Title: Metabolism of 5-Fluoro-2-Oxindole by Human Cytochrome P450s

Program of Study: Biochemistry

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Category: Basic

Abstract

A common structural motif in the realm of drug compounds is the double ringed oxindole. This derivative of the essential amino acid tryptophan is useful in drug targeting because of its ability to donate and accept hydrogen bonds. Additionally, rising number of compounds used in cancer treatment are fluorinated. Because many anti-cancer drugs are linked to negative side effects, it is important to understand the process by which the body metabolizes these compounds. The anti-cancerous effects of the compound 5-fluoro-2-oxindole are well documented. Characterization of the metabolism of this compound has clinical applications from a pharmaceutical perspective, but also has a unique chemical feature. The chemistry of this metabolic reaction is predicted to occur at the fluorinated site. There is a strong curative potential for the 5F2O compound and some cancer treatments that are in trial contain the 5-fluorooxindole structure. Therefore, a complete comprehension of this mechanism if vital. In a more general sense, the description of how fluorinated compounds are handled by CYPs is important. We have previously alluded to the fact that cytochrome p450BM3 metabolizes fluorophenol by forming a benzoquinone intermediate. This oxidative defluorination reaction is predictive of the mechanism by which cellular p450 isoforms would metabolism oxindole compounds. While a number of isoforms were examined for metabolite formation, only enzymes 1A2 and 2A6 were shown to be capable of defluorination. This is something the project aims to confirm via a comprehension of 5F2O

metabolic pathway. The project is also exploring the potential of a ‘suicide substrate’ inhibiting enzyme activity. This will be performed by intentional formation of a glutathione adduct in an attempt to define the intermediate state of the substrate in the reaction.