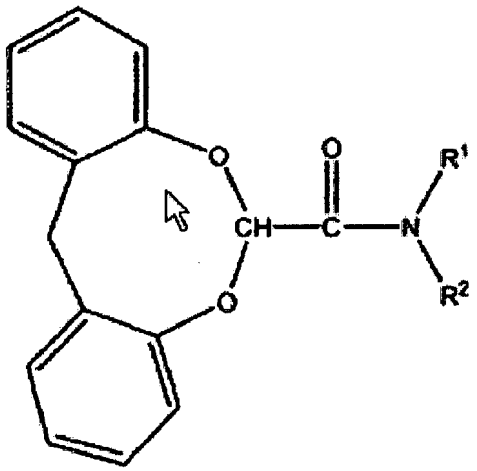
Exhibit 5
Part 2
To Third Declaration of
Joseph N. Hosteny

question of patentability as claims 1-5, 8-9, which question has not been decided in a previous examination of the Roth patent.

12. The Requester considers that a SNQ of claims 1-5, 8-9 of the Roth patent is raised by Hoefle II (US 4,647,576) in combination with Parker (US 3,931,173) under the judicially-created doctrine of non-statutory double patenting (pages 29-30 and the claim chart shown in Exhibit R of the request).

Hoefle II is as discussed in above paragraph 11.

Parker teaches a dioxocin carboxamide derivative of the following structural formula for treating hyperlipidemic states. Parker also teaches the process of making the carboxamide (column 4, lines 19-61).



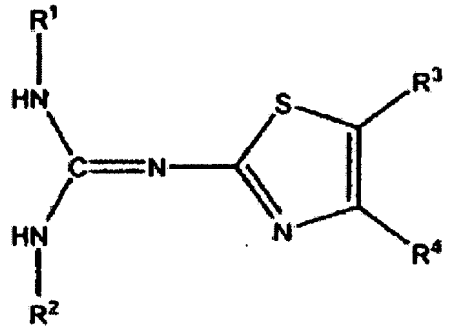
There is a substantial likelihood that a reasonable examiner would consider Hoefle II and Parker important in deciding the patentability of the present claims under the judicially-created

doctrine of non-statutory double patenting. These references were not cited during the prosecution of the application that became the Roth patent. Accordingly, these references raise a substantial new question of patentability as to claims 1-5, 8-9, which question has not been decided in a previous examination of the Roth patent.

13 The Requester considers that a SNQ of claims 1-5, 8-9 of the Roth patent is raised by Hoefle II (US 4,647,576) in combination with Ippen (US 4,581,453) under the judicially-created doctrine of non-statutory double patenting (pages 31-32 and the claim chart shown in Exhibit S of the request).

Hoefle II is as discussed in above paragraph 11.

Ippen teaches a guanidinothiazole derivative of the following structural formula for influencing lipid metabolism.



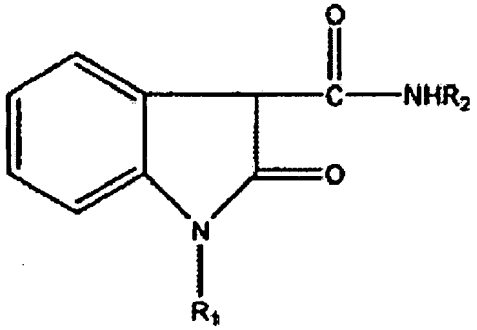
The compound of Example 17 (columns 7-8, Table 1) wherein R3 is a N-phenyl carboxamide causes significant reduction in the increase in liver cholesterol (column 21, lines 12-39).

There is a substantial likelihood that a reasonable examiner would consider Hoefle II and Ippen important in deciding the patentability of the present claims under the judicially-created doctrine of non-statutory double patenting. These references were not cited during the prosecution of the application that became the Roth patent. Accordingly, these references raise a substantial new question of patentability as to claims 1-5, 8-9, which question has not been decided in a previous examination of the Roth patent.

14. The Requester considers that a SNQ of claims 1-5, 8-9 of the Roth patent is raised by Hoefle II (US 4,647,576) in combination with McManus (US 3,634,453) under the judicially-created doctrine of non-statutory double patenting (pages 32-33 and the claim chart shown in Exhibit T of the request).

Hoefle II is as discussed in above paragraph 11.

McManus teaches an oxindole carboxamide compound of the following structural formula for use as an anti-inflammatory agent.



The compound wherein R2 is an optionally substituted phenyl is exemplified in Example 1V (column 9).

There is a substantial likelihood that a reasonable examiner would consider Hoefle II and McManus important in deciding the patentability under the judicially-created doctrine of non-statutory double patenting. These references were not cited during the prosecution of the application that became the Roth patent. Accordingly, these references raise a substantial new question of patentability as to claims 1-5, 8-9, which question has not been decided in a previous examination of the Roth patent.

Conclusion

15. The request for *ex partes* reexamination is ***granted.***

Claims 1-5, 8-9 of U.S. Patent 4,681,893 will be reexamined.

Extensions of Time

16. Extensions of time under 37 CFR 1.136(a) will not be permitted in these proceedings because the provisions of 37 CFR 1.136 apply only to "an applicant" and not to parties in a reexamination proceeding. Additionally, 35 U.S.C. 305 requires that *ex parte* reexamination proceedings "will be conducted with special dispatch" (37 CFR 1.550(a)). Extensions of time in *ex parte* reexamination proceedings are provided for in 37 CFR 1.550(c).

Ongoing Duty to Disclose

17. The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 6,96,773 throughout the course of this reexamination proceeding. The third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

Future Amendment

18. Patent owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37CFR 1.20(c).

Waiver of Right to File Patent Owner Statement

19. In a reexamination proceeding, Patent Owner may waive the right under 37 C.F.R. 1.530 to file a Patent Owner Statement. The document needs to contain a statement that Patent Owner waives the right under 37 C.F.R. 1.530 to file a Patent Owner Statement and proof of service in the manner provided by 37 C.F.R. 1.248, if request for reexamination was made by a

third party requester, see 37 C.F.R. 1.550(f). The Patent Owner may consider using the following statement in a document waiving the right to file a Patent Owner Statement:

Patent Owner waives the right under 37 C.F.R 1.530 to file a Patent Owner Statement.

NOTICE RE PATENT OWNER'S CORRESPONDENCE ADDRESS

20. Effective May 16, 2007, 37 CFR 1.33(c) has been revised to provide that:

The patent owner's correspondence address for all communications in an *ex parte* reexamination or an *inter partes* reexamination is designated as the correspondence address of the patent.

Revisions and Technical Corrections Affecting Requirements for Ex Parte and Inter Partes Reexamination, 72 FR 18892 (April 16, 2007)(Final Rule)

The correspondence address for any pending reexamination proceeding not having the same correspondence address as that of the patent is, by way of this revision to 37 CFR 1.33(c), automatically changed to that of the patent file as of the effective date.

This change is effective for any reexamination proceeding which is pending before the Office as of May 16, 2007, including the present reexamination proceeding, and to any reexamination proceeding which is filed after that date.

Parties are to take this change into account when filing papers, and direct communications accordingly.

In the event the patent owner's correspondence address listed in the papers (record) for the present proceeding is different from the correspondence address of the patent, it is strongly encouraged that the patent owner affirmatively file a Notification of Change of Correspondence Address in the reexamination proceeding and/or the patent (depending on which address patent owner desires), to conform the address of the proceeding with that of the patent and to clarify the record as to which address should be used for correspondence.

Telephone Numbers for reexamination inquiries:

Reexamination and Amendment Practice	(571) 272-7703
Central Reexam Unit (CRU)	(571) 272-7705
Reexamination Facsimile Transmission No.	(571) 273-9900

Future Correspondence

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 571-272-0686. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Jones can be reached on 571-272-1535. The fax phone number for the organization where this application or proceeding is assigned is 571-273-9900.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

All correspondence relating to this ex parte reexamination proceeding should be directed:

By Mail to:	Mail Stop ex parte Reexam Central Reexamination Unit Office of Patent Legal Administration United States Patent & Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450
By FAX to:	571-273-9900 Central Reexamination Unit
By Hand to:	Customer Service Window Randolph Building 401 Dulany St. Alexandria, VA 22314

Evelyn Huang
Primary Examiner
Art Unit 3991

Conferee Deborah Jones
SPE/3991

BENNETT M. CELSA
CRU EXAMINER - AU 3991

RANBAXY.023RX REEXAMINATION REQUEST

Please Direct All Correspondence to Customer Number **20995**

66548 U.S. PTO
90008727

07/02/07

TRANSMITTAL

In re U.S. Patent No. 4,681,893

Patentee.: Roth

Issued: July 21, 1987

Application No.: 06/868,867

For: Trans-6-[2-(3- or 4-carboxamido-substituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-one inhibitors of cholesterol synthesis

66548 U.S. PTO
07/02/07

CERTIFICATE OF MAILING

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on

June 29, 2007
(Date)

07/03/2007 MTHUYNH 00000005-111410 90008727
01 FC:1813 270.00 OP 2250.00 OP
Joseph M. Reisman, Reg. No. 43,878

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith for filing in the above-identified application are the following enclosures:

(X) Request for *Ex Parte* Reexamination in thirty-four (34) pages.

(X) Exhibits A through T.

(X) Check in the amount of $2,520.00 for *Ex Parte* Reexamination fee.

(X) Return prepaid postcard.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

Dated: June 29, 2007

By: _____

Joseph M. Reisman (Reg. No. 43,878)
Attorney for Requestor
Knobbe, Martens, Olson & Bear, LLP
2040 Main Street, 14th Floor
Irvine, CA 92614
Phone: 619-235-8550
Fax: 619-235-0176

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RANBAXY.023RX

REEXAMINATION REQUEST

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No.	4,681,893
Patentee.:	Roth
Issued:	July 21, 1987
Application No.:	06/868,867
For:	Trans-6-[2-(3- or 4-carboxamido-substituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-one inhibitors of cholesterol synthesis

CERTIFICATE OF MAILING
I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on

June 29, 2007
(Date)

Joseph M. Reisman, Reg. No. 43,878

REQUEST FOR *EX PARTE* REEXAMINATION

Mail Stop *Ex Parte* Reexam
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This is a request for *ex parte* reexamination pursuant to the provisions of 35 U.S.C. §§ 302-07 and 37 C.F.R. §§ 1.510-1.570 of U.S. Patent No. 4,681,893 ("the '893 Patent"), which issued on July 21, 1987 to Roth, and was extended pursuant to 35 U.S.C. §156 on July 15, 1998. The '893 Patent is still in-force, but only based upon that extension. A copy of the '893 Patent can be found in Exhibit A.

I. Claims for which reexamination is requested

Requester requests reexamination of Claims 1-5, 8, and 9 of the '893 Patent. Claim 1 is the only claim that does not refer back to another claim. Dependent Claims 2-5 depend either directly or indirectly from Claim 1. Dependent Claim 8 is a composition claim that requires the compound of Claim 1. Dependent Claim 9 is a method claim that requires a step of administering the composition of Claim 8.

II. Prior Art References Raising Substantial New Issues of Patentability

As is explained in detail in Section V, infra, the following references raise substantial new questions of patentability with respect to Claims 1-5, 8, and 9 of the '893 Patent:

1. European Patent Application Publication No. 0 179 559 ("the '559 EP Publication") - Exhibit B
2. United States Patent No. 3,931,173 (the '173 Patent") - Exhibit C
3. United States Patent No. 4,581,453 (the '1453 Patent") - Exhibit D
4. United States Patent No. 3,634,453 (the '4453 Patent") - Exhibit E
5. United States Patent No. 4,647,576 (the '576 Patent") - Exhibit F

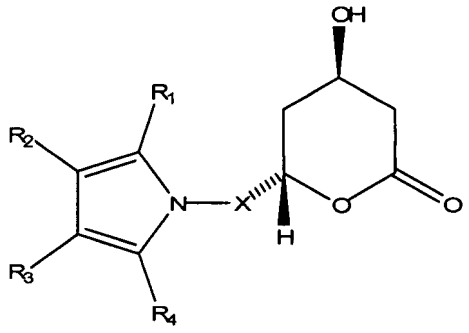
These references are listed on the attached Information Disclosure form and copies of the references are provided as Exhibits, as stated above.

The '559 EP Publication, the '173 Patent, the '1453 Patent, the '4453 Patent, and the '576 Patent (the "New Art") raise substantial new questions of patentability. None of these references was cited or applied during prosecution of the '893 Patent, and each either individually, or in combination (as explained in detail below), renders unpatentable the subject matter claimed in the '893 Patent.

III. Brief Description of the '893 Patent, the Prosecution History and the Claims

A. The '893 Patent

The '893 Patent is directed to certain trans-6-[2-(3- or 4-carboxamido-substituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones and the corresponding ring-opened acids derived therefrom. *See* Abstract of the '893 Patent. The broadest aspect of the '893 Patent provides compounds of structural formula I:



Formula I

wherein X is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH(CH_3)-$ (*See* column 2, lines 3-17), and each substituent R_1, R_2, R_3, and R_4 may be independently selected from a range of substituents (*See* column 2, lines 18-38). The '893 Patent also purports to provide methods for preparing various compounds encompassed by Formula I, pharmaceutical compositions, and a method of inhibiting cholesterol biosynthesis. *See* column 2, line 44 – column 3, line 33.

The compounds described in the '893 Patent are characterized as "a class of trans-6-[2-(3- or 4-carboxamidosubstituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones in which the pyran-2-one moiety is attached, through an alkyl chain, to the substituted pyrrole nucleus at the nitrogen, or 1-position, of the pyrrole." Column 3, lines 36-41. "The preferred reaction sequence which is used to prepare compounds [described in the '893 Patent] involves the cycloaddition of a disubstituted acetylene, in which one substituent is carboxamido or N-substituted carboxamido, to an appropriately substituted N-acylaminocarboxylic acid to form a substituted pyrrole." Column 4, lines 4-10. The '893 Patent describes four specific examples of such compounds and the method of their preparation. *See* column 10, line 40 – column 15, line 66.

The '893 Patent also describes two different methods for measuring the compounds' ability to inhibit the biosynthesis of cholesterol. *See* Column 7, lines 38-40. The first method is described as the "CSI screen" and is characterized as follows:

> [T]he level of HMG-CoA enzyme activity in standard laboratory rats is increased by feeding the rats a chow diet containing 5% cholestyramine for four days, after which the rats are sacrificed. The rat livers are homogenized, and the incorporation of cholesterol-^{14}C-acetate into nonsaponifiable lipid by the rat liver homogenate is measured. The micromolar concentration of compound required for 50% inhibition of sterol synthesis over a one-hour period is measured, and expressed as an IC_{50} value.

Column 7, line 40 – column 8, line 4. The second method is described as the "COR screen." "In [the second] method, the amount of ^{14}C-HMG-CoA converted to ^{14}C-mevalonate in the presence of a purified enzyme preparation of HMG-CoA reductase [is] measured. The micromolar concentration of compound required for 50% inhibition of cholesterol was measured and recorded as an IC_{50} value." Column 8, lines 7-13.

B. Prosecution History

The complete prosecution history of the '893 Patent is provided in Exhibit G. For the sake of brevity, only certain portions of the prosecution history are discussed in this request.

The '893 Patent was issued from Application No. 06/868,867 ("the '867 Application"). The '867 Application was filed on May 30, 1986 with 27 pages of written description and 10 claims. Claim 1 was independent and recited a compound of structural formula I. Claims 2-7 depended from Claim 1 and recited more specific limitations on the compound's structure. Claim 8 depended from Claim 1 and recited a pharmaceutical composition. Claim 9 depended from Claim 1 and recited a method of inhibiting cholesterol biosynthesis in a patient. Claim 10 was independent and recited a method of preparing a compound having structural formula I.

A first Office Action was mailed to the Applicant on October 2, 1986. The Examiner required election between two groups of inventions. The first group, Claims 1-9, was directed to chemical compounds, compositions containing the same, and cholesterol biosynthesis inhibition processes using the same. The second group, Claim 10, was directed to a chemical preparative mechanism. The Examiner asserted that the products of the first group could be made by another and materially different process. The Office Action noted that Applicant's representative elected the first group during a phone conversation on September 15, 1986. Claim 10 was therefore withdrawn from further consideration.

The Examiner also asserted that Claims 1-9 were inclusive of more than one patentably distinct species, noting that the claims presented a large number of possible compounds. Applicant's representative orally elected the species of the compound of Claim 5, which contained a pyrrole group and a 4-hydroxy-4-oxo-tetrahydro-2H-pyran-2-yl radical and no other heterocyclic group therein.

The Examiner rejected Claims 1-4 and 8-9 for containing an improper Markush group because the various substituents R_1, R_2, R_3, R_4, and X were so diffuse and different so as to overpower and overshadow the constant portion of the central nucleus formula. The Examiner rejected the use of Markush groups within Markush groups as trying to place too much subject matter into a single claim.

The Examiner rejected Claims 1-4 and 8-9 under 35 U.S.C. 112, first paragraph, because the claimed invention was not described in such full, clear, concise, and exact terms to enable a

person skilled in the art to make and use the invention. The Examiner also rejected Claims 1-4 and 8-9 under 35 U.S.C. 112, second paragraph for failing to particularly point out and distinctly claim the invention. The Examiner noted that the term hydroxy acid "derived from the opening of the lactone ring" was indefinite.

The Examiner indicated that Claims 5-7 were objected to for being dependent upon a rejected claim, but would be allowable if rewritten in independent form. The Examiner cited to various U.S. patents for the purpose of showing the state of the art.

Applicant responded with an amendment received by the PTO on January 5, 1987. Claim 1 was amended so that the R_1, R_2, and R_3 substituents could no longer be 2-, 3-, or 4-pyridinyl. Applicant asserted that this amendment overcame the improper Markush claim rejection. Claim 1 was amended to delete the "derived from the opening of the lactone ring" language and replace it with the "corresponding to the opened lactone ring" language. Applicant asserted that this amendment overcame the 35 U.S.C. 112, 1st and 2nd paragraph rejections. Claim 10 was cancelled.

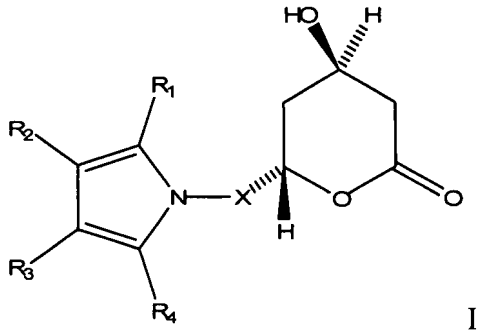
A Notice of Allowability was mailed to Applicant on March 16, 1987. Claims 1-9 were indicated as allowed. The Examiner cited some additional non-patent literature references, but did not give any reasons for the allowance. The '867 Application issued into the '893 Patent on July 21, 1987.

The term of the '893 Patent under 35 U.S.C. § 154 expired on May 30, 2006, the date that was 20 years after the filing of the '867 Application. On February 10, 1997, however, the Applicant had petitioned for a patent term extension under 35 U.S.C. § 156. A patent term extension of 1,213 days was granted, thereby extending the date of expiry to September 24, 2009.

C. The Claims of the '893 Patent

Claims 1-5, 8, and 9 recite:

1. A compound of structural formula I



I

wherein X is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH(CH_3)-$;
R_1 is
1-naphthyl;
2-naphthyl;
cyclohexyl;
norbornenyl;
phenyl;
phenyl substituted with
fluorine,
chlorine,
bromine,
hydroxyl,
trifluoromethyl,
alkyl of from one to four carbon atoms,
alkoxy of from one to four carbon atoms, or
alkanoyloxy of from two to eight carbon atoms;
either of R_2 or R_3 is $-CONR_5R_6$ where R_5 and R_6 are independently
hydrogen;
alkyl of from one to six carbon atoms;
phenyl;
phenyl substituted with
fluorine,
chlorine,
bromine,
cyano,
trifluoromethyl, or
carboalkoxy of from three to eight carbon atoms;
and the other of R_2 or R_3 is
hydrogen;
alkyl of from one to six carbon atoms;
cyclopropyl;
cyclobutyl;
cyclopentyl;
cyclohexyl;
phenyl; or

phenyl substituted with
fluorine,
chlorine,
bromine,
hydroxyl,
trifluoromethyl,
alkyl of from one to four carbon atoms,
alkoxy of from one to four carbon atoms, or
alkanoyloxy of from two to eight carbon atoms;

R_4 is
alkyl of from one to six carbon atoms;
cyclopropyl;
cyclobutyl;
cyclopentyl;
cyclohexyl; or
trifluoromethyl;

or a hydroxy acid or pharmaceutically acceptable salts thereof, corresponding to the opened lactone ring of the compounds of structural formula I above.

2. A compound as defined by claim 1 wherein X is $-CH_2CH_2-$.

3. A compound as defined by claim 2 wherein R_1 is phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoromethyl; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms.

4. A compound as defined by claim 2 wherein R_4 is alkyl of from one to six carbon atoms.

5. A compound as defined by claim 1 having the name trans-(±)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

8. A pharmaceutical composition, useful as a hypocholesterolemic agent, comprising a hypocholesterolemic effective amount of a compound in accordance with claim 1 in combination with a pharmaceutically acceptable carrier.

9. A method of inhibiting cholesterol biosynthesis in a patient in need of such treatment by administering a pharmaceutical composition as defined by claim 8.

Several of the claims of the '893 Patent have been, and are presently, the subject of litigations in United States District Courts, as discussed in the following section.

IV. Litigation

Several claims of the '893 Patent have been, and are presently, the subject of litigation. Specifically, *Pfizer Inc. et al. v. Ranbaxy Labs. Ltd. et al.*, Civil Action No. 03-209 (JJF) in the U.S. District Court for the District of Delaware (hereinafter "the Lipitor litigation") has concluded, and *Pfizer Inc. et al. v. Ranbaxy Labs. Ltd. et al.*, Civil Action No. 07-138 (JJF) in the U.S. District Court for the District of Delaware (hereinafter "the Caduet litigation") is now pending.

In the Lipitor litigation, the patentee (Warner Lambert Company) and its parent company, Pfizer, Inc. (collectively "Pfizer"), sued Ranbaxy Laboratories Limited and Ranbaxy Pharmaceuticals Inc. alleging infringement of two patents, including the '893 Patent, based on Ranbaxy's filing of an Abbreviated New Drug Application ("ANDA") seeking approval to market a generic version of Pfizer's Lipitor® product. In the Caduet litigation, Pfizer has sued Ranbaxy Laboratories Limited and Ranbaxy Inc. alleging infringement of two patents, including the '893 Patent, based on Ranbaxy's filing of an ANDA seeking approval to market a generic version of Caduet®, a product that combines atorvastatin calcium (the active ingredient in Lipitor®) and amlodipine besylate (the active ingredient in Norvasc®).

In the Lipitor litigation, only Claims 1-4, 8, and 9 of the '893 Patent were asserted. The district court rendered a judgment on January 3, 2006. The case was appealed to the Court of Appeals for the Federal Circuit (the "Federal Circuit") in Appeal No. 06-1179. The Federal Circuit issued its opinion on August 2, 2006. Petitions seeking rehearing and rehearing en banc by the Federal Circuit and certiorari to the United States Supreme Court were both denied. Relevant portions of the Federal Circuit's opinion are discussed below.

In the Lipitor litigation, Ranbaxy's pleadings alleged a defense and counterclaim of invalidity of the '893 Patent based on obviousness, but Ranbaxy chose not to present evidence of obviousness of the '893 Patent at trial. However, information revealed by Pfizer during the Lipitor litigation has given rise to a substantial new question of patentability. In particular, EP 0 179 559 (the "559 EP Publication") is now an important prior art reference that (optionally in combination with other references) renders several claims of the '893 Patent invalid for obviousness, as discussed in more detail in Section V.

The '559 EP Publication was not cited or applied during the prosecution of the '893 Patent, but it was cited, and formed the basis of a rejection in the prosecution of the European counterpart to the '893 Patent, EP 247 633 ("the '633 EP Patent"). Specifically the European Examiner rejected the claims as merely an obvious solution to the problem of providing active compounds similar to those described in the '559 EP Publication. *See* Lipitor litigation trial exhibit DTX-331 at RA017527-28, attached hereto as Exhibit H. The Examiner indicated, however, that if data were presented demonstrating that the claimed compounds showed surprising effectiveness compared to those in the '559 EP Publication, the claims would be allowed. *See id* at RA017528.

In response, Warner-Lambert accepted this position, stating:

> Applicants generally accept the Examining Division's arguments saying that a person skilled in the art would expect that the pyrazole [sic] ring was susceptible to further substitutions at the 3 and 4 position including other carboxy derivatives . . . without leading to a significant change in qualitative properties.

Id. at RA017516. To overcome the rejection, Warner-Lambert presented data allegedly showing unexpected results of the '893 Patent compounds over the '559 EP Publication compounds. *Id.* at RA017520. In presenting this data to the European Patent Office, Warner-Lambert represented that the data was from a test known as the "COR" test. (*Id.*).

During the Lipitor litigation, Pfizer admitted that the data that had been provided during prosecution of the '633 EP Patent purporting to be "COR" data was actually data from a completely different test known as the "CSI" test, and specifically from CSI screen 124. *See* Pfizer Reply Brief in Support of Motion to Dismiss and For Partial Judgment on the Pleadings Pursuant to Federal Rule of Civil Procedure 12(c) in Caduet litigation at 8-9, attached here as Exhibit I.

The accuracy and reliability of Pfizer's CSI data as a whole was disputed during the Lipitor litigation. *See, e.g.*, Lipitor litigation D.I. 292 (Ranbaxy's Opening Post-Trial Brief) at 40, attached here as Exhibit J. Furthermore, recognition that the data was CSI data, rather than COR data, leads to the conclusion that no unexpected results exist. *See, e.g.*, Lipitor litigation trial exhibit DTX-3347, attached here as Exhibit K.

Neither Ranbaxy nor Pfizer presented any evidence at trial, nor made any arguments on appeal, regarding the obviousness of the '893 Patent. Thus, while the '893 Patent was held not

invalid in the Lipitor litigation, obviousness of the '893 Patent was not decided. Further, MPEP §2642 (IV)(A), which is also discussed in the next section, states that "the existence of a final court decision of claim *validity* in view of the same or different prior art does not necessarily mean that no new question is present, because of the different standards of proof employed by the Federal District Courts and the Office." Moreover, "the determination of whether a substantial new question of patentability exists will be made independently of the court's decision on validity, because it is not controlling on the Office." *Id.*

The district court and the Federal Circuit did, however, resolve a claim construction dispute relating to the '893 Patent in the Lipitor litigation. In particular, the parties disagreed over whether Claim 1 covered enantiomeric forms of formula I, or was instead limited to racemic mixtures of the two possible trans isomers. In its opinion, the Federal Circuit upheld the district court's conclusion that each of the trans enantiomeric forms is covered by Claim 1. A copy of *Pfizer, Inc. v. Ranbaxy Labs. Ltd.*, 457 F.3d 1284 (Fed. Cir. 2006) is attached as Exhibit L. On this topic, the Federal Circuit looked to the specification of the '893 Patent, which states that:

> The compounds of structural formula I above possess two asymmetric carbon centers ... [which] gives rise to four possible isomers, two of which are the R-cis- and S-cis-isomers and the other two of which are the R-trans-and S-trans-isomers. This invention contemplates only the trans-form of the compounds of formula I above.

Id. at 1289 (quoting the '893 Patent at col. 3, ll. 45-54). The Federal Circuit then stated:

> We read this language to mean that the invention would otherwise encompass all four isomers of the compounds of structural formula I, but for the patentee's express disclaimer of the R-cis- and S-cis-isomers. There is no further disavowal of claim scope that would limit the '893 patent to trans-racemates. Indeed, as noted by the district court, the terms "racemate" or "racemic mixture" do not appear in the '893 patent; nor is claim 1, unlike claim 5, limited by a "trans-(±)" designation. In sum, the district court correctly found that no intrinsic evidence limits claim 1 of the '893 patent to trans-racemates, as opposed to an R-trans enantiomer, an S-trans enantiomer or any (equal or unequal) mixtures thereof.

Id. at 1289. The Federal Circuit thus concluded that "claim 1 was correctly construed to include the enantiomeric trans-forms of the compounds of structural formula I." *Id.* at 1290.

It should also be noted that throughout the Lipitor litigation, Pfizer attempted to rely on the commercial success of its Lipitor® product to support the non-obviousness of Claim 6 of U.S.

Patent No. 5,273,995. Pfizer continues to rely on this commercial success in support of that patent's now-pending reissue application, Reissue Application Serial No. 11/653,830. It would not be appropriate, under such circumstances, to infer the non-obviousness of *two* unrelated patents based on the success of a *single* commercial product. *See Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc.*, 395 F.3d 1364, 1376-77 (Fed. Cir. 2005).

The Caduet litigation is now pending, and the '893 Patent is one of the two asserted patents. Although the parties have submitted briefs relating to the application of *res judicata* and collateral estoppel based on the Lipitor litigation, no claim construction or validity briefing has occurred in the Caduet litigation to date.

V. The New Prior Art Raises Substantial New Questions of Patentability of Claims 1-5, 8, and 9 of the '893 Patent

Under MPEP §2642 (IV)(A), "the existence of a final court decision of claim *validity* in view of the same or different prior art does not necessarily mean that no new question is present, because of the different standards of proof employed by the Federal District Courts and the Office." Moreover, "the determination of whether a substantial new question of patentability exists will be made independently of the court's decision on validity, because it is not controlling on the Office." *Id.*

The '893 Patent issued from an application filed on May 30, 1986, and contains no priority claim to any earlier-filed domestic or foreign application. The '559 EP Publication was published on April 30, 1986, and is *prima facie* prior art under 35 U.S.C. § 102(a). The '173 Patent issued on January 6, 1976 and is prior art under 35 U.S.C. § 102(b). The '1453 Patent issued on April 8, 1986, with a filing date of May 9, 1983 and is *prima facie* prior art under 35 U.S.C. §§ 102(a) and (e). The '4453 Patent issued on January 11, 1972 and is prior art under 35 U.S.C. § 102(b). The '576 Patent issued on March 3, 1987, and because it has the same inventive entity and assignee as the '893 Patent, it is available as a reference and may support a reexamination request, under the judicially-created doctrine of non-statutory double patenting. *See In re Lonardo*, 119 F.3d 960 (Fed. Cir. 1997).

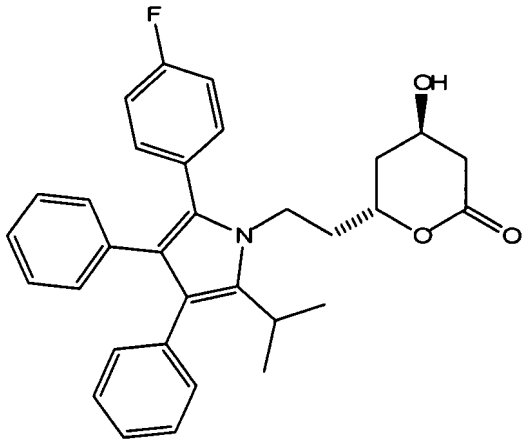
A. Claims 1-5, 8, and 9 are obvious under 35 U.S.C. §103 based on the '559 EP Publication

Claim 1 requires a compound of structural formula I with variously defined substituents R_1, R_2, R_3, R_4, and X, as defined above.

The '559 EP Publication teaches a variety of compounds of structural formula I having substituents that are identical, or structurally similar to the substituents R_1, R_2, R_3, R_4, and X as recited in Claim 1 of the '893 Patent. *See* page 3, line 22 – page 5, line 10. Specifically, the '559 EP Publication discloses compounds that satisfy the limitations of Claim 1 of the '893 Patent, except for the single limitation at column 16, line 30 that either of R_2 or R_3 be $-CONR_5R_6$.

However, the '559 EP Publication discloses other compounds that satisfy the limitations of Claim 1 of the '893 Patent, including the limitation that either of R_2 or R_3 be $-CONR_5R_6$, as discussed above, but excluding the limitation at column 16, lines 42-59 that the other R_2 or R_3 be one of the listed substituents.

Several examples provided in the '559 EP Publication disclose compounds that are structurally very similar to the compounds claimed in the '893 Patent.[1] For example, on page 13, lines 19-21, the '559 EP Publication recites the compound trans-6-[2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3,4-diphenyl-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one (hereinafter "Compound A"):

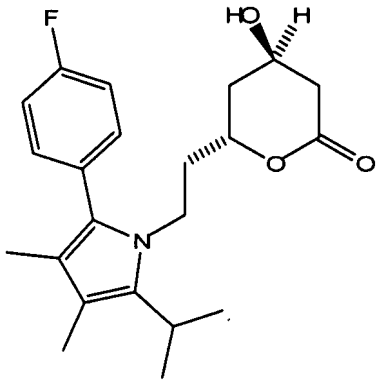


Compound A

[1] For the sake of brevity, not all of the relevant molecules of the '559 EP Publication are discussed. Rather, discussion is limited to a few exemplary molecules.

Prior art Compound A is largely encompassed by structural formula I, wherein X is $-CH_2CH_2-$, R_1 is phenyl substituted with fluorine, R_2 is phenyl, R_3 is phenyl, and R_4 is an alkyl of three carbon atoms. Compound A meets the claim limitations for X, R_1, R_2 and R_4. The only requirement of Claim 1 that is not met by Compound A is the limitation that either of R_2 or R_3 is $-CONR_5R_6$.[2]

On page 11, lines 29-31, the '559 EP Publication recites the compound trans-6-[2-[2-(4-Fluorophenyl)-3,4-dimethyl-5-(1-methylethyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one (hereinafter "Compound B"):



Compound B

Prior art Compound B is largely encompassed by structural formula I, wherein X is $-CH_2CH_2-$, R_1 is phenyl substituted with fluorine, R_2 is an alkyl of one carbon atom, R_3 is an alkyl of one carbon atom, and R_4 is an alkyl of three carbon atoms. Compound B meets the claim limitations for X, R_1, R_2 and R_4. The only requirement of Claim 1 that is not met by Compound B is the limitation that either of R_3 (or R_2) is $-CONR_5R_6$.

On page 11, lines 35-37, the '559 EP Publication recites the compound trans-2-(4-Fluorophenyl)-N^3,N^3,N^4,N^4-tetramethyl-5-(1-methylethyl)-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3,4-dicarboxamide (hereinafter "Compound C"):

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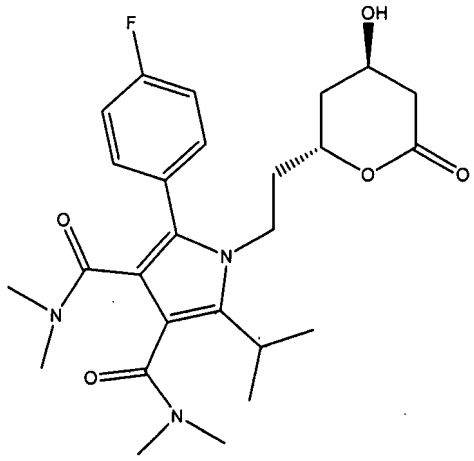
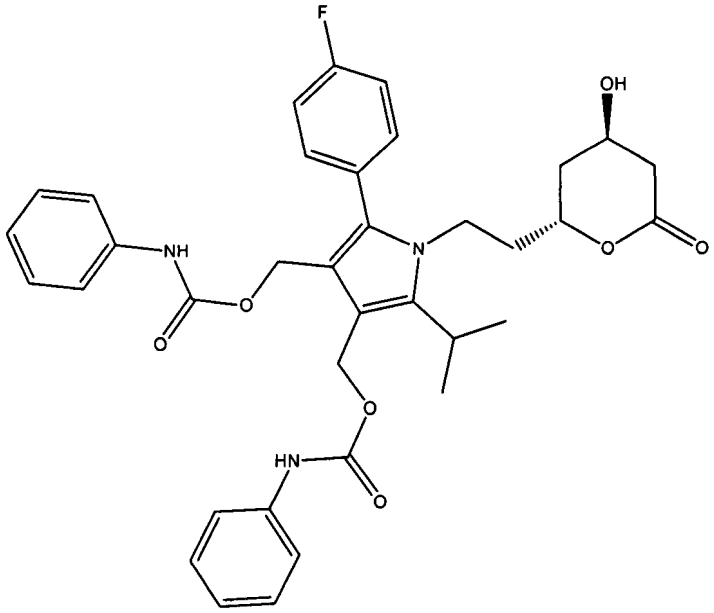
[2] While R_2 and R_3 are interchangeable in the analysis of the '559 EP Publication, in this request, structures in which R_3 is $-CONR_5R_6$ and R_2 is the "other" substituent are analyzed. This is done for the sake of simplicity and because the atorvastatin molecule (the subject of litigation in the Lipitor and Caduet litigations) follows that structure. This approach does not imply that Claim 1 requires that R_3 be $-CONR_5R_6$.



Compound C

Prior art Compound C is largely encompassed by structural formula I, wherein X is $-CH_2CH_2-$, R_1 is phenyl substituted with fluorine, R_2 is $-CONR_5R_6$ wherein R_5 and R_6 are both methyl, R_3 is $-CONR_5R_6$ wherein R_5 and R_6 are both methyl, and R_4 is an alkyl of three carbon atoms. Similar to Compounds A and B, Compound C meets the claim limitations for X, R_1, R_4, and one of the R_2 and R_3 substituents. Compound C describes a molecule wherein one of R_2 and R_3 is $-CONR_5R_6$. However, Compound C does not anticipate Claim 1 because the other of R_2 and R_3 does not meet the requirements of Claim 1. Thus, Compounds A and B meet the limitations for X, R_1, R_2, and R_4, but not R_3, whereas Compound C meets the limitations for X, R_1, R_3, and R_4, but not R_2.

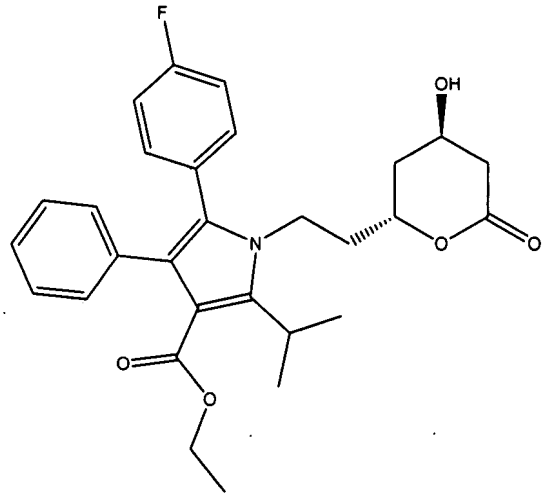
On page 14, lines 1-2, the '559 EP Publication recites the compound trans-6-[2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3,4-bis[[[(phenylamino)carbonyl]oxy]methyl]-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one (hereinafter "Compound D"):



Compound D

Prior art Compound D is largely encompassed by structural formula I, wherein X is $-CH_2CH_2-$, R_1 is phenyl substituted with fluorine, R_2 is $-CH_2OCONHR_7$ wherein R_7 is phenyl, R_3 is $-CH_2OCONHR_7$ wherein R_7 is phenyl, and R_4 is an alkyl of three carbon atoms. Compound D meets the claim limitations for X, R_1, and R_4. While Compound D does not meet the requirement of Claim 1 that either of R_2 or R_3 is $-CONR_5R_6$, the $-CH_2OCONHR_7$ substituent present on both R_2 and R_3 of Compound D serves as evidence that the '559 EP Publication contemplated a variety of possible substituents, including substituents comprising an amide group with a phenyl ring attached to the nitrogen atom.

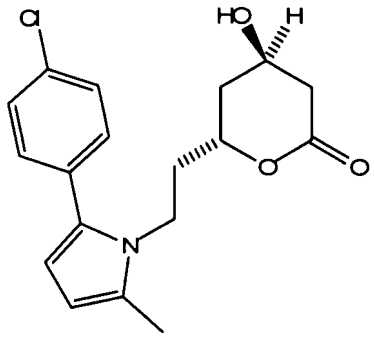
On page 13, lines 1-3, the '559 EP Publication recites the compound trans-Ethyl 5-(4-Fluorophenyl)-2-(1-methylethyl)-4-phenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxylate (hereinafter "Compound E"):



Compound E

Prior art Compound E is largely encompassed by structural formula I, wherein X is $-CH_2CH_2-$, R_1 is phenyl substituted with fluorine, R_2 is phenyl, R_3 is a carboalkoxy of two carbon atoms, and R_4 is an alkyl of three carbon atoms. Compound E meets the claim limitations for X, R_1, R_2 and R_4. Similar to Compounds A and B, the only requirement of Claim 1 that is not met by Compound E is the limitation that either of R_3 (or R_2) is $-CONR_5R_6$. While compound E does not meet the requirement of Claim 1 that either of R_2 or R_3 is $-CONR_5R_6$, the carboalkoxy of three carbon atoms present on R_3 of Compound E serves as evidence that the '559 EP Publication contemplated a wide variety of possible substituents, including substituents that are attached to the ring structure through a carbonyl group.

On page 11, lines 6-7, the '559 EP Publication recites the compound trans-6-[2-[2-(4-Chlorophenyl)-5-methyl-1H-pyrrol-1-yl]ethyl]tetrahydro-4-h ydroxy-2H-pyran-2-one (hereinafter "Compound F"):



Compound F

Compound F is largely encompassed by structural formula I, wherein X is $-CH_2CH_2-$, R_1 is phenyl substituted with chlorine, R_2 is hydrogen, R_3 is hydrogen, and R_4 is an alkyl group of one carbon atom. The only requirement of Claim 1 not met by Compound F is the limitation that either of R_2 or R_3 is $-CONR_5R_6$. However, Compound F serves of evidence that the '559 EP Publication contemplated a broad variety of substituents to attach to the ring.

Thus, the '559 EP Publication teaches molecules satisfying nearly all of the limitations of Claim 1, namely, the claimed structural formula I and the substituents for X, R_1, R_2, and R_4. The '559 EP Publication also teaches other molecules that satisfy the claimed structural formula I and the substituents for X, R_1, R_3, and R_4. The only difference between the disclosure of the '559 EP Publication and the compounds within the literal scope of Claim 1 lies in either the R_2 or R_3 substituent, depending on the molecule.

The '559 EP Publication specifically teaches that R_3 (or alternatively, R_2) can be $-CH_2OCONHR_7$, wherein R_7 is alkyl of from one to six carbon atoms, phenyl, or phenyl substituted with chlorine, bromine, or alkyl of from one to four carbon atoms. *See* page 8, lines 5-8. Compound D, illustrated above, is an example in which R_3 is $-CH_2OCONHR_7$. When compared to the R_3 substituent required in Claim 1 of the '893 Patent, the only difference is the presence of an $-OCH_2-$ linker group between the carbonyl group of the substituent and the central, five-membered ring structure.

Further, the '559 EP Publication specifically teaches that R_3 (or alternatively, R_2) can be carboalkoxy of two to eight carbon atoms (which means -COOR, wherein R is alkyl of from one to seven carbon atoms). *See* page 8, line 3. Compound E, illustrated above, is an example in which R_3 is –COOR, wherein R is alkyl of two carbons atoms (ethyl). When compared to the R_3 substituent required in Claim 1 of the '893 Patent, the only difference is the presence of an alkoxy group adjacent to the carbonyl group instead of an amine group adjacent to the carbonyl group.

The removal of a simple linker group (in this case, $-OCH_2-$) is a predictable and obvious variation, well within the ability of those having ordinary skill in the art. Similarly, the replacement of an ester with an amide group is also a predictable and obvious variation, well within the ability of those having ordinary skill in the art. As the Supreme Court has recently observed, if a person of ordinary skill can implement a predictable variation, § 103 likely bars its

patentability. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007). Similarly, as Warner-Lambert stated during prosecution of the European counterpart to the '893 Patent:

> Applicants generally accept the Examining Division's arguments saying that a person skilled in the art would expect that the pyrazole [sic] ring was susceptible to further substitutions at the 3 and 4 position including other carboxy derivatives . . . without leading to a significant change in qualitative properties.

Lipitor litigation trial exhibit DTX-331 at RA017516, attached here as Exhibit H. The '559 EP Publication discloses compounds that have essentially the same structure as those claimed in the '893 patent, and are taught to be useful for the same indication: lowering blood serum cholesterol. *See* page 1, lines 3-5.

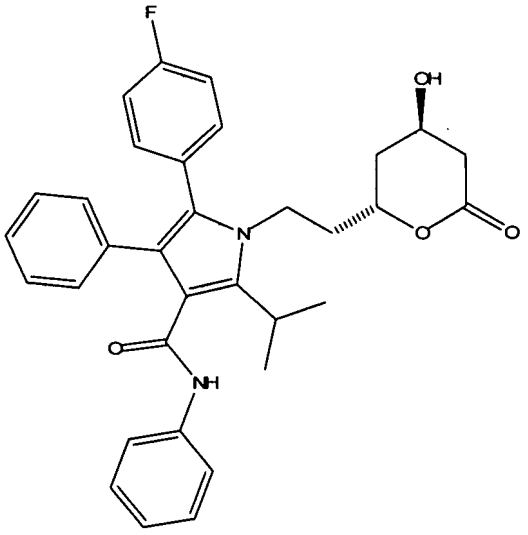
Furthermore, the '559 EP Publication itself teaches that a carboxamide substituent may be directly attached to the ring without using a $-OCH_2-$ linker group. Compound C, illustrated above, shows such an instance where the carboxamide is directly linked to the ring.

Where obtaining the same R_3 substituent merely represents selecting from a finite number of identified, predictable solutions available to one of ordinary skill in the art, as is the case here, obviousness under the *KSR* standard is easily found. *See KSR*, 127 S. Ct. at 1740-41. Moreover, obviousness can also be found where, as here, the claimed compound would have been obtained by applying well-known techniques to select an obvious alternative R_3 substituent. *Id.* It would have been obvious to a person having ordinary skill in the art to remove the $-OCH_2-$ linker group between the carbonyl group on the substituent and the ring structure or to modify the ester to an amide by applying the common knowledge of one of ordinary skill in the art to obtain a compound of Claim 1. The '559 EP Publication discloses a variety of useful substituents, including $-CONR_5R_6$, where R_5 and R_6 are alkyl *See, e.g.*, Compound C. It is easily within the purview of one having ordinary skill in the art to replace the R_3 ester substituent of Compound E with the R_3 amide substituent of Compound C, and thereby obtain a compound that falls within the scope of Claim 1.

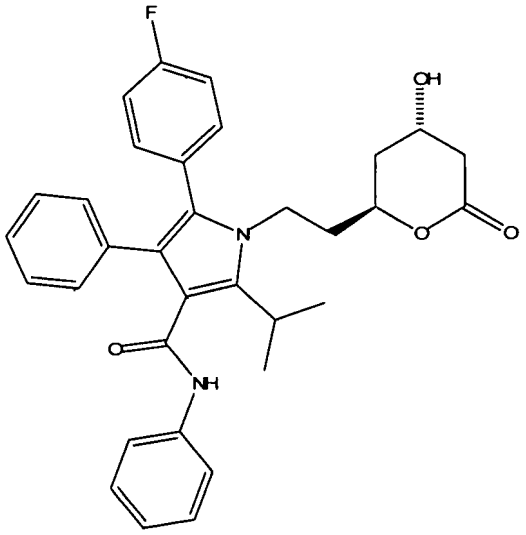
Regarding Claim 2, the '559 EP Publication also teaches the only additional limitation, that X is $-CH_2CH_2-$ in, for example, Compounds A-F. Regarding Claim 3, the '559 EP Publication teaches that R_1 is phenyl substituted with fluorine in, for example, Compounds A-E, and that R_1 is phenyl substituted with chlorine in, for example, Compound F. Regarding Claim

4, the '559 EP Publication teaches that R_4 is an alkyl of three carbon atoms in, for example, Compounds A-E, and that R_4 is an alkyl of one carbon atom in, for example, Compound F.

Claim 5 of the '893 Patent recites that the compound is trans-(±)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide. The recitation of "trans-(±)-" in Claim 5 refers to a racemic mixture that contains both the R-trans- and the S-trans-isomers.



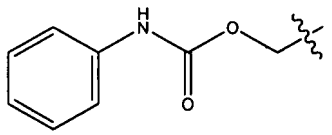
R-trans isomer



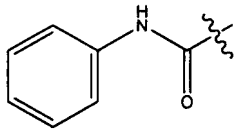
S-trans isomer

This compound of Claim 5 is a compound of structural formula I, wherein X is $-CH_2CH_2-$, R_1 is phenyl substituted with fluorine, R_2 is phenyl, R_3 is an N-phenyl carboxamide, and R_4 is an alkyl of three carbon atoms (isopropyl). As discussed above, the '559 EP Publication teaches several compounds of structural formula I, wherein X is $-CH_2CH_2-$, R_1 is phenyl substituted with fluorine, R_2 is phenyl, and R_4 is an alkyl of three carbon atoms (isopropyl). *See, e.g.*, page 8, line 36 to page 9, line 30; Compounds A and E. As for the racemic mixture aspect of Claim 5, the '559 EP Publication discloses "all of the compounds being in the trans racemate of the tetrahydropyran moiety." '559 EP Publication at page 5, lines 23-25. Therefore, the '559 EP Publication teaches molecules satisfying nearly all of the limitations of Claim 5. The only difference between the '559 EP Publication and the compound of Claim 5 lies in the R_3 substituent.

The '559 EP Publication teaches that R_3 (or alternatively, R_2) can be $-CH_2OCONHR_7$, wherein R_7 may be phenyl. *See* page 4, lines 13-14 and Compound D. Such an R_3 substituent has the following structure compared to the N-phenyl carboxamide substituent required in Claim 5 of the '893 Patent:

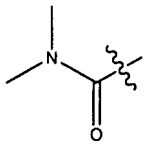


R3 substituent described in the '559 Publication

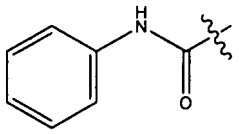


R3 substituent required by Claim 5 of the '893 Patent

The only difference between these two substituents is the presence of an $-OCH_2-$ linker group to the right side of the carbonyl. Thus, the obviousness analysis applied above with regard to Claim 1 also applies to Claim 5. The addition, or subtraction, of such a simple linker is a predictable and obvious variation, well-known to those of ordinary skill in the art. It thus, would have been obvious to remove the $-OCH_2-$ linker group by applying common knowledge of chemical substitution and obtain the compound recited in Claim 5. Specific motivation to remove this linker was present from the prior art '559 EP Publication, which describes a molecule wherein R_3 is $-CONR_5R_6$, and wherein R_5 and R_6 are methyl. *See* page 11, lines 35-37 and Compound C. Such an R_3 substituent has the following structure compared to the N-phenyl carboxamide substituent required in Claim 5 of the '893 Patent:



R3 substituent described in the '559 Publication



R3 substituent required by Claim 5 of the '893 Patent

Thus, the '559 EP Publication contemplated and taught that carboxamide substituents should be attached directly to the ring from the carbonyl atom. Therefore, the removal of the $-OCH_2-$ linker group in the above-referenced substituent was a predictable and obvious variation.

Further, the only difference between Compound E and the compound of Claim 5 is the presence of an ethoxy group instead of an N-phenyl amino group (adjacent to the carbonyl group in the R_3 substituent). Such a substitution is a predictable and obvious variation, well-known to those having ordinary skill in the art. Thus replacing the $-OCH_2CH_3$ group with a phenyl amine is merely a matter of applying common knowledge of chemical substitution, and thus obtaining

the compound recited in Claim 5. Evidence of motivation to use a phenyl amine adjacent to a carbonyl group in the R_3 substituent is provided, for example, by Compound D.

Regarding Claim 8, the '559 EP Publication discloses that "the present invention provides pharmaceutical compositions, useful as hypolipidemic or hypocholesterolemic agents, comprising a hypolipidemic or hypocholesterolemic affective amount of a compound in accordance with this invention ... in combination with a pharmaceutically acceptable carrier." '559 EP Publication at page 6, lines 23-28. Therefore, the '559 EP Publication teaches the additional limitations of Claim 8.

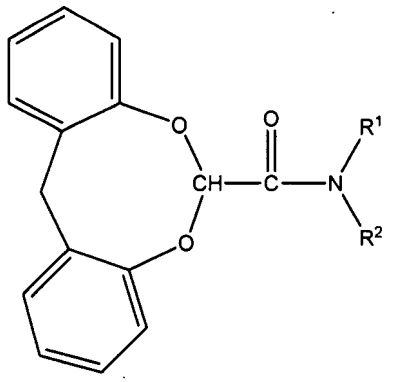
Regarding Claim 9, the '559 EP Publication discloses that "the present invention provides a method of inhibiting cholesterol biosynthesis in a patient in need of such treatment by administering a pharmaceutical composition." Page 6, lines 29-32. Therefore, the '559 EP Publication teaches the additional limitations of Claim 9.

Thus, as summarized above and in the claim chart in Exhibit M, Claims 1-5, 8, and 9 of the '893 Patent are rendered obvious over the teachings of the '559 EP Publication.

B. Claims 1-5, 8, and 9 are obvious under 35 U.S.C. §103 based on the '559 EP Publication in view of the '173 Patent

The '559 EP Publication teaches the structural framework of the claimed compounds, along with the specific, claimed substituents for X, R_1, R_2, and R_4. Where the '559 EP Publication does teach that R_3 is $-CONR_5R_6$ (thus meeting the Claim 1 limitation for R_3), then R_2 is a substituent that does not meet the claim limitations.

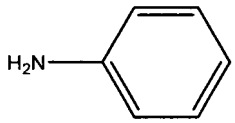
However, use of a $-CONR_5R_6$ substituent was well-known and commonly used in the art of pharmaceutical chemistry and, more specifically, with respect to compounds used to lower cholesterol levels. The prior art '173 Patent teaches dioxocin carboxamide derivatives useful in treating elevated cholesterol levels. *See* column 1, lines 4-10 and column 3, lines 40-54. The compounds taught by the '173 Patent are ring-containing compounds of the following formula:



wherein R^1 and R^2 may be independently selected to be hydrogen, lower alkyl of from 1 to 4 carbon atoms, benzyl, picolyl, cycloalkyl of from 3 to 6 carbon atoms, phenyl, or substituted phenyl in which case the substituents on the substituted phenyl are selected from lower alkyl of from 1 to 4 carbon atoms. *See* column 1, lines 27-57.

Thus, the '173 Patent taught a substituent on a central ring structure that corresponds to the claimed R_3 substituent of $-CONR_5R_6$. Therefore, it would have been obvious to a person having ordinary skill in the art to attach a $-CONR_5R_6$ substituent to the ring structure in the '559 EP Publication, as taught by the '173 Patent. Claim 1 is thus rendered obvious by this combination of art. Claims 2, 3, 4, 8, and 9 add nothing not also disclosed in the '559 EP Publication (as discussed previously), and are thus also rendered obvious.

Regarding Claim 5 and its limitation of an N-phenyl carboxamide R_3 substituent, the prior art '173 Patent teaches that the compound is formed by reaction of an acid halide having the ring structure shown above with an amine that creates the $-NR^1R^2$ substituent on the right side of the compound. *See* column 4, lines 19-61. The '173 Patent teaches that a typical amine that is reacted with the acid halide is aniline, column 4, line 57, which has the following structure:



After the aniline is reacted with the acid halide having the ring structure shown above, one of the R^1 and R^2 substituents is hydrogen and the other of the R^1 and R^2 substituents is phenyl in the compound of the '173 Patent. Thus, the ring structure is substituted with an N-phenyl carboxamide, which is the R_3 substituent of Claim 5. Therefore, it would have been obvious to a person having ordinary skill in the art to provide an N-phenyl carboxamide substituent to the ring structure in the '559 EP Publication, as taught by the '173 Patent, because

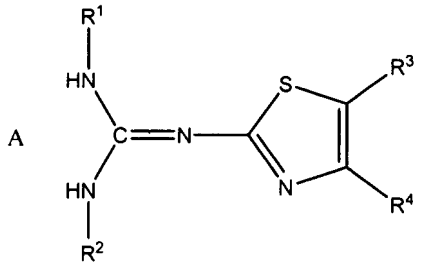
obviousness can be found where a claimed compound can be obtained by applying known chemical knowledge in the same field of endeavor to select the proper R_3 substituent. Claim 5 is thus rendered obvious by this combination of art as well.

Thus, as summarized above and in the claim chart in Exhibit N, Claims 1-5, 8, and 9 of the '893 Patent are rendered obvious by the combination of the '559 EP Publication and the '173 Patent.

C. Claims 1-5, 8, and 9 are obvious under 35 U.S.C. §103 based on the '559 EP Publication in view of the '1453 Patent

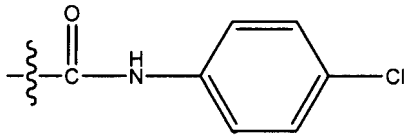
The '559 EP Publication teaches the structural framework of the claimed compounds, along with the specific, claimed substituents for X, R_1, R_2, and R_4. Where the '559 EP Publication teaches that R_3 is $-CONR_5R_6$ (thus meeting the Claim 1 limitation for R_3), then R_2 is a substituent that does not meet the claim limitations.

However, use of a $-CONR_5R_6$ substituent was well-known and commonly used in the art of pharmaceutical chemistry and, more specifically, with respect to compounds used to lower cholesterol levels. The '1453 Patent teaches compounds useful in influencing lipid metabolism and treating high cholesterol. *See* column 1, lines 6-10 and column 21, lines 12-45. The compounds taught by the '1453 Patent are ring-containing compounds of the following formula:



wherein R^3 may represent a carboxamide in which the amide group is substituted by an optionally substituted aryl. *See* column 1, lines 10-23 and column 2, lines 1-2. Thus, the reference teaches an N-phenyl carboxamide substituent on a central ring structure.

The '1453 Patent specifically teaches the use of a carboxamide where the nitrogen atom is substituted with an optionally substituted phenyl group is useful in the treatment of high cholesterol. *See* column 21, lines 12-46 and Example 17 from Table 1. This reference also discloses that Example 17 provides significant reduction in the increase in liver cholesterol. The R^3 substituent of Example 17 is an N-phenyl carboxamide that is substituted with chlorine:



It therefore would have been obvious to a person having ordinary skill in the art to attach a $-CONR_5R_6$ substituent to the ring structure in the '559 EP Publication, as taught by the '1453 Patent. Claim 1 is thus rendered obvious by this combination of art. Claims 2, 3, 4, 8, and 9 add nothing not also disclosed in the '559 EP Publication (as discussed previously), and are thus also rendered obvious.

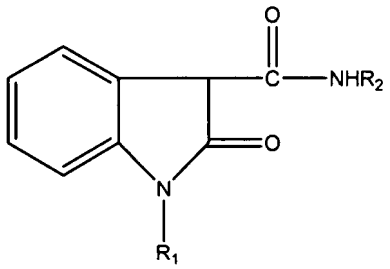
Regarding Claim 5 and its limitation of an N-phenyl carboxamide R_3 substituent, although the N-phenyl carboxamide substituent of Example 17 contains a chlorine atom, the inclusion of the chlorine atom is optional as described in the '1453 Patent. *See* column 2, lines 1-2. Thus, the '1453 Patent specifically teaches that N-phenyl carboxamide substituents are advantageous in ring-containing compounds designed to lower cholesterol. Therefore, it would have been obvious to a person having ordinary skill in the art to provide an N-phenyl carboxamide substituent to the ring structure in the '559 EP Publication, as taught by the '1453 Patent. Claim 5 is thus rendered obvious by this combination of art as well.

Thus, as summarized above and in the claim chart in Exhibit O, Claims 1-5, 8, and 9 of the '893 Patent are rendered obvious by the combination of the '559 EP Publication and the '1453 Patent.

D. Claims 1-5, 8, and 9 are obvious under 35 U.S.C. §103 based on the '559 EP Publication in view of the '4453 Patent

The '559 EP Publication teaches the structural framework of the claimed compounds, along with the specific, claimed substituents for X, R_1, R_2, and R_4. Where the '559 EP Publication teaches that R_3 is $-CONR_5R_6$ (thus meeting the Claim 1 limitation for R_3), then R_2 is a substituent that does not meet the claim limitations.

However, use of a $-CONR_5R_6$ substituent was well-known and commonly used in the art of providing safe and effective pharmaceutical ingredients. The prior art '4453 Patent teaches compounds useful in therapy as non-steroidal anti-inflammatory agents. *See* Abstract. The compounds taught by the '4453 Patent are ring-containing compounds of the following formula:



wherein R^2 may represent a phenyl group. *See* column 1, lines 47-67. Thus, the reference teaches a substituent on a central ring structure that is an N-phenyl carboxamide group.

The '4453 Patent also provides specific examples in which the carboxamide substituent of the ring has a phenyl or substituted phenyl as the R_2 substituent. *See* Table in Example IV. The '4453 Patent teaches that the carboxamide substituent is easily provided to therapeutic compounds and that preparation is facile, using methods well-known to those skilled in the art. *See* column 2, lines 40-66. Thus, the '4453 Patent specifically teaches that carboxamide substituents are advantageous in ring-containing compounds for use as safe and effective active pharmaceutical ingredients. Therefore, it would have been obvious to a person having ordinary skill in the art to attach a carboxamide substituent to the ring structure in the '559 EP Publication, as taught by the '4453 Patent. Claim 1 is thus rendered obvious by this combination of art. Claims 2, 3, 4, 8, and 9 add nothing that is not also disclosed in the '559 EP Publication (as discussed previously), and are thus also rendered obvious.

Regarding Claim 5, the '4453 Patent teaches numerous examples in which the R_2 substituent is phenyl. *See* Table in Example IV. Therefore, it would have been obvious to a person having ordinary skill in the art to provide an N-phenyl carboxamide substituent to the ring structure in the '559 EP Publication, as taught by the '4453 Patent. Claim 5 is thus rendered obvious by this combination of art as well.

Thus, as summarized above and in the claim chart in Exhibit P Claims 1-5, 8, and 9 of the '893 Patent are rendered obvious by the combination of the '559 EP Publication and the '4453 Patent.

E. Claims 1-5, 8, and 9 are not patentable under the judicially-created doctrine of non-statutory double patenting based on the claims of the '576 Patent

The duration of a patentee's right to exclude others from practicing a claimed invention is statutorily defined in 35 U.S.C. § 154(a)(2). The judicially-created doctrine of non-statutory

double patenting (also referred to as "obviousness-type double patenting") gives effect to that limited term by prohibiting a patentee from effectively obtaining an extension of the right to exclude through claims in a later patent that are not patentably distinct from claims in a commonly owned, earlier-expiring patent.[3] A later patent claim is not patentably distinct from an earlier patent claim if the later claim is obvious in view of the earlier claim. *See In re Longi*, 759 F.2d 887, 892, 896 (Fed. Cir. 1998) (affirming a holding of non-statutory double patenting because the claims at issue were obvious over claims in four prior art patents and explaining that, even though no explicit statutory basis exists for non-statutory double patenting, the doctrine is necessary to prevent a patent term extension through claims in a second patent that are not patentably distinct from those in the first patent).

In most circumstances, non-statutory double patenting requires a two step analysis. First, a court will construe the relevant claims of the two patents to determine the differences between the claimed subject matter. *Eli Lilly and Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001). Second, the court will determine whether the differences in subject matter between the two claims render the subject matter of the claims patentably distinct. *Id.* Under this so-called "one-way" double patenting test, a later claim that is not patentably distinct from an earlier claim in a commonly owned patent will be invalid for double patenting. *Id.* While the disclosure of the earlier patent may not be used as prior art, such disclosure may be used as an aid in the understanding the meaning of a claim term or of the nature of what is claimed. *See In re Vogel*, 422 F.2d 438 (C.C.P.A. 1970).

Claim 1 requires a compound of structural formula I with variously defined substituents R_1, R_2, R_3, R_4, and X, as defined above.

Claim 1 of the '576 Patent discloses compounds of the same structural formula I having substituent options that are identical to the R_1, R_2, R_4, and X as recited in Claim 1 of the '893 Patent. *See* Claim 1 of the '576 Patent. The following table shows the overlap in claimed substituents between the '576 Patent and the '893 Patent:

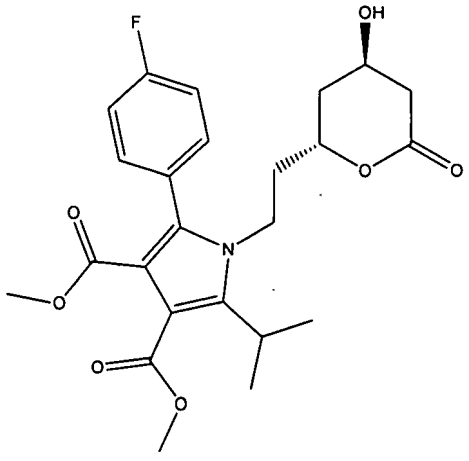
Substituent	Claim 1 of the '576 Patent	Claim 1 of the '893 Patent
X	$-CH_2-$, $-CH_2CH_2-$, - or	$-CH_2-$, $-CH_2CH_2-$, - or

[3] The '576 Patent expired on December 10, 2004, more than seventeen months before the original expiry of the '893 Patent under 35 U.S.C. § 154.

	$-CH_2CH(CH_3)-$	$-CH_2CH(CH_3)-$
R_1	1-naphthyl; 2-naphthyl; cyclohexyl; norbornenyl; phenyl; phenyl substituted by fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms	1-naphthyl; 2-naphthyl; cyclohexyl; norbornenyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms;
R_2	hydrogen; alkyl of from one to six carbon atoms; or phenyl	hydrogen; alkyl of from one to six carbon atoms; or phenyl
R_4	alkyl of from one to four carbon atoms; cyclopropyl; cyclobutyl; or trifluoromethyl	alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; or trifluoromethyl

However, Claim 1 of the '576 Patent does not disclose the single limitation that R_3 is $-CONR_5R_6$.

Claim 1 of the '576 Patent recites in column 31 line 66, that R_3 can be cyano, and recites in column 32, line 2, that R_3 can be carboalkoxy of from two to eight carbon atoms. Additionally, Claim 8 recites a compound, trans-dimethyl 2-(4-fluorophenyl)-5-(1-methylethyl)-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3,4-dicarboxylate, which shows R_3 as a carboalkoxy of two carbon atoms:



'576 Patent Claim 8 Compound

Claim 8 of the '576 Patent shows that the difference between the R_3 substituent in Claim 1 of the '576 Patent and the R_3 substituent in Claim 1 of the '893 Patent is an alkoxy group adjacent to the carbonyl (thus forming an ester) rather than an amino group adjacent to the

carbonyl (thus forming an amide). Alternatively, the difference between the R_3 substituent in Claim 1 of the '576 Patent and the R_3 substituent in Claim 1 of the '893 Patent is a nitrile group rather than an amide group.

Substitution of such a well-known and commonly used substituent would have been obvious to a person having ordinary skill in the art. As the Supreme Court has recently established, if a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007). Similarly, as Warner-Lambert stated during prosecution of the European counterpart to the '893 Patent:

> Applicants generally accept the Examining Division's arguments saying that a person skilled in the art would expect that the pyrazole [sic] ring was susceptible to further substitutions at the 3 and 4 position including other carboxy derivatives . . . without leading to a significant change in qualitative properties.

Lipitor litigation trial exhibit DTX-331 at RA017516, attached here as Exhibit H. Claim 1 of the '576 Patent discloses compounds that have essentially the same structure as those claimed in the '893 patent, and are taught to be useful for the same indication: lowering blood serum cholesterol. *See* Claims 18 and 19 of the '576 Patent.

Where, as here, obtaining the same R_3 substituent merely represents selecting from a finite number of identified, predictable solutions available to one of ordinary skill in the art, the claim is obvious under *KSR*. *See KSR*, 127 S. Ct. at 1740-41. Moreover, the claimed compound is obvious where it can be obtained by applying well-known chemical knowledge to select art-recognized R_3 substituents. *Id.* It therefore would have been obvious to a person having ordinary skill in the art to provide a $-CONR_5R_6$ substituent at R_3 in Claim 1 of the '576 Patent in order to obtain the compound of Claim 1 of the '893 Patent by applying common knowledge of chemical substitution.

Regarding Claims 2-4 of the '893 Patent, Claim 1 of the '576 Patent specifically recites each of these substituents for X, R_1, and R_4.

Regarding Claim 5 of the '893 Patent, the '576 Patent does not claim the R_3 substituent of an N-phenyl carboxamide. However, as explained above, N-phenyl carboxamide substituents were well-known and commonly used in the art. It therefore would have been obvious to a person having ordinary skill in the art to use an N-phenyl carboxamide at the R_3 substituent of Claim 1 of the '576 Patent in place of an ester or a nitrile substituent.

Regarding Claim 8 of the '893 Patent, Claim 18 of the '576 Patent recites a "hypocholesterolemic agent, comprising a hypocholesterolemic effective amount of a compound in accordance with claim 1 in combination with a pharmaceutically acceptable carrier." Therefore, the claims of the '576 Patent teach the additional limitations of Claim 8 of the '893 Patent.

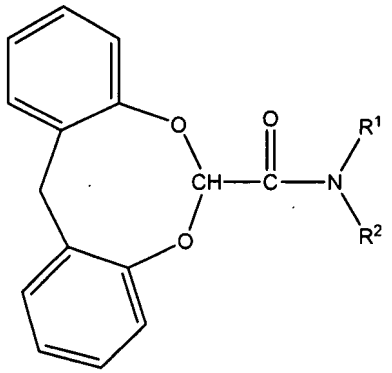
Regarding Claim 9 of the '893 Patent, Claim 19 of the '576 Patent recites a "method of treating inhibiting cholesterol biosynthesis in a patient in need of such treatment by administering a pharmaceutical composition in accordance with claim 18." Therefore, the claims of the '576 Patent teach the additional limitations of Claim 9 of the '893 Patent.

Thus, as summarized above and in the claim chart in Exhibit Q, Claims 1-5, 8, and 9 of the '893 Patent are rendered unpatentable over the claims of the '576 Patent.

F. Claims 1-5, 8, and 9 are not patentable under the judicially-created doctrine of non-statutory double patenting based on the claims of the '576 Patent in view of the '173 Patent

The claims of the '576 Patent teach the structural framework of the claimed compounds, along with the substituents for X, R_1, R_2, and R_4. The claims of the '576 Patent do not, however, expressly recite that R_3 is $-CONR_5R_6$.

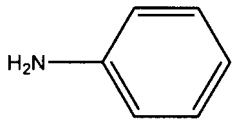
However, use of a $-CONR_5R_6$ substituent was common and well-known in the art of pharmaceutical chemistry, and more specifically, the art of lowering cholesterol levels. The '173 Patent teaches dioxocin carboxamide derivatives useful in treating elevated cholesterol. *See* column 1, lines 4-10 and column 3, lines 40-54. The compounds taught by the '173 Patent are ring-containing compounds of the following formula:



wherein R^1 and R^2 may be independently selected to be hydrogen, lower alkyl of from 1 to 4 carbon atoms, benzyl, picolyl, cycloalkyl of from 3 to 6 carbon atoms, phenyl, or substituted phenyl in which case the substituents on the substituted phenyl are selected from lower alkyl of from 1 to 4 carbon atoms. *See* column 1, lines 27-57.

Thus, the reference teaches a substituent on a central ring structure that corresponds to the claimed R_3 substituent of $-CONR_5R_6$. Therefore, it would have been obvious to attach a $-CONR_5R_6$ substituent to the ring structure in Claim 1 of the '576 Patent, as taught by the '173 Patent, because obviousness can be found where a claimed compound can be obtained by applying known chemical knowledge in the same field of endeavor to select the proper R_3 substituent. Claim 1 was thus unpatentable in view of this combination. Claims 2, 3, 4, 8, and 9 add nothing not also disclosed in the claims of the '576 Patent (as discussed previously), and are thus also unpatentable.

Regarding Claim 5 of the '893 Patent and its limitation of an N-phenyl carboxamide R_3 substituent, the '173 Patent teaches that the compound is formed by reaction of an acid halide having the ring structure shown above with an amine that creates the $-NR^1R^2$ substituent on the right side of the compound. *See* column 4, lines 19-61. The '173 Patent then teaches that a typical amine that is reacted with the acid halide is aniline, column 4, line 57, which has the following structure:



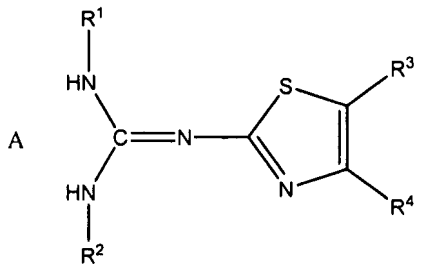
After the aniline is reacted with the acid halide having the ring structure shown above, one of the R^1 and R^2 substituents is hydrogen and the other of the R^1 and R^2 substituents is phenyl in the compound of the '173 Patent. Thus, the ring structure is substituted with an N-phenyl carboxamide, which is the R_3 substituent of Claim 5. Therefore, it would have been obvious to a person having ordinary skill in the art to provide an N-phenyl carboxamide substituent to the ring structure in Claim 1 of the '576 Patent, as taught by the '173 Patent. Claim 5 is thus unpatentable by this combination as well.

Thus, as summarized above and in the claim chart in Exhibit R, Claims 1-5, 8, and 9 of the '893 Patent are rendered unpatentable in view of the combination of the claims of the '576 Patent and the prior art '173 Patent.

G. Claims 1-5, 8, and 9 are not patentable under the judicially-created doctrine of non-statutory double patenting based on the claims of the '576 Patent in view of the '1453 Patent

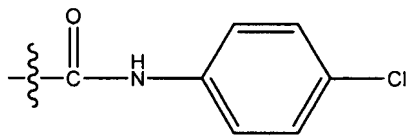
The claims of the '576 Patent teach the structural framework of the claimed compounds, along with the substituents for X, R_1, R_2, and R_4. The claims of the '576 Patent do not recite that R_3 is $-CONR_5R_6$.

However, use of a $-CONR_5R_6$ substituent was well-known and commonly used in the art of pharmaceutical chemistry, and more specifically related to compounds for lowering cholesterol levels. The '1453 Patent teaches compounds useful in influencing lipid metabolism and treating high cholesterol. *See* column 1, lines 6-10 and column 21, lines 12-45. The compounds taught by the '1453 Patent are ring-containing compounds of the following formula:



wherein R^3 may represent a carboxamide in which the amide group is substituted by an optionally substituted aryl. *See* column 1, lines 10-23 and column 2, lines 1-2. Thus, the reference teaches an N-phenyl carboxamide substituent on a central ring structure.

The '1453 Patent specifically teaches that a carboxamide where the nitrogen atom is substituted with an optionally substituted phenyl group is useful in the treatment of high cholesterol. *See* column 21, lines 12-46 and Example 17 from Table 1. There it is disclosed that Example 17 provides significant reduction in the increase in liver cholesterol. The R^3 substituent of Example 17 is an N-phenyl carboxamide that is substituted with chlorine:



It would have been obvious to a person having ordinary skill in the art to attach a $-CONR_5R_6$ substituent to the ring structure in Claim 1 of the '576 Patent, as taught by the '1453 Patent. Claim 1 is thus rendered unpatentable by this combination of art. Claims 2, 3, 4, 8, and 9

add nothing that is not also disclosed in the claims of the '576 Patent (as discussed previously), and are thus also rendered unpatentable.

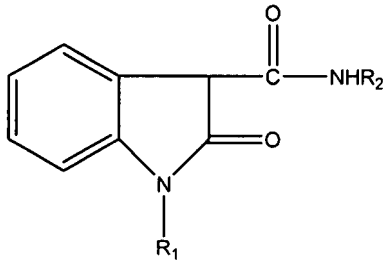
Regarding Claim 5 of the '893 Patent and its limitation of an N-phenyl carboxamide R_3 substituent, although the N-phenyl carboxamide substituent of Example 17 contains a chlorine atom, the inclusion of the chlorine atom is optional as described in the '1453 Patent. *See* column 2, lines 1-2. Thus, the '1453 Patent teaches that N-phenyl carboxamide substituents are advantageous in ring-containing compounds designed to lower cholesterol. Therefore, it would have been obvious to a person having ordinary skill in the art to provide an N-phenyl carboxamide substituent to the ring structure in Claim 1 of the '576 Patent, as taught by the '1453 Patent. Claim 5 is thus rendered unpatentable by this combination as well.

Thus, as summarized above and in the claim chart in Exhibit S, Claims 1-5, 8, and 9 of the '893 Patent are unpatentable in view of the combination of the claims of the '576 Patent and the prior art '1453 Patent.

H. Claims 1-5, 8, and 9 are not patentable under the judicially-created doctrine of non-statutory double patenting based on the claims of the '576 Patent in view of the '4453 Patent

The claims of the '576 Patent teach the structural framework of the claimed compounds, along with the substituents for X, R_1, R_2, and R_4. The claims of the '576 Patent do not recite that R_3 is $-CONR_5R_6$.

However, use of a $-CONR_5R_6$ substituent was common and well-known in the art of providing safe and effective pharmaceutical ingredients. The '4453 Patent teaches compounds useful in therapy as non-steroidal anti-inflammatory agents. *See* Abstract. The compounds taught by the '4453 Patent are ring-containing compounds of the following formula:



wherein R^2 may represent a phenyl group. *See* column 1, lines 47-67. Thus, the reference teaches a substituent on a central ring structure that is an N-phenyl carboxamide group.

The '4453 Patent also provides specific examples in which the carboxamide substituent of the ring has a phenyl or substituted phenyl as the R_2 substituent. *See* Table in Example IV. The '4453 Patent teaches that the carboxamide substituent is easily provided to therapeutic compounds and that preparation is easy, using methods well-known to those skilled in the art. *See* column 2, lines 40-66. Thus, the '4453 Patent clearly teaches that carboxamide substituents are advantageous in ring-containing compounds for use as safe and effective active pharmaceutical ingredients. Therefore, it would have been obvious to a person having ordinary skill in the art to attach a carboxamide substituent to the ring structure in Claim 1 of the '576 Patent, as taught by the '4453 Patent, because obviousness can be found where a claimed compound can be obtained by applying known chemical knowledge in the same field of endeavor to select the proper R_3 substituent. Claim 1 is thus rendered unpatentable by this combination. Claims 2, 3, 4, 8, and 9 add nothing not also disclosed in the claims of the '576 Patent (as discussed previously), and are thus also rendered unpatentable.

Regarding Claim 5, the '4453 Patent clearly teaches numerous examples where the R_2 substituent is phenyl. *See* Table in Example IV. Therefore, it would have been obvious to a person having ordinary skill in the art to provide an N-phenyl carboxamide substituent to the ring structure in Claim 1 of the '576 Patent, as taught by the '4453 Patent, because obviousness can be found where a claimed compound can be obtained by applying known chemical knowledge in the same field of endeavor to select the proper R_3 substituent. Claim 5 is thus rendered unpatentable by this combination as well.

Thus, as summarized above and in the claim chart in Exhibit T, Claims 1-5, 8, and 9 of the '893 Patent are rendered unpatentable in view of the combination of the claims of the '576 Patent and the '4453 Patent.

VI. Certificate of Service on the Patent Owner.

As certified on the Transmittal Form, a copy of that form and this request, including all attachments has been served in its entirety on:

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

Attorney of Record for Patentee.

CONCLUSION

Based on the foregoing, substantial new questions of patentability are raised with respect to the obviousness of the '893 Patent. Thus, reexamination of Claims 1, 2, 3, 4, 5, 8, and 9 of the '893 Patent is respectfully requested.

Pursuant to 37 CFR § 1.20(c)(1), a fee for filing of a request for *ex parte* reexamination is submitted herewith. Please charge any additional fees, or credit overpayment, to Deposit Account No. 11-1410.

Respectfully submitted,

Dated: June 29, 2007

By: _____

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