

Xenobiotic chemicals are chemicals foreign to life that are usually derived synthetically or from an abiotic process. The synthetic xenobiotic chemicals are often of enormous value to human society and are usually the majority of the chemicals in such important groups of substances as petrochemicals, pesticides, plastics and pharmaceuticals, where the term drug is usually applied when referring to xenobiotics. Biotransformation is a major mechanism for drug elimination, as they undergo biotransformation after they enter the body. Biotransformation, which almost always produces metabolites that are more polar than the parent compound, usually terminates the pharmacologic action of the parent drug and, via excretion, increases removal of the drug from the body. However, other consequences are possible, including similar or different pharmacologic activity, or toxicological activity.

The routes by which drugs may be biotransformed are many and varied and include oxidation, reduction, hydrolysis and conjugation reactions, among others. It is important that these pathways are understood, as the route of metabolism of a drug can determine its ultimate pharmacological or toxicological activity.

Drug biotransformation is divided into two phases: Phase I, or functionalisation reactions and Phase II, or conjugative reactions.

In addition to the physicochemical factors that affect xenobiotic metabolism, stereochemical factors play an important role in the biotransformation of drugs. This involvement is not unexpected because the xenobiotic-metabolizing enzymes are also the same enzymes that metabolize certain endogenous substrates, which for the most part are chiral molecules. Biotransformation of racemic drugs can be stereoselective, as the individual enantiomers undergo metabolism via different metabolic pathways. This stereoselectivity has been observed for both phase I and phase II reactions.

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Non-steroidal anti-inflammatory drugs, NSAID, are a group of analgesic, antiinflammatory and anti-pyretic drugs that are extensively used in rheumatology.

Although not all NSAIDs are chiral, all of the drugs in its major chemical class, the 2-arypropionic acid, possess a chiral centre. As a collective group, the chiral NSAIDs are perhaps one of the most studied classes for enantioselectivity in pharmacokinetics. This PhD project focused the study of Phase II Biotransformation of the potential NSAID Flobufen, structurally related to 2-arypropionic acids. As a chiral drug, this work investigated the ability of Flobufen and/or its metabolites to undergo enantioselective conjugation, employing techniques such as LC-MS to separate and identify the metabolites formed.