SYNTHESIS OF [^{18}F]-FLUOROETHYLFENOTEROL FOR IMAGING β2 RECEPTOR STATUS IN LUNG IN VIVO

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Summary: 5-(2-{2-[4-(2-[^{18}F]Fluoroethoxy)-phenyl]-1-methyl-ethylamino}-1-hydroxy-ethyl)-benzene-1,3-diol ([^{18}F]fluoroethylfenoterol) was synthesised from 4-(2-{benzyl-[2-(3,5-bis-benzyloxy-phenyl)-2-hydroxy-ethyl]-amino}-propyl)-phenol using 2-[^{18}F]fluoroethyltosylate (92% RCY) followed by reductive cleavage of the benzyl protecting groups. Preliminary *in vitro* tests showed [^{19}F]fluoroethylfenoterol to be as potent in relaxation of lung tissue as fenoterol itself.

Introduction: The β2 receptor system is important for the sympathetic innervation of the lung. Via the second messager cAMP, β2 agonists effect a relaxation of bronchial smooth muscle [1]. The importance of β2 adrenoceptor density for obstructive respiratory diseases such as asthma or chronic obstructive bronchitis is still not exactly clarified [2]. For understanding the pathogenesis, therapy and prognosis of such diseases, a non-invasive, quantifiable imaging of the β2 receptor in lung would be of considerable importance. The aim of this project was the synthesis of selective radiolabelled β2 ligands to visualise the β2 receptor status in lung.

Results and Discussion: We synthesised a fluoroethyl derivative of fenoterol, a β2 agonist commonly used as a therapeutic agent for asthma. As both the catechol phenol moieties, as well as the β-hydroxic function and the amine group are necessary for receptor binding, we aimed at fluoroethylating the 4-phenolic hydroxy function because this is unlikely to reduce the affinity of the molecule to the receptor (fig.1) [3]. For first labelling experiments, we synthesised both the labelling precursor and the standard compound as a racemate. An enantioselective synthesis is in progress to obtain the (R,R)-fluoroethylfenoterol, which is thought to be the most potent agonist of all the enantiomers [3]. The standard [^{19}F]fluorethylfenoterol (8) was synthesised from fenoterol hydrobromide (7) which was a gift of Boehringer Ingelheim Pharma KG (Berotec®). It was re-

acted with 2-fluoro-1-bromoethane to obtain 5-(2-{2-[4-(2-[^{19}F]fluoroethoxy)-phenyl]-1-methyl-ethylamino}-1-hydroxy-ethyl)-benzene-1,3-diol (8) (fig. 1).

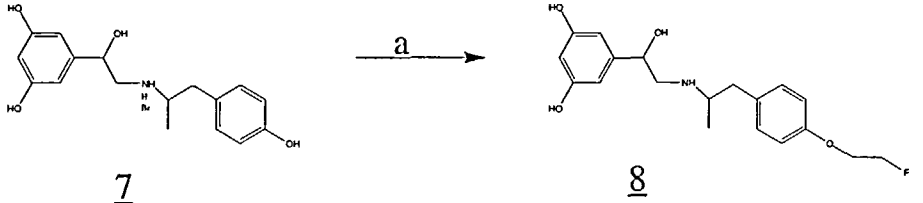

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Fig.1: synthesis of standard compound (7) (a: 2 eq. potassium methanolate, 2-bromo-1-fluoroethan)

The synthesis of the labelling precursor started from commercially available 3,5-dibenzyloxy acetophenone (1), which was brominated to obtain synthon 2 (fig. 2). For synthon 4, we reacted 4-hydroxy phenylacetone (3) with benzylamine in the presence of hydrogen at 5 bar in a Parr hydrogenator. Synthon 2 and 4 were then coupled and subsequently reduced with lithium aluminium hydride to obtain the benzyl protected labelling precursor 5 (fig.2). 5-(2-{2-[4-(2-[^{18}F]Fluoroethoxy)-phenyl]-1-methylethyl-amino}-1-hydroxy-ethyl)-benzene-1,3-diol (6) was obtained by reacting 10mg of the labelling precursor 5 with 2-[^{18}F]-fluoroethyltosylate in DMSO at 120°C (92%) and subsequent deprotection with hydrogen (2 bar) and 4% formic acid (fig. 3). All compounds were analysed with common spectroscopic methods such as ^{1}H-NMR, ^{13}C-NMR, mass spectroscopy and elemental analysis.
In first *in vitro* tests with guinea pig trachea it was proven whether the receptor binding properties of the fluoroethylfenoterol differed from the original compound fenoterol. Isolated guinea-pig tracheae were placed in organ baths horizontally under a tension of 1 g and contracted by the application of the muscarinic receptor agonist oxotremorine (100 nM). Cumulative concentration-response curves were established for fluoroethylfenoterol and fenoterol by stepwise increasing the concentration (factor $10^{1/2}$ or 10). The IC50 values for fenoterol and fluoroethylfenoterol were nearly identical (about 60 nM). Also the maximal degree of relaxation did not differ between both compounds (about 90%) in their relaxing potency and efficacy in isolated airways.

Conclusion: [^{18}F]fluoroethylfenoterol was synthesised and successfully evaluated as a potent derivative of fenoterol. [^{18}F]fluoroethylfenoterol and PET will now be used to quantify β2 adrenoceptor densities in vivo for understanding the pathogenesis, therapy and prognosis of various diseases.

References:

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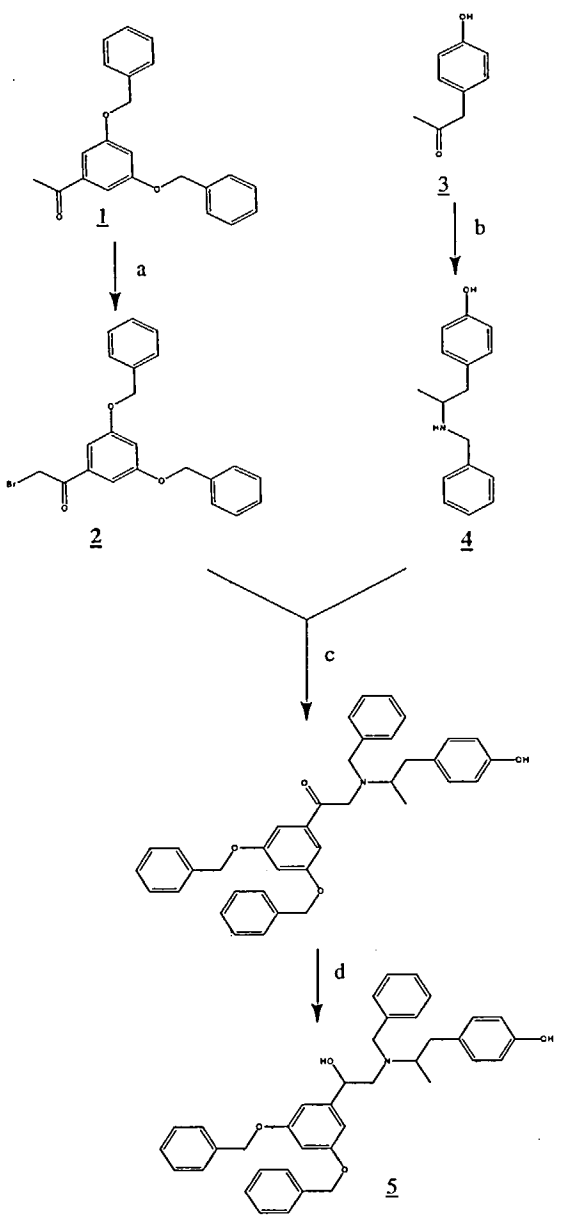

fig.2: synthesis of labelling precursor (5)(a: ether, bromine; b: benzylamine, hydrogen 5bar, Pd/C; c: THF reflux; d: $LiAlH_4$, THF

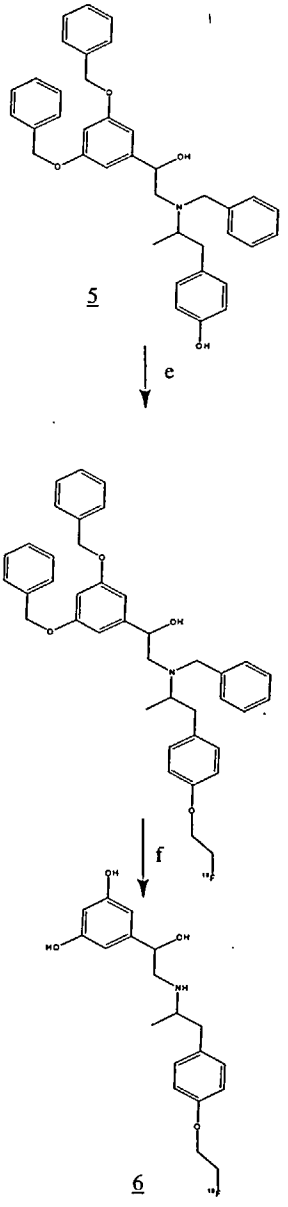

fig.3: labelling reaction(e: DMSO, 80°C, 10min, [^{18}F]fluoroethyltosylate, 92% RCA; f: hydrogen, 2bar, 4% formic acid