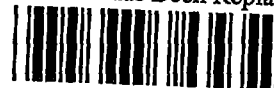


New Knoevenagel Condensation Products, Methods of their Production and their Use

Description

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The concerning invention refers to new Knoevenagel condensation products, methods of their production and their use for pharmaceutical and analytical purposes. Additionally, conjugates of the Knoevenagel condensates with biomolecules are disclosed.

In a publication of Feigl (Z. Anal. Chem. 74 (1928), 380-386) the use of p-dimethylaminobenzalrhodanine for the detection of silver is described. Escobar Godoy and Guiraum Perez (Analyst 111 (1986), 1297-1299) describe the use of the pyridoxal analogue (Z)-pyridoxylidenerhodanine for the spectrophotometric quantification of silver.

The basic problem of the concerning invention was to supply new compounds suitable particularly for pharmaceutical and analytical purposes. This task is fulfilled by the synthesis of the compound (Z)-5'-O-phosphono-pyridoxylidenerhodanine (3), representing a derivative of the vitamin B6 coenzyme pyridoxal 5'-phosphate (1).

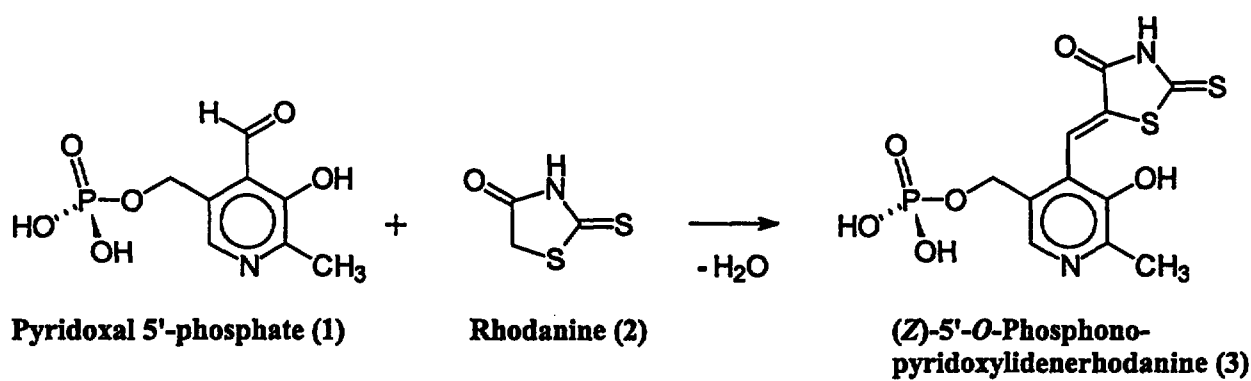
The preparation of the compound (3) is performed by reaction of (1) with the synthetic heterocyclic compound rhodanine (2) in a Knoevenagel condensation (see also Kesel et al., Tetrahedron 52 (18.11.1996), 14787-14800).

The compound 3 bears the nomenclature (Z)-5-[[[5-hydroxy-6-methyl-3-[(phosphonooxy)methyl]-4-pyridinyl]methylene]-2-thioxo-4-thiazolidinone. The rhodanine part of this molecule is able to bind to biomolecules like single-stranded nucleic acids. The charged phosphate group enables good water solubility.

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The compound 3 undergoes a (Z/E)-stereoisomerism to the (E)-isomer 4. This cis/trans-rearrangement is triggered by e. g. UV-irradiation with the wavelength 254 nm or/and 366 nm.

In polar aprotic solvents the originally yellow compound 3 is found as red 3-pyridinolates free acid 5 e. g. in pyridine or dimethylsulfoxide (DMSO).



The yellow compound 3 forms a deep-red monosodium salt. Its structure was determined by X-ray crystallography. It was crystallized as hemiheptadecahydrate (8.5 hydrate) and is found as (Z)-stereoisomer 6. The monosodium salt 6, if UV-irradiated, performs analogously a cis/trans-rearrangement to the red (E)-stereoisomer 7.

Derivatives of the compound 3 can be obtained with C₁₂-C₁₈ fatty acid chlorides at the OH group.

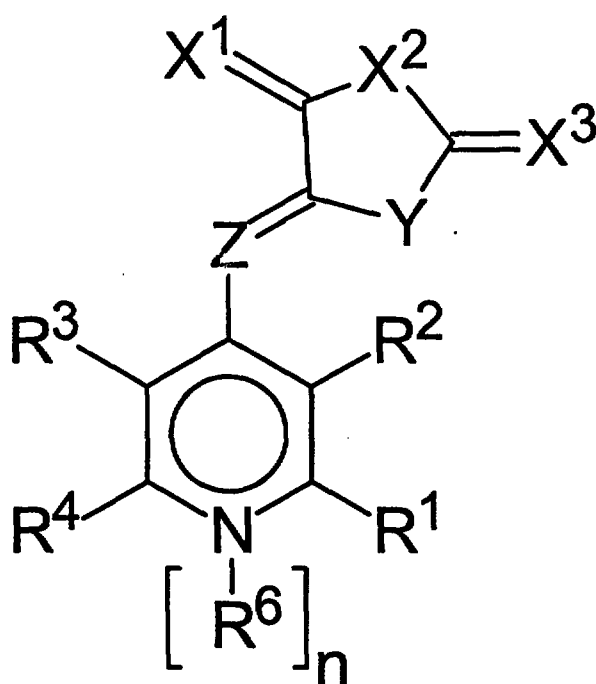
Furthermore, the concerning invention refers to compounds of the general formula (8).

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(8)

wherein:

X^1 , X^2 and X^3 are independently selected from O, S and NR^5 , respectively;

Y is O or S;

Z is CR^5 or N;

R^1 , R^2 , R^3 , R^4 and R^5 are independently selected from any substituents, respectively;

R^6 is selected from possibly substituted hydrocarbon derivatives and O, and n is 0 or 1;

also salts, e. g. salts with alkali metal, alkaline earth or ammonia ions, their hydrates and stereoisomers, with the condition that the compound is not pyridoxylidenerhodanine.

In the compounds of the general formula (8) X^1 is preferably O. X^2 is preferably NR^5 , wherein R^5 is hydrogen or C_1 - C_4 -alkyl and especially preferred hydrogen.

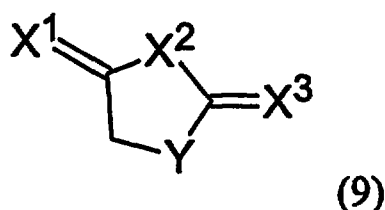
X^3 is preferably S. Y is preferably S. Z is preferably CR^5 , wherein R^5 is hydrogen or C_1 - C_4 -alkyl and especially preferred hydrogen.

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The substituents R^1 to R^4 in fact can be any substituents, if being compatible with the overall structure. If necessary, R^1 and R^2 or/and R^3 and R^4 can be bridged with each other. Examples for the substituents R^1 to R^4 are hydrogen, halogen, hydroxyl, amine and also, if necessary, substituted alkyl groups, e. g. C_1 - to C_6 -alkyl, aminoalkyl, hydroxyalkyl, alkoxy etc. Especially preferred at least one of the substituents R^1 to R^4 contains an under physiologic conditions negatively charged group, e. g. an acid group like phosphate, carboxylate, sulfonate etc.

Especially preferred the compounds of the general formula (8) represent the (Z)-5'-O-phosphonopyridoxylidenerhodanine (3), also its salts, hydrates and stereoisomers.

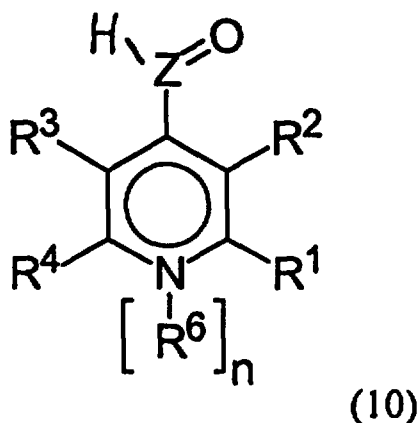
A further subject of the concerning invention is a process for the preparation of a compound of the general formula (8), characterized by the Knoevenagel condensation of a compound of the formula (9)



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with a compound of the formula (10)



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wherein X^1 , X^2 , X^3 , Y, Z, R^1 - R^5 and R^6 are defined as for the compounds 8. The reaction happens preferably in an essentially equimolar ratio of 9 to 10 in a suitable solvent or solvent mixture. The temperature is preferably room temperature to reflux temperature of the solvent.

The compounds of the general formula (8) surprisingly show pharmaceutical effects. So a further subject of the invention is a pharmaceutical composition containing as effective substance a compound as mentioned before (preferably without respect to the disclaimer in claim 1), and also, if necessary, pharmaceutically usual supplemental, supporting, carrier and diluting substances.

A first important application of the compounds according to the invention is the treatment of infective diseases, for example viral infections, parasitic diseases, fungal diseases or bacterial diseases. Especially preferred is the use for the treatment of viral infections, in particular of such viral infections which are caused by enveloped viruses like hepadnaviruses, herpesviruses or retroviruses e. g. HIV. Nevertheless, the compounds according to the invention proofed themselves suitable for the treatment of diseases which are caused by other viruses like influenza or papillomaviruses. Furthermore, the compounds according to the invention proofed themselves to be well suitable for the fighting of parasites like leishmania, plasmodia or trypanosoma. Mostly preferred are the compounds in the HIV therapy, for example in combination therapy with other drugs like AZT or DDI.

Furthermore, the compounds according to the invention are also suitable for the fighting of tumor diseases, for example leukemias, especially T cell leukemias, or of skin tumors like malignant melanoma or Kaposi's sarcoma. Surprisingly, they show a selective cytotoxic action against malignant cells, not against normal cells.

The compounds 8 also show immunomodulatory actions and, therefore, are suitable for the treatment of autoimmune diseases like multiple sclerosis, Alzheimer's disease, lupus

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erythematosus, myasthenia gravis, chronic arthritis, diabetes mellitus type I etc. and various neurodegenerative diseases.

Furthermore, the compounds 8 are suitable for the treatment of diseases connected with defects of vitamin B metabolism, e. g. as vitamin B6 antagonists.

A further use are diseases connected with defects of enzymatic reactions. The compounds according to the invention serve as effectors, e. g. activators, inhibitors or modifiers, on enzymatic reactions of the caspase system, and especially as inhibitors of nitric oxide synthases.

Furthermore, it was found that the compounds 8 influence the secretion of $\text{TNF}\alpha$ in T lymphocytes. In addition, they are able to bind to the cellular CD38 receptor, resulting in an inhibition of the binding of HIV gp41. In this way the signal transduction pathway of CD38 is decoupled, resulting in an inhibition of syncytia formation, of NO liberation, of T cell death by apoptosis, and of single cell lysis.

The compounds according to the invention can be as such used for therapeutical purposes. But they can be additionally used as chelates with polyvalent metal cations, or as non-covalent or/and covalent conjugates with biomolecules, e. g. nucleic acids, proteins, lipids, fatty acids etc.

The compounds according to the invention may be included in any form, e. g. as cream, ointment, injectable or orally applicable fluids, liposomal formulations, tablets, coated tablets, capsules etc. The application can be made e. g. locally or systemic, topic, orally or by injection. The dosage can be varied in wide ranges, e. g. 0.01 μg to 1 mg per kg body weight depending on the nature of the disease and application.

Furthermore, the compounds according to the invention are also suitable as analytical reagents. On the one hand they can be used in form of radioactive labelled derivatives, e. g. ^3H , ^{14}C , ^{32}P or ^{35}S . But preferred is the use in unlabelled form because its strong coloring and fluorescent

properties are enabling a simple detection in biological systems. Therefore, the compounds according to the invention are especially suitable for the detection of biomolecules, e. g. in diagnostic analysis, for example for the detection of single-stranded nucleic acids. In addition, the compounds are suitable for structure determination, e. g. for the sequencing of proteins or nucleic acids.

Furthermore, the compounds according to the invention can be used for electrochromic applications, e. g. as molecular digital switch substances or indicators for pH, temperature or solvents.

Furthermore, the compounds according to the invention and derivatives are suitable as absorber for ions, organic substances etc., or because of their intensive colors and reversible color changes for decorative purposes. Especially the alkaline earth salts, e. g. Mg- or Ca-salts of the compounds are to be noted appearing in the form of gels.

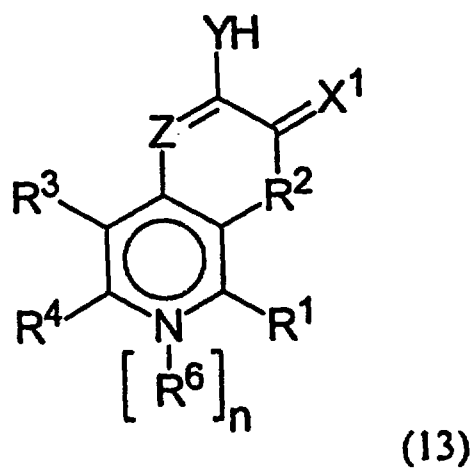
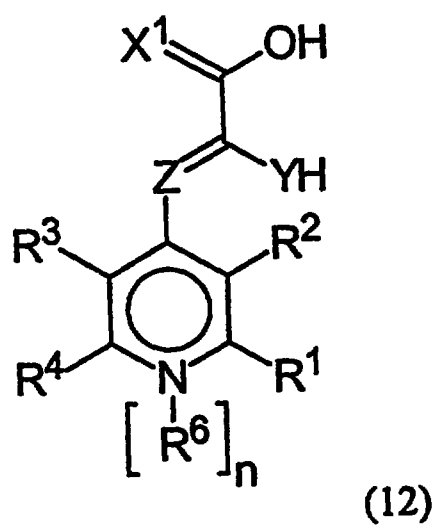
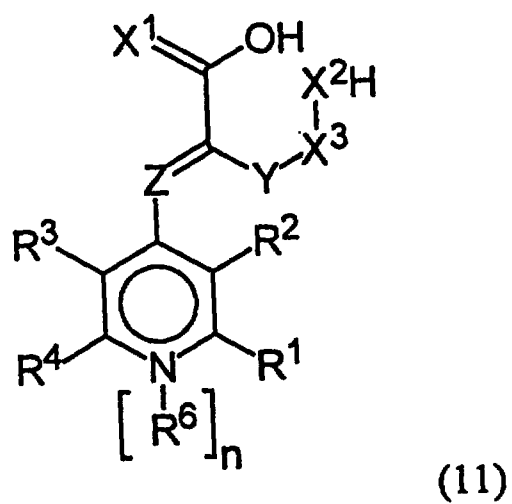
Also a further field of application is the nanotechnology. For example, laser system excited single fluorescent dye molecules and biomolecule derivatives can be detected and localized by sensitive detection systems, e.g. CCD cameras or avalanche detectors and optical techniques on thin layer plates, in membranes, cells, drops, capillares etc. Further possibilities of single molecule localization are the optical raster nearfield microscopy on minichips, the confocal microscopy in polyacrylamide gels, for example the two- or more-dimensional gel electrophoresis of nucleic acids.

Finally, the concerning invention refers to derivatives of compounds (8) which originate by hydrolytic degradation and represent for example the general formulas 11, 12 or 13:

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wherein X^1 , X^2 , X^3 , Y, Z, R^1 - R^5 and R^6 are defined as for the compounds 8.

Furthermore, the invention is explained by the following examples and figures. It shows:

Fig. 1: the by the compound (3) mediated protection of cells against a HIV-infection.

Fig. 2: an overall figure of hydrolytic side products which originate during synthesis of compound (3);

Examples

1. Preparation Method of 3

Preparation of the Crude Product:

3.83 g 2-thioxo-4-thiazolidinone (rhodanine) ($M = 133.18$ g/mol; $n = 28.76$ mmol) are dissolved in 150 ml of absolute ethanol in a 50 ml round bottomed flask with reflux condensor and 7.63 g of pyridoxal 5'-phosphate monohydrate ($M = 265.16$ g/mol; 28.78 mmol) are added. The pyridoxal 5'-phosphate monohydrate remains nearly undissolved in the cold.

It was refluxed under stirring on the water bath. The pyridoxal 5'-phosphate monohydrate dissolves now slowly and a firstly yellow, then orange, then red suspension emerges. After 20 min of refluxing through the condensor 150 ml of water are added because the suspension pushes up. It is still heated for 10 min and the red reaction product precipitates and pushes up. Then it is frozen for no more than 2 h at a temperature of -18°C .

Purification of the Crude Product

The orange product is filtered, collected with the mother liquor, and washed with 100 ml of icecold absolute ethanol. Vacuum drying in the desiccator over anhydrous calcium chloride;

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yield: 9.85 g orange-yellow crude product (Z)-5-[[5-Hydroxy-6-methyl-3-[(phosphonooxy)methyl]-4-pyridinyl]methylene]-2-thioxo-4-thiazolidinone. The product contains educts, side products and in spite of vacuum drying ethanol and water.

Purification of the Crude Product by Ion-Exchange-Repurification:

9.85 g crude product were suspended in 610 ml of water in a 2000 ml round bottomed flask. Under stirring 200 ml of an at room temperature (22°C) saturated solution [β (NaHCO_3) = 100 mg/ml] of anhydrous sodium bicarbonate [n (NaHCO_3) = 238.10 mmol] in several portions was added. This now red solution was titrated with 238.10 ml (238.10 mmol HCl) of a 1.0 M hydrochloric acid. The resulting mixture is stirred further for 15 min. At the end of the titration (pH 2) the color changed from red to yellow and the free acid 3 precipitated. It was collected in a filter flask and dried for 24 h at a pressure of 4 mbar and a temperature of 70°C. Then it was still dried at a pressure of 0.001 mbar in the oil pump vacuum at room temperature; yield: 8.70 g (83% for overall synthesis) yellow, amorphous powder (Z)-5-[[5-Hydroxy-6-methyl-3-[(phosphonooxy)methyl]-4-pyridinyl]methylene]-2-thioxo-4-thiazolidinone, content w > 96% (^1H -NMR).

The analytics of compound 3 includes ^1H NMR spectroscopy, ^{13}C NMR spectroscopy, ^{31}P NMR spectroscopy, RP18 HPLC, fast atom bombardment mass spectrometry (FAB MS), IR spectroscopy, UV spectrophotometry and fluorescence spectrophotometry. There follow typical analytical data of compound 3.

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$\text{C}_{11}\text{H}_{11}\text{N}_2\text{O}_6\text{P S}_2$, $M = 362.31$ g/mol.

mp 198–201°C (dec., uncorr.).

FAB MS (MH^+ calculated for m/z 362.99): m/z (rel.Int.) 363.0 (12.0%, MH^+), 227.4 (18.1%), 270.4 (8.7%), 171.2 (8.3%), 282.4 (7.1%), 267.1 (2.8%), 283.4 (2.1%), 265.1 (1.5%).

^1H NMR (TFA- d): δ 2.91 (s, 3 H, 2'-CH₃), 5.42 (d, $|^3J(^{31}\text{P}, ^1\text{H})| = 8.0$ Hz, 2 H, 5'-CH₂-OPO₃H₂), 7.76 (s, 1 H, 4'-CH), 8.47 (s, 1 H, 6-CH).

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^1H NMR (DMSO- d_6): δ 2.42 (s, 3 H, 2'-CH₃), 4.89 (d, $|^3J(^{31}\text{P}, ^1\text{H})| = 7.5\text{Hz}$, 2 H, 5'-CH₂-OPO₃H₂), 7.55 (s, 1 H, 4'-CH), 7.84 (s, 1 H, 6-CH).

^1H NMR (Pyridine- d_5): δ 2.72 (s, 3 H, 2'-CH₃), 5.62 (d, $|^3J(^{31}\text{P}, ^1\text{H})| = 8.0\text{Hz}$, 2 H, 5'-CH₂-OPO₃H₂), 8.36 (s, 1 H, 4'-CH), 8.53 (s, 1 H, 6-CH).

^{13}C NMR, proton-decoupled (TFA- d): δ 16.83 (s, 2'-CH₃), 65.75 (s, 5'-CH₂-OPO₃H₂), 121.04, 122.15 (2 s, C-4'), 133.34 (s, C-6), 136.85, 136.91 (2 s, $RR'\text{C-SR}''$), 138.54 (s, C-5), 142.05 (s, C-4), 147.64 (s, C-2), 153.03 (s, C-3), 171.93 (s, C=O), 193.39 (s, C=S). ^{31}P NMR (TFA- d): δ -4.24 (s, $R\text{-OPO}_3\text{H}_2$).

FT IR (KBr): 3430 (ν N—H, *m*), 1713 (ν C=O, *s*), 1213 (ν P=O in $R\text{-O(HO)PO}_2^-$, *s*), 1046 (ν C=S, in S-CS-N, *s*), 1024 (ν P=O in $R\text{-O(HO)PO}_2^-$, *s*).

UV/VIS (H₂O): λ_{max} , 1 = 232 nm [A (1%/1cm) = 373], λ_{max} , 2 = 308 nm [A (1%/1cm) = 271], λ_{max} , 3 = 353 nm [A (1%/1cm) = 413], λ_{max} , 4 = 454 nm [A (1%/1cm) = 227].

UV/VIS (MeOH): λ_{max} , 1 = 291 nm [A (1%/1cm) = 245], λ_{max} , 2 = 347 nm [A (1%/1cm) = 489].

UV/VIS (DMSO): λ_{max} = 518 nm [A (1%/1cm) = 98].

Fluorescence excitation (ex) and emission (em) spectra (DMSO): λ_{em} = 575 nm: λ_{ex} , max, 1 = 355 nm, λ_{ex} , max, 2 = 397 nm, λ_{ex} , max, 3 = 451 nm, λ_{ex} , max, 4 = 467 nm, λ_{ex} , max, 5 = 483 nm, λ_{ex} , max, 6 = 493 nm, λ_{ex} , max, 7 = 518 nm; λ_{ex} = 490 nm: λ_{em} , max = 575 nm.

Fluorescence excitation (ex) and emission (em) spectra (Pyridine): λ_{em} = 575 nm: λ_{ex} , max, 1 = 451 nm, λ_{ex} , max, 2 = 467 nm, λ_{ex} , max, 3 = 471 nm, λ_{ex} , max, 4 = 483 nm, λ_{ex} , max, 5 = 493 nm, λ_{ex} , max, 6 = 518 nm; λ_{ex} = 490 nm: λ_{em} , max = 575 nm.

2. Preparative Synthesis of 6

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2.1

A mass of 363 mg (Z)-5-[[5-Hydroxy-6-methyl-3-[(phosphonoxy)methyl]-4-pyridinyl]methylene]-2-thioxo-4-thiazolidinone (3) (1.0 mmol) was mixed with 20.0 ml of 0.10 M sodium hydroxide solution (2.00 mmol NaOH). After the mixing with 10.0 ml of absolute ethanol the mixture was frozen for 24 h at a temperature of -18°C. The fine crystalline needles were filtered;

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yield: 340 mg (63%) red (Z)-5-[[3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridinyl]methylene]-2-thioxo-4-thiazolidinone monosodium salt (8½) hydrate (6). Before elemental analysis this product was dried for two days at a pressure of 0.1 mbar and a temperature of 70°C; yield: deep red (Z)-5-[[5-Hydroxy-6-methyl-3-[(phosphonooxy)methyl]-4-pyridinyl]methylene]-2-thioxo-4-thiazolidinone monosodium salt-hemihydrate (2½) hydrate (6).

2.2

8.70 g dry compound 3 (24.00 mmol) were mixed with 240.00 ml of 0.10 M sodium hydroxide solution (24.00 mmol NaOH) and the addition of 124.00 ml of ethanol followed. The mixture was stored 24 h at a temperature of -18°C. The precipitated red crystals were filtered; yield: 7.55 g (73%) of compound 6.

mp 205–208°C (dec., uncorr.).

Anal. C₁₁ H₁₀ N₂ Na O₆ P S₂ x 2½ H₂O, M=429,33 g/mol; C 30.77% H 3.52% N 6.52%; found C 30.97% H 3.43% N 6.35%.

FT IR (KBr): 3277 (ν O—H, *m*, broad), 1700 (ν HN—C=O, *w*), 1229 (ν P=O in *R*-O(HO)PO₂⁻, *s*), 1198 (ν HN—C=S, *s*), 1090 (ν C=S, in S-CS-N, *s*), 973 (ν P—O—C in P-O-CH₂-aryl, 2).

3. Detection Method for Single-stranded Nucleic Acids

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The compounds 3 and 6 can be used in radioactive labelled form, e. g. labelled with ³H, ¹⁴C, ³²P or ³⁵S as probes for the detection of single-stranded nucleic acids.

The compounds 3/6 can be additionally used for the fluorescence detection of single-stranded DNA. The (E)-stereoisomer 4 shows fluorescence in DMSO, the (Z)-stereoisomer in water substantially less. In the case of binding of the (E)-stereoisomer 4 to single-stranded DNA fluorescence can be detected after the extraction with DMSO. The used excitation wavelength covers the range of 420 to 500 nm, the emission in DMSO or pyridine is found at 575 nm.

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The compounds 3, 4 and 6 show a non-covalent association to single-stranded DNA. This non-covalent binding can be fixated photochemically by irradiation with UV light of the wavelength 254 or/and 366 nm. There reacts 3 and 4 with a thymine nucleobase methyl group under splitting of H_2S .

4. Inhibition of Isoforms of the Enzyme Nitric Oxide Synthase

The substance 6 inhibits the neuronal, endothelial and immunologic/inducible isoforms of the nitric oxide synthase (NOS). The inhibition constant (IC_{50}) for nNOS is 61.25 μM . For eNOS and iNOS the inhibition constant (IC_{50}) is 50 μM . This values were obtained by measuring the transformation of (3H) arginine to (3H) citrulline with the use of recombinant human NOS isoforms from CHO cells.

5. Two-dimensional Nucleic Acid Electrophoresis

The substance 3 can be used in radioactively labelled or unlabelled form for two-dimensional electrophoretic separation of single-stranded nucleic acids. In the first dimension there can be a separation after charge and in the second dimension a separation after molecule size. The compound 3 can be coupled associative or covalent to the nucleic acid.

6. Therapeutical Use

The substance 3 and derivatives of it are effective as therapeutical agents, especially for influencing proliferative events of infectious agents, e. g. of such emerging in the host with intermediates of single-stranded DNA like retroviruses, herpesviruses or hepatoviruses.

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6.1 HIV-Inhibition

Myeloic HUT78 cells were exposed to an infection with HIV in absence or presence of 1.87 mM or 0.187 mM of compound 3. The HIV detection is made by photometric evaluation of p24 antigen. In Figure 1 is depicted that in the cells treated according to the invention no p24 was detectable, whereas the control from the 7th day shows a positive p24 test.

6.2 Treatment of Herpes

A patient (17, male) with herpes labialis was treated with an olive oil / water emulsion of the compound 3 (ca. 1 mg/ml). Few hours after local administration on the affected skin portions a total remission was found.

6.3 Treatment of Influenza

A patient (51, male) with viral influenza was treated orally with some drops of a H₂O/DMSO solution of the compound 3 (ca. 1 µg/ml). Over night the disease symptoms disappeared.

7. Temperature/Solvent Indicator

The (Z/E)-stereoisomerism of the compound 3 appears depending on temperature (thermochromism) and depending on solvent (solvatochromism). Therefore, 3 can be used as temperature indicator or/and solvent indicator.

8. Digital Switch Function

The (Z/E)-stereoisomerism of the compounds 3 and 4 appears depending on applying an electric field (electrochromism). Therefore, 3 can be used as digital switch element because of the different fluorescence spectroscopic properties against 4 e. g. on excitation with laser light of the

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wavelength 480 nm. Thereby, after applying an electric field on 3 rearrangement to 4 is performed, and it appears fluorescence emission at 575 nm after excitation at 480 nm.

9. Vitamin B6 Antagonism

The compound 3 is able to effect in metabolism as antagonist of the coenzyme pyridoxal 5'-phosphate by binding to enzymes depending on this coenzyme and, therefore, can show tumor suppressing properties.

10. Proliferation Control

The compound 3 can be used in proliferation control/chemotherapy/cytostasis therapy of malignant tumors in local application on skin tumors (malignant melanoma, Kaposi's sarcoma), if necessary, in connection with UV-irradiation, or/and for proliferation control of other skin diseases with increased cell division rate (e. g. psoriasis). The binding of compound 3 to replicatively active single-stranded DNA areas can be fixated photochemically and leads to locally restricted cytotoxicity.

11. Structure Determination

The compound 3 can be used because of its color and fluorescent properties and its ability to couple to biomolecules, e. g. proteins, for structure determination, e. g. for amino acid sequence determination of proteins or for DNA sequencing.

12. Detection of Hydrolysis Side Products

The hydrolysis side products which emerge during the synthesis of compound 3 are examined mass spectroscopically.

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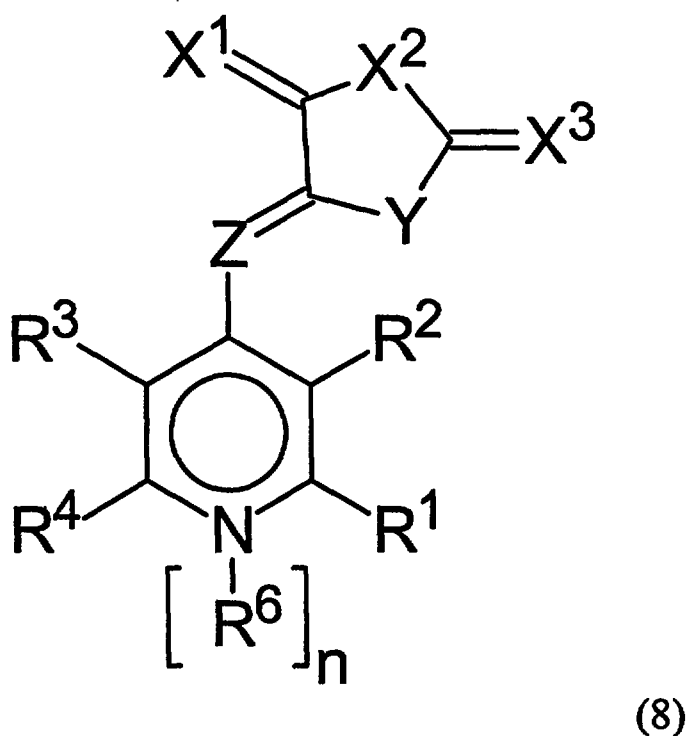


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The concerning compounds are listed in Fig. 2.

Claims

1. Compounds of the general formula (8)



wherein:

X^1 , X^2 and X^3 are independently selected from O, S and NR^5 , respectively;

Y is O or S;

Z is CR^5 or N;

R^1 , R^2 , R^3 , R^4 and R^5 are independently selected from any substituents, respectively;

R^6 is selected from possibly substituted hydrocarbon derivatives and O, and n is 0 or 1;

also salts, their hydrates and stereoisomers, with the condition that the compound is not pyridoxylidenerhodanine.

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2. Compounds according to claim 1,

wherein X^1 is O.



3. Compounds according to the claims 1 or 2,

wherein X^2 is NR^5 .

4. Compounds according to one of the previous claims,

wherein X^3 is S.

5. Compounds according to one of the previous claims,

wherein Y is S.

6. Compounds according to one of the previous claims,

wherein Z is CR^5 .

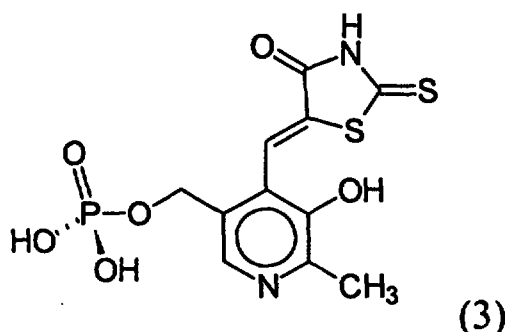
7. Compounds according to one of the previous claims,

wherein one of the substituents R^1 - R^4 contains a negatively charged group.

8. Compounds according to one of the previous claims,

choosed from (Z)-5-[[5-hydroxy-6-methyl-3-[(phosphonooxy)methyl]-4-pyridinyl]methylene]-2-thioxo-4-thiazolidinone of the formula (3)

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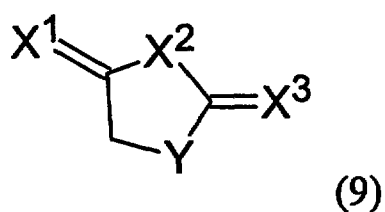


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and also salts, hydrates and stereoisomers of it.

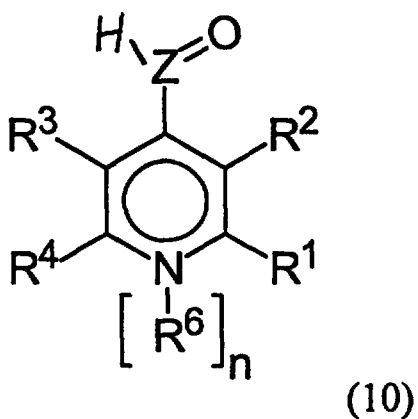
9. Processes for synthesis of a compound of the general formula (8),
characterized by

reacting a compound of the formula (9)



in a Knoevenagel condensation with a compound of the formula (10)

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wherein X^1 , X^2 , X^3 , Y , Z , R^1 - R^5 and R^6 are defined like in claim 1.

10. Processes for synthesis of a compound according to claim 8,
characterized by

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reacting pyridoxal 5'-phosphate in a Knoevenagel condensation with rhodanine.

11. Pharmaceutical composition,

characterized by

that it contains as effective agent a compound according to one of the claims 1 to 8, and also, if necessary, pharmaceutically usual supplemental, supporting, carrier and diluting substances.



12. Use of a compound according to one of the claims 1 to 8, for the preparation of a pharmaceutical composition for the treatment of infectious diseases, tumors and autoimmune diseases.

13. Use according to claim 12 for preparation of an anti-virus drug.

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14. Use according to claim 13 for the preparation of a drug for the treatment of viral infections caused by hepatoviruses, herpesviruses or retroviruses.

15. Use of a compound according to one of the claims 1 to 8, for the preparation of a pharmaceutical composition for the treatment of diseases which stand in connection with defects of the vitamin B metabolism.

16. Use of a compound according to one of the claims 1 to 8, for the preparation of a pharmaceutical composition for the treatment of diseases which stand in connection with defects of the immune system.

17. Use of a compound according to one of the claims 1 to 8, for the preparation of a pharmaceutical composition for the treatment of diseases which stand in connection with defects of enzymatic reactions.

18. Use according to claim 17 as effector of the enzymatic activity of nitric oxide synthases.

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19. Use of compounds according to one of the claims 1 to 8 as detecting agents.

20. Use according to claim 19 for the detection of biomolecules.

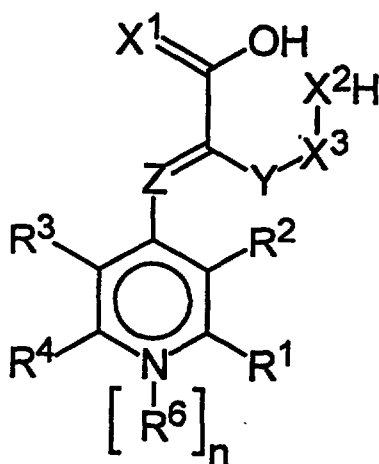


21. Use according to claim 20 for the detection of single-stranded nucleic acids.

22. Use of compounds according to one of the claims 1 to 8, for electrochromic applications.

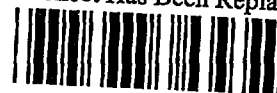
23. Conjugates of compounds according to one of the claims 1 to 8, with biomolecules.

24. Derivatives of compounds of the general formula (8) according to the general formulas (11), (12) or (13):

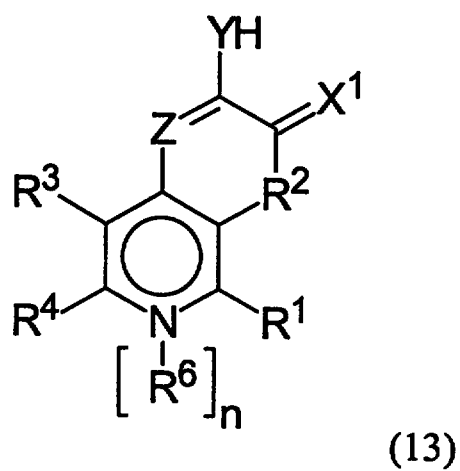
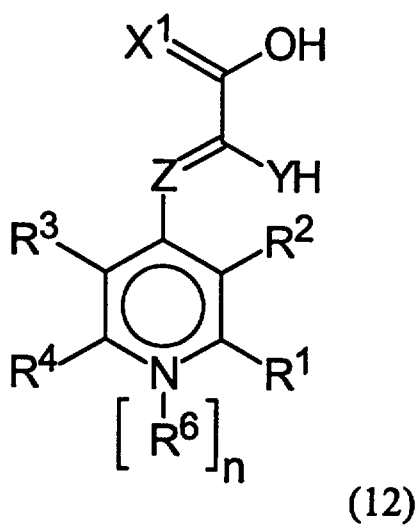


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wherein X^1 , X^2 , X^3 , Y, Z, R^1 - R^4 , R^5 and R^6 are defined as in claim 1.

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