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Laser beam resonant interaction of new hydantoin derivatives droplets for possible biomedical applications

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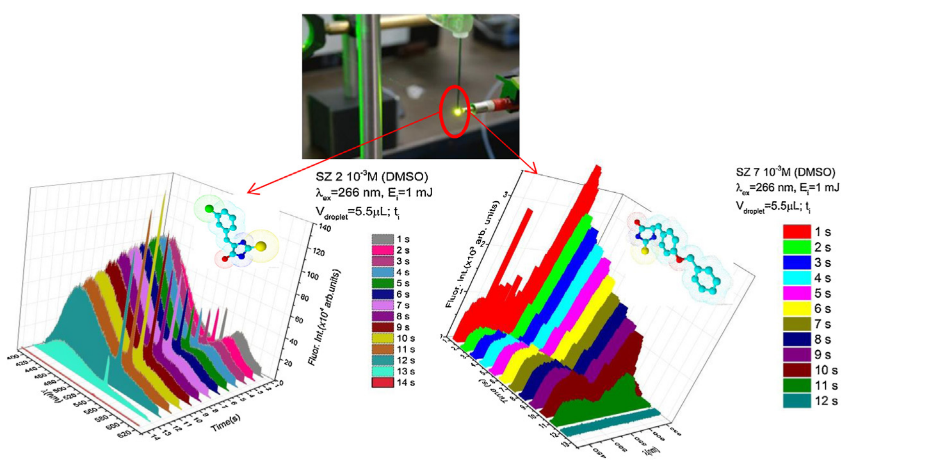
HIGHLIGHTS

- The investigated hydantoin derivatives molecules are photoreactive.
- Molecular changes in droplet are orders of magnitude faster than in bulk exposure.
- The fluorescence signal is amplified in microdroplets.
- Laser exposure may affect the cohesive strength of molecular droplets content.

GRAPHICAL ABSTRACT



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ABSTRACT

This paper deals with the rapid molecular changes induced by laser radiation on two novel hydantoin derivatives, generically named SZ-2 and SZ-7, having promising pharmaceutical properties as Szymanska et al. in 2002 and Subtelna et al. in 2010 have reported. Hydantoins solutions with concentration of 10^{-3} M in dimethyl sulfoxide were exposed both in droplets and bulk samples to coherent radiation emitted at 266 nm as the fourth harmonic of a Nd:YAG laser during different time intervals. The influence of exposure to laser radiation was highlighted by laser induced fluorescence. Also, dynamic wetting (in terms of surface tension and contact angle) measurements were performed in order to find information valuable for further development and modification of hydantoins. All these studies intend to provide physical data in order to better understand the behavior and the activity of this kind of potential drugs on biological targets. Experimental results prove that the investigated molecules are photoreactive. Changes produced in a pendant microdroplet are orders of magnitude faster than in the case of bulk exposure.

The surface tension values of unirradiated/irradiated hydantoin derivatives solutions in dimethyl sulfoxide are stable along the time interval of measurements, indicating that the molecules are evenly

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distributed in drop solution and they are not adsorbed at air–liquid interface. However, a very low gradient of dynamic surface tension values of the unirradiated samples, and the irradiated ones is registered for the SZ-2 compound. This suggests the modification of the cohesive strength of the molecules inside the droplets exposed to laser radiation.

The contact angles equilibrium values of droplets on hydrophobic surface show no remarkable differences for unirradiated/irradiated imidazolidines samples, though the small increase of the contact angle for irradiated SZ-7 confers it a more hydrophobic property.

1. Introduction

One of the current challenges in medicine is to identify new and possible unconventional ways to combat the failure of treatment of infectious diseases and cancer, induced by multidrug resistance (MDR) [1]. This regards not only the improvement of the medicines molecular and bactericide properties and the development of new and efficient molecular structures, but the development of new vectors to transport them to targets, as well.

The micro- and nano-droplets of different solutions of substances are possible means for drugs transportation and delivery. They may be used as individual droplets or as multiple (bunch of) droplets (like in aerosols) delivered on the tissues from surrounding media such as air, or as part of a multifunctional microsystem such as lab-on-a-chip. The direct use on tissues or their impregnation of specific materials (viz. textile) if performed in treatments of biological surfaces (skin, for instance) is of great interest [2]. By droplets exposure to laser radiation of certain characteristics (wavelength, frequency, energy, etc.) adapted to their molecular content, these may be structurally changed [3].

A group of chemicals whose pharmaceutical properties were recently studied is represented by the hydantoin class. The ring of hydantoin (2,4-imidazolidinedione) was firstly synthesized by Baeyer in 1861, but its structure was correctly assigned only in 1870 by Strecker [4]. Hydantoin derivatives are serious candidates in the medical field due to their pharmaceutical activity as anticonvulsants [5], but they found also many other medical applications as antiandrogen [6], antidiabetic [7], antimicrobial [8], anticancer and antimetastatic [9,10]. Several studies demonstrates radical uptake abilities of imidazolidine derivatives [11] compounds. Guanidine and spiroiminodihydantoins are known to mispair with adenine or guanine in consequence of their structural similarity to nitrogenous bases of DNA [12], features that can help in cancer control. Hydantoins like 5-hydroxyhydantoin and 5-methyl-5-hydroxyhydantoin seem to act as blocking lesions factors for DNA polymerases [13]. Some hydantoin derivatives are known to inhibit the *P*-glycoprotein efflux pump of mouse T-lymphoma cells, and act synergistically with anticancer drug doxorubicin [14]. 5-(2-Phenyl-3′-indolal)-2-thiohydantoin have shown inhibitory activity on several cancer lines organized into subpanels representing leukemia, melanoma, and cancer of lung, colon, kidney, ovary, breast, prostate and central nervous system in an anti-cancer drug screening program [15]. 5-benzylidene-hydantoin are known to interact with DNA via intrinsic and extrinsic pathways [16].

Besides medical applications, hydantoins and their derivatives have many other uses in agriculture, as fertilizers or pesticides [17] or in industry, as oxidizing biocides in paper or textile manufacturing [18,19]. Recent studies deal with the addition of antimicrobial hydantoins in industrial aqueous fluid media to reduce or inhibit the growth of microorganisms [20]. Also, new hydantoin derivatives acting as corrosion inhibitors for carbon steel N-80 in raw water were investigated [21]. In the chemical industry, various hydantoin derivatives are the basis of new generation of weatherproof high-temperature-stable epoxy resins [4].

The reason of this research is to find hydantoins that are modulators of efflux pumps in bacteria and cancer cells and finally to develop new pharmacological agents that reverse MDR. The survey shown in this article provides informations about photophysical and photochemical properties of two new hydantoin derivatives that are not investigated up to date. These data may be of use to better understand hydantoins biological activity and to improve their chemical structures for by-passing their side-effects.

In this paper the study covers the rapid molecular changes induced by laser radiation on two novel hydantoin derivatives that present promising antitumoral and antimycobacterial properties [22–24]. SZ-2 ((5Z)-5-(3-chlorobenzylidene)-2-thioxo-4-imidazolidinone) and SZ-7 ((5Z)-5-[4-(benzyloxy) benzylidene]-2-thioxo-4-imidazolidinone) prepared as solutions in dimethyl sulfoxide (DMSO) at different concentrations were kept in dark at about 4 °C. DMSO shows some advantages in biomedical applications especially as a permeation enhancer to improve drug delivery through the tissues epithelium [25], although side effects could appear [26].

The reported studies are devoted to the photophysical properties of SZ 2 and SZ-7 and not to their potential applications on biological targets. Some reports in this direction were already published [14,22–24].

Previous studies performed by us were focused on the biological activity on *P*-Glycoprotein of mouse lymphoma cells of thirty hydantoin derivatives, including SZ-2 and SZ-7 [14]. Also, recent works are focused on the potential efflux pump (EPI) activity of arylidene(thio) hydantoin derivatives. The obtained results confirm the important role of hydrophobic aromatic fragments for cancer efflux pump modulator properties [22]. SZ-2 and SZ-7 were tested along with other hydantoin derivatives as EPI of *Salmonella enterica*, SZ-7 showing promising results [23]. At the same time, similar chemical structures show in vitro antimycobacterial activity [24].

SZ-2 and SZ-7 solutions at 10^{-3} M in DMSO were exposed both in droplets and bulk to coherent radiation emitted at 266 nm as the fourth harmonic of a Nd:YAG laser for different time intervals.

Dynamic wetting (in terms of surface tension and contact angle) measurements of solutions were performed. Contact angle and interfacial tension knowledge provides the information needed for understanding the development and modification of liquids produced by exposure to laser radiation.

The influence of laser beam exposure of droplet/bulk samples was highlighted by laser induced fluorescence (LIF).

2. Materials and methods

2.1. Chemicals

(5Z)-5-(3-chlorobenzylidene)-2-thioxo-4-imidazolidinone ($C_{10}H_7ClN_2OS$, $M = 238.69$ g/mol), generically named SZ-2 (Fig. 1a) and (5Z)-5-[4-(benzyloxy) benzylidene]-2-thioxo-4-imidazolidinone generically named SZ-7 (Fig. 1b) were synthesized at Jagiellonian University, Cracow, Poland [27,28].