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United States Patent [19][11] **Patent Number:** **5,532,372****Saji et al.**[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.

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**

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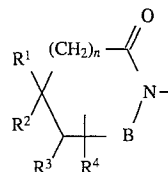
ABSTRACT

An imide compound of the formula:



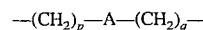
wherein

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:



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 antipsychotic 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-psychotic 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-psychotic 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 antipsychotic 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 |
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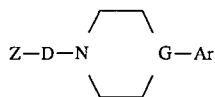
These conventional imide compounds are characteristic in that the imide portion and the piperazine or piperidine ring are bonded together with intervention of a straight alkylene

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

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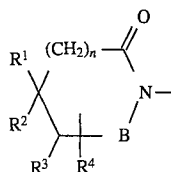
hydrocarbon ring has never been known. The present invention is based on the above findings.

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



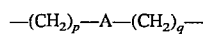
wherein

Z is a group of the formula:



in which B is a carbonyl group or a sulfonyl group R¹, R², R³ and R⁴ are each a hydrogen atom or a lower alkyl group, or R¹ and R² or R¹ and R³ may be combined together to make a non-aromatic hydrocarbon ring or R¹ and R³ 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:



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 biphenylmethylenidene 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

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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. —(CH₂)_p— and —(CH₂)_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, imidazothiofenyl, imidazofuryl, etc.

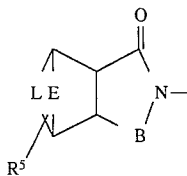
The present invention covers the acid addition salt formed between the imide compound (I) and an organic or inorganic acid. Examples of the inorganic acid are hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, etc., and examples of the organic acid are acetic acid, oxalic acid, citric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

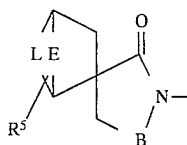
Among various groups represented by the symbol Ar, preferred are a bicyclic heterocyclic aromatic group, a naphthyl group, a benzoyl group, a phenoxy group, a phenylthio group, a biphenylmethylenidene group, etc., these groups being optionally substituted with at least one of lower alkyl, lower alkoxy 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

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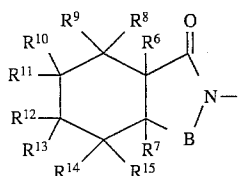
Preferred examples of the group represented by the symbol Z are those of the following formulas:



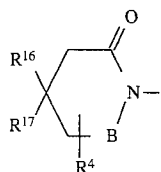
wherein L is $-\text{CH}_2-\text{CH}_2-$ or $-\text{CH}=\text{CH}-$, E is a lower alkylene group optionally substituted with lower alkyl or an oxygen atom, R^5 is a hydrogen atom or a lower alkyl group and B is a carbonyl group or a sulfonyl group,



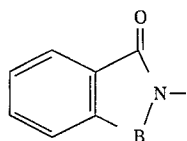
wherein L, E, R^5 and B are each as defined above,



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;

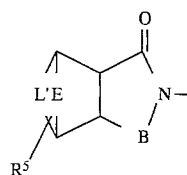


wherein R^{16} and R^{17} are each a hydrogen atom or a lower alkyl group, or they may be taken together to make a saturated hydrocarbon ring, preferably a cycloalkane ring having not more than 7 carbon atoms (e.g. cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane) and R^4 and B are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



wherein B is as defined above.

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

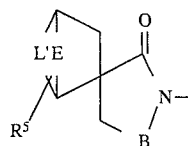


wherein L' is $-\text{CH}_2-\text{CH}_2-$ and E, R^5 and B are each as

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(Z-1)

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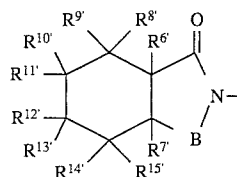


(Z-2)

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

(Z-3)

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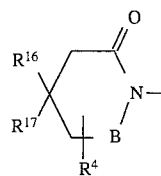
(Z-3)

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)

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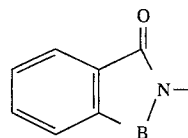


(Z-4)

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

(Z-5)

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(Z-5)

(Z-4)

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wherein B is as defined above.

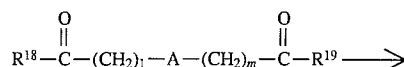
The imide compounds (I) of the invention are obtainable by various procedures, of which typical examples are as shown below.

Procedure (a):—

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

(II)

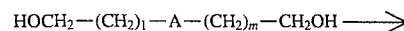
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(II)

(Z-5)

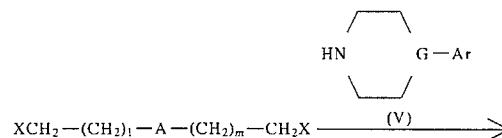
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(III)

(IV)

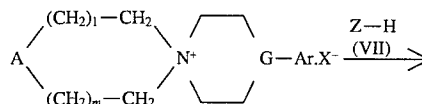
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(IV)

(Z-1')

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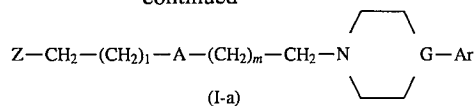


(VI)

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-continued



wherein A, G, Ar and Z are each as defined above and R¹⁸ and R¹⁹ 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. LiAlH₄, H₄, NaBH₄, Ca(BH₄)₂, LiAlH₂(OCH₂CH₂OCH₃)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-toluene-sulfonyl 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.

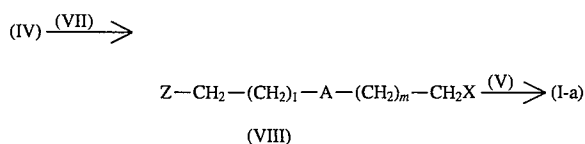
The compound (IV) is then reacted with the compound (V) to give the compound (VI). The reaction may be carried out in the presence of a base (e.g. potassium carbonate, sodium carbonate) in a solvent such as alcohol (e.g. methanol, ethanol, propanol, 2-propanol, butanol), acetonitrile or dimethylformamide 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 the 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)

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Procedure (b):—

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



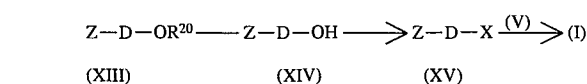
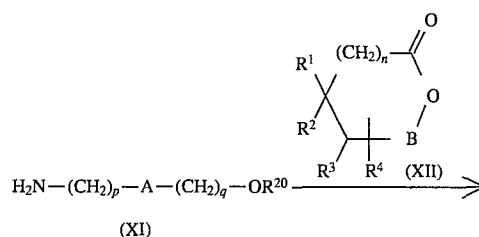
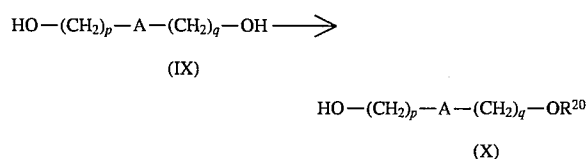
wherein X, A, Z, 1 and m are each as defined above.

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:



wherein R¹, R², R³, R⁴, n, p, q, D, A, B, X and Z are each as defined above and R²⁰ 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)

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