SAR OF H1-RECEPTOR ANTAGONISTS

SAR: STRUCTURE-ACTIVITY RELATIONSHIP

- The Structure-Activity Relationship (SAR) is the Relationship between the chemical or 3D structure of a Molecule and its biological, physicochemical and pharmacological activity.

- The analysis of SAR enables the determination of the Chemical groups responsible for evoking a target biological effect in the organism . This allows Modification of the effect or the potency of a bioactive Compound(a DRUG) by changing its chemical structure.

OTHER TERMS

- This method is refined to build mathematical relationships between the chemical structure and the biological activity, known as QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP(QSAR).
- Another related term is STRUCTURE AFFINITY RELATIONSHIP (SAFIR).

SAR OF H1 RECEPTOR ANTAGONISTS

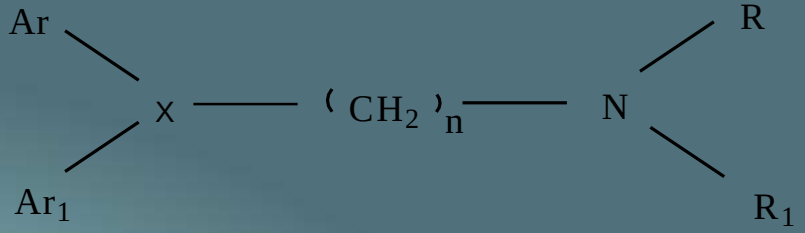
- Based on the Pharmacological Profile, the H1- antihistamines are divided into two major groups:

  1.FIRST GENERATION or CLASSICAL ANTIHISTAMINES.

  2.SECOND GENERATION or NON-SEDATIVE ANTIHISTAMINES.

- The SAR of antihistamines is discussed with reference to the First Generation antihistamines.

GENERAL STRUCTURE OF ANTIHISTAMINES



STRUCTURAL REQUIREMENTS:

- Ar is aryl: Phenyl, substituted phenyl,hetero aryl groups like 2- pyridyl.
- Ar_1: Second aryl (or) aryl methyl group.
- X: Connecting atom of O, C, (or) N.
- $(CH_2)n$: Carbon chain usually ethyl.
- NRR_1: Basic, terminal amine functional group.

1.ARYL GROUPS

1. The diaryl substitution is essential for significant H1-receptor affinity. The optimal antihistaminic activity depends upon the co-planarity of two aryl substitutions.

   Ar: Phenyl, substituted phenyl and heteroaryl group like 2-pyridyl.

2. Most of the H1-antihistamines possess substituents in one of the aryl rings (mainly in phenyl ring), and this influences the potency of the compound. Aryl rings may be linked,e.g: promethazine.

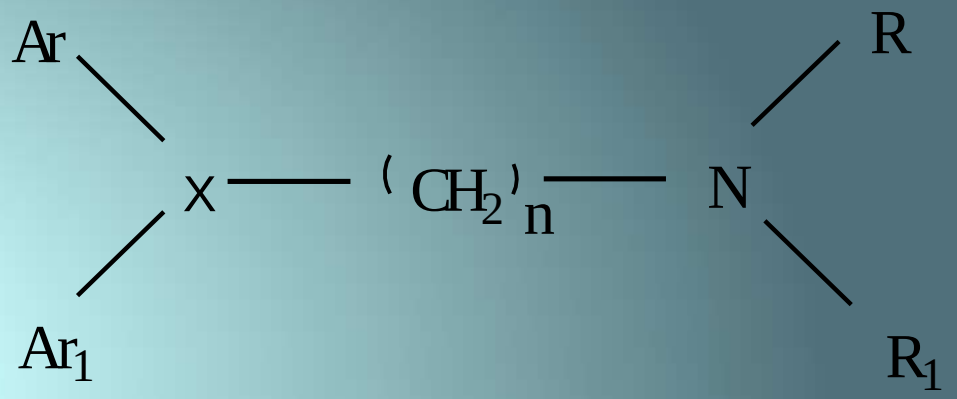
2. NATURE OF X

- The X-connecting moiety of H1-antihistamines may be simple carbon chain or saturated carbon-oxygen moiety, which serves as a spacer group for required pharmacophore.

  Antihistamines containing a carbon atom in the connecting moiety (e.g:carbinoxamine) exhibit chirality, which leads to stereo-selective binding at the receptor. X= oxygen (amino alkyl ether analogue), X=nitrogen (ethylene-diamine derivatives),X= carbon (mono amino propyl analogue).

3.ALKYL CHAIN

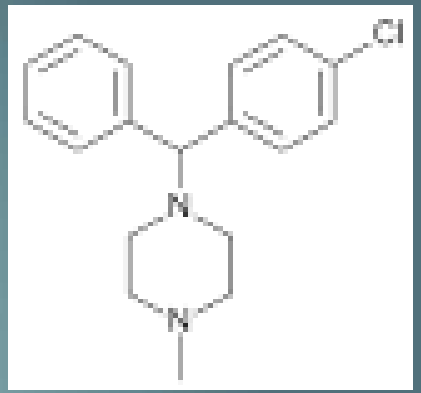
- The carbon chain consists of two or three atoms in H1-antihistamines, which leads to the distance between the central point of the diaryl ring system and the terminal nitrogen atom in the extended conformation of these compounds in he range of 5-6 Angstrom.



- Branching of this carbon chain leads decrease in antihistaminic activity. (exception is promethazine which is more potent than its nonbranched counterpart).
- If the carbon atom adjacent to the terminal nitrogen atom is branched, the possibility asymmetry exists. However it will not affect the binding affinity with the receptor.

4. TERMINAL NITROGEN ATOM(NRR')

- The terminal N-atom should be tertiary amine for maximum activity. The terminal nitrogen may be a part of heterocyclic ring, eg- chlorcyclizine which also retains high antihistaminic activity. The amino moiety deserves the protonation on interaction with H1 receptor due to the basicity with pKa 8.5-10.

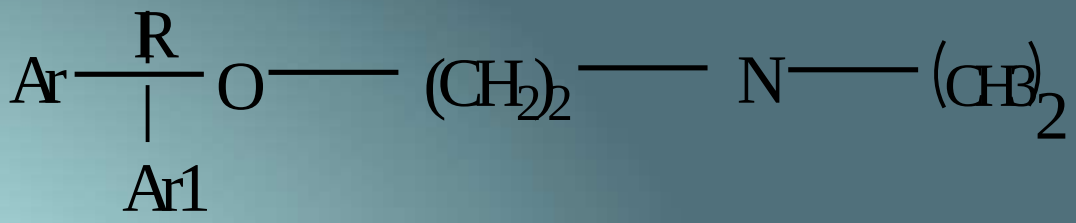


CLASSIFICATION:

a) Amino alkyl ethers.
b) Ethylenediamine derivatives.
c) Propyl amine derivatives.
d) Phenothiazine derivatives.
e) Piperazine derivatives.

AMINO ALKYL ETHERS (ETHANOLAMINES)

General structure:



STRUCTURE ACTIVITY RELATIONSHIP

a) These are characterized by presence of OXYGEN connecting moiety.

b) Most compounds in this series are simple N,N- dimethyl ethanolamine derivatives.

c) Most amino alkyl ethers are optically active.

d) This amino alkyl ethers have to penetrate the BBB and occupy central H_1 receptor resulting the DROWSINESS. eg: DOXYLAMINE

CONCLUSION

- Thus STRUCTURE-ACTIVITY RELATIONSHIP is important to evaluate the overall physicochemical

  properties of medicine.

  X-connecting moieties, and the nature of substitution in the alkyl side chain or terminal nitrogen among the various drugs account for differences observed in antihistaminic potency as well as pharmacological, biodisposition, and adverse reaction profiles.

THANK YOU