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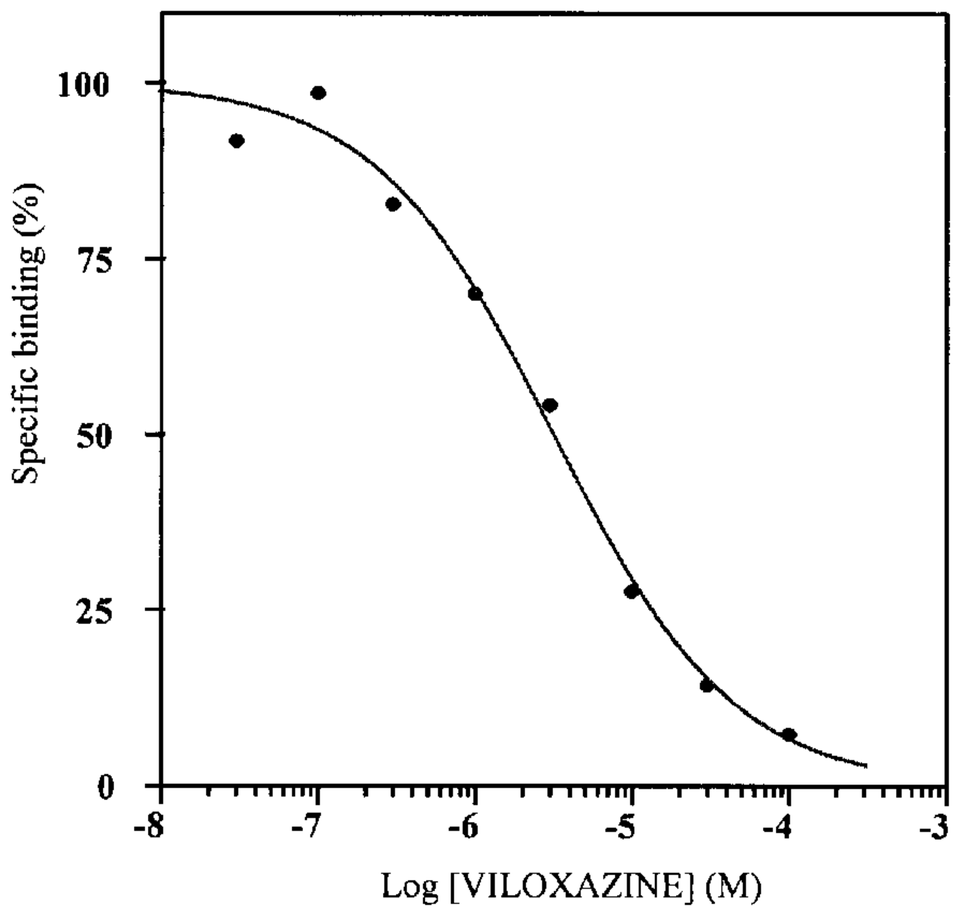
(54) **Titre : PROCEDE DE TRAITEMENT DE TROUBLE DEFICITAIRE DE L'ATTENTION AVEC HYPERACTIVITE (ADHD)**
(54) **Title: METHOD OF TREATMENT OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD)**

COMPETITION CURVE OBTAINED WITH VILOXAZINE
AT THE HUMAN 5-HT7 RECEPTOR

IC50 = 3.2E-06 M
nH = 0.8



(57) **Abrégé/Abstract:**
The invention comprises a method for treatment of ADHD or ADHD-related disorders by a pharmaceutical agent exhibiting combined serotonergic or no-radrenergic reuptake transporters and monoamine receptor activity.

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[Continued on next page]

(54) Title: METHOD OF TREATMENT OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD)

(57) Abstract: The invention comprises a method for treatment of ADHD or ADHD-related disorders by a pharmaceutical agent exhibiting combined serotonergic or noradrenergic reuptake transporters and monoamine receptor activity.

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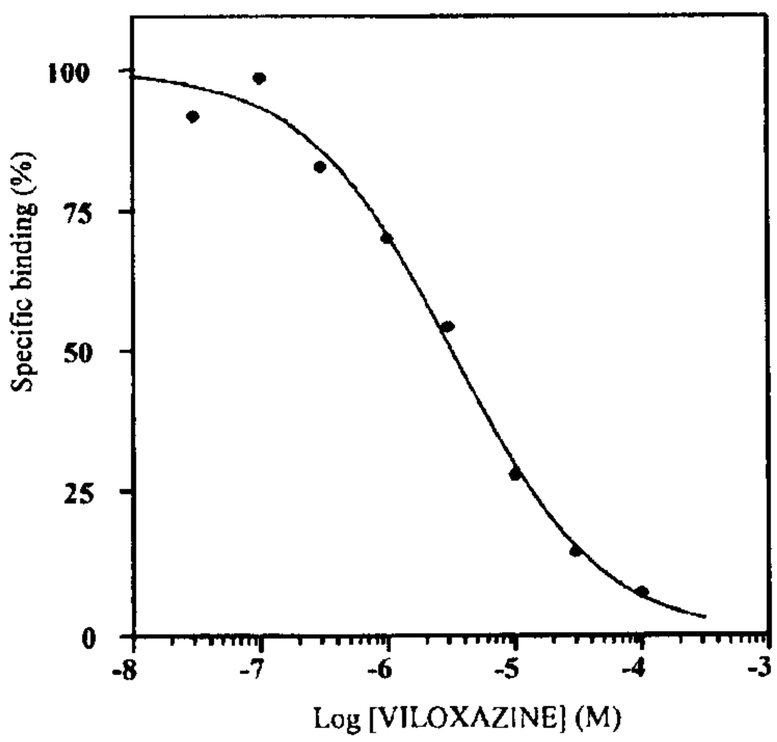

Figure 1

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METHOD OF TREATMENT OF ATTENTION DEFICIT / HYPERACTIVITY DISORDER (ADHD)

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority from U.S. Provisional Application No. 61/094,502, filed September 5, 2008.

BACKGROUND

[0002] Viloxazine (Emovit®, Vivalan®, Vivarin®, Vicilan®) is a bicyclic antidepressant morpholine derivative that inhibits the reuptake of norepinephrine. Viloxazine hydrochloride has been approved in Italy, Belgium, England, Ireland, Germany, Portugal, Spain, the former Yugoslavia, France, Slovakia, for the treatment of major depressive disorder.

[0003] Viloxazine is known to inhibit noradrenergic reuptake transporters (155 nM) and has very weak activity at the serotonin reuptake inhibitor (17.3 μm). (Tatsumi et al [1997] Eur J Pharmacol 340 (2-3): 249-58).

[0004] The present invention is predicated on the unexpected discovery that viloxazine may be effective in the treatment of ADHD in humans with nominal, if any, significant side effects.

SUMMARY OF THE INVENTION

[0005] In one embodiment of the invention, a method of treating ADHD and ADHD-related disorders in a mammal comprising administering to the mammal a pharmaceutical agent exhibiting 5HT1B and/or 5HT7 antagonistic activity is provided.

[0006] In another embodiment, the invention provides a method for treatment of ADHD and ADHD-related disorders in a mammal comprising administering to the mammal a pharmaceutical agent exhibiting a combination of at least two of the following: noradrenergic reuptake inhibitory activity, 5HT1B antagonistic activity, and 5HT7 antagonistic activity.

[0007] In yet another embodiment, the invention provides a method for treatment of ADHD and ADHD-related disorders in a mammal comprising administering to the mammal a pharmaceutical agent exhibiting a combination of at least two of the

following: noradrenergic reuptake inhibitory activity, α4/β2 antagonistic activity, and α7 antagonistic activity.

[0008] In still another embodiment, the invention provides a method for treatment of ADHD and ADHD-related disorders in a mammal comprising administering to the mammal a pharmaceutical agent exhibiting a combination of at least two of the following: 5HT1B antagonistic activity, 5HT7 antagonistic activity, α4/β2 antagonistic activity, and α7 antagonistic activity.

[0009] In another embodiment, the current invention provides a novel method for treatment of ADHD and related disorders by administering a formulation of viloxazine.

[0010] The invention also provides a method of identifying compounds for the treatment of ADHD and/or similar disorders.

[0010a] Specific aspects of the invention include:

- use of a therapeutically effective amount of a formulation of viloxazine as sole active ingredient for treatment of Attention Deficit/Hyperactivity Disorder (ADHD) in a human subject in need thereof;

- use of a therapeutically effective amount of a formulation of viloxazine as sole active ingredient for antagonizing 5HT1B and/or 5HT7;

- use of a therapeutically effective amount of a formulation of viloxazine as sole active ingredient for antagonizing inhibiting noradrenergic reuptake and antagonizing 5HTlB and/or 5HT7;

- use of a therapeutically effective amount of a formulation of viloxazine as sole active ingredient for inhibiting noradrenergic reuptake and antagonizing α4/β2 and/or α7; and

- use of a therapeutically effective amount of a formulation of viloxazine as sole active ingredient for antagonizing 5HT1B and/or 5HT7 and antagonizing α4/β2 and/or α7.

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BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Figure 1 shows a competition curve obtained with compound viloxazine with human 5-HT7 receptor.

[0012] Figure 2 shows the agonist effect of the compound viloxazine with human 5HT7 receptor.

[0013] Figure 3 shows the antagonist effect of the compound viloxazine with human 5HT7 receptor.

[0014] Figure 4 shows a competition curve obtained with compound viloxazine with human 5-HT1B receptor.

[0015] Figure 5 shows the agonist effect of the compound viloxazine with human 5HT1B receptor.

[0016] Figure 6 shows the antagonist effect of the compound viloxazine with human 5HTlB receptor.

DETAILED DESCRIPTION OF THE INVENTION

[0017] Unless otherwise specified, "a" or "an" means "one or more."

[0018] In one embodiment, the invention provides a method for treatment of ADHD and ADHD-related disorders. ADHD-related disorders include, but are not limited to, mood or affective disorders such as anxiety, depression or bipolar disorder; or

disorders where ADHD may be a co-morbid syndrome, such as obsessive compulsive disorder, Tourette's Syndrome, or Post Traumatic Stress Disorder. The method comprises the administration to a mammal diagnosed with ADHD or an ADHD-related disorder a pharmaceutical agent exhibiting a combination (at least 2) of: noradrenergic reuptake inhibitory activity, 5HT1B antagonistic activity, and 5HT7 antagonistic activity. In another embodiment, the invention comprises a method of treating any of the above-listed disorders with a pharmaceutical agent exhibiting a combination (at least 2) of: noradrenergic reuptake inhibitory activity, α4/β2 antagonistic activity, and α7 antagonistic activity. In still another embodiment, the invention comprises a method of treating any of the above-listed disorders with a pharmaceutical agent exhibiting a combination (at least 2) of: 5HT1B antagonistic activity, 5HT7 antagonistic activity, α4/β2 antagonistic activity, and α7 antagonistic activity.

[0019] The pharmaceutical agents suitable for invention are identified by a process comprising the steps of: (1) selecting one or a combination of active agents with known activity inhibiting either serotonin or noradrenergic reuptake transporters; (2) conducting a receptor screening assay on the selected agent(s) to identify activity on at least one nicotinic, dopaminergic, serotonergic or gabaergic receptor or binding site where the activity is known to be associated with ADHD;(3) determining if said activity is agonistic or antagonistic; (4) selecting among the screened active agents at least one that targets the most of the different types of ADHD-associated receptors; and (5) optimizing the total dosage of the selected active agent(s).

[0020] In a preferred embodiment of the invention, the pharmaceutical agent is viloxazine. The present inventor unexpectedly discovered that in addition to noradrenergic activity, viloxazine exhibits specific antagonist activity at the 5-HT7 (serotonin 7) and 5HT1B receptors. It was also discovered that viloxazine exhibits α4/β2 and/or α7 antagonistic activity. This heretofore unknown receptor activity of viloxazine was evaluated as follows:

I. Viloxazine activity on 5-HT receptors

[0021] A heterologous competition assay was used to determine the relative affinity of viloxazine for 5-HT receptors. Briefly, recombinant 5-HT1B OR 5-HT7 receptors were expressed in a CHO cell line. The receptors were then saturated with a tritiated receptor-specific ligand at concentrations known to be saturating. Thereupon, 10 μM viloxazine was added to the cells in the presence of non-specific ligand and incubated. In this way, viloxazine was allowed to "compete" with the receptor-specific ligand, such that greater displacement (i.e., % inhibition) is indicative of greater binding strength of viloxazine at a given receptor. "Specific binding" refers here to the difference in the binding of the ligand to the receptors in the presence or absence of an excess of the viloxazine. The conditions and results of the assays are summarized in the Table 1.

Table 1. Conditions of the displacement assay at select serotonin receptors for viloxazine

Receptor	Ligand	Conc.	Non-specific	Incubation	% Inhib.	Detection method
5-HT1A *(h)*	[3H]8-OH-DPAT	0.3 nM	8-OH-DPAT (10 μM)	60 min/22°C	66	Scintillation counting
5-HT1B	[125I]CYP (+ 30 μM (-)propranolol)	0.1 nM	serotonin (10 μM)	120 min/37°C	78	Scintillation counting
5-HT1D	[3H]serotonin	1 nM	serotonin (10 μM)	60 min/22°C	18	Scintillation counting
5-HT2A *(h)*	[3H]ketanserin	0.5 nM	ketanserin (1 μM)	60 min/22°C	-17*	Scintillation counting
5-HT2C *(h)*	[3H]mesulergine	1 nM	RS-102221 (10 μM)	60 min/37°C	56	Scintillation counting
5-HT3 *(h)*	[3H]BRL 43694	0.5 nM	MDL 72222 (10 μM)	120 min/22°C	18	Scintillation counting
5-HT4e *(h)*	[3H]GR 113808	0.3 nM	serotonin (100 μM)	60 min/37°C	16	Scintillation counting
5-HT5A *(h)*	[3H]LSD	1 nM	serotonin (100 μM)	60 min/37°C	15	Scintillation counting
5-HT6 *(h)*	[3H]LSD	2 nM	serotonin (100 μM)	120 min/37°C	6	Scintillation counting
5-HT7 *(h)*	[3H]LSD	4 nM	serotonin (10 μM)	120 min/22°C	70	Scintillation counting

* A negative number reflects negligible inhibition, i.e., a condition where the binding of the radioactive test ligand was greater in the presence of viloxazine. This reflects

either the variability in the radioactive control ligand binding or facilitation by the test ligand.

[0022] The affinity of viloxazine for 5-HT7 5-HT1B receptors was further characterized by determining the IC50 (i.e., the concentration of viloxazine that can inhibit 50% of control specific binding). For this experiment, a range of viloxazine concentrations was selected for the ligand blocking assay. The IC50 was determined using non-linear regression analysis of the competition curves using a Hill equation curve fitting ($Y = D + [(A - D)/(1 + (C/C50)nH)]$, where Y = specific binding, D = minimum specific binding, A = maximum specific binding, C = compound concentration, C50 = IC50, and nH = slope factor). The inhibition constants Ki were calculated using Cheng Prusoff equation. Ki is defined as the concentration of the competing ligand (viloxazine) that bound to half the binding sites at equilibrium in the absence of radioligand or other competitors. The results of the affinity assay are summarized in Tables 2 and 3, and in Fig. 1.

Table 2.

Receptor	Concentration(M)	% of Control Specific Binding		
		1st	2nd	Mean
5-HT1A *(h)*	3.0E-08	97.8	99.8	98.8
	1.0E-07	93.8	96.9	95.4
	3.0E-07	104.7	110.3	107.5
	1.0E-06	104.8	109.1	107.0
	3.0E-06	76.5	71.4	73.9
	1.0E-05	32.5	41.3	36.9
	3.0E-05	21.9	19.6	20.7
	1.0E-04	5.3	5.8	5.5
5-HT1B	3.0E-08	102.0	99.9	101.0
	1.0E-07	97.6	92.4	95.0
	3.0E-07	92.4	82.7	87.6
	1.0E-06	77.7	79.0	78.4
	3.0E-06	61.5	52.6	57.1
	1.0E-05	36.6	27.1	31.9
	3.0E-05	13.7	4.5	9.1
	1.0E-04	-10.4	-12.4	-11.4
5-HT2C *(h)*	3.0E-08	97.9	125.8	111.9
	1.0E-07	116.6	111.5	114.0
	3.0E-07	92.9	102.7	97.8
	1.0E-06	108.2	104.2	106.2
	3.0E-06	90.6	91.9	91.3
	1.0E-05	61.6	63.1	62.3
	3.0E-05	33.1	36.6	34.8
	1.0E-04	8.4	14.3	11.4
5-HT7 *(h)*	3.0E-08	90.6	92.7	91.7
	1.0E-07	102.9	94.2	98.5
	3.0E-07	80.4	85.1	82.7
	1.0E-06	73.5	66.5	70.0
	3.0E-06	48.2	60.2	54.2
	1.0E-05	27.3	27.9	27.6
	3.0E-05	15.3	13.2	14.3
	1.0E-04	6.5	8.1	7.3

Table 3. Summary of IC50 determination at select serotonin receptors for Viloxazine.

Assay	Reference compound	IC50 (M)	Ki (M)	n(H)
5-HT1A *(h)*	8-OH-DPAT	7.1E-06	4.5E-06	1.3
5-HT1B	serotonin	3.8E-06	2.3E-06	1.0
5-HT2C *(h)*	RS-102221	1.4E-05	6.4E-06	1.0
5-HT7 *(h)*	serotonin	3.2E-06	1.2E-06	0.8

[0023] The nature of the binding (i.e., agonist or antagonist) was next determined. Briefly, an assay was designed that examined the agonist effect on the 5HT7 or 5-HT1B receptor, i.e., the generation of cAMP or the blockade of this effect when stimulated by a 5HT7 agonist, serotonin. This was also done with a range of concentrations to determine the relative agonist versus antagonist binding Ki. The EC50 values (concentration producing a half-maximal specific response) and IC50 values (a concentration causing a half-maximal inhibition of the control-specific agonist response) were determined by a non-linear regression analysis of the concentration-response curves generated with mean replicate values using Hill equation curve fitting. The apparent dissociation constants for antagonists Kb were calculated using the modified Cheng Prusoff equation.

[0024] The conditions of the screening are represented in Table 4. Results of the functional assays are seen in Figures 2 (5-HT7 agonist assay) and 3 (5-HT7 antagonist assay). The agonist assay demonstrated no measurable response (Figure 2). The antagonist assay for 5-HT7 yielded a weak response with an IC50 greater than 3.0 x10-5 M.

Table 4. Conditions for 5HT7 Functional Assay

Assay	Reference compound	Incubation conditions	Reaction product	Method of detection
5-HT7 *(h) (agonist effect)*	none	45 min/37° C	cAMP	HTRF
5-HT7 *(h) (antagonist effect)*	serotonin	45 min/37° C	cAMP	HTRF
5-HT1B *(h) (agonist effect)*	none	30 min/37° C	cAMP	HTRF
5-HT1B *(h) (antagonist effect)*	serotonin	30 min/37° C	cAMP	HTRF

II. Viloxazine activity on nicotinic receptors

[0025] Conditions for the initial screen:

[0026] Membrane homogenates of rat cerebral tissue are incubated with 1.5 nM [3H]cystine (for nicotinic acetylcholine α4β2 screen) or 1 nM [125I]α-bungarotoxin (for nicotinic acetylcholine α7 screen) in the absence or presence of 10 μM test compound in buffer. Nonspecific binding is determined in the presence of 10 μM nicotine for α4β2 or 1μM α-bungarotoxin for α7. Following incubation, the samples are filtered rapidly under vacuum through glass fiber filters and rinsed several times. The filters are dried, then counted for radioactivity in a scintillation counter. The results can be expressed as a percent inhibition of the control radioligand specific binding. The standard reference compound is nicotine for α4β2 and α-bungarotoxin for α7, which is tested in each experiment at several concentrations to obtain a competition curve from which its IC50 can be calculated. Conditions for the IC50 determination can be the same as for the initial screen, except the test compound is assayed at 8 different concentrations between 10-9 and 10-4 M.

[0027] The effectiveness of viloxazine for ADHD treatment can be evaluated in a Five-Choice Serial Reaction Time Task (5-CSRTT) assay. This test in typically performed with rats and is designed to show brain regions and neural substrates involved in attention, information processing speed, impulsivity, hyperactivity and preservative behaviors (obsessive compulsive disorder-like). Pharmaceutical agents of the current invention, including but not limited to viloxazine, can be tested to

measure their effects on attention, impulsivity and reaction time and the outcome analyzed to determine their profile and application to treating ADHD.

[0028] An additional test, SmartCubeTM, can also be performed to obtain a "behavioral signature" for a given compound. The experimental platform of this test combines robotics, computer video capture and analysis (called computer vision), and bioinformatics to capture and analyze data.

[0029] An animal treated with the test compound under study is placed in an enclosure and presented with a non-invasive behavioral challenge, such as changing the floor's configuration. The animal's behavior is recorded using cameras and electro-mechanical sensors, and data from these recordings are processed using algorithms to reveal the compound's behavioral signature. This "signature" can then be screened against the company's database of signatures from reference compounds to identify candidates predicted to have utility in treating ADHD.

[0030] According to the invention, ADHD or ADHD-related disorders can be treated in human subjects by administering viloxazine in a total daily dose that is at least 10% lower than the current minimally effective dose of 2.14 mg/kg, which is used to treat major depressive disorder. In other embodiments, the dose is 15% lower, 25% lower, 35% lower, or 50% lower than the current dose. Dosage ranges of 1.1 mg/kg/day to 9.7 mg/kg/day or approximately 20 to 800 mg for pediatric (aged 6 to 17) and adult population are also provided.

[0031] According to the invention, viloxazine can be administered in the amount of from 10 to 600 mg/day. In another embodiment, the daily dose of viloxazine may be from 150 to 400 mg/day. In yet further embodiment of the invention, viloxazine is administered in the amount of up to 300 mg/day. The method of the current invention offers a safe and effective treatment of ADHD and related disorders in both children and adults. For the purposes of this invention, a term "viloxazine" includes viloxazine and all pharmaceutically acceptable salts thereof, as well as all isomers, stereomers and polymorphs thereof.

[0032] In another embodiment, the invention encompasses a method of treatment of ADHD or ADHD-related disorders with viloxazine that is characterized by an improved adverse effect profile. The adverse effects that are diminished by the method of the present invention include, but are not limited to, nausea, vomiting,

insomnia, loss of appetite, increased erythrocyte sedimentation, EKG and EEG anomalies, epigastric pain, diarrhea, constipation, vertigo, orthostatic hypotension, edema of the lower extremities, dysarthria, tremor, psychomotor agitation, mental confusion, inappropriate secretion of antidiuretic hormone, increased transaminases, seizure, and increased libido. Hence, the inventive method provides for the treatment of ADHD without, or at least with far less frequency than with conventional viloxazine-treatment, of one, two, six or more of these listed side effects. The efficacy and the adverse effect profile of the lower dose treatment of the current invention can be evaluated in a randomized, placebo controlled trial.

[0033] Whereas particular embodiments of the invention have been described herein for the purpose of illustrating the invention and not for the purpose of limiting the same, it will be appreciated by those of ordinary skill in the art that numerous variations of the details, materials and arrangement of parts may be made within the principle and scope of the invention without departing from the invention as described in the appended claims.

[0034] Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

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CLAIMS:

1. Use of a therapeutically effective amount of a formulation of viloxazine as sole active ingredient for treatment of Attention Deficit/Hyperactivity Disorder (ADHD) in a human subject in need thereof.

2. The use of claim 1, wherein the therapeutically effective amount is from about 10 to about 600 mg a day.

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

4. The use of claim 2, which provides an improved adverse effect profile.

5. Use of a therapeutically effective amount of a formulation of viloxazine as sole active ingredient for antagonizing 5HT1B and/or 5HT7.

6. Use of a therapeutically effective amount of a formulation of viloxazine as sole active ingredient for inhibiting noradrenergic reuptake and antagonizing 5HTlB and/or 5HT7.

7. Use of a therapeutically effective amount of a formulation of viloxazine as sole active ingredient for inhibiting noradrenergic reuptake and antagonizing α4/β2 and/or α7.

8. Use of a therapeutically effective amount of a formulation of viloxazine as sole active ingredient for antagonizing 5HT1B and/or 5HT7 and antagonizing α4/β2 and/or α7.

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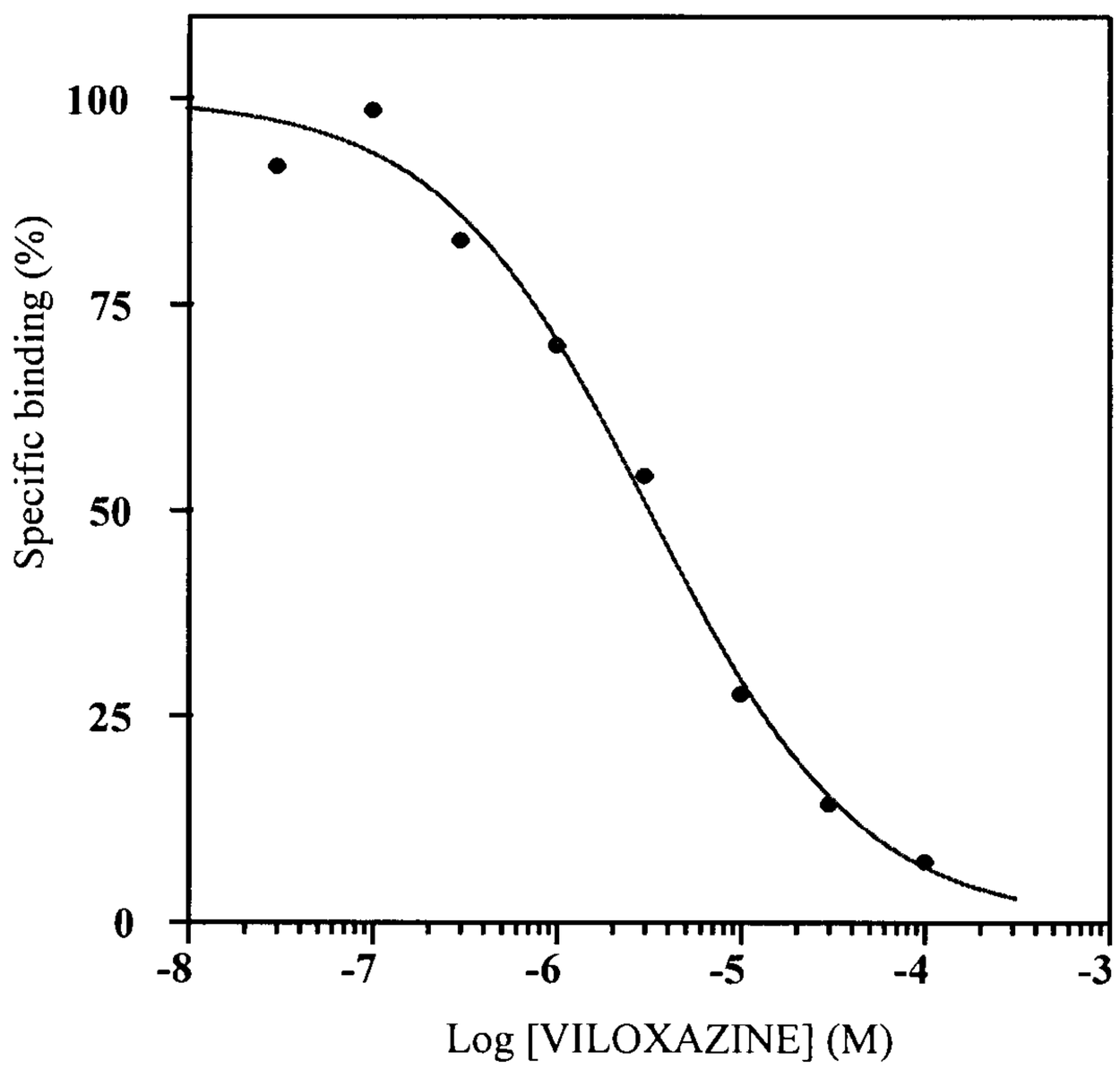

Figure 1

AGONIST EFFECT OF COMPOUND VILOXAZINE
AT THE HUMAN 5-HT7 RECEPTOR

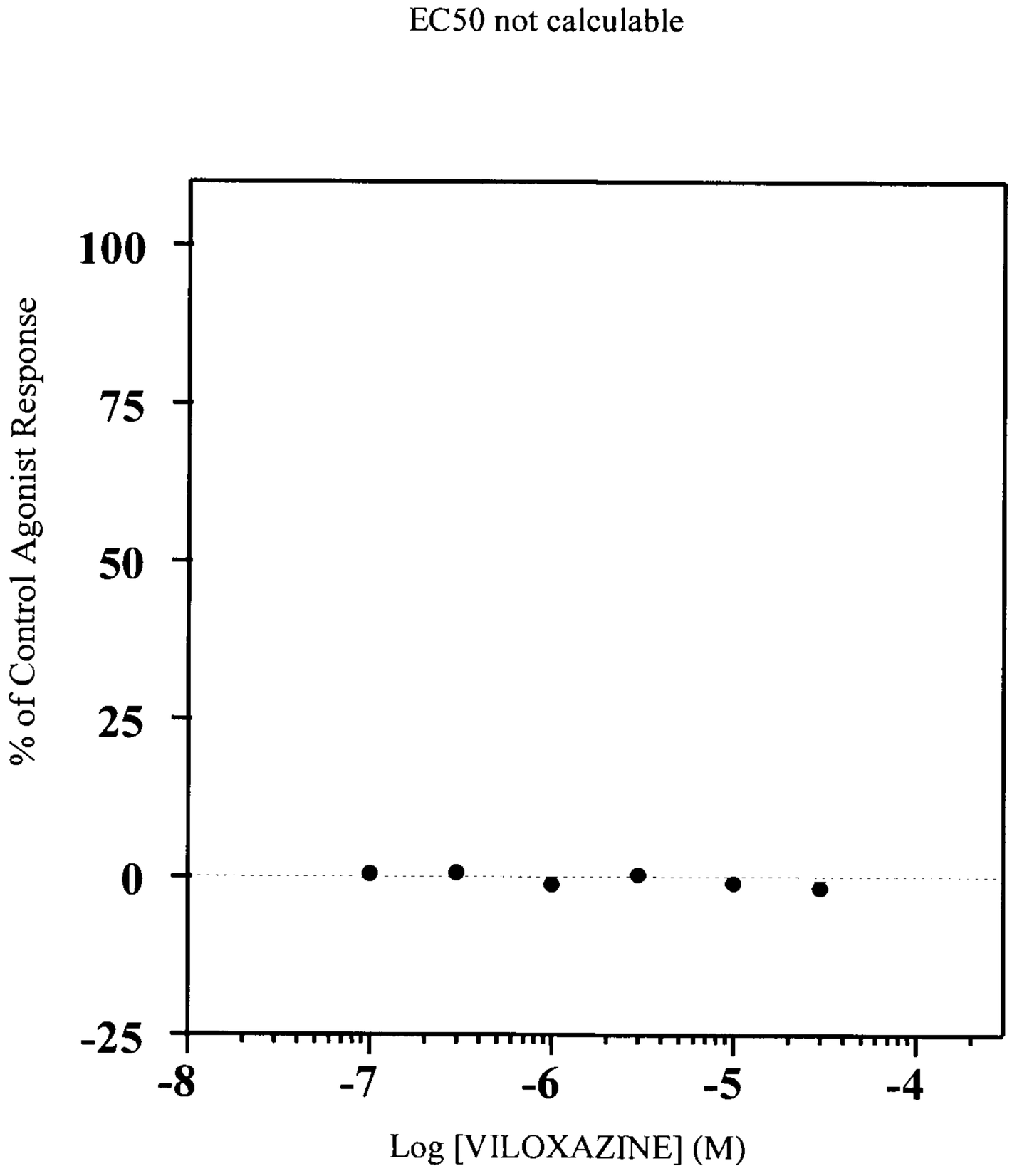

Figure 2

ANTAGONIST EFFECT OF VILOXAZINE
AT THE HUMAN 5-HT7 RECEPTOR

IC50 > 3.0E-05 M

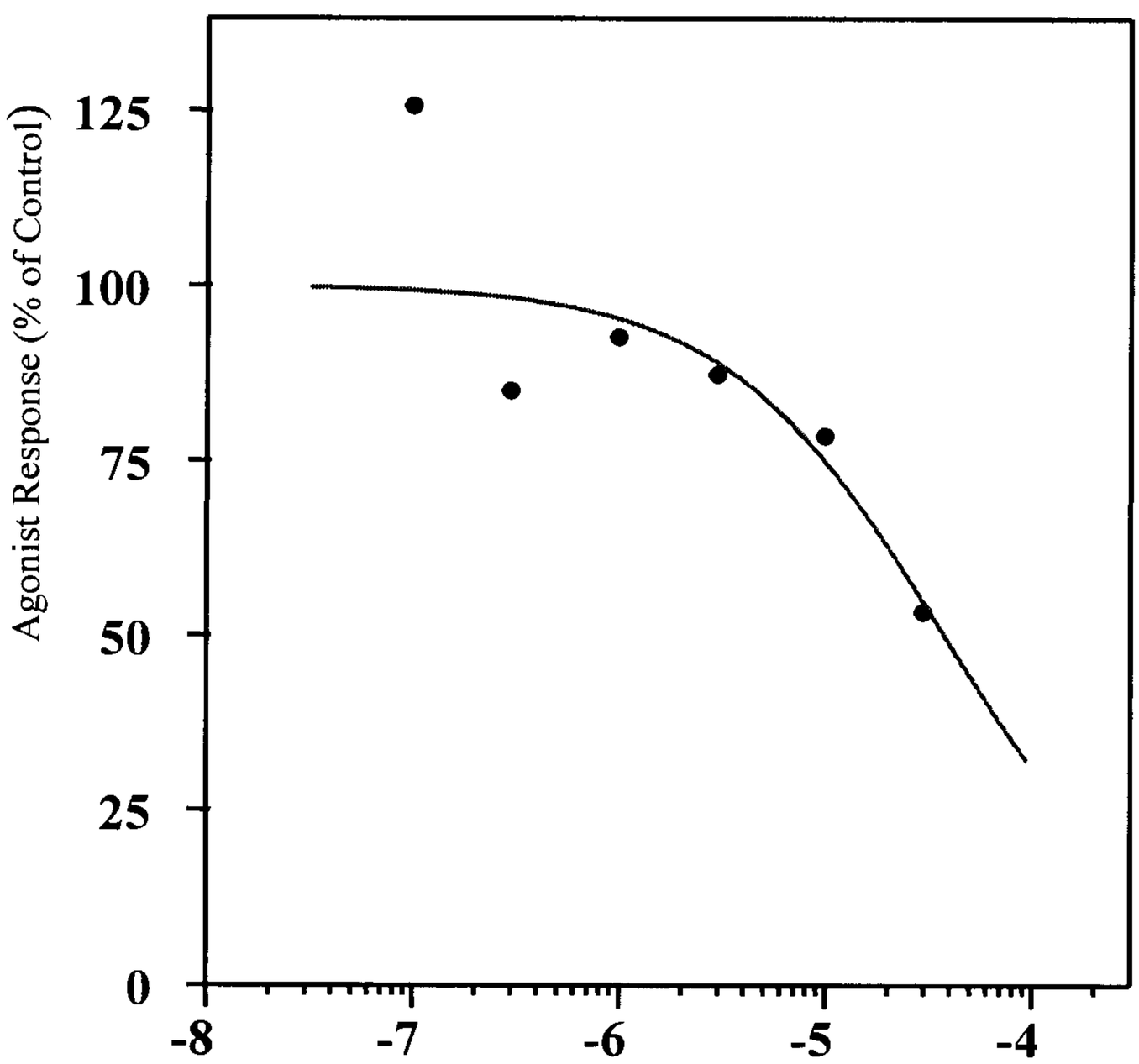

Figure 3

COMPETITION CURVE OBTAINED WITH VILOXAZINE
AT THE 5-HT1B RECEPTOR

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nH = 1.0

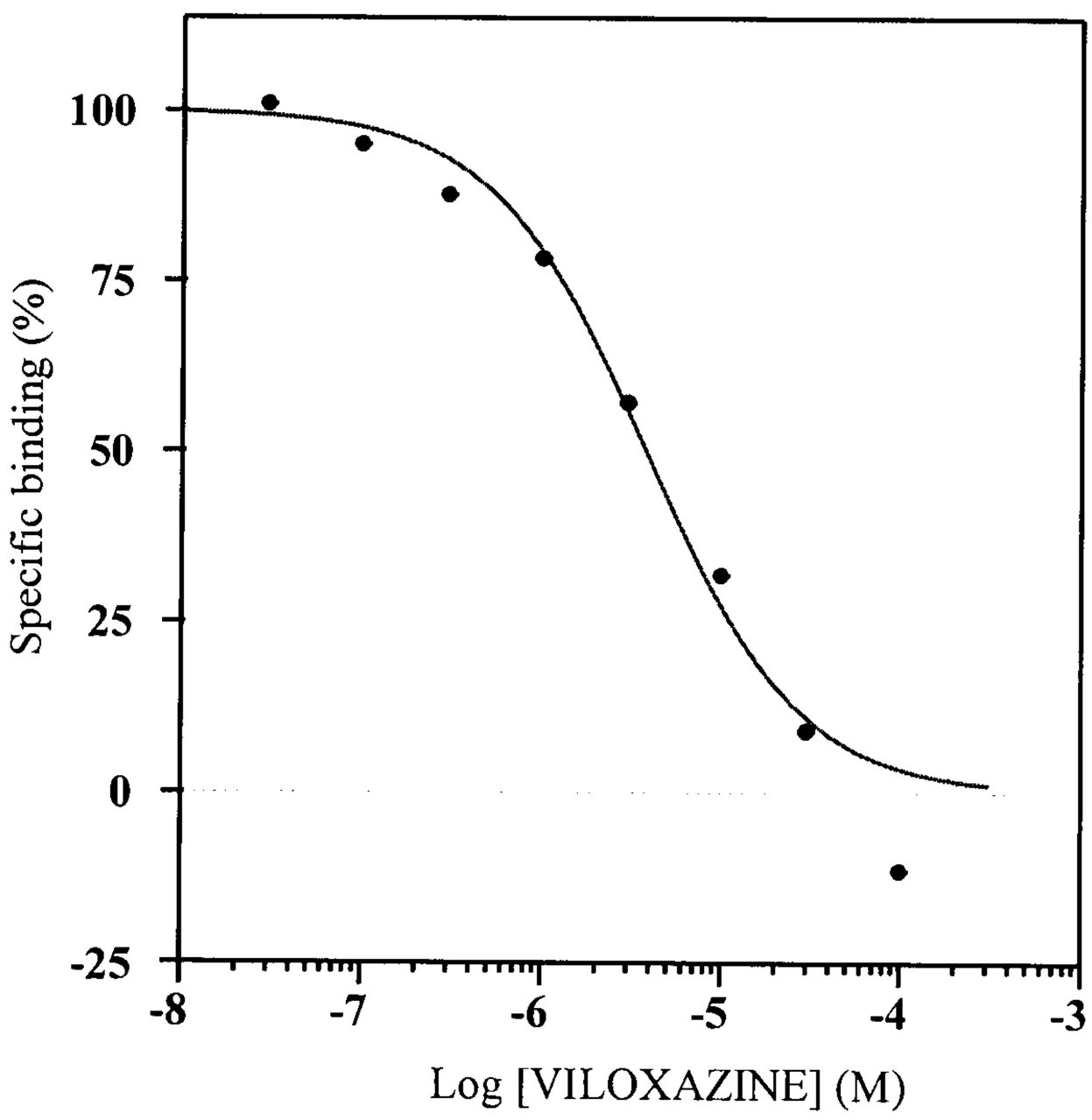

Figure 4

AGONIST EFFECT OF VILOXAZINE
AT THE 5-HT1B RECEPTOR

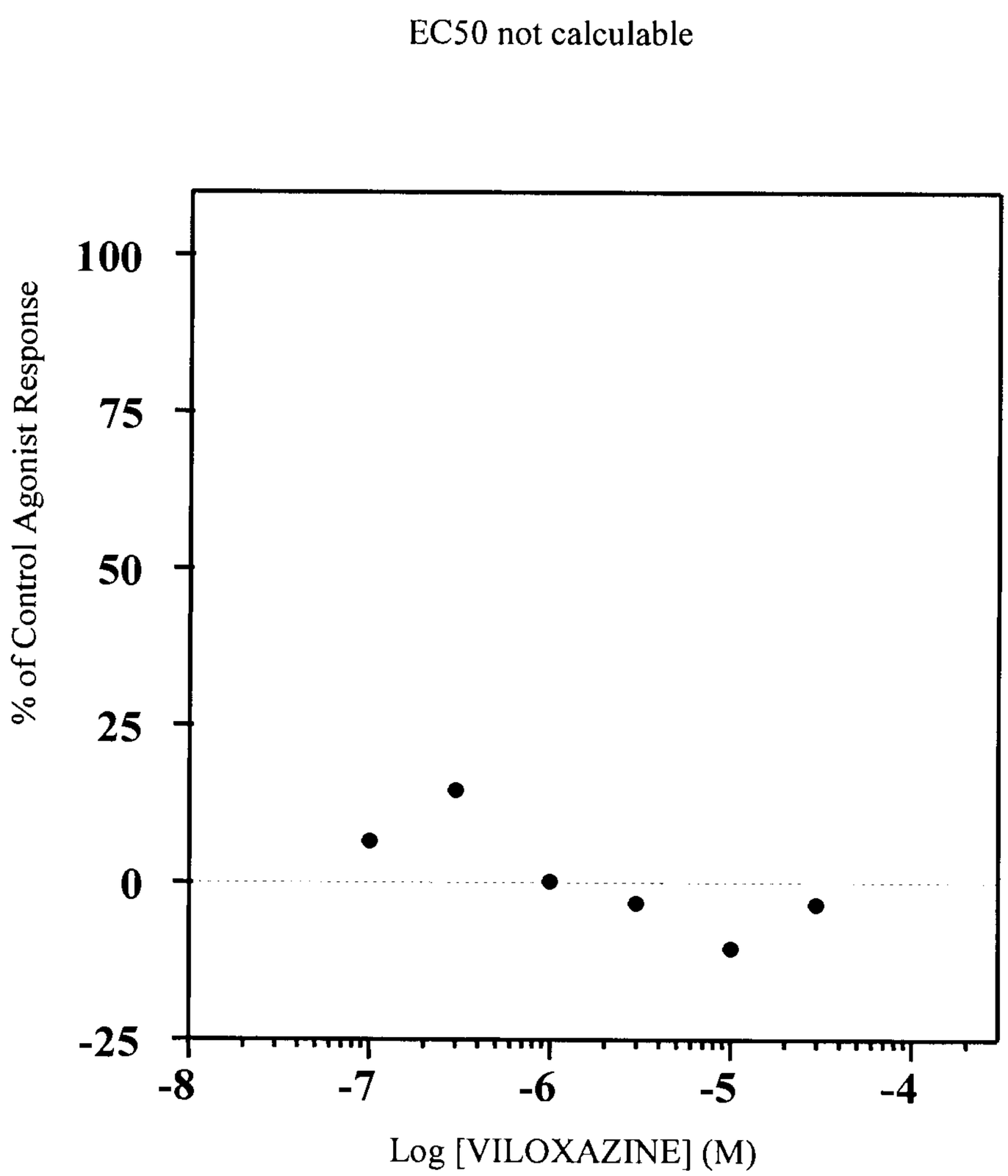

Figure 5

ANTAGONIST EFFECT OF VILOXAZINE
AT THE 5-HT1B RECEPTOR

IC50 = 1.8E-05 M

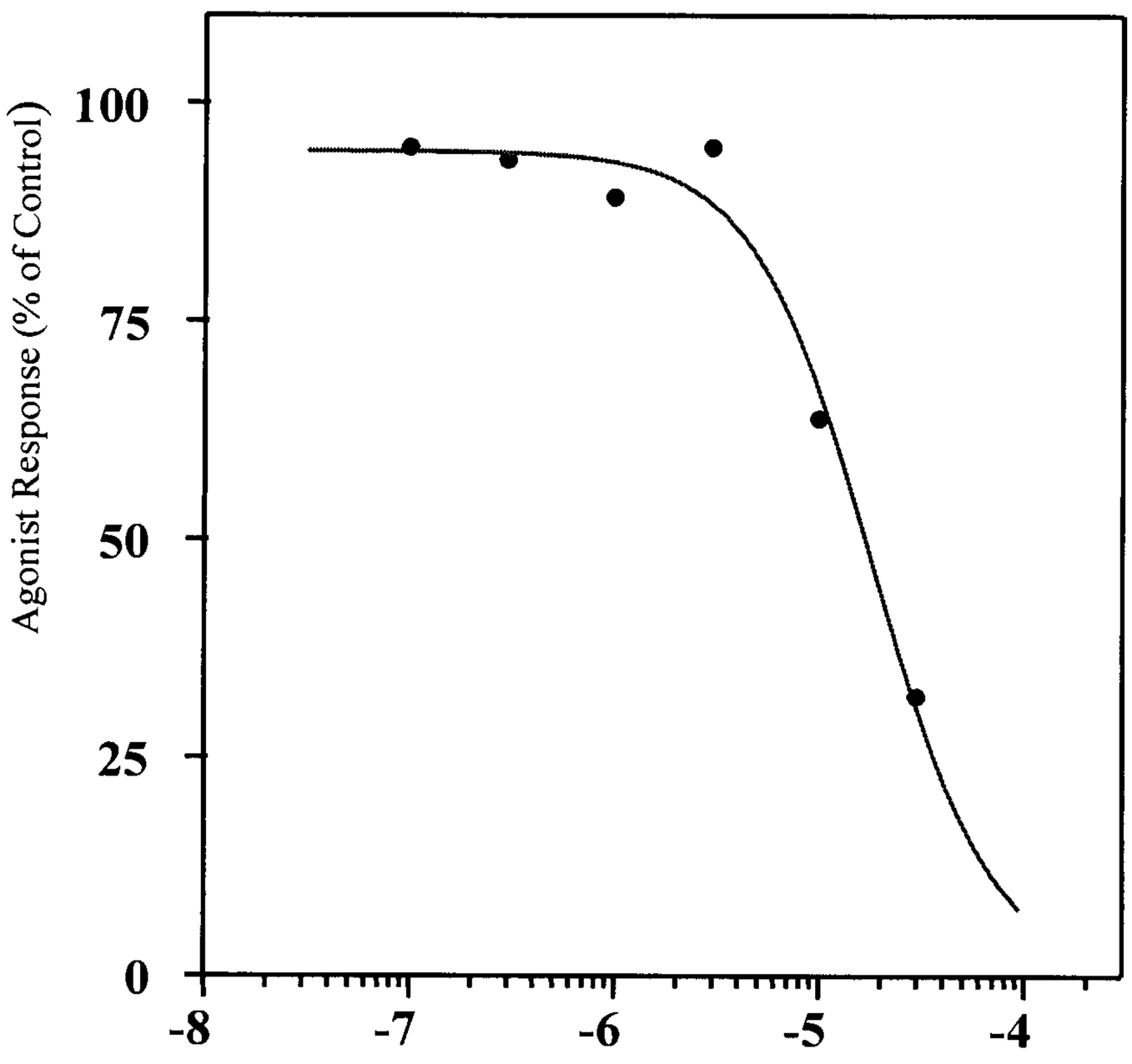

Figure 6

COMPETITION CURVE OBTAINED WITH VILOXAZINE
AT THE HUMAN 5-HT7 RECEPTOR

IC50 = 3.2E-06 M
nH = 0.8