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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-006378- -00004-0001

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Tra. 11 PATENTLIYII Eve: 344 DESGLOSE
Act. 411 PRESENTACION Folios: 1

jllc00@lloredacamacho.com

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: P1.-F. HOFFMANN LA ROCHE AG.- Patente de Invención en Fase
Nacional PCT para "COMBINACIÓN DE UN ANTAGONISTA DE
mGluR2 Y UN INHIBIDOR DE AChE PARA EL TRATAMIENTO DE
TRASTORNOS NEUROLÓGICOS AGUDOS Y/O CRÓNICOS".- Clase
A61K 31/551.-Expediente número 06-006.378.-

1. Me refiero a mi memorial de 19 de Septiembre de 2007.
2. Por medio del presente escrito, atentamente me permito solicitar a ese despacho, el desglose del recibo de pago allegado con mi memorial arriba mencionado, ya que por un error involuntario se presentó, siendo que este trámite solamente aplica para las solicitudes PCT Sin Publicar, según la respuesta emitida por ese Despacho al Derecho de Petición cuyo número es: 07-089.021.
3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad a la mayor brevedad posible.

Señor Superintendente,


ALICIA LLOREDA RICAURTE
T.P. 53.215

2020
Bogotá, D.C.,

Doctora:
Alicia Lloreda Ricaurte
Apoderada

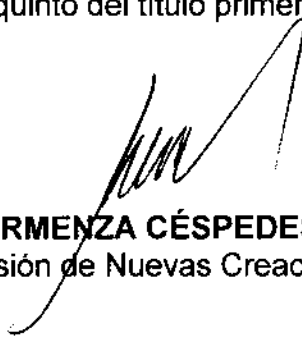
Oficio N°: 12618

ASUNTO:	Radicación PCT N°	06-6378
	Trámite	011
	Evento	344
	Actuación	330
	Folios	002

Atendiendo la solicitud contenida en el escrito de fecha 21 de septiembre del 2007 radicado bajo el número 06-006378-00004-0001, ordenase el desglose del recibo de caja N° 07-74,066 por valor de noventa y nueve mil pesos mcte (\$99.000.00), el cual obra a folio 157 del expediente administrativo, dejando copia dentro del mismo, previa entrega del original al solicitante para su aplicación a otro trámite ante esta Superintendencia.

Envíese copia del presente oficio a la División Financiera, para lo de su competencia.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.



ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe División de Nuevas Creaciones

El anterior oficio fue notificado por fijación en lista de fecha, _____.

202021

Recibo Desglose
Franca Elena Garcia

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-06378

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **564** DE

FECHA **31 DE MAYO DE 2006** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL 31 DE AGOSTO DE 2006

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

United States Patent [19]

Sugimoto et al.

US005100901A

[11] Patent Number: 5,100,901

[45] Date of Patent: Mar. 31, 1992

[54] CYCLIC AMINE COMPOUNDS AND PHARMACEUTICAL USE

[75] Inventors: Hachiro Sugimoto, Ushiku, Japan; Yutaka Tsuchiya, Fort Lee, N.J.; Kunizou Higurashi, Tokyo, Japan; Norio Karibe, Tsukuba, Japan; Youichi Iimura, Tsukuba, Japan; Atsushi Sasaki, Tsukuba, Japan; Yoshiharu Yamanishi, Ryugasaki, Japan; Hiroo Ogura, Tsuchiura, Japan; Shin Araki, Tsukuba, Japan; Takashi Kosasa, Tsukuba, Japan; Atsuhiko Kubota, Tsukuba, Japan; Michiko Kosasa, Tsukuba, Japan; Kiyomi Yamatsu, Kamakura, Japan

[73] Assignee: Eisai Co., Ltd., Tokyo, Japan

[21] Appl. No.: 423,349

[22] Filed: Oct. 18, 1989

Related U.S. Application Data

[62] Division of Ser. No. 209,339, Jun. 20, 1988, Pat. No. 4,895,841.

[30] Foreign Application Priority Data

Jun. 22, 1987 [JP] Japan 62-155058

[51] Int. Cl.⁵ A61K 31/445; C07D 241/36; C07D 211/06; C07D 217/18

[52] U.S. Cl. 514/319; 544/353; 546/206; 546/193; 546/194; 546/141; 546/149; 546/203; 546/205; 514/318; 514/325

[58] Field of Search 546/206, 193, 194, 141, 546/149, 205; 514/319; 544/353

[56] References Cited

PUBLICATIONS

CA 110:173102c Preparation . . . Inhibitors, Sugimoto et al. p. 763, Dec. 1988.

CA 111:232532p Synthesis of . . . Hydrochloride, Iimura et al, 1989.

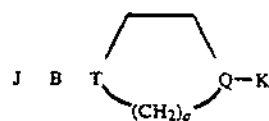
Primary Examiner—Mary C. Lee

Assistant Examiner—Joseph K. McKane

Attorney, Agent, or Firm—Flynn, Thiel, Boutell & Tanis

[57] ABSTRACT

A cyclic amine compound is defined by the formula:



in which J is indanyl, indanonyl, indenyl, indenonyl, indanedionyl, tetralonyl, benzosuberonyl, indanoly or a divalent group thereof, K is phenyl, an arylalkyl or cinnamyl, B is $-(CHR_{22})_r-$, R_{22} being H or methyl, $-\text{CO}-$ $(CHR_{22})_r-$, $=(\text{CH}-\text{CH}=\text{CH})_b-$, $=\text{CH}-(\text{CH}_2)_c-$ or $=(\text{CH}-\text{CH})_d=$ and the ring including T and Q is piperidine. The compound is useful to treat senile dementia.

17 Claims, No Drawings

SUMMARY OF THE INVENTION

The invention provides a cyclic amine compound having the following formula (XXV) and a pharmacologically acceptable salt thereof:

XXV

STATEMENT OF PRIOR ARTS

10

$$\begin{array}{c} \text{J} \quad \text{B} \quad \text{T} \qquad \text{Q-K} \\ \quad \quad \quad \curvearrowright (\text{CH}_2)_n \end{array}$$

in which J is

(a) a group, substituted or unsubstituted, selected from the group consisting of (1) phenyl, (2) pyridyl, (3) pyrazyl, (4) quinolyl, (5) cyclohexyl, (6) quinoxalyl and (7) furyl;

(b) a monovalent or divalent group, in which the phenyl may have a substituent(s), selected from the group consisting of (1) indanyl, (2) indanonyl, (3) indenyl, (4) indenonyl, (5) indanedionyl, (6) tetralonyl, (7) benzosuberonyl, (8) indanolyl and (9) $C_6H_5-CO-CH(CH_3)-$;

(c) a monovalent group derived from a cyclic amide compound;

(d) a lower alkyl or

(e) a group of $R^{21}-CH=CH-$ in which R^{21} is hydrogen or a lower alkoxy carbonyl;

B is $-(\text{CHR}^{22})_r-$, $-\text{CO}-(\text{CHR}^{22})_r-$, $-\text{NR}^4-(\text{CHR}^{22})_r$, R^4 being hydrogen, a lower alkyl, an acyl, a lower alkylsulfonyl, phenyl, a substituted phenyl, benzyl or a substituted benzyl, $-\text{CO}-\text{NR}^5-(\text{CHR}^{22})_r$, R^5 being hydrogen, a lower alkyl or phenyl, $-\text{CH}=\text{CH}-(\text{CHR}^{22})_r$, $-\text{OCOO}-(\text{CHR}^{22})_r$, $-\text{OOC}-\text{NH}-(\text{CHR}^{22})_r$, $-\text{NH}-\text{CO}-(\text{CHR}^{22})_r$, $-\text{CH}_2-\text{CO}-\text{NH}-(\text{CHR}^{22})_r$, $-(\text{CH}_2)_2-\text{CO}-\text{NH}-(\text{CHR}^{22})_r$, $-\text{CH}(\text{OH})-(\text{CHR}^{22})_r$, r being zero or an integer of 1 to 10, R^{22} being hydrogen or methyl so that one alkylene group may have no methyl branch or one or more methyl branch, $=(\text{CH}-\text{CH}=\text{CH})_b-$, b being an integer of 1 to 3, $=\text{CH}-(\text{CH}_2)_c-$, c being zero or an integer of 1 to 9, $=(\text{CH}-\text{CH})_d-$, d being zero or an integer of 1 to 5; $-\text{CO}-\text{CH}=\text{CH}-\text{CH}_2-$, $-\text{CO}-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-\text{CO}-\text{NH}-\text{CH}_2-$, $-\text{CH}=\text{CH}-\text{CO}-\text{NH}-(\text{CH}_2)_2-$, $-\text{NH}-\text{O}-$, $-\text{S}-$, a dialkylaminoalkylcarbonyl or a lower alkoxy carbonyl;

T is nitrogen or carbon;

Q is nitrogen, carbon or $>\text{N}\rightarrow\text{O}$; and

q is an integer of 1 to 3:

K is hydrogen, phenyl, a substituted phenyl, an arylalkyl in which the phenyl may have a substituent, cinnamyl, a lower alkyl, pyridylmethyl, a cycloalkylalkyl, adamantanemethyl, furylmethyl, a cycloalkyl, a lower alkoxycarbonyl or an acyl; and shows a single bond or a double bond.

In the compounds having the formula (XXV), it is preferable that J is (a) or (b). In the definition (b), monovalent groups of (2), (3) and (5) and divalent groups of (2) are preferable. In the definition of B, $-(\text{CHR}^{22})_r-$, $=(\text{CH}-\text{CH}=\text{CH})_b-$, $=\text{CH}-(\text{CH}_2)_c-$ and $=(\text{CH}-\text{CH})_d=$ are preferable. These preferable groups of (B) may be connected with (b) of J, in particular (2) of (b).

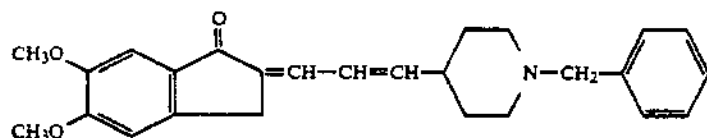
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It is preferable in the formula (XXV) that Q is nitrogen, T is carbon and q is 1 or 3; and Q is carbon, T is nitrogen q and is 2. It is most preferable that Q is nitrogen, T is carbon and q is 2.

It is preferable that K is a phenylalkyl or a phenylalkyl having a substituent(s) on the phenyl.

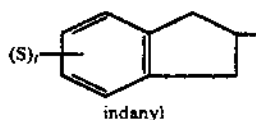
Preferable compounds of the invention include:

- 1-benzyl4-((5,6-dimethoxy-1-indanon)-2-yl)methyl-
piperidine, *Dupezilo*
1-benzyl4-((5,6-dimethoxy-1-indanon)-2-ylidenyl)methylpiperidine, 10
1-benzyl4-((5-methoxy-1-indanon)-2-yl)methylpiperidine,
1-benzyl4-((5,6-diethoxy-1-indanon)-2-yl)methylpiperidine, 15
1-benzyl4-((5,6-methylenedioxy-1-indanon)-2-yl)methylpiperidine,
1-(m-nitrobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine,
1-cyclohexylmethyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine, 20
1(m-florobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine,
1-benzyl4-((5,6-dimethoxy-1-indanon)-2-yl)propylpiperidine, 25
1-benzyl4-((5-isopropoxy-6-methoxy-1-indanon)-2-yl)methylpiperidine and
1-benzyl4-(5,6-dimethoxy-1-oxoindanon)-2-yl)propenylpiperidine, having the below shown formula, shown in Example 224. 30



In addition, the invention provides a therapeutical composition which comprises a pharmacologically effective amount of the cyclic amine compound having the formula (XXV) or a pharmacologically acceptable salt thereof and a pharmacologically acceptable carrier and then a method for preventing and treating a disease due to the acetylcholinesterase activity by administering to a human patient the cyclic amine compound having the formula (XXV) or a pharmacologically acceptable salt thereof.

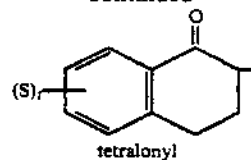
The preferable compound has the above shown formula in which J is (b). The group (b) includes ten groups having the respective formulae shown below. S is hydrogen or a substituent such as a lower alkyl having 1 to 6 carbon atoms and a lower alkoxy having 1 to 6 carbon atoms. Among the substituents, methoxy is most preferable. t is an integer of 1 to 4. The phenyl is most preferred to have 1 to 3 methoxy groups thereon. (S)_t may form methylene dioxy group or ethylene dioxy group on two adjacent carbon atoms of the phenyl group.



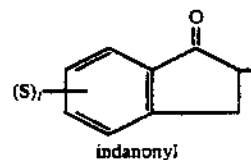
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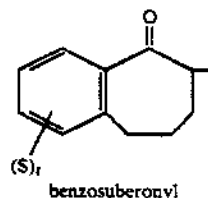
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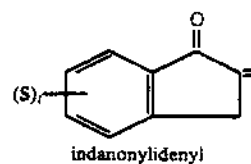
tetralonyl



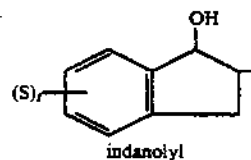
indanonyl



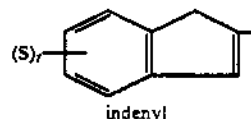
benzosuberonyl



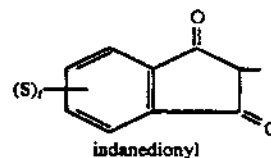
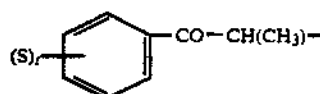
indanonylidenyl



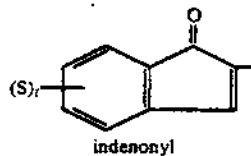
indanoyl



indenyl



indanedionyl



indenonyl

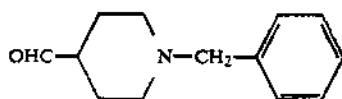
with an aqueous sodium hydroxide solution and extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate, and concentrated in vacuo. The resulting residue was purified by making use of a silica gel column (methylene chloride: methanol=500:1). The eluate was concentrated in vacuo, and the residue was dissolved in methylene chloride. A 10% solution of hydrochloric acid in ethyl acetate was added to the resulting solution, followed by concentration in vacuo to obtain 0.78 g (yield: 27%) of the title compound. 1.37 of diethyl 1-indanon-2-ylphosphorate was also recovered.

molecular formula; $C_{23}H_{25}NO \cdot HCl$.

^1H -NMR($CDCl_3$) δ : 1.10~2.13(7H,m), 2.26(2H,t), 2.88(2H,bd), 3.48(2H,s), 6.72~7.07(2H,m), 7.30(5H,s), 7.10~8.00(5H,m).

EXAMPLE 3

1-benzyl-4-piperidine-carbaldehyde having the formula:



was prepared in the following way.

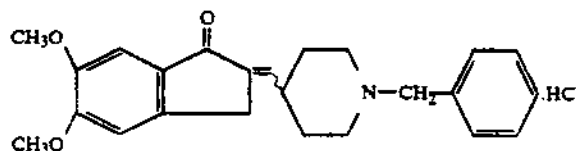
26 grams of methoxymethylene-triphenylphosphonium chloride was suspended in 200 ml of anhydrous ether. 1.6 M solution in hexane of n-butyl lithium was added dropwise to the suspension at the room temperature. The mixture was stirred at the room temperature for 30 minutes and cooled down to 0° C. Then 30 ml of a solution in anhydrous ether of 14.35 g of 1-benzyl-4-piperidone was added to the mixture. It was stirred at the room temperature for 3 hours and filtered to remove out the insoluble. The filtrate liquid was concentrated at a reduced pressure. The obtained concentrate was dissolved in ether and extracted with 1 N hydrochloric acid. An aqueous solution of sodium hydroxide was added to the extract to have pH value of 12. The resultant was extracted with methylene chloride. The extract was dried with magnesium sulfate and concentrated at a reduced pressure. The residue was purified with a column filled with silica gel to obtain 5.50 g of an oil with a yield of 33 percent.

The oil was incorporated into 40 ml of methanol and 40 ml of 1 N hydrochloric acid was added to the solution. It was heated so as to make reflux for 3 hours and then concentrated at a reduced pressure. The residue was dissolved in water. An aqueous solution of sodium hydroxide was added to the solution to have a pH value of 12 and the solution was extracted with methylene chloride. The extract was washed with saturated salt solution and dried with magnesium sulfate. It was further concentrated at a reduced pressure and the residue was purified in a column charged with silica gel. 2.77 g of the intended compound was obtained with a yield of 54 percent. In analysis, its molecular formula was found

to be $C_{13}H_{17}NO$ and ^1H -NMR ($CDCl_3$) δ , 1.40~2.40(7H,m), 2.78(2H, dt), 3.45(2H,S), 7.20(5H,S), 9.51(1H,d).

The compound may be produced according to the methods shown in (1) Arm. Kim. Zh., 36(9), 614~17 (1983) by R. A. Kuroyan, A. I. Markosyan, G. M. Snkhchyan and S. A. Vartangan and (2) Ind. Chim. Belge, 32, 64-5 (1967) by B. Hermans and P. Van Daele.

1-Benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl]-methylpiperidine hydrochloride



This reaction was conducted in an argon atmosphere.

2.05 ml of diisopropylamine was added to 10 ml of anhydrous THF, followed by addition of 9.12 ml of a 1.6 M solution of n-butyllithium in hexane at 0° C. The mixture was stirred at 0° C. for 10 min and then cooled to -78° C., and a solution of 2.55 g of 5,6-dimethoxy-1-indanone in 30 ml of anhydrous THF and 2.31 ml of hexamethyl-phosphoric amide were added thereto. The mixture was stirred at -78° C. for 15 min, and a solution of 2.70 g of 1-benzyl-4-piperidinecarbaldehyde in 30 ml of anhydrous THF was added thereto. The temperature of the mixture was gradually raised to room temperature, followed by stirring for 2 hr. An aqueous 1% ammonium chloride solution was added thereto, and the organic phase was separated. The water phase was extracted with ethyl acetate, and the organic phases were combined with each other. The combined organic phase was washed with a saturated saline solution, dried over magnesium sulfate, and concentrated in vacuo. The resulting residue was purified by making use of a silica gel column (methylene chloride: methanol=500:1~100:1). The eluate was concentrated in vacuo, and the residue was dissolved in methylene chloride. A 10% solution of hydrochloric acid in ethyl acetate was added to the resulting solution, followed by concentration in vacuo to obtain a crystal, which was recrystallized from methanol/IPE to obtain 3.40 g (yield: 62%) of the title compound having the following properties:

m.p. (° C.): 237°-238° C. (dec.).

elementary analysis: $C_{24}H_{27}NO_3 \cdot HCl$.

	C	H	N
calculated (%):	69.64	6.82	3.38
found (%):	69.51	6.78	3.30

EXAMPLE 4

1-Benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]-methylpiperidine hydrochloride

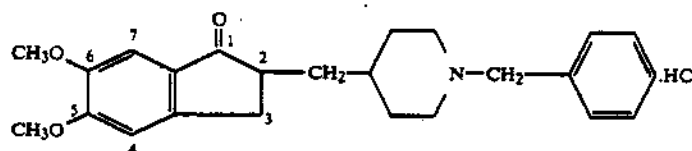


TABLE 1

Compound	AChE inhibitory activity IC ₅₀ (μM)
1	0.25
4	0.0053
5	0.10
6	0.017
8	0.013
9	0.051
10	0.009
11	0.063
12	0.040
13	0.026
14	0.038
15	0.094
17	0.052
18	0.68
19	0.064
20	0.54
21	50
23	0.072
24	1.1
26	24
27	0.41
29	0.15
31	0.025
33	0.030
45	0.36
48	0.019
52	0.80
54	1.0
56	0.017
62	0.0073
65	0.0016
67	0.10
70	0.28
72	0.020
89	0.018
90	0.035
95	0.085
101	0.11
120	0.19
124	2.8
176	0.004

EXPERIMENTAL EXAMPLE 2

Ex vivo acetylcholinesterase inhibitory action

A sample to detect was orally administered to rats. After one hour of the administration, the cerebral hemispheres were dissected and homogenized, followed by determination of the acetylcholinesterase activity. The group of rats treated with physiological saline was used as the control. Inhibition of AChE by samples ex vivo was expressed in terms of inhibition percent of the control value. Results are shown in Table 2.

EXPERIMENTAL EXAMPLE 3

Action on passive avoidance learning impairment induced by scopolamine

See Z. Boklanecy & Jarvik: Int. J. Neuropharmacol, 6, 217-222(1967).

Male Wistar rats were used as the test animal and a step-through light and dark box was used as an apparatus. A sample to detect was orally administered one hour before the training and the rats were treated with 0.5 mg/kg (i.p.) of scopolamine 30 min. before the training. In a training experiment, the animal was placed into a light room and, just after the animal had entered into a dark room, a guillotine door was closed, followed by delivery of an electric shock from the grid of the floor. After six hours, the animal was again placed into a light room for a retention experiment, and the time taken for

the animal to enter the dark room was measured for evaluation of the effect of the sample.

The difference in the response time between the physiological saline administration group and the scopolamine administration group was taken as 100%, and the effect of the sample was expressed in terms of the percentage antagonism by the sample (Reverse %).

The results are shown in Table 3.

TABLE 2

Compd. No.	Dose (mg/kg)	AChE inhibitory action (%)
Saline		0
4	1	5*
	3	17**
	10	36**
	30	47**
15	10	5
	30	14**
	100	18**

TABLE 3

Compd. No.	Dose (mg/kg)	Reverse %
4	0.125	55
	0.25	36
13	0.25	39
	0.5	27
15	1.0	51
	2.0	30
19	0.5	37
	1.0	39
69	0.5	22
	1.0	38

The number of animals per dose was 10 to 17. NE: non-effective.

The above-described pharmacological experiments revealed that the compound of the present invention had a potent acetylcholinesterase inhibitory action.

Among the compounds (I) of the present invention, the compound wherein R¹ is a group (II) or (III) derived from an indanone having an unsubstituted or substituted phenyl ring is preferable, and the compound wherein R¹ is a group represented by the general formula (II) are the most preferable. Specifically, particularly a compound wherein R¹ is a group derived from an indanone having an unsubstituted or substituted phenyl ring has characteristics such as remarkable difference from the conventional acetylcholinesterase inhibitor in the structure, advantages with respect to the manufacture of pharmaceutical preparations by virtue of the potent acetylcholinesterase inhibitory action, large width between the main and the side effects, persistent activity, high water solubility, excellent stability, advantage in formulating into preparations, high bioavailability and excellent penetration into the brain.

Therefore, the objects of the present invention are to provide a novel compound effective for various kinds of dementia and the sequelae of cerebrovascular diseases, to provide a process for preparing the same, and to provide a novel pharmaceutical comprising the same as an effective ingredient.

Representative compounds of the present invention (Compd. Nos. 4, 13, 15, 19, and 69 in the above Table 3) were applied to toxicity tests on rats. As a result, all the compounds exhibited a toxicity of 100 mg/kg or more, i.e., exhibited no serious toxicity.

The compound of the present invention is effective for treatment, prevention, remission, improvement, etc. of various kinds of senile dementia, particularly senile dementia of the Alzheimer type; cerebrovascular diseases accompanying cerebral apoplexy, e.g. cerebral hemorrhage or cerebral infarcts, cerebral arteriosclerosis, head injury, etc.; and aprosexia, disturbance of speech, hypobulia, emotional changes, recent memory disturbance, hallucinatory-paranoid syndrome, behavioral changes, etc. accompanying encephalitis, cerebral palsy, etc.

Further, the compound of the present invention has a strong and highly selective acetylcholinesterase action,

which renders the compound of the present invention useful also as a pharmaceutical based on this kind of action.

Specifically, the compound of the present invention is effective for, for example, Huntington's chorea, Pick's disease and delayed ataxia or tardive dyskinesia other than senile dementia of the Alzheimer type.

When the compound of the present invention is used as a pharmaceutical for these diseases, it may be orally or parenterally administered. In general, it is parenterally administered in the form of injections, such as intravenous, subcutaneous, and intramuscular injections, suppositories, or sublingual tablets. The doses will remarkably vary depending upon the symptom; age, sex, weight, and sensitivity of patients; method of administration; time and intervals of administration and properties, dispensing, and kind of pharmaceutical preparations; kind of effective ingredients, etc., so that there is no particular limitation with respect to the dose. Normally the compound may be administered in a dose of about 1.0 to 300 mg, preferably 1 to 100 mg, per day per adult, ordinarily in one to four portions.

Pharmaceutical preparations in the dosage form of, e.g., injections, suppositories, sublingual tablets, tablets, and capsules are prepared according to a method which is commonly accepted in the art.

In preparing injections, the effective ingredient is blended, if necessary, with a pH modifier, a buffer, a suspending agent, a solubilizing agent, a stabilizer, a tonicity agent, a preservative, etc., followed by preparation of an intravenous, subcutaneous, or intramuscular injection according to an ordinary method. In this case, if necessary, it is possible to lyophilize these preparations according to an ordinary method.

Examples of the suspending agents include methylcellulose, Polysorbate 80, hydroxyethylcellulose, acacia, powdered tragacanth, sodium carboxymethylcellulose, and polyoxyethylene sorbitan monolaurate.

Examples of the solubility agent include polyoxyethylene hydrogenated castor oil, Polysorbate 80, nicotinamide, polyoxyethylene sorbitan monolaurate, Macrogol, and an ethyl ester of castor oil fatty acid.

Examples of the stabilizer include sodium sulfite, sodium metabisulfite, and ether, and examples of the preservative include methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, sorbic acid, phenol, cresol, and chlorocresol.

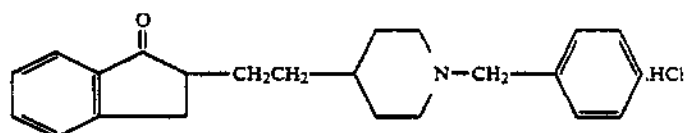
EXAMPLES

The present invention will now be described in more detail with reference to the following Examples. It is needless to say that the technical scope of the invention of the present invention is not limited to these Examples only.

In the following examples, all of the NMR values are those of the compounds measured in free form.

EXAMPLE 1

1-Benzyl-4-[2-[(1-indanon)-2-yl]]ethylpiperidine hydrochloride



0.37 g of 1-benzyl-4-[2-[(1-indanon)-2-yl]]-ethylpiperidine was dissolved in 10 ml of methanol, followed by addition of 0.1 g of 5% rhodium-carbon. The mixture was hydrogenated at room temperature under atmospheric pressure for 25 hr. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The residue was purified by making use of a silica gel column (methylene chloride:methanol=200:1). The eluate was concentrated in vacuo, and the residue was dissolved in methylene chloride. A 10% solution of hydrochloric acid in ethyl acetate was added to the resulting solution, followed by concentration in vacuo to obtain a crystal, which was recrystallized from methanol/IPE to obtain 0.33 g (yield: 80%) of the title compound having the following properties:

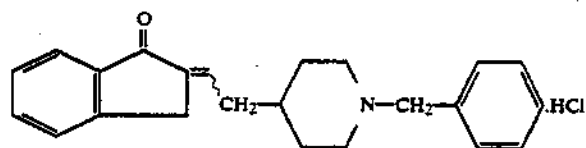
m.p. (° C.): 244°-225° C.

elementary analysis: $C_{23}H_{27}NO \cdot HCl$.

	C	H	N
calculated (%):	74.68	7.63	3.79
found (%):	74.66	7.65	3.77

EXAMPLE 2

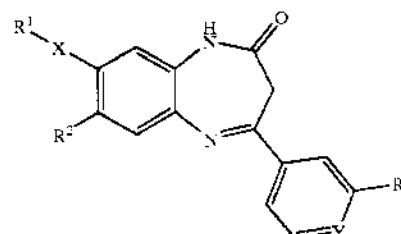
1-Benzyl-4-[2-[(1-indanon)-2-ylidenyl]]ethylpiperidine hydrochloride



0.32 g of 60% sodium hydride was washed with hexane, and 10 ml of THF was added thereto. A solution of 2.12 g of diethyl 1-indanon-2-ylphosphonate in 30 ml of THF was dropwise added thereto at 0° C. The mixture was stirred at room temperature for 30 min and again cooled to 0° C., followed by addition of a solution of 3.43 g of 1-benzyl-4-piperidineacetaldehyde in 10 ml of DMF. The mixture was stirred at room temperature for 2 hr and at 50° C. for 2 hr and then refluxed for 2 hr while heating the mixture. Methanol and 20% sulfuric acid were added at 0° C. to the reaction mixture. 10 min after the addition, the reaction mixture was made basic

(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2002/0193367 A1****Adam et al.**(43) **Pub. Date: Dec. 19, 2002**(54) **DIHYDRO-BENZO [B] [1,4] DIAZEPIN-2-ONE DERIVATIVES**(52) **U.S. Cl. 514/221; 540/567**(76) **Inventors: Geo Adam, Schopfheim (DE); Erwin Goetschi, Reinach (CH); Vincent Mutel, Brunstatt (FR); Juergen Wichmann, Steinen (DE); Thomas Johannes Woltering, Weil am Rhein (DE)**(57) **ABSTRACT**

This invention is a dihydro-benzo[b][1,4]diazepin-2-one derivative of the formula

Correspondence Address:
**HOFFMANN-LA ROCHE INC.
PATENT LAW DEPARTMENT
340 KINGSLAND STREET
NUTLEY, NJ 07110**(21) **Appl. No.: 10/115,826**(22) **Filed: Apr. 3, 2002**(30) **Foreign Application Priority Data**

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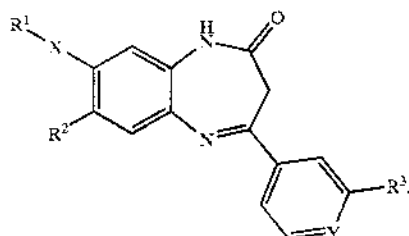
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wherein R^1 , R^2 , R^3 , X and Y are as defined in the specification. The invention includes pharmaceutical compositions containing these compounds, a process for their preparation, their use in preparation of pharmaceutical compositions and administration of an effective amount of the compounds for the treatment or prevention of acute and/or chronic neurological disorders to a patient in need of such treatment.

DIHYDRO-BENZO [B] [1,4] DIAZEPIN-2-ONE DERIVATIVES

FIELD OF INVENTION

[0001] This invention is a dihydro-benzo[b][1,4]diazepin-2-one derivative of the formula



[0002] The compounds of formula I are metabotropic glutamate receptor antagonists.

BACKGROUND

[0003] In the central nervous system (CNS) the transmission of stimuli takes place by the interaction of a neurotransmitter, which is sent out by a neuron, with a neuroreceptor.

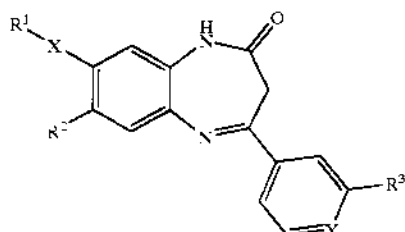
[0004] L-glutamic acid, the most commonly occurring neurotransmitter in the CNS, plays a critical role in a large number of physiological processes. The glutamate-dependent stimulus receptors are divided into two main groups. The first main group forms ligand-controlled ion channels. The metabotropic glutamate receptors (mGluR) form the second main group and, furthermore, belong to the family of G-protein-coupled receptors.

[0005] At present, eight different members of these mGluR are known and of these some even have sub-types. On the basis of structural parameters, the different influences on the synthesis of secondary metabolites and the different affinity to low-molecular weight chemical compounds, these eight receptors can be sub-divided into three sub-groups: mGluR1 and mGluR5 belong to group I, mGluR2 and mGluR3 belong to group II and mGluR4, mGluR6, mGluR7 and mGluR8 belong to group III.

[0006] Ligands of metabotropic glutamate receptors belonging to the group II can be used for the treatment or prevention of acute and/or chronic neurological disorders such as psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits.

SUMMARY

[0007] The present invention is a compound of formula I



[0008] wherein

[0009] X is a single bond or an ethynediyl group; wherein

[0010] when X is a single bond,

[0011] R¹ is selected from the group consisting of cyano, halogen, lower alkyl, C₃-C₆-cycloalkyl, lower alkoxy, fluoro-lower alkoxy, fluoro-lower alkyl, unsubstituted pyrrol-1-yl, and pyrrol-1-yl substituted by between one and three substituents selected from the group consisting of fluoro, chloro, cyano, $-(CH_2)_{1-4}$ -hydroxy, fluoro-lower alkyl, lower alkyl, $-(CH_2)_n$ -lower alkoxy, $-(CH_2)_n-C(O)O-R''$, $-(CH_2)_{1-4}-NR'R''$, hydroxy-lower alkoxy, and $-(CH_2)_n-CONR'R''$, unsubstituted phenyl, and phenyl substituted by one or two substituents selected from the group consisting of halogen, lower alkyl, fluoro-lower alkyl, lower alkoxy, fluoro-lower alkoxy and cyano;

[0012] when X is an ethynediyl group,

[0013] R¹ is unsubstituted phenyl, or phenyl substituted by between one and three substituents selected from the group consisting of halogen, lower alkyl, fluoro-lower alkyl, C₃-C₆-cycloalkyl, lower alkoxy and fluoro-lower alkoxy;

[0014] R² is selected from the group consisting of NR'R'', fluoro-lower alkoxy, unsubstituted 3-oxo-piperazin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, and 3-oxo-piperazin-1-yl, pyrrolidin-1-yl or piperidin-1-yl substituted by R'';

[0015] R' is selected from the group consisting of hydrogen, lower alkyl, C₃-C₆-cycloalkyl, fluoro-lower alkyl and 2-lower alkoxy lower alkyl;

[0016] R'' is selected from the group consisting of hydrogen, lower alkyl, C₃-C₆-cycloalkyl, fluoro-lower alkyl, 2-lower alkoxy lower alkyl, $-(CH_2)_2$ -4-di-lower alkylamino, $-(CH_2)_{2-4}$ -morpholinyl, $-(CH_2)_{2-4}$ -pyrrolidinyl, $-(CH_2)_{2-4}$ -piperidinyl and 3-hydroxy-lower alkyl;

[0017] Y is $-CH=$ or $=N-$;

[0018] R³ is selected from the group consisting of halogen, lower alkyl, fluoro-lower alkyl, lower alkoxy, cyano, $-(CH_2)_n-C(O)-OR''$, $-(CH_2)_n-C(O)-NR'R''$, unsubstituted five-membered aromatic heterocycle, and a five-membered aromatic heterocycle, substituted by halogen, fluoro-lower alkyl, fluoro-lower alkoxy, cyano, $-(CH_2)_n-NR'R''$, $-(CH_2)_n-C(O)-OR''$, $-(CH_2)_n-C(O)-NR'R''$, $-(CH_2)_n-SO_2-NR'R''$ lower alkyl, or lower alkyl substituted by a substituent selected from the group consisting of fluoro, hydroxy, lower alkoxy, cyano and carbamoyloxy; and

[0019] n is 0, 1, 2, 3 or 4;

[0020] or a pharmaceutically acceptable addition salt thereof.

[0021] It has surprisingly been found that the compounds of formula I are metabotropic glutamate receptor antagonists. Compounds of formula I are distinguished by valuable therapeutic properties.

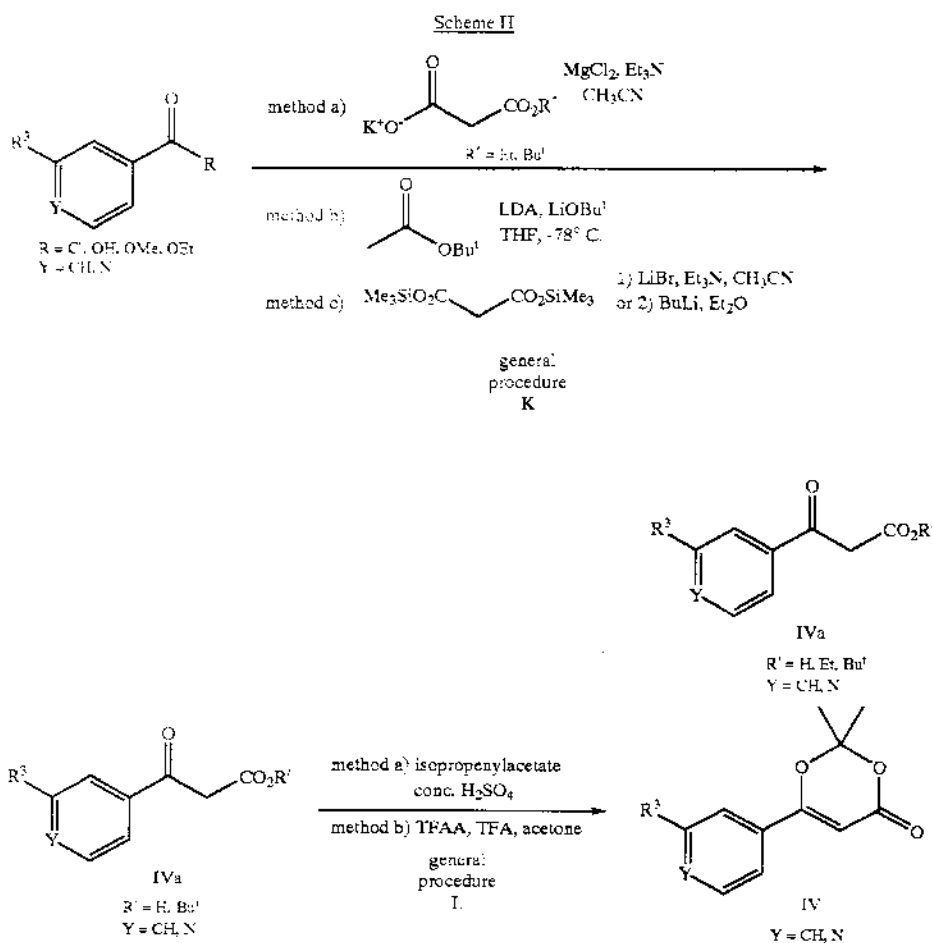
[0107] According to scheme G, compounds of formula II in which R^1 is as described above for compounds where X is an ethynediyl group can be prepared by different routes from the keto-compounds V, depending on the nature of R^1 and R^2 . As shown in scheme G, the transformation can for example be carried out by directly attaching the R^1 -alkynediyl-substituent to a compound of formula V via a Sonogashira-type coupling to produce compounds of the formula VIa followed by the reduction of the nitro group or by two stepwise Sonogashira-type couplings, in which first trimethylsilyl-acetylene is coupled to a compound of formula V to yield, after desilylation with sodium hydroxide in methanol, the intermediate X which then can be transformed via a second Sonogashira-type coupling with the appropriate reactant R^1 -I, R^1 -Br or R^1 -OSO₂CF₃ into compounds of the formula VIa and reduction of the nitro group leads to the desired compounds of formula II.

[0108] The exact conditions for the respective compounds can be found in the experimental part.

chlorides. The exact conditions for the corresponding compounds can be found in the experimental part.

[0110] The pharmaceutically acceptable salts can be manufactured readily according to known methods, taking into consideration the nature of the compound to be converted into a salt. Inorganic or organic acids such as, for example, hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid or citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like are suitable for the formation of pharmaceutically acceptable salts of basic compounds of formula I.

[0111] The compounds of formula I and their pharmaceutically acceptable salts are metabotropic glutamate receptor antagonists and can be used for the treatment or prevention of acute and/or chronic neurological disorders, such as psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits. Other treatable indications are restricted brain function caused by bypass operations or



[0109] According to Scheme II, the dioxinones and β -keto esters building blocks with the formula IV and IVa can be prepared by methods known to someone skilled in the art from the corresponding carboxylic acid derivatives R^2-COR , i.e. free acids, methyl or ethyl esters and acid

transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are acute and chronic pain, Huntington's chorea, ALS, dementia caused by AIDS, eye injuries, retinopathy, idiopathic par-

kinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficient functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, psychoses, opiate addiction, anxiety, vomiting, dyskinesia and depression.

[0112] The compounds of formula I or pharmaceutically acceptable salts thereof can be used as pharmaceutical compositions, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragees, hard and soft gelatine capsules, solutions, emulsions or suspensions. However, the administration can also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

[0113] The compounds of formula I or pharmaceutically acceptable salts thereof can be processed with pharmaceutically acceptable and therapeutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragees and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants, such as alcohols, polyols, glycerol, vegetable oils and the like, can be used for aqueous injection solutions of water-soluble salts of compounds of formula I, but as a rule are not necessary. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

[0114] In addition, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

[0115] As mentioned earlier, pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert, i.e., pharmaceutically acceptable, excipient are also an object of the present invention, as is a process for the production of such pharmaceutical compositions which comprises bringing one or more compounds of formula I or pharmaceutically acceptable salts thereof and, if desired, one or more other therapeutically valuable substances into a galenic dosage form together with one or more therapeutically inert carriers.

[0116] The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/kg/day being preferred for all of the indications described. The daily dosage for an adult human being weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

[0117] The present invention includes the use of compounds of formula I and of pharmaceutically acceptable salts

thereof for the production of pharmaceutical compositions, especially for the control or prevention of acute and/or chronic neurological disorders of the aforementioned kind.

[0118] The compounds of the present invention are group II mGlu receptor antagonists. The compounds show K_i values, as measured in the assay described below, of 10 μ M or less, typically 1 μ M or less, and ideally of 0.3 μ M or less.

[0119] In Table I below some specific K_i values of preferred compounds of the invention are presented. These values were obtained by indirect measurement of the affinity of the compounds for the recombinant rat mGluR2 expressed in CHO cells using a displacement binding assay with 3H-LY354740.

TABLE I

Compound	K_i mGlu2 (μ M)
3-(8-Dimethylamino-4-oxo-7-phenylethynyl)-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl-benzonitrile	0.030
8-(2,3-Difluoro-phenyl)-7-dimethylamino-4-(3-[1,2,3]triazol-1-yl-phenyl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.072
8-Chloro-7-[(2-methoxy-ethyl)-methyl-amino]-4-[3-(3-methyl-isoxazol-5-yl)-phenyl]-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.025
8-Chloro-7-dimethylamino-4-[3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.023
8-Chloro-7-dimethylamino-4-[3-(4-hydroxymethyl-thiazol-2-yl)-phenyl]-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.030
8-(2-Fluoro-phenyl)-4-[3-(3-methyl-isoxazol-5-yl)-phenyl]-7-(2,2,2-trifluoro-ethoxy)-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.03
8-Chloro-7-dimethylamino-4-[3-(4-hydroxymethyl-oxazol-2-yl)-phenyl]-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.039
8-Chloro-7-(methyl-propyl-amino)-4-[3-(5-hydroxymethyl-[1,2,3]triazol-1-yl)-phenyl]-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.030
8-Chloro-7-(diethyl-amino)-4-[3-(5-hydroxymethyl-[1,2,3]triazol-1-yl)-phenyl]-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.044
8-Chloro-4-[3-(5-hydroxymethyl-[1,2,3]triazol-1-yl)-phenyl]-7-pyrrolidin-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.019
8-Chloro-7-(cyclopropyl-methyl-amino)-4-[3-(5-hydroxymethyl-[1,2,3]triazol-1-yl)-phenyl]-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.16
8-Chloro-7-dimethylamino-4-(3-pyrazol-1-yl-phenyl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.11
7-Dimethylamino-4-[3-(3-morpholin-4-ylmethyl-isoxazol-5-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.125
7-Dimethylamino-4-[3-(2-methylsulfanyl-imidazol-1-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.019
4-[8-(Cyclopropylmethyl-methyl-amino)-4-oxo-7-trifluoromethyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-pyridine-2-carbonitrile	0.005
4-[3-(5-Cyclopropylaminomethyl-[1,2,3]triazol-1-yl)-phenyl]-7-dimethylamino-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.049
4-[4-Oxo-8-(2,2,2-trifluoro-ethoxy)-7-trifluoromethyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-pyridine-2-carbonitrile	0.004
3-[7-Methyl-8-(methyl-propyl-amino)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile	0.025
8-Chloro-4-[3-(5-hydroxymethyl-[1,2,3]triazol-1-yl)-phenyl]-7-(isobutyl-methyl-amino)-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.02
8-Diethylamino-2-[3-(3-methyl-isoxazol-5-yl)-phenyl]-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-7-carbonitrile	0.009