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TiO_2-modified MALDI target for *in vitro* modeling of the oxidative biotransformation of diclofenac

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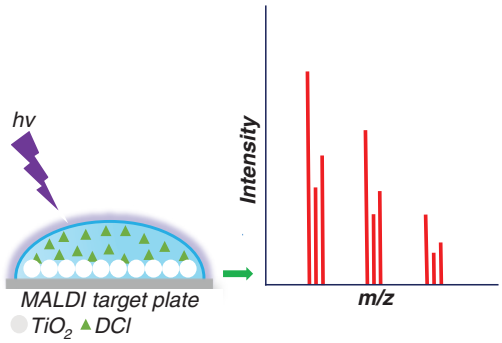
The UV-induced photocatalytic oxidation in the presence of TiO_2 nanoparticles (UV/TiO_2-PCO) is a more adequate approach than electrochemical oxidation to simulate the oxidative metabolism of diclofenac based on the comparative analysis of oxidation products using high-resolution tandem mass spectrometry. A simple and fast high-throughput technique is proposed for modeling the oxidative metabolism, which involves UV/TiO_2-PCO performed directly on a MALDI target and subsequent analysis by matrix-assisted laser desorption/ionization mass spectrometry. The ranges and yields of diclofenac oxidation products obtained by the conventional bulk UV/TiO_2-PCO and the proposed on-target version are in excellent agreement.



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The metabolic conversion of xenobiotics into reactive products, commonly referred to as bioactivation, is a major determinant of their unpredicted biological activities including adverse side effects. An analysis of the oxidative metabolism of xenobiotics is important for drug development as it allows one to predict the potential toxicity of novel pharmacological entities.[1]

Since biotransformation analysis with the use of biological systems (liver microsomes, hepatocytic cell lines, and laboratory animals) is laborious and time-consuming, fast and simple methods for the nonenzymatic *in vitro* modeling of oxidative metabolism have been developed.[2] Although electrochemical oxidation is the most popular method, the UV-induced photocatalytic oxidation in the presence of TiO_2 nanoparticles (UV/TiO_2-PCO), which is widely used for the degradation of pharmaceuticals and other pollutants in wastewater,[3–5] is highly promising for the comprehensive simulation of oxidative metabolism.[6–8]

The oxidation products obtained by UV/TiO_2-PCO are typically identified by mass spectrometry (MS) often coupled to high performance liquid chromatography (HPLC), which introduces pretreatment steps and thus slows down the overall analytical workflow. Therefore, the development of a fast and simple technique of UV/TiO_2-PCO coupled to MS for high-throughput analysis of oxidation products in multiple samples is of considerable current importance. Several sophisticated approaches for the online coupling of UV/TiO_2-PCO to electrospray ionization (ESI) MS have been suggested; they require special instrumentation and additional materials.[9–11] Here, we present a simple, rapid, and cost-effective technique for on-target UV/TiO_2-PCO followed by the direct analysis of oxidation products by matrix-assisted laser desorption/ionization mass spectrometry (MALDI MS). This technique involves the UV irradiation of a microvolume of analyte solution on a TiO_2-covered sample spot of a MALDI target, which serves as a common site for photocatalytic oxidation and MALDI (see Online Supplementary Materials). The use of a TiO_2 layer excludes the need for organic MALDI matrices.

Diclofenac (**1**), a non-steroidal anti-inflammatory drug whose photocatalytic degradation[10] and *in vivo* oxidative bioactivation[13,14] are well known, was used as a test compound. The oxidation products of diclofenac obtained using electrochemical oxidation, conventional photocatalytic oxidation and the suggested on-target photocatalytic oxidation† were analyzed and compared. The analysis of electrochemical oxidation and UV/TiO_2-PCO products was performed using HPLC-MS/MS on a high-resolution FT-ICR instrument.† On the basis of retention times and accurate mass measurements, the molecular structures of oxidation products were proposed (Scheme 1, Table 1 and Online Supplementary Materials).

Diclofenac was detected as the $[M - H]^-$ ion (*m/z* 294), and the base peak at *m/z* 310 was assigned to +O products identified as monohydroxylated derivatives (OH-diclofenac) **2a–c** (Scheme 1). As minor oxidation products, polyhydroxy (**2d–f**,) decarboxylated (**2g–j**), and quinone imine (**3a–d**) derivatives were detected, as well as deep destruction products **4a–f**. Compounds

† For oxidation and analysis procedures, see Online Supplementary Materials.

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