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An approach to develop personalized radiopharmaceuticals by modifying 2-[^{18}F]fluoro-2-deoxy-D-glucose (2-[^{18}F]FDG)

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Abstract

Background: A challenge for modern medicine is the development of clinical protocols for precise diagnosis and therapy. This study aimed to propose a simple method for modification of 2-[^{18}F]FDG used routinely in hospitals in a way, appropriate for patients' personalized radiopharmaceuticals approach.

Material and methods: For the purposes of the presented study chemo selective method for indirect radiofluorination was applauded to custom synthesized aminooxy- and hydrazine-functionalized tetrazines for ^{18}F-glycolation via oxime or hydrazone formation. 2-[^{18}F]FDG produced with medical baby cyclotron in Nuclear Medicine Clinic at the University Hospital St. Marina-Varna, was used. Thin layer chromatography (TLC) and radio TLC were used to follow the progress of synthesis and to determine radio chemical yield (RCY).

Results: The 2-[^{18}F]FDG was modified with two bifunctional tetrazines aminooxy-acetic acid-6-(2-aminooxy-acetoxy)-[1,2,4,5] tetrazin-3-yl ester (Tz1) and {3-[4-(6-phenyl-[1,2,4,5]tetrazin-3-yl)-phenoxy]-propyl}-hydrazine (Tz2) via oxime and hydrazone formation. The radiolabeling was carried out as one-pot reaction with following parameters: temperature 70–75°C; catalyst *p*- diaminobenzene (Cat.); pH = 4.2; time 30 minutes; RCY = 70–99%. The radiolabeled tetrazines are appropriate for further bioorthogonal (pretargeting) strategy by click reactions with trans-cyclooctene conjugated bioactive molecules. The methodology is applicable to standard clinical conditions.

KEY words: 2-[^{18}F]FDG; bifunctional compounds; tetrazine; hydrazone and oxime formation; personal medicine

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Introduction

Cancer continues to be one of the leading causes of death in the world. Despite significant improvements in current treatment options such as surgery, radiotherapy, chemotherapy, and immunotherapy, there are some shortcomings in the treatment of cancer [1]. Early diagnosis of malignant tumors plays a leading role in the choice of treatment approach and survival prognosis of cancer patients [2]. The use of molecular imaging agents is a key milestone in the advancement of medical procedures and is an essential part of ongoing research. At the forefront of molecular imaging is the use of positron emission tomography/computed tomography (PET/CT), which relies on a biomarker labeled with a short-lived positron-emitting radionuclide [3]. Molecular imaging aims to non-invasively visualize, characterize and quantify biological processes at the cellular and molecular level *in vivo* [4]. The technique can not only provide a comprehensive assessment of a patient's condition but also provide guidance for personalized therapy. It enables precise determination of the biopsy site to assess the effect of treatment already performed [5]. In recent years, strategies for the synthesis of (positron emission tomography) PET radiopharmaceuticals have been greatly improved, especially due to the development of various ^{18}F-labeled prosthetic groups designed mainly for chemoselective peptide labeling [6]. In some cases, it is not only desirable to use chemoselective and facile labeling methods, but also to be able to influence biodistribution and tracking characteristics.

A pretargeted PET imaging methodology based on the biorthogonal Diels–Alder click reaction between tetrazine and trans-cyclooctene has been proposed as an option for precision medicine [7].

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The development of this type of reaction offers the possibility of conducting them in a biological environment [8]. The high specificity, inertness to the biological environment, and an impressive rate constant of up to 10^7M-1s−1 compared to other bio-orthogonal reactions make tetrazine ligation the ideal tool for *in vivo* applications [9]. In imaging studies, this ability is necessary to more effectively contrast the target site with surrounding tissues, organs, and biological fluids [10]. The pretargeted methodologies have the potential to produce high uptake of activity in the tumor with extremely low levels of uptake of activity in non-target organs [11]. This allows the use of radionuclides with short half-lives, which are more suitable for clinical applications. Combined with the potential to be applied to imaging, pretargeting may be optimal for theranostic approaches. Pretargeting can also be used to trigger drug release [9]. Several pre-targeting approaches have been tested and have shown better tumor-to-background ratio and thus improved imaging and therapy compared to directly labeled antibodies [12].

The pre-targeting approach consists of two steps. First, target-specific molecules or immunoconjugates are injected and bound to the target site. Radiolabeled compounds are then added to selectively bind to the pretreated molecules at the target site [4]. In principle, pre-targeting can be considered as *in vivo* labeling, as specific molecules are labeled with a radionuclide in the target tissue after *in vivo* administration [13]. This strategy exploits the unique targeting properties of nanomedicines as well as the favorable pharmacokinetics of small molecules, and short-lived radionuclides with favorable radiophysical properties can be used [9]. Pretargeted PET imaging is an emerging and rapidly developing method for monitoring immuno-oncology strategies. In this approach, the time frame of monoclonal antibodies (mAbs) accumulation is temporally separated from the actual imaging process. In particular, a labeled mAb is administered days before a small molecule imaging agent is used to bioorthogonally react with the mAb label. Currently, the most promising reaction for pretargeted imaging is the ligation of tetrazine with trans-cyclooctene (TCO). From a clinical perspective, ^{18}F-labeled Tz would be ideal for PET applications because ^{18}F possesses almost perfect physical characteristics for molecular imaging [14]. The ^{18}F radionuclide can be pre-introduced into one of the two molecules involved in the click reaction, tetrazine or dienophile [15]. The synthesis of a fluorinated tetrazine starting from an ^{18}F-containing prosthetic group is necessary because tetrazines are unstable under the conditions commonly used for direct radiofluorination. The resulting fluorine-18 labeled tetrazine was used for pre-directed PET imaging [16, 17]. The 2-[^{18}F]fluoro-2-deoxy-D-glucose (2-[^{18}F]FDG) continues to be used as a major radiopharmaceutical for imaging glucose metabolism by positron emission tomography [18]. In addition to being a versatile PET radiopharmaceutical, 2-[^{18}F]FDG can also be used as a prosthetic group to indirectly label biomolecules such as peptides, proteins, and others under relatively mild reaction conditions [19]. The glycosylation of biomolecules such as peptides or proteins can improve in vivo pharmacokinetics and blood stability [20]. The 2-[^{18}F]FDG molecule has been reported as a suitable prosthetic group for indirect labeling of various aminooxy-functionalized peptides by chemoselective oxime formation [21]. Oxime and hydrazone formation represent another innovative tool for chemoselective bioconjugation reactions [22]. These reactions offer the ability to circumvent many of the difficulties associated with direct insertion of the [^{18}F]fluoride anion, including its weak nucleophilicity and limited reactivity in proton environments [23]. The oxime ligation is particularly attractive as it is a very efficient and chemoselective reaction proceeding in aqueous systems under mildly acidic conditions. It is compatible with most functionalities of biomolecules and water is the only by-product formed in this process [24]. The radiochemistry of oxime formation and the relatively high stability, both chemical and *in vivo*, allow the potential use of this approach to rapidly generate the desired ^{18}F-labelled macromolecules for application to PET imaging [25]. Combination of both chemoselective (click) reactions where functionalized tetrazines with a free hydroxylamine group capable to form an oxime bond were successfully applied for indirect radiofluorination of monoclonal antibodies [26]. These clickable bifunctional compounds are new-class conjugates with promising applications in nuclear medicine, providing a step towards the development of personalized medicine related to early and accurate diagnosis and precision therapy.

Our purpose is to develop a highly efficient and rapid method for indirect radiofluorination of bifunctional tetrazine moieties with hydroxylamine or hydrazine group by 2-[^{18}F]FDG conjugation, used in standard clinical laboratory settings.

Material and methods

It has become clear that 2-[^{18}F]FDG is the most commonly used radiopharmaceutical for the diagnosis of different types of cancers. At the Clinic of Nuclear Medicine at the University Hospital St. Marina — Varna (Bulgaria), 2-[^{18}F]FDG is the main radiotracer, which is produced on-site using a medical baby cyclotron (ABT Molecular Imaging biomedical, model ABT BG-75), complete with an automated radiochemical module and quality control system. All reagents were obtained commercially and were used without further purification. ^{18}O-enriched water (≥ 98%) ([^{18}O]-H2O) was obtained from Tajyo Nippon Sanso (Japan). Reagents used for 2-[^{18}F]FDG production were obtained from ABX GmbH (Radeberg, Germany). 2-[^{18}F]FDG synthesis cassettes were obtained from ABT Molecular Imaging (Knoxville, TN). 2-[^{18}F]FDG is produced by the more commonly used nucleophilic method for radiofluorination followed by acid hydrolysis with 2M HCl. The process is described in more detail in [27]. The reaction is shown in Figure 1.

The 2-[^{18}F]FDG do not fit the concept of the modern highly specific radiopharmaceutical, due to its glucose metabolism responsible for its unspecific radiolabeling which could be overcome by using radiolabel glucose as a prosthetic group (^{18}F-glycosylation). Conjugation of tetrazine with trans-cyclooctene shows promising rates of the synthesis process, making this click reaction concept very suitable for ^{18}F-labeling as well as for in vivo use in living systems [28]. Bifunctional compounds containing hydroxylamine or hydrazine groups ready to form an oxime or hydrazone bonds were chosen Tz1 and Tz2 (Fig. 2). The resulting radiolabelled Tz1 and Tz2 could be used for future click biorthogonal reactions with trans-cyclooctene bioactive conjugates under physiological conditions [29]. Simple one-pot syntheses carried out in mild conditions for a short time (^{18}F — 109 min) would be applicable to standard clinical conditions for labelling bifunctional tetrazine derivatives (Tz1, Tz2) with 2-[^{18}F]FDG by oxime or hydrazone formation. The developed

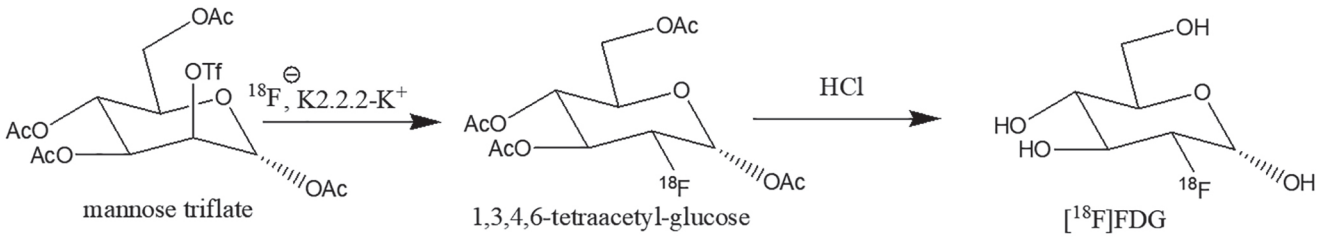

Figure 1. Synthesis of 2-[18F]FDG

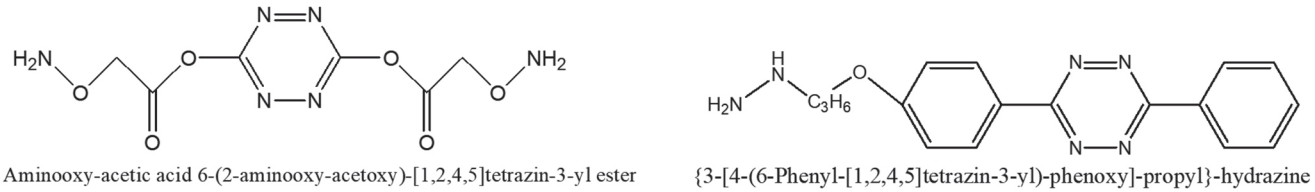

Figure 2. The structure of the used tetrazines; (**A**) Tz1 aminooxy-functionalized tetrazine; (**B**) Tz2 hydrazine-functionalized tetrazine

procedure uses only existing equipment in a hospital facility, which can be a useful tool for personalized diagnosis and treatment of the patient with radiopharmaceuticals.

Aminooxy- and hydrazine-functionalized tetrazines were used, which were custom synthesized, characterized, and provided for the needs of our experiment with corresponding structures shown in Figure 2. Tz1 moiety is appropriate for double labeling respectively will have higher specific activity and Tz2 moiety has a specific spacer that breaks the conjugation between the tetrazine chromophore and the hydrazone functional group. We used the corresponding tetrazines Tz1 and Tz2 for 2-[18F]FDG modification because they have similar physical parameters to the most popular commercially available tetrazine precursors. This suggests a similar effect on pharmacokinetics for *in vivo* pre-targeting and low lipophilicity, which will lead to rapid clearance from non-target tissues and organs. Tz1 is characterized by the following parameters: logarithm of the partition coefficient between n-octanol and water (LogKow) = −4.71; boiling point 402°C; melting point 166°C. And Tz2 with the following: LogKow = 0.64; boiling point 530°C; melting point 226°C. LogKow is a parameter related to the distribution of a substance in octanol/water. A lower value corresponds to better solubility in water. For comparison, we present the parameters of the commercially available Tetrazine-PEG5-NHS ester: LogKow = −5.18; boiling point 888°C; melting point 349°C. The values of the aminooxy-functionalized Tz1 are very similar to those of the presented example, and those of Tz2 are acceptable.

The syntheses were carried out in an approximate reagent ratio of 2-[18F]FDG: Tz1(Tz2) ratio 1–1.5:10^4 at 70°C and p-diaminobenzene was used as catalyst-buffer acidified with acetic acid to pH = 4.2. In the first step of the synthesis, 2-[18F]FDG (0.2 mL) with activity between 5 and 25 MBq and 50 mM buffered catalyst solution (0.5 mL) were mixed. The reaction mixture was heated for 15 min at the appropriate temperature, resulting in the activation of the carbohydrate molecule and the production of the Schiff base. Then 0.1 ml of a 25 μM solution of tetrazine (in acetonitrile) was added and heating was continued for another 15 minutes. Due to the fact that the available radio-HPLC is a component of the automated cyclotron complex, the final products were confirmed only by radio-TLC using ethyl acetate as eluent. The TLC analysis was performed on silica gel plates (ALUGRAM Sobent Silica G/UV254, 40 × 80 mm). After dropping of the samples and subsequent elution with the appropriate solvent, the plates were scanned using a Scan-Ram PET/SPECT radio TLC scanner using Laura software.

Results and discussion

According to the data from the literature the most appropriate conjugation for 2-[18F]FDG were through the formation of oxime and hydrazone bonds and the efficient and chemoselective reaction proceeded in aqueous media under mildly acidic conditions with the presents of catalyst were reported. The goal of the presented study was to check the applicability of such modification under standard clinical laboratory conditions and equipment. The optimal reaction parameters were taken from our previous studies and 50 mM p-diaminobenzene with pH = 4.2 was used as the media of reaction and catalyst [25]. The progress of conjugation was determined by radio TLC as a cheap and available analytical technique included in standard clinic facilities. The radiosyntheses were conducted under two different temperatures for both Tz1 and Tz2 with the idea to check the ability of radio TLC to follow the progress of the reactions. By forming an oxime bond, we modified aminooxy-acetic-6-(2-aminooxy-acetoxy)-[1,2,4,5]tetrazin-3-yl ester. Since the used tetrazine was symmetrically substituted, a mixture of the two 2-[18F]FDG-labelled products was expected. Figure 3 shows the reaction scheme of the synthesis process.

The eluent media (ethyl acetate) that was used allowed to determine each component of the reaction mixture: the color spot

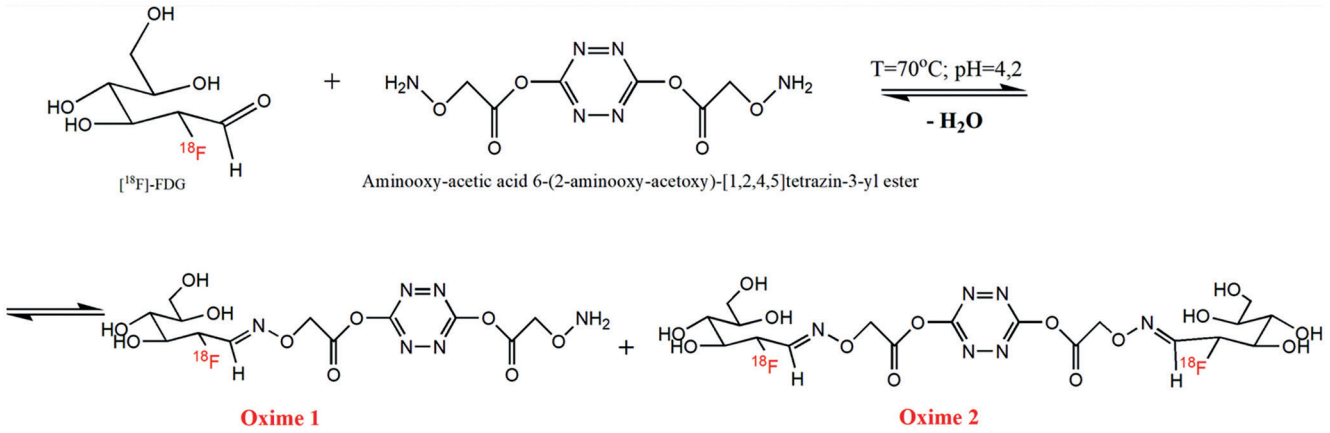

Figure 3. Modification of 2-[^{18}F]FDG by oxime formation

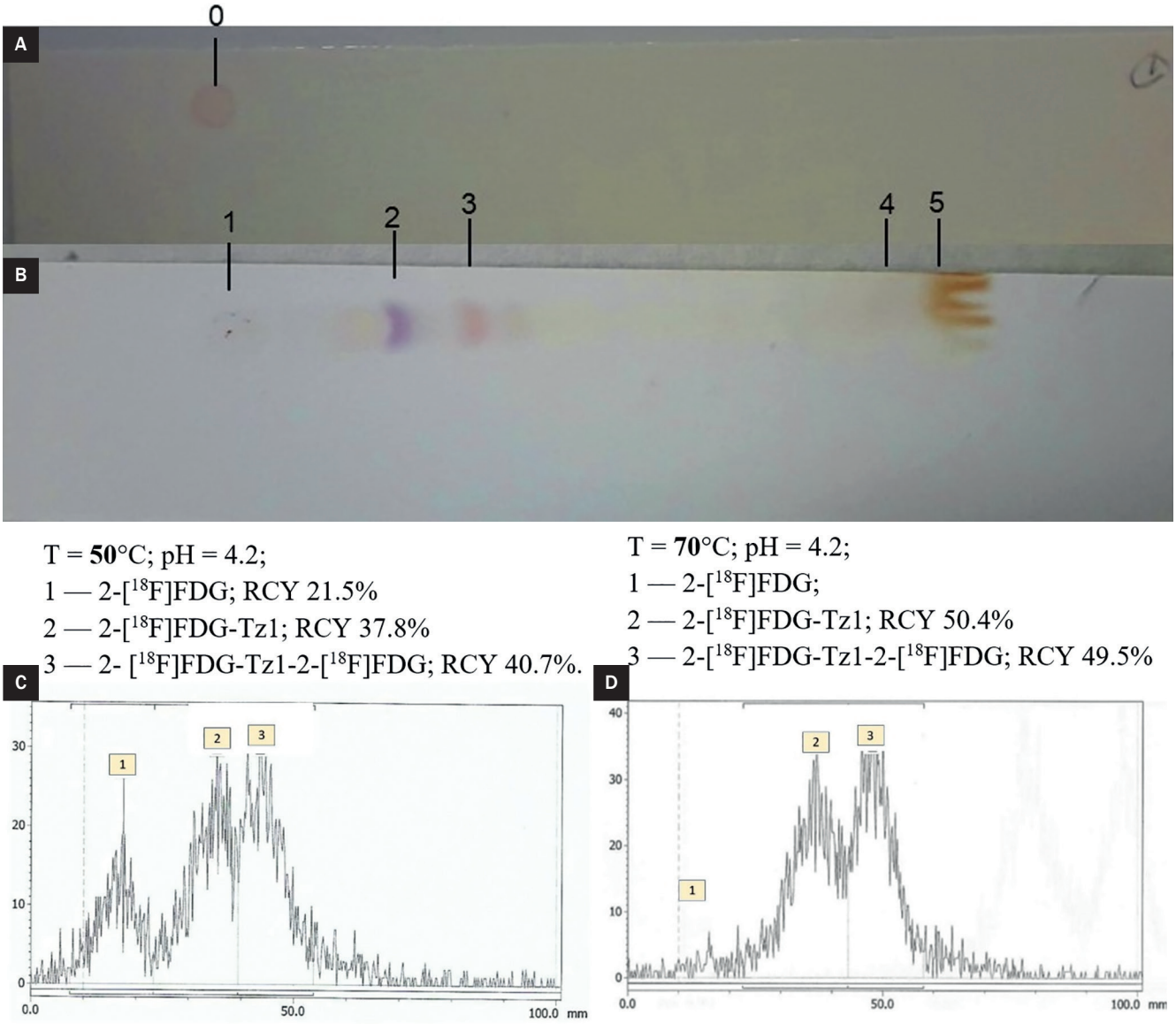

Figure 4. Radio-TLC analysis of the obtained oxime products: **A**) chromatogram before elution; **B**) chromatogram with spot distribution of the reaction components; **C**) radio chromatogram of synthesis at 50°C; **D**) radio chromatogram of synthesis at 70°C

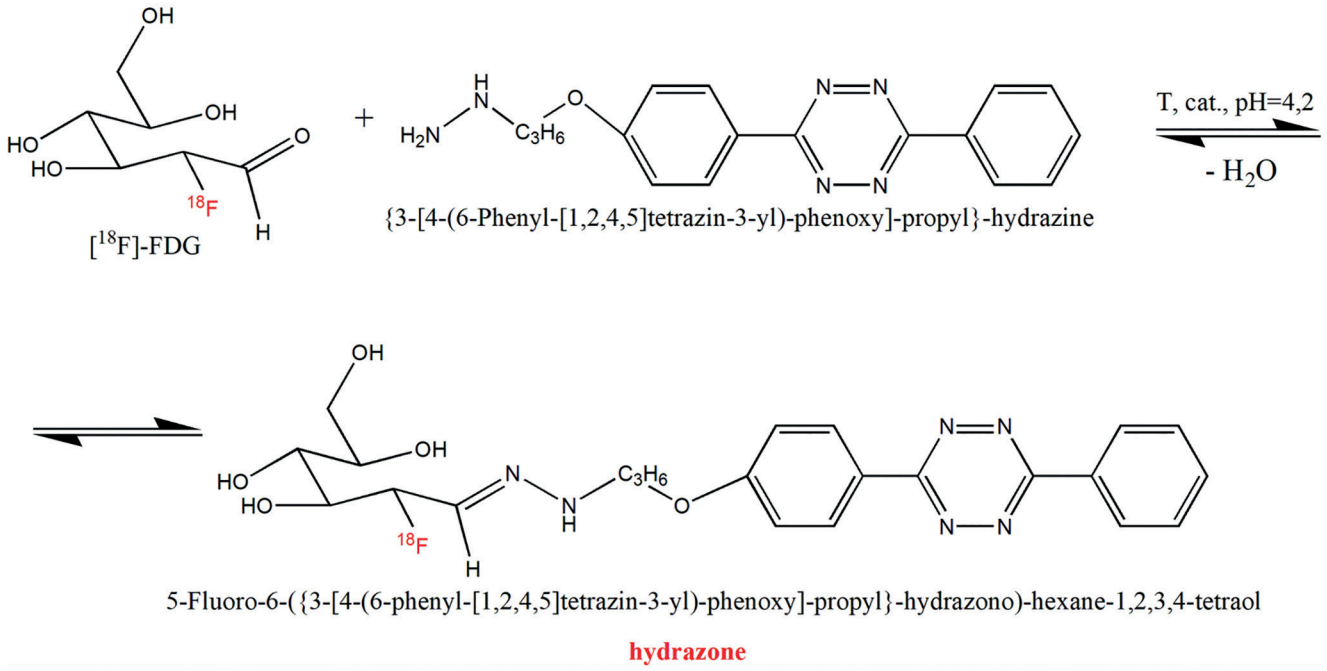

Figure 5. Modification of 2-[18F]FDG by hydrazone formation

of Cat. (brown) moved with the front, followed by a spot of Tz derivative (pink) and radiation peak shown that 2-[18F]FDG remained at the start and the desired products 2-[18F]FDG-Tz1 and 2-[18F]FDG-Tz1-2-[18F]FDG should have different positions of the spot on TLC plate with pink colors and joined radio-peaks. After dropping the samples onto TLC plates and elution them, the following distribution of reaction components was observed: catalyst (brown) and unreacted Tz1 (pink) moved to the front, the unlabeled 2-[18F]FDG (first radiopeak with Rf = 0.085) was retained at the start (at the drop point) and the radiolabeled tetrazines are observed as new colored spots shortly after the start of the plate (purple and light pink — radiopeaks with Rf = 0.282 and Rf = 0.0373). The spot distribution plate is shown in Figure 4. Figure 4a presents the chromatogram before elution, where the colored spot marked with 0 corresponds to the starting reaction mixture. Figures 4B, C, where 1 corresponds to 2-[18F]FDG, 2 and 3 are the resulting oxime products 2-[18F]FDG-Tz1 and 2-[18F]FDG-Tz1-2-[18F]FDG, 4 is Tz1 and 5 is the Cat used. Radio-TLC analyses successfully confirmed the formation of the oxime products with an overall RCY of 78.5% (64.95% decay corrected) and presented two expected products.

In the Figures 4C, D radiochromatograms of two syntheses carried out at different temperatures are compared and at 50°C the reaction does not proceed completely, but increasing the temperature to 70°C leads to excellent results — almost 100% of 2-[18F]FDG from reaction mixture converted. According to the big differences between the value of the Rf of reactants and two radiolabelled products obtained, application of standard column purification would be enough for separation of them and further biorthogonal click reactions application. Such purification was not performed in the presented study due to the small amounts (on the microscale) and low radioactivity that we used. The same algorithm of work was used for radiolabeling of {3-[4-(6--phenyl-[1,2,4,5]tetrazin-3-yl)-phenoxy]-propyl}-hydrazine via hydrazone bonding with 2-[18F]FDG. The reaction scheme is shown in Figure 5.

The radio-TLC analyses confirmed the formation of the hydrazone product. The spot distribution plate is shown in Figure 6A, where 1 and 5 correspond to unlabeled Tz2, 2 is 2-[18F]FDG, 3 is the resulting [18F]FDG-Tz2 product, and 4 corresponds to Cat. used. In the radiochromatograms (Figure 6B, C), the first radiopeak (with Rf = 0.065) is of the unlabelled 2-[18F]FDG, and the second (with Rf = 0.300) is of the obtained hydrazone product 2-[18F]FDG-Tz2.

Figures 6B, C show the radiochromatograms of syntheses carried out at different temperatures and the effect over reaction yield was the same as oxime formation. Negligible RCY at 30°C and increasing to about 70% (not decay corrected) at 70°C. In both temperatures presence of unreacted 2-[18F]FDG was observed in the reaction mixture and the reason comes due to the fact that the hydrazone bond under these conditions hydrolyzed. According to this result the hydrazone radiolabeling even if it was successful, could not be applied for further biorthogonal click reactions. Even though that obtained conjugates for Tz1 was mixture (2-[18F]FDG-Tz1 and [18F]FDG-Tz1-2-[18F]FDG) and for Tz2 (2-[18F]FDG-Tz2) was unstable, a simple protocol fully applicable for clinical laboratories for modification of 2-[18F]FDG via oxime and hydrazone formation was done, accomplished with appropriate technique for observation (radio TLC).

Conclusions

The main advantages of oxime formation via a click reaction between aminooxy- and carbonyl functional groups used for 18F-fluoroglycosylation are its high chemoselectivity, the application of unprotected aminooxy precursors, and the fact that coupling to the carbonyl component can be performed in aqueous media

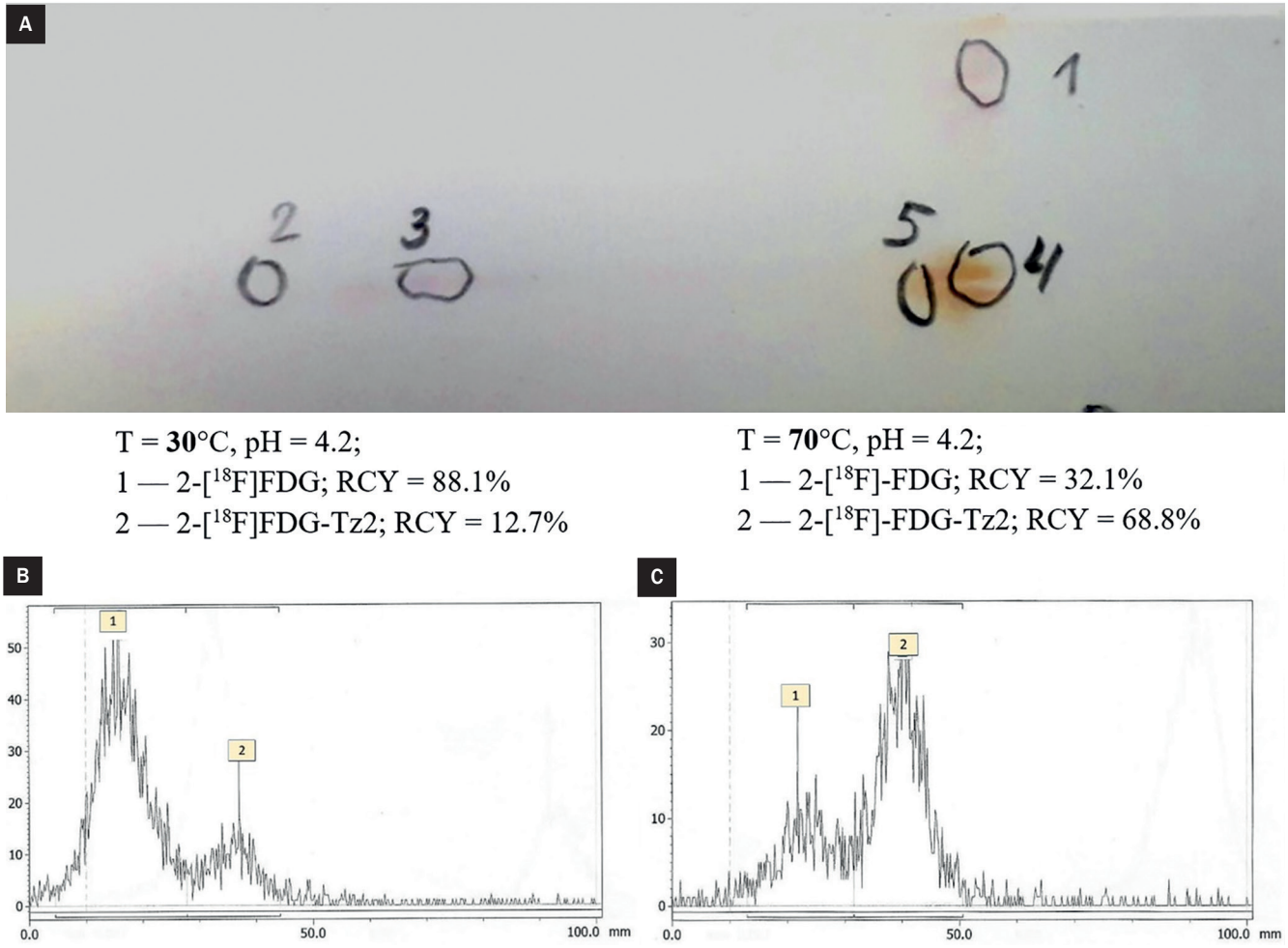

Figure 6. Radio-TLC analysis of the obtained hydrazone product: **A**) chromatogram with spot distribution of the reaction components; **B**) radio chromatogram of synthesis at 30°C; **C**) radio chromatogram of synthesis at 70°C

(pH 4–7) [20]. The acidic environment facilitates the deblocking of the acetal functional group as well as favors the formation of an oxime bond between the aldehyde and aminooxy group [30]. For the formation of oximes and hydrazones, a pH of around 4.5 is usually advantageous [31]. To achieve conjugation of 2-[^{18}F]FDG with peptides, the reaction must be performed at elevated temperature (up to 130°C) and low pH (e.g., pH 2.5) [32]. A facile, rapid, and efficient method for direct labeling of tetrazine derivative (clickable with trans cyclooctene moieties) with 2-[^{18}F]FDG under standard clinical laboratory settings was developed. The synthesis was carried out in a weakly acidic condition — pH = 4.2; at 70°C and in the presence of p-diaminobenzene as a catalyst. The progress of the reactions was monitored by radio-TLC. The temperature had a strong effect on the yield of radiolabeling via oxime and hydrazone conjugations, where RCY = 99.2 ± 0.5% for 2-[^{18}F]FDG-Tz1 + 2-[^{18}F]FDG-Tz1-2-[^{18}F]FDG and RCY = 68.8 ± 0.5% for 2-[^{18}F]FDG-Tz2 were obtained. Using existing facilities and equipment in clinics for specific modification of approved radiopharmaceutical as 2-[^{18}F]FDG will provide a unique toolbox in the hands of physicians and will forward a personalization of therapy in nuclear medicine.

Article information and declarations

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Conflict of interest

The authors declare that there is no conflict of interest regarding this research.

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