AO 120 (Rev. 08/10)

TO:	Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the Northern District of West Virginia on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:15 cv 13	1/27/2015	for the Northern District of West Virginia

PLAINTIFF	DEFENDANT
Pfizer Inc. UCB Pharma GMBH	Mylan Pharmaceuticals, Inc.

FILED
JAN 28 2015
U.S. DISTRICT COURT-WVND
CLARKSBURG, WV 26301

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,858,650 B1	2/22/2005	Schwarz Pharma AG
2	7,384,980, B2	6/10/2008	Schwarz Pharma AG
3	7,855,230 B2	12/21/2010	UCB Pharma GmbH
4	7,985,772 B2	7/26/2011	UCB Pharma GmbH
5	8,338,478 B2	12/25/2012	UCB Pharma GmbH

In the above---entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
Cheryl Dean Riley	J Mcglone	1/28/2015

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	1/23/2015	for the District of Delaware

PLAINTIFF	DEFENDANT
PFIZER INC. and UCB PHARMA GMBH	MYLAN PHARMACEUTICALS INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,858,650 B1	2/22/2005	UCB Pharma GmbH
2	7,384,980 B2	6/10/2008	UCB Pharma GmbH
3	7,855,230 B2	12/21/2010	UCB Pharma GmbH
4	7,985,772 B2	7/26/2011	UCB Pharma GmbH
5	8,338,478 B2	12/25/2012	UCB Pharma GmbH

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	6/21/2013	for the District of Delaware

PLAINTIFF	DEFENDANT
PFIZER INC. and UCB PHARMA GMBH	IMPAX LABORATORIES, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,858,650 B1	2/22/2005	UCB Pharma GmbH
2	7,384,980 B2	6/10/2008	UCB Pharma GmbH
3	7,855,230 B2	12/21/2010	UCB Pharma GmbH
4	7,985,772 B2	7/26/2011	UCB Pharma GmbH
5	8,338,478 B2	12/25/2012	UCB Pharma GmbH

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

Dismissed - See Attached

CLERK	(BY) DEPUTY CLERK	DATE
John A Cerino, Clerk United States District Court 844 N. King Street, Unit 18 Wilmington, DE 19801		9/2/14

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PFIZER INC. and UCB PHARMA GMBH, Plaintiffs, v. ALKEM LABORATORIES LTD., *et al.*, Defendants.	)	C.A. No. 13-1110 (GMS) **CONSOLIDATED**
PFIZER INC. and UCB PHARMA GMBH, Plaintiffs, v. IMPAX LABORATORIES, INC., Defendant.	)	C.A. No. 13-1158 (GMS)

STIPULATION AND ORDER OF DISMISSAL

WHEREAS, Plaintiffs Pfizer Inc. and UCB Pharma GmbH (collectively, "Plaintiffs") filed this action against Defendant Impax Laboratories, Inc. ("Impax") in connection with Impax's submission of Abbreviated New Drug Application Number ("ANDA") No. 20-4904 to the Food and Drug Administration, which included certifications pursuant to 21 U.S.C. §355(j)(2)(A)(vii)(IV) ("Paragraph IV") with respect to United States Patent Nos. 7,384,980 (the "'980 patent"), 7,855,230 (the "'230 patent"), 7,985,772 (the "'772 patent"), 8,338,478 (the "'478 patent"), and 6,858,650 (the "'650 patent") (collectively, the "patents in suit"); and

WHEREAS, Impax has asserted counterclaims against the patents in suit;

IT IS HEREBY STIPULATED by Plaintiffs and Impax pursuant to Federal Rule of Civil Procedure 41(a)(1)(A)(ii) and 41(c), subject to approval of the Court, that all claims and counterclaims between Plaintiffs and Impax are dismissed without prejudice;

IT IS HEREBY FURTHER STIPULATED by Plaintiffs and Impax, subject to approval of the Court, that this Stipulation and Order shall not act as an adjudication on the merits and that each party is responsible for its own costs and fees.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Maryellen Noreika

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Maryellen Noreika (#3208)
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P.O. Box 1347
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jblumenfeld@mnat.com
mnoreika@mnat.com

Attorneys for Pfizer Inc. and UCB Pharma GmbH

MORRIS JAMES LLP

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Mary B. Matterer (#2696)
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Wilmington, DE 19801
rherrmann@morrisjames.com
mmatterer@morrisjames.com
(302) 888-6800

Attorneys for Impax Laboratories, Inc.

SO ORDERED this 19th day of August 2014.

J.

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
C.A. No. 13-2022-GMS	12/11/2013	District of Delaware

PLAINTIFF	DEFENDANT
PFIZER INC. and UCB PHARMA GMBH	APOTEX INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,858,650 B1	2/22/2005	UCB Pharma GmbH
2	7,384,980 B2	6/10/2008	UCB Pharma GmbH
3	7,855,230 B2	12/21/2010	UCB Pharma GmbH
4	7,985,772 B2	7/26/2011	UCB Pharma GmbH
5	8,338,478 B2	12/25/2012	UCB Pharma GmbH

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY
2/3/2014	☐ Amendment ☑ Answer ☐ Cross Bill ☐ Other Pleading

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	7,807,715 B2	10/5/2010	UCB Pharma GmbH
2	8,088,398 B2	1/3/2012	UCB Pharma GmbH
3	8,501,723 B2	8/6/2013	UCB Pharma GmbH
4			
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	12/11/2013	for the District of Delaware

PLAINTIFF	DEFENDANT
PFIZER INC. and UCB PHARMA GMBH	HETERO USA INC. and HETERO LABS LIMITED

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,858,650 B1	2/22/2005	UCB Pharma GmbH
2	7,384,980 B2	6/10/2008	UCB Pharma GmbH
3	7,855,230 B2	12/21/2010	UCB Pharma GmbH
4	7,985,772 B2	7/26/2011	UCB Pharma GmbH
5	8,338,478 B2	12/25/2012	UCB Pharma GmbH

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

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AO 120 (Rev. 08/10)

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Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	12/11/2013	for the District of Delaware

PLAINTIFF	DEFENDANT
PFIZER INC. and UCB PHARMA GMBH	APOTEX INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,858,650 B1	2/22/2005	UCB Pharma GmbH
2	7,384,980 B2	6/10/2008	UCB Pharma GmbH
3	7,855,230 B2	12/21/2010	UCB Pharma GmbH
4	7,985,772 B2	7/26/2011	UCB Pharma GmbH
5	8,338,478 B2	12/25/2012	UCB Pharma GmbH

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT		
CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 121 (6/90)

TO:	
COMMISSIONER OF PATENTS AND TRADEMARKS (USPTO) P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OF DETERMINATION OF AN ACTION OR APPEAL REGARDING A COPYRIGHT

In compliance with the Act of July 19, 1952 (66 Stat. 814; 35 U.S.C. 290) you are hereby advised that a court action has been filed on the following patent(s) in the U.S. District Court:

DOCKET 13-cv-4628	FILED 6/24/2013	UNITED STATES DISTRICT COURT, NORTHERN DISTRICT OF ILLINOIS, EASTERN DIVISION
PLAINTIFF Pfizer Inc. et al		DEFENDANT Alkem Laboratories, LTD

PATENT NO.	DATE OF PATENT	PATENTEE
6,858,650 B1		Claus Meese
7,384,980 B2		Claus Meese, Bengt Sparf
7,855,230 B2		Claus Meese, Bengt Sparf
7,985,772 B2		Claus Meese, Bengt Sparf
8,338,478 B2		Claus Meese, Bengt Sparf

In the above-entitled case, the following patent(s) have been included:

DATE INCLUDED	INCLUDED BY [ ] Amendment [ ]Answer [ ] Cross Bill [ ] Other Pleading	
PATENT NO.	DATE OF PATENT	PATENT

In the above-entitled case, the following decision has been rendered or judgment issued:

DECISION/JUDGMENT		
CLERK Thomas G. Bruton	(BY) DEPUTY CLERK K. Johnson	DATE 6/25/2013

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
13-1110-GMS	6/21/2013	of Delaware

PLAINTIFF	DEFENDANT
Pfizer Inc. and UCB Pharma GmbH	Alkem Laboratories Ltd.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	US 6,858,650 B1	2/22/2005	UCB PHarma GmbH
2	US 7,384,980 B2	6/10/2008	UCB PHarma GmbH
3	US 7,855,230 B2	12/21/2010	UCB PHarma GmbH
4	US 7,985,772 B2	7/26/2011	UCB PHarma GmbH
5	US 8,338,478 B2	12/25/2012	UCB PHarma GmbH

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☑ Answer ☐ Cross Bill ☐ Other Pleading		
7/15/2013			
	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	US 7,807,715 B2	10/5/2010	UCB PHarma GmbH
2	US 8,088,398 B2	1/3/2012	UCB PHarma GmbH
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
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Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	6/21/2013	for the District of Delaware

PLAINTIFF	DEFENDANT
PFIZER INC. and UCB PHARMA GMBH	ACCORD HEALTHCARE INC., USA

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,858,650 B1	2/22/2005	UCB Pharma GmbH
2	7,384,980 B2	6/10/2008	UCB Pharma GmbH
3	7,855,230 B2	12/21/2010	UCB Pharma GmbH
4	7,985,772 B2	7/26/2011	UCB Pharma GmbH
5	8,338,478 B2	12/25/2012	UCB Pharma GmbH

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	6/21/2013	for the District of Delaware

PLAINTIFF	DEFENDANT
PFIZER INC. and UCB PHARMA GMBH	AMERIGEN PHARMACEUTICALS, INC. and AMERIGEN PHARMACEUTICALS LTD.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,858,650 B1	2/22/2005	UCB Pharma GmbH
2	7,384,980 B2	6/10/2008	UCB Pharma GmbH
3	7,855,230 B2	12/21/2010	UCB Pharma GmbH
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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	6/21/2013	for the District of Delaware

PLAINTIFF	DEFENDANT
PFIZER INC. and UCB PHARMA GMBH	IMPAX LABORATORIES, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,858,650 B1	2/22/2005	UCB Pharma GmbH
2	7,384,980 B2	6/10/2008	UCB Pharma GmbH
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4	7,985,772 B2	7/26/2011	UCB Pharma GmbH
5	8,338,478 B2	12/25/2012	UCB Pharma GmbH

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Mail Stop 8 **Director of the U.S. Patent and Trademark Office** **P.O. Box 1450** **Alexandria, VA 22313-1450**	

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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	6/28/2013	for the District of Delaware

PLAINTIFF	DEFENDANT
PFIZER INC. and UCB PHARMA GMBH	LUPIN LTD.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	US 6,858,650 B1	2/22/2005	UCB Pharma GmbH
2	US 7,384,980 B2	6/10/2008	UCB Pharma GmbH
3	US 7,855,230 B2	12/21/2010	UCB Pharma GmbH
4	US 7,985,772 B2	7/26/2011	UCB Pharma GmbH
5	US 8,338,478 B2	12/25/2012	UCB Pharma GmbH

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DECISION/JUDGEMENT

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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	6/21/2013	for the District of Delaware

PLAINTIFF	DEFENDANT
PFIZER INC. and UCB PHARMA GMBH	AMNEAL PHARMACEUTICALS, LLC

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,858,650 B1	2/22/2005	UCB Pharma GmbH
2	7,384,980 B2	6/10/2008	UCB Pharma GmbH
3	7,855,230 B2	12/21/2010	UCB Pharma GmbH
4	7,985,772 B2	7/26/2011	UCB Pharma GmbH
5	8,338,478 B2	12/25/2012	UCB Pharma GmbH

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	6/21/2013	for the District of Delaware

PLAINTIFF	DEFENDANT
PFIZER INC. and UCB PHARMA GMBH	SANDOZ INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,858,650 B1	2/22/2005	UCB Pharma GmbH
2	7,384,980 B2	6/10/2008	UCB Pharma GmbH
3	7,855,230 B2	12/21/2010	UCB Pharma GmbH
4	7,985,772 B2	7/26/2011	UCB Pharma GmbH
5	8,338,478 B2	12/25/2012	UCB Pharma GmbH

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Gregg Benson
Pfizer Inc.
Patent Department
Eastern Point Road
Groton, CT 06340

In Re: Patent Term Extension
Application for
U.S. Patent No. 6,858,650

Mailed by
AUG 24 2012
OPLA

Dear Mr. Benson:

A certificate under 35 U.S.C. § 156 is enclosed extending the term of U.S. Patent No. 6,858,650 for a period of 1,149 days. While a courtesy copy of this letter is being forwarded to the Food and Drug Administration (FDA), you should directly correspond with the FDA regarding any required changes to the patent expiration dates set forth in the Patent and Exclusivity Data Appendix of the Orange Book (Approved Drug Products with Therapeutic Equivalence Evaluations) or in the Patent Information set forth in the Green Book (FDA Approved Animal Drug Products). Effective August 18, 2003, patent submissions for publication in the Orange Book and Docket *95S-0117 need to be submitted on form FDA-3542 which may be downloaded from FDA's Electronic Forms Download Website: http://www.fda.gov/opacom/morechoices/fdaforms/default.html (http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3542.pdf).

Inquiries regarding this communication should be directed to the undersigned by telephone at (571) 272-7755, or by e-mail at mary.till@uspto.gov.

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Associate Commissioner
for Patent Examination Policy

cc: Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002

RE: TOVIAZ® (fesoteridine fumarate)
Docket No.: FDA-2009-E-0079

Attention: Beverly Friedman

UNITED STATES PATENT AND TRADEMARK OFFICE

(12) CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

(68)	PATENT NO.	:	6,858,650
(45)	ISSUED	:	February 22, 2005
(75)	INVENTOR	:	Claus Meese
(73)	PATENT OWNER	:	UCB Pharma GmbH
(95)	PRODUCT	:	TOVIAZ® (fesoteridine fumarate)

This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. 6,858,650 based upon the regulatory review of the product TOVIAZ® (fesoteridine fumarate) by the Food and Drug Administration. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) 1,149 days

from May 11, 2019, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156.

I have caused the seal of the United States Patent and Trademark Office to be affixed this 23rd day of August 2012.

David J. Kappos

David J. Kappos
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

MAR 26 2012

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Gregg Benson
Pfizer Inc.
Patent Department
Eastern Point Road
Groton, CT 06340

In Re: Patent Term Extension
Application for
U.S. Patent No. 6,858,650

NOTICE OF FINAL DETERMINATION

A determination has been made that U.S. Patent No. 6,858,650, claims of which cover the human drug product TOVIAZ® (fesoteridine fumarate), is eligible for patent term extension under 35 U.S.C. § 156. The period of extension has been determined to be 1,149 days.

A single request for reconsideration of this final determination as to the length of extension of the term of the patent may be made if filed within one month of the date of this notice. Extensions of time under 37 CFR § 1.136(a) are not applicable to this time period. In the absence of a request for reconsideration, the Director will issue a certificate of extension, under seal, for a period of 1,149 days.

The period of extension has been calculated using the Food and Drug Administration determination of the length of the regulatory review period published in the Federal Register of April 6, 2010 (75 Fed. Reg, 17414). Under 35 U.S.C. § 156(c):

Period of Extension	=	RRP - PGRRP - DD - ½ (TP - PGTP)[1]
	=	2,395 - 1,047 - 0 - ½ (1,445-1,047)
	=	1149 days (3.1 years)

Since the regulatory review period began April 13,2002, before the patent issued (February 22, 2005), only that portion of the regulatory review period occurring after the date the patent issued has been considered in the above determination of the length of the extension period 35 U.S.C. § 156(c). (From April 13, 2002, to and including February 22, 2005, is 1047 days; this period is subtracted from the number of days occurring in the testing phase according to the FDA determination of the length of the regulatory review period.) No determination of a lack of due diligence under 35 U.S.C. § 156(c)(1) was made.

Neither the limitations of 35 U.S.C. § 156(g)(6) nor 35 U.S.C. § 156(c)(3) operate to reduce the

[1] Consistent with 35 U.S.C. § 156(c), "RRP" is the total number of days in the regulatory review period, "PGRRP" is the number of days of the RRP which were on and before the date on which the patent issued, "DD" is the number of days of the RRP that the applicant did not act with due diligence, "TP" is the testing phase period described in paragraphs (1)(B)(i), (2)(B)(i), (3)(B)(i), (4)(B)(i), and (5)(B)(i) of subsection (g) of 35 U.S.C. § 156, and "PGTP" is the number of days of the TP which were on and before the date on which the patent issued, wherein half days are ignored for purposes of the subtraction of ½ (TP - PGTP).

period of extension determined above.

Upon issuance of the certificate of extension, the following information will be published in the Official Gazette:

U.S. Patent No.:	6,858,650
Granted:	February 22, 2005
Original Expiration Date[2]:	May 11, 2019
Applicant:	Claus Meese
Owner of Record:	UCB Pharma GmbH
Title:	Stable Salts of Novel Derivatives of 3,3-Diphenylpropylamines
Product Trade Name:	TOVIAZ® (fesoteridine fumarate)
Term Extended:	1,149 days
Expiration Date of Extension:	July 3, 2022

Any correspondence with respect to this matter should be addressed as follows:

By mail: Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450.

By FAX: (571) 273-7755

[2]Subject to the provisions of 35 U.S.C. § 41(b).

Telephone inquiries related to this determination should be directed to the undersigned at (571) 272-7755.

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Associate Commissioner
for Patent Examination Policy

cc: Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

RE: TOVIAZ® (fesoteridine fumarate)
Docket No.: FDA-2009-E-0079

Department of Health and Human Services | Public Health Service

Food and Drug Administration
Rockville, MD 20857

FEB 23 2011 10/130214

Re: Toviaz
Docket No. FDA-2009-E-0079

The Honorable David J. Kappos
Under Secretary of Commerce for Intellectual Property
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Kappos:

This is in regard to the patent term extension application for U.S. Patent No. 6,858,650 filed by Schwarz Pharma AG under 35 U.S.C. § 156. The patent claims Toviaz (fesoterodine fumarate), new drug application (NDA) 22-030.

In the April 6, 2010, issue of the Federal Register (75 Fed. Reg. 17414), the Food and Drug Administration published its determination of this product's regulatory review period, as required under 35 U.S.C. § 156(d)(2)(A). The notice provided that on or before October 4, 2010, 180 days after the publication of the determination, any interested person could file a petition with FDA under 35 U.S.C. § 156(d)(2)(B)(i) for a determination of whether the patent term extension applicant acted with due diligence during the regulatory review period.

The 180-day period for filing a due diligence petition pursuant to this notice has expired and FDA has received no such petition. Therefore, FDA considers the regulatory review period determination to be final.

Please let me know if we can provide further assistance.

Sincerely yours,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: Gregg C. Benson
Pfizer Inc.
Patent Department
Eastern Point Road
Groton, CT 06340

Collaborator fails to so notify Institution, or elects not to obtain an exclusive license, then Collaborator's option expires with respect to that Section B Invention, and Institution will be free to dispose of its interests in such Section B Invention in accordance with Institution's policies. If Institution and Collaborator fail to reach agreement within ninety (90) days (or such additional period as Collaborator and Institution may agree) on the terms for an exclusive license for a particular Subject B Invention, then for a period of six (6) months thereafter Institution agrees not to offer to license the Section B Invention to any third party on materially better terms than those last offered to Collaborator without first offering such terms to Collaborator, in which case Collaborator will have a period of thirty (30) days in which to accept or reject the offer. Institution retains the right to make and use any Section B Inventions for all non-profit research, including for educational purposes and to permit other educational and non-profit institutions to do so. If Collaborator elects to negotiate an exclusive commercial license to a Section B Invention, then Institution agrees to file and prosecute patent application(s) diligently and in a timely manner and to give Collaborator an opportunity to comment on the preparation and filing of any such patent application(s). Notwithstanding the above, Institution is under no obligation to file or maintain patent prosecution for any Section B Invention.

Inventions arising more than five years after the release of data on the primary end point of the NCI CTEP clinical trial that generated the clinical data and/or specimens will not be subject to the Section B (ii) IP Option.

C. The IP Option Described in This Section C Would Apply to Inventions Made by Institution's Investigator(s) or Any Other Employees or Agents of Institution, Which Are or May Be Patentable or Otherwise Protectable, as a Result of Research Utilizing the Agent(s) Outside the Scope of the NCI CTEP Funding Agreement (Unauthorized Inventions)

Institution agrees, at Collaborator's request and expense, to grant to Collaborator a royalty-free exclusive or co-exclusive license to Unauthorized Inventions.

D. Institution Notification

Institution agrees to promptly notify NCI CTEP (*NCICTEPpubs@mail.nih.gov*) and Collaborator(s) in writing of any Section A Inventions, Section B Inventions, and Unauthorized Inventions upon the earlier of: (i) Any submission of any invention disclosure to Institution of a Section A, Section B, or Unauthorized Invention, or (ii) the filing of any patent applications of a Section A, Section B, or Unauthorized Invention. Institution agrees to provide a copy of either the invention disclosure or the patent application to the Collaborator and to NCI CTEP which will treat it in accordance with 37 CFR part 401. These requirements do not replace any applicable reporting requirements under the Bayh-Dole Act, 35 U.S.C. 200–212, and implementing regulations at 37 CFR part 401.

III. Request for Comments

NCI CTEP is seeking comment not only from NCI CTEP funding recipients, but from the full range of academic, not-for-profit, government, and private sector participants in biomedical research and development. Widespread comment and participation by varied stakeholders in the biomedical research and development enterprise is critical if this language is to be effective in guiding the interactions of NIH funding recipients with external Collaborators in CTEP-funded studies.

Dated: March 30, 2010.

Jeffrey Abrams,

Associate Director, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, NCI, National Institutes of Health.

[FR Doc. 2010–7743 Filed 4–5–10; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2009–E–0079]

Determination of Regulatory Review Period for Purposes of Patent Extension; TOVIAZ

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for TOVIAZ and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of an application to the Director of Patents and Trademarks, Department of Commerce, for the extension of a patent which claims that human drug product.

ADDRESSES: Submit written comments and petitions to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http://www.regulations.gov.*

FOR FURTHER INFORMATION CONTACT: Beverly Friedman, Office of Regulatory Policy, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6222, Silver Spring, MD 20993–0002, 301–796–3602.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Public Law 100–670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of Patents and Trademarks may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human drug product TOVIAZ (fesoterodine fumarate). TOVIAZ is indicated for treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for TOVIAZ (U.S. Patent No. 6,858,650) from Schwarz Pharma AG, and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated September 29, 2009, FDA advised the Patent and Trademark

Office that this human drug product had undergone a regulatory review period and that the approval of TOVIAZ represented the first permitted commercial marketing or use of the product. Thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for TOVIAZ is 2,395 days. Of this time, 1,445 days occurred during the testing phase of the regulatory review period, while 950 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(i)) became effective*: April 13, 2002. FDA has verified the applicant's claim that the date the investigational new drug application became effective was on April 13, 2002.

2. *The date the application was initially submitted with respect to the human drug product under section 505(b) of the act*: March 27, 2006. The applicant claims March 17, 2006, as the date the new drug application (NDA) for TOVIAZ (NDA 22–030) was initially submitted. However, FDA records indicate that NDA 22–030 was submitted on March 27, 2006.

3. *The date the application was approved*: October 31, 2008. FDA has verified the applicant's claim that NDA 22–030 was approved on October 31, 2008.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the U.S. Patent and Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its application for patent extension, this applicant seeks 1,155 days of patent term extension.

Anyone with knowledge that any of the dates as published are incorrect may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments and ask for a redetermination by June 7, 2010. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by October 4, 2010. To meet its burden, the petition must contain sufficient facts to merit an FDA investigation. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Comments and petitions should be submitted to the Division of Dockets Management. Three copies of any mailed information are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments and petitions may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Dated: March 22, 2010.

Jane A. Axelrad,

Associate Director for Policy, Center for Drug Evaluation and Research.

[FR Doc. 2010–7679 Filed 4–5–10; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2009–E–0400]

Determination of Regulatory Review Period for Purposes of Patent Extension; FANAPT

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for FANAPT and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of an application to the Director of Patents and Trademarks, Department of Commerce, for the extension of a patent which claims that human drug product.

ADDRESSES: Submit written comments and petitions to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http://www.regulations.gov.*

FOR FURTHER INFORMATION CONTACT: Beverly Friedman, Office of Regulatory Policy, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6222, Silver Spring, MD 20993–0002, 301–796–3602.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Public Law 100–670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of Patents and Trademarks may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human drug product FANAPT (iloperidone). FANAPT is indicated for the acute treatment of schizophrenia in adults. Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for FANAPT (U.S. Patent No. RE39,198) from Aventis Holdings Inc., and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated September 2, 2009, FDA advised the Patent and Trademark Office that this human drug product had undergone a regulatory review period and that the approval of FANAPT represented the first permitted commercial marketing or use of the product. Thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for FANAPT is 6,552 days. Of this time, 5,964 days occurred during the testing phase of the regulatory review period, while 588 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(i)) became effective*: May 31, 1991. FDA has verified the applicant's claim that the date the investigational new drug application became effective was on May 31, 1991.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR 2 4 2010

Re: TOVIAZ
Docket No.: FDA-2009-E-0079

The Honorable David J. Kappos
Undersecretary of Commerce for Intellectual Property
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Kappos:

This is in regard to the application for patent term extension for U.S. Patent No. 6,858,650, filed by Schwarz Pharma AG, under 35 U.S.C. section 156 et seq. We have reviewed the dates contained in the application and have determined the regulatory review period for TOVIAZ (fesoterodine fumarate), the human drug product claimed by the patent.

The total length of the regulatory review period for TOVIAZ (fesoterodine fumarate) is 2,395 days. Of this time, 1,445 days occurred during the testing phase and 950 days occurred during the approval phase. These periods of time were derived from the following dates:

1. The date an exemption under subsection 505(i) of the Federal Food, Drug, and Cosmetic Act involving this drug product became effective: April 13, 2002.

   FDA has verified the applicant's claim that the date the investigational new drug application became effective was on April 13, 2002.

2. The date the application was initially submitted with respect to the human drug product under section 505 of the Federal Food, Drug, and Cosmetic Act: March 27, 2006.

   The applicant claims March 17, 2006, as the date the new drug application (NDA) for TOVIAZ (NDA 22-030) was initially submitted. However, FDA records indicate that NDA 22-030 was submitted on March 27, 2006.

3. The date the application was approved: October 31, 2008.

   FDA has verified the applicant's claim that NDA 22-030 was approved on October 31, 2008.

This determination of the regulatory review period by FDA does not take into account the effective date of the patent, nor does it exclude one-half of the testing phase as required by 35 U.S.C. section 156(c)(2).

Please let me know if we can be of further assistance.

Sincerely yours,

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: Gregg C. Benson
Pfizer Inc.
Patent Department
Eastern Point Road
Groton, CT 06340

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

NOV 23 2009

Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

Dear Ms. Axelrad:

Transmitted herewith is a copy of the application for patent term extension of U.S. Patent No. 6,858,650. The application was filed on December 10, 2008, under 35 U.S.C. § 156.

The patent claims a product that was subject to regulatory review under the Federal Food, Drug and Cosmetic Act. Subject to final review, the subject patent is considered to be eligible for patent term extension. Thus, a determination by your office of the applicable regulatory review period is necessary. Accordingly, notice and a copy of the application are provided pursuant to 35 U.S.C. § 156(d)(2)(A).

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Gregg Benson
Pfizer Inc.
Patent Department
Eastern Point Road
Groton, CT 06340

RE: TOVIAZ® (fesoteridine fumarate)
Docket No. FDA-2009-E-0079

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

SEP 29 2009

Re: Toviaz
Docket No. FDA-2009-E-0079

The Honorable David J. Kappos
Under Secretary of Commerce for Intellectual Property
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Kappos:

This is in regard to the application for patent term extension for U.S. Patent No. 6,858,650 filed by Schwarz Pharma AG, under 35 U.S.C. § 156. The human drug product claimed by the patent is Toviaz (fesoterodine fumarate), which was assigned new drug application (NDA) No. 22-030.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. § 156(a)(4). Our records also indicate that it represents the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. § 156(f)(1).

The NDA was approved on October 31, 2008, which makes the submission of the patent term extension application on December 10, 2008, timely within the meaning of 35 U.S.C. § 156(d)(1).

Should you conclude that the subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. § 156(d)(2)(A) we will then determine the applicable regulatory review period, publish the determination in the *Federal Register*, and notify you of our determination.

Please let me know if we can be of further assistance.

Sincerely yours,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: Gregg C. Benson
Pfizer Inc.
Patent Department
Eastern Point Road
Groton, CT 06340

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

JAN 21 2009

Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. 6,858,650 was filed on December 10, 2008, under 35 U.S.C. § 156.

The assistance of your Office is requested in confirming that the product identified in the application, TOVIAZ® (fesoteridine fumarate), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was timely filed within the sixty-day period beginning on the date the product was approved.[1] Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156.

[1]The filing of the application on December 10, 2008, was timely, given the NDA approval date of October 31, 2008. Applicant, however, misidentified at section 5 on page 3 of the application the last day the application may be submitted as December 30, 2008, pursuant to 37 C.F.R. § 1.740(a)(5). Under both 35 U.S.C. § 156(d)(1) and 37 C.F.R. § 1.720(f), a PTE applicant has sixty days to submit a PTE application, with the first day of that sixty-day period beginning on the FDA approval date. The absolute deadline for filing the present PTE Application is thus December 29, 2008, or sixty days from October 31, 2008, starting the count of the sixty-day period on October 31, 2008. The Federal Circuit in *Unimed, Inc. v. Quigg*, 12 USPQ2d 1644, 1646, made clear that "section 156(d)(1) admits of no other meaning than that the sixty-day period begins on the FDA approval date."

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Gregg Benson
Pfizer Inc.
Patent Department
Eastern Point Road
Groton, CT 06340

PATENT
12961/46301PTE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE: U.S. Patent No. 6,858,650

ISSUED: February 22, 2005

TO: Claus Meese

FOR: STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

Commissioner for Patents
P.O. Box 1450
Mail Stop: Hatch-Waxman PTE
Alexandria, VA 22313-1450

Sir:

The Commissioner is hereby authorized to charge Deposit Account No. 16-1445 the amount of $1,120.00 for the filing of the Request for Patent Term Extension Application which was filed on December 10, 2008 in the above-referenced United States Patent. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 16-1445.

Respectfully submitted,
SCHWARZ PHARMA AG

Date: January 14, 2009

Robert T. Ronau
Attorney for Applicant
Reg. No. 36,257
Tel.: (860) 441-5910

PFIZER INC.
Patent Department, MS 9114
Eastern Point Road
Groton, CT 06340
(860)441-5910

FACSIMILE

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DATE: January 14, 2009

TO: Mary Till

NUMBER OF PAGES: 2

FAX NO: 571-273-7755

RE: US Patent No. 6,858,650

FROM: ROBERT T. RONAU
PFIZER INC.
LEGAL DIVISION
EASTERN POINT ROAD, MS 9114
GROTON, CT 06340
(860) 441-5910

PATENT
12961/46301PTE

CERTIFICATE OF MAILING (37 C.F.R. §1.10)

Express Mail No. EV 607717833 US **Date of Deposit:** 12/10/08

I hereby certify that this transmittal, together with Application referred to below, is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. §1.10 on the date indicated above and is addressed to the Commissioner for Patents; P.O. Box 1450; Mail Stop: Hatch-Waxman PTE; Alexandria, VA 22313-1450.

Kristine Birkbeck
Name of Person Mailing Application

Kristine Birkbeck
Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE: U.S. Patent No. 6,858,650

ISSUED: February 22, 2005

TO: Claus Meese

FOR: STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

FROM: Serial No. 10/130,214

FILING DATE: May 14, 2002

Commissioner for Patents
P.O. Box 1450
Mail Stop: Hatch-Waxman PTE
Alexandria, VA 22313-1450

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PATENT EXTENSION
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01 FC:1457 1120.00 DA

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Sir:

Transmitted herewith is the Application of Schwarz Pharma AG for extension of the term of United States Patent No. 6,858,650, under 35 U.S.C. §156, together with exhibits and copies thereof.

Pursuant to 37 C.F.R. §1.20(j)(1), please charge Deposit Account No. 16-1445 the amount of $1,120.00 for the filing of the instant Application. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 16-1445.

Two copies of this paper are enclosed.

Respectfully submitted,

Date: December 10, 2008

Carl J. Goddard
Agent for Applicant
Reg. No. 39,203
Tel.: (860) 441-4902

PFIZER INC
Patent Department
Eastern Point Road
Groton, CT 06340
(860)441-4902

PATENT
12961/46301PTE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE: U.S. Patent No. 6,858,650

ISSUED: February 22, 2005

TO: Claus Meese

FOR: STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

FROM: Serial No. 10/130,214

OF: May 14, 2002

Commissioner for Patents
P.O. Box 1450
Mail Stop: Hatch-Waxman PTE
Alexandria, VA 22313-1450

DECLARATION ACCOMPANYING
APPLICATION FOR EXTENSION OF
PATENT TERM UNDER 35 U.S.C. §156

Sir:

I, Carl J. Goddard, declare as follows:

1. I am a Patent Attorney. I am a member in good standing of the Bar of the State of Connecticut and I am authorized to practice before the United States Patent and Trademark Office, Registration No. 39,203.

2. I am employed by PFIZER INC., a corporation organized and existing under the laws of the State of Delaware, having a place of business at 235 East 42nd Street, New York, NY 10017, and I have general authority from PFIZER INC. to act on its behalf in patent matters.

3. Pursuant to an Agreement dated April 12, 2006, Schwarz Pharma AG, owner of United States Patent No. 6,858,650, granted to PFIZER INC. the right to file on behalf of, and as Agent for, Schwarz Pharma AG an Application for extension of the term of U.S. Patent No. 6,858,650, based on a regulatory review of Toviaz™ (fesoterodine fumarate) referred to in the Application being submitted herewith.

4. Schwarz Pharma AG, a corporation organized and existing under the laws of Germany, with a principal place of business at Alfred-Nobel-Strasse 10, 40789 Monheim, Germany, is a subsidiary of UCB S.A., a corporation organized and existing under the laws of Belgium, with a principle place of business at Allée de la Recherche, 60 Bruxelles 1070, Belgium.

5. Attached hereto as EXHIBIT I is a copy of a Power of Attorney authorizing, *inter alia*, me to prepare, execute and file in the United States Patent and Trademark Office, on behalf of, and as Agent for, Schwarz Pharma AG, an Application under 35 U.S.C. §156 for extension of the term of U.S. Patent No. 6,858,650, based on the regulatory review of Toviaz™ (fesoterodine fumarate) referred to in the Application being submitted herewith.

6. I have reviewed and I understand the contents of the Application of Schwarz Pharma AG, dated December 10, 2008, which is being submitted herewith for extension of the term of United States Patent No. 6,858,650 under 35 U.S.C. §156 and 37 C.F.R. §1.730.

7. I believe that United States Patent No. 6,858,650 is subject to extension pursuant to 35 U.S.C. §156 and 37 C.F.R. §1.710.

8. I believe that the length of extension of term of United States Patent No. 6,858,650 being claimed by Schwarz Pharma AG is justified under 35 U.S.C. §156 and applicable regulations.

9. I believe that the patent for which extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. §156 and 37 C.F.R. §1.720.

I declare 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 are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the Application being submitted herewith or any extension of patent term granted thereon.

Signed this 10th day of December, 2008 at Groton, Connecticut.

Respectfully submitted,

Date: December 10, 2008

Carl J. Goddard
Agent for Applicant
Reg. No. 39,203
Tel.: (860) 441-4902

PFIZER INC
Patent Department
Eastern Point Road
Groton, CT 06340
(860)441-4902

PATENT
12961/46301PTE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE: U.S. Patent No. 6,858,650

ISSUED: February 22, 2005

TO: Claus Meese

FOR: STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

FROM: Serial No. 10/130,214

FILING DATE: May 14, 2002

Commissioner for Patents
P.O. Box 1450
Mail Stop: Hatch-Waxman PTE
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF UNITED STATES PATENT NO. 6,858,650 UNDER 35 U.S.C. §156

Sir:

Applicant, Schwarz Pharma AG, a corporation organized and existing under the laws of Germany, with a principal place of business at Alfred-Nobel-Strasse 10, 40789 Monheim, Germany, and a subsidiary of UCB S.A., a corporation organized and existing under the laws of Belgium, with a principle place of business at Allée de la Recherche, 60 Bruxelles 1070, Belgium, represents that it is the owner of the entire right, title, and interest in and to, Letters Patent of the United States No. 6,858,650 granted to Claus Meese on the 22nd day of February, 2005, for "STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-

DIPHENYLPROPYLAMINES", by virtue of the following. On May 2, 2002, Claus Meese assigned, *inter alia*, all of his right, title and interest in, and to, U. S. Patent Application Serial No. 10/130,214, filed May 14, 2002 and all United States Letters Patent which may be granted therefor to Schwarz Pharma AG, which assignment was recorded in the United States Patent and Trademark Office on May 14, 2002 at Reel 013122, Frame 0883.

Pursuant to the provisions of 35 U.S.C. §156, Applicant hereby applies for an extension of the term of said United States Patent No. 6,858,650 of 1,155 days based on the materials and accompanying papers set forth herein. In the materials following herein, paragraphs numbered "1" through "15" correspond to paragraph numbers "1" through "15" in 37 C.F.R. §1.740(a).

(1) The approved product is Toviaz™ (fesoterodine fumarate), further identified as follows:

Chemical Names

Propanoic acid, 2-methyl-, 2-[(1R)-3-[*bis*(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester, (2*E*)-2-butenedioate (1:1)(salt);

Isobutyric acid, 2-((R)-3-diisopropylammonium-1-phenylpropyl)-4-(hydroxymethyl)phenyl ester hydrogen fumarate;

R-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethyl)-phenylisobuyrate ester hydrogen fumarate.

CAS Registry Number

286930-03-8

Generic Name

Fesoterodine Fumarate

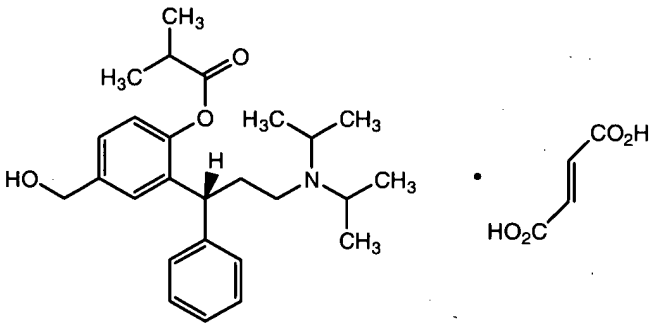
Molecular Formula

$C_{26}H_{37}NO_3 \cdot C_4H_4O_4$

Molecular Weight

527.65

Chemical Structure



Physical Characteristics

Toviaz™ exists as a white to off-white powder, or colorless flakes when recrystallized from cyclohexane/2-butanone (90:10), m.p. 103°C. It is freely water-soluble. Absorption max: 191, 193, 200, 220 nm (A_{1cm} 1% 1306, 1305, 1143, 456).

(2) Toviaz™ was subject to regulatory review under §505(b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355(b)).

(3) Toviaz™ received permission for commercial marketing or use under §505(b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355(b)) on October 31, 2008.

(4) The active ingredient in Toviaz™ is fesoterodine, in the form of its fumarate salt, which ingredient has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act.

(5) This Application is being submitted within the sixty-day period permitted for its submission pursuant to 37 C.F.R. §1.720(f). The last day on which this Application could be submitted is December 30, 2008.

(6) The patent for which an extension is being sought is identified as follows:

Inventor: Claus Meese

U.S. Patent No.: 6,858,650

Issued: February 22, 2005

Expires: May 11, 2019. The expiration date of U.S. Patent No. 6,858,650 is not evident on the face of the issued patent. According to the face of the patent, the date of expiration would be November 15, 2020. That a terminal disclaimer was filed during prosecution of the application resulting in the issuance of U.S. Patent No. 6,858,650 is not disclosed on the face of the patent. However, a terminal disclaimer based on U.S. Serial No. 09/700,094, now U.S. Patent No. 6,713,464, which expires on May 11, 2019 was filed on November 3, 2003. Accordingly, U.S. Patent No. 6,858,650 has a non-extended expiration date of May 11, 2019.

(7) A copy of U. S. Patent No. 6,858,650, the patent for which an extension is being sought, is attached hereto as EXHIBIT A.

(8) One receipt for a maintenance fee payment has issued for this patent, a copy of which is attached hereto as EXHIBIT B.

On November 3, 2003, a Terminal Disclaimer pursuant to 37 C.F.R. §1.321 was filed disclaiming the terminal portion of U.S. Patent No. 6,858,650 extending beyond the expiration date of any patent granted on co-pending U.S. Serial No. 09/700,094, filed internationally May 11, 1999, now U.S. Patent No. 6,713,464. Accordingly, as disclosed hereinabove, U.S. Patent No. 6,858,650 has a non-extended expiration date of May 11, 2019. A copy of the Terminal Disclaimer is attached hereto as Exhibit C.

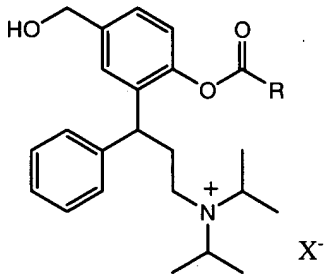
A Certificate of Correction was filed on June 21, 2005 correcting minor typographical errors. A copy of the Certificate of Correction is attached hereto as Exhibit D.

(9) U. S. Patent No. 6,858,650 claims the approved product, methods of manufacturing the approved product, and methods of using the approved product.

Claims 1 through 5, inclusive, claim the approved product. The manner in which each applicable claim reads on the approved product is as follows.

Claim 1 of U. S. Patent No. 6,858,650 claims the genus of chemical compounds of Formula I:

Formula I

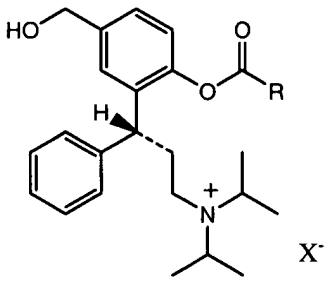


in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid. In fesoterodine fumarate, R is isopropyl, which is a C_3-alkyl, and X^- is the acid residue of the organic acid fumaric acid. Thus, claim 1 reads on the approved product.

Claim 2 of U. S. Patent No. 6,858,650 claims the compounds of claim 1 in which the definition of X^- may be an acid ester of fumaric acid, one member of a listed group of organic acids that includes fumaric acid. Thus, claim 2 reads on the approved product.

Claim 3 of U. S. Patent No. 6,858,650 claims compounds of claim 1, characterized by general formula 2:

Formula 2



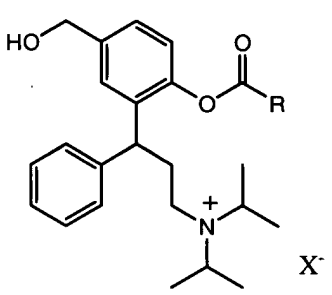
in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid. In fesoterodine fumarate, R is isopropyl, which is a C_3-alkyl, and X^- is the acid residue of the organic acid fumaric acid. Thus, claim 3 reads on the approved product.

Claim 4 of U. S. Patent No. 6,858,650 claims the compounds of claim 3 in which the definition of X^- may be fumaric acid. Thus, claim 4 reads on the approved product.

Claim 5 of U. S. Patent No. 6,858,650 claims a compound of claim 3, the compound characterized by the chemical name R-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethyl)-phenylisobuyrate ester hydrogen fumarate. This compound is fesoterodine fumarate. Thus, claim 5 reads on the approved product.

Claims 7 through 16, inclusive, and claims 19 and 20, claim methods of manufacturing the approved product. The manner in which each applicable claim reads on such methods is as follows.

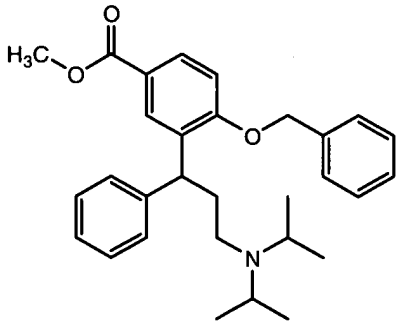
Claim 7 of U.S. Patent No. 6,858,650 claims a method for manufacturing compounds of general formula I



Formula I

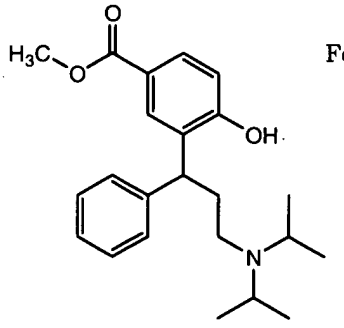
in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid, characterized in that

a) a compound of formula III



Formula III

is split with a hydrogenation agent to form a compound of Formula V

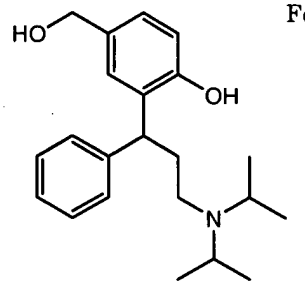


Formula V

whereupon

b) the compound of formula V so obtained is converted with a reducing agent, in order to give a compound of formula VI

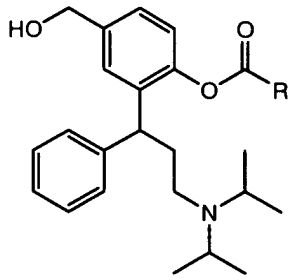
Formula VI



which

c) is converted with an acylating agent, in order to obtain a compound of formula A

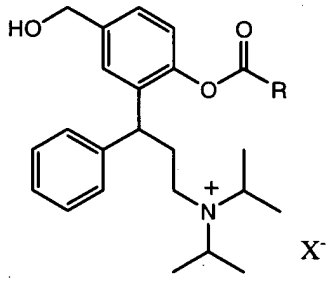
Formula A



in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula I

Formula I

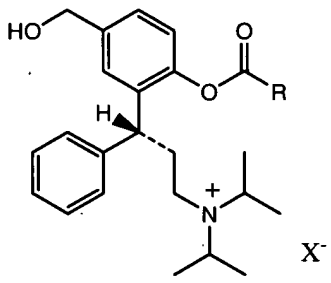


in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid. In fesoterodine fumarate, R is isopropyl, which is a C_3-alkyl, and X^- is the acid residue of the organic acid fumaric acid. Thus, claim 7 reads on a method for manufacturing the approved product.

Claim 8 of U.S. Patent No. 6,858,650 claims a method in accordance with claim 7, characterized in that one of the acids used may be fumaric acid, one acid among a listed group of organic acids. Thus, claim 8 reads on a method of manufacturing the approved product.

Claim 9 of U.S. Patent No. 6,858,650 claims a method for manufacturing compounds of general formula 2

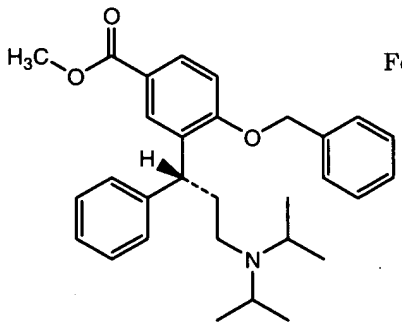
Formula 2



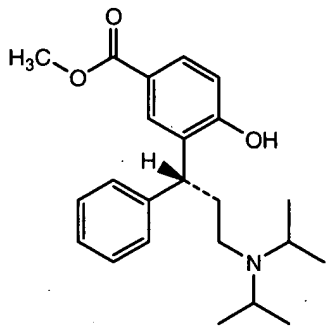
in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid, characterized in that

a) a compound of the formula 3

Formula 3



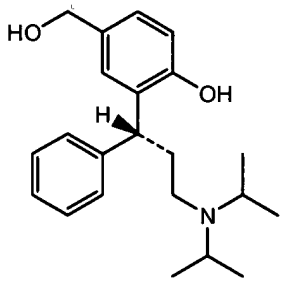
is split with a hydrogenation agent to form a compound of formula 5



Formula 5

whereupon

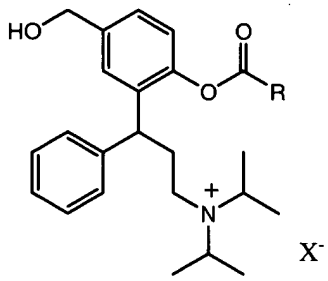
b) the compound of formula 5 so obtained is converted with a reducing agent in order to give a compound of formula 6



Formula 6

which

c) is converted with an acylating agent, in order to obtain a compound of formula I

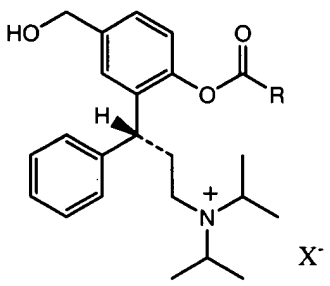


Formula I

in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula 2

Formula 2



in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid. In fesoterodine fumarate, R is isopropyl, which is a C_3-alkyl, and X^- is the acid residue of the organic acid fumaric acid. Thus, claim 9 reads on a method of manufacturing the approved product.

Claim 10 of U.S. Patent No. 6,858,650 claims a method in accordance with claim 9, characterized in that one of the acids used for the manufacture of the compounds of general formula 2 may be fumaric acid, one acid among a listed group of organic acids. Thus, claim 10 reads on a method of manufacturing the approved product.

Claim 11 of U.S. Patent No. 6,858,650 claims a method in accordance with claim 7, characterized in that as the hydrogenation agent Raney nickel/H_2 in methanol is preferably used as the solvent. Because it is directed to a method of manufacturing the approved product, claim 11 reads on a method of manufacturing the approved product.

Claim 12 of U.S. Patent No. 6,858,650 claims a method in accordance with claim 7, characterized in that for the reducing agent $NaBH_4$EtOH, preferably $LiAlH_4$/THF is used. Because it is directed to a method of manufacturing the approved product, claim 12 reads on a method of manufacturing the approved product.

Claim 13 of U.S. Patent No. 6,858,650 claims a method in accordance with claim 7, characterized in that for the acylation agent isobutyryl chloride and for the base triethylamine are used. Because it is directed to a method of manufacturing the approved product, claim 13 reads on a method of manufacturing the approved product.

Claim 14 of U.S. Patent No. 6,858,650 claims a method in accordance with claim 9, characterized in that a compound of general formula 6 is converted with an equivalent of isobutyryl chloride in the presence of triethylamine using ethyl acetate, dichloromethane, tetrahydrofuran, acetontitrile, or toluene regio- and chemoselectively into R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate. Because it is directed to a method of manufacturing the approved product, claim 14 reads on a method of manufacturing the approved product.

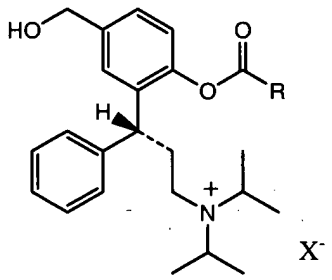
Claim 15 of U.S. Patent No. 6,858,650 claims a method in accordance with claim 9, characterized in that R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester and fumaric acid are converted with formation of the respective salt. Because it is directed to a method of forming the fumaric acid salt of fesoterodine, claim 15 reads on a method of manufacturing the approved product.

Claim 16 of U.S. Patent No. 6,858,650 claims a method in accordance with claim 9 for the manufacture of R-(+)-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-methylphenylisobutyrate ester hydrochloride hydrate, characterized in that the phenolic esterification of R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenol (6) is carried out without the addition of an

external base, in that solutions of (6) are dropped into solutions of isobutyryl chloride, that contain at least 1 mole equivalent of water, in order to directly obtain a corresponding stable, hydrate-containing hydrochloride. Because it is directed to a method of manufacturing the approved product, claim 16 reads on a method of manufacturing the approved product.

Claim 19 of U.S. Patent No. 6,858,650 claims a method of manufacture of salts of phenolic monoesters of general formula 2:

Formula 2



in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid, wherein the method comprises the steps of: providing a compound of claim 17; deprotecting the hydroxyl residues of the 4-hydroxy-benzyl alcohol residue; and acylating the phenol residue. In fesoterodine fumarate, R is isopropyl, which is a C_3-alkyl, and X^- is the acid residue of the organic acid fumaric acid. Thus, claim 19 reads on a method of manufacturing the approved product.

Claim 20 of U.S. Patent No. 6,858,650 claims a method of manufacture of R-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuyrate ester hydrogen fumarate or R-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuyrate ester hydrochloride hydrate, the method comprising the steps of:

providing a compound of claim 17; deprotecting the hydroxyl residues of the 4-hydroxy-benzyl alcohol residue; and acylating the phenol residue. Because the compound R-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuyrate ester hydrogen fumarate is fesoterodine fumarate, claim 20 reads on a method of manufacturing the approved product.

Claims 21 through 24, inclusive, claim methods of using the approved product. The manner in which each applicable claim reads on such methods is as follows.

Claim 21 of U.S. Patent No. 6,858,650 claims a method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 1. Because claim 21 claims a method of using a genus of compounds embracing fesoterodine fumarate, as described hereinabove for claim 1, claim 21 reads on a method of using the approved product.

Claim 22 of U.S. Patent 6,858,650 claims a method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 3. Because claim 22 claims a method of using a genus of compounds embracing fesoterodine fumarate, as described hereinabove for claim 3, claim 22 reads on a method of using the approved product.

Claim 23 of 6,858,650 claims a method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 5. Because claim 23 claims a method of using fesoterodine

fumarate, the compound of claim 5, claim 23 reads on a method of using the approved product.

Claim 24 of 6,858,650 claims a method of any one of claims 21-23, wherein the urinary incontinence disorder is urge incontinence. Because claim 24 claims a method of using a genus of compounds embracing fesoterodine fumarate, or a method of using fesoterodine fumarate specifically, claim 24 reads on a method of using the approved product.

(10) The relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(a) IND 51,232 was assigned to fesoterodine fumarate in a letter dated November 9, 2001. Applicant requested inactivation of IND 51,232 in a letter dated February 5, 2002. Applicant subsequently notified the FDA on March 12, 2002 of its intent to reactivate IND 51,232. Accordingly, the effective date of IND 51,232 is April 13, 2002, *i.e.*, thirty-days following Applicant's notification of March 12, 2002.

(b) An NDA under §505(b) of the Federal Food, Drug and Cosmetic Act for fesoterodine fumarate was submitted on March 17, 2006 as NDA 22-030.

(c) NDA No. 22-030 was approved on October 31, 2008.

(11) A brief description of the significant activities undertaken by, or for, the marketing Applicant during the applicable regulatory review period with respect to the approved product, and the significant dates applicable to such activities, is attached hereto as EXHIBIT E.

(12) Pursuant to the provisions of 35 U.S.C. §156, Applicant believes U. S. Patent No. 6,858,650 is eligible for an extension of 1,155 days.

The requirements of 35 U.S.C. §156(a) and (c)(4) have been satisfied as follows:

(a) U. S. Patent No. 6,858,650 claims the approved product, Toviaz™ (fesoterodine fumarate).

(b) U. S. Patent No. 6,858,650 has not yet expired. It is presently set to expire on May 11, 2019.

(c) The term of U. S. Patent No. 6,858,650 has never been extended.

(d) This Application is being submitted by Schwarz Pharma AG, the owner of record of U. S. Patent No. 6,858,650, through its Agent, PFIZER INC., in accordance with the requirements of 35 U.S.C. §156(d). A Power of Attorney from Schwarz Pharma AG to PFIZER INC. is attached hereto as Exhibit I.

(e) The approved product, Toviaz™ (fesoterodine fumarate), has been subject to a regulatory review period under §505(b) of the Federal Food, Drug and Cosmetic Act prior to its commercial marketing or use, and permission for said commercial marketing or use is the first permitted commercial marketing or use under the Federal Food, Drug and Cosmetic Act.

(f) No patent has, to this date, been extended, nor has any other extension been applied for, for the regulatory review period forming the basis for this Application for extension of the term of U. S. Patent No. 6,858,650.

The length of extension of the term of U. S. Patent No. 6,858,650 of 1,155 days claimed by applicant was

determined according to the provisions of 35 U.S.C. §156(c) and §156(g) as follows:

(a) The term of the regulatory review period, as defined in 35 U.S.C. §156(c)(2), is 195 days, *i.e.*, one-half of the 389 day period between the February 22, 2005 issue date of U.S. Patent No. 6,858,650 and the March 17, 2006 submission date of the NDA.

(b) The term of the NDA review period commencing on March 17, 2006, the date the NDA for the approved product was originally submitted, and ending October 31, 2008, the date on which the NDA was approved, is 960 days.

(c) The sum of paragraphs (a) and (b) of this subsection is 1,155 days.

(d) The sum shown in paragraph (c) is not limited under 35 U.S.C. 156(c)(3) since fourteen years from the NDA approval date of October 31, 2008, which is later than a 1,155 day extension of U.S. Patent No. 6,858,650, is October 31, 2022.

(e) The sum shown in paragraph (c) is also not limited under 35 U.S.C. 156(g)(6)(A) which states that if the patent involved is issued after the date of enactment of that section, the period of extension may not exceed five (5) years. The claimed period of extension is 1,155 days, which period is less than five (5) years.

(f) The sum in paragraph (c) is 1,155 days.

(g) Pursuant to 35 U.S.C. §156, Applicant herewith claims an extended expiration date of July 9, 2022, for U.S. Patent No. 6,858,650.

(13) Applicant acknowledges the duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information material to the determination of entitlement to the 1,155

day extension being sought to the term of U. S. Patent No. 6,858,650.

(14) The prescribed fee pursuant to 37 C.F.R. §1.20(j)(1) of $1,120.00 for receiving and acting upon this Application for extension of patent term is to be charged to Deposit Account No. 16-1445, as authorized in the transmittal letter.

(15) Please address all inquiries and correspondence relating to this Application to:

Gregg C. Benson
PFIZER INC.
Patent Department
Eastern Point Road
Groton, CT 06340
Tel.: (860)441-4901

Pursuant to 37 C.F.R. §1.740(15)(b) and M.P.E.P. §2753, one (1) original Application for Patent Term Extension of U. S. Patent No. 6,858,650, with accompanying exhibits, and four (4) copies of such papers and exhibits, are submitted herewith.

Respectfully submitted,
SCHWARZ PHARMA AG

Date: December 10, 2008

Carl J. Goddard
Agent for Applicant
Reg. No. 39,203
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EXHIBIT A

US006858650B1

(12) **United States Patent**
Meese

(10) **Patent No.: US 6,858,650 B1**
(45) **Date of Patent: Feb. 22, 2005**

(54) **STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES**

(75) Inventor: **Claus Meese**, Monheim (DE)

(73) Assignee: **Schwarz Pharma AG** (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/130,214**

(22) PCT Filed: **Nov. 15, 2000**

(86) PCT No.: **PCT/EP00/11309**

§ 371 (c)(1),
(2), (4) Date: **May 14, 2002**

(87) PCT Pub. No.: **WO01/35957**

PCT Pub. Date: **May 25, 2001**

(30) **Foreign Application Priority Data**

Nov. 16, 1999 (DE) 199 55 190

(51) **Int. Cl.**[7] **A01N 37/08**; A01N 37/12; A01N 37/44; A61K 31/215; A61N 31/24

(52) **U.S. Cl.** **514/530**; 514/531; 514/534; 514/548; 514/551; 560/61; 560/122; 560/123; 560/124; 560/138; 560/142; 560/250; 564/319

(58) **Field of Search** 514/530, 531, 514/534, 548, 551; 560/61, 122, 123, 124, 138, 142, 250, 37, 18, 42, 140; 564/319

(56) **References Cited**

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* cited by examiner

Primary Examiner—Richard L. Raymond
Assistant Examiner—Zachary C. Tucker
(74) *Attorney, Agent, or Firm*—Peter F. Corless; Christine C. O'Day; Edwards & Angell, LLP

(57) **ABSTRACT**

The present invention concerns highly pure, crystalline, stable compounds of novel derivatives of 3,3-diphenylpropylamines in the form of their salts, a method for the manufacture and highly pure, stable intermediate products.

The method is in particular characterized by regio- and chemoselectivity and high yield. Salts of phenolic monoesters of 3,3-diphenylpropylamines are provided, that are particularly well-suited for use in pharmaceutical formulations. Preferred compounds are R-(+)-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate and R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate. Furthermore, stable, crystalline intermediate products that are essential for obtaining the abovementioned salts are provided. A preferred intermediate product is R-(−)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester.

24 Claims, 1 Drawing Sheet

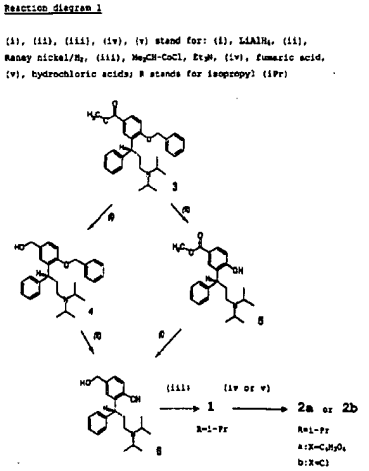
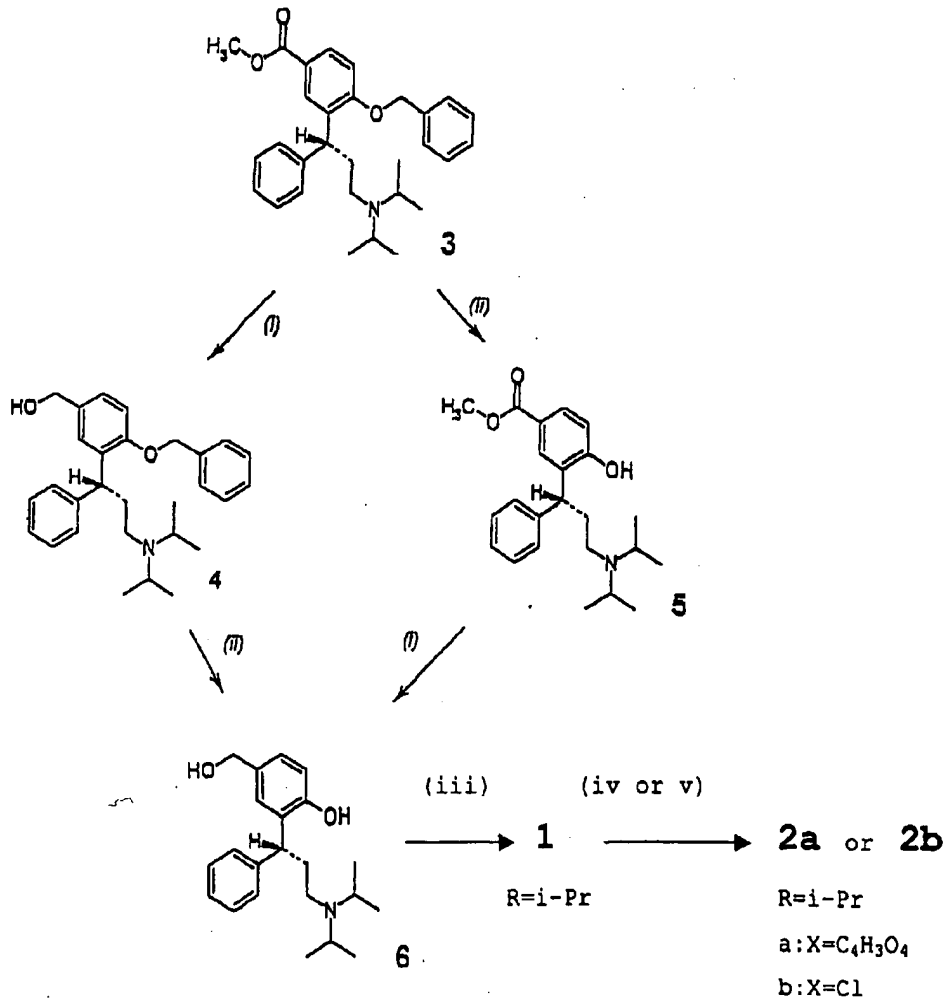


Figure 1

Reaction diagram 1

(i), (ii), (iii), (iv), (v) stand for: (i), $LiAlH_4$, (ii), Raney nickel/H_2, (iii), Me_2CH-CoCl, Et_3N, (iv), fumaric acid, (v), hydrochloric acids; R stands for isopropyl (iPr)



STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

This application was filed under 35 U.S.C. 371, and is the U.S. National Stage of PCT/EP00/11309, filed 5 Nov. 2000.

This patent application claims the benefit of priority under 35 U.S.C. §119 of German Patent Application No. 199 55 190.1, filed Nov. 16, 1999. German Patent Application No. 199 55 190.1 is incorporated herein in its entirety by reference.

The present invention concerns highly pure, crystalline, stable compounds of novel derivatives of 3,3-diphenylpropylamines in the form of their salts, a method for manufacturing these and highly pure, stable, intermediate products.

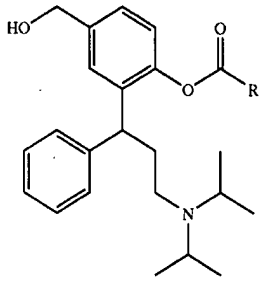
From document PCT/EP99/03212 novel derivatives of 3,3-diphenylproprylamines are known.

These are valuable prodrugn for the treatment of urinary incontinence and other spasmodic complaints, which overcome the disadvantage of the active substances available to date, namely inadequate absorption of the active substance by biological membranes or the unfavourale metabolism of these.

Furthermore these novel prodrugs have improved pharmacokinetic characteristics compared with Oxybutynin and Tolterodin.

Preferred compounds from the group of these novel derivatives of 3,3-diphenylpropylarines are esters of aliphatic or aromatic carboxylic acids with the general formula A referred to below

Formula A



in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl or unsubstituted or substituted phenyl. These can occur in their optical isomers form as racemic mixtures and in the form of their individual enantiomers.

Compounds with the structure of formula A do, however, have low solubility in water. This restricts their oral bioavailability.

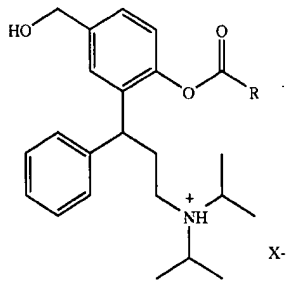
Finally, monoesters of the structure, as shown in formula A, have a tendency towards intermolecular transesterification. During long periods of storage, therefore, as the content of the compounds with the structure of general formula A drops an increase in diesters and free diol can be detected.

Basically salts of the compounds of general formula A can be obtained if solutions of the compounds of formula A (base component) are purified with solutions of acids in suitable solvents, but the salts obtained in the form of solid matter can prove to be altogether amorphous and/or hygroscopic and cannot be directly crystallized from the normal solvents either. Such salts have inadequate chemical stability to be galenically processed as valuable pharmaceutically active substances.

Surprisingly, it has now been found that the abovementioned disadvantages can be avoided if compounds with the structure of general formula A, once they have been prepared under a special reaction process, are converted with a physiologically compatible inorganic or organic acid with

general formula H-X, in which ^-X represents the respective acid residue, into their respective salt with general formula I.

Formula I



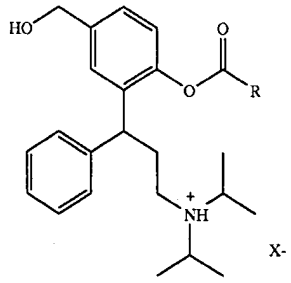
The problem for the present invention is therefore to provide highly pure, crystalline, stable compounds of novel derivatives of 3,3-diphenylpropylamines in the form of their salts, that avoid the stated disadvantages and are well suited to use in pharmaceutical-technical formulations and can be processed into these.

A further problem for the present invention is to provide a method for manufacturing such highly pure, crystalline, stable compounds in the form of their salts, as well as highly pure, stable intermediate products.

The final problem for the invention is to provide a method for manufacturing the abovementioned compounds with which a high yield of the products of the process and the respective intermediate products can be obtained chemo- or regioselectively.

This problem is solved in that highly pure, crystalline, stable compounds of the 3,3-diphenylpropylamines in the form of their salts with general formula I are provided,

Formula I



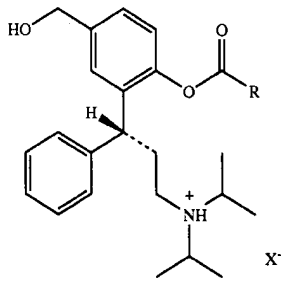
in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

In accordance with a design of the invention the salts of general formula I can contain the respective acid residue X^- of the acids mentioned below:

hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(−)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(−)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

In accordance with a further design form of the invention R-configured compounds with general formula 2 are provided

Formula 2



in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

In accordance with an advantageous design form of the invention the compounds in the form of their salts of general formula 2 can contain the respective acid residue X^- of the acids mentioned below:

hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(−)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(−)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

Preferred compounds of the present invention are the salts

R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate and

R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate.

Furthermore, compounds are preferred in which R stands for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-(1-cyclo-propyl-methanoyloxy)-phenyl, 4-(1-cyclobutyl-methanoyloxy)-phenyl, 4-(1-cyclohexyl-methanoyloxy)-phenyl or 4-(2,2-dimethyl-propanoyloxy)-phenyl and X denotes chloride.

Particular preference is for [(R)-3-(2-{1-[4-(1-cyclopropyl-methanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium chloride, [(R)-3-(2-{1-[4-(1-cyclobutyl-methanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium chloride, [(R)-3-(2-{1-[4-(1-cyclohexyl-methanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium chloride, [(R)-3-(2-{1-[4-(2,2-dimethyl-propanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium chloride, {(R)-3-[2-(1-cyclopropyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-propyl}-diisopropyl-ammonium chloride, {(R)-3-[2-(1-cyclobutyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-propyl}-diisopropyl-ammonium chloride, {(R)-3-[2-(1-cyclopentyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-propyl}-diisopropyl-ammonium chloride and {(R)-3-[2-(1-cyclohexyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-propyl}-diisopropyl-ammonium chloride.

In the compounds of the present invention the expression "alkyl" preferably stands for a straight-chain or branched-chain hydrogen group with between 1 and 6 C-atoms. Special preference is for methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl. The expression "cycloalkyl" designates cyclical hydrogen groups, that have between 3 and 10 hydrogen atoms, that may also contain suitable substitutes in place of the hydrogen atoms.

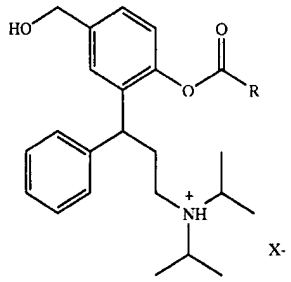
The expression "phenyl" designates a —C_6H_5-group that may be substituted or unsubstituted. Suitable substitutes can be, for example, alkyl, alkoxy, halogen, nitro and amine. The expression "alkoxy" has, with respect to the alkyl component, the same meaning as already given above for "alkyl". Suitable halogens are fluorine, chlorine, bromine and iodine atoms

The present invention also includes methods for manufacturing the compounds in accordance with the invention of general formula I as well as valuable intermediate products.

The method is characterised by chemo- and regioselectivity.

Compounds of General Formula I

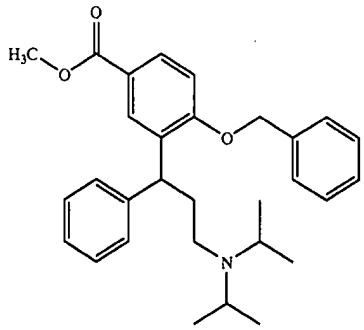
Formula I



in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid, are that

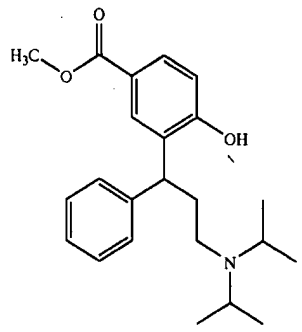
a) a compound of formula III

Formula III



is split with a hydrogenation agent to form a compound of formula V

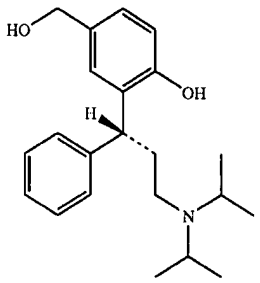
Formula V



whereupon

b) the compound of formula V so obtained is converted with agent, in order to give a compound of formula VI

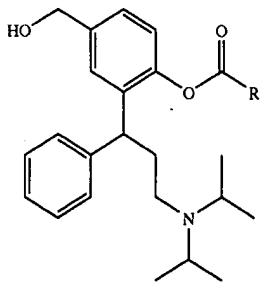
Formula VI



which

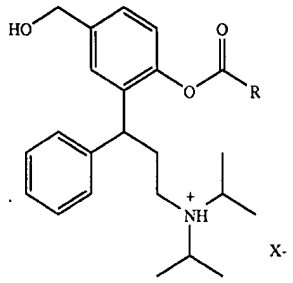
c) is converted with an acylation agent, in order to obtain of formula A

Formula A



in which R has the significance stated above, which d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula I

Formula I

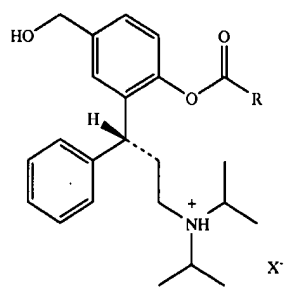


in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, unsubstituted or substituted phenyl and X– is the acid residue of a physiologically compatible inorganic or organic acid.

In accordance with the invention, for the manufacture of the compounds of general formula I hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(−)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(−)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

In accordance with an advantageous further development of the invention a method for the manufacture of R-configured compounds of the general formula 2 is described,

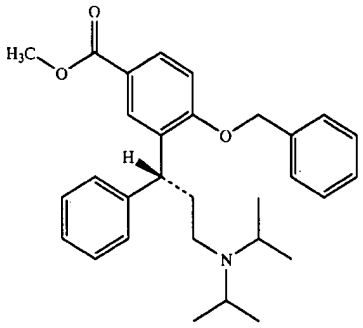
Formula 2



in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid, in that

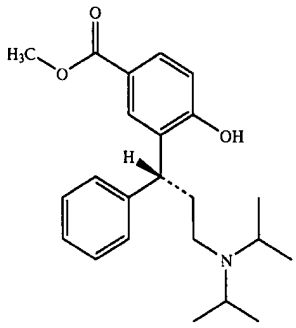
a) a compound of formula 3

Formula 3



is split with a hydrogenation agent to form a compound of formula 5

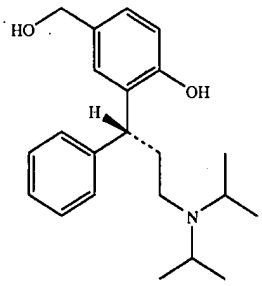
Formula 5



whereupon

b) the compound of formula 5 so obtained is converted with a reducing agent, in order to give a compound of formula 6

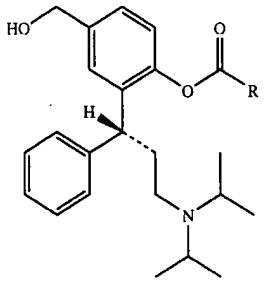
Formula 6



which

c) is converted with an acylation agent, in order to obtain a compound of formula 1

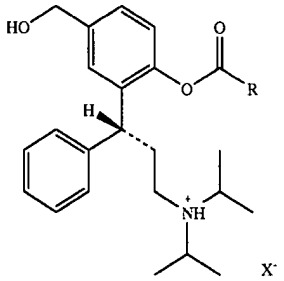
Formula 1



in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula 2

Formula 2



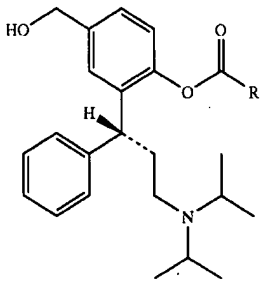
in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, unsubstituted or substituted phenyl and X– is the acid residue of a physiologically compatible inorganic or organic acid.

Advantageously in order to obtain compounds of general formula 2, in accordance with the method hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(−)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(−)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

Particular advantageously, on the basis of the crystalline R-(−)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)benzoic acid methyl ester, the highly pure, crystalline intermediate product R-(−)-3-(3-diisopropylamino-phenylpropyl)-4-hydroxy-benzoic acid methyl ester is prepared, which is reduced to R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol, is finally acylated in a suitable manner and is then converted with a physiologically compatible inorganic or organic acid under spontaneous crystallization to the respective highly pure, crystalline, stable salt.

Depending on the acid chloride used, compounds of general formula 1 are obtained,

Formula 1



in which R denotes C_1–C_6-alkyl, in particular isopropyl, C_3–C_{10}-cycloalkyl or unsubstituted or substituted phenyl.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to obtain the compounds in accordance with the invention in the form of their salts the special reaction process via particular intermediate stages and individually identifiable intermediate products is crucial.

This is explained using reaction diagram 1 (see FIG. 1), in which the conversions with R-configured compounds are described, but without this being restrictive.

In this:

3=R-(−)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid-methyl ester

4=R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol

5=R-(−)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester

6=R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

1=R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobutyrate ester

2a=R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobutyrate ester hydrogen fumarate

2b=R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobutyrate ester hydrochloride hydrate

In accordance with the reaction process explained in the embodiment the preliminary stage 3 (R-(−)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid-methylester) is prepared in crystalline, pure form.

Using normal methods—such as BBr_3, $AlCl_3$—but preferably by means of hydrogen gas via Raney nickel in methanol as the solvent at room temperature (RT), preliminary stage 3 is split into 5 (R-(−)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methylester. This develops in highly pure, crystalline form (melting point 143.7° C.).

Finally, using a suitable reducing agent—such as $NaBH_4$/EtOH—preferably $LiAlH_4$ 5 is reduced into an inert solvent at low temperature (−78° C. to +10° C.) and the compound 6 (R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol) is obtained. The compound 6 is obtained in a highly pure state and can be crystallised from a suitable solvent such as ethyl acetate. The colourless, compact grained material has a melting point of 102.3° C. This is surprising in that the compound 6 in the state of the art is described as an amorphous solid.

Compound 6 is now acylated with very good yield and regio- and chemoselectivity, into a phenolic ester. This reaction is performed at RT or low temperatures with an equivalent acid chloride in the presence of a base in a suitable solvent. Suitable solvents are ethyl acetate, dichloromethane, tetrahydrofurane, acetonitrile or toluene.

The reaction is preferably performed with isobutyrylchloride as the acid chloride and triethylamine as the base at the abovementioned temperatures. The 1 (R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester) then obtained, occurs with such purity that with solutions of the fumaric acid in suitable solvents spontaneous crystallisation starts with the formation of the hydrogen fumarate salt 2a.

This salt has a high melting point of 103° C., is stable at RT, is non-hygroscopic and does not contain crystallose agents. It can be recrystallised as often as desired.

If instead of fumaric acid anhydrous hydrochloric acid is used—for example as an etheric solution—salt formation also takes place with the crystalline product 2b (R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobutyrate ester hydrochloride hydrate being obtained.

Following a further recrystallisation the product 2b has a melting point range of 97–106° C.

Finally the product 2b can particularly advantageously be obtained by the following variants of the inverse reaction process, starting with the compound 6 of reaction diagram 1. The product 2b can thus be obtained without the addition of an external acid-intercepting base, as explained in the following.

Solutions of 6 (R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol) are dripped into solutions of isobutyrate chloride, so that under suitable polarity conditions the anhydrous product 2b rapidly crystallises out. 2b is very hygroscopic.

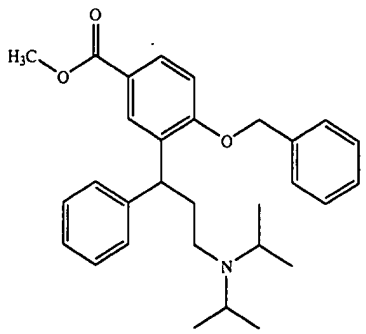
If the abovementioned reaction is carried out in a humid solvent, that contains at least one mole equivalent of water, a stable and crystalline, hydrate-containing product 2b is obtained, that has the abovementioned melting characteristics.

The compounds in accordance with the invention of general formulae 1 and 2 are suited to bulk material.

Of particular advantage are the highly pure compounds of general formulas III, V, VI, 3, 5, 6 and 7 which can be obtained.

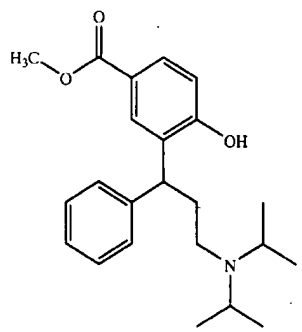
Compound of Formula III

Formula III



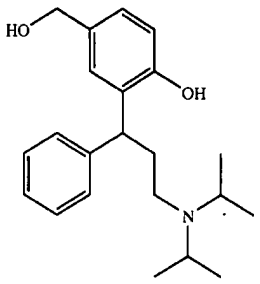
Compound of Formula V

Formula V



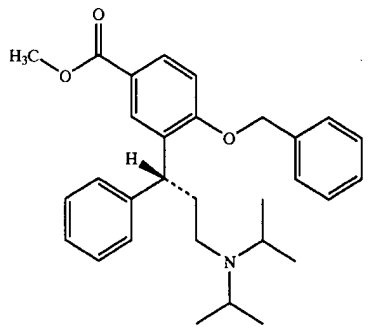
Compound of Formula VI

Formula VI



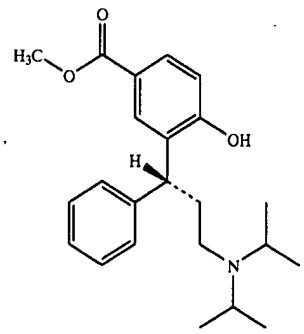
Compound of Formula 3

Formula 3



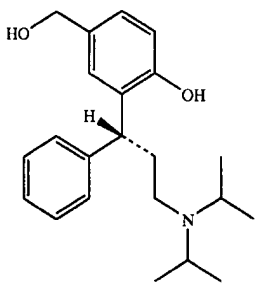
Compound of Formula 5

Formula 5



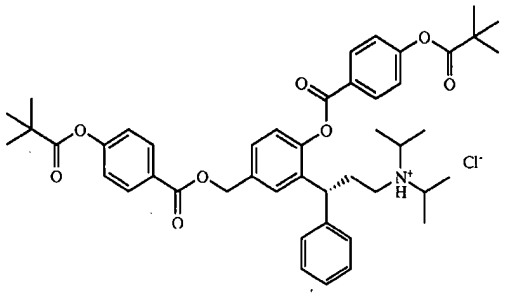
Compound of formula 6

Formula 6



Compound of Formula 7

Formula 7



[(R)-3-(2-{1-[4-(2,2-dimethyl-propanoyloxy)-phenyl]-methane-oyloxy}-5-{1-[4-(2,2-dimethyl-propanoyloxy)-phenyl]-methane-oyloxymethyl}-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium-chloride.

The abovementioned compounds III, V, VI, 3, 5, 6 and 7 are particularly suited to use in each case as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds.

Of particular advantage are compounds for use as an intermediate product in the manufacture of R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate and R -(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate.

Finally, the method can be carried out in a particularly advantageous way by converting a compound of general formula 6 (see reaction diagram 1) with an equivalent isobutyryl chloride in the presence of triethylamine using one of the respective solvents ethylacetate, dichloromethane, tetrahydrofurane, acetonitrile or toluene regio- and chemoselectively into R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester.

In accordance with the invention R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester is particularly suited to conversion with fumaric acid or hydrochloric acid with the formation of the respective salt.

The following embodiments explain the invention.

Experimental

I. General

All compounds have been fully characterised by ^{1}H and ^{13}C NMR-spectroscopy (Bruker DPX 200). The stated chemical displacements in the ^{13}C-NMR-spectra (50 MHz, ppm values stated) refer to the solvent resonances of $CDCl_3$ (77.10 ppm) ^{1}H NMR data ($CDCl_3$; 200 MHz, ppm) refer to internal tetramethylsilane).

Thin layer chromatography (DC, R_f given) was carried out on 5×10 cm E. Merck silica gel films (60F254), and the stains were revealed by fluorescence erasure or by spraying with alkaline potassium permanganate solution.

Absorbent systems were: (1), n-hexane/acetone/triethylamine (70/20/10, v/v-%); (2), toluene/acetone/methanol/acetic acid (70/5/20/5, v/v-%).

The optical rotations were measured at a wavelength of 589.3 nm (sodium D-line), at room temperature using ethanol as a solvent (apparatus: Perkin Elmer Polarimeter Type 241), melting points (in ° C.) are uncorrected and were determined on the Mettler FP apparatus, or by differential thermoanalysis (DSC) on the Perkin Elmer Model DSC7, using "Pyris" evaluation software.

UV/VIS measurements were carried out on the spectrophotometer. model Lambda 7 (Perkin-Elmer) with a layer thickness of 1 cm. The specific absorption stated is for a 1% solution ($A^{1\%}_{1\,cm}$)

IR spectra were recorded on a Perkin-Elmer FTIR spectrometer Series 1610 (resolution 4 cm^{-1}).

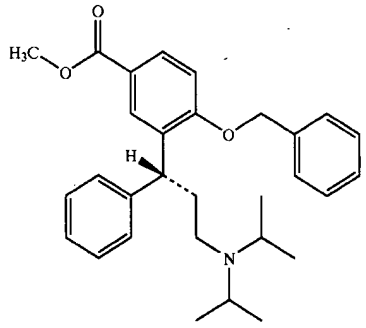
Gas chromatography mass spectrometry (GC-MS, m/z values and relative intensity with reference to the base ion (%) was carried out with a Finnigan TSQ 700 Triple Mass Spectrometer in positive (P-CI) or negative (N-CI) chemical ionization measurement mode with methane or ammonium as a reactant gas or via electron impact ionisation. Hydroxy compounds were measured as trimethylsilylether-derivatives.

Coupled liquid chromatography-mass spectrometry (LC-MS): Waters Integrity System, Thermabeam Mass Detector (EI, 70 eV), m/z-values and relative intensity (%) are given over a quantity range of 50–500 a.m.u.

II. Embodiments

The Arabic numerals in brackets (3), (4), (5), (6) refer to the identical designations in reaction diagram 1.

1. Preparation of R-(−)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid methyl-ester.(3)



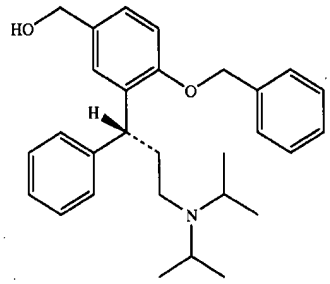
A solution of R-(−)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid hydrochloride (2.30 kg, 4.77 Mol) in 26.4 litres of methanol and 0.25 litre of concentrated sulphuric acid is heated for 16 hours with recycling. Then a third of the solvent is distilled off, cooled and under agitation mixed with 5 kg ice and 2.5 litres 25% aqueous sodium carbonate solution. The deposit is first extracted with 15 litres and then again with 5 litres of dichloromethane. The organic phases are purified and concentrated on the rotary evaporator until dry. 1.99 kg (90.7% of theoretical) dark yellow oil with a purity of approximately 90% (DC, NMR) are obtained.

DC (1): 0.58

^{13}C-NMR ($CDCl_3$): 20.55, 20.65, 36.83, 41.84, 43.63, 51.82, 70.12, 111.09, 122.46, 125.28, 127.49, 128.02, 128.35, 128.50, 129.22,129.49, 133.20, 136.39; 144.51, 159.87, 167.09.

Recrystallisation 69.0 oily raw material is dissolved in 150 ml boiling methanol. Following the addition of 15 ml distilled water it is left at 0° C., whereupon colourless crystals precipitate. These are filtered off, washed with a little cold methanol and vacuum-dried. Yield: 41.8 g (60.6% of theoretical) colourless crystals, melting point 89.8° C.; $[I]_D^{20}$=−30.7(c=1.0, ethanol).

2. Preparation of R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (4)

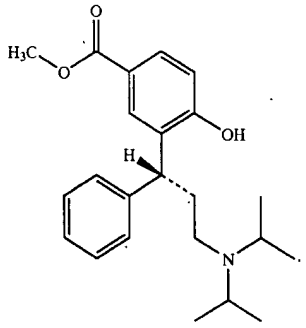


Raw product (3) (28 g) is dissolved in 230 ml pure diethylether and under agitation is dripped into a suspension of 1.8 g lithium-aluminium hydride in diethylether (140 ml). After 18 hours of agitation at room temperature, 4.7 ml of water are added in drop form. The organic phase is separated off, dried with anhydrous sodium sulphate, filtered and concentrated on the rotary evaporator until dry. 26 g (98.9% of theoretical) R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (4) are obtained as a colourless oil.

DC (2): 0.32; $[I]_D^{20}$=+6.3 (c=1.0, ethanol).

^{13}C-NMR ($CDCl_3$): 20.53, 20.61, 36.87, 41.65, 44.14, 48.82, 65.12, 70.09, 111.80, 125.77, 125.97, 126.94, 127.55, 128.08, 128.37, 128.44, 133.27, 134.05, 134.27, 137.21, 144.84.

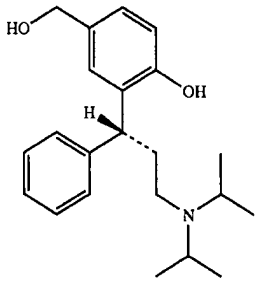
3. Preparation of R-(−)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester (5)



To an agitated suspension of 5 g Raney nickel (washed with water, then with methanol) in 200 ml methanol, 10 g (21.8 mmol) R-(−)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid methyl ester (3) are added. Following brief heating, in order to dissolve all (3) completely, the apparatus is placed under a hydrogen gas atmosphere. After three hours of agitation at normal pressure and room temperature, the thin layer chromatography demonstrates complete conversion. The deposit is rinsed with nitrogen gas and following addition of some active charcoal is filtered. Following concentration of the methanolic solution on the rotary evaporator 6.0 g (75% of theoretical) R-(−)-3-(3-diisopropylaminophenyl-propyl)-4-hydroxy-benzoic acid methyl ester (5) remains in the form of colourless crystals with a purity of 99.6% (HPLC).

Melting point 143.7° C.; DSC 144.7° C.
$[I]_D^{20}$=−26.6 (c=0.93, ethanol).
^{13}C-NMR ($CDCl_3$): 18.74, 19.21, 19.62, 33.12, 39.68, 42.36, 48.64, 51.42, 117.99, 120.32, 126.23, 127.81, 128.85, 129.39, 130.26, 132.21, 144.06, 162.43, 167.35.

4. Preparation of R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (6)



a) Starting from the intermediate stage (4), R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol

R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (19.7 g, 45.7 mmol) are dissolved in 220 ml methanol and Raney nickel (5 g). The apparatus is rinsed with hydrogen gas and the deposit is agitated for two days at room temperature. Following the addition of a further 5 g Raney nickel, agitation for a further two days at room temperature takes place under a hydrogen gas atmosphere, followed by filtration off from the catalyser and concentration until dry on the rotary evaporator. The oily, pale yellow residue is dissolved in 100 ml diethylether, washed twice with 100 ml water each time, dried via sodium sulphate, filtered and concentrated until dry. 14.1 g (90.4% of theoretical) R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol are obtained in the form of a cream-coloured, amorphous. solid. For recrystallisation see under c).

b) Starting from the intermediate stage (5); R-(−)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester

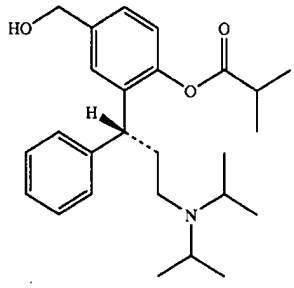
A solution of 370 mg (1.0 mmol) R-(−)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester in 20 ml anhydrous tetrahydrofurane is slowly and at room temperature dropped into an agitated mixture of dried tetrahydrofurane (10 ml) and a 1M solution of lithium-aluminium hydride in tetrahydrofurane (3 ml) (under a nitrogen protective gas atmosphere). Excess hydride is decomposed by the dropped addition of a saturated sodium carbonate solution. Following separation of the organic phase this is concentrated on the rotary evaporator and then dried in the high-vacuum. 274 mg (74% of theoretical) pale yellow oil is obtained, that slowly solidifies into an amorphous mass.

c) Recrystallisation

Raw product 6 (1.0 g) is dissolved in ethyl acetate and again concentrated on the rotary evaporator. The diol released in this way from foreign solvents (diethyl ether or tetrahydrofurane, see above) has 1.5 ml ethyl acetate added with slight heating. Agitation takes place until a clear solution results, followed by cooling at room temperature and addition of a few seed crystals. These are obtained by purifying raw 6 via HPLC, collecting the main fraction, concentrating this and drying the residue for a number of hours in the high-vacuum. Once clear crystallisation has definitely started, it is left at −10° C. The crystals are sucked off in the cold and dried in the vacuum. Colourless crystals with a yield of 84% are obtained.

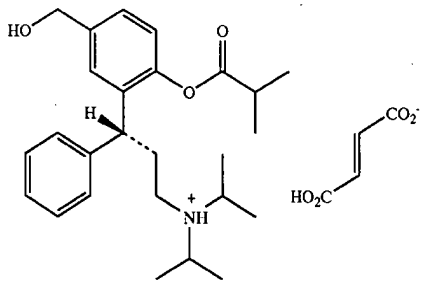
Melting point 102.3° C.
DC (1): 0.57
$[I]_D^{20}$=+21.3 (c=1.0, ethanol).
^{13}C-NMR ($CDCl_3$): 19.58, 19.96, 33.30, 39.52, 42.10, 48.00, 65.40, 118.58, 126.31, 126.57, 127.16, 127.54, 128.57, 132.63, 132.83, 144.55, 155.52.

5. Preparation of R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenolisobutyrate ester (1)



A solution of R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (6) (65.0 g, 190.3 mmol) and triethylamine (20.4 g, 201.7 mmol) in 750 ml dichloromethane has a solution of isobutyrate chloride (23.4 g, 201.7 mmol) in 250 ml dichloromethane added under agitation and cooling. Following addition agitation takes place for a further 15 minutes at 0° C., then for 30 minutes at room temperature and then one after another washing with water (250 ml) and 5% aqueous sodium hydrogen carbonate solution. The organic phase is separated and concentrated on the rotary evaporator until dry. The ester R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester is obtained as a colourless, viscous oil; yield: 77.1 g (98.4% of theoretical).
DC (1): 0.26; $[I]_D^{22}$=+2.7 (c=1.0, ethanol).
^{13}C-NMR ($CDCl_3$): 19.01, 19.95, 20.59, 21.12, 34.28, 36.89, 41.88, 42.32, 43.90, 48.78, 64.68, 122.57, 125:59, 126.16, 126.86, 127.96, 128.54, 136.88, 138.82, 143.92, 147.90, 175.96.

6. Preparation of R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenylisobutyrate ester hydrogen fumarate.



A solution of 41.87 g (102 mmol) R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester in 90 ml 2-butanone has fumaric acid (11.81 g, 102 mmol) added while heating. Following dissolution of the acid, cyclohexane (20–30 ml) is slowly added under agitation until the onset of turbidity. The colourless, homogenous deposit is initially left for 18 hours at room temperature, and then for several hours at 0° C. The colourless crystals that have precipitated are sucked off, washed with a little cyclohexane/2-butanone (90:10, vol.-%)and dried in the vacuum at 30° C. 44.6 g (83.1% of theoretical) hydrogen furate salt of R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-

hydroxymethylphenyl-isobutyrate ester in the form of colourless flakes are obtained.

Melting point 98.8° C., a second crystallisation from the same solvent mixture provides a product with a melting point of 103° C.

$[I]_D^{20}$=+6.0 (c=1.0, ethanol).

Elementary analysis: Calculated for $C_{30}H_{41}NO_7$ (molecular weight 527.66) C 68.29%, H 7.83%, N 2.65%, O 21.2%; found C, 68.29%; H, 7.90%; N, 2.72%; O, 21.0%.

UV/VIS at Σ in nm ($A^{1\%}_{1\ cm}$): 191 (1306), 193 (1305), 200 (1143), 220 (456).

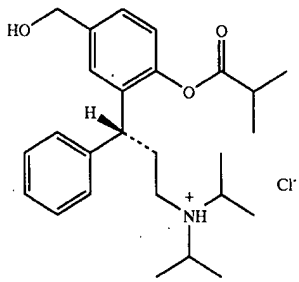
IR: 3380, 2978, 2939, 2878, 2692, 2514, 1756, 1702, 1680, 1618, 1496, 1468, 1226, 1040, 1019, 806,

^{1}H-NMR ($CDCl_3$): 1.198, 1.285, 1.287 (CH_3); 2.541 (CHC=O); 3.589 (NCH); 4.585 (CH_2OH); 6.832 (=CH, fumarate); 6.84–7.62 (aryl, =CH).

^{13}C-NMR ($CDCl_3$): 17.79, 18.95, 19.16 (CH_3); 31.63 ($CHCH_2$); 34.09 (CH—C=O); 41.87 ($CHCH_2$); 45.83 (NCH_2); 54.29 (NCH); 63.78 (OCH_2); 122.23, 126.48, 126.77, 127.56, 140.46, 140.52, 142.35, 147.54 (Aryl CH); 135.54 (=CH, fumarate); 170.48 (C=O, fumarate); 175.62 (i-Pr—C=O).

Ms in the direct inlet, m/z (%): 411 (1), 396 (9), 380 (1), 223 (2), 165 (2), 114 (100), 98 (4), 91 (3), 84 (3), 72 (10), 56 (7).

7. Preparation of R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenylisobutyrate ester hydrochloride hydrate



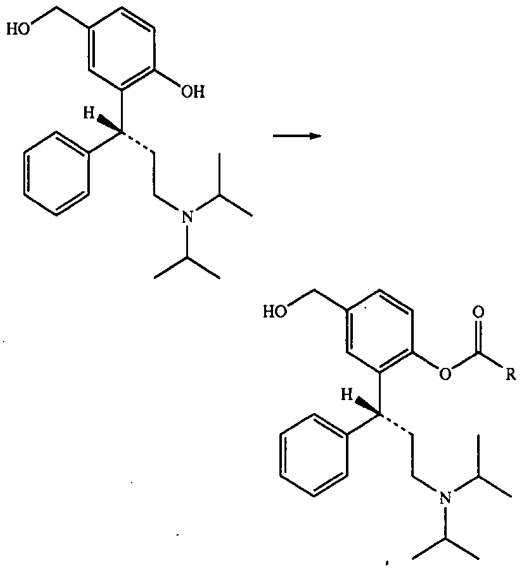
A solution of R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester (8.54 g, 25.0 mmol) in 50 ml dichloromethane is slowly dropped at 0° C. into an agitated solution of isobutyrate chloride (2.66 g, 25.0 mmol) in 100 ml dichloromethane. After an hour the cooling is removed and re-agitation takes place for an additional hour. Following the drawing off of the volatile components in the vacuum on the rotary evaporator a colourless, amorphous-solid foam remains. This residue is dissolved in acetone (17 ml), with 0.45 to 0.50 g water and diethyl ether is added (approx. 20–25 ml) until there is a definite onset of turbidity. Following brief treatment with ultrasound crystallisation starts spontaneously and under agitation a further 80 ml of diethyl ether are slowly added. The precipitated colourless crystals are sucked off and dried overnight in the vacuum via phosphorous pentoxide. 10.5 g (93.7% of theoretical) colourless crystalline R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate with a purity of 97.0% (HPLC) are obtained.

Melting point 97.1° C.

$[I]_D^{20}$=+4.3 (c=1.03, ethanol)

^{13}C-NMR ($CDCl_3$): 16.94, 17.35, 18.24, 18.40, 18.87, 19.05, 31.20, 33.99, 41.64, 45.41, 54.18, 54.42, 63.83, 122.25, 126.50, 126.70, 126.96, 127.34, 128.60, 133.80, 140.55, 142.17, 147.68, 175.79.

8. Phenolic Monoester



General Work Specification for the Manufacture of Phenolic Monoesters

Into a solution of 120.3 mg (0.352 mmol)R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxyphenol (6) in 5 ml dichloromethane, under agitation at 0° C., a solution of acid chloride (0.352 mmol) in 2 ml dichloromethane is dropped. Then triethylamine-dichloromethane (49.1 µl/0.353 mmol-2 ml) is added. After 18 hours at room temperature the thin layer chromatography shows that conversion is complete. The deposit is washed successively with 5 ml water, aqueous 0.1N-hydrochloric acid, 5 ml 5% aqueous sodium-hydrogen carbonate solution, 5 ml water, dried via sodium sulphate and following filtration concentrated until dry. Then it is dried in the high-vacuum until constant weight.

The following compounds are, by way of example, manufactured using this method:

R=$CH_2CH(CH_3)_2$

R-(+)-3-methylbutyric acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester

Colourless oil with 70% yield and >95% purity (NMR).

^{13}C-NMR ($CDCl_3$): 20.45, 20.59, 22.54, 25.70, 36,74, 42.18, 43.27, 43.96, 48.90, 64.67, 122.66, 125.60, 126.20, 126.79, 127.95, 128.37, 136.83, 138.86, 143.83, 147.82, 171.37.

DC (1): 0.76.

R=$CH_2C(CH_3)_3$

R-(+)-3.3-dimethylbutyric acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester, free base

Colourless oil with 69.7% yield and >95% purity (NMR).

^{13}C-NMR ($CDCl_3$): 20.40, 20.53, 29.73, 30.99, 36.62, 42.17, 44.01, 47.60, 49.01, 64.65, 122.64, 125.60, 126.20, 126.80, 127.96, 128.36, 136.85, 138.90, 143.80, 147.82, 170.55.

DC (1): 0.75.

R=$(CH_3)_3C$

R-(+)-3-pivalic . acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride.

Colourless crystals, melting point 165–6° C.

^{13}C-NMR (DMSO-d_6=39.7 ppm): 16.52, 16.68, 17.98, 18.11, 26.87, 31.46, 41.71, 45.33, 53.89, 53.98, 62.65, 122.61, 122.97, 125.94, 126.09, 126.57, 126.75, 127.87, 128.58, 131.80, 134.94, 141.02, 142.69, 147.17, 155.32, 163.92, 176.21.

R=c-C_3H_5

R-(+)-cyclopropane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride.

Colourless, waxy substance.

^{13}C-NMR (DMSO-d_6=39.7 ppm): 173.02, 172.49, 172.37, 153.10, 147.12, 142.72, 142.03, 140.78, 136.60, 134.79, 134.35, 129.55, 129.13, 128.80, 128.67, 127.87, 126.96, 126.74, 125.94, 125.84, 124.37, 123.71, 122.80, 62.64, 53.92, 45.34, 41.65, 31.44, 18.05, 16.66, 12.84, 9.58, 9.28, 8.49, 7.89.

R=c-C_4H_7

R-(+)-cyclobutane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless, waxy substance.

^{13}C-NMR (DMSO-d_6=39.7 ppm): 173.53, 147.12, 142.81, 140.74, 134.77, 128.65, 127.81, 126.74, 125.99, 125.87, 122.75, 62.63, 53.92, 45.34, 41.42, 37.38, 31.54, 25.04, 24.92, 18.03, 16.68, 16.61.

R=c-C_5H_9

R-(+)-cyclopentane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless, waxy substance.

^{13}C-NMR (DMSO-d_6=39.7 ppm): 174.80, 147.22, 142.86, 140.76, 134.72, 128.66, 127.80, 126.73, 126.04, 125.88, 122.71, 62.62, 53.94, 45.37, 43.24, 41.39, 31.54, 29.78, 29.59, 25.64, 25.59, 18.07, 16.64.

R=c-C_6H_{11}

R-(+)-cyclohexane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless, waxy substance.

^{13}C-NMR (DMSO-d_6=39.7 ppm): 174.08, 147.15, 142.85, 140.77, 134.78, 128.66, 127.77, 126.74, 126.06, 125.87, 122.69, 62.61, 53.91, 45.36, 42.26, 41.24, 31.53, 28.74, 28.62, 25.48, 25.04, 24.98, 18.05, 16.67, 16.60.

R=4-($C_2H_5CO_2$)-C_6H_4

R-(+)-4-ethylcarbonyloxy-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless crystals, melting point 195–8° C.

^{1}H-NMR (DMSO-d_6): 9.87 (s, 1H can be substituted with D_2O, NH), 8.19–8.12 (m, 2H, Phenyl-H), 7.55 (d, J=1.0 Hz, 1H, Phenyl-H3), 7.41–7.13 (m, 9H, Phenyl-H), 5.28 (br s, 1H can be substituted with D_2O, OH), 4.53 (s, 2H, CH_2), 4.23 (t, J=7.6 Hz, 1H, CH), 3.61–3.50 (m, 2H, 2×C<u>H</u>$(CH_3)_2$), 2.97–2.74 (m, 2H, CH_2), 2.67 (q, J=7.4 Hz, 2H, CH_2), 2.56–2.43 (m, 2H, CH_2), 1.23–1.13 (m, 15H, 2×CH($C\underline{H}_3)_2$, CH_3).

R=4-(i-$C_3H_7CO_2$)—C_6H_4

R-(+)-4-(isopropylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless crystals, melting point 202–4° C.

^{1}H-NMR (DMSO-d_6): 9.73 (s, 1H can be substituted with D_2O, NH), 8.19–8.12 (m, 2H, Phenyl-H), 7.55 (d, J=1.4 Hz, 1H, Phenyl-H_3), 7.42–7.14 (m, 9H, Phenyl-H), 5.27 (br s, 1H can be substituted with D_2O, OH), 4.53 (s, 2H, CH_2), 4.23 (t, J=7.5 Hz, 1H, CH), 3.61–3.50 (m, 2H, 2×C<u>H</u>$(CH_3)_2$), 2.99–2.78 (m, 3H, CH_2, C<u>H</u>$(CH_3)_2$), 2.54–2.47 (m, 2H, CH_2), 1.29–1.13 (m, 18H, 3×CH($C\underline{H}_3)_2$).

R=4-(t-$C_4H_9CO_2$)—C_6H_4

R-(+)-4-(t-butylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester, free base.

Colourless oil.

^{1}H-NMR (DMSO-d_6): 8.19–8.12 (m, 2H, phenyl-H), 7.45–7.33 (m, 3H, phenyl-H), 7.25–7.09 (m, 7H, phenyl-H), 5.20 (t, J=5.6 Hz, 1H, OH), 4.50 (d, J=5.6 Hz, 2H, CH_2), 4.20 (t, J=7.5 Hz, 1H, CH), 2.95–2.80 (m, 2H, 2×C<u>H</u>$(CH_3)_2$), 2.38–2.25 (m, 2H, CH_2), 2.09–2.03 (m, 2H, CH_2), 1.33 (s, 9H, $(CH_3)_3$), 0.82–0.76 (m, 12H, 2×CH($C\underline{H}_3)_2$).

Hydrochloride: colourless crystals, melting point 165–6° C.

^{1}H-NMR ($CDCl_3$): 8.22–8.16 (m, 2H, phenyl-H), 8.02 (d, J=1.8 Hz, 1H, phenyl-H), 7.27–7.02 (m, 9H, phenyl-H), 4.83–4.60 ('m', 2H, CH_2), 4.01–3.94 (m, 1H, CH), 3.66–3.54 (m, 2H), 3.18–2.80 (m, 3H), 2.53–2.44 (m, 1H) (2×CH_2, 2×C<u>H</u>$(CH_3)_2$), 1.43–1.25 (m, 21H, $(CH_3)_3$, 2×CH($C\underline{H}_3)_2$).

R=4-(c-$C_3H_5CO_2$)-C_6H_4

R-(+)-4-(cyclopropylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless crystals, melting point 208–213° C.

^{1}H-NMR (DMSO-d_6): 9.04 (s, 1H can be substituted with D_2O, NH), 8.15–8.09 (m, 2H, phenyl-H), 7.53 ('d', 1H, phenyl-H3), 7.42–7.13 (m, 9H, phenyl-H), 5.25 (br s, 1H can be substituted with D_2O, OH), 4.52 (s, 2H, CH2), 4.23 (t, J=7.5 Hz, 1H, CH), 3.62–3.53 (m, 2H, 2×C<u>H</u>(CH3)2), 3.05–2.70 (m, 2H, CH2), 2.51–2.37 (m, 2H, CH2), 2.01–1.89 (m, 1H, cyclopropyl-CH), 1.20–1.05 (m, 16H, 2×CH(C<u>H</u>3)2, 2×cyclopropyl-CH2).

^{13}C-NMR (DMSO-d_6=39.7 ppm): 172.71, 163.93, 154.92, 147.16, 142.69, 141.03, 134.97, 131.76, 128.60, 127.86, 126.76, 126.56, 126.06, 125.94, 122.95, 122.65, 62.65, 54.00, 53.89, 45.33, 41.63, 31.49, 18.10, 17.98, 16.69, 16.51, 12.86, 9.52.

R=4-(c-$C_4H_7CO_2$)-C_6H_4

R-(+)-4-(cyclobutylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless crystals, melting point 201–6° C.

^{1}H-NMR (DMSO-d_6): 9.50 (s, 1H can be substituted with D_2O, NH), 8.17–8.12 (m, 2H, phenyl-H), 7.54 (d, J=1.4 Hz, 1H, phenyl-H3), 7.42–7.14 (m, 9H, phenyl-H), 5.25 (br s, 1H can be substituted with D_2O, OH), 4.52 (s, 2H, CH_2), 4.23 (t, J=7.5 Hz, 1H, CH), 3.62–3.47 (m, 3H, cyclobutyl-CH), 2×C<u>H</u>$(CH_3)_2$), 3.00–2.70 (m, 2H, CH_2), 2.51–2.26 (m, 6H, CH_2, 2×cyclobutyl-CH_2), 2.10–1.85 (m, 2H, cyclobutyl-CH_2), 1.22–1.12 (m, 12H, 2×CH($C\underline{H}_3)_2$).

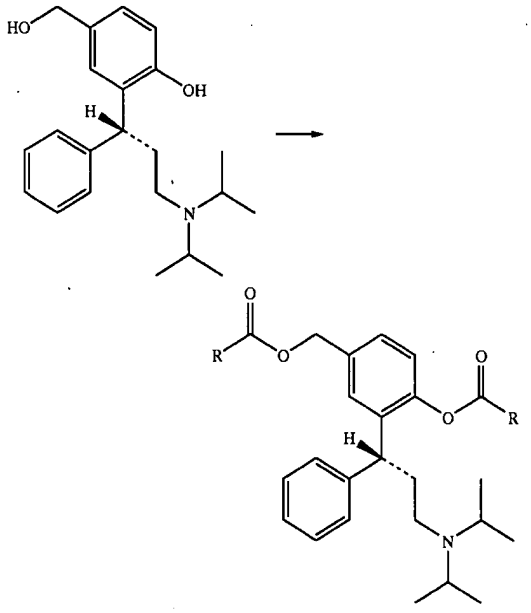
R=4-(c-$C_6H_{11}CO_2$)-C_6H_4

R-(+)-4-(cyclohexylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless crystals, melting point 212–217° C.

^{1}H-NMR (DMSO-d_6): 9.34 (s, 1H, can be substituted with D_2O, NH), 8.16–8.12 (m, 2H, phenyl-H), 7.54 (d, J=1.4 Hz, 1H, phenyl-H3), 7.39–7.14 (m, 9H, Phenyl-H), 5.26 ('t', 1H, can be substituted with D_2O), 4.53 (d, J=4.2 Hz, 2H, CH_2), 4.22 (t, J=7.5 Hz, 1H, CH), 3.62–3.48 (m, 2H, 2×C<u>H</u>$(CH_3)_2$), 3.00–2.60 (m, 3H, cyclohexyl-CH), CH_2), 2.51–2.40 (m, 2H, CH_2), 2.07–1.98 (m, 2H, cyclohexyl-CH_2), 1.80–1.11 (m, 20H, 4×cyclohexyl-CH_2), 2×CH($C\underline{H}_3)_2$)

9. Identical Diesters



General Work Specification for the Manufacture of Identical Diesters

Into a solution of 7.30 g (21.4 mmol)R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxyphenol (6) in 100 ml dichloromethane, under agitation at 0° C., a solution of acid chloride (49.2 mmol) in 50 ml dichloromethane is dropped. Then triethylamine-dichloromethane (6.86 ml/49.2 mmol-50 ml) is added. After 1–3 hours at room temperature the thin layer chromatography shows that conversion is complete. The deposit is washed successively with respectively 100 ml water, aqueous 0.1N-hydrochloric acid, 5 ml 5% aqueous sodium-hydrogen carbonate solution, 5 ml water, dried via, sodium sulphate and following filtration concentrated until dry. Then it is dried in the high-vacuum until constant weight.

The following compounds are, by way of example, manufactured using this method:

R=Methyl

R-(−)-acetic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-acetoxymethyl-phenyl-ester, free base

Pale yellow oil, purity (HPLC): 95.2%.

^{13}C-NMR ($CDCl_3$): 20.36, 20.69, 20.94, 20.99, 36.41, 42.27, 43.69, 48.79, 65.89, 122.89, 126.28, 127.17, 127.92, 128.36, 133.69, 136.95, 143.61, 148.46, 168.97, 170.76.

LC-MS: 425 (15%, M^+), 410 (97%), 382 (4%), 308 (3%), 266 (7%), 223 (27%), 195 (13%), 165 (8%), 114 (100%).

$[\alpha]_D^{20}$=−33.1 (c=1, CH_3CN).

DC (1): 0.79.

R=Cyclohexyl

R-(+)-cyclohexane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-cyclohexylcarbonyloxymethyl-phenyl-ester

Pale yellow oil, purity (NMR): >95%.

^{13}C-NMR ($CDCl_3$): 20.30, 25.17, 25.58, 25.73, 28.97, 29.12, 41.70, 43.15, 44.03, 48.64, 65.37, 122.67, 125.88, 126.24, 127.06, 127.31, 127.90, 128.37, 134,03, 136.85, 143.55, 148.33, 174.20, 175.72.

DC (1): 0.96.

R=Isopropyl

R-(+)-isobutyrate-2-(3-diisopropylamino-1-phenyl-propyl)-4-isobutyryloxymethyl-phenyl-ester

Free base: pale yellow oil, purity (HPLC): 95.6%.

^{13}C-NMR ($CDCl_3$): 18.96, 19.08, 20.59, 33.98, 34.20, 36.86, 41.72, 43.72, 48.72, 65.58, 122.65, 126.19, 126.73, 127.91, 128.11, 128.36, 133.91, 136.96, 143.81, 148.41, 175.15, 176.77.

DC (1): 0.74.

Hydrogen fumarate salt: colourless syrup, 94.4% HPLC purity.

^{13}C-NMR ($CDCl_3$): 17.89, 18.07, 18.94, 18.97, 19.07, 31.22, 33.93, 34.13, 41.78, 45.62, 53.93, 65.33, 122.93, 126.82, 127.45, 127.53, 127.91, 128.75, 134.74, 135.29, 135.42, 142.04, 148.44, 170.24, 175.71, 176.79.

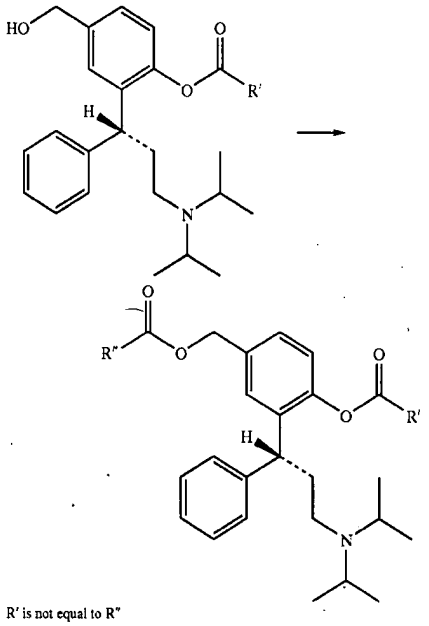
R=4-(t-C_4H_9 CO_2)-C_6H_4

R-4-(t-butylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-(4-t-butylcarbonyloxymethyl-benzoic acid)-phenyl-ester hydrochloride

Colourless crystals, melting point 105–7° C.

^{13}C-NMR (DMSO-d_6): 16.49, 16.71, 17.97, 18.06, 26.84, 31.36, 38.45, 41.70, 45.24, 53.79, 53.96, 55.09, 66.11, 122.47, 122.62, 123.59, 126.42, 126.83, 127.21, 127.70, 127.88, 128.02, 128.62, 131.17, 131.86, 134.48, 135.64, 142.52, 148.35, 154.86, 155.39, 163.80, 165.09, 176.14, 176.19.

10. Mixed Diesters



R' is not equal to R"

General Work Specification for the Manufacture of Mixed Diesters

Into a solution of 5.30 mmol phenolic monoester of general formula A in 40 ml dichloromethane under agitation at 0° C. a solution of acid chloride (5.83 mmol) in 15 ml dichloromethane is dropped. Then triethylamine-dichloromethane (0.589 g/5.82 mmol-15 ml) is added. After 18 hours at room temperature the thin layer chromatography shows that conversion is complete. The deposit is washed successively with respectively 50 ml water, aqueous 0.1N-hydrochloric acid, 5 ml 5% aqueous sodium-hydrogen carbonate solution, 5 ml water, dried via sodium sulphate and following filtration concentrated until dry. Then it is dried in the high-vacuum until constant weight.

The following example is manufactured using this method:

R'=$CH(CH_3)_2$

R"=CH_3

R-(+)-isobutyrate-2-(3-diisopropylamino-1-phenyl-propyl)-4-acetoxymethyl-phenyl-ester

Colourless oil.

DC (1): 0.56

^{13}C-NMR ($CDCl_3$): 19.12, 20.65, 21.05, 34.24, 37.02, 41.79, 43.79, 48.72, 65.98, 122.75, 125.98, 126.22, 127.94, 128.39, 128.84, 133.55, 137.04, 143.84, 148.58, 170.84, 175.18.

Hydrochloride: colourless crystals

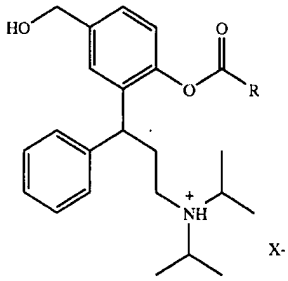
^{13}C-NMR ($CDCl_3$): 16.89, 17.04, 18.31, 18.92, 20.95, 31.49, 34.07, 41,64, 46.17, 54.55, 65.49, 122.91, 126.61, 126.93, 127.48, 127.83, 128.74, 134.50, 134.88, 141.61, 148.44, 170.67, 175.63.

$[\alpha]_D^{20}$=14.6 (c=1, $CHCl_3$).

What is claimed is:

1. Compounds of general formula I

Formula I

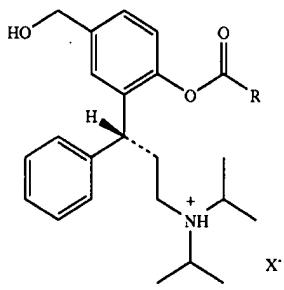


in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

2. Compounds in accordance with claim 1, characterised in that X^- in each case is an acid ester of hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(−)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+) -tartaric acid, D-(−)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

3. Compounds in accordance with claims 1, characterised in that they have general formula 2:

Formula 2



in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

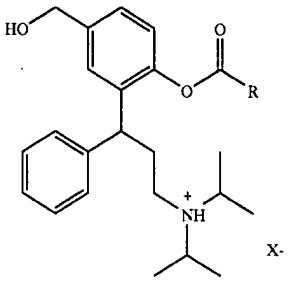
4. Compounds in accordance with claim 3, characterised in that X in each case is an acid ester of hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(−)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(−)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

5. Compounds in accordance with claims 3, characterised in that they are R-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethyl -phenylisobutyrate ester hydrogen fumarate, R-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester-hydrochloride hydrate.

6. Compounds in accordance with claims 3, characterised in that R stands for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-(1-cyclopropyl-methanoyloxy)-phenyl, 4-(1-cyclobutyl-methanoyloxy)-phenyl, 4-(1-cyclohexyl-methanoyloxy)-phenyl or 4-(2,2-dimethyl-propanoyloxy)-phenyl and X^- denotes chloride.

7. Method for manufacturing compounds of general formula I

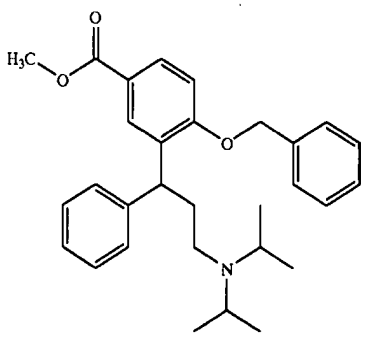
Formula I



in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X– is the acid residue of a physicologically compatible inorganic or organic acid, characterised in that

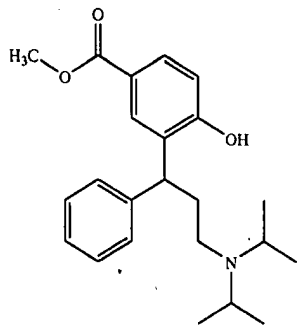
a) a compound of formula III

Formula III



is split with a hydrogenation agent to form a compound of Formula V

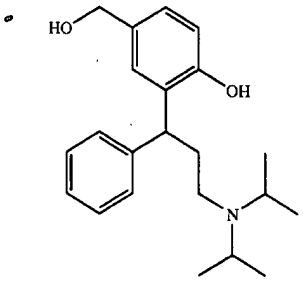
Formula V



whereupon

b) the compoud of formula V so obtained is converted with a reducing agent, in order to give a compound of formula VI

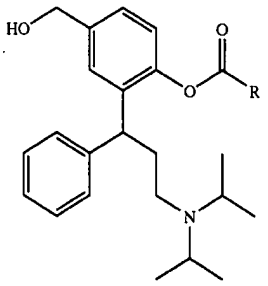
Formula VI



which

c) is converted with an acylation agent, in order to obtain a compound of formula A

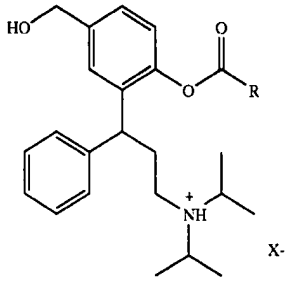
Formula A



in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula I

Formula I

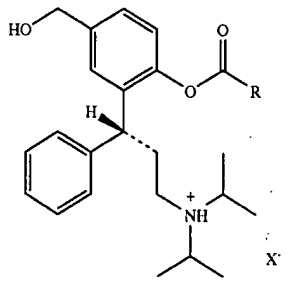


in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, unsubstituted or substituted phenyl and X– is the acid residue of a physiologically compatible inorganic or organic acid.

8. Method in accordance with claim 7, characterised in that for the manufacture of the compounds of general formula I hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(–)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(–)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-acetylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

9. Method for manufacturing compounds of general formula 2

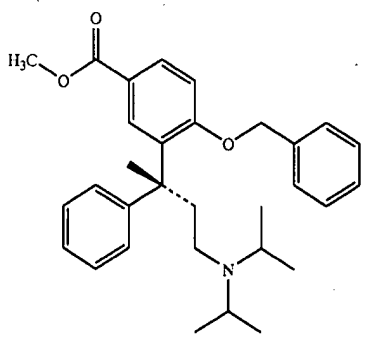
Formula 2



in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X– is the acid residue of a physiologically compatible inorganic or organic acid, characterised in that

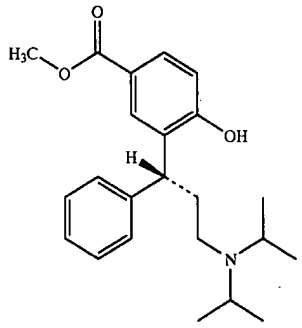
a) a compound of the formula 3

Formula 3



s split with a hydrogenation agent to form a compound of formula 5

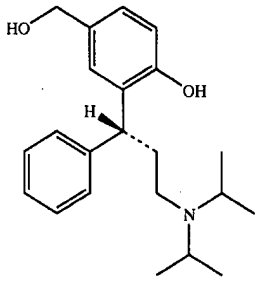
Formula 5



whereupon

b) the compound formula 5 so obtained is converted with a reducing agent, in order to give a compound of formula 6

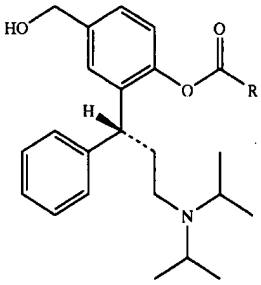
Formula 6



which

c) is converted with an acylation agent, in order to obtain a compound of formula 1

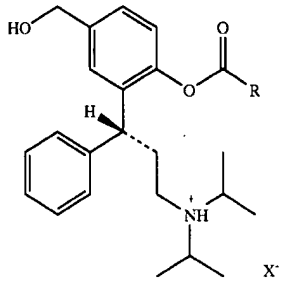
Formula 1



in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula 2

Formula 2



in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, unsubstituted or substituted phenyl and X– is the acid residue of a physiologically compatible inorganic or organic acid.

10. Method in accordance with claim **9**, characterised in that for the manufacture of the compounds of general formula 2 hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(−)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(−)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

11. Method in accordance with claims **7**, characterised in that as the hydrogenation agent, Raney nickel/H_2 in methanol is preferably used as the solvent.

12. Method in accordance with claims **7**, characterised in that for the reducing agent $NaBH_4$EtOH, preferably $LiAlH_4$/THF, is used.

13. Method in accordance with claims **7**, characterised in that for the acylation agent isobutyrylchloride and for the base triethylamine are used.

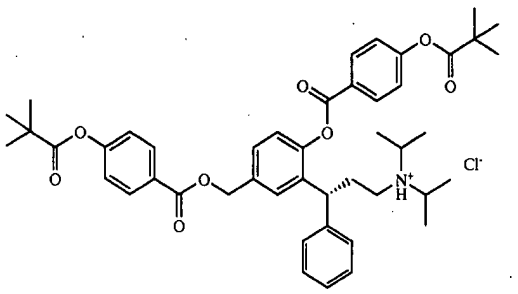
14. Method in accordance with claims **9**, characterised in that a compound of general formula 6 is converted with an equivalent isobutyryl chloride in the presence of triethylamine using one of the respective solvents ethylacetate, dichloromethane, tetrahydrofurane, acetonitrile or toluene regio- and chemoselectively into R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate.

15. Method in accordance with claims **9**, characterised in that R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester and fumaric acid or hydrochloric acid are converted with the formation of the respective salt.

16. Method in accordance with claims **9** for the manufacture of R-(+)-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-methylphenylisobutyrate ester hydrochloride hydrate, characterised in that the phenolic esterification of R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (6) is carried out without the addition of an external base, in that solutions of (6) are dropped into solutions of isobutyryl chloride, that contain at least 1 mole equivalent of water, in order to directly obtain a corresponding stable, hydrate-containing hydrochloride.

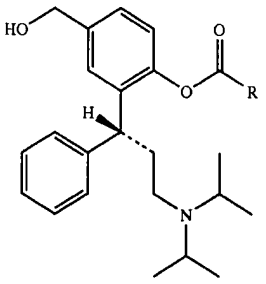
17. Compound of formula 7

Formula 7



18. A method of manufacture of phenolic monoesters of general formula 1

Formula 1



wherein the method comprises the steps of:

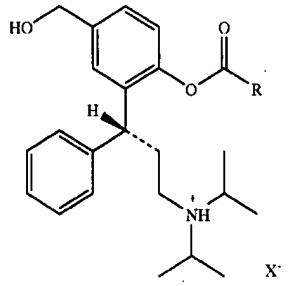
providing a compound of claim 17;

deprotecting the hydroxyl residues of the 4-hydroxybenzyl alcohol residue; and

acylating the phenol residue.

19. A method of manufacture of salts of phenolic monoesters of general formula 2:

Formula 2



in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physicologically compatible inorganic or organic acid, wherein the method comprises the steps of:

providing a compound of claim 17;

deprotecting the hydroxyl residues of the 4-hydroxybenzyl alcohol residue; and

acylating the phenol residue.

20. A method of manufacture of R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate or R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate, the method comprising the steps of;

providing a compound of claim 17;

deprotecting the hydroxyl residues of the 4-hydroxybenzyl alcohol residue; and

acylating the phenol residue.

21. A method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 1.

22. A method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 3.

23. A method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 5.

24. The method of any one of claims 21–23, wherein the urinary incontinence disorder is urge incontinence.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,858,650 B1
DATED : February 22, 2005
INVENTOR(S) : Meese

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1,
Line 17, please correct "prodrugn" to -- prodrugs --
Line 26, please correct "3,3-diphenylpropylarines" to -- 3,3-diphenylpropylamines --

Column 3,
Line 50, please correct "and X" to -- and X^- --

Column 4,
Lines 45-46, please correct "are that" to -- are manufactured in that --

Column 5,
Line 24, please correct "with agent" to -- with a reducing agent --

Column 13,
Line 14, please correct "photometer. model" to -- photometer model --
Line 64, please correct "43.63" to -- 43.83 --

Column 15,
Line 37, please correct "amorphous. solid" to -- amorphous solid --

Column 16,
Line 37, please correct "125:59" to -- 125.59 --

Column 17,
Line 6, please correct "$[I]_D^{20=+6.0}$" to -- $[I]_D^{20}$= +6.0 --
Line 23, please correct "Ms" to -- MS --

Column 23,
Line 13, please correct "=14.6" to -- = +14.6 --
Line 47, "please correct "claims" to -- claim --

Column 24,
Lines 15 and 21, please correct "claims" to -- claim --
Line 46, please correct "physicologically" to -- physiologically --

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,858,650 B1
DATED : February 22, 2005
INVENTOR(S) : Meese

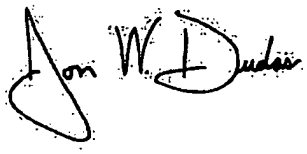
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 28,
Lines 35, 38, 41, 45, 53 and 58, please correct "claims" to -- claim --

Column 30,
Line 17, please correct "physicologically" to -- physiologically --

Signed and Sealed this

Ninth Day of August, 2005



JON W. DUDAS
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
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Alexandria, VA 22313-1450
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ISTMT

EXHIBIT B

EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON MA 02205

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,858,650	**$930.00**	**$0.00**	**08/13/08**	**10/130,214**	**02/22/05**	**05/14/02**	**04**	**NO**	**SCHWARZ PHARMA AG**

PTOL-439 (Rev. 09/2006)

EXHIBIT C

Practitioner's Docket No. 58827 (45107) *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	C. Meese		
Application No.:	10/130,214	GROUP:	1624
Filed:	May 14, 2002	EXAMINER:	Z. Tucker
For:	STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES		
[ ] *Patent No.:	Issue Date: Reexamination Date:		

**NOTE: Preferably also insert inventor's name and invention title.*

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

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION (37 C.F.R. SECTION 1.321(c))

Identification of Person(s) Making This Disclaimer

I, Christine C. O'Day

CERTIFICATE OF MAILING/TRANSMISSION (37 C.F.R. SECTION 1.8(a))

I hereby certify that, on the date shown below, this correspondence is being:

MAILING

[X] deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

FACSIMILE

[ ] transmitted by facsimile to the Patent and Trademark Office, (703) ___-____.

11/06/2003 SDENBOB1 00000030 10130214
01 FC:1814 110.00 OP

Date: November 3, 2003

Signature

Lee Dunkle

(type or print name of person certifying)

(type or print names of all inventors or assigns or name of attorney signing disclaimer)

(a) represent that I am

[ ] an inventor (applicant) of this invention.

[ ] an assignee of this invention.

WARNING: *"If the patent or patent application is assigned to an organization, such as a corporation, partnership, university, [g]overnment agency or similar entity, and the disclaimer is signed by the assignee, the assignee must comply with Section 3.73(b)." Notice of Oct. 15, 1993, 1156 O.G. 54-61 at 56, Section 1490, M.P.E.P., 7th Edition.*

[ ] a representative authorized to sign on behalf of the assignee identified below.

[ ] A statement under 37 C.F.R. Section 3.73(b) is attached.

WARNING: *See the above "WARNING".*

[X] the attorney of record for this invention.

NOTE: *The rules "permit an attorney or agent of record to sign a terminal disclaimer without the need to comply with Section 3.73(b)." Notice of Oct. 15, 1993, 1156 O.G. 54-61, at 56. See also Section 1490, M.P.E.P., 7th Edition.*

IDENTITY OF ASSIGNEE AND TITLE OF DISCLAIMANT
(if applicable)

The assignee is

Name of assignee Schwarz Pharma AG

Address of assignee Alfred-Nobel-Strasse 10, 40789 Monheim, Germany

Title of disclaimant authorized to sign on behalf of assignee n/a

EXTENT OF DISCLAIMANT'S INTEREST

The extent of the interest in this invention that the disclaimant owns is in:

[X] the whole of this invention.

[ ] a sectional interest in this invention, as follows:

(state the exact interest of the disclaimant)

RECORDAL OF ASSIGNMENT IN PTO
(if applicable)

[X] The assignment was recorded on: May 14, 2002

Reel 013122
Frame 0883

[ ] Authorization for recordal of the assignment is separately attached.

[ ] A separate [ ] "ASSIGNMENT (DOCUMENT) COVER SHEET" or
[ ] FORM PTO 1595 is also attached.

ESTABLISHING RIGHT OF ASSIGNEE TO TAKE ACTION
(if applicable)

[ ] Attached is a STATEMENT UNDER 37 C.F.R. Section 3.73(b) establishing the right of the assignee to take action in this case.

DISCLAIMER
(select one of the following)

(Provisional Obviousness-Type Double Patenting Rejection Over A Pending Application)

Petitioner hereby disclaims, except as provided below, the terminal part of any patent granted on the instant application, which would extend beyond the expiration date of any patent granted on Application No. 09/700,094, filed on January 2, 2001, as shortened by any terminal disclaimer. Petitioner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the above-listed application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors, or assigns.

In making the above disclaimer, disclaimant does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. Sections 154 to 156 and 173 of any patent granted on the application forming the basis of the double patenting rejection, namely, any patent granted on Application No.: 09/700,094, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of

competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. Section 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to expiration of its full statutory term as presently shortened by any terminal disclaimer, except for the separation of legal title stated above.

DISCLAIMER FEE (37 C.F.R. Section 1.20(d))

[X] Other than a small entity--fee $110.00

[ ] Small entity--fee $55.00

[ ] Small entity statement attached
[ ] Small entity statement already filed
[ ] in patent application __/ _____ on
(date)

OR

(Obviousness-Type Double Patenting Rejection Over A Prior Patent)

Petitioner hereby disclaims, except as provided below, the terminal part of any patent granted on the instant application, which would extend beyond the expiration date of Patent No. _____ as presently shortened by any terminal disclaimer. Petitioner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the above-listed patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors, or assigns.

In making the above disclaimer, disclaimant does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. Sections 154 to 156 and 173 of the patent forming the basis of the double patenting rejection, namely, Patent No.: _____, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. Section 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to expiration of its full statutory term as presently shortened by any terminal disclaimer, except for the separation of legal title stated above.

DISCLAIMER FEE (37 C.F.R. Section 1.20(d))

[ ] Other than a small entity--fee $110.00

[ ] Small entity--fee $55.00

[ ] Small entity statement attached
[ ] Small entity statement already filed

[ ] in patent application __/_____ on

(date)

OR

(Provisional Obviousness-Type Double Patenting Rejection Over A Pending Application--Reexamination Proceeding)

Petitioner hereby disclaims, except as provided below, the terminal part of any patent being reexamined, which would extend beyond the expiration date of any patent granted on Application No. __/_____, filed on _____, as shortened by any terminal disclaimer. Petitioner hereby agrees that any reexamination certificate issued on the instant patent being reexamined shall be enforceable only for and during such period that it and any patent granted on the above-listed application are commonly owned. This agreement runs with any reexamination certificate issued on the instant patent granted and is binding upon the grantee, its successors, or assigns.

In making the above disclaimer, disclaimant does not disclaim the terminal part of any reissue certificate granted on the instant patent being reexamined that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. Sections 154 to 156 and 173 of any patent granted on the application forming the basis of the double patenting rejection, namely, any patent granted on Application No.: ___/ _____, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. Section 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to expiration of its full statutory term as presently shortened by any terminal disclaimer, except for the separation of legal title stated above.

DISCLAIMER FEE (37 C.F.R. Section 1.20(d))

[ ] Other than a small entity--fee $110.00

[ ] Small entity--fee $55.00

[ ] Small entity statement attached
[ ] Small entity statement already filed
[ ] in patent application __/ _____ on

(date)

OR

(Provisional Obviousness-Type Double Patenting Rejection Over A Prior Patent--Reexamination Proceeding)

Petitioner hereby disclaims, except as provided below, the terminal part of the patent being reexamined, which would extend beyond the expiration date of Patent No. _____ as presently shortened by any terminal disclaimer. Petitioner hereby agrees that the patent for which a reexamination certificate is issued as a result of this proceeding shall be enforceable only for and during such period that it and the above listed patent granted are commonly owned. This agreement runs with any reexamination certificate issued on the instant patent and is binding upon the grantee, its successors, or assigns.

In making the above disclaimer, disclaimant does not disclaim the terminal part of any reexamination certificate granted on the instant patent that would extend to the expiration date of the full statutory term as defined in 35 U.S.C..Sections 154 to 156 and 173 of the patent forming the basis of the double patenting rejection, namely, Patent No.: _____, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. Section 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to expiration of its full statutory term as presently shortened by any terminal disclaimer, except for the separation of legal title stated above.

DISCLAIMER FEE (37 C.F.R. Section 1.20(d))

[ ] Other than a small entity--fee $110.00

[ ] Small entity--fee $55.00

[ ] Small entity statement attached
[ ] Small entity statement already filed
[ ] in patent application __/_____ on
(date)

FEE PAYMENT

[X] Attached is a check in the sum of $ 110.00.

[X] Charge Account 04-1105 for any fee deficiency.

[ ] Charge Deposit Account _____ the sum of $_____.
A duplicate of this disclaimer is attached.

Signature of disclaimant

Date: 11-3-03

SIGNATURE OF PRACTITIONER

Reg. No.: 38,256

Christine C. O'Day (Reg. No.: 38,256)
EDWARDS & ANGELL, LLP
P.O. Box 9169
Boston, MA 02209
Tel. (617) 439-4444

Customer No.: 21874

EXHIBIT D

10/130214
06-23-05
6858,650
copy

Application No. (if known): 10/130,214 Attorney Docket No.: 58827 (45107)

Certificate of Express Mailing Under 37 CFR 1.10

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail, Airbill No. EV654384971US in an envelope addressed to:

Attn: Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

on June 21, 2005
Date

Certificate
JUN 30 2005
of Correction

Judy Daley
Signature

Judy Daley
Typed or printed name of person signing Certificate

Registration Number, if applicable

(617) 439-4444
Telephone Number

Note: Each paper must have its own certificate of mailing, or this certificate must identify each submitted paper.

Certificate of Correction
Request for Certificate of Correction
Transmittal Letter

JUL 06 2005

Docket No.: 58827(45107)
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Claus Meese

US Patent No. 6,858,650

Issued: February 22, 2005

Application No.: 10/130,214 Group Art Unit: 1624

Filed: May 14, 2002 Examiner: R. L. Raymond

For: STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

TRANSMITTAL LETTER

Attention: Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Enclosed are the following items for filing in connection with the above-referenced Patent Application:

1. Request for Certificate of Correction; and

2. Certificate of Correction.

495617

JUL 0 6 2005

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. 58827(45107). A duplicate copy of this paper is enclosed.

Dated: June 21, 2005

Respectfully submitted,

By _____

Christine C. O'Day
Registration No.: 38,256
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 439-4444
Attorneys/Agents For Applicant

Attorney Docket No. 58827 (45107)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Claus Meese		
U.S.P.N.:	US 6,858,650	**ISSUED:**	February 22, 2005
U.S.S.N.:	10/130,214	**FILED:**	May 14, 2002
GROUP ART UNIT:	1624	**EXAMINER:**	R. L. Raymond
FOR:	STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES		

Attention: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION OF PATENT FOR PTO MISTAKE (37 C.F.R. SECTION 1.322(a))

Attached, in duplicate, is PTO/SB/44 (also Form PTO-1050), with at least one copy being suitable for printing.

NOTE: Form PTO—1050 (or PTO/SB/44), using the column and line number in the printed patent, should be used exclusively regardless of the length or complexity of the subject matter. M.P.E.P. section 1485, 7th ed.

NOTE: The patent grant should be retained by the patentee. The PTO does not attach the certificate of correction to the patentee's copy of the patent. The patent grant will be returned to the patentee if submitted. M.P.E.P. section 1485, 7th ed.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 1, line 17

Please correct:

" prodrugn"

to

—prodrugs--

Explanation of PTO error, and description of documentary support:

The recitation of "prodrugn" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 1, line 9.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 1, line 26

Please correct:

" 3,3-diphenylpropylarines "

to

-- 3,3-diphenylpropylamines --

Explanation of PTO error, and description of documentary support:

The recitation of "3,3-diphenylpropylarines" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 1, line 19.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 3, line 50

Please correct:

"and X "

to

-- and X$^-$ --

Explanation of PTO error, and description of documentary support:

The recitation of "and X" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 6, line 19.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 4, line 45-46

Please correct:

" are that "

to

-- are manufactured in that --

Explanation of application error, and description of documentary support:

The recitation of "are that" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 8, line 4-5.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 5, line 24

Please correct:

" with agent "

to

-- with a reducing agent --

Explanation of application error, and description of documentary support:

The recitation of "with agent" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 9, line 2-3.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 13, line 14

Please correct:

" photometer. model "

to

– photometer model --

Explanation of application error, and description of documentary support:

The recitation of "photometer. model" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 22, line 9-10.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 13, line 64

Please correct:

" 43.63 "

to

– 43.83 --

Explanation of application error, and description of documentary support:

The recitation of "43.63" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 24, line 1.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 15, line 37

Please correct:

" amorphous. solid "

to

– amorphous solid --

Explanation of application error, and description of documentary support:

The recitation of "amorphous. solid" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 27, line 10-11.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 16, line 37

Please correct:

" 125:59 "

to

– 125.59 --

Explanation of application error, and description of documentary support:

The recitation of "125:59" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 29, line 19.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 17, line 6

Please correct:

" $[I]_D^{20=+6.0}$ "

to

– $[I]_D^{20} = +6.0$ --

Explanation of application error, and description of documentary support:

The recitation of "$[I]_D^{20=+6.0}$" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 30, line 20.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 17, line 23

Please correct:

" Ms "

to

-- MS --

Explanation of application error, and description of documentary support:

The recitation of "Ms" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 31, line 11.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 23, line 13

Please correct:

" =14.6 "

to

-- = +14.6 --

Explanation of application error, and description of documentary support:

The recitation of "=14.6" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 44, line 19.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 23, line 47; column 24, line 15; column 24, line 21; column 28, line 35; column 28, line 38; column 28, line 41; column 28, line 45; column 28, line 53; column 28, line 58

Please correct:

" claims "

to

-- claim --

Explanation of application error, and description of documentary support:

The recitation of "claims" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the amendment filed November 3, 2003.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 24, line 46; column 30; line 17

Please correct:

" physicologically "

to

-- physiologically --

Explanation of application error, and description of documentary support:

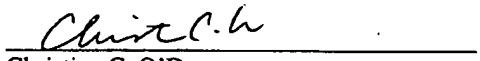
The recitation of "physicologically" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the amendment filed November 3, 2003.

NOTE: This information should be identified in this request, however, on Form PTO—1050, only the column and line number in the printed patent should be used. M.P.E.P. section 1485, 7th ed.

4. Please send the Certificate to:

Christine C. O'Day
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, MA 02205

Respectfully submitted,



Christine C. O'Day
Reg. No.: 38,256
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, Massachusetts 02205
Tel.: 617-439-4444
Fax: 617-439-4170
E-mail: coday@EdwardsAngell.com
Customer No.: 21874

Date: June 21, 2005

JUL 0 6 2005

PTO/SB/44 (04-04)
Approved for use through 04/30/2007. OMB 0651-0033
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,858,650

DATED : February 22, 2005

INVENTOR(S) : Claus Meese

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1, line 17

Please correct:

" prodrugn"

to

–prodrugs–

Column 1, line 26

Please correct:

" 3,3-diphenylpropylarines "

to

-- 3,3-diphenylpropylamines –

MAILING ADDRESS OF SENDER:
Christine C. O'Day
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, Massachusetts 02205

PATENT NO. 6,858,650

JUL 0 6 2005

PTO/SB/44 (04-04)
Approved for use through 04/30/2007. OMB 0651-0033
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.
(Also Form PTO-1050)

Column 3, line 50

Please correct:

"and X "

to

-- and X--

Column 4, line 45-46

Please correct:

" are that "

to

-- are manufactured in that --

Column 5, line 24

Please correct:

" with agent "

to

-- with a reducing agent --

Column 13, line 14

Please correct:

" photometer. model "

to

-- photometer model --

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P.O. Box 55874
Boston, Massachusetts 02205

PATENT NO. 6,858,650

JUL 0 6 2005

PTO/SB/44 (04-04)
Approved for use through 04/30/2007. OMB 0651-0033
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.
(Also Form PTO-1050)

Column 13, line 64

Please correct:

" 43.63 "

to

-- 43.83 --

Column 15, line 37

Please correct:

" amorphous. solid "

to

-- amorphous solid --

Column 16, line 37

Please correct:

" 125:59 "

to

-- 125.59 --

Column 17, line 6

Please correct:

" $[l]_D^{20=+6.0}$ "

to

-- $[l]_D^{20} = +6.0$ --

MAILING ADDRESS OF SENDER:
Christine C. O'Day
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, Massachusetts 02205

PATENT NO. 6,858,650

JUL 0 6 2005

PTO/SB/44 (04-04)
Approved for use through 04/30/2007. OMB 0651-0033
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

Column 17, line 23

Please correct:

" Ms "

to

-- MS --

Column 23, line 13

Please correct:

" =14.6 "

to

-- = +14.6 --

Column 23, line 47; column 24, line 15; column 24, line 21; column 28, line 35; column 28, line 38; column 28, line 41; column 28, line 45; column 28, line 53; column 28, line 58

Please correct:

" claims "

to

-- claim --

MAILING ADDRESS OF SENDER:
Christine C. O'Day
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, Massachusetts 02205

PATENT NO. 6,858,650

JUL 0 6 2005

PTO/SB/44 (04-04)
Approved for use through 04/30/2007. OMB 0651-0033
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

Column 24, line 46; column 30; line 17

Please correct:

" physicologically "

to

-- physiologically --

MAILING ADDRESS OF SENDER:
Christine C. O'Day
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, Massachusetts 02205

PATENT NO. 6,858,650

JUL 0 6 2005

EXHIBIT E

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY REVIEW PERIOD FOR TOVIAZ™ (FESOTERODINE FUMARATE)

Date	Activity	Comments
11/09/2001	Letter from FDA	IND No. 51,232 assigned.
11/20/2001	Telephone call to FDA	Clarification of IND number used in November 9, 2001 correspondence.
02/05/2002	Letter to FDA	Request to inactivate IND and obtain pre-IND recommendations on species and dosage selections.
02/11/2002	Letter from FDA	Acknowledgement of IND submission.
02/28/2002	Telephone call to FDA	Inquiry about progress of CAC review.
03/12/2002	Letter to FDA	Request under 21 C.F.R. §312.45 for reinstatement of IND 51,232. Submission of protocol numbers SP560, SP562, SP565, SP566, SP570, SP649, SP577.
03/14/2002	Facsimile from FDA	Response to Carcinogenicity Protocol Assessment Request re: Final CAC Report.
03/22/2002	Letter to FDA	Request for feedback on dose-reduction request in mice due to progressive mortality.
03/25/2002	Telephone call from FDA	FDA CAC response to March 22, 2002 letter.
03/25/2002	Letter from FDA	FDA letter regarding intent to reactivate IND.
04/03/2002	Telephone call from FDA	Request for information from Medical Reviewer.
04/05/2002	Letter to FDA	Response to FDA re: QTc intervals, ECG summary, and summary of QTc intervals from prior studies.
04/24/2002	Telephone call from FDA	Request for study design, demographic data, and treatment received at time of QTc

		assessment.
04/24/2002	Letter from FDA	FDA completion of chemistry review and comments.
05/06/2002	Letter to FDA	Submission to request for information about Protocol SP566.
06/11/2002	Letter to FDA	Initial Safety Report re: Protocol SP582.
06/12/2002	Letter to FDA	Reply to April 23, 2002 request for information.
06/13/2002	Letter to FDA	Submission of SAS datasets.
06/19/2002	Letter to FDA	Change in Protocol SP668 and new investigator.
07/01/2002	Letter to FDA	Initial Safety Report re: Protocol SP582.
07/03/2002	Letter to FDA	53-week interim report for study entitled "104-Week Carcinogenicity Study of SPM 8272 by Oral Administration to Sprague-Dawley Rats."
07/11/2002	Letter to FDA	Follow-Up Safety Report re: Protocol SP582.
07/17/2002	Letter to FDA	Change in investigator for Protocol SP668.
08/20/2002	Letter to FDA	Initial Safety Report re: Protocol SP668.
08/23/2002	Letter to FDA	Change in investigator for Protocol SP668.
08/27/2002	Facsimile from FDA	Amendment to Executive CAC minutes for March 12, 2002 meeting.
08/27/2002	Letter to FDA	Submission of ECG data from trials SP562, SP564, SP565, SP566, SP570, and SP649.
08/28/2002	Letter to FDA	Initial Safety Report re: Protocol SP668.
08/29/2002	Facsimile from FDA	Comments regarding clinical review of submission dated June 12, 2002.
09/05/2002	Letter to FDA	Amendment to Protocols SP669 and SP668.
09/13/2002	Facsimile to FDA	Submission concerning mortality in CD-1 mice carcinogenicity protocol.
09/18/2002	Letter to FDA	Change in Protocol SP668.

09/19/2002	Letter to FDA	Initial Safety Report re: Protocol SP582.
09/26/2002	Facsimile from FDA	Executive CAC amendments to minutes of March 12, 200 meeting.
09/27/2002	Letter to FDA	Change in investigator for Protocol SP668.
10/04/2002	Letter to FDA	Initial Safety Report re: Protocol SP582.
10/16/2002	Letter from FDA	Completion of pharmacology review of submissions dated March 12, 2002 and March 14, 2002.
10/23/2002	Letter to FDA	Change in investigator for Protocol SP668.
10/30/2002	Letter to FDA	Follow-up to June 11, 2002 safety report for Protocol SP582.
11/18/2002	Letter to FDA	Follow-up to September 19, 2002 safety report for Protocol SP582.
11/21/2002	Letter to FDA	Amendment to Protocol SP668.
11/22/2002	Letter to FDA	Response to FDA request for information pertaining to QTc intervals.
11/25/2002	Letter to FDA	Initial Safety Report re: Protocol SP582.
11/26/2002	Letter to FDA	Initial Safety Report re: Protocol SP668.
12/11/2002	Letter to FDA	Follow-up safety report re: Protocol SP582.
12/12/2002	Letter to FDA	Follow-up safety report re: Protocol SP582.
12/19/2002	Letter to FDA	Change in investigator for Protocol SP668.
01/07/2003	Letter to FDA	Follow-up report re: Protocol SP582.
01/22/2003	Letter to FDA	Change in investigator for Protocol SP668.
01/28/2003	Telephone call from FDA	Inquiry about QTc submission dated November 22, 2002.
02/04/2003	Letter to FDA	Change in Protocol SP668.
02/07/2003	Letter to FDA	Follow-up report re: Protocol SP582.
02/10/2003	Letter to FDA	Change in Protocol SP668.
02/13/2003	Telephone call from	Follow-up on a

	FDA	telephonic contact of January 31, 2003.
02/20/2003	Letter to FDA	Change in investigator for Protocol SP669.
02/27/2003	Letter to FDA	Request for change in emphasis of EOP2 meeting from QTc intervals to overall Phase 2 and Phase 3 protocols.
03/07/2003	Telephone call from FDA	Reply to letter of February 27, 2003 and request for teleconference.
03/13/2003	Letter to FDA	Initial Safety Report re: Protocol SP582.
03/17/2003	Letter from FDA	Acknowledgement of January 28, 2003 correspondence.
03/20/2003	Letter to FDA	Change in investigator for Protocol SP669.
03/20/2003	Letter to FDA	Follow-up Safety Report re: Protocol SP582.
03/25/2003	Letter to FDA	Confirmation of proposed April 3, 2003 teleconference to discuss QTc interval issue.
03/26/2003	Letter to FDA	Follow-up Safety Report re: Protocol SP669.
04/10/2003	Letter to FDA	Request for Type B meeting to discuss Phase 3 development.
04/15/2003	Letter to FDA	Summary of April 3, 2003 meeting minutes.
04/21/2003	Letter to FDA	Change in investigator for Protocol SP669.
04/28/2003	Facsimile to FDA	Request for reply to EOP2 submission dated April 10, 2003.
04/29/2003	Telephone call to FDA	Follow-up to April 28, 2003 request regarding EOP2 reply.
05/01/2003	Telephone call from FDA	EOP2 meeting request granted. Date to be determined.
05/01/2003	Letter to FDA	EOP2 meeting information package and proposal of meeting date.
05/05/2003	Facsimile to FDA	Confirmation of proposed June 16, 2003 meeting date.
05/09/2003	Letter from FDA	Information on scheduled Type B meeting.

05/21/2003	Letter to FDA	Change in investigator for Protocol SP669.
05/29/2003	Letter to FDA	Proposed amendments to EOP2 meeting package.
06/05/2003	Letter to FDA	Toxicology report pursuant to 37 C.F.R. §312.31.
06/05/2003	Letter to FDA	Change to Protocol SP669.
06/11/2003	Letter to FDA	Annual Report pursuant to 37 C.F.R. §312.33.
06/26/2003	Letter to FDA	Submission of Protocol SP854 for Special Protocol Assignment.
06/26/2003	Letter to FDA	Submission of Protocol SP853 for Special Protocol Assignment.
06/26/2003	Letter to FDA	Submission of Protocol SP854 for Special Protocol Assignment.
06/26/2003	Letter to FDA	Submission of Protocol SP853 for Special Protocol Assignment.
07/08/2003	Letter to FDA	Request for listing of FDA participants from June 16, 2003 EOP2 meeting.
07/14/2003	Letter to FDA	Submission of revised IB, dated June 2003.
07/16/2003	Facsimile from FDA	June 16, 2003 meeting minutes.
07/18/2003	Letter to FDA	June 16, 2003 EOP2 meeting minutes.
08/08/2003	Letter to FDA	Change to Protocol SP669.
08/14/2003	Letter from FDA	FDA comments and suggestions on proposed special protocol assessments for SP584 and SP583.
08/15/2003	Facsimile from FDA	Facsimile confirmation of August 15, 2003 letter.
08/21/2003	Letter to FDA	Change in investigator for Protocol SP669.
08/27/2003	Letter to FDA	Response to FDA comment recommending CYP2D6 and CYP3A4 studies.
08/28/2003	Letter to FDA	Request for comment to Item 3 of FDA letter of August 14, 2003 with comments on special protocol assessment of

		SP583 and SP584.
09/09/2003	Letter to FDA	Request for guidance on FDA comment No. 1 from special protocol assessment of August 15, 2003.
10/01/2003	Telephone call from FDA	Cancellation of proposed teleconference.
10/01/2003	Letter to FDA	Revision to protocol SP584.
10/10/2003	Letter to FDA	Submission pursuant to 21 C.F.R. §312.31 concerning revised chemistry, manufacturing, and control data, including new film-coated formulation for use in Phase 3 trials.
10/17/2003	Letter from FDA	FDA query concerning proposed criteria No. 6 in Protocols SP583 and SP584.
10/17/2003	Letter to FDA	Request for FDA comment on QTc trial discussed during June 16, 2003 EOP2 meeting and agreement that no cardiovascular studies are needed.
10/22/2003	Letter to FDA	Change in investigator for Protocol SP584.
10/29/2003	Telephone call to FDA	Status advisory of thorough QT study review serial 65.
11/12/2003	Telephone call from FDA	Request for teleconference.
11/20/2003	Letter to FDA	Change in investigator for Protocol SP584.
12/05/2003	Facsimile to FDA	Current list of attendees for scheduled December 10, 2003 teleconference.
12/18/2003	Letter to FDA	Change in investigator for Protocol SP584.
12/22/2003	Letter to FDA	Change in Protocol SP669.
01/09/2004	Facsimile from FDA	December 10, 2003 teleconference meeting minutes.
		Submission of reports requested by FDA in June 16, 2003 EOP2 meeting

01/09/2004	Letter to FDA	and justification for 2mg dose utilizing linear regression analysis and plan for populating pharmacokinetic analysis.
01/16/2004	Facsimile from FDA	Amendment to December 10, 2003 teleconference minutes.
01/20/2004	Letter to FDA	Change in investigator for Protocol SP584.
02/10/2004	Letter to FDA	Submission of information for selection of supratherapeutic dose and short report on SP569 in response to December 10, 2003 teleconference.
02/11/2004	Email to FDA	Question for CMC reviewer.
02/12/2004	Email from FDA	FDA response to question for CMC reviewer.
02/17/2004	Letter to FDA	Request for FDA comment on format of CMC amendment.
02/19/2004	Letter to FDA	Change in investigators for Protocol SP584.
03/18/2004	Letter to FDA	Changes in investigators for Protocol SP584 and SP669.
03/25/2004	Letter to FDA	Initial safety report Protocol SP584.
03/30/2004	Letter to FDA	New Protocol SP739.
03/31/2004	Email to FDA	Notification of error in title of last submission.
03/31/2004	Letter to FDA	Correction to title of new protocol SP739.
04/06/2004	Letter to FDA	Response to outstanding issues from December 10, 2003 teleconference and final protocol for QT trial.
04/12/2004	Letter to FDA	Follow-up safety report for Protocol SP584.
04/15/2004	Letter to FDA	Revised CMC data including updated stability information, revised specs and working regulations for DS and DP modification

		synthesis of DS and DP formulation.
04/20/2004	Letter to FDA	Change in investigators for Protocols SP584, SP669, and SP739.
04/30/2004	Letter to FDA	Submission under 21 C.F.R. §312.31 of new pharmacology, toxicology, and ADME reports.
05/05/2004	Letter to FDA	Change in Protocol SP584.
05/12/2004	Letter to FDA	Request for EOP2 (Type B) meeting to discuss CMC adequacy for Phase 3 trials and support of NDA.
05/14/2005	Letter to FDA	Request for status of review for QT protocol: justification for supratherapeutic dose selection, minimal dose of 2 mg and population analysis plan.
05/20/2004	Letter to FDA	Change in investigators for Protocols SP584, SP669, and SP739.
05/27/2004	Telephone call from FDA	Response to request for EOP2 CMC meeting.
05/27/2004	Letter from FDA	Confirmation of requested Type B meeting for July 13, 2004.
06/02/2004	Letter to FDA	Update on plans regarding Serial No. 79 (QTc protocol).
06/07/2004	Letter to FDA	Package for July 13, 204 EOP2 meeting.
06/08/2004	Letter to FDA	Clinical trial report submission pursuant to 21 C.F.R. §312.31 for Protocol SP677.
06/11/2004	Letter to FDA	Annual report pursuant to 21 C.F.R. §312.33.
06/15/2004	Telephone call from FDA	Request for teleconference to discuss QTc protocol and responses.
06/21/2004	Letter to FDA	Change in investigators for Protocols SP584 and SP739.
06/25/2004	Letter to FDA	Format correction to EOP2 CMC meeting package.

06/28/2004	Letter to FDA	Initial safety report for Protocol SP583.
07/01/2004	Letter to FDA	Initial safety report for Protocol SP583.
07/14/2004	Letter to FDA	Initial safety report for Protocol SP583.
07/20/2004	Letter to FDA	Change in investigators for Protocols SP584, and SP739.
07/20/2004	Letter to FDA	Initial safety report for Protocol SP583.
07/21/2004	Letter to FDA	Follow-up safety report for Protocol SP583.
07/29/2004	Letter to FDA	Follow-up safety report for Protocol SP583.
08/09/2004	Letter to FDA	Follow-up safety report for Protocol SP583.
08/10/2004	Letter to FDA	Meeting minutes from July 14, 2004 teleconference regarding QTc Protocol SP686.
08/19/2004	Letter to FDA	Submission pursuant to 21 C.F.R. §312.31 for Protocols SP560 and SP562.
09/26/2004	Facsimile to FDA	Minutes for EOP2 meeting of July 13, 2004.
08/26/2004	Letter to FDA	7-day initial safety report for Protocol SP583.
08/26/2004	Letter to FDA	Minutes for EOP2 meeting of July 13, 2004.
08/26/2004	Letter to FDA	Initial safety report for Protocol SP584.
09/01/2004	Letter to FDA	Follow-up safety report for Protocol SP583.
09/03/2004	Letter to FDA	Minutes for EOP2 meeting of July 13, 2004 and July 14, 2004 guidance meeting.
09/17/2004	Letter to FDA	Change in investigator for Protocol SP739.
09/21/2004	Letter to FDA	Follow-up safety report for Protocol SP583.
09/28/2004	Letter to FDA	Minutes from July 14, 2004 teleconference regarding QTc Protocol SP686.
10/04/2004	Letter to FDA	Changes to minutes of July 13, 2004 EOP2 meeting.
		Clinical trial report

10/05/2004	Letter to FDA	submission pursuant to 21 C.F.R. §312.31 for Protocols SP564, SP649, and SP677.
10/06/2004	Facsimile to FDA	Submission of meeting minutes not yet delivered by UPS.
10/12/2004	Letter to FDA	Initial safety report for Protocol SP739.
10/19/2004	Letter to FDA	Changes in investigators for Protocols SP584 and SP739.
10/28/2004	Letter to FDA	Initial safety report for Protocols SP583 and SP669.
10/28/2004	Letter to FDA	Follow-up safety report for Protocol SP739.
10/29/2004	Facsimile to FDA	Facsimile copy of Initial Safety Report 200400629.
11/16/2004	Letter to FDA	Initial safety report for Protocol SP583.
11/16/2004	Letter to FDA	Follow-up safety report for Protocols SP583 and SP584.
11/23/2004	Letter to FDA	Follow-up safety report for Protocols SP583.
12/13/2004	Letter to FDA	Submission of questions regarding pediatric waiver rule prior to submission of pediatric waiver request.
12/17/2004	Letter to FDA	Initial safety report for Protocols SP583 and SP669.
12/20/2004	Letter to FDA	Change in investigators for Protocol SP739.
12/21/2004	Letter to FDA	Follow-up safety report for Protocol SP583.
01/03/2005	Letter to FDA	Follow-up safety report for Protocol SP669.
01/06/2005	Letter to FDA	Follow-up safety report for Protocol SP584 and SP738.
01/19/2005	Letter to FDA	Follow-up safety report for Protocol SP669.
01/20/2005	Facsimile to FDA	Facsimile transmission of Safety Report 200400209.
01/20/2005	Letter to FDA	7-day initial safety report for Protocol SP583.

01/26/2005	Letter to FDA	Follow-up safety report for Protocols SP583 and SP669.
02/01/2005	Letter to FDA	Initial safety report for Protocol SP739.
02/07/2005	Letter to FDA	Follow-up safety report for Protocol SP669.
02/10/2005	Letter to FDA	Request for FDA comment on proposal to encode all Aes data in pooled sets using MedDRA and no recode or pool AE data Phase 1 studies that used WHO-ART.
02/14/2005	Letter to FDA	Request for FDA comment on proposal to provide ISE and ISS in CTD Section 5.3.5.3.
02/15/2005	Letter to FDA	Follow-up safety report for Protocol SP739.
02/18/2005	Letter to FDA	Follow-up safety report for Protocol SP669.
02/22/2005	Letter to FDA	Initial safety report for Protocol SP739.
02/25/2005	Letter to FDA	Request for DMETS review for two possible trade names prior to NDA submission.
02/28/2005	Telephone call from FDA	Message concerning IND Serial Nos. 132 and 133 regarding plans for encoding of AEs in NDA.
02/28/2005	Letter to FDA	Submission pursuant to 21 C.F.R. §312.31 of new pharmacology, toxicology, and ADME reports.
03/02/2005	Telephone call from FDA	Discussion of Serial No. 0137 re: request for trade name review.
03/02/2005	Letter to FDA	Request for DMETS review for two possible trade names prior to NDA submission with correct attachments.
03/07/2005	Letter to FDA	Follow-up safety report for Protocol SP739.
03/23/2005	Letter to FDA	Initial safety report for Protocol SP738.
04/06/2005	Letter to FDA	Follow-up safety report for Protocol SP738.
		Submission pursuant to 21 C.F.R. §312.31 of

04/08/2005	Letter to FDA	biopharmaceutic and human pharmacokinetic study reports.
04/15/2005	Letter to FDA	Follow-up safety report for Protocol SP584.
04/18/2005	Letter to FDA	Follow-up safety report for Protocol SP738.
04/19/2005	Letter to FDA	Change in investigators for Protocol SP584.
04/21/2005	Letter to FDA	Follow-up safety report for Protocol SP583.
04/27/2005	Telephone call to FDA	Discussion of latest target submission date for NDA.
04/27/2005	Letter to FDA	Submission pursuant to 21 C.F.R. §312.31 for Protocols SP565, SP567, SP568, and SP569.
05/02/2005	Letter to FDA	Initial safety report for Protocol SP738.
05/05/2005	Letter to FDA	Submission pursuant to 21 C.F.R. §312.31 for Protocol SP684.
05/12/2005	Letter to FDA	Request for Type B meeting to discuss proposed NDA filing, unresolved problems, pivotal trials, deferral of pediatric trials and general information.
05/17/2005	Letter to FDA	Follow-up safety report for Protocol SP738.
05/19/2005	Letter to FDA	Submission of pre-NDA meeting package.
05/19/2005	Letter to FDA	Change in investigators for Protocol SP668.
05/27/2005	Letter to FDA	7-day initial safety report for Protocol SP738.
06/01/2005	Letter to FDA	Submission of table of contents for mock shells for safety and efficacy missing from May 19, 2005 meeting package.
06/06/2005	Letter to FDA	Annual Report pursuant to 21 C.F.R. §312.33.
06/15/2005	Letter to FDA	Revised CMC data, including DS and DP specifications, analytical methods, and stability data.
06/16/2005	Letter to FDA	Follow-up safety report for Protocol SP738.

06/29/2005	Letter to FDA	Submission of SP561 clinical trial report pursuant to 21 C.F.R. §312.31.
07/07/2005	Letter to FDA	Submission of analytical Report No. 646-03 pursuant to 21 C.F.R. §312.31.
07/20/2005	Letter to FDA	Change in investigators for Protocol SP584.
07/20/2005	Letter to FDA	Change in investigators for Protocol SP584.
07/20/2005	Letter to FDA	Submission of MeDRA Version 7.0 codes for dry eyes.
07/22/2005	Letter to FDA	Minutes from July 18, 2005 pre-NDA meeting.
08/02/2005	Letter to FDA	Request for FDA review of proposed plans for submission of NDA datasets.
08/04/2005	Letter to FDA	Request for FDA concurrence with plans to code "dry eyes" as "Keratoconjunctivitis sicca" in CTRs.
08/10/2005	Letter to FDA	Initial safety report for Protocol SB738.
08/11/2005	Letter to FDA	Submission pursuant to 21 C.F.R. §312.31 of 104-week carcinogenicity study.
08/15/2005	Facsimile from FDA	Minutes from July 15, 2005 pre-NDA meeting.
08/15/2005	Letter to FDA	Minutes of August 9, 2005 teleconference regarding ophthalmology consult on Question 15 of pre-NDA
08/16/2005	Letter to FDA	Follow-up safety report for Protocol SP738.
08/17/2005	Letter to FDA	Request for feedback on experimental design of eye histology study in response to discussion of Question 15 from pre-NDA meeting package.
08/19/2005	Letter to FDA	Change in investigators for Protocol SP584, SP669, and SP739.
08/22/2005	Letter to FDA	Submission pursuant to 21 C.F.R. §312.31 of pharmacology and

		toxicology information.
08/23/2005	Letter to FDA	Follow-up safety report for Protocol SP738.
08/29/2005	Telephone call to FDA	Discussion of Serial Nos. 0165 and 0171.
08/29/2005	Letter to FDA	Revision to Protocol SP739.
09/06/2005	Letter to FDA	Request for pre-NDA meeting.
09/06/2005	Letter to FDA	Request for pre-NDA (Type B) CMC meeting.
09/09/2005	Telephone call to FDA	Inquiry about status of pre-NDA CMC meeting request.
09/09/2005	Facsimile to FDA	Withdrawal of Serial No. 0176 meeting request.
09/09/2005	Letter to FDA	Withdrawal of Serial No. 0176 meeting request.
09/14/2005	Letter to FDA	Revision to Protocol SP669.
09/15/2005	Letter to FDA	Submission pursuant to 21 C.F.R. §312.31 of pharmacology and toxicology information.
09/20/2005	Letter to FDA	Request for pre-NDA meeting to discuss drug manufacturing modifications.
09/21/2005	Telephone call to FDA	Follow-up on FDA responses and proposal on how to handle time lag from client cutoff date to new NDA submission date.
09/23/2005	Telephone call from FDA	Response to September 21, 2005 contact.
09/23/2005	Telephone call to FDA	Follow-up on previous call and September 21, 2005 contact.
10/03/2005	Letter to FDA	Request for teleconference to discuss acceptance and understanding of clinical trial datasets and NDA safety cutoff date.
10/05/2005	Letter from FDA	Confirmation of Type B meeting request. Scheduled for November 22, 2005.
10/05/2005	Letter to FDA	Revision to Protocol SP582.
10/06/2005	Letter from FDA	Confirmation of Type B

		meeting request.
10/11/2005	Letter to FDA	Pre-NDA CMC meeting package.
10/12/2005	Letter to FDA	Revision to Protocol SP686.
10/14/2005	Telephone call to FDA	Follow-up on outstanding matters.
10/17/2005	Letter from FDA	Completion of review of Serial No. 165 submission, with comments.
10/18/2005	Letter to FDA	Revision of Protocol SP683 and SP668.
10/19/2005	Facsimile from FDA	Completion of review of Serial No. 65 submission, with comments.
10/19/2005	Telephone call to FDA	Follow-up following receipt of reply to Serial No. 165 re: clinical trial datasets.
10/27/2005	Telephone call to FDA	Follow-up on outstanding matters.
11/09/2005	Telephone call to FDA	Follow-up on outstanding matters.
11/10/2005	Letter to FDA	Notification of new sponsor address and fax.
11/14/2005	Letter to FDA	Submission of clinical trial report for Protocol SP842.
11/18/2005	Facsimile from FDA	Preliminary draft comments for November 22, 2005 pre-NDA meeting.
11/18/2005	Facsimile from FDA	Preliminary draft comments for November 22, 2005 pre-NDA meeting.
11/18/2005	Facsimile to FDA	Cancellation of November 22, 2005 pre-NDA meeting.
11/18/2005	Facsimile from FDA	November 27, 2005 teleconference memo.
11/18/2005	Letter to FDA	Formal request to cancel November 22, 2005 meeting.
11/23/2005	Letter from FDA	Review of amendment Serial No. 171, with comments.
11/29/2005	Letter from FDA	Acknowledgement of November 10, 2005 notification of address change.

12/06/2005	Letter to FDA	Request for review and comment on proposed new drug product.
12/06/2005	Letter to FDA	Initial safety report for Protocol SP583.
12/08/2005	Letter to FDA	Clinical trial report for Protocols SP583 and SP584
12/12/2005	Letter to FDA	Submission pursuant to 21 C.F.R. §312.31 of pharmacology and toxicology information.
12/23/2005	Letter from FDA	Comments on request to review two trade names.
12/28/2005	Letter to FDA	Initial safety report for Protocol SP583.
01/16/2006	Letter to FDA	Submission pursuant to 21 C.F.R. §312.31 of pharmacokinetic, and toxicology, and ADME information.
01/30/2006	Letter from FDA	Comments on submission Serial No. 189.
01/31/2005	Letter to FDA	Submission pursuant to 21 C.F.R. §312.31 of revised chemistry, manufacturing, and control data.
02/01/2006	Letter to FDA	Submission pursuant to 21 C.F.R. §312.31 of ADME information.
02/08/2006	Letter to FDA	Initial safety report for Protocol SP738.
02/14/2006	Letter to FDA	Initial safety report for Protocol SP738.
03/01/2006	Letter to FDA	User Fee ID Notification
03/14/2006	Letter to FDA	Submission pursuant to 21 C.F.R. §312.31 of toxicology information.
03/17/2006	Letter to FDA	Initial Submission, NDA 22-030.
03/29/2006	Letter to FDA	7-day initial safety report for Protocol SP739.
04/12/2006	Telephone call from FDA	Verification that Schwarz Pharma Ltd., Shannon, Ireland is same facility as Sifa Ltd.
04/17/2006	Letter from FDA	Receipt of NDA.
04/20/2006	Telephone call from FDA	Request for location of NDA information.
		Change in investigator

04/20/2006	Letter to FDA	for Protocol SP669.
04/27/2006	Telephone call from FDA	Request for assistance in navigating CTD.
05/03/2006	Letter to FDA	Notification of change in pre-approval inspection readiness of API manufacturing.
05/11/2006	Email to FDA	Answer to agency request regarding CMC.
05/12/2006	Email to FDA	Communication of dissolution media information.
05/15/2006	Email from FDA	Recommendation for change in CMC study.
05/15/2006	Telephone call to FDA	Teleconference to discuss email regarding CMC testing.
05/15/2006	Letter to FDA	Update on PAI readiness.
05/17/2006	Letter to FDA	Written summary of May 15, 2006 teleconference concerning manufacturing inspection readiness.
05/22/2006	Telephone call from FDA	Request for further information following May 17, 2006 submission.
05/22/2006	Telephone call from FDA	Request for acceptability of PAI dates.
05/22/2006	Letter to FDA	Submission of revised IB, dated April 2006.
05/23/2006	Facsimile to FDA	Acceptance of proposed PAI date.
05/23/2006	Letter to FDA	Notification of September 27, 2006 PAI date.
05/23/2006	Telephone call to FDA	Confirmation of PAI date.
05/23/2006	Letter to FDA	Commitment to PAI date.
05/30/2006	Telephone call from FDA	Carcinogenicity data filed.
05/30/2006	Telephone call to FDA	Teleconference to discuss questions from carcinogenicity statistical reviewer.
05/31/2006	Letter to FDA	Submission of carciogenicity SAS transport datasets.
06/05/2006	Telephone call from FDA	Confirmation of receipt of SAS data transport sets and request for telephone numbers of clinical sites.

06/08/2006	Letter to FDA	Initial safety report for Protocol SP739.
06/08/2006	Letter to FDA	Annual Report pursuant to 21 C.F.R. §312.33.
06/09/2006	Letter to FDA	Initial safety report for Protocol SP739.
06/09/2006	Letter from FDA	Substantive filing review, with identification of clinical, pharmacological, and chemical issues.
06/12/2006	Facsimile from FDA	Communication summarizing issues of PAI readiness submission of May 15, 2006.
06/12/2006	Letter from FDA	Request for telephone numbers for Sites 156 and 075.
06/20/2006	Letter to FDA	Change in investigators for Protocols SP669 and SP739.
06/22/2006	Letter to FDA	Follow-up safety report for Protocol SP739.
06/27/2006	Letter to FDA	Follow-up safety report for Protocol SP739.
06/27/2006	Email to FDA	Advisory of plan to make Life Cycle submission to NDA.
06/27/2006	Facsimile from FDA	May 11, 2006 teleconference minutes.
06/27/2006	Facsimile from FDA	May 15, 2006 teleconference minutes.
06/27/2006	Facsimile from FDA	Further comment on May 22, 2006 teleconference.
06/27/2006	Letter to FDA	SAS datasets with samples from Phase I trials.
07/06/2006	Email to FDA	Request for finalization of scheduled site inspection visits.
07/12/2006	Facsimile from FDA	May 15, 2006 teleconference minutes.
07/13/2006	Email to FDA	Submission of dissolution profiles.
07/14/2006	Telephone call from FDA	Details concerning site inspection visits.
07/18/2006	Telephone call to FDA	Clarification on data request for narratives.
07/19/2006	Letter to FDA	Follow-up safety report for Protocol SP739.
		Change in investigators

07/20/2006	Letter to FDA	for Protocols SP669 and SP739.
07/20/2006	Telephone call to FDA	Notification of PAI status.
07/20/2006	Letter to FDA	Status of API readiness and Type A Meeting request.
07/21/2006	Letter to FDA	120-Day Safety update from trials SP669, SP738, and SP739.
07/21/2006	Letter to FDA	Response to request for investigator information for Trials SP583 and SP584.
07/27/2006	Telephone call to FDA	PAI meeting information.
07/27/2006	Email to FDA	Response to investigator information.
07/27/2006	Letter to FDA	Submission of information requested in July 14, 2006 teleconference concerning site visits.
07/28/2006	Letter from FDA	Acknowledgement of request for Type A meeting.
08/03/2006	Letter to FDA	Response to 74-day letter from FDA, re: CMC and pharmacology questions.
08/09/2006	Letter to FDA	Update to eCTD.
08/15/2006	Letter to FDA	Submission pursuant to 21 C.F.R. §312.31 of clinical trial report for Protocol SP857.
08/17/2006	Letter to FDA	Follow-up safety report for Protocol SP739.
08/21/2006	Letter to FDA	Change in investigators for Protocols SP669 and SP739.
08/26/2006	Letter to FDA	7-day initial safety report for Protocol SP583.
08/31/2006	Letter to FDA	Proposed questions for discussion and background prior to October 4, 2006 teleconference.
09/20/2006	Letter to FDA	7-day initial safety report for Protocol SP583.
09/22/2006	Email from FDA	Query about whether final report was

		included in last Life Cycle submission.
09/25/2006	Letter to FDA	Summary of results from clinical trial SP877.
09/29/2006	Email from FDA	Draft of preliminary comments for October 4, 2006 teleconference.
10/02/1006	Telephone call from FDA	Discuss FDA preliminary draft comments to October 4, 2006 teleconference and cancellation for meeting.
10/03/2006	Letter to FDA	Formal request for cancellation of Type C meeting.
10/06/2006	Letter to FDA	Request for review of proposed trade name "RENUAC™."
10/20/2006	Letter to FDA	Change in investigator for Protocol SP669.
10/23/2006	Letter to FDA	Mfg. Report No.: 000#5#2006-0417.
10/25/2006	Letter to FDA	Submission pursuant to 21 C.F.R. §312.31 of ADME information.
10/25/2006	Telephone call to FDA	NDA review discussion.
10/27/2006	Letter to FDA	74-day Letter response.
11/01/2006	Letter to FDA	74-day Letter to clinical request 3 and clinical trial report SP877.
11/16/2006	Letter to FDA	Submission of 12-month stability update in support of 24-month expiry date.
11/20/2006	Letter to FDA	Change in investigators for Protocol SP739.
11/22/2006	Letter to FDA	Submission of new and replacement carton and container labels for RENUAC™ extended release tablets.
12/13/2006	Letter to FDA	Authorization for FDA to accept, access, and retrieve information to/from Schwarz' fesoterodine IND on behalf of Pfizer Inc.
12/18/2006	Letter from FDA	Comments after review of CMC section of March 17, 2006 submission.

12/19/2006	Letter to FDA	Change in investigator for Protocol SP739.
12/21/2006	Letter to FDA	Submission of proposed Study Protocol A0221007 and CMC information.
12/27/2006	Email to FDA	Submission of trade name information.
01/04/2007	Letter to FDA	Mfg. Report No.: 000#5#2006-00509.
01/10/2007	Letter from FDA	FDA conclusion that Schwarz has adhered to applicable statutory requirements and FDA regulations governing conduct of investigations and protection of human subjects.
01/11/2007	Letter to FDA	Response to FDA request for information and revised package inserts.
01/12/2007	Letter to FDA	Submission pursuant to 21 C.F.R. §312.20 of new protocols A0221004 and A0221008.
01/17/2007	Email from FDA	CMC comments regarding labeling.
01/18/2007	Email to FDA	US labeling and graphic questions from Pfizer Inc., forwarded to FDA from Schwarz.
01/19/2007	Letter to FDA	Change in investigator for Protocol SP739.
01/24/2007	Telephone call to FDA	Submission of draft label information.
01/24/2007	Email from FDA	FDA revisions to labeling.
01/24/2007	Letter to FDA	Response to revised labeling provided by FDA.
01/25/2007	Letter to FDA	Follow-up safety report for Protocol SP738.
01/25/2007	Facsimile from FDA	Approvable action letter.
01/25/2007	Letter from FDA	Approvable action letter.
01/30/2007	Letter to FDA	Submission under 21 C.F.R. §314.110 of intent to file NDA amendment.
01/31/2007	Letter from FDA	Tentative acceptance of trade name "RENUAC™" and request for revisions to

		carton labeling.
02/05/2007	Letter to FDA	Amendment to Protocol A0221007-1001.
02/20/2007	Letter to FDA	Change in investigator for Protocol SP739.
02/27/2007	Letter to FDA	Change in investigators for Protocol A0221007.
03/01/2007	Letter to FDA	Submission under 21 C.F.R. 312.32(c) re: Mfg. Report No.: 000#5#2007-00070.
03/20/2007	Letter to FDA	Change in investigator for Protocol SP739.
03/23/2007	Letter to FDA	Change in investigator for Protocol A0221007.
03/28/2007	Letter to FDA	Submission under 21 C.F.R. 312.32(c) re: Mfg. Report No.: 000#5#2005-00274.
04/23/2007	Letter to FDA	Change in investigators for Protocol A0221007 and A00221008.
05/08/2007	Letter to FDA	Submission pursuant to 21 C.F.R. §312.31 of toxicology and ADME information.
05/16/2008	Meeting with FDA	FDA teleconference regarding PAI readiness of API manufacturer in Shannon, Ireland.
05/17/2007	Telephone call to FDA	Advisory that Dr. Robert Ryan will set up appointment to discuss response and filing of NDA.
05/18/2007	Letter to FDA	Change in investigators for Protocols SP669 and SP739.
05/22/2007	Telephone call to FDA	FDA decision following review of Schwarz submission on PAI.
05/24/2007	Letter to FDA	Change in investigators for Protocol A0221007-1011.
06/07/2007	Letter to FDA	Submission pursuant to 21 C.F.R. §312.32(c) re: Mfg. Report No.: 2007042502.
06/11/2007	Letter to FDA	Submission of Annual Report pursuant to 21 C.F.R. §312.33.
06/13/2007	Facsimile to FDA	Request for Type C meeting and information

		package.
06/13/2007	Letter to FDA	Request for Type C meeting and information package.
06/20/2007	Letter to FDA	Change in investigator for Protocol SP739.
06/20/2007	Letter to FDA	Change in investigators for Protocols A0221007 and A0221008.
06/27/2007	Letter from FDA	Acknowledgment of request for Type C meeting and schedule.
06/28/2007	Letter to FDA	Request for review of proposed trade name "TOVIAZ™."
07/03/2007	Letter from FDA	Copy of Establishment Inspection Report (EIR) for inspection conducted September 26-27, 2006.
07/03/2007	Letter from FDA	Establishment Inspection Report (EIR) for inspection conducted September 26-27, 2006.
07/18/2007	Letter to FDA	Submission pursuant to 21 C.F.R. §312.30 of new protocols A0221014 and A0221044.
07/24/2007	Facsimile to FDA	Request for attendees list and titles.
07/30/2007	Letter to FDA	Notification of change of ownership of fesoterodine NDA from Schwarz Pharma, Inc. to Pfizer, Inc.
07/31/2007	Letter to FDA	General correspondence in reference to Schwarz Pharma amendment to IND with letter dated July 30, 2007.
08/16/2007	Letter to FDA	Submission pursuant to 21 C.F.R. §§312.30 and 312.31.
08/27/2007	Letter from FDA	Notification that change of IND sponsorship from Schwarz to Pfizer is effective on August 1, 2007.
08/29/2007	Letter from FDA	Official minutes for cancelled August 27, 2007 meeting.
08/30/3007	Letter to FDA	Request for clarification to DRUP response to sponsor

		question 3 re: stability requirement.
08/31/2007	Letter to FDA	Acknowledgement of FDA authorization to transfer ownership of NDA from Schwarz Pharma to Pfizer Inc.
09/06/2007	Letter from FDA	Acknowledgement of receipt of August 31, 2007 notification of change of ownership.
09/13/2007	Letter to FDA	Amendment to protocols A0221008 and A0221014.
10/03/2007	Telephone call to FDA	Clarification questions regarding product description.
10/09/2007	Letter to FDA	Amendment to protocols A0221008 and A0221014.
10/23/2007	Letter to FDA	Amendment to protocols A0221008 and A0221014.
10/25/2007	Letter from FDA	FDA response to August 30, 2007 request for clarification of stability requirement.
11/07/2007	Letter from FDA	Obtain clarification for basis of stability requirement requesting addition of new API manufacturing site.
11/15/2007	Letter to FDA	Submission pursuant to 21 C.F.R. §312.30 of new protocol A0221046.
12/06/2007	Letter to FDA	Amendment to protocols A0221008 and A0221009.
12/10/2007	Letter to FDA	Reply to FDA October 25, 2007 letter; reply to request for structural elucidation, impurity profile, and stability data; and acceptability of proposal for addition of Ringaskiddy site.
12/18/2007	Letter to FDA	Amendment to protocols A0221008 and A0221009.
01/15/2008	Letter to FDA	Amendment to protocols A0221008, A0221009, and A0221046.
02/14/2008	Letter to FDA	Amendment to protocols A0221008, A0221009, and A0221046.
02/14/2008	Letter from FDA	Reply to December 10, 2007 inquiries.
03/14/2008	Letter to FDA	Amendment to protocol

		A0221008.
04/01/2008	Letter to FDA	Request for withdrawal of review of proposed trade name "RENUAC™."
04/08/2008	Letter to FDA	Amendment to Protocol A0221009.
05/01/2008	Letter to FDA	Complete response to FDA "Approvable Letter" of January 25, 2007.
05/08/2008	Letter to FDA	Submission of new Protocol A0221062 and amendment to Protocols A0221009 and A0221046.
05/08/2008	Email from NDA	FDA Reviewing Division request for point of contact information for all facilities in NDA.
05/09/2008	Letter to FDA	Submission of Annual Report pursuant to 21 C.F.R. §312.33.
05/12/2008	Letter from FDA	Tentative acceptance of proposed trade name "TOVIAZ™" and request for submission of container and carton labels.
05/19/2008	Letter from FDA	FDA request for formal submission confirming fesoterodine site readiness.
05/19/2008	Letter to FDA	Confirmation that manufacturing and testing facilities are ready for inspection.
05/20/2008	Letter to FDA	Submission of Safety Report No. 2008038883.
05/20/2008	Letter from FDA	Acknowledgement of May 1, 2008 resubmission of NDA.
06/05/2008	Letter to FDA	Submission of new Protocol A0221061.
06/18/2008	Letter to FDA	Method validation reports for studies A0221004, A0221015, A0221044. Method validation report and study specific bioanalytical reports of studies SP857 and SP877.
06/24/2008	Letter to FDA	Amendment to Protocol A0221061.
06/30/2008	Telephone call to	Request to file CBE-30 to include Ringaskiddy,

	FDA	Ireland as alternate API manufacturing site.
07/11/2008	Letter to FDA	Amendment to Protocols A0221009 and A0221046.
07/17/2008	Letter to FDA	Response to July 7, 2008 request for specific patient CRFs.
07/31/2008	Letter to FDA	Submission of follow-up to May 20, 2008 Safety Report No. 2008038883.
08/07/2008	Letter to FDA	Amendment to Protocols A0221008, A0221009, A0221046, and A0221061.
08/12/2008	Email to FDA	Inquire if Office of Compliance has scheduled, or will schedule, a PAI of API and product manufacturing sites listed in NDA.
08/20/2008	Letter to FDA	Submission of new Form FDA 3542a and eCTD updates.
08/26/2008	Letter to FDA	Proposal of CBE-30 post-approval supplement to include Ringaskiddy as alternate API manufacturing site.
09/04/2008	Letter to FDA	Amendment to Protocols A0221009 and A0221046.
09/10/2008	Communication to FDA	Submission of Pre-Launch Importation Request (PLAIR).
09/17/2008	Email from FDA	PLAIR approval.
09/22/2008	Letter to FDA	Amendment to Protocol A0221009.
10/07/2008	Letter to FDA	Withdrawal of labeling in Module 1: Toviaz™ bottle topper, Toviaz™ Move4ward brochure, and Toviaz™ Move4ward tracker.
10/17/2008	Letter to FDA	Amendment to Protocols A0221009 and A0221046.
10/20/2008	Letter to FDA	Submission of PI and PPI.
10/28/2008	Letter to FDA	Follow-up to May 20, 2008 Safety Report No. 2008038883 and submission of new Safety Report No. 2008086760.
10/31/2008	Letter from FDA	Marketing approval letter.

EXHIBIT I

POWER OF ATTORNEY

Schwarz Pharma AG ("Schwarz"), a corporation organized and existing under the laws of Germany, with a principal place of business at Alfred-Nobel-Strasse 10, 40789 Monheim, Germany, and a subsidiary of UCB S.A., a corporation organized and existing under the laws of Belgium, with a principle place of business at Allée de la Recherche, 60 Bruxelles 1070, Belgium, represents:

(1) that it is the owner of the entire right, title and interest in and to Letters Patent of the United States No. 6,858,650 by virtue of an Assignment recorded in the United States Patent and Trademark Office at Reel 013122, Frame 0883, on May 14, 2002;

(2) that said patent discloses and claims the chemical substance described therein as Toviaz™, known as fesoterodine fumarate;

(3) that Toviaz™ has undergone regulatory review by the United States Food and Drug Administration, prior to its commercial marketing or use;

(4) that by an Agreement dated April 12, 2006 (the "Agreement"), Schwarz granted to PFIZER INC. ("PFIZER"), a corporation organized and existing under the laws of the State of Delaware, and having its principle place of business at 235 East 42nd Street, New York, New York 10017, United States of America, an exclusive license under said patent;

(5) that under terms of the Agreement PFIZER may prepare, file and prosecute in the name of Schwarz an application for extension of the term of said patent pursuant

to 335 U.S.C. §156, based on said regulatory review of Toviaz™; and

Schwarz hereby appoints, authorizes and empowers the following individuals:

Raquel M. Alvarez, Reg. No. 45,807; Marie A. Aucoin, Reg. No. 59,414; S. Christopher Bauer, Reg. No. 42,305; Gregg C. Benson, Reg. No. 30,997; Brandon S. Boss, Reg. No. 46,567; Garth Butterfield, Reg. No. 36,997; B. Timothy Creagan, Reg. No. 39,156; J. Michael Dixon, Reg. No. 32,410; E. Victor Donahue, Reg. No. 35,492; Steven R. Eck, Reg. No. 36,126; Patricia K. Fitzsimmons, Reg. No. 52,894; Grover F. Fuller, Reg. No. 31,760; Martha A. Gammill, Reg. No. 31,820; Carl J. Goddard, Reg. No. 39,203; Mary J. Hosley, Reg. No. 48,324; Wendy Hsu, Reg. No. 42,794; Ye Hua, Reg. No. 53,042; Keith D. Hutchinson, Reg. No. 43,687; Seth H. Jacobs, Reg. No. 32,140; James T. Jones, Reg. No. 30,561; Robert M. Kennedy, Reg. No. 28,026; Sandra P. Kim, Reg. No. 58,212; Jennifer A. Kispert, Reg. No. 40,049; Gabriel L. Kleiman, Reg. No. 40,681; Kristina L. Konstas, Reg. No. 37,864; Julie M. Lappin, Reg. No. 46,612; Lorraine B. Ling, Reg. No. 35,251; Vincent P. Liptak, Reg. No. 53,225; Adrian G. Looney, Reg. No. 41,406; Deborah A. Martin, Reg. No. 44,222; John C. Martin, Reg. No. 42,843; Scott A. McNeil, Reg. No. 37,185; William F. Mulholland, Reg. No. 45,684; Martha G. Munchhof, Reg. No. 47,811; Arlene K. Musser, Reg. No. 37,895; Rona A. Nardone, Reg. No. 55,481; Carmella A. O'Gorman, Reg. No. 33,749; A. Dean Olson, Reg. No. 37,185; Bruce A. Pokras, Reg. No. 32,748; Philip B. Polster II, Reg. No. 43,864; Stephen D. Prodnuk, Reg. No. 43,020; Matthew J. Pugmire, Reg. No. 54,723; Joseph F. Reidy, Reg. No. 39,340; Robert T. Ronau, Reg. No. 36,257; Matthew J. Russo, Reg. No. 41,282; Pamela G. Salkeld, Reg. No. 38,607; Lisa A. Samuels, Reg. No. 43,080;

Nicholas I. Slepchuk, Reg. No. 32,174; Christian M. Smolizza, Reg. No. 46,319; Jason Tebbutt, Reg. No. 55,671; Jeffrey H. Tidwell, Reg. No. 47,995; Bruce S. Weintraub, Reg. No. 34,277; John A. Wichtowski, Reg. No. 48,032; Scott A. Williams, Reg. No. 39,876; Galina M. Yakovleva, Reg. No. 47,192; Lucy Yang, Reg. No. 40,259; Steve T. Zelson, Reg. No. 30,335; Austin W. Zhang, Reg. No. 48,061; and Brian C. Zielinski, Reg. No. 34,462,

who are members of the PFIZER Patent Department and have general authority to act on behalf of PFIZER in patent matters to prepare, sign, and file in the United States Patent and Trademark Office on behalf of, and as Agent for, Schwarz, an Application under 35 U.S.C. §156 and 37 C.F.R. §1.730 and §1.740 for extension of the term of United States Patent No. 6,858,650, based on said regulatory review of Toviaz™, and to take all actions and perform all duties with respect thereto and in support thereof that PFIZER deems necessary and proper to obtain an extension of the term of United States Patent No. 6,858,650, based on said regulatory review of Toviaz™, and to protect the rights of Schwarz and PFIZER.

Signed at Monheim, Germany, on this 14th day of November, 2008.

By: S. Krohn

Name: Sabine Krohn, PhD

Title: Associate General Patent Counsel, Schwarz Pharma AG

By: F. Dressen

Name: Frank Dressen, PhD

Title: Senior Patent Counsel, Schwarz Pharma AG

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/130,214	05/14/2002	Claus Meese	41946/32854

CONFIRMATION NO. 9833

21874
EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON, MA 02205

OC000000018325923

Date Mailed: 03/20/2006

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 09/01/2005.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

DESHAWN D DURHAM
OIPE (703) 308-9010

OFFICE COPY

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/130,214	05/14/2002	Claus Meese	12961/46301

CONFIRMATION NO. 9833

26646
KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

OC000000018325929

Date Mailed: 03/20/2006

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 09/01/2005.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

D. Durham

DESHAWN D DURHAM
OIPE (703) 308-9010

OFFICE COPY

COMPLETED

GCS

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER		Docket Number: 58827(45107) **(New Atty. Docket No.: 12961/46301)**	
Application Number **10/130,214**	Filing Date **May 14, 2002**	Examiner **R. L. RAYMOND**	Art Unit **1624**
Patent Number **6,858,650**	Issue Date **February 22, 2005**		
Invention Title **STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES**		Inventor(s) **Claus MEESE**	

Address to:
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

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

Date: AUGUST 29, 2005

Signature: Joseph A Coppola

Joseph A. Coppola (Reg. No. 38,413)

Sir:

Transmitted herewith for filing in the above-identified patent application is a Power of Attorney by Assignee of Entire Interest (Revocation of Prior Powers and Appointment of New Power) and 3.73(b) statement. Please note that two (2) copies are being submitted, each signed by separate authorized representatives of the assignee.

Please record the Power and change of address in the above application.

In addition, please change the Attorney Docket Number for the above-identified patent application from "58827(45107)" to -- **12961/46301** --.

Dated: AUGUST 29, 2005 By:	Joseph A Coppola Joseph A. Coppola (Reg. No. 38,413)
	KENYON & KENYON One Broadway New York, N.Y. 10004 (212) 425-7200 (telephone) (212) 425-5288 (facsimile) **Customer No. 26646**

NY01 1036107 v1

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		
REVOCATION OF PRIOR POWER OF ATTORNEY and APPOINTMENT OF NEW POWER OF ATTORNEY BY ASSIGNEE and 3.73(b) STATEMENT		Docket Number: **12961/46301**
Application Number: **10/130,214**	Filing Date: **May 14, 2002**	
Patent Number: **6,858,650**	Issue Date: **February 22, 2005**	
Invention Title: **STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES**		Inventor(s): **Claus MEESE**

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SIR:

SCHWARZ PHARMA AG, as assignee of the entire interest of the above-identified patent by virtue of executed assignments as indicated below, hereby revokes all powers of attorney previously given and appoints Bradford Paul Schmidt, Reg. No. 42,128, and the practitioners associated with Kenyon & Kenyon's customer number:

26646

to prosecute and transact all business in the Patent and Trademark Office connected therewith.

SCHWARZ PHARMA AG, is the assignee of the entire right, title and interest in U.S. Patent Application Serial No. 10/130,214 filed on May 14, 2002, now U.S. Patent No. 6,858,650 issued on February 22, 2005 by virtue of the following assignment of title from the inventor(s) to the current assignee as shown below:

From: Claus Meese

To: Schwarz Pharma AG

The document was recorded on May 14, 2002 in the United States Patent and Trademark Office at Reel 013122, Frame 0883.

Please send all correspondence and direct telephone calls to:

Jeffrey Ginsberg, Esq.

Kenyon & Kenyon
One Broadway
New York, NY 10004
Customer No: 26646

The undersigned are authorized to act on behalf of the assignee:

SCHWARZ PHARMA AG

Date: **August 22, 2005**

By: _____

Name: **Klaus Veitinger, MD**

Title: **Executive Board Member, Schwarz Pharma AG**

SCHWARZ PHARMA AG

Date:_____

By: _____

Name:_____

Title:_____

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		
REVOCATION OF PRIOR POWER OF ATTORNEY and APPOINTMENT OF NEW POWER OF ATTORNEY BY ASSIGNEE and 3.73(b) STATEMENT		Docket Number: **12961/46301**
Application Number: **10/130,214**	Filing Date: **May 14, 2002**	
Patent Number: **6,858,650**	Issue Date: **February 22, 2005**	
Invention Title: **STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES**		Inventor(s): **Claus MEESE**

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SIR:

SCHWARZ PHARMA AG, as assignee of the entire interest of the above-identified patent by virtue of executed assignments as indicated below, hereby revokes all powers of attorney previously given and appoints Bradford Paul Schmidt, Reg. No. 42,128, and the practitioners associated with Kenyon & Kenyon's customer number:

26646

to prosecute and transact all business in the Patent and Trademark Office connected therewith.

SCHWARZ PHARMA AG, is the assignee of the entire right, title and interest in U.S. Patent Application Serial No. 10/130,214 filed on May 14, 2002, now U.S. Patent No. 6,858,650 issued on February 22, 2005 by virtue of the following assignment of title from the inventor(s) to the current assignee as shown below:

From: Claus Meese

To: Schwarz Pharma AG

The document was recorded on May 14, 2002 in the United States Patent and Trademark Office at Reel 013122, Frame 0883.

Please send all correspondence and direct telephone calls to:

Jeffrey Ginsberg, Esq.
Kenyon & Kenyon
One Broadway
New York, NY 10004
Customer No: 26646

The undersigned are authorized to act on behalf of the assignee:

SCHWARZ PHARMA AG

Date: **August 22, 2005**

By: _____

Name: **Klaus Veitinger, MD**

Title: **Executive Board Member, Schwarz Pharma AG**

SCHWARZ PHARMA AG

Date: **August 24, 2005**

By: _____

Name: **Detlef Thielgen**

Title: **CFO and Member of the Executive Board, Schwarz Pharma AG**

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,858,650 B1
DATED : February 22, 2005
INVENTOR(S) : Meese

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1,
Line 17, please correct "prodrugn" to -- prodrugs --
Line 26, please correct "3,3-diphenylpropylarines" to -- 3,3-diphenylpropylamines --

Column 3,
Line 50, please correct "and X" to -- and X^- --

Column 4,
Lines 45-46, please correct "are that" to -- are manufactured in that --

Column 5,
Line 24, please correct "with agent" to -- with a reducing agent --

Column 13,
Line 14, please correct "photometer. model" to -- photometer model --
Line 64, please correct "43.63" to -- 43.83 --

Column 15,
Line 37, please correct "amorphous. solid" to -- amorphous solid --

Column 16,
Line 37, please correct "125:59" to -- 125.59 --

Column 17,
Line 6, please correct "$[I]_D^{20=+6.0}$" to -- $[I]_D^{20}$= +6.0 --
Line 23, please correct "Ms" to -- MS --

Column 23,
Line 13, please correct "=14.6" to -- = +14.6 --
Line 47, "please correct "claims" to -- claim --

Column 24,
Lines 15 and 21, please correct "claims" to -- claim --
Line 46, please correct "physicologically" to -- physiologically --

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,858,650 B1
DATED : February 22, 2005
INVENTOR(S) : Meese

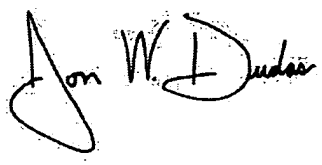
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 28,
Lines 35, 38, 41, 45, 53 and 58, please correct "claims" to -- claim --

Column 30,
Line 17, please correct "physicologically" to -- physiologically --

Signed and Sealed this

Ninth Day of August, 2005



JON W. DUDAS
Director of the United States Patent and Trademark Office

10/130214
06-23-05
6858,650
copy

Application No. (if known): 10/130,214 Attorney Docket No.: 58827 (45107)

Certificate of Express Mailing Under 37 CFR 1.10

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail, Airbill No. EV654384971US in an envelope addressed to:

Attn: Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate

on June 21, 2005
Date

JUN 3 0 2005

of Correction

Judy Daley
Signature

Judy Daley
Typed or printed name of person signing Certificate

Registration Number, if applicable

(617) 439-4444
Telephone Number

Note: Each paper must have its own certificate of mailing, or this certificate must identify each submitted paper.

Certificate of Correction
Request for Certificate of Correction
Transmittal Letter

Docket No.: 58827(45107)
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Claus Meese

US Patent No. 6,858,650

Issued: February 22, 2005

Application No.: 10/130,214 Group Art Unit: 1624

Filed: May 14, 2002 Examiner: R. L. Raymond

For: STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

TRANSMITTAL LETTER

Attention: Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Enclosed are the following items for filing in connection with the above-referenced Patent Application:

1. Request for Certificate of Correction; and

2. Certificate of Correction.

495617

JUL 0 6 2005

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. 58827(45107). A duplicate copy of this paper is enclosed.

Dated: June 21, 2005

Respectfully submitted,

By _____

Christine C. O'Day
Registration No.: 38,256
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 439-4444
Attorneys/Agents For Applicant

Attorney Docket No. 58827 (45107)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Claus Meese		
U.S.P.N.:	US 6,858,650	**ISSUED:**	February 22, 2005
U.S.S.N.:	10/130,214	**FILED:**	May 14, 2002
GROUP ART UNIT:	1624	**EXAMINER:**	R. L. Raymond
FOR:	STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES		

Attention: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION OF PATENT FOR PTO MISTAKE (37 C.F.R. SECTION 1.322(a))

Attached, in duplicate, is PTO/SB/44 (also Form PTO-1050), with at least one copy being suitable for printing.

NOTE: Form PTO—1050 (or PTO/SB/44), using the column and line number in the printed patent, should be used exclusively regardless of the length or complexity of the subject matter. M.P.E.P. section 1485, 7th ed.

NOTE: The patent grant should be retained by the patentee. The PTO does not attach the certificate of correction to the patentee's copy of the patent. The patent grant will be returned to the patentee if submitted. M.P.E.P. section 1485, 7th ed.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 1, line 17

Please correct:

" prodrugn"

to

–prodrugs--

Explanation of PTO error, and description of documentary support:

The recitation of "prodrugn" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 1, line 9.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 1, line 26

Please correct:

" 3,3-diphenylpropylarines "

to

-- 3,3-diphenylpropylamines --

Explanation of PTO error, and description of documentary support:

The recitation of "3,3-diphenylpropylarines" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 1, line 19.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 3, line 50

Please correct:

"and X "

to

-- and X^- --

Explanation of PTO error, and description of documentary support:

The recitation of "and X" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 6, line 19.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 4, line 45-46

Please correct:

" are that "

to

– are manufactured in that --

Explanation of application error, and description of documentary support:

The recitation of "are that" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 8, line 4-5.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 5, line 24

Please correct:

" with agent "

to

– with a reducing agent --

Explanation of application error, and description of documentary support:

The recitation of "with agent" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 9, line 2-3.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 13, line 14

Please correct:

" photometer. model "

to

-- photometer model --

Explanation of application error, and description of documentary support:

The recitation of "photometer. model" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 22, line 9-10.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 13, line 64

Please correct:

" 43.63 "

to

-- 43.83 --

Explanation of application error, and description of documentary support:

The recitation of "43.63" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 24, line 1.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 15, line 37

Please correct:

" amorphous. solid "

to

– amorphous solid --

Explanation of application error, and description of documentary support:

The recitation of "amorphous. solid" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 27, line 10-11.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 16, line 37

Please correct:

" 125:59 "

to

– 125.59 --

Explanation of application error, and description of documentary support:

The recitation of "125:59" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 29, line 19.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 17, line 6

Please correct:

" $[I]_D^{20=+6.0}$ "

to

– $[I]_D^{20} = +6.0$ --

Explanation of application error, and description of documentary support:

The recitation of "$[I]_D^{20=+6.0}$" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 30, line 20.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 17, line 23

Please correct:

" Ms "

to

-- MS --

Explanation of application error, and description of documentary support:

The recitation of "Ms" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 31, line 11.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 23, line 13

Please correct:

" =14.6 "

to

-- = +14.6 --

Explanation of application error, and description of documentary support:

The recitation of "=14.6" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the US application as originally filed, at page 44, line 19.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 23, line 47; column 24, line 15; column 24, line 21; column 28, line 35; column 28, line 38; column 28, line 41; column 28, line 45; column 28, line 53; column 28, line 58

Please correct:

" claims "

to

-- claim --

Explanation of application error, and description of documentary support:

The recitation of "claims" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the amendment filed November 3, 2003.

The exact column and line number where the error is shown incorrectly in the issued patent are:

Column 24, line 46; column 30; line 17

Please correct:

" physicologically "

to

-- physiologically --

Explanation of application error, and description of documentary support:

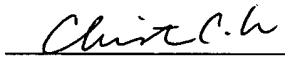
The recitation of "physicologically" of US 6,858,650 is incorrectly recited. The correct recitation can be found in the amendment filed November 3, 2003.

NOTE: This information should be identified in this request, however, on Form PTO—1050, only the column and line number in the printed patent should be used. M.P.E.P. section 1485, 7th ed.

4. Please send the Certificate to:

Christine C. O'Day
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, MA 02205

Respectfully submitted,



Christine C. O'Day
Reg. No.: 38,256
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, Massachusetts 02205
Tel.: 617-439-4444
Fax: 617-439-4170
E-mail: coday@EdwardsAngell.com
Customer No.: 21874

Date: June 21, 2005

PTO/SB/44 (04-04)
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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,858,650

DATED : February 22, 2005

INVENTOR(S) : Claus Meese

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1, line 17

Please correct:

" prodrugn"

to

--prodrugs--

Column 1, line 26

Please correct:

" 3,3-diphenylpropylarines "

to

-- 3,3-diphenylpropylamines --

MAILING ADDRESS OF SENDER:
Christine C. O'Day
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, Massachusetts 02205

PATENT NO. 6,858,650

JUL 0 6 2005

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(Also Form PTO-1050)

Column 3, line 50

Please correct:

"and X "

to

-- and X--

Column 4, line 45-46

Please correct:

" are that "

to

-- are manufactured in that --

Column 5, line 24

Please correct:

" with agent "

to

-- with a reducing agent --

Column 13, line 14

Please correct:

" photometer. model "

to

-- photometer model --

MAILING ADDRESS OF SENDER:
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EDWARDS & ANGELL, LLP
P.O. Box 55874
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PATENT NO. 6,858,650

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(Also Form PTO-1050)

Column 13, line 64

Please correct:

" 43.63 "

to

-- 43.83 --

Column 15, line 37

Please correct:

" amorphous. solid "

to

-- amorphous solid --

Column 16, line 37

Please correct:

" 125:59 "

to

-- 125.59 –

Column 17, line 6

Please correct:

" $[l]_D^{20=+6.0}$ „

to

-- $[l]_D^{20}$ = +6.0 --

MAILING ADDRESS OF SENDER:
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Column 17, line 23

Please correct:

" Ms "

to

-- MS --

Column 23, line 13

Please correct:

" =14.6 "

to

-- = +14.6 --

Column 23, line 47; column 24, line 15; column 24, line 21; column 28, line 35; column 28, line 38; column 28, line 41; column 28, line 45; column 28, line 53; column 28, line 58

Please correct:

" claims "

to

-- claim --

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Please correct:

" physicologically "

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P.O. Box 55874
Boston, Massachusetts 02205

PATENT NO. 6,858,650

JUL 0 6 2005

02-02-05

1624

DPW

PTO/SB/21 (09-04)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/130,214-Conf. #9833
Filing Date	May 14, 2002
First Named Inventor	Claus Meese
Art Unit	1624
Examiner Name	Z. C. Tucker
Total Number of Pages in This Submission	
Attorney Docket Number	58827(45107)

ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [x] Supplemental Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

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Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	EDWARDS & ANGELL, LLP		
Signature	Christine C. O'Day		
Printed name	Christine C. O'Day		
Date	January 31, 2005	Reg. No.	38,256

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Dated: January 31, 2005 Signature: Elisabeth Dunkle (Elisabeth Dunkle)

475730

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Dated: January 31, 2005 Signature: (Elisabeth Dunkle)

Docket No.: 58827(45107)
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Claus Meese

Application No.: 10/130,214 Confirmation No.: 9833

Filed: May 14, 2002 Art Unit: 1624

For: STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES Examiner: Z. C. Tucker

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (IDS)

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

Dear Sir:

Pursuant to 37 CFR 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08.

A copy of each reference on the PTO/SB/08 is attached. It also is noted that the cited document was identified during prosecution of a counterpart application.

This Supplemental Information Disclosure Statement is filed after payment of the Issue Fee. While it is understood that no documents may be considered and made of record following payment of the Issue Fee, Applicants nonetheless request that a copy of this submission be included in the USPTO file history for the referenced application.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper

hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. 58827(45107). A duplicate copy of this paper is enclosed.

Dated: January 31, 2005

Respectfully submitted,

By _____

Christine C. O'Day
Registration No.: 38,256
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 439-4444
Attorney for Applicant

PTO/SB/08a/b (08-03)
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Substitute for form 1449A/B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	10/130,214-Conf. #9833
Filing Date	May 14, 2002
First Named Inventor	Claus Meese
Art Unit	1624
Examiner Name	Z. C. Tucker
Attorney Docket Number	58827(45107)

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number: Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	BA	HU-212 729 B				
	BB	WO-89/06644	07-27-1989			

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ** CITE NO.: Those document(s) which are marked with an double asterisk (**) next to the Cite No. are not supplied because they were previously cited by or submitted to the Office in a prior application relied upon in this application for an earlier filing date under 35 U.S.C. 120. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

Examiner Signature		Date Considered	

475728

Application No. (if known): 10/130,214 Attorney Docket No.: 58827(45107)

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Date

Signature

Elisabeth Dunkle
Typed or printed name of person signing Certificate

Registration Number, if applicable

(617) 439-4444
Telephone Number

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Transmittal (1 page)
IDS (Citation) by Applicant (2 References)
Information Disclosure Statement

(19) Országkód:
HU

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MAGYAR SZABADALMI HIVATAL

SZABADALMI LEÍRÁS

(11) Lajstromszám:
212 729 B

(21) A bejelentés ügyszáma: 1069/89
(22) A bejelentés napja: 1989. 01. 20.
(30) Elsőbbségi adatok:
88/00207-6 1988. 01. 22. SE
(86) Nemzetközi bejelentési szám: PCT/SE 89/00016
(87) Nemzetközi közzétételi szám: WO 89/06644

(40) A közzététel napja: 1992. 01. 28.
(45) A megadás meghirdetésének dátuma a Szabadalmi Közlönyben: 1996. 10. 28.

(51) Int. Cl.[6]
C 07 C 215/54
C 07 C 217/62
C 07 D 207/06
C 07 D 207/12
C 07 D 211/14
C 07 D 211/40
A 61 K 31/135
A 61 K 31/395

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Mikiver, Lembit, Järna (SE)
Moses, Pinchas, Saltsjö-Boo (SE)
Nilvebrant, Lisbet, Bromma (SE)
Sparf, Bengt Ake, Trangsund (SE)

(73) Szabadalmas:
Pharmacia AB, Stockholm (SE)

(74) Képviselő:
ADVOPATENT Szabadalmi Iroda, Budapest

(54) Eljárás 3,3-difenil-propilamin-származékok és ilyen vegyületeket tartalmazó gyógyszerkészítmények előállítására

(57) KIVONAT

A találmány az (1) általános képlettel jellemzett új 3,3-difenil-propil-aminok és ilyen vegyületeket tartalmazó gyógyászati készítmények előállítására vonatkozik.

Az (1) általános képletben

R^1 jelentése hidrogénatom vagy metilcsoport,

R^2 jelentése hidrogénatom, halogénatom, hidroxil-, metil- vagy metoxicsoport,

R^3 jelentése hidrogénatom, halogénatom, hidroxil-, metil- vagy metoxicsoport,

R^4 jelentése hidrogénatom, halogénatom, hidroxil- vagy metoxicsoport,

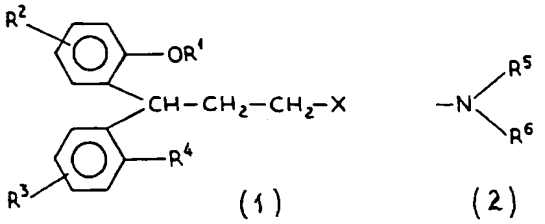
X jelentése (2) általános képletű csoport, amelyben

R^5 jelentése hidrogénatom vagy 1–4 szénatomos alkilcsoport, és

R^6 jelentése 1–6 szénatomos alkil-, 1–6 szénatomos hidroxi-alkil- vagy 1-adamantil-csoport, mimellett az R^5 és R^6 szubsztituensekben együttesen legalább 3 szénatom van, vagy

R^5 és R^6 együtt egy 4–6 szénatomos alkilénláncot képez, amely négy 1–4 szénatomos alkilcsoporttal és adott esetben egy hidroxilcsoporttal van helyettesítve.

Az új vegyületek és az ezeket tartalmazó gyógyszerkészítmények antikolinergiás hatásúak.



A leírás terjedelme: 28 oldal (ezen belül 5 lap ábra)

HU 212 729 B

A találmány tárgyát új, antikolinergiás hatású 3,3-difenil-propil-amin-származékok és ezeket tartalmazó gyógyászati készítmények előállítási eljárása képezi.

A 215 499 sz. svéd szabadalmi leírás ismertet néhány 3,3-difenil-propilamint, amelyek kedvező hatásúak a szívre és a vérkeringésre. Ezek a gyógyhatású 3,3-difenil-propilaminok szekunder aminok. Ugyanez a svéd szabadalmi leírás néhány köztiterméket is bemutat, amelyek az amin nitrogénjén aromás szubsztituenseket tartalmazó tercier aminok. Sem a végtermékeken (szekunder aminok), sem a köztitermékeken (tercier aminok) nincs a fenil-csoportokon orto-helyzetű hidroxil vagy metoxi csoport; a szabadalmi igény kifejezetten csak meta- és para-szubsztituensekre vonatkozik.

Ismeretes, hogy a kereskedelmileg kapható gyógyhatású szer, a terodilin az (A) szerkezeti képlettel jellemezhető, antikolinergiás hatású, és jól felszívódik a szervezetben. Biológiai felezési ideje azonban igen hosszú, és mint többféle hatású szer, eközben más farmakológiai szerepet is játszik, így kalcium-antagonista, noradrenalin antagonista, antihisztamin tulajdonságú és erős hatással van a szívre is.

A 3 446 901 sz. USA-beli, valamint az 1 169 944 és 1 169 945 sz. brit szabadalmi leírások is 3,3-difenil-propilaminokkal foglalkoznak, amelyeknek gyógyászati készítményei depresszióellenes hatásúak. Ilyen az N,N-dimetil-3-(2-metoxi-fenil)-3-fenil-propilamin, amely kémiai szerkezetét tekintve a legközelebbi hasonlóságot mutat a jelen találmány szerinti anyagokkal (lásd az összehasonlító próbákat a leírás végén). A 111 894 sz. dán szabadalmi leírás különleges eljárást mutat be egyes olyan difenil-alkil-aminok előállítására, amelyek hatással vannak a szívre és a vérkeringésre. Az itt szereplő vegyületek primer és szekunder aminok, és egyikükben sincs a fenil-gyűrűn orto-helyzetben sem hidroxil, sem alkoxi szubsztituens. A Chemical Abstracts 97, 120 105n (1982) leírásban szerepelnek olyan N-aril-alkil-izokinolinok, amelyekben lehet a fenil-gyűrűn orto-helyzetben hidroxil csoport. E vegyületek szimpatolitikus hatásúak, és az *aromás* szubsztituenseket a nitrogénatom hordozza.

A találmány célja olyan új típusú 3,3-difenil-propil-aminok előállítása, amelyek antikolinergiás hatása jobb, elsősorban az említett egyéb rendszerekéhez képest és akut toxikusságuk szempontjából.

A találmány célja tehát az (I) általános képletű, új 3,3-difenil-propil-amin-származékok előállítása; ebben a képletben

R^1 jelentése hidrogénatom vagy metilcsoport,

R^2 jelentése hidrogénatom, halogénatom, hidroxil-, metil- vagy metoxicsoport,

R^3 jelentése hidrogénatom, halogénatom, hidroxil-, metil- vagy metoxicsoport,

R^4 jelentése hidrogénatom, halogénatom, hidroxil- vagy metoxicsoport,

X jelentése (2) általános képletű csoport, amelyben

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R^5 és R^6 együtt egy 4–6 szénatomos alkilénláncot képez, amely négy 1–4 szénatomos alkilcsoporttal és adott esetben egy hidroxilcsoporttal van helyettesítve.

Az (I) általános képletű vegyületek sókat is alkothatnak fiziológiailag elfogadható, szerves és szervetlen savakkal, így a találmány a szabad bázisokon kívül ezek savaddíciós sóit is magában foglalja. Ilyen sóképző sav lehet például a sósav, a hidrogén-bromid, a hidrogén-fumarát és ezekhez hasonlók.

Ha az új vegyületek optikai izomereket alkothatnak, a találmány a racém keveréken kívül kiterjed az egyes enantiomerekre is önmagukban.

Az (I) általános képletben X helyén álló tercier amin-csoportok előnyös változatai az (a)–(f) képletűek, amelyek adott esetben egy vagy több hidroxilcsoportot is tartalmazhatnak.

Néhány példa az előnyös, (I) általános képletű vegyületekre:

- N,N-diizoporpil-3-(2-hidroxi-5-metil-fenil)-3-fenil-propilamin és ennek (+)-izomerje,
- N-metil-N-terc-butil-3-(2-hidroxi-fenil)-3-fenil-propilamin,
- N-metil-N-terc-butil-3-(2,4-dihidroxi-fenil)-3-fenil-propilamin,
- N-metil-N-terc-butil-3-(2-hidroxi-fenil)-propil-amin,
- N,N-diizopropil-3,3-bisz-(2-hidroxi-fenil)-propil-amin,
- N,N-diizopropil-3-(2,5-dihidroxi-fenil)-3-fenil-propilamin,
- N-metil-N-terc-butil-3-(2,5-dihidroxi-fenil)-3-fenil-propilamin,
- N,N-diizopropil-3-(2-metoxi-fenil)-3-fenil-propil-amin,
- N-[3-(2-metoxi-fenil)-3-fenil-propil]-2,2,6,6-tetrametil-piperidin.

Az (I) általános képletű vegyületeket a találmány értelmében oly módon állítjuk elő, hogy

a) egy (3) általános képletű, reaktív észterezéssel előállított 3,3-difenil-propanol származékot, ahol az R^1–R^4 szubsztituensek a fenti meghatározásoknak felelnek meg, az esetleges hidroxil csoportok védve lehetnek – előnyösen – metilezéssel vagy benzilezéssel, Y helyén pedig lecserélhető csoport, előnyösen halogén, alkil vagy aril-szulfonil-oxi csoport áll, reagáltatunk egy (4) általános képletű aminnal, amelyben X szubsztituens a fenti meghatározásnak felel meg; vagy

b) egy (5) általános képletű 3,3-difenil-propionamid származékot, amelyben az R^1–R^4 és X szubsztituensek a fenti meghatározásoknak felelnek meg, az esetleges hidroxil csoportok pedig védve lehetnek, előnyösen komplex fém-hidriddel redukálunk; vagy

c) egy (7a) vagy (7b) általános képletű 3,3-difenil-propil-amin származékot – ahol R^1, R^2, R^3, R^4 és X

jelentése egyezik a tárgyi körben megadottal és az adott esetben jelenlevő hidroxilcsoportok pedig védve is lehetnek, W helyén pedig hidroxilcsoport vagy halogénatom áll – redukálunk ; vagy

d) az X jelentésében R^5 helyén metilcsoportot, R^6 helyén pedig 2–6 szénatomos alkil-, 2–6 szénatomos hidroxi-alkil- vagy 1-adamantil-csoportot tartalmazó (1) általános képletű vegyületek előállítására egy (6) általános képletű szekunder 3,3-difenil-propil-amin származékot – a képletben R^1, R^2, R^3 és R^4 jelentése egyezik a tárgyi körben megadottal, és a vegyületben az esetleges hidroxilcsoportok védve lehetnek, Z helyén pedig a fenti meghatározások szerinti R^6 szubsztituensek egyike állhat metilcsoport kivételével – N-metilezünk;

majd

- kívánt esetben a kapott (1) általános képletű vegyületet fenilcsoporton halogénezzük,
- az adott esetben jelenlévő védőcsoportokat lehasítjuk;
- kívánt esetben a kapott, (I) általános képletnek megfelelő bázist fiziológiailag elfogadható savakkal savaddíciós sóvá alakítjuk át, vagy fordítva; és/vagy
- kívánt esetben az optikai izomerek kapott elegyét az egyedi enantiomerekre választjuk szét.

A fent leírt eljárási műveleteket önmagukban ismert módszerekkel és/vagy az alábbiakban ismertetett példák szerint, mindig a kívánt amino-csoportoknak és a benzolgyűrűkön lévő szubsztituenseknek megfelelően hajthatjuk végre.

A hidroxil-védőcsoportok eltávolítását például hidrogén-bromiddal, bór-tribromiddal való kezeléssel vagy katalitikus hidrogénezéssel hajthatjuk végre.

Az optikai izomerek elegyeinek szétválasztását egyedi enantiomerekre a királis savakkal alkotott sók frakcionált kristályosításával vagy királis oszlopon végzett kromatográfiás szétválasztással végezhetjük.

A (8) általános képletű vegyületek, amelyekben R^1–R^4 szubsztituensek a fenti meghatározásoknak felelnek meg, valamint a megfelelő védett vegyületek (ha védett hidroxil csoportokat tartalmaznak) alkalmas köztitermékek például az (I) általános képletű vegyületek előállításához. Ezek a vegyületek különféle, önmagukban ismert módszerekkel állíthatók elő, például úgy, hogy egy megfelelően helyettesített (9) általános képletű difenil-metánra valamely alkalmas bázis, például nátrium-amid jelenlétében a (10) képletű etilén-oxidot addicionáljuk.

A (8) általános képletű vegyületeket a megfelelő 3,3-difenil-propionsav származékok redukálásával is elő lehet állítani, előnyösen komplex fém-hidridek alkalmazásával.

A (8) általános képletű 3,3-difenil-propanolok kényelmesen átalakíthatók a megfelelő, (3) általános képletű, reaktívan észterezett származékokká önmagában ismert módszerrel, így a hidroxil csoport eltávolításával, pl. halogénatomra, alkil vagy aril-szulfonil-oxi-csoportra való kicserélléssel.

Az (5) általános képletű 3,3-difenil-aminokat használjuk a (b) eljárás kiindulási anyagaiként. Ezek előállíthatók pl. a fent említett 3,3-difenil-propionsav származékok és a megfelelő amin reagáltatásával.

A (d) eljárás kiindulási anyagaiként használt szekunder aminok kényelmesen előállíthatók, ha H_2N–Z általános képletű primer amint [amelyben Z jelentése egyezik a d) eljárásnál a (6) általános képletnél megadottal] reagáltatjuk a megfelelő, reaktívan észterezett 3,3-difenil-propanollal, az (a) eljárással analóg módon, vagy a megfelelő szekunder 3,3-difenil-propionamidok redukálásával, a (b) eljárás analógiájára.

Az említett szekunder aminok előállíthatók a (11) általános képletű, telítetlen hidroxi-aminok redukálásával, ahol R^1–R^4 és Z szubsztituensek a fenti meghatározásoknak felelnek meg. Ez végrehajtható egy lépésben, katalitikus hidrogénezéssel vagy a megfelelő telített hidroxi-amin redukciójával, előnyösen komplex fém-hidrid, így lítium-alumínium-hidrid alkalmazásával, majd a hidroxilcsoport eltávolításával katalitikus redukció segítségével. Más módon eljárva, először a hidroxilcsoportot víz alakjában lehasítjuk, majd a képződött telítetlen amint redukáljuk.

A (11) általános képletű, telítetlen hidroxi-aminok kényelmesen előállíthatók úgy, hogy a (13) általános képletű benzofenon-származékhoz, amelyben az R^1–R^4 szubsztituensek az előbbi meghatározásoknak felelnek meg, (12) általános képletű Schiff-bázist addícionálunk bázis, előnyösen lítiumorganikus bázis, így lítium-diizopropil-amid jelenlétében.

A találmány szerint az (1) általános képletű vegyületek szabad bázis vagy fiziológiailag elfogadható savval sóvá alakított formáit alkalmas gyógyszerkészítménnyé alakíthatjuk át, így orális alkalmazásra, injekció formájába vagy hasonlóba, a szokásos gyógyszerészeti eljárásokkal. Az ilyen, találmány szerinti gyógyszerkészítmények az (1) általános képletű vegyületet vele összeférhető hordozóanyagokkal vagy hígítószerekkel együtt tartalmazhatják, a szokásos szakmai ismeretek szerint . Hordozóként bármilyen iners anyag alkalmazható, akár szerves, akár szervetlen, amely alkalmas az emésztőrendszerbe, bőr alá vagy parenterálisan való bevitelre, így víz, zselatin, gumi arabicum, laktóz, mikrokristályos cellulóz, keményítő, nátrium-keményítő-glikolát, kalcium-hidrogén-foszfát, magnézium-sztearát, talkum, kolloid, szilícium-dioxid és hasonlók. A készítmények ezenkívül más, gyógyászatilag aktív szereket is tartalmazhatnak, így stabilizátorokat, nedvesítőanyagokat, emulgeátorokat, illatosítószereket, puffereket és hasonlókat.

A találmány szerinti készítmények orális alkalmazásra lehetnek szilárdak vagy folyékonyak, így tabletták, kapszulák, porok, szirupok, elixírek és hasonlók. Parenterális adagolásra lehetnek steril oldatok, szuszpenziók vagy emulziók és hasonlók.

A találmány szerinti vegyületek és készítmények alkalmazhatók kolin okozta rendellenességek, így kontrollálatlan vizeletcsurgás ellen. Mint ismeretes, az adagolás több tényezőtől függ, így a kiválasztott vegyület hatásosságától, a beadás módjától, a beteg életkorától és testsúlyától, állapota súlyosságától és hason-

lóktól. A napi adag például 0,05 mg és 4 mg között változhat testsúlykilogrammonként, amely beadható egy vagy több részletben, egy-egy részlet hatóanyagtartalma 0,05 és 200 mg között mozoghat.

A találmány szerinti eljárást az alábbi, nem korlátozó példákkal mutatjuk be.

Általános megjegyzések

A ^{1}H–NMR spektrumokat $CDCl_3$-ban vettük fel, JEOL PMX60 spektrométerrel. Egyes esetekben csak korlátozott számú csúcsot közlünk, amennyiben a jellemzéshez ezek elegendők.

A feltüntetett kitermelések legtöbbnyire olyan nyers termékekre vonatkoznak, amelyek kellő tisztaságúak a következő lépéshez való felhasználásra.

Oldószerekre vonatkozó rövidítések:
IPE = diizopropil-éter
PET = petroléter
éter = dietil-éter

Aminokra vonatkozó rövidítések:
IPA = diizopropil-amin
TBA = terc-butil-amin

Az olvadáspontokat Koeflerb-lokkon határoztuk meg.

A hőmérsékleteket °C-ban adjuk meg.

A mosási lépésekhez vizet használunk, kivéve, ha másképp határozzuk meg.

1. példa
4-Fenil-3,4-dihidrokumarinok előállítása

a) 4-(2-Metoxi-5-metil-fenil)-6-metil-3,4-dihidrokumarin (I)

96,0 g (0,5 mól) 2-metoxi-5-metil-fahéjsav, 108 g (1,0 mól) p-krezol, 200 ml tetralin és 20 g tömény kénsav elegyét lassan forrásig, 145–150 °C-ig melegítjük. 1,5–2 óra eltelte után az elegyet lehűtjük, dietil-éterben felvesszük, vízzel és nátrium-karbonát-oldattal mossuk, szárítjuk, és bepároljuk. 138 g (97%) nyers olaj marad vissza, amit acetonból két alkalommal átkristályosítunk. Így a kívánt laktont fehér kristályos anyagként kapjuk, amely 126–127 °C-on olvad.

Elemanalízis a $C_{18}H_{18}O_3$ (282,3) összegképlet alapján:
számított: C: 76,57%; H: 6,43%; O: 17,00%;
talált: C: 76,9%; H: 6,44%; O: 17,0%.

b) *6-Hidroxi-4-fenil-3,4-dihidrokumarint (II)* hasonló módon állítunk elő 97%-os hozammal fahéjsavból és hidrokinonból. Op. 138 °C (IPE-éter).

Elemanalízis a $C_{15}H_{12}O_3$ (240,3) összegképlet alapján:
számított: C: 76,57%; H: 6,43%; O: 17,00%;
talált: C: 76,4%; H: 6,31%; O: 17,2%.

c) *4-(2-Metoxi-4-metil-fenil)-7-metil-3,4-dihidrokumarint* hasonlóan állítunk elő 2-metoxi-4-metil-fahéjsavból és m-krezolból. Hozam: 58%; op. 147–148 °C (IPE-aceton).

Elemanalízis a $C_{18}H_{18}O_3$ (282,3) összegképlet alapján:
számított: C: 76,57%; H: 6,43%; O: 17,00%;
talált: C: 76,4%; H: 6,31%; O: 17,2%.

90 g (0,32 mól) fenti laktont 500 ml metilén-dikloridban 115 g (0,46 mól) bór-tribromiddal 24 órán át visszafolyatás közben forralunk, az oldatot bepároljuk, a maradékot dietil-éterben felvesszük, az oldatot nátrium-karbonát-oldattal és vízzel mossuk, szárítjuk és bepároljuk. 80 g (93%) szirup marad vissza, amely állás közben kristályosodik. IPE-PET elegyből végzett kristályosítás eredményeként

d) *4-(2-Hidroxi-4-metil-fenil)-7-metil-3,4-dihidrokumarint (III)* kapunk fehér kristályok formájában, op. 137 °C.

Elemanalízis a $C_{17}H_{16}O_3$ (268,3) összegképlet alapján:
számított: C: 76,10%; H: 6,01%; O: 17,89%;
talált: C: 76,2%; H: 6,30%; O: 17,0%.

e) *8-Hidroxi-4-fenil-3,4-dihidrokumarint (IV)* hasonló képpen kapunk fahéjsavból és katecholból, 18%-os hozamban. Op. 136 °C (IPE).

Elemanalízis a $C_{15}H_{12}O_3$ (240,2) összegképlet alapján:
számított: C: 74,99%; H: 5,04%; O: 19,98%;
talált: C: 75,0%; H: 5,01%; O: 19,90%.

f) *4-(2-Metoxi-fenil)-3,4-dihidrokumarint (V)* hasonló képpen állítunk elő metil-2-metoxi-cinnamátból és fenolból, 45%-os hozamban. A nyers reakcióelegyet metil-3-(4-hidroxi-fenil)-3-(2-metoxi-fenil)-propionát szennyezi. Ezen melléktermeket jéghideg nátrium-hidroxid-oldattal eltávolítjuk, így a cím szerinti vegyületet olajként, kielégítő tisztaságban kapjuk ahhoz, hogy a következő lépésben felhasználjuk.

2. példa
3,3-Difenil-propionsav-észterek előállítása

a) Metil-3-(2-metoxi-4-metil-fenil)-3-fenil-propionát (VI)

78 g (0,327 mól) 7-metil-4-fenil-3,4-dihidrokumarin, 150 ml metanol, 150 ml aceton, 100 g (0,7 mól) metil-jodid és 55 g (0,4 mól) kálium-karbonát elegyét 24 órán át visszafolyatás közben forraljuk, majd szűrjük, és az oldószert lepároljuk. A maradékot dietil-éterben oldjuk, az oldatot vízzel mossuk, szárítjuk és bepároljuk. 86 g (92%) viszkózus olajat kapunk.

NMR: δ 6,6–7,2 (m, 8H); 4,9 (t, 1H), 3,8 (s, 3H); 3,5 (s, 3H); 3,0 (d, 2H); 2,2 (s, 3H).

b) *Metil-3,3-bis(2-metoxi-fenil)-propionátot (VII)* hasonlóképpen kapunk az 1f) példa szerinti (V) laktonból 96%-os hozamban, op. 84–87 °C (IPE).

Elemanalízis a $C_{18}H_{20}O_4$ (300,4) összegképlet alapján:
számított: C: 71,98%; H: 6,71%; O: 21,3%;
talált: C: 71,4%; H: 6,67%; O: 21,6%.

c) *Metil-3-[2,3-di(benzil-oxi)-fenil]-3-fenil-propionátot (VIII)* hasonlóképpen állítunk elő kvantitatív hozamban az 1e) példa szerinti (IV) laktonból és benzil-kloridból metanolban. A kálium-karbonát mellett a reakcióelegy egy kevés nátrium-jodidot is tartalmaz. Op. 72 °C (IPE).

Elemanalízis a $C_{30}H_{28}O_4$ (452,5) összegképlet alapján:
számított: C: 79,63%; H: 6,24%; O: 14,14%;
talált: C: 79,9%; H: 6,15%; O: 14,1%.

d) *Metil-3-[2-(benzil-oxi)-fenil]-3-fenil-propionátot (IX)* hasonlóképpen állítunk elő 4-fenil-3,4-dihidrokumarinból és benzil-kloridból 81%-os hozamban, viszkózus olaj alakjában.

NMR: δ 7,2 (m, 14H); 4,9 (s, 2H, t, 1H); 3,5 (s, 3H); 3,0 (t, 2H).

d) *Metil-3-(2-metoxi-5-metil-fenil)-3-fenil-propionátot (X)* hasonlóképpen kapunk 6-metil-4-fenil-3,4-dihidrokumarinból, 96%-os hozamban.

NMR: δ 7,4 (m, 8H); 5,0 (t, 1H); 3,9 (s, 3H); 3,7 (s, 3H); 3,2 (d, 2H); 2,4 (s, 3H).

f) *Metil-3,3-bisz(2-metoxi-5-metil-fenil)-propionátot (XI)* hasonlóképpen kapunk kvantitatív hozamban az 1a) példa szerinti (I) laktonból és metil-jodidból.

NMR: δ 6,6–7,1 (m, 6H); 5,1 (t, 1H); 3,7 (s, 6H); 3,5 (s, 3H); 3,0 (d, 2H); 2,2 (s, 6H).

g) *Metil-3-[2,5-di(benzil-oxi)-fenil]-3-fenil-propionátot (XII)* hasonlóképpen kapunk 90%-os hozamban az 1b) példa szerinti (II) laktonból és benzil-kloridból.

NMR: δ 6,8–7,4 (m, 18H); 5,0 (s, 4H, t, 1H); 3,7 (s, 3H); 3,1 (d, 2H).

h) *Metil-3,3-bisz[2-(benzil-oxi)-4-metil-fenil]-propionátot (XIII)* hasonlóképpen kapunk 95%-os hozamban az 1d) példa szerinti (III) laktonból és benzil-kloridból. Gázkromatográfiásan a termék homogén, és a tömegspektruma helyes molekulatömeget mutat.

i) *Etil-3-(2,4-dimetoxi-fenil)-3-fenil-propionát (XIV)* 88 g (0,5 mól) etil-cinnanmát, 276 g (2,0 mól) dimetil-rezorcin és 50 g tömény kénsav elegyét forró vízfürdőn 2 órán át keverjük, majd az összes illékony anyagot vákuumban ledesztilláljuk. A maradék olajat dietil-éterben felvesszük, az oldatot nátrium-karbonát-oldattal mossuk, szárítjuk, majd bepároljuk. 101 g (64%) cím szerinti észtert kapunk viszkózus olaj formájában.

NMR: δ 6,4–7,2 (m, 8H); 4,9 (t, 1H); 4,0 (q, 2H); 3,7 (s, 6H); 3,0 (d, 2H); 1,1 (t, 3H).

j) *Metil-3,3-bisz(2,4-dimetoxi-fenil)-propionátot (XV)* hasonlóképpen állítunk elő metil-2,4-dimetoxi-cinnamátból és dimetil-rezorcinból. Az így kapott termék kb. 23% dimetil-rezorcint tartalmaz. A következő lépésben további tisztítás nélkül használjuk fel.

k) *Metil-3-(5-klór-2-metoxi-fenil)-3-fenil-propionát* 435 g (1,68 mól) T. Manimaran és V. T. Ramakrishnan által az Ind. J. Chem. B *18* (1979) 328 irodalmi helyen leírt módon előállított 6-klór-4-fenil-3,4-dihidrokumarint 140 g (3,5 mól) nátrium-hidroxid 500 ml vízzel készült forró oldatához adunk. Az oldatot 25 °C-ra hűtjük, és 442 g (3,5 mól) dimetil-szulfátot csepegtetünk hozzá 1 óra alatt, keverés és 25–35 °C-ra való hűtés közben. Az elegyet még 2 órán át keverjük, majd 100 g nátrium-hidroxid 500 ml vízzel készült oldatát adjuk hozzá, és addig keverjük az elegyet, amíg tiszta oldatot kapunk. Ehhez a metoxisav kicsapására feleslegben vett mennyiségű tömény sósavat adunk. A metoxi-sav olaj alakjában elkülönül, majd lassan kristályosodik. Kiszűrjük, vízzel mossuk, és szárítjuk. 2-Propanolból való kristályosítás eredményeként 455 g színtelen kristályos 3-(5-klór-2-metoxi-fenil)-3-fenil-propionsavat kapunk, amely 144 °C-on olvad.

291 g (1,0 mól) fenti sav, 1 liter metanol és 50 g tömény kénsav elegyét 8 órán át visszafolyatás közben forraljuk. Az oldószert ledesztilláljuk, a maradékot dietil-éterben felvesszük, vízzel és nátrium-karbonát-oldattal mossuk, szárítjuk, majd bepároljuk. 300 g (100%) nyers olaj marad vissza, amelyet IPE-ből átkristályosítunk, így a cím szerinti vegyületet fehér kristályos anyagként kapjuk, op. 65–66 °C.

Elemanalízis a $C_{17}H_{17}ClO_3$ (304,8) összegképlet alapján:

számított:	C: 67,0%;	H: 5,62%;	Cl: 11,63%;
talált:	C: 68,1%;	H: 5,82%;	Cl: 11,7%.

3. példa

3,3-Difenil-propanolok előállítása

3-(2-Metoxi-4-metil-fenil)-3-fenil-propanol (XVI)

84 g (0,295 mól) 2a) példa szerinti (VI) észter 150 ml száraz dietil-éterrel készült oldatát 11,3 g (0,295 mól) lítium-alumínium-hidrid 300 ml száraz dietil-éterrel készült szuszpenziójához csepegtetjük. Az elegyet egy éjszakán át keverjük, azután először 11 g víz óvatos adagolásával elbontjuk, majd 15%-os nátrium-hidroxid-oldatot adunk hozzá addig, amíg fehér szemcsés csapadék képződik. A keveréket szűrjük, a szűrletet vízzel mossuk, szárítjuk és bepároljuk. 71 g (91%) olaj marad vissza, amely állás közben kristályosodik. IPE-PET elegyből végzett átkristályosítás után fehér kristályos anyagot kapunk, amely 83 °C-on olvad.

Elemanalízis a $C_{17}H_{20}O_2$ (256,4) összegképlet alapján:

számított:	C: 79,65%;	H: 7,88%;	O: 12,48%;
talált:	C: 79,4%;	H: 7,89%;	O: 12,7%.

b) 3,3-Bisz(2-metoxi-fenil)-propanolt (XVII) hasonlóképpen kapunk kvantitatív hozamban, viszkózus olajként a 2b) példa szerinti (VII) észterből.

c) *3-[2,3-Di(benzil-oxi)-fenil]-3-fenil-propanolt (XVIII)* hasonlóképpen kapunk 96%-os hozamban, viszkózus olajként a 2c) példa szerinti (VIII) észterből.

d) *3-[2-(Benzil-oxi)-fenil]-3-fenil-propanolt (XIX)* hasonlóképpen kapunk olaj alakjában, 78%-os hozammal a 2d) példa szerinti (IX) észterből.

e) *3-(2-Metoxi-5-metil-fenil)-3-fenil-propanolt (XX)* hasonlóképpen kapunk olaj alakjában, kvantitatív hozamban, a 2e) példa szerinti (X) észterből.

f) *3,3-Bisz(2-metoxi-5-metil-fenil)-propanolt (XXI)* hasonlóképpen kapunk 98%-os hozamban a 2f) példa szerinti (XI) észterből. Op. 89 °C (IPE).

Elemanalízis a $C_{19}H_{24}O_3$ (300,4) összegképlet alapján:

számított:	C: 75,97%;	H: 8,05%;	O: 15,98%;
talált:	C: 75,9%;	H: 8,02%;	O: 16,1%.

g) *3-[2,5-Di(benzil-oxi)-fenil]-3-fenil-propanolt (XXII)* hasonlóképpen kapunk 88%-os hozamban a 2g) példa szerinti (XII) észterből. Op. 78 °C (IPE).

Elemanalízis a $C_{29}H_{28}O_3$ (424,5) összegképlet alapján:

számított:	C: 82,05%;	H: 6,65%;	O: 11,31%;
talált:	C: 82,0%;	H: 6,62%;	O: 11,2%.

h) *3,3-Bisz[2-(benzil-oxi)-4-metil-fenil]-propanolt (XXIII)* hasonlóképpen kapunk olaj formájában, 93%-os hozamban a 2h) példa szerinti (XIII) észterből.

i) *3-(2,4-Dimetoxi-fenil)-3-fenil-propanolt (XXIV)* aranyszínű olajként, 92%-os hozamban kapunk a 2i) példa szerinti (XIV) észterből.

NMR: δ 6,5–7,2 (m, 8H); 4,5 (t, 1H); 3,8 (s, 6H); 3,6 (m, 2H); 2,0–2,6 (m, 3H).

j) *3,3-Bisz(2,4-Dimetoxi-fenil)-propanolt (XXV)* hasonlóképpen kapunk a 2j) példa szerinti (XV) szennyezett észterből. Az NMR-spektrum szerint a termék kb. 20% dimetil-rezorcint tartalmaz.

k) *3-(4-Fluor-fenil)-3-(2-metoxi-fenil)-propanol (XXVI)* 93,5 g (0,5 mól) o-bróm-anizolból és 12 g (0,5 mól) magnéziumból 100 ml száraz dietil-éterben a szokásos módon Grignard-reagenst készítünk. 62 g (0,5 mól) p-fluor-benzaldehid 100 ml dietil-éterrel készült oldatát csepegtetjük az oldathoz. Kb. 1 óra eltelte után az elegyet ammónium-kloriddal megbontjuk, és feldolgozzuk. 100,6 g (87%) 4-fluor-2'-metoxi-difenil-metanolt kapunk. A terméket IPE-PET elegyből átkristályosítjuk, a fehér kristályok 88 °C-on olvadnak.

Elemanalízis a $C_{14}H_{13}FO_2$ (232,3) összegképlet alapján:

számított:	C: 72,40%;	H: 5,64%;
talált:	C: 72,9%;	H: 5,75%.

46,2 g (0,2 mól) fenti karbinolt 600 ml etanolban 4 g 5%-os szénhordozós palládiumkatalizátor jelenlétében hidrogénezzük. Mintegy 5–6 óra alatt a reakció teljesen végbemegy, és a reakcióelegyet feldolgozzuk. 40 g (93%) 4-fluor-2'-metoxi-difenil-metánt kapunk áttetsző olaj alakjában.

NMR: δ 6,8–7,2 (m, 8H); 4,0 (s, 2H); 3,8 (s, 3H).

71 g (0,33 mól) fenti metán-származékot 100 ml dietil-éterben 8,5 g (0,37 mól) nátriumból kb. 300 ml ammóniában in situ előállított nátrium-amid-oldathoz adunk. Kb. 1 óra eltelte után 17,5 g (0,395 mól) etilén-oxid 75 ml dietil-éterrel készült oldatát csepegtetjük a fenti elegyhez. A keverést 2 órán át folytatjuk, majd levegőárammal az ammónia nagy részét eltávolítjuk. Ezután szilárd ammónium-kloridot, majd vizet adunk a maradékhoz. A szerves fázist elválasztjuk, vízzel és 2N sósavval mossuk, szárítjuk és bepároljuk. 81,5 g (95%) cím szerinti vegyületet kapunk, amely 61 °C-on (IPE-PET) olvad.

Elemanalízis a $C_{16}H_{17}FO_2$ (260,3) összegképlet alapján:

számított:	C: 73,82%;	H: 6,58%;
talált:	C: 74,1%;	H: 6,77%.

l) 3-(5-Klór-2-metoxi-fenil)-3-fenil-propanol

91,5 g (0,3 mól) 2k) példa szerinti észter 500 ml száraz dietil-éterrel készült oldatát nitrogén alatt 11,4 g (0,3 mól) lítium-alumínium-hidrid és 200 ml száraz dietil-éter elegyéhez csepegtetjük. Az elegyet egy éjszakán át szobahőmérsékleten keverjük, majd 11 g víz és 11 g 15%-os nátrium-hidroxid-oldat hozzáadásával elbontjuk. Feldolgozás után 72,5 g (87,5%) színtelen olajat különítünk el. IPE-ből végzett átkristályosítás után a cím szerinti vegyületet fehér kristályos anyagként kapjuk, amely 80 °C-on olvad.

Elemanalízis a $C_{16}H_{17}ClO_2$ (276,8) összegképlet alapján:

számított:	C: 69,43%;	H: 6,19%;	Cl: 12,81%;
talált:	C: 70,1%;	H: 6,44%;	Cl: 12,9%.

4. példa

3,3-Difenil-propil-p-toluolszulfonátok előállítása

a) 3,3-Bisz(2-metoxi-fenil)-propil-p-toluolszulfonát (XXVII)

35 g (0,128 mól) 3b) példa szerinti (XVII) propanol, 100 ml kloroform és 30 ml piridin elegyét kb. –10 °C-ra hűtjük, és 29 g (0,15 mól) p-toluolszulfonil-kloridot adunk hozzá. Az elegyet egy éjszakán át hűtőszekrényben, kb. +5 °C-on állni hagyjuk, majd jeges vízbe öntjük. A szerves fázist vízzel és hideg 2N sósavval mossuk, szárítjuk, majd az oldószert 50 °C alatti hőmérsékleten ledesztilláljuk. Kvantitatív hozamban egy nyers olaj marad vissza, amelyet IPE-ből átkristályosítunk, így fehér kristályos anyagot kapunk, amelynek alacsony és határozatlan az olvadáspontja.

Elemanalízis a $C_{24}H_{26}O_5S$ (426,5) összegképlet alapján:

számított:	C: 67,58%;	H: 6,14%;	S: 7,52%;
talált:	C: 66,8%;	H: 6,22%;	S: 7,76%.

b) *3-(2-Metoxi-4-metil-fenil)-3-fenil-propil-p-toluol-szulfonátot (XXXI)* kvantitatív hozamban kapunk a 3a) példa szerinti (XVI) propanolból.

c) *3-[2,3-(Dibenzil-oxi)-fenil]-3-fenil-propil-p-toluol-szulfonátot (XXVIII)* hasonlóképpen kapunk sűrű olaj formájában, 88%-os hozamban a 3c) példa szerinti (XVIII) propanolból.

d) *3-[2-(Benzil-oxi)-fenil]-3-fenil-propil-p-toluolszulfonátot (XXIX)* hasonlóképpen kapunk 98%-os hozamban a 3d) példa szerinti (XIX) propanolból.

e) *3-(2-Metoxi-5-metil-fenil)-3-fenil-propil-p-toluol-szulfonátot (XXX)* kvantitatív hozamban kapunk a 3e) példa szerinti (XX) propanolból. Op. 64 °C (IPE-PET).

Elemanalízis a $C_{23}H_{24}O_4S$ (396,5) összegképlet alapján:

számított:	C: 69,67%;	H: 6,10%;	S: 8,09%;
talált:	C: 69,8%;	H: 6,20%;	S: 7,85%.

f) *3,3-Bisz(2-metoxi-5-metil-fenil)-propil-p-toluolszulfonátot (XXXII)* kvantitatív hozamban kapunk a 3f) példa szerinti (XXI) propanolból. Op. 117 °C (aceton-PET).

Elemanalízis a $C_{26}H_{30}O_5S$ (454,5) összegképlet alapján:

számított:	C: 68,7%;	H: 6,65%;	S: 7,05%;
talált:	C: 68,8%;	H: 6,66%;	S: 7,11%.

g) *3-[2,5-Di(benzil-oxi)-fenil]-3-fenil-propil-p-toluolszulfonátot (XXXIII)* hasonlóképpen kapunk kvantitatív hozamban a 3g) példa szerinti (XXII) propanolból.

h) *3,3-Bisz[2-(benzil-oxi)-4-metil-fenil]-propil-p-toluolszulfonátot (XXXIV)* hasonlóképpen kapunk 86%-os hozamban a 3h) példa szerinti (XXIII) propanolból.

i) *3-(2,4-Dimetoxi-fenil)-3-fenil-propil-p-toluolszulfonátot (XXXV)* hasonlóképpen kapunk 96%-os hozamban a 3i) példa szerinti (XXIV) propanolból.

j) *3,3-Bisz(2,4-dimetoxi-fenil)-propil-p-toluolszulfonátot (XXXVI)* hasonlóképpen kapunk a 3j) példa szerinti (XXV) propanolból. A terméket dimetil-rezorcin szennyezi.

b) N-(terc-Butil)-3-[2,3-di(benzil-oxi)-fenil]-3-fenil-propil-amin (LI) és hidrokloridja

A szabad bázist 78%-os hozamban kapjuk a 4c) példa szerinti (XXVIII) tozilátból. A hidrokloridsó 184–185 °C-on olvad (aceton-metanol-IPE).

Elemanalízis a $C_{33}H_{38}NO_2Cl$ (516,1) összegképlet alapján:

számított:	C: 76,79%;	H: 7,42%;	N: 2,71%;
	O: 6,20%;	Cl: 6,87%;	
talált:	C: 76,3%;	H: 7,30%;	N: 2,72%;
	O: 6,42%;	Cl: 6,81%.	

c) N-(terc-Butil)-3-[2-(benzil-oxi)-fenil]-3-fenil-propil-amin (LII) és hidrogén-oxalátja

A szabad bázist 84%-os hozamban kapjuk a 4d) példa szerinti (XXIX) tozilátból. Az oxálsavas só olvadáspontja 198 °C (aceton-éter).

Elemanalízis a $C_{28}H_{33}NO_5$ (463,6) összegképlet alapján:

számított:	C: 72,54%;	H: 7,18%;	N: 3,02%;
talált:	C: 71,8%;	H: 7,13%;	N: 2,95%.

d) N-(terc-Butil)-3-(2-metoxi-5-metil-fenil)-3-fenil-propil-amin (LIII) és hidrokloridja

A szabad bázist 90%-os hozamban kapjuk a 4e) példa szerinti (XXX) tozilátból. Éteres hidrogén-kloriddal való kezelés hatására némiképp higroszkópos só képződik, amely feltehetően 1/4 molekula vizet tartalmaz. Op. 171 °C (etanol-éter).

Elemanalízis a $C_{21}H_{29}NO \cdot HCl \cdot 1/4\ H_2O$ (352,5) összegképlet alapján:

számított:	C: 71,55%;	H: 8,74%;	N: 3,97%;
	O: 5,67%;	Cl: 10,06%;	
talált:	C: 71,8%;	H: 8,72%;	N: 4,05%;
	O: 5,57%;	Cl: 10,1%.	

e) N-(terc-Butil)-3-(2-metoxi-4-metil-fenil)-3-fenil-propil-amin (LIV) és hidrokloridja

A szabad bázist kvantitatív hozamban kapjuk a 4b) példa szerinti (XXXI) tozilátból. A hidrokloridsó olvadáspontja 138–139 °C (metanol-izopropanol). 3/4 mól vizet tartalmaz.

Elemanalízis a $C_{21}H_{30}NOCl \cdot 3/4H_2O$ (361,5) összegképlet alapján:

számított:

C: 69,77%; H: 8,80%; N: 3,88%; Cl: 9,81%;

talált:

C: 69,8%; H: 8,76%; N: 3,93%; Cl: 9,75%.

f) N-(terc-Butil)-3,3-bisz(2-metoxi-5-metil-fenil)-propil-amin (LV) és hidrokloridja

A szabad bázist kvantitatív hozamban kapjuk a 4f) példa szerinti (XXXII) tozilátból. A hidrokloridsó olvadáspontja 242 °C (aceton).

Elemanalízis a $C_{23}H_{34}NOCl$ (392,0) összegképlet alapján:

számított:

C: 70,47%; H: 8,74%; N: 3,57%; Cl: 9,05%;

talált:

C: 70,2%; H: 8,81%; N: 3,46%; Cl: 8,99%.

g) N-(terc-Butil)-3-[2,5-di(benzil-oxi)-fenil]-3-fenil-propil-amin (LVI) és hidrokloridja

A szabad bázist 85%-os hozamban kapjuk a 4g) példa szerinti (XXXIII) tozilátból. A hidrogén-klorid-só olvadáspontja 188 °C (etanol-éter).

Elemanalízis a $C_{33}H_{38}NO_2Cl$ (516,1) összegképlet alapján:

számított:	C: 76,79%;	H: 7,42%;	N: 2,71%;
	O: 6,20%;	Cl: 6,87%;	
talált:	C: 77,2%;	H: 7,50%;	N: 2,64%;
	O: 6,53%;	Cl: 6,85%.	

h) N-(terc-Butil)-3,3-bisz[2-(benzil-oxi)-4-metil-fenil]-propil-amin (LVII) és hidrokloridja

A szabad bázist 94%-os hozamban kapjuk a 4h) példa szerinti (XXXIV) tozilátból. A hidroklordsó olvadáspontja 210 °C (aceton-éter).

Elemanalízis a $C_{35}H_{42}NO_2Cl$ (544,2) összegképlet alapján:

számított:	C: 77,25%;	H: 7,78%;	N: 2,57%;
	O: 5,89%;	Cl: 6,52%;	
talált:	C: 77,6%;	H: 7,82%;	N: 2,35%;
	O: 6,08%;	Cl: 6,55%.	

i) N-(terc-Butil)-3-(2,4-dimetoxi-fenil)-3-fenil-propil-amin (LVIII) és hidrokloridja

A szabad bázist 84%-os hozamban kapjuk a 4i) példa szerinti (XXXV) tozilátból. A hidrogén-klorid-só olvadáspontja 196 °C (aceton-etanol-éter).

Elemanalízis a $C_{21}H_{30}NO_2Cl$ (363,9) összegképlet alapján:

számított:	C: 69,31%;	H: 8,31%;	N: 3,85%;
	O: 8,79%;	Cl: 9,74%;	
talált:	C: 69,3%;	H: 8,44%;	N: 3,80%;
	O: 8,89%;	Cl: 9,81%.	

j) N-(terc-Butil)-3,3-bisz(2,4-dimetoxi-fenil)-propil-amin (LIX) és hidrokloridja

A szabad bázist 60%-os hozamban kapjuk a 4j) példa szerinti (XXXVI) tozilátból. A hidrogén-klorid-só olvadáspontja 251 °C (metanol-aceton).

Elemanalízis a $C_{23}H_{34}NO_4Cl$ (424,0) összegképlet alapján:

számított:	C: 65,15%;	H: 8,08%;	N: 3,30%;
	O: 15,09%;	Cl: 8,36%;	
talált:	C: 64,5%;	H: 8,06%;	N: 3,57%;
	O: 15,3%;	Cl: 8,67%.	

k) N-(terc-Butil)-3-(4-fluor-fenil)-3-(2-metoxi-fenil)-propil-amin (LX) és hidrokloridja

A szabad bázist 89%-os hozamban kapjuk a 4k) példa szerinti (XXXVII) tozilátból. A hidrokloridsó olvadáspontja 194 °C (etanol-aceton).

Elemanalízis a $C_{20}H_{27}NOFCl$ (351,9) összegképlet alapján:

számított:

C: 68,26%; H: 7,73%; N: 3,98%; Cl: 10,08%;

talált:

C: 68,9%; H: 7,97%; N: 4,01%; Cl: 9,69%.

k) *3-(4-Fluor-fenil)-3-(2-metoxi-fenil)-propil-p-toluolszulfonátot (XXXVII)* hasonlóképpen kapunk 88%-os hozamban a 3k) példa szerinti (XXVI) propanolból. Op. 67 °C (IPE).
Elemanalízis a $C_{23}H_{23}FO_4S$ (414,5) összegképlet alapján:
számított: C: 66,65%; H: 5,59%; S: 7,74%;
talált: C: 67,1%; H: 5,69%; S: 7,78%.

l) 3-(2-Metoxi-fenil)-3-fenil-propil-p-toluolszulfonát (XLVIII)

1080 g (10 mól) anizol, 216 g (2 mól) benzil-alkohol és 40 g p-toluolszulfonsav elegyét 2 órán át visszafolyatás közben forraljuk egy vízleválasztóval ellátott készülékben. Az anizol feleslegét azután ledesztilláljuk, az olajos maradékot dietil-éterben oldjuk, vízzel és nátrium-karbonát-oldattal mossuk, szárítjuk és frakcionáltan desztilláljuk. Így 304 g (77%) halványsárga olajat kapunk, amely 53 Pa nyomáson 115–118 °C-on forr. Az NMR-spektrum alapján a termék o-metoxi- és p-metoxi-difenil-metán 1:1 arányú keveréke. Ezt az anyagot etilén-oxiddal a megfelelő propanolok keverékévé alakítjuk, amint azt a 3k) példában a (XXVI) propanol előállítására leírtuk. Ezt a propanolelegyet azután a fentebb leírt módon a p-toluolszulfonátok keverékévé alakítjuk át, amelyből a cím szerinti vegyületet 35%-os hozamban különítjük el IPE-ből végzett kétszeri átkristályosítással. Op. 108 °C.
Elemanalízis a $C_{23}H_{24}O_4S$ (396,5) összegképlet alapján:
számított: C: 69,67%; H: 6,10%; S: 8,09%;
talált: C: 69,3%; H: 6,00%; S: 8,17%.

m) 3-(5-Klór-2-metoxi-fenil)-3-fenil-propil-p-toluolszulfonát

66 g (0,24 mól) 3l) példa szerinti alkohol, 300 ml kloroform és 75 ml piridin elegyéhez részletekben 55 g (0,29 mól) hideg p-toluolszulfonil-kloridot adunk. Az elegyet 18 órán át 5 °C-on tartjuk, majd az oldószert vákuumban, 50 °C alatti hőmérsékleten lepároljuk. A maradékot dietil-éterben felvesszük. Vízzel és 2N sósavval mossuk, szárítjuk, majd bepároljuk. 100 g (97%) szalmasárga szirup marad vissza. IPE-ből végzett átkristályosítás eredményeként a cím szerinti vegyületet kapjuk, amely 89–90 °C-on olvad.
Elemanalízis a $C_{23}H_{23}ClO_4S$ (430,96) összegképlet alapján:
számított:
C: 64,10%; H: 5,38%; S: 7,44%; Cl: 8,23%;
talált:
C: 64,4%; H: 5,45%; S: 7,04%; Cl: 8,17%.

5. példa
Tercier 3,3-difenil-propil-aminok előállítása

a) N,N-Diizopropil-3,3-bisz(2-metoxi-fenil)-propil-amin (XXXVIII) és hidrogén-oxalátja

42,6 g (0,1 mól) 4a) példa szerinti (XXVII) tozilát, 100 ml acetonitril és 100 g (1,0 mól) diizopropil-amin elegyét nyomásálló lombikban 80 °C-on 4–6 napon át melegítjük. Ezután az illékony anyagokat lepároljuk, a maradékot feleslegben vett 2N nátrium-hidroxid-oldattal kezeljük, és dietil-éterrel extraháljuk. Az extraktumot vízzel mossuk, majd 2N sósavval extraháljuk. Ezt az extraktumot dietil-éterrel mossuk, meglúgosítjuk, dietil-éterrel extraháljuk, az extraktumot vízzel mossuk, szárítjuk, derítjük, szűrjük és bepároljuk. 24,0 g (68%) nyers olaj marad vissza. Ezt az olajat oxálsavas sóvá alakítjuk úgy, hogy a bázis acetonos oldatához 1 mól ekvivalens oxálsav acetonos oldatát adjuk. Op. 160–161 °C (aceton).
Elemanalízis a $C_{25}H_{35}NO_6$ (445,6) összegképlet alapján:
számított:
C: 67,39%; H: 7,92%; N: 3,14%; O: 21,55%;
talált:
C: 67,2%; H: 8,22%; N: 2,94%; O: 21,9%.

b) N,N-Diizopropil-3-[2,3-di(benzil-oxi)-fenil]-3-fenil-propil-amin (XXXIX)

A szabad bázist ugyanilyen módon kapjuk 75%-os hozammal a 4c) példa szerinti (XXVIII) tozilátból.
NMR: δ 6,9–7,2 (m, 18H); 5,0 (s, 4H); 0,9 (d, 12H).

c) N,N-Diizopropil-3-(2-metoxi-5-metil-fenil)-3-fenil-propil-amin (XL) és hidrogén-fumarátja

A szabad bázist 69%-os hozammal kapjuk a 4e) példa szerinti (XXX) tozilátból. A szokásos fumársavas sóvá alakítjuk. Op. 176 °C (aceton).
Elemanalízis a $C_{27}H_{37}NO_5$ (455,7) összegképlet alapján:
számított:
C: 71,17%; H: 8,20%; N: 3,07%; O: 17,6%;
talált:
C: 71,3%; H: 8,27%; N: 3,04%; O: 17,9%.

d) N,N-Diizopropil-3-(2-metoxi-4-metil-fenil)-3-fenil-propil-amin (XLI) és hidrogén-fumarátja

A szabad bázist 25%-os hozamban kapjuk a 4b) példa szerinti (XXXI) tozilátból. A fumársavas só olvadáspontja 147–148 °C (aceton).
Elemanalízis a $C_{27}H_{37}NO_5$ (455,7) összegképlet alapján:
számított:
C: 71,17%; H: 8,20%; N: 3,07% O: 17,6%;
talált:
C: 71,3%; H: 8,14%; N: 3,00%; O: 17,6%.

e) N,N-Diizopropil-3,3-bisz(2-metoxi-5-metil-fenil)-propil-amin (XLII) és hidrokloridja

A szabad bázist 78%-os hozamban kapjuk a 4f) példa szerinti (XXXII) tozilátból. Ezt dietil-éteres hidrogén-klorid-sóvá alakítjuk a szokásos módon. Op. 163–164 °C (aceton-éter).
Elemanalízis a $C_{25}H_{38}NO_2Cl$ (420,1) összegképlet alapján:
számított: C: 71,49%; H: 9,12%; N: 3,33%;
O: 7,61%; Cl: 8,44%;
talált: C: 71,6%; H: 9,08%; N: 3,27%;
O: 7,93%; Cl: 8,36%.

f) N,N-Diizopropil-3-[2,5-di(benzil-oxi)-fenil]-3-fenil-propil-amin (XLIII)

A szabad bázist 70%-os hozamban kapjuk a 4g) példa szerinti (XXXIII) tozilátból.

NMR: δ 6,6–7,2 (m, 18H); 5,0 (s, 4H); 4,5 (t, 1H); 1,0 (d, 12H).

g) N,N-Diizopropil-3,3-bisz[2-(benzil-oxi)-4-metil-fenil]-propil-amin (XLIV)

A szabad bázist 62%-os hozamban kapjuk a 4h) példa szerinti (XXXIV) tozilátból.

NMR: δ 6,8–7,2 (m, 16H); 4,8 (s, 4H, t, 1H); 0,9 (d, 12H).

h) N,N-Diizopropil-3-(2,4-dimetoxi-fenil)-3-fenil-propil-amin (XLV)

A szabad bázist 56%-os hozamban kapjuk a 4i) példa szerinti tozilátból.

NMR: δ 6,5–7,3 (m, 8H); 4,4 (t, 1H); 3,8 (s, 6H); 1,0 (d, 12H).

i) N,N-Diizopropil-3,3-bisz(2,4-dimetoxi-fenil)-propil-amin (XLVI)

A szabad bázist 34%-os hozamban kapjuk a 4j) példa szerinti (XXXVI) tozilátból.

NMR: δ 6,5–7,3 (m, 6H); 4,6 (t, 1H); 3,9 (s, 12H); 1,0 (d, 12H).

j) N,N-Diizopropil-3-(4-fluor-fenil)-3-(2-metoxi-fenil)-propil-amin (XLVII)

A szabad bázist 71%-os hozamban kapjuk a 4k) példa szerinti (XXXVII) tozilátból.

k) N,N-Diizopropil-3-(2-metoxi-fenil)-3-fenil-propil-amin (XLIX) és hidrogén-fumarátja

A szabad bázist 86%-os hozamban kapjuk a 4l) példa szerinti (XLVIII) ozilátból, majd a szokásos módon fumársavas sóvá alakítjuk. Op. 134–136 °C (aceton-IPE) vagy 163–164 °C (metanol).

Elemanalízis a $C_{26}H_{36}NO_5$ (441,6) összegképlet alapján:

számított:			
C: 70,72%;	H: 7,99%;	N: 3,28%;	O: 18,12%;
talált:			
C: 70,8%;	H: 7,93%;	N: 3,28%;	O: 18,1%.

l) N-[3-(2-Metoxi-fenil)-3-fenil-propil]-2,2,6,6-tetrametil-piperidin (LXIV)

Ezt a vegyületet ugyanígy kapjuk, 54%-os hozamban a 4l) példa szerinti (XLVIII) tozilátból és 2,2,6,6-tetrametil-piperidinből. Op. 100 °C (IPE).

Elemanalízis a $C_{25}H_{35}NO$ (365,6) összegképlet alapján:

számított:	C: 82,14%;	H: 9,65%;	N: 3,83%;
talált:	C: 82,0%;	H: 9,62%;	N: 3,57%.

m) N,N-Diizopropil-3-(5-klór-2-metoxi-fenil)-3-fenil-propil-amin

43,1 g (0,1 mól) 4m) példa szerinti tozilátot 4 napon át 50 g (0,5 mól) diizopropil-aminnal 100 ml acetonitrilben 80 °C-on melegítünk. Így 23 g (64%) nyers cím szerinti vegyületet kapunk, amely gázkromatográfiásan vizsgálva legalább 93%-os tisztaságú.

n) N-[3-[2-(Benzil-oxi)-fenil]-3-fenil-propil]-2,2,5,5-tetrametil-pirrolidin

Ezt a vegyületet hasonlóképpen állítjuk elő a 4d) példa szerinti (XXIX) tozilátból és 2,2,5,5-tetrametil-pirrolidinből. A terméket ragadós olajként kapjuk, amelyet további tisztítás nélkül alakítunk a hidroxi-analógjává [9ab) példa].

o) N-[3-[2-(Benzil-oxi)-fenil]-3-fenil-propil]-4-hidroxi-2,2,6,6-tetrametil-piperidin

Ezt a vegyületet hasonlóképpen állítjuk elő a 4d) példa szerinti (XXIX) tozilátból és 4-hidroxi-2,2,6,6-tetrametil-piperidinből. A terméket ragadós olaj formájában kapjuk, amelyet további tisztítás nélkül alakítunk a hidroxivegyületté [9ac) példa].

p) N-(2-Hidroxi-1,1,-dimetil-etil)-3-[2-(benzil-oxi)-fenil]-3-fenil-propil-amin

Ezt a vegyületet hasonlóképpen állítjuk elő a 4d) példa szerinti (XXIX) tozilátból és 2-amino-2-metil-propanolból. A szilárd termék diizopropil-éterből végzett kristályosítás után 103 °C-on olvad. Kiindulási anyagként használjuk a 7p) példában.

Elemanalízis a $C_{26}H_{31}NO_2$ (389,5) összegképlet alapján:

számított:			
C: 80,17%;	H: 8,02%;	N: 3,60%;	O: 8,22%;
talált:			
C: 80,0%;	H: 8,09%;	N: 3,69%;	O: 8,51%.

q) N-(1-Adamantil)-3-[2-(benzil-oxi)-fenil]-3-fenil-propil-amin

Ezt a vegyületet hasonlóképpen állítjuk elő a 4d) példa szerinti (XXIX) tozilátból és 1-amino-adamantánból. A 7q) példában kiindulási anyagként használjuk. A hidroklorid-szemihidrátja, amelyet acetonitrilben állítunk elő, 225 °C-on olvad.

Elemanalízis a $C_{32}H_{37}NO \cdot HCl \cdot 1/2\ H_2O$ (497,1) összegképlet alapján:

számított:	C: 77,31%;	H: 7,91%;	N: 2,82%;
	O: 4,83%;	Cl: 7,13%;	
talált:	C: 77,3%;	H: 8,23%;	N: 2,65%;
	O: 5,04%;	Cl: 7,14%.	

6. példa

Szekunder 3,3-difenil-propil-aminok előállítása

a) N-(terc-Butil)-3,3-bisz(2-metoxi-fenil)-propil-amin (L) és hidrogén-oxalátja

A 4a) példa szerinti (XXVII) tozilátot terc-butil-amin nagy feleslegével melegítjük az 5. példában leírt módon, így a szabad bázist 78%-os hozamban kapjuk, majd a szokásos módon oxálsavas sóvá alakítjuk. Op. 135–136 °C (aceton-éter).

Elemanalízis a $C_{21}H_{31}NO_6$ (417,5) összegképlet alapján:

számított:			
C: 66,17%;	H: 7,48%;	N: 3,36%;	O: 22,99%;
talált:			
C: 65,6%;	H: 7,31%;	N: 3,36%;	O: 23,4%.

l) N-(terc-Butil)-3-(2-metoxi-fenil)-3-fenil-propil-amin (LXI) és hidrokloridja

A szabad bázist 88%-os hozamban kapjuk a 4l) példa szerinti (XLVIII) tozilátból. A hidrokloridsó 205 °C-on olvad.

Elemanalízis a $C_{20}H_{28}NOCl$ (333,9) összegképlet alapján:

számított:
C: 71,94%; H: 8,45%; N: 4,20%; O: 4,79%;
talált:
C: 71,9%; H: 8,44%; N: 4,67%; O: 4,79%.

m) N-(1,1-Dimetil-propil)-3-(2-metoxi-5-metil-fenil)-3-fenil-propil-amin (LXII) és hidrokloridja

A szabad bázist 95%-os hozamban kapjuk a 4e) példa szerinti (XXX) tozilátból és terc-amil-aminból. A hidrokloridsó olvadáspontja 188–189 °C (etanol-aceton).

Elemanalízis a $C_{22}H_{32}NOCl$ (362,0) összegképlet alapján:

számított: C: 73,00%; H: 8,91%; N: 3,87%; O: 4,42%; Cl: 9,80%;
talált: C: 73,4%; H: 8,98%; N: 3,83%; O: 4,61%; Cl: 9,51%.

n) N-(1,1-Dimetil-propil)-3,3-bisz(2-metoxi-5-metil-fenil)-propil-amin (LXIII) és hidrokloridja

A szabad bázist 94%-os hozamban kapjuk a 4f) példa szerinti (XXXII) tozilátból és terc-amil-aminból. A hidrokloridsó olvadáspontja 210 °C (etanol-aceton).

Elemanalízis a $C_{24}H_{36}NO_2Cl$ (406.0) összegképlet alapján:

számított: C: 71,00%; H: 8,94%; N: 3,45%; O: 7,88%; Cl: 8,73%;
talált: C: 71,1%; H: 9,01%; N: 3,60%; O: 7,92%; Cl: 8,73%.

o) N-(terc-Butil)-3-(5-klór-2-metoxi-fenil)-3-fenil-propil-amin

43,1 g (0,1 mól) 4m) példa szerinti tozilátot 100 ml acetonitrilben 37 g (0,5 mól) terc-butil-aminnal nyomásálló lombikban 4 napon át 80 °C-on melegítünk. A szokásos feldolgozás után 32 g (100%) nyers cím szerinti vegyületet kapunk. A bázist dietil-éter és aceton elegyében dietil-éteres hidrogén-kloriddal kezeljük, így a hidrokloridsót kapjuk, amely 216–218 °C-on olvad.

Elemanalízis a $C_{20}H_{26}ClNO \cdot HCl$ (368,36) összegképlet alapján:

számított:
C: 65,21%; H: 7,39%; N: 3,80%; Cl: 19,25%;
talált:
C: 65,1%; H: 7,39%; N: 3,90%; Cl: 18,7%.

7. példa

Tercier 3,3-difenil-propil-aminok előállítása szekunder aminokból

a) N-Metil-N-(terc-butil)-3-(2-metoxi-fenil)-3-fenil-propil-amin (LXV) és hidrokloridja

29,7 g (0,1 mól) 6l) példa szerinti (LXI) szekunder amin, 13,8 g (0,3 mól) hangyasav és 12,5 g (0,12 mól) 37%-os formaldehid-oldat elegyét 18–24 órán át viszszafolyatás közben forraljuk. Ezután lehűtjük, nátrium-hidroxiddal meglúgosítjuk, és dietil-éterrel extraháljuk. Az extraktumot vízzel mossuk, szárítjuk, majd bepároljuk. 29,3 g (94%) nyers olaj marad vissza. A hidrogén-klorid-sót dietil-éteres hidrogén-kloriddal állítjuk elő a szokásos módon. Op. 199 °C.

Elemanalízis a $C_{21}H_{30}NOCl$ (347,9) összegképlet alapján:

számított:
C: 72,49%; H: 8,69%; N: 4,03%; Cl: 10,19%;
talált:
C: 71,9%; H: 8,79%; N: 4,23%; Cl: 10,1%.

b) N-Metil-N-(terc-butil)-3-(2-metoxi-5-metil-fenil)-3-fenil-propil-amin (LXVI) és hidrokloridja

A szabad bázist ugyanilyen módon kapjuk 89%-os hozammal a 6d) példa szerinti (LIII) aminból. A hidrokloridsó olvadáspontja 161 °C (aceton).

Elemanalízis a $C_{22}H_{32}NOCl$ (362,0) összegképlet alapján:

számított:
C: 73,00%; H: 8,91%; N: 3,87%; O: 4,42%; Cl: 9,08%;
talált: C: 73,0%; H: 8,96%; N: 3,94%; O: 4,59%; Cl: 9,77%.

c) N-Metil-N-(terc-butil)-3,3-bisz(2-metoxi-fenil)-propil-amin (LXVII) és hidrokloridja

A szabad bázist 96%-os hozamban kapjuk a 6a) példa szerinti (L) aminból. A hidrokloridsó olvadáspontja 187–190 °C (aceton-éter).

Elemanalízis a $C_{22}H_{33}NOCl$ (378,0) összegképlet alapján:

számított: C: 69,91%; H: 8,54%; N: 3,71%; O: 8,47%; Cl: 9,38%;
talált: C: 69,9%; H: 8,56%; N: 3,53%; O: 8,93%; Cl: 8,92%.

d) N-Metil-N-(terc-butil)-3-(2-metoxi-4-metil-fenil)-3-fenil-propil-amin (LXVIII)

A szabad bázist 96%-os hozamban kapjuk a 6e) példa szerinti (LIV) aminból. Op. 64 °C (IPE).

Elemanalízis a $C_{22}H_{31}NO$ (325,5) összegképlet alapján:

számított:
C: 81,17%; H: 9,60%; N: 4,30%; O: 4,92%;
talált:
C: 81,0%; H: 9,83%; N: 4,15%; O: 5,03%.

e) N-Metil-N-(terc-butil)-3,3-bisz(2-metoxi-5-metil-fenil)-propil-amin (LXIX)

A szabad bázist 97%-os hozamban kapjuk a 6f) példa szerinti (LV) aminból. Op. 95 °C (IPE).

Elemanalízis a $C_{24}H_{35}NO_2$ (370,0) összegképlet alapján:

számított:
C: 78,00%; H: 9,55%; N: 3,79%; O: 8,66%;
talált:
C: 78,1%; H: 9,57%; N: 3,70%; O: 8,80%.

f) N-Metil-N-(terc-butil)-3-(4-fluor-fenil)-3-(2-metoxi-fenil)-propil-amin (LXX) és hidrokloridja

A szabad bázist 82%-os hozamban kapjuk a 6k) példa szerinti (LX) aminból. A hidrokloridsó olvadáspontja 218 °C (etanol-aceton).

Elemanalízis a $C_{21}H_{29}NOClF$ (365,9) összegképlet alapján:

számított:
C: 68,93%; H: 7,99%; N: 3,83%; Cl: 9,69%;
talált:
C: 69,0%; H: 7,97%; N: 3,70%; Cl: 9,60%.

g) N-(1,1-Dimetil-propil)-N-metil-3-(2-metoxi-5-metil-fenil)-3-fenil-propil-amin (LXXI) és hidrokloridja

A szabad bázist 98%-os hozamban kapjuk a 6m) példa szerinti (LXII) aminból. A hidrogén-klorid-só olvadáspontja 176–177 °C (aceton).

Elemanalízis a $C_{23}H_{34}NOCl$ (376,0) összegképlet alapján:

számított:
C: 73,47%; H: 9,11%; N: 3,73%; Cl: 9,43%;
talált:
C: 73,4%; H: 9,15%; N: 3,73%; Cl: 9,41%.

h) N-(1,1-Dimetil-propil)-N-metil-3,3-bisz(2-metoxi-5-metil-fenil)-propil-amin (LXXII) és hidrokloridja

A szabad bázist 89%-os hozamban kapjuk a 6n) példa szerinti (LXIII) aminból. A hidrogén-klorid-só olvadáspontja 147 °C (aceton-éter).

Elemanalízis a $C_{25}H_{37}NO_2Cl$ (420,1) összegképlet alapján:

számított: C: 71,49%; H: 9,12%; N: 3,34%;
O: 7,62%; Cl: 8,44%;
talált: C: 70,8%; H: 9,20%; N: 3,63%;
O: 7,74%; Cl: 8,42%.

i) N-Metil-N-(terc-butil)-3-(2,4-dimetoxi-fenil)-3-fenil-propil-amin (LXXIII)

Ezt a vegyületet kvantitatív hozamban, olajként kapjuk a 6i) példa szerinti (LVIII) aminból.

NMR: δ 6,5–7,3 (m, 8H); 4,3 (t, 1H); 3,8 (s, 6H); 2,3 (s, 3H); 1,0 (s, 9H).

j) N-Metil-N-(terc-butil)-3-[2,3-di(benzil-oxi)-fenil]-3-fenil-propil-amin (LXXIV)

Ezt a vegyületet olajként, 95%-os hozamban kapjuk a 6g) példa szerinti (LVI) aminból.

k) N-Metil-N-(terc-butil)-3,3-bisz[2-(benzil-oxi)-4-metil-fenil]-propil-amin (LXXV) és hidrokloridja

A szabad bázist 92%-os hozamban kapjuk a 6k) példa szerinti (LVII) aminból. A hidrogén-klorid-só olvadáspontja 170–171 °C (aceton-éter).

Elemanalízis a $C_{36}H_{44}NO_2Cl$ (558,2) összegképlet alapján:

számított: C: 77,46%; H: 7,95%; N: 2,51%;
O: 5,73%; Cl: 6,35%;
talált: C: 77,6%; H: 7,86%; N: 2,42%;
O: 5,89%; Cl: 6,31%.

l) N-Metil-N-(terc-butil)-3,3-bisz(2,4-dimetoxi-fenil)-propil-amin (LXXVI) és hidrokloridja

A szabad bázist 96%-os hozamban kapjuk a 6j) példa szerinti (LIX) aminból. A hidrogén-klorid-só olvadáspontja 180–190 °C, és a vegyület feltehetően 1/4 mól vizet tartalmaz.

Elemanalízis a $C_{24}H_{36}NO_4Cl \cdot 1/4H_2O$ (447,0) összegképlet alapján:

számított: C: 64,48%; H: 8,34%; N: 3,13%;
O: 16,11%; Cl: 7,93%;
talált: C: 64,5%; H: 8,27%; N: 3,02%;
O: 16,2%; Cl: 8,19%.

m) N-Metil-N-(terc-butil)-3-[2,3-di(benzil-oxi)-fenil]-3-fenil-propil-amin (LXXVII)

Ezt a vegyületet olajként, 98%-os hozamban kapjuk a 6b) példa szerinti (LI) aminból.

NMR: δ 6,9–7,3 (m, 18H); 2,1 (s, 3H); 1,0 (s, 9H).

n) N-Metil-N-(terc-butil)-3-[2-(benzil-oxi)-fenil]-3-fenil-propil-amin (LXXVIII)

Ezt a vegyületet olajként, 97%-os hozamban kapjuk a 6c) példa szerinti (LII) aminból.

NMR: δ 6,9–7,3 (m, 14H); 5,0 (s, 4H); 4,5 (t, 1H); 2,2 (s, 3H); 0,9 (s, 9H).

o) N-Metil-N-(terc-butil)-3-(5-klór-2-metoxi-fenil)-3-fenil-propil-amin

25,3 g (0,076 mól) 6o) példa szerinti szekunder amint 18 órán át 9,2 g (0,2 mól) hangyasavval és 8,5 g (0,1 mól) 35%-os formaldehid-oldattal forralunk visszafolyatás közben. A feldolgozás után 25,6 g (97,5%) nyers bázist kapunk. Ezt acetonban oldjuk, ekvimoláris mennyiségű oxálsav acetonos oldatát adjuk hozzá. A cím szerinti vegyület hidrogén-oxalátja beige színű kristályok formájában válik ki, op. 165 °C.

Elemanalízis a $C_{21}H_{28}ClNO \cdot C_2H_2O_4$ (436,0) összegképlet alapján:

számított:
C: 63,37%; H: 6,94%; N: 3,21%; Cl: 8,13%;
talált:
C: 62,7%; H: 6,83%; N: 3,10%; Cl: 7,97%.

p) N-(2-Hidroxi-1,1-dimetil-etil)-N-metil-3-[2-(benzil-oxi)-fenil]-3-fenil-propil-amin

Ezt a vegyületet hasonlóképpen állítjuk elő az 5p) példa szerinti vegyületből. Ragadós olajként kapjuk, amelyet a 9ad) példa szerinti szabad hidroxi-vegyületté alakítunk.

q) N-(1-Adamantil)-N-metil-3-[2-(benzil-oxi)-fenil]-3-fenil-propil-amin

Ezt a vegyületet az 5q) példa szerinti vegyületből állítjuk elő. Ragadós olajként kapjuk, amelyet további tisztítás nélkül a 9ae) példa szerinti szabad hidroxivegyületté alakítunk.

8. példa

Előállítás olefines prekurzorokból

a) N-(terc-Butil)-3-(2,6-dimetoxi-fenil)-3-hidroxi-3-fenil-propil-amin (LXXIX)

10,1 g (0,1 mól) diizopropil-amin 100 ml száraz die-

til-éterrel készült oldatát –10 °C-ra hűtjük. Az oldathoz 65 ml (0,1 mól) hexános butil-lítium-oldatot adunk, és az elegyet –10 °C-on 20 percig leverjük. Ezután 10 g (0,1 mól) N-etilidén-terc-butil-amin 100 ml száraz dietil-éterrel készült oldatát adjuk hozzá, és a keverést 0 °C-on még 20 percig folytatjuk. –30 °C-ra való hűtés után 24,1 g (0,1 mól) 2,6-dimetoxi-benzofenon 100 ml száraz dietil-éterrel készült és 30 ml tetrahidrofuránt tartalmazó oldatát adjuk a fenti elegyhez, és környezeti hőmérsékleten 20 órán át keverjük, majd vízzel hidrolizáljuk. A szerves fázist vízzel mossuk, szárítjuk és bepároljuk. 32 g (94%) N-[3-(2,6-dimetoxi-fenil)-3-hidroxi-3-fenil-propilidén]-terc-butil-amint kapunk olaj alakjában.

Ezt az olajat 250 ml abszolút etanolban oldjuk, az oldatot –5 °C-ra hűtjük, és 5,7 g (0,15 mól) nátrium-bór-hidridet adunk hozzá részletekben. Az elegyet 0 °C-on 0,5 órán át, majd környezeti hőmérsékleten 3 órán át keverjük. Az oldószer nagy részét vákuumban ledesztilláljuk, a maradékot vízzel kezeljük, dietil-éterrel extraháljuk, vízzel mossuk, és 2N sósavval extraháljuk. Az extraktumot dietil-éterrel mossuk, nátrium-hidroxiddal meglúgosítjuk, dietil-éterrel extraháljuk, szárítjuk és bepároljuk. 30 g cím szerinti amint kapunk.

Úgy tűnik, hogy a hidrokloridsó, amelynek olvadáspontja 203–204 °C (aceton-éter), 1/4 mól vizet tartalmaz.

Elemanalízis a $C_{21}H_{29}NO_3 \cdot HCl \cdot 1/4H_2O$ (384,5) összegképlet alapján:

számított:				
C: 65,60%;	H: 8,01%;	N: 3,64%;	O: 13,52%;	
talált:				
C: 65,9%;	H: 8,11%;	N: 3,64%;	O: 13,7%.	

b) N-(terc-Butil)-3-(2,6-dimetoxi-fenil)-3-fenil-2-propén-1-amin (LXXX)

21 g (0,061 mól) fenti, a) lépésben előállított amint 20 ml (0,126 mól) 6,3 N kénsavhoz adunk. Az elegyet forró vízfürdőn 2 órán át keverjük, majd hűtjük, meglúgosítjuk és dietil-éterrel extraháljuk. Az extraktumot mossuk, szárítjuk és bepároljuk. 17,8 g (90%) cím szerinti olefint kapunk áttetsző olaj alakjában. A hidrogén-klorid-só 220–222 °C-on olvad, és 1/4 mól vizet tartalmaz.

Elemanalízis a $C_{21}H_{27}NO_2 \cdot HCl \cdot 1/4H_2O$ összegképlet alapján:

számított:	C: 68,82%;	H: 7,86%;	N: 3,82%;
	O: 9,82%;	Cl: 9,68%;	
talált:	C: 68,8%;	H: 7,89%;	N: 3,92%;
	O: 9,81%;	Cl: 9,44%.	

c) N-Metil-N-(terc-butil)-3-(2,6-dimetoxi-fenil)-3-fenil-propil-amin (LXXXI) és hidrogén-fumarátja

16,3 g (0,05 mól) b) lépésben előállított olefines amint 250 ml, 0,5 g 10%-os szénhordozós palládium-katalizátort tartalmazó metanolban, környezeti hőmérsékleten és nyomáson hidrogénezzük. Az elegyet celiten át szűrjük, a szűrletet szárazra pároljuk, így 16,3 g (100%) N-(terc-butil)-3-(2,6-dimetoxi-fenil)-3-fenil-propil-amint kapunk. A hidrokloridsó olvadáspontja 244 °C (etanol).

Elemanalízis a $C_{21}H_{29}NO_2 \cdot HCl$ (363,9) összegképlet alapján:

számított:	C: 69,31%;	H: 8,31%;	N: 3,85%;
	O: 8,79%;	Cl: 9,74%;	
talált:	C: 69,3%;	H: 8,29%;	N: 3,83%;
	O: 9,27%;	Cl: 9,75%.	

A fenti szekunder amint mint szabad bázist formaldehid-hangyasav elegyével a 7. példában leírt módon metilezzük, így 96%-os hozamban tercier amint kapunk. A fumársavas só olvadáspontja 185–190 °C (aceton).

Elemanalízis a $C_{26}H_{35}NO_6$ (457,6) összegképlet alapján:

számított:

C: 68,25%; H: 7,71%; N: 3,06%; O: 20,95%;

talált:

C: 67,8%; H: 7,59%; N: 3,05%; O: 21,6%.

9. példa

Az O-védőcsoportok eltávolítása

a) N,N-Diizopropil-3-(2-hidroxi-fenil)-3-fenil-propil-amin (LXXXII) és hidrokloridja

20,8 g (0,064 mól) 5k) példa szerinti (XLIX) amint 150 ml metilén-dikloridban 0 °C alá hűtünk. 64 ml (0,064 mól) 1N metilén-dikloridos bór-tribromid-oldatot csepegtetünk hozzá, és azután az oldatot hűtőszekrényben (5 °C) tartjuk 2–5 napig. Az illékony anyagokat 50 °C-nál alacsonyabb hőmérsékleten ledesztilláljuk. A maradék szirupot meglúgosítjuk, dietil-éterrel extraháljuk, az extraktumot vízzel mossuk, megszárítjuk és bepároljuk. Viszkózus szirupot kapunk. A hidrogén-klorid-só olvadáspontja 222 °C (metanol-éter), a hozam 31%.

Elemanalízis a $C_{21}H_{29}NO \cdot HCl$ (347,9) összegképlet alapján:

számított:	C: 72,49%;	H: 8,69%;	N: 4,03%;
	O: 4,60%;	Cl: 10,19%;	
talált:	C: 72,0%;	H: 8,72%;	N: 3,74%;
	O: 5,06%;	Cl: 10,3%.	

A következő vegyületeket ugyanilyen módon állítjuk elő.

b) N-[3-(2-Hidroxi-fenil)-3-fenil-propil]-2,2,6,6-tetrametil-piperidin (LXXXIII) és hidrogén-fumarátja

Az 5l) példa szerinti (LXIV) aminból, a nyers hozam 78%. A fumársavas só olvadáspontja határozatlan.

Elemanalízis a $C_{28}H_{37}O_5$ (467,6) összegképlet alapján:

számított:

C: 71,9%; H: 7,91%; N: 3,00%; O: 17,1%;

talált:

C: 71,8%; H: 8,41%; N: 3,01% O: 16,6%.

c) N,N-Diizopropil-3-(2-hidroxi-5-metil-fenil)-3-fenil-propil-amin (LXXXIV) és hidrokloridja

Az 5c) példa szerinti (XL) aminból a nyers hozam 85%, a hidrogén-klorid-só olvadáspontja 209–210 °C (aceton-éter).

Elemanalízis a $C_{22}H_{31}NO \cdot HCl \cdot 1/4H_2O$ (366,5) összegképlet alapján:

számított: C: 72,09%; H: 8,95%; N: 3,82%;
O: 5,46%; Cl: 9,67%;
talált: C: 72,3%; H: 8,95%; N: 3,71%;
O: 5,68%; Cl: 9,61%.

d) N-Metil-N-(terc-butil)-3-(2-hidroxi-5-metil-fenil)-3-fenil-propil-amin (LXXXV) és hidrokloridja

A 7b) példa szerinti (LXVI) aminból a nyers hozam 100%, a hidrogén-klorid-só olvadáspontja >260 °C (etanol).

Elemanalízis a $C_{21}H_{29}NO \cdot HCl$ (347,4) összegképlet alapján:

számított: C: 72,49%; H: 8,69%; N: 4,03%; Cl: 10,19%;
talált: C: 72,7%; H: 8,58%; N: 3,81%; Cl: 10,95%.

e) N,N-Diizopropil-3,3-bisz(2-hidroxi-fenil)-propil-amin (LXXXVI) és hidrokloridja

Az 5a) példa szerinti (XXXVIII) aminból a nyers hozam 57%, a hidrogén-klorid-só olvadáspontja 257 °C (etanol-éter).

Elemanalízis a $C_{21}H_{29}NO_2 \cdot HCl$ (363,9) összegképlet alapján:

számított: C: 69,31%; H: 8,31%; N: 3,85%;
O: 8,79%; Cl: 9,74%;
talált: C: 69,3%; H: 8,37%; N: 3,95%;
O: 9,23%; Cl: 9,40%.

f) N-Metil-N-(terc-butil)-3,3-bisz(2-hidroxi-fenil)-propil-amin (LXXXVII) és hidrokloridja

A 7c) példa szerinti (LXXVII) aminból. A nyers hozam 100%. Op. 190 °C, a hidrokloridsó olvadáspontja 252 °C (etanol).

Elemanalízis a $C_{20}H_{27}NO_2 \cdot HCl$ (349,9) összegképlet alapján:

számított: C: 68,65%; H: 8,06%; N: 4,00%; Cl: 10,13%;
talált: C: 64,8%: H: 8,06%; N: 4,17%; Cl: 9,59%.

g) N,N-Diizopropil-3-(2-hidroxi-4-metil-fenil)-3-fenil-propil-amin (LXXXVIII) és hidrokloridja

Az 5d) példa szerinti (XLI) aminból. A nyers hozam 90%. A hidrogén-klorid-só olvadáspontja 217 °C (etanol).

Elemanalízis a $C_{22}H_{31}NO \cdot HCl \cdot 1/4H_2O$ (366,5) összegképlet alapján:

számított: C: 72,09%; H: 8,96%; N: 3,82%;
O: 5,46%; Cl: 9,67%;
talált: C: 72,3%; H: 8,91%; N: 3,93%;
O: 5,27%; Cl: 9,46%.

h) N,N-Diizopropil-3,3-bisz(2-hidroxi-5-metil-fenil)-propil-amin (LXXXIX) és hidrokloridja

Az 5e) példa szerinti (XLII) aminból. A nyers hozam 93%, op. 166 °C. A hidrokloridsó olvadáspontja 220 °C (etanol).

Elemanalízis a $C_{23}H_{33}NO_2 \cdot HCl$ (392,0) összegképlet alapján:

számított: C: 70,47%; H: 8,74%; N: 3,57%; Cl: 9,05%;
talált: C: 70,6%; H: 8,78%; N: 3,71%; Cl: 8,93%.

i) N-Metil-N-(terc-butil)-3,3-bisz(2-hidroxi-5-metil-fenil)-propil-amin (XC) és hidrokloridja

A 7e) példa szerinti (LXIX) aminból. A nyers hozam 79%, op. 199–201 °C (IPE). A hidrokloridsó olvadáspontja 220 °C (aceton).

Elemanalízis a $C_{22}H_{31}NO_2 \cdot HCl$ (378,0) összegképlet alapján:

számított: C: 69,91%; H: 8,54%; N: 3,71%;
O: 8,47%; Cl: 9,38%;
talált: C: 69,9%; H: 8,70%; N: 3,75%;
O: 8,81%; Cl: 9,15%.

j) N-Metil-N-(terc-butil)-3-(2-hidroxi-4-metil-fenil)-3-fenil-propil-amin (XCI) és hidrokloridja

A 7d) példa szerinti (LXVIII) aminból. A nyers hozam 100%. A hidrogén-klorid-só olvadáspontja 240 °C (etanol).

Elemanalízis a $C_{21}H_{29}NO \cdot HCl$ (347,9) összegképlet alapján:

számított: C: 72,49%; H: 8,69%; N: 4,03%;
O: 4,60%; Cl: 10,19%;
talált: C: 72,5%; H: 8,75%; N: 4,06%;
O: 4,90%; Cl: 10,1%.

k) N,N-Diizopropil-3-(4-fluor-fenil)-3-(hidroxi-fenil)-propil-amin (XCII) és hidrokloridja

Az 5j) példa szerinti (XLVII) aminból. A nyers hozam 72%. A hidrogén-klorid-só olvadáspontja 183 °C (aceton-etanol).

Elemanalízis a $C_{21}H_{27}FNO \cdot HCl$ (364,9) összegképlet alapján:

számított: C: 69,12%; H: 7,73%; O: 3,83%;
talált: C: 69,1%; H: 8,09%; N: 3,82%.

l) N,N-Diizopropil-3-(2,4-dihidroxi-fenil)-3-fenil-propil-amin (XCIII) és hidrokloridja

Az 5h) példa szerinti (XLV) aminból. A nyers hozam 31%. A hidrogén-klorid olvadáspontja 205–210 °C (etanol-aceton-éter).

Elemanalízis a $C_{21}H_{29}NO_2 \cdot HCl$ (363,9) összegképlet alapján:

számított: C: 69,31%; H: 8,31%; N: 3,85%;
O: 8,79%; Cl: 9,74%;
talált: C: 69,5%; H: 8,33%; N: 3,72%;
O: 8,91%; Cl: 9,87%.

m) N-(1,1-Dimetil-propil)-N-metil-3,3-bisz(2-hidroxi-5-metil-fenil)-propil-amin (XCIV) és hidrokloridja

A 7h) példa szerinti (LXXII) aminból. A nyers hozam 100%, op. 190–195 °C. A hidrokloridsó olvadáspontja 235–240 °C (etanol-aceton-éter).

Elemanalízis a $C_{23}H_{33}NO_2 \cdot HCl$ (392,0) összegképlet alapján:

számított: C: 70,47%; H: 8,74%; N: 3,57%; Cl: 9,05%;
O: 8,16%;
talált: C: 70,0%; H: 8,96%; N: 3,54%;
O: 8,11%; Cl: 9,19%.

n) N-Metil-N-(terc-butil)-3-(2,4-dihidroxi-fenil)-3-fenil-propil-amin (XCV) és hidrobromidja

A 7i) példa szerinti (LXXIII) aminból. A nyers hozam 78%, op. 260 °C. A hidrogén-bromid olvadáspontja >260 °C (etanol).

Elemanalízis a $C_{20}H_{25}NO_2 \cdot HBr$ (394,4) összegképlet alapján:

számított:	C: 60,9%;	H: 7,16%;	N: 3,55%;
	O: 8,11%;	Br: 20,27%;	
talált:	C: 60,8%;	H: 7,18%;	N: 3,29%;
	O: 8,38%;	Br: 20,2%.	

o) N,N-Diizopropil-3,3-bisz(2,4-dihidroxi-fenil)-propil-amin (XCVI) és hidrokloridja

Az 5i) példa szerinti (XLVI) aminból. A hidroklorid amorf barna por, amely nem ad kielégítő elemanalízis eredményt a tökéletlen égés miatt.

p) N-Metil-N-(terc-butil)-3,3-bisz(2,4-dihidroxi-fenil)-propil-amin (XCVII) és hidrokloridja

A 7l) példa szerinti (LXXVI) aminból. A nyers hozam 87%, op. 260 °C. A hidrogén-klorid-só nem ad kielégítő elemanalízis eredményt a tökéletlen égés miatt.

q) N,N-Diizopropil-3-(2,5-dihidroxi-fenil)-3-fenil-propil-amin (XCVIII) és hidrokloridja

32,0 g (0,063 mól) szabad bázis formában levő 5f) példa szerinti (XLIII) amint 500 ml metanolban, 5 g 5%-os szénhordozós palládiumkatalizátor jelenlétében, környezeti hőmérsékleten és nyomáson hidrogénezzük. 2 óra alatt a reakció teljesen végbemegy. Az elegyet szűrjük, a szűrletet szárazra pároljuk, a maradékot acetonban oldjuk, és éteres hidrogén-kloriddal kezeljük. Így 19,8 g (87%) nyers sót kapunk, amely 260 °C-on olvad. Metanolból végzett átkristályosításkor fehér kristályok képződnek, op. 260 °C.

Elemanalízis a $C_{21}H_{29}NO_2 \cdot HCl \cdot 1/4H_2O$ (368,6) összegképlet alapján:

számított:	C: 68,44%;	H: 8,36%;	N: 3,80%;
	O: 9,77%;	Cl: 9,62%;	
talált:	C: 68,4%;	H: 8,40%;	N: 3,60%;
	O: 10,3%;	Cl: 9,42%.	

A következő vegyületeket hasonlóképpen állítjuk elő.

r) N-Metil-N-(terc-butil)-3-(2,5-dihidroxi-fenil)-3-fenil-propil-amin (XCIX) és hidrokloridja

A 7j) példa szerinti (LXXIV) aminból. A nyers hozam 90%. A hidrogén-klorid-só olvadáspontja >270 °C (metanol-víz).

Elemanalízis a $C_{20}H_{27}NO_2 \cdot HCl$ (349,9) összegképlet alapján:

számított:	C: 68,65%;	H: 8,06%;	N: 4,00%;
	O: 9,14%;	Cl: 10,13%;	
talált:	C: 68,9%;	H: 8,02%;	N: 3,93%;
	O: 9,60%;	Cl: 10,5%.	

s) N,N-Diizopropil-3,3-bisz(2-hidroxi-4-metil-fenil)-propil-amin (C) és hidrokloridja

Az 5g) példa szerinti (XLIV) aminból. A nyers hozam 100%. A hidrogén-klorid-só olvadáspontja 253 °C (metanol-éter).

Elemanalízis a $C_{23}H_{33}NO_2 \cdot HCl$ (392,0) összegképlet alapján:

számított:	C: 70,47%;	H: 8,74%;	N: 3,57%;
	O: 8,16%;	Cl: 9,05%;	
talált:	C: 70,5%;	H: 8,74%;	N: 3,55%;
	O: 8,47%;	Cl: 8,03%.	

t) N-Metil-N-(terc-butil)-3,3-bisz(2-hidroxi-4-metil-fenil)-propil-amin (CI) és hidrokloridja

A 7k) példa szerinti (LXXV) aminból. A nyers hozam 97%, sárga por. A hidrogén-klorid olvadáspontja 260 °C (metanol-aceton).

Elemanalízis a $C_{22}H_{31}NO_2 \cdot HCl$ (378,0) összegképlet alapján:

számított:	C: 69,91%;	H: 8,54%;	N: 3,71%;
	O: 8,47%;	Cl: 9,38%;	
talált:	C: 69,9%;	H: 8,68%;	N: 3,67%;
	O: 8,85%;	Cl: 9,24%.	

u) N,N-Diizopropil-3-(2,3-dihidroxi-fenil)-3-fenil-propil-amin (CII) és hidrokloridja

Az 5b) példa szerinti (XXXIX) aminból. A nyers hozam 100%. A hidrogén-klorid olvadáspontja 174–176 °C (aceton).

Elemanalízis a $C_{21}H_{29}NO_2 \cdot HCl$ (363,9) összegképlet alapján:

számított:	C: 69,31%;	H: 8,31%;	N: 3,85%;
	O: 8,79%;	Cl: 9,74%;	
talált:	C: 69,5%;	H: 8,33%;	N: 3,66%;
	O: 9,37%;	Cl: 9,63%.	

w) N-Metil-N-(terc-butil)-3-(2,3-dihidroxi-fenil)-3-fenil-propil-amin (CIII) és hidrokloridja

A 7m) példa szerinti (LXXVII) aminból. A nyers hozam 100%, fehér por. A hidrokloridsó olvadáspontja lassú melegítés mellett 209–210 °C (metanol-aceton).

Elemanalízis a $C_{20}H_{27}NO_2 \cdot HCl \cdot 1/4H_2O$ (358,9) összegképlet alapján:

számított:	C: 66,92%;	H: 8,14%;	N: 3,90%;
	O: 11,14%;	Cl: 9,88%;	
talált:	C: 66,9%;	H: 8,12%;	N: 3,76%;
	O: 11,8%;	Cl: 9,74%.	

x) N-Metil-N-(terc-butil)-3-(2-hidroxi-fenil)-3-fenil-propil-amin (CIV) és hidrokloridja

A 7n) példa szerinti (LXXVIII) aminból. A nyers hozam 100%. A hidrogén-klorid-só olvadáspontja 255 °C (aceton-éter).

Elemanalízis a $C_{20}H_{27}NO \cdot HCl$ (333,9) összegképlet alapján:

számított:

C: 71,94%; H: 8,45%; N: 4,20%; Cl: 10,62%;

talált:

C: 71,9%; H: 8,43%; N: 4,01%; Cl: 10,5%.

y) N-Metil-N-(terc-butil)-3-(2,6-dihidroxi-fenil)-3-fenil-propil-amin (CV) és hidrokloridja

A 8c) példa szerinti (LXXXI) aminból, bór-tribromiddal, alacsony hozamban. A hidrogén-klorid-só olvadáspontja 170 °C (etanol-éter).

Elemanalízis a $C_{20}H_{27}NO_2 \cdot HCl \cdot 1/2H_2O$ (358,9) összegképlet alapján:

számított:	C: 66,93%;	H: 8,14%;	N: 3,40%;
	O: 11,14%;	Cl: 9,87%;	
talált:	C: 67,4%;	H: 8,28%;	N: 3,63%;
	O: 10,9%;	Cl: 9,99%.	

z) N,N-Diizopropil-3-(5-Klór-2-hidroxi-fenil)-3-fenil-propil-amin

11,7 g (0,032 mól) 5m) példa szerinti bázist 7,6 g (0,096 mól) piridinnel és 13 g tömény sósavval reagáltatunk. Az elegyet vákuumban szárazra pároljuk, és a maradékot olajfürdőben 205–215 °C-on 1,5 órán át melegítjük. Az olvadékot valamennyire lehűtjük, vizet adunk hozzá, és forró vízfürdőben digeráljuk, majd lehűtjük. 2N sósavat adunk az elegyhez, a sót kiszűrjük, 2N sósavval mossuk, így 11,0 g (90%) fehér sót kapunk, amely 200 °C-on olvad. Acetonból végzett átkristályosítás után a cím szerinti vegyület olvadáspontja 202–203 °C.

Elemanalízis a $C_{21}H_{28}NO \cdot HCl$ (382,4) összegképlet alapján:

számított:

C: 65,96%; H: 7,64%; N: 3,66%; Cl: 18,54%;

talált:

C: 66,0%; H: 7,88%; N: 3,63%; Cl: 18,3%.

aa) N-Metil-N-(terc-Butil)-3-(5-klór-2-hidroxi-fenil)-3-fenil-propil-amin

10,5 g (0,03 mól) 7o) példa szerinti szabad bázist 7,0 g (0,09 mól) piridinnel és 12 g tömény sósavval reagáltatunk. Az elegyet vákuumban szárazra pároljuk, és a maradékot 205–215 °C-os olajfürdőben 1,5 órán át melegítjük. Az olvadékot kissé lehűtjük, 2N nátrium-hidroxidot adunk feleslegben hozzá, az elegyet dietil-éterrel extraháljuk, az extraktumot vízzel mossuk, szárítjuk és bepároljuk. 7,5 g (88%) nyers szirup marad vissza. Ezt dietil-éterben oldjuk, és éteres hidrogén-klorid-oldattal kezeljük, így 8 g (83%) hidrokloridsót kapunk. Aceton és 2N sósav elegyéből végzett átkristályosítás után a cím szerinti vegyület hidrogén-kloridja 260 °C-on olvad.

Elemanalízis a $C_{20}H_{26}NO \cdot HCl$ (368,4) összegképlet alapján:

számított:

C: 65,21%; H: 7,39%; N: 3,80%; Cl: 19,25%;

talált:

C: 65.0%; H: 7,30%; N: 3,73%; Cl: 18,9%.

ab) N-[3-(2-Hidroxi-fenil)-3-fenil-propil]-2,2,5,5-tetrametil-pirrolidin

Az 5n) példa szerinti nyers amint a 9q) példában leírt módon hidrogenolizáljuk. A szabad amint olaj alakjában kapjuk, majd hidrokloriddá alakítjuk, és 2-propanolból kristályosítjuk. Op. 250 °C.

Elemanalízis a $C_{23}H_{31}NO \cdot HCl$ (374,0) összegképlet alapján:

számított:	C: 73,86%;	H: 8,63%;	N: 3,75%;
	O: 4,28%;	Cl: 9,48%;	
talált:	C: 73,8%;	H: 8,71%;	N: 3,59%;
	O: 4,80%;	Cl: 9,45%.	

ac) N-[3-(2-Hidroxi-fenil)-3-fenil-propil]-4-hidroxi-2,2,6,6-tetrametil-piperidin

Az 5o) példa szerinti benzil-oxi-vegyületet a 9q) példában leírt módon hidrogenolizáljuk. A szabad bázist hidroklorid-szemihidráttá alakítjuk, majd acetonból kristályosítjuk. A vegyület bomlás közben kb. 150 °C-on olvad.

Elemanalízis a $C_{24}H_{33}NO_2 \cdot HCl \cdot 1/2H_2O$ (413,0) összegképlet alapján:

számított:	C: 69,79%;	H: 8,54%;	N: 3,39%;
	O: 9,68%;	Cl: 8,58%;	
talált:	C: 70,0%;	H: 8,67%;	N: 3,47%;
	O: 9,98%;	Cl: 8,13%.	

ad) N-(2-Hidroxi-1,1-dimetil-etil)-N-metil-3-(2-hidroxi-fenil)-3-fenil-propil-amin

A 7p) példa szerinti benzil-oxi-vegyületet a 9q) példában leírt módon hidrogenolizáljuk. A szabad hidroxi-amint üveges tömegként kapjuk, majd hidrokloriddá alakítjuk, amely etanolból dietil-éterrel kicsapva amorf szilárd formában válik ki.

Elemanalízis a $C_{20}H_{27}NO_2 \cdot HCl$ (349,9) összegképlet alapján:

számított:	C: 68,65%;	H: 8,06%;	N: 4,00%;
	O: 9,15%;	Cl: 10,13%;	
talált:	C: 68,25%;	H: 8,18%;	N: 3,98%;
	O: 9,12%;	Cl: 10,0%.	

ae) N-(1-Adamantil)-N-metil-3-(2-hidroxi-fenil)-3-fenil-propil-amin

A 7q) példa szerinti benzil-oxi-vegyületet a 9q) példában leírt módon hidrogenolizáljuk. A szabad hidroxi-amint üveges tömegként kapjuk. Vízmentes dietil-éterben oldjuk, és dietil-éteres hidrogén-klorid-oldat feleslegével kezeljük. A hidroklorid por alakjában válik ki, és bomlás közben kb. 220 °C-on olvad.

Elemanalízis a $C_{26}H_{33}NO \cdot HCl$ (412,0) összegképlet alapján:

számított:	C: 75,79%;	H: 8,32%;	N: 3,40%;
	O: 3,88%;	Cl: 8,61%;	
talált:	C: 75,3%;	H: 8,01%;	N: 3,22%;
	O: 3,45%;	Cl: 8,96%.	

10. példa
Amidok redukciója

a) N,N-Diizopropil-3-(2-metoxi-5-metil-fenil)-3-fenil-propil-amin

12,8 g (0,05 mól) 3-(2-metoxi-5-metil-fenil)-3-fenil-propionsavat (J. D. Simpson és H. Stephen, J. Chem. Soc. *1956*, 1382) és 50 ml tionil-kloridot vízfürdőn 3 órán át melegítünk. A tionil-klorid feleslegét csökkentett nyomáson ledesztilláljuk. A visszamaradó nyers 3-(2-metoxi-5-metil-fenil)-3-fenil-propionil-kloridot 50 ml metilén-dikloridban oldjuk, és cseppenként 20,2 g (0,20 mól) diizopropil-amin 200 ml metilén-dikloriddal készült oldatához csepegtetjük kb. 0 °C-on. Az oldatot 2 órán át állni hagyjuk, az oldószert ledesztilláljuk, és a visszamaradó anyagot vízzel kezeljük. A szilárd terméket, amely N,N-diizopropil-3-(2-metoxi-

5-metil-fenil)-3-fenil-propionamid, kiszűrjük, megszárítjuk, és kis részletekben 6,0 g (0,16 mól) lítium-alumínium-hidrid 700 ml száraz dietil-éterrel készült szuszpenziójához adjuk keverés közben. A hidrid feleslegét víz óvatos adagolásával elbontjuk, a dietil-éteres réteget elválasztjuk, és vízmentes nátrium-szulfáton szárítjuk. Szűrés után az oldatot feleslegben vett mennyiségű fumársav dietil-éteres oldatához adjuk. A kivált sót összegyűjtjük, és 2-propanolból kristályosítjuk. A *hidrogén-fumarát* 176 °C-on olvad.

b) *N-Metil-N-(terc-butil)-3-(2-metoxi-5-metil-fenil)-3-fenil-propil-amin*t hasonlóképpen állítunk elő. A *hidrokloridj*a 161 °C-on olvad.

11. példa

a) N-Metil-N-(terc-butil)-3-(5-klór-2-hidroxi-fenil)-3-fenil-propil-amin

7,1 g (0,10 mól) klór 500 ml ecetsavval készült oldatát cseppenként 29,7 g (0,10 mól) N-metil-N-(terc-butil)-3-(2-hidroxi-fenil)-3-fenil-propil-amin 200 ml ecetsavval készült oldatához adjuk keverés közben. 2 óra eltelte után az oldószert csökkentett nyomáson ledesztilláljuk, és a visszamaradó nyers *hidrokloridot* 2-propanolból kristályosítjuk. Op. 260 °C.

b) *N,N-Diizopropil-3-(5-klór-2-hidroxi-fenil)-3-fenil-propil-amin*t hasonlóképpen állítunk elő. A *hidrokloridj*a 202–3 °C-on olvad.

12. példa

A (+)- és (–)-enantiomerek elválasztása

31,1 g (0,10 mól) (±)-N,N-diizopropil-3-(2-hidroxi-fenil)-3-fenil-propil-amint 300 ml etanolban oldunk. Az oldathoz 15,0 g (0,10 mól) L(+)-borkősav 400 ml etanollal készült oldatát adjuk. Az elegyet forró vízfürdőn néhány percig melegítjük, és a főoldat egy kis mintájából hűtéssel és kaparással kapott kristállyal beoltjuk. Az elegyet kb. 4 °C-on tartjuk egy éjszakán át, ezután a kristályos csapadékot kiszűrjük, hideg etanollal mossuk, és etanolból több alkalommal átkristályosítjuk. Az így kapott tiszta *(–)-N,N-diizopropil-3-(2-hidroxi-fenil)-3-fenil-propil-amin-hidrogén-L-(+)-tartarát* $[\alpha]_D^{20}$ értéke –10,6° (c = 5%, metanol). A *szabad amin*t a vizes oldat lúgosításával, majd dietil-éteres extrakciójával, szárítással és az oldószer lepárlásával kapjuk. Ragadós olaj, $[\alpha]_D^{20} = -5,4°$ (c = 5%, metanol).

*(+)-N,N-Diizopropil-3-(2-hidroxi-fenil)-3-fenil-propil-amin*t hasonlóképpen állítunk elő D-(–)-borkősavval. A *hidrogén-D-(–)-tartarát* $[\alpha]_D^{20}$ értéke +10,0° (c = 5%, metanol). A szabad amin $[\alpha]_D^{20}$ értéke +5,6° (c = 5%, metanol).

13. példa

(Az 1. példa folytatása)

4-Fenil-3,4-dihidrokumarinok előállítása

g) 4-(2-Metoxi-fenil)-6-metil-3,4-dihidrokumarin (CVI)

178 g (1,0 mól) 2-metoxi-fahéjsav, 108 g (1,0 mól) p-krezol és 47,5 g (0,25 mól) p-toluolszulfonsav-monohodrát elegyét forró vízfürdőn kb. 2 órán át keverjük, ezalatt a rendszert vízsugárszivattyúval tartjuk összekapcsolva a képződött víz eltávolítására. A szilárd anyagot összetörjük, és vízzel mossuk. A darabos anyagot ezután nagy térfogatú telített nátrium-hidrogén-karbonát-oldattal mossuk, amely mintegy 10% acetont tartalmaz. A terméket kiszűrjük, mossuk, szárítjuk, és acetonból átkristályosítjuk. 167 g (62,5%) kívánt laktont kapunk fehér kristályos anyag formájában, amely 140 °C-on olvad.

Elemanalízis a $C_{17}H_{16}O_3$ (268,3) összegképlet alapján:

számított: C: 76,10%; H: 6,01%; O: 17,89%;
talált: C: 76,0%; H: 5,97%; O: 17,9%.

h) *6-Klór-4-(2-metoxi-fenil)-3,4-dihidrokumarint (CVII)* hasonlóképpen állítunk elő 49%-os hozamban, 2-metoxi-fahéjsavból és p-klór-fenolból. A reakcióhőmérséklet ez esetben 130 °C. Op. 172–173 °C (aceton).

14. példa

(A 2. példa folytatása)

3,3-Difenil-propionsav-észterek előállítása

l) Metil-3-(2-metoxi-fenil)-3-(2-metoxi-5-metil-fenil)-propionátot (CVIII) a 13g) példa szerinti (CVI) laktonból 75%-os hozamban, olaj formájában kapunk a 2a) példában a (VI) észter előállítására leírt módon.

m) *Metil-3-(5-klór-2-metoxi-fenil)-3-(2-metoxi-fenil)-propionátot (CIX)* ugyanilyen módon, 97%-os hozamban kapunk a 13. példa szerinti (CVII) laktonból.

15. példa

(A 3. példa folytatása)

3,3-Difenil-propanolok előállítása

m) *3-(5-Klór-2-metoxi-fenil)-3-(2-metoxi-fenil)-propanolt (CX)* 84%-os hozamban kapunk a 14m) példa szerinti (CIX) észterből a 3a) példában a (XVI) propanol előállítására leírt módon, azzal az eltéréssel, hogy a redukciót toluolban, és lítium-alumínium-hidrid helyett 10%-os moláris feleslegben vett 3,4 mólos toluolos nátrium-bisz(2-metoxi-etoxi)-alumínium-hidriddel (SMEAH) végezzük. Op. 70–72 °C (IPE).

n) *3-(2-Metoxi-fenil)-3-(2-metoxi-5-metil-fenil)-propanolt (CXI)* hasonlóképpen kapunk, kvantitatív hozamban a 14l) példa szerinti (CVII) észterből. A termék aranysárga színű olaj, gázkromatográfiásan vizsgálva 89%-os tisztaságú.

16. példa

(A 4. példa folytatása)

3,3-Difenil-propil-p-toluolszulfonátok előállítása

n) *3-(2-Metoxi-fenil)-3-(2-metoxi-5-metil-fenil)-propil-p-toluolszulfonátot (CXII)* a 15n) példa szerinti (CXI) propanolból ugyanolyan módon állítunk elő, mint (XXVII) tozilátot a 4a) példában, kloroform helyett metilén-dikloridot használva oldószerként. Hozam 100%, op. 101 °C (éter-IPE).

Elemanalízis a $C_{25}H_{26}O_5S$ (440,57) összegképlet alapján:

számított: C: 68,16%; H: 6,41%; S: 7,28%;
talált: C: 68,3%; H: 6,51%; S: 7,20%.

o) *3-(5-Klór-2-metoxi-fenil)-3-(2-metoxi-fenil)-propil-p-toluolszulfonátot (CXIII)* hasonlóképpen állítunk elő, kvantitatív hozamban a 15m) példa szerinti (CX) propanolból. Op. 97–98 °C (aceton-IPE).

Elemanalízis a $C_{24}H_{25}ClO_5S$ (460,92) összegképlet alapján:

számított:
C: 62,54%; H: 5,47%; S: 6,94%; Cl: 7,69%;
talált:
C: 63,0%; H: 5,65%; S: 6,95%; Cl: 7,70%.

17. példa
(Az 5. példa folytatása)
Tercier 3,3-difenil-propil-aminok előállítása

r) *N,N-Diizopropil-3-(5-klór-2-metoxi-fenil)-3-(2-metoxi-fenil)-propil-amint (CXIV)* 94%-os hozamban, olaj formájában kapunk a 16o) példa szerinti (CXIII) tozilátból, az 5a) példa szerinti (XXXVIII) aminra leírt módon. Gázkromatográfiásan a tisztaság = 99,9%.

s) *N,N-Diizopropil-3-(2-metoxi-fenil)-3-(2-metoxi-5-metil-fenil)-propil-amint (CXV)* ugyanilyen módon, 49%-os hozamban kapunk a 16n) példa szerinti (CXII) tozilátból. Szilikagél 60-ból készült oszlopon végzett kromatográfiás tisztítás után, amelyhez eluálószerként könnyű benzint használunk, a terméket olajként kapjuk, ennek tisztasága gázkromatográfiás vizsgálat alapján 100%-os.

t) *N-[2-(Benzil-oxi)-5-etil-3-fenil]-2,2,5,5-tetrametil-pirrolidint (CXVI)* 3-[2-(benzil-oxi)-5-metil]-3-fenil-propil-tozilátból és 2,2,5,5-tetrametil-pirrolidinből állítunk elő az 5a) példában adott útmutatásokat követve. A terméket ragadós olaj alakjában kapjuk, amelyet a 20aj) példában leírt módon szabad hidroxivegyületté alakítunk.

18. példa
(A 6. példa folytatása)
Szekunder 3,3-difenil-propil-aminok előállítása

p) *N-(terc-Butil)-3-(5-klór-2-metoxi-fenil)-3-(2-metoxi-fenil)-propil-amint (CXVII)* kvantitatív hozamban állítunk elő a 16o) példa szerinti (CXIII) tozilátból, a 6a) példában az (L) aminra leírt módon. A hidroklorid-só olvadáspontja >260 °C.

Elemanalízis a $C_{21}H_{28}ClNO_2 \cdot HCl$ (398,38) összegképlet alapján:

számított:
C: 63,3%; H: 7,43%; N: 3,52%; Cl: 17,80%;
talált:
C: 63,2%; H: 7,46%; N: 3,49%; Cl: 17,4%.

q) *N-(terc-Butil)-3-(2-metoxi-fenil)-3-(2-metoxi-5-metil-fenil)-propil-amint (CXVIII)* hasonlóképpen kapunk 89%-os hozamban a 16n) példa szerinti (CXII) tozilátból. A hidrokloridsó olvadáspontja 225 °C.

Elemanalízis:

számított: C: 69,91%; H: 8,54%; N: 3,71%; Cl: 9,38%; O: 8,47%;
talált: C: 69,8%; H: 8,73%; N: 3,60%; Cl: 9,45%; O: 8,79%.

19. példa
(A 7. példa folytatása)
Tercier 3,3-difenil-propil-aminok előállítása szekunder aminokból

r) *N-Metil-N-(terc-butil)-3-(5-klór-2-metoxi-fenil)-3-(2-metoxi-fenil)-propil-amint (CXIX)* 89%-os hozamban állítunk elő a 18p) példa szerinti (CXVII) aminból, a 7a) példában a (LXI) aminra leírt módon. A hidrogén-klorid-sót a szabad bázis acetonos oldatának hidrogén-kloridos kezelésével kapjuk. Op. 130 °C.

Elemanalízis a $C_{22}H_{30}ClO_2N \cdot HCl \cdot H_2O$ (430,42) összegképlet alapján:

számított:
C: 61,39%; H: 7,74%; N: 3,25%; Cl: 16,47%;
talált:
C: 62,0%; H: 7,93%; N: 3,26%; Cl: 16,5%.

s) *N-Metil-N-(terc-butil)-3-(2-metoxi-fenil)-3-(2-metoxi-5-metil-fenil)-propil-amint (CXX)* hasonlóképpen állítunk elő 98%-os hozamban a 18q) példa szerinti (CXVIII) aminból. A szabad bázis (olaj) tisztasága gázkromatográfiásan 96%.

20. példa
(A 9. példa folytatása)
O-védőcsoportok eltávolítása

af) *N,N-Diizopropil-3-(2-hidroxi-fenil)-3-(2-hidroxi-5-metil-fenil)-propil-amin (CXXI)*

26,5 g (0,072 mól) 17s) példa szerinti (CXV) amint metanolban tömény sósav kis feleslegével kezelünk. Az elegyet vákuumban szárazra pároljuk, 25,4 g (0,22 mól) piridínium-kloridot adunk hozzá, és 1,5 órán át 200–205 °C-on melegítjük. Ezután kb. 80 °C-ra hűtjük, 20 g acetont, majd kevés vizet adunk hozzá. A sót kiszűrjük, híg sósavval mossuk, és szárítjuk. Abszolút etanol/éter elegyből végzett átkristályosítással 17,5 g (64,3%) fehér sót kapunk, amelynek olvadáspontja >250 °C. A tisztaság gázkromatográfiásan 100%.

Elemanalízis a $C_{22}H_{31}NO_2 \cdot HCl$ (377,97) összegképlet alapján:

számított: C: 69,91%; H: 8,54%; N: 3,71%; O: 8,47%; Cl: 9,38%;
talált: C: 69,8%; H: 8,65%; N: 3,57%; O: 8,76%; Cl: 9,51%.

ag) *N,N-Diizopropil-3-(5-klór-2-hidroxi-fenil)-3-(2-hidroxi-fenil)-propil-amint (CXXII)* ugyanilyen módon állítunk elő 37%-os hozamban a 17r) példa szerinti (CXIV) aminból. A hidrogén-klorid-só olvadáspontja 214 °C (etanol).

Elemanalízis a $C_{21}H_{28}NO_2 \cdot HCl$ (398,38) összegképlet alapján:

számított: C: 63,31%; H: 7,34%; N: 3,52%; O: 8,03%; Cl: 17,80%;
talált: C: 63,1%; H: 7,34%; N: 3,40%; O: 8,15%; Cl: 17,8%.

ah) *N-Metil-N-(terc-butil)-3-(2-hidroxi-fenil)-3-(2-hidroxi-5-metil-fenil)-propil-amint (CXXIII)* ugyanilyen módon állítunk elő 30%-os hozamban a 19s) példa szerinti (CXX) aminból. A hidrogén-klorid-só olvadáspontja 240 °C (aceton).

Elemanalízis a $C_{21}H_{29}NO_2 \cdot HCl$ (363,94) összegképlet alapján:

számított:

C: 69,3%; H: 8,31%; N: 3,58%; Cl: 9,74%;

talált:

C: 69,0%; H: 8,55%; N: 3,65%; Cl: 9,76%.

ai) *N-Metil-N-(terc-butil)-3-(5-klór-2-hidroxi-fenil)-3-(2-hidroxi-fenil)-propil-amint (CXXIV)* ugyanilyen módon állítunk elő a 19r) példa szerinti (CXIX) aminból. Op. >250 °C.

Elemanalízis a $C_{20}H_{26}ClNO_2 \cdot HCl$ (384,36) összegképlet alapján:

számított:

C: 62,50%; H: 7,08%; N: 3,65%; Cl: 18,45%;

talált:

C: 62,5%; H: 7,09%; N: 3,63%; Cl: 18,4%.

ak) *N-[3-(2-Hidroxi-5-metil-fenil)-3-fenil-propil]-2,2,5,5-tetrametil-pirrolidint (CXXV)* úgy állítunk elő, hogy a 17t) példa szerinti (CXVI) O-benzilezett amint a 9q) példában leírt módon hidrogenolizáljuk. A hidroklorid 240 °C-on olvad.

Elemanalízis a $C_{24}H_{24}ClNO$ (388,0) összegképlet alapján:

számított:

C: 74,29%; H: 8,83%; N: 3,61%; Cl: 19,14%;

talált:

C: 73,9%; H: 8,90%; N: 3,52%; Cl: 9,48%.

21. példa

(A 10. példa folytatása)

Amidok redukciója

N,N-Diizopropil-3-(2-metoxi-fenil)-3-fenil-propionamin

N,N-Diizopropil-3-(2-metoxi-fenil)-3-fenil-propionaminot opálos sárga olajként, kvantitatív hozamban kapunk 3-(2-metoxi-fenil)-3-fenil-propionsavból a 10a) példa szerinti amidra leírt módon. 27 g (0,08 mól) ilyen amidot 50 g toluolban oldunk, és az oldatot szobahőmérsékleten 50 g (0,17 mól) 3,4 mólos toluolos SMEAH oldathoz csepegtetjük, amelyet előzőleg azonos tömegű toluollal hígítottunk. Az elegyet 60–70 °C-on 2 órán át keverjük, majd hűtjük, és 2N nátrium-hidroxid-oldat feleslegével kezeljük. A szerves fázist elválasztjuk, vízzel mossuk és 2N sósavval extraháljuk. A savas extraktumot dietil-éterrel mossuk, meglúgosítjuk, dietil-éterrel extraháljuk, szárítjuk és bepároljuk. 17,1 g (66%) szabad bázis marad vissza, amelyet 75 ml acetonban oldunk, és 6,6 g fumársav metanolos oldatával kezelünk. 20 g fumársavas sót kapunk, amely 163–164 °C-on olvad.

Elemanalízis a $C_{22}H_{31}ON \cdot C_4H_4O_4$ (441,58) összegképlet alapján:

számított:

C: 70,72%; H: 7,99%; N: 3,17%; O: 18,12%;

talált:

C: 70,7%; H: 7,96%; N: 3,13%; O: 18,0%.

22. példa

A (+)- és (–)-enantiomerek elválasztása

(+)-N,N-Diizopropil-3-(2-hidroxi-5-metil-fenil)-3-fenil-propil-amin-hidrogén-tartarát

48,8 g (0,15 mól) 9g) példa szerinti (LXXXVIII) racém amint 500 ml 95%-os etanolban oldunk, és az oldatot 22,5 g (0,15 mól) L(+)-borkősav 500 ml etanollal készült oldatával elegyítjük, majd egy éjszakán át +4 °C-on állni hagyjuk. A kivált sót szűréssel összegyűjtjük, és etanollal és dietil-éterrel mossuk. A nyers só hozama 34,3 g, $[\alpha]_{546}^{25}$ értéke +29,5° (c = 5%, metanol). Etanolból végzett átkristályosítás után 21,8 g sót kapunk, amelynek $[\alpha]_{546}^{25}$ értéke +36,0°.

Elemanalízis a $C_{26}H_{37}NO_7$ összegképlet alapján:

számított:

C: 65,66%; H: 7,84%; N: 2,95%; O: 23,55%;

talált:

C: 65,9%; H: 8,06%; N: 2,90%; O: 23,5%.

*(–)-N,N-Diizopropil-3-(2-hidroxi-5-metil-fenil)-3-fenil-propil-amin-hidrogén-D(–)-tartarát*ot hasonlóképpen állítunk elő D(–)-borkősavval. $[\alpha]_{\frac{D}{2}}^{25} = -35,8°$.

Elemanalízis:

talált:

C: 65,6%; H: 8,00%; N: 2,83%; O: 23,6%.

A találmány szerinti vegyületek közül néhányat megvizsgáltunk antikolinerg, anti-noradrenalin és antikalcium hatás, toxicitás és a szívverésre gyakorolt hatás szempontjából. A vizsgálati eljárásokat az alábbiakban írjuk le, és az eredményeket az 1. táblázatban foglaljuk össze. Összehasonlítás céljából megvizsgáltuk a kereskedelemben kapható terodilint és egy szerkezetileg hasonló vegyületet, az N,N-dimetil-3-(2-metoxi-fenil)-3-fenil-propil-amint, amelyet az US–A 3 446 901, GB–A–1 169 944 és BG–A–1 169 945 szabadalmi iratokban antidepresszánsként ismertettek. A vizsgálati eredmények világosan mutatják, hogy a találmány szerinti vegyületek felülmúlják az ismert vegyületeket, különösen a kívánt antikolinerg hatás és a nemkívánatos mellékhatások közötti szelektivitás vonatkozásában.

a) Antikolinerg hatás izolált húgyhólyagon

250–350 g testtömegű hím tengerimalacokat fejükre mért ütéssel leöltünk, és kivéreztettünk. Húgyhólyagukat gyorsan eltávolítottuk, és Na^+-Krebs fürdőbe helyeztük, és ebben tartottuk az egész boncolási eljárás során. A hólyagokat megszabadítottuk a rátapadt zsírtól és kötőszövetektől, majd felnyitottuk kétoldali bemetszéssel az aljától a tetejéig. Ollóval gondosan eltávolítottuk a nyálkahártyát. Négy, mintegy 3–5 mm hosszú csíkot vágtunk ki a hosszanti izomrostokkal párhuzamosan a hólyag mindkét feléből.

A hólyagcsíkokat azonnal belehelyeztük függőlegesen 5 ml olyan szövetfürdőbe, amely Na^+-Krebs oldatot tartalmazott, és a fürdőt folyamatosan karbogén gázzal levegőztettük, hogy a pH-ja 7,4 körüli érték maradjon. A 37 °C-os hőmérsékletet egy Lauda MS3 termosztát keringető szabályozta. A preparátumokat két horog közé helyeztük, ezek egyike egy Grass Instruments által gyártott FTO3 erőátalakítóhoz csatlako-

zot. A preparátumok izomer tenzióját Grass poligráffal (model 79D) regisztráltuk. A nyugalmi feszültség kb. 5 mN volt. A csíkokat legalább 45 percig hagytuk stabilizálódni. Ez idő alatt a nyugalmi feszültséget 5 mN-ra állítottuk be, és a preparátumokat ismételten mostuk.

Az előkísérletekben koncentráció – hatás görbéket vettünk fel karbachollal (karbamil-kolin-kloriddal), annak érdekében, hogy meghatározzuk a megfelelő agonista koncentrációt az antagonistával végzett gátlási vizsgálatokhoz. 3×10^{-6} karbachol koncentrációt választottunk, amely a maximálisnál kisebb (70%) összehúzódási választ adott. A gátlási vizsgálatokban a csíkokat minden 15 percben 3×10^{-6} M karbachollal érintkeztettük. A csíkokat három alkalommal mostuk minden agonista hozzáadása után. Ezt az eljárást addig ismételtük, amíg reprodukálható összehúzódási választ kaptunk. Három egymást követő összehúzódást, amennyiben az eltérés kb. 10%-os volt, reprodukálhatónak fogadtunk el.

Először minden antagonistát 10^{-6} M koncentrációban vizsgáltunk különböző tengerimalacokból származó két hólyagcsíkon. Amikor a 3×10^{-6} M karbachollal reprodukálható választ kaptunk, a csíkokat az antagonistával 15 percig inkubáltuk a következő karbachol hozzáadása előtt. Ha az antagonista a karbacholra adott választ 50%-nál nagyobb mértékben gátolta, akkor a teljes koncentráció – gátlás görbét is felvettük. A teljes gátlási görbék felvételekor a csíkokat 60 percig inkubáltuk egy meghatározott antagonista koncentráció mellett, a karbachol következő hozzáadása előtt. Az antagonisták hatását a kezdeti, agonista által indukált összehúzódások középértékének %-os gátlásaként számítottuk. A koncentráció – gátlás görbék elkészítéséhez az antagonistákat 6–8 koncentrációban vizsgáltuk, és mindegyik koncentrációhoz új hólyag-preparátumot használtunk, azaz a csíkokat csak egyszer tettük ki antagonista hatásának, majd kidobtuk.

b) Noradrenalin- és kalcium-antagonista hatás a portális vénán

Izolált patkány portális véna készítése

Állatok: hím albino patkányok, testtömeg kb. 200 g
Fürdőtérfogat: 5 ml
Puffer: K. E. Andersson által módosított Na^+-Krebs
Hőmérséklet: 37 °C
Gáz: karbogén (93,5% O_2 + 6,5% CO_2)
Izomtónus: 0,5 g

A patkányt a nyakára mért ütéssel leültük, majd lefejeztük. A hasüregét felnyitottuk, a vénát zsírmentesen kimetszettük, hosszirányban felvágtuk, és szervfürdőbe helyeztük. Az izometriás tenzió változásait egy erőelmozdulás átalakító segítségével regisztráltuk, amely erősítőhöz és író oszcillográfhoz csatlakozott.

Noradrenalin-antagonizmus portális vénán

Dózisok: noradrenalin 3×10^{-7} M

A választott dózisok kb. a maximális 70%-ának megfelelő választ adtak. Az agonistát 10 perces időközönként adtuk a fürdőhöz. Amikor reprodukálható összehúzódásokat kaptunk, a vizsgálandó anyag egy meghatározott koncentrációját adtuk a fürdőhöz. 10 perces inkubálási idő után történt a noradrenalin hozzáadása. A vizsgálandó anyag következő koncentrációját akkor adagoltuk, amikor az agonista eredeti válaszát kaptuk.

Az anyag antagonista hatását az agonista három egymást követő válaszának középértékére vonatkoztatott százalékos gátlásként fejeztük ki.

Ca-antagonista hatás portális vénán

10 mM K^+-oldatot adtunk a Krebs-pufferhez a véna spontán miogén hatásának stabilizálására. Az izomösszehúzódások amplitúdóját mérjük. A vizsgálandó anyagot kumulatív dózisokban addig adtuk a fürdőhöz, amíg teljes gátlást kaptunk.

c) Hisztamin-antagonizmus izolált ileumon

Izolált tengerimalac ileum készítése

Állatok: mindkét nemhez tartozó tengeri malacok, testtömeg kb. 350 g
Fürdőtérfogat: 5 ml
Puffer: K. E. Andersson által módosított Na^+-Krebs
Hőmérséklet: 37 °C
Gáz: karbogén (93,5% O_2 + 6,5% CO_2)
Izomtónus: 0,5 g

A tengerimalacot a nyakára mért ütéssel leöltük, majd lefejeztük. Felnyitottuk a hasüreget, és a csípőbeléből – a csípőbél és a vakbél csatlakozása fölött kb. 15 cm-rel – mintegy 2 cm-t kivágtunk. A kivágott ileumdarabot pufferrel mostuk, és szervfürdőbe helyeztük. Az izometriás feszültség változásait erő-elmozdulás átalakítóval regisztráltuk, amely erősítőhöz és író oszcillográfhoz csatlakozott.

Dózis: 3×10^{-7} M hisztamin

A kiválasztott hisztamin dózis a maximális válasz mintegy 70%-át adja. Az agonistát 3 perces időközönként adtuk a fürdőhöz. Amikor reprodukálható összehúzódásokat kaptunk, a vizsgálandó anyag egy meghatározott koncentrációját adtuk a fürdőhöz. 2–10 perces inkubálás után hisztaminnal egy új összehúzódást indukáltunk. A vizsgálandó anyag következő koncentrációját akkor adtuk a fürdőhöz, amikor az agonista eredeti válaszát kaptuk.

A vizsgálandó anyag agonista hatását három egymást követő hisztamin dózis válasz középértékére vonatkoztatott százalékos gátlásként számítottuk.

d) Akut toxicitás egérben

A vizsgálandó antagonistákat 0,9%-os nátrium-klorid-oldatban oldottuk. Azt az anyagot, amelyik 0,9%-os nátrium-klorid-oldatban nem oldódott, kétszeres mennyiségű desztillált vízben oldottuk. Az oldatokat a kísérlet napján készítettük.

Eljárás

25 g testtömegű fehér hím egereket egértartókba helyeztünk. A vizsgált vegyületeket intravénásan bólus dózisokban, a négy farokvéna egyikébe injektáltuk, 0,01 ml/g egér térfogatban. Mindegyik anyagkoncentrációt négy egérből álló csoportnak adtuk. Az antagonistákból 4–5 különböző koncentrációt készítettünk és vizsgáltunk.

Az akut letális dózis (LD_{11}) az antikolinerg hatóanyag azon legkisebb koncentrációja, amelynek hatá-

sára 4 vizsgált egérből a bólusz intravénás beadását követően 5 percen belül 4 elpusztult.

LD_{50}-tartomány: az LD_{50}-tartomány azon legmagasabb dózis, amelynek hatására 4 egér túléli a kísérletet és azon legalacsonyabb dózis között van, amelynek hatására 4 egér elpusztul a bólusz-dózis intravénás beadását követő 5 percen belül.

e) Eszméletnél levő patkányok szívritmusára gyakorolt hatás

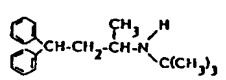
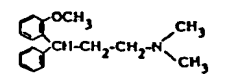
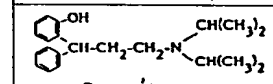
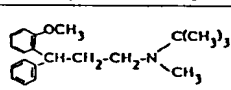
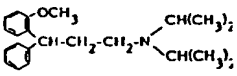
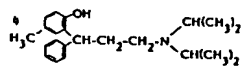
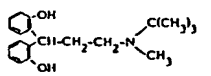
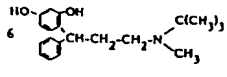
Az állatokat éterrel enyhén narkotizáltuk, és a farokvénába egy infúziós kanült vezettünk. A még alvó patkányokat egy durva, valamelyest rugalmas hálóból készült egyszerű szerkezetbe helyeztük, amely a patkányt egy állandó helyzetben rögzítette. A végtagokra elektródokat csatoltunk, és ezeket egy EKG-pulzus előerősítőhöz és egy Grass-poligráfhoz kapcsoltuk. Az EKG felvételével a szívritmust meghatározhattuk.

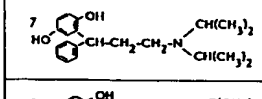
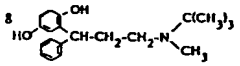
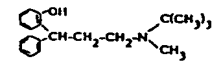
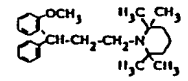
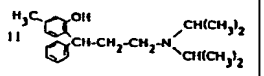
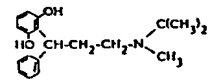
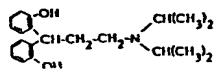
Addig semmilyen anyagot nem adtunk az állatnak, amíg az vissza nem nyerte eszméletét, és szívritmusa legalább 15 percig állandó nem maradt.

Az anyagokat intravénásan, az infúziós kanülön át adtuk be, és fiziológiás sóoldattal utánamostuk.

Az EKG-t 0,25, 0,5, 1, 2, 3 és 5 percenként vettük fel az injektálás befejezését követően, és minden 5 percben addig, amíg az eredeti szívritmus be nem állt.

1. táblázat

Anyag	Antikolinerg hatás IC_{50} (M)	Anti-noradrenalin hatás IC_{50} (M)	Anti-Ca hatás IC_{50} (M)	Anti-hisztamin hatás IC_{50} (M)	Akut toxicitás i.v. mg/kg	Letális dózis mg/kg	Hatás a szívritmusra Küszöbdózis mg/kg
 Terodilin (ismert vegyület)	$5,2 \times 10^{-7}$	$2,4 \times 10^{-6}$	10^{-5}	4×10^{-6}	15–20	20	1–3
 GB–A–1.169.944 (antidepresszáns)	$1,2 \times 10^{-6}$	$4,4 \times 10^{-6}$	$2,1 \times 10^{-5}$	$3,7 \times 10^{-7}$	10–15	15	
 Racemát	$1,8 \times 10^{-8}$	10^{-5}	$1,5 \times 10^{-5}$	7×10^{-6}	10–20	20	1–3
1a 1. vegyület (+)-izomerje	$1,8 \times 10^{-8}$						
1b 1. vegyület (–)-izomerje	$1,4 \times 10^{-8}$						
2 	$1,5 \times 10^{-7}$	$3,5 \times 10^{-6}$	9×10^{-6}		10–20	20	
3 	$2,4 \times 10^{-7}$	$3,6 \times 10^{-6}$	$>10^{-4}$		3–10	10	
	$1,5 \times 10^{-8}$	$5,5 \times 10^{-6}$	6×10^{-6}	10^{-5}	30–40	40	
4a. 4. tartarát (+)-izomerje	$1,3 \times 10^{-8}$		$6,5 \times 10^{-6}$		10–20	20	
4b. 4. tartarát (–)-izomerje	$1,3 \times 10^{-6}$		6×10^{-6}		10–20	20	
5 	$4,9 \times 10^{-9}$	$3,8 \times 10^{-5}$	3×10^{-5}	10^{-5}	30–45	45	1–3
6 	$2,0 \times 10^{-7}$	3×10^{-5}	$6,5 \times 10^{-5}$	$1,3 \times 10^{-5}$	>20	>20	

Anyag	Antikolinerg hatás IC_{50} (M)	Anti-noradrenalin hatás IC_{50} (M)	Anti-Ca hatás IC_{50} (M)	Anti-hisztamin hatás IC_{50} (M)	Akut toxicitás i.v. mg/kg	Letális dózis mg/kg	Hatás a szívritmusra Küszöbdózis mg/kg
7 	$1,9 \times 10^{-8}$	5×10^{-5}	$6,5 \times 10^{-5}$	3×10^{-6}	30–50	50	
8 	$3,1 \times 10^{-8}$	5×10^{-5}	$>5 \times 10^{-5}$	7×10^{-6}	>6	>6	
9 	$1,6 \times 10^{-8}$	5×10^{-5}	$2,5 \times 10^{-5}$	$1,2 \times 10^{-6}$		20	
10 	$6,2 \times 10^{-8}$	4×10^{-6}	7×10^{-6}	$2,5 \times 10^{-6}$			
11 	$1,0 \times 10^{-8}$	$5,5 \times 10^{-6}$	10^{-5}	$2,5 \times 10^{-6}$	10–20	20	
12 	$4,7 \times 10^{-7}$		$2,3 \times 10^{-5}$	$8,0 \times 10^{-6}$	15–30	30	
13 	$9,0 \times 10^{-9}$	3×10^{-5}	$1,5 \times 10^{-5}$	2×10^{-5}	5–10	10	

A) példa

Tabletták előállítása

Összetevők:	*mg/tabletta*
1. Az 1. táblázat 1. vegyülete	2,0
2. Cellulóz, mikrokristályos	57,0
3. Kalcium-hidrogén-foszfát	15,0
4. Nátrium-keményítő-glikolát	5,0
5. Szilícium-dioxid, kolloidális	0,25
6. Magnézium-sztearát	0,75
	80,0 mg

Az I. táblázat szerinti 1. vegyületet a 2., 3., 4. és 5. összetevőkkel kb. 10 percig keverjük. Ezután a magnézium-sztearátot adjuk hozzá, és a keveréket további 5 percig keverjük, majd filmbevonatú vagy anélküli tablettákká préseljük.

B) példa

Kapszulák előállítása

Összetevők:	*mg/kapszula*
1. Az 1. táblázat 1. vegyülete	2
2. Laktóz	186
3. Kukoricakeményítő	20
4. Talkum	15
5. Magnézium-sztearát	2
	225

Az I. táblázat szerinti 1. vegyületet a 2. és 3. komponensekkel összekeverjük, majd őröljük. A kapott keverékhez azután a 4. és 5. összetevőt is hozzákeverjük, majd megfelelő méretű kapszulákba töltjük.

SZABADALMI IGÉNYPONTOK

1. Eljárás (1) általános képletű 3,3-difenil-propil-aminok – ebben a képletben

R^1 jelentése hidrogénatom vagy metilcsoport,

R^2 jelentése hidrogénatom, halogénatom, hidroxil-, metil- vagy metoxicsoport,

R^3 jelentése hidrogénatom, halogénatom, hidroxil-, metil- vagy metoxicsoport,

R^4 jelentése hidrogénatom, halogénatom, hidroxil- vagy metoxicsoport,

X jelentése (2) általános képletű csoport, amelyben

R^5 jelentése hidrogénatom vagy 1–4 szénatomos alkilcsoport, és

R^6 jelentése 1–6 szénatomos alkil-, 1–6 szénatomos hidroxi-alkil- vagy 1-adamantil-csoport, mimellett az R^5 és R^6 szubsztituensekben együttesen legalább 3 szénatom van, vagy

R^5 és R^6 együtt egy 4–6 szénatomos alkilénláncot képez, amely négy 1–4 szénatomos alkilcso-

porttal és adott esetben egy hidroxilcsoporttal van helyettesítve –

és fiziológiai szempontból elfogadható savakkal képezett savaddíciós sóik, valamint optikai izomerek alakjában is létező vegyületek esetében racém elegyeik és enantiomer alakjaik előállítására, *azzal jellemezve*, hogy

a) egy (3) általános képletű 3,3-difenil-propanol származékot – a képletben R^1, R^2, R^3 és R^4 jelentése egyezik a tárgyi körben megadottal, Y egy lecserélhető csoportot képvisel, és a vegyületben az esetleges hidroxilcsoportok védve lehetnek – egy (4) általános képletű aminnal – ahol X jelentése egyezik a tárgyi körben megadotttal – reagáltatunk; vagy

b) egy (5) általános képletű 3,3-difenil-propionamid származékot – a képletben R^1, R^2, R^3, R^4 és X jelentése egyezik a tárgyi körben megadotttal és a vegyületben az esetleges hidroxilcsoportok védve lehetnek – redukálunk; vagy

c) egy (7a) vagy (7b) általános képletű 3,3-difenil-propil-amin származékot – ahol R^1, R^2, R^3, R^4 és X jelentése egyezik a tárgyi körben megadottal és az adott esetben jelenlevő hidroxilcsoportok pedig védve is lehetnek, W helyén pedig hidroxilcsoport vagy halogénatom áll – redukálunk; vagy

d) az X jelentésében R^5 helyén metilcsoport, R^6 helyén pedig 2–6 szénatomos alkil-, 2–6 szénatomos hidroxi-alkil- vagy 1-adamantil-csoportot tartalmazó (I) általános képletű vegyületek előállítására egy (6) általános képletű szekunder 3,3-difenil-propil-amin származékot – a képletben R^1, R^2, R^3 és R^4 jelentése egyezik a tárgyi körben megadotttal, és a vegyületben az esetleges hidroxilcsoportok védve lehetnek, Z helyén pedig a fenti meghatározások szerinti R^6 szubsztituensek egyike állhat metilcsoport kivételével – N-metilezünk;

majd

- kívánt esetben a kapott (I) általános képletű vegyületet fenilcsoporton halogénezzük,
- az adott esetben jelenlévő védőcsoportokat lehasítjuk;
- kívánt esetben a kapott, (I) általános képletnek megfelelő bázist fiziológiailag elfogadható savakkal savaddíciós sóvá alakítjuk át, vagy fordítva; és/vagy
- kívánt esetben az optikai izomerek kapott elegyét az egyedi enantiomerekre választjuk szét.

2. Az 1. igénypont szerinti eljárás olyan (I) általános képletű 3,3-difenil-propil-amin származékok előállítására, amelyekben X jelentésénél az R^5 és R^6 szubsztituensek egymástól függetlenül 1–4 szénatomos alkilcsoportot tartalmaznak vagy az R^6 adamantilcsoportot tartalmaz, mimellett az R^5 és R^6 szubsztituensekben együttesen legalább 3, előnyösen legalább 4 szénatom van, R^1, R^2, R^3 és R^4 jelentése egyezik az 1. igénypontban megadottal, *azzal jellemezve*, hogy megfelelően helyettesített kiindulási vegyületeket alkalmazunk.

3. Az 1. igénypont szerinti eljárás olyan (I) általános képletű vegyületek előállítására, amelyekben X jelentésénél az R^5 és R^6 szubsztituensek együtt egy 4–6 szénatomos, négy 1–4 szénatomos alkilcsoporttal helyettesített alkilénláncot képeznek, R^1, R^2, R^3 és R^4 jelentése egyezik az 1. igénypontban megadottal, *azzal jellemezve*, hogy megfelelően helyettesített kiindulási vegyületeket alkalmazunk.

4. Az 1. igénypont szerinti eljárás 3,3-difenil-propil-aminok származékok előállítására, amelyekben X jelentésénél az R^5 és R^6 szubsztituensek közül legalább az egyik elágazó szénláncú, *azzal jellemezve*, hogy megfelelően helyettesített kiindulási vegyületeket alkalmazunk.

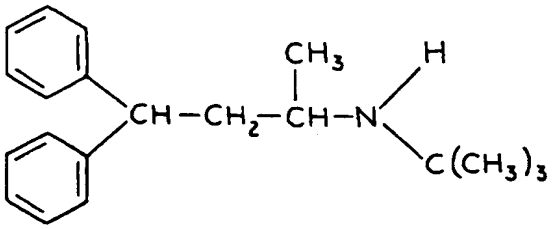
5. Az 1. igénypont szerinti eljárás az előző igénypontok bármelyike szerinti 3,3-difenil-propil-amin származékok előállítására, amelyekben X szubsztituensként az (a)–(f) képletű csoportok valamelyike szerepel vagy az (a)–(e) csoportok valamelyike legalább egy hidroxilcsoporttal van szubsztituálva, *azzal jellemezve*, hogy megfelelően helyettesített kiindulási vegyületeket alkalmazunk.

6. Az 1. igénypont szerinti eljárás az alább felsorolt vegyületek, azok fiziológiailag elfogadható savakkal alkotott sóinak, adott esetben racemátjainak, illetve egyedi enantiomerjeinek előállítására:

- N,N-diizopropil-3-(2-hidroxi-5-metil-fenil)-3-fenil-propilamin és ennek (+)-izomerje,
- N-metil-N-terc-butil-3-(2-hidroxi-fenil)-3-fenil-propilamin,
- N-metil-N-terc-butil-3-(2,4-dihidroxi-fenil)-3-fenil-propilamin,
- N-metil-N-terc-butil-3-(2-hidroxi-fenil)-propil-amin,
- N,N-diizopropil-3,3-bisz-(2-hidroxi-fenil)-propil-amin,
- N,N-diizopropil-3-(2,5-dihidroxi-fenil)-3-fenil-propilamin,
- N-metil-N-terc-butil-3-(2,5-dihidroxi-fenil)-3-fenil-propilamin,
- N,N-diizopropil-3-(2-metoxi-fenil)-3-fenil-propil-amin,
- N-[3-(2-metoxi-fenil)-3-fenil-propil]-2,2,6,6-tetrametil-piperidin,

azzal jellemezve, hogy megfelelően helyettesített kiindulási vegyületeket alkalmazunk.

7. Eljárás gyógyszerkészítmény előállítására, *azzal jellemezve*, hogy valamely az 1–6. igénypontok bármelyike szerinti eljárással előállított, (I) általános képletű 3,3-difenil-propil-amin származékot, amelynek a képletében R^1, R^2, R^3, R^4 és X jelentése az 1. igénypontban megadott, gyógyászatilag elfogadható vivőanyaggal keverünk össze és a keveréket gyógyszerkészítménnyé alakítjuk.



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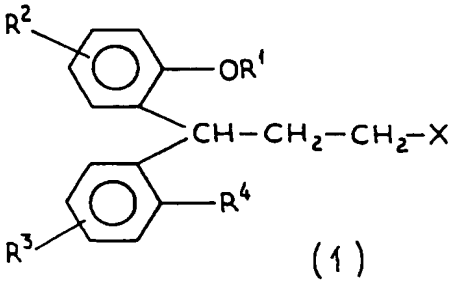

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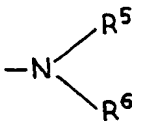

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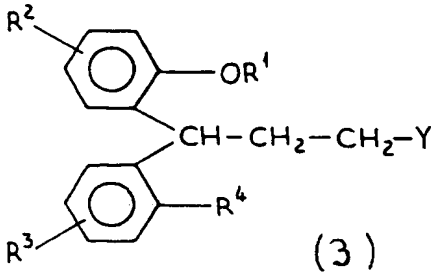
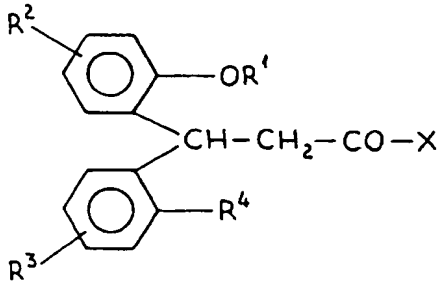


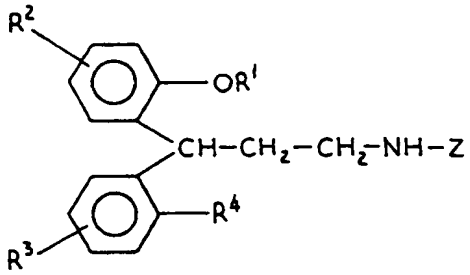
(3)

H–X

(4)



(5)



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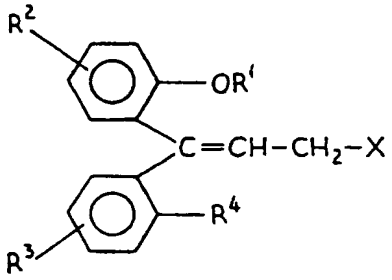
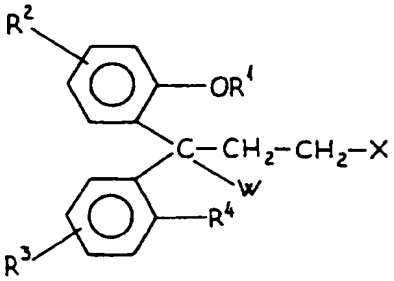
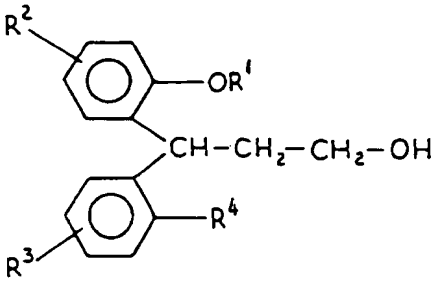


(7a)



(7b)



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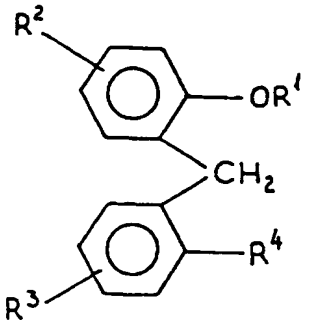

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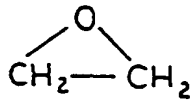

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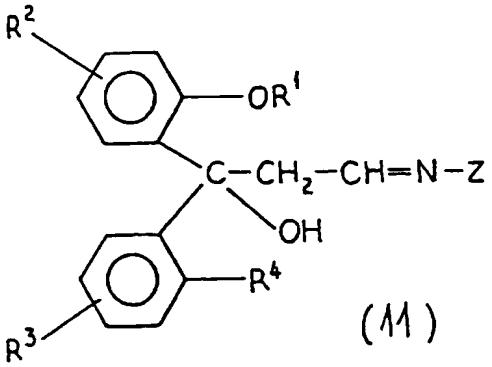
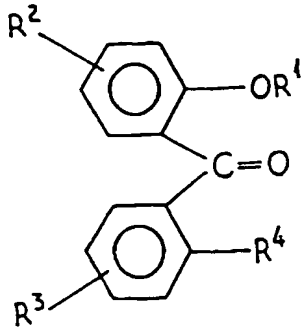


(11)

$CH_3-CH=N-Z$

(12)



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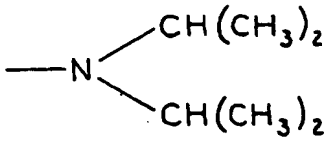
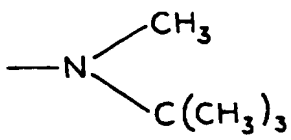
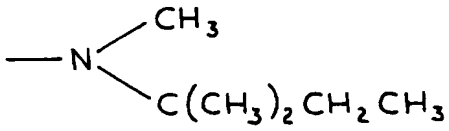


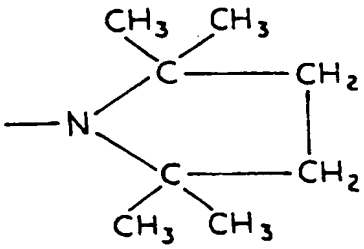
a)



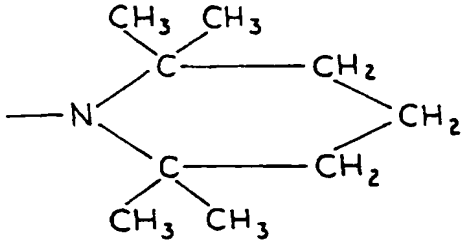
b)



c)



d)



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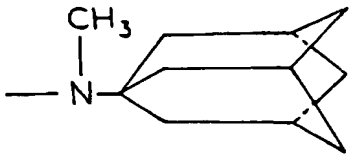
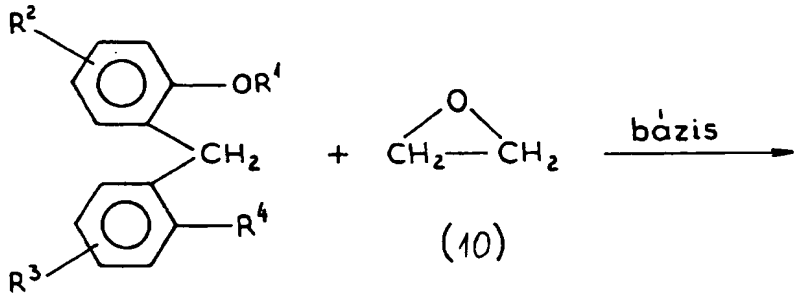


f)

(1) reakcióvázlat



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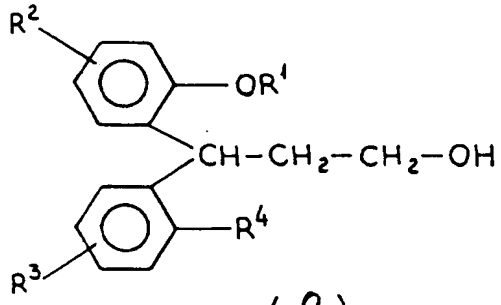

(8)

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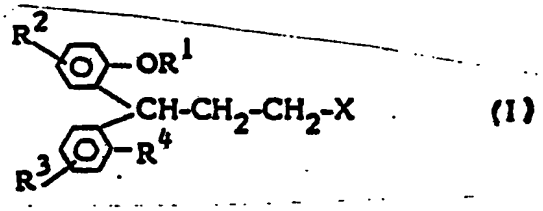
(54) Title: NEW AMINES, THEIR USE AND PREPARATION



(I)

(57) Abstract

Novel 3,3-diphenylpropylamines of formula (I) wherein R^1 signifies hydrogen or methyl, R^2, R^3 and R^4 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphanoyl or halogen, and X represents a tertiary amino group $-NR^5, R^6$, wherein R^5 and R^6 signify non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and which may form a ring together with the amine nitrogen, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers, their use as drugs, especially as anticholinergic agents, their use for preparing an anticholinergic drug, pharmaceutical compositions containing the novel amines, and methods for preparing the same.

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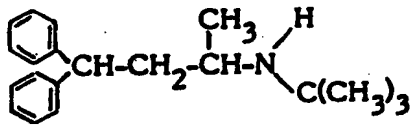
New amines, their use and preparation.

The present invention relates to novel 3,3-diphenylpropylamino derivatives, to pharmaceutical compositions containing the same, and to the use of said derivatives for preparing drugs.

Swedish patent No. 215 499 discloses certain 3,3-diphenylpropylyamines having an advantageous effect on the heart and circulation. These pharmacologically active 3,3-diphenylpropylamines are secondary amines. Said Swedish patent also discloses certain chemical intermediates which are tertiary amines carrying aromatic substituents on the amine nitrogen. Neither the end products (secondary amines) nor the intermediates (tertiary amines) have any hydroxy or methoxy groups as substituents in the ortho positions of the phenyl rings, but only meta and para substituents are specifically disclosed.

It is known that terodiline, a commercially available drug having the chemical formula

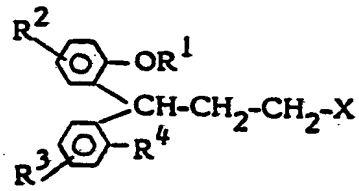


has anti-cholinergic properties, and is well resorbed in the body. However, this drug has a very long biological half-life and it is a multi-effect drug also having other pharmacological properties such as Ca-antagonist, noradrenaline antagonist and anti-histamine properties as well as a pronounced effect on the heart.

US-A-3.446.901, GB-A-1.169.944 and GB-A-1.169.945 disclose certain 3,3-diphenylpropylamine derivatives and pharmaceutical compositions having antidepressant activity, i.a. N,N-dimethyl-3-(2-methoxyphenyl)-3-phenylpropylamine, which is considered to be the closest prior art as regards chemical structure (see also the comparative tests reported at the end of this specification). DK-A-111.894 discloses a special process for preparing certain diphenylalkylamines having an effect on the heart and circulation. The specifically described compounds are primary or secondary amines, and none of them has any hydroxy or alkoxy substituent in ortho position of the phenyl rings. C.A. Vol. 97 (1982) 120105n discloses certain N-arylalkylisoquinolines which may have a hydroxy substituent in the ortho position of a phenyl ring. These compounds have sympatholytic activity and carry aromatic substituents on the nitrogen atom.

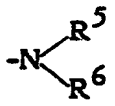
It is an object of the present invention to provide a novel class of 3,3-diphenylpropylamines having improved anti-cholinergic properties, especially in relation to the effects on these other systems and acute toxicity.

In a first aspect the invention provides novel 3,3-diphenylpropylamines of formula I



I

wherein R^1 signifies hydrogen or methyl, R^2, R^3 and R^4 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphanoyl or halogen, and X represents a tertiary amino group of formula II



II

wherein R^5 and R^6 signify non-aromatic hydrocarbol groups, which may be the same or different and which together contain at least three carbon atoms, preferably at least four carbon atoms, especially at least five carbon atoms, and wherein R^5 and R^6 may form a ring together with the amine nitrogen, said ring preferably having no other hetero atom than the amine nitrogen.

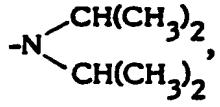
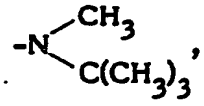
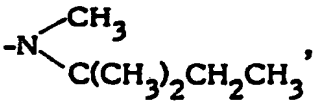
The compounds of formula I can form salts with physiologically acceptable acids, organic and inorganic, and the invention comprises the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride, hydrobromide, hydrogen fumarate, and the like.

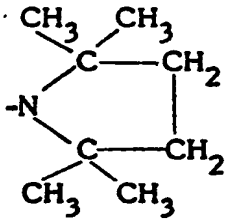
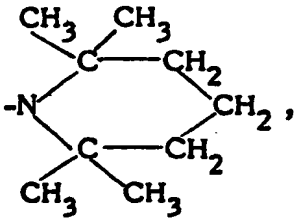
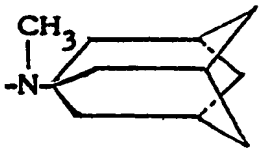
When the novel compounds can be in the form of optical isomers, the invention comprises the racemic mixture as well as the individual enantiomers as such.

A preferred sub-class of compounds according to the invention comprises tertiary amines of formula I, wherein each of R^5 and R^6 independently signifies C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^5 and R^6 together comprising at least three, preferably at least four carbon atoms. R^5 and R^6 may carry one or more hydroxy groups, and they may be joined to form a ring together with the amine nitrogen atom.

Presently preferred tertiary amino-groups X in formula I include the

following groups a) - f), each of which may carry one or more hydroxy groups.

a)  , b)  , c)  ,

d)  , e)  , f) 

The following are examples of presently preferred specific compounds of formula I:

N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine and its (+)-isomer,

N-methyl-N-tert.butyl-3-(2-hydroxyphenyl)-3-phenylpropylamine,

N-methyl-N-tert.butyl-3-(2,4-dihydroxyphenyl)-3-phenylpropylamine,

N-methyl-N-tert.butyl-3,3-bis-(2-hydroxyphenyl)propylamine,

N,N-diisopropyl-3,3-bis-(2-hydroxyphenyl)propylamine,

N,N-diisopropyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine,

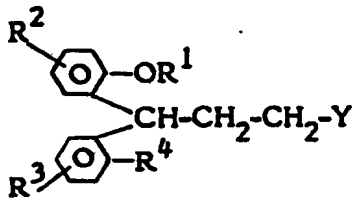
N-methyl-N-tert.butyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine,

N,N-diisopropyl-3-(2-methoxyphenyl)-3-phenylpropylamine,

N-[3-(2-methoxyphenyl)-3-phenylpropyl]-2,2,6,6-tetramethylpiperidine

In a second aspect the invention provides methods for preparing the compounds of formula I, especially the following methods:

a) reacting a reactively esterified 3,3-diphenylpropanol of formula III

 III

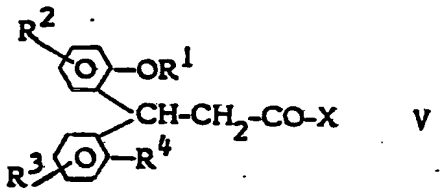
wherein R^1-R^4 are as defined above, and any hydroxy groups may be protected such as by methylation or benzylation, and wherein Y is a leaving group, preferably halogen or an alkyl or arylsulphonyloxy group,

with an amine of formula IV

H-X IV

wherein X is as defined above, or

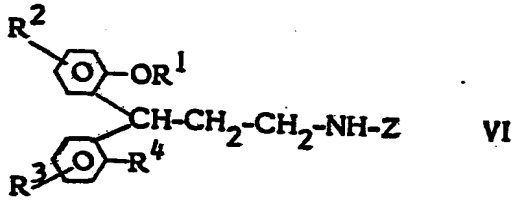
b) reducing a 3,3-diphenylpropionamide of formula V



V

wherein R^1-R^4 and X are as defined above and any hydroxy groups may be protected, preferably using a complex metal hydride,

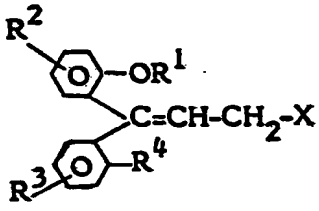
c) N-methylating a secondary 3,3-diphenylpropylamine VI



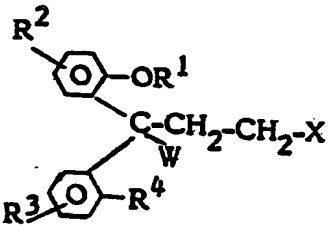
VI

wherein R^1-R^4 are as defined above and any hydroxy groups may be protected, and wherein Z has the same meaning as R^5 and R^6 with the exception of methyl, Z preferably being a hydrocarbyl group comprising at least three carbon atoms, the N-methylation preferably being carried out using formaldehyde or formic acid, or

d) reducing a 3,3-diphenylpropylamine of formula VIIa or VIIb



VIIa



VIIb

wherein R^1-R^4 and X are as defined above and any hydroxy groups may be protected, and W signifies a hydroxy group or a halogen atom, preferably by means of catalytic hydrogenation, and

i) when necessary splitting off hydroxy protecting groups in the compounds obtained, if desired after mono or di-halogenation of one or both of the phenyl rings, and/or

ii) if desired converting obtained bases of formula I into salts thereof with physiologically acceptable acids, or vice versa, and/or

iii) if desired separating an obtained mixture of optical isomers into the individual enantiomers, and/or

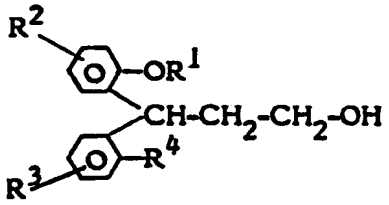
iv) if desired methylating an ortho-hydroxy group in an obtained compound of formula I, wherein R^1 is hydrogen and/or R^4 is hydroxy.

The above general methods can be carried out in a manner known per se and/or in accordance with the working examples described below, with due consideration of the desired amino groups and the substituents on the benzene rings.

The removal of hydroxy protecting groups according to i) above can e.g. be done by treatment with hydrobromic acid, borontribromide or by catalytic hydrogenation.

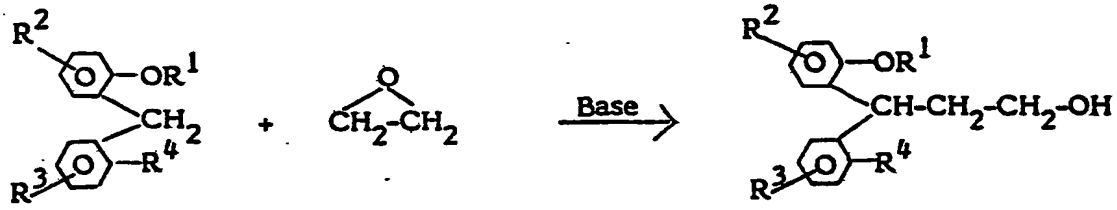
The separation of mixtures of optical isomers, according to ii) above, into the individual enantiomers can e.g. be achieved by fractional crystallization of salts with chiral acids or by chromatographic separation on chiral columns.

Novel compounds of formula VIII



VIII

wherein R^1-R^4 are as defined above, and the corresponding protected compounds (e.g. comprising protected hydroxy groups), are useful as chemical intermediates for the preparation of e.g. the compounds of formula I, and they can be prepared by means of several different methods which are known per se, such as by addition of ethylene oxide (X) to a correspondingly substituted diphenylmethane (IX) in the presence of a suitable base such as sodium amide:



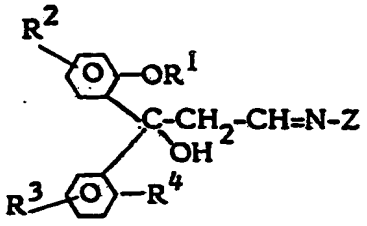
IX X VIII

The compounds VIII can also be prepared by reduction of the corresponding 3,3-diphenylpropionic acids, preferably using complex metal hydrides.

The 3,3-diphenylpropanols VIII can conveniently be converted into the corresponding reactively esterified derivatives III in a manner known per se by displacing the hydroxy groups with e.g. a halogen atom or an alkyl or arylsulphonyloxy group.

The 3,3-diphenylamides of formula V used as starting materials in method b), can e.g. be prepared by reacting the above mentioned 3,3-diphenylpropionic acids with an appropriate amine.

The secondary amines used as starting materials in method c) can conveniently be prepared by reacting a primary amine H_2N-Z (wherein Z is as defined above) with a corresponding reactively esterified 3,3-diphenylpropanol in analogy with method a) above, or by reduction of the corresponding secondary 3,3-diphenylpropionamides in analogy with method b) above. The secondary amines can also be prepared by reduction of unsaturated hydroxyamines XI



XI

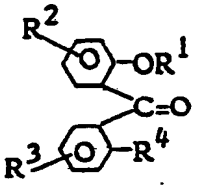
wherein R^1-R^4 and Z are as defined above, either in one step by catalytic hydrogenation, or by reduction to the corresponding saturated hydroxyamine, preferably using a complex metal hydride such as lithium aluminium hydride, followed by removal of the hydroxy group by catalytic reduction. As an alternative, the hydroxy group may first be split off as water, followed by reduction of the formed unsaturated amine.

The unsaturated hydroxy amines XI can conveniently be prepared by the

addition of a Schiff base of formula XII

$$CH_3\text{-}CH{=}N\text{-}Z \qquad \text{XII}$$

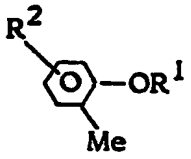
wherein Z is as defined above,
to a benzophenone of formula XIII



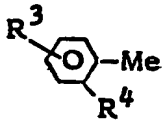
XIII

wherein R^1-R^4 are as defined above, in the presence of a base, preferably a lithium organic base such as lithium diisopropylamide.

Also the starting materials VIIa, VIIb for process d) can be prepared by methods known per se, such as by addition of an organometallic compound XIVa or XIVb

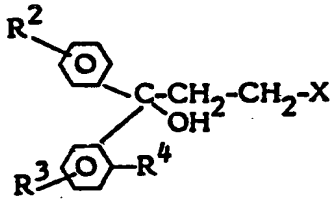


XIVa



XIVb

to a ketoamine XVa or XVb respectively to form a corresponding hydroxy amine XVI



XVI

and, if desired, splitting off water from compound XVI.

In formulae XIVa, XIVb, XVa, XVb, XVI, R^1-R^4 are as defined above, and Me signifies a metal such as magnesium or lithium.

In accordance with the invention the compounds of formula I, in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceuti-

cal compositions according to the invention comprise the compounds of formula I in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous or parenteral administration such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

The compositions according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, capsules, powders, syrups, elixirs and the like, in the form of sterile solutions, suspensions or emulsions for parenteral administration, and the like.

The compounds and compositions according to the invention can be used for treating cholin-mediated disorders such as urinary incontinence. As is well known, the dosage depends on several factors such as the potency of the selected specific compound, the mode of administration, the age and weight of the patient, the severity of the condition to be treated, and the like. The daily dosage may, for example, be from about 0.05 mg to about 4 mg per kilo of body weight, administered in one or more doses, e.g. containing from about 0.05 to about 200 mg each.

The invention will be further illustrated by the following non-limiting examples.

General

^{1}H-NMR spectra were run in $CDCl_3$ using a JEOL PMX60 spectrometer. In some cases, only a limited number of spectral peaks, useful for characterisation purposes, are reported.

Reported yields mostly refer to crude material of sufficient purity to be taken to the next stage.

Solvents are abbreviated as follows:

IPE = diisopropyl ether
PET = petroleum ether
Ether = diethyl ether

Amines are abbreviated as follows:

IPA = diisopropyl amine
TBA = tert.butyl amine

Melting points were taken on a Koefler bench.
Temperatures are in °C.
Water is used for the washing steps, unless otherwise stated.

Example 1

Preparation of 4-phenyl-3,4-dihydrocoumarins

a) 4-(2-Methoxy-5-methylphenyl)-6-methyl-3,4-dihydrocoumarin (I)

A mixture consisting of 2-methoxy-5-methylcinnamic acid (96.0 g, 0.5 mol), p-cresol (108 g, 1.0 mol), tetraline (200 ml), and conc. sulphuric acid (20 g) was heated slowly to refluxing temperature (145-150°). After 1 1/2 - 2 h, the mixture was cooled, taken up in ether, washed with water and sodium carbonate, dried and evaporated, giving 138 g (97%) crude oil. Two recrystallisations from acetone gave white crystals of the desired lactone, m.p. 126-127°.

$C_{18}H_{18}O_3$ (282.3) requires:	C	76.57	H	6.43	O	17.00
Found		76.9		6.44		17.0

b) 6-Hydroxy-4-phenyl-3,4-dihydrocoumarin (II) was prepared in a similar way in 97% yield from cinnamic acid and hydroquinone. M.p. 138° (IPE-Ether).

$C_{15}H_{12}O_3$ (240.3) requires:	C	74.99	H	5.04	O	19.98
Found		75.0		5.00		19.6

c) 4-(2-Methoxy-4-methylphenyl)-7-methyl-3,4-dihydrocoumarin was obtained in a similar way from 2-methoxy-4-methylcinnamic acid and m-cresol in 58%

yield. M.p. 147-148° (IPE-acetone).

$C_{18}H_{18}O_3$ (282.3) requires:	C	76.57	H	6.43	O 17.00
Found		76.4		6.31	17.2

The above lactone (90 g, 0.32 mol) in methylene chloride (500 ml) was refluxed with BBr_3 (115 g, 0.46 mol) for 24 h, the solution was concentrated, the residue was taken up in ether, the solution was washed with sodium carbonate and water, dried and evaporated, giving 80 g (93%) of a syrup which crystallized on standing. Crystallization from IPE-PET gave white crystals of

d) 4-(2-hydroxy-4-methylphenyl)-7-methyl-3,4-dihydrocoumarin (III), m.p. 137°.

$C_{17}H_{16}O_3$ (268.3) requires:	C	76.10	H	6.01	O 17.89
Found		76.2		6.30	17.0

e) 8-Hydroxy-4-phenyl-3,4-dihydrocoumarin (IV) was obtained in a similar way from cinnamic acid and catechol in 18% yield. M.p. 136° (IPE).

$C_{15}H_{12}O_3$ (240.2) requires:	C	74.99	H	5.04	O 19.98
Found		75.0		5.01	19.9

f) 4-(2-Methoxyphenyl)-3,4-dihydrocoumarin (V) was obtained in a similar way in 45% yield from methyl 2-methoxycinnamate and phenol. The crude reaction mixture was contaminated with methyl 3-(4-hydroxyphenyl)-3-(2-methoxyphenyl)-propionate. After removal of this by-product with ice-cold NaOH, the title compound was obtained as an oil of sufficient purity to be taken to the next step.

Example 2

Preparation of 3,3-diphenylpropionic acid esters

a) Methyl 3-(2-methoxy-4-methylphenyl)-3-phenylpropionate (VI)

7-Methyl-4-phenyl-3,4-dihydrocoumarin (78 g, 0.327 mol) in 150 ml methanol and 150 ml acetone containing methyl iodide (100 g, 0.7 mol) and K_2CO_3 (55 g, 0.4 mol) was refluxed for 24 h, filtered, and the solvent was evaporated. The residue was dissolved in ether, the solution was washed with water, dried and evaporated giving 86 g (92%) of a viscous oil.

NMR: δ 6.6-7.2 (m 8H), 4.9 (t 1H), 3.8 (s 3H), 3.5 (s 3H), 3.0 (d 2H), 2.2 (s 3H).

b) Methyl 3,3-bis-(2-methoxyphenyl)-propionate (VII) was obtained in the same way in 96% yield from the lactone (V) of Example 1f), m.p. 84-87° (IPE).

$C_{18}H_{20}O_4$ (300.4) requires:	C	71.98	H	6.71	O 21.3
Found		71.4		6.67	21.6

c) Methyl 3-(2,3-dibenzyloxyphenyl)-3-phenylpropionate (VIII) was obtained in a similar way in quantitative yield from the lactone (IV) of Example 1e) and benzyl chloride in methanol. In addition to K_2CO_3 the reaction mixture also contained some NaI. M.p. 72° (IPE).

$C_{30}H_{28}O_4$ (452.5) requires:	C	79.63	H	6.24	O	14.14
Found		79.9		6.15		14.1

d) Methyl 3-(2-benzyloxyphenyl)-3-phenylpropionate (IX) was obtained in a similar way as a viscous oil in 81% yield from 4-phenyl-3,4-dihydrocoumarin and benzyl chloride.

NMR: δ 7.2 (m 14H), 4.9 (s 2H, t 1H), 3.5 (s 3H), 3.0 (t 2H).

e) Methyl 3-(2-methoxy-5-methylphenyl)-3-phenylpropionate (X) was obtained in a similar way from 6-methyl-4-phenyl-3,4-dihydrocoumarin in 96% yield.
NMR: δ7.4 (m 8H), 5.0 (t 1H), 3.9 (s 3H), 3.7 (s 3H), 3.2 (d 2H), 2.4 (s 3H).

f) Methyl 3,3-bis-(2-methoxy-5-methylphenyl)propionate (XI) was obtained in a similar way in quantitative yield from the lactone (I) of Example 1a) and methyl iodide.
NMR: δ6.6-7.1 (m 6H), 5.1 (t 1H), 3.7 (s 6H), 3.5 (s 3H), 3.0 (d 2H), 2.2 (s 6H).

g) Methyl 3-(2,5-dibenzyloxyphenyl)-3-phenylpropionate (XII) was obtained in a similar way in 90% yield from the lactone (II) of Example 1b) and benzyl chloride.
NMR: δ 6.8-7.4 (m 18H), 5.0 (s 4H, t 1H), 3.7 (s 3H), 3.1 (d 2H).

h) Methyl 3,3-bis-(2-benzyloxy-4-methylphenyl)propionate (XIII) was obtained in a similar way in 95% yield from the lactone (III) of Example 1d) and benzyl chloride. By GLC the product is homogenous, and by MS it has the correct M.W.

i) Ethyl 3-(2,4-dimethoxyphenyl)-3-phenylpropionate (XIV)

A mixture of ethyl cinnamate (88 g, 0.5 mol), dimethyl resorcinol (276 g, 2.0 mol) and conc. sulphuric acid (50 g) was stirred on a boiling water-bath for 2 h, whereafter all the volatile material was distilled off in vacuum. The residual oil was dissolved in ether, the solution was washed with sodium carbonate, dried, and evaporated giving 101 g (64%) of the title ester in the form of a viscous oil.
NMR: δ 6.4-7.2 (m 8H), 4.9 (t 1H), 4.0 (q 2H), 3.7 (s 6H), 3.0 (d 2H), 1.1 (t 3H).

j) Methyl 3,3-bis-(2,4-dimethoxyphenyl)propionate (XV) was obtained in a similar way from methyl 2,4-dimethoxycinnamate and dimethyl resorcinol. The product thus obtained contained about 23% of dimethyl resorcinol. It was taken

to the next step without further purification.

k) Methyl-3-(5-chloro-2-methoxyphenyl)-3-phenylpropionate

6-Chloro-4-phenyl-3,4-dihydrocoumarin (435 g, 1.68 mol. Preparation: T. Manimaran & V.T. Ramakrishnan, Ind. J. Chem. B 18 (1979) 328) is added to a hot solution of sodium hydroxide (140 g, 3.5 mol) in water (500 ml). The solution is chilled to 25°C and dimethyl sulphate (442 g, 3.5 mol) is added dropwise during 1 h with stirring and cooling at 25-35°C. The mixture is stirred for an additional 2 h whereupon a solution of 100 g of sodium hydroxide in 500 ml of water is added and the mixture is stirred until a clear solution is obtained. An excess of concentrated hydrochloric acid is added to precipitate the methoxy acid, which separates as an oil which slowly crystallizes. It is filtered off, washed with water and dried. Crystallization from 2-propanol gives colourless crystals of 3-(5-chloro-2-methoxyphenyl)-3-phenyl propionic acid, m.p. 144°C. Yield 455 g.

The above acid (291 g, 1.0 mol) in 1 litre methanol containing 50 g concentrated sulphuric acid was refluxed for 8 h. The solvent was distilled off, the residue was taken up in ether, washed with water and sodium carbonat solution, dried and evaporated giving 300 g (100%) crude oil. Recrystallisation from IPE gave white crystals of the title compound, m.p. 65-66°.

$C_{17}H_{17}ClO_3$ (304,8) requires:	C 67.0	H 5.62	Cl 11.63
Found	68.1	5.82	11.7

Example 3

Preparation of 3,3-diphenylpropanols

a) 3-(2-Methoxy-4-methylphenyl)-3-phenylpropanol (XVI)

The ester (VI) of Example 2a) (84 g, 0.295 mol) in 150 ml dry ether was added dropwise to a suspension of $LiAlH_4$ (11.3 g, 0.295 mol) in 300 ml dry ether. The mixture was stirred overnight, then decomposed by the careful addition first of 11 g of water, then of 15% NaOH until a white granular precipitate was formed. The mixture was filtered, the filtrate was washed with water, dried, and evaporated giving 71 g (91%) of an oil which crystallized on standing. Recrystallization from IPE-PET gave white crystals, m.p. 83°.

$C_{17}H_{20}O_2$ (256.4) requires:	C 79.65	H 7.88	O 12.48
Found	79.4	7.89	12.7

b) 3,3-Bis-(2-methoxyphenyl)propanol (XVII) was obtained in a similar manner in quantitative yield as a viscous oil from the ester (VII) of Example 2b).

c) 3-(2,3-Dibenzyloxyphenyl)-3-phenylpropanol (XVIII) was obtained in a

similar way as a viscous oil in 96% yield from the ester (VIII) of Example 2c).

d) 3-(2-Benzyloxyphenyl)-3-phenylpropanol (XIX) was obtained in a similar way as an oil in 78% yield from the ester (IX) of Example 2d).

e) 3-(2-Methoxy-5-methylphenyl)-3-phenylpropanol (XX) was obtained in a similar way as an oil in quantitative yield from the ester (X) of Example 2e).
NMR: δ 6.8-7.4 (m 7H), 4.7 (t 1H), 3.8 (s 3H), 3.7 (m 2H), 2.3 (s 3H), 2.0-2.3 (m 2H).

f) 3,3-Bis-(2-methoxy-5-methylphenyl)propanol (XXI) was obtained in a similar way in 98% yield from the ester (XI) of Example 2f). M.p. 89° (IPE).

$C_{19}H_{24}O_3$ (300.4) requires:	C	75.97	H	8.05	O 15.98
Found		75.9		8.02	16.1

g) 3-(2,5-Dibenzyloxyphenyl)-3-phenylpropanol (XXII) was obtained in a similar way in 88% yield from the ester (XII) of Example 2g). M.p. 78° (IPE).

$C_{29}H_{28}O_3$ (424.5) requires:	C	82.05	H	6.65	O 11.31
Found		82.0		6.62	11.2

h) 3,3-Bis-(2-benzyloxy-4-methylphenyl)propanol (XXIII) was obtained in a similar way as an oil in 93% yield from the ester (XIII) of Example 2h).

i) 3-(2,4-Dimethoxyphenyl)-3-phenylpropanol (XXIV) was obtained as a golden oil in 92% yield from the ester (XIV) of Example 2i).
NMR: δ 6.5-7.2 (m 8H), 4.5 (t 1H), 3.8 (s 6H), 3.6 (m 2H), 2.0-2.6 (m 3H).

j) 3,3-Bis-(2,4-dimethoxyphenyl)propanol (XXV) was obtained in a similar way from the impure ester (XV) of Example 2j). By NMR, the product contains about 20% of dimethyl resorcinol.

k) 3-(4-Fluorphenyl)-3-(2-methoxyphenyl)propanol (XXVI)

A Grignard reagent was prepared in the usual manner from o-bromoanisole (93.5 g, 0.5 mol) and magnesium (12 g, 0.5 mol) in 100 ml dry ether. A solution of p-fluorobenzaldehyde (62 g, 0.5 mol) in 100 ml ether was added dropwise to this solution. After about 1 h, the mixture was decomposed with NH_4Cl and worked up, giving 100.6 g (87%) of 4-fluoro-2'-methoxy-diphenylmethanol. Recrystallization from IPE-PET gave white crystals, m.p. 88°.

$C_{14}H_{13}FO_2$ (232.3) requires:	C	72.40	H	5.64
Found		72.9		5.75

The obtained carbinol (46.2 g, 0.2 mol) in 600 ml ethanol was hydrogenated in the presence of 4 g of 5% Pd/C catalyst. After about 5-6 h, the

reaction was complete and the mixture was worked up giving 40 g (93%) of 4-fluoro-2'-methoxy-diphenylmethane as a clear oil.

NMR: 6.8-7.2 (m 8H), 4.0 (s 2H), 3.8 (s 3H).

The obtained methane derivative (71 g, 0.33 mol) in 100 ml ether was added to a solution of $NaNH_2$ prepared in situ from sodium (8.5 g, 0.37 mol) in about 300 ml of NH_3. After about 1 h, a solution of ethylene oxide (17.5 g, 0.395 mol) in 75 ml ether was added dropwise. The mixture was stirred for 2 h, and most of the ammonia was then removed with a stream of air. Solid NH_4Cl was then added, followed by the addition of water. The organic phase was separated, washed with water and 2N HCl, dried and evaporated, giving 81.5 g (95%) of the title compound. M.p. 61° (IPE-PET).

$C_{16}H_{17}FO_2$ (260.3) requires:	C	73.82	H	6.58	
Found		74.1		6.77	

l) 3-(5-Chloro-2-methoxyphenyl)-3-phenylpropanol

The ester from Example 2k) (91.5 g, 0.3 mol) in 500 ml dry ether was added dropwise under nitrogen to $LiAlH_4$ (11.4 g, 0.3 mol) in 200 ml dry ether. The mixture was stirred at room temperature overnight, then decomposed with 11 g water and 11 g 15% NaOH solution. Work up gave 72.5 g (87.5%) colourless oil. Recrystallization from IPE gave white crystals of the title compound, m.p. 80°.

$C_{16}H_{17}ClO_2$ (276.8) requires:	C	69.43	H	6.19	Cl	12.81
Found		70.1		6.44		12.9

Example 4

Preparation of 3,3-diphenylpropyl-p-toluene sulphonates

a) 3,3-Bis-(2-methoxyphenyl)propyl-p-toluene sulphonate (XXVII)

The propanol (XVII) of Example 3b) (35 g, 0.128 mol) in 100 ml chloroform containing 30 ml pyridine was cooled to about -10° and then treated with p-toluene sulphonyl chloride (29 g, 0.15 mol). After standing in the cooler (about +5°C) overnight, the mixture was poured into ice-water, the organic phase was washed with water and cold 2N HCl, dried, and the solvent was distilled off at < 50°C, giving a crude oil in quantitative yield. Recrystallization from IPE gave white crystals of low and indefinite m.p.

$C_{24}H_{26}O_5S$ (426.5) requires:	C	67.58	H	6.14	S	7.52
Found		66.8		6.22		7.76

b) 3-(2-Methoxy-4-methylphenyl)-3-phenylpropyl-p-toluene sulphonate (XXXI) was obtained in quantitative yield from the propanol (XVI) of Example 3a).

c) 3-(2,3-Dibenzyloxyphenyl)-3-phenylpropyl-p-toluene sulphonate (XXVIII) was obtained in a similar way as a thick oil in 88% yield from the propanol (XVIII) of Example 3c).

d) 3-(2-Benzyloxyphenyl)-3-phenylpropyl-p-toluene sulphonate (XXIX) was obtained in i similar way in 98% yield from the propanol (XIX) of Example 3d).

e) 3-(2-Methoxy-5-methylphenyl)-3-phenylpropyl-p-toluene sulphonate (XXX) was obtained in quantitative yield from the propanol (XX) of Example 3e). M.p. 64° (IPE-PET).

$C_{23}H_{24}O_4S$ (396.5) requires:	C	69.67	H	6.10	S	8.09
Found		69.8		6.20		7.85

f) 3,3-Bis-(2-methoxy-5-methylphenyl)-propyl-p-toluene sulphonate (XXXII) was obtained in quantitative yield from the propanol (XXI) of Example 3f). M.p. 117° (acetone-PET).

$C_{26}H_{30}O_5S$ (454.5) requires:	C	68.7	H	6.65	S	7.05
Found		68.8		6.66		7.11

g) 3-(2,5-Dibenzyloxyphenyl)-3-phenylpropyl-p-toluene sulphonate (XXXIII) was obtained in a similar manner in quantitative yield from the propanol (XXII) of Example 3g).

h) 3,3-Bis-(2-benzyloxy-4-methylphenyl)-propyl-p-toluene sulphonate (XXXIV) was obtained in a similar way in 86% yield from the propanol (XXIII) of Example 3h).

i) 3-(2,4-Dimethoxyphenyl)-3-phenylpropyl-p-toluene sulphonate (XXXV) was in the same way obtained in 96% yield from the propanol (XXIV) of Example 3i).

j) 3,3-Bis-(2,4-dimethoxyphenyl)-propyl-p-toluene sulphonate (XXXVI) was obtained in the same manner from the propanol (XXV) of Example 3j). The product was contaminated with dimethyl resorcinol.

k) 3-(4-Fluorphenyl)-3-(2-methoxyphenyl)-propyl-p-toluene sulphonate (XXXVII) was obtained in a similar way in 88% yield from the propanol (XXVI) of Example 3k). M.p. 67° (IPE).

$C_{23}H_{23}FO_4S$ (414.5) requires:	C	66.65	H	5.59	S	7.74	
Found		67.1		5.69		7.78	

l) 3-(2-Methoxyphenyl)-3-phenylpropyl-p-toluene sulphonate (XLVIII)

A mixture of anisole (1080 g, 10 mol), benzyl alcohol (216 g, 2 mol) and p-toluene sulphonic acid (40 g) was refluxed for 2 h in an apparatus equipped with a water separator. Excess of anisole was then distilled off, the oily residue was dissolved in ether, washed with water and sodium carbonate, dried and fractionated, giving 304 g (77%) of a pale yellow oil, b.p. 115-118°/0.4 Torr. By NMR, it is a 1:1 mixture of o-methoxy and p-methoxy diphenyl methane. This material was converted to a mixture of the corresponding propanols by reaction with ethylene oxide, as in the preparation of the propanol (XXVI) of Example 3k). This mixture of propanols was then converted as described above to a mixture of p-toluene sulphonates from which the title-compound could be isolated in 35% yield after two recrystallizations from IPE. M.p. 108°.

$C_{23}H_{24}O_4S$ (396.5) requires:	C	69.67	H	6.10	S	8.09	
Found		69.3		6.00		8.17	

m) 3-(5-Chloro-2-methoxyphenyl)-3-phenylpropyl-p-toluene sulphonate

The alcohol from Example 3l) (66 g, 0.24 mol) in 300 ml chloroform containing 75 ml pyridine was treated portionswise in the cold with p-toluene-sulphonyl chloride (55 g, 0.29 mol). The mixture was kept at 5°C for 18 h, solvent was evaporated under vacuum at < 50°, the residue was taken up in ether, washed with water and 2 N HCl, dried and evaporated giving 100 g (97%) of a straw-yellow syrup. Recrystallization from IPE gave the title compound, m.p. 89-90°.

$C_{23}H_{23}ClO_4S$ (430.96) requires:	C	64.10	H	5.38	S	7.44	Cl	8.23	
Found		64.4		5.45		7.04		8.17	

Example 5

Preparation of tertiary 3,3-diphenylpropylamines

a) N,N-Diisopropyl-3,3-bis-(2-methoxyphenyl)-propylamine (XXXVIII), hydrogen oxalate

The tosylate (XXVII) of Example 4a) (42.6 g, 0.1 mol) in 100 ml acetonitrile and 100 g (1.0 mol) diisopropylamine was heated in a pressure bottle at 80° for 4-6 days. Volatile material was then evaporated, the residue was treated with excess of 2N NaOH and extracted with ether. The extract was washed with water and extracted with 2N HCl. This extract was washed with ether, basified,

extracted with ether, washed with water, dried, decoloured, filtered, and evaporated, giving 24.0 g (68%) of a crude oil. This oil was converted to the oxalic acid salt by treating an acetone solution of the base with one equivalent of oxalic acid in acetone. M.p. 160-161° (acetone).

$C_{25}H_{35}NO_6$ (445.6) requires:	C	67.39	H	7.92	N	3.14	O	21.55
Found		67.2		8.22		2.94		21.9

b) N,N-Diisopropyl-3-(2,3-dibenzyloxyphenyl)-3-phenylpropylamine (XXXIX)

The free base was obtained in the same way in 75% yield from the tosylate (XXVIII) of Example 4c).

NMR: 6.9-7.2 (m 18H), 5.0 (s 4H), 0.9 (d 12H).

c) N,N-Diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine (XL), hydrogenfumarate

The free base was obtained in 69% yield from the tosylate (XXX) of Example 4e). It was converted to the fumaric acid salt in the usual manner. M.p. 176° (acetone).

$C_{27}H_{37}NO_5$ (455.7) requires:	C	71.17	H	8.20	N	3.07	O	17.6
Found		71.3		8.27		3.04		17.9

d) N,N-Diisopropyl-3-(2-methoxy-4-methylphenyl)-3-phenylpropylamine (XLI), hydrogenfumarate

The free base was obtained in 25% yield from the tosylate (XXXI) of Example 4b). The fumaric acid salt had m.p. 147-148° (acetone).

$C_{27}H_{37}NO_5$ (455.7) requires:	C	71.17	H	8.20	N	3.07	O	17.6
Found		71.3		8.14		3.00		17.6

e) N,N-Diisopropyl-3,3-bis-(2-methoxy-5-methylphenyl)propylamine (XLII), hydrochloride

The free base was obtained in 78% yield from the tosylate (XXXII) of Example 4f). It was converted to the hydrochloride with ethereal HCl in the ususal manner. M.p. 163-164° (acetone-ether).

$C_{25}H_{38}NO_2Cl$ (420.1) requires:	C	71.49	H	9.12	N	3.33	O	7.61	Cl	8.44
Found		71.6		9.08		3.27		7.93		8.36

f) N,N-Diisopropyl-3-(2,5-dibenzyloxyphenyl)-3-phenylpropylamine (XLIII)

The free base was obtained in 70% yield from the tosylate (XXXIII) of Example 4g).

NMR: δ 6.6-7.2 (m 18H), 5.0 (s 4H), 4.5 (t 1H), 1.0 (d 12H).

g) N,N-Diisopropyl-3,3-bis-(2-benzyloxy-4-methylphenyl)propylamine (XLIV)

The free base was obtained in 62% yield from the tosylate (XXXIV) of Example 4h).

NMR: δ6.8-7.2 (m 16H), 4.8 (s 4H, t 1H), 0.9 (d 12H).

h) N,N-Diisopropyl-3-(2,4-dimethoxyphenyl)-3-phenylpropylamine (XLV)

The free base was obtained in 56% yield from the tosylate (XXXV) of Example 4i).

NMR: 6.5-7.3 (m 8H), 4.4 (t 1H), 3.8 (s 6H), 1.0 (d 12H).

i) N,N-Diisopropyl-3,3-bis-(2,4-dimethoxyphenyl)propylamine (XLVI)

The free base was obtained in 34% yield from the tosylate (XXXVI) of Example 4j).

NMR: δ6.5-7.3 (m 6H), 4.6 (t 1H), 3.9 (s 12H), 1.0 (d 12H).

j) N,N-Diisopropyl-3-(4-fluorophenyl)-3-(2-methoxyphenyl)propylamine XLVII)

The free base was obtained in 71% yield from the tosylate (XXXVII) of Example 4k).

k) N,N-Diisopropyl-3-(2-methoxyphenyl)-3-phenylpropylamine (XLIX), hydrogen fumarate

The free base was obtained in 86% yield from the tosylate (XLVIII) of Example 4l) and was converted to the fumaric acid salt in the usual way. M.p. 134-136° (acetone-IPE) or 163-164° (methanol).

$C_{26}H_{36}NO_5$ (441.6) requires:	C	70.72	H	7.99	N	3.28	O 18.12
Found		70.8		7.93		3.28	18.1

l) N-[3-(2-Methoxyphenyl)-3-phenylpropyl]-2,2,6,6-tetramethyl-piperidine (LXIV)

This compound was obtained in the same way in 54% yield from the tosylate (XLVIII) of Example 4l) and 2,2,6,6-tetramethylpiperidine. M.p. 100° (IPE).

$C_{25}H_{35}NO$ (365.6) requires:	C	82.14	H	9.65	N	3.83
Found		82.0		9.62		3.57

m) N,N-diisopropyl-3-(5-chloro-2-methoxyphenyl)-3-phenylpropylamine

The tosylate from Example 4m) (43.1 g, 0.1 mol) was heated for 4 days at 80° with diisopropylamine (50 g, 0.5 mol) in 100 ml acetonitrile, giving 23 g (64%) of crude title compound. By GC, it is at least 93% pure.

n) N-[3-(2-Benzyloxyphenyl)-3-phenylpropyl]-2,2,5,5-tetramethyl-pyrrolidine

This compound was similarly prepared from the tosylate (XXIX) of Example 4d) and 2,2,5,5-tetramethylpyrrolidine. It was obtained as a sticky oil, which was converted to the hydroxy analogue without further purification (Example 9ab)).

o) N-[3-(2-Benzyloxyphenyl)-3-phenylpropyl]-4-hydroxy-2,2,6,6-tetramethylpiperidine

This compound was similarly prepared from the tosylate (XXIX) of Example 4d) and 4-hydroxy-2,2,6,6-tetramethylpiperidine, and it was obtained as a sticky oil which was converted to the hydroxy compound without further purification (Example 9ac)).

p) N-(2-Hydroxy-1,1-dimethylethyl)-3-(2-benzyloxyphenyl)-3-phenyl-propylamine

This compound was similarly prepared from the tosylate (XXIX) of Example 4d) and 2-amino-2-methylpropanol. The solid product was crystallized from diisopropyl ether and melted at 103°C. It was used as start material in Example 7p).

$C_{26}H_{31}NO_2$(389.5) requires:	C	80.17	H	8.02	N	3.60	O	8.22
Found		80.0		8.09		3.69		8.51

q) N-(1-Adamantyl)-3-(2-benzyloxyphenyl)-3-phenylpropylamine

This compound was similarly prepared from the tosylate (XXIX) of Example 4d) and 1-aminoadamantane. It was used as start material in Example 7q). The hydrochloridesemihydrate was prepared in acetonitrile and melted at 225°C.

$C_{32}H_{37}NO.HCl.1/2\ H_2O$ (497.1) requires:	C	77.31	H	7.91	N	2.82	O	4.83	Cl	7.13
Found:		77.3		8.23		2.65		5.04		7.14

Example 6

Preparation of secondary 3,3-diphenylpropylamines

a) N-tert.Butyl-3,3-bis-(2-methoxyphenyl)propylamine (L), hydrogen oxalate

The tosylate (XXVII) of Example 4a) was heated with a large excess of tert.butylamine as described in Example 5, giving the free base in 78% yield, which was converted to the oxalic acid salt in the usual manner. M.p. 135-136° (acetone-ether).

$C_{23}H_{31}NO_6$ (417.5) requires:	C	66.17	H	7.48	N	3.36	O	22.99	
Found		65.6		7.31		3.36		23.4	

b) N-tert.Butyl-3-(2,3-dibenzyloxyphenyl)-3-phenylpropylamine (LI), hydrochloride

The free base was obtained as above in 78% yield from the tosylate (XXVIII) of Example 4c). The HCl salt had m.p. 184-185° (acetone-methanol-IPE).

$C_{33}H_{38}NO_2Cl$ (516.1) requires:	C	76.79	H	7.42	N	2.71	O	6.20	Cl	6.87
Found		76.3		7.30		2.72		6.42		6.81

c) N-tert.Butyl-3-(2-benzyloxyphenyl)-3-phenylpropylamine (LII), hydrogen oxalate

The free base was obtained in 84% yield from the tosylate (XXIX) of Example 4d). The oxalic acid salt had m.p. 198° (acetone-ether).

$C_{28}H_{33}NO_5$ (463.6) requires:	C	72.54	H	7.18	N	3.02
Found		71.8		7.13		2.95

d) N-tert.Butyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine (LIII), hydrochloride

The free base was obtained in 90% yield from the tosylate (XXX) of Example 4e). When treated with ethereal HCl, it gave a somewhat hygroscopic salt which seems to be associated with 1/4 mol of water. M.p. 171° (ethanol-ether).

$C_{21}H_{29}NO.HCl.1/4\ H_2O$ (352.5) (requires):	C	71.55	H	8.74	N	3.97	O	5.67	Cl	10.06
Found		71.8		8.72		4.05		5.57		10.1

e) N-tert.Butyl-3-(2-methoxy-4-methylphenyl)-3-phenylpropylamine (LIV), hydrochloride

The free base was obtained in quantitative yield from the tosylate (XXXI) of Example 4b). The HCl-salt had m.p. 138-149° (methanol-isopropanol). It was associated with 3/4 mol of water.

$C_{21}H_{30}NOCl.3/4\ H_2O$ (361.5) requires:	C	69.77	H	8.80	N	3.88	Cl	9.81
Found		69.8		8.76		3.93		9.75

f) N-tert.Butyl-3,3-bis-(2-methoxy-5-methylphenyl)-propylamine (LV), hydrochloride

The free base was obtained in quantitative yield from the tosylate (XXXII) of Example 4f). The HCl-salt had m.p. 242° (acetone).

$C_{23}H_{34}NOCl$ (392.0) requires:	C	70.47	H	8.74	N	3.57	Cl	9.05
Found		70.2		8.81		3.46		8.99

g) N-tert.Butyl-3-(2,5-dibenzyloxyphenyl)-3-phenylpropylamine (LVI), hydrochloride

The free base was obtained in 85% yield from the tosylate (XXXIII) of Example 4g). The HCl salt had m.p. 188° (ethanol-ether).

$C_{33}H_{38}NO_2Cl$ (516.1) requires:	C	76.79	H	7.42	N	2.71	O	6.20	Cl	6.87
Found		77.2		7.50		2.64		6.53		6.85

h) N-tert.Butyl-3,3-bis-(2-benzyloxy-4-methylphenyl)-propylamine (LVII), hydrochloride

The free base was obtained in 94% yield from the tosylate (XXXIV) of Example 4h). The HCL-salt had m.p. 210° (acetone-ether).

$C_{35}H_{42}NO_2Cl$ (544.2) requires:	C	77.25	H	7.78	N	2.57	O	5.89	Cl	6.52
Found		77.6		7.82		2.35		6.08		6.55

i) N-tert.Butyl-3-(2,4-dimethoxyphenyl)-3-phenylpropylamine (LVIII), hydrochloride

The free base was obtained in 84% yield from the tosylate (XXXV) of Example 4i). The HCl-salt had m.p. 196° (acetone-ethanol-ether).

$C_{21}H_{30}NO_2Cl$ (363.9) requires:	C	69.31	H	8.31	N	3.85	O	8.79	Cl	9.74
Found		69.3		8.44		3.80		8.89		9.81

j) N-tert.Butyl-3,3-bis-(2,4-dimethoxyphenyl)-propylamine (LIX), hydrochloride

The free base was obtained in 60% yield from the tosylate (XXXVI) of Example 4j). The HCl-salt had m.p. 251° (methanol-acetone).

$C_{23}H_{34}NO_4Cl$ (424.0) requires:	C	65.15	H	8.08	N	3.30	O	15.09	Cl	8.36
Found		64.5		8.06		3.57		15.3		8.67

k) N-tert.Butyl-3-(4-fluorophenyl)-3-(2-methoxyphenyl)-propylamine (LX), hydrochloride

The free base was obtained in 89% yield from the tosylate (XXXVII) of Example 4k). The HCl-salt had m.p. 194° (ethanol-acetone).

$C_{20}H_{27}NOFCl$ (351.9) requires:	C	68.26	H	7.73	N	3.98	Cl	10.08		
Found		68.9		7.97		4.01		9.69		

l) N-tert.Butyl-3-(2-methoxyphenyl)-3-phenylpropylamine (LXI), hydrochloride

The free base was obtained in 88% yield from the tosylate (XLVIII) of Example 4l). The HCl-salt had m.p. 205°.

$C_{20}H_{28}NOCl$ (333.9) requires:	C	71.94	H	8.45	N	4.20	O	4.79	
Found		71.9		8.44		4.67		4.79	

m) N-(1,1-Dimethylpropyl)-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine (LXII), hydrochloride

The free base was obtained in 95% yield from the tosylate (XXX) of Example 4e) and tert. amylamine. The HCl-salt had m.p. 188-189° (ethanol-acetone).

$C_{22}H_{32}NOCl$ (362.0) requires:	C	73.00	H	8.91	N	3.87	O	4.42	Cl 9.80
Found		73.4		8.98		3.83		4.61	9.51

n) N-(1,1-Dimethylpropyl)-3,3-bis-(2-methoxy-5-methylphenyl)propylamine (LXIII), hydrochloride

The free base was obtained in 94% yield from the tosylate (XXXII) of Example 4f) and tert. amylamine. The HCl-salt had m.p. 210° (ethanol-acetone).

$C_{24}H_{36}NO_2Cl$ (406.0) requires:	C	71.00	H	8.94	N	3.45	O	7.88	Cl 8.73
Found		71.1		9.01		3.60		7.92	8.73

o) N-tert.Butyl-3-(5-chloro-2-methoxyphenyl)-3-phenylpropylamine

The tosylate from Example 4m) (43.1 g, 0.1 mol) in 100 ml acetonitrile was treated with tert.butylamine (37 g, 0.5 mol) and the mixture was heated in a pressure bottle at 80° for 4 days. The usual work-up afforded 32 g (100%) crude title compound. The base in ether-acetone was treated with ethereal HCl giving the hydrochloride salt, m.p. 216-218°.

$C_{20}H_{26}ClNO.HCl$ (368.36) requires:	C	65.21	H	7.39	N	3.80	Cl	19.25	
Found		65.1		7.39		3.90		18.7	

Example 7

Preparation of tertiary 3,3-diphenylpropylamines from secondary amines

a) N-Methyl-N-tert.butyl-3-(2-methoxyphenyl)-3-phenylpropylamine (LXV), hydrochloride

A mixture of the secondary amine (LXI) of Example 6l) (29.7 g, 0.1 mol), formic acid (13.8 g, 0.3 mol), and 37% formaldehyde solution (12.5 g, 0.12 mol) was refluxed for 18-24 h. The mixture was then cooled, basified with NaOH, and extracted with ether. The extract was washed with water, dried and evaporated, giving 29.3 g (94%) of a crude oil. The HCl-salt was prepared from ethereal HCl in the usual way, m.p. 199°.

$C_{21}H_{30}NOCl$ (347.9) requires:	C	72.49	H	8.69	N	4.03	Cl	10.19	
Found		71.9		8.79		4.23		10.1	

b) N-Methyl-N-tert.butyl-3-(2-methoxy-5-methylphenyl)-3-phenyl-propylamine (LXVI), hydrochloride

The free base was obtained in the same way in 89% yield from the amine (LIII) of Example 6d). The HCl-salt had m.p. 161° (acetone).

$C_{22}H_{32}NOCl$ (362.0) requires:	C	73.00	H	8.91	N	3.87	O	4.42	Cl 9.08
Found		73.0		8.96		3.94		4.59	9.77

c) N-Methyl-N-tert.butyl-3,3-bis-(2-methoxyphenyl)propylamine (LXVII), hydrochloride

The free base was obtained in 96% yield from the amine (L) of Example 6a). The HCl-salt had m.p. 187-190° (acetone-ether).

$C_{22}H_{33}NOCl$ (378.0) requires:	C	69.91	H	8.54	N	3.71	O	8.47	Cl 9.38
Found		69.9		8.56		3.53		8.93	8.92

d) N-Methyl-N-tert.butyl-3-(2-methoxy-4-methylphenyl)-3-phenylpropyl-amine (LXVIII)

The free base was obtained in 96% yield from the amine (LIV) of Example 6e). M.p. 64° (IPE).

$C_{22}H_{31}NO$ (325.5) requires:	C	81.17	H	9.60	N	4.30	O	4.92	
Found		81.0		9.83		4.15		5.03	

e) N-Methyl-N-tert.butyl-3,3-bis-(2-methoxy-5-methylphenyl)propyl-amine (LXIX)

The free base was obtained in 97% yield from the amine (LV) of Example 6f). M.p. 95° (IPE).

$C_{24}H_{35}NO_2$ (370.0) requires:	C	78.00	H	9.55	N	3.79	O	8.66	
Found		78.1		9.57		3.70		8.80	

f) N-Methyl-N-tert.butyl-3-(4-fluorophenyl)-3-(2-methoxyphenyl)-propylamine (LXX), hydrochloride

The free base was obtained in 82% yield from the amine (LX) of Example 6k). The HCl-salt had m.p. 218° (ethanol-acetone).

$C_{21}H_{29}NOClF$ (365.9) requires:	C	68.93	H	7.99	N	3.83	Cl	9.69	
Found		69.0		7.97		3.95		9.60	

g) N-(1,1-Dimethylpropyl)-N-methyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine (LXXI), hydrochloride

The free base was obtained in 98% yield from the amine (LXII) of Example 6m). The HCl-salt had m.p. 176-177° (acetone).

$C_{23}H_{34}NOCl$ (376.0) requires: C 73.47 H 9.11 N 3.73 Cl 9.43
Found 73.4 9.15 3.73 9.41

h) N-(1,1-Dimethylpropyl)-N-methyl-3,3-bis-(2-methoxy-5-methylphenyl)-propylamine (LXXII), hydrochloride

The free base was obtained in 89% yield from the amine (LXIII) of Example 6n). The HCl-salt had m.p. 147° (acetone-ether).

$C_{25}H_{37}NO_2Cl$ (420.1) requires: C 71.49 H 9.12 N 3.34 O 7.62 Cl 8.44
Found 70.8 9.20 3.63 7.74 8.42

i) N-Methyl-N-tert.butyl-3-(2,4-dimethoxyphenyl)-3-phenylpropyl-amine (LXXIII)

This compound was obtained as an oil in quantitative yield from the amine (LVIII) of Example 6i).

NMR: 6.5-7.3 (m 8H), 4.3 (t 1H), 3.8 (s 6H), 2.3 (s 3H), 1.0 (s 9H).

j) N-Methyl-N-tert.butyl-3-(2,5-dibenzyloxyphenyl)-3-phenylpropyl-amine (LXXIV)

This was obtained as an oil in 95% yield from the amine (LVI) of Example 6g).

k) N-Methyl-N-tert.butyl-3,3-bis-(2-benzyloxy-4-methylphenyl)propyl-amine (LXXV), hydrochloride

The free base was obtained in 92% yield from the amine (LVII) of Example 6k). The HCl-salt had m.p. 170-171° (acetone-ether).

$C_{36}H_{44}NO_2Cl$ (558.2) requires: C 77.46 H 7.95 N 2.51 O 5.73 Cl 6.35
Found 77.6 7.86 2.42 5.89 6.31

l) N-Methyl-N-tert.butyl-3,3-bis-(2,4-dimethoxyphenyl)propylamine (LXXVI), hydrochloride

The free base was obtained in 96% yield from the amine (LIX) of Example 6j). The HCl-salt had m.p. 180-190° and seems to be associated with 1/4 mol of water.

$C_{24}H_{36}NO_4Cl$ 1/4 H_2O (447.0) requires: C 64.48 H 8.34 N 3.13 O 16.11 Cl 7.93
Found 64.5 8.27 3.02 16.2 8.19

m) N-Methyl-N-tert.butyl-3-(2,3-dibenzyloxyphenyl)-3-phenylpropyl-amine (LXXVII)

This was obtained as an oil in 98% yield from the amine (LI) of Example 6b).

NMR: δ6.9-7.3 (m 18H), 2.1 (s 3H), 1.0 (s 9H).

n) N-Methyl-N-tert.butyl-3-(2-benzyloxyphenyl)-3-phenylpropyl-amine (LXXVIII)

This was obtained as an oil in 97% yield from the amine (LII) of Example 6c).

NMR: 6.9-7.3 (m 14H), 5.0 (s 4H), 4.5 (t 1H), 2.2 (s 3H), 0.9 (s 9H).

o) N-Methyl-N-tert.butyl-3-(5-chloro-2-methoxyphenyl)-3-phenylpropyl-amine

The secondary amine from Example 6o) (25.3 g, 0.076 mol) was refluxed for 18 h with formic acid (9.2 g, 0.2 mol) and 35% formaldehyde solution (8.5 g, 0.1 mol). Work-up gave 25.6 g, (97.5%) crude base. This was dissolved in acetone and treated with an equimolar quantity of oxalic acid in acetone giving beige crystals of the title compound, hydrogen oxalate, m.p. 165°.

$C_{21}H_{28}ClNO.C_2H_2O_4$ (436.0) requires:	C	63.37	H	6.94	N	3.21	Cl	8.13
Found		62.7		6.83		3.10		7.97

p) N-(2-Hydroxy-1,1-dimethylethyl)-N-methyl-3-(2-benzyloxyphenyl)-3-phenylpropylamine

This compound was similarly prepared from the compound of Example 5p). It was obtained as a sticky oil which was converted to the free hydroxy compound of Example 9ad).

q) N-1-Adamantyl-N-methyl-3-(2-benzyloxyphenyl)-3-phenylpropylamine

This compound was similarly prepared from the compound of Example 5q). It was obtained as a sticky oil which was converted to the free hydroxy compound of Example 9ae) without further purification.

Example 8

Preparation from olefinic precursors

a) N-tert.butyl-3-(2,6-dimethoxyphenyl)-3-hydroxy-3-phenylpropylamine (LXXIX)

A solution of diisopropylamine (10.1 g, 0.1 mol) in dry ether (100 ml) was cooled to -10°. A solution of butyl lithium in hexane (65 ml, 0.1 mol) was added, and the mixture was stirred at -10° for 20 min. A solution of N-ethylidene-tert.butylamine (10 g, 0.1 mol) in dry ether (100 ml) was added and the solution was stirred at 0° for 20 min. After cooling to -30° a solution of 2,6-dimethoxybenzophenone (24.1 g, 0.1 mol) in dry ether (100 ml), containing 30 ml THF, was added. The mixture was then stirred at ambient temperature for 20 h and hydrolized with water. The organic phase was washed with water, dried and evaporated, giving 32 g (94%) of N-(3-(2,6-dimethoxyphenyl)-3-hydroxy-3-phenyl-propylidene)tert.butylamine as an oil.

This oil was dissolved in absolute ethanol (250 ml), the solution was cooled to -5°, and $NaBH_4$ (5.7 g, 0.15 mol) was added portionwise. The mixture was stirred at 0° for 1/2 h, then at ambient temperature for 3 h. Most of the solvent was distilled off in vacuum, the residue was treated with water, extracted with ether, washed with water, and extracted with 2N HCl. The extract was washed with ether, basified with NaOH, extracted with ether, dried and evaporated, giving 30 g of the title amine.

The HCl-salt had m.p. 203-204° (acetone-ether) and seems to be associated with 1/4 mol of water.

$C_{21}H_{29}NO_3$.HCl.1/4 H_2O (384.5) requires: C 65.60 H 8.01 N 3.64 O 13.52
Found 65.9 8.11 3.64 13.7

b) N-tert.Butyl-3-(2,6-dimethoxyphenyl)-3-phenyl-2-propene-1-amine (LXXX)

The above amine from step a) (21 g, 0.061 mol) was added to 6.3N H_2SO_4 (20 ml, 0.126 mol). The mixture was stirred on a boiling water bath for 2 h, cooled, basified, and extracted with ether. The extract was washed, dried and evaporated, giving 17.8 g, (90%) of the title olefin as a clear oil. The HCl-salt had m.p. 220-22°, and was associated with 1/4 mol of water.

$C_{21}H_{27}NO_2$.HCl. 1/4 H_2O requires: C 68.82 H 7.86 N 3.82 O 9.82 Cl 9.68
Found 68.8 7.89 3.92 9.81 9.44

c) N-Methyl-N-tert.butyl-3-(2,6-dimethoxyphenyl)-3-phenylpropyl-amine (LXXXI), hydrogen fumarate

The olefinic amine from step b) (16.3 g, 0.05 mol) in methanol (250 ml) containing 0.5 g of a 10% Pd/C catalyst, was hydrogenated at ambient temperature and pressure. The mixture was then filtered through Celaton, the filtrate was taken to dryness, giving 16.3 g (100%) of N-tert.butyl-3-(2,6-dimethoxyphenyl)-3-phenylpropylamine. The HCl-salt had m.p. 244° (ethanol).

$C_{21}H_{29}NO_2$.HCl (363.9) requires: C 69.31 H 8.31 N 3.85 O 8.79 Cl 9.74
Found 69.3 8.29 3.83 9.27 9.75

The above secondary amine, as the free base, was methylated with formaldehydeformic acid as described in Example 7, giving the tertiary amine in 96% yield. The fumaric acid salt had m.p. 185-190° (acetone).

$C_{26}H_{35}NO_6$ (457.6) requires: C 68.25 H 7.71 N 3.06 O 20.95
Found 67.8 7.59 3.05 21.6

Example 9

Removal of O-protective groups

a) N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropylamine (LXXXII), hydrochloride

The amine (XLIX) of Example 5k) (20.8 g, 0.064 mol) in methylene chloride (150 ml) was cooled below 0°. A 1N solution of BBr_3 in CH_2Cl_2 (64 ml, 0.064 mol) was then added dropwise, the solution was then kept in the cooler (5°) for 2-5 days, and volatile material was distilled off at <50°. The residual syrup was basified, extracted with ether, the extract was washed with water, dried and evaporated, giving a viscous syrup. The HCl-salt had m.p. 222° (methanol-ether), yield 31%.

$C_{21}H_{29}NO.HCl$ (347.9) requires:	C	72.49	H	8.69	N	4.03	O	4.60	Cl 10.19
Found		72.0		8.72		3.74		5.06	10.3

The following compounds were obtained in the same way.

b) N-[3-(2-Hydroxyphenyl)-3-phenylpropyl]-2,2,6,6-tetramethyl-piperidine (LXXXIII), hydrogen fumarate

From the amine (LXIV) of Example 5l). Crude yield 78%. M.p. fumaric acid salt = indefinite.

$C_{28}H_{37}O_5$ (467.6) requires:	C	71.9	H	7.91	N	3.00	O	17.1
Found		71.8		8.41		3.01		16.6

c) N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine (LXXXIV), hydrochloride

From the amine (XL) of Example 5c). Crude yield 85%. HCl-salt, m.p. 209-210° (acetone-ether).

$C_{22}H_{31}NO.HCl.\ 1/4\ H_2O$ (366.5) requires:	C	72.09	H	8.95	N	3.82	O	5.46 Cl 9.67
Found		72.3		8.95		3.71		5.68 9.61

d) N-Methyl-N-tert.butyl-3-(2-hydroxy-5-methylphenyl)-3-phenyl-propylamine (LXXXV), hydrochloride

From the amine (LXVI) of Example 7b). Crude yield 100%. HCl-salt, m.p. >260° (ethanol).

$C_{21}H_{29}NO.HCl$ (347.4) requires:	C	72.49	H	8.69	N	4.03	Cl 10.19
Found		72.7		8.58		3.81	10.95

e) N,N-Diisopropyl-3,3-bis-(2-hydroxyphenyl)propylamine (LXXXVI), hydrochloride

From the amine (XXXVIII) of Example 5a). Crude yield 57%. HCl-salt, m.p. 257° (ethanol-ether).

$C_{21}H_{29}NO_2$.HCl (363.9) requires: C 69.31 H 8.31 N 3.85 O 8.79 Cl 9.74
Found 69.3 8.37 3.95 9.23 9.40

f) N-Methyl-N-tert.butyl-3,3-bis-(2-hydroxyphenyl)propylamine (LXXXVII), hydrochloride

From the amine (LXVII) of Example 7c). Crude yield 100%, m.p. 190°. HCl-salt, m.p. 252° (ethanol).

$C_{20}H_{27}NO_2$.HCl (349.9) requires: C 68.65 H 8.06 N 4.00 Cl 10.13
Found 68.4 8.06 4.17 9.59

g) N,N-Diisopropyl-3-(2-hydroxy-4-methylphenyl)-3-phenylpropylamine (LXXXVIII), hydrochloride

From the amine (XLI) of Example 5d). Crude yield 90%. HCl-salt, m.p. 217° (ethanol).

$C_{22}H_{31}NO$.HCl. 1/4 H_2O (366.5) requires: C 72.09 H 8.96 N 3.82 O 5.46 Cl 9.67
Found 72.3 8.91 3.93 5.27 9.46

h) N,N-Diisopropyl-3,3-bis-(2-hydroxy-5-methylphenyl)propylamine (LXXXIX), hydrochloride

From the amine (XLII) of Example 5e). Crude yield 93%, m.p. 166°. HCl-salt, m.p. 220° (ethanol).

$C_{23}H_{33}NO_2$.HCl (392.0) requires: C 70.47 H 8.74 N 3.57 Cl 9.05
Found 70.6 8.78 3.71 8.93

i) N-Methyl-N-tert.butyl-3,3-bis-(2-hydroxy-5-methylphenyl)propylamine (XC), hydrochloride

From the amine (LXIX) of Example 7e). Crude yield 79%, m.p. 199-201° (IPE). HCl-salt, m.p. 220° (acetone).

$C_{22}H_{31}NO_2$.HCl (378.0) requires: C 69.91 H 8.54 N 3.71 O 8.47 Cl 9.38
Found 69.9 8.70 3.75 8.81 9.15

j) N-Methyl-N-tert.butyl-3-(2-hydroxy-4-methylphenyl)-3-phenylpropylamine (XCI), hydrochloride

From the amine (LXVIII) of Example 7d). Crude yield 100%. HCl-salt, m.p. 240° (ethanol).

$C_{21}H_{29}NO$.HCl (347.9) requires: C 72.49 H 8.69 N 4.03 O 4.60 Cl 10.19
Found 72.5 8.75 4.06 4.90 10.1

k) N,N-Diisopropyl-3-(4-fluorophenyl)-3-(2-hydroxyphenyl)propylamine (XCII), hydrochloride

From the amine (XLVII) of Example 5j). Crude yield 72%. HCl-salt, m.p.

183° (acetone-ethanol).

$C_{21}H_{27}FNO.HCl$ (364.9) requires: C 69.12 H 7.73 N 3.83
Found 69.1 8.09 3.82

l) N,N-Diisopropyl-3-(2,4-dihydroxyphenyl)-3-phenylpropylamine (XCIII), hydrochloride

From the amine (XLV) of Example 5h). Crude yield 31%. HCl-salt, m.p. 205-210° (ethanol-acetone-ether).

$C_{21}H_{29}NO_2.HCl$ (363.9) requires: C 69.31 H 8.31 N 3.85 O 8.79 Cl 9.74
Found 69.5 8.33 3.72 8.91 9.87

m) N-(1,1-Dimethylpropyl)-N-methyl-3,3-bis-(2-hydroxy-5-methylphenyl)-propylamine (XCIV), hydrochloride

From the amine (LXXII) of Example 7h). Crude yield 100%, m.p. 190-195°. HCl-salt, m.p. 235-240° (ethanol-acetone-ether).

$C_{23}H_{33}NO_2.HCl$ (392.0) requires: C 70.47 H 8.74 N 3.57 O 8.16 Cl 9.05
Found 70.0 8.96 3.54 8.11 9.19

n) N-Methyl-N-tert.butyl-3-(2,4-dihydroxyphenyl)-3-phenylpropylamine (XCV), hydrobromide

From the amine (LXXIII) of Example 7i). Crude yield 78%, m.p. 260°. HBr-salt, m.p. >260° (ethanol).

$C_{20}H_{25}NO_2.HBr$ (394.4) requires: C 60.9 H 7.16 N 3.55 O 8.11 Br 20.27
Found 60.8 7.18 3.29 8.38 20.2

o) N,N-Diisopropyl-3,3-bis-(2,4-dihydroxyphenyl)propylamine (XCVI), hydrochloride

From the amine (XLVI) of Example 5l). The HCl-salt, consisting of an amorphous brown powder, did not give a satisfactory elemental analysis because of incomplete combustion.

p) N-Methyl-N-tert.butyl-3,3-bis-(2,4-dihydroxyphenyl)propylamine (XCVII), hydrochloride

From the amine (LXXVI) of Example 7l). Crude yield 87%, m.p. 260°. The HCl-salt did not give a satisfactory elemental analysis because of incomplete combustion.

q) N,N-Diisopropyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine (XCVIII), hydrochloride

The amine (XLIII) of Example 5f) in the form of the free base (32 g, 0.063 mol) in methanol (500 ml) containing 5 g of a 5% Pd/C catalyst was hydrogenated

at ambient temperature and pressure. After 2 h the reaction was complete. The mixture was filtered, the filtrate was taken to dryness, the residue was dissolved in acetone and treated with ethereal HCl, giving 19.8 g (87%) of a crude salt, m.p. 260°. Recrystallization from methanol gave white crystals, m.p. 260°.

$C_{21}H_{29}NO_2$.HCl. 1/4 H_2O (368.6) requires: C 68.44 H 8.36 N 3.80 O 9.77 Cl 9.62
Found 68.4 8.40 3.60 10.3 9.42

The following compounds were prepared in the same way.

r) N-Methyl-N-tert.butyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine (XCIX), hydrochloride

From the amine (LXXIV) of Example 7j). Crude yield 90%. HCl-salt, m.p. >270° (methanol-water).

$C_{20}H_{27}NO_2$.HCl (349.9) requires: C 68.65 H 8.06 N 4.00 O 9.14 Cl 10.13
Found 68.9 8.02 3.93 9.60 10.5

s) N,N-Diisopropyl-3,3-bis-(2-hydroxy-4-methylphenyl)propylamine (C), hydrochloride

From the amine (XLIV) of Example 5g). Crude yield 100%. HCl-salt, m.p. 253° (methanol-ether).

$C_{23}H_{33}NO_2$.HCl (392.0) requires: C 70.47 H 8.74 N 3.57 O 8.16 Cl 9.05
Found 70.5 8.74 3.55 8.47 8.03

t) N-Methyl-N-tert.butyl-3,3-bis-(2-hydroxy-4-methylphenyl)propylamine (CI), hydrochloride

From the amine (LXXV) of Example 7k). Crude yield 97%, a yellow powder. HCl-salt, m.p. 260° (methanol-acetone).

$C_{22}H_{31}NO_2$.HCl (378.0) requires: C 69.91 H 8.54 N 3.71 O 8.47 Cl 9.38
Found 69.9 8.68 3.67 8.85 9.24

u) N,N-Diisopropyl-3-(2,3-dihydroxyphenyl)-3-phenylpropylamine (CII), hydrochloride

From the amine (XXXIX) of Example 5b). Crude yield 100%. HCl-salt, m.p. 174-176° (acetone).

$C_{21}H_{29}NO_2$.HCl (363.9) requires: C 69.31 H 8.31 N 3.85 O 8.79 Cl 9.74
Found 69.5 8.33 3.66 9.37 9.63

w) N-Methyl-N-tert.butyl-3-(2,3-dihydroxyphenyl)-3-phenylpropylamine (CIII), hydrochloride

From the amine (LXXVII) of Example 7m). Crude yield 100%, a white powder. HCl-salt, m.p. 209-210°, slow heating, (methanol-acetone).

$C_{20}H_{27}NO_2$.HCl. 1/4 H_2O (358.9) requires: C 66.92 H 8.14 N 3.90 O 11.14 Cl 9.88
Found 66.9 8.12 3.76 11.8 9.74

x) N-Methyl-N-tert.butyl-3-(2-hydroxyphenyl)-3-phenylpropylamine (CIV), hydrochloride

From the amine (LXXVIII) of Example 7n). Crude yield 100%. HCl-salt, m.p. 255° (acetone-ether).

$C_{20}H_{27}NO$.HCl (333.9) requires: C 71.94 H 8.45 N 4.20 Cl 10.62
Found 71.9 8.43 4.01 10.5

y) N-Methyl-N-tert.butyl-3-(2,6-dihydroxyphenyl)-3-phenylpropylamine (CV), hydrochloride

From the amine (LXXXI) of Example 8c) with BBr_3, in low yield. HCl-salt, m.p. 170° (ethanol-ether).

$C_{20}H_{27}NO_2$.HCl. 1/2 H_2O (358.9) requires: C 66.93 H 8.14 N 3.40 O 11.14 Cl 9.87
Found 67.4 8.28 3.63 10.9 9.99

z) N,N-Diisopropyl-3-(5-chloro-2-hydroxyphenyl)-3-phenylpropylamine

The base from Example 5m) (11.7 g, 0.032 mol) was treated with pyridine (7.6 g, 0.096 mol) and conc. HCl (13 g). The mixture was taken to dryness in vacuum and the residue was heated in an oil-bath at 205-215° for 1 1/2 h. The melt was cooled somewhat, water was added, the mixture was digested in a boiling water bath and cooled. 2 N HCl was added, the salt was filtered off, washed with 2 N HCl and dried, giving 11.0 g (90%) white salt m.p. 200°. Recrystallization from acetone gave the hydrochloride of the title compound, m.p. 202-203°.

$C_{21}H_{28}ClNO$.HCl (382.4) requires: C 65.96 H 7.64 N 3.66 Cl 18.54
Found 66.0 7.88 3.63 18.3

aa) N-Methyl-N-tert.butyl-3-(5-chloro-2-hydroxyphenyl)-3-phenylpropylamine

The free base from Example 7o) (10.5 g, 0.03 mol) was treated with pyridine (7.0 g, 0.09 mol) and conc. HCl (12 g). The mixture was taken to dryness in vacuum and the residue was heated in an oil-bath at 205-215° for 1 1/2 h. The melt was cooled somewhat, excess of 2 N NaOH was added, the mixture was extracted with ether, the extract was washed with water, dried and evaporated giving 7.5 g (88%) crude syrup. This was dissolved in ether and treated with ethereal HCl giving 8 g (83%) of hydrochloride salt. Recrystallization from acetone-2 N HCl gave the hydrochloride of the title compound, m.p. 260°.

$C_{20}H_{26}ClNO.HCl$ (368.4) requires: C 65.21 H 7.39 N 3.80 Cl 19.25
Found 65.0 7.30 3.73 18.9

ab) N-[3-(2-Hydroxyphenyl)-3-phenylpropyl]-2,2,5,5-tetramethyl-pyrrolidine

The crude amine from Example 5n) was hydrogenolysed as described in Example 9q). The free amine was obtained as an oil which was converted to the hydrochloride and crystallized from 2-propanol. M.p. 250°C.

$C_{23}H_{31}NO.HCl$ (374.0) requires: C 73.86 H 8.63 N 3.75 O 4.28 Cl 9.48
Found 73.8 8.71 3.59 4.80 9.45

ac) N-[3-(2-Hydroxyphenyl)-3-phenylpropyl]-4-hydroxy-2,2,6,6-tetramethylpiperidine

The benzyloxy compound from Example 5o) was hydrogenolysed as described in Example 9q). The free base was converted to the hydrochloride semihydrate which was crystallized from acetone. The compound melts with decomposition at about 150°C.

$C_{24}H_{33}NO_2.HCl.\ 1/2\ H_2O$ (413.0) requires: C 69.79 H 8.54 N 3.39 O 9.68 Cl 8.58
Found: 70.0 8.67 3.47 9.98 8.13

ad) N-(2-Hydroxy-1,1-dimethylethyl)-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropylamine

The benzyloxy compound from Example 7p) was hydrogenolysed as described in Example 9q). The amine, obtained as a glassy mass, was converted to the hydrochloride which was obtained as an amorphous solid on precipitation from ethanol with ether.

$C_{20}H_{27}NO_2.HCl$ (349.9) requires: C 68.65 H 8.06 N 4.00 O 9.15 Cl 10.13
Found: 68.25 8.18 3.98 9.12 10.0

ae) N-1-Adamantyl-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropylamine

The benzyloxy compound from Example 7q) was hydrogenolysed as described in Example 9q). The free hydroxyamine was obtained as a glassy mass. It was dissolved in anhydrous ether and treated with an excess of hydrogen chloride in ether. The hydrochloride precipitated as a powder which decomposed at about 220°C.

$C_{26}H_{33}NO.HCl$ (412.0) requires: C 75.79 H 8.32 N 3.40 O 3.88 Cl 8.61
Found: 75.3 8.01 3.22 3.45 8.96

Example 10

Reduction of amides

a) N,N-Diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine

3-(2-Methoxy-5-methylphenyl)-3-phenylpropionic acid (12.8 g, 0.05 mol) (J.D. Simpson & H. Stehphen, J. Chem. Soc. 1956 1382) and thionyl chloride (50 ml) are heated on a water bath for 3 h. The excess of thionyl chloride is distilled off under reduced pressure. The remaining crude 3-(2-methoxy-5-methylphenyl)-3-phenylpropionyl chloride is dissolved in 50 ml of dichloromethane and added dropwise to a stirred solution of diisopropylamine (20.2 g, 0.20 mol) in 200 ml of dichloromethane at about 0°C. The solution is left for 2 h, the solvent is distilled off and the remaining material is treated with water. The solid product consisting of N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropionamide is filtered off, dried and added in small portions to a stirred suspension of lithium aluminium hydride (6.0 g, 0.16 mol) in dry ether (700 ml). The mixture is refluxed for 2 days. Excess of hydride is destroyed by the careful addition of water, the ether layer is separated and dried with anhydrous sodium sulfate. After filtration the solution is added to a solution of excess fumaric acid in ether. The precipitated salt is collected and crystallized from 2-propanol. The hydrogen fumarate melts at 176°C.

b) N-Methyl-N-tert.butyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine was similarly prepared. The hydrochloride melts at 161°C.

Example 11

a) N-Methyl-N-tert.butyl-3-(5-chloro-2-hydroxyphenyl)-3-phenylpropylamine

A solution of chlorine (7,1 g, 0,10 mol) in acetic acid (500 ml) is added dropwise to a stirred solution of N-methyl-N-tert.butyl-3-(2-hydroxyphenyl)-3-phenylpropylamine (29.7 g, 0.10 mol) in acetic acid (200 ml) with stirring. After 2 h the solvent is distilled off under reduced pressure and the crude hydrochloride left is recrystallized from 2-propanol. Melting point 260°C.

b) N,N-Diisopropyl-3-(5-chloro-2-hydroxyphenyl)-3-phenylpropylamine is similarly prepared. The hydrochloride melts at 202-3°C.

Example 12

Separation of (+)- and (-)-enantiomers

(±)-N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropylamine (31.1 g, 0.10 mol) is dissolved in 300 ml of ethanol. A solution of L(+)-tartaric acid (15.0 g, 0.10 mol) in 400 ml of ethanol is added. The mixture is heated a few minutes in a boiling water bath and seeded with crystals obtained by cooling and

scratching a small sample of the main solution. The mixture is chilled at about 4°C over-night whereupon the crystalline precipitate is filtered off, washed with cold ethanol and recrystallized repeatedly from ethanol. The pure (-)-N,N-diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropylamine hydrogen L-(+)-tartrate thus obtained has $[\alpha]_D^{20}$ -10.6° (c = 5% in methanol). The free amine is obtained by alkalisation of an aqueous solution, extraction into ether, drying and evaporation of the solvent. Sticky oil, $[\alpha]_D^{20}$ -5.4° (c = 5% in methanol).

(+)-N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropylamine is similarly prepared using D-(-)-tartaric acid. The hydrogen-D-(-)tartrate has $[\alpha]_D^{20}$ +10.0°. The free amine has $[\alpha]_D^{20}$ +5.6°, both measured as 5% solutions in methanol.

Example 13 (continuation of Example 1)

Preparation of 4-phenyl-3,4-dihydrocoumarins

g) 4-(2-Methoxyphenyl)6-methyl-3,4-dihydrocoumarin (CVI)

A mixture of 2-methoxycinnamic acid (178 g, 1.0 mol), p-cresol (108 g, 1.0 mol), and p-toluenesulphonic acid monohydrate (47.5 g, 0.25 mol) was stirred on a boiling water-bath for about 2 h during which time the system was evacuated with a waterpump to remove formed water. The solid was then broken up and washed copiously with water. The granular material was then stirred with a large volume of saturated $NaHCO_3$ solution containing some 10% acetone. The product was filtered off, washed, dried and recrystallised from acetone affording 167 g (62,5%) white crystals of the desired lactone, m.p. 140°.

$C_{17}H_{16}O_3$ (268.3) requires:	C 76.10,	H 6.01,	O 17.89
Found:	76.0	5.97	17.9

h) 6-Chloro-4-(2-methoxyphenyl)-3,4-dihydrocoumarin (CVII) was prepared in a similar way in 49% yield from 2-methoxycinnamic acid and p-chlorophenol, the reaction temperature being 130° in this case. M.p. 172-173° (acetone).

$C_{16}H_{13}O_3$ (288.7) requires:	C 66.56	H 4.54	O 16.62
Found:	66.8	4.45	16.5

Example 14 (continuation of Example 2)

Preparation of 3,3-diphenylpropionic acid esters

l) Methyl-3-(2-methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propionate (CVIII) was obtained as an oil in 75% yield from the lactone CVI of Example 13g in the manner described for the ester VI of Example 2a).

m) Methyl-3-(5-chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propionate (CIX) was obtained as an oil in the same way in 97% yield from the lactone CVII of Example 13.

Example 15 (continuation of Example 3)

Preparation of 3,3-diphenylpropanols

m) 3-(5-Chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propanol (CX) was obtained in 84% yield from the ester CIX of Example 14m in the manner described for the propanol XVI of Example 3a), except that the reduction was carried out in toluene with a 10% molar excess of a 3.4 M toluenic solution of sodium bis(2-methoxyethoxy)aluminium hydride (SMEAH) instead of $LiAlH_4$. M.p. 70-72° (IPE).

n) 3-(2-Methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propanol (CXI) was obtained in the same way in quantitive yield from the ester CVIII of Example 14l). The product consisted of a golden oil of 89% purity according to GC.

Example 16 (continuation of Example 4)

Preparation of 3,3-diphenylpropyl-p-toluenesulphonates

n) 3-(2-Methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propyl-p-toluenesulphonate (CXII) was prepared in the same way as the tosylate XXVII of Example 4a) in quantitative yield from the propanol CXI of Example 15n) using CH_2Cl_2 as solvent instead of chloroform. M.p. 101° (ether/IPE).

$C_{25}H_{28}O_5S$ (440.57) requires:	C 68.16	H 6.41	S 7.28	
Found:	68.3	6.51	7.20	

o) 3-(5-Chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propyl-p-toluenesulphonate (CXIII) was obtained in the same way in quantitative yield from the propanol CX of Example 15m. M.p. 97-98° (acetone/IPE).

$C_{24}H_{25}ClO_5S$ (460.92) requires:	C 62.54	H 5.47	S 6.94	Cl 7.69
Found:	63.0	5.65	6.95	7.70

Example 17 (continuation of Example 5)

Preparation of tertiary 3,3-diphenylpropylamines

r) N,N-Diisopropyl-3-(5-chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)-propylamine (CXIV) was obtained as an oil in 94% yield from the tosylate CXIII of Example 16o) in the manner described for the amine XXXVIII of Example 5a). Purity by GC = 99.9%.

s) N,N-Diisopropyl-3-(2-methoxyphenyl)-3-(2-methoxy-5-methylphenyl)-propylamine (CXV) was obtained in the same way in 49% crude yield from the tosylate CXV of Example 16n). After chromatographic purification on an Si-gel 60 column (eluation with light petroleum), the product (oil)

had a purity of 100% according to GC.

t) N-[(2-Benzyloxy-5-methyl)-3-phenyl]-2,2,5,5-tetramethylpyrrolidine (CXVI) was prepared from 3-(2-benzyloxy-5-methyl)-3-phenylpropyl tosylate and 2,2,5,5-tetramethylpyrrolidine following the directions given in Example 5a). It was obtained as a sticky oil which was converted to the free hydroxy compound of Example 20aj).

Example 18 (continuation of Example 6)

Preparation of secondary 3,3-diphenylpropylamines

p) N-tert.Butyl-3-(5-chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propylamine (CXVII) was prepared in quantitative yield from the tosylate CXIII of Example 16o) in the manner described for the amine L of Example 6a). The HCl-salt had m.p. >260°.

$C_{21}H_{28}ClNO_2.HCl$ (398.38) requires:	C 63.3	H 7.34	N 3.52	Cl 17.80
Found:	63.2	7.46	3.49	17.4

q) N-tert.Butyl-3-(2-methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propylamine (CXVIII) was obtained in a similar way in 89% crude yield from the tosylate CXII of Example 16n). The HCl-salt had m.p. 225°.

$C_{22}H_{31}O_2N.HCl$ (377.97)

Requires:	C 69.91	H 8.54	N 3.71	Cl 9.38	O 8.47
Found:	69.8	8.73	3.60	9.45	8.79

Example 19 (continuation of Example 7)

Preparation of tertiary 3,3-diphenylpropylamines from secondary amines

r) N-Methyl-N-tert.butyl-3-(5-chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propylamine (CXIX) was prepared in 89% yield from the amine CXVII of Example 18p) in the manner described for the amine LXI of Example 7a). The HCl-salt was prepared by treating an acetonic solution of the free base with conctrated hydrochloric acid. M.p. 130°.

$C_{22}H_{30}ClO_2N.HCl.H_2O$ (430.42)

Requires:	C 61.39	H 7.74	N 3.25	Cl 16.47
Found:	62.0	7.93	3.26	16.5

s) N-Methyl-N-tert.butyl-3-(2-methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propylamine (CXX) was prepared in a similar way in 98% yield from the amine CXVIII of Example 18q). The free base (oil) had a purity of 96% by GC.

Example 20 (continuation of Example 9)

Removal of O-protective groups

af) N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-(2-hydroxy-5-methylphenyl)-propylamine (CXXI)

The amine CXV from Example 17s) (26.5 g, 0.072 mol) in methanol was treated with a slight excess of concentrated hydrochloric acid. The mixture was taken to dryness in vacuum, pyridinium chloride (25.4 g, 0.22 mol) was added and the mixture was then heated at 200-205° for 1 ½ h. The mixture was cooled to about 80°, acetone (20 g) was added followed by addition of little water. The salt was filtered off, washed with diluted HCl and dried. Recrystallisation from absolute ethanol-/ether gave 17.5 g (64.3%) of a white salt, m.p. >250°. Purity by GC = 100%.

$C_{22}H_{31}NO_2$.HCl (377.97)

	C	H	N	O	Cl
Requires:	69.91	8.54	3.71	8.47	9.38
Found:	69.8	8.65	3.57	8.76	9.51

ag) N,N-Diisopropyl-3-(5-chloro-2-hydroxyphenyl)-3-(2-hydroxyphenyl)-propylamine (CXXII was prepared in the same way in 37% yield from the amine CXIV of Example 17r). The HCl-salt had m.p. 214° (ethanol).

$C_{21}H_{28}NO_2$.HCl (398.38)

	C	H	N	O	Cl
Requires:	63.31	7.34	3.52	8.03	17.80
Found:	63.1	7.34	3.40	8.15	17.8

ah) N-Methyl-N-tert.butyl-3-(2-hydroxyphenyl)-3-(2-hydroxy-5-methyl-phenyl)propylamine (CXXIII) was prepared in the same way in 30% yield from the amine CXX of Example 19s). The HCl-salt had m.p. 240° (acetone).

	C	H	N	Cl
$C_{21}H_{29}NO_2$.HCl (363.94) requires:	69.3	8.31	3.58	9.74
Found:	69.0	8.35	3.65	9.76

ai) N-Methyl-N-tert.butyl-3-(5-chloro-2-hydroxyphenyl)-3-(2-hydroxy-phenyl)propylamine (CXXIV) was prepared in the same way in 24% yield from the amine CXIX of Example 19r). M.p. >250°.

	C	H	N	Cl
$C_{20}H_{26}ClNO_2$.HCl (384.36) requires:	62.50	7.08	3.65	18.45
Found:	62.5	7.09	3.63	18.4

aj) N-[3-(2-Hydroxy-5-methylphenyl)-3-phenylpropyl]-2,2,5,5-tetramethylpyrrolidine (CXXV) was obtained when the O-benzylated amine CXVI of Example 17t) was hydrogenolyzed as described in Example 9q. The hydrochloride melts at 240°.

$C_{24}H_{34}ClNO$ (388.0) requires:	C 74.29	H 8.83	N 3.61	Cl 19.14
Found:	73.9	8.90	3.52	9.48

Example 21 (continuation of Example 10)

Reduction of amides

N,N-Diisopropyl-3-(2-methoxyphenyl)-3-phenylpropionamine

N,N-Diisopropyl-3-(2-methoxyphenyl)-3-phenylpropionamide was obtained as o pale yellow oil in quantitative yield from 3-(2-methoxyphenyl)-3-phenylpropionic acid in the manner described for the amide of Example 10a). This amide (27 g, 0.08 mol) in toluene (50 g) was added dropwise under r.t. to a 3.4 M toluenic solution of SMEAH (50 g, 0,17 mol) diluted with an equal weight of toluene. The mixture was stirred at 60-70° for 2 h, cooled, treated with excess od 2N NaOH. The organic phase was separated, washed with water and extracted with 2N HCl. The acidic extract was washed with ether, basified, extracted with ether, dried and evaporated giving 17.1 g (66%) free base. This was dissolved in acetone (75 ml) and treated with 6.6 g fumaric acid dissolved in methanol, affording 20 g of the fumaric acid salt, m.p. 163-164°.

$C_{22}H_{31}ON.C_4H_4O_4$ (441.58) requires:	C 70.72	H 7.99	N 3.17	O 18.12
Found:	70.7	7.96	3.13	18.0

Example 22

Separation of (+)- and (-)-enantiomers

(+)-N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine hydrogen tartrate

The racemic amine (LXXXVIII of Example 9g) (48.8 g, 0.15 mol) was dissolved in 500 ml of 95% ethanol and mixed with a solution of L(+)-tartaric acid (22.5 g, 0.15 mol) in 500 ml of ethanol. The mixture was left over night at +4°. The precipitated salt was collected by filtration and washed with ethanol and ether. The yield of crude salt with $[\alpha]_{546}^{25}$ +29.5° (C 5%, methanol) was 34,3 g. Two recrystallisations from ethanol afforded 21.8 g with $[\alpha]_{546}^{25}$ +36.0°.

$C_{26}H_{37}NO_7$ requires:	C 65.66	H 7.84	N 2.95	O 23.55
Found:	65.9	8.06	2.90	23.5

(-)-N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine hydrogen D(-)-tartrate was similarly prepared using D(-)-tartaric acid. $[\alpha]_{546}^{25}$ -35.8°.

Found:	C 65.6	H 8.00	N 2.83	O 23.6

Several of the compounds according to the invention were tested with regard to anti-cholinergic, anti-noradrenaline, and anti-calcium effects, toxicity and effect on the heart rate. The test procedures are described below, and the test results are reported in Table 1. For comparison purposes the testing also included the commercially available drug terodiline and a structurally similar compound, N,N-dimethyl-3-(2-methoxyphenyl)-3-phenylpropylamine, disclosed as an antidepressant in US-A-3.446.901, GB-A-1.169.944, and GB-A-1.169.945. The test results clearly show that the compounds according to the invention are superior to the known compounds especially as regards selectivity between the desired anti-cholinergic activity and the undesired side-effects.

a) Anticholinergic activity on isolated urinary bladder

Male guinea-pigs, weighing 250-350 g, were killed by a blow on the head and exsanguinated. The urinary bladders were quickly removed and placed in Na^+-Krebs, in which they were kept throughout the dissection procedure. The bladders were dissected free from adherent fat and connective tissue before they were cut open by an incision on each side from the base towards apex. The mucosa was carefully removed with a pair of scissors. Four strips, approximately 3-5 mm long were prepared by cutting in a parallel direction to the longitudinal muscle fibres, on each half of the bladder.

The bladder strips were immediately mounted vertically in 5 ml organ baths containing Na^+-Krebs solution aerated with carbogene gas to maintain the pH at about 7.4. The temperature, 37°C, was thermostatically controlled by a Lauda MS3 thermostatic circulator. The preparations were suspended between two hooks, one of which was connected to a Grass Instruments FTO3 force transducer. The isomeric tension of the preparations was recorded by a Grass polygraph model 79D. The resting tension was applied to approximately 5 mN. The strips were allowed to stabilize for at least 45 minutes. During this period the resting tension was adjusted to 5 mN and the preparations were repeatedly washed.

In the preliminary experiments concentration - effect curves for carbachol (carbamylcholin chloride) were studied, in order to determine a suitable agonist concentration for inhibition studies with antagonist. The carbachol concentration chosen, $3x10^{-6}$M, produced a submaximal contractant response (70%). In the inhibition studies, the strips were contracted with carbachol ($3x10^{-6}$M) every 15 minutes. The strips were washed three times after every agonist addition. This procedure was repeated until a reproducible contractant response was observed. A variation of about 10% for three subsequent contractions was accepted as reproducible.

Initially each antagonist was tested in a concentration of 10^{-6}M, on two bladder-strips from different guinea-pigs. When a reproducible response with $3x10^{-6}$M carbachol was obtained, the strips were incubated with the antagonist for 15 minutes before the next carbachol was added. If the antagonist produced more than 50% inhibition of the response to carbachol, a complete concentration-inhibition curve was also made. In the complete inhibition curves, the strips were then incubated for 60 minutes with a fixed concentration of the antagonist before the next addition of carbachol. The effect of the antagonists was calculated as per cent inhibition of the mean of the initial agonist-induced contractions. To generate concentration-inhibition curves the antagonists were studied in 6-8 concentrations and for each concentration a fresh preparation was used, i.e. the strips were only exposed to the antagonist once before they were discarded.

b) Antagonistic effect to noradrenaline and calcium on the portal vein

Preparation of isolated portal vein from rat

Animals: Albino, male rats, weighing about 200 g.

Bath volume: 5 ml

Buffer: Na^+-Krebs, modified by K.E. Andersson

Temperature: 37°C

Gas: Carbogene (93.5% O_2 + 6.5% CO_2)

Muscle tension: 0.5 g

The rat is killed by a blow on the neck and decapitated. The abdomen is opened, the vein is dissected free from fat, cut open longitudinally and mounted in an organ bath. Changes in isometric tension is registered by a force displacement transducer, connected to an amplifier and a writing oscillograph.

Noradrenaline - antagonism on portal vein

Doses: Noradrenaline $3x10^{-7}$M

The chosen doses give about 70% of maximal response. The agonist is

added to the bath at 10-minutes intervals. When reproducible contractions are obtained a fixed concentration of the test substance is added to the bath. After an incubation period of 10 minutes noradrenaline is added. The next concentration of the test substance is added when the original response of the agonist is obtained.

The antagonistic effect of the substance is calculated as per cent inhibition of the mean response by three preceding doses of the agonist.

Ca - antagonistic effect on portal vein

10 mM K^+-solution is added to the Krebs buffer to stabilize the spontaneous myogenic activity of the vein. The amplitude of the muscle contractions is measued. The test substance is added to the bath in cumulative doses until total inhibition is obtained.

c) Histamine - antagonism on isolated ileum

Preparation of isolated ileum from guinea pigs

Animals: Guinea pigs of both sexes, weighing about 350 g.
Bath volume: 5 ml
Buffer: Na^+-Krebs, modified by K.E. Andersson
Temperature: 37°C
Gas: Carbogene (93.5% O_2 + 6.5% CO_2)
Muscle tension: 0.5 g

The guinea pig is killed by a blow on the neck and decapitated. The abdomen is opened and about 2 cm of the ileum is cut off about 15 cm above the ileocaecal junction. The piece of ileum is washed with buffer and mounted in an organ bath. Changes in isometric tension is recorded by a force displacement transducer, connected to an amplifier and a writing oscillograph.
Dose: 5×10^{-7} M of histamine.

The chosen dose of histamine gives about 70% of maximal response. The agonist is added to the bath at 3-minutes intervals. When reproducible contractions are obtained a fixed concentration of the test substance is added to the bath. After an incubation period of 2-10 minutes a new contraction is induced by histamine. The next concentration of the test substance is added when the original response of the agonist is obtained.

The agonistic effect of the test substance is calculated as per cent inhibition of the mean response by three preceding doses of histamine.

d) Acute toxicity in mice

The antagonists to be tested were dissolved in 0.9% NaCl. If they were not soluble in 0.9% NaCl they were dissolved in double distilled water. The solutions were prepraed on the day of the experiment.

Procedure

White male mice, 25 g, were placed in a mouse holder. The tested compounds were given as i.v. bolus doses in one of the four tail-veins, with a volume of 0.01 ml/g mouse. Each substance concentration was given to a group of four mice. 4-5 different concentrations of the antagonists were made and tested.

The acute lethal dose (LD_{11}) was the lowest concentration of the anticholinergic drug where 4 mice of 4 tested died within 5 minutes after an i.v. bolus dose.

LD_{50}-interval: The LD_{50}-interval was between the highest dose where 4 mice survived and the lowest dose where 4 mice died within 5 minutes after an i.v. bolus dose.

e) Effect on heart rate in conscious rat

The animal is slightly anaestetized by ether and an infusion cannula is inserted into a tail vein. While still asleep the rat is placed in a simple device, made of a coarse, somewhat elastic net fixing the rat in a constant position. Electrodes are attached to the extremities and connected to an ECG-pulse pre-amplifier and a Grass polygraph. By recording the ECG, the heart rate can then be determined.

Before any substance is given the animal has regained consciousness and the heart rate has been constant for at least 15 minutes.

The substance is injected, i.v. in the infusion cannula and flushed with physiological saline.

ECG is recorded 0.25, 0.5, 1, 2, 3 and 5 minutes after completed injection and then every 5 minutes until the original heart rate is obtained.

Table I

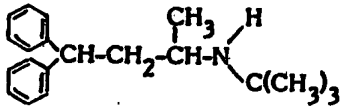
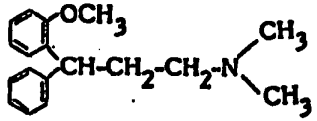
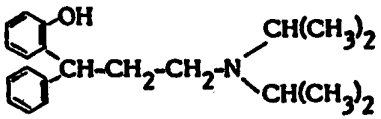
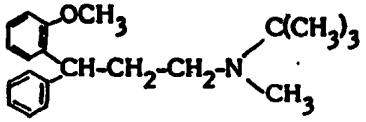
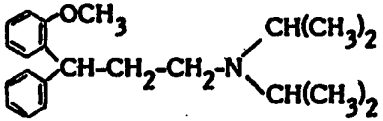
Substance	Antichol. effect IC_{50} (M)	Anti-N.A. effect IC_{50} (M)	Anti-Ca effect IC_{50} (M)	Anti-HI effect IC_{50} (M)	Acute toxicity i.v. mg/kg	Lethal dose mg/kg	Effect on heart rate threshold dose mg/kg
 Terodiline (prior art)	$5.2x10^{-7}$	$2.4x10^{-6}$	10^{-5}	$4x10^{-6}$	15-20	20	1-3
 GB-A-1.169.944 (antidepressant)	$1.2x10^{-6}$	$4.4x10^{-6}$	$2.1x10^{-5}$	$3.7x10^{-7}$	10-15	15	
1  Racemate	$1.8x10^{-8}$	10^{-5}	$1.5x10^{-5}$	$7x10^{-6}$	10-20	20	1-3
1a (+)-isomer of 1	$1.8x10^{-8}$						
1b (-)-isomer of 1	$1.4x10^{-8}$						
2 	$1.5x10^{-7}$	$3.5x10^{-6}$	$9x10^{-6}$		10-20	20	
3 	$2.4x10^{-7}$	$3.6x10^{-6}$	$>10^{-4}$		3-10	10	

Table I (cont.)

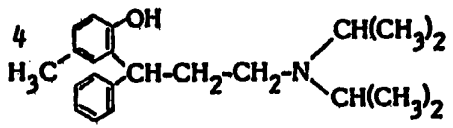
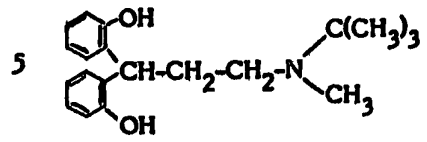
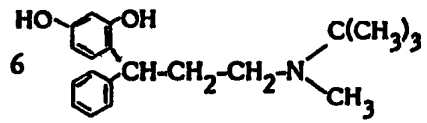
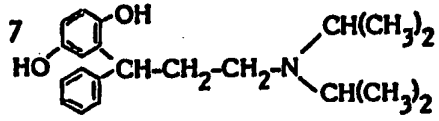
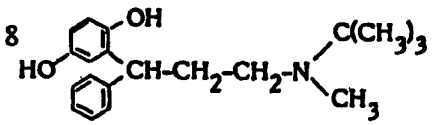
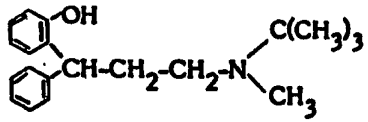
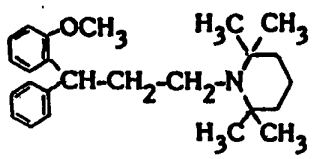
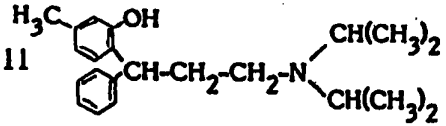
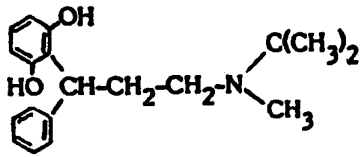
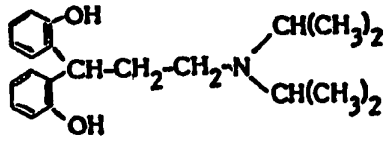
Substance	Antichol. effect IC_{50} (M)	Anti-N.A. effect IC_{50} (M)	Anti-Ca effect IC_{50} (M)	Anti-HI effect IC_{50} (M)	Acute toxicity i.v. mg/kg	Lethal dose mg/kg	Effect on heart rate threshold dose mg/kg
4 	1.5×10^{-8}	5.5×10^{-6}	6×10^{-6}	10^{-5}	30-40	40	
4a. (+)-isomer of 4 tartrate	1.3×10^{-8}		6.5×10^{-6}		10-20	20	
4b. (-)-isomer of 4 tartrate	1.3×10^{-6}		6×10^{-6}		10-20	20	
5 	4.9×10^{-9}	3.8×10^{-5}	3×10^{-5}	10^{-5}	30-45	45	1-3
6 	2.0×10^{-7}	3×10^{-5}	6.5×10^{-5}	1.3×10^{-5}	>20	>20	
7 	1.9×10^{-8}	5×10^{-5}	6.5×10^{-5}	3×10^{-6}	30-50	50	

Table I (cont.)

Substance	Antichol. effect IC_{50} (M)	Anti-N.A. effect IC_{50} (M)	Anti-Ca effect IC_{50} (M)	Anti-HI effect IC_{50} (M)	Acute toxicity i.v. mg/kg	Lethal dose mg/kg	Effect on heart rate threshold dose mg/kg
8 	$3.1x10^{-8}$	$5x10^{-5}$	$>5x10^{-5}$	$7x10^{-6}$	>6	>6	
9 	$1.6x10^{-8}$	$5x10^{-5}$	$2.5x10^{-5}$	$1.2x10^{-6}$		20	
10 	$6.2x10^{-8}$	$4x10^{-6}$	$7x10^{-6}$	$2.5x10^{-6}$			
11 	$1.0x10^{-8}$	$5.5x10^{-6}$	10^{-5}	$2.5x10^{-6}$	10-20	20	
12 	$4.7x10^{-7}$		$2.3x10^{-5}$	$8.0x10^{-6}$	15-30	30	
13 	$9.0x10^{-9}$	$3x10^{-5}$	$1.5x10^{-5}$	$2x10^{-5}$	5-10	10	

Example A

Preparation of tablets

	Ingredients	mg/tablet
1.	Compound 1 in Table 1	2.0
2.	Cellulose, microcrystalline	57.0
3.	Calcium hydrogen phosphate	15.0
4.	Sodium starch glycolate	5.0
5.	Silicon dioxide, colloidal	0.25
6.	Magnesium stearate	0.75
		80.0 mg

The compound 1 according to the invention is mixed with ingredients 2, 3, 4 and 5 for about 10 minutes. The magnesium stearate is then added, the resultant mixture being mixed for about 5 minutes and then compressed into tablet form with or without filmcoating.

Example B

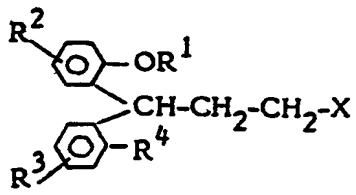
Preparation of capsules

	Ingredients	mg/capsule
1.	Compound 1 in Table 1	2
2.	Lactose	186
3.	Corn starch	20
4.	Talc	15
5.	Magnesium stearate	2
		225 mg

The compound I according to the invention is mixed with ingredients 2 and 3 and then milled. The resulting mixture is then mixed with ingredients 4 and 5 and then filled into capsules of appropriate size.

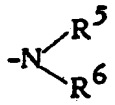
CLAIMS

1. 3,3-Diphenylpropylamines of formula I



I

wherein R^1 signifies hydrogen or methyl, R^2, R^3 and R^4 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphanoyl or halogen, and X represents a tertiary amino group of formula II



wherein R^5 and R^6 signify non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^5 and R^6 may form a ring together with the amine nitrogen,
their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

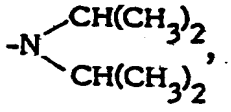
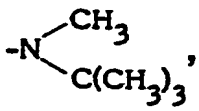
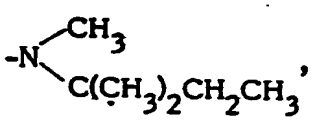
2. 3,3-Diphenylpropylamines according to claim 1, wherein each of R^5 and R^6 independently signifies a saturated hydrocarbyl group, especially saturated alifatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^5 and R^6 together comprising at least three, preferably at least four carbon atoms.

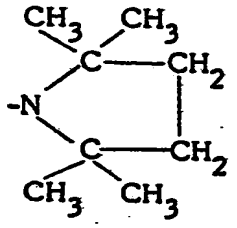
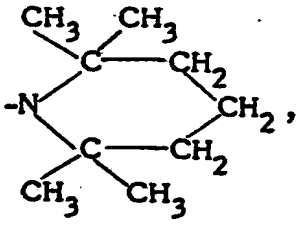
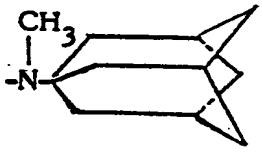
3. 3,3-Diphenylpropylamines according to claim 1 or 2, wherein R^5 and R^6 taken together form a ring with the amine nitrogen.

4. 3,3-Diphenylpropylamines according to claim 1, 2 or 3, wherein R^5 and/or R^6 carries at least one hydroxy substitutent.

5. 3,3-Diphenylpropylamines according to any one of the preceeding claims, wherein at least one of R^5 and R^6 comprises a branched carbon chain.

6. 3,3-Diphenylpropylamines according to any one of claims 1-5, wherein X signifies any of the following groups a) - f), each of which may carry at least one hydroxy substituent:

a)  , b)  , c)  ,

d)  , e)  , f) 

7. 3,3-Diphenylpropylamines according to claim 1, selected from the group consisting of the following compounds, their salts with physiologically acceptable acids and, where possible, their racemates and individual enantiomers:
N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine,
N-methyl-N-tert.butyl-3-(2-hydroxyphenyl)-3-phenylpropylamine,
N-methyl-N-tert.butyl-3-(2,4-dihydroxyphenyl)-3-phenylpropylamine,
N-methyl-N-tert.butyl-3,3-bis-(2-hydroxyphenyl)propylamine,
N,N-diisopropyl-3,3-bis-(2-hydroxyphenyl)propylamine,
N,N-diisopropyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine,
N-methyl-N-tert.butyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine,
N,N-diisopropyl-3-(2-methoxyphenyl)-3-phenylpropylamine,
N-(3-(2-methoxyphenyl)-3-phenylpropyl)-2,2,6,6-tetramethylpiperidine,
(+)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine.

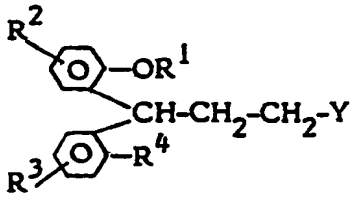
8. 3,3-Diphenylpropylamines according to any one of claims 1-7 for use as pharmaceutically active substances, especially as anticholinergic agents.

9. A pharmaceutical composition comprising a 3,3-diphenylpropylamine according to any one of claims 1-7 and a compatible pharmaceutical carrier.

10. Use of a 3,3-diphenylpropylamine according to any one of claims 1-7 for preparing an anticholinergic drug.

11. A method for preparing 3,3-diphenylpropylamines according to any one of claims 1-7, comprising:

a) reacting a reactively esterified 3,3-diphenylpropanol of formula III



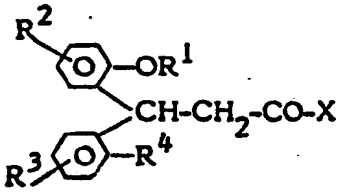
III

wherein R^1-R^4 are as defined above, any hydroxy groups may be protected and Y is a leaving group,
with an amine of formula IV

H-X IV

wherein X is as defined above, or

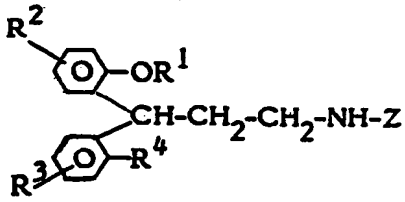
b) reducing a 3,3-diphenylpropionamide of formula V



V

wherein R^1-R^4 and X are as defined above and any hydroxy groups may be protected, or

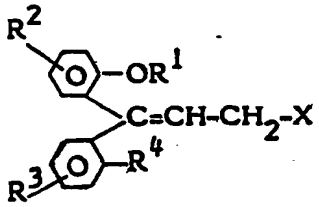
c) N-methylating a secondary 3,3-diphenylpropylamine VI



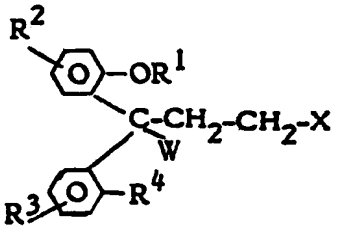
VI

wherein R^1-R^4 are as defined above and any hydroxy groups may be protected, and wherein Z has the same meaning as R^5 and R^6 with the exception of methyl, or

d) reducing a 3,3-diphenylpropylamine of formula VIIa or VIIb



VIIa



VIIb

wherein R^1-R^4 and X are as defined above and any hydroxy groups may be protected, and W signifies a hydroxy group or a halogen atom, and

i) when necessary splitting off hydroxy protecting groups in the compounds obtained, if desired after mono or di-halogenation of one or both of the phenyl rings, and/or

ii) if desired converting obtained bases of formula I into salts thereof with physiologically acceptable acids, or vice versa, and/or

iii) if desired separating an obtained mixture of optical isomers into the individual enantiomers, and/or

iv) if desired methylating an ortho-hydroxy group in an obtained compound of formula I, wherein R^1 is hydrogen and/or R^4 is hydroxy.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE89/00016

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

C 07 C 91/28, 93/14, A 61 K 31/135

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC 4	C 07 C 91/28, 91/30, 93/14; A 61 K 31/135
US Cl	260:568, 570.5, 571, 573; 564:316; 424:330; 514:648, 654

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	SE,A, 215 499 (FARBWERKE HOECHST AG VORMALS MEISTER LUCIUS & BRÜNING) 26 September 1976	1-11
X	DK,A, 111 894 (FARBWERKE HOECHST AG VORMALS MEISTER LUCIUS & BRÜNING) 21 October 1968 see page 1- page 2, line 9; the claim	1-11
X	US,A, 3 446 901 (ED. GEISTLICH SÖHNE AG FÜR CHEMISCHE INDUSTRIE) 27 May 1969 see column 1, line 29 - line 55 & GB, 1169945	1-2, 7-11
X	GB,A, 1 169 945 (ED. GEISTLICH SÖHNE AG FÜR CHEMISCHE INDUSTRIE) 5 November 1969 see the claims 1-2 & US, 3446901	1-2, 7-11

.../...

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1989-03-30	1989 -04- 05
International Searching Authority	**Signature of Authorized Officer**
Swedish Patent Office	Irja Berlin

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE /partly unsearchable

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [ ] Claim numbers ....., because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The expression "R^5 and R^6 may form a ring together with the amine nitrogen" (claims 1, 3, 4 and 8-11) is indefinite.

The search on claims 1, 3, 4 and 8-11 has therefore been incomplete.

3. [ ] Claim numbers ....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	GB, A, 1 169 944 (ED. GEISTLICH SÖHNE AG FUR CHEMISCHE INDUSTRIE) 5 November 1969 see the claims 1-2	1-2, 7-11
X	Chemical Abstracts Vol. 97 (1982) abstract 120105n, Biol. Zh. Arm. 1982, 35(2), 101-7 (Russ).	1,3, 8-10

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APPLICATION NUMBER	PATENT NUMBER	GROUP ART UNIT	FILE WRAPPER LOCATION
10/130,214		1624	06B0

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7590 01/28/2004

Peter F. Corless
P O Box 9169
Boston, MA 02209

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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO, on the date indicated below.

Lee Dunkle	(Depositor's name)
Lee Dunkle	(Signature)
April 27, 2004	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/130,214	05/14/2002	Claus Meese	41946/32854	9833

TITLE OF INVENTION: STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1330	$0	$1330	04/28/2004

EXAMINER	ART UNIT	CLASS-SUBCLASS
TUCKER, ZACHARY C	1624	514-530000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Peter F. Corless
Christine C. O'Day
EDWARDS & ANGELL, LLP

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

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(A) NAME OF ASSIGNEE: Schwarz Pharma AG

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Federal Republic of Germany

Please check the appropriate assignee category or categories (will not be printed on the patent); ☐ individual ☐ corporation or other private group entity ☐ government

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☐ Publication Fee

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Director for Patents is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

(Authorized Signature) Chris C. O'Day (Date) 4-27-04

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Practitioner's Docket No. 58827 (745107) *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: C. Meese

SERIAL NO.: 10/130,214 ART UNIT: 1624

FILED: May 14, 2002 EXAMINER: Z. Tucker

FOR: STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

Commissioner for Patents
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Alexandria, Virginia 22313-1450
MAIL STOP ISSUE FEE

TRANSMITTAL OF PAYMENT OF ISSUE FEE (37 C.F.R. SECTION 1.311)

1. Applicant hereby pays the issue fee for the attached Issue Fee Transmittal PTOL-85.

2. Fee (37 C.F.R. section 1.18(a) and (b)):

Application status is:	Regular	Design
[ ] small business entity fee	[ ] $ 660.00	[ ] $240.00
[X] other than a small entity fee	[X] $1,330.00	[ ] $480.00

3. Publication fee [ ] $ 300.00

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FACSIMILE

☐ transmitted by facsimile to the Patent and Trademark Office.

Lee Dunkle

Signature

Date: April 27, 2004

Lee Dunkle

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[X] Charge Account 04-1105 for any fee deficiency.

[ ] Charge Account _____ the sum of $ _____.

A duplicate of this request is attached.

Christine C. O'Day

SIGNATURE OF PRACTITIONER

Reg. No. 38,256

Christine C. O'Day
(type or print name of practitioner)

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FORM PTO-1449 INFORMATION DISCLOSURE STATEMENT	ATTY DOCKET NO. 58827(45107)	SERIAL NO. 10/130,214
	APPLICANT(S): Claus Meese	
	FILING DATE: May 14, 2002	ART UNIT: 1624

UNITED STATES PATENT DOCUMENTS

EXAM. INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILE DATE IF APPR
ZT	AA	5,686,464	11/11/97	R.A. Johansson et al.	514	315	

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	PUBLISHED DATE	COUNTRY	CLASS	SUB CLASS	TRAN YES/NO

OTHER DOCUMENTS (INCLUDING AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.)

Examiner: [signature]	Date: 29 APRIL 2004

Image 1624

Docket No. 58827 (45107)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: C. Meese

SERIAL NO.: 10/130,214 ART UNIT: 1624

FILED: May 14, 2002 EXAMINER: Z. Tucker

FOR: STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

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

Sir:

CERTIFICATE OF MAILING

I hereby certify that this correspondence along with any paper indicated as being attached hereto is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on 2/12/04.

By: Lee Dunkle
Lee Dunkle

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Pursuant to 37 C.F.R. §§ 1.97 and 1.98, applicant(s) hereby submit(s) an Information Disclosure Statement for consideration by the Examiner.

I. LIST OF PATENTS, PUBLICATIONS OR OTHER INFORMATION

The patents, publications or other information submitted for consideration by the Office are listed on PTO-1449, attached hereto.

II. COPIES

a. ☒ Submitted herewith is a legible copy of (i) each U.S and foreign patent; (ii) each publication or that portion which caused it to be listed; and (iii) all other information or that portion which caused it to be listed.

III. CONCISE EXPLANATION OF THE RELEVANCE

02/23/2004 BABRAHA1 00000072 10130214
01 FC:1806 180.00 OP