

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES**

202012
Bogotá, D.C., 09/sep/2010

Apoderado: James Ian Raisbeck

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-039668- -00005-0000

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Act. 519 TRASLADOINFORME Folios: 1

ASUNTO

Radicación 07-39668

Trámite 002

Evento 001

Actuación 430

Oficio

Folios

12005

Patente de Invención



Vía PCT (fase nacional)



Cap.I



Cap. II



No. Sol. Internacional

PCT/US2005/034015

Fecha de Presentación Internal.

WO2006/034414

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

1.1. Descripción: Folios: 179 a 469 Como se radicó inicialmente

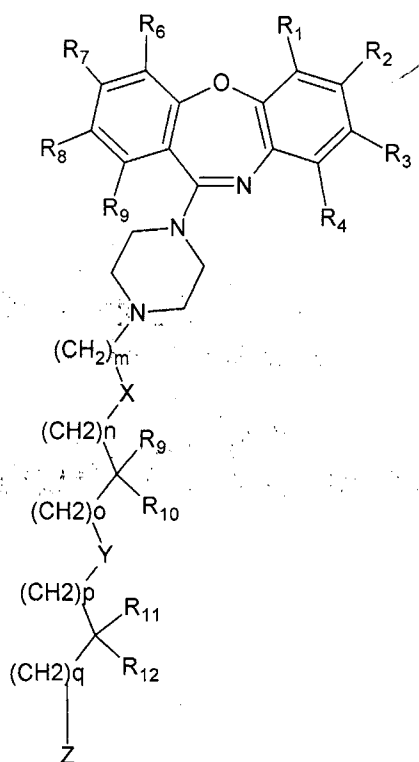
1.2. Reivindicaciones: Folios 470 a 485 Como se radicó inicialmente

1.3. Prioridad: Folio 1: 60/611.849; 21/sep/2004

2. Objeto de la invención

Título de la solicitud: ANALOGOS DE LOXAPINA Y MÉTODOS DE USO DE LOS MISMOS.

El objeto de la invención son los derivados 11-(piperazin-1-il)dibenzo[b,f][1,4]oxazepina de la fórmula:



- Reivindicaciones 1-22, 56-62: Procedimiento de tratamiento que consiste en administrar un compuesto a un paciente.
- Reivindicaciones 23-47: Un compuesto de la fórmula (I).
- Reivindicaciones 48-55: Composiciones que los contienen.

Se catalogó la invención, según la Clasificación Internacional de Patentes (IPC).
A61K31/553

3. De la solicitud de Patente

4.2 Reivindicaciones (artículo 30 de la Decisión 486 de la C.A.N. y/o art. 22 Tratado PCT).

-La reivindicación 37 no es clara ya que en las reivindicaciones debe aparecer explícitamente establecido los compuestos a que hace referencia con los números.

-Las reivindicaciones 47, 48 reclaman profármacos de compuestos. El término "profarmaco" mencionado conduce a un alcance no claro, porque el término profarmaco incluye compuestos obtenidos a partir de otro compuesto mediante reacciones químicas, para obtener estructuras que están estructuralmente alejadas del material de partida. Además, es un intento de definir la materia en términos de un resultado a conseguir. Son compuestos referenciados por una propiedad deseada, como es su capacidad de ser metabolizados en un fármaco.

Las reivindicaciones no cumplen con el requisito de claridad, concisión o sustento por la descripción de acuerdo al art. 30 de la Decisión 486.

4. Excepción a la patentabilidad (artículo 20 D486 literal d) de la C.A.N.)

-Las reivindicaciones 1-22, 56-62 se refieren a procedimiento de tratamiento que consiste en administrar un compuesto a un paciente, por lo tanto están comprendidas por el artículo 20 D486 literal d) de la C.A.N.

5. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el estado de la técnica fecha de presentación de la solicitud de la cual se reclama prioridad, 21/sep/2004.

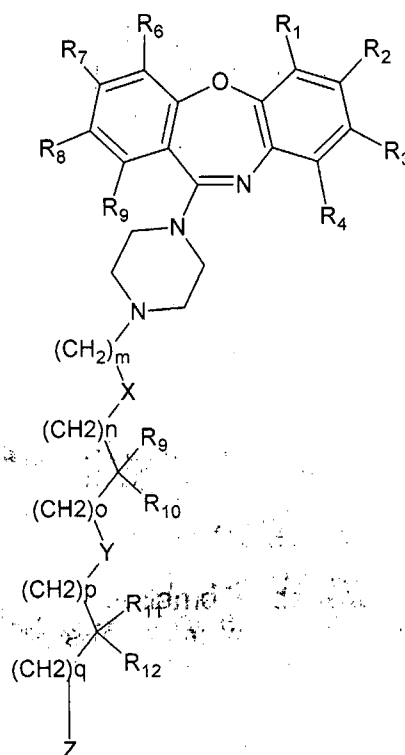
Teniendo en cuenta la fecha indicada se realizó la búsqueda del estado de la técnica, en bases de datos donde esta oficina tiene acceso libre, para búsqueda de documentos relacionados con la materia que se reclama como nueva e inventiva en presente solicitud, encontrándose los siguientes documentos más relevantes:

N°	Documento	Título	Fecha de Publicación*
D1	US3.546.226	11-basic-substituted dibenzoxazepines	08/dic/1970
D2	US5.344.828	Piperazinealkanoic acid and a pharmaceutical composition comprising the same	06/sep/1994
D3	WO200406182	Pesticidal dibenzo(hetero)azepine derivatives	08/jul/2004
D4	US3.845.074	Dibenzo[b,f]thiazepin[1,4]-11-yl amino alcanoic acids	29/oct/1974

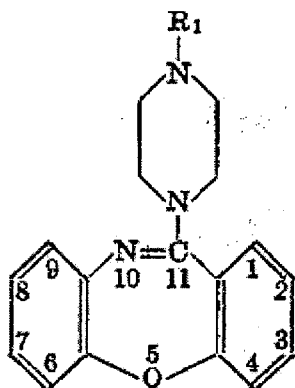
6. Análisis de patentabilidad (artículo 14 D486)

6.1. Novedad (artículo 16 D486 de la C.A.N.)

La solicitud en estudio reclama derivados de 11-(piperazin-1-il)dibenzo[b,f][1,4]oxazepina de la fórmula:

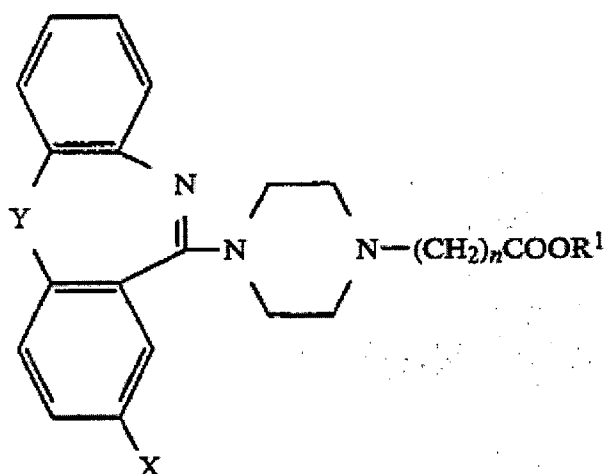


-D1 enseña 11-(piperazin-1-il)dibenzo[b,f][1,4]oxazepina, de fórmula:



Vease todo el documento especialmente, tabla II compuesto 35, por lo tanto la solicitud en estudio carece de novedad.

-D2 enseña 11-(piperazin-1-il)dibenzo[b,f][1,4]oxazepina, de la formula:



Y represents an oxygen

Vease todo el documento, ejemplos columna 4,5,7,8, ejemplos 1-50 y reivindicaciones, donde aparecen compuestos específicos de 11-(piperazin-1-il)dibenzo[b,f][1,4]oxazepina que son reclamados por la solicitud en estudio, por lo tanto la solicitud no cumple el requisito exigido en el artículo 16 D486 de la C.A.N.

D3 describe compuestos derivados de 11-(piperazin-1-il)dibenzo[b,f][1,4]oxazepina, véase todo el documento especialmente, pag.6 renglones 15-25; pag. 17 renglones 1-9; pag. 72 compuesto I-B 104, pag.74 compuestos I-B 133 a 136 y reivindicaciones, es materia que aparece reclamada en la presente solicitud como nueva e inventiva, por lo tanto la solicitud no cumple con el requisito exigido en el artículo 16 D486 de la C.A.N.

7. Conclusión:

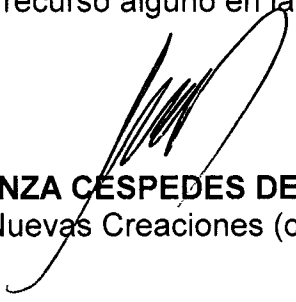
Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

*Una solicitud que no posee novedad obviamente no posee nivel inventivo.

Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	1-62	Novedad
D2	1-62	Novedad
D3	1-62	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.


ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha
17 SET. 2010

CONCEPTO TECNICO No. 3256 | **EXAMINADOR TECNICO Código No. 202012**

United States Patent Office

3,546,226

Patented Dec. 8, 1970

1

3,546,226

11-BASIC-SUBSTITUTED DIBENZOXAZEPINES

Jean Schmutz, Muri, near Bern, and Fritz Hunziker and Franz Martin Künzle, Bern, Switzerland, assignors to Dr. A. Wander, S.A., Bern, Switzerland, a corporation of Switzerland

No Drawing. Continuation-in-part of applications Ser. No. 371,123, May 28, 1964, and Ser. No. 712,956, Mar. 14, 1968. This application Feb. 6, 1969, Ser. No. 797,281 Claims priority, application Switzerland, May 30, 1963, 6,762/63; Sept. 27, 1963, 11,907/63; Mar. 13, 1967, 3,582/67; Mar. 22, 1967, 4,103/67; May 9, 1967, 6,557/67; July 14, 1967, 10,115/67; Nov. 3, 1967, 15,453/67

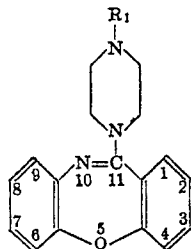
Int. Cl. C07d 51/70

U.S. Cl. 260—268

9 Claims 15

ABSTRACT OF THE DISCLOSURE

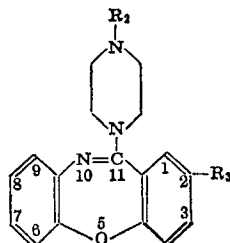
(A) 11-basic substituted dibenzoxazepines having the general Formula A:



wherein R_1 is a member of the class consisting of hydrogen, lower alkyl, lower hydroxyalkyl, acetylated lower hydroxyalkyl, and alkoxyalkyl having not more than 5 carbon atoms; and

(B) Derivatives of A substituted in the benzene nuclei by at least one member of the class consisting of halogen, trifluoromethyl, lower alkyl, lower alkoxy, and lower alkylthio; and

(C) 11-basic substituted dibenzoxazepines having the general Formula C:



wherein R_2 represents a member of the group consisting of hydrogen, allyl, alkyl containing not more than 3 carbon atoms, hydroxyalkyl containing not more than 3 carbon atoms, alkoxyalkyl containing not more than 6 carbon atoms and alkoxyloxyalkyl containing not more than 6 carbon atoms; and R_3 is a member of the group consisting of nitro, amino, aminosulphonyl of the formula $-\text{SO}_2\text{NR}_4\text{R}_5$ wherein R_4 and R_5 are the same or different members of the group consisting of hydrogen and methyl, alkylsulphonyl of the formula $-\text{SOR}_6$ wherein R_6 denotes alkyl with not more than 3 carbon atoms, and alkylsulphonyl of the formula $-\text{SO}_2\text{R}$ wherein R_6 denotes alkyl with not more than 3 carbon atoms; and

(D) The non-toxic pharmaceutically acceptable acid-addition salts of A, B and C.

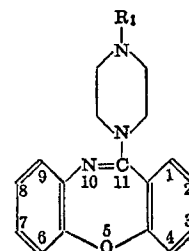
These compounds have a pronounced therapeutic effect on the central nervous system and are particularly active as neuroplegics, neuroleptics, neuroleptic antidepressants, antimetics, analgesics and sedatives.

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This is a continuation-in-part application of our co-pending patent application Ser. No. 371,123, filed May 28, 1964, and Ser. No. 712,956, filed Mar. 14, 1968 both now abandoned.

The object of the present invention is to provide 11-basic substituted dibenz[b,f][1,4]oxazepines having a pronounced therapeutic effect on the central nervous system.

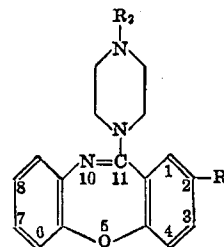
A further object of the invention is to provide 11-basic substituted dibenz[b,f][1,4]oxazepines having the above-mentioned action of the general formula:



(I)

wherein R_1 denotes hydrogen, lower alkyl, lower hydroxyalkyl, acetylated lower hydroxyalkyl, or alkoxyalkyl having not more than 5 carbon atoms, and which compounds are unsubstituted in the benzene nuclei or substituted by halogen, trifluoromethyl, lower alkyl, lower alkoxy or lower alkylthio; as well as acid addition salts of these basic compounds. Substituents in the benzene nuclei are preferably in the 2-, 4-, or 8-positions. The term "lower" alkyl etc. is intended to mean alkyl etc. having from 1 to 3 carbon atoms.

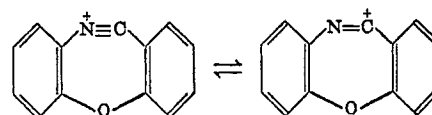
A further object of the invention is to provide 11-basic substituted dibenz[b,f][1,4]oxazepines having the above-mentioned action of the general formula:



(II)

and acid addition salts thereof. In Formula II R_2 represents hydrogen, allyl, alkyl containing not more than 3 carbon atoms, hydroxyalkyl containing not more than 3 carbon atoms, alkoxyalkyl containing not more than 6 carbon atoms or alkoxyloxyalkyl containing not more than 6 carbon atoms. R_3 denotes nitro; amino; aminosulphonyl of the formula $-\text{SO}_2\text{NR}_4\text{R}_5$ wherein R_4 and R_5 are the same or different and represent hydrogen or methyl; alkylsulphonyl of the formula $-\text{SOR}_6$ wherein R_6 denotes alkyl with not more than 3 carbon atoms; or alkylsulphonyl of the formula $-\text{SO}_2\text{R}_6$ in which R_6 represents alkyl with not more than 3 carbon atoms.

The compounds of Formula I are obtained by reacting a reaction mixture containing nitrilium or imonium cations of the formulae:



(III)

sodium sulphate and evaporated to dryness in vacuo. The residue is crystallized from acetone/petroleum ether to give 4.9 g. of 2-dimethylaminosulphonyl-11-(4-ethyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine of melting point 160-161° C.

EXAMPLE 13

4.63 g. of the same starting material as in Example 12 are dissolved in 80 ml. of isopropanol and treated with 1.6 g. of anhydrous potassium carbonate, then, while stirring and heating, treated dropwise with 3 g. of β -methoxyethyl-p-toluene sulphonic acid ester in 10 ml. of isopropanol. After the addition is complete the mixture is refluxed for 1.5 hours, then evaporated in vacuo. The residue is partitioned between dilute soda lye and ether and the ether extracts exhaustively shaken out with dilute hydrochloric acid. The acid extracts are made alkaline with concentrated soda lye and shaken out with ether. The ether extracts are washed with water, dried over sodium sulphate and evaporated in vacuo. The oily residue is dissolved in warm acetone together with 1.2 g. of maleic acid and crystallized by addition of ether. 4.9 g. of 2-dimethylaminosulphonyl-11-(4- β -methoxyethyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine maleate of melting point 124-140° C. (decomposition) are obtained.

EXAMPLE 14

4 g. of 2-dimethylaminosulphonyl-11-(4- β -hydroxyethyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine obtained according to Example 48 are mixed with 30 ml. of absolute pyridine and 15 ml. of acetic anhydride, left to stand for one hour at room temperature and then warmed for a short time on the steam bath. The reaction mixture is evaporated in vacuo and the residue diluted with water. The basic fraction is precipitated in the cold with concentrated soda lye and exhaustively extracted with ether. The ether phase is washed with water, dried over sodium sulphate and evaporated. The residue is dissolved in acetone and treated with 1.8 g. of maleic acid. After concentration of the solution and addition of ether crystals precipitate which are recrystallized from acetone/ether to give 3 g. of 2-dimethylaminosulphonyl-11-(β -acetoxyethyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine maleate of melting point 155-158° C.

In a like manner as in the examples previously mentioned there are obtained from the corresponding starting materials the products listed in the following Table II. R₁ or R₂, respectively, has the same meaning as mentioned above. In the last column *a* means acetone, *e* ether, *ch* chloroform, *m* methanol and *p* petroleum ether.

TABLE II

Example	R ₁ or R ₂ respectively	Substituents in the benzene nuclei	Physical constants
15.....	-CH ₃	7-Cl	M.P. of the base: 147-148° C. (from <i>p</i>).
16.....	-CH ₃	2,8-dichloro	M.P. of the base: 130-131° C. (from <i>e/p</i>).
17.....	-CH ₃	4,8-dichloro	M.P. of the base: 134-135° C. (from <i>e/p</i>).
18.....	-CH ₃	4-CH ₃	M.P. of the base: 179-182° C. (from <i>a/p</i>).
19.....	-CH ₃	2-CH ₃	M.P. of the base: 130-131° C. (from <i>e/p</i>).
20.....	-CH ₃	4-Cl	M.P. of the base: 173-174° C. (from <i>a/p</i>).
21.....	-CH ₃	6-Cl	M.P. of the base: 83-87° C. (from <i>p</i>).
22.....	-CH ₃	3-CH ₃	M.P. of the base: 103-105° C. (from <i>e/p</i>).
23.....	-CH ₃	2-Br	M.P. of the base: 95-99° C. (from <i>p</i>).
24.....	-CH ₃	3,4-dimethyl	M.P. of the base: 167-168° C. (from <i>a/p</i>).
25.....	-CH ₃	2-F	M.P. of the base: 81-86° C. (from <i>p</i>).
26.....	-CH ₃	1,4-dimethyl	M.P. of the base: 143-144° C. (from <i>e/p</i>).
27.....	-CH ₃	3-Cl	M.P. of the base: 122-124° C. (from <i>e/p</i>).
28.....	-(CH ₃) ₂ -O-1	2-Cl	M.P. of the dihydrochloride: 197-237° C. (from <i>m/e</i>).
29.....	-CH ₃	4-CH ₃ ; 8-Cl	M.P. of the base: 151-152° C. (from <i>e/p</i>).
30.....	H	2-Cl	M.P. of the base: 178-180° C. (from <i>a/p</i>).
31.....	-CH ₃	2-OCH ₃	M.P. of the base: 107-108° C. (from <i>e/p</i>).
32.....	-CH ₃	4-C ₂ H ₅	M.P. of the base: 128-130° C. (from <i>e/p</i>).
33.....	-CH ₃	2, 4-dichloro	M.P. of the base: 135-138° C. (from <i>a/p</i>).
34.....	-CH ₃	4-CH ₃ ; 7-Cl	M.P. of the base: 167-168° C. (from <i>a/e</i>).
35.....	-CH ₃ -CH ₂ -O-CO-CH ₃	2-Cl	M.P. of the dihydrochloride: 155-160° C. (from ethyl acetate <i>m/e</i>).
36.....	-CH ₃ -CH ₂ -OCH ₃	2-Cl	M.P. of the maleate: 180-181° C. (from ethanol/ <i>e</i>).
37.....	-CH ₃	2-SCH ₃	M.P. of the maleate: 198-201° C. (from ethanol/ <i>a/e</i>).
38.....	H	2-SCH ₃	M.P. of the base: 114-116° C. (from <i>a/p</i>).
39.....	-CH ₃	2-SC ₂ H ₅	M.P. of the base: 117-119° C. (from <i>e/p</i>).
40.....	H	2-SC ₂ H ₅	M.P. of the maleate: 161-162° C. (from <i>a/m/e</i>).
41.....	H	2-NO ₂	M.P. of the base: 190-192° C. (from <i>a/p</i>).
42.....	-CH ₃ -CH ₂ -OH	2-NO ₂	M.P. of the maleate: 155-156° C. (from <i>m/a</i>).
43.....	H	2-SO ₂ CH ₃	M.P. of the base: 189-191° C. (from <i>a/e/p</i>).
44.....	H	2-NH ₂	M.P. of the base: 181-183° C. (from ethyl acetate/ <i>e</i>).
45.....	-CH ₃	2-SO ₂ C ₂ H ₅	M.P. of the base: 196-197° C. (from <i>c/p</i>).
46.....	H	2-SO ₂ C ₂ H ₅	M.P. of the base: 130-133° C. (from <i>a/p</i>).

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TABLE II.—Continued

Example	R ₁ or R ₂ respectively	Substituents in the benzene nuclei	Physical constants
47.....	—CH ₂ —CH ₂ —OCH ₃	2-NO ₂	M.P. of the base: 102–104° C. (from a/p).
48.....	—CH ₂ —CH ₂ —OH	2-SO ₂ N(CH ₃) ₂	M.P. of the base: 164–166° C. (from a/p).
49.....	—CH ₂ —CH=CH ₂	2-SO ₂ N(CH ₃) ₂	M.P. of the base: 150–151° C. (from a/p).
50.....	II	2-SO ₂ N(CH ₃) ₂	M.P. of the base: 181–182° C. (from a/p).

Production of tablets

For the manufacture of tablets, the products of this invention can be mixed with lactose and granulated with water, 0.5% sodium alginate or 1% gelatine solution. The dried granulate is compressed into tablets in the presence of about 5% of talcum, 5% of corn starch and 0.1% of magnesium stearate. In this way, there are obtained, e.g. tablets of the following composition:

(A)

2 - chloro - 11 - (4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine	Mg.
Lactose	2
Corn starch	34
Talcum	2
Magnesium stearate	0.05

These 40 mg. tablets possess neuroleptic action. They are administered orally in a dosage of 3 to 6 tablets per day for the treatment of agitated conditions in psychotic patients.

(B)

11 - (4 - methyl - 1 - piperazinyl)-dibenz-[b,f][1,4]oxazepine	Mg.
Lactose	35
Corn starch	30
Talcum	160
Magnesium stearate	10
	10
	0.2
	40

These 210 mg. tablets possess neuroleptic action. They are administered orally in a dosage of 5 to 10 tablets per day for the treatment of agitated conditions in psychotic patients.

(C)

2 - nitro - 11 - (4 - methyl - 1 - piperazinyl)-dibenz[b,f][1,4]oxazepine	Mg.
Lactose	25
Corn starch	115
Talcum	7.5
Magnesium stearate	7.5
	0.15

These 155 mg. tablets, which are provided with a crack-line, can be administered orally in a dosage of one half to two tablets two to four times per day in the treatment of subjects suffering from any form of schizophrenia, any form of mania, severe psychotic and non-psychotic states of excitement, chorea, athetosis, and extrapyramidal movement disorders.

(D)

2 - nitro - 11 - (1 - piperazinyl) - dibenz[b,f][1,4]oxazepine	Mg.
Lactose	20
Corn starch	120
Talcum	7.5
Magnesium stearate	7.5
	0.15

These 155 mg. tablets, which are provided with a crack-line, can be administered orally in the dosage of one-half to two tablets two to five times, in some cases up to 5 times 4 tablets per day in the treatment of subjects suffering from states of mental depression and especially agitated forms of depression.

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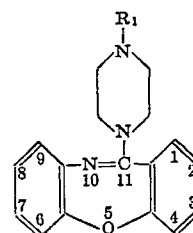
(E)

2 - dimethylaminosulphonyl - 11 - (4 - methyl - 1 - piperazinyl)-dibenz[b,f][1,4]oxazepine	Mg.
Lactose	10
Corn starch	70
Talcum	5
Magnesium stearate	5
	0.1

These 90 mg. tablets, which are provided with a crack-line, can be administered orally in a dosage of one half to two tablets one to three times per day in the treatment of subjects suffering from nausea and vomiting following operations or ray treatment or due to stomach or metabolism disorders, intoxications, drug incompatibility, pressure on the brain or pregnancy. These tablets may also be used prophylactically against post operative vomiting.

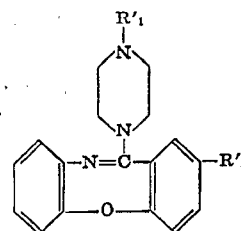
We claim:

1. A compound selected from the class consisting of (A): 11 - basic substituted dibenz[b,f][1,4]oxazepines having the general Formula A:



wherein R₁ is a member of the class consisting of hydrogen, lower alkyl, lower hydroxyalkyl, acetylated lower hydroxyalkyl, and alkoxyalkyl having not more than 5 carbon atoms; and (B) derivatives of (A) substituted in a benzene nucleus at the 2-position by a member of the class consisting of halogen, trifluoromethyl, lower alkyl, lower alkoxy, and lower alkythio; and (C) the non-toxic pharmaceutically acceptable acid addition salts of (A) and (B).

2. A compound selected from the consisting of (A): 11 - basic substituted dibenz[b,f][1,4]oxazepines having the general Formula A:



wherein R₁ is a member of the class consisting of alkyl having not more than 3 carbon atoms, hydroxyalkyl having not more than 3 carbon atoms, alkoxyalkyl having not more than 6 carbon atoms and alkoxyalkyl having not more than 6 carbon atoms, and R₂ is a member of the group consisting of halogen, lower alkyl, lower alkoxy, lower alkythio, and trifluoromethyl; and (B) the non-toxic pharmaceutically acceptable acid addition salts of (A).

United States Patent [19]

Sawanishi et al.

[11] Patent Number: 5,344,828

[45] Date of Patent: Sep. 6, 1994

[54] PIPERAZINEALKANOIC ACID AND A PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

[75] Inventors: Hiroyuki Sawanishi, Kanazawa; Yasuo Ito, Katsuyama; Hideo Kato, Fukui; Eiichi Koshinaka, Katsuyama; Nobuo Ogawa, Katsuyama; Kouji Morikawa, Katsuyama, all of Japan

[73] Assignee: Hokuriku Pharmaceutical Co., Ltd., Katsuyama, Japan

[21] Appl. No.: 663,154

[22] Filed: Mar. 1, 1991

[30] Foreign Application Priority Data

Mar. 5, 1990 [JP] Japan 2-51897
Mar. 5, 1990 [JP] Japan 2-51898
Aug. 29, 1990 [JP] Japan 2-225256

[51] Int. Cl.⁵ A61K 31/55; C07D 403/04; C07D 413/04; C07D 417/04

[52] U.S. Cl. 514/211; 514/217; 540/551; 540/587; 540/579

[58] Field of Search 540/547, 579, 587, 551; 514/211, 214, 217

[56] References Cited

U.S. PATENT DOCUMENTS

3,389,139 6/1968 Schmutz et al. 540/587
3,546,226 12/1970 Schmutz et al. 540/551
3,845,074 10/1974 Malen et al. 540/551
3,928,356 12/1975 Umio et al. 540/578

FOREIGN PATENT DOCUMENTS

0421823 4/1991 European Pat. Off. .
0505014 9/1992 European Pat. Off. .
1801523 6/1969 Fed. Rep. of Germany
8807997 10/1988 PCT Int'l Appl.

OTHER PUBLICATIONS

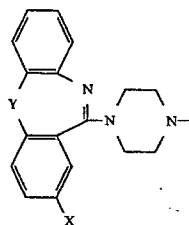
Kaspersen et al. Recd: Journal of the Royal Netherlands Chem. Soc., 102(10), pp. 457-460, (1983).
Chemical Abstract, vol. 100, No. 34501n, (1983), Kaspersen.
Chemical Abstract, 11th Collective Index, 1982-1986 Substance Index.
Stedman's Medical Dictionary, 24th Edition, (Publ. by Williams & Wilkins, p. 133, (1982).

(List continued on next page.)

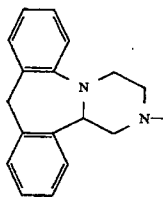
Primary Examiner—Mukund J. Shah
Assistant Examiner—Philip I. Datlow
Attorney, Agent, or Firm—Cushman, Darby & Cushman

ABSTRACT

Novel polycyclic compounds represented by the following formula: A—(CH₂)_n—COOR¹, wherein R¹ represents a hydrogen atom or a lower alkyl group; n represents an integer of from 0 to 5; and A is a group represented by the following formula:



wherein X represents a hydrogen atom or a halogen atom; and Y represents a methylene group, an oxygen atom, or a sulfur atom, or A is a group represented by the following formula:



and pharmacologically acceptable salts thereof are disclosed. Also disclosed are a method for preparing the same, a pharmaceutical composition comprising the same, an antiallergic agent and an agent for bronchial asthma comprising the same, and a method for treatment of an allergic disease or bronchial asthma comprising the step of administering the same.

10 Claims, No Drawings

those frequently observed clinically are, for example, psychoneurotic symptoms such as, tremor, hallucinosis, delirium, cerebaria, malaise, vertigo, or anticholinergic symptoms such as hydrodipsia, dysuria, or cycloplegia.

SUMMARY OF THE INVENTION

An object of the present invention is to provide novel compounds having a selective pharmacological activity.

Another object of the present invention is to provide novel compounds which extensively eliminate undesired adverse reactions.

A further object of the present invention is to provide a method for preparing said compounds.

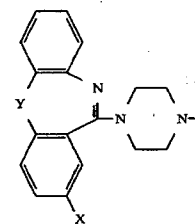
Yet another object is to provide a pharmaceutical composition comprising said compounds.

The inventor of the present invention have conducted various studies to achieve the foregoing objects and found that the objects can be effectively attained by providing novel polycyclic compounds of the present invention. These polycyclic compounds have selective pharmacological activity and reduced adverse reactions and are useful as antihistaminic agents, antiallergic agents, hypo-sedatives, psychoneurotic agents, analgetics, antiemetics, gastrointestinal tract hyperkinetics, antiarrhythmics, or antihypertensive agents.

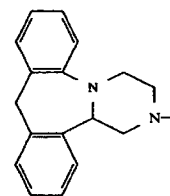
In accordance with the above objects, the present invention provides a compound represented by the following formula (I):



wherein R¹ represents a hydrogen atom or a lower alkyl group; n represents an integer of from 0 to 5; and A is a group represented by the following formula:



wherein X represents a hydrogen atom or a halogen atom; and Y represents a methylene group, an oxygen atom, or a sulfur atom, or A is a group represented by the following formula:



or a pharmacologically acceptable salt of the compound.

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In accordance with another embodiment of the present invention, the present invention provides a method for preparing the compound represented by formula (I).

In accordance with yet another embodiment of the present invention, the present invention provides a pharmaceutical composition comprising an effective amount of the compound represented by formula (I) together with a pharmaceutically acceptable carrier or coating.

In accordance with a further embodiment, the present invention provides a method for treating an allergic disease or bronchial asthma comprising the step of administering an effective amount of the compound represented by formula (I) to a mammal.

The present invention also provides an antiallergic agent, antihistaminic agent, and an agent for bronchial asthma comprising the compound represented by formula (I).

Further objects, features and advantages of the present invention will become apparent from the Description of the Preferred Embodiment which follows, when read in light of the attached Examples and Reference Examples.

DESCRIPTION OF THE PREFERRED EMBODIMENT

In the above formula (I), the lower alkyl group represented by R¹ may be, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl group, and the halogen atom represented by X may be, for example, a fluorine atom, a chlorine atom, a bromine atom, a iodine atom.

Preferred examples of the present invention include:

- 35 ethyl 4-(2-chlorodibenz[b,f][1,4]oxazepin-11-yl)-1-piperazinecarboxylate;
- ethyl 4-(2-chlorodibenz[b,f][1,4]oxazepin-11-yl)-1-piperazinepropionate;
- 40 ethyl 4-(2-chlorodibenz[b,f][1,4]oxazepin-11-yl)-1-piperazineacetate;
- ethyl 4-(2-chlorodibenz[b,f][1,4]oxazepin-11-yl)-1-piperazinebutyrate;
- ethyl 4-(2-chlorodibenz[b,f][1,4]oxazepin-11-yl)-1-piperazinevalerate;
- 45 ethyl 4-(2-chlorodibenz[b,f][1,4]oxazepin-11-yl)-1-piperazinecaproate;
- 4-(2-chlorodibenz[b,f][1,4]oxazepin-11-yl)-1-piperazineacetic acid;
- 4-(2-chlorodibenz[b,f][1,4]oxazepin-11-yl)-1-piperazinepropionic acid;
- 4-(2-chlorodibenz[b,f][1,4]oxazepin-11-yl)-1-piperazinebutyric acid;
- 4-(2-chlorodibenz[b,f][1,4]oxazepin-11-yl)-1-piperazinevaleric acid;
- 55 4-(2-chlorodibenz[b,f][1,4]oxazepin-11-yl)-1-piperazinecaproic acid;
- ethyl 4-(2-chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinecarboxylate;
- ethyl 4-(2-chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinepropionate;
- 60 ethyl 4-(2-chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazineacetate;
- ethyl 4-(2-chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinebutyrate;
- 65 ethyl 4-(2-chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinevalerate;
- ethyl 4-(2-chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinecaproate;

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4-(2-chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazineacetic acid;
 4-(2-chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinepropionic acid;
 4-(2-chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinebutyric acid;
 4-(2-chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinevaleric acid;
 4-(2-chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinecaproic acid;
 ethyl 4-(11H-dibenz[b,e]azepin-6-yl)-1-piperazinecarboxylate;
 ethyl 4-(11H-dibenz[b,e]azepin-6-yl)-1-piperazinepropionate;
 ethyl 4-(11H-dibenz[b,e]azepin-6-yl)-1-piperazineacetate;
 ethyl 4-(11H-dibenz[b,e]azepin-6-yl)-1-piperazinebutyrate;
 ethyl 4-(11H-dibenz[b,e]azepin-6-yl)-1-piperazinevalerate;
 ethyl 4-(11H-dibenz[b,e]azepin-6-yl)-1-piperazinecaproate;
 4-(11H-dibenz[b,e]azepin-6-yl)-1-piperazineacetic acid;
 4-(11H-dibenz[b,e]azepin-6-yl)-1-piperazinepropionic acid;
 4-(11H-dibenz[b,e]azepin-6-yl)-1-piperazinebutyric acid;
 4-(11H-dibenz[b,e]azepin-6-yl)-1-piperazinevaleric acid;
 4-(11H-dibenz[b,e]azepin-6-yl)-1-piperazinecaproic acid;
 ethyl 4-(1,2,3,4,10,14b-hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)formate;
 ethyl 3-(1,2,3,4,10,14b-hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)propionate;
 ethyl 2-(1,2,3,4,10,14b-hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)acetate;
 ethyl 4-(1,2,3,4,10,14b-hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)butyrate;
 ethyl 5-(1,2,3,4,10,14b-hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)valerate;
 ethyl 6-(1,2,3,4,10,14b-hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)caproate;
 2-(1,2,3,4,10,14b-hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)acetic acid;
 3-(1,2,3,4,10,14b-hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)propionic acid;
 4-(1,2,3,4,10,14b-hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)butyric acid;
 5-(1,2,3,4,10,14b-hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)valeric acid; and
 6-(1,2,3,4,10,14b-hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)caproic acid.

The compounds of the present invention represented by the above formula (I) may be converted to pharmacologically acceptable salts, if desired, and may then be reconverted to produce the free compound from the obtained salts.

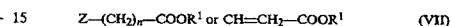
The pharmacologically acceptable salts of the compounds of the present invention represented by formula (I) may be acid addition salts or alkali addition salts. Examples of the acid addition salts include mineral acid addition salts such as, for example, hydrochloride, hydrobromide, sulfate, nitrate, phosphate, and organic acid addition salts such as, for example, acetate, maleate, fumarate, malate, citrate, oxalate, lactate, and tartrate. Examples of the alkali addition salts include metal salts such as, for example, sodium, potassium, calcium salt,

and organic alkali salts such as, for example, ammonium salts, methylamine, ethylamine, dimethylamine, triethylamine, ethanolamine, piperidine, and piperazine salts.

According to an embodiment of the present invention, the novel polycyclic compounds of the present invention represented by formula (I) can be prepared by the method comprising the steps reacting a compound represented by the following formula (VI):



wherein A is the same as that defined above, with a compound represented by the following formula (VII):



wherein R¹ and n are the same as those defined above, and Z represents a halogen atom, in a solvent or without solvent in the presence or absence of a base as a dehydrohalogenating agent, and followed by hydrolysis in a solvent by using an acid or a base, if necessary.

Any inert solvent may be used in the alkylation process of the present invention. Examples of the inert solvent include benzene, toluene, tetrahydrofuran, dioxane, acetone, acetonitrile, methanol, ethanol, isopropanol, n-butanol, dimethyl sulfoxide, and N,N-dimethylformamide.

Examples of the base used in the process of the present invention include potassium carbonate, sodium carbonate, pyridine, and triethylamine. The reaction may be carried out at from 0° to 200° C.

For the hydrolysis process, an acid such as, for example, hydrochloric acid or sulfuric acid, or a base such as, for example, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, or sodium bicarbonate may be used. A solvent used in the hydrolysis may be, for example, water, methanol, ethanol, acetone, or tetrahydrofuran, and the hydrolysis may be carried out at from 0° to 100° C.

In addition, the compounds represented by the above formula (VI), used as starting materials for the above process, are disclosed in *Helvetica Chimica Acta*, 50, 245-254; British Patent No. 1,006,156; and U.S. Pat. No. 4,217,452.

According to another embodiment of the present invention, the novel polycyclic compounds of the present invention represented by formula (I) wherein n is 0, can be prepared by the method comprising the steps of reacting a compound represented by the following formula (VIII):



wherein A is the same as that defined above, with a compound represented by the following formula (IX):



wherein R¹ and Z are the same as those defined above, in a solvent in the presence or absence of a base as a dehydrohalogenating agent.

Any inert solvent may be used in the alkylation process of the present invention. Examples of the inert solvent include benzene, toluene, tetrahydrofuran, dioxane, acetone, acetonitrile, methanol, ethanol, isopropanol, n-butanol, dimethyl sulfoxide, and N,N-dimethylformamide.

Examples of the base used in the process of the present invention include potassium carbonate, sodium carbonate, pyridine, and triethylamine. The reaction may be carried out at from 0° to 200° C.

The novel polycyclic compounds of the present invention represented by the above formula (I) and pharmacologically acceptable salts of the compounds are useful as antihistaminic agents, antiallergic agents, hypotensives, psychoneurotic agents, analgesics, antiemetics, gastrointestinal tract hyperkinetics, antiarrhythmics, or antihypertensive agents.

The novel polycyclic compounds of the present invention and their pharmacologically acceptable salts may be administered orally or parenterally to a patient as a pharmaceutical composition which comprises an effective amount of said compound or the salt thereof together with a pharmacologically acceptable carrier or coating.

The pharmaceutical composition suitable for oral administration may be, for example, tablet, capsule, powder, sublingual granule, granule, solution, or syrup. The pharmaceutical composition suitable for parenteral administration may be injection, suppository, inhalant, eye drop, nasal drop, ointment, or cataplasm. The pharmacologically acceptable carrier or coating used for the preparation of the pharmaceutical composition may be excipient, disintegrant or agent for accelerating disintegration, binder, lubricant, coating agent, pigment, diluent, base, solubilizing agent, solubilizer, isotonicity, pH adjusting agent, stabilizer, propellant, and adhesive.

For the preparation of the pharmaceutical composition suitable for oral administration, dermal administration, or mucosal application, the coating or carrier may comprise the following: an excipient such as, for example, glucose, lactose, D-mannitol, starch, or crystalline cellulose; a disintegrant or an agent for accelerating disintegration such as, for example, carboxymethylcellulose, starch, or calcium carboxymethylcellulose; a binder such as, for example, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, or gelatin; a lubricant such as, for example, magnesium stearate or talc; a coating agent such as, for example, hydroxypropylmethylcellulose, sucrose, polyethylene glycol, or titanium oxide; a base such as, for example, petrolatum, liquid paraffin, polyethyleneglycol, gelatin, kaolin, glycerin, purified water, or hard fat; a propellant such as, for example, from, diethyl ether, compressed gas; an adhesive such as, for example, sodium polyacrylate, polyvinylalcohol, methylcellulose, polyisobutylene, or polybutene; or a base sheet such as, for example, cloth or plastic sheet. The pharmaceutical composition suitable for injection may comprise the following: a solubilizing agent or a solubilizer, e.g., distilled water for injection, saline, or propylene glycol which is useful for an aqueous composition or a composition for preparing aqueous solution before use; an isotonicity agent such as, for example, glucose, sodium chloride, D-mannitol, or glycerin; and a pH adjusting agent such as, for example, an inorganic or organic acid or an inorganic or organic base.

The dose of the pharmaceutical composition of the present invention for an adult patient may generally be from about 1 to 500 mg per day for oral administration, which may be increased or decreased depending on the conditions of the patient to be treated.

The present invention will be further illustrated by the following Examples. The Examples are given by

way of illustration only and are not to be construed as limiting.

EXAMPLES

The following examples show the excellent effectiveness of the compounds of the present invention. The results of antihistaminic and antiallergic activities are summarized in Tables 1 and 2, respectively.

The reference compounds used were Amoxapine (II), Clothiapine (III), Perlapine (IV) and Mianserin (V).

1. Antihistaminic activity (Effect on the contractile response induced by histamine in isolated guinea-pig ileum)

Male Hartley guinea-pigs, 5-8 weeks of age, were sacrificed and the ileum was excised. An approximately 20 mm strip of isolated ileum was mounted vertically under a 0.5 g load in an organ bath containing 10 ml of Locke-Ringer solution (NaCl: 154 mM, KCl: 5.6 mM, CaCl₂·2H₂O: 2.2 mM, MgCl₂·6H₂O: 2.1 mM, NaHCO₃: 5.9 mM, glucose: 2.8 mM) maintained at 28° C. and bubbled with 95% O₂ and 5% CO₂. The contractile response was recorded on a recticorder an isotonic transducer. The concentration-contractile response curve to histamine was constructed before and after 30 min contact with test compounds. The dissociation constant K_B (M) of test compounds was calculated according to the method of Furchgott ("Catecholamines" Edited by Blaschko, H. and Muscholl, E., 283-335, Springer, Berlin; Heidelberg and New York, 1972).

The results are shown in Table 1.

TABLE 1

Antihistaminic Activity			
Test compound	-log K _B	Test compound	-log K _B
Example 2	7.92	Example 28	7.76
Example 4	8.31	Example 30	7.24
Example 5	7.98	Example 32	7.24
Example 6	8.51	Example 33	7.57
Example 8	7.30	Example 35	8.57
Example 9	7.32	Example 36	7.49
Example 10	7.26	Example 37	8.62
Example 13	7.29	Example 38	7.96
Example 15	7.52	Example 39	7.89
Example 16	7.33	Example 40	7.74
Example 17	7.26	Example 41	7.60
Example 19	7.28	Example 42	7.51
Example 20	7.24	Example 43	7.32
Example 21	7.23	Example 44	7.49
Example 22	7.46		
Example 24	8.05	Amoxapine	8.37
Example 25	7.34	Clothiapine	8.87
Example 26	7.87	Perlapine	9.15
Example 27	8.10	Mianserin	9.15

The compounds of the present invention exhibited excellent activities, though the activities were somewhat less potent than those of the reference compounds.

2. Antiallergic activity (48 hr homologous passive cutaneous anaphylaxis (PCA) in rat)

Male Wistar rats, 6 weeks of age, were passively sensitized by intracutaneous injection in the back of a volume of 0.1 ml of anti-DNP-As rat serum. Forty-eight hours later, the animals were administered an intravenous injection of 0.5 ml saline solution containing 1 mg of DNP-As and 5 mg of Evans blue. The animals were sacrificed 30 min after the injection and the extravasated dye was extracted with 1N KOH and acetone, neutralized with 1N H₃PO₄ and the absorbance at 620

nm was determined. The test compounds were administered orally in a dose of 1 mg/Kg 1 hr before antigen challenge. The inhibitory activity of a test compound was expressed as percent inhibition of PCA as compared with the control group. The results are shown in Table 2.

TABLE 2

Test compound	Antiallergic Activity	
	Inhibition rate (%)	Test compound
Example 8	88.6	Example 41
Example 9	95.8	Example 42
Example 10	84.1	Example 43
Example 11	86.4	Example 44
Example 19	64.6	
Example 20	77.7	Amoxapine
Example 21	78.5	Mianserin
Example 22	77.2	

The compounds of the present invention exhibited more potent antiallergic activity than the reference compounds.

The inhibitory activity of noradrenaline and 5-hydroxytryptamine uptake and anticholinergic activity were also examined. The compounds of the present invention showed little activity, while the reference compounds showed considerable activity.

Since the compounds of the present invention hardly have the above activity, these compounds, and because they cause no side effects such as, for example, psychogenesis, dyspnea and dysuria derived from these activities, are expected to be excellent, selective antihistaminic and antiallergic agents.

Example 1

Ethyl 4-(2-Chlorodibenzo[b,f][1,4]oxazepin-11-yl)-1-piperazinecarboxylate

A mixture of 2.20 g of 2-chloro-11-(1-piperazinyl)-dibenzo[b,f][1,4]oxazepine, 0.76 g of ethyl chloroformate and 0.97 g of potassium carbonate in 20 ml of N,N-dimethylformamide was stirred at 80° C. for 3 hrs. Ice water was added to the reaction mixture and extracted with ether. The etheral layer was washed with water, dried and concentrated. The residue was chromatographed on silica gel using a mixture of n-hexane and ethyl acetate (1:2) as eluents to give 2.62 g of colorless crystals, which were recrystallized from isopropyl ether to give colorless prisms, mp 121.5°-122.5° C.

Analysis for $C_{20}H_{20}ClN_3O_3$ Calculated C, 62.26; H, 5.22; N, 10.89 Found C, 62.36; H, 5.04; N, 11.00

Example 2

Ethyl 4-(2-Chlorodibenzo[b,f][1,4]oxazepin-11-yl)-1-piperazinepropionate

A mixture of 3.14 g of 2-chloro-11-(1-piperazinyl)-dibenzo[b,f][1,4]oxazepine and 1.20 g of ethyl acrylate in 16 ml of ethanol was refluxed for 2 hrs. The reaction mixture was concentrated and the residue was chromatographed on silica gel using a mixture of n-hexane and ethyl acetate (2:1 and 1:1) as eluents to give 3.68 g of yellow crystals, which were recrystallized from a mixture of isopropyl ether and n-pentane to give yellow prisms, mp 73°-75° C.

Analysis for $C_{22}H_{24}ClN_3O_3$ Calculated C, 63.84; H, 5.84; N, 10.15 Found C, 63.95; H, 5.86; N, 10.16

Example 3

Ethyl 4-(2-Chlorodibenzo[b,f][1,4]oxazepin-11-yl)-1-piperazineacetate

A mixture of 3.4 g of 2-chloro-11-(1-piperazinyl)-dibenzo[b,f][1,4]oxazepine, 2.00 g of ethyl bromoacetate and 1.38 g of potassium carbonate in 16 ml of N,N-dimethylformamide was stirred at 60°-70° C. for 3 hrs. After cooling, water was added to the reaction mixture and extracted with ether. The etheral layer was washed with water, dried and concentrated. The residue was chromatographed on silica gel using a mixture of n-hexane and ethyl acetate (2:1 and 1:1) as eluents to give 3.12 g of yellow crystals, which were recrystallized from n-hexane to give yellow prisms, mp 123°-123.5° C.

Analysis for $C_{21}H_{22}ClN_3O_3$ Calculated C, 63.07; H, 5.55; N, 10.51 Found C, 63.26; H, 5.56; N, 10.60

The compounds of Example 4 to 6 were prepared in the same manner as described in Example 3.

Example 4

Ethyl 4-(2-Chlorodibenzo[b,f][1,4]oxazepin-11-yl)-1-piperazinebutyrate

Yellow prisms, mp 86°-87° C. (n-hexane)

Analysis for $C_{23}H_{26}ClN_3O_3$ Calculated C, 64.56; H, 6.12; N, 9.82 Found C, 64.58; H, 6.20; N, 9.82

Example 5

Ethyl 4-(2-Chlorodibenzo[b,f][1,4]oxazepin-11-yl)-1-piperazinevalerate

Yellow prisms, mp 82.5°-84° C. (iso-Pr₂O-n-pentane)

Analysis for $C_{24}H_{28}ClN_3O_3$ Calculated C, 65.22; H, 6.39; N, 9.51 Found C, 65.18; H, 6.48; N, 9.36

Example 6

Ethyl 4-(2-Chlorodibenzo[b,f][1,4]oxazepin-11-yl)-1-piperazinecaproate

Pale yellowish viscous oil

IR spectrum ν (liq) cm^{-1} : 1738 (COO) NMR spectrum δ (CDCl₃) ppm:

1.10-2.80(14H,m), 1.28(3H,t, J=7.0 Hz), 3.40-3.75(4H,m), 4.19(2H,q, J=7.0 Hz), 7.00-7.65(7H,m)

High resolution mass spectrum for $C_{25}H_{30}ClN_3O_3$ Calculated m/z: 455.1976 Found m/z: 455.1994

Example 7

4-(2-Chlorodibenzo[b,f][1,4]oxazepin-11-yl)-1-piperazineacetic acid

2N Aqueous sodium hydroxide solution (5 ml) was added to a solution of 2.00 g of ethyl 4-(2-chlorodibenzo[b,f][1,4]oxazepin-11-yl)-1-piperazineacetate in 20 ml of methanol. The solution was refluxed for 30 min and then concentrated. The residue was dissolved in hot water and the solution was neutralized with 0.5N hydrochloric acid. The precipitates were collected by filtration to give 1.67 g of colorless crystals, which were recrystallized from aqueous ethanol to give colorless crystals, mp 210°-212° C.

IR spectrum ν (KBr) cm^{-1} : 1608 (COO-) Mass spectrum m/z: 371.373 (M+, 3:1) NMR spectrum δ (DMSO-d₆) ppm: 2.50-2.90(4H,m), 3.24(2H,s), 3.30-3.70(4H,m), 7.00-7.80(7H,m)

The compounds of Example 8 to 11 were prepared in the same manner as described in Example 7.

Example 8

4-(2-Chlorodibenzo[b,f][1,4]oxazepin-11-yl)-1-piperazinepropionic acid

Colorless crystals, mp 122°-124° C. (H₂O-EtOH). IR spectrum ν (KBr) cm^{-1} : 1604 (COO-) Mass spectrum m/z: 385.387 (M+, 3:1) NMR spectrum δ (DMSO-d₆) ppm: 2.30-2.80(8H,m), 3.30-3.70(4H,m), 6.90-7.80(7H,m) Example 9

4-(2-Chlorodibenzo[b,f][1,4]oxazepin-11-yl)-1-piperazinebutyric acid

Pale yellow crystals, mp 120°-122° C. (H₂O-EtOH). IR spectrum ν (KBr) cm^{-1} : 1604 (COO-) Mass spectrum m/z: 399.401 (M+, 3:1) NMR spectrum δ (DMSO-d₆) ppm: 1.50-2.00(2H,m), 2.10-2.70(8H,m), 3.30-3.70(4H,m), 7.00-7.80(7H,m) Example 10

4-(2-Chlorodibenzo[b,f][1,4]oxazepin-11-yl)-1-piperazinevaleric acid

Colorless crystals, mp 223°-226° C. (H₂O-EtOH). Analysis for $C_{22}H_{24}ClN_3O_3$ Calculated C, 63.84; H, 5.84; N, 10.15 Found C, 63.72; H, 5.89; N, 10.07

Example 11

4-(2-Chlorodibenzo[b,f][1,4]oxazepin-11-yl)-1-piperazinecaproic acid

Pale yellow crystals, mp 173°-175° C. (H₂O-EtOH)

Analysis for $C_{23}H_{26}ClN_3O_3$ Calculated C, 64.56; H, 6.12; N, 9.82 Found C, 64.54; H, 6.11; N, 9.83

Example 12

Ethyl 4-(2-Chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinecarboxylate

A mixture of 0.86 g of 2-chloro-11-(4-methyl-1-piperazinyl)dibenzo[b,f][1,4]thiazepine and 0.81 g of ethyl chloroformate in 5 ml of toluene was refluxed for 5 hrs. Ice water was added to the reaction mixture and made alkaline with sodium bicarbonate. The mixture was extracted with methylene chloride and the methylene chloride layer was washed with water, dried and concentrated. The residue was chromatographed on silica gel using methylene chloride as an eluent to give 0.70 g of colorless crystals, which were recrystallized from a mixture of isopropyl ether and n-pentane to give colorless prisms, mp 96.5°-97.5° C.

Analysis for $C_{20}H_{20}ClN_3O_3$ Calculated C, 59.77; H, 5.02; N, 10.46 Found C, 60.00; H, 5.06; N, 10.39

Example 13

Ethyl 4-(2-Chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinepropionate

A mixture of 3.30 g of 2-chloro-11-(1-piperazinyl)-dibenzo[b,f][1,4]thiazepine and 1.20 g of ethyl acrylate in 17 ml of ethanol was refluxed for 3 hrs. The reaction mixture was concentrated and the residue was chromatographed on silica gel using a mixture of n-hexane and ethyl acetate (1:1) as an eluent to give 4.04 g of yellow crystals, which were recrystallized from isopropyl ether to give colorless needles, mp 79°-80° C.

Analysis for $C_{22}H_{24}ClN_3O_3$ Calculated C, 61.47; H, 5.63; N, 9.77 Found C, 61.28; H, 5.81; N, 9.64

Example 14

Ethyl 4-(2-Chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazineacetate

A mixture of 3.30 g of 2-chloro-11-(1-piperazinyl)-dibenzo[b,f][1,4]thiazepine, 2.00 g of ethyl bromoacetate and 1.38 g of potassium carbonate in 17 ml of N,N-dimethylformamide was stirred at 70° C. for 3 hrs. After cooling, water was added to the reaction mixture and extracted with ether. The etheral layer was washed with water, dried and concentrated. The residue was

chromatographed on silica gel using a mixture of n-hexane and ethyl acetate (1:1) as an eluent to give 3.95 g of pale yellow crystals.

IR spectrum ν (KBr) cm^{-1} : 1744 (COO) NMR spectrum δ (CDCl₃) ppm: 1.27(3H,t, J=7 Hz), 2.50-3.00(4H,m), 3.27(2H,s), 3.40-3.85(4H,m), 4.20(2H,q, J=7 Hz), 6.70-7.60(7H,m)

High resolution mass spectrum for $C_{21}H_{22}ClN_3O_3$ Calculated m/z: 415.1121, 417.1092 Found m/z: 415.1097, 417.1087

The compounds of Example 15 to 17 were prepared in the same manner as described in Example 14.

Example 15

Ethyl 4-(2-Chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinebutyrate

Yellowish viscous oil

IR spectrum ν (liq) cm^{-1} : 1736 (COO) NMR spectrum δ (CDCl₃) ppm: 1.30(3H,t, J=7 Hz), 1.65-2.20(2H,m), 2.25-2.80(8H,m), 3.30-3.80(4H,m), 4.18(2H,q, J=7 Hz), 6.70-7.60(7H,m)

High resolution mass spectrum for $C_{23}H_{26}ClN_3O_3$ Calculated m/z: 443.1434, 445.1405 Found m/z: 443.1441, 445.1418

Example 16

Ethyl 4-(2-Chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinevalerate

Yellowish viscous oil

IR spectrum ν (liq) cm^{-1} : 1738 (COO) NMR spectrum δ (CDCl₃) ppm: 1.25(3H,t, J=7 Hz), 1.59-1.90(4H,m), 2.5-2.70(8H,m), 3.35-3.70(4H,m), 4.15(2H,q, J=7 Hz), 6.70-7.60(7H,m)

High resolution mass spectrum for $C_{24}H_{28}ClN_3O_3$ Calculated m/z: 457.1591, 459.1561 Found m/z: 457.1518, 459.1553

Example 17

Ethyl 4-(2-Chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinecaproate

Yellowish viscous oil.

IR spectrum ν (liq) cm^{-1} : 1740 (COO) NMR spectrum δ (CDCl₃) ppm: 1.25(3H,t, J=7 Hz), 1.30-2.00(6H,m), 2.00-2.80(8H,m), 3.40-3.80(4H,m), 4.15(2H,q, J=7 Hz), 6.70-7.60(7H,m)

High resolution mass spectrum for $C_{25}H_{30}ClN_3O_3$ Calculated m/z: 471.1747, 473.1718 Found m/z: 471.1753, 473.1746

Example 18

4-(2-Chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazineacetic acid

2N Aqueous sodium hydroxide solution (5 ml) was added to a solution of 2.08 g of ethyl 4-(2-chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazineacetate in 21 ml of methanol. The solution was refluxed for 30 min and then concentrated. The residue was dissolved in hot water and the solution was neutralized with 0.5N hydrochloric acid. The yellowish viscous precipitates were extracted with chloroform. The chloroform layer was washed with water, dried and concentrated to give 1.89 g of pale yellow crystals, which were recrystallized from ethanol to give pale yellow crystals, mp 139°-141° C.

Analysis for $C_{19}H_{18}ClN_3O_3 \cdot H_2O$ Calculated C, 56.22; H, 4.97; N, 10.35 Found C, 56.41; H, 4.71; N, 10.55

Example 19

4-(2-Chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinepropionic acid

2N Aqueous sodium hydroxide solution (5 ml) was added to a solution of 2.15 g of ethyl 4-(2-chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinepropionate in 22 ml of methanol. The solution was refluxed for 30 min and then concentrated. The residue was dissolved in hot water and the solution was neutralized with 0.5N hydrochloric acid. The precipitates were collected by filtration to give 1.84 g of pale yellow crystals, which were recrystallized from aqueous ethanol to give pale yellow crystals, mp 120°–121° C.

Analysis for $C_{20}H_{20}ClN_3O_2S \cdot 2H_2O$ Calculated C, 54.85; H, 5.52; N, 9.59 Found C, 54.76; H, 5.44; N, 9.46
The compounds of Example 20 to 22 were prepared in the same manner as described in Example 19.

Example 20

4-(2-Chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinebutyric acid

Colorless crystals, mp 112°–114° C. (H_2O -EtOH)
Analysis for $C_{21}H_{22}ClN_3O_2S \cdot H_2O$ Calculated C, 58.12; H, 5.57; N, 9.68 Found C, 57.95; H, 5.38; N, 9.75

Example 21

4-(2-Chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinevaleric acid

Colorless prisms, mp 220°–221° C. (H_2O -EtOH)
Analysis for $C_{22}H_{24}ClN_3O_2S$ Calculated C, 61.46; H, 5.63; N, 9.77 Found C, 61.40; H, 5.55; N, 9.72

Example 22

4-(2-Chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinecaproic acid

Pale yellow prisms, mp 186°–187° C. (H_2 -EtOH)
Analysis for $C_{23}H_{26}ClN_3O_2S$ Calculated C, 62.22; H, 5.90; N, 9.46 Found C, 62.02; H, 5.87; N, 9.32

Example 23

Ethyl 4-(11H-Dibenz[b,e]azepin-6-yl)-1-piperazinecarboxylate

A mixture of 3.33 g of 6-(1-piperazinyl)-11H-dibenz[b,e]azepine, 1.63 g of ethyl chloroformate and 1.66 g of potassium carbonate in 20 ml of N,N-dimethylformamide was stirred at 80° C. for 3 hrs. Ice water was added to the reaction mixture and extracted with ether. The ether layer was washed with water, dried and concentrated. The residue was chromatographed on silica gel using a mixture of n-hexane and ethyl acetate (1:2) as an eluent to give 3.14 g of colorless crystals, which were recrystallized from isopropyl ether to give colorless prisms, mp 137°–138° C.
Analysis for $C_{21}H_{23}N_3O_2$ Calculated C, 72.18; H, 6.63; N, 12.03 Found C, 71.94; H, 6.68; N, 11.96

Example 24

Ethyl 4-(11H-Dibenz[b,e]azepin-6-yl)-1-piperazinepropionate

A mixture of 2.77 g of 6-(1-piperazinyl)-11H-dibenz[b,e]azepine and 1.20 g of ethyl acrylate in 14 ml of ethanol was refluxed for 2 hrs. The reaction mixture was concentrated and the residue was chromatographed on silica gel using a mixture of n-hexane and ethyl acetate (1:1) as an eluent to give 3.25 g of colorless crystals, which were recrystallized from isopropyl ether to give colorless prisms, mp 133°–134° C.

Analysis for $C_{23}H_{27}N_3O_2$ Calculated C, 73.18; H, 7.21; N, 11.13 Found C, 73.15; H, 7.26; N, 11.10

Example 25

Ethyl 4-(11H-Dibenz[b,e]azepin-6-yl)-1-piperazineacetate

A mixture of 2.77 g of 6-(1-piperazinyl)-11H-dibenz[b,e]azepine, 2.00 g of ethyl bromoacetate and 1.38 g of potassium carbonate in 14 ml of N,N-dimethylformamide was stirred at 70° C. for 3 hrs. After cooling, water was added to the reaction mixture and extracted with ether. The etheral layer was washed with water, dried and concentrated. The residue was chromatographed on silica gel using a mixture of n-hexane and ethyl acetate (2:1 and 1:1) as eluents to give 2.91 g of colorless crystals, which were recrystallized from isopropyl ether to give colorless prisms, mp 107°–108° C.

Analysis for $C_{22}H_{25}N_3O_2$ Calculated C, 72.70; H, 6.93; N, 11.56 Found C, 72.76; H, 6.78; N, 11.53

The compounds of Example 26 to 28 were prepared in the same manner as described in Example 25.

Example 26

Ethyl 4-(11H-Dibenz[b,e]azepin-6-yl)-1-piperazinebutyrate

Pale yellow prisms, mp 106°–107° C. (iso-Pr₂O)
Analysis for $C_{24}H_{29}N_3O_2$ Calculated C, 73.63; H, 7.47; N, 10.73 Found C, 73.39; H, 7.54; N, 10.54

Example 27

Ethyl 4-(11H-Dibenz[b,e]azepin-6-yl)-1-piperazinevalerate

Colorless prisms, mp 57°–58° C. (iso-Pr₂O-n-pentane)
Analysis for $C_{25}H_{31}N_3O_2$ Calculated C, 74.04; H, 7.70; N, 10.36 Found C, 74.22; H, 7.81; N, 10.40

Example 28

Ethyl 4-(11H-Dibenz[b,e]azepin-6-yl)-1-piperazinecaproate

Colorless prisms, mp 62.5°–63° C. (iso-Pr₂O-n-pentane)
Analysis for $C_{26}H_{33}N_3O_2$ Calculated C, 74.43; H, 7.93; N, 10.02 Found C, 74.48; H, 7.83; N, 9.97

Example 29

4-(11H-Dibenz[b,e]azepin-6-yl)-1-Piperazineacetic acid

2N Aqueous sodium hydroxide solution (5 ml) was added to a solution of 1.82 g of ethyl 4-(11H-dibenz[b,e]azepin-6-yl)-1-piperazineacetate in 18 ml of methanol. The solution was refluxed for 30 min and then concentrated. The residue was dissolved in hot water and the solution was neutralized with 0.5N hydrochloric acid. The precipitates were collected by filtration to give 1.06 g of colorless crystals, which were recrystallized from ethanol to give colorless granules, mp 181°–183° C. (decomp.).

Analysis for $C_{20}H_{21}N_3O_2 \cdot H_2O$ Calculated C, 67.97; H, 6.56; N, 11.89 Found C, 67.74; H, 6.40; N, 11.82
The compounds of Example 30 to 33 were prepared in the same manner as described in Example 29.

Example 30

4-(11H-Dibenz[b,e]azepin-6-yl)-1-piperazinepropionic acid

Colorless prisms, mp 140°–141° C. (aq. EtOH)
Analysis for $C_{21}H_{23}N_3O_2 \cdot 2H_2O$ Calculated C, 65.44; H, 7.06; N, 10.90 Found C, 65.44; H, 7.02; N, 10.85

Example 31

4-(11H-Dibenz[b,e]azepin-6-yl)-1-piperazinebutyric acid

Colorless prisms, mp 207°–208° C. (aq. EtOH)
Analysis for $C_{22}H_{25}N_3O_2$ Calculated C, 72.70; H, 6.93; N, 11.56 Found C, 72.73; H, 7.13; N, 11.59

Example 32

4-(11H-Dibenz[b,e]azepin-6-yl)-1-piperazinevaleric acid

Colorless granules, mp 235°–237° C. (aq. EtOH)
Analysis for $C_{23}H_{27}N_3O_2$ Calculated C, 73.18; H, 7.21; N, 11.13 Found C, 73.01; H, 7.19; N, 11.20

Example 33

4-(11H-Dibenz[b,e]azepin-6-yl)-1-piperazinecaproic acid

Colorless prisms, mp 99°–100° C. (aq. EtOH)
Analysis for $C_{24}H_{29}N_3O_2 \cdot H_2O$ Calculated C, 70.39; H, 7.63; N, 10.26 Found C, 70.29; H, 7.54; N, 10.24

Example 34

Ethyl 4-(1,2,3,4,10,14b-Hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)formate

Ethyl chloroformate (19.53 g) was added dropwisely to a solution of 9.52 g of 1,2,3,4,10,14b-hexahydro-2-methylidibenzo[c,f]pyrazino[1,2-a]azepine in 48 ml of benzene at refluxed temperature and the mixture was refluxed for 5 hrs. Ice water was added to the reaction mixture and made alkaline with sodium bicarbonate. The mixture was extracted with benzene and the benzene layer was washed with water, dried and concentrated. The residue was chromatographed on silica gel using a mixture of n-hexane and ethyl acetate as an eluent (1:2) to give 8.70 g of pale yellow crystals, which were recrystallized from a mixture of isopropyl ether and n-pentane to give pale yellow prisms, mp 108.5°–109.5° C.
Analysis for $C_{20}H_{22}N_2O_2$ Calculated C, 74.51; H, 6.88; N, 8.69 Found C, 74.43; H, 7.06; N, 8.57

Example 35

Ethyl 3-(1,2,3,4,10,14b-Hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)propionate

A mixture of 2.50 g of 1,2,3,4,10,14b-hexahydrodibenzo[c,f]pyrazino[1,2-a]azepine and 1.20 g of ethyl acrylate in 13 ml of ethanol was refluxed for 3 hrs. The reaction mixture was concentrated and the residue was chromatographed on silica gel using a mixture of n-hexane and ethyl acetate (1:1) as an eluent to give 3.08 g of colorless crystals, which were recrystallized from isopropyl ether to give colorless needles, mp 159°–160° C.

Analysis for $C_{22}H_{26}N_2O_2$ Calculated C, 75.40; H, 7.48; N, 7.99 Found C, 75.35; H, 7.58; N, 7.79

Example 36

Ethyl 2-(1,2,3,4,10,14b-Hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)acetate

A mixture of 2.50 g of 1,2,3,4,10,14b-hexahydrodibenzo[c,f]pyrazino[1,2-a]azepine, 2.00 g of ethyl bromoacetate and 1.38 g of potassium carbonate in 13 ml of N,N-dimethylformamide was stirred at 70° C. for 3 hrs. After cooling, water was added to the reaction mixture and extracted with ether. The etheral layer was washed with water, dried and concentrated. The residue was chromatographed on silica gel using a mixture

of n-hexane and ethyl acetate (1:1) as an eluent to give 3.20 g of pale yellow crystals.

IR spectrum ν (KBr) cm^{-1} : 1748 (COO) NMR spectrum δ (CDCl₃) ppm: 1.27(3H, t, J=7 Hz), 2.30–3.70(7H, m), 3.30(2H, s), 4.00–4.40(3H, m), 4.82(1H, d, J=13 Hz), 6.65–7.25(8H, m)

High resolution mass spectrum for $C_{21}H_{24}N_2O_2$ Calculated m/z: 336.1837 Found m/z: 336.1803

The compounds of Example 37 to 39 were prepared in the same manner as described in Example 36.

Example 37

Ethyl 4-(1,2,3,4,10,14b-Hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)butyrate

Yellowish viscous oil
IR spectrum ν (liq) cm^{-1} : 1738 (COO) NMR spectrum δ (CDCl₃) ppm: 1.25(3H, t, J=7 Hz), 1.60–3.50(13H, m), 3.90–4.40(3H, m), 4.85(1H, d, J=13 Hz), 6.60–7.40(8H, m)

High resolution mass spectrum for $C_{23}H_{28}N_2O_2$ Calculated m/z: 364.2151 Found m/z: 364.2152

Example 38

Ethyl 5-(1,2,3,4,10,14b-Hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)valerate

Yellowish viscous oil
IR spectrum ν (liq) cm^{-1} : 1736 (COO) NMR spectrum δ (CDCl₃) ppm: 1.25(3H, t, J=7 Hz), 1.40–3.50(15H, m), 3.95–4.40(3H, m), 4.85(1H, d, J=13 Hz), 6.80–7.50(8H, m)

High resolution mass spectrum for $C_{24}H_{30}N_2O_2$ Calculated m/z: 378.2307 Found m/z: 378.2311

Example 39

Ethyl 6-(1,2,3,4,10,14b-Hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)caproate

Yellowish viscous oil
IR spectrum ν (liq) cm^{-1} : 1738 (COO) NMR spectrum δ (CDCl₃) ppm: 1.25(3H, t, J=7 Hz), 1.30–3.50(17H, m), 3.95–4.40(3H, m), 4.85(1H, d, J=13 Hz), 6.70–7.40(8H, m)

High resolution mass spectrum for $C_{25}H_{32}N_2O_2$ Calculated m/z: 392.2464 Found m/z: 392.2453

Example 40

2-(1,2,3,4,10,14b-Hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)acetic acid

2N Aqueous sodium hydroxide solution (5 ml) was added to a solution of 1.68 g of ethyl 2-(1,2,3,4,10,14b-hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)acetate in 17 ml of methanol. The solution was refluxed for 30 min and then concentrated. The residue was dissolved in hot water and the solution was neutralized with 0.5N hydrochloric acid. The precipitates were collected by filtration to give 1.33 g of colorless crystals, which were recrystallized from aqueous ethanol to give colorless needles, mp 162°–163° C.

Analysis for $C_{19}H_{20}N_2O_2 \cdot 2H_2O$ Calculated C, 66.26; H, 7.02; N, 8.13 Found C, 66.45; H, 6.88; N, 8.12

The compounds of Example 41 to 44 were prepared in the same manner as described in Example 40.

Example 41

3-(1,2,3,4,10,14b-Hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)propionic acid

Colorless crystals, mp 195°–197° C. (H_2O -EtOH)
Analysis for $C_{20}H_{22}N_2O_2 \cdot \frac{1}{2}H_2O$ Calculated C, 72.48; H, 6.99; N, 8.45 Found C, 72.34; H, 6.81; N, 8.45

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Example 42

4-(1,2,3,4,10,14b-Hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)butyric acid
Colorless crystals, mp 104°-105° C. (H₂O-EtOH)
Analysis for C₂₁H₂₄N₂O₂ Calculated C, 74.97; H, 7.19; N, 8.33 Found C, 74.95; H, 7.13; N, 8.35

Example 43

5-(1,2,3,4,10,14b-Hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)valeric acid
Colorless prisms, mp 218°-219° C. (H₂O-EtOH)
Analysis for C₂₂H₂₆N₂O₂ Calculated C, 75.40; H, 7.48; N, 7.99 Found C, 75.56; H, 7.56; N, 7.96

Example 44

6-(1,2,3,4,10,14b-Hexahydrodibenzo[c,f]pyrazino[1,2-a]azepin-2-yl)caproic acid
Colorless crystals, mp 181°-182° C. (H₂O-EtOH)
Analysis for C₂₃H₂₈N₂O₂ Calculated C, 75.79; H, 7.74; N, 7.69 Found C, 75.95; H, 7.79; N, 7.58

Example 45

Tablets of a pharmaceutical preparation according to the present invention are prepared in the usual manner using the following constituents:

Compound of the present invention	10 mg
Lactose	q.s.
Corn starch	34 mg
Magnesium stearate	2 mg
Hydroxypropylmethylcellulose	8 mg
Polyethylene glycol 6000	0.5 mg
Titanium oxide	0.5 mg

Example 46

Capsules of a pharmaceutical preparation according to the present invention are prepared in the usual manner using the following constituents:

Compound of the present invention	10 mg
Lactose	q.s.
Calcium carboxymethylcellulose	15 mg
Hydroxypropylcellulose	2 mg
Magnesium stearate	2 mg
	100 mg

Example 47

Powders of a pharmaceutical preparation according to the present invention are prepared in the usual manner using the following constituents:

Compound of the present invention	20 mg
Lactose	q.s.
D-Mannitol	500 mg
Hydroxypropylcellulose	5 mg
Talc	2 mg
	1000 mg

Example 48

Injectations of a pharmaceutical preparation according to the present invention are prepared in the usual manner using the following constituents:

Compound of the present invention	1 mg
Glucose	50 mg
Hydrochloric acid	q.s.
Distilled water for injection	q.s.
	2 ml

Example 49

Suppositories of a pharmaceutical preparation according to the present invention are prepared in the usual manner using the following constituents:

Compound of the present invention	5 mg
Hard fat	1295 mg
	1300 mg

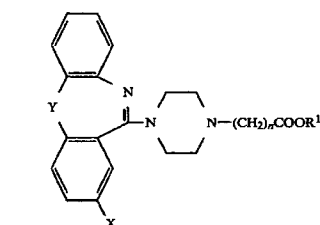
Example 50

Plasters of a pharmaceutical preparation according to the present invention are prepared in the usual manner using the following constituents:

Compound of the present invention	10 mg
Gelatin	1100 mg
Polyvinylalcohol	250 mg
Methylcellulose	100 mg
Glycerin	1500 mg
Kaolin	850 mg
Sodium polyacrylate	50 mg
Polybutene	150 mg
Purified water	990 mg
	5000 mg

What is claimed is:

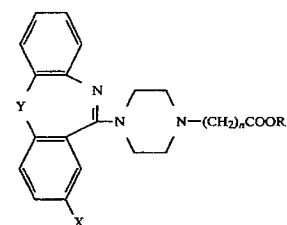
1. A polycyclic compound represented by the following formula:



wherein R¹ represents a hydrogen atom; n represents an integer of from 1 to 5; X represents a hydrogen atom or a halogen atom; and Y represents an oxygen atom or a sulfur atom;

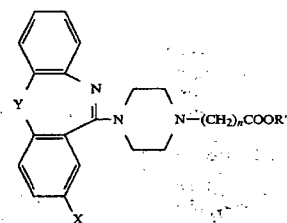
or a pharmacologically acceptable salt thereof.

2. A polycyclic compound represented by the following formula:



wherein R¹ represents a hydrogen atom; n represents an integer of from 1 to 5; X represents a hydrogen atom or a halogen atom; and Y represents a methylene group; or a pharmacologically acceptable salt thereof.

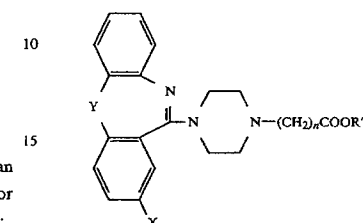
3. A pharmaceutical composition comprising an effective amount of a polycyclic compound represented by the following formula:



wherein R¹ represents a hydrogen atom; n represents an integer of from 1 to 5; X represents a hydrogen atom or a halogen atom; and Y represents an oxygen atom or a sulfur atom;

or a pharmacologically acceptable salt thereof, together with a pharmaceutically acceptable carrier or coating.

4. A pharmaceutical composition comprising an effective amount of a polycyclic compound represented by the following formula:



wherein R¹ represents a hydrogen atom; n represents an integer of from 1 to 5; X represents a hydrogen atom or a halogen atom; and Y represents a methylene group; or a pharmacologically acceptable salt thereof, together with a pharmaceutically acceptable carrier or coating.

5. 4-(2-Chlorodibenzo[b,f][1,4]oxazepin-11-yl)-1-piperazinepropionic acid and a pharmacologically acceptable salt thereof.

6. 4-(2-Chlorodibenzo[b,f][1,4]oxazepin-11-yl)-1-piperazinebutyric acid and a pharmacologically acceptable salt thereof.

7. 4-(2-Chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinepropionic acid and a pharmacologically acceptable salt thereof.

8. 4-(2-Chlorodibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinebutyric acid and a pharmacologically acceptable salt thereof.

9. 4-(11H-Dibenzo[b,c]azepin-6-yl)-1-piperazinepropionic acid and a pharmacologically acceptable salt thereof.

10. 4-(11H-dibenzo[b,c]azepin-6-yl)-1-piperazinebutyric acid and a pharmacologically acceptable salt thereof.

* * * * *

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(71) Applicant (for all designated States except US): BASF
AKTIENGESELLSCHAFT [DE/DE]; 67056 Lud-
wigshafen (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): STEINER, Gerd
[DE/DE]; Oberer Waldweg 1, 67281 Kirchheim (DE).
SCHMIDT, Thomas [DE/DE]; Pfarrgasse 8, 67433
Neustadt (DE). KORDES, Markus [DE/DE]; Bensheimer
Ring 13 d, 67227 Frankenthal (DE). VON DEYN, Wolf-
gang [DE/DE]; An der Bleiche 24, 67435 Neustadt (DE).
GÖTZ, Norbert [DE/DE]; Schöfferstr.25, 67547 Worms
(DE). HOFMANN, Michael [DE/DE]; Lutherstr.2,
67059 Ludwigshafen (DE). DE KRAMER, Jacobus
Jan [NL/DE]; Stettiner Str.4, 67691 Hochspeyer (DE).
HEFFERNAN, Gavin [GB/US]; 616 East Sixth Street,
Florence, NJ 08518 (US). CULBERTSON, Deborah
L. [US/US]; 6400 Vintage Ridge Lane, Fuquay Va-
rina, NC 27526 (US). TREACY, Michael, E. [US/US];
5333 High Bank Dr., Corpus Christi, TX 78413 (US).
OLOUMI-SADEGHI, Hassan [US/US]; 12105 Pawley's

Mill Circle, Raleigh, NC 27614 (US). EBUENGA, Cecille
[PI/PI]; Purok VI, Putho-Tuntungin, Los Banos, Laguna
(PI). TEDESCHI, Livio [IT/DE]; Kleinfeldstrasse 48a,
68165 Mannheim (DE). BUCCI, Toni [US/US]; 2629
Hidden Meadow Drive, Fuquay Varina, NC 27526 (US).
PARRA RAPADO, Liliana [ES/DE]; S 6, 29-31, 68161
Mannheim (DE). RACK, Michael [DE/DE]; Sandwingert
67, 69123 Heidelberg (DE). BAUMANN, Ernst [DE/DE];
Hakenstr. 6a, 67373 Dudenhofen (DE). PUHL, Michael
[DE/DE]; Bürstädter Str. 95, 68623 Lampertheim (DE).

(74) Common Representative: BASF AKTIENGE-
SELLSCHAFT; 67056 LUDWIGSHAFEN (DE).

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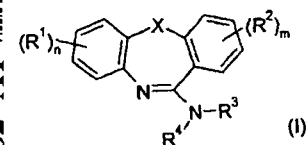
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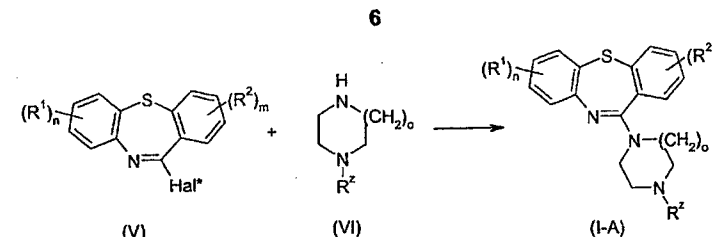
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(57) Abstract: Use of compounds of formula (I): wherein X is S, O, S=O,
SO₂, NR^a, or CR^aR^b; R¹, R² are halogen, OH, SH, NH₂, CN, NO₂, alkyl,
alkoxy, alkylamino, dialkylamino, alkylthio, alkenyl, alkenyloxy, alkenylamino,
alkenylthio, alkynyl, alkynyloxy, alkynylamino, alkynylthio, alkylsulfonyl,
alkylsulfoxyl, alkylsulfonyl, alkynylsulfoxyl, formyl, alkylcarbonyl,
hydroxycarbonyl, alkoxy carbonyl, carbonyloxy, alkylcarbonyloxy, phenyloxy,
alkylcarbonylamino, C(O)NR^aR^b, or (SO₂)NR^aR^b, or C=NOR^a-G^c-R^d, or a mono-
or bicyclic 5- to 10-membered aromatic or heteroaromatic ringsystem, optionally
substituted, which is unfused or fused to the aromatic group to which it is bonded and which, when unfused, is bonded directly or
through an O, S, alkyl, or alkoxy linkage, or cycloalkyl, wherein the carbon atoms in these groups may be substituted. R³, R⁴ are each
independently H, alkyl, haloalkyl, alkylamino, alkoxy, cycloalkyl, wherein the carbon atoms in these groups may be substituted,
or R³ and R⁴ together with the nitrogen atom to which they are attached form a saturated or partially saturated mono- or bicyclic
5- to 10-membered ringsystem or 5-membered heteraryl, phenyl or benzyl, wherein the rings are optionally sub-stituted, or R³ and
R⁴ together form the chains -(CH₂)₂N^a(O^a)(CH₂)₂- or -(CH₂)₃N^a(O^a)(CH₂)₂-; and R^a, R^b, R^c, R^d, R^e, R^f, G, and p are as defined
in the description; m is 0, 1, 2, 3 or 4; n is 0, 1, 2, 3 or 4; or the enantiomers or diastereomers, salts or esters thereof for combatting
insects, arachnids, or nematodes, methods for the control of these pests and of protecting growing plants from attack or infestation
by these pests by applying a pesticidally effective amount of compounds of formula (I), compounds of formula (I), processes for
preparing them, and compositions comprising them.

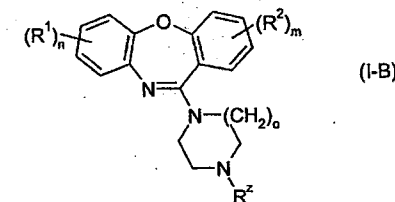


The reaction is usually carried out at temperatures of from 20°C to 250°C, preferably
from 80°C to 120°C, in an inert organic solvent or pure compound VI.

- 5 Suitable solvents are aromatic hydrocarbons such as toluene, o-, m- and p-xylene,
halogenated hydrocarbons, such as methylene chloride, chloroform and chloroben-
zene, ethers, such as diethylether, diisopropylether, tert.-butylmethylether, diglyme,
dioxane, anisol and tetrahydrofuran, and also dimethyl sulfoxide, dimethyl formamide
and dimethyl acetamide. Preferred solvents are toluene, xylene and dioxane. It is also
10 possible to use mixtures of the solvents mentioned.

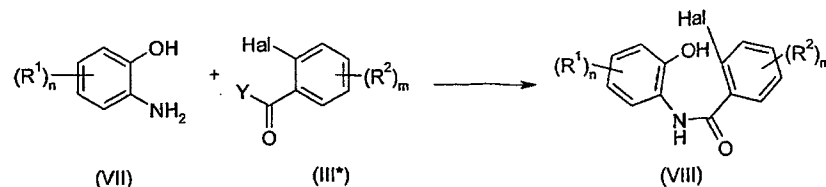
Compounds of formula VI are commercially available or can be prepared following
methods described in the literature [see e.g. J. Org. Chem. 31, p. 3867-3868 (1966)].

- 15 Compounds of formula I wherein X is oxygen are for example obtainable according to
the procedure described in J. Med. Chem. (1992), 35, 1887 or DE 1 645 954. These
processes encompass five to six steps. It was therefore also an object of the present
invention to provide a simpler process. Accordingly, the following process to com-
pounds of formula I-B wherein the variables and the indices have the meanings as
20 defined for formula I-A was found



wherein in a first step o-amino-phenol derivatives of formula VII are reacted with ben-
zoic acid derivatives III wherein Hal is halogen, preferably chloro or bromo, and Y is
hydroxy, halogen or C₁-C₆-alkoxy, preferably chloro or bromo, to give compounds VIII,
25 wherein the variables and the indices of the compounds III*, VII and VIII have the
meanings as defined for formula I.

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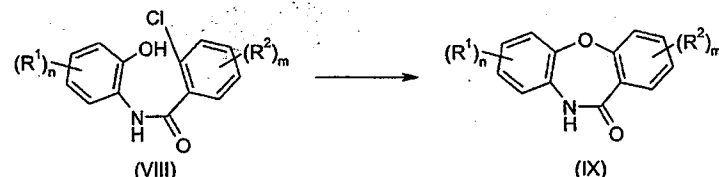


The reaction is usually carried out at temperatures of from 20°C to 250°C, preferably from 20°C to 100°C, in an inert organic solvent, in the presence of a water eliminating agent such as carbonyldiimidazol or dicyclohexylcarbodiimide if Y is hydroxy, and in the presence of a base such as a tertiary amine if Y is halogen.

Suitable solvents are aromatic hydrocarbons such as toluene, o-, m- and p-xylene, halogenated hydrocarbons, such as methylene chloride, chloroform and chlorobenzene, ethers, such as diethylether, diisopropylether, tert.-butylmethylether, diglyme, dioxane, anisol and tetrahydrofuran, and also dimethyl sulfoxide, dimethyl formamide and dimethyl acetamide. Preferred solvents are THF and toluene. It is also possible to use mixtures of the solvents mentioned.

Compounds of formula VII are obtainable by customary methods, or are commercially available [see e.g. Houben-Weyl, Methoden der organischen Chemie, 4th edition, Volume VI/1c, p. 53-54, p. 85-109, p. 477-480].

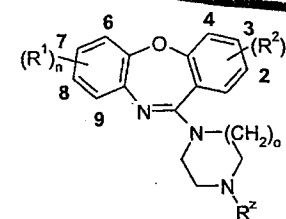
In a second step, compounds of formula VIII are transformed into compounds of formula IX, wherein the variables and the indices have the meanings as defined for formula I, by cyclization in the presence of a strong base.



The reaction is usually carried out at temperatures of from 20°C to 250°C, preferably from 20°C to 180°C, in an inert organic solvent.

Suitable solvents are aromatic hydrocarbons such as toluene, o-, m- and p-xylene, halogenated hydrocarbons, ethers, such as diglyme, and also dimethyl sulfoxide, dimethyl formamide and dimethyl acetamide. Preferred solvents are DMF, dimethyl acetamide or toluene, preferably dimethyl acetamide. It is also possible to use mixtures of the solvents mentioned.

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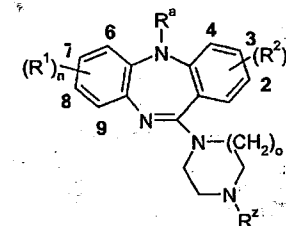
wherein R² and the indices n, m, and o are as defined for formula I-A and R¹ and R² each independently are halogen, C₁-C₆-alkyl, C₁-C₆-haloalkyl, methoxy, C₁-C₆-haloalkoxy, C₁-C₆-alkylthio, C₁-C₆-haloalkylthio, C₂-C₆-alkenylthio, or C₂-C₆-alkynylthio, with the proviso that

when R¹ is 2-chloro then R² is not 8-chloro or 8-methoxy; and

when R¹ is 4-chloro then R² is not 8-chloro; and

when R¹ is 4-methyl then R² is not 7-, 8-, or 9-chloro.

Furthermore, particular preference is given to compounds of formula I-C



wherein R^a is hydrogen or C₁-C₆-alkyl and the further variables and indices are as defined for formula I-B, with the proviso that

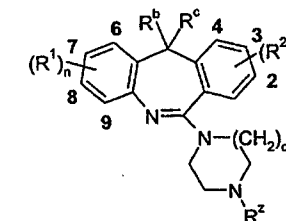
not both of R¹ or R² are halogen and

when R¹ is 2-chloro then R² is not 8-methyl, 8-methylthio, or 8-methoxy; and

when R¹ is 2-methoxy, then R² is not 8-chloro; and

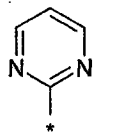
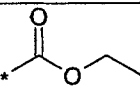
when R¹ is 2-methyl then R² is not 8-chloro.

Moreover, particular preference is given to compounds of formula I-D

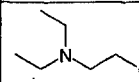
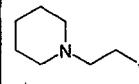
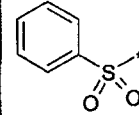
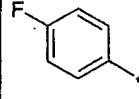
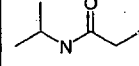
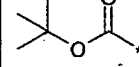


wherein R^b and R^c are each independently hydrogen, methyl or CR^bR^c represents C=CH₂, and the further variables and the indices are as defined for formula I-B.

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No.	X	(R ¹) _n	(R ²) _m	o	R ^z	Physical data (m.p.[°C] / ¹ H-NMR (CDCl ₃): δ [ppm]) / MS: m/z [M+H] ⁺
I-B.77	O	8-F	2-SCH ₃	1	(CH ₂) ₂ CH ₃	115-117
I-B.78	O	8-Cl	2-OH	1	CH ₃	247-249
I-B.79	O	8-CH ₃	2-Cl	1	(CH ₂) ₂ CH ₃	108-110
I-B.80	O	8-CH ₃	2-Cl	1	(CH ₂) ₂ CH ₃	61-63
I-B.81	O	8-CH ₃	2-Cl	1	CH ₂ CHCH ₂	129-131
I-B.82	O	8-CH ₃	2-Cl	2	CH ₃	61-63
I-B.83	O	8-CH ₃	2-Cl	1	CH ₂ CF ₃	115-119
I-B.84	O	8-CH ₃	2-Cl	1	CH(CH ₃) ₂	73-75
I-B.85	O	8-CH ₃	2-Cl	1	CH ₂ CCH	70-73
I-B.86	O	8-CH ₃	2-Cl	1	C ₆ H ₁₁	149-152
I-B.87	O	8-CH ₃	2-Cl	1	CH ₂ -cyclo-C ₃ H ₅	93-96
I-B.88	O	7-F	2-Br	1	CH ₃	79-81
I-B.89	O	7-F	2-Br	1	CH ₂ CH ₃	123-126
I-B.90	O	7-F	2-Br	1	(CH ₂) ₂ CH ₃	131-133
I-B.91	O	7-F	2-Br	1	CH ₂ CCH	166-169
I-B.92	O	8-Cl	2-SCF ₃	1	CH ₃	60-62
I-B.93	O	7-F	2-SCH ₃	1	CH ₂ CH ₃	143-145
I-B.94	O	7-F	2-SCH ₃	1	(CH ₂) ₂ CH ₃	99-102
I-B.95	O	7-F	2-SCH ₃	1	CH ₂ CCH	71-73
I-B.96	O	8-CH ₂ CH ₃	2-Cl	1	CH ₃	7.4 (dd), 7.3 (d), 7.2 (d), 7.0 (d), 6.9 (dd), 3.5 (s), 2.5 (m), 2.4 (s), 1.2 (t)
I-B.97	O	8-Cl	2-OCH ₂ CH ₃	1	CH ₃	133-135
I-B.98	O	8-Cl	2-OCH ₂ CH ₃	1	(CH ₂) ₂ CH ₃	oil
I-B.99	O	7-Cl	2-Cl	1	CH ₃	145-147
I-B.100	O	7-Cl	2-Cl	1	CH ₂ CH ₃	155-157
I-B.101	O	8-Br	2-CF ₃	1	CH ₃	73-75
I-B.102	O	8-Br	2-CF ₃	1	(CH ₂) ₂ CH ₃	oil
I-B.103	O	8-CH ₃	2-Cl	1		165-167
I-B.104	O	8-CH ₃	2-Cl	1		83-85
I-B.105	O	7-Cl	2-Cl	1	CH ₂ CCH	180-183
I-B.106	O	7-Cl	2-Cl	1	(CH ₂) ₂ CH ₃	157-160
I-B.107	O	8-F	2-Br	1	(CH ₂) ₂ CH ₃	oil

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No.	X	(R ¹) _n	(R ²) _m	o	R ^z	Physical data (m.p.[°C] / ¹ H-NMR (CDCl ₃): δ [ppm]) / MS: m/z [M+H] ⁺
I-B.131	O	8-CH ₃	2-Cl	1		MS: 427
I-B.132	O	8-CH ₃	2-Cl	1		MS: 439
I-B.133	O	8-CH ₃	2-Cl	1		MS: = 469
I-B.134	O	8-CH ₃	2-Cl	1		MS: 422
I-B.135	O	8-CH ₃	2-Cl	1		MS: 427
I-B.136	O	8-CH ₃	2-Cl	1		MS: 428
I-B.137	O	8-CH ₃	2-CONH ₂	1	CH ₃	122-124
I-B.138	O	7-F	2-NHCOCH ₃	1	CH ₂ CH ₃	102-104
I-B.139	O	8-CH ₃	2-CN	1	CH ₃	148-151
I-B.140	O	8-F	2-NO ₂	1	CH ₃	oil
I-B.141	O	8-F	2-NH ₂	1	CH ₃	78-79
I-B.142	O	7-F	2-NHCOCH ₃	1	CH ₃	120-122
I-C.1	NH	H	H	1	CH ₃	177-179
I-C.2	NH	H	H	1	CH ₂ CH ₃	164-166
I-C.3	NH	H	2-SCH ₃	1	CH ₃	82-84
I-C.4	NH	8-Cl	2-SCH ₃	1	CH ₃	182-184
I-C.5	NH	7-Cl	2-SCH ₃	1	CH ₃	138-140
I-C.6	NH	H	2-Br	1	CH ₃	193-195
I-C.7	NH	H	2-OCH ₃	1	CH ₃	89-91
I-C.8	NH	8-CH ₃	2-Cl	1	CH ₃	195
I-C.9	NH	7-F	2-SCH ₃	1	CH ₃	7.2 (m), 6.8 (m), 6.6 (m), 3.5 (s), 2.5 (s), 2.4 (s), 2.3 (s)
I-D.1	CH ₂	H	H	1	CH ₂ CHCH ₂	102-104
I-D.2	CH ₂	H	H	1	(CH ₂) ₃ CH ₃	90-92
I-D.3	CH ₂	H	H	1	CH ₂ CH ₂	96-98
I-D.4	CH ₂	H	H	1	(CH ₂) ₂ CH ₂	110-112