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Reagents Based on Silicon Nanoparticles and Therapeutic Nucleosides for Imaging and Targeted Exposure on Tumour Tissues

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Abstract

In recent years, resulting from research aimed at minimizing a harmful side effect on the patient, a new class of drugs that ensure both therapeutic effects on the tumour and its imaging has been developed. These drugs have been referred to as teranostics and the methodology for their use is defined as theranostics, *i.e.* an area of integrated medical science that combines therapy and diagnostics to treat diseases during the generic procedure. A wide variety of nanoconstructions for theranostics presented by different nanostructures, such as carbon nanotubes, magnetic, gold, polymeric nanoparticles, silica nanoparticles, *etc*., open up wide prospects for their use in oncology.

This review focuses on recent advances in the area of development of approaches towards making nanocomposite-based teranostics, whereat therapeutic nucleosides act as the main therapeutic agents, while silicon-based nanoparticles – as targeted delivery means. According to critical analysis results, generalizations about possible ways to improve the effectiveness of therapy and imaging of anticancer drugs based on the examined nanoconstructions have been made.

Keywords: teranostics, silica nanoparticles, chemical modification, azide-alkyne Huisgen cycloaddition, therapeutic nucleosides, tumour imaging

INTRODUCTION

Enhanced life time and simultaneous increased anthropogenic pressure on humans results in an increased portion of oncological diseases. In modern medical science, the standard of treatment of malignancies is a comprehensive multidisciplinary approach, including surgical tumour removal followed by the use of adjuvant methods of radiation and chemotherapy. Lately, due to the desire to minimize adverse side effects in patients, a new class of drugs that both ensure therapeutic action on tumour and its imaging has appeared. These drugs have been referred to as teranostics and the methodology for their use is defined as theranostics, *i.e.* an area of integrated medical science that combines therapy and diagnostics to treat diseases during the general procedure. A wide variety of nanostructures for theranostics, such as carbon nanotubes, magnetic, gold, polymeric nanoparticles, silica nanoparticles, *etc*., open up wide prospects for their use in oncology. Figure 1 gives the teranostic structure in the overall view.

Teranostics may contain both elements, each of which is responsible for a certain function (basic particle, such as a carrier, a therapeutic agent, a visualizing factor, a molecule accountable for directional delivery) and those

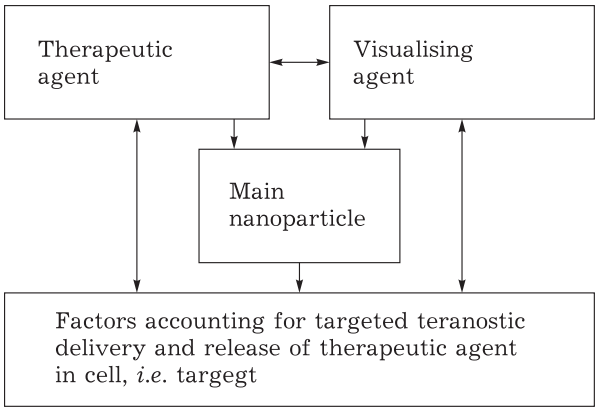


Fig. 1. Overall scheme for teranostic design.

that may account for several functions. In this connection, for example, the albumin molecule may act as the basic nanoparticle and a tumour-orienting function [1, 2].

The explosive nature of increasing the number of publications related to teranostics does not allow considering all aspects of their design, synthesis, and application. This review deals with the main approaches to synthesis of silica nanocomposite-based teranostics, where therapeutic nucleosides and their phosphorylated analogues are as the main therapeutic agents.

Silica nanoparticles as a framework to generate nanoscale anticancer teranostics

Attention to silica nanoparticles as a basic framework during making nanocomposite drugs is driven by a number of their properties. This is primarily due to low toxicity and biocompatibility [3–5] and wide-ranging capabilities of surface modification for immobilization by various compounds and, what is not unimportant, an opportunity to generate drugs for oral use based thereon [6].

Silica nanoparticles (SNP) used for biomedical applications may be classified as mesoporous or non-porous (solid) SNP. Mesoporous SNP characterized by the presence of pores of 2–50 nm in size are widely used when making nanoconstructions for the delivery of therapeutic agents due to physical or chemical adsorption [7, 8]. In the case of non-porous SNP, low-molecular-mass compounds are attached to the SNP surface by the covalent method. The targeted release of low-molecular-mass compounds from mesoporous SNP may be monitored by modifying the inner pore surface to change the affinity of binding [9], which may ensure the directed release of therapeutic agents under the influence of external triggers (*e.g.*, pH, redox potential, *etc.*) [10]. While in the case of porous silica, the cleavage of low-molecular-mass compounds is reached by means of cleavable linker groups. An opportunity to use mesoporous SNP for biomedical purposes is discussed in detail in reviews [11, 12]. Such nanoparticles have a much larger capacity due to a more developed surface, however, when designing therapeutic nanoconstructions and teranostics, there is a need for a monitored addition of several different ligands to the nanoparticle followed by the targeted release of only a therapeutic agent, which may be achieved only through covalent ligand addition to the nanoparticles through linker groups of different nature.

Nanoparticle size is a parameter of critical importance when selecting the basic platform. It is demonstrated that the size of tumour interendothelial contacts vary in a range from 40 to 80 nm, whereas in healthy tissues this parameter is less than 8 nm [13]. This and a number of other anatomical and pathophysiological differences of tumour and normal tissue ensure the accumulation of nanoparticles of a certain size due to the so-called effect of increased permeability and retention (EPR-effect, enhanced permeability and retention (EPR) effect) [14].

Currently, a series of investigations aimed at determination of the optimum shape and size of silicon nanoparticles have been carried out. For example, it has been demonstrated that SNP shape has a substantial effect on the time of their presence in blood flow and penetration efficiency into tumour cells. Spherical nanoparticles are quicker excreted from blood stream than spindle-shaped SNP or silicon nanotubes [15]. In addition, they as just worse penetrate into tumour tissues [16]. However, these differences are not dramatic. Given the fact that preparation of spherical DNA of a given size is much easier, their use in generating therapeutic nanoconstructions may be regarded justified.

Spherical SNP can be readily prepared on a large scale with discrete sizes of monodispersed particles resulting from the condensation reaction of tetraethylorthosilane (TEOS) or tetramethylsilane (TMOS). It was demonstrated in

[17] that condensation of TEOS or TMOS in an aqueous alcohol solution in the presence of NH_3 as a base, depending on the molar ratio of H_2O and NH_3, resulted in the formation of monodispersed SNP (Fig. 2). Research on the accumulation of different diameter silicon nanoparticles in tumour tissues [18–20] makes it possible to conclude that nanoparticles with sizes in the 20–50 nm range, depending on the type of tumour, are optimum. However, there are no data in the literature regarding the effect of the decoration with various ligands (*e.g.*, widely used polyethylene glycol) on the optimum SNP size.

The unique chemistry of silica allows readily modifying SNP surface by a wide range of functional groups [21]. Figure 3 gives some of them.

Paper [22] suggested a single-step procedure for the synthesis of epoxy group-containing SNP (Fig. 3, R = 3,4-epoxy cyclohexane, $n = 0$). Treatment of the resulting nanoparticles with proteins or nucleic acids results in the formation of stable bio-nano conjugates.

The introduction of azido groups [23], either directly or during primary ligation, or moieties with a terminal triple bond [24] additionally expands the range of ligands that may be attached to nanoparticle surface using azide-alkyne cycloaddition reactions.

Despite the fact that a series of works used also proposed other procedures for chemical modification of surface [25–27], the primary functionalization of silicon nanoparticles with aliphatic amino- groups became the most common [28]. The presence of amino groups allows you to enter a wide range of ligands using standard procedures; herewith, the presence of facile and

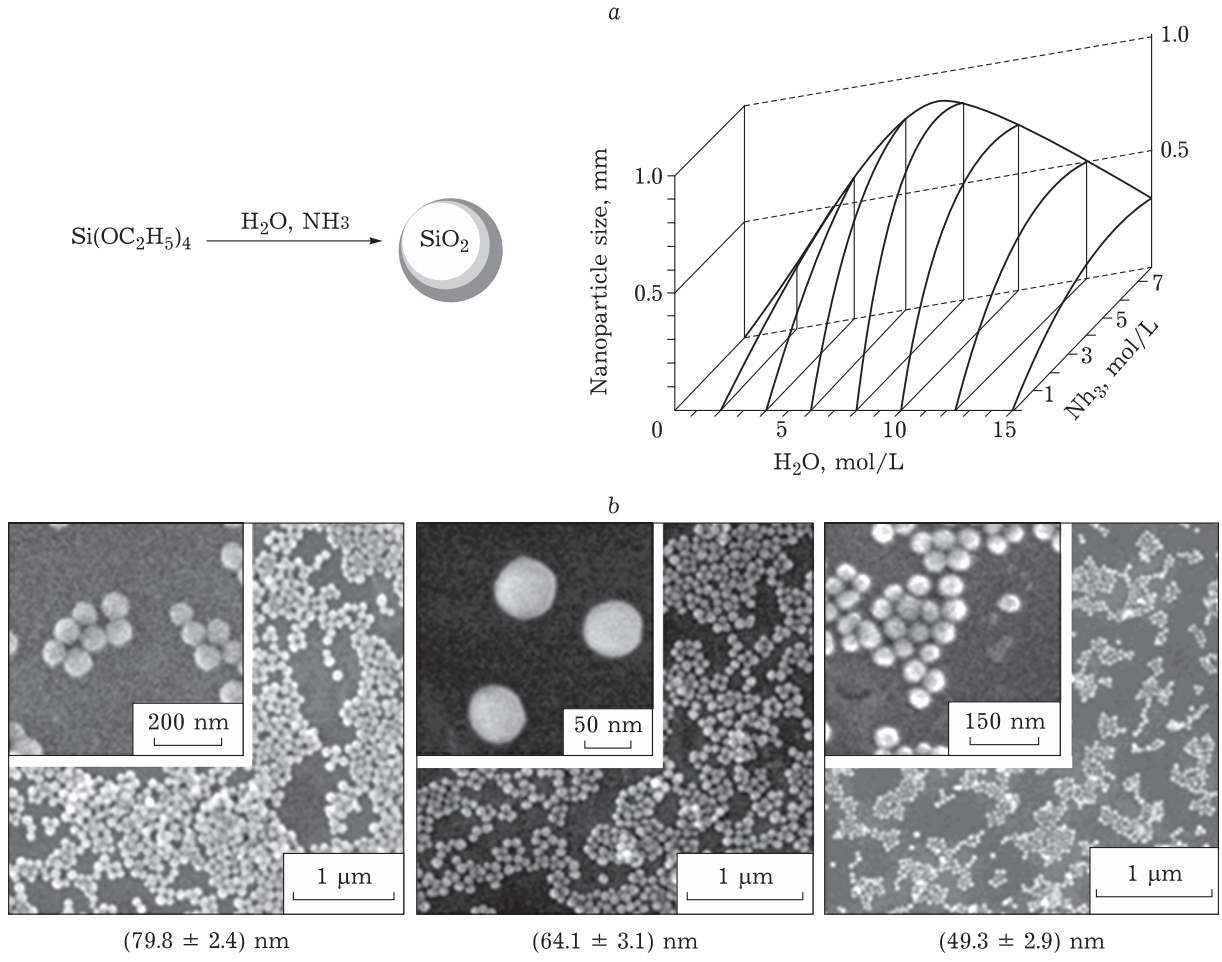


Fig. 2. Size of resulting silica nanoparticles in tetraethylortosilane hydrolysis versus the mole ratio of H_2O to NH_3 [17] (*a*), and also examples of generating monodispersed silica nanoparticles in a water-alcohol solution of tetraethylortosilane in the presence of ammonia [20] (*b*).

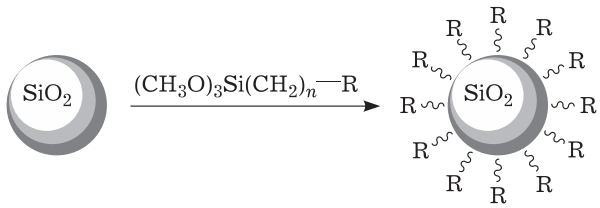


Fig. 3. Overall scheme for chemical doping of silica nanoparticles surface.

fairly accurate methods of determination of amino groups allows generating nanoconstructions with a controlled number of different ligands.

IMAGING AGENTS

Currently, several main methods are used for *in vivo*–tumour imaging. Each of them has its advantages and disadvantages [29] (Table. 1).

As the ideological roots of generating teranostics are based on the principle of side effect minimization, optical imaging and magnetic resonance imaging, where ionizing radiation is completely absent, should be recognized as the most acceptable methods. Fluorine-19 magnetic resonance imaging (^{19}F-MRI) instead of ^{1}H MRI opens up new diagnostic opportunities. The ^{19}F nucleus has a high gyromagnetic ratio (γ = 40.07 MHz/T) and a natural isotopic rate of 100 %. The ^{19}F-containing compounds are present in the human body entirely as solid salts, for example, in teeth and bones. As a consequence, T_2 relaxation time of endogenous ^{19}F atoms is very short, and the magnetic resonance signal is almost undetectable. Thus, exogenous contrast agents for ^{19}F MRI are detected as a hot spot on cold background. Herewith, there is no need for expensive and often toxic heavy metal-based contrast agents [2].

Teranostics, whereat ^{19}F MRI was proposed to be used for tumour tissue imaging, were

TABLE 1

Characteristics of various methods of *in vivo* tumour tissue imaging

Imaging method	Sample type	Sensibility (mole)	Resolution power (mm)	Advantages	Drawbacks
Optical imaging	Fluorescent dye, Quantum dots	10^{-9} – 10^{-12}	2–5	High sensibility Lack of ionizing radiation	Low resolution Limited depth of penetration into tissue
Computer tomography	Heavy element-based imaging agents	Lack of data	0.05–0.2	High spatial resolution Ability to distinguish between tissues. Low radiation dose	Toxic contrast agent is required. Ionizing radiation presence. High cost
MRI	Paramagnetic metal-based imaging agents (Gd, Mn, *etc.*)	10^{-3}–10^{-5}	0.025–0.1	High spatial resolution. Ability to distinguish between tissues. Ionizing radiation lack излучения	Toxic contrast agent is required. Ionizing radiation presence. High cost. Need for patient's lack of metal prostheses
Gamma scintigraphy PET and SPECT	Radioisotopes (F-18, In-111, Cu-64 *etc.*)	PET – 10^{-11}–10^{-12} SPECT – 10^{-10}–10^{-11}	1–2	Ability towards biochemical processes imaging	Radiation exposure. Low resolution. High cost

Note. PET is positron emission tomography and SPECT is single-photon emission computed tomography.

suggested in a series of papers [30–34], however, probably due to the lack of the wide distribution of appropriate equipment, this area has not yet become widely common. There are no data regarding silica particle-based teranostics with this imaging type in the literature.

On the contrary, the design of SNP-based teranostics with optical imaging is widespread [35]. Review [36] presents the main achievements of recent years in the area of fluorescent silicon nanoparticle-based probes for *in vivo* applications.

The introduction of a luminescent dye may be carried out according to the standard scheme of SNP surface modification using appropriate triethoxy(methoxy)silane derivatives [37, 38] (Fig. 4).

The preliminary introduction of amino groups onto the nanoparticles surface significantly expands opportunities for inserting a fluorescent label due to the use of a broad range of activated ethers of commercial dyes. Here, dye selection would be determined by the specific tasks for which the teranostic is generated (e.g., the range of wavelengths of excitation and fluorescence used in optical tomographs, fluorescent microscopes, flow cytometers, *etc.*).

To visualize a tumour by an *in vivo* non-invasive method, the dyes that fluoresce in the near IR range, where there is no tissue fluorescence, are optimum (compounds **3**, **4**, see Fig. 4). When determining tumour boundaries during surgery, a decisive factor is the light resistance of the dye. In this case, one may use BODIPY dyes that are characterized by high molar coefficients of extinction (in $3 \cdot 10^{-5}$ L/(mol · cm) and quantum fluorescence yields (typically in a range from 0.4 to 1), and also chemical inertness and high light stability [39].

TUMOUR-ORIENTING TERANOSTIC DEVICE

As noted above, a series of anatomical and pathophysiological differences between tumour and normal tissues ensure the accumulation of SNP of a certain size due to the EPR effect. This turns out to be sufficient in a number of cases to reliably detect tumour tissues. For example, silicon nanoparticles decorated with a dye fluorescing in the near IR range (see Fig. 4, compound **4**), were used to identify metastatic lymph nodes during surgery on model animals. It was demonstrated that the

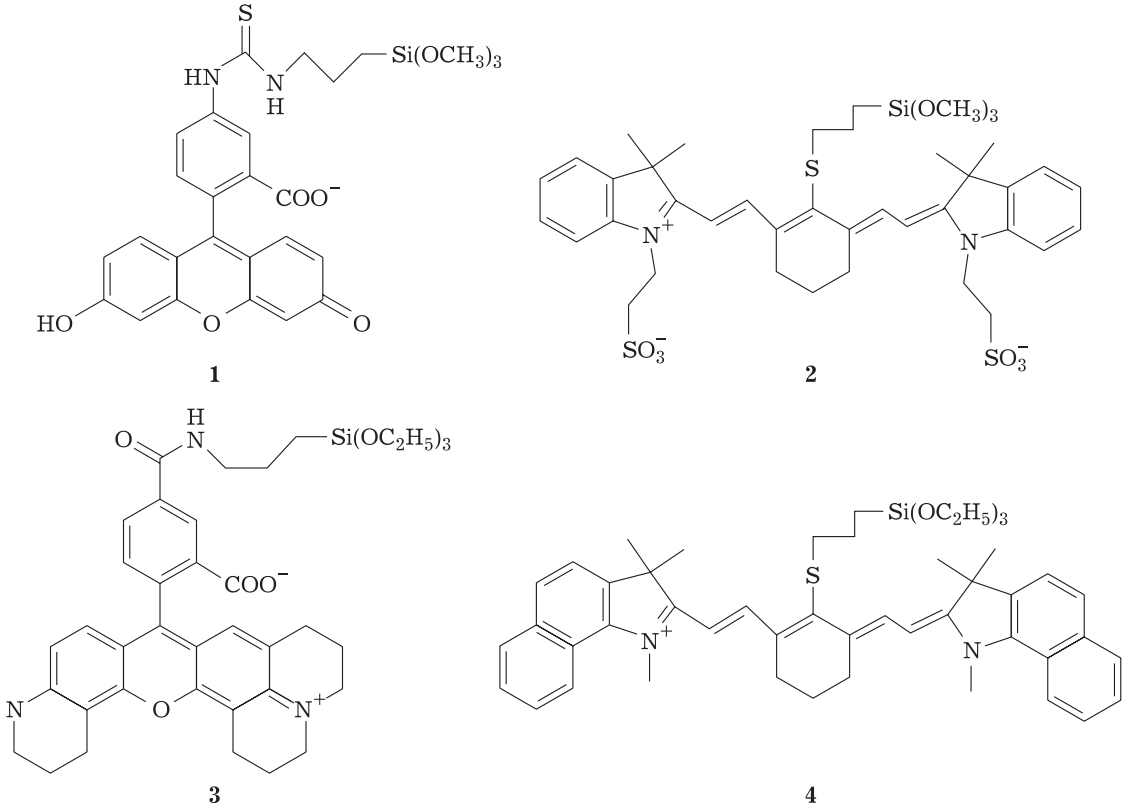


Fig. 4. Examples of dyes used for single-step modification of silicon nanoparticles.

additional introduction of polyethylene glycol residues improved mapping opportunities [38].

The efficiency of recognizing tumour cells may be enhanced by the additional introduction on the nanoparticles surface of low molecular mass compounds that are ligands of receptors of tumour cells hyperexpressed on the surface [40]. This approach is widely used to increase the affinity of nanoconstructions to tumour cells, however, most of the positive results were acquired *in vitro* experiments, herewith, and the reached effect is not always reproduced in the transition to experiments *in vivo* [41]. Thus, the introduction of a biotin molecule into the structure of an albumin-based teranostic, widely used as a tumour-oriented ligand [42], in experiments *in vivo* resulted in a decreased therapeutic effect [43].

Strong performance may be acquired when using tumour-specific aptamers. For example, conjugation of aptamers to SNP, pre-modified with fluorescein, allowed detecting hepatoma [44] and leukaemia [45] cells with the high *in vitro* and *in vivo* sensitivity. Reference [46] presents a facile method for synthesis of a nanoconstruction containing tumour-oriented aptamer and two labels for optical and positron emission tomography. The prospects of application of the proposed nanoconstructions to detect forming metastases in lymph nodes *in vivo* were demonstrated [46].

THERAPEUTIC NUCLEOSIDES

Review [47] of 2017 presents a broad range of compounds with antitumour activity that was used in the design of teranostics. Furthermore, the main types of split linker groups used for covalent attachment of therapeutic agents to various carriers are considered. The extensive bibliographic material presented in this review (more than 290 literature sources), eliminates the need for additional consideration of these aspects of designing teranostics. However, for some strange reason, the present review does not consider therapeutic nucleosides and nucleotides, as potential anticancer agents, although, there are examples of their use for this purpose in the literature [30, 32, 43, 48].

Nucleoside analogues present a group of antimetabolites most commonly used as antiviral and antitumour drugs. Several analogues of nucleosides and nucleotides that have undergone repositioning, that is, that they were initially approved as antiviral agents, are also known in practice. Furthermore, then it was demonstrated that they had promising antitumour properties [49–52]. Therapeutic nucleosides became most common in the treatment of hematological malignancies. The main mechanism of cytotoxicity of nucleoside analogues involves inhibition of essential enzymes of nucleotide metabolism and impairment of nucleic acid synthesis, which results in the induction of apoptosis. Currently, over 900 drugs on the basis of 19 antimetabolites based on analogues of nucleotides, nucleosides, and modified counterparts of heterocyclic bases are produced [53].

The vast majority of therapeutic nucleosides (TN) that show antitumour activity have common metabolic pathway: they are transferred through cell membranes by specific receptors that are carriers of nucleosides [54, 55] followed by phosphorylation with cellular kinases into their active, triphosphate forms [56].

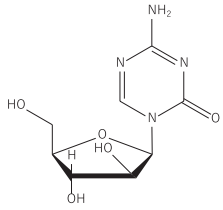
Table 2 presents the main TN structures that can potentially be used in the design of teranostics based thereon.

In general, the literature data on antitumour activity cannot unambiguously determine TN selection. Indeed, such essential parameters that determine their therapeutic effect, as the ability to penetrate through cell membranes and phosphorylation efficiency by intracellular nucleases would not be relevant for TN in nanoconstruction, as the mechanism of penetration of a low molecular mass compound and its conjugate with a nanoparticle is fundamentally different. The use of ready phosphorylated forms in the conjugate eliminates the need for their phosphorylation by intracellular kinases, which levels the efficiency factor of the limiting step of phosphorylation of a nucleoside analogue. Hereby, in the first phase of teranostic design, the decisive factor is the availability of a nucleoside analogue, the simplicity of its adherence to the core nanoparticle, an opportunity of its involvement in implementing other functions of the teranostic. In particular, the presence of fluorine atoms in TN, such as 5-fluorouridine, trifluorothymidine, gemcitabine (2′,2′-difluorocytidine) may be used for non-invasive control of drug accumulation in tumours by ^{19}F MRI [30, 32]. Despite the fact that most of the nucleoside analogues have common metabolic pathway, nevertheless, the details of

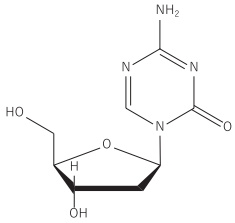
TABLE 2

Structures of therapeutic nucleosides and their application area

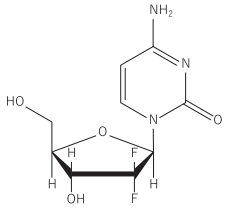
Cytidine analogues



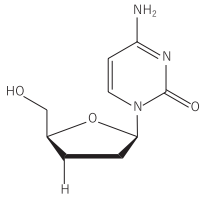
Cytarabine [57]
(leukaemia, lymphoma)



Decitabine [58]
(leukaemia)

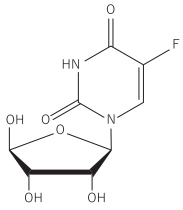


Gemcitabine [57]
(pancreatic, lung, and breast cancer)

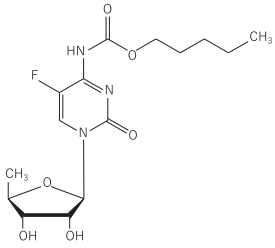


Zalcitabine [59, 60]
(HIV)

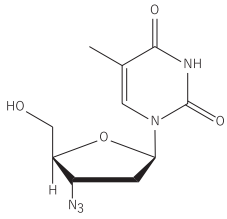
Uridine analogues



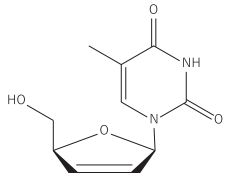
5-Fluorouridine [61–64]
(different kinds of cancer)



Capecitabine [65–67]
(leukaemia)

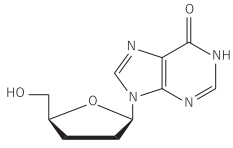


Azidothymidine [68–70]
(HIV)

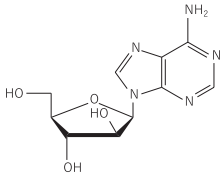


Stavudine [71]
(HIV)

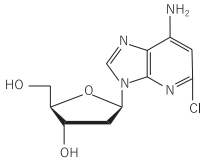
Purine analogues



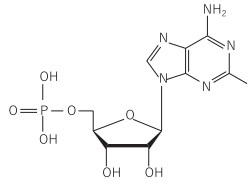
Dideoxyinosine [72]
(HIV)



Vidarabine [73]
(herpes virus)

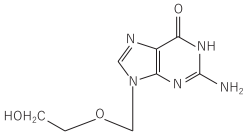


Cladribine [74]
(hematological malignancies)

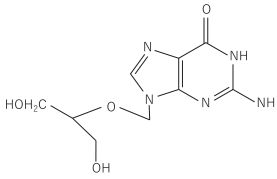


Fludarabine [75]
(hematological malignancies)

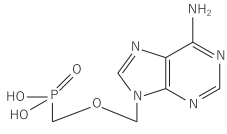
Other analogues



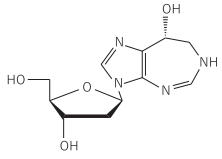
Acyclovir [76, 77]
(herpes virus)



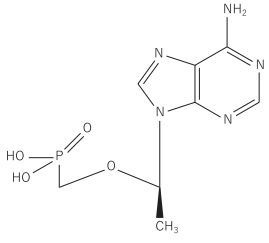
Ganciclovir [78–81]
(cytomegala virus)



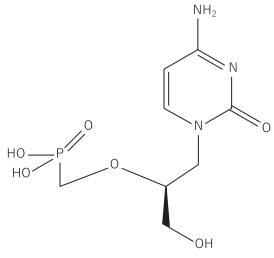
Adefovir [82–85]
(hepatitis B virus)



Pentostatin [86, 87] (cancer)



Tenofovir [88]
(HIV)



Cidofovir [89, 90]
(cytomegala virus)

mechanisms of inactivation of tumour cells by different therapeutic nucleosides may differ, which can be demonstrated by comparison of trifluorothymidine and gemcitabine.

Thus, the antitumour activity of trifluorothymidine is due to the formation of 5-trifluoromethyl-2′-deoxyuridine-5′-monophosphate (pdU^{CF3}), thymidylate synthase inhibitor, and also consecutive transformation of an antimetabolite of a pyrimidine nucleoside into a nucleoside 5-triphosphate analogue (see Fig. 5, *a*) [91].

Like trifluorothymidine, gemcitabine is sequentially phosphorylated by deoxycytidine kinase to mono- (dFdCMP), di- (dFdCDP), and triphosphate (dFdCTP). Herewith, gemcitabine triphosphate may get involved in both DNA and RNA preventing their further synthesis. Herewith, dFdCDP inhibits ribonucleotide reductase, which leads to a decrease in the level of deoxynucleotides (dCDP, dCTP), which in turn, leads to an increase in the probability of embedding modified nucleotides (dFdCTP) into DNA. It is likely that dFdCMP is subjected to dissemination to dFdU monophosphate (dFdUMP), that acts as thymidylate synthase inhibitor; dFdU may also be phosphorylated directly (most likely, by thymidine kinase **2**) to dFdUMP (see Fig. 5, *b*) [92].

Thus, other things being equal, gemcitabine is involved in a great number of metabolic pathways and would potentially have greater antitumour activity.

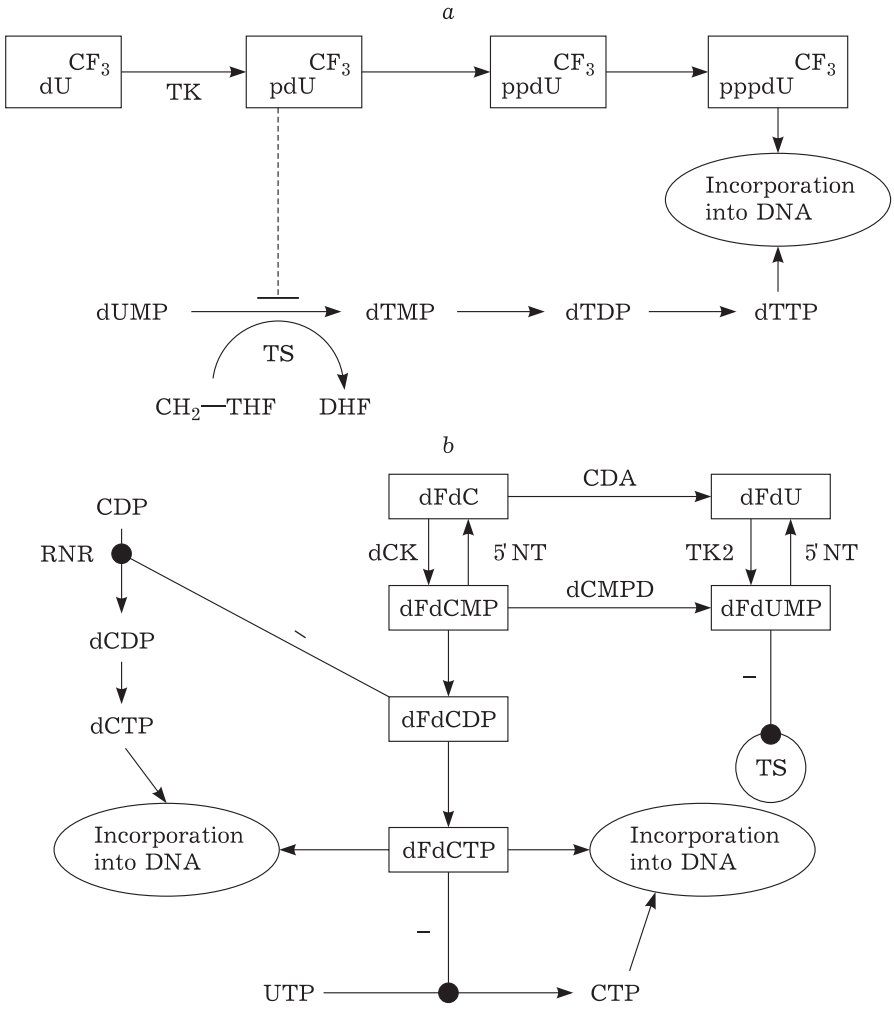


Fig. 5. Scheme for transformation of trifluorothymidine (dU^{CF3}) with generating antimetabolites of DNA pyrimidinium component (*a*) and gemcitabine (dFdC) (*b*). TK is thymidylate kinase, TS is thymidylate synthase; THF is tetrahydrofolate; DHF is dihydrofolate, CDA is cytidine deaminase; dCDP is deoxycytidine diphosphate; dCK is desoxycytidinekinase; dCMPD is deoxycytidine monophosphate deaminase; dCTP is desoxycytidine triphosphate; dFdCDP is diphosphate dFdC; dFdCMP is monophosphate dFdC; dFdCTP is dFdC triphosphate; dFdU is 2′,2′-difluoro-2′-deoxyuridine; dFdUMP is dFdU monophosphate; RNR is ribonucleotide reductase.

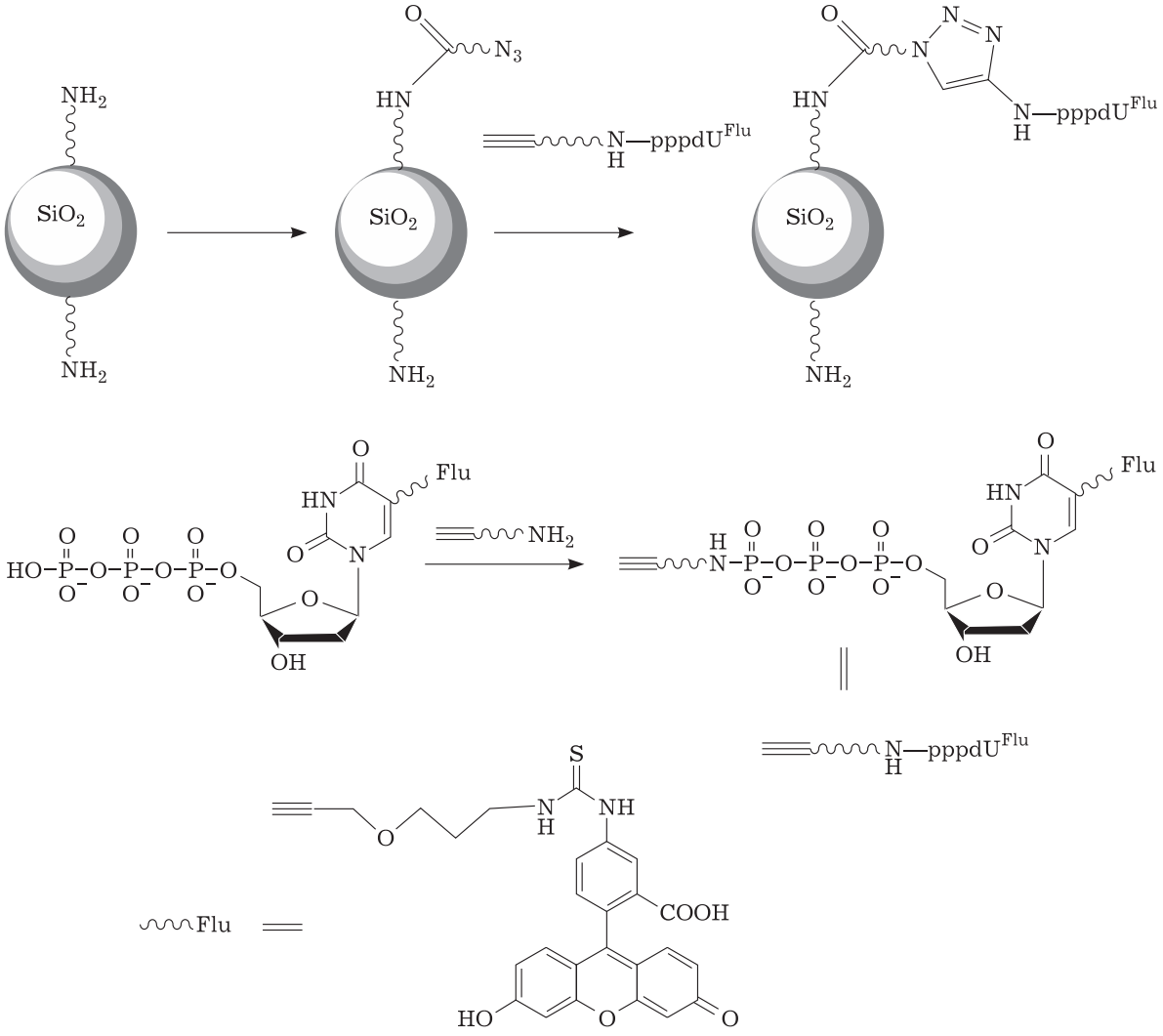


Fig. 6. Overall scheme for synthesis of silica nanoparticle-based teranostics and phosphorylated forms of therapeutic nucleosides.

The first examples of an opportunity to deliver the phosphorylated forms of nucleosides into tumour cells using SNP-based nanoconstructions were demonstrated in [93]. The authors of the paper used 20 nm in diameter commercial silica nanoparticles surface modified with aliphatic amino groups. Some amino groups were transformed into azido groups, at which derivatives of deoxyuridine containing a fluorescein residue were introduced (Fig. 6). Using confocal fluorescence microscopy, the authors demonstrated that nanoconstructions were able to penetrate into cells, while modified triphosphate retained the ability to embed in DNA.

In subsequent works [42, 94], using a similar approach, the authors obtained teranostics containing such therapeutic nucleosides, as azidothymidine, dideoxyuridine, zalcitabin, (dideoxycytidine), and lamivudine. As demonstrated, the resulting teranostics show higher antitumour activity compared to the initial therapeutic nucleosides taken in the equivalent amount. A fluorescent dye in paper [42] was introduced at both unused primary amino groups in the SNP surface and directly into the therapeutic nucleoside. This approach makes it possible to monitor nanoconstructions penetration to tumour cells and detaching phosphorylated forms of therapeutic nucleosides from nanoparticles in the intracellular medium.

CONCLUSION

Currently, there are all prerequisites to generate highly efficient modified silicon

nanoparticle-based teranostics for therapy and diagnostics of oncological diseases in the near future. The main methods for surface modification have been developed. They allow the introduction of imaging labels and therapeutic agents. Herewith, it has been demonstrated that silicon nanoparticles of certain sizes and shapes guarantee nanoconstructions accumulation in tumour tissues that is sufficient for efficient therapy and tumour mapping without introducing extra tumour-orienting ligands. At the same time, achievements in the area of synthesis of teranostics on a different basis, in particular, using fluorine-containing therapeutic nucleosides not only as therapeutic agents but also as labels for ^{19}F MRI open up prospects to generate teranostics that maximally meet medical needs.

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