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Radiosynthesis of [^{103}Pd]-di-actyl-bis (N^4-methylthio-semicarbazone): a potential therapeutic agent

A. R. Jalilian*, M. Sadeghi, Y.Y. Kamrani, A. Bahrami

Department of Cyclotron and Nuclear Medicine, Nuclear Research Center for Agriculture and Medicine (NRCAM), Atomic organization of Iran, Karaj, Iran

Background: Due to interesting tumor imaging properties of bis-thiosemicarbazones, [^{103}Pd]-di-acetyl-*bis* (N^4-methylthiosemicarbazone) ([^{103}Pd] $ATSM_2$) was prepared according to the analogy of radio copper homologues. ***Materials and Methods:*** Palladium-103 ($T_{1/2}$=16.96 d) was produced via the ^{103}Rh (p,n) ^{103}Pd nuclear reaction with proton energy 18 MeV. The final activity was eluted in form of Pd $(NH_4)_2Cl_2$ in order to react with bis-thiosemicarbazones to yield [^{103}Pd]-labeled compounds. Chemical purity of the final product was confirmed to be below the accepted limits by polarography. The labeled compound was purified by reverse phase column chromatography using C_{18} plus Sep-Pak. The partition co-efficient of the final complex was determined. The initial physico-chemical properties of the labeled compound was compared to those of their copper homologues. ***Results:*** Radiochemical purity of more than 99% using RTLC was obtained (specific activity of about 12500-13000 Ci/mol). The stability of the tracer was checked in final product and human serum, at 37˚C up to 48h. ***Conclusion:*** The labeled compound prepared in this study is probably one of the few new ^{103}pd-radiolabeled compounds which have a potential for future biological studies, regarding its suitable physicochemical stability. *Iran. J. Radiat. Res., 2006; 4 (1): 41-47*

Keywords: *Palladium-103, radiolabeling, bis-thiosemicarbazone complexes, $ATSM_2$, cyclotron.*

INTRODUCTION

Among cyclotron-produced radioisotopes, palladium-103 offers a unique characteristic of X-ray (20-22 keV), and abundant emission of Auger electrons suitable for radiotherapy in form of seeds for permanent interstitial implants [1, 2]. Palladium-103 is mainly produced by proton bombardment of rhodium via ^{103}Rh (p,n) ^{103}Pd reaction at cyclotrons [3].

It has been already shown that Pd-thiosemicarbazone complexes possess interesting anti-proliferative effects on human breast cancer [4, 5], as well as many other tumor cell lines [6-9] by apoptosis induction and/or inhibition on human topoisomerase II.

Moreover it has been shown that bis (thiosemicarbazone) palladium(II) complexes are very effective in inhibiting proliferation in several tumor cell lines sensitive (Hela, Vero, and Pam 212) and resistant to cis-DDP (Pam-ras cells) [10]. These results led us to study the possibility of the use of radiolabelled bis (thiosemicarbazones) palladium (II) complexes as possible therapeutic agents. Bis (4-methylthiosemicarbazonate) palladium (II) complexes have been synthesized previously reported [11], and their molecular structures have also been resolved by X-ray diffraction [10, 11].

As shown in figure 1 when the R1 and R2 groups are both aliphatic or non heterocyclic aromatic, the organic molecule acts as tetradentate ligand in anionic form, the coordination of the thiosemicarbazone results

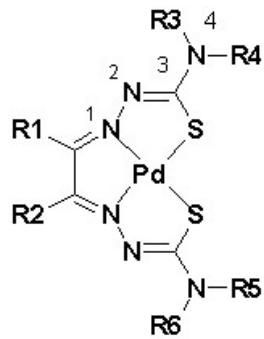

Figure 1. Pd(II) teteradentate thiosemicarbazone anionic complex, R1,R2=CH_3 or Phenyl, R3-R6 randomly can be H and/or CH_3.

Corresponding author:
Dr. Amir Reza Jalilian, Department of Cyclotron and Nuclear Medicine, Nuclear Research Center for Agriculture and Medicine (NRCAM), Atomic Energy Organization of Iran, P.O.Box: 31585-4395, Karaj, Iran.
Fax: *+98 261 4436397*
E-mail: *ajalilian@nrcam.org*

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in the formation of the three five-membered (PdSCNN, PdNCNN, and PdNNCS) chelate rings, all of which are planar within experimental error. The palladium (II) atom has a square planar geometry surrounded by two sulfur and two nitrogen atoms.

The metal environment is similar; thus, in many similar compounds containing various substituents on N^4. Two sulfur and two nitrogen atoms are involved in the coordination, but the coordinated nitrogen atoms are different.

There have been some publications on the antiviral activity of Pd-bis-thiosemicarbazones [12], as well as antitumor effects [13], but none of these studies focused on the production and evaluation of Pd-pyruvaldehyde-bis (N^4-methylthiosemicarbazone) ([Pd]-$ATSM_2$) as possible candidates for therapy in oncology.

According to our knowledge, Pd-103 labeled compounds are rare in the literature. Based on our previous works on the development of therapeutic metal complexes, the idea of developing a therapeutic complex containing an X-ray/Auger-electron radioisotope came into our attention [14]. Thus, we were interested in the preparation of [^{103}Pd]-diacetyl-bis (N^4-dimethylthiosemicarbazone) ([^{103}Pd]-$ATSM_2$) complex as possible therapeutic radiopharmaceutical (figure 2B).

We optimized ^{103}Pd complex formation conditions with $ATSM_2$, as well as developing a solid-phase based purification step suitable for automated production of similar lipophillic palladium-complexes. The lipophillic/hydrophilic constants, as well as 3 day serum stability of the labeled compound was determined.

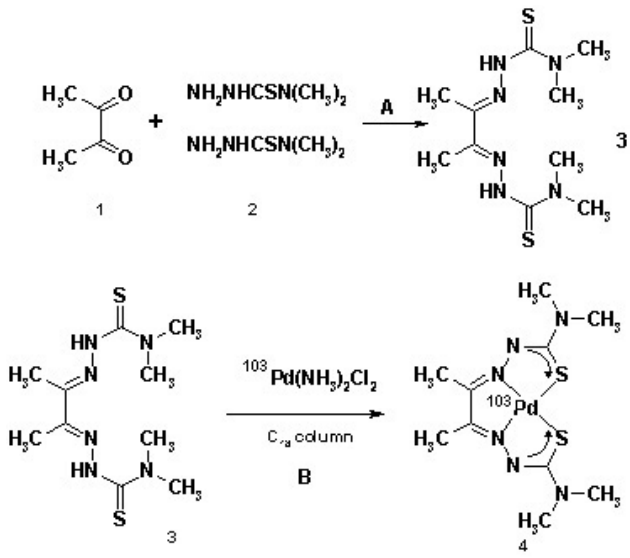

Figure 2. Scheme to the production of [^{103}Pd]ATSM2 3, A; 50°C, AcOH 5%, 2h, B; RT, 30 min, N_2, EtOH:DMSO (1:3).

MATERIALS AND METHODS

Production of ^{103}Pd was performed in the 30 MeV cyclotrons (Cyclone-30, IBA, Nuclear Research Center for Agriculture & Medicine, Karaj, Iran). Rhodium chloride and other chemicals with high purity were supplied by Aldrich Chemical Company (Germany). All exchange resins were provided commercially (Bio-Rad Laboratories, Canada). ^{1}H-NMR spectra were obtained on a FT-80 (80MHz) Varian instrument with tetramethylsilane based on as the internal standard. Infrared spectra were taken on a Perkin-Elmer 781 instrument (KBr disc). Mass spectra were recorded using a Finnigan Mat TSQ-70 spectrometer Thin layer chromatography (TLC) was performed on polymer-backed silica gel (F 1500/LS 254, 20×20 cm, TLC Ready Foil, Schleicher & Schuell®Germany). High purity ethanol and normal saline used for labeling. An authentic sample of Pd-$ATSM_2$ was prepared as standard. The purification of [^{103}Pd] $ATSM_2$ was performed by C_{18} plus Sep-Pak short columns (waters). Ultraviolet spectra were recorded by a Nicolette in methanol at the range of 200-800 nm. Melting points were determined on a Reichert-Jung hot stage microscope and are uncorrected. Radionuclide purity was checked by a Canberra™ high purity germanium (HPGe) detector (model GC1020-7500SL). All calculations and RTLC pieces counting were performed on the same HPGe detector compartment with a fixed geometry.

Production of palladium-103 in [^{103}Pd]Pd $(NH_4)_2Cl_2$ form

The production of Pd-103 in our center has been published recently [15]. On electroplated natural rhodium target on a copper backing

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plate was irradiated at an angle of 6 degrees toward the proton beam in order to achieve higher production yield. The target was dissolved in 6N HCl and purification using a Dowex1X8 (Cl^-)/100-200 mesh column (1.5×10 cm). The resulting high-purity [^{103}Pd]Pd $(NH_4)_2Cl_2$ solution was used directly in the labeling step.

Quality control of the product

Control of radionuclidic purity: The gamma spectroscopy of the dissolved target solution as well as the final sample purified by column chromatography was carried out by an HPGe detector coupled with a Canberra™ multi-channel analyzer.

Chemical purity control: The presence of Cu^{2+} was checked by polarography and colorimetric assays according to USP. The serial diluted copper standard solutions were checked up to our polarography apparatus limit of detection. For colorimetric assay, the limit of detection was 0.5 ppm. Standard copper concentrations were complexed by dithizone forming a pinkish complex [6].

Preparation of diacetyl-bis- N^{4}N^4-dimethylthiosemicarbazone

Bis-thiosemicarbazone was prepared according to the standard method. A stirring mixture 4,4-dimethyl-thiosemicarbazide (238 mg, 2 mmol) in acetic acid solution (5%, prepared by 99% AcOH and MilliQ-H_2O) was heated at 50°C until a transparent solution was formed. Then freshly distilled diacetyl (86mg, 1 mmol, 85µl) diluted (1:3) in acetic acid solution (5%) was added drop wise to the mixture during 5 min under a blanket of N_2. The mixture was stirred for 3-4 h at 50°C. The hot reaction mixture was filtered off through a bi-layer filter paper. The filtered mass was washed with MilliQ-H_2O (50 ml), rectified ethanol (25 ml) and finally heated in a vacuum oven overnight at 75°C. The dried powder was refluxed in 80% acetic acid solution (prepared with MilliQ-H_2O) for 2 h, than the hot mixture was filtered off and the precipitate was washed subsequently with MilliQ-H_2O (50 ml), rectified ethanol (25 ml) and heated at a vacuum oven overnight at 75°C again. The orange-colored fine powder was kept overnight in vacuum. Alternatively, the powder can be crystallized from boiling ethanol to give an orange brilliant powder. Thin layer chromatography showed an R_f of 0.78 using ethyl acetate as eluent (62%) m.p. 198-200°C. ^{1}H NMR (D_6-DMSO) δ (*ppm*) 9.26 (bs, 2H, 2 (NH-N^2)), 3.29 (s, 12H, 2 ($N(CH_3)_2$), 2.13 (s, 6H, 2(CH_3-C=N)). IR (KBr) λ_{max} 3322, 2922, 1527, 1364, 1313, 1199, 1158, 1123. Mass (electrospray) 288.2 (25%) M^+. UV (MeOH) ν_{max}: 319nm.

Preparation of Pd-diacetyl-bis-N^4, N^4-methylthiosemicarbazone complex

$Pd(OAc)_2$ (56 mg, 0.5 mmol) dissolved in ammonia solution (2.5-3 ml) was transferred to a 5 ml-conical borosilicate vial and heated to dryness using a flow of N_2 gas at 50-60°C. Methanol (2.5 ml) was added to the residue, and the mixture vortexed for 5 min at 50°C. H_2ATSM_2 (65 mg, 0.5 mmol) in MeOH (2.5 ml), dissolved in ultrasonic bath at 50°C, was added to the residue and the mixture was stirred at 55-65°C for 3 hours. A purple precipitate was formed just after the addition of the components. The mixture (about 1 ml) was then cooled in an ice bath and the dark precipitate was filtered and filtrate washed by the addition of MeOH and diethyl ether, respectively. The filtered mass was kept under vacuum for 4 hours. Thin layer chromatography of the dark solid in ethyl acetate as eluent showed an R_f of 0.97 (62%) m.p. 275°C. IR (KBr) λ_{max} 2908, 1508, 1378, 1249, 1139, 1083. Mass (electrospray) 258.2 (17%) M^+. UV (MeOH) ν_{max}: 222 nm.

Preparation of [^{103}Pd]-diacetyl-bis-N^4, N^4-methylthiosemicarbazone

[^{201}Pd]$PdCl_2(NH_3)_2$ (3-5 mCi) dissolved in ammoniacal medium obtained above (2.5-3 ml) was transferred to a 5 ml-conical borosilicate vial and heated to dryness using a flow of N_2 gas at 50-60°C. Rectified ethanol (150 µl) was added to the residue and the mixture vortexed for 5 min. Fifty microlitres of thiosemicarbazones in DMSO (1mg/ml, 4 m respectively) was added to the residue and vortxed at 25°C for 3-5 min. The mixture was

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then left at various temperatures (25, 50, 75 and 95°C) for 30 min up to 3 hours to optimize the reaction for best yield. The mixture (about 1 ml) was then cooled in an ice bath and mixed with water (1 ml), and rapidly injected into a C_{18} Sep-Pak column pretreated with 5 ml of ethanol and 2 ml of water. The column was washed with water (4 ml) and purged with a stream of dry N_2. The labeled compound was finally eluted using 500 µl-portions of absolute ethanol and the fractions were counted in Capintec radiometer. The vials containing the maximum radioactivity were mixed and evaporated to one-forth of the starting volume and finally diluted to a 5% solution by addition of normal saline. The active solution was checked for radiochemical purity. The final solution was then passed through a 0.22 µm filter and pH was adjusted to 5.5-7.

Radiochemical purity of [^{103}Pd]-labeled thiosemicarbazones

The RTLC was performed using polymer-backed silica gel layer chromatography using dry ethyl acetate as the mobile phase before (figure 3) and after (figure 4) solid phase purification for both ligands. After developing the TLC, it was cut into 0.5 cm pieces rapidly before drying and TLC pieces were counted in a Capintec radiometer compartment for the ^{103}Pd activity. The radio chromatogram showed a major and distinct radio peak at the R_f of 0.97. Uncomplexed ^{103}Pd in form of $^{103}Pd(NH_3)_2Cl_2$ eluted at R_f=0.0 (figure 3). Thus, the radiochemical yields (more than 98% in each case, number of runs=9) were determined by comparison of uncomplexed ^{103}Pd and the major radio peak at R_f= 0.97.

Stability of [^{103}Pd] labeled compounds in the final product

Stability tests were based on previous reported studies performed for radiolabelled copper complexes[17]. A sample of [^{103}Pd] labeled compounds (1 mCi) was kept at room temperature for 3 hours while checked by RTLC every half an hour. A micropipette sample (5 µl) was taken from the shaking mixture and the ratio of unlabelled radio palladium to [^{103}Pd]$ATSM_2$ was checked by radio thin layer chromatography (eluent: dry ethyl acetate).

Serum stability studies

500 µL of freshly prepared human serum was added to 36.1 MBq (976 µCi) of [^{103}Pd] labeled compounds. The resulting mixture was incubated at 37°C for 5 h, and 5-µL aliquots were analyzed by radio-TLC up to 24h of incubation to determine complex stability.

Determination of partition coefficient

Partition coefficient of [^{103}Pd] labeled compound was measured according to the reported methods [18, 19]. Briefly, [^{103}Pd]$PdATSM_2$ (3 mCi) was transferred to a 5 ml-vial containing 3M (4 ml) sodium following 1 min of vigorous vortex mixing of 1 mL of 1-octanol and 1 mL of isotonic buffered saline (pH=7) with approximately 100 µCi of the radiolabelled palladium complex at 37°C. Following centrifugation at >1200g for 5 min, the octanol and aqueous phases were sampled and counted in an automatic well counter. A 500 µL sample of the octanol phase from this partitioning was repartitioned two to three times with fresh buffer to ensure that trace hydrophilic ^{103}Pd impurities did not alter the calculated *P* values. The reported log *P* values are the average of the second and third extractions from three to four independent measurements, log *P* values represent the mean (standard deviation) of five measurements.

RESULTS AND DISCUSSION

^{103}Pd was prepared by 18 MeV proton bombardment of the ^{nat}Rh target. The target was bombarded with a current intensity of 200 µA for 15 hours (3000 µAh). The chemical separation process was based on a no-carrier-added method. The resulting activity of ^{103}Pd was 685 mCi at the end of bombardment (E.O.B.) and the production yield was 228.3 µCi/µAh.

In order to check the chemical purity, the

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concentration of copper (from target support) was determined by polarography and colorimetric assays. The colorimetric assays demonstrated that the copper concentration was below the internationally accepted levels, i.e. 5 ppm [20].

Since it has been shown that radiolabelled acetyl bisthiosemicarbazone complexes possesses tumor affinity and/or hypoxic seeking in human respectively, we postulated that radiolabelled Pd compound might be used in above studies.

It has already been observed that the combination of thiosemicarbazones with Pd(II) damage DNA and produces synergistic inhibition of tumor growth that may lead to improvements in the effectiveness of cancer chemotherapy [21, 22]. Using radio-palladium with therapeutic particles can enhance this effect.

The palladium complex was prepared in alcoholic/DMSO media. It can be assumed that the metal cation is connected with the ligand in PdL form (when, ATSM$_2$: L). On the other hand the spectral studies have suggested that in the solution, the palladium complexes mostly form planar tetra dentate complexes like cupric cation in a N_2S_2 chelation [6]. The real geometry and stoichiometry of the formed complexes are under investigation.

IR data suggested the N_2S_2 chelation resulting in the loss of 2 protons from the ligand after complex formation with the removal of 3322 cm^{-1}. A shift in UV maximum peaks was observed in ATSM$_2$ after production of Pd-ATSM$_2$, 322 for ATSM$_2$ and 220 for Pd-ATSM$_2$. The deep purple complex, Pd-ATSM$_2$, was soluble in methanol, ethanol and ethyl acetate while the free ligand, ATSM$_2$ showed no dissolution in above solvents. This compound was used as the standard TLC compound for radio thin layer chromatography.

Due to the engagement of several polar functional groups in its structure, labeling of ATSM$_2$ with Pd^{2+} cation affects its chromatographic properties and the final complex is lipophillic. In TLC studies, free palladium fractions, correlate to smaller R_fs (R_f =0.0-0.1), while the labeled complex migrates to the higher R_f (R_f =0.97) and the unlabelled ligand, ATSM$_2$, to the R_f of 0.7. The carrier Pd-ATSM$_2$ complex seems to be lipophillic (with a total charge of zero containing Pd^{2+}), and migrates in normal chromatographic stationary phase to higher R_fs in polar solvents such as acetonitrile and ethyl acetate which is in agreement with our RTLC experiments.

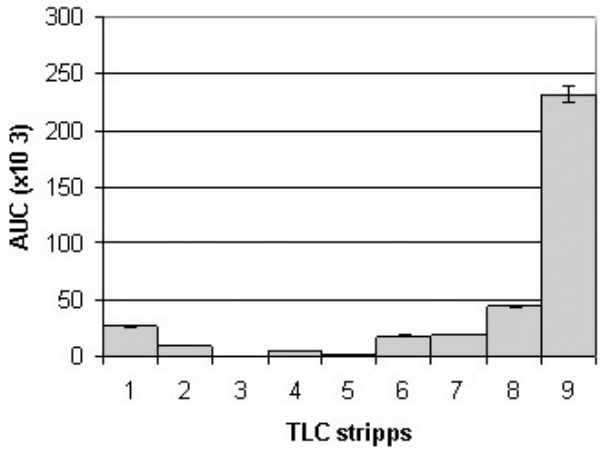

Figure 3. RTLC of the radiolabeling vial before injection into C_{18} Sep-Pak at optimized conditions for [^{103}Pd]ATSM$_2$ production.

Chelation of ATSM$_2$ using Pd seemed to be easily performed even at room temperature in about 30 min, most of the Pd activity incorporated into the ligand with very slight un-complexed free ion, which could be further purified by C_{18} Sep-Pak columns using ethanol as eluent (figure 4).

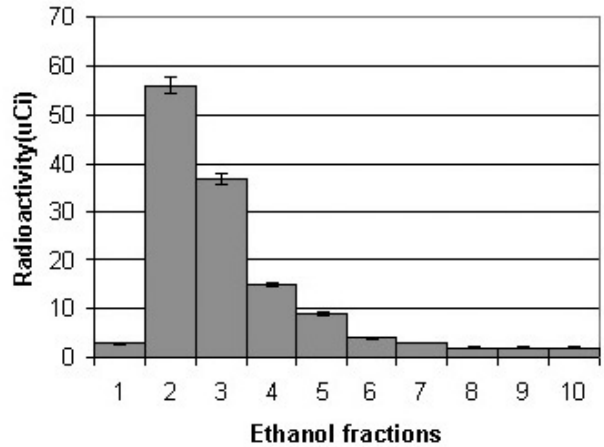

Figure 4. Radioactivity of eluted ethanol fractions from C_{18} at optimized conditions for [^{103}Pd]ATSM$_2$.

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In column elution, most of the radioactivity was eluted after 2-4 ml fractions, finally eluted to a 5% alcoholic solution, after the addition of the normal saline suitable for further biological studies.

The final radiolabelled complex, diluted in normal saline, was then passed through a 0.22 micron (Millipore) filter (filtration was used to sterilize the product). The chemical stability of [^{103}Pd]ATSM$_2$ was high enough at 37°C to perform further studies. RTLC of the final product showed no change in stability and the pattern for [^{103}Pd]ATSM$_2$ and it was not changed during 5 days.

[^{103}Pd]ATSM$_2$ incubated in freshly prepared human serum for 3 days at 37°C, and aliquots of the resulting mixtures were analyzed to determine the kinetic stability of the radiolabelled complex. No loss of ^{103}Pd from the complex was observed during the course of studies, and the radiochemical purity of complex remained at 99% for 3 days under physiologic conditions. Although the complex has a rather lipophil characteristic in purification and TLC, a log P. of 0.419 was measured in octanol/water system

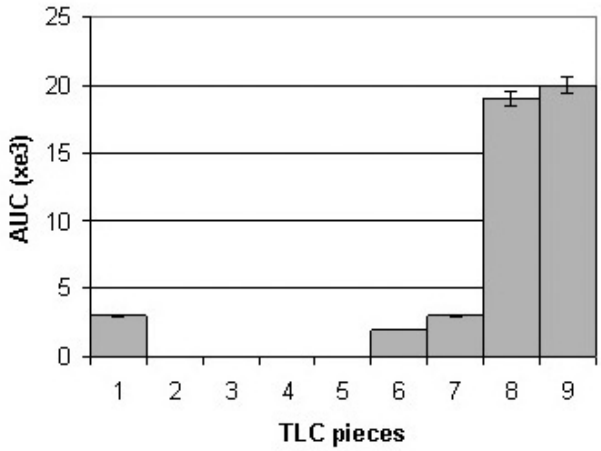

Figure 5. Serum stability of the [^{103}Pd]ATSM$_2$ complex in human serum at 37°C after 3 days incubation.

Total labeling and formulation of [^{103}Pd]ATSM$_2$ took about 30 minutes, with a radiochemical purity of higher than 99% using ^{103}Pd and ATSM$_2$ ligand in methanol:DMSO mixture at room temperature. A significant specific activity (≈12500 Ci/mol) was formed *via* insertion of [^{103}Pd] cation. No unlabelled and/or labeled by-products were observed upon RTLC analysis of the final preparation. The radiolabeled complex was stable in aqueous solutions, as well as human serum at 37°C for at least 24 hours with no significant amount of other radioactive species being detected by RTLC. No traceable amounts of [^{103}Pd]palladium species were traced by RTLC, which showed that radiochemical purity of the [^{103}Pd]ATSM$_2$ was higher than 99%. With respect to the anti-tumor properties of palladium-thiosemicarbazones, [^{103}Pd]ATSM$_2$, with an intermediate half-life, and significant chemical and biological stability, this compound in suitable formulations might be a possible candidate as a therapeutic agent for sensitive tumors, benefiting both from its chemotherapeutic and radio therapeutic properties.

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