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Full Length Article

Spectroscopic investigations of novel pharmaceuticals: Stability and resonant interaction with laser beam

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ABSTRACT

This paper presents data about photophysics of two novel thio-hydantoins that exhibit promising pharmaceutical properties in multidrug resistance control. Time stability studies are necessary to establish the proper use of these compounds in different applications. As for their administration as drugs, it is imperative to know their shelf life, as well as storage conditions.

At the same time, laser induced modified properties of the two new compounds are valuable to further investigate their specific interactions with other materials, including biological targets.

The two new thio-hydantoins under generic names SZ-2 and SZ-7 were prepared as solutions in dimethyl sulfoxide at different concentrations, as well as in deionised water. For the stability assay they were kept in various light/temperature conditions up to 60 days. The stability was estimates based on UV–vis absorption measurements.

The samples in bulk shape were exposed different time intervals to laser radiation emitted at 266 nm as the fourth harmonic of a Nd:YAG laser. The resonant interaction of the studied compounds with laser beams was analysed through spectroscopic methods UV–vis and FTIR absorption, as well as laser induced fluorescence spectroscopy.

As for stability assay, only solutions kept in dark at 4 °C have preserved the absorption characteristics, considering the cumulated measuring errors, less than one week.

The vibrational changes that occur in their FTIR and modified fluorescence spectra upon laser beam exposure are also discussed.

A result of the experimental analysis is that modifications are induced in molecular structures of the investigated compounds by resonant interaction with laser radiation. This fact evidences that the molecules are photoreactive and their characteristics might be shaped through controlled laser radiation exposure using appropriate protocols. This conclusion opens many opportunities both in the biomedical field, but also in other industrial activities involving the use of hydantoins.

1. Introduction

Multidrug resistance (MDR) has become a factor seriously limiting the success rate of various diseases treatment [1,2]. Large efforts are directed to design new drugs [3,4] or to enhance the potency of existing ones to combat MDR [5,6]. Recently, the scientific community attention was directed to evaluate the antimicrobial activity of new designed compounds belonging to hydantoin class [7].

Hydantoin or glycolilurea (2,4-imidazolidin-dione) is a heterocyclic chemical compound seldom found in nature. However, some natural products derived from this chemical structure are known [8]. For example, allantoin is a constituent of the urine and axinohydantoin is an alkaloid with antitumor pharmacological properties of the marine sponge *Axinella* sp.[9].

Although hydantoin was synthesized by Adolf von Baeyer in 1861, its structure was properly attributed only in 1870 by Strecker [10]. Many hydantoin derivatives were obtained over time. They are serious candidates in the medical field due to their pharmaceutical properties [11–14]. Promising results were obtained for some new designed hydantoins, including the compounds analysed in this study. They were tested as efflux pumps inhibitors of *S. enter-*

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ica [15]. Recent studies also indicated moderate properties against multidrug resistant *E. aerogenes* [4,16] and microbiological assays of some new hydantoins were developed to test their ability to enhance the action of a β-lactam antibiotics in *S. aureus* [7].

Besides medical applications, hydantoin and its derivatives have many other uses in agriculture, as fertilizers or pesticides [17] or in industry, as oxidizing biocides in paper [18] or textile manufacturing, [19]. New hydantoin derivatives are used as corrosion inhibitors for carbon steel N-80 in raw water [20] and recent studies deal with the addition of antimicrobial hydantoins in industrial aqueous fluid media to reduce or inhibit the growth of microorganisms [21]. In the chemical industry, various hydantoin derivatives are the basis of new generation of weatherproof high-temperature-stable epoxy resins [8].

An important aspect of MDR fighting is also drugs engineering using optical methods as manipulating agents, because the ultraviolet-visible (UV–vis) spectral range has the potential to change their structure. Some papers shown the increase of their treatment potency [6,22–24].

Exposure to laser radiation is recommended due to laser beams high energy and monochromaticity that quickly change drug molecules in solutions, developing new photoproducts with antibacterial activity, which can be effective against strains of bacteria resistant to treatments [25,6,26,27]. When an aromatic molecule absorbs light it suffers an electronic transition to an excited singlet state. Function of the molecular structure and the environment it can de-excite through physical or electronical processes, returning in the initial state or it can undergo a transition to the excited triplet state. Hence, molecule may lose energy reaching the ground state, or be involved in various chemical processes (e.g. redox) with the environment (Type I). Another process is the transfer of the molecule's energetic excess to molecular oxygen also found in the triplet state, allowing the formation of singlet oxygen (Type II). The ability of the molecule to be involved in redox reactions or generate singlet oxygen is conditioned by the accumulation of a sufficient population on the triplet state, which in turn depends on the extinction rate of both triplet and singlet excited states.

As for the optical properties of medicines, they depend also on their molecular structure. Most of them absorb light in the UV spectral range, but there are compounds that absorb on lower energy levels, in the visible. The action mechanism of the photosensitive drugs on target microorganisms may involve either only the degradation of the cell wall or other effects, such as breaking the chains of nucleic acids [28].

In this respect, this work presents the photophysics of two new chemical compounds belonging to hydantoin class, that exhibit promising pharmaceutical properties as antitumoral and antimycobacterial agents [15]. Time stability assay was conducted for the two new thio-hydantoin derivatives in different environment conditions up to 60 days, to further establish the proper use of drug solutions in different applications. The resonant interaction of hydantoin derivatives samples with laser radiation was investigated through spectroscopic techniques. The laser induced molecular changes were assigned based on both UV–vis and FTIR spectra acquired before and after exposure to optical beams emitted by a Nd:YAG laser at 266 nm for different time intervals. Laser induced fluorescence (LIF) spectra were also recorded in a specific experimental arrangement during laser irradiation experiments.

2. Materials and methods

The two novel thio-hydantoin derivatives generically called SZ-2 ($C_{10}H_7ClN_2OS$, M = 238.69 g/mol), and SZ-7 ($C_{17}H_{14}N_2O_2S$, M = 310 g/mol) shown in Fig. 1 were synthesized at Jagiellonian University, Cracow, Poland.

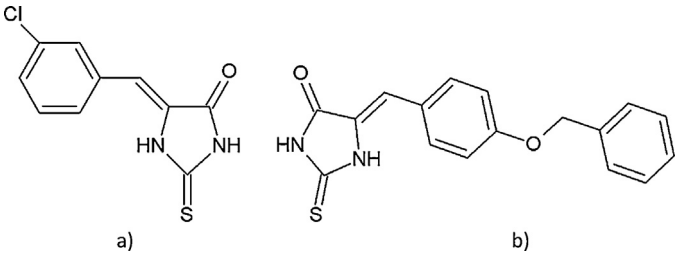

Fig. 1. 2D representations of SZ-2 (a) and SZ-7 (b) molecular structures.

The chemical compounds presenting as yellow powdered crystals were dissolved into dimethyl sulfoxide (DMSO) (Merck, purity ≥99%) and also in ultra-pure deionised water attained as described in [29]. They have been prepared samples between 10^{-5} M and 10^{-2} M concentration range. When DMSO is used as solvent, colourless to yellow clear solutions were obtained, whilst colloidal systems are observed for deionised water solvent. All the samples were 10 min sonicated (Sonorex Digitec, Bandelin Electronic GmbH, Germany), while only colloidal specimens were further mixed by 2000 rot/min spinning using Vortex Mixer wizard (VELP Scientifica, Italy).

SZ-2 and SZ-7 solution samples in DMSO were kept in different environmental conditions, as follows: at 4 °C in dark, at 22 °C in dark, and at 22 °C in white light. The time stability of the samples was determined based on their absorption spectra registered using the UV/vis/NIR spectrophotometer (Lambda 950, Perkin Elmer, USA). The used experimental spectral resolution was 0.05 nm for UV/vis domain and 0.2 nm for NIR spectral range. The cumulated measuring errors limit was ±1.045%, as described in [30].

For the assessment of laser beam resonant interaction with solutions of SZ-2 and SZ-7 into both solvents, the samples were subjected by turn to 266 nm irradiation using the 4th harmonic (FHG) of the Nd:YAG laser (Excel Technology, model Surelite II, Continuum, USA) fundamental beam in the experimental arrangement shown schematically in Fig. 2. Fresh solutions were prepared exclusively for these experimental sessions.

First of all, the solution samples were placed in quartz cuvettes (1.5 mL volume, 1 cm optical path) and agitated during the laser exposure by using a magnetic stirrer (AREC-X, VELP Scientifica, Italy) at 600 rpm, in order to avoid precipitation. The average energy of the laser beam was around 6 mJ, measured in real time by a powermeter (Gentec-EO, Canada). The laser pulse repetition rate was 10 Hz and the full time width at half maximum – 6 ns. Samples have been exposed to UV laser radiation for time intervals up to 60 min. After each exposure session, the influence of laser radiation on the investigated samples in bulk have been evaluated based on their FTIR absorption spectra recorded by a Nicolet IS50 spectrometer (Thermo Scientific, U.S.A.). The device operates with Omnic 9 Standard software and the used experimental spectral resolution was 4 cm^{-1}. 10 μL of each solution to be investigated was placed on KRS crystal and it was dried in direct air flux for 20 min.

Other experiments that intended to evaluate the laser beam resonant interaction with SZ-2 and SZ-7 solutions were carried out by measuring LIF spectra. The method makes possible to identify in real time the absorbents molecular structures modifications in the specimens. The LIF signal was collected at 90° with respect to the direction of the incident laser beam using an optical fiber (P400-1-UV–VIS, Ocean Optics, U.S.A.) with 400 μm core diameter; it was processed by a spectrometer (Spectra Pro SP-2750, Princeton Instruments, U.S.A.) coupled with an iCCD detector (IMAX 1024, Princeton Instruments, U.S.A.).

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