Synthesis of [^{11}C]methylfenoterol for imaging the β2 receptor status in lung *in vivo*

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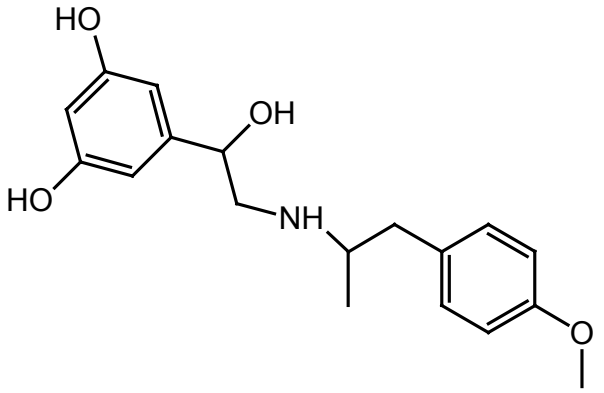
Introduction:
The β2 receptor system is important for the sympathetic innervation of the lung. Via the second messenger cAMP, β2 agonists effect a relaxation of bronchial smooth muscle [1]. The importance of β2 adrenoceptor density for obstructive respiratory diseases such as asthma or chronic obstructive bronchitis is still not exactly clarified [2]. For understanding the pathogenesis, therapy and prognosis of such diseases, a non-invasive, quantificable imaging of the β2 receptor in lung would be of considerable importance. There have already been several attempts, however mostly antagonists were labelled with carbon-11 [3]. We intent to label an agonist, so that only the high-affinity state of the receptor, which is believed to be involved in the above mentioned diseases, will be visualised by PET.

Results and Discussion:
We developed a more convenient synthesis of a methyl derivative of Fenoterol (1), a β2 agonist commonly used as a therapeutic agent for asthma. As both the catechol phenol moieties, as well as the beta-hydroxic function and the amine group are necessary for receptor binding, we aimed at methylating the 4-phenolic hydroxy function because this is unlikely to reduce the affinity of the molecule to the receptor [4].
For first labelling experiments, we synthesised both the labelling precursor and the standard compound as a racemate. The result of our synthetic pathway is a mixture of 4 stereoisomers, which form diastereomeric pairs of enantiomers. We have separated the diastereomers of the standard ^{12}C-compound. The separation of the enantiomers with the means of chiral HPLC has also been achieved. The new synthesis of the labelling precursor starts from commercially available 3,5-dibenzyloxy benzaldehyde, which is transferred to the first synthon, 2-(3,5-bis-benzyloxy-phenyl)-oxirane via reaction with trimethyl sulfonium iodide. For the second synthon, 4-(2-benzylamino-propyl)-phenol, we reacted 4-hydroxy phenylacetone with benzylamine in the presence of hydrogen at 5 bar in a Parr hydrogenator. Both synthons were then coupled to obtain the benzyl protected labelling precursor 4-(2-{benzyl-[2-(3,5-bis-benzyloxy-phenyl)-2-hydroxy-ethyl]-amino}-propyl)-phenol.
5-(2-{2-[4-(2-[^{11}C]Methoxy)-phenyl]-1-methylethyl-amino}-1-hydroxy-ethyl)-benzene-1,3-diol was obtained by reacting 10 mg of the labelling precursor with [^{11}C]-methyliodide. We optimized the reaction conditions as far as temperature, solvent, base, concentration of base and of precursor are concerned, the best parameters being 125°C in DMF with 0.9 equiv. sodiumhydroxide. The subsequent quantitative deprotection was carried out using hydrogen (1 bar) and Pd/C as catalyst. The overall radiochemical yield after purification is 30%. The standard [^{12}C]methyl-fenoterol was synthesised by reacting the first synthon (from the labelling precursor synthesis) with benzyl-{2-[4-(2-methoxy)-phenyl]-1-methyl-ethyl}-amine and subsequent deprotection with hydrogen and Pd/C as catalyst.

All compounds were analysed with common spectroscopic methods such as ^{1}H-NMR, ^{13}C-NMR, mass spectroscopy and elemental analysis.



References:
[1] Lulich K.M. et al. *Gen Pharmac* **19,3**: 307-311 (1988)
[2] Nijkamp F. et al. *Physiological Reviews* **72,2**: 323-367 (1992)
[3] Elsinga P. et al. *Nucl Med Biol* **23**: 159-167 (1996)
[4] MaloneyHuss K. et al. *J Med Biol* **225**: 859-871 (1992)