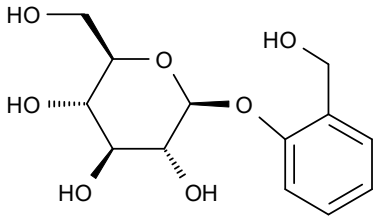
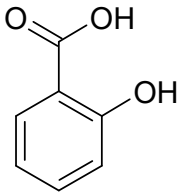
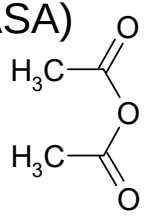
Drug patents and copying: generics versus biosimilars.
(How do patents and generics work)

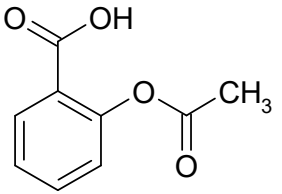
History of acetylsalicylic acid (ASA)



hydrolysis
oxidation







salicin
(2-hydroxymethylphenyl)-β-D-glucopyranoside

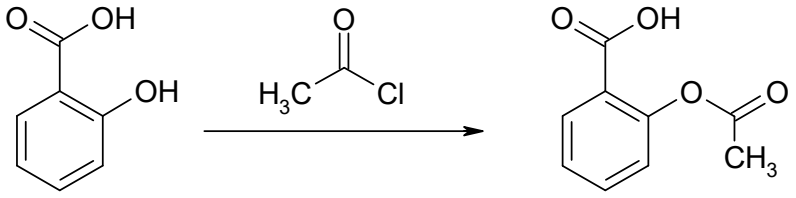
600 b.C. Hippocrates: chewig of willow bark
(*Cortex salicis - Salix sp.)*
1827 Leroux: isolation from willow bark

salicylic acid
2-hydroxybenzooic acid

1838 Piria: the first synthesis
Kolbe: efficient industrial synthesis
since 1878 used as antipyretic
and antirheumatic

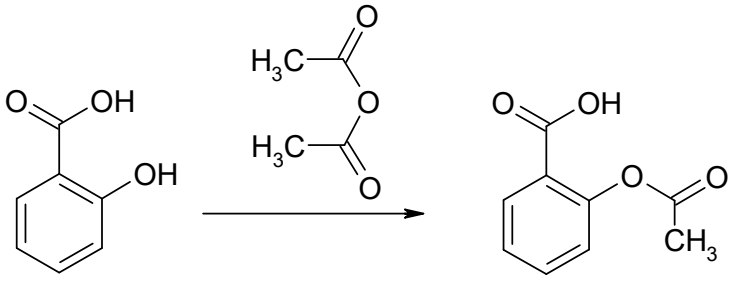
acetylsalicylic acid
2-acetoxybenzooic acid

1897 Felix Hoffmann - synthesis for industry
1899 - Aspirin(R) - Bayer



Gerhardt, Justus Liebigs Ann. Chem. **87**, 164 (1853)
Gilm, Justus Liebigs Ann. Chem. **112,** 181 (1859)
Kraut, Justus Liebigs Ann. Chem. **150**, 10 (1869)

is



Hoffmann

American version of Hoffmann´s patent

Felix Hoffmann

UNITED STATES PATENT OFFICE.

FELIX HOFFMANN, OF ELBERFELD, GERMANY, ASSIGNOR TO THE FARBENFABRIKEN OF ELBERFELD COMPANY, OF NEW YORK.

ACETYL SALICYLIC ACID.

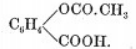
SPECIFICATION forming part of Letters Patent No. 644,077, dated February 27, 1900.

Application filed August 1, 1898. Serial No. 687,385. (Specimens.)

To all whom it may concern:

Be it known that I, FELIX HOFFMANN, doctor of philosophy, chemist, (assignor to the FARBENFABRIKEN OF ELBERFELD COMPANY, of New York,) residing at Elberfeld, Germany, have invented a new and useful Improvement in the Manufacture or Production of Acetyl Salicylic Acid; and I hereby declare the following to be a clear and exact description of my invention.

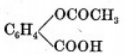
In the *Annalen der Chemie und Pharmacie*, Vol. 150, pages 11 and 12, Kraut has described that he obtained by the action of acetyl chlorid on salicylic acid a body which he thought to be acetyl salicylic acid. I have now found that on heating salicylic acid with acetic anhydride a body is obtained the properties of which are perfectly different from those of the body described by Kraut. According to my researches the body obtained by means of my new process is undoubtedly the real acetyl salicylic acid



Therefore the compound described by Kraut cannot be the real acetyl salicylic acid, but is another compound. In the following I point out specifically the principal differences between my new compound and the body described by Kraut.

If the Kraut product is boiled even for a long while with water, (according to Kraut's statement,) acetic acid is not produced, while my new body when boiled with water is readily split up, acetic and salicylic acid being produced. The watery solution of the Kraut body shows the same behavior on the addition of a small quantity of ferric chlorid as a watery solution of salicylic acid when mixed with a small quantity of ferric chlorid—that is to say, it assumes a violet color. On the contrary, a watery solution of my new body when mixed with ferric chlorid does not assume a violet color. If a melted test portion of the Kraut body is allowed to cool, it begins to solidify (according to Kraut's statement) at from 118° to 118.5° centigrade, while a melted test portion of my product solidifies at about 70° centigrade. The melting-points of the two compounds cannot be compared, because Kraut does not give the melting-point of his compound. It follows from these details that the two compounds are absolutely different.

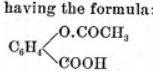
In producing my new compound I can proceed as follows, (without limiting myself to the particulars given:) A mixture prepared from fifty parts of salicylic acid and seventy-five parts of acetic anhydride is heated for about two hours at about 150° centigrade in a vessel provided with a reflux condenser. Thus a clear liquid is obtained, from which on cooling a crystalline mass is separated, which is the acetyl salicylic acid. It is freed from the acetic anhydride by pressing and then recrystallized from dry chloroform. The acid is thus obtained in the shape of glittering white needles melting at about 135° centigrade, which are easily soluble in benzene, alcohol, glacial acetic acid, and chloroform, but difficultly soluble in cold water. It has the formula



and exhibits therapeutical properties.

Having now described my invention and in what manner the same is to be performed, what I claim as new, and desire to secure by Letters Patent, is—

As a new article of manufacture the acetyl salicylic acid having the formula:



being when crystallized from dry chloroform in the shape of white glittering needles, easily soluble in benzene, alcohol and glacial acetic acid, difficultly soluble in cold water, being split by hot water into acetic acid and salicylic acid, melting at about 135° centigrade, substantially as hereinbefore described.

In testimony whereof I have signed my name in the presence of two subscribing witnesses.

FELIX HOFFMANN.

Witnesses:
R. E. JAHN,
OTTO KÖNIG.

What is possible to patent in medicines?

1) The chemical structure (or composition) of the active substance (or a group of chemically related substances).
   - a different activity of individual optical isomers of a chiral drug
   - polymorphs, i.e. different crystal modifications of the substance with possible different bioavailability
2) The procedure how the active substance is prepared (synthesis...)
3) The composition of the application form (tablet, injection…)
4) Indication(s) (= which disease(s) is/are intended to be treated with this medicine)

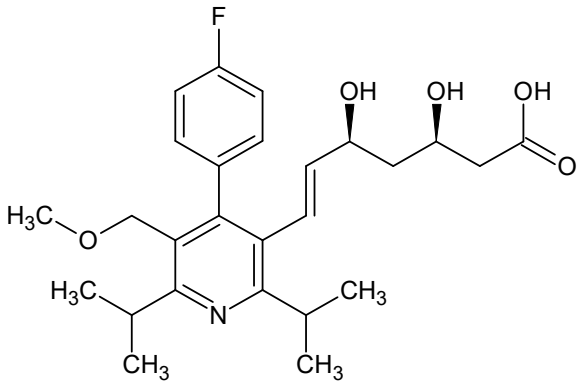
The maximum length of patent protection is 20 years. After this, it is possible to produce generics.

- promising compounds are often patented just as soon as the activity is detected by pre-clinical tests to avoid stealing them by concurrent companies, and protection period starts to run, although it takes several other years to develop the compound into a medicine capable to be used in therapy $\Rightarrow$ increase of the price of the original medicine
- generics can then be significantly cheaper

A patent example: antihypercholesterolemics

(1st page shown; the whole patent has 62 pages)

- the patent covers many compounds; among them



cerivastatin, Lipobay®

- tested and shortly used for hypercholesterolemia; withdrawn for lethal rhabdomyolysis

United States Patent [19]

Angerbauer et al.

[11] **Patent Number: 5,006,530**

[45] **Date of Patent: Apr. 9, 1991**

[54] **CERTAIN 7-[2,6-DIISOPROPYL-4-PHENYL-5-LOWER ALKOXYMETHYL-PYRID-3-YL]-3,5-DIHYDROXY-6-ENOATES AND DERIVATIVES USEFUL FOR TREATING CIRCULATORY DISEASES**

[75] Inventors: **Rolf Angerbauer; Peter Fey; Walter Hübsch,** all of Wuppertal; **Thomas Philipps,** Cologne; **Hilmar Bischoff,** Wuppertal; **Dieter Petzinna,** Duesseldorf; **Delf Schmidt,** Wuppertal, all of Fed. Rep. of Germany; **Günter Thomas,** Arese, Italy

[73] Assignee: **Bayer Aktiengesellschaft,** Leverkusen, Fed. Rep. of Germany

[21] Appl. No.: **298,549**

[22] Filed: **Jan. 17, 1989**

[30] **Foreign Application Priority Data**

Jan. 20, 1988 [DE] Fed. Rep. of Germany 3801406
Jul. 11, 1988 [IT] Italy 21317 A/88

[51] **Int. Cl.**[5] **C07F 7/02;** C07D 213/55; A61K 31/44

[52] **U.S. Cl.** **514/277;** 546/14; 546/268; 546/342

[58] **Field of Search** 546/318, 14, 342; 514/356, 277

[56] **References Cited**

U.S. PATENT DOCUMENTS

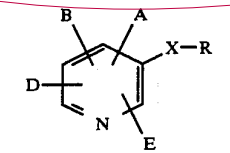
4,923,884 5/1990 Chandraratna 514/354

Primary Examiner—Alan L. Rotman

Attorney, Agent, or Firm—Sprung Horn Kramer & Woods

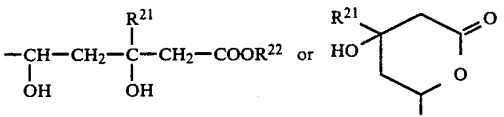
[57] **ABSTRACT**

Novel compounds for treating hyperproteinaemia, lipoproteinaemia or arteriosclerosis of the formula



(I)

in which
A, B, D and E can have varied meanings,
X is —CH_2—CH_2 or —CH=CH—, and
R is



wherein
R^{21} denotes hydrogen or alkyl and
R^{22}
denotes hydrogen,
denotes alkyl, aryl or aralkyl, or
denotes a cation,
and their oxidation products.

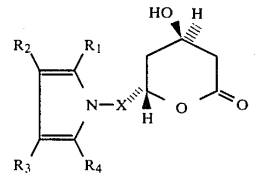
19 Claims, No Drawings

A patent example: antihypercholesterolemics

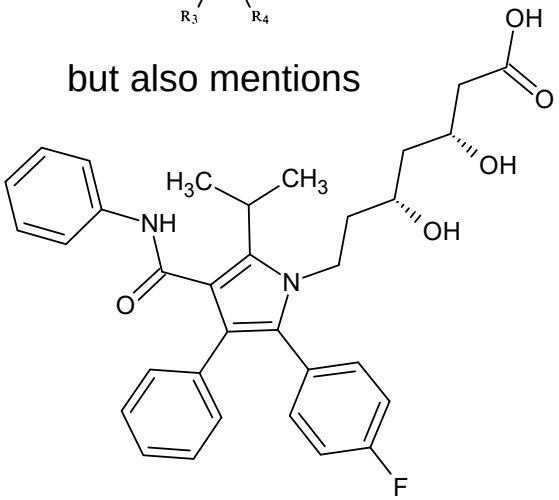
(1st page shown; the whole patent has 20 pages)

- the patent covers many compounds of the general formula

16



but also mentions



atorvastatin, originally intended rather as an open analogue a title compounds

United States Patent [19]

Roth

[11] **Patent Number: 4,681,893**

[45] **Date of Patent: Jul. 21, 1987**

[54] **TRANS-6-[2-(3- OR 4-CARBOXAMIDO-SUBSTITUTED PYRROL-1-YL)ALKYL]-4-HYDROXYPYRAN-2-ONE INHIBITORS OF CHOLESTEROL SYNTHESIS**

[75] Inventor: **Bruce D. Roth**, Ann Arbor, Mich.

[73] Assignee: **Warner-Lambert Company**, Morris Plains, N.J.

[21] Appl. No.: **868,867**

[22] Filed: **May 30, 1986**

[51] **Int. Cl.**[4] **A61K 31/40**; A61K 31/35; C07D 207/327

[52] **U.S. Cl.** **514/422**; 514/423; 546/256; 546/275; 548/517; 548/537

[58] **Field of Search** 548/517, 537; 514/422, 514/423

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,983,140	9/1976	Endo et al.	549/292
4,049,495	9/1977	Endo et al.	435/125
4,137,322	1/1979	Endo et al.	548/344 X
4,198,425	4/1980	Mitsui et al.	514/460
4,255,444	3/1981	Oka et al.	549/292 X
4,262,013	4/1981	Mitsui et al.	549/292 X
4,375,475	3/1983	Willard et al.	514/460

OTHER PUBLICATIONS

Singer, et al.; Proc. Soc. Exper. Biol. Med.; vol. 102, pp. 370–373, (1959).

Hulcher; Arch. Biochem. Biophys., vol. 146, pp. 422–427, (1971).

Brown, et al.; New England Jour. of Med., vol. 305, No. 9, pp. 515–517, (1981).

Brown, et al.; J. Chem. Soc. Perkin I, (1976), pp. 1165–1170.

Journal of the Americas Medical Assoc.; (1984), vol. 251, pp. 351–364, 365–374.

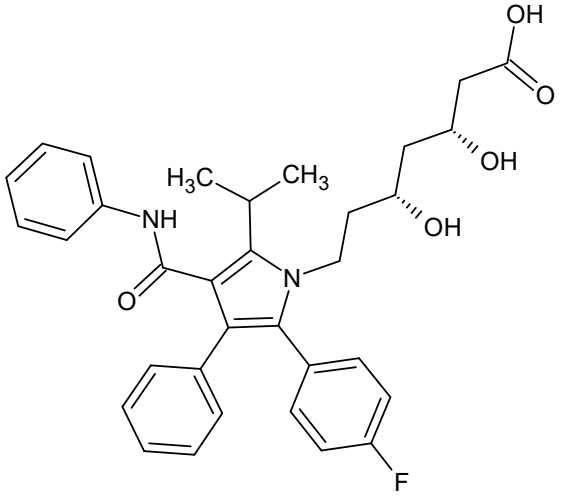
Primary Examiner—Joseph Paul Brust

Attorney, Agent, or Firm—Jerry F. Janssen

[57] **ABSTRACT**

Certain trans-6-[2-(3- or 4-carboxamido-substituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones and the corresponding ring-opened acids derived therefrom which are potent inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA reductase and are thus useful hypolipidemic or hypocholesterolemic agents. Pharmaceutical compositions containing such compounds, and a method of inhibiting the biosynthesis of cholesterol employing such pharmaceutical compositions are also disclosed.

9 Claims, No Drawings



atorvastatin [INN]; a HMG-CoA-reductase inhibitor, antihyperlipidemic
Lipitor®: original
17 generics currently approved and traded in ČR: Amedo, Amlator, Atoris, Atorstad, Atorvastatin Aurovitas, Atorvastatin Krka, Atorvastatin Mylan, Atorvastatin Ratiopharm GMBH, Caduet, Euvascor, Lipertance, Sortis, Torvacard Neo, Torvazin, Tulip, Zetovar, Zoletorv

EXAMPLE 2

Preparation of R*,R*-2-(4-fluoro-phenyl-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, sodium salt

A mixture of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (10 g, 18.5 mmol) and 0.74 g (18.5 mmol) of sodium hydroxide in 90 ml of a 1:2 mixture of tetrahydrofuran-water was cooled to 0° C. This mixture was allowed to warm slowly to 25° C., after which time it was concentrated and the residual solid dried under vacuum.

The infrared spectrum of the product exhibited principal absorption peaks at 3400, 1651, 1598, 1565, 1511, 1438, 1412, 1316, 1224, 1159, 844, 754, and 702 reciprocal centimeters.

The 90 MHz proton magnetic resonance spectrum of a hexadeutero dimethylsulfoxide solution of the product exhibited signals at 1.34 (doublet, J=7 Hz, 6H); 1.5 (multiplet, 4H); 1.80 (doublet of doublets, J=15, 8 Hz, 1H); 1.99 (doublet of doublets, J=15, 4 Hz, 1H); 3–4 (multiplet, 8H); 6.9–7.3 (multiplet, 12H); 7.50 (doublet, J=8 Hz, 2H); and 9.85 (singlet, 1H) parts per million downfield from tetramethylsilane.

A patent with atorvastatine polymorphs

US005969156A

United States Patent [19]

Briggs et al.

[11] **Patent Number: 5,969,156**

[45] **Date of Patent: *Oct. 19, 1999**

[54] **CRYSTALLINE [R- (R*,R*)]-2-(4-DFLUOROPHENYL)-β,δ-DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID HEMI CALCIUM SALT (ATORVASTATIN)**

[75] Inventors: **Christopher A. Briggs**; **Rex A. Jennings**; **Robert Wade**, all of Holland, Mich.; **Kikuko Harasawa**, Sagamihara, Japan; **Shigeru Ichikawa**, Machida, Japan; **Kazuo Minohara**; **Shinsuke Nakagawa**, both of Sagamihara, Japan

[73] Assignee: **Warner-Lambert Company**, Morris Plains, N.J.

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: **08/945,812**

[22] PCT Filed: **Jul. 8, 1996**

[86] PCT No.: **PCT/US96/11368**

§ 371 Date: **Oct. 2, 1997**

§ 102(e) Date: **Oct. 2, 1997**

[87] PCT Pub. No.: **WO97/03959**

PCT Pub. Date: **Feb. 6, 1997**

Related U.S. Application Data

[60] Provisional application No. 60/001,452, Jul. 17, 1995.

[51] **Int. Cl.**[6] **C07D 207/335**; A01N 43/36

[52] **U.S. Cl.** **548/537**; 514/423; 514/429

[58] **Field of Search** 548/537; 514/423, 514/429

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,316,765 5/1994 Folkers et al. 424/94.1

FOREIGN PATENT DOCUMENTS

0409281 7/1990 European Pat. Off. .
9416693 8/1995 WIPO .

OTHER PUBLICATIONS

Bocan, Thomas et al., Antiaherosclerotic activity of inhibitors of 3–hydroxy–3–methylgutaryl coenzyme A reductase, Atherosclerosis, 111, 127–142, Dec. 1994.

Tetrahedron Letters, vol. 33, No. 17, 1992, pp. 2283–2284, Baumann, et al.

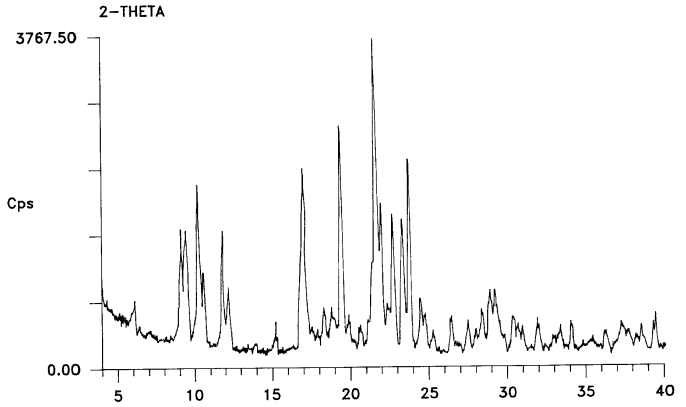
Pharmaceutical Research, vol. 10, No. 10, 1993, pp. 1461–1465, Kearney, et al.

Primary Examiner—Robert W. Ramsuer
Assistant Examiner—Dominic Keating
Attorney, Agent, or Firm—Francis J. Tinney

[57] **ABSTRACT**

Crystalline forms of atorvastatin and hydrates thereof are useful hypolipidemic and hypocholesterolemic agents.

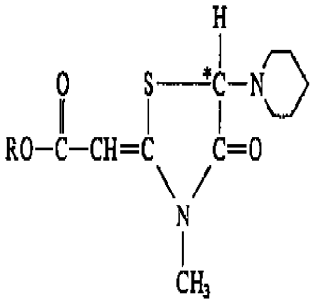
44 Claims, 6 Drawing Sheets



A patent devoted to diuretics and antihypertensives such as etozoline

Patentansprüche:

1. Rechtsdrehende Isomere von (3-Methyl-4-oxo-5-piperidino-thiazolidin-2-yliden)-essigsäureestern der allgemeinen Formel I



(I)

(19) BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENTAMT

(12) **Patentschrift**

(11) **DE 29 11 296 C 2**

(51) Int. Cl.³:
C 07 D 417/04
A 61 K 31/445

(21) Aktenzeichen: P 29 11 296.7-44
(22) Anmeldetag: 22. 3. 79
(43) Offenlegungstag: —
(44) Bekanntmachungstag: 24. 7. 80
(45) Veröffentlichungstag: 30. 7. 81

DE 29 11 296 C 2

(73) Patentinhaber:
Gödecke AG, 1000 Berlin, DE

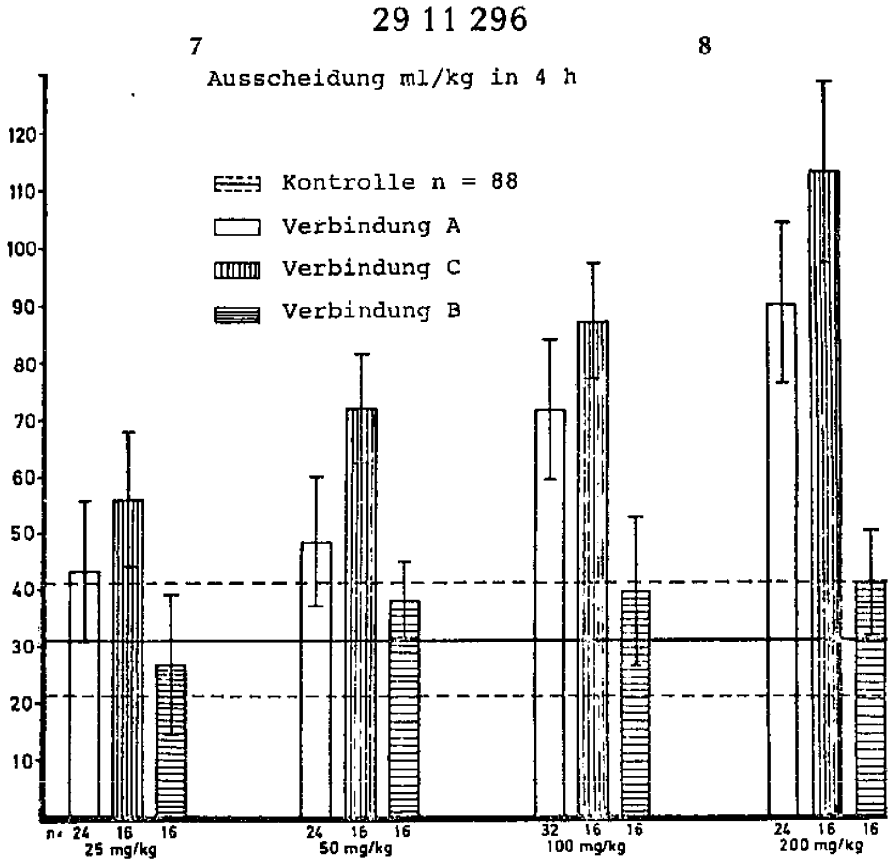
(61) Zusatz in: P 29 52 704.6
P 29 53 604.7

(72) Erfinder:
Herrmann, Dipl.-Chem. Dr., Wolfgang, 7802 Merzhausen, DE; Satzinger, Dipl.-Chem. Dr., Gerhard, 7809 Denzlingen, DE; Herrmann, Manfred, Dr., 7811 St. Peter, DE; Steinbrecher, Wolfgang, Dr., 7803 Gundelfingen, DE; Bahrmann, Heinrich, Dr., 7815 Kirchzarten, DE

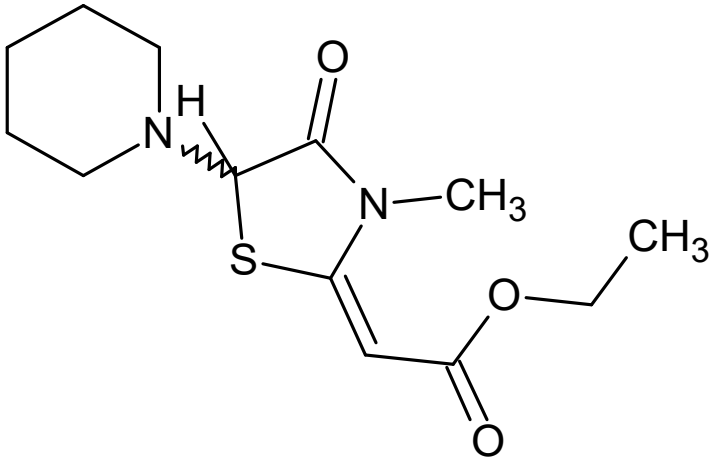
(56) Entgegenhaltungen:
NICHTS ERMITTELT

(54) **(+)-(3-Methyl-4-oxo-5- piperidinothiazolidin-2-yliden)-essigsäureester, Verfahren zu deren Herstellung und deren Verwendung bei der Bekämpfung der Hypertonie**

Diuretic effects of etozoline enantiomers in rats



Diurese an wachen Ratten bei intragastraler Verabreichung



A - (±)-(*R,S*) **etozoline**
B - (+)-(*S*) **dexetozoline**
C - (-)-(*R*)

Generics and biosimilars

Generics: small molecules – contain the same active compound as the original and reach 80 – 105 % of the bioavailability of the original

- bioavailability: % of administerd dose that absorbs into blood circulation (eg. from GIT)

„Biosimilars“ (EMA) = „follow-on proteins“ = „similar biotherapeutic products (WHO) = „similar biologics“ (India) etc. - contain the biologic drug prepared by the similar way and with the chemico-physical and analytical characteristics closely similar to the original (= „originator product“ or „innovator product“) but the same activity must be clinically demonstrated at least in its main indication

- also biosimilars can be manufactured when the original product´s patent expires

Committee for Medicinal Products for Human Use (CHMP) Guideline on Similar Biological Medicinal Products

(CHMP/437/04)

"It should be recognised that, **by definition, similar biological medicinal products are not generic medicinal products**, since it could be expected that there may be **subtle differences** between similar biological medicinal products from different manufacturers or compared with reference products, which **may not be fully apparent until greater experience in their use has been established**. Therefore, in order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified."

Biologics or biological drugs

•officially (WHO) „biological and biotechnological substances“

Main features of biologics

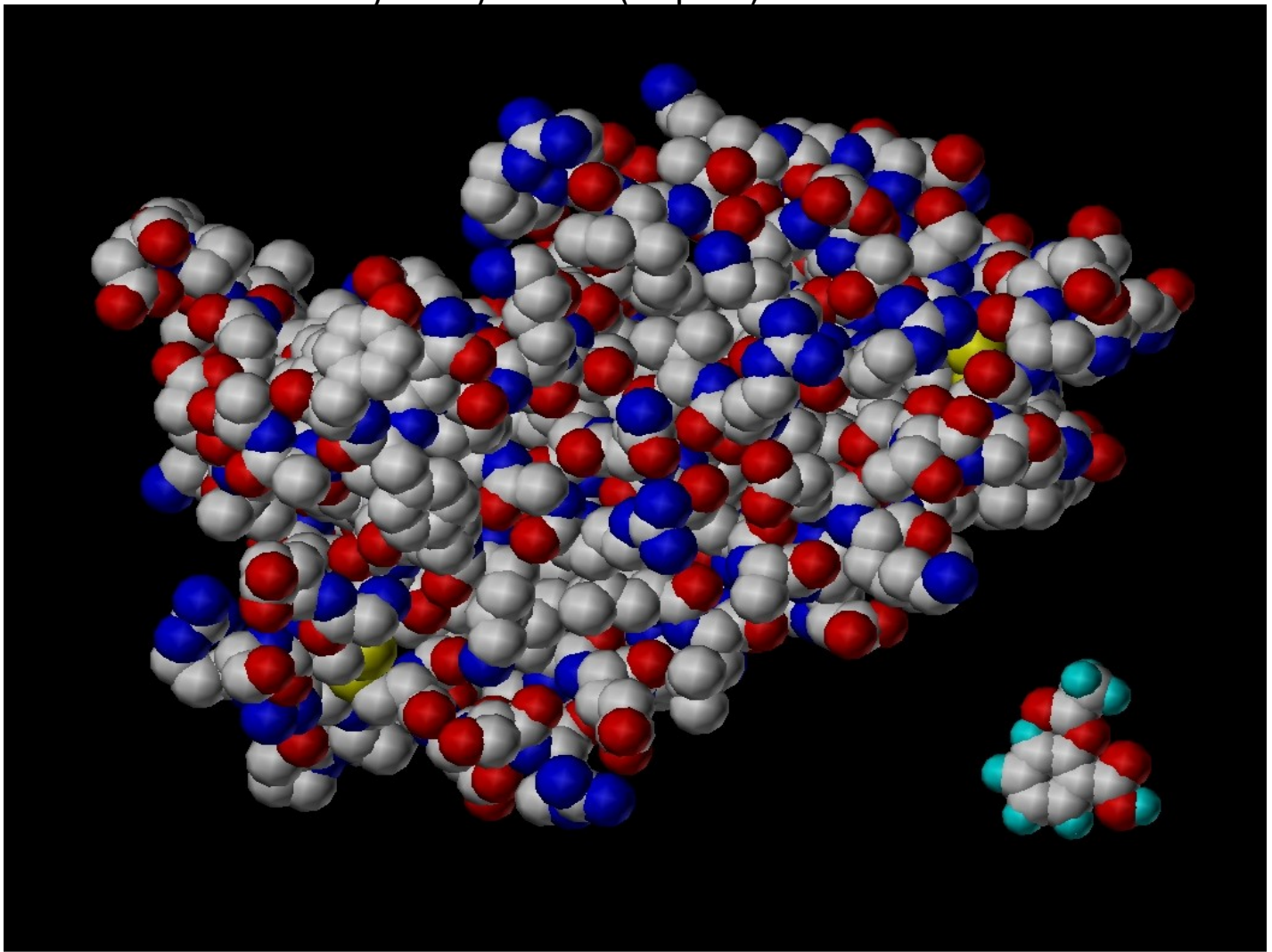
•typically obtained by other way than by classical chemical synthesis (semisynthetic modifications are possible)

•typically M_r > 1000 (up to 1000 „small molecules“) - greater, more complex, usually exhibit a *primary structure* (a sequence of amino acids or nucleotides), a *secondary structure* (α-helix, “folded sheet”, influence of -S-S- bridges), a *tertiary structure* (general space arrangement of a monomeric molecule), and a *quraternary structure* (grouping of monomers); many proteins are glycosylated

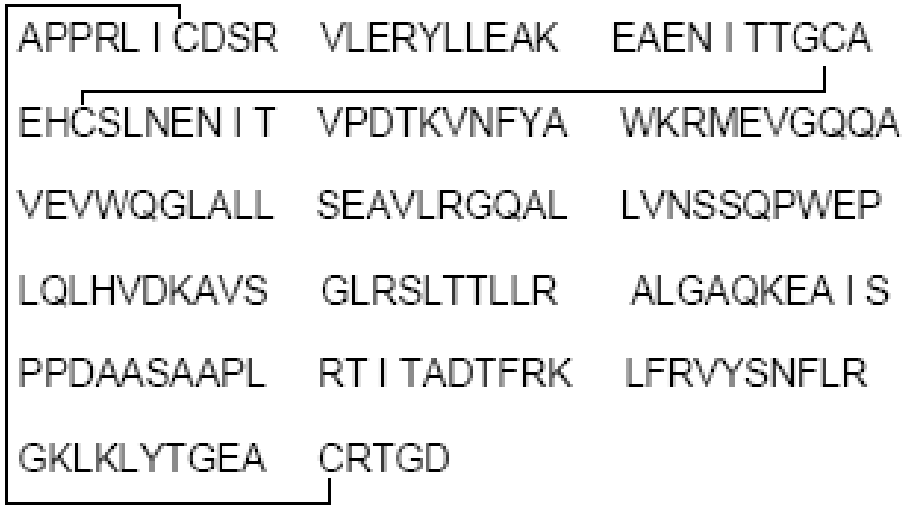
• due to their hydrophilicity and big M_r they cannot be absorbed from GIT and thus they must be administered parenterally (injections, infusions)

•but all the above conditions don´t have to be necessarily fulfilled for classification of a drug as biologic

An illustration of the difference between a biologic and a “small molecule”: erythropoietin and acetylsalicylic acid (Aspirin)



Blood factors of erythropoetine type



European pharmacopoeia, 10th edition

M_r about 30 600

erythropoietin (EPO)
= glycosylated protein from 165 AA
Erythropoietini solutio concentrata EP M_r asi 30 600 CAS 113427-24-0
= a solution containing a group of closely related glycoproteins, which are not to distinguish from the natural human erythopoietin (human urine erythropoietin, huEPO), from the point of view of 165 amino acids sequence and their average profile of glycosylation

- naturally released from kidneys of adults and in liver of foetus
- stimulates stem cells of bone marrow to proliferation and differentiation
- produced *in vitro* mostly in rodent cell lines by a method based on the recombinant DNA
- technology
- **INN names: epoetin + greek letter spelt in full** (eg. epoetin beta)
- various epoetins differ in glycosylation, complex branched oligomeric sugar chains are attached
- treatment of anaemia in chronic kidney failure, missused for doping in sports

Epoetin Alfa
(Genetical Recombination)

エポエチン　アルファ（遺伝子組換え）

Protein moiety

APPRLICDSR VLERYLLEAK EAENITTGCA EHCSLNENIT VPDTKVNFYA

WKRMEVGQQA VEVWQGLALL SEAVLRGQAL LVNSSQPWEP LQLHVDKAVS

GLRSLTTLLR ALGAQKEAIS PPDAASAAPL RTITADTFRK LFRVYSNFLR

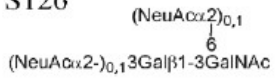
GKLKLYTGEA CRTGD

N24, N38, N83 and S126 : glycosylation

Carbohydrate moiety (structure of major glycans)

N24, N38 and N83

S126



$C_{809}H_{1301}N_{229}O_{240}S_5$: 18235.70 (Protein moiety)
[*113427-24-0*]

Epoetin Beta
(Genetical Recombination)

エポエチン　ベータ（遺伝子組換え）

Protein moiety

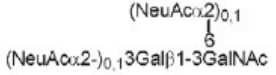
APPRLICDSR VLERYLLEAK EAENITTGCA EHCSLNENIT VPDTKVNFYA
WKRMEVGQQA VEVWQGLALL SEAVLRGQAL LVNSSQPWEP LQLHVDKAVS
GLRSLTTLLR ALGAQKEAIS PPDAASAAPL RTITADTFRK LFRVYSNFLR
GKLKLYTGEA CRTGD

N24, N38, N83 and S126: glycosylation

Carbohydrate moiety (structure of major glycans)

N24, N38 and N83

S126



$C_{809}H_{1301}N_{229}O_{240}S_5$: 18235.70 (Protein moiety)
[*122312-54-3*]

Overwiew of epoetins

INN name: epoetin	Year of discovery/approval	Production organism / tissue	Mr CAS	Glycosylation pattern	Originator product/biosimilar	Brand names ®, generic codes
alfa	2000	Chinese hamster ovary	113427-24-0	similar to uhEPO	orig/biosim	**Eprex**, Binocrit, Abseamed, Epoetin alfa Hexal
beta	1997	Chinese hamster ovary	122312-54-3		orig	Neorecormon
gama	1990	C127 murine cells transfected with huEPO cRNA	28 000-31 000 130455-76-4		orig	TYB-5220
delta	2002 - 2009	human fibrosarcoma cell line HT-1080	261356-80-3	less O-acetyls in O-glycan chains; similar to uhEPO	orig	Dynepo
epsilon	1995		154725-65-2		orig	
zeta	2007	Chinese hamster ovary	32 000-40 000 604802-70-2		biosim. of EPO alfa	Silapo, Retacrit
theta	2009	Chinese hamster ovary	762263-14-9	sugars represent 40 % of total Mr	orig	Biopoin, Eporatio
kappa	2010	Chinese hamster ovary	11096-26-7		biosim. of EPO alfa	Epoetin alfa BS injection ®
omega	1986	BHK-21 cells of Chinese hamster kidney	148363-16-0	greater sialylation of tetraantenary *N*-linked chains	orig	Epomax, Hemax

Remarks to biosimilars in epoetins

- epoetin alfa: **Eprex (originator)**, Binocrit, Abseamed (biosimilars)

⇒ epoetin kappa: Epoetin alfa BS injection ®

⇒epoetin theta: Biopoin ®, Eporatio ®

  - all above biosimilars are biosimilars of epoetin alfa, but they have been found to be so different from the original, that WHO nomenclature commission has given them other INNs

International patent application for 1st recombinant EPO production
(whole application has 76 pages)

- later named “epoetin omega”: Epomax®, Hemax®

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : C12P 21/00 — A1

(11) International Publication Number: WO 86/ 03520

(43) International Publication Date: 19 June 1986 (19.06.86)

(21) International Application Number: PCT/US85/02405

(22) International Filing Date: 3 December 1985 (03.12.85)

(31) Priority Application Numbers: 677,813; 688,622; 693,258

(32) Priority Dates: 4 December 1984 (04.12.84); 3 January 1985 (03.01.85); 22 January 1985 (22.01.85)

(33) Priority Country: US

(60) Parent Applications or Grants
(63) Related by Continuation
US 677,813 (CIP) Filed on 4 December 1984 (04.12.84)
US 688,622 (CIP) Filed on 3 January 1985 (03.01.85)
US 693,258 (CIP) Filed on 22 January 1985 (22.01.85)

(71) Applicant *(for all designated States except US)*: GENETICS INSTITUTE, INC. [US/US]; 87 CambridgePark Drive, Cambridge, MA 02140 (US).

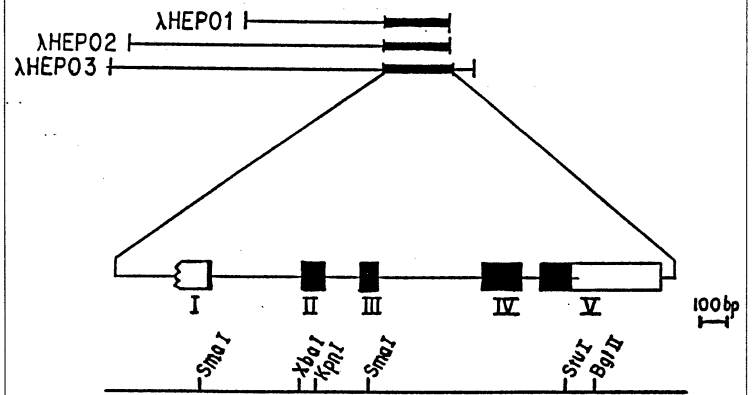
(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : FRITSCH, Edward [US/US]; 115 North Brand Road, Concord, MA 01742 (US). HEWICK, Rodney, M. [GB/US]; 16 Woodcliffe Road, Lexington, MA 02173 (US). JACOBS, Kenneth [US/US]; 151 Beaumont Ave., Newton, MA 02160 (US).

(74) Agent: BERSTEIN, David, L.; Genetics Institute, Inc., 87 CambridgePark Drive, Cambridge, MA 02140 (US).

(81) Designated States: AT (European patent), AU, BB, BE (European patent), BG, BR, CF (OAPI patent), CG (OAPI patent), CH (European patent), CM (OAPI patent), DE (European patent), DK, FI, FR (European patent), GA (OAPI patent), GB (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL (European patent), NO, RO, SD, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US, US, US.

Published
With international search report.
With amended claims.

(54) Title: METHOD FOR THE PRODUCTION OF ERYTHROPOIETIN

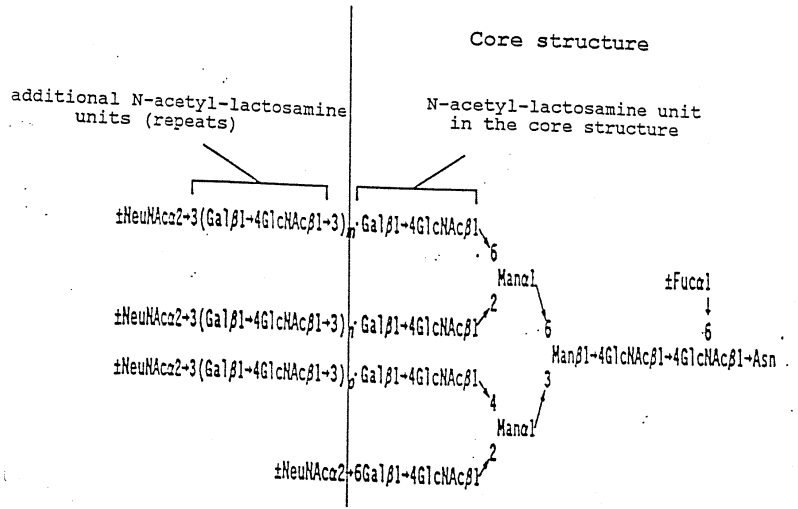


(57) Abstract

Cloned genes for human erythropoietin (EPO) obtained from human fetal liver that provide surprisingly high levels of expression. Also described is the expression of said genes *in vitro* to produce active human EPO.

A South African patent for an early epoetin

Figure 1: Tetraantennary N-linked carbohydrate structure with additional N-acetyl-lactosamine units (repeats) and sialic acids



REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978
PUBLICATION PARTICULARS AND ABSTRACT
[Section 32 (3) (a) - Regulations 22 (1) (g) and 31]

OFFICIAL APPLICATION NO.	LODGING DATE	ACCEPTANCE DATE
21 01 98/11003	22 02/12/98	43 2-6-2000

INTERNATIONAL CLASSIFICATION	Not for publication
51 A61K C07K	Classified by: GERMAN PATENT OFFICE

FULL NAME(S) OF APPLICANT(S)

71 ~~BOEHRINGER MANNHEIM GMBH~~ ROCHE DIAGNOSTICS GmbH
a German company
NAAM VERANDER
NAME CHANGED 15.3.99.

FULL NAME(S) OF INVENTOR(S)

72 JOSEF BURG, KARL-HEINZ SELLINGER,
ANTON HASELBECK, HANS KOLL

EARLIEST PRIORITY CLAIMED	COUNTRY	NUMBER	DATE
	33 DE	31 197 53 681.6	32 03/12/97

TITLE OF INVENTION

54 ERYTHROPOIETIN WITH HIGH SPECIFIC ACTIVITY

57 Abstract (not more than 150 words) and figure of the drawings to which the abstract refers, are attached.

Number of sheets: 70

Heading of an European patent for a chromatography purification of an epoetin (probably Binocrit® - a biosimilar of epoetin alfa)

(19) REPUBLIKA SLOVENIJA
MINISTRSTVO ZA GOSPODARSKI RAZVOJ IN TEHNOLOGIJO
URAD RS ZA INTELEKTUALNO LASTNINO

(10) SI/EP 1453857 T1

(12) **PREVOD ZAHTEVKOV EVROPSKEGA PATENTA**

(21) Številka predmeta: **200231050**
(22) Datum prijave: **26.11.2002**
(51) Int. Cl. (2014.01) **C07K 14/00**

(46) Datum objave prevoda zahtevkov: **30.01.2015**
(96) Evropska patentna prijava: **26.11.2002 EP 02803796.8**
(30) Prednostna pravica: **28.11.2001 US 333839**
(87) Objava mednarodne patentne prijave: **WO 2003/045996, 05.06.2003**
(86) Mednarodna patentna prijava: **26.11.2002 WO PCT/EP2002/013299**
(97) Objava evropskega patenta: **EP 1453857 B1, 13.08.2014**

(72) Izumitelja: **ALLIGER Peter, A-6330 Kufstein, AT;**
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(73) Imetnik: **Sandoz AG,**
Lichtstrasse 35, 4056 Basel, CH
(74) Zastopnik: **dr. Barbara Kunič, univ.dipl.kem., Verovškova 57, 1526 Ljubljana, SI**

(54) **KROMATOGRAFSKO ČIŠČENJE REKOMBINANTNEGA ČLOVEŠKEGA ERITROPOETINA**

SI/EP 1453857 T1

Patentni zahtevki

1. Postopek za pridobivanje in čiščenje rekombinantnega človeškega eritropoetina (rhEpo) iz gojišča celične kulture, ki vsebuje tudi gostiteljske celice, pri čemer postopek vključuje naslednje korake:

(a) odstranjevanje gostiteljskih celic, celičnih sestavin in ostankov iz gojišča celične kulture z izvedbo postopka, izbranega iz skupine, ki se sestoji iz (i), centrifugiranja, čemur sledi faza globinskega filtriranja, (ii) faze globinskega filtriranja, in (iii) centrifugiranja, da dobimo prečiščeni supernatant;
(b) naravnavanje prevodnosti supernatanta na 5 mS/cm ali manj, pH pa na vrednost med približno 7,0 in 8,0;
(c) nanašanje supernatanta iz koraka (b) na kolono, ki vsebuje nosilec za anionsko izmenjevalno kromatografijo, izpiranje kolone, eluiranje rhEpo iz kolone in zbiranje frakcij elucijskega vrha, ki vsebuje rhEpo;
(d) nanašanje združenih frakcij elucijskega vrha iz koraka (c) na reverzno fazno kromatografijo z uporabo nosilca, ki prenese srednje visoke tlake (<10 barov) in je odporen na visoke koncentracije NaOH, pri čemer se rhEpo elurira z linearnim gradientom organskega topila;
(e) nanašanje ene ali več frakcij, eluiranih v koraku (d), ki vsebujejo rhEpo, na kolono, ki vsebuje kromatografski nosilec za izmenjavo anionov, izpiranje kolone in eluiranje rhEpo z uporabo linearnega gradienta soli;
(f) izbiranje ene ali več v koraku (e) eluiranih frakcij, ki vsebujejo rhEpo, na temelju stopnje sialilacije rhEpo; in
(g) nanašanje ene ali več v koraku (f) eluiranih frakcij, ki vsebujejo rhEpo, v enem ali več korakov kromatografije z ločevanjem po velikosti z uporabo nosilca za gelsko filtracijo za odstranitev morebitnih dimerov in agregatov višjega reda in zbiranje eluata, ki vsebuje rhEpo.

Heading of a Japanese patent devoted to purification of an epoetin analog with pI < 4

(19)日本国特許庁(JP)　(12)公表特許公報(A)　(11)特許出願公表番号
特表2014-532080
(P2014-532080A)
(43)公表日　平成26年12月4日(2014.12.4)

(51)Int.Cl.		F I		テーマコード（参考）
C07K 1/18	(2006.01)	C07K	1/18	4H045
C07K 1/22	(2006.01)	C07K	1/22	
C07K 14/505	(2006.01)	C07K	14/505	

審査請求 有　予備審査請求 未請求　（全 28 頁）

(21)出願番号	特願2014-536972 (P2014-536972)
(86)(22)出願日	平成24年9月28日 (2012.9.28)
(85)翻訳文提出日	平成26年6月4日 (2014.6.4)
(86)国際出願番号	PCT/KR2012/007959
(87)国際公開番号	WO2013/058485
(87)国際公開日	平成25年4月25日 (2013.4.25)
(31)優先権主張番号	10-2011-0106230
(32)優先日	平成23年10月18日 (2011.10.18)
(33)優先権主張国	韓国 (KR)

(71)出願人　514052597
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(74)代理人　100107515
弁理士　廣田　浩一
(74)代理人　100107733
弁理士　流　良広
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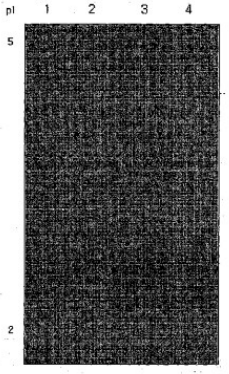
最終頁に続く

(54)【発明の名称】低い等電点を有するエリスロポエチン類似体の精製方法

(57)



How much “the same”, similar or different are individual epoetin originator products and biosimilars?

Differences in individual epotins' glycosylation pattern: capillary zone electrophoresis (CZE) in accordance with the European Pharmacopoea.

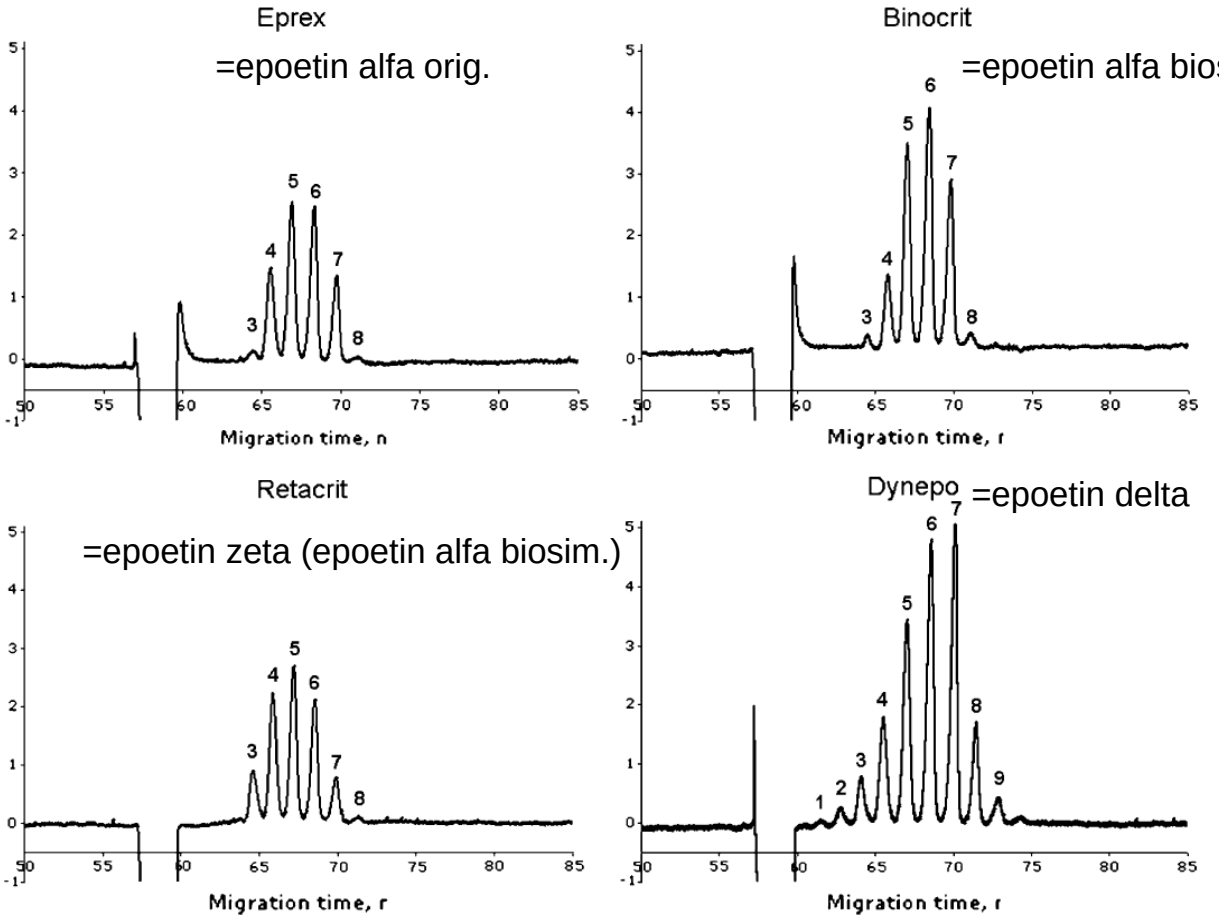


Fig. 3 CE-UV analysis of the four EPO products.

Brinks V. et al., Pharm. Res. 28, 386-393 (2011)

Monoclonal antibodies (MABs)

trastuzumab

Herceptin ® (originator); Ontruzant ® (biosimilar)

- humanized antibody
- IgG1 κ anti – HER2

•family of receptors for epidermal growth factor includes 4 structurally very similar receptors: Erb/HER (EGFR; HER-1, and ERBB1), human EGFR-2 (HER-2 and

•ERBB2), HER-3, a HER-4, transmembrane glycoproteins containing a domain binding an intracellular ligand and an intracellular receptor tyrosine kinase (RTK) domain

•deregulation of Erb/HER pathway by over-expression or by constitutive activation can trigger a cancer process including angiogenesis and metastasising and brings a bad prognosis in many types of human cancers

•

- early studies with trastuzumab as a single agent in HER-2-positive metastatic breast cancer achieved overall responses of 11.6 and 15% for patients who had progressed after chemotherapy. As a first-line treatment for metastatic breast cancer, trastuzumab showed response rates of 26% in HER-2-positive patients and responses of 35% in patients with 3+ HER-2 overexpression by immunohistochemistry and 34% in patients positive for HER-2 gene amplification by fluorescence in situ hybridisation (FISH).
- a pivotal phase III trial of trastuzumab in combination with chemotherapeutic agents demonstrated an overall response rate of approximately 50% (versus 32%), longer duration of response (time to progression; 7.4 versus 4.6 months), **longer survival (overall survival: 25.1 versus 20.3 months)** and a 20% reduction in risk of death compared to chemotherapy alone in HER-2 overexpressing metastatic breast cancer.

Main importance of both generics and biosimilars:

- lower price than in originals ⇒ better chance of availability of (relatively) modern medicines for more patients

  However, currently worsened availability of some medicines, mainly generics, for patients in ČR and whole Europe is mainly caused by moving of production of drug substances, and often the complete drug forms, to India and China. These countries prefer in a case of increased need their inner markets. Moreover, prices of drugs in ČR belong to the lowest ones in the Europe, that´s why other countries are favoured in supply of medicaments in times of their shortage. Furthermore, our country more or less tolerates re-export of medicines from us to other countries, where their prices are higher.

A new Chinese patent for a relatively old drug

(19)国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 116768697 A
(43)申请公布日 2023.09.19

(21)申请号 202211576011.5

(22)申请日 2022.12.09

(71)申请人 湖南大学
地址 410082 湖南省长沙市岳麓区麓山南路1号湖南大学

(72)发明人 胡艾希 李明芳 叶姣

(51)Int.Cl.
C07C 27/02(2006.01)
C07C 55/02(2006.01)
C07C 67/343(2006.01)
C07D 319/06(2006.01)
C07D 321/08(2006.01)
C07C 51/38(2006.01)
C07C 53/128(2006.01)

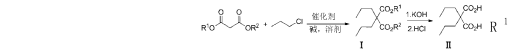
权利要求书2页 说明书7页

(54)发明名称

一种氯丙烷作烷化剂制备二丙基丙二酸的方法与应用

(57)摘要

本发明涉及化学结构式Ⅱ所示的二丙基丙二酸的制备方法:选择丙二酸二酯与1-氯丙烷,在碱作用下,催化二丙基化制得式Ⅰ所示的二丙基丙二酸二酯,后者水解制得二丙基丙二酸(Ⅱ);其制备反应如下:



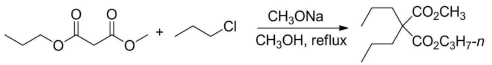
Ⅰ Ⅱ

选择:苄基、C1～C5直链烷基或C3～C5支链烷基;R^1和R^2相同或不同;催化剂由聚乙二醇、聚乙二醇单醚、聚乙二醇双醚、冠醚、三级胺、季铵盐和分子筛组成;溶剂选择:THF、DMF、DEF、DMC、DMSO、乙腈、丙腈、丁腈、1,4-二氧六环、乙二醇二甲醚、乙二醇二乙醚、二乙二醇二甲醚或二乙二醇二乙醚中的一种或二种。碱选自:固体MOH或固体M_2CO_3,其中M=Na、Li、Cs或K。二丙基丙二酸(Ⅱ)脱羧制得丙戊酸。

CN 116768697 A

[0079] 实施例10(对比实验)

[0080] 甲醇钠作为碱,甲醇作为反应溶剂,制备二丙基丙二酸甲酯丙酯。

[0081] 

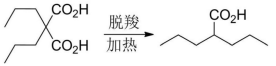
[0082] 按陶晶等[二丙基丙二酸二酯的制备方法.中国发明专利.CN103183612A,2013-07-03]

[0083] 描述的专利说明书中实施例8方法制备:

[0084] 500mL三口瓶中加入甲醇60mL,搅拌下加入丙二酸甲酯丙酯10g(62.5mmol)、1-氯丙烷30.6g(250mmol)、甲醇钠13.5g(250mmol),升温至回流,11h后补加1-氯丙烷7.6g(63.6mmol)和甲醇钠3.38g(63.6mmol),再反应3.5h,取样TLC检测反应完全,降至室温后抽滤,滤饼使用50mL乙酸乙酯洗涤,合并滤液,自来水洗滤液两次(50mL×2),饱和氯化钠水溶液洗滤液两次(50mL×2),无水硫酸钠干燥,旋干滤液,得粗品(二丙基丙二酸甲酯丙酯)10.77g,粗品收率70.5%。

[0085] 实施例11

[0086] 丙戊酸的制备

[0087] 

[0088] 按专利[一种制备2-丙基戊酸的方法,CN103183599B,2015-04-01]实施例1中的方法:将实施例1～9制得的二丙基丙二酸31g加入200mL圆底瓶中,用氮气置换三次,放入预先稳定的170℃油浴中反应,反应过程中放出CO_2,反应3h,降温,得23g丙戊酸。HPLC结果显示,纯度为99.84%。^{1}H NMR(400MHz,DMSO-d_6)δ:11.99(s,1H,COOH),2.24-2.18(m,1H,CH),1.53-1.44(m,2H,CH_2),1.39-1.34(m,2H,CH_2),1.32-1.22(m,4H,CH_2×2),0.86(t,J=7.2Hz,6H,CH_3×2)。

[0089] 在本说明书中,本发明已参照其特定的实施例作了描述。但是,很显然仍可以作出各种修改和变换而不背离本发明的精神和范围。因此,说明书应被认为是说明性的而非限制性的。

Patents are not only tools of the legal protection of an intellectual property, but they can also serve as an important resource of information for research and researchers. Moreover, they are freely available from data bases of patent offices.

Some interesting patent offices:

ČR ÚPV Úřad průmyslového vlastnictví
https://upv.gov.cz/informacni-zdroje/narodni-databaze/databaze-patentu-a-uzitnych-vzoru
- also links to foreign data bases

Europe EPO European patent office-Espacenet
https://worldwide.espacenet.com/advancedSearch?locale=en_EP
- search patents from virtually all countries including international patents

Germany DEPATIS https://depatisnet.dpma.de/DepatisNet/depatisnet?action=erweitert

USA USPTO United States Patent and Trademark Office https://www.uspto.gov/
- basic patent search: https://ppubs.uspto.gov/pubwebapp/static/pages/ppubsbasic.html

Japan Japan Patent Office JPO https://www.j-platpat.inpit.go.jp/

Thank you for your attention