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Dedicated to the 110th anniversary of M.I. Kabachnik's birth

2,5-Diamino-5,5-diphosphonovaleric Acid as a Ligand for an Osteotropic ^{188}Re Radiopharmaceutical

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Abstract—A modified method for the preparation of 2,5-diamino-5,5-diphosphonovaleric acid (DADP5) has been developed in the search for new synthetically available organic ligands to produce ^{188}Re radiopharmaceuticals with an increased accumulation in the bone tissue. Interaction of the obtained acid with ^{188}Re was studied by radio-TLC. An optimal system for separating unbound ^{188}Re and labeled complex in a yield of at least 95% was found. The biological distribution of ^{188}Re-DADP5 was studied based on direct radiometric data. The osteotropicity of ^{188}Re-DADP5 and its increased accumulation in bone fracture sites, which represent oncological pathology models, was detected at a level comparable to known radiopharmaceuticals.

Keywords: osteotropic radiopharmaceuticals, rhenium-188, 2,5-diamino-5,5-diphosphonovaleric acid, biological distribution

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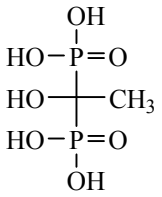
Radionuclide therapy of oncological diseases is one of the most intensively developing fields of nuclear medicine [1–3]. Due to its nuclear-physical characteristics ($T_{1/2}$ 16.7 h, E_β 2.12 MeV, 80%), radionuclide ^{188}Re falls under the definition of an ideal for use in radionuclide therapy. In addition, the presence of both the β- and γ-component (0.155 MeV) of ^{188}Re radiation allows, along with having the therapeutic effect, to perform visualization using commercially produced gamma cameras and, thus, to obtain information on the radiopharmaceutical distributions in the patient's body and the treatment results [1, 2, 4]. This has led to the appearence of a variety of ^{188}Re-based radiopharmaceuticals over the past decade. Radiopharmaceuticals containing radionuclide ^{188}Re are mainly used for the treatment of bone metastases, liver cancer, and brain carcinoma [5, 6].

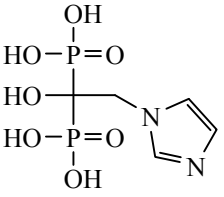
Complexes of phosphonic acids with various radionuclides are used for early diagnostics of bone metastases [7–10]. In view of phosphonate groups' ability to bind to hydroxyapatite, which is the main component of the inorganic matrix of bone, they are used as functional groups in organic ligands for the target delivery of radionuclides to bone tissues. In the international practice, ^{188}Re-HEDP based on 1-hydroxyethylidene diphosphonic acid (HEDP) became one of the most promising radiopharmaceuticals for palliative treatment of bone metastases [11, 12]. Phosphorene, ^{188}Re, a Russian radiopharmaceutical based on 1-hydroxyethylidene diphosphonic acid, is undergoing the final stage of clinical trials [13, 14]. There is another known osteotropic ^{188}Re radiopharmaceutical named "Zoleren, ^{188}Re" based on zoledronic acid also containing a geminal diphosphonic moiety [15–18]. Recently a study of a new organic ligand, specifically *trans*-1,2-cyclohexyl dinitrilotetramethylenephosphonic acid, as a component of both a ^{68}Ga-based diagnostic radiopharmaceutical and a ^{188}Re-based therapeutic medication was described [19].

Despite some progress in the development of osteotropic ^{188}Re radiopharmaceuticals, the search for new synthetically available organic ligands to obtain radiopharmaceuticals with increased specificity for bone tissues remains an urgent task.

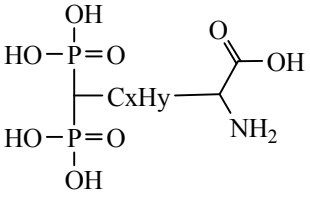
In order to find new osteotropic radiopharmaceuticals, the synthesis of organic ligands with a combination of aminocarboxylic and geminal diphosphonic moieties in one molecule (compound **1**) was described [20–24]. The obtained results suggest the investigation of new type compounds **2** that combine the aminodiphosphonic and aminocarboxylic groups in the molecule as potential ^{188}Re ligands. The synthesis of ligands **2** is distinguished by a relatively simple method for introducing an aminodiphosphonic function into the target molecule. In addition, an aminodiphosphonic moiety can be considered as a structural analog of an amino acid group containing a second phosphonic group, which can significantly affect the physiological and complexing activity of this class of compounds [21, 25].



HEDP



Zoledronic acid



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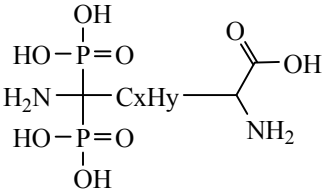


2

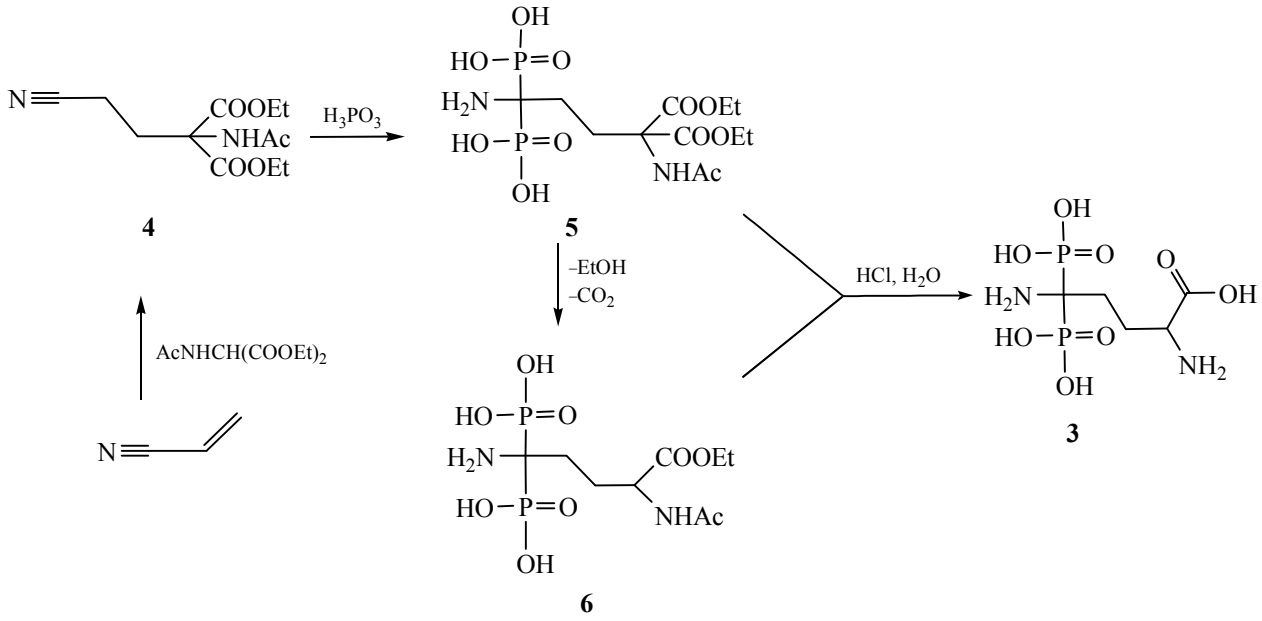
Aminodiphosphonic and amino acid groups in the ligand can both be involved in binding of the radionuclide and transport it to bone tissues. Therefore, radiopharmaceuticals containing this type of compounds can be promising for diagnostics and/or treatment of cancer, depending on the radionuclides used. In this paper, a modified method for the synthesis of 2,5-diamino-5,5-diphosphonovaleric acid (DADP5) **3** (Scheme 1) is proposed and, for the first time, the results of radiochemical and biological studies of a DADP5-based ^{188}Re radiopharmaceutical are reported.

The Michael addition of the acetamidomalonic ester to acrylonitrile results in the formation of nitrile **4** that contains a protected amino acid function as an acetamidomalonic ester moiety. The latter was converted to aminodiphosphonic acid **5** by addition of two phosphorous acid molecules according to a modification of an earlier published procedure [26].

Attempt to recrystallize acid **5** containing the acetamidomalonic moiety results in the loss of the ester group and decarboxylation with the formation of aminodiphosphonic acid **6** containing an *N*-acetylaminocarboxylic ester moiety. Acid hydrolysis of acid **5**, as well as of acid **6**, gives the desired acid **3** (Scheme 1).

The presence of two amino groups and several acid functions in the molecule of aminodiphosphonic aminocarboxylic acid **3** suggests its possible existence as various zwitterionic forms or salts in an aqueous solution, depending on the pH of the medium. In this view, it is of interest to recover the acid both as hydrochloride **3** and as free amino acid **3a**. It should be noted that, at the intrinsic pH ca. 1, only one form of the compound is present in the aqueous solution of free amino acid **3a**, as supported by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy data. In the ^{13}C NMR spectrum of amino acid **3a** a quite rare spin-spin coupling of the phosphorus nuclei with the carbons of the molecule (apart from the C^2 atom of the aminocarboxylic function) through 1, 2, 3, and even 5 bonds is observed. These signals are symmetrical triplets, which points at the magnetic equivalence of both phosphorus atoms in the free amino acid molecule **3a**. Unlike **3a**, spectral data of amino acid hydrochloride **3** indicate the presence of two amino acid forms with two nonequivalent phosphorus atoms, as supported by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy data. For example, the ^{13}C NMR spectrum of amino acid hydrochloride **3**, at intrinsic pH ca. 1, contains a carbon C^5 signal at 56.74 ppm as a doublet of doublets with characteristic coupling constants $^{1}J_{PC}$ = 137.6 and $^{1}J_{PC}$ = 138.4 Hz, which confirms the magnetic nonequivalence of phosphorus atoms at the fifth carbon atom. In addition, the presence of the second form is evidenced by the signals of all carbon atoms, including the carbonyl carbon atom of the aminocarboxylic moiety of amino

Scheme 1.



acid **3** (δ_{C^1} 169.16 and *171.42 ppm). The ^{1}H and ^{31}P NMR spectra also indicate the presence of two forms of amino acid hydrochloride **3**.

^{31}P NMR examination of free amino acid **3a** in aqueous solutions demonstrated a complex dependence of the chemical shift of the phosphorus nuclei signal on the pH of the medium, with diastereotopy of phosphorus atoms.

The preparation of acid **3** labeled with the radioisotope ^{188}Re was carried out by mixing solutions of 2,5-diamino-5,5-diphosphonovaleric acid **3**, sodium perrhenate ($Na^{188}ReO_4$) from the $^{188}W/^{188}Re$ generator GREN-1, and tin dichloride as a reducing agent, with a ligand:tin ratio of 3.5. The yield of the labeling reaction was determined by the known radio-TLC method [4, 27]. Thin-layer (TLC) and instant thin-layer (ITLC) chromatography in a silica-gel/acetone system, as well as paper chromatography in the Whatman 1–acetone and Whatman 3MM–0.9% NaCl were tried. It was found that the ITLC-acetone system on glass fiber strips impregnated with silica gel wherein the perrhenate ions move with the solvent front and the ^{188}Re complex remains at the start, demonstrates the best reproducibility of results and the separation of unbound ^{188}Re and labeled complex, the latter in a yield of at least 95%.

The ^{188}Re-DADP5 biological distribution was evaluated from direct radiometric data. The obtained pharmacokinetics data indicate the osteotropicity of the radiopharmaceutical and its increased accumulation in bone fracture sites representing oncological pathology models (see the table). The obtained coefficient of differential accumulation (CDA) [2, 5] for ^{188}Re-DADP5 is comparable with and even slightly higher than those for "Zoleren, ^{188}Re" and "Phosphorene, ^{188}Re."

EXPERIMENTAL

^{1}H, ^{31}P, and ^{13}C NMR spectra were recorded on a Bruker DPX-200 Fourier spectrometer, using TMS as an internal reference and 85% H_3PO_4 as an external reference. The melting points were determined on a block apparatus in an open capillary. The TLC of individual compounds and reaction masses was carried out on Silufol plates, on Merck glass plates with 0.2 mm layers of UV-254 silica gel (eluent 3–7% chloroform–isopropanol), as well as on Alufol (Kavalier) plates, with spots development in iodine vapor, under UV light, or using a ninhydrin solution for amino acids analysis.

Acrylonitrile, acetamidomalonic ester, and phosphorus tribromide were provided by Reacor Ltd. (Alfa Aesar). Phosphorous acid was thoroughly dried before use.

2-Cyanoethylacetamidomalonic ester (4). 0.05 g (2 mmol) of sodium metal was added, with stirring, to a mixture of 10.9 g (50 mmol) of acetamidomalonic

Distribution in the organs and tissues in rats with the bone pathology model in 1 and 3 h after the injection of "Zoleren, ^{188}Re," "Phosphorene, ^{188}Re," and ^{188}Re-DADP5, in % of injected activity

Organ	"Zoleren, ^{188}Re"		"Phosphorene, ^{188}Re"		DADP5, ^{188}Re	
	1 h	3 h	1 h	3 h	1 h	3 h
Blood,%/g	1.7	0.8	0.4	0.3	0.4	0.2
Liver	11.3	1.7	1.0	1.0	1.6	1.0
Kidneys	17.1	8.2	4.0	4.3	10.2	12.3
Stomach	2.4	1.9	1.8	2.7	3.1	3.7
Bladder	42.2	44.2	42.1	19.6	18.5	17.3
Thigh (norm)	0.6	0.3	0.8	0.9	0.3	0.2
Thigh (fracture)	1.0	0.6	1.8	1.6	0.7	0.5
Coefficient of differential accumulation	1.5	2.0	2.3	1.8	2.3	2.5

ester in 20 mL of ethanol, whereafter 3.6 mL (55 mmol) of freshly distilled acrylonitrile was slowly added dropwise. The resulting clear solution was stirred for 10–15 h. The reaction was monitored by TLC [until the acetamidomalonic ester spot disappeared (R_f 0.6–0.7, 5:1 chloroform:acetone)]. The reaction mixture was cooled, neutralized with a 2 N HCl solution to pH ca. 6–7 and evaporated *in vacuo*. The syrupy residue was partitioned between chloroform (50 mL) and water (20 mL). The organic phase was additionally washed with 20 mL of water, dried with sodium sulfate, and evaporated *in vacuo*. The residue was crystallized from diethyl ester. Yield 10.3 g (76%), mp 93–94°C (mp 92–94°C [28], 94–95°C [29]).

3-Amino-3,3-diphosphonopropylacetamidomalonic ester (5). 4.1 mL (44 mmol) of phosphorus tribromide was slowly added dropwise with stirring to a suspension of 3.6 g (44 mmol) of phosphorous acid and 6.0 g (22 mmol) of nitrile **4** in 30 mL of anhydrous dioxane at 5–10°C. The resulting mixture was stirred at room temperature and left without stirring for a day. The bulk of the dioxane over the resulting gelatinous product was decanted, and 15 mL of acetic acid was added to the residue at cooling. The resulting mixture was stirred for about 1 h, then poured onto ice (ca. 20 mL), and concentrated by evaporation *in vacuo*. 20 mL of ethanol was added to the oily residue and the resulting white powdery product was recrystallized from aqueous ethanol. Yield 5.3 g (56%), mp 192–193°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6 + drop of TFA), δ, ppm: 1.13 t (6H, CH_3, $^3J_{HH}$ = 6.9 Hz), 1.70–1.85 m (2H, CH_2), 1.88 s (3H, Ac), 2.35–2.50 m (2H, CH_2), 4.09 q (4H, CH_2O, $^3J_{HH}$ = 6.9 Hz). ^{31}P NMR spectrum (DMSO-d_6 + drop of TFA): δ_P 14.5 ppm.

Recrystallization of ester acid **5** from water resulted in a partial loss of the ester group and decarboxylation with the formation of aminodiphosphonic acid **6** containing an *N*-acetylaminocarboxylic ester moiety. ^{1}H NMR spectrum of acid mixture **5** + **6** (D_2O), δ, ppm: 1.12 t (CH_3, $^3J_{HH}$ = 7.3 Hz), 1.16* t (CH_3, $^3J_{HH}$ = 6.9 Hz), 1.88 s (Ac), 1.89* s (Ac), 2.10–2.45 m (CH_2) (**5** + **6**), 3.82* t (1H, CH, $^3J_{HH}$ = 6.9 Hz), 4.00–4.25 m (CH_2O) (**5** + **6**). ^{31}P NMR spectrum (D_2O), δ_P, ppm: 17.34*, 17.48, 17.90* [The signals marked with an *asterisk* correspond to acid **6** (8–25% depending on the duration of boiling in water)]. Acid hydrolysis of ester acid **5** and of acid mixture **5+6** results in the formation of desired amino acid **3**.

2,5-Diamino-5,5-diphosphonovaleric acid (DADP5, 3). A mixture of 4.3 g (10 mmol) of ester acid **5** and 15 mL of 6N HCl was boiled for 8–10 h. The reaction mixture was evaporated *in vacuo*, and the residue was co-evaporated with water and chromatographed using a cation exchanger (eluent 1 N HCl). Ninhydrin-positive eluate was evaporated *in vacuo*, and the residue was treated with 1N HCl–acetone (1 : 10), and 2.6 g (75%) of amino acid **3** were recovered as hydrochloride, mp 105–110°C (foaming followed by solidifying), 303–307°C (decomp.). ^{1}H NMR spectrum (D_2O, pH ca. 1), δ, ppm (the signals marked with an *asterisk* correspond to the second minor form): 1.72–2.17 m (4H, CH_2), 3.85 m and *4.00 m (1H, CH). ^{1}H NMR spectrum (D_2O + NH_4OH, pH ca. 9), δ, ppm: 1.97–2.42 m (4H, CH_2), 3.58 t (CH, $^3J_{HH}$ = 8.5 Hz). ^{13}C

NMR spectrum (D_2O, pH ca. 1), δ_C, ppm: 22.48, 22.85, *25.17, *27.92, 49.07, *52.67, 56.74 dd ($^1J_{PC}$ = 137.6, $^1J_{PC}$ = 138.4 Hz), 169.16, *171.42. ^{31}P NMR spectrum (D_2O, pH ca. 1), δ_P, ppm: *12.77, 17.51. Found, %: C 17.28, 17.22; H 5.13, 5.28. N 7.97, 7.88. $C_5H_{14}N_2O_8P_2 \cdot HCl \cdot H_2O$. Calculated, %: C 17.33; H 4.94; N 8.08.

Recovery of **3** as a free amino acid was accomplished by treating the amino acid hydrochloride with propylene oxide in an 1 : 2 aqueous ethanol solution. Additional crystallization from water allowed the recovery of free amino acid **3a**, mp 313–314°C. ^{1}H NMR spectrum (D_2O), δ, ppm: 2.07–2.52 m (4H, CH_2), 3.85 t (CH, $^3J_{HH}$ = 8.5 Hz). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 22.95 t ($^3J_{PC}$ = 4.1 Hz), 23.33 t ($^2J_{PC}$ = 3.0 Hz), 49.47, 57.33 t ($^1J_{PC}$ = 135.6 Hz), 169.48 t ($^5J_{PC}$ = 4.1 Hz). ^{31}P NMR spectrum (D_2O): δ_P 17.31 ppm. Found, %: C 20.18, 20.30; H 5.05, 4.96; N 9.67, 9.60. $C_5H_{14}N_2O_8P_2$. Calculated, %: C 20.56; H 4.83; N 9.59. Mass spectrum (LCMS), *m/z*: 293.1 $[M + H]^+$ (calculated for $C_6H_{16}N_2O_8P_2$: 292.1).

For radiochemical studies, a solution of [^{188}Re] sodium perrhenate obtained from the $^{188}W/^{188}Re$ generator GREN-1 (the Leypunsky Institute of Physics and Power Engineering, Russia) was used. To perform the labeling reaction 15 mg of ligand **3** was dissolved in 1 mL of water, and 3 mg of $SnCl_2 \cdot 2H_2O$, 1 mL of eluate from the generator with an activity of 37 MBq/mL, and 150 μL of 0.5M NaOH were added in an argon stream. The reaction mixture was held at room temperature for 30 min to complete the complexing reaction, and the pH was adjusted to 5 by adding 80 μL of 0.5 M NaOH to obtain a clear solution. The activity of the solution of the radiopharmaceutical composition was 16.6 MBq/mL, the ligand concentration 6.73 mg/mL (0.021 M), the concentration of $SnCl_2 \cdot 2H_2O$ 1.35 mg/mL (0.006 M).

The reaction yield of rhenium-188 labeling of acid **3** was determined by radio-TLC (see, e.g., [30] for the procedure details) using silica-gel impregnated glass fiber strips in acetone. The radiochemical purity (RCP) of the obtained ^{188}Re-DADP5 radiopharmaceutical was 95.1% (R_f 0–0.05 ^{188}Re-DADP5, R_f 1.0 $Na^{188}ReO_4$).

Biological behavior (distribution in organs and systems) of ^{188}Re-DADP5 was examined in non-linear female rats normally weighing 120–150 g and using a model of bone pathology similar to bone metastases of malignant timors in terms of physiological characteristics. The pathology was simulated by an osteotylus in the active stage after closed shin fracture. The manipulations with animals were carried out under chloral hydrate anesthesia. Animals were anesthetized with intraperitoneal injection of chloral hydrate in physiological saline, 400 mg per 1 kg of body weight. During the experiments, the animals were kept under standard conditions (special room, recommended diet, free access to drinking water, natural lighting). A solution of ^{188}Re-DADP5 with a volume activity of 16.6 MBq/mL was injected into the tail veins of animals in an amount of 0.2 mL (3.2 MBq per animal). The content of radiopharmaceuticals in organs and systems was determined by direct radiometry [1, 4] 1 and 3 h after the injection and indicated in % of the injected activity. Radiometry of organs and tissues was carried out using a Wizard 2480 gamma counter (USA). The results of the ^{188}Re-DADP5 biological behavior, as compared with those for "Zoleren, ^{188}Re" and "Phosphorene, ^{188}Re" are presented in the table above.

The work was performed in compliance with all applicable international, national, and institutional guidelines for the care and use of animals.

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CONFLICT OF INTEREST

No conflict of interests was declared by the authors.

REFERENCES

1. Knapp, F.F. and Dash, A., *Radiopharmaceuticals for Therapy*, New Delhi; Heidelberg; New York; Dordrecht; London: Springer, 2016. doi 10.1007/978-81-322-2607-9
2. *Clinical Applications of Nuclear Medicine Targeted Therapy*, Bombardieri, E., Seregni, E., Evangelista, L., Chiesa, C., and Chiti, A., Eds., Springer International Publishing AG, 2018, pt. 4, ch. 26, p. 345. doi 10.1007/978-3-319-63067-0_26
3. Pandit-Taskar, N., Batraki, M., and Divgi, C. R., *J. Nucl. Med.*, 2004, vol. 45, no. 8, p. 1358.
4. Kodina, G.E. and Krasikova, R.N., *Metody polucheniya*

radiofarmatsevticheskikh preparatov i radionuklidnykh generatorov dlya yadernoi meditsiny (Methods for Production of Radiopharmaceuticals and Radionuclide Generators for Nuclear Medicine), Moscow: Mosk. Energ. Inst., 2014.

5. Klimanov, V.A., *Radiobiologicheskoe i dozimetricheskoe planirovanie luchevoi i radionuklidnoi terapii* (Radiobiological and Dosimetric Planning of Radiotherapy and Radionuclide Therapy), Moscow: NRNU MEPhI, 2011, Part 2.
6. Sundram F.X., *Biomed. Imaging Interv. J.*, 2006, no. 2(3), p. e40. doi 10.2349/biij.2.3.e40
7. Kodina, G.E., Malysheva, A.O., and Klement'eva, O.E., *Russ. Chem. Bull.*, 2016, vol. 65, no. 2, p. 350. doi 10.1007/s11172-016-1308-0
8. Palma, E., Correia, J.D.G., Campello, M.P.C., and Santos, I., *Mol. BioSyst.*, 2011, vol. 7, no. 11, p. 2950. doi 10.1039/c1mb05242j
9. Fleisch, H., *Bisphosphonates in Bone Disease. From the Laboratory to the Patient*, New York: Academic Press, 2000.
10. Russell, R.G.G., *Bone*, 2011, vol. 49, no. 1, p. 2. doi 10.1016/j.bone.2011.04.022
11. Savio, E., Gaudiano, J., Robles, A.M., Balter, H., Paolino, A., Lo'pez, A., Hermida, J.C., De Marco, E., Martinez, G., Osinaga, E., and Knapp Jr., F.F., *BMC Nucl Med.*, 2001, vol. 1, no. 2. doi 10.1186/1471-2385-1-2
12. Scheffler, J., Derejko, M., Bandurski, T., and Romanowicz, G., *Nucl. Med. Rev.*, 2003, vol. 6, no. 1, p. 55.
13. Petriev, V.M. et al., RF Patent no. 2567728, 2014.
14. Krylov, V.V. and Kochetova, T.Yu., *Medical Radiology and Radiation Safety J.*, 2014, vol. 59, no. 6, p. 54.
15. Malysheva, A.O. et al., WO Patent no. 2010036140 A1, 2010.
16. Erfani, M., Tabatabaei, M., Doroudi, A., and Shafiei, M., *J. Radioanal. Nucl. Chem.*, 2018. doi 10.1007/s10967-018-5781-9
17. Kochetova, T., Krylov, V., Smolyarchuk, M., Sokov, D., Lunev, A., Shiryaev, S., Kruglova, O., Makeenkova, T., Petrosyan, K., Dolgova, A., Poluektova, M., Galkin, V., and Kaprin, A., *Int. J. Nucl. Med. Res.*, 2017, Special Issue, p. 92. doi 10.15379/2408-9788.2017.08
18. Voloznev, L.V., Klement'eva, O.E., Korsunskii, V.N., and Lysenko, N.P., *Mol. Med.,* 2013, no. 2, p. 45.
19. Jaswal, A.P., Meena, V.K., Prakash, S., Pandey, A., Singh, B., Mishra, A.K., and Hazari, P.P., *Front. Med.*, 2017, vol. 72, no. 4, p. 1. doi 10.3389/fmed.2017.00072
20. Yang, X.N., Zeng, J.C., Song, Y.C., Zhang, H., and Pei, F.X., *Eur. Rev. Med. Pharmacol. Sci.*, 2014, vol. 18, no. 15, p. 2116.
21. Xue, Z.-Y., Li, Q.-H., Tao, H.-Y., and Wang, C.-J., *J. Am. Chem. Soc.*, 2011, vol. 133, no. 30, p. 11757. doi 10.1021/ja2043563
22. Hosain, F., Spencer, R.P., Couthon, H.M., and Sturtz, G.L., *J. Nucl. Med.*, 1996, vol. 37, no. 1, p. 105.
23. Sturtz, G., Couthon, H., Fabulet, O., Mian, M., and Rosini, S., *Eur. J. Med. Chem.*, 1993, vol. 28, no. 11, p. 899. doi 10.1016/0223-5234(93)90043-E
24. Sturtz, G., Appere, G., Breistol, K., Fodstad, O., Schwartsmann, G., and Hendriks, H.R., *Eur. J. Med. Chem.*, 1992, vol. 27, no. 8, p. 825. doi 10.1016/0223-5234(92)90117-J
25. Dunford, J.E., Kwaasi, A.A., Rogers, M.J., Barnett, B.L., Ebetino, F.H., Russell, R.G.G., Oppermann, U., and Kavanagh, K.L., *J. Med. Chem.*, 2008, vol. 51, no. 7, p. 2187. doi 10.1021/jm7015733
26. Bandurina, T.A. et al., USSR Inventor's Certificate no. 798106, 1981.
27. Saha, G.B., *Fundamentals of Nuclear Pharmacy*, New York; Heidelberg; Dordrecht; London: Springer, 2010. doi 10.1007/9781441958600
28. Albertson, N.F. and Archer, S., *J. Am. Chem. Soc.*, 1945, vol. 67, no. 11, p. 2043. doi 10.1021/ja01227a501
29. Shimo, K. and Wakamatsu, S., *J. Org. Chem.*, 1961, vol. 26, no. 10, p. 3788. doi 10.1021/jo01068a039
30. Tsebrikova, G.S., Baulin, V.E., Kalashnikova, I.P., Ragulin, V.V., Zavel'skii, V.O., Maruk, A.Ya., Lunev, A.S., Klement'eva, O.E., Kodina, G.E., and Tsivadze, A.Yu., *Russ. J. Gen. Chem.*, 2015, vol. 85, no. 9, p. 2071. doi 10.1134/S1070363215090091