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Method for combating obesity

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PCT
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<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top; padding: 5px;"> (21) Internationales Aktenzeichen: PCT/EP98/07501 (22) Internationales Anmeldedatum: 21. November 1998 (21.11.98) (30) Prioritätsdaten: 197 54 082.1 5. Dezember 1997 (05.12.97) DE (71) Anmelder (für alle Bestimmungsstaaten ausser US): KNOLL AKTIENGESELLSCHAFT [DE/DE]; D-67061 Ludwigshafen (DE). (72) Erfinder; und (75) Erfinder/Anmelder (nur für US): MÜNTER, Klaus [DE/DE]; Karl-Ladenburg-Strasse 22, D-68163 Mannheim (DE). KIRCHENGAST, Michael [AT/DE]; Ifflandstrasse 16, D-68161 Mannheim (DE). (74) Anwälte: KARAU, Wolfgang usw.; BASF Aktiengesellschaft, D-67056 Ludwigshafen (DE). </td> <td style="width: 50%; vertical-align: top; padding: 5px;"> (81) Bestimmungsstaaten: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HU, ID, IL, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Veröffentlicht <i>Ohne internationalen Recherchenbericht und erneut zu veröffentlichen nach Erhalt des Berichts.</i> </td> </tr> </table>			(21) Internationales Aktenzeichen: PCT/EP98/07501 (22) Internationales Anmeldedatum: 21. November 1998 (21.11.98) (30) Prioritätsdaten: 197 54 082.1 5. Dezember 1997 (05.12.97) DE (71) Anmelder (für alle Bestimmungsstaaten ausser US): KNOLL AKTIENGESELLSCHAFT [DE/DE]; D-67061 Ludwigshafen (DE). (72) Erfinder; und (75) Erfinder/Anmelder (nur für US): MÜNTER, Klaus [DE/DE]; Karl-Ladenburg-Strasse 22, D-68163 Mannheim (DE). KIRCHENGAST, Michael [AT/DE]; Ifflandstrasse 16, D-68161 Mannheim (DE). (74) Anwälte: KARAU, Wolfgang usw.; BASF Aktiengesellschaft, D-67056 Ludwigshafen (DE).	(81) Bestimmungsstaaten: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HU, ID, IL, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Veröffentlicht <i>Ohne internationalen Recherchenbericht und erneut zu veröffentlichen nach Erhalt des Berichts.</i>
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(54) Title: METHOD FOR COMBATING OBESITY (54) Bezeichnung: METHODE ZUR BEKÄMPFUNG DER FETTLLEIBIGKEIT (57) Abstract The invention relates to the use of endothelin receptor antagonists for producing medicaments for combating obesity or for combating diseases caused by obesity. (57) Zusammenfassung Verwendung von Endothelin-Rezeptorantagonisten zur Herstellung von Arzneimitteln zur Bekämpfung von Fettleibigkeit bzw. von Krankheiten, die durch Fettleibigkeit hervorgerufen werden.				

A method for controlling obesity

Abstract

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The use of endothelin receptor antagonists for producing drugs for controlling obesity and diseases caused by obesity.

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A method for controlling obesity

The present invention relates to a method for controlling obesity and diseases caused by obesity. More particularly, the invention relates to a method for controlling hyperlipidemia.

The peptide hormone endothelin is known for its strong vasoconstrictor properties. Endothelin receptor antagonists are therefore mainly being tested in cardiovascular pathologies.

The invention relates to the use of endothelin receptor antagonists for producing drugs for controlling obesity and diseases caused by obesity. More particularly, the invention relates to the use of endothelin receptor antagonists for producing drugs for controlling hyperlipidemia.

The endothelin receptor antagonists which can be used are both endothelin_A and mixed endothelin_{A/B} receptor antagonists.

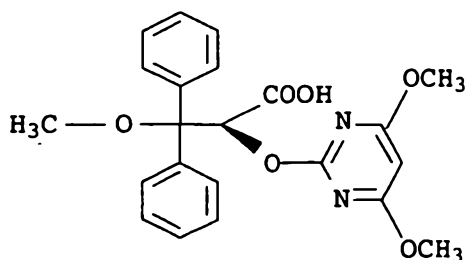
Particularly suitable endothelin receptor antagonists are

1. TBC-11251 (J. Med. Chem., 40, No. 11, 1690-97, 1997),
2. BMS-193884 (EP 558.258)
3. BMS-207940 (Pharmaprojects (13.06.97)),
4. BQ-123 (Exp. Opin. Invest. Drugs, 1997, 6, No. 5, 475-487),
5. SB-209670 (Exp. Opin. Invest. Drugs, 1997, 6, No. 5, 475-487),
6. SB-217242 (Exp. Opin. Invest. Drugs, 1997, 6, No. 5, 475-487),
7. SB-209598 (Trends in Pharmacol. Sci., 17, 177-81, 1996),
8. TAK-044 (Exp. Opin. Invest. Drugs, 1997, 6, No. 5, 475-487),
9. Bosentan (Trends in Pharmacol. Sci., 18, 408-12, 1997),
10. PD-156707 (J. Med. Chem., 40, No. 7, 1063-74, 1997),
11. L-749329 (Bioorg. Med. Chem. Lett., 7, No. 3, 275-280, 1997),
12. L-754142 (Exp. Opin. Invest. Drugs, 1997, 6, No. 5, 475-487),
13. ABT-627 (J. Med. Chem., 40, No. 20, 3217-27, 1997),
14. A-127772 (J. Med. Chem., 39, No. 5, 1039-1048, 1996),
15. A-206377 (213th American Chemical Society National Meeting, San Francisco, California, USA, 13 - 17 April, 1997, Poster, MEDI 193),
16. A-182086 (J. Med. Chem., 40, No. 20, 3217-27, 1997),
17. EMD-93246 (211th American Chemical Society National Meeting, New Orleans, USA, 1996, Poster, MEDI 143),
18. EMD-122801 (Bioorg. Med. Chem. Lett., 8, No. 1, 17-22, 1998),
19. ZD-1611 (Trends in Pharmacol. Sci., 18, 408-12, 1997),
20. AC-610612 (R&D Focus Drug News (18.05.98)),
21. T-0201 (70th Annual Meeting of the Japanese Pharmacological Society, Chiba, Japan, 22-25 March 1997, Lecture, O-133),
22. J-104132 (R&D Focus Drug News (15.12.97)) and, in particular,

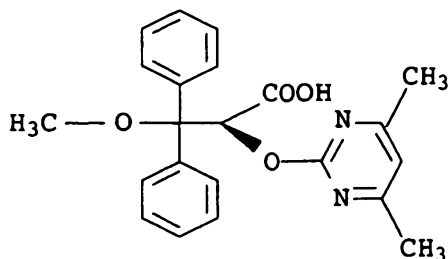


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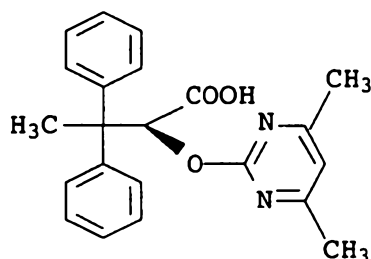
23:



24:

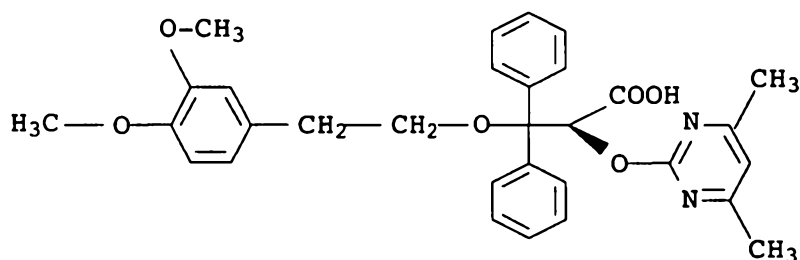


25:



and

26:



Obesity is the term used when the bodyweight is at least 20% over the normal weight. The causes of obesity are overeating or faulty utilization of food, for example familial hypercholesterolemia. Diseases caused by or frequently associated with obesity which should be specifically mentioned are hypertension, type 2 diabetes, hyperlipidemia, chronic kidney failure and arteriosclerosis and possibly also gout.

It has to date been possible only with great difficulty to simulate the pathological state of obesity in animal experiments (administration of extremely high cholesterol doses). However, recently, knockout mice lacking the gene for apolipoprotein E have been bred and can be employed for testing substances to counter obesity.



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The effect of the endothelin receptor antagonist substance 23 was investigated in the animal model of the apoE knockout mouse. In control rats, as was to be expected, the bodyweight of the animals on a high-fat diet increased greatly. This was associated with an increase in the size of the liver with simultaneous fatty degeneration of the liver. In a parallel group, the animals were treated with substance 23 (50 mg/kg/d). In this group, the increase in body and liver weight was completely prevented. The liver was also histologically unremarkable.

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The endothelin_A and endothelin_{A/B} receptor antagonists must be administered life-long. Their dosage is from 50 to 500 mg per patient and day.

15 Endothelin_A and endothelin_{A/B} receptor antagonists are generally administered orally, for example in the form of uncoated, lacquered and sugar-coated tablets, hard and soft gelatin capsules, solutions, emulsions or suspensions. However, administration may also take place rectally, for example in the form of suppositories, or parenterally, for example in the form of injection solutions.

To produce uncoated, lacquered and sugar-coated tablets and hard gelatin capsules, a combination according to the invention can be processed with pharmaceutically inert, inorganic or organic excipients. Excipients of these types which can be used for uncoated and sugar-coated tablets and hard gelatin capsules are lactose, corn starch or derivatives thereof, talc, stearic acid or its salts. Excipients suitable for soft gelatin capsules are vegetable oils, waxes, fats, semisolid and liquid polyols.

Excipients suitable for producing solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Excipients suitable for injection solutions are water, alcohols, polyols, glycerol, vegetable oils. Excipients suitable for suppositories are natural or hardened oils, waxes, fats, semiliquid or liquid polyols and the like.

The pharmaceutical preparations may moreover contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colors, aromatizing agents, salts to alter the osmotic pressure, buffers, coating agents and/or antioxidants.

45 The following examples illustrate the invention.



Example 1

Lacquered tablets of the following composition were produced:

5	Compound 23	300.0 mg
	Anhydrous lactose	30.0 mg
	Microcrystalline cellulose	30.0 mg
	Polyvinylpyrrolidone	20.0 mg
	Magnesium stearate	5.0 mg
10	Polyethylene glycol 6000	0.8 mg
	Yellow iron oxide	1.2 mg
	Titanium dioxide	0.3 mg
	Talc	0.7 mg

15 Compound 23, the lactose, the cellulose and the polyvinylpyrrolidone are wet-granulated and dried. The sieved granules are mixed with the magnesium stearate, and the mixture is compressed to oval tablet cores each weighing 390.0 mg. The cores are then lacquer-coated until the lacquered tablets have
20 reached a final weight of 400 mg.

Example 2

Lacquered tablets were produced in analogy to Example 1 but
25 contained 300 mg of Compound 26 in place of 300 mg of Compound 23.

Example 3

30 Production of hard gelatin capsules of the following composition:

	Compound 23	250.0 mg
	Crystalline lactose	18.0 mg
	Polyvinylpyrrolidone	15.0 mg
35	Microcrystalline cellulose	17.5 mg
	Sodium carboxymethyl starch	10.0 mg
	Talc	0.7 mg
	Magnesium stearate	3.0 mg

40 The first five ingredients are wet-granulated and dried. The granules are mixed with the sodium carboxymethyl starch, the talc and the magnesium stearate, and the mixture is packed into size 0 hard gelatin capsules.



THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. The use of endothelin receptor antagonists for producing drugs for controlling hyperlipidemia.
2. A method of controlling hyperlipidemia, the method including administering to a patient a therapeutically effective amount of an endothelin receptor antagonist, and one or more suitable carriers.
3. A therapeutic composition when used for controlling hyperlipidemia in a patient in need thereof, the composition including a therapeutically effective amount of a endothelin receptor antagonist, and one or more suitable carriers.

DATED this 18th day of July 2001

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