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D E C I S I O N
of 29 April 2004

Case Number: T 1280/01 - 3.3.1

Application Number: 94108968.2

Publication Number: 0629617

IPC: C07D 233/91

Language of the proceedings: EN

Title of invention:
Heteroatom-bearing ligands and metal complexes thereof

Patentee:
BRACCO International B.V.

Opponent:
Amersham plc

Headword:
Ligands and metal complexes thereof/BRACCO

Relevant legal provisions:
EPC Art. 54, 56, 100(b), 123(2)(3)

Keyword:
"Main request: amendments supported by the application as filed (no)"
"First auxiliary request: inventive step (yes) - non obvious solution"

Decisions cited:
T 0206/83, T 0166/90

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1280/01 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 29 April 2004

Appellant 1: (Opponent)
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Appellant 2: (Proprietor of the patent)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 8 October 2001 concerning maintenance of European patent No. 0629617 in amended form.**

Composition of the Board:

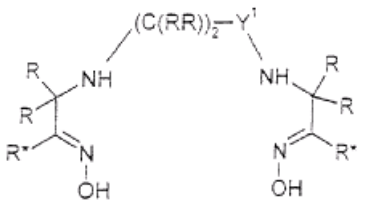
Chairman: A. J. Nuss
Members: P. F. Ranguis
S. C. Perryman

Summary of Facts and Submissions

I. Appellant 1 (Opponent) and Appellant 2 (Proprietor of the patent) each lodged an appeal against the decision of the Opposition Division to maintain the European patent 0 629 617 in amended form pursuant to Article 102(3) EPC.

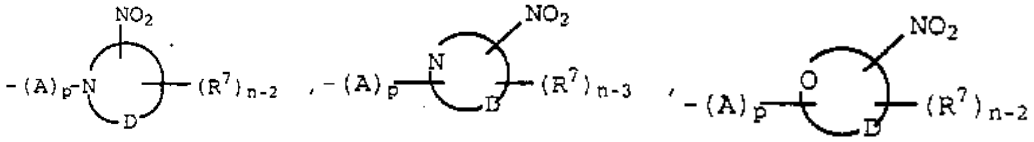
II. Claim 1 of the request as maintained read as follows:

"1. A compound of the following formula:



in which Y_1 is $-NR_0$ or -O- wherein R_0 is H or C_1-C_{12} alkyl and each of the groups R and R^* are, independently:
(i) R_2; (ii)halogen; (iii) $-OR_2$; (iv) $-CO-OR_2$; (v) $-CO-N(R_2)_2$; (vi) $-N(R_2)_2$; (vii) -alkylene-$CO-OR_2$; (viii) -alkylene-$CO-N(R_2)_2$; (ix) -alkylene-$N(R_2)_2$; (x) -arylene-$CO-OR_2$; (xi) -arylene-$CO-NR(R_2)_2$; (xii) -arylene-$N(R_2)_2$; (xiii) -acyl; (xiv) -acyloxy; (xv) -heterocyclo; (xvi) hydroxyalkyl; (xvii) $-SO_2-R_2$; (xviii) -alkyl-SO_2-R_2;(xix) $-(A)_p-R^3$, where A is a linker selected from -O-; -S; -CO-; -CS-; -NH-; $-NR_5$-; -HC=N-; $-CR_5$=N-; -heterocyclo-; -alkylenes- and -alkenylenes- such as $-CH_2$-, $-CHR_5$-, $-CR_5R_6$-, -CH=CH-, $-CHCR_5$-, $-CR_5=CR_6$-, in which R_5 and R_6 are independently alkyl-, alkenyl-, alkoxy-, aryl-, 5- or 6-membered N- or O-containing heterocycles, halogen-, HO- or hydroxyalkyl; -alkynylenes- such as -C≡C-; -cycloalkylene-; -cycloalkenylene-; -arylene- such as

unsubstituted or
HO-substituted phenylene; -arylalkylenes; -hydroxyalkylenes-, -aminoalkylenes-; -amidoalkylenes-; and alkylamino-alkylenes-; p is 0 to 20, and R^3 is a bioactive group selected from hypoxia localizing moieties of structures



wherein D is a group of atoms that forms, together with the N or O atoms to which it is bound, a 5- or 6-membered ring, n is the total number of substitution positions available on the ring, and one or more of the R_7 groups are independently H, halogen, alkyl, aryl, alkoxy, OH, hydroxyalkyl, hydroxyalkoxy, alkenyl, arylalkyl, alkylamido, arylalkylamido, alkylamino, and (alkylamino)-alkyl; or
(xx) two R groups, or one R and one R^*, taken together with the one or more atoms to which they are bound, form a saturated or unsaturated spiro or fused, carbocyclic or heterocyclic ring which may or not be substituted with one or more of the groups (i) to (xix), with the proviso that an R bearing C atom is not directly linked to more than one heteroatom; and with the further proviso that the compound contains one or more groups $-(A)_p-R^3$ where R^3 is a hypoxia-localizing moiety as defined herein; R_1 is H, a thiol protecting group, or the group $-(A)_p-R^3$ and R^2 is independently H, alkyl, alkenyl, alkynyl, or aryl".

III. The opposition sought revocation of the patent in suit on the ground that its subject-matter gave rise to objection under Article 100(a) EPC (lack of novelty and

inventive step) and Article 100(b) EPC. The following documents were cited, in that respect:

(3) EP-A-0 544 412

(4) US-A-5 101 041

(5) Nucl. Med. Biol., 19(7) 791-795 (1992)

(6) J. Nucl. Med., Vol. 32, No. 5, 985 (May 1991)

(7) Proceedings of the "Third International Symposium on Technetium in Chemistry and Nuclear Medicine", Padua (Italy) 1989, pp 585-593, "Pentadentate amino phenol complexes of ^{99m}Tc"

(8) Chem. Pharm. Bull., 39(1), 104-107 (1991).

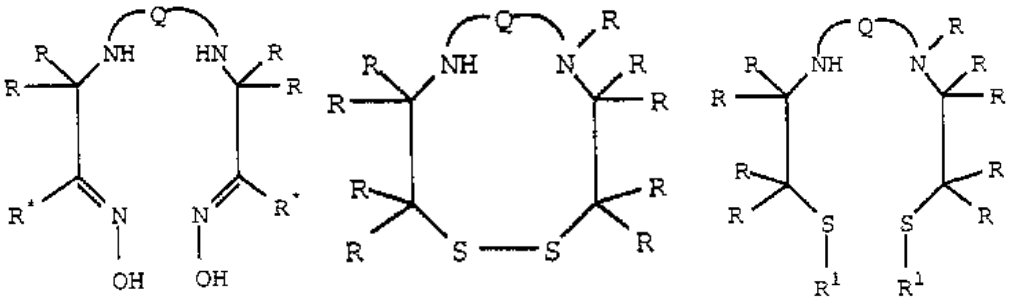
IV. In its decision, the Opposition Division held that the subject-matter of Claim 1 of the main request which was to maintain the patent as granted, lacked novelty in view of documents (4) to (7). Regarding the auxiliary request, the Opposition Division considered that in view of document (3), considered as the closest state of the art, the technical problem to be solved was to be seen in the provision of compounds which had higher selectivity for hypoxic tissue than the compounds disclosed in document (3). In view of the comparative data provided by the Patentee, it was credible that the technical problem was solved within the whole scope of Claim 1. Furthermore, none of the prior art cited suggested solving the technical problem in the way as defined in Claim 1 of the auxiliary request so that an inventive step could be acknowledged.

The subject-matter of the first auxiliary request also complied with the requirements of Article 83 EPC.

V. Oral proceedings before the Board took place on 29 April 2004. In the appeal proceedings, Appellant 2 no longer relied upon the set of claims maintained by the Opposition Division (cf. point II above) and submitted in lieu thereof two sets of claims as main request and first auxiliary request, respectively filed on 18 February 2002 and 17 January 2003.

The main request contained twenty five claims. Claim 1 read as follows:

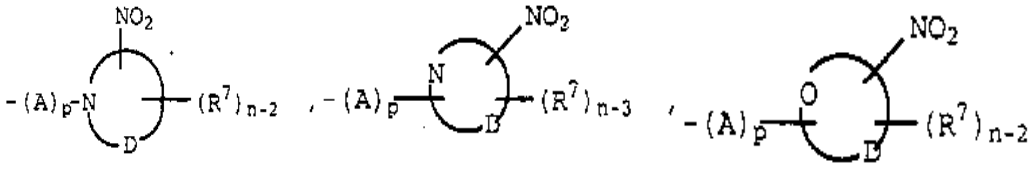
"1. A compound of the following formulae Ia, Ib or Ic



Ia Ib Ic

wherein Q is the group of formula $-(CRR)_{m1}-Y_1-(CRR)_{m2}-$, in which Y_1 is -NR-, -O-, -S-, -SO-, $-SO_2-$ or Se; and m_1 and m_2 are independently integers from 0 to 4, provided that $m_1 + m_2 > 0$ and m_1 or $m_2 = 0$; each of the groups R and R^* are, independently: (i) R_2; (ii)halogen; (iii) $-OR_2$; (iv) $-CO-OR_2$; (v) $-CO-N(R_2)_2$; (vi) $-N(R_2)_2$; (vii) -alkylene-$CO-OR_2$; (viii) -alkylene-$CO-N(R_2)_2$; (ix) -alkylene-$N(R_2)_2$; (x) -arylene-$CO-OR_2$; (xi) -arylene-$CO-NR(R_2)_2$; (xii) -arylene-$N(R_2)_2$; (xiii) -acyl; (xiv) -acyloxy; (xv) -heterocyclo; (xvi) hydroxyalkyl; (xvii) $-SO_2-R_2$; (xviii) -alkyl-SO_2-R_2;(xix)

$-(A)_p-R^3$, where A is a linker selected from -O-; -S; -CO-; -CS-; -NH-; $-NR_5$-; -HC=N-; $-CR_5$=N-; -heterocyclo-; -alkylenes- and -alkenylenes- such as $-CH_2$-, $-CHR_5$-, $-CR_5R_6$-, -CH=CH-, $-CHCR_5$-, $-CR_5$=CR_6-, in which R_5 and R_6 are independently alkyl-, alkenyl-, alkoxy-, aryl-, 5- or 6-membered N- or O-containing heterocycles, halogen-, HO- or hydroxyalkyl; -alkynylenes- such as -C≡C-; -cycloalkylene-; -cycloalkenylene-; -arylene- such as unsubstituted or HO-substituted phenylene; -arylalkylenes; -hydroxyalkylenes-, -aminoalkylenes-; -amidoalkylenes-; and alkylamino-alkylenes-; p is 0 to 20, and R^3 is a bioactive group selected from amphetamines, barbiturates, sulfonamides, monoamine oxidase substrates and inhibitors, hormones, enzymes, lipids, ligands for cell membrane receptors, antihypertensives, neurotransmitters, aminoacids and oligo-peptides, radiosensitizers, steroids, such as estrogen and estradiol, mono- and polyclonal antibodies as well as fragments thereof, sugars such as glucose derivatives, fatty acids, substrates for muscarine receptors such as 3-quinuclidinyl benzilate, substrates for dopamine receptors such as spiperone, biotin, chemotactic peptides, substrates for benzodiazepine receptors, and hypoxia localizing moieties of structures

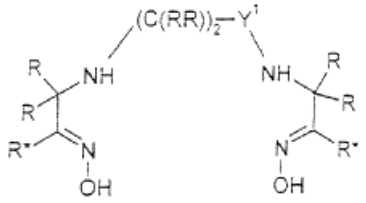


wherein D is a group of atoms that forms, together with the N or O atoms to which it is bound, a 5- or 6-membered ring, n is the total number of substitution positions available on the ring, and one or more of the R_7 groups are independently H, halogen, alkyl, aryl,

alkoxy, OH, hydroxyalkyl, hydroxyalkoxy, alkenyl, arylalkyl, alkylamido, arylalkylamido, alkylamino, and (alkylamino)-alkyl; or
(xx) two R groups, or one R and one R^*, taken together with the one or more atoms to which they are bound, form a saturated or unsaturated spiro or fused, carbocyclic or heterocyclic ring which may or not be substituted with one or more of the groups (i) to (xix), with the proviso that an R bearing C atom is not directly linked to more than one heteroatom; R_1 is H, a thiol protecting group, or the group $-(A)_p-R^3$ and R^2 is independently H, alkyl, alkenyl, alkynyl, or aryl".

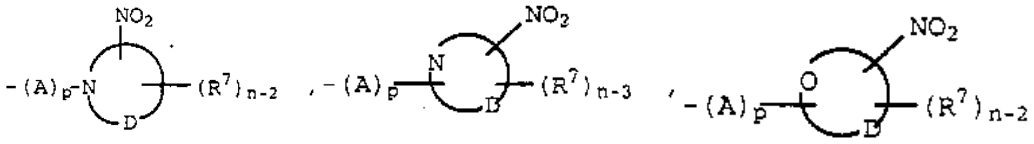
VI. The first auxiliary request contained twenty four claims. Independent Claims 1, 10, 16, 18, 19, 21 and 24 read as follows:

"1. A compound of the following formula:



in which Y_1 is $-NR_0$ or -O- wherein R_0 is H or C_1-C_{12} alkyl and each of the groups R and R^* are, independently:
(i) R_2; (ii)halogen; (iii) $-OR_2$; (iv) $-CO-OR_2$; (v) $-CO-N(R_2)_2$; (vi) $-N(R_2)_2$; (vii) -alkylene-$CO-OR_2$; (viii) -alkylene-$CO-N(R_2)_2$; (ix) -alkylene-$N(R_2)_2$; (x) -arylene-$CO-OR_2$; (xi) -arylene-$CO-NR(R_2)_2$; (xii) -arylene-$N(R_2)_2$; (xiii) -acyl; (xiv) -acyloxy; (xv) -heterocyclo; (xvi) hydroxyalkyl; (xvii) $-SO_2-R_2$; (xviii) -alkyl-SO_2-R_2;(xix) $-(A)_p-R^3$, where A is a linker selected from -O-; -S; -CO-; -CS-; -NH-; $-NR_5$-; -HC=N-; $-CR_5$=N-; -heterocyclo-; -alkylenes- and -alkenylenes- such

as $-CH_2-$, $-CHR_5-$, $-CR_5R_6-$, $-CH=CH-$, $-CHCR_5-$, $-CR_5=CR_6-$, in which R_5 and R_6 are independently alkyl-, alkenyl-, alkoxy-, aryl-, 5- or 6-membered N- or O-containing heterocycles, halogen-, HO- or hydroxyalkyl; -alkynylenes- such as $-C\equiv C-$; -cycloalkylene-; -cycloalkenylene-; -arylene- such as unsubstituted or HO-substituted phenylene; -arylalkylenes; -hydroxyalkylenes-, -aminoalkylenes-; -amidoalkylenes-; and alkylamino-alkylenes-; p is 0 to 20, and R^3 is a bioactive group selected from amphetamines, barbiturates, sulfonamides, monoamine oxidase substrates and inhibitors, hormones, enzymes, lipids, ligands for cell membrane receptors, antihypertensives, neurotransmitters, aminoacids and oligo-peptides, radiosensitizers, steroids, such as estrogen and estradiol, mono- and polyclonal antibodies as well as the fragments thereof, sugars such as glucose derivatives, fatty acids, substrates for muscarine receptors such as 3-quinuclidinyl benzilate, substrates for dopamine receptors such as spiperone, biotin, chemotactic peptides, substrates for benzodiazepine receptors, and hypoxia localizing moieties of structures



wherein D is a group of atoms that forms, together with the N or O atoms to which it is bound, a 5- or 6-membered ring, n is the total number of substitution positions available on the ring, and one or more of the R_7 groups are independently H, halogen, alkyl, aryl, alkoxy, OH, hydroxyalkyl, hydroxyalkoxy, alkenyl, arylalkyl, alkylamido, arylalkylamido, alkylamino, and (alkylamino)-alkyl; or

(xx) two R groups, or one R and one R^*, taken together with the one or more atoms to which they are bound, form a saturated or unsaturated spiro or fused, carbocyclic or heterocyclic ring which may or not be substituted with one or more of the groups (i) to (xix), with the proviso that an R bearing C atom is not directly linked to more than one heteroatom; and R^2 is independently H, alkyl, alkenyl, alkynyl, or aryl".

"10. A complex comprising a compound of claim 1 complexed with a metal."

"16. A complex as defined in claim 10 for use as a diagnostic."

"18. Use of a complex as defined in claim 10 for the preparation of a diagnostic composition for imaging hypoxic tissue."

"19. A complex as defined in claim 10 for use as a pharmaceutically active ingredient."

"21. A kit comprising a compound of claim 1 and a pharmaceutically acceptable reducing agent."

"24. A method for the stereoselective preparation of a compound of claim 9, comprising the steps of:
(i) reacting (S)-(+)-epichlorohydrin or (R)-(-)-epichlorohydrin with phthalimide to form a stereoisomer of 1-chloro-3-phthalimido-2-propanol;
(ii) contacting the product of (i) with an epoxide ring-forming agent to obtain a stereoisomer of N-(2,3-epoxypropyl)phthalimide;

(iii) contacting the product of (ii) with a base and 2-nitroimidazole to obtain a stereoisomer of 2-[2-hydroxy-2-(nitro-1H-imidazol-1-yl)ethyl]-1H-isoindole-1,3(2H)-dione;
(iv) contacting the product of (iii) with hydrazine, followed by a base and ditertiarybutyl dicarbonate, to obtain a stereoisomer of α-[(t-Boc-amino)methyl]-2-nitro-1H-imidazole-1-ethanol;
(v) contacting the product of (iv) with N-hydroxyphthalimide, triphenylphosphine and diethylazodicarboxylate to obtain a stereoisomer of 2-[1-[(t-Boc-amino)methyl]-2-(2-nitro-1H-imidazol-1-yl)ethoxy]1H-isoindole-1,3(2H)-dione;
(vi) contacting the product of (v) with hydrazine to obtain a stereoisomer of 1-[2-(aminooxy)-3-(t-Boc-amino)propyl]-2-nitro-1H-imidazole;
(vii) deprotecting the product of (vi) to obtain a stereoisomer of 1-[3-amino-2-(aminooxy)propyl]-2-nitro-1H-imidazole; and
(viii) contacting the product of (vii) with 3-chloro-3-methyl-2-nitrosobutane in the presence of a tertiary amine to obtain said compound of claim 9."

For ease of understanding, the wording of Claim 9 which is not an independent Claim is set out below:

"9. A compound of Claim 1 which is:
(R)-3,3,9,9-tetramethyl-6-[(2-nitro-1H-imidazol-1-yl)methyl]-5-oxa-4,8-diazaundecane-2,10-dione dioxime; or (S)-3,3,9,9-tetramethyl-6-[(2-nitro-1H-imidazol-1-yl)methyl]-5-oxa-4,8-diazaundecane-2,10-dione dioxime".

VII. In the written proceedings and at the oral proceedings, Appellant 1 submitted the following arguments:

The additional feature "m_1 or m_2 = 0" included in Claim 1 of the main request (cf. point V above) extended the claimed subject-matter beyond the content of the application as filed.

Regarding Claim 1 of the first auxiliary request (cf. point VI above), the feature "Y_1 is the group -NR_0- wherein R_0 is H or C_1-C_{12} alkyl" constituted new subject-matter not admissible under Article 123(2)(3) EPC. In that context, the passage of the description (cf. page 32, lines 6 to 8) referred to by Appellant 2 could not provide basis for such an amendment. The same arguments applied to Claims 2 to 7, 10 to 13 and 16 to 23 of this request.

The description of the patent in suit did not provide sufficient information to enable the person skilled in the art to prepare the claimed compounds within the whole scope of Claim 1. The definition of R^3 was too broad. In particular, only examples of preparation of compounds where R^3 was nitroimidazole or nitrofuran were provided. No process of preparation of compounds where R^3 was an antibody was given. In that context, documents (4) and (7) were not common general knowledge and could not be a proper basis to establish sufficiency of disclosure. Under such circumstances the burden of proof rested on the Patentee (Appellant 2).

In view of document (3) as the closest state of the art, the technical problem to be solved was to be seen in the provision of compounds which had higher selectivity for hypoxic tissue than the compounds disclosed in document (3). In view of the comparative

data provided by the Patentee (Dr Noon declaration), it was not credible that the technical problem was solved within the whole scope of Claim 1. Indeed, the compounds actually tested by Dr Noon were considerably narrower in scope than the overall scope of Claim 1. It was unreasonable to suggest that any compounds within Claim 1 would solve the above defined technical problem. Furthermore, if the technical problem to be solved was only to be seen as further compounds to localize in hypoxic tissue, it nevertheless turned out that the subject-matter of Claim 1 as a whole did not solve that problem since this claim encompassed compounds with or without hypoxia localizing moiety and it was impossible to localize compounds without hypoxia moiety in hypoxic tissue.

It would have been, furthermore, obvious to design the complexes comprising a compound of Claim 1 complexed with a metal according to this request. Indeed, document (3) taught on the one hand that the heteroatom, in particular the nitrogen atom, could be at any place. On the other hand, from the teachings of documents (4) to (8), there was an incentive to move the nitrogen atom at the location as defined in the chain $-(C(RR))_2-Y^1-$ of Claim 1. This was all the more true since it was clear that the nitrogen atom played no role in the formation of the coordination complex.

VIII. In the written proceedings and at the oral proceedings, Appellant 2 submitted the following arguments:

The additional feature "m_1 or m_2 = 0" present in Claim 1 of the main request (cf. point V above) was supported by the examples which disclosed compounds where either

m_1 or m_2 was equal to zero. Furthermore, various parts of the application as filed, in particular on page 13 (formulae IIa and IIb), page 17 (formulae IIc to IIf) page 40 and 41, Claims 3 and 14, showed preferred structures wherein either m_1 or m_2 is 0. In support thereof, decisions T 201/83 and T 166/90 were cited.

The subject-matter of Claim 1 of the auxiliary request was, in particular, supported by the application as filed on page 32, lines 6 to 8.

The methods of preparation of the claimed compounds were clearly described in the application as filed so that the burden of proof rested on the Appellant 2 which had brought no evidence in that respect. In particular, contrary to the Appellant's 1 assertion, there was no difficulty to achieve a bond between an antibody and the rest of the molecule, as taught by documents (4), (5), (6) and (7).

Regarding inventive step, the technical problem to be solved in view of document (3) could be seen in the provision of further complexes for use as diagnostic or therapeutic agents. The prior art as a whole did not direct in an obvious manner the person skilled in the art to design metal complexes as defined in Claim 10 (cf. point VI above) so that the requirement of Article 56 EPC was met.

IX. Appellant 1 requested that the decision under appeal be set aside and the patent be revoked.

Appellant 2 requested as main request and first auxiliary request that the decision under appeal be set

aside and that the patent be maintained on the basis of the claims of the main request submitted on 18 February 2002 or the first auxiliary request submitted on 17 January 2003.

X. At the end of the oral proceedings the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.

Main request

2. *Article 123(2) EPC - Amendments*

2.1 The question to be decided is whether or not the feature of Claim 1 "wherein Q is the group of formula -$(CRR)_{m1}$-Y_1-$(CRR)_{m2}$-, in which Y_1 is -NR-, -O-, -S-, -SO-, -SO_2-, or Se; and m_1 and m_2 are independently integers from 0 to 4, provided that $m_1 + m_2 > 0$ and m_1 or $m_2 = 0$" (cf. point V above) is subject-matter which extends beyond the content of the application as filed.

2.2 Appellant 2 argued, first, that this feature was based on Claim 1 as filed ("m_1, m_2 and m_3 are integers independently selected from 0 to 4, provided that the sum of m_1 and m_2 is greater than zero") in combination with the examples of the patent.

2.3 Claim 1 as filed, along with the description (cf. pages 2, line 13 to page 3, line 3), contains the following wording: " wherein Q is the group of formula-

$(CRR)_{m1}$-Y_1-$(CRR)_{m2}$-(Y_2-$(C(RR)_{m3})_n$, where Y_1 and Y_2 are independently -NR-, -O-, -S-, -SO-, -SO_2-, or Se; n is an integer selected from 0 or 1; and m_1, m_2 and m_3 are integers independently selected from 0 to 4, provided that the sum of m_1 and m_2 is greater than zero".

2.4 In the Board's judgment, from the application as filed there emerges unambiguously subject-matter wherein n is zero which leads to a group Q of formula-$(CRR)_{m1}$-Y_1-$(CRR)_{m2}$-, in which Y_1 is -NR-, -O-, -S-, -SO-, -SO_2-, or Se; and m_1 and m_2 are independently integers from 0 to 4, provided that the sum of m_1 and m_2 is greater than zero. This was not contested by the Appellant 1. However, the key issue to be decided is whether the supplemental condition that m_1 or m_2 = 0 present in Claim 1 of the main request can be directly and unambiguously derived from the content of the application as filed.

2.5 Appellant 2 argued that in all the examples m_1 or m_2 was equal to zero. However, even leaving aside the fact that the examples relate to specific molecules rendering it unlikely that their substituents can be neglected in order to construe a general teaching, it remains that all the examples disclose compounds wherein when m_1 is zero, m_2 is two or when m_1 is two, m_2 is zero. From this, it cannot be derived that when m_1 is zero, m_2 may be an integer from 1 to 4 or vice-versa. Also Claims 3 and 14 as originally filed invoked by the Appellant 2 only relate to formulas wherein m_1 is zero when m_2 is two.

2.6 Nor can the intermediate formulas IIa and IIb be used to rebut that finding since they define compounds wherein Y_1 is restricted to -O- or -NR-. In the absence

of any further source of disclosure in the application as filed, no generalization to compounds wherein Y_1 is as defined in Claim 1 is derivable from these formulas IIa and IIb.

2.7 Furthermore, in view of the disclosure that m_1 and m_2 are independently integers from 0 to 4, provided that $m_1 + m_2 > 0$ (cf. page 3, lines 1 to 3), the additional feature "m_1 or m_2 is zero" introduces an arbitrary limitation to eight specific combinations between m_1 and m_2 out of a total of twenty four possible combinations foreseen in the application as filed. This amounts to a multiple selection not admissible according to the jurisprudence of the Boards of Appeal.

2.8 As for the cited decisions T 206/83 (OJ EPO 1987, 5) and T 166/90 (not published in OJ EPO), the Board observes that they relate to limitations within quantitative ranges. As noted in point 10 of T 206/83, this situation is quite different from that relating to restrictions within a general formula of alternative components. The latter is, however, the case here since the selection of an integer for m_1 or m_2 corresponds to a specific sub-group of formula I.

2.9 Since the subject-matter of Claim 1 of the main request contravenes the requirements of Article 123(2) EPC and since the Board can only decide on a request as a whole, the main request is rejected

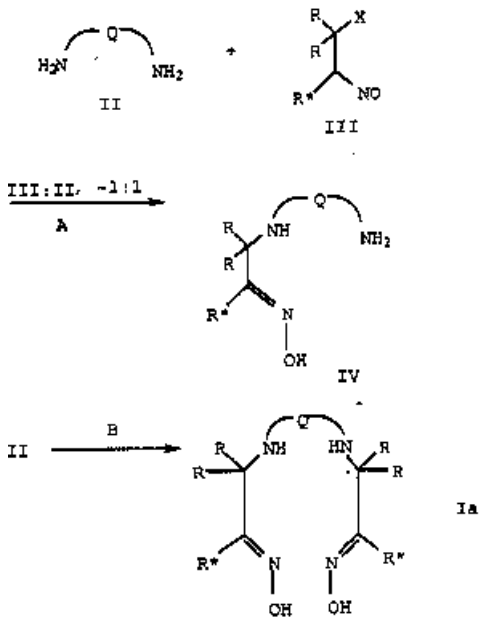
First auxiliary request

3. *Article 123(2)(3) EPC - Amendments*

3.1 In Claim 1 of the first auxiliary request, the substituent Y_1 is restricted to -O- or -NR_0-, wherein R_0 is H or C_1-C_{12} alkyl (cf. point VI above). The question to be decided is whether or not the thus restricted meaning of Y_1 constitutes an amendment which extends the claimed subject-matter beyond the content of the application as filed.

3.2 The Board concurs with the Appellant 1 that this amendment cannot be based on the passages of the description as filed stating that R or R^* groups which are not -$(A)_p$-R^3 are preferably hydrogen or alkyl groups" (cf. page 32, lines 7 to 8 and Claim 7). Present Claim 1 would constitute an intermediate generalization not unambiguously disclosed in the application as filed considering those passages only since in present Claim 1 only the group R carried by the nitrogen atom (Y_1= -NR_0-) is restricted to that preferred embodiment and not all the other R and R^* groups.

3.3 However, the Board observes that the description also discloses the compounds of formula Ia (cf. page V above). A method of their preparation involves the following reaction:



(cf. page 11).

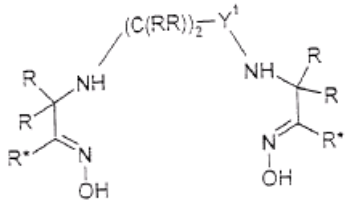
Preferred compounds of formula II are those of the following formulae IIa and IIb:

NH_2-$(C(RR))_{m1}$-NR-NH_2 (IIa)

NH_2-$(C(RR))_{m1}$-O-NH_2 (IIb)

especially where m1 is two (cf.page 13, lines 18 to 20).

It is concluded that a compound of formula Ia:



wherein Y_1 is -O- or -NR- and R, R^* have the general meanings disclosed in the description at pages 3 and 4 is explicitly disclosed in the application as filed. Selecting for **one** substituent, i.e. Y_1 = -NR-, the meanings H or C_1-C_{12} alkyl (R = R_0) amounts to a selection among a single list of substituents which does not extend the content of the application as filed. Furthermore, it is clear from the description

that the term alkyl has preferably 1 to 12 carbon atoms (cf. page 5, lines 6 to 11).

No objection under Article 123(2) EPC can, therefore, be raised against the subject-matter of Claim 1. Furthermore, the subject-matter of Claims 2 to 24 finds support in the application as filed (cf. Claims 2, 3, 5 to 25 respectively).

3.4 Regarding the compliance of the claimed subject-matter with the requirement of Article 123(3) EPC, Appellant 1 did not submit any additional arguments. It is not sufficient to object to amendments under Article 123(2) EPC and simply contend that the same arguments justify an objection under Article 123(3) EPC. The two sections of Article 123 EPC address different issues. Since Claim 1 relates to compounds of formula Ia of the patent as granted, wherein the meaning of the chain Q was additionally restricted, the Board considers that the claimed subject-matter of the first auxiliary request does not extend the scope of protection conferred by the patent.

3.5 The subject-matter of that request complies, therefore, with the requirements of Article 123(2)(3) EPC.

4. *Article 100(b) EPC - Sufficiency of disclosure*

4.1 At the oral proceedings before the Board, Appellant 1 argued for the first time that the description did not provide sufficient information for enabling the person skilled in the art to prepare the claimed compounds within the whole scope of Claim 1. In particular the

definition of R^3 of Claim 1 was objected to as being too large (cf. point VII above).

4.2 The question whether or not the claimed invention can be put into practice is not solely to be decided on the basis of the content of the claims but must be assessed on the basis of the whole content of the application.

4.3 The Board observes, in that context, that a general method for preparing the claimed compounds is disclosed in the application as filed (cf. page 11 to page 17). A description of the synthesis of the starting compounds of formula IIa, IIb and III (cf. point 3.3 above) is provided in that respect (cf. page 13, line 15 to page 17, line 17 and page 12, line 32 to page 13, line 14).

4.4 Appellant 1 never submitted any experimental results or an expert's report which would show that some of the claimed compounds could not be obtained by proceeding according to the technical knowledge in the domain of the organic synthesis and the information provided by the application as originally filed. The allegation that the person skilled in the art could not carry out the invention within the whole scope of Claim 1 is not backed up by facts that can be checked.

4.5 In accordance with the constant jurisprudence of the Boards of appeal, each party carries the separate burden of proof for any fact they allege. However, it turns out that the objections put forward by the Appellant 1 were based on non-supported arguments. Since the Appellant 1 has not discharged the burden of

proof which was upon him, his request must fail as far as his objection under Article 100(b) EPC is concerned.

4.6 For the above reasons, the Board holds that the patent in suit discloses the invention claimed in the form of the first auxiliary request in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

5. *Article 54 EPC - Novelty*

None of the prior art cited discloses ligands (or complexes thereof with a metal) having a bridging chain of formula $-(C(RR))_2-Y^1-$ (cf. point VI above). The subject-matter of the first auxiliary request is, therefore, novel. This was not contested by the Appellant 1.

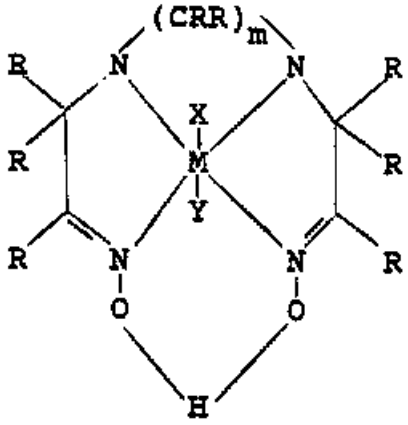
6. *Article 56 EPC - Inventive step*

6.1 The claimed invention relates to diagnostic and therapeutic agents (cf. page 2, lines 3 to 5 and page 3, lines 30 to 31 of the patent in suit). It is clear from the specification that these agents comprise a complex of a metal and a ligand in the form of a compound as defined in Claim 1 (cf. page 19, lines 54 to 56). Inventive step must be, therefore, assessed by reference to Claim 10 of the first auxiliary request (cf. point VI above), the ligands defined in Claim 1 being seen in that respect as intermediate compounds for preparing the complex as defined in Claim 10 intended for use as a diagnostic or therapeutic agent.

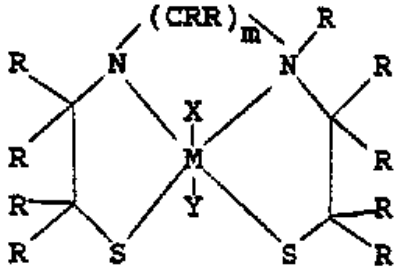
6.2 In order to determine the technical problem to be solved by the claimed invention, it is necessary to establish the closest state of the art. This "closest state of the art" is normally a prior art document disclosing subject-matter aiming at the same objective as the claimed invention and having the most relevant technical features in common.

6.2.1 Document (3) which discloses metal complexes of formula

Ia'



Ib'



wherein m is 2 to 5,
and diagnostic and therapeutic methods using such complexes (Cf. page 4, lines 15 to page 7, line 28), aims at the same objective as the patent in suit. Furthermore, the sole difference between the compounds disclosed therein and the claimed compounds resides in the bridging chain, namely $-(CRR)_m-$ in lieu of $-(C(RR))_2-Y^1-$ in the patent in suit (cf. point VI above). The Board concurs with the parties that document (3) is

the closest state of the art for defining the technical problem to be solved.

6.2.2 In the decision under appeal, the finding of lack of inventive step rested on the finding that the technical problem to be solved was to be seen in the provision of compounds which had higher selectivity for hypoxic tissue than the compounds disclosed in document (3) (cf. point 6 of the reasons). However, the Board can see no justification for formulating the technical problem in this way. Indeed, the Boards of Appeal have held on more than one occasion that an objective definition of the technical problem to be solved should normally start from the technical problem actually described in the patent in suit. Only if it turns out, for example, that an incorrect state of the art was used to define the technical problem or that the technical problem disclosed has in fact not been solved, can an inquiry be made as to which other technical problem objectively existed (Compendium of Case Law of the Boards of Appeal of the European Patent Office 4th edition 2001, I.D.4.3). In the present case, the Board sees no reason to deviate from this established jurisprudence.

6.2.3 It follows that the technical problem to be solved may be viewed in the provision of further metal complexes as diagnostic or therapeutic agents (cf. point 6.1 above).

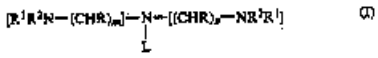
6.3 The Board, in view of the examples of the description, considers that the thus worded technical problem is credibly solved within the whole scope of Claim 10. No argument was put forward by the Appellant 2 against that finding.

6.4 It remains to be decided whether or not it would have been obvious for the person skilled in the art to solve the above technical problem in the claimed way.

6.4.1 Starting from document (3) disclosing metal complexes of formulae Ia' and Ib' as diagnostic and therapeutic agents (cf. point 6.2.1 above), the person skilled in the art would have considered modifying the structure of the complexes, while maintaining their properties.

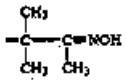
6.4.2 In order to preserve the stability of the coordination link between the metal and the ligands, it is clear, in the Board's judgment, that the four atoms participating in this bonding (the four nitrogen atoms in formula Ia', the two nitrogen atoms and the two sulphur atoms in formula Ib') were to be kept. Therefore, one of the possibilities was to vary the hydrocarbon bridging chain $-(CRR)_m-$. In that context, the disclosure of documents (4), (5), (6) and (7) would have been considered by the person skilled in the art trying to solve the above stated technical problem (cf. point 6.2.3 above).

Document (4) discloses metal complexes of ligands of formula



(I)

wherein R^2 may represent hydrogen, R^1 may be



L may be substituted cycloalkyl, aryl or aralkyl, m and n are independently integers from 2 to 4, as diagnostics or therapeutics agents.

That document actually invites the person skilled in the art to insert a nitrogen atom in the bridging chain but on condition that this nitrogen atom not be adjacent to one of the two nitrogen atoms participating in the coordination bonding.

6.4.3 Document (5) discloses the complex of 2,2,8,14,14-pentamethyl-4,8,12-triaza-dodecane-dithiol (MTADT) with technetium-99m for diagnostics (cf. pages 791 and 792, document (6) a technetium or rhenium complex of a 2,2,12,12-tetramethyl-4,7,10-triaza-7-p-aminobenzyl-1,13-tridecane dithiol for labelling monoclonal antibodies and document (7) a complex of 3,3,11,11-tetramethyl-4,7,10-triazatridecane-7-(p-aminobenzyl)-2,12-dionedioxime with ^{99m}Tc for labelling monoclonal antibodies (cf. pages 585 and 589).

Those documents confirm that a nitrogen atom may be inserted in the bridging chain in a non-adjacent position to one of the two nitrogen atoms participating in the coordination bonding.

6.4.4 Appellant 1 however argued that the discussion at the end of document (5) stating that:

"with this type of 3-carbon-3-nitrogen backbone ligand [and] there may be a possibility that the third nitrogen does take part in coordinating with the metal oxo core leading to the more favored 6-membered rings upon complexation with technetium",

implied *a contrario* that the insertion of the nitrogen atom at another location in the bridging chain would play no role in the coordination bond and it would be,

therefore, obvious to design further compounds having the same properties. That finding was considered to be confirmed by document (8) which disclosed Technetium-99^m complexes of pentane-2,4-dione bis(N-methylthiosemicarbazone) as diagnostic agents (cf. Figure 6) wherein a nitrogen atom was adjacent to the nitrogen atom involved in the coordination bonding.

6.4.5 However, the sole relevant material information that can be derived from document (5) is definitely to tell the person skilled in the art to preserve the so-called 3-carbon-3-nitrogen backbone which does not suggest to him the claimed complexes where a nitrogen atom of the bridging chain of the ligands is adjacent to the nitrogen atom participating in the coordination bonding (cf. point VI above).

6.4.6 Document (8) invoked by the Appellant 2 discloses two Technetium-99^m complexes of pentane-2,4-dione bis(N-methylthiosemicarbazone) as diagnostics agents, namely pentane-2,4-dione bis(N-methylthiosemicarbazone) (**PETS**), 3,3-dimethyl- pentane-2,4-dione bis(N-methylthiosemicarbazone) (**DM-PETS**). However, apart from the fact that those ligands appear to form a complex with technetium in the same manner as other well-known ligands in the field (cf. DADT complex), it remains that ligands having a pentane-2,4-dione bis (N-methylthiosemicarbazone) structure are structurally different from the ligands disclosed in documents (3) to (7), at the very least because the pentane-2,4-dione bis (N-methylthiosemicarbazone) is a total resonating structure which is not the case for any of the structures disclosed in documents (3) to (7). There is, therefore, no reason to combine those different

structures. In addition, document (8) does not teach insertion of a nitrogen atom in the bridging chain.

6.4.7 Since starting from document (3), and in the light of the other documents cited, the person skilled in the art would not have been directed in an obvious manner to the claimed solution in order to solve the technical problem defined above (cf. point 6.2.2 above), the subject-matter of Claim 10 meets the inventive step requirement. The same applies to dependent Claims 11 to 15 which represent particular embodiments of the subject-matter of Claim 10.

Independent Claims 1 to 9 relating to ligands useful for preparing metal complexes according to Claim 10 and Claims 21 to 23 relating to a kit containing said ligands and a pharmaceutically acceptable reducing agent are based on the same inventive concept and derive their patentability on the same basis as do Claims 10 to 15. Independent Claims 16 to 20 relating to various uses of the complexes of Claim 10 are based on the same inventive concept and derive their patentability on the same basis as do Claims 10 to 15. Claim 24 relating to a process of preparation of compounds of Claim 9 is based on the same inventive concept as Claim 9 (process by analogy).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of the claims of the first auxiliary request submitted on 17 January 2003 and a description to be adapted thereto.

The Registrar: The Chairman:

N. Maslin A. Nuss