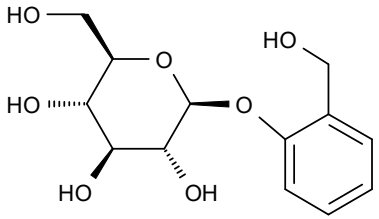
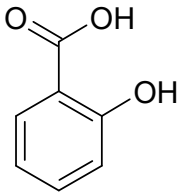
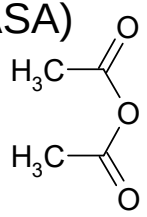
Drug patents and copying: generics versus biosimilars.
(How do patents and generics work)

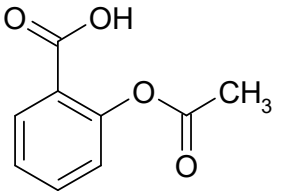
History of acetylsalicylic acid (ASA)



hydrolysis
oxidation







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

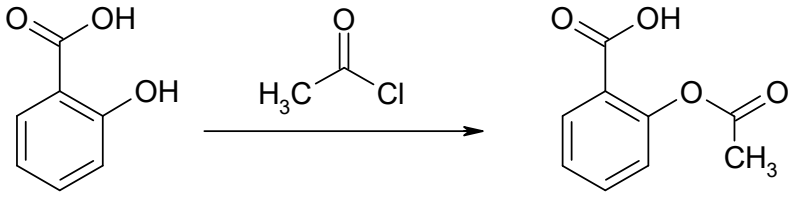
600 b.C. Hippocrates: chewig of willow bark
(*Cortex salicis - Salix sp.)*
1827 Leroux: isolation from willow bark

salicylic acid
2-hydroxybenzooic acid

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

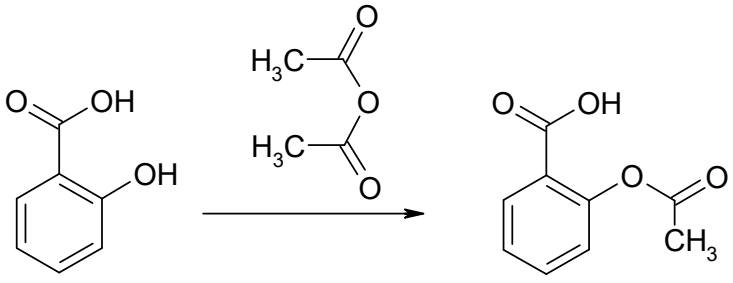
acetylsalicylic acid
2-acetoxybenzooic acid

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.

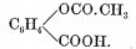
SPECIFICATION forming part of Letters Patent No. 644,077, dated February 27, 1900.

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.

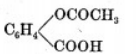
In the *Annalen der Chemie und Pharmacie*, Vol. 150, pages 11 and 12, Kraut has described that he obtained by the action of acetyl chlorid on salicylic acid a body which he thought to be acetyl salicylic acid. I have now found that on heating salicylic acid with acetic anhydride a body is obtained the 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.

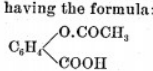
In producing my new compound I can proceed as follows, (without limiting myself to the particulars given:) A mixture prepared from fifty parts of salicylic acid and seventy-five parts of acetic anhydride is heated for about two hours at about 150° centigrade in a vessel provided with a reflux condenser. 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)

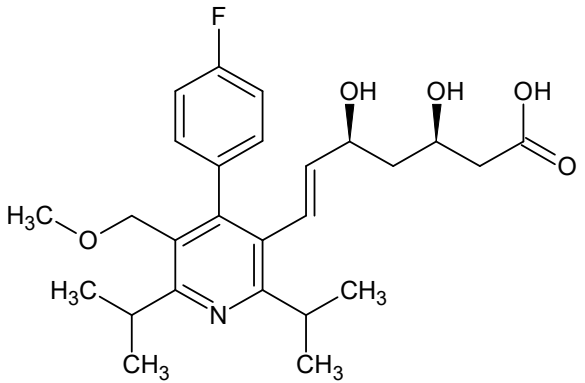
The maximum length of patent protection is 20 years. After this, it is possible to produce generics.

- 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

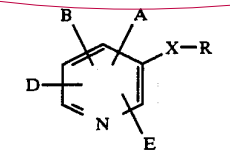
4,923,884 5/1990 Chandraratna 514/354

Primary Examiner—Alan L. Rotman

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

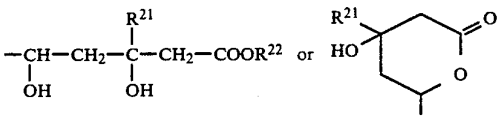
[57] **ABSTRACT**

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.

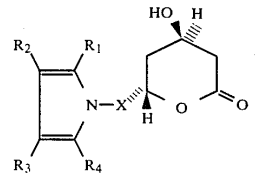
19 Claims, No Drawings

A patent example: antihypercholesterolemics

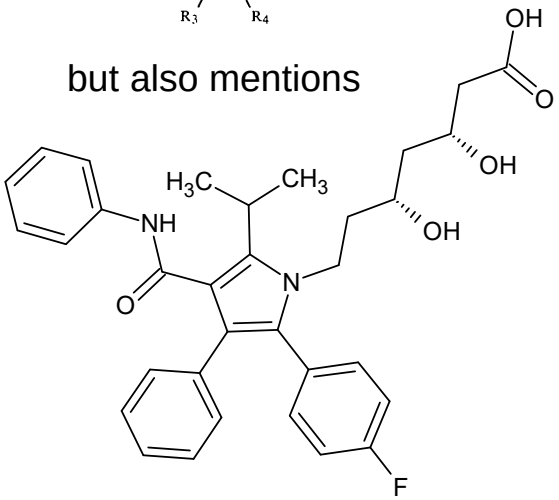
(1st page shown; the whole patent has 20 pages)

- 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**

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4,262,013	4/1981	Mitsui et al.	549/292 X
4,375,475	3/1983	Willard et al.	514/460

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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.

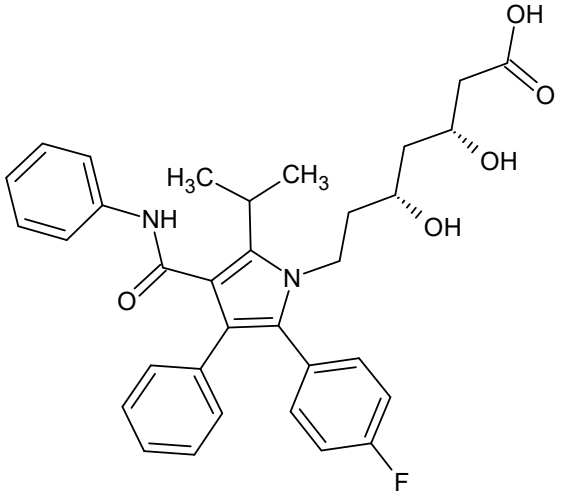
Primary Examiner—Joseph Paul Brust

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**

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

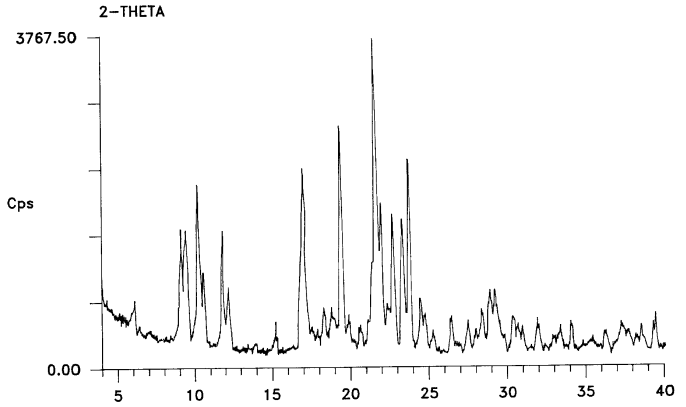
Pharmaceutical Research, vol. 10, No. 10, 1993, pp. 1461–1465, Kearney, et al.

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.

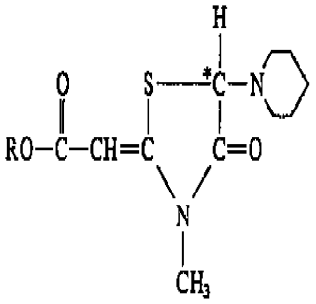
44 Claims, 6 Drawing Sheets



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

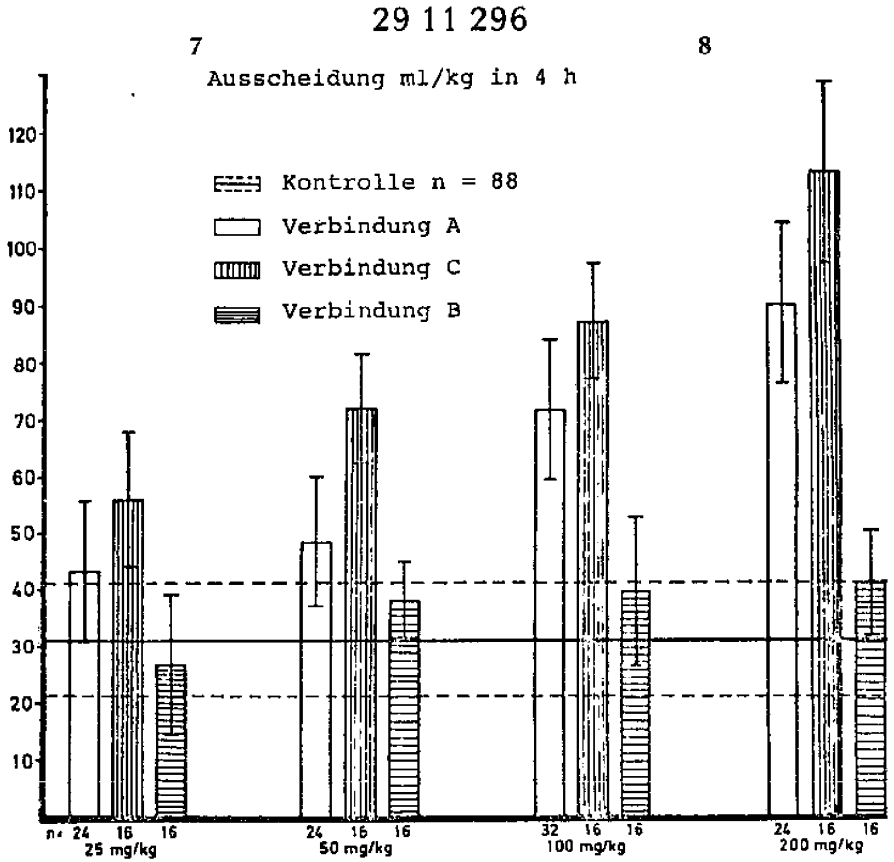
(61) Zusatz in: P 29 52 704.6
P 29 53 604.7

(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

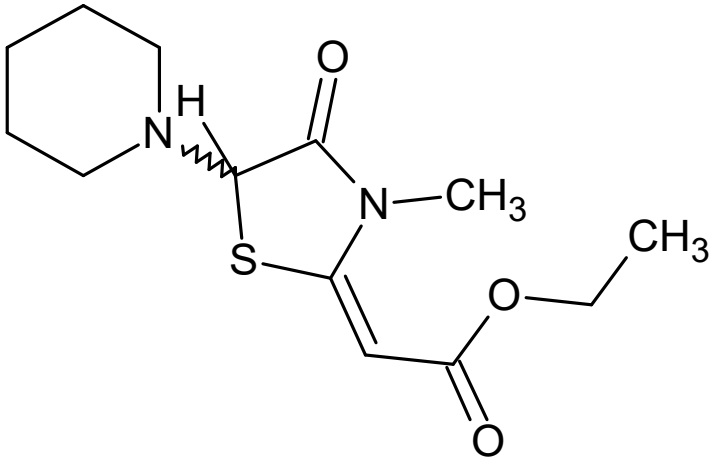
(56) Entgegenhaltungen:
NICHTS ERMITTELT

(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

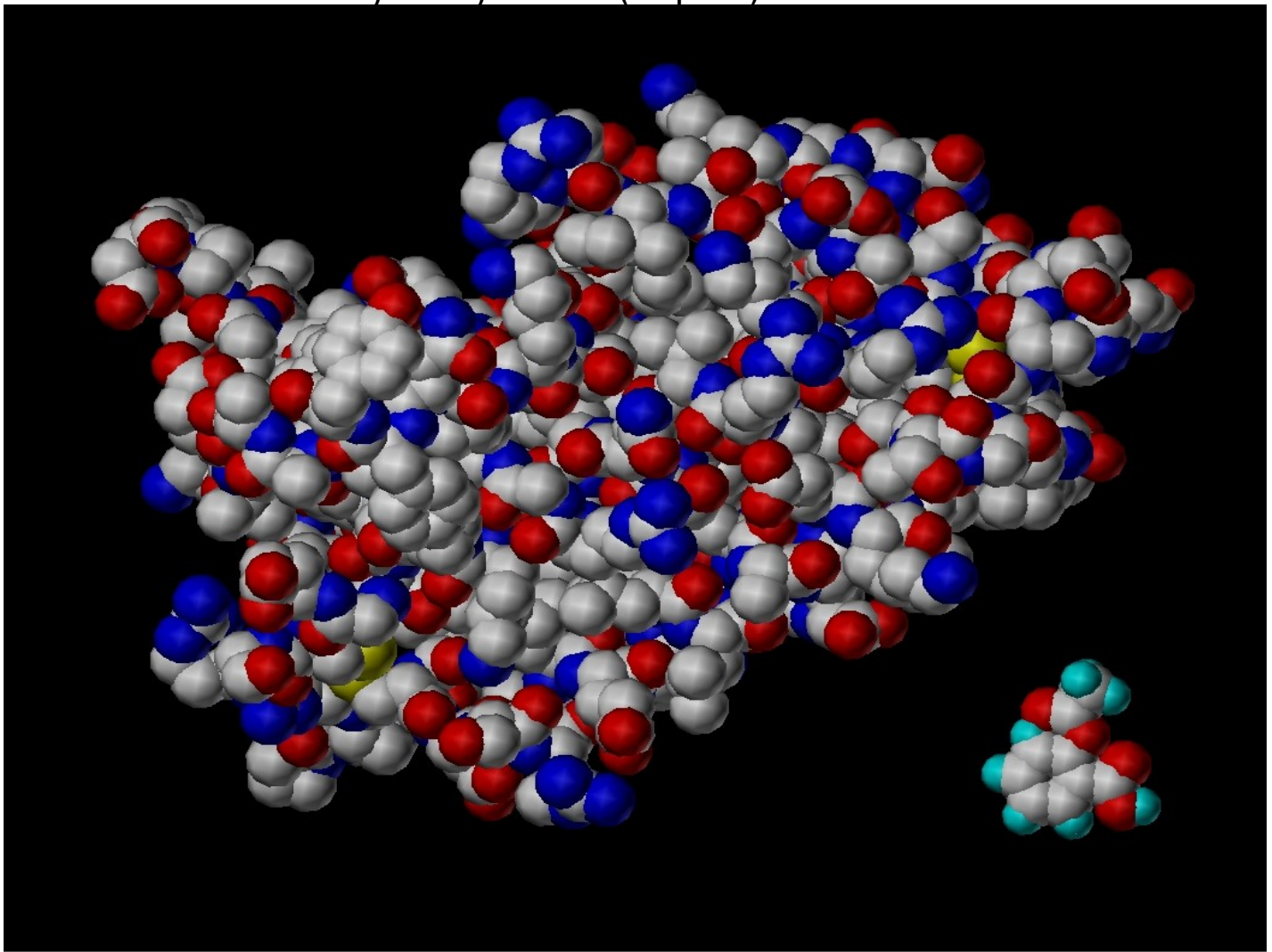
•typically obtained by other way than by classical chemical synthesis (semisynthetic modifications are possible)

•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

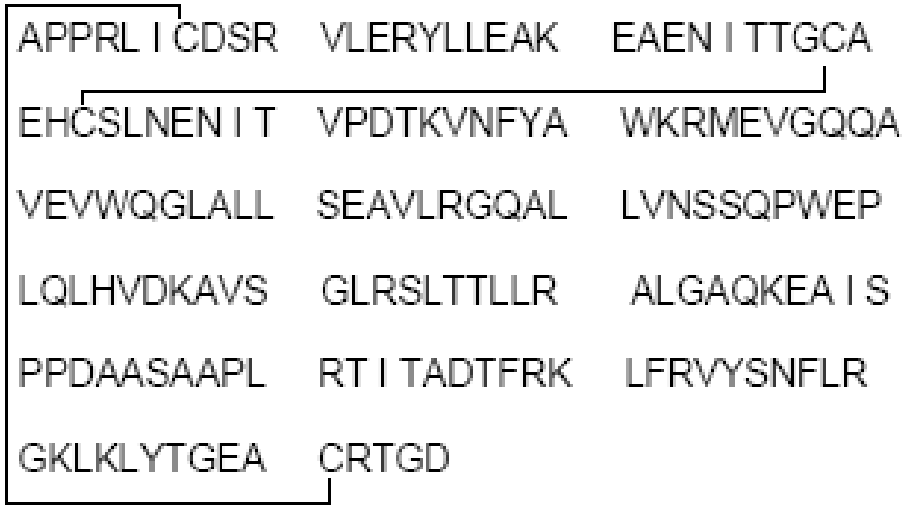
• due to their hydrophilicity and big M_r they cannot be absorbed from GIT and thus they must be administered parenterally (injections, infusions)

•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

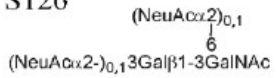
GKLKLYTGEA CRTGD

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

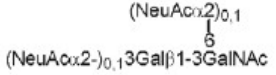
APPRLICDSR VLERYLLEAK EAENITTGCA EHCSLNENIT VPDTKVNFYA
WKRMEVGQQA VEVWQGLALL SEAVLRGQAL LVNSSQPWEP LQLHVDKAVS
GLRSLTTLLR ALGAQKEAIS PPDAASAAPL RTITADTFRK LFRVYSNFLR
GKLKLYTGEA CRTGD

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

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(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).

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(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
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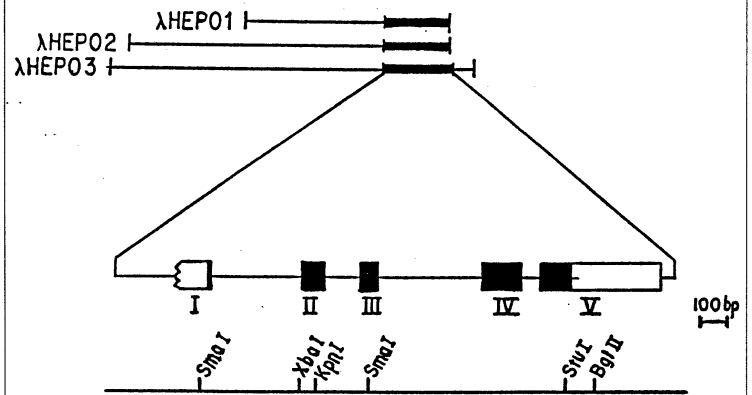
With amended claims.

(54) Title: METHOD FOR THE PRODUCTION OF ERYTHROPOIETIN

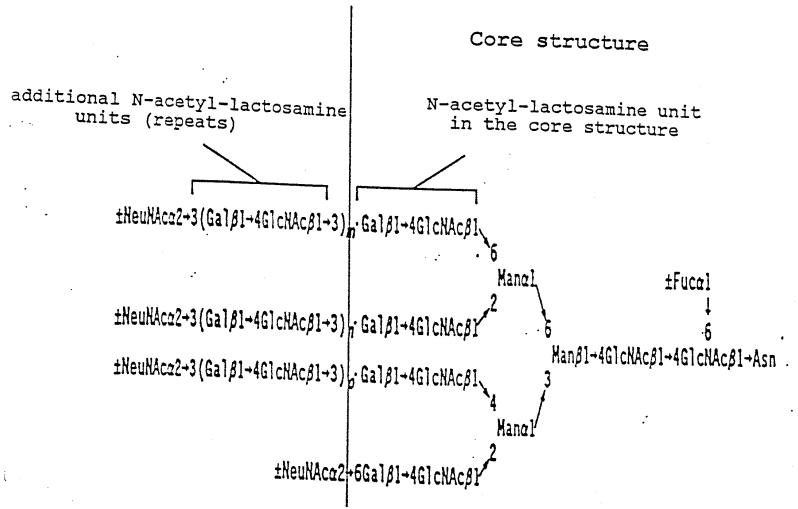


(57) Abstract

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]

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51 A61K C07K	Classified by: GERMAN PATENT OFFICE

FULL NAME(S) OF APPLICANT(S)

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NAME CHANGED 15.3.99.

FULL NAME(S) OF INVENTOR(S)

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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
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URAD RS ZA INTELEKTUALNO LASTNINO

(10) SI/EP 1453857 T1

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(51) Int. Cl. (2014.01) **C07K 14/00**

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(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**

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(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	
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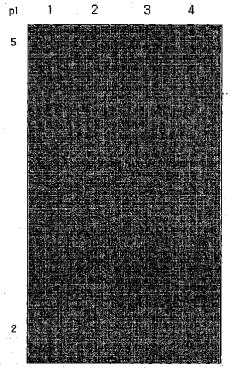
最終頁に続く

(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



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.

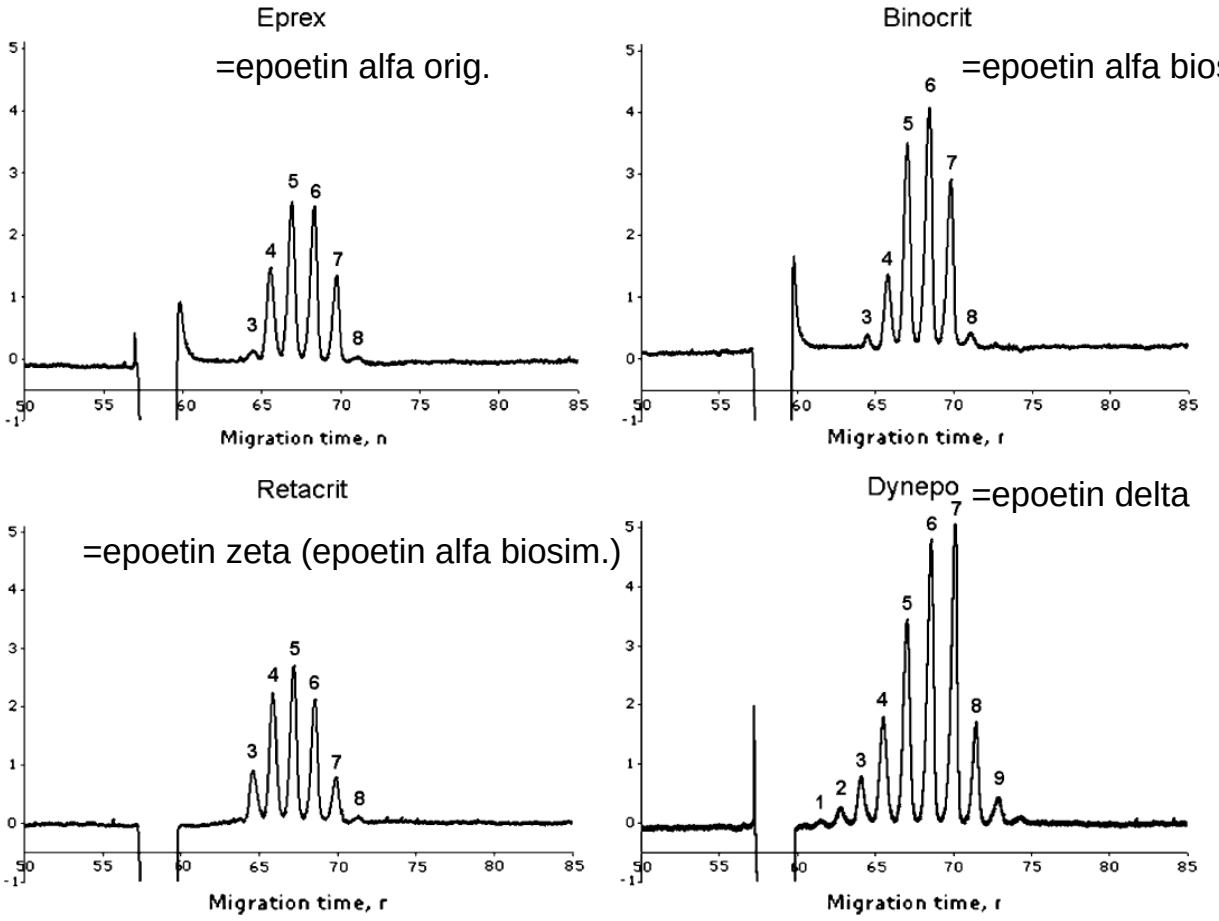


Fig. 3 CE-UV analysis of the four EPO products.

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.

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