Synthesis and Evaluation of (*S*)-4-(3-(2′-[^{11}C]Isopropylamino)-2-hydroxypropoxy)-2*H*-benzimidazol-2-one ((*S*)-[^{11}C]CGP 12388) and (*S*)-4-(3-((1′-[^{18}F]-Fluoroisopropyl)amino)-2-hydroxypropoxy)-2*H*-benzimidazol-2-one ((*S*)-[^{18}F]Fluoro-CGP 12388) for Visualization of β-Adrenoceptors with Positron Emission Tomography†

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The β-adrenoceptor antagonist (*S*)-[^{11}C]CGP 12177 (4-(3-(*tert*-butylamino)-2-hydroxypropoxy)-2*H*-benzimidazol-2[^{11}C]-one) is a generally accepted radioligand for cardiac and pulmonary PET studies. The synthesis of [^{11}C]CGP 12177 is a laborious and often troublesome procedure. Therefore, (*S*)-CGP 12388 (4-(3-(isopropylamino)-2-hydroxypropoxy)-2*H*-benzimidazol-2-one), **5**, the isopropyl analogue of CGP 12177, has been labeled with carbon-11 in the isopropyl group via a reductive alkylation by [^{11}C]acetone (**3**) of the corresponding (*S*)-desisopropyl compound **2**. The fluoro-substituted analogue of (*S*)-CGP 12388 was prepared by reacting **2** with [^{18}F]fluoroacetone (**4**). (*S*)-[^{11}C]CGP 12388 (**5**) was easily prepared via a one-pot procedure. The radiochemical yield of (*S*)-[^{11}C]CGP 12388 (600−800 Ci/mmol, EOS) was 18% (EOB) with a total synthesis time of 35 min, whereas (*S*)-[^{18}F]fluoro-CGP 12388 (**6**) (>2000 Ci/mmol, EOS) was synthesized in 105 min with a radiochemical yield of 12% (EOB). Biodistribution studies in rats demonstrated specific binding to β-adrenoceptors of (*S*)-[^{18}F]fluoro-CGP 12388 and (*S*)-[^{11}C]CGP 12388 in lung and heart. The lungs were clearly visualized with PET studies of rats. Total/nonspecific binding at 60 min postinjection was 5.6 for (*S*)-[^{11}C]CGP 12388 and 2.0 for the (*S*)-^{18}F compound. Due to its facile synthetic procedure and *in vivo* data, (*S*)-[^{11}C]CGP 12388 is a promising β-adrenoceptor ligand for clinical PET.

Introduction

With suitable radiopharmaceuticals, positron emission tomography (PET) offers the opportunity to probe β-adrenoceptors noninvasively. β-Adrenoceptor density (B_{max}) is altered under various pathophysiological conditions, like hypertension,[1] heart failure, ischemia,[2] airway infections, allergy and asthma,[3] schizophrenia,[4] and depression.[5] A suitable procedure for visualization and quantitation of cardiac, pulmonary, and cerebral β-receptors by PET would therefore be of great clinical interest.

Three suitable PET ligands are available for the investigation of β-adrenoceptors: i.e., (*S*)-[^{11}C]CGP 12177,[6−8] (*S*)-1′-[^{18}F]fluorocarazolol,[9−12] and (*S*)-[^{11}C]carazolol.[10,13] [^{11}C]CGP 12177, labeled with ^{11}C in the carbonyl group, is produced from [^{11}C]phosgene, a laborious and often troublesome procedure, which might be an important drawback to apply this tracer for clinical PET studies. [^{11}C]CGP 12177 is hydrophilic and therefore only binds to receptors on the cell surface and not to intracellular binding sites. Moreover, it is not possible to measure cerebral β-adrenoceptors, because (*S*)-[^{11}C]CGP 12177 has only a very limited ability to cross the blood−brain barrier. (*S*)-1′-[^{18}F]Fluorocarazolol and [^{11}C]carazolol are relatively lipophilic. The carazolol analogues not only bind to cell surface receptors but also to internalized receptors.[12] (*S*)-1′-[^{18}F]Fluorocarazolol passes the blood−brain barrier, which makes it possible to investigate cerebral β-adrenoceptors.[14] So far, only (*S*)-[^{11}C]CGP 12177 has been used to determine cardiac β-adrenoceptor density in animals[15] and humans[16,17] and pulmonary β-adrenoceptor density in humans.[18] Using a two-injection protocol (high and low specific activity), B_{max} can be calculated from a mathematical model.[19]

Because of the problems involved in routine production of [^{11}C]CGP 12177, it is worthwhile to develop another hydrophilic β-adrenoceptor PET ligand for clinical use. CGP 12388 (4-(3-(isopropylamino)-2-hydroxypropoxy)-2*H*-benzimidazol-2-one, **5**) was selected as a suitable candidate. CGP 12388 is the isopropyl analogue of the *tert*-butyl compound CGP 12177. *In vitro* experiments have indicated that racemic CGP 12388 is an almost equally potent antagonist as racemic CGP 12177 (isoprenaline antagonism, isolated guinea pig heart, chronotropy: ED_{50}(CGP 12388) = 0.0025 μg/mL, ED_{50}(CGP 12177) = 0.0017 μg/mL; unpublished results of Ciba-Geigy). CGP 12388 can be labeled using 2-[^{11}C]acetone (Scheme 1). This synthetic procedure is less troublesome and therefore more suitable for clinical use than the preparation of [^{11}C]CGP 12177 from [^{11}C]phosgene. Compared to carbon-11 (half-life is 20 min), the radioisotope fluorine-18 has advantages of higher specific activity and a longer half-life (110 min), which enables prolonged PET studies. A general labeling method using [^{18}F]fluoroacetone[9,11,20] to introduce

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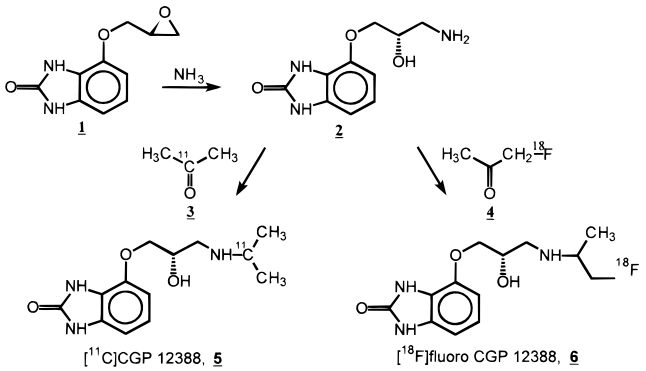
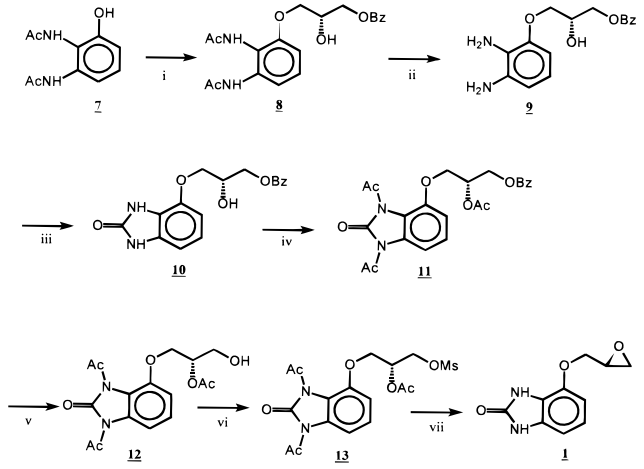
Scheme 1. Synthesis of (*S*)-[^{11}C]CGP 12388 (**5**) and (*S*)-[^{18}F]Fluoro-CGP 12388 (**6**)



Scheme 2. Synthesis of (*S*)-4-(2,3-Epoxypropoxy)-2*H*-benzimidazol-2-one (**1**)[a]



[a] Reagents: (i) epoxy benzyl ether, pyridine; (ii) KOH; (iii) phosgene; (iv) Ac_2O; (v) H_2/Pd; (vi) mesyl chloride, collidine; (vii) $NaOCH_3$, methanol.

^{18}F in the isopropyl group was applied to CGP 12388 (Scheme 1). Here we describe the radiolabeling and biodistribution studies in rats to evaluate the potential of [^{11}C]CGP 12388 and [^{18}F]fluoro-CGP 12388 as PET tracers.

Chemistry

The synthesis of the (*S*)-4-(2,3-epoxypropoxy)-2*H*-benzimidazol-2-one, **1**, is depicted in Scheme 2. It was not possible to synthesize CGP 12388 (**5**) using the conventional preparation methods of β-adrenergic antagonists. Usually, the epoxide precursors of those antagonists are prepared by reacting a phenolic intermediate with a reactive ester of glycidol in the presence of a base. We could not use this method because the nitrogen atoms of 1,3-dihydro-2*H*-benzimidazol-2-one react readily with electrophilic agents. Therefore, the synthesis of epoxide precursor was effected by using a protecting group strategy as outlined in Scheme 2. In the final reaction step, the epoxide is formed simultaneously with the removal of the protective groups. An analogous procedure has been applied earlier in the synthesis of (*S*)-prenalterol.[21]

The precursor for labeling reactions, (*S*)-4-(3-amino-2-hydroxypropoxy)-2*H*-benzimidazol-2-one, **2**, was prepared from the epoxide by ring opening with ammonia. The enantiomeric excess of (*S*)-desisopropyl compound **2** is assumed to be similar to that of the epoxide, since it is known that no racemization takes place upon nucleophilic attack by an amine.[8]

Table 1. Octanol/Water Partition Coefficients (log *P*)[a]

	[^{11}C]CGP 12388	[^{18}F]CGP 12388	[^{11}C]CGP 12177	[^{18}F]FCR
measured	−0.64	0.44	−0.50[30]	2.20[9]
calculated	0.20	0.10	0.68	2.98

[a] Calculated values by Pallas 1.2 (CompuDrug Chemistry Ltd.). $n = 5$ as measured by the procedure described in the Experimental Section. [^{18}F]FCR is (*S*)-1′-[^{18}F]fluorocarazolol.

(*S*)-[^{18}F]Fluoro-CGP 12388 (**6**) was prepared according to a procedure as described for (*S*)-[^{18}F]fluorocarazolol (Scheme 1). The radiochemical yield was 12% (corrected for decay) with a synthesis time of 105 min. Practical yields were 30−40 mCi. The majority of the radioactivity (60−80%) was lost in the [^{18}F]fluoroacetone (**4**) synthesis. The radiochemical yield of the reductive alkylation reaction was 50−70%. The specific activity was always >2000 Ci/mmol (EOS). It should be noted that two diastereomers of (*S*)-[^{18}F]fluoro-CGP 12388 are formed, because of the newly created stereogenic center in the fluoroisopropyl group. No efforts have been undertaken to separate the diastereomers, since previous studies with (*S*,*S*)- and (*S*,*R*)-1′-[^{18}F]fluorocarazolol demonstrated that the configuration at the stereogenic center in the fluoroisopropyl group is of minor influence on binding to the β-adrenoceptor.[11] Due to its hydrophilic character it was not possible to obtain "cold" reference material in pure form. No separation between **6** and salts derived from $NaCNBH_3$ could be achieved. Several attempts which included dichloromethane/water extractions, flash chromatography on silica gel, and selective precipitation of the salt in either dichloromethane, 2-propanol, diethyl ether, THF, acetone, methanol, or ethanol were not successful. For this reason, no proper elemental analysis of **6** could be obtained, and therefore two independent HPLC systems have been used for characterization (Experimental Section). From the elemental analysis data, an inorganic impurity of about 50% was calculated.

(*S*)-[^{11}C]CGP 12388 (**5**) was prepared by reaction of 2-[^{11}C]acetone (**3**) with (*S*)-desisopropyl CGP 12388, **2** (Scheme 1). In the literature[13,22,23] several preparations of β-blocking agents with ^{11}C in the isopropyl group by reaction with [^{11}C]acetone have been reported. In all cases, [^{11}C]acetone, prepared by trapping of $^{11}CO_2$ in a solution of MeLi in diethyl ether, was distilled into the precursor solution. By this distillation, the radiolabeled byproducts 1-[^{11}C]acetate and [^{11}C]-*tert*-butyl alcohol were removed. We developed a one-pot procedure without a distillation step and chose to remove radiolabeled byproducts by HPLC (10−25% of total radioactivity). The radiochemical yield of [^{11}C]CGP 12388 was 18% (corrected for decay) with a synthesis time of 35 min. The specific activity was 600−800 Ci/mmol (EOS).

Biological Results

Octanol/Water Partition Coefficient. The lipophilicity of [^{11}C]CGP 12388 and [^{18}F]fluoro-CGP 12388, **5** and **6**, was determined at pH = 7.4 and calculated with Pallas 1.2 (CompuDrug Chemistry Ltd.). The results are shown in Table 1. For comparison, the log *P* values for [^{11}C]CGP 12177 and [^{18}F]fluorocarazolol are included. Fluorine substitution increases the partition coefficient *P*. Therefore it is interesting to know whether

Table 2. Biodistribution of [18F]Fluoro-CGP 12388 in Male Wistar Rats[a]

tissue	controls (saline only) ($n = 4$)	propranolol-pretreated ($n = 4$)	P
	10 min Postinjection		
bone	0.51 ± 0.07	0.39 ± 0.03	<0.05
cerebellum	0.18 ± 0.06	0.17 ± 0.05	NS
cortex	0.16 ± 0.03	0.13 ± 0.01	NS
fat	0.16 ± 0.04	0.53 ± 0.53	NS
heart	1.98 ± 0.57	1.09 ± 0.25	<0.05
intestine	2.42 ± 0.41	1.52 ± 0.65	NS
kidney	3.71 ± 1.82	7.93 ± 2.73	<0.05
liver	1.41 ± 0.24	1.62 ± 0.16	NS
lung	4.29 ± 0.45	1.37 ± 0.41	<0.05
muscle	0.54 ± 0.10	0.42 ± 0.11	NS
plasma	0.45 ± 0.06	0.51 ± 0.06	NS
red blood cells	0.78 ± 0.07	0.57 ± 0.08	<0.05
spleen	2.19 ± 0.08	1.17 ± 0.27	<0.05
trachea	0.82 ± 0.15	0.70 ± 0.12	NS
	60 min Postinjection		
bone	0.42 ± 0.05	0.41 ± 0.05	NS
cerebellum	0.14 ± 0.04	0.12 ± 0.04	NS
cortex	0.13 ± 0.02	0.12 ± 0.04	NS
fat	0.14 ± 0.04	0.07 ± 0.02	<0.05
heart	1.09 ± 0.30	0.46 ± 0.19	<0.05
intestine	0.79 ± 0.36	0.87 ± 0.55	NS
kidney	0.91 ± 0.46	0.91 ± 0.60	NS
liver	0.52 ± 0.12	0.64 ± 0.15	NS
lung	3.66 ± 0.54	0.59 ± 0.14	<0.05
muscle	0.48 ± 0.07	0.30 ± 0.05	<0.05
plasma	0.25 ± 0.02	0.35 ± 0.13	NS
red blood cells	0.42 ± 0.07	0.39 ± 0.18	NS
spleen	1.26 ± 0.15	0.41 ± 0.07	<0.05
trachea	0.63 ± 0.10	0.37 ± 0.08	<0.05

[a] Data expressed as body-weight-standardized uptake values (DAR); mean ± SD of n experiments. Differences between groups were examined with the nonparametric Q-test of Wilcoxon.

[18F]fluoro-CGP 12388 passes the blood−brain barrier and may be a suitable ligand to study cerebral β-adrenoceptors.

Biodistribution Studies. The tissue distribution of [18F]fluoro-CGP 12388 and [11C]CGP 12388 *in vivo* in male Wistar rats is presented in Tables 2 and 3. The animals were sacrificed at 10 and 60 min postinjection. Blocking experiments were performed by iv injection of 500 μg of propranolol prior to injection of the radioligand. Uptakes are expressed as body-weight-standardized uptake values or differential absorption ratios (DAR), i.e., (counts in tissue/tissue weight) × (total body weight/total injected counts). Significant differences between control and propranolol-blocked rats were observed in lung, heart, and spleen. At 60 min postinjection total/nonspecific binding for [11C]CGP 12388 was 2.7 for heart and 9.5 for lung tissue. For [18F]fluoro-CGP 12388 these ratios were 2.4 and 6.2, respectively. Minor uptake was observed in brain for either the 18F or the 11C compound. No defluorination was observed, since uptake of 18F in bone was low.

PET Studies. The suitability of [18F]fluoro-CGP 12388 and [11C]CGP 12388 for visualization of β-adrenergic receptors was investigated by PET studies in male Wistar rats. With both tracers the lungs were clearly visualized and pulmonary uptake was blocked by pretreatment with propranolol. PET images looked similar as those obtained after injection of (*S*)-1′-[18F]fluorocarazolol.[11] Time−activity curves for lung are shown in Figures 1 and 2. After a rapid distribution phase, [11C]CGP 12388 was slowly washed out ($t_{1/2}$ about 130 min). The fluorinated analogue has a 2−3-fold faster washout, consistent with the loss of affinity resulting from fluorine substitution in the isopropyl group. The ratio total/nonspecific binding at 60 min postinjection was 5.6 for [11C]CGP 12388, whereas this ratio was 2.0 for the 18F-fluorinated analogue.

Table 3. Biodistribution of [11C]CGP 12388 in Male Wistar Rats[a]

tissue	controls (saline only) ($n = 4$, 10 min; $n = 6$, 60 min)	propranolol pretreated ($n = 4$)	P
	10 min Postinjection		
bone	0.29 ± 0.07	0.20 ± 0.08	NS
cerebellum	0.09 ± 0.04	0.09 ± 0.05	NS
cortex	0.10 ± 0.06	0.07 ± 0.05	NS
fat	0.32 ± 0.16	0.16 ± 0.06	NS
heart	2.52 ± 0.38	0.72 ± 0.18	<0.05
intestine	0.92 ± 0.07	0.55 ± 0.14	<0.05
kidney	4.73 ± 3.27	2.44 ± 0.42	NS
liver	1.83 ± 0.39	1.65 ± 0.65	NS
lung	8.65 ± 1.00	1.26 ± 0.56	<0.05
muscle	0.48 ± 0.07	0.23 ± 0.06	<0.05
plasma	0.42 ± 0.12	0.50 ± 0.18	NS
red blood cells	1.24 ± 0.47	0.70 ± 0.31	NS
spleen	3.28 ± 0.71	0.78 ± 0.18	<0.05
trachea	1.10 ± 0.13	0.70 ± 0.11	<0.05
	60 min Postinjection		
bone	0.32 ± 0.06	0.23 ± 0.06	<0.05
cerebellum	0.07 ± 0.06	0.26 ± 0.15	NS
cortex	0.07 ± 0.04	0.25 ± 0.09	<0.05
fat	0.28 ± 0.14	0.26 ± 0.06	NS
heart	2.71 ± 0.20	0.76 ± 0.23	<0.05
intestine	0.79 ± 0.36	1.14 ± 0.38	NS
kidney	1.28 ± 0.36	0.94 ± 0.45	NS
liver	0.80 ± 0.12	0.68 ± 0.09	NS
lung	10.3 ± 1.06	0.88 ± 0.16	<0.05
muscle	0.44 ± 0.12	0.36 ± 0.06	NS
plasma	0.11 ± 0.03	0.40 ± 0.26	<0.05
red blood cells	0.89 ± 0.38	0.49 ± 0.16	<0.05
spleen	3.11 ± 0.48	0.49 ± 0.05	<0.05
trachea	1.25 ± 0.28	0.86 ± 0.19	<0.05

[a] Data expressed as body-weight-standardized uptake values (DAR); mean ± SD of n experiments. Differences between groups were examined with the nonparametric Q-test of Wilcoxon.

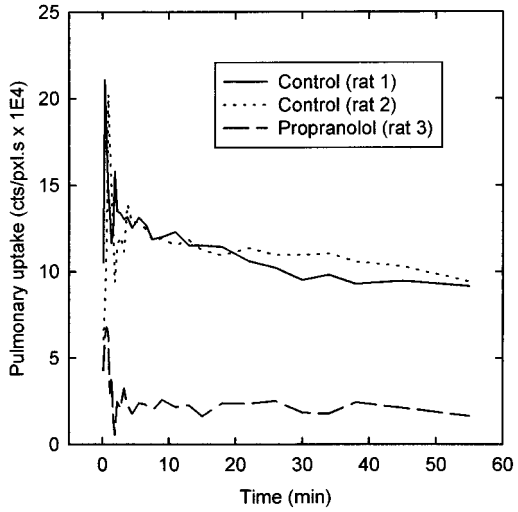


Figure 1. Time−activity curves of (*S*)-[11C]CGP 12388 in the right lung of a Wistar rat. Pulmonary uptake is expressed as (counts/pixel·s) × 10^4.

Discussion

(*S*)-[11C]CGP 12177 and (*S*)-[18F]fluorocarazolol are available to investigate β-adrenergic receptors *in vivo*. The advantages of [11C]CGP 12177 are its high meta-

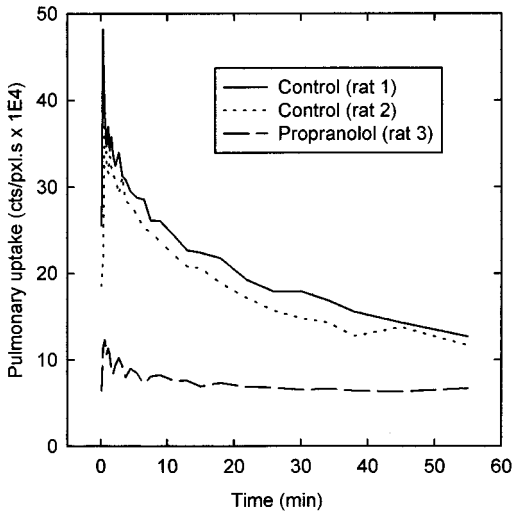


Figure 2. Time−activity curves of (*S*)-[^{18}F]fluoro-CGP 12388 in the right lung of a Wistar rat. Pulmonary uptake is expressed as (counts/pixel·s) × 10^4.

bolic stability, its hydrophilic character (log *P* −0.50), which enables mapping of only functional receptors at the cell surface, and the availability of a mathemathical model to quantify B_{max}. [^{18}F]Fluorocarazolol, on the other hand, allows the imaging of cerebral β-adrenoceptors due to its high log *P* of 2.2.[9] For investigating myocardial or pulmonary β-adrenoceptors, [^{11}C]CGP 12177 is preferred because of its lower nonspecific binding and selectivity for cell surface receptors. Because the preparation of the latter ligand is relatively complicated, we developed the radiosynthesis of its isopropyl analogue, i.e., (*S*)-CGP 12388. If (*S*)-[^{11}C]CGP 12388 (**5**) could be prepared from [^{11}C]acetone (**3**) by a one-pot procedure, (*S*)-[^{11}C]CGP 12388 might become the tracer of choice for clinical PET. The fluorinated analogue could be applied when prolonged PET studies are needed, and the tracer might be distributed to PET facilities without cyclotron. From previous studies it is known that fluorine substitution in the isopropyl group results in a 4−5-fold loss in affinity for β-adrenoceptors.[11,20]

Both [^{11}C]CGP 12388 and [^{18}F]fluoro-CGP 12388 (**5** and **6**, respectively) were conveniently synthesized from the desisopropyl compound **2** and the corresponding radiolabeled acetone derivative. Sufficient amounts of the tracer were obtained for patient studies. Especially, [^{11}C]CGP 12388 is very easily prepared via a one-pot procedure and is therefore suitable for clinical application. In literature [^{11}C]acetone is usually distilled into the precursor solution to remove the byproducts ^{11}C-labeled acetate and *tert*-butyl alcohol. However using reversed phase HPLC these radioactive byproducts are eluted much earlier than [^{11}C]CGP 12388.

As expected, the octanol/water partition coefficient for [^{11}C]CGP 12388 is similar to that of [^{11}C]CGP 12177 (Table 1). Both compounds show only minor penetration of the blood−brain barrier. Interestingly, [^{18}F]fluoro-CGP 12388 is more lipophilic and has a higher log *P* than pindolol (−0.33),[24] which is known to cross the blood−brain barrier.

Specific binding of [^{11}C]CGP 12388 and [^{18}F]fluoro-CGP 12388 to β-adrenoceptors was demonstrated in rats. [^{11}C]CGP 12388 is superior to the ^{18}F analogue as the uptake values in lung, heart, and spleen are higher. Nonspecific binding is similar for both compounds. The different biodistributions can be explained from the fluorine substitution in the isopropyl group. In previous studies with fluorinated metoprolol[20] and carazolol,[11] it was shown that substitution in the isopropyl group resulted in a 4−5-fold loss in affinity for β-adrenoceptors. The K_D for [^{18}F]fluoro-CGP 12388 is expected to exceed 1 nM, which is considered to be the maximal K_D for a suitable PET ligand for the visualization of β-adrenoceptors.[25] Uptake of [^{18}F]fluoro-CGP 12388 in the brain was very low. Factors other than log *P* probably determine cerebral uptake.

A comparison between the biodistribution data of the CGP 12388 analogues, [^{3}H]CGP 12177, and [^{18}F]fluorocarazolol is shown in Table 4. The administered mass of [^{3}H]CGP 12177 is similar to that of the PET-labeled compounds. At 10 min postinjection data of the CGP 12388 analogues are compared with [^{3}H]CGP 12177 only. Total/nonspecific binding of [^{11}C]CGP 12388 in lung (6.9) and heart (3.5) is comparable with that of [^{3}H]CGP 12177 (lung, 7.2; heart, 4.9). The ratios for the ^{18}F analogue are 2-fold lower. Comparison of data at 60 min postinjection with [^{18}F]fluorocarazolol results in higher total/nonspecific binding ratios for lung (13.8) and heart (4.3) as compared to [^{11}C]CGP 12388 (lung, 9.5; heart, 2.7). The higher ratios for [^{18}F]fluorocarazolol may be explained by its higher affinity and lipophilicity.

In PET studies of rats the lungs were clearly visualized with both radiolabeled CGP 12388 analogues, while the heart was not visible. Similar images have been obtained with (*S*)-[^{18}F]fluorocarazolol.[11] After treatment with propranolol the lungs were no longer visible. Time−activity curves in lung tissue are shown in Figures 1 and 2. The pulmonary uptake values are expressed as counts/pixel·s. In order to inject a constant mass, the administered dose of (*S*)-[^{18}F]fluoro-CGP 12388 (2 MBq) was twice the amount of (*S*)-[^{11}C]CGP 12388 (1 MBq). Therefore the pulmonary uptake values in Figures 1 and 2 cannot be compared directly.

The fluorinated analogue has a 2−3-fold faster washout than [^{11}C]CGP 12388, consistent with the loss of affinity resulting from fluorine substitution in the isopropyl group. The ratio total/nonspecific binding at 60 min postinjection for [^{11}C]CGP 12388 was 5.6, whereas this ratio was 2.0 for the ^{18}F-fluorinated analogue. For comparison, experiments with [^{11}C]CGP 12177 showed a similar ratio of total/nonspecific binding,[26] while after injection of [^{18}F]fluorocarazolol a ratio of 3.6 was observed.[11]

In conclusion, (*S*)-[^{11}C]CGP 12388 shows superior biodistribution data than its ^{18}F analogue. Due to its easy preparation and comparable *in vivo* behavior with established PET ligands such as (*S*)-[^{11}C]CGP 12177 and (*S*)-[^{18}F]fluorocarazolol, (*S*)-[^{11}C]CGP 12388 seems a very promising tracer for quantification and visualization of β-adrenoceptors in clinical PET.

Experimental Section

Materials. Unless noted otherwise, chemicals and solvents were obtained from commercial sources and were of analytical grade. Melting points were taken in open capillary tubes on a Tottoli apparatus (Buchi) and are uncorrected. Optical rotations: Perkin-Elmer-241 MC (589 nm) polarimeter. (±)-Propranolol was purchased from Sigma, St. Louis, MO. NMR spectra were performed on a Varian Gemini 200, 250, or 300

Table 4. Comparison between CGP 12388 Analogues, [3H]CGP 12177, and [18F]Fluorocarazolol[a]

		[11C]CGP 12388	[18F]CGP 12388	[3H]CGP 12177[31]	[18F]FCR[11]
			10 min Postinjection		
heart:	con	2.52 ± 0.38	1.98 ± 0.57	4.57 ± 1.43	nd
	prop	0.72 ± 0.18	1.09 ± 0.25	0.94 ± 0.16	
lung:	con	8.65 ± 1.00	4.29 ± 0.45	16.5 ± 2.7	nd
	prop	1.26 ± 0.56	1.37 ± 0.41	2.3 ± 0.3	
			60 min Postinjection		
heart:	con	2.03 ± 0.83	1.09 ± 0.30	nd	2.68 ± 0.16
	prop	0.76 ± 0.23	0.46 ± 0.19		0.62 ± 0.11
lung:	con	8.38 ± 2.62	3.66 ± 0.54	nd	15.9 ± 2.74
	prop	0.88 ± 0.16	0.59 ± 0.14		1.15 ± 0.30

[a] Uptake values expressed as DAR; $n = 4$ in each group, mean ± SD. con = control group, prop = propranolol-blocked group, nd = not determined. [18F]FCR is (*S*)-1′-[18F]fluorocarazolol. Administered mass of [3H]CGP 12177 was similar as those of the other ligands.[31]

MHz spectrometer. Chemical shifts are given in ppm relative to internal TMS signal; coupling constants *J* are in Hz. All temperatures are in °C. Alltima C-18 5U (250 × 10 mm) HPLC column was purchased from Alltech (Breda, The Netherlands). Ultron OVM HPLC column (150 × 4.6 mm) was from Astec (Whippany, NJ). Abbreviations: rt = room temperature, Ar = aryl, Bn = benzyl.

(*S*)-1-(2,3-Bis(acetylamino)phenoxy)-3′-(benzyloxy)propan-2′-ol, 8. A mixture of 2,3-bis(acetylamino)phenol, **7** (19.4 g, 93 mmol),[27] (*S*)-benzyl 2,3-epoxybenzyl ether (18.0 g, 110 mmol),[28] acetonitrile (55 mL), water (18 mL), and pyridine (0.7 mL) was refluxed for 24 h. Upon cooling and dilution with water (400 mL), crystals separated and were filtered off. After drying under vacuum, the product **8** was obtained (25.3 g, 73%): mp 156−157 °C; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.14 (s, 3H, CH_3CO), 2.15 (s, 3H, CH_3CO), 3.32 (s, 1H, OH), 3.60 (m, 2H, CH_2O), 3.95−4.20 (m, 3H, $ArOCH_2$, CH-O), 4.58 (s, 2H, CH_2Ar), aromatic protons 6.65 (d, 1H, $J = 8$), 7.13 (t, 1H, $J = 8$), 7.24−7.40 (m, 6H), 8.13 (s, 1H, NH), 8.80 (s, 1H, NH); $[\alpha]_D$ +13.6 ± 7.6° ($CHCl_3$). Anal. ($C_{20}H_{24}N_2O_5$) Calcd: C, 64.50; H, 6.50; N, 7.52. Found: C, 64.35; H, 6.58; N, 7.52.

(*S*)-1-(2,3-Diaminophenoxy)-3′-(benzyloxy)propan-2′-ol, 9. The diacetyl compound **8** (43.6 g, 117 mmol) was treated with a solution of KOH (67.5 g, 1.20 mol) in ethanol (210 mL) and water (30 mL) for 2 h at reflux temperature. The solution was evaporated, and the residue was taken up in water (400 mL). A precipitate formed which was filtered off and recrystallized from toluene. There were obtained off-white crystals of **9** (22.5 g, 65%): mp 80−82 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.58−3.74 (m, 2H, CH_2O), 4.07 (d, 2H, $J = 2.5$, CH_2OBn), 4.16−4.24 (m, 1H, CH-O), 4.58 (s, 2H, $ArCH_2$), aromatic protons 6.41 (d, 2H, $J = 6$), 6.65 (t, 1H, $J = 6$), 7.25−7.38 (m, 5H); $[\alpha]_D$ +12 ± 1.9° ($CHCl_3$). Anal. ($C_{16}H_{20}N_2O_3 \cdot 0.6H_2O$) Calcd C, 64.22; H, 7.14; N, 9.36. Found: C, 64.13; H, 6.94; N, 9.24.

(*S*)-4-(3′-(Benzyloxy)-2′-hydroxypropoxy)-2*H*-benzimidazol-2-one, 10. To a solution of the diamino compound **9** (28.8 g, 100 mmol) in CH_2Cl_2 (350 mL) was added 4 N sodium carbonate solution (63.0 mL, 126 mmol). The mixture was stirred at 0−5 °C, and a 1.93 M solution of phosgene in toluene (57.0 mL, 110 mmol) was added during 0.5 h. The cooling bath was removed, and the mixture was allowed to reach room temperature under continuous stirring. The precipitate which was formed during the reaction was filtered off, washed with water, and dried for 2 h at 70 °C under vacuum. Recrystallization from toluene yielded white crystals of **10** (27.5 g, 88%): mp 146−147 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 3.52−3.66 (m, 2H, CH_2O), 3.93−4.10 (m, 3H, $ArOCH_2$, CH-O), 4.52 (s, 2H, $ArCH_2O$), aromatic protons 6.56 (d, 1H, $J = 5$), 6.61 (d, 1H, $J = 5$), 6.84 (t, 1H, $J = 5$), 7.20−7.38 (m, 5H); $[\alpha]_D$ +7.1 ± 1.0° ($CHCl_3$). Anal. ($C_{17}H_{18}N_2O_4$) Calcd: C, 64.95; H, 5.77; N, 8.91. Found: C, 64.78; H, 5.68; N, 8.85.

(*S*)-4-((3′-(Benzyloxy)-2′-acetoxypropyl)oxy)-1,3-diacetyl-2*H*-benzimidazol-2-one, 11. To a solution of (*S*)-4-(3′-(benzyloxy)-2′-hydroxypropoxy)-2*H*-benzimidazol-2-one (**10**) (28.8 g, 91.6 mmol) in pyridine (74 mL) was added dropwise acetic anhydride (52.0 mL, 550 mmol) under stirring. During the addition, the temperature rose from rt to 32 °C. Stirring was continued at 60 °C for 48 h; then the excess reagents were removed under vacuum. The oily residue was dissolved in dichloromethane (500 mL) and washed with 1 N HCl and water. After drying over sodium sulfate and filtering off and evaporating the solvent, a brown oil (38.4 g) remained. Crystallization from 2-propanol furnished yellowish crystals of **11** (26.5 g, 66%): mp 73−75 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.13 (s, 3H, CH_3CO), 2.69 (s, 3H, CH_3CO), 2.75 (s, 3H, CH_3CO), 3.69−3.75 (m, 2H, CH_2O), 4.23−4.28 (m, 2H, $ArCH_2O$), 4.58 (d, 2H, $J = 3$, $ArOCH_2$), 5.34−5.61 (m, 1H, CH-O), aromatic protons 6.84 (d, 1H, $J = 5$), 7.20 (t, 1H, $J = 5$), 7.25−7.35 (m, 5H), 7.86 (d, 1H, $J = 5$); $[\alpha]_D$ −23.4 ± 0.9°. Anal. ($C_{23}H_{24}N_2O_7$) Calcd: C, 62.72; H, 5.49; N, 6.36. Found: C, 62.81; H, 5.58; N, 6.44.

(*S*)-4-(3′-Hydroxy-2′-acetoxypropoxy)-1,3-diacetyl-2*H*-benzimidazol-2-one, 12. A solution of the benzyl ether **11** (31.0 g, 70.4 mmol) in dioxane (700 mL) was hydrogenated at atmospheric pressure and rt over 5% palladium on carbon (4.0 g). A hydrogen uptake of 97% of the calculated amount was observed after 15 h. The catalyst was filtered off and the filtrate evaporated under vacuum. After crystallization of the residue from diethyl ether, white crystals of **12** (18.2 g, 74%) were obtained: mp 98−100 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 3H, CH_3CO), 2.74 (s, 3H, CH_3CO), 2.79 (s, 3H, CH_3CO), 3.87−3.94 (m, 2H, CH_2O), 4.25−4.34 (m, 2H, $ArOCH_2$), 5.19−5.26 (m, 1H, CH-O), aromatic protons 6.90 (d, 1H, $J = 5$), 7.24 (t, 1H, $J = 5$), 7.89 (d, 1H, $J = 5$); $[\alpha]_D$ −40 ± 6.3°. Anal. ($C_{16}H_{18}N_2O_7$) Calcd: C, 54.86; H, 5.18; N, 8.00. Found: C, 54.90; H, 5.25; N, 8.00.

(*R*)-4-((3′-((Methylsulfonyl)oxy)-2′-acetoxypropyl)oxy)-1,3-diacetyl-2*H*-benzimidazol-2-one, 13. To a solution of the above alcohol **12** (17.5 g, 50 mmol) in dichloromethane (500 mL) was added *s*-collidine (8.0 mL, 60 mmol). The solution was stirred at 0 °C, and methanesulfonyl chloride (4.7 mL, 60 mmol) was added dropwise. The reaction mixture was left overnight at rt. After being washed with 1 N HCl and water, the organic layer was dried over sodium sulfate, filtered, and evaporated. The oily residue gave colorless crystals of **13** (19 g, 89%) recrystallized from diethyl ether: mp 117−119 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 3H, CH_3CO), 2.74 (s, 3H, CH_3CO), 2.78 (s, 3H, CH_3CO), 3.10 (s, 3H, CH_3SO_2), 4.24 (d, 2H, $ArOCH_2$), 4.50−4.61 (m, 2H, CH_2O), 5.35−5.43 (m, 1H, CH-O), aromatic protons 6.85 (d, 1H, $J = 5$), 7.23 (t, 1H, $J = 5$), 7.90 (d, 1H, $J = 5$); $[\alpha]_D$ −27.0 ± 2.5°. Anal. ($C_{17}H_{20}N_2O_9S \cdot 0.5H_2O$) Calcd: C, 46.68; H, 4.84; N, 6.40; S, 7.33. Found: C, 46.80; H, 4.79; N, 6.51; S, 7.22.

(*S*)-4-((2′,3′-Epoxypropyl)oxy)-2*H*-benzimidazol-2-one, 1. The methanesulfonyl ester **13** (16.8 g, 39.2 mmol) was dissolved in $CHCl_3$ (350 mL) and MeOH (80 mL). The solution was cooled to 0−5 °C, and a 30% solution of sodium methoxide (7.3 mL, 39.2 mmol) in MeOH was added dropwise under stirring during 0.5 h. Stirring was continued for 2 h at rt. Evaporation under vacuum gave a residue which was triturated with cold water. The suspension obtained was filtered off, and the precipitate was washed and evaporated to dryness. After recrystallization from 2-propanol, there were obtained colorless crystals of **1** (6.7 g, 83%): mp 165−168 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.70−2.76 (m, 2H, oxirane CH_2), 3.33 (m, 1H, CH-O), 3.93 and 4.39 (both dd, 1H, $ArOCH_2$), aromatic protons 6.58 (d, 1H, $J = 5$), 6.63 (t, 1H, $J = 5$), 6.86 (t, 1H, $J = 5$), 10.60 (s, 1H, NH), 10.75 (s, 1H, NH); $[\alpha]_D$ +24.2 ± 1°.

Anal. ($C_{10}H_{10}N_2O_3 \cdot 0.5H_2O$) Calcd: C, 55.81; H, 5.15; N, 13.02. Found: C, 55.91; H, 4.92; N, 12.91.

Determination of Optical Purity. A sample of the epoxide **1** was converted by reaction with *tert*-butylamine to (*S*)-CGP 12177 as described with the racemic epoxide.[29] This was subjected to HPLC analysis (Ultron OVM 150 × 4.6 mm plus precolumn; eluent, 10 mM KH_2PO_4, pH = 4.6; flow rate, 0.5 mL/min; rt, UV_{212}). Retention time was 7.17−7.39 min. The optical purity as determined by derivatization to CGP 12177 was 99.3%.

(*S*)-Desisopropyl CGP 12388, 2. (*S*)-4-((2,3-Epoxypropyl)oxy)-2*H*-benzimidazol-2-one, **1** (50 mg, 0.24 mmol), was dissolved in methanol (8 mL). Ammonia gas was introduced during 1 h with a gas flow of 50 mL/min. After stirring for 4 days at room temperature, the solvent was evaporated under reduced pressure. Crude **2** was dissolved on methanol (0.5 mL) followed by addition of 0.48 M HCl (aqueous) in ethanol (5 mL). Acetone was added to precipitate **2**. (*S*)-Desisopropyl CGP 12388 (**2**) was filtered using a 0.5 μm filter: yield 53%; mp 226−227 °C; ^{1}H-NMR (200 MHz, CD_3OD) δ 3.18 (2H, m), 4.20 (3H, m), aromatic protons 6.72 (2H, d), 6.98 (1H, t); $[\alpha]_D$ −10.6 ± 1.2°. Anal. ($C_{10}H_{13}N_3O_3 \cdot HCl \cdot H_2O$) Calcd: C, 43.36; H, 5.77; N, 15.16. Found: C, 44.55; H, 5.47; N, 14.84.

In addition two HPLC systems were used for characterization: (1) Alltima C-18 column with eluent 0.9% NaCl containing 2 mM NaH_2PO_4/ethanol (88/12, pH = 2.3), with a flow rate of 4 mL/min, the retention time of **2** is 7 min; (2) silica gel Nova-PAK column (Waters, 150 × 3.9 mm) with eluent CH_2Cl_2/MeOH/H_2O/Et_3N (500/40/0.15/0.15, v/v/v/v), with a flow rate of 2 mL/min, the retention time of **2** is 14 min.

(*S*)-CGP 12388, 5. (*S*)-4-((2,3-Epoxypropyl)oxy)-2*H*-benzimidazol-2-one, **1** (31 mg, 0.15 mmol), and isopropylamine (0.3 mL, 3.53 mmol) were dissolved in 2-propanol (0.5 mL). The reaction mixture was heated for 2 h at 85 °C in a closed reaction tube. The solvent was evaporated, and the residue was dissolved in acetone. The HCl salt was formed by addition of ethereal HCl: yield 49%; mp 231−232 °C; ^{1}H-NMR (200 MHz, CD_3OD) δ 1.37 (6H, dd), 3.31 (2H, m), 3.42 (1H, m), 4.12 (2H, m), 4.29 (1H, m), aromatic protons 6.71 (2H, d), 7.00 (1H, t); $[\alpha]_D$ 19.6 ± 1.0°. Anal. ($C_{13}H_{19}N_3O_3 \cdot HCl$) Calcd: C, 51.91; H, 6.37; N, 13.97. Found: C, 51.46; H, 6.51; N, 13.63.

(*S*)-Fluoro-CGP 12388, 6. Fluoroacetone **4** (194 μL, 0.97 mmol) was added to a solution of (*S*)-desisopropyl CGP 12388, **2** (217 mg, 0.97 mmol), $NaCNBH_3$ (100 mg, 1.6 mmol), and glacial acetic acid (500 μL) in methanol (20 mL). The reaction mixture was heated at 110 °C for 2 h in a closed reaction tube. Subsequently the reaction mixture was evaporated under reduced pressure to an oil. The oil was dissolved in methanol (1 mL), and a solution of 0.48 M HCl in methanol was added (5 mL). Subsequently diethyl ether was added until precipitation was completed. The solid and white material was filtered off. Yield was 57%. Two HPLC systems were used for characterization: (1) Alltima C-18 column with eluent 0.9% NaCl containing 2 mM NaH_2PO_4/ethanol (88/12, pH = 2.3), with a flow rate of 4 mL/min, (*S*)-fluoro-CGP 12388 (**6**) was collected after 14 and 16 min as two diastereomers; (2) Waters RadPak silica gel column with eluent $CHCl_3$/methanol/25% NH_3(aq) (95/5/0.5), (*S*)-fluoro-CGP 12388 (**6**) was eluted after 20 min with a flow rate of 1 mL/min: ^{1}H-NMR (200 MHz, CD_3OD) δ 1.37 (d, 3H, CH_3), 3.27 (2H, m), 3.50−3.70 (1H, dm, J = 24), 4.13 (2H, m), 4.31 (1H, m), 4.30−4.80 (CH_2F, dm, J = 48), aromatic protons 6.69 (2H, dd), 6.95 (1H, dt).

(*S*)-[^{18}F]Fluoro-CGP 12388, 6. [^{18}F]Fluoride was produced by the $^{18}O(p,n)^{18}F$ nuclear reaction in an 0.8 mL silver target. The irradiated ^{18}O-enriched water was recovered by elution over an AG1-X8 ion exchange column (K_2CO_3 form). [^{18}F]Fluoride was eluted with a solution of K_2CO_3 (5 mg) in water (1 mL) into a vial containing Kryptofix 2.2.2. (10 mg). The resulting Kryptofix 2.2.2./^{18}F complex was dried by three successive evaporations of acetonitrile (1 mL). [^{18}F]Fluoride was reacted with acetol tosylate (4 mg) in acetonitrile (0.5 mL) at 110 °C as described previously.[9,11] The formed [^{18}F]fluoroacetone (**4**) was distilled into a solution containing (*S*)-desisopropyl CGP 12388, **2** (2 mg), $NaCNBH_3$ (1 mg), and glacial acetic acid (5 μL) in methanol (0.5 mL) followed by heating at 110 °C for 15 min. After evaporation of the solvent under reduced pressure, the residue was dissolved in HPLC eluent (1 mL, 0.9% NaCl containing 2 mM NaH_2PO_4/ethanol, 88/12, pH = 2.3). [^{18}F]Fluoro-CGP 12388, **6**, was purified by injection on HPLC with an Alltima C-18 column and eluent 0.9% NaCl containing 2 mM NaH_2PO_4/ethanol, 88/12, pH = 2.3. With a flow rate of 4 mL/min, [^{18}F]fluoro-CGP 12388, **6**, was collected after 16 min. Identity of **6** was confirmed by HPLC system 2 as described above. The radiotracer was injected in rats without further manipulations.

(*S*)-[^{11}C]CGP 12388, 5. [^{11}C]CO_2 was produced by the $^{14}N(p,\alpha)^{11}C$ nuclear reaction with 17 MeV protons. By trapping $^{11}CO_2$ in a solution of 5 μmol of MeLi in 100 μL of diethyl ether (dried from sodium) with a gas flow of 15 mL/min, [^{11}C]acetone (**3**) was formed. After evaporation of any residual diethyl ether, a solution of (*S*)-desisopropyl CGP 12388, **2** (1 mg), $NaCNBH_3$ (0.5 mg), and glacial acetic acid (2.5 μL) in methanol (250 μL) was added via a septum. Subsequently the reaction mixture was heated for 10 min at 110 °C in a closed reaction tube. After evaporation of the solvent, the residue was dissolved in HPLC eluent and applied onto HPLC. The eluent was 0.9% NaCl containing 0.02 M NaH_2PO_4/ethanol, 90/10, pH = 2.3, with a HPLC column Alltima C-18 5U. With a flow rate of 3 mL/min, the retention time was 19 min.

Octanol/Water Partition Coefficient (log *P*). An amount (50−100 μCi) of [^{11}C]- or [^{18}F]CGP 12388 was dissolved in 0.1 M phosphate buffer, pH = 7.4 (5 mL), whereafter *n*-octanol (5 mL) was added. Five mixtures were vigorously shaken at 37 °C for 30 min; 100 μL of the *n*-octanol layer and 100 μL of the water layer were counted in a Compugamma scintillation counter (LKB Wallac Compugamma 1282 CS, Turku, Finland). The partition coefficient was calculated according to the equation log P = −log(counts in octanol/counts in water).

***In Vivo* Studies with [^{11}C]CGP 12388 and [^{18}F]Fluoro-CGP 12388. 1. Tissue Distribution Studies.** All experiments were carried out in compliance with the Law on Animal Experimentation of The Netherlands. Male Wistar rats (200 ± 20 g) were anesthetized by intraperitoneal injection of pentobarbital (60 mg/kg of body weight). Maintenance doses of the anesthetics were normally not required, but in some cases (60 min biodistribution experiments) a small amount of pentobarbital (15−20 mg/kg of body weight) was injected shortly before tissue dissection to avoid animal suffering. Immediately (<1 min) before administration of the radioligand, the rats were treated either with saline (control group, n = 4) or with 500 μg (±)-propranolol (blocking experiments, n = 4) by iv injection. Subsequently [^{18}F]fluoro-CGP 12388 (2 MBq, 30 pmol) or [^{11}C]CGP 12388 (1 MBq, 30 pmol) was injected in a volume of 0.3 mL. After 10 or 60 min the rats were killed by extirpation of the heart, and several tissues were dissected. Plasma was obtained from blood by centrifugation (3 min, 1000*g*). Uptake values are expressed as differential absorption ratios (DAR = (cpm recovered/g of tissue)/(total dose injected in cpm/body weight in g)). Differences between groups were examined with the nonparametric *Q*-test of Wilcoxon.

2. PET Studies. PET studies were carried out with a Siemens ECAT 951/31 positron camera. Data acquisition was performed using a dynamic protocol and in the stationary mode. In this mode the in-plane spatial resolution amounts to 6 mm fwhm. During the reconstruction a zoom factor of 1.5 was applied, and the matrix size was 128 × 128 pixels. The rats were anesthetized as described above. In order to obtain sagittal sections, the long axis of the rat was positioned in the PET camera parallel to the transaxial plane of the tomograph. Subsequently [^{18}F]fluoro-CGP 12388 (2 MBq, 30 pmol) or [^{11}C]CGP 12388 (1 MBq, 30 pmol) dissolved in 0.3 mL of HPLC eluent as described above was administered by injection in a tail vein. The following frames were defined: 8 × 15, 2 × 30, 2 × 60, 4 × 300, and 3 × 600 s. Data analysis was performed using the Siemens ECAT software (V6.3 D) on a Sun workstation.

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