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Efficient and Practical Radiosynthesis of Novel [^{131}I]-Xanthine and [^{131}I]-Hypoxanthine

H. Wongso[1,2*], W. Nuraeni[3], E. Rosyidiah[3]

[1]*Research and Technology Center for Radioisotope, Radiopharmaceutical, and Biodosimetry - National Research and Innovation Agency (BRIN), Puspiptek Area Serpong, Tangerang Selatan 15314, Indonesia*

[2]*Research Collaboration Center for Theranostic Radiopharmaceuticals, National Research and Innovation Agency (BRIN), Jl. Raya Bandung Sumedang KM 21, Sumedang 45363, Indonesia*

[3]*Directorate of Laboratory Management, Research Facilities, and Science and Technology Park, National Research and Innovation Agency (BRIN), Jl. Tamansari 71 Bandung, West Java 40132, Indonesia*

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ABSTRACT

Natural products (NPs) have been the basis for the discovery and development of pharmacologically relevant drug-related molecules, including radiopharmaceuticals. Xanthine (3,7-dihydropurine-2,6-dione) and hypoxanthine (1,9-dihydro-6H-purin-6-one) are purine-based natural heterocyclic alkaloids that are generally found in some plants, animals, and the human body (e.g., muscle tissue, blood, and urine). The purpose of this study was to label xanthine and hypoxanthine with radioactive iodine-131 (a theranostic radionuclide) by a direct labeling method using chloramine-T as an oxidizing agent. Several experiments were performed to optimize the labeling efficiency by changing reaction conditions, including the ratio of starting material and chloramine-T, pH, solvent, temperature, and reaction time. Overall, labeling at acidic conditions in dimethyl sulfoxide (DMSO) resulted in considerable low radiochemical yields (RCYs) (< 4.0 %), and therefore the focus was shifted to exploit the alkaline reaction conditions. The optimized reaction condition: pH (10.5-11.0), xanthine:chloramine-T ratio (1:2), reaction temperature (27 ºC), and reaction time (30 min), provided [^{131}I]-xanthine with a RCY of 65.8 ± 0.1 %. After purification with extraction using chloroform ($CHCl_2$), the radiochemical purity (RCP) of 95.1 % was achieved, as indicated by radio-thin layer chromatography (radio-TLC) analysis. In addition, the labeling of hypoxanthine was accomplished in a maximum 60.3 ± 0.2 % RCY, and after purification a RCP of 94.2 % was obtained. The present results provide an efficient and practical labeling method for xanthine and hypoxanthine with iodine-131, suggesting that these radiolabeled compounds can be further investigated in in vitro and in vivo studies for their theranostics potential.

INTRODUCTION

Xanthine (3,7-dihydropurine-2,6-dione) and hypoxanthine (1,9-dihydro-6H-purin-6-one) are low molecular weight purine-based heterocyclic compounds found in nearly all living species, particularly in human body tissues, animals, and plants. Naturally, xanthine is generated from the catabolism of purine nucleotide. During the metabolic process, guanine and hypoxanthine were converted to xanthine by xanthine oxidase and guanase, following oxidation to produce uric acid (Fig. 1) [1,2]. Furthermore, molecular modifications of xanthine scaffold at R1, R2, R3, R4, and R5-position have shown various biological effects with well-known activities as adenosine receptor antagonists, inducers of histone deacetylase activity, and cystic fibrosis transmembrane conductance regulator (CFTR) activation [3].

Several xanthine derivatives found in plants have been extensively studied for human health, including caffeine, theophylline, theobromine, and paraxanthine (Fig. 2). These derivatives have brought considerable attention due to their pharmacologically effects in many diseases, such as respiratory tract diseases, neurodegenerative diseases, hypertension, cardiovascular diseases, and renal diseases [3].

Together with xanthine, hypoxanthine may provide a sensitive indicator for physiological

*Corresponding author.
E-mail address: hendriswongso@batan.go.id
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diseases, and therefore has been proposed as a biomarker for a diverse range of disease states, including Alzheimer's disease, multiple sclerosis, and colorectal cancer [4]. It is also found that local secretion of hypoxanthine by human adipose tissues was increased under hypoxia [5]. Previously, xanthine derivative has been radiolabeled with positron emission tomography (PET) isotopes (Fig. 3), namely carbon-11 for imaging the transient receptor potential channel subfamily member 5 (TRPC5) in the brain. In this study, the labeled xanthine derivative was synthesized with a good radiochemical yield (RCY) (25 ± 5 %), high chemical and radiochemical purity (> 99 %), and high specific activity (204–377 GBq μmol^{-1}). This labeled xanthine was found to have specific binding to TRCP5 and was able to cross the blood-brain barrier and sufficiently deposited in the brain [6]. Moreover, xanthine derivatives have been labeled with fluorine-18 (Fig. 3) to target Eph receptor tyrosine kinases, particularly EphA2 and EphB4 in cancers. The labeled compounds showed potent Eph receptor inhibitors with IC_{50} values ranging from 1 to 40 nM. Labeling using respective tosylate precursors generated labeled products with low RCY (± 5.0 %), but high radiochemical purity (> 98 %), and a molar activity of >10 GBq μmol^{-1} [7].

Some radionuclides such as iodine-131, iodine-125, technetium-99m, fluorine-18, gallium-68, and carbon-11 have been used for labeling numerous active compounds for their in vitro and in vivo biomedical applications [6,8-13]. Among them, radioiodines are very useful for labeling bioactive molecules containing phenol or imidazole groups [14]. Moreover, the introduction of iodine into the substrate negligibly alters the structure, and therefore could be crucial in maintaining biological activities [15]. Until recently, radioiodination of organic molecules has gained much attention among scientists in developing suitable radiotracers for the diagnosis and treatment of human ailments, such as cancer treatment (e.g., [^{125}I]-iodothioguanine, [^{131}I]- metaiodobenzylguanidine (MIBG), and [^{131}I]-anti-CD20) and cancer imaging (e.g., [^{123}I]-iodocelecoxib, [^{123}I]-MIBG) [16-18]. Although some xanthine derivatives have been explored for their potential as imaging or therapeutic agents in nuclear medicine, xanthine and hypoxanthine have not been radiolabeled with therapeutic radionuclides, especially iodine-131. Thus, it was of interest to investigate the potential of radioiodinated xanthine and hypoxanthine for use in nuclear medicine, in particular for the treatment of several serious diseases that affect global societies, such as cancers [19], inflammations [20], microbial infections [21], and neurodegenerative diseases [22]. Here, we report the radiosynthesis of new [^{131}I]-xanthine and [^{131}I]-hypoxanthine using efficient and practical labeling approaches. This study could provide a basis for the development of radiolabeled xanthine and hypoxanthine that may potentially be used as theranostic agents to target xanthine oxidase signaling involved in a number of diseases or other ailments. Hence, further studies including in vitro and in vivo evaluation of [^{131}I]-xanthine and [^{131}I]-hypoxanthine will be initiated in the near future.

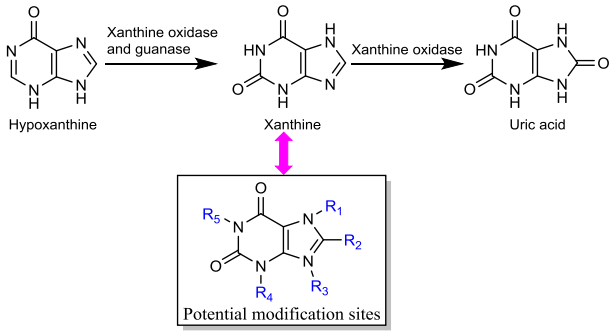

Fig. 1. The conversion route of hypoxanthine to uric acid, and the potential sites (R1, R2, R3, R4, and R5) for structural modifications of xanthine.

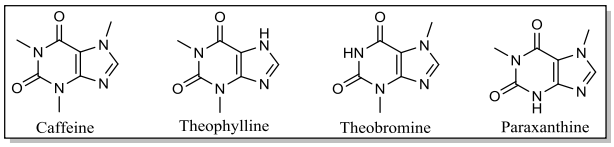

Fig. 2. The representative of xanthine derivatives.

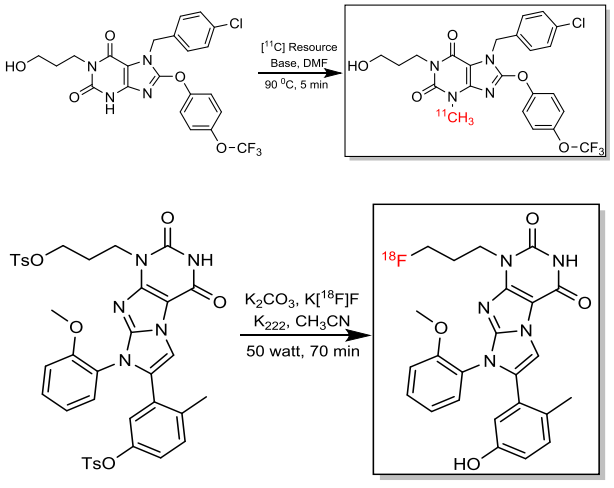

Fig. 3. Labeling procedure of xanthine derivatives with carbon-11 and fluorine-18.

METHODOLOGY

Materials and instruments

Unless stated otherwise, all chemicals were laboratory or reagent grade and were used as

received. All solvents were analytical and HPLC grade. 3,7-dihydropurine-2,6-dione (xanthine), hypoxanthine (1,9-dihydro-6H-purin-6-one), sodium hydroxide pellets (NaOH), dimethyl sulfoxide (DMSO), acetic acid (AcOH), ethanol (EtOH), methanol (MeOH), *N*-chloro-*p*-toluene sulfonamide salt (chloramine-T), chloroform ($CHCl_3$), ultrapure water (H_2O), Whatman paper no.3, pH paper, and sodium metabisulfite ($Na_2S_2O_5$) were purchased from Merck Singapore (2 Science Park Drive, Singapore). NaI-131 was obtained from Research and Technology Center for Radioisotope, Radiopharmaceutical, and Biodosimetry, National Research and Innovation Agency (BRIN) of Indonesia. Dose calibrator (Biodex; Shirley, NY, USA) was used to measure radioactivity, while radio-thin layer chromatography (radio-TLC) was performed on a Bioscan AR-2000 138 scanner (Washington, DC, USA) to determine radiochemical yield (RCY) and radiochemical purity (RCP).

Labeling under acidic conditions

Labeling of xanthine and hypoxanthine with iodine-131 was performed under acidic conditions employing the reported direct radioiodination method [15] with necessary modifications (n = 2). A solution of xanthine/hypoxanthine in DMSO/50 % AcOH (10:1, v/v) was stirred for 4 h to dissolve the starting material completely. To the mixture was slowly added an aqueous solution of chloramine-T, followed by NaI-131 solution (14.8-18.5 MBq). The resulting mixture was shaken in the mixer, followed by the addition of 0.5 M $Na_2S_2O_5$ (100 µL). To obtain the optimum reaction condition, the labeling was carried out by varying several parameters, including the ratio of xanthine/hypoxanthine and chloramine-T, pH, solvent, temperature, and reaction time.

Optimization of labeling conditions

To improve the labeling yield, radioiodination of xanthine and hypoxanthine was performed under alkaline conditions using the reported direct radioiodination method [15] with necessary modifications (n = 2). To a solution of xanthine/hypoxanthine in EtOH/H_2O (10:1, v/v) was slowly added an aqueous solution of NaOH (0.5 M) until pH reached 10.5-11.0, followed by chloramine-T and NaI-131 solution (14.8-18.5 MBq). The resulting mixture was shaken in the mixer, followed by the addition of 0.5 M $Na_2S_2O_5$ (100 µL). To obtain the optimum reaction condition, the labeling was carried out by varying several parameters, including the ratio of xanthine/hypoxanthine and chloramine-T, pH, solvent, temperature, and reaction time.

Purification

The crude [^{131}I]-xanthine and [^{131}I]-hypoxanthine were purified by extraction with $CHCl_3$. This method allows the separation between the radiolabeled compounds and free iodide (and other impurities). To the reaction mixture was added water (10 mL), followed by $CHCl_3$ (10 mL). The organic layer was separated, and the aqueous layer was further extracted with $CHCl_3$ (2 x 10 mL). The purified compounds were obtained by isolating the $CHCl_3$ layers. Finally, the combined solution of $CHCl_3$ was concentrated under a stream of nitrogen to give the pure labeled compounds.

Determination of Radiochemical Yield (RCY) and Radiochemical Purity (RCP)

Radio-TLC analysis was carried out for the crude and purified radiolabeled compounds. The labeled xanthine/hypoxanthine was subjected to paper chromatography using Whatman paper no.3 (10x1 cm) as the stationary phase and the mixture of MeOH:H_2O (25:75 %) as the mobile phase (n = 3). A volume of 2 µL isolated compound was placed on the start line. After reaching the TLC-strip's top line, the stationary phases were dried in the oven at 80 ºC for five minutes and assayed for radioactivity. The RCY and RCP of the labeled compounds were determined using radio-TLC. The first peak represents a radiolabeled compound, while the following peak reflects free iodine. The RCY and RCP were calculated as the percentage of the radioactivity in the labeled compounds relative to the total activity on the TLC strip.

RESULTS AND DISCUSSION

A number of radiotracers have been introduced to treat various diseases. In clinical settings, some radionuclides with high linear energy transfer (LET), such as alpha, beta, Auger, or low energy conversion electron emitters, could be used to destroy the diseased tissues [23-25]. Additionally, molecular imaging that exploits optical imaging and radiopharmaceuticals (radiolabeled compounds), or in combination (hybrid-imaging), has great potential for the measurement of pathological processes by targeting specific receptors in various diseases, including infections, inflammations, neurodegenerative diseases, and cancers [26,27].

Iodine-131 is gamma and beta emitters [28], and therefore can be used for both therapeutic and diagnostic purposes (theranostic). It has a half-life of 8.02 d and can be used for treating thyroid cancer [29]. The literature is rich with radioiodination methods for the synthesis of radiolabeled compounds from small molecules, peptides, and antibodies precursors [30]. Although there are some oxidizing agents that can be used in direct labelling, chloramine-T and iodogen are perhaps the most popular agents [31]. Labeling of xanthine and hypoxanthine with iodine-131 was investigated in various reaction conditions. The influence of pH values on the labeling yields was studied in acidic and alkaline reaction conditions. The data indicated that labeling at acidic conditions provided low RCYs (< 5.0 %) (Table 1). The radioiodination of xanthine and hypoxanthine was realized by replacing the hydrogen atom at imidazole functionality by an iodine atom through electrophilic substitution [32,33], thus the molecular structure of [^{131}I]-xanthine [^{131}I]-hypoxanthine were proposed as described in Fig. 4.

Table 1. Optimization of the reaction in acidic conditions (pH = 5.5-6.0; NaI-131 = 14.8-18.5 MBq)

Entry	Compound (mg)		Chloramine-T (mg)	Temp (°C)	Time (min)	Yield (%)
1	Xanthine	0.2	0.2	RT	5	NR
2		0.2	0.4	RT	5	NR
3		1.0	1.0	RT	30	NR
4		1.0	2.0	RT	30	NR
5		1.0	1.0	45	30	2.8 ± 0.1
6		1.0	2.0	45	30	2.1 ± 0.1
7		1.0	1.0	65	30	3.5 ± 0.3
8		1.0	2.0	65	30	2.0 ± 0.0
9	Hypoxanthine	1.0	1.0	65	30	3.1 ± 0.0
10		1.0	2.0	65	30	2.5 ± 0.3

RT = room temperature (□27 °C), min = minutes; NR = no reaction

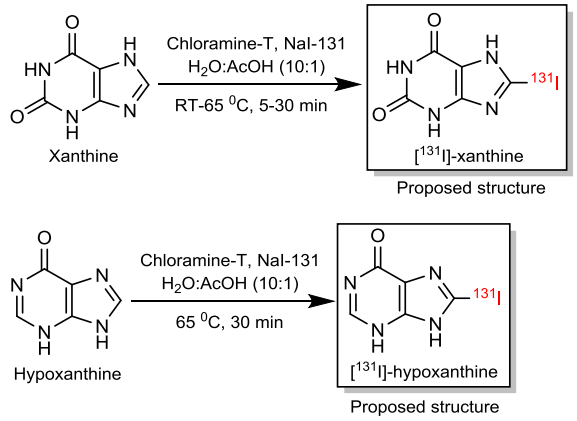

Fig. 4. General labeling strategy of xanthine and hypoxanthine with iodine-131 in acidic conditions, and the predicted outcomes. The radioiodine atom was attached to the imidazole ring system.

As indicated by radio-TLC analysis, a maximum RCY of 3.5 ± 0.3 % was achieved in Entry 7 (Fig. 5), while Entry 1-4 gave no conversion of starting material. The RCY was not significantly affected by increasing the temperature and the amount of chloramine-T (Entry 5-8) (Table 1). Similarly, labeling of hypoxanthine with iodine-131 under acidic conditions produced low RCYs (< 4.0 %), with a maximum yield of 3.1 ± 0.0 % (Entry 9). It is noteworthy that both xanthine and hypoxanthine were found to have poor solubility in DMSO/AcOH which may be attributed to the low RCYs. Hence, the focus was shifted to the use of EtOH and H_2O as a solvent system.

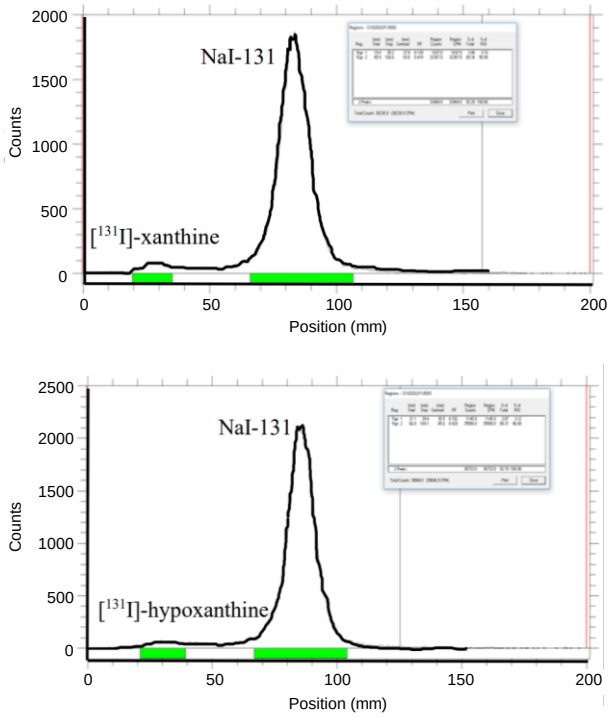

Fig. 5. TLC chromatogram of crude [^{131}I]-xanthine (Entry 7) and [^{131}I]-hypoxanthine (Entry 9) after reaction in acidic conditions (eluents = MeOH/H_2O (25:75 %)).

In an attempt to label xanthine and hypoxanthine with iodine-131 under alkaline conditions (Table 2), NaOH 0.5 M was added as a co-solvent to the solution of xanthine/hypoxanthine in H_2O, thus increasing the pH of the reaction mixture to 10.5-11.0. In alkaline solutions, xanthine and hypoxanthine were found to have better solubility than in acidic conditions. The first attempt of radioiodination of xanthine was performed using 1:1 ratio of xanthine:chloramine-T in EtOH:H_2O (10:1) at RT for 5 min to generate [^{131}I]-xanthine in 32.4 ± 1.1 % RCY (Entry 1). Increasing reaction time (Entry 2-5) and temperature (Entry 6-11) had no significant effect on the RCYs. Decomposition occurred when the reaction temperature increased to 90 °C, as suggested by radio-TLC analysis (Entry 12). The limited success of radioiodination using 1:1 ratio of xanthine:chloramine-T prompted

the search for more efficient reaction conditions by increasing the amount of chloramine-T. Recently, chloramine-T is widely used in radiolabeling of bioactive molecules through the halogenation procedure. During the reaction, chloramine-T has a crucial role in converting iodide to a more reactive form [34].

Table 2. Optimization of the reaction in alkaline conditions (pH 10.5-11.0; NaI-131 = 14.8-18.5 MBq).

Entry	Compound (mg)		Chloramine-T (mg)	Temp (ºC)	Time (min)	Yield (%)
1	Xanthine	0.5	0.5	RT	5	32.4 ± 1.1
2		0.5	0.5	RT	15	35.3 ± 0.2
3		0.5	0.5	RT	30	30.9 ± 0.4
4		0.5	0.5	RT	60	35.7 ± 0.3
5		0.5	0.5	RT	120	29.0 ± 0.6
6		0.5	0.5	45	30	30.7 ± 0.3
7		0.5	0.5	45	60	31.1 ± 0.1
8		0.5	0.5	45	120	22.1 ± 0.1
9		0.5	0.5	65	30	25.4 ± 0.5
10		0.5	0.5	65	60	37.5 ± 0.1
11		0.5	0.5	65	120	29.4 ± 0.4
12		0.5	0.5	90	30	Decomposed
13		0.5	1.0	RT	5	52.1 ± 0.1
14		0.5	1.0	RT	15	49.2 ± 0.2
15		0.5	1.0	RT	30	65.8 ± 0.1
16		0.5	1.0	RT	60	60.7 ± 0.1
17		0.5	1.0	RT	120	63.3 ± 0.3
18		0.5	1.0	90	15	Decomposed
19	Hypoxanthine	0.5	1.0	RT	60	60.3 ± 0.2
20		0.5	1.0	RT	120	59.6 ± 0.3

The number of attempts was performed by increasing the amount of chloramine-T (Entry 13-18). The results suggest that increasing the amount of chloramine-T significantly impacts the RCYs. Performing the reaction at RT with 1:2 ratio of xanthine:chloramine-T improved the RCY to 52.1 ± 0.1 % (Entry 13), and when the reaction time was prolonged to 15 and 30 min, the RCY of 49.2 ± 0.2 and 65.8 ± 0.1 % were obtained respectively (Entry 14-15). However, extending the reaction time to 60 and 120 min had no further effect on the RCYs. The final attempt to improve RCY was performed by increasing reaction temperature to 90 ºC, but no product was observed in TLC, probably due to thermal decomposition. On the other hand, labeling of hypoxanthine was achieved with a maximum yield of 60.3 ± 0.2 %, using 1:2 ratio of hypoxanthine:chloramine-T at rt for 60 min (Entry 19). Prolonging the reaction time to 120 min had no effect on the RCY (Entry 20).

During the reaction, radiochemical impurities may be present due to incomplete conversion of starting materials or decomposition products as a result of the presence of oxidizing agent (chloramine-T), radiolysis, or change of temperature and pH [35]. Analysis of the TLC chromatogram revealed that the source of impurity in the reaction mixtures was NaI-131. Accordingly, the crude solutions of Entry 15 ([^{131}I]-xanthine) and Entry 19 ([^{131}I]-hypoxanthine) were purified by extraction with chloroform ($CHCl_3$) to afford the desired labeled xanthine and hypoxanthine products with high RCP (95.1 and 94.2 %, respectively) (Fig.6).

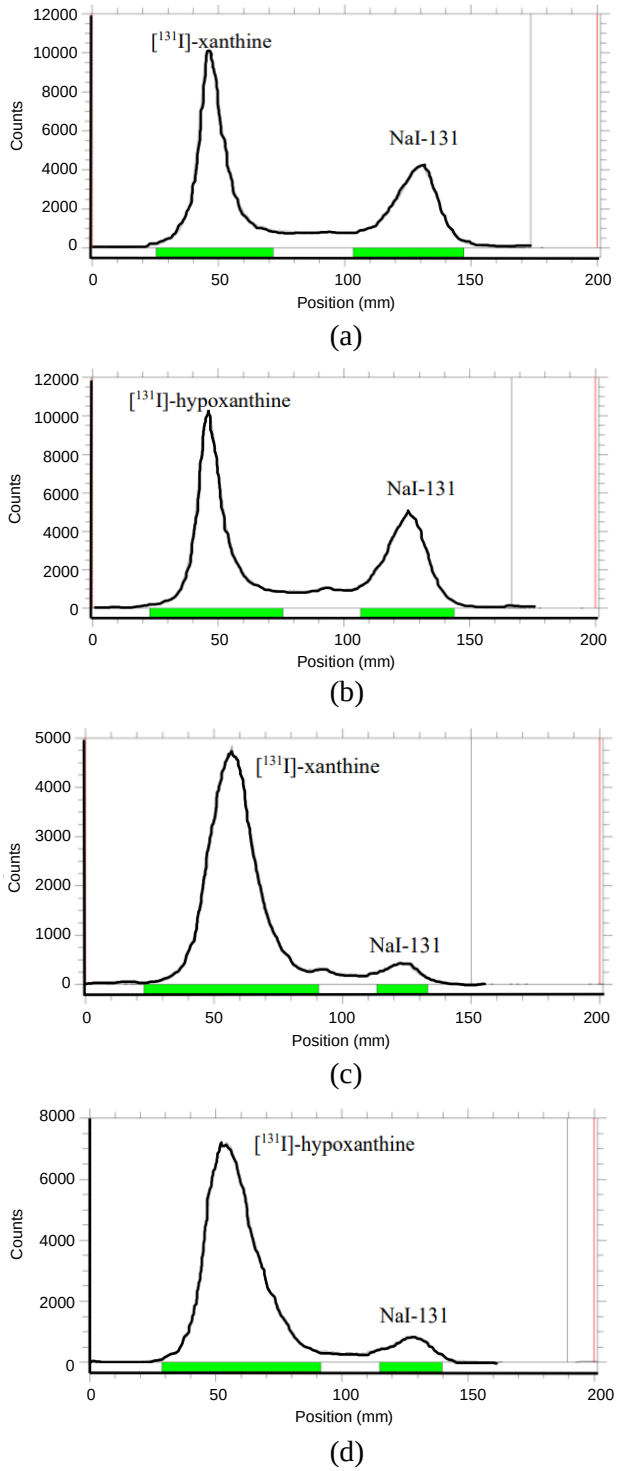

Fig. 6. TLC chromatogram of crude [^{131}I]-xanthine (Entry 15) (a) and [^{131}I]-hypoxanthine (Entry 19) (b) after reaction in alkaline condition (eluents = MeOH/H_2O (25:75 %). TLC chromatogram of isolated [^{131}I]-xanthine (Entry 15) (c) and [^{131}I]-hypoxanthine (Entry 19) (d) after purification by extraction using chloroform (eluents = MeOH/H_2O (25:75 %).

CONCLUSION

In the present study, novel [^{131}I]-3,7-dihydropurine-2,6-dione ([^{131}I]-xanthine) and [^{131}I]-1,9-dihydro-6H-purin-6-one ([^{131}I]-hypoxanthine) have been successfully radiosynthesized through efficient and practical radiolabeling procedures. Under alkaline reaction condition (pH = 10.5-11) and 1:2 ratio of starting materials:chloramine-T, the desired products were obtained with moderate RCYs (> 60 %) and high RCPs (~95.0 %). To the best of our knowledge, this is the first time that [^{131}I]-xanthine and [^{131}I]-hypoxanthine have been synthesized. These findings provide useful information and encourage us to develop xanthine and hypoxanthine-based radiopharmaceuticals for potential application as theranostic agents in nuclear medicine.

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AUTHOR CONTRIBUTION

Hendris Wongso contributed as the main contributor of this paper. All authors read and approved the final version of the paper.

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