

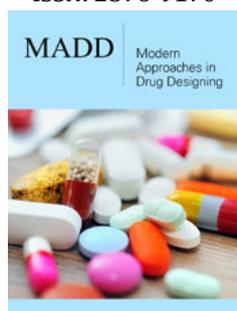
Molecular Modification: A Tool for Pruning the Molecule

John Sunil R^{1*}, Sridhar V¹, Sarbani Pal² and Jayashree A²

¹Department of Pharmaceutical Chemistry, India

²Department of Chemistry, India

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***Corresponding author:** John Sunil R,
Department of Pharmaceutical Chemistry,
Karimnagar, Telangana, India

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Abstract

Drug discovery is a process by which new drug molecules are discovered. Despite of advances in technology and understanding of biological systems, drug discovery is still a lengthy, expensive, difficult, and inefficient process with low rate of new therapeutic discovery so there is always needed to search for better drugs no matter how well the existing ones serve. Molecular modification is a revolution in contemporary drug development and still a major line of approach for the discovery of new drugs. Any alteration in the structure of known and previously characterized molecule for the purpose of enhancing its usefulness as drug is called as Molecular modification. The review article presents the significance of molecular modification and might be helpful in the development of the novel lead molecules to potential drug candidates for future.

Keywords: Drug discovery; Drug development; Better drugs; Molecular modification

Introduction

A. Any alteration in the structure of known and previously characterized molecule for the purpose of enhancing its usefulness as drug is called as Molecular modification [1].

B. Molecules obtained as a result of molecular modification are called as analogues or congeners.

C. The term molecular modification was coined by Hench.

D. It is also called as Molecular refinement, Molecular transformation, Molecular tailoring, Chemical modification, Chemical alteration, Pharmacomodulation and Method of variation.

E. It is one of tools of research in medicinal chemistry to refine molecules [2].

F. Molecular modifications of prototype (original) structures have yielded from no or little to moderate to significant improvements in their pharmacological potency.

G. Molecular modification by nature has been going on since the beginning of life.

H. Chemists have learned from nature about the effect of small changes in the structure of molecule on its biological activity.

I. Most of the molecules are modified either by altering its physical properties or by modifying the chemical structure.

Content

Types of molecular modification

- A. Natural: E.g., Morphine-Codeine
- B. Synthetic: E.g., Prontosil-Sulfanilamide

Purpose of molecular modification

- A. To improve or to alter the pharmacokinetics and Pharmacodynamics of the drug [3].

Criteria for molecular modification

- A. The molecule should be a known one.
- B. The molecule should be characterized one.

Overview of approaches in molecular modification

Conjunction approach:

- A. Molecular addition approach.
- B. Molecular replication approach.
- C. Molecular hybridization approach.

Disjunction approach:

Special approach:

- A. Bio isosteric replacement [4].
- B. Homologation [5].
- C. Change of position and orientation of some groups.
- D. Ring closing or ring opening methods.

Advantages of molecular modification [6]

- I. It enhances the selectivity or affinity of drug to a particular biological target.
- II. It increases the potency or efficacy of the drug.
- III. It improves the rate, extent of absorption and bioavailability of the drug.
- IV. It reduces the toxicity of the drug.
- V. It instills desired features in the drug.
- VI. It improves duration of action of the drug.
- VII. It decreases the cost of production of the drug.
- VIII. SAR studies of the drug can be undertaken.
- IX. It reduces the side effects of the drug.
- X. It increases metabolic stability or half-life of the drug.
- XI. It improves the overall safety of the drug.
- XII. It improves the formulation of the drug.
- XIII. It improves the acceptability of the drug by the patient.

Disadvantages of molecular modification

- I. It alters the shape of the drug molecule.
- II. It alters the solubility of the drug molecule.
- III. It may alter the polarity of the drug molecule.
- IV. It may alter the flexibility of the drug molecule.
- V. It alters the physico-chemical properties of the drug molecule.
- VI. It alters the bioactivity of the drug molecule (Table 1).

Table 1: Examples for molecular modification.

Sl. No	Lead Compound	Therapeutic Category of the Lead Compound	Analogue	Therapeutic Category of the Analogue	Comment
1	Sulfanilamide	Anti-bacterial	Probenecid Acetazolamide	Anti-gout Diuretic	There was change in the biological activity
2	Carbutamide	Anti-bacterial	Tolbutamide	Anti-diabetic	There was change in the biological activity
3	Chlorthiazide	Anti-hypertensive with diuretic side effect	Diazoxide	Anti-hypertensive without diuretic side effect	Activity was retained with the removal of side effect
4	Morphine	Analgetic	Pentazocine	Analgetic	Potency was increased Side effect was reduced
5	Cocaine	Local Anesthetic	Lidocaine	Local Anesthetic	Activity was improved Side effect was reduced

Summary and Conclusion

Molecular modification is a revolution in contemporary drug development and still a major line of approach for the discovery of new drugs. Molecular modification broadens the scope of usefulness of leads, but one has to be careful in measuring the effect of molecular modification of lead on its potency. To pave the way for

future research, there is a need to collect the latest information in this promising area.

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