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(54) Title: RADIOLABELLED PEPTIDE BASED COMPOUNDS AND USES THEREOF

(57) Abstract: The present invention relates to new radiolabelled peptide-based compounds and their use for diagnostic imaging using positron emission tomography (PET). Such compounds may thus be used for diagnosis or therapy of, for example, malignant diseases, heart diseases, endometriosis, inflammation-related diseases, rheumatoid arthritis and Kaposi's sarcoma.

Radiolabelled peptide based compounds and uses thereof

Field of the Invention

The present invention relates to new radiolabelled peptide-based compounds and their use for diagnostic imaging using positron emission tomography (PET). Such compounds may thus be used for diagnosis or therapy of, for example, malignant diseases, heart diseases, endometriosis, inflammation-related diseases, rheumatoid arthritis and Kaposi's sarcoma.

Background of the Invention

The application of radiolabelled bioactive peptides for diagnostic imaging is gaining importance in nuclear medicine. Biologically active molecules which selectively interact with specific cell types are useful for the delivery of radioactivity to target tissues. For example, radiolabelled peptides have significant potential for the delivery of radionuclides to tumours, infarcts, and infected tissues for diagnostic imaging and radiotherapy. ^{18}F, with its half-life of approximately 110 minutes, is the positron-emitting nuclide of choice for many receptor imaging studies. Therefore, ^{18}F-labelled bioactive peptides have great clinical potential because of their utility in PET to quantitatively detect and characterise a wide variety of diseases.

New blood vessels can be formed by two different mechanisms: vasculogenesis or angiogenesis. Angiogenesis is the formation of new blood vessels

by branching from existing vessels. The primary stimulus for this process may be inadequate supply of nutrients and oxygen (hypoxia) to cells in a tissue. The cells may respond by secreting angiogenic factors, of which there are many; one example, which is frequently referred to, is vascular endothelial growth factor (VEGF). These factors initiate the secretion of proteolytic enzymes that break down the proteins of the basement membrane, as well as inhibitors that limit the action of these potentially harmful enzymes. The other prominent effect of angiogenic factors is to cause endothelial cells to migrate and divide. Endothelial cells that are attached to the basement membrane, which forms a continuous sheet around blood vessels on the contralumenal side, do not undergo mitosis. The combined effect of loss of attachment and signals from the receptors for angiogenic factors is to cause the endothelial cells to move, multiply, and rearrange themselves, and finally to synthesise a basement membrane around the new vessels.

Angiogenesis is prominent in the growth and remodelling of tissues, including wound healing and inflammatory processes. Tumours must initiate angiogenesis when they reach millimetre size in order to keep up their rate of growth. Angiogenesis is accompanied by characteristic changes in endothelial cells and their environment. The surface of these cells is remodelled in preparation for migration, and cryptic structures are exposed where the basement membrane is degraded, in addition to the variety of proteins which are involved in effecting and controlling proteolysis. In the case of tumours, the resulting network of blood vessels is usually disorganised, with the formation of sharp kinks and also arteriovenous shunts. Inhibition of angiogenesis is also considered to be a promising strategy for antitumour

therapy. The transformations accompanying angiogenesis are also very promising for diagnosis, one example being malignant disease, but the concept also shows great promise in inflammation and a variety of inflammation-related diseases, including atherosclerosis, the macrophages of early atherosclerotic lesions being potential sources of angiogenic factors.

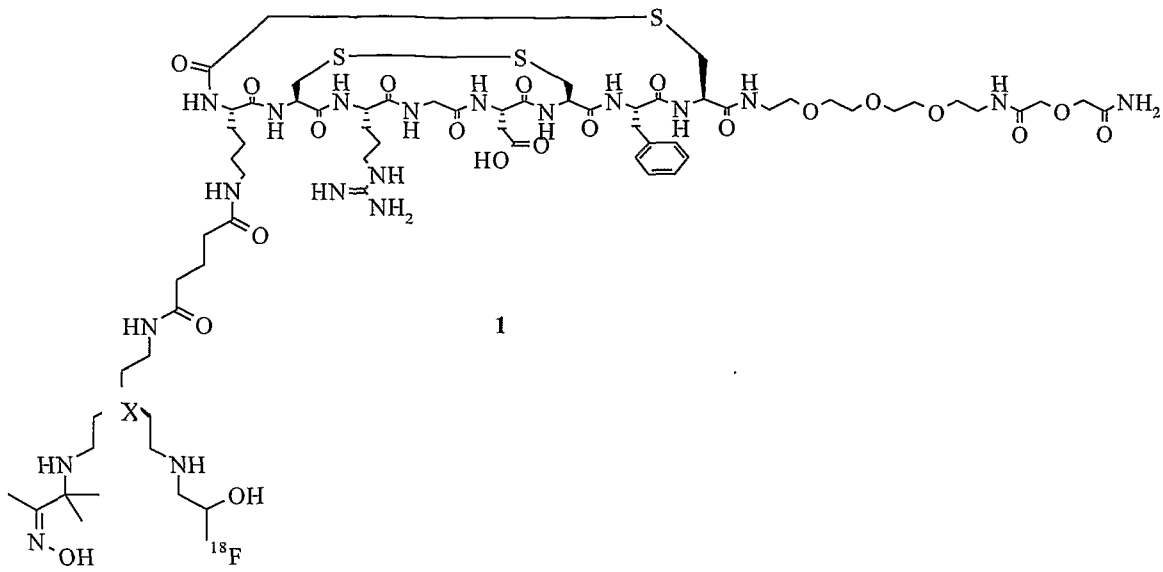
WO 2003/006491 describes peptide-based compounds which target integrin receptors associated with angiogenesis. International application PCT/GB2004/001052 describes methods suitable for labelling biologically active vectors with ^{18}F. However, there exists a need for further peptide-based compounds having utility for diagnostic imaging techniques such as PET.

Discussion or citation of a reference herein shall not be construed as an admission that such reference is prior art to the present invention.

Detailed Description of the Invention

The present invention relates to new peptide-based compounds and their use for diagnostic imaging using PET. The novel ^{18}F peptide based compounds discussed herein show a biodistribution (less binding in liver and other organs) that is about 15% higher in comparison to any relatively successful prior agents developed.

One embodiment of the present invention encompasses a compound of formula (1),



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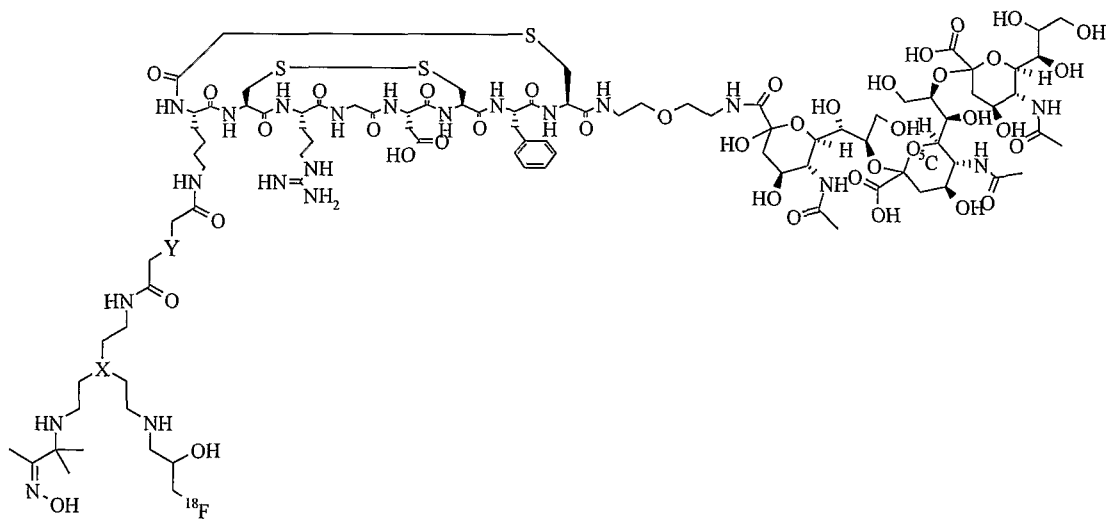
wherein X is a carbon or nitrogen.

Yet another embodiment of the invention entailes a compound of formula 2,



wherein Y is a carbon or oxygen and X is a nitrogen or carbon.

PET imaging agents. Compounds of formula (1) and (2) are prepared by standard methods of peptide synthesis, for example, solid-phase peptide synthesis, as described in Atherton, E. and Sheppard, R.C.; "Solid Phase Synthesis"; IRL Press: Oxford, 1989. Incorporation of the aminoxy group in a compound of formula (I) is achieved by formation of a stable amide bond formed by reaction of a peptide amine function with an activated acid and introduced either during or following the peptide synthesis.

Still a further embodiment of the invention depicts a radiopharmaceutical composition comprising an effective amount of a compound of formula 1 or 2, together with one or more pharmaceutically acceptable adjuvants, excipients or diluents.

Yet another embodiment of the present invention depicts a compound of formula 1 or 2 for medical use particularly in the in vivo diagnosis or imaging, for example by PET, of a disease or condition associated with angiogenesis.

The term "diseases and conditions associated with angiogenesis" includes those diseases and conditions referred to below. Reference is also made in this regard to WO 98/47541.

Diseases and conditions associated with angiogenesis include different forms of cancer and metastasis, for example, breast, skin, colorectal, pancreatic, prostate, lung or ovarian cancer.

Other diseases and conditions associated with angiogenesis are inflammation (for example, chronic inflammation), atherosclerosis, rheumatoid arthritis and gingivitis.

Further diseases and conditions associated with angiogenesis are arteriovenous alformations, astrocytomas, choriocarcinomas, glioblastomas, gliomas, hemangiomas (childhood, capillary), hepatomas, hyperplastic endometrium, ischemic myocardium, endometriosis, Kaposi sarcoma, macular degeneration, melanoma, neuroblastomas, occluding peripheral artery disease, osteoarthritis, psoriasis, retinopathy (diabetic, proliferative), scleroderma, seminomas and ulcerative colitis.

Still another embodiment of the present invention depicts a use of a compound of formula 1 or 2 for the manufacture of a radiopharmaceutical for use in the method of *in vivo* imaging.

Yet another embodiment of the present invention shows a method of generating an image of a human or animal body comprising administering a compound of claim 1 or 2 to said body and generating an image of at least a part of said body to which said compound has distributed using PET.

Another embodiment of the present invention shows a method of monitoring the effect of treatment of a human or animal body with a drug to combat a condition associated with cancer, preferably angiogenesis, said method comprising administering to said body a compound of formula 1 or 2 and detecting the uptake of

said compound by cell receptors said administration and detection optionally but preferably being effected before, during and after treatment with said drug.

Examples

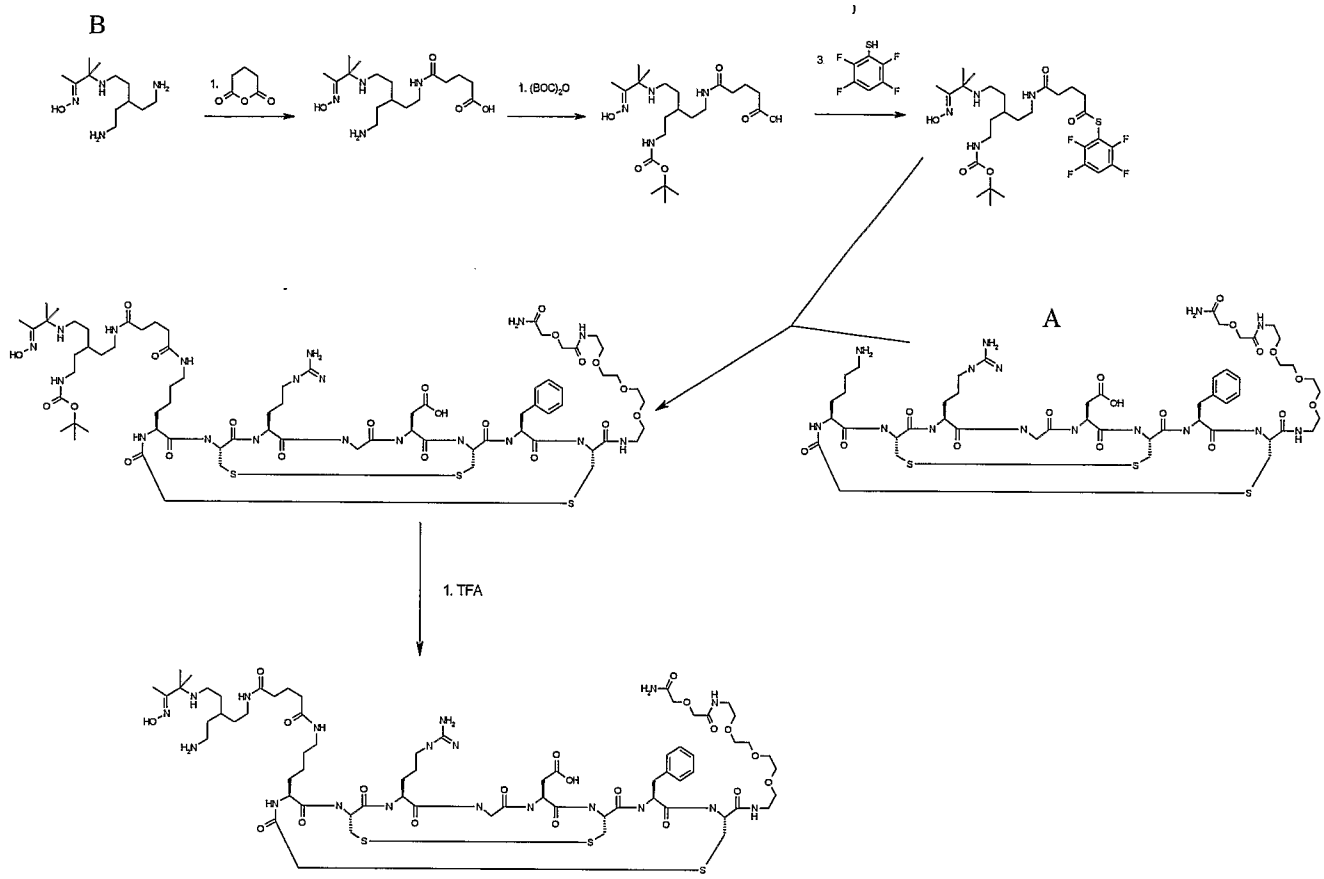
The invention is further described in the following example which is in no way intended to limit the scope of the invention.

The invention is illustrated by way of examples in which the following abbreviations are used.

NMR: nuclear magnetic resonance
TFA: trifluoroacetic acid
Boc: t-butoxycarbonyl

A precursor for the novel ^{18}F peptide based compounds are made from a reaction between A (available from Bachem) and a by-product from the synthesis of B (mono-alkylated by-product). See Scheme 1 below.

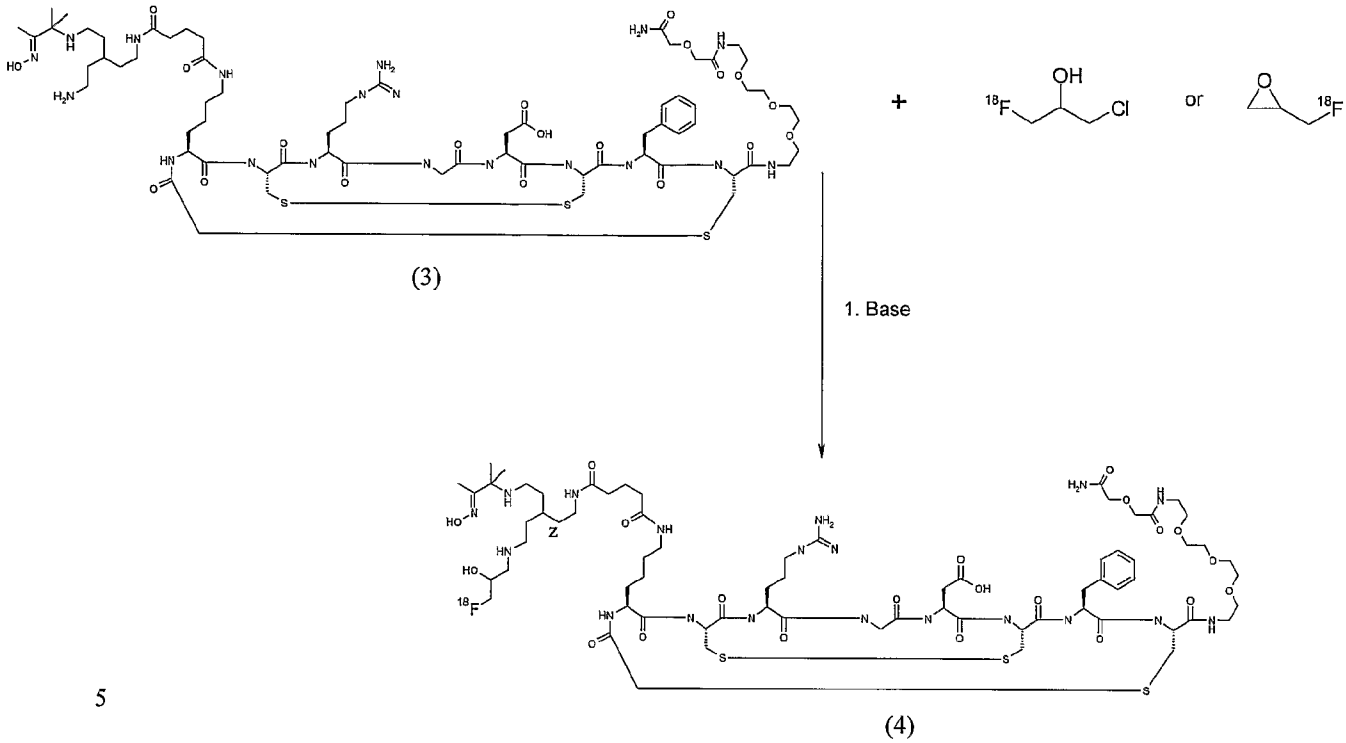
Scheme 1



(3)

The novel ^{18}F peptide based compound disclosed herein (4) wherein Z is carbon is made by reacting the precursor (3) shown above with ^{18}F epifluorohydrin or with 1-fluoro-3-chloro-propan-2-ol. See Scheme 2 below.

Scheme 2



The fact that starting materials are readily available and known can aid in reducing development time and costs. The present invention also suggests that the novel angiogenesis ^{18}F peptide based compounds have a superior biological profile/properties compared to other compounds. The novel ^{18}F peptide based compounds discussed herein show a biodistribution (less binding in liver and other organs) that is about 15% higher in comparison to any relatively successful prior agents developed.

The formation of the 3-chloro-2-hydroxy-1-^{18}fluoride at room temperature has been proved by both ^{19}F- and and a 400 MegaHertz ^{1}H-NMR spectrometer. The laboratory tests using the epoxide, as depicted above in scheme 2, to introduce ^{18}F

fluoride to an organic molecule was performed in water at room temperature and yielded a 30% relative amount of the organic fluoride target molecule. This amount obtained is about 2-3 times greater than the recovery amount of the organic fluoride target molecule compared to ^{18}F-labeling using tosyl (or a similar leaving group such as triflate or mesylate) as a leaving group.

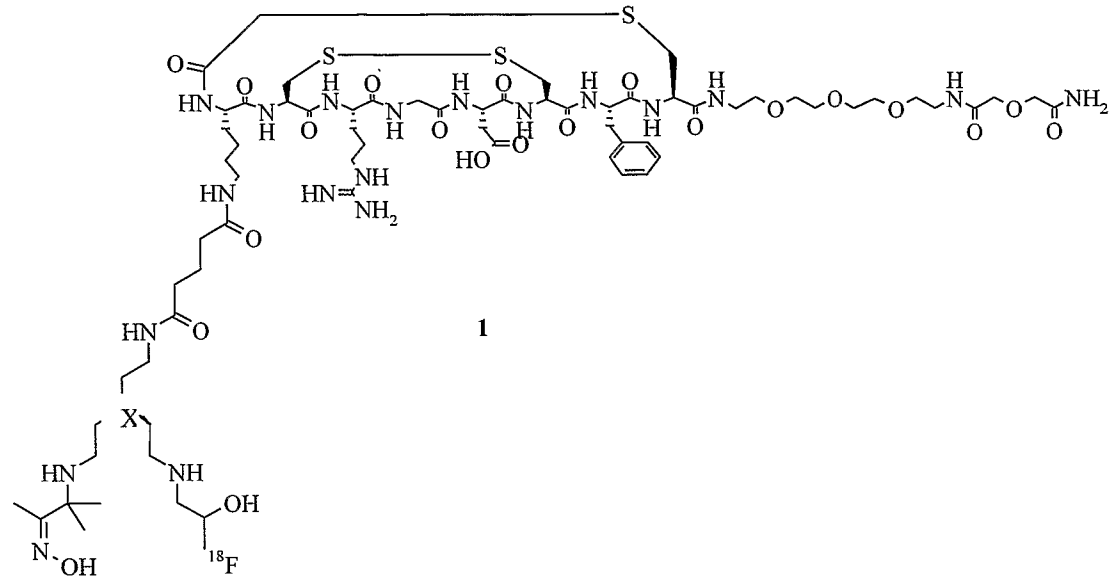
Specific Embodiments, Citation of References

The present invention is not to be limited in scope by specific embodiments described herein. Indeed, various modifications of the inventions in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

Various publications and patent applications are cited herein, the disclosures of which are incorporated by reference in their entireties.

What is claimed is:

1. A compound of formula (1) which is,



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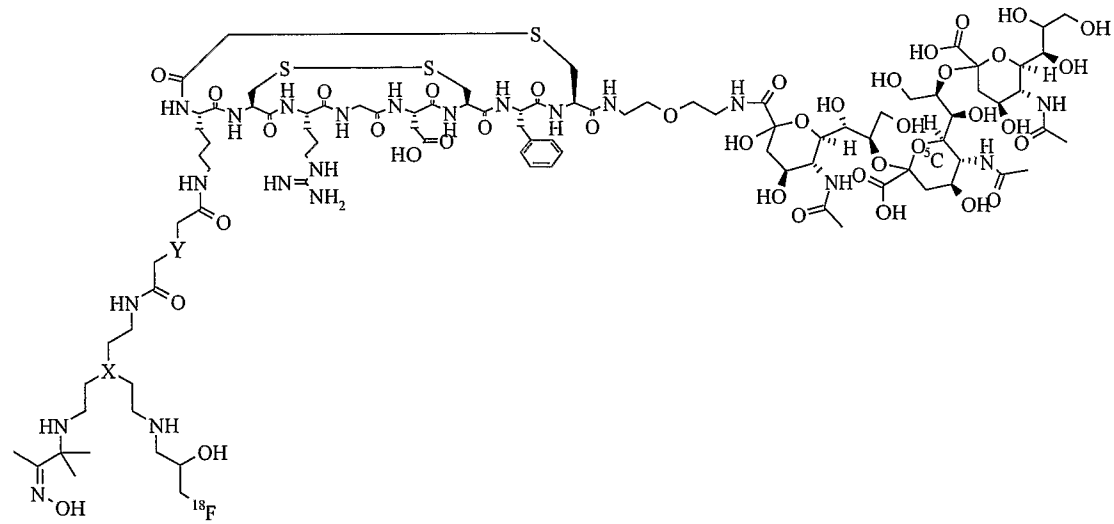
wherein X is a carbon or a nitrogen.

2. A compound of formula (2)



(2)

wherein Y is carbon or oxygen and X is nitrogen or carbon.

3. A radiopharmaceutical composition comprising an effective amount of a compound of claim 1 or 2, together with one or more pharmaceutically acceptable adjuvants, excipients or diluents.

4. A compound of claim 1 or 2 for medical use particularly in the in vivo diagnosis or imaging, for example by PET, of a disease or condition associated with angiogenesis.

5. Use of a compound of claim 1 or 2 for the manufacture of a radiopharmaceutical for use in the method of *in vivo* imaging.

6. A method of generating an image of a human or animal body comprising administering a compound of claim 1 or 2 to said body and generating an image of at least a part of said body to which said compound has distributed using PET.

7. A method of monitoring the effect of treatment of a human or animal body with a drug to combat a condition associated with cancer, preferably angiogenesis, said method comprising administering to said body a compound of claim 1 or 2 and detecting the uptake of said compound by cell receptors said administration and detection optionally but preferably being effected before, during and after treatment with said drug.