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[54] **INHIBITING AGGRESSIVE BEHAVIOR WITH 1,2,3-BENZOTRIAZIN-(3H)-ONE**

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[51] **Int. Cl.** **A61k 27/00**

[58] **Field of Search** 424/249

[56] **References Cited**

UNITED STATES PATENTS

2,935,445	5/1960	Hosler et al.	424/249
3,471,489	10/1969	Rigterink	424/249
3,652,560	3/1972	Livak	424/249

OTHER PUBLICATIONS

J. Org. Chem., Vol. 26, (1961), pp. 613–615.

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[57] **ABSTRACT**

1,2,3-benzotriazin-4(3H)-one is useful as an anti-aggression agent.

11 Claims, No Drawings

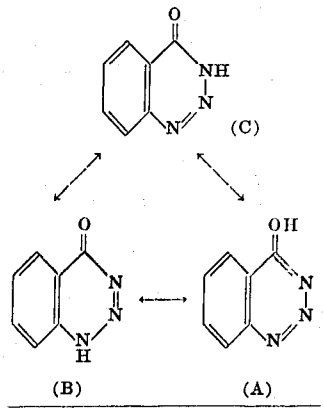
INHIBITING AGGRESSIVE BEHAVIOR WITH 1,2,3-BENZOTRIAZIN-(3H)-ONE

BACKGROUND OF THE INVENTION

1. Field of the Invention

The neurochemistry of aggression has recently attracted much attention, and it has long been recognized that aggressive behavior in animals and man can be produced by alterations in ordered brain function. In man, aggressive behavior is often associated with all types of mental diseases. Thus, aggression is a major side effect of most mental disorders.

This invention relates to 1,2,3-benzotriazin-4(3H)-one, (C) a known compound which is capable of tautomerism and exists in the following forms:



Form (A) is called 4-hydroxy-1,2,3-benzotriazine and form (B) is called 1,2,3-benzotriazin-4(1H)-one.

This compound has been found to be highly selective for the abolition of aggressive behavior at doses which cause little or no signs or symptoms of central nervous system depression or toxicity.

It is well accepted in neuropharmacology that there is no clear distinction between sedative-hypnotics and minor tranquilizers. All known minor tranquilizers which are effective in reducing anxiety also produce drowziness, ataxia (inability to coordinate muscular movements) and sleep when given in larger doses. All sedative-hypnotic drugs in small doses are "anxiolytic" (causing apprehension or anxiety). Sedative hypnotics such as alcohol and short-acting barbiturates tend to produce behavioral excitation prior to promoting drowziness and sleep. The sedative-hypnotics and minor tranquilizers produce discrete, predictable changes in behavior that can be applied to therapeutic advantage in neurotics. Aside from their ability to promote sleep, their major behavioral action of therapeutic advantage are their ability to slightly reduce the level of arousal-excitability, overcome passive avoidance (social withdrawal, suppressed or submissive) behavior, slightly diminish aggressive hostility, and increase the response to environmental stimuli. The effect, for example, of a "psychomimetic" (inducing psychosis like symptoms) drug on animal behavior such as LSD in rats and cats has been said to increase "excitement" and "aggression."

Currently, aggressive behavior in mental disease patients is usually controlled by such major tranquilizers as chlorpromazine. This approach to the problem of controlling mental disorders is not entirely satisfactory since patients under the influence of this type of medication are overtly depressed and are not able to return satisfactorily to society and to function normally. Chlorpromazine is a strong central nervous system (CNS) depressant, both in normal and schizophrenic patients. Its most salient feature, however, is the ability to inhibit aggressive behavior in abusive and destructive schizophrenics. It has been the drug of choice for the treatment of so-called "back-ward" schizophrenics, and is now used in out-patient therapy in cases of simple schizophrenia. The compounds have many side-effects, the most serious of which is that it causes depression at the same time that it alleviates the schizophrenic symptoms. Incidentally, it also has a disadvantage in that it is quite toxic and has caused liver damage and blood disorders.

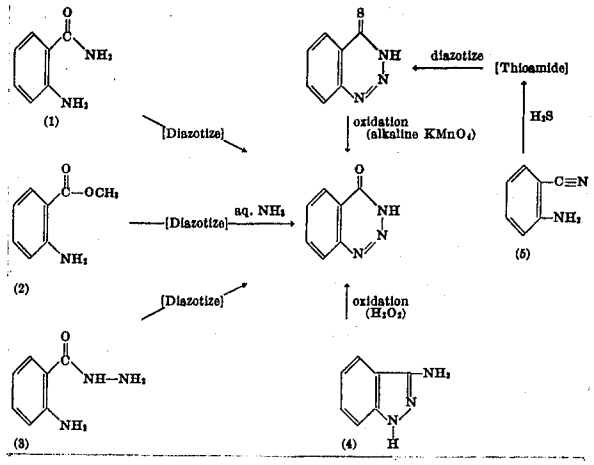
The abolition of aggressive behavior in schizophrenics without neurotoxicity, as characterized by depression, would be a most desirable feature for a new drug in the therapy of mental disease. The compound of the present invention has been found to be an agent which selectively blocks aggressive behavior but which does not cause depression.

Accordingly, the invention is a method of treating aggressive behavior comprising administering a therapeutically effective dose of 1,2,3-benzotriazin-4(3H)-one to an anxious animal.

2. Description of the Prior Art

1,2,3-benzotriazin-4(3H)-one is a known compound which was first described in the chemical literature in 1887 by A. Weddige and H. Finger, *Journ. fur prakt. Chem.* [2], 35, 262 (1887); and H. Finger, *Journ. fur prakt. Chem.* [2], 37, 431 (1888) with no mention of any pharmaceutical activity.

Several methods for preparing this compound are known. These methods are summarized in the following reaction schemes:



The above reaction schemes (1) to (5) are described in the literature as follows:

(1)	Weddige et al.	J. pr. [2],	35, 262 (1887)
	Finger	J. pr. [2],	37, 432 (1888)
(2)	Zacharias	J. pr. [2],	43, 446 (1891)
(3)	Thode	69, 103 (1856)	
	J. pr. [2],		
	Heller et al.	J. pr. [2],	116, (1927) 1904
(4)	Bamberger et al.	Ber.	31, 2637 (1898)
		Ann.	305, 359 (1899)
(5)	Reissert et al.	Ber.	42, 3710 (1909)

There are many compounds that are similar to 1,2,3-benzotriazin-4(3H)-one which are known to have pharmaceutical activity. For example, U.S. Pat. No. 3,316,262 discloses that certain 3-substituted-1,2,3-benzotriazin-4(3H)-ones have antiphlogistic, antipyretic, analgesic, and sedative activity coupled with low toxicity. This patent does not, however, disclose anti-aggression activity, i.e., the ability to selectively abolish aggressive behavior at doses which cause little or no signs or symptoms of CNS depression or toxicity.

In Shreekishna et al, J. Org. Chem. 26, 613 (1961), 1,2,3-benzotriazin-4(3H)-one is disclosed as having sedative activity (but not anti-aggression activity), while benz-halogenated and 3-dialkyl-aminoalkyl analogs thereof were found to be devoid of pharmacological activity.

Other references of interest are the following:

1. Cutting et al., Med. Pharmacol. Exptl. 15 (1), 7–16 (1966) which describes the present compound as being effective in decreasing the number of mice with litters by at least 50 percent.

2. "Benzo-1,2,3-triazines" — J. Org. Chem. 24, 272, (1959) discloses various derivatives of the present compound as possible pharmacologically active compounds.

3. A series of substituted derivatives of the present compound are reported in Gilmore et al., Journal Heterocyclic Chemistry 6, 809 (1969), and Stevens et al., J. Chem. Soc. (C) 765, (1970).

4. U.S. Pat. Nos. 2,758,115; 2,843,588; and 2,914,530, which disclose N-phosphate derivatives of the present compound as miticides and insecticides.

5. British Pat. No. 932,680 mentions a 3-aminobenzotriazinone N-carboxylic acid hydroxy-ethyl ester as a compound which possesses pronounced muscle relaxing and analgesic activity.

6. U.S. Pat. No. 3,075,982 discloses certain derivatives as having valuable pharmaceutical properties as narcotics.

7. U.S. Pat. No. 2,949,465 discloses 1,2,3-benzotriazin-4(3H)-one derivatives as plant fungicides.

8. U.S. Pat. No. 2,935,445 discloses N-trichloromethylthio derivatives as a nematocide.

9. U.S. Pat. No. 3,014,906 discloses 6-sulfamyl-3,7-disubstituted-1,2,3-benzotriazines as diuretics and for relief as pre-menstrual tension and similar periods of stress.

10. U.S. Pat. No. 3,471,489 discloses substituted 1,2,3-benzotriazin-4(3H)-ones as useful insecticides, herbicides and central nervous system depressants.

11. British Pat. No. 1,110,265 discloses 3-phenyl 1,2,3-benzotriazin-4-ones as pharmacologically active compounds useful as sedative-hypnotics, anticonvulsants and hypoglycemics.

12. U.S. Pat. No. 3,492,406 discloses 3-(2-fluorophenyl)-1,2,3-benzotriazin-4-ones as an anorexigenic agent in mammals.

13. Netherland Pat. No. 6,702,189 discloses derivatives of the present compound as central nervous system depressants.

14. Netherland Pat. No. 6,603,319 discloses derivatives of the present compound as having sedative activity and as being useful for treatment of psychoneurosis. The French equivalent is Pat. No. 1,552,801.

SUMMARY OF THE INVENTION

The present invention provides a method of inhibiting aggressive behavior in an anxious animal subject without causing the central nervous system depression which is a typical side effect of drugs heretofore used to treat aggressive behavior. This is achieved by administering to an anxious animal subject a therapeutically effective amount of 1,2,3-benzotriazin-4(3H)-one, either as such, or in the form of a pharmaceutical composition including said compound. Generally, the amount administered will be from about 2 to 100, preferably, from about 2 to 25 mg/kg/day of body weight. In humans, the amount will be from about 0.03 to 1.4, preferably, from about 0.03 to 0.3 mg/kg/day of body weight.

The pharmaceutical compositions which may be administered to an anxious animal subject in accordance with the invention comprise, in combination, a therapeutically effective amount of the compound of the present invention and a pharmaceutically acceptable carrier and/or diluent therefor.

For example, in the case of a tablet, the composition will comprise, in addition to the active ingredient, fillers, binders and diluents such as lactose, methylcellulose, talc, gum tragacanth, gum acacia, agar, polyvinylpyrrolidone, stearic acid and/or corn starch. In the case of a liquid suspension for oral administration, the composition will comprise, in addition to the active ingredients, a filler such as sodium carboxymethylcellulose and/or a syrup, e.g., a glycerine based syrup.

DETAILED DESCRIPTION OF THE INVENTION

The most outstanding property of the compound of the present invention is the highly selective abolition of aggressive behavior in doses which cause little or no signs or symptoms of central nervous system depression or toxicity. The compound can be classified as a psychotherapeutic agent, but it is unique in that no other agent of this class possesses the same spectrum of activity. The compound of the present invention has a Neuropharmacological Profile [Samuel Irwin, Science 136, 123 (1962)] in mice which resembles that of the major tranquilizers such as chlorpromazine. It differs from chlorpromazine, however, in that it is a much weaker depressant of motor activity in the mouse. It was very active in inhibiting aggressive behavior in three models of experimental aggression; namely, isolated fighting behavior in mice, electroshock-induced fighting in mice, and septal rat aggression. In a comparative study with a major tranquilizer, such as chlordiazepoxide, the compound of the present invention was found to be much more selective in inhibiting aggressive behavior than the latter. It does not possess significant anticonvulsant activity and in this respect it differs from chlordiazepoxide. It does, however, cause a significant hypothermia which indicates an activity resembling chlorpromazine and other major tranquilizers. It is a

weak potentiator of pentobarbital and is inactive in the dl-dopa fighting test from monoamine oxidase inhibitors. It apparently does not possess anti-depressant activity since it did not reverse tetrabenazine ptosis. The compound of the present invention is orally active in mice and rats and orally is less toxic than chlorpromazine or chlordiazepoxide.

The compound of the present invention was studied in the Neuropharmacological Profile, which is a standardized multidimensional observation technique used on mice to grade symptomatology and acute toxicity relative to dosage.

In a dose range of 3–300 mg/kg, the present compound produced depression, reduced motor activity, hyporeflexia and hypothermia. A loss of righting occurred at the 300 mg/kg dose level and no convulsions were observed at any level. Depending on the dosage used, the onset of action varied between 15 and 30 minutes and the effects lasted for approximately 30 minutes to several hours. The results of the Neuropharmacological Profile indicate that this compound is a central nervous system depressant having sedative properties.

The compound of the present invention and the two commonly used tranquilizers were subjected to the spontaneous locomotor activity test, in which six mice or rats per dose were placed in individual photocell activity cages 30 minutes (mice) or 60 minutes (rats) after i.p. (intraperitoneal) administration of the drug, for a 30 minute activity count. Table I shows the results obtained by comparing drug-treated groups with control activity. The SD_{50} being that dose causing a 50 percent reduction from control activity.

TABLE I

Spontaneous Locomotor Activity

I.P. SD_{50} (mg/kg)

	MICE	RATS
1,2,3-benzotriazin-4(3H)-one	44.0	82.5
Chlorpromazine	2.8	1.7
Chlordiazepoxide	12.8	14.0

The present compound appears to possess a much weaker depressant action in both mice and rats in comparison with chlorpromazine (major tranquilizer) and chlordiazepoxide (minor tranquilizer).

In addition, the present compound exhibited weak depressant activity when given orally with an SD_{50} of 140.0 mg/kg in mice and greater than 450 mg/kg in rats.

In the neurotoxicity test, the value (NTD_{50}) is defined as the dose necessary to cause 50 percent of mice or rats trained to walk a rotating wooden rod (5 rpm) to fall at the time of peak effect, and is a measure of drug effects on motor function or central nervous system toxicity. The results set forth in Table II were obtained when 1,2,3-benzotriazin-4(3H)-one was tested against chlorpromazine and chlordiazepoxide.

TABLE II

Neurotoxicity

	NTD_{50} (mg/kg)	(95% Confidence Limits)
I.P.	MICE	
1,2,3-benzotriazin-4(3H)-one	143.5	(99.1 – 207.0)
Chlorpromazine	0.7	(0.4 – 1.1)
Chlordiazepoxide	13.8	(7.1 – 27.0)
P.O.		
1,2,3-benzotriazin-4(3H)-one	320.0	(221.0 – 465.0)
Chlorpromazine	12.1	(8.5 – 17.3)
Chlordiazepoxide	54.0	(38.6 – 75.6)
I.P.	RATS	
1,2,3-benzotriazin-4(3H)-one	55.5	(34.6 – 89.0)
Chlorpromazine	5.3	(3.1 – 9.1)
Chlordiazepoxide	4.3	(2.6 – 7.1)
P.O.		
1,2,3-benzotriazin-4(3H)-one	214.0	(110.0 – 415.0)
Chlorpromazine	11.0	(6.1 – 19.9)
Chlordiazepoxide	11.5	(8.8 – 15.1)

The time of peak effect for each agent in both species was about 30–60 minutes after drug administration.

Again, 1,2,3-benzotriazin-4(3H)-one was considerably less potent than either reference drug. In addition, 1,2,3-benzotriazin-4(3H)-one appeared to be more centrally toxic in rats than in mice.

The compound of the present invention was compared with chlorpromazine and chlordiazepoxide for its anti-aggressive activity. Four models of experimentally-induced aggression in rodents were studied (R.D. Sofia, *Life Sciences* 8: 705, 1969). The results of these experiments are summarized in Table III.

TABLE III

Anti-Aggressive Activity

	ED_{50} (95% Confidence Limits) (mg/kg) I.P.			ED_{50} P.O.		
Agent	ED_{50}		NTD_{50}/ED_{50}	ED_{50}		$NTD_{50}ED_{50}$
	Isolated Mouse Aggression					
1,2,3-benzotriazin-4(3H)-one	6.7	(5.3–8.0)	21.7	17.0	(8.5–34.0)	18.8
Chlorpromazine	2.8	(2.0–3.9)	0.3	6.9	(5.1–9.4)	1.8
Chlordiazepoxide	20.5	(11.3–37.5)	0.7	35.0	(25.4–48.3)	1.5
	Electroshock-Induced Fighting in Mice					
1,2,3-benzotriazin-4(3H)-one	34.0	(20.7–55.9)	4.2	Weakly Active (approx. 100 mg/kg)		
Chlorpromazine	5.5	(3.1–9.9)	0.1	0.86	(0.39–1.88)	14.0
Chlordiazepoxide	4.2	(2.3–7.7)	3.3	3.0	(1.7–5.4)	18.0
	Septal Rat Aggression					

TABLE III

Anti-Aggressive Activity

Agent	I.P. ED_{50} (95% Confidence Limits) (mg/kg)		NTD_{50}/ED_{50}	P.O. ED_{50} (95% Confidence Limits) (mg/kg)		$NTD_{50}ED_{50}$
1,2,3-benzotriazin-4(3H)-one	8.8	(4.4–17.6)	6.3	9.4	(4.7–18.6)	22.8
Chlorpromazine	10.7	(4.5–25.7)	0.2	11.4	(6.1–21.4)	0.9
Chlordiazepoxide	25.8	(14.0–47.5)	0.4	23.7	(13.0–59.0)	0.5
	Killer Rat Aggression					
1,2,3-benzotriazin-4(3H)-one	85.0	(61.8 – 117.5)	0.65		—	—
Chlorpromazine	7.2	(4.3 – 11.8)	0.2	17.4	(10.1 – 29.8)	0.6
Chlordiazepoxide	36.3	(24.2 – 54.4)	0.3	74.0	(53.1 – 102.8)	0.2

When considering the results of these studies it should be understood that drug specificity is considered selective only when aggressive behavior is inhibited at doses which are significantly lower than those which impair rotarod performance (NTD_{50}) or result in a NTD_{50}/ED_{50} ratio of greater than 1. Based on the above criteria chlorpromazine and chlordiazepoxide are considered non-selective in abolishing aggression in the isolated mouse and septal rat assays, since these drugs give ratios of less than 1. The present compound gives ratios of 6.3 and 21.7 in septal rat and isolated mouse arrays when administered intraperitoneally, and 22.8 and 18.0 in the same assays when administered orally. These high ratios indicate a high degree of specificity for inhibiting experimentally-induced aggressive behavior. In addition, this degree of selectivity of the present compound for anti-aggressive activity is further supported by the fact that it is quite active at doses which are well below the doses inhibiting spontaneous locomotor activity. With respect to killer rat aggression, neither the present compound, chlorpromazine nor chlordiazepoxide were specific in inhibiting this type of aggression. This test is apparently selective for anti-depressants and stimulants, since reference agents from both these classes of drugs are selectively active (R.D. Sofia, *Life Science*, 8: 120, 1969).

The present compound is selectively active in blocking electroshock-induced fighting in mice; the ratio being 4.2 upon intraperitoneal injection. In this respect, it closely resembles chlordiazepoxide which gave a ratio of 3.3. Clorpromazine would be considered inactive in this respect since it did block electroshock-induced fighting, but only at neurotoxic doses.

Anti-convulsant activity was tested in the following procedures.

1. Maximal Electroshock Seizures (MES_{50})

Groups of ten mice each were injected i.p. with a vehicle and the test drug and placed in individual plexiglas squares. Thirty minutes after i.p. injection, each mouse was administered an electric shock transcorneally at 50mA intensity, 0.2 seconds duration (Swinyard, et al., *J. Pharmacol. Exptl. Ther.* 106: 319, 1952). The criterion for activity is protection against tonic extension of the hind limbs. The dose necessary to protect 50 percent of the mice (MES_{50}) was determined. The following results were obtained.

TABLE IV

Maximal Electroshock Seizures

Agent	I.P. MES_{50} mg/kg
1,2,3-benzotriazin-4(3H)-one	Inactive (100 mg/kg)
Chlorpromazine	Inactive (25 mg/kg)
Chlordiazepoxide	14.3 (8.4 – 24.3)

The present compound like chlorpromazine did not protect against MES even at very high doses. However, chlordiazepoxide did exhibit anti-convulsant activity.

2. Pentylenetetrazol Seizures (MET_{50})

Seizures were produced in mice by subcutaneous administration of 125 mg/kg of pentylenetetrazol. The endpoints measured were convulsions and death. The dose necessary to protect 50 percent of the mice (MET_{50}) for both parameters was determined. The following results were obtained.

TABLE V

Pentylenetetrazol Seizures

Agent	I.P. MET_{50} mg/kg
1,2,3-benzotriazin-4(3H)-one	Inactive (200 mg/kg)
Chlorpromazine	Inactive (100 mg/kg)
Chlordiazepoxide	7.1 (5.6 – 90) for convulsions 2.6 (2.2 – 3.1) for death

Of the drugs tested, only chlordiazepoxide exhibited antipentylenetetrazol activity.

Protection from d-amphetamine aggregation-induced lethality is usually afforded by alpha-adrenergic-blocking agents such as chlorpromazine, phenoxybenzamine, etc. Percent protection was determined for each compound and an ED_{50} value calculated. The results are summarized in Table VI.

TABLE VI

d-Amphetamine Aggregation

Agent	ED_{50} mg/kg
1,2,3-benzotriazin-4(3H)-one	Inactive (50 – 200 mg/kg)
Chlorpromazine	1.2 (0.8 – 1.8)
Chlordiazepoxide	Inactive (50 mg/kg)

The present compound and chlordiazepoxide were both inactive in this procedure. Chlorpromazine was very active and its activity is probably due in part to the alpha-adrenergic blocking activity of this compound.

1,2,3-benzotriazin-4(3H)-one, chlorpromazine, and chlordiazepoxide were compared in the following drug interaction studies.

1. Pentobarbital

1,2,3-benzotriazin-4(3H)-one, chlorpromazine, and chlordiazepoxide were administered at various doses intraperitoneally 30 minutes prior to a 50 mg/kp i.p. in-

jection of sodium pentobarbital. This procedure detects compounds which possess analeptic or potentiating properties. The duration of sleeping time, as measured by loss of righting reflex, was determined. The results are presented as percent of control sleeping time and are shown in Table VII.

TABLE VII

	% Increase in Control Sleep Time		
I.P. Dose mg/kg	1,2,3-benzotriazin-4(3H)-one	Chlorpromazine	Chlordiazepoxide
0.5		124	
1.0		240	
2.0		300	
2.5	22		
5.0	78		26
10.0	132		48
20.0			159
40.0			177

On a dose to dose relationship, the present compound appears to have approximately 1/20th the potency of chlorpromazine and twice the potency of chlordiazepoxide. Therefore, the compound of the present invention shows potentiation of barbiturate anesthesia.

2. Dihydroxyphenylalanine (dl-DOPA) Fighting Test

It is well known that when monoamine oxidase (MOA) inhibitors are administered prior to the administration of DOPA, which is a noradrenaline precursor, convulsions or excitation occur. In this study, the MAO inhibitor, pargyline, (80 mg/kg) was given 1, 2 and 4 hours prior to administering 200 mg/kg of dl-DOPA. Results of this experiment are manifested by excitation, salivation, jumping and fighting. When 1,2,3-benzotriazin-4 (3H)-one (60 – 140 mg/kg), chlorpromazine (5 mg/kg), or chlordiazepoxide (15 mg/kg) were administered instead of parglyine, these symptoms were not observed. This, in this procedure, none of the agents tested appear to be MOA inhibitors.

3. Yohimbine Potentiation

Potentiation of lethality induced by the alpha-adrenergic blocking agent, yohimbine, is considered to be a reliable procedure to classify possible antidepressant compounds. An ED_{50} in this test is defined as that dose of test drug which will cause the LD_1 (25 mg/kg, i.p.) of yohimbine to be converted to the LD_{50} value. Neither chlorpromazine (10 mg/kg) nor chlordiazepoxide (20 mg/kg) was active in this test. Since 1,2,3-benzotriazin-4(3H)-one was not selectively active in the killer rat aggression test, which appears to detect anti-depressant activity, it is possible that this agent might possess weak anti-depressant activity at doses which cause neurotoxicity. Hence, a third test for detection of anti-depressant activity was conducted.

4. Antagonism of Tetrabenazine-induced Ptosis

Groups of mice were given 32 mg/kg of tetrabenazine intraperitoneally 30 minutes after injection of 1,2,3-benzotriazin-4(3H)one (20 mg/kg). The degree of ptosis (eyelid drooping or closure) was then determined exactly 30 minutes after tetrabenazine administration. The compound of the present invention did not reverse tetrabenazine-induced ptosis as do the antidepressants, desipramine or amitriptyline.

5. Oxotremorine Antagonism

Antagonism of the pharmacological effects of oxotremorine, a potent cholinergic stimulant, was studied in mice after intraperitoneal administration of 1,2,3-benzotriazin-4(3H)-one (100 mg/kg). Peripheral anti-cholinergic activity was assessed by inhibition of salivation, and central activity by inhibition of tremors. At 100 mg/kg, the present compound was completely devoid of any anti-cholinergic activity.

Neuropharmacological Profile — Cat

1,2,3-benzotriazin-4(3H)-one was studied in cats to determine the neuropharmacological effects as well as the manner in which it is tolerated in cats. Neurotoxicity was also evaluated in this assay. Cats were administered the present compound at 20, 40 and 80 mg/kg orally in capsule form and were observed continuously for six hours using a standardized multidimensional observation technique to grade symptomatology. The scoring system is the same as that used in the mouse profile. At 20 and 40 mg/kg there were no signs or symptoms which appeared to be drug related. The drug was well tolerated and no emesis occurred. At 80 mg/kg there was relaxation of the nictitating membrane, accompanied by ptosis, and at four and six hour observation the animals appeared depressed and a tendency for sleep was observed. No emesis occurred at this dose and the animals appeared normal at 24 hours after dosing.

Evoked Hypothalamic Rage Response — Cats

The effect of the present compound on the hissing response elicited by hypothalamic stimulation in cats was studied in an effort to determine if it had properties similar to that of chlordiazepoxide and other anti-anxiety-like agents. Chlordiazepoxide has been shown by Baxter, *Life Sciences*, 3: 531, 1964, to increase the threshold of the hypothalamus to electrical stimulation. Cats with chronically implanted electrodes, stereotaxically plated in the perifornical region of the hypothalamus, were used in this study. Stimulation was accomplished in the unanesthetized, freely moving animal, and the threshold for the hissing response was determined with the following stimulus parameters: square wave stimulation of 150 Hz with a duration of 0.5 msec and voltage ranging from 5.4 to 30. The present compound was administered orally in capsule form. The present administration, the stimulation threshold for the hiss response was determined at 1, 2, 4, 6 and 24 hours. If an effect was observed, the stimulation was carried out daily until the thresholds returned to control values. The compound was administered in a dose range of 20 to 40 mg/kg. The compound was studied in four implanted cats; two cats administered 20 mg/kg and two at 40 mg/kg. The compound had no effect on hypothalamic stimulation at either dose. The rage response was not changed in intensity of character and the delay from stimulus to response was not changed. A few measurements were made in an effort to establish if this compound decreased the threshold for the

rage response, but this effect was not observed during the experiments. It can be concluded that the compound has no effect on hypothalamic excitability in cats and in this respect differs markedly from chlordiazepoxide.

Cardiovascular Activity

1,2,3-benzotriazin-4(3H)-one was also studied in the DOCA hypertensive rat, cardiovascular, and pharmacodynamic dog preparation. The compound was administered to groups of five rats made hypertensive by the administration of desoxycorticosterone acetate and saline. Blood pressures were recorded 4 and 24 hours after oral administration of 25 and 100 mg/kg. 1,2,3-benzotriazin-4(3H)-one had no effect on the systolic blood pressure of the hypertensive rat at 25 mg/kg; however, at 100 mg/kg two out of five animals experienced a fall in blood pressure of 24 mm Hg at the four-hour observation period. The apparent antihypertensive effect of the compound at the 100 mm/kg level is probably not significant, since it occurred at a dose twice that of the neurotoxic dose in rats.

The pharmacodynamic assay was performed using anesthetized dogs and recording blood pressure, electrocardiogram, and respiration. Responses to the following drugs were observed before and after the administration of 1,2,3-benzotriazin-4(3H)-one, epinephrine, norepinephrine, dimethylphenylpiperazinium iodide (DMPP), acetylcholine, tyramine, and histamine. After 1 mg/kg i.v. of 1,2,3-benzotriazin-4(3H)-one there was no change in blood pressure, electrocardiogram, respiration, or heart rate. Following the administration of 5 mg/kg i.v., there was a diminished response to the administration of epinephrine and norepinephrine; however, the response to the remaining challenging drugs were unchanged. An additional dose of 5 mg/kg i.v. caused a further suppression in epinephrine and norepinephrine responses; however, the other challenging drug responses were unchanged. Following an accumulative dose of 11 mg/kg there was no effect on blood pressure, heart rate, or respiration. It is concluded that the present compound has no effect on the cardiovascular system with respect to the parameters measured, except that a weak alpha-adrenergic blocking activity was observed after 5 mg/kg i.v.

Table VIII gives the results of five day lethality studies following single injections of a drug. All values presented represent tests conducted when animals were housed ten per cage. 1,2,3-benzotriazin-4(3H)-one is compared with chlorpromazine and chlordiazepoxide. In these and all the preceding calculations, the method of Litchfield and Wilcoxon (*J. Pharmacol. Exptl. Ther.* 96: 99, 1949) was used to estimate effective (ED_{50}) or lethal (LD_{50}) dose.

These data show that 1,2,3-benzotriazin-4(3H)-one is less toxic than chlorpromazine, but more toxic than chlordiazepoxide when administered to mice; however, when administered to rats, it is less toxic than either of the two standard reference drugs.

The compound of the present invention, either alone or in the form of a pharmaceutical composition, may be administered to an anxious animal subject in any of a number of forms and via any of several routes. Thus, the compound or compositions thereof may be orally administered in the form of tablets, pills, capsules, or in the form of a solution or liquid suspension. They may also be administered in the form of a parenteral suspension or solution. The compound or compositions thereof may also be administered rectally, in the form of a suppository.

When orally administering the compound or compositions, use can be made of a tablet, pill or capsule consisting entirely of the desired compound, although ordinarily, a composition comprising an effective amount of the compound and varying amounts of one or more physiologically inert materials such as carriers, vehicles, binders and the like will be used. Additionally, the compounds may be orally administered in the form of a suspension thereof in a suitable vehicle such as a syrup.

When parenterally administering the compound or compositions, use may be made of a parenteral solution or suspension of the compound in a suitable solvent or suspension medium.

The compound and compositions of the present invention may also be administered rectally in the form of a suppository comprising an effective amount of the desired compound and a suitable vehicle such as petroleum jelly.

The following Examples are specific formulations of compositions according to the invention:

EXAMPLE 1

Tablets may be prepared by the compression of a wet granulation containing the following:

Ingredients	In each
1,2,3-benzotriazin-4(3H)-one	20 mg
Polyvinylpyrrolidone	6 mg.
Lactose	25 mg.
Alcohol, 3A, 200 proof	1 ml.
Stearic acid	3 mg.
Talc	4 mg.
Corn starch	15 mg.

Dosage: 1 Tablet 3 times a day.

TABLE VIII

	LD_{50} (95% Confidence Limits) mg/kg			
	MICE		RATS	
Agent	I.P.	P.O.	I.P.	P.O.
1,2,3-benzotriazin-4(3H)-one	273 (239-311)	440 (441-471)	423 (326-550)	595 (419-841)
Chlorpromazine	136 (106-174)	280 (187-418)	137 (133-141)	357.7 (237.7-538.5)
Chlordiazepoxide	400 (265-604)	810 (688-958)	265 (224-313)	392.1 (235.5-753.5)

EXAMPLE 2

A liquid suspension for oral administration may be prepared in the following formulation:

Ingredients	In each 5 cc.
1,2,3-benzotriazin-4(3H)-one	20 mg.
Sodium carboxymethylcellulose	5 mg.
Syrup USP q.s. to	5 cc.
Dosage: 1 teaspoonful (5 cc.) every 4 to 6 hours.	

EXAMPLE 3

Dry filled capsules (DFC) consisting of two sections of hard gelatin may be prepared from the following formulation:

Ingredients	In each
1,2,3-benzotriazin-4(3H)-one	20 mg.
Lactose USP	q.s.
Dosage: 1 Capsule 3 times a day.	

EXAMPLE 4

A parenteral suspension for intra-muscular administration may be prepared in the following formulation:

Ingredients	In each
1,2,3-benzotriazin-4(3H)-one	10 mg.
Isotonic solution (0.85% saline)	5 cc.
Surfactant (a 1% solution of polysorbate 80 USP)	1 cc.

EXAMPLE 5

A suppository capsule formulated as below:

Ingredients	In each
1,2,3-benzotriazin-4(3H)-one	20 mg.
Cocoa butter	q.s.
Dosage: 1 suppository every 3 to 4 hours.	

Having thus described our invention, what we desire to claim and protect by letters patent is:

1. A method of inhibiting aggressive behavior in an anxious animal subject, said method comprising administering to an anxious animal subject, an amount of 1,2,3-benzotriazin-4(3H)-one which is effective to inhibit aggressive behavior in said animal subject without simultaneously causing depression.

2. The method of claim **1,** wherein said compound is administered in an orally administrable dosage form.

3. The method of claim **2,** wherein said orally administrable dosage form is a pill, tablet, capsule, solution or suspension.

4. The method of claim **1,** wherein said compound is administered in a parenterally administrable dosage form.

5. The method of claim **4,** wherein said parenterally administrable dosage form is a solution or suspension.

6. The method of claim **1,** wherein said compound is administered in a rectally administrable dosage form.

7. The method of claim **6,** wherein said rectally administrable dosage form is a suppository.

8. The method of claim **1,** wherein said effective amount is from about 2 to about 100 mg/kg of body weight of said animal per day.

9. The method of claim **8,** wherein said amount is from about 2 to about 25 mg/kg of body weight per day.

10. The method of claim **1,** wherein said effective amount is from about 0.03 to about 1.4 mg/kg of body weight per day.

11. The method of claim **10,** wherein said amount is from about 0.03 to about 0.3 mg/kg of body weight per day.

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