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Synthesis and Preliminary Evaluation of (*R,R*)(*S,S*) 5-(2-(2-[4-(2-[¹⁸F]fluoroethoxy)phenyl]-1-methylethylamino)-1-hydroxyethyl)-benzene-1,3-diol (¹⁸F]FEFE) for the In Vivo Visualisation and Quantification of the β 2-Adrenergic Receptor Status in Lung

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Abstract—The ¹⁸F-labeled β 2-adrenergic receptor ligand (*R,R*)(*S,S*) 5-(2-(2-[4-(2-[¹⁸F]fluoroethoxy)phenyl]-1-methylethylamino)-1-hydroxyethyl)-benzene-1,3-diol, a derivative of the original highly selective racemic fenoterol, was synthesized in an overall radiochemical yield of 20% after 65 min with a radiochemical purity higher than 98%. The specific activity was in the range of 50–60 GBq/ μ mol. In vitro testing of the non-radioactive fluorinated fenoterol derivative with isolated guinea pig trachea was conducted to obtain an IC₅₀ value of 60 nM. Preliminary ex vivo organ distribution and in vivo experiments with positron emission tomography (PET) on guinea pigs were performed to study the biodistribution as well as the displacement of the radiotracer to prove specific binding to the β 2-receptor.

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The obvious advance of positron emission tomography (PET) has led to the development of syntheses of biologically important tracer molecules labeled with the most common positron emitters carbon-11 and fluorine-18. The advantage of obtaining a high specific radioactivity of these radionuclides has opened up the possibility of visualising and quantifying the amount of specific biological receptors in vivo by utilizing labeled receptor ligands and PET. In particular, the investigation of the distribution and density of the dopaminergic receptors in the brain is an example of the potential of this technique in the determination of normal and diseased states in humans.¹

The knowledge on the interaction of radiolabeled neurotransmitter ligands with distinct subtypes of neuroreceptors in terms of chemistry, biochemistry, pharmacology, in vivo quantification and modeling can be transferred to peripheral ligand–receptor systems such as the human peripheral adrenoceptors of the heart, which have already been investigated.²

In humans, peripheral beta-adrenoceptors are widely distributed throughout the lung, with more than 70% of them being of the β 2-subtype. The β 2 receptors occur in bronchial epithelium, submucosal glands, immune cells and airway smooth muscle fibres.³

The β 2 receptor system is important for the neuronal and humoral regulation of the epithelial, glandular and muscular lung function. The β 2 agonists mediate a relaxation of the bronchial smooth muscle via the second

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messenger cAMP.⁴ The role of β_2 adrenoceptor density for obstructive respiratory diseases (such as asthma or chronic obstructive bronchitis) is still not clarified,⁵ although changes in beta-receptor function in the lung have been correlated to chronic obstructive lung disease and cystic fibrosis,⁵ and although beta-agonist drugs have been widely applied to treat asthma.

For understanding the pathogenesis, therapy and prognosis of such diseases, a non-invasive, quantifiable imaging of β_2 adrenoceptor density would be valuable. Consequently, a variety of radiolabeled ligands has been synthesized. However, only a few candidates have been introduced for direct quantification of the β_2 adrenoceptor density in lung in vivo via PET. Most of them were ¹¹C-labeled antagonists such as (*S*) [¹¹C]CGP 121777 (4-(3-*tert*-butylamino-2-hydroxy-propoxy)-1,3-dihydro-benzoimidazol-2-[¹¹C]one), which are not useful for the quantification of the high-affinity state of the β_2 adrenoceptor. Nevertheless, a similar compound, (*S*) [¹¹C]CGP 12388,⁸ was proposed to become the tracer of choice due to its facile synthesis and in vivo data.

Attempts to use ¹⁸F-labeled antagonists such as [¹⁸F]CGP12388 have so far resulted in a reduced affinity to the receptor.⁸ [¹⁸F]Carazolol was found to be of little subtype specificity.⁹ [¹⁸F]Fluoropropranolol has been evaluated and showed a rapid off-rate which could impair quantification.¹⁰

There have been attempts to characterize β_2 adrenoceptors with carbon-11 labeled agonists such as [¹¹C]formoterol¹¹ and [¹¹C]procaterol¹² but, to our knowledge, no fluorine-18 labeled agonists have been used so far.

Fenoterol represents a full β_2 receptor agonist, widely used as a short-acting escape medication in treatment of bronchoconstriction. In binding studies, fenoterol discriminates between β_1 and β_2 subtype with a ratio of >10 and binds with a rapid onset time directly to the receptor protein. In contrast, the more lipophilic compound salmeterol shows a slow dissociation and a binding to a specific exo-site domain of the β_2 receptor protein.

The aim of this study was to label a hydrophilic, highly selective subtype-specific agonist to image membrane-bound high-affinity state β_2 -receptors only.

Fenoterol is a highly subtype-specific high-affinity ligand with little lipophilicity.¹³ Thus, we intended to label fenoterol with fluorine-18, whose half-life of 109.6 min would allow longer measuring times with PET and improved scientific and clinical protocols compared to carbon-11 labeled analogues.

Chemistry

The non-radioactive standard compound (*R,R*)(*S,S*) 5-(2-(2-[4-(2-fluoroethoxy)phenyl]-1-methylethylamino)-1-hydroxy-ethyl)-benzene-1,3-diol [(*R,R*)(*S,S*)-6], required for in vitro evaluation and analytical purposes, was

synthesized in a convergent multistep synthesis starting from commercially available 4-hydroxyphenylacetone (**1**) which was reacted with 1-bromo-2-fluoroethane in acetone using K_2CO_3 as a base to yield **2**. Subsequent reductive amination with benzylamine under 5 bar hydrogen in an autoclave gave racemic benzyl-(2-[4-(2-fluoroethoxy)phenyl]-1-methylethyl)-amine (**3**) in an overall yield of 64%.¹⁴

2-(3,5-Bisbenzyloxyphenyl)oxirane (**5**) was synthesized starting from 3,5-bisbenzyloxybenzaldehyde (**4**), which was reacted with trimethylsulfonium iodide in DMF using sodium hydride as a base in a yield of 74%.¹⁵

Following analogous literature procedures, we attempted to couple **3** and **5** in DMSO at high reaction temperatures of 100–150 °C, but only small yields of the desired product (20%) could be obtained.¹⁶ A significant cleavage of the fluoroethyl-benzylether moiety was observed. To circumvent these difficulties, we applied ytterbium trifluoromethanesulfonate as a highly effective catalyst for the opening of the oxirane moiety at room temperature with amines.¹⁷ Using this method, the yield could be increased to 80%. Final cleavage of the benzyl protecting groups was achieved quantitatively with hydrogen on Pd/C-catalyst at 1 bar to give the two diastereomeric pairs (*R,R*)(*S,S*)-**6** and (*R,S*)(*S,R*)-**6** (Fig. 1).¹⁸

The two diastereomeric pairs (*R,R*)(*S,S*)-**6** and (*R,S*)(*S,R*)-**6** could be easily separated via column chromatography.¹⁹ To assign each separated compound its corresponding configuration, their ¹H NMR spectra were compared to the original (*R,R*)(*S,S*)-fenoterol[®] (Boehringer Ingelheim, Germany) and as a result (*R,R*)(*S,S*)-**6** could be clearly identified.²⁰ First labeling experiments starting from original (*R,R*)(*S,S*)-fenoterol[®] as a labeling precursor indicated that an additional by-product was formed in nearly the same radiochemical yields as the product which was assumed to be the ¹⁸F-fluoroethyl-resorcinol ether (*R,R*)(*S,S*)-[¹⁸F]**8** or the tertiary 2-fluoroethylamino compound (*R,R*)(*S,S*)-[¹⁸F]**14**. To identify the by-product, the two

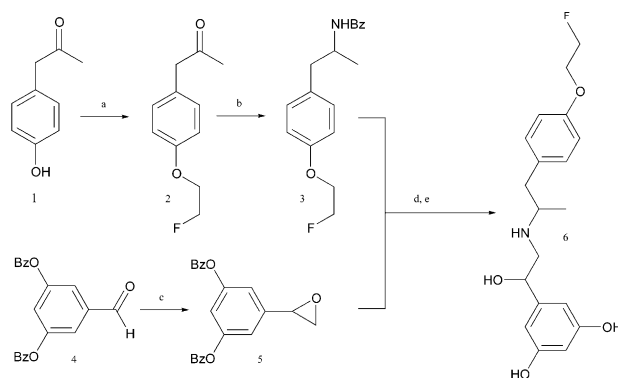


Figure 1. Synthesis of the non-radioactive standard compound (*R,R*)(*S,S*)-**6**; Reagents and conditions: (a) 1-bromo-2-fluoroethane (1.2 equiv), K_2CO_3 (2 equiv), acetone, reflux, 12 h (80%); (b) benzylamine (1.2 equiv), H_2 (5 bar), 5% Pt/C, ethanol, rt, 24 h (80%); (c) trimethylsulfonium iodide (1 equiv), NaH (1 equiv), DMF, rt, 1 h (74%); (d) ytterbium trifluoromethanesulfonate (0.1 equiv), dichloromethane, 1 h (78%); (e) 10% Pd/C, methanol, H_2 (1 bar), rt, 3 h (80%).

non-radioactive standard compounds (*R,R*)(*S,S*)-**8** and (*R,R*)(*S,S*)-**14** were synthesized according to Figure 2. In the case of (*R,R*)(*S,S*)-**8**, (*R,R*)(*S,S*)-fenoterol hydrobromide[®] was used for the synthesis. Unfortunately, the synthesis of (*R,R*)(*S,S*)-**6** could not be achieved via an analogous route because the obtained compound contained too many impurities for the in vitro evaluation which were not removable via column chromatography.

As in the case of (*R,R*)(*S,S*)-**6**, the diastereomeric pairs of **14** could be isolated via column chromatography²¹ and were identified by adding each of the isolated diastereomeric pairs to the crude labeling reaction mixture and comparing the UV-HPLC-chromatogram to the radioactive chromatogram. The HPLC analyses of both compounds (*R,R*)(*S,S*)-**8** and (*R,R*)(*S,S*)-**14** identified the by-product to be the tertiary 2-fluoroethyl amino compound (*R,R*)(*S,S*)-[¹⁸F]**14** and not the 2-fluoroethyl resorcinol ether (*R,R*)(*S,S*)-[¹⁸F]**8**.

The radioactive labeling was achieved using (*R,R*)(*S,S*)-fenoterol[®] (**15**) liberated from fenoterol hydrobromide[®]²² and the secondary labeling precursor 2-[¹⁸F]fluoroethyltosylate²³ (Fig. 3). The radiochemical yield of (*R,R*)(*S,S*)-[¹⁸F]**6** was 60% referring to the starting activity of 2-[¹⁸F]fluoroethyltosylate. The remaining 40% of detected radioactivity belonged to the 2-[¹⁸F]fluoroethylamino compound (*R,R*)(*S,S*)-[¹⁸F]**14**. The overall radiochemical yield was 20% referring to the end of bombardment (EOB). Incremental calculations suggested that the most acid H-atom is the HO-moiety of the resorcinol structure element.²⁴ After the

first deprotonating step using 1 N NaOH, the phenolic hydroxy-function should become more acidic than the remaining HO-moiety of the resorcinolate anion. However, extensive labeling experiments using varying equivalents of base (NaOH 1 N) for the deprotonation of the different aromatic HO-functions revealed that an amount of 0.9 equivalents of base led to the highest radiochemical yields of (*R,R*)(*S,S*)-[¹⁸F]**16**. This experimental outcome suggests that the phenolic hydroxy-function is more acidic than the resorcinol. Furthermore, after the use of more equivalents of base the formation of the 2-[¹⁸F]fluoroethyl-resorcinol ether (*R,R*)(*S,S*)-[¹⁸F]**8** also became a side-reaction.

The isolation of the radiotracer was achieved by high-performance liquid chromatography (HPLC).²⁵ The HPLC-chromatogram showed two peaks from which the first peak at 12 min could be related to (*R,R*)(*S,S*)-[¹⁸F]**6** whereas the second one at 16 min could be assigned to the tertiary 2-[¹⁸F]fluoroethylamino compound (*R,R*)(*S,S*)-[¹⁸F]**14** (Fig. 4).

After successful collection of the radiotracer, the liquid phase was diluted with water and passed through a solid phase column (C-18[®], Waters) which led to the fixation of the radiotracer. After drying with nitrogen the tracer was eluted from the solid phase with 1 mL of ethanol which was subsequently removed in vacuo. The radiotracer was dissolved in an appropriate amount of isotonic NaCl solution for further use.²⁶ Figure 5 shows the quality control chromatogram obtained by HPLC (radioactivity channel and UV-channel).

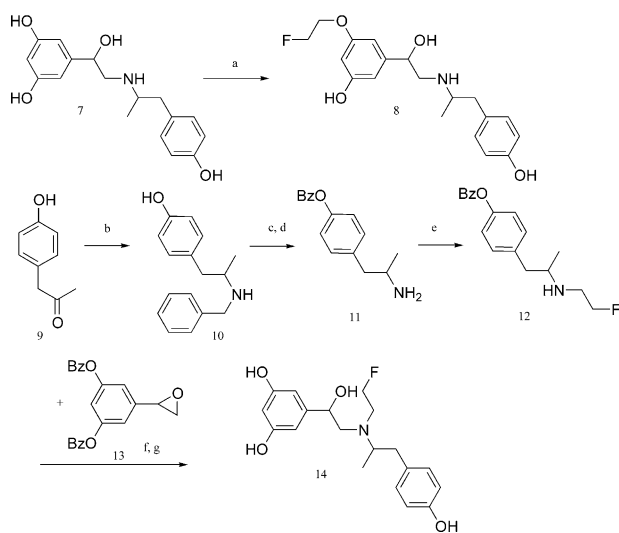


Figure 2. Synthesis of the non-radioactive by-products (*R,R*)(*S,S*)-**8** and (*R,S*)(*S,S*)-**14**; Reagents and conditions: (a) (*R,R*)(*S,S*)-fenoterol hydrobromide[®] (**15**) (Boehringer Ingelheim, Germany), potassium methanolate (2 equiv), methanol, 5 min, removal of methanol, DMF, 1-bromo-2-fluoroethane, 60 °C, 24 h (10%); (b) benzylamine, 5% Pt/C, H₂ (5 bar), ethanol, rt, 12 h (80%); (c) 10% Pd/C, H₂ (3 bar), ethanol, HCOOH (trace amount), rt, 6 h (60%); (d) benzylchloride (1 equiv), KOH (1 equiv), NaI (trace amount), ethanol/water, reflux, 48 h (60%); (e) 1-bromo-2-fluoroethane (1.2 equiv), K_i (trace amount), K₂CO₃ (2 equiv), acetone, reflux, 24 h (75%); (f) ytterbium trifluoromethanesulfonate (0.1 equiv), dichloromethane, rt, 2 h (25%); (g) 10% Pd/C, H₂ (1 bar), methanol, rt, 3 h (50%).

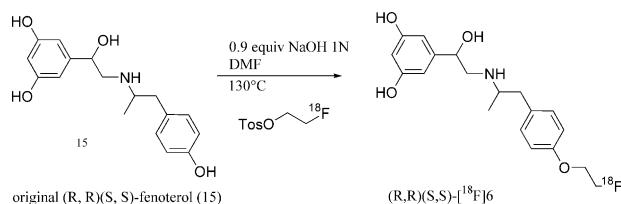


Figure 3. Radioactive labeling of (*R,R*)(*S,S*)-fenoterol[®] (**15**), Reagents and conditions: (a) NaOH 1 N (0.9 equiv), 2-[¹⁸F]fluoroethyltosylate, DMF, 130 °C, 8 min (60%).

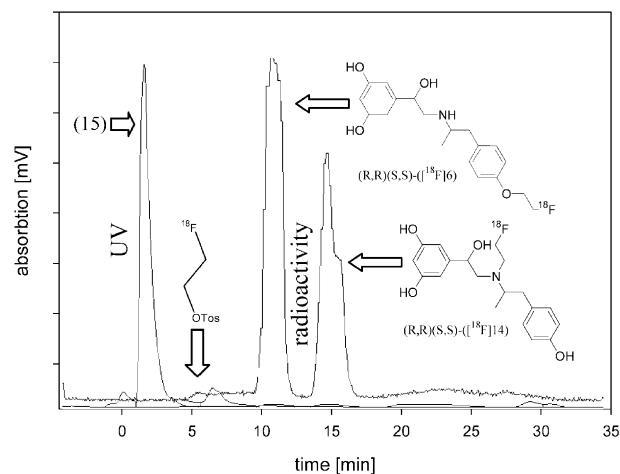


Figure 4. Radio- and UV-HPLC chromatogram of the crude reaction mixture (upper curve refers to the detected radioactivity; lower curve refers to the UV-absorption).

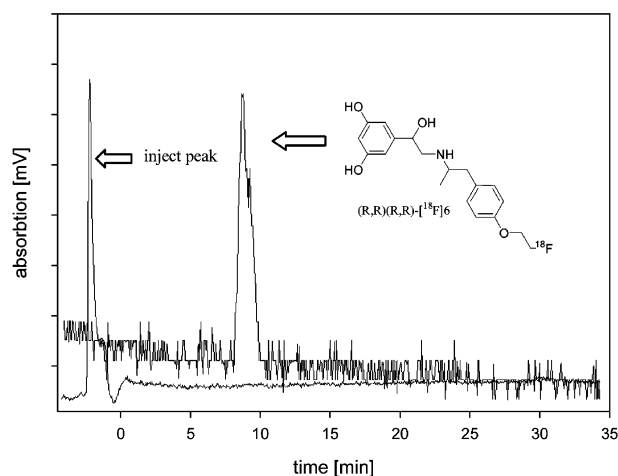


Figure 5. Radio- and UV-HPLC chromatogram of the isolated radiotracer $(R,R)(S,S)$ - $[^{18}\text{F}]6$ (upper curve refers to the detected radioactivity; lower curve refers to the UV-absorption).

Determination of the Partition Coefficient of $(R,R)(S,S)$ - $[^{18}\text{F}]6$

The lipid/water partition coefficient of compound $(R,R)(S,S)$ - $[^{18}\text{F}]6$ was measured by adding 5 μL of the radioactive compound in saline solution to a 2-mL vial containing 0.5 mL each of 1-octanol and pH 7.4 phosphate buffer. The vial was capped and vortexed vigorously for 10 min at room temperature. After reaching equilibrium, the organic phase was pipetted out and each phase was analyzed via radio-TLC on an Instant Imager (Packard Canberra). A partition coefficient of 0.5 ± 0.05 was calculated as $-\log$ [counts per min (cpm) in octanol/cpm in pH 7.4 phosphate buffer].

In Vitro Evaluation of the Non-radioactive Standard Compound $(R,R)(S,S)$ -6 Using Isolated Guinea Pig Trachea

Dunkin–Hartley guinea pigs of both genders were used. After execution, the trachea were removed and kept in a physiological saline solution through which a constant flow of carbogen, a mixture of 5% carbon dioxide in oxygen, was maintained at all times. The trachea was split in half and fixated in a special apparatus as described previously.²⁷ The pre-contraction of the trachea was achieved by treatment with oxotremorin, a muscarinic acetylcholine receptor ligand. Increasing concentrations of 1–1000 nM of either $(R,R)(S,S)$ -fenoterol[®] or the

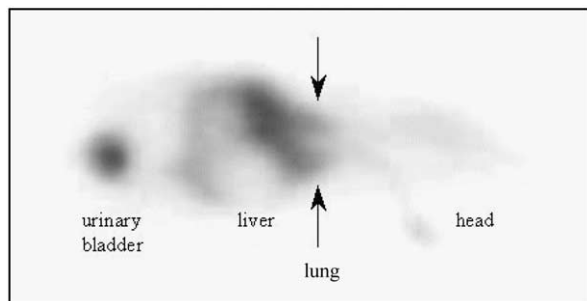


Figure 6. ^{18}F -FEFE PET of pulmonary β_2 -receptors of the lung (arrows) in guinea pigs (baseline study, 60 min p.i.).

fluoroethylated derivative $(R,R)(S,S)$ -6 were added and the relaxation measured analogously. The results showed that the IC_{50} value of $(R,R)(S,S)$ fenoterol and its fluoroethylated derivative 6 were both in the range of 60 nM. Thus the affinity of the ligand to the β_2 adrenoceptor did not change by the derivatisation within the accuracy of the measurement.

Ex Vivo Organ Distribution and In Vivo Evaluation of $(R,R)(S,S)$ - $[^{18}\text{F}]6$ on Guinea Pigs Using PET

The receptor binding of the compound and its organ distribution was assessed in Hartley guinea pigs (Charles River Wiga, Sulzfeld, Germany; body weight 400 g). All experimentation had previously been approved by the regional animal ethics committee and was conducted according to German federal law. Animals were anaesthetized with ketamine (10 mg/kg, Ketanest, Parke–Davis, Berlin, Germany) and xylazine (0.6 mg/kg, Rompun, Bayer, Leverkusen, Germany). A catheter was placed in the carotic artery and the jugular vein, respectively. Animals breathed spontaneously through a tracheal tube during the entire experiment. $(R,R)(S,S)$ - $[^{18}\text{F}]6$ was dissolved in isotonic saline and injected iv with an activity of 12–18 MBq. For the PET images the camera ECAT EXACT with axial resolution of 4.5 mm in the central field of view in 2D-mode was used. Dynamic PET studies over 60 min with $[^{18}\text{F}]FEFE$ were performed either as a baseline study (study group 1, $n=3$) or as a displacement study [study group 2, $n=3$; 2 mg/kg $(R,R)(S,S)$ -fenoterol 10 min post injection of $[^{18}\text{F}]FEFE$]. Partial volume correction was applied on iterative reconstructed images.²⁸ Figure 6 shows a coronal PET image (slice thickness: 6.7 mm) of the baseline study at 60 min pi. For the modeling of the β_2 -receptor binding potentials a region-of-interest (ROI) based reference tissue model was used.²⁹ Figure 7 shows a time–activity curve for one animal from study group 1. The unspecific activity correlates to a ROI in the neck area, where no β_2 adrenoceptors are located.

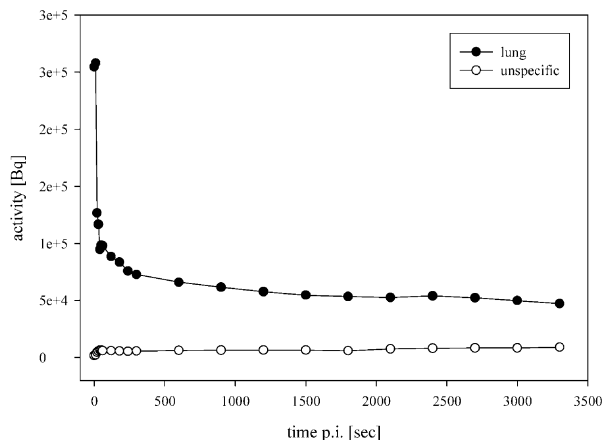


Figure 7. Time–activity curve for comparison of radioactivity uptake in lung versus neck area as a site of unspecific binding (one animal from study group 1).

At the end of the PET measurements, animals were sacrificed at 65 min pi and multiple organ samples were taken. The tissues were dissolved in KOH (4 N) at 75 °C for 30 min and the ^{18}F -organ activity was measured in a γ -counter. In the baseline study, group 1, ^{18}F organ uptake in % of injected activity/gram (%ID/g) of the lung, heart, liver, spleen, kidneys, brain, intestine and blood was 1.16 ± 0.05 , 0.49 ± 0.06 , 0.95 ± 0.1 , 0.84 ± 0.2 , 0.70 ± 0.1 , 0.02 ± 0.005 , 0.77 ± 0.08 and 0.22 ± 0.09 , respectively. [^{18}F]FEFE showed specific binding to pulmonary β_2 receptors (Fig. 6), which was displaceable by fenoterol by 50% of the baseline uptake (study group 2) as measured in vivo by means of PET. These results correlated well with the ex vivo measurements of the explanted lungs: $1.16 \pm 0.05\%$ ID/g baseline versus $0.42 \pm 0.07\%$ ID/g displacement.

Conclusion

The fluorine-18 labeled analogue of the β_2 subtype specific β -adrenoceptor ligand fenoterol was synthesized as racemic compound (*R,R*)(*S,S*) 5-(2-(2-[4-(2-[^{18}F]fluoroethoxy)phenyl]-1-methylethylamino)-1-hydroxyethyl)-benzene-1,3-diol ([^{18}F]FEFE) in an overall radiochemical yield of 20% after 65 min with a radiochemical purity higher than 98%. First in vitro, ex vivo and in vivo PET evaluation studies indicate that this compound binds specifically to the β_2 adrenoceptors of the lung of guinea pigs.

Thus, further evaluations with enantiomerically pure [^{18}F]FEFE are planned to elucidate its use in scientific and clinical studies using quantitative PET.

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- Column chromatography (Si-60): solvent = ethylacetate/methanol 9/1; [(*R,S*)(*S,R*)-6, $R_f = 0.15$]; [(*R,R*)(*S,S*)-6, $R_f = 0.1$]
- (*R,R*)(*S,S*) fenoterol[®]: ^1H NMR (400 MHz, DMSO- d_6) δ 9.0 (s, 3H), 6.9 (d, 2H), 6.7 (d, 2H), 6.2 (s, 2H), 6.0 (s, 1H), 5.0 (s, 1H), 4.4 (t, 1H), 3.4 (d, 2H), 2.7 (m, 1H), 2.6 (m, 2H), 2.2 (m, 1H), 0.8 (d, 3H); ^{13}C NMR (400 MHz, DMSO- d_6) δ 159.8, 156.3, 147.9, 130.1, 129.7, 116.5, 104.8, 102.3, 71.4, 56.1, 55.8, 48.5, 19.8; MS (FD): m/z (% rel. int.) 304.7 (100%, $[\text{M} + 1]^+$), additionally, elemental analysis (C, H, N), ^1H - ^{13}C 2D-NMR were performed for classification. Elemental analysis: calcd C 67.31, H 6.98, N 4.62; found C 67.28, H 7.00, N 4.61. (*R,R*)(*S,S*)-6: ^1H NMR (400 MHz, DMSO- d_6) δ 9.2 (s, 2H), 6.9 (d, 2H), 6.7 (d, 2H), 6.3 (s, 2H), 6.0 (s, 1H), 4.6 (t, 1H), 4.5 (t, 1H), 4.4 (t, 1H), 4.2 (t, 1H), 4.1 (t, 1H), 3.3 (m, 1H), 3.0 (m, 2H), 2.7 (m, 1H), 2.5 (d, 2H), 0.8 (d, 3H); ^{13}C NMR (400 MHz, DMSO- d_6) δ 159.5, 158.1, 131.7, 130.2, 129.8, 115.4, 104.9, 102.7, 81.6, 72.3, 67.8, 55.3, 55.1, 41.0, 20.4; ^{19}F NMR (400 MHz, DMSO- d_6) δ -224.2 (m, F); MS (FD): m/z (% rel. int.) 350.7 (100%, $[\text{M} + 1]^+$), additionally, elemental analysis (C, H, N), ^1H - ^{13}C and ^1H - ^{13}C 2D-NMR were performed for classification. Elemental analysis: calcd C 65.33, H 6.92, N 4.01; found C 65.31, H 6.96, N 4.11. (*R,S*)(*S,R*)-6: ^1H NMR (400 MHz, DMSO- d_6) δ 9.1 (s, 2H), 6.7 (d, 2H), 6.6 (d, 2H), 6.3 (s, 2H), 6.0 (s, 1H), 4.6 (t, 1H), 4.5 (t, 1H), 4.6 (t, 1H), 4.3 (t, 1H), 4.2 (t, 1H), 3.3 (m, 1H), 3.0 (m, 2H), 2.9 (m, 1H), 2.5 (d, 2H), 0.95 (d, 3H); ^{13}C NMR (400 MHz, DMSO- d_6) δ 159.4, 158.4, 131.4, 130.2, 129.4, 115.3, 104.5, 102.7, 81.6, 72.3, 67.6, 55.3, 55.1, 41.3, 20.2; ^{19}F NMR (400 MHz, DMSO- d_6) δ -224.2 (m, F); MS (FD): m/z (% rel. int.) 350.7 (100%, $[\text{M} + 1]^+$); Elemental analysis: calcd C 65.33, H 6.92, N 4.01; found C 65.28, H 6.98, N 4.07 (*chemical shifts which are underlined were used for assigning the diastereomers*).
- (*R,R*)(*S,S*)-8: ^1H NMR (400 MHz, DMSO- d_6) δ 9.2 (s, 1H), 9.1 (s, 1H), 6.9 (d, 2H), 6.7 (d, 2H), 6.3 (s, 2H), 4.6 (t, 1H), 4.5 (t, 1H), 4.4 (m, 1H), 4.2 (t, 1H), 4.1 (t, 1H), 3.0 (m, 2H), 2.7 (m, 1H), 2.5 (d, 2H), 0.85 (d, 3H); ^{13}C NMR (400 MHz, DMSO- d_6) δ 159.5, 158.1, 131.7, 130.2, 129.8, 115.4, 104.9, 102.7, 81.6, 72.3, 67.8, 55.3, 55.1, 41.0, 20.4; ^{19}F NMR (400 MHz, DMSO- d_6) δ -224.2 (m, F); MS (FD): m/z (% rel. int.) 350.5 (100%, $[\text{M} + 1]^+$); (*R,R*)(*S,S*)-14: ^1H NMR (400 MHz, DMSO- d_6) δ 9.0 (s, 3H), 6.9 (d, 2H), 6.7 (d, 2H), 6.2 (s, 2H), 6.0 (s, 1H), 5.0 (s, 1H), 4.3 (m, 2H), 4.3 (t, 1H), 2.8 (m, 2H), 2.7 (m, 1H), 2.6 (m, 2H), 2.5 (dd, 1H), 2.4 (dd, 1H), 0.8 (d, 3H); ^{13}C NMR (400 MHz, DMSO- d_6) δ 159.8, 156.3, 147.9, 130.1, 129.7, 116.5, 104.8, 102.3, 84.2, 71.4, 56.1, 55.8, 52.6, 48.5, 19.8; ^{19}F NMR (400 MHz, DMSO- d_6) δ

–198.2 (m, F); MS (FD): m/z (% rel. int.) 350.2 (100%, $[M + 1]^+$)

22. 5 g (3.5 mmol) Fenoterol hydrobromide[®] was dissolved in methanol (5 mL), NaOH (1.75 mL, 2N) was added and the mixture was stirred for 5 min. The solution was extracted with ether (3×25 mL) and the organic phase was dried over Na₂SO₄. After removing the solvent in vacuum the product could be obtained as a white powder (0.97 g, 90%).

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mm), flow: 1 mL/min, solvent: methanol/water (30/70 + 1% sodium dihydrogen phosphate-buffer), R_f (*R,R*)(*S,S*)-[¹⁸F]6 = 12 min.

26. In a typical experiment, 500 MBq of (*R,R*)(*S,S*)-[¹⁸F]6 could be obtained from 2.2–2.5 GBq [¹⁸F]fluoride starting activity.

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