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Synthesis and radiofluorination of novel fluoren-9-one based derivatives for the imaging of α7 nicotinic acetylcholine receptor with PET

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ABSTRACT

By structure–activity relationship studies on the tilorone scaffold, the 'one armed' substituted dibenzothiophenes and the fluoren-9-ones were identified as the most potential α_7 nAChR ligands. While the suitability of dibenzothiophene derivatives as PET tracers is recognized, the potential of fluoren-9-ones is insufficiently investigated. We herein report on a series of fluoren-9-one based derivatives targeting α_7 nAChR with compounds **8a** and **8c** possessing the highest affinity and selectivity. Accordingly, with [^{18}F]**8a** and [^{18}F]**8c** we designed and initially evaluated the first fluoren-9-one derived α_7 nAChR selective PET ligands. A future application of these radioligands is facilitated by the herein presented successful implementation of fully automated radiosynthesis.

Nicotinic acetylcholine receptors (nAChR) belong to the superfamily of ligand-gated ion channels and are known to modulate diverse physiological functions as well as to play a critical role in the pathophysiology of various diseases including Alzheimer's disease, schizophrenia, inflammatory conditions and cancer.[1,2] The broad spectrum of effects is a result of multiple pentameric α and β subunit arrangements as conferred by the 17 different combinations cloned so far.[3] Amongst them, the α_7 nAChR subtype has drawn considerable attention due its involvement in key intracellular signaling cascades eventually affecting cognition, learning, memory and attention-related processes in the central nervous system.[4] Despite of the poorly understanding of the underlying mechanisms of α_7 nAChR expression during disease progression, several α_7 nAChR-based therapies have reached clinical trials.[5,6] However, the inefficacy of the proposed α7 nAChR-targeted therapies in clinical use underline the need for a validation of α7 nAChR as biomarker for particular pathologies in preclinical research. With this regard, the selection of highly affine and selective new drug candidates has been greatly facilitated by advancements in molecular imaging tools such as positron emission tomography (PET).[7,8]

Various carbon-11 (^{11}C) and fluorine-18 (^{18}F) labelled quinuclidine PET ligands have been developed exhibiting affinity in a nanomolar range to α_7 nAChR.[7] However, with the exception of [^{11}C]CHIBA-1001 ($K_{i\alpha7}$ = 35 nM), none of them fulfilled the requirements for advancement to clinical trials (e.g., reasonable metabolic stability and suitable pharmacokinetics). The discovery of the interferon inducer tilorone as potent α_7 nAChR antagonists opened up new avenues for the development of PET ligands.[9,10] Structure-activity relationship studies (SAR) on this tricyclic pharmacophore revealed a subnanomolar α_7 nAChR binding affinity of the disubstituted fluoren-9-one derivative and the 'one armed' substituted dibenzothiophene (**A** and **B**, Fig. 1).[10] From the hit **A**, Horti et al.[11] developed the ^{11}C-labelled radiotracer [^{11}C]A-752274 (Fig. 1). However, pre-clinical evaluation in mice and baboon revealed a low brain penetration of [^{11}C]A-752274 due to an assumed low lipophilicity as a result of its dibasic structure. On the other hand, further insertion of fluorine on the hit **B** enabled the development of the corresponding ^{18}F-labelled derivatives (e.g., the ortho- and para-substituted, [^{18}F]ASEM and [^{18}F]DBT10, Fig. 1).[12,13] First-in-human studies with [^{18}F]ASEM[14] have been carried out and a comprehensive study comparing both radiotracers in non-human primates revealed nearly equivalent pharmacokinetic properties.[15] Further evaluation of [^{18}F]ASEM in healthy aging volunteers highlighted the potential of this class of compounds to monitor changes in α_7 nAChR distribution in the brain.[8]

The remarkable potential of tilorone derivatives prompted us to further investigate this compound class aiming at the development of a new ^{18}F-labelled α_7 nAChR PET tracer. Thus, confirming the data presented by Schrimpf et al.[10], the 'one armed' substituted

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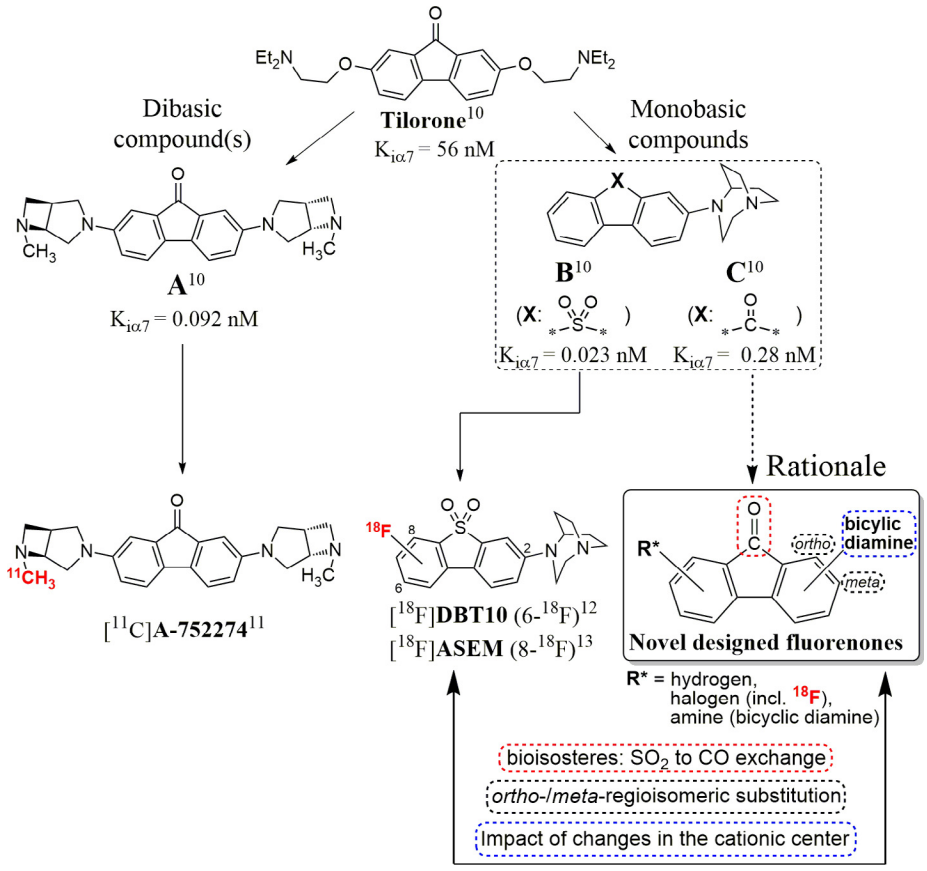


Fig. 1. Structure-activity relationship on the tilorone scaffold and the corresponding tilorone-based α_7 nAChR PET tracers. From the lead **C**, a schematic representation of the rationale for the development of the small series of fluoren-9-one bioisosteres.

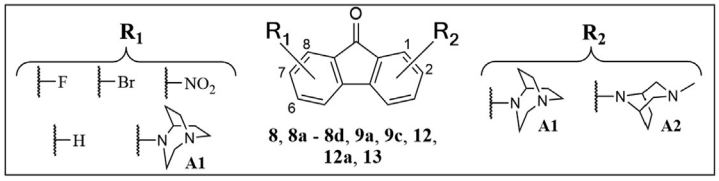
fluoren-9-one 2-((1*s*,5*s*)-1,4-diazabicyclo[3.2.2]nonan-4-yl)-9H-fluoren-9-one (**C**, Fig. 1) binds with low-nanomolar affinity to α_7 nAChR also in our *in house* assays.[16,17] By inserting fluorine in *ortho*- (*o*-), *meta*- (*m*-) and *para*- (*p*-) position to the carbonyl functionality we synthesized the fluoren-9-one derivatives **8a-d** (Table 1) and directly compared these novel sulfur-free bioisosteres with the corresponding dibenzothiophenes with regard to (i) the α_7 nAChR binding affinity and off-target selectivity towards the $\alpha_4\beta_2$ and $\alpha_3\beta_4$ nAChR subtypes as well as the serotonin receptor 5-HT_3, and (ii) the radiofluorination efficiency. To assess the impact of the *o*-substitution on binding affinities, we also synthesized the so far not reported *o*-regioisomeric derivatives **12** and **12a** (Table 1). Additionally, since symmetrical substitutions on the fluoren-9-one core are known to afford highly affine α_7 nAChR derivatives (**B**, Fig. 1),[10] we herein report on a new unsymmetrical dibasic fluoren-9-one **13,** which is *o*- and *m*-substituted with the 1,4-diazabicyclo[3.2.2]nonane pharmacophore. Eventually, we developed and translated to a fully automated procedure the ^{18}F-labelling of the most potent derivatives.

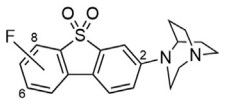
The four monobasic fluorofluoren-9-one derivatives **8a-d** were synthesized according to published data with minor modifications (see supporting information for full characterization of the final compounds).[12] As shown in scheme 1 the synthesis was carried out starting with the bromo-nitro substituted toluenes **1a** and **1c** to obtain the regioisomeric 1-nitro-fluoren-9-one **4a** and 3-nitro–fluoren-9-one **4c** in three steps.[18] The biphenyls **2a** and **2c** were obtained via Suzuki coupling of **1a** and **1c** with phenyl boronic acid in 93% and 84% yields, respectively. Subsequently, **2a** and **2c** were directly converted into their corresponding acids **3a** and **3c** via oxidation in presence of $KMnO_4$/pyridine. An acid promoted intramolecular Friedel-Crafts acylation led to the formation of the regioisomeric nitro fluoren-9-ones **4a** and **4c**. The 2-nitrofluoren-9-one **4b** was obtained in moderate yields starting from the *9H*-fluoren-9-one **4**.[19]

Regioselective bromination of **4a-c** was accomplished with *N*-bromosuccinimide (NBS) in a mixture of H_2SO_4 and trifluoroacetic acid to afford compounds **5a-c** in high yields. By exploiting the same fluorodenitration protocol we used for the corresponding dibenzothiophenes,[12] the fluorinated 7-bromo-fluoren-9-ones **6a**, **6c** and monofluoro derivative **6d** were accessed in reasonable yields in one step. Starting with **5b**, a three-step approach [(i) Zinin reaction, (ii) diazotization, (iii) Balz-Schiemann reaction] was carried out to obtain the corresponding 2-fluoro7-bromofluoren-9-one **6b** in 64% overall yield.

As shown in Scheme 2, the 7-bromo-fluoren-9-ones **6, 6a-c** were then reacted with the bicyclic diamines **7a** or **7b** under Pd-catalyzed Buchwald-Hartwig conditions to provide the reported non-fluorinated lead compound **8**[10] and the novel fluorinated derivatives **8a-d**. Unexpectedly, compound **8a** was obtained in a considerable lower yield (≈12%) and remained slightly impure according to ^{1}H NMR data. To circumvent this drawback, the carbonyl protected **10a** was synthesized from *o*-fluorofluoren-9-one **6a** via ketal formation (Scheme 3). After Buchwald-Hartwig coupling of **10a** with the 1,4-diazabicyclo[3.2.2]nonane **7a** to give the intermediate **11a**, deprotection under acidic conditions led to the hydrochloride of **8a** in 38% overall yield. The good leaving ability of fluorine substituted in the *o*-position to the electron withdrawing carbonyl group of **6a** in aromatic nucleophilic substitution (S_NAr) appeared to be responsible for the poor chemoselectivity. By contrast, neither impurities nor side products were observed for the *m*- and *p*-substituted derivatives **8b-d** according to the high yields and chemical purities (≥95%). Likewise, the nitro

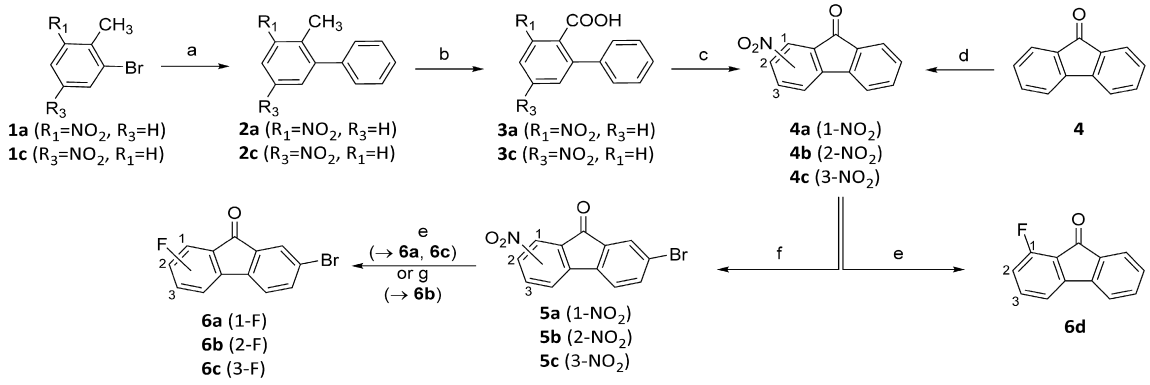
Table 1
In vitro binding affinities of compounds **8**, **8a** - **8d**, **9a**, **9c**, **12**, **12a**, **13** towards human homomeric α_7, heteromeric $\alpha_4\beta_2$ and $\alpha_3\beta_4$ nAChR subtypes, and human 5-HT_3 receptor, in comparison to **DBT10** and **ASEM**.



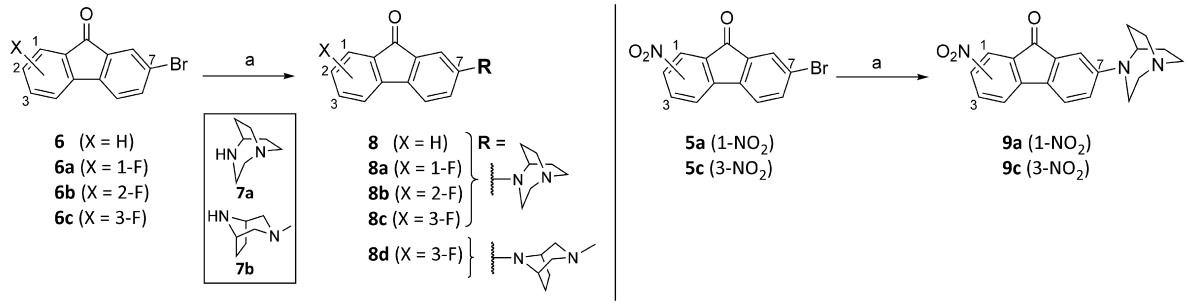


			Binding affinity (K_i, nM)				Selectivity (K_i ratio)	
Comp.	R_1	R_2	hα_7[a]	h$\alpha_4\beta_2$[b]	h$\alpha_3\beta_4$[b]	5-HT_3[c]	$\alpha_7/\alpha_4\beta_2$	$\alpha_7/\alpha_3\beta_4$
8 [d]	H	2-A1	1.91 ± 0.01	1660 ± 57.3	45.6 ± 3.69	49%	104	24
8a	8-F	2-A1	1.12 ± 0.14	1796 ± 231	33.2 ± 6.93	49%	>1000	29
8b	7-F	2-A1	2.09 ± 0.83	1315 ± 254	35.5 ± 1.20	23%	626	17
8c	6-F	2-A1	1.18 ± 0.36	1063 ± 371	65.4 ± 0.12	49%	244	39
8d	6-F	2-A2	15.4 ± 0.35	>10000	307 ± 11.3	n/a	>10000	16
9a	8-NO_2	2-A1	1.21 ± 0.30	1431 ± 52.3	63.3 ± 17.7	n/a	>1000	53
9c	6-NO_2	2-A1	84 ± 10.7	568 ± 33.2	44.3 ± 7.92	n/a	7	0.5
12	H	1-A1	466	>10000	454	n/a	21	1
12a	7-Br	1-A1	573 ± 254	3093 ± 155	251 ± 10.6	n/a	5	0.4
13	7-A1	1-A1	16.6 ± 8.41	722 ± 65.8	486 ± 107	n/a	42	28
DBT10[e]	–		0.60 ± 0.44	517 ± 375	119 ± 29.0	2%	862	198
ASEM[e]	–		0.84 ± 0.16	211 ± 108	42.3 ± 4.73	42%	251	50

[a] Human α_7 nAChR in stably transfected SH-SY5Y cells, with radiotracer [^{3}H]methyllycaconitine (0.5–1 nM), K_D = 2.0 nM.
[b] Human $\alpha_4\beta_2$ and $\alpha_3\beta_4$ nAChR in stably transfected HEK-293 cells, with radiotracer [^{3}H]epibatidine (0.5–1 nM), K_D = 0.025 nM for h$\alpha_4\beta$2 nAChR, K_D = 0.117 nM for h$\alpha_3\beta_4$ nAChR.
[c] Percentage of inhibition at 0.1 μM concentration of test compound; Human 5-HT_3 receptor recombinant-HEK293 cells, with radiotracer [^{3}H]GR65630 (working concentration n = 0.69 nM; K_D = 0.2 nM).
[d] Compound **8**[10].
[e] Binding affinity data.[12]



Scheme 1. Reagents and conditions: (a) Phenylboronic acid, K_2CO_3 (2.5 eq), DME/H_2O, $Pd(PPh_3)_4$, 100–102 °C, 6 h (**2a**, 93%, **2c**, 84%); (b) $KMnO_4$ (5–9 eq), pyridine/H_2O, 105–115 °C, 9–72 h (**3a**, 58%, **3c**, 86%); (c) 160–165 °C, 6 h, PPA (polyphosphoric acid) (**4c**, 91%), or H_2SO_4 (**4a**, 87%); (d) H_2O, H_2SO_4, HNO_3, 90 °C, 2.5 h (**4b**, 46%); (e) TMAF (azeotropically dried), DMSO/c-hexane, 95 °C, 6 h (**6a**, 75%, **6c**, 54%, **6d**, 58%); (f) NBS, TFA/H_2SO_4, 22 °C, 24 h (**5a**, 83%, **5b**, 94%, **5c**, 72%); or (g) for conversion **5b** → **6b** (i) $Na_2S{\cdot}9H_2O$, NaOH, EtOH/H_2O 110 °C, 4 h (2-amino derivative [not shown], 94%), (ii) HBF_4 (50% in H_2O), $NaNO_2$, H_2O, DMSO, 0–20 °C, 1 h; (iii) xylenes, 140 °C, 2 h (**6b**, 64% starting from **5b**).



Scheme 2. Reagents and conditions: (a) $Pd_2(dba)_3$, r-BINAP, Cs_2CO_3, **7a** (or **7b**), toluene, 90 °C, 24 h (**8**, 53%, **8a** [containing impurities as detected by ^{1}H NMR], ≈12%, **8b**, 70%, **8c**, 80%, **8d**, 81%, **9a**, 58%, **9c**, 56%).

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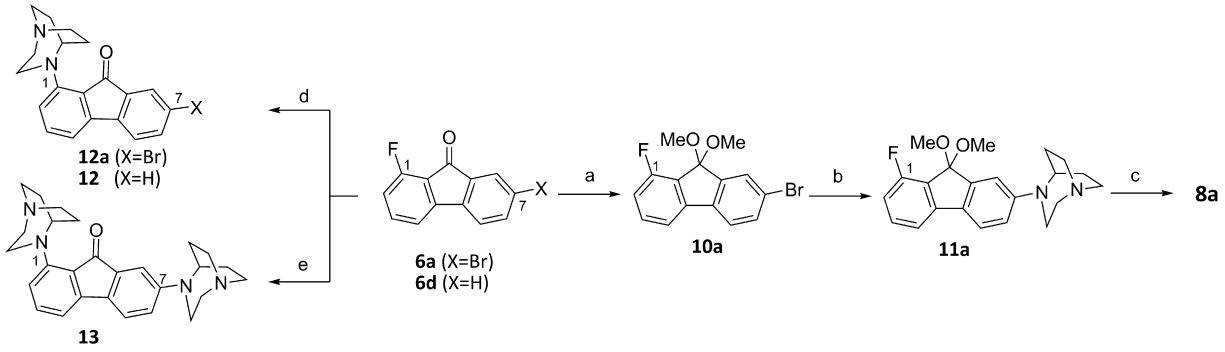


Scheme 3. Reagents and conditions: (a) Trimethylorthoformate, H_2SO_4 (cat.), MeOH, 14 d, 22 °C (**10a**, 57% [from **6a**]); (b) $Pd_2(dba)_3$, r-BINAP, Cs_2CO_3, **7a**, toluene, 90 °C, 24 h (**11a**, 76%); (c) MeOH/H_2O, HCl, 22 °C, 10 min (**8a**, 99%); (d) Cs_2CO_3, **7a**, toluene, 90–100 °C, 30 h (**12a**, 78% [from **6a**], **12**, 38% [from **6d**]); (e), Cs_2CO_3, **7a** (2.6 eq), $Pd_2(dba)_3$, r-BINAP, (2h after start of reaction), toluene, 90–100 °C, 48 h (**13**, 40% [from **6a**]).

precursors **9a** and **9c** for radiofluorination were synthesized using Buchwald-Hartwig coupling of **5a** and **5c** with the 1,4-diazabicyclo [3.2.2]nonane **7a** in 58% and 56% yields, respectively.

In order to assess the effect of the *o*-substitution on binding affinities, compounds **12**, **12a** and **13** were synthesized (Scheme 3). Although **12a** and **13** could be already detected by TLC during the synthesis of the *o*-fluorofluoren-9-one **8a**, their syntheses were scaled up to enable binding affinity measurements. Compound **12**, which is regioisomeric to **8**, was prepared from **6d** in 38% yield and compound **12a** from **6a** in 38% yield by exploiting the above-mentioned reactivity of the fluorine at the *ortho*-position to the carbonyl group. The 1,7-dihalofluorenone **6d** was reacted with amine **7a** under Pd-catalyzed Buchwald-Hartwig conditions to give the disubstituted derivative **13** in 40% yield.

The α_7 nAChR binding affinity and selectivity towards the off-target receptors $\alpha_4\beta_2$ and $\alpha_3\beta_4$ as well as 5-HT_3 is depicted in Table 1 (for methodology see supporting information). The α_7 nAChR binding affinity of the lead **8** ($K_{i\alpha7}$ = 1.91 ± 0.01 nM) was sevenfold lower than the previously reported by Schrimpf et al. ($K_{i\alpha7}$ = 0.28 nM).[10] Although these values cannot be directly compared due to the previously discussed impact of assay-related differences on binding affinities (e.g., radioligand, tissue),[13] our findings confirmed the potential of this tricyclic pharmacophore as α_7 nAChR agent. The sulfonyl (SO_2, $K_{i\alpha7}$ = 0.51 ± 0.32 nM)[12] to carbonyl (CO) exchange resulted in an approximately fourfold diminished affinity of the lead **8** ($K_{i\alpha7}$ = 1.91 ± 0.01 nM), which is less pronounced than the tenfold difference reported for the same matched pair under the same assay conditions (**B** vs **C**, Fig. 1).[10] Equivalent binding affinities ($K_{i\alpha7}$ in the range of 1.18–2.09 nM) were found for the *o*-, *m*- and *p*-fluoro substituted derivatives **8a-c** in comparison to the lead **8**. So we can conclude that the introduction of a fluorine atom at this part of the molecule does not affect the α_7 nAChR binding affinity as it is for the corresponding dibenzothiophene analogs ASEM and DBT10. The decrease in binding affinity obtained for **8d** ($K_{i\alpha7}$ = 15.4 ± 0.35 nM), where we introduced an azatropane ring instead of the 1,4-diazabicyclo[3.2.2]nonane, corresponds also to the dibenzothiophene bioisosteres.[12]

For compound **12**, the isomer of **8**, in which the 1,4-diazabicyclo [3.2.2]nonane is substituted at the *o*-position, we observed a remarkable loss in binding affinity ($K_{i\alpha7}$ = 466 nM). We hypothesize that this decline could be addressed to a steric hindrance caused by the proximity of the cationic center to the carbonyl group which act as hydrogen bond acceptor on the tricyclic pharmacophore.[20] The presence of an electron withdrawing group at the C-7 position of the tricyclic pharmacophore as in **12a** did not improve the affinity. However, as expected, restoring the 1,4-diazabicyclo[3.2.2]nonane as cationic center at the C-7 (*meta*-) position (compound **13**) of the tricyclic fluoren-9-one yielded a pronounced increase in binding affinity ($K_{i\alpha7}$ = 16.6 ± 8.41 nM).

The incorporation of fluorine in *o*-, *m*- and *p*-positions (**8a-c**) resulted in a $\alpha_4\beta_2$ nAChR selectivity ratio over 1000. Whilst the proposed changes in the cationic center were reported to positively contribute to the selectivity towards the $\alpha_4\beta_2$ subtype[12] as herein exhibited by **8d** ($K_{i\alpha4\beta2} \geq 10000$ nM), the diminished binding affinity towards the α_7 subtype led to the exclusion of this derivative for further ^{18}F-labelling.

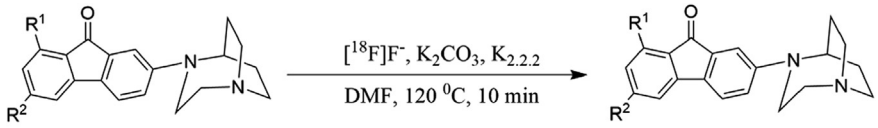
An overlap in the receptor expression of α_7 and $\alpha_3\beta_4$ nAChRs, in particular within autonomic neurons[21,22] makes the investigation of the selectivity of potential ligands towards this receptor subtype necessary. As summarized in Table 1, compound **8, 8a-c** showed only a modest $K_{i\alpha7}/K_{i\alpha3\beta4}$ selectivity ratio of about 24. The $\alpha_3\beta_4$ nAChR binding affinities remained in the same order of magnitude for the fluoren-9-one **8** ($K_{i\alpha3\beta4}$ = 45.6 ± 3.69 nM) compared to the corresponding non-fluorinated dibenzothiophene ($K_{i\alpha3\beta4}$ = 49.6 ± 14.7 nM[12], Fig. 1B). However, insertion of fluorine (**8a-c**) resulted in an increased $\alpha_3\beta_4$ nAChR affinity in comparison, for example, with their bioisosteres DBT10 and ASEM. Interestingly, for compound **8d** ($K_{i\alpha3\beta4}$ = 307 ± 11.30 nM) the deshielded *N*-methyl group of the cationic center greatly contributed to the selectivity towards the $\alpha_3\beta_4$ subtype in comparison to **8a-c**.

The *in vitro* binding affinity to 5-HT_3 was investigated by measuring the percentage of inhibition of binding of [^{3}H]GR65630 at 100 nM test compound. This analysis was performed only for compounds possessing the highest α_7 nAChR binding affinity and good nAChR off-target selectivity (**8, 8a-c**). With the exception of the *m*-fluoro substituted derivative **8b** (23%), the lead **8** and the fluoro isomers **8a** and **8c** exhibited percentages of inhibition in the range of 50%. These values are in the same order of magnitude as for ASEM. It is worth noticing that the neither non-specific binding nor undesirable pharmacological effects due to 5-HT_3 binding were reported in pre-clinical[15] and in clinical trials with [^{18}F]ASEM.[8,14] So we assume that the likelihood of potential 5-HT_3 cross-target issues for the corresponding radioligands of the fluoren-9-one derivatives **8a** and **8c** are rather small.

In summary, based on the pronounced α_7 nAChR binding affinity and sufficient off-target selectivity the fluoren-9-one derivatives **8a** and **8c** were selected for further ^{18}F-labelling.

To directly compare the radiofluorination efficiency of the fluoren-9-ones **8a** and **8c** with the corresponding bioisosteric dibenzothiophenes ASEM and DBT10, equivalent reaction conditions to those applied for the radiosynthesis of [^{18}F]**DBT10** were investigated (Table S.1, supporting information).[12] The initial screening was performed with regard to the solvent and the heating mode (conventional vs microwave) at 120 °C using minimal amount of the nitro precursors for radiolabeling (**9a** or **9c** ≅ 0.8 mg).[12,23] The radiochemical yields were determined via radio-TLC and radio-HPLC analysis of aliquots taken from the crude reaction mixture at different time points (up to 15 min) unless stated otherwise.

Table 2
Outcomes of the automated radiosynthesis of [^{18}F]**8a** and [^{18}F]**8c** and the corresponding experimental log$D_{7.4}$ values. Data represent mean ± SD (n = 3).



9a: R^1= NO_2, R^2=H
9c: R^1=H, R^2=NO_2

[^{18}F]**8a**: R^1= ^{18}F, R^2=H
[^{18}F]**8c**: R^1=H, R^2=^{18}F

	RCY(%)	RCP(%)	Am(GBq.μmol^{-1})	log$D_{(7.4)}$
[^{18}F]**8a**	37 ± 5	≥98	44 ± 3	1.2 ± 0.1
[^{18}F]**8c**	32 ± 3	≥98	31 ± 6	2.2 ± 0.1

Abbreviations. RCY: radiochemical yield; RCP: radiochemical purity; Am: molar activity.

[^{18}F]**8a** and [^{18}F]**8c** were obtained by nucleophilic aromatic substitution of the NO_2 leaving group by [^{18}F]fluoride in the presence of the kryptofix®($K_{2.2.2}$)/K_2CO_3 system. In dimethylsulfoxide (DMSO), S_NAr proceeded smoothly resulting in moderate radiochemical yields of 39% and 65%, respectively, for [^{18}F]**8a** and [^{18}F]**8c** under conventional heating at 10 min reaction time. While the use of microwave assisted radiofluorination in DMSO afforded a roughly twofold increase of radiochemical yield for [^{18}F]**8a** (73%), comparable yields were found for [^{18}F]**8c** (62%). When *N,N*-dimethylformamide (DMF) was used as solvent, radiochemical yields in the range of 70–90% under conventional and microwave heating were obtained for [^{18}F]**8a** and [^{18}F]**8c**. For all reactions, besides of unreacted [^{18}F]F^-, radioactive by products accounted for less than 3%.

It is worth noticing that the S_NAr for the fluoren-9-ones in DMF reached a plateau in very short reaction times (5 min), remaining constant up to 15 min independent of the heating method applied. This rapid nitro-to-[^{18}F]fluoro conversion was also observed for the corresponding dibenzothiophene matched pairs.[12] Interestingly, the superior electron withdrawing effect of the sulfonyl group of [^{18}F]DBT10 and [^{18}F]ASEM did not influence the radiofluorination efficiency in comparison to the corresponding radiolabeled carbonyl bioisosteres [^{18}F]**8a** and [^{18}F]**8c**.[24]

The manual radiosynthesis conditions were successfully translated to the TracerLab Fx-F_N automated module device (Table 2). For the labelling reaction of [^{18}F]**8a** and [^{18}F]**8c** radiochemical yields of about 67 ± 3% and 82 ± 4%, respectively were obtained.

After isolation via semi-preparative HPLC (Figure S.1 A-B, supporting information), [^{18}F]**8a** or [^{18}F]**8c** were trapped on a pre-conditioned Sep-Pak® C18 light cartridge, and formulated in isotonic saline containing 10% of EtOH (*v*/*v*). Starting with approximately 3–5 GBq, the average decay-corrected radiochemical yields for [^{18}F]**8a** and [^{18}F]**8c** were 37 ± 5% and 32 ± 3%, respectively, calculated at the end of the synthesis (EOS). Both radiotracers were obtained with a radiochemical purity of > 98% and molar activities of 44 ± 3 GBq·μmol^{-1} and 31 ± 6 GBq μmol^{-1} for [^{18}F]**8a** and [^{18}F]**8c**, respectively. Analytical radio-HPLC analysis of the final product co-eluted with the corresponding reference compound (**8a** or **8c**) confirmed the identity of the radiotracers (Fig. S.1C-D, supporting information). The distribution coefficient (log$D_{7.4}$, Table 2) in the *n*-octanol-PBS system was experimentally determined by the shake flask method (for methodology, see supporting information). With log$D_{7.4}$ values of 1.2 ± 0.1 and 2.2 ± 0.1, respectively for [^{18}F]**8a** and [^{18}F]**8c**, we assume that a passive diffusion through the blood–brain barrier is most likely.

We herein reported on the synthesis of a small series of fluoren-9-one derivatives exhibiting binding affinities to α_7 nAChR and off-target selectivities equivalent to the corresponding dibenztothiophenes bioisosteres.[12] From this series, the 'one armed' fluorinated fluoren-9-ones **8a** and **8c** exhibited the highest α_7 nAChR binding affinity and sufficient selectivity towards off-target receptors, and therefore were selected for further ^{18}F-labelling. With [^{18}F]**8a** and [^{18}F]**8c** we presented the first fluoren-9-one derived α_7 nAChR-targeting PET tracers, obtained in good radiochemical yields and with high radiochemical purities. The radiosyntheses were successfully translated to a rapid, versatile and reproducible automated process which will allow the accessibility of [^{18}F]**8a** and [^{18}F]**8c** for widespread production for further pre-clinical investigation.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bmcl.2018.03.081.

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