Proceedings of the 3rd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/98/2025.21467

Stereochemistry and Pharmacologic Action based on Plane Isomerism, Optical Isomerism and Conformational Isomerism

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Abstract: In a recent study, thalidomide has been proved to have positive pharmacological effects in the immune system, such as the treatment of lupus erythematosus and anti-tumor, but 60 years ago, because of its optical isomer, it led to many tragedies. This time, by collecting the data of papers, this paper mainly analyzes and summarizes the connection between stereochemistry and pharmacological action of drugs, and tried to find the main reasons for the isomers of different structures and their effects from the aspects of biology and medicine. 4-aminopyridine, 4-aminoquinoline, thalidomide, and macrolide compounds are mentioned in this article. It comes to the conclusion that the larger the plane structure area of some drugs, the better the efficacy; some drugs have therapeutic effects only in the R configuration and some drugs with different chiral structures have different pharmacological functions.

Keywords: Stereochemistry, drug activity, isomer, thalidomide

1. Introduction

In recent studies, more and more studies have shown that thalidomide has a very positive pharmacological effect in the immune system, and has become a popular drug, which can treat lupus erythematosus, multiple myeloma and other immune diseases, but also can strengthen the immune system to fight tumors or anti-inflammatory effects. In the history of drug development, stereochemistry and pharmacological effects seem to be closely linked. This study discussed the relationship between stereochemistry and pharmacological effects again by collecting previous papers and reorganizing research reports, and tried to classify and explain the different effects and influences of different isomers in living organisms. 4-aminopyridine, 4-aminoquinoline, thalidomide, macrolide compounds are mentioned in this article. It is believed that through detecting different mechanisms of action more effective drugs in a shorter period of time.

1.1. Overview of Stereochemistry

Stereochemistry was founded in the early 19th century. J.B. Biot was the first to observe the optical rotation of organic matter [1]. In 1848, L. Pasteur isolated two tartaric acid crystals, one hemihedral to the left and one hemihedral to the right. The former causes the plane polarized light to rotate to the left, while the latter causes it to rotate to the right at the same Angle [2]. In 1874, J.H. Van't Hoff and J.A.

DOI: 10.54254/2753-8818/98/2025.21467

Lebel respectively proposed the tetrahedral theory of carbon atoms [3], they believe that the molecule is A three-dimensional entity, the four valence bonds of carbon are symmetric in space, pointing to the four vertices of a tetrahedron, and the carbon atom is located in the center of the tetrahedron. When a carbon atom is connected with four different atoms or groups, it produces a pair of isomers, which are physical and mirror images of each other, this carbon atom is called an asymmetric carbon atom, and this pair of compounds are optical isomers of each other. The work of Van't Hoff and Lebel is the basis of stereochemistry. Since then, more and more scholars have joined the discipline and added to it.

1.2. The Relationship between Stereochemistry and Pharmacological Action

Arthur Robertson Cushny, one of the first scholars to find a connection to pharmacy in stereochemistry, proposed in his paper that optical isomers behave differently pharmacologically, just as they do with enzymes or react differently with substances with known structures such as alkaloids or acids [4]. They show the same variability here; for example, in cerebral supine and cerebral supine, the left-handed form is about 15 times more toxic than the right-handed form in some organs, where they are said to play a "special role," while in others, such as in the muscles or the nerve ends that supply it, the isomers are just as toxic and only weakly so.

2. Effect of Planoisomerism on Pharmacological Action

2.1. 4-aminopyridine and 4-amino-quinoline

4-aminopyridine and 4-aminoquinoline lack antibacterial activity, but the introduction of coplanar styrene groups into their molecules increases their antibacterial activity due to the increase of their planar surface area. The effect of the drug on the bacterial surface appears to be the ability to concentrate on inhibiting RNA polymerase. One of the necessary conditions for base pairing in RNA and DNA is coplanarity. Embedding drugs such as acridine and quinoline in a part of the DNA double helix between base pairs is only possible if the relative units have coplanarity. This not only guarantees the effective embedding of the drug, but also contributes to the stabilizing effect of the formed complex through van der Waals forces and charge transfer. In contrast, hydrogenation of an aromatic ring of 8-amino-acridine to 8-amino-1,2,3, 4-tetrahydroacridine destroys the planarity of the ring system and eliminates its strong interaction with DNA, resulting in a small reduction in antimicrobial activity.

2.2. Specific Causes of Antibacterial Activity

Actinomycin D binds to DNA to form complexes that inhibit RNA polymerase activity. Studies have shown that actinomycin D inhibits RNA synthesis very rapidly, especially in gram-positive bacteria such as Staphylococcus aureus [5]. Alanine also inhibits RNA and DNA synthesis, and its mechanism of action is similar to that of actinomycin D. Alanine also binds to DNA and exhibits competitive inhibition in RNA polymerase reactions [6].

3. Influence of Conformational Isomerism on Pharmacological Action

3.1. Hexachlorocyclohexane

Hexachlorobenzene has the effects of touch, fumigation and stomach toxicity on insects, and was once the largest tonnage agricultural drug in China. The acute toxicity of benzene hexachloride is relatively small, and the toxicity of all isomers is the highest in γ-hexachloride. After entering the body, benzene hexachloride mainly accumulates in the central nervous system and adipose tissue,

DOI: 10.54254/2753-8818/98/2025.21467

stimulates brain movement and cerebellum, and can also affect the vegetative nervous system and peripheral nerves through the cortex, and affect the oxidative phosphorylation of cells in the organs, causing nutritional disorders and degeneration and necrosis of the organs. It can induce hepatocyte microsomal oxidase, affect endocrine activity and inhibit ATPase. Only gamma-hexachlorobenzene has insecticidal ability.

3.2. The Difference of Hexachlorobenzene in Different Configurations

α-HCH:Melting point 159~160℃, boiling point 288℃, easily soluble in chloroform, benzene, etc., with a lasting spicy smell.

β-HCH:Melting point 314~315℃, density 1.89 g/cm 3 (19℃), sublimation after melting, slightly soluble in chloroform and benzene.

γ-HCH:Melting point 112~113℃, boiling point 323.4℃, soluble in acetone, benzene and ether, easily soluble in chloroform and ethanol, with mouldy odor and volatility.

δ-HCH:Melting point 112~113℃, boiling point 323.4℃, soluble in acetone, benzene and ether, easily soluble in chloroform and ethanol.

ε-HCH:Melting point 112~113℃, boiling point 323.4℃, soluble in acetone, benzene and ether, easily soluble in chloroform and ethanol [7].

4. Influence of Optical Isomerism on Pharmacological Action

4.1. Overview of Optical Isomerism and Pharmacological Effects

Because of the chiral optimization phenomenon, biological macromolecules, such as proteins, polysaccharides, enzymes, nucleic acids and receptors, which are important bases for life activities, are chiral, and enzymes only catalyze the reaction of specific chiral substrates, and receptors only bind to specific chiral small molecules. Therefore, in many cases, the pairs of enantiomers of subsexual drugs have different selective effects with biological macromolecules. There are significant differences in pharmacological activity, metabolic process, metabolic rate and toxicity in organisms.

4.2. Types of Drug Action of Different Enantiomers

One enantiomer is active and the other has no significant pharmacological effect. For example, salbutamol and terbutaline are two bronchodilating drugs whose R configurations are 80 to 200 times stronger than S configurations, respectively. It shows that the S enantiomers have no significant effect. The two enantiomers have the same or similar pharmacological activity. In this case there is no need to use a single enantiomer if the toxic effects are not different. Getifloxacin is an example; sometimes both enantiomers have similar activities, but a single enantiomer should be selected for overall balance. For example, two omeprazole enantiomers have similar activity in the treatment of gastric ulcers, but the individual difference of the racemes is large, the difference of the S-configuration enantiomers is small and the therapeutic index is high, so a single S-configuration should be used. The two enantiomers have completely different physiological activities; one of the two enantiomers is active, while the other is not only inactive, but also has toxic side effects.

4.3. Thalidomide

4.3.1. History of Thalidomide

Thalidomide was first synthesized in 1953 by Chemie Grünenthal, a German pharmaceutical company, and marketed in 1957. Initially, it was sold as a mild sedative and an effective treatment for

DOI: 10.54254/2753-8818/98/2025.21467

insomnia, anxiety, and nausea, particularly in pregnant women suffering from morning sickness. Its non-habit-forming nature and perceived safety made it extremely popular, and it was eventually distributed in more than 40 countries. By the early 1960s, thalidomide was recommended by doctors worldwide as a remedy for a variety of ailments, including gastrointestinal issues and colds.

However, its tragic side effects soon became apparent. By the early 1960s, reports began emerging of babies being born with severe birth defects, particularly phocomelia (a condition where limbs are shortened or absent). In 1961, Dr. Widukind Lenz, a German physician, linked the drug to these congenital malformations. His research found that the drug's teratogenic effects were most severe when taken by pregnant women during the first trimester [8].

In 1961, after widespread reports of birth defects, thalidomide was withdrawn from the market, and its use became restricted. It is estimated that approximately 10,000 babies were affected by the drug, with thousands dying in infancy. The global tragedy led to stricter drug regulation and testing procedures for pharmaceuticals, especially concerning the safety of medications during pregnancy.

4.3.2. Principle of Teratogenesis of Thalidomide Enantiomers

Thalidomide's chemical structure is simple yet unique. It is a racemic compound, meaning it consists of two mirror-image molecules. These two isomers (R-thalidomide and S-thalidomide) exhibit very different biological activities, which was one of the critical factors in understanding its teratogenic effects.

In the body, thalidomide undergoes metabolism in the liver, producing metabolites that can affect cellular processes. The S-isomer of thalidomide is primarily responsible for the teratogenic effects. While the exact mechanisms of thalidomide's teratogenicity were not initially understood, it was later discovered that the drug interferes with angiogenesis, the formation of new blood vessels, which is crucial for the development of limbs and other organs in the fetus. Thalidomide inhibits the growth of blood vessels, particularly in the developing limbs, resulting in the characteristic limb defects seen in babies exposed to the drug during pregnancy.

The drug's teratogenicity is likely related to its ability to bind to a specific protein, cereblon, which plays a role in regulating the immune system and cell growth. When thalidomide binds to cereblon, it disrupts various cellular pathways, leading to abnormal embryonic development. This discovery has been instrumental in understanding the molecular basis of thalidomide's harmful effects.

One of the reasons why thalidomide caused such widespread damage was its accessibility and the lack of proper regulatory oversight at the time. Additionally, the drug's long half-life in the body meant that even a small amount of thalidomide could cause significant harm if taken during critical periods of fetal development.

4.3.3. Current Principles of Neurological Disease Treatment

Despite its dark history, thalidomide has made a remarkable comeback in the medical world. In the 1990s, researchers began to explore its potential as a treatment for conditions beyond its initial use. Thalidomide's anti-inflammatory, immunomodulatory, and anti-angiogenic properties became the focus of new therapeutic applications. While its teratogenic effects remain a critical concern, modern medical protocols, rigorous safety guidelines, and advancements in drug testing have made it possible to use thalidomide safely in certain clinical settings. One of the most prominent areas where thalidomide has shown promise is in the treatment of neurological diseases, particularly those involving chronic inflammation or immune system dysregulation.

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4.3.3.1. Multiple Myeloma and Other Cancers

Thalidomide's re-emergence as a therapeutic agent began with its use in cancer treatment, particularly multiple myeloma. Multiple myeloma is a type of cancer that affects plasma cells in the bone marrow, leading to symptoms like bone pain, anemia, and kidney damage. In the early 2000s, studies showed that thalidomide could inhibit the growth of myeloma cells, promote the immune system's response against cancer cells, and reduce tumor burden. The drug's ability to inhibit angiogenesis plays a critical role in its antitumor effect, as tumors require a blood supply to grow and metastasize. Thalidomide, in combination with other chemotherapy drugs, has become part of the standard treatment for multiple myeloma. It is now widely used in clinical practice under strict monitoring guidelines to prevent its teratogenic effects.

4.3.3.2. Neurological Diseases

Thalidomide's neuroprotective properties have sparked significant interest in treating neurological conditions, especially those that involve inflammation and immune system dysfunction. Conditions, such as leprosy, where nerve damage results from chronic inflammation, have been effectively treated with thalidomide. The drug's immunomodulatory properties help reduce inflammation, which can alleviate symptoms and prevent further nerve damage in patients with leprosy. Halidomide is also being investigated for its potential in treating other neurodegenerative diseases, such as Alzheimer's disease and multiple sclerosis. In these conditions, inflammation plays a significant role in the progression of the disease. Thalidomide's ability to modulate the immune response and reduce inflammation may offer new therapeutic options. However, more research is needed to establish its safety and efficacy in these contexts.

4.3.3.3. Safety and Regulatory Measures

To address the serious concerns regarding thalidomide's teratogenic effects, modern medical protocols have been put in place to ensure its safe use. The most notable is the Thalidomide Risk Evaluation and Mitigation Strategy (REMS), which was implemented by the U.S. Food and Drug Administration (FDA) and other regulatory bodies worldwide. REMS ensures that thalidomide is only prescribed to patients with specific medical conditions, such as multiple myeloma and leprosy, and that patients are thoroughly informed of the risks, particularly the risk of birth defect. Female patients of childbearing potential must undergo regular pregnancy testing and use two forms of contraception during treatment. These measures are essential to prevent any accidental pregnancies during the use of the drug.

4.4. Other Optically Active Isomers

4.4.1. Terbutaline

Terbutaline selectively binds to and activates β2-adrenergic receptors in bronchial smooth muscle. When terbutaline activates these receptors, it leads to relaxation of bronchial smooth muscle through a series of biochemical reactions (such as increasing intracellular cAMP levels), thereby dilating the airway, reducing airway resistance, and relieving breathing difficulties due to bronchospasm.

4.4.2. Omeprazole

Omeprazole works by selectively inhibiting the hydropotassium ATPase (i.e., proton pump) within the cells of the gastric parietal, which is a key enzyme responsible for the secretion of stomach acid. When omeprazole binds to the proton pump, it inhibits its activity, resulting in a significant reduction

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in gastric acid secretion. This effect reduces the acidic environment in the stomach, helping to relieve acid-related symptoms and promote ulcer healing. Because omeprazole is an irreversible inhibitor, the activity of the proton pump is permanently suppressed after drug discontinuation until a new proton pump is synthesized [9].

5. Drugs that Interact with Optical Isomerism and Planar Isomerism

The activity of macrolides has a great relationship with its spatial configuration. The groups connected in the macrolides chain can not only help the macrolides to form a fixed conformation, but also bind to some structures in biological cells, thus assisting the macrolides to exert their biological activities [10].

As shown in Table 1, it can be found that the R-configuration compounds with different plane types have different inhibition rates against the rice thin line disease, among which 3-2j and 3-2m have the best inhibition effect.

Table 1: In vitro antibacterial bioactivity of facial chiral macrolide compounds

Compound	Microspora oryzae (Xoc)	
	Inhibition ratio (%)	
	100 (μg/mL)	50 (μg/mL)
(R_P)-3-2a	54.92±1.24	31.10±2.51
(R_P)-3-2b	0	0
(R_P)-3-2c	4.61±2.53	7.04±5.09
(R_P)-3-2d	0	0
(R_P)-3-2e	0	0
(R_P)-3-2f	0	0
(R_P)-3-2g	0	0
(R_P)-3-2h	38.41±2.54	25.36±3.07
(R_P)-3-2i	0	0
(R_p)-3-2j	55.02±1.55	24.19±3.18
(R_p)-3-2k	0	0
(R_p)-3-2l	13.09±2.60	5.21±4.44
(R_p)-3-2m	55.72±3.08	43.18±2.52
(R_p)-3-2n	0	0
(R_p)-3-2o	31.65±2.77	15.11±3.11
(R_p)-3-2p	41.21±1.94	35.06±2.88
(R_P)-3-2q	6.00±1.65	1.26±3.37
(R_P)-3-2t	9.40±4.22	4.42±4.18
(R_P)-3-7	31.77±2.08	26.60±1.58
(R_P)-3-9	0	0
(R_P)-3-11	32.77±3.11	9.17±2.48
Bismerthiazol	78.62±0.85	76.23±1.23
Thiediazole copper	35.54±1.24	26.62±1.58

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6. Conclusion

After the previous study, this paper found that the mechanism of action of different types of isomers is different, and even different drugs of the same type of isomers have different pharmacological effects due to their different groups or configurations. The description of thalidomide is to remind the current researchers that the poison may not be just a poison, it is more likely to become an important drug after research, and make outstanding contributions to the current medical field [11]. Stereochemistry plays a crucial role in pharmacological action, which not only affects the biological activity of drugs, but also determines the interaction between drugs and biological targets. Different stereoisomers may exhibit completely different pharmacological properties or even opposite effects, which makes the study of stereochemistry particularly important in the development of new drugs. By deeply understanding the three-dimensional structure of molecules and their interactions with the environment in the organism, scientists are able to more effectively design drugs with specific efficacy and fewer side effects. This not only promotes the development of medicinal chemistry, but also lays the foundation for the realization of personalized medicine. In the future, with the advancement of technology, the application of stereochemistry in drug research will be more extensive, and will certainly make greater contributions to the development of human health [12].

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