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Lead Discovery and Lead Optimization: A Useful Strategy in Molecular Modification of Lead Compound in Analog Design

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ABSTRACT: The current trend in the drug design is to develop new clinically effective agents through the molecular modification of a lead nucleus. A lead compound in drug discovery is a chemical compound that has pharmacological or biological activity. Lead optimization is the synthetic modification of a biologically active compound, to fulfill all stereoelectronic, physicochemical, pharmacokinetic and toxicologic required for clinical usefulness. The main objective of this review is to discuss the methods of lead discovery, lead optimization and its role in molecular modification of lead compound in analog design.

KEYWORDS: Lead discovery; Lead optimization; Molecular modification; Analog design

Introduction

Drug design is an integrated developing discipline which portends an era of tailored drug. It involves the study of effect of biologically active compounds on the basis of molecular interactions in terms of molecular structures or its physico-chemical properties involved[1].

The identification of high-quality hits and lead compounds is crucial in the drug discovery process. An understanding of structure–activity relationships and mechanistic aspects of action are key in selecting the best chemical class for further optimization. It is therefore essential to obtain sufficient high-quality data on affinity, kinetic, mechanistic and thermodynamic aspects of an interaction between potential drug candidates and their targets[2,5,6].

Analog design is as much an art as it is a science. The concept of analog design presupposes that a lead has been discovered; that is, a chemical compound has been identified that possesses some desirable pharmacological property. Analog design is most fruitful in the study of pharmacologically active molecules that are structurally specific; their biological activity depends on the nature and the details of their chemical structure.

The goal of analog design is to modify the chemical structure of the lead compound to retain or to reinforce the desirable pharmacologic effect while minimizing unwanted pharmacological (e.g., toxicity, side effects, or undesirable metabolism) and physical and chemical properties (e.g., poor solubility and solvent partition characteristics or chemical instability), which may result in a superior therapeutic agent and to use target analogs as pharmacological probes (i.e., tools used for the study of fundamental pharmacological and physiological phenomena to gain better insight into the pharmacology of the lead molecule and perhaps to reveal new knowledge of basic biology. Studies of analog structure-activity relationships may increase the medicinal chemist ability to predict optimum chemical structural parameters for a given pharmacological action[3].

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Methods of Lead Discovery

There are several approaches which can be employed for lead identification[7-11]. In order to identify a lead nucleus in a given series, the whole series should be analysed for a particular biological activity. Once the lead is identified, it can be structurally modified to improve the potency. Following are the important methods which can be used for lead identification.

Random screening

All compounds including synthetic chemicals, natural products of plant, marine and microbial origin from a given series are tested. Inspite of budgetary and manpower overuse, this method may be used to discover drugs or leads that have unexpected activities. Antibiotics like, streptomycin and tetracyclines were found out by this method.

Nonrandom screening

It is a modified form of random screening which was developed because of budgetary and manpower restrictions. In this method, only such compounds having similar structural skeletons with that of lead, are tested.

Drug metabolism studies

Metabolism of drug occurs as an attempt by metabolizing enzymes. Structural modifications are done in drug molecule by the enzymes to increase its polarity. The discovery of sulfanilamide is reported through the metabolic studies of prontosil.

The antipyretic action of acetanilide was discovered by chance when a nurse by mistake dispensed acetanilide to a patient. Due to its toxicities, acetanilide could not stand in the market. Metabolic studies showed that the toxicities are due to its in vivo metabolite, p-aminophenol. These observations led to development of phenacetin and paracetamol.

Clinical observations

Many times the drug possesses more than one pharmacological activities. The main activity is called as therapeutic effect while rest of the actions is known as side effects of the drug. Such drug may be used as lead compound for structural modifications to improve the potency of secondary effects.

A series of aminoalkyl derivatives of iminodibenzyl was synthesized as analgesics, sedative and antihistaminics by Hafliger and Schindler in 1951. Imipramine, one of the compounds, appeared to be potential antidepressant during clinical studies by Kuhn in 1957. Many tricyclic antidepressants therefore were synthesized.

Rational approaches to lead discovery

The knowledge about the receptors and their mode of interaction with drug molecules plays an important role in drug design. This knowledge may be used to develop conformationally bioactive skeletons having exact three-dimensional complementarity to a receptor. Greater potency, higher selectivity and less adverse effects are expected by reducing the flexibility of the drug structure. This approach is of greater importance in identification of lead nucleus. It involves the use of signs and symptoms of the disease.

Attempts were made to synthesize various insulin analogues by specific amino acid substitutions of the ß-chain of insulin molecules using recombinant DNA techniques. These analogues have different pharmacokinetic properties than the clinically used insulin. The monomeric insulin analogues appeared to be less immunogenic and allergic than insulin.

Methods of Lead Optimization in Analog Design

Once the lead nucleus is identified, it is easy to exploit. In analog design, molecular modifications of the lead compound[1, 3, 4] can involve one or more of the following strategies:

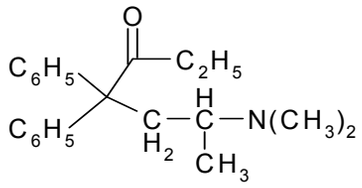
1. Identification of the active part (Pharmacophore).
2. Functional group optimization.
3. Structure activity relationship studies.
4. Bioisosteric replacement.
5. Design of rigid analogs.
6. Homologation of alkyl chains or alteration of chain branching, design of aromatic ring position isomers, alteration of ring size, and substitution of an aromatic ring for a saturated one or the converse.
7. Alteration of stereochemistry, or design of geometric isomers or stereoisomers.
8. Design of fragments of the lead molecule that contain the pharmacophoric group (bond disconnection).
9. Alteration of interatomic distances within the pharmacophoric group or in other parts of the molecule.

Identification of the active part (Pharmacophore)

Any drug molecule consists of both, essential and nonessential parts. Essential part is important in governing pharmacodynamic (drug receptor interactions) property while non-essential part influences pharmacokinetic features. The relevant groups on a molecule that interact with a receptor are known as bioactive functional groups. They are responsible for the activity. The schematic representation of nature of such bioactive functional groups along with their interatomic distances is known as pharmacophore.

Once such pharmacophore is identified, structural modifications can be done to improve pharmacokinetic properties of the drug. For example, the presence of a phenyl ring, asymmetric carbon, ethylene bridge and tertiary nitrogen are found to be minimum structural requirement for a narcotic analgesic to become active. Similarly the presence of two anionic sites and one cationic site must be present in cholinergic agent.

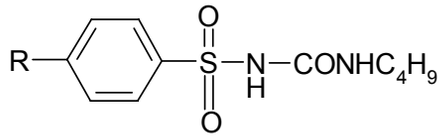
Morphine, the prototype narcotic agent has a pentacyclic structure. The complexity of structure leads to appearance of several side effects. Hence the pharmacophore of morphine has been recognized through molecular dissection and was used to develop still similar and even acyclic analogs. For example, methadone (1) is as potent as analgesic as morphine.



(1) Methadone

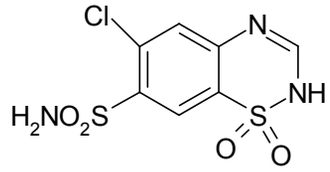
Functional group optimization

The activity of a drug can be correlated to its structure in terms of the contribution of its functional groups to the lipophilicity, electronic and steric features of the drug skeleton. Hence by selecting proper functional group, one can govern the drug distribution pattern and can avoid the occurrence of side-effects. For example, the amino group of carbutamide (2) (antibacterial agent) was replaced by a methyl group to give tolbutamide (3) (antidiabetic- agent).

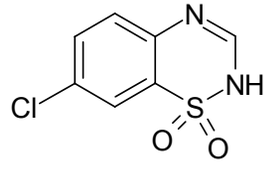


(2) R = NH_2: Carbutamide (3) R = CH_3: Tolbutamide

Similarly removal of sulfonamide side chain of chlorothiazide (4) (an antihypertensive drug with diuretic activity) helped to design diazoxide (5) (an antihypertensive drug without diuretic activity).



(4) Chlorothiazide



(5) Diazoxide

Structure activity relationship studies

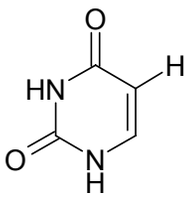
The physiological action of a molecule is a function of its chemical constitution. This observation is the basis of interpretation of activity in terms of the structural features of a drug molecule. Generalized conclusion is then can be made after examining a sufficient number of drug analogs. For example, Sulphonamides are found to be associated with diuretic and anti-diabetic activities in addition to their antibacterial activity.

Bioisosteric replacement

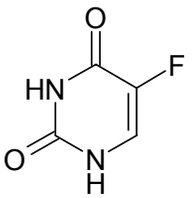
The concept of bioisosterism derives from Langmuir's observation that certain physical properties of chemically different substances (e.g., carbon monoxide and nitrogen, ketene and diazomethane) are strikingly similar. These similarities were rationalized on the basis that carbon monoxide and nitrogen both have 14 orbital electrons and, similarly, diazomethane and ketene both have 22 orbital electrons.

Bioisosteres are substituents or groups that have chemical or physical similarties and which produce broadly similar biological properties. Bioisosteres have been classified as either classical or nonclassical. Classical bioisosteres are those which have similar steric and electronic features and have the same number of atoms as the substituent moiety for which they are used as a replacement. Nonclassical bioisosteres do not obey the strict steric and electronic definition of classical isosteres and they do not have the same number of atoms as the substituent moiety for which they are used as a replacement. These isosteres are capable of maintaining similar biological activity by mimicking the spatial arrangement, electronic properties, or some other physicochemical property of the molecule or functional group that is critical for the retention of biological activity.

Substitution of a hydrogen atom by a fluorine atom is one of the most common classical monovalent bioisosteric replacement. The incorporation of fluorine into a drug allows simultaneous modulation of electronic, lipophilic and steric parameters, all can influence both the pharmacodynamic and pharmacokinetic properties of drugs. The difference in electronic effects is often the basis for the major differences in pharmacological properties, fluorine being the most electronegative element in the periodic table. A classical example of hydrogen replacement by fluorine is development of the antineoplastic agent 5-fluorouracil (7) from uracil (6) is shown as.



(6) Uracil

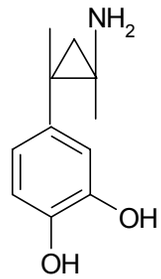


(7) 5-fluorouracil

Design of rigid analogs

Imposition of some degree of molecular rigidity on a flexible organic molecule (e.g., by incorporation of elements of the flexible molecule into a rigid ring system or by introduction of a carbon-carbon double or triple bond) may result in potent, biologically active agents that show a higher degree of specificity of pharmacological effect. There are two possible advantages to this technique, the three-dimensional geometry of the pharmacophore can be determined and the key functional groups are held in one steric disposition or, in the case of a semirigid structure, the key functional groups are constrained to a limited range of steric dispositions and interatomic distances. By the rigid analog strategy, it is possible to approximate "frozen" conformations of a flexible lead molecule that, if an enhanced pharmacological effect results, may assist in defining and understanding structure activity parameters.

The cyclopropane ring was employed to impart a degree of rigidity to the side chain of dopamine. Neither isomer displayed effects at dopamine receptors, but both were α-adrenoceptor agonists, with the (±)-trans-isomer (8) being approximately five times more potent than the (±)-cis-isomer (9).



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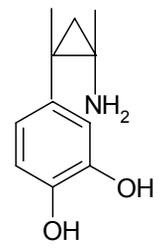
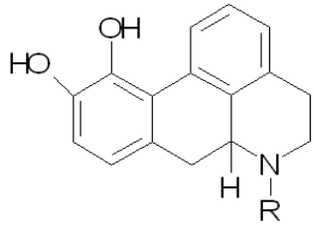


(9)

Homologation of alkyl chain or alteration of chain branching, Changes in ring size, and ring position isomers

Change in size or branching of an alkyl chain on a bioactive molecule may have profound and sometimes unpredictable effects on physical and pharmacological properties. Alteration of the size and or shape of an alkyl substituent can affect the conformational preference of a flexible molecule and may alter the spatial relationships of the components of the pharmacophore, which may be reflected in the ability of the molecule to achieve complementarily with its receptor or with the catalytic surface of a metabolizing enzyme. The alkyl group itself may represent a binding site with the receptor through hydrophobic interactions, and alteration of the chain may alter its binding capacity. Position isomers of substituents even alkyl groups on an aromatic ring may possess different pharmacological properties. In addition to their ability to affect electron distribution over an aromatic ring system, position isomers may differ in their complementarily to receptors, and the position of a substituent on a ring may influence the spatial occupancy of the ring system.

Homologation of the N-alkyl chain in norapomorphine (10) from methyl (11) to ethyl (12) to n-propyl (13) produced increases in emetic response in dogs and in stereotypy responses in rodents. The homolog, n-butyl (14) demonstrated a tremendous loss in potency and activity compared with the lower homologs.



(10) R= H (11) R= CH_3 (12) R= C_2H_5

(13) R= n-C_3H_7 (14) R=n-C_4H_9

Alteration of stereochemistry and design of stereoisomers and geometric isomers

In the case of chiral molecules one enantiomer would be expected to demonstrate pharmacological activity and the other enantiomer should be expected to be pharmacologically inert, is not valid.

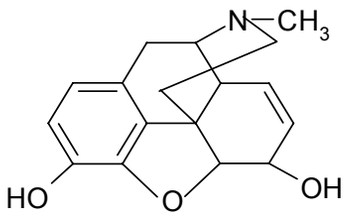
At high doses (R)-enatiomer selectively stimulated presynaptic dopaminergic receptor sites, while at lower doses it selectively stimulated postsynaptic receptor sites. In contrast, the (S)-enantiomer stimulated presynaptic dopamine receptors and at the same dose level, it blocked postsynaptic dopamine receptors. Thus, this enantiomer exhibits a bifunctional mode of doparninergic attenuation: that of presynaptic agonism and postsynaptic antagonism.

Fragments of the lead molecule

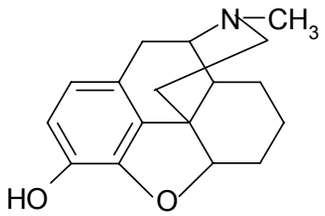
Design of fragments of a lead molecule is based on the premise that some lead molecules, especially polycyclic

natural products, may be much more structurally complex than is necessary for optimal pharmacologic effect. A bond disconnection strategy may be employed, in which bonds in the polycyclic structure are broken or removed to destroy one or more of the rings. The result may be a valuable drug that is more accessible (through chemical synthesis) than the original lead molecule.

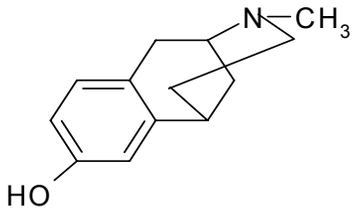
Morphine (15) can be cited as a lead molecule to illustrate fragment analog design. The analgesic pharmacophore of morphine has been defined as the basic nitrogen atom, the aromatic ring three carbon atoms from the nitrogen, and a quaternary carbon adjacent to the aromatic ring, which provides a region of molecular bulk. A bond disconnection strategy involved disruption of the hydrofuran ring to give rise to morphinan derivatives e.g., levorphanol (16), whose pharmacologic effects closely parallel those of morphine. Further simplification of the morphine ring system led to benzomorphan derivatives, typified by metazocine (17), in which morphine like analgesic activity is retained.



(15) Morphine



(16) Levorphanol

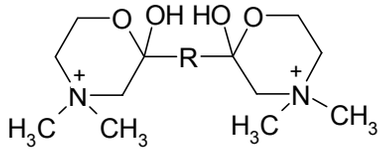


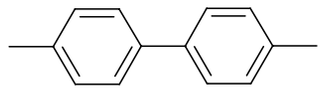
(17) Metazocine

Variation in interatomic distances

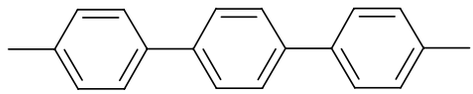
Alteration of distances between portions of the pharmacophore of a molecule or even between other portions of the molecule may produce profound qualitative and quantitative changes in pharmacological actions.

In a series of congeners of hemicholinium (18), the central biphenyl portion of the molecule was changed to ter-phenyl (19) and to p-phenylene (20). Both changes resulted in profound loss of the myoneural blocking activity. This result was described to alteration of the interquaternary nitrogen distance of 14.4 A^o in hemicholinium, to 18.4 A^o in the ter-phenyl analog, and to 10.2 A^o in the p-phenylene analog.

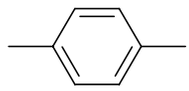




(18) R =



(19) R=



(20) R=

Conclusion

Lead Discovery and Lead Optimization aims to maximize the interactions of a drug with its target binding site in order to improve activity, selectivity, and to minimize side effects. Designing a drug that can be synthesized efficiently and cheaply is another priority. It is a powerful approach to the selection of lead compounds with potential for drug development. The lead discovery, lead optimization and process compares the properties of various lead compounds and provides information to help select the leads with the greatest potential to be developed into safe and effective medicines, and in alignment with corporate strategy.

Acknowledgements

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