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Case Number: T 0144/13 - 3.3.07

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Title of invention:
Blood pool agents for nuclear magnetic resonance diagnostics

Applicant:
Bracco Imaging S.p.A.

Relevant legal provisions:
EPC Art. 76(1), 123(2), 56

Keyword:
Inventive step - (yes)

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European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 0144/13 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 12 May 2016

Appellant: (Applicant)	Bracco Imaging S.p.A. Via E. Folli 50 20134 Milano (IT)
Representative:	Ravizza, Claudio Bracco Imaging SpA Intellectual Property Via Caduti di Marcinelle, 13 20134 Milan (IT)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 9 August 2012 refusing European patent application No. 08004643.6 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	D. Boulois
Members:	R. Hauss
	P. Schmitz

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division, posted on 9 August 2012, refusing European patent application No. 08 004 643.6 (a divisional of European patent application No. 99 963 556.8).

II. In the decision under appeal, which is based on the application as filed, the examining division found that the subject-matter of claims 1 to 4 did not involve an inventive step having regard to the disclosure of document D1 (WO 95/32741), in particular compound 29 disclosed therein.

III. The applicant (appellant) lodged an appeal against that decision and requested that a patent be granted on the basis of the application as filed.

IV. In the statement setting out the grounds of appeal, the appellant argued that the compounds defined by formula (IVa) in claim 1 of the application as filed represented a purposive selection within the range of compounds covered by document D1. Both the application in suit and document D1 related to contrast agents for magnetic resonance imaging (MRI). The technical effect provided by the compounds claimed in the application was their property, when administered as chelate complexes of gadolinium or manganese, of remaining in the vascular system for a sufficiently long time to permit magnetic resonance imaging of the vascular system to be carried out, while the compounds of D1 were said to be devised for the imaging of the hepatobiliary system (see D1: page 6, lines 14 to 24, claim 18). In support of the alleged technical effect, the appellant referred to example 18 of the application

and to additional experimental data submitted with the statement setting out the grounds of appeal.

V. In a communication issued in preparation for oral proceedings and advising the appellant of the board's preliminary opinion, the board observed that the available experimental data were limited in scope and did not appear to provide conclusive proof that an improvement, in the form of prolonged retention of the complexes in the vascular system, was achieved over the entire scope claimed (see point 1.7 of the board's communication).

VI. With letter dated 6 April 2016, the appellant filed a new main request and three auxiliary requests.

VII. Oral proceedings before the board took place on 12 May 2016.

During the oral proceedings, the appellant submitted an amended set of four claims to replace the previous main request.

The claims of the new **main request** read as follows:

"1. Chelating compounds selected from the group consisting of:

[3β(S),5β]-3-[[4-[bis[2-[bis(carboxymethyl)amino]ethyl]amino]-4-carboxy-1-oxobutyl]amino]cholan-24-oic acid; (compound 2)

[3β(R),5β,12α]-3-[[4-[bis[2-[bis(carboxymethyl)amino]ethyl]amino]-4-carboxy-1-oxobutyl]amino]-12-hydroxy-cholan-24-oic acid; (compound 10)

[3β(RS),5β,12α]-3-[[4-[bis[2-[bis(carboxymethyl)amino]ethyl]amino]-4-carboxy-1-oxobutyl]amino]-12-hydroxy-cholan-24-oic acid; (compound 11)

[3α(S),5β]-3-[[4-[bis[2-[bis(carboxymethyl)amino]ethyl] amino]-4-carboxy-1-oxobutyl]-amino]cholan-24-oic acid; (compound 4)

[3β(S),5β,12α]-3-[[4-[bis[2-[bis(carboxymethyl)amino] ethyl]amino]-4-carboxy-1-oxobutyl]amino]-12-hydroxy-cholan-24-oic acid; (compound 9)

[3α(S),5β,12α]-3-[[4-[bis[2-[bis(carboxymethyl)amino] ethyl]amino]-4-carboxy-1-oxobutyl]amino]-12-hydroxy-cholan-24-oic acid (compound 12);

the complexes thereof with gadolinium or manganese ions and the salts of the complexes with cations of bases selected from the group consisting of: ethanolamine, diethanolamine, morpholine, glucamine, N-methylglucamine, N,N-dimethylglucamine or from the group consisting of inorganic bases whose cations are sodium, potassium, magnesium and calcium.

2. Compounds according to claim 1 selected from the group consisting of:

[3β(S),5β]-3-[[4-[bis[2-[bis(carboxymethyl)amino] ethyl]-amino]-4-carboxy-1-oxobutyl]amino]cholan-24-oic acid;

[3β(S),5β,12α]-3-[[4-[bis[2-[bis(carboxymethyl)amino] ethyl]amino]-4-carboxy-1-oxobutyl]amino]-12-hydroxy-cholan-24-oic acid.

3. A compound according to claims 1 or 2 selected from:

[3β(S),5β,12α]-3-[[4-[bis[2-[bis(carboxymethyl)amino] ethyl]amino]-4-carboxy-1-oxobutyl]amino]-12-hydroxy-cholan-24-oic acid,

the complex thereof with gadolinium and the salts thereof with N-methylglucamine or sodium.

4. A contrastographic diagnostic pharmaceutical composition comprising at least one of the chelated

complexes, or a salt thereof, according to any one of the preceding claims from 1 to 3."

VIII. The appellant's arguments, in so far as relevant for the present decision, may be summarised as follows:

a) Compound 4 listed in claim 1 of the main request found its basis pursuant to Article 76(1) EPC in the chemical structure shown on page 11, line 17, of the parent application. While the chemical name used on page 11, lines 14 to 16, of the parent application to designate that structure differed from the name of compound 4 in claim 1 of the main request, the person skilled in the art would realise that it was not in line with the nomenclature which was consistently used in the parent application for the names of structurally closely related compounds having the same linker and "DTPA" ligand moieties (see for instance page 11, lines 2 to 13). Thus it was evident that the disclosure on page 11, lines 14 to 17 of the parent application related to the compound represented by the chemical structure rather than to the (incorrect) chemical name. The name had been corrected accordingly in the divisional application.

b) With regard to inventive step, the appellant argued that the definition of the chelating compounds in claim 1 had been restricted to compounds 2, 9 and 11, for which a technical effect (viz. increased blood concentration over time and improved relaxivity) had been demonstrated in comparison with compound 29 of D1. Compounds 4, 10 and 12, also listed in claim 1, were stereoisomers of compounds 2, 9 or 11 and would be regarded by the skilled person as equivalent, in terms of relaxivity and vascular residence time, to those compounds. The resulting improved suitability of the

claimed compounds for vascular MRI could not have been derived from the technical teaching of document D1, which focused on hepatobiliary imaging.

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claims of the main request, as filed during the oral proceedings before the board, or one of the first to third auxiliary requests, all filed with letter dated 6 April 2016.

Reasons for the Decision

1. Amendments - main request

1.1 Claims 1 and 2 of the present main request are directed to chelating compounds mentioned on pages 9 and 11 of the description as filed and in original claim 2 as filed, the complexes thereof with gadolinium or manganese ions and the salts of such complexes with specified cations, as defined, in the form of a general disclosure, in the description on page 5, lines 2 to 6; page 8, lines 2 to 3; page 23, line 8 to page 24, line 23. Dependent claim 3 and independent claim 4 are respectively based on claims 3 and 4 as filed.

1.2 Corresponding support is found in the parent application (published as WO 00/38738 A1) on pages 11, 13 and 14 showing the specific chelating compounds, page 9, lines 18 to 20; page 27, line 16 to page 29, line 13, and claim 24.

With regard to compound 4, the board accepts the appellant's view (see point VIII(a) above) that compound 4 finds support in the chemical structure shown on page 11, line 17 of the parent application,

and that the chemical name corresponding to that structure is the name recited in claim 1 of the present main request.

1.3 In view of the above, the requirements of Articles 123(2) and 76(1) EPC are met.

2. Inventive step - main request

Present application

2.1 The present application seeks to provide contrast agents for magnetic resonance imaging, in particular for the imaging of the vascular system (so-called "blood pool agents"); see page 1, lines 1 to 4, and page 3, line 13 to page 4, line 17 of the application.

2.2 As a solution to that problem, present claim 1 defines a list of six specified chelating compounds in which a lithocholic or deoxycholic bile acid residue is linked at the 3-position via a linker having the structure $-(CH_2-CH_2-CO-NH)-$ to DTPA (diethylene-triamino-pentaacetic acid) as a polyaminopolycarboxylic ligand, the complexes of those compounds with gadolinium or manganese ions and the salts of said complexes with specified organic or inorganic cations. Independent claim 4 is directed to a contrastographic diagnostic pharmaceutical composition comprising at least one chelated complex, or salt thereof, according to claims 1 to 3.

Closest prior art

2.3 Document D1 (cited in the application) is a suitable starting-point for the assessment of inventive step. This earlier application by the same applicant discloses bile acid conjugate MRI contrast agents of

the same general type as those defined in present claim 1, but with a more varied choice of the bile acid residue, linker, linking position and polyamino-polycarboxylic ligand (D1: claim 1). A desired property according to D1 is suitability of the contrast agent for targeting liver tissue, bile ducts and gall bladder (see D1: page 2, line 19 to page 3, line 5). D1 also includes a claim directed to contrast diagnostic pharmaceutical compositions comprising at least one of the complex chelates according to claims 1 to 14 or a salt thereof (see D1: claim 15).

2.4 The compounds according to present claim 1 are a subgroup of the compounds defined in prior-art document D1 (see D1: claim 1).

2.5 Compound 29 listed in claim 14 and shown on page 33 of document D1 is structurally very similar to the claimed compounds 2 and 9 of the present application; it differs from them solely in that the bile acid residue is derived from cholic acid instead of lithocholic or deoxycholic acid.

Technical problem and solution

2.6 According to the appellant, the chelating compounds listed in claim 1 of the main request represent a technical improvement over compound 29 of D1, because the claimed compounds yield complexes which are more suitable for vascular imaging, due to longer residence times in the vascular system after administration.

2.7 Based on the experimental data reported in example 18 of the present application and in table 2 provided with the statement setting out the grounds of appeal, the board accepts that the gadolinium complexes of compounds 2 and 9 have been shown to be retained

longer in the vascular system of test animals than the gadolinium complex of compound 29 of D1, which is the structurally most similar compound disclosed in document D1. Since compounds 4, 10, 11 and 12 are merely α-diastereomers or R enantiomers of compounds 2 or 9, it is plausible that those compounds would provide the same advantage as compounds 2 and 9. It has thus been rendered credible that the chelating compounds according to claim 1 yield gadolinium complexes with improved suitability for vascular imaging. Based on the available information, the board has moreover no reason to assume that complexes formed with manganese, as defined in claim 1, would behave differently, or that the choice of cations used for salification of the complexes would have any impact on the desired properties. Hence it can be accepted that the alleged technical effect is obtained over the entire scope claimed.

2.8 Accordingly, the technical problem to be solved is the provision of compounds with improved suitability as contrast agents for vascular MRI and of diagnostic compositions containing such compounds.

2.9 The board is satisfied that the technical problem is solved by the compounds and compositions defined in the present claims (see point 2.7 above).

Obviousness

2.10 Since document D1 does not discuss blood pool agents or vascular imaging, it gives no indication that the compounds according to present claim 1 might be particularly suitable for that purpose.

2.11 As a consequence, the claimed subject-matter involves an inventive step within the meaning of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to grant a patent on the basis of claims 1 to 4 of the main request, as filed during the oral proceedings before the board, and a description to be adapted.

The Registrar: The Chairman:

S. Fabiani D. Boulois

Decision electronically authenticated