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Optimization of Reaction Parameters for the Synthesis of ^{177}Lu-DOTAELA

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Abstract: *The article provides a comparison of the theoretically calculated and experimentally determined yield of the reaction ^{176}Lu (n, γ)^{177}Lu. Also, it provides the results of the studies on lutetium-177 labeling of a non-peptide antagonist of gonadotropin-releasing hormone (GnRH) elagolix (ELA) associated with a chelating DOTA (DOTAELA). The synthesized DOTAELA complex was labeled with the ^{177}Lu isotope.^{177}Lu was produced by the reaction (n, γ) using the enriched $LuCl_3$ target at the reactor WWR–K. Production of ^{177}Lu by the (n, γ) reaction from the enriched ^{176}Lu target achieved by irradiation for 17 days. All stages of the complex preparation were evaluated by paper chromatography. The optimal technological parameters for the synthesis of the complex ^{177}Lu-DOTAELA are: pH - 4.5, 90-100 °C and 40 min. The obtained optimal parameters made it possible to produce a labeled complex of ^{177}Lu–DOTAELA with a radiochemical yield of ≥ 95%.*

Keywords: *Lutetium-177; DOTAELA; labeling; radiochemical purity (RCP); triple-negative breast cancer*

1.Introduction

In women in many countries of the world, including Kazakhstan, breast cancer (BC) is the most common malignant neoplasm. On average, about 4,000 breast cancer patients are diagnosed annually in the Republic of Kazakhstan, and more than 1,380 women with breast cancer die [1]. Breast cancers registered in 2017 amounted to 24.5 per 100,000 of the population.

Triple negative breast cancer (TNBC) comprises about 8–20% of all breast tumors; it is more common in women up to 50 years of age before menopause, with early menarche, the first pregnancy at a younger age, a short period of breastfeeding, and a high body mass index. TNBC is characterized by a lack of expression of estrogen, progesterone and HER-2 receptors, which is characterized by an aggressive course, metastatic disease and reduction of life expectancy; the maximum risk of recurrence occurs during the first three years after surgical treatment [2-4].

Triple negative breast cancer expresses the receptors for gonadotropin-releasing hormone (GnRH) in more than 50% of cases [5]. Among several analogues (agonists and antagonists) of GnRH that have been studied for treatment of this type of cancer, the non-peptide antagonist elagolix (ELA) is of greatest interest. Elagolix is the first of a new class of GnRH inhibitors that have been designated as the second generation due to their non-peptide nature and oral bioavailability. In this regard, a DOTAELA molecule was synthesized, consisting of an elagolix bound to a chelating DOTA molecule via an ethylenediamine bridge to allow labeling with isotopes such as lutetium-177 and gallium-68.The substance has no analogues in the treatment of triple negative breast cancer and is the first in this field [6-8].

In recent years, ^{177}Lu has become a promising β-emitter with superficial tissue penetration. The depth of ^{177}Lu penetration into the tissue is equal to 2 mm, which is advantageous, especially for small metastases [9]. It can be used as an alternative to ^{131}I or as an addition to ^{90}Y.

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^{177}Lu [$T_{1/2}$ = 6.73 d, $E_{ßmax}$ = 0.497 MeV, E_{γ} = 113 KeV (6.4%) and 208 KeV (11%) are considered as alternatives for the development of new agents for peptide receptor radionuclide therapy [10-12]. At the same time, the low-energy gamma-ray photons of ^{177}Lu allow its use in the production of SPECT images [13]. The core of ^{l76}Lu has a large capture cross section of both thermal neutrons (2065 barns) and epithermal neutrons (1090 barns) [11]. This leads to the rapid achievement of the relatively high specific activity of ^{177}Lu.

Moderate flux reactors can be used to produce ^{177}Lu. The long-term half-life of ^{177}Lu provides logistical advantages. The main methods for producing ^{177}Lu of high specific activity are irradiation with neutrons of the reactor ^{l76}Lu or ^{l76}Yb by the reactions ^{176}Lu(n, γ)^{177}Lu and ^{l76}Yb(n, γ)^{177}Yb (β-decay)→^{l77}Lu.

Although the latter method allows the production of ^{177}Lu with no carrier, the radio-chemical separation of ^{177}Lu from the irradiated Yb target is difficult due to the similarity in chemical properties of the two side-by-side lanthanides in the series. The isotopic composition of the starting material has a significant impact on the specific activity of ^{177}Luproduced by the 'indirect' method. Commercially available ^{l76}Yb oxide can contain up to 2–3% of the isotope ^{l74}Yb [14]. The presence of this isotope in the starting material leads to the accumulation of ^{l75}Yb ($T_{1/2}$=4.18 days), which decays into ^{l75}Lu both during irradiation and at its end and thus reduces the specific activity of the^{177}Lu accumulated during irradiation [15]. In other words, the presence of a ^{l74}Yb impurity in the starting material actually eliminates the main advantage of the 'indirect' method of ^{177}Lu production. The solution to this problem is to minimize the accumulation of ^{l75}Lu by reducing the time between the end of irradiation and the processing of the irradiated material.

Various labelling procedures lead to different results. For example, ^{177}Lu- and ^{90}Y-DOTA-conjugated biomolecules (DOTATOC and PSMA-617) [16], ^{177}Lu-DOTA-Herceptin [17] and ^{177}Lu - DOTA-DN(PTX)-BN [18] were produced using various temperature, pH and time parameters, which resulted in slightly significant the radiochemical purity (RCP) values.

The main purpose of this research was to study the impact of the technological parameters of ^{177}Lu–DOTAELA synthesis on the radiochemical yield and quality of the product. The production of ^{177}Lu was carried out by reaction (n, γ) using the enriched $LuCl_3$ target in the reactor WWR-K with a moderate flux. The expected therapeutic effect consists in a certain degree of inhibition of cancer cell division and exposure to the cell by β-radiation.

2.Materials and methods

Lutetium oxide (82.0%, enriched by ^{176}Lu, with a spectroscopic purity of 99.99%) was used. DOTAELA was obtained from the University of Oslo in Norway, which coordinated the research project. All chemicals and solvents used were of analytical reagent grade and supplied by reputable chemical manufacturers. The radionuclide purity of ^{177}Lu was determined by gamma spectrometry with a high purity germanium detector (Ortec). The reference source^{152}Eu (OSGI) was used for calibration of the detector by energy and efficiency. A radiochromatogram-scanner Veenstra VCS-103 (Netherlands) was used. Chromatographic paper of the FN1 type (FILTRAK, Germany) and a well-type NaI (Tl) ionization chamber for total radioactivity measurement (CAPINTEC, INC., CRC.-2PR, USA) were used. A Shimadzu HPLC system (Shimadzu, Japan) equipped with a C18 reversed phase Shim-pack VP-ODS (5 μm, 4.6x250) column was used for HPLC analysis. HPLC was performed using a Shimadzu LC-10ADvp pump system coupled with UV (Shimadzu SPD-10Avp) and radiometric (Bioscan Inc., USA) detectors.

2.1^{177} Lu production

The isotope of lutetium-177 was produced by irradiation of 400 μg of lutetium-176 (82.0 %) with a flux of thermal neutrons $5.7 \cdot 10^{13}$ n/cm^{2}·s for 240, 252 and 408 h. After irradiation, the target was kept for 24–36 h; then the ampoules were opened in the hot cell, and the targets were dissolved in 2

mL of 0.01 M hydrochloric acid solution. The next step was quality control as described elsewhere [19].

Volume 3 of the State Pharmacopoeia of the Republic of Kazakhstan (2014) defines the purity of radionuclides, which should be more than 98% [20]. Radionuclide purity is checked by diluting the solution and the selection of aliquots with a micropipette at 2-5 µl. At least three samples should be measured to obtain the average result. A gamma spectrometer is used for radionuclide purity determination.

2.2 ^{177}Lu-DOTAELA preparation

2.2.1 Labeling of^{177}Lu with DOTAELA by optimization studies

Studies were performed on the optimal parameters for the process of producing the ^{177}Lu-DOTAELA (Figure 1) complex, including the influence of incubation time, temperature and *p*H, to obtain the maximum ^{177}Lu-DOTAELA during complexation. Keeping the reaction volume at 2 mL, the amount of DOTAELA remained constant. The labeled conjugate score and complexation yield were determined by paper chromatography in 1 M sodium citrate buffer solution with a *p*H of 5.0. The yield of ^{177}Lu-DOTAELA was evaluated by paper chromatography [21].

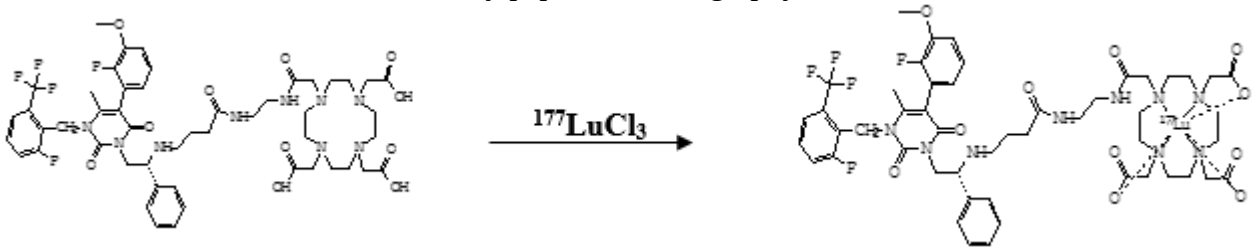


Figure 1. Synthesis scheme of ^{177}Lu-DOTAELA

2.2.2 Quality control

The results obtained using the HPLC method are consistent with the results obtained using the paper chromatography method. However, while it is possible to capture ^{177}Lu ions in the reverse phase of an HPLC column, this does not provide the necessary reliability in the analysis of radiochemical yield; therefore, in this case, the use of the paper chromatography method, which gives an idea of the content of the radiochemical forms of ^{177}Lu, is preferable.

Paper chromatography studies were carried out after passing 12 cm of the solvent front. For this purpose, 5–10 µL of test solution were applied at a 6–cm distance from the bottom of the paper strips, which were chromatographed in citrate buffer solution with *p*H=5.0. The strips were dried, and then a sticky tape was applied on both sides. After that, the distribution of activity on the strip was measured using a radiochromatogram scanner with an NaI detector. Validation of the location of Lu-177 DOTAELA as well as unbound Lu-177 is described elsewhere in this article [21]. The radiochemical yield percentage (B) of the complex was calculated by formula 1:

$$B = \frac{A(^{177}\text{Lu} - \text{DOTAELA})}{A_{^{177}Lu} + A(^{177}\text{Lu} - \text{DOTAELA})} * 100 \quad (1)$$

3.Results and discussions

3.1 Preparation of ^{177}Lu

^{177}Lu was obtained by irradiation with thermal neutrons of enriched lutetium (^{176}Lu, 82.0%) at the WWR-K reactor of the Institute of Nuclear Physics, Almaty. The radionuclide purity of ^{177}Lu was determined by analyzing the gamma spectrum, which was 99.975%.^{13177}Lu was estimated from grounded gamma lines at 113, 208, and 250 keV.

The 'direct' method of ^{177}Lu production is accompanied by a long-lived isomer ^{177m}Lu ($T_{1/2}$=160 days). To reduce the radiation load on the patient and the waste generated in clinics during 'lutetium' therapy, the content of ^{177m}Lu in the final product is limited. The estimates presented in the literature show that the problem of ^{177m}Lu build-up is successfully solved by the optimization of the irradiation conditions. Even under irradiation in a high-flux reactor for 10 days, the build-up of ^{177m}Lu remains at an acceptable level and does not exceed 0.02% [22]. The resulting gamma spectrum of the irradiated target did not show any significant peak corresponding to ^{177m}Lu (71, 128, 153, 228, 378, 414 and 418 KeV). This can be explained by the fact that the radioactivity of ^{177m}Lu is negligible compared to that of ^{177}Lu due to its long half-life and relatively low cross-section (2 barn) [11]. The level of ^{177m}Lu produced was determined by measuring the gamma spectrum of the sample initially having high activity after 100 days with increased sample volume. The average level of the radionuclide impurity load in ^{177}Lu due to ^{177m}Lu corresponds to 0.025% of the total activity produced.

The $LuCl_3$ target was irradiated at various available flow positions for different durations of time with thermal neutron flux positions of $5.7 \cdot 10^{13}$ n/cm^2·s. According to the irradiation schedule of the highly enriched target, the minimum irradiation time to reach the maximum yield is between 17 and 21 days.

The maximum specific activity was 760 GBq/mg, which was achieved under irradiation with a thermal neutron flux of $5.7 \cdot 10^{13}$n/cm^2·s for 408h. The data for ^{177}Lu irradiation were significantly higher than the theoretically calculated values, taking into account only the capture of thermal neutrons. The possible reason for obtaining such high values of practical activity in comparison with the theoretically calculated values can be explained by the contribution of epithermal neutrons, which are not taken into account in the theoretical calculations [23-25].

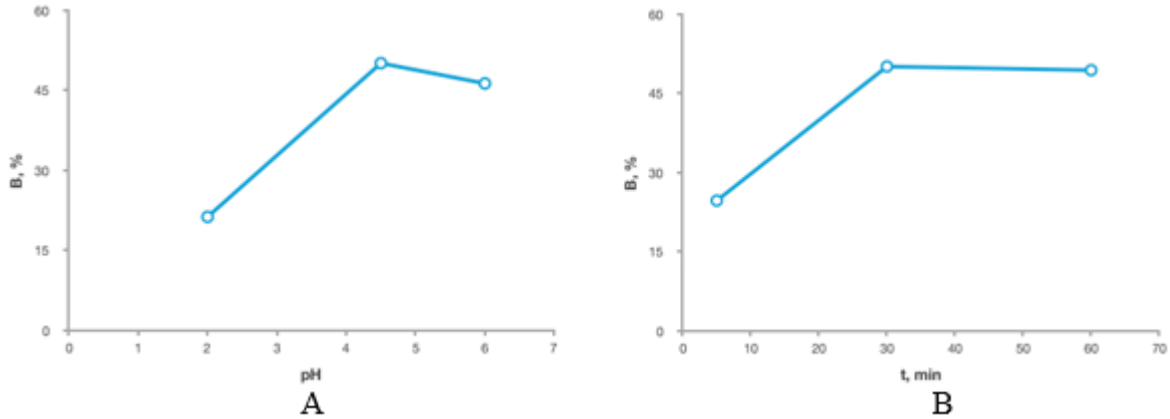
3.2 ^{177}Lu-DOTAELA radiochemical purity evaluation

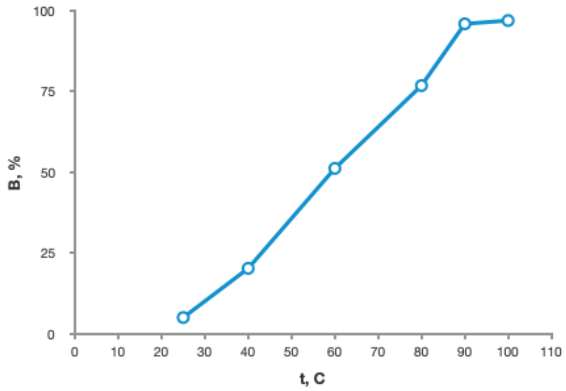
The main peak of ^{177}Lu-DOTAELA detected by the scintillation detector (NaI) after application as the mobile phase of an aqueous solution of sodium citrate is located on the start line (R_f=0), and the peak corresponding to the free Lu-177 moves along the chromatogram with the solvent front (R_f=1). The conclusion is that ^{177}Lu-DOTAELA does not interfere with the determination of the non-reacted Lu-177.

3.3 Optimization of the complexation yield of ^{177}Lu-DOTAELA

The optimal parameters of the process of producing the complex ^{177}Lu-DOTAELA were studied, including the influence of complexation time, temperature and *p*H, to obtain the maximum yield of ^{177}Lu-DOTAELA. Keeping the reaction volume of 2 mL, the amount of DOTAELA remained constant to determine the optimal parameters of time, temperature and *p*H to obtain maximum complexation.

The yield of ^{177}Lu-DOTAELA depending on pH, time and temperature is shown in Figures 2A, 2B and 2C respectively.





C

Figure 2. The dependence of the RCP of ^{177}Lu-DOTAELA:
A-pH, B-time and C-temperature

An important role is played by *p*H value in increasing the rate of complex formation. Considering the fact that lanthanide cations form insoluble hydroxides at *p*H=6 and above, the optimal pH for radioactive labeling is between 2 and 6, which is achieved by using buffer solutions. Radioactive Lu-177 in 0.01 M HCl solution (8 µL; 2.6-2.7 GBq) was added to the freshly prepared DOTAELA solution (71 µL) in ethanol and adjusted to *p*H values of 2–6 by the acetate buffer solution (125 µL); then the volume was adjusted to 2 ml with purified water.

According to the data obtained in the study about the influence of the *p*H of the synthesis on radiochemical purity, it was found that, with the growth of *p*H values from 2 to 4.5, the radiochemical yield value increases, and when *p*H drops to 6, the radiochemical yield value monotonically decreases. Radiolabeling was performed for 30 min at 60^{o}C. As a result, the optimal *p*H of the ^{177}Lu-DOTAELA complex synthesis is 4.5 (Figure 2A).

After determining the optimal pH parameter, we studied the reaction time mode (5, 30 and 60 min) (Figure 2B). The results indicate that the optimal time for complexing is 40 min since further increases in time do not affect the yield of the complex. Further, at a constant *p*H value of 4.5 and a time of 40 min, the dependence of radiochemical yield at different modes of complexation temperatures was studied (25, 40, 60, 80 and 100^{o}C (Figure 2C). As we can see in Figure 2C, with a temperature increase from 25° to 100°C, the value increases and reaches a maximum at 90–100°C. This temperature range is optimal.

The technological scheme was developed as a result of the research conducted to determine the optimum parameters for synthesis of the complex ^{177}Lu-DOTAELA (Figure 3).

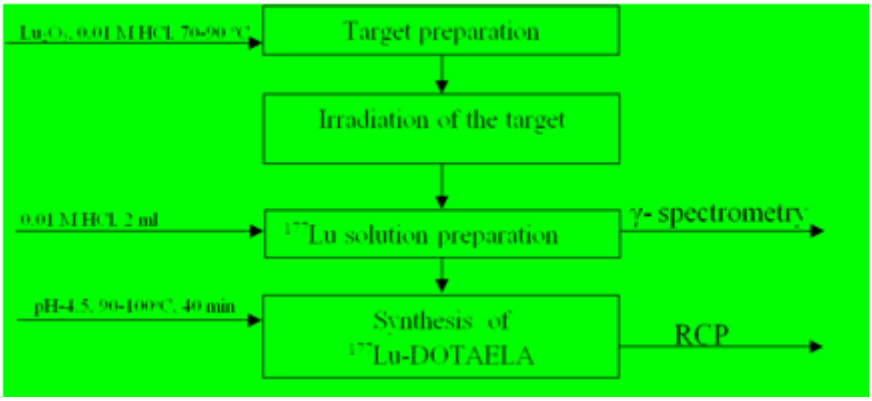


Figure 3. The technological scheme for ^{177}Lu-DOTAELA production

The control synthesis of DOTAELA radio labeling was performed in accordance with the developed technological scheme. One hundred µL of DOTAELA solution with a concentration of 1

mg/mL was placed in a 10-mL vial; then 125 µL of acetate buffer solution with a *p*H of 4.5 was added, followed by 50 µL of lutetium-177 chloride. The volume was adjusted to 2 mL with distilled water. The final mixture was placed in a glycerin bath at 90–95°C for 40 min.

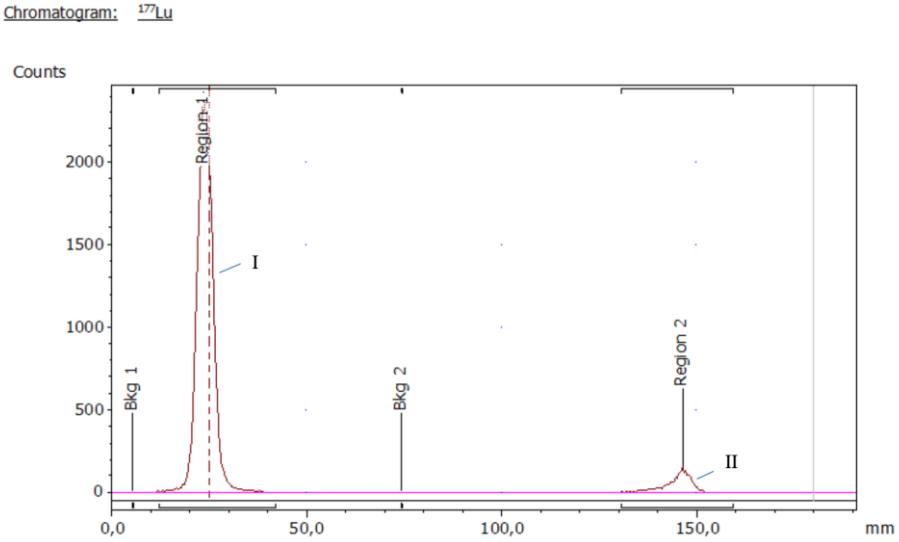


Figure 4. Radiochromatogram of ^{177}Lu-DOTAELA. I - ^{177}Lu-DOTAELA, II - $^{177}Lu^{3+}$

When performing the synthesis, after determining the optimal synthesis parameters, the radiochemical yield was 96% (Figure 4). Additional purification is described elsewhere in this article [26].

Typically, treatment of breast cancer can be performed using one or a combination of the following methods: hormonal therapy, surgery, chemotherapy and radiation therapy. Their side effects limit the effectiveness of chemo/radiotherapy, but they can be avoided, and much more effective therapy is possible if the preparations used have tumor selectivity, which includes the determination of the biochemical processes that distinguish the samples of tumor tissue from healthy tissue [27-30].

The required selectivity can be achieved by the development of targeted therapy using radiopharmaceuticals.

The development of radiopharmaceuticals obtained using radiometals for labeling or incorporating a radioactive isotope into a carrier molecule is a long and difficult process. There are many requirements for radiopharmaceuticals to be used for therapy as well as for diagnosis. Radiopharmaceuticals must have a high radiochemical purity and a high therapeutic dose, and the synthesis should preferably be simple and should not take a long time. In addition, highly qualified personnel, exact observance of the radio-labeling procedure in accordance with good manufacturing processes (GMP), adherence with pharmacopeia requirements and radiation safety are required.

Until recently, it was believed that TNBC cells have no or very few receptors on their surface. As a result, TNBC is characterized by a lack of expression for progesterone, estrogen and HER-2. Recent studies have shown that on the surface of TNBC cells, there are receptors expressing gonadotropin releasing hormone (GnRH) in more than 50% of cases. On this basis, we were attracted by an analogue of the gonadotropin-releasing hormone elagolix, which is non-protein in nature and has a small molecular weight relative to other analogues. Elagolix was bound to the DOTA chelating agent through the ethylenediamine bridge (DOTAELA), which allows radio-labeling with metal isotopes.

Due to the fact that the concentration of receptors on the tumor cell is limited, DOTAELA radiolabeling must be performed using high specific activity to deliver a therapeutic dose to the affected tissues.

Our goal was to determine the optimal technological parameters of the labeling of a synthesized substance with a high therapeutic dose. The strategy for the formation of the radiopharmaceutical

substance was to use a sodium acetate buffer solution, which is one of the most studied buffers for biological research as well as being safe and effective, to maintain a constant *p*H in the reaction mixture. This concept was used in studies on the effect of *p*H, temperature and time on the radiochemical purity of the resulting ^{177}Lu-DOTAELA complex. The obtained optimal parameters made it possible to produce a labeled complex with a radiochemical purity of ≥ 95%.

4.Conclusions

Production of ^{177}Lu by the (n, γ) reaction from an enriched ^{176}Lu target with specific activity of 740 GBq/mg was achieved by irradiation at the thermal neutron flux of $5.7 \cdot 10^{13}$ n/cm^2·s for 17 days. As a result of the experiments, the optimal *p*H of the synthesis of ^{177}Lu-DOTAELA is 4.5. The experiment showed that with a temperature increase from 25^o to 100^{o}C, the value of the RCP increases and reaches a maximum at 100^{o}C; this temperature is optimal. After determining the optimal temperature and pH parameters, the reaction time mode was studied. The results indicate that the optimal time for complexing is 40 minutes. The technological scheme was developed as a result of research to determine the optimal parameters of the ^{177}Lu-DOTAELA complex synthesis. According to this scheme, the radiochemical yield is ≥ 95 %.

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References

1.CHICHUA, N.A., TALAEVA, SH.ZH., OMARBAEV, N.A., *Oncology and radiology of Kazakhstan*, **12**, 2015, 26-31.
2.JOHN, E. M., L. M. HINES, L. M., PHIPPS, A. I., KOO, J., LONGACRE, T. A., INGLES, S. A., KATHY, B. B., MARTHA, L. S., WU, A. H., *International Journal of Cancer*, **142**(11), 2018, 2273-2285. **DOI**: 10.1002/ijc.31258
3.MA, H., URSIN, G., XU, X., LEE, E., TOGAWA, K., DUAN, L., LU, Y., MCDONALD, J.A., MALONE, K. E., SIMON, M. S., FOLGER, S. G., SULLIVAN-HALLEY, J., DEAPEN, D. M., PRESS, M. F., BERNSTEIN, L., *Breast Cancer Research*, **19**(1), 2017, 1-14. **DOI**: 10.1186/s13058-016-0799-9
4.ALMURADOVA, D.M., *Journal of Drug Delivery and Therapeutics*. **8**(5), 2018, 163-167.
DOI: 10.22270/jddt.v8i5.1827
5.JAMOUS, M., HABERKORN, U., MIER, W., *Molecules*, **18**(3), 2013, 3379-3409.
DOI: 10.3390/molecules18033379
6.KWOK, C.W., TREECK, O., BUCHHOLZ, S., SEITZ, S., ORTMANN, O., ENGEL, J.B., *Target Oncol*., **10**(3), 2015, 365-373. **DOI:** 10.1007/s11523-014-0340-y
7.DE LAURENTIIS, M., CIANNIELLO, D., CAPUTO, R., STANZIONE, B., ARPINO, G., CINIERI, S., LORUSSO, V., DE PLACIDO, S., *Cancer Treat. Rev*., **36**(Suppl 3), 2010, 80S-86S. **DOI:** 10.1016/S0305-7372(10)70025-6
8.DENT, R., TRUDEAU, M., PRITCHARD, K.I., HANNA, W. M., KAHN, H. K., SAWKA, C. A., NAROD, S. A., *Clin. Cancer Res*., **13**(15 Pt 1), 2007, 4429-4434. **DOI:** 10.1158/1078-0432.CCR-06-3045
9.MITTRA, E.S., *American Journal of Roentgenology*, **211**(2), 2018, 278-285.
DOI: 10.2214/ajr.18.19953
10.DE ARAÚJO, E.B., CALDEIRA, J.S., NAGAMATI, L.T., MURAMOTO, E., COLTURATO, M.T., COUTO, R.M, PUJATTI, P.B., MENGATTI, J., SILVA, C.P., *Appl. Radiat. Isot*., **67**(2), 2009, 227-233.
DOI: 10.1016/j.apradiso.2008.09.009

11.FIRESTONE, R., IN: SHIRLEY VS, (Ed.), Table of Isotopes. Eighth ed. New York, NY: Wiley; 2009.
12.DASH, A., PILLAI, M.R.A., KNAPP, F.F., *Nucl. Med. Mol. Imaging*, **49**(2), 2015, 85-107. **DOI:** 10.1007/s13139-014-0315-z
13.BEAUREGARD, J-M., HOFMAN, M.S., PEREIRA, J.M., EU, P., HICKS, R.J., *Cancer Imaging*, **11**(1), 2011, 56-66. **DOI**: 10.1102/1470-7330.2011.0012
14.KUZNETSOV, P.A, BOBROVSKAYA, K., SVETUHINA, A.H. *Radiochemistry*, **61**(4), 2019, 273-395. **DOI:** 10.1134/S1066362219040015
15.TARASOV, B.A., ROMANOV, E.R., KUZNETSOV, P.A., *Samarsk. scientific Center RAS*, **15**(4), 2013,1084.
16.IORI, M., CAPPONI, P. C., RUBAGOTTI, S., ESPOSIZIONE, L. R., SEEMANN, J. PITZSCHLER, R., DREGER, T., FORMISANO, D., GRASSI, E., FIORONI, F., VERSARI, A., ASTI, M., *Contrast Media & Molecular Imaging*, 1, 2017, 1-12. **DOI:** 10.1155/2017/8160134
17.WANG, T., PENG, Y., LI, X., LI, D., ZUO, CH., *J Nucl Med* **, 60(**no. supplement 1), 1055 (2019).
18.GIBBENS-BANDALA, B., MORALES-AVILA, E., FERRO-FLORES, G., SANTOS-CUEVAS, C.,LUNA-GUTIÉRREZ, M., RAMÍREZ-NAVA, G., OCAMPO-GARCÍA, B., *Polymers*, **11**(10)1572, 2019, 1-14. **DOI:** 10.3390/polym11101572
19.GURIN, A.N., RISS, P., CHAKROVA E.T., MATVEYEVA I.V., *International Journal of Biology and Chemistry*, **12**(2), 2019, 112-115. **DOI**: 10.26577/ijbch-2019-i2-14
20.***State Pharmacopoeia of the Republic of Kazakhstan. Almaty: Zhibek Zholy; 2014.
21.GURIN, A.N., SOLONINKINA, S.G., RISS, P., CHAKROVA, E.T., MATVEYEVA, I.V., *Chemical journal of Kazakhstan,* **2**, 2018, 151-154.
22.TOROPOV, Y.G., TARASOV, V.A., ANDREYEV, O.I., Report on the 1st research coordination meeting on «Development of Therapeutic Radiopharmaceuticals Based on ^{177}Lu for Radionuclide Therapy». Vienna: IAEA, 2006, P. 152.
23.KNAPP, F.F., AMBROSE, K.R., BEETS, A.L., LUO, H., MCPHERSON, D. W., MIRZADEH, S., Oak Ridge National Laboratory, ORNL/TM-13107, 1995.
24.PILLAI, M.R.A., CHAKRABORTY, S., DAS, T., VENKATECH, M., RAMAMOORTHY, N., *Appl. Radiat. Isot.*, **59**, 2003, 109-118.
DOI: 10.1016/S0969-8043(03)00158-1
25.NIR-EL, Y. *J. Radioanal. Nucl. Chem.,* **262**, 2005, 563-567. **DOI**: 10.1007/s10967-004-0476-9
26.GURIN, A.N., RISS, P., CHAKROVA, YE.T., MATVEYEVA, I. V., KADYRBAEV, E. A., *Pharmaceutical Chemistry Journal*, **54**(1), 2020 64-68. **DOI**: 10.1007/s11094-020-02157-3
27.HUIYAN, M., XINXIN, X., CLAGUE, J., LU, Y., TOGAWA, K., WANG, S. S., CLARKE, C.A., LEE, E., PARK, H. L., SULLIVAN-HALLEY, J., NEUHAUSEN, S. L., BERNSTEIN, L., *Breast Cancer Res*, **18**(1), 2016, 1-16. **DOI:** 10.1186/s13058-016-0723-3
28.FRIEDENREICH, C.M., CUST, A.E., Br. J. Sports. Med., 42(8), 2008, 636-647.
DOI: 10.1136/bjsm.2006.029132
*29.*MA, H. LUO, J., PRESS, M.F., WANG, Y., BERNSTEIN, L., URSIN, G., *Cancer Epidemiol Biomarkers Prev., 18(2), 2009, 479-485.* **DOI:** *10.1158/1055-9965.EPI-08-0805*
30.ANDERS, C.K., CAREY, L.A., *Clin. Breast Cancer*, **9** (Suppl 2), 2009, 73S-81S.
DOI: 10.3816/CBC.2009.s.008

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