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(54) Title: HEPARIN DERIVATIVES HAVING ANTIMETASTATIC ACTIVITY (57) Abstract Heparin fragments and fractions and/or derivatives having antimetastatic activity.		

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HEPARIN DERIVATIVES HAVING ANTIMETASTATIC ACTIVITY

The present invention relates to heparin derivatives, particular heparin fragments and fractions, and the use thereof as antimetastatic agents.

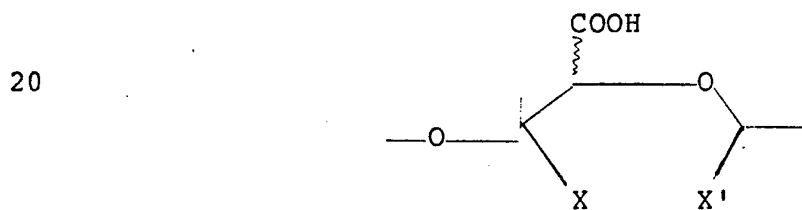
5 The antimetastatic activity of heparin has been known for some time (see, for example, Drago, J.R. et al., Anticancer Res., 4(3), 171-2, 1984), although some authors doubt its real efficacy in this field, assigning it, on the contrary, with a metastases-
10 stimulating effect (see, for example, S.Y. Chan, and M. Pollard, J.N.C.I., 64, n. 5, May 1980). Low molecular weight heparin also has antimetastatic activity, which some authors consider higher than that of normal heparin (Green, D. et al. The Lancet, 339, June 13,
15 1992). Nevertheless, the use of said molecules in this field is severely restricted by the marked anticoagulant and antithrombotic activities thereof.

Subsequently, studies have been directed to heparin derivatives. For example, WO 88/05301 reports
20 data about the antimetastatic activity of heparin, of N-desulfated N-acetylated heparin and of oxidized-reduced heparins: heparin as such turns out to be the mainly active compound, whereas its derivatives have quite a lower effect, reducing the number of metastases
25 by about 40-50%.

It should be noted, anyway, that N-desulfated N-acetylated heparin shows antithrombotic and fibrinolytic effects which could restrict its use as an antitumoral (see, EP-A-0 413 248).

Now it has surprisingly been found that other heparin derivatives and particular heparin fragments and fractions have a remarkable antimetastatic activity.

5 Therefore, the object of the present invention are heparin derivatives N-acylated with residues from aliphatic monocarboxylic acids having 3 to 20 carbon atoms, or with residues from aliphatic dicarboxylic acids having 3 to 10 carbon atoms, said derivatives
 10 having a molecular weight ranging from about 1,000 to about 30,000 daltons (Da), having a N-acylation degree, defined as the percent ratio of the number of N-acylated residues to the number of N-sulfated groups present in the heparin compound which they derive from,
 15 ranging from about 10 to about 100, said derivatives being further characterized in that they contain at least a unit of open D-iduronic or L-iduronic acid of formula I



I

wherein X and X' are independently a -CHO or -CH₂OH group; and in that the OH groups free from units of
 25 non-open D-glucuronic or L-iduronic acid and from D-glucosamine units can be acylated with the above mentioned acyl residues;
 and the salts thereof with alkali or alkaline-earth
 30 metal cations.

A further object of present invention relates to

the use of heparin derivatives characterized in that they contain at least a unit of formula I as antimetastatic compounds.

A further object of present invention relates to the use of heparin derivatives, or of fragments and fractions thereof, having a molecular weight ranging from 1,000 to about 30,000 Da, N-acylated with residues from aliphatic monocarboxylic acids having 3 to 20 carbon atoms, or with residues from aliphatic dicarboxylic acids having 3 to 10 carbon atoms, and having a N-acylation degree, defined as the percent ratio of the number of N-acylated residues to the number of N-sulfated groups present in the heparin compound which they derive from, ranging from about 10 to about 100, and the salts thereof, as antimetastatic compounds.

A still further object of present invention is the use of particular heparin fragments or fractions having an average molecular weight equal or lower than 3,000 Da, and the salts thereof, as antimetastatic compounds. By aliphatic monocarboxylic acid residues having 3 to 20 carbon atoms, residues are meant such as those from propionic, butyric, caproic, caprylic, capric, lauric, myristic, palmitic, stearic, crotonic, oleic, elaidic, stearolic, tetrolic, arachic acids and analogues. By aliphatic dicarboxylic acid residues having 3 to 10 carbon atoms, residues such as those from malonic, succinic, dimethylmalonic, glutaric, suberic, azelaic and sebacic acids and analogues are meant. These mono- or dicarboxylic acids can also be substituted with one or more hydroxy, amino or acylamino groups, thus

obtaining, for example, heparins N-acylated with residues from lactic, hydracrylic, tartaric, tartronic, malic, aspartic, glutamic, N-acetylaspartic, N-acetylglutamic acids and the like.

5 The heparin derivatives of present invention are commercially available products or they are prepared according to procedures well-known to those skilled in the art, or described in scientific and patent literatures.

10 The procedures for the synthesis of partially or completely N-desulfated and N-acylated heparin derivatives are disclosed in US-A-3,118,816, in WO 92/2258 (in the Applicant's name) and in GB Patent 2,078,768.

15 On the other hand, as far as the preparation of heparin derivatives characterized by at least a unit of formula I is concerned, the above mentioned partially or completely N-desulfated and N-acylated heparin derivatives are used as the starting compounds, which
20 are first oxidized with periodic acid or a salt thereof, according to the method described by Fransson L. et al., Carbohydrate Research, 80, 131-145 (1980), then reduced with a reducing agent, such as sodium borohydride, according to known methods (see, for
25 example, EP-A-0 287 477).

 Finally, the heparin fragments of average molecular weight equal or lower than 3,000 D are prepared according to the procedures described by Riesenfeld J. and Rodén L., Anal. Biochem., 188, 383-
30 389 (1990), and by Shively J.E. and Conrad E., Biochemistry, 15, N. 18, 3932-3942 (1976).

The following examples further illustrate the invention without limiting it.

EXAMPLE 1

100% N-succinylated N-desulfated heparin

5 a) N-desulfated heparin.

The preparation was carried out according to the procedure by Lloyd et al., Biochem. Pharm., 30, 637-648, 1971. An aqueous solution containing 1.1 g of porcine sodium heparin [Average MW - 13,600 Da; anti-Xa activity = 206 U/mg (chromogenic); APTT = 202 U/mg)] was percolated through a column thermostated at 4°C, containing 50 ml of Dowex^R 50 W X 8H cationic resin. The eluate (50 ml) containing the heparin acid, pH about 2, was placed into a round-bottom flask at 55°C for 24 hours, under mild stirring, at constant temperature. The solution was cooled to room temperature, neutralized to pH 7 with 1N NaOH, then freeze-dried to obtain the title product in form of a white powder. The desulfation degree was >95%, in agreement with the ¹³C-NMR analysis (shift of the C₁ signal of the amino sugar from 99.5 to 94 ppm, and shift of the C₂ signal from 60.5 to 66.8 ppm).

25 b) The product obtained in a) was dissolved in 100 ml of water (1% solution) under stirring. The solution was neutralized with 0.1N NaOH, and 2 g of solid succinic anhydride was added in 250 mg aliquots, always at room temperature. Each addition required pH to be adjusted from 5 to 7 with 0.1N NaOH. At the end of the reaction, the

insoluble succinate excess was filtered off, and the resulting clear solution was treated with 3 volumes of absolute ethanol, to obtain a white, solid precipitate, which was washed with absolute ethanol, then redissolved in water (5% solution), and the resulting solution was placed into dialysis membrane (SPECTRAPOR^R with cut-off 8,000 D) for 24 hours, against 2 l of water. The intradialysis solution was freeze-dried, to obtain the title product in form of white powder, having the following characteristics.

Sulfates/carboxyls = 0,91

Electrophoresis in barium acetate: R_f = unitary spot

Electrophoresis in HCl: R_f = 0.61

Anti-Xa activity < 1 U/mg

APTT = 26.4 U/mg

Average MW (HPLC) = 13,300 Da

Non-sulfated uronic acids (NMR) = 25.6%

EXAMPLE 2

20 50% N-succinylated N-desulfated heparin

Following the procedure described in Example 1a), but effecting the reaction at 40°C for 24 hours, a partially N-desulfated (>50%) heparin derivative was obtained, which desulfation degree was checked by means of ¹³C-NMR analysis as above described, and which was subjected to a succinylation reaction as described in Example 1b). The product, obtained in form of a white powder, has the following characteristics.

Sulfates/carboxyls = 1.2

Electrophoresis in barium acetate: R_f = 2 spots

Electrophoresis in HCl: R_f = 0.64

Anti-Xa activity < 1 U/mg

APTT = 18.3 U/mg

Average MW (HPLC) = 13,030 Da

Non-sulfated uronic acids (NMR) = 39.7%

5 **EXAMPLE 3**

30% N-succinylated N-desulfated heparin

Following the procedure described in Example 1a), but effecting the reaction at 35°C for 24 hours, a partially N-desulfated (>30%) heparin derivative was
10 obtained, which was subjected to a succinylation reaction as described in Example 1b). The product, obtained in form of a white powder, has the following characteristics.

Sulfates/carboxyls = 1.44

15 Electrophoresis in barium acetate: R_f = 2 spots

Electrophoresis in HCl: R_f = 0.68

Anti-Xa activity = 19.5 U/mg

APTT = 74.8 U/mg

Average MW (HPLC) = 13,300 Da

20 Non-sulfated uronic acids (NMR) = 30.4%

EXAMPLE 4

100% N-succinylated low molecular weight heparin

The procedure described in Example 1 was followed, starting from 1 g of a low molecular weight heparin
25 (Average MW = 5,000 Da; anti-Xa activity = 97 U/mg; APTT = 74 U/mg; Calbiochem). The purification of the N-succinylated derivative from the succinate excess was carried out in a dialysis membrane SPECTRAPOR^R with cut-off 1,000 D, according to what described in Example
30 1b). After freeze-drying, the title product is obtained in form of a white powder having the following

characteristics.

Sulfates/carboxyls = 1

Electrophoresis in barium acetate: R_f = unitary spot

Electrophoresis in HCl: R_f = 0.62

5 Anti-Xa activity < 1 U/mg

APTT - 4.9 U/mg

Average MW (HPLC) - 4,070 Da

Non-sulfated uronic acids (NMR) - 34.5%

EXAMPLE 5

10 50% N-succinylated low molecular weight heparin

Following the procedure described in Example 2, starting from 1 g of the heparin derivative used in Example 4, the title product is obtained in form of a white powder, having the following characteristics.

15 Sulfates/carboxyls - 1.1

Electrophoresis in barium acetate: R_f = unitary spot

Electrophoresis in HCl: R_f = 0.66

Anti-Xa activity < 1 U/mg

APTT < 1 U/mg

20 Average MW (HPLC) - 3,660 Da

Non-sulfated uronic acids (NMR) - 38%

EXAMPLE 6

100% N-succinylated very low molecular weight heparin

25 The procedure described in Example 1 was followed, starting from 1 g of a very low molecular weight heparin (Average MW < 3,000 Da; anti-Xa activity > 50 U/mg; APTT < 45 U/mg; Sigma). The purification of the N-succinylated derivative from the succinate excess was carried out by fractional precipitation, making use of

30 the selective formation of complexes with alkylammonium salts (see. Methods of Biochem. Anal., 8, 145-197,

1960): the 5% solution of N-succinylated very low molecular weight heparin was subjected to selective precipitation with 10% cetyl pyridinium chloride in the absence of salts, at 4°C, leaving to stand for about 2 hours, then centrifuging at 4,000xg for 20 minutes. The resulting precipitate was separated from the succinate excess in the solution, and after washing for 3 times with warm distilled water, was redissolved at 30-35°C in a 2M NaCl solution. Said solution was treated with 3 volumes of absolute ethanol, to precipitate the title product, having the following characteristics.

Sulfates/carboxyls = 0.9

Electrophoresis in barium acetate: R_f = unitary spot

Electrophoresis in HCl: R_f = 0.74

15 Anti-Xa activity < 1 U/mg

APTT - 2.4 U/mg

Average MW (HPLC) - 2,350 Da

EXAMPLE 7

20 50% N-desulfated and N-succinylated very low molecular weight heparin

The procedure described in Example 2 was followed, starting from 1 g of the heparin derivative used in Example 6. The purification of the product was carried out as described in Example 6, to obtain a compound having the following characteristics.

Sulfates/carboxyls = 1.1

Electrophoresis in barium acetate: R_f = unitary spot

Electrophoresis in HCl: R_f = 0.78

Anti-Xa activity < 1 U/mg

30 APTT < 1 U/mg

Average MW (HPLC) - 2,400 Da

EXAMPLE 8**50% N-succinylated N-desulfated heparin calcium salt**

The product of Example 2 (1 g) was percolated through a column thermostated at 4°C, containing 50 ml of cationic resin DOWEX^R 50WX8H⁺. The eluate containing the acid form of the intermediate was titred with a stoichiometric amount of calcium carbonate, and the solution was freeze-dried, to obtain the title product in form of a white powder, having the following characteristics.

Sulfates/carboxyls - 1.2

Electrophoresis in barium acetate: R_f - 2 spots

Electrophoresis in HCl: R_f = 0.64

Anti-Xa activity < 1 U/mg

APTT - 19 U/mg

Average MW (HPLC) - 13,300 Da

EXAMPLE 9**50% N-desulfated N-succinylated low molecular weight heparin**

The product of Example 5 (1 g) was treated as described in Example 8, to obtain the title product having the following characteristics.

Sulfates/carboxyls - 1.1

Electrophoresis in barium acetate: R_f = unitary spot

Electrophoresis in HCl: R_f = 0.74

Anti-Xa activity < 1 U/mg

APTT < 1 U/mg

Average MW (HPLC) - 3,660 Da

EXAMPLE 10

50% N-desulfated N-succinylated very low molecular weight heparin calcium salt

The product of Example 7 (1 g) was treated as described in Example 8, to obtain the title product, having the following characteristics.

Sulfates/carboxyls = 1.1

Electrophoresis in barium acetate: R_f = unitary spot

Electrophoresis in HCl: R_f = 0.78

Anti-Xa activity < 1 U/mg

APTT < 1 U/mg

Average MW (HPLC) = 2,400 Da

EXAMPLE 11

100% oxidized-reduced N-desulfated N-succinylated heparin

a) 100% oxidized N-desulfated N-succinylated heparin.

A solution of 10 g of the product of Example 1 in 500 ml of 50mM citric acid buffer, pH 3, added with 0.2M sodium perchlorate was cooled at 4°C and mixed with a solution of 4.29 g of sodium metaperiodate in 500 ml of the same buffer, previously cooled at 4°C. The mixture was reacted under stirring, in the dark, for 24 hours at 4°C, keeping pH at 3. At the end of the reaction (checked by photometric reading at 223 nm), 100 ml of an aqueous solution containing 11 ml of ethylene glycol added, then the mixture was neutralized with 1N NaOH. The product was recovered by precipitation from absolute ethanol (yield: 90%).

b) 450 ml of an aqueous solution of 9 g of the

product of step a) were added with 340 mg of sodium borohydride in 10 ml of water. The reaction mixture was left to react for 3 hours at room temperature, then the sodium borohydride excess was removed adjusting the solution to pH 5 with 1N HCl. After a night, the mixture was neutralized with 1N NaOH, and, by precipitation from 3 volumes of absolute ethanol, the product was recovered (yield: about 70%) having the following characteristics.

Sulfates/carboxyls - 0.97

Electrophoresis in barium acetate: R_f = unitary spot

Electrophoresis in HCl: R_f = 0.56

Anti-Xa activity < 1 U/mg

APTT - 21.9 U/mg

Average MW (HPLC) - 11,000 Da

Non-sulfated uronic acids (NMR) - 11.1%

EXAMPLE 12

30% oxidized-reduced N-desulfated N-succinylated
heparin

According to the procedure of Example 11, starting from 3 g of the compound of Example 3, the title product was obtained, having the following characteristics (yield: 10 g).

Sulfates/carboxyls - 1.55

Electrophoresis in barium acetate: R_f = unitary spot

Electrophoresis in HCl: R_f = 0.59

Anti-Xa activity < 1 U/mg

APTT - 29.0 U/mg

Average MW (HPLC) - 9,500 Da

Non-sulfated uronic acids (NMR) = 2%

EXAMPLE 13

100% oxidized-reduced N-desulfated N-succinylated low molecular weight heparin

According to the procedure of Example 11, starting
5 from 17 g of the compound of Example 4, the title product is obtained, having the following characteristics (yield: 13 g).

Electrophoresis in barium acetate: R_f = unitary spot

Electrophoresis in HCl: R_f = 0.59

10 Anti-Xa activity < 1 U/mg

Average MW (HPLC) = 4,000 Da

Non-sulfated uronic acids (NMR) = 12.8%

EXAMPLE 14

Very low molecular weight heparin

15 A 2% solution (2 g in 100 ml) of porcine sodium heparin [Average MW = 13,600 Da; anti-Xa activity = 206 U/mg (chromogenic); activity APTT = 202 U/mg]] was cooled to 4°C, and pH was adjusted to 2 with hydrochloric acid, then was added with a solution of
20 120 mg of sodium nitrite in 800 µl of water, quickly added. The pH was readjusted to 2, and the mixture was reacted for 15 minutes, then was neutralized with NaOH. 500 mg of 5 ml of sodium borohydride were added thereto and the mixture was left to react overnight, after that
25 the sodium borohydride excess was removed, pH was adjusted to 5, then, when effervescence was over, pH was readjusted to 7. The title product is precipitate with 3 volumes of ethanol, and dried in oven, under vacuum, at 35°C.

30 Electrophoresis in barium acetate: R_f = unitary spot

Electrophoresis in HCl: R_f = 0.73

Anti-Xa activity < 1 U/mg

APTT = 37 U/mg

Average MW (HPLC) = 2,100 Da

The compounds of present invention have
5 antimetastatic and antiproliferative activities,
therefore they are potentially useful in oncology.

The antiproliferative and antimetastatic
activities of the compounds will be illustrated by
means of the following test:

10 **INHIBITION OF METASTASES FORMATION**

Ten female mice C57BL/6 (18-20 g weight) were
inoculated subcutaneously with varying doses of some of
representative compounds of the invention, then, after
10 minutes, they were inoculated intravenously with
15 murine melanoma cells B16BL6 (10^5 cells/mouse). The
animals were observed for 21 days, then they were
killed. Following a general examination of the animal
to evaluate the presence of any extra-pulmonary
metastases, lungs were explanted, then fixed in a
20 suitable solution to count metastases under
stereoscopic microscopy. Only the tests in which the
animals of the control groups showed an average
metastases number higher than 100 were considered.

The compounds of present invention showed a
25 percent inhibition of the metastases number always
higher than 50%, at dosages generally higher or equal
to 100 µg/mouse. Moreover, to further prove the
antimetastatic activity, some compounds showed a 20%
inhibition of the tumour taking hold at the same doses
30 as above. In some representative tests, the compound of
Example 11 showed a percent inhibition of the

metastases number higher than 60%, at doses higher or equal to 200 µg/mouse, whereas the compound of Example 1 showed a slightly lower activity (about 50% percent inhibition of the metastases number) at the same doses.

5 The compound of Example 4 had a percent inhibition of the metastases number higher than 60% at doses higher than 200 µg/mouse, together with an inhibition of the tumour taking hold of about 20%. Finally, a commercial heparin having the following
10 characteristics: Average MW < 3,000 Da; anti-Xa activity > 50 U/mg; APTT < 45 U/mg; showed a percent inhibition of the metastases number higher than 80% at doses ranging from 100 to 400 µg/mouse, and a percent inhibition of the metastases number higher than 50%, at
15 doses of 50 µg/mouse; moreover it showed a inhibition of the tumour taking hold of about 20% even at a dose of 50 µg/mouse.

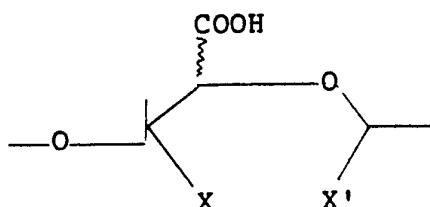
 The present invention relates to all the industrially applicable aspects related to the use of
20 the claimed compounds claimed as therapeutical agents. Therefore, a main object of the present invention is provided by pharmaceutical compositions of said salts together with conventional excipients or carriers.

 Particularly, a further object of the invention
25 relates to pharmaceutical preparations suitable to the parenteral and oral administrations, containing therapeutically effective amounts of a compound of present invention. Said compositions can be prepared according to techniques known to those skilled in the
30 art, as described, for example, in "Remington's Pharmaceutical Science Handbook", XVII Ed., Mack Pub.,

N.Y., USA. The posology, anyway, will be chose by the clinician, depending on the severity of the pathology to treat and the conditions, weight, age and sex of the patient.

CLAIMS

1. Heparin derivatives N-acylated with residues from aliphatic monocarboxylic acids having 3 to 20 carbon atoms, or with residues from aliphatic dicarboxylic acids having 3 to 10 carbon atoms, said derivatives having a molecular weight ranging from about 1,000 to about 30,000 daltons (Da), having a N-acylation degree, defined as the percent ratio of the number of N-acylated residues to the number of N-sulfated groups present in the heparin compound which they derive from, ranging from about 10 to about 100, said derivatives being further characterized in that they contain at least a unit of open D-iduronic or L-iduronic acids of formula I



20

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wherein X e X' are independently a -CHO or -CH₂OH group; and in that the OH groups free from non-open units of D-glucuronic or L-iduronic acids and from D-glucosamine units can be acylated with the acyl residues mentioned above; and the salts thereof with alkali or alkaline-earth metal cations.

25

2. The use of the heparin derivatives of claim 1 in the prevention of the formation of metastases in patients affected with neoplasias.

30

3. The use of the heparin derivatives of claim 1 in

the preparation of a medicament useful in the prevention of the formation of metastases in patients affected with neoplasias.

4. The use of the derivatives of heparin or of fragments and fractions thereof, having a molecular weight ranging from about 1,000 to about 30,000 Da, N-acylated with residues from aliphatic monocarboxylic acids having 3 to 20 carbon atoms, or with residues from aliphatic dicarboxylic acids having 3 to 10 carbon atoms, and having a N-acylation degree, defined as the percent ratio of the number of N-acylated residues to the number of N-sulfated groups present in the heparin compound which they derive from, ranging from about 10 to about 100, and the salts thereof, in the prevention of the formation of metastases in patients affected with neoplasias.

5. The use of the compounds according to claim 4 in the preparation of a medicament useful in the prevention of the formation of metastases in patients affected with neoplasias.

6. The use of heparin fragments or fractions, having an average molecular weight equal or lower than 3,000 Da, and the salts thereof, in the prevention of the formation of metastases in patients affected with neoplasias.

7. The use of the compounds according to claim 6 in the preparation of a medicament useful in the prevention of the formation of metastases in patients affected with neoplasias.