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Radioiodinated anastrozole and epirubicin as potential targeting radiopharmaceuticals for solid tumor imaging

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Abstract This study describes the preparation of radioiodinated anastrozole and epirubicin and their biological evaluation as potential solid tumor imaging gents. Radioiodinated anastrozole and epirubicin were successfully prepared via direct electrophilic substitution reaction at ambient temperature. The radiochemical yields for radioiodinated anastrozole and epirubicin were maximized to 92.9 ± 0.1 and 98.8 ± 0.1 %, respectively by studying different reaction parameters such as substrate amount, chloramine-T, pH of the reaction mixture, reaction temperature and reaction time. They showed in vitro stability up to 4 and 24 h, respectively. The preclinical evaluation and biodistribution in mice bearing solid tumor showed high retention and biological accumulation in solid tumor cells (12.4 and 25.3 % injected activity/g tissue) and high T/NT ratio equal to 4.7 ± 0.1 and 5.2 ± 0.1 at 2 and 1 h post-injection, respectively. Data described before could recommend radioiodinated anastrozole and radioiodinated epirubicin as potential targeting radiopharmaceuticals for solid tumor imaging.

Keywords Anastrozole · Epirubicin · Radioiodination · Solid tumor · Targeting

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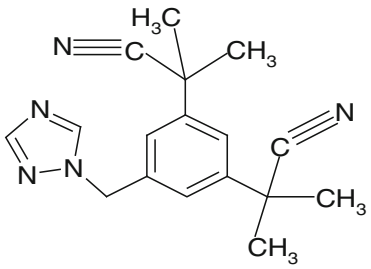
Introduction

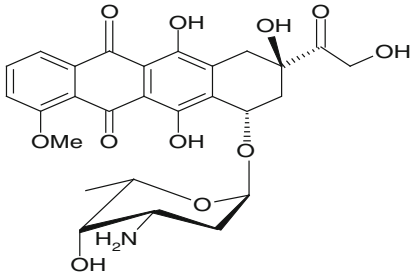
As tumor is one of the main death causes worldwide, many researches are directed to design and synthesize agents for tumor diagnosis and therapy [1, 2]. The early and accurate diagnosis of tumor will intensively improve the treatment plans for the patients. In-vivo imaging techniques could help in diagnosing and staging of tumors, optimizing drug scheduling, and predicting response to a therapeutic modality [3–5]. Tumor imaging agents based on radiotracers targeted to specific receptors have showed successful results, which demonstrate the utility of such targeting approaches for developing specific radiopharmaceuticals [6–8]. So, solid tumor can be imaged selectively using diagnostic radiopharmaceuticals. The main criteria of the radiopharmaceutical to be a selective tumor imaging agent is the high target/non target (T/NT) ratio [7]. This T/NT ratio expresses the ability of the pharmaceutical to target the radiotracer to specific receptor in the tumor cells [9, 10]. The literatures have considered that a radiopharmaceutical with target/non-target ratio greater than 1.5 (50 % greater capture in the target tissue) could be a potential diagnostic agent [9, 11]. Also, high target/blood (T/B) ratio plays an important role in increasing of the potentiality of diagnostic radiopharmaceutical for solid tumor imaging [6, 9].

Positron emission tomography (PET) agents are of great role in tumor imaging. [^{18}F]Fluoromisonidazole (FMISO), ^{18}F-fluoroazomycin arabinoside [^{18}F -FAZA] and ^{18}F-flortanidazole [^{18}F-HX4] [12–25] are examples for the tumor PET imaging agents, but ^{18}F applications are limited due to its high production cost and its short half life [25]. Single-photon emission computed tomography (SPECT) represents one of the standard technologies for most nuclear medicine departments [26, 27]. Research has focused on radioiodinated and ^{99m}Tc labeled

Fig. 1 Chemical structure of anastrozole and epirubicin



Anastrozole



Epirubicin

radiopharmaceutical for targeting solid tumor [6, 27–42]. The introduction of new radiopharmaceuticals, which target specific receptor in solid tumor, could potentially have high tumor uptake, high T/NT ratio and high T/B ratio which result in potential diagnostic radiopharmaceuticals [43].

Anastrozole is a potent third-generation highly selective non-steroidal aromatase inhibitor [44–47]. It inhibits selectively the conversion of androgens (produced by women in the adrenal glands) to estrogens by inhibiting the aromatase enzyme leading to a decreased tumor mass or delayed progression of tumor growth in some women [48, 49]. Hepatic metabolism accounts for approximately 85 % of anastrozole elimination and renal path way approximately 10 % of the total clearance [50]. Epirubicin is an anthracycline drug used for chemotherapy [51]. It prevents protein synthesis as a result of inhibition of RNA and inhibits topoisomerase II activity and polymerase activity [52]. Epirubicin and its major metabolites are eliminated through biliary excretion and, to a lesser extent, by urinary excretion [53]. So, anastrozole and epirubicin could play an important role as the potential targeting agents could deliver radiotracers to solid tumor.

This study aims to radioiodinate anastrozole and epirubicin (Fig. 1) to be evaluated as the potential solid tumor imaging radiopharmaceuticals. Factors affecting the iodination process, in vitro stability and biological biodistribution will be studied in details.

Experimental

Materials and equipments

Anastrozole ($C_{17}H_{19}N_5$, M.Wt = 293.4 g/mol) and epirubicin ($C_{27}H_{29}NO_{11}$, M.Wt = 543.519 g/mol) were obtained from Sigma-Aldrich laborchemikalien GmbH D-30918 seelze (Germany) with purity ≥98 %. All Chemicals were of analytical grade and were used directly without further purification. Deionized water was used in all experiments for the preparation of all solutions. Albino mice, each of 20–25 g, were used for the biological distribution study. A NaI (Tl) γ-ray scintillation counter (Scaler Ratemeter SR7 model, England) was used for the measurement of γ-ray radioactivity. Whatman No.1 paper chromatography (PC), Whatman International Ltd, Maidstone, Kent, UK. Shimadzu high performance liquid chromatography system (HPLC), which consists of pumps LC-9A and UV spectrophotometer detector (SPD-6A). Clear aqueous alkaline solution of sodium iodine ($Na^{125}I$) with specific activity 17,353 curies/gram was purchased from Institute of Isotopes Co., Ltd. (IZOTOP) Budapest, Hungary.

Radioiodination procedure

Radioiodinated anastrozole and epirubicin were synthesized by direct electrophilic substitution with ^{125}I under oxidative conditions in the presence of chloramine-T (CAT). ^{125}I was suitable for practical experimental as its $t_{1/2}$ = 59.4 days and it affords the ability to use high specific activity iodide without adding carrier iodine. The influence of various reaction parameters on radiochemical yield, such as the amount of oxidizing agent (chloramine-T), amount of substrate, pH of the reaction, reaction time and reaction temperature, were investigated and optimized in order to maximize the radiochemical yield.

The volume of reaction mixture was fixed to 500 μL. In an amber colored vial, 170 μL of aqueous solution anastrozole or epirubicin containing 0.08–1 mol (20–600 μg) of substrate was mixed with 170 μL of freshly prepared CAT solution in ethanol, containing 5–250 μg of CAT. pH was adjusted by using 150 μL of phosphate buffer solutions in the range of 2–10. Then, 10 μL of ^{125}I (4 MBq) was added to the reaction mixture. The reaction mixture was shaken by electric vortex and left at ambient temperature. Radioiodination was stopped at specific reaction time using drop of high concentration of sodium metabisulfite solution (10 mg/ml H_2O) to quench radioiodination reaction [54].

Quality control of ^{125}I-anastrozole and ^{125}I-epirubicin

The radiochemical yields and in vitro stability of ^{125}I-anastrozole and ^{125}I-epirubicin were determined using ascending paper chromatography (PC) and high performance liquid chromatography (HPLC).

Paper chromatography (PC) method was done using strips of Whatman paper number 1. On paper strip (1 cm width and 13 cm length), 2–3 drops of the reaction mixture were spotted at distance of 2 cm from the bottom and allowed to evaporate spontaneously. After developing the paper in fresh mixture of chloroform: methanol (8.5:1.5, v/v), it was removed, dried, and cut into 1 cm pieces. These pieces were counted using the NaI(Tl) γ-ray scintillation counter. The free radioiodide (I^-) remained near the origin ($R_f = 0$–0.1) while the ^{125}I-anastrozole and ^{125}I-epirubicin moved with the solvent front ($R_f = 0.8$).

For HPLC, the reaction mixtures (50 µl) were injected into a reversed-phase column (Lichrospher RP18, 4 mm × 250 mm; 5 µm).

The HPLC was operated for ^{125}I-anastrozole at a wavelength of 215 nm. The column was eluted with mobile phase of acetonitrile: water (45:55, v/v) and the flow rate were adjusted to 1 ml/min. In case of ^{125}I-epirubicin, the HPLC was operated at a wavelength of 254 nm using mobile phase of acetonitrile: water (15:85, v/v) and the flow rate was adjusted to 1 ml/min. Then fractions of 0.5 ml were collected separately using a fraction collector up to 10 ml and counted in a well-type γ-scintillation counter.

Biodistribution study

The study was approved by the animal ethics committee and was in accordance with the guidelines set out by the Egyptian Atomic Energy Authority.

The biodistrubition study was done in mice bearing solid tumor. Ehrlich ascites carcinoma (EAC) is one of the experimental breast tumor derived from a murine mammary carcinoma [55, 56]. The parent tumor line EAC had been derived from 7 days old donor female Swiss Albino mice and diluted with sterile physiological saline solution. Exactly 0.2 ml solution was then injected intramuscularly in the right thigh to produce a solid tumor evaluated in female Albino for 4–6 days [29–31].

The biodistribution assay of the radioiodinated anastrozole and epirubicin in albino mice bearing solid tumor of body mass 20–25 g ($n = 5$ mice/time point), were carried out at 20 min, 0.5, 1, 1.5, 2, 3, 3.5 and 24 h post injection (p. i). Mice housed in divided separated groups of five and provided with food and water. Radioiodinated anastrozole and epirubicin (3.7 MBq/10 µl) was injected via the tail vein of solid tumor mice. Animals were weighted, anaesthetized by chloroform and sacrificed at different time points. Samples of fresh blood, bone and muscle were collected in pre-weighed vials and counted. Blood, bone and muscles were assumed to be 7, 10 and 40 % of the total body weight, respectively [30, 57]. Organs and tissues were collected, rinsed with saline. The radioactivity of each sample as well as the back ground was counted in a well-type γ-counter NaI(Tl). A percentage of injected doses per gram tissue or organ (% ID/g) in a population of five mice for each time point were calculated for each sample. Solid tumor to normal muscle (T/NT) was calculated from % ID/g for solid tumor and normal muscle. Data were evaluated with one way ANOVA test. Results for p are reported and all the results are given as mean ± standard error (S.E) of a group of five mice. The level of significance was set at $p > 0.05$.

Results and discussion

The radioiodination reaction was done by electrophilic substitution. The free molecular iodine (I_2) has the structure of I^+–I^- in aqueous solution [58]. The hydrated iodonium ion (H_2OI^+) and the hypoiodous acid (HOI) are believed to be highly reactive electrophilic species resulting in iodination reaction through electrophilic substitution of a hydrogen ion in a molecule of interest (anastrozole or epirubicin) [59, 60] (Figs. 2, 3).

Quality control of ^{125}I-anastrozole and ^{125}I-epirubicin

HPLC analysis

The radiochemical yields were further confirmed by a Shimadzu HPLC, operated for ^{125}I-anastrozole and ^{125}I-epirubicin.

An HPLC radiochromatogram is presented in Fig. 4 It shows two peaks, one at fraction No. 1.2, which corresponds to free radioiodide (I^-), while the second peak was collected at fraction No. 4.7 for ^{125}I-anastrozole which was found to coincide approximately with its UV signal of anastrozole at retention time 4.6 min.

An HPLC radiochromatogram is presented in Fig. 4 It shows two peaks, one at fraction No. 3.3, which corresponds to free radioiodide (I^-), while the second peak was collected at fraction No. 6.6 for ^{125}I-epirubicin which was found to coincide approximately with its UV signal of epirubicin at retention time 6.4 min.

Effect of anastrozole and epirubicin amount

The reaction was performed at different amounts of anastrozole and epirubicin (20–600 µg). As shown in Fig. 5, the

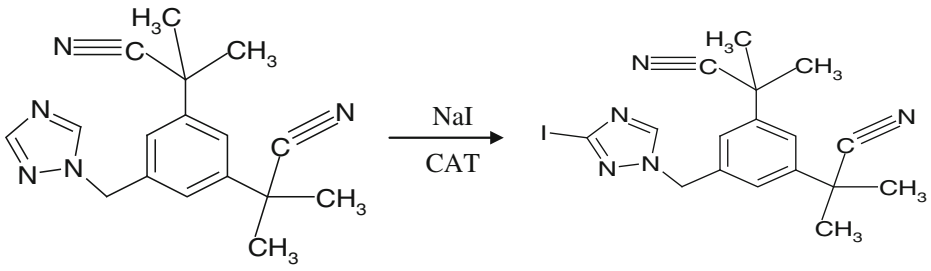


Fig. 2 The proposed structure of radioiodinated anastrozole

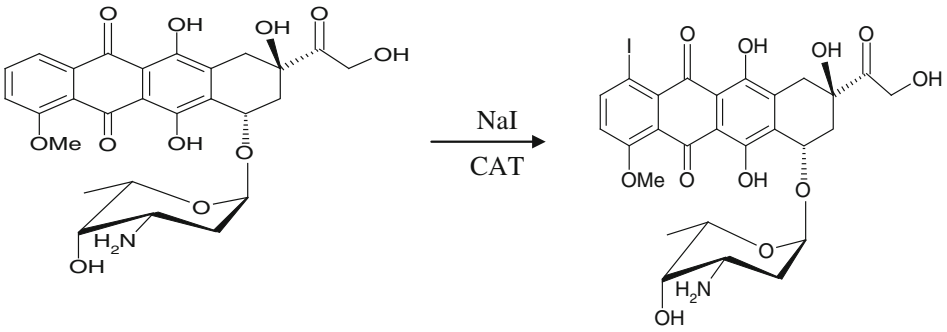


Fig. 3 The proposed structure of radioiodinated epirubicin

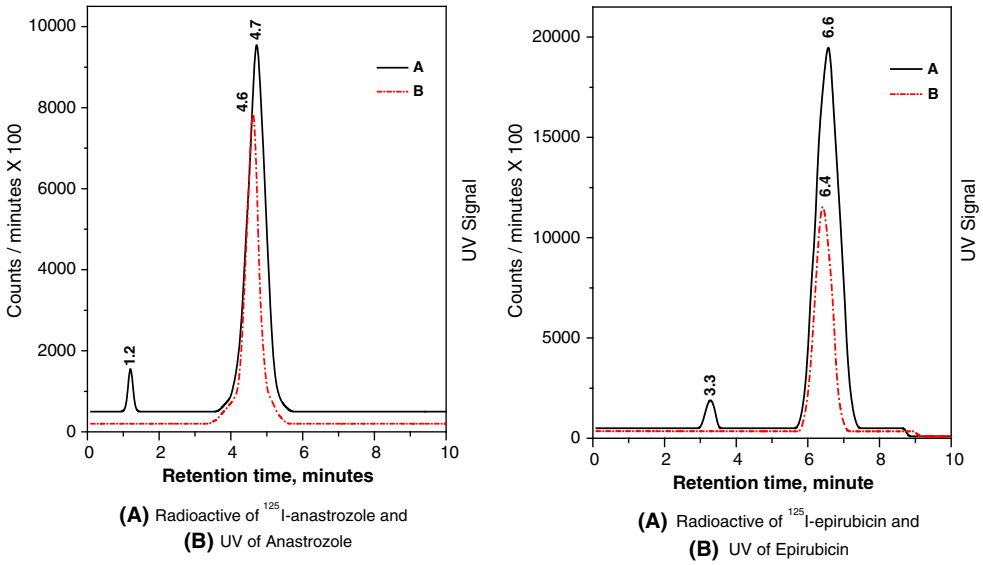


Fig. 4 HPLC radiochromatogram of ^{125}I-anastrozole and ^{125}I-epirubicin

radiochemical yields of ^{125}I-anastrozole and ^{125}I-epirubicin were small at low substrate amount where at 20 μg; the radiochemical yields were 65.4 ± 0.36 and 94.5 ± 0.11 %, respectively. By increasing the substrate amounts, the radiochemical yields were increased where maximum radiochemical yields of 92.9 ± 0.1 and 98.8 ± 0.1 % were obtained at 100 μg of anastrozole and epirubicin, respectively. The optimum amount 100 μg was equivalent to 0.34 and 0.18 mol of anastrozole and epirubicin, respectively. At substrate amounts higher than the optimum amounts, the radiochemical yields were slightly decreased again till reached 87.8 ± 0.22 and 96.4 ± 0.14 % at 600 μg, respectively.

Effect of chloramine-T (CAT) amount

Figure 6 shows the effect of CAT amount on the percent radiochemical yields of ^{125}I-anastrozole and ^{125}I-epirubicin.

Radioiodination of anastrozole and epirubicin has been performed by using CAT as a mild oxidizing agent,

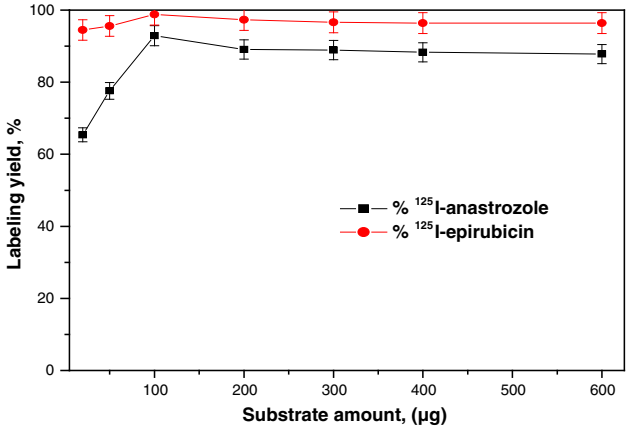


Fig. 5 Variation of the radiochemical yields of ^{125}I-anastrozole or ^{125}I-epirubicin as a function of different amounts of anastrozole or epirubicin. Reaction conditions: *X* µg of anastrozole or epirubicin, 150 µl phosphate buffer of pH 5 for anastrozole and pH 7 for epirubicin, 4 MBq of carrier-free Na^{125}I, 8 and 200 µg of CAT for anastrozole or epirubicin, respectively and the reaction mixtures were kept at room temperature for 30 min

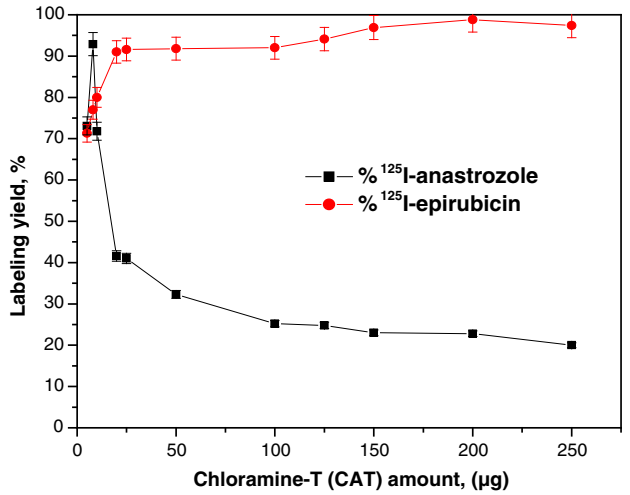


Fig. 6 Variation of the radiochemical yields of ^{125}I-anastrozole or ^{125}I-epirubicin as a function of CAT. Reaction conditions: 100 µg of anastrozole or epirubicin, 150 µl phosphate buffers of pH 5 for anastrozole and pH 7 for epirubicin, 4 MBq of carrier-free Na^{125}I, *X* µg of CAT and the reaction mixtures were kept at room temperature for 30 min

transforming iodide (I^-) to an electropositive form of iodine (oxidative state I^+), which allows a spontaneous electrophilic substitution with H^+ [61, 62]. When high specific activity radioiodide is oxidized in situ it generates an electropositive iodine, but it is unlikely to form I_2 because there is so little radioiodine present that statistically it is not possible for two iodine atoms to join together at the concentrations involved and because CAT (although it is a mild oxidizing agent) is strong enough to oxidize all I^- into I^+ without forming I_2 [62, 63].

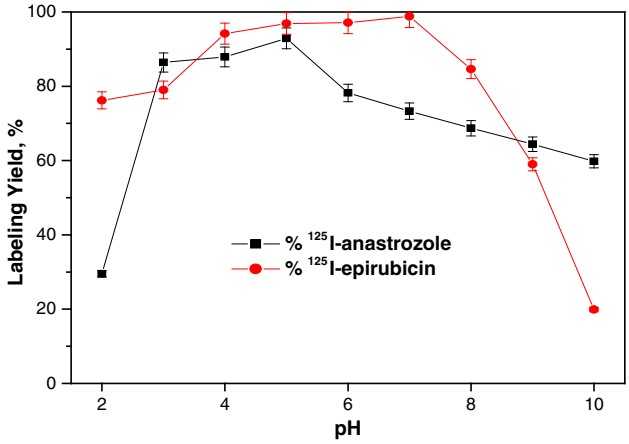


Fig. 7 Variation of the radiochemical yield of ^{125}I-anastrozole or ^{125}I-epirubicin as a function of pH. Reaction conditions: 100 µg of anastrozole or epirubicin, 150 µl phosphate buffer of different pH 2–10, 4 MBq of carrier-free Na^{125}I, 8 µg of CAT for anastrozole and 200 µg for epirubicin and the reaction mixtures were kept at room temperature for 30 min

At low CAT amounts 5 µg, the radiochemical yields of ^{125}I-anastrozole and ^{125}I-epirubicin were small and equal to 73.1 and 71.3 %, respectively. This may be due to the amount of CAT was not enough to reproduce the oxidative state of iodine (I^+) [62]. A high radiochemical yield of 92.9 ± 0.1 and 98.8 ± 0.1 % was achieved by increasing the amount of CAT to 8 in case of anastrozole and 200 µg for epirubicin.

Increasing the CAT amounts above these values lead to a decrease in the iodination yield which may be due to the formation of undesirable oxidative by-products like chlorination, polymerization and denaturation of anastrozole and epirubicin [63, 64]. The formation of these impurities may be attributed to the high reactivity and quantity of CAT [59]. So, the optimum amount of CAT is highly recommended in order to avoid the formation of any by-products and to obtain high radiochemical yields.

Effect of pH

The influences of pH of the reaction mixture on the radiochemical yields of ^{125}I-anastrozole and ^{125}I-epirubicin at different pH values (2–10) are shown in Fig. 7. The pH of reaction mixture was adjusted by using 150 µL of phosphate buffer solutions in the range of 2–10. The change in pH of reaction mixture may cause hydrolysis of radioiodinated compounds and may affect the efficiency of the oxidizing agent [59, 65].

At pH 2, the radiochemical yield was small and equal 29.5 and 76.2 % for ^{125}I-anastrozole and ^{125}I-epirubicin, respectively, which may be attribute to predominance of ICl species which have lower oxidation potential than

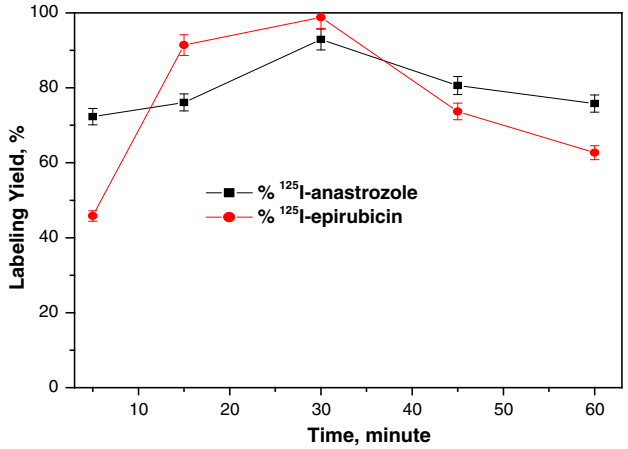


Fig. 8 Variation of the radiochemical yields of ^{125}I-anastrozole or ^{125}I-epirubicin as a function of reaction time. Reaction conditions: 100 μg of anastrozole or epirubicin, 150 μl phosphate buffer of pH 5 in case of anastrozole and pH 7 for epirubicin, 4 MBq of carrier-free Na^{125}I, 8 μg of CAT for anastrozole and 200 μg for epirubicin and the reaction mixtures were kept at room temperature for different time

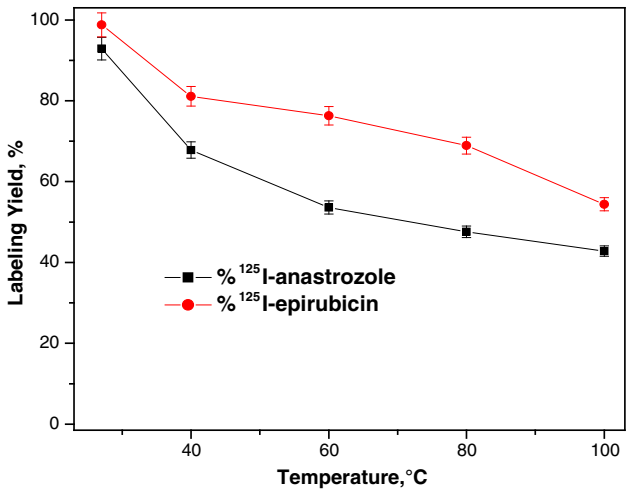


Fig. 9 Variation of the radiochemical yields of ^{125}I-anastrozole or ^{125}I-epirubicin as a function of reaction temperature. Reaction conditions: 100 μg of anastrozole or Epirubicin, 150 μl phosphate buffer of pH 5 for anastrozole and pH 7 for epirubicin, 4 MBq of carrier-free Na^{125}I, 8 μg of CAT in case of anastrozole and 200 μg of CAT for epirubicin and the reaction mixtures were kept at different temperature for 30 min

HOCl species [66]. At pH 5, for ^{125}I-anastrozole the yield was maximized (92.9 ± 0.07 %) while for ^{125}I-epirubicin, the maximized yield was 98.8 ± 0.12 % at pH 7. By increasing the pH towards alkaline side, the radiochemical yield decrease to 59.8 and 19.9 % at pH 10, respectively. The decrease in radiochemical yield at alkaline pH may be due to the formation of hypoiodite ion (IO^-) and iodate (IO_3^-), [69, 70] which are not the suitable forms for radioiodination of anastrozole and epirubicin [71].

Effect of reaction time

The radiochemical yield is strongly dependent on reaction time. It is clear from Fig. 8 that the radiochemical yields of ^{125}I-anastrozole and ^{125}I-epirubicin are increased with increasing the reaction time from 5 to 30 min. At shorter reaction time (5 min), the time required for reaction between chloramine-T and iodide to produce the iodonium ion is minimal. A reaction time of 30 min is needed to reach the maximum radiochemical yields of 92.9 ± 0.1 and 98.8 ± 0.1 % for ^{125}I-anastrozole and ^{125}I-epirubicin, respectively. Increasing the reaction time beyond the optimum values caused slight decrease in the radiochemical yield due to exposing the substrate to highly reactive CAT for long reaction time which can result in oxidative side reactions.

Effect of reaction temperature

The influence of the reaction temperature on the radiochemical yield of ^{125}I-anastrozole and ^{125}I-epirubicin are shown in Fig. 9. The reaction was carried out at room temperature (27 °C), 40, 60, 80 and 100 °C. The maximum radiochemical yields (92.9 ± 0.1 and 98.8 ± 0.1 %, respectively) were optimal at room temperature. The radiochemical yields were decreased by increasing temperature, this may be due to the thermal decomposition of the ^{125}I-anastrozole and ^{125}I-epirubicin.

In-vitro stability study

The effect of time on the in vitro stability of ^{125}I-anastrozole and ^{125}I-epirubicin were studied in order to determine the suitable time during which the preparation remain having high radiochemical yields without any undesired product which may be formed as result from the ionizing γ-radiation (radiolysis) of the labeled compound.

Figure 10 shows in vitro stability at different time post iodination. In-vitro stability tests carried out at different time post iodination which varied from 0 to 48 h and the radiochemical yields were calculated. The highest radiochemical yield of ^{125}I-anastrozole was stable up to 4 h While ^{125}I-epirubicin was stable up to 24 h.

Biodistribution studies

The biodistribution patterns of radioiodinated anastrozole and epirubicin in solid tumor bearing Albino mice at different time intervals (20 min, 0.5, 1, 1.5, 2, 3, 3.5 and 24 h) post injection (p.i.) were examined. The radioactivity levels are expressed as the average percent of injected dose per gram (% ID/g ± SEM) for five mice per group.

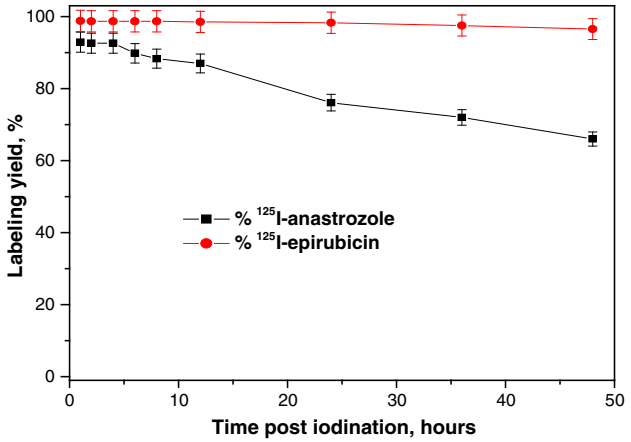


Fig. 10 Variation of the radiochemical yields of ^{125}I-anastrozole or ^{125}I-epirubicin In-vitro stability at different time post iodination. Reaction conditions: 100 μg of anastrozole or epirubicin, 150 μl phosphate buffer of pH 5 and 7, respectively, 4 MBq of carrier-free Na^{125}I, 8 μg of CAT for anastrozole and 200 μg for epirubicin and the reaction mixtures were kept at room temperature for 30 min

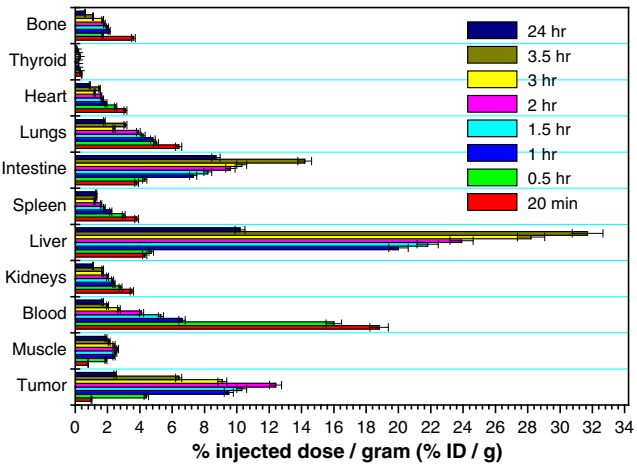


Fig. 11 Biodistribution of radioiodinated anastrozole at different time intervals post injection in albino mice bearing solid tumor

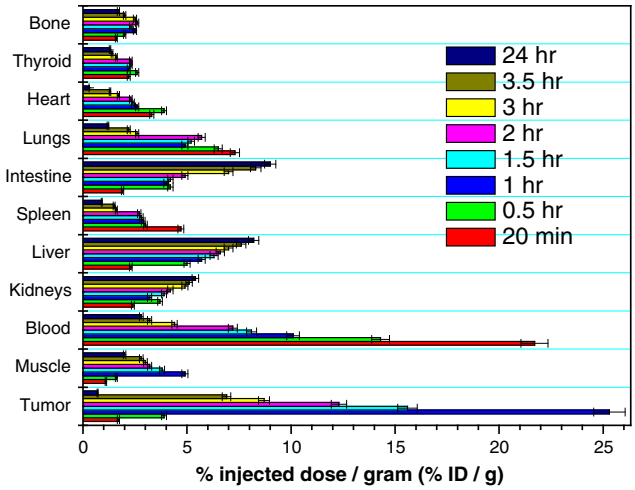


Fig. 12 Biodistribution of radioiodinated epirubicin at different time intervals post injection in albino mice bearing solid tumor

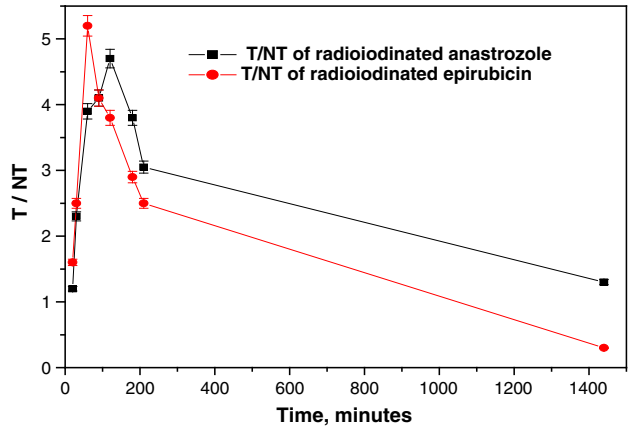


Fig. 13 T/NT of radioiodinated anastrozole or epirubicin at different time intervals post injection in albino mice bearing solid tumor

Data described in Figs. 11 and 12, showed significant high tumor uptake for radioiodinated anastrozole and epirubicin (12.4 % ID/g at 2 h p.i.) and (25.3 % ID/g at 1 h p.i.), respectively. Whole-body clearance of radioactivity was fast as the radioactivity levels for radioiodinated anastrozole and epirubicin in the blood were 6.6 ± 0.1 % ID/g at 1 h and 10.1 % ID/g at 1 h p.i. followed by a steady decline to 2.0 % at 3.5 h and 3.2 % at 3.5 h p.i., respectively. Radioiodinated anastrozole and epirubicin have high Tumor/Blood ratio (T/B) (3 at 2 h and 2.5 at 1 h p.i.), respectively. The high uptake of radioactivities in liver and intestine, clarify that the major elimination route for these compounds is the hepatobiliary system [50, 53]. The low thyroid uptakes of radioiodinated anastrozole and epirubicin confirm their in vivo stability [63]. Radioiodinated anastrozole and epirubicin have high T/NT ratio (4.7 ± 0.1 at 2 h p.i.) and (5.2 ± 0.1 at 1 h p.i.), respectively as shown in Fig. 13.

All the previous data showed a significant high affinity of radioiodinated anastrozole and epirubicin to the solid tumor. The main important properties of imaging radiopharmaceutical to be used as a potential targeting for solid tumor are high tumor uptake, high T/NT ratio and high T/B ratio [6, 9, 11].

Radioiodinated anastrozole and epirubicin have higher solid tumor uptake and T/NT ratio than many new SPECT tracers which have been developed in recent years [6, 12–42].

Some labeled pharmaceuticals such as [^{131}I] Iodomisonidazole (IMISO) and radioiodinated somatostatin analogue [Tyr3]octreotide showed high T/NT ratio but with

low tumor/blood ratio (0.75–1) resulting in restriction of their potentiality as tumor hypoxia imaging agents [6, 9, 11, 24, 43].

Various radiopharmaceuticals were used in detecting breast cancer as ^{99m}Tc-sestamibi (MIBI), which is the most popular agent [37, 72, 73] ^{99m}Tc-MIBI has many disadvantage such as: low T/B ratio, low tumor-to-muscle ratio [74], very rapid blood clearance (few minutes), and rapid tumor washout decreasing the net cellular uptake (2.8 % ID/g) [75].

These results could implement radioiodinated anastrozole and epirubicin as new potential targeting radiopharmaceuticals for solid tumor imaging being selectively accumulated in solid tumor (EAC) with high T/NT ratio and high T/B ratio.

Conclusion

Radioiodinated anastrozole and epirubicin were efficiently radiolabeled at room temperature with high radiochemical yields of 92.9 ± 0.1 and 98.8 ± 0.1 %, respectively. Biodistribution study for radioiodinated anastrozole and epirubicin showed high tumor uptake (12.4 and 25.3 ± 0.1 % ID/g at 2 and 1 h p.i., respectively), high T/NT ratio of 4.7 ± 0.1 at 2 h p.i. for radioiodinated anastrozole and 5.2 ± 0.1 at 1 h p.i. for radioiodinated epirubicin and high T/B ratio (3 at 2 h and 2.5 at 1 h p.i.), respectively. In addition, radioiodinated anastrozole and epirubicin showed in vitro and in vivo stability. So, this research article could implement new diagnostic radiopharmaceuticals (radioiodinated anastrozole and epirubicin) to be used as a selective potential solid tumor imaging agents.

References

1. Harrison L, Blackwell K (2004) Oncologist 9(Suppl 5):31–40
2. Chapman JD, Engelhardt EL, Stobbe CC, Schneider RF, Hanks GE (1998) Radiother Oncol 46:229–237
3. Vaupel P, Mayer A (2007) Cancer Metastasis Rev 26:225–239
4. Hu M, Polyak K (2008) Curr Opin Genet Dev 18:27–34
5. Kurihara H, Honda N, Kono Y, Arai Y (2012) Curr Med Chem 19(20):3282–3289
6. Junbo Z, Qian Y, Jinfeng H, Yan P, Sheng Y, Yining H, Tingting T, Chenchen Y, Xuebin W (2010) J Radioanal Nucl Chem 283:481–485
7. Santos-Cuevas CL, Ferro-Flores G, Murphy CA, Ramirez F, Luna-Gutiérrez MA, Pedraza-López M, Garcia-Becerra R, Ordaz-Rosado D (2009) Int J Pharm 375(1-2):75–83
8. Stober B, Tanase U, Herz M, Seidl C, Schwaiger M, Senekowitsch-Schmidtke R (2006) Eur J Nucl Med Mol Imaging 33(8):932–939
9. Kanchan K, Sudhanand P, Aruna K, Archana M, Manu J, Meera V, Ambikalmajan MRP, Rama M, Natesan R (2007) Appl Radiat Isot 65(4):382–396
10. Schottelius M, Wester H (2009) Methods 48(2):161–177
11. De Barros AL, Cardoso VN, Mota Ld, Leite EA, de Oliveira MC, Alves RJ (2010) Bioorg Med Chem Lett 20(8):2478–2480
12. Faintuch BL, Teodoro R, Duatti A, Muramoto E, Faintuch S, Smith CJ (2008) Nucl Med Biol 35(4):401–411
13. Yang DJ, Wallace S, Cherif A, Li C, Gretzer MB, Kim EE, Podoloff DA (1995) Radiology 194(3):795–800
14. Bakheet SM, Powe J (1998) Semin Nucl Med 28(4):352–358
15. Kubota R, Yamada S, Kubota K, Ishiwata K, Tamahashi N, Ido T (1992) J Nucl Med 33(11):1972–1980
16. Kubota R, Kubota K, Yamada S, Tada M, Takahashi T, Iwata R, Tamahashi N (1995) J Nucl Med 36(3):484–492
17. Yamada S, Kubota K, Kubota R, Ido T, Tamahashi N (1995) J Nucl Med 36(7):1301–1306
18. Sugawara Y, Gutowski TD, Fisher SJ, Brown RS, Wahl RL (1999) Eur J Nucl Med 26(4):333–341
19. Reinhard MJ, Kubota K, Yamada S, Iwata R, Yaegashi H (1997) J Nucl Med 38(2):280–287
20. Gutowski TD, Fisher SJ, Moon R, Wahl RL (1992) J Nucl Med 33:925–928
21. Wahl RL, Quint LE, Cieslak RD, Aisen AM, Koeppe RA, Meyer CR (1993) J Nucl Med 34(7):1190–1197
22. Furumoto S, Shinbo R, Iwata R, Ishikawa Y, Yanai K, Yoshioka T, Fukuda H (2013) J Nucl Med 54(8):1354–1361
23. Henley T, Reddy MP, Ramaswamy MR, Lilien DL (2004) Clin Nucl Med 29(5):322–323
24. Yang DJ, Ilgan S, Higuchi T, Zareneyrizi F, Oh CS, Liu CW, Kim EE, Podoloff DA (1999) Pharm Res 16(5):743–750
25. Carlin S, Zhang H, Reese M, Ramos NN, Chen Q, Ricketts SA (2014) J Nucl Med 55(3):515–521
26. Hoigebazar L, Jeong JM (2013) Recent Results Cancer Res 194:285–299
27. Larson SM (1994) J Nucl Med 35(10):1653–1655
28. Sakr TM, Motaleb MA, Ibrahim IT (2012) J Radioanal Nucl Chem 292(2):705–710
29. Sakr TM, El-Safoury DM, Awad GA, Motaleb MA (2013) J Label Compd Radiopharm 56(8):392–395
30. Sakr TM, Essa BM, El-Essawy FA, El-Mohty AA (2014) Radiochemistry 56(1):76–80
31. Wan W, Yang M, Pan S, Yu C, Wu N (2008) Drug Dev Res 69(8):520–525
32. De Barros AL, Mota Ld, Ferreira Cde A, Oliveira MC, Góes AM, Cardoso VN (2010) Bioorg Med Chem Lett 20(21):6182–6184
33. Mallia MB, Subramanian S, Mathur A, Sarma HD, Venkatesh M, Banerjee S (2010) J Label Comp Radiopharm 53(8):535–542
34. Wang J, Yang J, Yan Z, Duan X, Tan C, Shen Y, Wu w (2011) J Radioanal Nucl Chem 287(2):465–469
35. Machac J, Krynyckyi B, Kim C (2002) Semin Nucl Med 32(4):276–292
36. Hruska CB, Conners AL, Jones KN, Weinmann AL, Lingineni RK, Carter RE, Rhodes DJ, O'Connor MK (2014) Eur J Nucl Med Mol Imag Res 4(1):5–18
37. Hsia CC, Huang FL, Hung LH, Shen LH, Chen CL, Wang HE (2011) Appl Radiat Isot 69(4):649–655
38. Ding R, He Y, Xu J, Liu H, Wang X, Feng M, Qi C, Zhang J, Peng C (2012) Med Chem Res 21(4):523–530
39. Kuchar M, Oliveira MC, Gano L, Santos I, Kniess T (2012) Biorg Med Chem Lett 22(8):2850–2855
40. Rinku B, Dipak KN, Nabanita C, Kamal KH, Sanmoy K, Mita CD (2014) Chem Biol Drug Des 83(1):58–70
41. Breeman WAP, Hofland LJ, Bakker WH, Pluij M, Koetsveld PM, Jong M, Setyono-Han B, Kwekkeboom DJ, Visser TJ, Lamberts SWJ, Krenning EP (1993) Eur J Nucl Med 20(11):1089–1094
42. Du C, Ying H, Zhou J, Jiang J, Liu C, Chen J, Wang X, Hu C (2014) Med Oncol 31(2):833–842

43. Corsetti F, Chianelli M, Cornelissen B, Van de Wiele C, D'Alessandria C, Slegers G, Mather SJ, Di Mario U, Filetti S, Scopinaro F, Signore A (2004) Cancer Biother Radiopharm 19(1):57–63
44. http://www.rxlist.com/arimidex-drug.htm
45. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, Hoctin-Boes G, Houghton J, Locker GY, Tobias JS, Atac Trialists' G (2005) The Lancet 365(9453):60–62
46. Gallagher James (2013) *BBC News*.
47. Simpson ER (2003) J Steroid Biochem Mol Biol 86(3–5): 225–230
48. Iwata H, Masuda N, Ohno S, Rai Y, Sato Y, Ohsumi S, Hashigaki S, Nishizawa Y, Hiraoka M, Morimoto T, Sasano H, Saeki T, Noguchi S (2013) Breast Cancer Res Treat 139(2):441–451
49. Haque R, Ahmed SA, Fisher A, Avila CC, Shi J, Guo A, Craig Cheetham T, Schottinger JE (2012) Cancer Med 1(3):318–327
50. Cuzick J (2005) Anastrozole Drugs Today (Barc.) Pubmed 41(4):227-239.
51. Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L (2004) Pharmacol Rev 56(2):185–229
52. Gewirtz D (1999) Biochem Pharmacol 57(7):727–741
53. Yordanova G, Skrobanskab R, Evangelatovb A (2012) Colloids Surf B Biointerfaces 92:98–105
54. Lettŕe R, Paweletz N, Werner D, Granzow C (1972) Die Naturwissenschaften 59(2):59–63
55. Sheeja KR, Kuttan G, Kuttan R (1997) Amala Res Bull 17:73–76
56. Abu-Zeid M, Hori H, Nagasawa H, Uto Y, Inayama S (2000) Biol Pharm Bull 23(2):195–198
57. Rhodes BA (1974) Semin Nucl Med 4(3):281–293
58. Saha GB (2011) Fundamental of nuclear pharmacy, 5th edn. Springer, New York
59. Puttaswamy M, Sukhdev A, Shubha JP (2009) J Mol Cat A Chem 310(1–2):24–33
60. Valkonen J, Pitkanen I, Pajunen A (1985) Acta Chemical Scandinavca A 39:711–716
61. Adam MJ, Wilbur DS (2005) Chem Soc Rev 34(2):153–163
62. Motaleb MA, El-Kolaly MT, Rashed HM, Abd El-Bary A (2011) J Radioanal Nucl Chem 10:1499–1507
63. El-Azony KM (2010) J Radioanal Nucl Chem 285:315–320
64. Tolmachev V, Bruskin A, Sivaev I, Lundqvist H, Sjöberg S (2002) Radiochem Acta 90:229–235
65. Hunter WM, Greenwood FC (1963) Biochem J 89:114–123
66. Puttaswamy M, Vaz N (2003) Trans Met Chem 28:409–417
67. Ramalingaiah, Jagadeesh RV, Puttaswamy (2007) J Mol Cat A 265:70–79
68. Cynthia BF, Roger KD, Kaumann AJ, Theodore LS, Lutz B (1979) J Mol Pharmacol 12:328–332
69. Rayudu GVS (1983) Radiotracers for medical appl., CRS series in Radiotracers in Biology and Medicine 11.
70. Motaleb MA, Moustapha ME, Ibrahim IT (2011) J Radioanal Nucl Chem 10:1069–1076
71. Khalkhali I, Cutrone JA, Mena IG, Diggles LE, Venegas RJ, Vargas HI, Jackson BL, Khalkhali S, Moss JF, Klein SR (1995) Radiology 196(2):421–426
72. Palmedo H, Grunwald F, Bender H, Schomburg A, Mallmann P, Krebs D, Biersack HJ (1996) Eur J Nucl Med 23(8):940–946
73. Barbarics E, Kronauge JF, Davison A, Jones AG (1998) Nucl Med Biol 25(7):667–673
74. Wackers FJ, Berman DS, Maddahi J, Watson DD, Beller GA, Strauss HW, Boucher CA, Picard M, Holman BL, Fridrich R, Eugemo I, Bernard D, Angelika BD, Leopoldo C, Kenneth M (1989) J Nucl Med 30(3):301–311
75. Vecchio SD, Ciarmiello A, Potena MI, Carriero MV, Mainolfi C, Botti G, Thomas R, Cerra M, D'Aiuto G, Tsuruo T, Salvatore M (1997) Eur J Nucl Med 24(2):150–159