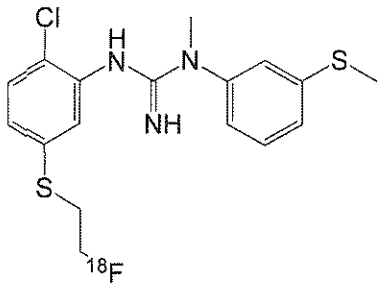
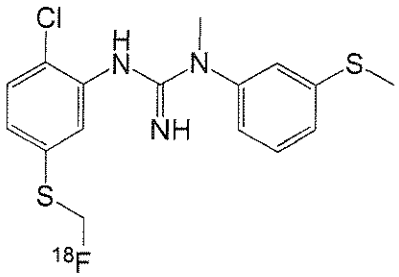
This method has also been recently reported by Robins *et al* (2010 Bioorg Med Chem Lett; 20: 1749-51) as a successful way to obtain the following ^{18}F-labelled *S*-fluoroalkyl diarylguanidines:





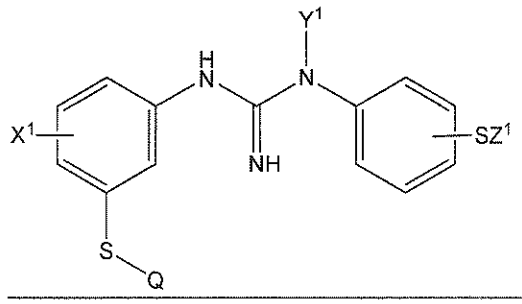
However, the above-described method of preparing the radiolabelling precursor of Formula (B) suffers from a number of problems. First of all, tin chloride is used in a reduction step used in the preparation of the compound of Formula (C) from sulfonylchloride starting material. Residual tin complicates the workup by gel forming tin hydroxides at pH >2. Furthermore, following this reduction step, a benzyl protective group is introduced at the thiol and this group has to be removed at the end of the synthesis, requiring use of $AlCl_3$ followed by flash chromatography. There is therefore a need for a method to prepare this radiolabelling precursor that overcomes these problems.

In addition, and not described in the prior art, the present inventors have found that the compound of Formula (B) wherein R^2 is hydrogen decomposes to form a disulfide impurity, even under what would be considered "inert" conditions, which complicates subsequent radiolabelling to obtain the corresponding compound of Formula (A). There is therefore an additional need for alternative strategies to obtain said compound of Formula (A) that do not suffer from this disadvantage.

Summary ~~of the Invention~~

The present ~~invention~~disclosure provides a method to prepare a radiolabelled guanidine derivative.

In a first aspect, there is provided a method to obtain a positron emission tomography (PET) tracer of Formula I:



(I)

wherein:

X^1 is an X group selected from C_{1-4} alkyl or halo;

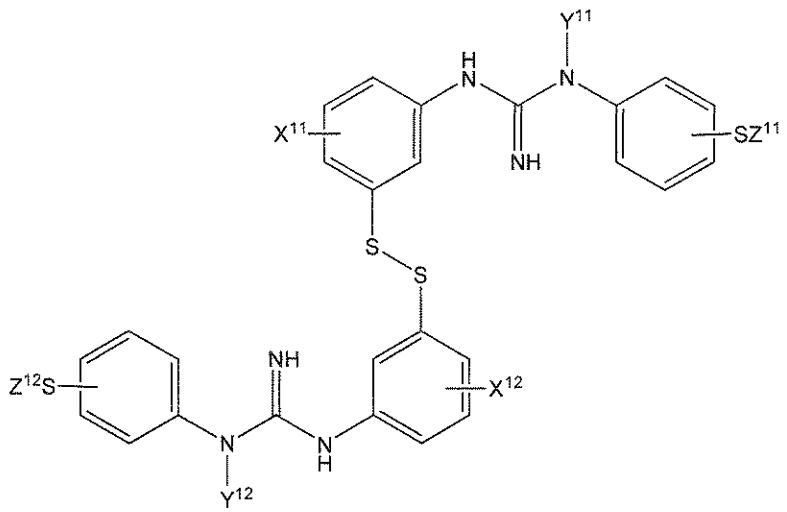
Y^1 is a Y group selected from hydrogen or C_{1-4} alkyl;

Z^1 is a Z group which is C_{1-4} alkyl; and,

Q is $[^{11}C]C_{1-4}$ alkyl- or $[^{18}F]$-C_{1-4}fluoroalkyl-;

wherein said method comprises:

(a) providing a compound of Formula II:



(II)

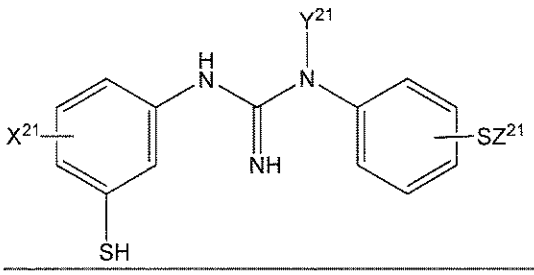
wherein:

X^{11} and X^{12} are the same and are both an X group as defined for X^1;

Y^{11} and Y^{12} are the same and are both a Y group as defined for Y^1; and,

Z^{11} and Z^{12} are the same and are both a Z group as defined for Z^1;

(b) reducing said compound of Formula II with a reducing agent to obtain a compound of Formula III:



(III)

X^{21} is an X group as defined for X^1;

Y^{21} is a Y group as defined for Y^1; and,

Z^{21} is a Z group as defined for Z^1;

(c) reacting the compound of Formula III as obtained in step (b), with either $[^{11}C]C_{1-4}$ alkyl-LG^1 or $[^{18}F]$-C_{1-4} fluoroalkyl-LG^2, wherein LG^1 and LG^2 are independently halo, or the group -O-SO_2-R^1 wherein R^1 represents an optionally-substituted C_{6-10} aryl, an optionally-substituted C_{1-4} alkyl, or C_{1-4} fluoroalkyl, wherein said reacting is carried out in a suitable solvent.

A novel intermediate and it's method of synthesis are also provided. In the method of the ~~invention~~disclosure, use of a step comprising iodine oxidation has the advantage that the iodine oxidises any tin present as a consequence of the

initial tin chloride reduction step. No protecting groups are required in the method of the ~~invention~~disclosure, thereby eliminating the need for a deprotection step. In addition, the method of the ~~invention~~disclosure overcomes the problem observed by the present inventors with formation of a disulphide impurity. The method of the ~~invention~~disclosure therefore overcomes a number of problems associated with known methods for the preparation of radiolabelled guanidine derivatives.

In a second aspect, there is provided a cassette for carrying out the method as defined above, wherein said cassette comprises:

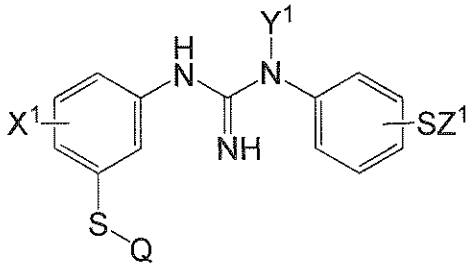
(i) a vessel containing the compound of Formula II as defined above;

(ii) means for reacting said compound of Formula II with a reducing agent to form a compound of Formula III as defined above; and,

(iii) means for reacting said compound of Formula III with either [^{11}C]C$_{1-4}$ alkyl-LG^1 or [^{18}F]-C$_{1-4}$ fluoroalkyl-LG^2 to obtain a PET tracer of Formula I, wherein LG^1, LG^2, and said PET tracer of Formula I are as defined above.

Detailed Description of the Invention

In one aspect, the present invention provides a method to obtain a positron emission tomography (PET) tracer of Formula I:



(I)

wherein:

X^1 is an X group selected from C$_{1-4}$ alkyl or halo;

Y^1 is a Y group selected from hydrogen or C_{1-4} alkyl;

Z^1 is a Z group which is C_{1-4} alkyl; and,

Q is $[^{11}C]C_{1-4}$ alkyl- or $[^{18}F]$-C_{1-4}fluoroalkyl-;

wherein said method comprises:

(a) providing a compound of Formula II: