Research Article

Journal of Labelled Compounds and Radiopharmaceuticals

Received 17 November 2009, Revised 30 December 2009, Accepted 4 January 2010 Published online 9 February 2010 in Wiley Interscience

(www.interscience.wiley.com) DOI: 10.1002/jlcr.1746

Synthesis and biodistribution of [^{11}C]SN-38

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SN-38 (7-ethyl-10-hydroxy camptothecin) is a topoisomerase I inhibitor that is the active chemotherapeutic agent of irinotecan, indicated for colon cancer. Because the rate of response to irinotecan treatment is low, it is of interest to have a prognostic indicator to identify and more selectively treat those who are likely to respond to treatment. We have therefore prepared SN-38 labeled with carbon-11. SN-38 was prepared by radical oxidation of 3-[^{11}C]propionaldehyde and subsequent radical addition of the ethyl fragment to 10-hydroxycamptothecin. Labeled propionaldehyde was prepared by reaction of methyl iodide with 2-lithiomethyl-1,3-dioxolane. Overall chemical yield was 34% from carbon dioxide. The murine biodistribution and radiation dosimetry of [^{11}C]SN-38 was measured by PET scanning in preparation for initial human studies. Biodistribution was fairly uniform except for hepatobiliary and urinary excretion.

Keywords: carbon-11; chemotherapy; cancer; PET; radiation dosimetry

Introduction

SN-38 (7-ethyl-10-hydroxy camptothecin) is an active metabolite of irinotecan,[1–8] a therapeutic drug that inhibits topoisomerase I and is mainly indicated for primary and metastatic colon and rectum cancer though it is used for other malignancies. Irinotecan is thought to primarily act as a prodrug through its rapid conversion to SN-38[9–11] via the cleavage by carboxyl esterase of a dipiperidinocarbamate substituent from the 10-position to leave the aromatic 10-hydroxyl noted in SN-38, the structure of which is shown in Scheme 1. Irinotecan is more water-soluble than SN-38,[12–14] which facilitates administration and biodistribution of the drug. SN-38 has been measured in various assays to be 2–2000 fold more potent than irinotecan (taken from labeling information, Camptosar). Multi-drug resistance appears to be a factor in the effectiveness of topoisomerase inhibitors, though there have been conflicting results in several *in vivo* studies as to whether concentration or time of exposure determines the effectiveness of the drug.[15] It remains a reasonable hypothesis that some degree of concentration of the active compound in tumors may be required for effectiveness, and therefore that PET scans of the active compound may provide a biomarker for drug effectiveness.

The rate of patient response to treatment with irinotecan is low[1,3,4,6,8] and it is typically used clinically in combination with other drugs such as 5-fluorouracil or anti-tumor antibodies. Depending on the type of tumor and the combination therapy, reported response rates range from 20 to 50%. At such a low response rate, many patients are subjected to the regimen, expense, and the potential for serious side effects (diarrhea, neutropenia, hypersensitivity, colitis, ileus, renal impairment including failure, and thromboembolism) of the treatment without receiving any benefit. However, it is currently impossible to predict which patients will benefit and which will not. It would clearly be of therapeutic, compassionate, and financial benefit to be able to predict the therapeutic response of patients who are candidates for irinotecan treatment.

In this work, SN-38 was prepared labeled with carbon-11 for use in PET scans to determine biodistribution of SN-38 in human subjects, potentially those who are candidates for irinotecan therapy. SN-38 was prepared (Scheme 1) by radical oxidation of 3-[^{11}C]-propionaldehyde and subsequent radical addition of the ethyl fragment to 10-hydroxycamptothecin. Labeled propionaldehyde was prepared by reaction of methyl iodide with 2-lithiomethyl-1,3-dioxolane. MicroPET scanning was used to measure biodistribution and radiation dosimetry of [^{11}C]SN-38 in mice.

Results and discussion

3-[^{11}C]Propionaldehyde (**3**) was synthesized by the I_2 catalyzed reaction of [^{11}C]methyl iodide with 2-lithiomethyl-1,3-dioxolane (**1**) in diethyl ether to form labeled 2-ethyl-1,3-dioxolane (**2**), which then afforded **(3)** upon acid hydrolysis. In tetrahydrofuran (THF), diglyme, dibutyl ether, and 1,4-dioxane, a major unidentified byproduct formed, accounting for $>50\%$ of the labeled material. This byproduct was not formed in diethyl ether, which therefore was the solvent of choice. Similarly, *in situ* preparation of (**1**) by exchange with *n*-butyllithium[16] proved unreliable to form the small quantity needed for radiolabeling. It was preferable to prepare (**1**) as a stock solution in diethyl ether, which had a shelf life of at least two weeks. However, the lithiation reaction of 2-bromomethyl-1,3 dioxolane did not proceed spontaneously in diethyl ether, so it was necessary to initiate reaction by addition of an aliquot of a solution prepared in dibutyl ether. As an alternative to (**1**), the corresponding Grignard reagent, (1,3-dioxolan-2-ylmethyl)-magnesium bromide, was also investigated. However, radiolabeling yields during initial comparative experiments to produce (**2**) were low (5–20%) from the

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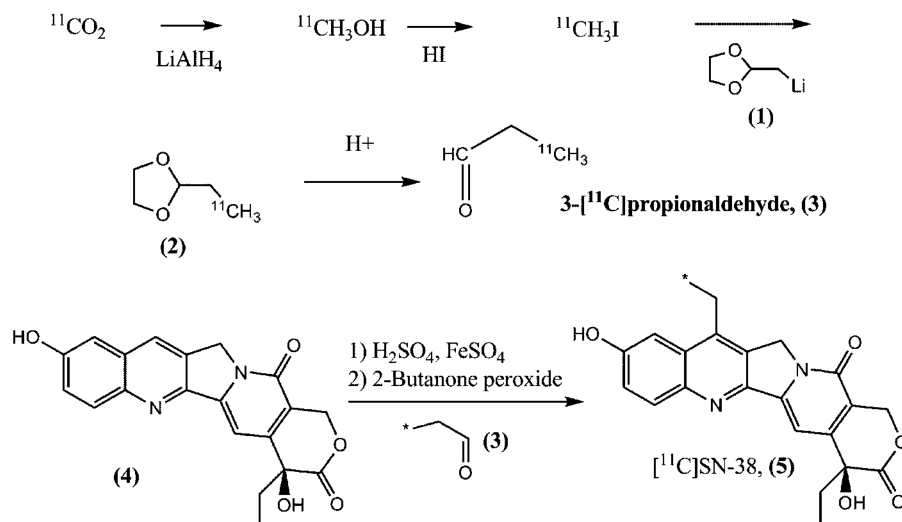

Scheme 1. Synthesis of [^{11}C]SN-38.

Grignard reagent compared to yields from (**1**) (20–50%) despite use of common catalytic additives[17] CuCN, CuI, Li_2CuCl_4,[18] Fe(acac), and NiCl.[19] Thereafter, reaction of (**1**) with methyl iodide without catalysis afforded yields of 18$\pm$5%, while use of catalytic iodine increased this to 49.6$\pm$9.3%. [^{11}C]Methyl iodide was generally obtained from [^{11}C]CO_2 in $>$95% yield, and propionaldehyde from methyl iodide in 40–60% yield.

Nascent propionaldehyde was distilled as the ethyl dioxolane (**2**) immediately upon methylation without prior quenching of (**1**), which, as a lithium salt, was not volatile. This provided a preliminary purification, leaving the relatively large amounts of lithio-methyl-1,3-dioxolane behind. If the lithium reagent was protonated by the addition of water or other proton donor, the resulting methyl-1,3-dioxolane distilled with the desired labeled ethyl-1,3-dioxolane (**2**). On hydrolysis, before or after distillation, these produced acetaldehyde and labeled propionaldehyde respectively. Both reacted similarly with 10-hydroxycamptothecin, with acetaldehyde producing 7-methyl-10-hydroxycamptothecin. The relatively large amount of (**1**) necessary to produce (**2**) rendered the method intractable, if protonation was allowed, by requiring and consuming additional precursor, reducing the radiolabeling yield, and complicating the final purification. Therefore, it was critical to distill (**2**) away from the unreacted and still lithiated (**1**). As (**2**) distilled into the reaction mixture for the production of SN-38, the sulfuric acid catalyst present for the SN-38 reaction also catalyzed the quantitative hydrolysis of the dioxolane to form propionaldehyde within one minute. However, an unavoidable consequence of this strategy was that some of the diethyl ether solvent also distilled into the reaction mixture for the production of SN-38.

[^{11}C]SN-38 was produced from labeled propionaldehyde and 10-hydroxycamptothecin, (**4**), (the *S* enantiomer, which is the same stereoconfiguration as irinotecan and as metabolically-produced SN-38) following the method of Collins[20] and by modifications of that method,[21] in which an aqueous reaction medium was used with a relatively large quantity (100 μL) of conc. sulfuric acid. The Collins method, using unlabeled propionaldehyde, provided yields of 30%, which further optimization raised to 55%. However, use of labeled propionaldehyde prepared as above afforded much lower yields (20%).

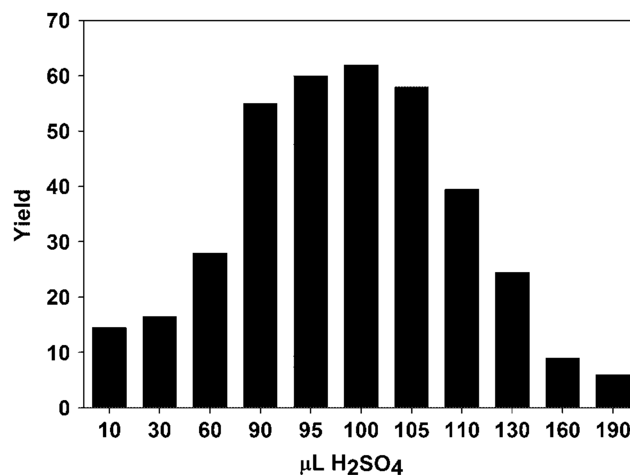

Figure 1. Dependence of SN-38 yield on sulfuric acid quantity (reaction in ether with 2-butanone peroxide).

It was demonstrated that the presence of diethyl ether in the reaction mixture reduced SN-38 yield. We postulated that this was due to the observed formation of two phases and separation of reactants, rather than inhibition of the reaction mechanism. Attempts to use 1,4-dioxane as solvent with hydrogen peroxide and sulfuric acid were unsuccessful in creating a single-phase reaction mixture or raising the yield. However, sulfuric acid alone was miscible in ether, and a single-phase reaction mixture could be obtained in ether with 2-butanone peroxide or benzoyl peroxide in place of hydrogen peroxide. Benzoyl peroxide was ineffective, but with 2-butanone peroxide a maximum product yield of 60% was obtained, which depended on the quantity of sulfuric acid used (Figure 1). While $FeSO_4 \cdot 7H_2O$ was not fully soluble in this medium, its presence was necessary and sufficient to provide the optimum yield. Purification by HPLC was straightforward, with the product being collected between 7 and 8 min with baseline resolution from small quantities of adjacent impurities. Starting material eluted at 4 min with good separation. The final product on

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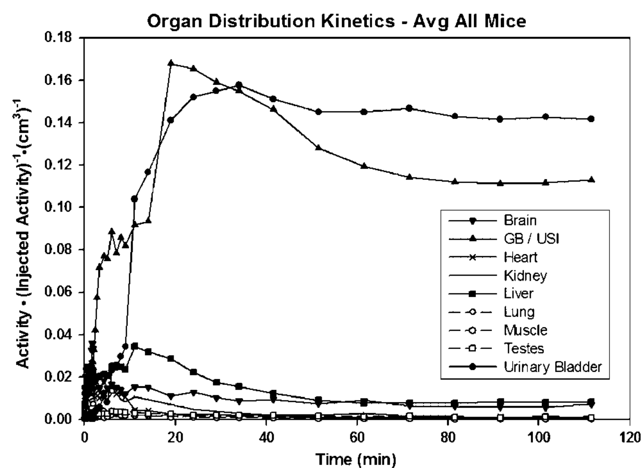

Figure 2. Average organ distribution kinetics of [^{11}C]SN-38 in mice.

analytical HPLC appeared as a single radioactive peak (8 min), with a mass impurity of 10-hydroxycamptothecin starting material (4.2 min), which contained less than 2% of mass present in the labeled product as the only detectable impurity. The 4-step, 3 pot, synthesis was complete at 70 min EOB, with chemical and radiochemical purity of 98+%, specific activity of 75–200 GBq (2–5 Ci) per micromole EOS, in overall chemical yield of 34% from carbon dioxide (radiochemical yield 3%). The chemical yield of the intermediate step of formation of propionaldehyde from methyl iodide was 60% and that of the ethylation of camptothecin by propionaldehyde was 60% (Scheme 1). A production beginning with 40 GBq (1 Ci, approx 30 μA 1 h) [^{11}C]CO_2 could produce 1.2 GBq (30 mCi) of SN-38 at 70 min EOB.

Biodistribution of [^{11}C]SN-38 was measured by MicroPET scans of 12 mice. Regions (volumes) of interest drawn on the scans were used to generate time–activity curves. Chosen representative decay-corrected organ uptake curves are shown in Figure 2. The prominent curve with the highest uptake is the upper small intestine, which proved to be the dose-limiting organ, indicating that hepatobiliary clearance was a major factor in the whole-body dose distribution. The remainder of the distribution noted in the PET images, aside from moderate uptake in brain relative to surrounding tissues, was rather uniform throughout the body and unremarkable, providing an image (in normal mice, without tumors) that contained very little information. The residence time was calculated for each organ (Table 1) as integrated region of interest data and input into OLINDA/EXM v.1.0, under the implicit assumption that the organ dose distribution as a percent of injected dose would be the same in the mouse and human. The human adult dosimetry model of the software was then used to calculate radiation dosimetry from the residence time data. The resulting calculated radiation dosimetry is tabulated in Table 1 in traditional and in SI units. With this model, the dose-limiting organ is the upper small intestine. Although the use of distribution data from mice has known drawbacks as an estimate of human radiation dosimetry, this data provides a preliminary indication of distribution and clearance as we move forward to human dosimetry studies. The dosimetry data was used in support of an IND application (approved) to investigate human radiation dosimetry of [^{11}C]SN-38 in a limited number of subjects in a preliminary study

Table 1. Calculated expected human radiation dosimetry of [^{11}C]SN-38, including organ residence time values (seconds) used as OLINDA input

Organ	mR/ mCi	uSv/ MBq	Res. time (s)
Adrenals	11.8	3.2	0.02
Brain	6.7	1.8	5.6
Breasts	5.5	1.5	0.47
Gall bladder	35.0	9.4	0.48
LLI	156.7	42.3	39
Small intestine	384.9	103.9	340
Stomach	36.7	9.9	7.8
ULI	138.2	37.3	39
Heart	56.5	15.1	12
Kidneys	32.0	8.6	5.6
Liver	24.8	6.7	26
Lungs	7.31	2.0	0.5
Muscle	11.8	3.2	33
Ovaries	59.8	16.1	0.16
Pancreas	18.9	5.1	0.5
Marrow	18.7	5.0	1.2
Skin	11.4	3.1	4.6
Spleen	14.3	3.9	0.73
Testes	14.6	3.9	0.65
Thymus	8.2	2.2	0.025
Thyroid	6.1	1.7	0.007
Urinary bladder	43.7	11.8	9.1
Uterus	39.2	10.6	0.27
Effective dose equivalent	66.5	17.9	
Effective dose	52.8	14.3	

toward the evaluation of the prognostic value of PET scans with this radiopharmaceutical.

Experimental

Reagents and solvents were obtained from Aldrich Chemical Co. and Fisher Scientific and used without further purification unless otherwise noted. Tetrahydrofuran and diethyl ether were freshly distilled from sodium/benzophenone ketal. 10-Hydroxycamptothecin starting material was obtained from Sigma-Aldrich with certificate of analysis that included certification of a stereochemical configuration equivalent to that of irinotecan.

Analyses were performed on a Hewlett-Packard 5890 Series II gas chromatograph with a $6' \times 1/8''$ Porapack N 80/100 column and flame ionization detection, He flow rate 20 mL/min; retention times (min): acetaldehyde 1.9, methyl iodide 2.2, propionaldehyde 4.5, methyl dioxolane 10.8, ethyl dioxolane 19.6, bromomethyl dioxolane – undetected (long). Radiochemical purification was performed using a Beckman 110B pump and Kratos Spectroflow 757 variable wavelength UV detector and an Alltech Econosphere 4.6×250 mm reverse phase C-18 column eluted with 20% aqueous acetonitrile/0.2% trifluoroacetic acid at 2 mL/min (Figure 3). Radioactivity was measured with a Beckman 170 flow-through detector. Retention times (min): propionaldehyde 2.5, H_2SO_4 and $FeSO_4$ 2-3, 10-OH-camptothecin 4.2, methyl iodide 4.9, SN-38 7.3, other unidentified non-radioactive materials in small amounts, presumably reaction of precursor with other nucleophiles 5.2, 6.2, 9.3,

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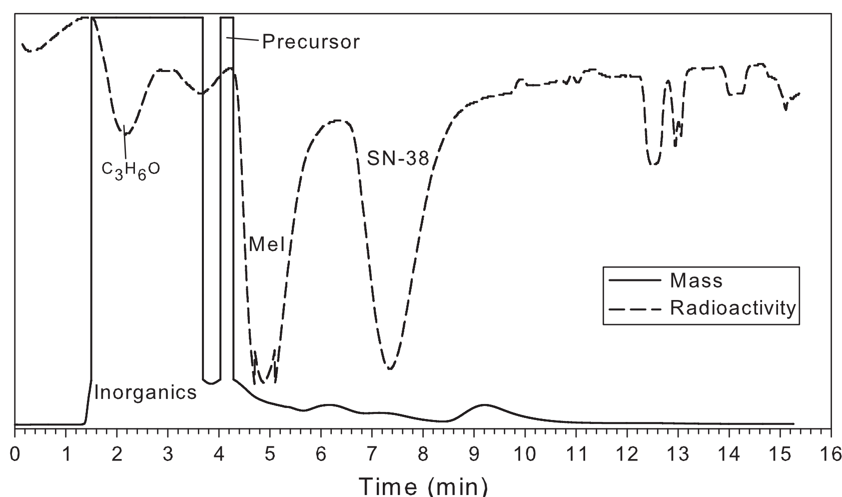

Figure 3. Sample radiochromatogram of SN-38 purification.

unidentified minor radioactive products 12.7, 13.2, 14.3, 15. HPLC for QC was performed on a Hewlett-Packard 1090 Series II instrument with autoinjector, diode array UV, and refractive index detection (Knauer), and a Grace Econosphere 4.6 × 250 mm reverse phase column eluted with 20% aqueous acetonitrile/0.2% trifluoroacetic acid at 2 mL/min; retention times (min): 10-hydroxycamptothecin 4.2, SN-38 8.2.

[^{11}C]CO2 was produced by the $^{14}N(p,\alpha)^{11}C$ reaction using a Siemens Eclipse 11 MeV cyclotron with the manufacturers standard target containing 2.5% O_2 in N_2 target gas and was trapped in a stainless steel coil cooled in liquid nitrogen.

[^{11}C]Methyl iodide

[^{11}C]CO_2 was released from the coil by a 30 mL/min helium flow and was trapped in a solution of $LiAlH_4$ (10 μmol) in 400 μL diethyl ether. The solvent was evaporated at 110°C, 400 μL 47% hydriodic acid added, and the vessel was heated for 5 min. NaOH (1 mL of 5 N) was added to neutralize the acid. The resulting [^{11}C]methyl iodide (>95% chemical yield) was purified by distillation through 1–2 mL bed volume of P_2O_5.

2-Lithiomethyl-1,3-dioxolane (1)

2-Lithiomethyl-1,3-dioxolane (**1**) in diethyl ether was prepared by reaction of lithium metal (8 mmol) and 2-bromomethyl-1,3 dioxolane (6.25 mmol) in 25 mL diethyl ether. The lithiation reaction was initiated in diethyl ether by addition of 0.1 mL of a solution of (**1**) previously prepared by an identical reaction performed in dibutyl ether. Formation of (**1**) was alternatively obtained by addition of *n*-butyllithium (104 μmol) to 2-bromomethyl-1,3-dioxolane (100 μmol) at −80°C in diethyl ether immediately preceding preparation of [^{11}C]methyl iodide.

2-(2-[^{11}C]-Ethyl)-1,3-dioxolane (2)

[^{11}C]Methyl iodide was distilled (into a solution containing (**1**) (100 μmol) in 400 μL diethyl ether at 0°C. One microliter of 1 mg/mL I_2 in diethyl ether solution was added and the reaction mixture was allowed to react for 10 min. (**2**) was then distilled from the reaction mixture. To prepare samples for intermediate analysis, 0.1 mL 1 N HCl was added to hydrolyze (**2**) to propionaldehyde.

[^{11}C]SN-38

2-(2-[^{11}C]-Ethyl)-1,3-dioxolane (**2**) was distilled into a solution of 200 μL diethyl ether, 100 μL H_2SO_4 (conc.), 100 μg 10-hydroxycamptothecin (0.27 mmol), and 4 mg $FeSO_4 \cdot 7H_2O$. After allowing 1 min to complete the rapid hydrolysis of (**2**) to produce 3-[^{11}C]propionaldehyde, the oxidative radical reaction was initiated by addition of 2 μL 2-butanone peroxide (Aldrich, 04390). After two minutes, an additional 2 μL 2-butanone peroxide was added. Addition and reaction was repeated for a total of 10 μL over 10 min. Then, 1 mL of 20% acetonitrile in 0.2% trifluoroacetic acid (HPLC solvent) was added and the product was purified by HPLC chromatography. The collected fraction was evaporated to dryness and then ethanol (1 mL) was added twice and evaporated to dryness to remove traces of HPLC solvent. The product was dissolved in sterile 5% EtOH/saline (USP) and sterile filtered for injection.

3-[^{11}C]-Propionaldehyde via Grignard reagent

A total of 200 μL of (1,3-dioxolan-2-ylmethyl)-magnesium bromide (0.5 M in tetrahydrofuran, 100 μmol) was dissolved in 200 μL tetrahydrofuran at −80°C (alternatively at 0°C or room temperature), optionally with added 10 μmol, NiCl, Li_2CuCl_4, LiCl, Fe(acac), or CuCN. Labeled methyl iodide was added and allowed to react for 5–30 min. The reaction was terminated by addition of 1 mL of 1 N hydrochloric acid and the vessel was heated for 10 min at 80°C to hydrolyze the dioxolane.

Biodistribution

Experiments were carried out with the approval of the UAMS IACUC in accordance with all applicable regulations. CD-1 Mice, 6 male, 6 female, were used. Under isoflurane anesthesia each mouse was injected with 15–40 MBq (0.3–1.0 mCi) of [^{11}C]SN-38. Dynamic PET imaging was performed. The microPET scanner was started immediately before injection. Dynamic reconstruction was performed, segmenting the data into image frames after the acquisition, and beginning at the time of injection of each mouse. The dynamic frame sequence was 6 × 5 s (30 s), 6 × 10 s (1.5 min), 3 × 20 s (2.5 min), 4 × 30 s (4.5 min), 6 × 60 s

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(10.5 min), 5 × 300 s (35.5 min), 10 × 600 s (135.5 min). Data were analyzed by integration of the observed organ dose distribution curves for all organs of interest (Table 1). In some cases, the organ was not clearly identifiable due to a uniform uptake throughout most areas of the body. In these cases, a representative region in the area of the body containing the organ, and possibly neighboring organs of similar uptake values, was used to represent the organ uptake. The uptake values, in units of uCi/cc, were multiplied by the organ volumes in the mouse and divided by the injected dose, to arrive at the total fraction of injected dose that was deposited in each organ at each time point. This data was integrated over time for each organ to give the 'residence time', or total deposited dose in units of (μCi/μCi injected) × (minutes). These residence time values were then input into the FDA-approved software package OLINDA/EXM v1.0 and used, applying the adult human radiation dose model, to calculate expected human radiation dosimetry. The method implicitly assumes that the relative organ uptake, as percent of injected dose deposited in each organ, is the same in a human as it is in a mouse.

Conclusion

[^{11}C]SN-38 was synthesized in 34±4.5% chemical yield from [^{11}C]CO_2 within 70 min from end of bombardment. Murine biodistribution was used as a preliminary indication of expected human radiation dosimetry, indicating that human studies would be feasible. Sufficient quantities, 370–1110 MBq (10–30 mCi), can be synthesized reproducibly for human use.

Acknowledgements

Valuable discussions with Dr. Timothy Tewson, University of Iowa, are gratefully acknowledged.

This project has been funded in whole or in part with Federal Funds from the U.S. National Cancer Institute, National Institutes of Health, under Contract No. NO1-CO-12400, SAIC-Frederick subcontract 27XS129. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

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