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Metabolism of Some Drugs Which Contain Carbonyl Group Make It Stereogenic Drug by Reductase Enzyme

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Abstract

The metabolism is biotransformation refers to the processes by which the body chemically alters drugs, transforming them into different chemical compounds called metabolites. One of these processes is reduction of the drugs by reductase enzyme which add hydrogen to the compound, e.g. acetohexamide (oral hypoglycemic drug), loxoprofen (analgesic), haloperidol (antipsychotic drug), oxisuran (immunosuppressive agent), bupropion (antidepressant drug). All of these drugs contain a carbonyl group, which is reduced by reductase enzyme and converted into a chiral carbon, which makes the drug stereogenic.

Keywords: metabolism, reductase enzyme, carbonyl group, stereogenic drug, chiral carbon

1. Introduction

The metabolism of a drug may convert the inactive drug to an active drug, pro-drug to an active drug, active drug to a more active drug… etc.

Stereochemistry of a drug is an arrangement of atoms and groups of the molecules (Drugs) in space, which is an important factor in determining how the drug interacts with various biological molecules (Enzymes, receptors, etc.) that it encounters in the body.

Acetohexamide is a sulfonylurea used to treat diabetes that undergoes metabolism by the reductase enzyme, which reduces the carbonyl group and makes it more active via this enzyme.

Loxoprofen is a prodrug, meaning it is inactive until metabolized in the body, the primary metabolic pathway by reductase enzyme, which converts the carbonyl group to a secondary alcohol. This metabolite is responsible for the

therapeutic effects of loxoprofen.

Haloperidol is an antipsychotic drug that contains a carbonyl group, which is reduced by reductase enzyme and makes it a stereogenic drug i.e., contains a chiral carbon after metabolism.

Oxisuran is an immunosuppressive drug; one of the metabolic pathways of this drug is reduction reactions, which convert the carbonyl group to a chiral carbon, where it contains a chiral carbon attached to the compound, resulting in a diastereoisomeric drug.

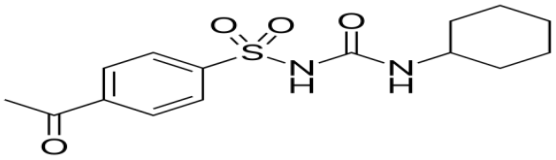
Bupropion is metabolized in the body by a reductase enzyme, which reduces the carbonyl group and plays a role in forming erythrohydrobupropion and threohydrobupropion, which are also pharmacologically active, and these metabolites make the compound easily excreted after glucuronidation in phase II metabolism.

From the previous introduction, the metabolism of the carbonyl group of some drugs through reduction by a reductase enzyme makes the drug stereogenic and may increase the activity of the drug, and the conversion of the carbonyl group into a secondary alcohol makes the drugs more easily excreted due to the presence of a hydroxyl group, which combines with glucuronic acid in the body (glucuronidation) and is excreted through the kidney.

N. b. Drug metabolism often converts drugs into more water-soluble forms and excretes them by the kidney, which prevents the drugs from building up in the body to toxic concentrations. The liver is the primary site of drug metabolism, where it contains enzymes like cytochrome P450.

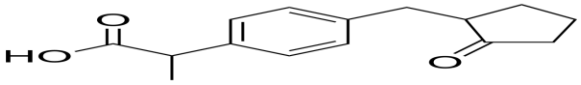
2. Pharmacology and Chemistry

Acetohexamide:



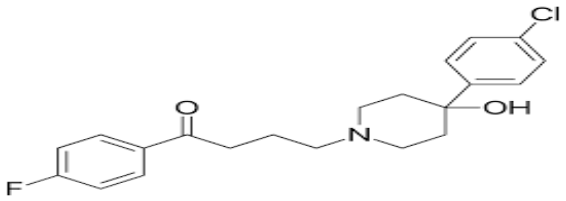
Acetohexamide is a first-generation sulfonylurea drug used to treat type 2 diabetes. It works by stimulating the pancreas to release insulin and enhancing the body's response to insulin. The primary active metabolite is hydroxyhexamide, which reduced in the liver, the hydroxyhexamide (the metabolite of acetohexamide) is more potent than acetohexamide X2; this metabolite becomes more easily excreted than the potent drug.

Loxoprofen:



Loxoprofen is a prodrug metabolized in the liver by carbonyl reductase enzyme to its active trans-alcohol metabolite and inactive cis alcohol metabolite of loxoprofen a prodrug when metabolized by reductase enzyme, which convert into the active metabolite, which gives the therapeutic effect as analgesic and anti-inflammatory and the hydroxyl group makes the metabolite easily excreted from the body.

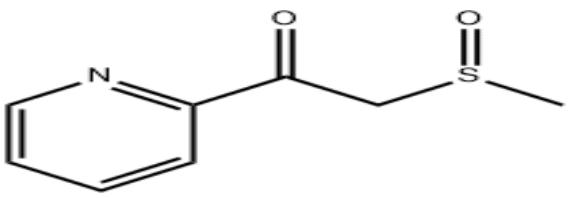
Haloperidol:



Haloperidol is an antipsychotic drug that acts on dopamine D2 receptors, resulting in extrapyramidal symptoms such as muscle rigidity and dystonia. Haloperidol blocks dopamine D2 receptors in the brain and exerts its antipsychotic action, where it manages the symptoms of schizophrenia, including hallucinations and delusions.

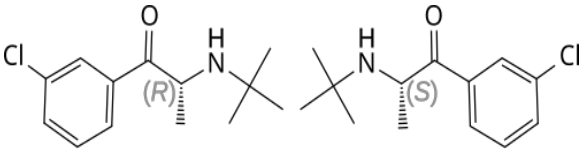
Haloperidol is metabolized by reductase enzyme, which converts the carbonyl group into a secondary alcohol, which makes the metabolite easily excreted from the body and prevents its accumulation in the body.

Oxisuran:



Oxisuran is an immunosuppressant drug that undergoes metabolism through a reduction reaction, which converts the carbonyl group to a secondary alcohol and may be further oxidized to oxisuran alcohol sulfon. This metabolic pathway makes the drug easily excreted from the kidneys.

Bupropion:



Bupropion is an antidepressant that works primarily as a norepinephrine and dopamine reuptake inhibitor. It is also used as a non-nicotine treatment for nicotine dependence.

Bupropion is extensively metabolized in the liver, with cytochrome being the major enzyme responsible for its initial metabolism to form the active metabolite hydroxybupropion. Other active metabolites, threohydroxybupropion and erythrohydroxybupropion, are formed through a non-CYP-mediated pathway.

Hydroxybupropion (Threo and Erythro) is all pharmacologically active with varying potencies compared to the parent drug hydroxybupropion, which is considered a major contributor to bupropion's overall pharmacological activity due to its higher plasma levels.

3. Conclusion

Drug activity, stereochemistry, and elimination are all significantly improved by the metabolic alteration of medicines by the reduction of carbonyl groups by reductase enzymes. Chiral centers are commonly formed as a result of this biotransformation, producing stereogenic medications with potentially distinct pharmacological profiles and better therapeutic results.

Acetohexamide, loxoprofen, haloperidol, oxisuran, and bupropion are examples of drugs that show how reductase enzymes change carbonyl-containing substances into secondary alcohols, frequently producing metabolites that are more active or pharmacologically relevant. For example, trans-alcohol (from loxoprofen) and hydroxyhexamide (from acetohexamide) are more potent than their parent molecules, whereas haloperidol and oxisuran undergo stereoselective metabolism, producing metabolites that are easier to excrete. Stereospecific metabolites of bupropion, including erythro- and threohydrobupropion, play a major role in overall antidepressant effect.

Furthermore, the presence of hydroxyl groups in these metabolites enhances water solubility, facilitating phase II conjugation reactions such as glucuronidation, and ultimately renal excretion, reducing the risk of drug accumulation and toxicity. The liver, being the central organ of metabolism, orchestrates these processes via a network of enzymatic pathways including cytochrome P450s and non-CYP reductases.

In conclusion, reduction of carbonyl groups by reductase enzymes not only contributes to the stereochemical complexity of drugs but also plays a crucial role in determining their pharmacodynamic and pharmacokinetic behavior, emphasizing the importance of stereochemistry in drug metabolism and therapeutic efficacy.

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