Wattanasin - recross

A. Yes.

Q. And your expectations weren't disappointed, were they? Your expectations were right on the money, weren't they, doctor?

A. I don't say it's right on the money but it's comparable, yes.

Q. Is there a general formula or thought process that you go through when determining when to submit a patent disclosure? I understand that you submitted this patent disclosure in question, 299/84, because at that point in time, you felt you could complete the rest of the compounds with some expectation of activity.

A. That's right.

MR. KELBER: I have nothing further.

REDIRECT EXAMINATION BY MR. VILA:

Q. Dr. Wattanasin, there seems to be a little uncertainty in your mind with regard to the submission of a publication clearance on the subject matter that became the subject of the patent application that was filed and I believe you testified you are not sure whether you may have submitted a request for publication prior to or

Wattanasin - redirect

after the filing of the patent application. Is that correct?

A. Yes.

Q. Would you be still uncertain whether that request was submitted before or after the "A" rating of the disclosure which took place in January 1988, would you have --

A. I would say definitely after, yes.

Q. After the "A" rating?

A. After, yes.

MR. VILA: I have no further questions.

MS. FURMAN: I would just like to ask the general question whether at any time between the synthesis of 63548 and 63549 --

THE WITNESS: 64548 and 64549.

MS. FURMAN: Correct, whether between that synthesis and the synthesis of 64933 and later compounds, whether in that period, you ever had the intention to abandon your invention?

THE WITNESS: No, as I said before, definitely not.

MR. KELBER: Thanks again, doctor. We appreciate it.

THE WITNESS: Thank you.

Wattanasin - redirect

MR. KELBER: Before we go off the record, different people have different styles. We have been operating under the situation where you identify an exhibit, you object to it. Just in case you operate under a different fashion, we have exhibits F-1 through F-8 and W-1 through 3. We have objected to W-2. Do you have any objections to any of F-1 through 8?

MS. FURMAN: No.

(Time noted is 2:30 p.m.)

Sompong Watt——n.
SOMPONG WATTANASIN 4/20/93.

Subscribed and Sworn to before me
This 20th day of April, 1993

Antoinette Lombardi
A Notary Public

ANTOINETTE LOMBARDI
Notary Public of New Jersey
My Commission Expires April 3, 1994

C E R T I F I C A T E

I, GARY M. TALPINS, a Notary Public and Certified Shorthand Reporter of the State of New Jersey, do hereby certify that prior to the commencement of the examination, SOMPONG WATTANASIN was duly sworn by me to testify the truth, the whole truth and nothing but the truth.

I DO FURTHER CERTIFY that the foregoing is a true and accurate transcript of the testimony as taken stenographically by and before me at the time, place and on the date hereinbefore set forth, to the best of my ability.

I DO FURTHER CERTIFY that I am neither a relative nor employee nor attorney nor agent of any of the parties to this action, and that I am neither a relative nor employee of such attorney or counsel, and that I am not interested directly or indirectly in the interference either as counsel, attorney, agent or otherwise.

Gary M. Talpins, C.S.R.
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WATTANASIN,

vs.

FUJIKAWA, et al.

DEPOSITION OF:
MELVYN M. KASSENOFF

Monday, March 22, 1993
Florham Park, New Jersey

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CERTIFIED TRANSCRIPT FOR Fujikawa

I N D E X

WITNESS	DIRECT	CROSS	REDIR	RECR
MELVYN M. KASSENOFF				
By Mr. Kelber		3		63
By Ms. Furman			51	

E X H I B I T S

FOR IDENT.	DESCRIPTION	PAGE
F-1	Declaration of Mr. Kassenoff	3
F-2	Handwritten document entitled Exhibit N	27
F-3	Handwritten document entitled Exhibit O	29
W-1	Patent Committee meeting minutes	51

(Before Gary M. Talpins, a Certified Shorthand Reporter and Notary Public of the State of New Jersey, held at the offices of Sandoz Corporation, Patent and Trademark Affairs Department, 25 Hanover Road, Florham Park, New Jersey, on Monday, March 22, 1993, commencing at 10:00 a.m.)

- - - - - - - - - - - - - - - - -

M E L V Y N M. K A S S E N O F F, 3 Shelley Terrace, West Orange, New Jersey 07052, Sworn.

MR. KELBER: Good morning. This is the cross examination of the Sandoz declaration witnesses. The first witness we have today is Mr. Kassenoff.

CROSS EXAMINATION BY MR. KELBER:

Q. Mr. Kassenoff, I'm going to hand you or hand the reporter a document that I would like labeled as F-1 and ask you to take a minute and take a look at that.

(Whereupon the document was received and marked F-1 for identification.)

Kassenoff - cross

Q. Do you recognize that document, Mr. Kassenoff?

A. Yes.

Q. And is that your signature at the end of the document on page six?

A. Yes.

Q. Let me turn your attention first to the very bottom of page one. You see the sentence starting "this project resulted in numerous patent disclosures." Do you have any feel in general numbers for how many disclosures of the type of compounds referred to as having utility as HMG-CoA reductase inhibitors?

A. No, I don't.

Q. You used the word "numerous" in your declaration.

A. Certainly over 10, possibly 20. It wouldn't surprise me; possibly even more than that.

Q. Turning to the top of page two of the declaration that is Exhibit F-1, there is a reference to a Mr. Fred Weinfeldt, who apparently shared the responsibility in that particular technology area. With whom did he share it, sir?

A. With me. In other words, initially he

was doing the work on it and then obviously, there were too many disclosures so I took over some of them and then eventually, I had primary responsibility.

Q. By primary responsibility, what would primary responsibility entail?

A. Just probably did more of them than anybody else at a particular time.

Q. If there was somebody else doing an application in that field at that particular time, let's pin it down, in the 1987-'88 framework, would you have responsibility for monitoring that other person?

A. Informally but not formally. In other words, I was not reviewing it but if somebody had a question on it, they would obviously come in to me.

Q. Are you familiar with the rating system that was used by the Sandoz Patent --

A. More or less.

Q. I know you know the answers to most of the questions I'm going to ask you but let me finish them for the reporter. I'm pretty clear when I finished the question.

Are you familiar with the rating system

Kassenoff - cross

that was used by the Sandoz Patent Committee during 1987 through '88?

A. Right.

Q. And by "right," you mean --

A. Yes.

Q. What did it mean if a disclosure received a "B" rating?

A. "B" I think is three months, it would come up again in three months.

Q. What criteria would be brought to bear to determine what rating a disclosure would get?

A. Probably ongoing work, it means it wasn't ripe for filing. More detailed than that, I'm not sure.

Q. It wasn't ripe for filing but --

A. It may have been ongoing work, for example.

Q. Would there be any other reasons that a disclosure would receive a "B" rating?

A. Sometimes it was the people there didn't feel qualified but usually that would be -- we would put it off a month if there was nobody there who felt comfortable in making a decision but usually, a "B" rating means it's ongoing work,

that's the principal reason.

Q. It's ongoing work. In other words, a disclosure would not be rated for more immediate action if the work was ongoing?

A. Well, unless, of course, you had something that was so hot that you had to file on it immediately.

Q. What would --

A. In other words, there are flexible standards involved. It's not an absolute.

Q. By assigning a "B" rating to a disclosure --

A. That means that the thing is of interest but it's not ready for filing yet because of, for example, ongoing work.

Q. Are there any other reasons for assigning it a "B" rating other than ongoing work?

A. I don't recall offhand. I'm not sure. There could be.

Q. You are currently Director of Patent and Trademark Affairs for Sandoz. Is that correct?

A. That's correct.

Q. Is there a Sandoz Patent Committee today?

Kassenoff - cross

A. Yes.

Q. Does it use the same rating system?

A. Yes, it does.

Q. As Director of Patent and Trademark Affairs, I would imagine one of your responsibilities --

A. Yes, I do attend the meetings and have attended on a regular basis for the last year.

Q. In your experience, have disclosures been rated "B" for any other reason than ongoing work?

A. I don't recall of any right now.

Q. You have been with Sandoz since 1972. Is that correct?

A. That's correct.

Q. Let's try and narrow it down. How about in the HMG-CoA reductase inhibitor field, do you recall during your tenure at Sandoz any other disclosure besides the one of interest, 299/84, in that field ever having been rated as "B"?

A. I don't recall. Frankly, I didn't attend the meetings on a regular basis. In fact, probably until the beginning of last year, over the previous 20 years, I probably attended the meeting

Kassenoff - cross

maybe twice and obviously, we have not had any ratings in that field, at least I don't think we have in the last year or so.

Q. If you didn't attend a meeting and a disclosure was rated "B", would you be informed of that fact?

A. Yes. The minutes are published.

Q. Have you reviewed the minutes of the Patent Committee --

A. I look at the minutes. I have got to see if anything is in my area, which I have to file on.

Q. In the period January 1, 1987, to December 31, 1988, did you see any other application --

A. I would not recall.

Q. Please let me finish the question, Mr. Kassenoff.

Do you recall seeing the disclosure 299/84 rated as "B" at any time?

A. I'm sure I saw it.

Q. But you don't recall seeing it now?

A. No.

Q. Are you sure that you might have seen

Kassenoff - cross

any other disclosure in your field rated "B"?

A. I'm sure I would have seen it there but on the other hand, I certainly wouldn't remember it because I would have no reason for remembering it because it didn't require any action.

Q. It didn't require any action. It didn't require any action on your part?

A. On my part.

Q. During the period 1987 through 1988, are you aware did Sandoz employ patent attorneys not employed by Sandoz Corporation directly as full-time employees for the preparation of patent applications?

A. Are you talking about outside?

Q. Outside counsel.

A. Not to write patent applications except possibly once in awhile, we may have an oddball case. Obviously, I wouldn't know about it. In other words, in the pharmaceutical area, I can tell you the answer is no except maybe possibly if there were a very complex interference or something like that but not for normal, we do not hire outside counsel for normal work.

Q. By normal, you would include drafting

Kassenoff - cross

applications?

A. Prosecution and application writing.

Q. Even if there is a crunch in the staff at Sandoz and it is not immediately up to it?

A. No, we don't do that unless -- the only exception being, for example, two years ago, we had -- it was not in the pharmaceutical area but we had a possible sale where we had to rush something, a filing on something which we were about to sell. In the U.S., we didn't have the problem but abroad, we would have had a filing if we didn't get it on filing immediately.

Q. And in that instance, you sent it to outside counsel?

A. Yes. This was not a pharmaceutical case because then you wouldn't have that kind of a problem.

Q. Is there a formal policy that you are aware of that would distinguish between pharmaceutical cases and --

A. There is no formal policy.

Q. How did you find out about the "A" rating that's referred to in paragraph four of the document that's --

Kassenoff - cross

A. The minutes are distributed anywhere from a few days to a week or two after the meeting.

Q. Are the minutes distributed to everybody in the department?

A. Everybody in the department receives the minutes.

Q. Again, I'm going to ask you to let me finish my sentence. I know you are ahead of me on this but you have got to give me a chance to catch up.

How was it determined who was responsible for a particular application that gets an "A" rating?

A. Usually one of the supervisors will decide and it usually will be decided before the meeting and usually it will be people have defined areas, although sometimes, as you can see here, people may share the same area. Obviously, if it's in somebody's area, it will go to that person. If it's in an area that's shared, usually the supervisor will decide who will get it. But things are not done on a formal basis and sometimes things are transferred afterwards.

Q. Was such a decision as to who would be

Kassenoff - cross

responsible for the disclosure that received an "A" rating referred to in paragraph four made?

A. Jody Giesser's initials were on the agenda as well as the minutes for that disclosure.

Q. Does that mean she had responsibility for the preparation of it?

A. That would mean generally she would have responsibility unless, of course, she transferred it to somebody else but at least initially, it was in her bailiwick.

Q. Let me direct you to the last sentence or actually the last phrase in paragraph four, where it indicates a backlog in unfiled HMG-CoA reductase disclosures have been developing. Do you have any idea of how large that backlog was?

A. No, I can't -- I have no idea.

Q. How do you know there was a backlog?

A. Because I can recall that there was some pressure involved in the area and that there were a number of disclosures that were floating around but I do not recall the number.

Q. Aren't there a number of disclosures floating around, weren't there a number of disclosures floating around throughout the 1981

Kassenoff - cross

through 1990 time period in that field?

A. At least through the beginning of that time period, probably not at the end of it.

Q. Probably not at the end of it. Let me direct your attention to paragraph five. Do you see the listing of cases that appears in that paragraph?

A. Correct.

Q. Many of those applications have a filing date of 1988 through 1990. Is that correct?

A. A number of them, correct.

Q. In fact, more than half. Isn't that correct?

A. Right, but most of those, if you notice, are CIP's or continuations and the like and would not be the result of new disclosures.

Q. Let's talk about that. The CIP application would not be the result of a new disclosure?

A. That's correct.

Q. How would a CIP application come to be docketed for filing?

A. It's not docketed, it's up to the attorney involved simply to file it without it

being docketed and usually the need for it will become apparent from discussions between the attorney involved and the inventor and/or others in Research and similarly, divisionals would simply come about, those would be decided on by the Patent Committee at the time an issue fee was paid for the earlier case in the series.

Q. Would you help me out. Could you take a look at the list of applications or list of cases, I'm sorry, that are recited there and tell me how many would have come from new disclosures.

A. If it does not have any letter or anything else after the number, that would be a new disclosure.

Q. Could you identify how many of those there are?

A. Starting from which one?

Q. All of the ones in this five, how many came from new disclosures?

A. 6951, 7013, 7015, 7022, 7025, 7028, 7035, 7041, 7050, 7064, 7087, 7101, 7104. There is also I see here 6955 but where is the original on that? There are a number of cases here that probably should be down there for completion but

Kassenoff - cross

are not here. For example, the 6955, what is down here is obviously a later application in the series.

Q. I'm sorry, 6955?

A. 55.

Q. Could you direct me to --

A. March 10th of '88. And there are also a number of other applications in the series which I can see are not down here.

Q. The ones that are down here, you identified 13 that resulted from new disclosures. Is that correct?

A. Correct. You counted them.

Q. That was my count but I'm asking you to confirm that for me.

A. That seems right.

Q. Of those 13 cases, do you have any feel for how many were part of the backlog that is referred to in paragraph four?

A. It was probably 7064 because I wrote that one, 7087, 7101, 7104 and of course, some of the CIP's involved, as well, although those weren't new disclosures but that's part of the backlog of work in this project.

Kassenoff - cross

Q. You indicated after you said 7064 that that would have been part of the backlog because you wrote it.

A. That's why I'm familiar with it.

Q. But you had shared responsibility for that field even before Mr. Weinfeldt's departure. Is that correct?

A. That's correct. I wrote some of the other cases in the series.

Q. Do you know for a fact that 7064 was part of the backlog?

A. Just from the time frame, I do.

Q. That application was filed January 27, 1988. Is that correct?

A. That's what it says here.

Q. But is it correct? You wrote it. Do you know?

A. I don't remember when I filed it. I have to assume that this is correct.

Q. Did you review any documents during the preparation and signing of this declaration?

A. Did I?

Q. Yes.

A. No. I relied on my memory.

Kassenoff - cross

Q. You don't have a memory of the statement that appears here now?

A. Not particularly, not in particular, no.

Q. Did you have a memory at the time you signed it?

A. No. It was to the best of my recollection, it was correct.

Q. And what is that recollection based on, sir?

A. What I remember.

Q. But you don't have a memory of doing it, do you?

A. I have a memory of writing that application and I know it was in that time frame but to say that it was definitely January 27th of '88, I don't know. But that seems right.

Q. Do you know as a matter of personal knowledge that 7064 was part of the backlog referred to in paragraph four?

A. Yes.

Q. 7064 appears to have been filed sometime about January of 1988, according to your recollection.

Kassenoff - cross

A. That's correct.

Q. Do you have any idea when you began preparation of the application at maturity of that filing?

A. No, I do not.

Q. Would it have begun prior to April 1987?

A. Probably not but I really -- without going into the file and looking at whatever notes I have, I can't answer that.

Q. Probably not. Do you have any feel for why you said probably not?

A. Because the time period would have been eight or nine months and I would not have been working on an application that long.

Q. That would be a longer time period than usual for you?

A. For me, yes.

Q. Let's look at 7087. Was that part of the backlog referred to?

A. Yes, it was.

Q. Did you work on that case?

A. Yes, I did.

Q. Do you know how long it had been

Kassenoff - cross

pending before you took over the preparation of that case?

A. No, I do not.

Q. You referred to a backlog in paragraph four and the backlog refers to unfiled disclosures had been accumulating. Is that correct?

A. That's correct.

Q. Were these disclosures that had been rated "A" for filing by the Patent Committee?

A. Yes, otherwise they wouldn't be part of the backlog.

Q. Can you give me an idea of the time delay between the "A" rating received and the delay until action on the disclosure so rated, give me an idea of that time delay involved in the backlog referred to?

A. I really cannot.

Q. What do you mean by "backlog"?

A. It means there were several disclosures which have been pending for more than a month or even probably more than two months.

Q. So your recollection suggests that the backlog was at least two months?

A. More than that, according to my

Kassenoff - cross

recollection, but I can't be more specific than that.

Q. I'm a little confused. Mr. Weinfeldt left in approximately April of 1987. Is that correct?

A. That sounds right.

Q. The backlog by January of 1988 had developed to as much as two months or more. Is that correct?

A. It was more than that, probably.

Q. Three months?

A. I'm sure that there were cases that -- in fact, I'm willing to bet that there were cases that were outstanding for longer than that which had not been filed on.

Q. You are willing to bet, is that bet based on your personal knowledge?

A. It's based on my knowledge of how things operate and how things operated in that period as well as currently.

Q. Do you have a specific recollection of a case or cases in that field, the reductase disclosures referred to, that had been pending for more than two months?

Kassenoff - cross

A. I am sure that 7064 was pending for more than two months because of the scope of the application. It was no way that that thing was filed within two months of its being rated "A"; also 7087, which is another case that I wrote, there was no way that that was filed within two months.

Q. We may be talking apples and oranges here. By backlog, I assume you refer to cases that had not been picked up for action. Is that correct?

A. By backlog, I mean cases that had been rated "A" and had not been filed on as yet.

Q. So if an attorney had a particularly difficult case, even though that was the only case the attorney was acting on, under this definition, that would be part of the backlog. Is that correct?

A. That's correct. That is the sense in which I have used the term.

Q. Were there any cases that had been rated "A" but had not received review or attention from an attorney for two months in that backlog?

A. I can't answer that. I can't answer --

Kassenoff - cross

Q. How about for cases assigned to you?

A. Again, I have to assume from the way I operate that within a few weeks of the "A" rating, I would have contacted the inventor and had the inventor or inventors at least start to send me the material required for the application. I would have contacted Biology to get their input and possibly, if relevant, Process Development to get any new processes which I would need for the best mode requirement on it.

Q. In fact, you contacted Dr. Wattanasin, is that the correct pronunciation?

A. Correct.

Q. You contacted Dr. Wattanasin as early as February 1988 regarding this disclosure. Is that correct?

A. That's what the notes in the file show.

Q. Is that customary for what is referred to as the backlog?

A. Yes. That's not saying that in every case, I would do it within a couple of weeks but in that case, I did do it.

Q. You identified earlier four cases that fell into that backlog, cases which had been

Kassenoff - cross

designated "A" but not yet filed. Is that correct?

A. That's correct.

Q. Do you recall, did you have personal responsibility for any other cases that might have been in that backlog?

A. No, I did not have any personal responsibility for any other cases.

Q. Besides --

A. In the new filings because filing new applications was only a very small part of my workload.

Q. Besides Ms. Giesser, was there anybody else at Sandoz with responsibility for the preparation of new applications and filing in this field?

A. In the HMG-CoA reductase application?

Q. That's correct.

A. Not to my recollection because I don't think -- Diane picked it up but I think it was after Jody had left.

Q. So for the period 1987 through 1988, after Mr. Weinfeldt's departure --

A. As far as my recollection, as far as I recall, that's correct.

Kassenoff - cross

Q. Do you have any knowledge or understanding of how many backlogged cases, as the term is used here, that Ms. Giesser might have had in this field?

A. No, I do not.

Q. You indicated that you knew from your own personal work that an eight to nine month delay between the receipt of an "A" rating on a disclosure and the filing would have been extraordinary, at least for yourself. Is that correct?

A. Yes. I don't think that I have any cases that were pending that long.

Q. Do you have any feeling for how quickly Miss Giesser would --

A. No, I do not.

Q. But you worked with Miss Giesser in this particular case, 299/84. Isn't that correct?

A. I did some of the spadework initially but that's as far as it goes.

Q. Why did you do the initial spadework if you had your own backlog of cases, sir?

A. Probably because I was ordering, it may have been that I was ordering things from Biology

for two different cases, it may have been she was so backlogged that I said okay, Jody, I will contact the people involved and start the ball rolling on it for you.

Q. But you don't know if she was backlogged or not?

A. I don't know her workload, if that's your question.

Q. You said she might have been backlogged. Do you have any knowledge that she was?

A. In this particular field?

Q. In this particular situation.

A. No, I really don't, bearing in mind, of course, that each of us has several distinct fields of responsibility.

Q. Let me refer you over for a minute to paragraph six. That spans pages three through four of the declaration that is F-1.

A. Right.

Q. You were in communication with Dr. Wattanasin?

A. That's correct.

Q. Was there communication other than written communication?

Kassenoff - cross

A. As far as this case, I cannot be certain but from the way I operate, that is likely.

Q. But you don't have any knowledge --

A. I don't keep records of my phone calls but I do know that I frequently request for information by telephone.

Q. But you don't have any knowledge of such request, personal knowledge of such a request?

A. No. There is no way I could remember that.

Q. Fair enough. Turning you to maybe two-thirds of the way down on page four, the very last paragraph of paragraph six, these notes indicated that you spoke to Dr. Wattanasin. I have Exhibit N which is referred to and I would like the reporter to mark that as F-2. Once he has done that, if you would take a brief look at that.

(Whereupon the document was received and marked F-2 for identification.)

A. Okay.

Q. Now if you look at the very last line of Exhibit N, is that line in your handwriting?

A. Yes, it is.

Q. And that does indicate "spoke with S.W."?

Kassenoff - cross

A. That's correct.

Q. And is there any other indication in Exhibit N that you spoke with Sompong Wattanasin?

A. No, that's the only indication, I have a date there and it says I spoke with him.

Q. Do you see the very last five words on that line?

A. Yes, I do.

Q. What do those say?

A. "Requested info will be sent."

Q. To what does the information on page b, 392b of Exhibit N, refer to?

A. 392b?

Q. If you look at the very top.

A. That's one of the synthetic routes to the compound, to the quinoline compounds.

Q. Was that the subject matter of your discussion?

A. It might have been but my discussion primarily, at least primarily relates to the material listed at the top of 392a.

Q. Was that the type of information requested, sir?

A. Yes, it was.

Kassenoff - cross

Q. And do you have any recollection of whether that information referred to at the very bottom of the first page of Exhibit N was ever sent?

A. I'm sure it was because I can recall -- let me put it this way: I have seen from the file that some of the material, the lab notebook pages were sent.

MR. KELBER: Let me ask the reporter to identify Exhibit O, this document, as F-3. It bears the legend at the top Exhibit O.

Q. And after the reporter has so identified it, if you would review it for a minute, sir.

(Whereupon the document was received and marked F-3 for identification.)

A. Okay.

Q. Mr. Kassenoff, is the material of Exhibit F-3 responsive to the information that is indicated was requested on Exhibit F-2?

A. Only partially.

Q. In your opinion, Mr. Kassenoff, was the information requested in Exhibit F-2 necessary for the preparation of a full patent application?

Kassenoff - cross

A. Yes, it was.

Q. Am I correct, then, in understanding that additional information that had been requested would have been necessary to prepare the application?

A. That is correct.

Q. And that information would have come from Dr. Wattanasin or somebody working with him. Is that correct?

A. That's correct.

Q. Did you take any further steps to secure that information that was not provided in the --

A. Either Jody did or I did.

Q. Do you have personal recollection of receiving the additional information necessary?

A. No, I do not. The only thing I do know is that in reviewing the file, but of course, this was recently, I did note that there were lab notebook pages in there which were received at a subsequent -- which I think were received at a subsequent time.

Q. This review was made subsequent to the preparation and signing of this declaration?

Kassenoff - cross

A. Or concurrently.

Q. You don't recall which?

A. Or both.

Q. Which was it? You executed this declaration on February 19.

A. Right. I did have to look through the file to see these handwritten notes and identify them. Obviously, when I'm looking through the file, I did see other papers there.

Q. But you did not identify those in this declaration? I'm sorry, you did not identify the papers incorporating the additional information that was requested in Exhibit F-2 in this declaration?

A. It doesn't appear there.

Q. Referring you to paragraph eight, Mr. Kassenoff, of Exhibit F-1, as of May 23, 1988, do you have any recollection as to whether you believed you had responsibility for case number 299/84?

A. No, I do not.

Q. Does the fact that you received data from the Sandoz Biology Department with respect to that indicate anything at all to you about who had

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responsibility for that case?

A. No, it does not. The only thing it does reveal is that there was a possibility that I would handle it. However, the case was assigned to Jody Giesser.

Q. Would Biology have known that the case was assigned to Jody Giesser?

A. No, absolutely not.

Q. Were you the only person to receive data from the Biology Department in this field?

A. No, whoever requested it would receive it.

Q. Did you request it?

A. Yes, I did. That's why it was sent to me.

Q. Why did you request it if the case had been assigned to Jody Giesser?

A. Possibly because either Jody was so tied up that I volunteered to do the legwork; possibly because I was asking, also asking for information on other cases; possibly because I might have taken over the case if I had the free time before she did.

Q. Do you have any recollection of which

of those possibilities it was?

A. No, I do not.

Q. Would a review of the case help refresh your recollection?

A. No. I did go through the case to see if I had any handwritten notes in there, which might help me.

Q. And were there any handwritten notes?

A. No, the only handwritten notes are what you see in front of you.

Q. Is it your custom, sir, to request biological data from the Sandoz Biology Department on cases for which you have no responsibility?

A. Only if there was a possibility that I might pick up the case or if they were tied to cases for which I did have responsibility.

Q. Do you have any feel, any recollection as to when you might have requested the data that is referred to in paragraph eight?

A. No, I do not. The only thing I can say, it was probably at least a week before May 23, 1988. It could have been, however, two months before that.

Q. Would it be customary to have a two

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month delay between a request for biological data and receipt of the same?

A. Usually not but if the person in Biology were tied up, it could be something he forgot about and then I would have to call back and say hey, what about the stuff that I requested.

Q. Do you know who the person in Biology was at this time period?

A. Yes, I would have spoken with Robert Engstrom.

Q. Do you recall what you did with the biological data report for kit PD 299/84?

A. I'm sure I just put it into the notes that I had, the material that I was collecting for this case.

Q. Did you advise Ms. Giesser of the receipt of that data?

A. I have no recollection but it's possible.

Q. But --

A. Because I'm sure that I would have given her everything that I have on the case.

Q. Why would you have done that?

A. Because there would be no -- if she had

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responsibility for the case, there certainly would be no sense in each of us having our own file. That would only lead to confusion. So I'm sure that anything I got relating to it, since she had primary responsibility, I would have given to her.

Q. So she had primary responsibility at this period in time?

A. For this particular case because it was assigned to her in the Patent Committee notes.

Q. In your review of the file -- I'm sorry, let me back up. Is it correct, then, that it would have been the practice at the time to have but a single file for the collection of materials for the preparation of the application for PD 299/84?

A. I would hope that would have been the case but I can't guarantee it.

Q. Do you have any familiarity with the procedure of the Sandoz Patent Department in general at that time?

A. There is no general procedure. Each one of us works as our own department.

Q. If each one of you works as your own department, how do you decide who has got primary

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responsibility for the case?

A. That's the Patent Committee's job, to assign the cases, or the supervisor, who will assign it before the Patent Committee meeting.

Q. Do you have any knowledge that Ms. Giesser had a file separate from the file that you reviewed?

A. No, I do not.

Q. In your review of the file that you referred to earlier, did you come across any communications from Ms. Giesser to anyone else at Sandoz regarding the PD 299/84 prior to May 23, 1988?

A. I don't recall, frankly.

MR. KELBER: Is the file available?

MS. FURMAN: Which one?

MR. KELBER: The file that Mr. Kassenoff is referring to.

THE WITNESS: The case file.

MS. FURMAN: Sure.

MR. KELBER: Can we get the case file with reasonable speed and have Mr. Kassenoff review it? I appreciate it. While we are getting that, we can ask some more questions.

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THE WITNESS: Let me just add something on that. Each of us had different methods of operating. What I would do is when I prepared an application, when it got filed, all of my notes relating to that case I would tuck into the file. I have no guarantee that anybody else did that. Some people had supplementary files, some of which were retained, some of which were disposed of; others did not.

Q. Mr. Kassenoff, take a minute to review that file.

A. Sure. Would you please rephrase your question so I know what I'm looking for.

Q. At this point, I'm asking you -- okay. Please review the file specifically with an eye towards determining if there are any written communications reflected there from Ms. Giesser to anybody else in Sandoz prior to May 23, 1988.

A. I don't even see my notes in there. There is nothing in the file here prior to that date, including my notes. I don't know where the originals --

MS. FURMAN: Your notes were not originally in the file.

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THE WITNESS: Where were they?

MS. FURMAN: A bunch of papers were separate from the file that Jody gave me.

THE WITNESS: I think it's clear that there was a supplemental file there of some other notes.

MR. KELBER: Let's go off the record for a minute.

(Whereupon a discussion took place off the record.)

Q. Just to preface the agreement, Mr. Kassenoff, is it correct that your review of the file does not indicate any written communication from Ms. Giesser in the file prior to May 23, 1988?

A. That's correct, nor does it reflect anything from me prior to that date.

MR. KELBER: Diane, we would appreciate it if you would search for any supplemental papers relevant to PD 299/84 and if there is anything in the file prepared by Ms. Giesser for communications to others at Sandoz prior to May 23, 1988, if you would forward us a copy. Is that agreeable to you?

MS. FURMAN: Yes, it is.

Q. To the best of your recollection, Mr.

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Kassenoff, did Ms. Giesser take any action with respect to PD 299/84 prior to May 23, 1988?

A. I have no recollection one way or the other.

Q. Let me direct your attention to paragraph nine of the declaration. You see the phrase "which was indicated for filing ahead of PD 299/84," the very first sentence of paragraph nine, middle of the page?

A. That's correct, yes.

Q. What does it mean to be indicated for filing ahead of?

A. It has no formal meaning, it just simply means that since this was, 7022/C was a CIP application, that I had decided to file it prior to filing, prior to picking up 7101.

Q. So you would work on 7022/C prior to picking up 299/84 if, in fact, you picked up 299 at all?

A. That's correct. I did not do anything as far as writing, that's clear.

Q. I'm trying to get a feeling for what you meant by "picking up" because obviously, you were involved with the file prior to that time.

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A. I was involved with gathering information, that's correct.

Q. You mean picking up for preparation of the application?

A. For preparation, that's correct.

Q. What was the basis of the determination to file 7022 prior to preparing 299 for preparation?

A. I don't recall other than the fact that it was a CIP application so I probably wanted to get that off my desk.

Q. Why?

A. I don't recall. I don't think there was any question of a statutory bar or anything like that. It was probably because I probably had an office action to respond to in the parent application or the parent application was about to issue and I had to get this CIP on file in lieu of a divisional. I don't recall that specifically but I think that's a valid assumption.

Q. Do you recall having prepared any other cases in this field between January 1987 and December 31, 1988?

A. It was clearly 7087; 7041/CIP/CIP was

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not a case I originally handled but I did prepare the most recent CIP in the case; 6955/XN/B/CONT/X was mine but that probably -- I'm not sure how much work I did on it in your time period; the one you just mentioned, 7022/C. Just referring to this list, those are the only ones on the list in that time period which I had prepared myself.

Q. Do you have personal recollection of preparing any other applications in this particular field, the HMG-CoA reductase field, in that time period?

A. In that time period, no.

Q. Let's look at 6955, the suffixes after it. What does the "CONT" designation mean?

A. Continuation.

Q. Would that have been a strict continuation application?

A. Yes.

Q. So no new preparation would have been involved. Is that correct?

A. That's correct.

Q. And 7041 was a CIP of a CIP. Is that correct?

A. That's correct.

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Q. Do you have any recollection of how much additional work was required?

A. That was quite a bit.

Q. By quite a bit, can you give me an idea of how many months it took to prepare the additional information?

A. It probably was about two, three days -- two days work but I don't know over what period of time. It was spread out because there was a significant amount of additional information, totally redrafting of the claims and a significant rewriting of the specification. It was probably more. If I said two days, that's probably incorrect, it probably took me a good three, four days of work on it, now that I'm thinking back on it.

Q. You mentioned 7087.

A. Correct.

Q. That was a new application. Is that correct?

A. That's correct.

Q. Do you have any recollection as to why you would have prepared and filed 7087 prior to 299/84?

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A. I'm not sure of when it was rated but I do know that it related to our potential commercial product, which is now being reviewed by the FDA. It was a process case and it had features that would have related to a commercial process. However, which case was rated "A" first, that I do not recall.

Q. Would the case to be rated first ordinarily receive attention first?

A. Unless there were a reason otherwise.

Q. Do you recall any reasons otherwise with respect to 299/84?

A. The only thing that I do recall is 7087 was a process case and it related to an advanced, at that time advanced research compound and also 7087 was initially assigned to me, whereas 7101 was not assigned to me. So under the totality of the facts, it was clear which one that I was working on first.

Q. In the absence of any reasons for proceeding differently, such as the commercial aspect of 7087, would a case that was rated "A" first get worked on first and then the case that was rated "A" after that get worked on second?

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A. If it were assigned to the same person?

Q. The same person, yes.

A. Probably but I wouldn't say that was always the case.

Q. Is there any standard for proceeding?

A. No.

Q. So --

A. Theoretically, at least, the case that was rated "A" first should be acted on first by the person to whom it's assigned but I would not guarantee that that was followed by everybody at all times.

Q. Was it followed by you?

A. I don't think I can say yes. I think I probably exercised some selection there.

Q. For instance, if a CIP was pending and you were running out of time in response to the parent case --

A. I would pick that up first. That I have no doubt about.

Q. Earlier, we discussed the new applications that had been filed in this time frame, in the 1987-'88 time frame. If the cases

were not prepared and filed by you, after April 1987 through December 31, 1988, is it a necessary conclusion that they would have had to have been prepared and filed by Miss Giesser?

A. After Mr. Weinfeldt left, yes, because I don't recall anybody else working in that area.

Q. I realize you have no personal knowledge but do you have any recollection as to how many more cases in this field, new cases in this field might have been filed than are represented here between April 1987 and December 31, 1988?

A. If there were any, and I'm not sure that there were any, it would have been probably very few.

Q. Did you assist in preparing this list that appears in paragraph five?

A. No, Diane prepared it on her own and I just went through it to make sure that everything there did -- everything listed was a case that was an HMG-CoA reductase case. I did not double-check the dates on them.

Q. Let me direct your attention to paragraph 11 of the declaration, penultimate

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paragraph of that form.

A. Okay.

Q. Is it possible for a disclosure never to receive an "A" rating?

A. Of course.

Q. And if that disclosure never receives an "A" rating -- I'm sorry, let me flip it around. Is it a requirement that a disclosure receive an "A" rating before it is prepared as an application for filing within Sandoz?

A. Generally, yes, but there are exceptions. Sometimes an application will be worked on before it actually is formally rated "A".

Q. Did you do any work on PD 299/84, to the best of your recollection, before it was rated "A"?

A. No, I did not. The only work done of which I have any recollection is that reflected by the notes in the file.

Q. Is it a correct statement, Mr. Kassenoff, that if Sandoz intends to file a United States patent application on the basis of a patent disclosure, it first or it simultaneously with that decision rates that disclosure "A"?

A. In the pharmaceutical area, yes.

Q. Mr. Kassenoff, when did you first become aware, if you recall, when did you first become aware that third parties other than Sandoz had filed for U.S. patent protection on compounds related to those of PD 299/84?

A. I assume it was after Warner-Lambert's patent issue sometime when somebody brought it to my attention or when I noticed it in the OG.

Q. Do you have any recollection as to whether that was before or after November 1987?

A. November --

Q. I'm sorry, November 1988? I apologize.

A. I don't know because if I recall correctly, Warner-Lambert's issue was in June or July or August?

Q. Your recollection is correct, I think it issued in June.

A. If it issued in June, it could have been brought to my attention anywhere from shortly after it issued to several months later. I really do not recall. If it was a question of my noticing it in the OG, I can tell you I did not notice it

immediately because as Bob will testify, I have a whole stack of OG's sitting around that I have not gone through. If somebody brought it to my attention, it could have been any time.

Q. Just for the record, when you refer to Bob, you are referring to --

A. Bob Honor.

Q. Do you have any recollection of whether you knew, prior to the time that PD 299/84 was filed in March of 1989, whether you knew that a third party had filed for patent protection?

A. Yes, I think I can recall, yes, I did know that.

Q. Have you been involved on behalf of Sandoz in the drafting of an application where you were aware that a third party had filed for patent protection on related subject matter?

A. It depends how you define "related."

Q. Related in the sense that the claims -- I'm sorry, forget claims, the subject matter disclosed in that third party's request for protection were obvious in the sense of 35 U.S.C. 103 with respect to the application you were preparing.

A. Not that I can recall.

Q. Besides PD 299/84, are you aware of any other situations similar to that within Sandoz?

A. Nothing comes to mind.

Q. As Director of Patent and Trademark Affairs at Sandoz, you attend the Patent Committee meetings as regularly as possible. Is that correct?

A. Yes. That's only since, though, January of last year.

Q. Is it a correct statement to say that you generally have input on how to rate a patent disclosure viewed by the Patent Committee?

A. I open my mouth when warranted.

Q. Fair enough. If you were aware that a third party had filed for U.S. patent protection on subject matter addressed in a disclosure before the Sandoz Patent Committee, would that influence in any way your judgment as to how to rate that disclosure?

A. It probably would.

Q. Give me one second. I'm sorry, one question I meant to ask. What other fields of technology did you have responsibility for besides

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the HMG-CoA reductase field in the period January 1987 through December 1988?

A. 90 percent of my workload at that time consisted of prosecution of dyestuff cases originating in Basle, Switzerland. If you look at my docket, almost all the cases on it would be dyestuff cases.

Q. Prior to Mr. Weinfeldt's retirement or I'm sorry, not retirement but departure from Sandoz, did you have any responsibility in the HMG-CoA reductase field?

A. Yes, I handled some disclosures as early as late 1982.

Q. Prior to Mr. Weinfeldt's departure, did anybody else in the Sandoz Patent Department handle the preparation of applications in the HMG field?

A. Other than me and Fred, no, to my best recollection.

MR. KELBER: Thank you, Mr. Kassenoff. Diane, your witness.

MS. FURMAN: Do you mind if we take a break before cross?

MR. KELBER: Sure.

(Whereupon a recess was taken.)

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MS. FURMAN: I would like to offer into evidence copies of Patent Committee minutes which have been masked as to their proprietary information but left unmasked with respect to information concerning patent disclosure 299/84.

MR. KELBER: Are these the records that are already of record in another declaration?

MS. FURMAN: These comprise exhibits M-1 through M-5 of the testimony already of record.

MR. KELBER: So that would be Rothwell. Go ahead and identify them.

MS. FURMAN: And that would be exhibit, the totality of that would be Exhibit F-4.

MR. KELBER: Can we make a distinction? These are going to be your exhibits to submit and maybe we ought to make it W-1.

MS. FURMAN: Fine.

(Whereupon the document was received and marked W-1 for identification.)

REDIRECT EXAMINATION BY MS. FURMAN:

Q. Mr. Kassenoff, do you recognize the copy of the minutes dated April 29, 1987?

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A. Yes.

Q. And what information is on the minutes concerning patent disclosure 299/84?

A. That it was rated "B" in April of 1987 and that it was originally assigned to Fred Weinfeldt.

Q. Now I call your attention to the minutes of July 29, 1987. Do you recognize information relating to patent disclosure 299/84?

A. Yes, that it was rated "B" and again, assigned to Fred Weinfeldt.

MR. VILA: Pardon me, is there an exhibit number on that?

MS. FURMAN: Yes, there is.

MR. KELBER: These are all part of W-1.

Q. Look now at the minutes of the October 28, 1987, Patent Committee meeting. What does it say about patent disclosure 299/84?

A. That it was rated "X" and assigned to Fred Weinfeldt.

Q. Again, the Patent Committee minutes of November 25, 1987, what is the rating thereon?

A. It was again rated "X" and is still assigned to Fred Weinfeldt.

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Q. Finally, I ask you to look at the minutes for the January 27, 1988, PCM. And what is the rating of PD 299/84?

A. It was rated "A" and assigned to Jody Giesser.

Q. To the best of your knowledge, what does a rating of "B" signify?

A. "B" signifies that it will be considered in three months.

Q. What would prompt a rating of "B", would it be not enough information is available to file a patent application or would it be that more information is intended to be developed for the patent?

MR. KELBER: Objection, leading. The question is okay but you can't feed him the answer.

MR. VILA: Cut the question off at the first part.

Q. What is the meaning of the rating of "B"?

A. Generally, it would mean that additional work is being performed on the case.

Q. And what about the rating of "X"?

A. "X" means that it will come up in one

month, it can mean one of two things, either one, that the people necessary or the people whose input is required before the disclosure is rated "A" are not at the meeting or that additional work is still ongoing and the results are expected within one month, such that it is anticipated that a decision will be made at the next Patent Committee meeting.

Q. At the time patent disclosure 299/84 was rated, was it within your responsibility to rate patent disclosures?

A. No, it was not.

Q. Once a patent disclosure has been rated by the Patent Committee, can you rerate that disclosure yourself?

A. I can bring it back to the Patent Committee if the need arises.

Q. Is it within your jurisdiction not to file on a patent disclosure that has been rated "A" by the Patent Committee?

A. No, it is not.

Q. Did you at any time intend after the rating of "A" of the patent disclosure not to file a patent application on it either yourself or by someone else in the department?

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MR. KELBER: Objection. You are asking him for knowledge as to other people's intentions.

Q. By yourself alone?

A. No.

Q. Is there any way to inactivate or retire a patent disclosure once it has been rated "A" by the Patent Committee?

A. The attorney in charge can bring it back to the Patent Committee and request a rerating of it for whatever reasons are deemed relevant.

Q. Absent that, is the patent disclosure considered active until --

A. Yes.

Q. -- the action is taken?

A. It's considered active until the application is filed.

Q. Mr. Kassenoff, I call your attention to your declaration previously made of record as Exhibit F-1 to the list of patent applications filed which is indicated on pages two and three. Do you know or is it within your reasonable belief that all of these applications have now been published in one way or another?

A. As far as I'm aware, every one has been

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published either in the U.S. or abroad.

Q. Is there a possibility that there may be some applications not on this list in the HMG-CoA area which have not published?

A. There is a possibility but I cannot recall of any specific ones. Actually, there is one that I think I can recall that's not on this list. Whether it was published or not, I don't know. I vaguely recall a case 7044.

Q. Other than that possibility of case 7044, this would constitute the entirety of the HMG-CoA filings?

A. That is not correct. There are a number of other cases that specifically have not been listed here. At least one that comes to mind is 6952. There are cases in the process area like 6957 and its progeny; there are some cases 694 -- I don't recall the last digit on them, some of the early cases. There could be others but I specifically remember those cases.

MS. FURMAN: That concludes my questioning.

MR. KELBER: I have a little bit of --

MR. VILA: Can I ask a couple of

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questions?

MR. KELBER: I have no objection.

BY MR. VILA:

Q. Mr. Kassenoff, I believe you said that you had a substantial involvement in dyestuffs besides the area in question which is the HMG-CoA reductase area. At that time, did you have any other areas of responsibility within the department?

A. Yes, I did.

Q. Would you enumerate those, please.

A. For example, I was keeping track of recent decisions and advising our parent company in Basle on recent decisions in U.S. patent law; I was involved in tracking pending legislation, rule changes and advising our parent company's Patent Department in that regard as well as other members of this department; I had several other projects, for example, in 19 -- it must have been 1987, when the record of understanding between the United States and the Republic of Korea was entered into, I was in charge of preparing all of the declarations. I think that was in early '87

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because if I recall correctly, the five year -- the initial five year period of exclusivity commenced on July 1st of 1987 and that took up a substantial amount of time in that period. There may have been others but those are the ones that come to mind.

Q. When Mr. Weinfeldt left in April of '87, I believe you testified that at that point in time, you and Mr. Weinfeldt had responsibility for the area in question.

A. That's correct.

Q. When Mr. Weinfeldt left, who had responsibility for that area?

A. I had, I would assume, primary responsibility and then Jody Giesser, and I'm not sure exactly when Jody came here, but Jody picked up a good deal of the responsibility sometime in that time period.

Q. Are you saying she picked up a responsibility for existing cases?

A. For existing cases as well as for new disclosures.

Q. And do we know approximately when Jody Giesser was employed?

A. If I recall correctly, it was at the

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time that Fred was on medical disability.

Q. I believe your declaration mentions that August of '87 is the time that Jody joined the department. Between April, when Mr. Weinfeldt left the department, and August, who else besides yourself would have been handling or responsible for this area?

A. I assume that you had some responsibility but I don't recall if you did any cases on that but other than that, no one.

Q. So as far as you know, you had responsibility for the entire area in that period?

A. As far as I know, that's correct.

Q. When Mrs. Giesser joined the department, did she have any prior experience in this area or in pharmaceutical applications, to your knowledge?

A. She may have had some in pharmaceuticals at the law firm or one of the law firms at which she was previously employed but certainly not in this specific area.

Q. I believe it's on the record that you have substantial long term experience in the pharmaceutical field. How would you describe the

degree of effort required in preparing cases in this area in general, would it be routine or easier than routine?

A. The cases were rather lengthy because this is not an area which one could synthesize the compounds in one step reactions. Many of the compounds required five, even ten step syntheses. Consequently -- and often not all of the compounds of a single disclosure could be made by a single route. Consequently, the process description was -- the required process description was extensive and the applications were lengthy.

For example, there were at least a couple of the applications that I wrote were well over a hundred pages and in fact, one may have been close to 150 pages. Of course, some of them were probably on the order of 40 or 50 pages. Those were the shorter ones.

Q. I believe it's been testified that when disclosure 299/84 was rated "A" in January of '88, it had Jody Giesser's initials on the Patent Committee minutes.

A. That's correct.

Q. Indicating the case was her

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responsibility. Was there some uncertainty as to who would prepare that case despite that notation?

A. I assume that it was in the back of our minds that there was a possibility that I might do it if I had no other -- if I had the available time because that's the only way I could explain the fact that I did request Dr. Wattanasin to send me some of the Chemical -- the information required from the Chemical side and I did request Biology to send me their input for the application.

Q. Would Mrs. Giesser have had experience in obtaining the type of information which you obtained in 1988 from the Pharmaceutical Research Group?

A. Probably not.

Q. If there were a decision after the "A" rating in January of 1988 not to file a patent application on 299/84, can you tell me what, if anything, would have happened to reflect that decision?

A. It would have been reflected in the subsequent minutes of the Patent Committee.

Q. And how would that procedure have taken place?

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A. The attorney in charge would have requested the Patent Committee to rewrite the disclosure from "A", either into "B", "C", "D" or "X", "D" meaning drop or dead and "X", "C" and "B" being various categories of bringing it up once again.

Q. If there had been a decision not to file the application, what would have been the rating in that case?

A. "D".

Q. Could anybody else other than the patent attorney bring that issue before the Patent Committee?

A. Yes, anybody, any member of the committee could bring it up but generally, it would be done through the attorney, at least directly through the attorney.

Q. Who were the members of the committee?

A. The people of the committee consists of the heads and assistant heads of the Patent Department and members representing Chemistry, Biology, Pharmacy and possibly some other groups in Pharmaceutical Research.

Q. Could members of the committee

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representing chemistry bring the disclosure back up once it had been rated "A"?

A. Yes, they could.

Q. Members of the Biology group?

A. Yes.

Q. To your knowledge, did anyone, either Patent Department, Chemistry, Biology or anyone else offer this disclosure back up to be given a category other than to be filed upon?

A. Not to my knowledge but then again, I was not participating in the Patent Committee at that time.

Q. If such an action had been taken, would you be aware of it through the Patent Committee minutes?

A. Yes, I would.

Q. Are you aware of any such action?

A. No, I'm not.

MR. VILA: I don't think I have any more questions.

RECROSS EXAMINATION BY MR. KELBER:

Q. Mr. Kassenoff, I believe you testified that between April and August of 1987, you were the

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sole patent attorney or agent at Sandoz responsible for the area of HMG-CoA reductase. Is that correct?

A. Yes, although there is a possibility that Dick Vila here, who is the supervisor of the group, might have filed some responses in some pending cases.

Q. Do you have knowledge of whether he did or not?

A. No, I don't have any knowledge of that.

Q. Between the period April and August of 1987, no patent attorney at Sandoz would have taken up PD 299/84 for any reason, would they have?

A. Between when?

Q. Between the period April and August of 1987.

A. No. It had not been rated "A".

Q. So even if Ms. Giesser had been here in April of 1987, she would have had no reason to pick up that disclosure?

A. That's correct, not until it received an "A" rating or was about to be rated "A".

Q. I believe you testified that at no time

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subsequent to the receipt of the "A" rating on 299/84, you were not aware -- I'm sorry, at no time subsequent to that "A" rating, you personally did not have any intention not to file an application --

A. That's correct.

Q. -- corresponding to PD 299/84. Is that correct?

A. That's correct.

Q. At any time prior to receipt of that rating, did you have any intention to file an application directed to PD 299/84?

A. No. There would be no reason to.

Q. Do you recall whether there was a Patent Committee meeting in December of 1987?

A. Unlikely. At least in the last few years, we have not had December meetings. The Patent Committee invariably meets the last Wednesday of the month and the last Wednesday in December is not a very conducive time to have a meeting.

Q. Are there cases where a disclosure has been rated "A" and additional work is continuing on that particular subject matter?

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subsequent to the receipt of the "A" rating on 299/84, you were not aware -- I'm sorry, at no time subsequent to that "A" rating, you personally did not have any intention not to file an application --

A. That's correct.

Q. -- corresponding to PD 299/84. Is that correct?

A. That's correct.

Q. At any time prior to receipt of that rating, did you have any intention to file an application directed to PD 299/84?

A. No. There would be no reason to.

Q. Do you recall whether there was a Patent Committee meeting in December of 1987?

A. Unlikely. At least in the last few years, we have not had December meetings. The Patent Committee invariably meets the last Wednesday of the month and the last Wednesday in December is not a very conducive time to have a meeting.

Q. Are there cases where a disclosure has been rated "A" and additional work is continuing on that particular subject matter?

Kassenoff - recross

A. Probably.

Q. Are you aware of any such cases personally?

A. Personally, no, but I'm pretty sure that that's the case.

Q. Isn't it the fact, Mr. Kassenoff, that in the case at issue here, PD 299/84, Dr. Wattanasin continued work in that subject matter subsequent to the "A" rating?

A. That's probably the case.

Q. So the fact that additional work is being performed on a case is not alone reason to rate it only "B" as opposed to "A"?

A. That's correct.

Q. There are other considerations that would go into rating a case as "B" as opposed to "A". Is that correct?

A. Probably.

Q. Can you name some of those other considerations?

A. Yes. For example, if the work done to date shows that the compounds, while being of interest, might not be as interesting as other compounds of the series, although of interest, they

could defer it. For example, if this were the best compound that we had and better than what was available, we would probably not wait for ongoing work. On the other hand, if this compound, that is, the lead compound of this particular series, were good but probably, let's say, maybe not better than anything we already had, we might delay it.

Q. Do you recall whether that was the situation in connection with PD 299/84?

A. I do recall that we had a compound in this series in advanced clinical research at the time and that this compound certainly did not appear to -- the lead compound of the quinoline series certainly did not appear to be better than the compound that was then in clinic. That I do recall.

Q. Is it your --

A. How it compared, it was probably -- I don't know but it was certainly no better.

Q. Is it your testimony, Mr. Kassenoff, that all other things being equal, that lead compound of a disclosure that is not as good, active, without toxicity --

A. Generally --

Kassenoff - recross

Q. Let me finish the sentence, the question.

-- that is not as active as another compound that is already developed and I presume the subject of a patent application, that the application as to the less active compound might be deferred?

A. Put it this way: One, as far as when the disclosures come to the Patent Committee, we generally do not have the tox information available so we are just dealing with the testing of the compound. We have information as to its activity but not as to tox. There are exceptions, of course.

Generally, we will-- I wouldn't say that the applications would be delayed. What I would say is that they wouldn't be expedited.

Q. Now I'm confused. Perhaps I used the wrong word in the term "delay." Would a disclosure be rated "B" for that reason alone?

A. For that reason alone?

Q. The reason you described, that is, less active than another case in testing.

A. No, it would simply mean that since the

Kassenoff - recross

work was ongoing, there was no rush to file it.

Q. If work was ongoing and the lead compound that was the subject of that work was not as active as another compound that you were currently pursuing, would that be sufficient in and of itself to rate a compound -- to rate a disclosure as "B"?

A. I don't know if I could really answer that question. I would say --

Q. What else do you need to know?

A. It was probably a factor but you are saying in and of itself, I really can't answer that.

Q. What other reasons would give rise to rating a disclosure "B"?

A. Other than the ongoing work, probably -- it either would be ongoing work or whether it was of sufficient interest but usually it's ongoing work, it's "B", because if the work had been incompleted, we would be able to make a rating of it.

Q. But PD 299/84 had ongoing work after it was rated "A", wasn't it?

A. That's correct.

Kassenoff - recross

Q. So ongoing work alone is not sufficient --

A. That's correct.

Q. -- to discriminate between "B" and "A". Is that correct?

A. That's correct.

Q. Do you have any idea why PD 299/84 was rated "B" or "X" prior to January of 1988?

A. If I had to make a guess, I would say it's probably because there was some biological testing on what was then the lead compound of the series that had not been completed yet.

Q. But you are guessing?

A. I'm guessing but I would say that's probably the case. It was probably the in vivo testing that had not been completed yet.

Q. Let's go back to the biological data that you requested from Sandoz Biology Department in March of 1988. Is that the type of data that you are talking about?

A. I'm not sure. That certainly is in vitro testing. Whether there was also in vivo testing at the time, I do not recall. If it was, I would have received it. Without looking at the

data, I can't tell you if that's strictly in vitro or whether there is also in vivo testing at that time.

Q. Why would a disclosure be rated "X"?

A. "X" generally means that it will come up in one month and usually either we expect some data to be received during the month or else it means that, in this case it probably would be two months because of the lack of a December meeting, or else it could mean that the people required to make the decision, either the lead person from Chemistry or Biology, without whose input you generally would not want to raise it, was not present at the meeting so it's strictly deferred for a month.

Q. Are there situations where a disclosure can be rated "X" and then not elevated to "A" subsequently?

A. Absolutely.

Q. How long does it take you to prepare the average pharmaceutical application that you spoke to earlier when you are preparing one on behalf of Sandoz?

A. Are you talking about in duration of

Kassenoff - recross

time or actual number of hours?

Q. I'm sorry, duration of time.

A. It really depends on my other workload.

Q. You were able to respond to an issue regarding average applications. Can you give me an average for the period in question?

A. My guess is that it would probably be -- the work would probably require about three months but obviously, I'm doing a lot more in that time period.

Q. Understood.

A. That's a ballpark figure.

MR. VILA: Pardon me.

MR. KELBER: Off the record.

(Whereupon a discussion took place off the record.)

Q. From the time you received notification of an "A" rating on a disclosure to the time you begin preparation of the application, generally how long a time period is that?

A. I don't think I could answer that. It can vary anywhere from days to a month, sometimes even longer.

Q. Why would it be longer?

Kassenoff - recross

A. Pressure of other work, particularly a huge docket of applications of office actions to respond to and/or other work. In other words, I'm fitting in my new disclosures on a time available basis between all of my other responsibilities.

Q. And you are careful to take things in turn. Is that correct?

A. As far as new disclosures?

Q. Your work in general.

A. I would give priority to responding to office actions unless there were a statutory bar involved.

Q. You indicated that all of these, almost all of the applications or patents listed in paragraph five of F-1 had, to the best of your recollection, been published by now.

A. Oh, yes.

Q. Do you have any knowledge whether any of them were published before their filing date?

A. Before their filing date?

Q. Before their filing date.

A. Absolutely not.

Q. So it would be the Sandoz policy not to publish material before the application --

Kassenoff - recross

A. Absolutely. That's a clear no-no.

Q. How about PD 299/84, do you have any knowledge specifically in that case as to whether there was any publication prior to its filing date?

A. I have to assume that there would be none because that would not be permitted by our publication clearance procedure. In other words, we will not clear a publication for release until either we filed on it, and generally we will not clear it until it's about to publish out either in the U.S. or abroad or unless the disclosure is rated "D".

Q. So if a disclosure would be rated "B" or "X" --

A. We would not permit a publication, no way.

Q. The synthesis data that you talked about on redirect examination that tends to make pharmaceutical cases lengthy --

A. At least in this particular area. I wouldn't want to generalize it.

Q. In this particular field, does much of that synthesis information come from the individuals responsible for the work on the

Kassenoff - recross

compounds?

A. Yes.

Q. And so that that would not have to be prepared ab initio by the attorney in question?

A. It would have to be prepared by the attorney in that one. Generally, we do not get written up procedures. We get lab notebook, at least I work from lab notebook pages, which means one, I have got to go into the lab notebook pages; two, I have got to, obviously, for the examples, write them up from the lab notebook pages; three, I have got to then check, write up general procedures for it. Sometimes they may come from the inventor, as was the case in this case.

Q. I'm sorry, which case is that, sir?

A. The 7101 case. As you can see, the material, one of the exhibits does have an outline. Then I have got to make sure that for the entire scope agreed upon, that the processes that were provided are operative and if they are not, either we have to modify the scope or we have to provide additional processes such that we have an enabling disclosure for the entire scope.

Q. Do you know offhand whether that was

necessary in 7101?

A. No, since the case was prepared by Miss Giesser.

Q. You testified, I believe, on redirect with respect to the experience Ms. Giesser had in obtaining data with respect to patent disclosures from other departments within Sandoz. Is that correct?

A. I said -- what I did say is that in all probability, since she was fairly new in the department, she did not have that experience. The basis for that is that most of the work that she did was nonpharmaceutical work. She was handling our seeds work and some agro, as well as some biotech work. She did not, other than the HMG-CoA reductase area, in which she just spent a small amount of her time, she did not spend very much in pharmaceuticals.

Q. But nonetheless, she was charged with responsibility in that field?

A. In these cases.

Q. How difficult is it to request the data in question?

A. Phone call.

Kassenoff - recross

Q. You worked with Ms. Giesser for a period of about two years, three years, is that correct, maybe more?

A. She was here for that period of time, yes.

Q. Did you have an opportunity to judge whether she had the ability to learn how to obtain that data in that period of time?

A. I'm sure to obtain the data didn't require any exercise.

Q. So even though she joined in August of 1987, it wouldn't have taken her too long to learn how to obtain that kind of data?

A. No, but I'm not sure, this could have been -- these probably were the first pharmaceutical cases that she was involved in.

Q. Do you know that one way or the other?

A. I don't know that as a fact but I think it's a valid assumption, since I'm not aware of any other area in which she did any pharmaceutical work.

Q. The applications that were prepared subsequent to April of 1987 in this field that were new cases that were not prepared by you would have

had to have been prepared by you, wouldn't they?

A. Yes, but if you look at the list, starting with April of 1987, you will see that there aren't very many actually new disclosures.

Q. But there are a few, aren't there?

A. There are a couple.

Q. And you weren't responsible for those entirely, were you?

MR. VILA: Can we go off the record a minute.

(Whereupon a discussion took place off the record.)

Q. You did not prepare all the cases that appear in this list that were filed subsequent to April of 1987. Is that correct?

A. That's correct.

Q. Do you have any knowledge of what type of input was provided to change the rating on PD 299/84 first from "B" to -- I'm sorry -- yes, first from "B" to "X"?

A. I don't know if there was any written input. It probably was oral input at the Patent Committee meeting.

Q. Do you have any knowledge as to what

Kassenoff - recross

that input was?

A. No. I did not attend the meeting at that time.

Q. Do you have any knowledge as to what caused the Patent Committee to change the rating from "X" to "A"?

A. No, I have no specific knowledge of that.

MR. KELBER: I have nothing further at this time.

MR. VILA: Let me clarify the question that was asked. I believe the question was addressed as to Jody Giesser's responsibilities subsequent to April of '87 in this area. Again, when did Miss Giesser join this department?

THE WITNESS: Later in '87, I think. Was it August? Sometime in August. I think it was August of '87.

MR. VILA: So your answer to that question only could have been with reference to the time she actually joined the department, which was later in 1987?

THE WITNESS: That's correct.

MR. KELBER: When Miss Giesser joined

in August of '87, were the patent disclosures rated "A" waiting to be prepared, assigned to her?

THE WITNESS: I really do not know.

MR. KELBER: Okay.

MS. FURMAN: I have nothing.

MR. KELBER: Thank you, Mr. Kassenoff. I appreciate it. Before we go off the record, we need each of the depositions to be taken today to be prepared in separate transcripts, according to the rules. Don't ask me why. There are lots of rules recited in the CFR about how they have to be prepared and filed.

MS. FURMAN: They are aware of them.

MR. KELBER: Did you take care of it?

MS. FURMAN: Yes.

MR. KELBER: Okay, thank you.

(Time noted is 11:45 a.m.)

Melvyn M. Kassenoff
MELVYN M. KASSENOFF

Subscribed and Sworn to before me
This 21st day of April, 1993

Antoinette Lombardi
A Notary Public

ANTOINETTE LOMBARDI
Notary Public of New Jersey
My Commission Expires April 3, 1994

ANTOINETTE LOMBARDI
Notary Public of New Jersey
My Commission Expires April 3, 1994

C E R T I F I C A T E

I, GARY M. TALPINS, a Notary Public and Certified Shorthand Reporter of the State of New Jersey, do hereby certify that prior to the commencement of the examination, MELVYN M. KASSENOFF was duly sworn by me to testify the truth, the whole truth and nothing but the truth.

I DO FURTHER CERTIFY that the foregoing is a true and accurate transcript of the testimony as taken stenographically by and before me at the time, place and on the date hereinbefore set forth, to the best of my ability.

I DO FURTHER CERTIFY that I am neither a relative nor employee nor attorney nor agent of any of the parties to this action, and that I am neither a relative nor employee of such attorney or counsel, and that I am not interested directly or indirectly in the interference either as counsel, attorney, agent or otherwise.

Gary M. Talpins, C.S.R.
License No. XI00561

ERRATA SHEET

Name of case: Wattanasin v. Fujikawa et al.
Deposition of: Melvyn M. Kassenoff
Date taken: March 22, 1993
Page 1

[I have marked the most important changes with an asterisk *.]

PAGE	LINE	CHANGE	REASON
*11	12	Change "filing" to "bar".	This is what I remember saying. Additionally, the sentence at ll. 11-13 makes no sense without this correction.
11	13	Change "filing" to "file".	I am certain I said "file". Also, this change would render the sentence grammatically correct.
14	24	Change the comma (",") to a period (".") and change "it's" to "It's".	This would clarify what I said and render the sentence grammatically correct.
22	4	Change "It" to "There".	This correction reflects what I remember actually saying. Additionally, the sentence at ll. 4-8 is clearly grammatically improper without this change.
23	22	Delete the comma (",") after case and insert a comma (",") after "weeks".	The meaning of my sentence is clarified by this change.
*24	17	Change "application?" to "inhibition field?".	This correction reflects what I remember saying. The word "application" is a clear transcriptional error, since the sentence at l. 17 makes no sense if left uncorrected.
25	13	Change "have" to "had".	This is what I remember saying. Also, without the correction, the sentence at ll. 13-14 does not make grammatical sense.

PAGE	LINE	CHANGE	REASON
31	9	Change "I'm looking" to "I looked".	This is what I remember saying. Also, without the correction, the sentence at ll. 9-10 does not make grammatical sense.
34	13	Delete "kit".	This word is meaningless in the context, and is clearly a transcriptional error. The meaning of the sentence at ll. 12-13 is clear without it.
25	13	Change "have" to "had".	This is what I remember saying. Also, without the correction, the sentence at ll. 13-14 does not make grammatical sense.
31	9	Change "I'm looking" to "I looked".	This is what I remember saying. Also, without the correction, the sentence at ll. 9-10 does not make grammatical sense.
34	13	Delete "kit".	This word is meaningless in the context, and is clearly a transcriptional error. The meaning of the sentence at ll. 12-13 is clear without it.
41	5	After "period;" insert "and".	This change is consistent with my recollection of what I said; the word "and" also provides a basis for my subsequent mention of case 7022/C.
42	4	Change "That" to "There".	This change is consistent with my recollection of what I said. Also, the sentence at l. 4 does not make grammatical sense without this change.

PAGE	LINE	CHANGE	REASON
42	12	Change "totally" to "a total".	This change is consistent with my recollection of what I said. Also, the sentence at ll. 10-13 does not make grammatical sense without this change.
43	16	After "advanced" insert a comma (",").	This insertion would clarify the meaning of my statement.
43	19	Change "working" to "to work".	This change is consistent with my recollection of what I said. Also, the change would clarify my statement.
47	8	After "was" insert "sometime".	This change is consistent with my recollection of what I said. The placement of the word "sometime" in line 9 is a transcriptional error, and it properly belongs in line 8.
47	9	Change "issue" to "issued" and delete "sometime".	This change is consistent with my recollection of what I said. Also, the change would clarify the sentence.
47	17	After "issue" insert "date".	This insertion is consistent with my recollection of what I said. Also, the insertion would clarify the sentence.
60	6	After "area" insert "in".	This insertion is consistent with my recollection of what I said. Also, the insertion would clarify the sentence.
60	12	After "was" (second occurrence) insert a double hyphen ("--").	This would clarify what I said and render the sentence grammatically correct.

60	15	After "wrote" insert "that".	This would clarify what I said and render the sentence grammatically correct.
*62	3	Change "rewrite" to "rerate".	This change is consistent with my recollection of what I said. Also, the sentence does not make sense in the present context without this change.
*69	21	Change "incompleted" to "completed".	This change is consistent with my recollection of what I said.
*71	14	Change "raise" to "rate".	This change is consistent with my recollection of what I said. Also, the word "raise" instead of "rate" would be meaningless in this context.

Melvyn M. Kassenoff
MELVYN M. KASSENOFF

SUBSCRIBED AND SWORN TO BEFORE ME

This 21st day of April, 1993

Antoinette Lombardi
A Notary Public

ANTOINETTE LOMBARDI
Notary Public of New Jersey
My Commission Expires April 3, 1994

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
CROSS-EXAMINATION

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

BOX INTERFERENCE

SIR:

Responsive to the filing of Wattanasin Consolidated Affidavit Testimony (Volume IV) bearing a filing date of February 22, 1993, Fujikawa hereby requests cross-examination of the following Affiants:

1. Sompong Wattanasin
2. Melvyn M. Kassenoff
3. Joanne M. Giesser

4. Linda Rothwell

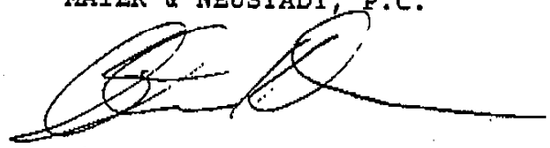
5. Lorraine M. Chesley

The cross-examination of Robert G. Engstrom will not be required.

The cross-examination will be as to all Declarations submitted by Sompong Wattanasin in this Interference. The remaining declarants are believed confined to Volume IV.

Respectfully submitted,

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



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

[redacted] [redacted]

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

WATTANASIN

v. Interference Nos. 102,648, 102,975

#28

FUJIKAWA et al. Examiner in Chief: M. Sofocleous

JOINT REQUEST FOR EXTENSION OF TIME

The parties Wattanasin and Fujikawa et al. jointly request an extension of time in which to complete taking of cross-examination and rebuttal testimony, as well as an extension of the dates currently set for taking subsequent action, in the above interferences.

The EIC and the parties have been in agreement that cross-examination of the junior party Wattanasin's affiants may run concurrently with the rebuttal testimony of senior party Fujikawa. The current closing date for cross-examination and rebuttal is set for March 25, 1993.

Fujikawa et al. have noticed five Wattanasin affiants for cross-examination, and will also take rebuttal testimony from one non-party witness.

However, owing to other commitments of the involved parties and their witnesses, it has been necessary to tentatively defer the dates for taking rebuttal testimony and certain of the cross-examination until after the current closing date of March 25, 1993[1], pending decision on this motion.

Therefore, the parties now jointly move to reset the relevant dates in the above interferences as follows:

Cross-examination of Wattanasin affiants to close April 15, 1993.
Rebuttal testimony for Fujikawa ..... to close April 15, 1993.
Filing and serving of the record due ..... May 15, 1993.
Wattanasin opening brief due ..... June 15, 1993.
Fujikawa brief due ..... July 15, 1993.
Wattanasin reply brief due ..... August 4, 1993.

Undersigned counsel for the party Wattanasin has discussed this matter with EIC Sofocleous, who indicated he would be agreeable to resetting the dates as set forth above. The courtesy of the EIC is gratefully acknowledged.

---

1. The rebuttal testimony of Dr. Holmlund is tentatively set for March 26, 1993, and cross-examination of Joanne M. Giesser, Esq. is tentatively scheduled for April 9, 1993. The cross-examination of the other Wattanasin affiants will be held on March 22, 1993.

Accordingly, grant of this joint motion is respectfully requested.

Respectfully submitted,

Diane Furman 3/17/93
Diane E. Furman
Attorney for the party Wattanasin
Registration No. 31,104
201-503-7332

Steven B. Kelber
Attorney for the party Fujikawa et al.
Registration No. 30,073
(703) 413-3000

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

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

WATTANASIN

v. Interference Nos. 102,648, 102,975

FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

DECLARATION OF MELVYN M. KASSENOFF PURSUANT TO 37 CFR §1.672

I, Melvyn M. Kassenoff, do hereby declare as follows:

1. All of the below-indicated activities took place in the United States.

2. I have been employed by Sandoz Corporation in the Patent and Trademark Department since 1972. My current position is Director, Patent and Trademark Affairs. I am an associate counsel of record in these interferences.

3. I have had responsibility for the filing and prosecution of Sandoz patent applications in the HMG-CoA reductase inhibitor area since 1982. However, this area was only a very small portion of my total workload, the bulk of which comprised prosecuting applications in the azo dye area originating from research done by Sandoz AG in Basle, Switzerland.

Since about 1981, Sandoz Research Institute has been engaged in a research effort to develop compounds having utility as HMG-CoA reductase inhibitors for use in the treatment of hypercholesterolemia. This project resulted in numerous patent disclosures being submitted to the Patent Department, including Patent Disclosure 299/84 of Dr. Wattanasin.

Prior to approximately April 1987, when he took permanent leave for health reasons, Mr. Fred Weinfeldt, a senior patent attorney in the Sandoz Patent Department, shared the responsibility of filing of patent applications in the HMG-CoA reductase inhibitor area. In August 1987, Mrs. Joanne M. Giesser joined the Department as a patent attorney and took over a portion of Mr. Weinfeldt's docket of patent disclosures to be filed.

4. Within a week or two following the January 27, 1988 Patent Committee meeting, I was aware that Patent Disclosure 299/84 of Sompong Wattanasin had received an "A" rating. It was my intention that the case would be filed by Mrs. Giesser or myself depending on who was available after existing filing priorities had been completed, inasmuch as following Mr. Weinfeldt's departure, a backlog in unfiled HMG-CoA reductase disclosures had been developing.

5. It is noted that the Sandoz U.S. filings in the HMG-CoA reductase area commenced in about 1982 and continued into 1991. For example, a representative list of Sandoz original (including CIP) U.S. patent application filings in the HMG-CoA reductase inhibitor area comprises the following:

Case 600-6951 filed Nov. 22, 1982 (abandoned)
Case 600-6951/B filed Nov. 4, 1983 (R60 of which) issued as U.S. 4,739,073 (1988)
Case 600-6951/C filed Nov. 22, 1982 (pending)
Case 600-7013 filed June 4, 1984 now U.S. 4,588,715 (1986)
Case 600-7015 filed June 22, 1984 (abandoned)
Case 600-7022 filed Dec. 4, 1984 (abandoned)
Case 600-7025 filed Apr. 12, 1985 (abandoned)
Case 600-7028 filed May 22, 1985 now U.S. 4,668,794 (1988)

Case 600-7015/B filed June 6, 1985 now U.S. 4,613,610 (1986)
Case 600-7035 filed Oct. 25, 1985 (abandoned)
Case 600-7022/B filed Mar. 7, 1986 (abandoned)
Case 600-7041 filed Apr. 30, 1986 (abandoned)
Case 600-7028/B filed May 14, 1986 (R60 of which) issued as U.S. 4,755,606 (1988)
Case 600-7035/B filed Oct. 15, 1986 now U.S. 4,851,427 (1989)
Case 600-7050 filed Dec. 23, 1986 now U.S. 4,751,235 (1988)
Case 600-7025/CIP filed May 5, 1987 (abandoned)
Case 600-7022/C filed Jul. 1, 1988 now U.S. 5,001,255 (1991)
Case 600-7025/CIP/CIP/CIP filed Oct. 6, 1988 (abandoned)
Case 600-7025/CIP/CIP/CIP/CIP filed Jan. 16, 1990 (pending)
Case 600-7041/CIP filed Mar. 6, 1987 (abandoned for R60)
Case 600-7064 filed Jan. 27, 1988 now U.S. 4,822,799 (1989)
Case 600-7041/CIP/CIP filed Mar. 10, 1988 (abandoned)
Case 600-6955/XN//B/CONT/X filed Mar. 10, 1988 now U.S. 4,876,1989 (1989)
Case 600-7087 filed Oct. 13, 1988 (abandoned)
Case 600-7101 filed Mar. 3, 1989 (abandoned for R60 cont.)
Case 600-7087/B filed May 8, 1989 (abandoned)
Case 600-7104 filed May 22, 1989 (abandoned)
Case 600-7041/CIP/CIP/II filed Jul. 13, 1989 now U.S. 4,870,199
Case 600-7104/CIP filed Feb. 20, 1990 (pending)
CAse 600-7087/C filed Sept. 5, 1990 (abandoned)
Case 600-7087/D filed Feb. 26, 1991 (pending)

Appendix Z hereto contains copies of the cover sheets of some of the above-indicated U.S. patents which issued on the above cases.

6. It is my best recollection that in February of 1988, I was in communication with Dr. Wattanasin concerning information

which was needed by the Patent Department in order to prepare an application based PD 299/84. (The application that was subsequently filed was designated as, and is referred to herein as, "Case 600-7101".)

Exhibit N hereto comprises a true copy of a page containing my handwritten notations concerning Case 600-7101 and a handwritten date of February 12, 1988.

These notes comprise a checklist of information items which needed to be developed or confirmed in order to draft Case 600-7101. The fact that these notes were made on the reverse side of the second attachment page to PD 299/84; and furthermore, that paragraph 2 discusses the scope of the disclosure and in sub-paragraph (c), refers to "other substitu [sic] on the quinoline ring," indicates their pertinence to the involved Wattanasin application.

These notes further indicate that I spoke with Sompong Wattanasin ("S.W.") on February 12, 1988 concerning his quinoline compounds and requested that he provide me with certain information.

7. On or about March 1, 1988, I received from Dr. Wattanasin certain reaction schemes which were to be included in case 600-7101.

Exhibit O comprises a copy of material which I received from Dr. Wattanasin for the preparation of Case 600-7101. This shows two different reaction routes to preparing quinoline compounds of the case.

8. It was my practice to request the Sandoz Biology Department to send me IC_{50} and ED_{50} values for compounds I was planning to cover in a patent application, as well as other biological information necessary to properly draft a patent application directed to a pharmaceutical.

Exhibit Q hereto comprises a Biological Data Report and computer printout which I received from the Sandoz Biology Department. The Wattanasin disclosure number, i.e. "299/84" is written in my handwriting on the front page, and the compounds of Patent Disclosure 295/84 as well as PD 299/84 are included in the printout.

The printout bears a date of May 23, 1988.

9. On July 1, 1988 I filed Case 600-7022/C based on PD 295/84, which was indicated for filing ahead of PD 299/84.

Exhibit R hereto comprises a copy of the front page of U.S. Patent No. 5,001,255, which issued on Case 600-7022/C, and indicates a filing date of July 1, 1988.

10. With reference to **Exhibit Y-2**: page 2 of this computer printout bears a date of January 11, 1989 written in my handwriting.

11. At no time subsequent to the "A" rating of Patent Disclosure 299/84 did I or, insofar as I am aware, any other member of the Patent and Trademark Department of Sandoz Corporation, ever have any intention not to file a United States patent application on the quinoline compounds of said patent disclosure in due course.

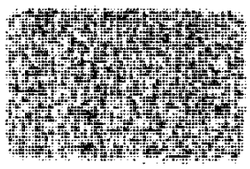
The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

I hereby subscribe my name to the foregoing Declaration this 19th day of February, 1993.

Melvyn M. Kassenoff

MELVYN M. KASSENOFF

Exhibit N 392a



want:

1) Typical example or lab notebook pages
2) Scope
   a) R_1 $R_{1'}$ R_2
   b) (E)-CH=CH- replacements
   c) other substituents on quinoline ring
3) which compds are known
4) Process condns for AA-AD
5) Unusual condns for std rxns
6) Anything unusual - lab, standard rxns that didn't work
7) Complete list of end products + NMR (tabulated) spectrum, mp. and isomeric compn of each

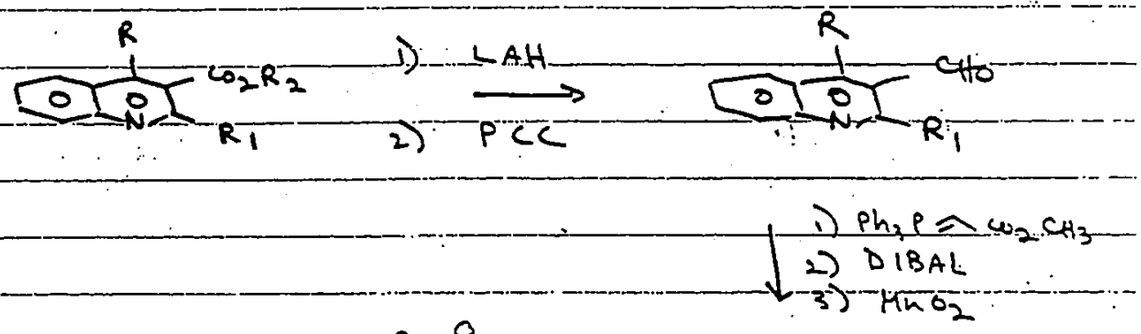
Scope same as naphthalene

X = (Z) or (E)-CH=CH $-CH_2CH_2-$, $-CH-$, $-(CH)_3-$

Substituents on alkyl
alkoxy
OH
$\phi CH=O$
CF_3
halo

Structure with S.W. 2-12-88; Requested info will be sent

Route II


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

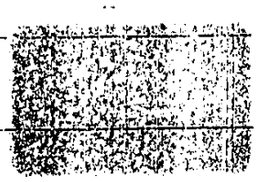
I

Exhibit O 393

sent to

M. Kasmikoff.

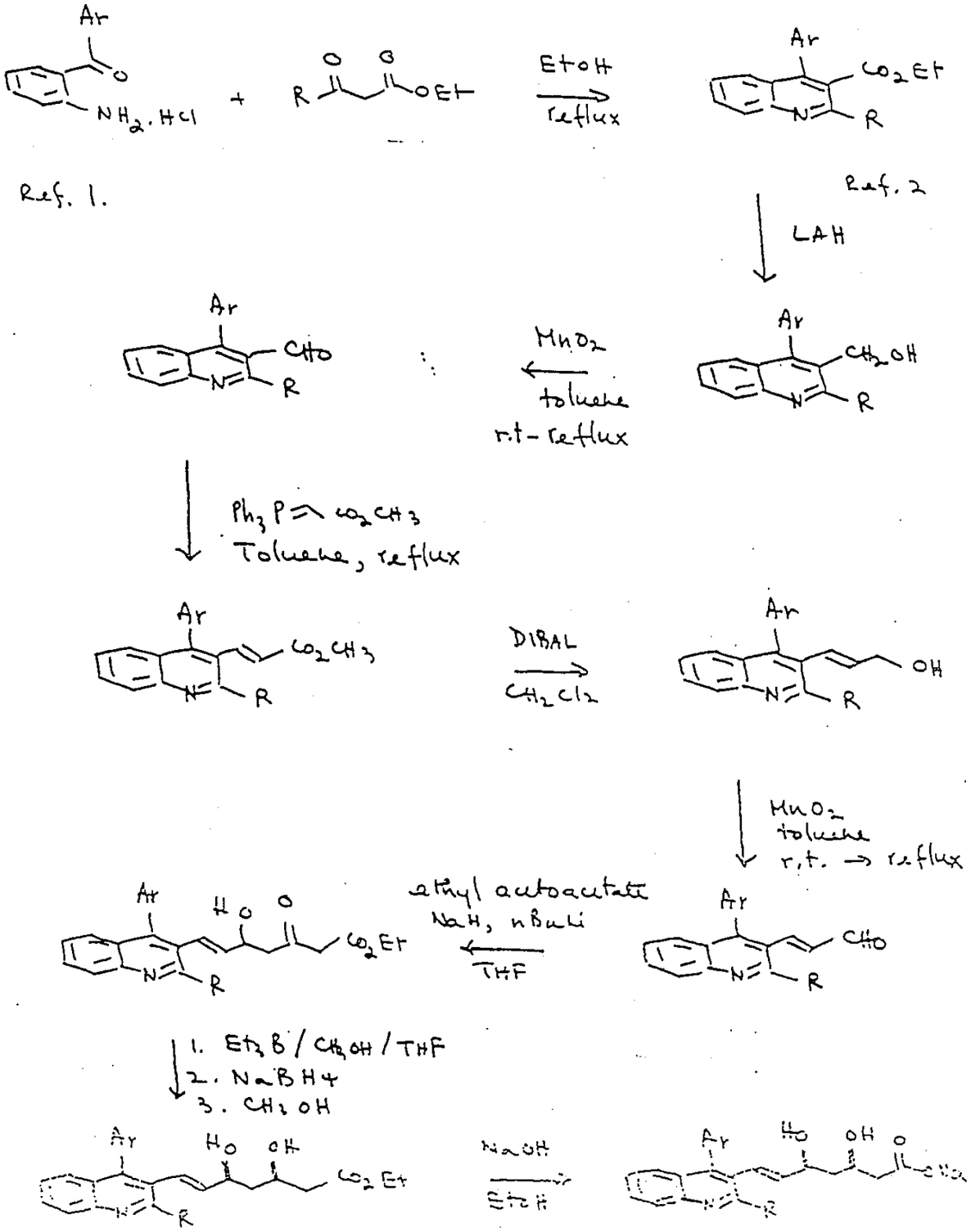
- 2/29/88.



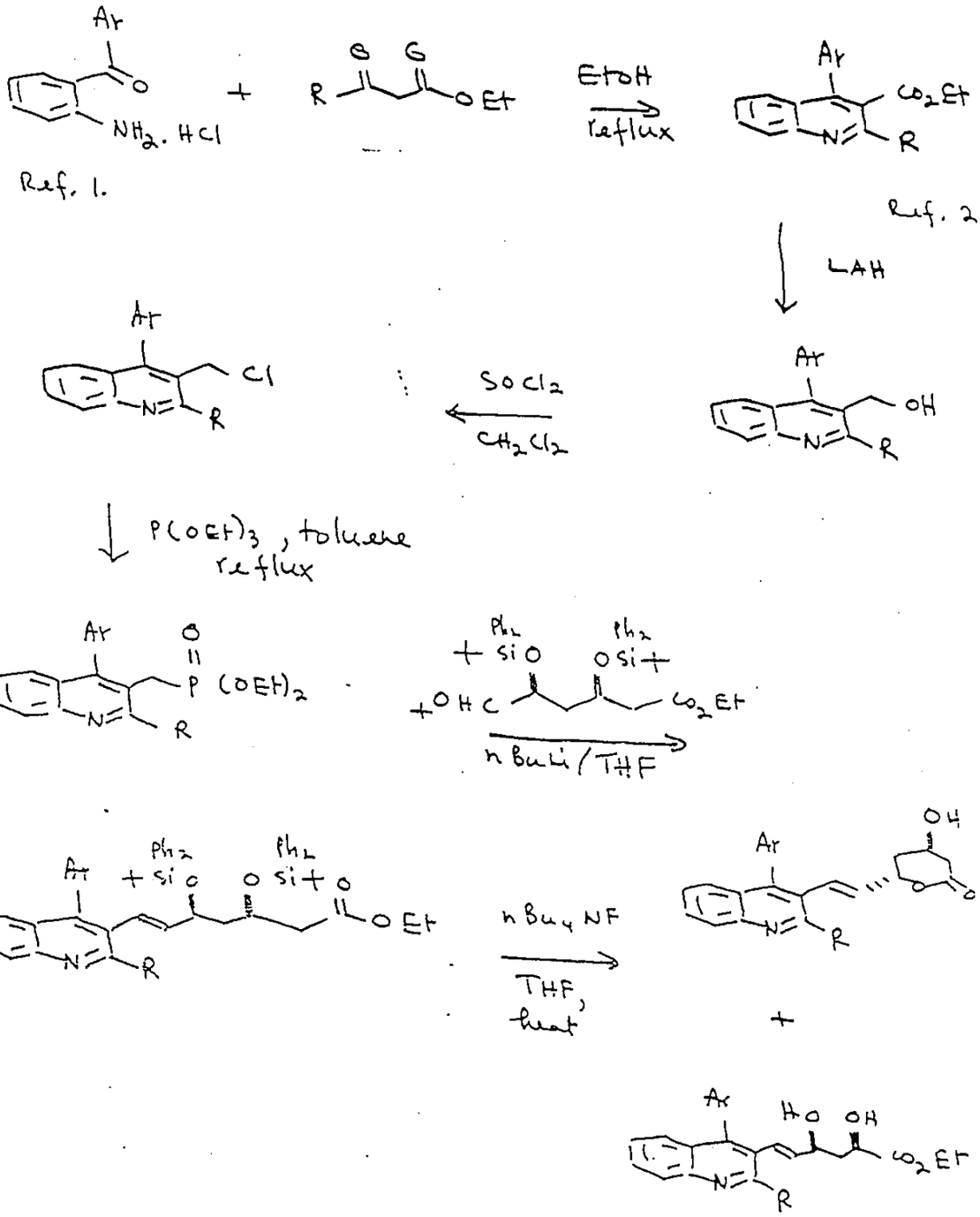
S. Wattanasin.
2/29/88

394

SCHEME I



SCHEME 2

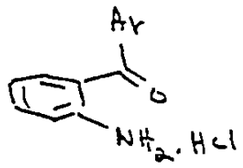

Ar
NH2. HCl
R
O
O
OEt
EtOH
reflux
CO2Et
N
R
Ref. 1.
Ref. 2
LAH
OH
SOCl2
CH2Cl2
Cl
P(OEt)3, toluene
reflux
P(OEt)2
Ph2
Si
OHC
nBuLi/THF
nBu4NF
THF,
heat
HO

References + Notes

1. A. Morrison and T.P. C. Mulholland, J. Chem. Soc. 2702 (1958)

2. E.A. Fehnel J. Heterocyclic Chem. 4, 565 (1968).

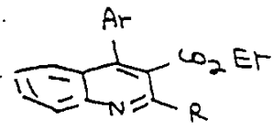
3. The starting aminoketones 1 are known compounds and prepared according to



1 Ar = Phenyl
= 3,5-dimethylphenyl
= p-Fluorophenyl

a procedure described in ref. 1.

4. The quinolines 2 were prepared by a modified procedure of ref. 2.



2

5. According to a search, only quinoline 2 where Ar = Ph and R = CH_3 is known

DR. D. CORNISH	DR. J. NADELSON	MR. J. BOROVIAN	MR. T. MC GOVERN
DR. J. FOLEY	DR. L. SALANS	MR. T. DOYLE	MRS. L. ROTHWELL
DR. G. HARDTMANN	DR. R. SAUNDERS	MR. R. HONOR	MR. G. SHARKIN
DR. W. HOULIHAN	DR. D. WEINSTEIN(2)	MR. W. JEWELL	MR. R. VILA
DR. F. KATHAWALA	DR. D. WINTER	MR. M. KASSENOFF	MR. F. WEINFELDT
BASLE (2)			

MINUTES

PATENT COMMITTEE MEETING

HELD WEDNESDAY, APRIL 29, 1987

* *

3. NOTICES OF ALLOWANCE:

3.1 Th
a

13

in-part;

3.2 Th
th

65

respecting

4. FINAL REJECTIONS:

4.1 T

5. DISCLOSURES:

5.1 The following disclosure has been rated "A":

5.2

"A" and a
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a separate
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5.3 The following disclosures have been rated "X":

5.4 The following disclosures have been rated "B":

299/84 WATTANASIN FHW

5.5

384

DR. D. CORNISH	DR. L. OSTBERG	MR. J. BOROVIAN	MR. T. MC GOVERN
DR. J. FOLEY	DR. L. SALANS	MR. T. DOYLE	MRS. L. ROTHWELL
DR. G. HARDTMANN	DR. R. SAUNDERS	MR. R. HONOR	MR. G. SHARKIN
DR. W. HOULIHAN	DR. D. WEINSTEIN(2)	MR. W. JEWELL	MR. R. VILA
DR. F. KATHAWALA	DR. D. WINTER	MR. M. KASSENOFF	MR. F. WEINFELDT
DR. J. NADELSON	BASLE (2)		

MINUTES

PATENT COMMITTEE MEETING

HELD WEDNESDAY, JULY 29, 1987

* *

5. DISCLOSURES:

5.1 The following disclosures are rated "X":

5.2 The following disclosures are rated "B":

299/84 WARRANASIN FHW

DR. D. CORNISH	DR. L. OSTBERG	MR. J. BOROVIAN	MR. T. MCGOVERN
DR. J. FOLEY	DR. L. SALANS	MR. T. DOYLE	MRS. L. ROTHWELL
DR. G. HARDTMANN	DR. R. SAUNDERS	MRS. J. GIESSER	MR. G. SHARKIN
DR. W. HOULIHAN	DR. D. WEINSTEIN(2)	MR. R. HONOR	MR. R. VILA
DR. F. KATHAWALA	DR. D. WINTER	MR. W. JEWELL	MR. F. WEINFELDT
DR. J. NADELSON	BASLE (2)	MR. M. KASSENOFF	

MINUTES OF THE

PATENT COMMITTEE MEETING

HELD WEDNESDAY, OCTOBER 28, 1987

* *

5.3 The following disclosures are rated X.

299/84 WATTANASIN FHW

5.4 The following disclosures are rated B.

V:lmc
/6/87

DR. D. CORNISH	DR. L. OSTBERG	MR. J. BOROVIAN	MR. M. KASSENOFF
DR. J. FOLEY	DR. L. SALANS	MR. T. DOYLE	MR. T. MC GOVERN
DR. G. HARDTMANN	DR. R. SAUNDERS	MRS.J. GIESSER	MRS.L. ROTHWELL
DR. W. HOULIHAN	DR. D. WEINSTEIN(2)	MR. R. HONOR	MR. G. SHARKIN
DR. F. KATHAWALA	DR. D. WINTER	MR. W. JEWELL	MR. R. VILA
DR. J. NADELSON	BASLE (2)		

MINUTES

PATENT COMMITTEE MEETING

HELD WEDNESDAY, NOVEMBER 25, 1987

* *

1A. FOREIGN FILINGS:

MEETINGS. (Cont.)

5. DISCLOSURES:

5.1 The following disclosures are rated "X":

299/84	WATTANASIN	FHW
6		
1		
8		
9		

DR. D. CORNISH	DR. L. OSTBERG	MR. J. BOROVIAN	MR. T. MCGOVERN
DR. J. FOLEY	DR. L. SALANS	MR. T. DOYLE	MRS. L. ROTHWELL
DR. G. HARDTMANN	DR. R. SAUNDERS	MRS. J. GIESSER	MR. G. SHARKIN
DR. W. HOULIHAN	DR. D. WEINSTEIN(2)	MR. R. HONOR	MR. R. VILA
DR. F. KATHAWALA	DR. D. WINTER	MR. W. JEWELL	
DR. J. NADELSON	BASLE (2)	MR. M. KASSENOFF	

MINUTES OF THE

PATENT COMMITTEE MEETING

HELD WEDNESDAY, JANUARY 27, 1988

* *

1.A. FOREIGN FILINGS:

DISCLOSURES:

5.1 The following disclosures are rated A.

.lity search
formed).

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only).

299/84 WATTANASIN JMG

BFY-lmc

#88

49-111-0

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

WATTANASIN	:	
V.	:	INTERFERENCE NO.: 102,648
	:	EXAMINER-IN-CHIEF:
FUJIKAWA ET AL	:	MICHAEL SOFOCLEOUS

FUJIKAWA ET AL SUBMISSION OF CERTIFIED TRANSCRIPT OF DEPOSITION OF CHESTER E. HOLMLUND

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

BOX INTERFERENCE

SIR:

Submitted herewith is the certified transcript of the deposition of Chester E. Holmlund.

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:

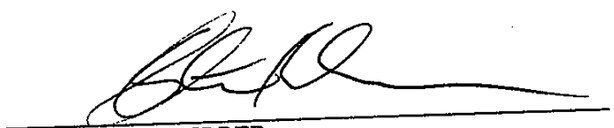
1. **FUJIKAWA ET AL SUBMISSION OF CERTIFIED TRANSCRIPT OF DEPOSITION OF CHESTER E. HOLMLUND**

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 28th day of APRIL, 1993.



STEVEN B. KELBER

ORIGINAL

TRANSCRIPT OF PROCEEDINGS

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 – #88
WATTANASIN v. FUJIKAWA, et al.	Interference No. 102,975 – #33

DEPOSITION OF CHESTER E. HOLMLUND

Arlington, Virginia

Friday, March 26, 1993

ACE - FEDERAL REPORTERS, INC.
Stenotype Reporters
1120 G Street, NW
Washington, D.C. 20005
(202) 347-3700

FOR Fujikawa

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
WATTANASIN v. FUJIKAWA, et al.	Interference No. 102,975

DEPOSITION OF CHESTER E. HOLMLUND

Arlington, Virginia

Friday, March 26, 1993

Deposition of CHESTER E. HOLMLUND, called for examination pursuant to notice of deposition, at the law offices of Oblon, Spivak, McClelland, Maier and Neustadt, 1755 Jefferson Davis Highway, Fourth Floor, at 10:05 a.m. before BRENDA M. SMONSKEY, a Notary Public within and for the District of Columbia, when were present on behalf of the respective parties:

-- continued --

APPEARANCES:

STEVEN B. KELBER, ESQ.
Oblon, Spivak, McClelland,
Maier & Neustadt, P.C.
Fourth Floor
1755 Jefferson Davis Highway
Arlington, Virginia 22202
On behalf of Fujikawa, et al.

RICHARD E. VILA, ESQ.
DIANE FURMAN, ESQ.
Sandoz Corporation
59 Route 10
East Hanover, New Jersey 07936
On behalf of Sandoz Corporation.

ALSO PRESENT:

F. G. KATHAWALA

C O N T E N T S

E X H I B I T S

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

NOTICE OF DEPOSITION

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

BOX INTERFERENCE

SIR:

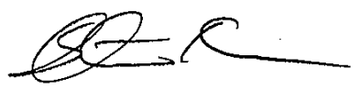
Pursuant to 37 CFR §1.673(a), Fujikawa et al hereby serve notice of the deposition of Dr. Chester E. Holmlund to be held at the offices of undersigned Counsel on March 26, 1993, beginning at 10:00 AM, and continuing from time-to-time until done. It is not expected that the deposition will last beyond a single day, but in the event it does, the deposition will be resumed March 29, 1993.

The current address for Dr. Holmlund is 9200 Edwards Way, Apartment 516, Adelphi, Maryland. The witness is expected to testify in a rebuttal capacity, as to the adequacy of the proof of the Junior Party with respect to conception and actual reduction to practice.

A true copy of the foregoing Notice of Deposition was served, by hand, on Diane Furman, Sandoz Corporation, on March 26, 1993, agreement as to the date of deposition and manner of notice having been earlier agreed upon.

Respectfully submitted,

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



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

49-111-0

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

WATTANASIN	:	
	:	INTERFERENCE NO.: 102,975
V.	:	EXAMINER-IN-CHIEF:
FUJIKAWA ET AL	:	MICHAEL SOFOCLEOUS

NOTICE OF DEPOSITION

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

BOX INTERFERENCE

SIR:

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Respectfully submitted,

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

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

PROCEEDINGS

MR. VILA: Let's put on the record we stipulate we can waive the requirements of Rule 672(b) and that references to matters already on the record or in evidence can be made without introducing these things for identification at the option of the side that is presenting the testimony.

Whereupon,

CHESTER E. HOLMLUND

was called as a witness and, having first been duly sworn, was examined and testified as follows:

MR. KELBER: Good morning. This is the deposition of Dr. C.E. Holmlund, a rebuttal witness for the party Fujikawa, et al. in Interferences 102,648 and 102,975. By prior agreement of the parties, we will be filing a consolidated record with regard to those two interferences.

Is that correct, Diane?

MS. FURMAN: That is correct.

EXAMINATION

BY MR. KELBER:

Q Could you state your full name and address for

the record.

A Chester Eric Holmlund, Apartment 516, 9200 Edwards Way, Adelphi, Maryland 20783.

MR. KELBER: I am going to hand a document to the reporter that I would like labeled as Exhibit F-10.

(Exhibit F-10 identified.)

BY MR. KELBER:

Q Doctor, take a minute and review Exhibit F-10 briefly.

Do you recognize that document?

A Yes, I do.

Q What is that document?

A It is a curriculum vitae prepared, I guess, in 1988.

Q To the best of your knowledge, is it accurate as of today?

A Yes, it is.

Q Doctor, do you have any experience in the field of cholesterol biosynthesis inhibition?

A Yes.

Q Could you describe that experience for me.

A For some time I have been interested in

generally in lipid metabolism, but most especially in the area of ~~sterile~~ sterol metabolism and have spent some time studying the effects of various inhibitors of ~~sterile~~ sterol synthesis insofar as they act upon microbial systems of several types. C24 C24

Q Does your experience involve work directly in the field?

A Yes.

Q Is that experience reflected in Exhibit F-10?

A It is.

Q Are you familiar with compounds intended to inhibit HMG-CoA reductase?

A Yes.

Q Can such compounds be used to reduce or inhibit cholesterol biosynthesis?

A Yes.

MR. KELBER: We offer Dr. Holmlund as an expert as to the art of cholesterol biosynthesis inhibition.

MR. VILA: We will reserve judgement on that until we have cross-examination.

BY MR. KELBER:

Q Prior to this proceeding, have you ever been

employed by Nissan Chemical Corporation?

A I have not.

Q Are you being paid for your services in connection with this proceeding?

A Yes.

MR. KELBER: I am going to hand the reporter a document entitled "Declaration of Terence J. Scallen Pursuant to 37 CFR Section 1.672" and ask that it be identified as Exhibit F-11.

(Exhibit F-11 identified.)

BY MR. KELBER:

Q If you would take a minute to review that.

MR. VILA: A declaration submitted like this without advance notice or seeing it, is that appropriate?

MS. FURMAN: That is our declaration.

MR. KELBER: You were also provided notice about the documents that would be referred to in the deposition.

BY MR. KELBER:

Q While you are reviewing that document, I am going to hand to the reporter for identification as Exhibits F-12 through 16 documents labeled Exhibit E-1, Exhibit E-2, Exhibit E-3, Exhibit E-4 and Exhibit E-5.

Those are exhibits to the Scallen declaration.

(Exhibits F-12 through F-16 identified.)

(Witness examined the documents.)

BY MR. KELBER:

Q Have you seen the documents that comprise Exhibits F-11 through F-16 prior to today?

A Yes.

Q In what context did you first see those documents?

A They were sent to me by you with respect to the action in which your company is now engaged.

Q Doctor, let me turn your attention to paragraph 4 of Exhibit F-11, which is the declaration itself. Do you see in paragraph 4, bridging the pages, the description of an assay protocol?

A Yes.

Q Are you familiar with in vitro assays of this type?

A Yes.

Q Let me direct your attention now back to paragraph 3 of that document that is Exhibit F-11. If you would take a minute to read that paragraph to yourself.

(Witness examined the document.)

A Yes.

Q Doctor, do you have sufficient knowledge, experience and expertise to have formed an opinion as to the validity of the conclusions set forth in paragraph 3 with respect to the second sentence of that paragraph; that is, the second sentence that reads "If a compound possesses this activity, it would be useful for lowering the blood cholesterol level in animals"?

A Short answer, yes.

Q Can you give me that opinion, sir.

A The problem that I have with that statement as it appears here is the declaration that such compounds would be useful. They may be, but they may not be.

Q Can you tell me under what situations compounds exhibiting in vitro activity as referred to would not be useful?

A Well, when a compound is administered to an intact animal, there are many other fates which can befall it before it interacts with its intended target, namely HMG-CoA reductase in this case.

Q Is it then your testimony that it is possible

for a compound to exhibit in vitro activity pursuant to the type of assay in paragraph 4 and still not exhibit reductase inhibition in vivo?

A Yes.

Q Let me direct your attention to the penultimate paragraph of F-11, which is the paragraph bridging pages 8 and 9 of that document.

A I don't see the pagination. The pagination on my copy is 75 on.

Q Looking at the pages numbered 82 and 83.

A Which paragraph?

Q The paragraph bridging those two pages at the bottom of page 82. If you would read that paragraph, sir, to yourself.

(Witness examined the document.)

A Yes.

Q Let me direct your attention specifically now to the sentence that begins at the very bottom of the page numbered 82, starts with the words "It was" and then continues on to the next page.

A Yes.

Q Would the testimony you just gave regarding the

correlation between in vitro and in vivo activity also apply to this statement?

A It would.

Q Do you see the reference in the paragraph that we have been discussing, to compounds 64-934/Na and 64-936/Na?

A Yes, I see them.

Q On the basis of your review of the documents provided, can you tell me the significance of the suffix "Na"?

A That is intended to indicate that it is the sodium salt of the compound that is being tested.

Q Doctor, on the basis of your knowledge, experience and expertise, can the in vivo activity shown by a sodium salt of a compound having reductase inhibition activity be different from the activity shown by the corresponding free acid?

A It can.

Q Let me direct your attention back now to the protocol that is set forth in paragraph 4 which begins on the page marked page 76. Doctor, can small changes in assays of this type affect the activity report obtained

from the assay?

A Yes.

Q Doctor, do you see that the top of the page marked 77, F-11, the reference to an article by Ackerman, et al?

A I see it.

MR. KELBER: For the record, the party Fujikawa takes objection to the declaration of Scallen with respect to paragraph 4 referring to a document not attached to the declaration.

MS. FURMAN: I may be incorrect in my recollection, but did you stipulate at the beginning of this session that you would be willing to consider any such documents referred to in declarations? That's what I thought I heard, that you were --

MR. KELBER: No. What Dick suggested is that we would be willing to stipulate to the use of documents that are of record in the interference already. If you would like, I can have the reporter read back that stipulation.

MS. FURMAN: No. I thought I heard something in connection with 672(b).

MR. KELBER: That's correct. That refers to

this deposition. In fact, the specific reference in 672(b) was to "A party shall not be entitled to rely on any document referred to in the affidavit unless a copy of the document is filed with the affidavit."

We were stating with reference to this particular deposition. I could obviously not have stipulated to the prior declaration, as it was signed and filed well before this discussion.

In any event, our objection goes to the fact that the Ackerman journal article was never made of record in any connection with this proceeding. The objection is made now only because it was made by declaration and we will not be talking at cross-examination to Dr. Scallen. If you prefer, we will make the objection in writing.

MS. FURMAN: I would prefer that.

MR. VILA: Do you have a copy of Ackerman? Have you obtained a copy of Ackerman?

MR. KELBER: No, sir, I have not.

MR. VILA: It so happens, we have brought a copy with us. If you want to take a few moments out, we will provide you with a copy. You may regard it as belated, but there certainly has been no intent to withhold that.

MR. KELBER: I didn't think there was. If you wish to use that in cross, that's perfectly acceptable. It would not cure my objection.

MR. VILA: I understand what you are saying.

Has the witness read Ackerman or is familiar with Ackerman?

MR. KELBER: Let's go off the record.

(Discussion off the record.)

MR. KELBER: I am going to hand the reporter a document I would like marked for the record as F-17 which is entitled "The Declaration of Robert G. Engstrom Pursuant to 37 CFR Section 1.672."

(Exhibit F-17 identified.)

MR. KELBER: While you are reviewing that, I will hand the reporter to mark as Exhibit F-18 a document that on the first page bears the legend "Exhibit K," it is, in fact, an exhibit to that document.

(Exhibit F-18 identified.)

MR. VILA: Let the record note that the opposing party has been provided with a copy of Ackerman at this point.

(Witness examined the document.)

BY MR. KELBER:

Q Doctor, have you seen Exhibits F-17 and F-18 before today?

A Yes, I have.

Q In what context did you first see these documents, Doctor?

A Again, these were documents submitted to me by you in connection with this action.

Q Do you see the protocol described on the second page of F-17 which bears the legend in the top right corner, "108"?

A Yes, I do.

Q Are you familiar with assays of this type?

A Yes.

Q Let me turn your attention now to Exhibit F-18. Doctor, based on your review of Exhibits F-17 and F-18, does the information contained in Exhibit F-18 reflect raw data collected according to the assay described in F-17?

A My answer to that would have to depend upon the definition of raw data, because the data that we see in F-18 have certainly been manipulated to some extent by the use of a computer program. So the data had to be entered

into the computer in order for the program to act upon it and come up with the figures that appear on F-18.

Q Is it a correct statement that the figures that do appear in F-18 would have had to have been calculated on the basis of the raw data?

A Yes, yes.

MR. KELBER: For the record, we will object to F-18, which is Exhibit K-1 and all reliance thereon on the grounds that it is a manipulation of raw data without the raw data having been made of record.

BY MR. KELBER:

Q Let me ask you, Doctor, what is the meaning of an ED_{50} value?

A This is the effective dosage in an in vivo assay, in this case, which would reduce the rate of cholesterol biosynthesis by 50 percent.

Q What is the meaning, then, of an ED_{50} value as being indicated as greater than 1.0?

A Well, I can't attach any significance to that whatsoever. The implication is that there would be activity if a dose greater than 1 milligram per kilogram were used. But without any experimental data confirming,

that deduction would seem to be meaningless.

Q Let me direct your attention to the page of F-17 that bears the legend 110 in the top right-hand corner.

Do you see, in about the middle of the page there, two entries for ED_{50} values of greater than 1.0?

A I do.

Q Would your comments a moment ago with regard to the meaning of an ED_{50} value of greater than 1.0 apply?

A They would.

Q Is it possible in the absence of further information that a reductase inhibitor having an ED_{50} value of greater than 1.0 may have no inhibition activity at all?

A Yes.

Q Doctor, would you take a moment and review Exhibit F-18 for information relevant to the compound identified as 64-933.

A Because the printing is so unclear, I would just ask for confirmation that I believe it is the bottom of page 338 and the top of 339 which provides the data for the 64-933.

Q That is correct, Doctor.

A I do see those data.

Q At what dosage levels was this compound tested as reflected in F-18?

A At 1.0, 0.3 and 0.1 milligrams per kilogram.

Q Does the data or information presented in Exhibit F-18 reflect activity for compound 64-933 at any of these levels?

A They do not.

Q Doctor, let me turn your attention back to F-17 for a moment, and specifically the indication on the last page of that document of an ED_{50} value for compound 64-933 of 0.49. On the basis of the information contained in K-1 alone, what, if any, is your opinion as to the validity of the assignment of an ED_{50} value of 0.49 for this compound?

A Your question referred to K-1?

Q I'm sorry. F-18.

A The data provided in F-18 with respect to compound 64-933 in no way can be used to provide a figure of 0.49, an ED_{50} of 0.49 for 64-933 as shown on page 110.

Q Can any ED_{50} value be assigned to this compound, 64-933 --

A No. Excuse me.

Q -- on the basis of F-18 alone?

A No.

Q Doctor, do you recall your earlier testimony today with respect to the reliability of in vitro testing as a certain predictor of in vivo activity?

A Yes.

Q In light of your testimony regarding the in vivo testing that you have just provided and the meaning of an ED_{50} value of greater than 1.0, can you draw any correlation between the in vitro tests addressed in F-11, that's the Scallen declaration, and the in vivo test results reflected in F-17, the Engstrom declaration?

A As I recall, in the Scallen declaration, all of these named compounds were described and shown to be active in the in vitro assay, and the statement was made that they would be active in vivo. Yet, the in vivo data here clearly indicate that that is certainly not the case for 64-933 and probably not the case for the other two compounds as well.

Q And that is probably not the case because?

A Because the data are so scattered for 64-935 and 64-936. There is no significant dose and activity

relationship.

Q Thank you, Doctor. Just one second.

(Pause.)

MR. KELBER: I have no further questions at this time.

MR. VILA: Can we have a break so we can review these records?

MR. KELBER: Sure.

(Recess.)

EXAMINATION

BY MR. VILA:

Q Doctor, during your testimony, you used the word "manipulated." Would it be fair to say that what you were really describing was the input of data into a computer that was programmed to calculate the results?

A Yes. I understand that the term manipulation could have adverse connotations, which was not intended.

Q Thank you. You have made a point in your testimony that certain things didn't seem to add up or allow certain conclusions. I would ask you if in preparation for these proceedings your attorney provided you with a copy of a supplemental declaration of Robert

Engstrom that was made of record in this interference.

A I believe so.

Q Can I ask you whether you considered that in the testimony that you gave?

A I have not reviewed it recently so that I would have to say --

Q Can I ask why, as this appears to do -- it corrects some of the basis for your testimony -- that this thing seems to have been ignored?

A Do you have an exhibit number that you could refer to so that I might review that document now?

MR. VILA: Let us put the supplemental Engstrom into evidence without objection, I assume, as Exhibit CR-1, we will call it. This includes the exhibit which I believe is Exhibit Q that was provided with this declaration.

MS. FURMAN: That Exhibit 2 is pages 418 to 422 of the report.

(Exhibit CR-1 identified.)

MR. VILA: The exhibits are 418 through 422 of our record. The declaration, supplemental declaration are pages 378 and 379.

MR. KELBER: Okay.

(Witness reviewed document.)

BY MR. VILA:

Q I believe the more relevant portion of this is on the last page, 422, of the record, the last two numbers where there are handwritten changes made.

A I would have to respond that to the best of my recollection, I don't believe that I have seen this before.

MR. VILA: I find it regrettable this was not provided to you because this was part of the record and did correct the record.

MR. KELBER: I understand your regret, but speech making is for a different time.

MR. VILA: Okay.

MR. KELBER: While he is reviewing it, we will object to the introduction of the exhibit that has been marked as CR-1 on the grounds that it was submitted well after the time for direct testimony and was submitted during a period confined to testimony intended to demonstrate an absence of abandonment, suppression or concealment.

But you may continue with the questioning.

MS. FURMAN: I would like to respond to that objection by directing the witness' testimony to page 340 of the testimony submitted in the direct testimony period, which he has previously referred to in Exhibit F-18.

MR. KELBER: Let's get some ground rules straight. I don't have a problem with anybody jumping in and asking questions. I made an objection, and you are going to respond to it by asking the witness questions when we were initiating questions on the first exhibit with Dick. You have to give the witness a chance to jump back and forth. That's all I ask.

MR. VILA: I don't believe the issue here today is abandonment, suppression and concealment.

MR. KELBER: The grounds for my objection is that the declaration was submitted out of time and that no special permission was sought to submit that declaration.

MR. VILA: It has been filed by us and we elected to submit our testimony by deposition and did not under the rules, have to take direct testimony.

MR. KELBER: I think you elected to present your testimony by declaration, and the order of the EIC

assigned specific times which were extended for the presentation of direct testimony. The supplemental declaration that we are talking about now was submitted well beyond the period of the close of that period and was submitted in the period, together with a bunch of other documents, which period was confined to the presentation of evidence directed to the issue of abandonment, suppression or concealment.

Therefore, to the extent that the exhibit goes to anything other than that, we would object to it.

Why don't you proceed with the response to the objection.

MR. VILA: Yes. With the response to the objection?

MR. KELBER: Diane was going to respond to the objection by directing the witness' attention to certain pages.

EXAMINATION

BY MS. FURMAN:

Q I would like to direct your attention, Dr. Holmlund, to page 340 of your testimony which I assume you have in hand now.

MR. KELBER: What is 340? He does not have a full copy of the record.

MS. FURMAN: It is a page from an exhibit that you have already made of record which is Exhibit F-18.

THE WITNESS: Yes.

MR. KELBER: 340 at the top of the page.

BY MS. FURMAN:

Q Going to compound number 64-933, approximately 1/3 from the bottom of the page.

A I do see it.

Q What is the ED_{50} value that is listed for that number?

A I have to assume that -- I see there is the title for the column. It is listed as 1.

Q That would be greater than 1?

A No, it would not. It would be 1, as indicated. There is no greater sign there. I'm sorry. It is customary to write those signs next to the number and not separate it by an interval of space here. So I did not see the greater than. I assume that the greater than,* 1 inch to the left,* does apply to the one and ~~the~~ that greater than 1 is the value.

* for clarification

Q The value for 64-935, the ED_{50} value for 64-935?

A Is written as .49.

Q Have you previously looked at this page when you prepared for this deposition?

A Yes.

Q In your opinion, would the values that are presented on page 340 be consistent with the data presented with respect to each compound on pages 336, 338 and 339 of the record?

A Let me take these one at a time, if I may. Page 336 provides the data for 64-936 which indicate that that compound was not significantly active at the dose levels of 1 and 0.1 milligram per kilogram but that it is active at the level of 0.3 milligrams per kilogram.

Q How would you define what would constitute activity? At what level of inhibition do you consider a compound to be active at 1 milligram per kilogram?

A This is on the basis of the statistical analysis which has been carried out by the individuals who carried out the analysis here.

Q Based on your expert opinion in the field.

A My expert opinion would indicate that it is

quite appropriate to apply these techniques of statistical analysis to evaluate the presumed activity or inactivity of a compound.

Q So the techniques themselves are valid?

A I have no quarrel at this point with the techniques for determining statistical activity as used for calculating these values.

Q Looking at line 48 on page 336, there is a value for percent change. What is the value for 64-936 on line 48?

A It is given as minus 9.0.

Q Looking to line 54, there is a value for 64-936 at .3 milligram.

A Correct. That is given as minus 39.2.

Q Looking to 64-935, which appears on page 339 of the record, at 1 milligram dosage provided on line 48 of that page, the amount of suppression or decrease in activity is what value?

A 65.8.

Q So the amount of decrease for 64-935 at 1 milligram is 65.8. The amount of decrease for 64-933 at 1 milligram is 36.3; is that correct?

A For 933 -- give me the relevant pages again.

Q Line 30 on page 338.

A Yes. I will repeat, line 30 on page 338 and this is for compound 64-933 at 1 milligram per kilogram, the reduction is given as minus 36.3, which, however, is not designated as a significant reduction.

Q Not designated as a significant reduction?

A That's correct.

EXAMINATION

BY MR. VILA:

Q I would ask you, Doctor, it seemed to me that it was your testimony with regard to the compound 64-936 on record page 336, I believe it was your testimony that the result of minus 39.2 is a significant result, a significant activity.

A I'm sorry. Page 336, which line?

Q It would be line 54. It would be line 54 for the compound 64-936, which gave a result of minus 39.2.

A Yes.

Q I believe it was your testimony that that was a significant result or activity?

A Based again upon the statistical analysis which

A For 933 -- give me the relevant pages again.

Q Line 30 on page 338.

A Yes. I will repeat, line 30 on page 338 and this is for compound 64-933 at 1 milligram per kilogram, the reduction is given as minus 36.3, which, however, is not designated as a significant reduction.

Q Not designated as a significant reduction?

A That's correct.

EXAMINATION

BY MR. VILA:

Q I would ask you, Doctor, it seemed to me that it was your testimony with regard to the compound 64-936 on record page 336, I believe it was your testimony that the result of minus 39.2 is a significant result, a significant activity.

A I'm sorry. Page 336, which line?

Q It would be line 54. It would be line 54 for the compound 64-936, which gave a result of minus 39.2.

A Yes.

Q I believe it was your testimony that that was a significant result or activity?

A Based again upon the statistical analysis which

was performed on the data.

Q Yet I believe that you are saying that a result of minus 36.3 for the compound 64-933 on record page 338 which differs only by 3 percent from the result for 936 is now an insignificant result?

A Yes. Again, based upon the statistical data and these differences bring dramatically to light the kind of biological variation which occurs in biological experiments.

Q Would it be fair to say that the compound 933 on pages 338 and 339 are showing activities statistically different from a control that would be inactive in the test at any of these dosages?

A You will have to rephrase that question, please, or repeat it.

Q I'm sorry. 64-933 on page 338 and 339, are any of these results showing an indication of activity which would be statistically above a level of a zero control?

A No.

Q But I take it that you have no reason to quarrel with the results obtained for 64-935 which from the other records projected an ED_{50} of .49?

MR. KELBER: Which records are you referring to, the other records you said?

MS. FURMAN: Page 340 of the record, which is a part of Exhibit F-18.

MR. KELBER: Could you reread that question.

(The reporter read the record as requested.)

MR. KELBER: I'm not sure that the question makes sense in terms of its literal phrasing. The witness can answer, if he wants to.

THE WITNESS: Well, my response would be that I have, and there is no indication given in any of the documents that I have seen which indicate how such a value of .49 is obtained. If one looks at the data for 64-935 given on page 339, one sees that there is significant activity for that compound in lowering the rate of cholesterol synthesis at both the levels of 1 and 0.1 milligrams per kilogram, but that it is not significantly effective at the intermediate dose of 0.3 milligrams per kilogram.

BY MR. VILA:

Q Would that compound 64-935 have, in your judgment, an ED_{50} less than 1 from this data?

A I would not be able to make any conclusions based upon the fact that, again, there is no understandable dose response curve obtainable from the three sets of data obtained. One would expect that there would be -- if the compound or any compound is active at a level of, let us say, 1 milligram per kilogram and at 0.1 milligrams per kilogram it should display an intermediate display of activity at an intermediate dose. It is the intermediate dose here which indicates there is no activity for the compound at that intermediate dose of 0.3 milligrams per kilogram.

Q Recognizing the variations that are likely to occur in any assay, is it your testimony that these results are totally meaningless or is it your testimony that this is a significantly active compound, but you simply cannot determine its ED_{50}?

MR. KELBER: Objection. You got a compound question there. There is a large range between totally meaningless and the specific -- you can ask him both. Ask them separately.

MR. VILA: Strike the whole question.

BY MR. VILA:

Q Is it your testimony this compound has significant activity?

A My testimony would be that it may have. Based upon the data that are presented, I cannot make a final conclusion on it.

Q Again, referring to the 64-935, the data on record page 339. If the result at .1 milligrams per kilogram were less than the result at .3, would you have the same difficulty with this data?

A No.

Q Would you say that the differences between those two results at .1 and .3 are possibly within the margin of variation of the tests?

A Not based upon the statistical analysis.

Q How would you explain the fact that the dosage at minus 36 is higher than 39?

A I have no explanation for it.

Q And you would not accept the fact that if we look at the dose at .3, the result there, and the dose at 1, that this compound is indicating a structural activity rate of relationship?

A I would say this, that one would be unable to

publish data such as presented here and claim activity for the compound that is demonstrably active.

Q Are you sufficiently familiar with the art of the HMG-CoA reductase inhibitors to know the ED_{50} of Compactin in vivo by the type of tests?

A I don't have those figures in my mind, no.

Q I'm going to approach the question this way and assume that the in vivo ED_{50} of Compactin is 3.5 or about 3.5 in the type of assays in question.

MR. KELBER: Which type of assays are those?

MR. VILA: An in vivo assay of the type that was described in the Sandoz patent application.

THE WITNESS: Would you give me the figure and the units, please, for your assumption.

BY MR. VILA:

Q That would be milligrams per kilogram.

A 3.5?

Q Right. In the same assay Lovastatin would be 0.414.

I would like to ask you if you would judge Compactin from what you know to be a compound of interesting activity in this area.

MR. KELBER: Objection as to the use of the word "interesting." Can you be specific in what you want him to consider.

BY MR. VILA:

Q Would this be a compound that a company might find worthy of further development based on its activity level?

MR. KELBER: Excuse me. I don't have a problem with the form of the question. But are you asking him a hypothetical on the basis of the numbers you have given?

MR. VILA: I will strike the question again and I will reask it.

BY MR. VILA:

Q Would you regard that as a significant level of activity in this field?

A Let me repeat what you have given me thus far. You have given me ED_{50} values in milligrams per kilogram for Compactin and for Lovastatin the values being 3.5 and 0.414. Now your question to me is would I regard such figures --

Q Compactin as involving a significant activity in this field.

A I can't respond to that on the basis of the numbers you have given me simply because it has been some years since I have looked at the ED_{50} values for Compactin and Lovastatin.

Q Are you familiar with Compactin and the history of Compactin and the activities that have surrounded Compactin in this field?

A I know that it functions as a competitive inhibitor for HMG-CoA reductase and that it is an effective one in vivo.

Q Do you know whether or not this compound was ever placed in clinical development by any company?

A I would have to speculate to say I am quite sure that it has been.

Q That confidence would be based on what, in your understanding?

A It would be based upon the fact that it is a reference compound for use in HMG-CoA reductase inhibition studies, and that I believe it has been used clinically. I'm not positive of that. But it has been in the literature for a good number of years.

Q Is that the same thing to say as it would be

considered as a standard in this field?

A Yes.

Q A standard in terms of research, would it be fair to say that that is a level to be met or exceeded?

A Yes. When you say "to be met or exceeded," the more active the compound, the lower the term.

Q By "exceeded" I mean bettered.

MR. KELBER: Let me just ask again for the record; I have no objection to the continuing line of questioning and the line that has gone forward, as long as I am correct in the assumption that these are hypothetical questions based on hypothetical values.

MR. VILA: I don't believe it is hypothetical.

MR. KELBER: Then I object to the entire line of questioning; assuming facts not in evidence.

MR. VILA: Could I have that objection again?

(The reporter read the record as requested.)

MR. VILA: Off the record.

(Discussion off the record.)

MR. VILA: I will ask the witness one more question. He seems to be unfamiliar at this point to some extent with Compactin.

MR. KELBER: I will ask you to ask questions but do not characterize the witness' testimony.

MR. VILA: I'm sorry.

BY MR. VILA:

Q Would it be your knowledge, based on your understanding in this art, that Compactin has been considered a standard or has been used as a standard?

A Yes.

Q But you are not familiar with its relative activity or absolute activity levels; you don't recall any values in mind?

A That's correct.

Q We will continue on the hypothetical.

MR. KELBER: You give me my continuing objection again; I won't interrupt.

BY MR. VILA:

Q If a person regarded the level of a standard such as Compactin to be 3.5 and was then running a test where the test could not reveal an ED_{50} better than 1, would it be fair to say that that person is setting a rather high standard for those compounds where he wanted to be able to determine an ED_{50}?

A Again, I am troubled by your use of the word "better than 1."

Q A more active compound.

A Repeat the question again, please.

Q A compound that would have equal or better activity than indicated by an ED_{50} of 1.

A May I rephrase it a bit and see if this is what you mean?

Q Sure.

A That if a compound is under investigation and it is found reproducibly to display an ED_{50} of less than 1.0 milligram per kilogram, would I consider that to be an active compound? Yes, I would. If Compactin were run at the same time under the same circumstances and displayed an ED_{50} of 3.5 --

Q Pardon me, Doctor, I think I am not getting the question across.

The ED_{50} in vivo tests that you see in the exhibits that were run by Sandoz based on your expertise in this area, is it fair to say that these compounds could only determine an ED_{50} for compounds that had an ED_{50} of 1 or more active?

A Or less. One or less, yes.

Q My question, therefore, is were they seeking through this assay to distinguish between compounds that were more active than Compactin?

MR. KELBER: Objection. You are asking the witness to make assumptions as to what they, whoever they were. You can ask him what the evidence represents. You can't ask him what they wanted.

MR. VILA: By "they" I mean the Sandoz researchers.

MR. KELBER: You can't ask him what the Sandoz researchers wanted to do. You can ask him what it says to him but you can't ask him what was in the mind of the researchers.

BY MR. VILA:

Q I believe if you were to do what we have just discussed, run an assay where the break point for ED_{50} is 1 and the ED_{50} of Compactin is 3.5, would it be your conclusion that you are running an assay for compounds that are considerably more active than Compactin?

A Yes.

Q So, it might be fair to say that you are setting

a rather high standard?

A Yes.

Q At least relative to Compactin.

With regard to the compounds, the data which has been discussed in this testimony, the 64-933, 64-935, 64-936, would it be fair to say that if the evaluation doses in milligram per kilogram were considerably greater than used here, that these compounds could have shown an ED_{50}?

A Of what value?

Q A value at a level higher than 1.

A Could have, yes.

Q If Compactin is a standard at 3.5, would it be your testimony that a compound with an ED_{50} of 3.5 in vivo or even higher would be considered an active compound?

A Again, I would have to rephrase. Even lower. 3.5 or lower.

Q No. I am saying higher.

A Repeat the question, then, again, please.

Q If a compound were revealed to have an ED_{50} of 3.5 in the in vivo assay, in other words, the same level as we have assumed for Compactin, would it be your

judgment that that would be an active compound in this field?

A Yes, it would be, provided that I'm assuming here that these would be an authentic, statistically significant value, this 3.5 figure that you cite. Under the circumstances, I would say yes.

Q That's a fair assumption, Doctor.

Would you say that there could be levels of activity above 3.5 where you could reach the same conclusion, 3.6, 3.7? I don't believe it is necessary to try and define what limits are, but higher than 3.5 could be considered an active useful compound in this field?

A Yes, by the very definition of ED_{50}.

I wonder if I might make an addendum to the answer that I gave you for the preceding question.

Q Yes.

A If the reporter would read back, please, the question that was asked of me.

(The reporter read the record as requested.)

THE WITNESS: That's the correction I wanted to make. I could consider that it would be active, but not necessarily useful.

BY MR. VILA:

Q Why would you conclude that?

A Because for any compound for any purpose, there is always the possibility of toxicity associated with the compound.

Q I can certainly give you that, Doctor. If the compound were free of toxicity or had a therapeutic ratio acceptable to the FDA, would something above 3.5 be considered useful?

A I think then as to whether it were useful or not would depend upon the economic factors involved, how high the dose would have to be, how expensive it would have to be to produce it and to prescribe it. I would certainly go along with saying it would be classified as an active compound. But the question of usefulness I think relates to these factors that I brought out.

Q But it would, nevertheless, in your mind at a dose bring the appropriate response in the body the same as Compactin might?

A It would be classified as an active compound.

Q As an HMG-CoA reductase inhibitor?

A Yes, in vivo.

Q I believe you started your testimony with a statement to the effect that a compound that would be active in vitro would not necessarily be active in vivo because of a number of things that can bear on the activity of a compound when administered to an in vivo system; is that correct?

A Yes.

Q Are you sufficiently familiar with the area of HMG-CoA reductase research to have an idea of how many compounds roughly have been tested in vitro and how many compounds have been tested in vivo?

A I couldn't give a number to that. I'm sure that a lot have been.

Q In any series of compounds in pharmaceutical research, if compounds active in vitro were found to be active in vivo subject to the exceptions that can always be encountered in research, would it be a fair assumption that for that given series, that it is likely that a compound active in vitro would be then active in vivo?

A You are referring to other members of a series of compounds, analogs.

Q Where there is substantial background in the

series of both in vivo and in vitro activity. We recognize that there are always exceptions.

A I would have to say yes.

Q Would you refer to Exhibit F-11, which is the Scallen declaration.

A Yes. I have the declaration. Is there anything in particular you would like me to refer to?

Q Yes. Paragraph 3, please.

A Yes.

Q Am I correct that it was in your previous testimony that you had a disagreement with this statement?

A With one word in the statement.

Q Which was that?

A "Would." The sentence starting with "If a compound possesses this activity, it would be useful for lowering."

Q You would change that to what word?

A "Might."

Q The first sentence of paragraph 3, I will read it to you, if that's appropriate. It refers to compounds sent to him by Sandoz. If Dr. Scallen had substantial background experience with compounds of general and

related classes, including compounds even of the class of the subject matter in this invention but with or without that experience with the compounds of this invention but with many compounds of this type of class, in particular heterocyclic derivatives, and was aware of the fact that to the extent it tested in vivo they were showing activity and that these compounds had been active in vitro in his own tests.

Would this statement then be a reasonably fair statement?

MR. KELBER: Can I have the question read back.

(The reporter read the record as requested.)

MR. KELBER: Can I ask you to rephrase it, please.

MR. VILA: Why don't you strike the whole question out.

BY MR. VILA:

Q If Dr. Scallen had a evaluated a large number of compounds in the general area of research involved here, HMG-CoA reductase of the type Compactin --

MR. KELBER: Let me jump in to avoid a long, frustrating activity. You are asking him to speculate as

to things that you are assuming.

MR. VILA: I'm not trying to assume anything.

MR. KELBER: You have to give him facts. You asked him to speculate if Dr. Scallen had done this, then that. If you want to give him a hypothetical, I have no strong objection other than hypotheticals don't bear on the questions at issue. You can give him a hypothetical but you have to give him facts, not speculation. If you want to set up a hypothetical situation and ask him to respond to that, I have no problem.

MR. VILA: Strike that and I will try it again. I will phrase it as a hypothetical question.

BY MR. VILA:

Q If Dr. Scallen had observed that many of the compounds in this area of research were in fact active both in vitro and in vivo, would the statement in paragraph 3 of the Scallen declaration be a fair statement?

A No.

Q Subject to the usual exceptions that can occur in biological research?

A I think adding that phrase nullifies the

statement that I think you are trying to make here. Let me rephrase my objection to this entire paragraph. As I said, it really applies to two uses of the word "would." In my mind, the word "would" implies complete, 100 percent assurance, no possible examples which would not fall into that category. That's where I take exception. I would accept either "might be useful." I would even accept "would probably be useful." Insertion of the word "probably" indicates that there is a reasonable element of doubt that some compounds may be encountered which are active in the in vitro assay but yet inactive in the in vivo assay.

Q Would you accept, subject to exceptions that might occur, that the failure to find that activity would be considered an exception, that there would be a reasonable expectancy against the background of the hypothetical I gave you?

A I think I probably would accept that.

Q Then if this statement were qualified to read that subject to exceptions, this is an acceptable statement to you?

A Yes. I think pretty much so, yes, recognizing

that exceptions can occur at any time, including the compounds that one is testing.

Q Is it a fair statement that you are able to criticize the results here because of absolute values of these compounds as determined in these assays, or is it possible that they can be criticized because the tests were run at a very stringent or a very high standard of pursuing compounds with an ED_{50} of 1 or less, 1 or higher?

MR. KELBER: I'm going to object to the question on the basis of the use of the pejorative term "criticizing." As far as I know, Dr. Holmlund has been asked specific questions and given answers in response to it. Criticize means a lot of things. If you can ask him what the testimony that you are concerned about and the basis for that, that would be fine.

BY MR. VILA:

Q Do you understand the question?

A Not completely. It seems as though we are shifting ground a bit because we are on page 76 dealing with paragraph 3 and it seemed to me that the line of questioning you now embarked upon extends beyond this. If

so, I would like to know what you are referring to.

Q I beg your pardon. I think we were concentrating on 3 and in your answer you made reference to the results that you had been previously testifying to here, that you said that these were probably in the category of the exceptions.

MR. KELBER: I don't think that is an accurate clarification of his testimony at all.

MR. VILA: Maybe we ought to read back his testimony, the last question.

(The reporter read the record as requested.)

MR. VILA: I'm assuming the compounds he is referring to are the ones he had testified about previously, 64-936.

THE WITNESS: That was not my intention.

BY MR. VILA:

Q It was not your intention to say these were an exception to your previous testimony?

A My understanding is that we were dealing with a hypothetical situation in terms of evaluating this statement. And hence my remark was addressed to that hypothetical situation, that in any hypothetical situation

where any list of compounds were being tested, that this statement as it stands here would not be acceptable.

Q If such a rule applied here, if that were in the background of Dr. Scallen's mind, you are not saying that the results in here are an exception or come under the exception that we discussed?

MR. KELBER: Again, you are asking him to speculate about what would be if something was in someone's mind. He can't get in somebody else's mind. Give him the hypothetical and ask him his opinion.

MR. VILA: Well, the hypothetical has been out there and I believe that he has testified that he would agree with Dr. Scallen here if the statement were qualified by saying "subject to exceptions." Some reference seems to have been made to the compounds on which we specifically took testimony today.

MR. KELBER: I think we have clarified that, Dick, twice now. If you want to go back and read it again, we can. It said that one is testing. He made it clear and said in response to your subsequent question that he was referring to the hypothetical that you had set up, not an actual example.

MR. VILA: Not the actual examples in the case, okay.

BY MR. VILA:

Q Prior to becoming involved in this interference, were you aware that Dr. Scallen was screening compounds for Sandoz?

A No, I was not.

Q Do you know Dr. Scallen?

A I don't know him personally. I certainly know him by reputation. I have heard him speak at several scientific meetings.

Q How would you regard that reputation?

A I would prefer not to respond to that.

MR. KELBER: We will be willing to stipulate for the record, if it helps, that he is a noted researcher in this field.

MR. VILA: Do you have any more questions?

MS. FURMAN: I have a couple of questions.

I am going to ask you another hypothetical. If you had the -- let me just refer to -- I would like to put into the record as Exhibit CR-2 pages 215 and 216 of the testimony which provide the IC_{50} values for the separate

compounds.

(Exhibit CR-2 identified.)

EXAMINATION

BY MS. FURMAN:

Q On page 216, an IC_{50} value is given for 64-936. That value is.53. If that were the best IC_{50} data you had in hand for a series of compounds, would you feel justified in believing that you could have in vivo activity over that whole series of compounds?

A I'm afraid I would be cautious enough to say again that I might have or would probably have. I would expect to have.

Q But there could be some question?

A Yes.

Q So you don't think it would be permissible for you to make a flat-out conclusion that you would have in vivo activity based on data such as this as your best data?

A That's correct.

MS. FURMAN: That's all I have on that.

BY MS. FURMAN:

Q I just have a couple of other questions going to

your background. I understand there is some informal relationship between you and Mr. Kelber, if I'm not mistaken. Have you known him for a number of years?

A I have not. It turns out that he called to my attention yesterday that he apparently had been a student in a class of mine which he didn't know when he contacted me and which I certainly did not know when I agreed to serve here.

Q Have you previously served as a witness for the Oblon, Fischer firm.

A No, I have not.

MR. KELBER: Let me correct the record. It is Oblon, Spivak.

MS. FURMAN: Oblon, Spivak.

BY MS. FURMAN:

Q You have numerous publications in the field of cholesterol biosynthesis based on your CV, which has been made of record.

A Is that a question?

Q No. Do you have publications in the field?

A Most of my publications with respect to inhibition relates to inhibition of ~~sterile~~ sterol synthesis. CEH

Because, as I indicated in my testimony earlier to Mr. Kelber, the types of organisms that most of my studies were done with were varying types of microorganisms, protozoan, a yeast, so forth.

Q Do you have any publications dealing with the HMG-CoA reductase enzyme?

A No publications, but I have had a graduate student who has worked upon that enzyme from a microorganism and purified it.

Q Have you done any work with HMG-CoA reductase inhibitor compounds?

A Again, it is restricted to the work that this one graduate student has done.

Q That comprises isolating the enzyme, did you say?

A Yes.

Q But not inhibiting it; is that correct?

A No. That was the example where I believe we used Compactin and found that it functioned as a competitive inhibitor for that enzyme from this particular source.

Q So, you have found in your own research that

Compactin is effective?

A Yes.

Q Did you perform an assay of the activity of Compactin?

A I did not.

Q But it was done in your lab?

A Yes.

Q Can you describe that assay for us.

A I probably can't give you complete details of it at this point in time because it was a number of years ago. But it was along the lines of I'm sure that what we did was to make use of radioactively labeled HMG-CoA, add the ingredients, including an ~~ED pH~~ NADPH generating system to the mixture, which comprised the enzyme ~~and the~~ in various stages of purification, and then allowed the reaction to proceed, terminate the reaction after a specific period of time, convert the mevalonic acid, which is the product, to the lactone thereof and then separated the lactone from the reaction mixture and determined the amount of radioactivity in that separated product.

Q Is that fairly consistent with the in vitro assay presented in the exhibits?

A Yes.

Q What would you think about an assay where the overall amount of radioactivity was measured not as to mevalonate but as to the end product of cholesterol.

MR. KELBER: Objection. I understand your question. But if you focus it. What do you think of it is awfully broad.

BY MS. FURMAN:

Q Would you find an assay which measured radioactivity levels in cholesterol end product as opposed to mevalonate, would you find that a precise assay for measuring HMG-CoA reductase inhibition activity?

A No.

Q You would not?

A Let me think about that for a moment. I would say no.

Q Why would you say no?

A I say that because if one starts and it will depend upon which substrate one starts with. One could start with something as simple as acetate because cholesterol is made from acetate, HMG-CoA is a product somewhere down the line in the overall process. Even

after the conversion of HMG-CoA to mevalonate, there are a large number of steps that must occur before the final product, cholesterol, is made.

In looking at such an assay and estimating the effect upon cholesterol, there are any one of a number of steps which could actually be the one where the inhibition occurs and not necessarily at the level of the reductase.

Q How many of such steps would actually follow the formation of mevalonate? Would it be on the order of 10?

A I suspect somewhat more than that. Between 10 and 20, I believe.

Q If someone provided an IC_{50} of .54, coming out of -- let me rephrase that question. If somebody provided an IC_{50} of 1 times 10 to the negative 8 micromolar, based on that assay --

A You want to restate that figure.

Q If someone offered you an in vitro assay result of 1 times 10 to the negative 8th micromolar, based on that assay where the amount of the cholesterol radioactivity was being determined, could you consider that result reliable?

MR. KELBER: Reliable as to what?

BY MS. FURMAN:

Q As to a level of HMG-CoA reductase inhibition activity.

THE WITNESS: I will rephrase the question or restate it so that I know what I am answering.

BY MS. FURMAN:

Q I'm sorry.

A If someone completed an in vitro assay and found an IC_{50} value of 1 times 10 to the minus 8th micromolar of such a compound, could I conclude what?

Q Let me qualify. An in vitro assay where the amount of product cholesterol was being quantified, not the mevalonate. Would the result be significant to you?

A I don't know that there is any in vitro assay, any in vitro assay which determines cholesterol as the final product.

Q You are not aware of such an assay that would measure the amount of radiolabeling in the product cholesterol of the entire pathway?

A You are again referring to an in vitro assay?

Q Correct. For HMG-CoA reductase inhibition.

A I think you are asking the same sort of question

you did before. Let me point out again that if you are going to deal with an in vitro assay and measure the amount of cholesterol which is produced, you have to have in that in vitro reaction mixture all of the enzymes, 30 or more enzymes depending on what your starting material is. If you start with acetate you would need that many, start with HMG-CoA you would need as I suggested around 10 to 20 enzymes, all of which would have to be active, all of which would have to be supplied with the necessary cofactors. It is almost impossible to be assured, to set up an in vitro assay where you can be assured that all those necessary requirements are present.

Q But if someone gave you the figure I just recited as a value determined by that assay, would you consider it significant?

A If your question -- this is an in vitro assay where the starting substrate is what?

Q Radiolabeled acetate, end product is radiolabeled cholesterol?

A And you find the value for IC_{50}. Obviously that value is significant, again, for the in vitro test.

Q Significant as to what?

A As to exerting an inhibitor effect on cholesterol biosynthesis.

Q How about HMG-CoA reductase inhibition?

A I don't think one can draw that conclusion directly upon the data you have presented me.

Q So you couldn't really predict based on that data whether a class of compounds could have in vitro activity as HMG-CoA reductase inhibitors?

A Not with that kind of a measurement.

MR. KELBER: Can I ask the relevance of this particular line of questioning? It is way beyond the scope of anything that was asked on direct.

MS. FURMAN: I think it is within the scope of establishing the credibility and the knowledge of the witness as an expert witness.

MR. KELBER: To the extent it is confined to that, I have no problem.

BY MS. FURMAN:

Q Just some further general questions. Were you aware of the Sandoz work in the HMG-CoA reductase area prior to this proceeding?

MR. KELBER: Let me object and ask, do you mean

published?

MS. FURMAN: The published work.

THE WITNESS: I don't recall having been aware of it. Let's put it that way.

BY MS. FURMAN:

Q So you don't really have any familiarity with the Sandoz literature in this area?

A No.

Q Do you have familiarity with any literature in this area, any published literature in the HMG-CoA reductase inhibition area?

A Yes.

Q Can you give me an example of some publications that you are aware of.

A I can't cite author and source, but certainly a number of papers involving the use of Compactin for this purpose, and I think I probably saw something with respect to Lovastatin as well. This is years ago.

Q Those would be hydrogenated naphthol derivatives?

A I cannot respond to that because I don't recall the structure of Compactin.

Q You don't recall the structure of Compactin?

A No.

Q Are you familiar with any heterocyclic inhibitors of HMG-CoA reductase?

A Not so that I could draw any structures for you.

Q Are you familiar with any of the findings in the art concerning these compounds, the activity levels of these compounds?

A I think I have already responded to that kind of questioning earlier, that I don't have any IC_{50} or ED_{50} values in mind for any of these compounds.

Q Do you know the structure of mevinolin?

A Close. It is fairly similar in structure to mevalonate lactone itself. But I don't recall its exact structure.

Q Are you examining the data presented in this testimony purely from an objective standpoint without any real background in the literature? Is that the case?

A No.

Q Are you able to interpret the data and the testimony in light of prior literature that you have

become familiar with?

MR. KELBER: Have you asked him a question with respect to that? You ask him a question with respect to prior literature and he will give you his answer.

BY MS. FURMAN:

Q Are you familiar with the Sandoz fluvastatin compound?

A No.

Q You do not know its structure?

A I do not.

Q Do you know its structure activity relationships which are in the literature?

A I do not.

MR. KELBER: Assuming facts not in evidence. But he is responding to your question without it.

BY MS. FURMAN:

Q Do you know the structure activity relationships for the Pyrazole HMG-CoA reductase inhibitor?

A No.

Q For the Pyrimidine?

A No.

Q So you yourself have never actually run an in

vitro or in vivo assay of an HMG-CoA reductase compound?

A That's correct.

MS. FURMAN: That's all.

MR. VILA: I just would like to take a couple of minutes and go back to Exhibit F-18, which is the data relating to ED_{50} determinations. I would like to refer you to the data on 336.

(Pause.)

MR. VILA: Strike that.

BY MR. VILA:

Q It is page 339. With regard to the data on the compound 64-935, I believe you said that you cannot accept the determination of an ED_{50} based on the data.

A There is no indication as to how -- I think this is the one for which an ED_{50} of .49 is given.

Q That's correct?

A There is no indication as to how that value is obtained.

Q Is there not a relatively standard way of determining ED_{50} from data?

A There is, but it can't be applied in this instance because the data obtained for the 0.3 milligram

per kilogram value are not significant.

Q Isn't it true from the record here that people doing these evaluations did find an ED_{50}?

MR. KELBER: I'm sorry? People? Doing these evaluations? Which people?

MR. VILA: Sandoz people.

MR. KELBER: You are asking him, again, to leap into the minds of people that we can't even identify by name.

BY MR. VILA:

Q Doesn't the record that you have seen today show an ED_{50} for this compound?

A Yes.

Q .49, as you indicate. But you disagree that an ED_{50} could be reasonably obtained from this information?

A There is no indication how the author of that figure of 0.49 obtained it.

Q Could he have been using a scientifically accepted method and come up with an ED_{50} on the basis of your experience?

A I find that difficult to accept on the basis of the fact that the intermediate dosage level of 0.3

milligrams per kilogram is not significant.

Q I would refer you to the result at 1 milligram per kilogram for this compound 64-935, the minus 65.8, I believe it is. Does that show that this compound is active at that dose?

A Yes.

Q I would like to ask you a question about the compound 64-933 as it appears on record pages 338 and 339. There are three results there. I believe here again you have testified that there is no ED_{50} for these compounds.

A There is no indication of any significant activity at any of the dose levels.

Q Can you say based on these tests that this compound would be inactive in vivo?

A At the dose levels tested, yes.

Q At a higher dose level? Can you make that statement?

A I could not make that statement.

Q Then that does not rule out the possibility this compound could be judged active at a higher dose than tested here?

A That's correct.

Q Would it be your same testimony for the compound 64-936 on record page 336?

A Yes, it would be. Since there are no testing results available there is always the possibility for any compound, that at a higher dose, it may manifest activity.

Q Do you regard this compound as showing significant activity at the dose level of .3 milligrams per kilogram?

A Yes.

MR. VILA: I have no further questions. I think maybe we should stop, take some kind of a break.

MR. KELBER: I will be done with redirect in about 15 minutes, if you want to push through.

MR. VILA: Sure.

EXAMINATION

BY MR. KELBER:

Q In cross-examination, you offered testimony with regard to the statistical analysis that was done with respect to the in vivo testing. Do you recall that testimony?

A Yes.

Q Did you perform that statistical analysis?

A No.

Q Is that statistical analysis, in fact, summarized as part of the exhibit?

A Yes.

Q Did you select the levels at which these compounds were to be tested?

A No.

Q Is it necessary to know the structure of a particular compound reflected in this in vivo assay to assess whether or not a reliable ED_{50} value is given by that assay?

A No.

Q In fact, the declaration that is F-17 does not reflect the structure of those compounds, does it?

A Does not.

Q Is it necessary to know the structure of a compound to assess whether or not data obtained from in vitro testing reflects activity for the identified compounds?

A No.

Q In fact, Dr. Scallen did not know the structure

of those compounds when he performed the testing reflected in Exhibit F-10, did he?

A That's correct.

Q Doctor, you testified at some length with regard to the connection between in vitro testing and activity in vivo. My question to you is testing, finding activity in vitro, without any follow-on in vivo testing, does that in vitro testing constitute a documentation of in vivo activity?

A No.

Q We talked about things that a researcher might or might not do in your testimony. Can you recount for me the level of skill of a researcher in this field of cholesterol biosynthesis inhibition.

A Well, for somebody to be well versed in the field, they should have a doctorate. It is certainly possible for people, even high school graduates for that matter, to be trained to perform an assay according to cookbook procedures. But to really understand all the ramifications and the significance of why things are done as they are requires a higher level of sophistication.

Q Do you recall offering testimony with regard to

the fact that compounds represented in the testing that is summarized in F-18 of the in vivo testing, although apparently not active at all levels of the 1.0 milligram per kilogram level might be active at higher levels? Do you recall that testimony?

A Yes.

Q Is it also a correct statement that they might not be active at any level?

A It is.

Q We have discussed one compound, and I believe that the number of that compound referred to in F-18 is 64-935, which the in vivo assay reported significant activity at the 1.0 milligram per kilogram and the 0.1 milligram per kilogram value but no significant activity at the 0.3 milligram per kilogram value.

Do you recall that testimony?

A Yes.

Q On the basis of your experience and knowledge, can you offer an explanation as to why the assay reflected activity at the higher and lower values but not in the intermediate values consistent with this assay?

A I really can't offer anything which would be

definitive. Under circumstances of this sort, what one does is to repeat the entire experiment at the indicated dose levels and perhaps even expand it to a couple of additional dose levels.

MR. KELBER: I have nothing further.

EXAMINATION

BY MR. VILA:

Q I believe on the reexamination you indicated that in your judgment a compound active in vitro would not be active in vivo.

MR. KELBER: I will object. I don't think that is a correct characterization of his testimony.

THE WITNESS: No.

MR. VILA: Could we go back and get that testimony.

MR. KELBER: I would be willing to offer you the latitude to go back and establish that testimony if you want to ask the foundation question. It is so far advanced in time from where we are now that it is difficult to identify from the stenographic record without having previously marked it.

MR. VILA: It was in response to the question

only about three or four minutes ago.

(The reporter read the record as requested.)

MR. VILA: My recollection must be faulty. I withdraw the question.

(Pause.)

MR. VILA: I don't think we have any further questions.

MR. KELBER: Before we go off the record, Doctor, I thank you for your attention. The transcript of this deposition will be prepared, forwarded to me and I will forward it on to you.

MS. FURMAN: We would appreciate a copy.

MR. KELBER: When you receive the transcript, you should review it to make sure that it is an accurate reflection of your testimony today. And there will be an errata sheet for indicating errors in the record and then you may sign and return it to me and we will attempt to file it.

(Whereupon, at 1:45 p.m., the deposition was concluded.)

Chester E. Holmlund

CHESTER E. HOLMLUND

Subscribed and sworn to before me this 6th day of April, 1993.

Notary Public

My Commission Expires June 1, 1996

CERTIFICATE OF NOTARY PUBLIC & REPORTER

I, BRENDA M. SMONSKEY, the officer before whom the foregoing deposition was taken, do hereby certify that the witness whose testimony appears in the foregoing deposition was duly sworn; that the testimony of said witness was taken in shorthand and thereafter reduced to typewriting by me or under my direction; that said deposition is a true record of the testimony given by said witness; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this deposition was taken; and, further, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

Brenda Smonskey
Notary Public in and for the
District of Columbia

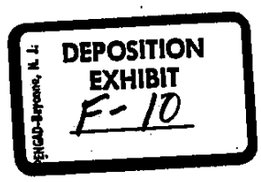
My Commission Expires APRIL 14, 1996

I. Notarization:

I have read the following and certify that this curriculum vita is a current and accurate statement of my professional record.

Chester E. Holmlund Date: 3/8/88

Chester E. Holmlund
Professor of Chemistry



II. Personal Information:

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Education:

B.S.	Worcester Polytechnic Institute	1943
M.S.	Worcester Polytechnic Institute	1951
Ph.D.	University of Wisconsin, Madison; Biochemistry	1954

Chester E. Holmlund

III. Academic Activities:

A. Percentage of official time (last three years) devoted to:

Instruction 25% Research 70% Other 5%

B. Positions held:

Higher Education:

Research Assistant, University of Wisconsin, Madison	1951-54
Associate Professor, Dept. of Chemistry, Univ. of Maryland	1967-70
Professor, Dept. of Chemistry, University of Maryland	1970-present

Other than higher education:

Research Chemist, E. I. DuPont deNemours Company	1946-47
Research Chemist, United States Envelope Co.	1948-51
Research Biochemist, Department of Mycology, Lederle Laboratories, American Cyanamid Co.	1954-57
Group Leader, Fermentation Biochemistry & Microbiology Departments, Lederle Laboratories, American Cyanamid Co.	1957-67

C. E. Holmlund - Publications

IV. Publications:

1. "Bacterial levans of Intermediate Molecular Weight, " J.R. Mattoon, C.E. Holmlund, S.A. Schepartz, J.J. Vavra, and M.J. Johnson, Appl. Microbiol. 3, 321 (1955).

2. "Chemical Hydroxylation of 12α-Deoxytetracycline," C.E. Holmlund, W.W. Andres and A.J. Shay, J. Am. Chem. Soc. 81, 4748 (1959).

3. "Microbiological Hydroxylation of 12α-Deoxytetracycline," C.E. Holmlund, W.W. Andres, and A.J. Shay, J. Am. Chem. Soc. 81, 4750 (1959).

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Chester E. Holmlund

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"Enhancement of Sterol Synthesis by Saturated and Monounsaturated Phosphatidylcholines in Culture of L-929 Cells," G.N. Thomaidis and C.E. Holmlund, 65th Annual Meeting, Federation of American Societies for Experimental Biology, Atlanta, Georgia, May 12-17, 1981.

"Phospholipid Composition and Sterol Efflux from L-929 Cells," Y. Son and C.E. Holmlund, 73rd Annual AOCS Meeting, Toronto, Canada, May 2-6, 1982.

"Isolation, Characterization, and Chemical Modification of Macrocyclic Trichothenes," B. B. Jarvis, G. P. Stahly, G. Pavanasasivam, C. E. Holmlund, E. P. Mazzola and R. Geohegan, 16th MARM, April 21-23 (1982).

"Effects of SICF-3301 on Growth and Composition of Free and Esterified Sterols in Saccharomyces cerevisiae," C. Jones and C.E. Holmlund, ASBC/AAI Annual Meeting, St. Louis, Mo., June 3-7, 1984.

"Metabolism of β-Hydroxy-β-Methylglutaryl Coenzyme A (HMG-6A) in Tetrahymena pyriformis: Presen e of HMG-CoA Lyase," K. Prasanna and C.E. Holmlund, ASBC/AAI Annual Meeting, St. Louis, MO. June 3-7 (1984).

"Analysis of Free and Esterified Sterols of Crithidia fasciculata at Various Times of Culture," C. Jones and C.E. Holmlund.

C. E. Holmlund - Curriculum Vita

B. Other Creative and Scholarly Activities:

PATENTS:

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2. 12α-hydroxytetracyclines. American Cyanamid Co., C.E. Holmlund, A. Green and A.J. Shay, Ger. 1,092,906. March 4, 1959.

3. Pregnanes. C.E. Holmlund, L.D. Feldman, H.M. Kissman, and M.J. Weiss, American Cyanamid Co., U.S., 3,047569, July 31, 1962.

4. 12α-hydroxylation of 12αdeoxytetracyclines. C.E. Holmlund and W.W. Andres. American Cyanamide Co. U.S., 3,043,877. July 10, 1962.

5. 16α-hydroxylation of Steroids by Staurophoma Species. C.E. Holmlund, R.J. Blank, and R.H. Evans, American Cyanamid Co. U.S., 3,071,516. January 1, 1963.

6. 6β-hydroxy Steroids. C.E. Holmlund, L.I. Feldman, R.H. Evans, S. Berstein, and J.P. Dusza. American Cyanamid Co. U.S., 3,071,516. January 1, 1963.

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9. Preparation of 1,2-Disubstituted Steroids. L.I. Feldman, C.E. Holmlund, and K.J. Sax. American Cyanamid Co. U.S., 3,297,687. January 19, 1967.

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11. Fusarium Fermentation, R.H. Evans, Jr., M.P. Kunstmann, C.E. Holmlund, and G.A. Ellestad. American Cyanamid Co. U.S. 3,546,073. December 8, 1970.

12. Preparation of 5,6-dihydro-5-hydroxy-6-propenyl-2-pyrone by Fermentation and Derivatives Thereof. R.H. Evans, J., and C.E. Holmlund, American Cyanamid Co. U.S. 3,701,787. October 31, 1972.

13. Tetracyclic Lactone Antifungal Agents. C.E. Holmlund, R.H. Evans, Jr., and G.E. Ellestad. American Cyanamid Co. U.S. 3,564,019. February 16, 1971.

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 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.

EXHIBIT E1

Sandoz HMG-Co-A Reductase
Screening Book VI
page 56-57

12-13-84

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Sandoz Compounds Tested for HMG-CoA Reductase

1) Following compounds weighed out to make 10^{-2} M dilution:

63-364 (25489)	1.30 mg	in 13.015 ml	DMA
63-365 (25490)	1.60 mg	in 18.836 ml	DMA
63-366 (25496)	1.50 mg	in 15.473 ml	DMA
63-369 (25512)	.5 mg	in 5.338 ml	DMA
63-162/3 (25500)	1.80 mg	in 19.284 ml	DMA
63-270/2 (25501)	.70 mg	in 15.411 ml	DMA

Following compounds saponified in 50° waterbath for 2 hrs:

2) Microsomes were made on 12-10-84 and kept frozen at -80° until thawed and rehomogenized for this experiment. Protein concentration of microsomes .180 X 10 X .68 = 1.18 mg/ml

3) Samples were pre-incubated 20 minutes in 37° waterbath.

4) 20µl 2mM NADPH added to each sample with repeating Eppendorf.

   20µl [^{14}C]HMG-CoA added to each sample with repeating Eppendorf.

5) Samples incubated 20 min in 37° waterbath.

6) Reaction stopped with addition of 50µl conc. HCL (12M).

7) 100µl [^{3}H]MVA added to each sample with pipetman.

8) Samples on benchtop 60 minutes before putting samples on columns.

9) Factor for calculations 48.44.

RESULTS OF EXPERIMENT:

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12-13-84

PROGRAM #. 10
REGION A. LL-UL= 0- 8 LCR= 0 BKG= [illegible]
REGION B. LL-UL= 24- 156 LCR= 0 BKG= [illegible]
NUCLIDE 1 = 0 NUCLIDE 2 = 0
TIME= 10.00 QIP= SIE/AEC SCR= B/A K= 1.000

93578 / 96269 x 50 = 45.49

³H Recounted

P#	S#	TIME	CPMA/K DPM1/K	%DEV	CPMB/K DPM2/K	%DEV	QIP	FLAGS	B/A	[illegible]	Notes		
10	1	10.00	20582.7 67534.5	.44	93.20 43.27	6.62	456.		[illegible]	[illegible]			1.18"
10	2	10.00	7170.75 0.00	.75	55512.3 56205.0	.27	501.		7.7[illegible]	[illegible]			
10	3	10.00	12318.5 62667.1	.57	194.60 267.29	4.35	433.		[illegible]	[illegible]	Blank		
10	4	10.00	10848.5 58428.8	.61	200.40 285.65	4.29	425.		[illegible]	[illegible]	Blank		
10	5	10.00	11003.1 57072.2	.60	3214.70 5551.65	1.11	427.		[illegible]	[illegible]	Buffer A .102		
10	6	10.00	11823.8 61181.7	.58	3211.50 5568.35	1.11	424.		[illegible]	[illegible]	Buffer A .102	1.00	
10	7	10.00	12406.5 64623.8	.57	3391.40 6315.88	1.08	422.		[illegible]	[illegible]	DMA .096		
10	8	10.00	12170.4 63821.3	.57	3156.30 5556.64	1.12	421.		[illegible]	[illegible]	DMA .096	.94	
10	9	10.00	11314.1 57756.3	.59	161.50 213.54	4.73	437.		[illegible]	[illegible]	Imm	.00	100
10	10	10.00	12186.1 65777.3	.57	256.70 384.87	3.81	424.		[illegible]	[illegible]	10^{-1}	.02	98
10	11	10.00	12123.3 64522.7	.57	519.80 880.36	2.73	427.		[illegible]	[illegible]	-2	.10	90
10	12	10.00	11927.2 61719.5	.58	1557.40 2823.10	1.59	430.		[illegible]	[illegible]	-3	.43	55
10	13	10.00	11836.3 60625.0	.58	2375.40 4737.52	1.24	425.		[illegible]	[illegible]	-4	.75	20 I
10	14	10.00	11727.9 60152.4	.58	2674.40 5310.16	1.18	427.		[illegible]	[illegible]	-5	.66	9 I
10	15	10.00	12721.4 64964.0	.56	3280.00 6060.68	1.10	426.		[illegible]	[illegible]	-6	.91	3 I
10	16	10.00	12866.7 66069.7	.56	3258.00 6023.92	1.11	427.		[illegible]	[illegible]	-7	.89	5 I
10	17	10.00	12062.2 61056.6	.58	3107.30 5725.33	1.13	430.	(24291) Compaction	[illegible]	[illegible]	-8	.92	2 I
10	18	10.00	11753.4 63062.9	.58	218.60 316.24	4.12	424.		[illegible]	[illegible]	10^{-2}	.01	99
10	19	10.00	11535.3 60525.9	.59	318.10 504.76	3.45	425.		[illegible]	[illegible]	-3	.04	96 I
10	20	10.00	11261.1 60390.9	.60	603.00 1045.56	2.54	425.		[illegible]	[illegible]	-4	.13	86 I
10	21	10.00	11621.5 61450.8	.59	1007.80 1803.62	1.98	426.		[illegible]	[illegible]	-5	.25	73
10	22	10.00	10583.5 56002.5	.60	2628.40 4642.96	1.23	429.		[illegible]	[illegible]	-6	.84	10 I
10	23	10.00	11265.4 58243.8	.60	2546.80 5468.86	1.16	425.		[illegible]	[illegible]	-7	.92	2 I
10	24	10.00	10555.7 54757.2	.61	2737.20 5028.53	1.21	432.	(24291) 62-320/Nov-4	[illegible]	[illegible]	-8	.90	4 I

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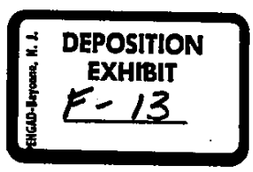
SA	TIME	CPMA/K CPM1/K	%DEV	CPMB/K CPM2/K	%DEV	DIP	FLAGS	FCR	[illegible]			
25	10.00	11971.1 60607.9	.56	2465.60 4511.66	1.27	432.	10^-2	[illegible]	[illegible]	.71	24 I	
26	10.00	12009.1 61665.6	.58	2502.20 5344.66	1.17	429.	-3	[illegible]	[illegible]	.86	9 I	
27	10.00	11970.3 61483.4	.56	3012.20 5572.15	1.15	426.	-7	[illegible]	[illegible]	.89	5 I	
28	10.00	11459.2 51076.7	.59	2656.90 5340.51	1.17	430.	-5	[illegible]	[illegible]	.90	4 I	
29	10.00	11745.5 59385.1	.58	2775.20 5164.65	1.20	431.	-6	[illegible]	[illegible]	.84	10 I	
30	10.00	11447.1 55962.5	.59	2603.50 5166.67	1.19	426.	-7	[illegible]	[illegible]	.86	9 I	
31	10.00	13366.9 65366.4	.55	3153.90 5838.62	1.12	425. (25489) 63-364	-8	[illegible]	[illegible]	.82	13 I	19
32	10.00	11544.3 62787.6	.58	246.70 367.48	3.89	430.		[illegible]	[illegible]	.02	98 I	
33	10.00	10624.9 55537.4	.61	412.50 667.23	3.05	431.		[illegible]	[illegible]	.08	92 I	
34	10.00	12111.1 67257.6	.57	716.00 1248.47	2.33	430.		[illegible]	[illegible]	.16	83 I	
35	10.00	11755.5 58365.1	.59	1952.70 3563.63	1.43	431.		[illegible]	[illegible]	.58	58 I	
36	10.00	12313.9 62437.3	.57	2925.50 5375.74	1.17	430.		[illegible]	[illegible]	.84	11 I	
37	10.00	11425.9 56365.1	.59	2682.70 4888.43	1.22	437.		[illegible]	[illegible]	.85	10 I	
38	10.00	12475.8 62511.6	.57	3041.80 5588.37	1.14	431. (25490) 63-365		[illegible]	[illegible]	.87	8 I	20
39	10.00	11757.? 60468.4	.58	655.00 1502.14	2.14	433.		[illegible]	[illegible]	.21	78 I	
40	10.00	11450.2 57757.9	.59	1963.50 3454.64	1.44	434.		[illegible]	[illegible]	.57	39 I	
41	10.00	12775.5 63608.6	.56	2880.70 5258.52	1.17	435.		[illegible]	[illegible]	.81	14 I	
42	10.00	12709.3 63746.6	.56	3125.20 5733.39	1.13	432.		[illegible]	[illegible]	.80	6 I	
43	10.00	12097.7 60685.8	.57	3059.30 5623.40	1.14	431.		[illegible]	[illegible]	.90	4 I	
44	10.00	11673.6 58151.1	.55	2683.80 5705.71	1.17	430.		[illegible]	[illegible]	.88	6 I	
45	10.00	12125.7 61611.9	.57	2971.50 5473.37	1.16	429. (25496) 63-366		[illegible]	[illegible]	.87	8 I	21
46	10.00	10997.4 54595.1	.60	235.10 352.63	3.91	430.		[illegible]	[illegible]	.02	98 I	
47	10.00	12319.0 63779.6	.57	473.10 1160.11	2.41	432.		[illegible]	[illegible]	.14	85 I	
48	10.00	11275.? 57110.2	.60	1478.90 2664.33	1.64	435.		[illegible]	[illegible]	.44	54 I	
49	10.00	10909.7 55645.3	.61	1966.70 3632.91	1.41	436.		[illegible]	[illegible]	.62	34 I	
50	10.00	[illegible]	.57	2562.30 4673.53	1.25	434.		[illegible]	[illegible]	.72	23 I	
	10.00	11109.9 55740.7	.60	2723.40 4920.73	1.21	435.		[illegible]	[illegible]	.87	8 I	

EXHIBIT E2



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- 0 LCR= 0 BKG= 11 X 2 SIGMA= .1
REGION B: LL-UL= 24- 156 LCR= 0 BKG= 17 X 1 SIGMA= .1
NUCLIDE 1 = 0 NUCLIDE 2 = 0
TIME= 10.00 QIP= SIE/AEC SCR= B/A K= 1.000

ST	TIME	CPMA/K CPM1/K	%DEV	CPMB/K CPM2/K	%DEV	QIP	FLAGS	SCR	MIN	
								81731/31376 x 46.2 = 120.35		
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	12240 [illegible]	[illegible]	0 4	1.95	428.		.085 .025	77	
8				1 -3	2.01	425.	DMA .029	.085 .026	11.47	
9	[illegible]	11842.3 62636.6	.58	187.90 258.19	4.42	429.		.016 .004	22	.00 100 H
10	10.00	12091.9 64859.9	.57	217.50 311.77	4.13	426.	10^{-1}	.018 .005	33	.02 96 H
11	10.00	11725.2 61948.2	.58	282.20 435.93	3.66	429.	-2	.024 .007	44	.06 88 H
12	10.00	12117.6 63918.1	.57	616.90 1061.13	2.51	428.	-3	.051 .017	55	.24 48 H
13	10.00	12445.1 64654.8	.57	954.10 1686.41	2.03	431.	-4	.077 .026	66	.41 12 H
14	10.00	12096.8 62627.3	.58	1028.60 1831.99	1.96	430.	-5	.088 .029	76	.47 100 C
15	10.00	11767.0 60883.5	.58	1003.20 1782.27	1.98	431.	-6	.085 .025	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 60665.8	.58	1010.70 1792.17	1.97	433.	-8 Compacting	.086 .030	109	.49 104 C
18	10.00	5972.70 29544.0	.82	64.00 73.74	7.03	442.	10^{-2}	.011 .002	120	.00 100 I
19	10.00	11719.0 61510.3	.58	215.10 310.10	4.15	431.	-3	.018 .005	130	.02 96 H
20	10.00	10876.4 56671.8	.61	331.00 533.04	3.39	432.	-4	.030 .009	141	.09 80 H
21	10.00	12112.8 64688.1	.57	470.40 787.87	2.86	426.	-5	.039 .012	195	.15 68 H
22	10.00	11203.1 57384.7	.60	701.80 1219.14	2.36	435.	-6	.063 .021	210	.32 32 H
[illegible]	[illegible]	12137.9	.57	995.80	1.99	430.	DMA -7	.082	220	.45 4 I

	31	10.00	12707.6 63610.8	..	1690.28									
	32	10.00	12229.2 62777.4	.57	223.30 321.20	4.08	436.							
	33	10.00	12060.9 62360.8	.58	346.00 551.10	3.32	434.							
	34	10.00	12161.0 63885.7	.57	754.10 1317.56	2.28	429.							
4	35	10.00	12069.6 62975.3	.58	695.00 1580.24	2.09	430.							
4	36	10.00	12133.6 63042.6	.57	987.90 1752.51	2.00	431.							
4	37	10.00	12321.3 63352.7	.57	1036.30 1836.46	1.95	433.							
4	38	10.00	12464.4 63599.6	.57	1038.50 1838.68	1.95	433.							
4	39	10.00	12399.8 64833.9	.57	202.40 281.02	4.27	432.							
5	40	10.00	12278.9 62975.6	.57	280.70 390.25	3.80	436.							
4	41	10.00	11232.7 [illegible]	.60	406.30 671.54	3.07	431.							
4				.58	598.00 1020.12									
4	43	10.00	[illegible] 63806.6	.57	929.20 1637.39	2.06	432.							
4	44	10.00	12288.0 64072.1	.57	1040.60 1851.99	1.94	430.							
4	45	10.00	12189.6 64052.5	.57	1042.40 1860.53	1.94	428.							
4	46	10.00	12119.8 63770.7	.57	432.00 713.38	2.98	429.							
6	47	10.00	12026.4 62744.7	.58	858.70 1512.64	2.14	430.							
4	48	10.00	12059.0 63125.5	.57	1016.70 1808.97	1.97	430.							
4	49	10.00	12212.9 62712.4	.57	1038.30 1840.44	1.95	433.							
4	50	10.00	12166.8 62337.9	.57	1002.90 1773.52	1.98	434.							
4	51	10.00	11720.1 60751.7	.58	988.50 1756.73	1.99	431.							
4	52	10.00	11999.0 62691.6	.58	999.90 1778.92	1.98	429.							
4	53	10.00	12032.0 62970.3	.58	556.20 946.02	2.64	430.							
7	54	10.00	11866.9 63061.2	.58	933.20 1662.26	2.05	426.							
4	55	10.00	11647.4 60781.4	.59	988.90 1760.63	1.99	429.							
4	56	10.00	12011.1 64054.0	.58	1021.80 1830.37	1.96	424.							
4	57	10.00	12067.7 63119.5	.58	1019.10 1815.00	1.96	429.							
4	58	10.00	12212.6 62328.7	.57	985.50 1738.75	2.00	433.							
4	59	10.00	11400.9 59940.9	.59	958.40 1708.98	2.03	428.							
4	60	10.00	11300.5 59446.6	.59	304.50 480.86	3.53	430.							
		10.00	11780.6 [illegible]	.58	674.40 1167.36	2.41	432.							

(RN 26039) 63-537 Wa

(RN 26075) 63-547

(RN 26080) 63-548

(RN 26082) 63-549

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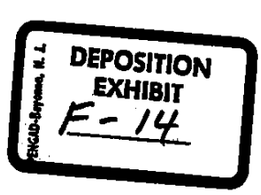
P#	S#	TIME	CPMA/K CPM1/K	%DEV	CPMB/K CPM2/K	%DEV	QIP	FLAGS
10	50	10.00	12404.4 62141.5	.57	2562.30 4673.53	1.15	434.	
10	51	10.00	11205.5 59748.7	.60	2723.40 4588.73	1.21	435.	
10	52	10.00	11793.4 60586.7	.58	2944.10 5444.66	1.16	427.	(25512) 63-369
10	53	10.00	11765.0 62249.7	.58	214.10 397.65	4.16	425.	
10	54	10.00	10746.4 55439.6	.61	226.20 338.05	4.66	435.	
10	55	10.00	11134.1 59682.0	.57	552.20 936.25	2.65	430.	
10	56	10.00	10750.4 55607.5	.61	721.60 1261.87	2.33	433.	
10	57	10.00	11566.4 61226.1	.58	2270.30 4154.15	1.32	436.	
10	58	10.00	12146.5 61534.5	.57	2764.50 5077.45	1.20	431.	(25500) 63-762/3
10	59	10.00	12035.4 60841.5	.58	2669.10 4893.27	1.22	431.	
10	60	10.00	12245.5 64662.5	.57	227.30 395.75	4.04	425.	
10	61	10.00	10550.8 56712.3	.60	324.60 521.15	3.42	426.	
10	62	10.00	11783.4 62115.6	.58	466.80 761.54	1.68	429.	
10	63	10.00	11978.5 61240.4	.58	1117.40 1550.45	1.38	433.	
10	64	10.00	12283.0 63370.6	.57	2545.80 4700.04	1.25	423.	
10	65	10.00	11051.4 57125.0	.60	2441.30 4500.65	1.28	427.	(25501) 63-270/2
10	66	10.00	11976.4 61324.6	.58	2728.50 5050.30	1.21	425.	

P#	S#	TIME	CPMA/K CPM1/K	%DEV	CPMB/K CPM2/K	%DEV	QIP	FLAGS
4	1	5.00	6666.00 0.00	1.03	52764.0 90561.8	.39	508.	
IN JAM	2	5.00	7371.60 0.00	1.04	55378.8 95646.8	.38	505.	

93 273.5

EXHIBIT E3



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	S.A.	% OF CONTROL	% OF INHIBITION	REMARKS
) Compactin (29299)	10/8/87	DMA				
1mM			.01	1	99	
10^{-1}			.04	3	97	
10^{-2}			.18	17	83	
10^{-3}			.62	61	39	
10^{-4}			.88	86	14	
10^{-5}			1.04	102	-	
10^{-6}			1.04	102	-	
10^{-7}			1.02	100	-	
10^{-8}			1.04	102	-	
) 62-320 (24135)	10/8/87	DMA				
10^{-2}			.01	1	99	
10^{-3}			.06	6	94	
10^{-4}			.20	20	80	
10^{-5}			.36	36	64	
10^{-6}			.83	82	18	
10^{-7}			1.02	100	-	
10^{-8}			1.02	100	-	
:) 64-906 (RN 30393)	10-8-87	DMA				
10^{-2}			.01	1	99	
10^{-3}			.01	1	99	
10^{-4}			.11	10	90	
10^{-5}			.27	26	74	
10^{-6}			.55	54	46	
10^{-7}			1.02	100	-	
10^{-8}			1.02	100	-	
1) 64-933 (RN 30441)	10-8-87	DMA				
10^{-2}			.20	20	80	
10^{-3}			.69	68	32	
10^{-4}			.99	98	2	
10^{-5}			1.04	102	-	
10^{-6}			.99	98	2	
10^{-7}			1.04	102	-	
10^{-8}			.99	98	2	

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COMPOUND	DATE	SOLVENT	RESP. S.A.	% OF CONTROL	% OF INHIBITION	REMARKS
5) 64-934/Na(RN 38442)	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= .
REGION B: LL-UL= 24- 156 LCR= 0 BKG= 10 ;; 2 SIGMA= .
NUCLIDE 1 = 0 NUCLIDE 2 = 0
TIME= 10.00 QIP= SIE/REC SCR= B/A K= 1.000 10-8-87

0.91 mg/ml

81965.9 / 32519.6 x 50.6 = 127.54

P#	S#	TIME	CPMA/K CPM1/K	%DEV	CPMB/K CPM2/K	%DEV	QIP	FLAGS	SCR	MIN		
10	1	10.00	3091.60 235.65	1.13	20162.1 32519.6	.45	623.		6.527 138.00	11		
10	2	10.00	25818.6 81965.9	.39	25.60 0.00	10.6	614.	1	.001 .000	23		
10	3	10.00	15376.8 57803.8	.51	118.30 152.01	5.58	536.	1	.008 .003	34		
10	4	10.00	14913.9 55504.1	.52	98.70 120.38	6.07	540.		.007 .002	45	S.A.	q:
10	5	10.00	15943.8 58737.5	.50	1667.70 2783.28	1.54	537.	1	.103 .047	88		
10	6	10.00	14562.0 53578.4	.52	1500.00 2501.69	1.63	538.	1	.103 .047	86	1.02	
10	7	10.00	15625.1 59001.1	.51	147.00 199.82	5.05	534.		.009 .003	77	.01	9:
10	8	10.00	14951.6 56705.7	.52	146.30 200.61	5.06	532.	1	.010 .004	88	.04	9'
10	9	10.00	16065.6 59499.6	.50	373.50 582.69	3.23	540.	1	.023 .010	99	.18	8:
10	10	10.00	16091.8 58934.3	.50	1038.90 1708.91	1.95	542.	1	.063 .026	110	.62	3'
10	11	10.00	15994.6 58487.0	.50	1410.50 2339.90	1.68	541.	1	.086 .040	121	.88	1'
10	12	10.00	14930.8 54627.5	.52	1525.80 2540.53	1.61	540.		.102 .047	132	1.04	1(
10	13	10.00	16937.4 63125.5	.49	1780.10 2979.86	1.49	533.	1	.108 .047	143	1.04	10
10	14	10.00	15441.7 57114.5	.51	1579.60 2637.63	1.59	536.		.102 .046	153	1.02	10
10	15	10.00	15874.9 58835.7	.50	1648.60 2755.17	1.55	535.		.104 .047	164	1.04	10
10	16	10.00	16273.6 62289.0	.50	150.40 202.79	4.99	529.	1	.003 .003	175	.01	99
10	17	10.00	15753.3 59828.1	.50	208.90 304.73	4.27	531.	1	.013 .005	186	.06	94
10	18	10.00	15849.2 58981.0	.50	418.40 660.16	3.06	538.	1	.028 .011	197	.20	80
10	19	10.00	15451.8 57686.1	.51	645.60 1048.57	2.47	536.	1	.049 .018	208	.36	64
10	20	10.00	15316.0 56089.6	.51	1287.10 2133.36	1.76	541.	1	.084 .038	219	.83	18
10	21	10.00	16492.1 60323.7	.49	1669.40 2778.83	1.54	540.	1	.101 .046	230	1.02	100
10	22	10.00	15743.7 57748.1	.50	1581.50 2633.97	1.59	539.		.100 .046	240	1.02	100
10	23	10.00	15611.7 58828.3	.51	132.80 175.79	5.29	535.		.009 .003	251	.01	99
10	24	10.00	15512.4 58030.1	.51	137.60 184.46	5.21	537.	1	.009 .003	262	.01	99

Blank
DMA control
Avg. .046
1mM
10^{-1}
10^{-2}
10μm
Competitive (29299)
(24135) 62-320

F#	S#	TIME	CPMA/K CPM1/K	%DEV	CPMB/K CPM2/K	%DEV	QIP	FLAGS	SCR	MIN		
10	25	10.00	16190.3 59961.2	.50	1161.30 392.02	3.84	541.		.016 -4 .007	173	.11	90I
10	26	10.00	16559.8 62307.7	.49	537.30 961.72	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 2752.02	1.55	536.	1	-7 .101 (RN 30393) .046	336	1.02	100C
10	29	10.00	16764.8 61637.3	.49	1705.70 2845.79	1.53	537.	1	-8 .101 64-906/Na .046	317	1.02	100C
10	30	10.00	16189.9 60617.9	0	405.30 688.63	3.00	536.	1	.2 .017 11 .010	336	.20	80I
10	31	10.00	16090.9 6[illegible]43.2	.50	1156.80 1918.69	1.35	534.	1	.072 -3 .032	339	.69	32I
10	32	10.00	16286.0 60443.6	.5	9.40 2721.69	1.56	535.	1	.100 -4 .043	350	.99	2 I
10	33	10.00	16217.7 59786.2	.50	1665.60 2766.53	1.55	544.	1	.103 -5 .047	349	1.04	102C
10	34	10.00	16174.1 59876.6	.50	1621.90 2704.09	1.57	537.		.100 -6 .043	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	361	1.04	102C
10	36	10.00	15984.6 58807.1	.50	1604.50 2674.30	1.57	538.	1	-8 .100 64-933 .043	393	.99	2 I
10	37	10.00	16010.2 60104.5	.50	457.90 727.94	2.52	535.		-2 .029 .012	284	.22	78I
10	38	10.00	15910.1 59943.1	.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	.095 -4 .043	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	408	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	466	1.28	121C
10	44	10.00	15261.6 57367.8	.51	310.10 478.64	3.53	535.	1	.020 -2 .008	484	.13	87 I
10	45	10.00	16345.3 61027.6	.49	580.20 947.92	2.59	536.	1	.036 -3 .016	491	.32	69 I
10	46	10.00	16369.7 60434.1	.49	1226.10 2030.00	1.80	538.	1	.079 -4 .034	501	.74	28I
10	47	10.00	16280.1 59712.9	.50	1515.40 2519.27	1.62	540.	1	.093 -5 .042	517	.92	9 I
10	48	10.00	16271.8 60108.7	.50	1562.10 2603.64	1.60	537.	1	.098 -6 .043	504	.95	7I
10	49	10.00	15953.0 59171.9	.50	1567.10 2616.07	1.59	535.	1	-7 .[illegible] (RN 30447) .[illegible]	[illegible]	.97	5I
10	50	10.00	15663.0 57617.7	.51	1590.00 2653.15	1.58	537.	1	-8 [illegible] 64-935 .042	47	1.02	100C
10	51	10.00	16311.6 60604.2	.50	184.40 282.19	4.54	533.	1	.011 -2 .004	[illegible]	.04	97I

F#	S#	TIME	CPMA/K CPM1/K	%DEV	CPMB/K CPM2/K	%DEV	QIP	FLAGS	SCR	MIN
10	52	10.00	15089.3 [illegible]	.51	545.90 [illegible]	2.68	534.		[illegible]	[illegible]

10	42	10.00	15893.3	.50	1685.20	1.57	538.	1		-7	.122	458			
			57784.7		2676.87				(RN 30442)		.046		1.02		230
10	43	10.00	17034.4	.48	2050.90	1.39	536.	1		-8	.120	369			
			62837.8		3434.60				64-934/Na		.055		1.23		121C
10	44	10.00	15281.6	.51	310.10	3.53	535.	1			.020	430			
			57367.8		478.64					-2	.008		.13		87 I
10	45	10.00	16345.3	.49	588.20	2.59	536.	1			.038	451			
			61027.6		947.92					-3	.016		.32		69 I
10	46	10.00	16369.7	.49	1226.10	1.80	538.	1			.075	301			
			60434.1		2830.00					-4	.034		.74		28I
10	47	10.00	16280.1	.50	1515.40	1.62	540.	1			.058	317			
			59712.9		2619.27					-5	.042		.92		9 I
	48	10.00	16271.8	.50	1562.10	1.60	537.	1			.056	324			
			60108.7		2603.64					-6	.043		.95		7 I
10	49	10.00	15932.0	.50	1567.10	1.59	535.	1			.054	330			
			59171.0		2616.07				(RN 30447)	-7	.044		.97		5 I
10	50	10.00	15663.0	.51	1596.00	1.58	537.	1			.046	47			
			57817.7		2653.19				64-935	-8	.047		1.02		100C
10	51	10.00	16311.6	.50	184.40	4.54	533.	1			.011				
			60604.2		262.19					-2	.008		.04		97I

P#	S#	TIME	CPMB/K CPM1/K	%DEV	CPMB/K CPM2/K	%DEV	DIP	FLAG							
10	52	10.00	15089.3	.51	545.90	2.68	534.				.034	347			
			56613.4		880.81					-3	.016		.32		69I
10	53	10.00	16394.2	.49	1082.90	1.91	533.	1			.066	578			
			61438.0		1792.44					-4	.028		.62		39I
	54	10.00	15760.3	.50	16.80	12.2	539.	1		-5	.001	799	-		—
			59017.1		0.00						.000				
10	55	10.00	15147.5	.51	14.10	12.8	537.	1			.001		-		—
			56791.0		0.00					-6	.000				
	56	10.00	15934.2	.51	1645.90	1.55	535.	1			.071				
			57776.3		2791.02				(RN 30448)	-7	.048		1.04		105C
10	57	10.00	15646.4	.51	1633.90	1.56	535.	1		-8	.047				
			58003.1		2731.11				64-936/Na		.047		1.04		102C
10	58	10.00	16494.4	.49	1675.70	1.54	537.	1			.072				
			60813.6		1795.44						.027				
10	59	10.00	16837.0	.49	1673.10	1.54	536.	1	Data		.071				
			62138.5		2791.43				control		.045				
10	60	10.00	16031.2	.50	1638.80	1.56	538.	1	10KM		.046				
			58941.1		2732.18						.046		1.02		100C

EXHIBIT E4

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
0^{-6}			.93	101	-
0^{-7}			1.00	108	-
10^{-8}			.98	106	-
1) 62-526/Na (29724)	10-13-87	DMA			
0^{-2}			.02	2	98
0^{-3}			.11	12	88
0^{-4}			.46	50	50
0^{-5}			.80	86	14
0^{-6}			.93	101	-
0^{-7}			.98	106	-
0^{-8}			.98	106	-

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COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL	% OF INHIBITION	REMARK
5) 64-727 (RN 30024)	10-13-87	DMA				
1mM			.05	5	95	
10^{-1}			.34	37	63	
10^{-2}			.82	88	12	
10^{-3}			.93	101	-	
10^{-4}			.95	103	-	
10^{-5}			.98	106	-	
10^{-6}			.93	101	-	
10^{-7}			.93	101	-	
10^{-8}			.95	103	-	
6) 64-948/Na(RA 30485)	10-13-87	DMA				
10^{-2}			.95	103	-	
10^{-3}			1.00	108	-	
10^{-4}			.95	103	-	
10^{-5}			.98	106	-	
10^{-6}			.95	103	-	
10^{-7}			.98	106	-	
7) 64-936/Na (RN 30448)	10-13-87	DMA				
10^{-2}			.07	7	93	
10^{-3}			.32	34	66	
10^{-4}			.73	79	21	
10^{-5}			.89	96	4	
10^{-6}			.93	101	-	
10^{-7}			.95	103	-	
10^{-8}			.95	103	-	

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RAM #: 10
GION A: LL-UL= 0- 8 LCR= 0 BKG= 15 % 2 SIGMA= .0
GION B: LL-UL= 24- 156 LCR= 0 BKG= 10 % 2 SIGMA= .0
CLIDE 1 = 0 NUCLIDE 2 = 0
"F= 10.00 DIP= SIE/REC SCR= B/A K= 1.000

10-13-87

S#	TIME	CPMA/K DPM1/K	%DEV	CPMB/K DPM2/K	%DEV	DIP	FLAGS	SCR	MIN		
								87022.6 / 33633.3 × 50.6-130.9			
1	10.00	3063.30	1.14	20864.8	.44	624.		6.811	11		
		0.00		33633.3				.000			
2	10.00	27939.4	.38	22.40	11.1	624.	1	.001	23		
		87022.6		0.00				.000			
3	10.00	14743.0	.52	89.10	6.35	546.	-1	.008	33		
		53933.1		105.03				.002			
4	10.00	15103.6	.51	91.20	6.29	544.	1	Blank .006	44	S.A.	
		55527.8		107.35				.002			
5	10.00	16545.8	.49	1543.10	1.60	545.	1	.093	55		
		59952.0		2557.41				.043 .043			
6	10.00	15478.8	.51	1569.50	1.59	544.		Dmk control .101	66	0.93	
		56015.2		2605.45				.047			
7	10.00	15921.3	.50	130.10	5.34	545.	1	.008	77		
		58454.7		170.53				1mM .003		.02	98 I
8	10.00	16044.9	.50	145.70	5.07	545.	1	.005	88		
		58913.1		196.57				16' .003		.02	98 I
9	10.00	14929.8	.52	340.10	3.38	549.	1	.023	99		
		54113.5		527.59				-2 .010		.18	80 I
10	10.00	15351.1	.51	1024.60	1.97	547.	1	.067	110		
		55587.1		1682.45				-3 .030		.64	31 I
11	10.00	15655.7	.51	1331.40	1.73	547.	1	.085	120		
		56431.5		2198.60				-4 .038		.84	9 I
12	10.00	16111.9	.50	1542.40	1.61	549.	1	.098	131		
		57735.5		2550.58				-5 .044		.95	103C
13	10.00	15710.6	.50	1606.60	1.57	545.	1	.102	142		
		56752.8		2666.29				-6 .047		1.02	110C
14	10.00	15175.0	.51	1491.70	1.63	542.	1	.098	153		
		55228.6		2478.83				(29299) -7 .043		.98	106C
15	10.00	15977.0	.50	1580.20	1.59	548.	1	-8.099	164		
		57579.1		2618.88				Compactin .045		.98	106C
16	10.00	16098.9	.50	135.80	5.24	547.	1	.008	175		
		58807.5		179.70				-2 .003		.02	98 I
17	10.00	14956.1	.52	159.80	4.65	545.	1	.011	186		
		54942.4		223.76				-3 .004		.05	95 I
18	10.00	15643.9	.51	383.20	3.19	544.	1	.024	197		
		57352.4		599.35				-4 .010		.18	80I
19	10.00	16031.6	.50	554.50	2.66	546.	1	.035	207		
		58424.5		886.95				-5 .015		.30	68 I
20	10.00	15638.5	.51	1368.20	1.70	545.	1	.087	218		
		56659.5		2263.93				-4 .040		.86	7 I
21	10.00	16301.4	.50	1602.40	1.58	550.	1	.098	229		
		58292.5		2650.00				(24135) -7 .045		.98	106C
22	10.00	15996.2	.50	1543.10	1.60	547.	1	-8.096	240		
		57666.1		2555.24				LoR-220 .044		.95	103C
23	10.00	16477.1	.49	1226.40	1.80	547.		.074	251		
		59531.6		2019.18				.034		.73	21 I
24	10.00	15445.1	.51	1483.40	1.64	547.	1	.096	262		
		55659.6		2456.75				.044		.95	103C

S#	TIME	CPMA/K CPM1/K	%DEV	CPMB/K CPM2/K	%DEV	QIP	FLAGS	SCR	MIN		
25	10.00	16087.8 58014.3	.50	1679.80 2787.82	1.54	546.	1	.104 .040	373	1.05	113C
26	10.00	16237.2 59026.8	.50	1487.80 2486.71	1.63	543.		.092 .042	384	.91	2I
27	10.00	15786.5 57067.1	.50	1481.70 2464.77	1.64	545.	1	.094 .043	390	.95	101C
28	10.00	16477.1 59148.7	.49	1640.10 2715.81	1.56	548.	1	.100 .046	386	1.00	108C
29	10.00	16689.9 59692.7	.49	1641.20 2714.32	1.56	550.	1	.098 .045	387	.98	106C
30	10.00	15073.5 54349.8	.51	110.10 139.60	5.77	553.	1	.007 .003	397	.02	98I
31	10.00	15986.5 57774.5	.50	281.30 425.84	3.71	551.	1	.018 .007	388	.11	88I
32	10.00	15010.4 54035.6	.52	795.50 1294.24	2.23	550.		.053 .024	389	.46	50I
33	10.00	15729.1 56993.4	.50	1289.60 2130.37	1.73	545.	1	.082 .037	380	.80	14I
34	10.00	16357.9 59060.3	.49	1533.10 2538.81	1.61	546.	1	.094 .042	371	.93	101C
35	10.00	15098.9 54628.8	.51	1476.00 2448.00	1.64	545.	1	.098 .045	382	.98	106C
36	10.00	14843.9 53956.7	.52	1442.70 2384.31	1.66	550.	1	.097 .045	393	.98	106C
37	10.00	15208.0 55123.7	.51	174.20 247.13	4.66	550.		.011 .004	404	.05	95I
38	10.00	15340.4 55110.1	.51	578.00 925.95	2.61	552.	1	.038 .017	418	.34	63I
39	10.00	15278.8 54718.9	.51	1274.30 2039.84	1.76	550.	1	.083 .038	415	.82	12I
40	10.00	15634.7 55800.0	.51	1463.40 2416.17	1.65	551.	1	.094 .043	419	.93	101C
41	10.00	15578.0 55720.7	.51	1495.90 2473.06	1.63	549.	1	.096 .044	411	.95	103C
42	10.00	16599.6 59378.4	.49	1614.90 2670.27	1.57	550.	1	.098 .045	411	.98	106C
43	10.00	15425.8 55637.3	.51	1460.60 2418.78	1.65	546.		.094 .043	411	.93	101C
44	10.00	15558.8 56231.7	.51	1508.10 2500.05	1.62	548.	1	.097 .044	411	.95	103C
45	10.00	16699.3 60049.5	.49	1660.60 2750.91	1.55	547.	1	.099 .045	411	1.00	108C
46	10.00	14803.4 53991.7	.49	1597.90 2648.30	1.58	545.	1	.096 .044	411	.95	103C
47	10.00	16754.7 60361.5	.49	1621.10 2686.67	1.57	547.	1	.097 .045	411	.98	106C
48	10.00	15341.0 55900.3	.51	1471.10 2435.34	1.64	547.	1	.096 .044	411	.95	103C
49	10.00	16056.6 58214.2	.50	1577.80 2612.46	1.59	544.	1	.096 .045	411	.98	106C
50	10.00	15068.4 54700.6	.51	1213.30 2000.23	1.81	548.	1	.081 .037	411	.80	14I
51	10.00	15549.0 56878.9	.51	199.60 289.47	4.37	546.	1	.013 .005	411	.07	93I

S#	TIME	CPMA/K CPM1/K	%DEV	CPMB/K CPM2/K	%DEV	QIP	FLAGS	SCR	MIN

(30461)
64-942/Na
(29724)
62-526/Na
64-727
(RN 30485
64-948/Wa

			20049.5		2750.91							
46	10.00	14603.4	.49	1597.90	1.58	545.	1					
		39991.7		2646.30								
47	10.00	14750.7	.49	1621.10	1.57	547.	1					
		40341.5		2666.67								
48	10.00	15341.0	.51	1471.10	1.64	547.	1					
		38790.3		2435.34								
49	10.00	14859.6	.50	1577.80	1.59	544.	1					
		38016.2		2618.46								
50	10.00	15368.4	.51	1213.20	1.81	548.	1					
		34128.6		2000.23								
51	10.00	15540.0	.51	199.60	4.37	546.	1					
		36878.9		285.47								

(RN 30485 64-948/Na)

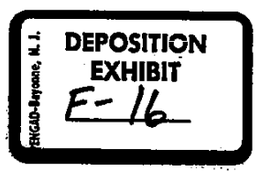
#	S#	TIME	CPMA/K CPM1/K	%DEV	CPMB/K CPM2/K	%DEV	QIP	FLAGS	SCR	MIN		
3	52	10.00	15816.7 57837.6	.50	574.60 922.29	2.62	545.	1	.036 -3.016	567	.32	66I
3	53	10.00	13180.4 54882.5	.51	1145.30 1886.68	1.86	547.	1	.075 -4.034	578	.73	21I
3	54	10.00	15774.1 57123.9	.50	1401.00 2318.80	1.68	545.	1	.089 -5.041	583	.89	4I
3	55	10.00	15900.1 57567.7	.50	1509.00 2501.44	1.62	545.	1	.095 -4.043	608	.93	101C
3	56	10.00	16502.8 59946.6	.49	1574.50 2612.55	1.59	543.	1	.095 -7.044	611	.95	103C
3	57	10.00	16387.2 58233.5	.49	1575.30 2611.10	1.59	545.	1	.096 -8.044	632	.95	103C
3	58	10.00	16200.5 58151.9	.50	1510.50 2497.36	1.62	548.	1	.093 -7.043	630	.93	101C
	59	10.00	15843.5 57283.5	.50	1512.80 2507.21	1.62	545.	1	.095 -8.044	643	.95	103C
3	60	10.00	16033.5 57707.8	.50	1514.70 2506.81	1.62	547.	1	.094 .043	634		
3	61	10.00	16912.0 61089.9	.49	1388.70 2292.13	1.69	547.	1	.082 .038	665		

(RN 30448 64-936/Na)

64-727

Drift Control

EXHIBIT E5



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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.

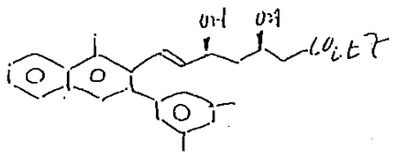
Microsomes were prepared from male Sprague-Dawley rats (180g ± 10) in Buffer A with 10 mM DTT and frozen at -80°C until thawed and used for experiment. 200 µl Aliquots of microsomal suspension (1.12-1.30 mg/ml) plus 10 µl of drug dilution were assayed for HMG-CoA reductase activity.

Compactin in DMA at various concentrations was assayed for inhibition and was indicated in the results. Buffer A, and DMA: DMSO:0.1M NaOH were also assayed by adding 10 µl of each to 31 200 µl of microsomal suspensions and they showed no significant inhibition of HMG-CoA reductase.

NOTE: That compound marked (SAP) was saponified in a 50° waterbath for 2 hr.

RECEIVED
DEC 20 1984

COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL	IC_{50}	% OF INHIBITION	REMARK
1) Compactin (24291)	12/4/84	DMA					
1mM			.02	4		96	
10^{-1}			.02	4		96	
10^{-2}			.09	18		82	
10^{-3}			.33	64	1.78	36	
10^{-4}			.51	98		2	
10^{-5}			.58	112		-	
10^{-6}			.61	118		-	
10^{-7}			--	--		-	
10^{-8}			.53	102		-	
2) 62-320/Na-4 (~~24291~~) 23531	12/4/84	DMA					
10^{-2}			.02	4		96	
10^{-3}			.04	8		92	
10^{-4}			.10	20		80	
10^{-5}			.18	34		66	
10^{-6}			.54	104	0.006	-	
10^{-7}			.59	114		-	
10^{-8}			.57	110		-	
3) 63-346(25467)(SAP)	12-4-84	DMSO:0.1M NaOH					
10^{-2}			.61	69		31	
10^{-3}			.85	96		4	
10^{-4}			.94	106	>10	-	
10^{-5}			.92	104		-	
10^{-6}			.95	108		-	
10^{-7}			.98	111		-	
10^{-8}			.97	110		-	
4) 63-346 (25467)	12/4/84	DMA					
10^{-2}			.50	96		4	
10^{-3}			.63	122		-	
10^{-4}			.65	126	>10	-	
10^{-5}			.59	114		-	
10^{-6}			.53	102		-	
10^{-7}			.60	116		-	
10^{-8}			.58	112		-	



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RESULTS

COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL		% OF INHIBITION	REMARK
5) 63-347/Na(25468)	12/4/84	Buffer A					
10^{-2}			.84	83		17	
10^{-3}			1.02	101		-	
10^{-4}			1.02	101	>10	-	
10^{-5}			.98	97		3	
10^{-6}			1.07	106		-	
10^{-7}			1.00	99		1	
10^{-8}			1.02	101		-	
6) 63-352/Na(25475)	12/4/84	DMA					
10^{-2}			.05	10		90	
10^{-3}			.25	48		52	
10^{-4}			.51	98	1.11	2	
10^{-5}			.56	108		-	
10^{-6}			.57	110		-	
10^{-7}			.60	116		-	
10^{-8}			.65	126		-	
7) 63-353 (25476)	12/4/84	DMA					
10^{-2}			.04	8		92	
10^{-3}			.20	38		62	
10^{-4}			.46	90	0.77	10	
10^{-5}			.56	108		-	
10^{-6}			.59	114		-	
10^{-7}			.57	110		-	
10^{-8}			.58	112		-	
8) 63-265/3 (25488)	12/4/84	DMA					
10^{-2}			.01	2		98	
10^{-3}			.03	6		94	
10^{-4}			.06	12	0.004	88	
10^{-5}			.13	26		74	
10^{-6}			.39	76		24	
10^{-7}			.55	106		-	
10^{-8}			.58	112		-	

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COMPOUND	DATE	SOLVENT	RES S.A.	% OF CONTROL		% OF INHIBITION	REMARKS
9) Compactin (24291)	12/12/84	DMA					
1mM			.00	-		100	
10^{-1}			.01	1		99	
10^{-2}			.10	9		91	
10^{-3}			.55	50	0.85	50	
10^{-4}			.90	83		17	
10^{-5}			1.01	93		7	
10^{-6}			1.12	103		-	
10^{-7}			1.06	97		3	
10^{-8}			1.04	96		4	
10) 62-320/Na-4 (24531)	12/12/84	DMA					
10^{-2}			.00	-		100	
10^{-3}			.04	3		97	
10^{-4}			.16	15	0.004	85	
10^{-5}			.37	34		66	
10^{-6}			-	-		-	
10^{-7}			1.03	95		5	
10^{-8}			1.03	95		5	
11) 63-361/Na (25481)	12/12/84	DMA					
10^{-2}			.00	-		100	
10^{-3}			.07	7		93	
10^{-4}			.31	28	0.016	72	
10^{-5}			.54	50		50	
10^{-6}			.98	91		9	
10^{-7}			1.01	93		7	
10^{-8}			1.02	94		6	
12) 62-562/Na(24908)	12/12/84	DMA					
10^{-2}			.00	-		100	
10^{-3}			.01	1		99	
10^{-4}			.08	8		92	
10^{-5}			.26	24	0.005	76	
10^{-6}			.94	06		14	
10^{-7}			.97	90		10	
10^{-8}			.99	91		9	

RESULTS

COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL		% OF INHIBITION	REMARK
13) 63-354 (25477)	12/12/84	DMA					
10^{-2}			.09	9		91	
10^{-3}			.48	44		56	
10^{-4}			.89	82	0.73	18	
10^{-5}			1.01	93		7	
10^{-6}			1.03	95		5	
10^{-7}			1.03	95		5	
10^{-8}			.93	85		15	
14) 63-355 (25474)	12/12/84	DMA					
10^{-2}			.26	24		76	
10^{-3}			.57	52		48	
10^{-4}			.94	86	1.35	14	
10^{-5}			.97	90		10	
10^{-6}			1.01	93		7	
10^{-7}			1.02	94		6	
10^{-8}			.99	91		9	
15) 63-356 (25480)	12/12/84	DMA					
10^{-2}			.00	-		100	
10^{-3}			.06	5		95	
10^{-4}			.26	24		76	
10^{-5}			.44	40	0.009	60	
10^{-6}			.92	85		15	
10^{-7}			.96	89		11	
10^{-8}			.98	91		9	
16) 62-265/3 (25488)	12/12/84	DMA					
10^{-2}			.00	-		100	
10^{-3}			.02	2		98	
10^{-4}			.11	10		90	
10^{-5}			.22	21	0.004	79	
10^{-6}			.84	78		22	
10^{-7}			.96	89		11	
10^{-8}			.96	89		11	

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COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL		% OF INHIBITION	REMARKS
17) Compactin (24291)	12/13/84	DMA					
1mM			.00	-		100	
10^{-2}			.02	2		98	
10^{-3}			.10	10		90	
10^{-4}			.43	45	0.72	55	
10^{-5}			.75	80		20	
10^{-6}			.86	91		9	
10^{-7}			.91	97		3	
10^{-8}			.89	95		5	
			.92	98		2	
18) 62-320/Na-4(~~24297~~ 23531)	12/13/84	DMA					
10^{-2}			.01	1		99	
10^{-3}			.04	4		96	
10^{-4}			.13	14	0.007	86	
10^{-5}			.25	27		73	
10^{-6}			.84	90		10	
10^{-7}			.92	98		2	
10^{-8}			.90	96		4	
19) 63-364 (24489)	12/13/84	DMA					
10^{-2}			.71	76		24	
10^{-3}			.86	91		9	
10^{-4}			.89	95		5	
10^{-5}			.90	96	> 10	4	
10^{-6}			.84	89		11	
10^{-7}			.86	91		9	
10^{-8}			.82	87		13	
20) 63-365 (25490)	12/13/84	DMA					
10^{-2}			.02	2		98	
10^{-3}			.08	8		92	
10^{-4}			.16	17	0.017	83	
10^{-5}			.58	62		38	
10^{-6}			.84	89		11	
10^{-7}			.85	90		10	
10^{-8}			.87	92		8	

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COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL		% OF INHIBITION	REMARK
21) 63-366 (25496)	12/13/84	DMA					
10^{-2}			.21	22		78	
10^{-3}			.57	61		39	
10^{-4}			.81	86	1.5%	14	
10^{-5}			.80	94		6	
10^{-6}			.90	96		4	
10^{-7}			.88	94		6	
10^{-8}			.87	92		8	
22) 63-369 (25512)	12/12/84	DMA					
10^{-2}			.02	2		98	
10^{-3}			.14	15		85	
10^{-4}			.44	46	0.035	54	
10^{-5}			.62	66		34	
10^{-6}			.72	77		23	
10^{-7}			.87	92		8	
10^{-8}			.88	94		6	
23) 63-162/3 (25500)	12/13/84	DMA					
10^{-2}			.01	1		99	
10^{-3}			.02	2		98	
10^{-4}			.11	11	0.007	89	
10^{-5}			.19	20		80	
10^{-6}			.65	97		3	
10^{-7}			.81	86		14	
10^{-8}			.78	83		17	
24) 63-270/2	12/13/84	DMA					
10^{-2}			.01	1		99	
10^{-3}			.05	5		95	
10^{-4}			.09	9	0.004	91	
10^{-5}			.28	30		70	
10^{-6}			.71	76		24	
10^{-7}			.77	82		18	
10^{-8}			.79	84		16	

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COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL		% OF INHIBITION	REMARK
25) Compactin (24291)	12/14/84	DMA					
1mM			.00	-		100	
10^{-1}			.00	-		100	
10^{-2}			.02	3		97	
10^{-3}			.38	46	0.87	54	
10^{-4}			.78	93		7	
10^{-5}			.85	101		-	
10^{-6}			.93	111		-	
10^{-7}			.89	107		-	
10^{-8}			.89	107		-	
26) 62-320/Na-4	12/14/84	DMA					
10^{-2}			.00	-		100	
10^{-3}			.00	-		100	
10^{-4}			.08	10	0.007	90	
10^{-5}			.21	25		75	
10^{-6}			.78	93		7	
10^{-7}			.88	106		-	
10^{-8}			.80	96		4	
27) 63-346 (25467)	12/14/84	DMSO:0.1M NaOH					
10^{-2}			.59	89		31	
10^{-3}			.89	104		-	
10^{-4}			.85	99	>10	1	
10^{-5}			.81	95		5	
10^{-6}			.85	99		1	
10^{-7}			.80	93		7	
10^{-8}			.83	97		3	
28) 63-347 (25468)	12/14/84	DMA					
10^{-2}			.76	82		18	
10^{-3}			.97	105		-	
10^{-4}			.97	105	>10	-	
10^{-5}			1.02	109		-	
10^{-6}			.97	105		-	
10^{-7}			.94	100		-	
10^{-8}			.96	103		-	

COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL		% OF INHIBITION	REMAI
29) 63-352 (25475)	12/14/84	DMA					
10^{-2}			.08	10		90	
10^{-3}			.29	35		65	
10^{-4}			.73	88	0.72	12	
10^{-5}			.83	100		-	
10^{-6}			.79	94		6	
10^{-7}			.80	96		4	
10^{-8}			.89	107		-	
30) Compactin (24291)	12/17/84	DMA					
1mM			.01	1		99	
10^{-1}			.03	3		97	
10^{-2}			.14	13		87	
10^{-3}			.61	55		45	
10^{-4}			1.00	90		10	
10^{-5}			1.09	98	1.17	2	
10^{-6}			1.22	109		-	
10^{-7}			1.18	105		-	
10^{-8}			1.23	110		-	
31) 62-320/Na-4(25480)	12/12/84	DMA					
10^{-2}			.01	1		99	
10^{-3}			.05	5		95	
10^{-4}			.18	17		83	
10^{-5}			.47	42	0.012	58	
10^{-6}			1.13	102		-	
10^{-7}			1.12	104		-	
10^{-8}			1.18	106		-	
32) 62-562/Na-2(25488)	12/17/84	DMA					
10^{-2}			.01	1		99	
10^{-3}			.04	4		96	
10^{-4}			.09	8	0.005	92	
10^{-5}			.25	22		78	
10^{-6}			.98	88		12	
10^{-7}			1.06	95		5	
10^{-8}			1.06	95		5	

COMPOUND	DATE	SOLVENT	S.I	CONTROL		INHIBITION
33) 63-361 (25485)	12/17/84	DMA				
10^{-2}			.01	1		99
10^{-3}			.08	7		93
10^{-4}			.31	28	0.017	72
10^{-5}			.50	45		55
10^{-6}			1.01	91		9
10^{-7}			1.10	99		1
10^{-8}			1.11	100		-
34) 63-162/3 (25500)	12/17/84	DMA				
10^{-2}			.01	1		99
10^{-3}			.04	4		96
10^{-4}			.14	13	0.005	87
10^{-5}			.25	22		78
10^{-6}			.96	86		14
10^{-7}			1.02	92		8
10^{-8}			1.01	91		9
35) 63-270/2 (25501)	12/17/84	DMA				
10^{-2}			.02	2		98
10^{-3}			.07	6		94
10^{-4}			.12	11	0.008	89
10^{-5}			.47	42		58
10^{-6}			.97	87		13
10^{-7}			1.04	94		6
10^{-8}			1.05	94		6
36) 62-265/3 (25488)	12/17/84	DMA				
10^{-2}			.01	1		99
10^{-3}			.01	1		99
10^{-4}			.07	6		94
10^{-5}			.18	17	0.001	83
10^{-6}			.55	50		50
10^{-7}			.99	89		11
10^{-8}			1.01	91		9

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

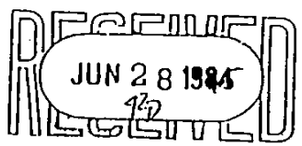
June 27, 1985

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 - 1.11mg/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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RESULTS

	COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL	IC50 (μM)	% OF INHIBITION	REMARKS
1)	Compactin (24291)	6/13/85	DMA					
	1mM			.00	-		100	
	10^{-1}			.02	4		96	
	10^{-2}			.06	12	1.041	88	
	10^{-3}			.24	52		48	
	10^{-4}			.41	88		12	
	10^{-5}			.47	100		-	
	10^{-6}			.47	100		-	
	10^{-7}			.43	92		8	
	10^{-8}			.49	104		-	
2)	62-320/Na-4(23531)	6/13/85	DMA					
	10^{-2}			.00	-		100	
	10^{-3}			.02	4		96	
	10^{-4}			.09	20		80	
	10^{-5}			.15	32	0.0038	68	
	10^{-6}			.32	68		32	
	10^{-7}			.45	96		4	
	10^{-8}			.47	100		-	
3)	63-518/2(RN 26020)	6/13/85	DMA					
	10^{-2}			.37	80		20	
	10^{-3}			.45	96		4	
	10^{-4}			.49	104	>10	-	
	10^{-5}			.45	96		4	
	10^{-6}			.51	100		-	
	10^{-7}			.49	104		-	
	10^{-8}			.49	104		-	
1)	63-537/Na(RN 26039)	6/13/85	DMA					
	10^{-2}			.02	4		96	
	10^{-3}			.09	20		80	
	10^{-4}			.32	68	0.169	32	
	10^{-5}			.39	84		16	
	10^{-6}			.45	96		4	
	10^{-7}			.47	100		-	
	10^{-8}			.47	100		-	

RESULTS

COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL		% OF INHIBITION	REMARKS
5) 63-547(RN 26075)	6/13/85	DMA					
10^{-2}			.00	-		100	
10^{-3}			.04	8	0.017	92	
10^{-4}			.13	28		72	
10^{-5}			.22	48		52	
10^{-6}			.41	88		12	
10^{-7}			.47	100		-	
10^{-8}			.47	100		-	
6) 63-548(RN 26080)	6/13/85	DMA					
10^{-2}			.13	28		72	
10^{-3}			.37	80		20	
10^{-4}			.47	100	3.775	-	
10^{-5}			.47	100		-	
10^{-6}			.45	96		4	
10^{-7}			.47	100		-	
10^{-8}			.45	96		4	
7) 63-549(RN 26082)	6/13/85	DMA					
10^{-2}			.21	44		56	
10^{-3}			.41	88		12	
10^{-4}			.47	100	7.31	-	
10^{-5}			.47	100		-	
10^{-6}			.47	100		-	
10^{-7}			.45	96		4	
10^{-8}			.47	100		-	
8) 63-550(RN 26083)	6/13/85	DMA					
10^{-2}			.07	16		84	
10^{-3}			.28	60		40	
10^{-4}			.41	88	1.348	12	
10^{-5}			.47	100		-	
10^{-6}			.47	100		-	
10^{-7}			.47	100		-	
10^{-8}			.47	100		-	

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RESULTS

COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL		% OF INHIBITION	REMARKS
9) Compactin (24291)	6/18/85	DMA					
1mM			.02	2		98	
10^{-1}			.02	2		98	
10^{-2}			.14	14		86	
10^{-3}			.54	52	0.978	48	
10^{-4}			.86	83		17	
10^{-5}			.94	91		9	
10^{-6}			.98	95		5	
10^{-7}			1.04	101		-	
10^{-8}			1.10	107		-	
10) 62-320/Na-4(23531)	6/18/85	DMA					
10^{-2}			.02	2		98	
10^{-3}			.04	4		96	
10^{-4}			.16	16		84	
10^{-5}			.38	37	0.0081	63	
10^{-6}			.90	87		13	
10^{-7}			1.00	97		3	
10^{-8}			.98	95		5	
11) 63-551(RN 26084)	6/18/85	DMA					
10^{-2}			.78	76		24	
10^{-3}			.96	93		7	
10^{-4}			1.00	97	>10	3	
10^{-5}			1.04	101		-	
10^{-6}			1.02	99		1	
10^{-7}			.98	95		5	
10^{-8}			1.00	97		3	
12) 63-552/Na(RN 26085)	6/18/85	DMA					
10^{-2}			.82	80		20	
10^{-3}			1.04	101		-	
10^{-4}			1.00	97	>10	3	
10^{-5}			1.00	97		3	
10^{-6}			.98	95		5	
10^{-7}			1.02	99		1	
10^{-8}			.98	95		5	

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COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL		% OF INHIBITION	REMARKS
13) 63-553(RN26086)	6/18/85	DMA					
10^{-2}			.36	35		65	
10^{-3}			.80	78		22	
10^{-4}			.94	91	4.479	9	
10^{-5}			1.02	99		1	
10^{-6}			1.00	97		3	
10^{-7}			1.04	101		-	
10^{-8}			1.00	97		3	
14) 63-554/Na(RN 26087)	6/18/85	DMA					
10^{-2}			.18	17		83	
10^{-3}			.64	62		38	
10^{-4}			.92	89	1.466	11	
10^{-5}			1.00	97		3	
10^{-6}			1.02	99		1	
10^{-7}			1.02	99		1	
10^{-8}			.98	95		5	
15) Compactin (24291)	6/19/85	DMA					
1mM			.04	4		96	
10^{-1}			.04	4		96	
10^{-2}			.14	15	1.241	85	
10^{-3}			.51	53		47	
10^{-4}			.90	93		7	
10^{-5}			.98	101		-	
10^{-6}			1.00	103		-	
10^{-7}			1.06	109		-	
10^{-8}			1.00	103		-	
16) 62-320/Na-4(23531)	6/19/85	DMA					
10^{-2}			.04	4		96	
10^{-3}			.08	8		92	
10^{-4}			.20	21	.0059	79	
10^{-5}			.45	46		54	
10^{-6}			.65	67		33	
10^{-7}			1.02	105		-	
10^{-8}			1.04	107		-	

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COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL		% OF INHIBITION	REMARKS
17) 63-550/Na(RN 26098)	6/19/85	DMA					
10^{-2}			.06	6		94	
10^{-3}			.31	32		68	
10^{-4}			.73	76	0.454	24	
10^{-5}			.96	99		1	
10^{-6}			1.02	105		-	
10^{-7}			.96	99		1	
10^{-8}			.98	101		-	
18) 63-559(RN 26106)	6/19/85	DMA					
10^{-2}			.12	13		87	
10^{-3}			.49	51		49	
10^{-4}			.90	93	1.144	7	
10^{-5}			.98	101		-	
10^{-6}			1.00	103		-	
10^{-7}			1.00	103		-	
10^{-8}			.92	95		5	
19) 63-550/2 Na(RN 26108)	6/19/85	DMA					
10^{-2}			.12	13		87	
10^{-3}			.53	55		45	
10^{-4}			.94	97	1.315	3	
10^{-5}			1.00	103		-	
10^{-6}			1.00	105		-	
10^{-7}			1.02	105		-	
10^{-8}			1.04	107		-	
20) 63-563(RN 26127)	6/19/85	DMA					
10^{-2}			.31	32		68	
10^{-3}			.80	82	4.365	18	
10^{-4}			.96	99		1	
10^{-5}			1.00	103		-	
10^{-6}			1.00	103		-	
10^{-7}			1.02	105		-	

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COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL		% OF INHIBITION	REMARK
21) 63-564/Na(26129)	6/19/85	DMA					
10^{-2}			.20	21		79	
10^{-3}			.67	69	2.48%	31	
10^{-4}			.96	99		1	
10^{-5}			1.02	105		-	
10^{-6}			1.00	103		-	
10^{-7}			1.04	107		-	
10^{-8}			1.04	107		-	
22) 63-565(RN 26128)	6/19/85	DMA					
10^{-2}			.10	11		89	
10^{-3}			.33	34		66	
10^{-4}			.78	80	0.573	20	
10^{-5}			.96	99		1	
10^{-6}			1.00	103		-	
10^{-7}			.96	99		1	
10^{-8}			.98	101		-	
23) Compactin (24291)	6/24/85	DMA					
1mM			.03	3		97	
10^{-1}			.03	3		97	
10^{-2}			.13	15	1.53%	85	
10^{-3}			.50	61		39	
10^{-4}			.81	97		3	
10^{-5}			.91	109		-	
10^{-6}			.96	115		-	
10^{-7}			.91	109		-	
10^{-8}			.88	106		-	
24) 62-320/Na-4(23531)	6/24/85	DMA					
10^{-2}			.00	-		100	
10^{-3}			.05	6		94	
10^{-4}			.15	18	0.01	82	
10^{-5}			.33	39		61	
10^{-6}			.78	94		6	
10^{-7}			.86	103		-	
10^{-8}			.88	106		-	

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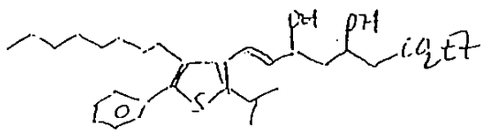
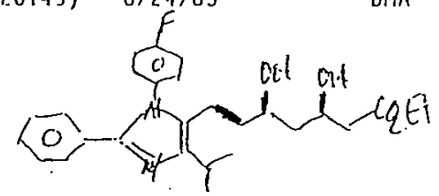
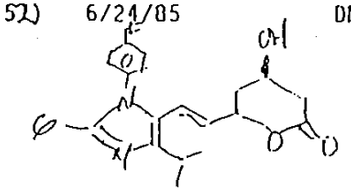
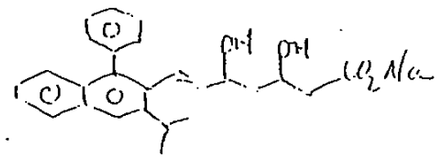
COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL		% OF INHIBITION	REMARK
25) 63-566(RN 26148)	6/24/85	DMA					
10^{-2}			.73	88		12	
10^{-3}			.86	103	>10	-	
10^{-4}			.91	109		-	
10^{-5}			.91	109		-	
10^{-6}			.83	100		-	
10^{-7}			.86	103		-	
10^{-8}			.91	109		-	
26) 63-567(RN 26149)	6/24/85	DMA					
10^{-2}			.23	27		73	
10^{-3}			.63	76		24	
10^{-4}			.70	85	2.734	15	
10^{-5}			.76	91		9	
10^{-6}			.78	94		6	
10^{-7}			.78	94		6	
10^{-8}			.76	91		9	
27) 63-568(RN 26152)	6/24/85	DMA					
10^{-2}			.03	3		97	
10^{-3}			.13	15		85	
10^{-4}			.28	33	0.086	67	
10^{-5}			.78	94		6	
10^{-6}			.81	97		3	
10^{-7}			.78	94		6	
10^{-8}			.78	94		6	
28) 63-560(RN 26107)	6/24/85	Buffer A					
10^{-2}			.08	9		91	
10^{-3}			.43	52		48	
10^{-4}			.73	88	0.981	12	
10^{-5}			.81	97		3	
10^{-6}			.81	97		3	
10^{-7}			.88	106		-	
10^{-8}			.86	103		-	

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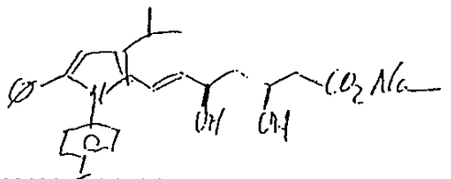
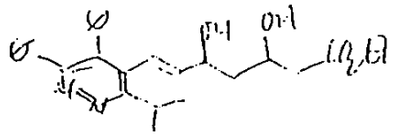
COMPOUND	DATE	SOLVENT	RESULTS S.A.	% OF CONTROL		% OF INHIBITION	REMARK
29) 63-555(RN 26088)	6/24/85	DMA					
10^{-2}			.00	-		100	
10^{-3}			.05	6		94	
10^{-4}			.20	24	0.014	76	
10^{-5}			.40	48		52	
10^{-6}			.70	85		15	
10^{-7}			.78	94		6	
10^{-8}			.78	94		6	
30) Compactin (24291)	6/26/85	DMA					
1mM			.00	-		100	
10^{-1}			.02	2		98	
10^{-2}			.11	12		88	
10^{-3}			.44	49	0.899	51	
10^{-4}			.74	84		16	
10^{-5}			.87	99		1	
10^{-6}			.90	101		-	
10^{-7}			.83	94		6	
10^{-8}			.87	99		1	
31) 62-320/Na-4(23531)	6/26/85	DMA					
10^{-2}			.00	-		100	
10^{-3}			.04	5		95	
10^{-4}			.13	15	0.008	85	
10^{-5}			.28	32		68	
10^{-6}			.81	91		9	
10^{-7}			.85	96		4	
10^{-8}			.90	101		-	
32) 63-556 (RN 26093)	6/26/85	DMA					
10^{-2}			.11	12		88	
10^{-3}			.44	49	0.753	51	
10^{-4}			.68	77		23	
10^{-5}			.83	94		6	
10^{-6}			.87	99		1	
10^{-7}			.90	101		-	
10^{-8}			.85	96		4	

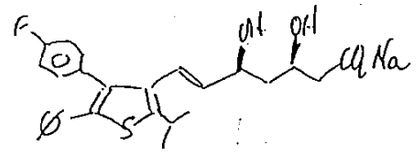
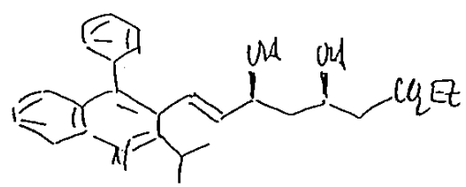
OCTOBER 8, 1987

DRUG INHIBITION STUDY FOR SANDOZ CONTRACT

Sandoz unknowns were dissolved in DMA (Dimethylacetamide from Sigma), and Buffer A
Dilution of each compound gave the concentrations indicated in the results.

Microsomes were prepared from male Sprague-Dawley rats (150 g) in Buffer A with 10 mM DTT and frozen at -80°C until thawed and used for experiment. 200 µl Aliquots of microsomal suspension (0.91 mg/ml) plus 10 µl of drug dilution were assayed for HMG-CoA reductase activity.

Compactin in DMA at various concentrations was assayed for inhibition also and is indicated in the results. Buffer A, and DMA were also assayed by adding 10 µl of each to 200 µl of microsomal suspension and they showed no significant inhibition of HMG-CoA reductase.

COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL		% OF INHIBITION	REMARKS
) Compactin (29299)	10/8/87	DMA					
1mM			.01	1		99	
10^{-1}			.04	3	1.37	97	
10^{-2}			.18	17		83	
10^{-3}			.62	61		39	
10^{-4}			.88	86		14	
10^{-5}			1.04	102		-	
10^{-6}			1.04	102		-	
10^{-7}			1.02	100		-	
10^{-8}			1.04	102		-	
) 62-320 (24135)	10/8/87	DMA					
10^{-2}			.01	1		99	
10^{-3}			.06	6	0.007	94	
10^{-4}			.20	20		80	
10^{-5}			.36	36		64	
10^{-6}			.83	82		18	
10^{-7}			1.02	100		-	
10^{-8}			1.02	100		-	
) 64-906 (RN 30393)	10-8-87	DMA					
10^{-2}		CHIRAL	.01	1		99	
10^{-3}			.01	1		99	
10^{-4}			.11	10	0.0012	90	
10^{-5}			.27	26		74	
10^{-6}			.55	54		46	
10^{-7}			1.02	100		-	
10^{-8}			1.02	100		-	
) 64-933 (RN 30441)	10-8-87	DMA					
10^{-2}			.20	20		80	
10^{-3}			.69	68	2.37	32	
10^{-4}			.99	98		2	
10^{-5}			1.04	102		-	
10^{-6}			.99	98		2	
10^{-7}			1.04	102		-	
10^{-8}			.99	98		2	

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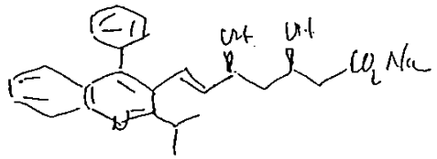
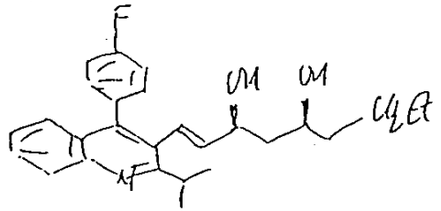
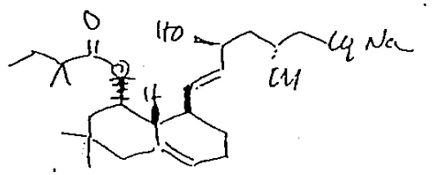
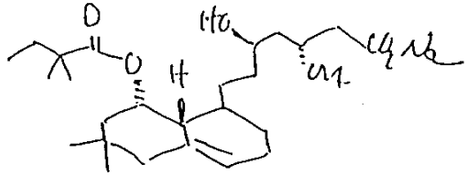
COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL		% OF INHIBITION	REMARKS
5) 64-934/Na(RN 30442)	10/8/87	DMA					
10^{-2}			.22	22		78	
10^{-3}			.71	70	2.61	29	
10^{-4}			.99	98		2	
10^{-5}			1.04	102		-	
10^{-6}			1.04	102		-	
10^{-7}			1.02	100		-	
10^{-8}			1.23	121		-	
6) 64-935 (RN 30447)	10/8/87	DMA					
10^{-2}			.13	13		87	
10^{-3}			.32	31	0.413	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	>10	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	0.73	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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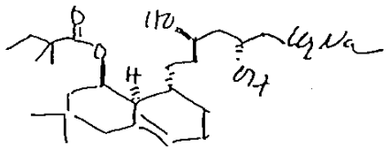
COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL	% OF INHIBITION	REMARK:
64-948/Na(RN 30485)	10/8/87	DMA				
10-2			.99	98	2	
10-3			.99	98	2	
10-4			1.02	100	-	
10-5			.97	95	5	
10-6			.99	98	2	
10-7			.99	98	2	
10-8			.95	93	7	



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OCTOBER 15, 1987

DRUG INHIBITION STUDY FOR SANDOZ CONTRACT

Sandoz unknowns were dissolved in DMA (Dimethylacetamide from Sigma), and Buffer A
Dilution of each compound gave the concentrations indicated in the results.

Microsomes were prepared from male Sprague-Dawley rats (150 g) in Buffer A with 10 mM DTT and frozen at -80°C until thawed and used for experiment. 200 µl Aliquots of microsomal suspension (0.96 mg/ml) plus 10 µl of drug dilution were assayed for HMG-CoA reductase activity.

Compactin in DMA at various concentrations was assayed for inhibition also and is indicated in the results. Buffer A, and DMA were also assayed by adding 10 µl of each to 200 µl of microsomal suspension and they showed no significant inhibition of HMG-CoA reductase.

COMPOUND	DATE	SOLVENT	S.A.	% OF CONTROL	% OF INHIBITION
1) Compactin (29299)	10-13-87	DMA			
1mM			.02	2	98
10^{-1}			.02	2	98
10^{-2}			.18	20	80
10^{-3}			.64	69	31
10^{-4}			.84	91	9
10^{-5}			.95	103	-
10^{-6}			1.02	110	-
10^{-7}			.98	106	-
10^{-8}			.98	106	-
2) 62-320 (24135)	10-13-87	DMA			
10^{-2}			.02	2	98
10^{-3}			.05	5	95
10^{-4}			.18	20	80
10^{-5}			.30	32	68
10^{-6}			.86	93	7
10^{-7}			.98	106	-
10^{-8}			.95	103	-
3) 64-942/Na (30461)	10-13-87	DMA			
10^{-2}			.73	79	21
10^{-3}			.95	103	-
10^{-4}			1.05	113	-
10^{-5}			.91	98	2
10^{-6}			.93	101	-
10^{-7}			1.00	108	-
10^{-8}			.98	106	-
1) 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	-

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Compound	DATE	SOLVENT	S.A.	% OF CONTROL	% OF INHIBITION	REMARK
5) 64-727 (RN 30024)	10-13-87	DMA				
mM						
10^{-1}			.05	5	95	
10^{-2}			.34	37	63	
10^{-3}			.82	88	12	
10^{-4}			.93	101	–	
10^{-5}			.95	103	–	
10^{-6}			.98	106	–	
10^{-7}			.93	101	–	
10^{-8}			.93	101	–	
			.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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Exhibit K

Date 10/22/87 Proj. H318

Cont'd from- 134

Title Cholesterol Synthesis Inhibition Screen

133

334

CHOLESTEROL BIOSYNTHESIS INH

LIPID METABOLISM DEPARTMENT
HMGR SCREENING UNIT
Sandoz Research Institute
To: Dr. D. Weinstein, Departmenthead
Mr. R. Slaughter, Responsible Technician
From: Mr. A. Engstrom, Responsible Investigator
CC: D.N., M.L.R., ARC

STUDY #: H318
STUDY ON 10/22/87
SK.REF. 917-83
APPROVAL
DATE 10/21/87
GEN. ARC#86-006

Title: In vivo single dose assay to test for inhibition of biosynthesis by compounds: 63-748, 64-844, 64-936

Purpose: Determine the invivo effects of test compounds in rats on cholesterol biosynthesis.

Experimental design: IN VIVO CHOLESTEROL BIOSYNTHESIS INHIBITION DT0065 invivo single dose assay 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. Animal use will be in compliance with ARC regulations. Duration = 1 hr. No/group = 6. No of groups = 14. WCR rats.

Rats	COMPOUND	REGNO	DOSE mg/kg	STOCK mg/20ml	WORKING SOLUTION ml stock q.s. to 15ml
1-6	Control	------	------	------	----------
7-12	63-748	26888	1	2	UNDILUTED
13-18	"	"	0.3	-	4.5
19-24	"	"	0.1	-	1.5
25-30	64-844	30290	0.3	2	4.5
31-36	"	"	0.1	-	1.5
37-42	"	"	0.03	-	0.45
43-48	64-936	30488	1	2	UNDILUTED
49-54	"	"	0.3	-	4.5
55-60	"	"	0.1	-	1.5
61-66	62-210	30859	0.3	2	4.5
67-72	"	"	0.1	-	1.5
73-78	"	"	0.03	-	0.45
79-84	Control	------	------	------	----------

Performed by- Todd A. Slaughter

Witness- R Engstrom

Cont'd to- 135

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Title- Cholesterol Synthesis Inhibition Screen

Date 10/22/87 Proj. 12

Cont'd From- 133

335

IN VIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN H316

	RAT	COMPOUND	REGNO	DOSE mg/kg	PO/IP	STATISTICS	
		BLANK				STD	7.6
		14C-STANDARD			20178	% EFFIC=	99
	1	CONTROL			492		
	2	CONTROL			677	MEAN =	537.7
	3	CONTROL			580	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	25688	1.00	170	MEAN =	155.9
	9	63-748	25688	1.00	278	STD =	73.1
	10	63-748	25688	1.00	113	SE =	32.7
	11	63-748	25688	1.00	113	t =	7.7
	12	63-748	25688	1.00	106	p	<.01
	7	63-748	25688	1.00	528*	%CHG =	-71
	13	63-748	25688	.300	358	MEAN =	316.3
	14	63-748	25688	.300	355	STD =	68.3
	15	63-748	25688	.300	391	SE =	39.5
	17	63-748	25688	.300	199	t =	4.0
	18	63-748	25688	.300	253	p	<.01
	16	63-748	25688	.300	794<	%CHG =	-40.8
	19	63-748	25688	.100	348	MEAN =	456.7
	20	63-748	25688	.100	725	STD =	213.5
	21	63-746	25688	.100	310	SE =	87.2
	22	63-748	25688	.100	650	t =	0.6
	23	63-748	25688	.100	536	p	N.S.
	24	63-748	25688	.100	178	%CHG =	-14.7
	25	64-844	30280	.300	286	MEAN =	185.8
	26	64-844	30280	.300	470	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 =	69.9
	33	64-844	30280	.100	195	SE =	39.9
	25	64-844	30280	.100	157	t =	6.7
	26	64-844	30280	.100	185	p	<.01
	31	64-844	30280	.100	656<	%CHG =	-59.1

Performed by- Todd R. Ashby-Mains

Witness- R Dyston

Cont'd to- 135

Date 10/22/87 Proj# 3,4

Cont'd From- 134

Title Cholesterol Synthesis Inhibition Screen

135

336

INVIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN HS18

RAT	COMPOUND REGNO	DOSE mg/kg	nCi/dl	STATISTICS	
37	64-844	30280	.030	354	MEAN = 419.7
38	64-844	30280	.030	518	STD = 138.6
39	64-844	30280	.030	639	SE = 56.6
40	64-844	30280	.030	245	t = 1.7
41	64-844	30280	.030	356	p N.S.
42	64-844	30280	.030	402	%CHG = -21.9
43	64-935	30488	1.00	590	MEAN = 489.4
44	64-935	30488	1.00	642	STD = 132.5
45	64-935	30488	1.00	290	SE = 54.2
46	64-935	30488	1.00	388	t = 0.7
47	64-935	30488	1.00	532	p N.S.
48	64-935	30488	1.00	513	%CHG = -9.0
49	64-935	30488	.300	167	MEAN = 326.7
50	64-935	30488	.300	332	STD = 165.0
51	64-935	30488	.300	566	SE = 67.4
52	64-935	30488	.300	378	t = 2.7
53	64-935	30488	.300	223	p <.02
54	64-935	30488	.300	473	%CHG = -39.2
55	64-935	30486	.100	485	MEAN = 416.5
56	64-935	30486	.100	181	STD = 166.8
57	64-935	30486	.100	339	SE = 68.9
58	64-935	30486	.100	486	t = 1.8
59	64-935	30486	.100	367	p N.S.
60	64-935	30486	.100	439	%CHG = -22.5
61	62-320	30559	.300	72	MEAN = 67.5
62	62-320	30559	.300	89	STD = 12.1
63	62-320	30559	.300	71	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 = 6.5
69	62-320	30559	.100	149	p <.01
72	62-320	30559	.100	138	%CHG = -69.3
73	62-320	30559	.030	333	MEAN = 351.2
74	62-320	30559	.030	380	STD = 173.9
75	62-320	30559	.030	77	SE = 70.8
76	62-320	30559	.030	578	t = 3.9
77	62-320	30559	.030	463	p <.05
78	62-320	30559	.030	277	%CHG = -34.7

* = rejected by "Q" test
= LACK OF SAMPLE

Computed 12-09-87

Performed by- Tom Slaughter

Witness- [signature]

Cont'd to-

136 Title- Cholesterol Synthesis Inhibition Screen

Date 10/29/87 Proj: 3

Cont'd From-

337

CHOLESTEROL BIOSYNTHESIS INHIBITION SCREEN

LIPID METABOLISM DEPARTMENT
HMGR SCREENING UNIT
Sandoz Research Institute

STUDY # H319
STUDY ON 10/29/87
BK.REF. 917-136
APPROVAL
DATE 10/28/87
GEN. ARC##-004

To: Dr. D. Weinstein, Departmenthead
Mr. R. Steuerle, Responsible Technician
From: Mr. R. Engstrom, Responsible Investigator
CC: D.N., M.L.S., ARC

Title: In vivo single dose assay to test for inhibition of biosynthesis by compounds: 84-298, 84-933, 83-935

Purpose: Determine the invivo effects of test compounds in rats on cholesterol biosynthesis.

Experimental design: IN VIVO CHOLESTEROL BIOSYNTHESIS INHIBITION CTO006 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 tied 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 al stock q.s. to 15ml
1-6	Control	------	------	------	----------
7-12	84-298	29377	1		2 UNDILUTED
13-18	"	"	0.3	-	4.5
19-24	"	"	0.1	-	1.5
25-30	84-933	30447	1		2 UNDILUTED
31-36	"	"	0.3	-	4.5
37-42	"	"	0.1	-	1.5
43-48	84-935	30441	1		2 UNDILUTED
49-54	"	"	0.3	-	4.5
55-60	"	"	0.1	-	1.5
61-66	83-920	30559	0.3	3	4.5
67-72	"	"	0.1	-	1.5
73-78	"	"	0.03	-	0.45
79-84	Control	------	------	------	----------

Performed by-

Witness- R Rastrom

Cont'd to- 337

Date 8/12/91 Proj.

Cont'd From-

Title-

137

338

IN VIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN H319

RAT	COMPOUND	REGNO	DOSE mg/kg	nCi/dl	STATISTICS		
	BLANK			7			
	14C-STANDARD			20176	% EFFIC=		SS
1	CONTROL			953			
2	CONTROL			515	MEAN =		671.8
3	CONTROL			648	STD =		211.0
4	CONTROL			578	SE =		80.9
5	CONTROL			934			
6	CONTROL			354			
79	CONTROL			756			
80	CONTROL			947			
81	CONTROL			814			
82	CONTROL			545			
83	CONTROL			872			
84	CONTROL			714			
7	84-296	28277	1.00	203	MEAN =		151.7
8	84-296	28277	1.00	381	STD =		113.6
9	84-296	28277	1.00	92	SE =		48.4
10	84-296	28277	1.00	78	t =		6.8
11	84-296	28277	1.00	71	p		<.01
12	84-296	28277	1.00	115	%CHG =		-77
13	84-296	28277	.300	311	MEAN =		335.1
14	84-296	28277	.300	284	STD =		81.4
15	84-296	28277	.300	257	SE =		33.2
16	84-296	28277	.300	307	t =		8.3
17	84-296	28277	.300	114	p		<.01
18	84-296	28277	.300	157	%CHG =		-66.0
19	84-296	28277	.100	381	MEAN =		385.7
20	84-296	28277	.100	387	STD =		81.5
21	84-296	28277	.100	268	SE =		33.3
22	84-296	28277	.100	392	t =		4.1
23	84-296	28277	.100	499	p		<.01
24	84-296	28277	.100	425	%CHG =		-42.1
25	84-933	30447	1.00	838	MEAN =		438.1
26	84-933	30447	1.00	275	STD =		253.4
27	84-933	30447	1.00	136	SE =		103.5
28	84-933	30447	1.00	584	t =		2.0
29	84-933	30447	1.00	258	p		N.S.
30	84-933	30447	1.00	447	%CHG =		-36.3
31	84-933	30447	.300	830	MEAN =		557.4
32	84-933	30447	.300	646	STD =		100.5
33	84-933	30447	.300	585	SE =		41.0
34	84-933	30447	.300	598	t =		1.6
35	84-933	30447	.300	366	p		N.S.
36	84-933	30447	.300	618	%CHG =		-17.0

Performed by-

138 Title-

Date

Cont'd From

INVIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN H319-4

RAT	COMPOUND	REGNO	DOSE mg/kg	nCi/dl	STATISTICS		
37	64-933	30447	.100	556	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	=	-16.6
43	64-935	30441	1.00	182	MEAN	=	230.0
44	64-935	30441	1.00	307	STD	=	78.2
45	64-935	30441	1.00	198	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	281	%CHG	=	-65.8
49	64-935	30441	.300	778	MEAN	=	472.2
50	64-935	30441	.300	282	STD	=	179.5
51	64-935	30441	.300	520	SE	=	73.3
52	64-935	30441	.300	413	t	=	2.1
53	64-935	30441	.300	344	P		N.S.
54	64-935	30441	.300	438	%CHG	=	-29.7
55	64-935	30441	.100	411	MEAN	=	428.2
56	64-935	30441	.100	320	STD	=	119.1
57	64-935	30441	.100	295	SE	=	46.8
58	64-935	30441	.100	425	t	=	8.1
59	64-935	30441	.100	821	P		<.02
60	64-935	30441	.100	495	%CHG	=	-38.5
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	=	8.6
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	=	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	225	P		<.01
72	62-320	30559	.100	804	%CHG	=	-50.8
73	62-320	30559	.030	421	MEAN	=	445.1
74	62-320	30559	.030	472	STD	=	64.1
75	62-320	30559	.030	571	SE	=	36.4
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 Stephen

Cont'd to-

340

64566	29651	280-85	>	1	09-JUN-87	917-065
64569	29652	280-85	=	.16	15-JUN-87	917-081
64602	29743	101-85	>	.3	05-MAY-87	917-050
64602	29743	101-85	>	.3	05-MAY-87	917-050
64604	29744	101-85	>	.3	05-MAY-87	917-051
64604	29744	101-85	>	.3	05-MAY-87	917-051
64604	29745	101-85	=	.48	14-JUL-87	917-086
64608	29756	298-85	>	7.5	15-MAY-87	917-056
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	917-155
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	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	917-136
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
917223	24022		>	16	20-MAR-84	812-183
980349	29591	102-82	>	10	18-AUG-87	917-098
980586	29588	102-82	>	10	18-AUG-87	917-098
980820	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

BIOLOGICAL ACTIVITY DATA REPORT (FOR PATENT DEPT.)

INVENTOR: S. Wattanasin DISCL. NO.: 399-84 4/8

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

User: STR -at pr0

<USERO2>ENGSTR>IC5 TA>PD295-84

419

299/84

295-84 &
299-84

Label: PRT002 -form

Pathname: <USERO2>ENGSTR>IC50DATA>PD295-84
File last modified: 88-05-23. 08:25:36. Mon

Spooled: 88-05-23 08:50:36. Mon [Spooler rev 19.4.6]
Started: 88-05-23 08:50:40. Mon on: 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	
SAH-063271	25208	295-84	0.0320	09-10-84	1069-055	SAPONIFIED
SAH-063271	25208	295-84	0.1450	09-12-84	1069-055	

SAH-064484	F	29413	I95-84	0.0320	11-24-86	1149-227
SAH-064744	E	30059	I95-84	0.0320	05-01-87	1149-293
SAH-064745	S	30060	I95-84	0.0030	05-01-87	1149-294
SAH-064745	S	30060	I95-84	0.0030	07-07-87	1149-297
SAH-064815	E	30198	I95-84	0.0220	07-07-87	1238-001
SAH-064816	S	30199	I95-84	0.0450	07-07-87	1238-002
SAH-063162	S	30203	I95-84	0.0080	07-07-87	1238-003
SAH-064745		30765	I95-84	0.0020	01-12-88	1238-030

→SAH-063366		25496	I99-84	1.5800	12-13-84	1069-113
→SAH-063549		26082	I99-84	7.3100	06-13-84	1069-197
→SAH-063548		26080	I99-84	3.7750	06-13-84	1069-198 —
→SAH-064933	E	30441	I99-84	2.3700	10-08-87	1238-013
→SAH-064934	S	30442	I99-84	2.6100	10-08-87	1238-014
→SAH-064935	E	30447	I99-84	0.4130	10-08-87	1238-015 —
→SAH-064936	S	30448	I99-84	0.5300	10-13-87	1238-016 —

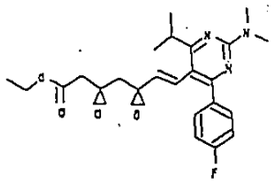
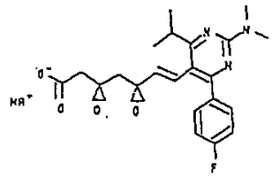
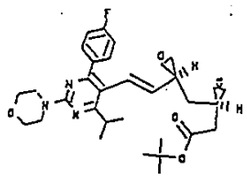
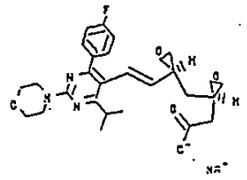
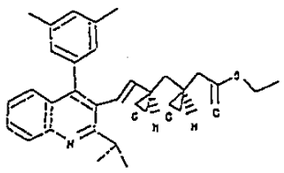
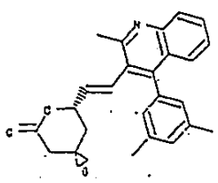
ED50 TABLE RAT INVIVO ACETATE INCORPORATION (CSIV-DT65)

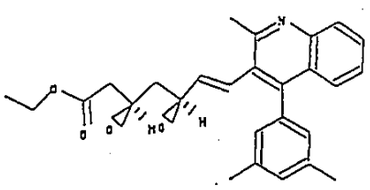
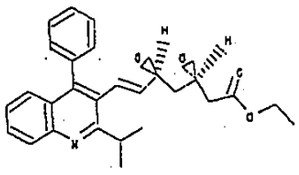
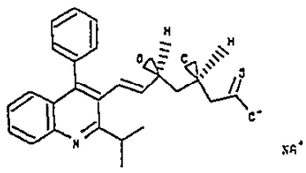
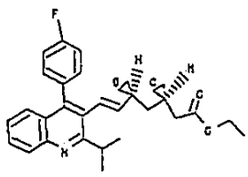
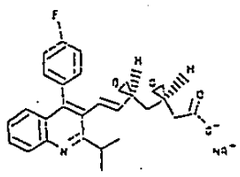
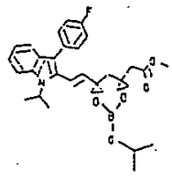
THIS FILE IS A CALCULATED ESTIMATE OF THE ED50 (DOSE WHICH REDUCES THE INCORPORATION OF 14C-ACETATE INTO CHOLESTEROL BY 50%) USING ALL THE STUDIES ON THE RELEVANT COMPOUNDS UP TO THE SORT DATE.

LAST UPDATE: 1-06-88 SORT BY: REGNO

COMPOUND	REGNO	CISCL	ED50 mg/kg	DATE mm-dd-yy	REF bk-pg	COMMENTS
SAH-064745	30060	I95-84 =	0.016	10-20-87	917-127	N=9
SAH-064745	30765	I95-84 =	0.016	02-19-88	917-154	N=3 BS BATCH
SAH-064745	ALL	I95-84 =	0.016	02-19-88	917-154	N=12 2BATCHES
SAH-063162	25500	I95-84 =	0.019	09-18-87	917-101	N=10
SAH-063162	ALL	I95-84 =	0.040	09-18-87		N=19 3BATCHES
SAH-063162	25085	I95-84 =	0.079	10-11-84	812-266	N=8
SAH-064119	27563	I95-84 =	0.08	05-16-86	869-228	N=6
SAH-064744	30059	I95-84 >	0.10	07-14-87	917-090	N=3 -21% @.10
SAH-064816	30199	I95-84 =	0.10	10-12-87	917-119	N=6
SAH-064483	29412	I95-84 =	0.13	02-06-87	917-024	N=3
SAH-064063	27424	I95-84 =	0.19	04-17-86	869-211	N=3
SAH-064309	28718	I95-84 =	0.19	11-03-86	869-283	N=3
SAH-063231	25079	I95-84 >	0.25	08-30-84	812-250	
SAH-064393	29163	I95-84 =	0.25	02-25-87	917-031	N=6
SAH-063161	24821	I95-84 >	0.250	11-29-84	812-293	-12@0.25
SAH-063989	27237	I95-84 =	0.28	04-04-86	869-195	N=6
AH-063425	25687	I95-84 >	0.3	03-20-85	869-046	N=3
SAH-064305	28701	I95-84 >	0.3	11-03-86	869-280	N=3 -34% @.3
SAH-064480	29404	I95-84 >	0.3	02-06-87	917-023	N=3 +3% @.3
SAH-063270	ALL	I95-84 =	0.308	02-07-85		N=11 2BATCHES
SAH-063270	25206	I95-84 =	0.33	10-11-84	812-267	
SAH-063270	25501	I95-84 =	0.362	01-21-85	869-018	
SAH-064307	28705	I95-84 =	0.47	02-06-87	917-020	N=6
SAH-063159	24810	I95-84 >	0.5	06-19-84	812-219	

SAH-063162	24822	E95-84	<	0.5	06-19-84	812-219	N=1 -87@0.5
SAH-063175	24866	E95-84	<	0.5	06-19-84	812-220	
SAH-063230	25078	E95-84	>	0.500	11-29-84	812-294	
SAH-064391	29161	E95-84	=	0.51	10-30-86	917-011	N=3
SAH-063035	24317	E95-84	>	0.6	05-07-84	812-201	
SAH-063145	24755	E95-84	>	0.6	05-18-84	812-208	
SAH-063146	24756	E95-84	>	0.6	05-18-84	812-208	
SAH-063174	24865	E95-84	=	0.706	06-19-84	812-220	
SAH-064481	29406	E95-84	>	1.0	02-06-87	917-024	N=3 -28% @1.0
SAH-064482	29411	E95-84	>	1.0	03-18-87	917-041	N=3 -41% @1.0
SAH-064064	27433	E95-84	=	1.05	07-17-86	869-263	N=6
SAH-064204	27793	E95-84	=	1.21	10-02-86	869-298	N=6
SAH-064141	27630	E95-84	>	1.25	02-24-87	917-029	N=6 -24% @1.25
SAH-064308	28717	E95-84	>	1.5	11-03-86	869-283	N=3 -16% @1.5
SAH-064193	27760	E95-84	>	2.4	07-24-86	869-269	N=3 -24% @2.4
SAH-063076	24449	E95-84	<	2.5	05-14-84	812-204	
SAH-063084	24512	E95-84	>	2.5	05-07-84	812-201	
→ SAH-064933	30441	E99-84	=	~~0.49~~ ≥1	12-09-87	917-138	N=3 -36 %@1.0
→ SAH-064935	30447	E99-84	≈	~~1=0~~ .99	12-09-87	917-138	N=3

SAH-064747 30067 1190-248-32 298-84		0.0820 05-03-87 1149-295
SAH-064748 30068 1190-257-26 298-84		0.0600 05-01-87 1149-296
SAH-064998 30622 1245-108-35 298-84	CHIRAL 	3.0400 11-17-87 1238-020
SAH-064999 30623 1245-120-30 298-84	CHIRAL 	0.0800 11-17-87 1238-021 BUFFER A
SAH-063366 25496 1079-111-19 299-84		1.5800 12-13-84 1059-113
SAH-063549 26082 1127-011-37 299-84		7.3100 06-13-84 1059-197

SAH-063548 26080 1127-011-34 299-84		IC50 (uM) - MICROSOMAL ASSAY 3.7750 DATE TESTED 06-13-84 REFERENCE 1069-198 COMMENTS
SAH-064933 30441 1206-176-43 299-84		IC50 (uM) - MICROSOMAL ASSAY 2.3700 DATE TESTED 10-08-87 REFERENCE 1238-013 COMMENTS
SAH-064934 30442 1206-179-30 299-84		IC50 (uM) - MICROSOMAL ASSAY 2.6100 DATE TESTED 10-08-87 REFERENCE 1238-014 COMMENTS
SAH-064935 30447 1206-190-41 299-84		IC50 (uM) - MICROSOMAL ASSAY 0.4130 DATE TESTED 10-08-87 REFERENCE 1238-015 COMMENTS
SAH-064936 30448 1206-201-30 299-84		IC50 (uM) - MICROSOMAL ASSAY 0.5300 DATE TESTED 10-13-87 REFERENCE 1238-016 COMMENTS
SAH-063224 25041 1036-087-41 431-54		IC50 (uM) - MICROSOMAL ASSAY 0.0019 DATE TESTED 07-26-84 REFERENCE 1069-053 COMMENTS

Deposition of CHESTER E. HOLMLUND, 26 March 1993.

CORRECTIONS TO DEPOSITION

Page	Line	Correction:
6	2&3	Change "sterile" to "sterol".
53	22	Change "sterile" to "sterol".
55	13	Change "ED pH" to "NAD-pH".
55	14	Change "and the" to "in".
25	20-21	For clarification:
		see the greater than. I assume that the greater than, 1 inch to the left, does apply to the one and that greater

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Certified Shorthand Reporters

1155 South Washington Street
Suite 201
Naperville, IL 60540
708-983-0030

FYI

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D-00581-93

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
INTERFERENCE NOS. 102,648 – #89
102,975 – #34

WATTANASIN,

vs.

FUJIKAWA, et al.

DEPOSITION OF:
JOANNE GIESSER, ESQ.

FRIDAY, APRIL 9, 1993
12:00 P.M. to 4:30 P.M.

A P P E A R A N C E S:

DIANE E. FURMAN, ESQ.
Sandoz Corporation
59 Route 10
East Hanover, New Jersey 07936
Attorneys for Wattanasin.

OBLON, SPIVAK, MC CLELLAND,
MAIER & NEUSTADT
1755 Jefferson Davis Highway
Fourth Floor
Arlington, Virginia 22202
BY: STEVEN B. KELBER, ESQ.,
Attorneys for Fujikawa.

CERTIFIED TRANSCRIPT FOR Wattanasin

I-N-D-E-X

E-X-H-I-B-I-T-S

Giesser - cross

(Before Paula M. Quetsch, a Certified Shorthand Reporter and Notary Public of the State of Illinois, held at the offices of Amoco Corporation, 55 Shuman Boulevard, Suite 600, Naperville, Illinois, on Friday, April 9, 1993, commencing at 12:00 p.m.)

- -

J O A N N E M. G I E S S E R, 55 Shuman Boulevard, Suite 600, Naperville, Illinois, Sworn.

MR. KELBER: Good morning. This is the cross examination deposition of Joanne Giesser, is that correct --

THE WITNESS: Uh-huh.

MR. KELBER: -- responsive to the declaration filed, I'm here on behalf of Fujikawa, and we have the witness and Diane Furman on behalf of Wattanasin.

CROSS EXAMINATION

By Mr. Kelber

Q. Ms. Giesser, I'm going to hand the reporter a document that I would like identified as F20, and that's just the declaration.

(Deposition Exhibit F20 marked for identification.)

Giesser - cross

Q. If you would, take just a couple of minutes to review that document.

A. Okay.

Q. Is that document familiar to you?

A. Yes, it is.

Q. And on the last page, which is page six of the document and bears the number 373 at the right-hand top corner, is that your signature?

A. Yes, it is.

Q. Did you review any documents before -- any other documents before signing F20?

A. Yes, I did.

Q. Could you describe those documents for me?

A. They were the ones referred to in the declaration.

Q. Were there any other documents that are not identified in the declaration that you reviewed prior to signing this exhibit?

A. Not that I recall.

Q. Let me turn your attention to paragraph three on the first page of that document. Do you see the reference to the involved Wattanasin continuation application and the parent application thereof?

Giesser - cross

A. Yes.

Q. Did you review that application or the parent application prior to signing this declaration?

A. No, I did not.

Q. Do you recall the specifics of that application?

A. I recall the generalities of it.

Q. What was the basis for your conclusion that you filed the involved continuation application if you did not review it?

A. I recall filing it.

Q. How was it -- I'm sorry, if you didn't see it, how was it identified for you?

A. I'm sorry, I don't understand.

Q. Well, you didn't review the actual application itself or the parent application. Did you recall it by serial number, or what was the mechanism for identifying that application?

A. Well, up at the corner of the document it says case 600-7101 continuation.

Q. And that was sufficient to recall it for you?

A. Yes.

Giesser - cross

Q. Ms. Giesser, when did you first become aware that a third party had filed for U.S. patent protection for subject matter similar to that claimed in case number 600-7101?

A. I don't remember the exact date.

Q. Do you remember who identified it for you?

A. Not exactly. I don't recall the specifics of it.

Q. Was the third-party claim brought to your attention by someone in the patent department, do you recall?

A. It would have been likely to have been Mel Kassenoff.

Q. Isn't it correct, Ms. Giesser, that in fact the existence of the third-party patent application was brought to your attention before preparation of the draft of the Wattanasin application?

A. No, that's not how I recall it.

Q. So you recall preparing the draft and then becoming aware of the third-party case?

A. I recall being involved in preparing the draft. It wasn't finished at the time when I learned about the third-party one.

Giesser - cross

Q. Was the initial -- do you have a recollection was the initial draft prepared before learning of it?

A. No, I was in the process of preparing it.

Q. So that would have been before December -- before December 14 --

A. Yes.

Q. -- of 1988?

A. Yes.

Q. At the time you were preparing the draft document for case number 600-7101, had you previously been involved in any interference contests?

A. I had been involved in a minor amount when I was a patent examiner at the patent office. A few cases which I was examining I helped set up the interference, but I didn't do any substantive work on them.

Q. Did anyone at the Sandoz patent and trademark department assist you in requesting the declaration of interference filed in 600-7101?

A. As I recall, I had conversations with Mel Kassenoff and Dick Vila concerning how you would go about setting up such a request and spoke with them

Giesser - cross

while I was compiling necessary documents and such.

Q. Were there any considerations that you took into account in drafting the case 600-7101 by reason of the fact that you would be requesting an interference declaration in connection therewith?

A. I don't recall handling the case any differently from any other case at that point.

Q. Let me turn your attention to page two of the declaration, which is -- and starting at the top at page five -- I'm sorry, paragraph five. Do you have a recollection of actually receiving a copy of the minutes referred to in that paragraph?

A. No, I don't.

Q. Why would you have received a copy?

A. They were routinely distributed to each member of the department after the meetings.

Q. Was there any routine separation between the date of the meeting and the time the minutes were distributed?

A. They were actually distributed within about a week or so, depending on how long it took the secretaries to compile them and type it up.

Q. Were there any occasions where you did not

Giesser - cross

receive minutes of the patent committee during your tenure at Sandoz?

A. No.

Q. How did you know, as stated in paragraph six of F20, that PD 299/84 had been assigned to you?

A. It said so in the minutes.

Q. Said so in the minutes. Was there a specific statement to that effect?

A. The minutes, they would rate the application, and if it was rated A, the attorney who would be responsible for it, their initials would appear.

MS. FURMAN: Not only if it was rated A.

Q. You see the reference to existing filing priorities in paragraph six of page two of the declaration?

A. Yes.

Q. What kind of existing filing priorities were there as of the time you received the assignment of PD 299/84?

A. Mel Kassenoff had a number of cases in the general HMG-CoA Reductase area which had been rated A and which had to be filed, as well.

Giesser - cross

Q. How about yourself?

A. At that time, no.

Q. Did you have any other cases other than case 600-7101 assigned to you for filing at the time that that particular case was assigned to you?

A. I don't recall specifically whether I had or not.

Q. Looking at paragraph six again, what other priorities existed that might preclude you from filing PD 299/84?

A. Well, there were certainly other cases around both from Pharma and for the other companies that I had responsibility for.

Q. Who is Pharma?

A. Sandoz Pharma Company.

Q. Now, by "other cases," other cases to prepare?

A. Yes.

Q. And those cases were assigned a priority in advance of 299/84?

A. I'm not sure whether all those cases were officially rated at that point or not.

Q. Okay. Well, what I'm a little confused

Giesser - cross

about is that paragraph six indicates that either Mr. Kassenoff or you would take care of it after existing filing priorities had been completed.

Now, you've testified that Mr. Kassenoff had some cases stacked up, if you will, in advance of PD 299/84. Would it be a correct conclusion that if you did not have filing priorities existing as of the time that case was assigned to you that you would have the primary responsibility for filing that case?

A. I did have the primary responsibility for filing this case.

Q. What other tasks or assignments did you have that would take priority on your resources before preparing 299/84 for filing?

A. Well, I was working for -- my responsibilities at Sandoz involved working for a number of different Sandoz companies. Aside from responsibilities in this area of Pharma, I also did a lot of work for the seed companies, which at that time were part of Sandoz' crop protection. I also was getting involved in work with a joint venture that Sandoz was involved called Repligen Sandoz

Giesser - cross

Research Corporation, or we call it RSRC.

I also had other -- aside from the HMG-CoA Reductase area, I also had other areas which I was responsible for in Pharma.

Q. Now, the other responsibilities that you had identified, and particularly the seed companies and the RSRC, did you have any filing responsibilities for them that would take priority over the filing responsibility for 600-7101?

A. Yes.

Q. Could you describe those responsibilities for me?

A. As it turned out, there were a number of applications which, out of the seed companies, although as of January 1988 had not been decided to be filed upon but later on as the year progressed were coming up against time bars.

Q. So as of January, those cases had not been assigned to you for preparation?

A. Right.

Q. Were they subsequently assigned to you for preparation?

A. Yes.

Giesser - cross

Q. And about when was that?

A. I'm not exactly sure. It was later in the year, though.

Q. Do you have a recollection of approximately how many -- would it have been as early as June?

A. Probably not the seed cases, but probably yes on a number of applications for Sandoz' crop protection.

Q. When you say a number, is that -- help me out. Is that more than five?

A. At least three.

Q. So these cases were designated A after -- and by A, I mean intended for filing -- after 600-7101 but were intended for filing before 600-7101; is that correct?

A. Yes.

Q. And they took priority over 7101 because --

A. Well, certainly, at least as I recall, I think some of the crop protection cases had -- either the scientists had wanted to publish or were scheduled to publish, so there were bars of that sort running on them.

Q. The scientists --

A. The inventors.

Q. The inventors had published?

A. No. I believe on the ones at that time they had either submitted, you know, like an abstract to a meeting or something like that -- I don't remember exactly, but I think there were publication concerns involved with some of those.

Q. How many applications did you prepare and file between January -- I'm sorry, between February '88 and March '89?

A. Including March?

Q. Let's take it through the end of February '89.

A. I don't remember exactly. Probably close to 15.

Q. And only one in the HMG-CoA Reductase field; is that correct?

A. No.

Q. What other cases were filed -- did you prepare and file in the HMG-CoA Reductase field?

A. There was a CIP, which I recall was a rather substantial CIP which was filed I believe in October of '88.

Giesser - cross

Q. Let me turn your attention to page three of F20, specifically paragraph 11.

A. Uh-huh.

Q. There is a case referred to there, 7025/CIP/CIP. Is that the case you're referring to?

A. Yes. I believe that date is incorrect. It should be October 6th, 1988, not November.

Q. And that's based on your memory?

A. No, I have since seen copies of a filing receipt for it.

Q. You have since seen copies of the filing receipt. You did not see the filing receipt at the time you signed this declaration?

A. No, I guess I did. It says here -- there's a reference to it here on Exhibit D.

Q. So you think you did see the filing receipt --

A. Uh-huh.

Q. -- at the time that you signed this declaration?

A. Right.

Q. Are there any documents referred to in the declaration that you might not have seen at the time

Giesser - cross

of signing?

A. Again, not that I recall.

MR. KELBER: I'm going to hand the reporter a document that I'd like identified as F21.

(Deposition Exhibit F21 marked for identification.)

Q. Ms. Giesser, is that in fact the filing receipt that you just referred to?

A. Yes, it is.

Q. And that reflects a filing date of when?

A. October 6th, 1988.

Q. My question I guess is, if you reviewed Exhibit T prior to signing this declaration, why does the declaration indicate November 6th?

A. Because it was a mistake.

Q. Are there any other possibilities of date mistakes in this declaration?

A. Not that I've noticed.

Q. If a document was received by the Sandoz patent department on a certain date, how long would it take to circulate to you specifically if you had been designated as a recipient?

A. Generally not very long.

Giesser - cross

Q. A few days?

A. Generally less than that.

Q. Were there instances where it might have been more than that?

A. That would have been very unusual.

Q. Do you have any actual recollection of any such delivery taking more than three days?

A. Not specifically, no.

Q. Let's return to paragraph six of the declaration.

Why was PD 299/84 assigned to you?

A. At that time one of my responsibilities was to help file cases in the HMG-CoA Reductase area.

Q. By "that time," you mean February of 1988?

A. Yes.

Q. Prior to that time, how many cases in the HMG-CoA Reductase field had you filed?

A. Prior to --

Q. Prior to February 1 of 1988.

A. None.

Q. So as of February 1, 1988, what activities had you undertaken in terms of assistance in the field of filing HMG-CoA Reductase cases?

Giesser - cross

A. None.

Q. So this was your first case in that field?

A. Well, it was not the first case that I ended up filing in that field.

Q. Was this the first case -- was this the first instance of assignment of a case to you in that field?

A. It might have been of a new case.

Q. So you had been assigned preexisting cases for re-filing in that field prior to February 1, 1988?

A. I don't recall.

Q. Had you worked on the preparation of any patent applications directed to the field of HMG-CoA Reductase prior to February 1, 1988?

A. By "worked on," you mean --

Q. Had you done work of any type in terms of preparation of a patent application to be filed?

A. Preparation, no.

Q. A patent application in the HMG-CoA Reductase field prior to February 1 of 1988?

A. No.

Q. What work had you undertaken in the HMG-CoA

Giesser - cross

Reductase field prior to February 1, 1988?

A. I don't remember exactly. It's possible I might have done some prosecution of existing -- of cases that had already been filed.

Q. Can you recall any of those cases either by docket number or subject matter or issued patent?

A. Not specifically, no.

Q. When did you first take any action of any type specific to 600-7101 after the assignment of responsibility of that case to you?

A. I don't recall.

Q. Do you recall ever discussing the status of 600-7101 with Linda Rothwell?

A. I don't recall.

Q. Were you acquainted with Linda Rothwell as of February 1, '88?

A. Yes, I was.

Q. And who was Ms. Rothwell?

A. She was our docket clerk.

Q. And do you recall whether or not Ms. Rothwell had responsibility for docketing the filing of new applications that you would be handling?

Giesser - cross

A. Yes, that would be part of her responsibility.

Q. And in fact, wasn't it customary as of February 1, '88, to docket new applications for a three-week date from the date of assignment?

A. I don't know if that was customary, no.

Q. Do you recall whether or not there was a customary date assigned for the filing of new applications? In other words, was there a time space designated from the date a case was assigned to the date it would be first docketed for filing?

A. By "docketed for filing," you mean --

Q. In other words, you indicated that Ms. Rothwell was at least partly responsible for docketing in the patent and trademark department?

A. Uh-huh.

Q. Would she be responsible for tracking the docketing of new applications; would she have been responsible as of February 1, 1988?

A. I'm not sure about the term "docketing of new applications."

Q. Was a date assigned within the patent and trademark department at Sandoz for the anticipation

of filing of a new application once that application was designated A and assigned to an attorney?

A. No specific date was given, no.

Q. Would anyone have responsibility for inquiring as to the status of an application to be filed from time to time?

A. I don't know if anyone was particularly responsible. People certainly did inquire, however.

Q. Do you recall anybody inquiring as to the status of 600-7101 between February 1, '88, and March 3, 1989?

A. Not any specific inquiries. Gerald Sharkin, who was the head of the patent department, used to come around periodically, and if he felt that an application has taken awhile to file, he would check on the status of it orally.

Q. Did Mr. Sharkin ever discuss this particular case, 600-7101, with you?

A. Yes.

Q. And was he concerned as to the length of time it was taking to file the case?

A. Yes.

Q. Do you recall when that conversation took

Giesser - cross

place?

A. I recall only one instance.

Q. Do you recall about when that one instance might have taken place?

A. It was at the filing, right when I had filed it.

Q. So he did not inquire prior to your actual filing of the application?

A. I don't recall specifically.

Q. You don't have recollection of anybody else inquiring as to the status of the case prior to March 3, 1989?

A. No specific recollection, no.

Q. Prior to February 1, 1988, had you prepared for filing any application in the field of pharmaceuticals?

A. No.

Q. Would you consider 600-7101 to be directed to pharmaceuticals?

A. Yes.

Q. Was the case that we discussed a moment ago, 600-7025/CIP/CIP, was that directed to pharmaceuticals?

Giesser - cross

A. Yes.

Q. During the period February 1, 1988, to March 3, 1989, did you prepare any other cases directed to pharmaceuticals?

A. Yes.

Q. Can you give me an idea of approximately how many?

A. Maybe three or four.

Q. And those would have been assigned to you after 600-7101; is that correct?

A. Probably.

Q. So they were assigned to you after 600-7101 but filed before 600-7101; is that correct?

A. I'm not sure when all of them were assigned to me, but that may be correct.

Q. Well, I want to double check, because -- and I may have misheard your earlier testimony.

As of February 1, 1988, did you have assigned to you responsibility for preparing and filing any new patent application other than 7101?

A. Not that I can recall.

Q. So any applications that you did prepare and file prior to 7101 -- in other words, prior to

Giesser - cross

March 3, 1989 -- would have been assigned to you after 7101 was assigned to you; is that correct?

A. That might be true. I really don't recall.

Q. But you do positively recall filing cases in the pharmaceutical field before March 3, 1989, and February 1, 1988; is that correct?

A. Yes.

Q. Besides the CIP/CIP case, were any of the other pharmaceutical cases directed to the HMG-CoA Reductase field?

A. Yes.

Q. The cases that you filed in that time period between February 1, 1988, and March 3, 1989, that were in the HMG-CoA Reductase field, why did they receive priority ahead of 600-7101?

A. One of them I believe had a time bar running on it.

Q. By "time bar," could you explain what you mean?

A. From what I recall on this case, the parent application had been allowed, but the research had progressed to where we wanted to add extra information to it, and so we were under a time bar to

Giesser - cross

get the CIP in prior to the paying of the allowance fee.

Q. So that was a CIP case?

A. Yes.

Q. How about the others in the HMG-CoA Reductase field that you prepared?

A. Well, I remember there was one that was specifically -- it was a process case, and I don't recall the circumstances of that one.

Q. Do you recall why it received priority ahead of 600-7101?

A. I believe I was working on the applications at the same time.

Q. But it was filed in advance of 7101?

A. Yes.

Q. Do you recall when that application was assigned to you, the one you were working on at about the same time?

A. No, I don't.

Q. But it was after February '88?

A. Probably.

Q. Was there a time bar involved in that other case, in that case that you were working on

Giesser - cross

simultaneously with 7101?

A. I don't recall the -- I'm sorry, the --

Q. You were working on another case in the HMG-CoA Reductase field at about the same time you were working on 7101; correct?

A. I was actually working on a few of them, yes.

Q. We talked about the one with the time bar involving an allowed parent application.

A. Right.

Q. And then you mentioned a process case.

A. Right. Oh, that one. I don't recall whether that had a time bar or not on there. I believe there might have been a publication that the inventors wanted to get out, but I couldn't -- that's just speculation on my part.

Q. Were there any publications involved with respect to 7101?

A. I don't recall.

Q. If a publication -- if a request for release of a publication had been filed, would that cause the priority assigned to that application to be advanced?

Giesser - cross

A. Generally, yes.

Q. Looking at paragraph seven, when did you receive Exhibit P?

A. Could I see Exhibit P again?

Q. Well, before looking at the exhibits that are described there, do you have any recollection of when you saw them?

A. Originally from Dr. Wattanasin, you mean?

Q. That's correct.

A. No, I don't recall.

Q. Let me hand you part of Exhibit P, which is Exhibit P-1 -- we don't have to make this part of the record -- and ask you if that refreshes your memory as to when you might have first received that document.

A. No, I don't recall.

Q. Do you remember requesting that document?

A. Not specifically, no.

Q. In fact, you didn't request that document at all; did you?

A. I don't think so.

Q. Let me hand you the rest of Exhibit P -- and we don't need to make these a record, either --

Giesser - cross

P-2 and P-3, and ask you if those refresh your recollection as to when you might have received Exhibit P.

A. No, they don't.

Q. Did you request P-2 and/or P-3?

A. I don't recall.

Q. What is your first recollection of actually taking action with respect to case 600-7101?

A. I don't recall the specific time.

Q. Let me direct your attention to paragraph ten, which is on page three of F20.

A. Yes.

Q. How do you know that you started writing the draft no later than October 1988?

A. Well, there was an exhibit that says it's a first draft Wattanasin that was early November. Exhibit U-1 says November 3rd, '88, was when Lorraine started typing it. Due to the other activities I was involved with at the time, it would have taken me at least a month, probably a lot longer -- in fact, I'm sure a lot longer -- to have drafted the application to where I would have had something to give to Lorraine by November 3rd to start typing.

Q. She wouldn't have begun typing the draft until you had completed it?

A. At least a large portion of it. It was not a finished draft when I gave it to her.

Q. And it's your recollection that it took you over a month to prepare the draft?

A. Yes.

Q. You indicated that you prepared and filed -- is it correct that you prepared and filed at least five different patent applications between the date February 1, 1988, and March 3, 1989, exclusive of 7101?

A. Yes.

Q. Can you give me an average time of how long it took you to prepare and file those cases from the date assigned to the filing date?

A. No, I couldn't.

Q. Well, you made reference to some other work that you were involved with prior to November 3, 1989. Can you describe for me that other work?

A. At that time I spent a large amount of time working for the seed companies, and it involved a large amount of travel. In fact, the most travel

Giesser - cross

I've done in my career so far basically took place during approximately this year, and so I was out of the office a lot and had to do a lot of preparation for these various trips I was making in relation with the seed companies. So, therefore, it would have taken an extra long time for patent applications to be filed just because of the circumstances of being out of the office so much.

Q. Let me direct your attention to paragraph nine, which lies on page three of F20. Looking at the dates that you were traveling on September and October --

A. Well, actually, the September 1 is a continuation of the August 29th trip.

Q. Okay. As I look at this, you were not out of the office at any time during November; is that correct -- on business travel?

A. Business travel, yes.

Q. During the month of October it seems to me that you were gone seven days on business travel; is that correct?

A. Let's see, it was the 9th through the 11th, 16, 17 and 27th, 28th.

Giesser - cross

Q. So that's about seven days?

A. Uh-huh.

Q. And is that the travel that you referred to a brief moment ago?

A. It's certainly part of it.

Q. And that was all on behalf of the seed companies?

A. Not all, but a lot of it was.

Q. Did the work involving the seed companies, was that assigned priority greater than the preparation and filing of 7101?

A. Yes, some of the deadlines involved were more pressing.

Q. Who assigned those priorities?

A. I'm not sure that things were formally assigned.

Q. Well, who made the determination that those things were more pressing than 7101?

A. Some of it came from management within the various companies, and also a lot of this had interaction with the patent department in Basle and other high-up departments in Basle -- or higher-up figures in Basle.

Giesser - cross

Q. So these management or higher figures in Basle or in the companies of interest would advise you that something had to be done as of a certain date?

A. Correct.

Q. Were these individuals aware that you had been assigned responsibility for 600-7101?

A. I doubt if they specifically knew that.

Q. Do you regard the time from assignment of 600-7101 to the time of filing as average time for you from the date of assignment to the date of preparation and filing of an application at Sandoz?

A. No.

Q. Is it longer than average?

A. Yes.

Q. Did you discuss with anybody at Sandoz at any time the fact that it was taking longer than average to prepare and file 600-7101?

A. No, I don't recall any specific discussions to that effect.

Q. Were you ever concerned with regard to the length of time it was taking to prepare 600-7101?

A. I don't recall specific concerns about it.

Giesser - cross

I knew that after the Warner-Lambert patent had issued that we were certainly under a time restraint to get this application in the office before the Warner-Lambert became 102-B.

Q. Were there any time restraints of any type that you were aware of prior to the Warner-Lambert patent information coming to you in connection with 7101?

A. Not specifically, no.

MR. KELBER: I'm going to hand you a document that I would like marked as F22.

(Deposition Exhibit F22 marked for identification.)

Q. Is in fact Exhibit F22 the document that is referred to in paragraph nine of F20 as Exhibit S?

A. Yes.

Q. Let's take the first page of that document. You see over the right-hand column there's reference to Northrup King, Rogers Brothers and--

A. Zoecon.

Q. -- Zoecon. Thank you. Who or what was Northrup King?

A. Northrup King is a seed company owned by

Giesser - cross

Sandoz.

Q. And Rogers Brothers?

A. Rogers Brothers is also a seed company owned by Sandoz.

Q. And Zoecon?

A. Zoecon is now a part of Sandoz Agro. It's a research facility in California.

Q. And it was a research facility at the time you visited it?

A. Yes.

Q. So you took the -- I'm sure you took the Northwest flight that stops at every city in the Greater Northwest on your way out there?

A. Something like that.

Q. Was it your habit to do business work while flying on behalf of Sandoz -- in other words, the time actually spent in the air?

A. Generally not.

Q. Rest assured, I'm not going to go through each one of these pages, but I do have questions on a few.

The second page which covers the period 3/1/88, what is the NACA patent committee?

Giesser - cross

A. National Agricultural Chemical Association. It's a trade group.

Q. And they have a patent committee?

A. It's a patent law committee.

Q. I see.

A. I was asked to represent Sandoz at one of their patent law committee meetings.

Q. Were you asked by someone within the Sandoz patent and trade department?

A. Yes.

Q. Would that individual have been aware that you had, prior to March 1, been assigned responsibility for 600-7101?

A. Yes.

Q. Let me turn your attention to the fourth page, which refers to a visit with seed committee. What was the seed committee?

A. This was a meeting in Des Plaines. Des Plaines is where the headquarters of what is now Sandoz Agro is. At that time, as I recall, the seed companies were considered part of Sandoz Agro. That's since changed.

During this time frame, the patent

Giesser - cross

office had started issuing patents to various varieties of hybrids which were not genetically engineered, and one of the questions which we were discussing throughout this time period is how this would affect our companies and whether we should look into this as part of the patent policy. This is what involved a lot of the people from very high management.

The seed committee, as it refers to on here, were people who were involved with the seed companies in establishing and recommending patent policies for them.

Q. Would that have included other patent attorneys in addition to yourself?

A. Probably, yes.

Q. So there was an actual meeting of this committee --

A. Yes.

Q. -- during this trip?

A. Uh-huh.

Q. Do you recall participating actively at that meeting?

A. Yes.

Giesser - cross

Q. Let's go actually to the next document -- or the next page in that document. What is the IBA?

A. Industrial Biotechnology Association. It's also a trade group.

Q. What was the nature of the meeting on or about May 2?

A. I don't recall exactly. They have periodic meetings of patent attorneys who are involved with biotechnology companies to discuss various issues of interest.

Q. Was it your habit to participate actively at those meetings?

A. Yes. I only went to a few of them on behalf of Sandoz.

Q. Were you requested by someone at Sandoz to attend those meetings?

A. Yes.

Q. Do you recall who that someone was?

A. Dick Vila.

Q. And he would have been aware of your responsibility for 600-7101; wouldn't he?

A. Yes.

Q. Before we leave the IBA, did anybody else

Giesser - cross

from Sandoz attend those meetings?

A. At that time, no.

Q. Let me turn your attention to the page -- I believe it's the seventh page. It covers the period 8/20 through 9/20/88. And you can identify it because it has in the comments Swiss franc exchange.

A. Yes, okay.

Q. Do you see the reference to Basle patent policy?

A. Yes.

Q. That was a meeting of Sandoz International?

A. It had members from -- the presidents of Northrup King and Rogers Brothers, myself, and members of the Basle patent department.

Q. Nobody else from the U.S. Sandoz patent and trademark department attended that meeting?

A. No.

Q. Let me direct your attention to fourth-from-the-last page; it covers the period 12/1 to 12/31, '88. Do you see the reference to you having delivered a patent lecture to Northrup King?

A. Right.

Giesser - cross

Q. Do you recall the nature of that lecture?

A. Yes, it was on general patent law. It took place at the American Seed Trade Association meetings, but it was a closed lecture to Northrup King personnel. A number of the Northrup King breeders who were stationed all over the country usually go to the Chicago meeting.

Q. Can you help me out with the dates over in the left-hand column? How long did this travel last?

A. Let's see, it looks like 12/6 through 12/8.

Q. Did you attend any other functions at the meeting other than delivering the patent lecture?

A. I went to a few of the lectures.

Q. The next-to-last page, which covers the time period February 1 to February 28, there's reference on that in column ten to a lecture to Rogers Brothers.

A. Right.

Q. What was the nature of that lecture?

A. General patent law and how it applied to questions that would arise in the seed industry.

Q. And you were the only person from the Sandoz patent and trademark department for that

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lecture; is that correct?

A. I think -- although I'm not sure, but I think Alan Norris, who is the manager of patents at Palo Alto, I believe he was there, also.

Q. Would he have delivered a lecture, also?

A. If he were there, he would possibly have spoken about international issues and the European system.

Q. Looking at the very last page, it wasn't much of a trip, but you went on up to New York City for the judges' dinner?

A. Yes.

Q. Was that on behalf of Sandoz?

A. Yes.

Q. Somebody at Sandoz suggested or requested that you go?

A. It was basically anyone in the department who wished to go could.

Q. Let me turn your attention to paragraph 14, page four of F20. You asked some information from Mr. Warhman?

A. Yes.

Q. Was that customary for you in the

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preparation of a patent application?

A. When it involved these kind of compounds, yes.

Q. Now, would you have needed that information to prepare the draft application -- the draft of the application in 7101?

A. As far as a completed draft, yes.

Q. Did you provide Mr. Warhman with any written information other than Exhibit V-1?

A. No. What I recall is I just drew the compounds that I wanted to get the correct technical chemical name for and just sent it over to him with a cover sheet.

Q. I'm going to hand you Exhibit V-1 -- I don't think we need to make this a record -- and ask if those are the compounds in question.

A. Yes, they are.

Q. How did you determine those specific compounds for inquiry?

A. As I recall, these were either intermediate or end products that were mentioned in the application.

Q. I'm going to hand you a document which has

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been previously identified in this proceeding as Exhibit F4 that's the application itself and ask you to take a look at that briefly. I'm going to ask you to turn to page 54 of Exhibit F4.

A. Okay.

Q. Do you see in the third line of the text -- I think it's the second line after the initial formula of that page -- the reference to C_{3-7}cycloalkyl?

A. Yes.

Q. Do you have any recollection as to whether that phrase appeared in the initial draft that you prepared?

A. I don't recall.

Q. Do you recall whether you identified that group as a suitable group for a substituent based on your own knowledge alone without reference to other documents?

A. It would not have been from my knowledge.

Q. Is there a name for the moiety or group that corresponds to C_{3-7}cycloalkyl?

A. I'm sorry?

Q. Let me back up and ask some foundation

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questions.

When the document refers to C_{3-7}cycloalkyl, is it correct to understand that that means any cycloalkyl moiety having three through seven carbon atoms?

A. Yes, that's what I intended it to mean.

Q. Do you have an estimate of whether or not those of ordinary skill in the art of making HMG-CoA Reductase field would have interpreted it similarly?

A. I think they would.

Q. Certainly that phrase identifies two possible compounds, one cycloalkyl compound with three carbon atoms and one with seven; is that correct?

A. Yes.

Q. If it had three carbon atoms, would that be cyclopropyl?

A. Yes.

Q. One of skill in this art you feel would similarly interpret it that way?

A. Yes.

Q. Do you recall discussing with anyone whether or not that would be an appropriate

recitation for the claim in -- that appears -- I guess it begins on page 54?

A. Not specifically, no.

Q. In general would you have discussed the appropriate substituents with anybody in the preparation of an application of this type?

A. Yes.

Q. What persons would that have included?

A. At least the inventor.

Q. I'm going to ask you to turn to page five of F20, which is the declaration. In particular my question pertains to the statements and comments with respect to the exhibit referred to as Y-2. I don't think we need to make that a record, but I will hand it to you for your review.

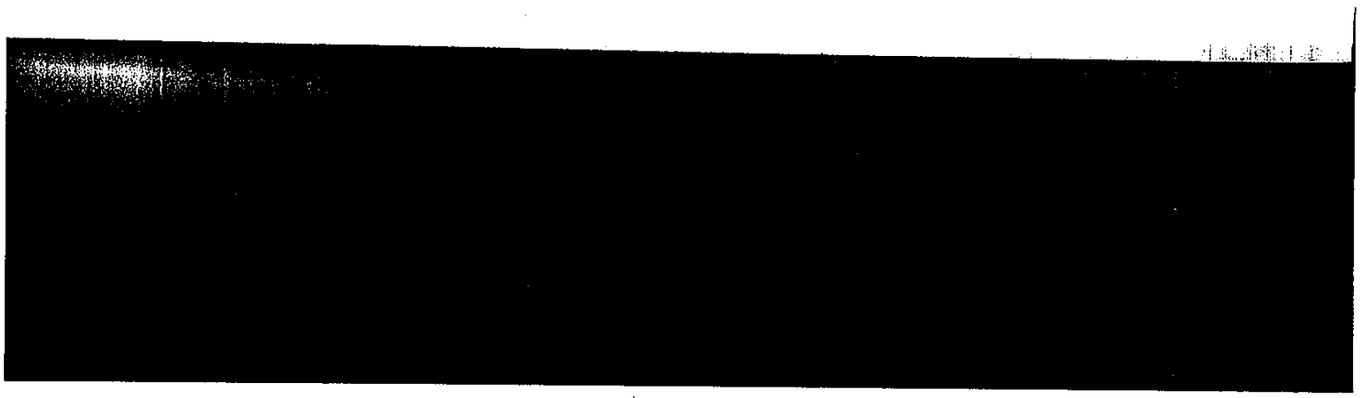
A. Okay.

Q. Did you obtain that computer printout for the preparation of 7101?

A. Yes.

Q. Why?

A. It was helpful for a number of different reasons. I thought the chemistry involved in this case was very difficult, and sometimes I felt more



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comfortable having very explicit detailed drawings so that I would get the structures right and wouldn't include wrong structures in the case; also, to make sure that I specifically covered all the specific compounds that we thought were important, and also to get the -- some of these had some kind of activity. I guess it's ED_{50s} only -- and IC_{50s}.

Q. Do you know who prepared that document, Y-2?

A. I believe it was -- it says on the document it was from Bob Angstrom. He was a person who did a lot of work in the activity area.

Q. Did you request that document?

A. I don't recall specifically.

Q. Ms. Giesser, can you recall any activity which you undertook between January 4, 1989, and March 3, 1989, with regard to case 600-7101?

A. I have no recollection.

Q. Do you recall receiving any changes, suggestions, additions, information of that type with respect to the draft of 600-7101 after documents that are referred to as Exhibit X, Y-1 and Y-2?

A. I'm sorry, could you repeat that?

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Q. Other than the Exhibits X, Y-1 and Y-2 referred to on page five of F20, do you recall receiving any documents relevant to case 600-7101 subsequent to January 4, 1989, but prior to March 3, 1989?

A. No, I don't recall.

Q. Do you recall reviewing any documents in connection with the preparation and signing of F20, the declaration, that you would have received between January 4 and March 3, 1989?

A. No, I don't.

Q. Would there have been any reason if the information necessary to file 7101 was in your possession as of January 4, 1989, to delay the filing to March 3, 1989, other than final preparation of the application?

A. I believe that at that point I was working on the final draft and getting comments from the inventor and things of that nature.

Q. But you don't recall any specific comments?

A. No.

Q. And you don't recall seeing any written documents to that effect?

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A. No.

MR. KELBER: In New Jersey, Diane, we had discussed the possibility of requesting the documents in the file. Any progress with regard to that?

MS. FURMAN: I have searched for the so-called supplemental file, and as I indicated at that deposition, I do have some -- I do have various papers relating to the case. None of such papers bear dates, however, so I do not know whether you would be interested in seeing them. If you are, I will provide them to you.

MR. KELBER: Please do. We had also asked for any requests for publication filed relative to this. Has the search for those documents been done?

MS. FURMAN: Yes, I have isolated two requests for publication, and if you wish, I can enter into evidence now as exhibits the isolated papers that I found on the one hand and the request for publication.

MR. KELBER: Well, I don't know about the need to -- well, let's go ahead and do that.

MS. FURMAN: I have seven loose pages obtained from documents left in the possession of

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Sandoz by Ms. Giesser which relate to case 600-7101, and I would like them marked as Exhibit S1.

(Deposition Exhibit S1 marked for identification.)

MS. FURMAN: Additionally, I have a second exhibit, S2, comprising, I believe, 22 pages which represent two publication requests related to the subject matter of case 600-7101 in response to Mr. Kelber's request of record.

(Deposition Exhibit S2 marked for identification.)

BY MR. KELBER:

Q. Do you have any feel for how it was determined that the patent and trademark committee of Sandoz, through the 1988 year, how it was determined who would have specific responsibility for a particular application?

A. From what I understood, generally attorneys or agents would be assigned a particular research area, and generally there wasn't too much overlap, the HMG-CoA Reductase area being rather an exception to that rule.

So if an invention disclosure came out

of a particular area, unless there was a reason not to, the attorney or agent who was normally working in that area would be assigned that application.

Q. And you had -- I'm sorry, correct me if I'm wrong. You had not previously been assigned responsibility for filing an application in the HMG-CoA Reductase field as of February 1; is that correct?

A. Right. I had not been at Sandoz for very long at that time.

Q. Did you have occasion to speak with anyone at Sandoz with regard to the volume of responsibility, the volume of work that had been assigned to you in the period February 1, '88, through March '89 -- I'm sorry, specifically with regard to 7101?

A. I don't recall.

Q. With regard to the CIP/CIP case, the 7025 case, did you discuss with anybody the possibility of filing a continuation application to maintain the case pending to allow preparation and filing of the 7101 file first?

A. We really didn't have an option to delay

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the 7025-CIP/CIP case.

Q. Why is that?

A. At that time, as I believe we were filing non-convention, foreign filing non-convention -- and I believe there was an outstanding office action where allowable subject matter had been indicated, but we needed to add some specifics to various other compounds in that case. I don't remember exactly, but I think there was some sort of time bar running vis-a-vis the foreign filing in that case.

Q. Would that have been a time bar in the sense of an outstanding publication imminent?

A. I don't believe there was a publication. I think it might have been -- I forget whether it was allowable subject matter had been indicated, and I know that there was -- I did an extensive amount of work on that case with one of the agents in Basle in preparing the foreign filing text on that one, and I don't remember exactly, but I know there was some sort of time pressure going on with that one.

Q. Were there any cases that you recall that were assigned to you after February 1, 1988, that you prepared and filed prior to March 3, 1989, that did

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not involve a time bar?

A. Yes.

Q. Can you describe the field that those applications pertained to?

A. One of them was a plant biotech case that originated in Basle, which they sent the draft over, and I basically had to review the draft and make any changes necessary for filing in the United States. While that had a time bar -- well, no, that was a priority United States filing.

Q. And that case was filed before March 3, '89?

A. Yes, I believe that was filed in December of '88. There were -- as I mentioned before, I believe there were pressures to file the Agro cases, but I don't remember exactly -- it's been awhile.

Q. With regard to the case that came over from Basle in draft form, any particular reason for assigning it a filing priority ahead of 7101?

A. It was a case that did not involve the -- nearly the amount of time or substantive work as 7101, and it was something I could get filed quickly.

Q. You spoke to some kind of pressure involved

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in the cases for the seed companies. Can you describe the pressure that was involved there?

A. In March there were 102-B on-use or on-sale bars.

Q. So the bar would have been complete in March of '89?

A. Yes.

Q. You don't recall whether that date would have been before or after March 3, 1989, do you?

A. I believe some were March 3. It was a rather hectic time.

Q. Do you recall during your tenure at Sandoz whether Sandoz ever employed outside patent attorneys, attorneys not regular employees of the patent and trademark department of Sandoz, for assistance in the preparation of patent applications?

A. Very rarely.

Q. Did you have any involvement with such outside attorneys?

A. No.

Q. In the rare cases when it did happen, do you recall why that would be done?

A. Usually it would be a circumstance where we

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were licensing a third party's technology and as part of the deal we were prosecuting the patent for them, so in order to avoid any kind of conflict, we'd have a third party do it.

Q. Did you ever encounter a situation where you were assigned a number of specific tasks that had to be completed by a certain date that you simply could not complete by that date -- I'm sorry, while you were at Sandoz?

A. I certainly recall multiple deadlines. Generally they'd all be met somehow.

Q. Did you ever seek help from another individual within Sandoz in that situation where you were facing multiple deadlines?

A. Yes.

Q. Did you ever attempt to seek help with regard to the preparation of 7101?

A. Not insofar as meeting a deadline, but general help involving the chemistry of the case, yes.

Q. Do you recall subsequent to February '88 ever discussing with the patent committee at Sandoz the decision to rate 7101 as A?

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A. I would have not have ever had discussions with the patent committee.

Q. I see. So you -- okay. Do you recall ever suggesting to somebody at the committee or somebody to suggest to somebody at the committee the question of the status of 7101?

A. I did not.

Q. Let me take you back again to the period between when you began at Sandoz and February 1, 1988. Regardless of the field to which it might have pertained, as of February 1, 1988, do you recall whether you had a backlog of cases to prepare and file?

A. I don't think I had a backlog, no.

MR. KELBER: I appreciate your patience with me, and I don't have any further questions at this time.

(WHEREUPON a recess was taken.)

RE-DIRECT EXAMINATION

MS. FURMAN

Q. I would like to ask you a couple of questions first about your experience prior to coming

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to Sandoz, which I believe was raised on cross.

Is it true that you had never written a pharmaceutical patent application prior to coming to Sandoz?

A. Yes.

Q. How would you rate the difficulty of case 600-7101, let's say on a scale of one to ten?

A. With ten being hard?

Q. Correct.

A. Ten.

Q. Why would you say that?

A. It was a multi-step procedure. There were -- it was a long reaction. It's a very complex compound; it has ring substituents as well as side chain substituents, and the stereochemistry is important and is involved.

Q. Were you required to work on other subject matter with which you had no prior familiarity before coming to Sandoz?

A. Yes.

Q. What did that comprise?

A. When I came to Sandoz, basically my first assignment was the prosecution docket from Fred

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Wienfeld, who was not working there at the time; he was on disability. And Fred's docket included a number of different kinds of chemical cases. I don't recall whether there were any HMG-CoA Reductase cases or not, but I do recall cases in areas such as fire retardants, polymers and other different types of chemicals.

Q. How long had you been at Sandoz before receiving case 600-7101 as a patent disclosure for filing?

A. Well, I started in mid August of '87, and the patent committee assigned this the end of January of '88. So middle of September, October, November, December, January -- about five-and-a-half months.

Q. Were you working on any pharmaceutical case as a prosecution matter during those prior five months?

A. I don't recall. It's quite possible, since Fred Wienfeld handled a number of HMG-CoA Reductase cases.

Q. How did you become aware of the A rating of patent disclosure 299/84 at issue?

A. I don't recall. Generally I would become

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aware of them when the minutes of the patent committee meeting would be circulated and I'd receive my copy. I don't recall an exception to that, so I assume that's how I found out.

Q. Was it within your responsibility to rate patent disclosures?

A. No.

Q. Did you have any influence on the patent committee in the rating of disclosures?

A. No.

Q. What rating did the patent committee assign to a disclosure which was not to be filed upon?

A. Ever?

Q. Correct.

A. It would be D.

Q. Did patent disclosure 299/84, to your knowledge, ever receive a D rating?

A. No.

Q. Having received patent disclosure 299/84 for filing, was it within your jurisdiction or ability to -- let me rephrase that -- within your jurisdiction or ability not to file a patent application?

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A. No.

Q. How would you characterize your obligation until the filing?

A. I had no choice but to draft the application.

Q. Is there any way to inactivate or retire a patent disclosure once rated A by the patent committee?

A. Yes.

Q. How is that?

A. You would have to have the disclosure brought up to the patent committee, and they would have to re-rate it.

Q. Did you at any time do that with respect to disclosure 299/84?

A. No.

Q. Did anyone at Sandoz carry out such a process?

A. No.

Q. You indicated that the involved application took perhaps longer to complete than applications you worked on for Sandoz?

A. Yes.

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Q. Can you explain that?

A. Well, it was a combination of factors. One, as I've mentioned before, I considered the chemistry difficult and was very concerned with making sure I had the correct chemistry at the time it actually got filed.

Secondly, I was out of the office a lot traveling on business matters, as went into before, and there were other cases and other issues which at the time seemed to need immediate attention.

And thirdly, this was a rather lengthy patent application. It was 50-some odd pages at least, and just the physical time it would take to write such an application would be long.

Q. Why did Mel Kassenoff collect information on the --

MR. KELBER: Objection, facts not in evidence.

BY MS. FURMAN:

Q. Did Mel Kassenoff collect information --

MR. KELBER: Objection. You're asking her to determine what Mel did. Anything that she says is going to be hearsay.

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BY MS. FURMAN:

Q. How did you receive information relating to case 600-7101?

A. I don't remember exactly. I think that some of it came from Mel, and some of it came from the inventor.

Q. The part that came from Mel, if the case was assigned to you, why did information relating to the case come from Mel?

A. I would expect because the scientists involved in this program were familiar with Mel, since he had been working with them for a number of years in this area.

MR. KELBER: Objection to the degree it's speculation.

Q. Were you familiar with the people to contact and procedures to follow to collect information needed to write case 600-7101 as of February 1988?

A. No.

Q. Did you receive any assistance from anyone in the patent department with respect to the case?

A. Yes.

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Q. Who provided such assistance?

A. Mel Kassenoff.

Q. What was the nature of that assistance?

A. I'm not sure if I can recall everything he did, but he certainly helped me with a lot of chemistry and would provide names of people I had to contact if I needed certain information. For instance, with regard to -- can we go off the record for a second?

MS. FURMAN: Off the record.

(WHEREUPON a discussion was held off the record.)

THE WITNESS: With regard to Exhibit V-1, which is page 448, it's the letter I wrote to Ziggy Warhman asking for the names of the compounds, that's the sort of thing Mel would direct me how to get that information.

BY MS. FURMAN:

Q. Otherwise you would not have known independently how to obtain such information?

A. Correct.

Q. Was it ever your intention not to file a patent application and patent disclosure for 299/84?

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A. No.

Q. What about the Warner-Lambert publication; what was your reaction to this publication, in your best recollection?

A. I don't remember too much about the specifics of finding out about it. I remember being, I guess upset is possibly the best word, when I heard about it.

Q. Why were you upset?

A. Because I knew that what would otherwise be a rather straight forward prosecution of an application suddenly was not.

Q. What is your impression as the involved patent attorney of the interest of the research in the subject matter in view of the Warner-Lambert patent?

MR. KELBER: I'm sorry, could you read that question back?

(The requested testimony was read by the reporter.)

MR. KELBER: Could you specify what you mean; whose interest and involved in what?

BY MS. FURMAN:

Giesser - re-direct

Q. After you became aware of the Warner-Lambert publication, did you request a re-rating of the subject patent disclosure?

A. No.

Q. Why?

A. I don't recall.

Q. Do you recall being directed by anyone in research to drop your work on the involved application?

A. I was never told to drop the work.

Q. You have referred to your activities during the period of February 1988 to March 1989 in the agricultural area for Sandoz. Do you have any special expertise in this area?

A. Yes.

Q. What does that comprise?

A. I hold a master's degree from the Department of Agronomy at Clemson University, and my subspecialty in that area was plant genetics.

Q. Did anyone else at Sandoz have a master's in that specialty?

A. Not that I was aware of; not in the patent department.

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Q. I would like to discuss some of your travel activity during the relevant time period.

You previously testified that you visited Northrup King, Rogers Brothers and Zoecon in February of 1988?

A. Yes.

Q. Approximately how many days -- how many working days were you out of the office in February of '88?

A. It appears from the 21st through the 26th.

Q. That would be how many days?

A. Probably an entire week, five working days.

Q. How many days of preparation for this trip do you estimate was required?

A. I don't recall exactly, but there was more than the usual business trip, since I was not alone on this trip. A member of the Basle patent department, Walter Smolders, who is currently the person in charge of Sandoz Agro and seed patent activities worldwide, accompanied me on this trip.

Q. Was this trip required of you by the Basle patent department?

A. I didn't have any choice in going, if

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that's what you meant.

Q. In March of 1988 you were occupied with patent committee meetings?

MR. KELBER: Objection as to the characterization of the testimony.

BY MS. FURMAN:

Q. What kind of travel activity were you involved in in March of 1988?

A. There was a trip to RSRC in Boston and also a trip to Palo Alto, California.

Q. In March of '88?

A. Yes. Also an one-day trip to Washington, D.C.

Q. Were you required to go on each of these trips in March of 1988?

A. Yes.

Q. Who required you to?

A. Again, it was not an official requirement. Dick Vila had asked me to attend a NACA meeting. I accompanied Dick up to the RSRC visit, and the visit to Palo Alto, I was alone, but it was certainly needed in connection with my activities with Sandoz' crop protection.

Giesser - re-direct

Q. Was there anyone who could substitute for you in the Sandoz patent department at the crop meetings?

A. Certainly Dick could. The point is he asked me to take this over.

Q. Approximately how many days were you out of the office on business in March of 1988?

A. Probably about seven.

Q. How many days of preparation would have been required in total for these trips?

A. The NACA meeting probably wouldn't have required much. I don't recall exactly, but there was certainly some amount of preparation for the RSRC and also the Palo Alto trips.

Q. By the way, you mentioned that Dick could possibly substitute for you. To your knowledge, did Dick Vila have a background in plant genetics?

A. No.

Q. To your knowledge, did he have a degree in agriculture?

A. No.

Q. Did he participate, to your knowledge, in drafting plant policy?

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A. Yes.

Q. In April of 1988 can you summarize how many days you were out of the office on business?

MR. KELBER: Summarize that?

BY MR. FURMAN:

Q. Can you indicate by number?

A. It looks like two.

Q. Two or three?

A. It was in a hotel. I have two nights; so probably three days.

Q. Can you do so similarly for May and June of 1988; can you give me the days out of the office on business?

A. It looks like May was one day; June looks like there was a one-day meeting to Washington and probably a two-day trip to California.

Q. That would be three?

A. Yeah.

Q. On your visit to Palo Alto, did you discuss whether patent disclosures needed to be filed?

MR. KELBER: Which visit is this?

MS. FURMAN: In June of 1988.

A. I don't remember exactly. That was a topic

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that was generally brought up when I was out in California.

Q. If patent disclosures needed to be filed for Palo Alto, who performed such filings?

A. This is a complicated question. There were basically two divisions of research in California, agricultural chemicals and plant biotechnology. The agricultural chemical filings were generally done by the person who was on site there. I think until March of '88 it was Jacqueline Larson. She left the site, and there was no one there for a few months until Alan Norris came over from Basle to take over, which was sometime in the late summer of '88, probably August.

So during that ensuing time, I'm not sure how the chemical cases got filed there, although I was -- I had filed one of the chemical ones. Jackie felt uncomfortable with a lot of the biotech applications, so the idea was that I would be working in that area.

Q. Did a backlog of biotech cases develop?

A. No.

Q. When Palo Alto decided to file a patent

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application and Alan Norris did not do it, who worked on that application?

A. Like I said, generally until Jackie left she handled all the chemical based cases. I was intended to work on the biological based cases from there.

Q. Did Dick Vila work on any of these cases?

A. I know he assisted in some of the biotech cases. I'm not sure of the time frame on those, though.

Q. When did you start writing cases for Palo Alto?

A. I don't remember exactly.

Q. Going to July of '88, how many days were you out of the office on business in that month?

A. It looks like I had a two-day trip to Des Plaines.

MR. KELBER: Can I hear the answer back again?

(The requested testimony was read by the reporter.)

BY MR. FURMAN:

Q. Let's go to August of '88. How many days

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were you out on business?

A. It looks like I had a three-night visit to Palo Alto, so that was probably four days. It was the week that overlapped the last week of August and the first week of September.

Q. In the course of your meetings on seed policy, do you remember when you were first assigned seed cases to work on?

A. Not exactly, no.

Q. Can you give me an estimate?

A. No, I don't recall when they first came up.

Q. Did these cases have statutory bars involved?

A. A number of them did.

Q. So there would have been a time constraint with respect to some of these cases?

A. Yes.

Q. How many such cases do you estimate there were, starting about June of 1988?

MR. KELBER: Objection. You're asking the witness to estimate when you haven't asked her if she knows the exact number.

BY MS. FURMAN:

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Q. Do you remember how many seed cases you worked on with a time constraint?

A. Not the exact number, no.

Q. Do you remember approximately how many?

A. There were quite a number of them. The ones that had bars coming up in March of '89 there were I think about six or so.

Q. These six cases had a required due date -- a filing date in order not to be --

A. They were coming up against the one-year in-public-use or on-sale bar.

Q. I would like to quickly finish up the number of days you were out of the office from September until -- September of 1988 until February of 1989, if you could quickly give me such an estimate for each month.

A. Well, September I had a trip to Basle, and that was four days. October I was out of the office a lot. There was another trip to California that looks like I had two days in a hotel, so probably three days out of the office. Then there was a trip to Wisconsin which looked like another two-day hotel, so probably three days out of the office, and then

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there was a trip do Boulder, Colorado, where there was -- I believe that was two days out of the office.

Q. In what month?

A. That was all October of '88.

Q. How many days in total for October?

A. Probably seven.

Q. November?

A. It looks like I got to stay home in November.

Q. Can you finish up with December through February?

A. Oh, December looks like a one-night -- so possibly two days out of the office in December. January it looks like three hotel nights, so possibly four days out of the office in January. February of '89 it looks like two hotel nights, so probably three days out of the office in February, and then in March of '89 one day -- or two days, one hotel night, so two days.

Q. The judges' dinner in March of '89 occurred after the filing date of the involved application; is that true?

A. Yes.

Giesser - re-direct

Q. Did you have any sick days, to your recollection, out of the office?

A. I don't recall.

Q. Now, what other pressures to file might exist besides a 102-B bar? You testified that you filed CIP applications under certain circumstances.

A. Well, there was the CIP that's 7025-CIP/CIP; I recall there was some sort of foreign filing deadline on that one.

Q. Well, I'm trying to refresh your recollection with Exhibit S3, which comprises a few pages from the prosecution history of --

MR. KELBER: I'm going to object to this exhibit and the questions based thereon as evidence of the type that should have been submitted in direct, but you can ask the witness questions with respect to it.

MS. FURMAN: Since we believe it's necessary for adequate re-direct, we will proceed.

(Deposition Exhibit S3 marked for identification.)

BY MR. FURMAN:

Q. Have you examined Exhibit S3?

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A. Yes.

Q. If you turn to the last page of that exhibit, do you recognize this page?

A. Yes.

Q. Can you describe it?

A. It's the first page of an office action to case number 600-7025/CIP, which is the parent case of 7025/CIP/CIP.

Q. What is the date of mailing?

A. May 11th, 1988.

Q. In order for this case not to go abandoned, under the patent office rules when would a response have had to be filed?

A. It would be six months from that day, or November 11th, '88, assuming the proper fees were paid.

Q. Did you have any interaction with the Basle patent department on this case?

A. Yes, I did.

Q. What did that concern?

A. There was a plan to have a foreign filing of the subject matter of 7025/CIP along with some additional subject matter was planned to be filed

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non-convention.

Q. Did Basle call upon you to assist in the preparation of such a foreign text?

A. Yes.

Q. Was it your responsibility to consult with the inventor in the United States on this case for Basle?

A. Yes.

Q. Did you then have to redraft the application for Basle?

A. No.

Q. How did the foreign text then come about?

A. I would convey any information or comments that the inventor had on the Basle case to the people in Basle. I believe it was Lucian Vallet.

Q. Did it occur to you that it would be necessary to file a continuation-in-part application on this case?

A. Yes.

Q. What would be the purpose of such a filing?

A. To include subject matter that wasn't already present in the parent.

Q. Would you have been required to consult

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with the inventor about that additional subject matter for the foreign text?

A. Yes.

Q. What would be the latest date that you could file a CIP on case 600-7025/CIP in response to the outstanding office action?

A. It appears that the case could have been extended beyond the 11th month if we had chosen to respond to the office action.

Q. Excuse me, the 11th month?

A. I'm sorry, November 11th, '88, would have been the last date we could file if we chose not to respond to the office action.

Q. By file, you mean file a CIP?

A. Right.

Q. Is it fair to say, then, that you were under some degree of time pressure concerning the filing of the CIP on case 600-7025/CIP?

A. Yes.

Q. Was there any standard way in the Sandoz patent department, to your knowledge, of deciding to give priority to an A rated disclosure or a CIP --

A. No.

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Q. -- that had to be filed?

A. I was not aware of any policy on that.

Q. Is it fair to say that you were required to give full time to this case prior to November of 1988 --

MR. KELBER: Which case is that, Diane?

Q. -- 600-7025 for the purpose of assisting Basle in filing the foreign text?

A. Yes.

Q. Is it fair to say that you would have needed the same information to file the CIP?

A. The same --

Q. The same information as needed by Basle?

A. Yes.

Q. Now, you also mentioned a case -- an HMG-CoA case where you were under time pressure because an issue fee was due; is that correct?

A. Yes.

Q. Do you remember the subject matter in particular of that case?

A. Not exactly. I know it was another different heterocycle compound.

MS. FURMAN: I'd like to introduce one

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further exhibit to refresh your recollection for purposes of re-direct, which will be Exhibit S4.

(Deposition Exhibit S4 marked for identification.)

MR. KELBER: I'm going to object to anything and everything with regard to S4. This is a case that's not even referred to in the declaration that constitutes the direct testimony in this case. It's beyond comprehension that it could possibly be necessary for adequate re-direct, since the scope of re-direct is necessarily narrower than the scope of direct.

If you give me a continuing objection, I'll let you ask your questions.

MS. FURMAN: Fine with me.

BY MS. FURMAN:

Q. Do you recognize the second page of this exhibit?

A. Yes.

Q. What does this page comprise?

A. It's the notice of allowance for case 600-7044/CONT.

Q. To your knowledge, was this case issued?

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A. No, this was allowed to go abandoned.

Q. Did you have any involvement in this case or a successor case?

MR. KELBER: Compound question. Why don't you ask them one at a time?

BY MS. FURMAN:

Q. Did you have any involvement in the writing of 600-7044/CONT?

A. I don't recall if I filed a continuation or whether I just received it off of Fred's docket.

MR. KELBER: Objection, that's not responsive to the question.

Q. Then you don't recall whether you were involved in 7044/CONT; is that correct?

A. That is correct.

Q. The second page of this exhibit -- what does this comprise?

A. The second page?

Q. Yes.

A. It's the notice of allowance and issue fee for 600-7044/CONT.

Q. In order to file a continuing application in this case, when would such action have had to be

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taken in order not to abandon the parent?

A. Well, to keep a chain going, it would have to have been by the due date of the issue fee, which would have been April 3rd of '89.

MR. KELBER: Can I hear that question and answer.

(The requested testimony was read by the reporter.)

MR. KELBER: Could you mark that for me?

BY MS. FURMAN:

Q. Did you in fact file a further application on 7044/CONT?

A. I filed a CIP.

Q. Is this the application you were referring to in your prior testimony concerning the need to file a case when an issue fee was due?

A. Yes.

Q. Do you recall when you filed that CIP application?

A. I believe it was in March of '89.

Q. You filed 600-7044/CONT/CIP in March of '89; correct?

A. To my best recollection, yes.

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Q. You filed 600-7025/CIP/CIP about when?

A. October of '88. It was the beginning of October.

Q. You filed how many seed cases under time constraint -- of the seed cases you filed in March 1989, how many were under time constraint?

A. I believe all of them were.

Q. I'm sorry, I don't remember the number you indicated.

A. I think it was five or six.

Q. Would you have had to have been working on the seed cases prior to March of '89 in order to have them on file that month?

A. Yes.

Q. When is your best estimate for beginning work on the earliest of the seed cases?

MR. KELBER: Which seed cases? Why don't you rephrase it?

BY MR. FURMAN:

Q. When do you think you started working on the six seed cases you just indicated were filed in March of 1989?

A. I don't recall.

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Q. Do you have any recollection of working on the seed cases in February of 1989?

A. Yes.

Q. Do you have any recollection in January of 1989?

A. I don't recall.

Q. If I can summarize your most recent testimony on re-direct, you filed case 7025 in October of 1988, and that was under time pressure?

A. Yes.

Q. You filed case 600 7044/CONT/CIP sometime before April of 1989?

A. Yes.

Q. Was that under time pressure?

A. Yes.

Q. The six seed cases that you filed in March of 1989 were under a time pressure, as well?

A. Yes.

Q. Who decided what cases you filed in the seed or Agro area?

A. At the earlier portion of this time period the seed companies would go through the Palo Alto patent committee. The results or the recommendations

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in the Palo Alto patent committee would be noted in the Pharma patent committee or the New Jersey patent committee.

Q. Did the New Jersey patent committee have any influence, to your knowledge, on the patent decisions of Palo Alto?

A. I'm not sure if they could veto something. I know they generally took the recommendations. In the later part of this period Northrup King started having its own -- well, it wasn't a full-blown patent committee, but patent issuings would be discussed at the research management committee meeting, and the results of that would be reported back through the New Jersey patent committee meeting.

Q. Do you recollect having conflicting priorities at times in the period of June of 1988 to February of 1989 between seed and Pharma?

A. There was certainly a lot of items that had to be taken care of within a very short period of time coming from all the different companies, so yes.

Q. An example of which would be patent filings to avoid statutory bars?

A. That would be one part.

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Q. In the period between February of 1988 and March of 1989, what was your general practice in the actual preparation of the patent application? More specifically, were you able to use a computer in drafting these applications?

A. The attorneys at that time didn't have individual work stations. The secretaries had a word processor, so you would have to basically write the application in longhand and give it to the secretary to type.

Q. Is that a practice you followed in connection with case 600-7101?

A. Yes.

Q. You indicated that you provided a substantially complete draft to your secretary to be typed?

A. Yes.

Q. Do you recollect about what date that was, based on the testimony of record?

A. I believe it was around November 3rd or so. According to the affidavit exhibit it was November 3rd of '88.

Q. If you provided to her a substantially

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complete copy on November 3rd, when do you think you might have started writing that draft?

A. I don't have a recollection of when I started that.

Q. Would it have taken more than two weeks, in your estimation?

A. Yes.

Q. A month?

A. I would say longer than that.

Q. Now, we are not talking about total activity exclusive of nothing else; we're talking about the time running from the day you started writing it to the day you handed it to your secretary.

A. Yes.

Q. Would it be more than a month?

A. Yes.

Q. What's your best estimate of the length of time it took you to complete the written draft?

MR. KELBER: Objection as to speculation. The witness has already testified she doesn't know.

BY MS. FURMAN:

Q. Would it have been more than a

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month-and-a-half?

A. Yes.

Q. How about two months?

A. I would say more than that.

Q. Well, that would bring us into December; correct?

MR. KELBER: Bring us where?

THE WITNESS: I think we're talking about different things.

MS. FURMAN: The length of time for you to hand write the draft that was given to your secretary to type on the 3rd.

THE WITNESS: I was counting backwards.

MS. FURMAN: That was my purpose.

MR. KELBER: Why don't you ask the questions?

BY MS. FURMAN:

Q. Counting backwards from November 3rd of 1988, how much time did it take to prepare the written draft?

A. I don't know exactly.

Q. What was the two-month figure that you just referred to?

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A. I know I was working on it for at least two months.

Q. Two months prior to November 3rd?

A. Right, which would have been September 3rd. I was working on this prior to that.

Q. Is that as far back before November 3rd that you can recall working on it?

A. As I said, I don't specifically recall. The date which I'm basing this on is I remember that when it came to light that Warner-Lambert had a patent application issued to the same subject matter -- or when their patent issued, I was in the process of writing this at that time.

Q. While you were writing the application, you had other obligations to the other Sandoz divisions; is that correct?

A. Yes.

Q. Do you recognize the pages that comprise Exhibit S1?

MR. KELBER: I'm going to object to reliance by the junior partner on Exhibit S1; you're beyond the scope.

BY MS. FURMAN:

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Q. Do you recognize those pages?

A. Some of them.

Q. What do they concern?

A. They are all pages that were part -- were either part of a draft of the application or in preparation of a draft in the application of 600-7101.

MR. KELBER: To what part of the cross does this questioning pertain?

MS. FURMAN: At some point you indicated whether or not work was being done during a certain time period, which I'm looking for at the moment, and I believe the testimony that -- the relevant period was between January 4th of 1989 and March 3rd of 1989, and my question of Mrs. Giesser is whether she can be certain that she did not generate any of that work during the time period.

MR. KELBER: You're asking her whether she couldn't have generated any of S1 in that time period?

MS. FURMAN: Whether it was -- whether she could be certain that none of it was done during the period of January 4, 1989, to March 3rd of 1989.

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THE WITNESS: I don't know when these papers were generated.

BY MS. FURMAN:

Q. Did you regard it as your continuing obligation to file a patent application on 299/84 as of the A rating of the underlying patent -- of that patent disclosure?

A. Yes.

Q. And that obligation, when was it fulfilled, on what date?

A. The date I filed the application was March 3rd of '89.

MS. FURMAN: That concludes my re-direct.

RE-CROSS EXAMINATION

By Mr. Kelber

Q. Ms. Giesser, you feel that you have at least a few years' experience in the matters of patent prosecution; is that correct?

A. Yes.

Q. When must a continuation application be on file with the United States Patent and Trademark Office in order to claim priority of an earlier U.S. application?

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A. As long as the earlier application is pending.

Q. So that means sometime before it issues; is that correct?

A. Yes.

MR. KELBER: Can you read back the question and answer that was marked earlier?

(The requested testimony was read by the reporter.)

BY MR. KELBER:

Q. Having heard that question and answer, do you still believe that the answer you gave is correct?

A. I think I'm getting confused. If the parent application is about to issue or go abandoned -- was it April 3rd -- then if you're going to file a continuation, it would have to be on file by that date, assuming that you were letting the parent go abandoned.

Q. So your assumption is that the parent was going to go abandoned; is that correct?

A. Yes.

Q. Let me direct your attention to the last

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page of that exhibit that constitutes S3 -- I'm sorry, not S3, S4.

A. That's 7044?

Q. 7044, that's correct.

A. Uh-huh.

Q. As of December 28, 1988, did you intend for the 7044/CONT to go abandoned?

A. I believe by that time that a CIP was going to be filed, so I believe that if not on December 21, '88, certainly after the time we had received the office action and had a chance to reflect upon it, we would have determined that we should abandon the parent.

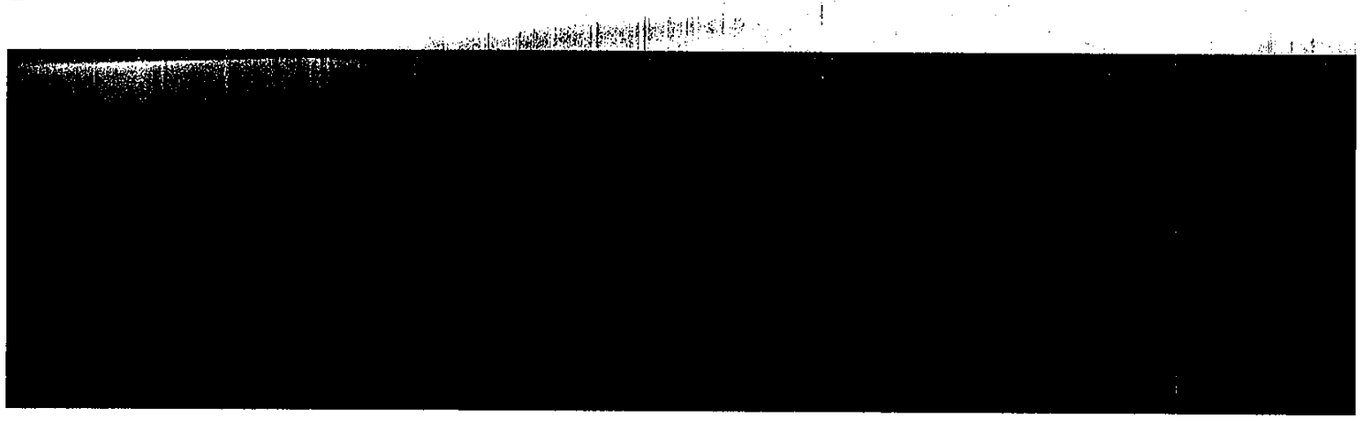
Q. My question to you is as of December 21, 1988, had you reached the conclusion that the parent was to be abandoned?

A. I don't recall.

Q. Well, in fact, you've read the last page of S4; is that correct?

A. Yes.

Q. The actions taken there are not exactly consistent with a determination to abandon the application; are they?



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A. At that point the question is whether we were going to abandon it on December 21st or whether we were going to abandon it eventually.

Q. So you authorized the examiner to undertake measures to place the case into condition for allowance knowing that you were going to abandon the case?

A. I'm not sure when the determination that the case was going to be abandoned was made.

Q. Would you say that the actions in the last page of Exhibit S4 are consistent with a determination to abandon the case?

A. It could be read as such.

Q. Do you see the reference to the cancelation of non-elected claims 18 and 19?

A. Yes.

Q. You could have in fact filed a divisional application directed to those claims consistent with patent office policy and then abandoned this application; couldn't you?

A. That was one option.

Q. That would have preserved the opportunity to file a CIP application tracing its priority back

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to the original application; wouldn't it?

A. You mean file a CIP off of the case containing only 18 and 19?

Q. That's correct.

A. I suppose that could have been an option.

Q. In fact, you could have re-filed 7044/CONT and subsequently filed a CIP off that re-filing and enjoyed claim to priority of the original case; correct?

A. I believe that could have been done.

Q. Let's turn to S3, which I believe is the notice of abandonment and related papers for 7025. Turning to S3, I believe your testimony was that the CIP of 7025/CIP was to be filed abroad as a non-convention case; is that correct?

A. That's the best of my recollection, yes.

Q. What was the nature of the time pressure involved if it was a non-convention case?

A. I think it might have had something to do with publication of the parent, but I couldn't be sure.

Q. Where was the parent being published?

A. Abroad, the parent abroad application.

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Q. Well, wouldn't that publication have an effective date as of May 5, 19 -- I'm sorry, as of May 5, 1987, abroad?

A. I'm sorry?

Q. Let's take the case of Europe. You indicated that the corresponding foreign application to 7025/CIP was about to be published?

A. I think that was what the -- part of what the time pressure was on it.

Q. Now, that would have constituted a bar to filing where?

A. It wouldn't have barred anything.

Q. So what was the nature of the time pressure?

A. It would have made -- part of the problem, I believe, was wanting to get the foreign application on file prior to the publication of the parent case for non-102 type reasons.

Q. You say you have recollection that there was a concern that there might be an objection abroad for a lack of availability of prior art; is that correct?

A. I believe that was one of the

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considerations.

Q. Were there other considerations?

A. I don't recall.

Q. Now, if you look at the third page of document S3, that's a request for extension of time; is that correct?

A. Yes.

Q. Why was the time period for response extended only two months?

A. I assume that was the only extension that was needed at that point.

Q. Needed for what?

A. To keep the parent -- keep the case from going abandoned.

Q. Is it correct, then, that the CIP would have been filed in the U.S. by that date?

A. Yes.

Q. So you actually filed the CIP sooner than you absolutely had to in the United States; is that correct?

A. Yes.

Q. Did you file that non-convention case in Europe before you filed the CIP in the U.S.?

Giesser - re-cross

A. I'm not sure exactly what the time frame was on that.

Q. Well, in fact --

A. It was right around the same time.

Q. Wasn't it your testimony that you did not draft the non-convention filing but rather communicated the information to Basle?

A. Yes.

Q. So you didn't have to actually prepare a rigid specification for that non-convention filing?

A. No, I did not. That was handled by the Basle patent department.

Q. And the filing of the CIP off 7025/CIP would have had no impact on the filing or entitlement -- I'm sorry, on the availability of the publication of the foreign filed parent on the European non-convention CIP; isn't that correct?

A. I'm not sure I understood what you said.

Q. I'm not sure I do, either.

Isn't it correct that the date of filing the CIP in the United States, the CIP of --

A. CIP two.

Q. Isn't it correct that the date of filing

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CIP two would have had no impact on whether or not prior art was available as against the non-convention document, the non-convention application filed abroad?

A. I don't know.

Q. In what way could it have affected the availability of prior art with respect to the non-convention application?

A. I don't know.

Q. Are you familiar with the practices of -- are you familiar with patent practices in Europe?

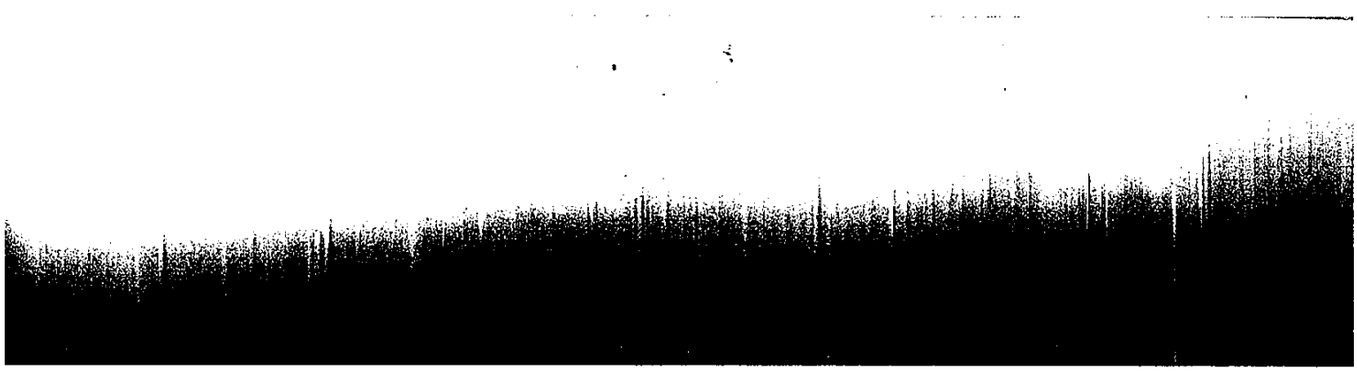
A. Yes.

Q. Can you imagine any situation where the filing of the CIP, of 7025/CIP, the filing date of that application would have impacted the availability of prior art as against a similar but non-convention application filed in Europe?

A. I'm sorry, I'm losing my focus here.

Q. You've told me that there was a time pressure to file the CIP of 7025/CIP, and you've told Diane the same thing, in part because there was a need to file an application abroad?

A. Yes.



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Q. And that application was a non-convention application?

A. Yes.

Q. My question to you is, how did the need to file that non-convention application impact the need to file the CIP application in the United States?

A. Well, certainly didn't want to file any information in Europe that hadn't been filed in the United States previously.

Q. Why?

A. We would not necessarily have permission to be under export license.

Q. Couldn't you have applied for export license without filing?

A. I suppose we could have.

Q. So it's your testimony that the 7025/CIP was in fact filed before the corresponding non-convention application?

A. I think it was.

Q. Under the Sandoz procedures that existed as of February 1988, could you have proceeded correctly with the preparation of a patent application on a disclosure and operated --

Giesser - re-cross

A. No that would have been incorrect procedure.

Q. So, in fact, it would not have been proper to proceed with the preparation of an application on 299/84 until sometime after January 27, 1988; is that correct?

A. Yes.

Q. I believe it was your testimony that you weren't familiar with the procedures at Sandoz necessary to obtain the information that was a prerequisite to drafting the application for 7101; is that correct?

A. Yes.

Q. In fact, weren't those procedures just a phone call to the person in question?

A. Well, that was the question, who is the person in question.

Q. And it's fairly easy to identify that by asking Mel; wasn't it?

A. That was part of it, yes.

Q. Of the meetings that you attended that are reflected in your schedule that you testified to about at length, what meetings were there that Dick

Giesser - re-cross

Vila could not have adequately represented the interests of Sandoz alone?

A. I'm sure Dick Vila can represent the interests of Sandoz whenever he chooses to.

Q. And would that representation, in your opinion, if he had so chosen, be adequate for the purposes of Sandoz' patent program?

A. Let me say Dick was at a number of these meetings.

Q. Let me turn your attention to paragraph ten on page three of F20, your declaration. I see that paragraph ten indicates you would have started writing the draft of 7101 no later than October 1988?

A. Yes.

Q. A few moments ago in response to questions from Diane you indicated that you must have started before September of 1988; is that correct?

A. Yes.

Q. What gave you the confidence that in fact it was no later than September rather than October as reflected in the declaration?

A. Well, with all the goings on at the office in October, i.e., the number of trips that I had to

Giesser - re-cross

make, particularly the trip to Madison and the trip to Boulder took up a lot of time, I remember being involved in drafting the application on this when the Warner-Lambert patent issued and we found out about it, and also just the general amount of time it would take to physically write this case leads me to believe that it would have been actually earlier than September.

Q. Now, of those three aspects of information you just described, which of them did you come into possession of after February 19th, 1993?

A. After February?

Q. Of this year.

A. None.

Q. So you had all that information in front of you, you were aware of all that information before February 19th of this year; weren't you?

A. Yes.

Q. Did you discuss the date on which you must have started drafting the application with Diane during the interval after your cross-examination by me?

A. No.

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Q. Did you consider anything in responding to Diane's questions on re-direct that you did not consider --

A. No.

Q. -- that you did not consider prior to signing your declaration of February 19, '93?

A. I'm sorry, what was that question again?

Q. Did you consider anything in responding to Diane's questions just a few minutes ago that you did not consider when signing the declaration that is F20 on February 19, 1993?

A. No.

Q. Your recollection is clearer now than it was then?

A. Yes.

Q. When did you receive notice of the Warner-Lambert -- issuance of the Warner-Lambert patent?

A. I don't recall exactly, but it was shortly after the patent issued.

Q. Was it in October?

A. No, it would have been shortly afterwards, possibly within a week or two after publication -- or

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after we received the Gazette.

Q. In response to a question I asked you this morning, I believe you testified that you didn't recall when you received notice of the Warner-Lambert patent or how that information came to you.

A. I don't have an exact recollection, no.

Q. You indicated that the receipt of the official Gazette would have been important in fixing the time on which you learned of the Warner-Lambert patent. Why is that?

A. Well, the general procedure would be that after the Gazette was received in the patent office, it would be circulated among the attorneys and agents for general knowledge.

Q. How many attorneys and agents were there in Sandoz in October of 1988?

A. Let me think. Let's see, October of '88, Mel, Tom Doyle, myself, Dick Vila, Bob Awna (phonetic), Gerry Sharkin, Barry Sullivan, Tom McGovern, Walt Jewel, and Jerry Robian (phonetic).

MS. FURMAN: For the record, Barry Sullivan is a trademark attorney.

Q. How long would each attorney take to review

the official Gazette?

A. It depended on the attorneys. The circulation was such that people who tended to be quick and pass them on would get them first, and people who were not as quick would get them last.

Q. Where did you fit in the scheme of things?

A. I tended to look at it quickly and pass it along.

Q. How long on average would it take that full rotation to complete?

A. I don't know about the full rotation. I tended to be at the top of the list of getting official Gazettes.

Q. Well, how long did it take for an official Gazette to get to you from its date of publication?

A. Generally within a week or so.

Q. Of its publication?

A. I'm sorry. Of its publication, I don't know. It would be about a week or so after we received it.

Q. How long would it take you to review the entire Gazette?

A. I would try to do it in an hour or so. I

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ignored the electrical section.

Q. You don't recall how you first became aware of the Warner-Lambert patent, do you?

A. No. It would either be by seeing it in the Gazette or hearing it from Mel, who had seen it in the Gazette.

Q. So you're certain it was either you or Mel?

A. Yes.

Q. Where did Mel fit in the pattern of obtaining it from the Gazette?

A. Since Mel was responsible for informing Basle of any substantive changes to U.S. patent law that would be proposed, he got the Gazettes either first or very close to it, so he would have been among the first ones to get it.

Q. And you knew this when you signed your declaration?

A. Yes.

Q. Do you ever dictate anything for transcription?

A. Not often, no.

Q. Anybody you know in the Sandoz office ever do that between January '88 and March '89?

Giesser - re-cross

A. Dick tended to dictate things a lot.

MS. FURMAN: For the record, his dictation was to his secretary.

MR. KELBER: You can ask her that. That's fact testimony.

THE WITNESS: Oh, were you talking about --

BY MR. KELBER:

Q. Dictation into a microphone?

A. Yeah, Dick tended to do that.

Q. Were you forbidden to do that?

A. No.

Q. That was just personal choice?

A. Yes.

Q. Do you at the present time feel incompetent to tackle the tasks assigned to you at Sandoz in the period January '88 through March '89 in a timely fashion?

A. No.

Q. Did you ever feel like there was a risk that you weren't going to get it all done?

A. At times, yes.

Q. Did you ever tell anybody about that?

A. Daily.

Giesser - re-cross

Q. Who did you tell?

A. I would talk to Dick a lot.

Q. Did you ever tell Dick that there was a chance that you might not get 7101 done and filed in time?

A. In time, meaning --

Q. Whatever you felt was an appropriate time.

A. I know that it was taking a long time to do it, and he was aware of that.

Q. But did you tell him it might take you too long?

A. I don't recall ever using those words.

Q. Dick was, to the best of your knowledge, satisfied with your progress with regard to that application; wasn't he?

A. He was certainly satisfied with my overall progress of handling things.

Q. Did he ever express any dissatisfaction with your progress with respect to 7101?

A. No.

Q. And he was aware that you were responsible for 7101?

A. Yes.

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Q. In fact, you talked to him on more than one occasion with respect to 7101 while you were preparing it; correct?

A. I would speak to him in general terms about it. For technical advice I would go to Mel.

Q. You testified that you had no choice but to file a patent application on the basis of the disclosure that became 7101; is that correct?

A. Yes.

Q. Did you have the option to determine when to file that application?

A. No, it was supposed to be given priority.

Q. Priority over what?

A. That's it. When a case was rated A, it meant it was ready to be filed and you were supposed to put forth all effort to file them.

Q. But in fact, there were other things that you had to put forth effort with respect to first?

A. Yes.

Q. Even as to your refreshed recollection of today between February of 1988 and September of 1988, you did not have the opportunity to begin drafting the application; is that correct?

Giesser - re-cross

A. I don't recall when I began drafting the application.

Q. How much of the application had you drafted when you learned of the Warner-Lambert patent?

A. I don't recall.

Q. Did you focus more attention on the application after you learned of the Warner Lambert patent?

A. Not any more than I had been -- I mean, I didn't treat it any differently after I found out than before I found out.

Q. Well, according to the best of your recollection, the best of your recollection tells you that you began drafting no later than September of 1988; is that correct?

A. No, I believe the best of my recollection is that it would have been earlier than that.

Q. August?

A. I would say yes, because I recall that I was working on it when I heard of the Warner-Lambert patent.

Q. July?

A. I don't know exactly.

Giesser - re-cross

Q. So the Warner-Lambert patent issuance really fixes in your mind the knowledge that you were working on the application?

A. Yes.

Q. That was an important event for you in connection with the application; is that correct?

A. Yes.

Q. Do you have any recollection as to whether you were working a long time on this application in terms of drafting before you learned of the Warner-Lambert application?

A. No, I don't have any recollection of that.

Q. So the best information that you have is sometime before the issuance of the Warner-Lambert application you began working?

A. Yes.

Q. That's quite a bit before October 1988; isn't that correct?

A. Yes.

Q. Would there have been any written records of your work of any type prior to October 1988?

A. I don't think there were any in existence then.

Giesser - re-cross

Q. No, I mean at the time.

A. Certainly my handwritten pages that I was drafting.

Q. Would anybody at Sandoz have known you were working on it at that time?

A. I'm sure Mel would have been generally aware that I was working on it. I don't know if he would recall any specific dates as to what I was doing. He was pretty busy with his own stuff at that point.

Q. How about your secretary?

A. I doubt if Lorraine would be able to distinguish between the various chemical cases I was working on in this area.

Q. So she wouldn't have known if you were working on this case or not?

A. I would say that's probably true.

Q. What happened to the case from January 27, 1988, until the time you began working on the draft?

A. From, I'm sorry, January 27th, 1988?

Q. 1988 until you began working on the draft.

A. Well, at that time Mel had collected some information on it. I don't know exactly when that

Giesser - re-cross

information went to him, but there was certainly some sort of information that I got from Mel that had been from the inventors, some preliminary --

Q. What did you do with that information?

A. I incorporated it into the draft.

Q. Before you began working on the draft, what did you do with that information?

A. I would have kept it until I began working on the draft.

Q. Do you recall reviewing it in detail?

A. Yes.

Q. Before working on the draft?

A. Yes.

Q. Do you know when that would have occurred?

A. No.

Q. You just recall reviewing it?

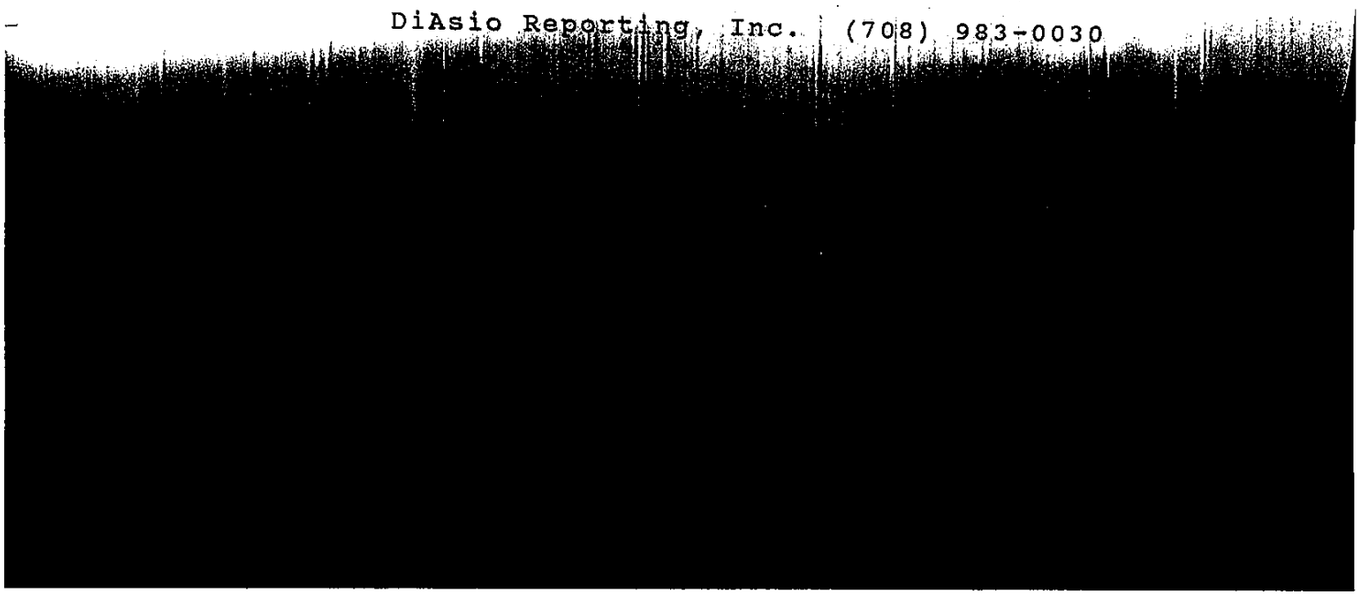
A. Yes.

Q. What was the nature of your review?

A. I was looking at it and trying very hard to understand it.

Q. Now, you said this was a very hard case to write; is that correct?

A. Yes.



Giesser - re-cross

Q. How much of the information on the synthesis did you obtain from the inventor?

A. I don't recall how much was directly from the inventor or how much was through Mel.

Q. Did you receive a lot of information from Mel, as well?

A. Yes.

Q. How much information with regard to the synthesis did you input yourself?

A. Possibly very little.

Q. How about the stereochemistry, the discussion of stereochemistry that appears in Exhibit S4, which is the application; did that come only from you?

A. I wrote that, but I remember discussing it with the inventor.

Q. Did anybody at Sandoz know that prior to the assignment of 7101 you had never written a pharmaceutical patent application?

A. Yes.

Q. Did Dick Vila know?

A. Yes.

Q. Did you feel at the time that you had

Giesser - re-cross

confidence in your ability to write this particular case?

A. Yes.

Q. Did you ever discuss that particular aspect of your experience with him in connection with 7101?

A. No.

Q. The seed cases that you filed in March of 1989, what were the nature of the time bars?

A. They were one of two, on-sale or in-public-use bars.

Q. And when did Sandoz' patent department learn of a need to file these applications?

A. I'm not sure what the time date was on that.

Q. Could it have been as early as January 1988?

A. No, it would have been later than that.

Q. Would it have been later than August of 1988?

A. I think it would have been, yes.

Q. So after you had begun drafting the application in question, was it necessary to put -- to interrupt that drafting in order to attend to the

Giesser - re-cross

seed cases?

A. I'm not sure whether I was -- I actually stopped working on it or whether I was working on it contemporaneously. The filing of the seed cases were in response to a policy change, and some of the discussions on the policy change were at the meeting in Basle in September, so the decision to file on these would have been after that.

Q. Do you recall how much of the application you had written before October -- draft application you had written before October of'88?

A. I would imagine it would have been relatively close to what I had given Lorraine on November 3rd, because I really wasn't in the office a whole lot or working on -- I was working on other projects for a large part of October.

Q. Well, you knew when you signed this declaration that is F20; correct?

A. Yes.

Q. Did you assign originally the date of October '88 as the date you had firm recollection of writing the first draft of 600-7101 that appears in paragraph ten?

Giesser - re-cross

A. I don't recall how that date came about.

Q. Did you receive a draft of the exhibit that is F20 and offer any corrections or advice with respect thereto?

A. Yes.

Q. In the draft that you received, was the date of October 1988 there?

A. I don't think it was.

Q. Was that date inserted in response to a suggestion from you?

A. I said I don't recall exactly the circumstances, but I remember that was an area that we had -- that there was a change from the original one.

Q. Well, it's not all that long ago compared with 1988. If the draft came to you without that information in it, isn't it reasonable to conclude that that information came from you?

A. I'm sorry.

Q. We're talking about a month-and-a-half from February 1993, and it's your testimony that you remember receiving a draft of this declaration that did not have the information in paragraph ten with

Giesser - re-cross

respect to October 1988; is that correct?

A. Yes. I recall that the original version was worded somewhat differently. I don't recall exactly what that wording was.

Q. Do you recall the effect of that wording?

A. I believe October '88 is an earlier deadline than what was originally in the first draft.

Q. An earlier date of starting?

A. Yes.

Q. Was the date of October 1988 suggested by you, then?

A. I don't recall.

Q. Who else besides you discussed the draft and changes thereto?

A. Well, I discussed them with Diane.

Q. Anybody else?

A. Not that I'm aware of. I don't know what Diane discussed.

Q. Do you recall suggesting to Diane that the date cited for beginning the draft was too late?

A. No.

Q. Somebody changed the date, though; is that correct?

Giesser - re-cross

A. Yes, that was changed.

Q. Did you give Diane documents in connection with changing the draft of this application?

A. I didn't send back a marked up document, no.

Q. I'm sorry, any other documents besides the draft declaration itself?

A. Well, she sent me copies of the other documents mentioned as exhibits.

Q. Did you send her any documents besides the documents --

A. Did I send her anything? No. I didn't take any papers connected with this case when I left Sandoz.

Q. The initial preparation of a declaration led to a date for beginning the draft of no than October 1988. You didn't consult any documents that Diane didn't give you in arriving at the date by February. Is it reasonable to conclude that the February 1988 came out of the discussions you had with Diane?

A. Yes.

Q. Isn't it necessary that the identification

Giesser - re-cross

of that date had to come from you? I mean, it was not so long ago you can't reconstruct that discussion?

A. I don't recall that discussion that clearly.

Q. Do you think if Diane knew you had begun as late as October 1988 -- strike that. It's objectionable even from me.

Did you recall when you were correcting the draft of Exhibit F20 that the Warner-Lambert patent of interest had issued while you were drafting the application?

A. Yes.

Q. But it is today your testimony that your drafting must have begun at least two months prior to the date that's reflected in your declaration?

A. Well, that is no later than October '88.

Q. It's your testimony it had to begin two months earlier than the date reflected in the declaration?

A. Yes.

Q. And you consulted no additional documents to arrive at that recollection?

Giesser - re-cross

A. Correct.

Q. Any of the other dates in here not as specifically fixed as they might be in light of your recollection of today?

A. Well, as we spoke earlier, there was a mistake on the filing date in paragraph 11.

Q. How about anything else?

A. Not that I recall.

Q. Is there any reason to believe that the other dates that are recited in here -- for instance, the date of December 14, 1988, that appears in paragraph 15, do you know for a fact that that date is correct?

A. I believe that was on a cover letter of an exhibit, so I would expect that it was correct.

Q. That was the date of the cover letter; is that correct?

A. Yes.

Q. Do you know that you sent it on the date the cover letter was dated?

A. Well, on or about that date.

Q. Could it have been as much as a week later?

A. I don't recall. I don't think so. I think

Giesser - re-cross

if -- it was my general practice that if a letter was delayed for that length of time, I would change the date on the letter to more accurately reflect when it would be sent.

Q. You spoke on re-direct with regard to the existence of conflicting obligations on your time and services between June '88 and March '89; do you recall that testimony?

A. Yes.

Q. How did you resolve those conflicting obligations when they occurred?

A. I would try and put the biggest fire out first.

Q. By "biggest fire," what do you mean?

A. The action that had the most pressing date or had the most possible adverse consequences.

Q. Missing that date would have the adverse --

A. Yes.

Q. The application that is 7101 was filed reasonably contemporaneously with the five or six seed cases that were filed in response to 102 bars in March; is that correct?

A. Yes.

Giesser - re-cross

Q. So they had the same date consequence?

A. Yes. At that point it was ready to be filed.

Q. It took you about three months to go from beginning to completion of the draft application; is that correct?

A. It appears that way, yes.

Q. Now, that's --

A. At least for completion of the first draft to filing.

Q. That's not my question. From initiating work on the first draft to completion of the first draft?

A. I don't remember exactly.

Q. It wasn't as long as four months, was it?

A. I don't recall.

Q. Forgive me for sounding a bit perturbed, but your recollection seems to come and go.

A. It's quite a while ago.

Q. It was a little bit better just a few minutes ago.

A. I remember I was working on the case when the Warner-Lambert patent issued. I don't recall how

long I was working on it.

Q. Did the issuance of the Warner-Lambert patent change the size of the fire, in your determination, with respect to 7101?

A. It certainly caused a lot of concern, because we were not expecting to see a Warner-Lambert patent issued to the same subject matter -- we were not expecting any patent to be issued to the same subject matter. As I said, my biggest recollection in finding out was thinking how it was going to complicate prosecution of an otherwise straight forward case.

Q. And you certainly had a time bar then with respect to the filing of the application?

A. Yes.

Q. When you signed the declaration that is F20, it was your recollection that you might have written the draft of the application that is 7101 in about a month's time; is that correct?

A. No.

Q. Well, it says no later than October 1988 you would have started writing the draft; that's correct?

Giesser - re-cross

A. Yes, that's correct.

Q. I apologize. I should have said about two months. Is that correct, it would have been two months from the -- your recollection on February 19, 1993, was that it could have been as little as two months from the beginning of the drafting to the completion of the first draft; is that correct?

A. No.

Q. Well, reading paragraph ten literally, it is consistent with the conclusion that you did not start earlier than October 1988; isn't that correct?

A. It seems consistent with the fact that October '88 would have been the latest possible date I could have started.

Q. And you know that you finished the draft prior to December 14; isn't that correct?

A. Well, I know that I gave a first handwritten version to Lorraine November 3rd.

Q. So that's just about a month; isn't it?

A. From October 1st to November 3rd is a little over a month, but as I've testified before, I was working on the application before.

Q. I understand that, but my question is, when

Giesser - re-cross

you signed this declaration, it was your recollection that it could have been as little as a month; isn't that correct?

A. No, when I signed the declaration, I knew that I had remembered working on the application when the Warner-Lambert patent came in.

Q. Did you know when the Warner-Lambert --

A. I knew it was vaguely in August. I don't know the exact date.

Q. It would have been possible to fix paragraph ten with more specificity if you had that information before you; wouldn't it?

A. It could have been possible to do a lot of things.

Q. That's not my question.

A. I didn't know you asked a question. I thought you were making a statement.

Q. It would have been possible to fix the date on which you would have started writing a draft of case 600-7101 with more specificity given the information you recall as of February 19, 1993; wouldn't it?

A. No, I don't recall when I started to work

Giesser - re-cross

on 600-7101.

Q. But you knew it was in fact earlier than September?

A. Yes.

Q. And you chose to recite October as the latest possible start date?

A. Yes.

Q. Any reason for that?

A. It seemed the most conservative.

Q. Is there still a question in your mind as to the possibility?

A. No.

Q. Was there a question in your mind as to the possibility?

A. No.

Q. What do you mean by "conservative" if you were certain that it started earlier than September?

A. I don't have a fixed date in my mind when I started writing it.

Q. But you didn't put a fixed date. You knew it was before September, you just testified?

A. That's true.

Q. So September 1988 would have been no more

Giesser - re-cross

or less conservative than October 1988; would it?

A. That could be true.

Q. Is it true?

A. Yes.

Q. Do you recall speaking to the inventor in this case with regard to 7101 between January 4 and March 3, 1989?

A. Yes.

Q. And what was the subject of those discussions?

A. I believe we went over the draft I gave him.

Q. Did you go over the changes that you had received?

A. Yes.

Q. Do you recall when you prepared the final draft?

A. Not exactly, no.

Q. When you were hired at Sandoz' patent and trademark department, do you have any reason to know -- I'm sorry, when you were hired at Sandoz' patent department, did you inform them of the nature of your prior experience in the patent field?

Giesser - re-cross

A. Yes.

Q. Is it a correct conclusion that for those meetings or trips that Dick Vila requested you to attend in the period reflected in your declaration that is F20 that he requested you to attend those having a general idea of your other obligations on behalf of Sandoz?

A. Yes.

Q. Is it correct to conclude that Sandoz -- or individuals in the Sandoz patent department made the decision to complete the drafting of the CIP application that bears the docket number 7025-CIP/CIP prior to completion of 7101 rather than filing a continuation?

A. I'm not sure that the weight of the two obligations were necessarily compared. I think it was basically decided that a CIP should be filed and should be filed now. I don't think it was --

Q. You had the responsibility for both; correct?

A. Yes.

Q. Do you remember making the decision with respect to that one way or the other?

A. At that time I was working on both applications. I was working on both the CIP of 7025 and also the draft of 7101.

Q. It's my understanding that of the two, you had to do the 7025 first.

A. Well, like I said, I was working on them contemporaneously.

Q. You filed 7025-CIP/CIP prior to October 11, 1988; correct?

A. Yes.

Q. If you had elected to file a continuation application or respond to the office action of May 11, '88 on 7025-CIP, thereby extending the time in which to file the CIP application, would you have had more time to work on 7101?

A. I'm not sure that was an election that I could have made at the time.

Q. If somebody at Sandoz had made that election, would you then have had more time?

A. If someone had decided that a continuation should be filed, then I would have had more.

Q. Do you recall ever being told that the 7101 case had to be on file by March of 1989?

Giesser - re-cross

A. Not specifically.

Q. That was just when you got to it?

A. That was when it was completed.

Q. And it was completed by you; correct?

A. Yes.

MR. KELBER: I have nothing further.

MS. FURMAN: I have a couple more questions.

RE-RE-DIRECT EXAMINATION

By Ms. Furman

Q. Going to case 600-7025, you earlier testified that you were writing the double CIP and transmitting information to Basle on the foreign text at the same time, roughly; is that correct?

A. Yes.

Q. In your opinion, would it have been a more economical use of your time for you to postpone filing the double CIP until sometime in the future?

A. Well, since I was working on the case with Basle, it probably would not have been.

Q. Did you need any information in filing the double CIP beyond that which you provided to Basle for the foreign text?

A. Are you asking whether I consulted the

Giesser - re-re-direct

inventors on this case?

Q. No, I'm asking whether the information that you got for foreign purposes was sufficient also for the double CIP. In other words, was drafting the double CIP very similar to preparing the draft of the foreign text?

MR. KELBER: Objection. I don't think she prepared the draft of the foreign.

BY MS. FURMAN:

Q. Was the content of the double CIP similar to the content of the foreign text?

A. As far as I recall, it was similar.

Q. It's my understanding that Basle imposed a deadline of October of '88 to file the foreign text; is that true?

A. As much as I can recommend -- excuse me, as much as I can recollect, yes.

Q. So you had no choice but to gather information, at least for preparing the foreign text, prior to October of 1988?

A. Yes.

Q. Are there structures in the involved patent application?

Giesser - re-re-direct

A. Yes.

Q. How did you dictate structures?

A. I would convey them by drawing them on the piece of paper that I gave to Lorraine. I didn't dictate this case.

Q. In fact, in a case such as this containing structures, would there be an advantage to writing out the case as opposed to dictating it?

MR. KELBER: Objection. The witness has already testified that she doesn't have much experience dictating cases. So how would she know?

MS. FURMAN: She can speculate.

MR. KELBER: Object strongly to any speculation, and the fact that you're inviting her to speculate I think is truly objectionable.

BY MS FURMAN:

Q. Does the phrase "no later than October 1988" include September of 1988?

A. Yes.

Q. Does it include August 1988?

A. Yes.

Q. Was it your intention between January 27th of 1988 and March 3rd of 1989 to file a patent

Giesser - re-re-direct

application on 299/84?

MR. KELBER: Asked and answered and far beyond the scope.

MS. FURMAN: If it's asked and answered--

A. Yes.

Q. What was the response?

A. Yes

Re-Re-Cross Examination

By Mr. Kelber

Q. What did you do to get the information for Basle's request?

A. I would have spoken with either or both Mel or the inventors of 7025-CIP/CIP.

Q. Did you actually do those things?

A. Yes.

Q. So you spoke with Mel. Couldn't Mel have sent that information on to Basle himself?

A. Well, it was my responsibility. It was not Mel's case.

Q. So you got some information from Mel, and you got some information from at least Dr. Kathawala; is that correct?

A. Yes.

Giesser - re-re-cross

Q. What did you do with that information?

A. I wrote a draft of 7025-CIP/CIP.

Q. I'm sorry, with respect to communication with Basle, what did you do?

A. I had communications in Basle, both on the phone and while I was over in Basle in September of '88.

Q. When you were in Basle for four days in September of '88?

A. Yes, I was there on -- well, on the weekdays it was Monday, Tuesday, Wednesday, and I came home on a Thursday.

Q. So three days. So the communication was over some part of those three days; is that correct?

A. Yes.

Q. How long did it take you to gather that information?

A. I don't recall exactly.

Q. As much as a day?

A. I'm sorry, to gather all the information needed to provide for the --

Q. To answer Basle's inquiry.

A. I'm sure it would have been longer than

Giesser - re-re-cross

that.

Q. Well, you talked to Mel, you said, and you talked to Mr. Kathawala. What else did you do?

A. That would have been it.

Q. I'm talking total time commitment in number of hours. How many hours did it take to talk to Mel and Dr. Kathawala?

A. As I recall, 7025-CIP/CIP was a rather extensive CIP; it was not a simple CIP, so there would have been a lot of information.

Q. I'm not referring to the CIP/CIP. You told me you needed to transmit some information to Basle with regard to additional information with regard to 7025/CIP; is that correct?

A. That was for them to write what would be the foreign counterpart of 7025-CIP/CIP.

Q. And it was your testimony that you did not write the foreign counterpart?

A. I did not write the foreign counterpart.

Q. So you collected the information and communicated it to Basle?

A. Yes. Usually the way that would work would be I would send a draft of my U.S. application, and

Giesser - re-re-cross

they would modify it for the European formats.

Q. In fact, that's not the way it worked on this case; is it?

A. No, this one, as I recall, was more contemporaneous writing of the applications by Basle and myself.

Q. And your discussions in Basle with regard to the information, that involved revising written documents?

A. I didn't do any revising of written documents over there, no.

Q. Did you write any documents over there?

A. Not that I recall.

Q. Your communication was purely oral there?

A. Yes.

Q. Did you write documents for Basle prior to going over there?

A. I don't recall. I imagine there was.

Q. You imagine there were. What type of documents would those have been?

A. Possibly transmitting technical information.

Q. Would you prepare that technical

Giesser - re-re-cross

information yourself?

A. I would compile it. For instance, diagrams of pathways, chemical pathways or such.

Q. Who would provide those pathway diagrams?

A. The inventor.

Q. So your involvement in written communication was the assembly of information received; is that correct?

A. Yes.

Q. And with regard to the non-convention case, you had some oral communication; is that correct?

A. Yes.

Q. Did you ever have another application at Sandoz that took more than a year from the date it was assigned as an A case to filing?

A. I don't recall. I would expect not.

Q. You would expect not?

A. Yes.

Q. You do recall more than one case where it took less than that amount of time?

A. Yes.

MR. KELBER: That's it.

MS. FURMAN: I have two more questions.

Giesser - re-re-re-direct

Re-Re-Re-Direct Examination

By Ms. Furman

Q. You indicated that 600-7025 CIP/CIP involved extensive work. The word extensive I believe is what you used?

A. Yes.

Q. Why do you use that word to describe it?

A. Well, the amount of material that was added, as I recall, was a lot. It wasn't just one extra example or something which you might put into a CIP. The amount of work involved was the equivalent to writing a new case, in my estimation.

Q. Would that be the same material that you needed to provide to Basle for the foreign text?

A. It would have involved the same material, yes.

Q. Do you recollect whether there was any commercial significance to the compounds covered by case 600-7025?

MR. KELBER: Objection, way beyond the scope of -- what are we, re-re-cross? Never even been raised in direct, let alone --

BY MS. FURMAN:

Giesser - re-re-re-direct

Q. Were there any other reasons for filing 7025-CIP/CIP as quickly as possible?

A. The subject matter was considered important.

MS. FURMAN: That's it. I have no more questions.

MR. KELBER: I couldn't improve on that answer myself. I appreciate your tolerance and your attention.

Are you going to take care of filing the original?

MS. FURMAN: Yes.

MR. KELBER: It continues to be your preference that we identify our objections to the declarations in writing?

MS. FURMAN: To the declarations, or the exhibits?

MR. KELBER: Yes, to both, other than Joanne's or the other ones that were subject to cross? Last time I tried to object to a declaration of yours during the deposition, and you said, quote, "we prefer the objections be made in writing." Is that still your desire?

Giesser - re-re-re-direct

MS. FURMAN: My request stands as indicated.

MR. KELBER: Okay. As far as I'm concerned, that's the end of the record.

(Whereupon the deposition was concluded.)

Giesser - re-re-re-direct

ERRATA SHEET

I have read the foregoing transcript of my deposition taken on April 9, 1992, and _____ It is a true and correct transcript of my deposition given on the day and date aforesaid.

[or]

_____ I wish to make the following changes to my deposition: See attached sheet

Page _____ Change _____

Page _____ Change _____

Page _____ Change _____

Page _____ Change _____

Page _____ Change _____

Page _____ Change _____

Page _____ Change _____

Page _____ Change _____

Subscribed and sworn to before me this 5th day of May, A.D. 1993.

Joanne M. Giesser

Thomas W. Tolpin

Notary Public

My commission expires: 4/9/97

[Seal]

ERRATA SHEET

Name of case: Wattanasin v. Fujikawa et al.
Deposition of: Joanne M. Giesser
Date taken: April 9, 1993
Page 1/1

PAGE	LINE	CHANGE	REASON
		The following changes are all of a typographical nature, and primarily are concerned with spelling or punctuation:	
7	15	Initial capitalize "patent office".	
7	19-20	Initial capitalize "patent and trademark department".	
10	16	Change "Pharma" to "Pharmaceutical".	
11	22	Initial capitalize "crop protection".	
11	24	After "involved" insert "in".	
13	8-9	Initial capitalize "crop protection".	
20	16	Initial capitalize "patent and trademark department".	
20	23-24	Initial capitalize "patent and trademark department".	
33	5	Change "102-B" to "102(b)".	
35	24	Initial capitalize "patent".	
36	2	Initial capitalize "office".	
38	16-17	Initial capitalize "patent and trademark department".	
39	24	Initial capitalize "patent and trademark department".	
40	12	Initial capitalize "judges' dinner".	
45	12	Change "Angstrom" to "Engstrom".	
52	4	Change "102-B" to "102(b)".	
52	16	Initial capitalize "patent and trademark department".	
56	2	Change "Weinfeld" to "Weinfeldt".	
56	20	Change "Weinfeld" to "Weinfeldt".	
60	23	Initial capitalize "patent department".	
62	12	Change "straight forward" to "straightforward".	
65	23	Delete the apostrophe following "Sandoz".	
65	24	Initial capitalize "crop protection".	
72	2	Change "do" to "to".	
72	21	Initial capitalize "judges' dinner".	
73	6	Change "102-B" to "102(b)".	
87	22	Change "partner" to "party".	
92	15	Change "cancelation" to "cancellation".	
103	19-20	Change "Awna" to "Honor" and delete "(phonetic)".	
103	20	Change "Sullivan" to "Solomon".	
103	21	Change "Jerry Robian (phonetic)" to "Joe Borovian".	
103	22	Change "Sullivan" to "Solomon".	

Joanne M. Giesser
JOANNE M. GIESSER, ESQ.

SUBSCRIBED AND SWORN TO BEFORE ME

This 5th day of May, 1993

My commission expires: 4/9/97

Thomas W Tolpin
A Notary Public

STATE OF ILLINOIS)
) SS.
COUNTY OF K A N E)

I, Paula M. Quetsch, C.S.R. No. 084-003733, a Notary Public in and for the County of Kane, State of Illinois, do hereby certify that JOANNE M. GIESSER, ESQ., was duly sworn by me to testify the truth; that the above deposition, Pages 1 through 140 was recorded stenographically be me and reduced to typewriting under my personal direction; and that the foregoing is a true and correct transcript of the testimony given by the said witness at the time and place previously specified.

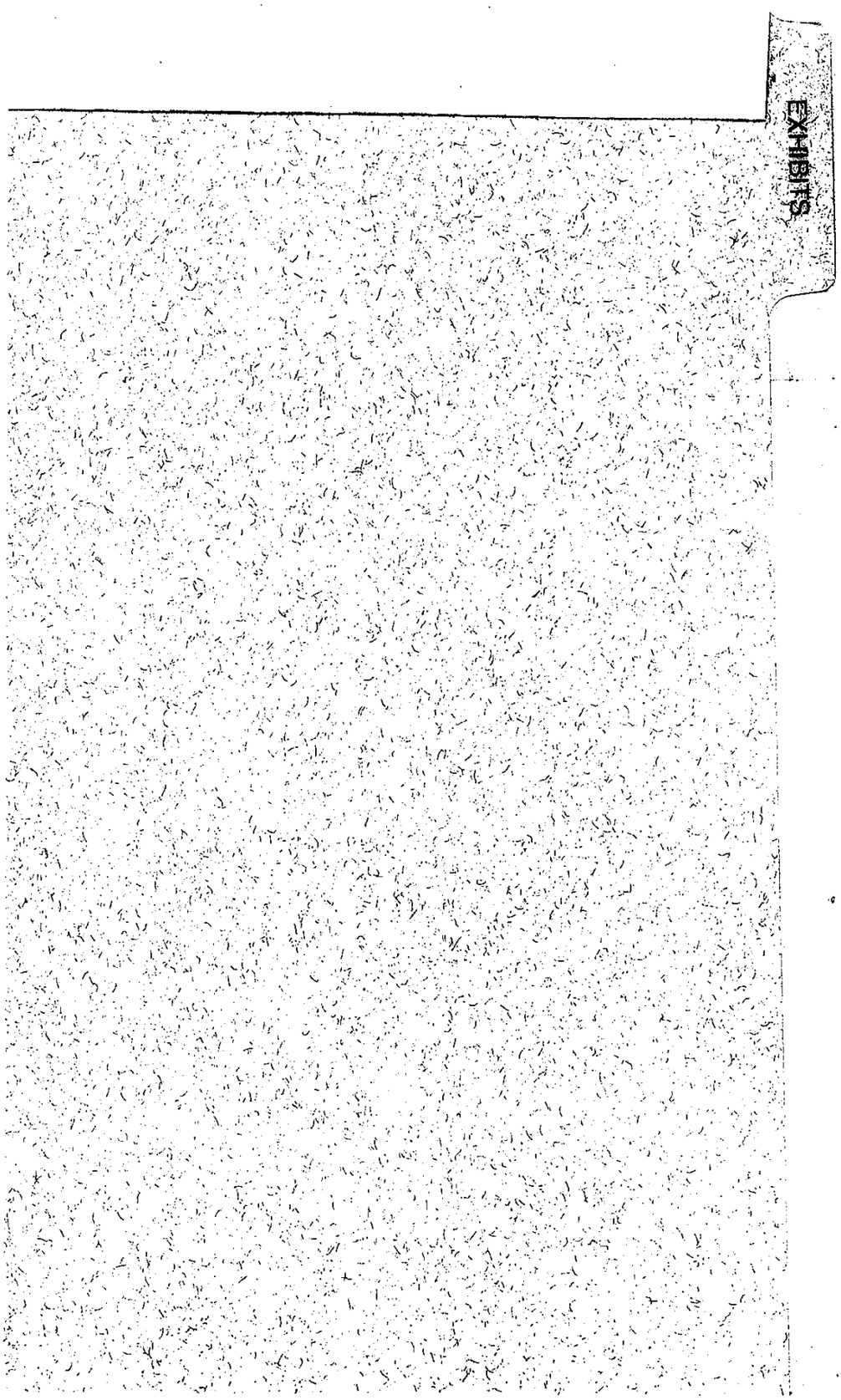
I further certify that I am not counsel for nor in any way related to any of the parties to this suit, nor am I in any way interested in the outcome thereof.

IN WITNESS WHEREOF I have hereunto set my hand and affixed by notarial seal this 14th day of April, 1993.

OFFICIAL SEAL
STATE OF ILLINOIS
PAULA QUETSCH
NOTARY PUBLIC

Notary Public

My Commission Expires: September 23, 1996


EXHIBITS

Case No. 600-7101/CONT/INT.
Patent

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

ORIGINAL

WATTANASIN NOTICE OF CROSS-EXAMINATION DEPOSITION 37 CFR §1.673(e)

By agreement of the parties, the cross-examination deposition of Joanne M. Giesser will be held on Friday, April 9, 1993 at the following address:

Amoco Corp.
55 Shuman Boulevard
"N Building"
Suite 600
Naperville, IL 60563

The starting time will be 12 noon.

Respectfully submitted,

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

SANDOZ CORPORATION
59 Route 10
East Hanover, NJ 07936

DEF:rmf
April 5, 1993
Encs: OVERVIEW MAP AND LOCAL MAPS A,B AND C

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 April 5, 1993
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Signature
4/5/93
Date of Signature

ORIGINAL

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

WATTANASIN NOTICE OF CROSS-EXAMINATION DEPOSITION 37 CFR §1.673(e)

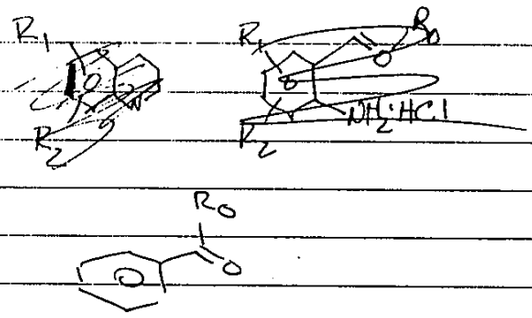
was served on counsel for the party Fujikawa et al., this 5th day of April 1993, by facsimile and by postage pre-paid first-class mail addressed to the following:

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
FAX: (703) 413-2220

Diane Furman

Diane E. Furman

Add before pg 4



A_1 ~~reflux~~ – condensation

X_1 = any alkyl group

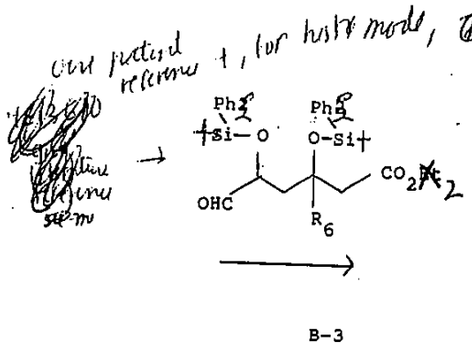
X_2 = R_{13} of indene

X_3 = any alkyl

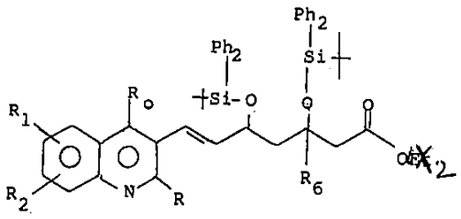
X_4 = any ethyl or methyl

R_6 as defined

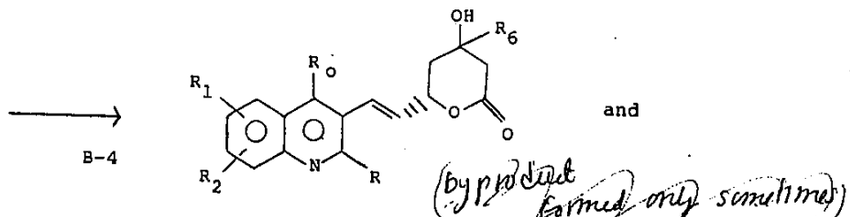
List of all var before table p11
incorp Rx scheme into example



B-3



(XVI)

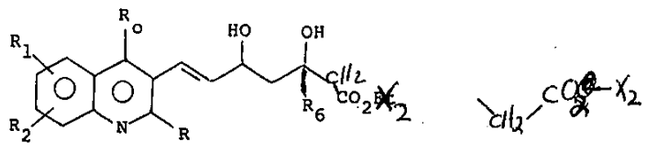


B-4

and

(by product formed only sometimes)

(II)



(I)

Compound I will give you an insight later on this

Need 1) Statement that when any compound of Formula A contains an hydroxy group as R_1-R_5, said hydroxy group is protected by a diphenyl/t-butyl/silyl group in the compounds of Formulae XIII - XI and XIV - XVI which group is cleaved at the end of the synthesis by Reaction B-4.

2) Hydrogenation reaction to get compounds wherein R is $-CH_2CH_2-$ over

(3) Process for obtaining compounds wherein X is 4-CH=CH- (cis). Add phosphonium wittig alkenalene to Reaction B-2

(4) Process for Q = -C(=O)- compound

(5) Process for ladenzalen, hydrolysis of lactone interconversion of esters, salts, free acid, etc.

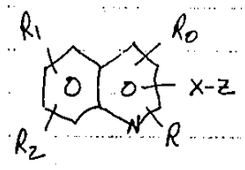
7064

Z-composition
-> method

Insert

but are not limited to the following

1) 1) ~~Those~~ Compounds which are included in ~~the~~ formula of ~~the~~ Proposed Count 1 including ~~such as~~ (referring to the formula of Proposed Count 1)



i) Compound 63-366, where R_1 = H; R_2 = H; R_D = 3,5-dimethylphenyl; R = isopropyl; X = -CH=CH-; ~~and~~ Z = (a); Q = $-\underset{OH}{C}-$; and R_g = ethyl

ii) Compound 63-548, where R_1 = H; R_2 = H; R_D = 3,5-dimethylphenyl; R = CH_3, X = -CH=CH-; Z = (a); Q = $-\underset{OH}{C}-$; and R_7 = ethyl.

iii) Compound 63-549, where R_1 = H; R_2 = H; R_D = 3,5-dimethylphenyl; R = CH_3, X = -CH=CH-; and Z = (b).

iv) Compound 64-933, where R_1 = H; [redacted]; R_D = phenyl; R = isopropyl; X = -CH=CH-; Z = (a); Q = $-\underset{OH}{C}-$ and R_g = ethyl

v) Compound 64-934, where R_1 = H; R_2 = H; R_D = phenyl; R = isopropyl; X = -CH=CH; Z = (a); Q = $-\underset{OH}{C}-$; R_7 = M; M = Na^+

vi) Compound 64-935, where R_1 = H; R_2 = H; R_D = 4-fluorophenyl, R = isopropyl; Z = (a); Q = $-\underset{OH}{C}-$; R_g = ethyl

BASLE

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/047,358	05/05/87	KATHAWALA	~~600-7025/CIP~~ 600-7025/CIP

07/047,358 5/5/87 KATHAWALA

GERALD D. SHARKIN
SANDOZ CORP.
59 ROUTE 10
EAST HANOVER, NJ 07936

PATENT AND TRADEMARK DEPT.
MAY 13 1988
JMG

EXAMINER	
BRISCOE,R	
BRISCOE,K	
ART UNIT	PAPER NUMBER
~~121~~ 121	4

DATE MAILED: ~~05/11/88~~ 5/11/88

This is a communication from the examiner in charge of your application.

COMMISSIONER OF PATENTS AND TRADEMARKS

August 11, 1988

☑ This application has been examined ☑ Responsive to communication filed on Jan. 19, 1988 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-23 and 26-32 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☑ Claims 1-23 and 26-29 are allowed.
4. ☑ Claims 30-32 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings which are acceptable for examination purposes until such time as allowable subject matter is indicated.
8. ☐ Allowable subject matter having been indicated, formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. These drawings are ☐ acceptable; ☐ not acceptable (see explanation).
10. ☐ The ☐ proposed drawing correction and/or the ☐ proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved. ☐ disapproved (see explanation). However, the Patent and Trademark Office no longer makes drawing changes. It is now applicant's responsibility to ensure that the drawings are corrected. Corrections MUST be effected in accordance with the instructions set forth on the attached letter "INFORMATION ON HOW TO EFFECT DRAWING CHANGES", PTO-1474.
12. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Case No. 600-7025/CIP
Serial No. (047,358

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :

FAIZULLA G. KATHAWALA : Art Unit: 121

Serial No. 07/047,358 : Examiner: K. BRISCOE

Filed: May 5, 1987 :

For: PYRIMIDINE DERIVATIVES :

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on October 11, 1988
(Date of Deposit)
Richard E. Vila
Name of applicant, assignee, or Registered Representative
/s/
Signature
October 11, 1988
Date of Signature

REQUEST FOR EXTENSION OF TIME

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

Dear Sir:

It is respectfully requested that the period for responding to the Office Action of May 11, 1988 or taking an appeal or further action in connection with the above-identified application, originally set to expire on August 11, 1988 , be extended for two (2) month(s) to October 11, 1988.

☐ A check in the amount of $ to cover the fee for this extension is enclosed.

☒ Please charge the extension fee of $170.00 required by 37 CFR 1.17(c) to Deposit Account No. 19-0134 in the name of Sandoz Corporation.

Respectfully submitted,

/s/
Richard E. Vila
Attorney for FAIZULLA G. KATHAWALA
(201) 503- 7852

JMG:lmc

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

Enclosures: Postcard; COM Stamp

SUBMITTED IN DUPLICATE

An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the Issue Fee.

Authorization for this Examiner's Amendment was given in a telephone interview with Ms. Giesser on December 21, 1988.

Non-elected claims 18 and 19 have been canceled without prejudice to the filing of one or more divisional applications drawn thereto.

Claim 16, line 3, after "compound" --according to claim 1-- has been inserted.

Claim 16, last line "; said compound of claim 1" has been canceled.

Any inquiry concerning this communication should be directed to Examiner Dentz at telephone number 703-557-3572.

12/22/88;df

JOHN M. FORD
EXAMINER
GROUP ART UNIT 121

Case No. 600-7101/CONT/INT.(3)
Patent

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

WATTANASIN
v.
FUJIKAWA et al.

Interference Nos. 102,648, 102,975
Examiner-in-Chief: M. Sofocleous

DECLARATION OF JOANNE M. GIESSER PURSUANT TO 37 CFR §1.672

I, Joanne M. Giesser, do hereby declare as follows:

1. All of the below-indicated activities took place in the United States.

2. I was employed by Sandoz Corporation as a patent attorney from August 16, 1987 to November 6, 1992, and during the time periods referred to herein was a member of the Patent and Trademark Department located in East Hanover, New Jersey. (On September 1, 1992, I transferred to the patent department of the Sandoz Crop Protection affiliate of Sandoz Corp. in Palo Alto, California.) I am currently employed as a patent attorney for Amoco Corporation in Naperville, Illinois.

3. I filed the involved Wattanasin continuation application, and I also drafted and filed the parent application thereof, Serial No. 07/318,773 filed on March 3, 1989. As of its filing date, the '773 application received internal docketing number 600-7101, and is hereinafter referred to as "Case 600-7101".

4. Case 600-7101 is based on Patent Disclosure No. 299/84 of Dr. Sompong Wattanasin.

5. At the January 27, 1988 meeting of the Sandoz Corporation Patent Committee, said PD 299/84 was rated "A" for filing. I would have received a copy of the Minutes of the meeting sometime in February 1988.

6. PD 299/84 was assigned to me, although Mr. Kassenoff of the Patent Department and I intended that the case would be filed by either one of us depending on who was available after existing filing priorities had been completed.

7. I received certain materials from Dr. Wattanasin in connection with the filing of Case 600-7101.

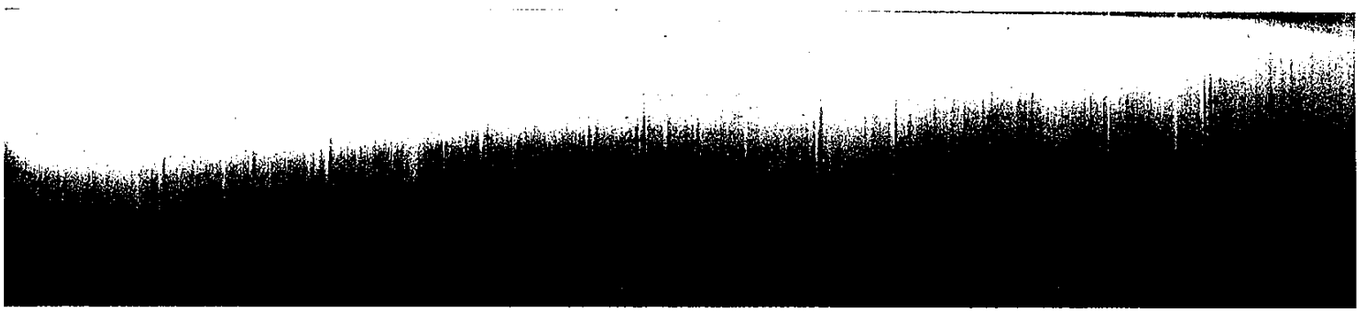
Exhibit P comprises a copy of material which the Patent Department received which related to the preparation of Case 600-7101. These materials comprise:

P-1: 4 pages containing handwritten reaction schemes and notes bearing the handwritten name of "S. Wattanasin" and a date of February 29, 1988 on the first page;

P-2: 7 pages of computer printouts of specific compounds containing handwritten notations of the Notebook pages on which they were prepared and relevant physical properties; and

P-3: 9 laboratory notebook pages numbered 130, 137, 145, 153, 158, 166, 172, 175 and 176.

8. When I received the pages which comprise Exhibit P, I made handwritten annotations on some of the pages, which appear on the pages of the Exhibits.



9. It will be noted that in the calendar year 1988, I compiled an airline travel mileage of approximately 75,000 miles. My travel and entertainment expense reports for the period of February 1, 1988 to March 3, 1989, indicate that I was required to be out of the office on business on at least the following dates:

February 21-26.
March 1, 15-16, 20 and 28-31.
April 20-22.
May 2
June 15-16, 24
July 12
August 29-31
September 1, 10-14
October 9-11, 16-17, 27-28
December 6-8
January 8-12
February 21, 28
March 1-2

Exhibit S hereto comprises true copies of travel and entertainment expense reports which I filed out and submitted to the Sandoz Travel Department to obtain reimbursement of my business travel expenses. Each of these reports is in my handwriting and bears my true signature.

10. No later than October 1988, I would have started writing a draft of Case 600-7101.

11. On November 6, 1988, I filed continuation-in-part application, Case 600-7025/CIP/CIP (Serial No. 07/466,083), which was indicated for filing ahead of PD 299/84.

Exhibit T hereto comprises a copy of the filing receipt for Case 600-7025/CIP/CIP/.

371

12. In early November of 1988, my secretary, Ms. Lorraine M. Chesley, began typing a draft of Case 600-7101.

Exhibit U-1 hereto appears to comprise a copy of the label of the computer disc on which this application is stored, which indicates a starting date of November 3, 1988 and a mailing date of March 3, 1989.

13. Also in about November of 1988, I received a memorandum from Dr. Wattanasin which outlined certain synthesis steps for preparing compounds of Case 600-7101.

Exhibit U-2 comprises a memorandum received from Dr. Wattanasin by the Patent Department, which comprises a cover page and 8 pages containing synthesis steps for preparing compounds covered by PD 299/84.

This memorandum bears a handwritten date of November 7, 1988 and was date stamped November 8, 1988 by the Patent Deparment.

14. On or before November 8, 1988, I requested Mr. Siegfied S. Warhman of Sandoz Information Services to provide correct nomenclature for various compounds of PD 299/84 and starting materials used in their synthesis.

Exhibit V-1 comprises a true copy of my handwritten request, which became the cover page of a responding memorandum from Mr. Henry Mah, also of Sandoz Information Services. The return memorandum is dated November 8, 1988; and the Patent Department date stamp on my request memo indicates that it was received by the Patent Department on November 9, 1988.

Exhibit V-2 is another memorandum which was received by the Patent Department from Mr. Henry Mah which bears a date of November 14, 1988 and is also date stamped November 14, 1988, which provides further nomenclature of the quinoline compounds of the PD 299/84 and their reaction intermediates.

15. On or about December 14, 1988, I sent a first draft of Case 600-7101 to Dr. Wattanasin for his review.

Exhibit W comprises a true copy of the cover letter for the draft application which I sent to Dr. Wattanasin.

15. Further information related to Case 600-7101 which is in the possession of the Patent Department comprises:

Exhibit X: which comprises four pages of reaction diagrams containing notations some of which are written in my handwriting, and the handwritten date of December 22, 1988.

Exhibit Y-1: a handwritten memorandum of changes in a draft of Case 600-7101 bearing a date of January 4, 1989;

Exhibit Y-2: a computer printout of the structures of the compounds of PD 299/84, with handwritten IC50 and/or ED50 values and a handwritten date of January 4, 1989.

16. On March 3, 1989, I filed Case 600-7101, the parent application of the involved Wattanasin application.

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.

Joanne M. Giesser

JOANNE M. GIESSER

PTO-103X
(Rev. 11-86)

Exhibit T 437

FILING RECEIPT

RE: CORRECTED

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTORNEY DOCKET NO.	DRWGS	TOT CL	IND CL
07/254,514	10/06/88	121	$ 450.00	600-7025/CIP/KIP	0	14	1

GERALD D. SHARKIN
SANDOZ CORPORATION
59 ROUTE 10
EAST HANOVER, NJ 07936

PATENT AND
TRADEMARK DEPT.

MAY 7 - 1990

Receipt is acknowledged of the patent application identified herein. It will be considered in its order and you will be notified as to the examination thereof. Be sure to give the U.S. SERIAL NUMBER, DATE OF FILING, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this transmittal.

Applicant(s) FAIZULLA G. KATHAWALA, MOUNTAIN LAKES, NJ.

CONTINUING DATA AS CLAIMED BY APPLICANT-
THIS APPLN IS A CIP OF. 07/047,358 05/11/88
WHICH IS A CIP OF 06/722,829 04/12/85 ABAN

FOREIGN FILING LICENSE GRANTED 12/29/88
TITLE
PYRIMIDINE DERIVATIVES

PRELIMINARY CLASS: 514

(see reverse)

0222/86

NAME: Joanne M. Giesser

BASE CITY: E. Hanover

CAR NO.: _____ REGION NO. _____

EMPLOYEE NUMBER: 05854

PERIOD COVERED

	MO.	DAY	YEAR
FROM	2	21	88
TO	2	26	88

COMMENTS:

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS MEALS (6)	BUSINESS ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1		Airplane tickets										visited Northrup King (Minneapolis), Rogers Brothers (Boise) and Zaccon (Palo Alto)
2		Newark - Minneapolis - Boise -										
3		San Francisco - Newark	939 00									
4												
5	2/21	Hotel - Minneapolis					114 60			19 99		
6	2/22	Shuttle bus to airport				15 00						
7	2/23							14 12				
8	2/23	Hotel - Boise					122 10			14 25		
9												
10	2/25	Hotel - Palo Alto					115 50					
11		Rental Car				49 67						
12												
13	2/26	Airport parking			2 00							
14												
15												
16												
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20												
21												
22												
23												
		TOTAL EXPENSES	939 00		2 00	64 67	355 20 (354.20)	14 02		34 24		

RECEIVED
Finance Division
APR 4 1988
Travel Expense Section

Exhibit No. 7241
Date 4/4/01
DiAsio Reporting

TOTAL EXPENSES (COLUMNS 1-9): $ 1409 13

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ 939 00

DUE EMPLOYEE → $ 470 13

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) C.U.

OFFICE USE: AP'd CW
Adj ded 1.00 col. 5

EMPLOYEE'S FULL SIGNATURE: Joanne M. Giesser

APPROVED BY:

OFFICE USE: AUDITED BY:

ODOMETER READING: END. _____ BEG. _____

COMPANY FLEET CARS – MILEAGE: PERSONAL → _____ BUSINESS → _____

FOR OFFICE USE

Exhibit 6

Sawai Ex 1005
Page 1896 of 4322

90222/86

NAME: Joanne M. Giesser

BASE CITY: E. Hanover

CAR NO.: _____ REGION NO. _____

EMPLOYEE NUMBER: 05854

PERIOD COVERED

	MO.	DAY	YEAR
FROM	3	1	88
TO	3	1	88

COMMENTS:

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS MEALS (6)	BUSINESS ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	3/1	Airplane tickets	158 00									Washington D.C., attended NASA patent committee meeting
2												
3		Subway tickets				3 60						
4												
5		Lunch + Dinner						19 50				
6												
7		Airport parking			4 00							
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22												
23												
		TOTAL EXPENSES	158 00		4 00	3 60		19 50				

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Finance Division
MAR 4 1988
Travel Expense Section

TOTAL EXPENSES (COLUMNS 1-9): $ 195 10

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ 158 00

DUE EMPLOYEE → $ 37 10

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) C.U.

OFFICE USE

EMPLOYEE'S FULL SIGNATURE: Joanne M. Giesser

APPROVED BY:

OFFICE USE — AUDITED BY: MM

ODOMETER READING — END. _____ BEG. _____

COMPANY FLEET CARS – MILEAGE — PERSONAL → _____ BUSINESS → _____

FOR OFFICE USE

90222/86

NAME: Jeanne M. Gieseker

BASE CITY: E. Hanover

CAR NO.: — REGION NO.

EMPLOYEE NUMBER: 05554

PERIOD COVERED

	MO	DAY	YEAR
FROM	3	15	88
TO	4	15	88

COMMENTS:

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL ~~& ENTERTAINMENT~~ EXPENSE REPORT

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS: MEALS (6)	BUSINESS: ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	3/15	Plane tickets	~~165.75~~									Boston - visit
2		Taxi	172.00			10.00						Repligen - Sandoz Res. Corp
3	3/16	Hotel					146.09	17.85		7.35		
4												
5												
6	3/28	Plane tickets EMP	690.00									Palo Alto, CA. visit
7		Rental car				~~177.99~~						Sandoz Crop Protection
8		Hotel (3 nights)					364.00	16.59		23.99		
9								10.03				
10								14.74				
11	3/31	Airport parking			2.00							
12												
13												
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	~~860.75~~		2.00	132.99	644.08	59.21		31.34		TOTAL EXPENSES (COLUMNS 1-9)
												$ ~~1743.62~~ 1738.62
												$ ~~869.00~~ 864.00
												$ ~~874.62~~ 874.62

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) C.U.

OFFICE USE 869.00

TOTAL PAID BY CO. AIR & RAIL (Col. 1) →

DUE EMPLOYEE →

EMPLOYEE'S FULL SIGNATURE: Jeanne M. Gieseker

APPROVED BY:

OFFICE USE AUDITED BY:

ODOMETER READING: END. / BEG.

COMPANY FLEET CARS – MILEAGE: PERSONAL → / BUSINESS →

APR 2-0-1988

FOR OFFICE USE: 1738.62 ~~869.00~~

426

90222/86

NAME: Joanne M. Giesser

BASE CITY: E. Hanover

CAR NO.: _____ REGION NO. _____

EMPLOYEE NUMBER: 05854

PERIOD COVERED

	MO.	DAY	YEAR
FROM	4	20	88
TO	4	23	88

COMMENTS:

TEAMSPIRIT

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS: MEALS (6)	BUSINESS: ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	4/20	Plane tickets	325 60									Des Plaines Ill
2	4/23											Visit with Seed
3												Committee &
4							88 80					crop protection
5	4/20-	Hotel (3 nights)					~~177 60~~			22 11		
6	4/23						88 80					
7												
8		Taxi (Newark - Morristown)				41 60	✓					
9												
10		Parking			10							
11												
12												
13												
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	325 00		10 00	41 60	177 60			22 11		

TOTAL EXPENSES (COLUMNS 1-9): $ 575 71

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) _____ C.U. _____

OFFICE USE

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ 325 00

DUE EMPLOYEE → $ 250 71

EMPLOYEE'S FULL SIGNATURE: Joanne M. Giesser

APPROVED BY: _____

OFFICE USE	ODOMETER READING	COMPANY FLEET CARS – MILEAGE
AUDITED BY:	END.	PERSONAL →
	BEG.	BUSINESS →

FOR OFFICE USE

MAY 13 1988

427

Sawai Ex 1005
Page 1899 of 4322

90222/86

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

NAME: Joanne M. Giesser

BASE CITY: E. Hanover

CAR NO.: _____ REGION NO. _____

EMPLOYEE NUMBER: 05854

PERIOD COVERED

	MO.	DAY	YEAR
FROM	5	2	88
TO	6	27	88

COMMENTS:

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS MEALS (6)	BUSINESS ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	5/3/88	Plane Tickets	178 00									Wash, DC
2		Taxi			3 00	3 25						IBA meeting
3												
4	6/15	Plane Tickets	690 00									Palo Alto - Visit
5		Hotel					245 00	25 05		32 67*		* Phone Sandoz Crop Protec.
6	6/16							18 75				
7		Airport parking			5 00							
8		Rental Car				95 27						
9												
10	6/24	Plane Tickets	178 00		3 00							Wash, DC
11		Metro Ticket				1 00						IBA Meeting
12												
13												
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	1,046 00		11 00	99 52	245 00	43 30		32 67		

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) _____ C.U. _____

OFFICE USE

TOTAL EXPENSES (COLUMNS 1-9): $ 1,474 49

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ 1,046 00

DUE EMPLOYEE → $ 428 49

EMPLOYEE'S FULL SIGNATURE: Joanne M. Giesser

OFFICE USE — AUDITED BY: _____

ODOMETER READING: END. _____ BEG. _____

COMPANY FLEET CARS – MILEAGE: PERSONAL → _____ BUSINESS → _____

FOR OFFICE USE

428

90222/86

NAME: Lexinne M. Giesser

BASE CITY:

CAR NO.: REGION NO.

EMPLOYEE NUMBER: 05554

PERIOD COVERED

FROM: MO. 07 DAY 12 YEAR 88

TO: 07 14 88

COMMENTS:

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS: MEALS (6)	BUSINESS: ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	7/12	Airline tickets	253 00									Des Plaines, Ill.
2		Cab (E. Hanover- Newark)				38						Sandoz Crop Protection
3		Cab to hotel				11 00						Patent Committee Meeting
4		Hotel					75 60	11 72		5 60		
5								2 50				(no receipt)
6		Cab (Newark- Morristown)				35 00						
7												
8												
9												
10												
11												
12												
13												
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	253 00			84 00	75 60	14 22		5 60		TOTAL EXPENSES (COLUMNS 1-9) $ 432 42

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JUL 25 1988
Travel Expense Section

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) C.U.

OFFICE USE

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ 253

DUE EMPLOYEE → $ 179 42

EMPLOYEE'S FULL SIGNATURE: Lexinne M. Giesser

APPROVED BY:

OFFICE USE AUDITED BY:

ODOMETER READING: END. BEG.

COMPANY FLEET CARS – MILEAGE: PERSONAL → BUSINESS →

FOR OFFICE US

JUL 22 1988

90222/BG

NAME: Jeanne M. Giesser

BASE CITY: E. Hanover

CAR NO.: _____ REGION NO. _____

EMPLOYEE NUMBER: 05854

PERIOD COVERED

	MO.	DAY	YEAR
FROM	08	30	88
TO	09	20	88

TEAMSPIRIT

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

COMMENTS: Swiss franc exchange rate - 1 Fr = $0.66.

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS MEALS (6)	BUSINESS ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	8/29	Plane tickets	690 00						/		/	Palo Alto - Patent
2	8/29-9/1	hotel room					115 50	12 34		23 15		Policy meeting w/ Dechert Price & Rhoads
3							115 50					
4		Airport parking			15 00		115 50					crop Protection
5							115 50				/	
6												
7	9/6	Passport								67 00		Basle - Patent policy (seeds) meeting (Authorization attached)
8		Passport photo (no receipt)								5 00		
9	9/10	Plane tickets	207 00						/			
10		Limo (Morristown - JFK)				91 20						
11	9/11-14	Hotel					59 40	6 60				
12		Limo (JFK - Morristown shared)				54 50	59 40					
13							59 40					
14							59 40					
15							59 40					
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	2789 00		15 00	145 70	584 10	18 94		95 15		

RECEIVED
Finance Division
SEP 20 1988
Travel Expense

TOTAL EXPENSES (COLUMNS 1-9) $ [illegible]

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ [illegible]

DUE EMPLOYEE → $ [illegible]

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) _____ C.U. _____

OFFICE USE

EMPLOYEE'S FULL SIGNATURE: Jeanne M. Giesser

OFFICE USE: AUDITED BY: VH

ODOMETER READING: END. _____ BEG. _____

COMPANY FLEET CARS – MILEAGE: PERSONAL → _____ BUSINESS → _____

SEP 23 1988

FOR OFFICE USE: 3647.3 / 7789 / 43

Sawai Ex 1005
Page 1902 of 4322

90222/86

NAME: Joanne M. Giesser

BASE CITY: E. Hanover

CAR NO.: _____ REGION NO. _____

EMPLOYEE NUMBER: 05854

PERIOD COVERED

	MO.	DAY	YEAR
FROM	9	20	88
TO	10	20	88

COMMENTS:

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS MEALS (6)	BUSINESS ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	10/9	Plane tickets	690 00									Palo Alto - Sandoz
2	10/7	Car rental				56 50						Crop Protection Patent
3	10/9-11	Hotel					121 00					Committee Meeting
4		Phone								21 90		
5		Food						6 72				
6	10/11	Taxi (Newark - Morristown)				35 00						
7												
8												
9	10/16	Plane Tickets	549 00									Madison, WI - visit
10	10/16-17	Hotel					70 56					Agrigenetics, return
11		Phone								4 77		via Wash. D.C.
12		Food					70 56	27 07				
13		Parking			18 00							
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	1239 00		18 00	91 50	383 12	33 79		26 57		

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Finance Division
OCT 21 1988
Travel Expense Section

TOTAL EXPENSES (COLUMNS 1-9) $ 1792 28

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ 1239 ✓ 00

DUE EMPLOYEE → $ 553 28

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) C.U.

OFFICE USE

EMPLOYEE'S FULL SIGNATURE: Joanne M. Giesser

APPROVED BY: _____

OFFICE USE — AUDITED BY:

ODOMETER READING — END. _____ BEG. _____

COMPANY FLEET CARS – MILEAGE — PERSONAL → _____ BUSINESS → _____

FOR OFFICE USE

EH 43

NAME: Joanne M. Giesser

BASE CITY: E. Hanover

CAR NO.: _____ REGION NO. _____

05854

PERIOD COVERED

	MO.	DAY	YEAR
FROM	10	20	88
TO	11	20	88

COMMENTS:

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS: MEALS (6)	BUSINESS: ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	10/27	Plane tickets	218 00									Boulder, CO - inspect patent files of Agrigenetics
2	10/27	Morristown - Newark				45 54						
3	10/27	Hotel					49 19					
4		Phone								2 11		
5	10/28	Rental car				51 07						
6	10/28	Newark - Morristown				57 54						
7												
8												
9												
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11												
12												
13												
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	218 00	+	+	154 15	49 19	+	+	2 11		

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Finance Division
NOV 02 1988
Travel Expense Section

TOTAL EXPENSES (COLUMNS 1-9) $ 423 45

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) _____ C.U. _____

OFFICE USE

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ 218 00

DUE EMPLOYEE → $ 205 45

EMPLOYEE'S FULL SIGNATURE: Joanne M. Giesser

APPROVED BY: FULL SIGNATURE _____

OFFICE USE — AUDITED BY: ✓

ODOMETER READING: END. _____ BEG. _____

COMPANY FLEET CARS – MILEAGE: PERSONAL → _____ BUSINESS → _____

FOR OFFICE USE

NOV 14 1988

90222/86

NAME: Joanne M. Giesser

BASE CITY: E. Hanover

CAR NO.: _____ REGION NO. _____

EMPLOYEE NUMBER 058574

PERIOD COVERED

	MO.	DAY	YEAR
FROM	12	1	83
TO	12	31	83

COMMENTS:

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS: MEALS (6)	BUSINESS: ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	12/02	Airline tickets	595 00									Chicago - delivered
2	12/03											patent lecture to
3	12/6	Hotel					157 36	7 44				Northrop King group
4	12/5									24 80		phone charges
5	12/6	cab to hotel				12 50						
6	12/8	van service to airport				9 75						no receipt available
7								4 80				
8	12/5	airport parking			15 00							
9												
10												
11												
12												
13												
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	595 00		15 00	22 25	157 36	12 24		24 80		TOTAL EXPENSES (COLUMNS 1-9) $ 826 65

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) _____ C.U. _____

OFFICE USE

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ 595 00

DUE EMPLOYEE → $ 231 65

EMPLOYEE'S FULL SIGNATURE: Joanne M. Giesser

APPROVED BY: _____

OFFICE USE — AUDITED BY: _____

ODOMETER READING — END. _____ BEG. _____

COMPANY FLEET CARS – MILEAGE — PERSONAL → _____ BUSINESS → _____

FOR OFFICE USE

DEC 20

43

90222/86

NAME: Joanne M. Gleason

BASE CITY: E. Hanover

CAR NO.: _____ REGION NO. _____

EMPLOYEE NUMBER 05854

PERIOD COVERED

	MO.	DAY	YEAR
FROM	1	1	89
TO	1	20	89

COMMENTS:

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS MEALS (6)	BUSINESS ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	1/4	Plane tickets	1078 00									Minneapolis (Northrup King Patent Committee)
2												Palo Alto (Zoecon Patent Committee)
3												
4												
5												
6	1/8	Taxi (Airport - Hotel)				30 00						
7	1/9	Taxi (Hotel - Northrup King)				6 00						
8	1/9	Hotel					60 42			8 52		(phone)
9	1/11	Rental Car				92 69						
10	1/11	Hotel					~~242 00~~ 242 00	7 06		24 27		(phone)
11	1/12	Parking at Airport			2 00	✓	121 00					no receipt
12						✓	121 00					
13												
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	1078 00		2 00	128 69	302 42	7 06		32 79		TOTAL EXPENSES (COLUMNS 1-9) $ 1550

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) C.U.

OFFICE USE

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ 1078

DUE EMPLOYEE → $ 472

EMPLOYEE'S FULL SIGNATURE: Joanne M. Gleason

OFFICE USE — AUDITED BY:

ODOMETER READING — END. _____ BEG. _____

COMPANY FLEET CARS – MILEAGE — PERSONAL → _____ BUSINESS → _____

FOR OFFICE USE

JAN 24 1989

434

90222/86

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

NAME: Joanne M. Giesser

BASE CITY: E. Hanover

CAR NO.: _____ REGION NO. _____

EMPLOYEE NUMBER: 05854

PERIOD COVERED

	MO.	DAY	YEAR
FROM	2	1	89
TO	2	28	89

COMMENTS:

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS MEALS (6)	BUSINESS ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	2/21	Plane tickets	844 00									Boise, Id. Patent
2												Lecture to Rogers Bros
3	2/28-	Hotel					84 40	35 87		6 39		phone
4	3/2						44 40	6 67				
5		Airport parking			2 00							No receipt available
6												
7												
8												
9												
10												
11												
12												
13												
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	844 00		2 00		88 80	42 49		6 39		

Finance Division

MAR 01 1989

Travel Expense

TOTAL EXPENSES (COLUMNS 1-9): $ 983 1,123

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) _____ C.U. _____

OFFICE USE

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ 844

DUE EMPLOYEE → $ 139

485 ✓

EMPLOYEE'S FULL SIGNATURE: Joanne M. Giesser

APPROVED BY: _____

OFFICE USE — AUDITED BY: _____

ODOMETER READING — END. _____ BEG. _____

COMPANY FLEET CARS – MILEAGE — PERSONAL → _____ BUSINESS → _____

FOR OFFICE USE: MAR 20 1989 BS

00222/86

NAME: Joanne M. Giesser

BASE CITY: E. Hanover

CAR NO.: — REGION NO.

EMPLOYEE NUMBER 05854

PERIOD COVERED

FROM MO. 03 DAY 2 YEAR 89

TO 03 31 89

COMMENTS:

Sandoz Pharmaceuticals Corporation

SANDOZ PHARMACEUTICALS

TRAVEL & ENTERTAINMENT EXPENSE REPORT

LINE NO.	DATE	NATURE OF EXPENSE	TRANSPORTATION EXPENSES: AIR & RAIL (1)	GAS & OIL (2)	PARKING & TOLLS (3)	SUNDRY (4)	OTHER EXPENSES: LODGING (5)	BUSINESS MEALS (6)	BUSINESS ENTERTAIN. (7)	SUNDRY (8)	AUTO REPAIRS ON FLEET CARS (9)	CITY VISITED & PURPOSE OF TRIP (10)
1	3/20	Plane tickets	422 00									Stanton, MN Northrup King Research Mgmt Comm. Meeting
2												
3	3/20	Car rental				94 45						
4												
5	3/20	Hotel					61 04	2 70		7 90		Phone
6								2 50				no receipt
7												
8	3/31	Parking			15 45							NYC - Judges Dinner
9		Tolls			4 00							
10												
11												
12												
13												
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
		TOTAL EXPENSES	422 00		19 45	94 45	61 04	5 20		7 90		TOTAL EXPENSES (COLUMNS 1-9) $ 610 04

TRANSFER OF EXPENSES APPROVED BY MANAGER (FULL SIGNATURE) C.U.

OFFICE USE

TOTAL PAID BY CO. AIR & RAIL (Col. 1) → $ 422 00

DUE EMPLOYEE → $ 188 04

EMPLOYEE'S FULL SIGNATURE: Joanne M. Giesser

APPROVED BY:

OFFICE USE — AUDITED BY:

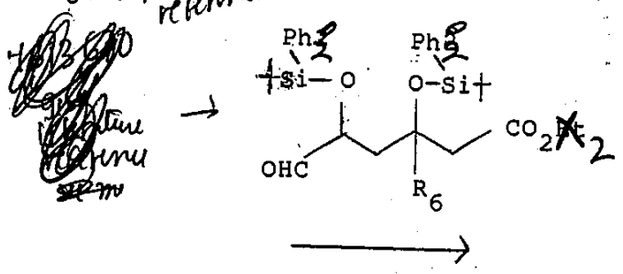
ODOMETER READING — END. / BEG.

COMPANY FLEET CARS – MILEAGE — PERSONAL → / BUSINESS →

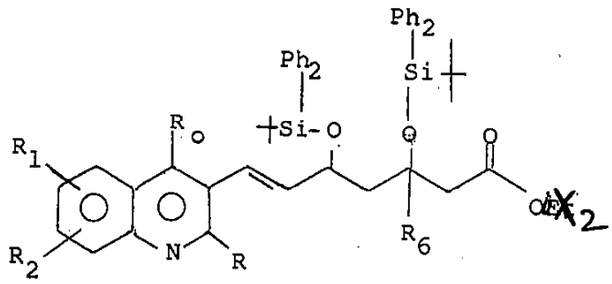
FOR OFFICE USE

RECEIVED APR 13 1989

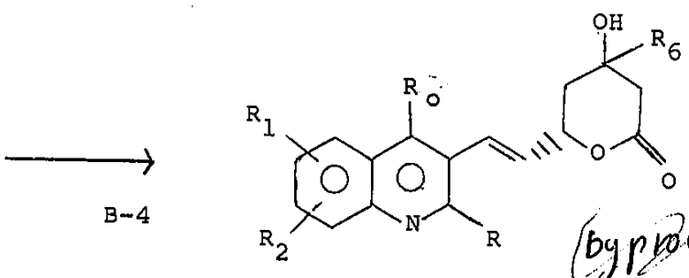
our patent reference +, for basic mode, B00-7064 procedure



B-3



(XVI)

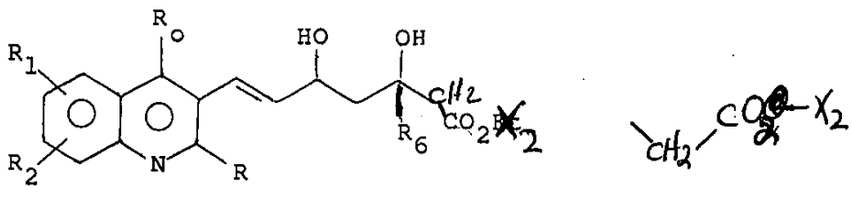


B-4

and

(by product formed only sometimes)

(II)



(I)

Lovastatine - Will give you an insert later on this

Need 1) Statement that when any compound of Formula A contains an hydroxy group as R_1-R_5, said hydroxy group is protected by a diphenyl/t-butylsilyl group in the compounds of formula XII - XI and XIV - XVI which group is cleaved at the end of the synthesis by Reaction B-4.

2) Hydrogenation reaction to get compounds wherein R is $-CH_2CH_2-$ over

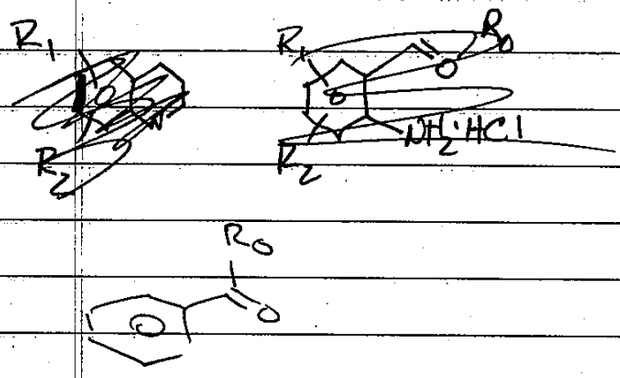
(3) Process for obtaining compounds wherein X is (Z)-CH=CH- (CIS). Add phosphonium Wittig alternative to Reaction B-2

(4) Process for Q = $-\overset{\overset{O}{\|}}{C}-$ compound

(5) Process for lactonization, hydrolysis of lactone interconversion of esters, salts, free acid, etc.

7064

Add before pg 4



A_1 ~~step~~ - condensation

X_1 = any alkyl group

X_2 = R_5 of indene

X_3 = any alkyl

$X'_{\#}$ = any ethyl or methyl

R_6 as defined

List of all var before table p11

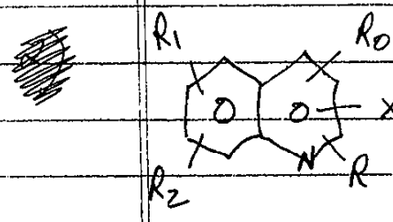
incorp Rx scheme into example

2-composition
- method

Insert

but are not limited to the following

1) 1) ~~Those~~ Compounds which are included in the formula of the Proposed Count 1 including ~~such as~~ (referring to the formula of Proposed Count 1)



i) Compound 63-366, where $R_1 = H$; $R_2 = H$; R_D = 3,5-dimethylphenyl; R = isopropyl; $X = -CH=CH-$; ~~and~~ $Z = (a)$; $Q = -\underset{OH}{C}-$; and R_8 = ethyl

ii) Compound 63-548, where $R_1 = H$; $R_2 = H$; R_D = 3,5-dimethylphenyl; $R = CH_3$, $X = -CH=CH-$; $Z = (a)$; $Q = -\underset{OH}{C}-$; and R_7 = ethyl.

iii) Compound 63-549, where $R_1 = H$; $R_2 = H$; R_D = 3,5-dimethylphenyl; $R = CH_3$, $X = -CH=CH-$; and $Z = (b)$.

iv) Compound 64-933, where $R_1 = H$; [redacted]; R_D = phenyl; R = isopropyl; $X = -CH=CH-$; $Z = (a)$; $Q = -\underset{OH}{C}-$ and R_8 = ethyl

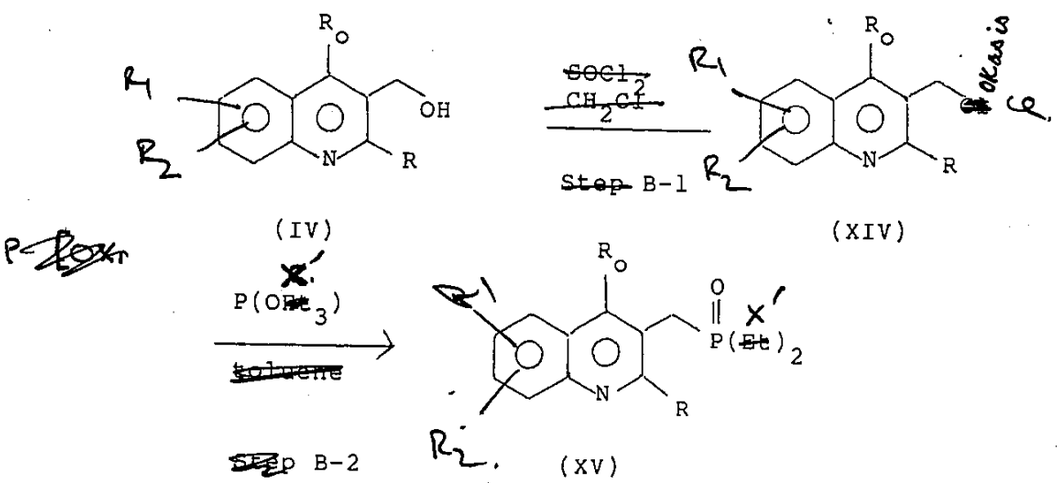
v) Compound 64-934, where $R_1 = H$; $R_2 = H$; R_D = phenyl; R = isopropyl; $X = -CH=CH$; $Z = (a)$; $Q = -\underset{OH}{C}-$; $R_7 = M$; $M = Na^+$

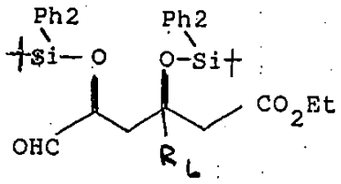
vi) Compound 64-935, where $R_1 = H$; $R_2 = H$; R_D = 4-Fluorophenyl, R = isopropyl; $Z = (a)$; $Q = -\underset{OH}{C}-$; R_8 = ethyl

Starting material III is known and can be obtained by methods described by Morrison and Mulholland, 1958, J. Chem. Soc. p. 2702, which is hereby incorporated by reference. Next, V is reduced with lithium aluminum hydride, (LAH) to give VI. This reaction has also been described by Fehnel, 1968. J. Heterocyclic Chem 4:565, which is also hereby incorporated by reference. In Step A-3, VI is oxidized to VII. Step A-4 is a Wittig reaction producing VIII. Compound VIII is then reduced using diisobutylaluminum hydride (DIBAL) to IX. In Step A-6, IX is oxidized to X. The aldehyde X is then reacted with ethyl acetoacetate in Step A-7 to give XI. Compound XI is reduced to give XII. Next, in Step A-9, XII is hydrolyzed to the salt form XIII.

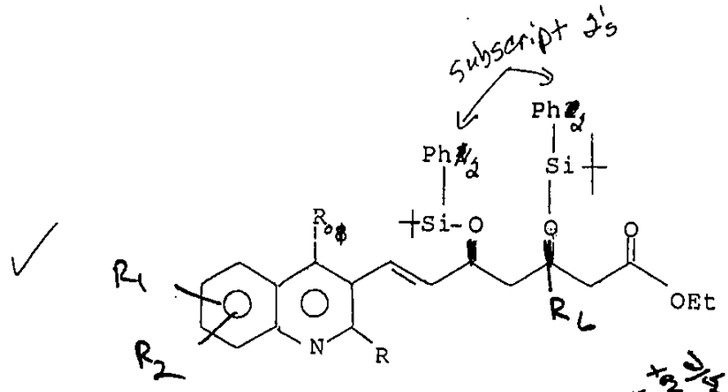
Compounds of both Formula I and II may be made according to Reaction Scheme B. Starting material for Reaction Scheme B is Compound VI from Reaction Scheme A.

REACTION SCHEME B





B-3



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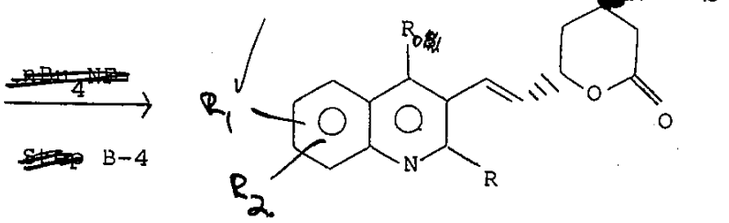
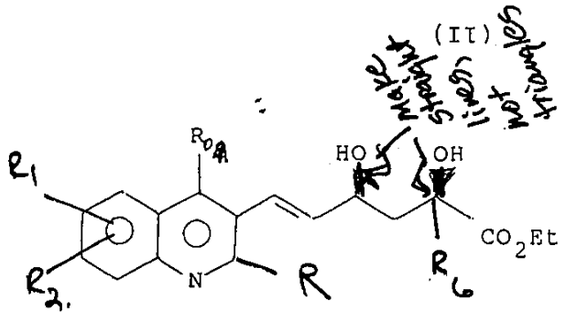


B-4

and



(I)

3A

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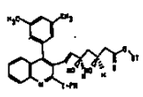
25496 D OR E OR C
1079-111-19
KATH 299-84
CSI



2

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SAH-063548
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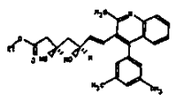
1127-011-34
KATH 299-84
CSI, CSTC, CSTV



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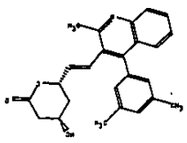
KATH 299-84
CSI



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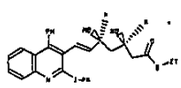
WATT 299-84
CSI CSIC CSIV



3B

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WATT 299-84
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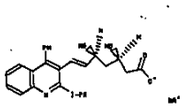

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WATT 299-84
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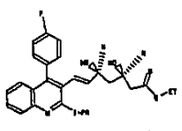

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WATT 299-84
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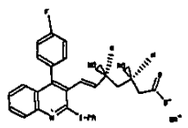

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KATH 299-84
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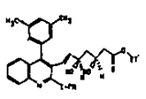

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WATT 299-84
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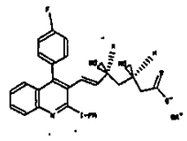

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26080 C OR D OR E
1127-011-34
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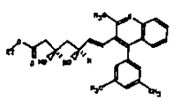
CSI, CSTC, CSIV



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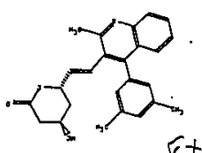
KATH 299-84
CSI



Ex 2

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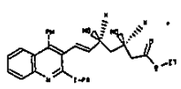
1206-176-43
WATT 299-84
CSI CSIC CSIV



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1206-179-30
WATT 299-84
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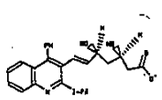

Ex 3B

09-21-87
MW 451.543
LD
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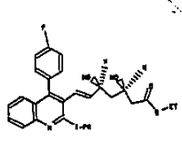
30447 D OR E OR C
1206-190-41
WATT 299-84
CSI CSIC CSIV



Ex 3C

DISCLOSURE
299-84

Bask mail 5/4/89

LIST FOR PUBLICATION CLEARANCES

1) Running number of publication: 4751 (Will be attributed by ST)

2) Names of all the authors:

S. WATTANASIN/F. G. KATHAWALA/R. PATEL/T. SCALLEN/
R. G. ENGSTROM/D. B. WEINSTEIN

3) Full title of the publication:

QUINOLINES AS HMG-CoA REDUCTASE INHIBITORS

4) Date of the receipt of the publication:

APRIL 4, 1989

5) Type of publication (lecture/article, poster/abstract or full publication) and proposed date of publication (if known):

POSTER - 5TH SCI-RSC MEDICINAL CHEMISTRY SYMPOSIUM CHURCHILL COLLEGE, CAMBRIDGE, SEPTEMBER 10-13, 1989

6) Bereiche: HANOVER,

7) SB Patent Department: MRS. J. M. GIESSER Joanne M. Giesser

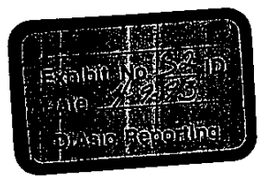
8) Subject matter ("Stichwort"), e.g. "Zaditen", "20-511", "Allylamines", "HPLC-apparatus" etc. and/or Case-No. if possible:
The compounds are covered in Case 600-7101
63-366 63-549 64-934 64-936
63-548 64-933 64-935

9) Date of return of the publication to source:

10) PA comments to source:

☐ No Objection

☐ Objection



Scientific Publication Release Request

SANDOZ

Name of Requestor: Dr. S. Wattanasin

Date: 3/30/89

I. STATEMENT OF REQUEST

I request release of the attached ☐ *manuscript,* ☐ *abstract,* ☐ *lecture* ☐ *other* Poster

By (names of all authors)
S. Wattanasin, F. G. Kathawala, R. Patel, T. Scallen
R. G. Engstrom, D. B. Weinstein

Entitled
Quinolines as HMG-CoA Reductase Inhibitors

For Disclosure in (periodical, symposium, meeting, correspondence, etc.) on (date, if known).
5th SCI-RSC Medicinal Chemistry Symposium
Churchill College, Cambridge September 10-13, 1989

Listed below in numerical order are SANDOZ compounds:

63-366	64-933	64-936
63-548	64-934	
63-549	64-935	

PATENT AND TRADEMARK DEPT.
APR 4 - 1989
JMG

II. CIRCULATION ORDER, RECOMMENDATIONS, AND ACTION

CO-AUTHOR APPROVAL (Initials)

				Date
1. Supervisor Dr. F. G. Kathawala	FGK	☒ Approve	☐ Withhold	4/3/89
2. Department Director Dr. F. G. Kathawala	FGK	☒ Approve	☐ Withhold	4/3/89
3. Patent Department Joanne M. Giesser		☒ Approve	☐ Withhold	4/19/89
4. V.P. Clinical or Preclinical Research		☐ Approve	☐ Withhold	Date

COMMENTS:

The material in this abstract is covered under Case No. 600-7101-U.S., Quinoline Analogs of Mevalonolactone and Derivatives Thereof, which was filed with the Patent Office on March 3, 1989.
SIMILAR WORK HAS APPEARED AFTER THE START OF OUR WORK & COMPLETION IN A PATENT FILED BY WARNER LAMBERT FGK.

5. President *SANDOZ RESEARCH INSTITUTE*	☐ Released	☐ Withheld	Date

86704/84

QUINOLINES AS HMG-CoA REDUCTASE INHIBITORS.

S. Wattanasin[1], F.G. Kathawala[1], R. Patel[1], T. Scallen[2], R.G. Engstrom[1], and D.B. Weinstein[1]

[1]Sandoz Research Institute, E. Hanover, New Jersey 07936

[2]Department of Biochemistry, School of Medicine, University of New Mexico, Albuquerque, New Mexico 87131

Inhibition of HMG-CoA reductase, the rate limiting enzyme in cholesterol biosynthesis, has proved to be an effective method of lowering serum low density lipoprotein(LDL-C) levels in both animals and man. Efforts at Sandoz Research Institute in the design and synthesis of new HMG-CoA reductase inhibitors have led to the discoverry of a number of classes of compounds which inhibit the enzyme HMG-CoA reductase. We present here the synthesis of quinolines as potent inhibitors of this enzyme *in vitro* and cholesterol biosynthesis *in vivo*.

April 19, 1989

Dr. S. Wattanasin/
Dr. F. Kathawala

Joanne M. Giesser

Abstract entitled:
"Quinolines as HMG-CoA Reductase Inhibitors"

The above abstract to be presented at the 5th SCI-RSC Medicinal Chemistry Symposium Churchill College, Cambridge, September 10-13 is approved by the Patent Department. However, the full text will still have to be reviewed and cleared by this department before presentation.

Joanne M. Giesser

JMG:lmc
Enc.

SANDOZ

Patent and Trademark Department
59 Route 10
E. Hanover, New Jersey 07936

Telex 240867
Telefax (201) 503-8807

May 4, 1989

SANDOZ LTD.
Patents and Trademarks Division
CH-4002
Basle, Switzerland

Re: Clearance for Abstract Entitled
"QUINOLINES AS HMG-CoA REDUCTASE
INHIBITORS"
Ref: 3700/RA

Dear Sirs:

Enclosed please find the Publication Clearance regarding the above-identified abstract.

We look forward to receiving the corresponding number in due course.

Very truly yours,

Linda C. Rothwell

LCR
Enc. Publication Clearance

Basle Mail 6/15/89

LIST FOR PUBLICATION CLEARANCES

1) Running number of publication: 4878 (Will be attributed by ST)

2) Names of all the authors:

S. WATTANASIN/F.G. KATHAWALA/R. PATEL/T. SCALLEN/
R.G. ENGSTROM/D.B. WEINSTEIN

3) Full title of the publication:

QUINOLINES AS HMG-CoA REDUCTASE INHIBITORS

4) Date of the receipt of the publication:

MAY 23, 1989

5) Type of publication (lecture/article, poster/abstract or full publication) and proposed date of publication (if known):

Poster for 5th SCI-RSC Medicinal Chemistry Symposium
Churchill College, Cambridge
September 10-13, 1989

6) Bereiche: HANOVER

7) SB Patent Department: MRS. GIESSER Joanne M. Giesser

8) Subject matter ("Stichwort"), e.g. "Zaditen", "20-511", "Allylamines", "HPLC-apparatus" etc. and/or Case-No. if possible:
The compounds are covered in Case 600-7101
63-366 64-933 64-936
63-548 64-934
63-549 64-935

9) Date of return of the publication to source:

10) PA comments to source:

☒ No Objection

☐ Objection

Scientific Publication Release Request

SANDOZ

Name of Requestor: Dr. S. Wattanasin

Date: 5/12/89 ~~3/30/89~~

I. STATEMENT OF REQUEST

I request release of the attached ☐ *manuscript,* ☐ *abstract,* ☐ *lecture* ☐ *other* Poster

By (names of all authors)

S. Wattanasin, F. G. Kathawala, R. Patel, T. Scallen

R. G. Engstrom, D. B. Weinstein

Entitled

Quinolines as HMG-CoA Reductase Inhibitors

For Disclosure in (periodical, symposium, meeting, correspondence, etc.) on (date, if known).

5th SCI-RSC Medicinal Chemistry Symposium

Churchill College, Cambridge September 10-13, 1989

Listed below in numerical order are SANDOZ compounds:

63-366	64-933	64-936
63-548	64-934	
63-549	64-935	

PATENT AND TRADEMARK DEPT.
MAY 23 1989
JMG

II. CIRCULATION ORDER, RECOMMENDATIONS, AND ACTION

CO-AUTHOR APPROVAL (Initials)

1. Supervisor Dr. F. G. Kathawala FGKathawala	☒ Approve	☐ Withhold	Date 5/19/89
2. Department Director Dr. F. G. Kathawala FGKathawala	☒ Approve	☐ Withhold	Date 5/19/89
3. Patent Department	☐ Approve	☐ Withhold	Date
4. V.P. Clinical or Preclinical Research	☐ Approve	☐ Withhold	Date

COMMENTS:

The material in this abstract is covered under Case No. 600-7101-U.S., Quinoline Analogs of Mevalonolactone and Derivatives Thereof, which was filed with the Patent Office on March 3, 1989.

The abstract of this poster had been approved.

5. President *SANDOZ RESEARCH INSTITUTE*	☐ Released	☐ Withheld	Date

86704/84

QUINOLINES AS HMG-CoA REDUCTASE INHIBITORS.

S. Wattanasin[1], F.G. Kathawala[1], R. Patel[1], T. Scallen[2], R.G. Engstrom[1], and D.B. Weinstein[1]

[1]Sandoz Research Institute, E. Hanover, New Jersey 07936

[2]Department of Biochemistry, School of Medicine, University of New Mexico, Albuquerque, New Mexico 87131

Inhibition of HMG-CoA reductase, the rate limiting enzyme in cholesterol biosynthesis, has proved to be an effective method of lowering serum low density lipoprotein(LDL-C) levels in both animals and man. Efforts at Sandoz Research Institute in the design and synthesis of new HMG-CoA reductase inhibitors have led to the discovery of a number of classes of compounds which inhibit the enzyme HMG-CoA reductase. We present here the synthesis of quinolines as potent inhibitors of this enzyme *in vitro* and cholesterol biosynthesis *in vivo*.

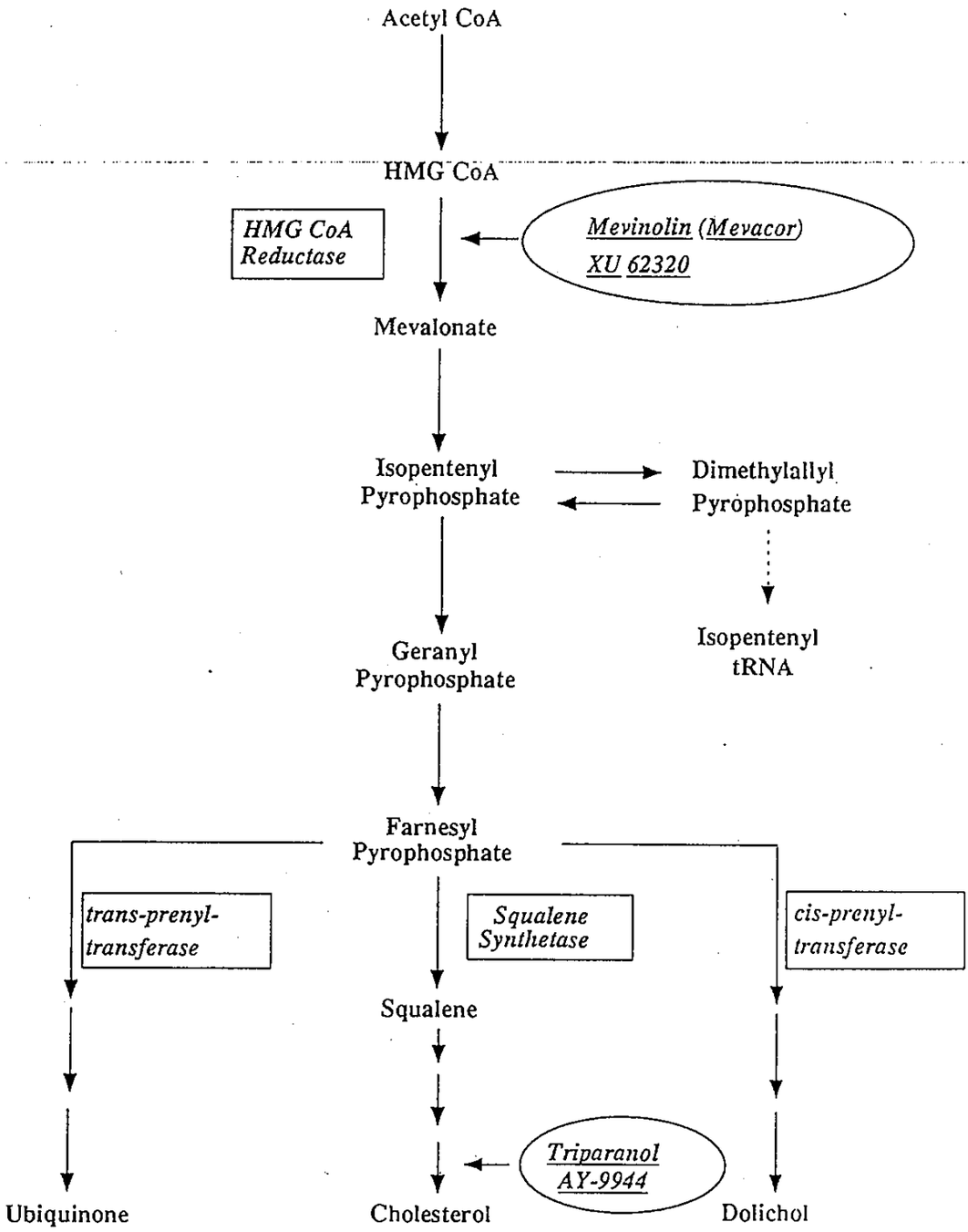
INTRODUCTION

Inhibition of 3-hydroxy-3-methylglutaryl-coenzymeA, the rate-limiting enzyme in cholesterol biosynthesis, has proved to be an effective method of lowering serum low density lipoprotein (LDL-C) levels in both animals and man. Epidemiological evidence implicating elevated LDL-C as a major risk factor for the development of coronary heart disease, have stimulated intensive efforts directed towards the development of agents affecting serum LDL-C levels.

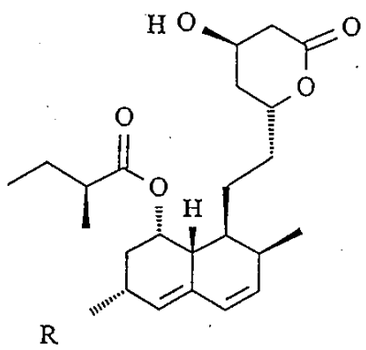
Recent reports have described XU 62-320, an indole analog of compactin and mevinolin, as one of the most potent HMG-CoA reductase inhibitors both in vitro and in vivo studies.

Discovery of XU 62-320 has prompted a search of a variety of new structural prototypes as potential inhibitors of HMG-CoA reductase. Described in this paper are the results of our initial study with a series of quinoline derivatives as HMG-CoA reductase inhibitors.

q-intro

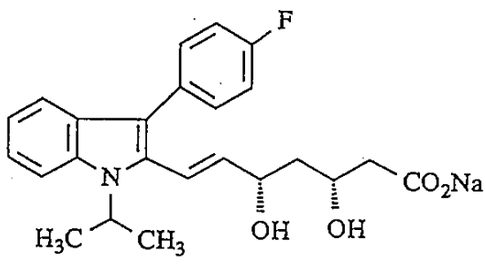

Acetyl CoA
HMG CoA
HMG CoA Reductase
Mevinolin (Mevacor)
XU 62320
Mevalonate
Isopentenyl Pyrophosphate
Dimethylallyl Pyrophosphate
Isopentenyl tRNA
Geranyl Pyrophosphate
Farnesyl Pyrophosphate
trans-prenyl-transferase
Squalene Synthetase
cis-prenyl-transferase
Squalene
Triparanol
AY-9944
Ubiquinone
Cholesterol
Dolichol

HMG-CoA REDUCTASE INHIBITORS



R = H; COMPACTIN

R = Me ; MEVINOLIN (LOVASTATIN)

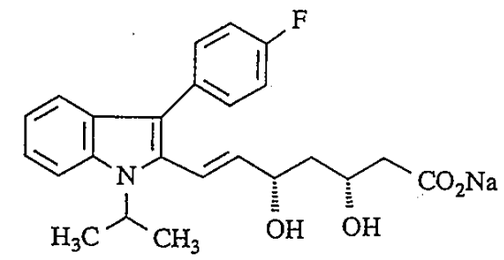


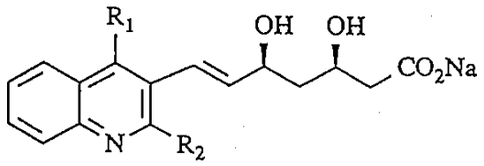
XU 62-320

q2
slide1

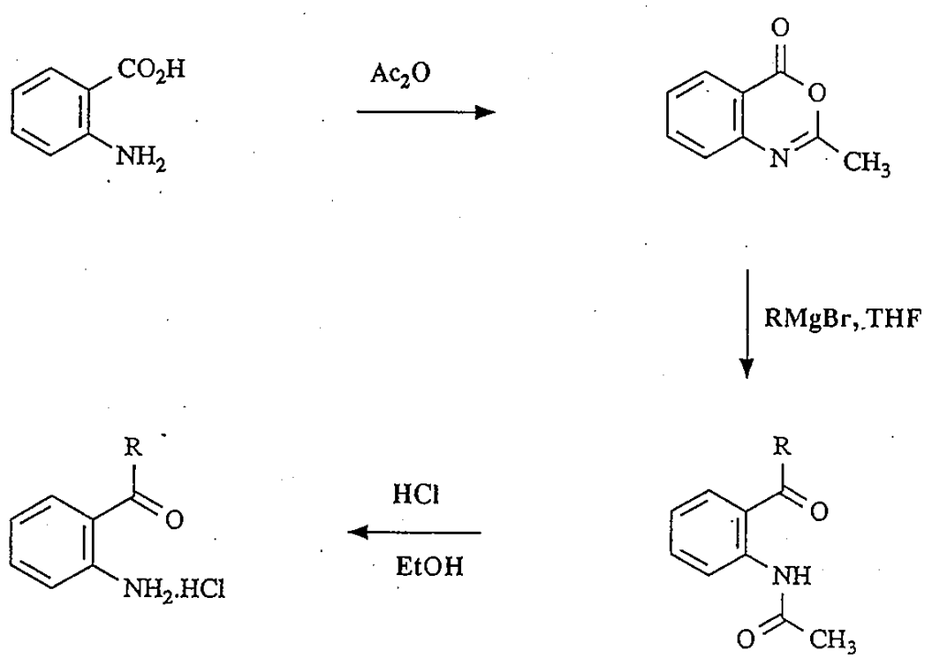
GENERATION OF NEW LEADS

INDOLE XU 62-320



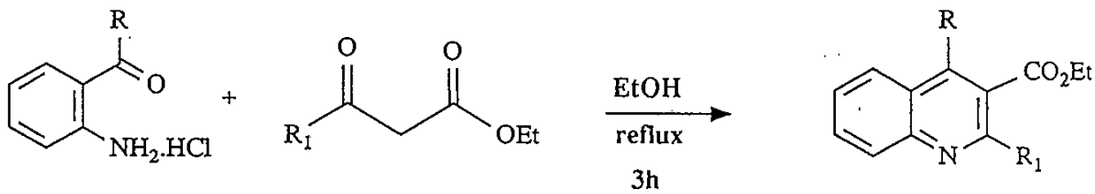


SYNTHESIS OF ortho-AMINO KETONES



R = 3,5-Dimethylphenyl
= isoPropyl
= 4-Fluorophenyl

SYNTHESIS OF 2,3,4-SUBSTITUTED QUINOLINES

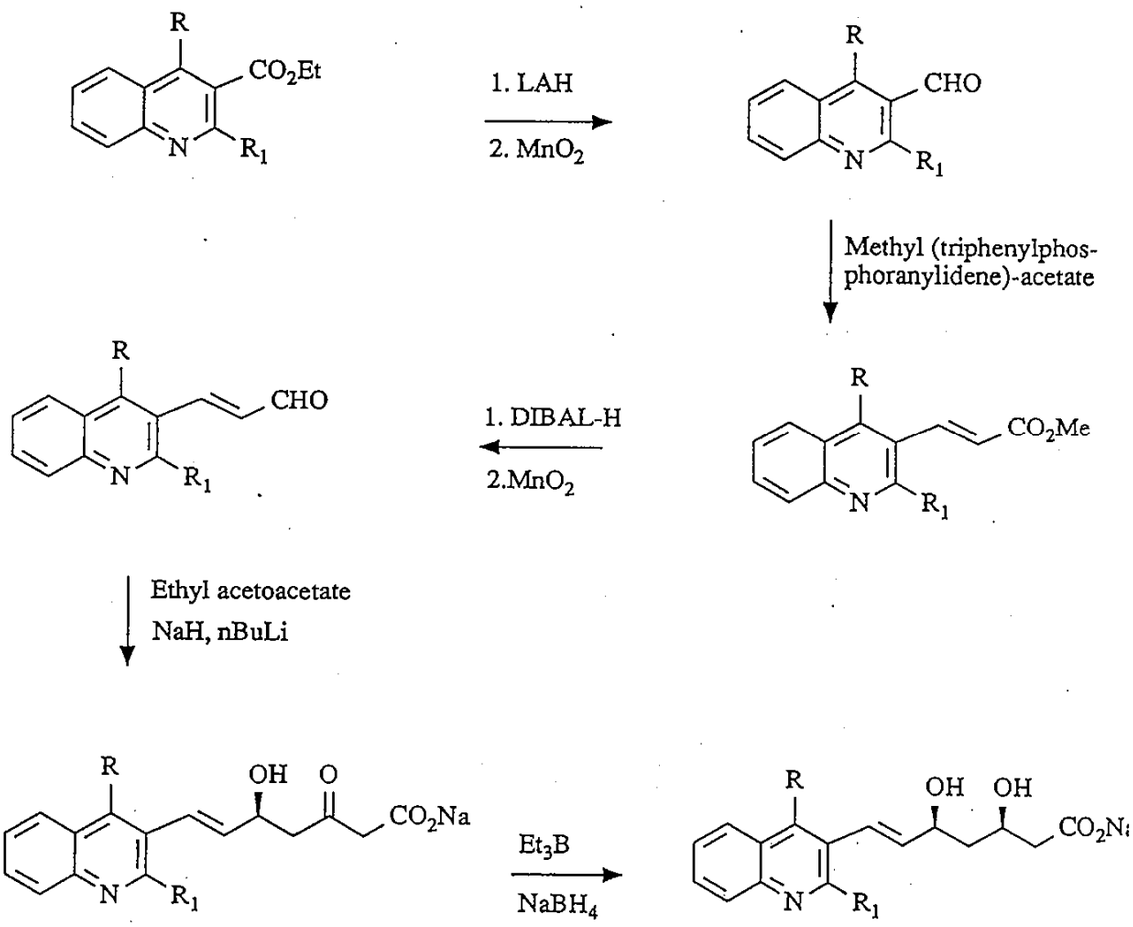


65-85%

R	R_1
i-Propyl	Me
Ph	i-Propyl
3,5-Dimethyl	4-Fluorophenyl
4-Fluorophenyl	

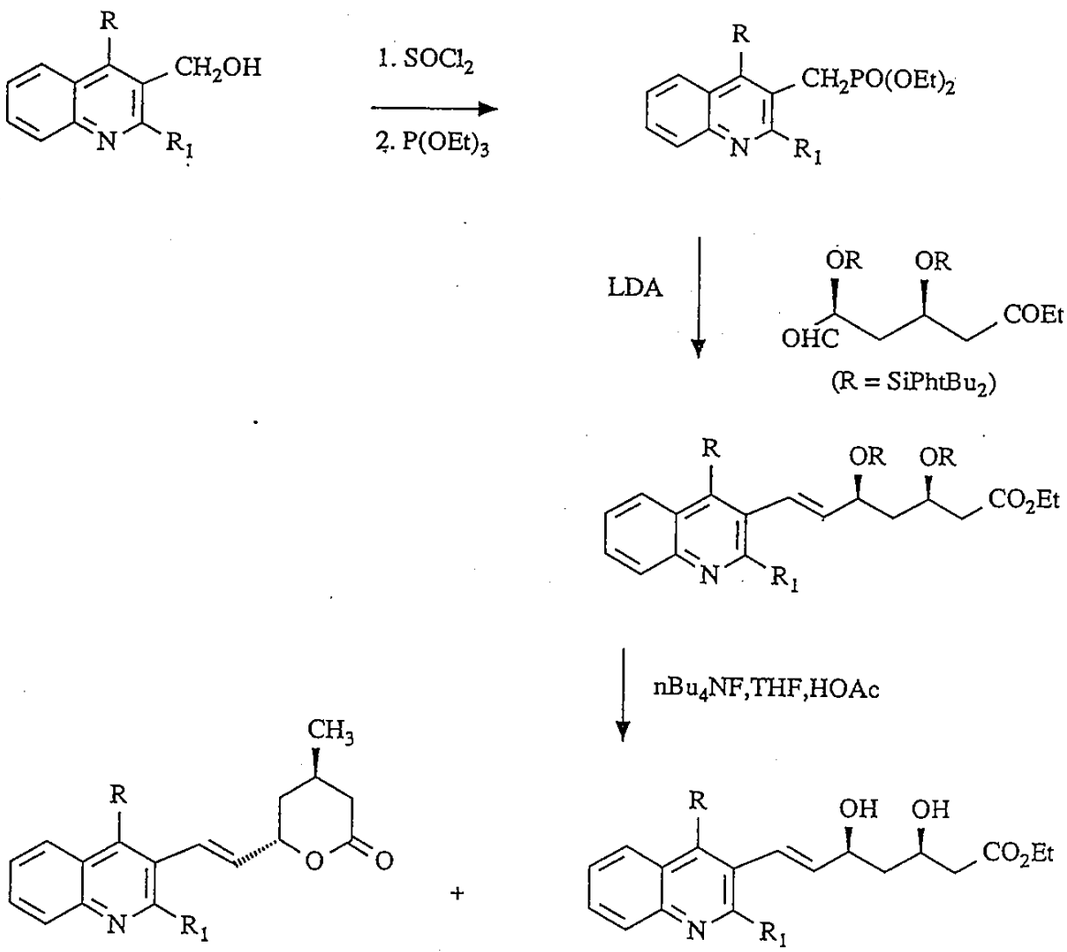
INTRODUCTION OF THE DIHYDROXY SIDECHAIN

A



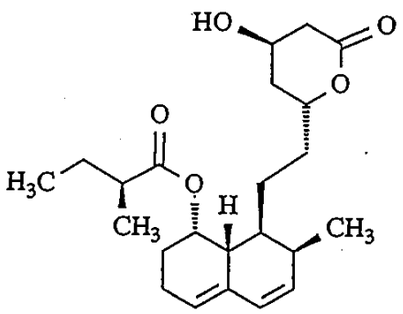
INTRODUCTION OF THE DIHYDROXY SIDECHAIN

B

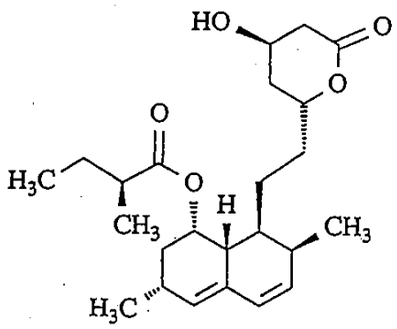


INHIBITORY EFFECT ON HMG-C0A REDUCTASE (Rat Liver Microsome)

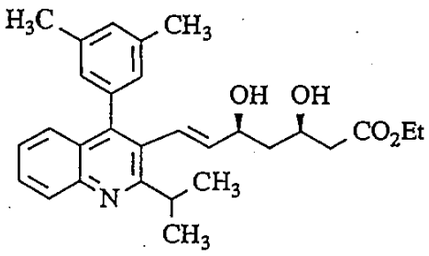
RELATIVE POTENCY*



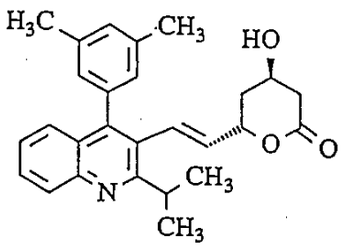
Compactin
1



Mevinoline
7.2



SDZ 63-366
0.64

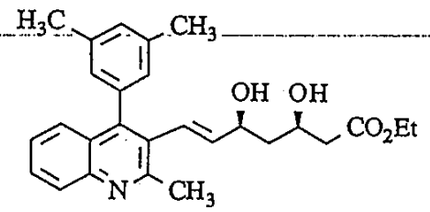


SDZ 63-549
0.14

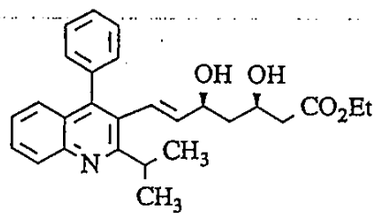
* The relative potency of the test compound was determined by comparing its IC_{50} value** with that of compactin, which was tested simultaneously and arbitrarily assigned a relative potency value of 1

** Method according to : Ackerman et.al. J. Lipid Res., 18 , 408-413 (1977)

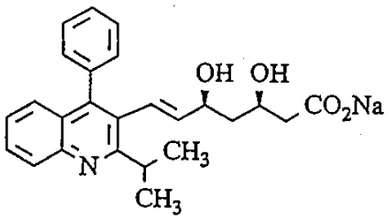
RELATIVE POTENCY*



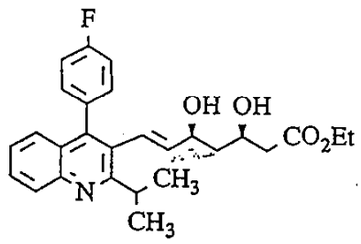
SDZ 63-548
0.27



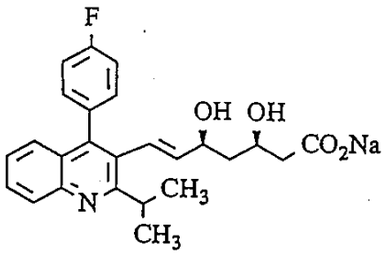
SDZ 64-933
0.43



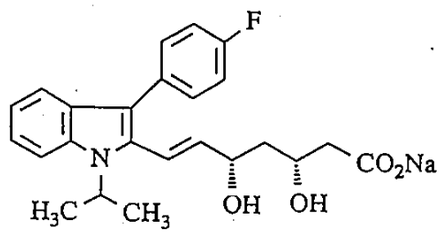
SDZ 64-934
0.39



SDZ 64-935
2.46

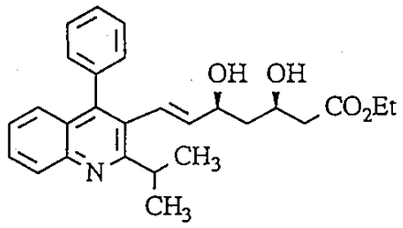


SDZ 64-936
1.9



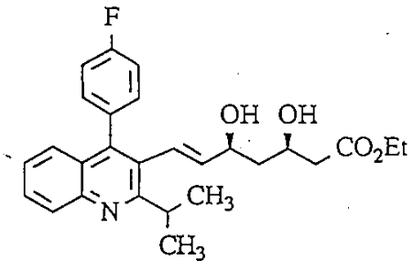
XU 62-620
146

INHIBITORY EFFECT ON CHOLESTEROL SYNTHESIS (RATS) ED_{50} (mg/Kg)



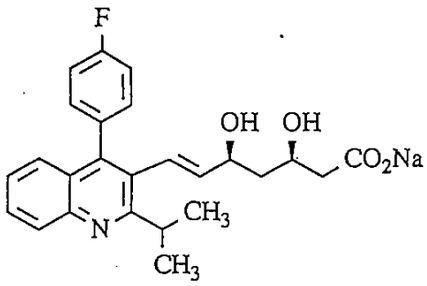
SDZ 64-933

>1.0



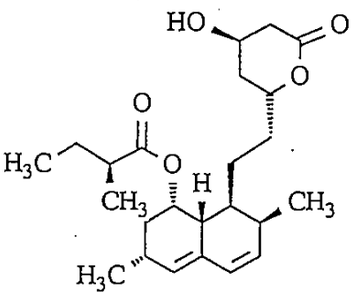
SDZ 64-935

0.49



SDZ 64936

>1.0



Mevinolin

0.38

CONCLUSION

1. QUINOLINE ANALOGS HAVE BEEN SYNTHESIZED AS NOVEL HMG-COA REDUCTASE INHIBITORS, BASED ON THE STRUCTURE AND SAR DATA OF XU 62-320

2. THESE ANALOGS ARE POTENT INHIBITORS OF HMG-COA REDUCTASE IN RAT MICROSOMAL ASSAYS AS WELL AS CHOLESTEROL BIOSYNTHESIS FROM C^{14}-ACETATE IN VIVO.

3. THE MOST ACTIVE COMPOUND (SDZ 64935) IS AS ACTIVE AS MEVINOLIN BUT IS FIVE FOLD LESS ACTIVE THAN XU 62-320 IN IN VIVO ASSAYS.

SANDOZ PATENT AND TRADEMARK DEPARTMENT

To: Dr. S. Wattanasin
Dr. F. Kathawala

From: Joanne M. Giesser

Date: June 13, 1989

Subject: Proposed publication "Quinolines as HMG-CoA Reductase Inhibitors" 5th SCI-RSC Medicinal Chemistry Symposium, Churchill College, Cambridge Sept. 10-13, 1989

The above-identified publication has been reviewed from a patent standpoint and is approved by the Patent and Trademark Department for publication.

Joanne M. Giesser

SANDOZ

Patent and Trademark Department
59 Route 10
E. Hanover, New Jersey 07936

Telex 240867
Telefax (201) 503-8807

June 15, 1989

SANDOZ LTD.
Patents and Trademarks Division
CH-4002
Basle, Switzerland

Re: Clearance for Poster Entitled
"QUINOLINES AS HMG-CoA REDUCTASE INHIBITORS"

Ref: 3700/RA

Dear Sirs:

Enclosed please find the Publication Clearance regarding the above-identified poster.

We look forward to receiving the corresponding number in due course.

Very truly yours,

Linda C. Rothwell

LCR
Enc. Publication Clearance

BASLE

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/047,358	5/5/87	KATHAWALA	600-7025/CIP

PATENT AND
TRADEMARK DEPT.

JAN 6 - 1989

JMG

EXAMINER	
ART UNIT	PAPER NUMBER
121	6

DATE MAILED: 1/3/89

NOTICE OF ABANDONMENT

This application is abandoned in view of:

1. ☒ Applicant's failure to respond to the Office letter, mailed Nov. 11, 1988.
2. ☐ Applicant's letter of express abandonment which is in compliance with 37 C.F.R. 1.138.
3. ☐ Applicant's failure to timely file the response received _____ within the period set in the Office letter.
4. ☐ Applicant's failure to pay the required issue fee within the statutory period of 3 months from the mailing date of _____ of the Notice of Allowance.
   - ☐ The issue fee was received on _____.
   - ☐ The issue fee has not been received in Allowed Files Branch as of _____.

   In accordance with 35 U.S.C. 151, and under the provisions of 37 C.F.R. 1.316(b), applicant(s) may petition the Commissioner to accept the delayed payment of the issue fee if the delay in payment was unavoidable. The petition must be accompanied by the issue fee, unless it has been previously submitted, in the amount specified by 37 C.F.R. 1.17 (l), and a verified showing as to the causes of the delay.

   If applicant(s) never received the Notice of Allowance, a petition for a new Notice of Allowance and withdrawal of the holding of abandonment may be appropriate in view of Delgar Inc. v. Schuyler, 172 U.S.P.Q. 513.
5. ☐ Applicant's failure to timely correct the drawings and/or submit new or substitute formal drawings by _____ as required in the last Office action.
   - ☐ The corrected and/or substitute drawings were received on _____.
6. ☐ The reason(s) below.

MARY C. LEE
SUPERVISORY PRIMARY EXAMINER
ART UNIT 121

PTO-1432 (REV. 5-83)

Serial No. 07/047,358
Date 1/6/89
Basic Reporting

PATENT AND TRADEMARK DEPT.
OCT 21 1988

The impressed Mail Room date stamp acknowledges receipt on the date indicated of

- ☐ Communication
- ☐ Claim of Priority
- ☐ Not. of Appeal
- ☐ Appeal Brief
- ☐ Prel. Amendment
- ☐ Amendment
- XX Ext. of Time in duplicate
- ☐ Req. for Recon.
- XX Postcard: COM Stamp

MAIL ROOM OCT 20 1988 PAT. & TRADEMARK OFF.

for Case No. 600-7025/CIP
Application of FAIZULLA G. KATHAWALA

Serial No. 07/047,358
Filed May 5, 1987

REV:lmc 10/11/88

BASLE

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/047,358	05/05/87	KATHAWALA	~~600-7025/CIP~~ 600-7025/CIP

07/047,358 5/5/87 KATHAWALA

GERALD D. SHARKIN
SANDOZ CORP.
59 ROUTE 10
EAST HANOVER, NJ 07936

PATENT AND TRADEMARK DEPT.
MAY 13 1988
JMG

EXAMINER	
BRISCOE, R	
BRISCOE, K	
ART UNIT	PAPER NUMBER
~~121~~ 121	4

DATE MAILED: ~~05/11/88~~ 5/11/88

This is a communication from the examiner in charge of your application.

COMMISSIONER OF PATENTS AND TRADEMARKS

August 11, 1988

☑ This application has been examined ☑ Responsive to communication filed on Jan. 19, 1988 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449
4. ☐ Notice of informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-23 and 26-32 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☑ Claims 1-23 and 26-29 are allowed.
4. ☑ Claims 30-32 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings which are acceptable for examination purposes until such time as allowable subject matter is indicated.
8. ☐ Allowable subject matter having been indicated, formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. These drawings are ☐ acceptable; ☐ not acceptable (see explanation).
10. ☐ The ☐ proposed drawing correction and/or the ☐ proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved. ☐ disapproved (see explanation). However, the Patent and Trademark Office no longer makes drawing changes. It is now applicant's responsibility to ensure that the drawings are corrected. Corrections MUST be effected in accordance with the instructions set forth on the attached letter "INFORMATION ON HOW TO EFFECT DRAWING CHANGES", PTO-1474.
12. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Case No. 600-7025/CIP
Serial No. (047,358

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :

FAIZULLA G. KATHAWALA : Art Unit: 121

Serial No. 07/047,358 : Examiner: K. BRISCOE

Filed: May 5, 1987 :

For: PYRIMIDINE DERIVATIVES :

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on October 11, 1988
(Date of Deposit)
Richard E. Vila
Name of applicant, assignee, or Registered Representative
/s/
Signature
October 11, 1988
Date of Signature

REQUEST FOR EXTENSION OF TIME

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

Dear Sir:

It is respectfully requested that the period for responding to the Office Action of May 11, 1988 or taking an appeal or further action in connection with the above-identified application, originally set to expire on August 11, 1988 , be extended for two (2) month(s) to October 11, 1988.

☐ A check in the amount of $ to cover the fee for this extension is enclosed.

☒ Please charge the extension fee of $170.00 required by 37 CFR 1.17(c) to Deposit Account No. 19-0134 in the name of Sandoz Corporation.

Respectfully submitted,

/s/
Richard E. Vila
Attorney for FAIZULLA G. KATHAWALA
(201) 503- 7852

JMG:lmc

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

Enclosures: Postcard; COM Stamp

SUBMITTED IN DUPLICATE

BASLE

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/165,456	03/08/88	ANDERSON	P 500-7049-7CON

GERALD D. SHARKIN
SANDOZ CORP.
59 ROUTE 10
E. HANOVER, NJ 07936

PATENT AND TRADEMARK DEPT.
JUN 15 1989
JMG

EXAMINER	
DENTZ B	
ART UNIT	PAPER NUMBER
121	17
DATE MAILED:	06/13/89

NOTICE OF ABANDONMENT

This application is abandoned in view of:

1. ☐ Applicant's failure to respond to the Office letter, mailed _____ .
2. ☐ Applicant's letter of express abandonment which is in compliance with 37 C.F.R. 1.138.
3. ☐ Applicant's failure to timely file the response received _____ within the period set in the Office letter.
4. ☒ Applicant's failure to pay the required issue fee within the statutory period of 3 months from the mailing date of 1-3-89 of the Notice of Allowance.
   - ☐ The issue fee was received on _____ .
   - ☐ The issue fee has not been received in Allowed Files Branch as of _____ .

   In accordance with 35 U.S.C. 151, and under the provisions of 37 C.F.R. 1.316(b), applicant(s) may petition the Commissioner to accept the delayed payment of the issue fee if the delay in payment was unavoidable. The petition must be accompanied by the issue fee, unless it has been previously submitted, in the amount specified by 37 C.F.R. 1.17 (i), and a verified showing as to the causes of the delay.

   If applicant(s) never received the Notice of Allowance, a petition for a new Notice of Allowance and withdrawal of the holding of abandonment may be appropriate in view of Delgar Inc. v. Schuyler, 172 U.S.P.Q. 513.
5. ☐ Applicant's failure to timely correct the drawings and/or submit new or substitute formal drawings by _____ as required in the last Office action.
   - ☐ The corrected and/or substitute drawings were received on _____ .
6. ☐ The reason(s) below.

DIRECT ANY INQUIRIES TO :
~~LARRY DORSEY~~
OR
MARCIA CAMPBELL
PUBLISHING DIVISION
(703) 557-~~2665~~
8190

PTO-1432 (REV. 5-83)

Exhibit No. 5-10
Date 4-4-2
Diane Ferring

PTOL-85 (REV 4 86)

BAUER

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

GERALD D. SHARKIN
SANDOZ CORP.
59 ROUTE 10
E. HANOVER, NJ 07936

PATENT AND TRADEMARK DEPT.
JAN 5 - 1989
JMG

April 3, 1989

All communications regarding this application should give the serial number, date of filing, name of applicant, and batch number.

Please direct all communications to the Attention of "OFFICE OF PUBLICATIONS" unless advised to the contrary.

The application identified below has been examined and found allowable for issuance of Letters Patent. PROSECUTION ON THE MERITS IS CLOSED.

SC/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT		DATE MAILED
07/165,656	03/08/88	017	DENTZ, B	121	01/03/89

First Named Applicant: ANDERSON, PAUL L.

TITLE OF INVENTION: AZAINDOLE DERIVATIVES USEFUL AS CHOLESTEROL BIOSYNTHESIS INHIBITORS (AS AMENDED)

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
600-7044/CONT	514-300.000	F15	UTILITY	NO	$560.00	04/03/89

The amount of the issue fee is specified in 37 C.F.R. 1.18. If the applicant qualified for and has filed a verified statement of small entity status in accordance with 37 C.F.R. 1.27, the issue fee is one-half the amount for non-small entities. The issue fee due printed above reflects applicant's status as of the time of mailing this notice. A verified statement of small entity status may be filed prior to or with payment of the issue fee. However, in accordance with 37 C.F.R. 1.28, failure to establish status as a small entity prior to or with payment of the issue fee precludes payment of the issue fee in the amount so established for small entities and precludes a refund of any portion thereof paid prior to establishing status as a small entity.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE as indicated above. The application shall otherwise be regarded as ABANDONED. The issue fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office. Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of the notice of allowance, the issue fee is charged to the deposit account at the time of mailing of this notice in accordance with 37 C.F.R. 1.311. If the issue fee has been so charged, it is indicated above.

In order to minimize delays in the issuance of a patent based on this application, **this Notice may have been mailed prior to completion of final processing.** The nature and/or extent of the remaining revision or processing requirements may cause slight delays of the patent. In addition, **if prosecution is to be reopened, this Notice of Allowance will be vacated and the appropriate Office action will follow in due course.** If the issue fee has already been paid and prosecution is reopened, the applicant may request a refund or request that the fee be credited to a deposit account. However, applicant may request that the previously submitted issue fee be applied. If abandoned, applicant may request refund or credit to a deposit account.

In the case of each patent issuing without an assignment, the complete post office address of the inventor(s) will be printed in the patent heading and in the Official Gazette. If the inventor's address is now different from the address which appears in the application, please fill in the information in the spaces provided on PTOL-85b enclosed. If there are address changes for more than two inventors, enter the additional addresses on the reverse side of the PTOL-85b.

The appropriate spaces in the ASSIGNMENT DATA section of PTOL-85b must be completed in all cases. If it is desired to have the patent issue to an assignee, an assignment must have been previously submitted to the Patent and Trademark Office or must be submitted not later than the date of payment of the issue fee as required by 37 C.F.R. 1.334. Where there is an assignment, the assignee's name and address must be provided on the PTOL-85b to ensure its inclusion in the printed patent.

Advance orders for 10 or more printed copies of the prospective patent can be made by completing the information in Section 4 of PTOL-85b and submitting payment therewith. If use of a deposit account is being authorized for payment, PTOL-85c should also be forwarded. The order must be for at least 10 copies and must accompany the issue fee. The copies ordered will be sent only to the address specified in section 1 or 1A of PTOL-85b.

☑ Note attached communication from the Examiner.

☐ This notice is issued in view of applicant's communication filed _____

IMPORTANT REMINDER

Patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. See 37 CFR 1.20 (e)—(j).

COPY - See reverse side for Issue Fee Record

PTOL 85b (REV 4 86)

U.S. Department of Commerce
Patent and Trademark Office

ISSUE FEE TRANSMITTAL

This form is provided in lieu of a formal transmittal and should be used for transmitting the Issue Fee. Sections 1A through 4 must be completed as appropriate.

INVENTOR(S) ADDRESS CHANGE | SC/SERIAL NO

INVENTOR S NAME

Street Address

City, State and ZIP Code

CO INVENTOR'S NAME

Street Address

City, State and ZIP Code

☐ Check if additional changes are on reverse side

MAILING INSTRUCTIONS

All further correspondence including the Issue Fee Receipt the Patent, and advanced orders will be mailed to the addressee entered in section 1 on PTOL-85c, unless you direct otherwise by specifying the appropriate name and address in 1A below. (Note: See box 5 below for correspondence concerning maintenance fee payments.)

2A. The COMMISSIONER OF PATENTS AND TRADEMARKS is requested to apply the Issue Fee to the application identified below.

(Signature of party in interest of record) | (Date)

Note: The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

	SC/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP/ART UNIT		DATE MAILED
	[illegible]	09/06/88	017	DENTZ, B	121	01/03/89

First Named Applicant: ANDERSON, PAUL L.

TITLE OF INVENTION: AZAINDOLE DERIVATIVES USEFUL AS CHOLESTEROL BIOSYNTHESIS INHIBITORS (AS AMENDED)

	ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
	600-7044/CON	514-300.000	P15	UTILITY	NO	$560.00	04/03/89

1A. Further correspondence to be mailed to the following:

2B. For printing on the patent front page, list the names of not more than 3 registered patent attorneys or agents OR, alternatively, the name of a firm having as a member a registered attorney or agent. If no name is listed, no name will printed.

1 _____
2 _____
3 _____

DO NOT USE THIS SPACE

3. ASSIGNMENT DATA (print or type)

A. (1) ☐ This application is NOT assigned.
(2) ☐ Assignment previously submitted to the Patent and Trademark Office.
(3) ☐ Assignment submitted herewith.

8. For Printing On The Patent: (Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data below is only appropriate when an assignment has been previously submitted to the PTO or is submitted herewith. Completion of this form is NOT a substitute for filing of an assignment as required by 37 C.F.R. 1.334).

(1) NAME OF ASSIGNEE:

(2) ADDRESS: (City & State or Country)

(3) STATE OF INCORPORATION, IF ASSIGNEE IS A CORPORATION:

4. The following fees are enclosed:
☐ Issue fee ☐ Advanced order ☐ Assignment recording

The following fees should be charged to deposit acc. no. _____
(PTOL-85c or additional copy of PTOL-85b must be enclosed)
☐ Issue fee ☐ Assignment recording
☐ Advanced order ☐ Any additional fees due

Number of advanced order copies requested. _____ (must be for 10 or more copies

5. All correspondence relating to maintenance fees will be addressed to the correspondence address unless a separate "Fee Address" is provided to the Patent and Trademark Office (37 C.F.R. 1.363). A "Fee Address" may be submitted by the owner of record with the payment of the issue fee or thereafter by using form PTO-1537.

TRANSMIT THIS FORM WITH FEE

An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the Issue Fee.

Authorization for this Examiner's Amendment was given in a telephone interview with Ms. Giesser on December 21, 1988.

Non-elected claims 18 and 19 have been canceled without prejudice to the filing of one or more divisional applications drawn thereto.

Claim 16, line 3, after "compound" --according to claim 1-- has been inserted.

Claim 16, last line "; said compound of claim 1" has been canceled.

Any inquiry concerning this communication should be directed to Examiner Dentz at telephone number 703-557-3572.

12/22/88;df

JOHN M. FORD
EXAMINER
GROUP ART UNIT 121

FYI

102648 - #89
102975 - #34

MAY 10 1993

RECEIVED IN
BOX INTERFERENCE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

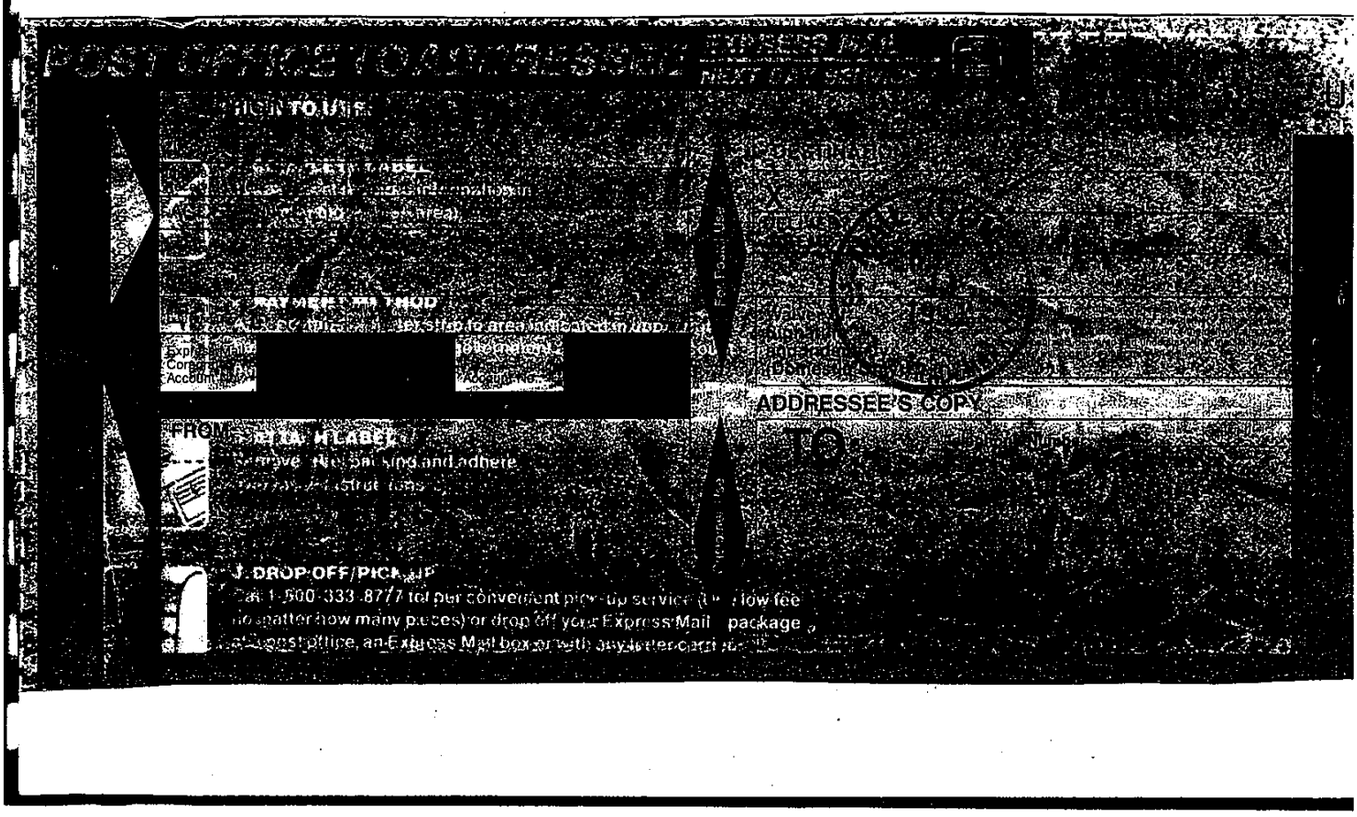
Express Mail Mailing Label Number GB500260662US

Date of Mailing 5/10/93 Interference Nos. 102,648, 102,975

I hereby certify that on the date indicated above, these materials, comprising the transcript of the deposition of Joanne M. Giesser, Esq. in Interference Nos. 102,648 and 102,975, are being deposited with the United States Postal Service as Post Office to Addressee Express Mail addressed to the Commissioner of Patents and Trademarks, Box Interference, Washington, D.C. 20231.

Connie S. Oubre
Signature of Person Mailing the Materials

Connie S. Oubre
Printed or Typed Name of Person Mailing the Materials



#90

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

WATTANASIN	:	
	:	INTERFERENCE NO.: 102,648
V.	:	EXAMINER-IN-CHIEF:
FUJIKAWA ET AL	:	MICHAEL SOFOCLEOUS

FUJIKAWA ET AL MOTION TO CONSOLIDATE THE RECORD

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231
BOX INTERFERENCE

SIR:

Pursuant to the provisions of 37 CFR §1.610(d)(e), as well as 37 CFR §1.635, Fujikawa et al hereby moves to consolidate the Record for Interferences 102,648 and 102,975, into a single Record, inasmuch as the Records are identical, the same testimony and exhibits being used for both Interferences. This is consistent with the understanding of the parties. For the convenience of the Patent Office, six copies of the Record are being filed, three for each Interference, 37 CFR §1.653(c).

It should be expressly noted that this Motion does not include consolidation of the Briefs. The Counts of the two Interferences appear to be patentably distinct, and in any event, raise different issues with regard to the necessary proof of priority, as well as potential other issues. Accordingly, the Briefs for each Interference shall be filed separately.

Pursuant to the provisions of Rule 637(b), this Motion and the circumstances involved were discussed extensively with Counsel for Wattanasin, Diane Furman, and Counsel is in agreement with this Motion.

The substance of this Motion was discussed by phone with EIC Sofocleous, who indicated that on the grounds set forth, the Motion would be granted. The assistance and cooperation of the EIC is deeply appreciated.

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 MOTION TO CONSOLIDATE THE RECORD**
2. **FUJIKAWA'S RECORD, VOLUMES 1-V, AND EXHIBIT**
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 FEDERAL EXPRESS, this 17TH day of MAY, 1993.

STEVEN B. KELBER

Interference 102,648

#91

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

WATTANASIN	:	
	:	INTERFERENCE NOS.:
V.	:	[redacted] AND 102,975
	:	EXAMINER-IN-CHIEF
FUJIKAWA ET AL	:	MICHAEL SOFOCLEOUS

THE RECORD FOR THE PARTY FUJIKAWA ET AL

VOLUME I
(Pages 1-99)

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

OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C.
1755 Jefferson Davis Highway
Arlington, Virginia 22202
(703) 413-3000

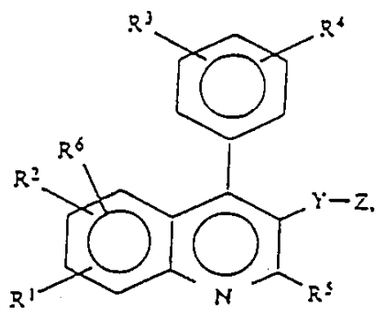
TABLE OF CONTENTS

LIST OF WITNESSES

RECORD VOLUMES

(SUBSTITUTE FOR COUNT 2 AS PROPOSED BY EIC IN PAPER NO. 40 MAILED AUGUST 7, 1993)

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,

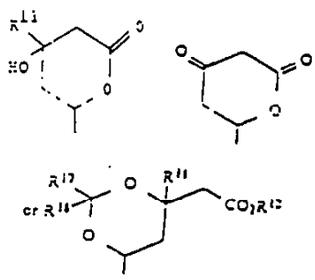
trifluoromethoxy,

difluoromethoxy,

II

(SUBSTITUTE FOR COUNT 2 AS PROPOSED BY EIC IN PAPER NO. 40 MAILED AUGUST 7, 1993)

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

III

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

(SUBSTITUTE FOR COUNT 2 AS PROPOSED BY EIC IN PAPER NO. 40 MAILED AUGUST 7, 1993)

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).

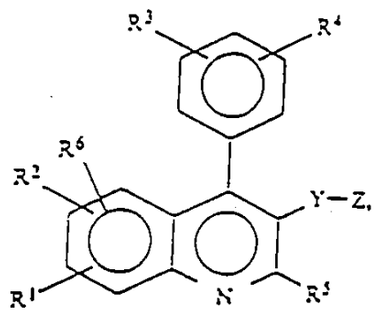
Y is
$-CH_2-$,
$-CH_2CH_2-$,
$-CH=CH-$,
$-CH_2-CH=CH-$, or
$-CH=CH-CH_2-$;

IV

as defined in combination with pharmaceutically acceptable carrier.

COUNT 1 **INTERFERENCE 102,975**

A compound of the formula:



wherein R^1, R^2, R^3, R^4 and R^5 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),

V

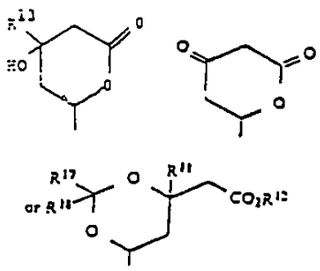
trifluoromethyl,
trifluoromethoxy,
difluoromethoxy,
fluoro,
chloro,
bromo,
phenyl,
phenoxy,
benzyloxy,
hydroxy,
hydroxymethyl,
$-O(CH_2)_\alpha OR^{19}$ (wherein R^{19} is hydrogen or C_{1-3}alkyl and α is 1, 2 or 3),
or when located at the ortho position to each other, R^3 and R^4 together optionally 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

$-CH_2-$,
$-CH_2CH_2-$,
$-CH=CH-$, **VI**
$-CH_2-CH=CH-$, 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;

VII

INDEX OF EXHIBITS

EXHIBIT NO.	DOCUMENT DESCRIPTION	RECORD PAGE IDENTIFIED	RECORD PAGE OFFERED INTO EVIDENCE
F-10	Curriculum Vitae of Chester E. Holmlund	182 ✓	182

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:

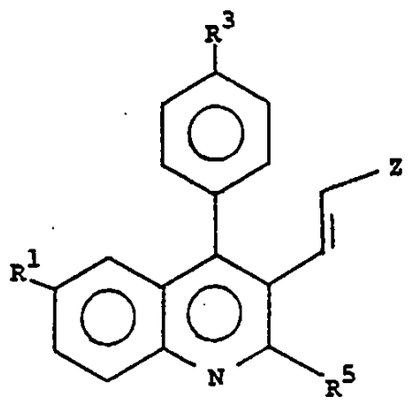
I, MASAKI KITAHARA, do hereby declare and state that:

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

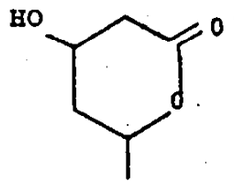
3

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
INTERFERENCE NOS. 102,648
102,975

WATTANASIN,

vs.

FUJIKAWA, et al.

DEPOSITION OF:
MELVYN M. KASSENOFF

Monday, March 22, 1993
Florham Park, New Jersey

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I N D E X

E X H I B I T S

(Before Gary M. Talpins, a Certified Shorthand Reporter and Notary Public of the State of New Jersey, held at the offices of Sandoz Corporation, Patent and Trademark Affairs Department, 25 Hanover Road, Florham Park, New Jersey, on Monday, March 22, 1993, commencing at 10:00 a.m.)

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M E L V Y N M. K A S S E N O F F, 3 Shelley Terrace, West Orange, New Jersey 07052, Sworn.

MR. KELBER: Good morning. This is the cross examination of the Sandoz declaration witnesses. The first witness we have today is Mr. Kassenoff.

CROSS EXAMINATION BY MR. KELBER:

Q. Mr. Kassenoff, I'm going to hand you or hand the reporter a document that I would like labeled as F-1 and ask you to take a minute and take a look at that.

(Whereupon the document was received and marked F-1 for identification.)

Kassenoff - cross

Q. Do you recognize that document, Mr. Kassenoff?

A. Yes.

Q. And is that your signature at the end of the document on page six?

A. Yes.

Q. Let me turn your attention first to the very bottom of page one. You see the sentence starting "this project resulted in numerous patent disclosures." Do you have any feel in general numbers for how many disclosures of the type of compounds referred to as having utility as HMG-CoA reductase inhibitors?

A. No, I don't.

Q. You used the word "numerous" in your declaration.

A. Certainly over 10, possibly 20. It wouldn't surprise me; possibly even more than that.

Q. Turning to the top of page two of the declaration that is Exhibit F-1, there is a reference to a Mr. Fred Weinfeldt, who apparently shared the responsibility in that particular technology area. With whom did he share it, sir?

A. With me. In other words, initially he

Kassenoff - cross

was doing the work on it and then obviously, there were too many disclosures so I took over some of them and then eventually, I had primary responsibility.

Q. By primary responsibility, what would primary responsibility entail?

A. Just probably did more of them than anybody else at a particular time.

Q. If there was somebody else doing an application in that field at that particular time, let's pin it down, in the 1987-'88 framework, would you have responsibility for monitoring that other person?

A. Informally but not formally. In other words, I was not reviewing it but if somebody had a question on it, they would obviously come in to me.

Q. Are you familiar with the rating system that was used by the Sandoz Patent --

A. More or less.

Q. I know you know the answers to most of the questions I'm going to ask you but let me finish them for the reporter. I'm pretty clear when I finished the question.

Are you familiar with the rating system

Kassenoff - cross

that was used by the Sandoz Patent Committee during 1987 through '88?

A. Right.

Q. And by "right," you mean --

A. Yes.

Q. What did it mean if a disclosure received a "B" rating?

A. "B" I think is three months, it would come up again in three months.

Q. What criteria would be brought to bear to determine what rating a disclosure would get?

A. Probably ongoing work, it means it wasn't ripe for filing. More detailed than that, I'm not sure.

Q. It wasn't ripe for filing but --

A. It may have been ongoing work, for example.

Q. Would there be any other reasons that a disclosure would receive a "B" rating?

A. Sometimes it was the people there didn't feel qualified but usually that would be -- we would put it off a month if there was nobody there who felt comfortable in making a decision but usually, a "B" rating means it's ongoing work,

Kassenoff - cross

that's the principal reason.

Q. It's ongoing work. In other words, a disclosure would not be rated for more immediate action if the work was ongoing?

A. Well, unless, of course, you had something that was so hot that you had to file on it immediately.

Q. What would --

A. In other words, there are flexible standards involved. It's not an absolute.

Q. By assigning a "B" rating to a disclosure --

A. That means that the thing is of interest but it's not ready for filing yet because of, for example, ongoing work.

Q. Are there any other reasons for assigning it a "B" rating other than ongoing work?

A. I don't recall offhand. I'm not sure. There could be.

Q. You are currently Director of Patent and Trademark Affairs for Sandoz. Is that correct?

A. That's correct.

Q. Is there a Sandoz Patent Committee today?

Kassenoff - cross

A. Yes.

Q. Does it use the same rating system?

A. Yes, it does.

Q. As Director of Patent and Trademark Affairs, I would imagine one of your responsibilities --

A. Yes, I do attend the meetings and have attended on a regular basis for the last year.

Q. In your experience, have disclosures been rated "B" for any other reason than ongoing work?

A. I don't recall of any right now.

Q. You have been with Sandoz since 1972. Is that correct?

A. That's correct.

Q. Let's try and narrow it down. How about in the HMG-CoA reductase inhibitor field, do you recall during your tenure at Sandoz any other disclosure besides the one of interest, 299/84, in that field ever having been rated as "B"?

A. I don't recall. Frankly, I didn't attend the meetings on a regular basis. In fact, probably until the beginning of last year, over the previous 20 years, I probably attended the meeting

Kassenoff - cross

maybe twice and obviously, we have not had any ratings in that field, at least I don't think we have in the last year or so.

Q. If you didn't attend a meeting and a disclosure was rated "B", would you be informed of that fact?

A. Yes. The minutes are published.

Q. Have you reviewed the minutes of the Patent Committee --

A. I look at the minutes. I have got to see if anything is in my area, which I have to file on.

Q. In the period January 1, 1987, to December 31, 1988, did you see any other application --

A. I would not recall.

Q. Please let me finish the question, Mr. Kassenoff.

Do you recall seeing the disclosure 299/84 rated as "B" at any time?

A. I'm sure I saw it.

Q. But you don't recall seeing it now?

A. No.

Q. Are you sure that you might have seen

Kassenoff - cross

any other disclosure in your field rated "B"?

A. I'm sure I would have seen it there but on the other hand, I certainly wouldn't remember it because I would have no reason for remembering it because it didn't require any action.

Q. It didn't require any action. It didn't require any action on your part?

A. On my part.

Q. During the period 1987 through 1988, are you aware did Sandoz employ patent attorneys not employed by Sandoz Corporation directly as full-time employees for the preparation of patent applications?

A. Are you talking about outside?

Q. Outside counsel.

A. Not to write patent applications except possibly once in awhile, we may have an oddball case. Obviously, I wouldn't know about it. In other words, in the pharmaceutical area, I can tell you the answer is no except maybe possibly if there were a very complex interference or something like that but not for normal, we do not hire outside counsel for normal work.

Q. By normal, you would include drafting

Kassenoff - cross

applications?

A. Prosecution and application writing.

Q. Even if there is a crunch in the staff at Sandoz and it is not immediately up to it?

A. No, we don't do that unless -- the only exception being, for example, two years ago, we had -- it was not in the pharmaceutical area but we had a possible sale where we had to rush something, a filing on something which we were about to sell. In the U.S., we didn't have the problem but abroad, we would have had a filing if we didn't get it on filing immediately.

Q. And in that instance, you sent it to outside counsel?

A. Yes. This was not a pharmaceutical case because then you wouldn't have that kind of a problem.

Q. Is there a formal policy that you are aware of that would distinguish between pharmaceutical cases and --

A. There is no formal policy.

Q. How did you find out about the "A" rating that's referred to in paragraph four of the document that's --

Kassenoff - cross

A. The minutes are distributed anywhere from a few days to a week or two after the meeting.

Q. Are the minutes distributed to everybody in the department?

A. Everybody in the department receives the minutes.

Q. Again, I'm going to ask you to let me finish my sentence. I know you are ahead of me on this but you have got to give me a chance to catch up.

How was it determined who was responsible for a particular application that gets an "A" rating?

A. Usually one of the supervisors will decide and it usually will be decided before the meeting and usually it will be people have defined areas, although sometimes, as you can see here, people may share the same area. Obviously, if it's in somebody's area, it will go to that person. If it's in an area that's shared, usually the supervisor will decide who will get it. But things are not done on a formal basis and sometimes things are transferred afterwards.

Q. Was such a decision as to who would be

Kassenoff - cross

responsible for the disclosure that received an "A" rating referred to in paragraph four made?

A. Jody Giesser's initials were on the agenda as well as the minutes for that disclosure.

Q. Does that mean she had responsibility for the preparation of it?

A. That would mean generally she would have responsibility unless, of course, she transferred it to somebody else but at least initially, it was in her bailiwick.

Q. Let me direct you to the last sentence or actually the last phrase in paragraph four, where it indicates a backlog in unfiled HMG-CoA reductase disclosures have been developing. Do you have any idea of how large that backlog was?

A. No, I can't -- I have no idea.

Q. How do you know there was a backlog?

A. Because I can recall that there was some pressure involved in the area and that there were a number of disclosures that were floating around but I do not recall the number.

Q. Aren't there a number of disclosures floating around, weren't there a number of disclosures floating around throughout the 1981

Kassenoff - cross

through 1990 time period in that field?

A. At least through the beginning of that time period, probably not at the end of it.

Q. Probably not at the end of it. Let me direct your attention to paragraph five. Do you see the listing of cases that appears in that paragraph?

A. Correct.

Q. Many of those applications have a filing date of 1988 through 1990. Is that correct?

A. A number of them, correct.

Q. In fact, more than half. Isn't that correct?

A. Right, but most of those, if you notice, are CIP's or continuations and the like and would not be the result of new disclosures.

Q. Let's talk about that. The CIP application would not be the result of a new disclosure?

A. That's correct.

Q. How would a CIP application come to be docketed for filing?

A. It's not docketed, it's up to the attorney involved simply to file it without it

Kassenoff - cross

being docketed and usually the need for it will become apparent from discussions between the attorney involved and the inventor and/or others in Research and similarly, divisionals would simply come about, those would be decided on by the Patent Committee at the time an issue fee was paid for the earlier case in the series.

Q. Would you help me out. Could you take a look at the list of applications or list of cases, I'm sorry, that are recited there and tell me how many would have come from new disclosures.

A. If it does not have any letter or anything else after the number, that would be a new disclosure.

Q. Could you identify how many of those there are?

A. Starting from which one?

Q. All of the ones in this five, how many came from new disclosures?

A. 6951, 7013, 7015, 7022, 7025, 7028, 7035, 7041, 7050, 7064, 7087, 7101, 7104. There is also I see here 6955 but where is the original on that? There are a number of cases here that probably should be down there for completion but

Kassenoff - cross

are not here. For example, the 6955, what is down here is obviously a later application in the series.

Q. I'm sorry, 6955?

A. 55.

Q. Could you direct me to --

A. March 10th of '88. And there are also a number of other applications in the series which I can see are not down here.

Q. The ones that are down here, you identified 13 that resulted from new disclosures. Is that correct?

A. Correct. You counted them.

Q. That was my count but I'm asking you to confirm that for me.

A. That seems right.

Q. Of those 13 cases, do you have any feel for how many were part of the backlog that is referred to in paragraph four?

A. It was probably 7064 because I wrote that one, 7087, 7101, 7104 and of course, some of the CIP's involved, as well, although those weren't new disclosures but that's part of the backlog of work in this project.

Kassenoff - cross

Q. You indicated after you said 7064 that that would have been part of the backlog because you wrote it.

A. That's why I'm familiar with it.

Q. But you had shared responsibility for that field even before Mr. Weinfeldt's departure. Is that correct?

A. That's correct. I wrote some of the other cases in the series.

Q. Do you know for a fact that 7064 was part of the backlog?

A. Just from the time frame, I do.

Q. That application was filed January 27, 1988. Is that correct?

A. That's what it says here.

Q. But is it correct? You wrote it. Do you know?

A. I don't remember when I filed it. I have to assume that this is correct.

Q. Did you review any documents during the preparation and signing of this declaration?

A. Did I?

Q. Yes.

A. No. I relied on my memory.

Kassenoff - cross

Q. You don't have a memory of the statement that appears here now?

A. Not particularly, not in particular, no.

Q. Did you have a memory at the time you signed it?

A. No. It was to the best of my recollection, it was correct.

Q. And what is that recollection based on, sir?

A. What I remember.

Q. But you don't have a memory of doing it, do you?

A. I have a memory of writing that application and I know it was in that time frame but to say that it was definitely January 27th of '88, I don't know. But that seems right.

Q. Do you know as a matter of personal knowledge that 7064 was part of the backlog referred to in paragraph four?

A. Yes.

Q. 7064 appears to have been filed sometime about January of 1988, according to your recollection.

Kassenoff - cross

A. That's correct.

Q. Do you have any idea when you began preparation of the application at maturity of that filing?

A. No, I do not.

Q. Would it have begun prior to April 1987?

A. Probably not but I really -- without going into the file and looking at whatever notes I have, I can't answer that.

Q. Probably not. Do you have any feel for why you said probably not?

A. Because the time period would have been eight or nine months and I would not have been working on an application that long.

Q. That would be a longer time period than usual for you?

A. For me, yes.

Q. Let's look at 7087. Was that part of the backlog referred to?

A. Yes, it was.

Q. Did you work on that case?

A. Yes, I did.

Q. Do you know how long it had been

Kassenoff - cross

pending before you took over the preparation of that case?

A. No, I do not.

Q. You referred to a backlog in paragraph four and the backlog refers to unfiled disclosures had been accumulating. Is that correct?

A. That's correct.

Q. Were these disclosures that had been rated "A" for filing by the Patent Committee?

A. Yes, otherwise they wouldn't be part of the backlog.

Q. Can you give me an idea of the time delay between the "A" rating received and the delay until action on the disclosure so rated, give me an idea of that time delay involved in the backlog referred to?

A. I really cannot.

Q. What do you mean by "backlog"?

A. It means there were several disclosures which have been pending for more than a month or even probably more than two months.

Q. So your recollection suggests that the backlog was at least two months?

A. More than that, according to my

Kassenoff - cross

recollection, but I can't be more specific than that.

Q. I'm a little confused. Mr. Weinfeldt left in approximately April of 1987. Is that correct?

A. That sounds right.

Q. The backlog by January of 1988 had developed to as much as two months or more. Is that correct?

A. It was more than that, probably.

Q. Three months?

A. I'm sure that there were cases that -- in fact, I'm willing to bet that there were cases that were outstanding for longer than that which had not been filed on.

Q. You are willing to bet, is that bet based on your personal knowledge?

A. It's based on my knowledge of how things operate and how things operated in that period as well as currently.

Q. Do you have a specific recollection of a case or cases in that field, the reductase disclosures referred to, that had been pending for more than two months?

Kassenoff - cross

A. I am sure that 7064 was pending for more than two months because of the scope of the application. It was no way that that thing was filed within two months of its being rated "A"; also 7087, which is another case that I wrote, there was no way that that was filed within two months.

Q. We may be talking apples and oranges here. By backlog, I assume you refer to cases that had not been picked up for action. Is that correct?

A. By backlog, I mean cases that had been rated "A" and had not been filed on as yet.

Q. So if an attorney had a particularly difficult case, even though that was the only case the attorney was acting on, under this definition, that would be part of the backlog. Is that correct?

A. That's correct. That is the sense in which I have used the term.

Q. Were there any cases that had been rated "A" but had not received review or attention from an attorney for two months in that backlog?

A. I can't answer that. I can't answer --

Kassenoff - cross

Q. How about for cases assigned to you?

A. Again, I have to assume from the way I operate that within a few weeks of the "A" rating, I would have contacted the inventor and had the inventor or inventors at least start to send me the material required for the application. I would have contacted Biology to get their input and possibly, if relevant, Process Development to get any new processes which I would need for the best mode requirement on it.

Q. In fact, you contacted Dr. Wattanasin, is that the correct pronunciation?

A. Correct.

Q. You contacted Dr. Wattanasin as early as February 1988 regarding this disclosure. Is that correct?

A. That's what the notes in the file show.

Q. Is that customary for what is referred to as the backlog?

A. Yes. That's not saying that in every case, I would do it within a couple of weeks but in that case, I did do it.

Q. You identified earlier four cases that fell into that backlog, cases which had been

Kassenoff - cross

designated "A" but not yet filed. Is that correct?

A. That's correct.

Q. Do you recall, did you have personal responsibility for any other cases that might have been in that backlog?

A. No, I did not have any personal responsibility for any other cases.

Q. Besides --

A. In the new filings because filing new applications was only a very small part of my workload.

Q. Besides Ms. Giesser, was there anybody else at Sandoz with responsibility for the preparation of new applications and filing in this field?

A. In the HMG-CoA reductase application?

Q. That's correct.

A. Not to my recollection because I don't think -- Diane picked it up but I think it was after Jody had left.

Q. So for the period 1987 through 1988, after Mr. Weinfeldt's departure --

A. As far as my recollection, as far as I recall, that's correct.

Kassenoff - cross

Q. Do you have any knowledge or understanding of how many backlogged cases, as the term is used here, that Ms. Giesser might have had in this field?

A. No, I do not.

Q. You indicated that you knew from your own personal work that an eight to nine month delay between the receipt of an "A" rating on a disclosure and the filing would have been extraordinary, at least for yourself. Is that correct?

A. Yes. I don't think that I have any cases that were pending that long.

Q. Do you have any feeling for how quickly Miss Giesser would --

A. No, I do not.

Q. But you worked with Miss Giesser in this particular case, 299/84. Isn't that correct?

A. I did some of the spadework initially but that's as far as it goes.

Q. Why did you do the initial spadework if you had your own backlog of cases, sir?

A. Probably because I was ordering, it may have been that I was ordering things from Biology

Kassenoff - cross

for two different cases, it may have been she was so backlogged that I said okay, Jody, I will contact the people involved and start the ball rolling on it for you.

Q. But you don't know if she was backlogged or not?

A. I don't know her workload, if that's your question.

Q. You said she might have been backlogged. Do you have any knowledge that she was?

A. In this particular field?

Q. In this particular situation.

A. No, I really don't, bearing in mind, of course, that each of us has several distinct fields of responsibility.

Q. Let me refer you over for a minute to paragraph six. That spans pages three through four of the declaration that is F-1.

A. Right.

Q. You were in communication with Dr. Wattanasin?

A. That's correct.

Q. Was there communication other than written communication?

Kassenoff - cross

A. As far as this case, I cannot be certain but from the way I operate, that is likely.

Q. But you don't have any knowledge --

A. I don't keep records of my phone calls but I do know that I frequently request for information by telephone.

Q. But you don't have any knowledge of such request, personal knowledge of such a request?

A. No. There is no way I could remember that.

Q. Fair enough. Turning you to maybe two-thirds of the way down on page four, the very last paragraph of paragraph six, these notes indicated that you spoke to Dr. Wattanasin. I have Exhibit N which is referred to and I would like the reporter to mark that as F-2. Once he has done that, if you would take a brief look at that.

(Whereupon the document was received and marked F-2 for identification.)

A. Okay.

Q. Now if you look at the very last line of Exhibit N, is that line in your handwriting?

A. Yes, it is.

Q. And that does indicate "spoke with S.W."?

Kassenoff - cross

A. That's correct.

Q. And is there any other indication in Exhibit N that you spoke with Sompong Wattanasin?

A. No, that's the only indication, I have a date there and it says I spoke with him.

Q. Do you see the very last five words on that line?

A. Yes, I do.

Q. What do those say?

A. "Requested info will be sent."

Q. To what does the information on page b, 392b of Exhibit N, refer to?

A. 392b?

Q. If you look at the very top.

A. That's one of the synthetic routes to the compound, to the quinoline compounds.

Q. Was that the subject matter of your discussion?

A. It might have been but my discussion primarily, at least primarily relates to the material listed at the top of 392a.

Q. Was that the type of information requested, sir?

A. Yes, it was.

Kassenoff - cross

Q. And do you have any recollection of whether that information referred to at the very bottom of the first page of Exhibit N was ever sent?

A. I'm sure it was because I can recall -- let me put it this way: I have seen from the file that some of the material, the lab notebook pages were sent.

MR. KELBER: Let me ask the reporter to identify Exhibit O, this document, as F-3. It bears the legend at the top Exhibit O.

Q. And after the reporter has so identified it, if you would review it for a minute, sir.

(Whereupon the document was received and marked F-3 for identification.)

A. Okay.

Q. Mr. Kassenoff, is the material of Exhibit F-3 responsive to the information that is indicated was requested on Exhibit F-2?

A. Only partially.

Q. In your opinion, Mr. Kassenoff, was the information requested in Exhibit F-2 necessary for the preparation of a full patent application?

Kassenoff - cross

A. Yes, it was.

Q. Am I correct, then, in understanding that additional information that had been requested would have been necessary to prepare the application?

A. That is correct.

Q. And that information would have come from Dr. Wattanasin or somebody working with him. Is that correct?

A. That's correct.

Q. Did you take any further steps to secure that information that was not provided in the --

A. Either Jody did or I did.

Q. Do you have personal recollection of receiving the additional information necessary?

A. No, I do not. The only thing I do know is that in reviewing the file, but of course, this was recently, I did note that there were lab notebook pages in there which were received at a subsequent -- which I think were received at a subsequent time.

Q. This review was made subsequent to the preparation and signing of this declaration?

Kassenoff - cross

A. Or concurrently.

Q. You don't recall which?

A. Or both.

Q. Which was it? You executed this declaration on February 19.

A. Right. I did have to look through the file to see these handwritten notes and identify them. Obviously, when I'm looking through the file, I did see other papers there.

Q. But you did not identify those in this declaration? I'm sorry, you did not identify the papers incorporating the additional information that was requested in Exhibit F-2 in this declaration?

A. It doesn't appear there.

Q. Referring you to paragraph eight, Mr. Kassenoff, of Exhibit F-1, as of May 23, 1988, do you have any recollection as to whether you believed you had responsibility for case number 299/84?

A. No, I do not.

Q. Does the fact that you received data from the Sandoz Biology Department with respect to that indicate anything at all to you about who had

Kassenoff - cross

responsibility for that case?

A. No, it does not. The only thing it does reveal is that there was a possibility that I would handle it. However, the case was assigned to Jody Giesser.

Q. Would Biology have known that the case was assigned to Jody Giesser?

A. No, absolutely not.

Q. Were you the only person to receive data from the Biology Department in this field?

A. No, whoever requested it would receive it.

Q. Did you request it?

A. Yes, I did. That's why it was sent to me.

Q. Why did you request it if the case had been assigned to Jody Giesser?

A. Possibly because either Jody was so tied up that I volunteered to do the legwork; possibly because I was asking, also asking for information on other cases; possibly because I might have taken over the case if I had the free time before she did.

Q. Do you have any recollection of which

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of those possibilities it was?

A. No, I do not.

Q. Would a review of the case help refresh your recollection?

A. No. I did go through the case to see if I had any handwritten notes in there, which might help me.

Q. And were there any handwritten notes?

A. No, the only handwritten notes are what you see in front of you.

Q. Is it your custom, sir, to request biological data from the Sandoz Biology Department on cases for which you have no responsibility?

A. Only if there was a possibility that I might pick up the case or if they were tied to cases for which I did have responsibility.

Q. Do you have any feel, any recollection as to when you might have requested the data that is referred to in paragraph eight?

A. No, I do not. The only thing I can say, it was probably at least a week before May 23, 1988. It could have been, however, two months before that.

Q. Would it be customary to have a two

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month delay between a request for biological data and receipt of the same?

A. Usually not but if the person in Biology were tied up, it could be something he forgot about and then I would have to call back and say hey, what about the stuff that I requested.

Q. Do you know who the person in Biology was at this time period?

A. Yes, I would have spoken with Robert Engstrom.

Q. Do you recall what you did with the biological data report for kit PD 299/84?

A. I'm sure I just put it into the notes that I had, the material that I was collecting for this case.

Q. Did you advise Ms. Giesser of the receipt of that data?

A. I have no recollection but it's possible.

Q. But --

A. Because I'm sure that I would have given her everything that I have on the case.

Q. Why would you have done that?

A. Because there would be no -- if she had

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responsibility for the case, there certainly would be no sense in each of us having our own file. That would only lead to confusion. So I'm sure that anything I got relating to it, since she had primary responsibility, I would have given to her.

Q. So she had primary responsibility at this period in time?

A. For this particular case because it was assigned to her in the Patent Committee notes.

Q. In your review of the file -- I'm sorry, let me back up. Is it correct, then, that it would have been the practice at the time to have but a single file for the collection of materials for the preparation of the application for PD 299/84?

A. I would hope that would have been the case but I can't guarantee it.

Q. Do you have any familiarity with the procedure of the Sandoz Patent Department in general at that time?

A. There is no general procedure. Each one of us works as our own department.

Q. If each one of you works as your own department, how do you decide who has got primary

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responsibility for the case?

A. That's the Patent Committee's job, to assign the cases, or the supervisor, who will assign it before the Patent Committee meeting.

Q. Do you have any knowledge that Ms. Giesser had a file separate from the file that you reviewed?

A. No, I do not.

Q. In your review of the file that you referred to earlier, did you come across any communications from Ms. Giesser to anyone else at Sandoz regarding the PD 299/84 prior to May 23, 1988?

A. I don't recall, frankly.

MR. KELBER: Is the file available?

MS. FURMAN: Which one?

MR. KELBER: The file that Mr. Kassenoff is referring to.

THE WITNESS: The case file.

MS. FURMAN: Sure.

MR. KELBER: Can we get the case file with reasonable speed and have Mr. Kassenoff review it? I appreciate it. While we are getting that, we can ask some more questions.

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THE WITNESS: Let me just add something on that. Each of us had different methods of operating. What I would do is when I prepared an application, when it got filed, all of my notes relating to that case I would tuck into the file. I have no guarantee that anybody else did that. Some people had supplementary files, some of which were retained, some of which were disposed of; others did not.

Q. Mr. Kassenoff, take a minute to review that file.

A. Sure. Would you please rephrase your question so I know what I'm looking for.

Q. At this point, I'm asking you -- okay. Please review the file specifically with an eye towards determining if there are any written communications reflected there from Ms. Giesser to anybody else in Sandoz prior to May 23, 1988.

A. I don't even see my notes in there. There is nothing in the file here prior to that date, including my notes. I don't know where the originals --

MS. FURMAN: Your notes were not originally in the file.

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THE WITNESS: Where were they?

MS. FURMAN: A bunch of papers were separate from the file that Jody gave me.

THE WITNESS: I think it's clear that there was a supplemental file there of some other notes.

MR. KELBER: Let's go off the record for a minute.

(Whereupon a discussion took place off the record.)

Q. Just to preface the agreement, Mr. Kassenoff, is it correct that your review of the file does not indicate any written communication from Ms. Giesser in the file prior to May 23, 1988?

A. That's correct, nor does it reflect anything from me prior to that date.

MR. KELBER: Diane, we would appreciate it if you would search for any supplemental papers relevant to PD 299/84 and if there is anything in the file prepared by Ms. Giesser for communications to others at Sandoz prior to May 23, 1988, if you would forward us a copy. Is that agreeable to you?

MS. FURMAN: Yes, it is.

Q. To the best of your recollection, Mr.

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Kassenoff, did Ms. Giesser take any action with respect to PD 299/84 prior to May 23, 1988?

A. I have no recollection one way or the other.

Q. Let me direct your attention to paragraph nine of the declaration. You see the phrase "which was indicated for filing ahead of PD 299/84," the very first sentence of paragraph nine, middle of the page?

A. That's correct, yes.

Q. What does it mean to be indicated for filing ahead of?

A. It has no formal meaning, it just simply means that since this was, 7022/C was a CIP application, that I had decided to file it prior to filing, prior to picking up 7101.

Q. So you would work on 7022/C prior to picking up 299/84 if, in fact, you picked up 299 at all?

A. That's correct. I did not do anything as far as writing, that's clear.

Q. I'm trying to get a feeling for what you meant by "picking up" because obviously, you were involved with the file prior to that time.

Kassenoff - cross

A. I was involved with gathering information, that's correct.

Q. You mean picking up for preparation of the application?

A. For preparation, that's correct.

Q. What was the basis of the determination to file 7022 prior to preparing 299 for preparation?

A. I don't recall other than the fact that it was a CIP application so I probably wanted to get that off my desk.

Q. Why?

A. I don't recall. I don't think there was any question of a statutory bar or anything like that. It was probably because I probably had an office action to respond to in the parent application or the parent application was about to issue and I had to get this CIP on file in lieu of a divisional. I don't recall that specifically but I think that's a valid assumption.

Q. Do you recall having prepared any other cases in this field between January 1987 and December 31, 1988?

A. It was clearly 7087; 7041/CIP/CIP was

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not a case I originally handled but I did prepare the most recent CIP in the case; 6955/XN/B/CONT/X was mine but that probably -- I'm not sure how much work I did on it in your time period; the one you just mentioned, 7022/C. Just referring to this list, those are the only ones on the list in that time period which I had prepared myself.

Q. Do you have personal recollection of preparing any other applications in this particular field, the HMG-CoA reductase field, in that time period?

A. In that time period, no.

Q. Let's look at 6955, the suffixes after it. What does the "CONT" designation mean?

A. Continuation.

Q. Would that have been a strict continuation application?

A. Yes.

Q. So no new preparation would have been involved. Is that correct?

A. That's correct.

Q. And 7041 was a CIP of a CIP. Is that correct?

A. That's correct.

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Q. Do you have any recollection of how much additional work was required?

A. That was quite a bit.

Q. By quite a bit, can you give me an idea of how many months it took to prepare the additional information?

A. It probably was about two, three days -- two days work but I don't know over what period of time. It was spread out because there was a significant amount of additional information, totally redrafting of the claims and a significant rewriting of the specification. It was probably more. If I said two days, that's probably incorrect, it probably took me a good three, four days of work on it, now that I'm thinking back on it.

Q. You mentioned 7087.

A. Correct.

Q. That was a new application. Is that correct?

A. That's correct.

Q. Do you have any recollection as to why you would have prepared and filed 7087 prior to 299/84?

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A. I'm not sure of when it was rated but I do know that it related to our potential commercial product, which is now being reviewed by the FDA. It was a process case and it had features that would have related to a commercial process. However, which case was rated "A" first, that I do not recall.

Q. Would the case to be rated first ordinarily receive attention first?

A. Unless there were a reason otherwise.

Q. Do you recall any reasons otherwise with respect to 299/84?

A. The only thing that I do recall is 7087 was a process case and it related to an advanced, at that time advanced research compound and also 7087 was initially assigned to me, whereas 7101 was not assigned to me. So under the totality of the facts, it was clear which one that I was working on first.

Q. In the absence of any reasons for proceeding differently, such as the commercial aspect of 7087, would a case that was rated "A" first get worked on first and then the case that was rated "A" after that get worked on second?

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A. If it were assigned to the same person?

Q. The same person, yes.

A. Probably but I wouldn't say that was always the case.

Q. Is there any standard for proceeding?

A. No.

Q. So --

A. Theoretically, at least, the case that was rated "A" first should be acted on first by the person to whom it's assigned but I would not guarantee that that was followed by everybody at all times.

Q. Was it followed by you?

A. I don't think I can say yes. I think I probably exercised some selection there.

Q. For instance, if a CIP was pending and you were running out of time in response to the parent case --

A. I would pick that up first. That I have no doubt about.

Q. Earlier, we discussed the new applications that had been filed in this time frame, in the 1987-'88 time frame. If the cases

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were not prepared and filed by you, after April 1987 through December 31, 1988, is it a necessary conclusion that they would have had to have been prepared and filed by Miss Giesser?

A. After Mr. Weinfeldt left, yes, because I don't recall anybody else working in that area.

Q. I realize you have no personal knowledge but do you have any recollection as to how many more cases in this field, new cases in this field might have been filed than are represented here between April 1987 and December 31, 1988?

A. If there were any, and I'm not sure that there were any, it would have been probably very few.

Q. Did you assist in preparing this list that appears in paragraph five?

A. No, Diane prepared it on her own and I just went through it to make sure that everything there did -- everything listed was a case that was an HMG-CoA reductase case. I did not double-check the dates on them.

Q. Let me direct your attention to paragraph 11 of the declaration, penultimate

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paragraph of that form.

A. Okay.

Q. Is it possible for a disclosure never to receive an "A" rating?

A. Of course.

Q. And if that disclosure never receives an "A" rating -- I'm sorry, let me flip it around. Is it a requirement that a disclosure receive an "A" rating before it is prepared as an application for filing within Sandoz?

A. Generally, yes, but there are exceptions. Sometimes an application will be worked on before it actually is formally rated "A".

Q. Did you do any work on PD 299/84, to the best of your recollection, before it was rated "A"?

A. No, I did not. The only work done of which I have any recollection is that reflected by the notes in the file.

Q. Is it a correct statement, Mr. Kassenoff, that if Sandoz intends to file a United States patent application on the basis of a patent disclosure, it first or it simultaneously with that decision rates that disclosure "A"?

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A. In the pharmaceutical area, yes.

Q. Mr. Kassenoff, when did you first become aware, if you recall, when did you first become aware that third parties other than Sandoz had filed for U.S. patent protection on compounds related to those of PD 299/84?

A. I assume it was after Warner-Lambert's patent issue sometime when somebody brought it to my attention or when I noticed it in the OG.

Q. Do you have any recollection as to whether that was before or after November 1987?

A. November --

Q. I'm sorry, November 1988? I apologize.

A. I don't know because if I recall correctly, Warner-Lambert's issue was in June or July or August?

Q. Your recollection is correct, I think it issued in June.

A. If it issued in June, it could have been brought to my attention anywhere from shortly after it issued to several months later. I really do not recall. If it was a question of my noticing it in the OG, I can tell you I did not notice it

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immediately because as Bob will testify, I have a whole stack of OG's sitting around that I have not gone through. If somebody brought it to my attention, it could have been any time.

Q. Just for the record, when you refer to Bob, you are referring to --

A. Bob Honor.

Q. Do you have any recollection of whether you knew, prior to the time that PD 299/84 was filed in March of 1989, whether you knew that a third party had filed for patent protection?

A. Yes, I think I can recall, yes, I did know that.

Q. Have you been involved on behalf of Sandoz in the drafting of an application where you were aware that a third party had filed for patent protection on related subject matter?

A. It depends how you define "related."

Q. Related in the sense that the claims -- I'm sorry, forget claims, the subject matter disclosed in that third party's request for protection were obvious in the sense of 35 U.S.C. 103 with respect to the application you were preparing.

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A. Not that I can recall.

Q. Besides PD 299/84, are you aware of any other situations similar to that within Sandoz?

A. Nothing comes to mind.

Q. As Director of Patent and Trademark Affairs at Sandoz, you attend the Patent Committee meetings as regularly as possible. Is that correct?

A. Yes. That's only since, though, January of last year.

Q. Is it a correct statement to say that you generally have input on how to rate a patent disclosure viewed by the Patent Committee?

A. I open my mouth when warranted.

Q. Fair enough. If you were aware that a third party had filed for U.S. patent protection on subject matter addressed in a disclosure before the Sandoz Patent Committee, would that influence in any way your judgment as to how to rate that disclosure?

A. It probably would.

Q. Give me one second. I'm sorry, one question I meant to ask. What other fields of technology did you have responsibility for besides

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the HMG-CoA reductase field in the period January 1987 through December 1988?

A. 90 percent of my workload at that time consisted of prosecution of dyestuff cases originating in Basle, Switzerland. If you look at my docket, almost all the cases on it would be dyestuff cases.

Q. Prior to Mr. Weinfeldt's retirement or I'm sorry, not retirement but departure from Sandoz, did you have any responsibility in the HMG-CoA reductase field?

A. Yes, I handled some disclosures as early as late 1982.

Q. Prior to Mr. Weinfeldt's departure, did anybody else in the Sandoz Patent Department handle the preparation of applications in the HMG field?

A. Other than me and Fred, no, to my best recollection.

MR. KELBER: Thank you, Mr. Kassenoff. Diane, your witness.

MS. FURMAN: Do you mind if we take a break before cross?

MR. KELBER: Sure.

(Whereupon a recess was taken.)

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MS. FURMAN: I would like to offer into evidence copies of Patent Committee minutes which have been masked as to their proprietary information but left unmasked with respect to information concerning patent disclosure 299/84.

MR. KELBER: Are these the records that are already of record in another declaration?

MS. FURMAN: These comprise exhibits M-1 through M-5 of the testimony already of record.

MR. KELBER: So that would be Rothwell. Go ahead and identify them.

MS. FURMAN: And that would be exhibit, the totality of that would be Exhibit F-4.

MR. KELBER: Can we make a distinction? These are going to be your exhibits to submit and maybe we ought to make it W-1.

MS. FURMAN: Fine.

(Whereupon the document was received and marked W-1 for identification.)

REDIRECT EXAMINATION BY MS. FURMAN:

Q. Mr. Kassenoff, do you recognize the copy of the minutes dated April 29, 1987?

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A. Yes.

Q. And what information is on the minutes concerning patent disclosure 299/84?

A. That it was rated "B" in April of 1987 and that it was originally assigned to Fred Weinfeldt.

Q. Now I call your attention to the minutes of July 29, 1987. Do you recognize information relating to patent disclosure 299/84?

A. Yes, that it was rated "B" and again, assigned to Fred Weinfeldt.

MR. VILA: Pardon me, is there an exhibit number on that?

MS. FURMAN: Yes, there is.

MR. KELBER: These are all part of W-1.

Q. Look now at the minutes of the October 28, 1987, Patent Committee meeting. What does it say about patent disclosure 299/84?

A. That it was rated "X" and assigned to Fred Weinfeldt.

Q. Again, the Patent Committee minutes of November 25, 1987, what is the rating thereon?

A. It was again rated "X" and is still assigned to Fred Weinfeldt.

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Q. Finally, I ask you to look at the minutes for the January 27, 1988, PCM. And what is the rating of PD 299/84?

A. It was rated "A" and assigned to Jody Giesser.

Q. To the best of your knowledge, what does a rating of "B" signify?

A. "B" signifies that it will be considered in three months.

Q. What would prompt a rating of "B", would it be not enough information is available to file a patent application or would it be that more information is intended to be developed for the patent?

MR. KELBER: Objection, leading. The question is okay but you can't feed him the answer.

MR. VILA: Cut the question off at the first part.

Q. What is the meaning of the rating of "B"?

A. Generally, it would mean that additional work is being performed on the case.

Q. And what about the rating of "X"?

A. "X" means that it will come up in one

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month, it can mean one of two things, either one, that the people necessary or the people whose input is required before the disclosure is rated "A" are not at the meeting or that additional work is still ongoing and the results are expected within one month, such that it is anticipated that a decision will be made at the next Patent Committee meeting.

Q. At the time patent disclosure 299/84 was rated, was it within your responsibility to rate patent disclosures?

A. No, it was not.

Q. Once a patent disclosure has been rated by the Patent Committee, can you rerate that disclosure yourself?

A. I can bring it back to the Patent Committee if the need arises.

Q. Is it within your jurisdiction not to file on a patent disclosure that has been rated "A" by the Patent Committee?

A. No, it is not.

Q. Did you at any time intend after the rating of "A" of the patent disclosure not to file a patent application on it either yourself or by someone else in the department?

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MR. KELBER: Objection. You are asking him for knowledge as to other people's intentions.

Q. By yourself alone?

A. No.

Q. Is there any way to inactivate or retire a patent disclosure once it has been rated "A" by the Patent Committee?

A. The attorney in charge can bring it back to the Patent Committee and request a rerating of it for whatever reasons are deemed relevant.

Q. Absent that, is the patent disclosure considered active until --

A. Yes.

Q. -- the action is taken?

A. It's considered active until the application is filed.

Q. Mr. Kassenoff, I call your attention to your declaration previously made of record as Exhibit F-1 to the list of patent applications filed which is indicated on pages two and three. Do you know or is it within your reasonable belief that all of these applications have now been published in one way or another?

A. As far as I'm aware, every one has been

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published either in the U.S. or abroad.

Q. Is there a possibility that there may be some applications not on this list in the HMG-CoA area which have not published?

A. There is a possibility but I cannot recall of any specific ones. Actually, there is one that I think I can recall that's not on this list. Whether it was published or not, I don't know. I vaguely recall a case 7044.

Q. Other than that possibility of case 7044, this would constitute the entirety of the HMG-CoA filings?

A. That is not correct. There are a number of other cases that specifically have not been listed here. At least one that comes to mind is 6952. There are cases in the process area like 6957 and its progeny; there are some cases 694 -- I don't recall the last digit on them, some of the early cases. There could be others but I specifically remember those cases.

MS. FURMAN: That concludes my questioning.

MR. KELBER: I have a little bit of --

MR. VILA: Can I ask a couple of

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questions?

MR. KELBER: I have no objection.

BY MR. VILA:

Q. Mr. Kassenoff, I believe you said that you had a substantial involvement in dyestuffs besides the area in question which is the HMG-CoA reductase area. At that time, did you have any other areas of responsibility within the department?

A. Yes, I did.

Q. Would you enumerate those, please.

A. For example, I was keeping track of recent decisions and advising our parent company in Basle on recent decisions in U.S. patent law; I was involved in tracking pending legislation, rule changes and advising our parent company's Patent Department in that regard as well as other members of this department; I had several other projects, for example, in 19 -- it must have been 1987, when the record of understanding between the United States and the Republic of Korea was entered into, I was in charge of preparing all of the declarations. I think that was in early '87

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because if I recall correctly, the five year -- the initial five year period of exclusivity commenced on July 1st of 1987 and that took up a substantial amount of time in that period. There may have been others but those are the ones that come to mind.

Q. When Mr. Weinfeldt left in April of '87, I believe you testified that at that point in time, you and Mr. Weinfeldt had responsibility for the area in question.

A. That's correct.

Q. When Mr. Weinfeldt left, who had responsibility for that area?

A. I had, I would assume, primary responsibility and then Jody Giesser, and I'm not sure exactly when Jody came here, but Jody picked up a good deal of the responsibility sometime in that time period.

Q. Are you saying she picked up a responsibility for existing cases?

A. For existing cases as well as for new disclosures.

Q. And do we know approximately when Jody Giesser was employed?

A. If I recall correctly, it was at the

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time that Fred was on medical disability.

Q. I believe your declaration mentions that August of '87 is the time that Jody joined the department. Between April, when Mr. Weinfeldt left the department, and August, who else besides yourself would have been handling or responsible for this area?

A. I assume that you had some responsibility but I don't recall if you did any cases on that but other than that, no one.

Q. So as far as you know, you had responsibility for the entire area in that period?

A. As far as I know, that's correct.

Q. When Mrs. Giesser joined the department, did she have any prior experience in this area or in pharmaceutical applications, to your knowledge?

A. She may have had some in pharmaceuticals at the law firm or one of the law firms at which she was previously employed but certainly not in this specific area.

Q. I believe it's on the record that you have substantial long term experience in the pharmaceutical field. How would you describe the

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degree of effort required in preparing cases in this area in general, would it be routine or easier than routine?

A. The cases were rather lengthy because this is not an area which one could synthesize the compounds in one step reactions. Many of the compounds required five, even ten step syntheses. Consequently -- and often not all of the compounds of a single disclosure could be made by a single route. Consequently, the process description was -- the required process description was extensive and the applications were lengthy.

For example, there were at least a couple of the applications that I wrote were well over a hundred pages and in fact, one may have been close to 150 pages. Of course, some of them were probably on the order of 40 or 50 pages. Those were the shorter ones.

Q. I believe it's been testified that when disclosure 299/84 was rated "A" in January of '88, it had Jody Giesser's initials on the Patent Committee minutes.

A. That's correct.

Q. Indicating the case was her

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responsibility. Was there some uncertainty as to who would prepare that case despite that notation?

A. I assume that it was in the back of our minds that there was a possibility that I might do it if I had no other -- if I had the available time because that's the only way I could explain the fact that I did request Dr. Wattanasin to send me some of the Chemical -- the information required from the Chemical side and I did request Biology to send me their input for the application.

Q. Would Mrs. Giesser have had experience in obtaining the type of information which you obtained in 1988 from the Pharmaceutical Research Group?

A. Probably not.

Q. If there were a decision after the "A" rating in January of 1988 not to file a patent application on 299/84, can you tell me what, if anything, would have happened to reflect that decision?

A. It would have been reflected in the subsequent minutes of the Patent Committee.

Q. And how would that procedure have taken place?

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A. The attorney in charge would have requested the Patent Committee to rewrite the disclosure from "A", either into "B", "C", "D" or "X", "D" meaning drop or dead and "X", "C" and "B" being various categories of bringing it up once again.

Q. If there had been a decision not to file the application, what would have been the rating in that case?

A. "D".

Q. Could anybody else other than the patent attorney bring that issue before the Patent Committee?

A. Yes, anybody, any member of the committee could bring it up but generally, it would be done through the attorney, at least directly through the attorney.

Q. Who were the members of the committee?

A. The people of the committee consists of the heads and assistant heads of the Patent Department and members representing Chemistry, Biology, Pharmacy and possibly some other groups in Pharmaceutical Research.

Q. Could members of the committee

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representing chemistry bring the disclosure back up once it had been rated "A"?

A. Yes, they could.

Q. Members of the Biology group?

A. Yes.

Q. To your knowledge, did anyone, either Patent Department, Chemistry, Biology or anyone else offer this disclosure back up to be given a category other than to be filed upon?

A. Not to my knowledge but then again, I was not participating in the Patent Committee at that time.

Q. If such an action had been taken, would you be aware of it through the Patent Committee minutes?

A. Yes, I would.

Q. Are you aware of any such action?

A. No, I'm not.

MR. VILA: I don't think I have any more questions.

RECROSS EXAMINATION BY MR. KELBER:

Q. Mr. Kassenoff, I believe you testified that between April and August of 1987, you were the

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sole patent attorney or agent at Sandoz responsible for the area of HMG-CoA reductase. Is that correct?

A. Yes, although there is a possibility that Dick Vila here, who is the supervisor of the group, might have filed some responses in some pending cases.

Q. Do you have knowledge of whether he did or not?

A. No, I don't have any knowledge of that.

Q. Between the period April and August of 1987, no patent attorney at Sandoz would have taken up PD 299/84 for any reason, would they have?

A. Between when?

Q. Between the period April and August of 1987.

A. No. It had not been rated "A".

Q. So even if Ms. Giesser had been here in April of 1987, she would have had no reason to pick up that disclosure?

A. That's correct, not until it received an "A" rating or was about to be rated "A".

Q. I believe you testified that at no time

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subsequent to the receipt of the "A" rating on 299/84, you were not aware -- I'm sorry, at no time subsequent to that "A" rating, you personally did not have any intention not to file an application --

A. That's correct.

Q. -- corresponding to PD 299/84. Is that correct?

A. That's correct.

Q. At any time prior to receipt of that rating, did you have any intention to file an application directed to PD 299/84?

A. No. There would be no reason to.

Q. Do you recall whether there was a Patent Committee meeting in December of 1987?

A. Unlikely. At least in the last few years, we have not had December meetings. The Patent Committee invariably meets the last Wednesday of the month and the last Wednesday in December is not a very conducive time to have a meeting.

Q. Are there cases where a disclosure has been rated "A" and additional work is continuing on that particular subject matter?

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A. Probably.

Q. Are you aware of any such cases personally?

A. Personally, no, but I'm pretty sure that that's the case.

Q. Isn't it the fact, Mr. Kassenoff, that in the case at issue here, PD 299/84, Dr. Wattanasin continued work in that subject matter subsequent to the "A" rating?

A. That's probably the case.

Q. So the fact that additional work is being performed on a case is not alone reason to rate it only "B" as opposed to "A"?

A. That's correct.

Q. There are other considerations that would go into rating a case as "B" as opposed to "A". Is that correct?

A. Probably.

Q. Can you name some of those other considerations?

A. Yes. For example, if the work done to date shows that the compounds, while being of interest, might not be as interesting as other compounds of the series, although of interest, they

could defer it. For example, if this were the best compound that we had and better than what was available, we would probably not wait for ongoing work. On the other hand, if this compound, that is, the lead compound of this particular series, were good but probably, let's say, maybe not better than anything we already had, we might delay it.

Q. Do you recall whether that was the situation in connection with PD 299/84?

A. I do recall that we had a compound in this series in advanced clinical research at the time and that this compound certainly did not appear to -- the lead compound of the quinoline series certainly did not appear to be better than the compound that was then in clinic. That I do recall.

Q. Is it your --

A. How it compared, it was probably -- I don't know but it was certainly no better.

Q. Is it your testimony, Mr. Kassenoff, that all other things being equal, that lead compound of a disclosure that is not as good, active, without toxicity --

A. Generally --

Kassenoff - recross

Q. Let me finish the sentence, the question.

-- that is not as active as another compound that is already developed and I presume the subject of a patent application, that the application as to the less active compound might be deferred?

A. Put it this way: One, as far as when the disclosures come to the Patent Committee, we generally do not have the tox information available so we are just dealing with the testing of the compound. We have information as to its activity but not as to tox. There are exceptions, of course.

Generally, we will-- I wouldn't say that the applications would be delayed. What I would say is that they wouldn't be expedited.

Q. Now I'm confused. Perhaps I used the wrong word in the term "delay." Would a disclosure be rated "B" for that reason alone?

A. For that reason alone?

Q. The reason you described, that is, less active than another case in testing.

A. No, it would simply mean that since the

Kassenoff - recross

work was ongoing, there was no rush to file it.

Q. If work was ongoing and the lead compound that was the subject of that work was not as active as another compound that you were currently pursuing, would that be sufficient in and of itself to rate a compound -- to rate a disclosure as "B"?

A. I don't know if I could really answer that question. I would say --

Q. What else do you need to know?

A. It was probably a factor but you are saying in and of itself, I really can't answer that.

Q. What other reasons would give rise to rating a disclosure "B"?

A. Other than the ongoing work, probably -- it either would be ongoing work or whether it was of sufficient interest but usually it's ongoing work, it's "B", because if the work had been incompleted, we would be able to make a rating of it.

Q. But PD 299/84 had ongoing work after it was rated "A", wasn't it?

A. That's correct.

Kassenoff - recross

Q. So ongoing work alone is not sufficient --

A. That's correct.

Q. -- to discriminate between "B" and "A". Is that correct?

A. That's correct.

Q. Do you have any idea why PD 299/84 was rated "B" or "X" prior to January of 1988?

A. If I had to make a guess, I would say it's probably because there was some biological testing on what was then the lead compound of the series that had not been completed yet.

Q. But you are guessing?

A. I'm guessing but I would say that's probably the case. It was probably the in vivo testing that had not been completed yet.

Q. Let's go back to the biological data that you requested from Sandoz Biology Department in March of 1988. Is that the type of data that you are talking about?

A. I'm not sure. That certainly is in vitro testing. Whether there was also in vivo testing at the time, I do not recall. If it was, I would have received it. Without looking at the

Kassenoff - recross

data, I can't tell you if that's strictly in vitro or whether there is also in vivo testing at that time.

Q. Why would a disclosure be rated "X"?

A. "X" generally means that it will come up in one month and usually either we expect some data to be received during the month or else it means that, in this case it probably would be two months because of the lack of a December meeting, or else it could mean that the people required to make the decision, either the lead person from Chemistry or Biology, without whose input you generally would not want to raise it, was not present at the meeting so it's strictly deferred for a month.

Q. Are there situations where a disclosure can be rated "X" and then not elevated to "A" subsequently?

A. Absolutely.

Q. How long does it take you to prepare the average pharmaceutical application that you spoke to earlier when you are preparing one on behalf of Sandoz?

A. Are you talking about in duration of

Kassenoff - recross

time or actual number of hours?

Q. I'm sorry, duration of time.

A. It really depends on my other workload.

Q. You were able to respond to an issue regarding average applications. Can you give me an average for the period in question?

A. My guess is that it would probably be -- the work would probably require about three months but obviously, I'm doing a lot more in that time period.

Q. Understood.

A. That's a ballpark figure.

MR. VILA: Pardon me.

MR. KELBER: Off the record.

(Whereupon a discussion took place off the record.)

Q. From the time you received notification of an "A" rating on a disclosure to the time you begin preparation of the application, generally how long a time period is that?

A. I don't think I could answer that. It can vary anywhere from days to a month, sometimes even longer.

Q. Why would it be longer?

Kassenoff - recross

A. Pressure of other work, particularly a huge docket of applications of office actions to respond to and/or other work. In other words, I'm fitting in my new disclosures on a time available basis between all of my other responsibilities.

Q. And you are careful to take things in turn. Is that correct?

A. As far as new disclosures?

Q. Your work in general.

A. I would give priority to responding to office actions unless there were a statutory bar involved.

Q. You indicated that all of these, almost all of the applications or patents listed in paragraph five of F-1 had, to the best of your recollection, been published by now.

A. Oh, yes.

Q. Do you have any knowledge whether any of them were published before their filing date?

A. Before their filing date?

Q. Before their filing date.

A. Absolutely not.

Q. So it would be the Sandoz policy not to publish material before the application --

Kassenoff - recross

A. Absolutely. That's a clear no-no.

Q. How about PD 299/84, do you have any knowledge specifically in that case as to whether there was any publication prior to its filing date?

A. I have to assume that there would be none because that would not be permitted by our publication clearance procedure. In other words, we will not clear a publication for release until either we filed on it, and generally we will not clear it until it's about to publish out either in the U.S. or abroad or unless the disclosure is rated "D".

Q. So if a disclosure would be rated "B" or "X" --

A. We would not permit a publication, no way.

Q. The synthesis data that you talked about on redirect examination that tends to make pharmaceutical cases lengthy --

A. At least in this particular area. I wouldn't want to generalize it.

Q. In this particular field, does much of that synthesis information come from the individuals responsible for the work on the

Kassenoff - recross

compounds?

A. Yes.

Q. And so that that would not have to be prepared ab initio by the attorney in question?

A. It would have to be prepared by the attorney in that one. Generally, we do not get written up procedures. We get lab notebook, at least I work from lab notebook pages, which means one, I have got to go into the lab notebook pages; two, I have got to, obviously, for the examples, write them up from the lab notebook pages; three, I have got to then check, write up general procedures for it. Sometimes they may come from the inventor, as was the case in this case.

Q. I'm sorry, which case is that, sir?

A. The 7101 case. As you can see, the material, one of the exhibits does have an outline. Then I have got to make sure that for the entire scope agreed upon, that the processes that were provided are operative and if they are not, either we have to modify the scope or we have to provide additional processes such that we have an enabling disclosure for the entire scope.

Q. Do you know offhand whether that was

Kassenoff - recross

necessary in 7101?

A. No, since the case was prepared by Miss Giesser.

Q. You testified, I believe, on redirect with respect to the experience Ms. Giesser had in obtaining data with respect to patent disclosures from other departments within Sandoz. Is that correct?

A. I said -- what I did say is that in all probability, since she was fairly new in the department, she did not have that experience. The basis for that is that most of the work that she did was nonpharmaceutical work. She was handling our seeds work and some agro, as well as some biotech work. She did not, other than the HMG-CoA reductase area, in which she just spent a small amount of her time, she did not spend very much in pharmaceuticals.

Q. But nonetheless, she was charged with responsibility in that field?

A. In these cases.

Q. How difficult is it to request the data in question?

A. Phone call.

Kassenoff - recross

Q. You worked with Ms. Giesser for a period of about two years, three years, is that correct, maybe more?

A. She was here for that period of time, yes.

Q. Did you have an opportunity to judge whether she had the ability to learn how to obtain that data in that period of time?

A. I'm sure to obtain the data didn't require any exercise.

Q. So even though she joined in August of 1987, it wouldn't have taken her too long to learn how to obtain that kind of data?

A. No, but I'm not sure, this could have been -- these probably were the first pharmaceutical cases that she was involved in.

Q. Do you know that one way or the other?

A. I don't know that as a fact but I think it's a valid assumption, since I'm not aware of any other area in which she did any pharmaceutical work.

Q. The applications that were prepared subsequent to April of 1987 in this field that were new cases that were not prepared by you would have

Kassenoff - recross

had to have been prepared by you, wouldn't they?

A. Yes, but if you look at the list, starting with April of 1987, you will see that there aren't very many actually new disclosures.

Q. But there are a few, aren't there?

A. There are a couple.

Q. And you weren't responsible for those entirely, were you?

MR. VILA: Can we go off the record a minute.

(Whereupon a discussion took place off the record.)

Q. You did not prepare all the cases that appear in this list that were filed subsequent to April of 1987. Is that correct?

A. That's correct.

Q. Do you have any knowledge of what type of input was provided to change the rating on PD 299/84 first from "B" to -- I'm sorry -- yes, first from "B" to "X"?

A. I don't know if there was any written input. It probably was oral input at the Patent Committee meeting.

Q. Do you have any knowledge as to what

Kassenoff - recross

that input was?

A. No. I did not attend the meeting at that time.

Q. Do you have any knowledge as to what caused the Patent Committee to change the rating from "X" to "A"?

A. No, I have no specific knowledge of that.

MR. KELBER: I have nothing further at this time.

MR. VILA: Let me clarify the question that was asked. I believe the question was addressed as to Jody Giesser's responsibilities subsequent to April of '87 in this area. Again, when did Miss Giesser join this department?

THE WITNESS: Later in '87, I think. Was it August? Sometime in August. I think it was August of '87.

MR. VILA: So your answer to that question only could have been with reference to the time she actually joined the department, which was later in 1987?

THE WITNESS: That's correct.

MR. KELBER: When Miss Giesser joined

Kassenoff - recross

in August of '87, were the patent disclosures rated "A" waiting to be prepared, assigned to her?

THE WITNESS: I really do not know.

MR. KELBER: Okay.

MS. FURMAN: I have nothing.

MR. KELBER: Thank you, Mr. Kassenoff. I appreciate it. Before we go off the record, we need each of the depositions to be taken today to be prepared in separate transcripts, according to the rules. Don't ask me why. There are lots of rules recited in the CFR about how they have to be prepared and filed.

MS. FURMAN: They are aware of them.

MR. KELBER: Did you take care of it?

MS. FURMAN: Yes.

MR. KELBER: Okay, thank you.

(Time noted is 11:45 a.m.)

MELVYN M. KASSENOFF

Subscribed and Sworn to before me
This day of , 1993

A Notary Public

C E R T I F I C A T E

I, GARY M. TALPINS, a Notary Public and Certified Shorthand Reporter of the State of New Jersey, do hereby certify that prior to the commencement of the examination, MELVYN M. KASSENOFF was duly sworn by me to testify the truth, the whole truth and nothing but the truth.

I DO FURTHER CERTIFY that the foregoing is a true and accurate transcript of the testimony as taken stenographically by and before me at the time, place and on the date hereinbefore set forth, to the best of my ability.

I DO FURTHER CERTIFY that I am neither a relative nor employee nor attorney nor agent of any of the parties to this action, and that I am neither a relative nor employee of such attorney or counsel, and that I am not interested directly or indirectly in the interference either as counsel, attorney, agent or otherwise.

Gary M. Talpins, C.S.R.
License No. XI00561

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
INTERFERENCE NOS. 102,648
102,975

WATTANASIN,

vs.

FUJIKAWA, et al.

DEPOSITION OF:
LINDA ROTHWELL

Monday, March 22, 1993
Florham Park, New Jersey

A P P E A R A N C E S:

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-and-
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I N D E X

E X H I B I T S

(Before Gary M. Talpins, a Certified Shorthand Reporter and Notary Public of the State of New Jersey, held at the offices of Sandoz Corporation, Patent and Trademark Affairs Department, 25 Hanover Road, Florham Park, New Jersey, on Monday, March 22, 1993, commencing at 2:35 p.m.)

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L I N D A R O T H W E L L, 2 Rambling Woods Drive, Morris Township, New Jersey 07960, Sworn.

CROSS EXAMINATION BY MR. KELBER:

Q. Good afternoon, Linda.

A. Hello.

Q. I'm going to have the reporter mark as an Exhibit F-9, a document, and after he marks it and hands it to you, if you would review it briefly.

(Whereupon the document was received and marked F-9 for identification.)

A. Okay.

Q. Is that your signature on page four?

A. Yes, it is.

Rothwell - cross

Q. And did you review this document prior to signing it?

A. Yes.

Q. Miss Rothwell, are you a patent attorney or agent?

A. No, administrator.

Q. If you would turn to page one of that document, F-9, you describe a couple of the responsibilities you have as patent administrator. I would like to focus on the one described in paragraph three, the responsibility to docket patent disclosures. Can you elaborate on that? What is involved in docketing the patent disclosures?

A. Once it's been rated, if it's been rated "A", then it's docketed for three weeks for filing and that's what the docketing procedure is. They get little blue cards.

Q. And after you have docketed it for three weeks, do you have follow-up responsibility?

A. Yes.

Q. Can you describe that?

A. I just go in and check with the attorney.

#91

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

WATTANASIN	:	
	:	INTERFERENCE NOS.:
V.	:	102,618 AND 102,975
	:	EXAMINER-IN-CHIEF
FUJIKAWA ET AL	:	MICHAEL SOFOCLEOUS

THE RECORD FOR THE PARTY FUJIKAWA ET AL

VOLUME II
(Pages 100-199)

Steven B. Kelber
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Rothwell - cross

Q. And if the application has not been prepared, what happens? Let's suppose, I will give you a hypothetical, you docket it for three weeks and do you go in and discuss with the attorney, and the application hasn't been prepared for lack of sufficient information from the inventor, is any further date set for docketing review?

A. No. I would just move it maybe another three weeks or two weeks, if he knows when he is going to get more information.

Q. If he doesn't have any idea when he is going to get more information, is a further date set?

A. No, I would just go back in a couple of weeks.

Q. And do you keep on checking until --

A. Yes.

Q. Do you keep on checking until the application is filed?

A. Yes.

Q. At paragraph four on page one of F-9, you make reference to 299/84. Did you have responsibility for docketing that disclosure for filing after it had been rated "A"?

Rothwell - cross

A. I believe so, yes.

Q. Do you recall checking, as you have just described, with the attorney responsible after the first three weeks in that disclosure?

A. To the best that I can remember, yes.

Q. Do you know who that attorney was?

A. I think at the time, it was Fred Weinfeldt, unless it had already been turned over.

Q. Do you recall checking with any other attorney besides Mr. Weinfeldt with regard to 299/84?

A. It would have to be whoever took over the disclosure.

Q. You don't have a recollection as to who that was?

A. No.

Q. Is there anybody else in the Sandoz Patent Department with responsibility for docketing applications for filing?

A. No.

Q. Just yourself. You mentioned a three week date. Is that generally given all applications?

A. Just if it's rated "A" at the meeting.

Rothwell - cross

Q. I see. So in the course of performing those responsibilities with regard to docketing, have you developed an approximation of on average how long it takes from the time a disclosure is rated "A" to the time an application is filed? Do you have a feeling for that?

A. Not really because some of them are filed quick and others take a little longer for one reason or another.

Q. Would a year be an unusually long time?

A. Yes.

Q. If you are familiar with the procedure, when a disclosure is rated "B" and supplemental information is provided, is it provided to you?

A. No. I would just automatically bring it up at the next meeting.

MR. KELBER: Thank you very much. I appreciate it. I have no further questions. Diane?

MS. FURMAN: I have no questions.

REDIRECT EXAMINATION BY MR. VILA:

Q. You were asked a question with regard to essentially the average time that it would take to file a patent application from the time of an

Rothwell - redirect

"A" rating to disclosure. Would that vary in pattern as you might recognize it among different attorneys in the department?

A. Yes.

Q. With regard to Mr. Kassenoff, would you say that he filed in the average time slower than average, faster than average?

A. Some he would do real quick and others, he would just get held up by some of the inventors.

Q. Were there other reasons for him to be --

A. Not that I would know of.

Q. But in some cases, it would be a longer than average time?

A. Yes.

Q. With regard to Jody Giesser, concerning pharmaceutical patent applications that had been assigned to her, would you have ever had an opportunity to form a judgment there?

A. No.

MR. VILA: Thank you very much.

THE WITNESS: Okay, thank you.

(Time noted is 2:45 p.m.)

LINDA ROTHWELL

Subscribed and Sworn to before me
This day of , 1993

A Notary Public

C E R T I F I C A T E

I, GARY M. TALPINS, a Notary Public and Certified Shorthand Reporter of the State of New Jersey, do hereby certify that prior to the commencement of the examination, LINDA ROTHWELL was duly sworn by me to testify the truth, the whole truth and nothing but the truth.

I DO FURTHER CERTIFY that the foregoing is a true and accurate transcript of the testimony as taken stenographically by and before me at the time, place and on the date hereinbefore set forth, to the best of my ability.

I DO FURTHER CERTIFY that I am neither a relative nor employee nor attorney nor agent of any of the parties to this action, and that I am neither a relative nor employee of such attorney or counsel, and that I am not interested directly or indirectly in the interference either as counsel, attorney, agent or otherwise.

Gary M. Talpins, C.S.R.
License No. XI00561

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
INTERFERENCE NOS. 102,648
102,975

WATTANASIN, :
:
vs. : DEPOSITION OF:
: SOMPONG WATTANASIN
FUJIKAWA, et al. :
:
---------- :

Monday, March 22, 1993
Florham Park, New Jersey

A P P E A R A N C E S:

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I N D E X

E X H I B I T S

(Before Gary M. Talpins, a Certified Shorthand Reporter and Notary Public of the State of New Jersey, held at the offices of Sandoz Corporation, Patent and Trademark Affairs Department, 25 Hanover Road, Florham Park, New Jersey, on Monday, March 22, 1993, commencing at 11:55 a.m.)

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S O M P O N G W A T T A N A S I N, 11 DiVito Trail, Hopatcong, New Jersey, Sworn.

MR. VILA: Dr. Wattanasin, speak up so everyone here can hear you.

CROSS EXAMINATION BY MR. KELBER:

Q. Doctor, I'm going to hand you a multi-paged document which you can feel free to disassemble as necessary.

MR. KELBER: I would ask the reporter first to mark it as Exhibit F-4, I believe.

(Whereupon the document was received and marked F-4 for identification.)

Q. If you would take a moment to review

Wattanasin - cross

the document.

Q. Dr. Wattanasin, do you recognize the document that has been identified as Exhibit F-4?

A. That's something that I have to check because I don't think I remember all of the numbers and so on.

Q. Do you recall seeing a document like this?

A. Oh, yes, definitely, yes.

Q. And can you identify it for me?

MS. FURMAN: By subject matter.

Q. Dr. Wattanasin, is this a patent application prepared by Sandoz?

A. Yes.

Q. And to your recollection, does it name you as an inventor?

A. Yes.

Q. Would you turn to page 54 of F-4.

A. Okay.

Q. Do you see the rather lengthy written passage numbered one there? It continues on to the next page of the document.

A. Yes.

Q. And do you see that that passage, which

Wattanasin - cross

begins with the number one, describes a certain genus of compounds?

A. Yes.

Q. Doctor, when did you first learn that another company had filed for United States patent protection on compounds similar to those set forth in the passage numbered one?

A. From my recollection, I think I saw a patent maybe at the end of '88 from I think Warner-Lambert.

Q. Did you receive an initial draft of the document that's been identified as F-4 prior to its completion in the form it's been presented to you?

A. I believe so.

Q. Do you recall if you became aware of the patent, I believe you identified it as Warner-Lambert patent before you received that draft copy of the application?

A. I don't think so.

Q. Do you recall who first brought the Warner-Lambert patent to your attention?

A. I think my supervisor, I believe so, because we have review, you know, it's a routine process in the department that we review the patent

Wattanasin - cross

applications not only from Warner-Lambert, from other companies that work on HMG-CoA reductase inhibitor at that time.

Q. Do you know whose responsibility it was to secure those patents of other companies?

A. As I say, it's routine practice in our department to circulate abstracts.

Q. Did you draw the existence of the Warner-Lambert patent, did you draw the attention of anybody in the Patent Department at Sandoz to the fact that the Warner-Lambert patent had issued?

A. I may or may not have called someone in the Patent Department saying that okay, this is the patent from Warner-Lambert similar to our case. From a scientific point, I really have no interest in the Warner-Lambert patent.

Q. Do you have any recollection as to what attorney in the Patent Department of Sandoz prepared --

A. At that time, maybe Jody Giesser, I believe, Jody Giesser.

Q. Do you recall at all discussing the Warner-Lambert patent with her?

A. I believe probably just mentioned that

Wattanasin - cross

this is the patent from Warner-Lambert, that's all.

Q. Doctor, I'm going to hand you an exhibit that I would like identified as F-5. It's paper number two from the file, the request for declaration of interference.

(Whereupon the document was received and marked F-5 for identification.)

Q. If you would take just a minute to look at that, doctor.

MR. VILA: Pardon me, can we go off the record.

(Whereupon a discussion took place off the record.)

Q. Doctor, I obtained the document that's been identified as F-5 from the records of the United States Patent and Trademark Office in an application 318773, which identifies you as an inventor, and my question to you is do you recall seeing F-5 prior to this day?

A. I don't think so.

Q. You never saw it prior to today, to the best of your recollection?

A. Yes.

Wattanasin - cross

Q. Do you recall, doctor, at any time discussing the need to bring the Warner-Lambert patent to the attention of the United States Patent and Trademark Office in connection with your application?

A. Yes, I did discuss it sometime, yes, at some point.

Q. Do you recall whether that discussion was before or after the application was filed?

A. Which application?

Q. The original application that is embodied in Exhibit F-4.

A. I did not recall.

Q. Could you take a look at page one of F-5, doctor, the very first page. Do you see the date stamp circle at the very top of the left-hand corner of that page?

A. Yes.

Q. What is that? Can you make out the date that's in there, doctor?

A. March 3, 1989?

Q. Doctor, do you have any knowledge as to whether any patent application besides the application involved in this interference naming

Wattanasin - cross

you as an inventor has ever been involved in an interference in the United States Patent and Trademark Office?

A. Yes.

Q. Would that other application and other interference have occurred prior to the interference that you are testifying in today?

A. Excuse me? I didn't quite understand.

MS. FURMAN: Off the record.

(Whereupon a discussion took place off the record.)

Q. Doctor, has any application for patent been filed by Sandoz Corporation naming you as an inventor other than the application involved in today's interference of --

A. Yes.

Q. Any of those other applications filed naming you as an inventor by Sandoz, of those aplications, to the best of your knowledge, has any been involved in an interference before the United States Patent and Trademark Office?

A. No, I don't think so.

Q. Do you have any recollection of discussing with Ms. Giesser the need for an

Wattanasin - cross

interference in connection with the application involved in today's proceeding prior to its actual filing?

A. Maybe. I cannot say for sure. Maybe, yes, because -- yes.

Q. It's the only interference you have ever been involved in. Is that correct?

A. Yes.

Q. Are you familiar with the nature of an interference, what an interference is?

A. I'm not fully familiar with the legal process.

Q. Did you ever discuss with Ms. Giesser the need to establish a date of invention prior to the Warner-Lambert patent filing date?

A. Yes, I think so.

Q. Do you recall whether that discussion was prior to March 3, 1989?

A. That I don't recall.

Q. Would you flip back to page 54 of F-4, doctor. Do you see the third text line, the second line after the initial formula on that page, where it says, "C3-7cycloalkyl or"? Do you see that line?

Wattanasin - cross

A. C3 --

Q. I'm sorry, counting from the Arabic numeral one on page 54, the third line of text.

A. Okay.

Q. Do you see the recitation C3-7?

A. Yes.

Q. Do you recall having an understanding of what you meant by C3-7 at the time this application was originally filed?

A. I believe so, yes.

Q. What was that understanding, doctor?

A. What understanding, can be anything, anything that contains cyclics, having carbon 3 to carbon 7 in it.

Q. That would be five compounds, actually, wouldn't it, doctor, independent of substitutions, that would be five?

A. Yes.

Q. Can you name those compounds for me, what five basic compounds are encompassed by that group C3 to C7 cycloalkyl?

A. The name?

Q. The name of the compound.

A. It should be cyclopropane, cyclobutane,

cyclopentane, cyclohexane and cycloheptane.

Q. Thank you, doctor. Do you have any knowledge as to the level of skill that an initial, an entry category researcher would have in the field of HMG-CoA reductase, what kind, in general, of educational level would be required of such a researcher? By that I mean -- go ahead.

A. I would say it depends on -- I would say at least a Bachelor's degree.

Q. In chemistry?

A. In chemistry, yes.

Q. Would such an individual understand that C3, in your opinion, that C3-C7cycloalkyl included those five basic compounds?

A. Yes.

Q. Thank you, doctor. Doctor, I'm going to hand you a declaration--sorry, a paper that I would like identified as F-6 and ask you to review that. This one is of record in volume four.

(Whereupon the document was received and marked F-6 for identification.)

MR. VILA: What record page number is that?

MS. FURMAN: Which is it?

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MR. KELBER: Here is my copy.

MS. FURMAN: His declaration.

MR. KELBER: I prefer we not identify what the document is until the witness has a chance to identify it.

MS. FURMAN: Fine.

Q. Doctor, do you recognize this document that's been marked F-6?

A. Yes.

Q. Can you recall the first circumstances under which you saw this document?

A. This is the application that had been filed.

Q. In fact, this document was prepared in connection with this interference, wasn't it, doctor?

A. Yes.

Q. I should say interferences. By interference, I mean Interference 102,648 and 102,975.

A. Right.

Q. Doctor, how many applications, if you know, have been filed by Sandoz naming you as an inventor or co-inventor directed to the field of

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HMG-CoA reductase?

A. At least three including the quinoline case.

Q. Let me turn your attention, doctor, to paragraph seven, page two of Exhibit F-6. Why did you submit patent disclosure 299/84 in late March of 1987?

A. Because I believe that at that time, we felt that we should be able to complete most of the key compounds involved in the quinoline cases.

Q. I'm sorry, doctor, I didn't catch your full response. You thought that you could --

A. At that time, we felt that we should be able to finish making most of the key compounds involved in this case.

Q. In general, why do you file a patent disclosure, submit a patent disclosure to the Patent Department? What criteria do you use to determine when to file a patent disclosure?

A. When we feel that we have a class of compound that we can use --

Q. I'm sorry, if you could continue the answer. When you feel you have a class of compounds that can be used?

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A. For this particular objective in our department to find inhibitor of HMG-CoA reductase.

Q. Does that represent a determination by you that these compounds are new?

A. Yes.

Q. Does it represent a determination to you that these compounds may be valuable to the corporation?

A. Yes, that's right.

Q. Did any event subsequent to March of 1987 indicate to you that your decision that the compounds identified in 299/84 were not either new or valuable to Sandoz Corporation?

A. I don't think so.

Q. Let me turn your direction to paragraph eight, doctor. Do you know why during the period April through November of 1987, the Sandoz disclosures were rated, let's take the rating "B" first -- not the Sandoz disclosure, your disclosure, PD 299/84, was rated "B" by the Patent Committee?

A. I'm not in the Patent Committee but I understand it bears on the factor that further information on this case would be needed before the

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application can be filed so more work needs to be done, I think that's the bottom line.

Q. Did you receive notification that the disclosure had been rated "B"?

A. This is by oral, by verbally.

Q. But you did receive that notification?

A. Yes.

Q. What type of extra work needed to be done?

A. Basically, we have to complete the whole set of compounds that need to be prepared.

Q. And why was that, doctor, why did you have to complete the whole set?

A. I think the objective of making, working on any class of compound is to insure that we come up with an optimum structure. In this particular case, we just making only partially part of the set, we are not complete the whole set yet.

Q. Did you expect to find in the set, part of the set that had not been completed a difference, qualitative difference in the compounds in terms of their value to Sandoz Corporation? In other words, you had completed some of the compounds but not all of the compounds of the set.

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A. True.

Q. Did you have a personal expectation as to the activity you anticipated from the rest of the compounds?

A. Yes.

Q. And what was that expectation, doctor?

A. My expectation is I expect that I may come up with some compounds that show better activity.

Q. Did you expect that some of the compounds in the set to be completed might have worse activity?

A. Yes, that can be the case.

Q. Did, in fact, you come up with compounds subsequent to March of 1987 that had better activity than the compounds identified in the disclosure?

A. Yes. That's normal.

Q. Did you come up with compounds that were worse?

A. Oh, yes, I come up with a compound worse and compound better.

Q. Let's turn now to the "X" rating. When you received notification that your disclosure has

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been rated "X", what does that mean to you, what does "X" indicate?

A. I think it indicates the same thing to me. I mean as I say, I'm not the one who made this thing but it indicates the same thing, more information will be needed to complete, to complete the whole application process of this case.

Q. Was the information needed in response to an "X" rating different, in your opinion, than the information needed for a "B" rating?

A. No, I don't think so.

Q. Do you see the reference in paragraph nine to additional synthesis and testing between July and December of 1987?

A. Yes.

Q. Was that additional synthesis and testing done responsive to the "B" or "X" rating that your disclosure received?

A. No.

Q. You would have done that, anyway?

A. I would have done that, anyway, yes.

Q. Thank you, doctor. If the disclosure had been rated "A", would you have continued that testing that's referred to in paragraph nine?

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A. Yes, I believe so.

Q. Thank you, doctor. In the other applications naming you as an inventor completed by or on behalf of Sandoz Corporation, do you have a recollection as to how long it took between the time you learned that the disclosure had been rated "A" and the time you received the first draft of that application? Do you have any idea?

A. No, I cannot give you that honestly.

Q. Can you tell me was it more than six months?

A. I would say about six months, yes.

Q. About six months?

A. About six months.

Q. Do you know does Sandoz have a written policy regarding responding to questions from the Patent Department for additional information?

A. Yes.

Q. It does have a written policy?

A. Yes, policy as to you have to comply with requests from the Patent Department.

Q. There is such a written policy, you think?

A. I think so, yes.

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Q. If there is such a policy, can you send us a copy to the extent it's not privileged?

THE WITNESS: I --

Q. That's okay, they will get a chance to ask you all about it in not too long a period of time.

Do you have an appreciation based on the experiences of other researchers at Sandoz as to the time it takes for the preparation of a draft application from the time a disclosure is rated "A"? Do you have a general idea?

A. No, no idea.

Q. Let me turn your attention to paragraph 11 on page three of F-6, doctor. Why did you send certain information to Melvyn Kassenoff about February 29 of 1988?

A. I believe that I was requested by Mr. Kassenoff for subsequent information.

Q. You already knew that your disclosure had been rated "A". Is that correct?

A. At that time, yes.

Q. Was it your understanding that the material you sent to Mr. Kassenoff was required or requested -- I'm sorry, requested for the purposes

of preparing that application?

A. Yes.

Q. Did you have occasion, do you recall, to speak with anybody in the Patent Department between February 29 of 1988 and the end of May 1988 regarding the patent application to be prepared on your disclosure?

A. Yes, I think so.

Q. Do you recall who you spoke with?

A. Either Mel Kassenoff or Jody Giesser.

Q. Do you recall the substance of those discussions?

A. Mostly related to specific information as far as the compound, you know, included in the patent.

Q. Did you at any time ask when you might expect a patent application to be prepared?

A. I don't think so.

Q. Let me turn your attention to paragraph 12, pages three and four of F-6. Why did you send that information to the Patent Department?

A. Again, I was requested from the Patent Department for some information.

Q. Do you recall when you sent that

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information?

A. I don't recall when I received the actual copy of the thing I sent to the Patent Department. Generally I would know what date I sent it on the copy.

MS. FURMAN: Could you repeat your last sentence, please.

THE WITNESS: In general, I don't exactly remember the date that I sent any material to anyone but in general, before I send something to someone, I would note the page, I would date the page.

MS. FURMAN: You would date the page.

Q. Let's take them one at a time. I'm going to hand the reporter a document I would like identified as F-7. I will ask you to review that document briefly, doctor.

(Whereupon the document was received and marked F-7 for identification.)

Q. Doctor, does your review of P-2 enable you to determine in any way about when you might have sent that material to the Patent Department?

A. I can tell you that this is after February 29, 1988.

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Q. Do you know would it have been before May of 1988?

A. No.

Q. Did you send it in response to a request from the Patent Department?

A. Yes.

Q. Do you recall who the request came from?

A. I think this is from Mel Kassenoff.

Q. Let me hand you a document, P-3, for identification as Exhibit F-8.

(Whereupon the document was received and marked F-8 for identification.)

Q. Does F-8 contain documents that were sent to the Patent Department as described in paragraph 12 of your declaration?

A. Yes, I think so, yes.

Q. Does review of that document enable you in any way to fix the time you sent those documents to the Patent Department?

A. No.

Q. But you know they were before February of 1988 -- I'm sorry, after February of 1988?

A. After, yes, definitely, yes.

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Q. And you know you sent them in response to a request by Mr. Kassenoff?

A. Yes.

Q. After submission of those documents, but prior to November of 1988, do you recall having any further written or oral communications with the attorneys in the Patent Department at Sandoz regarding your disclosure 299/84?

A. Yes, I think so, yes.

Q. Do you have an actual recollection of it?

A. No, I don't have actual recollection.

Q. Do you have an actual recollection of anything that might have been said or written at that time?

A. Mostly anything that related to the draft or something on it, I see something where they have seen some question that needs to be clarified, I think in general.

Q. But you did not see a draft until November of 1988. Isn't that correct?

A. Yes.

Q. In fact, you didn't see the draft until December of 1988. Is that correct, doctor?

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A. Yes.

Q. Isn't it correct, doctor, that you didn't receive the draft declaration until after you had learned of the existence of a Warner-Lambert patent?

MR. VILA: The declaration?

MR. KELBER: I'm sorry.

Q. Isn't it correct, doctor, that you had received the draft memorandum of your patent application after you had learned of the existence of the Warner-Lambert patent?

A. Let me check the date again. That may be the case, yes.

Q. Do you recall exchanging in writing any communications with Ms. Giesser concerning the Warner-Lambert patent?

A. In writing, no, I don't think so.

Q. Anybody else at the Patent Department, did you exchange correspondence concerning the Warner-Lambert patent?

A. No.

Q. Do you recall publishing the subject matter at item one of page 54-55 of your application, the document that's been marked F-4,

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prior to March of 1989?

A. I don't think so.

Q. You had completed the initial set of compounds back in March of 1987. Is that correct?

A. Can you repeat that again?

Q. You had completed the initial set of compounds to which PD 299/84 and subsequently, your application document F-4, pertained, you had completed that initial set of compounds by March of 1987. Is that correct?

A. By March, yes.

Q. And you didn't publish information regarding those compounds until after March of 1989. Is that correct?

A. Yes.

Q. Compounds were interesting to you?

A. Compounds were interesting to me, of course, yes.

Q. Do you think the compounds would have been interesting to other researchers in the field?

A. Of course.

Q. Was there any reason for not publishing that information until after March of 1989?

A. There is no particular reason, I don't

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think so.

Q. When did you become aware that Nissan Chemical Corporation had filed for U.S. patent protection on compounds similar to those identified at item one of page 54 of your application?

A. I don't remember the date exactly but I think it happened after we already, you know, talking about a patent application of this case.

Q. So after the application was filed or before?

A. I don't recall the date. I cannot give you the definite time.

Q. Do you recall having discussed the existence of the Nissan Chemical Company's request for patent protection with Ms. Giesser?

A. Yes.

Q. Subsequent to the classification of your disclosure as "A" in January of 1988, did you at any time express any concern to anyone about the progress made in preparing the application corresponding to that disclosure?

A. No, I don't think so.

Q. In your experience at Sandoz Corporation, the period of January of 1988 till

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March of 1989, is it customary to take that 14 months for preparation of the patent application?

A. That is unusual. That is unusual.

Q. During that time period, were any other applications naming you as an inventor or coinventor filed by Sandoz Corporation, January of '88 through March of 1989? Do you recall were any other applications naming you as an inventor or co-inventor filed?

A. There are a couple -- I would say there are two other patents involving HMG-CoA reductase inhibitor but I don't recall the exact date.

Q. Have those, either of those patent applications been issued as a U.S. patent?

A. Yes.

Q. Do you know the number offhand?

A. We are in one of four.

MR. KASSENOFF: Off the record.

(Whereupon a discussion took place off the record.)

Q. I want to return just to one subject and that's the question of the information needed in response to a "B" or "X" classification by the Patent Committee. We talked about the need to

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provide more information in response to a "B" classification. What specific type of information is necessary? The synthesis of the compounds, is that required?

A. I think at this time, let me say when you set up on any class of compound, you want to make a few of the compound to find optimum structure and I think at that point in time, we know we are not complete the whole set of compound yet and I think until then, I think we still need further information.

Q. So synthesis and testing of the compound would be required?

A. Synthesis and testing of the compound.

Q. Any of the compounds that are identified in the original disclosure, PD 299/84, did any of those compounds show the type of activity that suggested they might have utility as HMG-CoA reductase inhibitors?

A. Certainly.

Q. Did anything occur between March of 1987 and March of 1989 that suggested that that might not be true, they did not have sufficient activity?

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A. No, I don't think so.

MR. KELBER: Doctor, I really appreciate your patience with me in being here this morning. I have no more questions at this time.

THE WITNESS: Thank you.

MR. VILA: Do you want to take lunch break?

MR. KASSENOFF: Let me ask one question on redirect.

MR. KELBER: I have no objection -- I have discomfort with a witness crossing.

MR. VILA: We will take that question up later.

MR. KELBER: Okay.

MR. VILA: It's a matter of clarifying some things.

MR. KELBER: My only concern is keeping the good doctor longer than we need to. If you have got a lot --

MR. VILA: He is invited to lunch.

MR. KELBER: I kind of hoped you would feed him.

(Whereupon the luncheon recess was taken.)

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REDIRECT EXAMINATION BY MS. FURMAN:

Q. Dr. Wattanasin, referring to your testimony concerning the C3 to C7 cycloalkyl substituents on the quinoline ring, you testified that that would include, among others, cyclopropyl and you testified that a person of skill in the art would recognize it to include cyclopropyl. Do you think that a person of skill in the art would regard cyclopropyl as being obvious as that structure being obvious in view of isopropyl?

MR. KELBER: Objection. I don't know that the witness -- I don't know how you are using the term "obvious" but I don't know that the witness has demonstrated a knowledge under the 103 sense, if you could rephrase it.

Q. Dr. Wattanasin, do you understand what the term "obvious" means under the patent law or can you give me your definition of the term "obvious"?

A. The obvious, in my term, in the medicinal chemistry term, is a kind of, what do you call it, kind of group that you like to make to cover your hypothesis.

Q. Do you think that someone knowing about

an isopropyl substituted compound, based on that information alone, would be led to prepare a cyclopropyl compound?

A. That's what I mean by obvious because in medicinal chemistry, cyclopropyl would be an obvious analogue of cyclopropyl group. If you look at some of the --

Q. Excuse me, I didn't understand you. Cyclopropyl would what?

A. Cyclopropyl, cyclopropane group would be obvious analogue of cyclopropyl group. Do you understand the word analogue?

Q. Yes. If someone in your lab knew about an isopropyl compound, do you think based on that information, they would be led to prepare a cyclopropyl compound?

MR. KELBER: Objection. You are now asking his opinion as to what others in the laboratory would do.

Q. Would you be led to prepare a cyclopropyl compound?

A. Yes, definitely.

Q. Why would you be led to prepare a cyclopropyl compound?

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A. Because of the, this is according to scientific, basically, when you put the group on any structure, you are looking for two things, two things you are looking for, two properties of that group, sterically and electronically and in this case, cyclopropyl, and cyclopropyl are very similar.

Q. I am talking about cyclopropyl versus isopropyl. Is cyclopropyl similar in chemistry to isopropyl sterically?

A. What I'm saying is sterically and electronically, cyclopropyl group would be very similar to isopropyl group and not only that, you can see from the scheme of the chemistry, chemistry scheme, we have the hardware that can make both compounds quite easily.

MS. FURMAN: I would like to put into evidence as W-2 the declarations that were submitted in this interference of Mr. Kitahara.

MR. KELBER: I will wait until your question but I would object to the extent they would go to anything in the nature of direct questioning.

Q. Dr. Wattanasin, do you recognize the

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structure on page two of the Kitahara declaration?

A. Yes, I do.

Q. What is that structure?

A. This is the structure of isoquinoline derivative.

Q. The R-5 substituent, what is the R-5 substituent?

A. In this case, R-5 can be cyclopropyl or isobutyl.

Q. Going to the test on that declaration, which compares the activity of cyclopropyl with the isopropyl compound, what is your opinion of this activity information?

MR. KELBER: Before you answer, doctor, I'm going to object to that on the grounds that this is in the nature of direct testimony and if you had wanted to submit it, it should have been submitted together with the remainder of your direct testimony. As far as I'm aware, this is our cross on direct and you have not requested rebuttal response or the opportunity to cross our own declarant. I can't stop you from asking your questions but I do definitely object to further questions on this issue.

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MR. VILA: Can I conference with you outside?

MS. FURMAN: Yes.

(Whereupon a brief recess was taken.)

MS. FURMAN: I will go on to a different line of questioning.

BY MS. FURMAN:

Q. Dr. Wattanasin, the patent disclosure on your quinoline compound is numbered 299/84. Do you know how this number was assigned to your patent disclosure?

A. I think this number was assigned on an annual basis, I believe. Before the end of the year, one of the secretaries here send you the patent disclosure form for the next year.

Q. A blank patent disclosure --

A. A blank patent disclosure.

Q. With the number appearing at the top?

A. Yes.

Q. And that was sent to you when?

A. Around the end of the year, in December.

Q. In December of --

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A. Of '83.

Q. Of '83. You synthesized at least one compound by the end of 1984. Is that correct?

A. Yes.

MR. KELBER: Just for clarification, we are talking about the compounds of the disclosure or compounds in general or what?

THE WITNESS: The first compound we are making, one of the first compounds we are making in this case.

Q. After that compound was synthesized, what additional work was done in relation to your quinoline patent disclosure? After the synthesis of 63366, what compounds did you synthesize?

A. There are a number of compounds we synthesized during that period. At that time, we were still working on basically all of them. All of them are HMG-CoA reductase inhibitors and two more compounds, two more compounds were synthesized, the number I believe is 64548 and 64549.

MS. FURMAN: I would like to put into evidence as Exhibit W-3 pages --

MR. KELBER: We started to talk about

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W-2 but we never did get around to marking it. Do you want to have W-2 in or do you want to just mark those as W-2?

MS. FURMAN: Yes, let's put W-2 in.

(Whereupon the document was received and marked W-2 for identification.)

MS. FURMAN: I would like to put into the record as W-3 pages 164 through 166 of the Wattanasin testimony.

(Whereupon the document was received and marked W-3 for identification.)

Q. Dr. Wattanasin, do you recognize those pages?

A. Yes, I do.

Q. Can you describe them?

A. This is reaction, this is a notebook, from my notebook, the synthesis of one of the compounds that later on is designated as 64548.

Q. And what is the date at the top of the page?

A. 5/7/85.

Q. What would the date at the top of the page signify?

A. This is the date that I start doing

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this particular reaction that leads to the synthesis of this particular compound 64548.

Q. So you had synthesized 64548 sometime on or after May 7, 1988?

A. Yes.

Q. Is there an additional compound that you synthesized around that time?

A. The next compound we synthesized is the compound 64549.

Q. Was that also synthesized --

A. Around this date.

Q. Around May of 1985?

A. '85, yes.

Q. Your patent disclosure, which is numbered 299/84, when was that submitted to the Patent Committee by you?

A. I think by March, in March '88.

Q. March of --

A. March of 1988.

Q. Submitted to the Patent --

A. I'm sorry, March of 1987.

Q. What made you submit the patent disclosure in March of '87? Why did you not submit the patent disclosure after you made 64548 or 49?

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A. I think the reason for that is because of we are not complete the whole set of this class of compound yet.

Q. Why had you not completed the whole set?

A. The reason is because, I think one of the key reasons is because of a lack of manpower at that time because I'm the only one working at that time on the HMG-CoA reductase in this lab.

Q. Your lab was the only lab synthesizing quinoline compounds?

A. Yes.

Q. When did you realize you lacked manpower to proceed with the whole series?

A. Actually, at that time, actually 1985 because we are dealing with different classes of HMG-CoA reductase inhibitor compound, quinoline is not the only compound we are making. We are making other, different kind of heterocyclics, as well.

MR. KELBER: I don't know that it raises to the level of an objection, Diane, but to what part of the cross does this line of questioning go to?

MS. FURMAN: I believe you did ask him

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about his activities in that time period.

MR. KELBER: I asked him if anything occurred with regard to the period between the submission and the "A" rating, I asked him if anything occurred to change his mind.

MS. FURMAN: You were discussing the initial set of compounds, you asked whether they were completed by March of 1987 and I was trying to develop that testimony.

MR. KELBER: Okay.

Q. When did you realize there was a manpower shortage?

A. I think around this time, I think sometime in 1985.

Q. How long did it take you to find somebody to fill that position or positions?

A. Normally to get someone, you have got to have approval from your boss and then subsequently, you have got to get approval by your department head and then it also depends on whether or not the opening is available at that time and when you got the actual head count, the opening, then you have got to get approval from your boss, from your department head and then from the head

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of -- from the president of SRI. And then you have to recruit the person. It takes a long time, actually.

Q. How long did it take?

A. You have an opening, after you have an opening, then you have to place an ad and looking for someone, I would say at least six months.

MR. KELBER: I'm going to object because I'm not sure but I don't think the answer was responsive to the question. I think the answer was general and you had a very specific question.

Q. Can you answer the question more specifically. How long did it take you in this case to find somebody?

A. In this case, a whole year.

Q. When did you ultimately find somebody?

A. I got someone to join my lab in January 1987.

Q. What was the name of that person?

A. Miss Patel.

Q. Can you spell out the full name?

A. Rajeshvari Patel, R-a-j-e-s-h-v-a-r-i P-a-t-e-l.

Q. Was she assigned to your lab exclusively?

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A. Yes.

Q. Did you supervise her work?

A. Yes.

MS. FURMAN: Do you want to continue with questioning or do you want to leave it open?

MR. VILA: Are you finished completely or do you want to come back later?

MS. FURMAN: I'm going to come back later.

BY MR. VILA:

Q. Was there any relationship or significance to the timing of the submission of the patent disclosure to the Patent Department relative to this lack of manpower that you mentioned?

A. Yes, because --

Q. What would that be?

A. Because if I did have the manpower before 1987, some key compounds should have been synthesized before that date, before March 3, 1987.

Q. You mentioned this Miss Patel and she was hired in January of --

A. 1987.

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Q. -- '87. Do you recall what assignments she was given when she was hired?

A. There were a number of assignments given to her, key projects were given to her and this quinoline project is one of them.

Q. From the start, she --

A. From the start, yes.

Q. -- she was assigned this?

A. Yes.

Q. Having not submitted that disclosure previously, why would you have at that particular time submitted the disclosure?

MR. KELBER: I think that has been asked and answered.

THE WITNESS: Yes.

Q. You can answer it. Go ahead.

A. Because at that time, with additional manpower, I felt that we should be able to complete the whole set of this quinoline case, that's why I file the patent disclosure at that time.

Q. You had testified in response to questions on cross examination with regard to publication of the subject matter of this patent disclosure in this patent application. Would you

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have published on this subject matter prior to March of '89 when the patent application was actually filed?

A. No, I wouldn't.

Q. Why would you have not done that?

MR. KELBER: I'm going to object just to the form. Is the question did he or would he have? I don't understand the subjective tense of the question.

MR. VILA: Would he have. I believe he testified before that he could have --

MR. KELBER: If he didn't, he wouldn't. I mean I don't understand the nature of what -- is there a difference between did and would?

MR. VILA: Yes.

MR. KELBER: Are you asking for a hypothetical situation? We know what he would have done, he did it in this situation. Are you asking --

MR. VILA: Let's go off the record a second.

(Whereupon a discussion took place off the record.)

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Q. I will simply ask you did you make any publication on the subject matter of that patent application prior to its filing?

A. No.

Q. Can you explain why you did not make a publication on that subject matter?

A. If I understand, you cannot disclose the information related to the patent disclosure until it was approved by the Patent Department, until it be cleared by the Patent Department.

Q. I believe you testified on cross examination that there was a written policy or you thought there was a written policy with regard to communications with the Patent Office and in particular, responding to requests by the Patent Department.

A. Yes.

Q. Have you ever seen such a written policy?

A. What I meant in that time is this is part of what you call the job description, that you are supposed to comply with all of the requests, information related to the patent application of your discovery.

Wattanasin - redirect

BY MS. FURMAN:

Q. You testified concerning the activity of the compounds in the quinoline series. In response to questioning, you indicated that after you did the earliest work, you would have expected some compounds would come up with better activity or worse activity. Is that true?

A. I cannot predict that but it can be seen from the IC50 of one of the first compounds, I believe 63366, the IC50 of 1.5 micromolar. That, in my judgment, that is comparable to IC50 of Compactin and established HMG-CoA reductase inhibitor.

Q. And established HMG-CoA reductase inhibitor?

A. Yes.

Q. So based on the first compound you made, what was the likelihood that the later compounds would have activity in vitro as an HMG-CoA reductase inhibitor?

MR. KELBER: Objection. What later compounds?

MS. FURMAN: 64933, 934, 935 and 936.

A. I cannot predict activity of those

Wattanasin - redirect

compounds before I make them. However, based on the information, we have learned from closely related analogue of this quinoline compound, I would say that we would have very good chance of being active and as you can see from the IC50 of those compounds, again, they are comparable again to Compactin and as you know, going back to the in vivo, as you know, Compactin has a good potency, not only in vitro but also in vivo, as well. So when some of those compounds have IC50 similar to Compactin, one would predict that to have a good activity in vivo, as well.

Q. Predicted?

A. One would expect that.

Q. Expect it?

A. Yes.

Q. What level of assurance would you have? How high would be your expectation?

A. Actually, I would say it I would be very certain that the compound should have activity in vivo, as well.

BY MR. VILA:

Q. Would that statement that you just made

Wattanasin - redirect

apply to 63933, which is part of your mention on page 27 of your original declaration, results on page 27 of the record? Do you know the structure of the compound I referred to as 63933?

A. Yes, I do.

Q. Would that statement apply to that compound?

A. I'm not quite sure. That's project 933, 64933. If I recall, IC50 of 64933 is somewhat less active than the first compound I made. However, the statement would apply to the later compound, the number is 64935, which we have better IC50 and also have very good potency based on ED50 based on in vivo testing.

Q. We know the IC50's now, I think we are going back to the point when you prepared these compounds and before they were tested, you said that you would have a very high degree of confidence that they would exhibit activity. We don't know the level of the activity.

A. Yes.

Q. Would that high degree of confidence apply to 63933?

A. Yes, I think so.

Wattanasin - redirect

Q. And the compound -- I'm sorry, is that --

A. 64933.

Q. I'm sorry, I beg your pardon, correct the record, I'm referring to 64933, correct?

A. Yes.

Q. And that's a compound you know the structure of?

A. Yes.

Q. It's in the record. I would ask the same question with regard to compound 64934. Do you know the structure of that compound?

A. Yes.

Q. Would you have or not have that same degree of confidence as to the activity of that compound at the time it was prepared and before you tested it?

A. I would have the same degree of confidence.

Q. And 64935?

A. Yes.

Q. The same?

A. Same degree of confidence.

Q. In the record that I have observed

Wattanasin - redirect

here, the compound 64933 and 64934 allegedly were prepared --

A. In August, I believe.

Q. -- sometime in July or August of '89.

A. No, '87.

Q. '87, I'm sorry. Yet they were not sent for testing at that point.

MR. KELBER: Objection, assuming facts not in the record of today's deposition. The fact that you may have submitted them elsewhere doesn't make them of record here.

MS. FURMAN: Off the record.

(Whereupon a discussion took place off the record.)

BY MR. VILA:

Q. You testified those compounds were prepared sometime in August of '87 from your recollection.

A. Yes.

Q. Do you recall when they were submitted for testing?

A. I think it's in one of these exhibits. It's definitely. I do recall, yes. I believe it

Wattanasin - redirect

was submitted for testing on October 2nd, 1987.

Q. And by submitted for testing, what does that mean to you, October 2 of '87?

A. What do you mean this means to me?

Q. You say they were submitted for testing and I asked you what do you mean by submitting, what event took place on October 2, 1987?

A. On October 2, 1987, the compound was shipped to Professor Terry, T-e-r-r-y, Scallen, S-c-a-l-l-e-n.

Q. These compounds were prepared in August, as you say, and they were sent in October. Why weren't they submitted earlier? Do you have a recollection on why they were not submitted earlier to Dr. Scallen?

A. There are basically two key reasons. First of all, doing the process, the compound has to be made and the -- doing the process of the compound being synthesized and purification and characterization, I went to a meeting in New Orleans for over a week and when I came back, I was aware that the next shipment would be on October 2nd and so even though these last three compounds were made before that October 2nd, I would like all

Wattanasin - redirect

of these compounds to ship for testing together so I can have a better comparison of the potency in the same study.

Q. When you say all of these compounds, you are referring to which ones?

A. 933, 64933, 64934 and 64935 and 64936, as well.

Q. Could you tell me whether you had any particular procedures or arrangements for sending compounds to Dr. Scallen?

A. Yes. Normally after you finish the synthesis and the compound has been purified and the compound had been submitted to different measurements in the physical chemistry department to identify the identity of the compound, then we would, we, I mean the chemists in my lab would then submit the compound to the drug room and then there would be one person responsible for registering the compound into the system and then after the compound had been registered into the system, there would be another person who would be responsible for collecting all of this compound and ship it, ship them for testing.

MR. KELBER: I'm going to renew my

Wattanasin - redirect

objection to this line of questioning at this time. I know I didn't go into anything regarding in vivo testing and the procedures therefor on direct.

MR. VILA: I believe you have been into the questions of abandonment and diligence in this area and I think --

MR. KELBER: Certainly not diligence, never. With respect to abandonment, suppression, concealment, that's an issue but it's hardly anything that gives rise to a free-for-all in determining what kind of activities. My understanding of the rules provide that you can ask in areas developed on redirect that were initially explored on cross. I just want to make my objection for the record because the rule requires it to be made now rather than later.

MR. VILA: All right. I think that we are probably finished with that line.

BY MR. VILA:

Q. In January of 1988, your disclosure 299/84 was rated "A" by the Patent Committee, I believe you have testified to that. As a result of

Wattanasin - redirect

that rating, what would have been your expectancy with regard to the subject matter in that disclosure?

MR. KELBER: The witness can answer if he can but I admit, I'm totally confused by your question. What is his expectation with regard to this subject matter?

Q. What did that rating mean to you?

A. I think I already answered that question this morning, that the rating doesn't mean to me, it's only my intention to complete the synthesis of one of the key compounds in the quinoline case.

Q. I believe it was also testified this morning that the "A" rating would signal the filing of a patent application.

A. Yes, you are right.

Q. And I would ask you whether that created a certain expectancy in your mind with regard to that filing of a patent application?

A. Yes.

Q. And what would that expectancy be?

A. The expectation would be that the compound should be finished as soon as possible.

Wattanasin - redirect

Q. I'm referring to the "A" rating of the decision to file a patent application, whether that decision created a certain expectancy in your mind. Would you have expected that a patent application would have been filed as a result of that "A" rating?

A. Yes.

Q. I would ask you, then, from the period January of 1988, when that was rated "A", and March of 1989, when the patent application was actually filed, whether anything occurred that would have changed your expectancy that a patent application would have been filed?

A. Nothing.

Q. Do you want to verbalize the answer.

A. Can you repeat the question? I'm not quite really understanding the point. Can you repeat the question again, please?

MR. VILA: Do you want to read him the question.

(Whereupon the record was read.)

A. Nothing.

MR. VILA: Let's go off the record for a minute.

Wattanasin - redirect

(Whereupon a discussion took place off the record.)

Q. You just testified that you expected a patent application to file. Are you aware of any activities on the part of anybody else that may have indicated any kind of a decision not to file a patent application on that disclosure which had been rated "A" in January of --

A. I was not aware of any.

BY MS. FURMAN:

Q. Did either Mel Kassenoff or Jody Giesser ever indicate to you an intention not to file a patent application?

A. No, definitely not.

Q. You testified earlier that you spoke with Jody Giesser about the Warner-Lambert patent and possibly about the Nissan application. Is that correct?

A. Yes.

Q. I want to ask you again whether you can remember exactly when you spoke to her about those publications. Do you remember for certain that you spoke with her before the filing of the patent

Wattanasin - redirect

application?

A. I believe so, yes.

Q. Do you remember exactly when that was?

A. I don't remember exactly when.

Q. Did you arrive at any conclusion based on your talk with her about that?

A. Conclusion about what?

Q. The Warner-Lambert patent. Had you been working on the patent application already when you spoke with her about the Warner-Lambert?

A. Yes.

Q. You were working with her on the draft before you spoke with her about the Warner-Lambert?

A. Yes.

Q. You received a draft of the application in, I believe, December of 1988.

A. December or November.

Q. November of 1988.

A. Yes.

Q. Were you in communication with Jody Giesser before that date concerning the patent application?

A. Yes.

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Q. Were you in communication with her between February and November at any time?

A. Of what year?

Q. 1988.

MR. KELBER: Asked and answered. He said before that day.

MS. FURMAN: More specifically, between February and November.

A. Yes.

Q. Were those communications oral or written?

A. Mostly I believe oral, over the phone.

Q. Dr. Wattanasin, is English your first language?

A. No.

Q. What is your first language?

A. Thai.

Q. Thai?

A. Yes.

Q. Did Jody Giesser ever have trouble understanding you?

A. I don't think so.

Q. You don't think so.

MS. FURMAN: That's about it.

Wattanasin - redirect

MR. VILA: I just have one final question.

BY MR. VILA:

Q. During the period sometime in 1985, after you had made the three compounds, the first three compounds, those being, according to the record, 63366, 63548, 63549, that synthesis ending sometime in 1985, and early 1987, when the activities resumed on this quinoline series, was it ever your intention that that earlier work would be considered abandoned in your mind in the sense that it would be no longer of interest?

A. No, definitely not.

Q. And how would you describe the interest that you had in those compounds during that period?

A. My interest in those compounds, I would say very high but as I stated before, that the reason that the gap is somewhat apart is because of two reasons. The first one is because of the manpower that I mentioned before. I think the second thing is because of the priority and the priority is sometimes set by me and most of the time set by my supervisors.

Wattanasin - redirect

MR. VILA: I don't think I have any more questions.

MR. KELBER: I have just a few, doctor. I'm sorry to belabor you but I do understand you clearly, I don't think there is a problem there.

RECROSS EXAMINATION BY MR. KELBER:

Q. The very last answer you gave had to do with the manpower shortage and the priority being set on things. Did you set the priority with regard to the compounds in question that you just testified to?

A. The priority was set either by myself or my boss.

Q. In this particular case, do you recall who set the priority?

A. In this particular case, I think -- actually both, I will say both. You see, I mentioned before this is not the only compound, only class of compound we are working with. We are working on different classes of compounds during the HMG-CoA reductase and probably as you have seen from the patent, as well, we have two key

Wattanasin - recross

compounds, very important compounds, indole and indene.

Q. Did those projects receive a higher priority than the project in question?

A. Yes, according to my supervisor, yes.

Q. You also mentioned the kind of arduous process that anybody with supervisory authority is involved with hiring somebody new and you couldn't find anybody for over a year. Is that correct?

A. No, what I'm saying is the process, because of, first of all, before you can hire anyone, you have got to get approval from different people first and once you got approval for hiring someone, then it would take at least six months before you actually get someone to join your lab.

Q. Understood. This manpower shortage, if you will, that was a fairly big problem for you in connection with this?

A. Big problem because I'm the only one working in the lab on a number of compounds, on a number of projects.

Q. Did you speak to anybody in the chain of command, your boss or above, regarding expediting the process of bringing in somebody?

Wattanasin - recross

A. Yes, I did speak many times with my bosses about this issue, yes.

Q. To the best of your knowledge, did anybody do anything to expedite it?

A. As I say, the decision not only depend on my boss.

Q. But the decision also included those above your boss?

A. Yes.

Q. And do you recall today making a decision to expedite the search for manpower in this particular case? Did they move faster than the regular procedure in the case that was eventually satisfied by Dr. Patel?

A. That I don't have information to tell you.

Q. Did you ever submit a disclosure relevant to the quinoline derivatives that we have been talking about today for clearance by the Patent Department?

A. Beside quinoline cases?

Q. Besides the patent application and patent disclosure itself, I'm sorry, let me go backwards, during redirect, you spoke that a

Wattanasin - recross

disclosure outside of a patent application can't be released until it's cleared by the Patent Department. Do you recall that testimony?

A. Yes.

Q. Did you, yourself, ever submit a publication for clearance by the Patent Department relative to the subject matter of the application involved?

A. Yes, I prepared some, yes.

Q. And that would have been prior to the filing date?

A. After the filing dates.

Q. You did not submit a disclosure prior to the filing date?

A. That I'm not quite sure. I have to check my record before I can answer to you definitely.

MR. KELBER: Can we ask you to check those records and get back to us.

Q. You testified, doctor, that on the basis of your initial work reflected in the patent disclosure, you had a reasonably high expectation as to the issue of whether the compounds later prepared would exhibit activity.

Wattanasin - recross

A. Yes.

Q. And your expectations weren't disappointed, were they? Your expectations were right on the money, weren't they, doctor?

A. I don't say it's right on the money but it's comparable, yes.

Q. Is there a general formula or thought process that you go through when determining when to submit a patent disclosure? I understand that you submitted this patent disclosure in question, 299/84, because at that point in time, you felt you could complete the rest of the compounds with some expectation of activity.

A. That's right.

MR. KELBER: I have nothing further.

REDIRECT EXAMINATION BY MR. VILA:

Q. Dr. Wattanasin, there seems to be a little uncertainty in your mind with regard to the submission of a publication clearance on the subject matter that became the subject of the patent application that was filed and I believe you testified you are not sure whether you may have submitted a request for publication prior to or

Wattanasin - redirect

after the filing of the patent application. Is that correct?

A. Yes.

Q. Would you be still uncertain whether that request was submitted before or after the "A" rating of the disclosure which took place in January 1988, would you have --

A. I would say definitely after, yes.

Q. After the "A" rating?

A. After, yes.

MR. VILA: I have no further questions.

MS. FURMAN: I would just like to ask the general question whether at any time between the synthesis of 63548 and 63549 --

THE WITNESS: 64548 and 64549.

MS. FURMAN: Correct, whether between that synthesis and the synthesis of 64933 and later compounds, whether in that period, you ever had the intention to abandon your invention?

THE WITNESS: No, as I said before, definitely not.

MR. KELBER: Thanks again, doctor. We appreciate it.

THE WITNESS: Thank you.

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MR. KELBER: Before we go off the record, different people have different styles. We have been operating under the situation where you identify an exhibit, you object to it. Just in case you operate under a different fashion, we have exhibits F-1 through F-8 and W-1 through 3. We have objected to W-2. Do you have any objections to any of F-1 through 8?

MS. FURMAN: No.

(Time noted is 2:30 p.m.)

SOMPONG WATTANASIN

Subscribed and Sworn to before me
This day of , 1993

A Notary Public

C E R T I F I C A T E

I, GARY M. TALPINS, a Notary Public and Certified Shorthand Reporter of the State of New Jersey, do hereby certify that prior to the commencement of the examination, SOMPONG WATTANASIN was duly sworn by me to testify the truth, the whole truth and nothing but the truth.

I DO FURTHER CERTIFY that the foregoing is a true and accurate transcript of the testimony as taken stenographically by and before me at the time, place and on the date hereinbefore set forth, to the best of my ability.

I DO FURTHER CERTIFY that I am neither a relative nor employee nor attorney nor agent of any of the parties to this action, and that I am neither a relative nor employee of such attorney or counsel, and that I am not interested directly or indirectly in the interference either as counsel, attorney, agent or otherwise.

Gary M. Talpins, C.S.R.
License No. XI00561

TRANSCRIPT OF PROCEEDINGS

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
WATTANASIN v. FUJIKAWA, et al.	Interference No. 102,975

DEPOSITION OF CHESTER E. HOLMLUND

Arlington, Virginia

Friday, March 26, 1993

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DEPOSITION OF CHESTER E. HOLMLUND

Arlington, Virginia

Friday, March 26, 1993

Deposition of CHESTER E. HOLMLUND, called for examination pursuant to notice of deposition, at the law offices of Oblon, Spivak, McClelland, Maier and Neustadt, 1755 Jefferson Davis Highway, Fourth Floor, at 10:05 a.m. before BRENDA M. SMONSKEY, a Notary Public within and for the District of Columbia, when were present on behalf of the respective parties:

-- continued --

APPEARANCES:

STEVEN B. KELBER, ESQ.
Oblon, Spivak, McClelland,
Maier & Neustadt, P.C.
Fourth Floor
1755 Jefferson Davis Highway
Arlington, Virginia 22202
On behalf of Fujikawa, et al.

RICHARD E. VILA, ESQ.
DIANE FURMAN, ESQ.
Sandoz Corporation
59 Route 10
East Hanover, New Jersey 07936
On behalf of Sandoz Corporation.

ALSO PRESENT:

F. G. KATHAWALA

C O N T E N T S

E X H I B I T S

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

NOTICE OF DEPOSITION

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

BOX INTERFERENCE

SIR:

Pursuant to 37 CFR §1.673(a), Fujikawa et al hereby serve notice of the deposition of Dr. Chester E. Holmlund to be held at the offices of undersigned Counsel on March 26, 1993, beginning at 10:00 AM, and continuing from time-to-time until done. It is not expected that the deposition will last beyond a single day, but in the event it does, the deposition will be resumed March 29, 1993.

The current address for Dr. Holmlund is 9200 Edwards Way, Apartment 516, Adelphi, Maryland. The witness is expected to testify in a rebuttal capacity, as to the adequacy of the proof of the Junior Party with respect to conception and actual reduction to practice.

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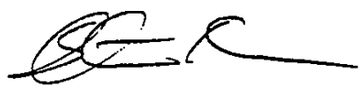
CHESTER E. HOLMLUND

A true copy of the foregoing Notice of Deposition was served, by hand, on Diane Furman, Sandoz Corporation, on March 26, 1993, agreement as to the date of deposition and manner of notice having been earlier agreed upon.

Respectfully submitted,

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



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

49-111-0

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

WATTANASIN	:	
	:	INTERFERENCE NO.: 102,975
V.	:	EXAMINER-IN-CHIEF:
FUJIKAWA ET AL	:	MICHAEL SOFOCLEOUS

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Respectfully submitted,

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

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

P R O C E E D I N G S

MR. VILA: Let's put on the record we stipulate we can waive the requirements of Rule 672(b) and that references to matters already on the record or in evidence can be made without introducing these things for identification at the option of the side that is presenting the testimony.

Whereupon,

CHESTER E. HOLMLUND

was called as a witness and, having first been duly sworn, was examined and testified as follows:

MR. KELBER: Good morning. This is the deposition of Dr. C.E. Holmlund, a rebuttal witness for the party Fujikawa, et al. in Interferences 102,648 and 102,975. By prior agreement of the parties, we will be filing a consolidated record with regard to those two interferences.

Is that correct, Diane?

MS. FURMAN: That is correct.

EXAMINATION

BY MR. KELBER:

Q Could you state your full name and address for

the record.

A Chester Eric Holmlund, Apartment 516, 9200 Edwards Way, Adelphi, Maryland 20783.

MR. KELBER: I am going to hand a document to the reporter that I would like labeled as Exhibit F-10.

(Exhibit F-10 identified.)

BY MR. KELBER:

Q Doctor, take a minute and review Exhibit F-10 briefly.

Do you recognize that document?

A Yes, I do.

Q What is that document?

A It is a curriculum vitae prepared, I guess, in 1988.

Q To the best of your knowledge, is it accurate as of today?

A Yes, it is.

Q Doctor, do you have any experience in the field of cholesterol biosynthesis inhibition?

A Yes.

Q Could you describe that experience for me.

A For some time I have been interested in

generally in lipid metabolism, but most especially in the area of sterile metabolism and have spent some time studying the effects of various inhibitors of sterile synthesis insofar as they act upon microbial systems of several types.

Q Does your experience involve work directly in the field?

A Yes.

Q Is that experience reflected in Exhibit F-10?

A It is.

Q Are you familiar with compounds intended to inhibit HMG-CoA reductase?

A Yes.

Q Can such compounds be used to reduce or inhibit cholesterol biosynthesis?

A Yes.

MR. KELBER: We offer Dr. Holmlund as an expert as to the art of cholesterol biosynthesis inhibition.

MR. VILA: We will reserve judgement on that until we have cross-examination.

BY MR. KELBER:

Q Prior to this proceeding, have you ever been

employed by Nissan Chemical Corporation?

A I have not.

Q Are you being paid for your services in connection with this proceeding?

A Yes.

MR. KELBER: I am going to hand the reporter a document entitled "Declaration of Terence J. Scallen Pursuant to 37 CFR Section 1.672" and ask that it be identified as Exhibit F-11.

(Exhibit F-11 identified.)

BY MR. KELBER:

Q If you would take a minute to review that.

MR. VILA: A declaration submitted like this without advance notice or seeing it, is that appropriate?

MS. FURMAN: That is our declaration.

MR. KELBER: You were also provided notice about the documents that would be referred to in the deposition.

BY MR. KELBER:

Q While you are reviewing that document, I am going to hand to the reporter for identification as Exhibits F-12 through 16 documents labeled Exhibit E-1, Exhibit E-2, Exhibit E-3, Exhibit E-4 and Exhibit E-5.

Those are exhibits to the Scallen declaration.

(Exhibits F-12 through F-16 identified.)

(Witness examined the documents.)

BY MR. KELBER:

Q Have you seen the documents that comprise Exhibits F-11 through F-16 prior to today?

A Yes.

Q In what context did you first see those documents?

A They were sent to me by you with respect to the action in which your company is now engaged.

Q Doctor, let me turn your attention to paragraph 4 of Exhibit F-11, which is the declaration itself. Do you see in paragraph 4, bridging the pages, the description of an assay protocol?

A Yes.

Q Are you familiar with in vitro assays of this type?

A Yes.

Q Let me direct your attention now back to paragraph 3 of that document that is Exhibit F-11. If you would take a minute to read that paragraph to yourself.

(Witness examined the document.)

A Yes.

Q Doctor, do you have sufficient knowledge, experience and expertise to have formed an opinion as to the validity of the conclusions set forth in paragraph 3 with respect to the second sentence of that paragraph; that is, the second sentence that reads "If a compound possesses this activity, it would be useful for lowering the blood cholesterol level in animals"?

A Short answer, yes.

Q Can you give me that opinion, sir.

A The problem that I have with that statement as it appears here is the declaration that such compounds would be useful. They may be, but they may not be.

Q Can you tell me under what situations compounds exhibiting in vitro activity as referred to would not be useful?

A Well, when a compound is administered to an intact animal, there are many other fates which can befall it before it interacts with its intended target, namely HMG-CoA reductase in this case.

Q Is it then your testimony that it is possible

for a compound to exhibit in vitro activity pursuant to the type of assay in paragraph 4 and still not exhibit reductase inhibition in vivo?

A Yes.

Q Let me direct your attention to the penultimate paragraph of F-11, which is the paragraph bridging pages 8 and 9 of that document.

A I don't see the pagination. The pagination on my copy is 75 on.

Q Looking at the pages numbered 82 and 83.

A Which paragraph?

Q The paragraph bridging those two pages at the bottom of page 82. If you would read that paragraph, sir, to yourself.

(Witness examined the document.)

A Yes.

Q Let me direct your attention specifically now to the sentence that begins at the very bottom of the page numbered 82, starts with the words "It was" and then continues on to the next page.

A Yes.

Q Would the testimony you just gave regarding the

correlation between in vitro and in vivo activity also apply to this statement?

A It would.

Q Do you see the reference in the paragraph that we have been discussing, to compounds 64-934/Na and 64-936/Na?

A Yes, I see them.

Q On the basis of your review of the documents provided, can you tell me the significance of the suffix "Na"?

A That is intended to indicate that it is the sodium salt of the compound that is being tested.

Q Doctor, on the basis of your knowledge, experience and expertise, can the in vivo activity shown by a sodium salt of a compound having reductase inhibition activity be different from the activity shown by the corresponding free acid?

A It can.

Q Let me direct your attention back now to the protocol that is set forth in paragraph 4 which begins on the page marked page 76. Doctor, can small changes in assays of this type affect the activity report obtained

from the assay?

A Yes.

Q Doctor, do you see that the top of the page marked 77, F-11, the reference to an article by Ackerman, et al?

A I see it.

MR. KELBER: For the record, the party Fujikawa takes objection to the declaration of Scallen with respect to paragraph 4 referring to a document not attached to the declaration.

MS. FURMAN: I may be incorrect in my recollection, but did you stipulate at the beginning of this session that you would be willing to consider any such documents referred to in declarations? That's what I thought I heard, that you were --

MR. KELBER: No. What Dick suggested is that we would be willing to stipulate to the use of documents that are of record in the interference already. If you would like, I can have the reporter read back that stipulation.

MS. FURMAN: No. I thought I heard something in connection with 672(b).

MR. KELBER: That's correct. That refers to

this deposition. In fact, the specific reference in 672(b) was to "A party shall not be entitled to rely on any document referred to in the affidavit unless a copy of the document is filed with the affidavit."

We were stating with reference to this particular deposition. I could obviously not have stipulated to the prior declaration, as it was signed and filed well before this discussion.

In any event, our objection goes to the fact that the Ackerman journal article was never made of record in any connection with this proceeding. The objection is made now only because it was made by declaration and we will not be talking at cross-examination to Dr. Scallen. If you prefer, we will make the objection in writing.

MS. FURMAN: I would prefer that.

MR. VILA: Do you have a copy of Ackerman? Have you obtained a copy of Ackerman?

MR. KELBER: No, sir, I have not.

MR. VILA: It so happens, we have brought a copy with us. If you want to take a few moments out, we will provide you with a copy. You may regard it as belated, but there certainly has been no intent to withhold that.

MR. KELBER: I didn't think there was. If you wish to use that in cross, that's perfectly acceptable. It would not cure my objection.

MR. VILA: I understand what you are saying.

Has the witness read Ackerman or is familiar with Ackerman?

MR. KELBER: Let's go off the record.

(Discussion off the record.)

MR. KELBER: I am going to hand the reporter a document I would like marked for the record as F-17 which is entitled "The Declaration of Robert G. Engstrom Pursuant to 37 CFR Section 1.672."

(Exhibit F-17 identified.)

MR. KELBER: While you are reviewing that, I will hand the reporter to mark as Exhibit F-18 a document that on the first page bears the legend "Exhibit K," it is, in fact, an exhibit to that document.

(Exhibit F-18 identified.)

MR. VILA: Let the record note that the opposing party has been provided with a copy of Ackerman at this point.

(Witness examined the document.)

BY MR. KELBER:

Q Doctor, have you seen Exhibits F-17 and F-18 before today?

A Yes, I have.

Q In what context did you first see these documents, Doctor?

A Again, these were documents submitted to me by you in connection with this action.

Q Do you see the protocol described on the second page of F-17 which bears the legend in the top right corner, "108"?

A Yes, I do.

Q Are you familiar with assays of this type?

A Yes.

Q Let me turn your attention now to Exhibit F-18. Doctor, based on your review of Exhibits F-17 and F-18, does the information contained in Exhibit F-18 reflect raw data collected according to the assay described in F-17?

A My answer to that would have to depend upon the definition of raw data, because the data that we see in F-18 have certainly been manipulated to some extent by the use of a computer program. So the data had to be entered

into the computer in order for the program to act upon it and come up with the figures that appear on F-18.

Q Is it a correct statement that the figures that do appear in F-18 would have had to have been calculated on the basis of the raw data?

A Yes, yes.

MR. KELBER: For the record, we will object to F-18, which is Exhibit K-1 and all reliance thereon on the grounds that it is a manipulation of raw data without the raw data having been made of record.

BY MR. KELBER:

Q Let me ask you, Doctor, what is the meaning of an ED_{50} value?

A This is the effective dosage in an in vivo assay, in this case, which would reduce the rate of cholesterol biosynthesis by 50 percent.

Q What is the meaning, then, of an ED_{50} value as being indicated as greater than 1.0?

A Well, I can't attach any significance to that whatsoever. The implication is that there would be activity if a dose greater than 1 milligram per kilogram were used. But without any experimental data confirming,

that deduction would seem to be meaningless.

Q Let me direct your attention to the page of F-17 that bears the legend 110 in the top right-hand corner.

Do you see, in about the middle of the page there, two entries for ED_{50} values of greater than 1.0?

A I do.

Q Would your comments a moment ago with regard to the meaning of an ED_{50} value of greater than 1.0 apply?

A They would.

Q Is it possible in the absence of further information that a reductase inhibitor having an ED_{50} value of greater than 1.0 may have no inhibition activity at all?

A Yes.

Q Doctor, would you take a moment and review Exhibit F-18 for information relevant to the compound identified as 64-933.

A Because the printing is so unclear, I would just ask for confirmation that I believe it is the bottom of page 338 and the top of 339 which provides the data for the 64-933.

Q That is correct, Doctor.

A I do see those data.

Q At what dosage levels was this compound tested as reflected in F-18?

A At 1.0, 0.3 and 0.1 milligrams per kilogram.

Q Does the data or information presented in Exhibit F-18 reflect activity for compound 64-933 at any of these levels?

A They do not.

Q Doctor, let me turn your attention back to F-17 for a moment, and specifically the indication on the last page of that document of an ED_{50} value for compound 64-933 of 0.49. On the basis of the information contained in K-1 alone, what, if any, is your opinion as to the validity of the assignment of an ED_{50} value of 0.49 for this compound?

A Your question referred to K-1?

Q I'm sorry. F-18.

A The data provided in F-18 with respect to compound 64-933 in no way can be used to provide a figure of 0.49, an ED_{50} of 0.49 for 64-933 as shown on page 110.

Q Can any ED_{50} value be assigned to this compound, 64-933 --

A No. Excuse me.

Q -- on the basis of F-18 alone?

A No.

Q Doctor, do you recall your earlier testimony today with respect to the reliability of in vitro testing as a certain predictor of in vivo activity?

A Yes.

Q In light of your testimony regarding the in vivo testing that you have just provided and the meaning of an ED_{50} value of greater than 1.0, can you draw any correlation between the in vitro tests addressed in F-11, that's the Scallen declaration, and the in vivo test results reflected in F-17, the Engstrom declaration?

A As I recall, in the Scallen declaration, all of these named compounds were described and shown to be active in the in vitro assay, and the statement was made that they would be active in vivo. Yet, the in vivo data here clearly indicate that that is certainly not the case for 64-933 and probably not the case for the other two compounds as well.

Q And that is probably not the case because?

A Because the data are so scattered for 64-935 and 64-936. There is no significant dose and activity

relationship.

Q Thank you, Doctor. Just one second.

(Pause.)

MR. KELBER: I have no further questions at this time.

MR. VILA: Can we have a break so we can review these records?

MR. KELBER: Sure.

(Recess.)

EXAMINATION

BY MR. VILA:

Q Doctor, during your testimony, you used the word "manipulated." Would it be fair to say that what you were really describing was the input of data into a computer that was programmed to calculate the results?

A Yes. I understand that the term manipulation could have adverse connotations, which was not intended.

Q Thank you. You have made a point in your testimony that certain things didn't seem to add up or allow certain conclusions. I would ask you if in preparation for these proceedings your attorney provided you with a copy of a supplemental declaration of Robert

Engstrom that was made of record in this interference.

A I believe so.

Q Can I ask you whether you considered that in the testimony that you gave?

A I have not reviewed it recently so that I would have to say --

Q Can I ask why, as this appears to do -- it corrects some of the basis for your testimony -- that this thing seems to have been ignored?

A Do you have an exhibit number that you could refer to so that I might review that document now?

MR. VILA: Let us put the supplemental Engstrom into evidence without objection, I assume, as Exhibit CR-1, we will call it. This includes the exhibit which I believe is Exhibit Q that was provided with this declaration.

MS. FURMAN: That Exhibit 2 is pages 418 to 422 of the report.

(Exhibit CR-1 identified.)

MR. VILA: The exhibits are 418 through 422 of our record. The declaration, supplemental declaration are pages 378 and 379.

MR. KELBER: Okay.

(Witness reviewed document.)

BY MR. VILA:

Q I believe the more relevant portion of this is on the last page, 422, of the record, the last two numbers where there are handwritten changes made.

A I would have to respond that to the best of my recollection, I don't believe that I have seen this before.

MR. VILA: I find it regrettable this was not provided to you because this was part of the record and did correct the record.

MR. KELBER: I understand your regret, but speech making is for a different time.

MR. VILA: Okay.

MR. KELBER: While he is reviewing it, we will object to the introduction of the exhibit that has been marked as CR-1 on the grounds that it was submitted well after the time for direct testimony and was submitted during a period confined to testimony intended to demonstrate an absence of abandonment, suppression or concealment.

#91

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

WATTANASIN	:	
	:	INTERFERENCE NOS.:
V.	:	[redacted] AND 102,975
	:	EXAMINER-IN-CHIEF
FUJIKAWA ET AL	:	MICHAEL SOFOCLEOUS

THE RECORD FOR THE PARTY FUJIKAWA ET AL

VOLUME III
(Pages 200-299)

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But you may continue with the questioning.

MS. FURMAN: I would like to respond to that objection by directing the witness' testimony to page 340 of the testimony submitted in the direct testimony period, which he has previously referred to in Exhibit F-18.

MR. KELBER: Let's get some ground rules straight. I don't have a problem with anybody jumping in and asking questions. I made an objection, and you are going to respond to it by asking the witness questions when we were initiating questions on the first exhibit with Dick. You have to give the witness a chance to jump back and forth. That's all I ask.

MR. VILA: I don't believe the issue here today is abandonment, suppression and concealment.

MR. KELBER: The grounds for my objection is that the declaration was submitted out of time and that no special permission was sought to submit that declaration.

MR. VILA: It has been filed by us and we elected to submit our testimony by deposition and did not under the rules, have to take direct testimony.

MR. KELBER: I think you elected to present your testimony by declaration, and the order of the EIC

assigned specific times which were extended for the presentation of direct testimony. The supplemental declaration that we are talking about now was submitted well beyond the period of the close of that period and was submitted in the period, together with a bunch of other documents, which period was confined to the presentation of evidence directed to the issue of abandonment, suppression or concealment.

Therefore, to the extent that the exhibit goes to anything other than that, we would object to it.

Why don't you proceed with the response to the objection.

MR. VILA: Yes. With the response to the objection?

MR. KELBER: Diane was going to respond to the objection by directing the witness' attention to certain pages.

EXAMINATION

BY MS. FURMAN:

Q I would like to direct your attention, Dr. Holmlund, to page 340 of your testimony which I assume you have in hand now.

MR. KELBER: What is 340? He does not have a full copy of the record.

MS. FURMAN: It is a page from an exhibit that you have already made of record which is Exhibit F-18.

THE WITNESS: Yes.

MR. KELBER: 340 at the top of the page.

BY MS. FURMAN:

Q Going to compound number 64-933, approximately 1/3 from the bottom of the page.

A I do see it.

Q What is the ED_{50} value that is listed for that number?

A I have to assume that -- I see there is the title for the column. It is listed as 1.

Q That would be greater than 1?

A No, it would not. It would be 1, as indicated. There is no greater sign there. I'm sorry. It is customary to write those signs next to the number and not separate it by an interval of space here. So I did not see the greater than. I assume that the greater than 1 inch to the left does apply to the one and the greater than 1 is the value.

Q The value for 64-935, the ED_{50} value for 64-935?

A Is written as .49.

Q Have you previously looked at this page when you prepared for this deposition?

A Yes.

Q In your opinion, would the values that are presented on page 340 be consistent with the data presented with respect to each compound on pages 336, 338 and 339 of the record?

A Let me take these one at a time, if I may. Page 336 provides the data for 64-936 which indicate that that compound was not significantly active at the dose levels of 1 and 0.1 milligram per kilogram but that it is active at the level of 0.3 milligrams per kilogram.

Q How would you define what would constitute activity? At what level of inhibition do you consider a compound to be active at 1 milligram per kilogram?

A This is on the basis of the statistical analysis which has been carried out by the individuals who carried out the analysis here.

Q Based on your expert opinion in the field.

A My expert opinion would indicate that it is

quite appropriate to apply these techniques of statistical analysis to evaluate the presumed activity or inactivity of a compound.

Q So the techniques themselves are valid?

A I have no quarrel at this point with the techniques for determining statistical activity as used for calculating these values.

Q Looking at line 48 on page 336, there is a value for percent change. What is the value for 64-936 on line 48?

A It is given as minus 9.0.

Q Looking to line 54, there is a value for 64-936 at .3 milligram.

A Correct. That is given as minus 39.2.

Q Looking to 64-935, which appears on page 339 of the record, at 1 milligram dosage provided on line 48 of that page, the amount of suppression or decrease in activity is what value?

A 65.8.

Q So the amount of decrease for 64-935 at 1 milligram is 65.8. The amount of decrease for 64-933 at 1 milligram is 36.3; is that correct?

A For 933 -- give me the relevant pages again.

Q Line 30 on page 338.

A Yes. I will repeat, line 30 on page 338 and this is for compound 64-933 at 1 milligram per kilogram, the reduction is given as minus 36.3, which, however, is not designated as a significant reduction.

Q Not designated as a significant reduction?

A That's correct.

EXAMINATION

BY MR. VILA:

Q I would ask you, Doctor, it seemed to me that it was your testimony with regard to the compound 64-936 on record page 336, I believe it was your testimony that the result of minus 39.2 is a significant result, a significant activity.

A I'm sorry. Page 336, which line?

Q It would be line 54. It would be line 54 for the compound 64-936, which gave a result of minus 39.2.

A Yes.

Q I believe it was your testimony that that was a significant result or activity?

A Based again upon the statistical analysis which

was performed on the data.

Q Yet I believe that you are saying that a result of minus 36.3 for the compound 64-933 on record page 338 which differs only by 3 percent from the result for 936 is now an insignificant result?

A Yes. Again, based upon the statistical data and these differences bring dramatically to light the kind of biological variation which occurs in biological experiments.

Q Would it be fair to say that the compound 933 on pages 338 and 339 are showing activities statistically different from a control that would be inactive in the test at any of these dosages?

A You will have to rephrase that question, please, or repeat it.

Q I'm sorry. 64-933 on page 338 and 339, are any of these results showing an indication of activity which would be statistically above a level of a zero control?

A No.

Q But I take it that you have no reason to quarrel with the results obtained for 64-935 which from the other records projected an ED_{50} of .49?

MR. KELBER: Which records are you referring to, the other records you said?

MS. FURMAN: Page 340 of the record, which is a part of Exhibit F-18.

MR. KELBER: Could you reread that question.

(The reporter read the record as requested.)

MR. KELBER: I'm not sure that the question makes sense in terms of its literal phrasing. The witness can answer, if he wants to.

THE WITNESS: Well, my response would be that I have, and there is no indication given in any of the documents that I have seen which indicate how such a value of .49 is obtained. If one looks at the data for 64-935 given on page 339, one sees that there is significant activity for that compound in lowering the rate of cholesterol synthesis at both the levels of 1 and 0.1 milligrams per kilogram, but that it is not significantly effective at the intermediate dose of 0.3 milligrams per kilogram.

BY MR. VILA:

Q Would that compound 64-935 have, in your judgment, an ED_{50} less than 1 from this data?

A I would not be able to make any conclusions based upon the fact that, again, there is no understandable dose response curve obtainable from the three sets of data obtained. One would expect that there would be -- if the compound or any compound is active at a level of, let us say, 1 milligram per kilogram and at 0.1 milligrams per kilogram it should display an intermediate display of activity at an intermediate dose. It is the intermediate dose here which indicates there is no activity for the compound at that intermediate dose of 0.3 milligrams per kilogram.

Q Recognizing the variations that are likely to occur in any assay, is it your testimony that these results are totally meaningless or is it your testimony that this is a significantly active compound, but you simply cannot determine its ED_{50}?

MR. KELBER: Objection. You got a compound question there. There is a large range between totally meaningless and the specific -- you can ask him both. Ask them separately.

MR. VILA: Strike the whole question.

BY MR. VILA:

Q Is it your testimony this compound has significant activity?

A My testimony would be that it may have. Based upon the data that are presented, I cannot make a final conclusion on it.

Q Again, referring to the 64-935, the data on record page 339. If the result at .1 milligrams per kilogram were less than the result at .3, would you have the same difficulty with this data?

A No.

Q Would you say that the differences between those two results at .1 and .3 are possibly within the margin of variation of the tests?

A Not based upon the statistical analysis.

Q How would you explain the fact that the dosage at minus 36 is higher than 39?

A I have no explanation for it.

Q And you would not accept the fact that if we look at the dose at .3, the result there, and the dose at 1, that this compound is indicating a structural activity rate of relationship?

A I would say this, that one would be unable to

publish data such as presented here and claim activity for the compound that is demonstrably active.

Q Are you sufficiently familiar with the art of the HMG-CoA reductase inhibitors to know the ED_{50} of Compactin in vivo by the type of tests?

A I don't have those figures in my mind, no.

Q I'm going to approach the question this way and assume that the in vivo ED_{50} of Compactin is 3.5 or about 3.5 in the type of assays in question.

MR. KELBER: Which type of assays are those?

MR. VILA: An in vivo assay of the type that was described in the Sandoz patent application.

THE WITNESS: Would you give me the figure and the units, please, for your assumption.

BY MR. VILA:

Q That would be milligrams per kilogram.

A 3.5?

Q Right. In the same assay Lovastatin would be 0.414.

I would like to ask you if you would judge Compactin from what you know to be a compound of interesting activity in this area.

MR. KELBER: Objection as to the use of the word "interesting." Can you be specific in what you want him to consider.

BY MR. VILA:

Q Would this be a compound that a company might find worthy of further development based on its activity level?

MR. KELBER: Excuse me. I don't have a problem with the form of the question. But are you asking him a hypothetical on the basis of the numbers you have given?

MR. VILA: I will strike the question again and I will reask it.

BY MR. VILA:

Q Would you regard that as a significant level of activity in this field?

A Let me repeat what you have given me thus far. You have given me ED_{50} values in milligrams per kilogram for Compactin and for Lovastatin the values being 3.5 and 0.414. Now your question to me is would I regard such figures --

Q Compactin as involving a significant activity in this field.

A I can't respond to that on the basis of the numbers you have given me simply because it has been some years since I have looked at the ED_{50} values for Compactin and Lovastatin.

Q Are you familiar with Compactin and the history of Compactin and the activities that have surrounded Compactin in this field?

A I know that it functions as a competitive inhibitor for HMG-CoA reductase and that it is an effective one in vivo.

Q Do you know whether or not this compound was ever placed in clinical development by any company?

A I would have to speculate to say I am quite sure that it has been.

Q That confidence would be based on what, in your understanding?

A It would be based upon the fact that it is a reference compound for use in HMG-CoA reductase inhibition studies, and that I believe it has been used clinically. I'm not positive of that. But it has been in the literature for a good number of years.

Q Is that the same thing to say as it would be

considered as a standard in this field?

A Yes.

Q A standard in terms of research, would it be fair to say that that is a level to be met or exceeded?

A Yes. When you say "to be met or exceeded," the more active the compound, the lower the term.

Q By "exceeded" I mean bettered.

MR. KELBER: Let me just ask again for the record; I have no objection to the continuing line of questioning and the line that has gone forward, as long as I am correct in the assumption that these are hypothetical questions based on hypothetical values.

MR. VILA: I don't believe it is hypothetical.

MR. KELBER: Then I object to the entire line of questioning; assuming facts not in evidence.

MR. VILA: Could I have that objection again?

(The reporter read the record as requested.)

MR. VILA: Off the record.

(Discussion off the record.)

MR. VILA: I will ask the witness one more question. He seems to be unfamiliar at this point to some extent with Compactin.

MR. KELBER: I will ask you to ask questions but do not characterize the witness' testimony.

MR. VILA: I'm sorry.

BY MR. VILA:

Q Would it be your knowledge, based on your understanding in this art, that Compactin has been considered a standard or has been used as a standard?

A Yes.

Q But you are not familiar with its relative activity or absolute activity levels; you don't recall any values in mind?

A That's correct.

Q We will continue on the hypothetical.

MR. KELBER: You give me my continuing objection again; I won't interrupt.

BY MR. VILA:

Q If a person regarded the level of a standard such as Compactin to be 3.5 and was then running a test where the test could not reveal an ED_{50} better than 1, would it be fair to say that that person is setting a rather high standard for those compounds where he wanted to be able to determine an ED_{50}?

A Again, I am troubled by your use of the word "better than 1."

Q A more active compound.

A Repeat the question again, please.

Q A compound that would have equal or better activity than indicated by an ED_{50} of 1.

A May I rephrase it a bit and see if this is what you mean?

Q Sure.

A That if a compound is under investigation and it is found reproducibly to display an ED_{50} of less than 1.0 milligram per kilogram, would I consider that to be an active compound? Yes, I would. If Compactin were run at the same time under the same circumstances and displayed an ED_{50} of 3.5 --

Q Pardon me, Doctor, I think I am not getting the question across.

The ED_{50} in vivo tests that you see in the exhibits that were run by Sandoz based on your expertise in this area, is it fair to say that these compounds could only determine an ED_{50} for compounds that had an ED_{50} of 1 or more active?

A Or less. One or less, yes.

Q My question, therefore, is were they seeking through this assay to distinguish between compounds that were more active than Compactin?

MR. KELBER: Objection. You are asking the witness to make assumptions as to what they, whoever they were. You can ask him what the evidence represents. You can't ask him what they wanted.

MR. VILA: By "they" I mean the Sandoz researchers.

MR. KELBER: You can't ask him what the Sandoz researchers wanted to do. You can ask him what it says to him but you can't ask him what was in the mind of the researchers.

BY MR. VILA:

Q I believe if you were to do what we have just discussed, run an assay where the break point for ED_{50} is 1 and the ED_{50} of Compactin is 3.5, would it be your conclusion that you are running an assay for compounds that are considerably more active than Compactin?

A Yes.

Q So, it might be fair to say that you are setting

a rather high standard?

A Yes.

Q At least relative to Compactin.

With regard to the compounds, the data which has been discussed in this testimony, the 64-933, 64-935, 64-936, would it be fair to say that if the evaluation doses in milligram per kilogram were considerably greater than used here, that these compounds could have shown an ED_{50}?

A Of what value?

Q A value at a level higher than 1.

A Could have, yes.

Q If Compactin is a standard at 3.5, would it be your testimony that a compound with an ED_{50} of 3.5 in vivo or even higher would be considered an active compound?

A Again, I would have to rephrase. Even lower. 3.5 or lower.

Q No. I am saying higher.

A Repeat the question, then, again, please.

Q If a compound were revealed to have an ED_{50} of 3.5 in the in vivo assay, in other words, the same level as we have assumed for Compactin, would it be your

judgment that that would be an active compound in this field?

A . Yes, it would be, provided that I'm assuming here that these would be an authentic, statistically significant value, this 3.5 figure that you cite. Under the circumstances, I would say yes.

Q That's a fair assumption, Doctor.

Would you say that there could be levels of activity above 3.5 where you could reach the same conclusion, 3.6, 3.7? I don't believe it is necessary to try and define what limits are, but higher than 3.5 could be considered an active useful compound in this field?

A Yes, by the very definition of ED_{50}.

I wonder if I might make an addendum to the answer that I gave you for the preceding question.

Q Yes.

A If the reporter would read back, please, the question that was asked of me.

(The reporter read the record as requested.)

THE WITNESS: That's the correction I wanted to make. I could consider that it would be active, but not necessarily useful.

BY MR. VILA:

Q Why would you conclude that?

A Because for any compound for any purpose, there is always the possibility of toxicity associated with the compound.

Q I can certainly give you that, Doctor. If the compound were free of toxicity or had a therapeutic ratio acceptable to the FDA, would something above 3.5 be considered useful?

A I think then as to whether it were useful or not would depend upon the economic factors involved, how high the dose would have to be, how expensive it would have to be to produce it and to prescribe it. I would certainly go along with saying it would be classified as an active compound. But the question of usefulness I think relates to these factors that I brought out.

Q But it would, nevertheless, in your mind at a dose bring the appropriate response in the body the same as Compactin might?

A It would be classified as an active compound.

Q As an HMG-CoA reductase inhibitor?

A Yes, in vivo.

Q I believe you started your testimony with a statement to the effect that a compound that would be active in vitro would not necessarily be active in vivo because of a number of things that can bear on the activity of a compound when administered to an in vivo system; is that correct?

A Yes.

Q Are you sufficiently familiar with the area of HMG-CoA reductase research to have an idea of how many compounds roughly have been tested in vitro and how many compounds have been tested in vivo?

A I couldn't give a number to that. I'm sure that a lot have been.

Q In any series of compounds in pharmaceutical research, if compounds active in vitro were found to be active in vivo subject to the exceptions that can always be encountered in research, would it be a fair assumption that for that given series, that it is likely that a compound active in vitro would be then active in vivo?

A You are referring to other members of a series of compounds, analogs.

Q Where there is substantial background in the

series of both in vivo and in vitro activity. We recognize that there are always exceptions.

A I would have to say yes.

Q Would you refer to Exhibit F-11, which is the Scallen declaration.

A Yes. I have the declaration. Is there anything in particular you would like me to refer to?

Q Yes. Paragraph 3, please.

A Yes.

Q Am I correct that it was in your previous testimony that you had a disagreement with this statement?

A With one word in the statement.

Q Which was that?

A "Would." The sentence starting with "If a compound possesses this activity, it would be useful for lowering."

Q You would change that to what word?

A "Might."

Q The first sentence of paragraph 3, I will read it to you, if that's appropriate. It refers to compounds sent to him by Sandoz. If Dr. Scallen had substantial background experience with compounds of general and

related classes, including compounds even of the class of the subject matter in this invention but with or without that experience with the compounds of this invention but with many compounds of this type of class, in particular heterocyclic derivatives, and was aware of the fact that to the extent it tested in vivo they were showing activity and that these compounds had been active in vitro in his own tests.

Would this statement then be a reasonably fair statement?

MR. KELBER: Can I have the question read back.

(The reporter read the record as requested.)

MR. KELBER: Can I ask you to rephrase it, please.

MR. VILA: Why don't you strike the whole question out.

BY MR. VILA:

Q If Dr. Scallen had a evaluated a large number of compounds in the general area of research involved here, HMG-CoA reductase of the type Compactin --

MR. KELBER: Let me jump in to avoid a long, frustrating activity. You are asking him to speculate as

to things that you are assuming.

MR. VILA: I'm not trying to assume anything.

MR. KELBER: You have to give him facts. You asked him to speculate if Dr. Scallen had done this, then that. If you want to give him a hypothetical, I have no strong objection other than hypotheticals don't bear on the questions at issue. You can give him a hypothetical but you have to give him facts, not speculation. If you want to set up a hypothetical situation and ask him to respond to that, I have no problem.

MR. VILA: Strike that and I will try it again. I will phrase it as a hypothetical question.

BY MR. VILA:

Q If Dr. Scallen had observed that many of the compounds in this area of research were in fact active both in vitro and in vivo, would the statement in paragraph 3 of the Scallen declaration be a fair statement?

A No.

Q Subject to the usual exceptions that can occur in biological research?

A I think adding that phrase nullifies the

statement that I think you are trying to make here. Let me rephrase my objection to this entire paragraph. As I said, it really applies to two uses of the word "would." In my mind, the word "would" implies complete, 100 percent assurance, no possible examples which would not fall into that category. That's where I take exception. I would accept either "might be useful." I would even accept "would probably be useful." Insertion of the word "probably" indicates that there is a reasonable element of doubt that some compounds may be encountered which are active in the in vitro assay but yet inactive in the in vivo assay.

Q Would you accept, subject to exceptions that might occur, that the failure to find that activity would be considered an exception, that there would be a reasonable expectancy against the background of the hypothetical I gave you?

A I think I probably would accept that.

Q Then if this statement were qualified to read that subject to exceptions, this is an acceptable statement to you?

A Yes. I think pretty much so, yes, recognizing

that exceptions can occur at any time, including the compounds that one is testing.

Q Is it a fair statement that you are able to criticize the results here because of absolute values of these compounds as determined in these assays, or is it possible that they can be criticized because the tests were run at a very stringent or a very high standard of pursuing compounds with an ED_{50} of 1 or less, 1 or higher?

MR. KELBER: I'm going to object to the question on the basis of the use of the pejorative term "criticizing." As far as I know, Dr. Holmlund has been asked specific questions and given answers in response to it. Criticize means a lot of things. If you can ask him what the testimony that you are concerned about and the basis for that, that would be fine.

BY MR. VILA:

Q Do you understand the question?

A Not completely. It seems as though we are shifting ground a bit because we are on page 76 dealing with paragraph 3 and it seemed to me that the line of questioning you now embarked upon extends beyond this. If

so, I would like to know what you are referring to.

Q I beg your pardon. I think we were concentrating on 3 and in your answer you made reference to the results that you had been previously testifying to here, that you said that these were probably in the category of the exceptions.

MR. KELBER: I don't think that is an accurate clarification of his testimony at all.

MR. VILA: Maybe we ought to read back his testimony, the last question.

(The reporter read the record as requested.)

MR. VILA: I'm assuming the compounds he is referring to are the ones he had testified about previously, 64-936.

THE WITNESS: That was not my intention.

BY MR. VILA:

Q It was not your intention to say these were an exception to your previous testimony?

A My understanding is that we were dealing with a hypothetical situation in terms of evaluating this statement. And hence my remark was addressed to that hypothetical situation, that in any hypothetical situation

where any list of compounds were being tested, that this statement as it stands here would not be acceptable.

Q If such a rule applied here, if that were in the background of Dr. Scallen's mind, you are not saying that the results in here are an exception or come under the exception that we discussed?

MR. KELBER: Again, you are asking him to speculate about what would be if something was in someone's mind. He can't get in somebody else's mind. Give him the hypothetical and ask him his opinion.

MR. VILA: Well, the hypothetical has been out there and I believe that he has testified that he would agree with Dr. Scallen here if the statement were qualified by saying "subject to exceptions." Some reference seems to have been made to the compounds on which we specifically took testimony today.

MR. KELBER: I think we have clarified that, Dick, twice now. If you want to go back and read it again, we can. It said that one is testing. He made it clear and said in response to your subsequent question that he was referring to the hypothetical that you had set up, not an actual example.

MR. VILA: Not the actual examples in the case, okay.

BY MR. VILA:

Q Prior to becoming involved in this interference, were you aware that Dr. Scallen was screening compounds for Sandoz?

A No, I was not.

Q Do you know Dr. Scallen?

A I don't know him personally. I certainly know him by reputation. I have heard him speak at several scientific meetings.

Q How would you regard that reputation?

A I would prefer not to respond to that.

MR. KELBER: We will be willing to stipulate for the record, if it helps, that he is a noted researcher in this field.

MR. VILA: Do you have any more questions?

MS. FURMAN: I have a couple of questions.

I am going to ask you another hypothetical. If you had the -- let me just refer to -- I would like to put into the record as Exhibit CR-2 pages 215 and 216 of the testimony which provide the IC_{50} values for the separate

compounds.

(Exhibit CR-2 identified.)

EXAMINATION

BY MS. FURMAN:

Q On page 216, an IC_{50} value is given for 64-936. That value is.53. If that were the best IC_{50} data you had in hand for a series of compounds, would you feel justified in believing that you could have in vivo activity over that whole series of compounds?

A I'm afraid I would be cautious enough to say again that I might have or would probably have. I would expect to have.

Q But there could be some question?

A Yes.

Q So you don't think it would be permissible for you to make a flat-out conclusion that you would have in vivo activity based on data such as this as your best data?

A That's correct.

MS. FURMAN: That's all I have on that.

BY MS. FURMAN:

Q I just have a couple of other questions going to

your background. I understand there is some informal relationship between you and Mr. Kelber, if I'm not mistaken. Have you known him for a number of years?

A I have not. It turns out that he called to my attention yesterday that he apparently had been a student in a class of mine which he didn't know when he contacted me and which I certainly did not know when I agreed to serve here.

Q Have you previously served as a witness for the Oblon, Fischer firm.

A No, I have not.

MR. KELBER: Let me correct the record. It is Oblon, Spivak.

MS. FURMAN: Oblon, Spivak.

BY MS. FURMAN:

Q You have numerous publications in the field of cholesterol biosynthesis based on your CV, which has been made of record.

A Is that a question?

Q No. Do you have publications in the field?

A Most of my publications with respect to inhibition relates to inhibition of sterile synthesis.

Because, as I indicated in my testimony earlier to Mr. Kelber, the types of organisms that most of my studies were done with were varying types of microorganisms, protozoan, a yeast, so forth.

Q Do you have any publications dealing with the HMG-CoA reductase enzyme?

A No publications, but I have had a graduate student who has worked upon that enzyme from a microorganism and purified it.

Q Have you done any work with HMG-CoA reductase inhibitor compounds?

A Again, it is restricted to the work that this one graduate student has done.

Q That comprises isolating the enzyme, did you say?

A Yes.

Q But not inhibiting it; is that correct?

A No. That was the example where I believe we used Compactin and found that it functioned as a competitive inhibitor for that enzyme from this particular source.

Q So, you have found in your own research that

Compactin is effective?

A Yes.

Q Did you perform an assay of the activity of Compactin?

A I did not.

Q But it was done in your lab?

A Yes.

Q Can you describe that assay for us.

A I probably can't give you complete details of it at this point in time because it was a number of years ago. But it was along the lines of I'm sure that what we did was to make use of radioactively labeled HMG-CoA, add the ingredients, including an ED pH generating system to the mixture, which comprised the enzyme and the various stages of purification, and then allowed the reaction to proceed, terminate the reaction after a specific period of time, convert the mevalonic acid, which is the product, to the lactone thereof and then separated the lactone from the reaction mixture and determined the amount of radioactivity in that separated product.

Q Is that fairly consistent with the in vitro assay presented in the exhibits?

A Yes.

Q What would you think about an assay where the overall amount of radioactivity was measured not as to mevalonate but as to the end product of cholesterol.

MR. KELBER: Objection. I understand your question. But if you focus it. What do you think of it is awfully broad.

BY MS. FURMAN:

Q Would you find an assay which measured radioactivity levels in cholesterol end product as opposed to mevalonate, would you find that a precise assay for measuring HMG-CoA reductase inhibition activity?

A No.

Q You would not?

A Let me think about that for a moment. I would say no.

Q Why would you say no?

A I say that because if one starts and it will depend upon which substrate one starts with. One could start with something as simple as acetate because cholesterol is made from acetate, HMG-CoA is a product somewhere down the line in the overall process. Even

after the conversion of HMG-CoA to mevalonate, there are a large number of steps that must occur before the final product, cholesterol, is made.

In looking at such an assay and estimating the effect upon cholesterol, there are any one of a number of steps which could actually be the one where the inhibition occurs and not necessarily at the level of the reductase.

Q How many of such steps would actually follow the formation of mevalonate? Would it be on the order of 10?

A I suspect somewhat more than that. Between 10 and 20, I believe.

Q If someone provided an IC_{50} of .54, coming out of -- let me rephrase that question. If somebody provided an IC_{50} of 1 times 10 to the negative 8 micromolar, based on that assay --

A You want to restate that figure.

Q If someone offered you an in vitro assay result of 1 times 10 to the negative 8th micromolar, based on that assay where the amount of the cholesterol radioactivity was being determined, could you consider that result reliable?

MR. KELBER: Reliable as to what?

BY MS. FURMAN:

Q As to a level of HMG-CoA reductase inhibition activity.

THE WITNESS: I will rephrase the question or restate it so that I know what I am answering.

BY MS. FURMAN:

Q I'm sorry.

A If someone completed an in vitro assay and found an IC_{50} value of 1 times 10 to the minus 8th micromolar of such a compound, could I conclude what?

Q Let me qualify. An in vitro assay where the amount of product cholesterol was being quantified, not the mevalonate. Would the result be significant to you?

A I don't know that there is any in vitro assay, any in vitro assay which determines cholesterol as the final product.

Q You are not aware of such an assay that would measure the amount of radiolabeling in the product cholesterol of the entire pathway?

A You are again referring to an in vitro assay?

Q Correct. For HMG-CoA reductase inhibition.

A I think you are asking the same sort of question

you did before. Let me point out again that if you are going to deal with an in vitro assay and measure the amount of cholesterol which is produced, you have to have in that in vitro reaction mixture all of the enzymes, 30 or more enzymes depending on what your starting material is. If you start with acetate you would need that many, start with HMG-CoA you would need as I suggested around 10 to 20 enzymes, all of which would have to be active, all of which would have to be supplied with the necessary cofactors. It is almost impossible to be assured, to set up an in vitro assay where you can be assured that all those necessary requirements are present.

Q But if someone gave you the figure I just recited as a value determined by that assay, would you consider it significant?

A If your question -- this is an in vitro assay where the starting substrate is what?

Q Radiolabeled acetate, end product is radiolabeled cholesterol?

A And you find the value for IC_{50}. Obviously that value is significant, again, for the in vitro test.

Q Significant as to what?

A As to exerting an inhibitor effect on cholesterol biosynthesis.

Q How about HMG-CoA reductase inhibition?

A I don't think one can draw that conclusion directly upon the data you have presented me.

Q So you couldn't really predict based on that data whether a class of compounds could have in vitro activity as HMG-CoA reductase inhibitors?

A Not with that kind of a measurement.

MR. KELBER: Can I ask the relevance of this particular line of questioning? It is way beyond the scope of anything that was asked on direct.

MS. FURMAN: I think it is within the scope of establishing the credibility and the knowledge of the witness as an expert witness.

MR. KELBER: To the extent it is confined to that, I have no problem.

BY MS. FURMAN:

Q Just some further general questions. Were you aware of the Sandoz work in the HMG-CoA reductase area prior to this proceeding?

MR. KELBER: Let me object and ask, do you mean

published?

MS. FURMAN: The published work.

THE WITNESS: I don't recall having been aware of it. Let's put it that way.

BY MS. FURMAN:

Q So you don't really have any familiarity with the Sandoz literature in this area?

A No.

Q Do you have familiarity with any literature in this area, any published literature in the HMG-CoA reductase inhibition area?

A Yes.

Q Can you give me an example of some publications that you are aware of.

A I can't cite author and source, but certainly a number of papers involving the use of Compactin for this purpose, and I think I probably saw something with respect to Lovastatin as well. This is years ago.

Q Those would be hydrogenated naphthol derivatives?

A I cannot respond to that because I don't recall the structure of Compactin.

Q You don't recall the structure of Compactin?

A No.

Q Are you familiar with any heterocyclic inhibitors of HMG-CoA reductase?

A Not so that I could draw any structures for you.

Q Are you familiar with any of the findings in the art concerning these compounds, the activity levels of these compounds?

A I think I have already responded to that kind of questioning earlier, that I don't have any IC_{50} or ED_{50} values in mind for any of these compounds.

Q Do you know the structure of mevinolin?

A Close. It is fairly similar in structure to mevalonate lactone itself. But I don't recall its exact structure.

Q Are you examining the data presented in this testimony purely from an objective standpoint without any real background in the literature? Is that the case?

A No.

Q Are you able to interpret the data and the testimony in light of prior literature that you have

become familiar with?

MR. KELBER: Have you asked him a question with respect to that? You ask him a question with respect to prior literature and he will give you his answer.

BY MS. FURMAN:

Q Are you familiar with the Sandoz fluvastatin compound?

A No.

Q You do not know its structure?

A I do not.

Q Do you know its structure activity relationships which are in the literature?

A I do not.

MR. KELBER: Assuming facts not in evidence. But he is responding to your question without it.

BY MS. FURMAN:

Q Do you know the structure activity relationships for the Pyrazole HMG-CoA reductase inhibitor?

A No.

Q For the Pyrimidine?

A No.

Q So you yourself have never actually run an in

vitro or in vivo assay of an HMG-CoA reductase compound?

A That's correct.

MS. FURMAN: That's all.

MR. VILA: I just would like to take a couple of minutes and go back to Exhibit F-18, which is the data relating to ED_{50} determinations. I would like to refer you to the data on 336.

(Pause.)

MR. VILA: Strike that.

BY MR. VILA:

Q It is page 339. With regard to the data on the compound 64-935, I believe you said that you cannot accept the determination of an ED_{50} based on the data.

A There is no indication as to how -- I think this is the one for which an ED_{50} of .49 is given.

Q That's correct?

A There is no indication as to how that value is obtained.

Q Is there not a relatively standard way of determining ED_{50} from data?

A There is, but it can't be applied in this instance because the data obtained for the 0.3 milligram

per kilogram value are not significant.

Q Isn't it true from the record here that people doing these evaluations did find an ED_{50}?

MR. KELBER: I'm sorry? People? Doing these evaluations? Which people?

MR. VILA: Sandoz people.

MR. KELBER: You are asking him, again, to leap into the minds of people that we can't even identify by name.

BY MR. VILA:

Q Doesn't the record that you have seen today show an ED_{50} for this compound?

A Yes.

Q .49, as you indicate. But you disagree that an ED_{50} could be reasonably obtained from this information?

A There is no indication how the author of that figure of 0.49 obtained it.

Q Could he have been using a scientifically accepted method and come up with an ED_{50} on the basis of your experience?

A I find that difficult to accept on the basis of the fact that the intermediate dosage level of 0.3

milligrams per kilogram is not significant.

Q I would refer you to the result at 1 milligram per kilogram for this compound 64-935, the minus 65.8, I believe it is. Does that show that this compound is active at that dose?

A Yes.

Q I would like to ask you a question about the compound 64-933 as it appears on record pages 338 and 339. There are three results there. I believe here again you have testified that there is no ED_{50} for these compounds.

A There is no indication of any significant activity at any of the dose levels.

Q Can you say based on these tests that this compound would be inactive in vivo?

A At the dose levels tested, yes.

Q At a higher dose level? Can you make that statement?

A I could not make that statement.

Q Then that does not rule out the possibility this compound could be judged active at a higher dose than tested here?

A That's correct.

Q Would it be your same testimony for the compound 64-936 on record page 336?

A Yes, it would be. Since there are no testing results available there is always the possibility for any compound, that at a higher dose, it may manifest activity.

Q Do you regard this compound as showing significant activity at the dose level of .3 milligrams per kilogram?

A Yes.

MR. VILA: I have no further questions. I think maybe we should stop, take some kind of a break.

MR. KELBER: I will be done with redirect in about 15 minutes, if you want to push through.

MR. VILA: Sure.

EXAMINATION

BY MR. KELBER:

Q In cross-examination, you offered testimony with regard to the statistical analysis that was done with respect to the in vivo testing. Do you recall that testimony?

A Yes.

Q Did you perform that statistical analysis?

A No.

Q Is that statistical analysis, in fact, summarized as part of the exhibit?

A Yes.

Q Did you select the levels at which these compounds were to be tested?

A No.

Q Is it necessary to know the structure of a particular compound reflected in this in vivo assay to assess whether or not a reliable ED_{50} value is given by that assay?

A No.

Q In fact, the declaration that is F-17 does not reflect the structure of those compounds, does it?

A Does not.

Q Is it necessary to know the structure of a compound to assess whether or not data obtained from in vitro testing reflects activity for the identified compounds?

A No.

Q In fact, Dr. Scallen did not know the structure

of those compounds when he performed the testing reflected in Exhibit F-10, did he?

A That's correct.

Q Doctor, you testified at some length with regard to the connection between in vitro testing and activity in vivo. My question to you is testing, finding activity in vitro, without any follow-on in vivo testing, does that in vitro testing constitute a documentation of in vivo activity?

A No.

Q We talked about things that a researcher might or might not do in your testimony. Can you recount for me the level of skill of a researcher in this field of cholesterol biosynthesis inhibition.

A Well, for somebody to be well versed in the field, they should have a doctorate. It is certainly possible for people, even high school graduates for that matter, to be trained to perform an assay according to cookbook procedures. But to really understand all the ramifications and the significance of why things are done as they are requires a higher level of sophistication.

Q Do you recall offering testimony with regard to

the fact that compounds represented in the testing that is summarized in F-18 of the in vivo testing, although apparently not active at all levels of the 1.0 milligram per kilogram level might be active at higher levels? Do you recall that testimony?

A Yes.

Q Is it also a correct statement that they might not be active at any level?

A It is.

Q We have discussed one compound, and I believe that the number of that compound referred to in F-18 is 64-935, which the in vivo assay reported significant activity at the 1.0 milligram per kilogram and the 0.1 milligram per kilogram value but no significant activity at the 0.3 milligram per kilogram value.

Do you recall that testimony?

A Yes.

Q On the basis of your experience and knowledge, can you offer an explanation as to why the assay reflected activity at the higher and lower values but not in the intermediate values consistent with this assay?

A I really can't offer anything which would be

definitive. Under circumstances of this sort, what one does is to repeat the entire experiment at the indicated dose levels and perhaps even expand it to a couple of additional dose levels.

MR. KELBER: I have nothing further.

EXAMINATION

BY MR. VILA:

Q I believe on the reexamination you indicated that in your judgment a compound active in vitro would not be active in vivo.

MR. KELBER: I will object. I don't think that is a correct characterization of his testimony.

THE WITNESS: No.

MR. VILA: Could we go back and get that testimony.

MR. KELBER: I would be willing to offer you the latitude to go back and establish that testimony if you want to ask the foundation question. It is so far advanced in time from where we are now that it is difficult to identify from the stenographic record without having previously marked it.

MR. VILA: It was in response to the question

only about three or four minutes ago.

(The reporter read the record as requested.)

MR. VILA: My recollection must be faulty. I withdraw the question.

(Pause.)

MR. VILA: I don't think we have any further questions.

MR. KELBER: Before we go off the record, Doctor, I thank you for your attention. The transcript of this deposition will be prepared, forwarded to me and I will forward it on to you.

MS. FURMAN: We would appreciate a copy.

MR. KELBER: When you receive the transcript, you should review it to make sure that it is an accurate reflection of your testimony today. And there will be an errata sheet for indicating errors in the record and then you may sign and return it to me and we will attempt to file it.

(Whereupon, at 1:45 p.m., the deposition was concluded.)

CHESTER E. HOLMLUND

CERTIFICATE OF NOTARY PUBLIC & REPORTER
CHESTER E. HOLMLUND

I, BRENDA M. SMONSKEY, the officer before whom the foregoing deposition was taken, do hereby certify that the witness whose testimony appears in the foregoing deposition was duly sworn; that the testimony of said witness was taken in shorthand and thereafter reduced to typewriting by me or under my direction; that said deposition is a true record of the testimony given by said witness; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this deposition was taken; and, further, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

Brenda Smonskey
Notary Public in and for the
District of Columbia

My Commission Expires APRIL 14, 1996

D-00581-93

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
INTERFERENCE NOS. 102,648
102,975

WATTANASIN,
vs.
FUJIKAWA, et al.

DEPOSITION OF:
JOANNE GIESSER, ESQ.

FRIDAY, APRIL 9, 1993
12:00 P.M. to 4:30 P.M.

A P P E A R A N C E S:

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I-N-D-E-X

E-X-H-I-B-I-T-S

Giesser - cross

(Before Paula M. Quetsch, a Certified Shorthand Reporter and Notary Public of the State of Illinois, held at the offices of Amoco Corporation, 55 Shuman Boulevard, Suite 600, Naperville, Illinois, on Friday, April 9, 1993, commencing at 12:00 p.m.)

- -

J O A N N E M. G I E S S E R, 55 Shuman Boulevard, Suite 600, Naperville, Illinois, Sworn.

MR. KELBER: Good morning. This is the cross examination deposition of Joanne Giesser, is that correct --

THE WITNESS: Uh-huh.

MR. KELBER: -- responsive to the declaration filed, I'm here on behalf of Fujikawa, and we have the witness and Diane Furman on behalf of Wattanasin.

CROSS EXAMINATION

By Mr. Kelber

Q. Ms. Giesser, I'm going to hand the reporter a document that I would like identified as F20, and that's just the declaration.

(Deposition Exhibit F20 marked for identification.)

Giesser - cross

Q. If you would, take just a couple of minutes to review that document.

A. Okay.

Q. Is that document familiar to you?

A. Yes, it is.

Q. And on the last page, which is page six of the document and bears the number 373 at the right-hand top corner, is that your signature?

A. Yes, it is.

Q. Did you review any documents before -- any other documents before signing F20?

A. Yes, I did.

Q. Could you describe those documents for me?

A. They were the ones referred to in the declaration.

Q. Were there any other documents that are not identified in the declaration that you reviewed prior to signing this exhibit?

A. Not that I recall.

Q. Let me turn your attention to paragraph three on the first page of that document. Do you see the reference to the involved Wattanasin continuation application and the parent application thereof?

Giesser - cross

A. Yes.

Q. Did you review that application or the parent application prior to signing this declaration?

A. No, I did not.

Q. Do you recall the specifics of that application?

A. I recall the generalities of it.

Q. What was the basis for your conclusion that you filed the involved continuation application if you did not review it?

A. I recall filing it.

Q. How was it -- I'm sorry, if you didn't see it, how was it identified for you?

A. I'm sorry, I don't understand.

Q. Well, you didn't review the actual application itself or the parent application. Did you recall it by serial number, or what was the mechanism for identifying that application?

A. Well, up at the corner of the document it says case 600-7101 continuation.

Q. And that was sufficient to recall it for you?

A. Yes.

Giesser - cross

Q. Ms. Giesser, when did you first become aware that a third party had filed for U.S. patent protection for subject matter similar to that claimed in case number 600-7101?

A. I don't remember the exact date.

Q. Do you remember who identified it for you?

A. Not exactly. I don't recall the specifics of it.

Q. Was the third-party claim brought to your attention by someone in the patent department, do you recall?

A. It would have been likely to have been Mel Kassenoff.

Q. Isn't it correct, Ms. Giesser, that in fact the existence of the third-party patent application was brought to your attention before preparation of the draft of the Wattanasin application?

A. No, that's not how I recall it.

Q. So you recall preparing the draft and then becoming aware of the third-party case?

A. I recall being involved in preparing the draft. It wasn't finished at the time when I learned about the third-party one.

Giesser - cross

Q. Was the initial -- do you have a recollection was the initial draft prepared before learning of it?

A. No, I was in the process of preparing it.

Q. So that would have been before December -- before December 14 --

A. Yes.

Q. -- of 1988?

A. Yes.

Q. At the time you were preparing the draft document for case number 600-7101, had you previously been involved in any interference contests?

A. I had been involved in a minor amount when I was a patent examiner at the patent office. A few cases which I was examining I helped set up the interference, but I didn't do any substantive work on them.

Q. Did anyone at the Sandoz patent and trademark department assist you in requesting the declaration of interference filed in 600-7101?

A. As I recall, I had conversations with Mel Kassenoff and Dick Vila concerning how you would go about setting up such a request and spoke with them

Giesser - cross

while I was compiling necessary documents and such.

Q. Were there any considerations that you took into account in drafting the case 600-7101 by reason of the fact that you would be requesting an interference declaration in connection therewith?

A. I don't recall handling the case any differently from any other case at that point.

Q. Let me turn your attention to page two of the declaration, which is -- and starting at the top at page five -- I'm sorry, paragraph five. Do you have a recollection of actually receiving a copy of the minutes referred to in that paragraph?

A. No, I don't.

Q. Why would you have received a copy?

A. They were routinely distributed to each member of the department after the meetings.

Q. Was there any routine separation between the date of the meeting and the time the minutes were distributed?

A. They were actually distributed within about a week or so, depending on how long it took the secretaries to compile them and type it up.

Q. Were there any occasions where you did not

Giesser - cross

receive minutes of the patent committee during your tenure at Sandoz?

A. No.

Q. How did you know, as stated in paragraph six of F20, that PD 299/84 had been assigned to you?

A. It said so in the minutes.

Q. Said so in the minutes. Was there a specific statement to that effect?

A. The minutes, they would rate the application, and if it was rated A, the attorney who would be responsible for it, their initials would appear.

MS. FURMAN: Not only if it was rated A.

Q. You see the reference to existing filing priorities in paragraph six of page two of the declaration?

A. Yes.

Q. What kind of existing filing priorities were there as of the time you received the assignment of PD 299/84?

A. Mel Kassenoff had a number of cases in the general HMG-CoA Reductase area which had been rated A and which had to be filed, as well.

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Q. How about yourself?

A. At that time, no.

Q. Did you have any other cases other than case 600-7101 assigned to you for filing at the time that that particular case was assigned to you?

A. I don't recall specifically whether I had or not.

Q. Looking at paragraph six again, what other priorities existed that might preclude you from filing PD 299/84?

A. Well, there were certainly other cases around both from Pharma and for the other companies that I had responsibility for.

Q. Who is Pharma?

A. Sandoz Pharma Company.

Q. Now, by "other cases," other cases to prepare?

A. Yes.

Q. And those cases were assigned a priority in advance of 299/84?

A. I'm not sure whether all those cases were officially rated at that point or not.

Q. Okay. Well, what I'm a little confused

Giesser - cross

about is that paragraph six indicates that either Mr. Kassenoff or you would take care of it after existing filing priorities had been completed.

Now, you've testified that Mr. Kassenoff had some cases stacked up, if you will, in advance of PD 299/84. Would it be a correct conclusion that if you did not have filing priorities existing as of the time that case was assigned to you that you would have the primary responsibility for filing that case?

A. I did have the primary responsibility for filing this case.

Q. What other tasks or assignments did you have that would take priority on your resources before preparing 299/84 for filing?

A. Well, I was working for -- my responsibilities at Sandoz involved working for a number of different Sandoz companies. Aside from responsibilities in this area of Pharma, I also did a lot of work for the seed companies, which at that time were part of Sandoz' crop protection. I also was getting involved in work with a joint venture that Sandoz was involved called Repligen Sandoz

Giesser - cross

Research Corporation, or we call it RSRC.

I also had other -- aside from the HMG-CoA Reductase area, I also had other areas which I was responsible for in Pharma.

Q. Now, the other responsibilities that you had identified, and particularly the seed companies and the RSRC, did you have any filing responsibilities for them that would take priority over the filing responsibility for 600-7101?

A. Yes.

Q. Could you describe those responsibilities for me?

A. As it turned out, there were a number of applications which, out of the seed companies, although as of January 1988 had not been decided to be filed upon but later on as the year progressed were coming up against time bars.

Q. So as of January, those cases had not been assigned to you for preparation?

A. Right.

Q. Were they subsequently assigned to you for preparation?

A. Yes.

Giesser - cross

Q. And about when was that?

A. I'm not exactly sure. It was later in the year, though.

Q. Do you have a recollection of approximately how many -- would it have been as early as June?

A. Probably not the seed cases, but probably yes on a number of applications for Sandoz' crop protection.

Q. When you say a number, is that -- help me out. Is that more than five?

A. At least three.

Q. So these cases were designated A after -- and by A, I mean intended for filing -- after 600-7101 but were intended for filing before 600-7101; is that correct?

A. Yes.

Q. And they took priority over 7101 because --

A. Well, certainly, at least as I recall, I think some of the crop protection cases had -- either the scientists had wanted to publish or were scheduled to publish, so there were bars of that sort running on them.

Q. The scientists --

Giesser - cross

A. The inventors.

Q. The inventors had published?

A. No. I believe on the ones at that time they had either submitted, you know, like an abstract to a meeting or something like that -- I don't remember exactly, but I think there were publication concerns involved with some of those.

Q. How many applications did you prepare and file between January -- I'm sorry, between February '88 and March '89?

A. Including March?

Q. Let's take it through the end of February '89.

A. I don't remember exactly. Probably close to 15.

Q. And only one in the HMG-CoA Reductase field; is that correct?

A. No.

Q. What other cases were filed -- did you prepare and file in the HMG-CoA Reductase field?

A. There was a CIP, which I recall was a rather substantial CIP which was filed I believe in October of '88.

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Q. Let me turn your attention to page three of F20, specifically paragraph 11.

A. Uh-huh.

Q. There is a case referred to there, 7025/CIP/CIP. Is that the case you're referring to?

A. Yes. I believe that date is incorrect. It should be October 6th, 1988, not November.

Q. And that's based on your memory?

A. No, I have since seen copies of a filing receipt for it.

Q. You have since seen copies of the filing receipt. You did not see the filing receipt at the time you signed this declaration?

A. No, I guess I did. It says here -- there's a reference to it here on Exhibit D.

Q. So you think you did see the filing receipt --

A. Uh-huh.

Q. -- at the time that you signed this declaration?

A. Right.

Q. Are there any documents referred to in the declaration that you might not have seen at the time

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of signing?

A. Again, not that I recall.

MR. KELBER: I'm going to hand the reporter a document that I'd like identified as F21.

(Deposition Exhibit F21 marked for identification.)

Q. Ms. Giesser, is that in fact the filing receipt that you just referred to?

A. Yes, it is.

Q. And that reflects a filing date of when?

A. October 6th, 1988.

Q. My question I guess is, if you reviewed Exhibit T prior to signing this declaration, why does the declaration indicate November 6th?

A. Because it was a mistake.

Q. Are there any other possibilities of date mistakes in this declaration?

A. Not that I've noticed.

Q. If a document was received by the Sandoz patent department on a certain date, how long would it take to circulate to you specifically if you had been designated as a recipient?

A. Generally not very long.

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Q. A few days?

A. Generally less than that.

Q. Were there instances where it might have been more than that?

A. That would have been very unusual.

Q. Do you have any actual recollection of any such delivery taking more than three days?

A. Not specifically, no.

Q. Let's return to paragraph six of the declaration.

Why was PD 299/84 assigned to you?

A. At that time one of my responsibilities was to help file cases in the HMG-CoA Reductase area.

Q. By "that time," you mean February of 1988?

A. Yes.

Q. Prior to that time, how many cases in the HMG-CoA Reductase field had you filed?

A. Prior to --

Q. Prior to February 1 of 1988.

A. None.

Q. So as of February 1, 1988, what activities had you undertaken in terms of assistance in the field of filing HMG-CoA Reductase cases?

Giesser - cross

A. None.

Q. So this was your first case in that field?

A. Well, it was not the first case that I ended up filing in that field.

Q. Was this the first case -- was this the first instance of assignment of a case to you in that field?

A. It might have been of a new case.

Q. So you had been assigned preexisting cases for re-filing in that field prior to February 1, 1988?

A. I don't recall.

Q. Had you worked on the preparation of any patent applications directed to the field of HMG-CoA Reductase prior to February 1, 1988?

A. By "worked on," you mean --

Q. Had you done work of any type in terms of preparation of a patent application to be filed?

A. Preparation, no.

Q. A patent application in the HMG-CoA Reductase field prior to February 1 of 1988?

A. No.

Q. What work had you undertaken in the HMG-CoA

Giesser - cross

Reductase field prior to February 1, 1988?

A. I don't remember exactly. It's possible I might have done some prosecution of existing -- of cases that had already been filed.

Q. Can you recall any of those cases either by docket number or subject matter or issued patent?

A. Not specifically, no.

Q. When did you first take any action of any type specific to 600-7101 after the assignment of responsibility of that case to you?

A. I don't recall.

Q. Do you recall ever discussing the status of 600-7101 with Linda Rothwell?

A. I don't recall.

Q. Were you acquainted with Linda Rothwell as of February 1, '88?

A. Yes, I was.

Q. And who was Ms. Rothwell?

A. She was our docket clerk.

Q. And do you recall whether or not Ms. Rothwell had responsibility for docketing the filing of new applications that you would be handling?

Giesser - cross

A. Yes, that would be part of her responsibility.

Q. And in fact, wasn't it customary as of February 1, '88, to docket new applications for a three-week date from the date of assignment?

A. I don't know if that was customary, no.

Q. Do you recall whether or not there was a customary date assigned for the filing of new applications? In other words, was there a time space designated from the date a case was assigned to the date it would be first docketed for filing?

A. By "docketed for filing," you mean --

Q. In other words, you indicated that Ms. Rothwell was at least partly responsible for docketing in the patent and trademark department?

A. Uh-huh.

Q. Would she be responsible for tracking the docketing of new applications; would she have been responsible as of February 1, 1988?

A. I'm not sure about the term "docketing of new applications."

Q. Was a date assigned within the patent and trademark department at Sandoz for the anticipation

Giesser - cross

of filing of a new application once that application was designated A and assigned to an attorney?

A. No specific date was given, no.

Q. Would anyone have responsibility for inquiring as to the status of an application to be filed from time to time?

A. I don't know if anyone was particularly responsible. People certainly did inquire, however.

Q. Do you recall anybody inquiring as to the status of 600-7101 between February 1, '88, and March 3, 1989?

A. Not any specific inquiries. Gerald Sharkin, who was the head of the patent department, used to come around periodically, and if he felt that an application has taken awhile to file, he would check on the status of it orally.

Q. Did Mr. Sharkin ever discuss this particular case, 600-7101, with you?

A. Yes.

Q. And was he concerned as to the length of time it was taking to file the case?

A. Yes.

Q. Do you recall when that conversation took

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place?

A. I recall only one instance.

Q. Do you recall about when that one instance might have taken place?

A. It was at the filing, right when I had filed it.

Q. So he did not inquire prior to your actual filing of the application?

A. I don't recall specifically.

Q. You don't have recollection of anybody else inquiring as to the status of the case prior to March 3, 1989?

A. No specific recollection, no.

Q. Prior to February 1, 1988, had you prepared for filing any application in the field of pharmaceuticals?

A. No.

Q. Would you consider 600-7101 to be directed to pharmaceuticals?

A. Yes.

Q. Was the case that we discussed a moment ago, 600-7025/CIP/CIP, was that directed to pharmaceuticals?

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A. Yes.

Q. During the period February 1, 1988, to March 3, 1989, did you prepare any other cases directed to pharmaceuticals?

A. Yes.

Q. Can you give me an idea of approximately how many?

A. Maybe three or four.

Q. And those would have been assigned to you after 600-7101; is that correct?

A. Probably.

Q. So they were assigned to you after 600-7101 but filed before 600-7101; is that correct?

A. I'm not sure when all of them were assigned to me, but that may be correct.

Q. Well, I want to double check, because -- and I may have misheard your earlier testimony.

As of February 1, 1988, did you have assigned to you responsibility for preparing and filing any new patent application other than 7101?

A. Not that I can recall.

Q. So any applications that you did prepare and file prior to 7101 -- in other words, prior to

Giesser - cross

March 3, 1989 -- would have been assigned to you after 7101 was assigned to you; is that correct?

A. That might be true. I really don't recall.

Q. But you do positively recall filing cases in the pharmaceutical field before March 3, 1989, and February 1, 1988; is that correct?

A. Yes.

Q. Besides the CIP/CIP case, were any of the other pharmaceutical cases directed to the HMG-CoA Reductase field?

A. Yes.

Q. The cases that you filed in that time period between February 1, 1988, and March 3, 1989, that were in the HMG-CoA Reductase field, why did they receive priority ahead of 600-7101?

A. One of them I believe had a time bar running on it.

Q. By "time bar," could you explain what you mean?

A. From what I recall on this case, the parent application had been allowed, but the research had progressed to where we wanted to add extra information to it, and so we were under a time bar to

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get the CIP in prior to the paying of the allowance fee.

Q. So that was a CIP case?

A. Yes.

Q. How about the others in the HMG-CoA Reductase field that you prepared?

A. Well, I remember there was one that was specifically -- it was a process case, and I don't recall the circumstances of that one.

Q. Do you recall why it received priority ahead of 600-7101?

A. I believe I was working on the applications at the same time.

Q. But it was filed in advance of 7101?

A. Yes.

Q. Do you recall when that application was assigned to you, the one you were working on at about the same time?

A. No, I don't.

Q. But it was after February '88?

A. Probably.

Q. Was there a time bar involved in that other case, in that case that you were working on

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simultaneously with 7101?

A. I don't recall the -- I'm sorry, the --

Q. You were working on another case in the HMG-CoA Reductase field at about the same time you were working on 7101; correct?

A. I was actually working on a few of them, yes.

Q. We talked about the one with the time bar involving an allowed parent application.

A. Right.

Q. And then you mentioned a process case.

A. Right. Oh, that one. I don't recall whether that had a time bar or not on there. I believe there might have been a publication that the inventors wanted to get out, but I couldn't -- that's just speculation on my part.

Q. Were there any publications involved with respect to 7101?

A. I don't recall.

Q. If a publication -- if a request for release of a publication had been filed, would that cause the priority assigned to that application to be advanced?

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A. Generally, yes.

Q. Looking at paragraph seven, when did you receive Exhibit P?

A. Could I see Exhibit P again?

Q. Well, before looking at the exhibits that are described there, do you have any recollection of when you saw them?

A. Originally from Dr. Wattanasin, you mean?

Q. That's correct.

A. No, I don't recall.

Q. Let me hand you part of Exhibit P, which is Exhibit P-1 -- we don't have to make this part of the record -- and ask you if that refreshes your memory as to when you might have first received that document.

A. No, I don't recall.

Q. Do you remember requesting that document?

A. Not specifically, no.

Q. In fact, you didn't request that document at all; did you?

A. I don't think so.

Q. Let me hand you the rest of Exhibit P -- and we don't need to make these a record, either --

Giesser - cross

P-2 and P-3, and ask you if those refresh your recollection as to when you might have received Exhibit P.

A. No, they don't.

Q. Did you request P-2 and/or P-3?

A. I don't recall.

Q. What is your first recollection of actually taking action with respect to case 600-7101?

A. I don't recall the specific time.

Q. Let me direct your attention to paragraph ten, which is on page three of F20.

A. Yes.

Q. How do you know that you started writing the draft no later than October 1988?

A. Well, there was an exhibit that says it's a first draft Wattanasin that was early November. Exhibit U-1 says November 3rd, '88, was when Lorraine started typing it. Due to the other activities I was involved with at the time, it would have taken me at least a month, probably a lot longer -- in fact, I'm sure a lot longer -- to have drafted the application to where I would have had something to give to Lorraine by November 3rd to start typing.

Giesser - cross

Q. She wouldn't have begun typing the draft until you had completed it?

A. At least a large portion of it. It was not a finished draft when I gave it to her.

Q. And it's your recollection that it took you over a month to prepare the draft?

A. Yes.

Q. You indicated that you prepared and filed -- is it correct that you prepared and filed at least five different patent applications between the date February 1, 1988, and March 3, 1989, exclusive of 7101?

A. Yes.

Q. Can you give me an average time of how long it took you to prepare and file those cases from the date assigned to the filing date?

A. No, I couldn't.

Q. Well, you made reference to some other work that you were involved with prior to November 3, 1989. Can you describe for me that other work?

A. At that time I spent a large amount of time working for the seed companies, and it involved a large amount of travel. In fact, the most travel

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I've done in my career so far basically took place during approximately this year, and so I was out of the office a lot and had to do a lot of preparation for these various trips I was making in relation with the seed companies. So, therefore, it would have taken an extra long time for patent applications to be filed just because of the circumstances of being out of the office so much.

Q. Let me direct your attention to paragraph nine, which lies on page three of F20. Looking at the dates that you were traveling on September and October --

A. Well, actually, the September 1 is a continuation of the August 29th trip.

Q. Okay. As I look at this, you were not out of the office at any time during November; is that correct -- on business travel?

A. Business travel, yes.

Q. During the month of October it seems to me that you were gone seven days on business travel; is that correct?

A. Let's see, it was the 9th through the 11th, 16, 17 and 27th, 28th.

Giesser - cross

Q. So that's about seven days?

A. Uh-huh.

Q. And is that the travel that you referred to a brief moment ago?

A. It's certainly part of it.

Q. And that was all on behalf of the seed companies?

A. Not all, but a lot of it was.

Q. Did the work involving the seed companies, was that assigned priority greater than the preparation and filing of 7101?

A. Yes, some of the deadlines involved were more pressing.

Q. Who assigned those priorities?

A. I'm not sure that things were formally assigned.

Q. Well, who made the determination that those things were more pressing than 7101?

A. Some of it came from management within the various companies, and also a lot of this had interaction with the patent department in Basle and other high-up departments in Basle -- or higher-up figures in Basle.

Giesser - cross

Q. So these management or higher figures in Basle or in the companies of interest would advise you that something had to be done as of a certain date?

A. Correct.

Q. Were these individuals aware that you had been assigned responsibility for 600-7101?

A. I doubt if they specifically knew that.

Q. Do you regard the time from assignment of 600-7101 to the time of filing as average time for you from the date of assignment to the date of preparation and filing of an application at Sandoz?

A. No.

Q. Is it longer than average?

A. Yes.

Q. Did you discuss with anybody at Sandoz at any time the fact that it was taking longer than average to prepare and file 600-7101?

A. No, I don't recall any specific discussions to that effect.

Q. Were you ever concerned with regard to the length of time it was taking to prepare 600-7101?

A. I don't recall specific concerns about it.

Giesser - cross

I knew that after the Warner-Lambert patent had issued that we were certainly under a time restraint to get this application in the office before the Warner-Lambert became 102-B.

Q. Were there any time restraints of any type that you were aware of prior to the Warner-Lambert patent information coming to you in connection with 7101?

A. Not specifically, no.

MR. KELBER: I'm going to hand you a document that I would like marked as F22.

(Deposition Exhibit F22 marked for identification.)

Q. Is in fact Exhibit F22 the document that is referred to in paragraph nine of F20 as Exhibit S?

A. Yes.

Q. Let's take the first page of that document. You see over the right-hand column there's reference to Northrup King, Rogers Brothers and--

A. Zoecon.

Q. -- Zoecon. Thank you. Who or what was Northrup King?

A. Northrup King is a seed company owned by

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Sandoz.

Q. And Rogers Brothers?

A. Rogers Brothers is also a seed company owned by Sandoz.

Q. And Zoecon?

A. Zoecon is now a part of Sandoz Agro. It's a research facility in California.

Q. And it was a research facility at the time you visited it?

A. Yes.

Q. So you took the -- I'm sure you took the Northwest flight that stops at every city in the Greater Northwest on your way out there?

A. Something like that.

Q. Was it your habit to do business work while flying on behalf of Sandoz -- in other words, the time actually spent in the air?

A. Generally not.

Q. Rest assured, I'm not going to go through each one of these pages, but I do have questions on a few.

The second page which covers the period 3/1/88, what is the NACA patent committee?

Giesser - cross

A. National Agricultural Chemical Association. It's a trade group.

Q. And they have a patent committee?

A. It's a patent law committee.

Q. I see.

A. I was asked to represent Sandoz at one of their patent law committee meetings.

Q. Were you asked by someone within the Sandoz patent and trade department?

A. Yes.

Q. Would that individual have been aware that you had, prior to March 1, been assigned responsibility for 600-7101?

A. Yes.

Q. Let me turn your attention to the fourth page, which refers to a visit with seed committee. What was the seed committee?

A. This was a meeting in Des Plaines. Des Plaines is where the headquarters of what is now Sandoz Agro is. At that time, as I recall, the seed companies were considered part of Sandoz Agro. That's since changed.

During this time frame, the patent

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office had started issuing patents to various varieties of hybrids which were not genetically engineered, and one of the questions which we were discussing throughout this time period is how this would affect our companies and whether we should look into this as part of the patent policy. This is what involved a lot of the people from very high management.

The seed committee, as it refers to on here, were people who were involved with the seed companies in establishing and recommending patent policies for them.

Q. Would that have included other patent attorneys in addition to yourself?

A. Probably, yes.

Q. So there was an actual meeting of this committee --

A. Yes.

Q. -- during this trip?

A. Uh-huh.

Q. Do you recall participating actively at that meeting?

A. Yes.

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Q. Let's go actually to the next document -- or the next page in that document. What is the IBA?

A. Industrial Biotechnology Association. It's also a trade group.

Q. What was the nature of the meeting on or about May 2?

A. I don't recall exactly. They have periodic meetings of patent attorneys who are involved with biotechnology companies to discuss various issues of interest.

Q. Was it your habit to participate actively at those meetings?

A. Yes. I only went to a few of them on behalf of Sandoz.

Q. Were you requested by someone at Sandoz to attend those meetings?

A. Yes.

Q. Do you recall who that someone was?

A. Dick Vila.

Q. And he would have been aware of your responsibility for 600-7101; wouldn't he?

A. Yes.

Q. Before we leave the IBA, did anybody else

Giesser - cross

from Sandoz attend those meetings?

A. At that time, no.

Q. Let me turn your attention to the page -- I believe it's the seventh page. It covers the period 8/20 through 9/20/88. And you can identify it because it has in the comments Swiss franc exchange.

A. Yes, okay.

Q. Do you see the reference to Basle patent policy?

A. Yes.

Q. That was a meeting of Sandoz International?

A. It had members from -- the presidents of Northrup King and Rogers Brothers, myself, and members of the Basle patent department.

Q. Nobody else from the U.S. Sandoz patent and trademark department attended that meeting?

A. No.

Q. Let me direct your attention to fourth-from-the-last page; it covers the period 12/1 to 12/31, '88. Do you see the reference to you having delivered a patent lecture to Northrup King?

A. Right.

Giesser - cross

Q. Do you recall the nature of that lecture?

A. Yes, it was on general patent law. It took place at the American Seed Trade Association meetings, but it was a closed lecture to Northrup King personnel. A number of the Northrup King breeders who were stationed all over the country usually go to the Chicago meeting.

Q. Can you help me out with the dates over in the left-hand column? How long did this travel last?

A. Let's see, it looks like 12/6 through 12/8.

Q. Did you attend any other functions at the meeting other than delivering the patent lecture?

A. I went to a few of the lectures.

Q. The next-to-last page, which covers the time period February 1 to February 28, there's reference on that in column ten to a lecture to Rogers Brothers.

A. Right.

Q. What was the nature of that lecture?

A. General patent law and how it applied to questions that would arise in the seed industry.

Q. And you were the only person from the Sandoz patent and trademark department for that

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lecture; is that correct?

A. I think -- although I'm not sure, but I think Alan Norris, who is the manager of patents at Palo Alto, I believe he was there, also.

Q. Would he have delivered a lecture, also?

A. If he were there, he would possibly have spoken about international issues and the European system.

Q. Looking at the very last page, it wasn't much of a trip, but you went on up to New York City for the judges' dinner?

A. Yes.

Q. Was that on behalf of Sandoz?

A. Yes.

Q. Somebody at Sandoz suggested or requested that you go?

A. It was basically anyone in the department who wished to go could.

Q. Let me turn your attention to paragraph 14, page four of F20. You asked some information from Mr. Warhman?

A. Yes.

Q. Was that customary for you in the

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preparation of a patent application?

A. When it involved these kind of compounds, yes.

Q. Now, would you have needed that information to prepare the draft application -- the draft of the application in 7101?

A. As far as a completed draft, yes.

Q. Did you provide Mr. Warhman with any written information other than Exhibit V-1?

A. No. What I recall is I just drew the compounds that I wanted to get the correct technical chemical name for and just sent it over to him with a cover sheet.

Q. I'm going to hand you Exhibit V-1 -- I don't think we need to make this a record -- and ask if those are the compounds in question.

A. Yes, they are.

Q. How did you determine those specific compounds for inquiry?

A. As I recall, these were either intermediate or end products that were mentioned in the application.

Q. I'm going to hand you a document which has

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been previously identified in this proceeding as Exhibit F4 that's the application itself and ask you to take a look at that briefly. I'm going to ask you to turn to page 54 of Exhibit F4.

A. Okay.

Q. Do you see in the third line of the text -- I think it's the second line after the initial formula of that page -- the reference to C3-7cycloalkyl?

A. Yes.

Q. Do you have any recollection as to whether that phrase appeared in the initial draft that you prepared?

A. I don't recall.

Q. Do you recall whether you identified that group as a suitable group for a substituent based on your own knowledge alone without reference to other documents?

A. It would not have been from my knowledge.

Q. Is there a name for the moiety or group that corresponds to C3-7cycloalkyl?

A. I'm sorry?

Q. Let me back up and ask some foundation

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questions.

When the document refers to C3-7cycloalkyl, is it correct to understand that that means any cycloalkyl moiety having three through seven carbon atoms?

A. Yes, that's what I intended it to mean.

Q. Do you have an estimate of whether or not those of ordinary skill in the art of making HMG-CoA Reductase field would have interpreted it similarly?

A. I think they would.

Q. Certainly that phrase identifies two possible compounds, one cycloalkyl compound with three carbon atoms and one with seven; is that correct?

A. Yes.

Q. If it had three carbon atoms, would that be cyclopropyl?

A. Yes.

Q. One of skill in this art you feel would similarly interpret it that way?

A. Yes.

Q. Do you recall discussing with anyone whether or not that would be an appropriate

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recitation for the claim in -- that appears -- I guess it begins on page 54?

A. Not specifically, no.

Q. In general would you have discussed the appropriate substituents with anybody in the preparation of an application of this type?

A. Yes.

Q. What persons would that have included?

A. At least the inventor.

Q. I'm going to ask you to turn to page five of F20, which is the declaration. In particular my question pertains to the statements and comments with respect to the exhibit referred to as Y-2. I don't think we need to make that a record, but I will hand it to you for your review.

A. Okay.

Q. Did you obtain that computer printout for the preparation of 7101?

A. Yes.

Q. Why?

A. It was helpful for a number of different reasons. I thought the chemistry involved in this case was very difficult, and sometimes I felt more

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comfortable having very explicit detailed drawings so that I would get the structures right and wouldn't include wrong structures in the case; also, to make sure that I specifically covered all the specific compounds that we thought were important, and also to get the -- some of these had some kind of activity. I guess it's ED50s only -- and IC50s.

Q. Do you know who prepared that document, Y-2?

A. I believe it was -- it says on the document it was from Bob Angstrom. He was a person who did a lot of work in the activity area.

Q. Did you request that document?

A. I don't recall specifically.

Q. Ms. Giesser, can you recall any activity which you undertook between January 4, 1989, and March 3, 1989, with regard to case 600-7101?

A. I have no recollection.

Q. Do you recall receiving any changes, suggestions, additions, information of that type with respect to the draft of 600-7101 after documents that are referred to as Exhibit X, Y-1 and Y-2?

A. I'm sorry, could you repeat that?

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Q. Other than the Exhibits X, Y-1 and Y-2 referred to on page five of F20, do you recall receiving any documents relevant to case 600-7101 subsequent to January 4, 1989, but prior to March 3, 1989?

A. No, I don't recall.

Q. Do you recall reviewing any documents in connection with the preparation and signing of F20, the declaration, that you would have received between January 4 and March 3, 1989?

A. No, I don't.

Q. Would there have been any reason if the information necessary to file 7101 was in your possession as of January 4, 1989, to delay the filing to March 3, 1989, other than final preparation of the application?

A. I believe that at that point I was working on the final draft and getting comments from the inventor and things of that nature.

Q. But you don't recall any specific comments?

A. No.

Q. And you don't recall seeing any written documents to that effect?

Giesser - cross

A. No.

MR. KELBER: In New Jersey, Diane, we had discussed the possibility of requesting the documents in the file. Any progress with regard to that?

MS. FURMAN: I have searched for the so-called supplemental file, and as I indicated at that deposition, I do have some -- I do have various papers relating to the case. None of such papers bear dates, however, so I do not know whether you would be interested in seeing them. If you are, I will provide them to you.

MR. KELBER: Please do. We had also asked for any requests for publication filed relative to this. Has the search for those documents been done?

MS. FURMAN: Yes, I have isolated two requests for publication, and if you wish, I can enter into evidence now as exhibits the isolated papers that I found on the one hand and the request for publication.

MR. KELBER: Well, I don't know about the need to -- well, let's go ahead and do that.

MS. FURMAN: I have seven loose pages obtained from documents left in the possession of

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Sandoz by Ms. Giesser which relate to case 600-7101, and I would like them marked as Exhibit S1.

(Deposition Exhibit S1 marked for identification.)

MS. FURMAN: Additionally, I have a second exhibit, S2, comprising, I believe, 22 pages which represent two publication requests related to the subject matter of case 600-7101 in response to Mr. Kelber's request of record.

(Deposition Exhibit S2 marked for identification.)

BY MR. KELBER:

Q. Do you have any feel for how it was determined that the patent and trademark committee of Sandoz, through the 1988 year, how it was determined who would have specific responsibility for a particular application?

A. From what I understood, generally attorneys or agents would be assigned a particular research area, and generally there wasn't too much overlap, the HMG-CoA Reductase area being rather an exception to that rule.

So if an invention disclosure came out

#91

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

WATTANASIN	:	
	:	INTERFERENCE NOS.:
V.	:	[redacted] AND 102,975
	:	EXAMINER-IN-CHIEF
FUJIKAWA ET AL	:	MICHAEL SOFOCLEOUS

THE RECORD FOR THE PARTY
FUJIKAWA ET AL

VOLUME IV
(Pages 300-399)

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"RIBBON COPY FOR PARTY" Fujikawa et. al.

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of a particular area, unless there was a reason not to, the attorney or agent who was normally working in that area would be assigned that application.

Q. And you had -- I'm sorry, correct me if I'm wrong. You had not previously been assigned responsibility for filing an application in the HMG-CoA Reductase field as of February 1; is that correct?

A. Right. I had not been at Sandoz for very long at that time.

Q. Did you have occasion to speak with anyone at Sandoz with regard to the volume of responsibility, the volume of work that had been assigned to you in the period February 1, '88, through March '89 -- I'm sorry, specifically with regard to 7101?

A. I don't recall.

Q. With regard to the CIP/CIP case, the 7025 case, did you discuss with anybody the possibility of filing a continuation application to maintain the case pending to allow preparation and filing of the 7101 file first?

A. We really didn't have an option to delay

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the 7025-CIP/CIP case.

Q. Why is that?

A. At that time, as I believe we were filing non-convention, foreign filing non-convention -- and I believe there was an outstanding office action where allowable subject matter had been indicated, but we needed to add some specifics to various other compounds in that case. I don't remember exactly, but I think there was some sort of time bar running vis-a-vis the foreign filing in that case.

Q. Would that have been a time bar in the sense of an outstanding publication imminent?

A. I don't believe there was a publication. I think it might have been -- I forget whether it was allowable subject matter had been indicated, and I know that there was -- I did an extensive amount of work on that case with one of the agents in Basle in preparing the foreign filing text on that one, and I don't remember exactly, but I know there was some sort of time pressure going on with that one.

Q. Were there any cases that you recall that were assigned to you after February 1, 1988, that you prepared and filed prior to March 3, 1989, that did

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not involve a time bar?

A. Yes.

Q. Can you describe the field that those applications pertained to?

A. One of them was a plant biotech case that originated in Basle, which they sent the draft over, and I basically had to review the draft and make any changes necessary for filing in the United States. While that had a time bar -- well, no, that was a priority United States filing.

Q. And that case was filed before March 3, '89?

A. Yes, I believe that was filed in December of '88. There were -- as I mentioned before, I believe there were pressures to file the Agro cases, but I don't remember exactly -- it's been awhile.

Q. With regard to the case that came over from Basle in draft form, any particular reason for assigning it a filing priority ahead of 7101?

A. It was a case that did not involve the -- nearly the amount of time or substantive work as 7101, and it was something I could get filed quickly.

Q. You spoke to some kind of pressure involved

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in the cases for the seed companies. Can you describe the pressure that was involved there?

A. In March there were 102-B on-use or on-sale bars.

Q. So the bar would have been complete in March of '89?

A. Yes.

Q. You don't recall whether that date would have been before or after March 3, 1989, do you?

A. I believe some were March 3. It was a rather hectic time.

Q. Do you recall during your tenure at Sandoz whether Sandoz ever employed outside patent attorneys, attorneys not regular employees of the patent and trademark department of Sandoz, for assistance in the preparation of patent applications?

A. Very rarely.

Q. Did you have any involvement with such outside attorneys?

A. No.

Q. In the rare cases when it did happen, do you recall why that would be done?

A. Usually it would be a circumstance where we

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were licensing a third party's technology and as part of the deal we were prosecuting the patent for them, so in order to avoid any kind of conflict, we'd have a third party do it.

Q. Did you ever encounter a situation where you were assigned a number of specific tasks that had to be completed by a certain date that you simply could not complete by that date -- I'm sorry, while you were at Sandoz?

A. I certainly recall multiple deadlines. Generally they'd all be met somehow.

Q. Did you ever seek help from another individual within Sandoz in that situation where you were facing multiple deadlines?

A. Yes.

Q. Did you ever attempt to seek help with regard to the preparation of 7101?

A. Not insofar as meeting a deadline, but general help involving the chemistry of the case, yes.

Q. Do you recall subsequent to February '88 ever discussing with the patent committee at Sandoz the decision to rate 7101 as A?

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A. I would have not have ever had discussions with the patent committee.

Q. I see. So you -- okay. Do you recall ever suggesting to somebody at the committee or somebody to suggest to somebody at the committee the question of the status of 7101?

A. I did not.

Q. Let me take you back again to the period between when you began at Sandoz and February 1, 1988. Regardless of the field to which it might have pertained, as of February 1, 1988, do you recall whether you had a backlog of cases to prepare and file?

A. I don't think I had a backlog, no.

MR. KELBER: I appreciate your patience with me, and I don't have any further questions at this time.

(WHEREUPON a recess was taken.)

RE-DIRECT EXAMINATION

MS. FURMAN

Q. I would like to ask you a couple of questions first about your experience prior to coming

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to Sandoz, which I believe was raised on cross.

Is it true that you had never written a pharmaceutical patent application prior to coming to Sandoz?

A. Yes.

Q. How would you rate the difficulty of case 600-7101, let's say on a scale of one to ten?

A. With ten being hard?

Q. Correct.

A. Ten.

Q. Why would you say that?

A. It was a multi-step procedure. There were -- it was a long reaction. It's a very complex compound; it has ring substituents as well as side chain substituents, and the stereochemistry is important and is involved.

Q. Were you required to work on other subject matter with which you had no prior familiarity before coming to Sandoz?

A. Yes.

Q. What did that comprise?

A. When I came to Sandoz, basically my first assignment was the prosecution docket from Fred

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Wienfeld, who was not working there at the time; he was on disability. And Fred's docket included a number of different kinds of chemical cases. I don't recall whether there were any HMG-CoA Reductase cases or not, but I do recall cases in areas such as fire retardants, polymers and other different types of chemicals.

Q. How long had you been at Sandoz before receiving case 600-7101 as a patent disclosure for filing?

A. Well, I started in mid August of '87, and the patent committee assigned this the end of January of '88. So middle of September, October, November, December, January -- about five-and-a-half months.

Q. Were you working on any pharmaceutical case as a prosecution matter during those prior five months?

A. I don't recall. It's quite possible, since Fred Wienfeld handled a number of HMG-CoA Reductase cases.

Q. How did you become aware of the A rating of patent disclosure 299/84 at issue?

A. I don't recall. Generally I would become

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aware of them when the minutes of the patent committee meeting would be circulated and I'd receive my copy. I don't recall an exception to that, so I assume that's how I found out.

Q. Was it within your responsibility to rate patent disclosures?

A. No.

Q. Did you have any influence on the patent committee in the rating of disclosures?

A. No.

Q. What rating did the patent committee assign to a disclosure which was not to be filed upon?

A. Ever?

Q. Correct.

A. It would be D.

Q. Did patent disclosure 299/84, to your knowledge, ever receive a D rating?

A. No.

Q. Having received patent disclosure 299/84 for filing, was it within your jurisdiction or ability to -- let me rephrase that -- within your jurisdiction or ability not to file a patent application?

Giesser - re-direct

A. No.

Q. How would you characterize your obligation until the filing?

A. I had no choice but to draft the application.

Q. Is there any way to inactivate or retire a patent disclosure once rated A by the patent committee?

A. Yes.

Q. How is that?

A. You would have to have the disclosure brought up to the patent committee, and they would have to re-rate it.

Q. Did you at any time do that with respect to disclosure 299/84?

A. No.

Q. Did anyone at Sandoz carry out such a process?

A. No.

Q. You indicated that the involved application took perhaps longer to complete than applications you worked on for Sandoz?

A. Yes.

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Q. Can you explain that?

A. Well, it was a combination of factors. One, as I've mentioned before, I considered the chemistry difficult and was very concerned with making sure I had the correct chemistry at the time it actually got filed.

Secondly, I was out of the office a lot traveling on business matters, as went into before, and there were other cases and other issues which at the time seemed to need immediate attention.

And thirdly, this was a rather lengthy patent application. It was 50-some odd pages at least, and just the physical time it would take to write such an application would be long.

Q. Why did Mel Kassenoff collect information on the --

MR. KELBER: Objection, facts not in evidence.

BY MS. FURMAN:

Q. Did Mel Kassenoff collect information --

MR. KELBER: Objection. You're asking her to determine what Mel did. Anything that she says is going to be hearsay.

Giesser - re-direct

BY MS. FURMAN:

Q. How did you receive information relating to case 600-7101?

A. I don't remember exactly. I think that some of it came from Mel, and some of it came from the inventor.

Q. The part that came from Mel, if the case was assigned to you, why did information relating to the case come from Mel?

A. I would expect because the scientists involved in this program were familiar with Mel, since he had been working with them for a number of years in this area.

MR. KELBER: Objection to the degree it's speculation.

Q. Were you familiar with the people to contact and procedures to follow to collect information needed to write case 600-7101 as of February 1988?

A. No.

Q. Did you receive any assistance from anyone in the patent department with respect to the case?

A. Yes.

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Q. Who provided such assistance?

A. Mel Kassenoff.

Q. What was the nature of that assistance?

A. I'm not sure if I can recall everything he did, but he certainly helped me with a lot of chemistry and would provide names of people I had to contact if I needed certain information. For instance, with regard to -- can we go off the record for a second?

MS. FURMAN: Off the record.

(WHEREUPON a discussion was held off the record.)

THE WITNESS: With regard to Exhibit V-1, which is page 448, it's the letter I wrote to Ziggy Warhman asking for the names of the compounds, that's the sort of thing Mel would direct me how to get that information.

BY MS. FURMAN:

Q. Otherwise you would not have known independently how to obtain such information?

A. Correct.

Q. Was it ever your intention not to file a patent application and patent disclosure for 299/84?

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A. No.

Q. What about the Warner-Lambert publication; what was your reaction to this publication, in your best recollection?

A. I don't remember too much about the specifics of finding out about it. I remember being, I guess upset is possibly the best word, when I heard about it.

Q. Why were you upset?

A. Because I knew that what would otherwise be a rather straight forward prosecution of an application suddenly was not.

Q. What is your impression as the involved patent attorney of the interest of the research in the subject matter in view of the Warner-Lambert patent?

MR. KELBER: I'm sorry, could you read that question back?

(The requested testimony was read by the reporter.)

MR. KELBER: Could you specify what you mean; whose interest and involved in what?

BY MS. FURMAN:

Giesser - re-direct

Q. After you became aware of the Warner-Lambert publication, did you request a re-rating of the subject patent disclosure?

A. No.

Q. Why?

A. I don't recall.

Q. Do you recall being directed by anyone in research to drop your work on the involved application?

A. I was never told to drop the work.

Q. You have referred to your activities during the period of February 1988 to March 1989 in the agricultural area for Sandoz. Do you have any special expertise in this area?

A. Yes.

Q. What does that comprise?

A. I hold a master's degree from the Department of Agronomy at Clemson University, and my subspecialty in that area was plant genetics.

Q. Did anyone else at Sandoz have a master's in that specialty?

A. Not that I was aware of; not in the patent department.

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Q. I would like to discuss some of your travel activity during the relevant time period.

You previously testified that you visited Northrup King, Rogers Brothers and Zoecon in February of 1988?

A. Yes.

Q. Approximately how many days -- how many working days were you out of the office in February of '88?

A. It appears from the 21st through the 26th.

Q. That would be how many days?

A. Probably an entire week, five working days.

Q. How many days of preparation for this trip do you estimate was required?

A. I don't recall exactly, but there was more than the usual business trip, since I was not alone on this trip. A member of the Basle patent department, Walter Smolders, who is currently the person in charge of Sandoz Agro and seed patent activities worldwide, accompanied me on this trip.

Q. Was this trip required of you by the Basle patent department?

A. I didn't have any choice in going, if

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that's what you meant.

Q. In March of 1988 you were occupied with patent committee meetings?

MR. KELBER: Objection as to the characterization of the testimony.

BY MS. FURMAN:

Q. What kind of travel activity were you involved in in March of 1988?

A. There was a trip to RSRC in Boston and also a trip to Palo Alto, California.

Q. In March of '88?

A. Yes. Also an one-day trip to Washington, D.C.

Q. Were you required to go on each of these trips in March of 1988?

A. Yes.

Q. Who required you to?

A. Again, it was not an official requirement. Dick Vila had asked me to attend a NACA meeting. I accompanied Dick up to the RSRC visit, and the visit to Palo Alto, I was alone, but it was certainly needed in connection with my activities with Sandoz' crop protection.

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Q. Was there anyone who could substitute for you in the Sandoz patent department at the crop meetings?

A. Certainly Dick could. The point is he asked me to take this over.

Q. Approximately how many days were you out of the office on business in March of 1988?

A. Probably about seven.

Q. How many days of preparation would have been required in total for these trips?

A. The NACA meeting probably wouldn't have required much. I don't recall exactly, but there was certainly some amount of preparation for the RSRC and also the Palo Alto trips.

Q. By the way, you mentioned that Dick could possibly substitute for you. To your knowledge, did Dick Vila have a background in plant genetics?

A. No.

Q. To your knowledge, did he have a degree in agriculture?

A. No.

Q. Did he participate, to your knowledge, in drafting plant policy?

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A. Yes.

Q. In April of 1988 can you summarize how many days you were out of the office on business?

MR. KELBER: Summarize that?

BY MR. FURMAN:

Q. Can you indicate by number?

A. It looks like two.

Q. Two or three?

A. It was in a hotel. I have two nights; so probably three days.

Q. Can you do so similarly for May and June of 1988; can you give me the days out of the office on business?

A. It looks like May was one day; June looks like there was a one-day meeting to Washington and probably a two-day trip to California.

Q. That would be three?

A. Yeah.

Q. On your visit to Palo Alto, did you discuss whether patent disclosures needed to be filed?

MR. KELBER: Which visit is this?

MS. FURMAN: In June of 1988.

A. I don't remember exactly. That was a topic

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that was generally brought up when I was out in California.

Q. If patent disclosures needed to be filed for Palo Alto, who performed such filings?

A. This is a complicated question. There were basically two divisions of research in California, agricultural chemicals and plant biotechnology. The agricultural chemical filings were generally done by the person who was on site there. I think until March of '88 it was Jacqueline Larson. She left the site, and there was no one there for a few months until Alan Norris came over from Basle to take over, which was sometime in the late summer of '88, probably August.

So during that ensuing time, I'm not sure how the chemical cases got filed there, although I was -- I had filed one of the chemical ones. Jackie felt uncomfortable with a lot of the biotech applications, so the idea was that I would be working in that area.

Q. Did a backlog of biotech cases develop?

A. No.

Q. When Palo Alto decided to file a patent

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application and Alan Norris did not do it, who worked on that application?

A. Like I said, generally until Jackie left she handled all the chemical based cases. I was intended to work on the biological based cases from there.

Q. Did Dick Vila work on any of these cases?

A. I know he assisted in some of the biotech cases. I'm not sure of the time frame on those, though.

Q. When did you start writing cases for Palo Alto?

A. I don't remember exactly.

Q. Going to July of '88, how many days were you out of the office on business in that month?

A. It looks like I had a two-day trip to Des Plaines.

MR. KELBER: Can I hear the answer back again?

(The requested testimony was read by the reporter.)

BY MR. FURMAN:

Q. Let's go to August of '88. How many days

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were you out on business?

A. It looks like I had a three-night visit to Palo Alto, so that was probably four days. It was the week that overlapped the last week of August and the first week of September.

Q. In the course of your meetings on seed policy, do you remember when you were first assigned seed cases to work on?

A. Not exactly, no.

Q. Can you give me an estimate?

A. No, I don't recall when they first came up.

Q. Did these cases have statutory bars involved?

A. A number of them did.

Q. So there would have been a time constraint with respect to some of these cases?

A. Yes.

Q. How many such cases do you estimate there were, starting about June of 1988?

MR. KELBER: Objection. You're asking the witness to estimate when you haven't asked her if she knows the exact number.

BY MS. FURMAN:

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Q. Do you remember how many seed cases you worked on with a time constraint?

A. Not the exact number, no.

Q. Do you remember approximately how many?

A. There were quite a number of them. The ones that had bars coming up in March of '89 there were I think about six or so.

Q. These six cases had a required due date -- a filing date in order not to be --

A. They were coming up against the one-year in-public-use or on-sale bar.

Q. I would like to quickly finish up the number of days you were out of the office from September until -- September of 1988 until February of 1989, if you could quickly give me such an estimate for each month.

A. Well, September I had a trip to Basle, and that was four days. October I was out of the office a lot. There was another trip to California that looks like I had two days in a hotel, so probably three days out of the office. Then there was a trip to Wisconsin which looked like another two-day hotel, so probably three days out of the office, and then

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there was a trip do Boulder, Colorado, where there was -- I believe that was two days out of the office.

Q. In what month?

A. That was all October of '88.

Q. How many days in total for October?

A. Probably seven.

Q. November?

A. It looks like I got to stay home in November.

Q. Can you finish up with December through February?

A. Oh, December looks like a one-night -- so possibly two days out of the office in December. January it looks like three hotel nights, so possibly four days out of the office in January. February of '89 it looks like two hotel nights, so probably three days out of the office in February, and then in March of '89 one day -- or two days, one hotel night, so two days.

Q. The judges' dinner in March of '89 occurred after the filing date of the involved application; is that true?

A. Yes.

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Q. Did you have any sick days, to your recollection, out of the office?

A. I don't recall.

Q. Now, what other pressures to file might exist besides a 102-B bar? You testified that you filed CIP applications under certain circumstances.

A. Well, there was the CIP that's 7025-CIP/CIP; I recall there was some sort of foreign filing deadline on that one.

Q. Well, I'm trying to refresh your recollection with Exhibit S3, which comprises a few pages from the prosecution history of --

MR. KELBER: I'm going to object to this exhibit and the questions based thereon as evidence of the type that should have been submitted in direct, but you can ask the witness questions with respect to it.

MS. FURMAN: Since we believe it's necessary for adequate re-direct, we will proceed.

(Deposition Exhibit S3 marked for identification.)

BY MR. FURMAN:

Q. Have you examined Exhibit S3?

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A. Yes.

Q. If you turn to the last page of that exhibit, do you recognize this page?

A. Yes.

Q. Can you describe it?

A. It's the first page of an office action to case number 600-7025/CIP, which is the parent case of 7025/CIP/CIP.

Q. What is the date of mailing?

A. May 11th, 1988.

Q. In order for this case not to go abandoned, under the patent office rules when would a response have had to be filed?

A. It would be six months from that day, or November 11th, '88, assuming the proper fees were paid.

Q. Did you have any interaction with the Basle patent department on this case?

A. Yes, I did.

Q. What did that concern?

A. There was a plan to have a foreign filing of the subject matter of 7025/CIP along with some additional subject matter was planned to be filed

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non-convention.

Q. Did Basle call upon you to assist in the preparation of such a foreign text?

A. Yes.

Q. Was it your responsibility to consult with the inventor in the United States on this case for Basle?

A. Yes.

Q. Did you then have to redraft the application for Basle?

A. No.

Q. How did the foreign text then come about?

A. I would convey any information or comments that the inventor had on the Basle case to the people in Basle. I believe it was Lucian Vallet.

Q. Did it occur to you that it would be necessary to file a continuation-in-part application on this case?

A. Yes.

Q. What would be the purpose of such a filing?

A. To include subject matter that wasn't already present in the parent.

Q. Would you have been required to consult

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with the inventor about that additional subject matter for the foreign text?

A. Yes.

Q. What would be the latest date that you could file a CIP on case 600-7025/CIP in response to the outstanding office action?

A. It appears that the case could have been extended beyond the 11th month if we had chosen to respond to the office action.

Q. Excuse me, the 11th month?

A. I'm sorry, November 11th, '88, would have been the last date we could file if we chose not to respond to the office action.

Q. By file, you mean file a CIP?

A. Right.

Q. Is it fair to say, then, that you were under some degree of time pressure concerning the filing of the CIP on case 600-7025/CIP?

A. Yes.

Q. Was there any standard way in the Sandoz patent department, to your knowledge, of deciding to give priority to an A rated disclosure or a CIP --

A. No.

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Q. -- that had to be filed?

A. I was not aware of any policy on that.

Q. Is it fair to say that you were required to give full time to this case prior to November of 1988 --

MR. KELBER: Which case is that, Diane?

Q. -- 600-7025 for the purpose of assisting Basle in filing the foreign text?

A. Yes.

Q. Is it fair to say that you would have needed the same information to file the CIP?

A. The same --

Q. The same information as needed by Basle?

A. Yes.

Q. Now, you also mentioned a case -- an HMG-CoA case where you were under time pressure because an issue fee was due; is that correct?

A. Yes.

Q. Do you remember the subject matter in particular of that case?

A. Not exactly. I know it was another different heterocycle compound.

MS. FURMAN: I'd like to introduce one

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further exhibit to refresh your recollection for purposes of re-direct, which will be Exhibit S4.

(Deposition Exhibit S4 marked for identification.)

MR. KELBER: I'm going to object to anything and everything with regard to S4. This is a case that's not even referred to in the declaration that constitutes the direct testimony in this case. It's beyond comprehension that it could possibly be necessary for adequate re-direct, since the scope of re-direct is necessarily narrower than the scope of direct.

If you give me a continuing objection, I'll let you ask your questions.

MS. FURMAN: Fine with me.

BY MS. FURMAN:

Q. Do you recognize the second page of this exhibit?

A. Yes.

Q. What does this page comprise?

A. It's the notice of allowance for case 600-7044/CONT.

Q. To your knowledge, was this case issued?

Giesser - re-direct

A. No, this was allowed to go abandoned.

Q. Did you have any involvement in this case or a successor case?

MR. KELBER: Compound question. Why don't you ask them one at a time?

BY MS. FURMAN:

Q. Did you have any involvement in the writing of 600-7044/CONT?

A. I don't recall if I filed a continuation or whether I just received it off of Fred's docket.

MR. KELBER: Objection, that's not responsive to the question.

Q. Then you don't recall whether you were involved in 7044/CONT; is that correct?

A. That is correct.

Q. The second page of this exhibit -- what does this comprise?

A. The second page?

Q. Yes.

A. It's the notice of allowance and issue fee for 600-7044/CONT.

Q. In order to file a continuing application in this case, when would such action have had to be

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taken in order not to abandon the parent?

A. Well, to keep a chain going, it would have to have been by the due date of the issue fee, which would have been April 3rd of '89.

MR. KELBER: Can I hear that question and answer.

(The requested testimony was read by the reporter.)

MR. KELBER: Could you mark that for me?

BY MS. FURMAN:

Q. Did you in fact file a further application on 7044/CONT?

A. I filed a CIP.

Q. Is this the application you were referring to in your prior testimony concerning the need to file a case when an issue fee was due?

A. Yes.

Q. Do you recall when you filed that CIP application?

A. I believe it was in March of '89.

Q. You filed 600-7044/CONT/CIP in March of '89; correct?

A. To my best recollection, yes.

Giesser - re-direct

Q. You filed 600-7025/CIP/CIP about when?

A. October of '88. It was the beginning of October.

Q. You filed how many seed cases under time constraint -- of the seed cases you filed in March 1989, how many were under time constraint?

A. I believe all of them were.

Q. I'm sorry, I don't remember the number you indicated.

A. I think it was five or six.

Q. Would you have had to have been working on the seed cases prior to March of '89 in order to have them on file that month?

A. Yes.

Q. When is your best estimate for beginning work on the earliest of the seed cases?

MR. KELBER: Which seed cases? Why don't you rephrase it?

BY MR. FURMAN:

Q. When do you think you started working on the six seed cases you just indicated were filed in March of 1989?

A. I don't recall.

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Q. Do you have any recollection of working on the seed cases in February of 1989?

A. Yes.

Q. Do you have any recollection in January of 1989?

A. I don't recall.

Q. If I can summarize your most recent testimony on re-direct, you filed case 7025 in October of 1988, and that was under time pressure?

A. Yes.

Q. You filed case 600 7044/CONT/CIP sometime before April of 1989?

A. Yes.

Q. Was that under time pressure?

A. Yes.

Q. The six seed cases that you filed in March of 1989 were under a time pressure, as well?

A. Yes.

Q. Who decided what cases you filed in the seed or Agro area?

A. At the earlier portion of this time period the seed companies would go through the Palo Alto patent committee. The results or the recommendations

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in the Palo Alto patent committee would be noted in the Pharma patent committee or the New Jersey patent committee.

Q. Did the New Jersey patent committee have any influence, to your knowledge, on the patent decisions of Palo Alto?

A. I'm not sure if they could veto something. I know they generally took the recommendations. In the later part of this period Northrup King started having its own -- well, it wasn't a full-blown patent committee, but patent issuings would be discussed at the research management committee meeting, and the results of that would be reported back through the New Jersey patent committee meeting.

Q. Do you recollect having conflicting priorities at times in the period of June of 1988 to February of 1989 between seed and Pharma?

A. There was certainly a lot of items that had to be taken care of within a very short period of time coming from all the different companies, so yes.

Q. An example of which would be patent filings to avoid statutory bars?

A. That would be one part.

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Q. In the period between February of 1988 and March of 1989, what was your general practice in the actual preparation of the patent application? More specifically, were you able to use a computer in drafting these applications?

A. The attorneys at that time didn't have individual work stations. The secretaries had a word processor, so you would have to basically write the application in longhand and give it to the secretary to type.

Q. Is that a practice you followed in connection with case 600-7101?

A. Yes.

Q. You indicated that you provided a substantially complete draft to your secretary to be typed?

A. Yes.

Q. Do you recollect about what date that was, based on the testimony of record?

A. I believe it was around November 3rd or so. According to the affidavit exhibit it was November 3rd of '88.

Q. If you provided to her a substantially

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complete copy on November 3rd, when do you think you might have started writing that draft?

A. I don't have a recollection of when I started that.

Q. Would it have taken more than two weeks, in your estimation?

A. Yes.

Q. A month?

A. I would say longer than that.

Q. Now, we are not talking about total activity exclusive of nothing else; we're talking about the time running from the day you started writing it to the day you handed it to your secretary.

A. Yes.

Q. Would it be more than a month?

A. Yes.

Q. What's your best estimate of the length of time it took you to complete the written draft?

MR. KELBER: Objection as to speculation. The witness has already testified she doesn't know.

BY MS. FURMAN:

Q. Would it have been more than a

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month-and-a-half?

A. Yes.

Q. How about two months?

A. I would say more than that.

Q. Well, that would bring us into December; correct?

MR. KELBER: Bring us where?

THE WITNESS: I think we're talking about different things.

MS. FURMAN: The length of time for you to hand write the draft that was given to your secretary to type on the 3rd.

THE WITNESS: I was counting backwards.

MS. FURMAN: That was my purpose.

MR. KELBER: Why don't you ask the questions?

BY MS. FURMAN:

Q. Counting backwards from November 3rd of 1988, how much time did it take to prepare the written draft?

A. I don't know exactly.

Q. What was the two-month figure that you just referred to?

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A. I know I was working on it for at least two months.

Q. Two months prior to November 3rd?

A. Right, which would have been September 3rd. I was working on this prior to that.

Q. Is that as far back before November 3rd that you can recall working on it?

A. As I said, I don't specifically recall. The date which I'm basing this on is I remember that when it came to light that Warner-Lambert had a patent application issued to the same subject matter -- or when their patent issued, I was in the process of writing this at that time.

Q. While you were writing the application, you had other obligations to the other Sandoz divisions; is that correct?

A. Yes.

Q. Do you recognize the pages that comprise Exhibit S1?

MR. KELBER: I'm going to object to reliance by the junior partner on Exhibit S1; you're beyond the scope.

BY MS. FURMAN:

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Q. Do you recognize those pages?

A. Some of them.

Q. What do they concern?

A. They are all pages that were part -- were either part of a draft of the application or in preparation of a draft in the application of 600-7101.

MR. KELBER: To what part of the cross does this questioning pertain?

MS. FURMAN: At some point you indicated whether or not work was being done during a certain time period, which I'm looking for at the moment, and I believe the testimony that -- the relevant period was between January 4th of 1989 and March 3rd of 1989, and my question of Mrs. Giesser is whether she can be certain that she did not generate any of that work during the time period.

MR. KELBER: You're asking her whether she couldn't have generated any of S1 in that time period?

MS. FURMAN: Whether it was -- whether she could be certain that none of it was done during the period of January 4, 1989, to March 3rd of 1989.

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THE WITNESS: I don't know when these papers were generated.

BY MS. FURMAN:

Q. Did you regard it as your continuing obligation to file a patent application on 299/84 as of the A rating of the underlying patent -- of that patent disclosure?

A. Yes.

Q. And that obligation, when was it fulfilled, on what date?

A. The date I filed the application was March 3rd of '89.

MS. FURMAN: That concludes my re-direct.

RE-CROSS EXAMINATION

By Mr. Kelber

Q. Ms. Giesser, you feel that you have at least a few years' experience in the matters of patent prosecution; is that correct?

A. Yes.

Q. When must a continuation application be on file with the United States Patent and Trademark Office in order to claim priority of an earlier U.S. application?

Giesser - re-cross

A. As long as the earlier application is pending.

Q. So that means sometime before it issues; is that correct?

A. Yes.

MR. KELBER: Can you read back the question and answer that was marked earlier?

(The requested testimony was read by the reporter.)

BY MR. KELBER:

Q. Having heard that question and answer, do you still believe that the answer you gave is correct?

A. I think I'm getting confused. If the parent application is about to issue or go abandoned -- was it April 3rd -- then if you're going to file a continuation, it would have to be on file by that date, assuming that you were letting the parent go abandoned.

Q. So your assumption is that the parent was going to go abandoned; is that correct?

A. Yes.

Q. Let me direct your attention to the last

Giesser - re-cross

page of that exhibit that constitutes S3 -- I'm sorry, not S3, S4.

A. That's 7044?

Q. 7044, that's correct.

A. Uh-huh.

Q. As of December 28, 1988, did you intend for the 7044/CONT to go abandoned?

A. I believe by that time that a CIP was going to be filed, so I believe that if not on December 21, '88, certainly after the time we had received the office action and had a chance to reflect upon it, we would have determined that we should abandon the parent.

Q. My question to you is as of December 21, 1988, had you reached the conclusion that the parent was to be abandoned?

A. I don't recall.

Q. Well, in fact, you've read the last page of S4; is that correct?

A. Yes.

Q. The actions taken there are not exactly consistent with a determination to abandon the application; are they?

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A. At that point the question is whether we were going to abandon it on December 21st or whether we were going to abandon it eventually.

Q. So you authorized the examiner to undertake measures to place the case into condition for allowance knowing that you were going to abandon the case?

A. I'm not sure when the determination that the case was going to be abandoned was made.

Q. Would you say that the actions in the last page of Exhibit S4 are consistent with a determination to abandon the case?

A. It could be read as such.

Q. Do you see the reference to the cancelation of non-elected claims 18 and 19?

A. Yes.

Q. You could have in fact filed a divisional application directed to those claims consistent with patent office policy and then abandoned this application; couldn't you?

A. That was one option.

Q. That would have preserved the opportunity to file a CIP application tracing its priority back

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to the original application; wouldn't it?

A. You mean file a CIP off of the case containing only 18 and 19?

Q. That's correct.

A. I suppose that could have been an option.

Q. In fact, you could have re-filed 7044/CONT and subsequently filed a CIP off that re-filing and enjoyed claim to priority of the original case; correct?

A. I believe that could have been done.

Q. Let's turn to S3, which I believe is the notice of abandonment and related papers for 7025. Turning to S3, I believe your testimony was that the CIP of 7025/CIP was to be filed abroad as a non-convention case; is that correct?

A. That's the best of my recollection, yes.

Q. What was the nature of the time pressure involved if it was a non-convention case?

A. I think it might have had something to do with publication of the parent, but I couldn't be sure.

Q. Where was the parent being published?

A. Abroad, the parent abroad application.

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Q. Well, wouldn't that publication have an effective date as of May 5, 19 -- I'm sorry, as of May 5, 1987, abroad?

A. I'm sorry?

Q. Let's take the case of Europe. You indicated that the corresponding foreign application to 7025/CIP was about to be published?

A. I think that was what the -- part of what the time pressure was on it.

Q. Now, that would have constituted a bar to filing where?

A. It wouldn't have barred anything.

Q. So what was the nature of the time pressure?

A. It would have made -- part of the problem, I believe, was wanting to get the foreign application on file prior to the publication of the parent case for non-102 type reasons.

Q. You say you have recollection that there was a concern that there might be an objection abroad for a lack of availability of prior art; is that correct?

A. I believe that was one of the

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considerations.

Q. Were there other considerations?

A. I don't recall.

Q. Now, if you look at the third page of document S3, that's a request for extension of time; is that correct?

A. Yes.

Q. Why was the time period for response extended only two months?

A. I assume that was the only extension that was needed at that point.

Q. Needed for what?

A. To keep the parent -- keep the case from going abandoned.

Q. Is it correct, then, that the CIP would have been filed in the U.S. by that date?

A. Yes.

Q. So you actually filed the CIP sooner than you absolutely had to in the United States; is that correct?

A. Yes.

Q. Did you file that non-convention case in Europe before you filed the CIP in the U.S.?

Giesser - re-cross

A. I'm not sure exactly what the time frame was on that.

Q. Well, in fact --

A. It was right around the same time.

Q. Wasn't it your testimony that you did not draft the non-convention filing but rather communicated the information to Basle?

A. Yes.

Q. So you didn't have to actually prepare a rigid specification for that non-convention filing?

A. No, I did not. That was handled by the Basle patent department.

Q. And the filing of the CIP off 7025/CIP would have had no impact on the filing or entitlement -- I'm sorry, on the availability of the publication of the foreign filed parent on the European non-convention CIP; isn't that correct?

A. I'm not sure I understood what you said.

Q. I'm not sure I do, either.

Isn't it correct that the date of filing the CIP in the United States, the CIP of --

A. CIP two.

Q. Isn't it correct that the date of filing

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CIP two would have had no impact on whether or not prior art was available as against the non-convention document, the non-convention application filed abroad?

A. I don't know.

Q. In what way could it have affected the availability of prior art with respect to the non-convention application?

A. I don't know.

Q. Are you familiar with the practices of -- are you familiar with patent practices in Europe?

A. Yes.

Q. Can you imagine any situation where the filing of the CIP, of 7025/CIP, the filing date of that application would have impacted the availability of prior art as against a similar but non-convention application filed in Europe?

A. I'm sorry, I'm losing my focus here.

Q. You've told me that there was a time pressure to file the CIP of 7025/CIP, and you've told Diane the same thing, in part because there was a need to file an application abroad?

A. Yes.

Giesser - re-cross

Q. And that application was a non-convention application?

A. Yes.

Q. My question to you is, how did the need to file that non-convention application impact the need to file the CIP application in the United States?

A. Well, certainly didn't want to file any information in Europe that hadn't been filed in the United States previously.

Q. Why?

A. We would not necessarily have permission to be under export license.

Q. Couldn't you have applied for export license without filing?

A. I suppose we could have.

Q. So it's your testimony that the 7025/CIP was in fact filed before the corresponding non-convention application?

A. I think it was.

Q. Under the Sandoz procedures that existed as of February 1988, could you have proceeded correctly with the preparation of a patent application on a disclosure and operated --

Giesser - re-cross

A. No that would have been incorrect procedure.

Q. So, in fact, it would not have been proper to proceed with the preparation of an application on 299/84 until sometime after January 27, 1988; is that correct?

A. Yes.

Q. I believe it was your testimony that you weren't familiar with the procedures at Sandoz necessary to obtain the information that was a prerequisite to drafting the application for 7101; is that correct?

A. Yes.

Q. In fact, weren't those procedures just a phone call to the person in question?

A. Well, that was the question, who is the person in question.

Q. And it's fairly easy to identify that by asking Mel; wasn't it?

A. That was part of it, yes.

Q. Of the meetings that you attended that are reflected in your schedule that you testified to about at length, what meetings were there that Dick

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Vila could not have adequately represented the interests of Sandoz alone?

A. I'm sure Dick Vila can represent the interests of Sandoz whenever he chooses to.

Q. And would that representation, in your opinion, if he had so chosen, be adequate for the purposes of Sandoz' patent program?

A. Let me say Dick was at a number of these meetings.

Q. Let me turn your attention to paragraph ten on page three of F20, your declaration. I see that paragraph ten indicates you would have started writing the draft of 7101 no later than October 1988?

A. Yes.

Q. A few moments ago in response to questions from Diane you indicated that you must have started before September of 1988; is that correct?

A. Yes.

Q. What gave you the confidence that in fact it was no later than September rather than October as reflected in the declaration?

A. Well, with all the goings on at the office in October, i.e., the number of trips that I had to

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make, particularly the trip to Madison and the trip to Boulder took up a lot of time, I remember being involved in drafting the application on this when the Warner-Lambert patent issued and we found out about it, and also just the general amount of time it would take to physically write this case leads me to believe that it would have been actually earlier than September.

Q. Now, of those three aspects of information you just described, which of them did you come into possession of after February 19th, 1993?

A. After February?

Q. Of this year.

A. None.

Q. So you had all that information in front of you, you were aware of all that information before February 19th of this year; weren't you?

A. Yes.

Q. Did you discuss the date on which you must have started drafting the application with Diane during the interval after your cross-examination by me?

A. No.

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Q. Did you consider anything in responding to Diane's questions on re-direct that you did not consider --

A. No.

Q. -- that you did not consider prior to signing your declaration of February 19, '93?

A. I'm sorry, what was that question again?

Q. Did you consider anything in responding to Diane's questions just a few minutes ago that you did not consider when signing the declaration that is F20 on February 19, 1993?

A. No.

Q. Your recollection is clearer now than it was then?

A. Yes.

Q. When did you receive notice of the Warner-Lambert -- issuance of the Warner-Lambert patent?

A. I don't recall exactly, but it was shortly after the patent issued.

Q. Was it in October?

A. No, it would have been shortly afterwards, possibly within a week or two after publication -- or

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after we received the Gazette.

Q. In response to a question I asked you this morning, I believe you testified that you didn't recall when you received notice of the Warner-Lambert patent or how that information came to you.

A. I don't have an exact recollection, no.

Q. You indicated that the receipt of the official Gazette would have been important in fixing the time on which you learned of the Warner-Lambert patent. Why is that?

A. Well, the general procedure would be that after the Gazette was received in the patent office, it would be circulated among the attorneys and agents for general knowledge.

Q. How many attorneys and agents were there in Sandoz in October of 1988?

A. Let me think. Let's see, October of '88, Mel, Tom Doyle, myself, Dick Vila, Bob Awna (phonetic), Gerry Sharkin, Barry Sullivan, Tom McGovern, Walt Jewel, and Jerry Robian (phonetic).

MS. FURMAN: For the record, Barry Sullivan is a trademark attorney.

Q. How long would each attorney take to review

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the official Gazette?

A. It depended on the attorneys. The circulation was such that people who tended to be quick and pass them on would get them first, and people who were not as quick would get them last.

Q. Where did you fit in the scheme of things?

A. I tended to look at it quickly and pass it along.

Q. How long on average would it take that full rotation to complete?

A. I don't know about the full rotation. I tended to be at the top of the list of getting official Gazettes.

Q. Well, how long did it take for an official Gazette to get to you from its date of publication?

A. Generally within a week or so.

Q. Of its publication?

A. I'm sorry. Of its publication, I don't know. It would be about a week or so after we received it.

Q. How long would it take you to review the entire Gazette?

A. I would try to do it in an hour or so. I

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ignored the electrical section.

Q. You don't recall how you first became aware of the Warner-Lambert patent, do you?

A. No. It would either be by seeing it in the Gazette or hearing it from Mel, who had seen it in the Gazette.

Q. So you're certain it was either you or Mel?

A. Yes.

Q. Where did Mel fit in the pattern of obtaining it from the Gazette?

A. Since Mel was responsible for informing Basle of any substantive changes to U.S. patent law that would be proposed, he got the Gazettes either first or very close to it, so he would have been among the first ones to get it.

Q. And you knew this when you signed your declaration?

A. Yes.

Q. Do you ever dictate anything for transcription?

A. Not often, no.

Q. Anybody you know in the Sandoz office ever do that between January '88 and March '89?

Giesser - re-cross

A. Dick tended to dictate things a lot.

MS. FURMAN: For the record, his dictation was to his secretary.

MR. KELBER: You can ask her that. That's fact testimony.

THE WITNESS: Oh, were you talking about --

BY MR. KELBER:

Q. Dictation into a microphone?

A. Yeah, Dick tended to do that.

Q. Were you forbidden to do that?

A. No.

Q. That was just personal choice?

A. Yes.

Q. Do you at the present time feel incompetent to tackle the tasks assigned to you at Sandoz in the period January '88 through March '89 in a timely fashion?

A. No.

Q. Did you ever feel like there was a risk that you weren't going to get it all done?

A. At times, yes.

Q. Did you ever tell anybody about that?

A. Daily.

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Q. Who did you tell?

A. I would talk to Dick a lot.

Q. Did you ever tell Dick that there was a chance that you might not get 7101 done and filed in time?

A. In time, meaning --

Q. Whatever you felt was an appropriate time.

A. I know that it was taking a long time to do it, and he was aware of that.

Q. But did you tell him it might take you too long?

A. I don't recall ever using those words.

Q. Dick was, to the best of your knowledge, satisfied with your progress with regard to that application; wasn't he?

A. He was certainly satisfied with my overall progress of handling things.

Q. Did he ever express any dissatisfaction with your progress with respect to 7101?

A. No.

Q. And he was aware that you were responsible for 7101?

A. Yes.

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Q. In fact, you talked to him on more than one occasion with respect to 7101 while you were preparing it; correct?

A. I would speak to him in general terms about it. For technical advice I would go to Mel.

Q. You testified that you had no choice but to file a patent application on the basis of the disclosure that became 7101; is that correct?

A. Yes.

Q. Did you have the option to determine when to file that application?

A. No, it was supposed to be given priority.

Q. Priority over what?

A. That's it. When a case was rated A, it meant it was ready to be filed and you were supposed to put forth all effort to file them.

Q. But in fact, there were other things that you had to put forth effort with respect to first?

A. Yes.

Q. Even as to your refreshed recollection of today between February of 1988 and September of 1988, you did not have the opportunity to begin drafting the application; is that correct?

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A. I don't recall when I began drafting the application.

Q. How much of the application had you drafted when you learned of the Warner-Lambert patent?

A. I don't recall.

Q. Did you focus more attention on the application after you learned of the Warner Lambert patent?

A. Not any more than I had been -- I mean, I didn't treat it any differently after I found out than before I found out.

Q. Well, according to the best of your recollection, the best of your recollection tells you that you began drafting no later than September of 1988; is that correct?

A. No, I believe the best of my recollection is that it would have been earlier than that.

Q. August?

A. I would say yes, because I recall that I was working on it when I heard of the Warner-Lambert patent.

Q. July?

A. I don't know exactly.

Giesser - re-cross

Q. So the Warner-Lambert patent issuance really fixes in your mind the knowledge that you were working on the application?

A. Yes.

Q. That was an important event for you in connection with the application; is that correct?

A. Yes.

Q. Do you have any recollection as to whether you were working a long time on this application in terms of drafting before you learned of the Warner-Lambert application?

A. No, I don't have any recollection of that.

Q. So the best information that you have is sometime before the issuance of the Warner-Lambert application you began working?

A. Yes.

Q. That's quite a bit before October 1988; isn't that correct?

A. Yes.

Q. Would there have been any written records of your work of any type prior to October 1988?

A. I don't think there were any in existence then.

Giesser - re-cross

Q. No, I mean at the time.

A. Certainly my handwritten pages that I was drafting.

Q. Would anybody at Sandoz have known you were working on it at that time?

A. I'm sure Mel would have been generally aware that I was working on it. I don't know if he would recall any specific dates as to what I was doing. He was pretty busy with his own stuff at that point.

Q. How about your secretary?

A. I doubt if Lorraine would be able to distinguish between the various chemical cases I was working on in this area.

Q. So she wouldn't have known if you were working on this case or not?

A. I would say that's probably true.

Q. What happened to the case from January 27, 1988, until the time you began working on the draft?

A. From, I'm sorry, January 27th, 1988?

Q. 1988 until you began working on the draft.

A. Well, at that time Mel had collected some information on it. I don't know exactly when that

Giesser - re-cross

information went to him, but there was certainly some sort of information that I got from Mel that had been from the inventors, some preliminary --

Q. What did you do with that information?

A. I incorporated it into the draft.

Q. Before you began working on the draft, what did you do with that information?

A. I would have kept it until I began working on the draft.

Q. Do you recall reviewing it in detail?

A. Yes.

Q. Before working on the draft?

A. Yes.

Q. Do you know when that would have occurred?

A. No.

Q. You just recall reviewing it?

A. Yes.

Q. What was the nature of your review?

A. I was looking at it and trying very hard to understand it.

Q. Now, you said this was a very hard case to write; is that correct?

A. Yes.

Giesser - re-cross

Q. How much of the information on the synthesis did you obtain from the inventor?

A. I don't recall how much was directly from the inventor or how much was through Mel.

Q. Did you receive a lot of information from Mel, as well?

A. Yes.

Q. How much information with regard to the synthesis did you input yourself?

A. Possibly very little.

Q. How about the stereochemistry, the discussion of stereochemistry that appears in Exhibit S4, which is the application; did that come only from you?

A. I wrote that, but I remember discussing it with the inventor.

Q. Did anybody at Sandoz know that prior to the assignment of 7101 you had never written a pharmaceutical patent application?

A. Yes.

Q. Did Dick Vila know?

A. Yes.

Q. Did you feel at the time that you had

Giesser - re-cross

confidence in your ability to write this particular case?

A. Yes.

Q. Did you ever discuss that particular aspect of your experience with him in connection with 7101?

A. No.

Q. The seed cases that you filed in March of 1989, what were the nature of the time bars?

A. They were one of two, on-sale or in-public-use bars.

Q. And when did Sandoz' patent department learn of a need to file these applications?

A. I'm not sure what the time date was on that.

Q. Could it have been as early as January 1988?

A. No, it would have been later than that.

Q. Would it have been later than August of 1988?

A. I think it would have been, yes.

Q. So after you had begun drafting the application in question, was it necessary to put -- to interrupt that drafting in order to attend to the

Giesser - re-cross

seed cases?

A. I'm not sure whether I was -- I actually stopped working on it or whether I was working on it contemporaneously. The filing of the seed cases were in response to a policy change, and some of the discussions on the policy change were at the meeting in Basle in September, so the decision to file on these would have been after that.

Q. Do you recall how much of the application you had written before October -- draft application you had written before October of'88?

A. I would imagine it would have been relatively close to what I had given Lorraine on November 3rd, because I really wasn't in the office a whole lot or working on -- I was working on other projects for a large part of October.

Q. Well, you knew when you signed this declaration that is F20; correct?

A. Yes.

Q. Did you assign originally the date of October '88 as the date you had firm recollection of writing the first draft of 600-7101 that appears in paragraph ten?

Giesser - re-cross

A. I don't recall how that date came about.

Q. Did you receive a draft of the exhibit that is F20 and offer any corrections or advice with respect thereto?

A. Yes.

Q. In the draft that you received, was the date of October 1988 there?

A. I don't think it was.

Q. Was that date inserted in response to a suggestion from you?

A. I said I don't recall exactly the circumstances, but I remember that was an area that we had -- that there was a change from the original one.

Q. Well, it's not all that long ago compared with 1988. If the draft came to you without that information in it, isn't it reasonable to conclude that that information came from you?

A. I'm sorry.

Q. We're talking about a month-and-a-half from February 1993, and it's your testimony that you remember receiving a draft of this declaration that did not have the information in paragraph ten with

Giesser - re-cross

respect to October 1988; is that correct?

A. Yes. I recall that the original version was worded somewhat differently. I don't recall exactly what that wording was.

Q. Do you recall the effect of that wording?

A. I believe October '88 is an earlier deadline than what was originally in the first draft.

Q. An earlier date of starting?

A. Yes.

Q. Was the date of October 1988 suggested by you, then?

A. I don't recall.

Q. Who else besides you discussed the draft and changes thereto?

A. Well, I discussed them with Diane.

Q. Anybody else?

A. Not that I'm aware of. I don't know what Diane discussed.

Q. Do you recall suggesting to Diane that the date cited for beginning the draft was too late?

A. No.

Q. Somebody changed the date, though; is that correct?

Giesser - re-cross

A. Yes, that was changed.

Q. Did you give Diane documents in connection with changing the draft of this application?

A. I didn't send back a marked up document, no.

Q. I'm sorry, any other documents besides the draft declaration itself?

A. Well, she sent me copies of the other documents mentioned as exhibits.

Q. Did you send her any documents besides the documents --

A. Did I send her anything? No. I didn't take any papers connected with this case when I left Sandoz.

Q. The initial preparation of a declaration led to a date for beginning the draft of no than October 1988. You didn't consult any documents that Diane didn't give you in arriving at the date by February. Is it reasonable to conclude that the February 1988 came out of the discussions you had with Diane?

A. Yes.

Q. Isn't it necessary that the identification

Giesser - re-cross

of that date had to come from you? I mean, it was not so long ago you can't reconstruct that discussion?

A. I don't recall that discussion that clearly.

Q. Do you think if Diane knew you had begun as late as October 1988 -- strike that. It's objectionable even from me.

Did you recall when you were correcting the draft of Exhibit F20 that the Warner-Lambert patent of interest had issued while you were drafting the application?

A. Yes.

Q. But it is today your testimony that your drafting must have begun at least two months prior to the date that's reflected in your declaration?

A. Well, that is no later than October '88.

Q. It's your testimony it had to begin two months earlier than the date reflected in the declaration?

A. Yes.

Q. And you consulted no additional documents to arrive at that recollection?

Giesser - re-cross

A. Correct.

Q. Any of the other dates in here not as specifically fixed as they might be in light of your recollection of today?

A. Well, as we spoke earlier, there was a mistake on the filing date in paragraph 11.

Q. How about anything else?

A. Not that I recall.

Q. Is there any reason to believe that the other dates that are recited in here -- for instance, the date of December 14, 1988, that appears in paragraph 15, do you know for a fact that that date is correct?

A. I believe that was on a cover letter of an exhibit, so I would expect that it was correct.

Q. That was the date of the cover letter; is that correct?

A. Yes.

Q. Do you know that you sent it on the date the cover letter was dated?

A. Well, on or about that date.

Q. Could it have been as much as a week later?

A. I don't recall. I don't think so. I think

Giesser - re-cross

if -- it was my general practice that if a letter was delayed for that length of time, I would change the date on the letter to more accurately reflect when it would be sent.

Q. You spoke on re-direct with regard to the existence of conflicting obligations on your time and services between June '88 and March '89; do you recall that testimony?

A. Yes.

Q. How did you resolve those conflicting obligations when they occurred?

A. I would try and put the biggest fire out first.

Q. By "biggest fire," what do you mean?

A. The action that had the most pressing date or had the most possible adverse consequences.

Q. Missing that date would have the adverse --

A. Yes.

Q. The application that is 7101 was filed reasonably contemporaneously with the five or six seed cases that were filed in response to 102 bars in March; is that correct?

A. Yes.

Giesser - re-cross

Q. So they had the same date consequence?

A. Yes. At that point it was ready to be filed.

Q. It took you about three months to go from beginning to completion of the draft application; is that correct?

A. It appears that way, yes.

Q. Now, that's --

A. At least for completion of the first draft to filing.

Q. That's not my question. From initiating work on the first draft to completion of the first draft?

A. I don't remember exactly.

Q. It wasn't as long as four months, was it?

A. I don't recall.

Q. Forgive me for sounding a bit perturbed, but your recollection seems to come and go.

A. It's quite a while ago.

Q. It was a little bit better just a few minutes ago.

A. I remember I was working on the case when the Warner-Lambert patent issued. I don't recall how

Giesser - re-cross

long I was working on it.

Q. Did the issuance of the Warner-Lambert patent change the size of the fire, in your determination, with respect to 7101?

A. It certainly caused a lot of concern, because we were not expecting to see a Warner-Lambert patent issued to the same subject matter -- we were not expecting any patent to be issued to the same subject matter. As I said, my biggest recollection in finding out was thinking how it was going to complicate prosecution of an otherwise straight forward case.

Q. And you certainly had a time bar then with respect to the filing of the application?

A. Yes.

Q. When you signed the declaration that is F20, it was your recollection that you might have written the draft of the application that is 7101 in about a month's time; is that correct?

A. No.

Q. Well, it says no later than October 1988 you would have started writing the draft; that's correct?

Giesser - re-cross

A. Yes, that's correct.

Q. I apologize. I should have said about two months. Is that correct, it would have been two months from the -- your recollection on February 19, 1993, was that it could have been as little as two months from the beginning of the drafting to the completion of the first draft; is that correct?

A. No.

Q. Well, reading paragraph ten literally, it is consistent with the conclusion that you did not start earlier than October 1988; isn't that correct?

A. It seems consistent with the fact that October '88 would have been the latest possible date I could have started.

Q. And you know that you finished the draft prior to December 14; isn't that correct?

A. Well, I know that I gave a first handwritten version to Lorraine November 3rd.

Q. So that's just about a month; isn't it?

A. From October 1st to November 3rd is a little over a month, but as I've testified before, I was working on the application before.

Q. I understand that, but my question is, when

Giesser - re-cross

you signed this declaration, it was your recollection that it could have been as little as a month; isn't that correct?

A. No, when I signed the declaration, I knew that I had remembered working on the application when the Warner-Lambert patent came in.

Q. Did you know when the Warner-Lambert --

A. I knew it was vaguely in August. I don't know the exact date.

Q. It would have been possible to fix paragraph ten with more specificity if you had that information before you; wouldn't it?

A. It could have been possible to do a lot of things.

Q. That's not my question.

A. I didn't know you asked a question. I thought you were making a statement.

Q. It would have been possible to fix the date on which you would have started writing a draft of case 600-7101 with more specificity given the information you recall as of February 19, 1993; wouldn't it?

A. No, I don't recall when I started to work

Giesser - re-cross
on 600-7101.

Q. But you knew it was in fact earlier than September?

A. Yes.

Q. And you chose to recite October as the latest possible start date?

A. Yes.

Q. Any reason for that?

A. It seemed the most conservative.

Q. Is there still a question in your mind as to the possibility?

A. No.

Q. Was there a question in your mind as to the possibility?

A. No.

Q. What do you mean by "conservative" if you were certain that it started earlier than September?

A. I don't have a fixed date in my mind when I started writing it.

Q. But you didn't put a fixed date. You knew it was before September, you just testified?

A. That's true.

Q. So September 1988 would have been no more

Giesser - re-cross

or less conservative than October 1988; would it?

A. That could be true.

Q. Is it true?

A. Yes.

Q. Do you recall speaking to the inventor in this case with regard to 7101 between January 4 and March 3, 1989?

A. Yes.

Q. And what was the subject of those discussions?

A. I believe we went over the draft I gave him.

Q. Did you go over the changes that you had received?

A. Yes.

Q. Do you recall when you prepared the final draft?

A. Not exactly, no.

Q. When you were hired at Sandoz' patent and trademark department, do you have any reason to know -- I'm sorry, when you were hired at Sandoz' patent department, did you inform them of the nature of your prior experience in the patent field?

Giesser - re-cross

A. Yes.

Q. Is it a correct conclusion that for those meetings or trips that Dick Vila requested you to attend in the period reflected in your declaration that is F20 that he requested you to attend those having a general idea of your other obligations on behalf of Sandoz?

A. Yes.

Q. Is it correct to conclude that Sandoz -- or individuals in the Sandoz patent department made the decision to complete the drafting of the CIP application that bears the docket number 7025-CIP/CIP prior to completion of 7101 rather than filing a continuation?

A. I'm not sure that the weight of the two obligations were necessarily compared. I think it was basically decided that a CIP should be filed and should be filed now. I don't think it was --

Q. You had the responsibility for both; correct?

A. Yes.

Q. Do you remember making the decision with respect to that one way or the other?

Giesser - re-cross

A. At that time I was working on both applications. I was working on both the CIP of 7025 and also the draft of 7101.

Q. It's my understanding that of the two, you had to do the 7025 first.

A. Well, like I said, I was working on them contemporaneously.

Q. You filed 7025-CIP/CIP prior to October 11, 1988; correct?

A. Yes.

Q. If you had elected to file a continuation application or respond to the office action of May 11, '88 on 7025-CIP, thereby extending the time in which to file the CIP application, would you have had more time to work on 7101?

A. I'm not sure that was an election that I could have made at the time.

Q. If somebody at Sandoz had made that election, would you then have had more time?

A. If someone had decided that a continuation should be filed, then I would have had more.

Q. Do you recall ever being told that the 7101 case had to be on file by March of 1989?

Giesser - re-cross

A. Not specifically.

Q. That was just when you got to it?

A. That was when it was completed.

Q. And it was completed by you; correct?

A. Yes.

MR. KELBER: I have nothing further.

MS. FURMAN: I have a couple more questions.

RE-RE-DIRECT EXAMINATION

By Ms. Furman

Q. Going to case 600-7025, you earlier testified that you were writing the double CIP and transmitting information to Basle on the foreign text at the same time, roughly; is that correct?

A. Yes.

Q. In your opinion, would it have been a more economical use of your time for you to postpone filing the double CIP until sometime in the future?

A. Well, since I was working on the case with Basle, it probably would not have been.

Q. Did you need any information in filing the double CIP beyond that which you provided to Basle for the foreign text?

A. Are you asking whether I consulted the

Giesser - re-re-direct

inventors on this case?

Q. No, I'm asking whether the information that you got for foreign purposes was sufficient also for the double CIP. In other words, was drafting the double CIP very similar to preparing the draft of the foreign text?

MR. KELBER: Objection. I don't think she prepared the draft of the foreign.

BY MS. FURMAN:

Q. Was the content of the double CIP similar to the content of the foreign text?

A. As far as I recall, it was similar.

Q. It's my understanding that Basle imposed a deadline of October of '88 to file the foreign text; is that true?

A. As much as I can recommend -- excuse me, as much as I can recollect, yes.

Q. So you had no choice but to gather information, at least for preparing the foreign text, prior to October of 1988?

A. Yes.

Q. Are there structures in the involved patent application?

Giesser - re-re-direct

A. Yes.

Q. How did you dictate structures?

A. I would convey them by drawing them on the piece of paper that I gave to Lorraine. I didn't dictate this case.

Q. In fact, in a case such as this containing structures, would there be an advantage to writing out the case as opposed to dictating it?

MR. KELBER: Objection. The witness has already testified that she doesn't have much experience dictating cases. So how would she know?

MS. FURMAN: She can speculate.

MR. KELBER: Object strongly to any speculation, and the fact that you're inviting her to speculate I think is truly objectionable.

BY MS FURMAN:

Q. Does the phrase "no later than October 1988" include September of 1988?

A. Yes.

Q. Does it include August 1988?

A. Yes.

Q. Was it your intention between January 27th of 1988 and March 3rd of 1989 to file a patent

Giesser - re-re-direct

application on 299/84?

MR. KELBER: Asked and answered and far beyond the scope.

MS. FURMAN: If it's asked and answered--

A. Yes.

Q. What was the response?

A. Yes

Re-Re-Cross Examination

By Mr. Kelber

Q. What did you do to get the information for Basle's request?

A. I would have spoken with either or both Mel or the inventors of 7025-CIP/CIP.

Q. Did you actually do those things?

A. Yes.

Q. So you spoke with Mel. Couldn't Mel have sent that information on to Basle himself?

A. Well, it was my responsibility. It was not Mel's case.

Q. So you got some information from Mel, and you got some information from at least Dr. Kathawala; is that correct?

A. Yes.

Giesser - re-re-cross

Q. What did you do with that information?

A. I wrote a draft of 7025-CIP/CIP.

Q. I'm sorry, with respect to communication with Basle, what did you do?

A. I had communications in Basle, both on the phone and while I was over in Basle in September of '88.

Q. When you were in Basle for four days in September of '88?

A. Yes, I was there on -- well, on the weekdays it was Monday, Tuesday, Wednesday, and I came home on a Thursday.

Q. So three days. So the communication was over some part of those three days; is that correct?

A. Yes.

Q. How long did it take you to gather that information?

A. I don't recall exactly.

Q. As much as a day?

A. I'm sorry, to gather all the information needed to provide for the --

Q. To answer Basle's inquiry.

A. I'm sure it would have been longer than

Giesser - re-re-cross

that.

Q. Well, you talked to Mel, you said, and you talked to Mr. Kathawala. What else did you do?

A. That would have been it.

Q. I'm talking total time commitment in number of hours. How many hours did it take to talk to Mel and Dr. Kathawala?

A. As I recall, 7025-CIP/CIP was a rather extensive CIP; it was not a simple CIP, so there would have been a lot of information.

Q. I'm not referring to the CIP/CIP. You told me you needed to transmit some information to Basle with regard to additional information with regard to 7025/CIP; is that correct?

A. That was for them to write what would be the foreign counterpart of 7025-CIP/CIP.

Q. And it was your testimony that you did not write the foreign counterpart?

A. I did not write the foreign counterpart.

Q. So you collected the information and communicated it to Basle?

A. Yes. Usually the way that would work would be I would send a draft of my U.S. application, and

Giesser - re-re-cross

they would modify it for the European formats.

Q. In fact, that's not the way it worked on this case; is it?

A. No, this one, as I recall, was more contemporaneous writing of the applications by Basle and myself.

Q. And your discussions in Basle with regard to the information, that involved revising written documents?

A. I didn't do any revising of written documents over there, no.

Q. Did you write any documents over there?

A. Not that I recall.

Q. Your communication was purely oral there?

A. Yes.

Q. Did you write documents for Basle prior to going over there?

A. I don't recall. I imagine there was.

Q. You imagine there were. What type of documents would those have been?

A. Possibly transmitting technical information.

Q. Would you prepare that technical

Giesser - re-re-cross

information yourself?

A. I would compile it. For instance, diagrams of pathways, chemical pathways or such.

Q. Who would provide those pathway diagrams?

A. The inventor.

Q. So your involvement in written communication was the assembly of information received; is that correct?

A. Yes.

Q. And with regard to the non-convention case, you had some oral communication; is that correct?

A. Yes.

Q. Did you ever have another application at Sandoz that took more than a year from the date it was assigned as an A case to filing?

A. I don't recall. I would expect not.

Q. You would expect not?

A. Yes.

Q. You do recall more than one case where it took less than that amount of time?

A. Yes.

MR. KELBER: That's it.

MS. FURMAN: I have two more questions.

Giesser - re-re-re-direct

Re-Re-Re-Direct Examination

By Ms. Furman

Q. You indicated that 600-7025 CIP/CIP involved extensive work. The word extensive I believe is what you used?

A. Yes.

Q. Why do you use that word to describe it?

A. Well, the amount of material that was added, as I recall, was a lot. It wasn't just one extra example or something which you might put into a CIP. The amount of work involved was the equivalent to writing a new case, in my estimation.

Q. Would that be the same material that you needed to provide to Basle for the foreign text?

A. It would have involved the same material, yes.

Q. Do you recollect whether there was any commercial significance to the compounds covered by case 600-7025?

MR. KELBER: Objection, way beyond the scope of -- what are we, re-re-cross? Never even been raised in direct, let alone --

BY MS. FURMAN:

Giesser - re-re-re-direct

Q. Were there any other reasons for filing 7025-CIP/CIP as quickly as possible?

A. The subject matter was considered important.

MS. FURMAN: That's it. I have no more questions.

MR. KELBER: I couldn't improve on that answer myself. I appreciate your tolerance and your attention.

Are you going to take care of filing the original?

MS. FURMAN: Yes.

MR. KELBER: It continues to be your preference that we identify our objections to the declarations in writing?

MS. FURMAN: To the declarations, or the exhibits?

MR. KELBER: Yes, to both, other than Joanne's or the other ones that were subject to cross? Last time I tried to object to a declaration of yours during the deposition, and you said, quote, "we prefer the objections be made in writing." Is that still your desire?

Giesser - re-re-re-direct

MS. FURMAN: My request stands as indicated.

MR. KELBER: Okay. As far as I'm concerned, that's the end of the record.

(Whereupon the deposition was concluded.)

Giesser - re-re-re-direct

ERRATA SHEET

I have read the foregoing transcript of my deposition taken on _____, and _____ It is a true and correct transcript of my deposition given on the day and date aforesaid.

[or]

_____ I wish to make the following changes to my deposition:

Page _____ Change _____

Page _____ Change _____

Page _____ Change _____

Page _____ Change _____

Page _____ Change _____

Page _____ Change _____

Page _____ Change _____

Page _____ Change _____

Subscribed and sworn to before me this _____ day of _____, A.D. 1993.

_____

Notary Public

[Seal]

STATE OF ILLINOIS)
) SS.
COUNTY OF K A N E)

I, Paula M. Quetsch, C.S.R. No. 084-003733, a Notary Public in and for the County of Kane, State of Illinois, do hereby certify that JOANNE M. GIESSER, ESQ., was duly sworn by me to testify the truth; that the above deposition, Pages 1 through 140 was recorded stenographically be me and reduced to typewriting under my personal direction; and that the foregoing is a true and correct transcript of the testimony given by the said witness at the time and place previously specified.

I further certify that I am not counsel for nor in any way related to any of the parties to this suit, nor am I in any way interested in the outcome thereof.

IN WITNESS WHEREOF I have hereunto set my hand and affixed by notarial seal this 14th day of April, 1993.

_____
Notary Public

My Commission Expires: September 23, 1996

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

NOTICE, 37 CFR §1.682

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

BOX INTERFERENCE

SIR:

Fujikawa et al hereby serves notice pursuant to the provisions of 37 CFR §1.682 that the following printed publications are introduced into evidence:

1. Medicinal Research Reviews, Vol. 11, No. 2, 121-146 (1991)
2. J Med. Chem. 1990, 33, No. 1, 21-31
3. J Med. Chem. 1990, 33, No. 1, 31-38
4. J Med. Chem. 1990, 33, No. 1, 52-60
5. J Med. Chem. 1990, 33, No. 1, 61-70
6. J Med. Chem. 1990, 33, No. 2, 758-765

7. J Med. Chem. 1991, 34, No. 1, 357-366

8. J Med. Chem. 1991, 34, No. 1, 367-373

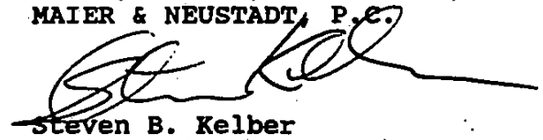
9. J Med. Chem. 1991, 34, No. 9, 2804-2815

The publications 1-9 referenced above are relevant to the issue of actual reduction to practice, and conception, of the subject matter of the Count in the above-captioned Interference. Specifically, these publications relate to measurements of the activity of specific HMG-CoA reductase inhibitors, the demonstration of which is a prerequisite to demonstration of an actual reduction to practice, purportedly shown by the Junior Party in the above-captioned Interference.

Pursuant to the provisions of Rule 682(a)(4) and Rule 682(b), copies of the publications identified above accompany this notice, and have been served on the Junior Party.

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

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

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

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

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

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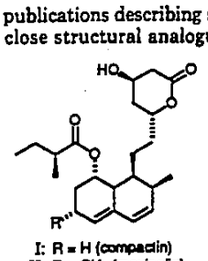
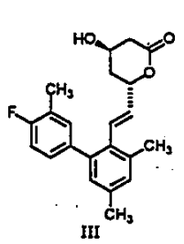
A novel series of *trans*-6-(2-pyrrol-1-ylethyl)-4-hydroxypyran-2-ones and their dihydroxy acid derivatives were prepared and evaluated for their ability to inhibit the enzyme HMG-CoA reductase in vitro. A systematic study of substitution at the 2- and 5-positions of the pyrrole ring revealed that optimum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

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



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



III

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

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

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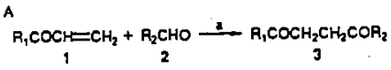
(3) (a) Therapeutic response to Lovastatin (Mevinolin) in Non-Familial Hypercholesterolemia. *J. Am. Med. Assoc.* 1986, 256, 2829. (b) Vega, L.; Grundy, S. *J. Am. Med. Assoc.* 1987, 257(1), 33–38 and references contained therein.

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

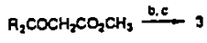
0022-2623/90/1833-0021$02.50/0

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.

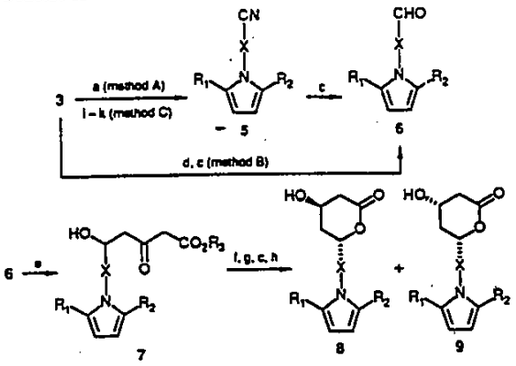
feature possessed by all of these agents was a large lipophilic group held in a particular spatial relationship with respect to the 4-hydroxypyran-2-one moiety. Indeed, examination of CPK models of these inhibitors suggested that the ortho phenyl ring might occupy the same space as the isobutyric ester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

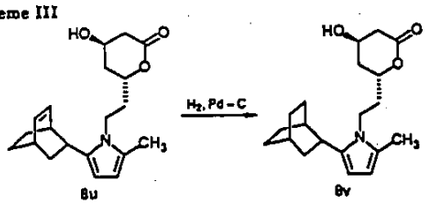
Our general synthetic strategy entailed the preparation of a suitable 1,4-diketone (3, Table I), either by the thiazolium salt chemistry developed by Stetter (Scheme I, method A)[8] or by alkylation of a β-keto ester with an α-halo ketone followed by hydrolysis and decarboxylation (method B). The Stetter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

Scheme II[a]

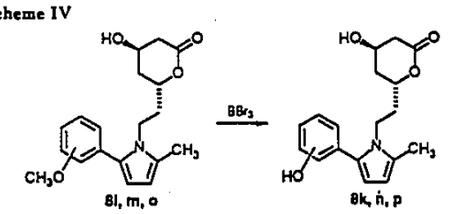


[a] (a) H_2N–X–CN, HOAc, reflux. (b) DIBAL-H, toluene, −78 °C. (c) aqueous HCl. (d) H_2N–X–$CH(OEt)_2$, toluene, cat. p-TSA, reflux. (e) $^-CH_2CO^-CHCH_2CH_3$, THF, −78 °C. (f) n-Bu_3B, $NaBH_4$, −78 °C. (g) H_2O_2, OH^-. (h) Toluene, reflux. (i) H_2N–X–OH, HOAc. (j) CH_3SO_2Cl, pyr. (k) KCN, DMF–H_2O, 100 °C.

Scheme III



Scheme IV



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

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

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

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

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

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

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

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

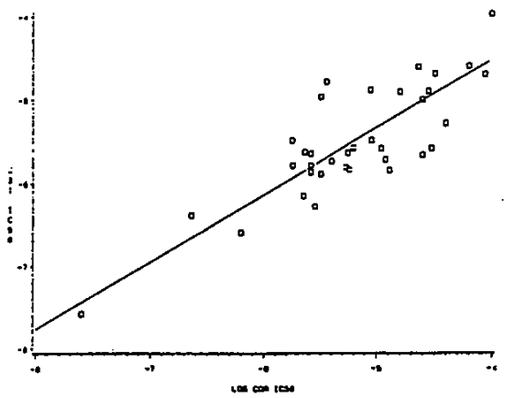


Figure 1. Correlation between CSI and COR IC_{50}'s.

Table I. Substituted 1,4-Diketones

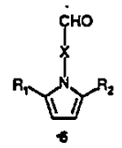
$R_1COCH_2CH_2COR_2$
3

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

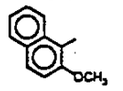
[a] All spectral data were consistent with assigned structures. [b] Purified by silica gel chromatography.

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

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



6

no.	X	R_1	R_2	% yield[a,b] (method)
6a		4-FC_6H_4	CH_3	63 (A)
6b		4-FC_6H_4	CH_3	56 (A)
6c		4-FC_6H_4	CH_3	35 (A)
6d	$-CH_2CH_2CH_2-$	4-FC_6H_4	CH_3	65 (A)
6e	$-CH(CH_3)CH_2-$	4-FC_6H_4	$CH(CH_3)_2$	34 (C)
6f	$-CH_2CH_2-$	4-FC_6H_4	CH_3	45 (A)
6g	$-CH_2CH_2-$	Ph	CH_3	27 (A)
6h	$-CH_2CH_2-$	4-PhC_6H_4	CH_3	60 (A)
6i	$-CH_2CH_2-$	4-$CH_3OC_6H_4$	CH_3	32 (A)
6j	$-CH_2CH_2-$	4-ClC_6H_4	CH_3	56 (A)[c]
6k	$-CH_2CH_2-$	3-$F_3CC_6H_4$	CH_3	37 (A)
6l	$-CH_2CH_2-$	3-$CH_3OC_6H_4$	CH_3	68 (A)
6m	$-CH_2CH_2-$	2-$CH_3OC_6H_4$	CH_3	58 (A)
6n	$-CH_2CH_2-$	2-naphthyl	CH_3	50 (A)
6o	$-CH_2CH_2-$	1-naphthyl	CH_3	23 (A)
6p	$-CH_2CH_2-$	cyclohexyl	CH_3	60 (A)
6q	$-CH_2CH_2-$		CH_3	63 (A)
6r	$-CH_2CH_2-$		CH_3	22 (A)
6s	$-CH_2CH_2-$	Ph_2CH	CH_3	32 (A)
6t	$-CH_2CH_2-$	4-FC_6H_4	$CH(CH_3)_2$	92 (A)
6u	$-CH_2CH_2-$	4-FC_6H_4	$C(CH_3)_3$	42 (C)
6v	$-CH_2CH_2-$	4-FC_6H_4	$CH(C_2H_5)_2$	46 (A)
6w	$-CH_2CH_2-$	4-FC_6H_4	cyclopropyl	25 (A)
6x	$-CH_2CH_2-$	4-FC_6H_4	cyclobutyl	34 (A)
6y	$-CH_2CH_2-$	4-FC_6H_4	cyclohexyl	22 (A)[d]
6z	$-CH_2CH_2-$	4-FC_6H_4	CF_3	55 (A)
6aa	$-CH_2CH_2-$	3-FC_6H_4	$CH(CH_3)_2$	29 (A)
6bb	$-CH_2CH_2-$	2-FC_6H_4	$CH(CH_3)_2$	17 (A)
6cc	$-CH_2CH_2-$	2,4-$F_2C_6H_3$	$CH(CH_3)_2$	20 (A)
6dd	$-CH_2CH_2-$	2-$CH_3OC_6H_4$	$CH(CH_3)_2$	42 (A)
6ee	$-CH_2CH_2-$	2,6-$(CH_3O)_2C_6H_3$	$CH(CH_3)_2$	36 (A)[e]
6ff	$-CH_2CH_2-$	2,5-$(CH_3)_2C_6H_3$	$CH(CH_3)_2$	43 (A)
6gg	$-CH_2CH_2-$	2-[$(CH_3)_2CHO$]C_6H_4	$CH(CH_3)_2$	79 (A)
6hh	$-CH_2CH_2-$	2-ClC_6H_4	$CH(CH_3)_2$	46 (A)
6ii	$-CH_2CH_2-$		$CH(CH_3)_2$	41 (C)
6jj	$-CH_2CH_2-$	$CH(C_2H_5)_2$	$CH(C_2H_5)_2$	60 (A)

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

Biological Results

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

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

(13) McOmie, J.; Watts, M.; West, D. *Tetrahedron* 1968, *24*, 2289.
(14) Dugan, R.; Slakey, L.; Briedis, A.; Porter, J. *Arch. Biochim. Biophys.* 1972, *152*, 21–7.

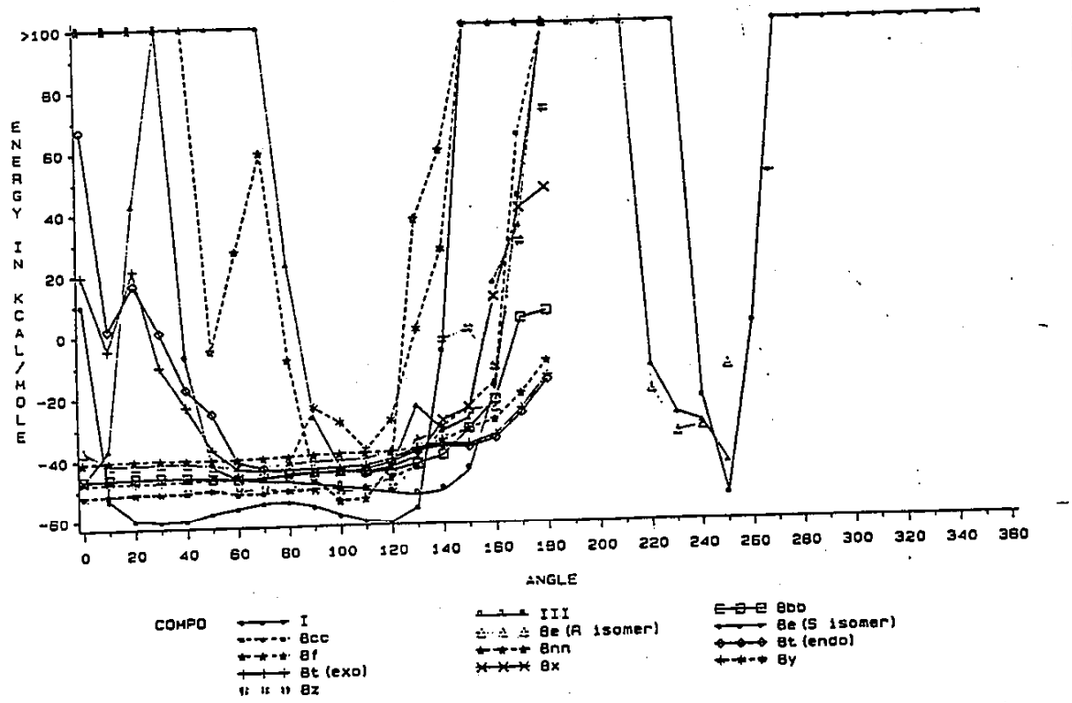


Figure 2. CAMSEQ-II energies calculated for comparable orientations of the lactone side chain. Dashed lines represent less potent analogues (8j, 8z, 8bb, 8cc, and 8nn; CSI $IC_{50} > 5$ μM).

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

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

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

Structure–Activity Relationships

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

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

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

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

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

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

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

#91

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

WATTANASIN	:	
	:	INTERFERENCE NOS.:
V.	:	[redacted] AND 102,975
	:	EXAMINER-IN-CHIEF
FUJIKAWA ET AL	:	MICHAEL SOFOCLEOUS

THE RECORD FOR THE PARTY FUJIKAWA ET AL

VOLUME V
(Pages 400-496)

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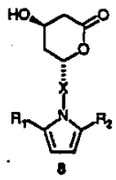
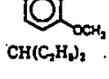
"RIBBON COPY FOR PARTY" Fujikawa et al.

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



8

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

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

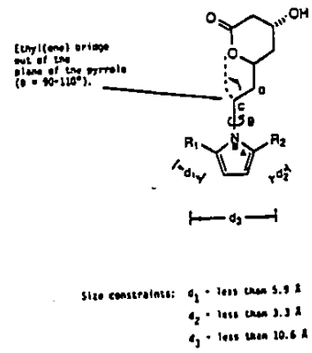


Figure 3. Summary of conclusions from the molecular modeling study.

Molecular Modeling

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

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

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

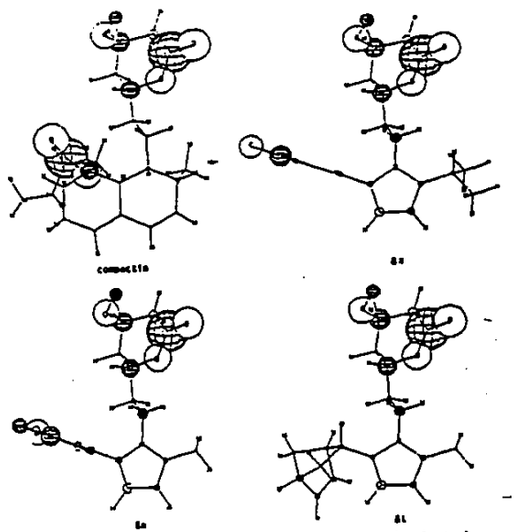


Figure 4. Charge distribution of compactin and selected analogues. Hatched and open spheres represent positive and negative charges, respectively. Sphere size is proportional to the magnitude of the atomic charge.

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

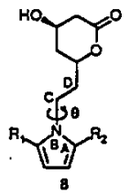
The maximum lengths of R_1 and R_2 and the overal width of the molecule across the parent ring system from R_1 to R_2 are given in Table IV. The calculations show a clear dependence of CSI potency on all three distance summarized in Figure 3. High potency ($IC_{50} < 1.6$ μM is observed only for those analogues whose (a) maximun length of R_1 (Figure 3, d_1) is <5.9 Å (Table IV: compar 8f and 8j), (b) maximum length of R_2 (Figure 3, d_2) is <3. Å (compare 8x and 8z or 8nn), and (c) overall widt (Figure 3, d_3) is <10.6 Å (compare 8y and 8bb). Othe analogues not included in Table IV reinforce the lengt constraints at R_1: the 2-naphthyl analogue 8q (d_1 = 6.4 Å) is less potent than the 1-naphthyl (d_1 = 4.20 Å), an the para-substituted derivatives 8h and 8i possess reduce potency.

Charge Distribution. Initially, it was hypothesize that the spatial orientation of polar regions with relative large partial charges within the molecule might be co nected to CSI potency. Compactin contains two distin regions of relatively large partial charges correspondi to the 4-hydroxypyran-2-one ring and the isobutyric est side chain (Figure 4). The potent inhibitors 8f and also present relatively large partial charges, albeit weak in strength, in roughly the same region as this side cha However, attempts to increase potency by more close mimicking the polar regions associated with the isobuty ester of compactin with the more polar 2- and 3-(metho and hydroxy)phenyl analogues 8m–p resulted in equi

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

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

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



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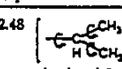
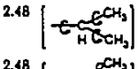
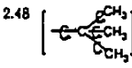
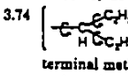
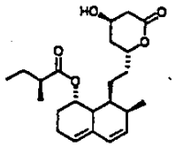
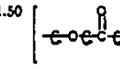
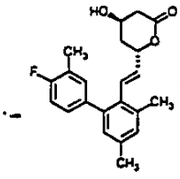
no.	R_1	R_2	IC_{50},[a] μM	lactone side chain rotations, CAMSEQ energies[b] 0°	90°	180°	min en conf	maximum overall width, Å (R_1 to R_2)	maximum lengths, Å R_1	R_2	other rotations[c]
8e	4-FC_6H_4 (α-Me)[d]	$CH(CH_3)_2$	5.0	−37.10[e]	−41.43[e]	100[e]	60°, −42.92[e]	10.12	5.58	2.48	 : also bond from α-Me to lactone side chain from 0° to 60° by 20°
8e	4-FC_6H_4 (α-Me)[f]	$CH(CH_3)_2$	5.0	−46.93[e]	−27.09[e,g]	100[e]	0°, −46.93[f]	10.12	5.58	2.48	as above
8f	4-FC_6H_4	CH_3	0.51	−40.92	−39.27	−10.03	0°, −40.92	7.66	5.58	1.50	methyl group (R_2) from 0° to 60° by 10°
8j	4-ClC_6H_4	CH_3	10					9.33	5.89	1.50	as above
8t[h]		CH_3	1.4	67.11	−44.98	−16.40	90°, −44.98	7.22	3.64	1.50	bond from R_1 to pyrrole from 0° to 360° by 20°
8t[i]		CH_3	1.4	19.63	−43.65	−15.01	70°, −44.65	7.87	4.27	1.50	as above
8x	4-FC_6H_4	$CH(CH_3)_2$	0.40	−46.64	−45.06	46.29	0°, −46.64	10.12	5.58	2.48	
8y	4-FC_6H_4	$C(CH_3)_3$	1.6	−47.77	−24.10[f]	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	5.59	3.35	bond from R_2 to pyrrole from 0° to 360° by 20°
8cc	4-FC_6H_4	cyclohexyl	100	−51.76	−50.31	100	0°, −51.76	11.92	5.58	4.33	bond from R_2 to pyrrole from 0° to 360° by 20°
8nn	$CH(C_2H_5)_2$	$CH(C_2H_5)_2$	100	100	−47.28	100	100°, −54.31	9.41	3.74	3.74	see compound 8z above
I			0.026	10.17[f]	−56.04[f]	100[f]	120°, −61.74[f]	8.81	5.66	1.50	 : terminal alkyl groups set to a staggered conformation
III			0.01	100	−48.89	100	130°, −52.92	8.74	5.52	1.50	bond from R_2 (Me) to phenyl from 0° to 60° by 20°; bond from R1 (4-F,3-MeC_6H_3) to phenyl from 0° (biphenyl coplanar) to 90° by 15°

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

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

Conclusions

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

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

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

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

Experimental Section

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

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

Alternate Synthesis of 3p. A mixture of 2-methyl-4-penten-4-one[84] (2.0 g, 20 mmol), 4-fluorobenzaldehyde (2.4 g, 20 mmol), 2 mL (14 mmol) of triethylamine, and 1.0 g (4 mmol) of 2-(2-hydroxyethyl)-3-methyl-4-benzylthiazolium chloride was stirred under nitrogen for 5 h at 70 °C, cooled to room temperature, and partitioned between ether (200 mL) and water (50 mL). The water layer was extracted with ether (200 mL). The ether extracts were combined, washed successively with water (50 mL), 2 M HCl (50 mL), and brine (50 mL), and dried. After concentration to dryness in vacuo, the residue was flash chromatographed on silica gel with hexane–ethyl acetate (20:1 v/v) as eluant, affording 2.6 g of 3p, mp 47–49 °C.

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

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

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

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

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

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 3 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 totol, 84%).

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

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

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

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

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

Liver homogenates were prepared by use of five to six passes of a Teflon pestle in a 50-mL glass homogenizer. The homogenates were pooled and centrifuged at 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 98 μmol of sodium acetate as cold carrier. When [^{3}H]-mevalonate was used, the amount of 0.5 μCi per sample with cold carrier was added to make a total of 0.2 μmol per sample. Volume of radiolabel per sample was 100 μL. After receiving radiolabel, samples were incubated at 37 °C for 1 h and treated with 2.5 mL of 10% KOH in ethanol, and the saponification was carried out at 70 °C for 2 h in a water bath. After cooling to room temperature, the nonsaponifiable lipids (cholesterol accounts for approximately 80% of nonsaponifiable lipids; the remainder are methyl sterols) were extracted by shaking the samples with 4.2 mL of hexane for 10 min. After phase separation, 2 mL of the hexane layer was diluted with 8 mL of Handifluor and counted.

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

HMG CoA Reductase Inhibition Assay 2: Co-A Reductase Inhibition Screen (COR). This procedure is a modification of that reported by Kita et al.[15] Male Charles River (CD) rats weighing 200–300 g were fed a chow diet containing cholestyramine (5%) for 3 days in order to increase levels of liver microsomal HMG–CoA reductase. Between 9 a.m. and 10 a.m., fed animals were anesthetized with ether prior to a midline incision to open the abdomen. Traverse cuts were made to the left and right of abdominal cavity exposing the hepatic portal vein. A syringe with a 22-gauge needle containing 10 mL of exsanguinating buffer (40 mM Tris, 0.25 M sucrose, 0.3 mM EDTA, 5 mM dithiothreitol (DTT), pH 7.2) was injected into the portal vein after cutting the inferior vena cava. Prior to excision, the liver was cleared of blood by perfusion with exsanguinating buffer. Immediately after excision, the liver was added to ice-cold (4 °C) pH 7.4 buffer (0.3 M sucrose, 5 mM DTT, 50 mM leupeptin, 5 mM EGTA, 1 mM PMSF). Approximately 1 g samples were taken from the largest lobe and homogenized with 10 strokes of a tight-fitting Potter-Elvehjem homogenizer. Each homogenate was centrifuged for 15 min at 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[1b] X-ray data; the structure of pyrrole came from a compendium[20] of minimized structures. Coordinates for other groups were extracted from the library of fragments within CAMSEQ-II. Structures III and 8 were built to attaching the side chain containing the 4-hydroxypyran-2-one ring (coordinates for which were copied from the X-ray structure of compactin) to the benzene and pyrrole rings, respectively, and adding the other substituents. Side chains were rotated to remove steric contacts.

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

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

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

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Registry No. 1 (R_1 = Ph), 768-03-6; 1 (R_1 = 4-F-C_6H_4), 51594-59-3; 1 (R_1 = 4-Ph-C_6H_4), 42575-11-1; 1 (R_1 = 4-Cl-C_6H_4), 7448-87-5; 1 (R_1 = 4-CH_3O-C_6H_4), 7448-86-4; 1 (R_1 = 3-F_3C-C_6H_4), 123184-14-5; 1 (R_1 = 3-CH_3O-C_6H_4), 51594-60-6; 1 (R_1 = 2-CH_3O-C_6H_4), 77942-10-0; 1 (R_1 = 2-naphthyl), 4452-06-6; 1 (R_1 = 1-naphthyl), 22422-69-1; 1 (R_1 = bicyclo[2.2.1]-hept-5-en-2-yl), 100234-78-4; 1 (R_1 = bicyclo[2.2.2]-oct-5-en-2-yl), 123184-15-6; 1 (R_1 = cyclohexyl), 2177-34-6; 1 (R_1 = Ph_2CH), 93021-71-7; 1 (R_1 = $CH(C_2H_3)_2$), 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 = $CH(C_2H_3)_2$), 97-96-1; 2 (R_2 = cyclopropyl), 1489-69-6; 2 (R_2 = cyclobutyl), 2987-17-9; 2 (R_2 = cyclohexyl), 2043-61-0; 2 (R_2 = $C(CH_3)_3$), 630-19-3; 2 (R_2 = 4-F-C_6H_4), 459-57-4; 2 (R_2 = C_2H_5), 123-38-6; 3a, 583-05-1; 3b, 123183-95-9; 3c, 63472-37-7; 3d, 53842-12-9; 3e, 2108-54-5; 3f, 123183-96-0; 3g, 123183-97-1; 3h, 104562-48-3; 3i, 123183-98-2; 3j, 123263-79-6; 3k, 70353-45-6; 3l, 123183-99-3; 3m, 61771-79-7; 3n, 123184-00-9; 3o, 123184-01-0; 3p, 104568-68-5; 3q, 123184-02-1; 3r, 123184-03-2; 3s, 123184-04-3; 3t, 123184-05-4; 3u, 123184-06-5; 3v, 123184-07-6; 3w, 123184-08-7; 3x, 123184-09-8; 3y, 123184-10-1; 3z, 123184-11-2; 3aa, 123184-12-3; 3bb, 123184-13-4; 5a, 123184-20-3; 5b, 123184-21-4; 5c, 123184-22-5; 5d, 123184-23-6; 5e, 123184-89-4; 5f, 123184-24-7; 5g, 123184-25-8; 5h, 123184-26-9; 5i, 123184-27-0; 5j, 123184-28-1; 5k, 123184-29-2; 5l, 123184-30-5; 5m, 123184-31-6; 5n, 123184-32-7; 5o, 123184-33-8; 5p, 123184-34-9; 5q, 123184-35-0; 5r, 123184-36-1; 5s, 123184-37-2; 5t, 104568-69-6; 5u, 123184-88-3; 5v, 123184-38-3; 5w, 123184-39-4; 5x, 123184-40-7; 5y, 123184-41-8; 5z, 104568-91-4; 5aa, 104568-69-6; 5bb, 123184-42-9; 5cc, 123184-43-0; 5dd, 123184-44-1; 5ee, 123184-45-2; 5ff, 123184-46-3; 5gg, 123184-47-4; 5hh, 123184-48-5; 5ii, 123184-49-6; 5jj, 123184-50-9; 6a, 123184-51-0; 6b, 123184-52-1; 6c, 123184-53-2; 6d, 123184-54-3; 6e, 123184-55-4; 6f, 123184-56-5; 6g, 123184-57-6; 6h, 123184-58-7; 6i, 123184-59-8; 6j, 123184-60-1; 6k, 123184-61-2; 6l, 123184-62-3; 6m, 123184-63-4; 6n, 123184-64-5; 6o, 123184-65-6; 6p, 123184-66-7; 6q, 123184-67-8; 6r, 123184-68-9; 6s, 123184-69-0; 6t, 104568-70-9; 6u, 123184-70-3; 6v, 123184-71-4; 6w, 123184-72-5; 6x, 123184-73-6; 6y, 123184-74-7; 6z, 123184-75-8; 6aa, 123184-76-9; 6bb, 123184-77-0; 6cc, 123184-78-1; 6dd, 123184-79-2; 6ee, 123184-80-5; 6ff, 123184-81-6; 6gg, 123184-82-7; 6hh, 123184-83-8; 6ii, 123184-84-9; 6jj, 123184-85-0; 7a, 123184-90-7; 7b, 123184-91-8; 7c, 123184-92-9; 7d, 123184-93-0; 7e, 123184-94-1; 7f, 123184-95-2; 7g, 123184-96-3; 7h, 123184-97-4; 7i, 123184-98-5; 7j, 123184-99-6; 7l, 123185-00-2; 7m, 123185-01-3; 7o, 123185-02-4; 7q, 123185-03-5; 7r, 123185-04-6; 7s, 123185-05-7; 7t, 123185-06-8; 7u, 123185-07-9; 7w, 123185-08-0; 7x, 104568-71-0; 7y, 123185-09-1; 7z, 123185-10-4; 7aa, 123185-11-5; 7bb, 123185-12-6; 7cc, 123185-13-7; 7dd, 123185-14-8; 7ee, 123185-15-9; 7ff, 123185-16-0; 7gg, 123185-17-1; 7hh, 123185-18-2; 7ii, 123185-19-3; 7jj, 123185-20-6; 7kk, 123185-21-7; 7ll, 123185-22-8; 7mm, 123185-23-9; 7nn, 123185-24-0; 8a, 123185-25-1; 8b, 123185-26-2; 8c, 123185-27-3; 8d, 123185-28-4; 8e (stereoisomer 1), 123185-29-5; 8e (stereoisomer 2), 123185-49-9; 8f, 104568-74-3; 8g, 105356-37-4; 8h, 104568-81-2; 8i, 104568-78-7; 8j, 123185-30-8; 8k, 123185-31-9; 8l, 104568-80-1; 8m, 123185-32-0; 8n, 123185-33-1; 8o, 104568-77-6; 8p, 123185-34-2; 8q, 104568-83-4; 8r, 104568-82-3; 8s, 104568-79-8; 8t (stereoisomer 1), 123355-04-4; 8t (stereoisomer 2), 123283-97-6; 8u, 123185-35-3; 8v, 123185-36-4; 8w, 104568-85-6; 8x, 104568-73-2; 8y, 104568-76-5; 8z, 123185-37-5; 8aa, 104568-75-4; 8bb, 123185-38-6; 8cc, 123185-39-7; 8dd, 104568-92-5; 8ee, 123185-40-0; 8ff, 123185-41-1; 8gg, 123185-42-2; 8hh, 105356-38-5; 8ii, 123185-43-3; 8jj, 123185-44-4; 8kk, 123185-45-5; 8ll, 123185-46-6; 8mm, 123185-47-7; 8nn, 123185-48-8; $EtCOCH_2CO_2Me$, 30414-53-0; $CF_3COCH_2CO_2Me$, 83643-84-9; m-$FC_6H_4COCH_2Br$, 53631-18-8; $(CH_3)_2CHCH_2CO_2Me$, 42558-54-3; p-$FC_6H_4COCH_2Br$, 403-29-2; 2,6-$(MeO)_2C_6H_3COCH_2Br$, 123184-19-0; 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride, 4568-71-2; 2-(2-hydroxyethyl)-3-methyl-4-benzylthiazolium chloride, 123184-18-9; 3-aminopropionitrile $^1/_2$-fumarate, 2079-89-2; 2-[2-(4-fluorophenyl)-5-(1,1-dimethylethyl)-1*H*-pyrrol-1-yl]-2-ethanol, 123184-86-1; 2-[2-(4-fluorophenyl)-5-(1,1-dimethylethyl)-1*H*-pyrrol-1-yl]-2-ethyl methanesulfonate, 123184-87-2; methyl acetoacetate, 105-45-3; cholesterol, 57-88-5.

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

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

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

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

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

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

0022-2623/90/1833-0031$02.50/0

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

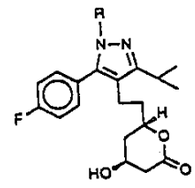
We previously described a series of 2,5-disubstituted pyrrole mevalonolactones whose 3,5-dihydroxyheptanoic acid derivatives were shown to possess varying degrees of intrinsic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity in vitro.[1] Structure–activity relationships (SAR) for this 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

Table I. Physical Properties and in Vitro HMG-CoA Reductase Inhibitory Actives of Pyrazole Mevalonolactones I

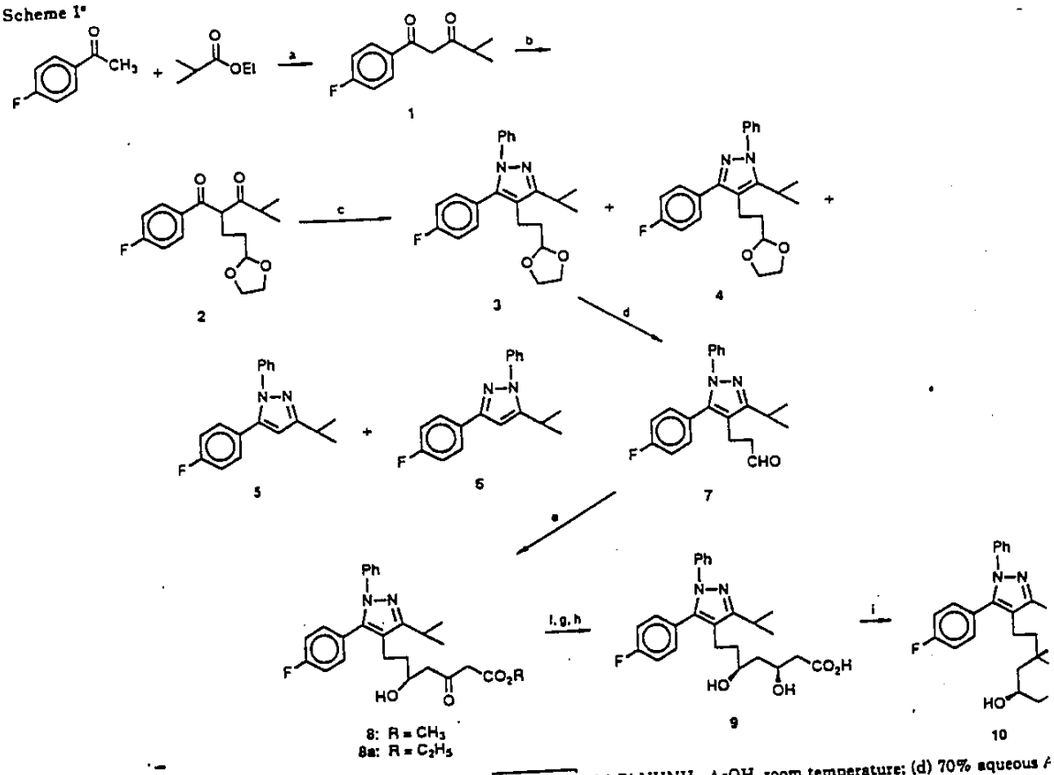


I

no.	R	mp, °C	formula[a]	method of prep	CSI IC_{50},[d] μM	rel (CSI) potenc
10	Ph	165–167	$C_{25}H_{27}FN_2O_3$	A, B	0.035	83.0
25	4-fluorophenyl	138–142	$C_{25}H_{26}F_2N_2O_3$	A	0.032	62.0
26	4-methylphenyl	152–153	$C_{26}H_{29}FN_2O_3$	A	0.040	49.0
27	4-tolylsulfonyl	foam	$C_{26}H_{29}FN_2O_5S$	B	0.660	4.5
28	4-methoxyphenyl	134–139	$C_{26}H_{29}FN_2O_4$[e]	A	0.039	75.8
29	benzyl	145–148	$C_{26}H_{29}FN_2O_3$[f]	A	0.158	12.6
30	1-naphthyl	75–81	$C_{29}H_{29}FN_2O_3$[g]	B	0.234	19.6

[a] Analytical results are within ±0.4% of the theoretical values unless otherwise noted. [b] Potency of compactin arbitrarily assigned a val of 100, and the IC_{50} value of the test compound was compared with that of compactin determined simultaneously. [c] Anal. Calcd: C, 69.(Found: C, 68.30. >98% pure by HPLC. [d] Anal. Calcd: H, 6.70. Found: H, 7.22. Calcd: N, 6.42. Found: N, 5.85. >98% pure by HPL [e] Anal. Calcd: C, 73.21. Found: C, 72.46. >98% pure by HPLC. [f] Cholesterol synthesis inhibition (CSI). Assays of each inhibi concentration were performed in triplicate and the precision for compactin was 37%. See ref 1. [g] All compounds tested had a diaster metric purity of >95% of the trans diastereomer as determined by HPLC and/or 200-MHz NMR.

Scheme I[a]



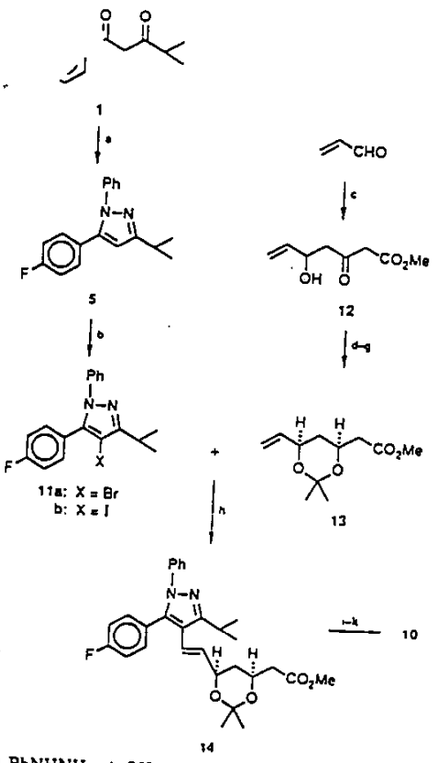
8: R = CH_3
8a: R = C_2H_5

[a] (a) NaH, DMF, 80 °C; (b) NaH, DMF, NaI, $BrCH_2CH_2CHO(CH_2)O$; (c) $PhNHNH_2$, AcOH, room temperature; (d) 70% aqueous A Δ; (e) $^-CH_2CO^-CHCO_2R$; (f) BR_3, air; (g) $NaBH_4$, −78 °C; (h) H_2O_2, ^-OH; (i) tol, Δ.

improved inhibitory potencies compared to the pyrrole mevalonolactones.

Chemistry

The target lactones, listed in Table I, were prepared by the general synthetic routes outlined in Schemes I a: The general method (method A) employed for the struction of the pyrazole nucleus was condensatio 1,3-dicarbonyl compound with a suitably substitute drazine. Two regioisomers can theoretically arise, b



[a] (a) $PhNHNH_2$, AcOH, room temperature; (b) NBS or NIS, DMF, 0 °C; (c) $^-CH_2CO^-CHCO_2Et$; (d) Bu_3B, air; (e) $NaBH_4$; (f) H_2O_2/OH^-; (g) $(CH_3)_2C(OCH_3)_2$, CSA, acetone; (h) $(Ph_3P)_2PdCl_2$, Et_3N, DMF, 70 °C; (i) H_2, Pd/C; (j) HCl, NaOH; (k) Tol, Δ.

judicial choice of solvent and reaction temperature, one regioisomer can predominate. Initial studies began with the incorporation of the preferred substituents (4-fluorophenyl and isopropyl) discovered in the SAR of the pyrrole mevalonolactones.[1] The requisite 1,3-diketone 1 was synthesized by a Claisen type acylation of 4-fluoroacetophenone with ethyl isobutyrate.[3] This product, which was almost completely enolized (86% by NMR), was alkylated with 2-(2-bromoethyl)-1,3-dioxolane[4] to give the C-alkylated 1,3-diketone 2 in 58% yield, together with a small amount of material presumed to be the O-alkylated product. Condensation with phenylhydrazine in acetic acid at room temperature afforded predominantly one regioisomer (~90%), tentatively assigned structure 3 in which the aryl groups exist in a 1,5-relationship (rather than 1,3). NMR studies[5] on 1,3- and 1,5-diphenylpyrazoles have shown that the chemical shifts of phenyl groups in the 1,3-regioisomer extend from δ 7.0 to 8.1 ppm. In our case, downfield resonances at δ 8.0 ppm were barely discernible. The majority of the aryl proton resonances were found in the region from δ 7.0 to 7.3 ppm which was in accordance with resonances published for 1,5-diphenylpyrazole. This regiochemistry was confirmed by an X-ray crystallographic analysis of the eventual target lactone derived from 3 (vide

(3) Levine, R.; Conroy, J. A.; Adams, J. T.; Hauser, C. R. *J. Am. Chem. Soc.* **1945**, *67*, 1516.
(4) Buchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122.
(5) Ruu, T.; LeStrat, G. *Bull. Soc. Chem. Fr.* **1975**, *5–6*, 1375.

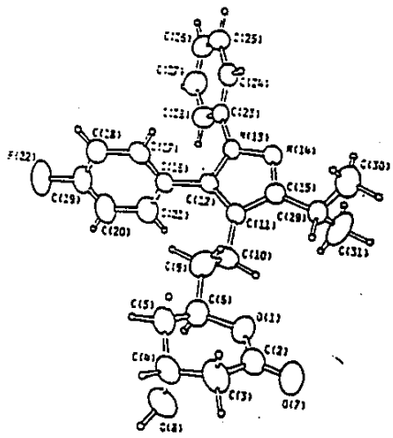


Figure 1. ORTEP view of lactone 10. Solid-state conforma and crystallographic atom numbering scheme; small circles de hydrogen atoms.

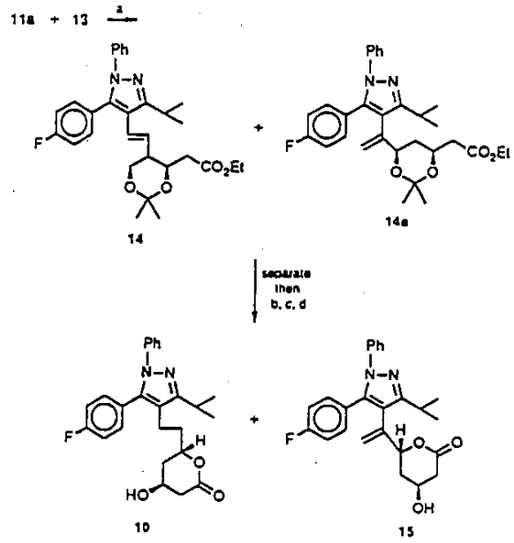
supra).[6] An ORTEP drawing of the solid-state conforma of compound 10 is shown in Figure 1. Increased amou of the 1,3-regioisomer 4 were obtained by changing reaction solvent to absolute ethanol or by raising the action temperature (regardless of solvent choice). U either (4-chlorophenyl)hydrazine or (4-fluorophen hydrazine in absolute ethanol at reflux, the regioiso ratio of pyrazoles obtained was 5:1 (1,5:1,3), this ratio improved (~10:1) by changing solvent to acetic acid. isolated from this reaction was an oil later identifiec NMR and independent synthesis[7] as a 5:1 mixture of razole regioisomers 5 and 6 which was presumably deri from the O-alkylated material present from the prev reaction.

Acidic hydrolysis of the acetal 3 provided aldehyd which was condensed with the dianion of methyl ac acetate.[8] Reduction of the resulting δ-hydroxy-β-keto e 8 was achieved by the boron chelation method of Naras and Pai.[9] Thus, compound 8 was complexed with tr butylborane prior to treatment with sodium borohydr The resulting boronate ester was hydrolyzed with 3 hydrogen peroxide and base to give a mixture of syn and anti 1,3-dihydroxy acids, which were lactonise refluxing toluene with azeotropic removal of water to predominantly the trans lactone 10 in good yield. HI analysis of the lactone 10 showed that the stereoselecti achieved (3.3:1 trans:cis diastereomers) was not as hig that achieved in the pyrrole series (10:1 trans:cis).[1] improvement in stereoselectivity was found on addi of an extra equivalent of n-Bu_3B, ruling out the possib of competitive chelation with the pyrazole free nitro atom; thus the reason for this lack of stereoselectivit the pyrazole series remains unclear. Excellent stere lectivity (>20:1 trans:cis) was achieved by employing ethylborane as chelating agent with pivalic acid catal and methanol as cosolvent.[10]

An alternative route (Scheme II) was devised in wl the key step was the palladium-catalyzed vinylation

(6) Prof. A. T. McPhail. Personal communication.
(7) Katritzky, A. R.; Rees, C. W. *Comprehensive Heteroc Chemistry*; Pergamon: Elmsford, NY, 1984; Vol. 5, p
(8) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1981**, *96*, 1
(9) (a) Narasaka, K.; Pai, H. C. *Chem. Lett.* **1980**, 1415. (b) I *Tetrahedron* **1984**, *40*, 2233.
(10) Verhoeven, T. R. *Eur. Pat.* 0164, 049, 1985.

Scheme III

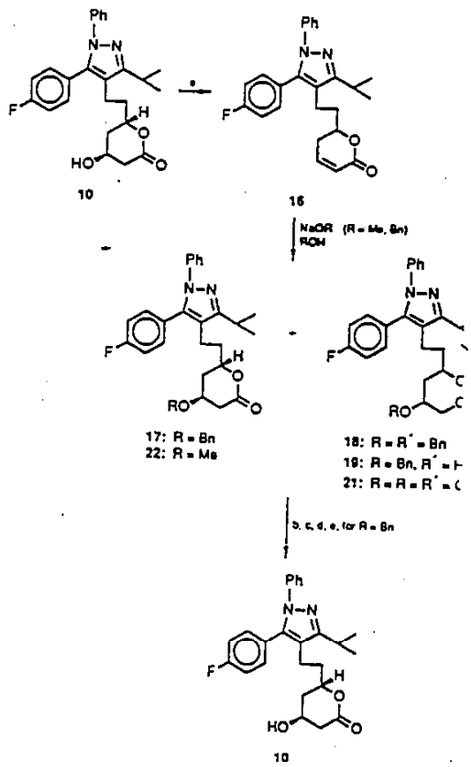


[a] (a) $(PPh_3)_2PdCl_2$, DMF, Et_3N; (b) H_2, Pd/C; (c) HCl, NaOH; (d) Tol, Δ, $-H_2O$.

halopyrazole (11a,b) with the intact lactone side chain (13).[11] This route had the advantages of being convergent and providing products of satisfactory stereochemical purity (method B). The heterocyclic halides 11a,b were prepared by condensation of 1,3-diketone 1 with phenylhydrazine in acetic acid at room temperature followed by halogenation of the resulting pyrazole 5 with either NBS or NIS in DMF at 0 °C. The alkene portion (13) was constructed via aldol condensation of acrolein with the dianion of methyl (or ethyl) acetoacetate,[12] reduction as before gave the diol, which was protected as the acetonide 13 (25:1 trans:cis diastereomers). Although treatment of 11a with 13 under the standard conditions described by Heck[11] did in fact provide a modest (50%) yield of 14, this reaction proved capricious. A variety of catalysts were employed (e.g., $(Ph_3P)_2PdCl_2$, $Pd(OAc)_2$, 10% Pd/C, polymer-supported catalysts, etc.), and it was concluded that 2–6 mol % of $(Ph_3P)_2PdCl_2$ was the preferred catalyst. A number of bases (e.g., tri-*n*-butylamine, diisopropylethylamine, and triethylamine) and solvents (e.g., DMF and acetonitrile) were examined, and the best yields were obtained with triethylamine and DMF as solvents. Changing the heterocyclic halide from bromide (11a) to iodide (11b) gave increased amounts of the dehalogenated pyrazole 5. Although it has been reported that use of a more hindered phosphine ligand on the catalyst reduces this side reaction, replacement of $(Ph_3P)_2PdCl_2$ with $[(o\text{-}CH_3Ph)_3P]_2PdCl_2$ provided no improvement in yield.[11] The 200-MHz NMR showed the formation of predominantly the trans alkene 14 (J_{trans} = 15 Hz). A minor product was produced by addition to the more substituted carbon atom of the double bond (Scheme III), giving the olefin 14a. This structure was confirmed by HETCOR NMR[13] on the resulting lactone 15. Catalytic reduction of olefin 14, removal of the protecting groups, and lac-

(11) Heck, R. F. *Org. React. (N.Y.)* 1982, *27*, 345.
(12) Brussani, G.; Ley, S. V.; Wright, J. L.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* 1986, 303.
(13) Benn, R.; Günther, H. *Angew. Chem., Int. Ed. Engl.* 1983, *22*, 350.

Scheme IV[a]



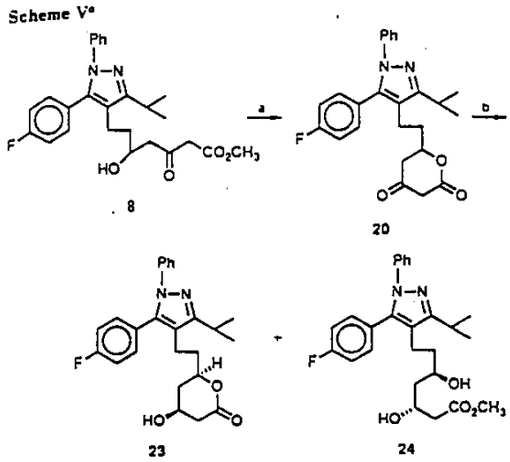
[a] (a) Ac_2O, DBU, CH_2Cl_2; (b) NaOH, (c) H^+; (d) H_2, Pd/C, OAc; (e) Tol, Δ.

tonization afforded lactone 10 as a mixture of diastereomers (64:1 trans:cis).

In order to avoid the very low temperature reducti compound 8 in Scheme I and the capricious nature c Heck reaction shown in Scheme II, an alternative synt was devised in which the required 1,3-asymmetry w troduced by the stereospecific 1,4-conjugate additi an alkoxide.[14] Thus, elimination of water from the ture of lactone diastereomers 10 produced by borohy reduction or from the cis lactone 23 obtained fron catalytic reduction of compound 20 produced the unsaturated lactone 16 in 68% yield (Scheme IV). dition of sodium benzylate in benzyl alcohol afforc mixture of products thought to consist mainly of pounds 17 and 18. After base hydrolysis the mixtur acidified to predominantly hydroxy acid 19. This ma was then hydrogenated over 10% Pd/C and the rest material lactonized to give compound 10 as a mixtu diastereomers (8:1 trans:cis by HPLC). In a si fashion, sodium methoxide was added to lactone 16 to after base hydrolysis, acidification, and lactonizatio 4-methoxy lactone 22 as a mixture of diastereomers trans:cis by HPLC). The cis diastereomer 23 was obt as the predominant product by catalytic hydrogenati ketone 20, which was prepared by base hydrolysis of pound 8 (Scheme V). Catalytic reduction of comp 20 gave, after chromatography, a mixture of ester 2 lactone 23 (4:1 cis:trans diastereomers).

(14) Roth, B. D.; Roark, W. H. *Tetrahedron Lett.* 1988, 12

Scheme V[a]



[a](a) NaOH then H+; (b) 10% Ru–C, H_2, MeOH, room temperature.

Table II. In Vitro Inhibitory Potencies against HMG-CoA Reductase

no.	CSI IC_{50},[a,c] μM	rel potency[b]
15	17.8	0.17
20	10.0	0.32
22	3.16	1.00
23	0.7	4.40

[a]Cholesterol synthesis inhibition (CSI). Assays of each inhibitor concentration were performed in triplicate and the precision for compactin was 37%. See ref 1. [b]Potency of compactin arbitrarily assigned a value of 100, and the IC_{50} value of the test compound was compared with that of compactin determined simultaneously. See ref 1. [c]The diastereomeric purities of compounds 22 and 23 are indicated in the Experimental Section. Compound 15 had a diastereomeric purity of >95% of the trans diastereomer as indicated by 200-MHz NMR.

Biological Results

The target lactones and related compounds listed in Tables I and II were saponified to the hydroxy acids and tested for their ability to inhibit the enzyme HMG-CoA reductase by employing a crude liver homogenate derived from rats fed a chow diet containing 5% cholestyramine.[1,15] This screen was designated CSI (cholesterol synthesis inhibition screen). The biological activities are displayed in Tables I and II as an IC_{50} (i.e., the concentration needed to inhibit enzyme activity by 50%). Compactin was employed as the internal standard in each testing protocol.

The optimum distance between the lactone and the heterocyclic ring in the pyrrole series was achieved by a two-carbon bridging unit.[1] This feature was incorporated in all the pyrazole derivatives described here apart from compound 15, in which the pyrazole and lactone portions are separated by only one carbon atom. This compound is relatively inactive.

Modification of the lactone portion generally decreases the activity and confirms the strict structural requirements found by others.[16] Methyl ether 22 exhibited about $^1/_{100}$ potency of compactin whereas the racemic hydroxy compound 10 was nearly equipotent; if resolved, this compound would be expected to be more potent than compactin. The keto analogue 20 also exhibited low potency.[17] Th lactone stereoisomer 23 (a 4:1 mixture of cis:trans di reomers by HPLC) also displayed significantly red biological activity.[16] The residual biological activity probably due to the presence of the trans diastereo:

As previous studies suggested that the 5-(4-fluorophe and 3-(1-methylethyl) substituents afforded optir potency, we focused our attention on variations in pos 1 of the pyrazole ring. A number of (para-substitu phenyl)hydrazines were employed, and it was den strated that in the limited series of compounds prepa varying the electronic distribution in the phenyl ring not, in general, have deleterious effects on in vitro pote Electron-withdrawing, e.g., 25, and electron-donating, 26 and 28, groups were equally tolerated; however, c pound 27, which has a hydrophilic electron-withdra group present, was considerably less potent. Replacer by naphthyl (e.g., 30) caused a significant decreas potency as did replacement by an alkyl group, e.g..

Conclusion

A small series of pyrazole mevalonolactones were pared and evaluated for their ability to inhibit the enz HMG-CoA reductase in vitro. By focusing on compou possessing the 5-(4-fluorophenyl)-3-(1-methylethyl) stitution found to be optimum in previous studies, a c pound (10) was rapidly identified that was almost e potent to compactin. Additional modification of th phenyl ring of 10 did not improve activity in vitro.

Experimental Section

Unless otherwise noted, materials were obtained from c mercial suppliers and used without further purification. T hydrofuran (THF) was distilled from sodium and benzophen Melting points were determined on a Thomas-Hoover mel point apparatus and are uncorrected. Infrared spectra determined on a Nicolet MX-1 FT-IR spectrophotometer. clear magnetic resonance spectra were determined on eith Varian EM-390 or a Varian XL-200 spectrometer. Chemical s are expressed as parts per million downfield from internal ramethylsilane. Elemental analyses were determined on a kin-Elmer 240C elemental analyzer. HPLC analyses were formed on a Varian 5500 HPLC with a UV 200 detector (w length was 251 nm). The detailed protocol of the biological a is described in ref 1.

1-(4-Fluorophenyl)-4-methyl-1,3-pentanedione (1). mixture of 4-fluoroacetophenone (150 g, 1.09 mol) and e isobutyrate (126 g, 1.09 mol) in dioxane (1.5 L) was added drop under a nitrogen atmosphere to a vigorously stirred suspen of hexane-washed sodium hydride (133 g, 58.8% NaH, 3.25 in dioxane (3.0 L). Vigorous evolution of gas ensued, after w the mixture was heated to 80–90 °C for 4 h. The mixture then allowed to cool to room temperature, after which it poured into ice-cold 2 M hydrochloric acid (6 L) with vigo stirring and extracted with ethyl acetate (4 × 1 L). The comb ethyl acetate extracts were washed with water (2 × 500 mL) brine (2 × 500 mL) and dried ($MgSO_4$). The solution was filt and the filtrate concentrated under vacuum. Distillation o residue yielded compound 1: bp 100–110 °C/1 mm (116 g, 5C ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.30 (s, 3 H), 2.60 (m, 1 = 7 Hz), 6.1 (s, 1 H), 7.15 (m, 2 H), 7.9 (m, 2 H), and 16.2 (1 H) ppm. IR (thin film) 2973, 2825, 1653, 1603, 1578, 1509, 1 1240, 1160, 1069, 851, and 793 cm^{-1}. Anal. ($C_{12}H_{13}FO_2$) C F.

2-[2-(1,3-Dioxolan-2-yl)ethyl]-1-(4-fluorophenyl methyl-1,3-pentanedione (2). To a suspension of hexane-was sodium hydride (22.8 g, 58% NaH, 0.56 mol) in anhydrous methylformamide (DMF) (750 mL) was added dropwise, v

(15) Dugan, R.; Slakey, L. L.; Briedis, A. V.; Porter, J. W. *Arch. Biochem. Biophys.* 1972, *152*.
(16) Stokker, G. E.; Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J.; Deana, A. A.; Gilfillan, J. L.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* 1985, *28*, 347.

(17) One possible explanation for this lack of activity may h been that during the biological assay procedure, base tr ment of compound 20 may not have produced the open form. We thank the reviewer for this suggestion.

vigorous stirring under a nitrogen atmosphere, a solution of 1 (116 g, 0.56 mol) in anhydrous DMF (450 mL). Vigorous effervescence ensued. When gas evolution had ceased, sodium iodide (21.0 g, 0.14 mol) was added, followed by the dropwise addition of 2-(2-bromoethyl)-1,3-dioxolane[4] (100.9 g, 0.56 mol) in anhydrous DMF (450 mL). The resulting mixture was heated at 80–90 °C for 36 h after which it was cooled to room temperature and poured into ice–water (2 L). This was extracted with ethyl acetate (4 × 1 L), and the combined organic extracts were washed successively with water (500 mL) and brine (500 mL) and dried ($MgSO_4$). The solution was filtered and the filtrate was concentrated under vacuum. The residue was flash chromatographed on silica gel, eluting with 25% ethyl acetate–hexane to yield 2 (100 g, 58%); ^1H NMR ($CDCl_3$) δ 1.1 (s, 3 H), 1.15 (s, 3 H), 1.7 (m, 2 H), 2.2 (m, 2 H), 2.8 (m, 1 H), 3.9 (m, 4 H), 4.7 (t, 1 H), 4.9 (t, 1 H), 7.2 (m, 2 H), and 8.1 (m, 2 H) ppm; IR (thin film) 2972, 1723, 1676, 1600, 1509, 1411, 1237, 1160, and 1037 cm^{-1}. Anal. ($C_{17}H_{21}FO_4$) C, H, F.

4-[2-(1,3-Dioxolan-2-yl)ethyl]-5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1*H*-pyrazole (3). To solution of 2 (104.75 g, 0.34 mol) in absolute ethanol under nitrogen (1 L) was added dropwise, with stirring, phenylhydrazine (40.45 g, 0.374 mol). When addition was complete, the solution was heated under reflux for 5 days[18] and then cooled to room temperature. The solution was concentrated under vacuum and chromatographed on silica gel. Elution with 15% ethyl acetate–hexane gave a yellow oil (9.7 g, R_f 0.55 (15% EtOAc–hexane)) identified by NMR and synthesis as a 5:1 mixture of regioisomers 5 and 6. Further elution gave a 10:1 regioisomer mixture of pyrazoles 3 and 4 (NMR shows two sets of isopropyl methyl groups at δ 1.4 and 1.2 ppm in a 10:1 ratio). This mixture solidified and was recrystallized (hexane) to give 3: mp 98–100 °C (hexane) (50.85 g, 40%); ^1H NMR ($CDCl_3$) δ 1.4 (s, 3 H), 1.35 (s, 3 H), 1.8 (m, 2 H), 2.7 (m, 2 H), 3.1 (t, 1 H), 3.9 (m, 4 H), 4.8 (t, 1 H), and 7.2 (m, 9 H) ppm; IR (KBr) 2950, 2900, 1596, 1566, 1511, 1440, 1377, 1227, 1158, 1143, 1058, 970, and 842 cm^{-1}. Anal. ($C_{23}H_{25}FN_2O_2$) C, H, N.

3(or 5)-(4-Fluorophenyl)-5(or 3)-(1-methylethyl)-1-phenyl-1*H*-pyrazoles (5 and 6). To a solution of 1 (1 g, 0.0048 mol) in absolute ethanol (10 mL) was added via a syringe, with stirring, phenylhydrazine (0.52 mL, 0.0053 mol). The solution was heated to reflux for 24 h and then cooled to room temperature. The solution was concentrated under vacuum and then chromatographed on silica gel. Elution with 5% ethyl acetate–hexane gave a yellow oil (1.1 g, R_f 0.24 (5% EtOAc–hexane)) identified by NMR as a 5:1 regioisomer mixture of 5 and 6. The oil solidified and was recrystallized (hexane) to give a 5:1 mixture of regioisomers: mp 67–70 °C (0.5 g, 37%); ^1H NMR ($CDCl_3$) δ 1.2 (d, 6 H, $(CH_3)_2CH$, regioisomer (6) (ht = 1)), 1.3 (d, 6 H, $(CH_3)_2CH$, regioisomer (5) (ht = 5)), 3.1 (m, 1 H), 6.35 (s, 1 H, 4 H regioisomer (5) (ht = 5)), 6.5 (s, 1 H, 4 H regioisomer (6) (ht = 1)) and 6.9–7.4 (m, 9H) ppm; IR (KBr) 3450, 3053, 2964, 1594, 1510, 1440, 1374, 1302, 1222, 1164, 996, and 849 cm^{-1}. Anal. ($C_{18}H_{17}FN_2$) C, H, N.

5-(4-Fluorophenyl)-3-(1-methylethyl)-1-phenyl-1*H*-pyrazole-4-propanal (7). A solution of 3 (50.85 g, 0.134 mol) in 70% aqueous acetic acid (1.0 L) was heated under reflux for 48 h with stirring. The solution was then cooled to room temperature and partitioned between ethyl acetate (1.0 L) and water (1.0 L). The phases were separated, and the aqueous phase was reextracted with ethyl acetate (1.0 L). The combined organic layer was washed successively with saturated sodium bicarbonate solution (250 mL), water (250 mL), and brine (250 mL). The ethyl acetate solution was dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was flash chromatographed on silica gel, eluting with 15% ethyl acetate–hexane. The eluted material solidified and was recrystallized (hexane) to give 7: mp 86–88 °C (hexane) (29.0 g, 65%); ^1H NMR ($CDCl_3$) δ 1.3 (s, 3 H), 1.35 (s, 3 H), 2.4 (t, 2 H), 2.7 (t, 2 H), 3.05 (m, 1 H), 7.2–7.6 (m, 9 H), and 9.6 (s, 1 H) ppm. IR (KBr) 2961, 2869, 1728, 1609, 1598, 1498, 1439, 1376, 1334, 1224, 1159, 971, 840, and 767 cm^{-1}. Anal. ($C_{15}H_{17}FN_2O$) H, N; C: calcd, 69.21; found, 68.51.

(±)-Methyl 5-(4-Fluorophenyl)-δ-hydroxy-3-(1-methylethyl)-β-oxo-1-phenyl-1*H*-pyrazole-4-heptanoate (8). Methyl acetoacetate (11.48 mL, 0.106 mol) in anhydrous THF (100 m was added dropwise to a stirred suspension of sodium hydri (58.6% oil suspension, 4.56 g, 0.116 mol) in anhydrous THF (1 mL) at 0 °C under an N_2 atmosphere. When gas evolution w complete, a 2.6 M solution (40.9 mL, 0.106 mol) of *n*-butyllithiu in hexane was added over 30 min. The resulting solution w stirred for an additional 60 min at 0 °C and then cooled to − °C (dry ice/acetone). This was then treated with a solution 7 (23.8 g, 0.0709 mol) in anhydrous THF (100 mL) added dropw over 60 min. The resulting orange solution was stirred 30 m at −78 °C and then at 0 °C for an additional 30 min befc quenching with glacial acetic acid (35 mL) and 2 M aqueous H (70 mL) with vigorous stirring. The resulting mixture was th partitioned between diethyl ether (750 mL) and water (250 m. After separation of phases, the aqueous layer was reextracted w diethyl ether (200 mL), and the combined organic extracts w washed successively with 0.2 M HCl (200 mL), water (200 m saturated sodium bicarbonate solution (3 × 150 mL), and br (200 mL). The ether solution was dried ($MgSO_4$), filtered, a concentrated in vacuo to yield a yellow oil, which was then fl chromatographed on silica gel. Elution with 40% ethyl acet gave 8 (32.3 g, 84%): ^1H NMR ($CDCl_3$) δ 1.3 (s, 3 H), 1.4 (s H), 1.45 (m, 2 H), 2.47 (d, 2 H), 2.7 (m, 2 H), 3.1 (m, 1 H), (s, 3 H), 3.38 (s, 2 H), 3.9 (m, 1 H), and 6.8–7.2 (m, 9 H) pp The ethyl ester 8a was also synthesized in comparable yield w ethyl acetoacetate: ^1H NMR ($CDCl_3$) δ 1.27 (t, 3 H), 1.36 (s H), 1.40 (s, 3 H), 1.45 (m, 2 H), 2.6 (d, 2 H), 2.4–2.7 (m, 2 H), (m, 1 H), 3.4 (s, 2 H), 3.9 (m, 1 H), 4.2 (q, 2 H), and 7.0–7.2 9 H) ppm; IR (thin film) 2965, 1743, 1714, 1654, 1599, 1559, 1 1500, 1374, 1227, 1160, and 844 cm^{-1}; HPLC indicated, 10 purity (retention time 23.2 min). Anal. ($C_{25}H_{29}FN_2O_4$) C, H calcd, 6.19; found, 5.73.

(±)-*trans*-6-[2-[5-(4-Fluorophenyl)-3-(1-methylethyl phenyl-1*H*-pyrazol-4-yl]ethyl]tetrahydro-4-hydroxy- pyran-2-one (10). **(i) Use of Tri-*n*-butylborane and Activation.** Through a THF (150 mL) solution of tri-*n*-bu borane (76.5 mL, 1 M, 0.076 mol) and 8 (31.48 g, 0.070 mol) bubbled air (125 mL), and the solution was stirred at room t perature under a nitrogen atmosphere for 24 h. The solution then cooled to −78 °C, and sodium borohydride (3.15 g, 0.0 mol) was added in one portion. The mixture was allowed to w to −20 °C over 2 h and then to 0 °C where it was stirred for The reaction was then quenched by the addition of glacial a acid (14.6 mL, 0.205 mol) and water (17 mL). When gas evolu had ceased, 2 N sodium hydroxide (167 mL) was added follc by the dropwise addition of 30% hydrogen peroxide (25.7 0.25 mol) over 1 h. The resulting mixture was allowed to w to room temperature overnight and then partitioned between (500 mL) and water (500 mL). The aqueous layer was separ and the ether layer was washed with 3 N NaOH (2 × 200 The combined aqueous layers were then cooled to 0 °C acidified with ice-cold 6 N HCl. This was then extracted ethyl acetate (4 × 200 mL). The combined organic extracts then washed with water (200 mL) and brine (2 × 200 mL), (($MgSO_4$), filtered, and concentrated under vacuum to yield g, 95%) as a mixture of 3*R*,5*R*/3*S*,5*S* and 3*S*,5*R*/3*R*,5*S* racem This material was dissolved in toluene (500 mL) and heated t reflux with azeotropic removal of water for 3 h. The mixtur cooled to room temperature and concentrated in vacuo. residue was flash chromatographed on silica gel, eluting with ethyl acetate–hexane to produce 10 (16.6 g, 60%) as a colc solid: mp 157–159 °C (5:1 cyclohexane:chloroform).

^1H NMR ($CDCl_3$) δ 1.3 (s, 3 H), 1.4 (s, 3 H), 1.6–1.9 (m, 2.2 (br s, 1 H), 2.5–2.8 (m, 4 H), 3.1 (m, 1 H), 4.3 (m, 1 H (m, 1 H), and 7.0–7.3 (m, 9 H) ppm; IR (KBr) 3400, 2962, 1707, 1598, 1511, 1440, 1376, 1252, 1225, 1052, 972, 843, an cm^{-1}.

HPLC (stationary phase, Altex C 18 column; mobile p 50:50 0.05 M citric acid (pH = 4.0)/CH_3CN) indicated a mixture of trans (t_R = 13.1 min)/cis (t_R = 12.0 min) diastere Anal. ($C_{25}H_{27}FN_2O_4$) C, H, N. The cis diastereomer was by NMR; the H6 and H4 protons appeared as a broad mu at δ 4.1 ppm.

(ii) Use of Triethylborane with Pivalic Acid Cata To a room temperature solution of triethylborane (2.5 m 1 M THF solution (0.002 14 mol)) under a nitrogen atmos

(18) Use of acetic acid as solvent greatly reduces reaction times.

was added, with stirring, a catalytic amount of pivalic acid (0.022 g, 0.00021 mol). The resulting solution was stirred at room temperature for 1 h before a THF (7 mL) solution of 8a (1 g, 0.00214 mol) was added dropwise. The resulting solution was stirred at room temperature for a further 1 h before cooling to −78 °C. Methanol (1 mL) was added followed by the addition of sodium borohydride (0.0893 g, 0.00236 mol) in one portion. Vigorous gas evolution ensued. This mixture was stirred at −78 °C for 2.5 h. It was then poured into an excess of ice-cold 30% hydrogen peroxide (10 mL) and extracted with ethyl acetate. The organic layer was then washed extensively with water and brine, dried ($MgSO_4$), filtered, and evaporated to yield 1.0 g of the corresponding 1,3-diol (quantitative) as a 23:1 mixture of 3*R*,5*R*/3*S*,5*S*; and 3*S*,5*R*/3*R*,5*S* racemates. (HPLC indicated that the 3*R*,5*R*/3*S*,5*S* racemate had a retention time of 13.5 min and the 3*R*,5*R*/3*R*,5*S* racemate had a retention time of 11.7 min.)

5-(4-Fluorophenyl)-3-(1-methylethyl)-1-phenyl-1*H*-pyrazole (5). To a solution of 1 (10.6 g, 0.0509 mol) in glacial acetic acid (100 mL) was added at room temperature phenylhydrazine (6.04 g, 0.0559 mol). The mixture was stirred overnight at room temperature and then poured into ice-cold saturated aqueous sodium bicarbonate (200 mL). An oil precipiteted, which then crystallized. These crystals were collected and redissolved in hexane. The hexane solution was washed with water (100 mL) and brine (100 mL) and then dried ($MgSO_4$). The solution was then concentrated to one-quarter of its original volume and cooled to yield 5 as colorless crystals: mp 70–72 °C (hexane) (12.0 g, 84%); ^{1}H NMR δ ($CDCl_3$) 1.34 (s, 3 H), 1.38 (s, 3 H), 3.1 (m, 1 H), 6.3 (s, 1 H), 6.9–7.3 (m, 9 H) ppm; IR (KBr) 3052, 2964, 1594, 1510, 1440, 1374, 1302, 1222, 1164, 1089, 995, and 849 cm^{-1}. Anal. ($C_{18}H_{17}FN_2$) C, H, N.

4-Bromo-5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1*H*-pyrazole (11a). *N*-Bromosuccinimide (6.21 g, 0.0348 mol) was added to a solution of 5 (11.3 g, 0.0348 mol) in DMF (130 mL) at 0 °C under a nitrogen atmosphere. After 1 h, a solid was deposited, which was filtered and washed extensively with water. This solid was recrystallized from toluene to yield 11a: mp 126–128 °C (toluene) (8.1 g, 56%); ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3 H), 1.42 (s, 3 H), 3.1 (m, 1 H), 7.0–7.3 (m, 9 H); IR (KBr) 1593, 1551, 1496, 1376, 1304, 1227, 1160, 1109, 1036, 968, and 843 cm^{-1}. Anal. ($C_{18}H_{16}BrFN_2$) C, H, N.

5-(4-Fluorophenyl)-4-iodo-3-(1-methylethyl)-1-phenyl-1*H*-pyrazole (11b). *N*-Iodosuccinimide (4.81 g, 0.0214 mol) was added in one portion to a stirred solution of 5 (5.0 g, 0.0178 mol) in DMF (100 mL) cooled to 0 °C under a dry nitrogen atmosphere. The mixture was allowed to warm to room temperature overnight and then recooled to 0 °C before more *N*-iodosuccinimide (0.24 g, 0.0011 mol) was added. This was then allowed to warm to room temperature and then poured into water (500 mL). This aqueous mixture was extracted with diethyl ether (2 × 250 mL). The ether extracts were diluted with hexane (200 mL) and washed with water (100 mL), 10% aqueous sodium bisulfite (100 mL), and brine (100 mL) and dried ($MgSO_4$). Filtration and concentration afforded 11b (6.8 g, 94%) as orange/tan needles (mp 141–143 °C) (hexane): ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3 H), 1.42 (s, 3 H), 3.1 (m, 1 H), and 7.0–7.3 (m, 9 H) ppm; IR (KBr) 2929, 1600, 1542, 1500, 1460, 1427, 1373, 1298, 1229, 1159, 1028, 968, and 845 cm^{-1}. Anal. ($C_{18}H_{16}FIN_2$) C, H, N.

Methyl 5-hydroxy-3-oxo-6-heptenoate (12) was prepared as described by Ley et al.[12] Ethyl 5-hydroxy-3-oxo-6-heptenoate was prepared similarly in 94% yield: 12: ^{1}H NMR ($CDCl_3$) δ 1.2 (tr, 3 H), 2.78 (d, 2 H, 4-H, *J* = 6.3 Hz), 3.4 (s, 2 H, 2-H), 4.2 (q, 2 H), 4.6 (dt, 1 H, 5-H, *J* = 6.0, 6.3 Hz), 5.07–5.35 (m, 2 H, 7-H), and 5.88 (ddd, 1 H, 6-H, *J* = 16.3, 10.0, 6.0 Hz) ppm.

Methyl 6-Ethenyl-2,2-dimethyl-1,3-dioxane-4-acetate (13). Air (20 mL) was bubbled through a solution of triethylborane (64 mL, 1 M THF, 0.064 mol) and 12 (10 g, 0.058 mol) in anhydrous THF (50 mL) under a nitrogen atmosphere. The resulting solution was stirred overnight at room temperature and then cooled to −78 °C. Sodium borohydride (2.64 g, 0.0696 mol) was added in one portion, and the vigorously stirred suspension was allowed to warm slowly to 0 °C over 2 h. (Vigorous gas evolution was noticed at −50 °C.) The reaction was quenched by the dropwise addition of glacial acetic acid (15 mL) followed by addition of water (20 mL) and methanol (20 mL). After all the solid had been consumed, saturated aqueous sodium bicarbonate solution (50 mL) was added carefully, followed by the dropwise addition of 30% hydrogen peroxide (19.2 mL). This solution was stirred for 1 h and then poured into ether (800 mL). The organic phase was washed with water (2 × 160 mL) and brine (100 mL). It was dried ($MgSO_4$), filtered, and evaporated. The residue was flash chromatographed on silica gel, eluting with ethyl acetate–hexane (50:50), to give methyl 3,5-dihydroxy-6-heptenoate (7.05 g, 69%) as a mixture of 3*R*,5*R*/3*S*,5*S* and 3*S*,5*R*/3*R*,5*S* racemates, which was used in the subsequent step without further purification. The crude mixture (7.0 g, 0.04 mol) was dissolved in a mixture of dichloromethane (100 mL) and 2,2-dimethoxypropane (20 mL, 0.162 mol). A catalytic amount of camphorsulfonic acid (0.05 g) was added and the solution was stirred overnight at room temperature. Concentration and flash chromatography on silica gel (eluting with 25% ethyl acetate–hexane) of the resulting residue gave 13 (4.25 g, 50%) as a 25:1 mixture of 3*R*,5*R*/3*S*,5*S* and 3*S*,5*R*/3*R*,5*S* racemates (HPLC indicated that the 3*R*,5*R*/3*S*,5*S* racemate had a retention time of 8.5 min and the 3*S*,5*R*/3*R*,5*S* racemate had a retention time of 8.4 min): ^{1}H NMR ($CDCl_3$) 1.2–1.3 (m, 1 H, 5-H), 1.38 (s, 3 H), 1.45 (s, 3 H), 1.60 (m, 1 H, 5-H'), 2.36 (dd, 1 H, *J* = 14, 6 Hz), 2.56 (dd, 1 H, *J* = 14, 6 Hz), 3.6 (s, 3 H), 4.3–4.5 (m, 2 H, 4-H, 6-H), 5.1–5.3 (m, 2 H), 5.8 (m, 1 H) ppm; IR (thin film) 2994, 1743, 1439, 1382, 1316, 1261, 1211, 1170, 1099, 1001, and 926 cm^{-1}. Anal. ($C_{11}H_{18}O_4$) H; C: calcd 61.66; found, 60.12.

(*E*)-Methyl 6-[2-[5-(4-Fluorophenyl)-3-(1-methylethyl-1-phenyl-1*H*-pyrazol-4-yl]ethenyl]-2,2-dimethyl-1,3-dioxane-4-acetate (14). A solution of 11a (1.07 g, 0.003 mol), 13 (1 g, 0.0051 mol), and bis(triphenylphopshine)palladium(II) chloride (0.042 g, 0.00006 mol, 2 mol %) in 6 mL of a 50:50 mixture of triethylamine and DMF was stirred and heated at reflux overnight under a nitrogen atmosphere. The solution was cooled to room temperature and diluted with ether (100 mL) and washed with water (100 mL), 2 M hydrochloric acid (50 mL), water (100 mL), saturated aqueous sodium bicarbonate (100 mL), and brine (50 mL). The organic extracts were dried ($MgSO_4$), filtered, and evaporated. The residue was flash chromatographed on silica gel eluting with 10% ethyl acetate–hexane, to give 14 (0.74 g, 50%) as yellow crystals, mp 136–137 °C, together with small amount of 5: ^{1}H NMR ($CDCl_3$) δ 1.25–1.6 (m, 14 H), 2.36 (dd, 1 H, *J* = 14, 6 Hz), 2.56 (dd, 1 H, *J* = 14, 6 Hz), 3.20 (m, 1 H), 3.7 (s, 3 H), 4.3 (m, 2 H), 5.7 (dd, 1 H, *J* = 15 Hz, 7 Hz), 6.23 (d, 1 H, *J* = 15 Hz), and 7.0–7.3 (m, 9 H) ppm; IR (KBr) 2914, 1739, 1600, 1597, 1546, 1510, 1441, 1379, 1276, 1225, 1160, 1078, 974, and 836 cm^{-1}; HPLC indicated a 59:1 mixture of 4*R*,6*R*/4*S*,6*S* and 4*S*,6*R*/4*R*,6*S* racemates (the 4*R*,6*R*/4*S*,6*S* racemate had a retention time of 12.57 min, and the 4*S*,6*R*/4*R*,6*S* racemate had a retention time of 13.87 min). Anal. ($C_{29}H_{33}FN_2O_4$) C, H, N.

(±)-*trans*-6-[2-[5-(4-Fluorophenyl)-3-(1-methylethyl)-phenyl-1*H*-pyrazol-4-yl]ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (10). A solution of 14 (0.63 g, 0.00128 mol) in ethyl acetate (10 mL) was hydrogenated under a balloon of hydrogen gas with 10% palladium on charcoal as catalyst at 25 °C for 5 days. The catalyst was then removed by filtration through Celite and the filtrate was concentrated and redissolved in 50:50 THF–2 M HCl (30 mL). This was stirred for 5 h at room temperature and then 25% sodium hydroxide was added until the solution was basic (pH ~10). After stirring for 30 min, the mixture was diluted with water and extracted with ether. The aqueous solution was then acidified with 2 M hydrochloric acid and extracted with ethyl acetate. The organic extracts were then washed with brine and dried ($MgSO_4$). Filtration and concentration provided the crude dihydroxy acid, which was lactonized with azeotropic removal of water by refluxing in toluene for 3 h. The cooled solution was concentrated to ca. 10 mL and allowed to stand. Pure lactone 10 crystallized as a white solid (0.35 g, 65%) (mp 163–165 °C, 165–167 °C): HPLC indicated a 64:1 mixture of trans (t_R = 11 min)/cis (t_R = 12.3 min) diastereomers. Anal. ($C_{25}H_{27}FN_2O_3$) C, H, N.

(±)-*trans*-6-[1-[5-(4-Fluorophenyl)-3-(1-methylethyl)-phenyl-1*H*-pyrazol-4-yl]ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (15). A mixture of crude 14 (34 g, 0.067 mol) and 10% Pd/C (1 g) in absolute EtOH (100 mL) was hydrogenated for 2 days at atmospheric pressure and room temperature. The catalyst was removed by filtration through Celite. After concentration, the filtrate residue was dissolved in 3:2:1 THF–2

HCl–MeOH (600 mL) and the mixture stirred for 3 days at room temperature. This was made alkaline (25% aqueous NaOH) and partitioned between ether and water. The aqueous layer was then acidified (2 M HCl) and extracted with ethyl acetate (2 × 250 mL). The combined organic extracts were then washed with brine (100 mL), dried ($MgSO_4$), filtered, and evaporated. The residue was dissolved in toluene and refluxed with azeotropic removal of water for 2 h. Concentration and flash chromatography on silica gel provided a first fraction identified as 15 (1.5 g, 5.3%; mp 157–158 °C) and a second fraction of 10 (6 g, 22%; mp 156–157 °C): ^{1}H NMR ($CDCl_3$) δ 1.3 (s, 6 H), 1.5 (m, 1 H), 1.7 (m, 1 H), 2.1 (br s, 1 H), 2.4 (m, 1 H), 2.7 (m, 1 H), 3.1 (m, 1 H), 4.1 (m, 1 H), 4.9 (dd, 1 H), 5.4 (d, 1 H), 5.7 (d, 1 H), and 7.0–7.4 (m, 9 H) ppm; IR (KBr) 2931, 1725, 1642, 1598, 1546, 1510, 1438, 1379, 1229, 1159, 1071, 1045, 975, 845, and 766 cm^{-1}. Anal. ($C_{25}H_{25}FN_2O_3$) C, H, N.

6-[2-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-phenyl-1*H*-pyrazol-4-yl]ethyl]-5,6-dihydro-2*H*-pyran-2-one (16). A solution of 10 (3.3:1 mixture of trans:cis isomers) (20 g, 0.0473 mol) was dissolved in anhydrous dichloromethane (50 mL) under a nitrogen atmosphere. Acetic anhydride (5.3 g, 0.052 mol) and DBU (15.8 g, 0.104 mol) were added dropwise to the solution. The reaction mixture was stirred overnight and then diluted with ether (150 mL) and washed with 2 M HCl (100 mL), saturated aqueous sodium bicarbonate solution (100 mL), and brine (100 mL), and dried ($MgSO_4$). Filtration and concentration gave a residue (17 g), which was passed through silica gel. Elution with hexane gave 16 (13 g, 63%) as a white solid (mp 69 °C (hexane)): ^{1}H NMR ($CDCl_3$) δ 1.36 (d, 6 H), 1.6–1.9 (m, 2 H), 2.2 (m, 2 H), 2.7 (m, 2 H), 3.0 (m, 1H), 4.3 (m, 1 H), 6.0 (dd, 1 H), 6.8 (m, 1 H), and 7.0–7.3 (m, 9 H) ppm; IR (KBr) 2961, 2868, 1723, 1596, 1562, 1511, 1439, 1376, 1336, 1248, 1159, 1094, 1043, 970, and 844 cm^{-1}. Anal. ($C_{25}H_{25}FN_2O_2$) C, H, N.

6-[2-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-phenyl-1*H*-pyrazol-4-yl]ethyl]dihydro-2*H*-pyran-2,4(3*H*)-dione (20). Ethyl acetoacetate (1.14 mL, 0.0089 mol) in anhydrous THF (15 mL) was added dropwise to a stirred suspension of hexane-washed sodium hydride (58.8% oil suspension) (0.225 g) in anhydrous THF (20 mL) at 0 °C under an N_2 atmosphere. When gas evolution was complete, a solution of *n*-butyllithium in hexane (3.9 mL, 0.0089 mol, 2.3 M) was added over 30 min. The resulting solution was stirred an additional 30 min at 0 °C and then cooled to −78 °C. This was then treated with a solution of 7 (2.0 g, 0.0059 mol) in anhydrous THF (15 mL). The resulting solution was stirred at −78 °C for an additional 40 min and then at 0 °C for 30 min. This was then poured into 25% aqueous NaOH (50 mL). The resulting mixture was then washed with ether (to remove starting aldehyde) and then acidified with ice-cold 6 M HCl. This was then extracted with ethyl acetate, the organic extract was washed with water and brine, dried ($MgSO_4$), filtered, and evaporated. Recrystallization from Et_2O–hexane (1:10) provided 20 (1.62 g, 65%): mp 141–143 °C; ^{1}H NMR ($CDCl_3$) δ 1.3 (d, 6 H), 1.6–1.9 (m, 2 H), 2.4 (m, 2 H), 2.8 (m, 2 H), 3.1 (m, 1 H), 3.3 (d, 2 H), 4.5 (m, 1 H), 7.1–7.3 (m, 9 H) ppm; IR (KBr) 2900, 1599, 1511, 1440, 1376, 1273, 1226, 1159, 842, and 766 cm^{-1}. Anal. ($C_{25}H_{25}N_2O_3F$) H, N; C: calcd, 71.41; found, 70.93.

Addition of Benzyl Alcohol to Compound 16. To a solution of 16 (6 g, 0.0148 mol) in benzyl alcohol (45 mL) at 0 °C was added sodium benzylate in benzyl alcohol (5.9 mL, 0.5 M). The reaction was allowed to warm to room temperature and then stirred for 24 h. The solution was then diluted with methanol and made alkaline (0.02 mol, 3 M NaOH). The resulting aqueous layer was washed with ether, acidified with 2 M HCl, and extracted with ethyl acetate. The organic extracts were washed with water and brine and dried ($MgSO_4$). Filtration and concentration yielded a crude mixture of products (7.8 g) consisting mainly of the benzyl ether dihydroxy acid 19 and a small amount of lactone 17. T material was dissolved in ethyl acetate (30 mL) and 10% Pd (0.5 g) added. This was then hydrogenated at 1 atm of pressu for 2 days. The catalyst was then removed by filtration and t filtrate concentrated. The residue was dissolved in toluene (mL) and heated to reflux with azeotropic removal of water. T solution was cooled and the product (10) crystallized (3.8 g, 60 HPLC showed a 8:1 trans:cis mixture of diastereomers.

Addition of Methanol to Compound 16. To a solution compound 16 (1.1 g, 0.0027 mol) in methanol (25 mL) at ro temperature under a nitrogen atmosphere was added sodi methoxide (0.017 g, 0.0003 mol). Reaction was almost instan neous. TLC showed the formation of two products, the m product was presumably the ring opened methyl ether 21. minor product was the lactone 22. This was then made alka with 25% NaOH and concentrated in vacuo. The residue extracted with hexane and the remaining aqueous solution acidified (0 °C, 12 N, HCl). The solution was then extracted ethyl acetate and the organic solution was washed with water brine and dried ($MgSO_4$). Filtration and concentration yiel crude product (1.1 g). This was dissolved in toluene (100 and heated under reflux with azeotropic removal of water f h. Flash chromatography on silica gel eluting with 40% e acetate–hexane gave 6-[2-[5-(4-fluorophenyl)-3-(1-met ethyl)-1-phenyl-1*H*-pyrazol-4-yl]ethyl]tetrahydro-4-methoxy pyran-2-one (22) (0.89 g, 75%): mp 86–88 °C; HPLC indic a 7.4:1 mixture of trans (t_R = 23.9 min):cis (t_R = 21.8 min) stereomers; ^{1}H NMR ($CDCl_3$) δ 1.25 (d, 6 H), 1.4–1.9 (m, 4 2.4–2.6 (m, 4 H), 3.0 (m, 1 H), 3.2 (s, 3 H), 3.6 (m, 1 H), 4. 1 H), 6.9–7.1 (m, 9 H) ppm; IR (KBr) 2958, 1744, 1595, 1565, 1439, 1376, 1253, 1224, 1157, 1098, 1071, and 840 cm^{-1}. ($C_{26}H_{29}FN_2O_3$) C, H, N.

(±)-*cis*-6-[2-[5-(4-Fluorophenyl)-3-(1-methylethyl phenyl-1*H*-pyrazol-4-yl]ethyl]tetrahydro-4-hydroxy pyran-2-one (23). A methanolic solution (25 mL) of 20 0.0024 mol) was hydrogenated at atmospheric pressure and temperature using 10% Ru/C as catalyst. This was stirr room temperature for 5 days, filtered, and concentrated to 1.3 g of crude material. Flash chromatography on silica gel, el with 40% ethyl acetate–hexane provided a first fraction iden as 24 (0.55 g, 51%): mp 92–94 °C; ^{1}H NMR ($CDCl_3$) δ 1. 6 H), 1.5 (m, 4 H), 2.4–2.7 (m, 4 H), 3.1 (m, 1 H), 3.7 (s, 3 H (m, 1 H), 4.2 (m, 1 H), and 7.0–7.2 (m, 9 H) ppm; IR (KBr) 2867, 1735, 1595, 1562, 1511, 1439, 1325, 1337, 1222, 1159, 983, and 840 cm^{-1}. Anal. ($C_{26}H_{31}FN_2O_4$) C, H, N.

A second fraction gave material identified as 23 (0.13 g, mp 145–147 °C; HPLC indicated a 4:1 mixture of cis (t_R = min):trans (t_R = 11.41 min) diastereomers; ^{1}H NMR (CD 1.3 (d, 6 H), 1.4–2.0 (m, 4 H), 2.3–2.9 (m, 4 H), 3.1 (m, 1 H (m, 2 H), and 7.0–7.2 (m, 4 H) ppm. Anal. ($C_{25}H_{27}FN_2O_3$) N.

The other diastereomer exhibits peaks at δ 4.5 ppm (H6 4.3 ppm (H4'); IR (KBr) 3400, 2950, 1700, 1605, 1511, 137 845 cm^{-1}.

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Supplementary Material Available: Preliminary crystallographic data for lactone 10 (4 pages). Orderin mation is given on any current masthead page.

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

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

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

Acknowledgment. This work was supported by Polish Project CPBR 11.5 and by Italian Ministero della Pubblica Instruzione (Fondi 60%). We thank E. Augustin for the determination of cytotoxic activity against HeLaS$_3$ cells in tissue culture, K. Maturska for skillful technical assistance in animal experiments, and F. Lupidi for NMR spectra.

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

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

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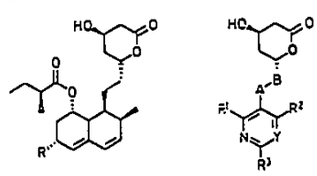
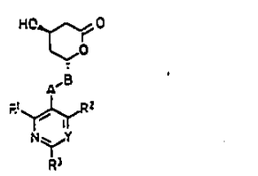
Lactones of pyridine- and pyrimidine-substituted 3,5-dihydroxy-6-heptenoic (-heptanoic) acids 2–4 have been synthesized. Extensive exploration of structure-activity relationships led to several compounds exceeding the inhibitory activity of mevinolin (1b) on HMG-CoA reductase, both in vitro and in vivo.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

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



1a: R = H

1b: R = CH_3



2: A–B = (E)-CH=CH; Y = CH, N

3: A–B = (Z)-CH=CH; Y = CH, N

4: A–B = CH_2-CH_2; Y = CH, N

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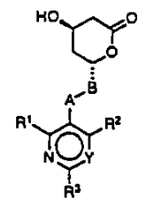
0022-2623/90/1833-0052$02.50/0

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



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

no.	Y	R^1	R^2	R^3	purifcn[a]	% yield[b]	formula	mp, °C	anal.[c]	IC_{50},[d] nM
1b	–	–	–	–	–	–	–	–	–	8
2a	CH	CH_3	4-FC_6H_4	CH_3	A	16	$C_{20}H_{20}FNO_3$	205	C, H, F, N	260
2b	CH	CH_3	4-ClC_6H_4	CH_3	A	15	$C_{20}H_{20}ClNO_3$	oil	C, H, Cl, N	94
2c	CH	CH_3	4-FC_6H_4	C_6H_5	B	13	$C_{25}H_{22}FNO_3$	149	C, H, F, N	38
2d	CH	C_2H_5	4-FC_6H_4	C_6H_5	C	13	$C_{26}H_{24}FNO_3$	oil	C, H, F, N	40
2e	CH	i-C_3H_7	4-FC_6H_4	CH_3	C	23	$C_{22}H_{24}FNO_3$	oil	C, H, F, N	9
2f	CH	i-C_3H_7	4-FC_6H_4	i-C_3H_7	C	28	$C_{24}H_{28}FNO_3$	137–140	C, H, F, N	3
2g	CH	i-C_3H_7	4-FC_6H_4	t-C_4H_9	C	16	$C_{25}H_{30}FNO_3$	158–160[e]	C, H, F, N	1
2h	CH	i-C_3H_7	4-FC_6H_4	c-C_6H_{11}	C	13	$C_{27}H_{32}FNO_3$	135–138	C, H, F, N	4
2i	CH	i-C_3H_7	4-FC_6H_4	C_6H_5	C	24	$C_{27}H_{26}FNO_3$	141[f,g]	C, H, F, N	3
2j	CH	i-C_3H_7	4-FC_6H_4	4-FC_6H_4	C	22	$C_{27}H_{25}F_2NO_3$	oil	C, H, F, N	2
2k	CH	i-C_3H_7	4-FC_6H_4	2,5-$(CH_3)_2C_6H_3$	C	28	$C_{29}H_{30}FNO_3$	oil	C, H, F, N	5
2l	CH	i-C_3H_7	4-FC_6H_4	3,5-$(CH_3)_2C_6H_3$	C	26	$C_{29}H_{30}FNO_3$	80	C, H, F, N	8
2m	CH	i-C_3H_7	4-$CH_3OC_6H_4$	C_6H_5	C	30	$C_{28}H_{29}NO_4$	oil	C, H, N	13
2n	CH	i-C_3H_7	4-$CF_3C_6H_4$	C_6H_5	C	21	$C_{28}H_{26}F_3NO_3$	oil	C, H, F, N	36
2o	CH	t-C_4H_9	4-FC_6H_4	C_6H_5	C	19	$C_{28}H_{28}FNO_3$	oil	C, H, F, N	18
2p	CH	c-C_6H_{11}	4-FC_6H_4	C_6H_5	C	11	$C_{30}H_{30}FNO_3$	196–198	C, H, F, N	30
2q	CH	4-FC_6H_4	i-C_3H_7	C_6H_5	C	25	$C_{27}H_{26}FNO_3$	oil	C, H, F, N	4
2r	N	CH_3	4-FC_6H_4	CH_3	D	18	$C_{19}H_{18}FN_2O_3$	174–176[h]	C, H, F, N	500
2s	N	CH_3	4-ClC_6H_4	CH_3	D	20	$C_{19}H_{19}ClN_2O_3$	oil	C, H, Cl, N	600
2t	N	i-C_3H_7	4-FC_6H_4	i-C_3H_7	E	13	$C_{23}H_{27}FN_2O_3$	oil	C, H, F, N	3
2u	N	i-C_3H_7	4-FC_6H_4	c-C_6H_{11}	C	19	$C_{26}H_{31}FN_2O_3$	128	C, H, F, N	1
2v	N	i-C_3H_7	4-FC_6H_4	C_6H_5	D	18	$C_{26}H_{25}FN_2O_3$	164–166[i]	C, H, F, N	3
2w	N	i-C_3H_7	4-FC_6H_4	4-FC_6H_4	C	22	$C_{26}H_{24}F_2N_2O_3$	138–140	C, H, F, N	1
3a	CH	CH_3	4-FC_6H_4	CH_3	A	8	$C_{20}H_{20}FNO_3$	188	C, H, F, N	>1000
3c	CH	CH_3	4-FC_6H_4	C_6H_5	B	6	$C_{25}H_{22}FNO_3$	216	C, H, F, N	100
3s	N	CH_3	4-ClC_6H_4	CH_3	D	18	$C_{19}H_{19}ClN_2O_3$	165–166	C, H, Cl, N	>1000
4d	CH	C_2H_5	4-FC_6H_4	C_6H_5	–	17	$C_{26}H_{26}FNO_3$	53–55	C, H, F, N	3
4i	CH	i-C_3H_7	4-FC_6H_4	C_6H_5	–	22	$C_{27}H_{28}FNO_3$	oil	C, H, F, N	19
4r	N	CH_3	4-FC_6H_4	CH_3	–	18	$C_{19}H_{21}FN_2O_3$	170–172	C, H, F, N	1000

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

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

(7) (a) Stokker, G. E.; Hoffmann, W. F.; Alberts, A. W.; Cragoe, E. J., Jr.; Deana, A. A.; Gilfillan, J. L.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* 1985, *28*, 347. (b) Hoffmann, W. F.; Alberts, A. W.; Cragoe, E. J., Jr.; Deana, A. A.; Evans, B. E.; Gilfillan, J. L.; Gould, N. P.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Rittle, K. E.; Smith, R. L.; Stokker, G. E.; Willard, A. K. *J. Med. Chem.* 1986, *29*, 159. (c) Stokker, G. E.; Alberts, A. W.; Anderson, P. S.; Cragoe, E. J., Jr.; Deana, A. A.; Gilfillan, J. L.; Hirshfield, J.; Holtz, W. F.; Hoffmann, W. F.; Huff, J. W.; Lee, T. J.; Novello, F. C.; Prugh, J. D.; Rooney, C. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* 1986, *29*, 170. (d) Hoffmann, W. F.; Alberts, A. W.; Anderson, P. S.; Chen, J. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* 1986, *29*, 849. (e) Stokker, G. E.; Alberts, A. W.; Gilfillan, J. L.; Huff, J. W.; Smith, R. L. *J. Med. Chem.* 1986, *29*, 852.

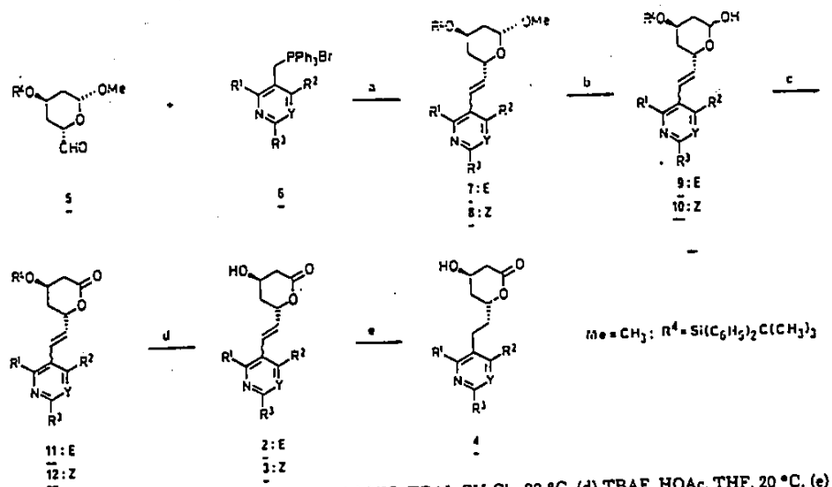
(8) (a) Sandoz, patent WO 84/02131, 1984. (b) Sandoz, patent WO 86/00307, 1986. (c) Sandoz, patent WO 86/07054, 1986. (d) Sandoz, European Application EP-A-0221025, 1987.

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

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

(11) (a) Bartmann, W.; Beck, G.; Granzer, E.; Jendralla, H.; v. Kerekjarto, B.; Wess, G. *Tetrahedron Lett.* 1986, *27*, 4709. (b) Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Jendralla, H.; Kesseler, K.; Wess, G.; Schubert, W.; Granzer, E.; v. Kerekjarto, B.; Krause, R. *Tetrahedron Lett.* 1988, *29*, 929.

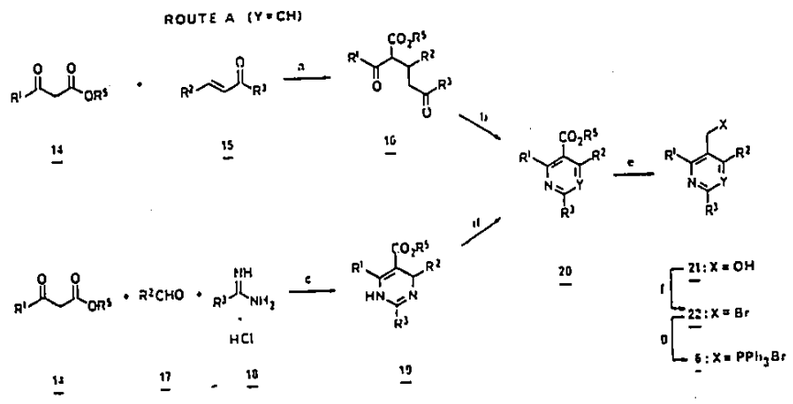
Scheme I[a]



Me = CH_3; R^4 = $Si(C_6H_5)_2C(CH_3)_3$

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

Scheme II[a]



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

heteroaromatic groups with basic properties.

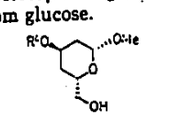
Chemistry

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

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

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

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



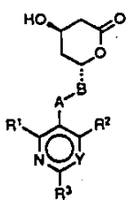
13

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

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

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

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



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

no.	Y	R^1	R^2	R^3	IC_{50}, nM	rel potency[b]
1b	–	–	–	–	50	1.00
2a	CH	CH_3	4-FC_6H_4	CH_3	2000	0.03
2c	CH	CH_3	4-FC_6H_4	C_6H_5	90	0.56
2e	CH	*i*-C_3H_7	4-FC_6H_4	CH_3	50	1.00
2g	CH	*i*-C_3H_7	4-FC_6H_4	*t*-C_4H_9	20	2.50
2h	CH	*i*-C_3H_7	4-FC_6H_4	*c*-C_6H_{11}	9.5	5.26
2i	CH	*i*-C_3H_7	4-FC_6H_4	C_6H_5	5.0	10.00
2j	CH	*i*-C_3H_7	4-FC_6H_4	4-FC_6H_4	7.5	6.67
2k	CH	*i*-C_3H_7	4-FC_6H_4	2,5-$(CH_2)_2$-C_6H_3	20	2.50
2m	CH	*i*-C_3H_7	4-$CH_3OC_6H_4$	C_6H_5	150	0.33
2p	CH	*c*-C_6H_{11}	4-FC_6H_4	C_6H_5	>5000	>0.01
2q	CH	4-FC_6H_4	*i*-C_3H_7	C_6H_5	10	5.00
2t	N	*i*-C_3H_7	4-FC_6H_4	*i*-C_3H_7	4.8	10.42
2u	N	*i*-C_3H_7	4-FC_6H_4	*c*-C_6H_{11}	26	1.92
2y	N	*i*-C_3H_7	4-FC_6H_4	C_6H_5	5	10.00
2w	N	*i*-C_3H_7	4-FC_6H_4	4-FC_6H_4	18	2.78
3c	CH	CH_3	4-FC_6H_4	C_6H_5	5000	0.08
4i	CH	*i*-C_3H_7	4-FC_6H_4	C_6H_5	370	0.14

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

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

Biological Results and Discussion

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

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

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

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

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

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

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

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

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

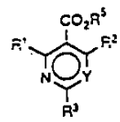
A graphical representation of the fit of 2i against 1b is shown in Figure 1. If the lactone moieties are oriented the same way in both conformers, the isopropyl group of 2i occupies partly the region of the hexahydronaphthalene system of 1b. At the same time the 4-fluorophenyl group of 2i occupies most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

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

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

(20) Results will be published separately.

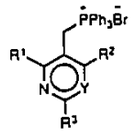
Table III. Physical Properties of Esters 20



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

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

Table IV. Physical Properties of Phosphonium Salts 6



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

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

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

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

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

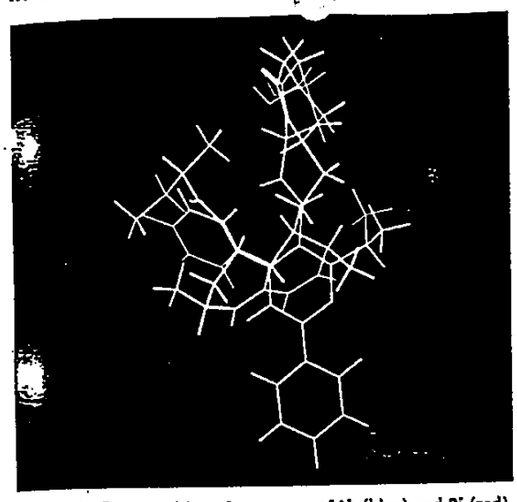


Figure 1. Superposition of structures of 1b (blue) and 2i (red). Except for the phenyl ring, 2i occupies the same regions of space as 1b.

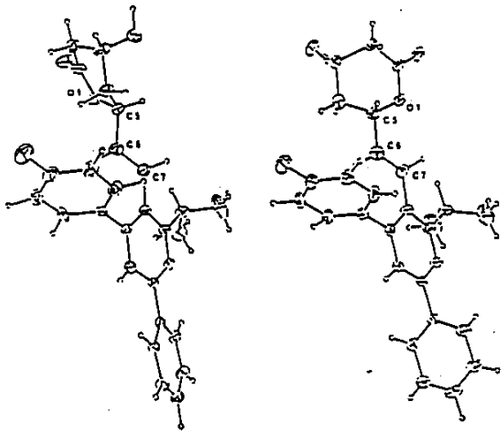


Figure 2. Computer-generated ORTEP drawings of conformers A (left) and B (right) of compound 2i forming an asymmetrical unit within the unit cell.

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

X-ray Crystallography for 2i

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

Conclusion

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

Experimental Section

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

NO_3 m/e = 433 (M^+). Anal. ($C_{27}H_{28}FNO_3$)

.ys. **HMG-CoA Reductase Inhibition Assay.** .tivity of compounds 2–4 on rat liver HMG-CoA estimated with soluble-enzyme preparations ob- ıe microsomal fraction.[22] The test was performed he method described by Avigan.[23] The complete ı contained the following in a total volume of 0.2 M; EDTA, 2.5 mM; DTT 2.5, mM; NADP, 50 mM; phate, 50 mM; glucose 6-phosphate dehydrogenase, G-CoA, 0.91 mM containing 100 nCi (3.7 kBq) of oA (New England Nuclear); partially purified en- ılution, 50 μL. Test compounds 2–4 as well as 1b ision to their corresponding potassium 3(*R*),5(*S*)- oxylates through reaction with 1 equiv of potassium ethanol) were added to the assay system in 10-μL ulticoncentration levels. The complete assay was 37 °C with shaking during 20 min and the reaction y addition of 75 μL of 2 N $HClO_4$. After 1 h at room ınd 10 min in an ice bath, 75 μL of 3 N potassium 50 μL of water were added, and the precipitate was The supernatant (250 μL) was applicated to an 0.6 ımn containing 100–200-mesh AG 1×8, Cl form levalonolactone was eluted with 3.5 mL of Milli-Q mL portions of the eluate were mixed with 10 mL 212 (Zinsser) for measurement in a Beckman ounter. The assay was carried out in triplicate; the values was calculated for the percentage inhibition. ere obtained by plotting the percentage inhibition ompound concentration.

ı of Acetate Incorporation in Cholesterol in HEP G2 Cells. Monolayers of HEP G2 cells in edium (Flow) with 10% delipidated fetal calf serum ıated for 1 h with suitable concentrations of the test 3, or 4. After addition of ^{14}C-labeled sodium acetate, ı was continued for 3 h. [^{3}H] Cholesterol was added standard and an aliquot of the cells was saponified he lipids were extracted with chloroform/methanol dition of carrier cholesterol, the lipid mixture was paratively on TLC plates using chloroform/acetone esterol zone was visualized with iodine vapor and scanner and scraped out. The amount of [^{14}C] s determined scintigraphically. With another aliquot ıyers, cell proteins were determined for calculation terol biosynthesis per milligram of cell protein. The ıre was done at three different inhibitor concen- cells of the same culture, and additionally without ı with a test compound (solvent control).

ompound, IC_{50} values were calculated by plotting ween the relative amount of [^{14}C] cholesterol syn- hibitor-treated cells and in solvent controls against centrations. Relative potencies were calculated on .b as external standard.

esterolemic Activity in Rabbits. Normolipemic ew Zealand rabbits (3–5.5 kg) in groups of four to eceived the compounds, suspended in 1% aqueous yl)cellulose (Tylose) daily in the morning by stomach trol groups were given only Tylose. In samples of , taken every 3–4 days 20 h after the oral adminis- ı total cholesterol was enzymatically determined by tion of Boehringer-Mannheim (CHOD-PAP high- method). The serum cholesterol level of drug-treated ompared with that of control groups. After the time cation" a time of "withdrawal" followed.

ıtional Analysis and Structural Comparison of 1b and 2i. A computer-assisted conformational and 2i was carried out using a commercially available order to determine their low-energy conformations. conformation of 1b was modeled from the confor- mpactin (1a) as determined by X-ray crystallogra- ystematic conformational search with rotatable bonds

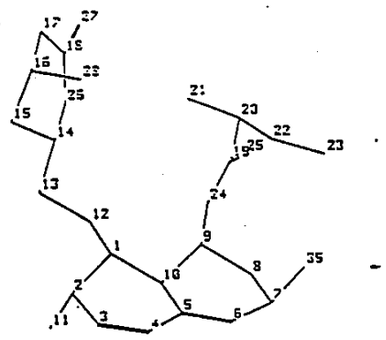


Figure 3. Low-energy conformation of 1b as determined by computer-assisted analysis (hydrogen atoms omitted).

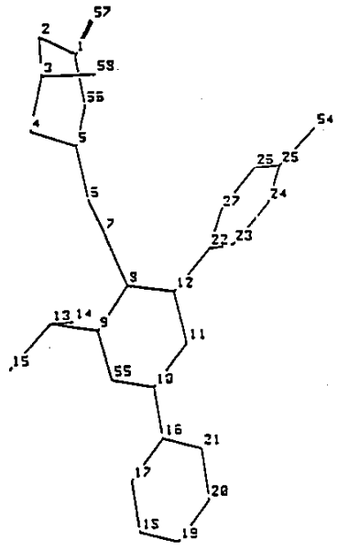


Figure 4. Low-energy conformation of 2i as determined by computer-assisted analysis (hydrogen atoms omitted).

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

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

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(26) Since the crystal structure of 1b is not known, 1a was used for analysis. Compactin differs from 1b by just one methyl group, suggesting that the conformational energies of both compounds should be similar.

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

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

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

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

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

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

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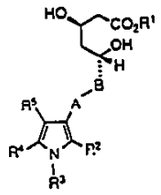
A series of 7-(1*H*-pyrrol-3-yl)-substituted-3,5-dihydroxyhept-6(*E*)-enoates (-heptanoates) 1 and 2 have been prepared and tested for inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. The most potent compounds exceeded mevinolin's activity in vitro and in vivo.

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



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

Chemistry

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

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

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

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

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

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

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

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

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

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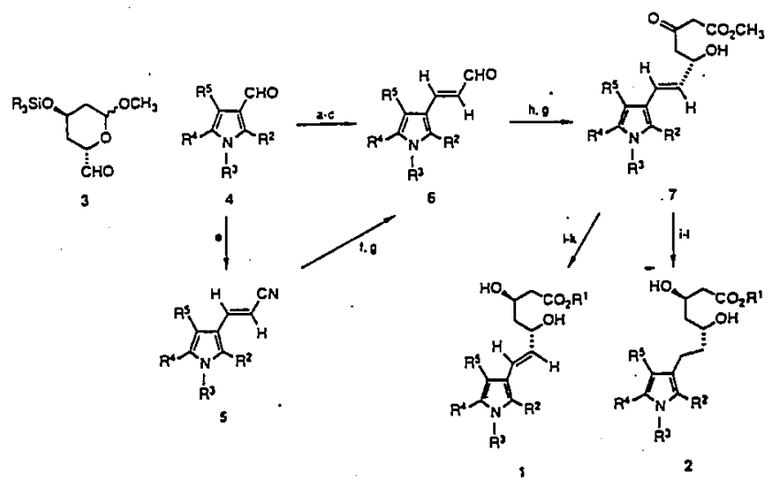
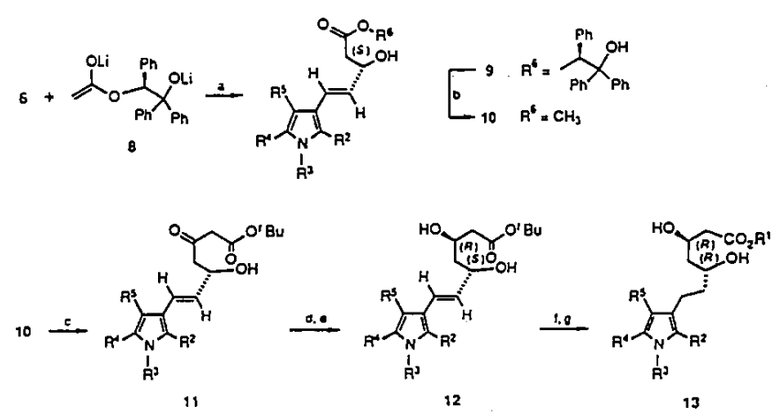
Scheme I[a]



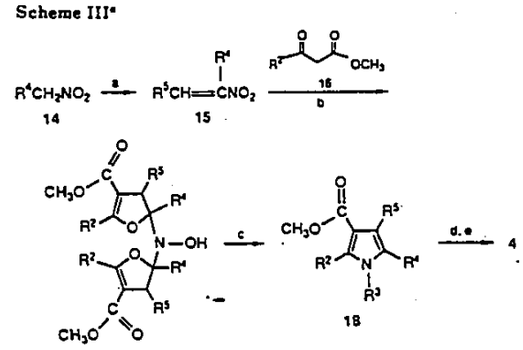
[a] (a) EtOCH=CHSn(*n*-Bu)$_3$;[2] (b) *n*-BuLi/−70 °C; (c) NH_4Cl/H_2O; (d) $TsOH/H_2O$; (e) $NCCH_2PO(O\text{-}i\text{-}Pr)_2/NaH$/0 °C; (f) $(i\text{-}Bu)_2AlH$; (g) NaH_2PO_4/H_2O; (h) $CH_3COCH_2CO_2CH_3/NaH/n$-BuLi/−15 °C; (i) Et_3B; (j) $NaBH_4$/−75 °C; (k) $NaOH/H_2O/CH_3OH$; (l) $Pd/C/H_2$.

Scheme II[a]



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

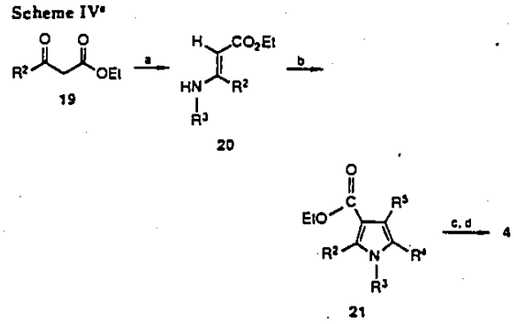
Scheme III[a]



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

with enamino esters 20 (Scheme IV). When substituent R^2 was not sterically demanding (e.g. $R^2 = CH_3$), 20 were

Scheme IV[a]



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

easily obtained by addition of 1 equiv of amine to the β-keto ester 19 under acid catalysis.

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