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Relationship of Stereochemistry and Activity of Drugs

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Abstract

The stereochemistry is important to drug action because the shape of the drug molecule is an important factor in determining how it interacts with various biological molecules (Enzymes – Receptors… etc.) e.g. dextromethorphan and levomethorphan, the dextromethorphan is antitussive and levomethorphan is opioid due to this difference of pharmacological activity is due to stereochemistry of methorphan (Dextro – Levo), cisplatin and transplatin, cisplatin is anti cancer, which is more active than transplatin, trans diethylstilbestrol and cis diethylstilbestrol, the trans form is more active than cis form, escitalopram is pure enantiomer for treat anxiety and depression, which is more active and more fast than citalopram which is mixture of two enantiomers of citalopram, cetirizine and levocetirizine are antihistaminic but the levo cetirizine is more safe and faster action than cetirizine, erythro ephedrine and threo ephedrine which is used in common rhinitis disease under names pseudo ephedrine, levodopa and dopa the levodopa used in treatment of parkinsonism, which is more active than dopa, levothyroxine and dextrothyroxine the levothyroxine used in hypothyroidism but the dextro inactive or less active, and levetiracetam which is levo enantiomer which used in treatment of epilepsy, the levo-enantiomer is more active than dextro enantiomer.

Keywords: stereochemistry, pharmacological action, dextro, levo, cis, trans, erythro, threo, enantiomers, isomers

1. Introduction

Dextromethorphan is the dextro enantiomer, which is used to treat cough and levomethorphan is the levo enantiomer, which is used potent analgesic. Levo methorphan is a prodrug is levorphanol, which is used opioid analgesic. The two enantiomers differ in binding with receptors according to their stereochemistry and give different pharmacological actions.

The difference between cis and trans platin lies in the spatial arrangement of their ligands which

significantly impacts their biological activity and effectiveness as anticancer drug, cisplatin with its two chloride ligands and two ammonia ligands position in the same side (cis of the platinum atom) is a widely used as a chemotherapy drug, while the transplatin, these ligands are opposite each other, so inactive as anticancer agent.

The trans-diethylstilbestrol and cis-diethylstilbestrol are geometrical isomers of diethylstilbestrol, where the trans form is more effective and active to estrogen receptors than the cis form due to the binding with receptors, where the trans form binds with the estrogen receptors very well.

Citalopram is used in the treatment of depression, while escitalopram, which is a pure isomer of citalopram (S-form), which approved for generalized anxiety disorder (GAD) in adults and children; this characteristic over citalopram is due to the stereochemistry of citalopram.

Cetirizine and levocetirizine are both antihistaminic drugs; levocetirizine is the active enantiomer of cetirizine and is more potent due to the levo enantiomer of cetirizine, due to a higher affinity for histamine H1 receptors than cetirizine, meaning it binds more strongly to these receptors, which are involved in allergic reactions.

Ephedrine has two chiral carbons, which make the ephedrine diastereomers, which may be erythro or threo. The erythro form refers to one of the diastereomers where the substituents on the chiral carbons are on the same side, but the threo form and the substituents are on opposite sides. The threo isomer is called pseudoephedrine, which is used in the treatment of the common cold, but the erythro ephedrine used in the treatment of bronchial asthma, where it acts as a sympathomimetic agent, where it act on adrenergic receptors.

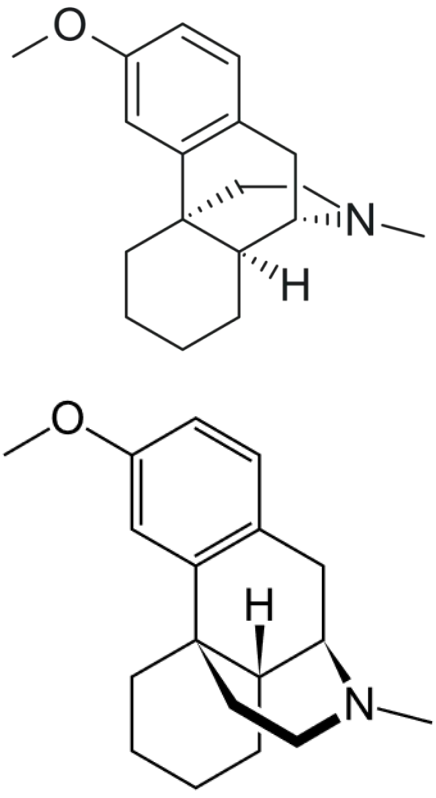
Levodopa is the levo enantiomer of dopa, which used in treatment of parkinsonism, where the levo enantiomer is able to cross the blood-brain barrier once in the brain it is converted into dopamine and treatment of parkinsonism, the dopamine is a neurotransmitter but can not cross the blood-brain barrier hence the levo isomer is more effective than dopa, hence the stereochemistry tell us the pharmacological action depend on the stereochemistry of drug.

Levothyroxine and D-Thyroxine are both synthetic thyroid hormones, but they have different properties and uses. L-Thyroxine is a more common and widely used form for the treatment of hypothyroidism, while dextrothyroxine was previously used for cholesterol reduction but has been largely discontinued due to its side effects.

Levetiracetam has one chiral center, making it exist as two enantiomers (S)-(-)-Levetiracetam, the active drug due to its stereochemistry which appear in levo form, and (R)-(+)-Etiracetam, the levetiracetam is anticonvulsant agent active, while etiracetam not active as anticonvulsant agent due to its stereochemistry.

2. Pharmacology and Chemistry

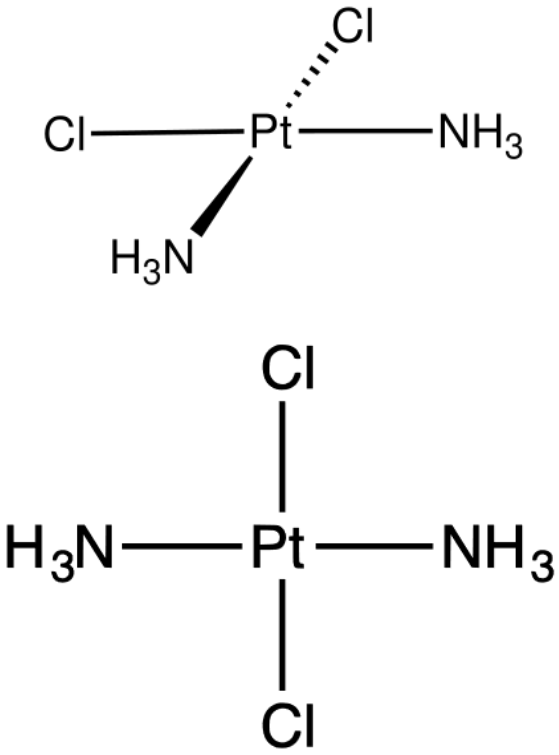
Dextromethorphan and Levomethorphan



Dextromethorphan and Levomethorphan are stereoisomers with distinct pharmacological profiles. Dextro-form acts as an antitussive (cough suppressant) at low doses and, at higher doses is a potent opioid analgesic roughly five times stronger than morphine. This enantiomer gives different pharmacological actions according to its doses, while Levomethorphan is an opioid analgesic at any dose.

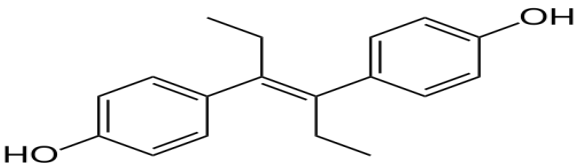
The stereochemistry of methorphan explains the pharmacological action of dextromethorphan and levomethorphan.

Cisplatin and Transplatin



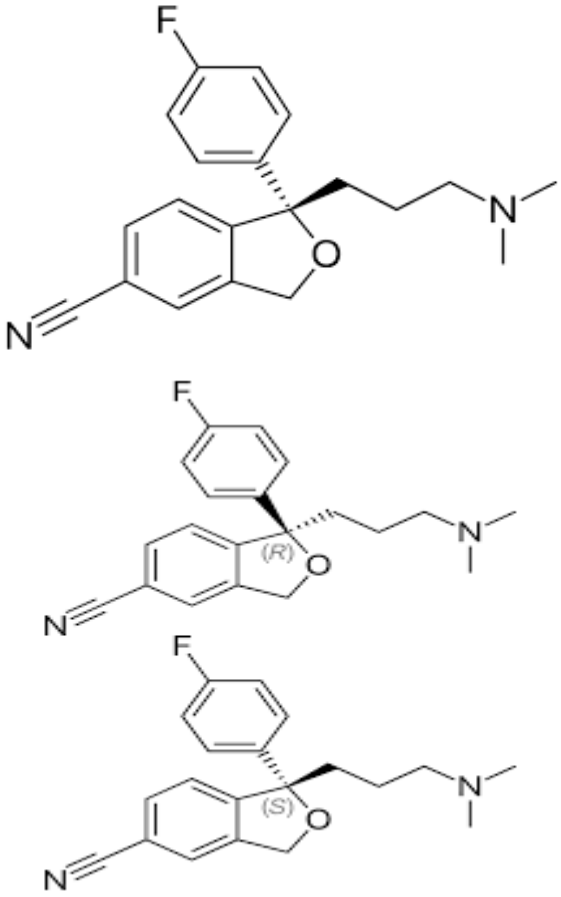
Cisplatin is widely use as chemotherapy drug where as transplatin its transisomer is largely in effective anticancer agent, this difference is largely attributed to their distinct ability to form DNA adducts with cisplatin (cis configuration allowing for more effective) DNA cross-linking, so the cisplatin is antitumor agent and transplatin has minimal to no antitumor activity in most cancer models, these enantiomers difference are in stereochemistry explain the pharmacological action of both isomers.

Cis Diethylstilbestrol and Trans Diethylstilbestrol



Diethylstilbestrol (DES) exists as two stereoisomers, cis and trans. The trans isomer is more biologically active for and cis isomer can convert to the transform invivo contributing to its observed tereogenic effects, both isomers are synthetic estrogens but the transform is more potent due to its structural similarity to estradiol, the transform is binding to estrogen receptors in cells more than cis isomer, where the trans resemble estradiol hormone, also the trans isomer is more stable while the cis isomer tend to convert to the transform.

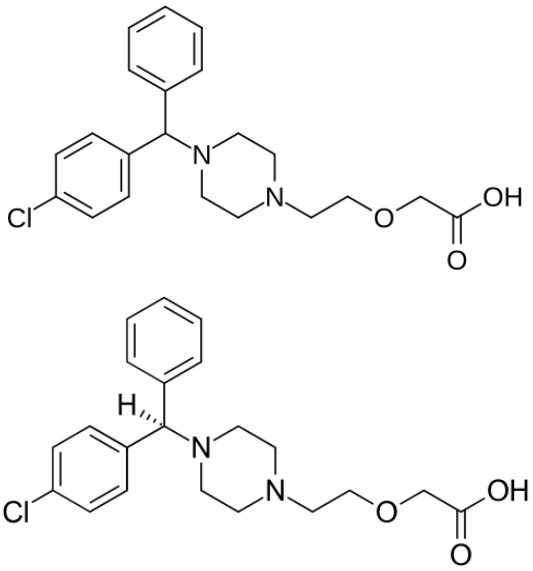
Escitalopram and Citalopram



Escitalopram is the (S)-isomer of citalopram, which is approximately 150 times more potent than the (R)-isomer of citalopram and is responsible (S) for the vast majority of citalopram's clinical activity, with some evidence suggesting the (R)-enantiomer of racemic citalopram actively dampens the activity of escitalopram.

Escitalopram is the (S) enantiomer of citalopram, which is used in the treatment of anxiety and depression for adults and children, while the citalopram ((R) form or racemic mixture) is not used for children, not used for anxiety; hence, the pharmacological action differs between citalopram and escitalopram, and the tolerance by children.

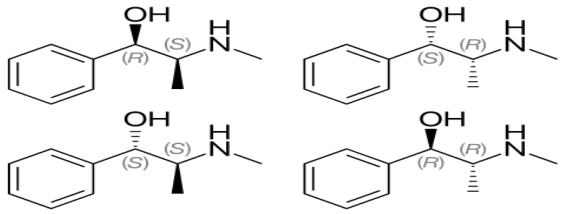
Cetirizine and Levocetirizine



Cetirizine and levocetirizine are both antihistaminic are used to treat allergy symptoms, but levo isomer is active enantiomer of cetirizine i.e. it is a more potent form, levo cetirizine is essentially used half dose of cetirizine and clinical studies suggest it maybe more effective at low doses and potentially loss sedating than cetirizine, where the dose of levocetirizine less than cetirizine.

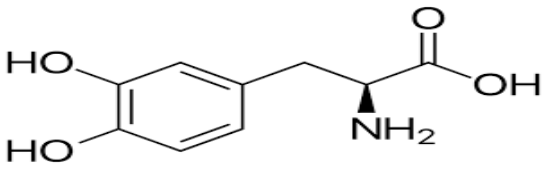
Cetirizine may be a dextro or racemic mixture, but the levo is a pure enantiomer. The stereochemistry of cetirizine explains the potency of the drug, where the dose of levocetirizine is half the dose of cetirizine.

Erythro Ephedrine and Threo Ephedrine



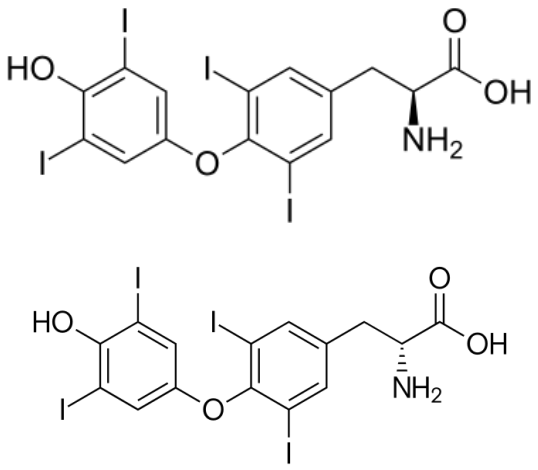
Ephedrine, both natural and synthetic, exists as two pairs of stereo isomers categorized as erythro and threo (pseudo ephedrine) the term of erythro refers to the stereo isomer where the substituents on the chiral carbon are on the same side and the threo ephedrine refers to isomer where the substituents on the two chiral carbons are on opposite side of molecule. Ephedrine is a sympatho-mimetic amine with stimulant properties used for conditions like asthma, high potential and as a decongestant, while both erythro and threo forms have a pharmacological activity, the erythro-form specifically the (-)-ephedrine enantiomer is more commonly used in medical applications like CNS stimulant and treatment of asthma while the pseudo ephedrine used as decongestant agent.

Dopa and Levodopa



Levodopa and dextrodopa are both forms of the molecule 3,4-Dihydroxyphenylalanine, but they differ in their optical activity. L-Dopa is biologically active and used to treat parkinson's disease because it is a precursor to dopamine, which is deficient in parkinson's patients. D-Dopa, the enantiomer of L-Dopa, is biologically inactive due to L-Dopa is able to cross the blood-brain barrier and increase the dopamine in the brain, while the dextro dopa unable to penetrate the blood-brain barrier; hence, the stereochemistry of Dopa explains the mechanism of action and pharmacology of L-Dopa as antiparkinson's agent.

Levothyroxine and Dextrothyroxine



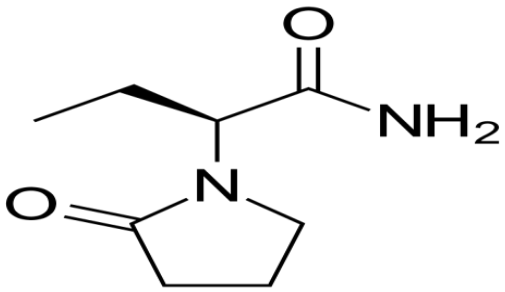
Levothyroxine has pharmacological action when it is used in the treatment of hypothyroidism, where the levo isomer is more active than the dextro isomer.

Dextrothyroxine is used to lower cholesterol levels, particularly triglycerides, in patients with hypercholesterolemia. It can also reduce LDL,

cholesterol and increase HDL.

The stereochemistry of thyroxine explains the activity and the pharmacological action of thyroxine, where the action of levo differs than dextro.

Levetiracetam



Levetiracetam is a drug used to treat epilepsy and it is the (S)-enantiomer of a molecule, the (R)- enantiomer called etiracetam has no anticonvulsant activity while levetiracetam (S-enantiomer) has anticonvulsant activity, levetiracetam is administer as a single enantiomer, where it binds to synaptic vesicle protein (SV2A), which is believed to play a role in neurotransmitter release, this binding is thought to reduce the release of neurotransmitter thus inhibiting the propagation of seizure activity, so the (S)-enantiomer explain the pharmacology of levetiracetam as anticonvulsant agent and the (R)-enantiomer has no anticonvulsant activity.

3. Conclusion

Stereochemistry plays a critical role in determining the pharmacological efficacy, safety, and overall therapeutic profile of pharmaceutical agents. The spatial arrangement of atoms within a drug molecule directly influences its interaction with biological targets such as receptors, enzymes, and transporters. This research highlights several clinically relevant examples where enantiomers and geometric isomers exhibit significantly different pharmacodynamic and pharmacokinetic profiles, emphasizing the importance of stereoselectivity in drug design and clinical application.

From the antitussive and opioid effects of dextromethorphan and levomethorphan, to the selective anticancer activity of cisplatin over transplatin, and the improved potency and safety of drugs like escitalopram, levocetirizine, and levetiracetam, it is evident that the stereochemical configuration dictates both the mechanism of action and therapeutic outcomes. Furthermore, the ability of only certain enantiomers, such as levodopa, to cross physiological barriers and exert their intended effect underscores the necessity for stereochemically pure formulations in achieving optimal treatment responses.

As pharmaceutical science advances, greater emphasis must be placed on chiral synthesis, enantioselective drug development, and precise stereochemical characterization to ensure the efficacy and safety of future medications. Understanding and leveraging stereochemistry is not merely a chemical concern but a clinical imperative that shapes modern pharmacotherapy.

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