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Synthesis and Preliminary Affinity Testing of ^{123}I/^{125}I-*N*-(3-Iodophenyl)-2-methylpyrimidine-4,6-diamine as a Novel Potential Lung Scintigraphic Agent[1]

T. M. Sakr

Radioactive Isotopes and Generator Department, Hot Laboratories Center, Atomic Energy Authority, P.O. Box 13759, Cairo, Egypt; e-mail: Tamer_sakr78@yahoo.com

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Abstract—Radioiodinated *N*-(3-iodophenyl)-2-methylpyrimidine-4,6-diamine (radioiodinated IPMPD), a potential lung scintigraphic agent, was synthesized via direct electrophilic substitution. Factors affecting the radiochemical yield were studied in detail. High radiochemical yield (92.3 ± 2.3%) was reached. The compound is stable in vitro for 24 h. Radioiodinated IPMPD was biologically evaluated in normal Albino mice. The compound demonstrated high lung uptake (21.4 ± 1.7% of injected dose per gram organ at 15 min) and thus shows promise for lung perfusion scintigraphy.

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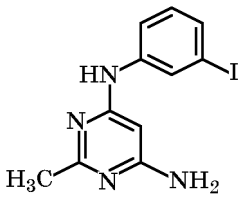
Lung diseases represent one of the most widespread diseases in the world. Early detection and correct diagnosis for these pulmonary clinical cases are essential for definite treatment and better outcome for lung patients [1]. Lung scintigraphy is designed to evaluate the ventilation and perfusion pattern. The ventilation/perfusion lung scintigraphy (V/Q lung scan) is a type of medical modality which uses medical radioisotopes to evaluate the circulation of air and blood within patient's lungs, which will assist in the regional assessment of lung function in a variety of diseases [2–5]. The ventilation scintigraphy, which evaluates the ability of air to reach all parts of the lungs, can be performed by using radioactive gases such as ^{133}Xe, ^{127}Xe, and ^{81m}Kr [6–11] or radioactive aerosols such as ^{99m}Tc-DTPA [12, 13]. The perfusion scintigraphy, which evaluates the ability of blood to circulate well within the lungs, can be accomplished by the injection of radiolabeled particles in peripheral veins. The most currently used radiopharmaceutical for lung perfusion scintigraphy is ^{99m}Tc-human albumin macroaggregates (^{99m}Tc-MAA) of size 10–40 μm. It, however, has some disadvantages as it is a blood component derived from human donors, so there is high possibility of contamination by infective agents such as hepatitis B, hepatitis C, and HIV; furthermore, it needs additional processing to ensure specific particle size, and it is contraindicated in patients with a history of hypersensitivity to products containing human serum albumin [14–19]. ^{67}Ga is also one of lung perfusion scintigraphic agents. Its half-life, however, is as long as 3.26 days, which increases the radiation hazard for the patients [2, 20]. Therefore, many new researches are aimed to develop new lung scintigraphic agents, which have high lung uptake and high radiochemical yield, are easily available, and are not human blood products. ^{99m}Tc(CO)$_5$I, ^{99m}Tc-5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydro(1*H*)pyrimidine-2-one, and ^{125}I-paroxetine, with lung uptake of 12.8, 10.12 and 27.9 ± 1.0% injected dose per gram organ at 1 h, 5 min, and 15 min, respectively, are examples of recently discovered potential lung perfusion scintigraphic agents [19, 21, 22]. ^{123}I, one of the commonly used SPECT radioisotopes, has a photon energy of 159 keV with an abundance of 83.4% and half-life of 13.22 h [23–32]. The medical importance of the pyrimidine group as the main nucleus of many drugs such as antimicrobial, analgesic, antiviral, anti-inflammatory, anti-HIV, antitubercular, antitumor, anti-malarial, diuretic, cardiovascular agents and hypnotic drugs is reported [33, 34]; therefore, many researches are focusing on the synthesis of new compounds containing the pyrimidine moiety. This research was aimed to develop a potential lung perfusion imaging agent. A new organic compound, *N*-(3-iodo-

[1] The text was submitted by the author in English.

phenyl)-2-methylpyrimidine-4,6-diamine (IPMPD, see below) was successfully synthesized and radioiodinated via direct electrophilic substitution. The radioiodinated IPMPD was biologically evaluated in mice as a lung perfusion scintigraphic agent.

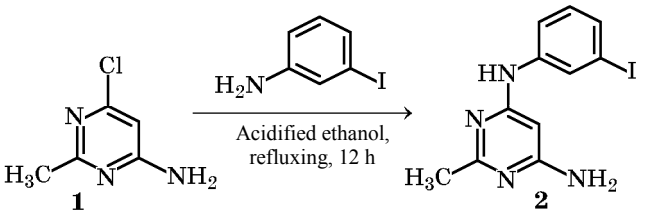


IPMPD

EXPERIMENTAL

All chemicals were purchased from Merck and were of AR grade. Double-distilled water was used for solution preparation. ^{125}I (pH 9.7, radionuclidic purity 99.99%, radiochemical purity 99.99%), was obtained as a gift from the Radioisotope Production Facility, Atomic Energy Authority, Egypt. A NaI(Tl) γ-ray scintillation counter (Scaler Ratemeter SR7 model, the United Kingdom) was used for the measurement of γ-ray radioactivity. HPLC was performed with a Hitachi device equipped with an Alphabond C18 125A 10U column with i.d. 3.9 and length 300 mm (Japan). Melting points (°C, uncorrected) were determined in open glass capillaries using a Barnstead 9001 Electrothermal melting point apparatus. The IR spectra were recorded on a Perkin–Elmer FT-IR Spectrum BX spectrometer in the cm^{-1} scale using KBr discs. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 500 MHz spectrometer; chemical shifts are expressed in δ scale (ppm) relative to TMS. The mass spectra were run at 70 eV on a Hewlett–Packard 5890 GC/MS spectrometer, using the electron impact (EI) technique. Elemental analyses (C, H, N) were carried out at the Microanalytical Data Center, Faculty of Science, Cairo, Egypt, and were in full agreement with the proposed structures within ±0.4% of the theoretical values. Thin layer chromatography was performed on precoated (0.75 mm) silica gel GF254 plates (Merck, Germany). The plates were visualized by UV illumination (254 nm).

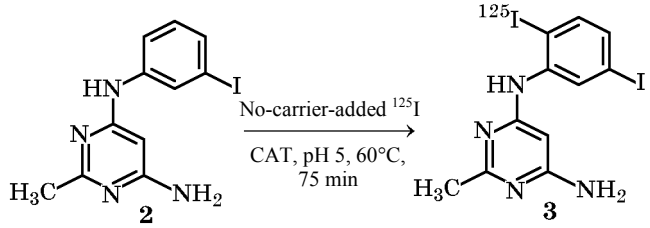
Synthesis of *N*-(3-iodophenyl)-2-methylpyrimidine-4,6-diamine (IPMPD). 4-Amino-2-methyl-6-chloropyrimidine (**1**) was prepared using the previously published procedures [35, 36]. A mixture of 4-amino-2-methyl-6-chloropyrimidine (**1**) (1.55 g, 0.01 mol) and 3-iodoaniline (2.19 g, 0.01 mol) in absolute ethanol (10 mL), with a drop of HCl added, was refluxed for 12 h. The reaction mixture was cooled and poured onto ice water. The precipitate that formed was filtered off, washed several times with water, and recrystallized from ethanol to give compound **2** in a yield of 55% (1.79 g); mp, °C: 262–264. IR, ν, cm^{-1}: 3299 (NH_2), 3069 (NH), 1380 and 1469 (CH_3), 660 (C–I). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.37 s (3H, CH_3), 5.99 s (1H, NH), 7.07–8.22 m (5H, aromatic protons), and 7.91 br.s (2H, NH_2). ^{13}C NMR (DMSO-d_6), δ_C, ppm: 21.48 (CH_3), 94.72 (C–I), 120.92–159.20 (C^{Ar}). MS, *m*/*z*, %: 326 (100), M^+.



Preparation of ^{125}I-IPMPD. *Radioiodination procedure*. IPMPD was radioiodinated with ^{125}I via direct electrophilic substitution under oxidative conditions in the presence of chloramine-T (CAT) [37].

$$R–H + H_2O + {}^{125}I^+ \rightleftarrows R–{}^{125}I + HI + H_2O.$$

The reaction mixture volume was fixed at ~600 μL. In an amber-colored vial, 40–250 μg of IPMPD in 100 μL of ethanol was placed. A freshly prepared solution of 40–250 μg of CAT in 100 μL of ethanol was added. Then, 350 μL of appropriate buffer solution was added to adjust pH. After that, 30 μL of a ^{125}I solution (7.2 MBq) was added to the reaction mixture. The reaction mixture was vortexed and left for 5–105 min at various temperatures in the range 20–100°C. A drop of saturated aqueous sodium metabisulfite solution (10 mg mL^{-1}) was added to quench the reaction [38].



Radiochemical yield assessment. The radiochemical yield of ^{125}I-IPMPD was assessed by paper chromatog-

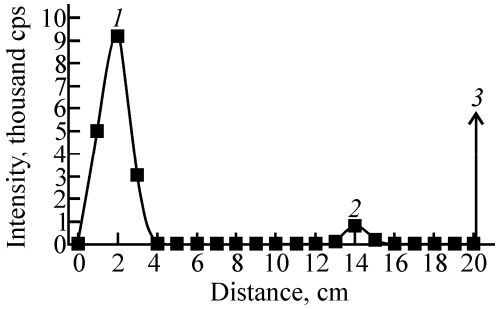


Fig. 1. Electrophoresis pattern of ^{125}I-IPMPD. (*1*) ^{125}I-IPMPD and (*2*) free $^{125}I^-$; (*3*) anode.

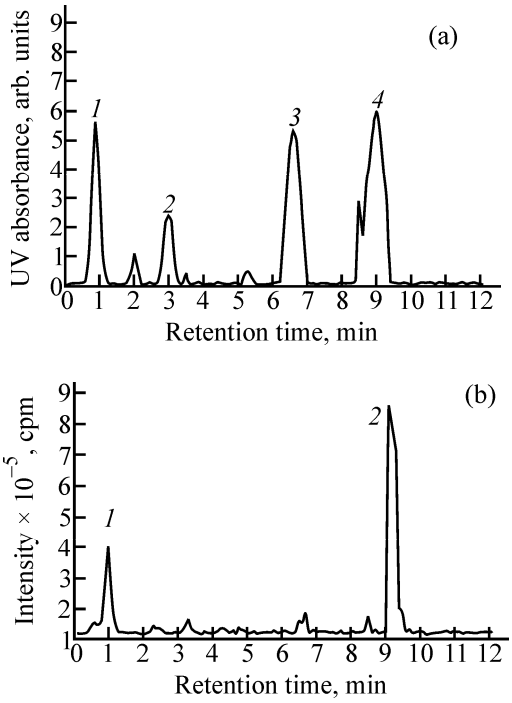


Fig. 2. HPLC patterns of reaction mixtures. (a) Cold iodination of IPMPD: (*1*) iodide, (*2*) CAT, (*3*) IPMPD, and (*4*) iodinated IPMPD; (b) iodination with ^{125}I: (*1*) free $^{125}I^-$ and (*2*) ^{125}I-IPMPD.

raphy and paper electrophoresis with further check using HPLC.

The paper chromatography was performed with strips of Whatman no. 1 paper (Whatman International Ltd, Maidstone, Kent, the United Kingdom). 1–2 μL of the reaction mixture was placed 2 cm above the lower edge of a paper strip (1 cm wide and 13 cm long), and the solvent was allowed to evaporate spontaneously. Then the paper strips were developed with a fresh methylene chloride–ethyl acetate (2 : 1) mixture as a mobile phase. In the process, radioiodide (I^-) remained near the origin (R_f = 0–0.1), whereas ^{125}I-IPMPD moved with the solvent front (R_f = 0.9).

For the paper electrophoresis, 1–2 μL of the reaction mixture was placed at a distance of 12 cm from the cathode edge of a Whatman no. 1 paper strip (2 cm wide and 47 cm long). Electrophoresis was carried out for 1 h at voltage of 300 V using normal saline (0.9% w/v NaCl solution) as electrolyte source solution. In the process, free radioiodide and ^{125}I-IPMPD moved to different distances from the spotting point toward the anode depending on the molecular weight of the species (distance from the spotting point 14 and 2 cm, respectively, Fig. 1).

After the complete development, the paper strips were removed, dried, and cut into segments, 1 cm wide each, and each segment was counted in a well type γ-ray counter.

The radiochemical yield was calculated as the percent ratio of the radioactivity of ^{125}I-IPMPD to the total activity.

The HPLC analysis (Fig. 2) of IPMPD cold iodination product and of ^{125}I-IPMPD was done by injecting a 10-μL sample filtered through 0.22 μm Millipore filter into a column (RP-18, 300 × 3.9 mm^2, Alphabond), with detection by UV absorption (SPD-6A detector adjusted to a wavelength of 254 nm) and radioactivity. The column was eluted with 0.1 M phosphate buffer (pH 7.4)–ethanol (30 : 70) mixture at a flow rate of 0.5 mL min^{-1}. Fractions of volume 0.25 mL were collected separately using a fraction collector up to a total volume of 12 mL and were counted in a well-type NaI(Tl) detector connected to a single-channel analyzer. The retention times of cold-iodinated IPMPD and ^{125}I-IPMPD were 9 and 9.1 min, respectively.

In vitro stability study of ^{125}I-IPMPD. The reaction mixture was left at ambient temperature for 24 h, and 1–2-μL samples were taken at different time intervals. The relative content of ^{125}I-IPMPD was determined by paper chromatography and paper electrophoresis.

Biodistribution of ^{125}I-IPMPD in normal mice. The biological studies were done in accordance with the guidelines set out by the Egyptian Atomic Energy Authority and were approved by the Animal Ethics Committee, Radioisotopes and Generator Department.

Prior to the study, normal Swiss Albino mice (17–

25 g) were housed in groups of five and provided with food and water. Aliquots of 10 μL containing 3.7 MBq of ^{125}I-IPMPD were injected into each mouse via the tail vein. The mice were weighed and anaesthetized with chloroform at 15, 40, 60 and 120 min post injection (five animals for each time point). Samples of fresh blood, bones, and muscles were collected in preliminarily weighed vials and counted. The weights of blood, bones and muscles were assumed to be 7, 10, and 40% of the total body weight, respectively [39–42]. Organs and tissues were rinsed with saline, collected in plastic containers, and weighed. The radioactivity of each sample as well as the background was counted in a well-type NaI(Tl) crystal counter coupled to an SR-7 scaler ratemeter. The percentages of the injected dose per gram (% ID/g) were calculated. The results of replicate measurements with five mice were averaged. Data were evaluated with one-way ANOVA test. The results are reported and as mean ± SEM. The level of significance was set at $P < 0.05$.

RESULTS AND DISCUSSION

Preparation of ^{125}I-IPMPD. For the experiments, it is preferable to use ^{125}I because of its longer half-life ($t_{1/2}$ = 59.4 days), whereas ^{123}I is more suitable for medical applications because of its favorable physical characteristics (photon energy of 159 keV with an abundance of 83.4%, half-life of 13.22 h) and availability in high specific activity.

The influence of reaction conditions (substrate and oxidant amounts, pH, reaction time) on the radioiodination efficiency was investigated, and the conditions were optimized to reach the highest radiochemical yield. The results are discussed below.

IPMPD amount. The dependence of the radiochemical yield on the IPMPD amount (40–250 μg) is shown in Fig. 3. At 40 μg, the radiochemical yield was low (34 ± 3%). By increasing IPMPD amount, the radiochemical yield was increased to reach a maximum, 92.3 ± 2.3%, at 150 μg. As the IPDMD amount was increased further, the radiochemical yield did not change noticeably.

Oxidizing agent (CAT) amount. Chloramine-T oxidizes I^- ions to I^+ without forming I_2. The influence of the CAT amount on the radiochemical yield of ^{125}I-IPMPD is shown in Fig. 4. At low CAT amount (40 μg), the radiochemical yield of ^{125}I-IPMPD was low: 70.1 ± 2.1%. The maximum radiochemical yield

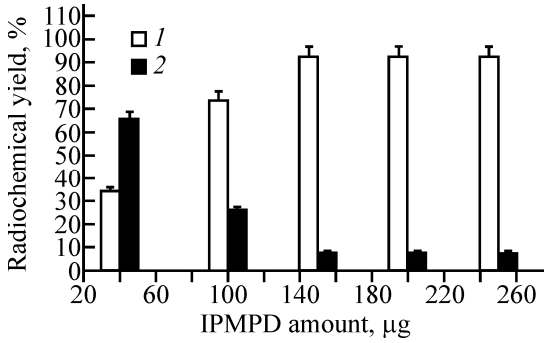


Fig. 3. Radiochemical yield of ^{125}I-IPMPD as a function of IPMPD amount. Reaction conditions: 10 μL (~3.7 MBq) of Na^{125}I solution, 100 μg of CAT, pH 5, 60°C, 75 min. (*1*) ^{125}I-IPMPD and (*2*) free $^{125}I^-$; the same for Figs. 4–6.

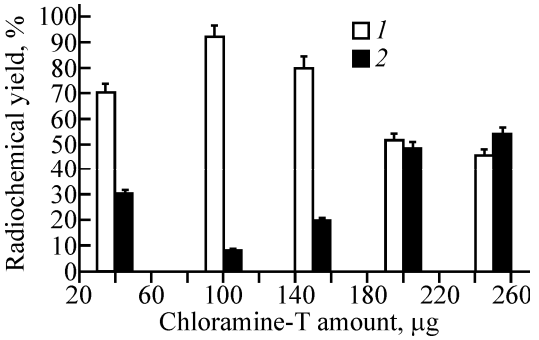


Fig. 4. Radiochemical yield of ^{125}I-IPMPD as a function of CAT amount. Reaction conditions: 10 μL (~3.7 MBq) of Na^{125}I solution, 150 μg of IPMPD, pH 5, 60°C, 75 min.

(92.3 ± 2.3%) was achieved at the CAT amount increased to 100 μg. Increasing the CAT amount above this value leads to a decrease in the radiochemical yield, which may be due to the formation of undesirable by-products of IPMPD chlorination and oxidative polymerization under the action of excess CAT [43, 44].

pH. The potential of CAT decreases with an increase in pH [45], which is associated with the dependence of the nature of active oxidizing species on pH of the medium and on the reaction conditions. When dissolving CAT in ethanol, it decomposes to $ArSO_2NCl^-$, which undergoes hydrolysis in acidic medium to give HOCl. The hypochlorous acid can undergo protonation to H_2OCl^+. The possible oxidizing species in acidified CAT solutions are HOCl and H_2OCl^+, and in alkaline solutions of CAT these are HOCl and ClO^-. The HOCl or H_2OCl^+ generated oxidizes iodide in acidic solutions to iodonium ions I^+, which rapidly react with IPMPD

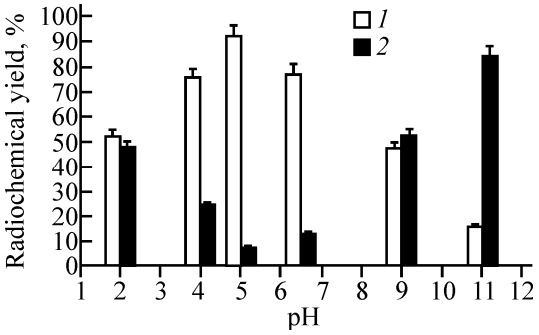


Fig. 5. Radiochemical yield of ^{125}I-IPMPD as a function of pH. Reaction conditions: 10 μL (~3.7 MBq) of Na^{125}I solution, 150 μg of IPMPD, 100 μg of CAT, 60°C, 75 min.

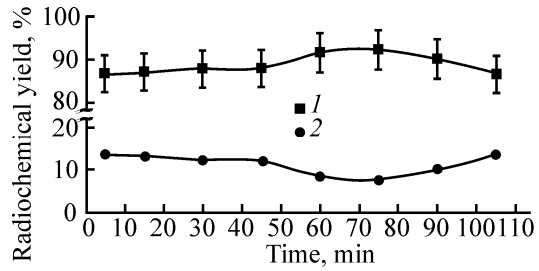


Fig. 6. Radiochemical yield of ^{125}I-IPMPD as a function of reaction time. Reaction conditions: 10 μL (~3.7 MBq) of Na^{125}I solution, 150 μg of IPMPD, 100 μg of CAT, pH 5, 60°C.

at the site that is the most reactive in electrophilic substitution [45–47].

The influence of pH of the reaction mixture on the radiochemical yield of ^{125}I-IPMPD is shown in Fig. 5. At pH 5, the radiochemical yield was maximal (92.3 ± 2.3%). The yield decreases both with a decrease (to 52 ± 1.4% at pH 2) and with an increase in pH (to 15.8 ± 1.1% at pH 11). The latter trend can be attributed to the formation of hypoiodite ion (IO^-) and iodate (IO_3^-), which do not enter into the radioiodination process [48].

Reaction time. Figure 6 shows that 75 min is required to reach the maximum radiochemical yield (92.3 ± 2.3%). At longer reaction times, the radiochemical yield slightly decreased, which may be due to side oxidative reactions occurring on prolonged exposure of IPMPD to highly reactive CAT.

Temperature. The influence of the reaction mixture temperature was studied in the range 20–100°C. The radiochemical yield was the highest at 60°C (92.3 ± 2.3%) and slightly decreased at lower and higher temperatures.

In vitro stability of ^{125}I-IPMPD was studied in order to determine the suitable time for injection to avoid the formation of the undesired products that result from the radiolysis of the labeled compound and may be accumulated in nontarget organs. The results of stability tests showed that ^{125}I-IPMPD was stable for up to 24 h.

Biodistribution of ^{125}I-IPMPD in normal mice. Data on the biodistribution of ^{125}I-IPMPD in normal mice at 15, 40, 60, and 120 min post injection are given in the table. ^{125}I-IPMPD showed a high uptake in

Biodistribution of ^{125}I-IPMPD in normal Swiss Albino mice at different time intervals post injection (% ID/g ± SEM, n = 5)

Organs and body fluids	15 min	40 min	60 min	120 min
Blood	3.4 ± 0.4	3.7 ± 0.4	4.3 ± 0.4	2.5 ± 0.3
Kidneys	11.2 ± 1.0	16.1 ± 1.6	6.1 ± 0.6	5.2 ± 0.5
Liver	11.9 ± 1.0	13.1 ± 1.3	4.4 ± 0.4	5.0 ± 0.5
Spleen	6.0 ± 0.6	6.4 ± 0.6	3.5 ± 0.4	3.4 ± 0.3
Intestine	4.1 ± 0.5	12.5 ± 1.2	20.9 ± 1.9	22.4 ± 2.0
Lungs	21.4 ± 1.7	15.4 ± 1.5	7.8 ± 0.7	5.5 ± 0.5
Heart	7.6 ± 0.6	7.1 ± 0.9	2.8 ± 0.3	3.4 ± 0.3
Thyroid	6.2 ± 0.6	5.7 ± 0.5	4.3 ± 0.4	2.08 ± 0.17
Muscle	6.0 ± 0.5	8.1 ± 0.8	1.18 ± 0.09	3.9 ± 0.4
Bone	3.5 ± 0.3	7.8 ± 0.7	2.9 ± 0.3	4.9 ± 0.5
Brain	3.6 ± 0.4	2.8 ± 0.3	0.83 ± 0.06	0.49 ± 0.03
Lung/blood	6.36	4.22	1.82	2.2
Lung/heart	2.81	2.19	2.81	1.6

the lung tissues (21.4 ± 1.7% ID/g at 15 min) in comparison with the recently developed radiopharmaceuticals such as $^{99m}Tc(CO)_5I$, ^{99m}Tc-5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydro(1*H*)pyrimidine-2-one, and ^{125}I-paroxetine [19, 21, 22]. In addition, ^{125}I-IPMPD showed high lung/blood and lung/heart % ID/g ratios (6.36 ± 0.3 and 2.81 ± 0.13 at 15 min, respectively), which enhances the imaging quality. Biodistribution showed rapid withdrawal of the radioactivity from the lungs (7.8 ± 0.7% ID/g at 60 min and 5.5 ± 0.5% ID/g at 120 min). These results indicate that radioiodinated IPMPD could be a very promising lung perfusion scintigraphic agent.

The radioactivity uptake of liver, intestine, and kidneys indicates that excretion of ^{125}I-IPMPD occurs mainly via the hepatobiliary route and to a lesser extent via urinary route.

The low radioactivity uptake of the thyroid gland indicates that the ^{125}I-IPMPD is stable against in vivo deiodination.

Finally, radioiodinated IPMPD as a new lung perfusion agent shows advantages in that it is not a blood component and does not require additional processing related to the particle size. The radiation hazard to the patient is decreased when using ^{123}I.

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