

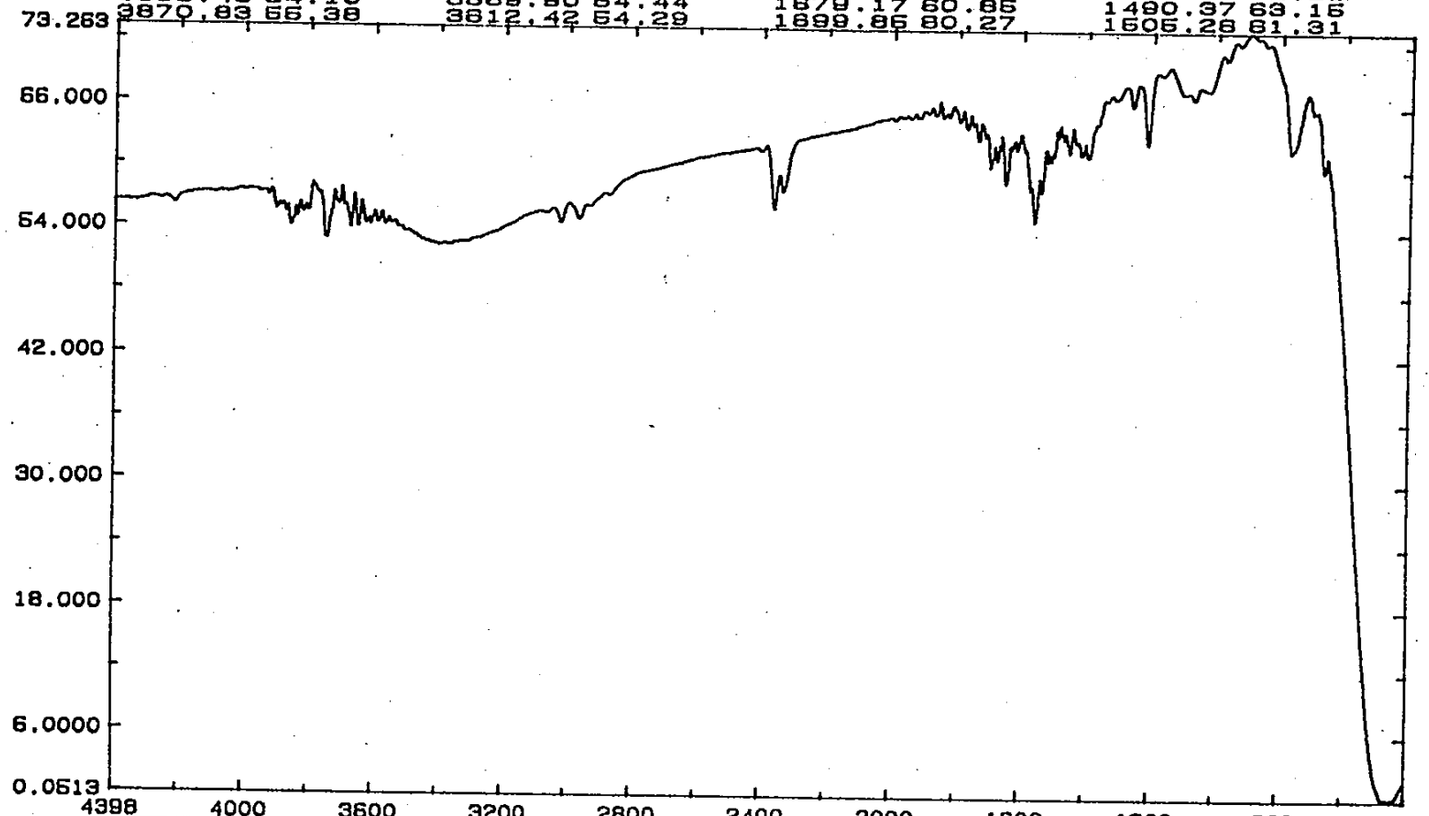
Cont'd to-

CM-1	%T	CM-1	%T	CM-1	%T
				488.45	0.45
				739.00	0.38
				910.64	0.24
				976.43	5.67
				2501.90	12.69



FILE NAME : 1206-179-30 1093	GAIN : 2	ANALECT FX-6160
#SCANS : 64	DET : TGS	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		

CM-1	%T	CM-1	%T	CM-1	%T	CM-1	%T
3625.31	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	865.02	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	64.99	1215.79	62.57
3746.57	62.96	2964.39	54.94	1575.14	57.99	1396.97	61.28
3801.88	66.53	3020.64	54.68	1618.32	61.95	1419.62	61.43
3817.22	65.39	3397.92	52.96	1662.49	68.69	1456.21	61.67
3837.12	64.98	3585.71	64.32	1689.61	82.00	1473.60	62.98
3855.46	64.10	3589.90	64.44	1679.17	60.65	1490.37	63.15
3870.83	66.38	3812.42	64.29	1899.86	80.27	1505.28	61.31



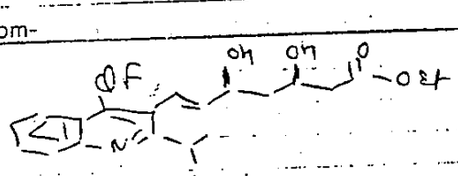
FILE NAME : 1206-179-30/1085	GAIN : 2	ANALECT FX-6160
#SCANS : 64	DET : TGS	ORD : %T
#BKG : 64	RES : 4 CM-1	ABSC: WAVENUMBER
APOD : HAPP-GENZEL	DATE : 07/30/87	TIME: 12:27:50
COMMENT : thin film wattanasin/r.p.lab#358 fm		

Small Sample

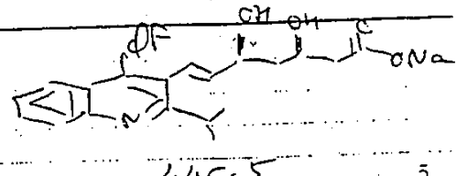

SAMPLE NO. 1206-179-30
SOLVENT CDCl3/CD3OD
REFERENCE TMS
TEMP. RT °C TUBE 5 mm
OBSERVE NUCLEUS 1H
MENU NO. 4
IRMOD NON
IRR. POWER
PUMOD
NO. of ACCUM. 120
DATA POINTS 16K
SPECTRAL WIDTH 2KHz
DATE 29 Jul 87
OPERATOR
FX 90
SPECTRUM NO. 3967-R
8 7 6 5 4 3 2 1 0
200 150 100 50
87355/81 (Rev. 1)

Date 8-25-87 Proj. Title-

Cont'd From-



451

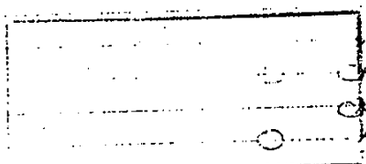


445.5

451 120G-190-41 = 100mg (0.2217294 mmole)
1N NaOH = 217.3 ml (0.2217294 mmole)
abs. eton = 3ml + 2ml

Ref: 120G-179

To 120G-190-41 in abs. eton at 0°C with stirring was added dropwise 1N NaOH. The mixt was stirred at 0°C (11 3c = 2 3c) → 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 (120G-201-nmr, ms, mino → not too good MH+=446)

Theory: 98.7 mg (87.5%)

Doesn't melt up to 225°C

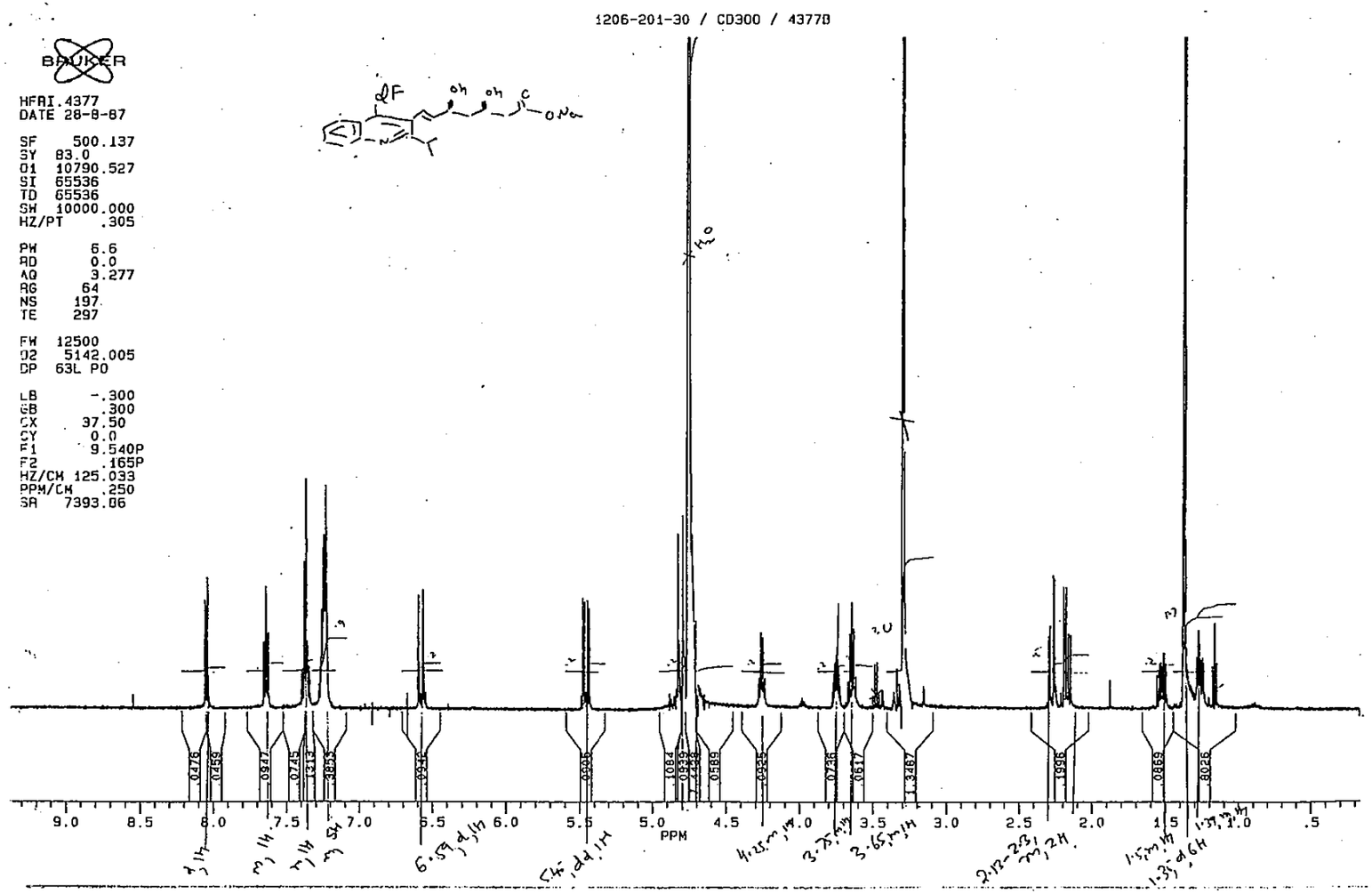
10-6-87 Submitted for solubility study (20 mg.) to minzlab

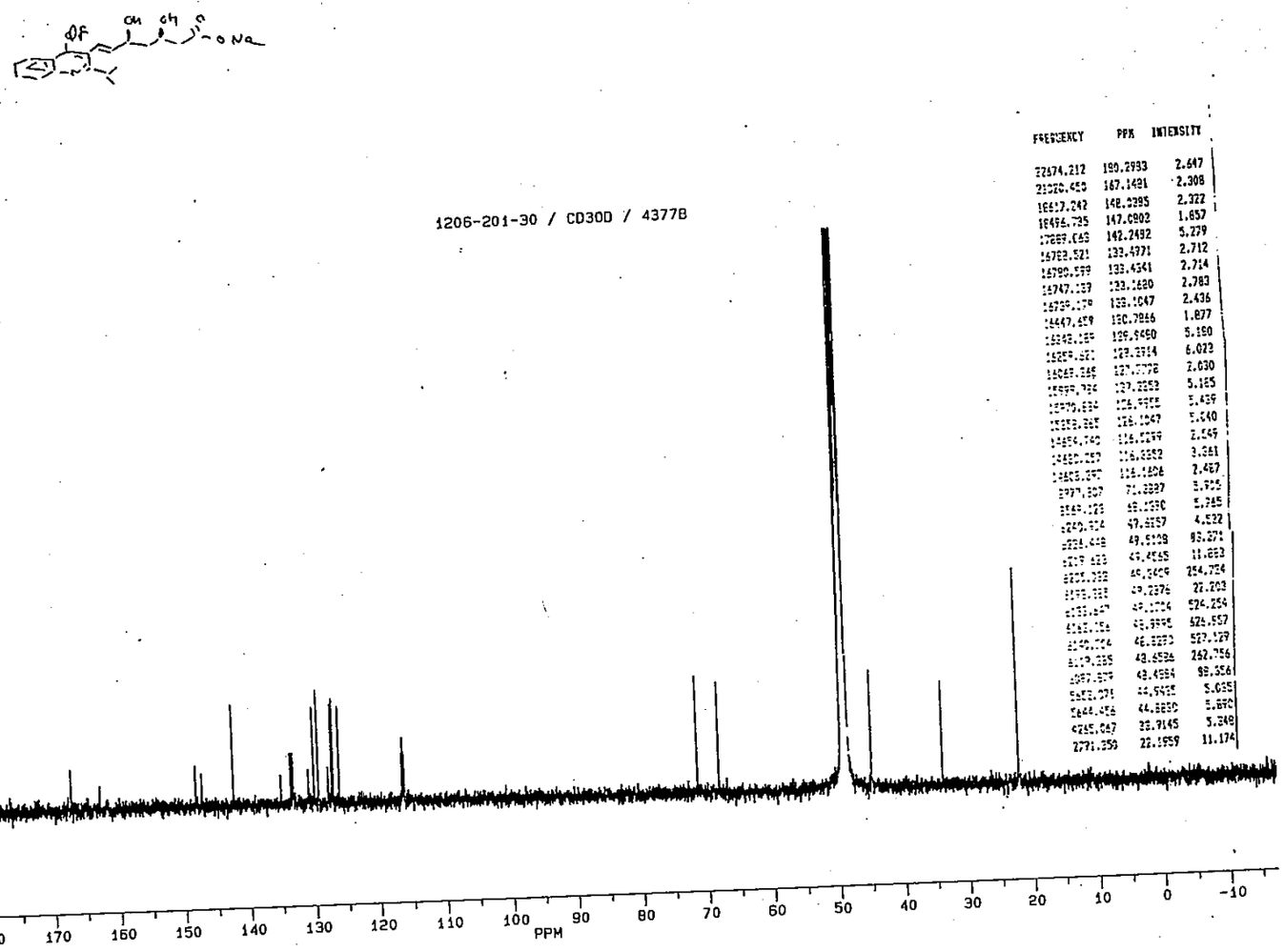
10-7-87 Solubility = 0.0958 mg./ml

Performed by- Roy Patel 9-1-87

Witness- L Perez

Cont'd to-


1206-201-30 / CD300 / 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 7393.06
PPM


1206-201-30 / CD30D / 4377B
BRUKER
AU280F.102
AU PROG:
X02.AU
DATE 27-8-87
SF 125.759
SY 93.0
O1 1740.234
SI 65536
TD 65536
SW 29411.765
HZ/PT .098
PW 0.0
RD 0.0
AQ 1.114
RG 800
NS 14000
TE 297
FW 36800
O2 10387.995
DP 15H 00
LB 2.000
GB .010
GX 37.50
GY 0.0
F1 207.582P
F2 -17.412P
HZ/CM 754.538
PPM/CM 6.000
SR -10532.68
FREQUENCY PPM INTENSITY
PPM


H

Date: 10/22/87 Proj. H318

Cont'd From- 134

Title- Cholesterol Synthesis Inhibition Screen

133

CHOLESTEROL BIOSYNTHESIS INHIBITION SCREEN

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: 83-748, 84-844, 84-936

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	83-748	26688	1	2	UNDILUTED
13-18	"	"	0.3	-	4.5
19-24	"	"	0.1	-	1.5
25-30	84-844	30280	0.3	2	4.5
31-36	"	"	0.1	-	1.5
37-42	"	"	0.03	-	0.45
43-48	84-936	30488	1	2	UNDILUTED
49-54	"	"	0.3	-	4.5
55-60	"	"	0.1	-	1.5
61-66	82-320	30259	0.3	2	4.5
67-72	"	"	0.1	-	1.5
73-78	"	"	0.03	-	0.45
79-84	Control	------	------	------	------

Performed by- Tod R. Slaughter

Witness- R Engstrom

Cont'd to- 135

AUG-27-1992 14:55 FROM BLD 405 3RD FLOOR TO 8807 P.06

134

Title- Cholesterol Synthesis Inhibition Screen

Date 10/22/87 Prot 1431

Cont'd From- 133

IN VIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN H318

RAT	COMPOUND	REGNO	DOSE mg/kg	nCi/dpm	STATISTICS	
	BLANK			6		
	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			318		
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
16	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 =	0.8
23	63-748	26688	.100	538	p	N.S.
24	63-748	26688	.100	178	%CHG =	-14.7
25	64-844	30280	.300	268	MEAN =	165.8
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 =	-69.2
31	64-844	30280	.100	308	MEAN =	219.8
32	64-844	30280	.100	273	STD =	66.9
33	64-844	30280	.100	195	SE =	29.9
35	64-844	30280	.100	157	t =	6.7
36	64-844	30280	.100	186	p	<.01
34	64-844	30280	.100	696*	%CHG =	-59.1

Performed by- Todd A. Slaughter

Witness- R Eggleston

Cont'd to- 135

Date 10/22/87 Proj# 3.8

Cont'd From- 134

Title- Cholesterol Synthesis Inhibition Screen

135

INVIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN H318

RAT	COMPOUND	REGNO	DOSE mg/kg	nC1/d1	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	30488	1.00	580	MEAN =	489.4
44	64-936	30488	1.00	642	STD =	132.8
45	64-936	30488	1.00	280	SE =	54.2
46	64-936	30488	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	30488	.300	232	STD =	165.0
51	64-936	30488	.300	586	SE =	67.4
52	64-936	30488	.300	378	t =	2.7
53	64-936	30488	.300	223	p	<.02
54	64-936	30488	.300	473	%CHG =	-38.2
55	64-936	30488	.100	485	MEAN =	416.5
56	64-936	30488	.100	181	STD =	166.8
57	64-936	30488	.100	339	SE =	68.9
58	64-936	30488	.100	695	t =	1.6
59	64-936	30488	.100	367	p	N.S.
60	64-936	30488	.100	439	%CHG =	-22.5
61	62-320	30559	.300	72	MEAN =	67.5
62	62-320	30559	.300	89	STD =	13.1
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	238	STD =	51.1
70	62-320	30559	.100	198	SE =	22.8
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	333	MEAN =	361.2
74	62-320	30559	.030	360	STD =	173.8
75	62-320	30559	.030	77	SE =	70.8
76	62-320	30559	.030	579	t =	2.3
77	62-320	30559	.030	483	p	<.05
78	62-320	30559	.030	277	%CHG =	-34.7

Computed 12-09-87

* = rejected by "Q" test

^ =LACK OF SAMPLE

Performed by- Rod K. Slaughter

Witness- D Engelhorn

Cont'd to-

136 Title- Cholesterol Synthesis Inhibition Screen

Date 10/29/87 Proj: 3.9

Cont'd From-

CHOLESTEROL BIOSYNTHESIS INHIBITION SCREEN

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 # H319
STUDY ON 10/29/87
BK.REF. 917-136
APPROVAL R.E.
DATE 10/29/87
GEN. ARC#86-008

Title: In vivo single dose assay to test for inhibition of biosynthesis by compounds: 64-298, 64-933, 63-935

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 of inhibition of Reference method: TA0/001. 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	64-298	29377	1	1	UNDILUTED
13-18	"	"	0.3	-	4.5
19-24	"	"	0.1	-	1.5
25-30	64-933	30447	1	1	UNDILUTED
31-36	"	"	0.3	-	4.5
37-42	"	"	0.1	-	1.5
43-48	63-935	30441	1	1	UNDILUTED
49-54	"	"	0.3	-	4.5
55-60	"	"	0.1	-	1.5
61-66	62-320	30556	0.3	2	4.5
67-72	"	"	0.1	-	1.5
73-78	"	"	0.03	-	0.45
79-84	Control	------	------	------	----------

Performed by- [signature]

Witness- R Engstrom

Cont'd to- 137

64568	29651	280-85	>	1	09-JUN-87	917-065
64569	29652	280	5 =	.16	15-JUN-87	17-081
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	18-MAY-87	917-056
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>

Date 10/2/92 Proj.

Cont'd From-

Title- [illegible]

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			947		
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	264	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 =	386.7
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	426	%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	286	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	585	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-

138

Title-

Date 12/24/87 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	558	MEAN =	547.0
38	64-933	30447	.100	735	STD =	147.2
39	64-933	30447	.100	370	SE =	60.1
40	64-933	30447	.100	378	t =	1.5
41	64-933	30447	.100	591	p	N.S.
42	64-933	30447	.100	652	%CHG =	-18.6
43	64-935	30441	1.00	162	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 =	-85.8
49	64-935	30441	.300	776	MEAN =	472.2
50	64-935	30441	.300	282	STD =	179.5
51	64-935	30441	.300	580	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	426	t =	3.1
59	64-935	30441	.100	621	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	225	p	<.01
72	62-320	30559	.100	804	%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- R Eberhorn

Cont'd to-

#57

49-111-0

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 MODIFICATION OF
REQUEST FOR RECONSIDERATION

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

BOX INTERFERENCE

SIR:

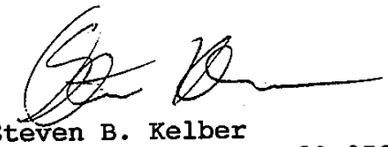
In Fujikawa's Request for Reconsideration of August 21, 1992, Section II, pages 16-21, is devoted to seeking reconsideration of the sua sponte action of the EIC in proposing a second Interference. That request was based on the concern that both Interferences would present Counts patentably indistinguishable, directed to compounds, and having overlapping scope.

The Redeclaration of the Interference, mailed the day the Request for Reconsideration was filed, resolves this issue by

striking Count 1 of this Interference, something that was not indicated in the earlier Decision on Motions of the EIC. Accordingly, Section II of the Fujikawa Request for Reconsideration need not be treated, as resolved by the Redeclaration of the Interference, Paper No. 26.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

Fourth Floor
1755 South Jefferson Davis Highway
Arlington, Virginia 22202
703-521-5940

CERTIFICATE OF SERVICE

I hereby certify that true copies of:

1. **FUJIKAWA MODIFICATION OF REQUEST FOR FOR RECONSIDERATION**

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 first-class mail, postage prepaid, this 3rd day of September, 1992.

STEVEN B. KELBER

Paper No. 58
MS/gjh

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Patent Interference No. 102,648

Wattanasin v. Fujikawa et al.

Reconsideration

R Smith, Sofocleous and Caroff, Examiners-in-Chief.

Sofocleous, Examiner-in-Chief.

On August 21, 1992, Fujikawa et al. (Fujikawa) filed a request (Paper No. 50) for reconsideration of the Examiner-in-Chief's (EIC's) Decision on Preliminary Motions, dated August 7, 1992 (Paper No. 40) with respect to the denial of Fujikawa's preliminary motion to redefine the interfering subject matter by adding proposed counts 3 and 4 and their corresponding proposed claims 41 to 44 and the dismissal of Fujikawa's preliminary motion to be accorded the benefit of a previously filed application in Japan and the EIC's sua sponte action. In the modification (Paper No. 57) to the request, Fujikawa has withdrawn his request seeking reconsideration with respect to the EIC's sua sponte action.

Preliminarily, we note that Wattanasin filed a response (Paper No. 54) to the Fujikawa request for reconsideration. Since the EIC did not request that the response be filed, the response is dismissed as being an unprovided for paper. 37 CFR § 1.641(c).

The request for reconsideration was filed pursuant to 37 CFR 1.640(c), which requires that a request shall specify the points believed to have been misapprehended or overlooked in rendering the decision. We have reviewed the request and agree with Fujikawa that the EIC should not have dismissed Fujikawa's preliminary motion (Paper No. 16) to be accorded benefit since the motion seeks the benefit of a previously filed application in Japan whose benefit Fujikawa was not accorded in the notice of interferences. We do not agree with Fujikawa that the EIC overlooked any matters in the denial of the preliminary motion to add proposed counts 3 and 4 and their corresponding proposed claims 41 to 44.

In denying the preliminary motion to add proposed counts 3 and 4, the EIC agreed with Wattanasin's opposition that his application did not support the claims suggested by Fujikawa to correspond to the proposed counts. Fujikawa's position concerning Wattanasin's purported support for the proposed claims was before the EIC, but he did not agree with Fujikawa. In our view, the EIC did not overlook any matters in denying the motion since he considered the arguments raised by Fujikawa. A disagreement with the EIC's

decision under these circumstances is not a matter for reconsideration under 37 CFR 1.640(c) but rather is a matter which Fujikawa may seek review at final hearing.

The EIC did not enter Fujikawa's amendment proposing claims 41 to 44 since the entry of the amendment was contingent upon the granting of Fujikawa's preliminary motion to add proposed counts 3 and 4 to this proceeding. See pages 8 and 9 of the motion. In the motion, Fujikawa urged that the subject matter of the proposed counts is directed to a separate patentable invention. Fujikawa now requests that the amendment be entered and that the proposed claims be designated as corresponding to the count. The present request is contrary to the allegations in Fujikawa's motion to redefine which urged that these claims were directed to a separate patentable invention, i.e., were patentably distinct from the counts of the interference and the claims corresponding thereto. In any event, since Fujikawa did not request in the motion that the claims be designated as corresponding to the counts of this interference, the EIC could not have overlooked the matter. The EIC could not have overlooked the matter not presented before him.

The request for reconsideration is granted to the extent that the interference is remanded to the EIC to consider Fujikawa's

Interference No. 102,648

motion to be accorded benefit.

RECONSIDERATION GRANTED TO THE FOREGOING EXTENT.

Ronald H. Smith
Examiner-in-Chief

Michael Sofocleous
Examiner-in-Chief

Marc L. Caroff
Examiner-in-Chief

BOARD
OF
PATENT APPEALS
AND
INTERFERENCES

Paper No. 59

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.

Pursuant to the Decision on Reconsideration, the interference has been remanded to the examiner-in-chief (EIC) for a decision on Fujikawa et al.'s preliminary motion (Paper No. 16) under 37 CFR 1.633(f) to be accorded benefit.

For the reasons stated therein, the motion is granted. Accordingly, Fujikawa et al. are accorded the benefit of Japanese Patent Application 193606, filed August 3, 1988 with respect to count 3 and with respect to the count of the additional interference, now Interference No. 102,975.

It is now appropriate to set times for taking testimony. In setting the times for taking testimony below, the EIC has only set Fujikawa et al. rebuttal testimony. A possible issue in this interference is whether Fujikawa et al.'s preliminary motion (Paper No. 15) to redefine by adding proposed counts should have been granted. Should Fujikawa et al. desire to have the denial of this motion reviewed at final hearing and to rely upon the evidence

presented during the motion period, they should notify in writing the EIC before the start of the junior party's testimony. The testimony times are set as follows:

Testimony-in-chief of the junior party Wattanasin for deposition testimony, including cross-examination of witnesses, to open October 1, 1992 and to close December 15, 1992.

Testimony-in-chief of the junior party Wattanasin for affidavit testimony (affidavits pursuant to 37 CFR 1.671(e) and 1.672(b) must be filed) to close November 15, 1992.

Cross-examination of any junior party's affiants to close December 15, 1992.

Rebuttal testimony of the senior party Fujikawa et al. for deposition testimony, including cross-examination of witnesses, to open January 5, 1993 and to close February 25, 1993.

Testimony of the senior party Fujikawa et al. for affidavit testimony (affidavits pursuant to 37 CFR 1.671(e) and 1.672(b) must be filed) to close January 30, 1993.

Cross-examination of any senior party's affiants to close February 25, 1993.

For filing and serving the record to close March 25, 1993.

The brief times are set as follows:

Junior party's brief due April 25, 1993.

Senior party's brief due May 25, 1993.

Junior party's reply brief due June 15, 1993.

Additional Discovery

Most interferences do not require motions for additional discovery (37 CFR 1.687(c)). Therefore, no period for filing such motions has been set. If additional discovery is deemed necessary, the parties should attempt to resolve the matter by agreement under 37 CFR 1.687(d) before filing a motion for additional discovery. If either party deems such a motion to be necessary, the party should contact the examiner-in-chief (EIC) via a conference call, including opposing counsel, within 20 days after the date of this order.

Other Evidence

If either party intends to rely on an affidavit filed by him during ex parte prosecution, an affidavit under 37 CFR 1.608 or an affidavit under 37 CFR 1.639(c), he must comply with the provisions of 37 CFR 1.671(e) by the close of his testimony-in-chief for affidavit testimony. If either party intends to present the testimony of a witness by affidavit, the affidavit must be filed by the close of his testimony-in-chief for affidavit testimony.

Any motion under 37 CFR 1.671(g), 1.683(a) and 1.684(a) must be filed sufficiently far in advance of the end of the testimony period that the motion (including any opposition) can be acted upon,

and any resultant testimony taken or filed, prior to the end of the testimony period. Compliance with the provisions of 37 CFR 1.673(a), (b) and (g) must be completed within a reasonable time from the opening of the testimony period so as to ensure that testimony will be taken within the time set.

Cross-Examination

If either party wishes to cross-examine any of his opponent's affiants, the party should file a pro forma request therefor (37 CFR 1.672(b)) and proceed during the time set. After such request, it becomes the responsibility of the opponent to notice the depositions of his affiants during the period set for cross-examination, arrange for the court reporter and file the certified transcript of the deposition (37 CFR 1.673(e and 1.672(b)). Failure to notice the depositions during the period set may result, upon a motion from the party, in according the affidavit testimony no weight at final hearing (37 CFR 1.616).

Record and Testimony

A certified transcript of a deposition must be filed by the time set in 37 CFR 1.678.

Suggestion for Negotiations

The parties are strongly encouraged to make contact with each other, prior to the start of Simon et al.'s testimony period,

and attempt to settle this interference or, failing that, to narrow down, as much as possible, the issues for final hearing. The EIC can be expected to cooperate in allowing reasonable time for a bona fide attempt at such negotiations.

Michael Sofocleous
Examiner-in-Chief
(703) 557-4066

gjh

#60

49-111-0

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 REQUEST FOR
PRESERVATION OF ISSUES AND EVIDENCE

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

BOX INTERFERENCE

SIR:

Pursuant to Paper No. 59, Orders of the EIC setting times for taking testimony, Fujikawa hereby requests denial of Fujikawa's Motion to Redefine the Interference by the addition of proposed Counts and Fujikawa's Claims 41-44 be reviewed at Final Hearing, and Fujikawa further indicates its desire to rely upon the evidence presented during the Motion Period. This notification is made pursuant to the Order of the EIC in Paper No. 59, page 2.

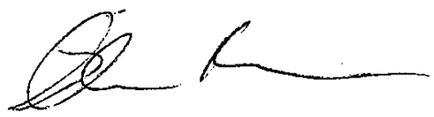
With respect to companion Interference 102,975, it is believed

that a similar issue should be preserved in that Interference as well, as Fujikawa's Motion to Redefine included a proposed Count with respect to the compound, and the method of administration. Appropriate relief is requested in Interference 102,975 as well. It is further submitted that it may be appropriate to combine the evidence, records and Briefs into a single body for the Interferences involved, as the issues raised in the two Interferences appear, in many cases, to be inextricably tied, one to the other.

Appropriate relief is respectfully requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

Fourth Floor
1755 South Jefferson Davis Highway
Arlington, Virginia 22202
703-521-5940

CERTIFICATE OF SERVICE

I hereby certify that true copies of:

1. **FUJIKAWA ET AL REQUEST FOR PRESERVATION OF ISSUES AND EVIDENCE**

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 first-class mail, postage prepaid, this 30th day of September, 1992.

STEVEN B. KELBER

SANDOZ CORPORATION
59 ROUTE 10, EAST HANOVER NJ 07936

PATENT AND TRADEMARK DEPARTMENT
TELEX 240867
TELEFAX 201 503 8807

October 29, 1992

BY PRIORITY MAIL

Steven B. Kelber, Esq.
Oblon, Spivak, McClelland,
Maier & Neustadt, P.C.
1755 Jefferson Davis Highway
Crystal Square 5, Ste. 400
Arlington, VA 22202

Re: Interference Nos. [redacted] 102,975:
WATTANASIN Declarations and
Exhibits Pursuant to 37 CFR 1.608

Dear Steve:

Per our phone conversation yesterday, enclosed please find a true copy of the above papers from the file of Wattanasin Application Serial No. 07/498,301, which were mailed to the PTO on May 25, 1990.

Very truly yours,

Diane Furman

Diane E. Furman

DEF:rf

cc: M. Sofocleous, EIC
w/o Encs.

TABLE OF CONTENTS

DECLARATIONS AND EXHIBITS SUBMITTED
PURSUANT TO 37 C.F.R. 1.608 IN
WATTANASIN PATENT APPLICATION SERIAL NO. 07/498,301

EXHIBITS: (CONT.)

#61

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN

V.

FUJIKAWA et al.

Interference No. 102,975

Examiner-in-Chief: M. Sofocleous

WATTANASIN REPLY TO
FUJIKAWA OPPOSITION TO
WATTANASIN PROPOSED FINDINGS OF FACT

FYI

SEP 22 1993

RECEIVED IN
BOX INTERFERENCE

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

Fujikawa have opposed the Wattanasin Proposed Findings of Fact filed with the Wattanasin opening brief on July 16, 1993.

First of all, Wattanasin notes that under 37 CFR 1.656(g), proposed findings of fact and/or conclusions of law are not mandatory, and it is solely within the discretion of the Board to adopt them in whole or in part or not to adopt them at all irrespective of whether or not they fully comply with the rules.

With respect to the grounds of the Fujikawa opposition, Wattanasin responds as follows:

1. There was no abandonment, supression or concealment of the Wattanasin invention between June 1985 (by which time he had reduced to practice by testing in vitro the "initial phase" compounds 63-366, 63-548 and 63-549), and March 1987, when work was resumed on the "second phase" compounds, because during this period Wattanasin was involved in continuing synthesis work within

the generic invention of HMG-CoA inhibitors and furthermore suffered from a manpower shortage in his laboratory which prevented him from completing the quinoline series, although it remained his intention to do so (WB[1] at 28-30, 67-68).

2. Additional testing was not needed for a reduction to practice of the "second phase" compounds 64-933, 64-934/NA, 64-935, and 64-936/NA, because their practical utility was already known to Wattanasin from the prior testing of the "initial phase" compounds (WB at 27-28).

3. Even if testing of the second phase compounds was required for a reduction to practice, diligence in making and testing the second phase compounds is shown by Wattanasin from just prior to the Fujikawa benefit date of August 20, 1987 to the in vitro testing carried out on October 8 and 13, 1987 by Dr. Scallen (WRB at 35-43).

4. The in vitro testing constituted a renewed reduction to practice within the count because it confirmed the practical utility of the "second phase" compounds, and because the activity in vitro could be reasonably correlated with activity in vivo. If arguendo the Board finds that the Wattanasin in vitro testing of Wattanasin does not prove a reduction to practice and requires in vivo testing, then the Board should sua sponte also restrict Fujikawa to, at the earliest, their priority date of August 3, 1988, when they first introduced in vivo test results in their priority filing (WRB at 11-19).

---

1. "WB" is the Wattanasin opening brief; "WRB" is the Wattanasin reply brief; "WR" is the Wattanasin record.

5. In vivo testing of compounds 64-933, 64-935 and 64-936/NA was also pursued with diligence down to October 22 and 29, 1987; and culminated in further activity for the count comprising entry of ED_{50}'s for 64-933, 64-935 and 64-936/NA into the Sandoz database on December 9, 1987 (WB at 43-45; WRB at 19-29). In vivo administration to rats of carboxymethylcellulose solutions or suspensions of test compounds (WR at 204) met the limitations of the count (WRB at 24, WR at 204).

6. Wattanasin did not at any time abandon, suppress or conceal the invention, and nothing in the record supports such an inference. On the contrary, in view of the January 1988 recommendation of the Sandoz Patent Committee to file a patent application on the Watttanasin invention, there was an outstanding obligation to file, and attorney activity toward that objective, through to the filing date of March 3, 1989, which was 14 months after the last activity for the count (WB at 45-57; WRB at 24-25).

7. Accordingly, it is submitted that Wattanasin has proved priority by a preponderance of the evidence, or by clear and convincing evidence, over Fujikawa.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

DEF:rmf
September 7, 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 Sept. 7, 1993
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
9/7/93
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN REPLY TO
FUJIKAWA OPPOSITION TO
WATTANASIN PROPOSED FINDINGS OF FACT

was served on counsel for the party Fujikawa et al., this 7th day of September 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

#61

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN

v. Interference No. 102,975

FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

WATTANASIN OPPOSITION
TO FUJIKAWA MOTION TO SUPPRESS EVIDENCE

FYI

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

Fujikawa have moved to supress the Declaration and Supplemental Declaration of Robert E. Engstrom, the Sandoz researcher who conducted in vivo testing of the Wattanasin compounds in rats, together with Exhibits K-1 and Q which accompany his respective declarations. For the convenience of the Board, copies of these declarations and exhibits (as well as the companion Rodney Slaughter declaration) are appended hereto.

Fujikawa are apparently objecting to the ED_{50} data in the Engstrom declaration (WR 206) because they "constitute the results of not one but two computer manipulations."

Whatever, Fujikawa intend by this, the following things are evident from these declaration and exhibit pages:

1. Pages 334 and 337 (see upper right hand corner of exhibit page) are summary pages generated for each of the screenings carried out starting October 22 and October 29, 1987, respectively, and simply record the type of test solutions utilized;

2. Pages 335-336 and 338-339 show the actual counts in nanocuries per 100 ml. of rat serum obtained for each in vivo testing.

As described more fully by Engstrom at WR 204, the rats were administered the test substance dissolved or as a suspension in a formulation comprising carboxymethylcellulose. The rats were therafter injected with a given amount of radiolabeled sodium acetate. Serum samples were then obtained, the sterols were precipitated, and their radioactivity detected by liquid scintillation spectrometry.

The count in nanoCuries per 100 ml. rat serum is listed down the fifth column of the WX K-1 computer printout. This is the actual raw data obtained from the experiments. From the nanoCurie values received for the six rats in each testing, various computations were made including a "% change" in nanoCurie count. A % change greater than 50% would indicate activity in the assay. (This is a quite stringent assay, where the industry standard, compactin, itself had an ED50 of 3.5, as described by Wattanasin in the Reply Brief at 21-22.)

This data were then inputed into a computer program which generated an ED_{50} number for each compound tested, and the ED_{50} was downloaded in the Sandoz database maintained in the ordinary course of business. (Notice that the database accepted only ED_{50} values which were smaller than 1.) However, in Exhibit Q (at page 418), a Biological Activity Data Report on the Wattanasin compounds shows that compound 64-933 was also calculated to have a specific ED_{50} value of 2.40.

Calculation of ED_{50} in this manner was hardly new to the art as of December 1987. In fact, the whole Engstom in vivo testing procedure appears almost verbatim at page 33 of the Kathawala 1984 European patent publication on fluvastatin, EP 114,027 which was cited as "technological background" against the involved Fujikawa '930 patent (copy of relevant pages also appended).

Even the Fujikawa rebuttal witness, Dr. Homlund, acknowledged that he had "no quarrel with the techniques for determining statistical activity" used by Wattanasin (FR at 204).

Given the art-recognized status of this in vivo assay, it is hard to understand why Fujikawa insist on being provided with computer programs or logorithms so that they can trace the exact progress of each byte of information.

The Board has discretion in applying the rules of evidence, and there is submitted to be no convincing argument that a "rule of reason" should not apply here where the raw data is attested to by the individuals who actually performed the experiments, and the resulting ED_{50} calculation was generated thereon by Sandoz in the ordinary course of business.

Fujikawa affect discomfort that the ED_{50} data for one of 64-933 and 64-936/NA was inadvertently "switched" at page 206 of the original Engstrom declaration. Regardless of whether this typographical error is related in any way to an acknowledged Engstrom "goof" showing up in Exhibit Q, all of the other Wattanasin Exhibits are uniform in assigning an ED_{50} value to

compound 64-935, alone, of 0.49 (see, e.g., Exhibit S-1 (relevant page also appended))[1].

Like any other business or technical information maintained in the ordinary course of business by Sandoz, the ED_{50} data in a sense speaks for itself, and should not be invalidated by a purported lack of foundation, particularly since the underlying computer programs or logorithms are not themselves likely to be comprehensible.

Accordingly, the Fujikawa motion to suppress should be denied.

SANDOZ CORP.
50 route 10
E. Hanover, NJ 07936
Attachments as noted
September 7, 1993

Respectfully submitted,

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231, on Sept. 7, 1993
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
Sept. 7, 1993
Date of Signature

1. Fujikawa also attempt an argument surrounding the absence of a sodium salt indication, i.e. "NA", from the Sandoz database printout for 64-936(NA) included in Wattanasin Exhibit K-1 (at 336). However, notice that on pages 203, 205 and 209 of the Wattanasin record "64-936" is used interchangeably with the designation "64-936/NA", just as the Sandoz fluvastatin compound, a sodium salt (technically, "62-320/NA"), is typically referred to as, simply, 62-320 (WR at 484), without the added sodium designation. It is hard to see how Fujikawa could allege difficulty with practices that are customary in the art, and manifested throughout the Wattanasin record in relation to compounds of known strucutre such as fluvastatin.

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN OPPOSITION
TO FUJIKAWA MOTION TO SUPPRESS EVIDENCE

and the attachments thereto were served on counsel for the party Fujikawa et al., this 7th day of September 1993, by postage pre-paid first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
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Diane Furman
Diane E. Furman

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 114 027**
A1

600 - 6951

(12) # EUROPEAN PATENT APPLICATION

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04.11.83 US 548850

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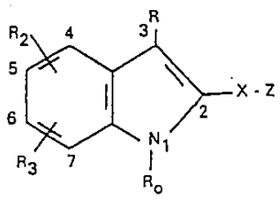
(84) Designated Contracting States: AT

(72) Inventor: Kathawala, Faizulla Gulamhusein, 39 Woodland Avenue, Mountain Lakes, N.J., 07946 (US)

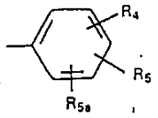
(54) **Analogs of mevalolactone and derivatives thereof, processes for their production, pharmaceutical compositions containing them and their use as pharmaceuticals.**

(57) Compounds of formula I



(I)

wherein one of R and R_o is



and the other is primary or secondary C_{1-6}alkyl, C_{3-6}-cycloalkyl or phenyl-$(CH_2)_m$-,

wherein

R_4 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, (except t-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

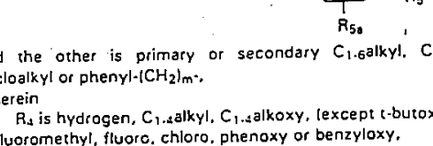
m is 1, 2, or 3,

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_{1-4}alkyl, C_{3-6}cycloalkyl, C_{1-4}alkoxy, (except t-butoxy), trofluoromethyl, 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 $-CH=CH-$ (n = 0, 1, 2 or 3),



(II)

wherein R_6 is hydrogen or C_{1-3}alkyl in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in salt form.

These compounds are indicated for use as pharmaceuticals particularly for inhibiting cholesterol biosynthesis and treating atherosclerosis.

EP 0 114 027 A1

The isomer of Yang et al. and the isomer disclosed in Reaction Scheme III yield lactones having the 4R,6S configuration and, as a result of epimerization in Reaction X, such compounds having the 4R,6R configuration. Lactones having the 4S,6R and 4S,6S configuration may be obtained from the other isomer whose synthesis is disclosed in Rection Scheme III.

The availability of these intermediates enables synthesis of optically pure end products.

Reaction products both intermediale and final can be isolated and purified in conventional mannr whereby intermediates can where appropriately be employed directly in a subsequent reaction

Mixtures of stereoisomers (cis, trans and optical) may be separated by conventional means at whatever stage of synthesis is appropriate. Such methods include re-crystalisation, chromatography, formation of esters with optically pure acids and alcohols or of amides and salts (cf also Sommer et al. J.A.C. S 80, 3271 (1958)) with subsequent reconversion under retention of optical purity. For example diastereoisomeric (-)-α-naphthyl-phenylmethylsilyl derivatives of a lactone type end product of formula I may be separated on a silica solumn having covalently bound L-phenylglycine (eluant n-hexane/acetate : 1/1).

Salts may be prepared in conventional manner from free acids, lactones and esters and vice-versa. Whilst all salts are covered by the invention pharmaceutically acceptable salts especially sodium, potassium and ammonium particularly sodium salts are preferred.

The various forms of the compounds of formula I are by virtue of their interconvertability useful as intermediates in addition to the use set out below.

Also within the scope of this invention are the intermediates of formulae V, X, XI, XII, XX, XXIV, XXVI-XXVIII and XXIXB-XXIXD. The preferences for each variable are the same as those set forth for the compounds of formula I, with the preferred groups of such compounds including those that correspond to Groups (i)-(xiii) and (xxxix)-lxxxviii) (for

formulae V, X-XII, XX and XXIXB-XXIXD) and Groups (xiv)-(xx), (xxxiii)-(xxxviii) and (lxxxix)-(cxiv) for formulae XXVI-XXVIII) to the extent consistent therewith.

The compounds of formula I possess pharmacological activity in particular they are inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase and as a consequence inhibitors of cholesterol biosynthesis as demonstrated in the following three tests.

Test A: In Vitro Microsomal Assay of HMG-CoA Reductase Inhibition:

200 ul. aliquots (1.08-1.50 mg./ml.) of rat liver microsomal suspensions, freshly prepard from male Spargue-Dawley rats (150-225 g. body weight), in Buffer A with 10 mmol. dithiothreitol are incubated with 10 ul. test substance dissolved in dimethylacetamide and assayed for HMG-CoA reductase activity as described by Ackerman et al., J. Lipid Res. 18, 408-413 (1977). In the assay the microsomes are the source of the HMG-CoA reductase enzyme which catalyses the reduction of HMG-CoA to mevalonate. The assay employs a chloroform extraction to separate the product, [^{14}C]mevalonolactone, formed by the HMG-CoA reductase reaction from the substrate, [^{14}C]HMG-CoA. [^{3}H]mevalono-lactone is added as an internal reference. Inhibition of HMG-CoA reductase is calculated from the decrease in specific activity [^{14}C/^{3}H]mevalonate) of test groups compared to controls.

Test B: In Vitro Cell Culture Cholesterol Biosynthesis Screen:

The cell culture is prepared as follows: Stock monolayer cultures of the Fu5AH rat hepatoma cell line (originally obtained from G. Rothblat; see Rothblat, Lipids 9, 526-535 (1974) are routinely maintained in Eagle's Minimum Essential Medium (EMEM) supplemented with 10% fetal bovine serum (FBS) in 75 cm^2 tissue culture flasks. For these studies, when the cultures reach

confluence, they are removed by mild enzymatic treatment with 0.25% trypsin in Hanks' balanced salt solution (without calcium and magnesium). After centrifugation of the cell suspension and aspiration of the enzymatic solution, a cell pellet is resuspended in an appropriate volume of media for seeding into 60 mm. tissue culture dishes. The cultures are incubated at 37°C in an atmosphere of high humidity and 5% carbon dioxide. When the cultures are confluent (approximately 5 days), they are ready for use. The culture media is aspirated from the dishes and replaced with 3 ml of EMEM suplemented with 5 mg/ml of dilipidized serum protein (DLSP) prepared by the method of Rothblat et al., In Vitro 12, 554-557 (1976). Replacement of the FBS with DLSP has been shown to stimulate the incorporation of [^{14}C]acetate into sterol by removing the exogenous sterol supplied by the FBS, thereby requiring the cells to synthesized sterol. Enthanced 3-hydroxy-3-methylglutaryl Coenzyme A reductase (HMG-CoA reductase) activity is measurable in the cells in response to the lack of exogenous sterol. Following approximately 24 hours incubation at 37°C in the DLSP supplemented media, the assay is initiated by the addition of 3μCi of [^{14}C]acetate and the test substances solubilized in dimethylsulfoxide (DMSO) or distilled water. Solvent controls and compactin-treated controls are always prepared. Triplicate 60mm. tissue culture dishes are run for each group. After 3 hours incubation at 37°C, the cultures are examined microscopically using an inverted phase contrast microscope. Notations are made of any morphological changes which may have occurred in the cultures. The media is aspirated and the cell layer is gently washed twice with 0.9% sodium chloride solution (saline). The cell layer is then harvested in 3 ml. of 0.9% saline by gentle scraping with a rubber policeman and transferred to a clean glass tube with Teflon lined cap. The dishes are rinsed with 3 ml. of 0.9% saline and rescraped, and the cells are combined with the first harvest. The tubes are centrifuged at 1500 r.p.m. for 10 minutes

in an IEC PR-J centrifuge, and the supernatant is asperated.

The cells are then extracted as follows: One ml. of 100% ethanol is added to the cell pellet followed by sonication for 10 seconds with a "LO" setting of 50 on a Bronwell Biosonik IV. One hundred ul. are taken for protein determination. One ml. of 15% potassium hydroxide (KOH) is added, and the samples are thoroughly vortexed. Saponification is accomplished by heating the ethanol-KOH treated samples at 60°C for 60 minutes in a water bath. Following dilution of the samples with 2ml. of distilled water, they are extracted three times with 7 ml. of petroleum ether. The petroleum ether extracts are then washed three times with 2 ml. of distilled water and finally taken to dryness under a stream of nitrogen.

The obtained samples are then analyzed by thin layer chromatography (TLC) as follows: Residues from the petroleum ether extraction are taken up in a small volume of hexane and spotted on silica gel 60 TLC plates (E. Merck). Development of the plates is carried out in a 150 parts by volume hexane: 50 parts by volume diethyl ether: 5 parts by volume galcial acetic acid solvent system using a three phase development procedure. Visualization is accomplished in an iodine vapor chamber. The plates are divided into five sections such that each section contains the molecules having the following approximate Rf values: section 1- 0-0.4, section 2- 0.4-0.55, section 3- 0.55-0.7, section 4- 0.7-0.9 and section 5- 0.9-1.0. Section 2 contains the non-saponifiable sterols. The five sections of the TLC plates are scraped into scintillation vials. Blanks are also prepared from scrapings of chromatographed non-labelled standards. ACS® scintillation cocktail is added, and the radioactivity is determined in a liquid scintillation spectrometer. [^{14}C]hexadecane standards are used to determine counting efficiencies. The total protein content of the samples is determined employing the Bio-Rad Protein Assay System.

The results are reported as disintegrations per minute per mg protein (d.p.m./mg protein) for each of the live TLC sections. Mean d.p.m./mg protein ± standard error of the mean are compared for percentage change (%Δ) and statistical significance with solvent control means. TLC section 2 data is taken as a measure of HMG-CoA reductase activity inhibition.

Test C: In Vivo Cholesterol Biosynthesis Inhibition Tests: In vivo studies utilize male Wistar Royal Hart rats weighing 150±20 g which have been kept for 7-10 days on an altered light cycle (6:30 a.m. - 6:30 p.m. dark) housed two per cage and fed powdered Purina Rat Chow and water ad libitum. Three hours before the diurnal maximum of cholesterol synthesis at mid-dark, the rats are administered the test substances dissolved or as a suspension in 0.5% carboxymethylcellulose in a volume of 1 ml/100 g body weight. Controls receive vehicle alone. One hour after receiving the test substance, the rats are injected intraperitoneally with about 25 μCi/100 g body weight of sodium [1-^{14}C]acetate 1-3 mCi/mmol. Two hours after mid-dark, blood samples are obtained under sodium hexobarbitol anesthesia and the serum separated by centrifugation.

Serum samples are saponified and neutralized, and the 3β-hydroxy sterols are precipiated with digitonin basically as described by Sperry et al., J. Biol. Chem. 187, 97 (1950). The [^{14}C]digitonides are then counted by liquid scintillation spectrometry. After correcting for efficiencies, the results are calculated in nCi (nanocuries) of sterol formed per 100 ml of serum. Inhibition of sterol synthesis is calculated from the reduction in the nCi of sterols formed from test groups compared to controls.

The compounds are thus indicated for use as hypolipoproteinemic and anti-atherosclerotic agents.

An indicated suitable daily dosage for use in the treatment of hyperlipoproteinemia and atherscleroses is from about

1 to 2000 mg preferably 1.5 to 100 mg suitably administered in divided dosages of 0.25 to 1000 mg preferably 0.4 to 50 mg two to four times daily or in retard form.

They may be administered in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form whereby the various forms have activities in the same range.

The invention therefore also concerns a method of treating hyperlipoproteinemia or atherosclerosis by administration of a compound of formula I in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form as well as such compounds for use as pharmaceuticals e.g. as hypolipoproteinemic and anti-atherosclerotic agents.

The compounds may be administered alone, or in admixture with a pharmaceutically acceptable diluent or carrier, and, optionally other excipients, and administered orally in such forms as tablets, elixirs, capsules or suspensions or parenterally in such forms as injectable solutions or suspensions.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules.

Such compositions also form part of the invention.

The following examples, in which all temperatures are in °C illustrate the invention.

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, 102,975
Examiner-in-Chief: M. Sofocleous

DECLARATION OF ROBERT G. ENGSTROM PURSUANT TO 37 CFR §1.672

I, Robert G. Engstrom, do hereby declare as follows:

(1) That I have been employed by Sandoz Pharmaceuticals Corporation since 1964 as a Research Scientist. Among my responsibilities has been supervising the testing of new HMG Co-A reductase inhibiting compounds synthesized by Sandoz chemists.

(2) That all activities referred to in this Declaration took place in the United States.

IN VIVO TESTING OF
WATTANASIN COMPOUNDS 64-933, 64-935 and 64-936/Na

1. On or before October 29, 1987, in my laboratory under my supervision, Rodney Slaughter began performing the below-indicated protocol on compounds 64-933, 64-935 and 64-936/Na:

In vivo studies utilized male Wistar Royal Hart rats weighing 150 ± 20 g. which have been kept for 7-10 days on an altered light cycle (6:30 A.M. - 6:30 P.M. dark) housed two per cage and fed powdered Purina Rat Chow and water ad libitum. Three hours before the diurnal maximum of cholesterol systhesis at mid-day the rats were administered the test substances dissolved or as a suspension in 0.5% carboxymethylcellulose in a volume of 1 ml./100 g. body weight. Controls received vehicle alone. One hour after receiving the test substance, the rats were injected intraperitoneally with about 25 μCi/100 g. body weight of sodium [1-^{14}C]acetate 1-3 mCi/mmol. Two hours after mid-dark, blood samples were obtained under sodium hexobarbitol anesthesia, and the serum was separated by centrifugation. The resulting serum samples were saponified and neutralized, and the 3β-hydroxy sterols were precipitated with digitonin basically as described by Sperry et al., J. Biol. Chem. 187,97(1950). The [^{14}C]digitonides were counted by liquid scintillation spectrometry. The assay is based on the conversion of ^{14}C-acetate to ^{14}C-cholesterol in vivo.

2. The counts in DPM of digitonin precipitable sterol (β-hydroxy sterol, mostly cholesterol in the rat) were entered by Rodney Slaughter into my computer program, which converted them to nCi of sterol found per 100 ml. of serum at 4 hours after the injection of the ^{14}C-acetate.

3. I have reviewed Exhibit K-1 hereto, which comprises true copies of pages 133, 134, and 135, 136, 137 and 138 of R. Slaughter's Laboratory Notebook #917. I witnessed Rodney Slaughter's signature on each of these pages, and each page bears my true signature as a witness.

4. Notebook pages 133-135 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H318, which was commenced on October 22, 1987. I initialed the first page of this computer printout on or before October 22, 1987. This computer printout on page 135 indicates that an in vivo assay of compound 64-936 was started on October 22, 1987.

5. Notebook pages 136-138 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H319, which was commenced on October 29, 1987. I initialed the first page of this computer printout on page 136 on or prior to October 29, 1987. This computer printout on page 137-138 indicates that an in vivo assay of compound 64-933 and 64-935 was started on October 29, 1987.

6. Both studies were completed on or prior to December 9, 1987, the date indicated at the bottom of pages 135 and 138.

7. It was my responsibility to enter the nCi/dl data into a separate computer program which calculates the ED_{50} values of a compound tested in vivo from the reduction in the nCi of sterols formed from test groups compared to controls for each assay, and forms a database of the ED_{50} values. On or before December 9, 1987, I entered the data for compounds 64-933, 64-935 and 64-936/Na.

8. The 1st page of Exhibit K-1 comprises a true copy of part of the ED_{50} database. This page indicates that the ED_{50} for compounds 64-933, 64-935 and 64-936/Na was in the system as of December 9, 1987. Therefore, the information was available to other Sandoz employees having access to the computer database as of December 9, 1987.

The ED50 for these compounds are:

COMPOUND	ED_{50} (mg/kg)
64-933	0.49
64-935	>1.0
64-936	>1.0

. . .

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 13 day of November 1992.

Robert G. Engstrom

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v. Interference Nos. 102,648, 102,975
FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

DECLARATION OF RODNEY SLAUGHTER PURSUANT TO 37 CFR §1.672

I, Rodney Slaughter, do hereby declare as follows:

(1) That I have been employed by Sandoz Pharmaceuticals Corporation since 1982, and during the time periods referred to herein, I worked in the Department of Lipid Metabolism.

(2) That it has been my responsibility to carry out an in vivo testing program of various HMG-CoA reductase inhibitor compounds, including Wattanasin compounds 64-933, 64-935 and 64-936.

(3) That all of the below-indicated activities took place in the United States.

IN VIVO TESTING OF
WATTANASIN COMPOUNDS 64-933, 64-935 and 64-936

1. On or before October 29, 1987, I carried out the below-indicated protocol on compounds 64-933, 64-935 and 64-936:

In vivo studies utilized male Wistar Royal Hart rats weighing 150 ± 20 g. which have been kept for 7-10 days on an altered light cycle (6:30 A.M. - 6:30 P.M. dark) housed two per cage and fed powdered Purina Rat Chow and water ad libitum. Three hours before the diurnal maximum of cholesterol systhesis at mid-day the rats were administered the test substances dissolved or as a suspension in 0.5% carboxymethylcellulose in a volume of 1 ml./100 g. body weight. Controls received vehicle alone. One hour after receiving the test substance, the rats were injected intraperitoneally with about 25 μCi/100 g. body weight of sodium [1-^{14}C]acetate 1-3 mCi/mmol. Two hours after mid-dark, blood samples were obtained under sodium hexobarbitol anesthesia, and the serum was separated by centrifugation. The resulting serum samples were saponified and neutralized, and the 3β-hydroxy sterols were precipitated with digitonin basically as described by Sperry et al., J. Biol. Chem. 187,97(1950). The [^{14}C]digitonides were counted by liquid scintillation spectrometry. The assay is based on the conversion of ^{14}C-acetate to ^{14}C-cholesterol in vivo.

2. I entered the counts in DPM of digitonin precipitable sterol (β-hydroxy sterol, mostly cholesterol in the rat) into a computer program, which converted them to nCi of sterol found per 100 ml. of serum at 4 hours after the injection of the ^{14}C-acetate.

3. I have reviewed Exhibit K-1 hereto, which comprises true copies of pages 133, 134, 135, 136, 137 and 138 of my Laboratory Notebook #917.

4. Notebook pages 133-135 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H318, which I started on October 22, 1987. These pages contain the date of 10/22/87 at the top in my handwriting.

5. Notebook pages 136-138 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H319, which I started on October 29, 1987. These pages contain the date of 10/29/87 at the top in my handwriting.

6. Both studies were completed on or prior to December 9, 1987, the date indicated at the bottom of the computer printouts on pages 135 and 138.

7. It was my practice to paste the computer printouts into my notebook and to sign the notebook page when I did this.

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 13 day of November 1992.

Rodney Slaughter

Date: 10/22/87 Proj. #318

Title: Cholesterol Synthesis Inhibition Screen

135

334

From: 134

CHOLESTEROL BIOSYNTHESIS (HMG)

LIPID METABOLISM DEPARTMENT
HMGR SCREENING UNIT
Sandoz Research Institute

STUDY #: 318
STUDY ON: 10/22/87
SK.REF. 917-83
APPROVAL
DATE 10/21/87
GEN. ARC88S-006

To: Dr. D. Weinstein, Departmenthead
Mr. R. Slaughter, Responsible Technician
From: Mr. R. Engstrom, Responsible Investigator
CC: D.N., M.L.R., ARC

Title: In vivo single dose assay to test for inhibition of biosynthesis by compounds: 63-748, 64-844, 64-886

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: 340/001. Stock solutions and dilutions prepared in 0.5% CMC, administered p.o. at 1ml/100gm weight. Rats bled via carotid incision using hexobarbital anesthesia. Amical use will be in compliance with ARC regulations. Duration = 1 hr. No/group = 5. No of groups = 14. UCR 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	30688	1	2	UNDILUTED
13-18	"	"	0.3	-	4.5
19-24	"	"	0.1	-	1.5
25-30	64-844	30250	0.3	2	4.5
31-36	"	"	0.1	-	1.5
37-42	"	"	0.03	-	0.45
43-48	64-886	30484	1	2	UNDILUTED
49-54	"	"	0.3	-	4.5
55-60	"	"	0.1	-	1.5
61-66	62-210	30259	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- [signature]

Witness- [signature]

Cont'd to- 135

134 Title- Cholesterol Synthesis Inhibition Screen

Date 10/27/88 Proj 12

Cont'd From- 135

335

INVIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN H318

RAT	COMPOUND	REGNO	DOSE	PC1/dL	STATISTICS
				x̄/x̄₅	
	BLANK				
	TAC-STANDARD			20178 x EFFIC=	.99
1	CONTROL			492	
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	26588	1.00	113	SE = 32.7
11	63-748	26688	1.00	115	t = 7.7
12	63-748	26588	1.00	106	P <.01
7	63-748	26668	1.00	528x	%CHG = -71
13	63-748	26682	.300	358	MEAN = 319.3
14	63-748	26688	.300	356	STD = 68.3
15	63-748	26686	.300	391	SE = 39.5
17	63-748	26668	.300	199	t = 4.0
18	63-748	26668	.300	253	P <.01
16	63-748	26682	.300	794x	%CHG = -40.6
19	63-748	26688	.100	348	MEAN = 456.7
20	63-748	26668	.100	725	STD = 213.5
21	63-748	26688	.100	310	SE = 67.2
22	63-748	26668	.100	650	t = 0.8
23	63-748	26688	.100	536	P N.S.
24	63-748	26686	.100	178	%CHG = -14.7
25	64-844	30280	.300	256	MEAN = 185.6
26	64-844	30280	.300	170	STD = 57.3
27	64-844	30280	.300	155	SE = 23.4
28	64-844	30280	.300	128	t = 6.5
29	64-844	30280	.300	174	P <.01
30	64-844	30280	.300	101	%CHG = -69.2
31	64-844	30280	.100	306	MEAN = 219.8
32	64-844	30280	.100	273	STD = 69.9
33	64-844	30280	.100	195	SE = 38.9
35	64-844	30280	.100	157	t = 6.7
36	64-844	30280	.100	185	P <.01
34	64-844	30280	.100	696x	%CHG = -55.1

Performed by- Tod R. Mayhew

Witness- R Dutton

Cont'd to- 135

Date 10/22/87 Proj# 3,1,x

Title- Cholesterol Synthesis Inhibition Screen

135

Cont'd From- 134

336

IN VIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN H818

RAT	COMPOUND REGNO	DOSE mg/kg	nCi/dl	STATISTICS	
37	64-844	30280	.030	354	MEAN = 418.7
38	64-844	30280	.030	518	STD = 136.6
39	64-844	30280	.030	639	SE = 56.6
40	64-844	30280	.030	245	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	590	MEAN = 489.4
44	64-936	30486	1.00	542	STD = 132.8
45	64-936	30486	1.00	280	SE = 54.2
46	64-936	30486	1.00	328	t = 0.7
47	64-936	30486	1.00	532	p N.S.
48	64-936	30482	1.00	513	%CHG = -9.0
49	64-936	30486	.300	167	MEAN = 325.7
50	64-936	30486	.300	333	STD = 165.0
51	64-936	30486	.300	566	SE = 87.4
52	64-936	30486	.300	278	t = 2.7
53	64-936	30488	.300	328	p <.02
54	64-936	30482	.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	359	SE = 68.9
58	64-936	30488	.100	696	t = 1.6
59	64-936	30482	.100	357	p N.S.
60	64-936	30485	.100	439	%CHG = -33.5
61	62-320	30559	.300	72	MEAN = 67.5
62	62-320	30559	.300	89	STD = 12.1
63	62-320	30559	.300	73	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	238	STD = 51.1
70	62-320	30559	.100	198	SE = 22.9
71	62-320	30559	.100	109	t = 8.5
69	62-320	30559	.100	149	p <.01
72	62-320	30559	.100	156	%CHG = -89.3
73	62-320	30559	.030	333	MEAN = 381.2
74	62-320	30559	.030	380	STD = 173.3
75	62-320	30559	.030	77	SE = 70.8
76	62-320	30559	.030	575	t = 3.2
77	62-320	30559	.030	483	p <.05
78	62-320	30559	.030	377	%CHG = -34.7

* = rejected by "Q" test Computed 12-09-87
= LACK OF SAMPLE.

Performed by- [signature]

Witness- [signature]

Cont'd to-

136 Title- Cholesterol Synthesis Inhibition Screen

Date 10/29/87 Proj: 3.5

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.E., ARC

STUDY # H319
STUDY ON 10/29/87
BK.REF. 917-135
APPROVAL
DATE 10/29/87
GEN. ARC#86-004

Title: In vivo single dose assay to test for inhibition of biosynthesis by compounds: 64-298, 64-933, 63-935

Purpose: Determine the invivo effects of test compounds in rats on cholesterol biosynthesis.

Experimental design: IN VIVO CHOLESTEROL BIOSYNTHESIS INHIBITION DT0069 Invivo single dose assay of 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. UCR rats.

RATS	COMPOUND	REGNO	DOSE mg/kg	STOCK mg/20ml	WORKING SOLUTION ml stock q.s. to 15ml
1-6	Control	------	------	------	------
7-12	64-298	29277	1	1	UNDILUTED
13-18	"	"	0.3	-	4.5
19-24	"	"	0.1	-	1.5
25-30	64-933	30447	1	1	UNDILUTED
31-36	"	"	0.3	-	4.5
37-42	"	"	0.1	-	1.5
43-48	64-935	30481	1	1	UNDILUTED
49-54	"	"	0.3	-	4.5
55-60	"	"	0.1	-	1.5
61-66	63-935	30555	0.3	1	4.5
67-72	"	"	0.1	-	1.5
73-78	"	"	0.03	-	0.45
79-84	Control	------	------	------	------

Performed by-

Witness-

Cont'd to- 337

Title- 137

Proj. 338

IN VIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN H315

RAT	COMPOUND	REGNO	DOSE mg/kg	nCi/dl	STATISTICS	
	BLANK			7		
	14C-STANDARD			20176	X EFFIC=	98
1	CONTROL			953		
2	CONTROL			515	MEAN =	671.8
3	CONTROL			646	STD =	211.0
4	CONTROL			578	SE =	80.9
5	CONTROL			934		
6	CONTROL			354		
78	CONTROL			756		
80	CONTROL			847		
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	381	STD =	118.8
9	64-298	28277	1.00	82	SE =	48.1
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 =	8.3
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	245	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	426	%CHG =	-42.1
25	64-933	30447	1.00	838	MEAN =	626.1
26	64-933	30447	1.00	275	STD =	253.4
27	64-933	30447	1.00	138	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 =	-38.3
31	64-933	30447	.300	830	MEAN =	587.4
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	366	P	N.S.
36	64-933	30447	.300	815	%CHG =	-17.0

performed by-

Title- 138

Date 12/[illegible]/87 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	555	MEAN =	547.0
38	64-933	30447 .100	735	STD =	147.2
39	64-933	30447 .100	370	SE =	60.1
40	64-933	30447 .100	378	t =	1.5
41	64-933	30447 .100	581	p	N.S.
42	64-933	30447 .100	552	%CHG =	-18.8
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	166	SE =	31.9
46	64-935	30441 1.00	321	t =	8.4
47	64-935	30441 1.00	124	p	<.01
48	64-935	30441 1.00	281	%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	342	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	256	SE =	48.8
58	64-935	30441 .100	426	t =	3.1
59	64-935	30441 .100	621	p	<.02
60	64-935	30441 .100	495	%CHG =	-38.3
61	62-320	30559 .300	50	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 =	8.8
65	62-320	30559 .300	217	p	<.01
66	62-320	30559 .300	327	%CHG =	-75.3
67	62-320	30559 .100	282	MEAN =	331.7
68	62-320	30559 .100	434	STD =	185.7
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 =	-50.9
73	62-320	30559 .030	421	MEAN =	448.1
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 =	-33.5

Computed 12-09-87

Performed by-

Witness- R Elsyton

Cont'd to...

64566	29851 280-8	>	.1	09-JUN-87	917-065
64569	29852 290-8	=	.16	15-JUN-87	.7-081
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	917-085
64608	29756 298-86	>	7.5	13-MAY-87	917-055
64636	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		.5S	16-DEC-87	917-141
64722	30004 280-85	=	.2	23-OCT-87	917-125
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	917-155
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	220-85	=	.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	917-136
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
380349	29591	102-82	>	10	18-AUG-87	917-098
380586	29588	102-82	>	10	18-AUG-87	917-098
380820	29589	102-82	>	10	18-AUG-87	917-098

140 records selected.

SQL>

Case No. 600-7101/CONT/INT.(5)
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

SUPPLEMENTAL DECLARATION OF ROBERT G.ENGSTROM PURSUANT TO 37 CFR §1.672

I, Robert G. Engstrom, do hereby declare as follows:

All of the below-indicated activities took place in the United States.

Exhibit Q comprises a true copy of a Biological Activity Data Report dated May 24, 1988 which I sent to the Patent Department concerning the compounds of PD 299/84, together with a computer printout of the Sandoz database dated May 23, 1988. The printout contains IC_{50} and some ED_{50} values for compounds of Patent Disclosure 295/84 and compounds of the subject Patent Disclosure 299/84.

(I note that I became aware of a computer entry error comprising the inadvertent "switching" of the ED_{50} data for compounds 64-933 and 64-935. The corrections on the printout are in my handwriting and would have been made on or about May 23, 1988.).

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 19 day of February, 1993.

Robert Engstrom

Robert Engstrom

Q

BIOLOG AL ACTIVITY DATA REPORT (R PATENT DEPT.)

4/8

INVENTOR: S. Wattanasin DISCL. NO.: 299-84

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 THAI 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 DESIGNATEI 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

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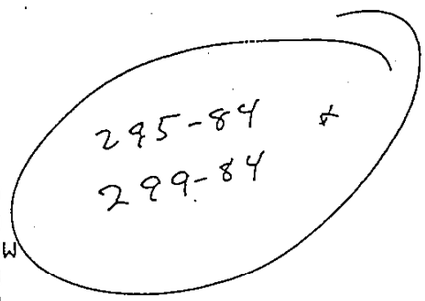
<USER02>ENGSTR>IC5 TA>PD295-84

419

299/84.



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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: PRO by: PRO

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	SAPONIFIED
SAH-063271	25208	295-84	0.0320	09-10-84	1069-055	
SAH-063271	25208	295-84	0.1450	09-12-84	1069-055	

SAH-064484	F	29413	95-84	0.0320	11-24-86	1149-227
SAH-064744	E	30059	95-84	0.0320	05-01-87	1149-293
SAH-064745	S	30060	95-84	0.0030	05-01-87	1149-294
SAH-064745	S	30060	95-84	0.0030	07-07-87	1149-297
SAH-064815	E	30198	95-84	0.0220	07-07-87	1238-001
SAH-064816	S	30199	95-84	0.0450	07-07-87	1238-002
SAH-063162	S	30203	95-84	0.0080	07-07-87	1238-003
SAH-064745		30765	95-84	0.0020	01-12-88	1238-030
SAH-063366		25496	99-84	1.5800	12-13-84	1069-113
SAH-063549		26082	99-84	7.3100	06-13-84	1069-197
SAH-063548		26080	99-84	3.7750	06-13-84	1069-198
SAH-064933	E	30441	99-84	2.3700	10-08-87	1238-013
SAH-064934	S	30442	99-84	2.6100	10-08-87	1238-014
SAH-064935	E	30447	99-84	0.4130	10-08-87	1238-015
SAH-064936	S	30448	99-84	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	DISCL	ED50 mg/kg	DATE mm-dd-yy	REF bk-pg	COMMENTS
SAH-064745	30060	95-84	= 0.016	10-20-87	917-127	N=9
SAH-064745	30765	95-84	= 0.016	02-19-88	917-154	N=3 BS BATCH
SAH-064745	ALL	95-84	= 0.016	02-19-88	917-154	N=12 2BATCHES
SAH-063162	25500	95-84	= 0.019	09-18-87	917-101	N=10
SAH-063162	ALL	95-84	= 0.040	09-18-87		N=19 3BATCHES
SAH-063162	25085	95-84	= 0.079	10-11-84	812-266	N=8
SAH-064119	27563	95-84	= 0.08	05-16-86	869-228	N=6
SAH-064744	30059	95-84	> 0.10	07-14-87	917-090	N=3 -21% @.10
SAH-064816	30199	95-84	= 0.10	10-12-87	917-119	N=6
SAH-064483	29412	95-84	= 0.13	02-06-87	917-024	N=3
SAH-064063	27424	95-84	= 0.19	04-17-86	869-211	N=3
SAH-064309	28718	95-84	= 0.19	11-03-86	869-283	N=3
SAH-063231	25079	95-84	> 0.25	08-30-84	812-250	
SAH-064393	29163	95-84	= 0.25	02-25-87	917-031	N=6
SAH-063161	24821	95-84	> 0.250	11-29-84	812-293	-12@0.25
SAH-063989	27237	95-84	= 0.28	04-04-86	869-195	N=6
SAH-063425	25687	95-84	> 0.3	03-20-85	869-046	N=3
SAH-064305	28701	95-84	> 0.3	11-03-86	869-280	N=3 -34% @.3
SAH-064480	29404	95-84	> 0.3	02-06-87	917-023	N=3 +3% @.3
SAH-063270	ALL	95-84	= 0.308	02-07-85		N=11 2BATCHES
SAH-063270	25206	95-84	= 0.33	10-11-84	812-267	
SAH-063270	25501	95-84	= 0.362	01-21-85	869-018	
SAH-064307	28705	95-84	= 0.47	02-06-87	917-020	N=6
SAH-063159	24810	95-84	> 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 -3% @1.0
SAH-064935	30447	E99-84	=	~~1=0.49~~	12-09-87	917-138	N=3

Case No. 600-7101/CONT/Int.(1)
Patent

#62

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v.
FUJIKAWA et al.

[redacted]
Examiner-in-Chief: M. Sofocleous

WATTANASIN
v.
FUJIKAWA et al.
v.
FUJIKAWA et al.

Interference No. 102,975
Examiner-in-Chief: M. Sofocleous

FYI

NOV 19 1992

RECEIVED IN
FOX INTERFERENCE

WATTANASIN MOTION TO CONSOLIDATE RECORD

Wattanasin hereby moves to consolidate the record for the above-numbered interferences, the counts of which are directed to essentially the same subject matter.

The undersigned counsel for Wattanasin has conferred with counsel for Fujikawa et al., who take no exception to the present motion to consolidate (however, without forfeiting the right to oppose in the event of unspecified changed circumstances in the future).

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 Nov. 16, 1992
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
11/16/92
Date of Signature

Respectfully submitted,

Diane Furman
Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

DEF:rmf
November 16, 1992

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN MOTION TO CONSOLIDATE RECORD

was served on counsel for the party Fujikawa et al., this 16th day of November, 1992, 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

Case No. 600-7...1/CONT/Int. (3)
Patent

#63

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v.
FUJIKAWA et al.

[redacted]
Examiner-in-Chief: M. Sofocleous

WATTANASIN
v.
FUJIKAWA et al.
v.
FUJIKAWA et al.

Interference No. 102,975
Examiner-in-Chief: M. Sofocleous

FYI

NOV 19 1992

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COX INTERFERENCE

WATTANASIN MOTION FOR EXTENSION OF TIME UNDER 37 CFR §1.635

It is respectfully requested that the party Wattanasin be permitted an extension of time of ten (10) days, from November 15, 1992[1], i.e. until November 25, 1992, to file and serve: (1) an executed copy of the Declaration of Lawrence B. Perez pursuant to 37 CFR 1.672; and (2) an original of the executed copy of the Declaration of Rajeshvari Patel pursuant to 37 CFR §1.672.

With regard to the Perez declaration, it was discovered today by the undersigned that the original and copies of Dr. Perez's signed declaration have regrettably been misplaced. It has also been learned that Dr. Perez, who is a Sandoz employee, is on vacation and is therefore unavailable to sign from Friday, November 13 to at least Wednesday, November 18, 1992, inclusive.

1. The Wattanasin deadline for filing and serving testimony in the above interferences.

An unexecuted copy of the Perez declaration is today being filed and served in the above interferences.

With respect to the declaration of Rajeshvari Patel, who is no longer employed by Sandoz: inadvertently, only a facsimile copy of the execution page of the signed declaration is currently available, perhaps owing to miscommunication between the declarant and undersigned counsel, who expected to receive the original by mail today. The facsimile copy of the Patel declaration is today being filed and served in the above interferences.

Counsel for Fujikawa et al. have been apprised of the above, and have indicated to the undersigned that they will not oppose the introduction of the Patel declaration; but they are reserving the right to oppose introduction of the Perez declaration.

Acccordingly, it is respectfully requested that Wattanasin be permitted to file a signed copy of the Perez declaration, and an original of the signed copy of the Patel declaration, on or before November 25, 1992.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORP.
59 Route 10
E. Hanover, NJ 07936
DEF:rmf
November 16, 1992

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 Nov. 16, 1992
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
11/16/92
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN MOTION FOR EXTENSION OF TIME

was served on counsel for the party Fujikawa et al., this 16th day of November, 1992, 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

#63

Case No. 600-7101/CONT
Serial No. 07/498,301
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :

SOMPONG WATTANASIN : Art Unit:

Serial No. 07/498,301 : Examiner:

Filed: March 2, 1990 :

For: QUINOLINE ANALOGS OF :
MEVALONOLACTONE AND :
DERIVATIVES THEREOF :

FYI

NOV 19 1992

RECEIVED IN
BOX INTERFERENCE

DECLARATION OF LAWRENCE B. PEREZ PURSUANT TO 37 C.F.R. §1.608

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Dear Sir:

I, Lawrence B. Perez, Ph.D. do hereby declare that:

1) I am an Assistant Fellow employed by Sandoz Pharmaceuticals Corporation. In the course of my employment I synthesize compounds, including HMG-CoA reductase inhibiting compounds, and I am familiar with the chemistry employed to make such compounds. All activities referred to in this Declaration took place in the United States.

2) I reviewed Rajeshvari Patel's Laboratory Notebook #1206, pages 179 and 201.

3) I signed the aforementioned Laboratory Notebook pages prior to December 7, 1987.

4) Exhibit F-1 contains true copies, except that the dates have been deleted of Rajeshvari Patel's Notebook #1206, pages 179 and 201, bearing my signature. The dates which have been deleted are prior to December 7, 1987.

5) 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 day of 5/8, 1990.

Lawrence B Perez

Lawrence B. Perez, Ph.D.

#63

Case No. 600-7101/CONT
Serial No. 07/498,301
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :

SOMPONG WATTANASIN : Art Unit:

Serial No. 07/498,301 : Examiner:

Filed: March 23, 1990 :

For: QUINOLINE ANALOGS OF MEVALONOLACTONE AND DERIVATIVES THEREOF :

FYI

NOV 19 1992

RECEIVED IN
BOX INTERFERENCE

DECLARATION OF RAJESHVARI PATEL PURSUANT TO 37 C.F.R. §1.608

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Dear Sir:

I, RAJESHVARI PATEL, do hereby declare that:

1) I am a chemist, who was employed by Sandoz Pharmaceuticals Corporation, 59 Route 10, East Hanover, N.J. during the time when Dr. Sompong Wattanasin was in the process of reducing to practice compounds claimed in U.S. Patent Application Serial Number 07/498,301. One of my job responsibilities included the synthesis of certain compounds under the direction and supervision of Dr. Wattanasin. All activities referred to in this Declaration took place in the United States of America.

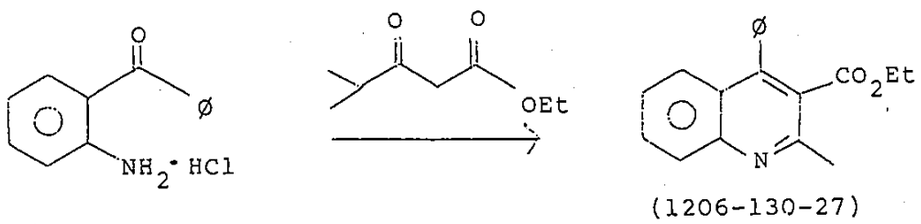
2) I kept a record of this activity in my Laboratory Notebook #1206. Exhibit F-1 is a true copy of my Laboratory Notebook #1206, Pages 130, 137, 145, 153, 158, 166, 172, 175, 176, 179 and 201,

except that dates have been deleted. The activity recorded in these notebook pages and the recordation of this activity both took place prior to December 7, 1987.

3) To determine molecular weight, mass spectrometry was performed. The molecular weight which was determined is the weight of the molecular ion, or $M-H^+$, where M is the compound of interest. Thus, to calculate the molecular weight of the compound rather than its ion, one must subtract the molecular weight of hydrogen (1) from the molecular weight of the ion. In the notebook pages, I recorded the molecular weight of the ion. Thus, the molecular weight of the compound is 1 less than what I recorded in my notebook.

4) The spectra and microanalyses were not performed by me, but were performed by an employee of the Physical Organic Chemistry Department of Sandoz Pharmaceuticals Corporation. Upon receipt of the spectra from the Physical Organic Chemistry Department, I filed them in their own folder arranged by their compound number. Reference is made to the Declaration of Dr. Sandor Barcza which accompanies this Declaration for details concerning analysis procedures.

Notebook #1206, Page 130, documents the following reaction which I performed.



(1206-130-27)

Ø = phenyl group

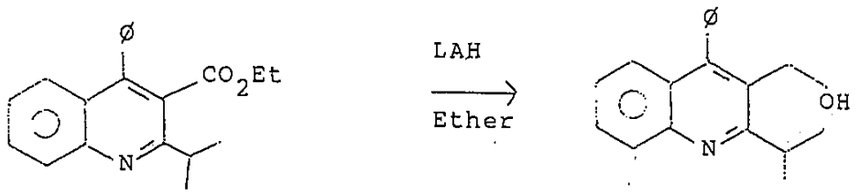
(1206-129-18)

The compound on the left side of the equation was designated 1206-129-18. A mixture of 11.5 g (0.04930 mol) of 1206-129-18,

11.93 ml (0.073958 mol; 1.5 equivalents) of
and 105 ml EtOH was heated to reflux for six hours (10:00 A.M. to 4:00 P.M.) and then stirred at room temperature overnight.

The following day, the reaction mixture was evaporated to dryness to give a yellow oil with the rotary evaporator, basified with NH_4OH and extracted with ether, and the ether extract was washed with H_2O and then brine, dried with anhydrous sodium sulfate, and filtered. The filter cake was washed with ether and the washing was combined with the initial filtrate and evaporated to give 10.21 g of an orange-yellow solid, designated 1206-130-27. IR and NMR spectra were performed and follow Laboratory Notebook #1206, page 130. Yield was calculated to be 64.86%. The spectra were judged by me and Dr. Wattanasin to be consistent with the desired product (1206-130-27).

Notebook #1206, Page 137, documents the following reaction which I performed.

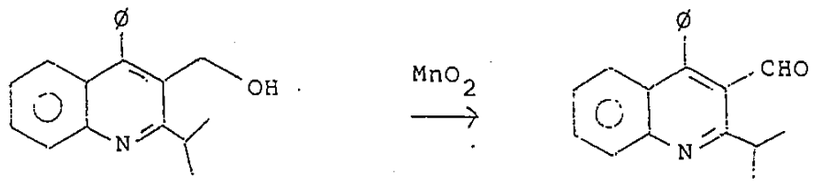


(1206-130-27) (1206-137-31)

To 10.21 g (0.0319621 mol) of 1206-130-27 in 100 ml dry ether with cooling was added 2.43 g (0.063242 mol) LAH (lithium aluminum hydride) portion-wise. The reaction was exothermic and foaming occurred. The mixture was stirred at room temperature for three hours (9:35 A.M. to 12:35 P.M.).

The reaction mixture was poured into ice water (the reaction was strongly exothermic). The result was extracted with ether and the ether extract was washed with water and then brine, dried with anhydrous sodium sulfate and filtered. The filter cake was washed with ether, and the washing was combined with the initial filtrate. Evaporation gave 8.5 g of a yellow solid, designated 1206-137-31. IR and NMR spectra were performed and the results follow Laboratory Notebook #1206, page 137. The spectra were judged by me and Dr. Wattanasin to be consistent with the desired product (1206-137-31). Yield was calculated at 95.8% of theoretical.

Notebook #1206, Page 145, documents the following reaction which I performed.



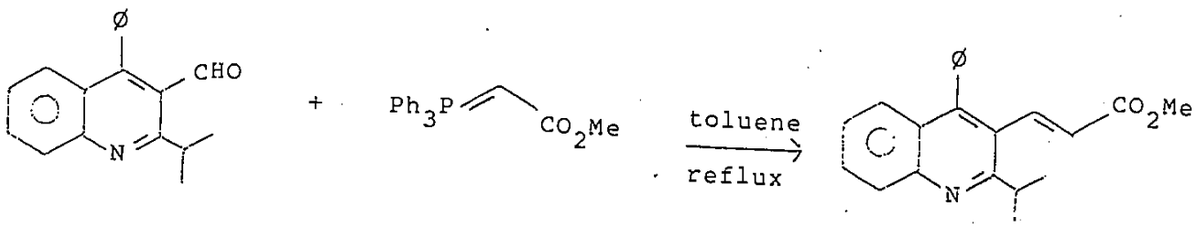
(1206-137-31) (1206-145-25)

To 8.0 g (0.0288392 mol) of 1206-137-31 in 150.0 ml toluene was added 16.0 g activated MnO_2. This was heated to reflux for approximately 3-3/4 hours (11:00 A.M. to 2:45 P.M.). The result

was filtered through a pad of silica gel. During filtration, it separated into two bands, which were then filtered separately and evaporated separately. Both were yellow solids: (a) 2.6518 g designated 1206-145-25 with a molecular weight of 276, which was determined to be the desired product; and (b) 4.4663 g, designated 1206-145-26, with a molecular weight of 278, which was determined to be the starting material. IR and NMR spectra were performed on 1206-145-25 and the results follow Laboratory Notebook #1206, page 145. The spectra were judged by me and Dr. Wattanasin to be consistent with the desired product (1206-145-25).

This process was repeated with 1206-145-26 as recorded in Laboratory Notebook #1206, page 148, and 3.26 g of the same compound as 1206-145-25 was obtained, and designated 1206-148-33. Thus total yield was calculated as 2.6518 g + 3.26 g = 5.91 g. Theoretical yield was 7.91 g, yield was therefore 74.52%.

Laboratory Notebook #1206, Page 153, documents the following reaction which I performed.



(1206-145-25)
(1206-148-33)

(1206-153-40)

Ph = phenyl group
Me = methyl group

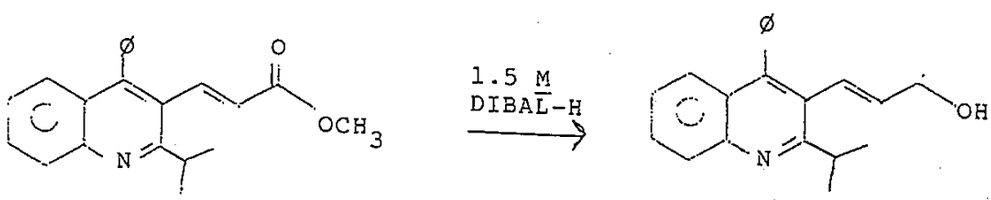
5.91 g of the combination of 1206-145-25 and 1206-148-33

(0.0214909 mol), 8.6135 g of Ph_3P=CO_2Me(0.025789 mol) and 85 ml of toluene were heated to reflux for 1.5 hours. (Before heating this was a yellow heterogeneous mixture). It was then stirred at room temperature overnight.

The following day, the reaction mixture was diluted with 50% ether/petroleum ether and filtered through a pad of silica gel. The filter cake was washed with 50% ether/petroleum ether, the washing was combined with the initial filtrate and evaporated to dryness to give 8.6 g of a yellow crystalline solid. Trituration with methanol gave 5.5198 g of an off-white solid, designated 1206-153-31, molecular weight 331; yield was 77.6%. The mother liquor was evaporated to dryness, leaving a 2.7593 g of a yellow oil, designated 1206-153-34.

Trituration of 1206-153-34 with methanol gave 761.6 mg of a light yellow solid, designated 1206-153-37, with a molecular weight of 331. Evaporation of the mother liquor to dryness resulted in a yellow solid, designated 1206-153-38. 1206-153-31 and 1206-153-37 were combined and designated 1206-153-40. The melting point of 1206-153-40 was found to be 128-130°C. Spectra were run on 1206-153-31 (NMR), 1206-153-37 (NMR) and 1206-153-34 (IR) and the results follow Laboratory Notebook #1206, page 153. The spectra of 1206-153-31 and 1206-153-37 were judged by me and Dr. Wattanasin to be consistent with the desired product.

Laboratory Notebook #1206, Page 158, documents the following reaction which I performed.

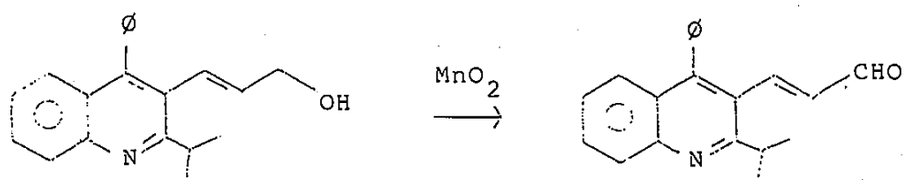


(1206-153-40) (1206-158-41)

To a solution of 6.25 g of 1206-153-40 (0.0188821 mol) in 75 ml CH_2Cl_2 at -78°C was added 25.18 ml of 1.5 M DIBAL-H (diisobutyl-aluminum hydride) (0.0377642 mol; 2 equivalents) in toluene. This was stirred at -78°C for about three hours (12:15 P.M. to 3:10 P.M.). The reaction was then quenched with 12.5 ml 2 N NaOH, diluted with EtOAc, and stirred at room temperature overnight. A white solid (gel) came out of solution.

The following day, the reaction product was filtered through a pad of silica gel, washed with EtOAc, water, and then brine, dried with anhydrous sodium sulfate and evaporated to dryness. The result was 5.42 g of an off-white solid, designated 1206-158-35. Yield was 73.7% theoretical yield. The solids were dissolved in Et_2O, and the insoluble portion (aluminum oxide) was filtered off. The solution was evaporated to dryness, resulting in 5.22g of white-yellow solids designated 1206-158-37. The solids were dissolved in Et_2O, and the insoluble portion (aluminum oxide) was filtered off. The resulting solution was evaporated to dryness, resulting in 4.2117 g of a yellowish solid, designated 1206-158-41, with a molecular weight of 303 and a melting point of 119-121°C. NMR and IR spectra were run on 1206-158-41 and the results follow Laboratory Notebook #1206, page 158. The spectra were judged by me and Dr. Wattanasin to be consistent with the desired product (1206-158-41).

Laboratory Notebook #1206, page 166, documents the following reaction, which I performed.



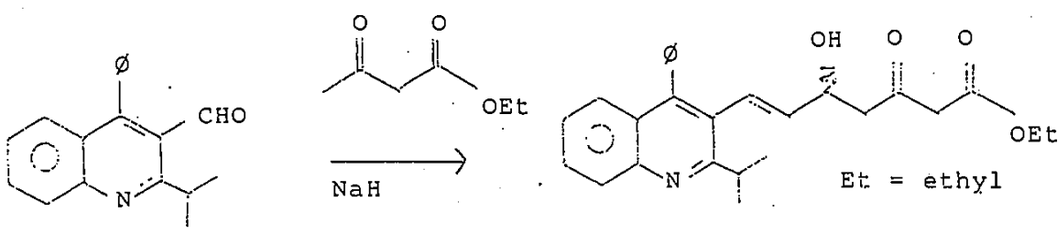
(1206-158-41) (1206-166-30)

To 4.0 g of 1206-158-41 (0.0132013 mol) in 50 ml toluene was added 8.0 g activated MnO_2. This was heated to reflux for one hour (2:00 P.M. to 3:00 P.M.), then stirred at room temperature overnight.

The following day, the reaction product was filtered through a pad of silica gel. Evaporation to dryness gave 3.4946 g of a yellow crystalline material, designated 1206-166-30, with a molecular weight of 301. NMR and IR spectra were run on 1206-166-30 and the results follow Laboratory Notebook #1206, page 166. Yield was 88% theoretical yield. The spectra were judged by me and Dr. Wattanasin to be consistent with the desired product (1206-166-30).

Twelve days later, a microanalysis was performed. Two days later, the melting point was determined to be 98-101°C.

Laboratory Notebook #1206, Pages 172 and 175 document the following reaction which I performed.



(1206-166-30) (1206-175-4)

To a solution of 3.5 g (0.0116279 mol) of 1206-166-30 in 40 ml dry THF at -5°C to -10°C was added 38 ml of a previously prepared solution of the dianion of ethyl acetoacetate, the details of the preparation of which are set forth below. The color changed

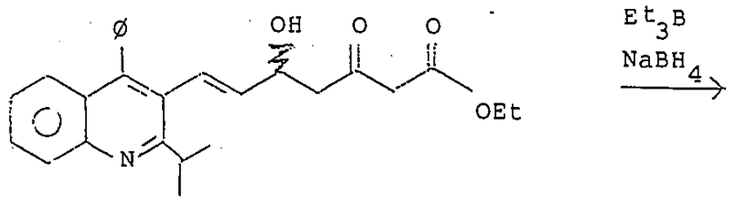
from yellow to orange to dark red, suggesting that the reaction had occurred. A TLC (using 50% ether/petroleum ether) run after 15 minutes indicated the reaction was complete. The reaction mixture was stirred for 30 minutes.

The reaction mixture was quenched with NH_4Cl solution, extracted with EtOAc, resulting in two layers. The organic layer was separated and was washed with water then brine, dried with anhydrous sodium sulfate and filtered. Evaporation gave 5.9188 g of a yellow oil, designated 1206-172-41. Yield was 67.87% theoretical.

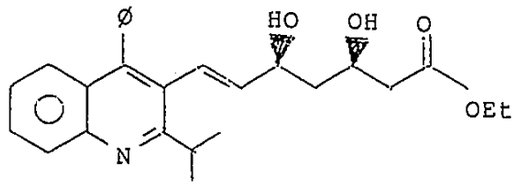
To make the dianion solution used above, the following procedure was used. A solution of 5 ml ethyl acetoacetate in 50 ml dry THF was added 1.9 g of 50% NaH in THF at -5° to 0°C. This was stirred for 15 minutes (the solution was foaming as H_2 was evolved). At -10° to -15°C, 27 ml of 1.6 M n-butyllithium/hexane was added and the mixture was stirred for 20 minutes at -10°C. 92 ml of a yellow homogeneous solution resulted (0.04 mol).

Flash chromatography through silica gel (25% ether/petroleum ether) of 1206-172-41 gave 3.4004 g of a yellow solid, designated 1206-175-4. Melting point was 84-87°C. Yield was 68%. A microanalysis was performed and the results are shown. NMR and IR spectra were run on 1206-175-4 and the results follow Laboratory Notebook #1206, page 172. The spectra were judged by me and Dr. Wattanasin to be consistent with the desired product (1206-175-4).

Laboratory Notebook #1206, Page 176, documents the following reaction which I performed.



(1206-175-4)



(1206-176-41)

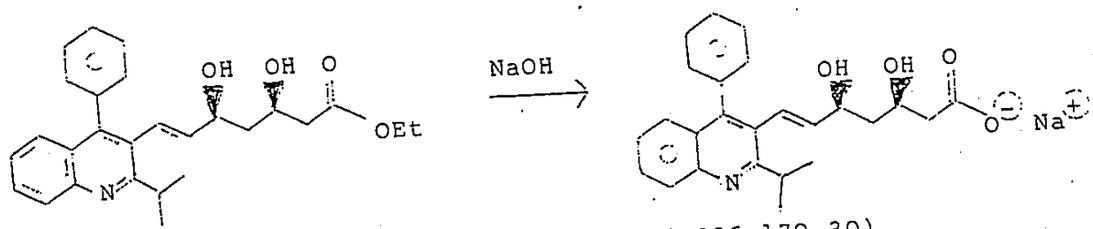
To a homogeneous solution of 1.0 g (0.0023201 mol) 1206-175-4 in 10 ml dry THF and 2.5 ml methanol was added 3.5 ml 1 M Et_3B (0.0034801 mol; 1.5 equivalents) in THF. This was stirred at room temperature for one hour (9:45 A.M. to 10:45 A.M.). Then the solution was cooled to -78°C. 0.1315 g of $NaBH_4$ (0.0034810 mol; 1.5 equivalents) was added portion-wise. This was then stirred at -78°C for four hours (11:00 A.M. to 3:00 P.M.).

The reaction was quenched with 5 ml acetic acid at -78°C. Ethyl acetate was then added and the mixture was allowed to warm to room temperature. The organic layer was washed with saturated sodium bicarbonate solution, water, and brine. It was then dried, filtered and evaporated to dryness. The residue was redissolved in methanol and evaporated to dryness. The evaporation process (in methanol) was repeated until TLC showed the desired product was obtained, 1.0914 g of an orange oil, designated 1206-176-39.

Flash chromatography on silica gel (80% ether/petroleum ether) gave two products: (a) $F_{4-6'}$ 0.4043 g of a yellow solid, designated 1206-176-41 with a molecular weight of 433 and M.P. 104-106°C, which was shown by HPLC to be 98.3% pure; and (b) $F_{7-13'}$ 0.510 g of a yellow solid designated 1206-176-43, with a molecular weight of 433, which was shown to be 93.2% pure by HPLC. IR and NMR spectra were run on both 1206-176-41 and 1206-176-43 and follow Laboratory Notebook #1206, page 176. Based on these spectra, compound 1206-176-41 was determined to be the desired product. Compound 1206-176-41 was eventually renamed 64-933.

A sample of 64-933 was sent to Dr. Scallen for biological testing in his <u>in vitro</u> microsomal assay for HMG-CoA reductase inhibition activity. It was shown by Dr. Scallen to possess inhibition activity prior to December 7, 1987. I learned of this activity from Dr. Damon. Thus, prior to December 7, 1987, I knew that 64-933 was useful as an anti-cholesterol biosynthesis agent, and would be useful in treating atherosclerosis and other conditions resulting from excessive cholesterol biosynthesis.

Laboratory Notebook #1206, page 179, documents the following reaction which I performed.

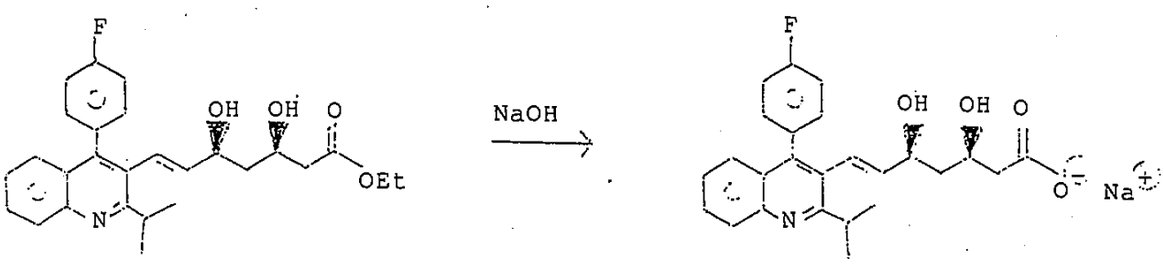


(1206-176-41) (1206-179-30)

To 200.0 mg 1206-176-41 in 5 ml absolute ethanol at 0°C. was added approximately 439 µml of 0.5N NaOH. This was stirred at 0°C. for approximately 1 hour. A yellow oil resulted. The mixture was diluted with ether and evaporated to a yellow oil. This was re-diluted with ether and solids precipitated out of solution. The solids were washed with ether, the ether was decanted, and the solids were dried under vacuum to obtain 178.8 mg of yellow solids designated 1206-179-30. NMR and IR spectra and a microanalysis were performed. The spectra appear after Notebook #1206, page 179, and were judged by me and Dr. Wattanasin to be consistent with the desired product (1206-179-30). The product shrunk at 187°C and the melting point was above 210°C.

1206-179-30 was re-named 64-934. It was submitted to Dr. Scallen for biological testing in his above-mentioned <u>in vitro</u> microsomal assay and was found to be active.

Laboratory Notebook #1206, page 201, documents the following reaction which I performed.



(1206-190-41)

(1206-201-30)

The compound on the left side of the equation was synthesized and designated 1206-190-41. To 100 mg 1206-190-41 in 5 ml absolute ethanol, at 0°C with stirring was added approximately 217.3 µml 1N

NaOH dropwise. The mixture was stirred at 0°C for approximately 3 hours, resulting in a yellow oil.

This was diluted with ether, and evaporated to dryness to produce a yellow oil. Upon the addition of ether, yellow solids precipitated out. These were filtered, washed and dried to give 86.4 mg of a yellow solids designated 1206-201-30.

NMR and a microanalysis were performed on 1206-201-30. The spectrum appears after Notebook #1206, page 201. It was judged by me and Dr. Wattanasin to be consistent with the desired product (1206-201-30). Its melting point was greater than 225°C.

1206-201-30 was renamed 64-936. It was submitted to Dr. Scallen for biological testing in his above-mentioned microsomal assay and was found to be active prior to December 7, 1987.

Thus, prior to December 7, 1987, I knew that both 64-934 and 64-936 were useful as anti-cholesterol biosynthesis agents, and would be useful in treating atherosclerosis and other conditions resulting from excessive cholesterol biosynthesis.

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 7th day of May, 1990.

Rajeshvari D Patel

RAJESHVARI PATEL

Case No. 600-7101/CONT/Int. (4)
Patent

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 - #64
Examiner-in-Chief: M. Sofocleous

WATTANASIN
v.
FUJIKAWA et al.

Interference No. 102,975 - #6
Examiner-in-Chief: M. Sofocleous

v.
FUJIKAWA et al.

FYI

NOV 19 1992

RECEIVED IN
BOX INTERFERENCE

WATTANASIN RULE 671(e) NOTIFICATION

Contingent on the denial of the Wattanasin Motion for Extension of Time of even date herewith, the party Wattansin hereby gives notice of intent to rely on the Rule 608 Declaration of Lawrence B. Perez (if the above-mentioned Motion is denied as to Perez), and/or the Rule 608 Declaration of Rajeshvari Patel (if the above-mentioned Motion is denied as to Patel) filed in Wattanasin application Serial No. 07/318,773 on May 25, 1990. A copy of each of the Perez and Patel Rule 608 Declarations is enclosed herewith.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

DEF:rmf
November 16, 1992
Encs: Rule 608 Declaration of Lawrence B. Perez
Rule 608 Declaration of Rajeshvari Patel

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 Nov. 16, 1992
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
11/16/92
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN RULE 671(e) NOTIFICATION

together with the enclosures appended to said paper, were served on counsel for the party Fujikawa et al., this 16th day of November, 1992, 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

WATTANASIN

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NOV 19 1992

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VOLUME I

Interference No. 102,648 - #65

Interference No. 102,975 - #7

WATTANASIN Consolidated

Affidavit Testimony

and Exhibits

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v. Interference Nos. 102,648, 102,975
FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

DECLARATION OF SOMPONG WATTANASIN PURSUANT TO 37 CFR §1.672

I, Sompong Wattanasin, Ph.D., do hereby declare as follows:

(1) That I am the inventor of the subject matter contained in U.S. patent application Serial Number 07/498,301.

(2) That based upon the information provided in this Declaration, I believe that I am entitled to a judgment relative to Fujikawa et al., U.S. patent application Serial No. 07/233,752.

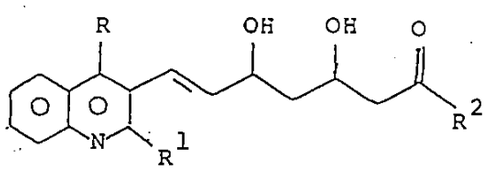
(3) That I am currently a Senior Associate Fellow employed by Sandoz Pharmaceuticals Corporation, 59 Route 10, East Hanover, New Jersey. At the time during which I conceived and reduced the invention of the above-identified patent application to practice, I was a Senior Scientist A. My job responsibilities included the invention and synthesis of compounds which are inhibitors of 3-hydroxy-3-methyl- glutarylcoenzyme A reductase (HMG-CoA Reductase), an enzyme which is involved in cholesterol biosynthesis.

(4) That prior to August 20, 1987, I conceived and reduced to practice my invention in the United States.

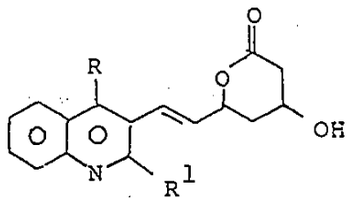
All the activities described in this Declaration took place in the United States.

I. CONCEPTION PRIOR TO AUGUST 20, 1987

(1) On or before November 28, 1983, I conceived of the following compounds:



(I)



(II)

where R = phenyl, 3,5-dimethylphenyl, 4-fluorophenyl, or isopropyl

R^1 = methyl, isopropyl, or 4-fluorophenyl

R^2 = an ester group, a salt, an acid

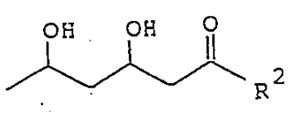
It was preferred that the open chain compounds be in the form of the 3R,5S isomer, or be in the erytho racemic form. For lactone compounds, I preferred the 4R,6S isomer or the trans racemic form.

(2) I made the first drawing or written description of the invention on or before November 28, 1983, when I proposed to Dr. Kathawala to synthesize compounds of the invention from previously synthesized intermediates and commercially available compounds for formulation into compositions for use as HMG-CoA reductase inhibitors.

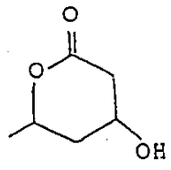
Exhibit A-1 documents my first drawing or written description of my invention, and is a true copy of a research report I authored.

The pages which comprise Exhibit A-1 are written in my handwriting. The first page contains my signature and the date of November 28, 1983 in my handwriting. I sent a copy of this report to Dr. Kathawala on November 28, 1983 and also orally disclosed the substance of the report to Dr. Faizulla Kathawala on or before November 28, 1983.

This exhibit outlines the following year's projects. It explains that the coordinated search for compounds having HMG-CoA reductase activity should be centered in four major areas. On the last page, a compound designated compound 14, which makes up part of this invention is proposed. In this proposal's formulae, "L" indicates either of the side chains:



and



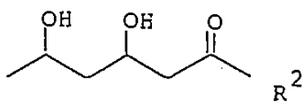
where R^2 = an acid, a salt or an ester.

I also intended that the preferred open chain form be the 3R,5S form or the erythro racemate, and the 4R,6S or trans racemate for lactones.

Exhibit A-2 documents a further written description of my invention, and is a true copy of another research report I authored.

The pages which comprise Exhibit A-2 are written in my handwriting. The first page contains my signature and the date of November 19, 1984 in my handwriting. I sent a copy of this report to Dr. Kathawala on November 19, 1984 and also orally disclosed the substance of the report to Dr. Faizulla Kathawala on or before November 19, 1984.

This report outlines plans for the following year's research. On the first page, the following compounds are proposed. In this proposal's formulae, "L" again indicates these side chains, with R^2 and the stereochemistry the same as above.



and

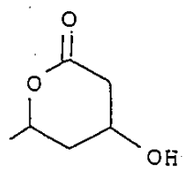
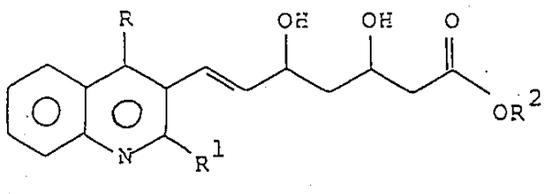
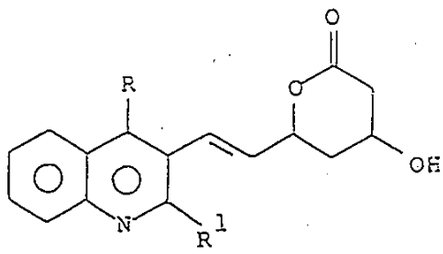


Exhibit A-3 comprises a true copy of an Invention Disclosure Form which I authored. The Form contains my signature and my date of signature of March 16, 1987. I had this document witnessed by Dr. Faizulla Kathawala. I then sent this document to the Sandoz Patent and Trademark Department. Two representative formulae are presented, as follows:



(I)



(II)

where R = 3,5-dimethylphenyl or isopropyl (abbreviated i-Pr)

R^1 = methyl, isopropyl or 4-fluorophenyl

R^2 = ethyl (abbreviated Et)

The second and third pages of the Invention Disclosure were also authored by me and are in my handwriting. I attached these pages to the Invention Disclosure Form before sending it to the Patent and Trademark Department. Two methods of synthesizing compounds are shown on these pages. The method of the second page yields both compounds of Formula I and II, whereas the method on the third page yields only compounds of Formula I.

While the Invention Disclosure Form only indicates the ester compounds, I intended the ester to be a shorthand designation for salts and acids as well. Since the salts and acids are easily made from the esters (i.e. by simple hydrolysis), and since these types of reactions were fully explained in other patent applications on which I am a named inventor, I did not include these in the

Invention Disclosure although I considered them part of my invention. Also at this time, and based on my experience with the chemistry of other HMG-CoA reductase inhibitors, I expected that for a given compound, the lactone would be less active than an open side chain and that the acid form, ester form and salt form would show approximately the same activity. Therefore, I considered the acids, esters and salts to be equivalents and for brevity's sake would only generally draw one of them when referring to all three.

II. ACTUAL REDUCTION TO PRACTICE OF MY INVENTION PRIOR TO AUGUST 20, 1987

(1) Compounds of my invention were actually reduced to practice by me and by chemists working under my supervision in the United States prior to August 20, 1987.

(2) For details of work performed under my supervision, and not by me personally, reference is made to Exhibits F-1 and L-1 hereto, which I have reviewed and which to my knowledge comprises the notebook pages of Rajeshvari Patel.

(3) For details concerning the biological activities of compounds of my invention, reference is made to Exhibit E-1 to E-5 hereto which I have reviewed and which to my knowledge contains the assay work of Dr. Terence Scallen

of the University of New Mexico and Dr. Robert Damon of Sandoz; and to Exhibit K-1 hereto, which I have reviewed and which to my knowledge contains the in vivo data obtained by Mr. Robert Engstrom of Sandoz.

A. FIRST ACTUAL REDUCTION TO PRACTICE PRIOR TO AUGUST 20, 1987

(1) Synthesis of Compound 63-366

On or before May 31, 1984, I began to reduce my invention to practice.

On or before November 15, 1984, I synthesized compound 1079-111-19 (subsequently redesignated compound 63-366, comprising an erythro racemate), a compound within the scope of my invention.

In accordance with standard company procedures, I recorded my laboratory activities relating to the preparation of compounds of the invention in a laboratory notebook. It was my practice to sign and date each notebook page on the same day the work described on the page was performed.

Exhibits B-1 and B-2 hereto comprise true copies of my laboratory notebook pages, which include copies of NMR spectra for the final product synthesized, as well as the intermediates. (On some of the notebook pages, micro-

analysis data were affixed to the laboratory notebook page subsequent to the date the actual synthesis was performed.)

Detailed Description of Laboratory Notebook Pages

i. Designation of Compounds:

Intermediates and final compounds are referred to in the notebooks by a three part number. The first number is the notebook number, the second is the page of the notebook where the compound appears, and the third number is the line of the page. Thus, compound 1049-237-19 is the entity appearing in Laboratory Notebook 1049, page 237, line 19.

ii. Spectra, Microanalyses and TLC:

The spectra and microanalyses were not performed by me, but were performed by an employee of the Physical Organic Chemistry Department of Sandoz Pharmaceuticals Corporation.

Procedures used to obtain these spectra and microanalyses are detailed in Section V below. Reference is also made to Exhibits C-2, C-3, D-2, G-1, G-2 and H-1 hereto which I have reviewed, and which to my knowledge reflects work performed under the supervision of Dr. S. Barcza of Sandoz.

The copies of the spectra which follow the relevant notebook pages are to my best knowledge, true copies of the results I received from the Physical Organic Chemistry Department. When I received a spectrum from the Physical Organic Chemistry Department, I would file it according to its compound number. For convenience in this Declaration, the spectra have been placed after the relevant notebook pages.

All spectra in Exhibits B-1 and B-2 bear dates prior to August 20, 1987. For microanalyses, the percentages obtained by the Physical Organic Chemistry Department were sent to me and I copied these values into my notebook pages.

All microanalyses in Exhibits B-1 and B-2 were performed prior to August 20, 1987.

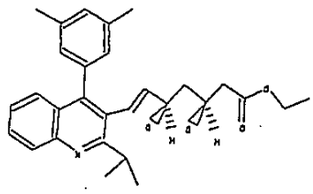
Thin Layer Chromatography (TLC) was performed by me. The entries in the laboratory notebook pages are my drawings of the results I obtained. All the TLCs in Exhibits B-1 and B-2 were performed by me or under my supervision and were recorded in my notebooks prior to August 20, 1987.

Additionally, Section VI. below describes the Sandoz procedure for assigning company numbers to compounds, which I followed; and Section VII. describes the procedures used for determining biological activity of the compounds of the invention.

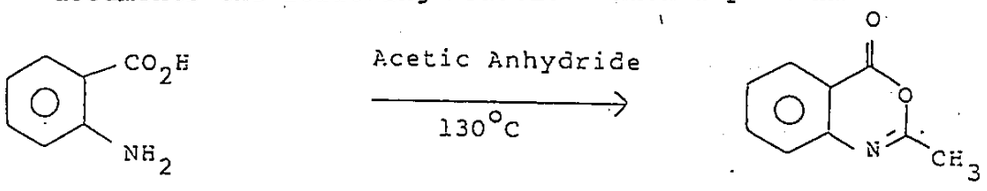
EXHIBIT B-1

Exhibit B-1 comprises true copies of my Laboratory Notebook #1049, pages 237, 241, 248, 251 and Laboratory Notebook #1079, pages 22, 24, 27, 30, 33, 34, 39, 105, 106, 110 and 111 along with copies of spectra, and microanalysis data corresponding to the intermediate and final products.

These pages show the synthesis of the following compound, which was given the designation 63-366:



Notebook #1049, page 237 contains my signature and the date of May 29, 1984 in my handwriting. This page documents the following reaction which I performed.

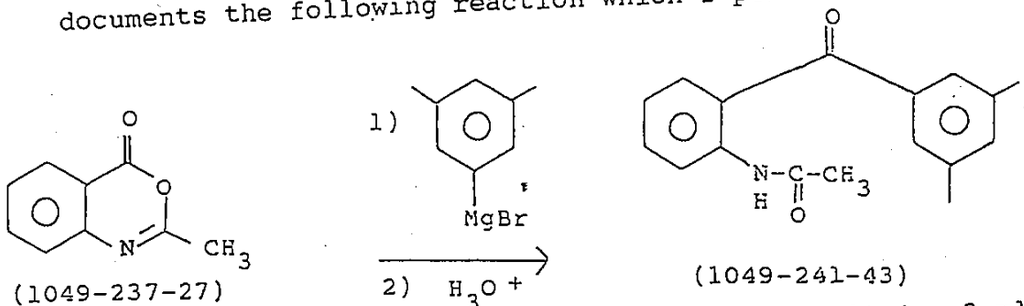


(1049-237-27)

A mixture of 10 g anthranilic acid and 54 ml acetic anhydride was heated at 130°C for 30 minutes at 12:00 P.M.

Then, approximately 30 ml of the acetic anhydride was removed. The residue was cooled to give a yellow solid. Recrystallization from acetic anhydride gave 8.9 g of a pale yellow solid, designated 1049-237-19. 1049-237-19 was dissolved in ether and filtered through a pad of silica gel. Evaporation gave 7.0 g of a colorless solid, melting point 76-78°C, designated 1049-237-27. NMR, IR, and microanalysis were performed on 1049-237-27. The spectra follow page 237, and the results of the microanalysis is reported on page 237. The spectra and microanalysis were judged by me to be consistent with the desired product.

Notebook #1049, page 241 contains my signature and the date of May 31, 1984 in my handwriting. This page documents the following reaction which I performed:



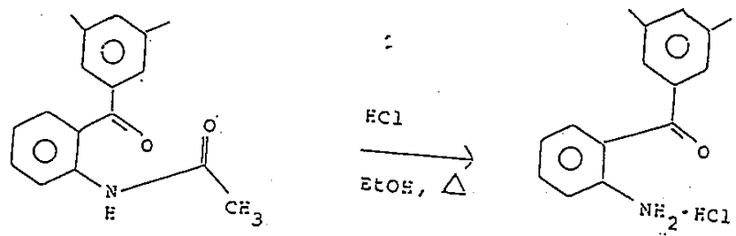
(1049-237-27) (1049-241-43)

To a suspension of 446 mg Mg (0.0186 mol) in 2 ml ether and a few drops of I_2 at room temperature was added a few drops of 1,2-dibromoethane, followed by a solution of 3.44 g (0.0186 mol) 5-bromo-m-xylene in 8 ml ether dropwise (at a rate such that the reaction mixture refluxed gently). This began at 9:05 A.M. and continued until 9:45 A.M. The reaction mixture was then heated at

reflux for 3 hours. Then the Grignard reagent was withdrawn by syringe (approximately 8 ml) and added to a solution of 2 g 1049-237-27 (0.0124 mol) in 10 ml benzene and 2 ml ether dropwise (via a funnel).

The next morning, the reaction mixture was quenched with 3N HCl and extracted with EtOAc and evaporated to give a 3.6 g of a yellow oil, designated 1049-241-31. Preparative TLC of 300 mg of 1049-241-31 gave two products: (a) 128 mg of a colorless oil, designated 1049-241-34; and (b) 24 mg of a white solid designated 1049-241-37. HPLC of the 1049-241-31 gave 1.6 g of a product, designated 1049-241-43. An NMR spectrum was performed on 1049-241-34 and follows Laboratory Notebook #1049, page 241. The spectra was judged by me to be consistent with the desired product.

Notebook #1049, page 248 contains my signature and the date of June 6, 1984 in my handwriting. This page documents the following reaction which I performed:

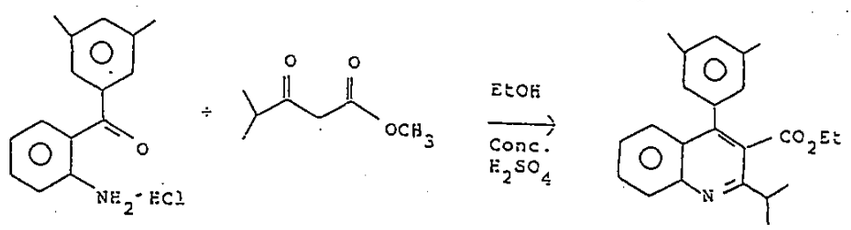


(1049-241-43) (1049-248-24)

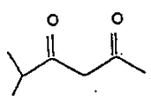
A solution containing 1.6 g of 1049-241-43, 20 ml ethyl alcohol, and 0.5 ml concentrated HCl was heated at 90°C. This began at 8:50 AM and lasted until 4:00 P.M. A TLC showed that there was a very small amount of starting material remaining. The solution was concentrated and the

residue was extracted in ether and filtered to give 1.15 g of a pale yellow solid, which was designated 1049-248-24.

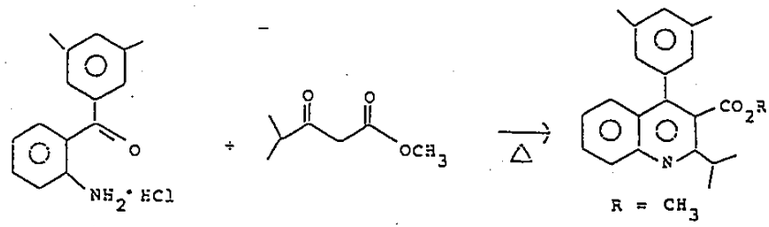
Notebook #1049, page 251 contains my signature and the date of June 8, 1984 in my handwriting. This page documents the following reaction which I performed:



(1049-248-24) (1049-251-29)

500 mg (0.001912 mol) of 1049-248-24, 412 mg of  , 20 ml of ethyl alcohol, and 0.1 ml concentrated HCl were reacted according to the same procedure as set forth in Notebook #1049, page 245 (which is set forth below). The reaction was started at 8:50 A.M. and continued until 12:30 P.M. The product was concentrated, basified with NH_4OH, diluted with H_2O, extracted with ether and evaporated to give 720 mg of an oil. A preparative TLC using 20% ether-petroleum ether showed one main band. The yield was 565 mg which upon standing in the refrigerator solidified into a pale yellow solid with a melting point of 82-83°C, which was designated 1049-251-29. Microanalysis was performed on 1049-251-29 and the results were recorded on page 251. The results of the microanalysis were judged by me to be consistent with the desired product.

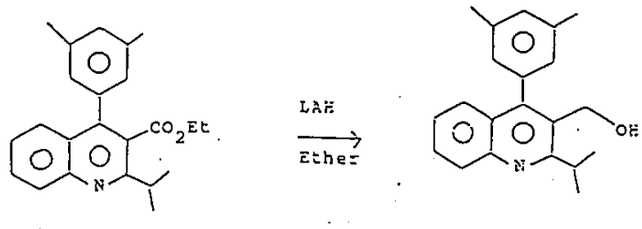
Notebook #1049, page 245, contains my signature and the date of June 5, 1984 in my handwriting. This page documents the following reaction which I performed:



(1049-244-24) (1049-245-23)

The compound on the far left side of the above equation was synthesized and designated 1049-244-24. A solution containing 20 mg of 1049-244-24 (0.0000766 mol), 11 mg (0.000011 mol) of methyl 4-methyl-3-oxopentanoate , 2 ml ethyl alcohol and 1 drop of concentrated H_2SO_4 was heated at reflux. This started at 9:30 A.M. and continued until 5:00 P.M. The product was concentrated, basified with NH_4OH and extracted with ether. The crude oil so obtained was purified by preparative TLC (1:1 ether/petroleum ether) and evaporated to give 17 mg of a colorless oil, designated 1049-245-23. A NMR spectrum was run on 1049-245-23 and follows Laboratory Notebook #1049, page 245. The spectrum was judged by me to be consistent with the desired product.

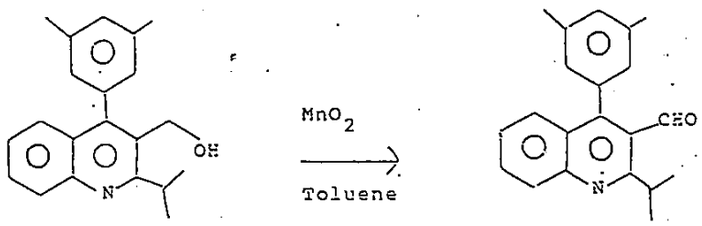
Notebook #1079, page 22 contains my signature and a date of August 10, 1984 in my handwriting. This page documents the following reaction which I performed:



(1049-251-29) (1079-22-28)

To a solution of 535 mg (0.00154 mol) of 1049-251-29 in 8 ml dry ether at room temperature was added 117 mg (0.0091 mol) LAH (lithium aluminum hydride) portion-wise. The mixture was stirred at room temperature and TLC was performed to check the progress of the reaction. The reaction began at 9:15 A.M. and was stopped at 10:15 A.M. when TLC showed that the reaction was complete. The reaction was quenched by pouring into cold water. The product was extracted with ether and evaporated. It solidified upon standing to give 427 mg of a colorless solid with a melting point of 115-118°C, designated 1079-22-28. The IR spectrum of 1079-22-28 was run and the results follow Laboratory Notebook #1074, page 22. The spectrum was judged by me to be consistent with the desired product.

Notebook #1079, page 24 contains my signature and a date of August 10, 1984 in my handwriting. This page documents the following reaction which I performed:

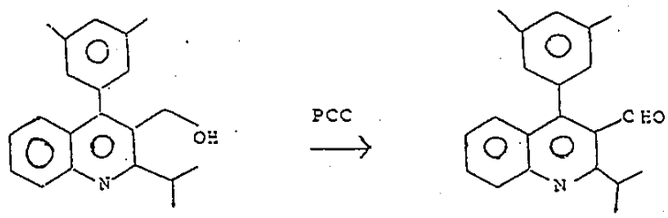


(1079-22-28) (1079-24-24)

A mixture of 420 mg of compound 1079-22-28 and 500 mg of MnO_2 in 6 ml toluene was stirred at room temperature. TLC was performed after 2 days to monitor the progress of

the reaction. The mixture was diluted with ether and filtered through a pad of silica gel. Upon evaporation, a pale yellow solid was obtained, designated 1079-24-24. An NMR spectrum of 1079-24-24 and the results following page 24 indicated that no reaction occurred. A TLC showed that mainly starting material was present, so the crude product, 1079-24-24 was used directly in the reaction set forth below.

Notebook #1079, page 27 contains my signature and the date of August 14, 1984 in my handwriting. This page documents the following reaction which I performed.



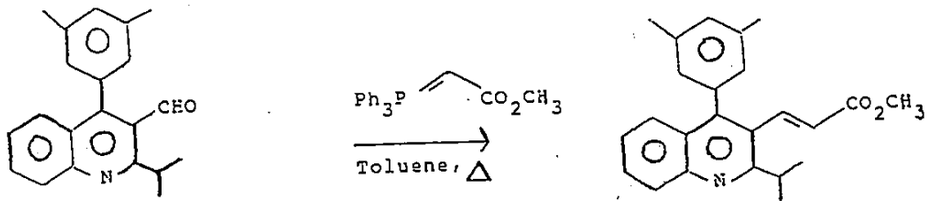
(1079-24-24) (1079-27-25)

382 mg of 1079-24-24, 400 mg DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) and 4 ml toluene are stirred at room temperature overnight. The reaction mixture (a dark red color) was diluted with ether and filtered through a pad of silica gel. Evaporation resulted in a dark red foam gum. TLC indicated no reaction had occurred.

The above gum was dissolved in 10 ml CH_2Cl_2 and 400 mg PCC (pyridinium chlorochromate) and 1 g neutral alumina were added. The mixture was stirred at room temperature

for one hour. TLC showed a complete reaction. The mixture was diluted with ether and filtered through 5 g silica gel. Evaporation of the filtrate gave a pale yellow oil (137 mg) which was designated 1079-27-25. NMR and IR spectra were run on 1079-27-25 and the results follow Laboratory Notebook #1079, page 27. The spectra were judged by me to be consistent with the desired product.

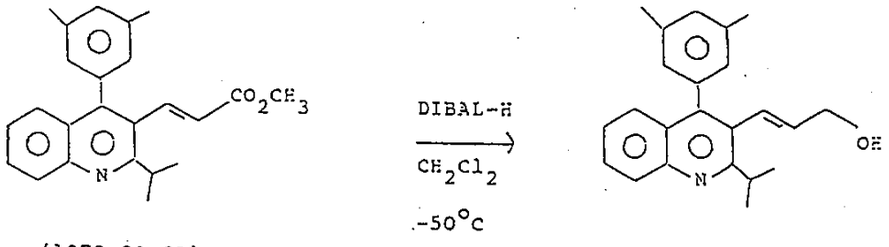
Notebook #1079, page 30 contains my signature and the date of August 17, 1984 in my handwriting. This page documents the following reaction which I performed:



(1079-27-25) (1079-30-23)

140 mg of 1079-27-25, 200 mg of methyl(triphenyl phosphoranylidene)acetate (abbreviated as Ph_3P CO_2CH_3) and 5 ml toluene were heated and refluxed for 3 hours. After cooling, the mixture was diluted with ether and filtered through a pad of silica gel. Concentration gave a semisolid which was further purified by preparative chromatography to give 140 mg of a colorless solid with a melting point of 110-112°C. The product was given the designation 1079-30-23. An NMR spectrum was performed on 1079-30-23 and the results follow Laboratory Notebook #1079, page 30. The spectrum was judged by me to be consistent with the desired product.

Notebook #1079, page 33, contains the date of August 22, 1984 in my handwriting. This page documents the following reaction which I performed:

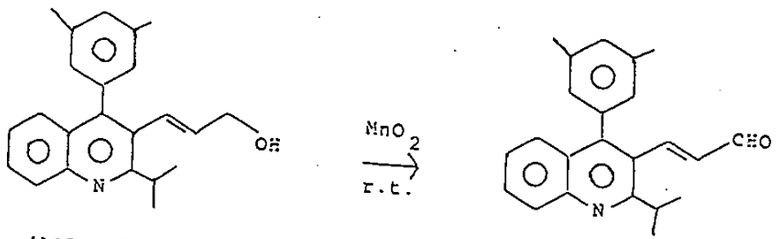


(1079-30-23) (1079-33-19)

To a solution of 130 mg (0.0003768 mol) of 1079-30-23 in 5 ml dry CH_2Cl_2 at -50°C was added 0.5 ml (0.007136 mol) of DIBAL-H. DIBAL-H is the abbreviation I use for diisobutylaluminum hydride. The mixture was stirred at -50°C for 0.5 h. TLC showed that the reaction was complete.

The reaction product was diluted with ether and filtered through a pad of silica gel. Evaporation gave 135 mg of a crude gel which was directly used in the next step. TLC of this crude oil showed only one spot. The reaction product was designated 1079-33-19.

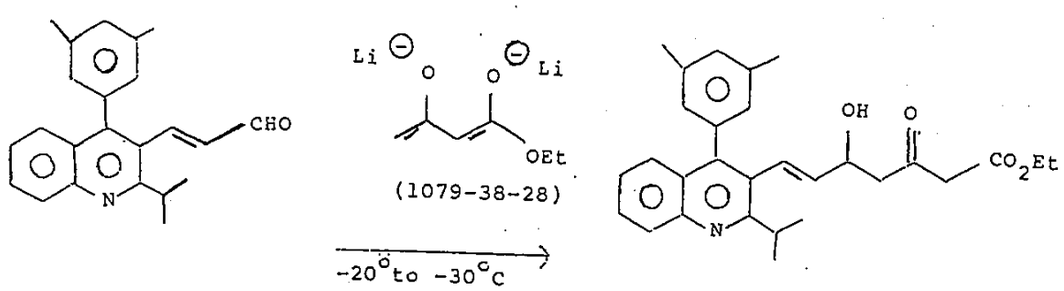
Notebook #1079, page 34 contains my signature and the date of August 23, 1984 in my handwriting. This page documents the following reaction which I performed:



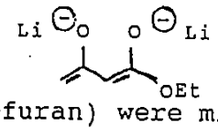
(1079-33-19) (1079-34-17)

A mixture of 135 mg of 1079-33-19 and 300 mg MnO_2 in 5 ml toluene was stirred at room temperature overnight. The result was 107 mg of a pale yellow oil which was designated 1079-34-17. An NMR spectrum was performed on 1079-34-17 and follows Laboratory Notebook #1079, page 34. The spectrum was judged by me to be consistent with the desired product.

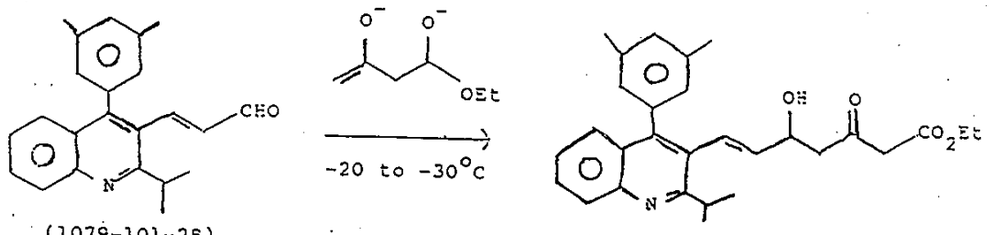
Notebook #1079, page 39 contains my signature and the date of September 5, 1984 in my handwriting. This page documents the following reaction which I performed.



(1039-34-17) (1079-38-28) (1079-39-18)

At 10:00 A.M., 100 mg of 1079-34-17 (0.0003039 mol), 5 ml of the dianion from 1079-38-28, (≃0.0014 mol) the structure of which is 
and 4 ml THF (tetrahydrofuran) were mixed. By 10:50 A.M. the reaction was complete, as evidenced by one spot on the TLC. The reaction was quenched with saturated NH_4Cl, extracted with ethyl acetate (EtOAc) and evaporated. The result was 177 mg of a yellow oil, which was designated 1079-39-18. The crude 1079-39-18 was reduced in the next step directly without further purification.

Notebook #1079, page 105 contains my signature and the date of November 8, 1984 in my handwriting. This page documents the following reaction which I performed (This is the same reaction described in Notebook #1079, page 39):



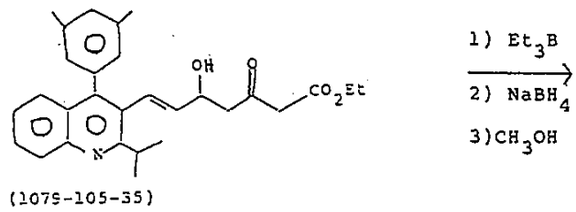
(1079-101-28) (1079-105-35)

The list of reagents on Page 105 includes 0.5 ml (0.00334 mol) diisopropylamine and 1.6 M n-BuLi (2 ml, 0.00334 mol). Upon mixing these reagents, lithium diisopropylamide would be formed, and could be used as set forth below. However, I found that the commercially available lithium diisopropylamide in cyclohexane gave equally satisfactory results compared to the lithium diisopropylamide which I synthesized. Therefore, I used the commercially available reagent.

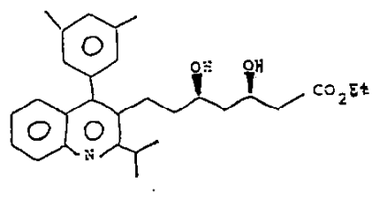
To a solution of lithium diisopropylamide (1.8M in cyclohexane, 1.8 ml) (a commercially available reagent) in THF at -25°C was added 0.22 ml ethyl acetoacetate. The resulting yellow solution was stirred at -20° to -30° for 30 minutes.

4 ml of the above solution was withdrawn by a syringe and added to a solution of 110 mg of the aldehyde designated 1079-101-28 (which was prepared as described for 1079-34-17) in 2 ml THF at -30°C. The solution was stirred at -30° to -10°C for about 20 minutes. The reaction was quenched with 2 ml of saturated NH_4Cl and extracted with EtOAc to give 290 mg of a yellow oil. Prep TLC (1:1 ether-petroleum ether) and evaporation gave 112 mg of a yellow oil, designated 1079-105-35. NMR and IR spectra were performed on this compound and the results follow Laboratory Notebook #1079, Page 105. The results of the spectra were judged by me to be consistent with the desired product.

Notebook #1079, page 106 contains my signature and the date of November 12, 1984 in my handwriting. This page documents the following reaction which I performed:



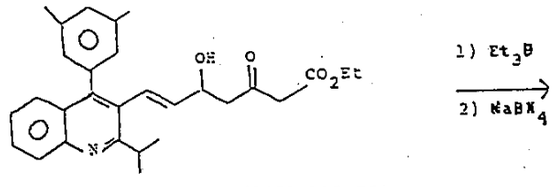
(1079-105-35)



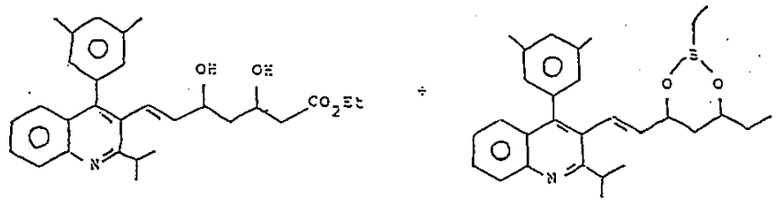
(1079-106-36)

To a solution of 55 mg 1079-105-35 in 2 ml THF at room temperature was added 1M Et_3B (0.0001437 mol) and 1 ml air (by syringe). The solution was stirred at room temperature for 1.5 hr. The solution was then cooled to -78°C and 10 mg $NaBH_4$ was added. The reaction mixture was stirred at -78°C from 10:30 A.M. until 8:30 A.M. the next morning. TLC showed the presence of starting material. 15 mg $NaBH_4$ was added and stirring was continued at -78°C. At approximately 3:20 P.M., the reaction was quenched with dilute HCl and extracted with EtOAc to obtain 50 mg of a crude product designated 1079-106-36, which was used directly in the next step. The crude product probably contained, in addition to the structure shown in the above reaction, some boron-intermediate designated infra as 1079-110-33, and some by-products of the reaction of 1079-106-36 with HCl. 1079-106-36 was believed to be the erythro racemate with the proportion of the 3R,5S isomer to be at least 85% or greater.

Notebook #1079, page 110 contains my signature and the date of November 14, 1984 in my handwriting. This page documents the following reaction which I performed, which is similar to that of Laboratory Notebook #1079, page 106:



(1079-105-35)

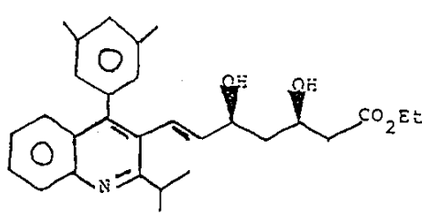


(1079-110-33)

To a solution of 50 mg 1079-105-35 in 2 ml THF at room temperature was added 0.2 ml of 1M Et_3B and 1 ml air (by syringe). The solution was stirred at room temperature from 2:30 to 3:30 P.M., then cooled to -78°C. The following day, the almost colorless reaction mixture was diluted with 4 ml CH_3OH after the cooling bath was removed. After 10 minutes, a slightly fluorescent color occurred, and 1 ml H_2O and a few drops of acetic acid was added. After the evolution of H_2 subsided, the reaction mixture was concentrated. Water was added, the mixture was extracted with ether, and evaporated. The result, 40 mg of an oil which was pale yellow and with some florescence, was designated 1079-110-33 and was used directly in the next step. The oil was believed to contain the two compounds shown, the ester was believed to be the erythro racemate, with at least approximately 85% being the 3R,5S isomer.

Notebook #1079, page 111 contains my signature and the date of November 15, 1984 in my handwriting. This page documents the following reaction which I performed:

1079-110-33 $\xrightarrow{CH_3OH}$



(1079-111-19)

A solution of 40 mg 1079-110-33 in 4 ml CH_3OH was stirred at room temperature for 3 days. TLC (1:1 ether-petroleum ether) showed one main spot of the product. Prep. TLC gave 25.6 mg of a pale yellow oil designated 1079-111-19. IR and NMR spectra were performed on 1079-111-19 and follow Laboratory Notebook, Page 111. The spectra were judged by me to be consistent with the desired product. Compound 1079-11-19 was subsequently redesignated compound 63-366. This redesignation occurred prior to December 13, 1984.

III. TESTING OF COMPOUND 63-366 FOR HMG-COA REDUCTASE INHIBITOR PRIOR TO AUGUST 20, 1987

On or before December 31, 1984, I learned the results of *in vitro* testing of compound 63-366 in an assay for HMG-CoA reductase activity.

Page 111 of my laboratory notebook indicates that on or before November 26, 1984, 14.5 mg of compound 63-366 were sent to Dr. Terence Scallen of the University of New Mexico for testing in his *in vitro* microsomal assay for HMG-CoA reductase inhibition activity.

Compound 63-366 was shown by Drs. Scallen and Damon to inhibit HMG-CoA reductase activity by having an IC_{50} of 1.58.

Having reviewed Exhibit E-5 hereto, my best recollection is that Dr. Damon of Sandoz informed me of this activity either orally or by sending me a copy of the computer printout included in Exhibit E-5 on or before December 31, 1984.

Thus on or before December 31, 1984, I knew that 63-366 had activity in an assay for HMG-CoA reductase activity.

Furthermore, it was my judgment on or before December 31, 1984 that it was likely that said compound 63-366 would have activity in vivo as an HMG-CoA reductase inhibitor, and therefore would have activity when administered to a patient to treat atherosclerosis and other conditions resulting from excessive cholesterol biosynthesis.

By way of background, since prior to December 31, 1984, I had been receiving from Dr. Damon the IC_{50} data he calculated from Dr. Scallen's assays for various other Sandoz compounds being investigated for HMG-CoA reductase inhibitor activity besides the quinoline compounds of my invention.

These other compounds have the same 3,5-dihydroxy heptenoic acid, ester, or salt side chain, or alternatively, lactone form, as the quinoline compounds of my invention. However, these compounds differ by having an organic radical substituent other than a quinoline.

For example, Sandoz compounds containing a substituted napthyl or indole radical, were tested at approximately the same time as compound 63-366, as shown on Exhibit E-5, hereto.

Additionally, on or before December 31, 1984, I knew the IC_{50} values for the compound Mevastatin (Compactin) which was a known HMG-CoA reductase inhibitor for administration to a patient to treat hypercholesterolemia or atherosclerosis. These values were obtained from data generated by Dr. Scallen in the same assays as used to test the quinoline compounds of my invention. (See Exhibit E-5 hereto).

Also, on or before December 31, 1984, I was knew the IC_{50} values for Sandoz compound 62-320/Na (fluvastatin sodium) (see Exhibit E-5), which I knew to be very active in vivo.

Further, on or prior to December 31, 1984, I further knew that there was typically a high correlation between *in vitro* activity and *in vivo* activity of Sandoz compounds which had been tested.

Based on my knowledge and experience, it was my judgment since on or prior to December 31, 1984, that Wattanasin compound 63-366 would have activity when administered *in vivo* to a patient for the treatment of hypercholesteremia or atherosclerosis, and would have activity when administered to a human patient in in a dosage amount recited in my specification at page 35.

It was also my judgment upon receiving the IC_{50} data for each of compounds 63-548, 63-549, 64-933, 64-934/Na, 63-935, and 64-936/Na (0.53), that the quinoline compounds of my invention would have activity as an HMG-CoA reductase inhibitor when administered to a patient, and when administered to a human patient within the dosage amounts taught in my application.

IV. CONTINUING EXPERIMENTAL ACTIVITY UNDER MY SUPERVISION PRIOR TO AND AFTER AUGUST 20, 1987

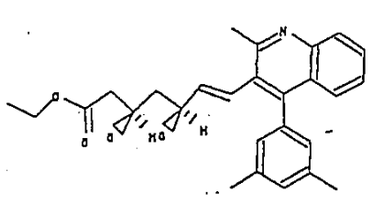
(1) Compounds 53-548 and 53-549

Prior to August 20, 1987, I synthesized compounds 63-548 and 63-549 of the invention.

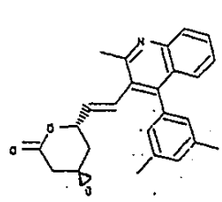
EXHIBIT B-2

Exhibit B-2 comprises true copies of my Laboratory Notebook #1127, pages 5, 9, and 11 along with copies of spectra corresponding to the intermediate and final products. These pages show the synthesis of compounds 63-548 and 63-549. 63-548 is a racemic mixture, with at least 95% being the 3R,5S isomer. Similarly, 63-549 is also a racemic mixture with at least 95% being the 4R,6S isomer. The structures of these compounds are as follows:

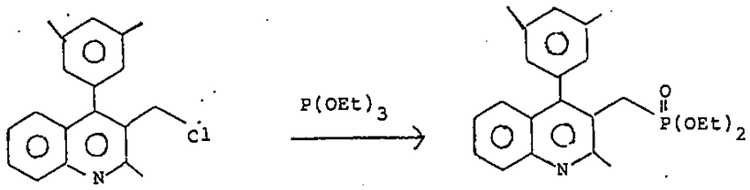
63548



63549



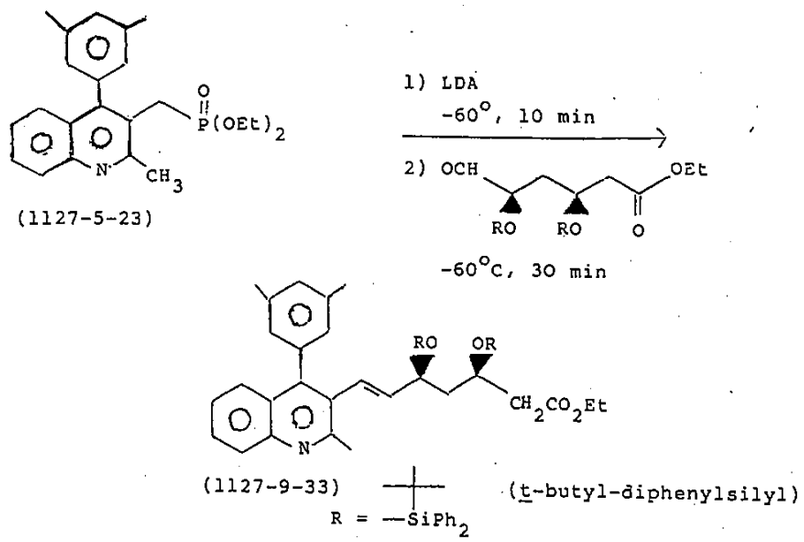
Notebook #1127, page 5 contains my signature and the date of May 2, 1985 in my handwriting. This page documents the following reaction which I performed.



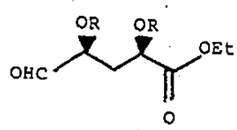
(1079-296-35) (1127-5-23)

The compound on the left was synthesized by me and given the designation 1079-296-35. A mixture of 1079-296-35 (150 mg) and triethyl phosphite (0.3 ml) in toluene (2 ml) was heated at reflux for approximately 2 hrs. TLC indicated no reaction had occurred. An additional 0.5 ml of triethyl phosphite was added. The reaction was heated at 100°C for 20 hrs. TLC showed a complete reaction. Concentration by distillation at reduced pressure gave 160 mg of an oil which solidified on standing to an almost colorless solid, designated 1127-5-23. Melting point was 105-107° C. NMR and IR spectra were performed on 1127-5-23 and the results follow Laboratory Notebook #1127, page 5. The spectra were judged by me to be consistent with the desired product.

Notebook #1127, page 9 contains my signature and the date of May 6, 1985 in my handwriting. This page documents the following reaction which I performed:



To a solution of 150 mg (0.0003778 mol) of 1127-5-23 in 3 ml THF (tetrahydrofuran) at -55°C was added 0.27 ml (1.2 equivalents) of 1.7 M LDA (lithium diisopropyl amide) in cyclohexanes. The resulting dark orange solution was then stirred at -55°C to -60°C for 10 minutes, from 9:50 A.M. to 10:00 A.M.

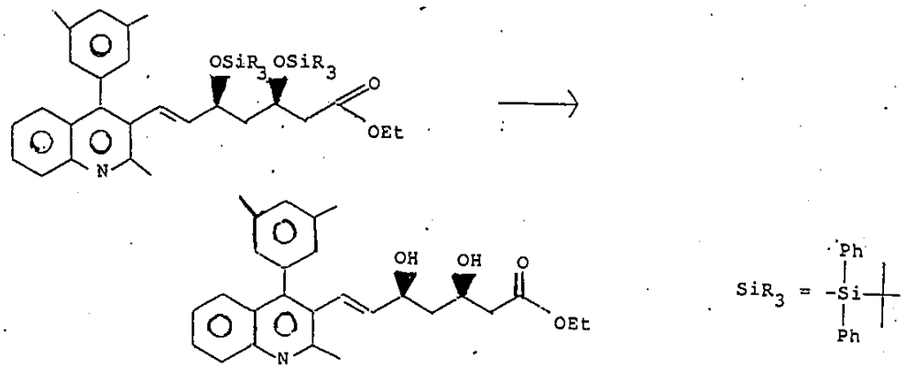
The aldehyde having the structure 

where R=  $-SiPh_2$

is termed the "Prasad aldehyde", referring to another chemist at Sandoz, Dr. Prasad Kapa, who made this molecule.

A solution containing 293 mg (0.0004534 mol) of the aldehyde and 2 ml THF is added to the above dark orange solution. A TLC performed after 20 minutes indicated that there was mainly one product formed. After 30 minutes, the reaction was quenched at -60°C with 0.5 ml acetic acid. Then, dilute HCl and H_2O were added, the solution was extracted with EtOAc, and evaporated to yield 500 mg of a yellow oil, designated 1127-9-30. A preparative TLC (1:1 ether/petroleum ether) gave 100 mg of a yellow oil designated 1127-9-33. A NMR was performed on 1127-9-33 and the results follow Laboratory Notebook #127, page 9. The spectrum was judged to be consistent with the desired product.

Notebook #1127, page 11 contains my signature and the date of May 7, 1985 in my handwriting. This page documents the following reaction which I performed:



A mixture of 90 mg (0.0001012 mol) 1127-9-33, 0.61 ml (0.000607 mol) 1M Bu_4NF (tetra-n-butylammonium fluoride) in THF, 0.03 ml (0.0005 mol) HOAc, and 2 ml THF was stirred at room temperature. This began at 9:00 A.M. and a TLC was performed the next morning at 9:00, which indicated that the reaction was not complete. Additional 0.6 ml in Bu_4NF and 0.02 ml of HOAc were added. A second TLC run five days later at 8:30 A.M. indicated that there was a mixture of starting materials and product. The solution was heated at 9:00 A.M. to 50°C to 60°C. A TLC at 11:00 A.M. still showed a mixture of spots. The reaction was stopped at 5:30 P.M. The reaction product was concentrated and the crude oil was purified by a preparative TLC (using ether/HOAc). Two products were obtained; (a) 10 mg of a colorless oil designated 1127-11-34 and (b) 10 mg of an oil designated 1127-11-37. IR and NMR spectra were performed on both of 1127-11-34 and 1127-11-37. The spectra follow Laboratory Notebook #1127, page 11. The spectra were judged by me to be consistent with the desired products.

Compound 1127-11-34 was subsequently renumbered 63-548 and Compound 1127-11-37 was subsequently renumbered 63-549; the renumbering of both compounds occurred on or before March 20, 1985.

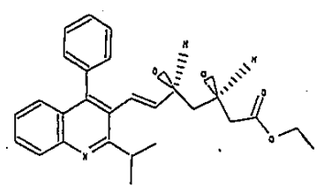
On or prior to May 17, 1985, I sent compounds 63-548 and 63-549 to Dr. Scallen for testing in his in vitro microsomal assay for HMG-CoA reductase inhibition activity. Both compounds were shown by Drs. Scallen and Damon to possess inhibitory activity. Having reviewed Exhibit E-5 hereto, my best recollection is that I learned of the activity of compounds 63-548 and 63-548 from Dr. Damon on or before June 30, 1985.

Based on the in vitro data, it was also my judgment on or before June 30, 1985 that it would be likely that the quinoline compounds of my invention would have activity in vivo as an HMG-CoA reductase inhibitor, and therefore would have activity when administered to a patient to treat atherosclerosis and other conditions resulting from excessive cholesterol biosynthesis.

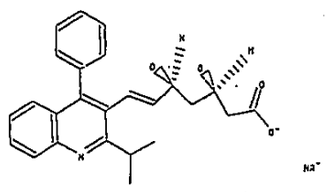
(2) Synthesis of Compounds 64-933, 64-934/Na, 64-935 and 64-936/Na:

Compounds 64-933 and 64-934/Na were synthesized under my direction by Rajeshvari Patel prior to August 20, 1987. These compounds have the following structures:

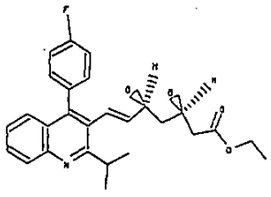
64933



64934



64935



64936

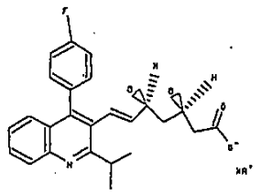


EXHIBIT F-1

Exhibit F-1 comprises pages 130, 137, 145, 153, 158, 166, 172, 175, 176 and 179 of Laboratory Notebook #1206 of Rajeshvari Patel. Each of these pages (except page 179) bear my true signature as a witness.

I witnessed the work performed by Rajeshvari Patel on the pages which I signed. I read and understood the above-numbered laboratory pages which I signed.

Exhibit F-1 indicates that the synthesis of compounds 64-933 and 64-934/Na was commenced on or before June 1, 1987 and was completed on or before August 5, 1987. This is consistent with my general recollection.

I have also reviewed pages 190 and 201 of notebook #1206, which also comprise Exhibit F-1, and Exhibit L-1, hereto. These show the synthesis of compounds 64-935 and 64-936/Na. These pages indicate that the final steps of the synthesis commenced on or prior to August 10, 1987, and it was completed by September 1, 1987. Although I did not perform the work performed on these pages, this time period is consistent with my general recollection as the laboratory supervisor of Rajeshvari Patel.

Testing of Compounds 64-933, 64-934/Na, 64-935 and 64-936/Na

I learned the results of testing of compounds 64-933, 64-934/Na, 64-935 and 64-936/Na in an in vitro asssay for HMG-CoA reductase activity.

Compounds 64-933, 64-934/Na, 64-935, and 64-936/Na were sent to Dr. Scallen for testing in his in vitro microsomal assay for HMG-CoA reductase inhibition activity. They were shown by Dr. Scallen to possess inhibitory activity.

Having reviewed Exhibit E-5 hereto, my best recollection is that Dr. Damon of Sandoz informed me of this activity either orally or by sending me a copy of the computer printout included in Exhibit E-5 on or before October 31, 1987.

Based on the in vitro data, it was my judgment on or before October 31, 1987 that it was likely that the quinoline compounds of my invention would have activity in vivo as HMG-CoA reductase inhibitors, and therefore would have activity when administered to a patient to treat atherosclerosis and other conditions resulting from excessive cholesterol biosynthesis, and would have activity when administered to a human patient under the dosage conditions recited in my patent application.

I have also reviewed Exhibit K-1 hereto, which contains rat cholesterol biosynthesis data for compounds 64-933, 64-935 and 64-936/Na which were tested by Robert Engstrom. I believe I learned of this data on or before December 9, 1987. This data indicate that the quinoline compounds of my invention would have activity as an HMG-CoA reductase inhibitor when administered to a patient for treatment of hypercholesteremia or atherosclerosis.

V: PROCEDURES FOR OBTAINING SPECTRA AND MICROANALYSES AND MAINTENANCE OF RESULTS

All IR and NMR spectra as well as microanalyses are performed by the Sandoz Physical Organic Chemistry Department. The Department has developed procedures to follow when submitting samples of materials which are to be analyzed. These procedures, described below, were in place prior to and after August 20, 1987, including the time periods referred to herein, and these are the procedures which I followed when I submitted samples of compounds which I made for analysis. For details concerning procedures of the Physical Organic Chemistry Department, reference is made to the work of Dr. Sandor Barcza of Sandoz.

Approximately 1 to 20 mg of the sample was placed in a vial and the vial was labeled with the three-part numerical designation used in the notebooks. A Request Sheet was filled out in duplicate by me or under my supervision, on which it was indicated, among other things, the type of analyses I wished to have performed, and the sample number of the vial.

Exhibit C-1 comprises a copy of a blank Request Sheet.

Upon receipt of the form and sample, the Physical Organic Chemistry Department notes the date of receipt on the form, and assigns its own number to each spectrum run.

This procedure was followed prior to and after August 20, 1987 for each of compounds 64-366, 63-548, 63-549, 64-933, 64-934/Na, 64-935 and 64-936/Na.

Exhibit C-2 comprises true copies of the Sandoz Physical Organic Chemistry Department's Request Sheets for spectra and/or microanalysis before and after the sheets were received and the compounds were assigned a spectrum number. (For the compounds synthesized in Exhibits B-1 and B-2, I was the Requestor. For the compounds synthesized in Exhibits F-1 and L-1, M. Patel is listed as the Requestor.)

Exhibits B-1 and **B-2** contain copies of the spectra for the compounds of the invention which I received from the Physical Organic Chemistry Department.

VI. PROCEDURE FOR ASSIGNING COMPANY NUMBERS TO COMPOUNDS

When an end product has been made, an official company number is assigned to the compound and information concerning the compound is entered into the company's computerized database. There is an established procedure in effect for this, both prior to and after August 20, 1987, including the time periods referred to herein, which I followed.

I filled out a "Chemical Information" form for each end product which included such information as the chemical structure, molecular weight, empirical formula, and synthesis procedure as well as the three part number used in the notebook.

Exhibit D-1 comprises a blank "Chemical Information" form.

This form is sent to the Drug Room, which is part of the Sandoz Physical Organic Chemistry Department. Upon receipt of this form, the Drug Room personnel assign the compound a number.

Exhibit D-2 comprises copies of forms submitted by me or under my supervision to the Drug Room for the compounds of the invention. I note that the page for compounds 63-548 and 63-549 bears a date of May 15, 1985 in my handwriting.

Exhibit D-3 comprises a copy of the information which is assembled by the Drug Room personnel and made accessible on the computer database. The "SAH" number is the official compound number. The large type number in the second box in the left column is the internal registry number. The three-part number in the third box in the left column is the notebook, page, and line number. The two-part number in the fourth box in the left column is the number of the patent disclosure which covers the compound.

VI. PROCEDURES FOR DETERMINING BIOLOGICAL ACTIVITY

Sandoz has an established procedure for determining whether end products possess biological activity of interest, e.g. HMG-CoA reductase inhibitor activity which would indicate that they inhibit the biosynthesis of cholesterol and are useful in the treatment of atherosclerosis and other related diseases in a patient.

These procedures were in place prior to and after August 20, 1987, including the time periods referred to herein, and these were the procedures which were followed in determining whether the compounds I invented had such activity.

After the official company number has been assigned to an end product, the compound is tested for biological activity. The Physical -Organic Chemistry Department submits the sample of the compounds for biological testing. Some tests are performed in-house; others are performed outside the company. The in vitro testing of my compounds was done by a person who is not employed by Sandoz, Professor Terence Scallen, Department of Biochemistry, School of Medicine, University of New Mexico, Albuquerque, New Mexico 87131.

Dr. Scallen reported his results to Dr. Robert E. Damon at Sandoz. Upon receipt of the reports, Dr. Damon would draw the chemical structure of each test compound on

the report, and calculate the IC_{50} value of each test compound and would write this on the report. Dr. Damon then sent copies of these reports to researchers involved in the project.

Exhibit E-5 comprises true copies of Dr. Scallen's reports which I received, with what I believe to be Dr. Damon's handwritten structures and IC_{50} values, for compounds 63-366, 63-548, 63-549, 64-933, 64-934/Na, 64-935 and 64-936/Na.

. . .

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 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 13th day of November, 1992.

Sompong Wattanasin

SOMPONG WATTANASIN, Ph.D

BARCZA

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 SANDOR BARCZA PURSUANT TO 37 CFR §1.672

I, Sandor Barcza, Ph.D., do hereby declare as follows:

(1) That I am employed by Sandoz Pharmaceuticals Corporation. My position, both prior to August 20, 1987 and during the time periods thereafter which are referred to herein, was Director of the Department of Physical Organic Chemistry.

(2) That all activities referred to in this Declaration took place in the United States, under my supervision.

(3) That it was the responsibility of personnel working under my supervision to perform various analyses of samples prepared by Sandoz chemists, including the determination or confirmation of chemical structure and purity.

(4) That individuals working under my direction initialed and dated the pages of the IR and NMR spectra which they personally recorded. I have reviewed B-1, B-2 and F-1 hereto, and in my best recollection, the following initials are those of the following named individuals.

S.D.: Susan DiCataldo; Karl G.: Karl Gunderson; MXK: Michael X. Kolpak; F.M.: Frances McCrink; J.B.: (?); none of whom are now employed by Sandoz.

M.J.S.: Michael J. Shapiro, Fellow, Senior Scientific Staff, and head of the NMR laboratory.

Exhibits B-1, B-2 and F-1 contain true copies of IR and Spectra generated by the Physical Organic Chemistry Department under my supervision.

I. ANALYSIS OF WATTANASIN COMPOUNDS

Sandoz has established procedures which researchers must follow in order for my department to perform various analyses of compounds and mixtures. These procedures are outlined below and were company policy at the time when the samples of Exhibits B-1, B-2, and F-1 were analyzed, i.e., prior to August 20, 1987 and during the other time periods referred to herein.

When a scientist wants to have material analyzed, he completes a Request Sheet.

General Description of Exhibits C-1, C-2, C-3; D-2; G-1, G-2 and H-1

Exhibit C-1 comprises a blank Request Sheet, and is the same as that used during the time that the compounds of this patent application were analyzed, i.e., prior to

August 20, 1987 and during the other time periods referred to herein. Referring to Exhibit C-1, there are areas on the Request Sheet where the type of analysis can be requested, including IR spectrum, NMR spectrum, and microanalysis. Also, there is a space on the Request Sheet where the compound is identified by reference to its notebook number, page number and line number. In addition to filling out the form, the scientist provides a sample of the material in a vial which is also labeled with the notebook number, page number, and line number. The personnel who actually perform the analyses rely on the notebook number-page number-line number designation for identification of the sample, and then assign their own number to the analysis (spectrum).

Exhibit C-2 comprises true copies of the Physical Organic Chemistry Department's copies of Request Sheets for IR spectra.

Upon receipt of a completed Request Sheet and its accompanying sample, the Optical Spectroscopy Laboratory (Infra Red) Laboratory records each request in a laboratory logbook. The Infra Red Laboratory's logbook is kept in a three ring binder. Each sample is treated as a separate entry and is entered sequentially, into two sequential lines.

Exhibit C-3 comprises copies of the Physical Organic Chemistry Department's copies of Request Sheets for NMR spectra.

Exhibit D-2 comprises completed copies of Chemical Information forms for compounds of the invention.

Exhibit G-1 comprises copies from the Infra Red Laboratory's logbook.

Exhibit G-2 contains copies of the Microanalysis Laboratory logbook.

Exhibit H-1 comprises copies of printouts of entries of the computer database. The dates are the dates on which the structures and data were entered.

To my knowledge, the papers which comprise these Exhibits are true copies.

Compounds 63-366, 63-548, 63-549, 64-934/Na, 64-935 and 64-936/Na

The spectra of compounds 63-366, 63-548, 63-549, 64-934/Na, 64-935 and 64-936/Na were recorded under my supervision. The above-listed exhibits show the following:

Exhibit G-1 documents receipt of the Wattanasin compounds by the Infra Red Laboratory on the following dates:

Compounds from Exhibit B-1

Line 1377:	receipt of compound 1049-237-27 on	5/31/84
Line 2009:	receipt of compound 1079-22-28 on	8/10/84
Line 2029:	receipt of compound 1079-27-25 on	8/14/84
Line 2514:	receipt of compound 1079-105-35 on	11/ 9/84
Line 2589:	receipt of compound 1079-111-19 on	11/21/84

Compounds from Exhibit B-2

Line 1012: receipt of compound 1127-5-23 on 5/ 6/85
Line 1094: receipt of compound 1127-11-34 on 5/17/85
Line 1095: receipt of compound 1127-11-37 on 5/17/85

Compounds from Exhibit F-1

Line 899: receipt of compound 1206-130-27 on 7/ 5/87
Line 922: receipt of compound 1206-137-31 on 7/12/87
Line 1007: receipt of compound 1206-153-34 on 7/16/87
Line 1037: receipt of compound 1206-158-41 on 7/21/87
Line 1052: receipt of compound 1206-175-4 on 7/23/87
Line 1084: receipt of compound 1206-166-30 on 7/30/87
Line 1087: receipt of compound 1206-176-41 on 7/30/87
Line 1093: receipt of compound 1206-179-30 on 7/31/87

The line number of the logbook becomes the assigned spectrum number. The spectrum number is written on the request sheet in the box on the right side marked "do not fill in" by the person who would be running the spectrum, along with that person's initials.

Exhibit C-2 contains the assigned numbers for the compounds:

Compounds from Exhibit B-1:

1049-237-27, assigned spectrum number 1377
1079-22-28, assigned spectrum number 2009
1079-27-25, assigned spectrum number 2029
1079-105-35, assigned spectrum number 2514
1079-111-19, assigned spectrum number 2589

Compounds from Exhibit B-2:

1127-5-23, assigned spectrum number 1012
1127-11-34, assigned spectrum number 1094
1127-11-37, assigned spectrum number 1095

Compounds from Exhibit F-1

1206-130-27, assigned spectrum number 899
1206-137-31, assigned spectrum number 922
1206-153-34, assigned spectrum number 1007
1206-158-41, assigned spectrum number 1037
1206-186-30, assigned spectrum number 1084
1206-175-4, assigned spectrum number 1052
1206-176-41, assigned spectrum number 1087
1206-179-30, assigned spectrum number 1085
1206-179-30, assigned spectrum number 1093

The NMR Laboratory assigns spectra numbers in the following manner: Upon receipt of a Request Sheet and accompanying sample, the request sheet is stamped "Received" with an automatic stamper which dates the request sheet and assigns it a number in sequential order.

Exhibit C-3 contain the assigned spectrum number in the box marked "do not fill in.":

Compounds from Exhibit B-1
1049-237-27, : spectrum number 4716 received on 5/30/84
1049-241-34, : spectrum number 4751 received on 6/ 1/84
1079- 22-28, : spectrum number 6255 received on 8/13/84
1079- 27-25, : spectrum number 6288 received on 8/14/84
1079- 30-23, : spectrum number 6404 received on 8/22/84
1079- 34-17, : spectrum number 6597 received on 9/ 5/84

Compounds from Exhibit B-2
1127- 5-23, : spectrum number 2517 received on 5/ 6/85
1127- 9-33, : spectrum number 2538 received on 5/ 7/85
1127- 11-34, : spectrum number 2683 received on 5/14/85
1127- 11-37, : spectrum number 2686 received on 5/14/85

Compounds from Exhibit F-1

1206-130-27:	spectrum number	3256	received on 6/ 5/87
1206-137-31:	spectrum number	3326	received on 6/12/87
1206-145-25:	spectrum number	3450	received on 6/19/87
1206-145-26:	spectrum number	3451	received on 6/19/87
1206-153-31:	spectrum number	3596	received on 7/ 2/87
1206-153-37:	spectrum number	3615	received on 7/ 7/87
1206-158-41:	spectrum number	3677	received on 7/10/87
1206-166-30:	spectrum number	3793	received on 7/16/87
1206-175- 4:	spectrum number	3874	received on 7/22/87
1206-176-41:	spectrum number	3934	received on 7/27/87
1206-176-43:	spectrum number	3933	received on 7/27/87

Exhibit G-2 contains copies of the Microanalysis Laboratory's logbook containing the sample numbers listed below. Each sample is entered on one line in a sequential manner and the line number becomes the analysis number:

Compounds from Exhibit F-1:

Line 518:	receipt of compound	1206-153-31	on 7/ 9/87
Line 524:	receipt of compound	1206-158-41	on 7/15/87
Line 545:	receipt of compound	1206-175- 4	on 7/23/87
Line 560:	receipt of compound	1206-166-30	on 7/28/87
Line 563:	receipt of compound	1206-179-30	on 7/29/87
Line 634:	receipt of compound	1206-201-30	on 8/26/87

Compounds from Exhibit B-1:

Line 813: receipt of compound 1049-237-27 on 5/31/84

Upon completion of an IR or NMR spectrum, the chemist is provided with the original spectrum, and no copies are retained by the Physical Chemistry Department. Each spectrum contains information identifying the sample, including the sample's notebook number-page number-line number; the date, the operator, and any other notes which are relevant.

The chemist who requested the sample is primarily responsible for the interpretation of the structure based on the data provided by my department; however, my Department can provide assistance if necessary.

II. PROCEDURES FOR ASSEMBLING THE DATABASE

Another responsibility of the Physical Organic Chemistry Department was the assembly of a computerized database for use only by Sandoz employees which contains information regarding compounds produced by the chemists. The database information regarding the compounds of this patent application were assembled in the following manner. This procedure was the one in use when the compounds of this patent application were submitted.

Upon verification of the structure and purity of a sample, a "Chemical Information" form is completed, and an accompanying sample of the compound is submitted.

Exhibit D-1 is a blank Chemical Information form. The "Date" box at the upper right hand side of the form is filled in by the person registering the compound, and the Compound Number is assigned sequentially by the person registering the compound. (The initials of the person who is registering the compound is recorded on the computer database).

The Chemical Information form also includes a list of "screens" which are standard biological tests which the chemist may request. Abbreviations which appear on the forms (either printed or handwritten in the blank spaces) are as follows: AO= anti-obesity, GHI= growth hormone inhibition, GLUC= glucagon, HG= hypoglycemic, HL= hypolipidemia, PL= platelet, TC= tissue culture cholesterol absorption inhibition test, AM/AV= anti-microbial and/or anti-viral, Tr= Tripanosoma, Agro= agricultural, CSI= cholesterol synthesis inhibition, CSIV= cholesterol synthesis inhibition *in vivo*.

The Chemical Information Form also includes, at the bottom, a "Chem. No." which is the laboratory notebook-page number-line number of the sample.

Exhibit D-2 contains copies of Chemical Information forms for compounds which are contained in the above-identified patent application. These forms were submitted for compound registration in the database.

Upon receipt of the Chemical Information Form and sample, personnel under my direction enter this information into the Sandoz computer database.

Exhibit H-1 contains copies of printouts of entries of the computer database. The date which is recorded in the database is automatically supplied by the computer; it is not manually entered by the operator, and is not changed once it is generated.

Codes used in the databank are as follows. INT.REG.NO is the unique internal registry number, the number assigned sequentially to this compound in the Sandoz internal database. Information recorded across the top of the printout is as follows. SAH.NO is the "Sandoz Number" or the official Sandoz number for the compound. These numbers are assigned sequentially, and are never deleted. SALTCODE is the code of the type of salt form, if the compound is a salt. CHEM.NO. is the laboratory notebook-page number-line number designation of the sample. SUBMITTED is the date the data were entered into the database. DISCL is the number of the Invention Disclosure form which was submitted to the Patent and Trademark Department.

Each chemist who submits a compound for entry into the database must proofread the entry. The data in the database are considered accurate by the scientists at Sandoz, and the data as recorded in the database are relied upon in the course of further research, testing, and development.

Upon assignment of an official number, the samples are marked with their "SAH" number and are stored in the Drug Room.

III. STORAGE AND INVENTORY PROCEDURES

The Sandoz Drug Room is responsible for the storage of samples of compounds that are catalogued in the database.

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 12th day of November, 1992.

Sandor Barcza

SANDOR BARCZA, Ph.D.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN

v. Interference Nos. 102,648, 102,975

FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

DECLARATION OF RAJESHVARI PATEL PURSUANT TO 37 C.F.R. §1.672

I, Rajeshvari Patel, do hereby declare as follows:

(1) That I am a chemist, who was employed by Sandoz Pharmaceuticals Corporation, 59 Route 10, East Hanover, N.J. during the time when Dr. Sompong Wattanasin was in the process of reducing to practice compounds claimed in U.S. Patent Application Serial Number 07/498,301.

(2) That one of my job responsibilities included the synthesis of certain compounds under the direction and supervision of Dr. Wattanasin.

(3) That all activities referred to in this Declaration took place in the United States of America.

A. SYNTHESIS OF COMPOUNDS 64-933, 64-934/Na, 64-935 AND 64-936/Na

Under the supervision of Sompong Wattanasin, I synthesized compounds 64-933, 64-934/Na, 64-935 and 64-936/Na of the invention. I kept a record of this activity in my Laboratory Notebook #1206.

Exhibit F-1 comprises a true copy of my Laboratory Notebook #1206, Pages 130, 137, 145, 153, 158, 166, 172, 175, 176, 179, 190 and 201.

It was my practice to date the top of each laboratory notebook page on the date I started the experiment reported on the page, and to sign the page and date my signature after the experiment was completed.

General Description of Laboratory Notebook Pages

i. Molecular Weight:

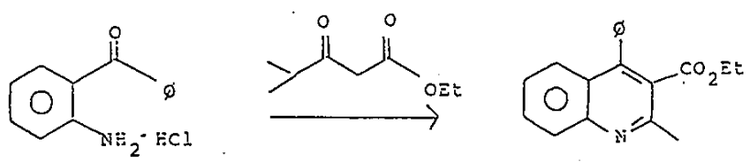
To determine molecular weight of each compound and its intermediates, mass spectrometry was performed. The molecular weight which was determined is the weight of the molecular ion, or $M-H^+$, where M is the compound of interest. Thus, to calculate the molecular weight of the compound rather than its ion, one must subtract the molecular weight of hydrogen (1) from the molecular weight of the ion. In the notebook pages, I recorded the molecular weight of the ion. Thus, the molecular weight of the compound is 1 less than what I recorded in my notebook.

ii. Spectra and Microanalyses:

The spectra and microanalyses were not performed by me, but were performed by an employee of the Physical Organic Chemistry Department of Sandoz Pharmaceuticals

Corporation. Upon receipt of the spectra from the Physical Organic Chemistry Department, I filed them in their own folder arranged by their compound number. Reference is made to the work of Dr. Sandor Barcza for details concerning analysis procedures.

Notebook #1206, page 130 is dated June 1, 1987 at the top in my handwriting, and contains my dated signature of June 8, 1987, at the bottom of the page. This page documents the following reaction which I performed:



(1206-130-27)

Ø = phenyl group

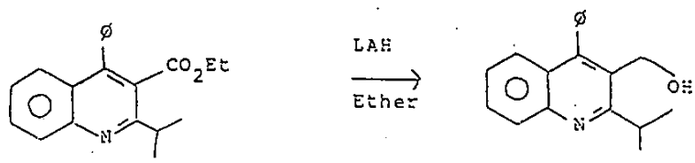
(1206-129-18)

The compound on the left side of the equation was designated 1206-129-18. A mixture of 11.5 g (0.04930 mol) of 1206-129-18, 11.93 ml (0.073958 mol; 1.5 equivalents) of and 105 ml EtOH was heated to reflux for six hours (10:00 A.M. to 4:00 P.M.) and then stirred at room temperature overnight.

The following day, the reaction mixture was evaporated to dryness to give a yellow oil with the rotary evaporator, basified with NH_4OH and extracted with ether, and the ether extract was washed with H_2O and then brine, dried with anhydrous sodium sulfate, and filtered. The filter cake was washed with ether and the washing was

combined with the initial filtrate and evaporated to give 10.21 g of an orange-yellow solid, designated 1206-130-27. IR and NMR spectra were performed and follow Laboratory Notebook #1206, page 130. Yield was calculated to be 64.86%. The spectra were judged by me and Dr. Wattanasin to be consistent with the desired product (1206-130-27).

Notebook #1206, page 137 is dated June 9, 1987 at the top in my handwriting, and contains my dated signature of July 2, 1987 at the bottom of the page. This page documents the following reaction which I performed:



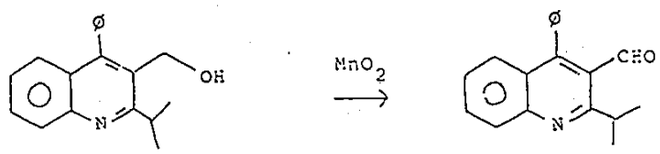
(1206-130-27) (1206-137-31)

To 10.21 g (0.0319621 mol) of 1206-130-27 in 100 ml dry ether with cooling was added 2.43 g (0.063242 mol) LAH (lithium aluminum hydride) portion-wise. The reaction was exothermic and foaming occurred. The mixture was stirred at room temperature for three hours (9:35 A.M. to 12:35 P.M.).

The reaction mixture was poured into ice water (the reaction was strongly exothermic). The result was extracted with ether and the ether extract was washed with water and then brine, dried with anhydrous sodium sulfate and filtered. The filter cake was washed with ether, and

the washing was combined with the initial filtrate. Evaporation gave 8.5 g of a yellow solid, designated 1206-137-31. IR and NMR spectra were performed and the results follow Laboratory Notebook #1206, page 137. The spectra were judged by me and Dr. Wattanasin to be consistent with the desired product (1206-137-31). Yield was calculated at 95.8% of theoretical.

Notebook #1206, page 145 is dated June 17, 1987 at the top in my handwriting, and contains my signature. This page documents the following reaction which I performed:



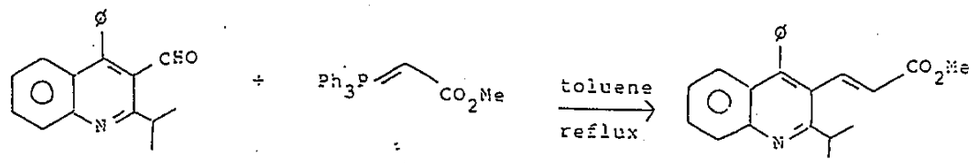
(1206-137-31) (1206-145-25)

To 8.0 g (0.0288392 mol) of 1206-137-31 in 150.0 ml toluene was added 16.0 g activated MnO_2. This was heated to reflux for approximately 3-3/4 hours (11:00 A.M. to 2:45 P.M.). The result was filtered through a pad of silica gel. During filtration, it separated into two bands, which were then filtered separately and evaporated separately. Both were yellow solids: (a) 2.6518 g designated 1206-145-25 with a molecular weight of 276, which was determined to be the desired product; and (b) 4.4663 g, designated 1206-145-26, with a molecular weight of 278, which was determined to be the starting material.

IR and NMR spectra were performed on 1206-145-25 and the results follow Laboratory Notebook #1206, page 145. The spectra were judged by me and Dr. Wattanasin to be consistent with the desired product (1206-145-25).

This process was repeated with 1206-145-26 as recorded in Laboratory Notebook #1206, page 148, and 3.26 g of the same compound as 1206-145-25 was obtained, and designated 1206-148-33. Thus total yield was calculated as 2.6518 g + 3.26 g = 5.91 g. Theoretical yield was 7.91 g, yield was therefore 74.52%.

Notebook #1206, page 153 is dated June 30, 1987 at the top in my handwriting, and contains my dated signature of July 6, 1987. This page documents the following reaction which I performed:



(1206-145-25)
(1206-148-33)

(1206-153-40)

Ph = phenyl group
Me = methyl group

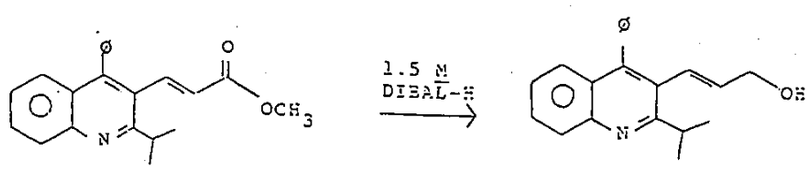
5.91 g of the combination of 1206-145-25 and 1206-148-33 (0.0214909 mol), 8.6135 g of Ph_3P CO_2Me(0.025789 mol) and 85 ml of toluene were heated to

reflux for 1.5 hours. (Before heating this was a yellow heterogeneous mixture). It was then stirred at room temperature overnight.

The following day, the reaction mixture was diluted with 50% ether/petroleum ether and filtered through a pad of silica gel. The filter cake was washed with 50% ether/petroleum ether, the washing was combined with the initial filtrate and evaporated to dryness to give 8.6 g of a yellow crystalline solid. Trituration with methanol gave 5.5198 g of an off-white solid, designated 1206-153-31, molecular weight 331; yield was 77.6%. The mother liquor was evaporated to dryness, leaving a 2.7593 g of a yellow oil, designated 1206-153-34.

Trituration of 1206-153-34 with methanol gave 761.6 mg of a light yellow solid, designated 1206-153-37, with a molecular weight of 331. Evaporation of the mother liquor to dryness resulted in a yellow solid, designated 1206-153-38. 1206-153-31 and 1206-153-37 were combined and designated 1206-153-40. The melting point of 1206-153-40 was found to be 128-130°C. Spectra were run on 1206-153-31 (NMR), 1206-153-37 (NMR) and 1206-153-34 (IR) and the results follow Laboratory Notebook #1206, page 153. The spectra of 1206-153-31 and 1206-153-37 were judged by me and Dr. Wattanasin to be consistent with the desired product.

Notebook #1206, page 158 is dated July 7, 1987 at the top in my handwriting, and contains my dated signature of July 17, 1987. This page documents the following reaction which I performed:

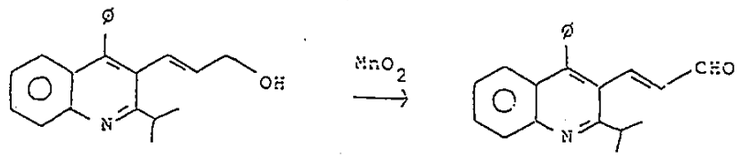


(1206-153-40) (1206-158-41)

To a solution of 6.25 g of 1206-153-40 (0.0188821 mol) in 75 ml CH_2Cl_2 at -78°C was added 25.18 ml of 1.5 M DIBAL-H (diisobutylaluminum hydride) (0.0377642 mol; 2 equivalents) in toluene. This was stirred at -78°C for about three hours (12:15 P.M. to 3:10 P.M.). The reaction was then quenched with 12.5 ml 2 N NaOH, diluted with EtOAc, and stirred at room temperature overnight. A white solid (gel) came out of solution.

The following day, the reaction product was filtered through a pad of silica gel, washed with EtOAc, water, and then brine, dried with anhydrous sodium sulfate and evaporated to dryness. The result was 5.42 g of an off-white solid, designated 1206-158-35. Yield was 73.7% theoretical yield. The solids were dissolved in Et_2O, and the insoluble portion (aluminum oxide) was filtered off. The solution was evaporated to dryness, resulting in 5.22g of white-yellow solids designated 1206-158-37. The solids were dissolved in Et_2O, and the insoluble portion (aluminum oxide) was filtered off. The resulting solution was evaporated to dryness, resulting in 4.2117 g of a yellowish solid, designated 1206-158-41, with a molecular weight of 303 and a melting point of 119-121°C. NMR and IR spectra were run on 1206-158-41 and the results follow Laboratory Notebook #1206, page 158. The spectra were judged by me and Dr. Wattanasin to be consistent with the desired product (1206-158-41).

Notebook #1206, page 166 is dated July 15, 1987 at the top in my handwriting, and contains my dated signature of July 20, 1987. This page documents the following reaction, which I performed:



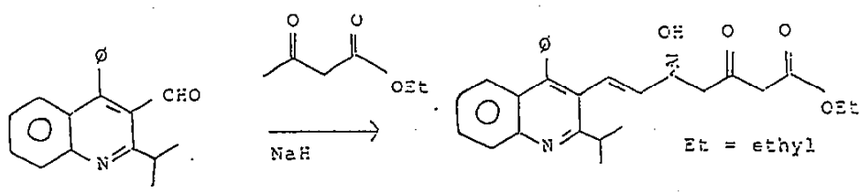
(1206-158-41) (1206-166-30)

To 4.0 g of 1206-158-41 (0.0132013 mol) in 50 ml toluene was added 8.0 g activated MnO_2. This was heated to reflux for one hour (2:00 P.M. to 3:00 P.M.), then stirred at room temperature overnight.

The following day, the reaction product was filtered through a pad of silica gel. Evaporation to dryness gave 3.4946 g of a yellow crystalline material, designated 1206-166-30, with a molecular weight of 301. NMR and IR spectra were run on 1206-166-30 and the results follow Laboratory Notebook #1206, page 166. Yield was 88% theoretical yield. The spectra were judged by me and Dr. Wattanasin to be consistent with the desired product (1206-166-30).

Twelve days later, a microanalysis was performed. Two days later, the melting point was determined to be 98-101°C.

Notebook #1206, page 172 is dated July 20, 1987 at the top in my handwriting, and contains my dated signature of July 21, 1987. Notebook #1206, page 175 is dated July 22, 1987 at the top in my handwriting, and contains my dated signature of August 5, 1987. These pages document the following reaction which I performed:



(1206-166-30) (1206-175-4)

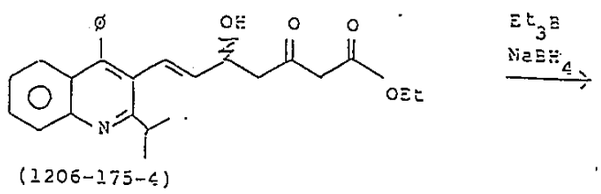
To a solution of 3.5 g (0.0116279 mol) of 1206-166-30 in 40 ml dry THF at -5°C to -10°C was added 38 ml of a previously prepared solution of the dianion of ethyl acetoacetate, the details of the preparation of which are set forth below. The color change from yellow to orange to dark red, suggesting that the reaction had occurred. A TLC (using 50% ether/petroleum ether) run after 15 minutes indicated the reaction was complete. The reaction mixture was stirred for 30 minutes.

The reaction mixture was quenched with NH_4Cl solution, extracted with EtOAc, resulting in two layers. The organic layer was separated and was washed with water then brine, dried with anhydrous sodium sulfate and filtered. Evaporation gave 5.9188 g of a yellow oil, designated 1206-172-41. Yield was 67.87% theoretical.

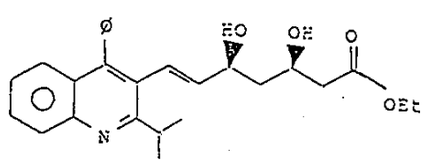
To make the dianion solution used above, the following procedure was used. A solution of 5 ml ethyl acetoacetate in 50 ml dry THF was added 1.9 g of 50% NaH in THF at -5° to 0°C. This was stirred for 15 minutes (the solution was foaming as H_2 was evolved). At -10° to -15°C, 27 ml of 1.6 M n-butyllithium/hexane was added and the mixture was stirred for 20 minutes at -10°C. 92 ml of a yellow homogeneous solution resulted (0.04 mol).

Flash chromatography through silica gel (25% ether/petroleum ether) of 1206-172-41 gave 3.4004 g of a yellow solid, designated 1206-175-4. Melting point was 84-87°C. Yield was 68%. A microanalysis was performed and the results are shown. NMR and IR spectra were run on 1206-175-4 and the results follow Laboratory Notebook #1206, page 172. The spectra were judged by me and Dr. Wattanasin to be consistent with the desired product (1206-175-4).

Notebook #1206, page 176 is dated July 23, 1987 at the top in my handwriting, and contains my dated signature of August 5, 1987. This page documents the following reaction which I performed:



(1206-175-4)



(1206-176-41)

To a homogeneous solution of 1.0 g (0.0023201 mol) 1206-175-4 in 10 ml dry THF and 2.5 ml methanol was added 3.5 ml 1 M Et_3B (0.0034801 mol; 1.5 equivalents) in THF. This was stirred at room temperature for one hour (9:45 A.M. to 10:45 A.M.). Then the solution was cooled to -78°C. 0.1315 g of $NaBH_4$ (0.0034810 mol; 1.5 equivalents) was added portion-wise. This was then stirred at -78°C for four hours (11:00 A.M. to 3:00 P.M.).

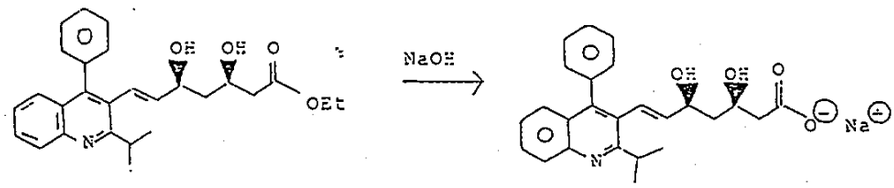
The reaction was quenched with 5 ml acetic acid at -78°C. Ethyl acetate was then added and the mixture was allowed to warm to room temperature. The organic layer was washed with saturated sodium bicarbonate solution, water, and brine. It was then dried, filtered and evaporated to dryness. The residue was redissolved in methanol and evaporated to dryness. The evaporation process (in methanol) was repeated until TLC showed the desired product was obtained, 1.0914 g of an orange oil, designated 1206-176-39.

Flash chromatography on silica gel (80% ether/ petroleum ether) gave two products: (a) F_{4-6}, 0.4043 g of a yellow solid, designated 1206-176-41 with a molecular weight of 433 and M.P. 104-106°C, which was shown by HPLC to be 98.3% pure; and (b) F_{7-13}, 0.510 g of a yellow solid designated 1206-176-43, with a molecular weight of 433, which was shown to be 93.2% pure by HPLC. IR and NMR spectra were run on both 1206-176-41 and 1206-176-43 and follow Laboratory Notebook #1206, page 176. Based on these spectra, compound 1206-176-41 was determined to be

the desired product. Compound 1206-176-41 was eventually renamed 64-933.

A sample of 64-933 was sent to Dr. Scallen for biological testing in his in vitro microsomal assay for HMG-CoA reductase inhibition activity. It was shown by Dr. Scallen to possess inhibition activity prior to December 7, 1987. I learned of this activity from Dr. Damon. Thus, prior to December 7, 1987, I knew that 64-933 was useful as an anti-cholesterol biosynthesis agent, and would be useful in treating atherosclerosis and other conditions resulting from excessive cholesterol biosynthesis.

Notebook #1206, page 179 is dated July 28, 1987 at the top in my handwriting, and contains my dated signature of August 5, 1987. This page documents the following reaction which I performed:

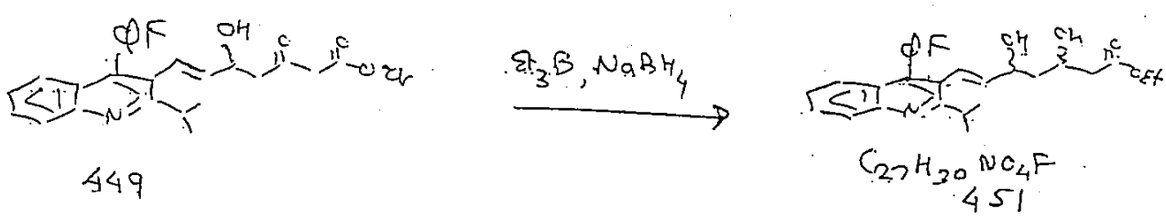


(1206-176-41) (1206-179-30)

To 200.0 mg 1206-176-41 in 5 ml absolute ethanol at 0°C. was added approximately 439 µml of 0.5N NaOH. This was stirred at 0°C. for approximately 1 hour. A yellow oil resulted. The mixture was diluted with ether and evaporated to a yellow oil. This was re-diluted with ether and solids precipitated out of solution. The solids were washed with ether, the ether was decanted, and the solids were dried under vacuum to obtain 178.8 mg of yellow solids designated 1206-179-30. NMR and IR spectra and a microanalysis were performed. The spectra appear after Notebook #1206, page 179, and were judged by me and Dr. Wattanasin to be consistent with the desired product (1206-179-30). The product shrunk at 187°C and the melting point was above 210°C.

1206-179-30 was re-named 64-934. It was submitted to Dr. Scallen for biological testing in his above-mentioned in vitro microsomal assay and was found to be active.

Notebook #1206, page 190 is dated August 10, 1987 at the top in my handwriting, and contains my dated signature of September 1, 1987. This page documents the following reaction which I performed:



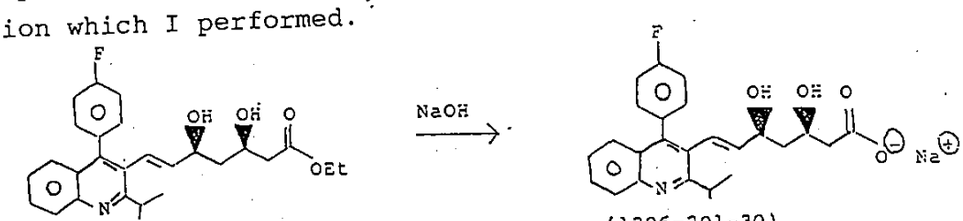
449

$C_{27}H_{30}NO_4F$
451

To a solution of 400 mg 1206-187-18 in 133.6 ml THF at room temperature was added 1M Et_3B (0.0001437 mol) and 1 ml air (by syringe). The solution was stirred at room temperature for 1 hr. The solution was then cooled to -78°C and 10 mg $NaBH_4$ was added. The reaction mixture was cooled to -78°C, 51 mg $NaBH_4$ was added and stirring was continued at -78°C from 12 noon to 3 p.m. The reaction was quenched and extracted with EtOAc, and washed with saturated $NaHCO_3$, dried, filtered, washed with MeOH five times to give a yellow oil which was chromatographed to give a yellow-orange oil,, 1206-190-38, which was dried over high vacuum to give 206.6 mg of 1206-190-41 which was believed to be the <u>erythro</u> racemate.

1206-190-41 was re-named 64-935. It was submitted to Dr. Scallen for biological testing in his above-mentioned <u>in vitro</u> microsomal assay and was found to be active.

Notebook #1206, page 201 is dated <u>August 25, 1987</u> at the top in my handwriting, and contains my dated signature of September 1, 1987. This page documents the following reaction which I performed.



(1206-190-41) (1206-201-30)

To 100 mg 1206-190-41 in 5 ml absolute ethanol, at 0°C with stirring was added approximately 217.3 µml 1N NaOH dropwise. The mixture was stirred at 0°C for approximately 3 hours, resulting in a yellow oil.

This was diluted with ether, and evaporated to dryness to produce a yellow oil. Upon the addition of ether, yellow solids precipitated out. These were filtered, washed and dried to give 86.4 mg of a yellow solids designated 1206-201-30.

NMR and a microanalysis were performed on 1206-201-30. The spectrum appears after Notebook #1206, page 201. It was judged by me and Dr. Wattanasin to be consistent with the desired product (1206-201-30). Its melting point was greater than 225°C.

1206-201-30 was renamed 64-936.

Compounds 64-933, 64-934/Na, 64-935 and 64-936/Na were sent to Dr. Scallen for biological testing in his in vitro microsomal assay for HMG-CoA reductase inhibition activity.

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 13th day of November, 1992.

Rajeshvari D Patel
RAJESHVARI PATEL

70

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN

v. Interference Nos. 102,648, 102,975

FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

SUPPPLEMENTAL DECLARATION OF RAJESHVARI PATEL
PURSUANT TO 37 C.F.R. §1.672

I, Rajeshvari Patel, do hereby declare as follows:

(1) That I am a chemist, who was employed by Sandoz Pharmaceuticals Corporation, 59 Route 10, East Hanover, N.J. during the time when Dr. Sompong Wattanasin was in the process of reducing to practice compounds claimed in U.S. Patent Application Serial Number 07/498,301, and during the time periods referred to in my Declaration pursuant to 37 CFR 1.672 and this Supplemental Declaration pursuant to 37 CFR 1.672.

(2) That one of my job responsibilities included the synthesis of certain compounds under the direction and supervision of Dr. Wattanasin.

(3) That all activities referred to in this Declaration took place in the United States of America.

(4) The contents of my Declaration made Pursuant to Rule 37 CFR 1.672 are hereby incorporated by reference in their entirety.

SYNTHESIS OF COMPOUND 64-935

Under the supervision of Sompong Wattanasin, I synthesized compound 64-935 of the invention. I kept a record of this activity in my Laboratory Notebook #1206.

Exhibit F-1 comprises a true copy of my Laboratory Notebook #1206, Pages 130, 137, 145, 153, 158, 166, 172, 175, 176, 179, 190 and 201.

Exhibit L-1 hereto comprises a true copy of my Laboratory Notebook #1206, Pages 86, 99, 103, 119, 178, 181, 183, 185, 186, and 187.

These pages show the complete synthesis of compound 64-935.

It was my practice to date the top of each laboratory notebook page on the date I started the experiment reported on the page, and to sign the page and date my signature after the experiment was completed.

Notebook #1206, page 86 is dated April 13, 1987 in my handwriting and contains my dated signature of April 14, 1987 at the bottom of the page. This page documents the synthesis of compound 1206-86-387 from benzoxazine according to the method of Suzuki et al., JOC, 1961, 2239, 2241.

Notebook #1206, page 99 is dated April 13, 1987 at the top in my handwriting, and contains my dated signature of April 14, 1987 at the bottom of the page. This page documents the synthesis of compound 1206-99-26 by a process analogous to the one recorded in Notebook #1079, Page 248 in Exhibit B-1.

Notebook #1206, page 103 is dated May 4, 1987 at the top in my handwriting, and contains my dated signature of May 5, 1987 at the bottom of the page. This page documents the synthesis of compound 1206-103-28 by a process analogous to the one recorded my Notebook #1206, Page 130 in Exhibit F-1.

Notebook #1206, page 119 is dated May 20, 1987 at the top in my handwriting, and contains my dated signature of May 27, 1987 at the bottom of the page. This page documents the synthesis of compound 1206-119-30 by a process analogous to the one recorded in my Notebook #1206, Page 137 in Exhibit F-1.

Notebook #1206, page 178 is dated July 27, 1987 at the top in my handwriting, and contains my dated signature of August 5, 1987 at the bottom of the page. This page documents the synthesis of compound 1206-178-31 by a process analaogous to the one recorded in my Notebook #1206, page 145 in Exhibit F-1.

Notebook #1206, page 181 is dated July 29, 1987 at the top in my handwriting, and contains my dated signature of August 5, 1987 at the bottom of the page. This page documents the synthesis of compound 1206-181-26 by a method analogous to the one recorded in my Notebook #1206, page 153 in Exhibit F-1.

Notebook #1206, page 183 is dated August 3, 1987 at the top in my handwriting, and contains my dated signature of August 5, 1987 at the bottom of the page. This page documents the synthesis of compound 1206-181-26 by a method analogous to the one recorded in my Notebook #1206, page 158 in Exhibit F-1.

Notebook #1206, page 185 is dated August 4, 1987 at the top in my handwriting. This page documents the synthesis of compound 1206-185-31 by a method analogous to the one recorded in my Notebook #1206, page 166 in Exhibit F-1.

Notebook #1206, page 186 is dated August 5, 1987 at the top in my handwriting, and contains my dated signature of August 5, 1987 at the bottom of the page. Notebook #1206, page 187 is dated August 5, 1987 at the top in my handwriting and contains my dated signature of September 1, 1987. These pages document the synthesis of compound 1206-187-18 by a method analogous to the one recorded in my Notebook #1206, pages 172 and 175 in Exhibit F-1.

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 16th day of November, 1992.

Rajeshvari D Patel
RAJESHVARI PATEL

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 TERENCE J. SCALLEN PURSUANT TO 37 CFR §1.672

I, Terence J. Scallen, M.D., Ph.D., do hereby declare as follows:

(1) That I am a Professor of Biochemistry in the Department of Biochemistry, School of Medicine, University of New Mexico, Albuquerque, New Mexico 87131.

(2) That all activities referred to in this Declaration took place in the United States.

BIOLOGICAL ACTIVITY OF WATTANASIN COMPOUNDS

1. I have done extensive research in the area of cholesterol biosynthesis inhibition and am familiar with compounds which possess cholesterol biosynthesis inhibition activity.

2. I have performed tests of biological activity on compounds supplied to me by Sandoz Pharmaceuticals Corporation both since 1980, and I have reported the results back to Sandoz. The compounds I receive are labeled with only their compound number, and no structural identification of these compounds is given until the testing is completed.

3. The compounds sent to me by Sandoz were tested to determine whether they are competitive inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase, the rate limiting enzyme in cholesterol biosynthesis, and therefore inhibitors of cholesterol biosynthesis. If a compound possesses this activity, it would be useful for lowering the blood cholesterol level in animals; e.g., mammals and especially larger primates. A compound with this activity would therefore be a hypolipoproteinemic and anti-atherosclerotic agent.

4. There was an established protocol which was used in my laboratory for assaying the samples which I received, which is described on the first page of each of Exhibits E-1 to E-4 (and also for each group of test results in E-5) appended hereto.

In general, the test which I use to determine whether a compound has HMG-CoA reductase inhibition activity is as follows:

> 200 µl aliquots (1.08 - 1.50 mg/ml) of rat liver microsomal suspensions are prepared from male Sprague-Dawley rats (150-225g body weight), in Buffer A with 10 mM dithiothreitol (DTT). "Buffer A" is 0.04M potassium phosphate, pH 7.4, 0.05M KCl, 0.03M EDTA and 0.25M sucrose; (The microsomes were frozen before use.)

The microsomal suspension is incubated with 10 µl of a solution of the test compound in dimethylacetamide (DMA), as described by Ackerman, et al. 1977 J. Lipid Res. v. 18 p. 408-413. In the assay, the rat microsomes are the source of HMG-CoA reductase enzyme which catalyzes the reduction of HMG-CoA to mevalonate. Rather than using a chloroform extraction procedure as described by Ackerman, et al., supra, a Dowex^{R} 1X8 (200-400 mesh, formate form) ion exchange column is used to separate the product, [^{14}C]mevalonolactone, which is formed by the HMG-CoA reductase reaction from the substrate, [^{14}C]HMG-CoA. [^{3}H]mevalonolactone is added as an internal reference. Inhibition of HMG-CoA reductase is calculated from the decrease in specific activity ([^{14}C/^{3}H]mevalonate ([^{3}H]MVA))) of test groups compared to controls.

5. In vitro assays of biological activity as an HMG-CoA reductase inhibitor, were performed in my laboratory under my supervision on compounds 63-366, 63-548, 63-549, 64-933, 64-934/Na, 64-935 and 63-366/Na; and I reported the results to Dr. Robert Damon of Sandoz.

Compound 63-366

On or before December 13, 1984, an in vitro biological assay of compound 63-366 was performed in my laboratory. I reviewed the results of the assay, and

determined that the compound has HMG-CoA reductase activity. On or before December 20, 1984, I communicated this result to Dr. R. Damon of Sandoz.

Exhibit E-1 comprises true copies of the testing protocol utilized and the Laboratory Notebook pages which recorded the data for compound 63-366.

The first two pages of Exhibit E-1 bear the date of December 13, 1984. It was the practice in my laboratory to date these pages with the date on which the testing of the compound was performed.

The third page of Exhibit E-1 shows the data I obtained for 63-366.

Compounds 63-548 and 63-549

On or before June 13, 1985, in vitro biological assays of Compounds 63-548 and 63-549 were performed in my laboratory. I reviewed the results of the assays, and determined that these compounds have HMG-CoA reductase activity. On or before June 30, 1985, I communicated those results to Dr. R. Damon of Sandoz.

Exhibit E-2 contains a true copy of the description of the procedure and the printout showing the data for 63-548 and 63-549. The printout pages bear a date of June 13, 1985. The practice in my laboratory was to date these pages with the date on which the testing of the compound was performed.

The data for compounds 63-548 and 63-549 are on the third page of Exhibit E-2.

Compounds 64-933, 64-934/Na, 64-935 and 64-936/Na

On or before October 8, 1987, *in vitro* biological assays of compounds 64-933, 64-934/Na, and 64-935 were performed in my laboratory. I reviewed the results of the assays, and determined that these compounds have HMG-CoA reductase activity. On or before October 20, 1987, I communicated these results to Dr. R. Damon of Sandoz.

On or before October 13, 1987, an *in vitro* biological assay of compound 64-936/Na was performed in my laboratory. I reviewed the results of the assay, and determined that this compound has HMG-CoA reductase activity. On or before October 20, 1987, I communicated these results to Dr. R. Damon of Sandoz.

Exhibit E-3 contains a true copy of the report I sent to Dr. Damon summarizing my results and the printouts for compounds 64-933, 64-934/Na and 64-935. The printout pages bear the date of October 8, 1987. The practice in my laboratory was to date these pages with the date on which the testing of the compound was performed.

Exhibit E-4 contains a true copy of the report I sent to Dr. Damon summarizing my results and the printout for compound 64-936/Na. The printout pages bear the date of October 13, 1987. The practice in my laboratory was to date these pages with the date on which the testing of the compound was performed.

Exhibit E-5 contains true copies (except that structures and IC_{50} values have been added), of the summary of the results of a series of assays which I performed on compounds including 63-366, 63-548, 63-549, 64-933, 64-934/Na, 64-935, and 64-936/Na which I sent to Dr. Damon.

It has been my judgment since prior to August 20, 1987, that the level of in vivo activity of a compound as a cholesterol inhibitor or anti-atherosclerotic when administered to a patient, is typically highly correlatable to its in vitro activity in my HMG-CoA reductase inhibitor assays.

As demonstrated by Exhibit E-5 hereto, since on or prior to December 31, 1984, I was involved in the testing of numerous Sandoz compounds in substantially the same assay as used for the quinoline compounds, to determine in vitro HMG-CoA reductase activity.

These other compounds have the same 3,5-dihydroxy heptenoic acid, ester, or salt side chain, or alternatively have internal ester, i.e. lactone form, as the Wattanasin quinoline compounds at issue. However, these compounds differ by having a different organic radical substituent of the side chain.

For example, I performed in vitro assays of Sandoz compounds having a substituted napthyl or indole substituent, at or about the same time as compound 63-366, as indicated by Exhibit E-5, hereto.

Therefore, I have substantial experience in testing compounds for HMG-CoA reductase activity in vitro; and I

was familiar with the in vivo activity of many of these compounds as a result of my discussions with Dr. Damon and Mr. Engstrom of Sandoz.

On or before December 31, 1984, I also used the assay described herein to determine IC_{50} values for the compound Mevastatin (Compactin) which was a known HMG-CoA reductase inhibitor for administration to a patient to treat hypercholesterolemia or atherosclerosis.

Additionally, on or before December 31, 1984, I determined the IC_{50} values for Sandoz compound 62-320/Na (fluvastatin sodium), which I also knew to be active in vivo on or prior to December 31, 1984.

Therefore, I was able to compare the IC_{50} values for the quinoline compounds to the IC_{50} values for mevastatin and fluvastatin sodium, both of which were known to be active in vivo.

Based on my knowledge and experience, it was my judgment since on or prior to December 31, 1984, that Wattanasin compound 63-366 would be active when administered in vivo to a patient for the treatment of hypercholesteremia or atherosclerosis, in a dosage amount recited by Wattanasin in his patent application. It was

also my judgment after determining the in vitro assay data for each of compounds 63-548, 63-549, 64-934/Na, 63-935 and 64-936/Na, that each of these compounds would also be active in vivo, and would be active when administered to a human patient in the dosage amounts recited in the Wattanasin specification.

. . .

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 day of November, 1992.

Terence J. Scallen 11/13/92
TERENCE J. SCALLEN, M.D., Ph.D.

PAOLELLA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v. Interference Nos. 102,648, 102,975
FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

DECLARATION OF NICHOLAS A. PAOLELLA PURSUANT TO 37 C.F.R. §1.672

I, Nicholas A. Paolella, do hereby declare as follows:

(1) That I was a Senior Scientist A employed by Sandoz Pharmaceuticals Corporation from 1960 to 1991. In the course of my employment I synthesized compounds, including HMG-CoA reductase inhibiting compounds and I am familiar with the chemistry employed to make such compounds.

(2) That all activities referred to in this Declaration took place in the United States.

(3) That I have reviewed Sompong Wattanasin's Laboratory Notebook #1049 pages 237, 241, 248, 251, 245, Laboratory Notebook #1079 pages 22, 24, 27, 30, 33, 34, 39, 105, 106, 110 and 111.

(4) That I understood the experiments reported on these pages, and read and understood the aforementioned Laboratory Notebook pages, which I signed as a witness prior to August 20, 1987.

Exhibit B-1 contains true copies of Sompong Wattanasin's Notebook #1049, pages 237, 241, 248, 251, 245 and Notebook #1079, pages 22, 24, 27, 30, 33, 34, 39, 105, 106, 110 and 111 which bear my signature.

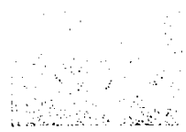
It is my recollection that I signed these pages prior to August 20, 1987.

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 6th day of November 1992.

Nicholas A. Paolella
NICHOLAS A. PAOLELLA

KATHAWALA



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v. Interference Nos. 102,648, 102,975
FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

DECLARATION OF FAIZULLA G. KATHAWALA PURSUANT TO 37 CFR §1.672

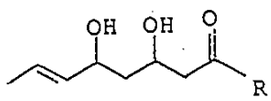
I, Faizulla G. Kathawala, Ph.D., do hereby declare as follows:

(1) That I am employed by Sandoz Pharmaceuticals Corporation as Director of Medicinal Chemistry -- Lipoprotein Metabolism. I am the supervisor of Dr. Sompong Wattanasin. All activities referred to in this Declaration took place in the United States.

(2) For over a decade Sandoz has been involved in an intense effort to discover compounds which have HMG-CoA reductase inhibiting activity. This project began in 1979 when I was named the section head, supervising one other Ph.D. and his technician. Our research team expanded until there are five laboratory units each headed by a Ph.D. and also staffed by 12-15 other scientists. Sompong Wattanasin joined the project in 1982 as a Post-Doctoral level scientist working under my direction, and was later appointed as head of one of the five laboratory units.

(3) That prior to and during the same time as the invention of the quinoline-HMG-CoA reductase inhibitory compounds claimed in the Wattanasin patent application

Serial Number 07/498,301, I and/or other scientists in my department had invented other HMG-CoA reductase inhibitors which were chemically analogous to such quinolines except that the quinoline moiety was replaced by another moiety which included: the pyrazole, pyrimidine, indene, pyrrole, naphthalene and indole systems. By "system" I mean the compound either had the following side chain



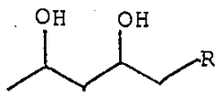
and was a salt form, an acid form, or an ester form, or the compound was in a lactone form. Additionally, it included the 3R,5S forms as well as racemates. Based on the chemistry we learned from these other systems, we expected that if one of these forms showed biological activity, the other forms could be expected to show activity as well. Thus, when a scientist referred to compounds in a generic manner, it was understood by everyone involved to include salts, acids, esters and lactones, even if only one of these was actually drawn.

(4) That when a scientist had an idea for making a new system, he would review the idea with me prior to the start of the synthesis. The proposed synthetic pathways would also be discussed. Dr. Wattanasin reviewed his idea for making a quinoline system with me prior to the synthesis of the first quinoline.

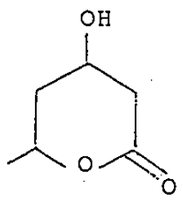
WATTANASIN CONCEPTION PRIOR TO AUGUST 20, 1987

1. On or before November 28, 1983, the subject invention was disclosed to me by Dr. Sompong Wattanasin. On November 28, 1983, I received a report from Dr. Wattansin in which compounds of the Wattanasin patent application were proposed for synthesis.

Exhibit A-1 comprises a true copy of the report I received. I understood the "L" in structure 14 to include the following side chain (where R indicates an acid, salt or ester) and also the lactone form.



and

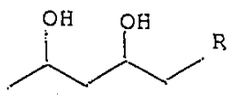


I understood that the open chain compounds were preferably in the 3R,5S form or in an racemic mixture, and that the lactone was preferably in the 4R,6S form or in a trans racemic mixture.

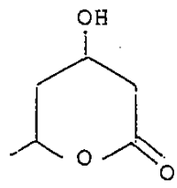
2. On November 19, 1984, I received a report from Dr. Wattanasin, proposing the synthesis of additional compounds which form the subject of this invention.

Exhibit A-2 comprises a true copy of the report I received. For each of the structures drawn on page 1 of Exhibit A-2, I understood "L" to include the following

chain (where R indicates an acid, salt or ester) and also the lactone form.



and



I understood that the open chain compounds were preferably in the 3R,5S form or in an erythro racemic mixture, and that the lactone was preferably in the 4R,6S form or in a trans racemic mixture.

3. On March 16, 1987 I reviewed, understood, and signed and dated as a witness, a disclosure of invention prepared by Dr. Wattanasin for the compounds of this patent application.

Exhibit A-3 is a true copy of the disclosure of invention, bearing my signature as a witness. I understood Compound I of Exhibit A-3 to include the salt and acid forms as well as the ester form shown: I also understood that the preferred stereochemistry for the open chain compound was the 3R,5S or the erythro racemate, and that for the lactone, the 4R,6S form or the trans racemate was preferred.

4. During the time that Drs. Wattanasin and Patel made the compounds described in their laboratory notebooks, I observed their work in my laboratory, and I was in contact with them on a frequent basis concerning their progress and results. Dr. Wattanasin spent a considerable amount of time and effort on this project.

WATTANASIN ACTUAL REDUCTION TO PRACTICE

1. To the best of my knowledge and belief, the Laboratory notebook pages which form Exhibits B-1, B-2, and F-1 are accurate reflections of the work performed in my laboratory.

2. I was aware that certain of the Wattanasin compounds were sent to Dr. Scallen for in vitro biological testing prior to August 20, 1987. I was aware that Dr. Scallen reported the results he obtained to Dr. Robert Damon. Dr. Damon reported these results to me.

Exhibit E-5 contains true copies of reports of activities of compounds which Dr. Damon sent to me and other investigators involved in the HMG-CoA reductase project.

3. That based on the in vitro biological activity, I knew, prior to August 20, 1987, that compounds according to this invention were HMG-CoA reductase inhibitors. I therefore knew that they possessed utility as anti-cholesterol synthesis agents, and therefore as hypolipoproteinemic and anti-atherosclerotic compounds.

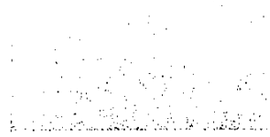
4. I also believed, prior to August 20, 1987, based on the in vitro data for compound 63-366, that compound 63-366 and other compounds of the invention would also have activity as an HMG-CoA reductase inhibitor when administered in vivo, to a patient.

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 12 day of Nov. , 1992.

Faizulla G. Kathawala
FAIZULLA G. KATHAWALA, Ph.D.

KAPA



92

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN

v.

FUJIKAWA et al.

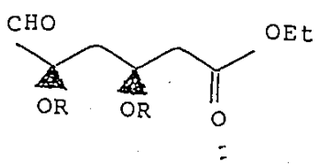
Interference Nos. 102,648, 102,975
Examiner-in-Chief: M. Sofocleous

DECLARATION OF PRASAD KAPA PURSUANT TO 37 CFR §1.672

I, Prasad Kapa, do hereby declare as follows:

(1) That I am a chemist employed by Sandoz Pharmaceuticals Corporation in the Process Research and Development Group. All activities referred to in this Declaration took place in the United States.

(2) That on or prior to July 31, 1983, I synthesized the following racemic compound:



R = t-butyl-diphenyl silyl

(3) That on or prior to May 6, 1985, I supplied this racemate to Dr. Sompong Wattanasin for use in his synthesis of HMG-CoA reductase inhibiting compounds; and that this is the compound referred to as the "Prasad Aldehyde" in Dr. Wattanasin's notebook #1127, page 9, which I have reviewed.

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 12 th day of November 1992.

PRASAD KAPA, Ph.D.

DAMON

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v. Interference Nos. 102,648, 102,975
FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

DECLARATION OF ROBERT E. DAMON PURSUANT TO 37 CFR §1.672

I, Robert E. Damon, II, Ph.D., do hereby declare as follows:

(1) That I am a chemist employed by Sandoz Pharmaceuticals Corporation. Among my responsibilities is coordination of the shipping of compounds to Dr. Terence Scallen and receiving data from him concerning the biological activity of new HMG-CoA reductase inhibiting compounds synthesized by Sandoz chemists.

(2) That all activities referred to in this Declaration took place in the United States.

TESTING OF WATTANASIN COMPOUNDS

1. Under my direction, Mrs. Honora Lukas of Sandoz sent samples of compounds stored in the Drug Room to Dr. Scallen for biological activity assaying.

Exhibit I-1 comprises what appear to be true copies of covering sheets accompanying shipments of compounds 63-366, 63-548, 63-549, 64-933, 64-934/Na, 64-935 and 64-936/Na to Dr. Scallen.

2. When Dr. Scallen performed assays on Sandoz compounds, including 63-366, 63-548, 63-549, 64-933, 64-934/Na, 64-935 and 64-936/Na, he sent the data to me.

Exhibit E-5 comprises true copies of reports that I received from Dr. Scallen reporting the results of his assay on the Wattanasin compounds (bearing structures and IC_{50} data handwritten by me after receipt).

As soon as I received the reports, I date-stamped them and initialed the date. The structures and IC_{50} numbers appearing on the reports were also written by me.

The first report I date-stamped on December 20, 1984.

The June 27, 1985 report I date-stamped June 28, 1985.

The October 8, 1987 report I date-stamped October 20, 1987.

The October 20, 1987 report I date stamped October 20, 1987.

3. IC_{50} Data: Based on the data supplied to me in the reports which make up Exhibit E-5, I calculated the IC_{50} value for each compound. IC_{50} is the concentration of the test substance in the assay system calculated to produce a 50% inhibition of HMG-CoA reductase activity. The smaller the IC_{50} value, the more active the compound was in the assay.

4. I wrote the structural formulae and IC_{50} value for the compounds tested by Dr. Scallen on the reports received from Dr. Scallen.

5. My practice was that, within at most three or four days of receiving a report from Dr. Scallen, I would send the report (containing my handwritten structures and IC_{50} data) to Dr. Wattanasin and other researchers working in the HMG-CoA reductase inhibitor area.

6. I also recorded the data from Dr. Scallen in my laboratory notebooks.

Exhibit J-1 comprises true copies of my Laboratory Notebook #1069, pages 113, 197, 198, and Laboratory Notebook #1238, pages 13, 14, 15, and 16.

It was my practice after receiving a report from Dr. Scallen, to prepare a form containing the structural formula of a compound which was tested by Dr. Scallen. I retrieved the structural formula from the Sandoz computerized database. I affixed the form to a page of my laboratory notebook, and wrote on the form the assay data (including the IC_{50} data) received from Dr. Scallen. Each page bears a date in my handwriting which is the date that Dr. Scallen tested the compound, which I obtained from Dr. Scallen's reports.

Laboratory notebook #1069, page 113, records the biological activity of 63-366. Its IC_{50} (in μM) is 1.58. This page bears a date of December 13, 1984 in my handwriting.

Laboratory notebook #1069, page 197, records the biological activity of 63-549. Its IC_{50} (in μM) is 7.3100. This page bears a date of June 13, 1985 in my handwriting.

Laboratory notebook #1069, page 198, records the biological activity of 63-548. Its IC_{50} (in μM) is 3.7750. This page bears a date of June 13, 1985 in my handwriting.

Laboratory notebook #1238, page 13, records the biological activity of 64-933. Its IC_{50} (in μM) is 2.3700. This page bears a date of October 8, 1987 in my handwriting.

Laboratory notebook #1238, page 14, records the biological activity of 64-934/Na. Its IC_{50} (in μM) is 2.6100. This page bears a date of October 8, 1987 in my handwriting.

Laboratory notebook #1238, page 15, records the biological activity of 64-935. Its IC_{50} (in μM) is 0.4130. This page bears a date of October 8, 1987 in my handwriting.

Laboratory notebook #1238, page 16, records the biological activity of 64-936/Na. Its IC_{50} (in μM) is 0.5300. This page bears a date of October 13, 1987 in my handwriting.

7. On or prior to December 31, 1984, I had already received from Dr. Scallen the in vitro assay data for various other Sandoz compounds being investigated for HMG-CoA reductase inhibitor activity, and had computed the IC_{50} values for such compounds.

These other compounds have the same 3,5-dihydroxy heptenoic acid side chain, or ester, salt or internal lactone form as the Wattanasin quinoline compounds 63-633 et al. However, these compounds differ by having a different organic radical substituent of the side chain. Some of these other compounds were tested approximately the same time as compound 63-366, as indicated by Exhibit E-5, hereto.

I compared the IC_{50} values of the Wattanasin quinoline compounds and other compounds tested by Dr. Scallen to IC_{50} values for the compound Mevastatin (Compactin) which was a known HMG-CoA reductase inhibitor for administration to patients to inhibit cholesterol biosynthesis. Exhibit E-5 also indicates that prior to December 31, 1984, I calculated the IC50 values for Sandoz compound 62-320/Na (fluvastatin sodium), which I also knew to be active in vivo on or prior to December 31, 1984.

Based on my knowledge and experience, it was my judgment on or prior to December 31, 1984, that there was a high probability that Wattanasin compound 63-366 would be active when administered in vivo to a patient to inhibit cholesterol biosynthesis, i.e. for the treatment of hypercholesteremia or atherosclerosis. It was also my judgment based on the in vitro assay data for the other tested quinoline compounds, that there was a high probability that the compounds of Dr. Wattanasin's invention would have activity when administered to a patient to inhibit cholesterol biosynthesis, i.e. for the treatment of hypercholesteremia or atherosclerosis, etc.

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 13th day of November, 1992.

Robert E. Damon

ROBERT E. DAMON, II, Ph.D.

WEINSTEIN

101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v. Interference Nos. 102,648, 102,975
FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

DECLARATION OF DAVID WEINSTEIN PURSUANT TO 37 CFR §1.672

I, David Weinstein, do hereby declare as follows:

(1) That I am employed by Sandoz Pharmaceuticals Corporation. Presently I am Head of the Department of Lipid and Lipoprotein Metabolism. During the time when Dr. Wattanasin invented the compounds of his invention, I was in charge of the "Drug Room", which is the facility where samples of compounds produced by Sandoz chemists are stored.

(2) That all activities referred to in this Declaration took place in the United States.

TESTING OF WATTANASIN COMPOUNDS

1. That at the time when Dr. Wattanasin supplied the Drug Room with samples of compounds of his invention, both prior to and after August 20, 1987, the following procedure was in place:

A sample of the compound, labeled with its official Sandoz number, was given to the Drug Room personnel, and its receipt was recorded in the computer database.

Exhibit H-1 contains true copies of printouts of the database entries for various compounds of the invention.

Compound 63-366 was entered on November 26, 1984.
Compound 63-548 was entered on May 17, 1985.
Compound 63-549 was entered on May 17, 1985.
Compound 64-933 was entered on September 21, 1987.
Compound 64-934 was entered on September 21, 1987.
Compound 64-935 was entered on September 21, 1987.
Compound 64-936 was entered on September 22, 1987.

At the bottom right hand column of the printout is a box entitled "AMOUNTS,mg". This is the amount of compound which was deposited in the Drug Room. There are also notations in this box if samples were sent to biologists for testing, and whether the Drug Room currently has any of the compound on hand.

Referring to the printout for 63-366, the notation means that a 14.5 mg sample of the compound (the entire amount deposited in the Drug Room) was sent to Dr. Terence Scallen.

For compound 63-548, a 2.0 mg sample (from a total deposit of 4.8 mg) was sent to Dr. Scallen.

For 63-549, the entire 2.0 mg deposit was sent to Dr. Scallen.

For other compounds encompassed by this invention:

64-933: 50.0 mg deposited; 50 mg sent to Dr. Scallen
64-934: 50.0 mg deposited; 50 mg sent to Dr. Scallen
64-935: 20.0 mg deposited; 20 mg sent to Dr. Scallen
64-936: 20.0 mg deposited; 20 mg sent to Dr. Scallen

2. In addition to recording in the computer database, the Drug Room also recorded when a sample was sent to a researcher.

Exhibit I-1 is a true copy of the Drug Room records documenting that Dr. Terence Scallen was sent samples of the compounds as follows:

63-366: December 3, 1984
63-548 and 63-549: June 3, 1985
64-933, 64-934/Na, 64-935 and 64-936/Na: October 2, 1987

3. It has been Drug Room policy, in force since before the dates in question, that when a sample of a compound leaves the Drug Room, it may not be returned to the Drug Room. This policy is meant to eliminate the risk of mis-identifying samples, and prevent contamination of compounds on deposit with the Drug Room. Thus, when a sample is sent from the Drug Room to a researcher, the researcher may rely on the identity of the compound, its purity, and the fact that it has not deteriorated.

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 12th day of November, 1992.

David Weinstein

DAVID WEINSTEIN, Ph.D.

PEREZ

105

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v. Interference Nos. 102,648, 102,975
FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

DECLARATION OF LAWRENCE B. PEREZ PURSUANT TO 37 CFR §1.672

I, Lawrence B. Perez, Ph.D. do hereby declare as follows:

(1) I am an Associate Fellow employed by Sandoz Pharmaceuticals Corporation since July 1987. In the course of my employment I synthesize compounds, including HMG-CoA reductase inhibiting compounds, and I am familiar with the chemistry employed to make such compounds. All activities referred to in this Declaration took place in the United States.

(3) I reviewed and and understood the experiments reported in Rajeshvari Patel's Laboratory Notebook #1206, pages 179, 190 and 201, before signing these pages.

(4) I reviewed and and understood the experiments reported in Rajeshvari Patel's Laboratory Notebook #1206, 86, 99, 103, 119, 124, 167, 173, 177, 178, 180, 181, 183, 185, 186 and 187, before signing these pages.

Exhibit F-1 comprises true copies of Rajeshvari Patel's Notebook #1206, pages 179 and 201, bearing my signature.

Exhibit L-1 comprises true copies of Rajeshvari Patel's Notebook #1206, pages 86, 99, 103, 119, 124, 167, 173, 177, 178, 180, 181, 183, 185, 186 and 187, bearing my signature.

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 day of November, 1992.

Lawrence B. Perez, Ph.D.

ENGSTROM

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN

v. Interference No. 102,648, 102,975

Fujikawa et al. Examiner-in-Chief: M. Sofocleous

DECLARATION OF ROBERT G. ENGSTROM PURSUANT TO 37 CFR §1.672

I, Robert G. Engstrom, do hereby declare as follows:

(1) That I have been employed by Sandoz Pharmaceuticals Corporation since 1964 as a Research Scientist. Among my responsibilities has been supervising the testing of new HMG Co-A reductase inhibiting compounds synthesized by Sandoz chemists.

(2) That all activities referred to in this Declaration took place in the United States.

IN VIVO TESTING OF
WATTANASIN COMPOUNDS 64-933, 64-935 and 64-936/Na

1. On or before October 29, 1987, in my laboratory under my supervision, Rodney Slaughter began performing the below-indicated protocol on compounds 64-933, 64-935 and 64-936/Na:

In vivo studies utilized male Wistar Royal Hart rats weighing 150 ± 20 g. which have been kept for 7-10 days on an altered light cycle (6:30 A.M. - 6:30 P.M. dark) housed two per cage and fed powdered Purina Rat Chow and water ad libitum. Three hours before the diurnal maximum of cholesterol systhesis at mid-day the rats were administered the test substances dissolved or as a suspension in 0.5% carboxymethylcellulose in a volume of 1 ml./100 g. body weight. Controls received vehicle alone. One hour after receiving the test substance, the rats were injected intraperitoneally with about 25 μCi/100 g. body weight of sodium [1-^{14}C]acetate 1-3 mCi/mmol. Two hours after mid-dark, blood samples were obtained under sodium hexobarbitol anesthesia, and the serum was separated by centrifugation. The resulting serum samples were saponified and neutralized, and the 3β-hydroxy sterols were precipitated with digitonin basically as described by Sperry et al., J. Biol. Chem. 187,97(1950). The [^{14}C]digitonides were counted by liquid scintillation spectrometry. The assay is based on the conversion of ^{14}C-acetate to ^{14}C-cholesterol in vivo.

2. The counts in DPM of digitonin precipitable sterol (β-hydroxy sterol, mostly cholesterol in the rat) were entered by Rodney Slaughter into my computer program, which converted them to nCi of sterol found per 100 ml. of serum at 4 hours after the injection of the ^{14}C-acetate.

3. I have reviewed **Exhibit K-1** hereto, which comprises true copies of pages 133, 134, and 135, 136, 137 and 138 of R. Slaughter's Laboratory Notebook #917. I witnessed Rodney Slaughter's signature on each of these pages, and each page bears my true signature as a witness.

4. Notebook pages 133-135 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H318, which was commenced on October 22, 1987. I initialed the first page of this computer printout on or before October 22, 1987. This computer printout on page 135 indicates that an in vivo assay of compound 64-936 was started on October 22, 1987.

5. Notebook pages 136-138 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H319, which was commenced on October 29, 1987. I initialed the first page of this computer printout on page 136 on or prior to October 29, 1987. This computer printout on page 137-138 indicates that an in vivo assay of compound 64-933 and 64-935 was started on October 29, 1987.

6. Both studies were completed on or prior to December 9, 1987, the date indicated at the bottom of pages 135 and 138.

7. It was my responsibility to enter the nCi/dl data into a separate computer program which calculates the ED_{50} values of a compound tested in vivo from the reduction in the nCi of sterols formed from test groups compared to controls for each assay, and forms a database of the ED_{50} values. On or before December 9, 1987, I entered the data for compounds 64-933, 64-935 and 64-936/Na.

8. The 1st page of Exhibit K-1 comprises a true copy of part of the ED_{50} database. This page indicates that the ED_{50} for compounds 64-933, 64-935 and 64-936/Na was in the system as of December 9, 1987. Therefore, the information was available to other Sandoz employees having access to the computer database as of December 9, 1987.

The ED50 for these compounds are:

COMPOUND	ED_{50} (mg/kg)
64-933	0.49
64-935	>1.0
64-936	>1.0

. . .

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 13 day of November 1992.

Robert G. Engstrom

///

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v. Interference Nos. 102,648, 102,975
FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

DECLARATION OF RODNEY SLAUGHTER PURSUANT TO 37 CFR §1.672

I, Rodney Slaughter, do hereby declare as follows:

(1) That I have been employed by Sandoz Pharmaceuticals Corporation since 1982, and during the time periods referred to herein, I worked in the Department of Lipid Metabolism.

(2) That it has been my responsibility to carry out an in vivo testing program of various HMG-CoA reductase inhibitor compounds, including Wattanasin compounds 64-933, 64-935 and 64-936.

(3) That all of the below-indicated activities took place in the United States.

IN VIVO TESTING OF
WATTANASIN COMPOUNDS 64-933, 64-935 and 64-936

1. On or before October 29, 1987, I carried out the below-indicated protocol on compounds 64-933, 64-935 and 64-936:

In vivo studies utilized male Wistar Royal Hart rats weighing 150 ± 20 g. which have been kept for 7-10 days on an altered light cycle (6:30 A.M. - 6:30 P.M. dark) housed two per cage and fed powdered Purina Rat Chow and water ad libitum. Three hours before the diurnal maximum of cholesterol systhesis at mid-day the rats were administered the test substances dissolved or as a suspension in 0.5% carboxymethylcellulose in a volume of 1 ml./100 g. body weight. Controls received vehicle alone. One hour after receiving the test substance, the rats were injected intraperitoneally with about 25 μCi/100 g. body weight of sodium [1-^{14}C]acetate 1-3 mCi/mmol. Two hours after mid-dark, blood samples were obtained under sodium hexobarbitol anesthesia, and the serum was separated by centrifugation. The resulting serum samples were saponified and neutralized, and the 3β-hydroxy sterols were precipitated with digitonin basically as described by Sperry et al., J. Biol. Chem. 187,97(1950). The [^{14}C]digitonides were counted by liquid scintillation spectrometry. The assay is based on the conversion of ^{14}C-acetate to ^{14}C-cholesterol in vivo.

2. I entered the counts in DPM of digitonin precipitable sterol (β-hydroxy sterol, mostly cholesterol in the rat) into a computer program, which converted them to nCi of sterol found per 100 ml. of serum at 4 hours after the injection of the ^{14}C-acetate.

3. I have reviewed **Exhibit K-1** hereto, which comprises true copies of pages 133, 134, 135, 136, 137 and 138 of my Laboratory Notebook #917.

4. Notebook pages 133-135 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H318, which I started on October 22, 1987. These pages contain the date of 10/22/87 at the top in my handwriting.

5. Notebook pages 136-138 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H319, which I started on October 29, 1987. These pages contain the date of 10/29/87 at the top in my handwriting.

6. Both studies were completed on or prior to December 9, 1987, the date indicated at the bottom of the computer printouts on pages 135 and 138.

7. It was my practice to paste the computer printouts into my notebook and to sign the notebook page when I did this.

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 13 day of November 1992.

Rodney Slaughter

FYI

Case No. 600-7101/CONT/Int. (2)
Patent

NOV 19 1992

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

RECEIVED IN
INTERFERENCE

WATTANASIN
v.
FUJIKAWA et al.

Interference No. 102,648 - #65
Examiner-in-Chief: M. Sofocleous

WATTANASIN
v.
FUJIKAWA et al.
v.
FUJIKAWA et al.

Interference No. 102,975 - #7
Examiner-in-Chief: M. Sofocleous

NOTICE OF THE FILING OF WATTANSIN CONSOLIDATED AFFIDAVIT TESTIMONY PURSUANT TO 37 CFR 1.672

Appended is the consolidated affidavit testimony of the party Wattanasin for the above-numbered interferences.

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 Nov. 16, 1992
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
11/16/92
Date of Signature

Respectfully submitted,

Diane Furman
Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

DEF:rmf
November 16, 1992

Enclosures: Volume I (pages 1-114)
Declaration of S. Wattanasin
Declaration of S.Barcza

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PAT. & TRADEMARK OFF.

Enclosures (continued):

Declaration of R. Patel
Supplemental Declaration of R. Patel
Declaration of T. Scallen
Declaration of N. Paolella
Declaration of F. Kathawala
Declaration of R. Damon
Declaration of D. Weinstein
Declaration of L. Perez
Declaration of R. Engstrom
Declaration of R. Slaughter

Volume II (pages 115-262)
Exhibits A-1, A-2, A-3
Exhibits B-1, B-2
Exhibits C-1, C-2, C-3
Exhibits D-1, D-2, D-3
Exhibits E-1, E-2, E-3, E-4, E-5

Volume III (pages 263-355)
Exhibit F-1
Exhibits G-1, G-2
Exhibit H-1
Exhibit I-1
Exhibit J-1
Exhibit K-1
Exhibit L-1

. . . .

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

NOTICE OF THE FILING OF CONSOLIDATED WATTANSIN AFFIDAVIT TESTIMONY PURSUANT TO 37 CFR 1.672

together with the declarations and exhibits appended to said paper, were served on counsel for the party Fujikawa et al., this 16th day of November, 1992, 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

Exhibit A

FYI

NOV 17 1992

RECEIVED IN
BOX INTERFERENCE

VOLUME II

Interference No. 102,648 - #66

Interference No. 102,975 - #8

WATTANASIN Consolidated

Affidavit Testimony

and Exhibits

VOLUME II

Interference No. 102,648

Interference No. 102,975

WATTANASIN Consolidated
Affidavit Testimony
and Exhibits

(3) copy to Dr. Kathawala 115

1984 Proposal

Sompong Wattanasi
November 28, 1983

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

We will conduct the work in the approximat 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

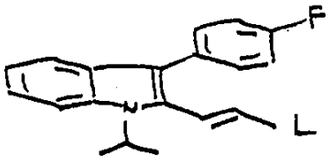
② Synthesis of "restricted rotation" Indole analogues,

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



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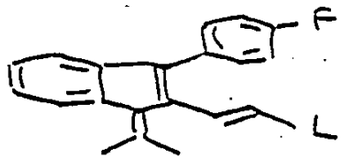
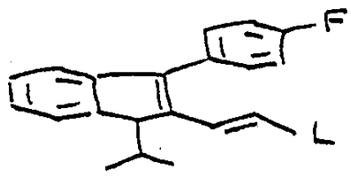


2

L = Lactone



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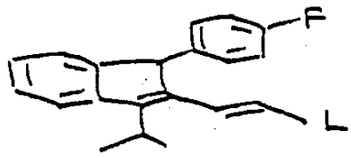
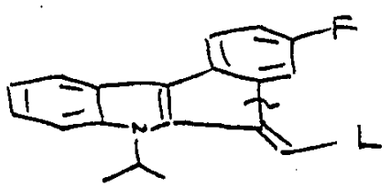


4

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



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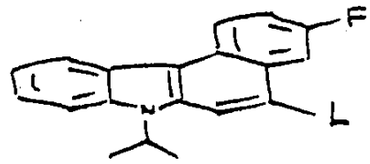
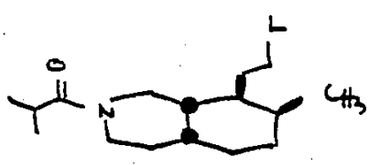


6

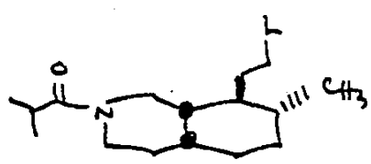
Analogues 5 and/or 6 are proposed as probes of the rotation requirements of the para-fluorophenyl group and the double bond side chain of the lactone. Nothing is currently known in this regard.

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

A) Asymmetric Synthesis of an aza analogue of compactin



7



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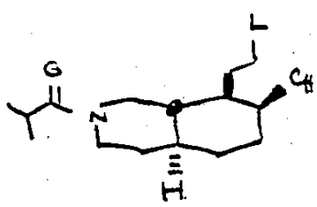
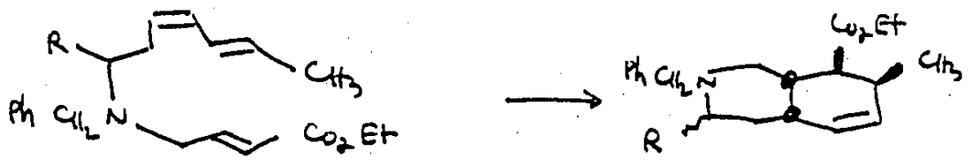


9

The racemic compounds 7 - 9, aza analogues 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.

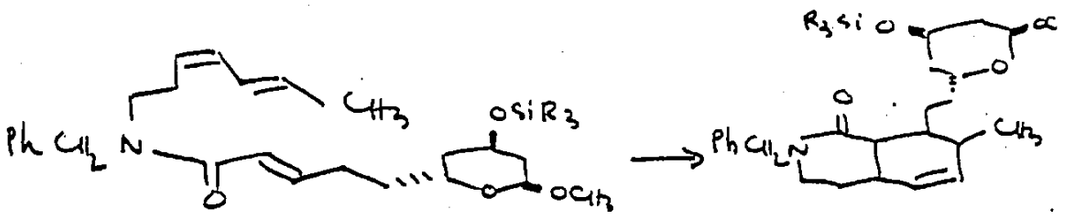


10

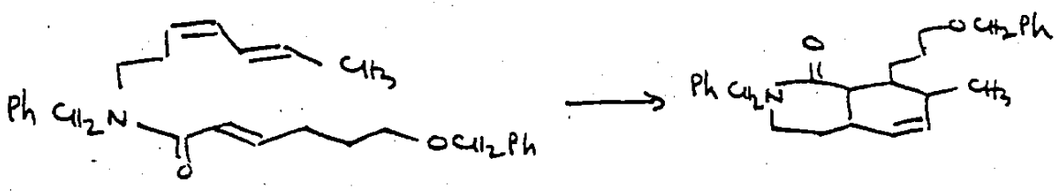
The highly stereospecific and the usefulness of the method in the synthesis of this type of compounds makes us feel necessary to demonstrate the followings:

(a) Effect of the R group (R = CH3 rather than H) in the cyclisation.

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

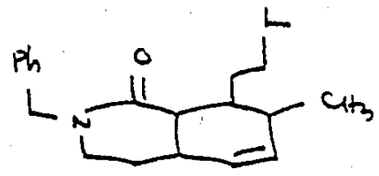


stereochemistry



C). Synthesis of the analogue 11.

Compound 11 is a close relative of the aza analogues of compactin 7 – 9, but might be more readily obtainable by the route shown above.

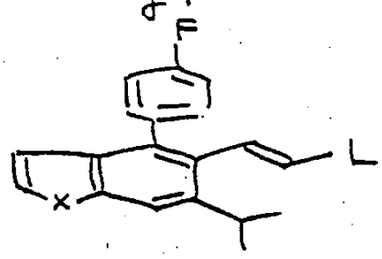


11

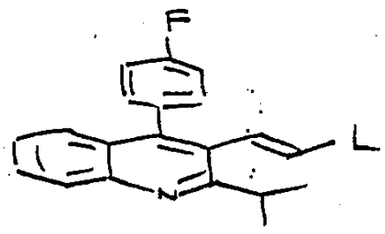
In addition, computer modellings show a better overlapping between compactin and 11 than those of 7 – 9

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.

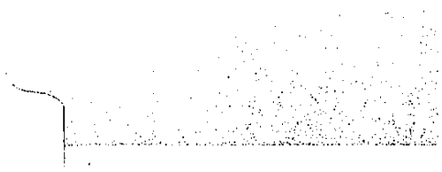


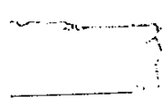
12 X = NR
13 X = S



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)

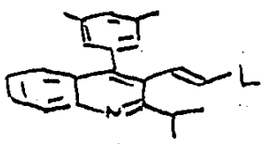
Sompong Wattanasin

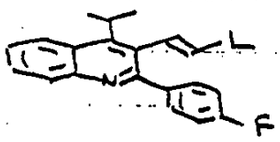
Nov. 19, 1984.

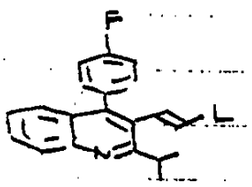
1985 Proposal

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

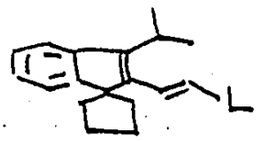


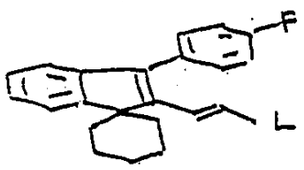


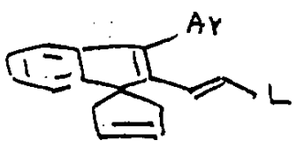


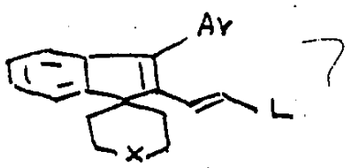
a few modifications might need to be prepared, because of their appearent ease of synthesis.

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



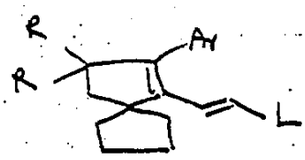




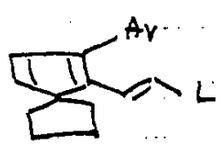


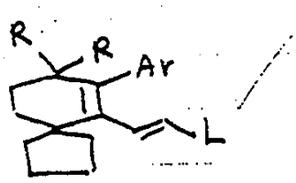
X = O, NR, S

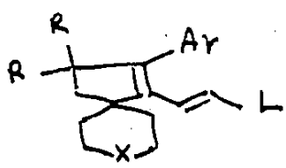
(3) New Analogs of Indenes.



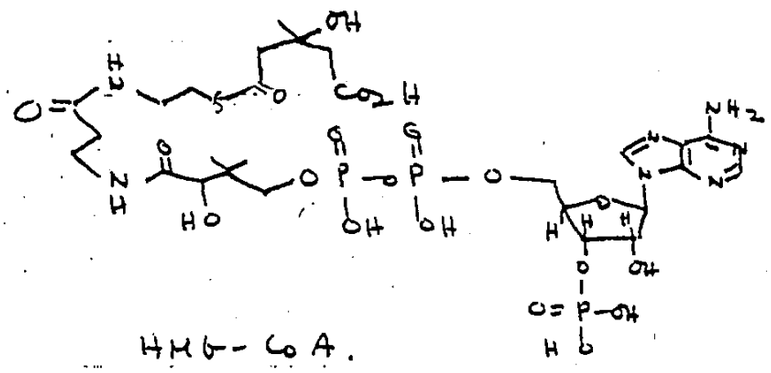
R = Aryl, alkyl groups.
X = O, NR, S





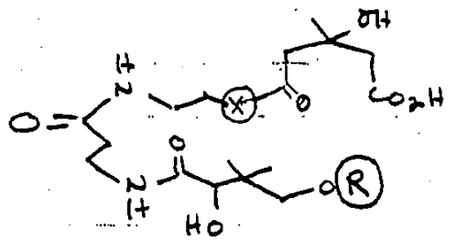


(4) X-ray structure of crystalline HMG-CoA derivatives.

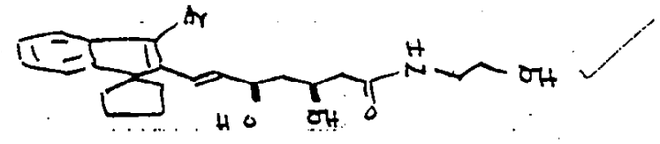


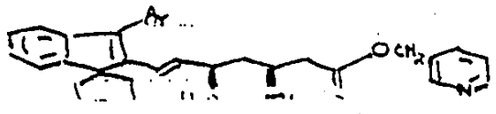
HMG-CoA.

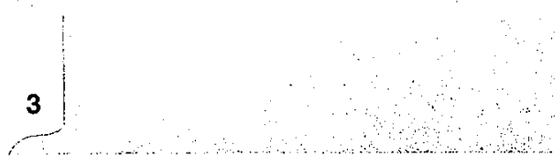
Derivatives vary R & X



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






3

B-July 87 X-Oct 91 Y-11/87

DISCLOSURE OF INVENTION

124

General Subject Matter: (CLASS 544)
QUINOLINES

Invention pertains to: (check all applications)
- [X] NEW PRODUCT
- [ ] NEW PROCESS
- [ ] NEW FORMULATION
- [ ] NEW USE

FOR PATENT DEPARTMENT

Pat. Comm. Rating	Disclosure No.
	299/84
Assigned to: JMC HW	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 18 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

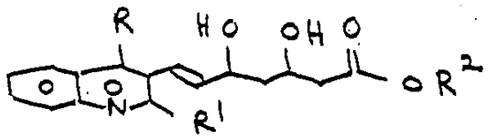
All other pertinent Notebook Pages

Notebook	Page(s)	Notebook	Page(s)
1049	237, 239, 241, 243,	1079	22, 24, 29, 30, 33, 34, 39, 41, 83, 91, 101, 111
	244, 245, 248, 251	1127	11, 13

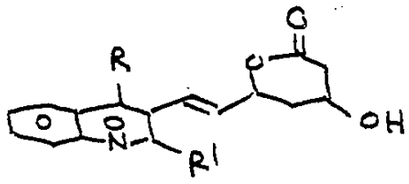
All other pertinent Memos and Reports

Date	From	To
11/28/83	S. WATTANASIN	F. G. KATHAWALA
11/15/85	S. WATTANASIN	F. G. KATHAWALA

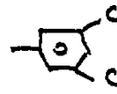
Description of Invention: (include flow sheet where applicable, applicable conditions, critical features, if any, advantages of invention, contemplated scope, products prepared)



I



II

R =  , (i-Pr)

R¹ = 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 ;6 ;6 ;6

List Closest Prior Art

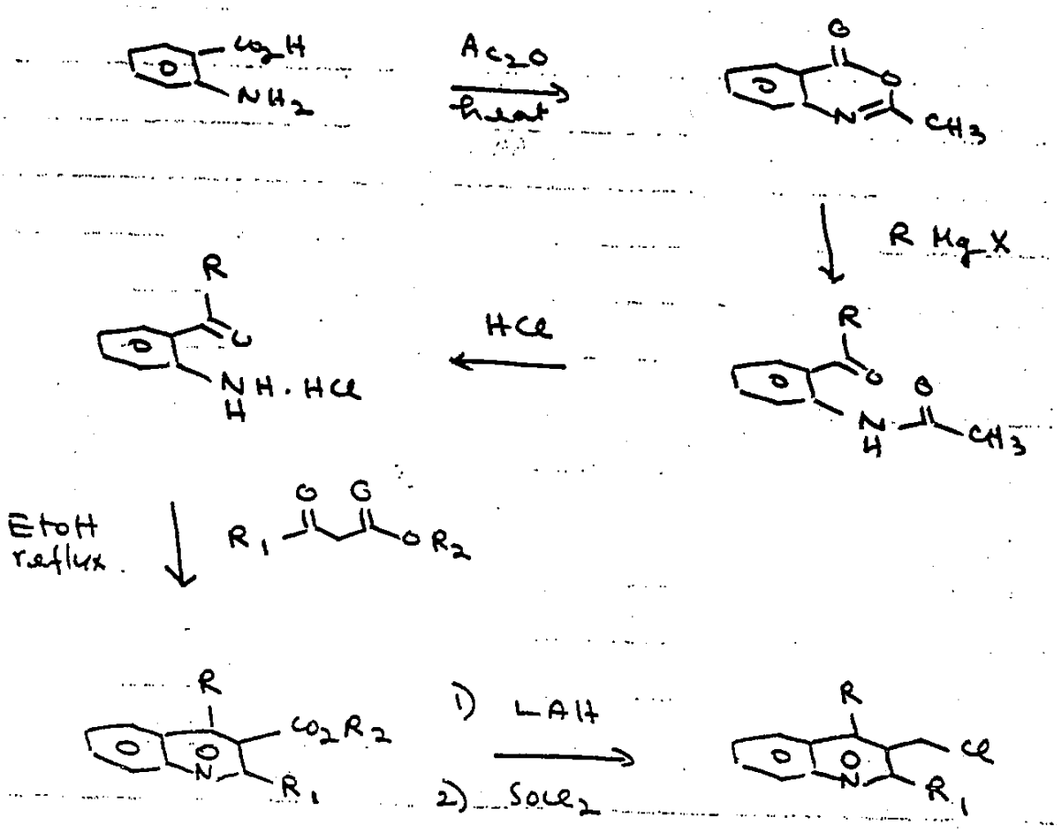
L & D Report No.

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

Witnessed by: J. F. Kathawala Date: 3/16/87

13 Re 8

Route I


CO2H
NH2
Ac2O
heat
CH3
R MgX
R
HCl
NH · HCl
NH
CH3
EtOH
reflux
R1
R2
CO2R2
1) LAH
2) SOCl2
Cl
P(OEt)3
1) LDA
I + II
Ph2
OSi
OHC
CO2R3
3) nBu4NF
P(OEt)2

Route II

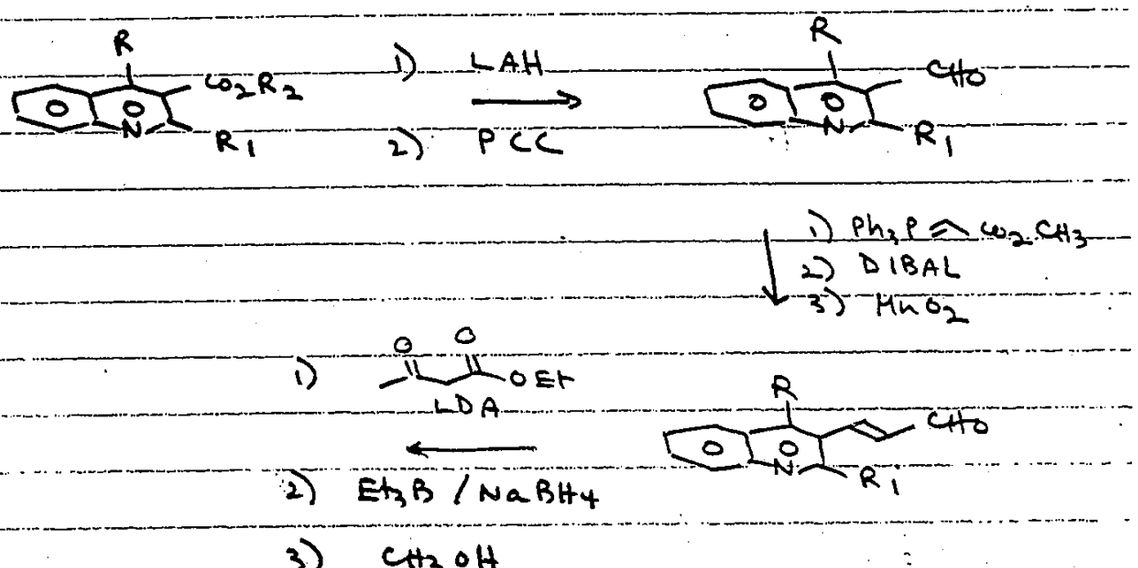
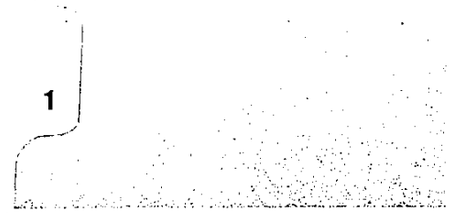
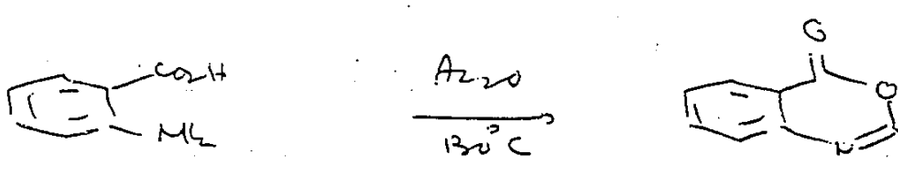

R
CO_2R_2
R_1
1) LAH
2) PCC
CHO
1) $Ph_3P=CO_2CH_3$
2) DIBAL
3) MnO_2
I
1)
OEt
LDA
2) Et_3B / $NaBH_4$
3) CH_3OH

Exhibit B


1

See. JCS 2702 C(9 F)



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 MeOH gave a pale yellow solid = 8.9 g C(1049-237-19)

nmr

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

nmr IR micro

$C_9H_7O_2N$ 161.161

	C	H	N	O		
Calc.	67.08	4.38	8.69			
Found						
	66.80	4.41	8.71			

Performed by- S. Wattanasin
Witness- M. Rockelle
Cont'd to-

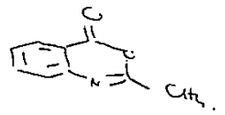
[redacted]

128

SAMPLE NO. 1049 - 237-27
SOLVENT CDCl3
REFERENCE TMS
TEMP. °C TUBE 5 mm
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOD u
IRR. POWER
PUMOD
NO. of ACCUM. 80
DATA POINTS
SPECTRAL WIDTH
DATE 5/31/84
OPERATOR SO
FX 90Q
SPECTRUM NO. R 4716
11.25ppm
0
50
100
1H
13C

ABSORBANCE
TRANSMITTANCE (%)
WAVENUMBER (cm⁻¹)
THRESHOLD?
DATE 5-31-84
SPECTRUM NO. 1317
OPERATOR
SAMPLE 1049-232-23
PHASE KBr
THICKNESS
NOTES: Gastric Juice B: 049-232-23
Smooth NC
Bsly
Dr. Hallaran
STORED ( ) INTERLEAVED ( ) BKG
NO. SCAN PAIRS (SAM/BKG) (32/4)
AUXILIARY DISPLAY
TRANS. ( ) ABSORBANCE ( )
VERT. ORIGIN 0 SPAN 120
HOR. ORIGIN 4m SPAN 4m
SANDOZ

129



SAMPLE NO. 1049-237-2
SOLVENT $CDCl_3$
REFERENCE $CDCl_3$ (77)
TEMP. °C TUBE 5
OBSERVE NUCLEUS 13
MENU NO. 11
IRMOD
IRR. POWER
PUMOD
NO. of ACCUM. 4,145
DATA POINTS 16k
SPECTRAL WIDTH 12k
OATE 6/1/84
OPERATOR mzk
FX 200
SPECTRUM NO. R-047

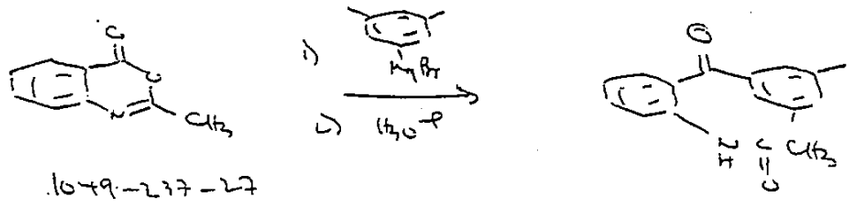
87355/81 (Rev

130

Date 5/31/84. Proj. | Title- (~17) | 241

Cont'd From-

cf. P. 158. 131



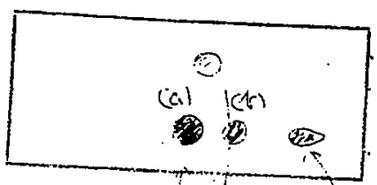
1049-237-27

161	1049-237-27	=	2 g (0.0124 mol)
(15ml)	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 few drop of I_2 at r.t, was added a few drops of 1,2-dibromoethane, followed by a soln of 5-bromo-m-xylene in ether (5 ml) dropwise (at a rate that the reaction mixture refluxes gently). 9.05 am. ~~9.44~~ 9.45 am. The reaction mixture was then heated at reflux for 3 h. Then the Grignard reagent was withdrawn by a syringe (5 ml) and added to a soln of 1049-237-27 in Phit (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 μg) (1:1 eth—pet.) gave

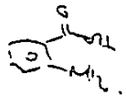


SM. (a): white oil = 128 mg (1049-241-34)

NMR

(b): white solid = 24 mg (1049-241-32)

Show weak KMnO4 ppt. Come from hydrolysis of S.M.



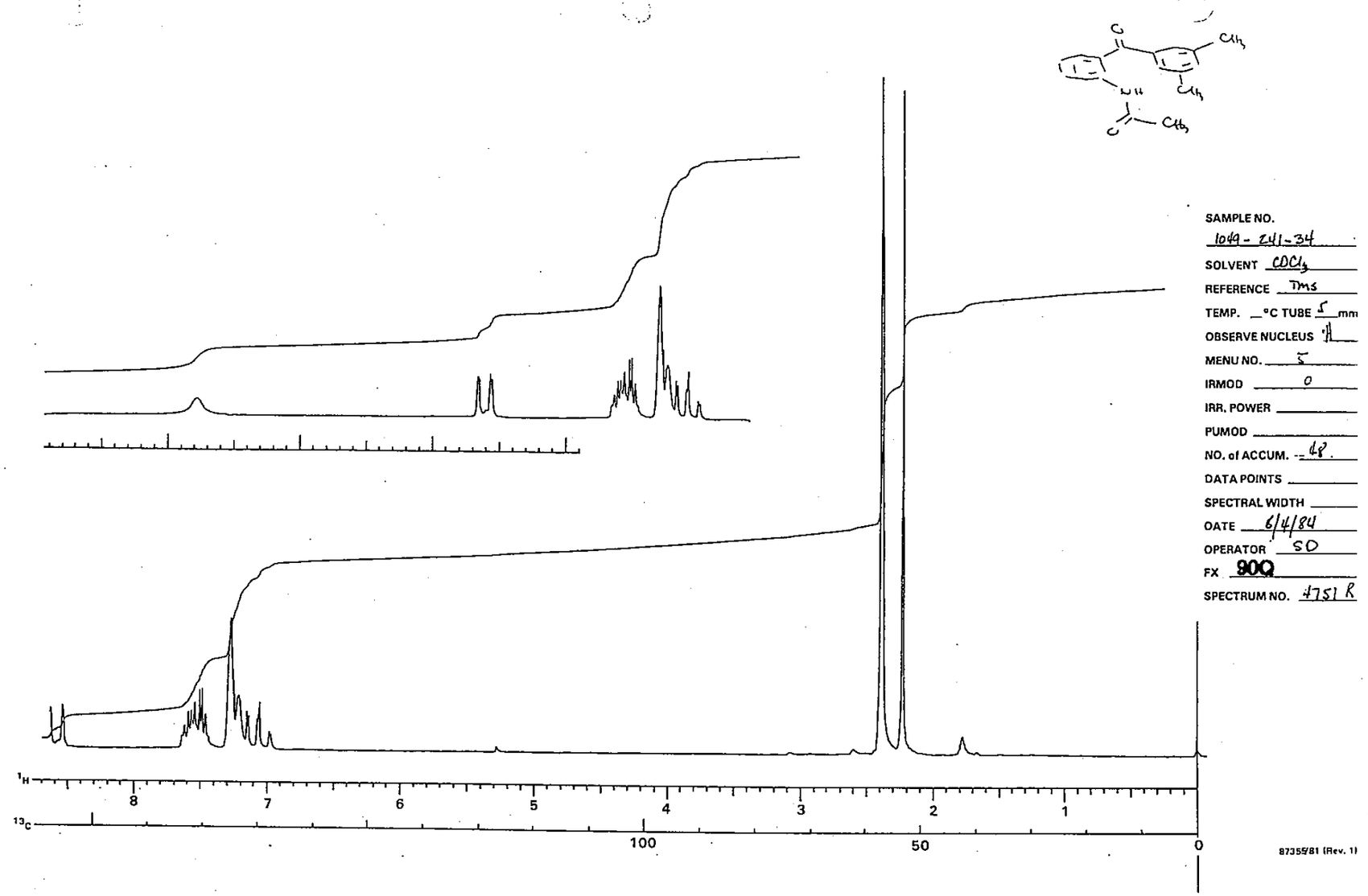
HPLC of the rest gave the product = 1.6 g (1049-241-43)

Performed by- S. Wattanasin

Witness- M. Rabello

Cont'd to-

[redacted]

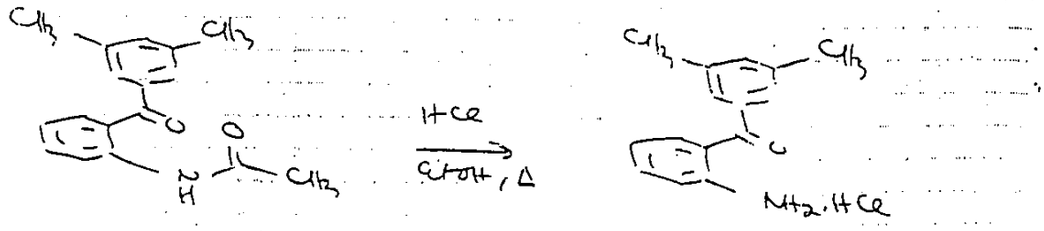


132

Title- 1049

Date 6/6/84 Proj.

Cont'd From- 133



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.

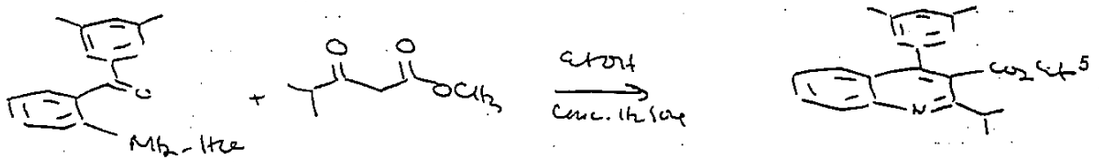
stop 4.00 pm TLC showed very small amt of the starting material.

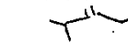
The soln was concentrated and the residue was taken up in ether and filtered to give a pale yellow solid = 1.15 g (1049 – 145 – 24)

Performed by: S Wattanasin

Witness: M. Ruckelle

Cont'd to-

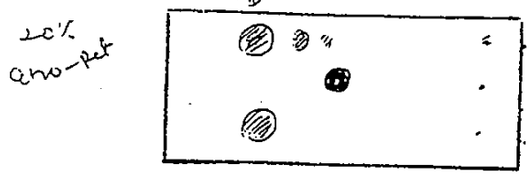


(261.5) 1049 = 248 – 24 = 500 mg (0.001912 mol)
(144)  = 412 mg (0.00286 mol)
EtOH = 20 ml.
Conc H2SO4 = 0.1 ml.

Procedure Same → 1049-245 Rx. 15

Start reflux. @ 10 am:

Tlc 12.30 pm. Stop 12.30 pm. 20



Concentrated, basified with NH4OH, diluted with H2O & extracted with ether to give an oil = 420 mg Prep Tlc (20% eno-petrol) gave one main band. 25

= 565 mg which on standing in the fridge solidified: pale yellow solid. (1049-245(-29)) 30

m.p. 82–83°C

$C_{22}H_{24}N_2O_2$ micro

	C	H	N	O
Calc.	78.57	7.14	4.03	
Found	78.78	6.83	4.30	
	80.3	7.01	4.32	

35

40

Performed by- S. Wattanasin

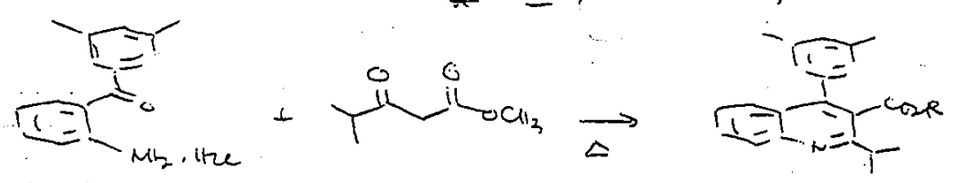
Witness- M. Rapella

Cont'd to-

[redacted]

135

cf. J. Het. Chem. 7 (85 (1970)
J. Prakt. Chem. [4] 34, 295 (1966)

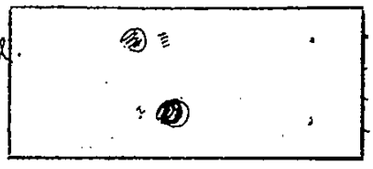


(261.5) 1049-244-24 = 20 mg (0.0000766 mol)
(144) = 11 mg (0.0000811 mol).
⇒ EtOH = 2 ml. → 0.02 ml.
conc. H2SO4 = 1 drop.

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

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

(a) (b)

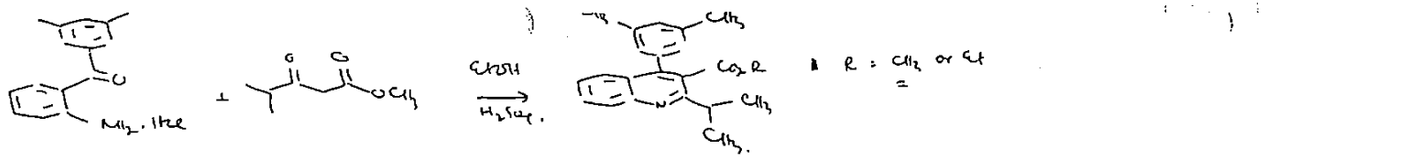


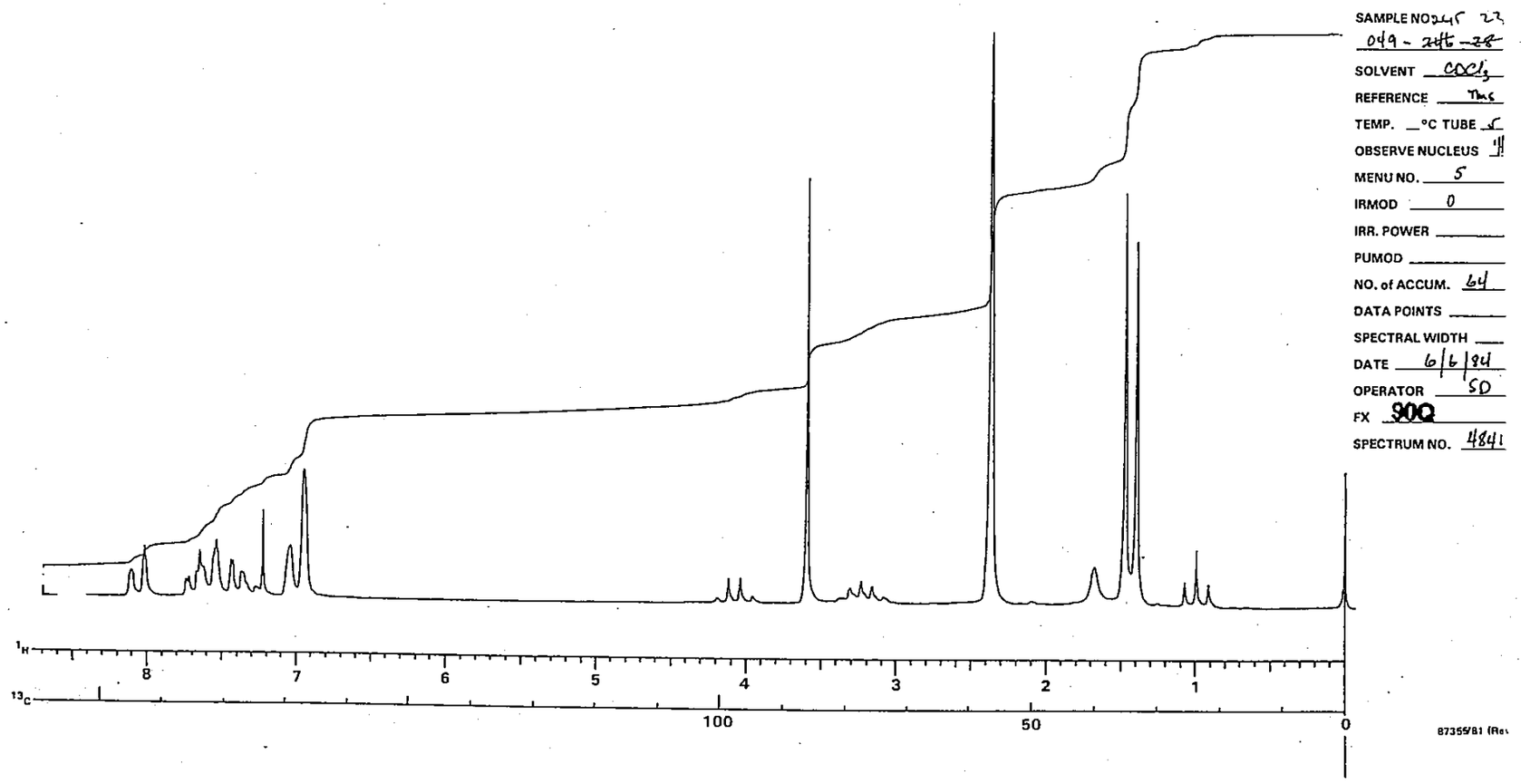
1:1 ether-petrol.
R2
SM. (ketoester)

colorless oil
(a) 12 17 mg (1049-244-24)
nmr ✓ ⇒ perfect.

Performed by- G. Wattanasin
Witness- M. Barbella
Cont'd to-

[redacted]





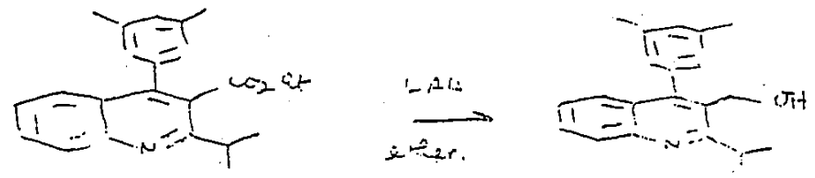
136

Title- # 1079

Date 8/10/84. Proj.

Cont'd From-

137



$C_{13}H_{14}O_2N$

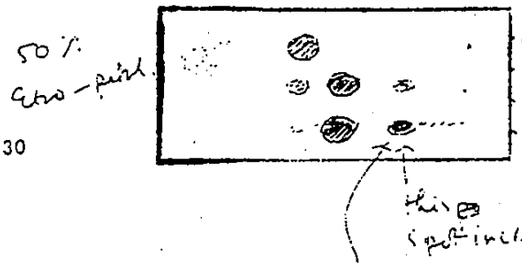
(347) . 1049-271-29 : 535 mg (0.00154 mol)
(38) LAH : 117 g. (0.0031 mol)
ether : 8 ml

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 T.L.C.

9.15 am:

T.L.C after 10 min ⇒ 2 spots mainly the product.

9.50 10.15 am



The reaction was quenched with the addition with ether, to give a crude (1049-22-29) as white solid 427 mg

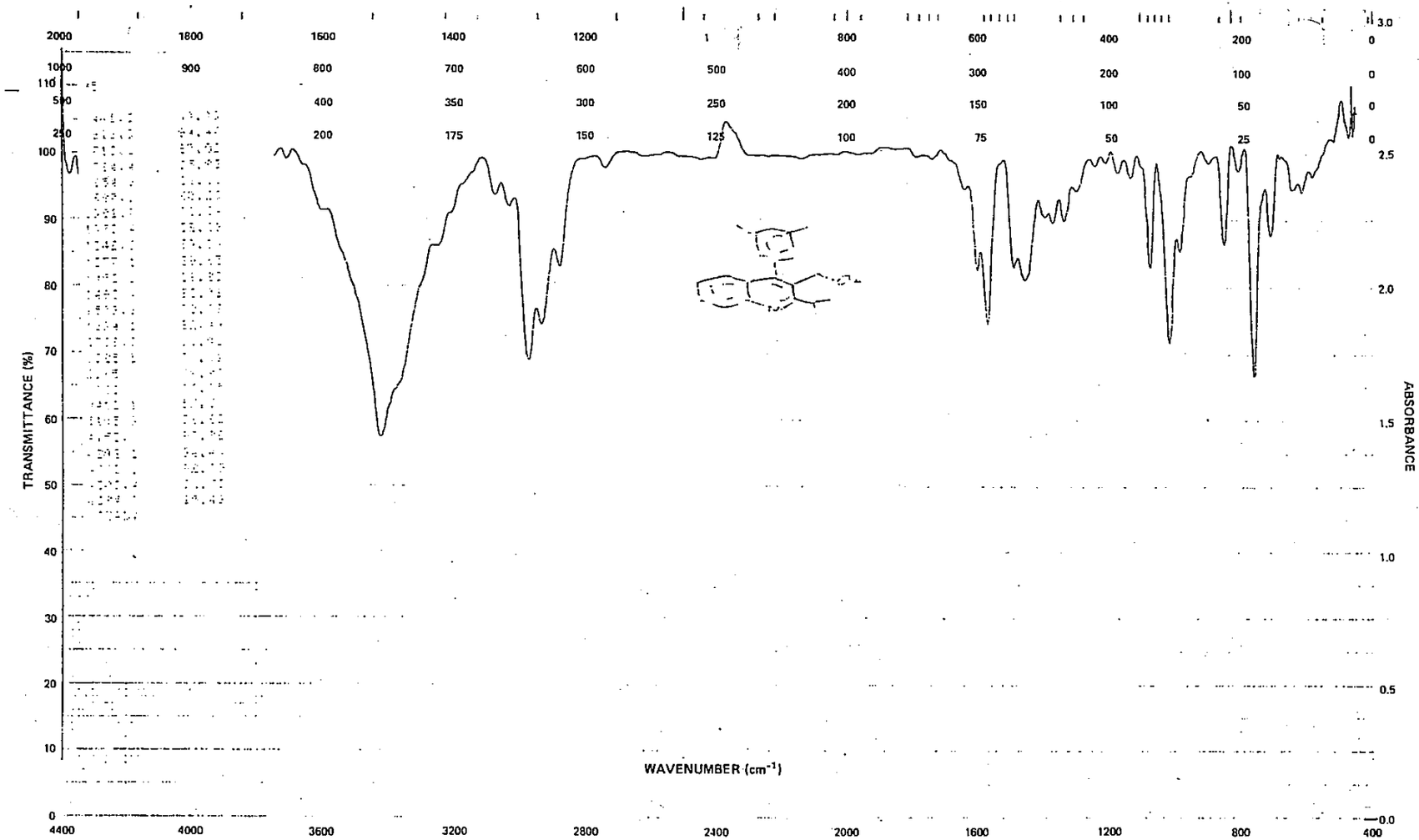
mp 112-113°C (Stable on standing)

IR ⇒ (all what not polar)

Performed by- S. Watanabe

Witness- M. Perfetti

Cont'd to-



DATE 8-10-84	SAMPLE 1079-22-28	NOTES: Prep: Tech. B: 1079-22-28	STORED (INTERLEAVED (TBKG	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 Pr Wafer	BSLN	AUXILIARY DISPLAY	HOR. ORIGIN 440 SPAN 440

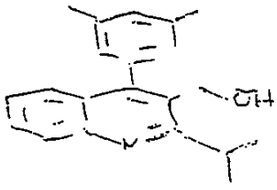
SANDOZ

138

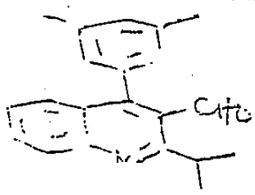
Title- # 1079

Date 8/10/94 Proj.

Cont'd From-



MnO_2 → Toluene



10.79 - 2.2 - 2.1 = 4.20 mg

Mass = 5.00 mg

Theor = 6.6 mg. (Ind.)

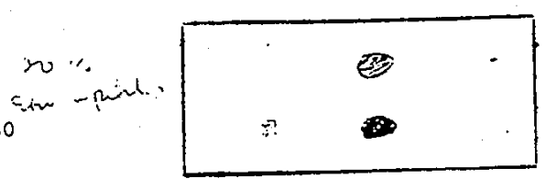
A melt of $C_{10}H_{14}O_2$ and more in toluene was stirred at R.T / ~~day~~, Crude then. (1 ST am).

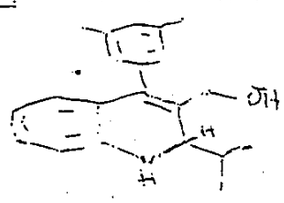
TLC after 2 days still S.M.

The reaction was diluted with CH_2Cl_2 and filtered through a pad of silica gel (5 cm) Evap gave a pale yellow oil = 4.2 mg ($C_{10}H_{14}O_2$ - 2 H - 2 H).

92.9 % pure

N.M.R GC MS ⇒ M^+ 207 ?

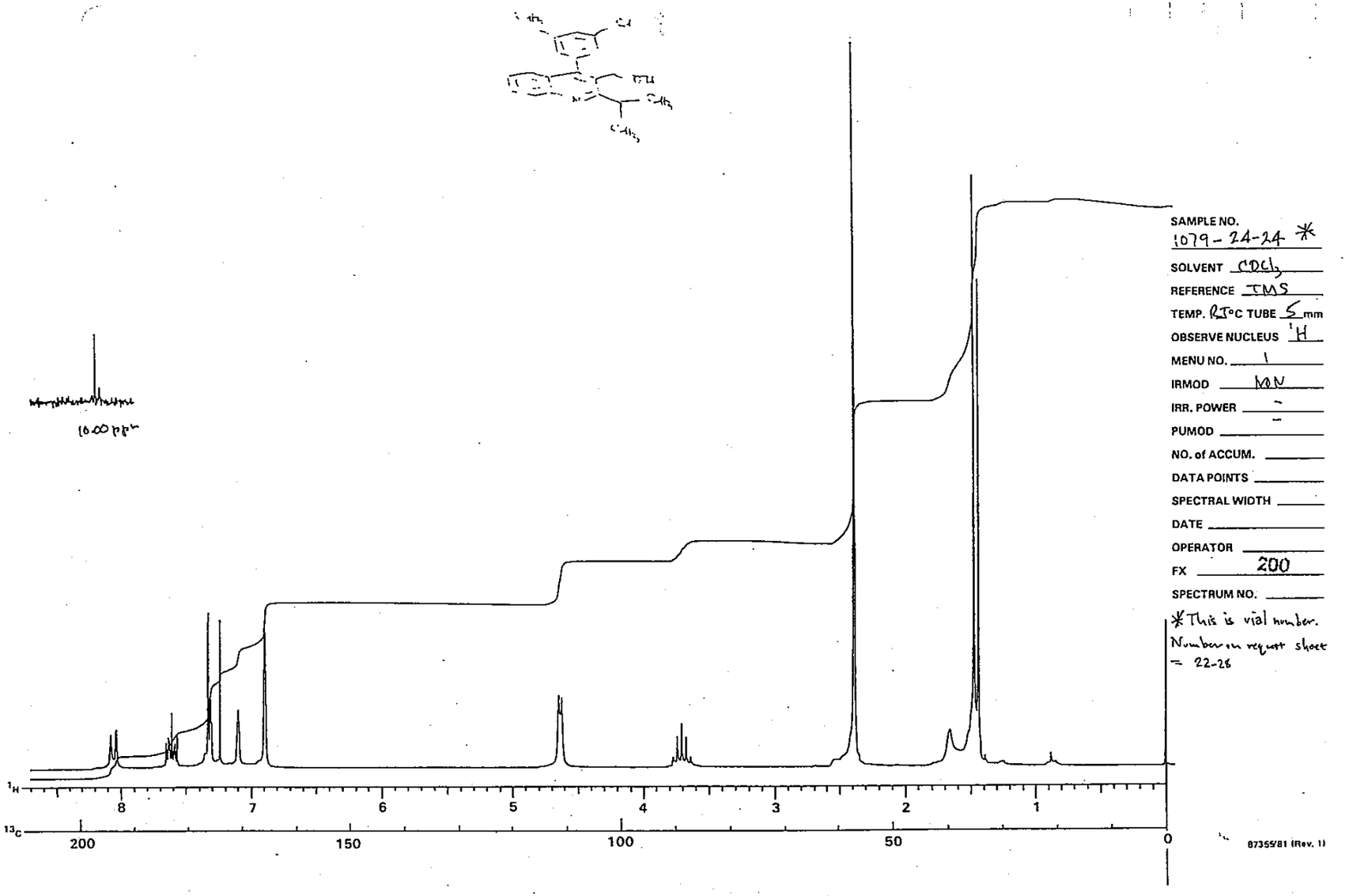




Performed by- S. Wattanmaniwat

Witness M. Padilla

Cont'd to-



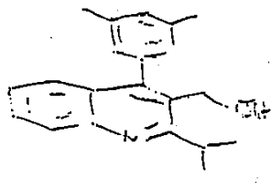
140

Date Proj.

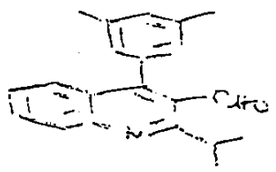
Cont'd From-

Title # 1079

27 1/11



PCC.



DDQ =

Toluene =

⇒ The mixt. was stirred at r.t. overnight. TLC no r.a.

The reaction mixt. (dark red color) was diluted with water and filtered through a pad of silica gel. Evap. gave a dark red gum. TLC ⇒ no change.

⇒ The crude gum was dissolved in 1:1 CH_2Cl_2 / PCC (400 mg), and vacuum column for 1½ hr at r.t. The mixt. was stirred ⇒ TLC ⇒ complete rx. Diluted with ether, filtered through silica gel (3 g). Evap. gave a red solid (1079 — 27 — 14 — 151 mg). M.M.P., IR. Submitted for biological testing.

Cmpd-retrif

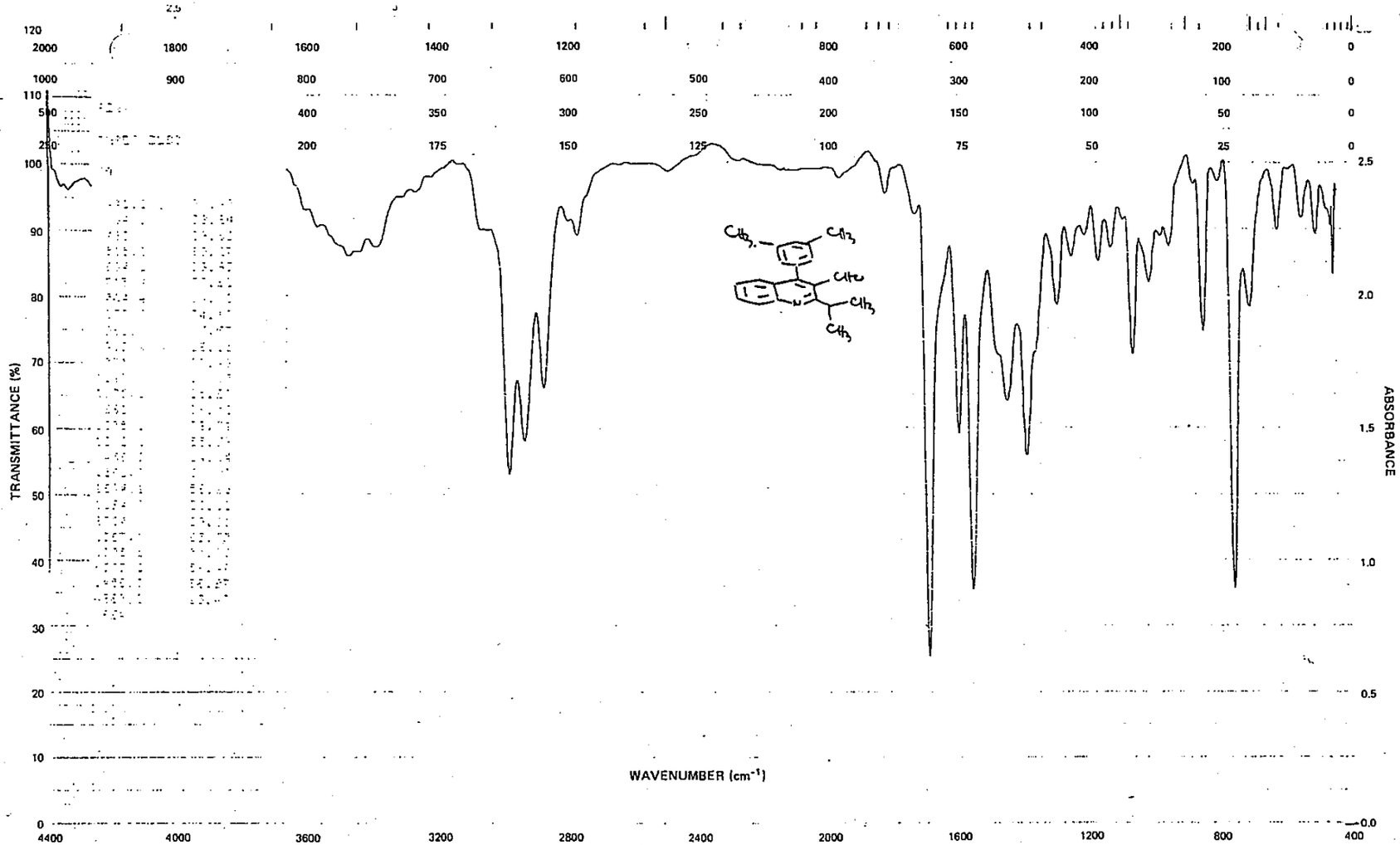
cm.

mm.

Performed by- S. Wattanasin

Witness- M. Parlelle

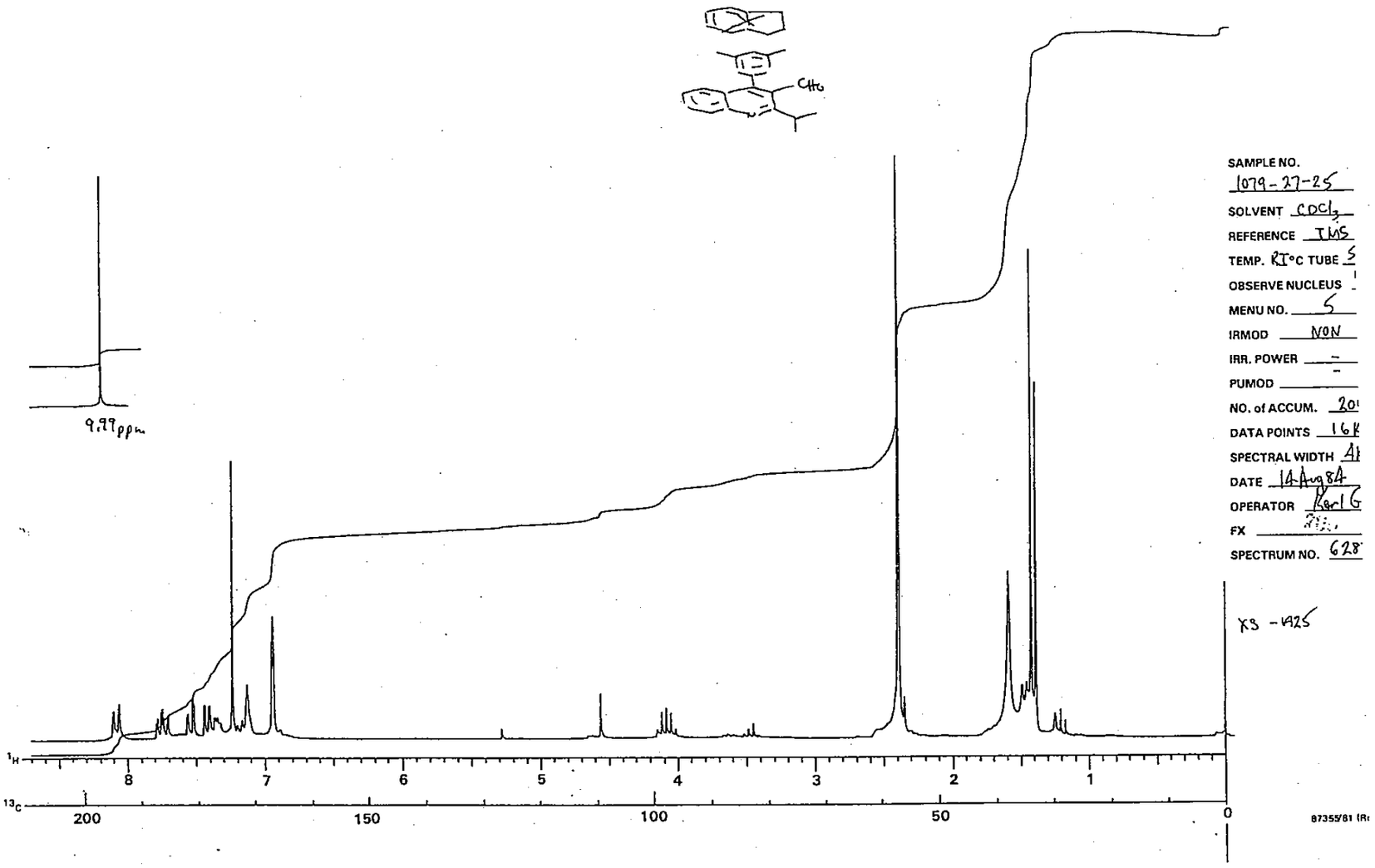
Con'd to-



DATE 9-14-84	SAMPLE 1079-27-25	NOTES Jim Flate. B: 1075-27-25	STORED (INTERLEAVED (BKG	TRANS. (ABSORBANCE ( )
SPECTRUM NO. 2029	PHASE KBr	Smooth 15	NO. SCAN PAIRS (SAM/BKG) 32/64	VERT. ORIGIN 0 SPAN 120
OPERATOR J.M.	THICKNESS — Dr. Wallenfels	Bs/N	AUXILIARY DISPLAY	HOR. ORIGIN 440 SPAN 4400

SANDOZ

142



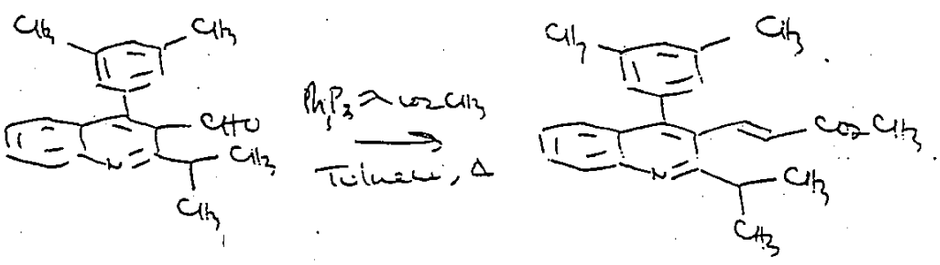
143

Title #1079

Date 8/17/94 Proj.

Cont'd From-

144



1079-27-2 = 140 mg
the ylide = 200 mg
toluene = 5 ml.

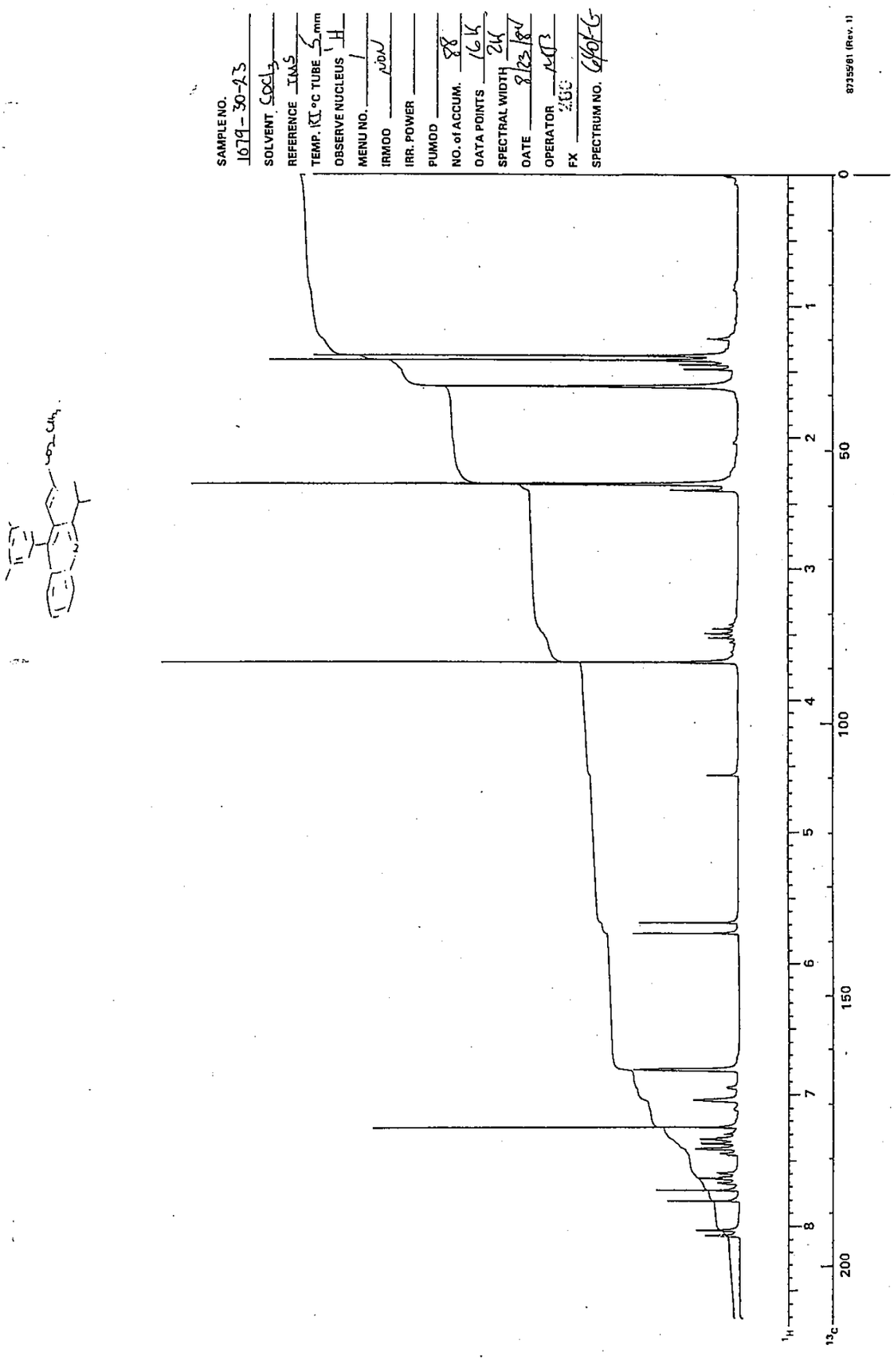
The mixt. was heated at reflux for 3 h. After cooling the reaction mixt. was diluted with ether and filtered through a pad of silica gel. Concentration gave a semisolid, which was purified by prep. TLC to give a colorless solid = 140 mg (1079-30-23) IR nmr ✓ mp 110-112°C

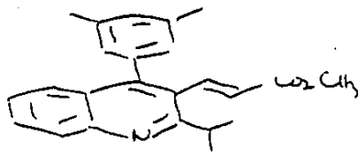
TLC => only one main band of product

Performed by- S. Wattanasin

Witness- M. Mobelli

Con'd to-


SAMPLE NO. 1679-30-A3
SOLVENT CDCl3
REFERENCE TMS
TEMP. RT °C TUBE 5mm
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOD non
IRR. POWER
PUMOD
NO. of ACCUM. 8
DATA POINTS 16K
SPECTRAL WIDTH 24
DATE 8/23/84
OPERATOR MT3
FX
SPECTRUM NO. GP01-C
8735/81 (Rev. 1)
1H
13C
0
1
2
3
4
5
6
7
8
50
100
150
200



1079-30-23 = 130 mg (0.0003768 mol)
DIBAL-H = 0.5 ml. (0.0007536 ml).
CH_2Cl_2 = 5 ml.

To a Solution of (1079-30-23) in dry CH_2Cl_2 at -50°C was added DIBAL-H. The mixt. was then stirred at -50°C

11.30 am :
12.00 pm ⇒ complete reaction

The reaction was diluted with ether and filtered through a pad of silica gel. Evapn gave a crude oil = 135 mg which was used directly in the next step (1079-33-19) TLC ⇒ one spot

1:1 Etro-petrol.

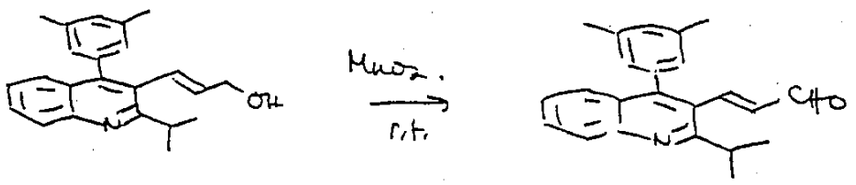
Performed by-
Witness- R. Parelle
Cont'd to-

Title- # 1079

Date 5/23/89 Proj.

Cont'd From-

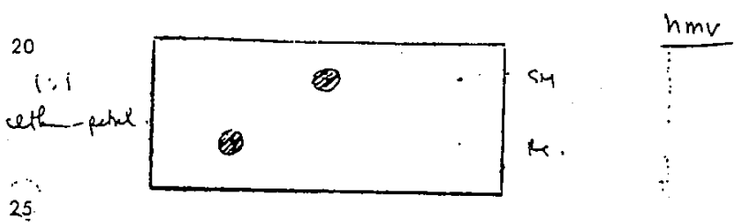
147



1079-33-19 = 135 mg
MnO2 = 300 mg
Toluene = 5 ml.

A mixture of (1079-33-(9) and MnO2 in toluene was stirred at r.t. overnight

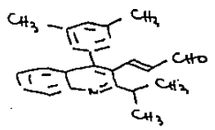
petrol ether 1:1 ⇒ 104 mg (1079-34-17)

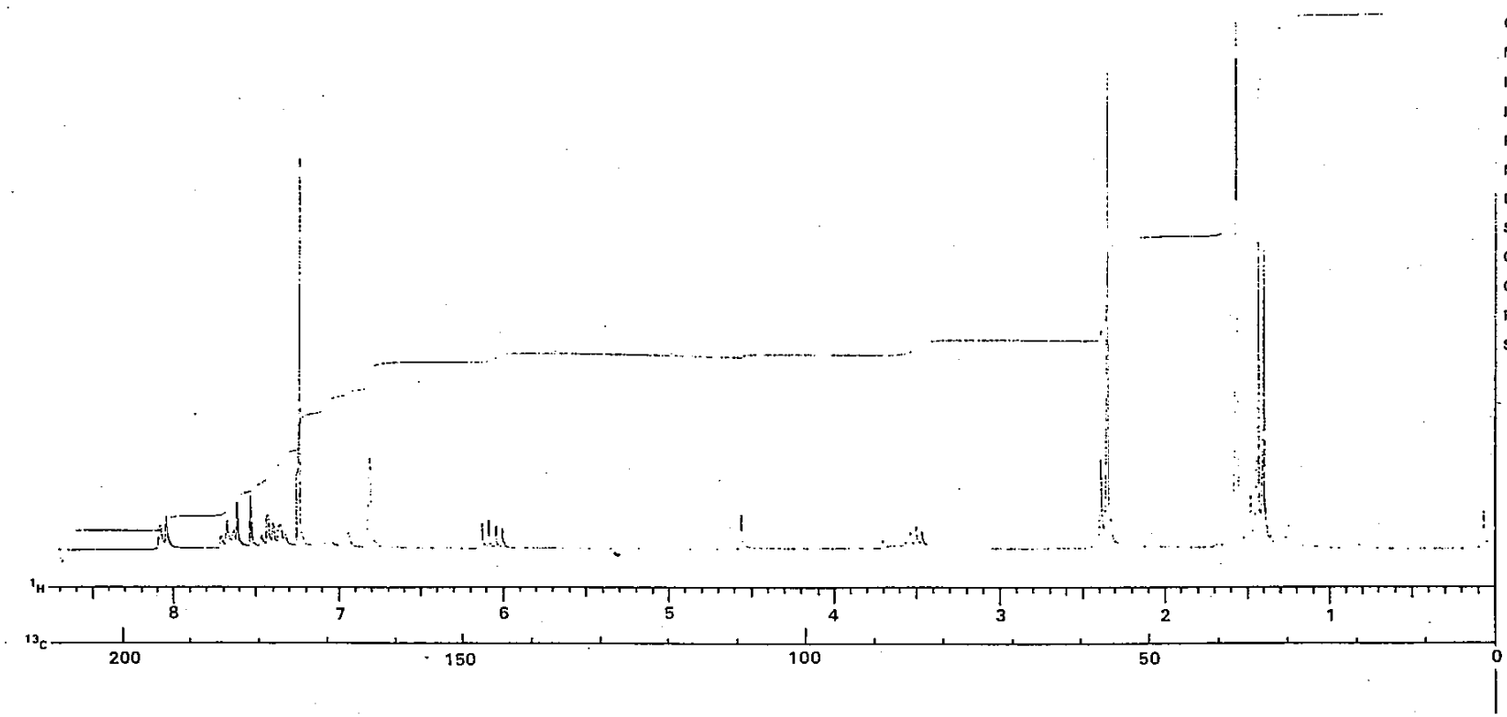


Performed by- S Wattamwar

Witness- N. Padella

Cont'd to-





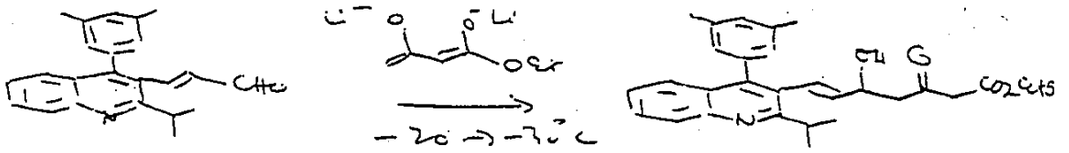
84/148

Date 9/5/89. Proj.

Cont'd From-

Title- # 1079

149



(3eq) 1079-34-17 = 100 mg (0.0003039 mol).
the diamine from
1079-38-21 = 5 ml (≈ 0.0014 mol).
THF = 4 ml.

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

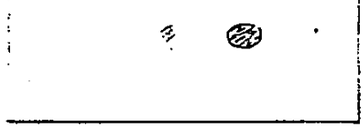
to give an yellow oil = 177 mg (1079-39-1F)

The crude p. was reduced directly without further purification

see P. ~~40~~, 41

The ⇒ one major spot.

1:1 EtOAc-Pet.



Performed by- S. Wattanasin.

Witness- M. Rodeller

Cont'd to-

[redacted]

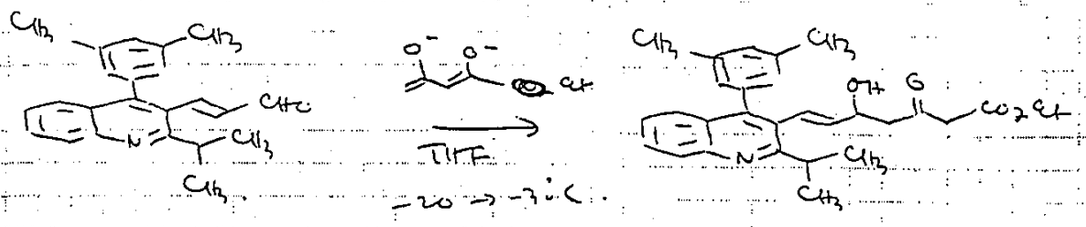
Date 11/8/84. Proj.

Title- 22.57 wt = 1.8 M = 1.8 eq. N2 ml.

Cont'd From-

105

150



(329)	1079 - 101 - 28	=	110 mg (0.0003343 mol)
10.19, .322	Diisopropylamine	=	0.5 ml. (0.00334 mol)
	1.6 M n BuLi	=	2 ml. (0.00334 mol).
130.14, 1.021	Ethyl acetoacetate	=	0.22 ml. (0.000 (67 ml)
	THF	=	4 ml.

commercially available

To a soln of diisopropylamide (1.8 M in cyclohexane, 1.8 ml) in THF (4 ml) at -3°C, was added ethylacetoacetate (0.22 ml). The resulting yellow soln was stirred at -20 → -3°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 -3°C. → -10°C

4.40 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 ether

Et-pet (1:1) (1-) (a) Rf gave a yellow oil = 290 mg
Prep TLC. (1:1 ether - petrol)

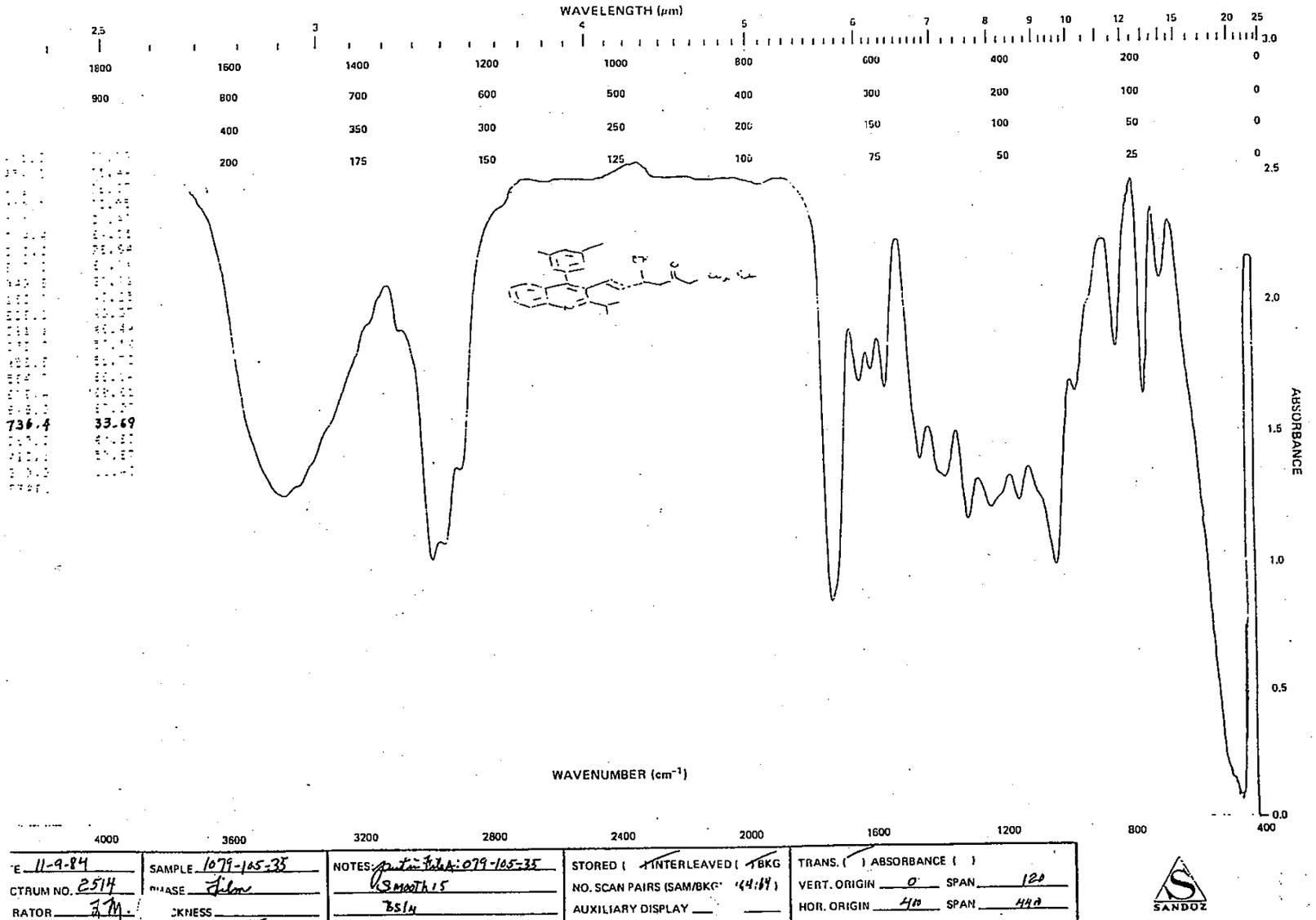
SM

(a) : yellow oil = 112 mg (1079-101-35)
n.mr ✓ I.R. ✓

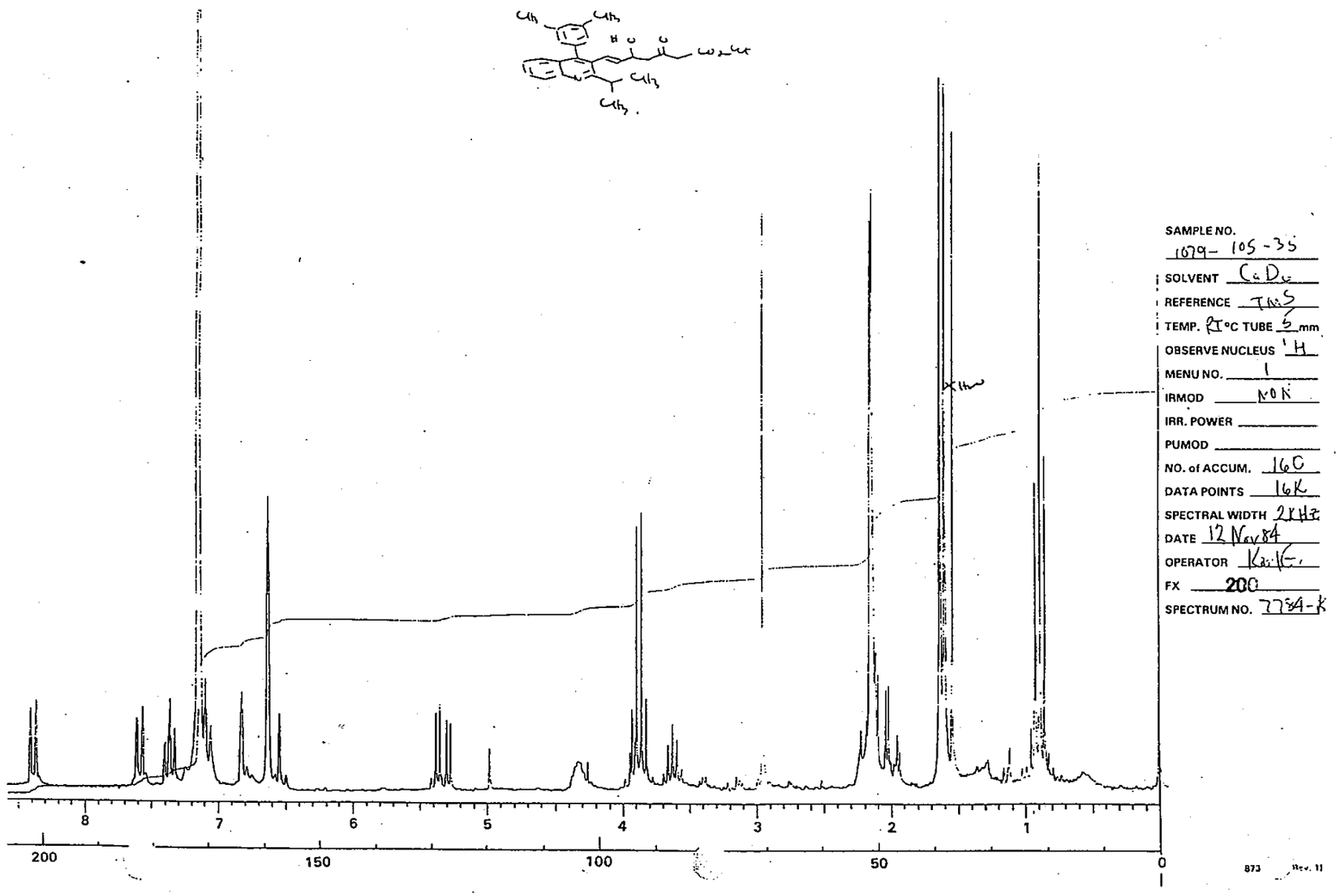
Performed by- S. Wallace

Witness- M. Rodella

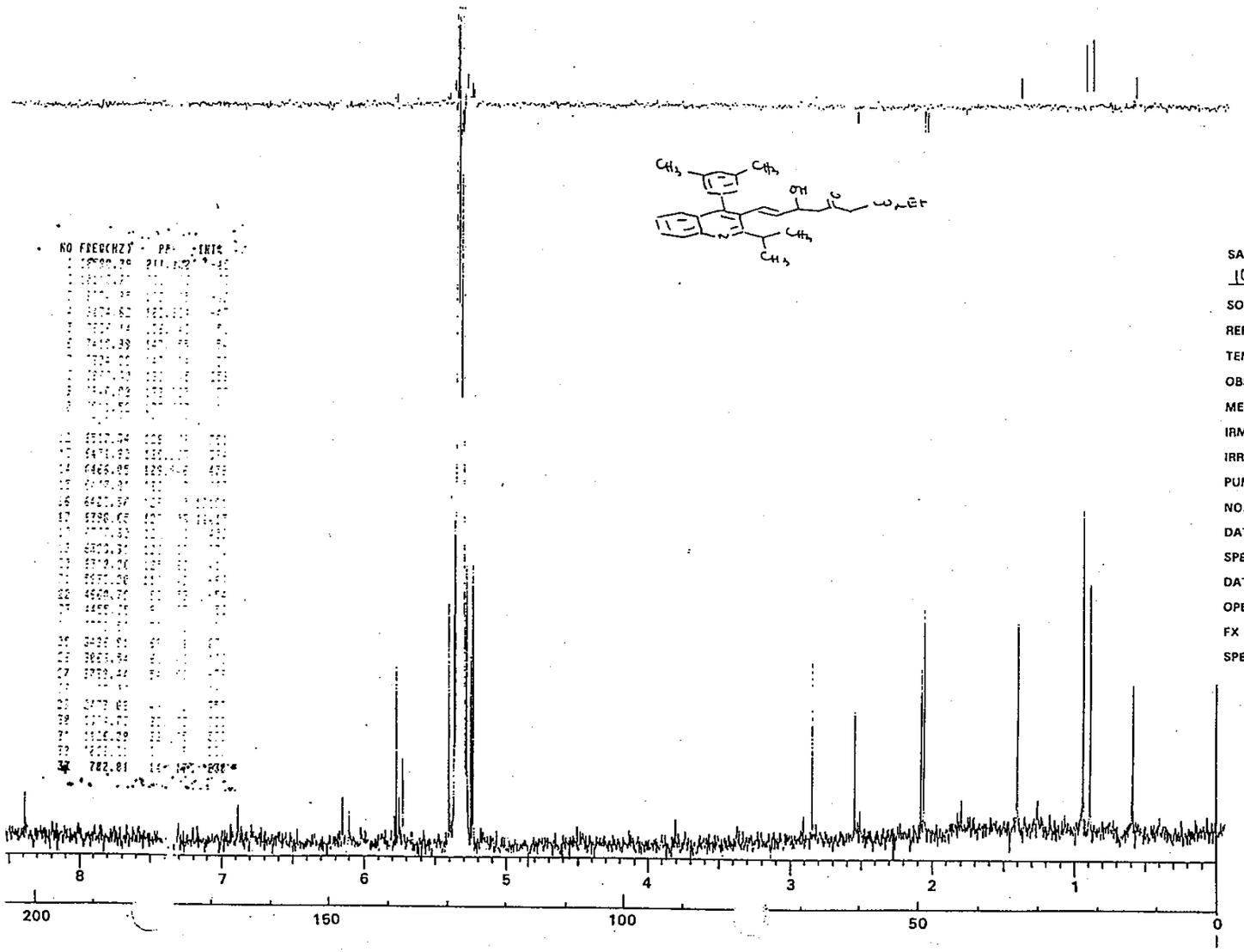
Cont'd to-


WAVELENGTH (μm)
2.5
3
4
5
6
7
8
9
10
12
15
20
25
3.0
1800
1600
1400
1200
1000
800
600
400
200
0
900
800
700
600
500
400
300
200
100
0
400
350
300
250
200
150
100
50
0
200
175
150
125
100
75
50
25
0
736.4
33.69
2.5
2.0
1.5
1.0
0.5
0.0
ABSORBANCE
WAVENUMBER (cm⁻¹)
4000
3600
3200
2800
2400
2000
1600
1200
800
400
E 11-9-84
CTRUM NO. 2514
RATOR JM.
SAMPLE 1079-105-35
PHASE Film
CKNESS
DR. Wallingford
NOTES: Jantin Lab: 079-105-35
Smooth 15
BSLN
STORED ( ) INTERLEAVED ( ) BKG
NO. SCAN PAIRS (SAM/BKG 64:64)
AUXILIARY DISPLAY
TRANS. ( ) ABSORBANCE ( )
VERT. ORIGIN 0 SPAN 120
HOR. ORIGIN 410 SPAN 440
SANDOZ

151


SAMPLE NO.
1079-105-35
SOLVENT C6D6
REFERENCE TMS
TEMP. RT °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 KAK
FX 200
SPECTRUM NO. 7784-K
8
7
6
5
4
3
2
1
200
150
100
50
0
873 Rev. 11

151



SAMPLE NO. 1079-105-35
SOLVENT C_6D_6
REFERENCE C_6D_6
TEMP. RT °C TUBE 5 mm
OBSERVE NUCLEUS ^{13}C
MENU NO. #22/23
IRMOD COM/DEPT
IRR. POWER
PUMOD
NO. of ACCUM. 28K/2.6K
DATA POINTS 16K/16K
SPECTRAL WIDTH 12KHz
DATE 13 Nov 84
OPERATOR Kalig.
FX
SPECTRUM NO. 1784-R

87365

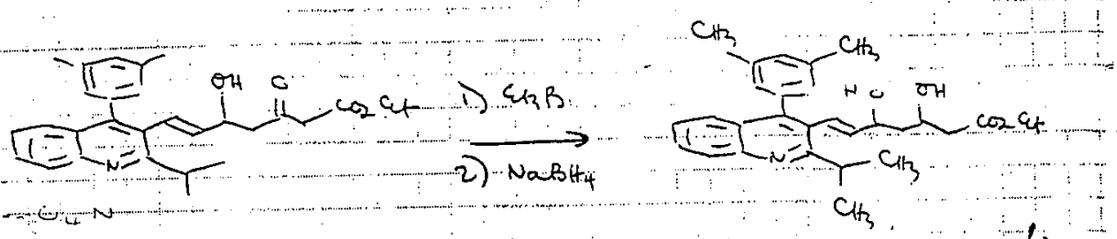
153

Title-

Date 11/12/94 Proj.

Cont'd From-

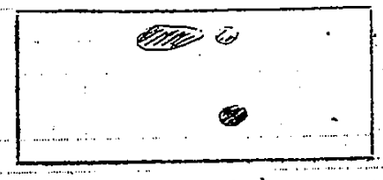
154



(479) 1079-105-35 = 57 mg (0.000119.8 mol)
1 M Et_3B in THF = 0.15 (0.000143.7 mol)
THF = 2 ml.

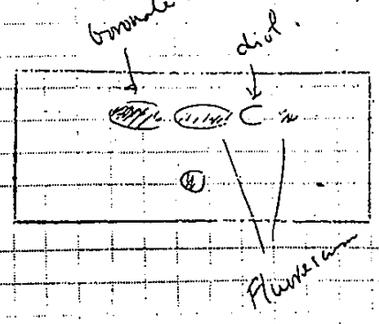
To a soln of (1079-105-35) in THF (2 ml) at r.t. was added 1M Et_3B a (1 ml) of air by syringe. The soln was stirred for 15h.
9.00 am.
10.30 am. At -78°, $NaBH_4$ (10 mg) was added.

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 removed from dry ice bath, acidified 3N HCl was added until aq. layer (pH-check), diluted with Et2O during this period reaction mixt. turned to fluorescence (, dehydration ??).



The crude product (70 mg) was used directly in the next step (1079-106-36)

Performed by- S. Wattanasin

Witness- M. Balasubramanian

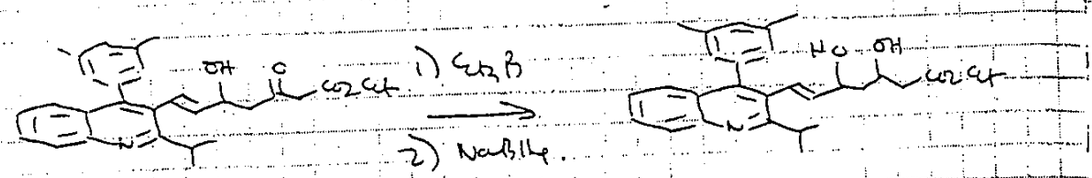
Cont'd to-

Title-

110

Date : 11/14/89 Proj.

Cont'd From- 155



avoid HCl treatment.

107g - 105 - 3 =	50	kg
1M Et_2B	= 0.2	l.
THF	= 2	l.
$NaBH_4$	= 20	g.

1) 2.30 pm:

2) 3.30, -78°C

11/15/89: The reaction mixt. almost colorless ... was diluted with 4 ml CH_3OH, after the cool bath was removed. After 10 min.* (ml thin a few mps of Hz, was added. After the evolution of H2 subsided. The reaction mixt. was concentrated the was added & extracted with ether * slightly fluorescent color occured.

see TLC P. 109 => mixture of boronate + diol ?

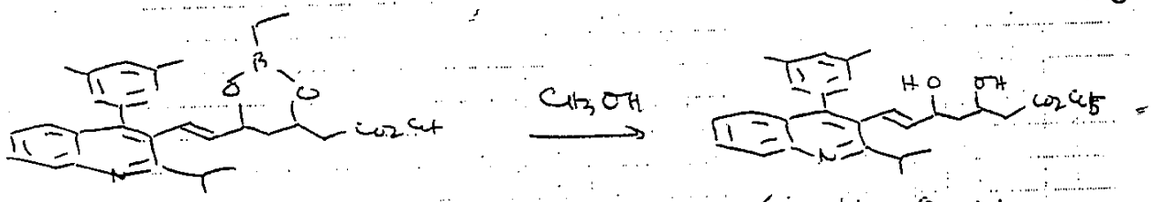
=> pale yellow + sm fluorescent oil = 40 mg (109-110-33) which was used directly in the next step.

Performed by- S. Wattanasin.

Witness- M. Ravella

Cont'd to-

156



$C_{29}H_{37}O_4N$

1079 – 110 – 33 = 40 mg

CH_3OH = 4 ml.

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

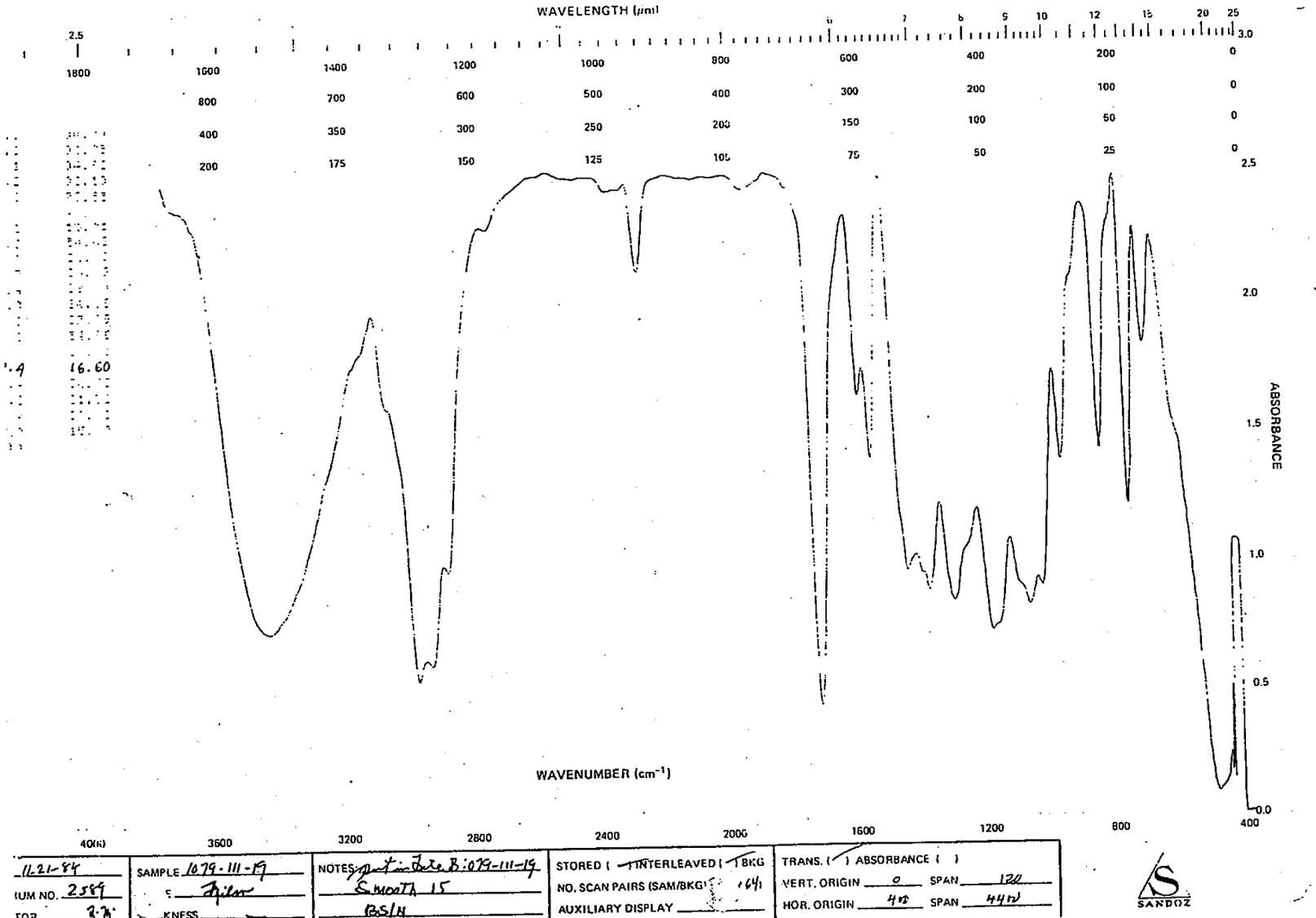
~~9.30 am.~~

TLC ⇒ showed one main spt (1:1 eth–petrol).

Prep TLC ⇒ (1079–111–19) pale yellow oil = 27–6 mg

nmr 10 mg.

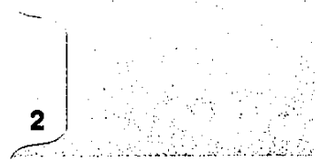
11/16/84. T. Scallen 14.5 mg.


WAVELENGTH (μm)
2.5
3.0
1800
1600
1400
1200
1000
800
600
400
200
800
700
600
500
400
300
200
100
400
350
300
250
200
150
100
50
200
175
150
125
100
75
50
25
0
2.5
2.0
1.5
1.0
0.5
0.0
ABSORBANCE
16.60
WAVENUMBER (cm⁻¹)
4000
3600
3200
2800
2400
2000
1600
1200
800
400
11-21-84
SAMPLE 1079-111-19
NOTES: put in Date B:079-111-19
SMOOTH 15
BS/4
STORED ( ) INTERLEAVED ( ) BKG
NO. SCAN PAIRS (SAM/BKG) 64/
AUXILIARY DISPLAY
TRANS. ( ) ABSORBANCE ( )
VERT. ORIGIN 0 SPAN 120
HOR. ORIGIN 4m SPAN 4420
SANDOZ

157

158

SAMPLE NO.
679-111-9
SOLVENT CDCl3
REFERENCE TMS
TEMP. 18°C TUBE 5mm
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOD NON
IRR. POWER
PUMOD
NO. of ACCUM. 160
DATA POINTS 16K
SPECTRAL WIDTH 2KHz
DATE 21 Nov 84
OPERATOR Karl G.
FX 200
SPECTRUM NO. 2897-6
0
50
100
150
200
1
2
3
4
5
6
7
8


2

Date 5/2/95 Proj.

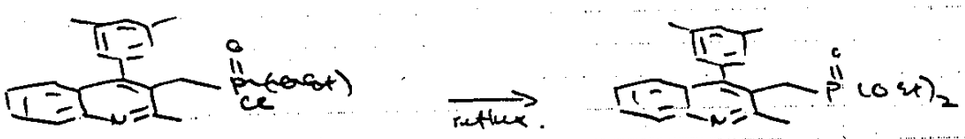
Cont'd From-

Title

5

159

cf. P. 1079-55.



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

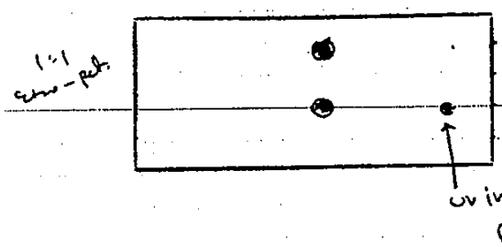
(295) 1079-296-35 = 150 mg
$P(OEt)_3$ = 0.3 ml.
Toluene = 2 ml.

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 (127-5-23) mp 101-102 (almost colorless solid)

NMR ✓ : desired P.

micro ✓ OH

MS M^+ 397 ✓

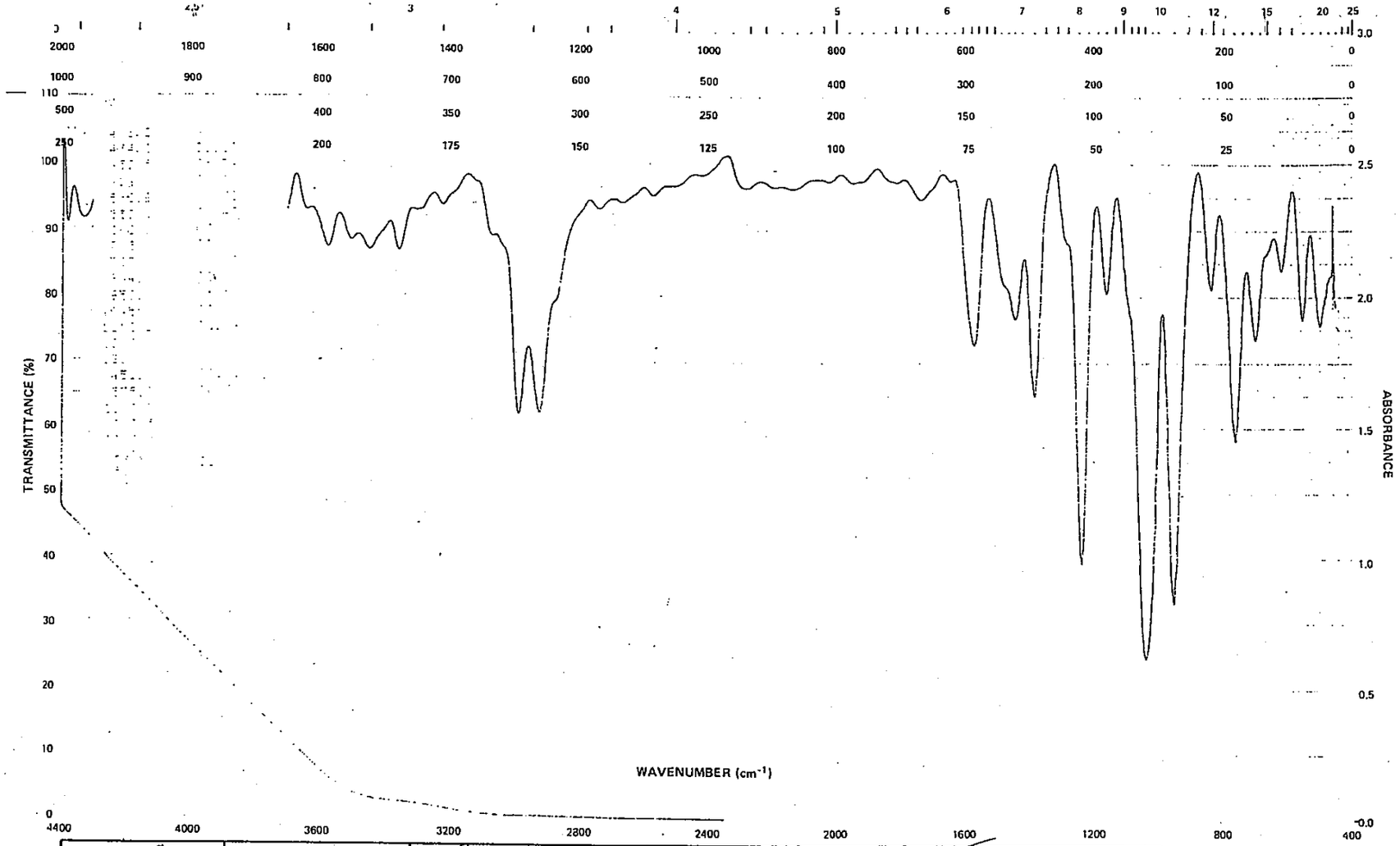
Performed by- S. Wallace

Witness- Stuart W. Mason 12/12/89

Con'd to-

160

SAMPLE NO. 122-5-23
SOLVENT CDCl3
REFERENCE TMS
TEMP. RT °C TUBE 5 mm
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOD VAN
IRR. POWER
PUMOD
NO. of ACCUM. 120
DATA POINTS 16K
SPECTRAL WIDTH 2KHz
DATE 7 May 85
OPERATOR Bailey
FX 300
SPECTRUM NO. 1517-B
87359/81 (Rev. 1)
1H
13C



DATE 5-4-95	SAMPLE 1127-5-23	NOTE Gut-Tube A: 1127-5-23 Smooth 11	STORED ( ) INTERLEAVED (✓) BKG	TRANS. (✓) ABSORBANCE ( )
SPECTRUM NO. 1012	PHASE KBr		NO. SCAN PAIRS (SAM/BKG) 64/64	VERT. ORIGIN 0 SPAN 120
OPERATOR [illegible]	THICKNESS Dr. Wallanagi	SCAN 1-8	AUXILIARY DISPLAY	HOR. ORIGIN 4m SPAN 4488

SANDOZ

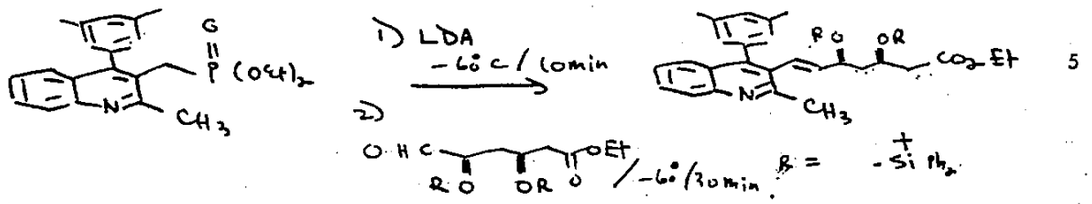
16

Date 5/6/85 Proj.

Cont'd From-

Title- 9

162

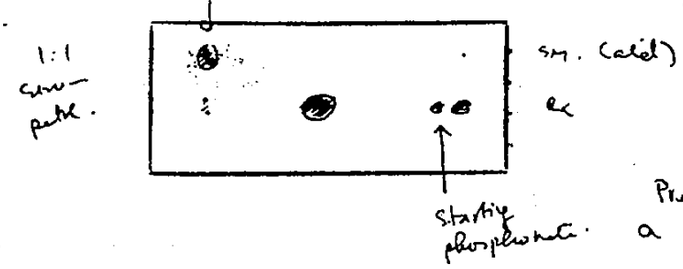


(397) 1127-5-23 = 150 mg (0.0003728 mol)
647 Prac ad ald. = 293 mg (0.0004534 mol)
1.7M LDA = 0.27 ml. 1.2 eq.
THF = 3 ml.

To a solution of 1127-5-23 in THF (3 ml) at -55°c was added LDA. The resulting dark orange soln was then stirred at -5°→-6°c for ~~20~~ 10 min.
9.50 am — 10.00 am.

Then a soln of aldehyde in THF (2 ml) was added

TLC after 20 min. ⇒ mainly one product



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

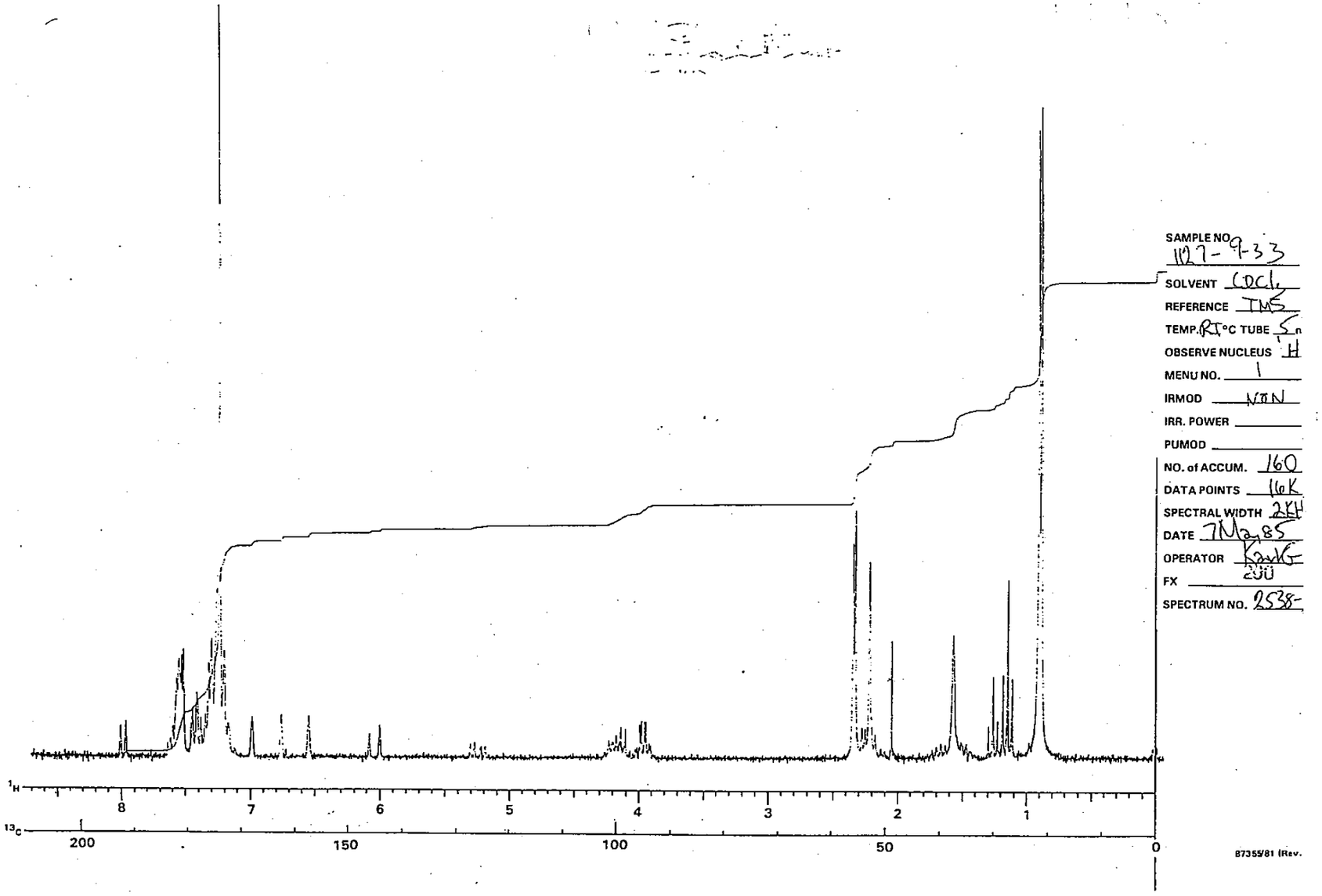
Prep TLC (1:1 cyclo-petrol) gave a yellow oil = 100 mg (to 1127-9-33)

Nmr ✓

Performed by- S. Wattanasin.

Witness- [signature] 12/12/89

Cont'd to-


SAMPLE NO 1127-9-33
SOLVENT CDCl3
REFERENCE TMS
TEMP. RT °C TUBE 5mm
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOD NON
IRR. POWER
PUMOD
NO. of ACCUM. 160
DATA POINTS 16K
SPECTRAL WIDTH 2KH
DATE 7May85
OPERATOR KaWG
FX 200
SPECTRUM NO. 2538
1H
8
7
6
5
4
3
2
1
0
13C
200
150
100
50
0
87355/81 (Rev.

163

Date 5/7/85 Proj.

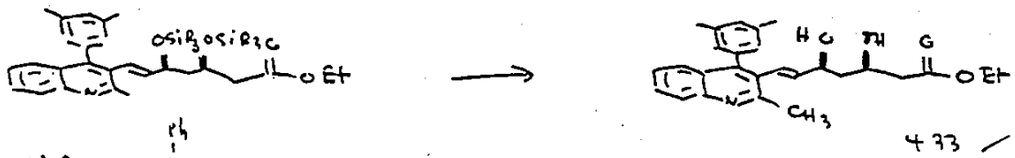
Cont'd From-

Title- Book # 1127

11

cf. 1079-97

164



433 ✓
$C_{27}H_{31}O_4N$

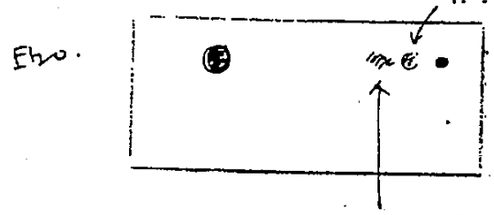
SiR_3 : Ph, Si, Ph

(1289) 1127-9-33 = 90 mg (0.0001012 mol)
1M Bu4NF = 0.61 ml. (0.000607 mol) 1e
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: | - Bu4NF 0.6
- " - 0.6
- HOAc 0.05 ml |

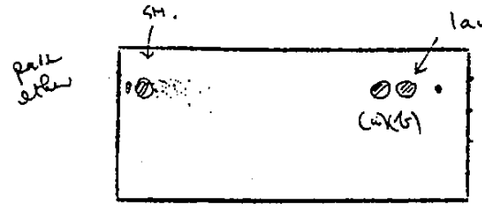
TLC 5/8/85 9.00 am.



TLC 5/13/85 : 8.30 am ⇒ a mixt of SM + P(s)
The solu was heated at 50°C

9.00 am:

TLC 11.00 pm : mixt. of 2 spots.
stop 5.30 pm



concentrated on the cyclic ✓
was purified by prep TLC (ether + CH2Cl2 + HOAc)

(a) : colorless oil = 10 mg
(= 1127-11-34)
nmr MS ✓ M^+ 433 ✓

(b) : oil = 10 mg (1127-11-37)
nmr ms ✓ M^+ 387 ✓
$C_{25}H_{33}O_3N$

5/17/85. 1127-11-34 { 2 mg CSI
48 mg CSTU, CSTC
1127-11-37 { 2 mg CSI

Performed by- S. Wattanasin

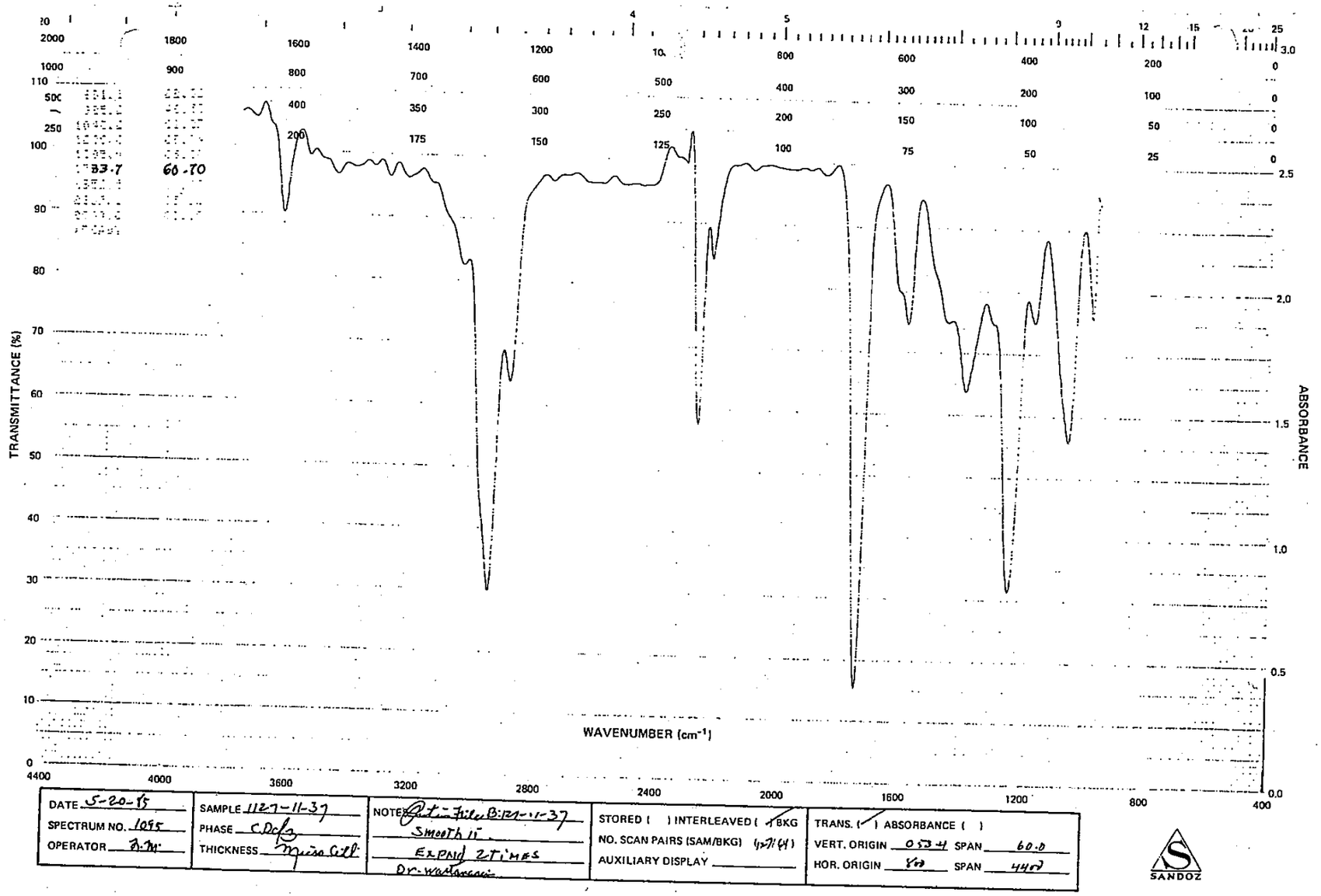
Witness-

Cont'd to-

165

ABSORBANCE
TRANSMITTANCE (%)
WAVENUMBER (cm-1)
DATE 5-17-94
SPECTRUM NO. 1014
OPERATOR B.M.
SAMPLE 11-27-11-34
PHASE CDCl3
THICKNESS Macerated
Dr-Wallenius
NOTE Batch: Fine A: 11-27-11-34
Scal 1.8
Evaporated Sample dry
STORED ( ) INTERLEAVED ( )
NO. SCAN PAIRS (SAM/BKG)
AUXILIARY DISPLAY
TRANS. ABSORBANCE ( )
VERT. ORIGIN SPAN
HOR. ORIGIN SPAN
SANDOZ

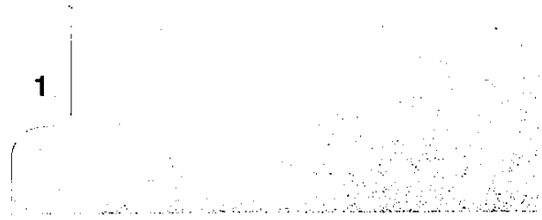
SAMPLE NO. -1127-11-34
SOLVENT CDCl3
REFERENCE TMS
TEMP. RT °C TUBE 5 mm
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOD VOM
IRR. POWER
PUMOD
NO. of ACCUM. 640
DATA POINTS 16K
SPECTRAL WIDTH 2KHz
DATE 15 May 85
OPERATOR Kaelin
FX 300
SPECTRUM NO. 2683-G
8735/81 (Rev. 1)
H2O
OEt
1H
13C

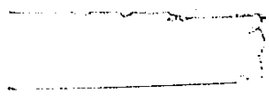


167

SAMPLE NO.
1127-11-37
SOLVENT Silt CDCl3
REFERENCE TMS
TEMP. RT °C TUBE 5 mm
OBSERVE NUCLEUS 1H
MENU NO. 1
IRMOD NON
IRR. POWER
PUMOD
NO. of ACCUM. 296
DATA POINTS 16K
SPECTRAL WIDTH 2kHz
DATE 15 May 85
OPERATOR
FX
SPECTRUM NO. 2486
8735/81 (Rev. 1)
0
50
100
150
200
1H
13C

Exhibit C


1



circle

IR UV-Vis OR NMR90 200 500 Micro Misc **Request Sheet** 169

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:

SAMPLE WEIGHT

Required for 200 or 500 mHz

☐ 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

mol. wt.

req. ____ ____

drying

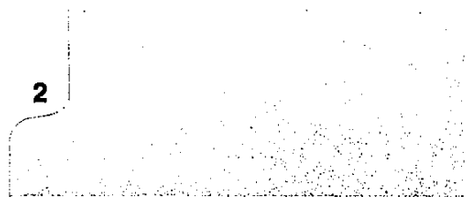
done ____ °C ____ hrs.

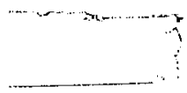
formula	C	H	N	O				
calc.								
found								

misc. & comments:

sample # book #

87147/81 (Rev. 3)

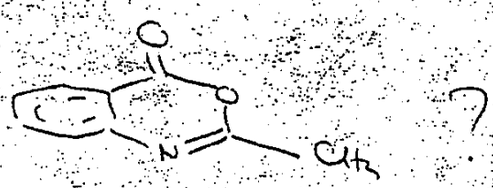

2



IR UV-Vis OR NMR60 90 200 Micro Misc Request Sheet 190

1377

synthetic pathway:
reagents, solvents
esp. last solvent:



suspected structures
in order of prob.:

models available

T_1	^{13}C
WT	^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. °C hrs.
done

misc. & comments:

calc.								
found								

IR UV-Vis OR NMR 60 90 200 Micro Misc — circle requests

Request Sheet

171

FTm.
KBr.

solvent or medium

empirical formula

mp

bp

sample # / book / page / line
1079-22-28

IW-AW-KP
☐ pure ☐ crude

unit head

requestor

bldg. 409 lab 356 ext

date submitted

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

1	^{13}C		
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

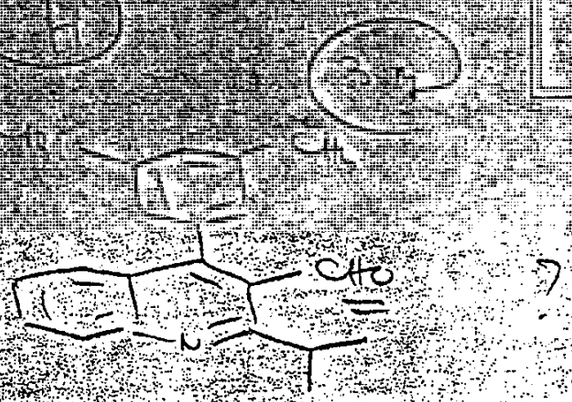
mol. wt.

drying req. °C hrs.
done

formula	C	H	N	O				
calc.								

misc. & comments:

IR UV Vis OR NMR60 90 200 Micro Misc Request Sheet



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.

drying req. °C hrs.
done

formula	C	H	N	O				
calc.								
found								

misc. & comments:

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

Circle requests

173

empirical formula C606

mp.

solvent of rxn

bp

requestor Sawaya

book page line

W-AW-X?

plate crude

bldg. lab. 365 ext. 8404

1079-101-35

date submitted

do not fill

2514 A.M.

problem statement or specific instructions:

17 mg

synthetic pathway: reagents, solvents esp. last solvent:

suspected structures in order of prob.:

Samples 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

count

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

fill in # & circle requested elements

formula C H N O

calc.

mol.wt.

drying req. °C hrs.

done

misc. & comments

circle

IR UV-Vis OR NMR60 90 200 Micro Misc Request Sheet 174

F. lm					C_6D_6	

solvent or medium

empirical formula

mp. ____ °C

bp

sample # book page line: 1079-111-19

IW-AW-KP ☒ pure ☐ crude

unit head

requestor S. Sarkar

bldg. lab. ext.

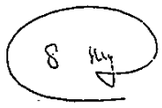
date submitted 8+04

sensitivities:

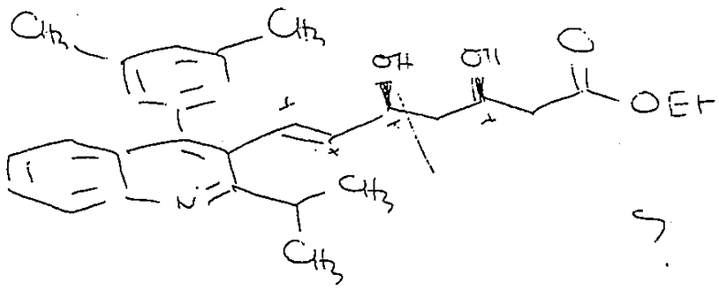
hazards:

do not fill in 2589 2.74

nature of request: problem statement or specific instructions:



synthetic pathway: reagents, solvents esp. last solvent:



suspected structures in order of prob.:

— Sample in the fridge.

models available

— expand vinylic protons & methine protons.

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

mol. wt.

drying req. ____ °C ____ done ____ hrs.

formula	C	H	N	O				
calc.								
found								

misc. & comments:

sample # book #

87147/81 (Rev. 1)

circle requests

IR / UV-Vis / OR / NMR 60 / 90 / 200 / Micro / Misc — **Request Sheet** 175

KBr — $CDCl_3$ — solvent or medium

empirical formula

mp.

bp

sample # / book / page / line: 1127-5-23

IW-AW-KP ☐ pure ☐ crude

unit head

requestor: S. Wakabayashi

bldg. lab. ext.

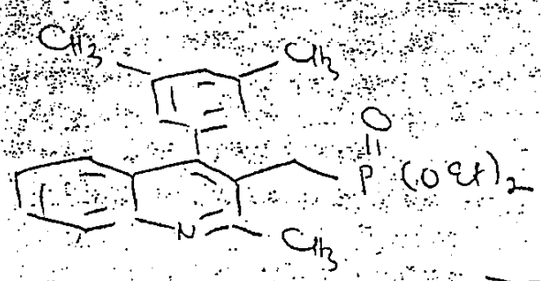
date submitted 3-6-84

sensitivities:

hazards: H

do not fill in: 10-12

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



synthetic pathway: reagents, solvents esp. last solvent:

77

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

count

other measurements	IR	UV	H nmr	micro	MS		

fill in # & circle requested elements

formula C H N O

calc.								

mol. wt.

drying req. °C hrs. done

misc. & comments:

circle r

IR UV-Vis OR NMR60 90 200 Micro Misc **Request Sheet** 176

~~Film~~ $CDCl_3$ — solvent or medium — $CDCl_3$

empirical formula

mp. °C

bp

sample # book page line: 1127-11-34

IW-AW-KP ☒ pure ☐ crude

unit head

requestor S. Wattanasin

bldg. lab. 36 ext. 8404

date submitted

sensitivities:

hazards:

do not fill in

1044

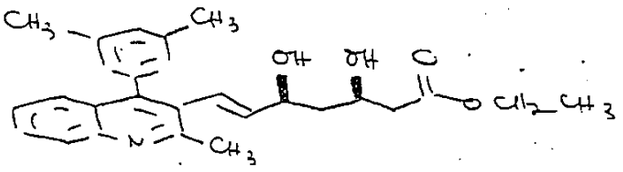
nature of request: problem statement or specific instructions:

1 H

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
it 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						

count

other measurements	IR	UV	H nmr	micro	MS		

fill in # & circle requested elements

formula C H N O

mol. wt.

drying req. °C hrs. done

misc. & comments:

sample # book #

calc.								
found								

87147/81 (Rev. 1)

circle requests

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

CDCl3 — filtered

solvent or medium

empirical formula

mp. 177

bp

sample # book page line 1127-11-37

IW-AW-KP ☐ pure ☐ crude

unit head

requestor S. Wattanasin

bldg. lab. 36 ext. 8404

date submitted

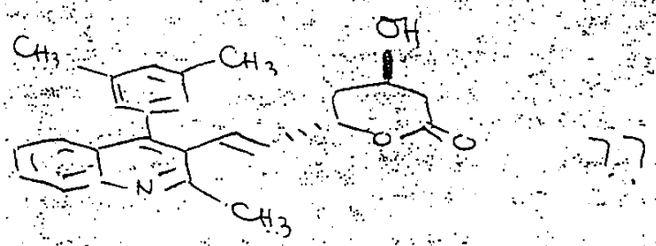
do not fill in 1095

sensitivities: 1127-11-37

hazards: H, 1 mg

nature of request: problem statement or specific instructions:

Sample from NMR



77

synthetic pathway: reagents, solvents esp. last solvent:

Sample in the fridge

Testing sample, please get a good S/N

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							

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 (Rev. 1)

Hexane 6.206 13027

circle requests

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

Th 13
5 1m

CDCl3
solvent or medium

empirical formula

mp.

bp

sample # book page line
206 130 27

IW-AW-KP
☐ pure ☒ crude

unit head S. Watt requestor R. Reid

bldg. lab. ext. 8578

date submitted 6-5-87

sensitivities:

hazards:

SAMPLE WEIGHT

Required for 200 or 500 mHz

do not fill in

899

☒ routine ☒ ^{1}H ☐ ^{13}C ☐ ^{31}P

☐ expand spectral region from to

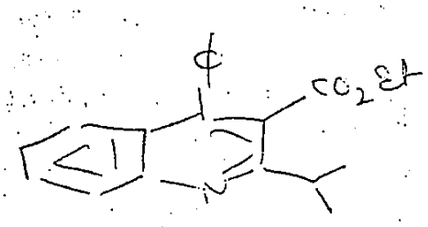
☐ assign for ☐ ^{1}H (500) ☐ ^{13}C

☐ 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

mol. wt.

drying req. °C hrs.
done

formula C H N O

calc.									
found									

misc. & comments:

sample # book #

87147/81 (Rev. 2)

Hit in Plate B 206/137/31

circle requests

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

film | CDCl3 | solvent or medium | empirical formula | mp. °C | bp

sample # book page line: 206-137-31

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

922

☒ routine ☒ ^{1}H ☐ ^{13}C ☐ ^{31}P

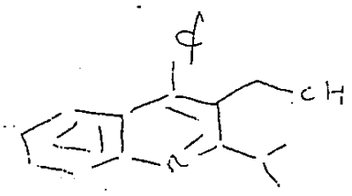
☐ expand spectral region from to

☐ assign for ☐ ^{1}H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level) %

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

formula C H N O

calc.								
found								

mol. wt.

drying req. °C hrs. done

misc. & comments:

sample # book #

87147/81 (Rev. 2)

circle re

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

pellet CDCl3

solvent or medium

empirical formula

mp. °C

bp

sample # book page line

1-cr-168-34

1206

IW-AW-KP

☒ pure ☐ crude

unit head Smith requestor

bldg. lab. 352 ext.

date submitted 7-22-87

sensitivities: hazards:

SAMPLE WEIGHT

5mg

Required for 200 or 500 mHz

do not fill in

1007 gaa

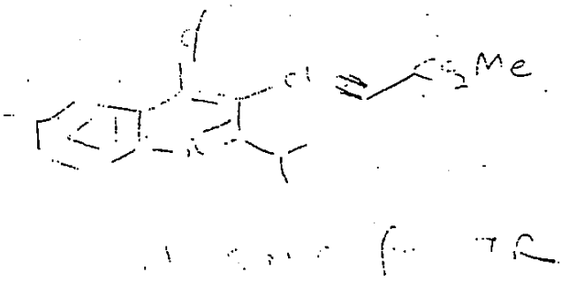
☒ routine ☒ ^{1}H ☐ ^{13}C ☐ ^{31}P

☐ 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

061533 1

Save-a, a:0615331

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 #

circle requests

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

(CDCl3 or thin film)

solvent or medium

empirical formula

mp. 181

bp

sample # book page line 1206-158-41

IW-AW-KP ☐ pure ☒ crude

unit head S. Watt requestor R. Patel

bldg. 464 lab. 357 ext.

date submitted 7-29-87

SAMPLE WEIGHT

Required for 200 or 500 mHz

do not fill in 1037 pac

sensitivities: hazards:

☐ routine ☐ ^{1}H ☐ ^{13}C ☐ ^{31}P

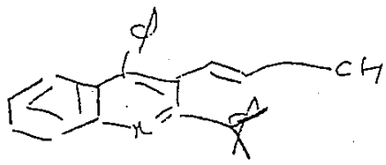
☐ expand spectral region from to

☐ assign for ☐ ^{1}H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level)

%



synthetic pathway:
reagents, solvents
esp. last solvent:

suspected structures in order of prob.:

models available

save_d,a: 615841

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 #

82147/81 (Rev. 2)

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

Request Sheet 182

empirical formula

mp.

bp

solvent or medium

sample # book page line

IW-AW-KP
☒ pure ☐ crude

unit head S. L. Hanson requestor R. Rabel

bldg. 404 lab. 3 5 ext. 5218

date submitted 7-28-89

sensitivities: hazards:

SAMPLE WEIGHT
Required for 200 or 500 mHz

do not fill in
1084-274

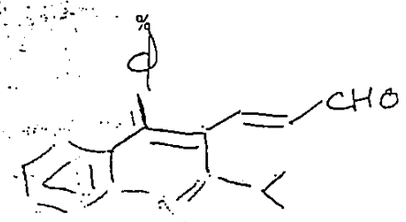
☐ routine ☐ ^{1}H ☐ ^{13}C ☐ ^{31}P

☐ 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: 616630

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 #

87/47/81 (Rev. 2)

ci ...uests

IR UV-Vis OR NMR90 200 500 Micro Misc **Request Sheet** 183

thin film

solvent or medium

empirical formula

mp. °C

bp

sample # book page line 12061 175-88

IW-AW-KP ☒ pure ☐ crude

unit head requestor R. Rabbat

bldg. lab. ext.

date submitted 12-22-89

sensitivities: hazards:

SAMPLE WEIGHT Required for 200 or 500 mHz

do not fill in 1052 pac

☐ 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)

Fig.

synthetic pathway:
reagents, solvents
esp. last solvent:

suspected structures in order of prob.:

models available

save. d, a; 061754

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

mol. wt.

drying req. °C hrs. done

calc.								
found								

misc. & comments:

sample # book #

87147/B1 (Rev. 2)

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

Request Sheet

184

solvent or medium

empirical formula

mp.

bp

sample # book page line: (206-176-41)

IW-AW-KP ☒ pure ☐ crude

unit head

requestor Rolat

bldg. lab. ext.

date submitted 7/29/8

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

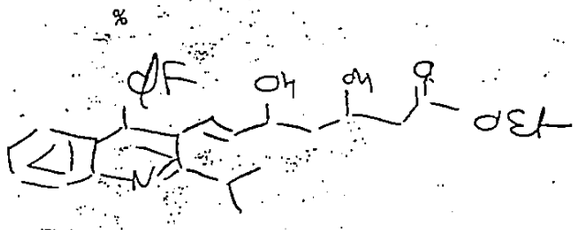
☐ assign for ☐ ^{1}H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level)

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.:

Save - d, a: 617641

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.

drying req. ____ °C ____ hrs. done ____

misc. & comments:

sample # book #

7147/81 (Rev. 2)

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

thin film KBr

CDCl3

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

mp. 185 °C

bp

solvent or medium

sample # book page line

120-179-30

IW-AW-KP

☒ pure ☐ crude

unit head

requestor

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.:

Structure id: 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	LSR
RELA	T1
	VT
MOL	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 hrs. done

calc.

misc. & comments:

circle requests

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

thin film

solvent or medium

empirical formula

mp. 186 °C

bp

sample # book page line

12C6-179-30

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

1093 9.2

☐ routine ☐ ^{1}H ☐ ^{13}C ☐ ^{31}P

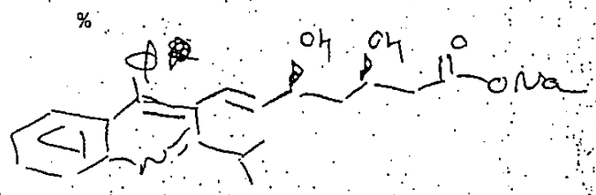
☐ expand spectral region from to

☐ 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.:

June_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								

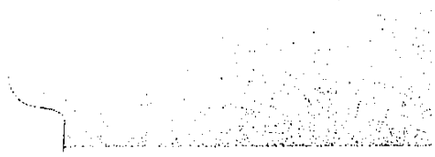
mol. wt.

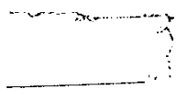
drying req. °C hrs.
done

misc. & comments:

sample # book #

87147/81 (Rev. 2)





circle requests

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

KBr, | | | $CDCl_3$ | empirical formula | mp. ____ °C | bp

solvent or medium

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:

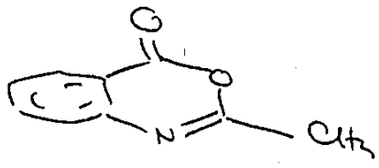
hazards:

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

2 count

other measurements	IR	UV	H nmr	micro	MS		

fill in # & circle requested elements

formula C H N O

mol. wt.

drying req. ____ °C ____ done ____ hrs.

calc.								
found								

misc. & comments:

sample # book #

87147/81

circle req 188

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

				CD_3CN			

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. 409 lab. 361 ext. 8409

date submitted

sensitivities:

hazards:

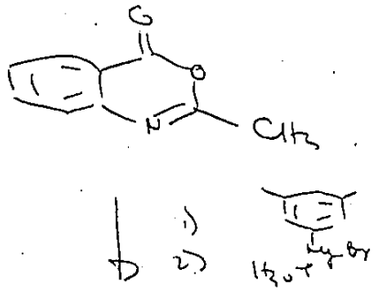
nature of request:
problem statement or
specific instructions:

1H

15 mg

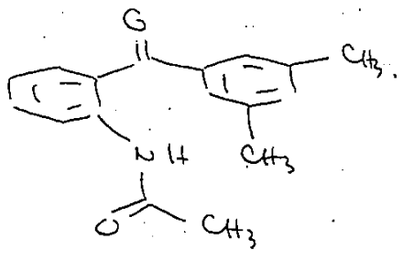
do not fill in
RECEIVED
1751 JUN. - 1. 84
INSTRUMENTAL ANALYSIS

synthetic pathway:
reagents, solvents
esp. last solvent:



suspected structures
in order of prob.:

models available



?

T_1	13_C
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

mol. wt.

drying req. ____ °C ____ hrs.
done ____

formula	C	H	N	O				
calc.								
found								

misc. & comments:

sample # book #

87147/81

circle requi

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

bldg. 404 | lab. 361 | ext. 8404 | date submitted

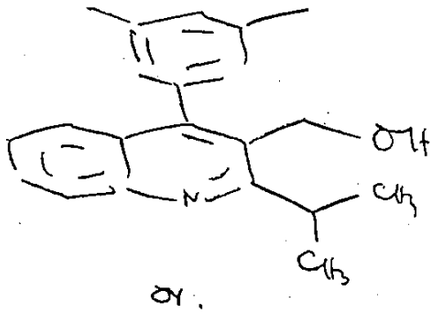
sensitivities: #ounds = 1079-24-24 hazards:

'H | 4 mg

do not fill in

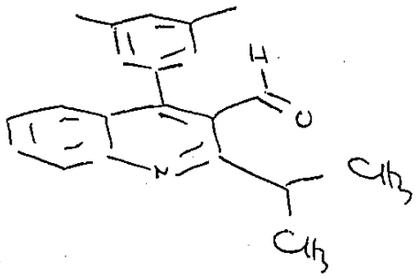
RECEIVED
8255 AUG. 13.84
INSTRUMENTAL ANALYSIS

nature of request:
problem statement or
specific instructions:



or.

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

mol. wt.

drying req. °C hrs. done

formula	C	H	N	O				
calc.								
found								

misc. & comments:

sample # book #

87147/81

circle requests

IR UV-Vis OR NMR60 90 200 Micro Misc **Request Sheet** 190

KBr | | | | | CDCl3

solvent or medium

empirical formula

mp. ____ °

bp

sample # book page line: 1079-27-25

IW-AW-KP ☐ pure ☐ crude

unit head

requestor S. Wattanasin

bldg. 400 lab. 365 ext. 5600

date submitted

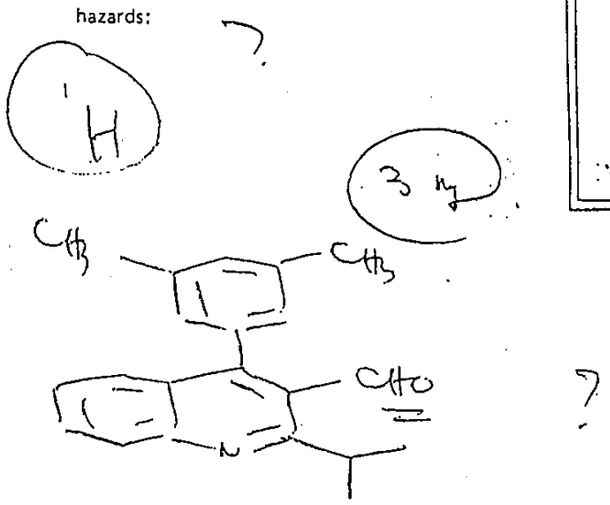
sensitivities:

hazards:

do not fill in

RECEIVED
0288 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

circle requests

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

191

(CBr)				$CDCl_3$	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. 36F ext. 8404

date submitted

sensitivities: ?

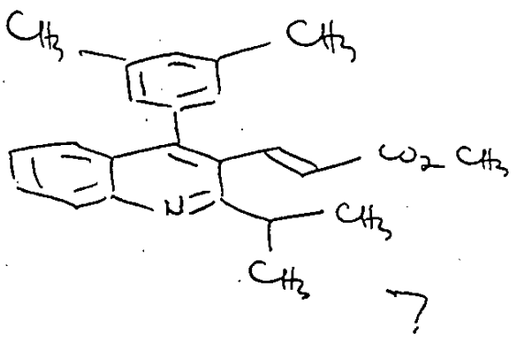
hazards: ?

4 mg

do not fill in

RECEIVED
6404 AUG.22.84
INSTRUMENTAL ANALYSIS

nature of request:
problem statement or
specific instructions:



?

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

mol. wt.

drying req. ____ °C ____ hrs. done ____

formula	C	H	N	O				
calc.								
found								

misc. & comments:

sample # book #

87147/81

circle requests

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

solvent or medium: CH_2Cl_2

empirical formula

mp. °C

bp

sample # book page line: 1079-34-17

IW-AW-KP ☒ pure ☐ crude

unit head

requestor: S. Wattanazin

bldg. 404 lab. 365 ext. 8204

date submitted

sensitivities:

hazards:

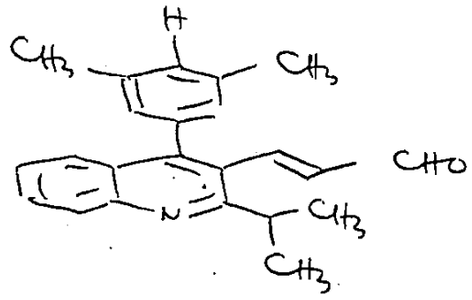
^1H

~ 3 mg

do not fill in

RECEIVED
SEP. - 5. 84
ANALYSIS

nature of request:
problem statement or
specific instructions:



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

mol. wt.

drying req. °C hrs.
done

formula	C	H	N	O				
calc.								
found								

misc. & comments:

sample # book #

87147/81.

circle 193

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

KBr. | | | | | $C_{16}H_{23}$ | empirical formula | mp. ____ °C

solvent or medium | bp

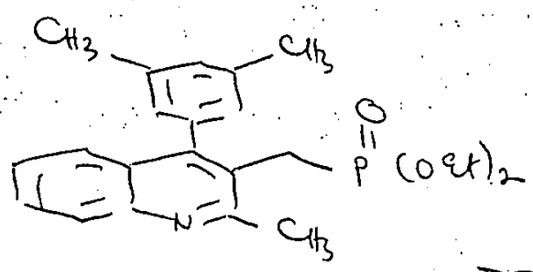
sample # book page line: 1127-5-23 | IW-AW-KP ☐ pure ☐ crude | unit head | requestor S. Kattamuri

bldg. | lab. 365 | ext. 8404 | date submitted

sensitivities: | hazards: 1 H

do not fill in
RECEIVED
1987 MAY -6 P 3:55
ENVIRONMENTAL ANALYSIS

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	^{31}P						
COM	LSR						
OPR	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)

circle requests

IR UV-Vis OR NMR60 90 200 Micro Misc **Request Sheet** 194

solvent or medium: $CDCl_3$

empirical formula

mp.

bp

sample # book page line: 1127-9-33

IW-AW-KP ☑ pure ☐ crude

unit head

requestor: S. Watanabe

bldg. lab. ext.: 365 8404

date submitted

sensitivities:

hazards:

do not fill in

RECEIVED
2538 MAY -7 85
INSTRUMENTAL ANALYSIS

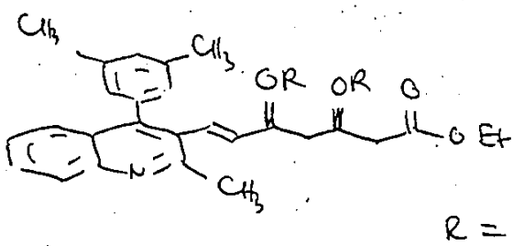
nature of request: problem statement or specific instructions:

1H

3 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:



R = Si(Ph)(Ph)(t-Bu)

77

suspected structures in order of prob.:

models available

- Sample in the fridge.
- please keep sample in

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)

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

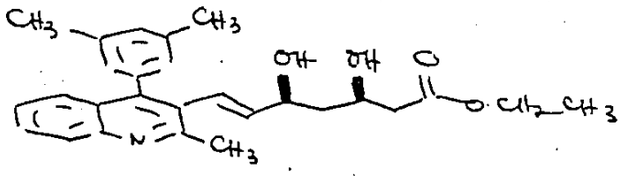
nature of request:
problem statement or
specific instructions:

^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

mol. wt.

drying req. ____ °C ____ hrs.
done ____

calc.									
found									

misc. & comments:

sample # book #

87147/81 (Rev. 1)

cir

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

Film | | | | $CDCl_3$ — filtered | empirical formula | mp. ____ °C

solvent or medium | bp

sample # book page line: 1127-11-37 | IW-AW-KP: ☒ pure ☐ crude | unit head | requestor: S. Wattanasin

bldg. | lab. 365 | ext. 8404 | date submitted

sensitivities: 1127-11-37

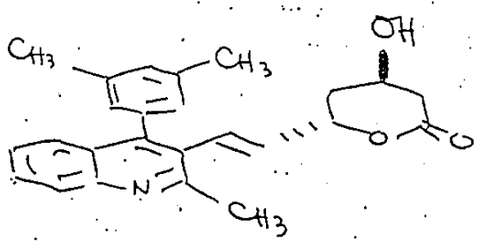
hazards: 1 H | 1 mg

do not fill in

RECEIVED
2686 MAY 14 05
INSTRUMENTAL ANALYSIS

nature of request:
problem statement or
specific instructions:

synthetic pathway:
reagents, solvents
esp. last solvent:



77

suspected structures
in order of prob.:

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

models available

T_1	^{13}C
VT	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 ____

calc.								
found								

misc. & comments:

sample # book #

87147/81 (Rev. 1)

circle 196

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

thin film		$CDCl_3$	empirical formula	mp. ____ °C
		solvent or medium		bp

sample # book page line: 126 130-27

IW-AW-KP ☐ pure ☒ crude

unit head S. Wath 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

RECEIVED
3256 JUN-5 87
INSTRUMENTAL ANALYSIS

☒ routine ☒ ^1H ☐ ^{13}C ☐ ^{31}P

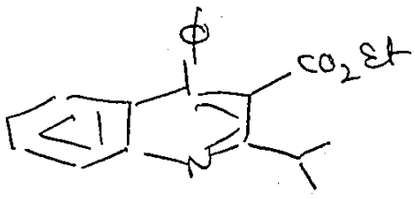
☐ expand spectral region from to

☐ assign for ☐ ^1H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level) %

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)

circle re 192

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

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
ANALYTICAL ANALYSIS

☒ routine ☒ ^1H ☐ ^{13}C ☐ ^{31}P

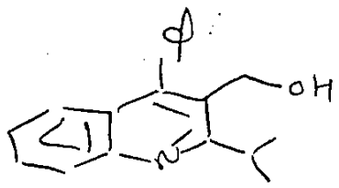
☐ expand spectral region from to

☐ 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

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

circle r

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

INSTRUMENTAL ANALYSIS

☐ routine ☐ ^{1}H ☐ ^{13}C ☐ ^{31}P

☐ expand spectral region from to

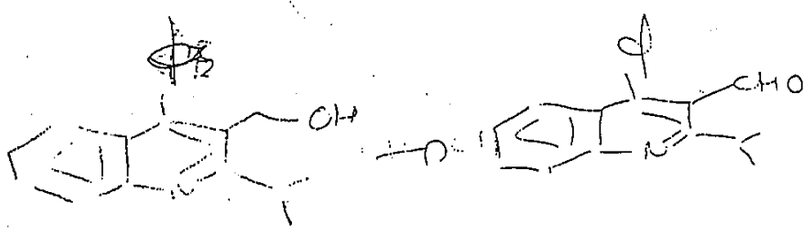
☐ assign for ☐ ^{1}H (500) ☐ ^{13}C

☐ 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

formula C H N O

calc.								
found								

mol. wt.

drying req. °C hrs.
done

misc. & comments:

sample # book #

87147/81 (Rev. 2)

circle

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

solvent or medium $CDCl_3$

empirical formula

mp. °C

bp

sample # book page line 1-66-145-26

IW-AW-KP ☐ pure ☒ crude

unit head Swalen requestor R Patel

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

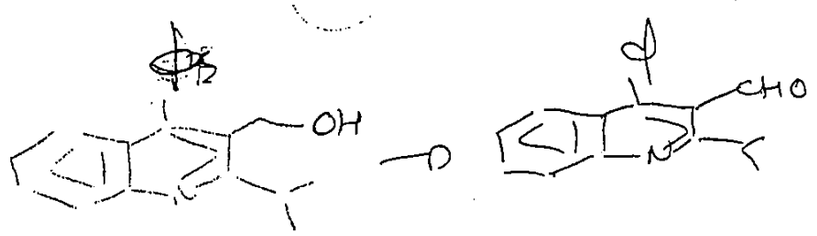
☐ expand spectral region from to

☐ 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 OEC	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)

circle 200

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

Pelleh

solvent or medium

empirical formula

mp. °C

bp

sample # book page line -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
9596 JUL.-2 87
INSTRUMENTAL ANALYSIS

☐ routine ☒ ^{1}H ☐ ^{13}C ☐ ^{31}P

☐ expand spectral region from to

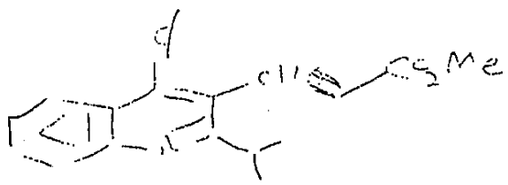
☐ assign for ☐ ^{1}H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level) %

SAVE

synthetic pathway: reagents, solvents esp. last solvent:



If save for IR

suspected structures in order of prob.:

models available

90	^{1}H J
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

formula C H N O

calc.								
found								

mol. wt.

drying req. °C hrs. done

misc. & comments:

sample # book #

87147/81 (Rev. 2)

circle 201

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

$CDCl_3$

solvent or medium

empirical formula

mp. ____ °C

bp

sample # book page line: 120G 153-37

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

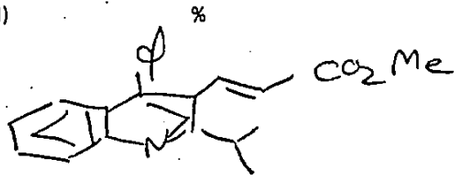
☒ routine ☒ ^1H ☐ ^{13}C ☐ ^{31}P

☐ 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	HDM 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** circle re 202

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

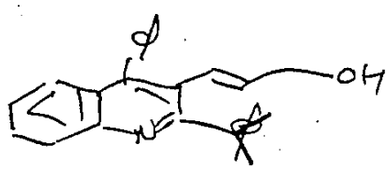
☐ routine ☐ ^{1}H ☐ ^{13}C ☐ ^{31}P

☐ 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

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

circle requested

Request Sheet 203

solvent or medium $CDCl_3$

empirical formula

mp. °C

bp

sample # book page line 1206 166 30

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

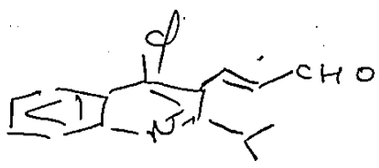
☐ expand spectral region from to

☐ 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.

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** 204

solvent or medium: — $CDCl_3$

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

mp. ____ °C

bp

sample # book page line: 12675-4

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

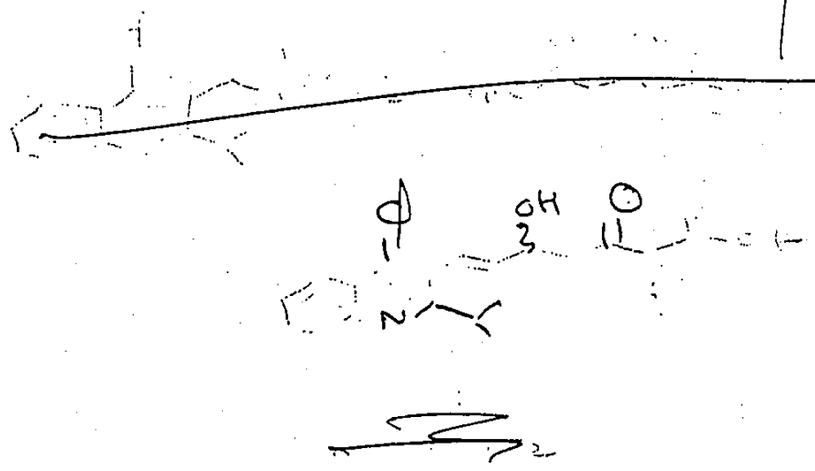
☐ expand spectral region from to

☐ 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
	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 NMR90 200 500 Micro Misc **Request Sheet** circ 205

thin film — $CDCl_3$ — solvent or medium

empirical formula

mp. °C

bp

sample # book page line: 120 176-41

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

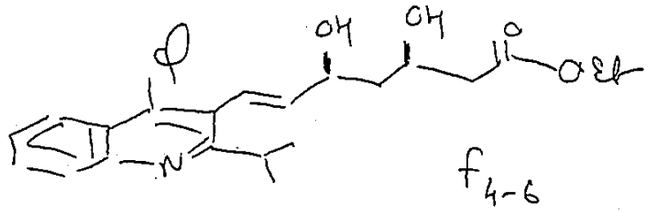
☐ expand spectral region from to

☐ 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. same for ~~same~~ IR

expanded 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

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 90 200 500 Micro Misc Request Sheet circ! 206

solvent or medium

empirical formula

mp. °C

bp

sample # book page line

IW-AW-KP ☐ pure ☐ crude

unit head requestor

bldg. 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

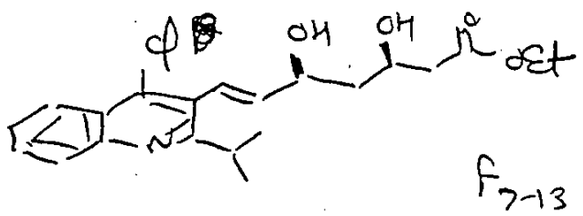
☐ expand spectral region from to

☐ assign for ☐ ^{1}H (500) ☐ ^{13}C

☐ save on tape if pure

☐ check for impurities (state level) %

synthetic pathway:
reagents, solvents
esp. last solvent:



f_{7-13}

Pl. save for I.R.:

Pl. extrapolate region δ 5-7

Rest

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
	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

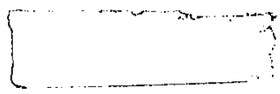
misc. & comments:

sample # book #

87147/81 (Rev. 2)

Exhibit D


1



207

SANDOZ

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:

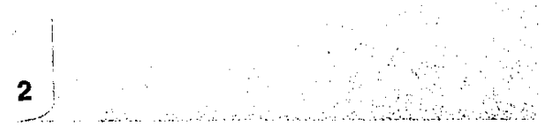
Preparation of Physiol. Solution:

Synthesis:

Chemist:

Chem. No.:

83520 74 Rev. 7


2

RESEARCH DEPARTMENT

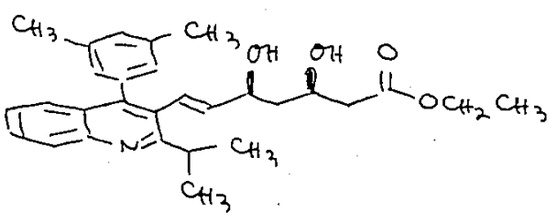
SANDOZ HANOVER

CHEMICAL INFORMATION

Date:

Compound No.: 63-366 208

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. —

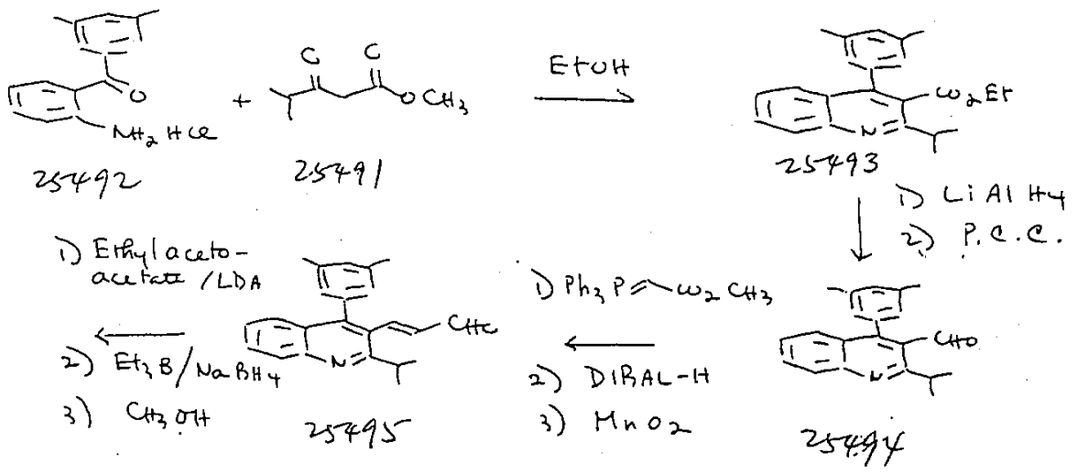
Known ___ Unknown X

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:



Product.

Chemist: S. WATTANASIN / F.G. KATHAWALA.

Chem. No.: 1079-111-19

83520/74 Rev: 6

RESEARCH DEPARTMENT

SANDOZ HANOVER

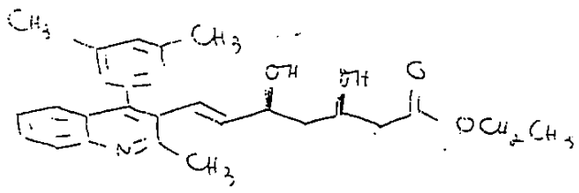
209

Date: 4/16/85

CHEMICAL INFORMATION

Compound No.: 63-548

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		[illegible]	✓
GHI		[illegible]	✓
GLUC		[illegible]	✓
HG			
HL			
PL		AM/AV	
TC		Tr	
		Agro	

Compare With: [illegible]

Pat. Disclosure No. 299/84

L & D No. 13329

Known ___ Unknown ✓

Remarks: DF Stallion 5.0 mg
- pure and the compound
- Keep in ref.

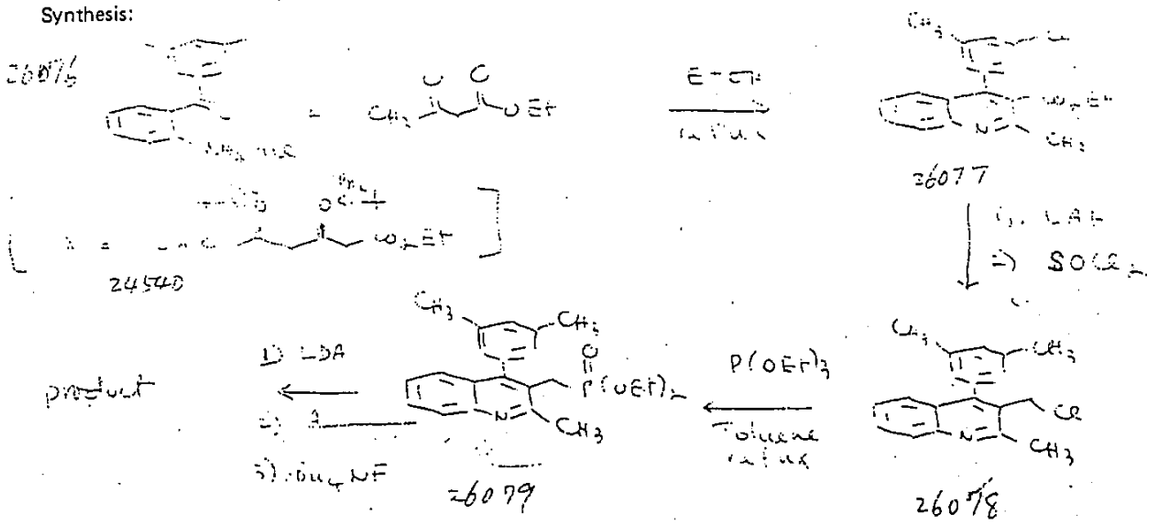
Preparation of Physiol. Solution:

DMA 5

EtOH E

CMC [illegible] C

Synthesis:



Chemist: S. WATANASIN & F. G. KATHAWALA

Chem. No.: 123-11-34

83520/74 Rev. 6

RESEARCH DEPARTMENT

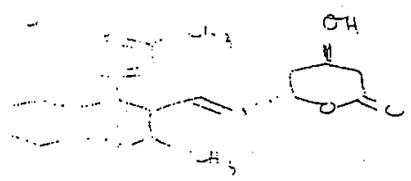
SANDOZ HANOVER

CHEMICAL INFORMATION

Date: [illegible] 210

Compound No.: 43-549

Structure:



1082

Emp. Form :	$C_{25}H_{32}O_3N$
Mol. Wt. :	392
m.p. :	
b.p. :	
*Others :	~1.
Hanover :	—
AM/AV :	
Tr :	
Agro :	

Name:

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

Compare With:

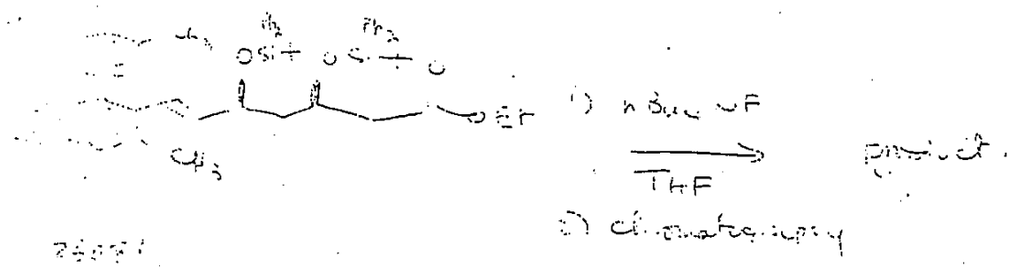
Pat. Disclosure No. 299/64
L & D No. 13329
Known ___ Unknown ✓

Remarks: Dissertation during
— pure 3-oxo lactone
— contains some impurities
— Key intermediate

Preparation of Physiol. Solution:

DMA 5
EtOH 5
Cmc suspension ad 100

Synthesis:



Chemist: S. VENKATARAMAN & F. C. KATRAWALA

Chem. No.: 43-11-37

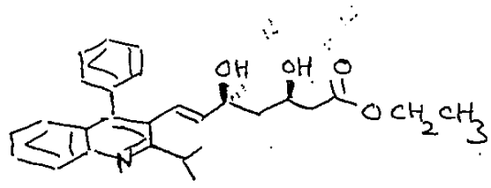
83520/74 Rev. 6

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

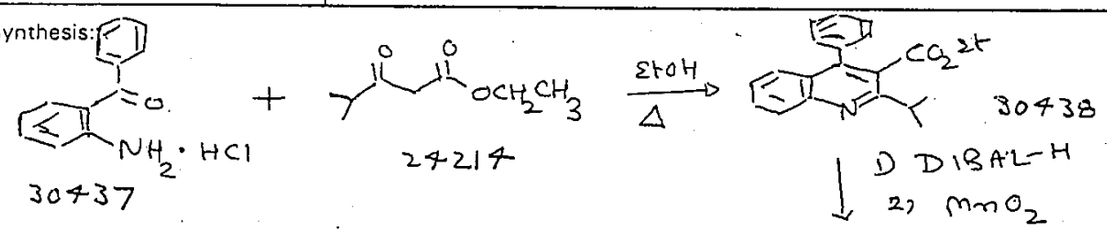
Pat. Disclosure No. 299/84
L & D No.
Known ____ Unknown X

Remarks: Dv. Scallen 50mg
erythro : threo > 95 : 5
keep refrigerate.

Preparation of Physiol. Solution:

DMA D
or
EtOH E
or
CMC suspension C

Synthesis:



Chemist: S. Wattanasin / R. Patel

Chem. No.: 1206-176-43

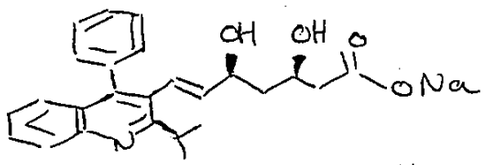
83520/74 Rev. 7

SANDOZ RESEARCH INSTITUTE
EAST HANOVER, NEW JERSEY
CHEMICAL INFORMATION

Date:

Compound No.: 64-934/Na

Structure:



30442

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

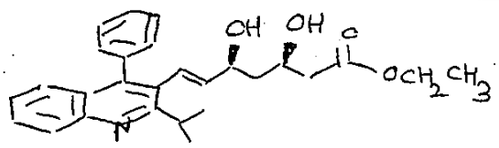
Pat. Disclosure No. 299 184
L & D No.
Known ___ Unknown X

Remarks: Dr. Scallen 50 mg 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

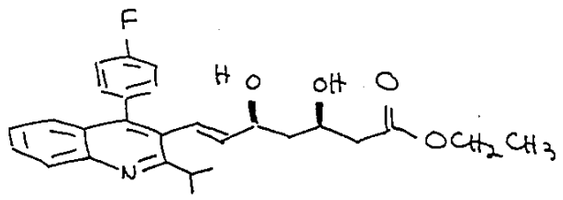
83520/74 Rev. 7

SANDOZ RESEARCH INSTITUTE
EAST HANOVER, NEW JERSEY
CHEMICAL INFORMATION

Date:

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		CSI	✓
GHI		CSTC	✓
GLUC		CSTV	✓
HG			
HL			
PL		AM/AV	
TC		Tr	
		Agro	

Compare With: 62-320

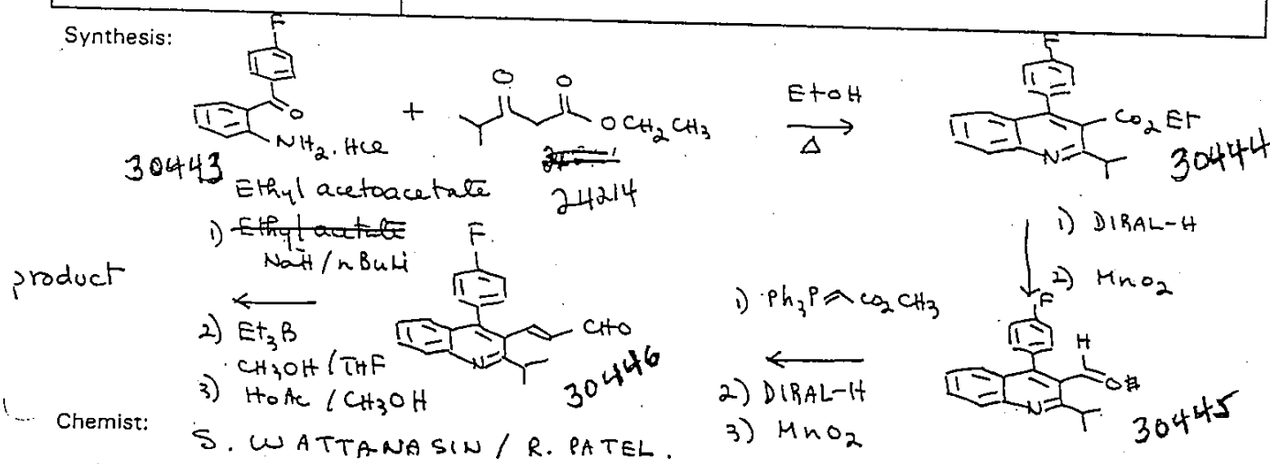
Pat. Disclosure No. 29984
L & D No. —
Known ____ Unknown X

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

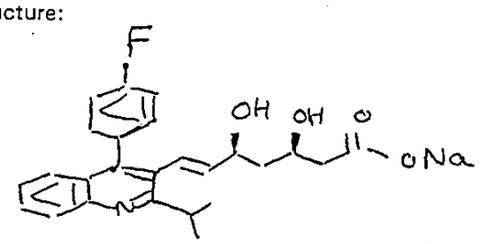
214

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

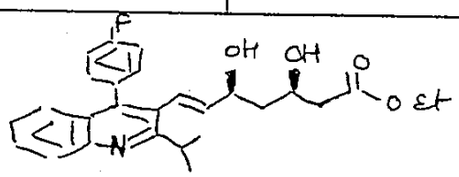
Pat. Disclosure No. 299/84
L & D No.
Known ___ Unknown X

Remarks: Dr. Scallen 20 mg
erythro : threo > 95 : 5
Keep refrigerate

Preparation of Physiol. Solution:

DMA D
or
EtOH E
or
Cme Suspension C

Synthesis:

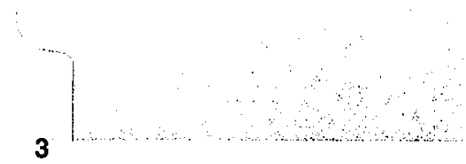


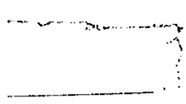
30447

$\xrightarrow[0^\circ C]{NaOH}$ Product.

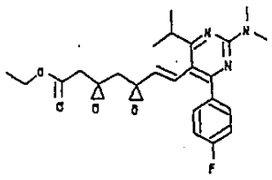
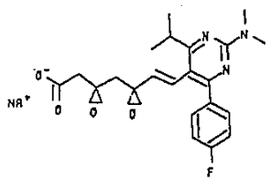
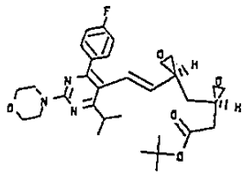
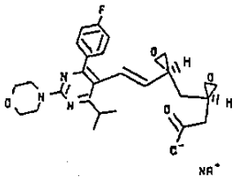
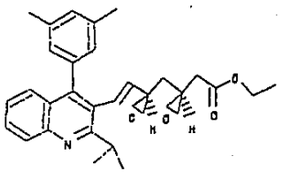
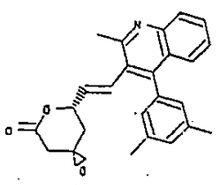
Chemist: S. Wattanasin / R. Patel
Chem. No.: 1206-201-30

83520/74 Rev. 7


3



(2 215

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 R
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

249

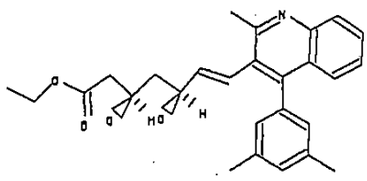
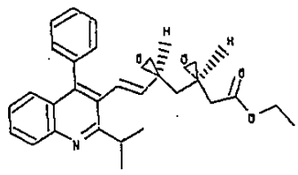
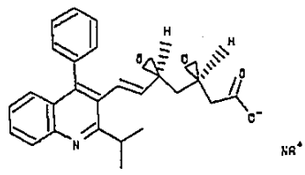
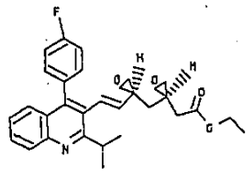
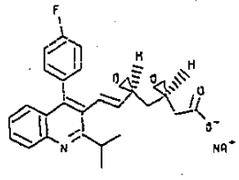
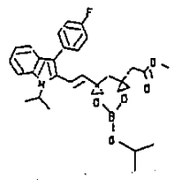
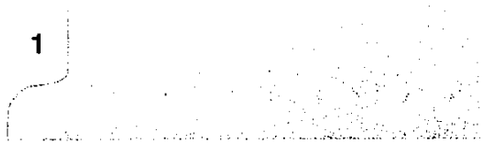
SAH-063548 26080 1127-011-34 299-84		ICSO (UM) - MICROSOMAL ASSAY 3.7750 DATE TESTED 06-13-84 REFERENCE 1069-198 COMMENTS
SAH-064933 30441 1206-176-43 299-84		ICSO (UM) - MICROSOMAL ASSAY 2.3700 DATE TESTED 10-08-87 REFERENCE 1238-013 COMMENTS
SAH-064934 30442 1206-179-30 299-84		ICSO (UM) - MICROSOMAL 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 1036-087-41 431-64		ICSO (UM) - MICROSOMAL ASSAY 0.0019 DATE TESTED 07-26-84 REFERENCE 1069-033. COMMENTS

Exhibit E


1

Sandoz HMG-Co-A Reductase Screening Book VI page 5 217

12-13-84

Sandoz Compounds Tested for HMG-CoA Reductase

1) Following compounds weighed out to make 10 mM dilution:

63-364 (25489)	1.30 mg	in 13.015 ml DMA
63-345 (25490)	1.60 mg	in 18.836 ml DMA
63-346 (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.

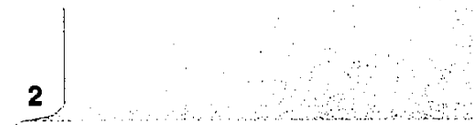
RESULTS OF EXPERIMENT:

PROGRAM #: 10
REGION A: LL-UL= 0- 8 LCR= 0 BKG= 12 1 2 sigma
REGION B: LL-UL= 24- 156 LCR= 0, BKG= 17 1 2 sigma
NUCLIDE 1 = 0 NUCLIDE 2 = 0
TIME= 10.00 QIP= SIE/AEC SCR= B/A K= 1.000

12-13-84

P#	S#	TIME	CPMA/K CPM1/K	%DEV	CPMB/K CPM2/K	%DEV	QIP	FLAGS	SCR	MIN		
								93178 / 96309 x SD =		48.44		
				³H Recounted								1.18 mg
10	1	10.00	20582.7	.44	93.20	6.62	490.		.000	11		
			67534.5		43.27				.000			
10	2	10.00	7170.70	.75	55512.3	.27	501.		7.742	33		
			0.00		56209.0				.000			
10	3	10.00	12318.5	.57	194.60	4.35	433.		.014	33		
			62667.1		267.29				.004			
10	4	10.00	10848.5	.61	200.40	4.29	425.	Blank	.010	44		
			58428.8		289.65				.007			
10	5	10.00	11003.1	.60	3214.70	1.11	423.		.293	50		
			57072.2		5991.65				.100			
10	6	10.00	11623.8	.58	3211.50	1.11	424.	Buffer A .102	.277	44	1.00	
			61181.7		5968.35				.098			
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	3196.30	1.12	421.	DMA .096	.269	87	.94	
			63821.3		5955.84				.093			
10	9	10.00	11314.1	.59	161.50	4.73	437.		.014	99		
			57798.3		213.54				.004		.00	100 I
10	10	10.00	12186.1	.57	256.70	3.82	424.	1mm 10^{-1}	.021	169		
			65777.5		384.87				.005		.02	98 I
10	11	10.00	12123.3	.57	519.80	2.73	427.	10^{-2}	.043	120		
			64522.7		880.30				.014		.10	90 I
10	12	10.00	11927.2	.58	1557.40	1.59	430.	10^{-3}	.131	153		
			61715.5		2823.10				.046		.43	55 I
10	13	10.00	11836.3	.58	2575.40	1.24	426.	10^{-4}	.218	141		
			60625.0		4737.92				.076		.75	20 I
10	14	10.00	11727.9	.58	2674.40	1.18	427.	10^{-5}	.228	152		
			60152.4		5310.16				.081		.86	9 I
10	15	10.00	12721.4	.56	3280.00	1.10	428.	10^{-6}	.258	143		
			64964.0		6060.68				.091		.91	3 I
10	16	10.00	12886.7	.56	3258.00	1.11	427.	10^{-7}	.253	174		
			66069.7		6023.92				.091		.89	5 I
10	17	10.00	12062.2	.58	3107.30	1.13	430. (24291)	10^{-8}	.258	167		
			61956.6		5725.33		Compaction		.092		.92	2 I
10	18	10.00	11793.4	.58	218.60	4.12	426.	10^{-2}	.014	199		
			63082.9		316.24				.005		.01	99 I
10	19	10.00	11535.3	.59	318.10	3.45	429.	10^{-3}	.021	206		
			60925.9		504.78				.006		.04	96 I
10	20	10.00	11261.1	.60	603.00	2.54	425.	10^{-4}	.037	217		
			60390.9		1045.56				.013		.13	86 I
10	21	10.00	11621.5	.59	1007.80	1.98	426.	10^{-5}	.067	224		
			61450.8		1803.62				.025		.25	73 I
10	22	10.00	10983.8	.60	2628.40	1.23	429.	10^{-6}	.239	221		
			56002.5		4642.96				.084		.84	10 I
10	23	10.00	11265.4	.60	2946.80	1.16	425.	10^{-7}	.261	198		
			58243.0		5468.88				.092		.92	2 I
10	24	10.00	10899.7	.61	2737.20	1.21	432. (24291)	10^{-8}	.249	221		
			54797.2		5028.53		62-320/Nic-4		.090		.90	4 I

S#	TIME	CPMA/K CPM1/K	%DEV	CPMB/K CPM2/K	%DEV	DIP	FLAGS	SCR	MIN		
25	10.00	11971.1 60603.4	.58	2465.80 4511.86	1.27	432.		.206 .087	373	.71	24 I
	10.00	12009.1 61065.6	.58	2902.20 5344.66	1.17	429.		.242 .061	283	.86	9 I
27	10.00	11570.3 61493.4	.58	3012.20 5572.15	1.15	426.		.252 .041	353	.89	5 I
28	10.00	11459.2 59078.7	.59	2898.90 5340.51	1.17	430.		.237 .052	340	.90	4 I
29	10.00	11746.6 59385.1	.58	2779.20 5104.85	1.20	431.		.227 .066	315	.84	10 I
30	10.00	11443.1 58662.5	.59	2803.50 5186.67	1.19	426.		.240 .054	334	.86	9 I
31	10.00	13384.9 69386.4	.55	3153.90 5838.62	1.12	425.	(25489) 63-364	.256 .064	397	.82	13 I
32	10.00	11944.3 62787.8	.58	246.70 367.48	3.69	430.		.021 .004	101	.02	98 I
33	10.00	10624.9 55037.4	.61	412.50 687.83	3.05	431.		.033 .013	351	.08	92 I
34	10.00	12111.1 63287.6	.57	716.00 1248.47	2.33	430.		.057 .020	349	.16	83 I
35	10.00	11395.5 58355.1	.59	1952.70 3563.63	1.43	431.		.171 .041	380	.58	38 I
36	10.00	12013.9 62437.3	.57	2925.50 5379.74	1.17	430.		.236 .056	391	.84	11 I
37	10.00	11429.5 56369.1	.59	2682.70 4888.43	1.22	437.		.203 .047	402	.85	10 I
38	10.00	12475.8 62911.9	.57	3041.80 5588.37	1.14	431.	(25490) 63-365	.244 .035	413	.87	8 I
	10.00	11757.3 60468.4	.58	855.00 1502.14	2.14	433.		.073 .022	421	.21	78 I
40	10.00	11450.2 57757.5	.59	1903.50 3454.64	1.44	434.		.166 .060	434	.57	39 I
41	10.00	12775.5 63608.8	.56	2880.70 5258.52	1.17	435.		.225 .033	445	.81	14 I
42	10.00	12709.3 63746.6	.56	3125.20 5733.35	1.13	432.		.246 .030	406	.80	6 I
43	10.00	12097.7 60889.8	.57	3059.30 5623.40	1.14	431.		.237 .031	411	.90	4 I
44	10.00	11673.6 59168.1	.59	2683.80 5306.71	1.17	430.		.211 .050	411	.88	6 I
45	10.00	12125.7 61611.9	.57	2971.50 5473.37	1.16	429.	(25496) 63-366	.233 .043	411	.87	8 I
46	10.00	10967.4 54555.1	.60	255.10 352.83	3.96	434.		.021 .004	101	.02	98 I
47	10.00	12310.9 61770.6	.57	673.10 1160.11	2.41	431.		.052 .018	347	.14	85 I
48	10.00	11275.4 57110.2	.60	1472.90 2664.33	1.64	435.		.131 .044	371	.44	54 I
49	10.00	10509.7 53015.3	.61	1985.70 3636.91	1.41	430.		.189 .062	371	.62	34 I
50	10.00	12466.4 61941.9	.57	2562.30 4673.53	1.25	434.		.206 .046	411	.72	23 I
	10.00	11205.9 55740.7	.60	2725.40 4980.73	1.21	435.		.243 .049	401	.87	8 I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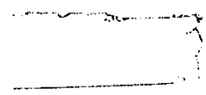

8/20/85

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).

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6-13-85
1.07 mg/ml

GRAM #: 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

	SE	TIME	CPMA/K DPM1/K	%DEV	CPMB/K DPM2/K	%DEV	QIP	FLAGS	SCR	MIN	
	1	10.00	19925.7 81731.8	.45	74.00 21.71	6.63	502.		.004 .000	11	
	2	10.00	2275.30 0.00	1.32	18306.4 31376.4	.47	515.		8.046 .000	23	
	3	10.00	12008.9 63316.8	.58	187.40 255.96	4.42	430.		.016 .004	33	
	4	10.00	11819.5 62654.8	.58	183.40 249.90	4.47	429.	B1	.016 .004	44	
	5	10.00	12376.4 65114.9	.57	987.30 1755.36	2.00	428.	Buffer .020	.080 .027	55	
	6	10.00	6022.80 29724.8	.81	495.30 866.74	2.79	443.		.082 .029	66	.49
	7	10.00	12248. [illegible]	.58	0 4	1.95	428.		.085 .029	77	
	8				3 .3	2.01	425.	DMA .029	.085 .029	11.47	
	9		11642.3 62636.8	.58	187.90 258.19	4.42	429.		.016 .004	22	
1	10	10.00	12091.9 64859.9	.57	217.50 311.77	4.13	426.	1MR 10'	.018 .005	33	.00 100 I .02 96 I
	11	10.00	11725.2 61948.2	.58	282.20 435.93	3.66	429.	-2	.024 .007	44	.06 88 I
	12	10.00	12117.6 63918.1	.57	616.90 1061.13	2.51	428.	-3	.051 .017	55	.24 48 I
	13	10.00	12445.1 64654.8	.57	954.10 1686.41	2.03	431.	-4	.077 .026	66	.41 12 I
	14	10.00	12006.8 62627.3	.58	1028.60 1831.99	1.96	430.	-5	.086 .029	76	.47 100 C
	15	10.00	11767.0 60883.9	.58	1003.20 1782.27	1.98	431.	-6	.085 .029	87	.47 100 C
	16	10.00	884.10 4239.44	2.11	67.20 116.16	6.89	451.	-7	.076 .027	98	.43 8 I
	17	10.00	11813.5 60665.0	.58	1010.70 1792.17	1.97	433.	-8 Compactin	.086 .030	109	.49 104 C
	18	10.00	5972.70 29944.0	.82	64.00 73.74	7.03	442.	10^{-2}	.011 .002	120	.00 100 I
2	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
	21	10.00	12112.8 64688.1	.57	470.40 787.87	2.86	426.	-5	.039 .012	199	.15 68 I
	22	10.00	11203.1 57384.7	.60	701.80 1219.14	2.36	435.	-6	.063 .021	210	.32 32 I
4	23	10.00	12137.9 [illegible]	.57	995.80 1768.37	1.99	430.	DMA	.082 .028	220	.45 4 I

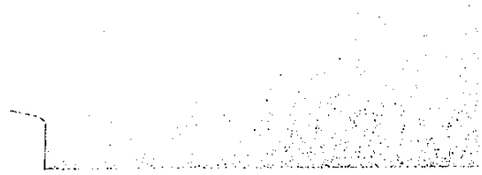
4	31	10.00	12389.0										
			63810.8		1890.28								
4	32	10.00	12229.2	.57	223.30	4.08	436.	.016					
			62777.4		321.20			10² .005		.02	46 I		
4	33	10.00	12060.9	.58	346.00	3.32	434.	.029	55				
			62360.8		551.10			.009		.09	80 I		
	34	10.00	12161.0	.57	754.10	2.28	429.	.062	66				
			63889.7		1317.56			-4 .021		.32	32 I		
	35	10.00	12069.8	.58	895.00	2.09	430.	.074	77				
			62939.3		1580.24			-5 .025		.39	16 I		
4	36	10.00	12133.6	.57	987.90	2.00	431.	.081	88				
			63042.8		1752.51			-6 .028		.45	4 I		
4	37	10.00	12321.3	.57	1036.30	1.95	433.	.084	98				
			63352.7		1836.46			-7 .029		.47	100C		
4	38	10.00	12464.4	.57	1038.50	1.95	433.	(RN 26039)					
			63999.6		1838.68			63-537/Wa -8 .029	109	.47	100C		
4	39	10.00	12399.5	.57	202.40	4.27	432.	.016	120				
			64833.9		281.02			10² .004		.00	100 I		
5	40	10.00	12278.9	.57	260.70	3.80	436.	.021	131				
			62975.6		390.25			-3 .006		.04	92 I		
4	41	10.00	11232.7	.60	406.30	3.07	431.						
			[illegible]		671.54			-4 .036	142	.13	72 I		
4				.58	598.00								
					1020.12			-5		.22	52 I		
4	43	10.00	[illegible]	.57	929.20	2.06	433.	.075	23				
			63806.6		1637.39			-6 .026		.41	12 I		
4	44	10.00	12288.0	.57	1040.60	1.94	430.	.085	34				
			64072.1		1851.99			-7 .029		.47	100C		
4	45	10.00	12189.6	.57	1042.40	1.94	428.	(RN 26075)					
			64092.5		1860.53			63-547 -8 .086 .029	44	.47	100C		
4	46	10.00	12119.8	.57	432.00	2.98	429.	.036	55				
			63770.7		713.38			10² .011		.13	72 I		
6	47	10.00	12026.4	.58	858.70	2.14	430.	.071	66				
4			62744.7		1512.64			-3 .024		.37	20 I		
4	48	10.00	12099.0	.57	1016.70	1.97	430.	.084	77				
			63125.5		1808.97			-4 .029		.47	100C		
4	49	10.00	12212.9	.57	1038.30	1.95	433.	.085	88				
			62712.4		1840.44			-5 .029		.47	100C		
4	50	10.00	12166.8	.57	1002.90	1.98	434.	.082	98				
			62337.9		1773.52			-6 .028		.45	4 I		
4	51	10.00	11720.1	.58	988.90	1.99	431.	(RN 26080)					
			60751.7		1756.73			63-548 -7 .029	109	.47	100C		
4	52	10.00	11999.0	.58	999.90	1.98	429.	.082	120				
			62691.6		1778.92			-8 .028		.45	4 I		
4	53	10.00	12032.0	.58	556.20	2.64	430.	.036					
			62970.3		946.02			10² .011		.21	56 I		
7	54	10.00	11866.9	.58	933.20	2.05	426.	.071					
4			63061.2		1662.26			-3 .024		.41	12 I		
4	55	10.00	11647.4	.59	988.90	1.99	429.	.084					
			60781.4		1760.63			-4 .029		.47	100C		
4	56	10.00	12011.1	.58	1021.80	1.96	424.	.085	164				
			64054.0		1830.37			-5 .029		.47	100C		
4	57	10.00	12067.7	.58	1019.10	1.96	429.	.084	174				
			63119.5		1815.00			-6 .029		.47	100C		
4	58	10.00	12212.6	.57	985.50	2.00	435.	.081	185				
			62328.7		1738.75			-7 .028		.45	4 I		
4	59	10.00	11400.9	.59	958.40	2.03	428.	(RN 26082)					
			59940.9		1708.98			63-549 -8 .084 .029	194	.47	100C		
4	60	10.00	11300.5	.59	304.50	3.53	430.						
			59446.6		480.86			10²		.07	84 I		
4	61	10.00	11780.8	.58	674.40	2.41	432.						
			61152.5		1167.36			-3		.28	40 I		
			[illegible]	.58	909.30	2.08	428.	-4		.41	12 I		
			[illegible]		[illegible]					.47	100C		

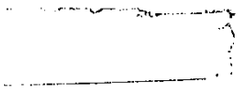
10	50	10.00	12404.4 62141.9	.57	2562.30 4673.53	1.25	434.		.341 .005		.72	23 I	224
10	51	10.00	11205.5 55740.7	.60	2723.40 4980.73	1.21	435.		.343 .005		.87	8 I	

P#	S#	TIME	CPMA/K DPM1/K	%DEV	CPMB/K DPM2/K	%DEV	DIP	FLAGS	SCR	MIN			
								(25512)					
10	52	10.00	11793.4 60586.7	.58	2944.10 5444.86	1.16	427.	63-369	.350 .006	564	.88	6 I	22
10	53	10.00	11759.0 62249.7	.58	214.10 397.89	4.16	429.		.016 .000	575	.01	99 I	
10	54	10.00	10746.4 55439.6	.61	226.20 338.05	4.06	435.		.021 .006	566	.62	98 I	
10	55	10.00	12134.1 63682.0	.57	552.20 936.29	2.65	430.		.045 .015	557	.11	89 I	
10	56	10.00	10750.4 55607.9	.61	721.60 1261.87	2.33	433.		.057 .020	466	.19	80 I	
10	57	10.00	11588.4 61226.1	.58	2270.30 4154.19	1.32	430.		.169 .008	411	.65	31 I	
10	58	10.00	12140.5 61534.3	.57	2764.90 5077.09	1.20	431.	(25500)	.220 .003	424	.81	14 I	
10	59	10.00	12035.4 60845.5	.58	2569.10 4893.27	1.22	431.	-63-162/3	.332 .010	440	.78	17 I	23
10	60	10.00	12245.9 64652.3	.57	227.80 329.78	4.04	429.		.015 .000	551	.01	99 I	
10	61	10.00	10555.8 59712.3	.60	324.60 522.15	3.42	426.	-3	.030 .005	663	.05	95 I	
10	62	10.00	11783.4 62219.8	.58	466.80 781.94	2.88	429.	-4	.040 .013	673	.13	91 I	
10	63	10.00	11538.9 61266.4	.58	1117.40 1950.45	1.88	433.	-5	.054 .032	687	.28	70 I	
10	64	10.00	12183.0 63370.5	.57	2545.80 4700.04	1.25	425.	-6	.207 .074	695	.71	24 I	
10	65	10.00	11091.6 57123.0	.60	2441.30 4500.65	1.28	427.	(25501) -7	.316 .075	707	.77	18 I	
10	66	10.00	11576.4 62224.6	.58	2728.90 5050.30	1.21	425.	63-270/2	.328 .031	718	.79	16 I	

			DPM1/K	%DEV	CPMB/K DPM2/K	%DEV	DIP	FLAGS	SCR	MIN
	1	5.00	6688.00	1.09	52764.0	.39	508.		7.605	9
PIN JAM			0.00		90901.8			avg	.000	
	2	5.00	7371.80	1.04	55378.8	.38	505.	BH	7.713	12
PIN JAM			0.00		95646.8			93273.5	.005	

93 273.5





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	.01	1	99	
1mM			.04	3	97	
10^{-1}			.18	17	83	
10^{-2}			.62	61	39	
10^{-3}			.88	86	14	
10^{-4}			1.04	102	-	
10^{-5}			1.04	102	-	
10^{-6}			1.02	100	-	
10^{-7}			1.04	102	-	
10^{-8}						
) 62-320 (24135)	10/8/87	DMA	.01	1	99	
10^{-2}			.06	6	94	
10^{-3}			.20	20	80	
10^{-4}			.36	36	64	
10^{-5}			.83	82	18	
10^{-6}			1.02	100	-	
10^{-7}			1.02	100	-	
10^{-8}						
3) 64-906 (RN 30393)	10-8-87	DMA	.01	1	99	
10^{-2}			.01	1	99	
10^{-3}			.11	10	90	
10^{-4}			.27	26	74	
10^{-5}			.55	54	46	
10^{-6}			1.02	100	-	
10^{-7}			1.02	100	-	
10^{-8}						
4) 64-933 (RN 30441)	10-8-87	DMA	.20	20	80	
10^{-2}			.69	68	32	
10^{-3}			.99	98	2	
10^{-4}			1.04	102	-	
10^{-5}			.99	98	2	
10^{-6}			1.04	102	-	
10^{-7}			.99	98	2	
10^{-8}						

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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	

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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/AEC SCR= B/A K= 1.000

10-8-87

0.91 mg/ml

81965.9 / 32519.6 × 50.6 = 127.54

P#	S#	TIME	CPMA/K DPM1/K	%DEV	CPMB/K DPM2/K	%DEV	QIP	FLAGS	SCR	MIN		
10	1	10.00	3091.60	1.13	20162.1	.45	623.		6.522	11		
			235.65		32519.6				138.00			
10	2	10.00	25818.6	.39	25.60	10.6	614.	1	.001	23		
			81965.9		0.00				.000			
10	3	10.00	15376.8	.51	118.30	5.58	536.	1	.008	34		
			57003.8		152.01				.003			
10	4	10.00	14913.9	.52	98.70	6.07	540.		.007	45		
			55504.1		120.38				.002		S.A.	%I
10	5	10.00	15943.8	.50	1667.70	1.54	537.	1	.105	55		
			58737.5		2783.28				.047	Avg. .046		
10	6	10.00	14562.0	.52	1500.00	1.63	538.	1	.103	66	1.02	
			53578.4		2501.69				.047			
10	7	10.00	15625.1	.51	147.00	5.05	534.		.009	77		
			59001.1		199.82				1mM .003		.01	99I
10	8	10.00	14951.6	.52	146.30	5.06	532.	1	.010	88		
			56705.7		200.61				10^{-1} .004		.04	97I
10	9	10.00	16065.6	.50	373.50	3.23	540.	1	.023	99		
			59499.6		582.69				10^{-2} .010		.18	83I
10	10	10.00	16091.8	.50	1038.90	1.95	542.	1	.065	110		
			58934.3		1708.91				10^{-3} .029		.62	39I
10	11	10.00	15994.6	.50	1410.50	1.68	541.	1	.088	121		
			58487.0		2339.90				10^{-4} .040		.88	14I
10	12	10.00	14930.8	.52	1525.80	1.61	540.		.102	132		
			54627.5		2540.53				10^{-5} .047		1.04	102
10	13	10.00	16937.4	.49	1780.10	1.49	533.	1	.105	143		
			63125.5		2979.86				10^{-6} .047		1.04	102
10	14	10.00	15441.7	.51	1579.60	1.59	536.		.102	153		
			57114.5		2637.63				10^{-7} .046		1.02	100
10	15	10.00	15874.9	.50	1648.60	1.55	535.	(29299)	.104	164		
			58835.7		2755.17			Competin	10^{-8} .047		1.04	102
10	16	10.00	16273.6	.50	150.40	4.99	529.	1	.009	175		
			62289.0		202.79			10µm	10^{-2} .003		.01	99I
10	17	10.00	15753.3	.50	208.90	4.27	531.	1	.013	186		
			59820.1		304.73				10^{-3} .005		.06	94I
10	18	10.00	15849.2	.50	418.40	3.06	538.	1	.026	197		
			58981.0		660.18				10^{-4} .011		.20	80I
10	19	10.00	15451.8	.51	645.60	2.47	536.	1	.042	208		
			57686.1		1048.57				10^{-5} .018		.36	64I
10	20	10.00	15316.0	.51	1287.10	1.76	541.	1	.084	219		
			56089.6		2133.36				10^{-6} .038		.83	18I
10	21	10.00	16492.1	.49	1669.40	1.54	540.	1	.101	230		
			60323.7		2778.83				10^{-7} .046		1.02	100
10	22	10.00	15743.7	.50	1581.50	1.59	539.	(24135)	.100	240		
			57748.1		2633.97			62-320	10^{-8} .046		1.02	100
10	23	10.00	15611.7	.51	132.80	5.29	535.		.009	251		
			58828.3		175.79				10^{-2} .003		.01	99I
10	24	10.00	15512.4	.51	137.60	5.21	537.	1	.009	262		
			58030.1		184.46				10^{-3} .003		.01	99I

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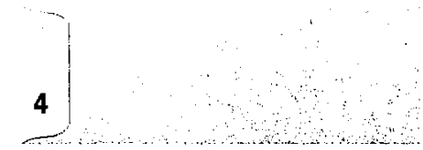
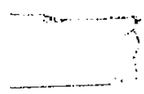
P#	S#	TIME	CPMA/K DPM1/K	%DEV	CPMB/K DPM2/K	%DEV	QIP	FLAGS	SCR	MIN	
10	25	10.00	16190.3 59961.2	.50	261.30 392.02	3.84	541.		.016 -4 .007	273 .11	70-
10	26	10.00	16559.8 62307.7	.49	537.30 861.72	2.70	534.	1	.032 -5 .014	284 .27	74I
10	27	10.00	16551.0 61974.6	.49	984.30 1623.19	2.01	534.	1	.059 -6 .026	295 .55	46I
10	28	10.00	16260.6 60033.6	.50	1649.80 2753.02	1.55	536.	1	-7 .101 (RN 30393) .046	306 1.02	100C
10	29	10.00	16764.8 61837.3	.49	1705.70 2845.79	1.53	537.	1	-8 .102 64-906/Na .046	317 1.02	100C
10	30	10.00	16189.0 60617.9	.50	435.30 688.63	3.00	536.	1	-2 .027 11 .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	16206.0 60445.6	.5	79.40 2721.69	1.56	535.	1	.100 -4 .048	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 (RN 30441) .047	382 1.04	102C
10	36	10.00	15984.6 58807.1	.50	1604.50 2674.30	1.57	538.	1	-8 .100 64-933 .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	.075 -3 .033	415 .71	30I
10	39	10.00	15210.9 56444.4	.51	1511.00 2523.37	1.62	535.	1	.099 -4 .045	426 .99	2I
10	40	10.00	15940.7 58354.9	.50	1630.10 2714.63	1.56	540.	1	.102 -5 .047	437 1.04	102C
10	41	10.00	15797.7 58542.5	.50	1640.90 2742.23	1.56	535.	1	.104 -6 .047	448 1.04	102C
10	42	10.00	15693.3 57754.7	.50	1605.20 2676.87	1.57	538.	1	-7 .102 (RN 30442) .046	458 1.02	100C
10	43	10.00	17034.4 62837.8	.48	2050.90 3434.60	1.39	536.	1	-8 .120 64-934/Na .055	469 1.23	121C
10	44	10.00	15281.6 57367.8	.51	310.10 478.64	3.53	535.	1	.020 -2 .008	480 .13	87I
10	45	10.00	16345.3 61027.6	.49	588.20 947.92	2.59	536.	1	.036 -3 .016	491 .32	69I
10	46	10.00	16369.7 60434.1	.49	1226.10 2030.00	1.80	538.	1	.075 -4 .034	502 .74	28I
10	47	10.00	16280.1 59712.9	.50	1515.40 2519.27	1.62	540.	1	.093 -5 .042	513 .92	9I
10	48	10.00	16271.8 60108.7	.50	1562.10 2603.64	1.60	537.	1	.096 -6 .043	524 .95	7I
10	49	10.00	15953.0 59171.0	.50	1567.10 2616.07	1.59	535.	1	-7 .098 (RN 30447) .044	535 .97	5I
10	50	10.00	15663.0 57817.7	.51	1590.00 2653.15	1.58	537.	1	-8 .100 64-935 .045	547 1.02	100C
10	51	10.00	16011.6 60604.2	.50	184.40 262.19	4.54	533.	1	-2 .011 .004	[illegible] .04	97I

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.		.036 -3 .016	567 .32	69I
10	53	10.00	16394.2	.48	888.20	1.79	533.				

10	42	10.00	15693.3	.50	1605.20	1.57	538.	1		-7	.102	458		
			57754.7		2676.87				(RN 30442)		.046		1.02	100
.0	43	10.00	17034.4	.48	2050.90	1.39	536.	1		-8	.120	469		
			62837.8		3434.60				64-934/Na		.055		1.23	12 230
10	44	10.00	15281.6	.51	310.10	3.53	535.	1			.020	480		
			57367.8		478.64					-2	.008		.13	87 I
.0	45	10.00	16345.3	.49	588.20	2.59	536.	1			.036	491		
			61027.6		947.92					-3	.016		.32	69 I
.0	46	10.00	16369.7	.49	1226.10	1.80	538.	1			.075	502		
			60434.1		2030.00					-4	.034		.74	28 I
10	47	10.00	16280.1	.50	1515.40	1.62	540.	1			.093	513		
			59712.9		2519.27					-5	.042		.92	9 I
	48	10.00	16271.8	.50	1562.10	1.60	537.	1			.096	524		
			60108.7		2603.64					-6	.043		.95	7 I
10	49	10.00	15953.0	.50	1567.10	1.59	535.	1			.098	535		
			59171.0		2616.07				(RN 30447)	-7	.044		.97	5 I
.0	50	10.00	15663.0	.51	1590.00	1.58	537.	1			.102	547		
			57817.7		2653.15				64-935	-8	.042		1.02	100C
.0	51	10.00	16011.6	.50	184.40	4.54	533.	1			.011	557		
			60604.2		262.19					-2	.004		.04	97I

P#	S#	TIME	CPMA/K CPM1/K	%DEV	CPMB/K CPM2/K	%DEV	DIF	FLAGS					
10	52	10.00	15089.3	.51	545.90	2.68	534.			.036	567		
			56615.4		880.81				-3	.016		.32	69I
0	53	10.00	16394.2	.49	1082.90	1.91	533.	1	-4	.029	578	.62	39 I
			61438.0		1792.44								
10	54	10.00	15760.3	.50	16.80	12.2	539.	1	-5	.001	589	-	—
			58017.1		0.00					.000			
.0	55	10.00	15147.5	.51	14.10	12.8	537.	1	-6	.001	600	-	—
			56761.0		0.00					.000			
	56	10.00	15504.2	.51	1645.90	1.55	535.	1		.106	611		
			57376.3		2751.02				(RN 30448)	.046		1.06	105C
10	57	10.00	15646.4	.51	1633.90	1.56	535.	1	-8	.104	621		
			58003.1		2731.11				64-936/Na	.047		1.04	102C
10	58	10.00	16494.4	.49	1675.70	1.54	537.	1		.103	632		
			60823.6		2795.44				Data	.046			
10	59	10.00	16837.0	.49	1673.10	1.54	536.	1		.097	644		
			62238.5		2791.43				omitted	.045			
.0	60	10.00	16031.2	.50	1638.80	1.56	538.	1	10xm	.101			
			58941.1		2732.18					.046		1.02	100C


4



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.

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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	REMAR
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	-	

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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
T: T= 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 x 50.6 = 130.9			
L0	1	10.00	3063.30 0.00	1.14	20864.8 33633.3	.44	624.		6.911 .000	11		
L0	2	10.00	27939.4 87022.6	.38	22.40 0.00	11.1	624.	1	.001 .000	23		
L0	3	10.00	14743.0 53935.1	.52	89.10 105.03	6.35	546.	1	.006 .002	33		
L0	4	10.00	15103.6 55527.8	.51	91.20 107.35	6.29	544.	1	Blank .006 .002	44	S.A.	
L0	5	10.00	16545.8 59952.0	.49	1543.10 2557.41	1.60	545.	1	.093 .043	55	.043	
L0	6	10.00	15478.0 56015.2	.51	1569.50 2605.45	1.59	544.		Dmt control .101 .047	66	0.93	
L0	7	10.00	15921.3 58454.7	.50	130.10 170.59	5.34	545.	1	.008 1mM .003	77	.02	98 I
L0	8	10.00	16044.9 58913.1	.50	145.70 196.57	5.07	545.	1	.009 16' .003	88	.02	98 I
L0	9	10.00	14929.8 54113.5	.52	340.10 527.59	3.38	549.	1	.023 -2 .010	99	.18	80 I
L0	10	10.00	15351.1 55587.1	.51	1024.60 1682.45	1.97	547.	1	.067 -3 .030	110	.64	31 I
L0	11	10.00	15655.7 56431.5	.51	1331.40 2198.60	1.73	547.	1	.085 -4 .039	120	.84	9 I
L0	12	10.00	16111.9 57735.5	.50	1542.40 2550.58	1.61	549.	1	.096 -5 .044	131	.95	103C
L0	13	10.00	15710.6 56752.8	.50	1606.60 2666.29	1.57	545.	1	.102 -6 .047	142	1.02	110C
L0	14	10.00	15175.0 55220.6	.51	1491.70 2478.83	1.63	542.	1	-7 .098 .045	153	.98	106C
L0	15	10.00	15977.0 57579.1	.50	1580.20 2618.88	1.59	546.	1	(29299) -8 .099 Compaction .045	164	.98	106C
L0	16	10.00	16098.9 58807.5	.50	135.80 179.70	5.24	547.	1	.008 -2 .003	175	.02	98 I
L0	17	10.00	14956.1 54842.4	.52	159.80 223.76	4.85	545.	1	.011 -3 .004	186	.05	95 I
L0	18	10.00	15643.9 57352.4	.51	383.20 599.35	3.19	544.	1	.024 -4 .010	197	.18	80I
L0	19	10.00	16031.6 58424.5	.50	554.50 886.95	2.66	546.	1	.035 -5 .015	207	.30	68 I
L0	20	10.00	15638.5 56659.5	.51	1368.20 2263.93	1.70	545.	1	.087 -6 .040	218	.86	7 I
L0	21	10.00	16301.4 58292.5	.50	1602.40 2650.00	1.58	550.	1	(24135) -7 .098 .045	229	.98	106C
L0	22	10.00	15996.2 57[illegible].1	.50	1543.10 2[illegible].84	1.60	547.	1	-8 .096 6x2=320 .044	240	.95	103C
L0	23	10.00	16477.1 59531.6	.49	1226.40 2019.18	1.80	547.		.074 .034	251	.73	21 I
L0	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 58614.3	.50	1679.80 2787.82	1.54	546.	1	.104 .048	273	1.05	113C
0	26	10.00	16237.2 59020.8	.50	1487.80 2466.71	1.63	543.		.092 .042	284	.91	2I
10	27	10.00	15786.5 57087.1	.50	1481.70 2454.77	1.64	545.	1	.094 .043	295	.93	101C
10	28	10.00	16477.1 59148.7	.49	1640.10 2715.81	1.56	548.	1	.100 .046	306	1.00	108C
10	29	10.00	16689.9 59692.7	.49	1641.20 2714.32	1.56	550.	1	.098 .045	317	.98	106C
1	30	10.00	15893.5 54349.8	.51	110.10 139.60	5.77	553.	1	10^{-2} .007 .003	327	.02	98I
1	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	15010.4 54035.6	.52	795.50 1294.24	2.23	550.		-4 .053 .024	349	.46	50I
1	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 59060.3	.49	1533.10 2538.81	1.61	546.	1	-4 .094 .043	371	.93	101C
1	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	15208.0 55123.7	.51	174.20 247.13	4.66	550.		.011 10^{-1} .004	404	.05	95I
1	38	10.00	15340.4 55110.1	.51	578.00 925.95	2.61	552.	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
1	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 2473.06	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
0	43	10.00	15425.8 55637.3	.51	1460.60 2418.79	1.65	546.		-6 .096 .044	468	.93	101C
10	44	10.00	15558.8 56231.7	.51	1508.10 2500.05	1.62	545.	1	10^{-2} .097 .044	479	.95	103C
0	45	10.00	16699.3 60849.5	.49	1660.60 2750.91	1.55	547.	1	-3 .099 .045	490	1.00	108C
10	46	10.00	16603.4 59991.7	.49	1597.90 2648.30	1.58	545.	1	-4 .096 .044	501	.95	103C
0	47	10.00	16750.7 60761.5	.49	1622.10 2686.67	1.57	547.	1	-5 .097 .045	511	.98	106C
10	48	10.00	15341.0 55700.3	.51	1471.10 2435.34	1.64	547.	1	-4 .096 .044	522	.95	103C
10	49	10.00	16059.6 58218.2	.50	1577.80 2618.46	1.59	544.	1	-7 .098 .045	533	.98	106C
10	50	10.00	15068.4 54260.6	.51	1213.30 2000.23	1.81	548.	1	-8 .081 .037	544	.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 DPM1/K	%DEV	CPMB/K DPM2/K	%DEV	QIP	FLAGS	SCR	MIN

(30461) 64-942/Na

(29724) 62-526/Na

64-727

(RN 30485 64-948/Na