Investigation of iodine-123-labelled amino acid derivatives for imaging cerebral gliomas: uptake in human glioma cells and evaluation in stereotactically implanted C6 glioma rats

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Abstract. In developing iodine-123-labelled amino acid derivatives for imaging cerebral gliomas by single-photon emission tomography (SPET), we compared p-[123I]iodo-L-phenylalanine (IPA), L-[123I]iodo-1,2,3,4-tetrahydro-7-hydroxyisoquinoline-3-carboxylic acid (ITIC) and L-3-[123I]iodo-α-methyltyrosine (IMT) with regard to their uptake in human glioblastoma T99 and T3868 cells, and thereafter studied the mechanisms promoting the cellular uptake. The potential of the 123I-iodinated agents for use as SPET radiopharmaceuticals was evaluated in healthy experimental rats as well as in rats with stereotactically implanted C6 gliomas. The radiopharmaceutical uptake into glioblastoma cells was rapid, temperature and pH dependent, and linear during the first 5 min. Equilibrium was reached after 15–20 min, except in the case of ITIC, the initial uptake of which gradually decreased from 15 min onwards. The radioactivity concentration in glioma cells following 30-min incubation at 37°C (pH 7.4) varied from 11% to 35% of the total activity per million cells (ITIC < IMT ≤ IPA). Competitive inhibition experiments using α-(methylamino)-isobutyric acid and 2-amino-2-norbornane-carboxylic acid, known as specific substrates for systems A and L, respectively, as well as representative amino acids preferentially transported by system ASC, indicated that IPA, like IMT, is predominantly mediated by the L and ASC transport systems, while no significant involvement of the A transport system could be demonstrated. By contrast, none of the three principal neutral amino acid transport systems (A, L and ASC) appear to be substantially involved in the uptake of ITIC into glioblastoma cells. Analysis of uptake under conditions that change the cell membrane potential, i.e. in high K⁺ medium, showed that the membrane potential plays an important role in ITIC uptake. Alteration of the mitochondrial activity by means of valinomycin or nigericin induces a slight increase or decrease in the radiopharmaceutical uptake, suggesting a minor contribution of the mitochondria in the uptake. IPA, IMT and ITIC passed the blood-brain barrier, and thereafter showed efflux from the brain. The radioactivity concentration in healthy rat brain 15 min following intravenous injection varied from 0.07% (ITIC) to 0.27% ID/g (IPA). In comparison, the brain uptake in the stereotactically implanted C6 glioma rats was substantially higher (up to 1.10% ID/g 15 min p.i.), with tumour-to-background ratios greater than 4. These data indicate that IPA and ITIC, like IMT, exhibit interesting biological characteristics which hold promise for in vivo brain tumour investigations by SPET.

Key words: Single-photon emission tomography – Iodine-123-labelled amino acids – Amino acid transport – Cerebral glioma


Introduction

Development of non-invasive methods to identify qualitatively and quantitatively differences between normal tissue and neoplastic tissue is crucial to the understanding of cancer and to the improvement of cancer treatment. One promising technique that appears more sensitive and accurate than other brain imaging modalities, including magnetic resonance imaging (MRI) and computer tomography (CT), is the use of positron emission tomography (PET) to study the physiological process asso-
associated with the utilization of nutrients in tumours [1, 2, 3, 4]. In particular, PET with radiolabelled amino acids such as \(L^{-11}C\)methionine (MET) allows the accurate delineation of viable tumour extent, yielding important diagnostic information in patients with brain tumours [5, 6, 7], and may also represent a rapid and sensitive indicator of response to therapy. However, the major limitation of MET is that the half-life of \(^{11}C\) is only 20 min. In addition to therapy. However, the major limitation of MET is that the half-life of \(^{11}C\) is only 20 min. In addition, the availability of PET with MET remains limited. Consequently, research has concentrated on developing amino acid analogues labelled with fluorine-18 \([8, 9, 10]\) for PET or with single-photon-emitting radionuclides such as iodine-123 \([11, 12]\), suitable for widespread clinical application with single-photon emission tomography (SPET). In recent years, the amino acid derivative \(L^{-3-\[123\]I}iodo-\alpha\)-methyltyrosine (IMT) has been introduced as a SPET radiopharmaceutical for brain tumour imaging \([13, 14, 15]\). In a previous comparative study of PET with MET and SPET with IMT in patients with cerebral gliomas, the imaging of the tumour extent was identical and there was a significant correlation between the tumour-to-brain (T/B) ratios of the two tracers within 1 h post injection (p.i.). However, T/B ratios were significantly lower for IMT than for MET \([16]\). In an attempt to improve the amino acid-based radiotracers available for the non-invasive diagnosis of brain tumours with SPET, we prepared \(p^{-123}\)Iiodo-\(L\)-phenylalanine (IPA) and \(L^{-123}\)Iiodo-tetrahydroisooquinoline-3-carboxylic acid (ITIC) and studied their uptake in human glioblastoma cells in comparison with that of IMT. Furthermore, following intravenous administration we evaluated the ability of the radiopharmaceuticals to penetrate the blood-brain barrier and their organ distribution in both healthy experimental rats and rats with stereotactically implanted C6 gliomas. In addition, the mechanism of uptake of the radiopharmaceuticals into human glioma cells was elucidated.

**Materials and methods**

**Reagents.** \(L\)-Alanine, \(L\)-serine, \(L\)-cysteine, 2-amino-2-norbornane-carboxylic acid (BCH), \(\alpha\)-(methylamino)-isobutyric acid (MeAIB), nigerin and valinomycin, as well as \(\alpha\)-methyl-\(L\)-p-tyrosine (MT) and 4-bromo-\(L\)-phenylalanine (BrPA), used as precursors for the radioiodination, were purchased from Sigma-Aldrich (Deisenhofen, Germany). \(L^{-1,2,3,4}\)-Tetrahydro-7-hydroxyisooquinoline-3-carboxylic acid (TIC) was obtained from Novabiochem (Bad Soden, Germany). Carrier-free sodium \(^{123}\)Iodine for radioiodination was obtained from FZK (Karslsruhe, Germany) in 10–15 µl of 0.1 N NaOH solution. Unless otherwise stated, all other solvents were of analytical or clinical grade and purchased via the local university hospital pharmacy.

**Preparation of the radiopharmaceuticals.** \(L^{-3-\[123\]I}iodo\-\alpha\)-methyltyrosine (IMT) was prepared by direct electrophilic radioiodination of \(\alpha\)-methyl-\(L\)-p-tyrosine in 1 N hydrochloric acid in the presence of KIO\(_3\) \([15]\). \(p^{-\[123\]I}iodo-\(L\)-phenylalanine (IPA) was obtained by non-isotopic Cu(I)-assisted \([123\]Iiododebromination of \(p\)-bromophenylalanine \([17]\) while \(L^{-123}\)Iiodo-\(L\)-1,2,3,4-tetrahydro-

![Fig. 1. Structures of \(L^{-[123]I}\)iodo-1,2,3,4-tetrahydro-7-hydroxyisooquinoline-3-carboxylic acid (ITIC), \(p^{-[123]I}\)iodo-\(L\)-phenylalanine (IPA) and \(L^{-3-[123]I}\)iodo-\(\alpha\)-methyltyrosine (IMT)](image)

isoquinoline-3-carboxylic acid (ITIC) was prepared by the Iodogen method \([18]\), starting from TIC. IMT, IPA and ITIC (Fig. 1) were isolated from unreacted starting materials and radioactive impurities by isocratic reverse-phase high-performance liquid chromatography (HPLC), and the fraction containing the radiopharmaceutical was collected into a sterile tube, buffered with PBS (pH 7.4) and sterile-filtered through a 0.22-µm filter into an evacuated sterile tube prior to studies. Details concerning the radiosynthesis have been described previously \([19]\).

**Cell cultures.** Human T99 and T3868 glioma cells (primary human glioblastoma multiforme) were obtained from the oncological research laboratory and human genetic research laboratory of the Saarland University Medical Centre (Homburg, Germany) and cultivated in RPMI-1640 medium (phenol red-free, Gibco-BRL) and Dulbecco’s modified Eagle medium (sodium pyruvate-free, supplemented with \(L\)-glucose and pyridoxine), respectively, supplemented with penicillin (50 U/ml), streptomycin (50 µg/ml), 10% fetal calf serum and 50 µl insulin (10 µg/ml) at 37°C in a humidified atmosphere of 5% CO\(_2\) in an incubator. Cells were passaged routinely every 5 days, and the medium changed every 2 days. Before the experiment, subconfluent cells were trypsinized with a solution of 0.05% trypsin and 0.02% EDTA in PBS without Ca\(^{2+}\) and Mg\(^{2+}\). The suspension was mixed thoroughly, transferred to a 50-ml centrifuge tube (Falcon, Becton Dickinson, USA) and counted on a haemocytometer, and the viability of the cells was assessed using trypsin blue. Cells were centrifuged for 5 min at 200 × g; the resulting supernatant was removed and the pellet re-suspended in serum-free Dulbecco’s modified Eagle medium and then transferred to 1.5-ml Eppendorf tubes at concentrations of 500,000 and 10\(^6\) cells/ml for the experiment.

**Cellular uptake.** To minimize non-specific binding of the radioiodinated agents to plastic tubes, they were presaturated with a freshly prepared solution of 1% bovine serum albumin in 0.1 M PBS (pH 7.4) for 30 min followed by three washes in PBS. Control experiments showed that the radiopharmaceutical binding to plastic tubes was always less than 1% of total radioactivity for incubation periods up to 120 min. All experiments were performed in a protein-free medium simultaneously with 500,000 and 10\(^6\) cells. Before the incubation with the radiopharmaceuticals, the cells were pre-incubated for 15 min in 500 µl medium at 37°C in 1.7-ml Eppendorf centrifuge tubes. Aliquots of 30–50 µl (10\(^5–1.5 \times 10^6\) cpm) freshly prepared IPA, ITIC or IMT were added and cells were incubated at 37°C for 1, 15, 30, 60 and 90 min while shaking. After stopping the tracer uptake with 1 ml ice-cold PBS (pH 7.4) and an additional 2-min
stay in an ice bath, the cells were centrifuged for 2 min at 300 × g, the supernatant removed and the pellet washed three times with ice-cold PBS. Radioactivity in the cells was measured on a Berthold LB951 gamma counter. The results were expressed either as percent of the applied dose per 10^6 cells or as cpm/1000 cells after correction for the amount of radioactivity retained in wells without cells (1%). All activities were corrected for decay.

**Study of the effect of pH and temperature and the influence of plasma and mitochondrial membrane potentials on radiopharmaceutical uptake.** In separate experiments the uptake of IPA, ITIC and IMT in suspensions of 10^6 glioblastoma cells was examined at 4°C (pH 7.4) and 37°C (pH 5.0–9.0), as well as in cell suspensions in high K^+ medium (135 mM KCl), to determine the temperature and pH dependence and the influence of cell membrane potential on radiopharmaceutical uptake. Furthermore, in order to evaluate the contribution of the mitochondria, the radiopharmaceutical uptake was examined in the presence of the ionophores valinomycin and nigerinic (5 mM/l, 250 µl), which are known to disrupt the metabolism of mitochondria. Radioactivity in the tumour cells was determined as described above after a 30-min incubation at 37°C/pH 7.4.

**Competitive inhibition studies and pre-loading with naturally occurring amino acids.** Inhibition investigations were carried out to characterize the uptake mechanisms involved in the uptake of the radiopharmaceuticals into human glioma cells. The following specific amino acid carrier inhibitors were used: BCH, MeAIB and alanine-serine-cysteine mixture for the carrier systems L, A and ASC, respectively. Cell suspensions containing 10^6 cells were pre-incubated with 250 µl of the amino acid carrier inhibitors (10 mM medium). After 15 min at 37°C, 30–50 µl (10^5–1.5×10^6 cpm) of the freshly prepared radiopharmaceutical was added, followed by incubation at 37°C/pH 7.4 for 30 min.

In addition, cell suspensions containing 10^6 cells were pre-loaded with 250 µL of L-aminino acid (5 mM/l) and allowed to remain at 37°C for 15 min, followed by addition of 30–50 µl (10^5–1.5×10^6 cpm) of the radiopharmaceutical and incubation at 37°C/pH 7.4 for 30 min. The following L-amino acids were used: L-alanine, L-phenylalanine, L-tyrosine, L-proline and L-serine. After stopping the tracer uptake with 1 ml ice-cold PBS (pH 7.4), the cells were centrifuged for 2 min at 300 × g, the supernatant removed and the pellet washed three times with ice-cold PBS, followed by measurement of the radioactivity on a gamma counter.

**Animal experiments.** Two different in vivo evaluations of the radiodinated amino acid derivatives were performed in this study, namely investigation of the blood-brain barrier penetration and initial organ distribution in healthy rats and assessment of the biodistribution of the radiopharmaceuticals in C6 glioma-bearing rats. The studies were carried out on young adult male Sprague-Dawley and Wistar rats (Charles River Wiga, Sulzfeld, Germany) weighing 220–250 g. The experiments were performed in accordance with the principles of laboratory animal care in the context of scientific research and the German law, and were approved by the district governments (Saarpfalz-Kreis and Rheinland-Pfalz, Germany No. K 110/180–07 109/7 and 177–07/999–10 02/99).

C6 rat glioma cells (10^6) were stereotactically implanted [20, 21] into the left frontal region of male Wistar rats while under chloralhydrate anaesthesia. The tumour was allowed to grow for 10 days. Intracranial C6 tumour-bearing rats presented signs of apathy and the presence of the tumour was confirmed by cranial MRI prior to in vivo investigation. The animals were anaesthetized by diethyl ether or chloralhydrate. Thereafter 1.5–3.0 MBq of the radiopharmaceutical in 0.3–0.4 ml injectable solution was intravenously administered via a Teflon catheter in the inferior vena cava. The animals were held in metabolic cages and sacrificed 5, 15, 30 and 60 min p.i. Blood samples were obtained by cardiac puncture. Organs of interest were excised, blotted dry and weighed. Activity in the organs was counted on a Berthold LB951 gamma scintillation counter after a reference sample of the injected dose had been prepared and counted. After correction for physical decay, percent injected dose per gram organ (% ID/g) was calculated for each organ. At the end of the experiments the brain tissue of all C6 glioma-bearing rats was analysed histopathologically. In separate experiments, the blood-brain barrier penetration and the whole-body distribution of the radiopharmaceuticals were visualized with a gamma camera (Multispec II, Siemens), starting immediately after intravenous administration of 7–8 MBq of the radiopharmaceutical in chloralhydrate-anaesthetized rats.

**Blood kinetic and plasma analysis.** Blood samples were collected at 5, 15, 30 and 60 min after injection of the radiopharmaceutical. Radioactivity in whole blood and plasma (obtained by centrifugation at 5000 × g) was measured against a known standard sample in a scintillation counter. Plasma analysis was performed after methanol or acetonitrile extraction through Sep-Pak C18 cartridges, followed by HPLC analysis of the supernatant on a Nucleosil C4 column (4×250 mm) with 1% acetic acid–ethanol (90:10, v/v) as eluent, and additionally by thin-layer chromatography analysis using two different chromatographic systems: silica gel plates (Gelman ITLC-SG) and ethanol/1% acetic acid, 40/60 (v/v), as mobile phase, and silica gel plates (Merck) with methanol:acetic acid (99:1, v/v) as solvent system.

**Results**

**Cellular uptake and determination of the uptake mechanisms**

Data regarding the uptake kinetics of the investigated radioiodinated amino acid analogues in two primary human glioblastoma cell lines are provided in Fig. 2, and the results of the competitive inhibition studies are shown in Fig. 3. IPA, IMT and ITIC showed rapid uptake in the human T99 and T3868 glioblastoma cells for the first 2 min under physiological conditions, followed by a steady state in the case of IMT and a moderate increase in IPA. The radioactivity concentration in the tumour cells at 37°C and pH 7.4 varied from 11% to 35% of the total incubated activity per 10^6 cells (105–335 cpm/1000 cells). ITIC exhibited the lowest cellular uptake, which gradually decreased from 15 min of incubation onwards. The initial uptake of ITIC into T99 and T3868 glioblastoma cells had decreased by up to 20% and 50% after 30 and 60 min, respectively, suggesting a possibly efflux of ITIC from the cells. Compared with the uptake at 37°C, that at 4°C was inhibited by up to 95%. Lowering the medium pH (from 7.4 to 5.5) resulted in a reduction in the uptake of the radiopharmaceutical by up to 60% (Fig. 3).
As shown in Fig. 3A, depolarizing the plasma membrane potential in high K⁺ buffer resulted in a reduction in the cellular accumulation of IPA and IMT, whereas the uptake of ITIC significantly increased (Fig. 3B). In addition, alteration of the mitochondria membrane potential, using the ionophores valinomycin and nigericin, induced a slight alteration in the cellular uptake of the radiopharmaceuticals, suggesting that plasma and mitochondrial membrane potentials play a minor role in the uptake.

Competitive inhibition experiments using BCH and L-alanine-serine-cysteine mixture resulted in a reduction in the cellular accumulation of IPA and IMT by up to 90%, while MeAIB induced no significant alteration (Fig. 3), indicating that the uptake of IPA and IMT into glioblastoma cells is predominantly mediated by neutral amino acid carrier systems L and ASC. By contrast, none of the three principal neutral amino acid transport systems, A, L and ASC [22, 23], appear to be significantly involved in the cellular uptake of ITIC.

Preloading the tumour cells with neutral L-amino acids such as L-alanine, L-cysteine, L-phenylalanine, L-proline and L-tyrosine (data not shown) resulted in a reduction in the cellular uptake of IPA and IMT by up to 92%.

Animal studies

Table 1 shows the biodistribution of IPA, IMT and ITIC at 15, 30 and 60 min after intravenous administration in healthy experimental rats. Radioactivity concentration in blood decreased rapidly over time. The blood uptake 5 min p.i. was up to 2.3% ID/g, decreasing to less than 0.5% ID/g after 60 min, except in the case of IPA. Chromatographic analysis of the plasma showed that more than 90% of the extracted activity was unchanged radioligand, thus confirming the metabolic stability of the investigated amino acid derivatives. Accumulation of IMT (16.8% ID/g) and ITIC (8.2% ID/g) in the kidney 15 min post injection was greater than in all other organs. In contrast, the highest IPA accumulation occurred in the pancreas (5.5% ID/g) 15 min p.i. A representative example of an in vivo study of the blood-brain barrier penetration and whole-body distribution under a gamma camera is given in Fig. 4. The three 123I-iodinated agents cross the blood-brain barrier, followed by efflux from the
brain. Radioactivity uptake in normal brain tissue was moderate, the concentration remaining less than 0.28% ID/g 15 min post injection. In contrast, radioactivity uptake in the brain of C6 glioma-bearing rats was 0.28%–1.10% ID/g, significantly higher than in normal brain tissue, attesting to the excellent tumour uptake of the new radioiodinated compounds in vivo. In Fig. 5 the brain uptake of IPA, IMT and ITIC in healthy rats is compared with that in the C6 glioma-bearing rats, 10 days following the stereotactic implantation. In all cases, IPA showed the highest cerebral uptake and retention.

All C6 glioma-bearing brains included in this study were additionally analysed histopathologically. The histological evaluation of thin brain sections confirmed the presence of tumour tissue at the site of implantation but also showed local extension along the subarachnoid space; thus excellent agreement between tumour extent and activity distribution after radiopharmaceutical administration could be shown. An example of an MRI analysis and IPA uptake in the same C6 glioma-bearing rat brain is given in Fig. 6.

Discussion

Due to the favourable properties of iodine-123 for routine imaging purposes using SPET, including its 13-h half-life, ideal emission energy and general high availability in high purity, extensive efforts have been made to develop 123 I-labelled agents with high tumour affinity that satisfy the requirements for routine clinical application with SPET. The goal of this work was to investigate the uptake of the 123 I-labelled amino acid derivatives p-[123 I]iodo- L -phenylalanine (IPA) and L -[123 I]iodo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (ITIC) in human gliomas in vitro and in vivo in comparison with L -3-[123 I]iodo-α-methyltyrosine (IMT), with a view to applying these radiopharmaceuticals for non-invasive in vivo investigations of cerebral tumours by means of SPET. As shown in in vitro experiments, the new 123 I-iodinated agents accumulate highly and selectively in human glioblastoma cells. We found that the cellular accumulation was obviously lower at 4°C than at 37°C and was pH dependent. IPA revealed similar high human glioma affinity and tumour retention to IMT. In contrast, the initial uptake of ITIC in glioma cells decreased significantly with time, suggesting a possible efflux from the cells.

Previous studies have characterized a number of distinct systems for the transport of amino acids inside mammalian cells [24, 25]. The neutral amino acid uptake into mammalian cells occurs predominantly through the A, L and ASC carrier-mediated transport systems [22, 23]. We therefore investigated the mechanisms involved in the cellular uptake of IPA, ITIC and IMT by competitive inhibition experiments using α-(methylamino)-isobutyric acid (MeAIB) and 2-amino-2-norbornane carboxylic acid (BCH), known to be specific substrates for
systems A and L [26, 27], as well as the representative amino acid mixture L-alanine/L-serine/L-cysteine, which is preferably transported by system ASC [27, 28, 29]. We were able to demonstrate that IPA and IMT are both predominantly taken up by the L and ASC transport systems into human glioblastoma cells, while the A transport system is not involved in their uptake. By contrast, none of the three principal neutral amino acid transport systems, A, L and ASC, appeared to be significantly involved in the cellular uptake of ITIC into glioblastoma cells.

Analysis of uptake under conditions that change the plasma membrane potential, i.e. in high K+ medium, showed a significant reduction in the cellular uptake of IPA and IMT. By contrast, depolarizing the plasma membrane potential in high K+ buffer induced an increase in the uptake of ITIC into tumour cells. Thus, the plasma membrane potential plays an important role in ITIC uptake.

In order to evaluate the contribution of the mitochondria to tumour cell uptake, we further examined the effect of the ionophores valinomycin and nigericin, which are known to disrupt the metabolism of mitochondria. In this study no significant increase or decrease in the cellular uptake was observed, suggesting that the contribution of the mitochondria to radiopharmaceutical accumulation in human glioblastoma cells is minor.

A frequently asked question is whether the increased uptake of amino acids in cerebral gliomas is mainly caused by a disruption of the blood-brain barrier. It has been shown for MET, as well as for IMT, that uptake is also increased in low-grade gliomas without disruption of the blood-brain barrier [30, 31]. Therefore, we studied the ability of IPA and ITIC to cross the blood-brain barrier following intravenous administration in healthy rats. Our results showed that IPA and ITIC, like IMT, passed the blood-brain barrier, followed by efflux from the brain. Analysis of the radioactivity accumulation in healthy experimental rat organs (Table 1) revealed that ITIC, like IMT, displays high renal accumulation and rapid renal excretion. Accumulation of IMT (16.8% ID/g) and ITIC (8.2% ID/g) in the kidney 15 min p.i. was greater than in all other organs. By contrast, the highest IPA accumulation 15 min p.i. occurred in the pancreas (5.5% ID/g).

**Fig. 4.** Gamma camera determination of the blood-brain barrier penetration and whole-body distribution of ITIC in a healthy experimental rat within the first 24 min after i.v. administration of 7 MBq ITIC, showing good blood-brain barrier penetration of the radiopharmaceutical, followed by efflux from the brain and renal excretion.
Fig. 5. Radioactivity accumulation in C6 glioma-bearing rat brains (Tum) compared with the accumulation in the brains of healthy rats following intravenous administration of IMT (A), IPA (B) and ITIC (C).
Evaluation of IPA, ITIC and IMT in rats with stereotactically implanted C6 gliomas (10 days after implantation) showed marked uptake of radioactivity in C6 glioma-bearing rat brains (up to 1.20% ID/g brain). In comparison, the radiopharmaceutical uptake in normal rat brain tissue remained less than 0.28% ID/g. This marked difference in tumour to background (T/B) ratios indicates that the investigated radioiodinated amino acid derivatives should give sufficient contrast for in vivo detection of gliomas. The effect was more strongly expressed for IPA than for IMT and ITIC. In general, IPA revealed the highest brain uptake and retention in the present study, while the brain clearance of ITIC was more pronounced within the first 30 min.

In conclusion, this study demonstrates that IPA and ITIC, like IMT, show high accumulation in human glioblastomas, whereas their incorporation into normal brain tissue is low. IPA, ITIC and IMT showed marked uptake and sufficient retention in the C6 glioma-bearing rat brain. In addition to its high tumour uptake in vitro and in vivo, IPA revealed the highest tumour retention in this study. The T/B ratios of IPA and ITIC were similar to that of IMT, and should be sufficient for clinical application. These data indicate that the investigated iodine-123 amino acid derivatives exhibit interesting characteristics that hold promise for in vivo brain tumour investigation with SPET. Additional studies and clinical evaluations of IPA and ITIC as tumour imaging agents are currently in progress.

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References


