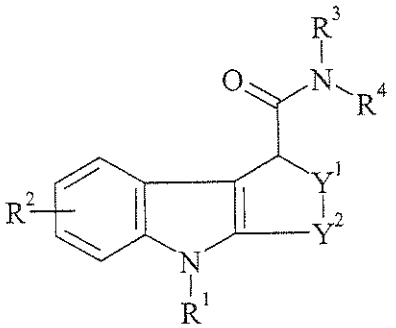
In addition, co-pending patent application PCT/EP2009/062827 describes tetracyclic indole-derived *in vivo* imaging agents similar to those of WO 2007/057705.

The tetracyclic indole derivatives described in WO 2007/057705 and in co-pending patent application PCT/EP2009/062827 have good affinity for the PBR receptor, and a high proportion of radioactivity in the brain at 60 minutes post-injection represents the parent *in vivo* imaging agent. Although these tetracyclic indole derivatives also achieve a reasonable initial concentration in the rat brain in biodistribution studies, the uptake is still relatively low and could be improved upon. The present inventors have also found that the relative retention in the olfactory bulb (the brain region having the highest concentration of PBR receptor) of these prior art tetracyclic indole derivatives is not as high as desirable for *in vivo* imaging. There is therefore scope for a PBR *in vivo* imaging agent that retains the advantageous properties of the above-described prior art tetracyclic indole *in vivo* imaging agents, but that has improved brain uptake and improved specific binding to the PBR receptor.

Summary ~~of the Invention~~

The present ~~invention~~disclosure provides a novel tricyclic indole compound suitable for use as an *in vivo* imaging agent.

In a first aspect, there is provided an *in vivo* imaging agent of Formula I:



(I)

wherein:

R^1 is C_{1-3} alkyl or C_{1-3} fluoroalkyl;

R^2 is hydrogen, hydroxyl, halo, cyano, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} fluoroalkyl, or C_{1-3} fluoroalkoxy;

R^3 and R^4 are independently C_{1-3} alkyl, C_{7-10} aralkyl, or R^3 and R^4, together with the nitrogen to which they are attached, form a nitrogen-containing C_{4-6} aliphatic ring optionally comprising 1 further heteroatom selected from nitrogen, oxygen and sulfur;

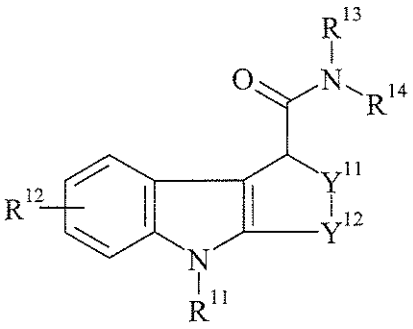
Y^1 is CH_2; and,

Y^2 is CH_2, CH_2-CH_2, $CH(CH_3)$-CH_2 or CH_2-CH_2-CH_2;

and wherein Formula I as defined comprises an atom which is a radioisotope suitable for *in vivo* imaging.

The present ~~invention~~disclosure also provides a precursor compound useful in the synthesis of the *in vivo* imaging agent of the ~~invention~~disclosure, as well as a method for synthesis of said precursor compound.

In a second aspect, there is provided a precursor compound for the preparation of the *in vivo* imaging agent as defined above wherein said precursor compound is of Formula II:

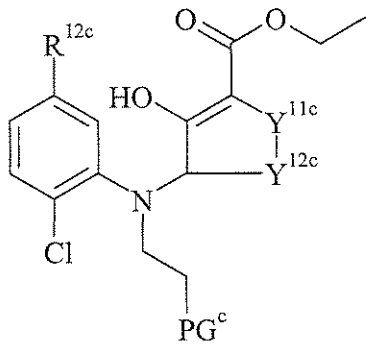


(II)

wherein one of R^{11} and R^{12} comprises a chemical group that reacts with a suitable source of the radioisotope as defined above, such that said *in vivo* imaging agent is formed upon reaction of said precursor compound with said suitable source of said radioisotope, and the other of R^{11} and R^{12} is as defined above for R^1 and R^2, respectively, and optionally comprises a protecting group; and,

R^{13-14} and Y^{11-12} are as defined for R^{3-4} and Y^{1-2}, respectively, above, and optionally each further comprises a protecting group.

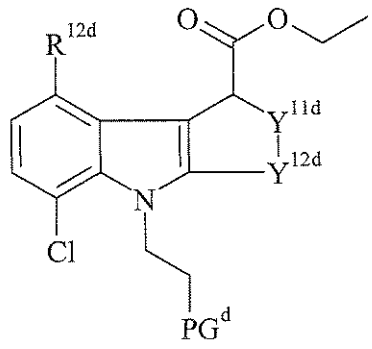
In a third aspect, there is provided a method for the preparation of a precursor compound of Formula IIb as defined above, wherein said method comprises reaction with $ZnCl_2$ of a compound of Formula IIc:



IIc

wherein R^{12c}, Y^{11c} and Y^{12c} are as defined above for R^{12}, Y^{11} and Y^{12}, respectively, and PG^c is a protecting group;

to form a compound of Formula IId:



IId

wherein R^{12d}, Y^{11d}, Y^{12d} and PG^d are as defined for R^{12c}, Y^{11c}, Y^{12c} and PG^c, respectively;

wherein said reaction is carried out in a solvent system comprising diethyl ether.

In a fourth aspect, there is provided a method for the preparation of the *in vivo* imaging agent as defined above comprising:

(i) providing a precursor compound as defined above;

(ii) providing a suitable source of said radioisotope as defined above;

(iii) reacting the precursor compound of step (i) with the radioisotope of step (ii) to obtain said *in vivo* imaging agent.

In a fifth aspect, there is provided a kit for carrying out the method as defined above comprising the precursor as defined above.

A method for the preparation of the *in vivo* imaging agent is also provided comprising use of the precursor compound of the ~~invention~~disclosure. A pharmaceutical composition comprising the *in vivo* imaging agent of the ~~invention~~disclosure is additionally provided, in addition to a kit suitable for the facile preparation of the pharmaceutical composition. In a further ~~aspect~~embodiment, use of the *in vivo* imaging agent for *in vivo* imaging of a condition associated with abnormal PBR expression is provided. The *in vivo* imaging agent of the present ~~invention~~disclosure retains the advantageous properties of known tetracyclic *in vivo* imaging agents, in conjunction with improved brain uptake and specificity for the peripheral benzodiazepine receptor.

In a sixth aspect, there is provided a cassette for carrying out the method as defined above comprising:

(i) a vessel containing the precursor compound as defined above;

and,

(ii) means for eluting the vessel of step (i) with a suitable source of a radioisotope suitable for *in vivo* imaging as defined above.

In a seventh aspect, there is provided a radiopharmaceutical composition comprising the *in vivo* imaging agent as defined above together with a biocompatible carrier in a form suitable for mammalian administration.

In an eighth aspect, there is provided an *in vivo* imaging method for determining the distribution and/or the extent of PBR expression in a subject comprising:

(i) administering to said subject an *in vivo* imaging agent as defined above;

(ii) allowing said *in vivo* imaging agent to bind to PBR in said subject;

(iii) detecting by an *in vivo* imaging procedure signals emitted by the radioisotope of said *in vivo* imaging agent;

(iv) generating an image representative of the location and/or amount of said signals; and,

(v) determining the distribution and extent of PBR expression in said subject wherein said expression is directly correlated with said signals emitted by said *in vivo* imaging agent.