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^{68}Ga-Labelled Tropane Analogues for the Visualization of the Dopaminergic System

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The development of radiometal-labelled pharmaceuticals for neuroimaging could offer great potential due to easier handling during labelling and availability through radionuclide generator systems. Nonetheless, to date, no such tracers are available for positron emission tomography, primarily owing to the challenge of crossing the blood–brain barrier (BBB) and loss of affinity through chelator attachment. We have prepared a variety of ^{68}Ga-labelled phenyltropanes showing that, through a simple hydrocarbon-linker, it is possible to introduce a chelator onto the lead structure while maintaining its high affinity for hDAT (human dopamine transporter) and simultaneously achieving adequate lipophilicity. One of the candidates, [^{68}Ga]Ga-HBED-hexadiyne-tropane, showed an IC_{50} value of 66 nM, together with a $\log D_{7.4}$ of 0.96. A μPET study in a hemiparkinsonian rat model showed a fast wash-out of the tracer, and no specific uptake in the brain, thus implying an inability to penetrate the BBB.

Introduction

The development of radioactively labelled tracers for the diagnosis of neurological diseases is becoming more and more important with the increasing incidence of neurodegenerative diseases as the population ages.[1] Together with positron emission tomography (PET), they offer a sensitive, non-invasive imaging method for the diagnosis (from early detection to control of disease progression) of diseases of the central nervous system (CNS).[2] Of particular interest is the dopaminergic system, which due to its high functionality plays a major role in a variety of disorders such as Parkinson's disease,[3] Alzheimer's disease,[4] schizophrenia,[5] depression,[6] epilepsy,[7] substance use disorders[8] and many others. The dopamine transporter (DAT) is located on dopaminergic neurons and represents a common target due to its major role in the dopaminergic pathway, providing information about its integrity. Most radiopharmaceuticals for such questions are currently based on the cocaine-derived tropane structure with cyclotron-produced nuclides such as ^{11}C, ^{18}F or ^{123}I. First attempts were made by labelling cocaine itself with carbon-11 (**1**), readily replaced by the phenyltropanes such as [^{18}F]β-CFT (**2**), because of their superior affinity and stability *in vivo*. Since then, considerable effort has been placed on the development of novel radioligands, providing high selectivity for the human DAT (hDAT) with high striatum-to-cerebellum ratios. Representative derivatives include the clinical established [^{123}I]FP-β-CIT (DATSan®; **3**), [^{18}F]LBT-999 (**4**) and, more recently, [^{18}F]PR04.MZ (**5**).

However, the development of a radiometal-labelled CNS tracer would be advantageous due to the simpler labelling chemistry, lower costs and greater availability through radionuclide generator systems. Progress has been made with the ^{99m}Tc-labelled tropane derivatives TRODAT-1 (**6**) and technepine (**7**) which have already been evaluated to make DAT imaging accessible to radiometal-labelled tracers. Despite the size and the chemical influence of the attached chelator unit, remarkable affinities to the DAT could be achieved, and encouraging *in vivo* properties have been demonstrated in human studies.[9,10]

However, a disadvantage of using SPECT nuclides over PET is the loss of the ability to quantify the radiotracer concentration in tissue *in vivo*. In addition, the maximum spatial resolution of modern clinical PET/MRT scanners is 3 mm,[11] whereas the resolution of modern SPECT/CT scanners is in the range of approx. 1 cm.[12] To date, however, there is no DAT tracer labelled with a generator-produced PET nuclide that has been successfully tested *in vivo*.[13]

Gallium-68 is one of the most widely used PET radiometals. Its practical half-life of 68 min and above all its simple and cost-effective non-carrier-added (n.c.a.) availability via the ^{68}Ge/^{68}Ga

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radionuclide generator often makes it the nuclide of choice for a variety of applications.

We have therefore synthesized and evaluated a set of chelator-coupled derivates based on the phenyltropane lead structure. For the chelators DO3A, as a readily available and established chelating agent, and HBED, for its lipophilic character, enhancing the possibility of blood–brain barrier (BBB) perfusion, were chosen. Despite HBED being an acyclic chelator, it is well known for its high stability constant for the Ga^{3+} complex ($\log K_{GaL} = 38.51$), which is reflected in its high *in vivo* stability.[14,15] The tropane target vector was connected to the chelators via various linker structures, to examine their influence on receptor binding. This report details the synthesis of the labelling precursors, radiolabelling with gallium-68, $\log D_{7.4}$ lipophilicity measurements, uptake studies in human embryonic kidney (HEK293) cell lines expressing the hDAT and initial μPET studies.

Results and Discussion

The phenyltropane target vector was synthesized from commercially available cocaine as described in literature (Section S1.1 in the Supporting Information).[16,17] Demethylation of the bridge-nitrogen provided the accessibility for the linkage to the respective chelators. By using a one-pot synthesis strategy, consisting of i) the protected chelator, ii) the di-halogenated/trifluoromethan-sulfonylated linker and iii) the phenyltropane target vector (if possible), was developed to prepare a variety of different precursors. Initially four DO3A derivatives with a selection of aliphatic linkers (namely C_2, C_3, butyne and hexadiyne) were synthesized (compounds **8** to **11**, Figure 2; Section S1.2). The corresponding ^{nat}Ga complexes were prepared (Section S1.4). The pharmacological properties for these ^{nat}Ga-labelled compounds to hDAT were determined in a cell-based uptake inhibition assay, using HEK293 cells stably expressing hDAT, using the tritiated DAT substrate *N*-[^{3}H]Methyl-4-phenylpyridin ([^{3}H]MPP^+) according to published

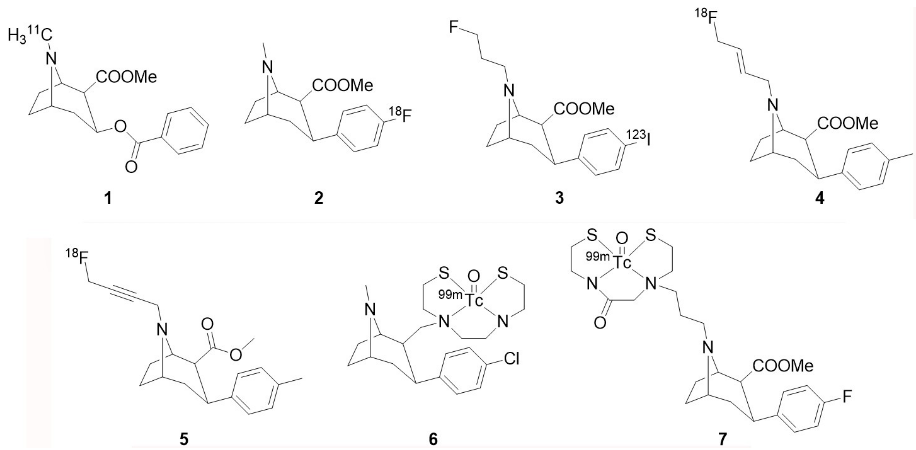

Figure 1. Representative tropane derivates established for PET imaging of the hDAT.

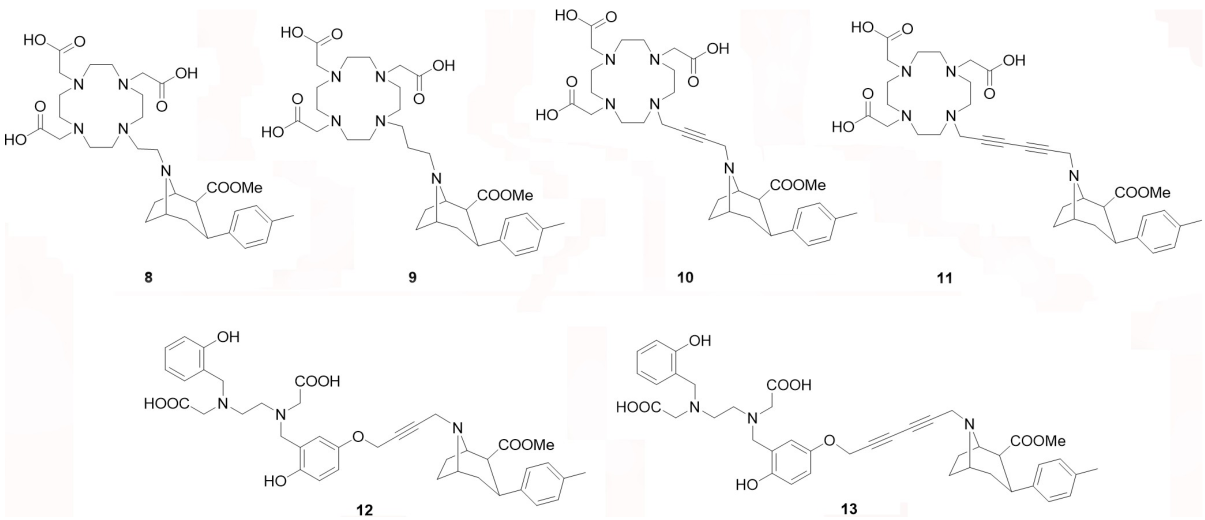

Figure 2. DO3 A- and HBED-coupled tropane derivates for ^{68}Ga labelling.

procedures.[18] As reference, PR04.MZ (**5**) and cocaine were determined as well. The resulting IC_{50} values from the experiments as well as a comparison to some representative phenyltropanes are shown in Table 1 (regarding the cell assay, compounds **8**–**13** refer to the ^{nat}Ga-labelled derivatives; inhibition curves and further data: Section S2.3).

For the DO3A derivatives, the linker length between chelator and tropane unit shows a significant increase in hDAT affinity with increasing chain length ($C_2 < C_3 < C_4 < C_6$). Whereas the flexible linker structures (**8** and **9**) with two and three CH_2 units still show insufficient affinities in the micromolar range, a clear improvement to nanomolar values can be observed by introducing the alkyne structures in **10** and **11** with chain lengths of C_4 and C_6 respectively. It can therefore be assumed that the binding pocket for the phenyltropane in the immediate vicinity of the binding site does not tolerate larger molecule groups such as the ^{nat}Ga-labelled chelator in this case. Comparing **9** with [^{99m}Tc]technepine **7** shows the Ga-DO3A chelator is larger than its Tc-MAMA (monoamine–monoamide dithiol) counterpart. Although a larger ligand field is formed by the longer Tc–S bonds (~2.25 Å) compared to Ga–O (~1.93 Å), the Ga-DO3A complex is octahedral compared to the square-pyramidal Tc–MAMA complex, occupying much more space on the *z*-axis through the carboxy groups lying opposite.[19,20] The C_3 linker therefore seems to be the breakpoint. With the help of the hexadiyne structure in **11**, an IC_{50} value of 157 nM comparable to cocaine could be achieved.

To increase the lipophilicity of the radiotracers the corresponding HBED derivatives were prepared (Section S1.3). Following the affinity assay, the most promising lead structures utilising the butyne (**10**) and the hexadiyne (**11**) linker were chosen (Figure 2). The exchange of the chelator to HBED led to a further affinity increase in the two-digit nanomolar range (Table 1). An extension of the linker from C_4 (**12**) with 47 nM to C_6 (**13**) with 66 nM did not result in a noticeable change. The direct comparison with DO3A suggests that the lipophilic HBED structure might fit better to the amino acid sequence in the binding pocket area and that a hydrophobic interaction might be advantageous here. Thus, the ^{nat}Ga-labelled HBED compounds of **12** and **13** prove to be promising candidates due to their affinities comparable with those known in literature, such as FP-β-CIT (**3**) and LBT-999 (**4**).

Table 1. IC_{50}(hDAT, 95% confidence interval) and $\log D_{7.4}$ values of the ^{nat}Ga-labelled compounds of 8–13 compared to representative phenyltropanes.

Compound	IC_{50} (K_i) hDAT [nM]	$\log D_{7.4}$ ($\log P$)
cocaine **1**	188.2[a] / 230[b][21]	1.31 ± 0.01[22]
[^{18}F]β-CFT **2**	14.2[b],[23]	–
[^{123}I]FP-β-CIT **3**	(28)[b],[24]	–
LBT-999 **4**	(26) [b],[25]	–
PR04.MZ **5**	20.07[a] / 3.3[b][26]	2.70 ± 0.20[27]
TRODAT-1 **6**	oxo isomers: 8.42 and 13.87[b],[28]	(0.29 ± 0.04)[29]
technepine **7**	5.99[b],[30]	–
[^{nat}Ga]Ga-**8**	72082[a]	−2.06 ± 0.11
[^{nat}Ga]Ga-**9**	12951[a]	−2.01 ± 0.09
[^{nat}Ga]Ga-**10**	209.1[a]	−2.21 ± 0.17
[^{nat}Ga]Ga-**11**	156.7[a]	−1.93 ± 0.23
[^{nat}Ga]Ga-**12**	47.11[a]	−0.07 ± 0.05
[^{nat}Ga]Ga-**13**	66.46[a]	0.96 ± 0.20

[a] Values obtained by cell assay (quadruplicate determination; $n = 3$). [b] Taken from reference. $\log D_{7.4}$ values (triplicate determination; $n = 4$; ±SD).

All precursors (**8**–**13**) were labelled with gallium-68 obtained from a ^{68}Ge/^{68}Ga-generator utilizing the acetone post procession.[31] The free chelators were exposed to $^{68}GaCl_3$ in NaOAc buffer (0.2 M, pH 4.5) at 45 °C (for HBED) or 95 °C (for DO3A), respectively. After a reaction time of 15 min the radiolabelled products were purified by HPLC and isolated by solid-phase extraction on a C_{18} cartridge. The sterile formulation was obtained through elution of the resin with ethanol, followed by isotonic saline solution, yielding the radioligands in radiochemical purities of 97–99% (Section S3.1).

Stability studies for all radiolabelled compounds were performed in PBS solution and human serum as triplicates. The radiotracers remained intact in both solutions over a period of 2 h, suitable for distribution and neurological *in vivo* studies with gallium-68 (Section S3.2).

The lipophilicity of all compounds was determined by the "shake flask" method. The radioactively labelled tracer is added to a two-phase mixture of *n*-octanol and PBS (pH 7.4) and then its distribution across the two phases is determined. The lipophilicity is expressed by the distribution coefficient $\log D_{7.4}$. All experiments were carried out as quadruplicates with three extractions, whereby the values of the first ones were rejected, since these are afflicted with the largest error (Section S3.3). Obtained $\log D_{7.4}$ values are shown in Table 1 (compounds **8**–**13**).

If the values obtained are compared with the values known from literature for cocaine ($\log D = 1.31$ (±0.01)) or PR04.MZ (**5**) ($\log D = 2.7$ (±0.2)), it becomes clear that the coupling with the DO3A chelator drastically shifts the original lipophilicity of the tropane lead structure into the hydrophilic range. All DO3A conjugates show lipophilicities of about −2. The Ga^{3+}-DO3A complex is hexacoordinated and therefore negatively charged.[19] Together with the high polarity of the ionic bonds and the carboxyl groups this causes a high polarity/water solubility. In contrast, the HBED conjugates show significantly higher $\log D_{7.4}$ values of 0–1. Again, the polarity of the Ga^{3+} complex is reflected in the lower $\log D$ values compared to the lead compounds. However, the lipophilic influence of the phenol groups is evident, as they are supposed to shield the complex charge from the outside. In addition, the HBED chelator has two fewer heteroatoms than the DO3A chelator resulting in a lesser amount of hydrogen bridge bonds. In comparison to DO3A, a 100-fold higher lipophilicity could be achieved with the tropane-butyne-HBED (**12**) and even a 1000-fold higher lipophilicity with the tropane-hexadiyne-HBED (**13**).

With regard to overcoming the BBB, the "Lipinski's rule of five" for oral bioavailability has established itself as a guideline for brain-active molecules, where the HBED derivatives in particular proved to be very promising.[32] Both compounds have only one hydrogen bridge donor, less than 10 hydrogen bridge acceptors and a sufficient lipophilicity. Only their molecular weight is higher than the desired <500 g/mol. However, "Lipinski's rule of five" is only a rule of thumb, so breaking one or more of these rules does not necessarily result in a missing or low brain uptake. For instance, the molecular weights of the tracers [^{99m}Tc]TRODAT-1 (**6**; 540 g/mol) and [^{99m}Tc]technepine (**7**; 610 g/mol) still allow a sufficient brain uptake. Furthermore, the lipophilicity of [^{99m}Tc]TRODAT-1 (**6**) shows a value of 0.29 ($\pm$0.04) and thus is also comparable with the HBED conjugates **12** and **13**.

Out of the six radiotracers examined, HBED-hexadiyne-tropane **13** showed the most promising results regarding hDAT affinity and lipophilicity, and was therefore further evaluated. A dynamic, *in vivo* μPET study was conducted on a hemi-parkinsonian (hemi-PD) animal model on male Wistar rats (Figure 3; Section S4).

Unfortunately, no brain uptake of the radiopharmaceutical was observed, either in target, reference or other brain regions; nor in 6-OHDA- or in sham-6-OHDA-rats (6-hydroxydopamine model). Figure 4 depicts the time activity curve (TAC) of the uptake of the radiopharmaceutical for right and left striatum of a 6-OHDA-rat showing a rapid influx followed by an equally quick wash-out of the tracer.

The PET study indicates an inability of the tracer [^{68}Ga]Ga-**13** to penetrate the BBB, despite all previous obtained data seemed promising. This might be caused by several reasons. On one hand, the tracer might be a target for efflux transporters

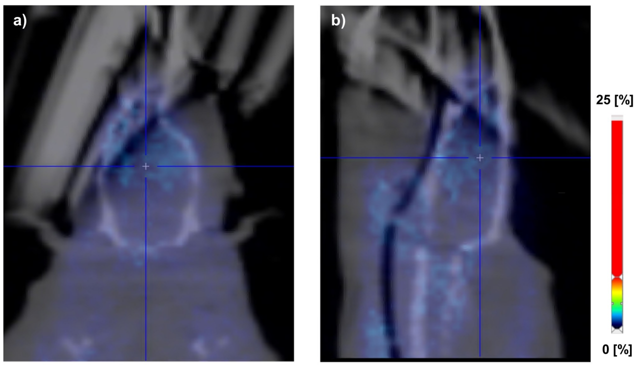

Figure 3. μPET/CT images of [^{68}Ga]Ga-HBED-hexadiyne-tropane 13 in a 6-OHDA-rat 60 min p.i.; a) coronal; b) sagittal.

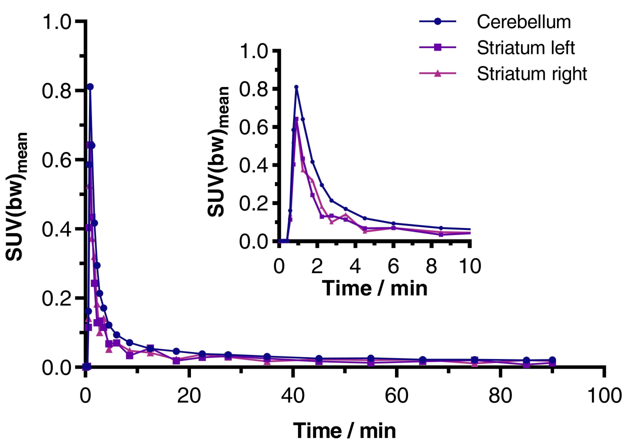

Figure 4. TAC for [^{68}Ga]Ga-HBED-hexadiyne-tropane 13 for right and left striata.

(e.g., P-glycoprotein (P-gp) or other multidrug-resistant proteins).[33] In addition, the transport of radiopharmaceuticals across the BBB is mainly reliant on passive membrane diffusion, for which the lipophilicity of the tracer might not be high enough to allow intercalation into the lipid bilayer of the endothelial cells. On the other hand, the achieved IC_{50} value of 66 nM might not be high enough because, for a highly perfused organ with strong metabolism rates such as the brain, even lower values are typically beneficial to prevent a rapid wash-out. In general, the required tracer affinity is modulated by a number of factors, such as receptor/transporter density, the concentration and number of endogenous ligand, which makes it difficult to predict the optimal affinity.[2] In addition, neither too low affinities (insufficient enrichment, fast kinetics) nor too high affinities (low kinetics) are desirable. However, considering that cocaine was successfully used as a PET tracer despite its IC_{50} of about 200 nM, an IC_{50} of 66 nM should be enough to achieve at least some accumulation in the striatum, which could not be observed.[34] Therefore, the affinity of compound **13** should not be the primary problem for the insufficient accumulation in the brain.

Conclusion

The possibility to use ^{68}Ga-labelled PET tracers for neurological questions represents a huge advantage for the improvement of neurological imaging. Based on their simpler labelling chemistry, lower costs and greater availability through the ^{68}Ge/^{68}Ga radionuclide generator system, they can support the need to make CNS diagnosis more accessible. However, in consequence of the radiochemistry of radiometals they require a suitable chelator, which can be challenging due to its high impact on the pharmacophore regarding target affinity and BBB penetration. We have shown that with a simple hydrocarbon-linker it is possible to introduce a chelator onto a phenyltropane lead structure while maintaining its high affinity for the hDAT. Using alkyne moieties based on the model of [^{18}F]PR04.MZ (**5**) in the case of the HBED chelator, affinities comparable to established DAT tracers like LBT-999 (**4**) or [^{123}I]FP-β-CIT (**3**) could be achieved. All prepared precursors were labelled successfully with [^{68}Ga]Ga^{3+} in radiochemical yields of >97 %. Lipophilicity studies revealed the strong impact of the polar DO3A chelator, resulting in $\log D_{7.4}$ values of about −2 for all compounds, which is unfavourable for a BBB perfusion *in vivo*. On the other hand, the HBED-coupled tracers **12** and **13** showed improved lipophilicity, comparable to the attested brain tracer [^{99m}Tc]TRODAT-1 (**6**). The most promising candidate [^{68}Ga]Ga-HBED-hexadiyne-tropane **13** was labelled in a radiochemical yield of 98 % and formulated after HPLC purification in a radiochemical purity of 98 %. Based on the conducted lipophilicity and affinity studies, this tracer had a high potential to serve as a ^{68}Ga-labelled PET imaging agent for neurological questions. Unfortunately, no specific uptake into the brain could be observed, presuming the inability of the tracer to penetrate the BBB. Nevertheless, we could show that high affinities at hDAT can be achieved by adequate spacing between pharmacophore and chelator. In future studies, further improvements will therefore be attempted by using chelators with lower molecular weight and/or higher lipophilicity, such as NS_3 (tris(2-mercaptobenzyl)amine)) or TACN-TM (1,4,7-triazacyclononane-1,4,7-trimercaptoethane).[35,36]

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Conflict of Interests

The authors declare no conflict of interests.

Keywords: dopamine transporters · gallium-68 · imaging agents · lipophilicity · radiopharmaceuticals · tropane

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