(CONVENTION. By one or more persons and/or a Company.) Form 4

607811

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1969

CONVENTION APPLICATION FOR A PATENT

APPLICATION ACCEPTED AND AMENDMENTS

ALLOWED 11.12.90

(1) Here insert (in full) Name or Names of Applicant or Applicants, followed by Address (es).

~~We~~ I (1) EGIS GYOGYSZERGYAR,
1475 Budapest, Kereszturi ut 30-38,
Hungary.

hereby apply for the grant of a Patent for an invention entitled: (2)
(2-THIENYL-METHYL)-THIOUREA DERIVATIVES

which is described in the accompanying complete specification. This application is a Convention application and is based on the application numbered (3)
4437/87

for a patent or similar protection made in (4) Hungary on
2nd October, 1987.

~~My~~ Our address for service is Messrs. Edwd. Waters & Sons, Patent Attorneys, 50 Queen Street, Melbourne, Victoria, Australia.

DATED this 29th day of September, 19 88

(5) Signature (s) of Applicant (s) or Seal of Company and Signatures of its Officers as prescribed by its Articles of Association.

(5) EGIS GYOGYSZERGYAR

BY:

LOUIS C. GEBHARDT.
Registered Patent Attorney

M0032 30/09/88

(CONVENTION Company.) Form 8

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1969

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

(1) Here insert (in full) Name of Company.

In support of the Convention Application made by(1) EGIS GYOGYSZERGYAR

(hereinafter referred to as the applicant) for a Patent

(2) Here insert title of Invention.

for an invention entitled:(2) (2-THIENYL-METHYL)-THIOUREA DERIVATIVES

(3) Here insert full Name and Address, of Company official authorized to make declaration.

We ~~I~~,(3) CSABA KISS and ATTILA MANDI, both of 1475 Budapest, Keresztúri út 30-38, Hungary

do solemnly and sincerely declare as follows:

1. We are ~~I am~~ authorised by the applicant for the patent to make this declaration on its behalf.

(4) Here insert basic Country or Countries followed by date or dates and basic Applicant or Applicants.

2. The basic application as defined by Section 141 of the Act was made in(4) Hungary on the 2nd day of October 1987, by EGIS GYOGYSZERGYAR

~~on the XXXX day of XXXXX 19XXXXXXXX, by~~

(5) Here insert (in full) Name and Address of Actual Inventor or Inventors.

3.(5) ILDIKO RATZ, 1126 Budapest, Tartsay u. 26, EDIT BERENYI, 1111 Budapest, Bartok Bela ut 36-38, PAL BENKO, 1126 Budapest, Tartsay u. 7, DANIEL BOZSING, 1141 Budapest, Vezer u. 116, and KAROLY MAGYAR, 1012 Budapest, Attila ut 131, Hungary

~~is~~/are the actual inventor~~s~~ of the invention and the facts upon which the applicant is entitled to make the application are as follow:

The applicant is the assignee of the said actual inventors

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED at Budapest, Hungary

this 29th day of September 19 88

(12) PATENT ABRIDGMENT (11) Document No. AU-B-23329/88
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 607811

(54) Title
(2-THIENYL-METHYL)-THIOUREA DERIVATIVES

International Patent Classification(s)
(51)[4] **C07D 333/20 A23K 001/16 C07D 409/12**

(21) Application No. : **23329/88** (22) Application Date : **30.09.88**

(30) Priority Data

(31) Number (32) Date (33) Country
4437/87 02.10.87 HU HUNGARY

(43) Publication Date : **06.04.89**

(44) Publication Date of Accepted Application : **14.03.91**

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(56) Prior Art Documents
AU 11450/88 C07D 409/12
GB 1020611

(57) This invention relates to new (2-thienyl-methyl)--thiourea derivatives, a process for the preparation thereof, feed additives comprising the same and the use of the said compounds in animal husbandry.

The compounds of the general Formula I possess useful weight gain increasing properties - particularly on pig, poultry, ruminants, especially on lamb and chicken - which is accompanied by a valuable fodder utilization improving effect.

CLAIM

1. 2-(thienyl-methyl)-thiourea derivatives of the general Formula I

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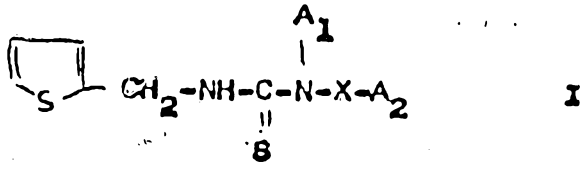


I

(wherein

A_1 stands for hydrogen, C_{1-4} alkyl or C_{4-8} cycloalkyl;

A_2 represents C_{3-10} alkyl, C_{3-10} alkenyl, C_{4-8} cycloalkyl, phenyl-C_{1-4} alkyl, phenyl-C_{2-4} alkenyl; phenyl optionally substituted by one or more C_{1-4} alkyl, C_{1-4} alkoxy or hydroxy; naphthyl; pyridyl optionally substituted by C_{1-4} alkyl; or furfuryl; and

X is a valency bond or a -CO- group;

with the proviso that if X stands for a valency bond, A_2 is other than phenyl).

607811

Form 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-69

COMPLETE SPECIFICATION

(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority :

Related Art :

This document contains the amendments made under Section 49 and is correct for printing

Name of Applicant : EGIS GYOGYSZERGYAR

Address of Applicant : 1475 Budapest, Kereszturi ut 30-38, Hungary.

Actual Inventor: ILDIKO RATZ, EDIT BERENYI, PAL BENKO, DANIEL BOZSING and KAROLY MAGYAR.

Address for Service : EDWD. WATERS & SONS,
50 QUEEN STREET, MELBOURNE, AUSTRALIA, 3000.

Complete Specification for the invention entitled:

(2-THIENYL-METHYL)-THIOUREA DERIVATIVES

The following statement is a full description of this invention, including the best method of performing it known to :- us

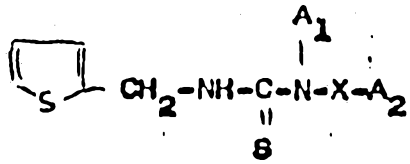
(2-THIENYL-METHYL)-THIOUREA DERIVATIVES

This invention relates to new (2-thienyl-methyl)--thiourea derivatives, a process for the preparation thereof, feed additives comprising the same and the use of the said compounds in animal husbandry.

In European patent specification No. 0207358 compounds exhibiting weight gain increasing effect on several animal species (domestic animals, wild animals, reptiles, hobby animals) - among others 2-thienyl-thiourea derivatives - are disclosed. The patent specification contains however no activity data on any of the animal species.

In US patent specifications Nos. 4,267,191 and 4,313,885 (2-furfuryl)-thiourea derivatives useful as weight gain increasing agents on lamb, pig and chicken are disclosed. The activity of the said (2-furfuryl)--thiourea derivatives is however inferior to that of the compounds of the present invention.

According to an aspect of the present invention there are provided (2-thienyl-methyl)-thiourea derivatives of the general Formula I



I

(wherein

A_1 stands for hydrogen, C_{1-4} alkyl or C_{4-8} cycloalkyl;

A_2 represents C_{3-10} alkyl, C_{3-10} alkenyl, C_{4-8} cycloalkyl, phenyl-C_{1-4} alkyl, phenyl-C_{2-4} alkenyl; phenyl optionally substituted by one or more C_{1-4} alkyl, C_{1-4} alkoxy or hydroxy; naphthyl; pyridyl optionally substituted by C_{1-4} alkyl; or furfuryl; and

X is a valency bond or a -CO- group;

with the proviso that if X stands for a valency bond, A_2 is other than phenyl).

The term "alkyl" relates to straight or branched chain alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, tert.butyl, n-decyl etc.). The "alkoxy" groups are alkyl ether groups comprising the above-defined alkyl groups (e.g. methoxy, ethoxy, tert. butoxy). The term "C_{4-8} cycloalkyl" covers straight or branched cyclic alkyl groups (e.g. cyclopentyl, cyclohexyl). As representatives of the phenyl-C_{1-4} alkyl and phenyl-C_{2-4} alkenyl groups e.g. the benzyl, β-phenyl-ethyl, 4-phenyl--butyl, phenyl-vinyl, phenyl-propenyl group, respectively, can be mentioned. The "alkenyl group" may be e.g. allyl, butenyl etc.

Preferred representatives of the compounds of the general Formula I are the following derivatives:

N-benzoyl-N'-(2-thienyl-methyl)-thiourea;

N-benzyl-N'-(2-thienyl-methyl)-thiourea;

N-(p-methoxy-benzoyl)-N'-(2-thienyl-methyl)-thiourea;

N-cyclohexyl-N'-(2-thienyl-methyl)-thiourea;

N-(2,6-dimethyl-phenyl)-N'-(2-thienyl-methyl)-thiourea;

N-(β-phenyl-acryloyl)-N'-(2-thienyl-methyl)-thiourea.

A particularly advantageous representative of the compounds of the general Formula I is the following compound:

N,N-dicyclohexyl-N'-(2-thienyl-methyl)-thiourea.

According to a further aspect of the present invention there is provided a process for the preparation of the compounds of the general Formula I (wherein

A_1 stands for hydrogen, C_{1-4} alkyl or C_{4-8} cycloalkyl;

A_2 represents C_{3-10} alkyl, C_{3-10} alkenyl, C_{4-8} cycloalkyl, phenyl-C_{1-4} alkyl, phenyl-C_{2-4} alkenyl; phenyl optionally substituted by one or more C_{1-4} alkyl, C_{1-4} alkoxy or hydroxy; naphthyl; pyridyl optionally substituted by C_{1-4} alkyl; or furfuryl; and

X is a valency bond or a -CO- group;

with the proviso that if X stands for a valency bond, A_2 is other than phenyl),

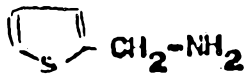
which comprises

a) for the preparation of compounds of the general Formula I, wherein X is a valency bond and A_1 and A_2 are as stated above,

a_1) reacting an isothiocyanate of the general Formula II

A_2-NCS (II)

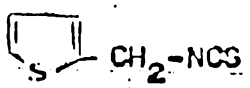
with a-thenyl amine of the Formula III;



III

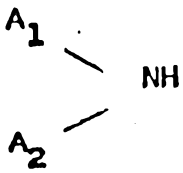
or

a_2) reacting (2-thienyl-methyl)-isothiocyanate of the Formula V



V

with an amine of the general Formula VI;



VI

or

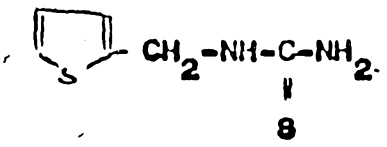
b) for the preparation of compounds of the general Formula I, wherein X stands for a -CO- group; A_1 is hydrogen and A_2 is as stated above,

b_1) reacting 2-thienyl amine of the Formula III with an acyl-isothiocyanate of the general Formula IV;

A_2-CO-NCS (IV)

or

b_2) reacting N-(2-thienyl-methyl)-thiourea of the Formula VII



VII

with a carboxylic acid of the general Formula VIII

$$A_2 - COOH \qquad (VIII)$$

or a reactive derivative thereof (in which Formulae A_1, A_2 and X are as stated above).

According to method a_1) an isothiocyanate of the general Formula II is reacted with 2-thenyl-amine of the Formula III. The reactants may be preferably used in equimolar amount. The reaction may be preferably accomplished in an inert solvent (e.g. ethanol, petrol, ether, dichloro methane, tetrahydrofurane etc.). Petrol and ethanol proved to be particularly suitable reaction media. The reaction may be accomplished at a temperature between 0 ^{o}C and 100 ^{o}C, particularly at room temperature. The compound of the general Formula I may be isolated from the reaction mixture by filtration and/or evaporation.

According to method a_2) an amine of the general Formula VI is reacted with (2-thienyl-methyl)-isothiocyanate of the Formula V. The reaction may be carried out in an inert solvent, preferably in a solvent

enumerated in connection with method a_1). It is preferred to use petrol or ethanol as solvent. The reaction may be advantageously accomplished at room temperature. The compound of the general Formula I may be isolated by filtration or evaporation.

According to process b_1) (2-thenyl)-amine of the Formula III is reacted with an acyl isothiocyanate of the general Formula IV. The reaction may be carried out in an inert organic solvent, preferably acetone. The reaction may be accomplished at a temperature between 40 °C and the boiling point of the reaction mixture. It is preferred to work at the boiling point of the solvent used. One may preferably proceed by preparing the acyl isothiocyanate of the general Formula IV by reacting ammonium rhodanide with the corresponding acyl chloride. The compound of the general Formula I may be isolated by methods known per se (e.g. by pouring the reaction mixture into water).

According to process b_2) (2-thienyl-methyl)-thiourea of the Formula VII is acylated with a carboxylic acid of the general Formula VIII or a reactive derivative thereof. It is preferred to use an acyl halide (particularly acyl chloride) as reactive acyl derivative. The reaction may be accomplished in an inert organic solvent (e.g. acetonitrile, methylene chloride, aromatic hydrocarbons etc.). Benzene proved to be a particularly suitable reaction medium. The reaction may be carried out under warming, at a temperature between 40 °C and the boiling

point of the reaction mixture. One may preferably work at the boiling point of the solvent used.

All the reactions a_1, a_2, b_1 and b_2 are carried out by methods known per se.

The starting materials of the general Formulae II, III, VI and VIII are commercially available products. The starting materials of the general Formula II can be prepared by the methods described in Houben-Weyl: Methoden der organischen Chemie IX, pages 867-878. The acyl-isothiocyanates of the general Formula IV can be prepared by the method disclosed in Houben-Weyl: Methoden der organischen Chemie II. Pages 878-879.

The (2-thienyl-methyl)-isocyanate of the Formula V can be prepared in an analogous manner to J. Chem. Soc. Perkin I. (1976) page 139.

The (2-thienyl-methyl)-thiourea of the Formula VII can be prepared by the process disclosed in Houben-Weyl: Methoden der organischen Chemie Bd E4, pages 484-505 (Georg-Thieme Verlag 1983).

The compounds of the general Formula I possess useful weight gain increasing properties - particularly on pig, poultry, ruminants, especially on lamb and chicken - which is accompanied by a valuable fodder utilization improving effect.

The biological activity of the compounds of the general Formula I is shown by the following tests:

1. Tests carried out on lambs

As test animals lambs are used, the feeding period being 40 days. The lambs are fed with the following basic fodder mixture

Component	Amount %
Maize grits	70.0
II. class alfalfa meal	24.0
Urea	3.0
Fodder lime	0.5
Monocalcium phosphate	1.0
Crystalline sodium sulfate	0.5
Fodder salt	0.5
Lamb premix XIX (manufacturer: Phylaxia)	0.5
	100.00 %

The test compound is admixed with the above fodder in a concentration of 50 ppm.

All the lambs are Hungarian merino lambs.

Each group consists of 12 lambs and 3 groups are used per treatment.

During the 40 days' experimental period the lambs are individually weighed, namely at the beginning of the test, every 10th day, the last time on the 40th day, always at the same time. The evaluated data are the weighed body weight; no deductions appear in the evaluation. The amount of the consumed fodder is given

for each decade and group. The results obtained are summarized in Table I. The weight gain increase and fodder utilization is expressed as the average of three experiments.

Table I

Treatment	Control	4.	5.	3.	1.	2.	6.
Average daily weight gain increase							
in g.	254.3	287.9	283.9	279.6	266.7	275.2	276.2
in %.	100	113.6	112.0	110.3	105.2	108.2	108.9
Specific fodder utilization							
in kg./kg.	3.95	3.57	3.57	3.66	3.79	3.72	3.68
in %.	100	90.4	90.4	92.7	95.9	94.9	93.2

It clearly appears from the above data that the compounds of the general Formula I significantly improve fodder utilization i.e. 1 kg. of weight gain can be achieved with a considerably smaller amount of fodder.

2) Test carried out on broyler

The test is carried out on broylers (both male and

female). The results are summarized in Table II.

Table II

Age: 28 days

Test compound	Dose mg./kg. fodder	Live weight g.	Difference from the control in g.	in %.
Example No. 12	50	827	+52	106.7
Zinc bacitracin	20	796	+31	103.9
Control	0	775	-	100.0
Age: 42 days				
Example No. 12	50	1545	+91	106.3
Zinc bacitracin	20	1510	+56	103.9
Control	0	1454	-	100.0
Age: 49 days				
Example No. 12	50	1979	+154	108.4
Zinc bacitracin	20	1878	+53	102.9
Control	0	1825	-	100.0

At the age of 49 days 2.3 % of fodder can be saved as compared to the control group - related to 1 kg. of live weight.

The compounds of the general Formula I exhibit no antibiotic effect and are for this reason void of the disadvantages which appear when antibiotics are used.

A very important advantage of the compounds of the general Formula I is that they do not show any mutagenic effect. This fact constitutes a significant advantage in use in animal husbandry. It is namely known that several known weight gain increasing agents can be used only to a limited extent or their application is even banned because of the mutagenic effects thereof.

According to a further feature of the invention there are provided compositions - particularly fodder additives and fodders - comprising as active ingredient an amount of 1 ppm. to 85 % by weight of a compound of the general Formula (I), wherein A_1, A_2 and X are as defined above, in admixture with inert solid or liquid carriers or diluents.

According to a further feature of the invention there is provided a process for the preparation of fodder additives and fodders, characterized by admixing a compound of the general formula (I), wherein A_1, A_2 and X are as defined above, or a biologically acceptable salt thereof, with suitable edible solid or liquid carrier or diluent or additive generally used in the production of fodder additives and fodders.

As carrier or diluent any substance of vegetable or animal origin applicable in the feeding of animals or serving as fodder can be used. For this purpose e.g. wheat, barley, maize, soybean, oats, rye, alfalfa, can be used in appropriate forms (grits, groats, meal, bran, etc.), furthermore fish meal, meat meal, bone meal or

mixtures thereof can be applied as well. One may advantageously use a fibre-free green plant fodder concentrate with high protein content (e.g. VEPEX^{R}).

As additives e.g. silicic acid, antioxidants, starch, dicalcium phosphate, calcium carbonate, sorbic acid, etc. can be used. As wetting agent e.g. non-toxic oils, preferably soybean oil, maize oil or mineral oil can be applied. Various alkylene glycols can also be used as wetting agent. The starch used may be wheat, maize or potato starch.

The fodder additives and concentrates may contain usual vitamins (e.g. vitamin A, B_1, B_2, B_3, B_6, B_{12}, E, K) and trace elements (e.g. Mn, Fe, Zn, Cu, J), too.

The active ingredient content of the compositions may vary within wide ranges. The fodder additives may contain about 5 to 80 % by weight, preferably about 10 to 50 % by weight, particularly about 20 to 50 % by weight of the active ingredient of the general formula (I). The active ingredient content of the animal fodders ready for use may be about 1 to 400 ppm, preferably about 10 to 100 ppm.

The fodder additives and concentrates are diluted with suitable fodder components or are incorporated into suitable animal feeds to provide animal feeds ready for use.

The fodders according to the present invention can be used for the increase of weight gain of various domestic animals, such as pigs, lambs, ruminants and

poultry, particularly lambs and chicken.

Further details of the present invention can be found in the following Examples without limiting the scope of protection to the said Examples.

Example 1

N-benzoyl-N'-(2-thienyl-methyl)-thiourea

To a solution of 38.08 g. (0.5 mole) of ammonium rhodanide and 500 ml. of hot acetone 70.08 g. (0.5 mole) of benzoyl chloride are added dropwise under stirring and heating to boiling within 10 minutes. White crystals precipitate.

To the suspension thus obtained a solution of 56.6 g. (0.5 mole) of 2-thenyl-amine and 300 ml. of hot acetone is added dropwise. The addition having been completed the reaction mixture is heated to boiling for 20 minutes, then cooled, poured into 4 liter of icecold water. The precipitated crystals are filtered and washed with water. In form of light beige crystals 103.8 g. of the desired compound are obtained, yield 75.1 %, mp.: 118-119 ^{o}C (from methanol).

Example 2

N-benzyl-N'-(2-thienyl-methyl)-thiourea

97.0 g. (0.65 mole) of benzyl-isothiocyanate are added dropwise under stirring to an emulsion of 73.56 g. (0.65 mole) of 2-thenyl-amine and 500 ml. of petrol.

The reaction mixture is stirred at room temperature for 4 hours, the precipitate is filtered and washed with petrol. Thus 152.75 g. of the desired compound are obtained, yield 89.6 %, mp.: 108-109 °C (from methanol).

Example 3

N-(p-methoxy-benzoyl)-N'-(2-thienyl-methyl)thiourea

One proceeds in an analogous manner to Example 1 by using 38.08 g. (0.5 mole) of ammonium rhodanine, 85.3 g. (0.5 mole) of anisoyl chloride and 56.6 g. (0.5 mole) of 2-thenyl-amine. Thus 118.5 g. of the desired compound are obtained, yield 77.3 %, mp.: 124--125 °C (from a 3:1 mixture of methanol and benzene).

Example 4

N-cyclohexyl-N'-(2-thienyl-methyl)-thiourea

One proceeds in an analogous manner to Example 2 by reacting 82.46 g. (0.7 mole) of 2-thenyl-amine and 98.86 g. (0.7 mole) of cyclohexyl-isothiocyanate. Thus 171.6 g. of the desired compound are obtained, yield 96.4 %, mp.: 112-113 °C (from methanol).

Example 5

N-(2,6-dimethyl-phenyl)-N'-(2-thienyl-methyl)--thiourea

A solution of 15.5 g. (0.1 mole) of (2-thienyl--methyl)-isothiocyanate and 200 ml. of petrol is added dropwise to a solution of 12.1 g. (0.1 mole) of 2,6-

-dimethyl-aniline and 100 ml. of petrol at room temperature under stirring. The reaction mixture is stirred for 4 hours, the precipitated crystals are filtered and washed with petrol. Thus 22.55 g. of the desired compound are obtained, yield 81.7 %, mp.: 147-148 °C.

Example 6

N-(β-phenyl-acryloyl)-N'-(2-thienyl-methyl)--thiourea

One proceeds in an analogous manner to Example 1 by reacting 76.1 g. (1 mole) of ammonium rhodanine, 166.6 g. (1 mole) of cinnamoyl chloride and 113.2 g. (1 mole) of 2-thenyl-amine. Thus 210 g. of the desired compound are obtained, yield 59,5 %, mp.: 181-182 °C (from methyl cellosolve).

Example 7

N-(1-naphthyl)-N'-(2-thienyl-methyl)-thiourea

In an analogous manner to Example 2 2.26 g. (0.02 mole) of 2-thenyl-amine are reacted with 3.7 g. (0.02 mole) of 1-naphthyl-isothiocyanate. Thus 5.85 g. of the desired compound are obtained, yield 98 %, mp.: 147-148 °C (from ethanol).

Example 8

N-(β-phenyl-ethyl)-N'-(2-thienyl-methyl)-thiourea

In an analogous manner to Example 5 15.5 g.

(0.1 mole) of (2-thienyl-methyl)-isothiocyanate are reacted with 12.1 g. (0.1 mole) of β-phenyl-ethyl-amine. Thus 22.4 g. of the desired compound are obtained, yield 81 %, mp.: 88-89 °C (from ethanol).

Example 9

N-pivaloyl-N'-(2-thienyl-methyl)-thiourea

In an analogous manner to Example 1 38 g. (0.5 mole) of ammonium rhodanine, 60.3 g. (0.5 mole) of pivaloyl chloride and 58.5 g. (0.5 mole) of 2--thienyl amine are reacted. Thus 91.5 g. of the desired compound are obtained, yield 71.3 %, mp.: 90-91 °C (from ethanol).

Example 10

N-(2-pyridinyl)-N'-(2-thienyl-methyl)-thiourea

To a suspension of 27.0 g. (0.29 mole) of 2--amino-pyridine and 300 ml. of petrol 45 g. (0.29 mole) of (2-thienyl-methyl)-isothiocyanate are added dropwise. The reaction mixture is stirred at room temperature for 5 hours, whereby the oily precipitate becomes crystalline. The product is filtered. Thus 66.74 g. of the desired compound are obtained, yield 92.3 %, mp.: 115 °C (from ethanol).

Example 11

N-(4-methyl-2-pyridinyl)-N-(2-thienyl-methyl)--thiourea

One proceeds in an analogous manner to Example 10 by reacting 10.8 g. (0.1 mole) of 2-amino-4-methyl--pyridine and 15.5 g. (0.1 mole) of (2-thienyl-methyl)-isothiocyanate. Thus 17.1 g. of the desired compound are obtained, yield 65.2 %, mp.: 139-140 °C.

Example 12

N,N-dicyclohexyl-N'-(2-thienyl-methyl)-thiourea

One proceeds in an analogous manner to Example 10 by reacting 18.13 g. (0.1 mole) of dicyclohexyl amine and 15.5 g. (0.1 mole) of (2-thienyl-methyl)-isothiocyanate. Thus 25.5 g. of the desired compound are obtained, yield 75,8 %, mp.: 119-120 °C.

Example 13

N-allyl-N'-(2-thienyl-methyl)-thiourea

One proceeds in an analogous manner to Example 10 by using 17.1 g. (0.3 mole) of allyl amine and 46.5 g. (0.3 mole) of (2-thienyl-ethyl)-isothiocyanate. Thus 47.1 g. of the desired compound are obtained, yield 73,8 %, mp.: 88 °C (from benzene).

Example 14

N-(3-hydroxy-phenyl)-N'-(2-thienyl-methyl)-thiourea

To a solution of 7.76 g. (0.05 mole) of (2-thienyl--methyl)-isothiocyanate and 50 ml. of tetrahydrofurane 5.46 g. (0.05 mole) of m-amino-phenol are added. The reaction mixture is stirred at room temperature for

5 hours. The precipitated beige powdery crystals are filtered. Thus 8.83 g. of the desired compound are obtained, yield 66.9 %, mp.: 175-176 °C.

Example 15

N-benzoyl-N'-(2-thienyl-methyl)-thiourea

To a suspension of 1.7 g. (0.01 mole) of (2-thienyl--methyl)-thiourea and 30 ml. benzene 1.4 g. (0.01 mole) of benzoyl chloride are added dropwise. The reaction mixture is refluxed under stirring for 16 hours. The solution is clarified and evaporated. The residual oil is treated with 3 ml of cold isopropanol. Thus 1.57 g. of a crystalline product are obtained, yield 56.7 %, mp.: 118 °C.

Example 16

N-(n-butyl)-N'-(2-thienyl-methyl)-thiourea

3.88 g. (0.025 mole) of (2-thienyl-methyl)-isothiocyanate are added dropwise to a solution of 1.82 g. (0.025 mole) of n-butyl amine and 50 ml. of ethanol. The temperature of the reaction mixture rises from 25 °C to 40 °C. The reaction mixture is stirred at room temperature for 5 hours. The precipitated crystals are filtered. Thus 4.4 g. of the desired compound are obtained, yield 77.1 %, mp.: 55-56 °C (from a mixture of methanol and water).

Example 17

N-(n-decyl)-N'-(2-thienyl-methyl)-thiourea

One proceeds in an analogous manner to Example 16 by reacting 3.88 g. (0.025 mole) of (2-thienyl-methyl)-isothiocyanate and 3.93 g. (0.025 mole) of n-decyl amine. Thus 7.25 g. of the desired compound are obtained, yield 92.8 %, mp.: 77-78 °C (from ethanol).

Example 18

N-(2-furfuryl)-N'-(2-thienyl-methyl)-thiourea

One proceeds in an analogous manner to Example 16 by reacting 9.72 g. (0.1 mole) of furfuryl amine and 15.5 g. (0.1 mole) of (2-thienyl-methyl)-isothiocyanate. Thus 17.46 g. of the desired compound are obtained, yield 69,2 %, mp.: 89 °C (from a mixture of ethanol and water).

Example 19

A premix for supplementing pig fodder is prepared with the following composition:

Components	Amounts
Vitamin A	3,000,000 IU
Vitamin D_3	600,000 IU
Vitamin E	4,000 IU
Vitamin K_3	400 mg.
Vitamin B_1	600 mg.
Vitamin B_2	800 mg.
Vitamin B_3	2,000 mg.

Components	Amounts
Vitamin B_6	800 mg.
Vitamin B_{12}	10 mg.
Niacine	4,000 mg.
Choline chloride	60,000 mg.
Active agent according to Example 12	10,000 mg.
Butylhydroxytoluene (antioxidant)	30,000 mg.
Flavouring substances	8,000 mg.
Sodium saccharate	30,000 mg.
Trace elements:	
Mn	8,000 mg.
Fe	30,000 mg.
Zn	20,000 mg.
Cu	6,000 mg.
I	100 mg.
Twice-ground bran ad	1,000 g.

This premix of vitamins and trace elements is admixed with the basal fodder in a concentration of 0.5 kg. per 100 kg.

Example 20

A premix for supplementing piglet fodder is prepared with the following composition:

Components	Amounts
Vitamin A	1,200,000 IU
Vitamin D_3	300,000 IU
Vitamin E	2,000 IU
Vitamin B_2	600 mg.

Components	Amounts
Vitamin B_3	2,000 mg.
Vitamin B_{12}	5 mg.
Niacine	3,000 mg.
Choline chloride	40,000 mg.
Active agent according to Example 12	10,000 mg.
Butylhydroxytoluene (antioxidant)	30,000 mg.
Trace elements:	
Mn	6,000 mg.
Fe	10,000 mg.
Zn	15,000 mg.
Cu	30,000 mg.
I	100 mg.
Twice-ground bran ad	1,000 g.

This premix of vitamins and trace elements is admixed with the basal fodder in a concentration of 0.5 kg. per 100 kg.

Example 21

0.5 kg. of a premix as described in Example 19 are admixed with 100.0 kg. of a basal fodder with the following composition:

Components	Amounts, kg
Maize	37.6
Barley	25.4
Wheat	6.0
Oats	5.0
Soybean	13.0

Components	Amounts, kg.
Fish meal	6.0
Bran	2.4
Fat powder	1.5
Premix of minerals[x]	1.0
Lime (fodder quality)	1.0
Sodium chloride (fodder quality)	0.5
Biolisine	0.1
Premix according to Example 19	0.5
Total weight:	100.0 kg.

The active agent content of the resulting pig fodder is 50 ppm.

[x]The composition of the premix of minerals is as follows:

Components	Amounts, %
Dicalcium phosphate	55.0
Monocalcium phosphate	40.0
Calcium carbonate	5.0

Example 22

0.5 kg. of a premix as described in Example 20 are admixed with 100.0 kg. of a basal fodder with the following composition:

Components	Amounts, kg.
Maize	25.0
Wheat	34.0
Extracted soybean	18.0

Components	Amounts, kg.
Milk powder	9.9
Fish meal	4.0
Yeast (fodder quality)	2.0
Fat powder	3.4
Premix of minerals according to Example 20	1.8
Lime (fodder quality)	1.0
Sodium chloride (fodder quality)	0.4
Premix according to Example 20	0.5
Total weight:	100.0 kg.

The active agent content of the resulting piglet fodder is 50 ppm.

Example 23

400 kg. of a pre-ground soybean meal are filled into a mixer, 3.1 kg. of soybean oil are added under stirring, and the mixture is stirred until the solids get coated with oil. Thereafter 9.1 kg. of an active agent according to Example 1 are added and the mixture is stirred until a homogeneous blend is obtained. Finally 9.0 kg. of soybean oil are added, and the mixture is homogenized again.

Example 24

0.5 kg. of an active agent according to Example 2

are added to 40 kg. of corn meal under stirring, and simultaneously 3.0 kg. of propylene glycol are sprayed into the mixture. Thereafter 1.4 kg. of dicalcium phosphate are added and the mixture is homogenized.

Example 25

10 kg. of alfalfa meal and 15 kg. of VEPEX^{R} are stirred for 20 hours, thereafter 1 kg. of maize oil is started to spray into the mixture with an even speed so that spraying is continued during the introduction of the following additional components: 2.5 kg. of an active agent according to Example 3, 10 kg. of maize starch, 2.5 kg. of the above active agent, 0.3 kg. of silicon dioxide, 0.6 kg. of ascorbic acid, 9 kg. of maize starch and 2.5 kg. of the above active agent. Thereafter the mixture is stirred for additional 5 minutes.

Example 26

One proceeds as described in Example 23 with the difference that butylene glycol is applied as wetting agent instead of soybean oil.

Example 27

A.) 3.5 kg. of potato starch are admixed with 2.9 kg. of an active agent according to Example 5. 0.05 kg. of mineral oil are sprayed into the mixture, thereafter 0.2 kg. of sorbic acid, 0.4 kg. of silicon

dioxide and 0.1 kg. of calcium propionate are added, and the mixture is stirred for additional 2 minutes.

B.) 4.2 kg. of fish meal are admixed with 22 kg. of rye bran, 0.6 kg. of mineral oil are sprayed into the mixture, thereafter 4 kg. of a mixture prepared according to point A), 10 kg. of maize meal, 4 kg. of a mixture prepared according to point A) and 9 kg. of maize meal are introduced under stirring. Finally 0.6 kg. of mineral oil are sprayed into the mixture.

Example 28

100 kg. of wheat bran, 10 kg. of an active agent according to Example 6, 2.5 kg. of calcium carbonate, 0.15 kg. of α-tocopherol and 0.4 kg. of calcium propionate are homogenized with 4 kg. of propylene glycol.

Example 29

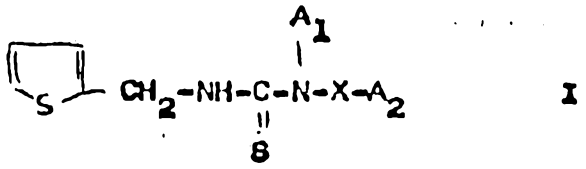
10 kg. of soybean meal and 0.6 kg. of an active agent according to Example 8 are homogenized with 2.5 kg. of butylene glycol.

Example 30

50 kg. of soybean meal, 6 kg. of an active agent according to Example 12, 0.5 kg. of silicon dioxide and 0.2 kg. of calcium propionate are homogenized with 1.6 kg. of soybean oil.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:
~~XXXXXXXXXXXXXXXXXXXXXXXX~~
~~What we claim is:~~

1. 2-(thienyl-methyl)-thiourea derivatives of the general Formula I



I

(wherein

A_1 stands for hydrogen, C_{1-4} alkyl or C_{4-8} cycloalkyl;

A_2 represents C_{3-10} alkyl, C_{3-10} alkenyl, C_{4-8} cycloalkyl, phenyl-C_{1-4} alkyl, phenyl-C_{2-4} alkenyl; phenyl optionally substituted by one or more C_{1-4} alkyl, C_{1-4} alkoxy or hydroxy; naphthyl; pyridyl optionally substituted by C_{1-4} alkyl; or furfuryl; and

X is a valency bond or a -CO- group;

with the proviso that if X stands for a valency bond, A_2 is other than phenyl).

2. N,N-dicyclohexyl-N'-(2-thienyl-methyl)-thiourea.

3. N-benzoyl-N'-(2-thienyl-methyl)-thiourea;

N-benzyl-N'-(2-thienyl-methyl)-thiourea;

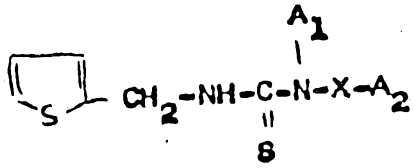
N-(p-methoxy-benzoyl)-N'-(2-thienyl-methyl)--thiourea;

N-cyclohexyl-N'-(2-thienyl-methyl)-thiourea;

N-(2,6-dimethyl-phenyl)-N'-(2-thienyl-methyl)--thiourea;

N-(β-phenyl-acryloyl)-N'-(2-thienyl-methyl)-thiourea.

4. Process for the preparation of 2-(thienyl--methyl)-thiourea derivatives of the general Formula I



I

(wherein

A_1 stands for hydrogen, C_{1-4} alkyl or C_{4-8} cycloalkyl;

A_2 represents C_{3-10} alkyl, C_{3-10} alkenyl, C_{4-8} cycloalkyl, phenyl-C_{1-4} alkyl, phenyl-C_{2-4} alkenyl; phenyl optionally substituted by one or more C_{1-4} alkyl, C_{1-4} alkoxy or hydroxy; naphthyl; pyridyl optionally substituted by C_{1-4} alkyl; or furfuryl; and

X is a valency bond or a -CO- group;

with the proviso that if X stands for a valency bond, A_2 is other than phenyl),

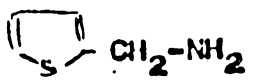
which comprises

a) for the preparation of compounds of the general Formula I, wherein X is a valency bond and A_1 and A_2 are as stated above,

a_1) reacting an isothiocyanate of the general Formula II

$$A_2\text{-NCS} \qquad \text{(II)}$$

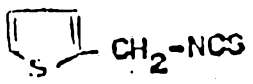
with a thenyl amine of the Formula III;



III

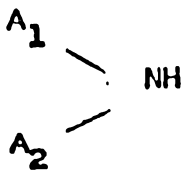
or

a_2) reacting (2-thienyl-methyl)-isothiocyanate of the Formula V



V

with an amine of the general Formula VI;



VI

or

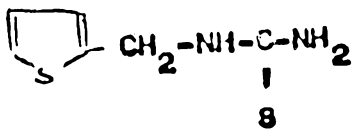
b) for the preparation of compounds of the general Formula I, wherein X stands for a -CO- group; A_1 is hydrogen and A_2 is as stated above,

b_1) reacting a 2-thenyl amine of the Formula III with an acyl-isothiocyanate of the general Formula IV;

$$A_2\text{-CO-NCS} \qquad \text{(IV)}$$

or

b_2) reacting N-(2-thienyl-methyl)-thiourea of the Formula VII



VII

with a carboxylic acid of the general Formula VIII

$$A_2\text{-COOH} \qquad \text{(VIII)}$$

or a reactive derivative thereof

(in which Formulae A_1, A_2 and X are as stated above).

5. Process according to variant b_1) or Claim 4, which comprises forming the acyl-isothiocyanate of the general Formula IV by reacting ammonium rhodanine with the corresponding acyl halide.

6. Compositions for use in animal husbandry comprising an effective amount of a compound of the general Formula I in admixture with suitable inert solid carriers or liquid diluents.

7. Fodder additives and fodders having weight gain increasing effect, comprising an effective amount of a compound of the general Formula I in admixture with suitable inert solid carriers or liquid diluents.

8. Fodders for use in animal husbandry having weight gain increasing effect, comprising as

active ingredient an effective amount of a compound of the general Formula I in admixture with suitable inert solid carriers or liquid diluents.

9. Compositions according to any of Claims 6-8 comprising as carrier substances of vegetable or animal origin applicable in the feeding of animals or serving as fodder, preferably wheat, oats, maize, soybean, rye or alfalfa in the form of grits, groats or meal, furthermore fish meal or meat meal.

10. Compositions according to any of Claims 6-9, comprising N,N-dicyclohexyl-N'--(2-thienyl-methyl)-thiourea.

11. A process for the preparation of compositions according to any of Claims 6-10, which comprises admixing a compound of the general Formula I with suitable inert carriers or liquid diluents.

12. A method for improving weight gain and fodder utilization of animals, which comprises feeding the animals with a fodder or feed additive according to any of Claims 6-10.

DATED this 29th day of September 1988.

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I certify that this and the preceding 30 pages are a true and correct copy of pages of the specification originally lodged.