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Molecular Hybridization - An Emanating Tool in Drug Design

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Abstract

Most of the diseases are multifactorial in nature. Moreover, the exploration of new drugs with appropriate absorption, distribution, metabolism, and excretion along with effective pharmacological activity and less toxicity for the treatment and cure of multifactorial diseases is a herculean task. There is new hope for the treatment of multifactorial diseases like cancer in recent years with the advent of Molecular hybridization. It is one of the approaches in the molecular modification of drug designing which involves the refinement of molecules. Chemists had learned well from nature about the significance of small changes in structures of drugs and its effect on biological activity. Molecular modification by nature has been going on since the beginning of life. Molecular hybridization is based on the combination of pharmacophores of different bioactive substances to produce a hybrid compound with improved affinity and efficacy when compared to the parent drugs. This strategy results in compounds with a modified selectivity profile, with different and/or dual modes of action and reduced undesired side effects. This technique focuses on the modulation of the pharmacophores giving rise to innovative hybrids. Molecular hybridization is a cropping up approach in drug discovery and development of medicinal chemistry during the latest years. The review article presents insights into the concept of molecular hybridization in designing better drugs.

Keywords: Drug design; Molecular modification; Molecular hybridization; Molecular hybrids

Introduction

The process of drug discovery for diseases with complex pathogenic factors has been facing significant challenges since the traditional "one molecule, one target" drug discovery paradigm is not adequately addressing many diseases. The architecture of new drugs with better physicochemical properties like appropriate absorption, distribution, metabolism, and excretion, effective pharmacological activity and less toxicity is also a herculean task. Besides the exploitation of new targets, there is another approach in drug discovery which involves combining two or more pharmacophore or drugs into a single molecule. The review article presents insights into molecular hybridization in designing drugs.

Literature Review

Molecular modification

Molecular modification is the chemical amendment of a known and previously characterized lead compound for the purpose of enhancing its usefulness as a drug. It is one of the approaches in the molecular modification of drug designing which involves the refinement of molecules [1,2]. It is also called as molecular manipulation or method of variation or chemical modification or chemical alteration. Molecular modifications of prototype (original) structures have yielded from no or little to moderate to significant improvements in pharmacological potency. Molecular modification enhances the specificity of a lead compound for a particular body target site, increases the potency of a lead compound, improves the rate and extent of absorption of the lead compound, reduces the toxicity of a lead compound, and changes the physical-chemical and biological properties of the lead compound. Molecular modification by nature has been going on since the beginning of life.

Approaches of molecular modification

The general approach of molecular modification involves:

- **Molecular disjunction approach:** It involves breaking of molecules.
- **Molecular conjunction approach:** It involves joining of molecules.

Types of molecular conjunction approach

- **Molecular addition approach:** It involves the association of two or more identical or non-identical molecules through weak forces of attraction.
- **Molecular replication approach:** It involves the association of two or more identical molecules through covalent bonding.
- **Molecular hybridization approach**: It involves the association of two or more non-identical molecules through hybridization.

Special approaches

- Ring closure/opening
- Formation of lower or higher homologs
- Introduction of double bonds
- Introduction of chiral centers
- Introduction or removal or replacement of bulky groups
- Ring equivalents

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- Isosteric substitutions
- Change of position or orientation of certain groups
- Introduction of alkylating moiety
- Modification toward inhibition or promotion of various electronic states

Molecular hybridization

Molecular hybridization is a process that involves the formation of molecular hybrids from two or more than two non-identical molecules having different characteristics with the help of a covalent bond. It is also defined as a combination of Pharmacophores of two or more than different bioactive substances of natural or synthetic origin to produce a hybrid compound with improved affinity and efficacy when compared to the parent drugs. It is abbreviated as MH. It is also called as Hybrid drug design, covalent bi-therapy, Molecular amalgamation, Molecular crossing, Molecular fusion, Molecular association, etc. It is a multi-targeted drug design. Molecular hybrids are the products of molecular hybridization. Hybrid compounds can be defined as chemical entities with two or more structural moieties with different biological functions. Molecular hybrids are also called as multi-target directed compounds, multi-functional compounds, dual-acting compounds, me-better drugs, multiple ligands combi molecules, double-drugs, combinational drugs, dual -drugs multiple-drugs, bifunctional drugs, bivalent ligands, drugs with two heads, etc. [3-6]. Hybrid compounds can be constructed by linking Pharmacophores subunits directly or indirectly using linkers or spacers in molecular hybridization.

The concept of molecular hybridization was first introduced by Nicki in the year 1886. The term molecular hybridization was proposed by Morphy et al. Phenolic esters of carboxylic acids are the first molecular hybrids synthesized by Nicki by the esterification reaction of carboxylic acids using phenols. In the designing of new drugs, the concept of molecular hybridization is an attractive strategy. It is a useful tool in the design of new drug prototypes. These merged Pharmacophores addresses the active site of different target and offer the possibility of overcoming drug resistance. It is a new concept in drug designing and drug development. The hybridization process is closely related to the strategy of obtaining a mutual pro-drug, with the main difference being that the pro-drug action is dependent on its *in vivo* cleavage while hybrid compounds can also act "per se" at their specific receptors or targets Molecular modification is a structural modification strategy useful in the design of new optimized ligands and prototypes with new molecular architectures composed of two or more known bioactive derivatives, through the adequate fusion of these sub-unities. The molecular hybridization can be useful to improve the main unsuccessful causes of fail in drug discovery such as lack of efficacy and poor safety. It is a pharmaco-modulation focused on new innovative hybrid compounds. It is an extension of the concept of a fixed-dose combination of two or more drugs in a single tablet. Molecular hybridization is a molecular modification approach to obtain multiple-ligands/compounds with pharmacokinetic advantages over concomitant administration of two different drugs [7].

Types of molecular hybridization

Drug-drug molecular hybridization which involves hybridization between the drugs

A. Directly linked drug-drug molecular hybridization

- Merged type
- Fused type

B. Indirectly linked drug-drug molecular hybridization

- Linked by a flexible linker
- Linked by a rigid linker

Pharmacophore hybridization which involves hybridization between pharmacophores

A. Directly linked pharmacophore hybridization

- Merged type
- Fused type

B. Indirectly linked pharmacophore hybridization

- Linked by flexible linker
- Linked by a rigid linker

Classification of molecular hybrids

Conjugates are the molecular hybrids that contain pharmacophores for each target and separated by a distinct linker group that is not found in either of the individual drugs. Most conjugates comprise of a metabolically stable linker. Cleavable conjugates are the molecular hybrids with a linker designed to be metabolized to release the two drugs that interact independently with each target. Fused hybrids are the non-super posed molecular hybrids with the decreased size of the linker such that the scaffold of the pharmacophores just touches each other. Merged hybrids are the superposed molecular hybrids with merged frameworks by taking benefit of commonalities in the structures of the starting compounds, which give rise to smaller and simpler molecules

Examples of molecular hybrids and their uses

- **Streptoniazid:** Streptomycin and isoniazid-antitubercular and antibiotics.
- **Quinine Acetyl Salicylate:** Quinine and acetylsalicylic acid -Antipyretic, Analgetic, Antimalarial.
- **Acetamino Salol:** Salicylic acid and Acetamido Phenol-Analgetic.
- **Guaicyl Phenyl Cinchoninate:** Guaiacol and Cinchophen-Expectorant.

Advantages of molecular hybrids

- Screening of the molecular hybrid is not necessary all the time.
- They are versatile.
- They can create new pharmacological properties.
- They improve patient's compliance.
- They are more affordable.
- They reduce the risk of drug-drug interactions.
- The efficacy of parent drugs is restored.
- They improve Pharmacokinetic properties.
- They improve Pharmacodynamic properties.
- They change the bioavailability profile
- They have better physicochemical properties
- The toxicity of parent drugs is minimized

- They possess a different mode of action
- They possess dual modes of action [8,9]
- They have the ability to address more than one target [10,11]
- One need not take many drugs at a time
- They reduce the undesirable side effects of the parent drugs.
- They enhance the specificity of a drug for a particular body target site
- They increase the potency of the drug
- They allow prolonged patent life of some parent drugs
- They modify the time course of the drug in the body
- They change the physical or chemical properties of the drug to provide the desired features.
- They protect active substances from enzymatic degradation
- Drug resistance can be avoided by the use of molecular hybrids

Disadvantages of molecular hybrids

- The chemical structures of the parent molecules have to be optimized before subjecting them for molecular hybridization.
- Altering the structure of parent molecules may affect their affinity, selectivity and metabolism profiles.
- Molecular hybrids require activity in similar concentration range.
- Molecular hybrids with flexible structure may reduce the target binding efficacy.
- The high molecular weight of molecular hybrids may lower oral bioavailability.
- Molecular hybrids lose the ability to cross the blood-brain barrier.

Discussion and Conclusion

The growing efforts to discover hybrid drugs resulting from the combination of Pharmacophoric moieties of different known lead compounds of synthetic or natural origin have brought new hope for the treatment of multifactorial diseases in recent years. It is evident that the future is optimistic and that this type of design will lead to important drugs with higher activity, better selectivity, and lower toxicity than the traditional combination therapies. This review article describes possible ways of exploring molecular hybridization strategies to plan new effective molecular hybrids.

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