

PATENT SPECIFICATION

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(54) NEW MOLECULAR COMPLEXES AND THEIR USE IN ANIMAL HUSBANDRY

(71) We, HETEROCHEMICAL CORPORATION, a Corporation organised and existing under the laws of the State of New York, United States of America, of 111 East Hawthorne Avenue, Valley Stream, New York 11580, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

This invention relates to new molecular complexes and to their use in animal husbandry.

More specifically, this invention relates to novel and useful molecular complexes comprising a bis-(5-nitrofurfurylidene)-acetone-guanyldrazone or acid addition salts thereof and an amine and to feed additive premixes and feed compositions containing them.

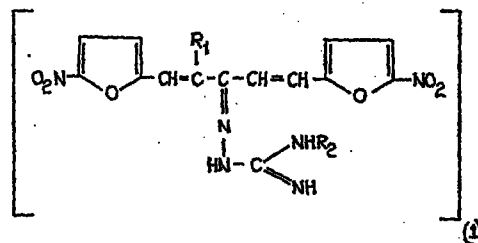
The novel molecular complexes of the present invention are utilized as animal feed additives and as such are highly desirable. Numerous additives have been utilized in animal feed compositions in an attempt to accelerate the growth of young domestic animals, e.g. cattle, swine, sheep, chickens, turkeys and ducklings. A rapid growth rate in domestic animals is of great economic importance because the more rapid the growth the greater the proportion of feed which is transformed into meat. Animal feed additives are also utilized to afford protection against certain infectious diseases. The molecular complexes of the present invention exhibit a surprisingly high activity when utilized to promote growth and anti-infection properties in animal feed compositions.

Bis - (5 - nitrofurfurylidene) - acetone-guanyldrazone and its addition salts have been utilized as animal feed additives as disclosed in United States Patent No. 3,264,112. We are, however, unaware of any prior art [Price 25p]

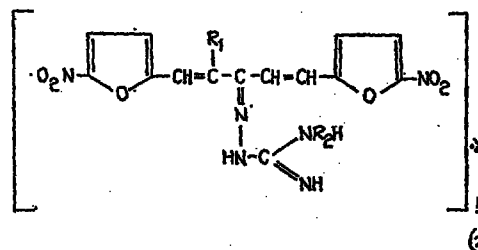
which discloses the molecular complexes of the present invention or their surprisingly high activity in promoting growth and anti-infection properties.

Accordingly the present invention provides a molecular complex comprising

A) a bis-(5-nitrofurfurylidene)-acetone-guanyldrazone or addition salt thereof of the general formula:—



OR



respectively, in which general formulae:—

R_1 is a hydrogen or halogen atom or an alkyl group having 1 to 4 carbon atoms;

R_2 is a hydrogen atom or an alkyl group having 1 to 4 carbon atoms;

X is a mono-, di-, or tribasic acid;

and n is 1, 2 or 3;

with the proviso that when X is monobasic

n is 1, when X is dibasic n is 1 or 2 and when X is tribasic n is 1, 2 or 3; and

B) an aliphatic, aromatic or heterocyclic amine.

- 5 A preferred bis-(5-nitrofurfurylidene)-acetoneguanyldiazide acid addition salt is the hydrochloride commercially available under the name "Nitrovin" from the American Cyanamid Company. A preferred bis-(5-nitro-
- 10 furfurylidene)-acetoneguanyldiazide is the compound in which R_1 and R_2 are both hydrogen.

- Suitable amines which can be utilized include primary, secondary and tertiary amines and these may be aliphatic, aromatic or heterocyclic. They may be mono-, di-, tri- or poly-
- 15 amines. Specific amines which can be utilized in the present invention include phenylene diamine; piperazine; hydroxyethyl piperazine; N-alkyl piperazines, e.g., N-methyl, N-ethyl, N-propyl, N-butyl, N-cetyl and N-lauryl; N-(aryl substituted) alkyl piperazines, e.g. N-benzyl piperazine; guanidine; aminoethyl
- 20 piperazine; p-aminobenzoic acid; nicotinic acid; picolinic acid; nicotinic acid amide; pyrrolidine; triethylamine; methyl aniline, 2-hydroxy, 2-hydroxy-4,6-dimethylpyrimidine; n-hexylamine; α -picoline; pyrrole; amino-cyclohexane; glycine; and
- 25 lysine. A preferred amine is 2-hydroxy-4,6-dimethylpyrimidine.

- The invention further provides a process for the production of the new molecular complexes comprising reacting a bis-(5-nitro-
- 35 furfurylidene)-acetoneguanyldiazide or an acid addition salt thereof of the general formula (1) or (2) with the appropriate amine.

- A preferred method of preparing the molecular complexes of the present invention comprises dissolving the amine in a suitable solvent e.g., methanol, and then adding the bis-
- 40 (5-nitrofurfurylidene)-acetoneguanyldiazide or an acid addition salt thereof. The resulting mixture is stirred at room temperature, preferably for about sixteen hours, and the resulting product is then filtered, e.g. by suction, washed and dried to yield the desired molecular complex.

- The molecular complex compounds of this invention may be utilized alone or in admixture with suitable carriers. They may be
- 50 utilized with their acid or alkaline carriers because of their extreme stability. Numerous carriers are available and one is normally selected on the basis of cost, inertness to the molecular complex and tolerance by the particular animal. The following list contains but a few of the nutritive materials which have been or may be employed as carriers: corn
- 55 meal, corn cob meal, milo, soybean oil meal, alfalfa meal, dried whey, wheat shorts, distillers' dried solubles, salt, meat scraps, calcite, feather meal, poultry by-products wheat
- 60

middlings, dextrose, lactose meal, dried kelp, linseed oil meal, oatmeal, dried yeast, wheat bran, soybean meal.

The compounds of this invention may be provided as premixes or as concentrated mixtures which may then be used to prepare the complete feed mixture. The premix is usually prepared to contain 4 grams of the molecular complex per pound; however, multiple strength premixes, e.g., those containing 8, 12, 16, 24, 32 and 64 grams of the molecular complex per pound, can also be prepared and utilized. The premix can then be combined with other ingredients to form a complete feed, e.g., about one-quarter pound of premix with about one ton of other ingredients will form a complete chicken feed. Complete feeds for other animals can be similarly formulated. A complete feed composition can also be directly prepared containing from about 1 gram to about 20 grams of the desired molecular complex per ton of composition without utilizing the premix composition.

The invention includes within its scope a method of treating a domestic animal comprising administering to the animal a molecular complex according to the invention either alone or in admixture with an ingestible carrier or feedstuff.

The following Examples illustrate in detail the manner in which the invention may be practiced.

Example I.

1.98 g (0.016 mole) of 2-hydroxy-4,6-dimethylpyrimidine were dissolved in 10 ml. of methanol and with continuous stirring 3.97 g (0.01 mole) of "Nitrovin" were slowly added in small portions. The resulting mixture was stirred at room temperature for a period of 16 hours and then filtered by suction on a glass-sintered filter. The filtered product was then washed with a small amount of methanol and dried at about 40°C. yielding 4.85 g of an orange-brown powder. Analysis of the product confirmed the structure to be the desired molecular complex.

Example II.

1.98 g (0.016 mole) of 2-hydroxy-4,6-dimethylpyrimidine were dissolved in 10 ml. of methanol and with continuous stirring 3.61 g (0.01 mole) of bis-(5-nitrofurfurylidene)-acetoneguanyldiazide were slowly added in small portions. The resulting mixture was stirred at room temperature for a period of 16 hours and then filtered by suction on a glass-sintered filter. The filtered product was then washed with a small amount of methanol and dried at about 40°C. yielding 4.40 g of a purple-black powder. Analysis of the product confirmed the structure to be the desired molecular complex.

Example III.

A feed premix composition is prepared by intermixing the components shown below.

intermixing the components shown below.

5	Soybean meal	2.2 lbs.
	Choline chloride	13.2 lbs.
	Nicotinic acid	500 g.
	Calcium pantothenate	200 g.
	Thiamin	40 g.
	Riboflavin	100 g.
10	α -Tocopherol acetate	120 g.
	Molecular complex of Example I	40 g.

	Yellow corn meal	1200 lbs.	20
	Soybean meal	700 lbs.	
	Bone meal	50 lbs.	
	Limestone flour	30 lbs.	
	Iodized salt	20 lbs.	
	Manganese sulfate	0.06 lbs.	25
	Cod liver oil concentrate	0.4 lbs.	
	Sulfaquinoxaline	0.30 lbs.	
	Riboflavin	3 g.	
	molecular complex of Example I	1 g.	

15 A substantially similar feed premix composition is prepared when the molecular complex of Example II is substituted on an equal weight basis for the molecular complex of Example I in the above composition.

A substantially similar poultry feed composition is prepared when the molecular complex of Example II is substituted on an equal weight basis for the molecular complex of Example I in the above composition.

The characteristics of the molecular complex of nitrovin and 2-hydroxy-4,6-dimethylpyrimidine, hereinafter called neo-nitrovin, compare with the characteristics of nitrovin as follows:

Example IV.

A poultry feed composition is prepared by

	Nitrovin	Neo-Nitrovin
Physical Form—	Amorphous brownish yellow powder	Orange-brown powder
Melting Point—	+295°C Decomposition	+235°C Decomposition
Density—	0.30	0.47
Extinction coefficient of 1 cm. length at 305 microns—	380	None
Extinction coefficient of 1 cm. length at 387 microns—	712	936

To show the improved activity of neo-nitrovin as compared to nitrovin, tests were run in which groups of broilers were fed with a basal diet for eight weeks to determine the

amount of feed required to produce a kilogram of weight at eight weeks of age. The composition of the basal ration was as follows:

COMPOSITION OF BASAL RATION:

Ingredient	Percent
Yellow corn	57.40
Animal fat	3.00
49% Soybean Meal	31.00
60% Protein Fish Meal	5.00
17% Dehydrated Alfalfa Meal	1.00
Dicalcium Phosphate (18.32)	1.50
Ground Limestone	.50
Salt	.30
Vitamin Premix	.25
Methionine (MHA)	.05
TOTAL	100.00

Calculated Ration Characteristics:

Protein	28.87
Metabolizable Energy	1425
Calcium	1.00

Phosphorus (Available)	.499
Methionine	.459
Methionine + Cystine	.840
Lysine	1.383

Different groups of chickens were fed the basal ration, the basal ration mixed with varying amounts of nitrovin and the basal

ration mixed with varying amounts of neo-nitrovin. The results were as follows:

5

Amount of Nitrovin or Neo-nitrovin	Kilograms of Feed Utilized for Each Kilogram of Weight at Eight Weeks		
	Control	Nitrovin	Neo-Nitrovin
0	2.13		
5.5 parts/million		2.13	1.99
11 parts/million		2.32	2.06
22 parts/million		2.07	2.06

10 Since the results are reported on a statistical basis, it is apparent that the results obtained with lower levels, i.e. 5 and 11 parts per million, of neo-nitrovin are significantly better than those obtained without any supplement and with nitrovin.

Tests conducted on the comparative stability of nitrovin and neo-nitrovin on a carrier

15 commonly used, calcium carbonate, showed that neo-nitrovin is superior. Thus, separate lots of nitrovin mixed with calcium carbonate and neo-nitrovin mixed with calcium carbonate were prepared and the lots were stored in a chamber at 20°C. and 75% relative humidity. The results were as follows:

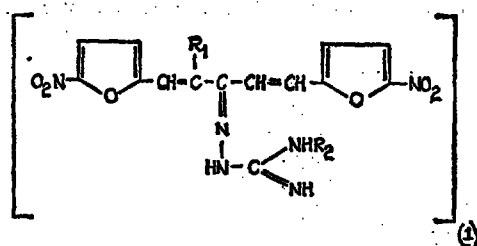
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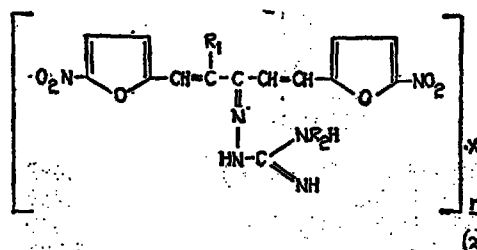
Storage Time	% Retention	
	Nitrovin	Neo-Nitrovin
7 days	95%	100%
60 days	77%	96%

WHAT WE CLAIM IS:—

- 25 1. A molecular complex comprising
A) a bis-(5-nitrofurfurylidene)-acetone-guanyldrazone or addition salt thereof of the general formula:—



or



respectively, in which general formulae:—

30

R_1 is a hydrogen or halogen atom or an alkyl group having 1 to 4 carbon atoms;

R_2 is a hydrogen atom or an alkyl group having 1 to 4 carbon atoms;

X is a mono-, di-, or tribasic acid;

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and n is 1, 2 or 3;

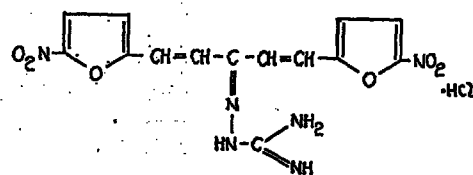
with the proviso that when X is monobasic n is 1, when X is dibasic n is 1 or 2 and when X is tribasic n is 1, 2 or 3; and

B) an aliphatic, aromatic or heterocyclic amine.

40

2. The molecular complex of claim 1 in which the bis-(5-nitrofurfurylidene)-acetone-guanyldrazone compound is of the formula:—

45



3. The molecular complex of claim 1 in which the bis-(5-nitrofurfurylidene)-acetone-guanyldrazone compound is of the formula

Different groups of chickens were fed the basal ration, the basal ration mixed with varying amounts of nitrovin and the basal

ration mixed with varying amounts of neo-nitrovin. The results were as follows:

5

Kilograms of Feed Utilized for Each Kilogram of Weight at Eight Weeks

Amount of Nitrovin or Neo-nitrovin	Control	Nitrovin	Neo-Nitrovin
0	2.13		
5.5 parts/million		2.13	1.99
11 parts/million		2.32	2.06
22 parts/million		2.07	2.06

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Tests conducted on the comparative stability of nitrovin and neo-nitrovin on a carrier

commonly used, calcium carbonate, showed that neo-nitrovin is superior. Thus, separate lots of nitrovin mixed with calcium carbonate and neo-nitrovin mixed with calcium carbonate were prepared and the lots were stored in a chamber at 20°C. and 75% relative humidity. The results were as follows:

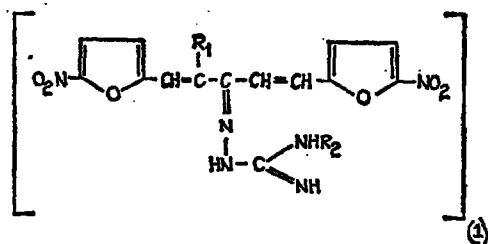
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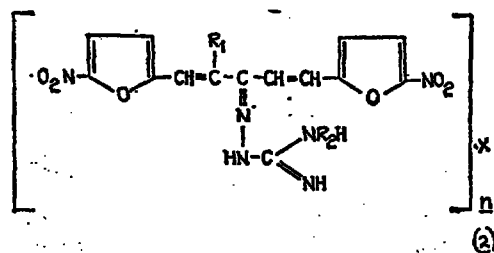
Storage Time	% Retention	
	Nitrovin	Neo-Nitrovin
7 days	95%	100%
60 days	77%	96%

WHAT WE CLAIM IS:—

- 25 1. A molecular complex comprising
A) a bis-(5-nitrofurfurylidene)-acetone-guanyldiazone or addition salt thereof of the general formula:—



OR



respectively, in which general formulae:—

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R₁ is a hydrogen or halogen atom or an alkyl group having 1 to 4 carbon atoms;

R₂ is a hydrogen atom or an alkyl group having 1 to 4 carbon atoms;

X is a mono-, di-, or tribasic acid;

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and n is 1, 2 or 3;

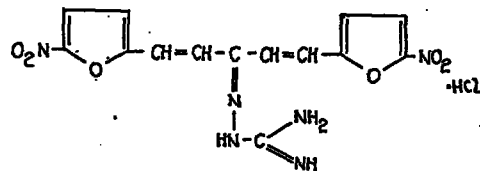
with the proviso that when X is monobasic n is 1, when X is dibasic n is 1 or 2 and when X is tribasic n is 1, 2 or 3; and

B) an aliphatic, aromatic or heterocyclic amine.

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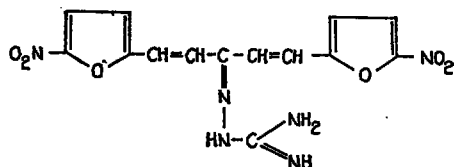
2. The molecular complex of claim 1 in which the bis-(5-nitrofurfurylidene)-acetone-guanyldiazone compound is of the formula:—

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3. The molecular complex of claim 1 in which the bis-(5-nitrofurfurylidene)-acetone-guanyldiazone compound is of the formula





4. The molecular complex of claim 1, 2 or 3 in which the amine is 2-hydroxy-4,6-dimethylpyrimidine.
5. The molecular complex of claim 1 in which the bis-(5-nitrofurfurylidene)-acetoneguanylylhydrazone and the amine are selected from those hereinbefore specifically mentioned in the description.
6. A process for the production of a molecular complex of any preceding claim comprising reacting a bis-(5-nitrofurfurylidene)-acetoneguanylylhydrazone or acid addition salt thereof of the general formula (1) or (2) with the appropriate aliphatic, aromatic or heterocyclic amine.
7. The process of claim 6 in which the amine is dissolved in a solvent and the bis-(5-nitrofurfurylidene)-acetoneguanylylhydrazone or acid addition salt thereof is added thereto, and the resulting mixture stirred without heating or cooling and then filtered.
8. The process of claim 6 or 7 substantially as hereinbefore described, or as illustrated in Example I or II.
9. The molecular complexes of any of claims 1 to 5 whenever produced by the process of claim 6, 7 or 8.

10. A composition containing from 4 to 64 gm/lb, referred to the total premix, of a molecular complex of any of claims 1 to 5 and 9 in admixture with an animal ingestible carrier.

11. The composition of claim 10 in which the carrier is one of those hereinbefore specifically mentioned.

12. The composition of claim 10 or 11 substantially as hereinbefore described, or as illustrated in Example III.

13. A composition containing from 1 to 20 gm/ton referred to the total composition, of a molecular complex of any of claims 1 to 5 and 9 in admixture with an animal feedstuff.

14. The composition of claim 13 substantially as hereinbefore described, or as illustrated in Example IV.

15. A method of treating a domestic animal comprising administering to the animal a molecular complex of any of claims 1 to 5 and 9 either alone or in admixture with an ingestible carrier or feedstuff.

16. The method of claim 15 in which a composition of claim 13 or 14 is administered to the animal.

17. The method of claim 15 or 16 substantially as hereinbefore described.

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