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Molecular Modification: A Strategy in Drug Discovery and Drug Design

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ABSTRACT

Drug discovery and design is a complex and expensive process. The cost of developing a new drug can reach billions of dollars, and the success rate is very low. One way to improve the efficiency of drug discovery is to use molecular modification. Molecular modification is the process of chemically altering a known drug molecule to improve its physical, chemical, and pharmacological properties. This can be done to increase the drug's potency, to improve solubility, improve its selectivity, or reduce its side effects. Molecular modification is a powerful tool that can be used to improve the efficacy and safety of existing drugs. It is a relatively simple and inexpensive technique, and it can be used to rapidly generate many new drug candidates. Molecular modification has been used to develop a few successful drugs, including the anti-cancer drug, Cyclophosphamide and the paclitaxel. In this paper, we review the principles of molecular modification and discussed its applications in drug discovery. We also discussed the challenges and limitations of molecular modification, and we provide an overview of the current state of the field.

Keywords: Molecular Modification; Drug Discovery; Drug Design; Efficiency; Potency; Selectivity; Side Effects; Cyclophosphamide; Paclitaxel

Introduction

What is Molecular Modification?

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. Term molecular modification was coined by Hench. It is also called as Molecular refinement, Molecular transformation, Molecular tailoring, Chemical modification, Chemical alteration, Pharmacomodulation and Method of variation. It is one of tools of research in medicinal chemistry to refine molecules. Molecules obtained as a result of molecular modification are called as analogues or congeners [1].

What is Drug Design?

Drug design is the inventive process of finding new medications based on the knowledge of a biological target [2]. In the most basic sense, drug design involves the design of molecules that are complementary in shape and charge to the molecular target with which they interact and bind [3]. Drug design frequently but not necessarily relies on computer modelling techniques and bioinformatics approaches in the big data era [3,4]. Molecules obtained because of molecular modification are called as analogues or congeners [1].

What is Drug Discovery?

Drug discovery is the process through which potential new therapeutic entities are identified, using a combination of computational, experimental, translational, and clinical models [3,5,6].

The General Approach of Molecular Modification Involves [1]:

I Molecular disjunction approach: It involves breaking of molecules [7].

II Molecular conjunction approach: It involves joining of molecules.

III Special Approaches

I Molecular Disjunction Approach:

Disjunction comes in where there is the systematic formulation of analogues of a prototype agent. Analogues have partly structure of the prototype agent. The method of disjunction is usually employed in three different manners, namely:

(i) Un-Joining of certain bonds.

(ii) Substitution of aromatic cyclic system for saturated bonds 28

(iii) Decrease in the size of the hydrocarbon portion of the parent molecule.

Example: The extensive study on the estrogenic activity of oestradiol via drug design throughdisjunction ultimately rewarded in the crowning success of the synthesis and evaluation of trans-diethylstilbestrol as depicts in the (Figure 1).

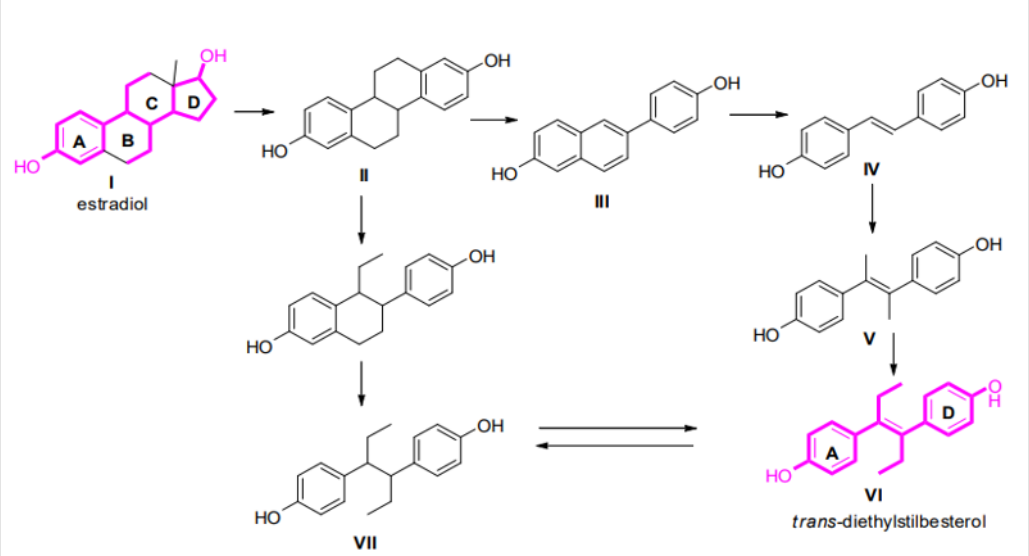

Figure 1.

The Observations Include:

i. Various steps in design of II to III to IV designate nothing but successive simplification through total elimination of the rings B and C in oestradiol (I).

ii. The above manner of drug design finally led to successively fewer active products (i.e., II, III, IV).

iii. Upon plotting oestrogenic activity against various structures (I to VII) it was quite evident that the maximal activity in this series was attributed to transdiethylstilbesterol [7] as illustrated in the (Figure 2)

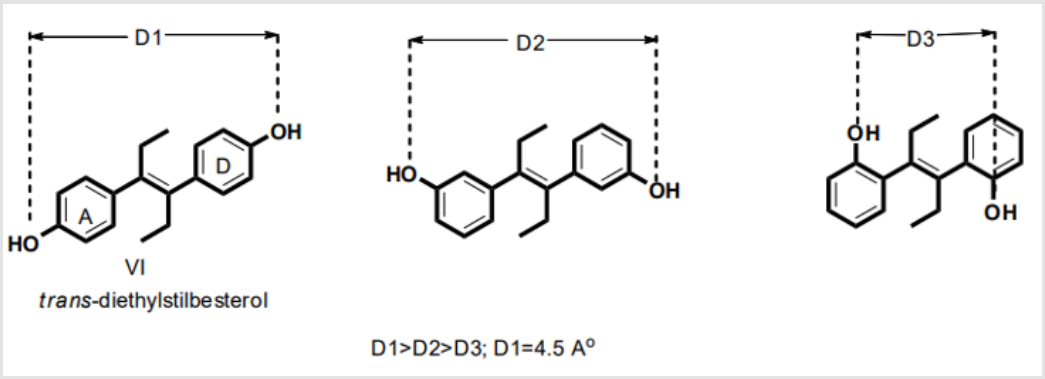

Figure 2.

II Molecular Conjunction Approach

Types of Molecular Conjunction Approach

1. Molecular addition approach: It involves the association of two or more identical or non-identical molecules through weak forces of attraction.

2. Molecular replication approach: It involves the association of two or more identical molecules through covalent bonding [8].

3. Molecular hybridization approach: It involves the association of two or more non-identical molecules through hybridization.

III Special Approaches

1. Ring closure/opening

2. Formation of lower or higher homologs

3. Introduction of double bonds

4. Introduction of chiral centers

5. Introduction or removal or replacement of bulky groups

6. Ring equivalents

7. Isosteric substitutions

8. Change of position or orientation of certain groups

9. Introduction of alkylating moiety

10. Modification toward inhibition or promotion of various electronic states

A Molecular Conjunction Approach

1. Molecular Addition Approach [9]: The molecular addition approach of molecular modification is a method of altering the structure of a drug by adding new chemical groups to the molecule. This can be done to improve the drug's properties in several ways, such as:

- Increasing the drug's solubility in water, which can make it easier to absorb and distribute throughout the body.
- Enhancing the drug's selectivity for its target molecule, which can improve its potency and reduce its side effects.
- Changing the drug's metabolism, which can affect its half-life and how long it remains in the body.
- The molecular addition approach can be used to modify a wide variety of drugs, including small molecules, peptides, and proteins. It is a versatile and powerful tool that has been used to develop many of the drugs that are used today.

Here are some examples of molecular addition approaches that have been used to modify drugs:

- The addition of a hydroxyl group to a drug can increase its solubility in water. For example, the addition of a hydroxyl group to the amino acid phenylalanine produces the amino acid tyrosine, which is more soluble in water.
- The addition of a lipophilic group to a drug can increase its affinity for a target molecule. For example, the addition of a lipophilic group to the drug loperamide increases its affinity for the mu-opioid receptor, which makes it a more potent pain reliever.
- The addition of a chemical group that is metabolized differently than the original drug can change the drug's half-life. For example, the addition of a methyl group to the drug acyclovir increases its half-life, which means that it remains in the body for a longer period.

2. Molecular Replication Approach:

The molecular replication approach involves designing and synthesizing small molecules that mimic or replicate the structural features and functional properties of a target biomolecule. This approach aims to develop synthetic molecules that can interact with biological targets in a manner similar to endogenous ligands, proteins, or nucleic acids. The molecular replication approach can be employed in various areas of drug discovery and development, including the design of enzyme inhibitors, receptor agonists or antagonists, and nucleic acid-binding molecules [10].

An overview of the Molecular Replication Approach:

a. Rational Design: Rational design involves analysing the structure and functional aspects of the target biomolecule to identify key interactions and binding sites. Based on this analysis, synthetic molecules are designed with specific structural features and chemical functionalities to replicate or mimic the binding interactions and functional properties of the target [11].

b. Fragment-Based Approaches: Fragment-based approaches involve the identification and assembly of small molecular fragments that can individually bind to the target biomolecule. These fragments are then linked or elaborated upon to form larger molecules that mimic the target's binding mode and interactions. This approach allows for the stepwise optimization of binding affinity and selectivity [12].

c. Combinatorial chemistry techniques: such as parallel synthesis or library screening, can be employed to generate diverse collections of molecules with structural diversity. These libraries are then screened against the target biomolecule to identify molecules that replicate or mimic the desired interactions. Iterative rounds of synthesis and screening can be performed to refine and optimize the replicating molecules [13].

d. Scaffold Hopping: Scaffold hopping involves identifying structurally distinct molecules that possess similar biological ac-

tivities to the target biomolecule. By analyzing the key interactions and pharmacophoric features of the target, structurally distinct molecules are selected and modified to replicate the desired binding interactions and functional properties [14].

e. Virtual Screening and Molecular Modelling: Virtual screening techniques, such as molecular docking and molecular dynamics simulations, can be employed to predict and evaluate the binding interactions and properties of synthetic molecules with the target biomolecule. This computational approach aids in the identification and optimization of replicating molecules before their synthesis and experimental testing [15].

3. Molecular Hybrid Approach [16,7]:

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 multitargeted 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, bi-functional drugs, bivalent ligands, drugs with two heads, etc. Hybrid compounds can be constructed by linking Pharmacophores subunits directly or indirectly using linkers or spacers in molecular hybridization.

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

Examples of molecular hybrids and their uses

- Streptoniazid: Streptomycin and isoniazid-antitubercular and antibiotics.
- Quinine Acetyl Salicylate: Quinine and acetylsalicylic acid -Antipyretic, Analgesic, Antimalarial.
- Acetamino Salol: Salicylic acid and AcetamidoPhenol Analgetic.
- Guaicyl Phenyl Cinchoninate: Guaiacol and CinchophenExpectorant.

III. Special Approaches

1. Ring closure and Ring Opening: Ring opening and ring closure reactions are important processes in medicinal chemistry that involve breaking or forming a cyclic structure. These reactions can have significant implications in drug synthesis and metabolism [17].

a. Ring Opening Reaction: Carbamazepine is largely metabolized in the liver. CYP3A4 hepatic enzyme is the major enzyme that metabolizes carbamazepine to its active metabolite, carbamazepine-10,11-epoxide 12, which is further metabolized to its trans-diol form by the enzyme epoxide hydrolase [18] as shown in (Figure 3).

b. Ring Closure Reaction: Intramolecular Cyclization; synthesis of the drug taxol (paclitaxel), an anticancer agent. Taxol contains a complex taxane ring system. The key step in the synthesis of taxol involves an intramolecular cyclization reaction. A ring closure reaction is utilized to form the taxane ring system, involving the formation of multiple new bonds to generate the desired cyclic structure as shown in (Figure 4).

2. Formation of Lower or Higher Homologs

a. Lower Homolog Drug Example: Ibuprofen and Naproxen belong to propionic acid derivatives and are structurally similar and are synthesized from propionic acid

b. Higher Homolog Drug Example: Atorvastatin and Rosuvastatin are cholesterol-lowering drugs belonging to the class of statins. They are used to reduce the levels of LDL cholesterol in the bloodstream [19] as illustrates in (Figure 5).

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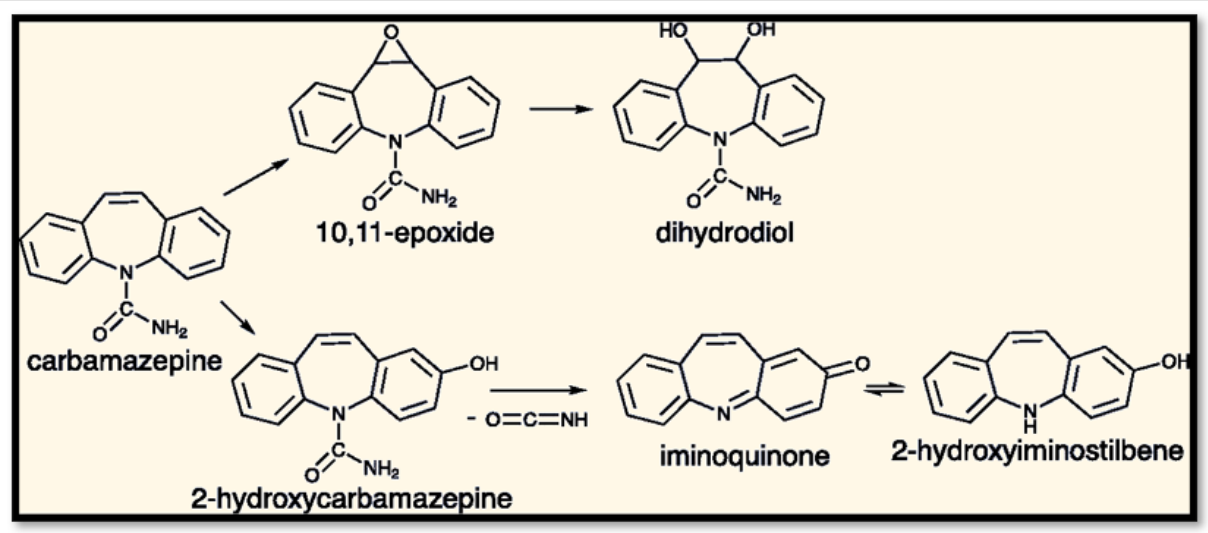

Figure 3.

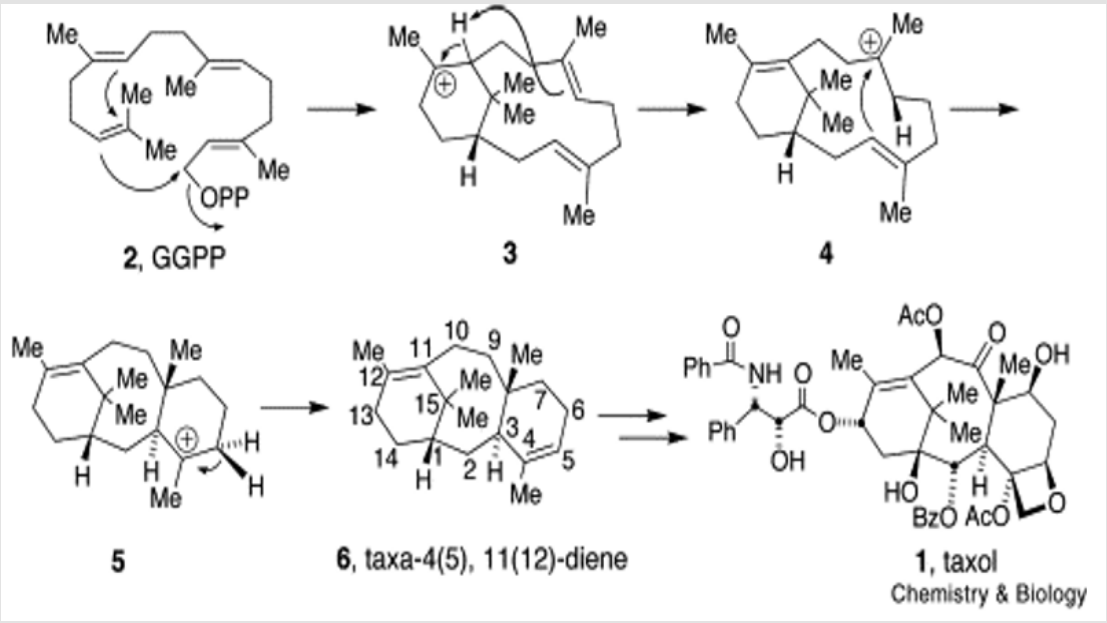

Figure 4.

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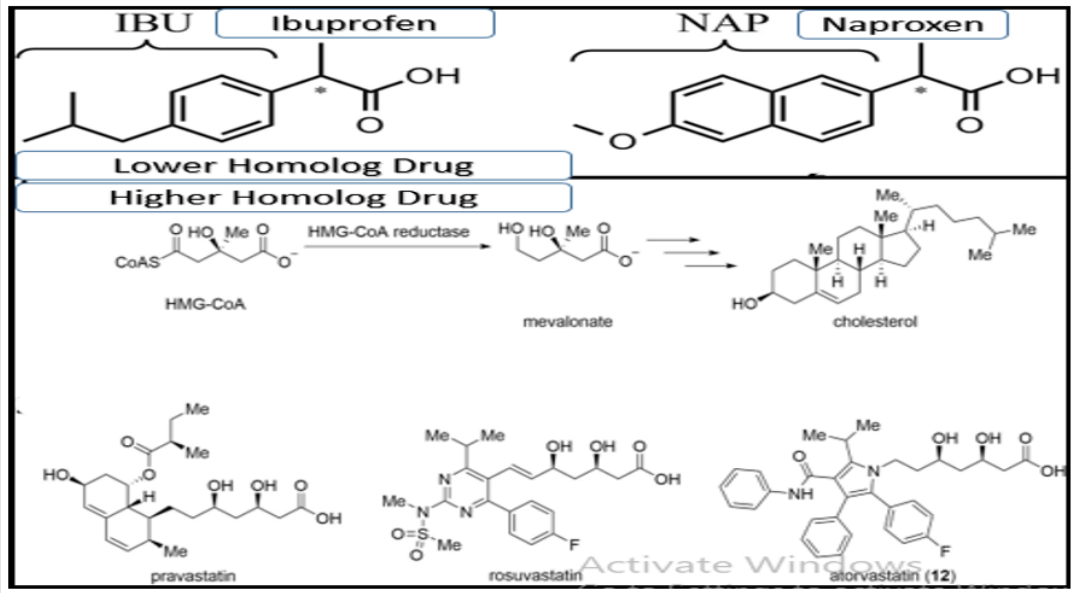

Figure 5.

3. Double Bonds Introduction

- Synthesis of Progesterone: Progesterone is a natural hormone involved in the female reproductive system and is used in various pharmaceutical formulations [20].
- Here's a simplified synthesis pathway for progesterone that involves the introduction of a double bond as shown in (Figure 6).

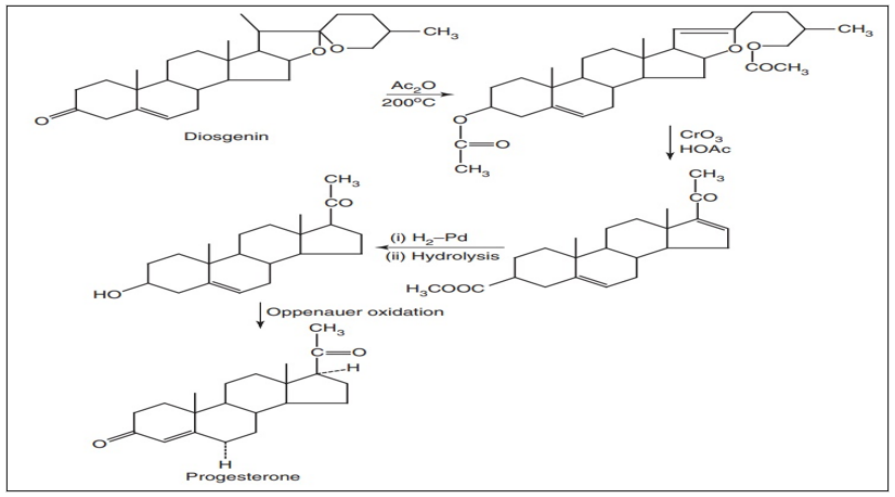

Figure 6.

4. Introduction of Chiral Center

- Synthesis of Chiral Drug from Achiral Starting Material: Propranolol is a chiral drug used as a non-selective beta blocker [21]. It can be synthesized from an achiral starting material through an asymmetric synthesis approach as shown in the (Figure 7).

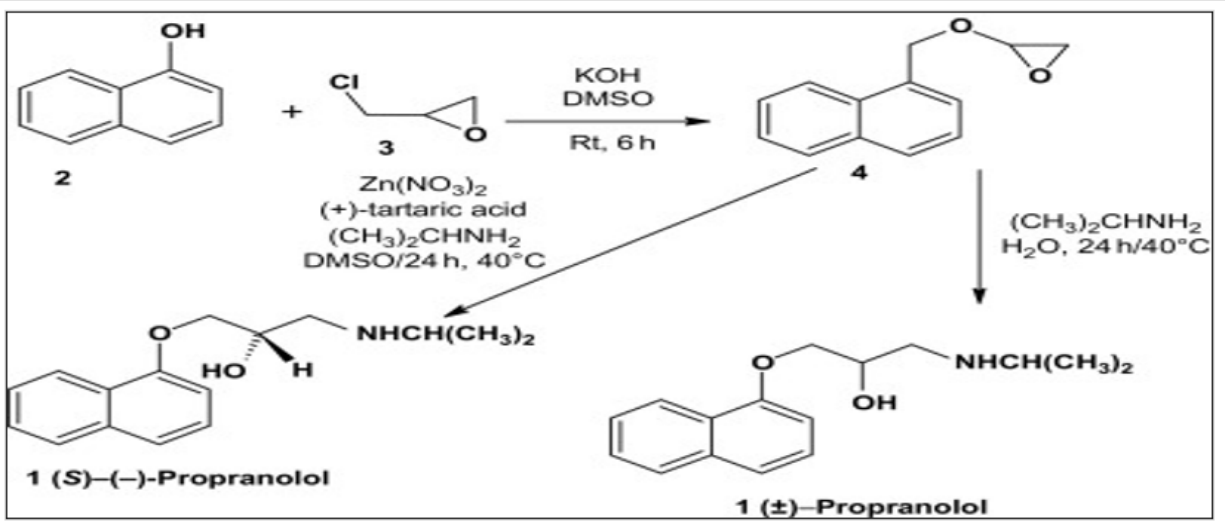

Figure 7.

5. Introduction of Removal or Replacement of Bulky Groups

Introduction, removal, or replacement of bulky groups in drugs is a common strategy used in medicinal chemistry to modify the properties and activities of drug molecules. Bulky groups can impact drug-target interactions, metabolic stability, pharmacokinetics, and other factors. Here are a few examples:Introducing aryl groups, such as phenyl or naphthyl, can increase lipophilicity and improve binding interactions with hydrophobic pockets on the target protein. Adding alkyl or alkoxy groups, such as tert-butyl or methoxy, can increase steric hindrance and improve selectivity by blocking off-target interactions [22].

a. Removal of Bulky Groups: Removing bulky groups from a drug molecule can reduce its size, improve metabolic stability, or minimize off-target effects. For example:Removing large substituents can decrease steric hindrance and improve drug-like properties, such as solubility and permeability.Eliminating highly lipophilic groups can enhance water solubility and reduce the potential for nonspecific binding.

b. Replacement of Bulky Groups: Substituting bulky groups with other functional groups can alter drug properties, such as lipophilicity, charge, or polarity. For example:Replacing a bulky alkyl group with a polar functional group, such as a hydroxyl or amino group, can enhance water solubility and facilitate renal clearance.Swapping a large lipophilic substituent with a smaller, more polar group can improve metabolic stability and decrease the risk of adverse effects.

6. Ring Equivalents:

- Ring equivalents are structural motifs or groups that possess similar or equivalent ring-like characteristics in terms of shape, size, and properties. They can be used to replace or mimic rings in drug molecules, providing similar or improved pharmacological properties [23]. Here are some examples of ring equivalents used in drugs as shown in the (Figure 8).

7. Bioisosteres of Aromatic Rings: Aromatic rings are common in drug molecules and contribute to their activity. However, aromatic rings can be susceptible to metabolism, Replacement of an aromatic ring with a Bioisosteres, such as a heteroaromatic ring (e.g., pyridine, pyrimidine), can retain the aromatic character while introducing different electronic and steric properties. This substitution is often used to optimize binding interactions or improve metabolic stability. Zolpidem, used for the treatment of insomnia, contains a pyridine ring as a bioisostere of an aromatic ring [24].

- Lactams and lactones are common ring structures in drugs. they can be prone to hydrolysis or have limited conformational flexibility. Ring equivalents can be used to replace lactams or lactones while maintaining their functionality. Replacing a lactam or lactone ring with a bioisostere, such as a cyclic urea or carbamate, can retain similar hydrogen-bonding capabilities while improving metabolic stability and physicochemical properties. Montelukast, used for the treatment of asthma and allergies, contains a cyclic urea as a ring equivalent of a lactam.

8. Isosteric Substitutions

• Isosteric substitutions involve replacing a functional group or moiety in a molecule with another group or moiety that has similar size, shape, and electronic properties, while maintaining or modifying the overall pharmacological activity. Isosteric substitutions are often employed in drug design and optimization to achieve specific goals, such as improving metabolic stability, enhancing binding interactions, or addressing toxicity issues [25]. Here are some examples of isosteric substitutions in drug molecules:

• Bioisosteric Replacement of Functional Groups:Bioisosteres are groups or moieties that have similar shape and physicochemical properties, allowing them to mimic the biological activity of a specific functional group. An example illustrated in the (Figure 9).

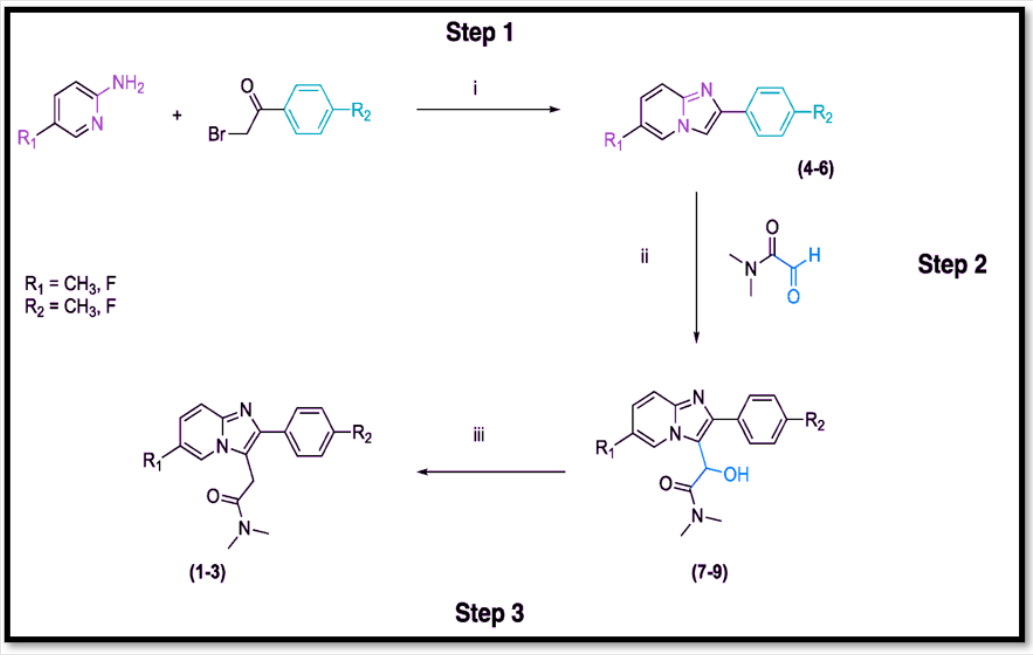

Figure 8.

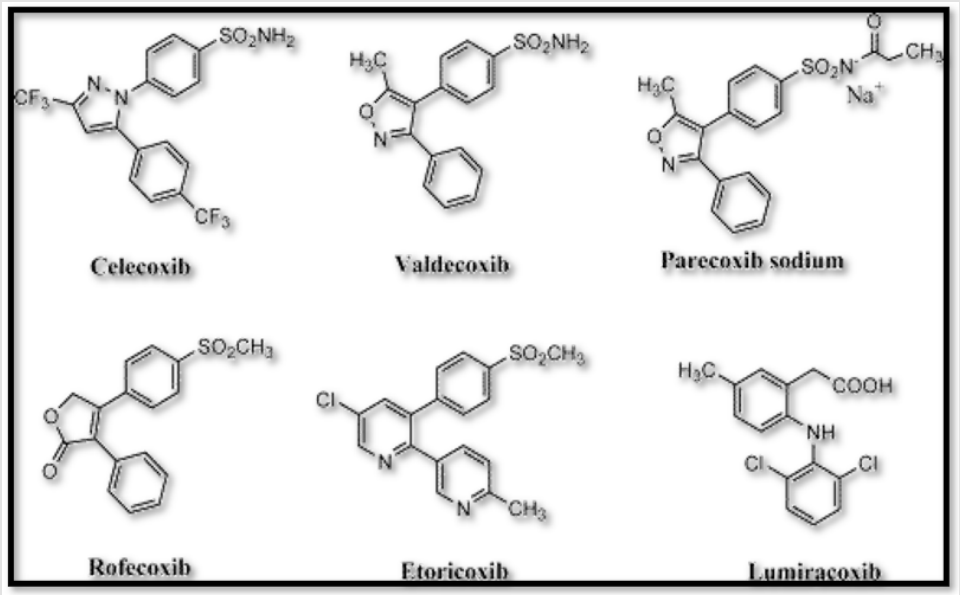

Figure 9.

9. Change of Position or Orientation of Certain Groups

Changing the position or orientation of certain groups in drug molecules can have a significant impact on their pharmacological properties, including potency, selectivity, and metabolic stability. Here are some examples of how altering the position or orientation of specific groups can influence drug properties:

a. Positional Isomerism: Positional isomerism involves changing the location of a functional group or substituent within a drug molecule. This can affect the interactions with the target and alter the drug's pharmacological profile. For example: The drug Warfarin exists as two positional isomers: R-warfarin and S-warfarin, which have different pharmacokinetic and anticoagulant properties. S-warfarin is also 5 times more potent as a blood anticoagulant than the R-form [27] as shown in (Figure 10).

b. Stereoisomerism: Stereoisomerism refers to the different spatial arrangements of atoms in a molecule. Changing the stereochemistry or orientation of specific groups can have a profound impact on drug activity and selectivity. For example: Swapping the stereochemistry of chiral centres can result in enantiomers with different pharmacological profiles. This can include variations in binding affinity, metabolic stability, or side effects. Changing the orientation of functional groups in a cyclic molecule, such as in cis-trans isomerism, can affect the shape, rigidity, and interactions with the target. Salbutamol (Albuterol) is a bronchodilator that exists as a racemic mixture of (R)- and (S)-enantiomers. The (R)-enantiomer exhibits higher affinity for the target receptor, while the (S)-enantiomer contributes to adverse effects [28] as shown in (Figure 11).

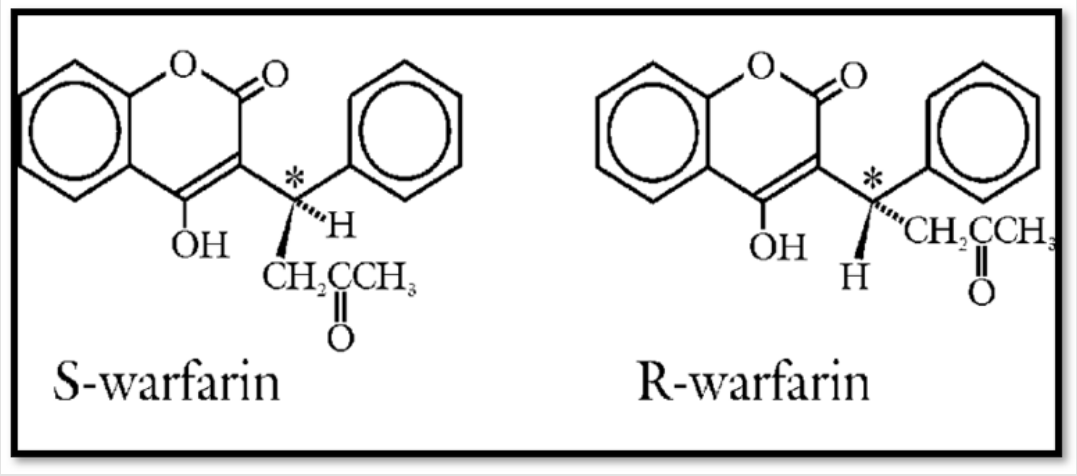

Figure 10.

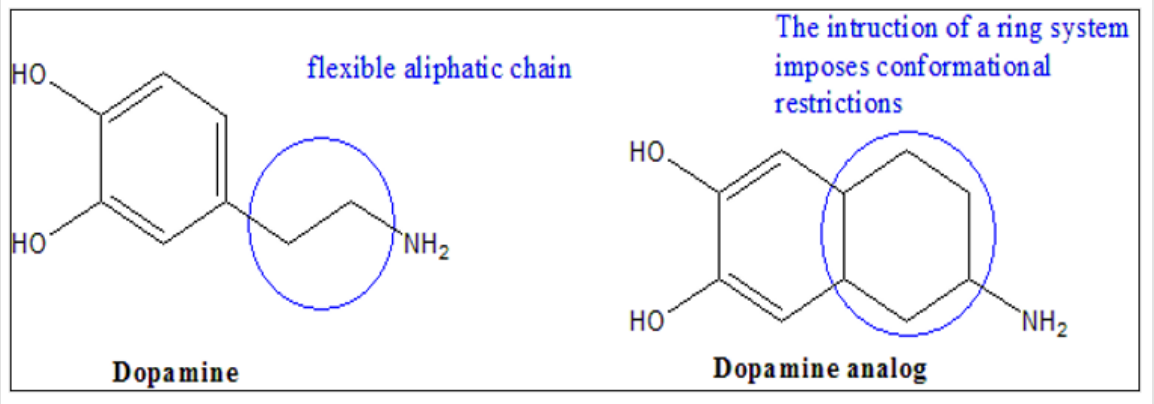

Figure 11.

c. Conformational Isomerism: Conformational isomerism involves altering the conformation or spatial arrangement of atoms in a molecule without changing the connectivity. This can impact the molecule's shape, flexibility, and binding interactions. For example: Modifying the torsional angles between atoms can influence the overall shape and conformational stability of the molecule, affecting interactions with the target protein. Changing the rotatable bonds or ring conformations can impact the flexibility and rigidity of the drug molecule, potentially affecting its binding affinity and pharmacokinetic properties. Sertraline, an antidepressant, exists in different conformations due to rotation around single bonds, which can influence its interaction with the serotonin transporter protein. The conformation of sertra- line has two planar phenyl rings that are approximately perpendicular to each other, and an unsaturated ring in a half-chair conformation [29].

10. Introduction of Alkylating Moiety

- The introduction of an alkylating moiety to a drug molecule can result in the formation of covalent bonds with cellular targets, leading to altered or enhanced pharmacological activities. Alkylating agents are commonly used in cancer chemotherapy to inhibit the growth of rapidly dividing cells [30]. Here are a few examples of drugs that incorporate alkylating moieties: Mechlorethamine: Mechlorethamine, also known as mustine, is an alkylating agent used in the treatment of certain types of cancers, including Hodgkin's lymphoma and non-Hodgkin's lymphoma. It contains a chloroethyl group as its alkylating moiety. The chloroethyl group can react with nucleophilic sites on DNA, leading to DNA cross-linking and inhibition of DNA replication [31].

- Cyclophosphamide: Cyclophosphamide is an alkylating agent widely used in chemotherapy for various types of cancers, including breast cancer and lymphomas. It undergoes metabolic activation in the body, forming active alkylating metabolites. These metabolites contain a phosphoramide mustard group, which can form covalent bonds with DNA, leading to DNA damage and inhibition of cell division [32].

11. Modification Toward Inhibition or Promotion of Various Electronic States (Electron-Withdrawing Groups):

Modifying drugs to inhibit or promote various electronic states can have significant implications for their pharmacological activities. Altering the electronic states can impact factors such as binding affinity, reactivity, or redox potential. Here are a few examples of modifications that can influence electronic states in drugs:

a. Electron-Withdrawing Groups: Introducing electron-withdrawing groups into a drug molecule can increase its electron deficiency and modify its electronic state. This can affect several aspects of drug activity, such as: Enhancing the acidity of a functional group, such as a carboxylic acid, by withdrawing electron density, which can influence interactions with targets or enzymes. Increasing the polarity of a drug molecule, which can affect solubility, distribution, and pharmacokinetics. Example: The drug Warfarin contains an electron-withdrawing aromatic ring that contributes to its anticoagulant properties by inhibiting vitamin K epoxide reductase [33].

b. Electron-Donating Groups: Incorporating electron-donating groups into a drug molecule can increase its electron density and modify its electronic state. This can impact various aspects of drug activity, such as: Modulating the basicity of a functional group, such as an amine, by donating electron density, which can affect binding interactions and receptor activation. Lowering the redox potential of a drug, which can influence its reactivity and potential as an antioxidant or pro-oxidant. Example: The drug Morphine contains electron-donating functional groups, such as hydroxyl groups, that contribute to its analgesic properties by interacting with opioid receptors [34].

c. Conjugated Systems: Conjugated systems involve the presence of alternating single and multiple bonds, allowing for delocalization of electrons. Modifying the extent or nature of conjugation in a drug molecule can affect its electronic state and properties. For example: Expanding or contracting the conjugated system in a chromophore can influence its absorption and fluorescence properties, which are relevant in photodynamic therapy or fluorescent imaging. Altering the extent of conjugation in a drug molecule can influence its electronic delocalization and stability, impacting reactivity or metabolic susceptibility [35]. Example: The drug Tamoxifen contains a conjugated system that contributes to its estrogen receptor binding affinity and selective Estrogen receptor modulator (SERM) activity.

11.1. Chemical Modification: A Unique Solution to Solubility Problem

Almost 40% of the new chemical entities at present are poorly water-soluble drugs. Solubility is one of the most important parameters to give desired concentration of drug in systemic circulation to get its pharmacological response. Orally administered drugs obtained completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. The solubility and dissolution properties of drugs perform a valuable role in the process of formulation development. Enhancement of solubility of drug is the most challenging job in drug development process.

- Solubilization may be affected by co solvent water interaction, micellar solubilization, reduction in particle size, inclusion complexes, solid dispersion, and change in polymorph. Solubility enhancement with special emphasis on Chemical modification methods like Salt formation, Co-crystallization, Co-solvency, Hydrotropy, use of novel solubilizeretc along with physical modification techniques [36].

11.2. Chemical Modification on Polarity and Solubility

- The relative solubility of a drug in both aqueous and non-polar media plays a major role in the ability of the body to absorb and transport the active molecule to its action site. Most of the time, the drug must be hydrophilic enough to be able transported in the blood, but also lipophilic enough to travel through a membrane. We must consider that polarity (and therefore solubility in polar and non-polar media) is a synergistic effect, and is the combined effect of functional groups and molecular geometry that will determine the polarity of a drug candidate. The presence of flexible or rigid groups can affect the molecular shape and therefore the ability of the drug to bind a specific ligand in the body [37]. For example, the introduction of unsaturated groups and ring systems generate more structurally rigid analog than aliphatic systems. Figure 11 shows the structure of dopamine and a more structurally rigid analog. The biological effects induced by changes in the molecular flexibility are difficult to predict. Every single new analog needs to be retested to determine its pharmacological properties and compare them with the lead compound. A more rigid molecule tends to create a stronger binding to its biological target (receptor). However, when the target receptor has a more flexible binding site, increasing molecular rigidity might decrease the ability of the drug to enter this site [38-40].

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