

**(12) PATENT  
(19) AUSTRALIAN PATENT OFFICE**

**(11) Application No. AU 200114402 B2  
(10) Patent No. 775885**

(54) Title  
**Use of 1-aminoindan derivatives for treatment of mania in bipolar mood disorder**

(51)<sup>7</sup> International Patent Classification(s)  
**A61K 031/16**

(21) Application No: **200114402** (22) Application Date: **2000.10.27**

(87) WIPO No: **WO01/30339**

(30) Priority Data

(31) Number **60/161817** (32) Date **1999.10.27** (33) Country **US**

(43) Publication Date : **2001.05.08**  
(43) Publication Journal Date : **2001.07.26**  
(44) Accepted Journal Date : **2004.08.19**

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(56) Related Art  
**US 3637740**  
**US 3886168**  
**US 4096173**

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
3 May 2001 (03.05.2001)

PCT

(10) International Publication Number  
WO 01/30339 A1(51) International Patent Classification<sup>7</sup>: A61K 31/16 (74) Agent: WHITE, John, P.; Cooper & Dunham LLP, 1185 Avenue of the Americas, New York, NY 10036 (US).

(21) International Application Number: PCT/US00/29618

(22) International Filing Date: 27 October 2000 (27.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/161,817 27 October 1999 (27.10.1999) US

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GF, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

## Published:

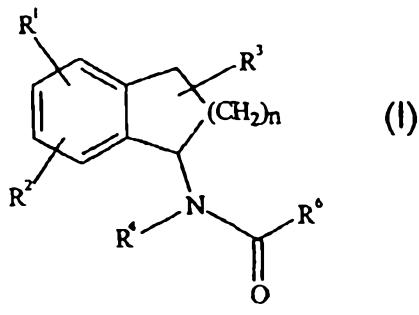
- With international search report.
- Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF 1-AMINOINDAN DERIVATIVES FOR TREATMENT OF MANIA IN BIPOLAR MOOD DISORDER

(57) Abstract: The subject invention provides a method of treating mania in bipolar disorder in a subject comprising administering to the subject a therapeutically effective amount of derivatives of 1-aminoindan or their racemic mixtures, enantiomers, or salts, of general formula (I).

WO 01/30339 A1



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**USE OF 1-AMINOINDAN DERIVATIVES**  
**FOR TREATMENT OF MANIA IN BIPOLAR MOOD DISORDER**

This application claims the priority of U.S. Provisional  
5 Application No. 60/161,817, filed October 27, 1999, the  
contents of which are incorporated into this application.

Throughout this application, various references are  
identified by authors and full citations. Disclosures of  
10 these publications in their entireties are hereby  
incorporated by reference into this application to more  
fully describe the state of the art to which this invention  
pertains.

15 The reference to any prior art in this specification is not,  
and should not be taken as, an acknowledgment or any form of  
suggestion that that prior art forms part of the common  
general knowledge in Australia.

20 Throughout this specification and the claims which follow,  
unless the context requires otherwise, the word "comprise",  
and variations such as "comprises" and "comprising", will be  
understood to imply the inclusion of a stated integer or  
step or group of integers or steps but not the exclusion of  
25 any other integer or step or group of integers or steps.

**Background of the Invention**

Bipolar mood disorder commonly begins with depression and is  
30 characterized by at least one elated period sometime during  
the course of the illness. In bipolar I disorder, full  
blown manic and major depressive episodes alternate. In

- 1A -

bipolar II disorder, depressive episodes alternate with hypomanias (i.e., mild, nonpsychotic periods of excitement) of relatively short duration. Although insomnia and poor appetite do occur during the depressive phase of bipolar 5 illness, such atypical depressive signs as hypersomnia and overeating are more characteristic and may recur on a seasonal basis (e.g., in the autumn or winter).

In full blown manic psychosis, the mood typically is one of 10 elation, but irritability and frank hostility are not uncommon. The patient's lack of insight and inordinate capacity for activity lead to a dangerously explosive

psychotic state, in which the individual is impatient, intrusive, and meddlesome and responds with aggressive irritability when crossed. Interpersonal friction results and may lead to secondary paranoid delusional 5 interpretations of being persecuted. Audio and visual hallucinations are sometime present, occur at the high mania, and are usually understandably linked with the morbid mood. The need for sleep is decreased. Manic persons are inexhaustibly, excessively, and impulsively involved in 10 various activities without recognizing the inherent social dangers.

Mixed states are labile mixtures between depressive and manic manifestations or rapid alternation from one state to 15 the other and commonly occur in manic depressive at one time or another. (The Merck Manual 16<sup>th</sup> edition, 1992, p. 1592, 1593, 1599). Bipolar disorder (BP) affects 1-2% of the population.

20 The classical psychopharmaceuticals effective in the treatment of mood disorders can be grouped into three classes: the heterocyclic antidepressants (HCA), monoamine oxidase inhibitors (MAOI) and lithium salts. (Merck, p. 1603). While HCA and MAOI drugs are indicated for the 25 depressive phase of the bipolar disorder, lithium is known to attenuate the bipolar mood swings.

Only around 70% of the patients are considered to respond to the treatment with HCA or lithium drugs (Merck, p. 1604, 30 1607). For the resistant and refractory disease, combinations of drugs are used, increasing even more the panel of characteristic side effects.

In light of this situation, there is a continuous search for new drugs aimed to solve the problems of drug resistance and severe side effects. Lately, drugs like valproic acid, carbamazepin, verapamil, propanolol, clonidine and adenylyl cyclase inhibitors have been found to be beneficial either alone or as adjunct therapy for manic patients. (O. Kaufman and R.H. Belmaker, P. Soubrie, ed.: *Anxiety, Depression and Mania. Anim. Models Psychiatr. Disord.*, Basel, Karger, 1991, 3, pp. 103-121).

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In order to discover new drugs, rodent models relevant to the manic phase, like amphetamine, amphetamine with chlordiazepoxide, morphine or desmethylimipramine induced hyperactivity or to the depression phase like immobilizations, are usually used (D.L. Murphy, *Anim. Mod. Psych. Neur.*, 1977, pp. 211-225).

These mania models focus on an induced increase in the activity level of the animal (e.g., locomotor or/and vertical activity) as a parallel to the hyperactivity of the maniac patient. The reversal of the induced hyperactivity in rodents by their pretreatment with a drug of interest indicates the possible efficacy of this drug in the treatment of human mania.

25

A variety of substituted 1-aminoindans have been proposed to have some activity in the central nervous system (CNS). This group of compounds has a wide range of activities, for example, U.S. Patent No. 4,096,173 discloses 1-aminoindans with ring chloro substituents as having anti-allergic, anti-spasmodic and local anesthetic activities, whereas U.S. Patent No. 3,886,168 discloses the anti-inflammatory and

vasodilatory activity of certain 1-aminoindans.

It is hypothesized therein that the activity may be based in the CNS though no evidence is provided or suggested to support the hypothesis. British Patent No. 852,735 discloses 1-aminoindans with a lower alkoxy group in the five position as being active in dilating coronary blood vessels.

10 U.S. Patent No. 3,637,740 discloses *dl*-1-*N,N*-dimethylamino-4-methoxy-7-chloroindane as an antidepressant and/or an antianxiety agent. However, no clear evidence is provided of either activity.

15 Horne et al. (J. Pharm. Exp. Ther. 1972, 180(3), p. 523) have shown that 2-aminoindan is a far superior inhibitor of catecholamine uptake than 1-aminoindan and therefore dismissed the latter as a candidate for use in the treatment of Parkinson's Disease. Martin et al. (J. Med. Chem. 1973, 20 16(2), p. 147; J. Med. Chem. 1974, 17(4), p. 409) describe experiments wherein *N*-methyl-5-methoxy derivatives of 1-aminoindan are investigated as having monoamine oxidase (MAO) inhibitory activity.

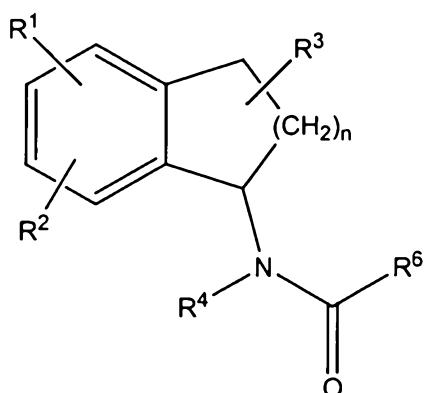
25 Oshiro et al. (J. Med. Chem. 1991, 34, pp. 2004-2013) disclose a wide range of 7-hydroxy-1-aminoindan derivatives that they subjected to screening for use as cerebroprotective agents using an antihypoxic test and as CNS stimulatory agents using a cerebral trauma test. In the 30 resultant structure-activity-analysis, it was found that replacement of the 7-hydroxy group by a methoxy group resulted in loss of activity in the antihypoxic test but not

in the cerebral trauma test. Their conclusion was that the 7-hydroxy is essential to obtain the desired activity. This is evident from their subsequent paper wherein a broader range of 7-hydroxy derivatives are screened (J. Med. Chem. 5 1991, 34, 2014-2020). These 7-hydroxy-1-aminoindans are defined in U.S. Patent Nos. 4,788,130; 4,792,628; 4,895,847; 5,055,474; and 5,242,919, all assigned to Otsuka Pharmaceutical Co., Japan.

10 Cohen et al. describe the use of a series of aminoindans for the treatment of Parkinson's disease, dementia, epilepsy, convulsions or seizures and neurotrauma and disclose the preparation of certain novel representatives of that class. (U.S. Patent Nos. 5,877,221; 5,880,159; 5,877,218).

Summary of the Invention

The subject invention describes a method of treating mania in the bipolar mood disorder in a subject comprising 5 administering to the subject a therapeutically effective amount of a compound of the structure:



10 wherein n is 0 or 1;  
 each of R<sup>1</sup> and R<sup>2</sup> are hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, or halogen;  
 R<sup>3</sup> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, hydroxy, or C<sub>1</sub>-C<sub>4</sub> alkoxy;  
 R<sup>4</sup> is hydrogen, or C<sub>1</sub>-C<sub>4</sub> alkyl;  
 R<sup>6</sup> is hydrogen, substituted or unsubstituted C<sub>1</sub>-C<sub>12</sub> alkyl, C<sub>6</sub>-15 C<sub>12</sub> aryl, C<sub>7</sub>-C<sub>12</sub> aralkyl or A-N-R<sup>9</sup>R<sup>10</sup>, provided that R<sup>6</sup> is not methyl when R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are hydrogen atoms,  
 wherein A is substituted or unsubstituted C<sub>1</sub>-C<sub>12</sub> alkyl,  
 substituted or unsubstituted C<sub>6</sub>-C<sub>12</sub> aryl, or substituted  
 or unsubstituted C<sub>7</sub>-C<sub>12</sub> aralkyl, and  
 20 each of R<sup>9</sup> and R<sup>10</sup> are independently hydrogen, C<sub>1</sub>-C<sub>12</sub> alkyl, C<sub>6</sub>-C<sub>12</sub> aryl, C<sub>7</sub>-C<sub>12</sub> aralkyl, COOtBu, or indanyl;  
 or a racemic mixture, enantiomer, or salt thereof.

Description of the Figures

FIG. 1 shows four specific compounds discussed in the experiments: (R)-N-acetyl aminoindan (1), (S)-N-indanyl 5 glycinamide HCl (2), (rac)-N-(2-aminoacetyl)-1-aminoindan HCl (3), (S)-N-formyl aminoindan (4).

FIG. 2A-5B hereinafter describe the means  $\pm$ SE for activity counts measured for each group for 30 minutes, at 10 minute 10 time intervals. The asterisk "\*" denotes a significant difference from the control. Drug administration is interperitoneal (IP).

FIG. 2A shows the locomotor activity level for rats which 15 have been administered (R)-N-acetyl aminoindan (1) as compared to the control.

FIG. 2B shows the vertical activity level for rats which have been administered (R)-N-acetyl aminoindan (1) as 20 compared to the control.

FIG. 3A shows the locomotor activity level for rats which have been administered (S)-N-indanyl glycinamide HCl (2) as compared to the control.

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FIG. 3B shows the vertical activity level for rats which have been administered (S)-N-indanyl glycinamide HCl (2) as compared to the control.

30 FIG. 4A shows the locomotor activity level for rats which have been administered (rac)-N-(2-aminoacetyl)-1-aminoindan (3) as compared to the control.

FIG. 4B shows the vertical activity level for rats which have been administered (rac)-N-(2-aminoacetyl)-1-aminoindan (3) as compared to the control.

5 FIG. 5A shows the locomotor activity level for rats which have been administered (S)-N-formyl aminoindan (4) as compared to the control.

FIG. 5B shows the vertical activity level for rats which 10 have been administered (S)-N-formyl aminoindan (4) as compared to the control.

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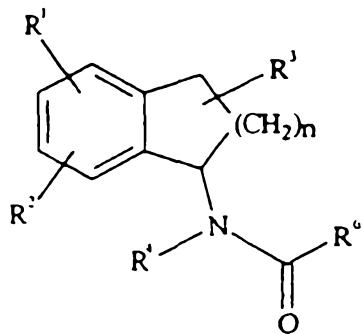
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### Detailed Description of the Invention

It has now been surprisingly observed that a particular class of 1-aminoindan derivatives decrease the amphetamine-induced hyperactivity levels while another class increases this hyperactivity.

This invention provides a method for the treatment of mania in bipolar mood disorder using derivatives of 1-aminoindan 10 or their racemic mixtures, enantiomers, and salts thereof.

In particular, the present invention discloses a method of treating mania in bipolar mood disorder in a subject comprising administering to the subject a therapeutically effective amount of a compound of the structure:



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wherein  $n$  is 0 or 1;

each of  $R^1$  and  $R^2$  are hydrogen,  $C_1$ - $C_4$  alkyl, or halogen;  
25  $R^3$  is hydrogen,  $C_1$ - $C_4$  alkyl, hydroxy, or  $C_1$ - $C_4$  alkoxy;  $R^4$  is hydrogen, or  $C_1$ - $C_4$  alkyl;  $R^5$  is hydrogen, substituted or unsubstituted  $C_1$ - $C_{12}$  alkyl,  $C_6$ - $C_{12}$  aryl,  $C_7$ - $C_{12}$  aralkyl or  $A$ - $N$ - $R^9R^{10}$ , provided that  $R^6$  is not methyl when  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are hydrogen atoms,

30 wherein A is substituted or unsubstituted C<sub>1</sub>-C<sub>12</sub> alkyl, substituted or unsubstituted C<sub>6</sub>-C<sub>12</sub> aryl, or substituted or

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unsubstituted C<sub>7</sub>-C<sub>12</sub> aralkyl, and each of R<sup>9</sup> and R<sup>10</sup> are independently hydrogen, C<sub>1</sub>-C<sub>12</sub> alkyl, C<sub>6</sub>-C<sub>12</sub> aryl, C<sub>7</sub>-C<sub>12</sub> aralkyl, COOtBu, or indanyl;  
or a racemic mixture, enantiomer, or salt thereof.

5

In another embodiment of the invention, there is provided a method of treating mania in bipolar mood disorder in a subject comprising administering to the subject a therapeutically effective amount of a compound selected from 10 the group consisting of (rac)-N-(2-aminoacetyl)-1-aminoindan HCl, (R)-N-acetyl aminoindan, a salt of (R)-N-acetyl aminoindan, (S)-N-formyl aminoindan, and a salt of (S)-N-formyl aminoindan.

15 In one embodiment of the invention, the subject is a human subject.

In a further embodiment of the invention, the compound is a salt selected from the group consisting of a hydrochloride 20 salt, a mesylate salt, an ethylsulfonate salt, and a sulfate salt.

In a specific embodiment of the invention, the salt is a hydrochloride salt.

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In one embodiment of the invention, the administration is selected from the group consisting of oral, intraperitoneal, parenteral, topical, transdermal, rectal, nasal, and buccal administration.

- 10A -

In yet another embodiment of the invention, the therapeutically effective amount is an amount from 30 mg/kg to 150 mg/kg.

5 In a further embodiment of the invention, the therapeutically effective amount is an amount from 30 mg/kg to 100 mg/kg.

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In a preferred embodiment of the invention, the therapeutically effective amount is an amount from 30 mg/kg to 75 mg/kg.

### 5 Experimental Details

#### I. Synthesis of Compounds

Cohen et al. disclose the preparation of the (R)-1-aminoindan starting material, and certain novel 10 representatives of aminoindan (U.S. Patents 5,877,221; 5,880,159; 5,877,218). The R- and S- enantiomers of each compound may be obtained by optical resolution of the corresponding racemic mixtures. Such a resolution can be accomplished by any conventional resolution method also 15 disclosed in Cohen et al.

#### II. Experimental Examples

Evaluation of possible anti-bipolar effects of compounds 1 to 4 was effected by an amphetamine-induced hyperactivity 20 model of mania in rats. Each of the compounds was examined in a separate experiment and compared with a control group, treated with the same dose of amphetamine.

Twenty Sprague Dawley rats, weighing 200-250 g served for 25 each of the four (4) experiments. Rats were housed in a colony room with constant temperature (22°C), 12 h light/dark cycle and free access to food and water. Each experiment consisted of two groups (n=10 per group), one group was treated with the compound (1 to 4) and the other with 30 vehicle solution. In experiments 1-4, the drugs were administered intraperitoneally (IP). All experimental procedures were conducted during the light phase of the

light/dark cycle.

Amphetamine (0.5 mg/kg, sub-cutaneous (s.c.), diluted in de-ionized water) was injected into all rats (both groups of 5 each experiment) immediately prior to behavioral testing. In experiments 1 to 4, compounds (R)-N-acetyl aminoindan (1); (S)-N-indanyl glycaminamide HCl (2); (rac)-N-(2-aminoacetyl)-1-aminoindan HCl (3); and (S)-N-formyl aminoindan (4) were injected twice intraperitoneally (IP) at 10 a dose of 75 mg/kg, 19 h and 3 h prior to behavioral testing in experiments. All compounds were suspended in a 5% methyl cellulose solution. The vehicle solution was administered to the control animals.

15 Immediately after amphetamine injection, rats were placed in automated activity monitors and their activity levels were scored every 10 minutes in the 30 minute time span for experiments 1 to 4. Activity scores included separate measurements of horizontal (locomotion) and of vertical 20 (rearing) activity.

#### Statistical analysis

Repeated ANOVA measurements were used to examine the effects of compounds 1 to 4 on locomotor and on vertical activity. 25 One factor measured the treatment of the rats using compounds 1 to 4 or the control vehicle; the repeated measure factor was time (three 10 minute intervals). Post hoc LSD (least significant difference) tests were used to determine whether significant differences occurred in 30 different time periods, where relevant.

**A. (R)-N-acetyl aminoindan (1)**

The results of the experiment employing (R)-N-acetyl aminoindan (1) are shown in Tables 1 and 2, as well as FIG. 2A and 2B. Table 1 compares the activity counts for rats which have been administered intraperitoneal (R)-N-acetyl aminoindan (1) to control rats for three 10 minute intervals. FIG. 2A shows the locomotor activity level for rats which have been administered intraperitoneally (R)-N-acetyl-aminoindan (1) as compared to the control. FIG. 2B shows the vertical activity level for rats which have been administered intraperitoneally (R)-N-acetyl-aminoindan (1) as compared to the control.

Subacute treatment with 75 mg/kg (R)-N-acetyl aminoindan significantly reduced locomotion following amphetamine treatment (FIG. 2A) (ANOVA: Drug effect:  $F(1)=10.85$ ,  $p<0.005$ ; Time effect:  $F(2)=7.03$ ,  $p<0.003$ ; Interaction:  $F(2)=0.63$ , NS). Post hoc analysis indicates that the effect of the drug was significant at all time points (FIG. 2A). Similar effects were observed for vertical activity (ANOVA: Drug effect:  $F(1)=7.44$ ,  $p<0.02$ ; Time effect:  $F(2)=2.96$ , NS; Interaction:  $F(2)=2.32$ , NS). Post hoc analysis indicates significant differences during the first and second 10 minute time periods (FIG 2B).

TABLE 1. Effect of (R)-N-acetyl aminoindan (1) on Activity  
Levels

LOCOMOTOR ACTIVITY					
	10 min	20 min	20-10 min	30 min	30-20 min
5	control 830	1341	511	2026	685
	control 723	1245	522	1899	654
	control 810	1231	421	1727	496
	control 565	1102	537	1525	423
10	control 569	1196	627	1798	602
	control 551	1053	502	1640	587
	control 687	1447	758	2091	644
	control 606	1359	753	2067	708
15	control 496	1059	563	1428	369
	control 850	1566	716	2295	729
	mean 668.9	1259.9	591	1849.6	590
	std err 40	52	36	86	38
	10 min	20 min	20-10 min	30 min	30-20 min
20	(1) 600	930	330	1436	506
	(1) 448	677	229	1027	350
	(1) 718	1125	407	1653	528
	(1) 740	1026	286	1317	291
	(1) 570	1147	577	1776	629
25	(1) 426	802	376	1230	428
	(1) 395	800	405	1053	253
	(1) 462	794	332	1150	356
	(1) 681	1361	680	2064	703
	(1) 413	796	383	1250	454
30	mean 545.3	945.8	400.5	1395.6	449.8
	std err 42	67	42	105	45

VERTICAL ACTIVITY (cumulative and non cumulative counts)						
	10 min	20 min	20-10 min	30 min	30-20 min	
5	control	80	115	35	132	17
	control	29	48	19	52	4
	control	40	47	7	52	5
	control	10	19	9	31	12
	control	34	76	42	120	44
10	control	9	19	10	31	12
	control	27	92	65	112	20
	control	25	66	41	79	13
	control	14	29	15	34	5
	control	69	130	61	179	49
15	mean	33.7	64.1	30.4	82.2	18.1
	std err	8	12	7	16	5
	10 min	20 min	20-10 min	30 min	30-20 min	
(1)	27	34	7	62	28	
20	(1)	9	12	3	18	6
	(1)	16	18	2	20	2
	(1)	29	29	0	31	2
	(1)	20	37	17	53	16
	(1)	16	28	12	38	10
25	(1)	5	12	7	12	0
	(1)	10	11	1	21	10
	(1)	6	39	33	76	37
	(1)	4	5	1	7	2
	mean	14.2	22.5	8.3	33.8	11.3
30	std err	3	4	3	7	4

**B. (S)-N-indanyl glycinnamide HCl (2)**

The results of the experiment employing (S)-N-indanyl glycinnamide HCl (2) are shown in Table 2, FIG. 3A and FIG. 3B. Table 2 compares the activity counts for rats which 5 have been administered (S)-N-indanyl glycinnamide HCl (2) to control rats for three 10 minute intervals. FIG. 3A shows the locomotor activity level for rats which have been administered (S)-N-indanyl glycinnamide HCl (2) as compared to the control. FIG. 3B shows the vertical activity level 10 for rats which have been administered (S)-N-indanyl glycinnamide HCl (2) as compared to the control.

Subacute treatment with (S)-N-indanyl glycinnamide HCl (75mg/kg) did not have a significant effect on amphetamine-15 induced locomotor activity (ANOVA: Drug effect:  $F(1)=0.89$ , NS; Time effect:  $F(2)=15.923$ ,  $p<0.001$ ; Interaction:  $F(2)=1.5$ , NS; FIG. 3A). Contrary to expectations, the compound significantly increased the level of vertical activity (ANOVA: Drug effect:  $F(1)=5.499$ ,  $p=0.031$ ; Time 20 effect:  $F(2)=8.533$ ,  $p=0.001$ ; Interaction:  $F(2)=2.537$ , NS). Post hoc analysis indicates that the difference between the groups was significant during the first and second 10 minute time periods (FIG. 3B).

TABLE 2. Effect of (S)-N-indanyl glycaminamide HCl (2) on Activity Levels

LOCOMOTOR ACTIVITY						
	10 min	20 min	20-10 min	30 min	30-20 min	
5	control	560	1009	449	1487	478
	control	604	1232	628	1719	687
	control	504	1055	551	1560	505
	control	466	920	454	1324	422
	control	556	1233	677	1640	407
	control	631	1205	574	1680	475
	control	790	1572	782	2252	680
	control	737	1328	591	1862	534
	control	659	1273	614	1837	564
	control	714	1275	561	1726	451
10	mean	622.1	1210.2	588.1	1708.7	520.3
	std err	33	57	31	80	31
15		10 min	20 min	20-10 min	30 min	30-20 min
	(2)	531	1096	565	1547	451
	(2)	603	1197	594	1606	409
	(2)	604	1334	730	1964	630
	(2)	619	1140	521	1598	458
	(2)	663	1525	862	1908	383
	(2)	616	1508	892	2038	530
	(2)	670	1366	696	1670	304
	(2)	643	1272	629	1608	336
	(2)	648	1325	677	2047	722
20	(2)	663	1016	353	1419	403
	mean	626	1277.9	651.9	1740.5	462.6
	std err	13	53	50	71	41
25		10 min	20 min	20-10 min	30 min	30-20 min
	(2)	531	1096	565	1547	451
	(2)	603	1197	594	1606	409
	(2)	604	1334	730	1964	630
	(2)	619	1140	521	1598	458
	(2)	663	1525	862	1908	383
	(2)	616	1508	892	2038	530
	(2)	670	1366	696	1670	304
	(2)	643	1272	629	1608	336
	(2)	648	1325	677	2047	722
30	(2)	663	1016	353	1419	403
	mean	626	1277.9	651.9	1740.5	462.6
	std err	13	53	50	71	41

VERTICAL ACTIVITY						
	10 min	20 min	20-10 min	30 min	30-20 min	
5	control	35	41	6	57	16
	control	26	38	12	46	8
	control	24	59	35	73	14
	control	7	8	1	25	17
	control	10	14	4	19	5
	control	40	62	22	91	29
	control	42	70	28	89	19
	control	41	50	9	61	11
	control	44	60	16	80	20
	control	65	86	21	111	25
10	mean	33.4	48.8	15.4	65.2	16.4
	std err	5	8	3	9	2
15		10 min	20 min	20-10 min	30 min	30-20 min
	(2)	32	51	19	75	24
	(2)	82	133	51	168	35
	(2)	31	62	31	98	36
	(2)	38	84	46	96	12
	(2)	38	101	63	104	3
	(2)	95	236	141	321	85
	(2)	66	118	52	126	8
	(2)	38	50	12	58	8
	(2)	30	70	40	116	46
20	(2)	43	58	15	88	30
	mean	49.3	96.3	47	125	28.7
	std err	7	18	12	23	8
25		10 min	20 min	20-10 min	30 min	30-20 min
	(2)	32	51	19	75	24
	(2)	82	133	51	168	35
30	(2)	31	62	31	98	36
	(2)	38	84	46	96	12
	(2)	38	101	63	104	3
35	(2)	95	236	141	321	85
	(2)	66	118	52	126	8
	(2)	38	50	12	58	8
40	(2)	30	70	40	116	46
	(2)	43	58	15	88	30
	mean	49.3	96.3	47	125	28.7
45	std err	7	18	12	23	8

**C. (rac)-N-(2-aminoacetyl)-1-aminoindan HCl (3)**

The results of the experiment employing (rac)-N-(2-aminoacetyl)-1-aminoindan HCl (3) are shown in Table 3, FIG. 4A and FIG. 4B. Table 3 compares the activity counts for 5 rats which have been administered (rac)-N-(2-aminoacetyl)-1-aminoindan HCl (3) to control rats for three 10 minute intervals. FIG. 4A shows the locomotor activity level for rats which have been administered (rac)-N-(2-aminoacetyl)-1-aminoindan HCl (3) as compared to the control. FIG. 4B shows the vertical activity level for rats which have been administered (rac)-N-(2-aminoacetyl)-1-aminoindan HCl (3) as compared to the control.

Injections of (rac)-N-(2-aminoacetyl)-1-aminoindan HCl (75 mg/kg), 19 and 3 hours prior to testing significantly reduced locomotor activity of rats treated with amphetamine (ANOVA: Drug effect:  $F(1)=9.32$ ,  $p<0.007$ ; Time effect:  $F(2)=11.29$ ,  $p<0.002$ ; Interaction:  $F(2)=0.21$ , NS). Post hoc comparisons indicated that the difference was significant at 20 all time periods (FIG. 4A). A similar, albeit non-significant, effect was demonstrated for vertical activity (FIG. 4B).

TABLE 3. Effect of (rac)-N-(2-aminoacetyl)-1-aminoindan HCl  
(3) on Activity Levels

LOCOMOTOR ACTIVITY						
	10 min	20 min	20-10 min	30 min	30-20 min	
5	control	713	1647	934	2101	454
	control	685	1635	950	2138	503
	control	580	990	410	1243	253
	control	642	1303	661	1910	607
	control	645	1246	601	1950	704
	control	594	1164	570	1558	394
	control	746	1470	724	2099	629
	control	668	1442	774	2107	665
	control	778	1414	636	2011	597
	control	629	1090	461	1563	473
10	mean	668	1340	672.1	1868	527
	std err	20	69	56	96	43
15		10 min	20 min	20-10 min	30 min	30-20 min
	(3)	379	1214	835	1678	464
	(3)	525	1196	671	1507	311
	(3)	338	621	283	691	70
	(3)	553	1303	750	1619	316
	(3)	449	862	413	1112	250
	(3)	349	663	314	917	254
	(3)	584	1104	520	1576	472
	(3)	614	1349	735	1810	461
	(3)	537	1095	558	1758	663
20	(3)	616	963	347	1306	343
	mean	494.4	1037	542.6	1397.4	360.4
	std err	34	79	62	118	51
25		10 min	20 min	20-10 min	30 min	30-20 min
	(3)	379	1214	835	1678	464
	(3)	525	1196	671	1507	311
30		10 min	20 min	20-10 min	30 min	30-20 min
	(3)	338	621	283	691	70
	(3)	553	1303	750	1619	316
	(3)	449	862	413	1112	250
	(3)	349	663	314	917	254
	(3)	584	1104	520	1576	472
	(3)	614	1349	735	1810	461
	(3)	537	1095	558	1758	663
	(3)	616	963	347	1306	343
	mean	494.4	1037	542.6	1397.4	360.4
	std err	34	79	62	118	51

VERTICAL ACTIVITY					
	10 min	20 min	20-10 min	30 min	30-20 min
5	control	47	99	52	110
	control	44	62	18	64
	control	25	28	3	28
	control	3	75	72	94
	control	42	76	34	117
10	control	23	43	20	53
	control	66	113	47	141
	control	18	28	10	28
	control	59	78	19	107
	control	55	82	27	93
15	mean	38.2	68.4	30.2	83.5
	std err	6	9	7	12
		10 min	20 min	20-10 min	30 min
		30-20 min			
20	(3)	0	0	0	1
	(3)	17	33	16	35
	(3)	7	11	4	11
	(3)	27	91	64	101
	(3)	11	26	15	35
25	(3)	5	5	0	5
	(3)	36	66	30	75
	(3)	58	1	-57	100
	(3)	16	21	5	38
	(3)	54	66	12	82
30	mean	23.1	32	8.9	48.3
	std err	6	10	9	12

D. (S)-N-formyl aminoindan (4)

The results of the experiment employing (S)-N-formyl aminoindan (4) are shown in Table 4, FIG. 5A and FIG. 5B. Table 4 compares the activity counts for rats which have been administered (S)-N-formyl aminoindan (4) to control rats for three 10 minute intervals. FIG. 5A shows the locomotor activity level for rats which have been administered (S)-N-formyl aminoindan (4) as compared to the control. FIG. 5B shows the vertical activity level for rats which have been administered (S)-N-formyl aminoindan (4) as compared to the control.

(S)-N-formyl aminoindan significantly reduced amphetamine-induced locomotor activity (ANOVA: Drug effect:  $F(1)=8.18$ ,  $p<0.011$ ; Time effect:  $F(2)=5.2$ ,  $p<0.011$ ; Interaction:  $F(2)=0.42$  NS). Post hoc analysis indicates difference at all time points (FIG. 5A). Similar significant effects were demonstrated for vertical activity (ANOVA: Drug effect:  $F(1)=14.1$ ,  $p<0.002$ ; Time effect:  $F(2)=10.64$ ,  $p<0.0003$ ; Interaction:  $F(2)=0.58$ , NS). Post hoc analysis indicated a difference at all time points (FIG. 5B).

TABLE 4. Effect of (S)-N-formyl aminoindan (4) on Activity  
Levels

LOCOMOTOR ACTIVITY						
	10 min	20 min	20-10 min	30 min	30-20 min	
5	control	621	1167	546	1773	606
	control	647	1426	779	2200	774
	control	615	1294	679	1944	650
	control	627	1034	407	1504	470
	control	550	1029	479	1438	409
	control	750	1497	747	2274	777
	control	703	1374	671	1877	503
	control	700	1363	663	2007	644
	control	716	1347	631	1976	629
	control	631	1244	613	1819	575
10	mean	656	1278	622	1881	604
	std err	19	50	36	83	38
15		10 min	20 min	20-10 min	30 min	30-20 min
	(4)	453	919	466	1371	452
	(4)	589	1099	510	1632	533
	(4)	482	896	414	1253	357
	(4)	508	840	332	1031	191
	(4)	596	1179	583	1789	610
	(4)	558	1113	555	1730	617
	(4)	481	923	442	1422	499
	(4)	551	988	437	1422	434
	(4)	691	1306	615	2061	755
20	(4)	619	1088	469	1519	431
	mean	553	1035	482	1523	488
	std err	23	46	27	92	49
25						
30						

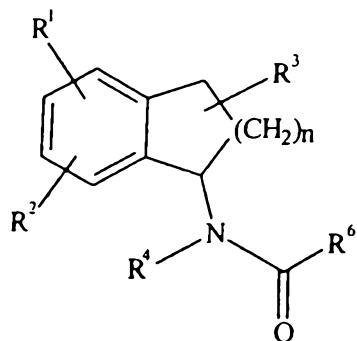
VERTICAL ACTIVITY						
	10 min	20 min	20-10 min	30 min	30-20 min	
5	control	51	77	26	125	48
	control	71	142	71	210	68
	control	20	27	7	31	4
	control	28	34	6	44	10
	control	25	52	27	66	14
10	control	60	114	54	167	53
	control	49	69	20	81	12
	control	34	58	24	106	48
	control	62	95	33	128	33
	control	43	55	12	93	38
15	mean	44	72	28	105	33
	std err	5	11	7	17	7
	10 min	20 min	20-10 min	30 min	30-20 min	
(4)	9	10	1	15	5	
20	(4)	30	40	10	55	15
	(4)	13	21	8	26	5
	(4)	7	7	0	7	0
	(4)	12	30	18	30	0
	(4)	12	17	5	31	14
25	(4)	21	27	6	38	11
	(4)	3	4	1	14	10
	(4)	34	37	3	83	46
	(4)	30	43	13	46	3
	mean	17	24	7	35	11
30	std err	3	4	2	7	4

Summary and Conclusion

Significant effects on behavior were demonstrated in the present experiment for the compounds (R)-N-acetyl aminoindan 5 (1), (S)-N-indanyl glycinate HCl (2), (rac)-N-(2-aminoacetyl)-1-aminoindan HCl (3) and (S)-N-formyl aminoindan (4). Interestingly, while (R)-N-acetyl-aminoindan (1), (rac)-N-(2-aminoacetyl)-1-aminoindan HCl (3) and (S)-N-formyl aminoindan (4) reduced the activity levels 10 of rats, by contrast, (S)-N-indanyl glycinate HCl (2) surprisingly increased activity. From the tested model, the compounds (R)-N-acetyl aminoindan (1), (rac)-N-(2-aminoacetyl)-1-aminoindan HCl (3) and (S)-N-formyl aminoindan (4) show anti-manic potential in humans. The 15 compound (S)-N-indanyl glycinate HCl (2) does not show anti-manic potential based on the tested model and doses.

**THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:**

1. A method of treating mania in bipolar mood disorder in a subject comprising administering to the subject a therapeutically effective amount of a compound of the structure:



wherein  $n$  is 0 or 1;

each of R<sup>1</sup> and R<sup>2</sup> are hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, or halogen;

$R^3$  is hydrogen,  $C_1-C_4$  alkyl, hydroxy, or  $C_1-C_4$  alkoxy;

R' is hydrogen, or C<sub>1</sub>-C<sub>4</sub> alkyl;

$R^6$  is hydrogen, substituted or unsubstituted  $C_1$ - $C_{12}$  alkyl,  $C_6$ - $C_{12}$  aryl,  $C_7$ - $C_{12}$  aralkyl or  $A-N-R^9R^{10}$ , provided that  $R^6$  is not methyl when  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are hydrogen atoms,

wherein A is substituted or unsubstituted  $C_1-C_{12}$  alkyl, substituted or unsubstituted  $C_6-C_{12}$  aryl, or substituted or unsubstituted  $C_7-C_{12}$  aralkyl, and

each of  $R^9$  and  $R^{10}$  are independently hydrogen,  $C_1$ - $C_{12}$  alkyl,  $C_6$ - $C_{12}$  aryl,  $C_7$ - $C_{12}$  aralkyl,  $COOtBu$ , or indanyl;

or a racemic mixture, enantiomer, or salt thereof.

2. A method of treating mania in bipolar mood disorder in a subject comprising administering to the subject a therapeutically effective amount of a compound selected from the group consisting of (rac)-N-(2-aminoacetyl)-1-aminoindan HCl, (R)-N-acetyl aminoindan, a salt of (R)-N-acetyl aminoindan, (S)-N-formyl aminoindan, and a salt of (S)-N-formyl aminoindan.

3. The method of claim 1, wherein the subject is a human subject.

4. The method according to claim 1, wherein the compound is a salt selected from the group consisting of a hydrochloride salt, a mesylate salt, an ethylsulfonate salt, and a sulfate salt.
5. The method according to claim 4, wherein the salt is a hydrochloride salt.
6. The method according to claim 1, wherein the administration is selected from the group consisting of oral, intraperitoneal, parenteral, topical, transdermal, rectal, nasal, and buccal administration.
7. The method according to claim 1, wherein the therapeutically effective amount is an amount from 30 mg/kg to 150 mg/kg.
8. The method according to claim 7, wherein the therapeutically effective amount is an amount from 30 mg/kg to 100 mg/kg.
9. The method according to claim 8, wherein the therapeutically effective amount is an amount from 30 mg/kg to 75 mg/kg.
10. The method of claim 2, wherein the compound is (rac)-N-(2-aminoacetyl)-1-aminoindan HCl.
11. The method of claim 2, wherein the compound is (S)-N-formyl aminoindan or a salt of (S)-N-formyl aminoindan.
12. The method of claim 2, wherein the compound is (R)-N-acetyl aminoindan or a salt of (R)-N-acetyl aminoindan.
13. The method according to claim 2, wherein the subject is a human subject.
14. The method according to claim 2, wherein the compound is a salt selected from the group consisting of a hydrochloride salt,

a mesylate salt, an ethylsulfonate salt, and a sulfate salt.

15. The method according to claim 14, wherein the salt is a  
5 hydrochloride salt.

16. The method according to claim 2, wherein the administration is selected from the group consisting of oral, intraperitoneal, parenteral, topical,  
10 transdermal, rectal, nasal, and buccal administration.

17. The method according to claim 2, wherein the therapeutically effective amount is an amount from 30 mg/kg to 150 mg/kg.

15

18. The method according to claim 11, wherein the compound is a salt selected from the group consisting of a hydrochloride salt, a mesylate salt, an ethylsulfonate salt, and a sulfate salt.

20

19. The method according to claim 12, wherein the compound is a salt selected from the group consisting of a hydrochloride salt, a mesylate salt, an ethylsulfonate salt, and a sulfate salt.

25

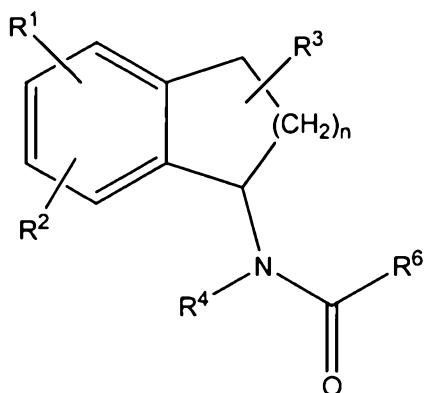
20. The method according to claim 18, wherein the salt is a hydrochloride salt.

30

21. The method according to claim 19, wherein the salt is a hydrochloride salt.

22. The method according to claim 1 or claim 2, substantially as hereinbefore described with reference to the Examples.

5 23. Use of a compound of the structure:



wherein n is 0 or 1;

10 each of R<sup>1</sup> and R<sup>2</sup> are hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, or halogen;  
 R<sup>3</sup> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, hydroxy, or C<sub>1</sub>-C<sub>4</sub> alkoxy;  
 R<sup>4</sup> is hydrogen, or C<sub>1</sub>-C<sub>4</sub> alkyl;  
 R<sup>6</sup> is hydrogen, substituted or unsubstituted C<sub>1</sub>-C<sub>12</sub> alkyl, C<sub>6</sub>-C<sub>12</sub> aryl, C<sub>7</sub>-C<sub>12</sub> aralkyl or A-N-R<sup>9</sup>R<sup>10</sup>, provided that R<sup>6</sup> is not methyl when R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are hydrogen atoms,

15 wherein A is substituted or unsubstituted C<sub>1</sub>-C<sub>12</sub> alkyl, substituted or unsubstituted C<sub>6</sub>-C<sub>12</sub> aryl, or substituted or unsubstituted C<sub>7</sub>-C<sub>12</sub> aralkyl, and  
 each of R<sup>9</sup> and R<sup>10</sup> are independently hydrogen, C<sub>1</sub>-C<sub>12</sub> alkyl, C<sub>6</sub>-C<sub>12</sub> aryl, C<sub>7</sub>-C<sub>12</sub> aralkyl, COOtBu, or indanyl;

20 or a racemic mixture, enantiomer, or salt thereof;  
 in the manufacture of a medicament for treating mania  
 25 in bipolar mood disorder.

- 30 -

24. Use of a compound selected from the group consisting of  
(rac)-N-(2-aminoacetyl)-1-aminoindan HCl, (R)-N-acetyl  
aminoindan, a salt of (R)-N-acetyl aminoindan, (S)-N-  
formyl aminoindan, and a salt of (S)-formyl aminoindan  
5 in the manufacture of a medicament for treating mania  
in bipolar mood disorder.

DATED this 4<sup>th</sup> day of June, 2004

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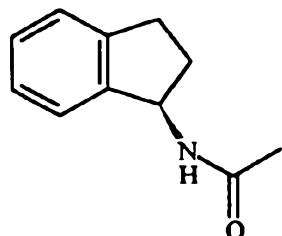
**Teva Pharmaceutical Industries Ltd.**

By DAVIES COLLISON CAVE  
Patent Attorneys for the Applicants

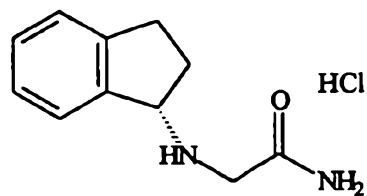


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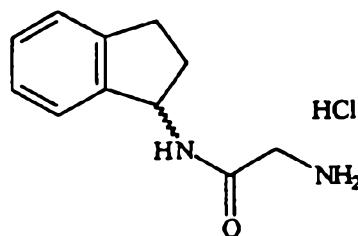
FIG. 1



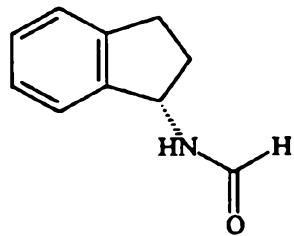
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3



4

FIG. 2

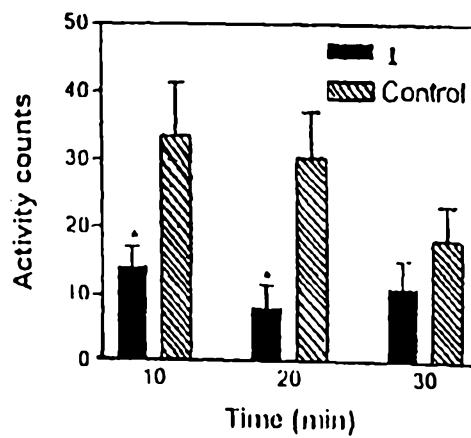
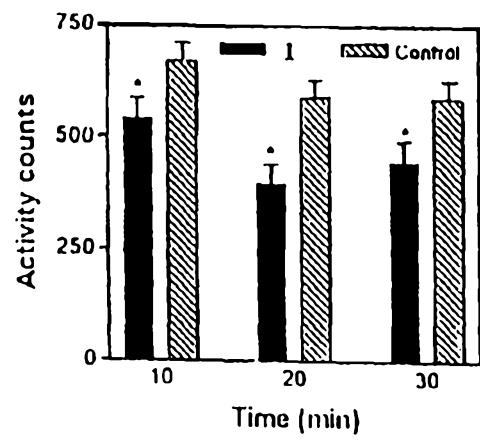
FIG. 2B  
Vertical activityFIG. 2A  
Locomotor activity

FIG. 3

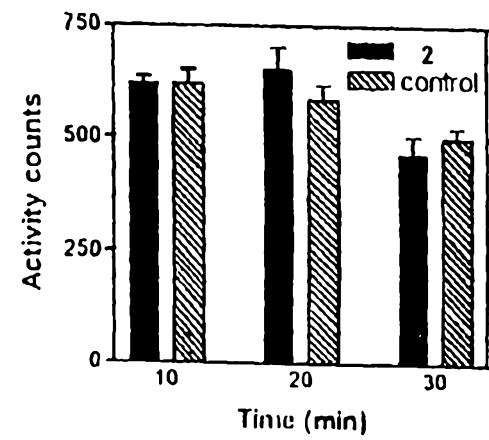
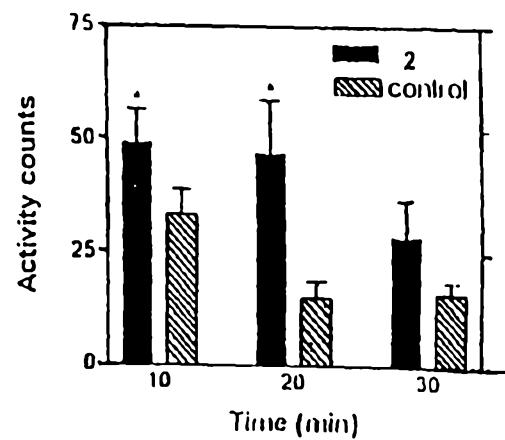
FIG. 3A  
Locomotor activityFIG. 3B  
Vertical activity

FIG. 4

FIG. 4A  
Locomotor activity

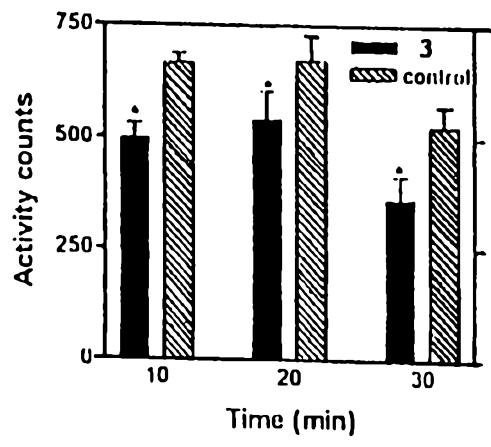


FIG. 4B  
Vertical activity

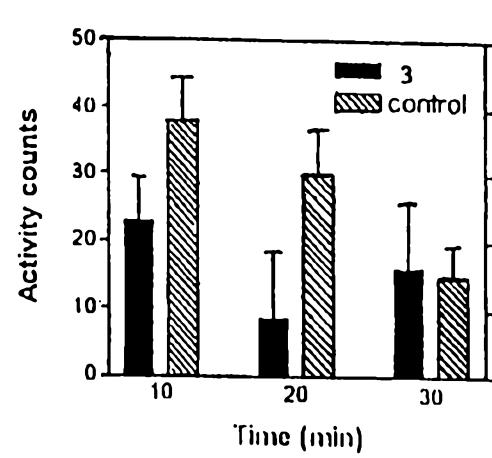
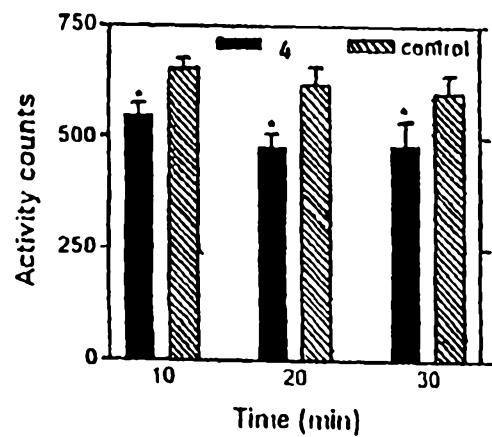


FIG. 5

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FIG. 5A  
Locomotor activityFIG. 5B  
Vertical activity