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Photolytic and photocatalytic degradation of tandospirone: Determination of kinetics, identification of transformation products and *in silico* estimation of toxicity

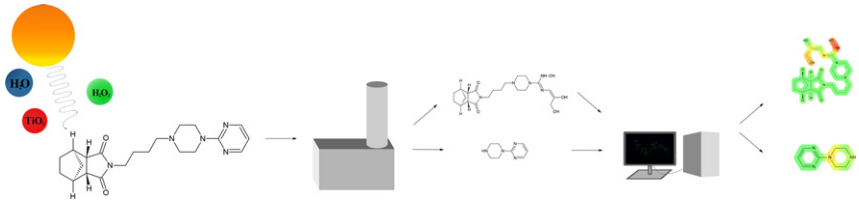
Jakub Trawiński *, Robert Skibiński

Department of Medicinal Chemistry, Faculty of Pharmacy, Medical University of Lublin, Jaczewskiego 4, 20-090 Lublin, Poland

HIGHLIGHTS

- Direct photolysis and photocatalysis with the use of TiO_2 and H_2O_2 of tandospirone were studied
- Kinetics parameters of reactions were compared
- Eighteen photoproducts were detected, and their structures were elucidated
- Toxicity of phototransformation products was assessed with the use of computational methods, and compared by PCA

GRAPHICAL ABSTRACT



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ABSTRACT

The photolytic and photocatalytic transformation of tandospirone with the use of TiO_2 and H_2O_2 was investigated. A micro-scale method for simultaneous irradiation with simulated full solar spectrum of multiple samples in photostability chamber was proposed. RP-UHPLC-DAD coupled with ESI-Q-TOF mass spectrometer was used for the quantitative and qualitative analysis of the processes. The developed method was fully validated and the kinetic parameters of tandospirone photodegradation were compared. The structures of eighteen photoproducts as well as phototransformation pathways were proposed. Based on the elucidated structures, computational toxicity assessment with the use of various software was performed and most of the photoproducts were found as less or similarly toxic to the parent compound. Nevertheless, several products, including one of the drug main metabolites, were significantly more toxic than the parent drug. The multivariate chemometric method (principal component analysis) was used to compare the toxicity of phototransformation products as well as the toxicity of the assessment methods.

1. Introduction

Numerous routes by which pharmaceuticals, as well as their metabolites, can reach environment were identified, for instance humans' and animals' excretions, agriculture, medical or industrial waste (Evgenidou et al., 2015; Silva et al., 2015). According to many studies, a lot of drugs are detected in various wastes samples, such as wastewater (WW), wastewater effluents or sludge, and municipal solid wastes (Musson and Townsend, 2009; Peysson and Vulliet, 2013; Prieto-Rodriguez et al., 2012; Subedi and Kannan, 2015). Occurrence of low concentrations of active pharmaceutical substances was also frequently reported in surface waters (river, coastal waters) or even drinking water (Azuma et al., 2015; Moreno-González et al., 2014; Petrović et al., 2014). In the light of the lack of regulations or directives concerning the removal

* Corresponding author.
E-mail address: jakub.trawinski@umlub.pl (J. Trawiński).

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Table 1
Adsorption of Tandospirone on the TiO_2 surface (catalyst loading = 100 mg L^{-1}).

Time [min]	Tandospirone concentration [mg L^{-1}]
0	8.57
15	8.35
30	8.63
45	8.34
60	8.40

of pharmaceuticals from wastewaters, they are still classified as the emerging contaminants. One of the most important issues in this case is low effectiveness of traditionally applied WW treatment methods (two steps: physico-chemical and biological) (Rivera-Utrilla et al., 2013). Hence other, more efficient, methods which could be linked with those commonly used (tertiary treatment) are actively studied recently. Their concept is usually based on generation of the highly reactive oxygen species (ROS), mainly hydroxyl radicals, and they are assembled in the group named "advanced oxidation processes" (AOPs) (Silva et al., 2015). Most of AOPs utilize catalysis processes, and they can be divided into two groups – homogeneous (*e.g.* Fenton process and its variant coupled with UV–Vis radiation, or UV/H_2O_2) and heterogeneous (Trawiński and Skibiński, 2017). In the latter case ROS are generated as a consequence of interaction of UV–Vis radiation with surface of semiconductors, namely creation of electron-hole pair (Prieto-Rodriguez et al., 2012). The most frequently studied material for this purpose is TiO_2, mainly Degussa 25 consisting of 25% rutile and 75% anatase, possessing better photochemical properties than rutile or anatase alone (Hurum et al., 2003). Nevertheless many authors studied modifications of TiO_2 surface, mainly in order to enhance its photoreactivity (*e.g.* metal or nitrogen doping, mixing with carbon nanomaterials) and facilitate its use on a scale larger than laboratory (immobilization on various materials) (Di Paola et al., 2012; He et al., 2016). The effectiveness of other semiconductors, such as zinc, tungsten, zirconium, vanadium, bismuth, molybdenum or iron compounds were also studied and results were promising in some particular cases, however TiO_2 is still considered as an optimal choice (Di Paola et al., 2012).

It should be noted that studying of photodegradation process only in the term of contaminant removal may be insufficient. In some cases formed phototransformation products (TPs) may be more toxic than the parent compound (Isidori et al., 2005), thus identification of photoproducts should be an essential part of the process investigation. According to the European Pharmacopoeia over 250 of pharmaceuticals listed there are considered as photolabile (Tonnesen, 2004). In the light of this fact, sunlight in certain cases can be used as an effective method of pharmaceutical removal. However this statement refers only to substances absorbing radiation over 290 nm wavelength (the lower border of solar spectrum). On the other hand formation of possibly problematic TPs after release of pharmaceutical substance to the environment must be taken into account.

Another reason justifying necessity of structural elucidation of TPs formed in photolytic and photocatalytic processes, however not connected with environmental aspect, is identification of metabolites of pharmaceuticals. Since on the surface of irradiated catalyst particle electron-hole pairs are created, it possesses both oxidative and reductive properties, which is sometimes used for *in vitro* simulation of pharmaceuticals metabolism (Ruokolainen et al., 2016, 2014). Sometimes compounds formed in phototransformation experiments are identical with identified impurities, *e.g.* product of N-oxidation of pyrrolidine fragment, formed under UV-A irradiation of amisulpride shares the structure with F impurity described in the European Pharmacopoeia 7 (Skibiński, 2011).

As it was mentioned, pharmaceuticals are problematic contaminants, and psychotropic drugs are not the exception – they belong to the third best selling group of pharmaceuticals. Taking into consideration that treatment of mental illnesses usually demands long-term pharmacological therapy, and fact that consumption of drugs affecting nervous system (especially antidepressants) is still increasing (Norwegian Institute of Public Health, 2015), numerous reports concerning detection of these pharmaceuticals in the environmental samples were published (Trawiński and Skibiński, 2017).

Tandospirone, a $5HT_{1A}$ receptor partial agonist (Uehara et al., 2014), belongs to the second generation of azapirone anxiolytic drugs, and is used for treatment of general anxiety disorder (Gogas et al., 2007). It was also reported as effective in treatment of social anxiety disorder (results comparable with sertraline) (Huang et al., 2013) and anorexia nervosa (Okita et al., 2013). Chronic intake of tandospirone may also increase hippocampal neurogenesis (Mori et al., 2014).

Although tandospirone, along with benzodiazepines and benzodiazepine-like pharmaceuticals, belongs to the group of the most widely prescribed anxiolytic drugs (Lee et al., 2017), any paper describing its environmental occurrence and concentrations, biodegradation processes, or behavior under UV–Vis radiation (including photocatalytic processes or removal from environmental samples, such as wastewater), has not been published until now. However, taking into account measured concentrations of other representatives of this pharmacological group, for instance 560 ng L^{-1} in tap water or 390 ng L^{-1} of oxazepam in surface waters (Trawiński and Skibiński, 2017), occurrence of tandospirone in the environment may be also problematic. Results of study of photocatalytic transformation of buspirone, drug sharing structure almost identical to tandospirone, with the use of TiO_2 suggested usefulness of this method in removal of compounds belonging

Table 2
Validation of the quantitative method.

Parameters	Results
Linearity	
Concentration range [mg L^{-1}]	(0.1:14)
Slope	2.3034
SD of slope	0.0226
Intercept	0.0418
SD of intercept	0.0188
Correlation coefficient (*r*)	0.9999
LOD (mg L^{-1})	0.03
LOQ (mg L^{-1})	0.09
Precision (RSD%)	
Intra-day (n = 12)	0.89
Inter-day (n = 21)	0.69
Accuracy	
% Recovery	100.87
RSD (%)	0.42

Table 3
Summary of the phototransformation kinetics.

Matrix	Model	Fit (*r*)	*k* [min^{-1}]	$t_{1/2}$ [min]
TiO_2	Pseudo-first order	0.9996	0.01445	47.97
H_2O_2	Pseudo-first order	0.9986	0.01032	67.16
H_2O	Pseudo-first order	0.9986	0.00384	180.46