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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

SUMITOMO DAINIPPON PHARMA CO., LTD. and SUNOVION PHARMACEUTICALS INC., Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES, LTD., Defendants.	**Civil Action No. _____** **COMPLAINT FOR PATENT INFRINGEMENT** **(Filed Electronically)**

Plaintiffs Sumitomo Dainippon Pharma Co., Ltd. and Sunovion Pharmaceuticals Inc. (collectively, "Sunovion" or "Plaintiffs"), for their Complaint against Defendants Teva Pharmaceutical Industries, Ltd. (hereinafter "Teva Ltd.") and Teva Pharmaceuticals USA, Inc. (hereinafter "Teva USA") (together with Teva Ltd., "Teva" or "Defendants"), hereby allege as follows:

THE PARTIES

1. Plaintiff Sumitomo Dainippon Pharma Co., Ltd. is a Japanese corporation, having its primary place of business at 6-8, Doshomachi 2-chome, Chuo-ku, Osaka, Osaka 541-0045, Japan.

2. Plaintiff Sunovion Pharmaceuticals Inc. is a corporation having its principal place of business at 84 Waterford Drive, Marlborough, Massachusetts 01752.

3. Upon information and belief, Defendant Teva USA is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 1090 Horsham Road, North Wales, Pennsylvania 19454.

4. Upon information and belief, Teva USA has appointed Corporate Creations Network Inc., 811 Church Road Suite 105, Cherry Hill, New Jersey, 08002, as its agent in New Jersey authorized to accept service of process for this actions filed in this Judicial District.

5. Upon information and belief, Teva USA has at least three places of business in the State of New Jersey, including, but not limited to, the following business addresses: (1) 400 Chestnut Ridge Road, Woodcliff Lake, New Jersey 07677-7604; (2) 208 Passaic Avenue, Suite 1, Fairfield, New Jersey 07004-3515; and (3) 8 Gloria Lane, Fairfield, New Jersey 07004-3306.

6. Upon information and belief, Defendant Teva USA is a wholly-owned subsidiary and agent of Defendant Teva Ltd.

7. Upon information and belief, Defendant Teva Ltd. is an Israeli corporation having a place of business at 5 Basel Street, P.O. Box 3190, Petah Tikva 49131, Israel.

8. Upon information and belief, Teva Ltd., by itself or through its wholly-owned subsidiary Teva USA, develops, manufactures, and/or imports generic pharmaceutical versions of branded products for sale and use throughout the United States, including in this Judicial District. Upon information and belief, Teva Ltd., by itself or through its wholly-owned subsidiary and agent Teva USA, markets, distributes, and/or sells generic pharmaceutical versions of branded products throughout the United States, including in the State of New Jersey.

JURISDICTION AND VENUE

9. This is a civil action for infringement of United States Patent No. 5,532,372 ("the '372 patent"). This action arises under the Patent Laws of the United States, 35 U.S.C. § 100 *et seq.*

10. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

11. Venue is proper in this Court under 28 U.S.C. §§ 1391(b)-(d) and 1400(b).

12. This Court has personal jurisdiction over both Teva USA and Teva Ltd. because, *inter alia*, both Teva USA and Teva Ltd. have availed themselves of the legal protections of the State of New Jersey and consented to personal jurisdiction in this Judicial District. *See, e.g.*, *Teva Pharmaceuticals USA, Inc., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 15-471 (CCC)(MF) (D.N.J. Jan. 22, 2015); *Teva Pharmaceuticals USA,*

Inc., et al. v. Synthon Pharmaceuticals Inc., et al., Civil Action No. 15-472 (CCC)(MF) (D.N.J. Jan. 22, 2015); *Teva Pharmaceuticals USA, Inc., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 14-5672 (MAS)(TJB) (D.N.J. Sept. 11, 2014).

13. This Court also has personal jurisdiction over Defendants because, *inter alia*, Defendants have committed, or aided, abetted, contributed to, or participated in the commission of, tortious acts of patent infringement, including acts in the State of New Jersey, that have led to foreseeable harm and injury to Plaintiffs in the State of New Jersey. Defendants sent a Paragraph IV Certification Notice Letter to Sunovion, dated July 13, 2015 ("Notice Letter").

14. Teva's Notice Letter states that Defendants filed Abbreviated New Drug Application ("ANDA") No. 208060 seeking approval from the United States Food and Drug Administration ("FDA") to commercially manufacture, use, market, or sell generic lurasidone hydrochloride tablets 20 mg, 40 mg, 60 mg, 80 mg, and 120 mg in the United States (including, upon information and belief, in the State of New Jersey), prior to the expiration of the '372 patent.

15. This Court also has personal jurisdiction over Defendants because, upon information and belief, *inter alia*: (1) Defendants have affiliations with the State of New Jersey that are pervasive, continuous, and systematic, including the direct marketing, distribution, or sale of generic pharmaceutical drugs within the State of New Jersey and to residents of the State of New Jersey by Defendants; (2) Teva USA is registered to do business in the State of New Jersey under entity ID # 0100250184; (3) Teva USA has at least three places of business in New Jersey; (4) Teva USA is licensed by the State of New Jersey as a "wholesaler" and "manufacturer and wholesaler" of generic pharmaceutical products in New Jersey with License

Nos. 5003436 and 5000583, respectively; (5) Teva Ltd. holds Drug Master File ("DMF") No. 28178 for the active pharmaceutical ingredient in Teva's infringing ANDA products (as defined in Paragraph 22, *infra*), lurasidone hydrochloride; (6) Teva Ltd. controls Teva USA; (7) Teva Ltd. makes its generic drug products available in this State through Teva USA; (8) Defendants maintain a broad distributorship network within this State; (9) Defendants intend to market, sell, and/or distribute Teva's infringing ANDA products; and (10) Defendants enjoy substantial income from sales of its generic pharmaceutical products in this State.

16. Defendants have previously consented and submitted to the jurisdiction of this Court. *See, e.g., Boehringer Ingelheim Pharma GmbH & co. KG, et al. v. Teva Pharmaceuticals USA, Inc., et al.*, Civil Action No. 14-7811 (MLC)(TJB) (D.N.J. Dec. 15, 2014); *Helsinn Healthcare, S.A., et al. v. Teva Pharmaceuticals USA, Inc., et al.*, Civil Action No. 14-6341 (MLC)(DEA) (D.N.J. Oct. 13, 2014); *United Therapeutics Corp. v. Teva Pharmaceuticals USA, Inc.*, Civil Action No. 14-5498 (PGS)(LHG) (D.N.J. Sept. 2, 2014); *Novo Nordisk Inc., et al. v. Teva Pharmaceuticals USA, Inc.*, Civil Action No. 14-4248 (MAS)(DEA) (D.N.J. July 3, 2014); *Amarin Pharma, Inc., et al. v. Teva Pharmaceuticals USA, Inc.*, Civil Action No. 14-3558 (MLC)(TJB) (D.N.J. Jun. 4, 2014); *Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 11-3962 (MLC)(DEA) (D.N.J. Jul. 8, 2011); *Teva Pharmaceutical Industries ,Ltd., et al. v. Glenmark Generics, Inc. USA, et al.*, Civil Action No. 08-4355 (GEB)(DEA) (D.N.J. Aug. 29, 2008).

17. Alternatively, to the extent the above facts are not found to establish personal jurisdiction over Teva Ltd., this Court may exercise jurisdiction over Teva Ltd. pursuant to Federal Rule of Civil Procedure 4(k)(2) because: (1) Sunovion's claims arise under federal law; (2) Teva Ltd. would be a foreign defendant not subject to personal jurisdiction in the courts

of any state; and (3) Teva Ltd. has sufficient contacts with the United States as a whole, including, but not limited to, manufacturing and selling generic pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Teva Ltd. satisfies due process.

THE PATENT-IN-SUIT

18. Plaintiff Sunovion Pharmaceuticals Inc. holds approved New Drug Application ("NDA") No. 200603, under which the FDA granted approval for 20 mg, 40 mg, 60 mg, 80 mg, and 120 mg lurasidone HCl tablets marketed in the United States under the trade name LATUDA®.

19. The LATUDA® (lurasidone HCl) tablets approved in NDA No. 200603 are indicated for the treatment of (1) depressive episodes associated with Bipolar I Disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate; and (2) the treatment of schizophrenia.

20. Plaintiff Sumitomo Dainippon Pharma Co., Ltd. owns the '372 patent titled "Imide derivatives, and their production and use." The '372 patent was duly and legally issued on July 2, 1996. A copy of the '372 patent is attached as Exhibit A.

21. The '372 patent is listed in the FDA publication entitled *Approved Drug Products with Therapeutic Equivalence Evaluations* ("the Orange Book") for LATUDA®.

DEFENDANTS' ANDA AND NOTICE LETTER

22. Upon information and belief, Defendants submitted ANDA No. 208060 ("Teva's ANDA") to the FDA, including a certification with respect to the '372 patent under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) ("Paragraph IV Certification"), seeking approval to engage in the commercial manufacture, use,

sale, or offer for sale within the United States, or importation into the United States, of generic lurasidone hydrochloride tablets 20 mg, 40 mg, 60 mg, 80 mg, and 120 mg (collectively, "ANDA Products") prior to expiration of the '372 patent.

23. Upon information and belief, on or about July 13, 2015, Teva sent its Notice Letter to Plaintiffs. In the Notice Letter, Teva represented that ANDA No. 208060 for the ANDA Products was filed, including a Paragraph IV Certification with respect to the '372 patent, and that Teva sought approval of ANDA No. 208060 prior to the expiration of the '372 patent. Plaintiffs first received Teva's Notice Letter on or about July 14, 2015.

24. Plaintiffs commenced this action within 45 days of the date of receipt of Teva's Notice Letter.

DEFENDANTS' INFRINGEMENT OF THE '372 PATENT

25. Plaintiffs repeat and re-allege paragraphs 1-24 as if fully set forth herein.

26. By seeking approval of its ANDA No. 208060 to engage in the commercial manufacture, use, sale, or offer for sale within the United States, or importation into the United States, of the ANDA Products prior to the expiration of the '372 patent, Defendants have infringed that patent under 35 U.S.C. § 271(e)(2)(A).

27. Defendants are jointly and severally liable for infringement of the '372 patent under 35 U.S.C. § 271(e)(2)(A). This is because, upon information and belief, Defendants actively and knowingly caused to be submitted, assisted with, participated in, contributed to, or directed the submission of Defendants' ANDA seeking to engage in the commercial manufacture, use, sale, or offer for sale within the United States, or importation into the United States, of the ANDA products prior to the expiration of the '372 patent.

28. If Defendants manufacture, use, offer to sell, or sell within the United States, or import into the United States, the ANDA Products prior to the expiration of the '372 patent, Defendants will infringe one or more claims of this patent under 35 U.S.C. § 271(a), (b), or (c).

29. Sunovion is entitled to relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of Defendants' ANDA be a date that is not earlier than the expiration date of the '372 patent, or any later expiration of any patent term extension or exclusivity for the '372 patent to which Sunovion is or becomes entitled.

30. Sunovion is entitled to a declaration that, if Defendants commercially manufacture, use, offer for sale, or sell the ANDA Products within the United States, import the ANDA Products into the United States, or induce or contribute to such conduct, Defendants will infringe the '372 patent under 35 U.S.C. § 271(a), (b), or (c).

31. Sunovion will be irreparably harmed by Defendants' infringing activities unless those activities are enjoined by this Court. Sunovion does not have an adequate remedy at law.

PRAYER FOR RELIEF

Sunovion requests that the Court grant the following relief:

A. An Order adjudging and decreeing that Defendants have infringed the '372 patent by submitting Defendants' ANDA to the FDA;

B. A permanent injunction pursuant to 35 U.S.C. § 271(e)(4)(B) or 35 U.S.C. § 283 restraining and enjoining Defendants, their directors, officers, agents, attorneys, affiliates, divisions, successors and employees, and those acting in concert with them, from infringing the

'372 patent by the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any drug product claimed in the '372 patent;

C. An Order pursuant to 35 U.S.C. § 271(e)(4)(A) decreeing that the effective date of any approval of Defendants' ANDA be a date that is not earlier than the expiration date of the '372 patent, or any later expiration of any patent term extension or exclusivity for the '372 patent to which Sunovion is or becomes entitled;

D. That Sunovion be awarded monetary relief to the extent Defendants commercially manufacture, use, offer for sale, or sell within the United States, or import into the United States any product that infringes or induces or contributes to the infringement of the '372 patent within the United States prior to the expiration of the '372 patent, including any later expiration of any patent term extension or exclusivity for the patent to which Sunovion is or becomes entitled, and that any such monetary relief be awarded to Sunovion with prejudgment interest;

E. An Order be entered that this case is exceptional, and that Sunovion is entitled to reasonable attorneys' fees pursuant to 35 U.S.C. § 285; and

F. Such other and further relief as the Court may deem just and proper.

Dated: August 24, 2015

Respectfully submitted,

By: s/ Charles M. Lizza

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CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

I hereby certify that the matters captioned *Sumitomo Dainippon Pharma Co., Ltd., et al. v. Emcure Pharmaceuticals Limited, et al.*, Civil Action No. 15-280 (SRC)(CLW) and *Sumitomo Dainippon Pharma Co., Ltd., et al. v. InvaGen Pharmaceuticals, Inc.*, Civil Action No. 15-281 (SRC)(CLW), which have been consolidated for discovery purposes, are related to the matter in controversy because the matter in controversy involves the same patent and defendants who filed Abbreviated New Drug Applications seeking to market generic versions of the same drug product.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: August 24, 2015

Respectfully submitted,

By: s/ Charles M. Lizza

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EXHIBIT A

US005532372A

United States Patent [19]

Saji et al.

[11] **Patent Number: 5,532,372**

[45] **Date of Patent: Jul. 2, 1996**

[54] **IMIDE DERIVATIVES, AND THEIR PRODUCTION AND USE**

[75] Inventors: **Ikutaro Saji**; **Masayuki Muto**; **Norihiko Tanno**; **Mayumi Yoshigi**, all of Osaka, Japan

[73] Assignee: **Sumitomo Pharmaceuticals Company, Ltd.**, Osaka, Japan

[21] Appl. No.: **113,320**

[22] Filed: **Aug. 30, 1993**

Related U.S. Application Data

[63] Continuation of Ser. No. 726,172, Jul. 5, 1991, abandoned.

[30] **Foreign Application Priority Data**

Jul. 6, 1990 [JP] Japan 2-180271

[51] **Int. Cl.**[6] **C07D 417/14**; A61K 31/495

[52] **U.S. Cl.** **544/368**; 546/17; 546/16; 546/199; 546/200; 546/198; 546/201; 546/225; 546/243; 544/230; 544/231; 514/255; 514/321

[58] **Field of Search** 544/368

[56] **References Cited**

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4,745,117	5/1988	Ishizumi et al.	544/368
4,812,461	3/1989	Antoku et al.	546/198
4,843,078	6/1989	Ishizumi et al.	544/295
4,937,249	6/1990	Antoku et al.	546/187

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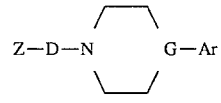
Primary Examiner—Robert T. Bond

Attorney, Agent, or Firm—Birch, Stewart, Kolasch & Birch

[57] **ABSTRACT**

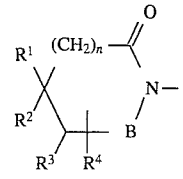
An imide compound of the formula:



(I)

wherein

Z is a group of the formula:



in which the substituents are defined herein, and n is an integer of 0 to 1;

D is a group of the formula:

$$-(CH_2)_p-A-(CH_2)_q-$$

in which A is a non-aromatic hydrocarbon ring optionally bridged with a lower alkylene group or an oxygen atom, said non-aromatic hydrocarbon ring and said lower alkylene group being each optionally substituted with at least one lower alkyl, and p and q are each an integer of 0, 1 or 2; and

Ar is an aromatic group, a heterocyclic aromatic group, a benzoyl group, a phenoxy group or a phenylthio group and G is >N—, >CH— or >COH— or Ar is a biphenylmethylidene group and G is >C═, all of the above groups being each optionally substituted with at least one of lower alkyl, lower alkoxy and halogen; and its acid addition salts, useful as an antipsycotic agent.

20 Claims, No Drawings

IMIDE DERIVATIVES, AND THEIR PRODUCTION AND USE

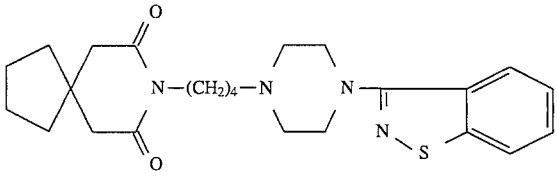
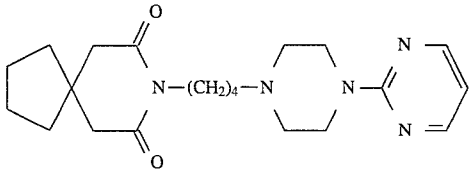
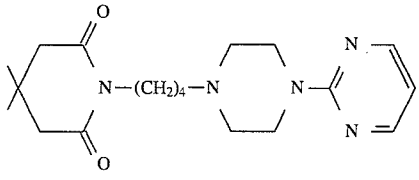
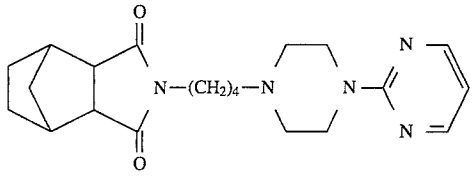
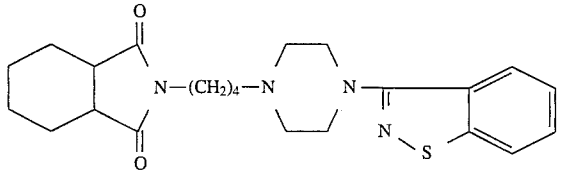
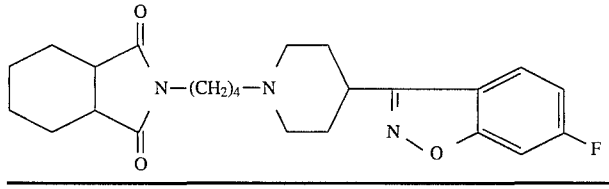
This application is a continuation, of application Ser. No. 07/726,172 filed on Jul. 5, 1991, now abandoned.

The present invention relates to imide derivatives, and their production and use. More particularly, it relates to novel imide compounds and their acid addition salts, and their production processes and their use as anti-psycotic agents (neuroleptic agents, anti-anxiety agents), especially for therapy of schizophrenia, senile insanity, manic-depressive psychosis, neurosis, etc.

There are known some imide compounds having an anti-psycotic activity, of which typical examples are as follows:

Conventional antipsychotic agents are generally accompanied by a central or peripheral system side effect such as extrapyramidal motor disturbance (e.g. Parkinsonism) and depression of blood pressure (e.g. orthostatic hypotension) and produce a great problem on clinic (e.g. L. S. Goodman et al.: The Pharmacological Basis of Therapeutics, New York, p. 387 (1985); Gendai Iryo (Modern Medical Therapy), 22, p. 22 (1990)).

The problem underlying the present invention is to provide an excellent psychotic agent suppressed in the above side effect as generally observed on the conventional anti-psychotic agents. An extensive study has been made. As the result, it has been found that imide compounds wherein the imide portion and the piperazine or piperidine ring are bonded with intervention of an alkylene chain comprising a

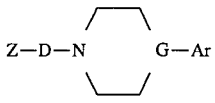
Structure	Remarks
	Tiaspirone; JP-A-61-251683, JP-A-58-110576
	Buspirone; The Merck Index, 11, 229 (1989)
	Gepirone The Merck Index, 11, 689 (1989)
	JP-B-01-28756
	US-A-4,745,117
	JP-A-01-199967

These conventional imide compounds are characteristic in that the imide portion and the piperazine or piperidine ring are bonded together with intervention of a straight alkylene chain.

non-aromatic hydrocarbon ring therein show the desired pharmacological action. Any imide compound wherein the alkylene chain present between the imide portion and the piperazine or piperidine ring comprises a non-aromatic

hydrocarbon ring has never been known. The present invention is based on the above findings.

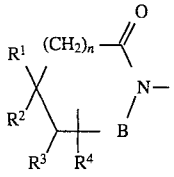
Accordingly, an object of the present invention is to provide an imide compound of the formula:



(I)

wherein

Z is a group of the formula:



in which B is a carbonyl group or a sulfonyl group R^1, R^2, R^3 and R^4 are each a hydrogen atom or a lower alkyl group, or R^1 and R^2 or R^1 and R^3 may be combined together to make a non-aromatic hydrocarbon ring or R^1 and R^3 may be combined together to make an aromatic ring, said non-aromatic hydrocarbon ring being optionally bridged with a lower alkylene group or an oxygen atom therein and said aromatic hydrocarbon ring, said non-aromatic hydrocarbon ring and said lower alkylene group being each optionally substituted with at least one lower alkyl, and n is an integer of 0 or 1;

D is a group of the formula:

$$—(CH_2)_p—A—(CH_2)_q—$$

in which A is a non-aromatic hydrocarbon ring optionally bridged with a lower alkylene group or an oxygen atom, said non-aromatic hydrocarbon ring and said lower alkylene group being each optionally substituted with at least one lower alkyl, and p and q are each an integer of 0, 1 or 2; and

Ar is an aromatic group, a heterocyclic aromatic group, a benzoyl group, a phenoxy group or a phenylthio group and G is >N—, >CH— or >COH— or Ar is a biphenylmethylidene group and G is >C═, all of the above groups being each optionally substituted with at least one of lower alkyl, lower alkoxy and halogen; and its acid addition salts.

In the above significances, the term "lower" is intended to mean generally a group having not more than 8 carbon atoms, particularly not more than 5 carbon atoms, unless otherwise specified. The term "lower alkyl" includes an alkyl group preferably having not more than 4 carbon atoms (e.g. methyl, ethyl, propyl, 2-propyl, butyl). The term "lower alkoxy" covers an alkoxy group preferably having not more than 4 carbon atoms (e.g. methoxy, ethoxy, propoxy, 2-propoxy, butoxy). The term "lower alkylene" covers an alkylene group preferably having not more than 3 carbon atoms (e.g. methylene, ethylene, trimethylene). The term "halogen" includes chlorine, bromine, iodine and fluorine.

The non-aromatic hydrocarbon ring includes particularly the one having not more than 7 carbon atoms such as a cycloalkane ring having not more than 7 carbon atoms or a cycloalkene ring having not more than 7 carbon atoms. Examples of the cycloalkane ring include cyclopropane, cyclobutane, cyclopentane, cyclohexane and cycloheptane. Examples of the cycloalkene ring are cyclopentene, cyclohexene, cycloheptene, etc.

The non-aromatic hydrocarbon ring bridged with a lower alkylene group or an oxygen atom may be, for instance, the one having not more than 10 ring carbon atoms and includes specifically bicyclo[1.1.1]pentane, bicyclo[-2.1.1]hexane, bicyclo[2.1.1]hex-2-ene, bicyclo[2.2.1]heptane, bicyclo [2.2.1]hept-2-ene, bicyclo[2.2.2]octane, bicyclo[2.2.2]oct-2-ene, bicyclo[4.1.1]octane, bicyclo[-4.1.1]oct-2-ene, bicyclo[4.1.1]oct-3-ene, bicyclo[3.2.1]octane, bicyclo [3.2.1]oct-2-ene, bicyclo[3.2.1]oct-3-ene, bicyclo[3.2.1]oct-6-ene, bicyclo[3.2.2]nonane, bicyclo[3.2.2]non-2-ene, bicyclo[3.2.2]non-3-ene, bicyclo[3.2.2]-non-6-ene, 2-oxabicyclo[1.1.1]butane, 2-oxabicyclo[2.1.1]pentane, 2-oxabicyclo[2.1.1]pent-4-ene, 7-oxabicyclo[2.2.1]hexane, 7-oxabicyclo[2.2.1]hex-2-ene, 7-oxabicyclo[4.1.1]heptane, 7-oxabicyclo[4.1.1]hept-2-ene, 7-oxabicyclo[4.1.1]-hept-3-ene, 8-oxabicyclo[3.2.1]heptane, 8-oxabicyclo[3.2.1]-hept-2-ene, 8-oxabicyclo[3.2.1]hept-3-ene, 8-oxabicyclo[3.2.1] hept-6-ene, etc.

The aromatic ring may be, for instance, any one having not more than 10 carbon atoms, of which specific examples are benzene and naphthalene.

The non-aromatic hydrocarbon ring represented by its both sides, i.e. $—(CH_2)_p—$ and $—(CH_2)_q—$, at the 1- and 1-positions, the 1- and 2-positions, the 1- and 3-positions, the 1- and 4-positions or the like.

The aromatic group represented by the symbol Ar may be monocyclic, bicyclic or the like and have usually not more than 10 carbon atoms, and its specific examples are phenyl, naphthyl, etc. The heterocyclic aromatic group represented by the symbol Ar may be also monocyclic, bicyclic or the like. The monocyclic heterocyclic aromatic group may be the one, for instance, having not more than 6 carbon atoms and not more than 4 hetero atoms chosen from nitrogen, oxygen and sulfur, and its specific examples are pyridyl, pyrimidinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, furyl, imidazolyl, etc. The bicyclic heterocyclic aromatic group may be the one, for instance, having not more than 10 carbon atoms and not more than 5 hetero atoms chosen from nitrogen, oxygen and sulfur, and its specific examples are a benzologous condensed ring group (e.g. benzisothiazolyl, benzisoxazolyl, benzofuryl, quinolyl, isoquinolyl, indolyl, indazolyl, benzimidazolyl, benzoxazolyl), naphthyridinyl, pteridinyl, thienofuryl, imidazothiophenyl, imidazofuryl, etc.

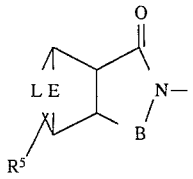
The present invention covers the acid addition salt formed between the imide compound (I) and an organic or inorganic acid. Examples of the inorganic acid are hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, etc., and examples of the organic acid are acetic acid, oxalic acid, citric acid, malic acid, tartaric acid, maleic acid, fumaric acid, etc.

The imide compound (I) can have stereo and optical isomers, and this invention involves these isomers or their mixtures as well.

Among various groups represented by the symbol Ar, preferred are a bicyclic heterocyclic aromatic group, a naphthyl group, a benzoyl group, a phenoxy group, a phenylthio group, a biphenylmethylidene group, etc., these groups being optionally substituted with at least one of lower alkyl, lower alkoxy and halogen. More preferred are a benzologous condensed ring group, a naphthyl group, a benzoyl group, a phenoxy group, a phenylthio group, etc., these groups being optionally substituted with at least one of lower alkyl, lower alkoxy and halogen. The most preferred are benzisothiazolyl, benzisoxazolyl, indazolyl, indolyl, benzoyl, phenoxy, phenylthio, etc., which are optionally substituted with at least one of lower alkyl, lower alkoxy and halogen.

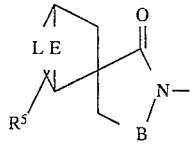
Preferred examples of the group represented by the symbol Z are those of the following formulas:

(Z-1)



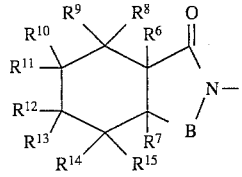
wherein L is $—CH_2—CH_2—$ or $—CH=CH—$, E is a lower alkylene group optionally substituted with lower alkyl or an oxygen atom, R^5 is a hydrogen atom or a lower alkyl group and B is a carbonyl group or a sulfonyl group,

(Z-2)



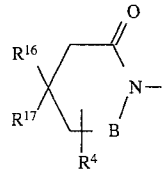
wherein L, E, R^5 and B are each as defined above,

(Z-3)



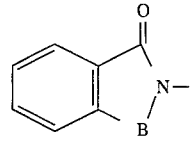
wherein R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are each a hydrogen atom or a lower alkyl group, or two of those present at the neighbouring positions each other may be combined together to make a bond (i.e. forming a double bond between said two positions) and B is as defined above;

(Z-4)



wherein R^{16} and R^{17} are each a hydrogen atom or a lower alkyl group, or they may be taken together to make a saturated hydrocarbon ring, preferably a cycloalkane ring having not more than 7 carbon atoms (e.g. cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane) and R^4 and B are each as defined above, and

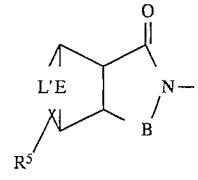
(Z-5)



wherein B is as defined above.

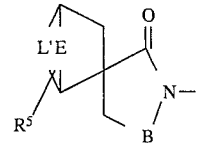
More preferred examples of the group represented by the symbol Z are those of the following formulas:

(Z-1')



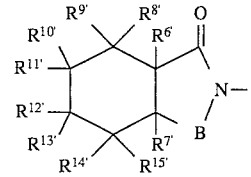
wherein L' is $—CH_2—CH_2—$ and E, R^5 and B are each as defined above,

(Z-2')



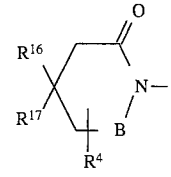
wherein L', E, R^5 and B are each as defined above,

(Z-3')



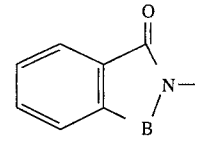
wherein $R^{6'}$, $R^{7'}$, $R^{8'}$, $R^{9'}$, $R^{10'}$, $R^{11'}$, $R^{12'}$, $R^{13'}$, $R^{14'}$ and $R^{15'}$ are each a hydrogen atom or a lower alkyl and B is a defined above;

(Z-4')



wherein R^4, R^{16}, R^{17} and B are each as defined above, and

(Z-5')

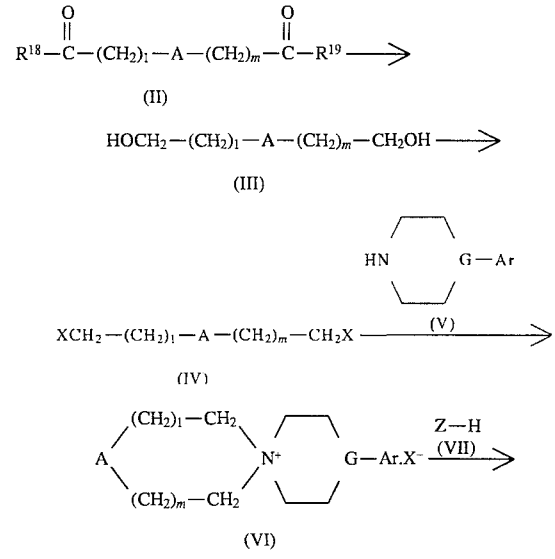


wherein B is as defined above.

The imide compounds (I) of the invention are obtainable by various procedures, of which typical examples are as shown below.

Procedure (a):—

The imide compound (I) is obtainable according to the following scheme:



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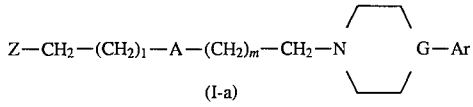


(I-a)

wherein A, G, Ar and Z are each as defined above and R^{18} and R^{19} are each a hydroxy group or a lower alkoxy group, or they may be taken together to represent an oxygen atom, X is a leaving group such as halogen, lower alkylsulfonyloxy (e.g. methanesulfonyloxy), arylsulfonyloxy (e.g. p-toluene-sulfonyloxy, benzenesulfonyloxy) and 1 and m are each an integer of 0 or 1.

Namely, the compound (II) is reduced to give the compound (III). The reduction may be carried out by treatment with a reducing agent (e.g. $LiAlH_4$, H_4, $NaBH_4$, $Ca(BH_4)_2$, $LiAlH_2(OCH_2CH_2OCH_3)_2$) in an inert solvent at a temperature of 0° C. to the reflux temperature of the reaction mixture to give the compound (III). The reducing agent is usually employed in an amount of about 1 to 10 mol to one mol of the compound (II). As the inert solvent, there may be used an ethereal solvent such as diethyl ether or tetrahydrofuran.

The hydroxy groups in the compound (III) are then converted respectively into leaving groups to give the compound (IV). When the leaving group is a halogen atom (e.g. chlorine, bromine), the conversion may be carried out by reacting the compound (III) with thionyl halide (e.g. thionyl chloride, thionyl bromide), optionally in the presence of a base (e.g. pyridine). This reaction is preferably performed in a solvent (e.g. pyridine, tetrahydrofuran, dichloromethane) at a temperature of about 0° to 30° C. The molar proportion of the compound (III) and thionyl halide may be usually about 1:2–4.

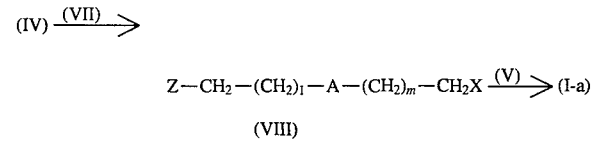
When the leaving group is sulfonyloxy, the conversion may be effected by reacting the compound (III) with a sulfonyl halide such as alkylsulfonyl halide (e.g. methanesulfonyl chloride) or arylsulfonyl halide (e.g. p-toluenesulfonyl chloride, benzenesulfonyl chloride), optionally in the presence of a base (e.g. triethylamine). This reaction is favorably performed in a solvent (e.g. pyridine, tetrahydrofuran, dichloromethane, chloroform) at a temperature of about 0° to 30° C. The molar proportion of the compound (III) and the sulfonyl halide is usually about 1:2–4.

The compound (IV) is then reacted with the compound (V) to give the compound (VI). The reaction may be carried out in the presence of a base (e.g. potassium carbonate, sodium carbonate) in a solvent such as alcohol (e.g. methanol, ethanol, propanol, 2-propanol, butanol), acetonitrile or dimethylformamide at a temperature around the boiling point of the solvent. The base and the compound (V) may be used respectively in amounts of about 0.5 to 2 mol and of about 1 to 1.5 mol to one mol of the compound (IV).

The compound (VI) is then reacted with the compound (VII) to give the compound (I-a). This reaction is carried out optionally in tile presence of a catalyst and a base (e.g. potassium carbonate, sodium carbonate, sodium hydride, potassium hydride) in an aromatic solvent (e.g. toluene, xylene, chlorobenzene) at a temperature around the boiling point of the solvent. As the catalyst, a crown ether such as dibenzo-18-crown-6-ether may be used, and its amount is normally from about 0.1 to 10% by weight based on the compound (VI). The molar proportion of the compound (VI) and the compound (VII) to be used is usually about 1:1–1.5.

Procedure (b):—

The imide compound (I) is also produced according to the following scheme:



(VIII)

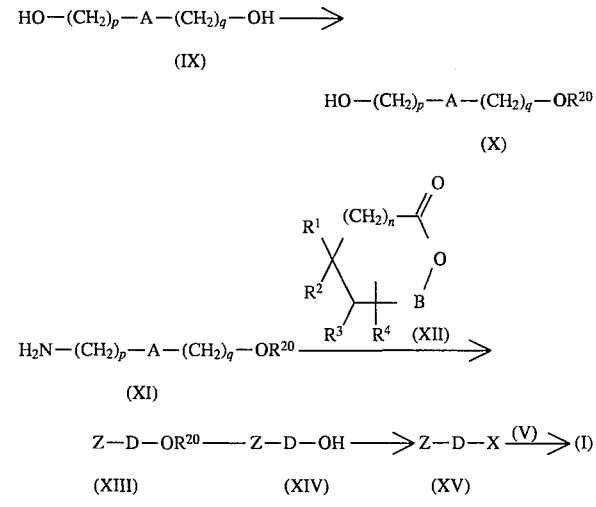
wherein X, A, Z, l and m are each as defined above.

The compound (IV) is reacted with the compound (VII) in the presence of a base such as an inorganic base (e.g. potassium carbonate, sodium carbonate, sodium hydride, potassium hydride) to give the compound (VIII). The reaction is usually carried out in a solvent (e.g. alcohol, dimethylformamide, acetonitrile); optionally in the coexistence of a reaction aid such as an alkali metal iodide (e.g. potassium iodide, sodium iodide), at a temperature around the boiling point of the solvent. The amounts of the base, the reaction aid and the compound (VII) may be respectively from about 1 to 2 mol, from about 0.1 to 1 mol and from about 0.1 to 1 mol to one mol of the compound (IV).

The compound (VIII) is then reacted with the compound (V) in the presence of a base (e.g. potassium carbonate, sodium carbonate, sodium hydride, potassium hydride) to give the compound (I-a). The reaction is normally carried out in a solvent (e.g. alcohol, dimethylformamide, acetonitrile), optionally in the coexistence of a reaction aid such as an alkali metal iodide (e.g. potassium iodide, sodium iodide), at a temperature around the boiling point of the solvent. The amounts of the base and the reaction aid may be respectively from about 1 to 2 mol and from about 0.1 to 1 mol to one mol of the compound (VIII). The molar proportion of the compound (VIII) and the compound (V) may be usually about 1:1–1.5.

Procedure (c):—

The imide compound (I) is further obtainable according to the following scheme:



(XIII) (XIV) (XV)

wherein R^1, R^2, R^3, R^4, n, p, q, D, A, B, X and Z are each as defined above and R^{20} is a protective group for hydroxy (e.g. benzyl, halogen, methoxy or nitro-substituted benzyl, methoxymethyl, methoxyethoxymethyl, tetrahydrofuranyl).

The compound (IX) is converted into the compound (X) by application of a per se conventional protection procedure

(g.g. T. W. Greene: *"Protective Group in Organic Synthesis"*, John Willey & Sons, pages 10–39 (1981)) to the former. Examples of the protective group for hydroxy thus introduced are benzyl, substituted benzyl (e.g. halogen-, methoxy- or nitro-substituted benzyl), methoxymethyl, methoxyethoxymethyl, tetrahydrofuryl, etc.

The compound (X) is then subjected to oxidation, oximation (i.e. oxime formation) and reduction in this order to give the compound (XI). The oxidation may be carried out by reacting the compound (X) with an oxidizing agent such as chromic acid or its salt (e.g. chromic anhydride, bichromic acid). The oximation may be carried out by reacting the oxidized product with hydroxylamine in an alcohol at a temperature of about 0° to 30° C. Hydroxylamine is normally used in an amount of about 1 to 2 mol to one mol of the compound (X). The reduction may be carried out by reacting the oximated product with a reducing agent (e.g. lithium aluminum hydride) in an inert solvent (e.g. diethyl ether or tetrahydrofuran) at a temperature around the boiling point of the solvent. The amount of the reducing agent is usually from about 1 to 10 mol to one mol of the compound (X).

The compound (XI) thus obtained is reacted with the compound (XII) in a solvent (e.g. pyridine, toluene, xylene, chlorobenzene) at a temperature around the boiling point of the solvent to give the compound (XIII). The amount of the compound (XII) is ordinarily from about 1 to 3 mol to 1 mol of the compound (XI).

The compound (XIII) is then subjected to elimination of the protecting group by a per se conventional procedure (e.g. T. W. Greene: *"Protective group in organic synthesis"*, John Wiley & Sons, pages 10–39 (1981)) to give the compound (XIV).

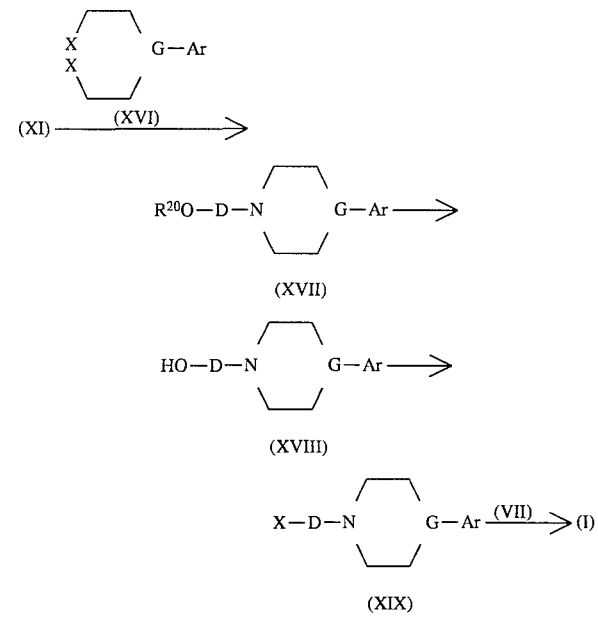
Conversion of the compound (XIV) into the compound (XV) is accomplished by introduction of a leaving group into the former. When the leaving group is halogen (e.g. chlorine, bromine), the compound (XIV) may be reacted with thionyl halide (e.g. thionyl chloride, thionyl bromide) in the presence of a base (e.g. pyridine) in a solvent (e.g. pyridine, tetrahydrofuran, dichloromethane) at a temperature of about 0° to 30° C. The amount of the thionyl halide is normally from about 2 to 4 mol to 1 mole of the compound (XIV).

When the leaving group is sulfonyloxy, the compound (XIV) is reacted with a sulfonyl halide such as alkylsulfonyl halide (e.g. methanesulfonyl chloride) or arylsulfonyl halide (e.g. benzenesulfonyl chloride, p-toluenesulfonyl chloride) in the presence of a base (e.g. triethylamine). This reaction is usually carried out in a solvent (e.g. pyridine, tetrahydrofuran, dichloromethane, chloroform) at a temperature of about 0° to 30° C. The amount of the sulfonyl halide is normally from about 2 to 4 mol to one mol of the compound (XIV).

The compound (XV) thus produced is reacted with the compound (V) in the presence of a base in the coexistence of a reaction aid to give the compound (I). The reaction is normally performed in a solvent (e.g. alcohol, dimethylformamide, acetonitrile) at a temperature around the boiling point of the solvent. As the base, there may be used an inorganic base (e.g. potassium carbonate, sodium carbonate, sodium hydride, potassium hydride). As the reaction aid, an alkali metal iodide (e.g. potassium iodide, sodium iodide) is usable. The amounts of the base, the reaction aid and the compound (V) are respectively from about 1 to 2 mol, from about 0.1 to 1 mol and from about 1 to 1.5 mol to one mol of the compound (XV).

Procedure (d):—

The imide compound (I) is further obtainable according to the following scheme:



wherein R^{20}, D, G, X and Ar are each as defined above.

The compound (XI) is reacted with the compound (XVI) in the presence of a base in a solvent (e.g. alcohol, diglyme, toluene, chlorobenzene) at a temperature around the boiling point of the solvent to give the compound (XVII). As the base, there may be used an inorganic base (e.g. potassium carbonate, sodium carbonate), and its amount is normally from about 1 to 2 mol to one mol of the compound (XI). The compound (XVI) is used ordinarily in an amount of about 1 to 1.5 mol to one mol of the compound (XI).

The compound (XVII) is subjected to elimination of the protecting group by a per se conventional procedure (e.g. T. W. Greene: *"Protective Group in Organic Synthesis"*, John Wiley & Sons, pages 10–39 (1981)) to give the compound (XVIII).

Introduction of a leaving group into the compound (XVIII) affords the compound (XIX). When the leaving group is halogen (e.g. chlorine, bromine), the compound (XVIII) is reacted with thionyl halide (e.g. thionyl chloride, thionyl bromide), optionally in the presence of a base (e.g. pyridine). The reaction is normally carried out in a solvent (e.g. pyridine, tetrahydrofuran, dichloromethane) at a temperature of about 0° to 30° C. The amount of the thionyl halide may be from about 2 to 4 mol to 1 mol of the compound (XVIII).

When the leaving group is sulfonyloxy, the compound (XVIII) is reacted with a sulfonyl halide such as an alkylsulfonyl halide (e.g. methanesulfonyl chloride) or an arylsulfonyl chloride (e.g. p-toluenesulfonyl chloride, benzenesulfonyl chloride), optionally in the presence of a base (e.g. triethylamine). The reaction is normally carried out in a solvent (e.g. pyridine, tetrahydrofuran, dichloromethane, chloroform) at a temperature of about 0° to 30° C. The amount of the sulfonyl halide may be from about 2 to 4 mol to one mol of the compound (XVIII).

The compound (XIX) is reacted with the compound (VII) in the presence of a base (e.g. potassium carbonate, sodium carbonate, sodium hydride, potassium hydride) in a solvent (e.g. alcohol, acetonitrile, dimethylformamide) at a tempera-

ture around the boiling point of the solvent to give the compound (I). The amounts of the base and the compound (VII) may be respectively from about 0.5 to 2 mol and from about 1 to 1.5 mol to 1 mol of the compound (XIX).

The products in Procedures (a) to (d), i.e. the compounds (I) and (I-a), may be each purified by a per se conventional procedure such as recrystallization from a suitable solvent (e.g. alcohol, diethyl ether, ethyl acetate, hexane) or chromatography on a column of silica gel. It is also possible to convert the products into their acid addition salts and then purify by recrystallization from a proper solvent (e.g. acetone, diethyl ether, alcohol).

Throughout Procedures (a) to (d), the introduction of a protective group is accomplished by a per se conventional procedure. When, for instance, the protective group is benzyl, substituted benzyl (e.g. halogen-, methoxy- or nitro-substituted benzyl) or methoxymethyl, the starting compound into which the protective group is to be introduced may be reacted with a protective group-introducing reagent such as benzyl halide, substituted benzyl halide or methoxymethyl halide in the presence of a basic substance such as an alkali metal hydride (e.g. sodium hydride, potassium hydride) or an organic base (e.g. triethylamine, dimethylaminopyridine) in an organic solvent (e.g. tetrahydrofuran, dimethylformamide) at a temperature of about −10° to 30° C. The amount of the protective group-introducing reagent may be from about 1 to 2 mol to one mol of the starting compound.

Elimination of the protective group may be also carried out by a per se conventional procedure. When, for instance, the protective group is benzyl or substituted benzyl, the elimination may be effected by hydrogenation using a noble metal catalyst (e.g. Pd-C, PtO, Pt-C) under a hydrogen pressure of 1 to 3 atm. When the protective group is benzyl, substituted benzyl or methoxymethyl, the elimination may be accomplished by treatment with a strong acid (e.g. CF_3COOH, HBr, HBr—CH_3COOH).

Optical resolution of the compound (I) can be accomplished by dissolving in an inert solvent (e.g. acetonitrile, alcohol), adding an optically active acid thereto to form the optically active salt between the compound (I) and the acid, precipitating the formed salt, collecting the precipitated salt and treating the collected salt with a base to make the optically active compound (I) in a free form.

As the optically active acid, there may be used, for instance, L-tartaric acid, D-tartaric acid, D-camphanic acid, L-mandelic acid, L-pyroglutamic acid, D-10-CSA (D-10-camphor-sulfonic acid), D-quinic acid, L-malic acid, dibenzoyl-L-tartaric acid, etc., among which preferred are L-tartaric acid and D-tartaric acid. No particular limitation is present on the temperature at which the salt formation is to be carried out, and the salt formation may be effected within a wide range from room temperature to the refluxing temperature of the reaction system. For enhancement of the optical purity, however, it is favored that the reaction system is once heated to the refluxing temperature. Before collection of the precipitated salt by filtration, the mixture may be once cooled so as to increase the yield. The amount of the optically active acid as the resolving agent may be from 0.5 to 2.0 equivalents, preferably around one equivalent, to the substrate. When desired, the collected salt may be recrystallized from a proper solvent such as alcohol to give the optically active salt with a higher purity. The thus obtained salt may be treated with a base to release an optical isomer of the compound (I) in a free form.

For the therapeutic use as an antipsychotic agent, the imide compound (I) or its pharmaceutically acceptable salt may be used as such, but it is usually formulated into a pharmaceutical preparation such as tablets, capsules, syrups, suspension, solutions, emulsions and suppositories by a per se conventional procedure. Depending upon the administration route such as parenteral or non-parenteral administration (e.g. oral administration, intravenous administration, rectal administration), an appropriate preparation form may be employed. In order to make said pharmaceutical preparation, the imide compound (I) or its pharmaceutically acceptable salt may be combined, if necessary, with any suitable additive(s) such as carriers, diluents, filters, binders and stabilizers. In case of an injectionable preparation, pharmaceutically acceptable buffers, solubilizers, isotonizers, etc. may be incorporated therein.

While the dosage of the imide compound (I) or its pharmaceutically acceptable salt varies greatly with the symptom, age and weight of the patient, the dosage form, the administration mode and the like, it may be generally given to an adult at a daily dose of from about 1 to 1000 mg, preferably from about 5 to 100 mg, in case of oral administration and at a daily dose of from about 0.1 to 100 mg, preferably from about 0.3 to 50 mg, in case of intraveous injection. Said dose may be applied in a single time or dividedly in two or more times.

As stated above, the imide compound (I) and its pharmaceutically acceptable salts exert a significant anti-psychotic activity. Yet, they are very weak in side effects as observed on the conventional neuroleptic drugs.

The above facts are well evidenced by the pharmacological test data as set forth below.

(i) Dopamine D_2 receptor binding assay (in vitro)

It is known that there is a correlation between the anti-psychotic activity and the dopamine D_2 receptor binding activity. This assay is therefore to examine an affinity of the test compound to dopamine D_2 receptor in membrane fractions of corpus striatum taken out from rat brain according to the method as described in T. Kuno et al: J. Neurochem., 41, 841 (1983).

Fresh corpus striatum taken out from rat brain is homogenized in a 30-fold volume of Tris-HCl buffer solution (pH, 7.4; 0.05 M) and centrifuged (31,360×g) for 10 minutes to give the membrane fractions, which are washed with the same volume of the buffer solution twice to give the membrane fractions for assay.

The membrane fractions as above obtained (containing 5 mg of protein) are incubated at 37° C. for 30 minutes in a buffer solution comprising [^{3}H] raclopride (0.45 nM), sodium chloride (120 mM), 1 mM magnesium chloride, 5 mM potassium chloride, 2 mM calcium chloride, Tris-HCl (pH, 7.4; 50 mM), 0.01% ascorbic acid, 1 mM pargyline and the test compound (10^{-9} to 10^{-5} M). Upon termination of the reaction, the membrane fractions are collected through a Whatman GF/B glass filter and number of [^{3}H] raclopride bound to membranes is measured by the aid of a liquid scintillation counter. Number of [^{3}H] raclopride binding specific to the D_2 receptor in a designed concentration of the test compound is calculated according to the following equation and the IC_{50} and Ki are determined on the basis of a hill plot according to the method as described in Life Sci., .23, 1781–1784 (1978). As the representative anti-phychotic drug, Haloperidol is used as control.

Number of specific binding=

(Total number of bindings)—(Number of non-specific bindings, e.g. number of bindings in co-existence of 10^{-6} M (+)Butaclamol)

$Ki\ (nM)=IC_{50}/(1+S/K_D)$

S: concentration of [^{3}H] raclopride on assay

K_D: dissociation constant of [^{3}H] raclopride

The results are shown in Table 2.

TABLE 2

Compound No.	Ki (nM)
101	1.6
105	1.0
Haloperidol	0.57

Further, the anti-psychotic activity (e.g. inhibition of [^{3}H] raclopride binding to D_2 receptors) of the designated compound at the concentration of 0.01 μM is observed, of which the results are shown in Table 3.

TABLE 3

Compound No.	Antipsychotic activity (% inhibition)
101	60
106	90
107	71
161	24
163	11

(ii) Anti-climbing activity (in vivo)

This activity is examined through the anti-climbing behavior test, i.e. the test for suppressing the climbing behavior induced by apomorphine in mice.

A designed amount of the test compound is orally administered to several groups of ddY strain male mice (body-weight, 20 to 25 g; one group, 5 mice), and each of the animals is placed in an individual column cage of 12 cm in diameter and 14 cm in height having metal poles (each pole, 2 mm in diameter) vertically installed and arranged along the periphery with intervals of 1 cm. After 60 minutes, apomorphine (1.0 mg/kg) is subcutaneously injected, and the behavior is observed during 10 to 20 minutes. Evaluation is made on the basis of the following criteria [P. Protais et al.: Psychopharmacology, 50, 1–6 (1976)]:

Score	Evaluation
0	All the paws are on the floor
1	only forepaws seize the pole of the cage
2	All the paws seize the pole of the cage; climbing behavior observed discontinuously
3	Continuous climbing behavior observed

Inhibition percentage of climbing behavior per each dose is calculated by the following equation, and ED_{50} (50% suppressive dose) is determined thereon:

$$\text{Inhibition percentage (\%)} = \frac{\text{Total score in control group} - \text{Total score in tested group}}{\text{Total score in control group}} \times 100$$

The results are shown in Table 4 in which the representative psychotic drugs such as Haloperidol and Chlorpromazine are used for control.

TABLE 4

Compound No.	ED_{50} (mg/Kg)
101	10.3
107	26.5
Haloperidol	0.67

TABLE 4-continued

Compound No.	ED_{50} (mg/Kg)
Chlorpromazine	4.2

(iii) Side-effect

a) Catalepsy inducing activity

The catalepsy inducing activity, which is the typical central nervous system side-effect, i.e. extrapyramidal side-effect, on clinical use of the psychotic drug, is observed.

A designated amount of the test compounds is orally administered to male mice, and one hour later a pair of forepaws are forcedly hanged on an iron pipe (diameter, 2.5 mm) horizontally set at a height of 5 cm. At least one cataleptic state of more than 30 second per three trials is regarded as positive. The results are shown in Table 5.

TABLE 5

Test compound	ED_{50} (mg/kg)	Ratio to anti-apomorphine activity
Compound No. 101	747	72.5
Haloperidol	3.1	4.6
Chlorpromazine	18	4.3

Ptosis inducing activity

Since the blocking activity of α_1 adrenergic receptor inherent to the anti-psychotic drug has a correlation with cardiovascular organ side-effect such as orthostatic hypotension, a ptosis inducing test is conducted to evaluate the α_1-receptor blocking activity.

The designated compound is orally administered to mice and after one hour blepharoptosis is scored, of which the results are shown in Table 6.

TABLE 6

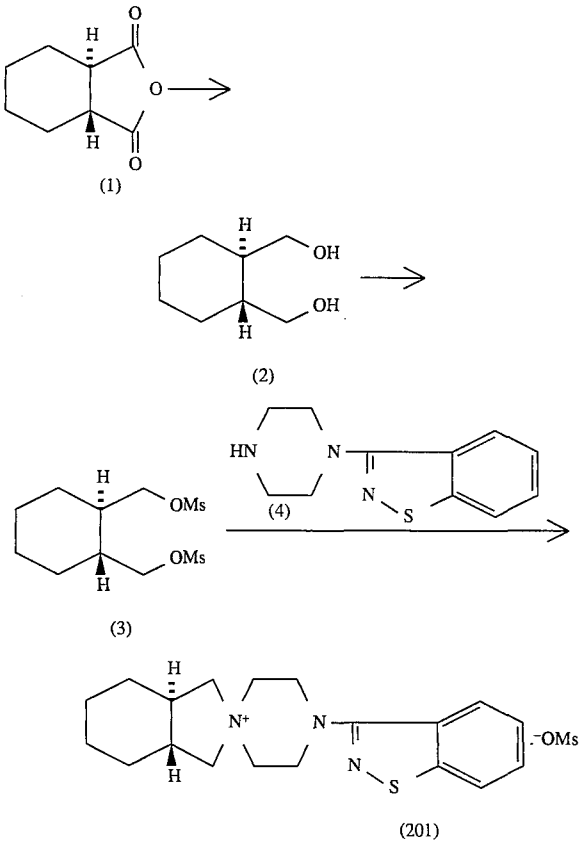
Test compound	ED_{50} (mg/kg)	Ratio to anti-apomorphine activity
Compound No. 101	>1000	>97
Haloperidol	4.1	6.0
Chlorpromazine	6.0	1.4

The above pharmacological data support that the imide derivatives (I) and their acid addition salts according to the invention show an excellent anti-psychotic activity. Further, the efficacy ratio of the anti-psychotic activity (i.e antiapomorphine activity) to the side-effect induction reveals that they have least central and peripheral nervous system side-effects in comparison with the conventional drugs.

Practical and presently preferred embodiments of the invention are illustratively shown in the following Examples wherein the abbreviations have the following meanings: Ms, methanesulfonyl; Et, ethyl; Ph, phenyl.

Reference Example 1-(a)

Production of trans-3a,7a-octahydroisoindolium-2-spiro-1'-[4'-(1,2-benzisothiazol- 3-yl)]piperazine methanesulfonate (Compound No. 201):-



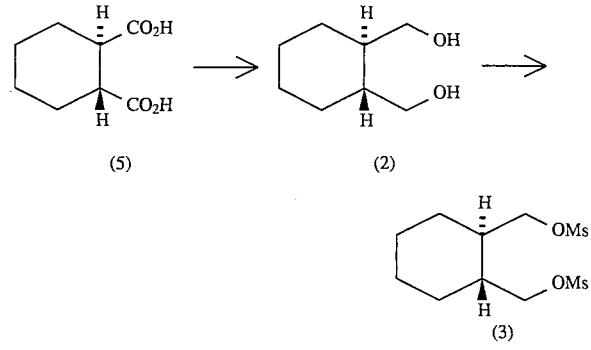
To a mixture of lithium aluminum hydride (2.85 g; 75 mmol) and diethyl ether (50 ml), a solution of trans-1,2-cyclohexanedicarboxylic acid anhydride (1) (7.71 g; 50 mmol) in diethyl ether (150 ml) is dropwise added, and the resultant mixture is allowed to react at room temperature for 3 hours and then heated under reflux for 2 hours. After cooling, wet ether is dropwise added to the reaction mixture, followed by addition of water. The organic layer is collected by decantation, followed by concentration to give trans-1,2-bis(hydroxymethyl)cyclohexane (2) (5.1 g).

The thus obtained compound (2) (5.1 g; 35.4 mmol) is dissolved in triethylamine (10.37 g; 103 mmol) and acetonitrile (127 ml), and methanesulfonyl chloride (8.13 g; 71 mmol) is dropwise added thereto under ice-cooling. The resultant mixture is ice-cooled for 1 hour and allowed to react at room temperature for 3 hours. The reaction mixture is washed with water, dried and concentrated, followed by addition of diethyl ether. Precipitated crystals are collected by filtration to give trans-1,2-bis(methanesulfonyloxymethyl)cyclohexane (3) (5.4 g).

A mixture of the compound (3) (3.06 g; 10.2 mmol), 3-(1-piperazinyl-1,2-benzisothiazole (4) (2.19 g; 10 mmol), sodium carbonate (1.05 g; 10 mmol) and acetonitrile (45 ml) is refluxed for 23 hours. The reaction mixture is filtered while hot, and the filtrate is concentrated to give the objective compound (Compound No. 201) (4.3 g). m.p., 220°–225° C.

Reference Example 1-(b)

Production of trans-1,2-bis (methanesulfonyloxymethyl) cyclohexane (3) :—

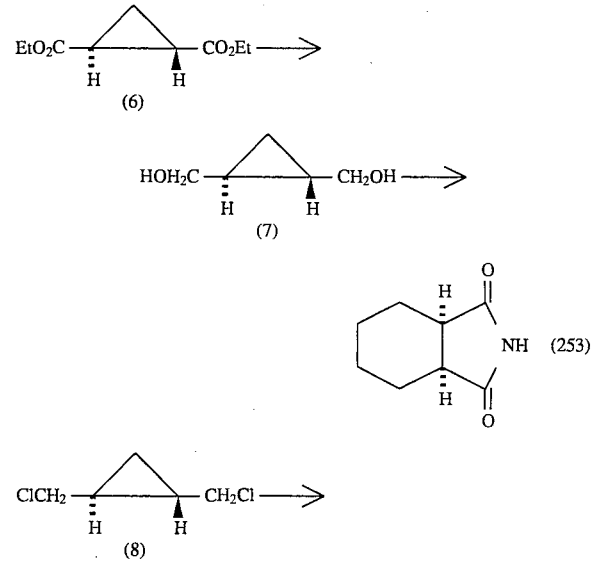


To a mixture of lithium aluminum hydride (52.22 g; 1,374 mol) and tetrahydrofuran (500 ml), a solution of trans-1,2-cyclohexanedicarboxylic acid (5) (118.18 g; 0.687 mol) in tetrahydrofuran (2 liters) is dropwise added under reflux, and the resultant mixture is allowed to react under reflux for 3 hours. After completion of the reaction, the reaction mixture is cooled, and wet tetrahydrofuran and ether are dropwise added thereto, followed by filtration. The filtrate is concentrated under reduced pressure to give trans-1,2-bis(hydroxymethyl)cyclohexane (2) (71.86 g).

To a solution of the compound (2) (71.86 g; 0.499 mol) and triethylamine (151.21 g; 1.497 mol) in chloroform (1 liter), methanesulfonyl chloride (114.27 g; 0.998 mol) is dropwise added under ice-cooling, and the resultant mixture is stirred at room temperature for 6 hours. The reaction mixture is washed with water, dried and concentrated under reduced pressure. Diethyl ether is added to the residue for crystallization, and the precipitated crystals are collected to give trans-1,2-bis(methanesulfonyloxymethyl)cyclohexane (3) (88.57 g).

Reference Example 2

Production of N-[(2-chloromethyl)cyclopropylmethyl]cyclohexane-1,2-dicarboximide (Compound No. 202):—



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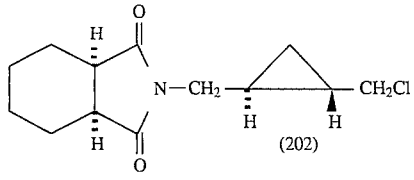


(202)

To a mixture of lithium aluminum hydride (6.65 g; 175 mmol) and diethyl ether (1000 ml), a solution of diethyl 1,2-cyclopropanedicarboxylate (6) (25.0 g; 134 mmol) in diethyl ether (250 ml) is dropwise added, and the resultant mixture is refluxed for 5 hours, followed by cooling. Wet ether is dropwise added to the reaction mixture, followed by addition of water. The organic layer is collected by decantation and dried. Concentration under reduced pressure gives 1,2-bis(hydroxymethyl)cyclopropane (7) (24.8 g).

To a solution of the compound (7) (3.0 g; 29.4 mmol) in pyridine (4.64 g), thionyl chloride (10.5 g; 88.2 mmol) is dropwise added, and the resultant mixture is stirred at a temperature of 0° to 5° C. for 30 minutes and at room temperature for 2 hours. The reaction mixture is concentrated, and to the residue diethyl ether and ethyl acetate (1:1) are added. After filtration of insoluble materials, the filtrate is concentrated to give 1.2-bis(chloromethyl)cyclopropane (8) (2.51 g).

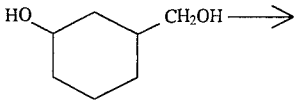
^{1}H-NMR ($CDCl_3$) δ: 6: 0.75 (2 H, m), 1.25 (2 H, m), 3.45 (4 H, m).

A mixture of the compound (8) (0.3 g; 2.2 mmol), cyclohexane-1,2-dicarboximide (253) (66 rag; 0.43 mmol), potassium carbonate (0.3 g; 2.2 mmol), potassium iodide (0.3 g; 1.8 mmol) and acetonitrile (20 ml) is refluxed for 5 hours, and the reaction mixture is, after cooling, concentrated under reduced pressure. Chloroform is added to the residue, which is washed with water, dried, concentrated under reduced pressure and chromatographed on a silica gel column to give the objective compound (Compound No. 202) (0.11 g).

^{1}H-NMR ($CDCl_3$) δ: 0.60 (2 H, m), 0.95 (2 H, m), 1.45 (4 H, m), 1.85 (4 H, m), 2.85 (2 H, m), 3.20 (2 H, m), 3.55 (2 H, m).

Reference Example 3

Production of N-(3-methanesulfonyloxymethylcyclohexyl) bicyclo[2.2.1]heptane-2-exo-3-exo-dicarboximide (Compound No. 203):-



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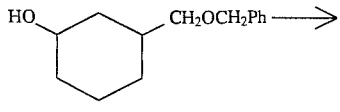
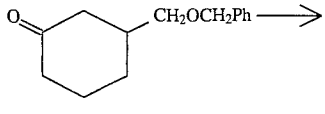


(10)



(11)

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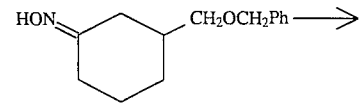
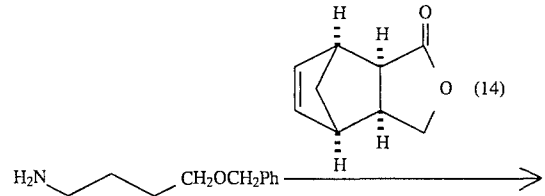
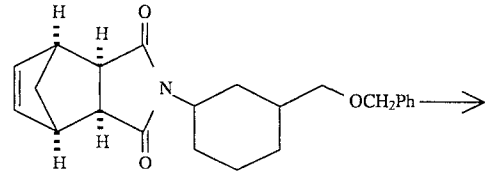


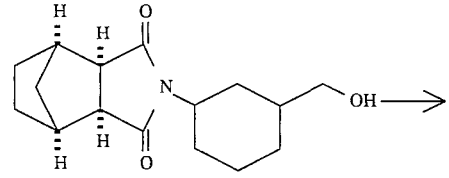
(12)



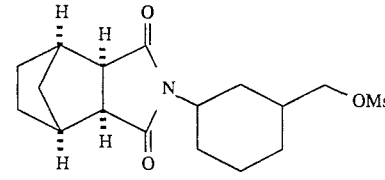
(13)



(15)



(16)



(203)

50% Sodium hydride (5.77 g; 120 mmol) is washed with n-hexane, and dimethylformamide (50 ml) is added thereto. To the resultant mixture, 3-hydroxymethylcyclohexanol (9) (10.0 g; 76.8 mmol) is dropwise added under ice-cooling, and then benzyl bromide (13.15 g; 76.8 mmol) is dropwise added thereto under ice-cooling. The resulting mixture is stirred at a temperature of 0° to 10° C. for 5 hours. The reaction mixture is poured into ice-water, extracted with toluene. The organic layer is washed with water, dried and concentrated under reduced pressure. The residue is chromatographed on a silica gel column to give 3-benzyloxymethylcyclohexanol (10) (9.55 g).

^{1}H-NMR ($CDCl_3$) δ: 0.8–2.1 (9 H, m), 3.35 (2 H, s), 3.60 (1 H, m), 4.50 (2 H, s), 7.35 (5 H, m).

To a solution of the compound (10) (4.9 g; 22.2 mmol) in acetone (90 ml), Jones reagent (chromic anhydride acid-sulfuric acid) (0.07 mol) is dropwise added, and the resultant mixture is stirred at a temperature of 0° to 10° C. for 2 hours. Methanol is dropwise added to the reaction mixture, which is poured into ice-water and extracted with chloroform. The extract is washed with water, dried and concentrated under

reduced pressure. The residue is chromatographed on a silica gel column to give 3-benzyloxymethylcyclohexanone (11).

^{1}H-NMR ($CDCl_3$) δ: 1.15–2.50 (9 H, m), 3.38 (2 H, d), 4.50 (2 H, s), 7.30 (5 H, m).

To a solution of the compound (11) (1.0 g; 4.6 mmol), in ethanol (25 ml), sodium acetate (0.754 g; 9.2 mmol) and hydroxylamine hydrochloride (0.384 g; 5.5 mmol) are added, and the resultant mixture is stirred at room temperature for 3 hours. The reaction mixture is poured into ice-water, extracted with chloroform, washed with water and dried. After concentration under reduced pressure, the residue is chromatographed on a silica gel column to give 3-benzyloxymethylcyclohexanone oxime (12) (0.8 g).

^{1}H-NMR ($CDCl_3$) δ: 1.2–1.55 (2 H, m), 1.65–2.15 (5 H, m), 2.45 (1 H, m), 3.25 (1 H, m), 3.38 (2 H, m), 4.50 (2 H, s), 7.30 (5 H, m).

To a solution of the compound (12) (0.75 g; 3.2 mmol) in diethyl ether (30 ml), lithium aluminum hydride (0.75 g; 20 mmol) is added, and the resultant mixture is refluxed for 3 hours. After cooling, wet ether is dropwise added to the reaction mixture, and the organic layer is collected by decantation and dried, followed by concentration under reduced pressure to give 3-benzyloxymethylcyclohexylamine (13) (0.61 g).

^{1}H-NMR ($CDCl_3$) δ: 0.8–2.2 (9 H, m), 3.15 (1 H, s), 3.20 (1 H, s), 3.35 (2 H, m), 4.50 (2 H, s), 7.30 (5 H, m).

To a solution of the compound (13) (0.57 g; 2.6 mmol) in pyridine (30 ml), bicyclo[2.2.1]hept-5-ene-2-exo-3-exo-dicarboxylic acid anhydride (14) (854 rag; 5.2 mmol) is added, and the resultant mixture is refluxed for 7 hours. Pyridine is removed under reduced pressure, and chloroform is added to the residue and washed with water. The thus obtained residue is chromatographed on a silica gel column and further on a silica gel thin layer to give N-(3-benzyloxymethylcyclohexyl) bicyclo[2.2.1]hept-5-ene-2-exo-3-exodicarboximide (15) (0.23 g).

^{1}H-NMR ($CDCl_3$) δ: 0.9–2.45 (11 H, m), 2.60 (2 H, s), 3.25 (2 H, s), 3.30–3.52 (2 H, m), 4.00 (1 H, m), 4.55–4.65 (2 H, m), 6.30 (2 H, s), 7.30 (5 H, m).

To a solution of the compound (15) (0.21 g; 57.5 mmol) in methanol (10 ml), one drop of conc. hydrochloric acid and 10% palladium-carbon (210 mg) are added at room temperature to perform catalytic reduction. After completion of the reaction, the catalyst is removed. Removal of methanol under reduced pressure gives N-(3-hydroxymethylcyclohexyl) bicyclo[2.2.1]hept-2-exo-3-exo-dicarboximide (16) quantitatively.

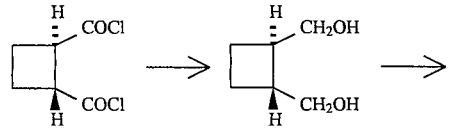
H-NMR ($CDCl_3$) δ: 0.9–2.25 (15 H, m), 2.55 (2 H, s), 2.70 (2 H, s), 3.68 (2 H, brs), 4.08 (1 H, brs).

To a solution of the compound (16) (133 rag; 0.61 mmol) in pyridine (5 ml), methanesulfonyl chloride (82.4 mg; 0.92 mmol) is dropwise added under ice-cooling, and the resultant mixture is stirred at room temperature for 1.5 hours. Pyridine is removed under reduced pressure, and chloroform is added to the residue and washed with water. The chloroform solution is dried and concentrated under reduced pressure to give the objective compound (Compound No. 203).

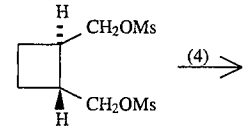
H-NMR ($CDCl_3$) δ: 1.0–2.2 (15 H, m), 2.55 (2 H, s), 2.70 (2 H, s), 3.00 (3 H, s), 4.02 (3 H, m).

Reference Example 4

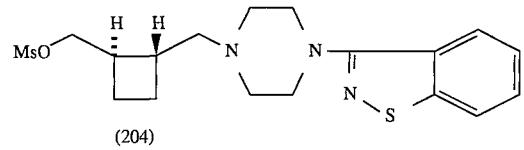
Production of Compound No. 204:-



(17) (18)



(19)



(204)

To a mixture of lithium aluminum hydride (11.86 g; 0.312 tool) and diethyl ether (300 ml), a solution of trans-1,2-bis(chlorocarbonyl)cyclobutane (17) (18.90 g; 0.104 mol) in diethyl ether (200 ml) is dropwise added under reflux, and the resultant mixture is refluxed for 3 hours. After cooling, wet tetrahydrofuran is dropwise added to the reaction mixture, followed by filtration. The filtrate is concentrated under reduced pressure to give trans-1,2-bis-(hydroxymethyl)cyclobutane (18) (8.76 g).

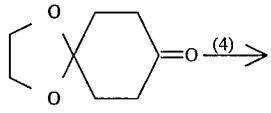
To a solution of the compound (18) (8.50 g; 0.0733 mol) and triethylamine (22.20 g; 0.22 mol) in chloroform (100 ml), methanesulfonyl chloride (16.79 g; 0.147 tool) is dropwise added under ice-cooling, and the resultant mixture is stirred for 7 hours at room temperature. The reaction mixture is washed with water, dried and concentrated under reduced pressure to give trans-1,2-bis (methanesulfonyloxymethyl-)cyclobutane (19) (18.50 g). m.p., 60° to 62° C. (crystallized from ether).

A mixture of the compound (19) (10.00 g; 0.0368 tool), 3-(1-piperazinyl)-1,2-benzisothiazole (4) (7.25 g; 0.0331 mol), sodium carbonate (3.90 g; 0.0368 mol) and acetonitrile (300 ml) is refluxed for 13 hours, and the reaction mixture is cooled, followed by filtration. The filtrate is concentrated under reduced pressure and chromatographed on a silica gel column to give the objective compound (Compound No. 204) (2.84 g).

^{1}H-NMR ($CDCl_3$) δ: 1.5–2.15 (4 H, m), 2.3–2.69 (8 H, m), 3.02 (3 H, s), 3.54 (4 H, t, J=5 Hz), 4.25 (2 H, d, J=5.6 Hz), 7.32–7.50 (2 H, m), 7.83–7.92 (2 H, m).

Reference Example 5

Production of Compound No. 205:-



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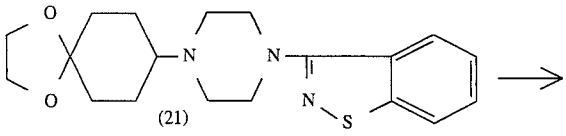
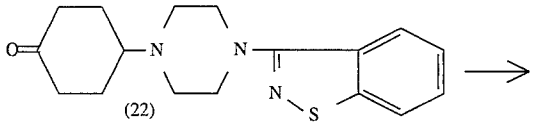
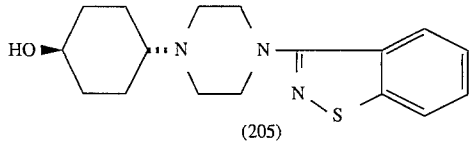


(21)



(22)



(205)

A mixture of 3- (1-piperazinyl) -1,2-benzisothiazole (4) (12.7 g; 0.058 mol), 1,4-cyclohexanedione monoethylene ketal (20) (10 g; 0.064 mol), p-toluenesulfonic acid (0.55 g; 0.0029 mol) and toluene (200 ml) is refluxed for 7 hours, and potassium carbonate (0.8 g; 0.0058 mol) is added thereto at room temperature. The resultant mixture is stirred for 1 hour and concentrated under reduced pressure. To the residue tetrahydrofuran (250 ml), methanol (20 ml) and sodium borohydride (2.19 g; 0.058 mol) are added, followed by stirring at room temperature for 15 hours. The reaction mixture is concentrated under reduced pressure, followed by addition of chloroform. The resultant solution is washed with water and dried. The solution is concentrated under reduced pressure and chromatographed on a silica gel column to give the compound (21) (1.57 g). m.p., 105° to 106° C.

A solution of the compound (21) (2.5 g; 0.007 mol) in 1 N hydrochloric acid (20 ml) and tetrahydrofuran (20 ml) is refluxed for 10 hours, and the reaction mixture is concentrated under reduced pressure. The residue is made alkali with aqueous potassium carbonate, extracted with ethyl acetate, dried and concentrated under reduced pressure to give the compound (22) (2.06 g).

To a solution of the compound (22) (2 g; 0.0063 tool) in methanol (200 ml), sodium borohydride (0.24 g; 0.0063 mol) is added under ice-cooling, followed by stirring for 30 minutes. The reaction mixture is concentrated under reduced pressure, followed by addition of water and extraction with ethyl acetate. The extract is dried and concentrated under reduced pressure to give the objective compound (Compound No. 205). m.p., 155° to 160° C.

^{1}H-NMR ($CDCl_3$) δ: 1.2–2.1 (9 H, m), 2.3–2.45 (1 H, m), 2.7–2.85 (4 H, m), 3.5–3.7 (5 H, m), 7.32–7.5 (2 H, m), 7.81 (1 H, d, J=8 Hz), 7.91 (1 H, d, J=8 Hz).

Reference Example 6

In the same manner as in Reference Examples 1 to 5, the compounds as shown in Table 7 are obtainable.

TABLE 7

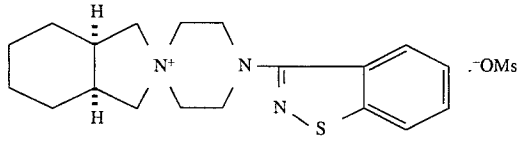
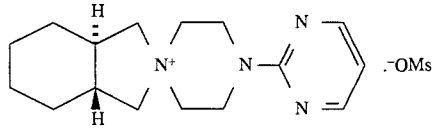
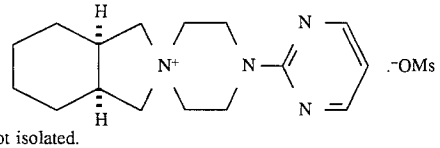
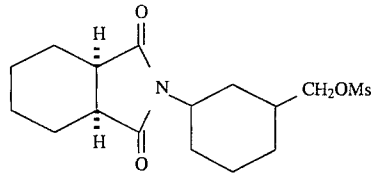
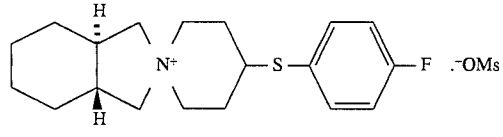
Compound No.	Structure	Physical constant	
206		Melting point:	222–225° C.
207		Melting point: ^{1}H-NMR ($CDCl_3$) δ:	269–272° C. 1.2–1.4(4H, m), 1.7–2.2(6H, m), 2.70(3H, s), 3.35(2H, t, J=12Hz), 3.6–3.9(4H, m), 4.0–4.3(6H, m), 6.63(1H, t, J=5Hz), 8.33(2H, d, J=5Hz).
208			
Note: not isolated.			
209		^{1}H-NMR ($CDCl_3$) δ: EI-MS m/e:	1.0–2.2(17H, m), 2.80(2H, m), 3.05(3H, s), 4.05(3H, m). 343 (M^+)
210		Melting point: ^{1}H-NMR ($CDCl_3$) δ:	193–195° C. 1.1–1.4(4H, m), 1.65–2.0(8H, m), 2.1–2.3(2H, m), 2.72(3H, s), 2.93(1H, t, J=11Hz), 3.25(1H, t, J=11Hz), 3.4–3.65(3H, m), 3.74(1H, dd, J=6 and 11Hz), 3.9–4.2(3H, m), 6.9–7.1(2H, m), 7.3–7.5(2H, m).

TABLE 7-continued

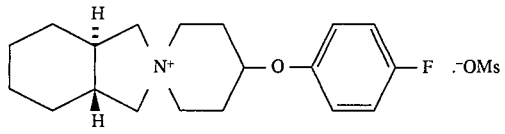
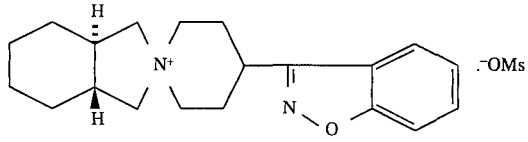
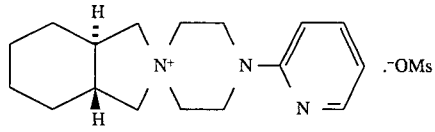
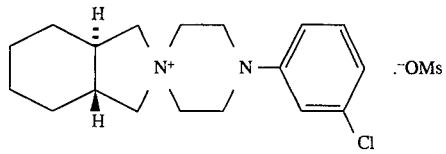
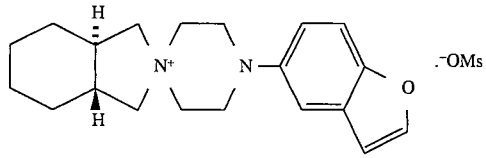
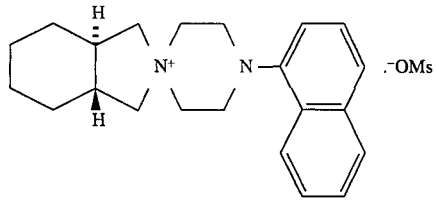
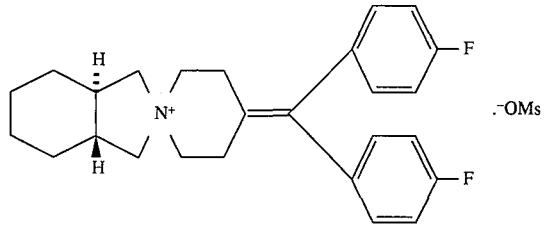
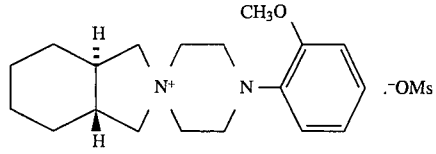
Compound No.	Structure	Physical constant	
211		Melting point: ^{1}H-NMR ($CDCl_3$) δ:	182–184° C. 1.1–1.5(4H, m), 1.7–2.2(8H, m), 2.25–2.55(2H, m), 2.74(3H, s), 3.10(1H, t, J=11Hz), 3.27 (1H, t, J=11Hz), 3.5–3.7(1H, m) , 3.75–3.9(1H, m), 3.9–4.1 (1H, m), 4.1–4.25(1H, m), 4.77 (1H, m), 6.85–7.0(4H, m).
212		Melting point: ^{1}H-NMR ($CDCl_3$) δ:	178–180° C. 1.1–1.45(4H, m), 1.7–2.05(6H, m), 2.05–2.35(2H, m), 2.35–2.6(2H, m), 2.79(3H, s), 2.97 (1H, t, J=12Hz), 3.30(1H, t, J=12Hz), 3.54(1H, dd, J=13 and 26Hz), 3.87(1H, dd, J=6 and 12Hz), 4.0–4.2(1H, m), 4.26(1H, dd, J=6 and 12Hz), 4.4–4.6(1H, m), 7.07(1H, dt, J=2 and 7Hz), 7.19(1H, dd, J=2 and 8Hz), 7.91(1H, dd, J=5 and 9Hz).
213		Melting point: ^{1}H-NMR ($CDCl_3$) δ:	223–225° C. 1.15–1.45(4H, m), 1.7–2.2 (6H, m), 2.71(3H, s), 3.32(2H, t, J=12Hz), 3.65–4.1(10H, m), 6.65–6.8(2H, m), 7.52(1H, m), 8.15(1H, m).
214		Melting point: ^{1}H-NMR ($CDCl_3$) δ:	164–167° C. 1.1–1.4(4H, m), 1.75–2.2 (6H, m), 2.74(3H, s), 3.31(2H, t, J=2Hz), 3.45–3.65(4H, m), 3.75–3.95(4H, m), 4.0(1H, dd, J=2 and 11Hz), 6.75–7.0(3H, m), 7.15–7.2(1H, m).
215		Melting point: ^{1}H-NMR ($CDCl_3$) δ:	176–179° C. 1.27(4H, m), 1.7–2.1(6H, m), 2.75(3H, s), 3.31(2H, t, J=2Hz), 3.45(4H, brs), 6.69(1H, m), 6.95(1H, dd, J=2 and 9Hz), 7.13(1H, d, J=2Hz), 7.38(1H, d, J=9Hz), 7.58(1H, d, J=2Hz).
216		Melting point: ^{1}H-NMR ($CDCl_3$) δ:	226–229° C. 8.11(1H, d, J=9Hz), 7.82–7.86(1H, m), 7.63(1H, d, J=8Hz), 7.36–7.53(3H, m), 7.15 (1H, d, J=7Hz), 3.9–4.1(6H, m), 3.4–3.5(6H, m), 2.78(3H, s), 1.2–2.2(10H, m).
217		Melting point: ^{1}H-NMR ($CDCl_3$) δ:	226–229° C. 6.98–7.15(8H, m), 4.0–4.1 (2H, m), 3.7–3.8(4H, m), 3.2–3.3(2H, m), 2.76(3H, s), 2.6–2.7(4H, m), 2.8–3.0(8H, m), 1.2–1.4(2H, m).
218		Melting point: ^{1}H-NMR ($CDCl_3$) δ:	176–179° C. 6.8–7.1(4H, m), 3.9–4.0(2H, m), 3.7–3.8(7H, m), 3.35–3.45 (6H, m), 2.77(3H, s), 1.8–2.2 (6H, m), 1.3–1.4(4H, m).

TABLE 7-continued

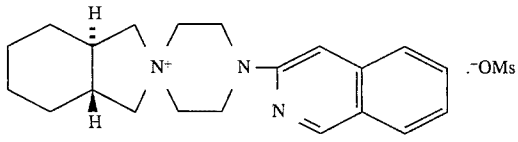
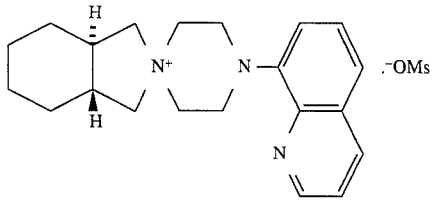
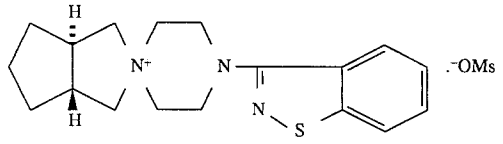
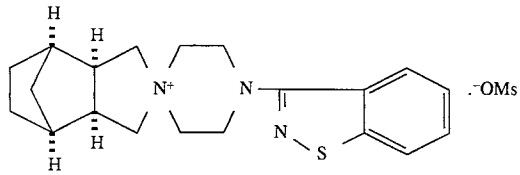
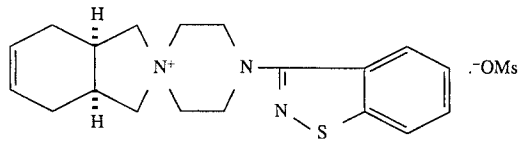
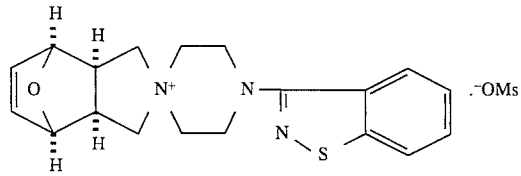
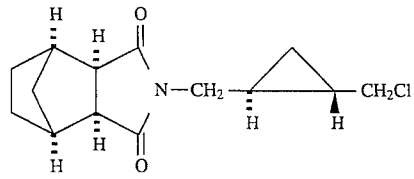
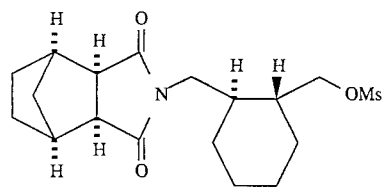
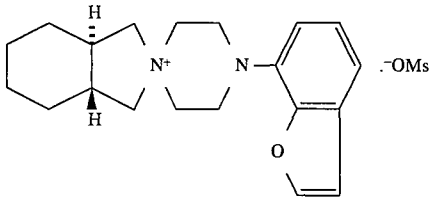
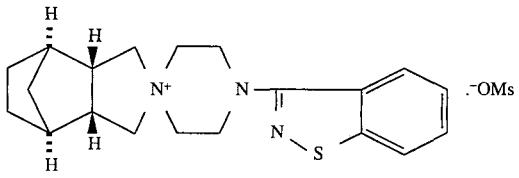
Compound No.	Structure	Physical constant	
219		Melting point: ^{1}H-NMR ($CDCl_3$) δ:	215–216° C. 1.1–1.5(4H, m), 1.8–2.2(6H, m), 2.77(3H, s), 3.3–3.5(2H, m), 3.7–4.1(10H, m), 6.94(1H, s), 7.3–7.37(1H, m), 7.51–7.65(2H, m), 7.78(1H, d, J=8 Hz), 8.89(1H, s).
220		Melting point: ^{1}H-NMR ($CDCl_3$) δ:	112–113° C. 1.2–1.4(4H, m), 1.8–2.2(6H, m), 2.78(3H, s), 3.4–3.5(2H, m), 3.7–4.1(10H, m), 7.2–7.3 (1H, m), 7.4–7.6(3H, m), 8.1–8.2(1H, m), 8.8–8.9(1H, m).
221		Melting point: ^{1}H-NMR ($CDCl_3$) δ:	194–195° C. 1.51(2H, quint, J=10Hz), 1.90 (2H, m), 2.19–2.27(2H, m), 2.57 (2H, m), 2.76(3H, s), 3.47(2H, t, J=11Hz), 3.92–4.08(10H, m), 7.38–7.53(2H, m), 7.83(1H, d, J=8Hz), 7.95(1H, d, J=8Hz).
222		Melting point: ^{1}H-NMR ($CDCl_3$) δ:	224–227° C. 1.1–1.3(3H, m), 1.60(2H, m), 1.89(1H, d, J=15Hz), 2.25(2H, brs), 2.47(2H, m), 2.71(3H, s), 3.20(2H, m), 3.60–3.70(2H, m), 3.80–3.90(4H, m), 4.0–4.2(4H, m), 7.3–7.5(2H, m), 7.79(1H, d, J=8Hz), 7.96(1H, d, J=8Hz).
223		^{1}H-NMR ($CDCl_3$) δ:	2.0–2.1(2H, m), 2.3–2.45(2H, m), 2.76(3H, s), 2.95–3.1(2H, m), 3.25–3.4(2H, m), 3.87(4H, brs), 3.96(4H, brs), 4.15–4.25 (2H, m), 5.90(2H, brs), 7.38–7.53(2H, m), 7.82(1H, d, J=8 Hz), 7.99(1H, d, J=8Hz).
224		^{1}H-NMR ($CDCl_3$) δ:	2.75(3H, s), 3.0–3.15(4H, m), 3.8–4.0(8H, m), 4.4–4.5(2H, m), 4.87(2H, s), 6.44(2H, s), 7.41–7.50(2H, m), 7.82(1H, d, J=8Hz), 7.98(1H, d, J=8Hz).
225		^{1}H-NMR ($CDCl_3$) δ:	0.45(1H, m), 0.90(1H, m), 1.1–1.8(8H, m), 2.62(2H, m), 2.72 (2H, brs), 3.20(2H, m), 3.50(2H, m).
226		^{1}H-NMR ($CDCl_3$) δ:	1.0–2.0(16H, m), 2.62(2H, brs), 2.70(2H, brs), 3.08(3H, s), 3.37 (1H, dd, J=8Hz and 13Hz), 3.60 (1H, dd, J=8Hz and 13Hz), 4.25–4.37(2H, m).

TABLE 7-continued

Compound No.	Structure	Physical constant
227		
Note: not isolated.		
228		Melting point: 216–218° C. ^{1}H-NMR ($CDCl_3$) δ: 1.55–1.9(6H, m), 2.35–2.45 (2H, m), 2.75(3H, s), 2.95–3.05(2H, m), 3.35–3.5(2H, m), 3.75–4.0(8H, m), 4.1–4.2(2H, m), 7.38–7.53(2H, m), 7.82(1H, d, J=8Hz), 8.01(1H, d, J=8Hz).

Reference Example 7

According to the methods as described in JP-A-63-83085, J. Med. Chem., 28, 761–769 (1985) or ibid., 32, 1024–1033 (1989), the compounds as shown in Table 8 are obtained.

TABLE 8

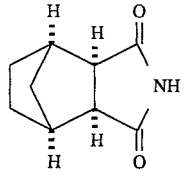
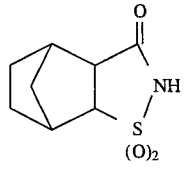
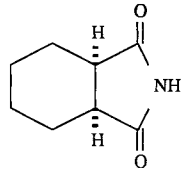
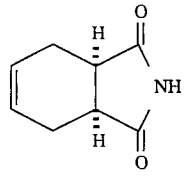
Compound No.	Structure
251	
252	
253	
254	

TABLE 8-continued

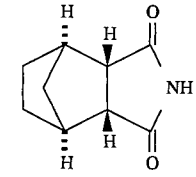
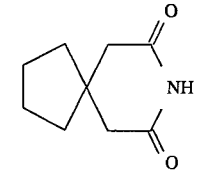
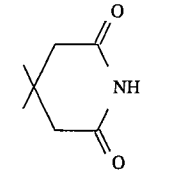
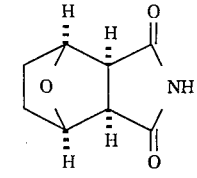
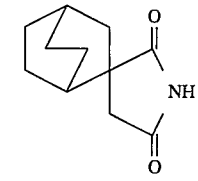
Compound No.	Structure
255	
256	
257	
258	
259	

TABLE 8-continued

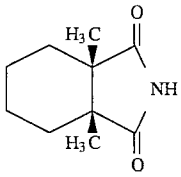
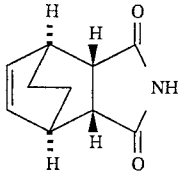
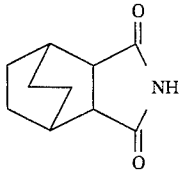
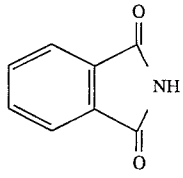
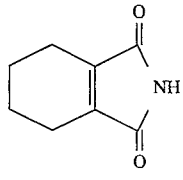
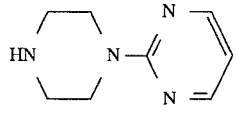
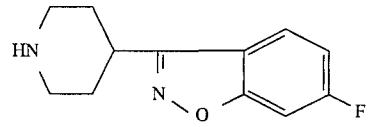
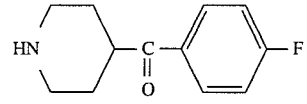
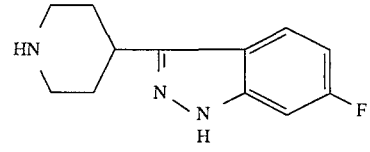
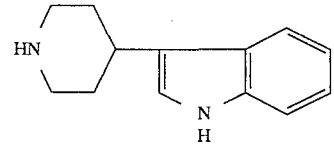
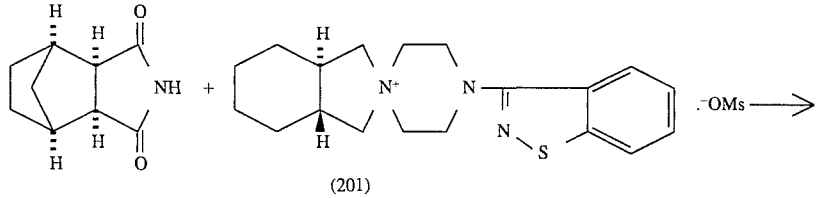
Compound No.	Structure
260	
261	
262	
263	
264	
265	

TABLE 8-continued

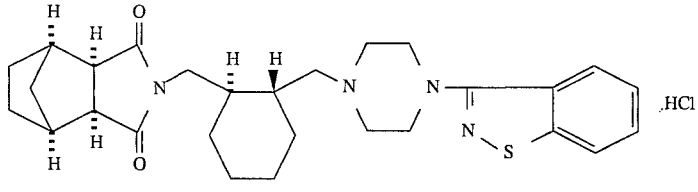
Compound No.	Structure
266	
267	
268	
269	

Example 1- (a)

Production of Compound No. 101:—



(251) (201)



(101)

A mixture of the compound (201) (1.44 g; 3.4 mmol), bicyclo[2.2.1]heptane-2-exo-3-exo-dicarboximide (251) (0.84 g; 5.1 mmol), potassium carbonate (0.68 g; 5.0 mmol), dibenzo-18-crown-6-ether (4 mg; 0.01 mmol) and xylene (20 ml) is refluxed #or 16 hours, followed by removal of the solvent. The residue is chromatographed on a silica gel column and treated with hydrogen chloride-2-propanol to give the objective compound (Compound No. 101) in the form of hydrochloride. m.p., 215° to 217° C.

Example 1- (b)

A mixture of the compound No. 101 in the free form (145.0 g) and methanol (1350 ml) is heated at 60° C., and a solution of L-tartaric acid (44.4 g) in methanol (100 ml) is dropwise added thereto, and the resultant mixture is refluxed for 30 minutes. After allowing to cool to 20° to 30° C., the reaction mixture is stirred for 2 hours, and precipitated crystals are collected by filtration and dried under reduced pressure. The resulting crystals (103.5 g) are recrystallized from methanol two times to give a (+)-isomer of Compound No. 101 in the form of L-tartrate, i.e. Compound No. 102, (71.3 g). m.p., 129° C. $[\alpha]^{25}_{D}$=+18.2 (c=1.0, dimethylformamide (DMF))

Example 1-(c)

The mother liquor after collection of the first crystals by filtration in Example 1-(b) is concentrated under reduced pressure, followed by addition of dichloromethane (500 ml) and aqueous sodium bicarbonate (200 ml). The organic layer is washed with aqueous sodium bicarbonate and aqueous sodium chloride (500 ml) two times in order, dried and concentrated under reduced pressure. To the residue, methanol (3300 ml) and D-tartaric acid (20.2 g) are added, and the resultant mixture is stirred under reflux, followed by cooling. Stirring is continued at 20° to 30° C. for 2 hours, and precipitated crystals are collected and dried under reduced pressure to give crystals (88.0 g). The thus obtained crystals are recrystallized from methanol to give a (−)-isomer of Compound No. 101 in the form of D-tartrate, i.e. Compound No. 103, (67.5 g). m.p., 129° C. $[\alpha]_{D}^{25}$=−18.3 (c=1.0, DMF).

Example 1- (d)

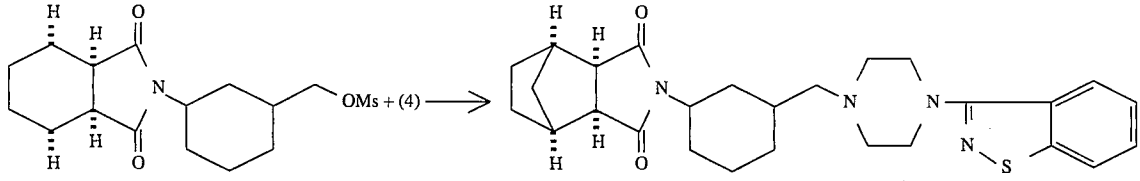
A solution of Compound No. 102 (70.0 g) as obtained in Example 1-(b) in chloroform (500 ml) is washed with aqueous sodium bicarbonate (200 ml) two times and aqueous sodium chloride two times in order, dried and concentrated under reduced pressure. To the residue, acetone (270 ml) and 13.7% 2-propanol solution of hydrogen chloride (31.9 g) are added, and the mixture is stirred at 20° to 30° C. for 2 hours. Precipitated crystals are collected by filtration and dried under reduced pressure to give a (+)-isomer of Compound No. 101 in the form of hydrochloride, i.e. Compound No. 104, (55.9 g). m.p., 268° C. $[\alpha]^{25}_{D}$=+45.7° (c=1.0, methanol)

Example 1- (e)

Compound No. 103 as obtained in Example 1-(c) (65.0 g) is treated in the same manner as in Example 1-(d) to give a (−)-isomer of Compound No. 101 in the form of hydrochloride, i.e. Compound No. 105. m.p., 268° C. $[\alpha]^{25}_{D}$=−45.8 (c=1.0, methanol).

Example 2

Production of Compound No. 106:—



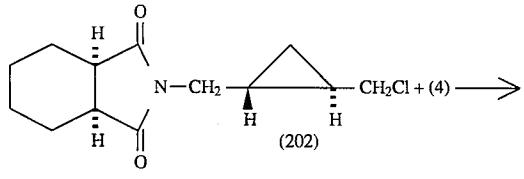
(203) (106)

A solution of the compound (203) (90 mg; 0.25 mmol), sodium carbonate (90 rag; 0.85 mmol) and 3-(1-piperazinyl)-1,2-benzisothiazole (4) (180 mg; 0.82 mmol) in acetonitrile (5 ml) is refluxed for 30 hours. After removal of the solvent, chloroform is added to the reaction mixture. The resultant solution is washed with water, dried and concentrated. The residue is chromatographed on a silica gel column to give the objective compound (Compound No. 106).

^{1}H-NMR ($CDCl_3$) δ: 0.9–2.0 (14 H, m), 2.05–2.35 (3 H, m), 2.55 (2 H, s), 2.65 (4 H, brs), 2.75 (2 H, s), 3.55 (4 H, brs), 4.00 (1 H, m), 7.33–7.50 (2 H, m), 7.80 (1 H, d, J=8 Hz), 7.90 (1 H, d, J=8 Hz).

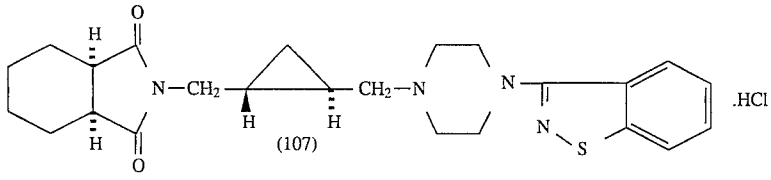
Example 3

Production of Compound No. 107:—



(202)

-continued

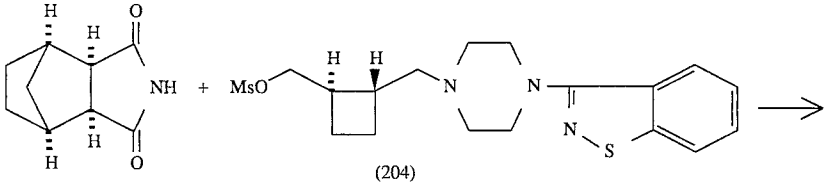


(107)

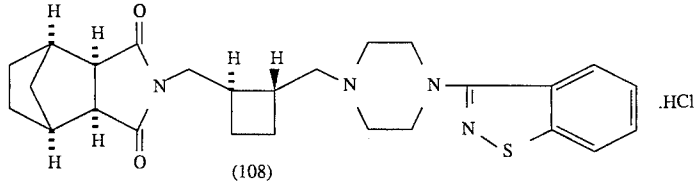
A mixture of the compound (202) (0.1 g; 0.39 mmol), 3-(1-piperazinyl)-1,2-benzisothiazole (4) (0.129 g; 0.58 mmol), potassium carbonate (0.1 g; 0.72 mmol), potassium iodide (0.1 g; 0.60 mmol) and acetonitrile (5 ml) is refluxed for 5.5 hours. The reaction mixture is concentrated under reduced pressure, and chloroform is added to the residue, which is washed with water, dried and concentrated under reduced pressure. The residue is chromatographed on a silica gel thin layer to give the objective compound (Compound No. 107) in the form of hydrochloride. m.p., 207° C.

Example 4

Production of Compound No. 108:—



(251) (204)



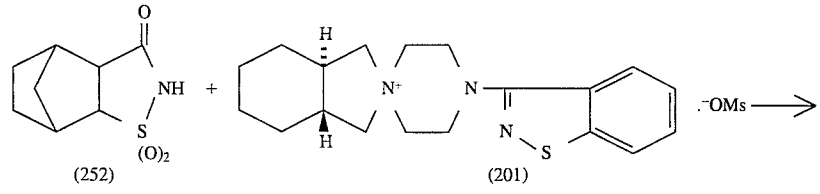
(108)

A solution of the compound (204) (1.18 g; 0.0030 mol), bicyclo[2.2.1]heptane-2-exo-3-exo-dicarboximide (251) (0.49 g); 0.0030 tool), potassium carbonate (0.41 g; 0.0030 mol) and dibenzo-18-crown-6-ether (10 mg) in xylene (30 ml) is refluxed for 20 hours. The reaction mixture is filtered, and the filtrate is concentrated under reduced pressure. The residue is chromatographed on a silica gel column and treated with hydrogen chloride-2-propanol to give the objective compound (Compound No. 108) in the form of hydrochloride. m.p., 208° to 210° C.

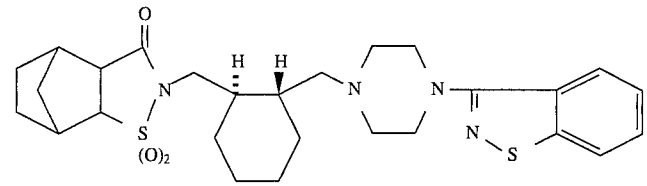
^{1}H-NMR ($CDCl_3$) δ: 1.08–2.1 (10 H, m), 2.2–2.68 (12 H, m), 3.5–3.6 (6 H, m), 7.30–7.48 (2 H, m), 7.80 (1 H, d, J=8.3 Hz), 7.90 (1 H, d, J=8.3 Hz).

Example 5

Production of Compound No. 109:—



(252) (201)



(109)

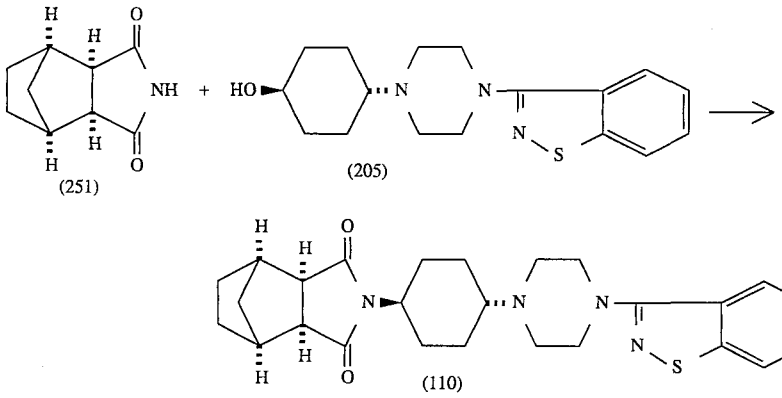
A mixture of the compound (201) (0.46 g; 0.0011 mol), the compound (252) (0.20 g; 0.00099 mol), potassium carbonate (0.14 g; 0.0011 mol), dibenzo-18-crown-6-ether (1 mg) and dimethylformamide (5 ml) is refluxed for 6 hours, followed by concentration under reduced pressure. The residue is chromatographed on a silica gel column to give the objective compound (Compound No. 109).

^{1}H-NMR ($CDCl_3$) δ: 0.95–1.9 (15 H, m), 2.1–2.3 (2 H, m), 2.5–2.7 (5 H, m), 2.9 (2 H, brs), 3.33 (0.5 H, dd, J=10 and 14.6 Hz), 3.42 (0.5 H, dd, J=10 and 14.2 Hz), 4.12 (0.5 H, dd, J=4.6 and 14.2 Hz), 4.2 (0.5 H, dd, J=4.6 and 14.6 Hz), 7.27–7.49 (2 H, m), 7.80 (1 H, d, J=8 Hz), 7.91 (1 H, d, J=8 Hz).

EI-MS m/e: 528.

Example 6

Production of Compound No. 110:—



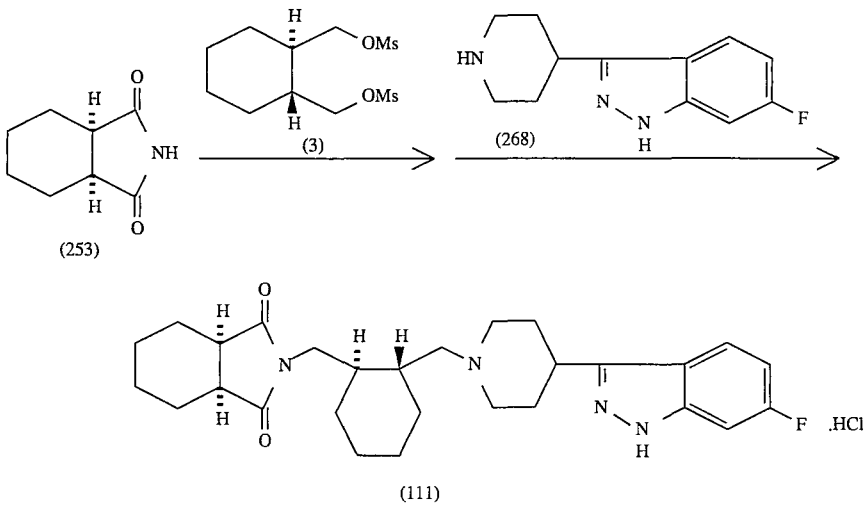
(251) (205) (110)

To a solution of the compound (205) (0.7 g; 2.2 mmol), bicyclo[2.2.1]heptane-2-exo-3-exo-dicarboximide (251) (0.73 g; 4.4 mmol) and triphenylphosphine (0.69 g; 2.6 mmol) in tetrahydrofuran (50 ml), a solution of diethyl azodicarboxylate (0.11 g; 2.6 mmol), in tetrahydrofuran (10 ml) is dropwise added at room temperature, followed by stirring at the same temperature for 3 hours. The reaction mixture is concentrated under reduced pressure, and the residue is chromatographed on a silica gel column to give the objective compound (Compound No. 110). m.p., 200° to 201° C.

^{1}H-NMR ($CDCl_3$) δ: 1.05–1.7 (10 H, m), 2.05–2.25 (2 H, m), 2.25–2.35 (1 H, m), 2.5–2.75 (10 H, m), 3.5–3.7 (4 H, m), 3.95–4.1 (1 H, m), 7.32–7.49 (2 H, m), 7.81 (1 H, d, J=8 Hz), 7.92 (1 H, d, J=8 Hz).

Example 7

Production of Compound No. 111:—



(253) (3) (268) (111)

A mixture of cyclohexane-1,2-dicarboximide (253) (2 g; 0.013 mol), trans-1,2-his (methanesulfonyloxymethyl) cyclohexane (3) (5.88 g; 0.02 tool), potassium carbonate (1.8 g; 0.013 tool) and acetonitrile (50 ml) is refluxed for 2.5

hours. To the reaction mixture, there is added 6-fluoro-3-(4-piperidinyl)-1 H-indazole (268) (4.39 g; 0.02 tool), and the mixture is refluxed for additional 6 hours. The reaction mixture is filtered, and the filtrate is concentrated under reduced pressure. The residue is chromatographed on a silica gel column and treated with hydrogen chloride-2-propanol to give the objective compound (Compound No. 111) in the form of hydrochloride. m.p., 169° to 170° C.

^{1}H-NMR ($CDCl_3$) δ: 1.0–2.2 (25 H, m), 2.5–2.6 (1 H, m), 2.8–2.9 (2 H, m), 2.9–3.1 (3 H, m), 3.2–3.4 (1 H, m), 3.96 (1 H, dd, J=4 and 13 Hz), 6.85–6.93 (1 H, m), 7.07 (1 H, dd, J=2 and 9 Hz), 7.71 (1 H, dd, J=5 and 9 Hz), 9.78 (1 H, brs).

Examples 8 to 72

In the same manner as in Examples 1 to 7, the compounds as shown in Table 9 are obtained. The physical constants of these compounds are given in Table 10.

TABLE 9

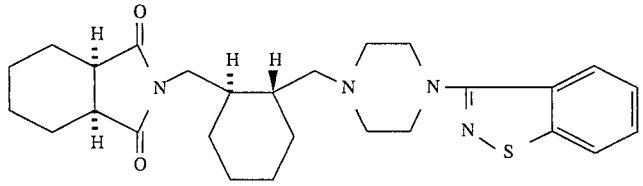
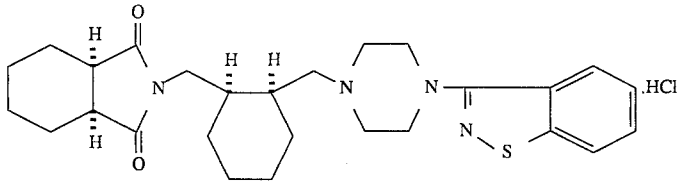
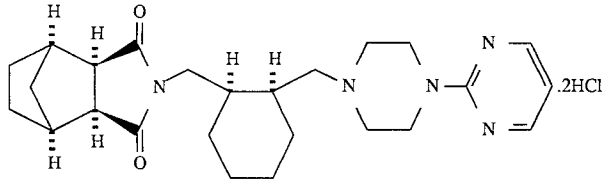
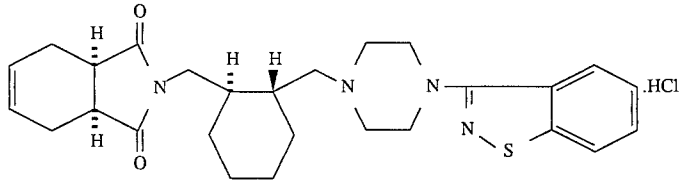
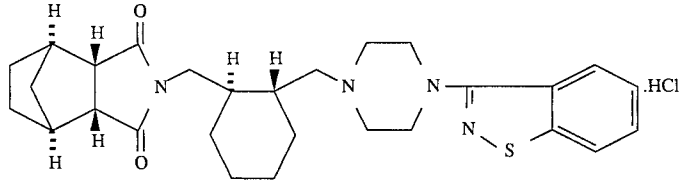
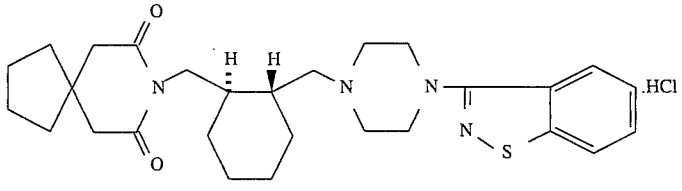
Example No.	Starting Compound No.	Objective Compound No.	Structure
8	253 + 201	112	
9	253 + 206	113	
10	251 + 208	114	
11	254 + 201	115	
12	255 + 201	116	
13	256 + 201	117	

TABLE 9-continued

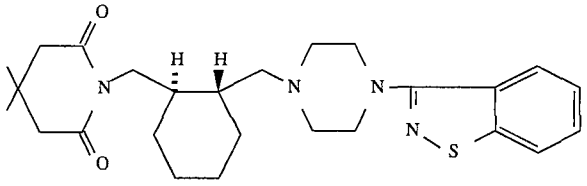
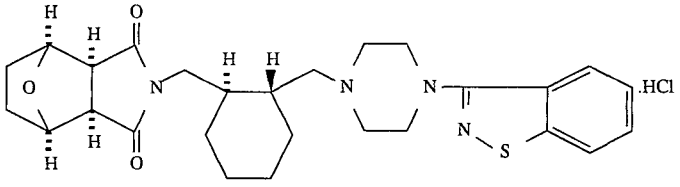
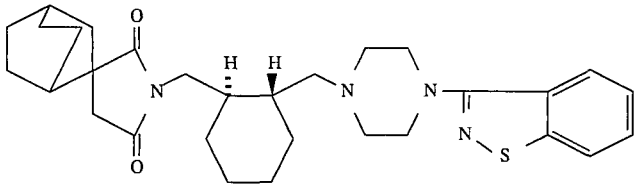
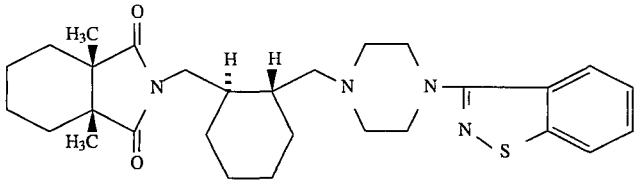
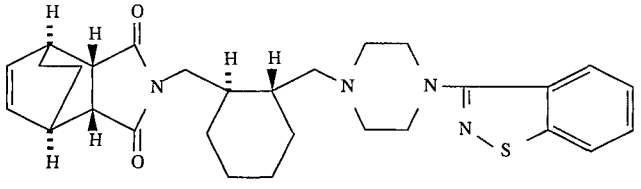
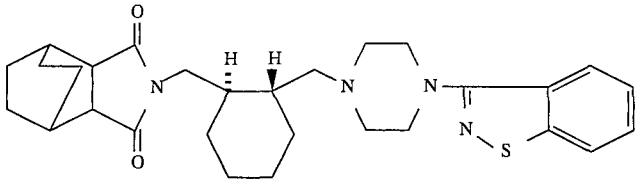
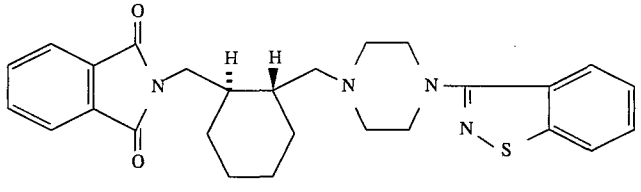
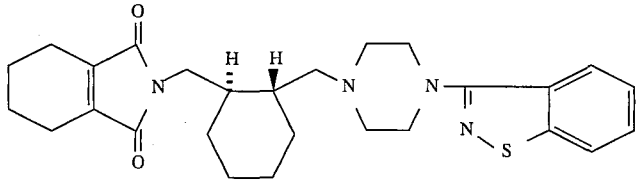
Example No.	Starting Compound No.	Objective Compound No.	Structure
14	257 + 201	118	
15	258 + 201	119	
16	259 + 201	120	
17	260 + 201	121	
18	261 + 201	122	
19	262 + 201	123	
20	263 + 201	124	
21	264 + 201	125	

TABLE 9-continued

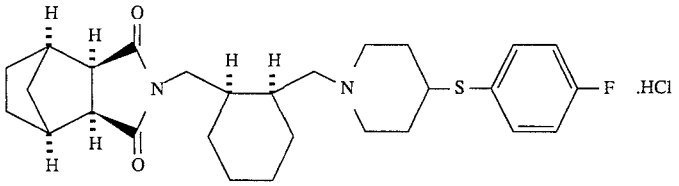
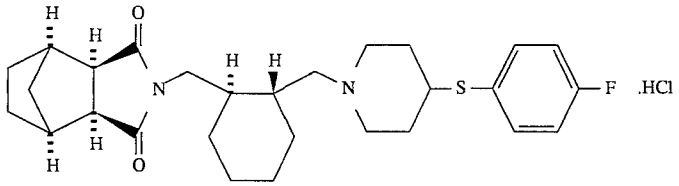
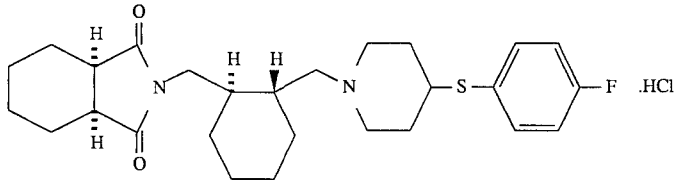
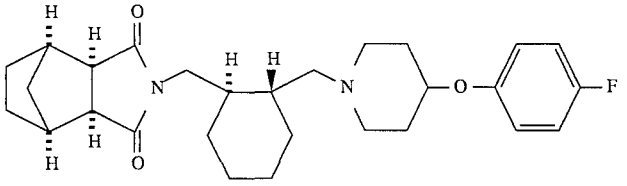
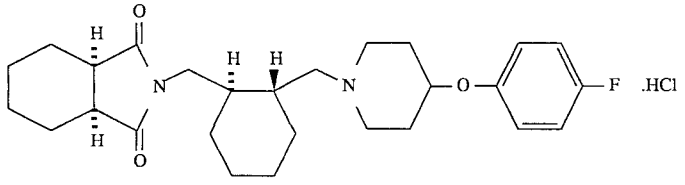
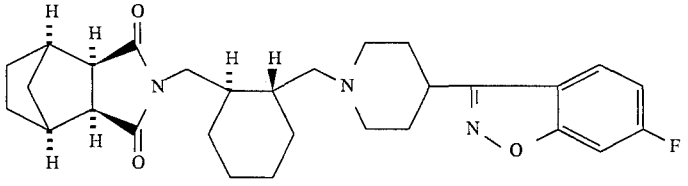
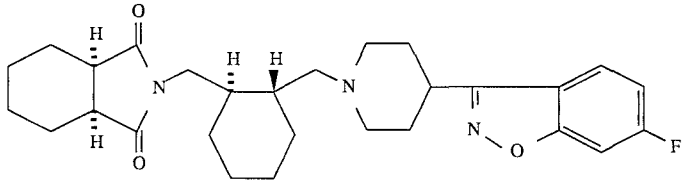
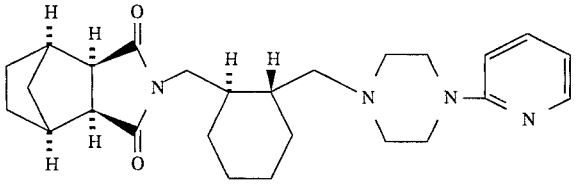
Example No.	Starting Compound No.	Objective Compound No.	Structure
22	251 + 206	126	
23	251 + 210	127	
24	253 + 210	128	
25	251 + 211	129	
26	253 + 211	130	
27	251 + 212	132	
28	253 + 212	132	
29	251 + 213	133	

TABLE 9-continued

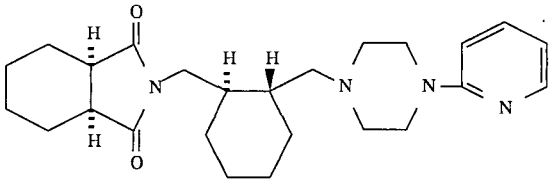
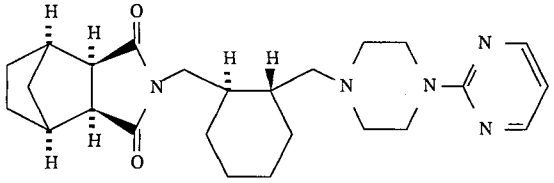
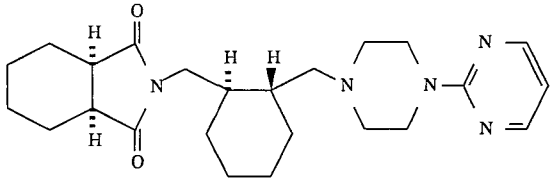
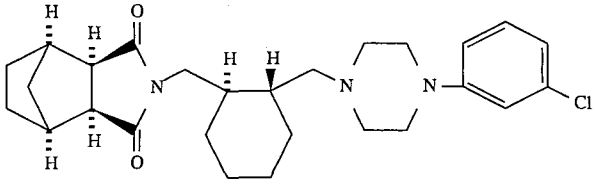
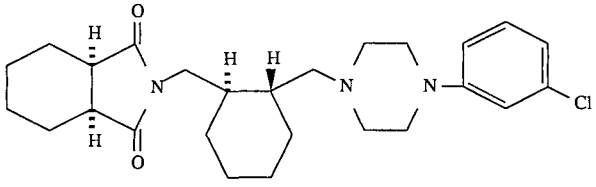
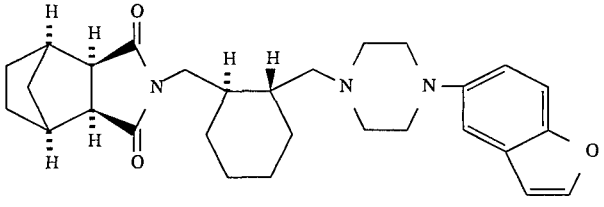
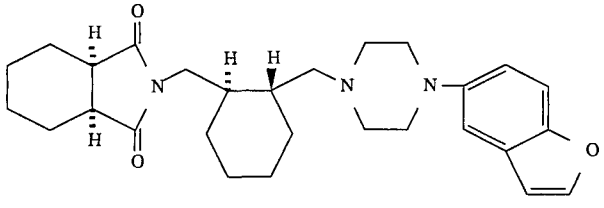
Example No.	Starting Compound No.	Objective Compound No.	Structure
30	253 + 213	134	
31	251 + 207	135	
32	253 + 207	136	
33	251 + 214	137	
34	253 + 214	138	
35	251 + 215	139	
36	253 + 215	140	

TABLE 9-continued

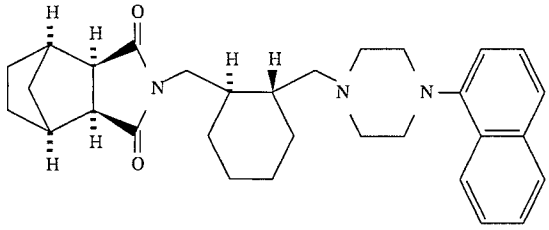
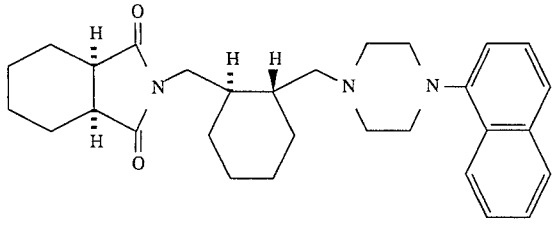
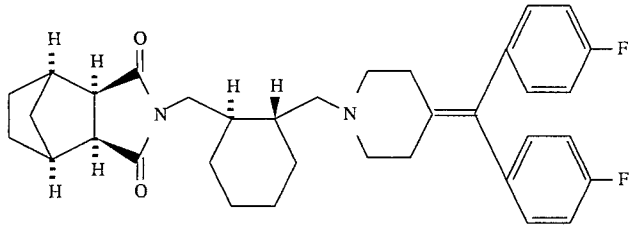
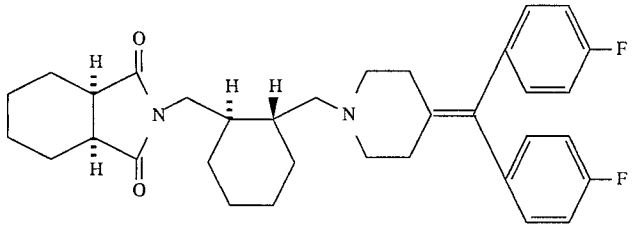
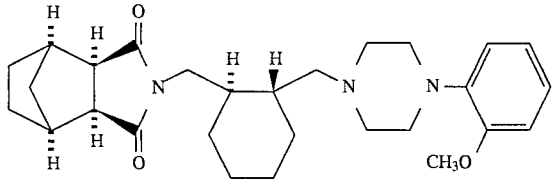
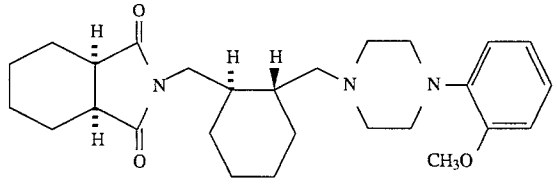
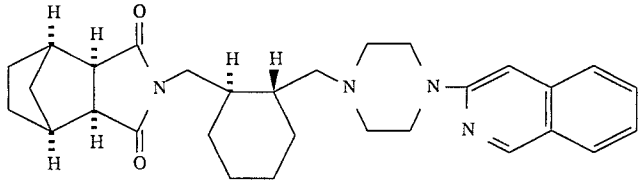
Example No.	Starting Compound No.	Objective Compound No.	Structure
37	251 + 216	141	
38	253 + 216	142	
39	251 + 217	143	
40	253 + 217	144	
41	251 + 218	145	
42	253 + 218	146	
43	251 + 219	147	

TABLE 9-continued

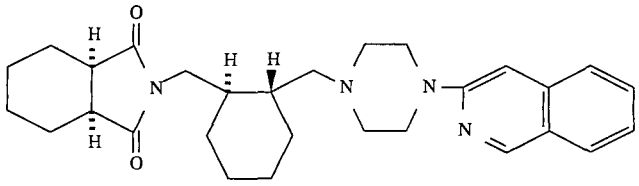
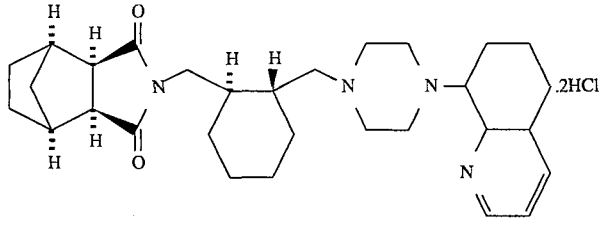
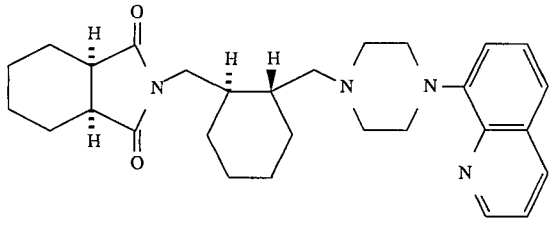
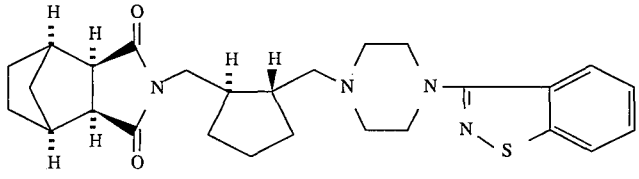
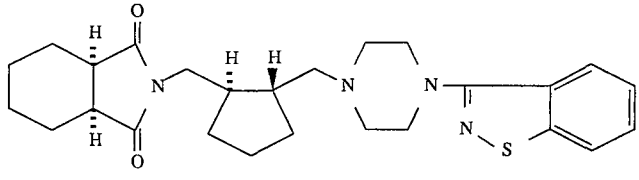
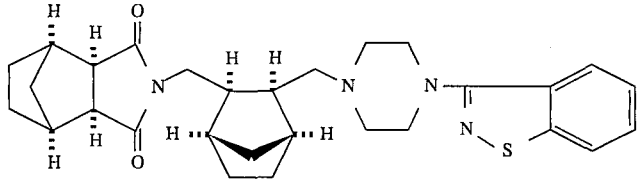
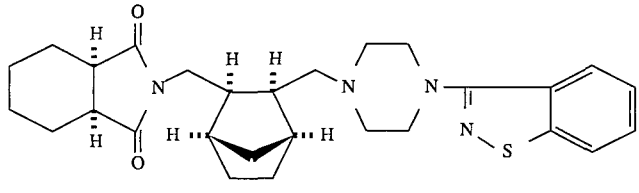
Example No.	Starting Compound No.	Objective Compound No.	Structure
44	253 + 219	148	
45	251 + 220	149	
46	253 + 220	150	
47	251 + 221	151	
48	253 + 221	152	
49	251 + 222	153	
50	253 + 222	154	

TABLE 9-continued

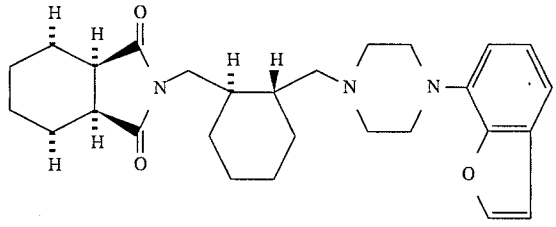
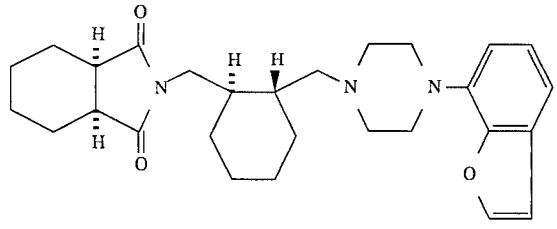
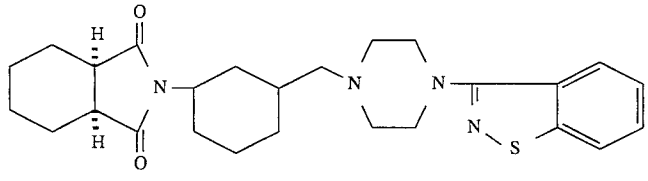
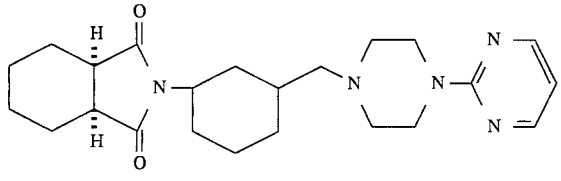
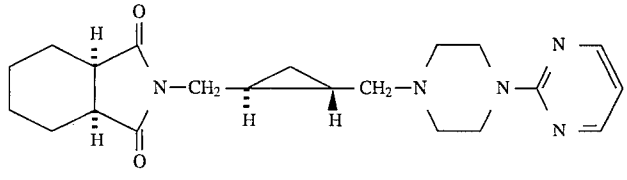
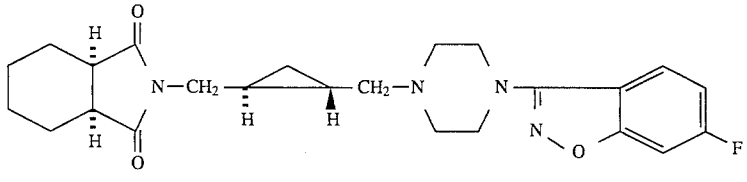
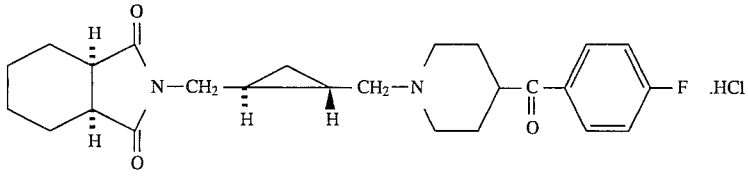
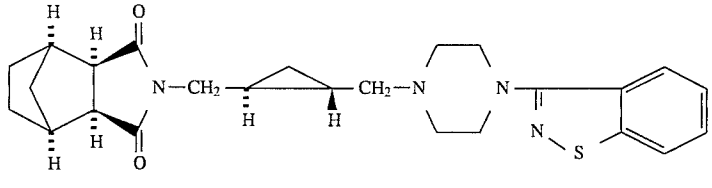
Example No.	Starting Compound No.	Objective Compound No.	Structure
51	251 + 227	155	
52	253 + 227	156	
53	209 + 4	157	
54	209 + 265	158	
55	202 + 265	159	
56	202 + 266	160	
57	202 + 267	161	
58	225 + 4	162	

TABLE 9-continued

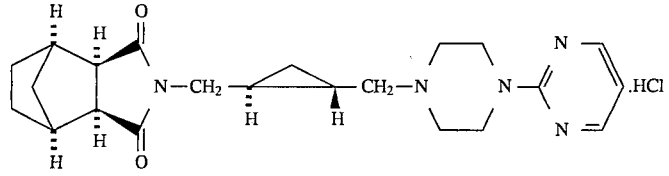
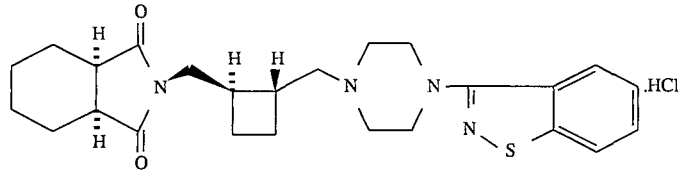
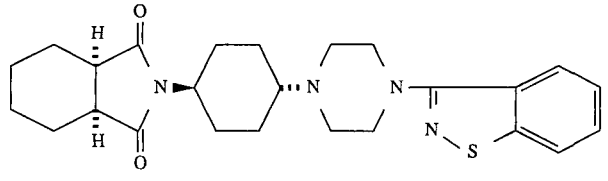
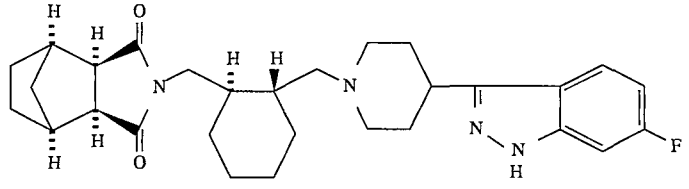
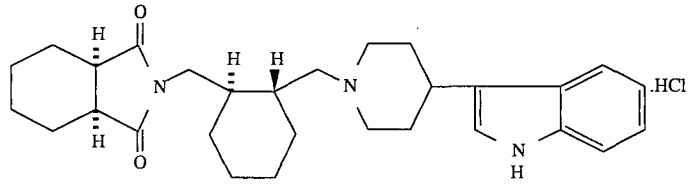
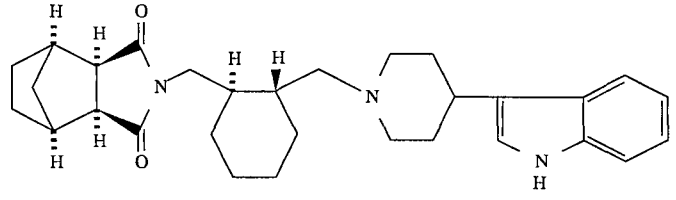
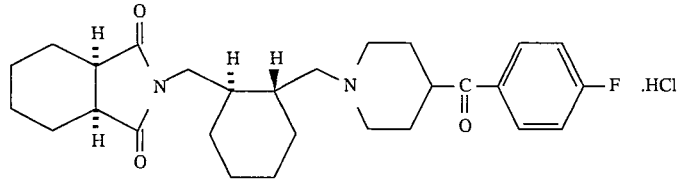
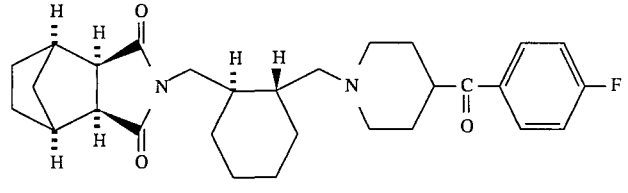
Example No.	Starting Compound No.	Objective Compound No.	Structure
59	225 + 265	163	
60	253 + 204	164	
61	253 + 205	165	
62	251 + 3 + 268	166	
63	253 + 3 + 269	167	
64	251 + 3 + 269	168	
65	253 + 3 + 267	169	
66	251 + 3 + 267	170	

TABLE 9-continued

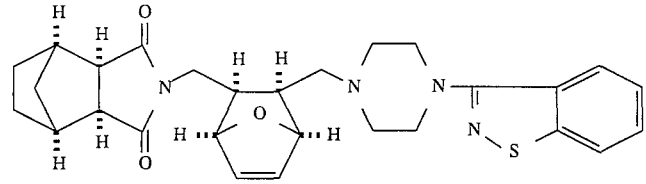
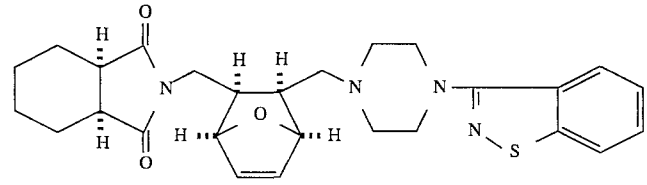
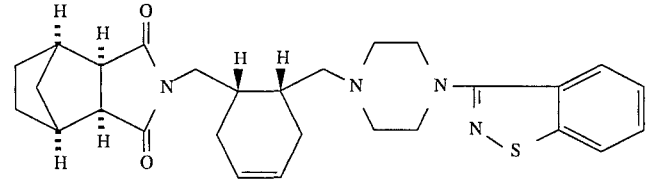
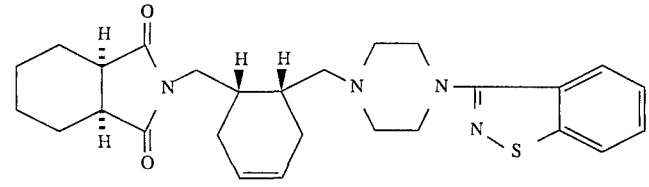
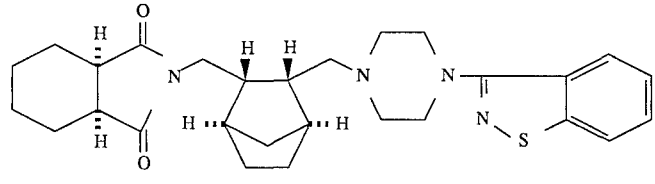
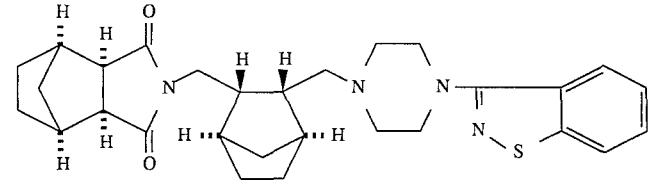
Example No.	Starting Compound No.	Objective Compound No.	Structure
67	251 + 224	171	
68	253 + 224	172	
69	251 + 223	173	
70	253 + 223	174	
71	253 + 228	175	
72	251 + 228	176	

TABLE 10

Example No.	Compound No.	Melting point (°C.)	^{1}H-NMR ($CDCl_3$) δ (free form)
8	112	140	
9	113	145–150	
10	114	230	
11	115	107–110	0.92–1.9(10H, m), 2.19–2.26(3H, m), 2.58–2.64(7H, m), 3.07(2H, t, J=3Hz), 3.32(1H, dd, J=13 and 10 Hz), 3.52(4H, t, J=4Hz), 3.91(1H, dd, J=13 and 4Hz), 5.90(2H, t, J=3Hz), 7.32–7.49(2H, m), 7.78–7.92

TABLE 10-continued

Example No.	Compound No.	Melting point (°C.)	^{1}H-NMR ($CDCl_3$) δ (free form)
			(2H, m).
12	116	231–233	1.03–1.91(16H, m), 2.24(1H, dd, J=12 and 7Hz), 2.60–2.76(7H, m), 3.07(2H, t, J=2Hz), 3.32(1H, dd, J=13 and 10Hz), 3.52(4H, t, J=5Hz), 3.95(2H, dd, J=13 and 4Hz), 7.32–7.49 (2H, m), 7.78–7.92(2H, m).
13	117	212–214	0.96–1.9(18H, m), 2.24(1H, dd, J=12 and 7Hz), 2.53–

TABLE 10-continued

Example No.	Compound No.	Melting point (°C.)	^{1}H-NMR ($CDCl_3$) δ (free form)
			2.65(9H, m), 3.53(4H, t, J=5Hz), 3.77(1H, dd, J=13 and 10Hz), 4.07(1H, dd, J=13 and 4Hz), 7.32–7.49(2H, m), 7.78–7.92(2H, m).
14	118	124–125	0.85–1.9(16H, m), 2.23(1H, dd, J=12 and 7Hz), 2.44–2.66(9H, m), 3.52(4H, t, J=5Hz), 3.78(1H, dd, J=13 and 10Hz), 4.10(1H, dd, J=13 and 4Hz), 7.32–7.49(2H, m), 7.78–7.92(2H, m).
15	119	217–219	0.9–1.9(14H, m), 2.24(1H, m), 2.63(5H, brs), 2.86(2H, s), 3.32(1H, dd, J=13 and 10Hz), 3.52(4H, brs), 3.90 (1H, brd, J=9Hz), 4.87 (2H, s), 7.32–7.48(2H, m), 7.78–7.92(2H, m).
16	120	118–120	1.9–2.0(20H, m), 2.1–2.3 (3H, m). 2.4–2.5(1H, m), 2.5–2.8(5H, m), 2.96(1H, d, J=18Hz), 3.32(1H, dd, J=10 and 13Hz), 3.5–3.6(4H, m), 3.88–3.94(1H, m), 7.32–7.49(2H, m), 7.79–7.92(2H, m).
17	121	173–174	1.15(6H, s), 1.0–2.0(18H, m), 2.2–2.3(1H, m), 2.5–2.7(5H, m), 3.3(1H, t, J=11Hz), 3.5–3.6(4H, m), 3.8 (1H, d, J=13Hz), 7.33–7.49(2H, m), 7.79–7.93(2H, m).
18	122	146–147	0.8–1.8(14H, m), 1.8–1.9 (1H, m), 2.2–2.3(1H, m), 2.5–2.7(4H, m), 2.85(2H, m), 3.1–3.2(2H, m), 3.25 (1H, dd, J=10 and 13Hz), 3.45–3.6(4H, m), 3.85(1H, dd, J=3 and 13Hz), 6.14–6.2(2H, m), 7.33–7.49(2H, m), 7.79–7.92(2H, m).
19	123	157–158	1.0–1.8(17H, m), 1.9–2.0 (1H, m), 2.1–2.2(2H, m), 2.25(1H, dd, J=7 and 13Hz), 2.6–2.7(5H, m), 2.8(2H, s), 3.38(1H, dd, J=10 and 13Hz), 3.5–3.6(4H, m), 4.0 (1H, dd, J=3 and 13Hz), 7.32–7.49(2H, m), 7.79–7.93(2H, m).
20	124	160–162	1.0–2.0(10H, m), 2.29(1H, dd, J=13 and 7Hz), 3.48–3.54(5H, m), 4.16(1H, dd, J=13 and 4Hz), 7.33–7.49 (2H, m), 7.70–7.94(6H, m).
21	125	183–184	0.8–1.8(13H, m), 1.9–2.0 (1H, m), 2.2–2.4(5H, m), 2.6–2.7(4H, m), 3.3(1H, dd, J=10 and 13Hz), 3.5–3.6(4H, m), 3.89–3.93(1H, m), 7.32–7.49(2H, m), 7.79–7.93(2H, m).
22	126	235–236	1.1–1.7(12H, m), 1.8–2.1 (4H, m), 2.3–2.75(10H, m), 3.35–3.6(6H, m), 7.32–7.49 (2H, m), 7.80(1H, d, J=8Hz), 7.91(1H, d, J=8Hz).
23	127	107–110	0.8–2.0(22H, m), 2.07(1H, dd, J=7 and 13Hz), 2.46(1H, dd, J=6 and 13Hz), 2.58(2H, s), 2.67(2H, brs), 2.75–3.0 (3H, m), 3.25(1H, dd, J=10 and 13Hz), 3.84(1H, dd, J=4 and 13Hz), 6.9–7.1(2H, m), 7.3–7.5(2H, m).
24	128	169–171	0.8–2.0(22H, m), 2.07(1H, dd, J=7 and 12Hz), 2.45(1H, dd, J=7 and 12Hz), 2.7–3.0 (7H, m), 3.26(1H, dd, J=10 and 13Hz), 3.84(1H, dd, J=4 and 14Hz), 6.95–7.02(2H, m), 7.36–7.43(2H, m).
25	129	115–117	0.8–2.0(20H, m), 2.0–2.3 (3H, m), 2.51(1H, dd, J=6 and 12Hz), 2.59(2H, s), 2.70 (4H, brs), 3.28(1H, dd, J=10 and 13Hz), 3.88(1H, dd, J=4 and 13Hz), 4.17(1H, m), 6.8–7.0(4H, m).
26	130	145–148	0.8–2.0(22H, m), 2.0–2.3 (3H, m), 2.51(1H, dd, J=6 and 12Hz), 2.6–2.9(4H, m), 3.31(1H, dd, J=10 and 13Hz), 3.89(1H, dd, J=4 and 13Hz), 4.17(1H, m), 6.75–7.0 (4H, m).
27	131	121–123	0.9–1.8(15H, m), 1.8–1.95 (1H, m), 1.95–2.15(6H, m), 2.17(1H, dd, J=7 and 13Hz), 2.56(1H, dd, J=6 and 12Hz), 2.60(2H, s), 2.70(2H, s), 2.9–3.1(3H, m), 3.30(1H, dd, J=10 and 13Hz), 3.91 (1H, dd, J=4 and 13Hz), 7.04 (1H, dt, J=2 and 9Hz), 7.23 (1H, dd, J=2 and 9Hz), 7.68 (1H, dd, J=5 and 8Hz).
28	132	104–107	0.9–2.0(18H, m), 2.0–2.2 (6H, m), 2.17(1H, dd, J=7 and 13Hz), 2.56(1H, dd, J=6 and 13Hz), 2.8–2.9(2H, m), 2.95–3.1(3H, m), 3.33 (1H, dd, J=10 and 14Hz), 3.92(1H, dd, J=4 and 13Hz), 7.05(1H, dt, J=2 and 9Hz), 7.23(1H, dd, J=3 and 9Hz), 7.68(1H, m).
29	133	161–163	0.9–1.75(15H, m), 1.8–1.95 (1H, m), 2.18(1H, dd, J=7 and 13Hz), 2.4–2.65(7H, m), 2.69(1H, brs), 3.29(1H, dd, J=10 and 13Hz), 3.50(4H, t, 5Hz), 3.90(1H, dd, J=4 and 13Hz), 6.55–6.7(2H, m), 7.46(1H, m), 8.17(1H, m).
30	134	106–108.5	0.9–2.0(18H, m), 2.18(1H, dd, J=7 and 13Hz), 2.4–2.6 (5H, m), 2.75–2.9(2H, m), 3.32(1H, dd, J=10 and 13Hz), 3.50(4H, t, J=5Hz), 3.90(1H, dd, J=4 and 13Hz), 6.55–6.7(2H, m), 7.45(1H, m), 8.17(1H, m).
31	135	145–147	0.9–1.75(15H, m), 1.8–1.95 (1H, m), 2.16(1H, dd, J=7 and 13Hz), 2.35–2.65(7H, m), 2.70(2H, brs), 3.30(1H, dd, J=10 and 13Hz), 3.78 (4H, t, J=5Hz), 3.88(1H, dd, J=4 and 13Hz), 6.46(1H, t, J=5Hz), 8.29(2H, d, J=5Hz).
32	136	92–94	0.9–2.0(18H, m), 2.17(1H, dd, J=7 and 12Hz), 2.35–2.55(4H, m), 2.54(1H, dd, J=6 and 13Hz), 2.75–2.9 (2H, m), 3.32(1H, dd, J=10 and 13Hz), 3.79(4H, t, J=5Hz), 3.89(1H, dd, J=4 and 14Hz), 6.44(1H, t, J=5Hz), 8.29(2H, d, J=5Hz).

TABLE 10-continued

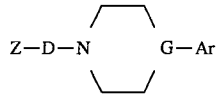
Example No.	Compound No.	Melting point (°C.)	^{1}H-NMR ($CDCl_3$) δ (free form)
33	137	134–136.5	0.9–1.8(15H, m), 1.8–1.95 (1H, m), 2.18(1H, dd, J=7 and 12Hz), 2.45–2.65 (7H, m), 2.70(2H, brs), 3.16(4H, m), 3.29(2H, dd, J=10 and 13Hz), 3.89(1H, dd, J=4 and 13Hz), 6.7–6.9(3H, m), 7.15(1H, m).
34	138	89–91.5	0.9–2.0(18H, m), 2.19(1H, dd, J=7 and 13Hz), 2.45–2.65(5H, m), 2.84(2H, m), 3.16(4H, m), 3.32(1H, dd, J=10 and 13Hz), 3.9(1H, dd, J=7 and 13Hz), 6.7–6.9 (3H, m), 7.15(1H, m).
35	139	185–186	0.9–1.75(15H, m), 1.75–1.95(1H, m), 2.21(1H, dd, J=7 and 13Hz), 2.5–2.75(9H, m), 3.14(4H, m), 3.30(1H, dd, J=10 and 13Hz), 3.91(1H, dd, J=4 and 13Hz), 6.68(1H, m), 6.99(1H, dd, J=2 and 9Hz), 7.08(1H, d, J=2Hz), 7.38(1H, d, J=9Hz), 7.56 (1H, d, J=2Hz).
36	140	147.5–149	0.9–2.0(18H, m), 2.22(1H, dd, J=7 and 13Hz), 2.5–2.7(5H, m), 2.84(2H, m), 3.14 (4H, m), 3.33(1H, dd, J=10 and 13Hz), 3.92(1H, dd, J=4 and 13Hz), 6.68(1H, m), 6.99 (1H, dd, J=3 and 9Hz), 7.09 (1H, d, J=2Hz), 7.38(1H, d, J=9Hz), 7.56(1H, d, J=2Hz).
37	141	106–107	1.0–1.8(16H, m), 1.9–2.0 (1H, m), 2.27(1H, dd, J=6 and 13Hz), 2.5–2.8(8H, m), 3.0–3.2(4H, m), 3.3(1H, dd, J=10 and 13Hz), 3.94(1H, dd, J=4 and 13Hz), 7.07(1H, d, J=7Hz), 7.36–7.55(4H, m), 7.8–7.9(1H, m), 8.18–8.21(1H, m).
38	142	100–101.5	1.0–2.0(19H, m), 2.26(1H, dd, J=7 and 12Hz), 2.6–2.9 (6H, m), 3.0–3.2(4H, m), 3.36(1H, dd, J=10 and 13Hz), 3.95(1H, dd, J=4 and 13Hz), 7.07(1H, d, J=7Hz), 7.36–7.55(4H, m), 7.8–7.83 (1H, m), 8.18–8.21(1H, m).
39	143	106–107	1.0–1.7(14H, m), 1.8–1.9 (1H, m), 2.12(1H, dd, J=7 and 13Hz), 2.3–2.6(10H, m), 2.59(2H, s), 2.69(2H, s), 3.29(1H, dd, J=10 and 13Hz), 3.86(1H, dd, J=3 and 13Hz), 6.9–7.1(8H, m).
40	144	100–101.5	1.0–2.0(18H, m), 2.13(1H, dd, J=7 and 13Hz), 2.3–2.6 (9H, m), 2.8–2.9(2H, m), 3.31(1H, dd, J=4 and 10Hz), 3.87(1H, dd, J=4 and 13Hz), 6.93–7.07(8H, m).
41	145	79–80	0.9–1.7(16H, m), 1.8–1.9 (1H, m), 2.21–2.29(1H, m), 2.5–2.75(8H, m), 2.9–3.1 (4H, m), 3.2–3.3(1H, m), 3.86(3H, s), 3.9–4.0(1H, m), 6.8–7.0(4H, m).
42	146	78–79	0.9–2.0(18H, m), 2.21(1H, dd, J=12 and 7Hz), 2.5–2.6(5H, m), 2.7–2.8(2H, m), 2.9–3.1(4H, m), 3.32 (1H, dd, J=13 and 10Hz), 3.86(3H, s), 3.9–4.0(1H, m), 6.8–7.0(4H, m).
43	147	187–188	1.0–1.75(15H, m), 1.8–2.0 (1H, m), 2.21(1H, dd, J=12 and 7Hz), 2.5–2.8(9H, m), 3.31(1H, dd, J=13 and 10Hz), 3.45–3.65(4H, m), 3.92 (1H, dd, J=13 and 4Hz), 6.75 (1H, s), 7.22–7.28(1H, m), 7.46–7.59(2H, m), 7.77(1H, d, J=8Hz), 8.93(1H, s).
44	148	139–140	0.9–2.0(18H, m), 2.2(1H, dd, J=12 and 7Hz), 2.5–2.7 (5H, m), 2.8–2.95(2H, m), 3.3(1H, dd, J=13 and 10Hz), 3.45–3.65(4H, m), 3.93(1H, dd, J=9 and 4Hz), 6.75(1H, s), 7.22–7.28(1H, m), 7.46–7.6(2H, m), 7.78(1H, d, J=8Hz), 8.93(1H, s).
45	149	268–270	1.0–2.0(16H, m), 2.27(1H, dd, J=12 and 7Hz), 2.6–2.9(9H, m), 3.3–3.5(5H, m), 3.94(1H, dd, J=13 and 4Hz), 7.11–7.15(1H, m), 7.3–7.5 (3H, m), 8.1(1H, d, J=8Hz), 8.87–8.89(1H, m).
46	150	108–109	1.0–2.0(18H, m), 2.28(1H, dd, J=7 and 12Hz), 2.6–2.9 (7H, m), 3.3–3.5(5H, m), 3.95(1H, dd, J=13.5 and 4Hz), 7.11–7.15(1H, m), 7.34–7.47(3H, m), 8.1(1H, dd, J=8 and 2Hz), 8.87(1H, dd, J=4 and 2Hz).
47	151	94–97	1.1–2.0(14H, m), 2.3–2.4 (2H, m), 2.5–2.71(8H, m), 3.42(1H, dd, J=13 and 9Hz), 3.54(4H, t, J=5Hz), 3.35 (1H, dd, J=5 and 13Hz), 7.32–7.49(2H, m), 7.81(1H, d, J=8Hz), 7.91(1H, d, J=8Hz).
48	152	91–93	1.28–2.1(16H, m), 2.35(2H, m), 2.6–2.71(4H, m), 2.8–2.9(2H, m), 3.44(1H, dd, J=13 and 9Hz), 3.54(4H, t, J=5Hz), 3.66(1H, dd, J=13 and 6Hz), 7.32–7.49(2H, m), 7.78–7.93(2H, m).
49	153	195–197	1.0–1.75(13H, m), 1.8–2.05 (3H, m), 2.15(1H, brs), 2.2–2.5(2H, m), 2.5–2.8(7H, m), 3.3–3.65(5H, m), 3.83(1H, dd, J=3 and 13Hz), 7.30–7.50(2H, m), 7.8(1H, d, J=8Hz), 7.91(1H, d, J=8Hz).
50	154	164–167	1.0–1.25(3H, m), 1.3–2.1 (14H, m), 2.16(1H, brs), 2.2–2.45(2H, m), 2.55–2.75 (4H, m), 2.75–2.95(2H, m), 3.35–3.65(5H, m), 3.84(1H, dd, J=4 and 13Hz), 7.3–7.5 (2H, m), 7.8(1H, d, J=8Hz), 7.91(1H, d, J=8Hz).
51	155	136–138	0.9–1.75(15H, m), 1.8–1.95 (1H, m), 2.23(1H, dd, J=7 and 12Hz), 2.5–2.8(9H, m), 3.2–3.4(5H, m), 3.92(1H, dd, J=4 and 13Hz), 6.7–6.8 (2H, m), 7.05–7.25(2H, m), 7.60(1H, d, J=2Hz).
52	156	120–123	0.9–2.0(18H, m), 2.24(1H, dd, J=7 and 13Hz), 2.5–2.75(5H, m), 2.75–2.95(2H, m), 3.2–3.4(5H, m), 3.93

TABLE 10-continued

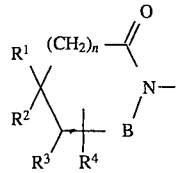
Example No.	Compound No.	Melting point (°C.)	^{1}H-NMR ($CDCl_3$) δ (free form)
			(1H, dd, J=4 and 13Hz), 6.7–6.8(2H, m), 7.05–7.25 (2H, m), 7.60(1H, d, J=2Hz).
53	157		1.0(1H, m), 1.3–1.9(15H, m), 2.10(1H, m), 2.30(2H, brs), 2.80(2H, m), 2.65(4H, brs), 3.55(4H, brs), 4.00 (1H, m), 7.33–7.49(2H, m), 7.80(1H, d, J=8Hz), 7.90 (1H, d, J=8Hz).
54	158		0.95(1H, m), 1.3–1.9(15H, m), 2.10(1H, m), 2.20(2H, brs), 2.45(4H, brs), 2.80 (2H, m), 3.80(4H, brs), 4.00 (1H, m), 6.48(1H, t, J=4.6Hz), 8.35(2H, d, J=4.6Hz).
55	159	92	
56	160	107	
57	161	190–192	
58	162	238	
59	163	252	
60	164	141–143	1.4–2.1(12H, m), 2.30–2.51 (4H, m), 2.62(4H, t, J=5Hz), 2.8–2.9(2H, brs), 3.51–3.60(6H, m), 7.31–7.48(2H, m), 7.79(1H, d, J=8.3Hz), 7.90(1H, d, J=8.3Hz).
61	165	212–213	1.25–1.95(14H, m), 2.05–2.35(3H, m), 2.5–2.85(8H, m), 3.55–3.7(4H, m), 3.9–4.1(1H, m), 7.32–7.49(2H, m), 7.81(1H, d, J=8Hz), 7.93(1H, d, J=8Hz).
62	166	143–145	0.9–2.2(23H, m), 2.5–2.6 (1H, m), 2.6(2H, s), 2.7(2H, s), 2.9–3.1(3H, m), 3.3(1H, dd, J=13 and 10Hz), 4.0(1H, dd, J=13 and 4Hz), 6.85–6.93(1H, m), 7.07(1H, dd, J=2 and 9Hz), 7.7(1H, dd, J=5 and 8Hz), 9.79(1H, brs).
63	167	215–216	1.0–2.2(28H, m), 2.5–2.6 (1H, m), 2.7–3.1(5H, m), 3.34(1H, dd, J=13 and 10Hz), 3.9(1H, dd, J=13 and 4Hz), 6.95(1H, d, J=1Hz), 7.06–7.21(2H, m), 7.36(1H, d, J=8Hz), 7.64(1H, d, J=8Hz), 7.97(1H, brs).
64	168	180–181	0.9–2.2(24H, m), 2.52–2.58 (1H, m), 2.59(2H, s), 2.7(2H, s), 2.75–2.85(1H, m), 2.9–3.1(2H, m), 3.31(1H, dd, J=10 and 13Hz), 3.9(1H, dd, J=4 and 13Hz), 6.94(1H, d, J=1Hz), 7.06–7.2(2H, m), 7.34 (1H, d, J=8Hz), 8.0(1H, brs).
65	169	209–210	0.9–2.2(25H, m), 2.5–2.6 (1H, m), 2.8–3.4(6H, m), 3.9–4.0(1H, m), 7.1–7.17 (2H, m), 7.94–7.99(2H, m).
66	170	129–130	0.9–2.2(21H, m), 2.45–2.6 (1H, m), 2.6(2H, s), 2.7(2H, s), 2.9–3.35(4H, m), 3.85–3.95(1H, m), 7.17–7.17(2H, m), 7.94–7.99(2H, m).
67	171	186–187	1.0–1.4(4H, m), 1.65–1.75 (2H, m), 1.9–2.0(2H, m), 2.5–2.6(2H, m), 2.6–2.8 (8H, m), 3.5–3.65(5H, m), 3.83(1H, d, J=12Hz), 3.8–3.9(1H, m), 4.62(1H, brs), 4.90(1H, brs), 6.22(1H, dd, J=1.6 and 6Hz), 6.38(1H, dd, J=1.6 and 6Hz), 7.33–7.50(2H, m), 7.81(1H, d, J=8Hz), 7.91(1H, d, J=8Hz).
68	172	124–125	1.3–2.0(10H, m), 2.5–2.6 (2H, m), 2.6–2.8(4H, m), 2.8–3.0(2H, m), 3.5–3.7 (5H, m), 3.86(1H, d, J=14Hz), 4.63(1H, brs), 4.9(1H, brs), 6.22(1H, dd, J=1.7 and 6Hz), 6.38(1H, brd, J=6Hz), 7.33–7.50(2H, m), 7.82(1H, d, J=8Hz), 7.92 (1H, d, J=8Hz).
69	173	119–120	1.1–1.75(6H, m), 1.8–2.2 (6H, m), 2.3–2.8(10H, m), 3.4–3.65(6H, m), 5.6–5.7 (2H, m), 7.33–7.49(2H, m), 7.81(1H, d, J=8Hz), 7.92 (1H, d, J=8Hz).
70	174	89–90	1.35–2.25(14H, m), 2.3–2.9 (8H, m), 3.4–3.7(6H, m), 5.5–5.7(2H, m), 7.33–7.49 (2H, m), 7.81(1H, d, J=8Hz), 7.92(1H, d, J=8Hz).
71	175	149–151	1.2–1.9(16H, m), 2.2–2.45 (4H, m), 2.55–2.7(4H, m), 2.8–2.9(2H, m), 3.5–3.8 (6H, m), 7.32–7.49(2H, m), 7.80(1H, d, J=8Hz), 7.91 (1H, d, J=8Hz).
72	176	189–191	1.1–1.9(4H, m), 2.2–2.7 (12H, m), 3.5–3.8(6H, m), 7.33–7.49(2H, m), 7.8(1H, d, J=8Hz), 7.91(1H, d, J=8Hz).

What is claimed is:

1. An imide compound of the formula:

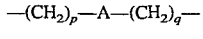


wherein Z is a group of the formula:



in which B is a carbonyl group or a sulfonyl group, R^1, R^2, R^3 and R^4 are each a hydrogen atom or an alkyl group having 1–4 carbon atoms with a proviso that R^1 and R^2 or R^1 and R^3 are combined together to make a non-aromatic hydrocarbon ring having at most 7 carbon atoms and being un-substituted or substituted with at least one alkyl group having 1–4 carbon atoms, and n is an integer of 0 or 1;

D is a group of the formula:



in which A is a non-aromatic hydrocarbon ring having at most 7 carbon atoms or a non-aromatic hydrocarbon ring having at most 7 carbon atoms which is bridged with an alkylene group having not more than 3 carbon atoms or an oxygen atom, and p and q are each an integer of 0, 1 or 2;

Ar is a benzisothiazolyl group being unsubstituted or substituted with at least one of an alkyl group having 1–4 carbon atoms, an alkoxy group having 1–4 carbon atoms and a halogen atom; and G is >N—; or an acid addition salt thereof.

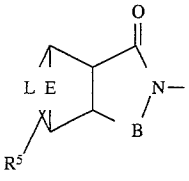
2. The imide compound according to claim **1**, wherein said non-aromatic hydrocarbon ring in Z is further bridged with an alkylene group having 1–3 carbon atoms and being un-substituted or substituted with at least one alkyl group having 1–4 carbon atoms, or an oxygen atom; or an acid addition salt thereof.

3. The imide compound according to claim **1**, wherein said non-aromatic hydrocarbon ring in D is further bridged with an alkylene group having 1–3 carbon atoms and being unsubstituted or substituted with at least one alkyl group having 1–4 carbon atoms, or an oxygen atom; or an acid addition salt thereof.

4. The imide compound according to claim **1**, wherein said non-aromatic hydrocarbon rings in Z and D are further bridged with an alkylene group having 1–3 carbon atoms and being unsubstituted or substituted with at least one alkyl group having 1–4 carbon atoms, or an oxygen atom; or an acid addition salt thereof.

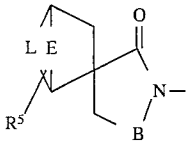
5. The imide compound according to claim **1**, wherein Z is one of the following formulas:

(Z-1)



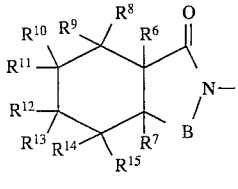
wherein L is $—CH_2—CH_2—$ or —CH=CH—, E is an alkylene group having not more than 3 carbon atoms and being un-substituted or substituted with an alkyl group having not more than 4 carbon atoms or an oxygen atom, R^5 is a hydrogen atom or an alkyl group having not more than 4 carbon atoms and B is a carbonyl group or a sulfonyl group;

(Z-2)



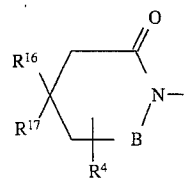
wherein L, E, R^5 and B are each as defined above;

(Z-3)



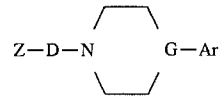
wherein R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are each a hydrogen atom or an alkyl group having not more than 4 carbon atoms, or two of those present at the neighboring positions each other may be combined together to make a bond and B is as defined above; and

(Z-4)



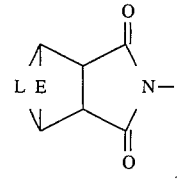
wherein R^4 is a hydrogen atom or an alkyl group having not more than 4 carbon atoms, R^{16} and R^{17} are combined together to make a saturated hydrocarbon ring having not more than 7 carbon atoms, and B is as defined above; or an acid addition salt thereof.

6. An imide compound of the formula:



wherein

Z is a group of the formula:



wherein L is $—CH_2—CH_2—$ or —CH=CH—, E is an alkylene group having not more than 3 carbon atoms;

D is a group of the formula:

$$—(CH_2)_p—A—(CH_2)_q—$$

wherein A is a cycloalkane ring having not more than 7 carbon atoms or a cycloalkane ring having not more than 7 carbon atoms which is bridged with an alkylene group having not more than 3 carbon atoms, or an oxygen atom, p and q are each an integer of 0, 1 or 2;

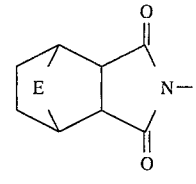
Ar is a benzisothiazolyl group; and

G is >N—

or an acid addition salt thereof.

7. The imide compound according to claim **7**, wherein said cycloalkane ring in D is further bridged with an alkylene group having 1–3 carbon atoms; or an acid addition salt thereof.

8. The imide compound according to claim **7** or **8**, wherein Z is a group of the formula:



wherein E is a methylene group or an ethylene group; or an acid addition salt thereof.

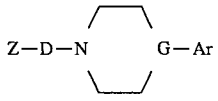
9. The imide compound according to claim **7** or **8**, wherein D is a group of the formula:

$$—CH_2—A—CH_2—$$

wherein A is as defined above; or an acid addition salt thereof.

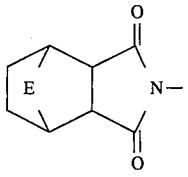
10. The imide compound according to claim **10**, wherein A is a cyclohexane ring; or an acid addition salt thereof.

11. The imide compound of the formula:



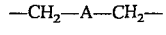
wherein

Z is a group of the formula:



wherein E is a methylene group or an ethylene group;

D is a group of the formula:



wherein A is a cycloalkane ring having not more than 7 carbon atoms or a cycloalkane ring having not more than 7 carbon atoms which is bridged with an alkylene group having not more than 3 carbon atoms, or an oxygen atom;

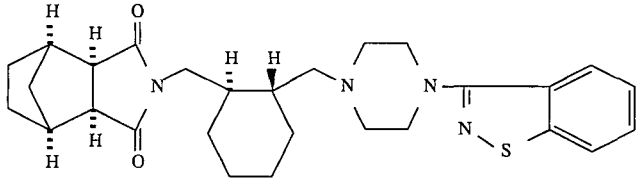
Ar is a benzisothiazolyl group; and

G is >N—; or an acid addition salt thereof.

12. The imide compound according to claim **14**, wherein E is a methylene group; or an acid addition salt thereof.

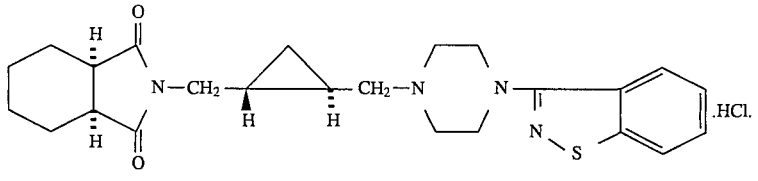
13. The imide compound according to claim **14** or **15**, wherein A is a 1,2-cyclohexane-diyl group; or an acid addition salt thereof.

14. The imide compound of the formula:

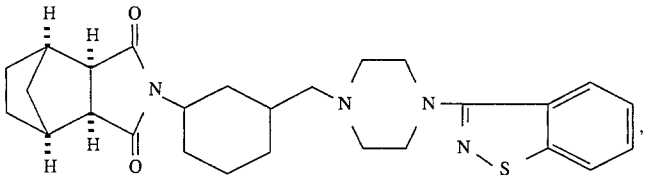


or an acid addition salt thereof.

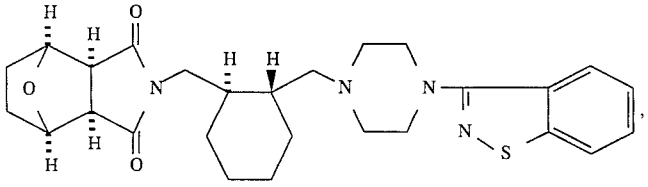
15. The imide compound of the formula:



16. The imide compound of one of the following formulae:

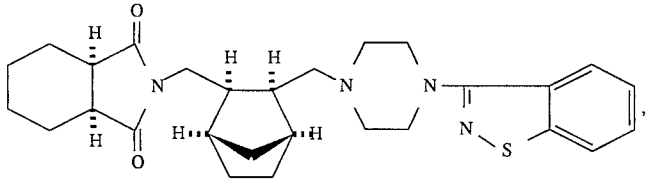


17. The imide compound of the formula:



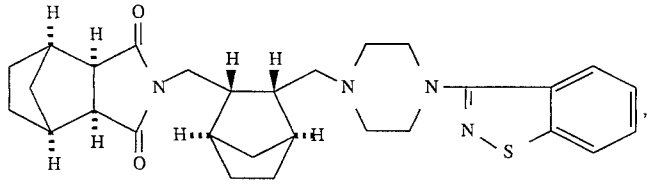
or an acid addition salt thereof.

18. The imide compound of the formula:



or an acid additional salt thereof.

19. The imide compound of the formula:



or an acid addition salt thereof.

20. The imide compound according to claim **1**, wherein said non-aromatic hydrocarbon ring and said alkylene group in the definition of A are each substituted with at least one alkyl group having 1–4 carbon atoms.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,532,372
APPLICATION NO. : 08/113320
DATED : July 2, 1996
INVENTOR(S) : Ikutaro Saji et al.

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

Col. 62 Line 45-49 in Claim 7, the line reading "The imide compound according to claim 7, wherein" should read --The imide compound according to claim 6, wherein--.

Col. 62 Line 49-50 in Claim 8, the line reading "The imide compound according to claim 7 or 8," should read --The imide compound according to claim 6 or 7,--.

Col. 62 Line 61-62 in Claim 9, the line reading "The imide compound according to claim 7 or 8," should read --The imide compound according to claim 6 or 7,--.

Col. 63 Line 1-2 in Claim 10, the line reading "The imide compound according to claim 10, wherein" should read --The imide compound according to claim 9, wherein--.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,532,372
APPLICATION NO. : 08/113320
DATED : July 2, 1996
INVENTOR(S) : Ikutaro Saji et al.

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

Col. 63 Line 31-32 in Claim 12, the line reading "The imide compound according to claim 14, wherein" should read --The imide compound according to claim 11, wherein--.

Col. 63 Line 34-35 in Claim 13, the line reading "The imide compound according to claim 14 or 15," should read --The imide compound according to claim 11 or 12,--.

Signed and Sealed this

Twenty-fourth Day of November, 2009

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office