Research for New Production Method of no carrier added I-131 MIBG

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1. Introduction

The β-particle emitters I-131, lutetium-177 and yttrium-90 have been introduced and commonly used over the last 40 years. They are the most frequently used emission type for Radiopharmaceutical therapy (RPT) agents

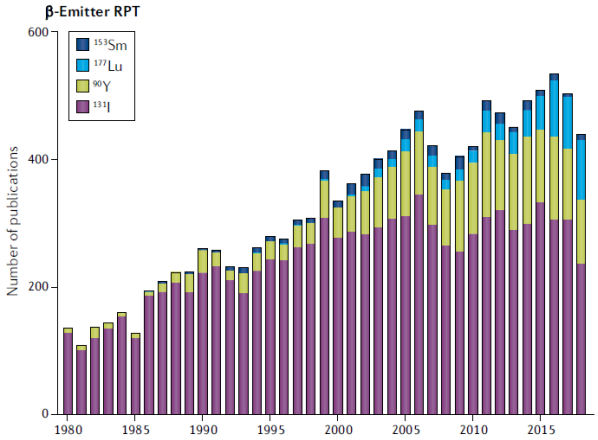


Fig. 1 Publications per year related to RPT

Metaiodobenzylguanidine (MIBG) contains a benzyl and a guanidine group. MIBG is a substrate of the norepinephrine transporter (NET).

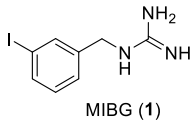


Fig. 2 Molecular structure of MIBG

I-131 MIBG was introduced in the 1980s as a potential systemic therapy for patients with progressive and/or symptomatic malignant pheochromocytomas and paragangliomas (MPPGs) that express the NET in the tumor cell membranes. At the beginning of the 21st century, a purified, high–specific-activity (HSA) I-131 MIBG was developed for the treatment of MPPG. HSA I-131 MIBG was approved by the US Food and Drug Administration (FDA) in 2018. In this manuscript we wanted to design a better process by comparing the synthetic method of 131-I MIBG that is currently being produced in KAERI with other company's method.

2. Synthetic Method

KAERI have been produced I-131 MIBG using isotopic and halogen exchanges. Direct replacement of stable iodine isotopes on dimer **2** by a radioiodine isotope, known as the carrier added (CA) method, is a well-known procedure. Through the above methods, low-specific-activity (LSA) I-131 MIBG with a low content of radioiodine was obtained.

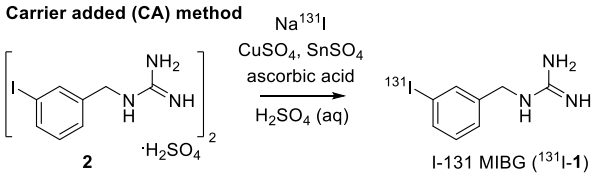


Fig. 3 Synthetic method of LSA I-131 MIBG

Organotin compounds are highly toxic. But iododestannylation of polymeric precursor **3** using the no carrier added (NCA) method, which involves a monomer, releases high-specific-activity (HSA) I-131 MIBG into solution, while the toxic tin-containing by-products remain bound to the insoluble polymer.

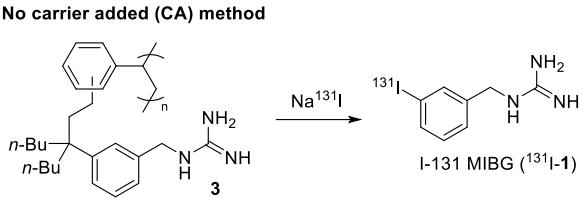


Fig. 4 Synthetic method of HSA I-131 MIBG

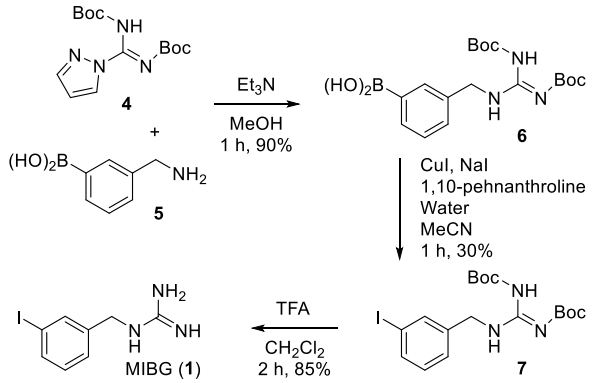
3. New Production Plan

We conducted a process development to switch from CA to NCA method in the synthesis of MIBG. We were looking for a process that can reduce the elemental impurities, and we wanted to improve the side effects caused by cold MIBG through the CA process.

Characteristics	LSA I-131 MIBG	HAS I-131 MIBG
Manufacturing process	Simple isotope exchange methodology	Solid phase precursor Ultra-trace process
Unlabeled MIBG in each dose	Large amount	None
Potential efficacy	Low levels of radioactivity delivered to tumor per dose	High levels of radioactivity delivered to tumor per dose
Potential safety	Excess cold MIBG and increased risk for cardiovascular issues	No cold MIBG, low cardiovascular risk

Table 1. Differences between LSA and HSA I-131 MIBG

Through an SN2-type reaction involving pyrazole **4** and boronic acid benzylamine **5**, compound **6** was synthesized (90%). Attempting nucleophilic iodination via Cu_2O, but an unidentified compound predominantly formed, deviating from Zhang's work. Despite varying reaction conditions, the desired compound **7** remained elusive. Notably, when CuI was substituted for Cu_2O, the Boc-MIBG **7** was obtained with a low yield of 30%. Subsequently, MIBG (**1**) was successfully synthesized via a TFA (85%). Considering the potential for interference from iodine ions present in the CuI catalyst during radioiodine labeling, we are currently investigating alternative copper-based catalysts and conditions.



Scheme 1 Synthesis of MIBG (**1**)

4. Conclusion

We designed and conducted experiments to produce MIBG by NCA method using iododeboronation. We wanted to derive the synthetic method of 131-I MIBG that is applicable to the current production facility.

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