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Determination of Impurities and Degradation Products/Causes for *m*-Iodobenzylguanidine Using HPLC-Tandem Mass Spectrometry

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Abstract

m-Iodobenzylguanidinium hemisulfate (MIBGHS) is a precursor in the preparation of radioiodine-labeled *m*-iodobenzylguanidine (MIBG), which is used as a radio-imaging and therapy agent for neuroendocrine tumors and myocardial sympathetic nerve function. To ensure the quality and efficacy of the medicine and prevent side effects, the precursor purity, source of impurity, and derivatives have to be determined. In this study, the purity of synthesized MIBGHS and the amount of contaminants therein were determined by high-performance liquid chromatography and ultraviolet detection, gradient eluted by ammonium formate aqueous solution and acetonitrile mobile phase on both C8 and phenyl type column. The impurities were identified on the basis of molecular and fragmented ion mass spectra using of electrospray ionization triple quadrupole tandem mass spectrometry. The results revealed the presence of process-related impurities including *m*-bromobenzylguanidine (MBrBG) and overreacted byproducts. Stress test results indicated that MIBGHS is stable under acidic and dry thermal conditions for at least 72 h but MIBG aqueous solution was deteriorated slowly when exposed to UV light, thermal, oxidative and alkaline environments. Thus, *m*-iodobenzylamine, the starting material intended for the synthesis of MIBGHS should be analyzed to ensure that it is free from *m*-bromobenzylamine impurity. Stored under normal condition (−18˚C), MIBGHS is stable for at least 12 months. The chemically labile guanidine and amine groups in MIBGHS are the major causes of its instability, while iodide loss from the phenyl group is a minor cause.

Keywords

MIBG, *m*-Iodobenzylguanidine, Neuroendocrine Tumor, Degradation

Derivative, Impurity Identification, Tandem Mass Spectrometry

1. Introduction

m-Iodobenzylguanidine (MIBG, **Figure 1**) is structurally similar to the neurotransmitter norepinephrine (NE) and acts as an adrenergic neuron blocker. Therefore, it is easily absorbed by cells rich in sympathetic neurons, such as those of the heart and neuroendocrine glands, via an active uptake process regulated by the NE transporter (NET) which is responsible for shuttling NE into cells [1] [2] [3]. When MIBG is labeled with radioactive iodine ($^{123/124/131}$I-MIBG), it is employed as a radiopharmaceutical agent in pathology diagnosis of various neuroendocrine gland tumors, including neuroblastoma, paragonglioma, pheochromocytoma, malignant glioma, thyroid medullary carcinoma, malignant schwannoma, and myocardial imaging by single-photon emission computed tomography (SPECT) and positron emission tomography (PET). Furthermore, ^{131}I-MIBG is employed in neuroendocrine glands tumors therapy applications [4]-[8]. As neuroendocrine gland tumors overexpress NET and enrich *I-MIBG in disorder organs and emission radiation there [9]. Neuroblastoma accounts for 8% of childhood malignant tumor [9]. Thus, radioiodine-labeled MIBG species are multiple purpose radiopharmaceuticals. They have been approved by the USA FDA (2008) [7] [9] and are extensively applied clinically around the world [10] [11] [12] [13] with commercial name as "AdreView" [14].

A common method used to prepare radioactive-iodine labeled MIBG involves the isotope replacement reaction of cold-MIBG (^{127}I-MIBG) with radioactive iodide [1] [15]. The precursor is mixed and reacted with a solution of the sodium salt of $^{123/124/131}$I containing ammonium sulfate, sodium acetate, glacial acetic acid, and sodium phosphate buffer, at 175˚C for 1 h. The product $^{123/124/131}$I-MIBG is then chromatographically separated from the solution on a C-18 preparative column.

Four methods for preparing the cold-MIBG hemisulfate salt (MIBGHS) precursor have been reported in the literature. Synthesis method 1 (**Figure 1**) is followed by the Institute of Nuclear Energy Research (INER), Taiwan [16]. A new drug application (NDA) license from the Food and Drug Administration, Taiwan (TFDA) for radiopharmaceutical MIBG was approved in Sep., 2019.

In order to ensure the quality and safety of an active pharmaceutical ingredient (API), determination of its purity level and identification/quantification of impurities in the precursor are required by International Council for Harmonisation (ICH) to follow "Guidance for Industry—Q3A Impurities in New Drug Substances" [17], and the Pharmaceutical Inspection Co-operation Scheme Good Manufacturing Practice (PIC/S-GMP) of medicinal products for humans. If impurities contaminated with the API, their unexpected effects on the patient may result in health impactions, or at least reduce efficacy dose of medicine; for

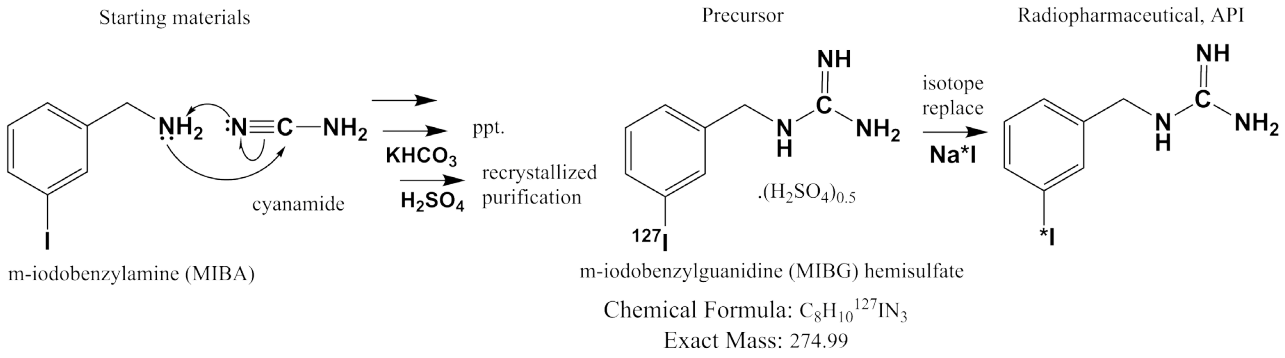


Figure 1. Synthesis route for MIBG.

imaging agent, impurities might affect resolution. Furthermore, the stabilities of the precursor during storage, transport, and reaction, as well as the potential degradation derivatives and causes for MIBG are issues that have to be addressed but have not been reported previously in the literatures.

MIBG contains a free guanidine group, which is a very strong organic base (pKa between 13 and 13.6 depending on substituents) [18] [19] [20] that is readily protonated to the guanidinium form. The guanidine group exists widely in various natural products and synthetic pharmaceutically active compounds [18]-[22]. Its bioactivities come from binding through charge pairing, hydrogen bonding with proteins and nitrogen coordination to metalloproteinases [22]. Some guanidine compounds, including MIBG itself, also have aromaticity, allowing interaction with enzymes or cell receptors by π-π bonding interaction [18]. These types of interaction enhance recognition specificity and affinity with target proteins and uptake by cells. Characterizing the behaviors of bioactive molecules such as MIBG under various conditions is vital for their proper use.

The aims of this study were to determine the purity and stability of the cold-MIBG precursor synthesized at the INER, and to identify the contaminants and their sources, as well as the degradation derivatives and causes under various conditions, including thermal, acidic or alkaline hydrolysis, oxidization, and photolysis. This was achieved by C8- and phenyl-type reversed-phase HPLC-MS/MS analysis. The results also provide information on the chemical characteristics of radioiodine-labeled MIBG, the API for radio-imaging or therapy.

2. Materials and Methods

2.1. Chemicals and Standards

MIBGHS standard reference material was purchased from European Pharmacopeia (EP). Analytical reference materials including *m*-bromobenzylguanidine (MBrBG), *m*-bromobenzylamie (MBrBA), and *m*-iodobenzylamine (MIBA) hydrochloride were purchased from Abcr, GmbH (Germany), Alfa Aesar (USA) and Sigma-Aldrich (USA), respectively. Several different batches of MIBGHS

were synthesized and purified by the Chemistry Division at the INER and stored at −18˚C - −20˚C until analysis. The HPLC analytical columns for analysis of MIBG were reversed-phase C8 (150 × 4.6 mm, particle size 5 μm, Agilent Eclipse XBD) and phenyl-type (100 × 2.1 mm, particle size 3 μm, Hypersil Gold phenyl, Thermo Fisher, USA).

2.2. Instrumentation

2.2.1. HPLC-MS/MS

The purity and stabilities in degradation studies of the synthesized MIBGHS were obtained using an HPLC system (Agilent 1100/1200 series, Palo Alto, CA, USA) with an online degasser, binary pump, autosampler, temperature controlled column oven and diode array detector (DAD, detection wavelength at 229 nm). Data were acquired and processed using Agilent ChemStation 10.02 software. The HPLC system was coupled with an MS/MS apparatus (4000 QTRAP, AB Sciex, Concord, ON, Canada), operated using Analyst 1.6.2 software. The mass spectrometer was equipped with an electrospray ionization source and a triple quadrupole linear ion trap mass detector. It was operated in positive-ion detection mode.

2.2.2. Other Equipment

Thermal decomposition was surveyed using a temperature programmable (±1˚C) digital oven (FD 53, Binder GmbH, Tuttlingen, Germany) equipped with a forced convection unit. Photolysis light source (253.7 nm, 20 W) at a distance 15 cm. test was studied under UV irradiation using a low-pressure mercury lamp as the light source (253.7 nm, 20 W) at a distance 15 cm.

2.3. Analytical Methods

2.3.1. HPLC

Intially, MIGB was eluted on a C8 column with an isocratic mobile phase at a flow rate of 1.5 mL/min for 7 min, per injection solution volume of 10 μL by an autosampler. Mobile phase made up 4.1 mL triethylamine (TEA, 99%), 1 mL trifluoroacetic acid (TFA) in 1 L ddH_2O/CH_3CN (3:1, v/v), and was altered to pH 4.0 with phosphoric acid.

Later, a new method that improved the MIBG peak shape was developed. This method employed a phenyl-type column with an eluent composed of mobile phase A (4 mM ammonium formate, 0.5 mL acetic acid in 1 L deionized water, pH 4.9 - 5.0) and mobile phase B (4 mM ammonium formate dissolved in acetonitrile, 100%) by the gradient program given in **Table 1** at a flow rate of 0.5 mL/min and a sample solution volume of 5 μL. The turnaround time for the analyses was 14 min.

2.3.2. Mass Spectrometry

Tandem mass spectra [including enhance product ion (EPI), neutral loss (NL), precursor ion (PI) and MS/MS mode] of MIBG and its contaminants or derivatives were acquired by infusion sample solution with a micro syringe

Table 1. Gradient program for chromatographic separation of MIBG and its derivatives on phenyl type column.

Time, min	Pump A (%)	Pump B (%)
0.0	85	15
1.0	80	20
3.0	70	30
8.0	20	80
11.0	20	80
11.1	85	15

pump at 10 μL/min into 4000QTRAP. Molecular ion mass spectra (MS^1) of prepared MIBGHS product and incubated MIBG stress tests solutions were acquired by leading in-HPLC eluant into the mass spectrometer. Acquisition parameters for the instrument were listed in Table 2.

2.3.3. Stress Tests

The effects of acidic, alkaline, and oxidative factors on MIBG were determined by adding 50 μL of HCl (30%), 10 μL of TEA (99%), or 50 μL of hydrogen peroxide (30%), respectively, to an aqueous MIBG solution (1 mg in 0.5 mL) and incubating it at 25˚C with shaking until analysis. The incubated MIBG solutions were diluted 1:1 with mobile phase A to prepare the sample solutions.

The effects of thermal and photolytic conditions on MIBG were examined both as a powder and dissolved in deionized water. MIBGHS powder (0.5 mg) and its aqueous solution (0.5 mg in 0.5 mL) were incubated in a fan oven (80˚C C) or irradiated with a UV lamp at room temperature.

3. Results and Discussion

3.1. MS/MS Spectra and Fragmentation of MIBG

To identify the impurities in MIBG, determining suitable mass spectrometer parameters and fragmentation patterns for MIBG is the first issue. A solution of MIBG (EP standard reference material) in aqueous ammonium formate (5 mM) and acetonitrile (1:1) was supplied to the 4000QTRAP. The intensity was optimized at DP 10 - 30 V, curtain gas 10 - 30 psi, IS 4800 - 5200 V, CE 20 - 60 V, EP 10 - 30 V, and GS1, GS2 both 10 psi.

The *m/z* values of the moleculr ions of MIBG are 276 and 277 and those of the fragmentation product ions of MIBG (*m/z* 276) were 259, 234, 217, 149, and 90, which indicated the fragmentation scheme of MIBG outlined in Figure 2. These results indicate that the weak chemical bonds in MIBG include the phenyl-iodide and C-N bonds, because the parent ion possesses I·, NH_3, cyanamide, and guanidinium leaving groups ($\Delta m/z$ = −127, −17, −42, and −59, respectively) that results in product ions with more delocalized and stable structures. An interesting point here is that when the iodo-radical leaves from

Table 2. Analytical parameters of mass spectrometer used for the identification of impurities and derivatives in MIBG and MIBGHS.

Mass spectrometry	ESI-QqQ LIT
Source temperature, TEM (˚C),	
LC eluent	400
10 μL/min by micro syringe pump	Not specified
Ionization voltage, IS (V)	5200
Ion source gas 1, GS1 (psi)	10
Ion source gas 2, GS2 (psi)	10
Detector polarity	Positive ion
Scanning mass range, MS^1	100 - 700
MS^2	85 - 600
Resolution, Q1 and Q3	Unit
Curtain gas, CUR (psi)	20
Collision gas, CAD (psi), MS^1	0
MS^2	Medium
Declustering potential, DP (V)	30
Collision energy, CE (V)	20 - 40
Collision exit potential, CXP (V)	15
Entrance potential, EP (V)	10

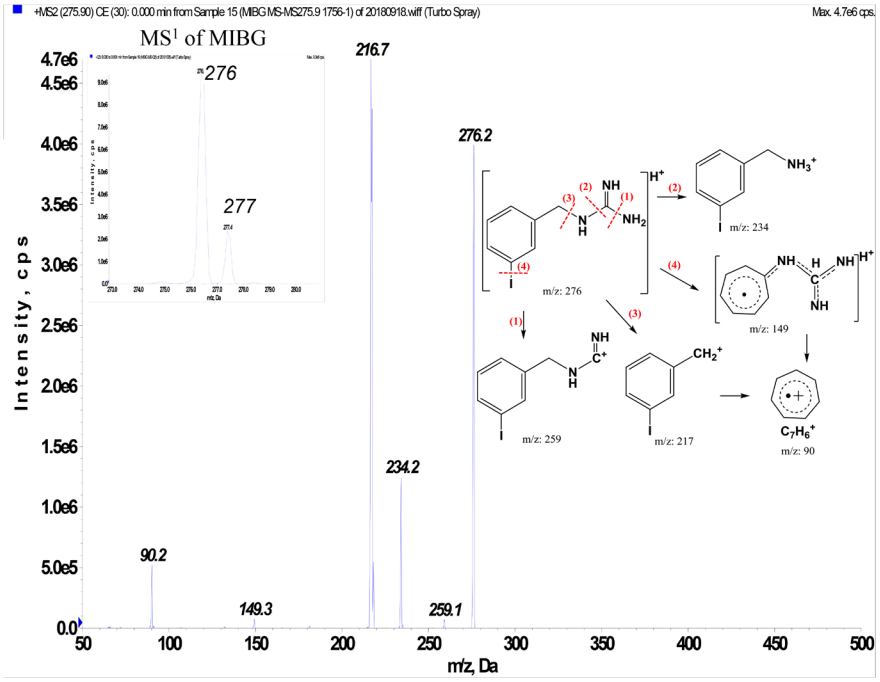


Figure 2. MS^1, MS^2 and fragmentation scheme for MIBG.

phenyl group, a transient seven-member aromatic conjugated radical cation is formed.

3.2. Purity of MIBG and Determination of Process Related Impurities

Analytical methods for determining the purity of MIBG are reported in the U.S. Pharmacopeia (USP) [23], and ^{131}I-MIBG metabolites in the plasma of patients with metastatic pheochromocytoma are separated on a reversed phase C18 column [24] [25] and detected by UV absorbance. In those studies, the mobile phase contained phosphoric acd and TEA as ion pair agents because of the high polarity and positive charge of the guanidinium group. However, phosphate and TEA suppress electrospray ionization efficiency and reduce mass spectra signals [26]. No HPLC-MS/MS method for MIBG and its derivatives has been reported yet. Consequently, we initially tried to separate the impurity in our lab-synthesized MIBG on a C18 column with an isocratic mobile phase comprising a phosphoric acid-TEA aqueous buffer and acetonitrile (9:1) (USP method), but no contaminants were observed in the chromatogram (**Figure 3**) by UV detection.

Thus, we initially employed an HPLC method involving a C8 column and phosphate, TEA mobile phase to determine MIBG purity and allow tandem MS analysis, but we also later developed a method without phosphate and TEA using a phenyl column to determine the MIBG impurities and derivatives by mass spectrometry.

The starting materials used in our MIBG synthesis included *m*-iodobenzylamine hydrochloride (MIBA. HCl), cyanamide ($N\equiv C\text{-}NH_2$), and potassium bicarbonate, which were refluxed, and the product was then precipitated and recrystallized as the hemisulfate salt. The purities of MIBGHS over different preparative batches were all above 99.0% according to analysis using the C8 column and isocratic elution. A major impurity peak (0.3% - 0.5%) was observed with molecular ions of *m*/*z* 230 and 228 (isotope distribution ratio ca. 1:1, indicating that it contains Br). The fragmentation ion mass spectra of the impurity showed signal for 230 → 213, 188, 171, and 90; and 228 → 211, 186, 169, and 90. Therefore the impurity was determined to be the bromo-substituted analog, MBrBG (**Figure 4**), where the iodo of MIBG is substituted with a bromo. Therefore, the MIBA starting materal was analyzed by HPLC (C8 column), and the chromatogram showed a peak area at retention time (t_R) 6.1 min of 99.8% and a trace impurity (t_R 4.1 min, 0.2%). The *m/z* values of the impurity molecular ion were 188 and 186, and those of their fragmentation product ions pairs were 171, 90 and 169, 90 respectively (**Figure 5**). Therefore the impurity in MIBA was MBrBA. The HPLC and MS results were also confirmed using purchased reference materials, MBrBA and MBrBG. Based on our conclusions, it is indicated that the starting material MIBA should be analyzed for impurity before the first time it is employed to prepare MIBG. A new batch (#0000000624, replacing the previously used #101582951) of the MIBA. HCl agent was employed

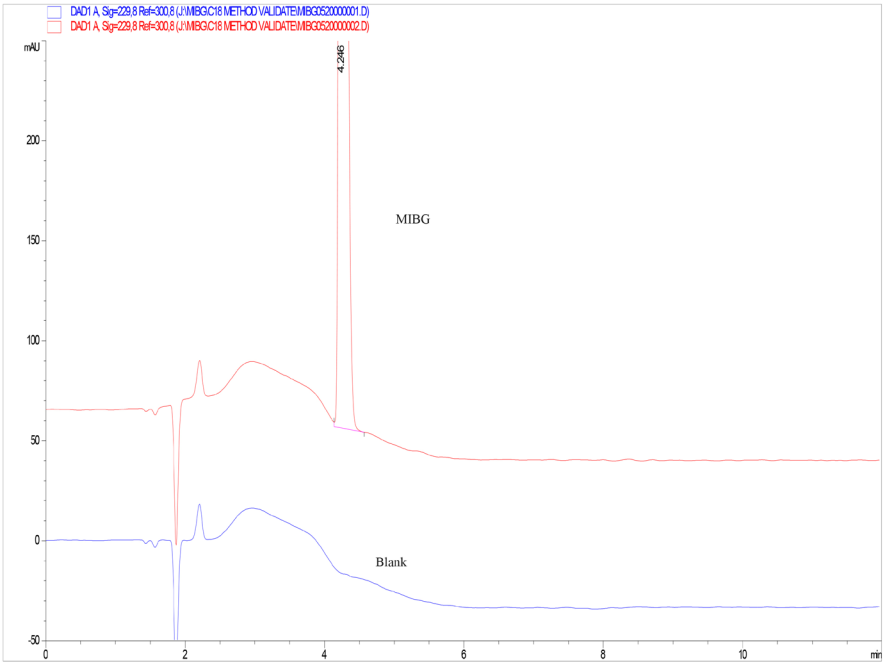


Figure 3. Chromatogram of MIBG provided using a C18 column.

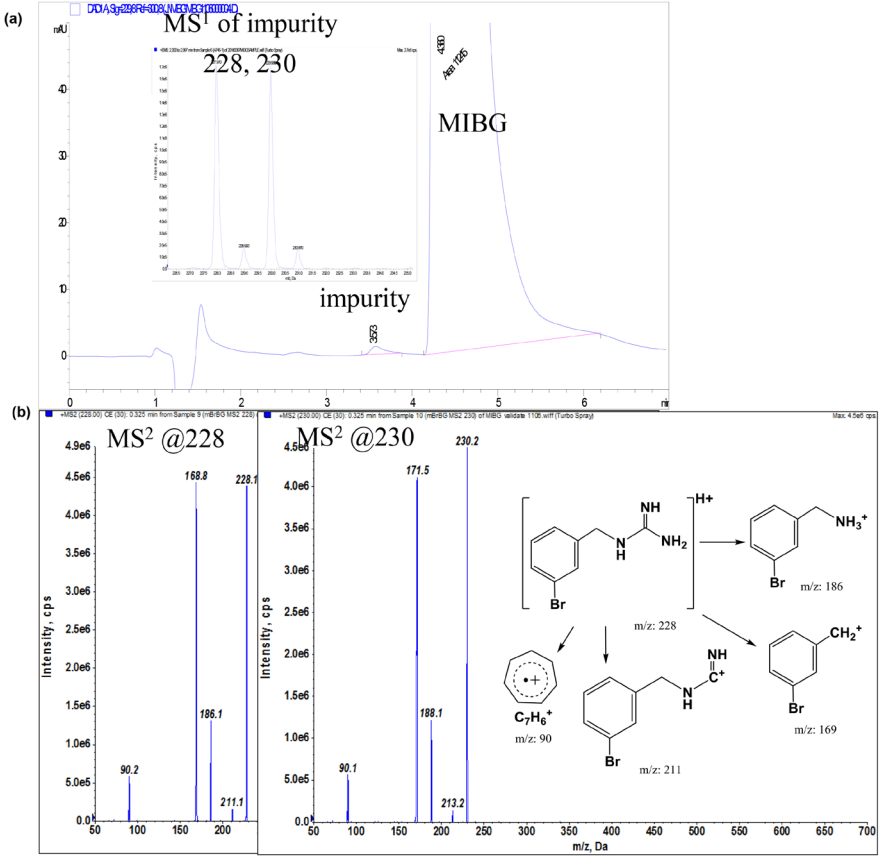


Figure 4. Chromatogram of MIBG provided using a C8 column and MS^1 of the impurity peak (a). MS^2 (MS^1 = 228, 230) and fragment structures of the impurity MBrBG in MIBG (b).

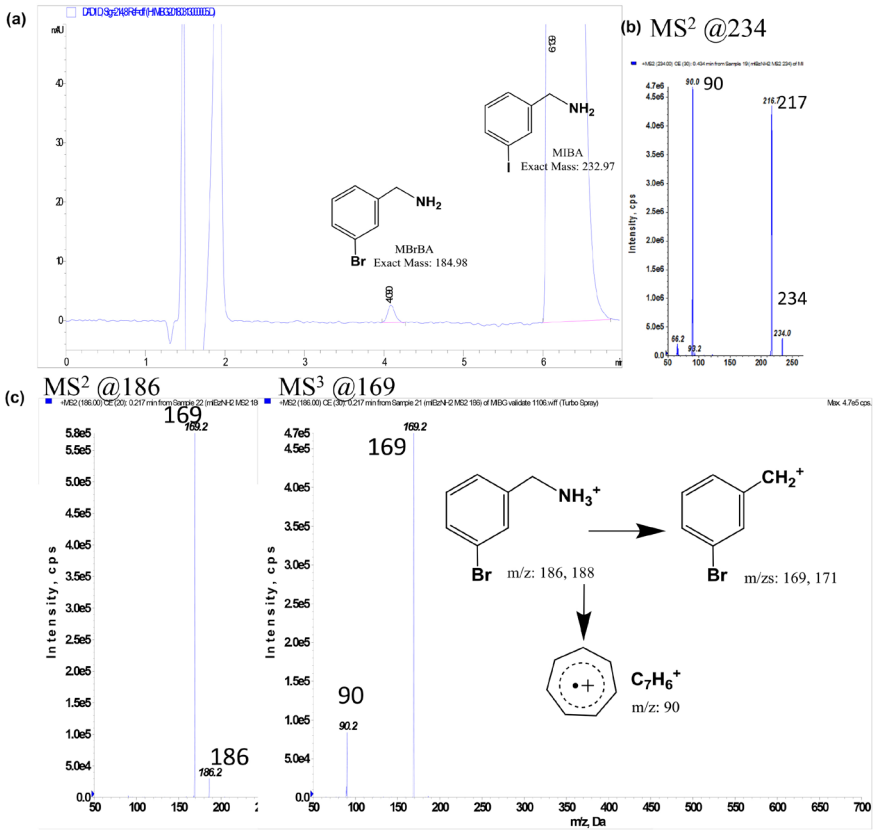


Figure 5. Chromatogram of MIBA with trace impurity MBrBA (a); MS/MS sprctra for MIBA (b), and MBrBA (c).

to prepare the later batches of MIBG, and neither the MIBG product nor the MIBA starting material contained bromo-sunstituted analogs.

In order to improve chromatographic efficiency and thus analyze more complex derivatives of MIBG, an HPLC-MS/MS method without TEA, TFA and phosphoric acid in the mobile phase, which interfere with mass spectrometry analysis, was developed. In this method, a reversed-phase column with phenyl groups (Hypersil Gold phenyl column) was employed, as π-π interaction between analytes and stationary phase enhances the separation efficiency of MIBG [27]. **Figure 6** shows the resultant chromatogram of MIBG (purity > 99.4%) with the number of theoretical plates (N) at 10,000 and a retention time of 4.8 min. The peak is sharp and thus very easily distinguished from impurities. Consequently, this chromatographic method was later applied to study the stability and degradation products/ causes.

The short-term stability of MIBG strored at 25˚C ± 3˚C under a relative humidity of less than 75% in the dark for 1, 2, 3, 6 months, and the long-term stability of MIBG stored at −18˚C ± 2˚C, in the dark for 3, 6, 9 and 12 months were evaluated. The chromatograms of MIBG were steady (>99%) without observable degeneration over 6 months and 12 months, respectively. Thus, MIBGHS is stable for at least six and twelve months under room temperature and frozen storage conditions. There were two major impurities constantly

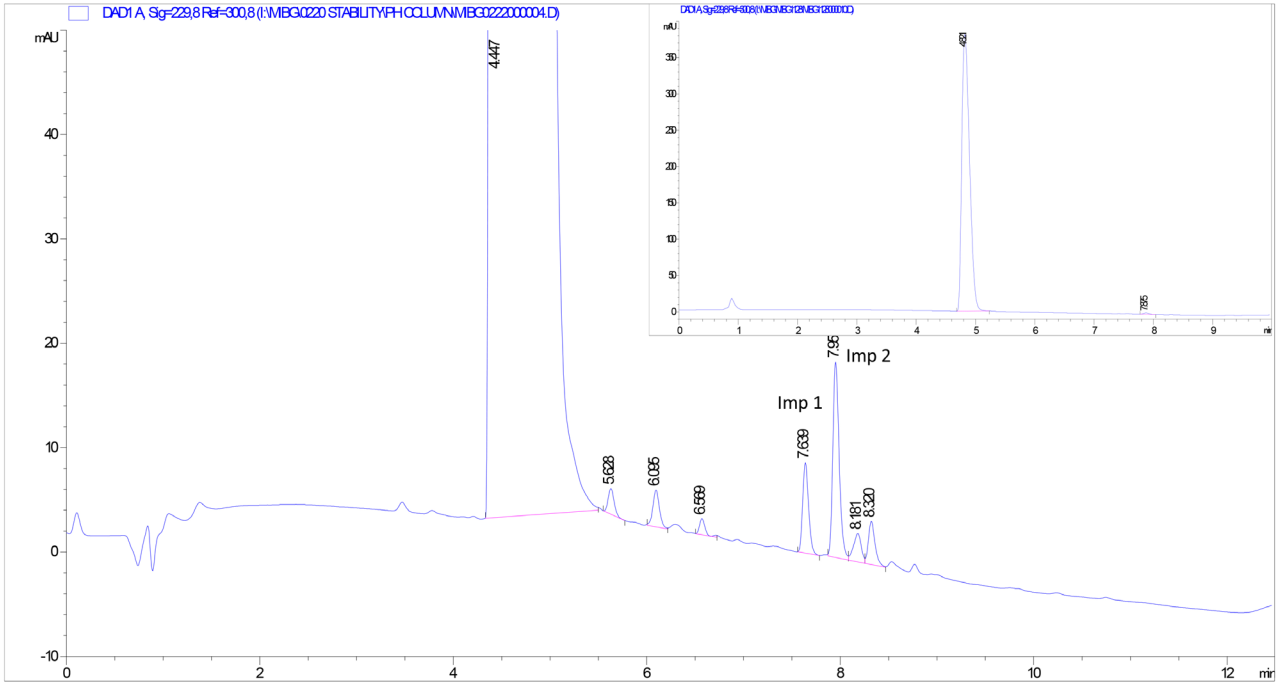


Figure 6. Chromatogram of synthesized MIBG contaminated with impurities provided using a phenyl column.under normal storage condition.

existed since initial MIBGHS (termed Imp 1 and 2) but the amount didn't increase over storage periods. The retention time, molecular ion mass (MS^1), and peak aera % for the impurities were 7.7 min, 532, 0.1% - 0.2% and 7.95 min, 492, 0.25% - 0.35%, respectively. (The MS^1 values for the impurities were confirmed by extraction ion count (XIC) to be 532 - 533 and 492 - 493 in LC-MS chromatogram of MIBG).

The identities of the impurities were determined by fragmentation structures based on the MS/MS spectra. (**Figure 7(a)**, **Figure 7(b)**). Imp 1, N^3,N^5-bis(3-iodobenzyl)-4H-1,2,4-triazole-3,5-diamine, is a dimer of two MIBG molecules coupled through condensation of the guanidine groups, where an ammonia molecule and tow protons are eliminated to form a five-memberd ring, *i.e.*, a triazole-diamine compound. Imp 2, 1,3-bis(3-iodobenzyl)guanidine, is the coupling product of MIBG with MIBA via a condensation reaction that eliminates an ammonia molecule. Furthermore, there were several trace impurities shown in the MIBG chromatogram with peak areas < 0.1%, but their mass spectra (MS^1) were covered by background noise. Hence, an MIBG solution was perfused into the mass spectrometer inorder to identify more contaminants.

Contaminants with MS^1 values of *m*/*z* 494, 534, 551, 649, and 671 were found and their enhanced product ion (EPI) scans all contained signals for *m*/*z* 276, 259, 234, 217, and 90. Furthermore, the precursor ion scan for *m*/*z* 276 including 534, 551, and 649 shows that they are MIBG adducts. The identities of the contaminants with MS^1 534 and 494 may possibly be di(3-iodobenzyl)guanid-inylamine (MS^2 534 → 517, 492, 475, 450, 276, etc.) and N,N'-bis(3-iodobenzyl)

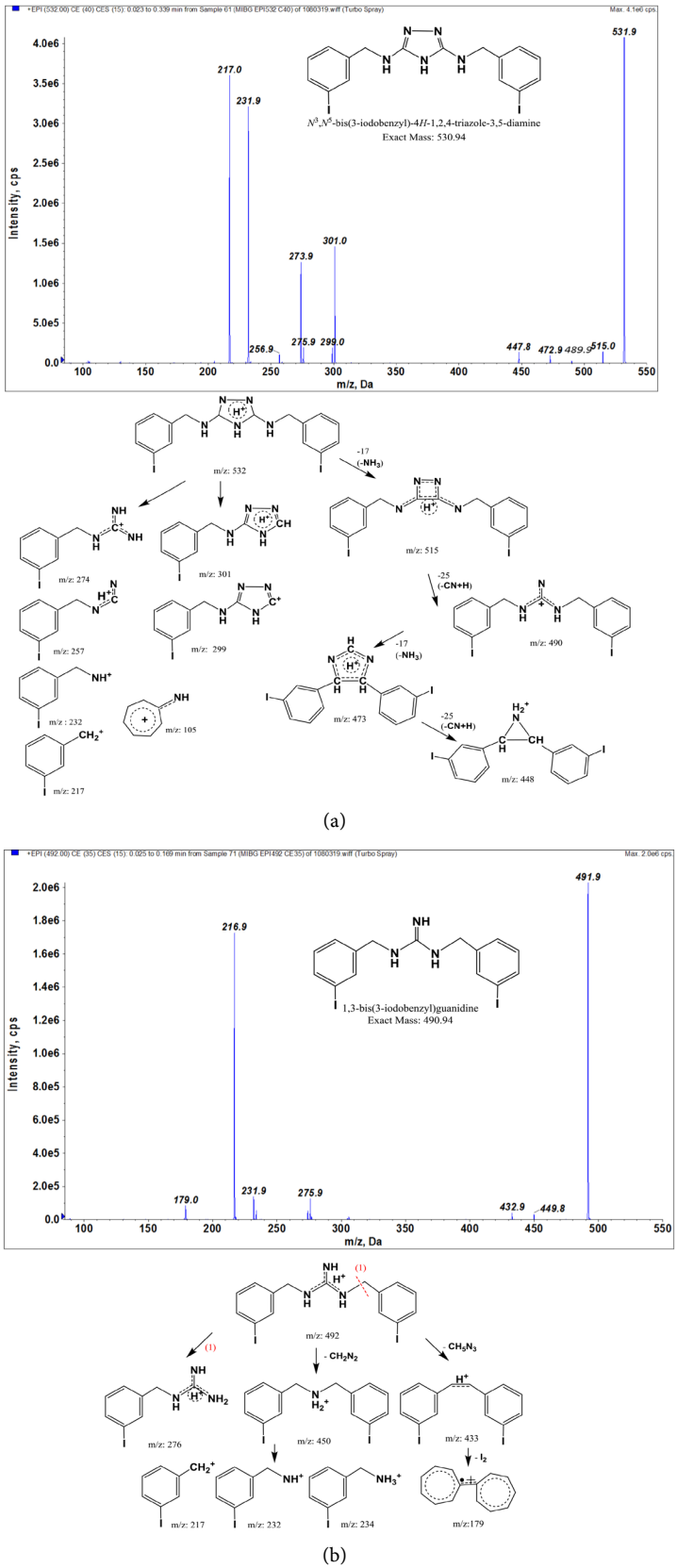


Figure 7. Tandem mass spectra and fragmentation ion structures of over-reacted products Imp 1 (a) and Imp 2 (b) in MIBG.

methanetriamine (MS^2 494 → 477, 452, 434, 276, etc.), respectively (**Figure 8(a)**, **Figure 8(b)**). Both are analogs of Imp 1 and 2. The contaminants with MS^1 551, 649, and 671 are $MIBG_2{\cdot}H^+$, $MIBG_2{\cdot}H_2SO_4{\cdot}H^+$, and $MIBG_2{\cdot}H_2SO_4{\cdot}Na^+$, respectively. Thus these three molecular ions should be seen as representing MIBG itself instead of its derivatives. It is believed that contaminants Imp 1 and 2 and two other analogs in MIBGHS come from byproducts formed during synthesis due to guanidine or amino group overreaction and are not formed during storage.

3.3. Degeneration Products and Causes

The potential derivatives of MIBGHS upon improper storage and transport or reprocess were investigated by forced degradation under harsh conditions, including acidic/alkaline, oxidative, thermal, and UV photolysis factors. The chromatograms of MIBG incubated under acidic condition (HCl 3%) show that it is stable over 72 h without spoilage. This is reasonable as MIBG is recrystalizated as the hemisulfate salt after adding diluted H_2SO_4. For alkaline condition ($TEA_{(aq)}$, 2%), the purity remains at > 98% for the first 24 h, but falls to 90% by 72 h. Two degradation products are detected in the chromatogram (DP_b1, t_R = 3.97 min, 5.4% and DP_b2, t_R = 5.26 min, 3.5%). Their MS/MS data are DP_b1: 234 → 217, and DP_b2: 346 → 328, 302, 276, 260, 232, and 217. The mass spectra and fragmentation structures of DP_b2 are shown in **Figure 9**. Therefore, DP_b1 and DP_b2 were determined to be *m*-iodobenzylamine (MIBA) and 4-hydroxy-1,3-diazet-2-yl(3-iodobenzyl)carbamate.

After exposure to oxidative surrounding for 24 h, an oxidized product ($DP_{ox}1$, t_R = 5.0 min, 1%) with MS^1 292 (ΔMS = +16 cf. MIBG) and fragment ion masses of 275, 250, 233, and 217. The mass spectra and fragment structures of $DP_{ox}1$ are shown in **Figure 10**. It is supposed that oxidization occurs on the iodide to form a hydroxyiodonium species, which is similar to the oxidization behavior of epidepride [28].

For MIBGHS powder stayed in a thermal environment (80˚C for 72 h), MIBG does not spoil and no derivatives are produced. However, in aqueous solution, the purity falls to 96.9% (24 h) and one derivative is produced, *i.e.*, $DP_{th}1$, which has m/z = 234 and MS^2 = 217. Thus, $DP_{th}1$ is MIBA (2.5%). This indicates that MIBG may decompose a little during the radioiodine substitution reaction at 175˚C (provide activation energy to induce isotope replacement) for 1 h, although thermal decomposition might result in MIBG losing cyanamide, especially promoted by the aqueous environment. However, MIBGHS powder is inert to thermal effects. Trace MIBA may contaminate the radiolabeled product *I-MIBG and reduce its effective dose.

When the MIBG solution is exposed to UV light for 22 and 42 h, the amount of MIBG decreases to 95% and 91%, respectively. Three decomposition products are observed in the chromatograms, and their fragmentation mass spectra revealed the transitions $DP_{UV}1$: 150 → 133, 108, 91 (benzylguanidine, t_R = 1.1 min), $DP_{UV}2$: 166 → 149, 131, 124, 117, 107, 103 (hydroxybenzylguanidine), and

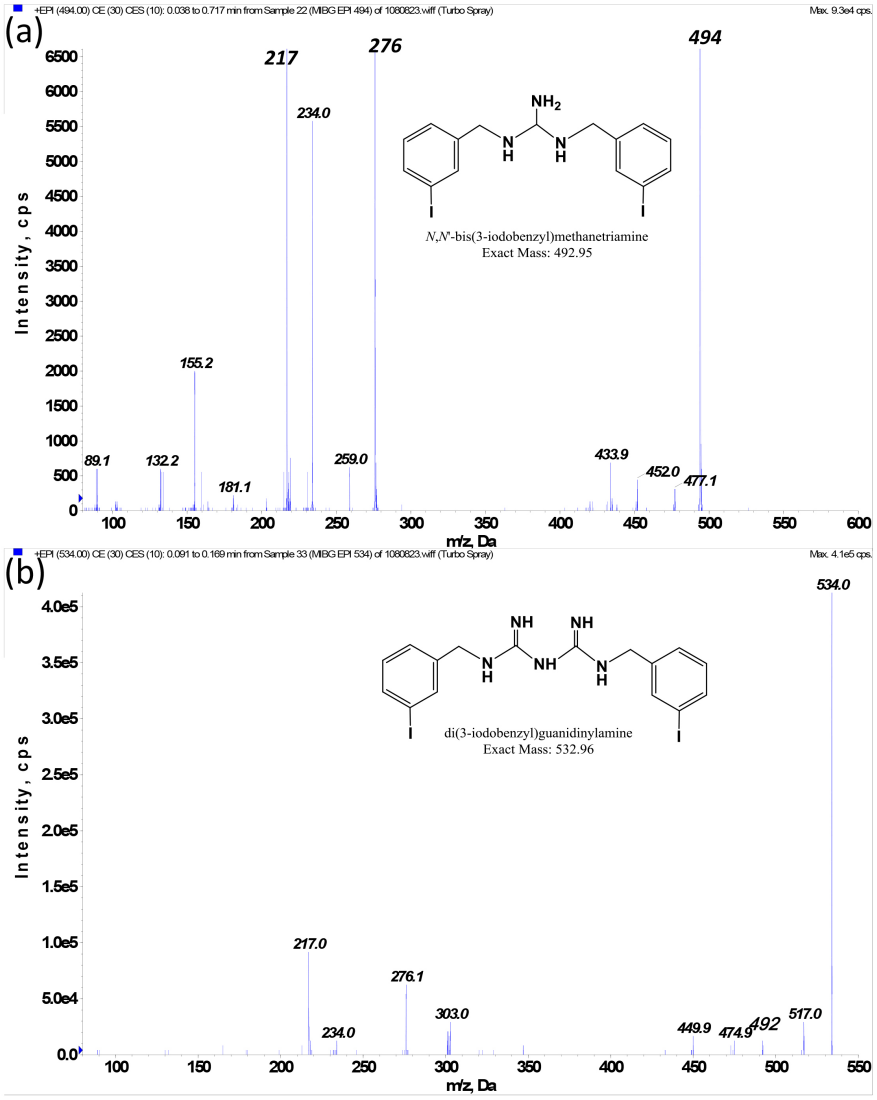


Figure 8. Tandem mass spectra and fragmentation ion structures for MS^1 494 (a) and 534 (b).

$DP_{UV}3$: 164 → 147, 135, 122, 120, 119 [(hydroxybenzylidene)guanidine)]. $DP_{UV}2$ and $DP_{UV}3$ co-eluate at t_R = 1.4 min. However, the MIBGHS powder is more stable under UV irradiation (>97% till 42 h) than the aqueous solution, with only $DP_{UV}1$ being produced. The result indicates the weakness of the iodo-phenyl bond, which is partially broken under UV irradiation, then hydroxide filling the resultant vacancy. The mass spectra and fragment structures of $DP_{UV}1$ - 3 are shown in **Figures 11(a)-(c)**.

4. Conclusion

The causes of contaminants, derivatives and decomposition products of MIBG (or MIBGHS) are summarized in **Figure 12** to highlight its chemical characteristics. The source of impurities included trace MBrBA in the starting material MIBA resulted in MBrBG pollute in MIBG/MIBGHS, and a few

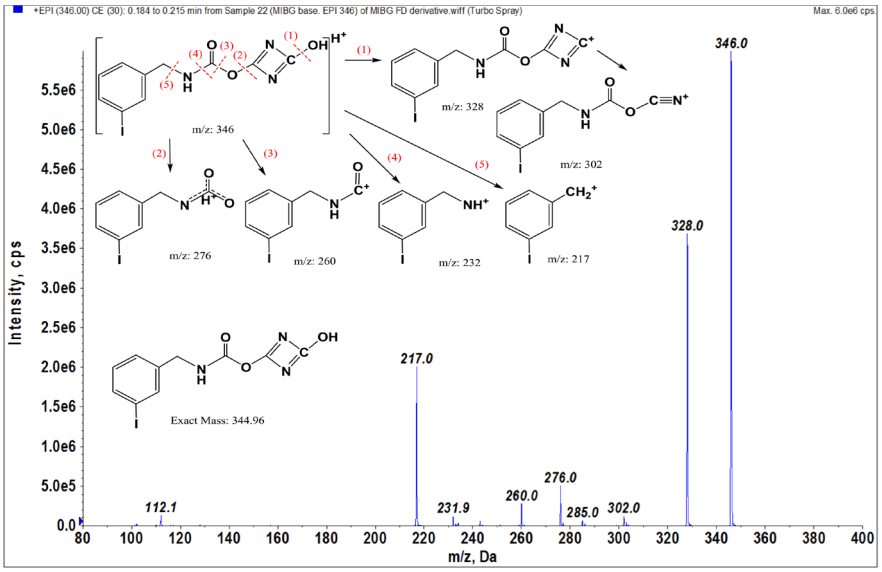


Figure 9. Tandem mass spectra and fragmentation ion structures for identification of DP_b2.

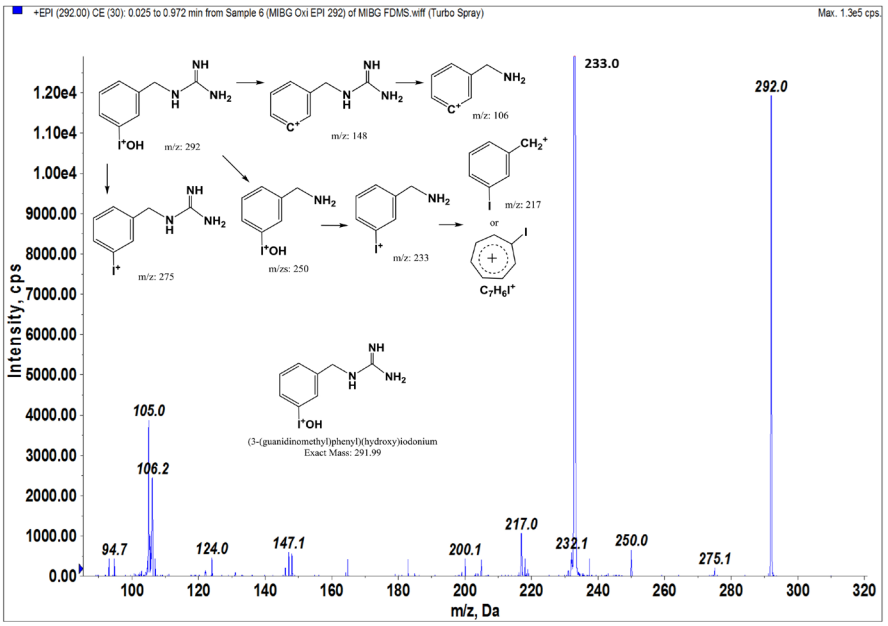
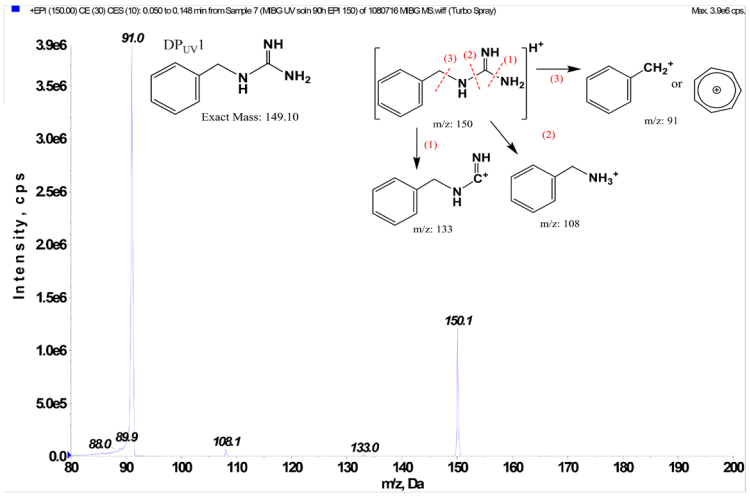
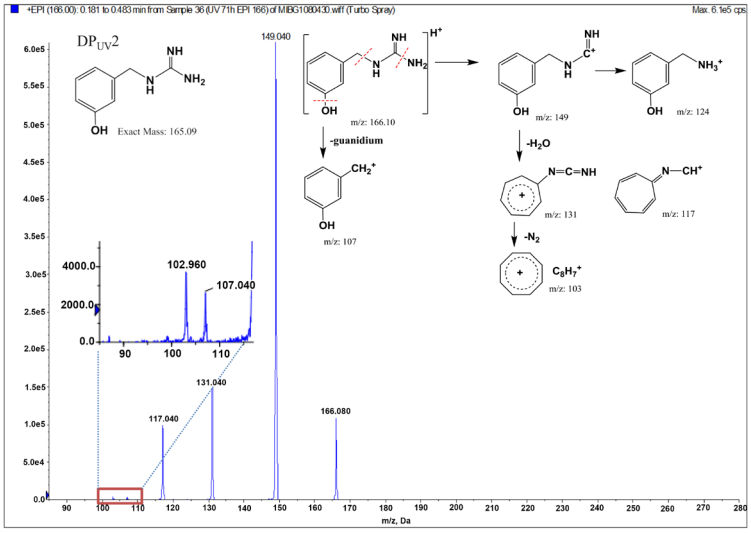


Figure 10. Tandem mass spectra and fragmentation ion structures of oxidative degraded product $DP_{ox}1$.

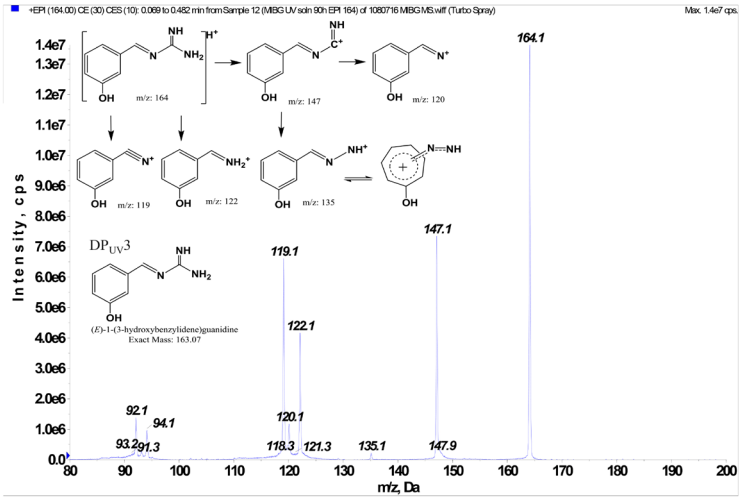
overreacted byproducts which arise from condensation reaction of amino groups. MIBGHS is stable, without degeneration under normal storage condition for at least 6 months (at dark and room temperature) and 12 months (at dark, frozen environment). MIBG solution is spoiled and degenerated partially under alkaline conditions, UV irradiation, oxidization, and thermal factors. Thus, this study provides directions for the proper preparation of the precursor and API, and well defines the chemical behavior for MIBG radio-medicine. All contaminants, derivatives, and degenerates derived from the



(a)



(b)



(c)

Figure 11. Identification of UV photolysis products of MIBG based on MS^2 spectra of $DP_{UV}1$ (a), $DP_{UV}2$ (b), and $DP_{UV}3$ (c).

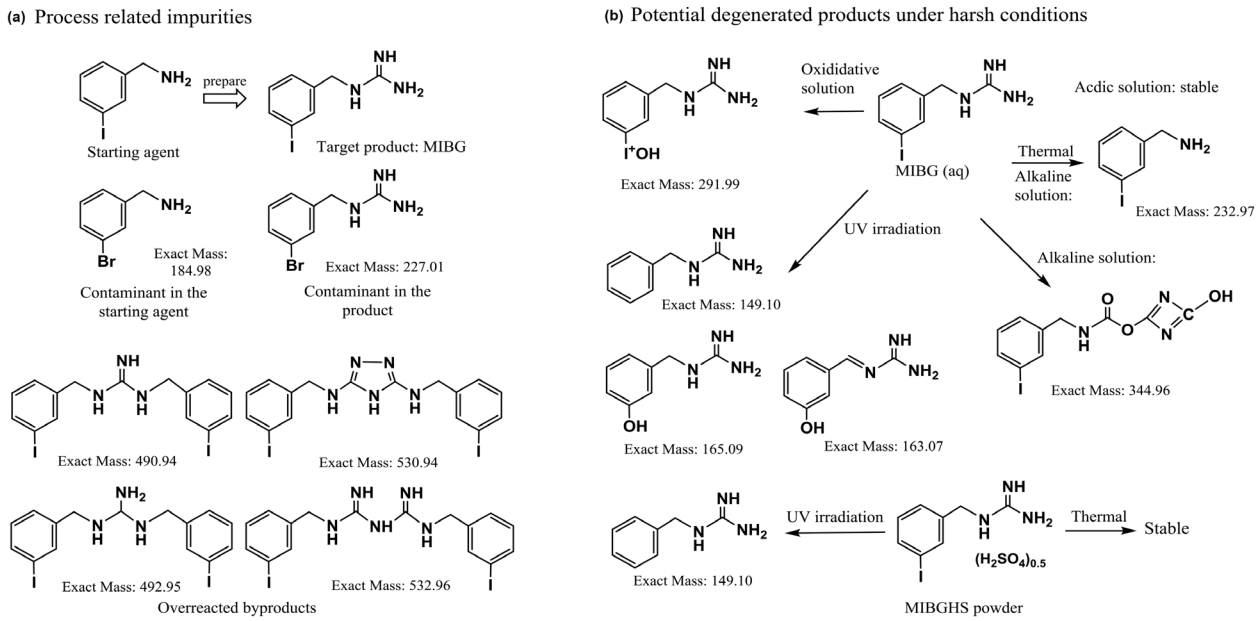


Figure 12. Sources and causes of MIBG impurities.

reaction activity of the guanidine or amine groups, and the weak phenyl-iodine bond of MIBG, they are non-toxic under normal medicinal dose, but may reduce the effective dose of radioiodine-labeled MIBG.

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Conflicts of Interest

The authors declare no conflicts of interests regarding the publication of this paper.

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