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Chemical Delivery System of MIBG to the Central Nervous System: Synthesis, ^{11}C-Radiosynthesis, and *in Vivo* Evaluation

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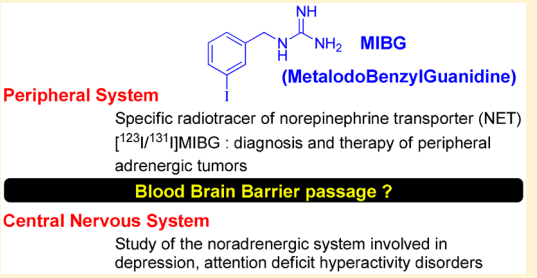
Supporting Information

ABSTRACT: The norepinephrine transporter (NET) plays an important role in neurotransmission and is involved in a multitude of psychiatric and neurodegenerative diseases. [^{123}I/^{131}I]*meta*-iodobenzylguanidine (MIBG) is a widely used radiotracer in the diagnosis and follow-up of peripheral neuroendocrine tumors overexpressing the norepinephrine transporter. MIBG does not cross the blood−brain barrier (BBB), and we have demonstrated the "proof-of-concept" that 1,4-dihydroquinoline/quinolinium salt as chemical delivery system (CDS) is a promising tool to deliver MIBG to the brain. To improve BBB passage, various substituents on the 1,4-dihydroquinoline moiety and a linker between CDS and MIBG were added. A series of CDS-MIBGs **1a−d** was synthesized, labeled with carbon-11, and evaluated *in vivo* into rats. The *in vivo* results demonstrated that, although adding substituents on CDS in **1a−c** is of no benefit for brain delivery of MIBG, the presence of a linker in CDS-MIBG **1d** greatly improved both brain penetration and the release rate of MIBG in the central nervous system.



KEYWORDS: *Central nervous system, norepinephrine transporter, MIBG, radiosynthesis, redox chemical delivery system, 1,4-dihydroquinolines carriers*

The *in vivo* expression of norepinephrine transporter (NET) is mostly established in the central and peripheral sympathetic nervous system. Several different radiotracers for clinical imaging of NET expression were developed.

Among them, *meta*-iodobenzylguanidine (MIBG) is structurally similar to the neurotransmitter norepinephrine, and [^{123}I]MIBG single photon emission computed tomography (SPECT) imaging studies are the most accurate method for detection of catecholamine-secreting tumors including neuroendocrine tumors such as pheochromocytoma and neuroblastoma.[1−3]

Moreover, MIBG was also radiolabeled with iodine-131 for radiotherapy to treat neuroendocrine tumors. Positron emission tomography (PET) is more accurate and has the potential to be more sensitive and to provide better image resolution. In this context, efforts to develop MIBG analogs labeled with a positron emitter remain of great interest, and several ^{18}F-labeled benzylguanidine analogs have already been developed for PET imaging of NET expression. Recently, the radiotracer *meta*-[^{18}F]Fluorobenzylguanidine ([^{18}F]MFBG) has shown to be a very promising PET candidate leading to successful clinical investigations.[4−7] Dysregulation of NET is implicated in various neuropsychiatric disorders such as depression, anxiety, attention deficit hyperactivity disorders (ADHD), Parkinson's disease, Alzheimer's disease, and epilepsy. As the NET plays an important role in the central nervous system (CNS), the use of MIBG or MIBG analogs in brain imaging needs to be explored. However, MIBG is unable to cross the blood−brain-barrier (BBB). Guilloteau et al. have compared the uptake and release of radioiodinated *meta*-iodobenzylguanidine ([^{125}I]MIBG) and tritiated norepinephrine ([^{3}H]NE) in different regions of the rat brain. The authors found comparable regional distribution of [^{3}H]NE and [^{125}I]MIBG uptake in the rat brain.[8] A chemical delivery system (CDS) designed for MIBG able to cross the BBB would provide a potential imaging marker to visualize the NET in the brain (Figure 1). In the literature, Bodor et al. have developed an interesting CDS based on a lipophilic 1,4-dihydropyridine able to cross the lipophilic BBB.[9,10] Then, the 1,4-dihydropyridine system is oxidized into the CNS to a hydrophilic pyridinium species. which cannot cross back the BBB (named as "the locked in effect"). A subsequent

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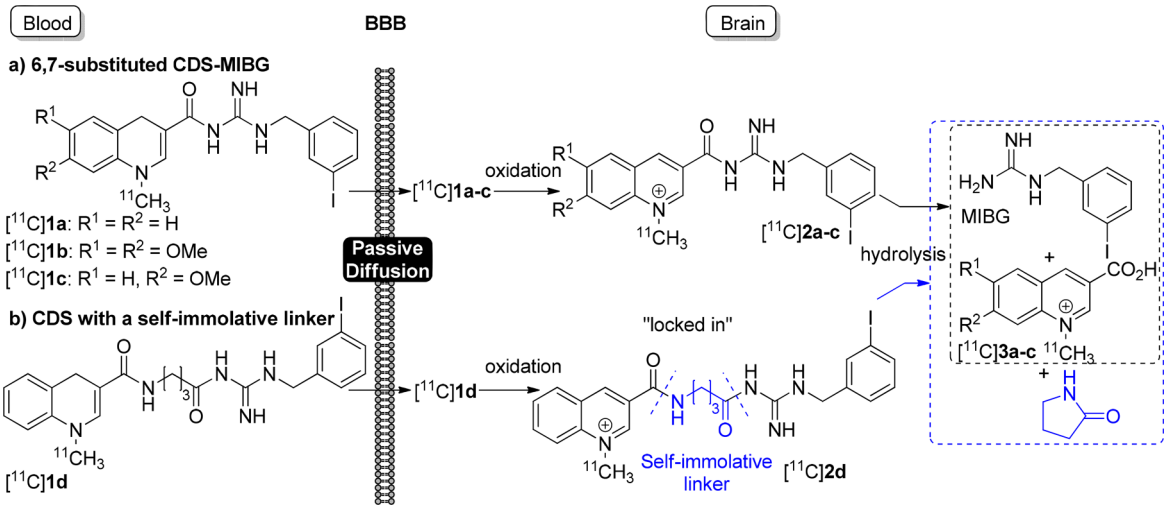
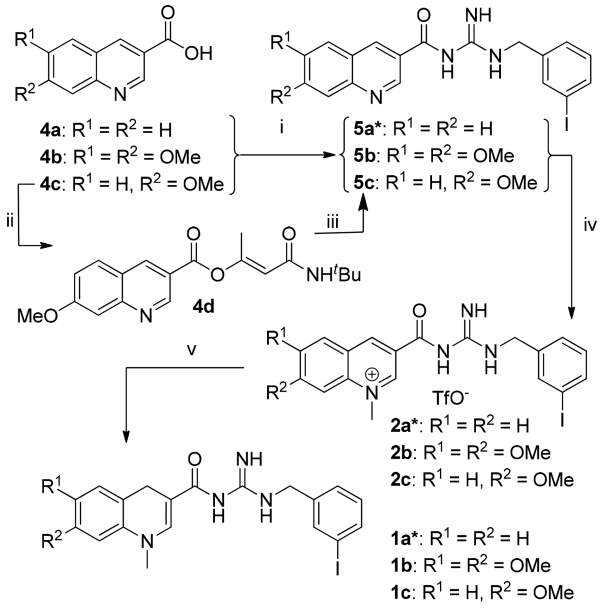


Figure 1. Development of a ^{11}C-chemical delivery system of MIBG into the CNS.

hydrolysis releases the active compound, which can then act directly on the target into the CNS. By using this approach, Bodor et al. have targeted many drugs to the CNS.[11−14] Later, Levacher et al. have solved many drawbacks related to this CDS by means of 1,4-dihydroquinolines instead of 1,4-dihydropyridines. However, although mainly drugs were successfully targeted using this strategy, very few reports deal with the use of this CDS to target radiotracers into the brain. A survey of the literature indicated that, aside from our previous work on MIBG,[15,16] only a single research article[17] explored the potential of this appealing CDS approach to deliver a radiolabeled agent into the CNS. As far as our preliminary research work on MIBG is concerned, our initial work focused on the radiolabeling with carbon-11 of the CDS in order to validate the concept described previously. The results of the *in vivo* studies were highly encouraging, supporting our working hypothesis that the dihydroquinoline system may possibly be a promising CDS to target MIBG to brain tissues. Indeed, after *in vivo* injection into rats of [^{11}C]CDS-MIBG ([^{11}C]**1a**), the passage of [^{11}C]**1a** through the BBB has been demonstrated as well as the presence of MIBG in the brain. However, this chemical delivery system has some limitations: (1) a moderate brain penetration has been measured, and (2) the oxidation kinetics of [^{11}C]**1a** was quite slow since more than 50% was still present in rat brain at 45 min post injection. For these reasons, this CDS still needed to be optimized before being applied to radioiodinated MIBG. This Letter will focus on the preparation and *in vivo* evaluation of new 1,4-dihydroquinoline-MIBG systems [^{11}C]**1b,c** bearing methoxy groups to tune the redox potential of the CDS. The preparation and *in vivo* evaluation of a 1,4-dihydroquinoline [^{11}C]**1d** having a self-immolative linker between the CDS and MIBG will be also reported (Figure 1).

To perform the radiosynthesis and *in vivo* study of our systems, it was first necessary to synthesize the precursors for radiolabeling and references that will be used to identify compounds in radio-HPLC. We have previously described the synthesis of the targeting system **1a** starting from quinoline **4a** (Scheme 1).[15] We decided to adopt the same approach to prepare **1b,c**. Thus, a coupling reaction from quinolines **4b,c**[18,19] and MIBG using CDI led to the corresponding quinolines **5b,c** in moderate yields (36% and 30%, respectively). Alternatively, quinoline **5c** could be prepared

Scheme 1. Synthesis of the Redox CDS-MIBG 1a−c[a]



[a]Reagents and conditions: (i) CDI, DMF, 20 °C, 1 h then MIBG, 20 °C, 1 h for **5a*** (60%) and **5b** (36%) and **5c** (30%); (ii) NBI, NEt_3, DMF, 20 °C, 12 h (74%); (iii) MIBG, DMF, 140 °C, 7 h (76%); (iv) CH_3OTf, CH_2Cl_2, 20 °C, 2 h for **2a*** (50%), 3 h for **2b** (60%) and **2c** (81%); (v) BNAH, CH_2Cl_2, 20 °C, 12 h for **1a*** (95%), **1b** (32%), **1c** (70%). **1a***, **2a***and **5a*** results are from ref 15.

by reacting MIBG with the activated enol ester[20] **4d** (76%), the latter having been obtained by reacting **4c** with NBI (74%). Then, quinolines **5b,c** were easily transformed into their corresponding quinolinium salts **2b,c** (60% and 81%, respectively) in the presence of methyl triflate. Finally, the desired CDS-MIBG **1b,c** were successfully obtained after regioselective reduction of quinolinium salts **2b,c** by means of BNAH (32% and 70%, respectively).

We next turned our attention to the synthesis of a CDS having a γ-aminobutyric acid (GABA) self-immolative linker group.[21−23] We envisaged the synthesis of quinoline **9** from GABA derivative **6a** (Scheme 2, route A). So, neutralization of hydrochloride amine salt **6a** and subsequent coupling reaction with carboxylic acid **4a** using BOP reagent led to quinoline **7a**

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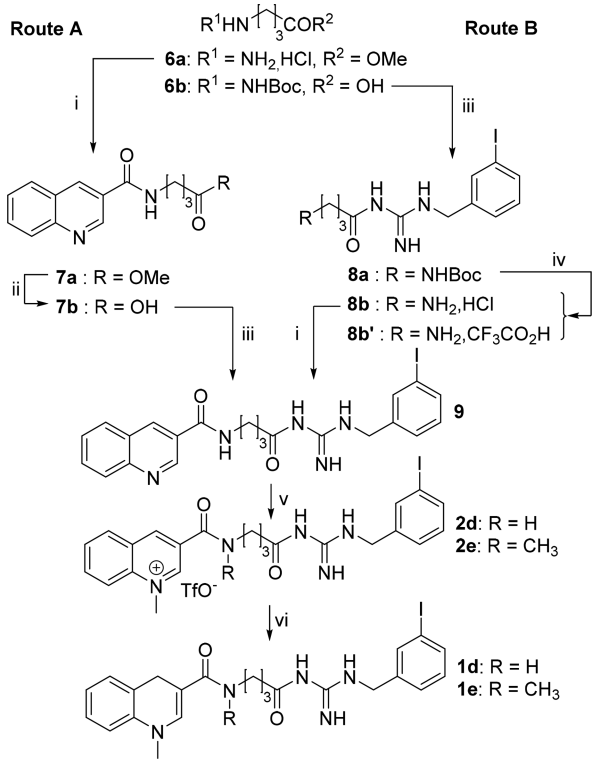
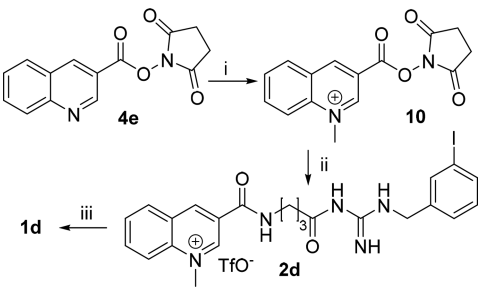
Scheme 2. Initial Routes To Synthesize the Targeting System 1d[a]



[a]Reagents and conditions: (i) NaOH then **4a**, BOP, NEt_3, DMF, 20 °C, 12 h (79% for **7a**, 25% for **9**); (ii) LiOH, THF, MeOH, H_2O, 20 °C, 3 h (96%); (iii) BOP, MIBG, NEt_3, DMF, 20 °C, 12 h (25% for **8a**, 4% for **9**); (iv) CH_3COCl, MeOH, 20 °C, 1 h for **8b** (95%) or TFA, CH_2Cl_2, −5 °C, 1 h for **8b′** (98%); (v) CH_3OTf, CH_2Cl_2, 20 °C, 12 h (44% for **2d** and 23% for **2e** determined by ^1H NMR); (vi) BNAH, CH_2Cl_2, 20 °C, 12 h.

(79% yield). The methyl ester functional group was hydrolyzed by LiOH to give carboxylic acid **7b** (96% yield). The latter was subsequently involved in a coupling reaction with MIBG using BOP to give **9** in a very low yield (4% yield). We also investigated other activation strategies of carboxylic acid **7b** by means of CDI, ClCOOEt, (COCl), NBI, or NHS/DCC. Unfortunately, we failed to obtain **9** by using these reagents. Alternatively, *N*-protected GABA **6b** and MIBG were reacted in the presence of BOP reagent to furnish the coupling product **8a** in 25% yield (Scheme 2, route B). Then, *N*-Boc deprotection was carried out by using either acetyl chloride/MeOH or TFA to lead, respectively, to the desired ammonium salts **8b** and **8b′** (95% and 98% yields). One may note that 20 equiv of acetyl chloride/MeOH or TFA were required during the course of the *N*-Boc deprotection to prevent from the formation of the undesired γ-lactam ring resulting from the cyclization reaction of the self-immolative linker. Thereafter, ammonium **8b** was neutralized back to pH 7 with sodium hydroxide before being converted into the desired amide **9** in 25% yield by means of a coupling reaction between **4a** and BOP reagent. The quaternization reaction of **9** with methyl triflate afforded a mixture of **2d,e** (44% and 23%, respectively, estimated by ^1H NMR). We then proceeded to a classical reduction of the mixture of quinolinium salts **2d,e** with BNAH. However, LC/MS analysis of the crude reaction medium revealed the presence of both 1,4-dihydroquinolines **1d,e** and quinolinium salts **2d,e**, which turned out to be extremely difficult to separate. Given this result, we decided to explore another route to obtain exclusively 1,4-dihydroquinoline **1d**. To overcome the alkylation reaction leading to undesirable compound **2e**, quinoline **4e** was first quaternized with methyl triflate to give the key intermediate **10** in 96% yield (Scheme 3). The resulting NHS-activated quinolinium **10**[24] was

Scheme 3. Alternative Route to the Redox CDS-MIBG 1d[a]



[a]Reagents and conditions: (i) CH_3OTf, CH_2Cl_2, 20 °C, 4 h (96%); (ii) polymer-bound DBU, **8b′**, THF, 20 °C, 12 h (58%); (iii) BNAH, CH_2Cl_2, 20 °C, 4 h (77% determined by ^1H NMR).

smoothly reacted with linker-MIBG derivative **8b′** to yield compound **2d** (58%). Finally, a classical reduction reaction with BNAH led to the desired MIBG-targeting system **1d** (77% determined by ^1H NMR).

Radiosyntheses of [^{11}C]**1b,c** were carried out as depicted in Scheme 4 according to a two-step synthetic procedure.[15,16,25] The structures of the ^{11}C-labeled products were confirmed by comparing their retention time with the corresponding nonradioactive standard compounds using reverse-phase HPLC. Thus, the quaternization reaction of quinolines **5b,c** with [^{11}C]methyl triflate afforded quinolinium salts [^{11}C]**2b,c**. Reduction of [^{11}C]**2b,c** was conducted with BNAH for 5 min at 100 °C to provide the corresponding 1,4-dihydroquinolines [^{11}C]**1b,c** (respectively, 68% and 61% relative percentages determined by radio-HPLC). The same procedure was applied to the radiosynthesis of [^{11}C]**1d**. However, radio-HPLC analyses demonstrated that [^{11}C]**2d** was not stable enough under these high dilution reaction conditions. To circumvent the poor stability of [^{11}C]**2d**, we decided to add the reducing agent BNAH and the alkylating agent [^{11}C]CH_3OTf simultaneously. Then, the reaction mixture was left to react 5 min at 20 °C. To prevent [^{11}C]**1d** from oxidation during the purification step, basic HPLC conditions were required. So, by adding triethylamine in HPLC eluent, 1,4-dihydroquinoline [^{11}C]**1d** was obtained with a radiochemical purity of 50% (based on HPLC analysis of the crude product). A TRACERlab FX-MeI and FX-M radiosynthesis module was used to achieve a fully automated radiosynthesis of [^{11}C]**1b−d** using a two-step reaction as shown in Scheme 4. The total synthesis time of the fully automated process was approximately 50 min. Activity levels in the final product ranged from 592 to 814 MBq for [^{11}C]**1b**; 259−444 MBq for [^{11}C]**1c**; and 148−518 MBq for [^{11}C]**1d**. The radiochemical purities of [^{11}C]**1b−d** were >95%.

Then, biological studies were conducted in rats to determine, *in vivo*, the cerebral penetration through the BBB of the different MIBG-targeting systems [^{11}C]**1b−d** by measuring the radioactivity of the cerebral samples obtained after sacrifice of the animals (Figure 2). Last but not least, we

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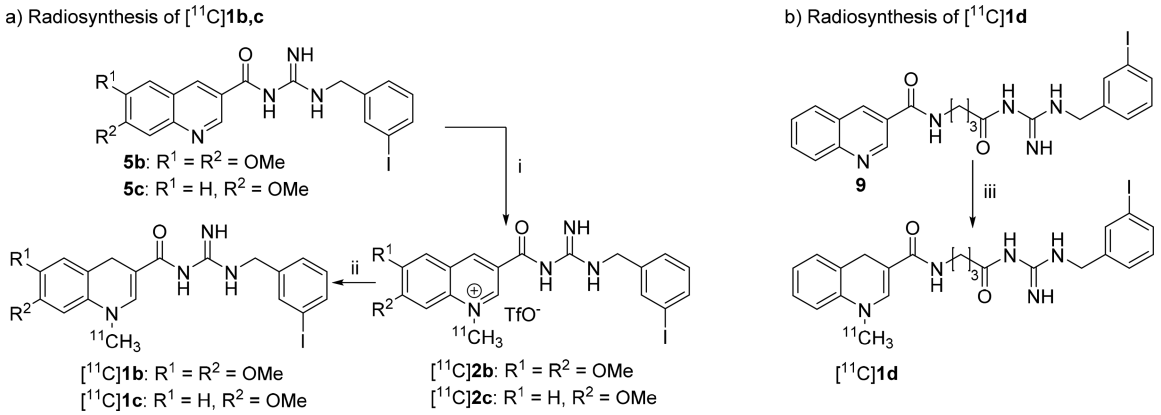
Scheme 4. Radiosyntheses of [^{11}C]1b−d[a]



[a]Reagents and conditions: for [^{11}C]**1b,c** from **5b,c**: (i) [^{11}C]CH_3OTf, CH_3CN, 20 °C, 5 min; (ii) BNAH, CH_3CN, 100 °C, 5 min; for [^{11}C]**1d** from **9**: (iii) [^{11}C]CH_3OTf, CH_3CN, 20 °C and BNAH, then 10 min, 20 °C.

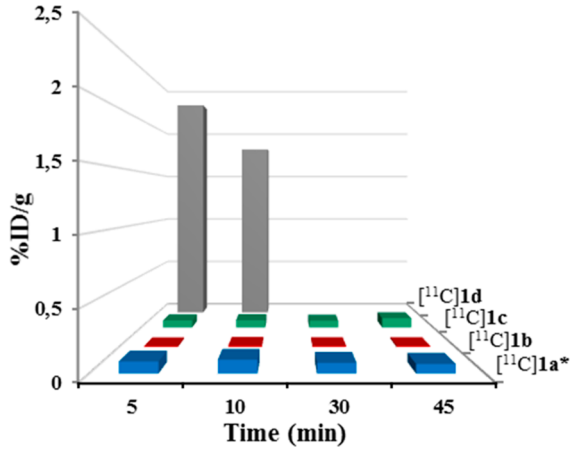


Figure 2. *Ex vivo* biodistribution of the radioactivity in rat brain at different time intervals following tail vein injection of [^{11}C]**1a−d** (5, 10, 30, and 45 min for [^{11}C]**1a−c**; 5 and 10 min for [^{11}C]**1d**). Results are expressed in percent of injected dose per gram (%ID/g, mean, n = 2 for each point). [^{11}C]**1a*** results are from ref 15.

were also interested (both in brain and plasma) in the oxidation rates of [^{11}C]**1b−d** into the corresponding quinolinium salts [^{11}C]**2b−d**, which subsequently led to the cleavage of MIBG from the carrier through hydrolysis. The results will be compared to those already obtained from [^{11}C]**1a**[15] in order to select the most promising CDS to target MIBG to the CNS.

Then, the monitoring of both oxidation and MIBG cleavage steps in the CNS were investigated from brain samples, which were analyzed by radio-HPLC after radiotracer injection. Both CDS-MIBG [^{11}C]**1b** and [^{11}C]**1c** proved to be rather stable since 87% and 90% of 1,4-dihydroquinolines [^{11}C]**1b,c**, respectively, were detected at 10 min after injection, together with 12% and 5% of quinolinium salts [^{11}C]**2b,c**, respectively, but with no traces of carboxylic acids [^{11}C]**3b,c** (Figure 3b,c). Regarding CDS-MIBG [^{11}C]**1a** previously investigated,[15] the percentage of carboxylic acid [^{11}C]**3a** reached 11% at 10 min after injection, highlighting a faster cleavage of MIBG from the quinolinium salt **2a** (Figure 3a). We can therefore draw the conclusion that the presence of methoxy groups on the carrier do not increase the oxidation rates of [^{11}C]**1b,c** in the brain compared to [^{11}C]**1a** and even seems to delay the cleavage of MIBG from the resulting quinolinium salts [^{11}C]**2b,c**.

At this stage, it seems that in terms of brain uptake, oxidation, and hydrolysis rates, CDS-MIBG [^{11}C]**1a** remains the best candidate among the three CDS-MIBG [^{11}C]**1a−c**. In

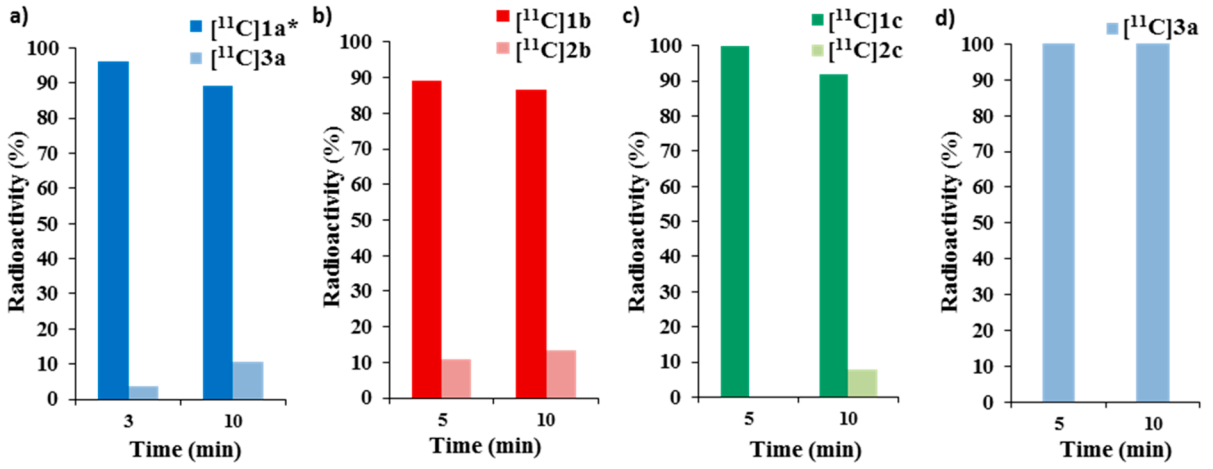


Figure 3. Percentage of the expected [^{11}C]radioactive species in brain after injection into rat of (a) [^{11}C]**1a**, (b) [^{11}C]**1b**, (c) [^{11}C]**1c**, and (d) [^{11}C]**1d** (mean, n = 2 for each time point). [^{11}C]**1a*** results are from ref 15.

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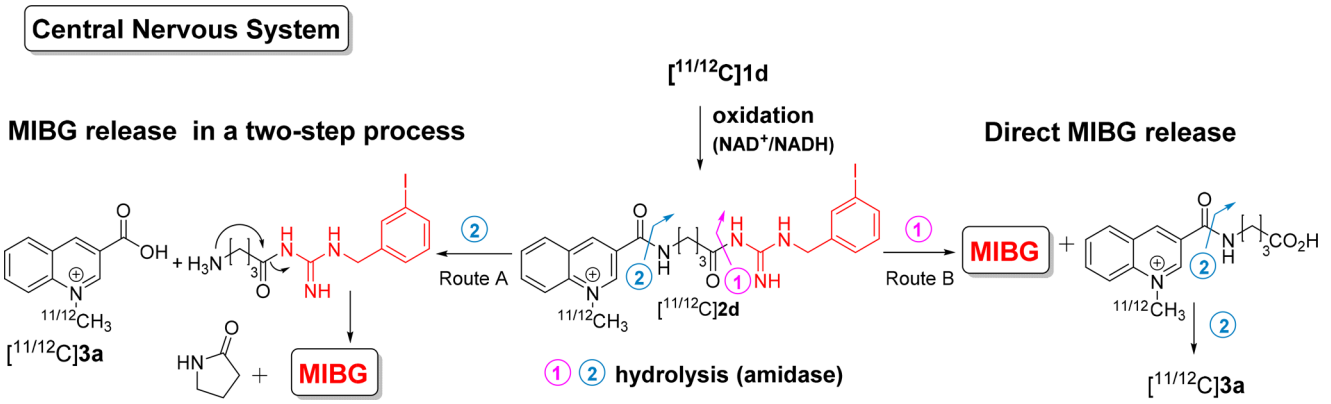
Scheme 5. Schematic Representation for MIBG Release from Carrier-linker-MIBG 1d



contrast, HPLC analyses of both brain and plasma samples at 5 min after injection of 1,4-dihydroquinoline [^{11}C]**1d** revealed the presence of only one polar radioactive compound corresponding to the carboxylic acid [^{11}C]**3a** (Figure 3d). These data indicate a fast *in vivo* oxidation of [^{11}C]**1d** followed by hydrolysis of the resulting quinolinium salt [^{11}C]**2d** leading to the release of carboxylic acid [^{11}C]**3a** along with the linker-MIBG intermediate, which would undergo cyclization to produce desired MIBG along with γ-lactam as byproduct. This scenario depicted in Scheme 5 (route A) is backed up by the fact that during the preparation of **8b,b′**, a fast cyclization process of the corresponding free amine was observed leading to MIBG and γ-lactam products. At this stage, a second scenario cannot be ruled out in which hydrolysis would occur at the carbonyl group attached to MIBG as shown in Scheme 5 (route B) to release MIBG in a single step. In light of our results, it might be concluded that the presence of a linker between the 1,4-dihydroquinoline moiety and MIBG increases notably not only the BBB passage and oxidation rate of [^{11}C]**1d** but also the release of MIBG from the carrier in the brain.

In this study, we successfully synthesized and labeled with carbon-11 various [^{11}C]CDS-MIBG ([^{11}C]**1b–d**). We also examined *in vivo* their potential to deliver MIBG into the central nervous system. A preclinical evaluation showed high BBB permeability of the carrier-linker-MIBG [^{11}C]**1d** as demonstrated by the high percentage of radioactivity measured in the brain, whereas the two other CDS-MIBG [^{11}C]**1b,c** exhibited poor BBB passage. Once in the brain, fast oxidation of the 1,4-dihydroquinoline [^{11}C]**1d** and prompt cleavage of MIBG from the resulting quinolinium salt [^{11}C]**2d** take place as evidenced by the only presence of carboxylic acid [^{11}C]**3a** in brain samples after 5 min. In light of these promising *in vivo* profiles observed with [^{11}C]**1d**, this work paves the way to the use of the CDS-radiolabeled-MIBG as an appealing imaging tool for the study of cerebral adrenergic nerve endings within the brain.[26272829]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.8b00642.

Experimental procedures and characterization of all compounds, radiosyntheses and procedures for *in vivo* experiments (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript;

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

MIBG, *meta*-iodobenzylguanidine; NET, norepinephrine transporter; BBB, blood–brain barrier; CDS, chemical delivery system; SPECT, single photon emission computed tomography; PET, positron emission tomography; CNS, central nervous system; ADHD, attention deficit hyperactivity disorder

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