

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 June 2010 (03.06.2010)

(10) International Publication Number
WO 2010/060941 A2

(51) International Patent Classification:
C07C 237/08 (2006.01) *A61K 49/04* (2006.01)
A61K 31/166 (2006.01)

(21) International Application Number:
PCT/EP2009/065865

(22) International Filing Date:
26 November 2009 (26.11.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
08170041.1 27 November 2008 (27.11.2008) EP

(71) Applicant (for all designated States except US): **GE HEALTHCARE AS** [NO/NO]; P.O. Box 4220 Nydalen, Nycoveien 1-2, N-0401 Oslo (NO).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **WISTRAND, Lars-Göran** [SE/NO]; GE Healthcare AS, P.O. Box 4220 Nydalen, Nycoveien 1-2, N-0401 Oslo (NO).

(74) Agent: **WULFF, Marianne, W.**; GE Healthcare AS, P.O. Box 4220 Nydalen, Nycoveien 1-2, N-0401 Oslo (NO).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: CONTRAST AGENTS

(57) Abstract: The present invention relates to a class of compounds and to diagnostic compositions containing such compounds where the compounds are iodine containing compounds. More specifically the iodine containing compounds are chemical compounds containing two linked iodinated phenyl groups of the general formula $R-N(CO-CH_2R^1)-X-N(CO-CH_2R^1)-R$ and salts or optical active isomers thereof, wherein each R^1 independently denotes a hydrogen or a C_1 to C_4 alkoxy moiety provided that at least one R^1 denotes a C_1 to C_4 alkoxy moiety; X denotes a C_3 to C_{10} straight or branched alkylene moiety which may be further substituted, and each R denotes a triiodinated phenyl residue further substituted by hydrophilic moieties. The invention also relates to the use of such compounds and diagnostic compositions as contrast agents in diagnostic imaging and in particular in X-ray imaging.



WO 2010/060941 A2

Title: Contrast Agents**Technical Field of the Invention**

The present invention relates to a class of compounds and to diagnostic compositions containing such compounds where the compounds are iodine containing compounds. More specifically the iodine containing compounds are chemical compounds containing two linked iodinated phenyl groups.

The invention also relates to the use of such diagnostic compositions as contrast agents in diagnostic imaging and in particular in X-ray imaging, and to contrast media containing such compounds.

Description of Related art

All diagnostic imaging is based on the achievement of different signal levels from different structures within the body. Thus in X-ray imaging for example, for a given body structure to be visible in the image, the X-ray attenuation by that structure must differ from that of the surrounding tissues. The difference in signal between the body structure and its surroundings is frequently termed contrast and much effort has been devoted to means of enhancing contrast in diagnostic imaging since the greater the contrast between a body structure and its surroundings the higher the quality of the images and the greater their value to the physician performing the diagnosis. Moreover, the greater the contrast the smaller the body structures that may be visualized in the imaging procedures, i.e. increased contrast can lead to increased spatial resolution.

The diagnostic quality of images is strongly dependent on the inherent noise level in the imaging procedure, and the ratio of the contrast level to the noise level can thus be seen to represent an effective diagnostic quality factor for diagnostic images. Achieving improvement in such a diagnostic quality factor has long been and still remains an important goal. In techniques such as X-ray, magnetic resonance imaging (MRI) and ultrasound, one approach to improving the diagnostic quality factor has been to introduce contrast enhancing materials formulated as contrast media into the body region being imaged. Thus, in X-ray early examples of contrast agents were insoluble inorganic barium salts which enhanced X-ray attenuation in the body zones into which they distributed. For the last 50 years the field of X-ray

contrast agents has been dominated by soluble iodine containing compounds. Commercial available contrast media containing iodinated contrast agents are usually classified as ionic monomers such as diatrizoate (marketed e.g. under the trade name Gastrografen™), ionic dimers such as ioxaglate (marketed e.g. under the trade name Hexabrix™), nonionic monomers such as iohexol (marketed e.g. under the trade name Omnipaque™), iopamidol (marketed e.g. under the trade name Isovue™), iomeprol (marketed e.g. under the trade name Iomeron™) and the non-ionic dimer iodixanol (marketed under the trade name and Visipaque™).

The most widely used commercial non-ionic X-ray contrast agents such as those mentioned above are considered safe. Contrast media containing iodinated contrast agents are used in more than 20 millions of X-ray examinations annually in the USA and the number of adverse reactions is considered acceptable. However, since a contrast enhanced X-ray examination will require up to about 200 ml contrast media administered in a total dose, there is a continuous drive to provide improved contrast media.

The utility of the contrast media is governed largely by its toxicity, by its diagnostic efficacy, by adverse effects it may have on the subject to which the contrast medium is administered, and by the ease of storage and ease of administration. Since such media are conventionally used for diagnostic purposes rather than to achieve direct therapeutic effect, it is generally desirable to provide media having as little as possible effect on the various biological mechanisms of the cells or the body as this will lead to lower toxicity and lower adverse clinical effect. The toxicity and adverse biological effects of a contrast medium are contributed to by the components of the formulation medium, e.g. the solvent or carrier as well as the contrast agent itself and its components such as ions for the ionic contrast agents and also by its metabolites. The major contributing factors to the toxicity of the contrast medium are identified as the chemotoxicity of the contrast agent, the osmolality of the contrast medium and the ionic composition or lack thereof of the contrast medium.

Desirable characteristics of an iodinated contrast agent are low toxicity of the compound itself (chemotoxicity), low viscosity of the contrast medium wherein the compound is dissolved, low osmolality of the contrast medium and a high iodine content (frequently measured in mg iodine per ml of the formulated contrast medium for administration). The iodinated contrast agent must also be completely soluble in

the formulation medium, usually an aqueous medium, and remain in solution during storage. The osmolalities of the commercial products, and in particular of the non-ionic compounds, is acceptable for most media containing dimers and non-ionic monomers although there is still room for improvement. In coronary angiography for example, injection into the circulatory system of a bolus dose of contrast medium has caused severe side effects. In this procedure contrast medium rather than blood flows through the system for a short period of time, and differences in the chemical and physiochemical nature of the contrast medium and the blood that it replaces can cause undesirable adverse effects such as arrhythmias, QT prolongation and reduction in cardiac contractive force. Such effects are seen in particular with ionic contrast agents where osmotoxic effects are associated with hypertonicity of the injected contrast medium. Contrast media that are isotonic or slightly hypotonic with the body fluids are particularly desired. Low osmolar contrast media have low renal toxicity which is particularly desirable. The osmolality is a function of the number of particles per volume unit of the formulated contrast medium.

In patients with acute renal failure, nephropathy induced by contrast medium remains one of the most clinically important complications of the use of iodinated contrast medium. Aspelin, P et al, The New England Journal of Medicine, Vol. 348:491-499 (2003) concluded that nephropathy induced by contrast medium may be less likely to develop in high risk patients when iodixanol is used rather than a low-osmolar, non-ionic contrast medium. The part of the patient population considered as high risk patients is increasing. To meet the need for continuous improvement of in vivo X-ray diagnostic agents for the entire patient population, there is a continuous drive in finding X-ray contrast agents that have improved properties, also with regards to contrast induced nephrotoxicity (CIN).

To keep the injection volume of the contrast media as low as possible it is highly desirable to formulate contrast media with high concentration of iodine/ml, and still maintain the osmolality of the media at a low level, preferably below or close to isotonicity. The development of non-ionic monomeric contrast agents and in particular non-ionic bis(triiodophenyl) dimers such as iodixanol (EP patent 108638) has provided contrast media with reduced osmotoxicity allowing contrast effective iodine concentration to be achieved with hypotonic solution, and has even allowed correction of ionic imbalance by inclusion of plasma ions while still maintaining the contrast medium Visipaque™ at the desired osmolality (WO 90/011094 and WO 91/13636).

The X-ray contrast media at commercial high iodine concentration have relative high viscosity, ranging from about 15 to about 60 mPas at ambient temperature. Generally, contrast media where the contrast enhancing agent is a dimer has higher viscosity than the corresponding contrast media where the contrast enhancing agent is the monomer corresponding to the dimer. Such high viscosities may pose problems to the administrators of the contrast medium, requiring relatively large bore needles or high applied pressure, and are particularly pronounced in pediatric radiography and in radiographic techniques which require rapid bolus administration, e.g. in angiography.

X-ray contrast media containing a chemical compound as the active pharmaceutical ingredient(s) having two triiodinated phenyl groups linked by a linking group are usually referred to as dimeric contrast agents or dimers. During the years a wide variety of iodinated dimers have been proposed. Relevant patent publications include EP 1186305, EP 686046, EP108638, EP 0049745, EP 0023992, WO2005087272, WO 2003080554, WO2000026179, WO 1997000240, WO 9208691, US3804892, US4239747, US3763226, US3763227 and US3678152. In particular, EP 108638 describes a small group of non-ionic dimers where the two triiodinated phenyl groups are linked by linking groups of the formulas $-N(COCH_3)-CH_2-CH(OH)-CH_2-(COCH_3)N-$ and $-N(COCH_3)-CH_2-CH(OH)-CH(OH)-CH_2-(COCH_3)N-$, and wherein the carboxamide substituents of the triiodinated phenyl groups contain either two $-CH(CH_2-OH)_2$ groups or two $-CH_2-CH(OH)-CH_2-OH$ groups. Four compounds, denoted A, B, C and D are prepared, of which compound A is known under the INN name of iodixanol.

At this time, one contrast medium having an iodinated non-ionic dimer as the active pharmaceutical ingredient is on the market, the product Visipaque™ containing the compound iodixanol mentioned above. The compound Hexabrix™, containing the ionic dimeric compound ioxaglic acid is also on the market.

Hence there still exists a desire to develop contrast agents that solve one or more of the problems discussed above. Such agents should ideally have improved properties over the soluble iodine containing compounds on the market in one or more of the following properties: renal toxicity, osmolality, viscosity, solubility,

injection volumes/iodine concentration and attenuation/radiation dose and any additional adverse effect known or discovered for such iodinated compounds.

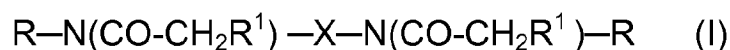
Summary of the Invention

The present invention provides compounds useful as contrast media having improved properties over the known media with regards to at least one of the criteria mentioned above and in particular to renal toxicity, osmolality, viscosity and solubility. The contrast media comprises iodine containing contrast enhancing compounds where the iodine containing compounds are chemical compounds containing two linked iodinated phenyl groups. The iodine containing contrast enhancing compounds can be synthesized from commercially available and relatively inexpensive starting materials.

Detailed Description of the Invention

The new compounds of the invention, diagnostic compositions comprising the compounds, and their use as X-ray contrast agents, are specified in the attached claims and in the specification hereinafter.

The contrast enhancing compounds are synthetic chemical compounds of formula (I)



Formula (I)

and salts or optical active isomers thereof,

wherein

each R^1 independently denotes a hydrogen or a C_1 to C_4 alkoxy moiety provided that at least one R^1 denotes a C_1 to C_4 alkoxy moiety;

X denotes a divalent linking moiety with 3 to 10 bridge elements of carbon, oxygen, sulphur or nitrogen separating the nitrogen atoms and which may be further substituted by hydroxyl groups, by C_1 to C_4 alkyl moieties optionally substituted by hydroxyl groups, by C_1 to C_4 alkoxy groups, by amino groups and by C_1 to C_4 alkylamino groups, and wherein 2 or 3 carbon bridge elements together with alkyl or

alkoxy groups may form a cyclopentane, cyclohexane, pentahydropyran or tetrahydrofuran entity which may be alkyl- or hydroxyalkyl- substituted

and

each R independently are the same or different and denote a triiodinated phenyl group, preferably a 2,4,6-triiodinated phenyl group, further substituted by two groups R^2 at the remaining 3 and 5 positions in the phenyl moiety, and wherein each R^2 are the same or different and denote a hydrogen atom or a non-ionic hydrophilic moiety, provided that at least one R^2 group in the compound of formula (I) is a hydrophilic moiety.

Each R^1 denotes a hydrogen atom or a straight or branched C_1 to C_4 alkoxy moiety preferably selected from the group of methoxy, ethoxy, propoxy, isopropoxy and linear or branched butoxy groups. Most preferred are methoxy and ethoxy groups. Methoxy moieties are particularly preferred. The two R^1 moieties in the compound of formula (I) may be the same or different, preferably however the R^1 groups are the same and more preferably they both denote C_1 to C_4 alkoxy moieties, particularly methoxy moieties.

In a preferred embodiment, X denotes a C_3 to C_{10} straight or branched alkylene moiety optionally with one or two CH_2 moieties replaced by oxygen atoms, sulphur atoms or NR^3 groups and wherein the alkylene moiety optionally is substituted by up to six $-OR^3$ groups, wherein R^3 denotes a hydrogen atom or a C_1 to C_4 straight or branched alkyl group. The C_3 to C_{10} alkylene moiety is preferably substituted by one to four hydroxyl groups, and in addition up to 4 carbon atoms of the C_3 to C_{10} alkylene moiety may be replaced by oxygen atoms. Preferably none of the hydroxyl groups are on carbon atoms vicinal to a nitrogen atom.

Still more preferably the divalent linker group X comprises a straight alkylene moiety with 3 to 10 carbon atoms substituted by 1, 2 or 3 hydroxy groups where none of the hydroxyl groups are on a carbon atom vicinal to the bridge nitrogen atom. More preferably X denotes a straight C_3 to C_5 alkylene chain substituted by one or two OH groups and/or methyl and/or hydroxymethyl moieties. More preferably X is substituted by one or two such substituents, and most preferably X denotes divalent entities of the following formulas:

$-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-$;
 $-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}(\text{OH})-\text{CH}_2-$;
 $-\text{CH}_2-\text{C}(\text{OH})(\text{CH}_3)-\text{CH}_2-$;
 $-\text{CH}_2-\text{C}(\text{OH})(\text{CH}_2\text{OH})-\text{CH}_2-$; and
 $-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-$.

For the bridging group X, further examples of preferred hydroxylated alkylene groups are the 2,3,4- trihydroxy-pentylene and 2,7-dihydroxy-octylene moieties.

Also preferred are the divalent linker groups X comprising a straight alkylene moiety wherein 1 or 2 of the 3 to 10 carbon atoms are replaced by oxygen atoms and where the linker may be further substituted by 1, 2 or 3 hydroxy groups where none of the hydroxyl groups are on a carbon atom vicinal to a nitrogen atom. Examples of such divalent linker groups are 2,6-dihydroxy-4-oxa-heptylene and 2,9-dihydroxy-4,7-dioxa-decylene.

When the bridging group X comprises a cyclic group element, this is preferably a heterocyclic group element such as pentahydropyrane.

Each of the triiodinated R groups can be the same or different and preferably denote a 2,4,6-triiodinated phenyl group, further substituted by two groups R^2 in the remaining 3 and 5 positions in the phenyl moiety. The non-ionic hydrophilic moieties (R^2) may be any of the non-ionizing groups conventionally used to enhance water solubility. Hence, the R^2 substituents may be the same or different and shall preferably all denote a non-ionic hydrophilic moiety comprising esters, amides and amine moieties, optionally further substituted by a straight chain or branched chain C_{1-10} alkyl groups, preferably C_{1-5} alkyl groups, where the alkyl groups also may have one or more CH_2 or CH moieties replaced by oxygen or nitrogen atoms. The R^2 substituents may also further contain one or more groups selected from oxo, hydroxyl, amino or carboxyl derivative, and oxo substituted sulphur and phosphorus atoms. Each of the straight or branched alkyl groups preferably contains 1 to 6 hydroxy groups and more preferably 1 to 3 hydroxy groups. Therefore, in a further preferred aspect, the R^2 substituents are the same or different and are mono or

polyhydroxy C₁₋₅ alkyl, hydroxyalkoxyalkyl with 1 to 5 carbon atoms and hydroxypolyalkoxyalkyl with 1 to 5 carbon atoms, and are attached to the iodinated phenyl group via an amide or a carbamoyl linkage, preferably carbamoyl linkages.

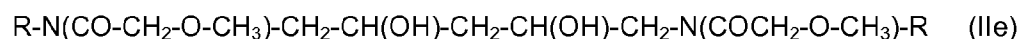
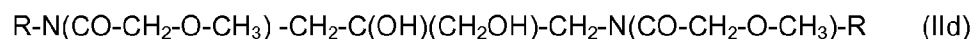
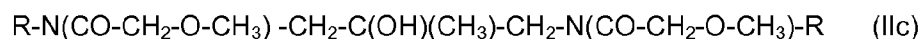
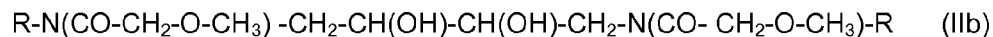
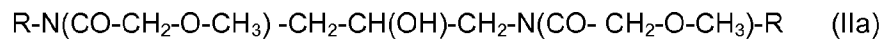
The R² groups of the formulas listed below are particularly preferred:

-CONH-CH₂-CH₂-OH;
 -CONH-CH₂-CHOH-CH₂-OH;
 -CON(CH₃)CH₂-CHOH-CH₂OH;
 -CONH-CH-(CH₂-OH)₂;
 -CON-(CH₂-CH₂-OH)₂;
 -CONHCH₃;
 -CONH-CH₂-CH₂-O-CH₃;
 -CONH-O-CH₃;
 -CONH-CH₂-CHOH-CH₂-O-CH₃;
 -CONH-CH₂-CHOCH₃-CH₂-OH;
 -CON (CH₂-CHOH-CH₂-OH) (CH₂-CH₂-OH);
 -CONH-C(CH₂-OH)₂CH₃;
 -CONH-C(CH₂-OH)₃;
 -CONH-CH (CH₂-OH) (CHOH -CH₂-OH) ;
 -NHCOCH₂OH;
 -N(COCH₃)H;
 -N(COCH₃) C₁₋₃ alkyl;
 -N(COCH₃) – mono, bis or tris-hydroxy C₁₋₄ alkyl;
 -N(COCH₂OH) – hydrogen, mono, bis or tris-hydroxy C₁₋₄ alkyl;
 -N(CO-CHOH-CH₂OH) - hydrogen, mono, bis or trihydroxylated C₁₋₄ alkyl;
 -N(CO-CHOH-CHOH-CH₂OH) - hydrogen, mono, bis or trihydroxylated C₁₋₄ alkyl;
 -N(CO-CH-(CH₂OH)₂) - hydrogen, mono, bis or trihydroxylated C₁₋₄ alkyl; and
 -N(COCH₂OH)₂.

Even more preferably the R² groups will be equal or different and denote one or more moieties of the formulas -CONH-CH₂-CHOH-CH₂-OH, -CON(CH₃)CH₂-CHOH-CH₂-OH, -CONH-CH-(CH₂-OH)₂, -CON-(CH₂-CH₂-OH)₂, and -CONH-CH₂-CH₂-OH. It will be understood that in each of the two groups R in formula (I) each of the two R² substituents may be the same or different.

Still more preferably both R groups are the same and the R² groups in each R are the same or different and have the meanings above.

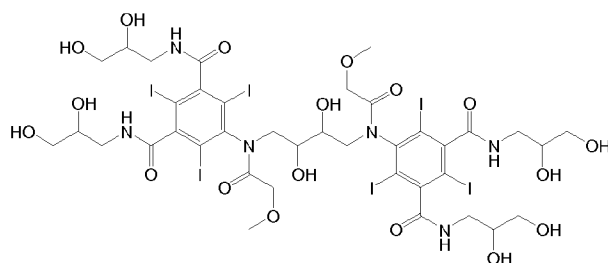
Thus, preferred structures according to the invention include the compounds of formulas (II):



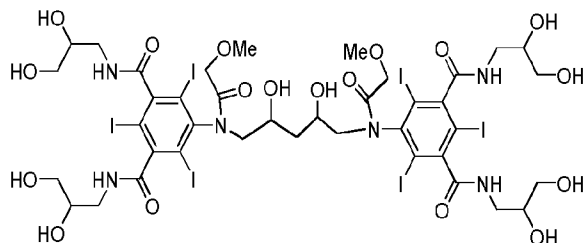
Formulas (II)

In formulas (II) each group R has the meaning above, more preferably both triiodinated phenyl groups R are the same and the R² groups all denote non-ionic hydrophilic moieties, and preferably the R² groups are linked to iodinated phenyl moiety by carbamoyl linkages.

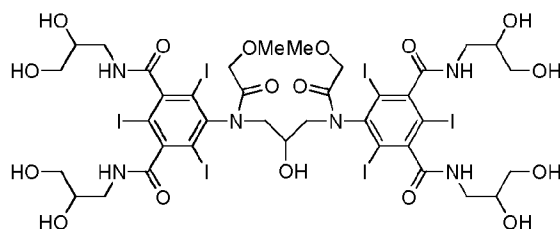
Preferred examples of compounds according to the invention include the compounds of formulas (IIIa), (IIIb) and (IIIc) below.



Formula (IIIa)



Formula (IIIb)



Formula (IIIc)

At an iodine concentration of 320 mg/ml, which is a common concentration for commercially available iodinated contrast media, the concentration of the compound of formula (I) will be approximately 0.42 M (Molar). The contrast medium will also be hypoosmolar at this iodine concentration, and this is an advantageous property with regards to the nephrotoxicity of the contrast medium. It is also possible to add electrolytes to the contrast medium to lower the cardiovascular effects as explained in WO 90/011094 and WO 91/13636.

Compounds of formula (I) also have optical active isomers and may exist in several isomeric forms due to chiral carbon atoms. In addition, the compounds exhibit exo/endo isomerism due to the restricted rotation of the N-CO bond in the alkoxyated acetyl functions caused by the proximity of the bulk iodine atom. Both enantiomerically pure products as well as mixtures of optical isomers are included.

The compounds of the invention may be used as contrast agents and may be formulated with conventional carriers and excipients to produce diagnostic contrast

media. Thus viewed from a further aspect the invention provides a diagnostic composition comprising a compound of formula (I) as described above together with at least one physiologically tolerable carrier or excipient, e.g. in aqueous solution for injection optionally together with added plasma ions or dissolved oxygen.

The contrast agent composition of the invention may be in a ready to use concentration or may be in concentrated form for dilution prior to administration. Generally compositions in a ready to use form will have iodine concentrations of at least 100 mg I/ml, preferably at least 150 mg I/ml, with concentrations of at least 300 mg I/ml, e.g. 320 mg I/ml being preferred. The higher the iodine concentration, the higher is the diagnostic value in the form of X-ray attenuation of the contrast media. However, the higher the iodine concentration the higher is the viscosity and the osmolality of the composition. Normally the maximum iodine concentration for a given contrast media will be determined by the solubility of the contrast enhancing agent, e.g. the iodinated compound, and the tolerable limits for viscosity and osmolality. For contrast media administered by injection or infusion, the desired upper limit for the solution's viscosity at ambient temperature (20°C) is about 30 mPas, however viscosities of up to 50 to 60 mPas and even more than 60 mPas can be tolerated. For contrast media given by bolus injection, e.g. in angiographic procedures, osmotoxic effects must be considered and preferably the osmolality should be below 1 Osm/kg H₂O, preferably below 850 mOsm/kg H₂O and more preferably about 300 mOsm/kg H₂O. With the compounds of the invention such viscosity, osmolality and iodine concentrations targets can be met. Indeed, effective iodine concentrations can be reached with hypotonic solutions. It may thus be desirable to make up the solution's tonicity by the addition of plasma cations so as to reduce the toxicity contribution that derives from the imbalance effects following bolus injection. Such cations will desirably be included in the ranges suggested in WO 90/011094 and WO 91/13636.

In particular, addition of sodium and calcium ions to provide a contrast medium isotonic with blood for all iodine concentrations is desirable and obtainable. The plasma cations may be provided in the form of salts with physiologically tolerable counterions, e.g. chloride, sulphate, phosphate, hydrogen carbonate etc., with plasma anions preferably being used.

In a further embodiment the invention provides diagnostic agents comprising a compound of formula (I) or diagnostic compositions comprising a compound of formula (I) together with pharmaceutically acceptable carriers or excipients. The diagnostic agents and composition are preferably for use in X-ray diagnosis.

The contrast media containing compounds of formula (I) can be administered by injection or infusion, e.g. by intravascular administration. Alternatively, contrast media containing compounds of formula (I) may also be administered orally. For oral administration the contrast medium may be in the form of a capsule, tablet or as liquid solution.

Hence, the invention further embraces use of a diagnostic agent and a diagnostic composition comprising a compound of formula (I) in X-ray contrast examinations.

Another embodiment is use of a compound of formula (I) for the manufacture of a diagnostic composition for use as an X-ray contrast agent.

A method of diagnosis comprising administration of compounds of formula (I) to the human or animal body, examining the body with a diagnostic device and compiling data from the examination is also provided. In the method of diagnosis the body may also be preadministered with compounds of formula (I).

Furthermore, a method of imaging, specifically X-ray imaging is provided, which comprises administration of compounds of formula (I) to the human or animal body, examining the body with a diagnostic device and compiling data from the examination and optionally analysing the data. In the method of imaging the body may also be preadministered with compounds of formula (I).

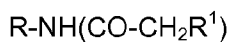
Preparation

The compounds of the general formula (I) can be synthesized by multistep procedures from starting materials that are either known from the state of art or that are commercially available or can readily be produced from commercially available

materials. The known synthesis for the production of iodixanol (see e.g. EP 108638) can generally be adapted to produce compounds of formula (I).

General procedure for preparation of compounds of formula (I):

Compounds of formula (IV)



Formula (IV)

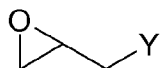
are reacted with a reactive linker group of formula (V)



Formula (V)

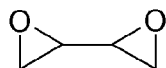
wherein Y and Y' are readily eliminatable atoms or groups and X has the above meaning as defined for formula I or a hydroxyl protected derivative thereof, or a corresponding epoxide in which one or both of the substituents Y and Y' are replaced by -O-. If required, the reaction is followed by removal of protecting groups. The groups Y and Y' may be selected from halogen atoms, e.g. chloride, bromine or iodine, or sulphate hydrocarbylsulphonyloxy groups, e.g. alkyl- or aryl-sulphonyloxy groups such as tosyloxy or mesyloxy. R and R¹ have the same meaning as for formula (I).

Examples of suitable compounds of formula (V) are compounds of formulas (Va) to (Vh):

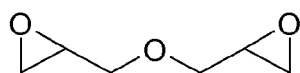


Formula (Va)

wherein Y is a readily eliminatable atom or group.

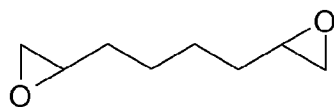


Formula (Vb)



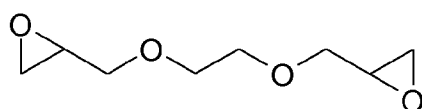
2-[(Oxiran-2-ylmethoxy)methyl]oxirane

Formula (Vc)



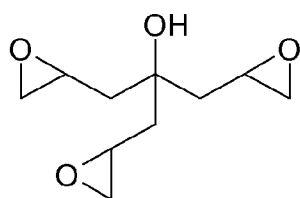
2-(4-Oxiran-2-ylbutyl)oxirane

Formula (Vd)



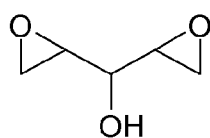
2-[[2-(Oxiran-2-ylmethoxy)ethoxy]methyl]oxirane

Formula (Ve)



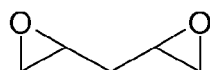
1,3-Dioxiran-2-yl-2-(oxiran-2-ylmethyl)propan-2-ol

Formula (Vf)



Dioxiran-2-ylmethanol

Formula (Vg)



2-(Oxiran-2-ylmethyl)oxirane

Formula (Vh)

or any precursor that can form terminal epoxides under basic conditions like

1,5-Dichloro-pentane-2,4-diol, see Scott D. Rychnovsky, J George Griesgraber, Sam Zeller, and Donald J. Skalitzy, *J. Org. Chem.* 1991, 56, 5161-5169 or 2,4-Dibromo-pentane-1,5-diol, see Schreiber, Stuart L.; Goulet, Mark T.; Schulte, Gayle; *J. Am. Chem. Soc.*; EN; 109; 15; 1987; 4718-4720.

Suitable compounds of formula (V) may thus be epichlorohydrin, butadiene epoxide or any precursor that can form butadiene diepoxide under basic conditions like 1,4-dichloro-2,3-dihydroxybutane.

Further, compounds of formula (V) providing a bridge with 3 carbon atoms are described in Bjørsvik, H-R., and Priebe, H. *Acta Chem. Scand.* 49 (1995) 446-456, "Multivariate data analysis of molecular descriptors estimated by using semi-empirical quantum chemistry methods. Principal properties for synthetic screening of 2-chloromethyl-oxirane and analogues bis-alkylating C3 moieties".

The hydroxyl groups present in the R groups and in the X group may, if desired, be in a hydroxyl protected form. Suitable protecting groups include acyl groups such as acetyl or, where adjacent hydroxyl groups are present, as cyclic ketal or acetal groups.

The reaction between compounds of formulas (IV) and (V) is preferably effected in the presence of an acid binding agent, for example an organic or inorganic base preferably in aqueous or alcoholic medium or mixtures thereof such as water and/or an alkanol or glycol; an alkali metal alkoxide such as sodium metoxide or an alkali metal hydroxide such as sodium and potassium hydroxide may be used as base.

Any protecting group may be removed by standard methods, for example by hydrolysis. The compounds of formula (IV) may be prepared by acetylation of the corresponding compounds having free amino groups. In this reaction, hydroxyl groups in the substituents R may also be protected by acylation.

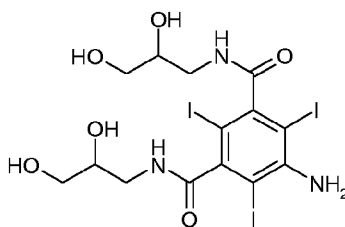
The compounds of formula (I) may be purified in any convenient manner, e.g. by preparative chromatography or by recrystallisation.

Alternatively, the compounds of formula (I) can be prepared employing the method described in Priebe et.al. (*Acta Radiol.* 36 (1995), Suppl. 399, 21-31 and also by adapting other methods described for the synthesis of iodixanol in the state of art.

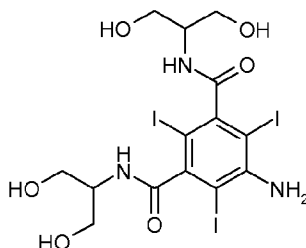
Preparation of intermediates

The precursors to the compounds of formulas (IV) the tri-iodinated phenyl groups having a free amino group are commercially available or can be produced following procedures described or referred to e.g. in WO95/35122 and WO98/52911. 5-amino-2,4,6-triiodo - isophthalic acid for example is available e.g. from Aldrich and 5-amino-2,4,6-triiodo-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide is commercially available e.g. from Fuji Chemical Industries, Ltd.

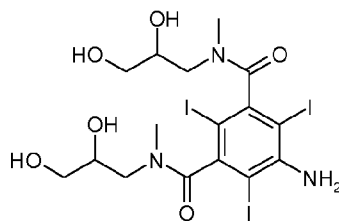
Examples of precursors of the compounds of formulas (IV), either commercially available or previously described in the literature include:



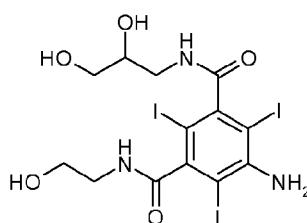
5-amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide



5-amino-N,N'-bis[1,3-dihydroxy-2-propyl]-2,4,6-triiodo-1,3-benzenedicarboxamide
(WO2002044125)



5-amino-N,N'-bis(2,3-dihydroxypropyl)-N,N'-dimethyl-2,4,6-triiodo-1,3-benzenedicarboxamide



5-amino-N-(2,3-dihydroxypropyl)-N'-(2-hydroxyethyl)-2,4,6-triiodo-1,3-benzenedicarboxamide (WO 8700757)

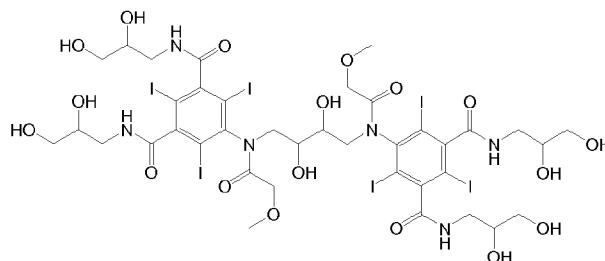
The compounds of formulas (IV) may be prepared by acylation of the corresponding compounds having free amino groups. In this reaction, hydroxyl groups in the substituents R may also be protected by acylation.

The acylation may be effected by any convenient method, e.g. by use of activated acetic acid such as acetic anhydride or mixed anhydrides which can be prepared by a variety of methods described in the literature, see e.g. K. M. R. Pillai, G. Diamantidis, L. Duncan and R. S. Ranganathan J. Org. Chem. 1994, 59, 1344-1350.

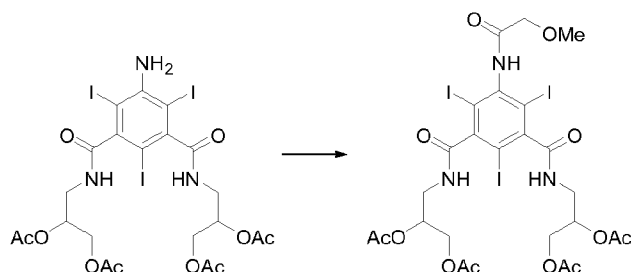
Examples

Example 1

Preparation of 5,5'-(2-hydroxypropane-1,3-diyl)bis(methoxyacetylazanediy)bis (N1,N3-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide)



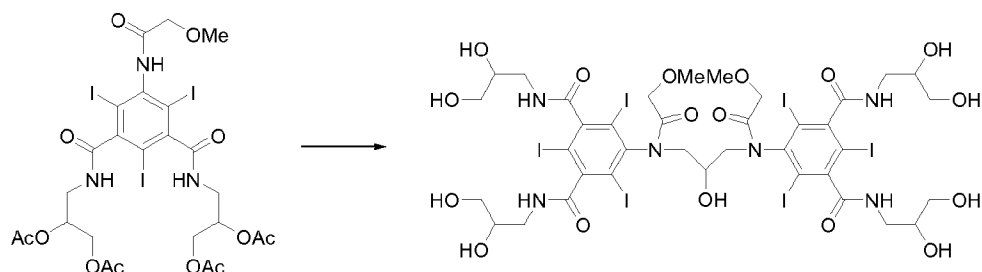
a) 5-Methoxyacetylamino-N,N'-bis(2,3-diacetoxypropyl)-2,4,6-triiodo-1,3-Benzenedicarboxamide



5-amino-N,N'-bis(2,3-diacetoxypropyl)-2,4,6-triiodo-1,3-Benzenedicarboxamide (10 g, 11.45 mmol) was dissolved in dimethylacetamide (10 ml) under a nitrogen atmosphere at ambient temperature. Methoxyacetylchloride (3.73 g, 34.35 mmol) was added drop wise over 10 minutes while stirring and the mixture was left stirring for 12 h.

The reaction mixture was poured into diethyl ether (100 ml) under stirring. The ether phase was decanted and the gummy residue was dissolved in a biphasic mixture of ethyl acetate (75 ml) and sodium bicarbonate, 1M (75 ml). The organic phase was separated and washed with water (4 x 100 ml) and dried over magnesium sulphate. After evaporation a light yellow foam was obtained which was used directly in the next step.

b) 5,5'-(2-hydroxypropane-1,3-diyl)bis(methoxyacetylazanediy)bis(N1,N3-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide)



5-Methoxyacetylamino-N,N'-bis(2,3-diacetoxypropyl)-2,4,6-triiodo-1,3-

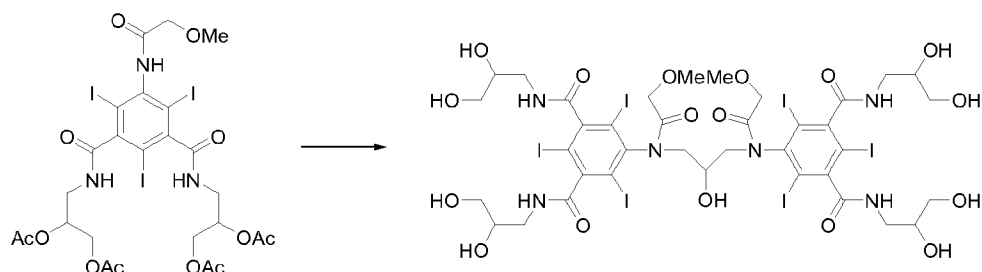
Benzenedicarboxamide (2.0 g, 2.12 mmol) was dissolved in a mixture of methanol (1 ml) and water (1 ml). The mixture was cooled to 17 °C and potassium hydroxide 10M (1.3 ml) was added drop wise. The pH was adjusted to 12 with hydrochloric acid 6M and the mixture was cooled to 15 °C. 1,3-butadienediepoxy (91 mg, 1.06 mmol) was added, the pH was maintained between 12.0 and 12.6 with hydrochloric acid over 8 h and the mixture was then left stirring over the night. The following day the mixture was diluted with water (10 ml) and treated with ion exchangers (AMB 200C, H⁺ and IRA-67, OH⁻) to zero conductivity. The ion exchangers were filtered off and rinsed with water and the combined filtrates were freeze-dried and purified by preparative HPLC (column Phenomenex Luna C18 10 µm 250 x 75.0 mm, solvents: A = water and B = acetonitrile; gradient 5 % isocratic for 5 min, 5-15 % B over 35 min; flow 175.0 ml/ min, UV detection at 254 nm). After freeze-drying 450 mg 5,5'-(2,3-dihydroxybutane-1,3-diyl)bis(methoxyacetylazanediy)bis(N1,N3-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide) was obtained (26 % yield).

LC-MS: (ESI Ion-Trap, m/e): 1610.3 [M+H]⁺

¹H-NMR 500 MHz (solvent: DMSO-d₆, ref.: TMS=0.00ppm). All protons are leading to multiple resonances due to isomerism.

8.6ppm – 7.8 ppm (NH, m, 4H); 5.0 ppm – 4.4 ppm (OH, m, 10H); 4.4 ppm – 2.9 ppm (CH, CH₂, CH₃, m, 36H)

3.29 ppm (OCH₃).

Example 3Preparation of 5,5'-(2-hydroxypropane-1,3-diyl)bis(methoxyacetylazanediy)bis(N1,N3-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide)

5-Methoxyacetyl amino-N,N'-bis(2,3-diacetoxypentyl)-2,4,6-triiodo-1,3-Benzenedicarboxamide (2.0 g, 2.12 mmol) obtained from example 1a) is dissolved in a mixture of methanol (1 ml) and water (1 ml). The mixture is cooled to 17 °C and potassium hydroxide 10M (1.3 ml) is added drop wise. The pH is adjusted to 12 with hydrochloric acid 6M or KOH 10 M as needed and the mixture is then cooled to 15 °C. Epichlorohydrin (98 mg, 1.06 mmol) is added and the pH is maintained between 12.0 and 12.6 with hydrochloric acid over 8 h and the mixture is then left stirring over the night. The following day the mixture is diluted with water (10 ml) and treated with ion exchangers (AMB 200C, H⁺ and IRA-67, OH⁻) to zero conductivity. The ion exchangers is filtered off and rinsed with water and the combined filtrates is freeze-dried. Purified is done by preparative HPLC (column Phenomenex Luna C18 10 µm 250 x 75.0 mm, solvents: A = water and B = acetonitrile; with UV detection at 254 nm). Relevant fractions are collected and freeze-dried to furnish 5,5'-(2-hydroxypropane-1,3-diyl)bis(methoxyacetylazanediy)bis(N1,N3-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide).

Claims

1. Compounds of formula (I)



Formula (I)

and salts or optical active isomers thereof,

wherein

each R^1 independently denotes a hydrogen or a C_1 to C_4 alkoxy moiety provided that at least one R^1 denotes a C_1 to C_4 alkoxy moiety;

X denotes a C_3 to C_{10} straight or branched alkylene moiety optionally with one or two CH_2 moieties replaced by oxygen atoms, sulphur atoms or NR^3 groups and wherein the alkylene moiety optionally is substituted by up to six $-OR^3$ groups, wherein R^3 denotes a hydrogen atom or a C_1 to C_4 straight or branched alkyl group;

and

each R independently are the same or different and denote a triiodinated phenyl group, preferably a 2,4,6-triiodinated phenyl group, further substituted by two groups R^2 at the remaining 3 and 5 positions in the phenyl moiety, and wherein each R^2 are the same or different and denote a hydrogen atom or a non-ionic hydrophilic moiety, provided that at least one R^2 group in the compound of formula (I) is a hydrophilic moiety.

2. Compound as claimed in claim 1 wherein each R^1 independently denotes a hydrogen atom or a methoxy, ethoxy, propoxy, isopropoxy or a linear or branched butoxy group.
3. Compound as claimed in claims 1 or 2 wherein each R^1 independently denotes a hydrogen atom or a methoxy or ethoxy group.

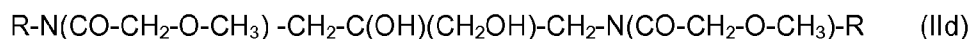
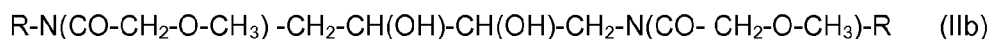
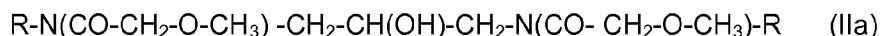
4. Compound as claimed in claims 1 to 3 wherein both R^1 are the same and denote C_1 to C_4 alkoxy moieties.
5. Compound as claimed in claim 4 wherein both R^1 are methoxy groups.
6. Compound as claimed in any of the preceding claims wherein X denotes a straight alkylene moiety with 3 to 10 carbon atoms separating the nitrogen atoms wherein the alkylene moiety is substituted by one to four hydroxyl groups.
7. Compound as claimed in any of the preceding claims wherein X denotes divalent entities selected from the following formulas:
- CH₂-CH(OH)-CH₂-;
- CH₂-CH(OH)-CH(OH)-CH₂-;
- CH₂-C(OH)(CH₃)-CH₂-;
- CH₂-C(OH)(CH₂OH)-CH₂-; and
- CH₂-CH(OH)-CH₂-CH(OH)-CH₂-.
8. Compounds as claimed in any of the preceding claims wherein each of the R^2 groups are the same or different and denote a non-ionic hydrophilic moiety comprising esters, amides and amine moieties, optionally further substituted by a straight chain or branched chain C_{1-10} alkyl groups, preferably straight chain or branched chain C_{1-5} alkyl groups, optionally with one or more CH₂ or CH moieties replaced by oxygen or nitrogen atoms and optionally substituted by one or more groups selected from oxo, hydroxyl, amino or carboxyl derivative, and oxo substituted sulphur and phosphorus atoms.
9. Compounds as claimed in claim 8 wherein each of the R^2 groups are the same or different and denote a non-ionic hydrophilic moiety comprising esters, amides and amine moieties, further substituted by a straight chain or branched chain C_{1-5} alkyl groups substituted by 1 to 3 hydroxy groups.

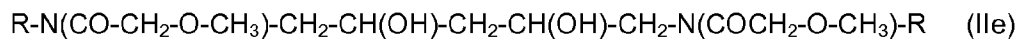
10. Compounds as claimed in any of the preceding claims wherein each of the R^2 groups are the same or different and are selected from groups of the formulas

-CONH-CH₂-CH₂-OH;
 -CONH-CH₂-CHOH-CH₂-OH;
 -CON(CH₃)CH₂-CHOH-CH₂OH;
 -CONH-CH-(CH₂-OH)₂;
 -CON-(CH₂-CH₂-OH)₂;
 -CONHCH₃;
 -CONH-CH₂-CH₂-O-CH₃;
 -CONH-O-CH₃;
 -CONH-CH₂-CHOH-CH₂-O-CH₃;
 -CONH-CH₂-CHOCH₃-CH₂-OH;
 -CON (CH₂-CHOH-CH₂-OH) (CH₂-CH₂-OH);
 -CONH-C(CH₂-OH)₂CH₃;
 -CONH-C(CH₂-OH)₃;
 -CONH-CH (CH₂-OH) (CHOH -CH₂-OH) ;
 -NHCOCH₂OH;
 -N(COCH₃)H;
 -N(COCH₃) C₁₋₃ alkyl;
 -N(COCH₃) – mono, bis or tris-hydroxy C₁₋₄ alkyl;
 -N(COCH₂OH) – hydrogen, mono, bis or tris-hydroxy C₁₋₄ alkyl;
 -N(CO-CHOH-CH₂OH) - hydrogen, mono, bis or trihydroxylated C₁₋₄ alkyl;
 -N(CO-CHOH-CHOH-CH₂OH) - hydrogen, mono, bis or trihydroxylated C₁₋₄ alkyl;
 -N(CO-CH-(CH₂OH)₂) - hydrogen, mono, bis or trihydroxylated C₁₋₄ alkyl; and
 -N(COCH₂OH)₂.

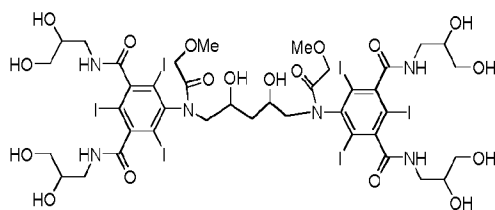
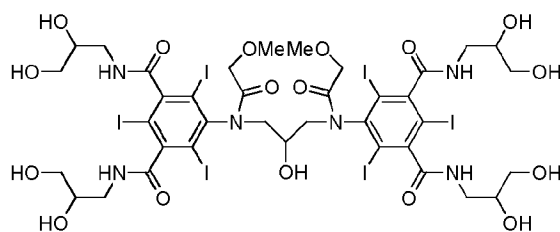
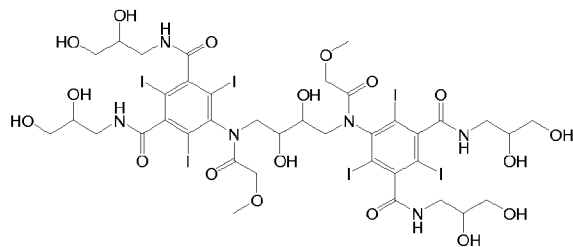
11. Compounds as claimed in any of the preceding claims wherein the R^2 groups are attached to the iodinated phenyl group via carbamoyl linkages.

12. Compounds as claimed in any of the preceding claims and of formulas (IIa) to (IIe)





13. Compounds as claimed in the preceding claims being of the formulas



14. A diagnostic agent comprising a compound of formula (I) as defined in any of the preceding claims.

15. An X-ray diagnostic composition comprising a compound of formula (I) as defined in claims 1 to 13 together with a pharmaceutically acceptable carriers or excipients.

16. Use of a diagnostic agent or a diagnostic composition comprising a compound of formula (I) as defined in claims 1 to 13 in X-ray contrast examinations.

17. Use of a compound of formula (I) as defined in claims 1 to 13 for the manufacture of a diagnostic composition for use as an X-ray contrast agent.

18. A method of diagnosis comprising administration of compounds of formula (I) as defined in claims 1 to 13 to the human or animal body, examining the body with a diagnostic device and compiling data from the examination.

19. A method of imaging, specifically X-ray imaging, comprising administration of compounds of formula (I) as defined in claims 1 to 13 to the human or animal body, examining the body with a diagnostic device and compiling data from the examination and optionally analysing the data.