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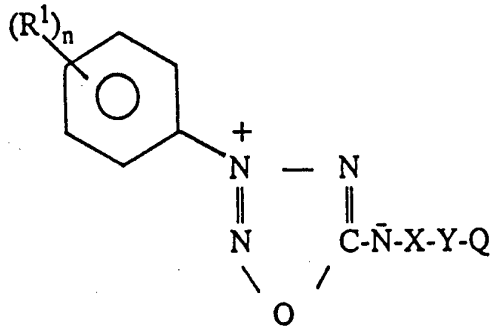
(54) Virsraksts: **3- un 5-Aizvietoti 1,2,3,4-oksatriazol-5-imīna savienojumi, to iegūšanas metode, tos saturošs farmaceitisks preparāts un to izmantošana medikamentu iegūšanai**

(57) Kopsavilkums: Izgudrojums attiecas uz 1,3- un 5-aizvietotiem 1,2,3,4-oksatriazol-5-imīna savienojumiem, kas var būt aktīvā sastāvdaļa astmu ārstējošos medikamentos, asnīšu agregācijas inhibēšanas medikamentos, kā arī impotences ārstēšanas un preteklampsijas medikamentos.

3- UN 5-AIZVIETOTI 1,2,3,4-OKSATRIAZOL-5-IMĪNA SAVIENOJUMI, TO IEGŪŠANAS METODE, TOS SATUROŠS FARMACEITISKS PREPARĀTS UN TO IZMANTOŠANA MEDIKAMENTU IEGŪŠANAI

PATENTA FORMULA

1. 3- un 5-aizvietoti 1,2,3,4-oksatriazol-5-imīna savienojumi ar kopīgo formulu I



(I),

atšķirīgi ar to, ka R^1 ir vienādas vai dažādas grupas un apzīmē alkil- vai alkoksigrupas ar 1 līdz 3 oglekļa atomiem, halogenu, trifluormetil-, nitro-, ciano-, fenil- vai alkilsulfonilgrupas, n ir 1 līdz 3, pie tam R^1 nav halogens vai alkilgrupa, kad n = 1,

X ir $-SO_2$ vai - C(O)NH-,

Y ir $-(CHR^2)_m-$, kur m = 1 līdz 4 un R^2 apzīmē $-CH_2$-aril-, alkilgrupu, ūdeņradi vai tiešo saiti un

Q apzīmē 10-kamforil-, -C(O)O-alkil-, aril-, $-SO_2$-alkil- vai $-SO_2$-arilgrupu, kur aril- apzīmē fenil- vai 4-alkil-1,3-tiazol-5-il grupu un arilgrupa ir aizvietota ar 1 līdz 3 Z grupām, kur Z apzīmē

-NH-C(O)-C_{1-6}alkil-, -C(O)O-C_{1-6}alkil- vai -O-$(CHR^3)_p$-OH grupu, kur p = 1 līdz 4 un R^3 apzīmē H vai OH un Z vēl var apzīmēt metoksigrupu, kad -SO_2-arilgrupas arilgrupa ir fenilgrupa.

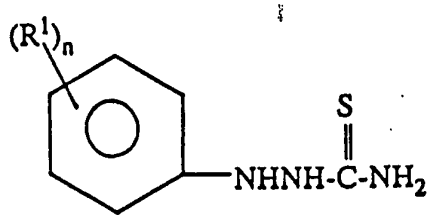
2. Savienojums, saskaņā ar 1. punktu,
atšķirīgs ar to, ka tas ir 3-(3-hlor-2-metilfenil)-1,2,3,4-oksatriazol-5-(N-(1S)-(+)-10-kamforilsulfamoil) imīns.

3. Savienojums, saskaņā ar 1. punktu,
atšķirīgs ar to, ka tas ir 3-(3-hlor-2-metilfenil)-1,2,3,4-oksatriazol-5-(N-2-acetamido-4-metil-5-tiazol sulfamoil) imīns.

4. Savienojums, saskaņā ar 1. punktu,
atšķirīgs ar to, ka tas ir 3-(3-hlor-2-metilfenil)-1,2,3,4-oksatriazol-5-(N-4-(metoksifenil sulfonil karbamoil) imīns.

5. Farmaceitisks preparāts,
atšķirīgs ar to, ka tas satur 1. punkta kopīgās formulas I savienojumu kā aktīvo ingredientu kopā ar farmaceitiski pieņemamu nesēju vai šķīdinātāju.

6. 3- un 5-aizvietotu 1,2,3,4-oksatriazol-5-imīna savienojumu ar kopīgo formulu I, saskaņā ar 1. punktu, iegūšanas metode,
atšķirīga ar to, ka 1-ariltiosemikarbazīda atvasinājuma ar kopīgo formulu II



(II),

kur R^1 un n ir ar tām pašām nozīmēm kā formulā I, ciklizē, apstrādājot to ar alkilnitrītu ar 1 līdz 6 oglekļa atomiem vai ar sārmu metāla nitrītu skābos apstākļos pie 0 līdz 10°C, pēc kā iegūto sāli

pārvērš atbilstošā brīvā savienojumā, kuru pēc tam ievada reakcijā ar $ClSO_2$-Y-Q vai O=C=N-Y-Q tipa savienojumu, kur Y un Q ir ar tām pašām nozīmēm kā formulā I.

7. 3- un 5-aizvietotu 1,2,3,4-oksatriazol-5-imīna savienojumu ar kopīgo formulu I, saskaņā ar 1. punktu, izmantošana astmu ārstējoša medikamenta iegūšanai.

8. 3- un 5-aizvietotu 1,2,3,4-oksatriazol-5-imīna savienojumu ar kopīgo formulu I, saskaņā ar 1. punktu, izmantošana tāda medikamenta iegūšanai, kas inhibē asins plāksnīšu agregāciju.

9. 3- un 5-aizvietotu 1,2,3,4-oksatriazol-5-imīna savienojumu ar kopīgo formulu I, saskaņā ar 1. punktu, izmantošana tāda medikamenta iegūšanai, kas ir efektīvs pret impotenci.

10. 3- un 5-aizvietotu 1,2,3,4-oksatriazol-5-imīna savienojumu ar kopīgo formulu I, saskaņā ar 1. punktu, izmantošana tāda medikamenta iegūšanai, kas ir efektīvs pret preeklampsiju.

Title: 3- and 5-substituted 1,2,3,4-oxatriazole-5-imine compounds, a process for the preparation thereof, a pharmaceutical preparation containing said compounds and the use of said compounds for the preparation of medicaments

Technical Field

The present invention relates to hitherto unknown 3- and 5-substituted 1,2,3,4-oxatriazole-5-imine compounds having biological effects making them suitable for treatment of cardiovascular diseases (blood clots) and asthma, a process for the preparation thereof and a pharmaceutical preparation containing said compounds. Furthermore, the invention relates to the use of said compounds for the preparation of medicaments.

Background Art

N.G. Finnegan et al., J. Org. Chem. 30, pages 567-575 (1965) discloses the compound 3-cyclohexyl-1,2,3,4-oxatriazole-5-imino-hydrochloride. However, no biological effect of said compound is mentioned.

K. Masuda et al., Chem. Pharm. Bull. 19 (3) pages 559-563 (1971) discloses 3-aryl-1,2,3,4-oxatriazole-5-imine compounds and acyl derivatives thereof, wherein the aryl group may be monosubstituted by methyl or halogen. Even though these compounds were synthesized in the hope of finding new hypotensive agents, no biological effects of the compounds are described.

C. Christophersen et al., Acta Chemica Scandinavica, 25, pages 625-630 (1971), discloses 3-substituted 1,2,3,4-oxatriazole-5-imino compounds, wherein the 3-substituent may be propyl or phenyl or cyclohexyl. However, no biological effects of said compounds are described.

Hanley et al., J.C.S. Perkin Trans I, 736-740 (1979), discloses 3-aryl-1,2,3,4-oxatrizole-5-imine compounds, wherein the aryl group may be monosubstituted by methyl or halogen. However, no biological effects of the compounds are described.

The JP Patents Nos. 20904/70 and 21102/70 disclose 3-substituted 1,2,3,4-oxatriazole-5-imine salts and acyl derivatives thereof, wherein the 3-substituent may be aryl, optionally monosubstituted by chlorine or methyl. The vasodepressor activity of said compounds is stated as a biological effect.

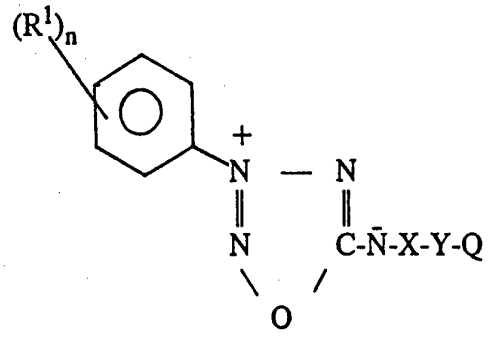
GB patent specification No. 2 015 878 discloses 3-phenyl-1,2,3,4-oxatriazole-5-imine compounds, for which a pesticidal and/or pest ovicidal and/or hebicidal activity has been found.

US patent specification No. 4,329,355 discloses anhydro-5-imino-1,2,3,4-oxatriazolium hydroxides of a structure similar to the structure of the compounds of the present invention. However, the compounds known from this patent specification are only mentioned as being useful in the treatment of cancer.

Furthermore, from J.C.S. Perkin Trans I, 747-751 (1979) compounds of a structure similar to the structure of the compounds of the present invention are known. However, no biological effects of said compounds have been stated.

Disclosure of the Invention

The present invention relates to hitherto unknown 3- and 5-substituted 1,2,3,4,-oxatriazole-5-imine compounds of the general formula I



(I)

being characterised in that R^1 is the same or different groups and represents alkyl or alkoxy groups having 1 to 3 carbon atoms, halogen, trifluoromethyl, nitro, cyano, phenyl or alkylsulphonyl groups, n is 1 to 3, whereby R^1 is not halogen or alkyl, when n = 1,

X is $-SO_2$ or - C(O)NH-,

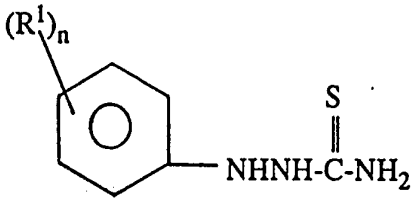
Y is $-(CHR^2)_m-$, wherein m = 1 to 4, and R^2 means $-CH_2$-aryl, alkyl, hydrogen or a direct bond, and

Q means 10-camphoryl, -C(O)O-alkyl, aryl, $-SO_2$-alkyl or $-SO_2$-aryl, where aryl means phenyl or 4-alkyl-1,3-thiazole-5-yl and the aryl group is substituted by 1 to 3 groups Z, where Z means -NH-C(O)-C_{1-6}alkyl, -C(O)O-C_{1-6}alkyl or -O-$(CHR^3)_p$-OH, wherein p = 1 to 4 and R^3 means H or OH, where Z may further mean methoxy, when the aryl group in $-SO_2$-aryl is a phenyl group.

The compounds according to the invention differ from the above prior art compounds by their chemical constitution, as they have a different substitution in the 3-position and/or in the 5-position of the oxatriazole ring, and they differ from the compounds known from the above patents with respect to their biological effect, as they inhibit the blood platelet aggregation and have a relaxation effect on the trachea.

The invention further relates to a pharmaceutical preparation being characterised in that it comprises as an active ingredient a compound of formula I together with a pharmaceutically acceptable carrier or diluent.

Moreover, the invention relates to a process for the preparation of said 3- and 5-substituted 1,2,3,4-oxatriazole-5-imine compounds of the general formula I, said process being characterised by ring closing a 1-arylthiosemicarbazide derivative of the general formula II



(II)

wherein R^1 and n have the same meaning as in formula I, by treatment with alkyl nitrite having 1 to 6 carbon atoms or alkali metal nitrite under acidic conditions at 0 to 10°C, whereafter the resulting salt is converted into the corresponding free compound, which is subsequently reacted with a compound of the type $ClSO_2$-Y-Q or O=C=N-Y-Q, wherein Y and Q have the same meaning as in formula I.

The ring closure reaction by the use of alkyl nitrite having 1 to 6 carbon is hitherto unknown and is preferred for the preparation of the compounds according to the invention, as a quantitative yield prior to purification is obtained hereby.

In the process according to the invention it is preferred to use ethyl nitrite as alkyl nitrite having 1 to 6 carbon atoms, and sodium nitrite is preferred as an alkali metal nitrite.

It is known per se to cyclize 1,4-disubstituted thiosemicarbazides with nitrous acid (sodium nitrite and acid) to form 3-substituted 1,2,3,4-oxatriazole-5-imines. The

yields at this reaction are stated to be between 18 and 57%.

For reacting 1 equivalent of the 1-aryl-thiosemicarbazide derivative with alkyl nitrite having 1 to 6 carbon atoms, it is preferred to use 2 to 2.5 equivalents of alkyl nitrite in a suitable solvent, such as alkyl alcohol having 1 to 6 carbon atoms, to obtain a 3-arylsubstituted 1,2,3,4-oxatriazole-5-imine salt in a substantially quantitative yield. After filtration of the precipitated sulphur and evaporation of the solvent, the product is, if necessary, recrystallized from for instance alkyl alcohol having 1 to 6 carbon atoms, acetonitrile or nitromethane, whereby the yields of the pure product obtained are usually between 60 and 95%.

As alkyl alcohol having 1 to 6 carbon atoms methanol or ethanol is preferred.

The necessary starting compounds of the general formula II may be prepared in a manner known per se by reacting the corresponding arylhydrazine hydrochloride with an alkali thiocyanate or an ammonium thiocyanate in a suitable solvent, such as alcohol or water, using reflux for 6 to 18 hours, for instance as described by Houben-Weyl: "Methoden Der Organischen Chemie E4", page 513.

PREPARATION OF THE STARTING MATERIALS

Preparation of 1-(3-chloro-2-methylphenyl)thiosemicarbazide

19.3 g (0.1 mole) of 3-chloro-2-methylphenylhydrazine-hydrochloride were dissolved in 200 ml of absolute ethanol. 11.64 g (0.12 mole) of potassium thiocyanate were added to the solution, and the mixture was heated during reflux for 16 hours. The mixture was then cooled, whereby the product was partially precipitated, and the mixture was subsequently evaporated to dryness on a rotatory evaporator. The product was recrystallized from 200 ml water and 250 ml

methanol, separated by filtration and washed thoroughly with water.

Yield: 17.8 g = 82.5%
Melting point: 192-193°C.

Elemental analysis: $C_8H_{10}ClN_3S$:

Calculated	C: 44.54%	H: 4.67%	N: 19.48%	S:14.86%
Found	C: 44.22%	H: 4.58%	N: 19.60%	S:14.67%

500 MHz ^1H NMR (d_6-DMSO):
δ 9.33 (br s, 1H, NH), δ 7.80 (br s, 1H, NH), δ 7.72 (br s, 1H, NH), δ 7.52 (br s, 1H, NH), δ 6.80 (m, 3H, ArH), δ 2.18 (s, 3H, CH_3).

Preparation of 3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-imine hydrochloride

8.6 g (40 mmole) of 1-(3-chloro-2-methylphenyl)thiosemicarbazide were dissolved in 100 ml of methanol and 5 ml of 37% hydrochloric acid while being stirred at room temperature. The mixture was cooled to 0 to 5°C by means of an ice bath, and 6.3 g (7 ml) of ethyl nitrite were subsequently added in small quantities over a period of approximately 5 minutes. The mixture became dark coloured by the nitrous vapours, but turned light after a few minutes at the same time as free sulphur precipitated. The mixture was stirred for 10 minutes, and additional 0.9 g (1 ml) of ethyl nitrite was then added, and the reaction mixture was then left for about 20 minutes while being stirred. The sulphur was separated by filtration and the mixture was evaporated on a rotating evaporator at a bath temperature of 30°C. If necessary, the mixture was dehydrated by evaporation together with toluene/ethanol. The crystals were stirred with diethyl ether, separated by filtration and washed further with small amounts of diethyl ether.

Yield: 9.2 g = 94%

Melting point: 194-195°C (decomposes)

IR: 1700 cm^{-1}.

Elemental analysis $C_8H_7ClN_4O$, HCl, ¼H_2O:

Calculated	C: 38.19%	H: 3.41%	N: 22.28%	Cl:28.18%
Found	C: 38.07%	H: 3.19%	N: 22.30%	Cl:28.58%

500 MHz ^1H NMR (D_2O):

δ 7.52 (m, 3H, ArH), δ 2.38 (s, 3H, CH_3)

Example 1

3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-(N-phenyl sulphonyl carbamoyl) imine

4.94 g (20 mml) of 3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-imine-hydrocloride were dissolved in 100 ml of water and 2.1 g (25 mmole) of sodium hydrogencarbonate were subsequently added while being stirred. After terminated development of carbon dioxide 100 ml of chloroform were added, whereafter the precipitated substance dissolved. Under vigorous stirring 3.85 g (21 mmole) of benzene sulphonyl isocyanate were added to the mixture and stirring was continued for 60 minutes, whereby a precipitate was formed. This precipitate was separated by filtration and the chloroform phase was washed thrice with 50 ml of 1N hydrochloric acid and subsequently with water, whereafter it was concentrated. The product formed by the concentration was mixed with the precipitate separated by filtration and this mixture was subsequently stirred with a small quantity of ether, whereafter the mixture was separated by filtration and dried.

Yield: 6.7 g = 84.6%

Melting point: 163-165°C

IR: 1695 cm^{-1}, 1685 cm^{-1}, 1330 cm^{-1}, 1160 cm^{-1} (N^{-}-SO_2-); 1650 cm^{-1} (N^{-}-CO-NH).

Elemental analysis $C_{15}H_{22}ClN_5SO_4$:

Calculated	C: 45.46%	H: 3.07%	N: 17.79%	S: 8.14%
Found	C: 45.46%	H: 3.14%	N: 17.31%	S: 7.92%

Example 2

3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-(N-2-acetamido-4-methyl-5-thiazole sulphamoyl)imine

1.95 g (7.9 mmole) of 3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-imine hydrochloride were dissolved/suspended in 30 ml of pyridine, and 2.0 g (7.9 mmole) of 2-acetamido-4-methyl-5-thiazole sulphonyl chloride were subsequently added while being stirred. The mixture was stirred for 75 minutes at room temperature, whereafter it was poured into 350 ml of water while being stirred vigorously. The precipitated product was separated by filtration, washed thoroughly with water and diethyl ether and dried under vacuum.

Yield: 1.71 g = 50.4%

Melting point: 158-159°C

IR: 1690 cm^{-1} (-NH-CO-); 1610 cm^{-1}, 1320 cm^{-1}, 1155 cm^{-1} (N^{-}-SO_2-)

Elemental analysis $C_{14}H_{12}ClN_6O_4S_2,H_2O$:

Calculated	C: 37.61%	H: 3.38%	N: 18.81%	S:14.34%
Found	C: 37.63%	H: 3.32%	N: 18.84%	S:14.60%

Example 3

3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-(N-4-acetylamino phenyl sulphamoyl)imine

4.94 g (20 mmole) of 3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-imine hydrochloride were dissolved/suspended in 70 ml of pyridine, and 4.67 g (20 mmole) of N-acetyl sulphanyl chloride were subsequently added, while being stirred. The mixture was then stirred for 75 minutes at room temperature and subsequently poured into 900 ml of water while being stirred vigorously. The precipitated product was separated by filtration, then washed thoroughly with water and diethyl ether and dried under vacuum.

Yield: 6.87 g = 84.2%
Melting point: 224-225°C
IR: 1700 cm^{-1} (-NH-CO-); 1630 cm^{-1}, 1320 cm^{-1}, 1155 cm^{-1} (N^{-}-SO_2-)

Elemental analysis $C_{16}H_{14}ClN_5SO_4$:

Calculated	C: 47.12%	H: 3.46%	N: 17.18%	S: 7.86%
Found	C: 47.10%	H: 3.28%	N: 16.83%	S: 7.98%

Example 4

3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-(N-(1S)-(+)-10-camphoryl sulphamoyl)imine

4.94 g (20 mmole) of 3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-imine hydrochloride were dissolved in 70 ml of water and 4.2 g (50 mmole) of sodium hydrogencarbonate were subsequently added while being stirred. After terminated

development of carbon dioxide 70 ml of dichloromethane were added, whereafter the precipitated product dissolved. 5.02 g (20 mmole) of (1S)-(+)-camphor-10-sulphonic acid chloride were added to the mixture under vigorous stirring, and the mixture was then stirred for 16 hours. The organic phase was separated and then washed with 1N hydrochloric acid and subsequently with water, whereafter it was concentrated into an oil, and left to stand in a small quantity of ethanol said oil slowly formed a precipitate, which was separated by filtration and then dried under vacuum.

Yield: 3.76 g = 43.0%

Melting point: 126-128°C

IR: 1740 cm^{-1} (-CO-); 1630 cm^{-1}, 1315 cm^{-1}, 1150 cm^{-1} (N^{-}-SO_2-)

Elemental analysis $C_{18}H_{21}ClN_4SO_4$:

Calculated	C: 50.88%	H: 4.98%	N: 13.19%	S: 7.55%
Found	C: 50.80%	H: 4.96%	N: 13.14%	S: 7.69%

Example 5

3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-(N-4-carbethoxy phenyl carbamoyl)imine

4.9 g (20 mmole) of 3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-imine hydrochloride were dissolved in 50 ml of water, to which 2.0 g (24 mmole) of sodium hydrogencarbonate were subsequently added while being stirred. After terminated development of carbon dioxide 50 ml of dichloromethane were added, whereafter the precipitated product dissolved. 3.82 g (20 mmole) of 4-isocyanato-benzoic acid ethyl ester were added to said mixture under vigorously stirring, whereby the end product precipitated almost instantaneously. The mixture was

stirred for a further 30 minutes, whereafter the precipitated product was separated by filtration, washed thoroughly with water and subsequently with diethyl ether, and dried under vacuum.

Yield: 7.07 g = 88.0%

Melting point: 183-185°C

IR: 1680 cm^{-1}, 1270 cm^{-1}, 1110 cm^{-1} (ester); 1635 cm^{-1} (N-CO-NH).

Elemental analysis $C_{18}H_{16}ClN_5O_4$, ⅓ H_2O

Calculated	C: 53.01%	H: 4.12%	N: 17.18%
Found	C: 53.03%	H: 4.04%	N: 16.83%

Example 6

3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-(N-4-methoxy-phenylsulphonyl carbamoyl)imine

4.94 g (20 mmole) of 3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-imine hydrochloride were dissolved in 70 ml of water, to which 2.5 g (30 mmole) of sodium hydrogencarbonate were subsequently added while being stirred. After terminated development of carbon dioxide 70 ml of dichloromethane were added, whereafter the precipitated product dissolved. 4.5 g (21 mmole) of 4-methoxy benzene sulphonyl isocyanate were added to the mixture under vigorous stirring, and the mixture was then stirred for 2 hours, whereafter the organic phase was separated. The organic phase was washed trice with 50 ml of 1N hydrochloric acid and subsequently with water, whereafter ithe mixture was concentrated. The residue was stirred thoroughly with 100 ml of diethyl ether, whereafter the product was separated by filtration and dried.

Yield: 6.34 g = 72.7%

Melting point: 135°C

IR: 1690 cm^{-1}, 1330 cm^{-1}, 1160 cm^{-1} (N^{-}-SO_2-); 1620 cm^{-1} (N^{-}-CO-NH); 1260 cm^{-1} (OCH_3).

Elemental analysis $C_{16}H_{14}ClN_5O_5S$:

Calculated	C: 45.34%	H: 3.33%	N: 16.53%	S: 7.36%
Found	C: 45.05%	H: 3.34%	N: 16.38%	S: 7.23%

Example 7

3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-(N-carbethoxy-carbamoyl)imine

2.47 g (10 mmole) of 3-(3-chloro-2-methylphenyl)-1,2, 3,4-oxatriazole-5-imine hydrochloride were dissolved in 30 ml of water and 0.9 g (10.7 mmole) of sodium hydrogen carbonate were subsequently added while being stirred. After the development of carbon dioxide was terminated, 30 ml of dichloromethane were added, whereafter the precipitated product dissolved. 1.15 g (10 mmole) of carbethoxy ethyl isocyanate were added to the mixture during vigorous stirring, whereafter the mixture was stirred for 30 minutes. The organic phase was separated and washed with water, whereafter the mixture was concentrated and the residue was washed with ether. The product was subsequently separated by filtration and dried.

Yield: 2.55 g = 78.3%

Melting point: 123 to 127°C

IR: 1770 cm^{-1}, 1200 cm^{-1} (ester); 1640 cm^{-1} (N^{-}-CO-NH).

Elemental analysis $C_{12}H_{12}ClN_5O_4$:

Calculated	C: 44.25%	H: 3.71%	N: 21.50%
Found	C: 44.18%	H: 3.72%	N: 21.08%

Example 8

3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-(N-carbethoxy methylcarbamoyl)imine

4.9 g (20 mmole) of 3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-imine hydrochloride were dissolved in 60 ml of water and 1.8 g (21 mmole) of sodium hydrogencarbonate were subsequently added while being stirred. After terminated development of carbon dioxide 60 ml of dichloromethane were added, whereafter the precipitated product dissolved. 2.5 g (20 mmole) of ethoxy carbonyl methyl isocyanate were added to the mixture under vigorous stirring, whereafter the mixture was stirred for 30 minutes, whereby a precipitate was formed. Dichloromethane was added causing the precipitate to dissolve. The organic phase was separated and subsequently washed with water and concentrated, wherafter the residue was stirred with a small quantity of ether, separated by filtration and dried.

Yield: 5.9 g = 86.8%

Melting point: 163-165°C

IR: 1755 cm^{-1}, 1200 cm^{-1} (ester); 1645 cm^{-1}, 1635 cm^{-1} (N^--CO-NH).

Elemental analysis $C_{13}H_{14}ClN_5O_4$:

Calculated	C: 45.96%	H: 4.15%	N: 20.61%
Found	C: 46.10%	H: 4.22%	N: 20.36%

Example 9

3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-(N-2-carbamoyl-3-phenyl propionic acid ethyl ester)imine

4.9 g (20 mmole) of 3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-imine hydrochloride were dissolved in 60 ml of water and 1.8 g (24 mmole) of sodium hydrogencarbonate were subsequently added while being stirred. After terminated development of carbon dioxide 60 ml of dichloromethane were added, whereafter the precipitated product dissolved. 4.38 g (20 mmole) of 2-isocyanato-3-phenyl-propionic acid ethyl ester were added to the mixture being stirred vigorously, whereupon the mixture was stirred for 30 minutes. The organic phase was separated and then washed with 1N hydrochloric acid and subsequently with water, whereafter it was concentrated. The residue was washed with a small quantity of diethyl ether, then separated by filtration and dried under vacuum.

Yield: 5.0 g = 58.2%

Melting point: 127-128°C

IR: 1745 cm^{-1}, 1190 cm^{-1} (ester); 1670 cm^{-1}, 1630 cm^{-1} (N^{-}-CO-NH).

Elemental analysis $C_{20}H_{20}ClN_5O_4$:

Calculated	C: 55.88%	H: 4.69%	N: 16.29%
Found	C: 55.79%	H: 4.53%	N: 16.04%

Example 10

3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-(N-2-carbamoyl propionic acid methyl ester)imine

4.9 g (20 mmole) of 3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-imine hydrochloride were dissolved in 60 ml of water and 1.8 g (24 mmole) of sodium hydrogencarbonate were subsequently added while being stirred. After terminated development of carbon dioxide 60 ml of dichloromethane were added, whereafter the precipitated product dissolved. 2.58 g (20 mmole) of 2-isocyanate propionic acid methyl ester were added to the mixture being stirred vigorously, whereupon the mixture was stirred for 30 minutes. The organic phase was separated and then washed with 1N hydrochloric acid and subsequently with water, whereafter it was concentrated. The residue was washed with a small quantity of diethyl ether, then separated by filtration and dried under vacuum.

Yield: 3.5 g = 51.5%

Melting point: 66-69°C

IR: 1745 cm^{-1}, 1200 cm^{-1} (ester); 1670 cm^{-1}, 1635 cm^{-1} (N^--CO-NH).

Elemental analysis $C_{13}H_{14}ClN_5O_4$:

Calculated	C: 45.96%	H: 4.15%	N: 20.61%
Found	C: 45.54%	H: 4.14%	N: 20.11%

PHARMACOLOGiCAL TESTS

1. Inhibition of blood platelet aggregation

Compounds according to the invention were tested for their inhibition of clumping together (aggregation) of blood platelets (thrombocytes), which is the first phase of the formation of blood clots (thrombi). Such an inhibition may prevent the formation of blood clots and inhibit the development of new thrombi after a diagnosed thrombus.

The method of demonstrating this effect is a so-called aggregometer measurement, which was first described by Born (Nature (Lond.) 194, 927-929, 1962). Citrate stabilized (0.38% of sodium citrate, final concentration) venous blood from healthy testees is used, who have not used medicine for at least 8 days. Slight centrifugation (160 x g for 10 minutes) results in PRP (blood plasma rich in platelets) which is pipetted. PPP (blood plasma poor in platelets) is obtained by an intense centrifugation (3000 x g for 10 minutes) of the remaining blood. The light transmission is measured by the aggregometer (CHRONOLOG). PRP allows nearly no light transmission, while PPP allows complete transmission of light. The PRP is placed in the aggregometer at 37°C while being stirred by a magnet. Addition of a pro-aggregating substance causes the PRP to aggregate gradually and an increasing light transmission takes place at the same time. At complete aggregation a light transmission corresponding to PPP is obtained. Adenosine diphosphate (ADP) is used as pro-aggregating substance, said substance representing a basic biochemical mechanism for aggregation of blood platelets. The test substances are incubated for three minutes in PRP placed in the aggregometer at 37°C during magnetic stirring. A predetermined positively aggregating dosage of adenosine diphosphate (ADP) (2 to 4 μM) is then added. At least three different concentrations of the test substances are tested to demonstrate dosage-dependent inhibition of the aggregation. A so-called IC_{50}-value (that is the concentration inhibiting the aggregation by 50% relative to the control aggregation) is calculated for each test substance by linear regression analysis (log concentration μM as constant ad abscissa and % inhibition as variable ad ordinate). The following known reference substances have been used: nitroglycerine (GTN), sodium nitroprusside (NNP) and SIN-1 (the active metabolite of molsidomine).

The results for ten compounds according to the invention and three reference substances appear from Table 1.

It appears from Table 1 that the compounds according to the invention in general are substantially superior to the best of the reference substances. Nitroglycerine appears to be inactive in this test.

Table 1 INHIBITION OF BLOOD PLATELET AGGREGATION

Compound	IC_{50}, μM
GTN	100
NNP	2.7
SIN-1	3.9
Compound prepared according to Example No.	
1	0.49
2	0.37
3	1.01
4	0.08
5	2.98
6	0.67
7	0.16
8	7.60
9	7.90
10	2.31

2. Relaxation effect on the trachea

Compounds according to the invention were tested for their ability to relax a pre-contracted trachea. A contraction of the respiratory passages in combination with a swelling of the mucuos membrane therein presents a vital factor at asthmatic conditions. Relaxation or dilation of the contracted respiratory passages will improve the asthmatic condition.

The method of demonstrating relaxation of a pre-contracted trachea is described

by Emmerson & MacKay (J. Pharm. Pharmacol 31, 798, 1979). An isolated trachea from a guinea pig is used. After preparation of a strip which has maintained the circular musculature, the organ strip is divided into two parts of equal size. The two tracheal strips are suspended in their respective organ bath and connected to a transducer recording the contraction and relaxation of the organ by means of a recorder. The two tracheal strips are continuously bathed in a Krebs buffer at 37°C, constantly bubbled with carbogen (95% 0_2 and 5% CO_2). After an equilibration time of about 3 hours the organ strips are tested for their sensitivity (contractility) to carbamylcholine, a bolus being added directly to the bath (0.3 μM). If the contraction is satisfactory, the organ strips are transferred to the Krebs buffer containing the same concentration of carbamylcholine. The organ strips are now constantly exposed to the carbamylcholine and slowly develop a permanent contraction ("asthma"). The test compounds are added directly to the organ bath in bolus form. Having reached maximum effect (relaxation), the added substances are rinsed out of the system and the tracheal strip reverts to its permanent contraction state. At least three different concentrations of the test compounds are tested to demonstrate a dose-dependent relaxation of the organ. An EC_{50}-value (that is the concentration relaxing the organ by 50% relative to the maximum relaxation) is calculated for each test compound by means of a linear regression analysis (log concentration (μM) as a constant ad abscissa and % relaxation as variable ad ordinate). Sodium nitroprusside (NNP) and SIN-1 are used as reference compounds.

The results for ten compounds according to the invention and for the two reference compounds appear from Table 2.

It appears from Table 2 that the compounds according to the invention have a strong relaxing effect on the pre-contracted tracheal strips, said effect being in agreement with the effect of NNP and SIN-1. In addition, however, the com-

pounds according to the invention have a longer lasting effect than the reference compounds.

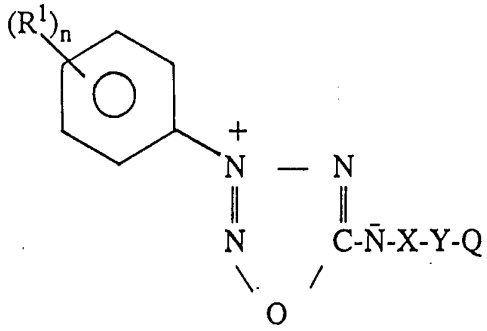
Table 2 RELAXATION OF THE TRACHEA

Compound	IC_{50} μM
NNP	2.5
SIN-1	18.3
Compound prepared according to Example No.	
1	3.9
2	13.9
3	11.1
4	0.90
5	34
6	3.9
7	3.0
8	11
9	37
10	23

The invention has been described with reference to preferred embodiments. Many modifications may, however, be carried out without thereby deviating from the scope of the invention.

Claims

1. 3- and 5-substituted 1,2,3,4-oxatriazole-5-imine compounds of the general formula I



(I)

c h a r a c t e r i s e d in that

R^1 is the same or different groups and represents alkyl or alkoxy groups having 1 to 3 carbon atoms, halogen, trifluoromethyl, nitro, cyano, phenyl or alkylsulphonyl groups, n is 1 to 3, whereby R^1 is not halogen or alkyl, when n = 1,

X is $-SO_2$ or - C(O)NH-,

Y is $-(CHR^2)_m-$, wherein m = 1 to 4, and R^2 means $-CH_2$-aryl, alkyl, hydrogen or a direct bond, and

Q means 10-camphoryl, -C(O)O-alkyl, aryl, $-SO_2$-alkyl or $-SO_2$-aryl, where aryl means phenyl or 4-alkyl-1,3-thiazole-5-yl and the aryl group is substituted by 1 to 3 groups Z, where Z means -NH-C(O)-C_{1-6}alkyl, -C(O)O-C_{1-6}alkyl or -O-$(CHR^3)_p$-OH, wherein p = 1 to 4 and R^3 means H or OH, and Z may further mean methoxy, when the aryl group in $-SO_2$-aryl is a phenyl group.

2. A compound as claimed in claim 1, c h a r a c t e r i s e d in that it is 3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-(N-(1S)-(+)-10-camphorylsul-

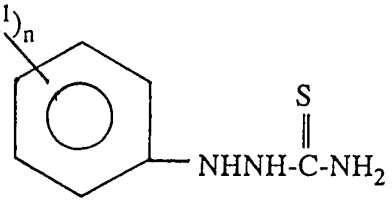
phamoyl)imine.

3. A compound as claimed in claim 1, c h a r a c t e r i s e d in that it is 3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-(N-2-acetamido-4-methyl-5-thiazole sulphamoyl)imine.

4. A compound as claimed in claim 1, c h a r a c t e r i s e d in that it is 3-(3-chloro-2-methylphenyl)-1,2,3,4-oxatriazole-5-(N-4-(methoxyphenyl sulphonyl carbamoyl)imine.

5. A pharmaceutical preparation, c h a r a c t e r i s e d in that it comprises a compound of the general formula I according to claim 1 as an active ingredient together with a pharmaceutically acceptable carrier or diluent.

6. A process for the preparation of 3- and 5-substituted 1,2,3,4 oxatriazole-5-imine compounds of the general formula I according to claim 1, c h a r a c t e r i s e d by ring closing a 1-arylthiosemicarbazide derivative of the general formula II



(II)

wherein R^1 and n have the same meaning as in formula I, by treatment with alkyl nitrite having 1 to 6 carbon atoms or alkali metal nitrite under acidic conditions at 0 to 10°C, whereafter the resulting salt is converted into the corresponding free compound, which is subsequently reacted with a compound of the type $ClSO_2$-Y-Q or O=C=N-Y-Q, wherein Y and Q have the same meaning as in formula I.

7. The use of 3- and 5-substituted 1,2,3,4,-oxatriazole-5-imine compounds of the general formula I according to claim 1 for the preparation of a medicament for the treatment of asthma.

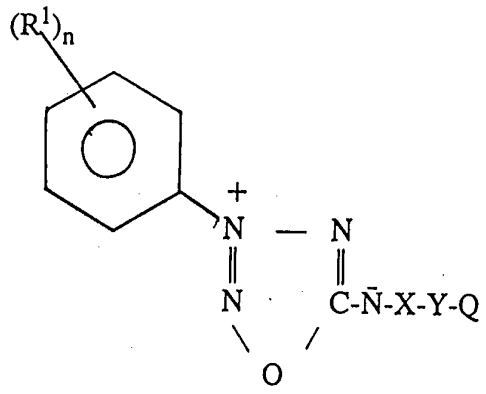
8. The use of 3- and 5-substituted 1,2,3,4-oxatriazole-5-imine compounds of the general formula I according to claim 1 for the preparation of a medicament having an inhibiting effect on the blood platelet aggregation.

9. The use of 3- and 5-substituted 1,2,3,4-oxatriazole-5-imine compounds of the general formula I according to claim 1 for the preparation of a medicament being effective against impotence.

10. The use of 3- and 5-substituted 1,2,3,4-oxatriazole-5-imine compounds of the general formula I according to claim 1 for the preparation of a medicament being effective against pre-eclampsia.

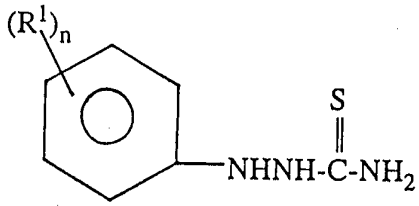
Abstract

3- and 5-substituted 1,2,3,4-oxatriazole-5-imine compounds of the general formula I



(I)

wherein R^1 is the same or different groups and represents alkyl or alkoxy groups having 1 to 3 carbon atoms, halogen, trifluoromethyl, nitro, cyano, phenyl or alkylsulphonyl groups, n is 1 to 3, whereby R^1 is not halogen or alkyl, when n = 1, X is $-SO_2$ or - C(O)NH-, Y is $-(CHR^2)_m-$, wherein m = 1 to 4, and R^2 means $-CH_2$-aryl, alkyl, hydrogen or a direct bond, and Q means 10-camphoryl, --C(O)O-alkyl, aryl, $-SO_2$-alkyl or $-SO_2$-aryl, where aryl means phenyl or 4-alkyl-1,3-thiazole-5-yl and the aryl group is substituted by 1 to 3 groups Z, where Z means -NH-C(O)-C_{1-6}alkyl, -C(O)O-C_{1-6}alkyl or -O-$(CHR^3)_p$-OH, wherein p = 1 to 4 and R^3 means H or OH, and Z may futher means methoxy, when the aryl group in $-SO_2$-aryl is a phenyl group, are prepared by ring closing a 1-aryl-thiosemicarbazide derivative of the general formula II



(II)

wherein R^1 and n have the same meaning as in formula I, by treatment with alkyl

nitrite having 1 to 6 carbon atoms or alkali metal nitrite under acidic conditions at 0 to 10°C, whereafter the resulting salt is converted into the corresponding free compound, which is subsequently reacted with a compound of the type $ClSO_2$-Y-Q or O=C=N-Y-Q, wherein Y and Q have the same meaning as in formula I.

The compounds of the general formula I may form part of a pharmaceutical preparation in association with a pharmaceutically acceptable carrier or diluent. The compounds of the general formula I may be used for the preparation of a medicament for the treatment of asthma, a medicament having an inhibiting effect on the blood platelet aggregation, a medicament being effective against impotence and a medicament being effective against pre-eclampsia.