IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

"THE ROLE OF STEREOCHEMISTRY IN STEROIDAL DRUG DEVELOPMENT"

RAHAT KATOON[1], JITENDRA KUMAR[2]
S.N COLLEGE OF PHARMACY, JAUNPUR

Abstract:
Stereochemistry plays a pivotal role in the design, optimization, and clinical performance of steroidal drugs. Due to the highly specific nature of steroid-receptor interactions and the stereoselective nature of enzyme-mediated metabolism, the stereochemical configuration of steroids can significantly affect their therapeutic efficacy, side effects, and pharmacokinetic profiles. This review explores the impact of stereochemistry in steroidal drug development, focusing on the importance of chirality, receptor binding, metabolic pathways, and the design of selective compounds. We also discuss how stereochemical considerations influence the synthesis of steroidal drugs, the challenges associated with chirality in drug design, and future directions in the development of stereochemically optimized steroid-based therapies.

Keywords:
Steroidal drugs, Stereochemistry, Chirality, Receptor binding, Drug metabolism, Selectivity, Pharmacodynamics, Corticosteroids, SARMs, Steroid synthesis.

Introduction
Steroids are the class of naturally occurring organic compounds with four rings arranged in a specific molecular configuration. Steroids exhibit two principal biological functions such as important components of cell membranes which alter membrane fluidity and as signaling molecules. Steroidal drugs have revolutionized medicine, from anti-inflammatory corticosteroids to hormonal therapies and anabolic steroids. The structural backbone of these drugs consists of steroidal rings, with small modifications often influencing their pharmacological properties. Among the most important of these modifications is stereochemistry. This review examines the role of stereochemistry in steroidal drug development and how it affects the drug's performance, receptor specificity, and metabolic processes.

Classification of Steroids
Anabolic Steroids: Interact with androgen receptor and enhance muscle mass and male sex hormones
Glucocorticoids: Regulate metabolism and immune function and anti-inflammatory activity
Mineralocorticoids: Maintain blood volume and renal excretion
Progestins: Development of female sex organs
Phytosteroids: Plant steroids
Ergosteroids: Steroids of the fungi and vitamin D

Nomenclature of steroids
Beginning in the 1950s, nomenclature rules for steroids were being developed, and the most recent IUPACIUB Joint Commission rules for systematic steroid nomenclature were published in 1989. The steroid core structure is composed of seventeen carbon atoms (C17), bonded in four "fused" rings. Three six-member cyclohexane rings (rings A, B and C in the first illustration) and one five-member cyclopentane ring (the D ring) (Fig. 2). Steroids vary by the functional groups attached to this four ring core and by the oxidation state of the rings

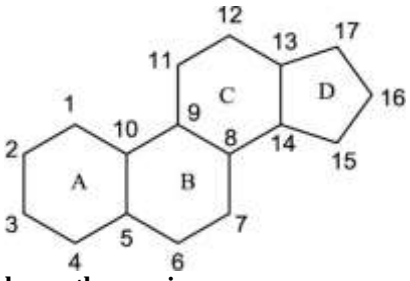
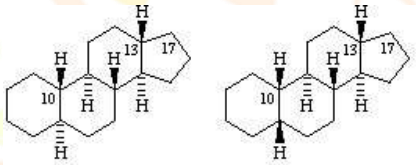


Fig.1: Structure of Cyclopentanoperhydrophenanthrene ring.

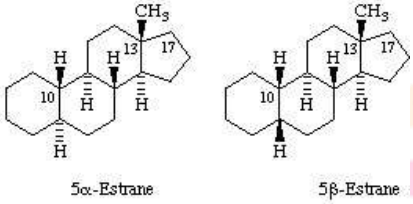
Almost all steroids are named as derivatives of any one of the following basic steroidal ring.

- Solid line indicates groups above the plane of the nucleus (β-configuration) and dotted line denote groups below the plane (α- configuration).
- The configuration of the hydrogen (-H) at C-5 position is always indicate in the name.
- Compounds with 5-α cholestane belong to the 'allo series' while compounds derived from the 5-β- cholestane belongs to the 'normal series'.
- If the double bond is not between sequence numbered carbon, in that case both carbons are indicated in the name.
- The symbol Δ (delta) is used to indicate C=C bond in steroids.
- When a methyl group is missing from the side chain, these are not indicated by the prefix 'nor' with the number of the carbon atom which is disappear.

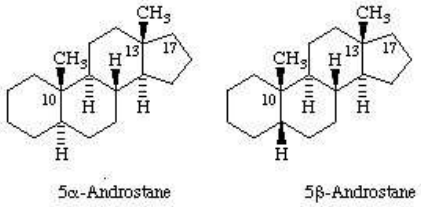
Gonane: The parent tetracyclic hydrocarbon without methyl groups at C-10 and C-13 and without a side chain at C-17 is named gonane. E.g. 5 (α or β) gonane (C =17) (**Fig. 2**).



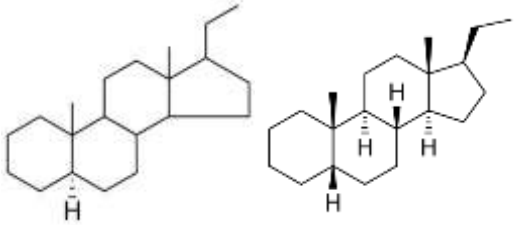
Estrane: The hydrocarbon with a methyl group at C-13 but without a methyl group at C-10 and without a side chain at C-17 is named as estrane (**Fig. 3**). E.g. 5 (α or β) estrane (C =18)



Androstane: The hydrocarbon with methyl groups at C-10 and C-13 but without a side chain at C-17 is named as androstane (**Fig. 4**). E.g. 5 (α or β) androstane. (C =19)



Pregnane: The hydrocarbon with methyl groups at C-10 and C-13, with a side chain at C-17 upto C-21 containing is named Pregnane (**Fig. 5**). It is a parent hydrocarbon for two series of steroids stemming from 5α-pregnane and 5β-pregnane (C=21).

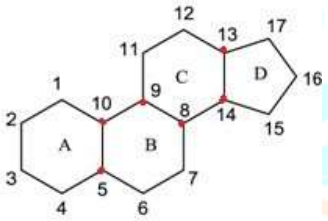


5α-pregnane 5β-pregnane

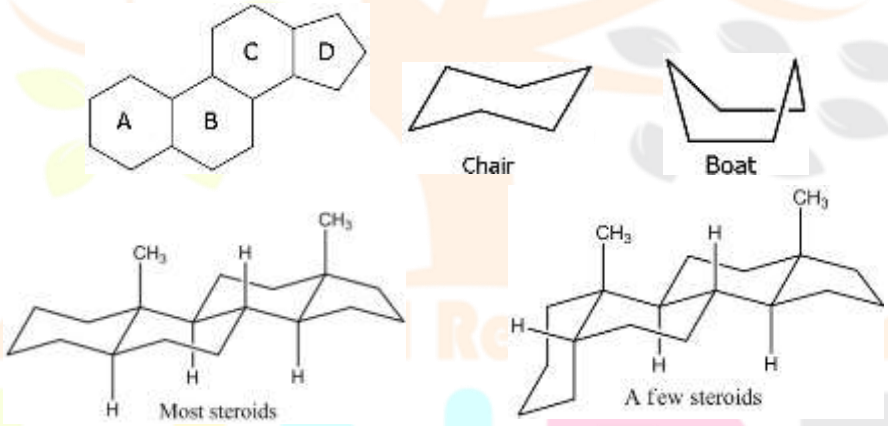
Cholane & Cholestane: The hydrocarbon with methyl groups at C-10 and C-13, with a side chain at C-17 upto Carbon chain 24 is named Cholane and upto Carbon chain 27 named Cholestane (**Fig. 6**).

Stereochemistry of steroids

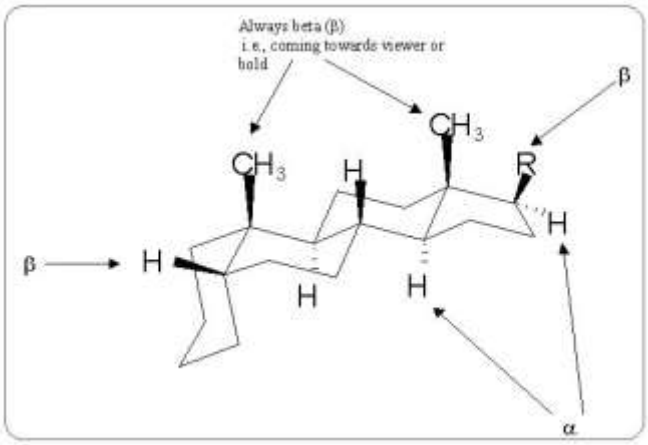
There are six asymmetric carbon atoms 5,8,9,10,13,14 in the nucleus, therefore 64 optically active forms are possible (**Fig. 7**).



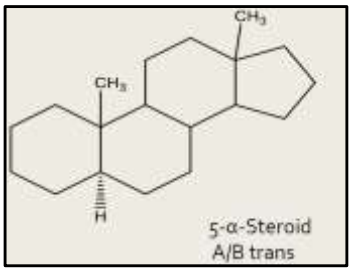
Cholestane , androstane and pregnane exist in two conformations such as chair form and boat form. Chair form is more stable then boat form due to less angle strength, therefore all cyclohexane ring in steroid nucleus exist in the chair form (**Fig. 8**).

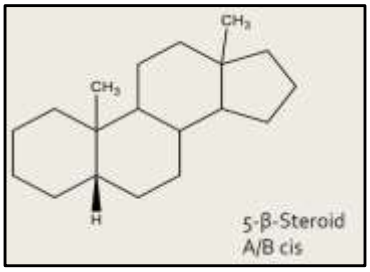


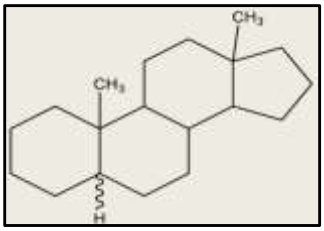
The absolute stereochemistry of the molecule and any substituent is shown with solid bond (β-configuration) and dotted bond (α-configuration) (**Fig. 9**).



The aliphatic side chain at C-17 position is always assumed to be β- configuration. The term cis and trans are sometimes used to indicate the backbone stereochemistry between the rings (**Fig. 10**).
Example; 5-α- steroid are A/B Trans and 5-β- steroids are A/B Cis.







If A/B fusion cis and trans both position possible or position is unknown, it is indicated by waving lines/bonds (**Fig. 11**).

Chirality in Steroidal Drugs

Chirality refers to the presence of non-superimposable mirror image forms, known as enantiomers. The presence of stereocenters in the steroid molecule means that different enantiomers can have vastly different biological effects: Impact on Receptor Binding: Enantiomers interact differently with their target receptors, where one might exert a desired therapeutic effect, while the other could be inactive or harmful. Enzyme-Mediated Metabolism: Stereoisomers often undergo different metabolic processes, leading to variations in drug half-life, bioavailability, and clearance.

Steroid-Receptor Interactions

Steroid hormones like glucocorticoids, estrogens, and androgens act by binding to specific nuclear receptors, where their stereochemical configuration is crucial for proper receptor binding and activation:

Selective Binding: The stereochemistry of steroids influences how well they bind to their respective receptors, such as androgen or estrogen receptors, leading to either agonist or antagonist effects.

Conformational Influence: The 3D structure of steroids impacts their ability to induce conformational changes in the receptor, thus triggering the desired cellular response. Even subtle changes in stereochemistry can lead to reduced or increased efficacy.

Pharmacodynamics and Stereochemistry

Pharmacodynamics refers to how a drug produces its effects at the receptor level, and stereochemistry is central to this process:

Activation vs. Inhibition: A steroid's stereochemical configuration determines whether it acts as an agonist, stimulating receptor activity, or as an antagonist, blocking receptor function.

Steroidal Conformations: Steroids exhibit rigid polycyclic structures, with slight alterations in ring or side-chain configurations leading to different pharmacological effects.

Steroid Metabolism and Stereochemistry

The body's metabolism of steroidal drugs is heavily influenced by their stereochemical structure: Enzymatic Metabolism: Cytochrome P450 enzymes, responsible for drug metabolism, are highly stereoselective. The stereochemical differences between enantiomers can lead to different metabolic pathways and rates of clearance. Toxicity and Drug Interactions: Stereochemical variations can also influence the likelihood of drug-drug interactions or toxicities, which is especially important when drugs are metabolized via similar pathways.

Applications in Steroidal Drug Development

Corticosteroids: The design of corticosteroids, such as prednisone and dexamethasone, has focused on optimizing their anti-inflammatory effects while minimizing undesirable mineralocorticoid activity. Stereochemistry plays a major role in this balance. Oral Contraceptives and Hormonal Therapy: The development of synthetic estrogens and progestins has relied on precise stereochemical modifications to achieve selective receptor binding and control over fertility or menopausal symptoms.

Selective Androgen Receptor Modulators (SARMs): SARMs represent a class of steroidal drugs with selective tissue activity. Stereochemistry is key to ensuring that these compounds selectively activate androgen receptors in muscle and bone without exerting negative effects on the prostate or other tissues.

Challenges in Steroidal Drug Synthesis

The synthesis of stereochemically pure steroidal drugs presents significant challenges:

Asymmetric Synthesis: The production of pure enantiomers often requires advanced synthetic techniques such as chiral catalysis or asymmetric synthesis. The development of cost-effective methods for synthesizing stereochemically defined steroids is a major focus in drug design.

Chiral Separation: In some cases, stereoisomers need to be separated and isolated, which can be both time-consuming and costly.

Regulatory and Safety Considerations

The regulatory approval of stereochemically distinct steroid drugs requires careful characterization of each enantiomer:

Safety Profiles: Clinical trials must assess the efficacy and safety of each enantiomer, with special attention to side effects such as liver toxicity, cardiovascular issues, or endocrine disruption.

Chiral Drug Regulation: Regulatory agencies such as the FDA and EMA may require detailed stereochemical data, including studies on pharmacokinetics, pharmacodynamics, and toxicology, before approving new steroidal drugs.

Future Directions in Steroidal Drug Development

Stereochemical Optimization: Advances in computational chemistry and structure-based drug design offer new opportunities for optimizing steroid molecules to improve selectivity, potency, and safety. Biologics and Steroids: The integration of biologics with steroidal therapies, such as monoclonal antibodies or gene editing technologies, may also benefit from stereochemical insights to enhance efficacy.

Conclusion

Stereochemistry is a critical factor in the design, development, and clinical performance of steroidal drugs. By understanding how small changes in the stereochemical configuration of steroid molecules affect their interactions with receptors, enzymes, and metabolic pathways, researchers can develop more selective, effective, and safe therapies. As new synthetic methodologies and computational tools emerge, the ability to tailor steroidal drugs to specific therapeutic needs will continue to improve.

References

1. John A. Thomas, Principles of Endocrine Pharmacology, Plenum medical Book Company, New York and London,1986, 1-14.
2. Tripathi KD, Essentials of Medical Pharmacology, Seventh Edition: 2013, Jaypee Brothers medical Publishers (P) Ltd, Page no-306-311.
3. Pharmacology and pharmacotherapeutics by R.S satoskar, 21st edition, 2012, Popular prakashan, 935-942.
4. Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, 25th Ed., 2010,Chapter-20, 666-701.
5. Foye's Principles of Medicinal Chemistry, Lippincott Williams & Wilkins, 7th Ed., 2012, 576-588.
6. Clark JH, Hardin JW, Mc Cormack SA (1979). "Mechanism of action of estrogen agonists and antagonists". J. Anim. Sci. 49 Suppl 2: 46–65.
7. Kenneth L. Becker (2001). Principles and Practice of Endocrinology and Metabolism. Lippincott Williams & Wilkins. pp. 932, 989, 1061. ISBN 978-0-7817-1750-2.
8. Razdan Balkishen, Medicinal Chemistry, First Edition: 2010, CBS publishers & Distributors Pvt. Ltd., Page No. 497-500.
9. Tomlinson E.S, Maggs J.L, Park B.K, Back D.J: Dexamethasone metabolism in-vitro: species differences. J Steroid Biochem Mol Biol. 1997, 62(4):345-52.
10. Baker GB, Prior TI. Stereochemistry and drug efficacy and development: relevance of chirality to antidepressant and antipsychotic drugs. Ann Med. 2002;34(7-8):537-43. doi: 10.1080/078538902321117742. PMID: 12553493.
11. Chhabra, N., M.L. Aseri, and D. Padmanabhan, A review of drug isomerism and its significance. International journal of applied & basic medical research, 2013. 3(1): p. 16-18.
12. Song, W. and S. Si, The rare ethambutol-induced optic neuropathy: A case-report and literature review. Medicine, 2017. 96(2): p. e5889-e5889.
13. Rivas, A. Thalidomide Birth Defect Victims Settle Class-Action Suit For $81 Million, Decades After Morning Sickness Pill Was Pulled Off The Market. 2013; Available from: https://www.medicaldaily.com/thalidomide-birth-defect-victims-settle-class-action-suit-81-million-decades-after-morning-sickness.
14. Yartsev, A. Enantiomerism. 2018; Available from: https://derangedphysiology.com/main/cicm-primary-exam/required-reading/pharmaceutics/Chapter%202.0.1/enantiomerism.