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Radiosynthesis of 4-[^{18}F]fluoro-L-tryptophan by isotopic exchange on carbonyl-activated precursors

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ABSTRACT

Several ^{18}F-labeled aromatic amino acids have been developed primarily for tumor imaging with positron-emission-tomography (PET). Also, ^{18}F-labeled tryptophan derivatives were synthesized by electrophilic ^{18}F-fluorination or by introducing a [^{18}F]fluoroalkyl group. Here, a 3-step method for a nucleophilic radiosynthesis of 4-[^{18}F]fluoro-L-tryptophan was developed. A carbonyl activated precursor containing a chiral amino acid building block was radiofluorinated by isotopic exchange, followed by removal of the activating formyl group by reductive decarbonylation and subsequent cleavage of the building block under acidic conditions. The title compound was obtained within 100 min with a radiochemical yield of about 13%, a molar activity of >70 MBq/mmol and an enantiomeric excess of >99%.

1. Introduction

The indole moiety is one of the most frequently occurring heterocycles in natural products.[1] It is, for example, part of the essential amino acid L-tryptophan, its metabolite skatol, the plant growth factor 3-indolylacetic acid (heteroauxin) and the neurotransmitter serotonin.[2] There is also a broad variety of plant alkaloids that contain indole, for example, strychnine and ellipticin. Many of those plant alkaloids are highly toxic but may also have properties that are very valuable for special medicinal considerations.

Recent studies revealed that many tumors up-regulate the enzyme tryptophan dioxygenase to stimulate the consumption of tryptophan. Hence, the uptake of tryptophan of those tumor cells increases. This is because the primary product of tryptophan dioxygenase is kyneurine which is known to be an endogenous ligand for the aryl hydrocarbon receptor and as mediator of invasive tumor growth.[3]

Furthermore, tryptophan is the precursor for serotonin[4] which is involved in a series of neurological regulations and diseases such as depression[5] and migraine.[6]

Hitherto, only a few tryptophan derivatives have been radiolabeled with positron emitters.[7] First radiofluorinated tryptophan derivatives were realized by the Balz-Schiemann reaction,[8] but with low radiochemical yield (RCY), or by electrophilic ^{18}F-fluorination.[9] Recently, a more efficient radiolabeling has been performed by ^{18}F-fluoroalkylation in different positions of tryptophan.[10–12]

The major aim of this study was to find out, whether an activation of the carbocycle of the indole moiety is possible in such a way that isotopic ^{18}F-exchange via a nucleophilic aromatic substitution (S_NAr) becomes possible. For this, the influence of the substitution pattern of the fluorine and the activating carbonyl group on the RCY and chemical stability were of high interest. To examine the influence of the position of activating carbonyl function and of the fluorine leaving group on the exchange rate, indole derivatives with various protecting groups at the indole nitrogen were synthesized and labeled with fluorine-18. Further, a corresponding precursor for the radiosynthesis of 4-[^{18}F]fluoro-L-tryptophan had to be designed and prepared and the radiosynthesis had to be optimized.

2. Results and discussion

2.1. Radiolabeling of indole derivatives with fluorine-18

2.1.1. Synthesis of precursors for labeling of indole-1*H*-carbaldehydes

Four different *ortho*- and *para* substituted indolecarbaldehydes **1**–**4** (Scheme 1) were prepared following a modified procedure from lit.[2]

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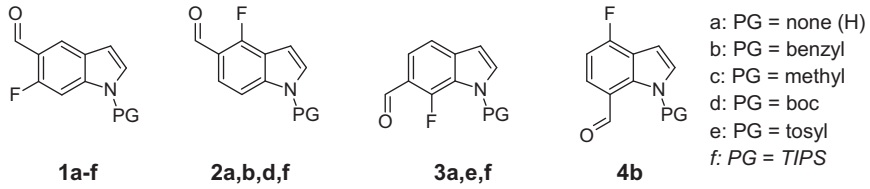


Scheme 1. Fluoro-1*H*-indole-carbaldehydes (PG: protecting group).

In the first step the amino group of the *ortho*-substituted indolecarbaldehydes **1**–**3** was protected by the triisopropylsilyl-group (TIPS) which proceeded quantitatively. This was the protecting group of choice, since TIPS is a bulky group that is able to avoid the ordinary deprotonation of the intrinsically most acidic 2-position of indoles by the consecutive lithiation reaction.[2] Next, the formyl group was introduced in *ortho* position to the fluorine (**1**–**3**). This was accomplished by *N*,*N*-dimethylformamide (DMF) as electrophile instead of carbon dioxide, referring to the procedure from lit.[2] The formylation gave yields of about 65% with all fluoro-1*H*-indole derivatives. Hereby, it was essential to use at least four equivalents of DMF, otherwise much lower yields were obtained. The removal of TIPS from the nitrogen was performed with tetrabutylammonium fluoride (TBAF) giving yields of >90%. Finally, different protecting groups were then attached to the indole nitrogen of the fluoro-1*H*-indolecarbaldehydes, namely the benzyl, the methyl, the *tert*-butoxycarbonyl (Boc) and the tosyl group.

Except for the *N*-benzylation, all protection procedures were performed as described in lit.[13–15] Accordingly, *N*-benzylations of indoles proceeded in good yields when tetrahydrofuran (THF) or dimethylsulfoxide (DMSO) was used as solvent. However, the use of DMF as solvent for the benzylation of all indole compounds described here (**1a**–**3a**) was essential otherwise a decomposition of the final product was observed. With DMF as solvent the benzylation succeeded in good yields of about 85%. The methylation gave moderate yields of about 58% while tosylation and Boc-protection led to the desired products in 80% and 90% yields, respectively. The total synthetic pathway for derivatives of compounds **1** to **3** is shown in Scheme 2, with 6-fluoro-1*H*-indole-5-carbaldehyde (**1b**–**e**) as an example.

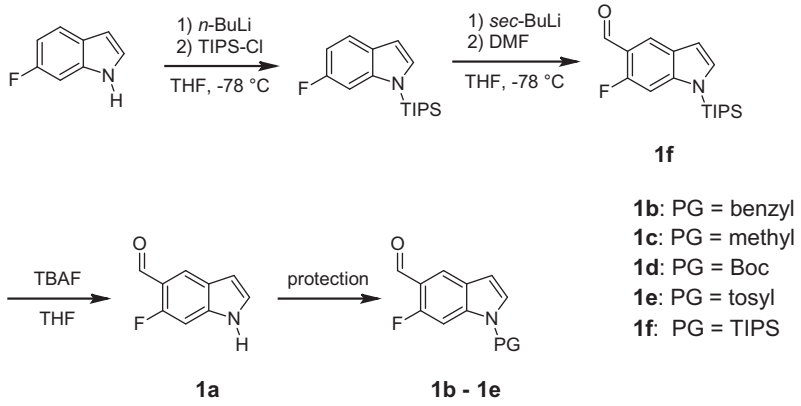
The *para*-substituted precursor **4b** was differently synthesized, following a three-step linear pathway starting from 1-bromo-4-fluoro-2-nitrobenzene. The total synthetic route is shown in Scheme 3. The first step therein was the formation of the indole via a Bartoli reaction[16] giving 7-bromo-4-fluoro-1*H*-indole in 52% yield. The subsequent benzylation reaction was carried out with NaH and benzyl bromide under similar conditions as for the indole compounds **1b**–**3b**, giving the desired product in yields of about 81%. The formylation was here the final step, carried out in THF with *n*-butyllithium and DMF and providing finally the precursor **4b** with about 39% yield.

2.1.2. Isotopic exchange with [^{18}F]fluoride and subsequent decarbonylation

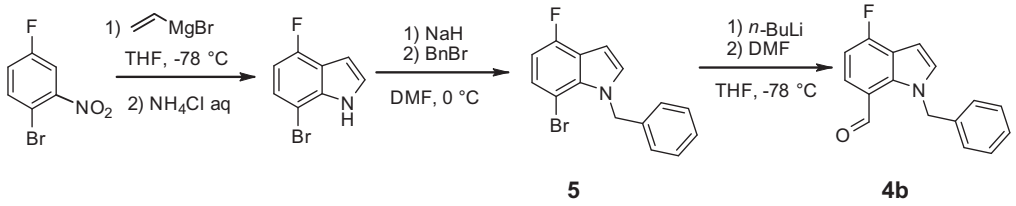
The first step in the preparation of radiofluorinated indoles was an ^{18}F-for-^{19}F isotopic exchange reaction. Previous work on nucleophilic aromatic substitution had shown that DMF as solvent and temperatures above 100 °C gave the best radiochemical yield (RCY) with fluorobenzaldehydes.[17,18] These conditions were adapted to study the influence of different protecting groups on the radiolabeling reaction. For this purpose, the ^{18}F-fluorination was carried out with different protected 6-fluoro-indole-1*H*-5-carbaldehydes **1a**–**e** (cf. Scheme 4) using [^{18}F]TBAF at 130 °C for 15 min. All reactions were analyzed by radio HPLC and the results obtained are listed in Table 1.

The radiolabeling was not possible at all when the nitrogen of the 6-fluoro-1*H*-indole-5-carbaldehyde (**1a**) was not protected or when it was protected with a tosyl group. The latter is not surprising since de-tosylation of indoles is commonly carried out with TBAF.[19] The best radiochemical yields were obtained with the benzyl- and methyl-protected indole derivatives **1b** and **1c** (25% and 20%, respectively). Due to higher RCY the benzyl group was therefore preferred to the methyl group for further reactions.

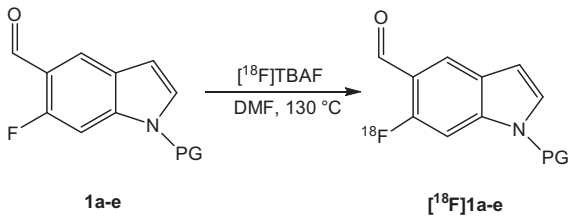
Next, the dependence of radiolabeling on the temperature was examined. For this, the benzyl-protected precursors (**1b**–**4b**) were first radiofluorinated at 150 °C for 15 min using DMF as solvent. Since the RCY at this temperature was higher than 90% for 1-benzyl-4-fluoro-1*H*-indole-5-carbaldehyde (**2b**), it was tested out how far the temperature could be reduced until the RCY would decrease significantly. That happened at 60 °C. Alternatively, DMSO and acetonitrile were tested as solvents, but a RCY higher than 8–10% could not be obtained. Moreover, reaction times longer than 15 min did not increase the RCY. The other benzyl-protected indolecarbaldehydes (**1b**, **3b**, and **4b**) were also tested at



Scheme 2. Synthetic pathway for the preparation of the *ortho*-substituted indole precursors, exemplified for 6-fluoro-1*H*-indole-5-carbaldehyde.



Scheme 3. Synthetic pathway for the preparation of 1-benzyl-4-fluoro-1*H*-indole-7-carbaldehyde (**4b**).



Scheme 4. Radiofluorination of 6-fluoro-indole-1*H*-5-carbaldehydes **1a–e**.

temperatures between 60 and 150 °C. Surprisingly, the 1-benzyl-fluoro-1*H*-indolecarbaldehydes with different *ortho*- and *para*-substitution patterns gave a varying RCY. They also showed a very different chemical stability toward elevated temperatures.

The maximum RCYs were found in the range of 55–94% depending on the substitution pattern of the used fluoro-1*H*-indolecarbaldehydes. The RCY of 1-benzyl-4-[^{18}F]fluoro-1*H*-indole-7-carbaldehyde (**4b**) and 1-benzyl-7-[^{18}F]fluoro-1*H*-indole-6-carbaldehyde (**3b**) was maximum at 80 °C and 95 °C, respectively, and decreased with increasing temperatures due to decomposition of the compounds. In contrast, 1-benzyl-4-[^{18}F]fluoro-1*H*-indole-5-carbaldehyde (**2b**) and 1-benzyl-6-[^{18}F]fluoro-1*H*-indole-5-carbaldehyde (**1b**) did not show any decomposition at all, even at temperatures as high as 150 °C. The results are graphically shown in Figure 1.

It can be concluded that the substitution pattern has an influence on the results of the corresponding isotopic exchange reactions. However, not only the position of the fluorine influences the isotopic exchange, but also the position of the formyl group, a fact significantly exemplified by the different results found with the compounds examined. Both **2b** and **4b** have the fluorine atom attached in the 4-position, while the compounds **1b** and **2b** both have the formyl group in the 5-position with a different substitution pattern of the other substituent, respectively.

The subsequent reductive decarbonylation was performed with chlorotris(triphenylphosphine)rhodium(I) ('Wilkinson's catalyst', $Rh(PPh_3)_3Cl$). Due to the fact that during this reaction the formation of stable $Rh(PPh_3)_2(CO)Cl$ occurs as a secondary product it is necessary to use stoichiometric amounts of Wilkinson's catalyst. This reaction was at first tested with 1-benzyl-6-[^{18}F]fluoro-1*H*-indole-5-carbaldehyde ([**^{18}F**]**1b**) under conditions previously described.[18,20,21] Good results were obtained using the method described by Castillo et al.[21] giving a RCY of 85 ± 2%. Increasing the amount of Wilkinson's catalyst to 3 equiv and the reaction time to 120 s, however, led to optimum conditions with a RCY of 95%. The results are summarized in Table 2. Those latter conditions were then applied to all indole compounds **1b–4b** leading to similar RCYs.

Following debenzylation reactions were studied using ammonium formate (NH_4HCO_2)[22] and hydrogen gas[23] with palladium on charcoal, respectively, or $AlCl_3$ in benzene.[24] The use of triphosgene also proved to convert the benzylamine into the corresponding carbamoyl chloride that should be hydrolyzed under acidic conditions.[25] However, all methods tested gave no debenzylated indole derivative, only the $AlCl_3$ method gave radiolabeled side products. Since all of these attempts failed for the debenzylation of the indole compounds, the 4-fluoro-1*H*-indole-5-carbaldehyde (**2a**) which gave the best results regarding RCY and chemical stability was also protected with a Boc-group. Although the isotopic exchange reaction with the Boc-protected derivative **1d** gave a RCY of only 6% (cf. Table 1), the Boc-group offers, in principle, the possibility of its easy removal. Therefore, 1-boc-4-fluoro-1*H*-indole-5-carbaldehyde (**2d**) was labeled with fluorine-18 at temperatures between 70 °C and 110 °C, showing a maximum RCY of 28% at a reaction temperature of 80 °C after 15 min. The deprotection of this compound proceeded quantitatively with 2 M HCl at room temperature (cf. Scheme 5).

Table 1
Dependence of the radiochemical yield of 6-[^{18}F]fluoro-indole-1*H*-5-carbaldehydes **1a–e** on different protecting groups ($n = 3$)

Compound	Protecting group	RCY [%]
1a	None	0
1b	Benzyl	25 ± 7
1c	Methyl	20 ± 4
1d	Boc	6 ± 2
1e	Tosyl	0

Conditions: 1 mL DMF, $TBAHCO_3$ [18 μmol], reaction time 15 min 130 °C.

2.2. Radiosynthesis of 4-[^{18}F]fluoro-L-tryptophan

A previous report on the labeling of aromatic amino acids described the radiosynthesis of 2-[^{18}F]fluoro-L-phenylalanine and 2-[^{18}F]fluoro-L-tyrosine in a three step synthesis.[21] The concept of this synthesis was adapted to the precursor **16** described above, following the same synthetic procedures: isotopic exchange, reductive decarbonylation, and cleavage of the amino acid auxiliary (Scheme 6).

2.2.1. Precursor synthesis

The above described results on [^{18}F]fluoroindolecarbaldehydes have shown that indoles should preferably be radiofluorinated in the 4-position. Therefore, a synthetic route was developed to prepare a suitable precursor for the radiosynthesis of 4-[^{18}F]fluoro-L-tryptophan. The selected precursor was synthesized in an 11 step linear synthesis starting from 4-fluoroindole with an overall yield of 8% (see Scheme 7) following a modified route to the one described by Konas et al.[15]

As the first step, 4-fluoroindole was *N*-protected with TIPS-Cl (94%). A regioselective iodination of **6** was performed as previously described by Schlosser et al.[2] using diiodoethane instead of elemental iodine followed by deprotection with TBAF, giving ca. 65% of the deprotected iodoindole **8**. The formylation in the 3-position was carried out under standard Vilsmeier-Haack conditions.[26]

The resulting aldehyde (**9**) was isolated in 88% yield by filtration and used as obtained without further purification. A tosyl-group was introduced (83%) and the protected aldehyde (**10**) reduced quantitatively by $NaBH_4$ yielding the corresponding alcohol (**11**)

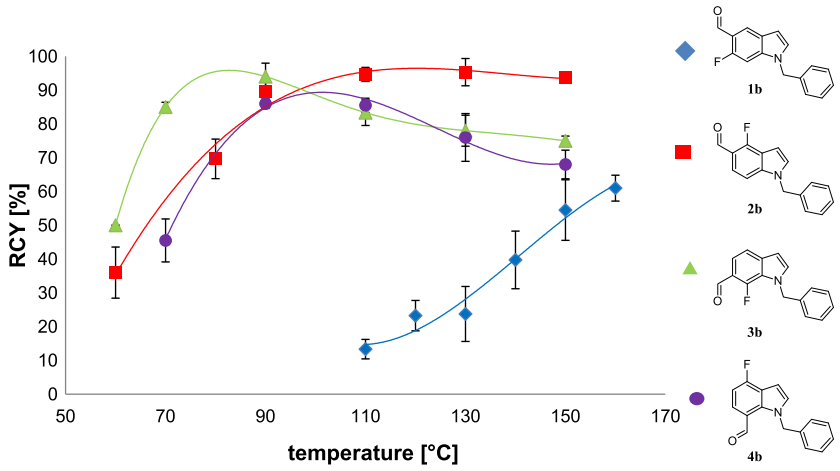
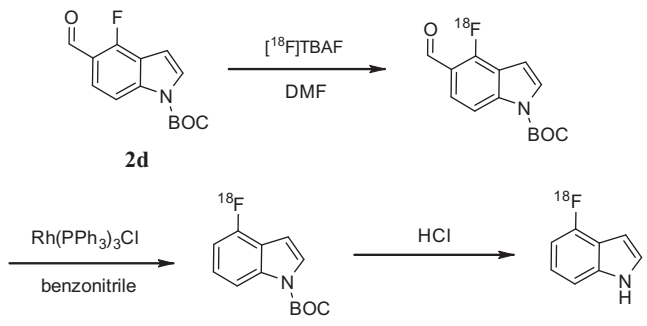


Figure 1. Influence of the temperature on the isotopic ^{18}F-exchange on fluoro-1*H*-indolecarbaldehydes with an *ortho*- and *para*-substitution pattern. Conditions: precursors **1b**–**4b** [20 μmol], 1 mL DMF, $TBAHCO_3$ [18 μmol], reaction time 15 min, (n = 3). Each solid curve is an eye-guide.

Table 2
Reductive decarbonylation of 1-benzyl-6-[^{18}F]fluoro-1*H*-indole-carbaldehyde (**1e**) (n = 3)

Solvent	Equivalents of Wilkinson catalyst	Conditions	Conversion (%)	RCY (%)
Benzonitrile	3	150 °C, 20 min[18]	>99	95 ± 6
Benzonitrile	3	100 W, 50 s[21]	85 ± 2	85 ± 2
Benzonitrile	3	100 W, 120 s	>99	95 ± 3
Dioxane	2	150 °C, 20 min[20]	29 ± 4	6 ± 3

which was brominated in an Appel reaction with PPh_3 and CBr_4 (78%).[27] The resulting bromide (**12**) was immediately coupled with Seebach's chiral amino acid auxiliary (73%). The imidazolidinone (**13**) obtained was formylated via an iodine formyl exchange in a Grignard like reaction using *i*-PrMgBr and DMF, providing 72% of the corresponding benzaldehyde **14**. Further, the tosyl-group was removed and replaced by a Boc-group, since it is known that *N*-tosylindoles can be easily detosylated by nucleophilic fluoride. The subsequent removal of the tosyl-group was performed with TBAF leading to the unprotected indolecarbaldehyde **15** in 53% yield,[19] and eventually the introduction of the Boc-group (94%)[14] led to the desired precursor benzyl (2*S*,5*S*)-2-*tert*-butyl-5-[(1-boc-4-fluoro-5-formyl-1*H*-indol-3-yl)methyl]-3-methyl-4-oxoimidazolidine-1-carboxylate (**16**) with an overall yield of about 8%.



Scheme 5. Reaction sequence to 4-[^{18}F]fluoro-1*H*-indole.

2.2.2. Isotopic exchange with [^{18}F]fluoride

The first step in the radiosynthetic pathway is again the isotopic ^{18}F-for-^{19}F exchange. The previous studies on nucleophilic exchange of indoles indicated, that the use of DMF as solvent and temperatures between 80 °C and 130° gave the highest RCY. Thus, the optimum temperature for the isotopic exchange of precursor **16** was tested by heating the reaction mixture to temperatures between 60 and 120 °C for 15 min (see Fig. 2).

The temperature range is very narrow, over which a good RCY of above 40% could be obtained and extends from 75 to 85 °C, with an optimum RCY of 51% at about 80 °C. At temperatures higher than 90 °C the precursor decomposed rapidly. The exchange radiolabeling was also tested in DMSO and MeCN, but the desired compound could not be obtained in both solvents. Furthermore, a kinetic measurement of the isotopic exchange was performed at the optimum temperature of 80 °C. The maximum RCY was reached between 10 and 15 min, while again decomposition of the labeled intermediate occurred with reaction times longer than 20 min. As it is known from literature that only highly activated aromatic systems will allow a nucleophilic aromatic substitution reaction with [^{18}F]fluoride at room temperature,[28] the reaction here was not studied under room temperature conditions.

Furthermore, in order to improve the process of the isotopic exchange, a microwave assisted reaction was tested. Microwave

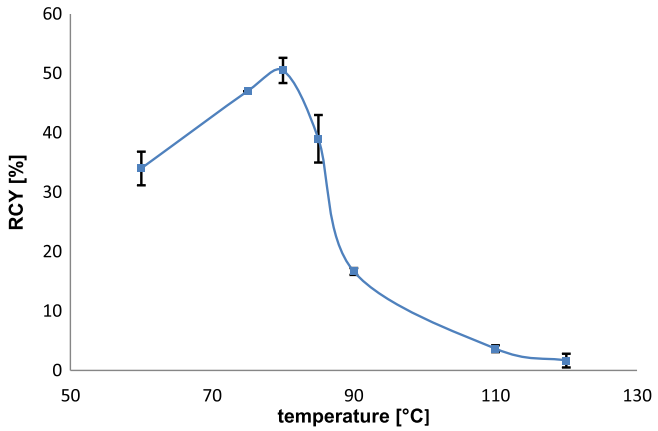
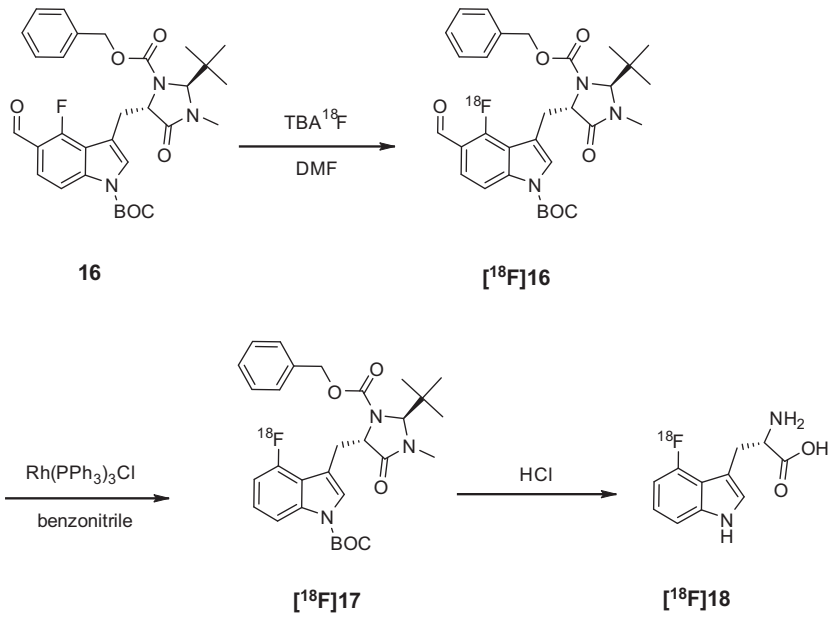


Figure 2. Influence of temperature on the isotopic ^{18}F-exchange on precursor **16**. Conditions: 1 mL DMF, $TBAHCO_3$ [18 μmol], 15 min, each experiment was carried out at least in triplicate. The solid curve is an eye-guide.



Scheme 6. Synthetic route for the radiosynthesis of 4-[^{18}F]fluoro-L-tryptophan.

irradiation produces efficient internal heating (in-core volumetric heating) by direct coupling of microwave energy with the molecules (solvents, reagents, catalysts) that are present in the reaction mixture, resulting in an inverted temperature gradient compared to conventional thermal heating.[29] While the total RCY could not be increased by the use of this technique in comparison to conventional heating, the reaction time could be reduced to 1 min. The best results using a microwave assisted reaction were obtained by a power of 40 W and a reaction time of 1 min with a RCY of about 49%.

2.2.3. Reductive decarbonylation and hydrolysis

The aldehyde function was removed with the help of Wilkinson's catalyst. This reaction was tested under the conditions that gave the best RCY with the indoles (**1b–4b**) as described above, and it was optimized regarding the equivalents of catalyst, solvent, temperature and time. The reaction was also carried out under microwave assisted heating. It turned out that under conventional heating (CH) only a moderate RCY of **[^{18}F]17** of about 45% could be achieved which is probably due to decomposition. Under microwave assisted heating (MH) a RCY of about 75% was obtained. However, the formation of a polar side product could not be avoided, but be limited to about 20%, when using 3 or 4 equiv of Wilkinson's catalyst. Under microwave heating it could also not be accomplished to get the decarbonylated intermediate without removing the Boc-group from the indole-nitrogen which, however, is not a problem in this case. Moreover, the use of microwave assisted heating led to almost quantitative chemical conversion of **[^{18}F]17**, whereas 35 ± 9% of **[^{18}F]17** were left unchanged under conditions of conventional heating. The fractions of non-converted intermediate **[^{18}F]17** were examined by HPLC analysis. The conversions were examined by HPLC analysis. The results are summarized in Table 3.

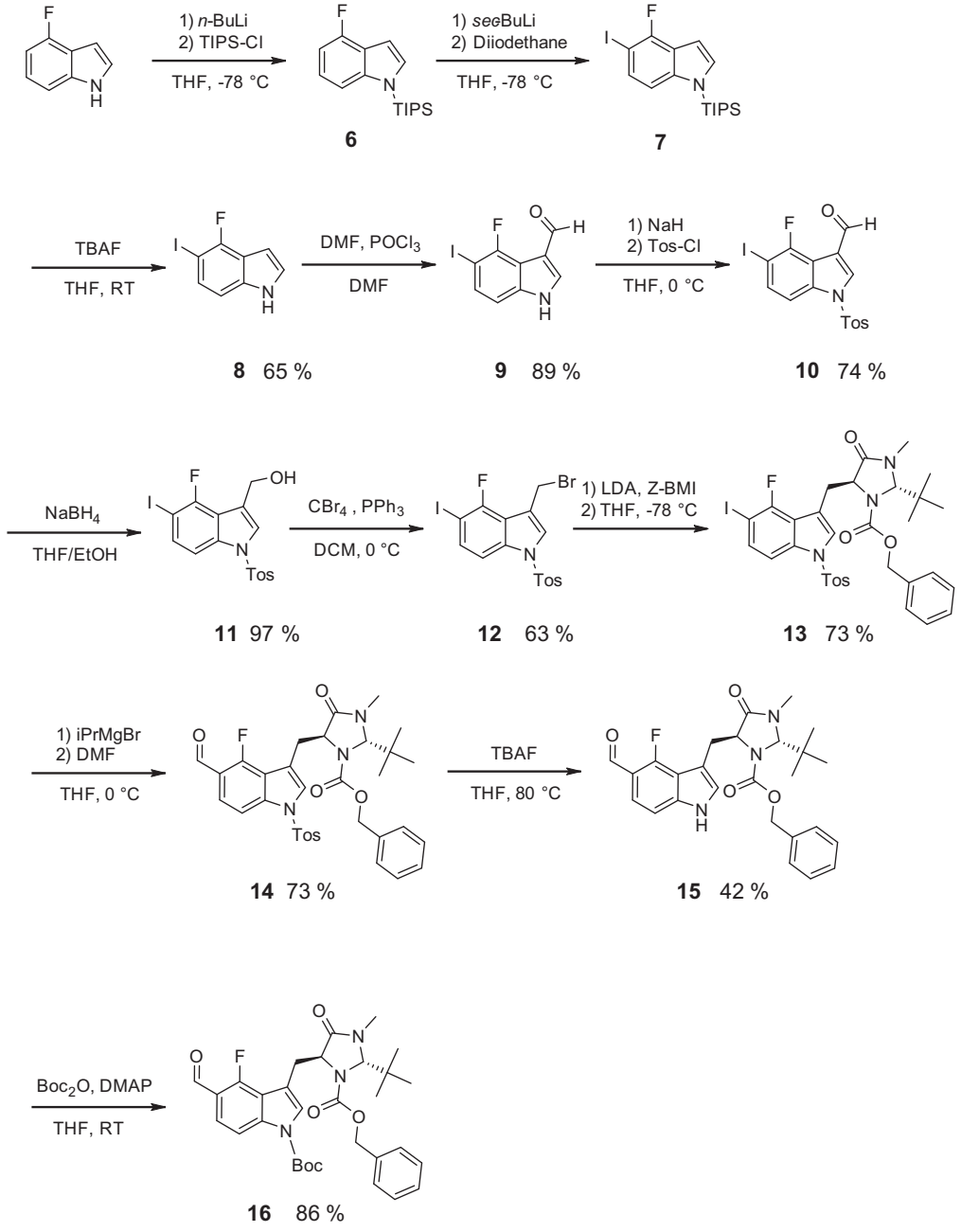
The amide bond in Seebach's auxiliary requires harsh conditions for hydrolysis. In previous studies this was done using concentrated HBr or HI and temperatures as high as 150 °C or even 200 °C.[17,30] In another work concentrated HCl and heating to 150 °C for 30 min proved sufficient for the hydrolysis of the Boc-protected derivative of Seebach's auxiliary.[21] In the study here, those conditions were adapted to give a RCY of **[^{18}F]18** of approximately 34% for this deprotection reaction. Each experiment was carried out at least in triplicate. The final purification was performed by HPLC using 10% ethanol in water which can directly be used for first animal experiments.

The reactions performed under conventional heating yielded the desired product in an overall RCY of **[^{18}F]18** of approximately 8%. The application of a microwave assisted synthesis increased the total RCY to about 13% due to the higher yields that were obtained for the decarbonylation reaction with microwave heating. Furthermore, the total preparation time of 4-[^{18}F]fluoro-L-tryptophan (**[^{18}F]18**) could be reduced to 27 min, yielding the product in an enantiomeric purity of >99%. None of the D-enantiomer could be observed by chiral HPLC.

The specific activity obtained by isotopic exchange reactions is a function of both the amount of precursor and the amount of radioactivity of [^{18}F]fluoride. The maximum amount of carrier is limited by the quantity of precursor that is used; in this study here 9 μmol. When a starting activity of approximately 250 MBq was used the molar activity was always >70 MBq/mmol which is in the region of specific activities obtained under electrophilic fluorination conditions. Thus, it can be expected that with a higher starting activity of [^{18}F]fluoride the molar activity of the product would increase considerably and will thereby be much higher than that obtained with electrophilic ^{18}F-fluorination. An animal toxicological study of 4-[^{18}F]fluoro-L-tryptophan is in progress, however, in earlier tests with bacteria no toxicity of the compound was observed.[31]

3. Summary

An influence of the positions of fluorine and of the formyl group on the isotopic exchange in the carbocyclic ring of indole was observed with several fluoro-1*H*-indolecarbaldehydes, each bearing a different protecting group at the indole nitrogen. The best results regarding radiochemical yield and chemical stability were obtained with 1-benzyl-4-fluoro-1*H*-indole-5-carbaldehyde (**2e**). However, it was not possible to remove the benzyl protection group from this compound. Thus, the Boc-protected derivative 4-[^{18}F]fluoro-L-tryptophan was best prepared by the three step radiosynthesis, consisting of an isotopic exchange, a reductive



Scheme 7. Synthesis pathway of precursor **16** for radiosynthesis of 4-[^{18}F]fluoro-L-tryptophan.

decarbonylation with $Rh(PPh_3)_3Cl$ and the hydrolysis of the protecting groups with HCl. After optimization of this procedure, 4-[^{18}F]fluoro-L-tryptophan could be isolated in a total radiochemical yield of about 13%, an enantiomeric excess of >99% and a molar activity of >70 MBq/mmol within about 100 min total synthesis time. Hence, a new and more efficient nucleophilic radiosynthesis of 4-[^{18}F]fluoro-L-tryptophan was developed which makes the tracer now available for preclinical evaluation studies.

4. Experimental

4.1. General

Chemicals were purchased from Sigma-Aldrich (Taufkirchen), Merck (Darmstadt), and ABCR (Karlsruhe) (all Germany). 1-Triisopropylsilyl-6-fluoro-1*H*-indole-5-carbaldehyde, 4-fluoro-1-(triisopropylsilyl)-1*H*-indole, 7-bromo-4-fluoroindole, 7-fluoro-1-(triisopropylsilyl)-1*H*-indole and 4-fluoro-1-triisopropyl-1*H*-indole (**6**) were prepared as described in lit.[2]

Experiments under microwave heating were performed using a CEM Discover (Matthews, USA) single-mode microwave reactor system. Thin layer chromatography (TLC) was performed on precoated plates of silica gel 60 F254 (Merck, Darmstadt, Germany) and the compounds were detected at 254 nm. Radioactivity on radio-TLC was detected on a Raytest minigita device (Raytest, Straubenhardt, Germany). High-performance liquid chromatography (HPLC) separations were achieved with a Knauer pump, a Knauer K-2500 UV/VIS detector (Knauer, Berlin, Germany), a manual Rheodyne injector (20 μL or 1.0 mL loop), and a NaI(Tl) well-type scintillation detector (EG&G Ortec; model 276 Photomultiplier Base) with an ACE Mate Amplifier and BIAS supply (all from Ortec Ametek, Meerbusch, Germany) for radioactivity

detection. Data acquisition and interpretation were performed with Gina software (Raytest, Version 2.18).

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Varian Inova 400 MHz spectrometer using $CDCl_3$ or d_6-DMSO as solvents. All chemical shifts are given below in δ ppm using the signals of the appropriate solvent as a reference. HRMS spectra were obtained on an FTICR 'LTQ FT Ultra' (Thermo Fisher Scientific, Germany). Optical rotation was measured using a Perkin Elmer (Rodgau, Germany) Model 341 Polarimeter at a wavelength of 589 nm.

4.2. Chromatographic systems

System A

Analytical HPLC of the ^{18}F-labeled indole derivatives was performed with a Kromasil 5 µm C18 column (250 × 4 mm; CS Chromatographieservice Langerwehe, Germany). Elution was performed at a constant flow rate of 1 mL min^{-1} with an acetonitrile water mixture (65:35).

System B

Semi-preparative HPLC was carried out with a Synergi 4 µm Hydro-RP 80 Å column (250 × 10 mm; Phenomenex, Aschaffenburg, Germany). The mobile phase was 10% ethanol in water, and the flow rate was 4 mL min^{-1}.

System C

The enantiomeric purity of the radiolabeled compounds was determined by HPLC using a Supelco chirobiotic™ T column, 250 × 4.6 mm (Sigma-Aldrich, Diedenhofen, Germany). Elution was performed with a methanol-water mixture (30:70) at a constant flow rate of 1 mL min^{-1}.

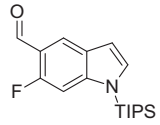
System D

Analytical HPLC was carried out with a Synergi 4 µm Hydro-RP 80 Å column (250 × 4 mm; Phenomenex). The mobile phase was 10% ethanol in water, and the flow rate was 1 mL min^{-1}. The k'-values of important radiolabelled compounds together with the corresponding separation systems are summarized in Table 4.

4.3. Precursor syntheses

Following 10 fluoroindole carbaldehydes were synthesized according to Schlosser et al.[2]

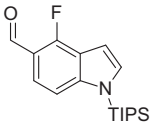
4.3.1. 1-Triisopropylsilyl-6-fluoro-1*H*-indole-5-carbaldehyde (1f)



A solution of 6-fluoro-1-(triisopropylsilyl)-1*H*-indole (4.0 g, 14 mmol) in 30 mL tetrahydrofuran was cooled to −78 °C, and a 1.4 M solution of *sec*-butyllithium in hexanes (14 mmol) was added dropwise. The resulting mixture was stirred for 2 h at −78 °C before 5 mL dimethylformamide were added slowly. The reaction was allowed to warm up to room temperature and stirred for 2 more hours. Water was added and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered and the solvents were evaporated in vacuo. The crude residue was purified by flash chromatography (2% ethyl acetate (EA)/petroleum ether (PE), R_f = 0.30) giving 2.5 g (7.8 mmol, 64%) of the desired product as a colorless oil.

^{1}H NMR ($CDCl_3$) δ 10.38 (s, 1H), 8.17 (d, ^{3}J = 7.0 Hz, 1H), 7.32 (d, ^{4}J = 3.3 Hz, 1H), 7.24 (dd, ^{3}J = 12.6 Hz, ^{4}J = 0.7, 1H), 6.74 (dd, ^{4}J = 2.4 Hz, ^{4}J = 0.9 Hz, 1H), 1.72 (hept, ^{3}J = 7.6 Hz, 3H), 1.19 (d, ^{3}J = 7.4 Hz, 18H); ^{13}C NMR ($CDCl_3$) 187.1 (d, $^{3}J_{CF}$ = 6.4 Hz), 161.13 (d, $^{1}J_{CF}$ = 247), 144.8 (d, $^{3}J_{CF}$ = 12 Hz), 133.4 (d, $^{4}J_{CF}$ = 3 Hz), 128.2 (d, $^{5}J_{CF}$ = 1 Hz), 121.7 (d, $^{4}J_{CF}$ = 4Hz), 118.4 (d, $^{3}J_{CF}$ = 11Hz), 106.5, 100.4 (d, $^{2}J_{CF}$ = 25.2 Hz), 18.0(6C), 12.7(3C); ^{19}F NMR ($CDCl_3$) δ −130.1; HRMS: $C_{18}H_{26}FNOSi$ $[M+H]^+$ calcd: 320.1840; found: 320.1839.

4.3.2. 1-Triisopropylsilyl-4-fluoro-1*H*-indol-5-carbaldehyd (2f)



Analogously prepared as the aldehyde **1f**, while starting from 4-fluoro-1-(triisopropylsilyl)-1*H*-indole giving the desired product as a colorless solid in 66% yield.

Mp: 61–63 °C.

^{1}H NMR (DMSO-d_6) δ 10.26 (s, 1H), 7.51–7.48 (m, 3H), 6.85 (d, ^{4}J = 3.2 Hz), 1.73 (hept, 3H, ^{3}J = 7.6 Hz), 1.02 (d, 18H, ^{3}J = 7.6 Hz); ^{13}C NMR (DMSO-d_6) δ 187.3 (d, $^{3}J_{CF}$ = 6 Hz), 158.9 (d, $^{1}J_{CF}$ = 259 Hz), 147.3 (d, $^{2}J_{CF}$ = 12 Hz), 134.2, 120.9, 119.7 (d, $^{2}J_{CF}$ = 19 Hz), 115.8 (d, $^{3}J_{CF}$ = 5 Hz), 111.5, 102.3, 18.1 (6C), 12.2(3C); ^{19}F NMR (DMSO-d_6) δ −128,78; HRMS: $C_{18}H_{26}FNOSi$ $[M+H]^+$ calcd 320.1840; found: 320.1842; elemental analysis calcd for $C_{18}H_{26}FNOSi$: C, 67.67; H, 8.20; N, 4.38; found: C, 67.68; H, 8.25; N, 4.35.

Table 3
Conditions and results for the reductive decarbonylation of precursor **16**

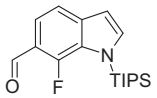
Conditions	Equivalents of $Rh(PPh_3)_3Cl$	Time (min)	Conversion (%)	RCY (%)
CH, 150 °C	2	20	22 ± 8	15 ± 6
CH, 150 °C	3	20	65 ± 9	45 ± 8
CH, 150 °C	4	20	45 ± 6	35 ± 3
MH, 100 W	1	2	>99	58 ± 11
MH, 100 W	2	2	>99	69 ± 9
MH, 100 W	3	2	>99	75 ± 7
MH, 100 W	4	2	>99	78 ± 6

CH: conventional heating; MH: microwave assisted heating; Each experiment was carried out at least in triplicate.

Table 4
k'-Values of the labeled compounds analyzed by radio-HPLC

Compound	HPLC System	k'
[^{18}F]1b	A	5.18
[^{18}F]2b	A	5.26
[^{18}F]3b	A	5.38
[^{18}F]4b	A	6.60
[^{18}F]16	A	14.68
[^{18}F]17	A	5.18
[^{18}F]18	B	3.44
[^{18}F]18	C	6.18
[^{18}F]18	D	2.99

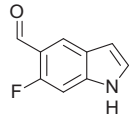
4.3.3. 1-Triisopropylsilyl-7-fluoro-1*H*-indol-5-carbaldehyd (3f)



Analogously prepared as the aldehyde **1f**, but starting from 7-fluoro-1-(triisopropylsilyl)-1*H*-indole giving the desired product as colorless oil in 63% yield.

^{1}H NMR (DMSO-d_6) δ 10.32 (s, 1H), 7.71 (d, 1H, ^4J = 2.6 Hz), 7.52 (dd, 1H, ^3J = 8.2 Hz, ^3J = 12.6 Hz), 7.51 (d, 1H, ^3J = 7.1 Hz), 6.82 (s, 1H), 1.69 (sept, 3H, ^3J = 7.2 Hz), 1.07 (d, 18H, ^3J = 7.5 Hz); ^{13}C NMR (DMSO-d_6) δ 187.5 (d, $^3J_{CF}$ = 8.3 Hz), 153.1 (d, $^1J_{CF}$ = 257 Hz), 140.9 (d, $^3J_{CF}$ = 8 Hz), 138.4, 126.9 ($^2J_{CF}$ = 9 Hz), 119.6, 117.4, 106.8, 18.3(6C), 13.1 (3C) ($^5J_{CF}$ = 5 Hz); ^{19}F NMR (DMSO-d_6) δ −133.15; HRMS: $C_{18}H_{26}FNOSi$ [M+H]$^+$ calcd 320.1840; found: 320.1840; elemental analysis calcd for $C_{18}H_{26}FNOSi$: C, 67.67; H, 8.20; N, 4.38; found: C, 67.42; H, 8.24; N, 4.35.

4.3.4. 6-Fluoro-1*H*-indole-5-carbaldehyde (1a)

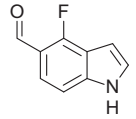


4.1 mL of a 1.0 M solution of TBAF in THF were added to a solution of 1.3 g (4.0 mmol) of 1-triisopropylsilyl-6-fluoro-1*H*-indole-5-carbaldehyde (**1f**) in 5 mL THF. The reaction mixture was stirred for 5 min at room temperature, quenched by the addition of water and extracted repeatedly with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed in vacuo. Purification by column chromatography (PE/EA = 3:2) delivered 560 mg (3.4 mmol, 86%) of the desired 6-fluoro-1*H*-indole-5-carbaldehyde (**1d**) as a colorless solid.

Mp: decomposition at 125–128 °C.

^{1}H NMR (DMSO-d_6) δ 11.60 (s, 1H), 10.16 (s, 1H), 8.06 (d, 1H, ^3J = 6.8 Hz), 7.47 (t, 1H, ^3J = 3.0 Hz), 7.28 (d, 1H, ^3J = 12.0 Hz), 6.61 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 188.2 (d, $^3J_{CF}$ = 5 Hz), 160.2 (d, $^1J_{CF}$ = 246 Hz), 139.7 (d, $^3J_{CF}$ = 13 Hz), 128.8 (d, $^4J_{CF}$ = 3 Hz), 124.9, 123.2 (d, $^4J_{CF}$ = 4 Hz), 117.9 (d, $^3J_{CF}$ = 11 Hz), 103.7, 98.4 (d, $^2J_{CF}$ = 25 Hz); ^{19}F NMR (DMSO-d_6) δ −130.24; HRMS: C_9H_6FNO [M+H]$^+$ calcd 164.0506; found: 164.0506; elemental analysis calcd for C_9H_6FNO: C, 66.26; H, 3.71; N, 8.59; found: C, 65.80; H, 3.75; N, 8.55.

4.3.5. 4-Fluoro-1*H*-indole-5-carbaldehyde (2a)

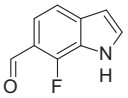


Analogously prepared as compound **1a**, while starting from 1-triisopropylsilyl-4-fluoro-1*H*-indol-5-carbaldehyd (**2f**); colorless solid; yield 89%.

Mp: decomposition at 61–67 °C.

^{1}H NMR (DMSO-d_6) δ 11.89 (s, 1H), 10.27 (s, 1H), 7.49 (t, 2H, ^3J = 6.8 Hz), 7.33 (d, 1H, ^3J = 8.4 Hz), 6.68 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 187.2 (d, $^3J_{CF}$ = 7 Hz), 159.5 (d, $^1J_{CF}$ = 26 Hz), 142.8 (d, $^2J_{CF}$ = 13 Hz), 128.2, 120.5, 116.2 (d, $^2J_{CF}$ = 21 Hz), 115.2 (d, $^3J_{CF}$ = 5 Hz), 109.4 (d, $^4J_{CF}$ = 3 Hz), 99.33; ^{19}F NMR (DMSO-d_6) δ −129,01; HRMS: C_9H_6FNO [M+H]$^+$ calcd 164.0506; found: 164.0506; elemental analysis calcd for C_9H_6FNO: C, 66.26; H, 3.71; N, 8.59; found: C, 65.76; H, 3.73; N, 8.54.

4.3.6. 7-Fluoro-1*H*-indole-6-carbaldehyde (3a)

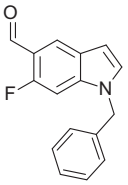


Analogously prepared as aldehyde **1a**, but starting from 1-triisopropylsilyl-7-fluoro-1*H*-indol-5-carbaldehyd (**3f**) giving the desired product as a colorless solid in 88% yield.

Mp: 132 °C.

^{1}H NMR (DMSO-d_6) δ 10.28 (s, 1H), 7.67–7.34 (m, 2H), 7.41–7.37 (m, 1H), 6.59 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 187.3 (d, $^3J_{CF}$ = 7 Hz), 152.7 (d, $^1J_{CF}$ = 259 Hz), 137.0 (d, $^3J_{CF}$ = 8 Hz), 131.6, 123.2 (d, $^2J_{CF}$ = 11 Hz), 117.9, 117.0 (d, $^4J_{CF}$ = 3 Hz), 116.5 (d, $^4J_{CF}$ = 3 Hz), 103.7 (d, $^4J_{CF}$ = 1 Hz); ^{19}F NMR (DMSO-d_6) δ −140.48; HRMS: C_9H_6FNO [M+H]$^+$ calcd 164.0506; found: 164.0505; elemental analysis calcd for C_9H_6FNO: C, 66.26; H, 3.71; N, 8.59; found: C, 65.89; H, 3.75; N, 8.62.

4.3.7. 1-Benzyl-6-fluoro-1*H*-indole-5-carbaldehyde (1b)

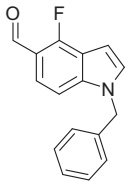


A solution of 270 mg (1.7 mmol) of 6-fluoro-1*H*-indole-5-carbaldehyde (**1a**) in 5 mL DMF was cooled to 0 °C, and 100 mg (2.5 mmol) of a 60% dispersion of NaH in mineral oil were added. The resulting solution was stirred for 20 min at 0 °C before 296 μL (2.5 mmol) benzyl bromide were added. Then, the reaction mixture was warmed to room temperature and stirred for 12 h. Water was added, followed by repeated extraction with Et_2O. The combined organic layers were dried over Na_2SO_4, and the solvent was evaporated in vacuo. Purification by column chromatography gave 371 mg (1.46 mmol, 86%) of 1-benzyl-6-fluoro-1*H*-indole-5-carbaldehyde (**1e**) as a colorless solid.

Mp: 100–101 °C.

^{1}H NMR (DMSO-d_6) δ 10.17 (s, 1H), 8.08 (d, 1H, ^3J = 6.8 Hz), 7.63 (d, 1H, $^4J_{CF}$ = 3.1 Hz), 7.54 (d, 1H, $^3J_{CF}$ = 12.5 Hz), 7.32–7.22 (m, 5H), 5.43 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 188.1 (d, $^3J_{CF}$ = 5 Hz), 160.3 (d, $^1J_{CF}$ = 246 Hz), 139.6 (d, $^2J_{CF}$ = 13 Hz), 137.9, 132.7 (d, $^4J_{CF}$ = 3 Hz), 129.1, 128.1(2C), 127.6(2C), 125.3, 123.6 (d, $^4J_{CF}$ = 4 Hz), 118.0 (d, $^3J_{CF}$ = 11 Hz), 104.1, 97.7 (d, $^2J_{CF}$ = 26 Hz), 49.8; ^{19}F NMR (DMSO-d_6) δ −128.90; HRMS: $C_{16}H_{12}FNO$ [M+H]$^+$ calcd 254.0976; found: 254.0975; elemental analysis calcd for $C_{16}H_{12}FNO$: C, 75.88; H, 4.78; N, 5.53; found: C, 75.27; H, 4.86; N, 5.27.

4.3.8. 1-Benzyl-4-fluoro-1*H*-indole-5-carbaldehyd (2b)

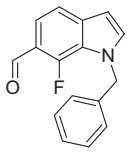


Analogously prepared as the aldehyde **1b**, while starting from 4-fluoro-1*H*-indole-6-carbaldehyde (**2a**) giving the desired product as a colorless solid in 88% yield.

Mp: 96–97 °C.

^{1}H NMR (DMSO-d_6) δ 10.26 (s, 1H), 7.68 (d, 1H, ^4J = 3.2 Hz), 7.49 (dd, 1H, ^3J = 8.8 Hz, ^3J = 8.4 Hz), 7.30–7.20 (m, 5H), 6.75 (d, 1H, ^4J = 2.8 Hz), 5.47 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 187.2 (d, $^3J_{CF}$ = 6 Hz), 159.2 (d, $^1J_{CF}$ = 260 Hz), 142.3 (d, $^3J_{CF}$ = 13 Hz), 137.8, 132.0 (2C), 129.0 (d, $^2J_{CF}$ = 21 Hz), 128.1 (d, $^3J_{CF}$ = 8 Hz), 127.5 (2C), 116.8 (d, $^2J_{CF}$ = 21 Hz), 115.4 (d, $^3J_{CF}$ = 5 Hz), 108.2 (d, $^4J_{CF}$ = 3 Hz), 99.6, 49.9; ^{19}F NMR (DMSO-d_6) δ −128.90; HRMS: $C_{16}H_{12}FNO$ [M+H]$^+$ calcd 254.0976; found: 254.0975; elemental analysis calcd for $C_{16}H_{12}FNO$: C, 75.88; H, 4.78; N, 5.53; found: C, 75.27; H, 4.86; N, 5.27.

4.3.9. 1-Benzyl-7-fluoro-1*H*-indole-6-carbaldehyd (3b)

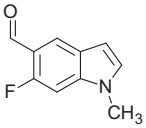


Analogously prepared as the aldehyde **1b**, but starting from 7-fluoro-1*H*-indole-6-carbaldehyde (**3a**) giving the desired product as a colorless solid in 82% yield.

Mp: 90–91 °C.

^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1H), 7.52 (dd, 1H, ^3J = 5.9 Hz, ^4J = 2.1 Hz), 7.39 (d, 1H, ^3J = 8.3 Hz), 7.33–7.24 (m, 4H), 7.13 (d, 2H, ^3J = 7.0 Hz), 6.58 (s, 1H), 5.51 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 187.0 (d, $^3J_{CF}$ = 9 Hz), 153.7 (d, $^1J_{CF}$ = 259 Hz), 137.8 (d, $^3J_{CF}$ = 7 Hz), 137,4, 133.9, 128.9, 128(2C), 126.7(2C), 123 (d, $^3J_{CF}$ = 8 Hz), 118.4, 117.6 (d, $^4J_{CF}$ = 5 Hz), 117.1 (d, $^4J_{CF}$ = 3 Hz), 103.7 (d, $^4J_{CF}$ = 1 Hz), 52.7 (d, $^4J_{CF}$ = 6 Hz); ^{19}F NMR ($CDCl_3$) δ −148.05; HRMS: $C_{16}H_{12}FNO$ [M+H]$^+$ calcd 254.0976; found: 254.0976; elemental analysis calcd for $C_{16}H_{12}FNO$: C, 75.88; H, 4.78; N, 5.53; found: C, 75.57; H, 4.80; N, 5.49.

4.3.10. 1-Methyl-6-fluoro-1*H*-indole-5-carbaldehyde (1c)

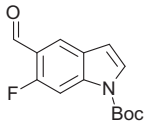


A solution of 80 mg (0.5 mmol) of 6-fluoro-1*H*-indole-5-carbaldehyde (**1a**) in 5 mL DMF was cooled to 0 °C, and 30 mg (0.75 mmol) of a 60% dispersion of NaH in mineral oil were added. The resulting solution was allowed to stir for 20 min at 0 °C, before 100 μL (1.6 mmol) iodomethane were added. The reaction mixture was allowed to reach room temperature and then stirred for further 12 h. Water was added, followed by repeated extraction with Et_2O. The combined organic layers were dried over Na_2SO_4, and the solvent was evaporated in vacuo. Purification by column chromatography gave 52 mg (0.29 mmol, 58%) of 1-methyl-6-fluoro-1*H*-indole-5-carbaldehyde (**1c**) as an off-white solid.

Mp: 108–110 °C.

^{1}H NMR (DMSO-d_6) δ 10.21 (s, 1H), 8.09 (d, 1H, ^3J = 6.8 Hz), 7.52–7.46 (m, 2H), 6.67 (dd, 1H, ^4J = 3.2 Hz, ^5J = 0.9 Hz), 3.82 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 188.2 (d, $^3J_{CF}$ = 5 Hz), 160.3 (d, $^1J_{CF}$ = 246 Hz), 140.2 (d, $^2J_{CF}$ = 13 Hz), 133.1 (d, $^4J_{CF}$ = 3 Hz), 125.1 (d, $^5J_{CF}$ = 1 Hz), 123.5 (d, $^3J_{CF}$ = 4 Hz), 117.8 (d, $^3J_{CF}$ = 11 Hz), 103.4, 97.3 (dd, $^2J_{CF}$ = 25, 33 Hz); ^{19}F NMR (DMSO-d_6) δ −129.49; HRMS: $C_{10}H_8FNO$ [M+Na]$^+$ calcd 200.0482; found: 200.0482; elemental analysis calcd for $C_{10}H_8FNO$: C, 67.79; H, 4.55; N, 7.91; found: C, 66.42; H, 4.61; N, 7.61.

4.3.11. 1-Boc-6-fluoro-1*H*-indole-5-carbaldehyde (1d), according to de Koning et al.[14]

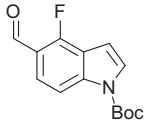


7.3 mg (0.06 mmol) DMAP and 152 mg (0.7 mmol) Boc_2O were added to a solution of 100 mg (0.61 mmol) of 6-fluoro-1*H*-indole-5-carbaldehyde (**1a**) in 7 mL THF. The resulting solution was stirred for 4 h at room temperature. Water was added, followed by repeated extraction with Et_2O. The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuo. Purification by column chromatography gave 136 mg (0.48 mmol, 72%) of 1-Boc-6-fluoro-1*H*-indole-5-carbaldehyde (**1d**) as a colorless solid.

Mp: 91–93 °C.

^{1}H NMR (DMSO-d_6) δ 10.38 (s, 1H), 8.05 (d, 1H, ^3J = 6.7 Hz), 7.95 (d, 1H, ^3J = 11.2 Hz), 7.62 (d, 1H, ^4J = 3.6 Hz), 6.63 (d, 1H, ^4J = 3.8 Hz), 1.68 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 187.4 (d, $^3J_{CF}$ = 6.8 Hz), 162.6 (d, $^1J_{CF}$ = 249.8 Hz), 149, 139.1 (d, $^3J_{CF}$ = 13.2 Hz), 128.0 (d, $^4J_{CF}$ = 3.1 Hz), 127.0, 121.3 (d, $^4J_{CF}$ = 3.1 Hz), 120.8 (d, $^3J_{CF}$ = 10.1 Hz), 107.8, 102.9 (d, $^2J_{CF}$ = 28.1 Hz), 85.0, 28.1(3C); ^{19}F NMR (DMSO-d_6) δ −126.44; HRMS: $C_{16}H_{12}FNO_3S$ [M+Na]$^+$ calcd 286.0849; found: 286.0849; elemental analysis calcd for $C_{16}H_{12}FNO_3S$: C, 63.87; H, 5.36; N, 5.32; found: C, 63.71; H, 5.38; N, 5.23.

4.3.12. 1-Boc-4-fluoro-1*H*-indole-5-carbaldehyde (2d), according to Koning et al.[14]

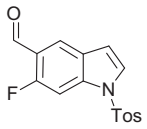


Analogously prepared as the aldehyde **1d**, but starting from 7-fluoro-1*H*-indole-6-carbaldehyde (**3a**), giving the desired product as a colorless solid in 82% yield.

Mp: 112–114 °C.

^{1}H NMR ($CDCl_3$) δ 10.48 (s, 1H), 8.06 (d, ^3J = 8.7 Hz, 1H), 7.82 (dd, ^3J = 8.7 Hz, ^3J = 6.5 Hz, 1H), 7.67 (d, ^4J = 3.8 Hz, 1H), 6.81 (d, ^4J = 3.8 Hz, 1H), 1.73 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 186.9 (d, $^3J_{CF}$ = 7 Hz), 158.7 (d, $^1J_{CF}$ = 247), 149.8, 141.6, 127.3, 123.6 (d, $^4J_{CF}$ = 2 Hz), 119.3 (d, $^2J_{CF}$ = 21 Hz), 118.2 (d, $^3J_{CF}$ = 6 Hz), 111.9 (d, $^4J_{CF}$ = 4 Hz), 103.4, 85.2, 28.1(3C); ^{19}F NMR ($CDCl_3$) δ −129.58; HRMS: $C_{16}H_{12}FNO_3S$ [M+Na]$^+$ calcd 286.0849; found: 286.0850; elemental analysis calcd for $C_{16}H_{12}FNO_3S$: C, 62.77; H, 5.36; N, 5.32; found: C, 63.31; H, 5.22; N, 5.21.

4.3.13. 1-Tosyl-6-fluoro-1*H*-indole-5-carbaldehyde (1e), according to Konas et al.[15]

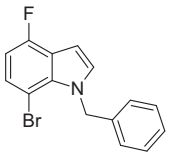


A solution of 150 mg (0.92 mmol) of 6-fluoro-1*H*-indole-5-carbaldehyde (**1a**) in 5 mL DMF was cooled to 0 °C, and 55 mg (1.38 mmol) of a 60% dispersion of NaH in mineral oil were added. The resulting solution was allowed to stir for 20 min at 0 °C, before 263 mg (1.38 mmol) of tosyl chloride were added. The reaction mixture was allowed to reach room temperature and stirred for further 12 h. Water was added, followed by repeated extraction with Et_2O. The combined organic layers were dried over Na_2SO_4, and the solvent was evaporated in vacuo. Purification by column chromatography gave 239 mg (0.75 mmol, 82%) of 1-tosyl-6-fluoro-1*H*-indole-5-carbaldehyde (**1e**) as an off-white solid.

Mp: 130–132 °C.

^{1}H NMR (DMSO-d_6) δ 10.15 (s, 1H), 8.06 (d, 1H, ^3J = 6.8 Hz), 7.94 (d, 2H, ^3J = 8.4 Hz), 7.90 (d, 1H, ^3J = 3.5 Hz), 7.81 (d, 1H, ^3J = 11.4 Hz), 7.37 (d, 1H, ^3J = 8.0 Hz), 6.93 (d, 1H, ^3J = 3.4 Hz), 2.27 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 187.9 (d, $^3J_{CF}$ = 5 Hz), 161.4 (d, $^1J_{CF}$ = 251 Hz), 146.6(2C), 137.6 (d, $^3J_{CF}$ = 13 Hz), 134.1, 130.9, 129.4 (d, $^4J_{CF}$ = 4 Hz), 127.4 (d, $^4J_{CF}$ = 4 Hz), 127.4(2C), 123.7 (d, $^4J_{CF}$ = 4 Hz), 121.0 (d, $^3J_{CF}$ = 11 Hz), 110.2, 101.4 (d, $^2J_{CF}$ = 27 Hz), 21.5; ^{19}F NMR (DMSO-d_6) δ −124.12; HRMS: $C_{16}H_{12}FNO_3S$ [M+H]$^+$ calcd 318.0595; found: 318.0594; elemental analysis calcd for $C_{16}H_{12}FNO_3S$: C, 60.56; H, 3.81; N, 4.41; found: C, 60.35; H, 3.95; N, 4.46.

4.3.14. 1-Benzyl-7-bromo-4-fluoro-1*H*-indole (5)

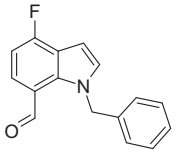


A solution of 612 mg (2.9 mmol) of 7-bromo-4-fluoro-1*H*-indole in dry DMF was cooled to 0 °C, and 173 mg (4.3 mmol) of a 60% dispersion of NaH in mineral oil were added. After 20 min 510 μL (735 mg, 4.3 mmol) benzyl bromide were added and the reaction mixture was allowed to warm up to room temperature and stirred overnight. Water was added, and the aqueous phase was repeatedly extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by column chromatography (100% PE R_f = 0.29) yielding 711 mg (2.4 mmol, 81%) of 1-benzyl-7-bromo-4-fluoro-1*H*-indole (**4d**) as colorless oil.

Mp: 65 °C.

^{1}H NMR (DMSO-d_6) δ 7.33–7.25 (m, 4H), 7.12–7.03 (m, 3H), 6.71 (dd, 2H, ^3J = 10.5 Hz, ^3J = 9.4 Hz), 5.87 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 159.9 (d, $^1J_{CF}$ = 243 Hz), 139.7, 134.4 (d, $^3J_{CF}$ = 11 Hz), 133.6, 129.0, 127.6(2C), 127.1 (d, $^3J_{CF}$ = 8), 126.2(2C), 120.4 (d, $^2J_{CF}$ = 24 Hz), 106.4 (d, $^2J_{CF}$ = 20 Hz), 98.0 (d, $^4J_{CF}$ = 3), 98.1, 50.8; ^{19}F NMR (DMSO-d_6) δ −124.11; E.A.: calcd C, 63.87; H, 5.36; N, 5.32; found: C, 63.71; H, 5.38; N, 5.23.

4.3.15. 1-Benzyl-4-fluoro-1*H*-indole-7-carbaldehyde (4b)

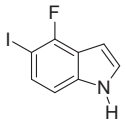


A solution of 420 mg (1.4 mmol) of **4d** in 5 mL THF was cooled to −78 °C, and 560 μL (1.4 mmol) of a 2.5 M solution of *n*-BuLi in hexane were added. The mixture was stirred for 30 min, before 500 μL DMF were added, followed by warming to room temperature and stirring for 3 h. Water was added, and the aqueous phase was repeatedly extracted with Et_2O. The combined organic fractions were dried over Na_2SO_4, and the solvent was evaporated in vacuo. The crude product was purified by column chromatography yielding 134 mg (0.5 mmol, 39%) of 1-benzyl-4-fluoro-1*H*-indole-7-carbaldehyde (**4e**) as a colorless solid.

Mp: 75–77 °C.

^{1}H NMR (DMSO-d_6) δ 10.05 (s, 1H), 7.81 (dd, ^3J = 8.4 Hz, ^4J = 5.7 Hz, 1H), 7.71 (d, ^3J = 3.2 Hz, 1H), 7.21–7.10 (m, 6H), 6.98 (d, $^3J_{FH}$ = 21.0 Hz, 1H), 6.90 (d, ^4J = 1.3 Hz), 6.82 (d, ^3J = 3.3 Hz), 5.97 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 190.3, 159.9 (d, $^1J_{CF}$ = 154 Hz), 138.6, 136.2 (d, $^3J_{CF}$ = 13 Hz), 132.1, 132.1 (d, $^3J_{CF}$ = 10 Hz), 129.1, 127.7(2C), 126.5(2C), 120.5, 105.4 (d, $^2J_{CF}$ = 20 Hz), 98.9, 53.7, 28.5; ^{19}F NMR (DMSO-d_6) δ −111.47; elemental analysis calcd for $C_{16}H_{12}FNO$: C, 63.87; H, 5.36; N, 5.32; found: C, 63.71; H, 5.38; N, 5.23.

4.3.16. 4-Fluoro-5-iodo-1*H*-indole (8)



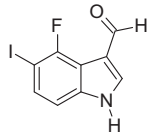
sec-BuLi in hexane (20 ml, 28 mmol, 1.4 M) was added to solution of 8.0 g (27.5 mmol) 4-fluoro-1-triisopropylsilyl-1*H*-indole (**7**) and 5.8 mL N,N,N′,N″,N″-pentamethyldiethylenetriamine (4.9 g, 27.5 mmol) in 40 mL THF at −78 °C. The solution was stirred at this temperature for 6 h before 7.8 g (27.5 mmol) of diiodoethane were added. The reaction mixture was slowly warmed to room temperature and stirred overnight. Water was added and the aqueous phase was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product, a brownish oil, was dissolved in 30 mL THF and 7.1 g (27.1 mmol) TBAF·H_2O were added. The mixture was stirred for 30 min at room temperature before water was added. The aqueous phase was extracted with Et_2O and the organic layer dried over Na_2SO_4, filtered and the solvent evaporated in vacuo. The crude residue was purified by flash chromatography (PE/EA = 4:1;

R_f = 0.45) giving 4.7 g (17.9 mmol, 65%) of the desired product as a light green solid.

Mp: 58–60 °C.

^{1}H NMR ($CDCl_3$) δ 8.30 (broad s, 1H), 7.42 (dd, ^3J = 8.4 Hz, ^4J = 6.0 Hz, 1H), 7.14 (t, ^3J = 2.7 Hz, 1H), 6.99 (d, ^3J = 8.5 Hz, 1H), 6.61 (t, ^3J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 155.2 (d, $^1J_{CF}$ = 245 Hz), 138.3 (d, $^3J_{CF}$ = 11 Hz), 131.1, 124.7, 117.9 (d, $^2J_{CF}$ = 24 Hz), 109.2 (d, $^4J_{CF}$ = 4 Hz), 98.8 (d, $^3J_{CF}$ = 6 Hz), 68.3 (d, $^2J_{CF}$ = 23 Hz); ^{19}F NMR ($CDCl_3$) δ −101.74; elemental analysis calcd for C_8H_5FIN: C, 36.81; H, 1.93; N, 5.37; found: C, 37.64 H, 2.17; N, 5.14.

4.3.17. 4-Fluoro-5-iodo-1*H*-indole-3-carbaldehyde (9)

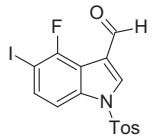


5.7 mL $POCl_3$ (35.5 mmol) were added to 16.0 mL DMF at 0 °C. The mixture was stirred at this temperature for 15 min before 4.1 g (15.6 mmol) of 4-fluoro-5-iodo-*1H*-indole (**7**) were added in 37 mL of DMF. The solution was warmed to room temperature and stirred until it became an opaque paste (approximately 1 h). It was added 10% $NaOH_{aq}$ until the pH of the solution was greater than 10. The suspension was heated to reflux for 10 min before it was cooled to 0 °C. The precipitate was filtered and washed with water and Et_2O. After drying under reduced pressure at 50 °C, the desired product was obtained as an off-white solid (89%, 4.03 g, 13.9 mmol).

Mp: decomposition at 246–249 °C.

^{1}H NMR (DMSO-d_6) δ 12.60 (s, 1H), 10.02 (d, ^4J = 3.3 Hz, 1H), 8.30 (d, ^4J = 2.9 Hz, 1H), 7.60 (dd, ^3J = 8.6 Hz, ^3J = 5.8 Hz, 1H), 7.23 (d, ^3J = 8.5 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 184.1 (d, $^4J_{CF}$ = 2 Hz), 155.1 (d, $^1J_{CF}$ = 245 Hz), 140.1 (d, $^3J_{CF}$ = 11 Hz), 136.8, 132,8, 116.8 (d, $^3J_{CF}$ = 7 Hz), 113.8 (d, $^2J_{CF}$ = 25 Hz), 111.7 (d, $^4J_{CF}$ = 4 Hz), 73.2 (d, $^2J_{CF}$ = 24 Hz); ^{19}F NMR (DMSO-d_6) δ −92.94; HRMS: C_9H_5FINO $[M-H]^+$ calcd 289.9473; found: 289.9477; elemental analysis calcd for C_9H_5FINO: C, 37.40; H, 1.74; N, 4.85; found:: C, 37.86; H, 1.84; N, 5.22.

4.3.18. 4-Fluoro-5-iodo-1-tosyl-1*H*-indole-3-carbaldehyde (10)

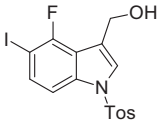


A solution of 3.8 g (13.3 mmol) 4-fluoro-5-iodo-1*H*-indole-3-carbaldehyde (**8**) in 40 mL of THF was cooled to 0 °C and 480 mg (20 mmol) of a 60% dispersion of NaH in mineral oil was added. The resulting solution was stirred for 20 min at 0 °C. Subsequently, 3.8 g (20 mmol) of Tos-Cl was added. The reaction mixture was warmed to room temperature and stirred for another 2 h. Water was added and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed in vacuo. Purification by flash chromatography (PE/EA = 4:1 R_f = 0.38) gave the desired product as a colorless solid (74%, 4.4 g, 9.8 mmol).

Mp: decomposition at 148–153 °C.

^{1}H NMR ($CDCl_3$) δ 10.02 (s, 1H), 8.65 (d, 1H, ^3J = 6.2 Hz), 8.19 (s, 1H), 7.83 (d, 2H, ^3J = 8.1 Hz), 7.69 (d, 1H, ^3J = 8.3 Hz), 7.32 (d, 2H, ^3J = 8.1 Hz), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 184.7, 159.5 (d, $^1J_{CF}$ = 242 Hz), 146.6(2C), 136.5 (d, $^4J_{CF}$ = 3 Hz), 135.3 ($^3J_{CF}$ = 11.2 Hz), 133.7(2C), 132.6 ($^4J_{CF}$ = 2.8 Hz), 130.5, 127.1, 124.2 (d, $^4J_{CF}$ = 2 Hz), 120.9 (d, $^5J_{CF}$ = 1 Hz), 100.7 (d, $^2J_{CF}$ = 31 Hz), 78.4 (d, $^2J_{CF}$ = 27 Hz), 21.6; ^{19}F NMR ($CDCl_3$) δ −89.70; HRMS: $C_{16}H_{11}FINO_3S$ $[M+H]^+$ calcd 443.9561; found: 443.9561; elemental analysis calcd for $C_{16}H_{11}FINO_3S$: C, 43.36; H, 2.50; N, 3.16; found: C, 43.05; H, 2.59; N, 3.11.

4.3.19. (4-Fluoro-5-iodo-1-tosyl-1*H*-indol-3-yl)methanol (11)

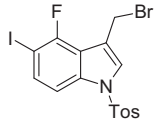


541 mg (14.3 mmol) $NaBH_4$ were added to a solution of 4.2 g (9.5 mmol) of **9** in 150 mL THF/EtOH (2:1) at 0 °C. The resulting solution was warmed to room temperature and stirred for 30 min. Saturated NH_4Cl_{aq} was added and the mixture was extracted with Et_2O. The combined organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the desired product as a colorless solid (97%, 4.1 g, 9.2 mmol).

Mp: 131–132 °C.

^{1}H NMR (DMSO-d_6) δ 7.87 (d, ^3J = 8.4 Hz, 2H), 7.70 (dd, ^3J = 8.6 Hz, ^3J = 6.0 Hz, 1H), 7.63 (s, 1H), 7.61 (d, ^3J = 8.7 Hz, 1H), 7.40 (d, ^3J = 8.2 Hz, 2H), 5.26 (t, ^3J = 5.4 Hz, 2H), 4.63 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 154.6 (d, $^1J_{CF}$ = 245 Hz), 145.9 (2C), 136.7 (d, $^3J_{CF}$ = 10 Hz), 134.3, 133.7(2C), 130.4, 126.8, 124.4, 121.7 (d, $^3J_{CF}$ = 5 Hz), 118.0 (d, $^2J_{CF}$ = 23 Hz), 111.6 (d, $^4J_{CF}$ = 4 Hz), 74.9 (d, $^2J_{CF}$ = 24 Hz), 55.5 (d, $^4J_{CF}$ = 2 Hz), 21.0; ^{19}F NMR (DMSO-d_6) δ −100.88; HRMS: $C_{16}H_{13}FINO_3S$ $[M+Na]^+$ calcd 467.9537; found: 467.9539; elemental analysis calcd for $C_{16}H_{13}FINO_3S$: C, 43.16; H, 2.94; N, 3.15; found: C, 43.40; H, 3.03; N, 3.15.

4.3.20. (3-(Bromomethyl)-4-fluoro-5-iodo-1-tosyl)-1*H*-indole (12)



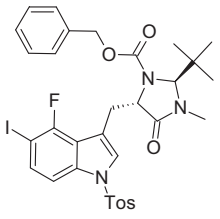
A solution of the alcohol **10** (2.0 g, 4.5 mmol) was cooled to 0 °C before PPh_3 (1.3 g, 5.0 mmol) and CBr_4 (1.7 g, 5.0 mmol) were added subsequently. The mixture was stirred at 0 °C and the progress of reaction monitored by TLC (PE/EA = 4:1, R_f = 0.72). After approximately 30 min the reaction was finished and the solvent was partially removed in vacuo at room temperature. The oily residue was applied to a silica column eluted with a mixture of PE/EE (4:1). Removal of the solvents under reduced pressure gave the desired product as a colorless solid (63%, 1.4 g, 2.8 mmol).

Mp: decomposition at 166–168 °C.

^{1}H NMR (DMSO-d_6) δ 8.08 (s, 1H), 7.88 (d, ^3J = 8.4 Hz, 2H), 7.75 (dd, ^3J = 8.7 Hz, ^3J = 6.0 Hz, 1H), 7.62 (d. ^3J = 8.8 Hz, 1H), 7.42 (d, ^3J = 8.2 Hz, 2H), 4.82 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 154.3 (d, $^1J_{CF}$ = 247 Hz), 146.2(2C), 136.3 (d, $^3J_{CF}$ = 9 Hz), 134.9, 133.3, 130.4, 126.7(2C), 124.3, 117.4 (d, $^2J_{CF}$ = 23 Hz), 117.0 (d, $^4J_{CF}$ = 4 Hz), 111.6 (d, $^4J_{CF}$ = 4 Hz), 75.6 (d, $^2J_{CF}$ = 24 Hz), 55.4 (d,

$^4J_{CF}$ = 2 Hz), 20.9; ^{19}F NMR (DMSO-d_6) δ −102.13; HRMS: $C_{16}H_{12}BrFINO_2S$ $[M-Br]^-$ calcd 427.9617; found: 427.9636; elemental analysis calcd for $C_{16}H_{12}BrFINO_2S$: C, 37.82; H, 2.38; N, 2.73; found: C, 38.12; H, 2.38; N, 2.64.

4.3.21. Benzyl (2*S*,5*S*)-2-*tert*-butyl-5-[(4-fluoro-5-iodo-1-tosyl-1*H*-indol-3-yl)methyl]-3-methyl-4-oxoimidazolidine-1-carboxylate (13)

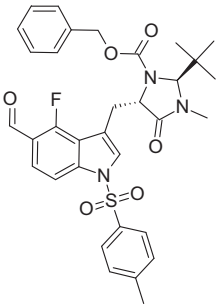


n-BuLi in hexane (1.24 mL, 3.1 mmol) was added to a solution of diisopropylamine (435 μL, 3.1 mmol) in 3 mL of THF at −78 °C. The resulting solution was stirred for 30 min before a solution of Z-BMI (772 mg, 2.7 mmol) in 3 mL of THF was added. After another 30 min of stirring at -78 °C a solution of bromide **11** in 4.5 mL THF was added. The reaction was slowly warmed to room temperature and stirred overnight. The reaction was quenched with saturated NH_4Cl_{aq}. Water was added and the aqueous phase was extracted with diethyl ether. The combined organic extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (PE/EA = 7:3; R_f = 0.4) gave the desired product as a colorless solid (73%, 1.4 g, 2.0 mmol).

Mp: 76–78 °C.

^{1}H NMR ($CDCl_3$) δ 7.73 (broad s, 2H), 7.52 (dd, ^3J = 8.7 Hz, ^4J = 5.7 Hz, 1H), 7.47 (d, ^3J = 8.6 Hz, 1H), 7.25 (broad s, 2H), 7.15–6.60 (broad m, 6H), 5.18 (broad s, 1H), 4.84 (d, ^4J = 6.1 Hz, 2H), 4.38 (s, 1H), 3.76 (broad s, 1H), 3.40 (d, ^3J = 14.4 Hz, 1H), 3.06 (s, 3H), 2.32 (s, 3H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.1, 155.4 (d, $^1J_{CF}$ = 249 Hz), 145.5(2C), 136.5 (d, $^3J_{CF}$ = 9 Hz), 134.9(2C), 134.7, 134.2, 130.1, 128.5(2C), 128.3(2C), 128.3, 127.1, 122.2, 120.2 (d, $^2J_{CF}$ = 21 Hz), 115.0 (d, $^4J_{CF}$ = 3 Hz), 111.2 (d, $^4J_{CF}$ = 4 Hz), 81.2, 73.8 (d, $^2J_{CF}$ = 24 Hz), 67.6, 60.4, 58.3, 40.9, 32.1, 26.3, 21.6, 21.1(3C); ^{19}F NMR ($CDCl_3$) δ −100.94; HRMS: $C_{33}H_{32}FIN_3O_5S$ $[M+Na]^+$ calculated 740.1061; found: 740.1053; elemental analysis calcd for $C_{33}H_{32}FIN_3O_5S$: C, 53.56; H, 4.64; N, 5.86; found: C, 53.83; H, 4.84; N, 5.60, $[\alpha]_D^{20}$ +57 (c 10mg/mL, MeOH).

4.3.22. Benzyl (2*S*,5*S*)-2-*tert*-butyl-5-[(4-fluoro-5-formyl-1-tosyl-1*H*-indol-3-yl)methyl]-3-methyl-4-oxoimidazolidine-1-carboxylate (14)

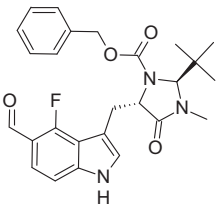


1.7 mL of a 2.9 M solution of isopropyl magnesium bromide in THF was added to a solution of the iodide **12** (1.8 g, 2.5 mmol) in 5 mL of THF at 0 °C. The resulting solution was stirred for 1 h at 0 °C before 770 μL of DMF (10 mmol) were added. The reaction was warmed to room temperature and stirred for another 3 h. Saturated NH_4Cl_{aq} was added, and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. Flash chromatography (PE/EA = 7:3, R_f = 0.27) of the crude mixture gave the desired product as a colorless solid (73%, 1.1 g, 1.8 mmol).

Mp: 73–75 °C.

^{1}H NMR ($CDCl_3$) δ 10.34 (s, 1H), 7.81–7.71 (m, 4H), 7.31 (d, ^3J = 7.7 Hz, 2H), 7.02–6.87 (m, 6H), 5.16 (s, 1H), 4.93 (s, 2H), 4.45 (s, 1H), 4.16 (d, ^3J = 7.1 Hz, 1H), 3.53 (d, ^4J = 17.2 Hz, 1H), 3.05 (s, 3H), 2.37 (s, 3H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 186.6 (d, $^3J_{CF}$ = 8 Hz), 171.0, 160.0 (d, $^1J_{CF}$ = 264 Hz), 145.8(2C), 140.0 (d, $^3J_{CF}$ = 11 Hz), 134.9, 134.6(2C), 130.2, 128.4(2C), 128.3(2C), 127.2, 123.9, 119.5 (d, $^2J_{CF}$ = 17 Hz), 118.8 ($^4J_{CF}$ = 5 Hz), 116.0, 109.9 (d, $^4J_{CF}$ = 4 Hz), 81.3, 67.6, 40.8, 32.1, 26.6, 21.3(3C); ^{19}F NMR ($CDCl_3$) δ −129.12, HRMS: $C_{33}H_{34}FN_3O_6S$ $[M+Na]^+$ calcd 642.2044; found: 642.2030, elemental analysis calcd for $C_{33}H_{34}FN_3O_6S$: C, 63.96; H, 5.53; N, 6.78; found: C, 63.91; H, 5.63; N, 6.48.

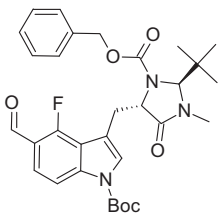
4.3.23. Benzyl (2*S*,5*S*)-2-tert-butyl-5-[(4-fluoro-5-formyl-1*H*-indol-3-yl)methyl]-3-methyl-4-oxo-imidazolidine-1-carboxylate (15)



3.5 mL of 1.0 M solution of TBAF in THF was added to a solution of 432 mg (0.7 mmol) of **13** in 10 mL THF. The resulting mixture was heated to reflux for 3 h, then cooled to room temperature and the solvent was evaporated in vacuo. Flash chromatography of the crude mixture gave the desired product as a colorless solid (42%, 140 mg, 0.3 mmol). The compound decomposed rapidly, as a result of which the data of elemental analysis were not in agreement.

^{1}H NMR (DMSO-d_6) δ 11.53 (s, 1H), 10.27 (s, 1H), 7.48 (dd, ^3J = 8.4 Hz, ^3J = 6.2 Hz, 1H), 7.27 (d, ^3J = 8.5 Hz, 1H), 7.19–7.14 (m, 3H), 7.08 (d, ^3J = 7.2 Hz, 2H), 6.72 (s, 1H), 5.19 (s, 1H), 5.00 (d, ^2J = 12.3 Hz, 1H), 4.79 (d, ^2J = 12.3 Hz, 1H), 4.50 (d, ^3J = 4.4 Hz, 1H), 3.97–3.94 (broad s, 1H), 3.38 (d, ^4J = 15.4 Hz, 1H), 2.93 (s, 3H), 0.93 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 187.2 (d, $^3J_{CF}$ = 8 Hz), 171.0, 160.8 (d, $^1J_{CF}$ = 263 Hz), 142.6 (d, $^2J_{CF}$ = 14 Hz), 136.3, 128.6(2C), 128.3(2C), 123.6, 120.5, 115.8 (d, $^2J_{CF}$ = 16 Hz), 115.2 (d, $^3J_{CF}$ = 5 Hz), 109.9, 109.2, 80.4, 66.9, 58.7, 31.8, 26.5; ^{19}F NMR (DMSO-d_6) δ −130.47; HRMS: $C_{26}H_{28}FN_3O_4$ $[M+Na]^+$ calculated 488.1956; found: 488.1992; elemental analysis calcd for $C_{26}H_{28}FN_3O_4$: C, 67.08; H, 6.06; N, 9.03; found: C, 65.20; H, 5.92; N, 8.60.

4.3.24. Benzyl (2*S*,5*S*)-2-*tert*-butyl-5-[(1-boc-4-fluoro-5-formyl-1*H*-indol-3-yl)methyl]-3-methyl-4-oxoimidazolidine-1-carboxylate (16)



60 mg (0.27 mmol) of Boc_2O was added to a solution of **14** (110 mg, 0.23 mmol) and of DMAP (3 mg, 24 μmol) in 5 mL THF. The resulting solution was stirred for 1 h at room temperature. The solvent was evaporated under reduced pressure. Purification of the crude mixture by flash chromatography yielded the desired product as a colorless solid (86%, 112 mg, 0.20 mmol).

Mp: 133–136 °C.

^{1}H NMR ($CDCl_3$) δ 10.37 (s, 1H), 7.92 (d, ^3J = 8.8 Hz, 1H), 7.74 (dd, ^3J = 8.7 Hz, ^4J = 6.5 Hz, 1H), 7.39–7.03 (m, 5H), 6.98 (s, 1H), 5.14–4.89 (m, 3H), 4.49 (d, ^4J = 1.2 Hz, 1H), 4.03 (d, ^2J = 16.8 Hz, 1H), 3.59 (d, ^2J = 17.2 Hz), 3.11 (s, 3H), 1.58 (s, 9H), 0.99 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 187.5 (d, $^3J_{CF}$ = 7 Hz), 170.9, 160.6 (d, $^1J_{CF}$ = 261 Hz), 148.5(2C), 140.5 (d, $^2J_{CF}$ = 12 Hz), 136.3, 128.3 (d, $^3J_{CF}$ = 5 Hz), 124.6(2C), 123.2, 118.8, 118.5, 118.4, 114.5 (d, $^4J_{CF}$ = 3 Hz), 111.9, 85.5, 80.8, 66.8, 58.1, 32.0, 28.0, 26.4(3C); ^{19}F NMR ($CDCl_3$) δ −130.61; HRMS $C_{31}H_{36}FN_3O_4$ $[M+Na]^+$ calcd 588.2480; found: 588.2461; elemental analysis calcd for $C_{31}H_{36}FN_3O_4$: C, 65.83; H, 6.42; N, 7.43; found: C, 66.10; H, 6.57; N, 7.26, $[\alpha]_D^{20}$ −3.1 (c 10 mg/mL, $CHCl_3$).

4.4. Radiochemistry

4.4.1. Preparation of [^{18}F]TBAF

N.c.a. [^{18}F]fluoride was produced via the ^{18}O(p,n)^{18}F nuclear reaction by bombardment of an isotopically enriched [^{18}O]water target with 17 MeV protons at the JSW cyclotron BC 1710 (INM-5, Forschungszentrum Jülich).[32] An aliquot of the aqueous [^{18}F]fluoride was added to a solution containing 150 μL of a 0.13 M tetrabutylammonium bicarbonate ($TBAHCO_3$) solution.[33] 1.0 mL of dry acetonitrile was added to the mixture. The solvent was evaporated under a stream of argon at 75 °C and 600 mbar. The azeotropic evaporation was repeated twice with each 1.0 mL of acetonitrile and followed by evacuating the vial for 5 min at 10–20 mbar.

4.4.2. General procedure for the radiosynthesis of 1-benzyl-[^{18}F]fluoro-1*H*-indoles ([^{18}F]1-4b) under conventional heating

A solution of 20 μmol of the corresponding precursor was dissolved in 1.0 mL DMF and added to a Reacti-Vial™ containing the dried residue of [^{18}F]TBAF. The reaction mixture was heated to the optimum temperature for 15 min. After labeling the solution was diluted with 10.0 mL of water and passed through a previously conditioned LiChrolut RP-18e cartridge (Merck). Thereafter, the adsorbed labeled compound was eluted with 2.0 mL acetonitrile into a second vial and the solvent subsequently evaporated. A solution containing 3 equiv of Wilkinson's catalyst in 1.0 mL benzonitrile was added, and the mixture was heated to 150 °C for 20 min.

4.4.3. General procedure for the radiosynthesis of 1-benzyl-[^{18}F]fluoro-1*H*-indoles ([^{18}F]1-4b) under microwave heating

A solution of 20 μmol of the corresponding precursor was dissolved in 1.0 mL DMF and added to a Reacti-Vial™ containing the dried residue of [^{18}F]TBAF. The reaction mixture was irradiated with 50 W microwaves during 1 min. After labeling, the solution was diluted with 10.0 mL water and passed through a previously conditioned LiChrolut RP-18e cartridge (Merck). Then, the adsorbed labeled compound was eluted with 2.0 mL acetonitrile into a second Reacti-Vial™ and the solvent subsequently evaporated. A solution containing 3 equiv of Wilkinson's catalyst in 1.0 mL benzonitrile was added, and the mixture was irradiated with 120 W microwaves during 2 min.

4.4.4. General procedure for the radiosynthesis of 4-[^{18}F]fluoro-L-tryptophan ([^{18}F]18)

Conventional heating. A solution of 8–9 μmol of the corresponding precursor was dissolved in 1.0 mL DMF and added to a Reacti-Vial™ containing the dried residue of [^{18}F]TBAF. The reaction mixture was heated to 80 °C for 15 min. After labeling, the reaction mixture was diluted with 1.0 mL acetonitrile and 9.0 mL water and passed through a previously conditioned LiChrolut RP-18e cartridge (Merck, Germany). Thereafter the cartridge was eluted with 2.0 mL acetonitrile and the solvent was evaporated. A solution containing 2 equiv of Wilkinson's catalyst in 1.0 mL benzonitrile was added and the reaction mixture was heated to 150 °C for 20 min. The mixture was diluted with 1.0 mL of a solution of ethyl acetate in petroleum ether (5% EA/PE) and filtered through a silica cartridge (600–700 mg silica gel in a 3 mL polyethylene filtration tube). Subsequently the desired compound was eluted with a solution of ethyl acetate in petroleum ether (60% EA/PE). The solvents were evaporated, then 0.5 mL of concentrated hydrochloric acid was added, and the reaction mixture was heated to 150 °C for 30 min. The product was purified by semi-preparative HLPC (System B).

Microwave heating. A solution of 8–9 μmol of the corresponding precursor was dissolved in 1.0 mL DMF and added to a vial containing the dried residue of [^{18}F]TBAF. The reaction mixture was irradiated with 40 W microwaves for 1 min. After labeling, the reaction mixture was diluted with 1.0 mL acetonitrile and 9.0 mL water and passed through a previously conditioned LiChrolut RP-18e cartridge (Merck, Germany). Thereafter the cartridge was eluted with 2.0 mL acetonitrile and the solvent was evaporated. A solution containing 2 equiv of Wilkinson's catalyst in 1.0 mL benzonitrile was added and the reaction mixture irradiated with 100 W microwaves during 2 min. The mixture was diluted with 1.0 mL of a solution of ethyl acetate in petroleum ether (5% EA/PE) and filtered through a silica cartridge (600–700 mg silica gel in a 3 mL polyethylene filtration tube). Subsequently, the desired compound was eluted with a solution of ethyl acetate in petroleum ether (60% EA/PE). The solvents were evaporated, then 0.5 mL of concentrated hydrochloric acid was added, and the reaction mixture was heated to 150 °C for 30 min. The product was purified by semi-preparative HLPC (System B).

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