Review Article

Essentiality of Different Functional Groups and their mechanisms involved in Binding

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ABSTRACT

The role of functional groups in binding of the drug with the targeted site is discussed. For different functional groups and their analogues various binding interactions are possible for its synthesis, to indicate whether these groups are helpful in binding or not. Hydrophobic interactions and van der Waals are commonly involved interactions with the binding site containing flat hydrophobic regions as they are planar and hydrophobic in nature. Many of the studied medicinal chemistry structures the ketone group is a common one. The carboxyl oxygen present in the planar group facilitates the hydrogen bonding with the binding site by acting as a hydrogen bond acceptor. Alkenes are hydrophobic and planar like that of aromatic rings. Alkenes can interact by interacting with the hydrophobic regions with the binding site by means of van der Waals hydrophobic interactions. Atoms or group of atoms possessing same valency in outer shell configuration with similar chemical and physical characteristics are referred to as isosteres. Studying of the binding interactions of various groups provides us with the ability to reduce the non required or the additional groups which have no specific activity within a compound and can lead to cause adverse effects of the compounds by binding with the undesired site of action.

Keywords: Functional groups, binding interactions, lead compound, targeted site.

INTRODUCTION

Binding Interactions

For different functional groups and their analogues various binding interactions are possible for its synthesis, to indicate whether these groups are helpful in binding or not. The role of functional groups in binding of the drug with the targeted site is discussed in detail in the below sections.

Aromatic ring

Hydrophobic interactions and van der Waals are commonly involved interactions with the binding site containing flat hydrophobic regions as they are planar and hydrophobic in nature. Any other analogues in which the ring gets less flatten as in the case of cyclohexane, the poor interaction between the molecule and the hydrophobic region can be seen (Fig 1). Cyclohexane when compared to an aromatic ring is bulky in its structure and is not capable to fit into the hydrophobic region of the binding site unlike aromatic ring which fits in perfectly due to the narrow slot rather its planar surface.

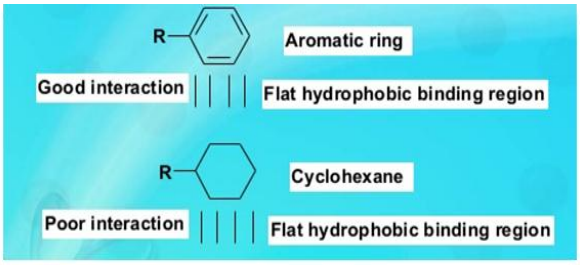

Fig. 1: comparison of aromatic ring and cyclohexane interactions

The amino acids such as Phenylalanine, tyrosine and tryptophan are highly hydrophobic due to hydrophobic nature of aromatic rings.For most of the lead compounds, the aromatic rings cannot be easily converted into cyclohexane rings, and such analogues can be prepared normally by full synthesis method. By means of hydrogen bonding or induced dipole interactions, the interacting of aromatic rings with an ammonium ion is possible. For cyclohexyl analogue these interactions are not possible.

Ketones and Aldehydes

Many of the studied medicinal chemistry structures the ketone group is a common one. The carboxyl oxygen present in the planar group facilitates the hydrogen bonding with the binding site by acting as a hydrogen bond acceptor. Because of the presence of two lone pairs of electrons, two such hydrogen bonding interactions are possible at the carbonyl oxygen. These lone pairs are in the same plane as that of functional group as they are sp2 hybridized (Fig 2).

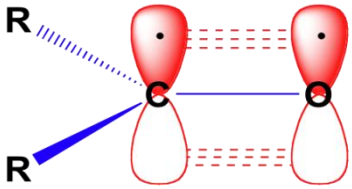

Fig. 2: hydrogen bonding at the carbonyl oxygen (sp2 hybridized- lone pairs at same plane)

The carbonyl oxygen of the ketone group also shows significant dipole moment making the dipole-dipole interaction possible at the binding site. In a lead compound it is possible to reduce a ketone group into an alcohol group by direct reaction. Tetrahedral geometry of an alcohol group from a planar one can be obtained due to changes in geometry of the functional group. Due to changes in the geometry, the magnitude and the orientation are altered for the dipole moment leading to the weakening of the existing hydrogen bond as well as dipole-dipole interactions. Many reactions are available which removes the oxygen completely by reducing a ketone group into an alkane one, but in the case of lead compounds these reactions are unpractical in medicinal chemistry studies. Due to high susceptibility of oxidation to carboxylic acids, aldehydes are the uncommon group in the drugs. However, they possess same reactivity as such of ketones and studying of similar analogues is possible (Fig 3).

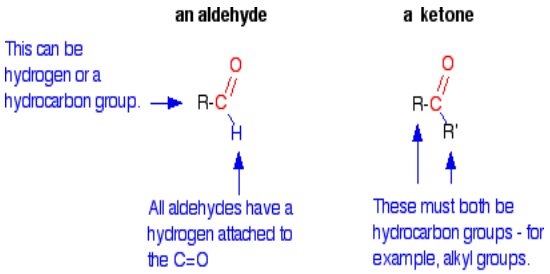

Fig. 3: showing oxidation in an aldehyde and a ketone group

Alcohols and Phenols

Many drugs contain alcohols and phenols as their functional groups which are generally involved in hydrogen bonding interactions. The hydrogen atom of the OH group acts as a hydrogen bond donor, whereas oxygen atom acts as acceptor of hydrogen bond. The hydrogen bond is indicated with an arrow mark. One or all the possible interactions may play an essential role in the binding of the drug to its binding site. Synthesis of methyl ether or ester analogue will be applicable in testing this, because they are possible chances of disruption of bonding in either analogue. The hydroxyl group contains a proton which is involved in hydrogen bonding as it acts as hydrogen bond donor, and if the proton is removed it leads to the loss of hydrogen bond. This is one of the two reasons because of which the ether might prevent the formation of hydrogen bond. The second reason is that due to the removal of proton, the oxygen atom present in the molecule may act as hydrogen bond acceptor but not to the same extend as to that of an original compound because the increase in the methyl group may obstruct the close approach to that of a previous one and disrupts the hydrogen bonding. Complete disruption or prevention of hydrogen bond is not done but the bond may be weakened when compared to that of original molecule. The same case can be seen with that of an ester analogue that is, it cannot act as hydrogen bond donor but still there is a possibility of ester analogue to act as hydrogen bond acceptor, but the increased acyl group than that the methyl group disrupts the hydrogen bonding interactions as that of original one. Difference can be seen in the electronic properties of an alcohol and an ester. A resonance structure is formed due to the weak pull on electrons by the carboxyl group from the adjacent oxygen. This interaction will be less effective than the hydrogen bond acceptor as lone pair of electrons is involved. The carbonyl oxygen present in the molecule may act as hydrogen bond acceptor, but the carbonyl group is relatively in different positive in the molecule and is not able to form such interaction as that of hydrogen bond present at the binding site in original molecule. Alcohols and phenols can be easily acetylated to esters such as in case of morphine. Ethers and esters can be formed from both alcohols and phenols to observe the effect on binding. OH interacting with the binding site is been seen, but aromatic ring can also take part in interactions at intermolecular levels.

Alkenes

Alkenes are hydrophobic and planar like that of aromatic rings. Alkenes can interact by interacting with the hydrophobic regions with the binding site by means of van der Waals hydrophobic interactions (Fig 4).

Fig. 4: hydrophobic interactions in alkenes

The activity of saturated analogue which is equivalent to original molecule is worth testing, because the alkyl region which is saturated is in excess and is unable to approach the adjacent binding site region so closely. Alkenes can be reduced easily than the aromatic rings; therefore it is possible to synthesize the saturated analogue from lead compound directly.

Amines

Many drugs in medicinal chemistry contain amines as a functional group and it is an extremely important one. Their interactions involve hydrogen bond donor and hydrogen bond acceptor facilitating hydrogen bonding. One lone pair of electron is present in the nitrogen atom of amine group and interacts by hydrogen bonding by acting as hydrogen bond acceptor (Fig 5).

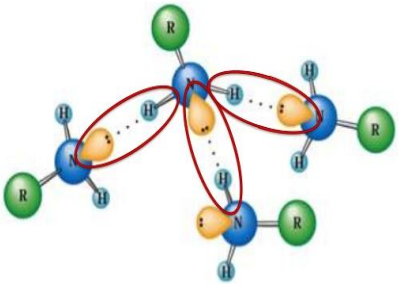

Fig. 5: Presence of lone pair of electrons in nitrogen atom (hydrogen bonding between amines)

N-H groups are present in primary (10) and secondary (20) amines and they act as hydrogen bond donors. As the lone pair present in the heteroaromatic and aromatic amines interact with the heteroaromatic and aromatic ring, so these amine can act as hydrogen bond donors only. When the interaction of amine at target binding site occurs, the amines are protonated i.e. they are ionized and loses the property of hydrogen bond acceptor. But it can still form a stronger hydrogen bond because it still acts as hydrogen bond donor; the hydrogen bond is stronger than of unionized. An amide analogue can be studied to test whether interactions are hydrogen bonding or ionic. In this the lone pair of nitrogen attaches with the adjacent carbonyl group preventing it to act as hydrogen bond acceptor. Possibility of the ionic interactions to take place can be observed as the protonation is prevented. Primary (1^0) and secondary amines (2^0) can relatively form secondary (2^0) and tertiary (3^0) amines respectively, and these direct reactions are possible for lead compounds. The secondary (2^0) amide formed is obstructed to act as hydrogen bond donor inspite of N-H group present, due to the excess of acyl group present. Amides cannot be formed directly from the tertiary (3^0) amines, but if a methyl group is present as an alkyl group it can be easily removed using vinyloxycarbonyl chloride (VOC-Cl) in the formation of secondary (2^0) amide which later can be converted to amide. Positive effects have been seen in morphine analogues synthesis by this demethylation reaction (Fig 6) and this reaction is an extremely used reaction.

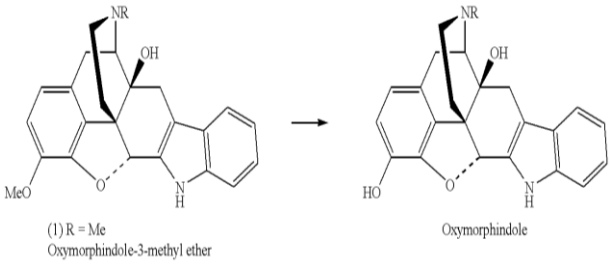

Fig. 6: demethylation of morphine analogues

Amides

Peptides and polypeptides are the commonly studied lead compounds in medicinal chemistry, consists of amino acids which are linked by amide or peptide bonds. Amides with the binding sites are likely to interact by hydrogen bonding. The carbonyl oxygen has the ability to form 2 hydrogen bonds as it behaves as a hydrogen bond acceptor. The lone pairs are similar to that of amide group as they are in the same plane as sp2 hybridized orbitals. The nitrogen as it interacts with the adjacent carbonyl group is unable to behave as a hydrogen bond acceptor. N-H group is present in primary (1^0) and secondary (2^0) amides, allowing the possibility to act as hydrogen bond donor. Secondary amide is the most common amide among the peptide lead

compounds. Certain analogues can be prepared for the testing of possible binding interactions.Except the amines (10, 20) almost all the analogues can be used to identify whether amide group acts as hydrogen bond donor, to identify whether amide acts as hydrogen bond acceptor amines and alkenes can be tested. Due to the partial double bond the amide group does not rotate and is planar. At equivalent position secondary amine, tertiary amine and ketone analogues poses single bond which can rotate. Due to this the relative positions of amide group on either side of binding groups is altered leading to binding loss even if amide group itself is uninvolved in binding. Hence, activity loss does not definitely mean that amide group is essential as binding group. With the above groups, it is right to say that NH2 group is not is important if the activity is preserved. Similarly no activity can be found by carboxylic acid and primary amine, mainly due to loss of essential binding groups at one half of molecule. These specific analogues can only be worth for taking in consideration if the peripheral part of molecule contains amide group. Alkenes acts as a useful test analogue as it cannot rotate i.e. planar and can neither act as hydrogen bond acceptor nor hydrogen bond donor. Hence the above described analogues should be prepared by means of full synthesis several analogues of amide can be attained directly from the lead compound as amides are stable functional groups in relation to other groups.

Thiols and Ethers

The (S-H) thiol group acts as a good ligand in relation to zinc ion and is thus incorporated into many drugs which are designed for inhibiting enzymes which contain zinc cofactor. These enzymes are called as zinc metallo proteinases. If the thiol group is present in lead compound, the relative alcohol can be tested. This leads to weak interactions with transition metal like zinc.An ether group (ROR) acts as hydrogen bond acceptor between oxygen atoms. The test can be carried out by on neighboring alkyl group by increasing the size to see if it reduces the capability of group to participate in hydrogen bonding. Significant decrease in binding affinity is seen in analogues where oxygen is used in place methylene (CH2) isostere.

Alkyl Groups and Carbon Skeleton

The carbon skeleton and alkyl substituent's of lead compound is hydrophobic in nature and binds to hydrophobic regions through hydrophobic interactions and Vander Waals forces to the binding site. The relation between alkyl substituent and binding site can be known by the synthesis of analogue lacking the substituent. These analogues if attached with carbon skeleton of molecule should generally be synthesized by full synthesis. If oxygen or nitrogen are present attached with the alkyl group it can be possible to detach the alkyl group from lead compound (for eg. demethylation of methyl ether using hydrogen bromide HBr). Thus the activity of analogue is expected to get reduced if alkyl group undergone important hydrophobic interactions.

Other Functional Groups

Lead compounds may possess other functional groups in vast variety which shows no direct binding, but is important in other aspects. Functional groups such as nitro groups or nitriles have influenced on electronic properties of molecules. Whereas alkynes restrict the conformation or shape of molecule and functional groups such as aryl halides acts as metabolic blockers.

Quaternary Ammonium Salts

Quaternary ammonium salts interacts by ionic interactions with the carboxylate groups as they are ionized it can also interact between aromatic ring in binding site and quaternary ammonium ion by induced dipole interaction. The electron availability in the aromatic ring is decreased by the positively charged nitrogen atom thereby inducing dipole effect. The slightly positive edges, slightly negative ring face is observed in such a ring leading to possibility of interaction between quaternary ammonium positive ion and slightly negative aromatic ring faces. An analogue is been synthesized possessing a tertiary amine group replacing quaternary ammonium group exhibiting the necessity of these interactions. There is a possibility of a group to get ionized by protonation; this can be prevented by converting an amine group to amide. Acetylcholine a common neurotransmitter possessing quaternary ammonium group is assumed to bind with its target receptor at the binding site by means of induced dipole interactions and/or by ionic bonding exhibited by change in the ion channel (Fig 7).

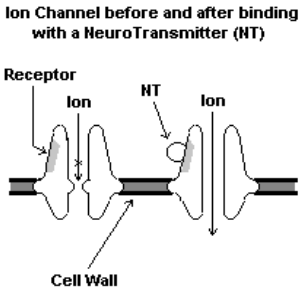

Fig. 7: Neurotransmitter e.g. – acetylcholine

Alkyl and Aryl Halides

Chlorine, iodine or bromine involved in alkyl halides tend to posses chemical reactivity as the halide ion are good leaving group. Due to this the drug possessing alkyl halide is easily capable of reacting with any of the nucleophilic group; targeting and making it covalently/permanently bonded i.e. an alkylation reaction (e.g. alkylation of enolates Fig 1.3.l) takes place. This reactivity is slightly problematic as the drugs are capable for alkylating wide range of macromolecules possessing nucleophillic group in it and also for amino group in nucleic acids and proteins. The problem in the reactivity can be moderated to a certain extent leading to severe side effects as selectivity is still a major problem. Therefore these drugs are not used in treatment of common diseases and are preserved for usage in life threatening diseases e.g. cancer. Alkyl group containing fluorides i.e. alkyl fluorides does not act as alkylating agents due to the presence of stronger C-F bond which cannot be easily broken. Fluorine due to its same size to that of proton is used to replace it but posses' different electronic properties. It has the ability to protect the molecules from undergoing metabolism.Aryl halides are not able to act as alkylating agents as the halogen substituents present in it are electron withdrawing groups affecting electron density, influencing binding nature of aromatic ring. Due to hydrophobic nature chlorine and bromine are favorable for interaction at binding site through hydrophobic pockets. Hence hydrogen bonding is not essential. Halogen substituents, halide ions are poor, strong hydrogen bond acceptors respectively.

Esters

An ester functional group is able to bind at the binding site only as a hydrogen bond acceptor. The carbonyl oxygen present in the functional group is more capable than alkoxy oxygen for acting as a hydrogen bond acceptor due to its less hindrance sterically and greater electron density. Fully synthesized equivalent ether can play an important role in testing carbonyl group. Esterases are the esters which can hydrolyze by metabolic enzymes in vivo. Due to this nature, the lead compounds containing esters (important for binding) may susceptible to problems decreasing the drug life-time in vivo. Ester groups are present in several drugs stabilizing itself towards metabolism mainly due to electronic or steric factors protecting esters. The hydrolysis of esters in the blood releasing the active drug is referred to as prodrug strategy. Aspirin exhibits an anti inflammatory action by inhibiting the cyclooxygenase enzyme (essential for the synthesis of prostaglandin). It also acts as acylating agent by covalently attaching to serine residue at COX active site (Fig 8). Aspirin is considered as a prodrug generating salicylic acid inhibiting enzyme by non covalent interactions.

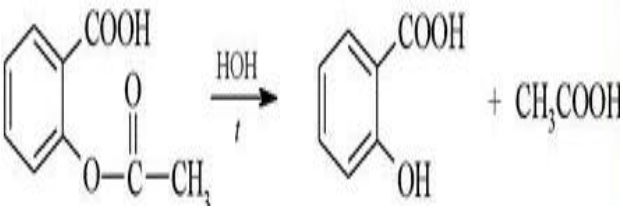

Fig. 8: aspirin- acylating agent

Carboxylic Acids

Carboxylic acid group is commonly present in many drugs it acts as both hydrogen bond acceptor and donor in various ways. It can also exist as carboxylate ion allowing the possibility of acting as hydrogen bond acceptor. Carboxylate ion for zinc ions acts as a good ligand, present in zinc metalloproteinases enzymes as a cofactor. Primary amides, primary alcohols, esters and ketones are the basic analogues synthesized and used for testing the carboxylic acid interactions. The above analogues are incapable to get ionized, indicating the importance of ionic bond at the time of loss of activity. Primary alcohol indicates that carbonyl oxygen participates in hydrogen bonding. In ester and ketone a hydroxyl group present in the carboxylic acid participates in hydrogen bonding. From lead compound ester and amide analogues can be synthesized directly but harsher conditions are required for reducing carboxylic acid to primary alcohol, therefore this analogue must be prepared through full synthesis. Ketone can also be prepared by full synthesis.

Isosteres

Atoms or group of atoms possessing same valency in outer shell configuration with similar chemical and physical characteristics are referred to as isosteres.-Univalent isosteres, Bivalent isosteres, Trivalent isosteres and Ring equivalents.

For hydroxyl group OH isosteres are CH3, NH2 and SH. For oxygen O isosteres are CH2 (dimethoxy isosteres (Fig 9), NH and S. isosteres function mainly in determination of the importance of a particular group in binding. By altering the groups the character can be effectively controlled. Replacement of CH2 by O makes a little difference in analogue size. Replacement shows a marked change in bonding, electronic distribution and polarity. Replacement of OH by larger SH influences steric factors and not the electronic character. In hydrogen bonding a particular group involved can be determined by the isosteric groups. For example consider OH replaced by CH3 eliminates the hydrogen bonding, whereas the replacement of OH by NH2 does not eliminate it.

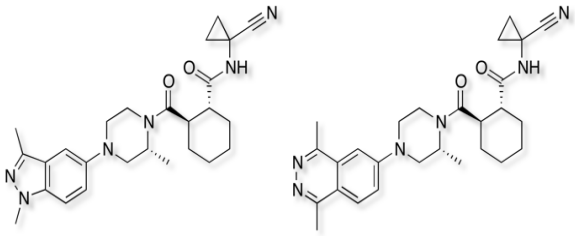

Fig. 9: Dimethoxy isosteres

An ether linkage is present in β blocker propranolol (Fig 10). OCH2 segment is replaced with CH=CH/CH2 CH2/SCH2 isosteres demolishes its activity completely. Whereas NHCH2 when replaced reduces yet retains its activity. These are indicative that ether oxygen is essential and is involved in hydrogen bonding of drug with the receptor.

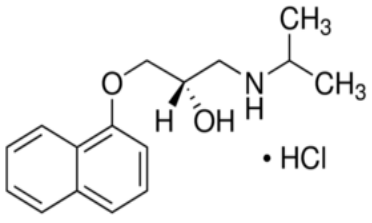

Fig. 10: propranolol

Heterocycles

In lead compounds large varieties of heterocyclic groups are present. These are the structures which contain hetero atoms (nitrogen, sulfur and oxygen) in their cyclic ring. Nitrogen containing heterocyclic compounds is common in nature. Heterocyclic compounds may either aromatic or aliphatic and are capable to bind and interact with variety of binding forces at the binding sites. When taken individually, the heteroatoms like sulfur, nitrogen and oxygen are capable to interact by hydrogen bonding at the binding site. Whereas overall compound can bind and interact through hydrophobic and van der waals forces. In hydrogen bonding, aspects such as the orientation of ring and position of heteroatom are essential in determining the interaction stability (good or weak). Consider purine structure, it possesses 3 hydrogen bond acceptors and donors permitting 6 hydrogen bond interactions but in an ideal direction. In the purine ring vander waal interactions are possible above and below binding regions of ring system. Some heterocycles involves hydrogen binding intricate networks within binding site. Methotrexate, an anticancer drug can be considered as an example containing pteridine ring system which basically interacts with binding site.If the heterocyclic ring is present in lead compound, analogues are to be synthesized exploring the necessity of these heteroatoms. Tautomers formed due to complication of heterocycles plays essential a role in determining DNA structure. Nucleic acid bases which are heterocyclic in nature are paired with double stranded helix constituting DNA structure. Guanine and cytosine are paired with three hydrogen bonds, and adenine and thymine are paired with two hydrogen bonds. Coplanar rings are involved in base pairing allowing ideal orientation for hydrogen bond acceptors and donors. The above arrangement leads to stacking of base pairs one above another, allowing the faces of base pairs for van der waal interactions. It is essential to determine the tautomers preferred by the heterocycles to ease the understanding of drugs interacting at the binding sites. A conjugated system is formed by hydrogen bond acceptors and donors of heterocyclic compounds. Enhancement of the hydrogen bond can be facilitated by bond cooperatively in conjugated system caused by polarization of electrons; this phenomenon is referred to as resonance-assisted hydrogen bonding possible for nucleic acid base pairs hydrogen bond acceptors and donors.

CONCLUSION

The functional groups are essential for increasing the activity of the compounds as they lead to enhanced reactivity with the other compounds. Studying of the binding interactions of various groups provides us with the ability to reduce the non required or the

additional groups which have no specific activity within a compound and can lead to cause adverse effects of the compounds by binding with the undesired site of action. So, the binding interaction studying is beneficial in pharmaceutical terms for compounding a drug.

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