

DESIGN, SYNTHESIS, AND BIOLOGICAL TRACING OF ^{99m}Tc-DPDQA AS A POTENTIAL MARKER FOR TUMOR IMAGING

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ABSTRACT

Thalidomide is a sedative drug discovered at the end of the 50s, it showed high anticancer activity so attempts were made to synthesize thalidomide analogs that had fewer side effects than the parent compound. DPDQA showed higher anticancer activities than thalidomide. Labeling of a DPDQA with ^{99m}Tc using Na₂S₂O₄ as reducing agent was performed. The dependence of the radiolabeling yield on the concentrations of DPDQA and reducing agent, pH of the reaction mixture, reaction time, and reaction temperature was studied. Bio-distribution studies in mice with tumor induced in the right thigh were carried out. The tumor infected thigh/contralateral thigh uptake ratio (T/NT) was evaluated. The time for the maximum accumulation of the ^{99m}Tc-DPDQA in the tumor site was evaluated after administration of the compound.

Keywords: Technetium-99m; Thalidomide; labeling; nuclear medicine bio-distribution; Tumor imaging.

Introduction

Molecular imaging is a well-defined technique which can visualize, characterize, and measure the biological processes at the molecular and cellular levels in humans and other living systems. Radioisotope applications become involved in many life disciplines like industry, agriculture, biology, chemistry, and nuclear medicine (Sakr et al. 2014). Nuclear medicine field is interested in the design and synthesis of new radiolabeled agents for diagnosis and therapy (Jurisson et al. 1993). The oxygen level in tissues is a key factor for the evaluation of the criticality of the disease progress and the treatment planning; however, its accurate noninvasive *in vivo* measurement is difficult. Nuclear medicine techniques introduce very good tools able to give informative images about deep and superficial hypoxic tumors using single photon emission computed tomography (SPECT) and positron emission tomography (PET). The corresponding equipment is already in routine use in many cancer centers (Gambhir 2002; Phelps et al. 1975). The development of tumor-sensitive radiotracer markers for noninvasive nuclear medicine imaging will allow hypoxic tumors to be revealed in early stages. Among such markers are ^{99m}Tc -citrofolate (Altiparmak et al. 2010), ^{99m}Tc -N₂S₂-Tat(49–57)-bombesin (Santos-Cuevas et al. 2009), ^{18}F fluoromisonidazole (FMISO) (Rasey et al. 1996; Rischin et al. 2006), ^{123}I -iodoazomycin arabinoside (IAZA) (Parliament et al. 1992), ^{99m}Tc -bombesin (de Barros et al. 2013), and ^{99m}Tc -meropenem (Sakr, Motaleb, and Ibrahim 2012). Due to the excellent physical properties of ^{99m}Tc (ideal half-life of 6.02 h and ideal γ -ray energy of 140 keV and to its low cost and good availability, researchers interest in ^{99m}Tc -labeled compounds as hypoxic tumor radiotracer markers increases (Dilworth and Parrott 1998; Jurisson and Lydon 1999).

Thalidomide is a synthetic glutamic acid derivative originally marketed as a sedative and antiemetic in 1954. However, in 1961 it was quickly withdrawn from distribution when its teratogenic properties were discovered (Franks, Macpherson, and Figg 2004; Bartlett, Dredge, and Dalglish 2004). Speculation that thalidomide teratogenicity is linked to the repression of angiogenesis (D'Amato et al. 1994) resulted in a new wave of clinical investigations that expanded the use of thalidomide for the treatment of various malignancies, including multiple myeloma (MM), melanoma, renal-cell carcinoma and prostate cancer (Thomas and Kantarjian 2000). Therefore, it is hardly surprising that not long after the discovery of the anti-angiogenic properties of thalidomide, and given its obvious clinical benefits, attempts were made to synthesize thalidomide analogs that had fewer side effects than the parent compound (Bartlett, Dredge, and Dalglish 2004). This work is a continuation to our previous efforts of design and synthesis of new anticancer agents (El-Naggar et al. 2017; Eldehna et al. 2017; El-Naggar et al. 2020; Mahdy et al. 2020; El-Helby, Sakr, Eissa, Al-Karmalawy, et al. 2019; El-Helby, Sakr, Eissa, Abulkhair, et al. 2019; Elmetwally et al. 2019; Gaber et al. 2018; Eissa, El-Naggar, and El-Hashash 2016; Eissa et al. 2018; Ibrahim et al. 2018; Eissa et al. 2019; El-Adl et al. 2020; El-Helby et al. 2020; Abbass et al. 2020; Eissa et al. 2020; El-Zahabi et al. 2020).

This research is directed to radiolabel thalidomide analog Fig. 1 for non-invasive assessment of tumor development. The compound was labelled using ^{99m}Tc *via* direct labelling method. Followed by its preclinical biological evaluation in male mice models.

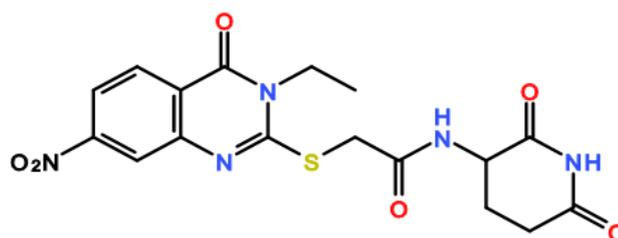


Fig. 1: *N*-(2,6-dioxopiperidin-3-yl)-2-((3-ethyl-7-nitro-4-oxo-3,4-dihydroquinazolin-2-yl)thio)acetamide (DPDQA)

Experimental

Materials and equipment

All chemicals were purchased from Merck Company of AR grade and bi distilled water was used for solution preparation. Deionized water was used in all experiments for the preparation of all solutions. The compound (DPDQA) was obtained as a gift from El Azhar university. Technetium-99m was eluted as $^{99m}\text{TcO}_4^-$ from a $^{99}\text{Mo}/^{99m}\text{Tc}$ generator (radionuclidic and radiochemical purity 99.99 %).

A NaI (Tl) γ -ray scintillation counter (Scaler Ratemeter SR7 model, England) was used for the measurement of gamma-ray radioactivity. Whatman No.1 paper chromatography (PC), Whatman International Ltd, Maidstone, Kent, UK. To determine the radiochemical yield.

Animals.

Swiss Albino mice (male) weighing 20–30 g were purchased from the Institute of Eye Research (Cairo, Egypt). The animals were kept under constant environmental and nutritional conditions throughout the experimental period at room temperature ($22 \pm 2^\circ\text{C}$) with a 12 h on/off light schedule. Animals were kept with free access to food and water all over the experiment.

Labeling procedure.

An accurately weighed portion of DPDQA was transferred to an evacuated penicillin vial. The required amount of the $\text{Na}_2\text{S}_2\text{O}_4$ was added, and the required pH of the mixture was adjusted with 0.1 N NaOH and phosphate buffer, after which the volume of the mixture was adjusted to 1 mL with nitrogen-purged distilled water. 1 mL of freshly eluted $^{99m}\text{TcO}_4^-$ (~ 400 MBq) was added. The reaction mixture was vigorously shaken and allowed to react at room temperature for 15 min (**Sanad, El-Tawoosy, and Ibrahim 2017**). When studying the effect of various factors on the reaction, all the variables were kept constant except the factor being studied.

Labeling yield assay

The labeling yield and the in vitro stability of ^{99m}Tc -DPDQA complex were assessed by ascending paper chromatography (PC) to evaluate the percent of ^{99m}Tc -DPDQA, free $^{99m}\text{TcO}_4^-$ and reduced hydrolyzed ^{99m}Tc colloid species as follows (Motaleb 2007; Hall et al. 1998; Kashani, Cooper, and Das 2004).

For each labeling experiment, ascending chromatography was carried out using two strips of Whatman No.1 paper chromatography (13 cm long and 0.5 cm wide). Two drops of the reaction product were spotted on line (origin) at distance of 2 cm from the bottom. One strip was developed with acetone and other strip was developed with ethanol: water: ammonium hydroxide mixture (2:5:1, v/v/v). After complete development, the two strips were dried, cut into 1 cm pieces and separately counted using the NaI(Tl) gamma-ray scintillation counter to determine the ratio of the hydrolyzed ^{99m}Tc , free $^{99m}\text{TcO}_4^-$ and ^{99m}Tc -DPDQA complex. Each experiment was repeated three times.

Acetone, as developing solvent, was used to develop one paper strip where the free $^{99m}\text{TcO}_4^-$ moved with the solvent front ($R_f = 1$), while ^{99m}Tc -DPDQA and reduced hydrolyzed technetium colloid remained at the origin. A mixture of ethanol: water: ammonium hydroxide (2:5:1, v/v/v) as developing solvent to develop another paper strip where reduced hydrolyzed technetium colloid remained at the origin ($R_f = 0$) while free $^{99m}\text{TcO}_4^-$ and ^{99m}Tc -DPDQA species migrated with the solvent front ($R_f = 1$). The labeling yield percent of ^{99m}Tc -DPDQA complex was determined as follows:

$$\% \text{labeling yield} = 100\% - (\% \text{Free } ^{99m}\text{TcO}_4 + \% \text{Reduced hydrolyzed } ^{99m}\text{Tc colloid})$$

In vitro stability of ^{99m}Tc -substrate complex

The in vitro stability of ^{99m}Tc -DPDQA complex was investigated as a function of time up to 24 h post labeling.

Bio distribution 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.

Tumor hypoxia induction in mice

The bio-distribution study was done in tumor hypoxia bearing mice. The parent tumor line (Ehrlich Ascites Carcinoma) was withdrawn from 7 days old donor male Swiss Albino mice and diluted with sterile physiological saline solution to give 12.5×10^6 cells/ml. Exactly 0.2 ml solution was then injected intramuscularly in the right thigh to produce a solid tumor evaluated in male Albino Swiss mice weighting 20–30 g. The animals were maintained till the tumor development was apparent (4–6 days).

Bio distribution study

Target organ uptake of ^{99m}Tc -DPDQA was evaluated in male Albino Swiss mice weighing 20–30 g. A volume of 0.2 mL of ^{99m}Tc -DPDQA containing 185–1850 kBq was intravenously injected in the tail vein of mice. The animals were anesthetized by chloroform at the predesigned time interval and their body organs and fluids were separated, weighted and their radioactivities were assayed using a NaI(Tl) gamma-ray scintillation counter. Biological distribution of ^{99m}Tc -DPDQA in mice organs and fluids was studied as a function of time, 30, 60, 120 and 180 min post injection. The percentages of the injected dose/g organ or fluids were calculated. T/NT ratio are calculated and compared.

Results and discussion

Factors affecting the percent labeling yield of ^{99m}Tc -DPDQA complex

Effect of substrate amount

DPDQA was labeled with technetium-99m using the direct technique, As shown in Fig. 2, at low DPDQA amount (0.1 mg) the labeling yield was small $75 \pm 0.6\%$. This low labeling yield was due to the DPDQA amount was insufficient to react with the reduced form of technetium-99m forming ^{99m}Tc -DPDQA complex so; the remaining reduced form of technetium-99m was converted to reduced hydrolyzed technetium colloid. By increasing the DPDQA amount to 0.5 mg, the labeling yield was maximized to become $92 \pm 0.3\%$ which was significantly higher than other yields. By increasing the DPDQA amount over the optimum values, the labeling yield was slightly decreased to $91.5 \pm 0.2\%$ at .6 mg DPDQA.

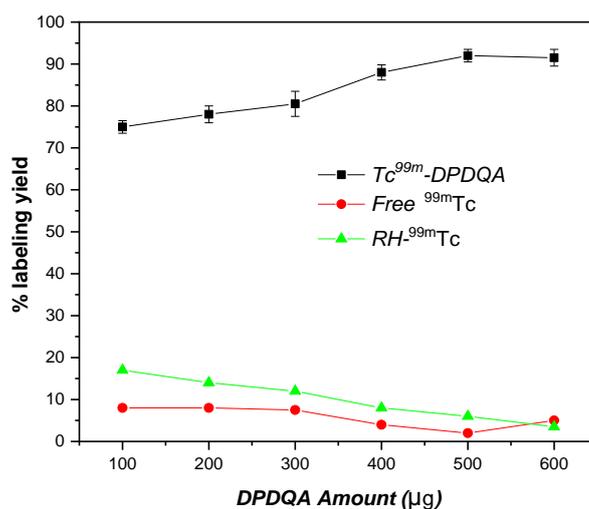


Fig. 2: Variation of the labeling yield of ^{99m}Tc -DPDQA as a function of DPDQA amount.

Reducing agent ($\text{Na}_2\text{S}_2\text{O}_4$) amount.

The effect of the reducing agent ($\text{Na}_2\text{S}_2\text{O}_4$) amount on the yield of $^{99\text{m}}\text{Tc}$ -DPDQA is shown in Fig. 3. At the $\text{Na}_2\text{S}_2\text{O}_4$ amount of 100 mg, the yield of $^{99\text{m}}\text{Tc}$ -DPDQA was low, $64 \pm 1.5\%$, because of incomplete reduction of $^{99\text{m}}\text{TcO}_4^-$ (the relative content of free $^{99\text{m}}\text{TcO}_4^-$ was $25 \pm 1.5\%$). The labeling yield significantly increased as the $\text{Na}_2\text{S}_2\text{O}_4$ amount was increased from 100 to 500 mg, reaching a maximum of $92 \pm 0.6\%$. With a further increase in the $\text{Na}_2\text{S}_2\text{O}_4$ amount, the labeling yield decreased (to $86 \pm 1.1\%$ at 600 mg of $\text{Na}_2\text{S}_2\text{O}_4$).

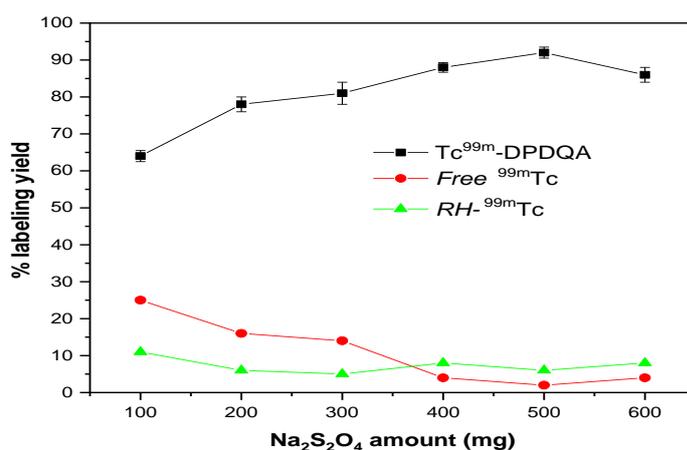


Fig. 3: Effect of $\text{Na}_2\text{S}_2\text{O}_4$ amount on the formation of $^{99\text{m}}\text{Tc}$ -DPDQA complex

Effect of pH of the reaction mixture

Data presented in Fig. 4 reflects the results obtained from the labeling of DPDQA with technetium-99m at different pH values (5–11). The labeling yield of the $^{99\text{m}}\text{Tc}$ -DPDQA is maximum and significantly higher than other yields ($p < 0.001$) at pH 8 ($92 \pm 0.3\%$). At pH below or above the optimum pH, the labeling yield is significantly decreased by forming reduced hydrolyzed technetium-99m and free technetium-99m which are the main radiochemical impurities.

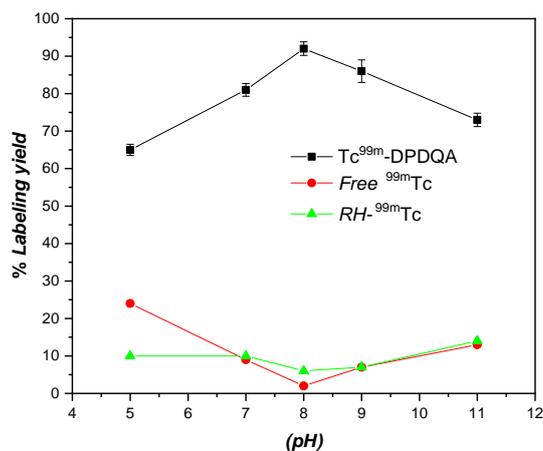


Fig. 4: Effect of pH of the reaction medium on the percent labeling yield of ^{99m}Tc–DPDQA complex

Effect of reaction time

The labeling yield of ^{99m}Tc–DPDQA complex was studied at different reaction times (5–60 min). Figure 5 shows that the formation of ^{99m}Tc–DPDQA complex has started relatively slowly with labeling yield of 80 ± 0.19 % at 5 min. The maximum yield of ^{99m}Tc–DPDQA complex (92 ± 0.03 % at 15 min) is significantly higher than yields at 5 min ($p < 0.001$) and not significantly difference with yields at 45 and 60 min ($p > 0.05$) because the labeling yield reaches the saturation value and not affected by increasing the reaction time above 15 min.

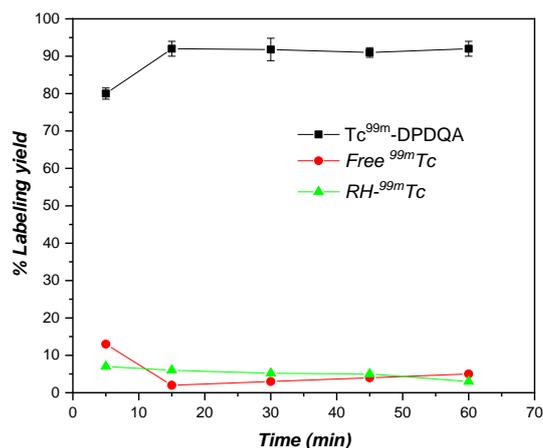


Fig.5 Radiochemical yield of ^{99m}Tc-DPDQA as a function of time.

Effect of reaction temperature.

As shown in Fig. 6, the radiochemical yield of ^{99m}Tc -DPDQA complex was maximal (92%) at room temperature (25°C) and gradually decreased with increasing temperature, reaching 82% at 60°C.

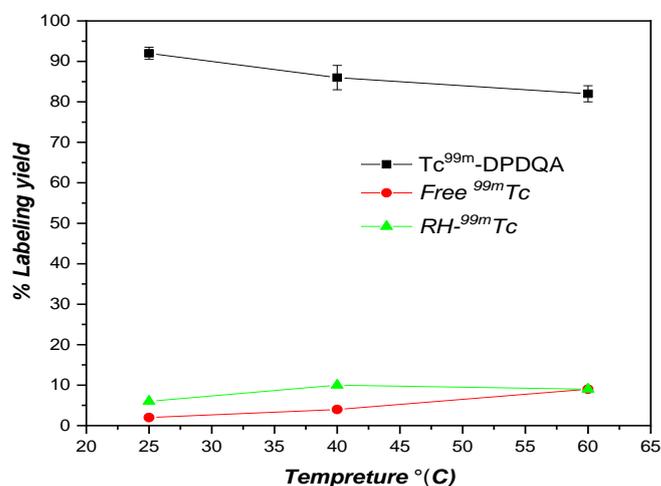


Fig. 6. Radiochemical yield of ^{99m}Tc -DPDQA as a function of reaction temperature.

***In-vitro* stability of ^{99m}Tc -DPDQA complex**

The stability of ^{99m}Tc -DPDQA complex was studied in order to determine the suitable time for injection to avoid the formation of the undesired products that result from the radiolysis and oxidation of ^{99m}Tc -DPDQA during storage time post labeling with technetium, besides to the effect of ionizing gamma-radiation (radiolysis). These undesired radioactive products may be accumulated in non-target organs. The results show that ^{99m}Tc -DPDQA complex was stable at a maximum yield of $92 \pm 0.3\%$ with no significant decrease up to 24 h ($p [0.05]$).

Bio-distribution.

Table 1 shows the bio-distribution of ^{99m}Tc -DPDQA in tumor bearing mice (% ID/g) at 30, 60, 120 and 240 min post injection. As can be seen, ^{99m}Tc -DPDQA was mainly excreted via both urinary and hepatobiliary pathways, as kidneys showed $15.5 \pm 0.7\%$ ID/g at 30 min, liver showed $13.6 \pm 0.4\%$ ID/g at 30 min, and intestine showed $10.4 \pm 0.4\%$ ID/g at 240 min. ^{99m}Tc -DPDQA was not specifically accumulated in any organs other than the tumor tissue. The main parameter for evaluating the selectivity and sensitivity of ^{99m}Tc -DPDQA as tumor imaging agent is the target/non target (T/NT) ratio between the tumor muscle (mouse right leg muscle) and normal muscle (mouse left leg muscle). Table 1 shows the T/NT ratio of ^{99m}Tc -DPDQA in tumor bearing mice, which indicates that ^{99m}Tc -DPDQA is highly selective to the tumor cells.

The T/NT ratio reaches the highest value of ~ 19 at 30 min post injection. Thus, ^{99m}Tc -DPDQA as a potential radiotracer marker for tumor is not inferior to many other agents (the T/NT ratio and time post injection, respectively, are indicated: ^{99m}Tc -BnAO-NI

(2.59, 2 h), $^{99m}\text{Tc}(\text{CO})_3$ -labeled chlorambucil analog (3.2, 3 h), $^{99m}\text{TcN-MAG-AMCPP}$ (1.83, 1 h), $^{99m}\text{TcDETA}$ (2.47, 4 h), $^{99m}\text{Tc-TETA}$ (2.45, 4 h), $^{99m}\text{TcTEPA}$ (2.91, 4 h), [$^{99m}\text{Tc}(\text{CO})_3(\text{IDA-PEG3-CB})_2$] (3.45, 3 h), and $^{99m}\text{Tc-nitride-pyrazolo}[1,5-a]\text{pyrimidine}$ (2.2, 60 min) (Mallia et al. 2010; Wang et al. 2011; Satpati et al. 2009; Ding et al. 2012).

Table 1: *In vivo* bio-distribution study of ^{99m}Tc - DPDQA in tumor bearing Albino mice at different time intervals post injection.

	30 min	1 hr	2 hr	4 hr
Organs	gm	gm	gm	Gm
Blood	14.367681	9.20042	6.204793	4.50922
Kidneys	15.55	26.5169	52.71813	15.3975
Liver	13.686357	7.77152	5.734043	7.89652
Spleen	4.0661527	2.3109	2.338	1.78791
Intestine	5.0060673	6.18985	6.486986	10.4966
Stomach	3.032861	4.02577	4.268558	6.30051
Lungs	9.5695064	3.75494	3.462275	4.50854
Heart	5.6877382	2.63965	2.661199	1.39136
Bone	1.395553	1.60748	2.053596	4.54141
Muscle	0.2414248	0.74208	1.120148	1.36539
Tumor	4.7489072	4.80114	7.46982	3.27379
T/NT	19.705	6.47	6.669	2.398

Conclusion.

The thalidomide analog (DPDQA) was radiolabeled with ^{99m}Tc by the direct labeling technique with a high yield, $92 \pm 1\%$. The complex ^{99m}Tc - DPDQA showed high *in vitro* stability and selective uptake in tumor cells (T/NT ~ 19 at 30 min post injection). ^{99m}Tc - DPDQA shows promise for clinical non-invasive evaluation of tumor *in vivo*.

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التصميم والتشيد والتتبع البيولوجى للمركب التكنسيوم-99م-DPDQA كعامل محتمل لتصوير الاورام

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الملخص :

الثاليدوميد هو عقار مهدئ اكتشف فى الخمسينيات و اكتشف ان له تاثر مضاد للسرطان لذا قد تمت محاولات لتخليق نظائر لهذا العقار لها اثار جانبية اقل. و قد اظهر النظير DPDQA تاثير مضاد للسرطان اقوى من الثاليدوميد. و تم ترقيم DPDQA باستخدام ^{99m}Tc بواسطة Na₂S₂O₄ كعامل مختزل. و تمت دراسة تاثير تركيز DPDQA و تركيز Na₂S₂O₄ و تاثير ال PH و تاثير زمن التفاعل و درجة الحرارة على ناتج الترقيم. و قد تمت دراسة التوزيع الحيوي للعقار فى فئران مصابه بالسرطان فى عضله الفخذ الايمن. و قياس نسبة تشبع العضله المصابه الى نسه تشبع العضله السليمه بالعقار. و قياس الزمن الازم للوصول الى اعلى نسبه من العقار فى المكان المصاب.

كلمات المفتاح: تكنسيوم-99م - ثاليدوميد - ترقيم - طب نووى - توزيع حيوى - تصوير الورم