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Radiosynthesis and Biological Evaluation of ^{99m}Tc Nitrido-Levetiracetam as a Brain Imaging Agent

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Abstract—^{99m}Tc nitrido-Levetiracetam was prepared using the ^{99m}Tc nitrido core for labeling. The reaction conditions were optimized to get the highest radiochemical purity (98%): substrate amount 2 mg, Sn(II) (reducing agent) amount 50 μg, pH 7, 30 min, ambient temperature. The biodistribution studies revealed high brain uptake of ^{99m}Tc nitride-Levetiracetam, reaching a maximum of 9% ID/g at 30 min post injection (p.i.). The complex deserves further analysis as a candidate brain imaging agent.

Keywords: ^{99m}Tc nitrido core, Levetiracetam, biodistribution, complexation, brain imaging

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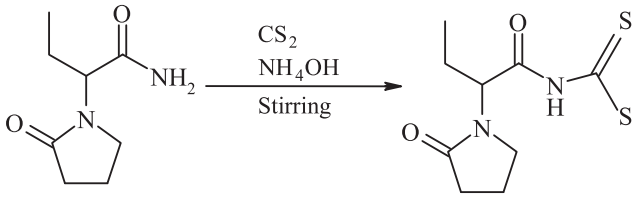
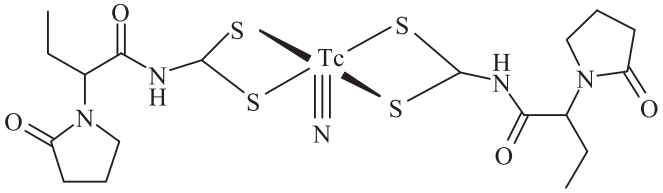
INTRODUCTION

Levetiracetam (Leve) is utilized for many diseases like epilepsy or tonic–clonic seizures [1]. In addition, Levetiracetam is a drug that has the ability to treat focal epilepsy, which has been newly diagnosed in adults. It also reduces most of the focal seizures by a high rate of 50% or more as an additional drug [2–4]. Since the 1980s, many studies have been conducted in the sciences related to the nervous system, such as neuroscience and psychology, as well as human medicine [5–7]. Various techniques have been used to image brain such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) [8]. Imaging brain diseases requires compounds that have high binding affinity for specific receptors. Therefore, many studies have been conducted to find how such compounds bind to a receptor inside the body to perform their function. These studies led to a conclusion that Levetiracetam is related to the so-called SV2A, which is a glycoprotein with a synaptic vesicle; it can also inhibit pre-synaptic calcium channels, reduce the release of the neurotransmitter, and act as a neurotransmitter. Accordingly, it is believed that this drug obstructs the impulse conduction through the synapses [9–11]. Although many radiotracers have been tested in this area [12–23], brain imaging is still a critical point in this field because of lack or low level of the brain uptake. To overcome these problems, we prepared the Leve dithiocarbamate derivative (Scheme 1) and tested it in combination with the ^{99m}Tc nitrido core. ^{99m}Tc nitrido-Leve (Scheme 2) was prepared under optimum conditions in a high radiochemical yield. This radiotracer was intravenously injected into Swiss

Scheme 1. Synthesis of Levetiracetam (Leve) dithiocarbamate.



Scheme 2. Assumed structure of ^{99m}TcN-Levetiracetam.



Albino mice as suitable experimental animals to detect its uptake in the target organ, brain.

EXPERIMENTAL

General. Levetiracetam, succinic dihydrazide, propylenediaminetetraacetic acid (PDTA), aqueous ammonia solution, and carbon disulfide were purchased from Sigma–Aldrich (the United States). All the chemicals were of analytical or clinical grade and were used without further purification unless otherwise stated. Elemental analyses were carried out with an ELEMENTAR viro EL instrument (Germany) at the Microanalytical Center, National Research Center (Cairo, Egypt). The mass spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer at 70 eV. A well-type NaI scintillation γ-counter (model Scalar Ratemeter SR7, Nuclear Enterprises Ltd., the United States) was used for radioactivity measurement. Paper electrophoresis (PE) apparatus from E.C. Corporation (Albany, Oregon, the United States) was used. ^{99m}Tc nitrido-Leve was purified by HPLC using a Shimadzu SpD-6A chromatograph equipped with a LiChrosorb column (RP-C_{18}, 250 mm × 4.6 mm, 5 μm), LC-9A pumps, Rheodyne injector, a radioactivity detector, and a UV spectrophotometer detector operating at 256 nm wavelength. An isocratic elution system consisting of H_2O and methanol (90 : 10 v/v) was used. The mobile phase was fed at flow rate of 1.0 mL min^{-1}. The radiotracer, ^{99m}Tc nitrido-Leve, was collected by using a fraction collector, and its activity was counted with a well-type NaI(Tl) detector connected to a single-channel analyzer. In addition, ^{99m}Tc nitrido core was determined using a LiChrosorb RP-C_{18} column (Lichrosorb, 150 mm × 4.6 mm, 5 μm) and a gradient elution system in which the mobile phase consisted of water (solvent A) and acetonitrile (solvent B): 100% A/0% B, linear gradient to 0% A/100% B from 0 to 30 min. The flow rate was 1.0 mL min^{-1} [24]. Thin-layer chromatography (TLC) SG-60 F_{254} aluminum sheets (20 × 25 cm) were supplied by Merck. The ^{99m}Tc nitrido core was detected using TLC sheets, which were marked 2 cm from the base and lined into fragments 1 cm each up to 14 cm with a non-pointed pencil. A combination of two different solvent systems was used: normal saline (0.9%) and ethanol : chloroform : toluene : 0.5 M ammonium acetate (6 : 3 : 3 : 0.5 v/v). A spot (5 μL) of the reaction mixture was applied with a micropipette, and then the strip was developed in the ascending manner in a closed jar filled with N_2 gas to prevent the oxidation of the labeled spot. The strip was developed using the eluting solvent system, dried, and cut into 1-cm segments, and the radioactivity associated with each segment was recorded using a well-type NaI(Tl) detector. The colloidal impurities were separated by filtration of the reaction mixture through a 0.22 μm Millipore filter at a suitable pressure [12–14].

Synthesis of Levetiracetam dithiocarbamate. 0.5 mL of a carbon disulfide solution in ethanol (1 : 4 v/v) was added to a precooled solution of Leve (5 mg, 29.375 μmol) in aqueous ammonia (2 mL) at 0°C with stirring. The mixture was stirred overnight at ambient temperature. After the reaction completion, the solvent was vacuum-evaporated, and the residue, Leve dithiocarbamate, was recrystallized from solvents and characterized by mass spectrometry and elemental analysis. Yield 45%, melting point 155–157°C.

Synthesis and characterization of Levetiracetam dithiocarbamate. The composition of Leve dithiocarbamate ($C_9H_{13}N_2O_2S_2$) was confirmed by mass spectrometry (a peak at *m*/*z* 213.33 [M–S] was observed) and elemental analysis. Calculated, %: C 44.10, H 5.31, N 11.43. Found, %: C 44.22, H 5.32, N 11.45.

Synthesis of technetium-99m nitride core. A mixture of $SnCl_2 \cdot 2H_2O$ solution (50 μL, 50 μg) in aqueous HCl, 5 mg of succinic dihydrazide, 5 mg of propylenediaminetetraacetic acid (PDTA), sodium dihydrogen phosphate (0.5 mg), and disodium hydrogen phosphate (5.8 mg) was prepared. Then, 1 mL of pertechnetate (38 MBq, 1 mCi) was added, and the mixture was kept at ambient temperature for 30 min. The technetium-99m nitrido core was characterized by TLC and HPLC (Fig. 1).

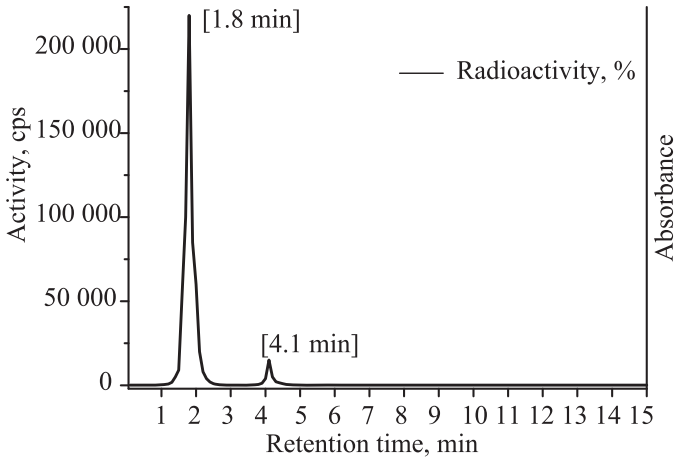


Fig. 1. HPLC of ^{99m}Tc nitrido core >99%, t_R =1.80 min.

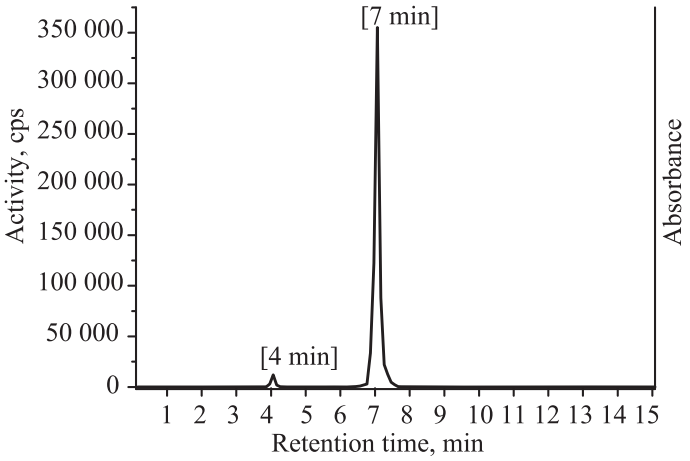


Fig. 2. HPLC of ^{99m}TcN-Leve (>98%).

Factors affecting on the radiochemical yield. To optimize the sinthesis of ^{99m}Tc nitrido-Levetiracetam, we varied the substrate amount, pH of reaction mixture, and reaction time according to [12, 13]. Trials and errors were performed to obtain the best result. The experiment was reiterated, keeping the factors on the optimum level except the factor being varied, until the optimization was reached [12, 13].

Preparation of the radiotracer, ^{99m}Tc nitrido-Leve complex. The complex was synthesized from 0.5 mL of a solution of the freshly prepared technetium-99m nitrido core and 2 mg of Leve dissolved in ethanol (0.5 mL). The product was thoroughly vortexed and kept at ambient temperature at pH 7 for 30 min. The radiochemical purity of the complex was evaluated by RP-HPLC (Fig. 2). The structure was assumed in accordance with the previously published data [12, 13].

Serum stability. A 0.3 mL portion of the radiotracer, ^{99m}Tc nitrido-Leve complex, was mixed with 1.7 mL of rat serum and kept at ambient temperature for 24 h. To determine the relative content of the radiotracer, ~50-μL samples were taken and analyzed by HPLC [12, 13].

Biodistribution study. Five groups, each consisting of five mice, were taken to determine the biodistribution at 5, 15, 30, 60, and 120 min post injection (p.i.). About 0.2 mL of the radiotracer, ^{99m}Tc nitrido-Leve complex (220–300 KBq), was injected according to [12, 13]. The subsequent operations were done as described in [25–30]. Differences in the data were evaluated with the Student *t*-test. The results for *P* using the 2-tailed test are reported, and all the results are given as mean ± SEM. The level of significance was set at $P < 0.05$.

Partition coefficient determination. The octanol/water partition coefficient ($P_{o/w}$) of ^{99m}Tc nitride-Leve complex was determined at pH 7.4 by measuring its distribution between octanol and phosphate-buffered saline. A 100-μL sample was added to a system of immiscible liquids consisting of phosphate buffered saline (900 μL, pH 7.4) and n-octanol (1 mL); then, after 5-min vigorous vortexing, the mixture was incubated for 30 min at room temperature. Centrifugation at 5000 rpm for 5 min ensured complete separation of the organic and the aqueous layers. An aliquot (100 μL) from each layer was measured with a γ-counter. The experiment was repeated 5 times. The partition coefficient value is expressed as log $P_{o/w}$ [31–33].

Study of drug inhibition for ^{99m}Tc nitrido-Leve complex. Different amounts of unlabeled Leve were used in the range of 0 to 1000 μg. It was injected to the mice 5 min prior to the administration of the radiotracer, ^{99m}Tc nitrido-Leve complex, and the percent of brain uptake was estimated at 5 min post injection of ^{99m}Tc nitrido-Leve ($n = 5$) [34–36].

RESULTS AND DISCUSSION

Evaluation of radiochemical yield and purity of the radiotracer, ^{99m}Tc nitrido-Leve complex. The colloidal impurities such as technetum-99m–tin colloid, hydrated technetium dioxide, and stannous dihydroxide were removed using a 0.22 μm Millipore filter. The radiochemical yield of the intermediate, technetium-99m

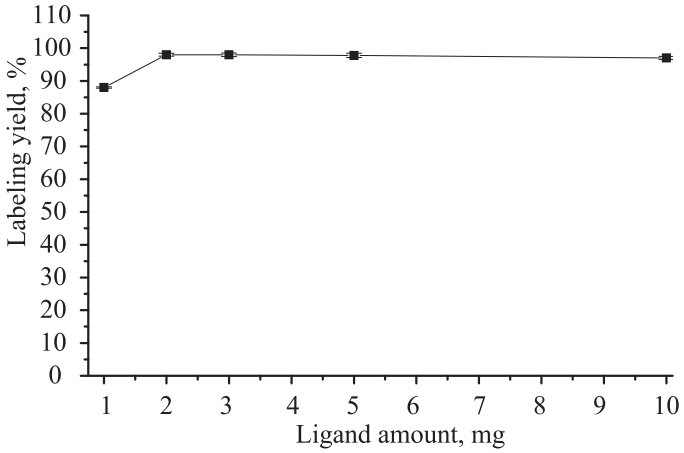


Fig. 3. Effect of Leve amount on the radiochemical yield of ^{99m}TcN-Leve complex. Conditions: 1–10 mg of Leve, 100 μg of Sn(II), pH 7, 30 min (mean yield ± SD, n = 3).

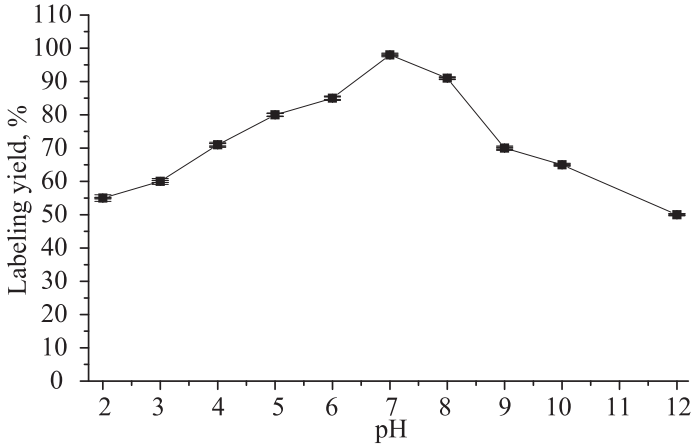


Fig. 4. Effect of pH on the radiochemical yield of ^{99m}TcN-Leve complex. Conditions: 2 mg of Leve, 50 μg of Sn (II), 30 min (mean yield ± SD, n = 3).

nitrido core, was estimated by TLC. There are two main species, $[^{99m}Tc{\equiv}N]^{2+}$ and free pertechnetate, to determine; the nitrido core had R_f = 0–0.1 with normal saline (0.9%) as the mobile phase and R_f = 0.8–1 with ethanol : chloroform : toluene : 0.5 M ammonium acetate (6 : 3 : 3 : 0.5 v/v) as the mobile phase. The relative content of the technetium-99m nitrido core can be estimated at >98%. The free pertechnetate impurity was characterized by R_f = 0.4–0.6. The radiochemical yields are the mean values of five experiments. In paper electrophoresis (PE), the radiotracer, ^{99m}Tc nitrido-Leve complex, stayed at the spotting point; i.e., the complex was neutral. Free pertechnetate moved toward the anode to a distance of 11 cm, whereas the technetium-99m nitrido core moved toward the cathode. The optimum radiochemical yield of ^{99m}Tc nitrido-Leve complex, according to PE, was >98%. In addition, HPLC was also performed to determine the purity of the radiotracer, ^{99m}Tc nitrido-Leve complex and its core. The purity of the core intermediate (technetium-99m nitrido core) was found to be more than 99% (R_t = 1.8 min; for free pertechnetate, R_t = 4.1 min, Fig. 1). The R_t value of ^{99m}Tc nitrido-Leve complex was 7 min (Fig. 2).

Table 1. In vitro stability in serum of ^{99m}TcN-Leve complex[a]

Time, h	^{99m}TcN-Leve	$[^{99m}Tc{\equiv}N]^{2+}$ core
4	98.0 ± 0.6	2.0 ± 0.3
7	97.5 ± 0.3	2.5 ± 1.0
10	97.1 ± 1.2	2.9 ± 0.4
12	96.5 ± 0.11	3.5 ± 0.4
24	95.0 ± 0.7	5.0 ± 0.3

[a] Mean ± SEM, n = 3.

Reaction optimization. The factors affecting the labeling process were optimized totally to give the maximum radiochemical yield at ambient temperature. The effect of the substrate amount is shown in Fig. 3. The maximal radiochemical conversion to ^{99m}Tc nitrido-Leve complex (98%) was reached with 2 mg of Leve at 7.5 MBq of the $[^{99m}Tc{\equiv}N]^{2+}$ core at the other parameters kept constant [12, 13]. pH is also an important factor in labeling process (Fig. 4) which needs to be controlled; pH 7 proved to be optimum (radiochemical yield 98%) [36–38]. The optimum radiochemical yield significantly decreased at both lower and higher pH values [25], which may reflect in part the stability of ^{99m}Tc nitrido-Leve complex. The optimum reaction time was found to be 30 min (Fig. 5). Additionally, the radiochemical yield significantly increased up to a ceiling, 98%, at 50 μg tin(II) content (optimum content). Higher tin(II) amounts may lead to the formation of undesirable colloid [39–41].

Evaluation of the in vitro stability (Table 1) in rat serum has shown that the ^{99m}Tc nitrido-Leve complex is quite stable (96.5% in 12 h and 95% in 24 h). The partition coefficient of the ^{99m}Tc nitrido-Leve was log P = 0.70 ± 0.01. This value is within the canonical range (0.5–2.5) for passing through the blood–brain barrier.

Inhibition study. Drug inhibition experiments were made to show the binding affinity of the complex. It decreased to 0.8% ID/g (Fig. 6) at 30 min due to blocking of AMPA receptors. This decrease confirmed the

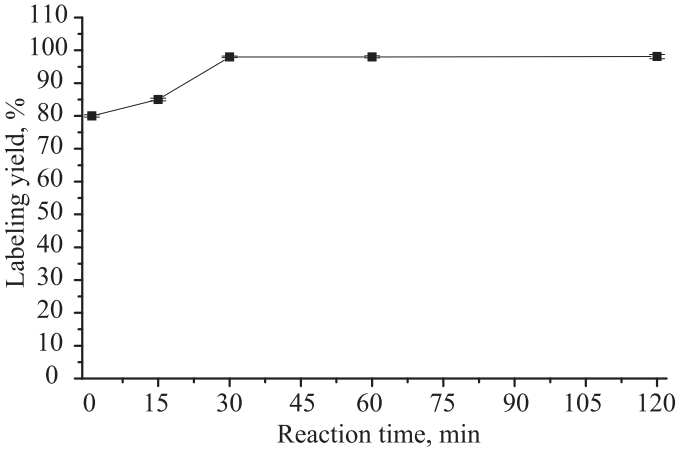


Fig. 5. Effect of reaction time on the radiochemical yield of ^{99m}TcN-Leve complex. Conditions: 2 mg of Leve, 50 μg Sn(II), pH 7 (mean yield % ± SD, n = 3).

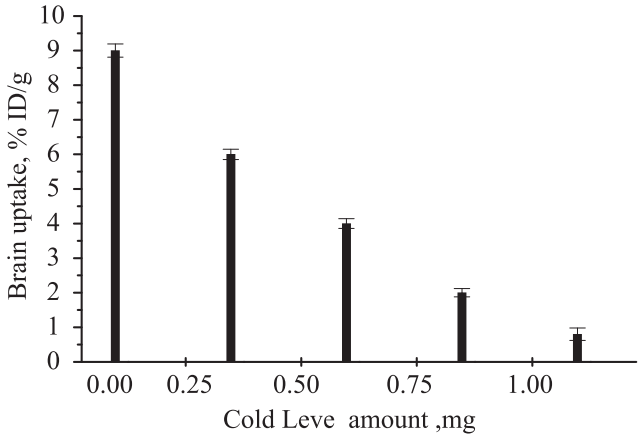


Fig. 6. Inhibition of ^{99m}TcN-Leve brain uptake in normal male Swiss Albino mice at 15 min post injection (ID/g, % ± SEM, n = 5).

selectivity and high binding affinity of the complex to its receptor located in brain [24, 25]. The drug binds to SV2A, a synaptic vesicle glycoprotein, and inhibits presynaptic calcium channels, reducing the neurotransmitter released and acting as a neuromodulator. This is believed to impede impulse conduction across synapses.

Biodistribution. Table 2 shows the biodistribution of ^{99m}Tc nitrido-Leve in different body organs and fluids. The complex is rapidly accumulaed in kidneys, blood, intestine, etc., at 5 min p.i. The kidney uptake increased to 17.9% at 0.5 h post injection and then decreased to 3.12% at 2 h post injection. Thus, ^{99m}Tc nitrido-Leve is excreted through urinary pathways. In addition, the liver uptake increased to 7.10% at 1 h p.i. and decreased to 3.12% at 2 h p.i. After 60 min, the radiotracer uptake decreased

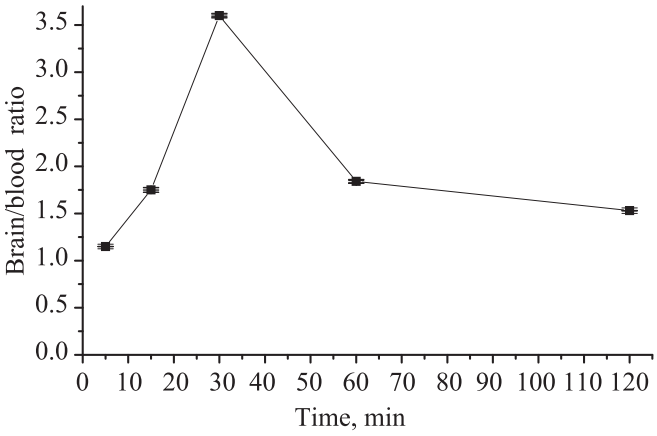


Fig. 7. Brain/blood ratio of ^{99m}TcN-Leve in normal male Swiss Abino mice as a function of time (mean ratio ± SD, n = 5).

Table 2. Biodistribution of 99mTcN-Leve in normal mice at different times[a]

Organs and body fluids	% ID/g at indicated time post injection				
	5 min	15 min	30 min	60 min	120 min
Blood	3.90 ± 0.18	3.20 ± 0.12	2.50 ± 0.10	2.11 ± 0.15	1.80 ± 0.15
Bones	1.21 ± 0.11	1.20 ± 0.20	1.00 ± 0.17	0.95 ± 0.12	0.90 ± 0.02
Muscles	2.30 ± 0.11	2.50 ± 0.02	2.10 ± 0.01	1.5 ± 0.01	1.10 ± 0.01
Brain	4.50 ± 0.11	5.60 ± 0.15	9.00 ± 0.15	3.9 ± 0.22	2.75 ± 0.18
Heart	1.10 ± 0.11	1.00 ± 0.01	0.95 ± 0.02	0.91 ± 0.01	0.85 ± 0.00
Liver	4.00 ± 0.11	5.11 ± 0.12	7.10 ± 0.18	5.00 ± 0.22	3.12 ± 0.01
Kidneys	5.13 ± 0.11	8.15 ± 0.14	17.90 ± 0.95	11.12 ± 0.11	3.12 ± 0.01
Spleen	1.10 ± 0.02	1.20 ± 0.03	1.00 ± 0.01	0.95 ± 0.01	0.92 ± 0.02
Intestine	2.99 ± 0.12	3.80 ± 0.01	5.60 ± 0.01	3.11 ± 0.01	2.21 ± 0.01
Stomach	1.11 ± 0.02	1.12 ± 0.01	1.00 ± 0.04	0.92 ± 0.02	0.90 ± 0.00
Brain/blood	1.15	1.75	3.60	1.84	1.53

[a] Mean ± SEM (mean of five experiments).

in most of organs, as in [12, 13]. The radiotracer, ^{99m}Tc nitrido-Leve, gave maximum accumulation in brain of 9% at 30 min, exceeding the levels reached with ^{99m}Tc nitrido-histamine and ^{99m}Tc nitrido-piracetam (4.50 ± 0.91 and 7.15 ± 0.29% ID/g, respectively [12, 13]). The brain/blood ratio for ^{99m}Tc nitrido-Leve at 30 min p.i. is 3.6, which also exceeds the levels reached with ^{99m}Tc nitrido-histamine and ^{99m}Tc nitrido-piracetam (1.8 and 1.4, respectively, Fig. 7) [12, 13]. It is worth noting that this radiotracer, ^{99m}Tc nitrido-Leve, exhibits higher % ID/g ± SD values than many of the radiotracers reported previously do [12–22]. In addition, ^{99m}Tc nitrido-Leve surpasses two main approved radiotracers used in brain imaging. Namely, [^{99m}Tc]ECD gives 4.7% ID/g at 24 h p.i. in monkeys, and [^{99m}Tc]HMPAO gives 3.50% ID/g at 30 min. p.i. in rats [19, 20].

CONCLUSIONS

This study shows that Levetiracetam is easily radiolabeled by technetium-99m nitrido core with a high radiochemical yield (98%). Biodistribution studies show that ^{99m}Tc nitrido-Levetiracetam complex is concentrated in brain to give the uptake of 9% ID/g at 30 min. p.i. and is retained for 2 h (2.75%). This radiotracer outperforms many radiotracers mentioned previously [12–22]. However, this complex needs further analysis as a candidate brain imaging agent.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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