STRUCTURE ACTIVITY RELATIONSHIP (SAR)

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SAR is the relationship between the chemical or 3D structure of a molecule and its biological activity.

OR

The analysis of the dependence of biological effects of a chemical upon its molecular
structure.

OR

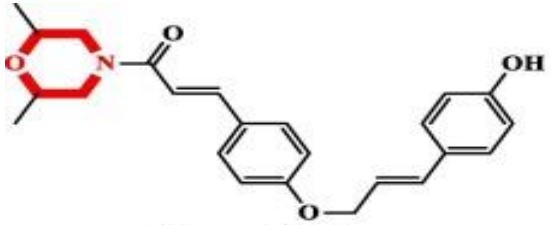
Molecular structure and biological activity are correlated by observing the results of systematic structural modification on defined biological endpoints.

Quantitative SARs (QSAR)as a special case of SARs (when relationships become quantified)

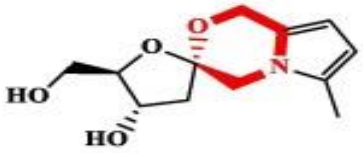
Pharmacophore

The precise arrangement of atoms, groups, or functionalities in a small molecule required for specific interactions with its biological target and its activity.

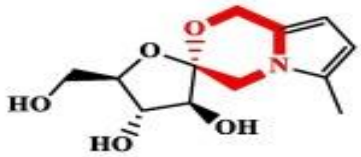
A pharmacophore model consists of a few features organized in a specific 3D pattern. Each feature is typically represented as a sphere (although variants exist) with a radius determining the tolerance on the deviation from the exact position . The features can be labeled as a single feature or any logic combination consisting of “AND,” “OR,” and “NOT” to combine different interaction patterns within one label. Additional features can describe forbidden volume interactions (typically to represent the receptor boundary).



Polygonafolin 1
(Antileishmanial)

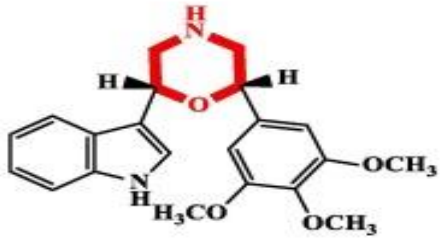


Acotartarin A 2
(Appetite stimulant)

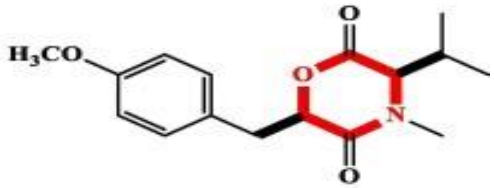


Acotartarin C 3
(Appetite stimulant)

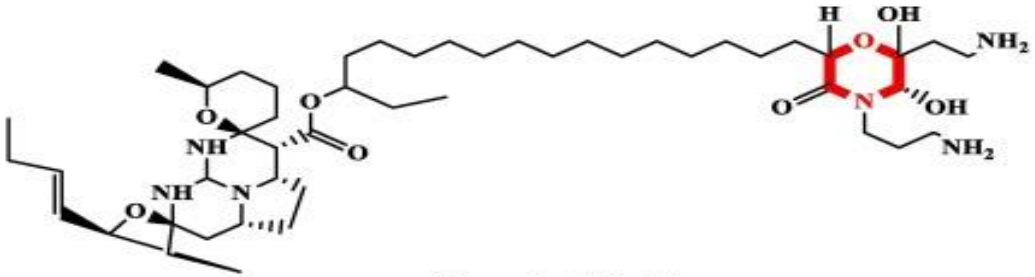
Chelonin A 4
(Antiinflammatory &
Antimicrobial)



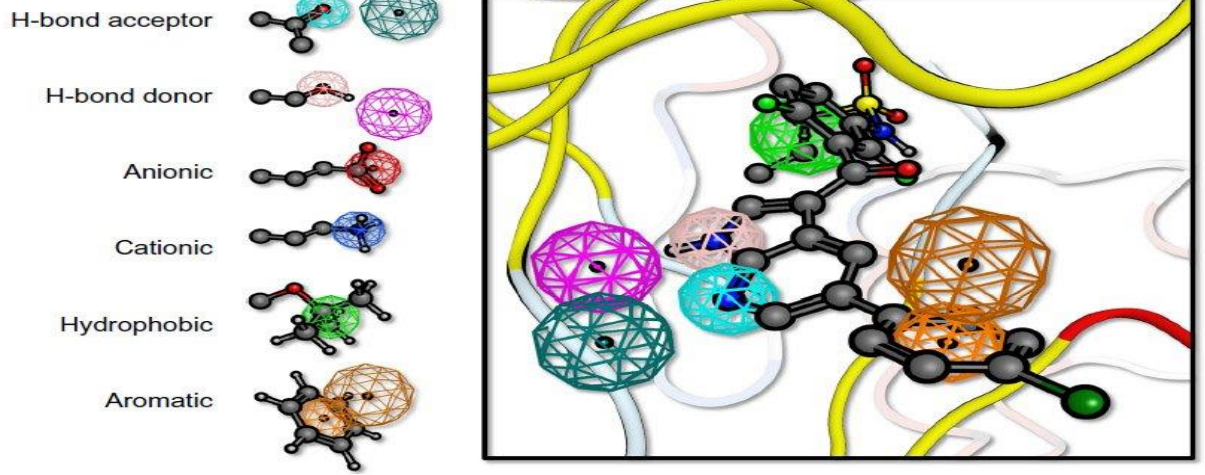
Chelonin C 5
(Antiinflammatory &
Antimicrobial)



syn-3-isopropyl-6-(4-methoxybenzyl)-4-methylmorpholine-2,5-dione 6
(Anticancer)

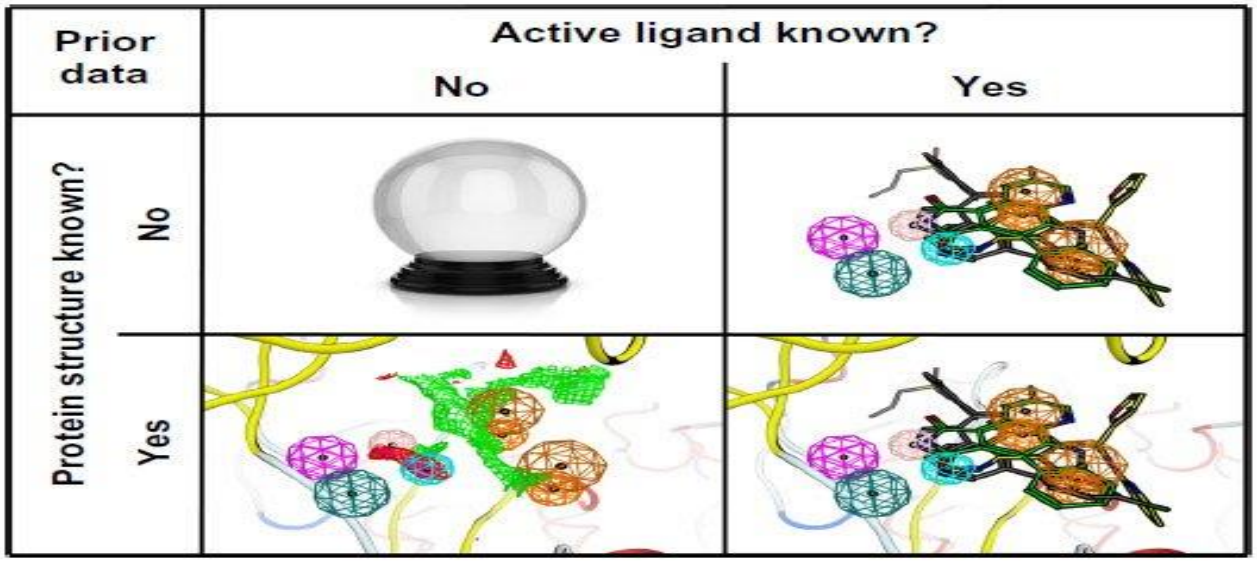


Monanchocidin A 7
(Anticancer)



Pharmacophore query.

Notes: A pharmacophore query is comprised of different features. The features represent molecular recognition motifs such as hydrogen bond acceptors or donors, anionic, cationic, hydrophobic, and aromatic groups. The radius of the sphere determines the strictness of the geometric constraint. For features where the correct orientation of the interaction is important such as hydrogen bonds and the aromatic plane, a second feature can be used indicating the vector of the interaction (or the normal of the plane). A pharmacophore query can combine any of these features, with different radii and logic operations such as “AND,” “OR,” and “NOT.” On the left a hypothetical pharmacophore query for BRAF kinase is given



Four different situations for the pharmacophore search.

Notes: The figure shows the four different situations that may be encountered when starting a virtual screening. The situations include the absence of both the ligand and protein structure information, where except for divination, experimental screening is the only option. The second option is the presence of active ligands, but the protein structure is unknown, where pharmacophores can be used for ligand-based virtual screening. The best situation is when binding ligand and structural information is present. The most challenging option is when only a protein structure is available.

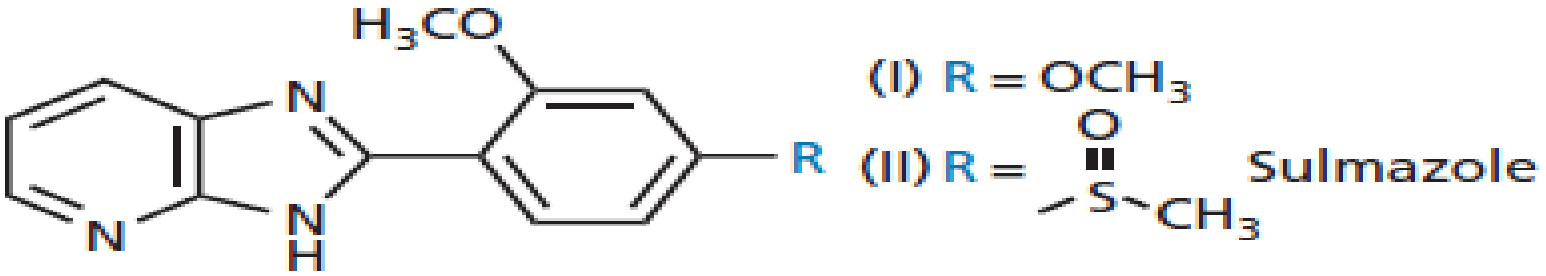
Physicochemical properties

QSAR studies on a variety of totally different structures are relatively rare and are limited to studies on hydrophobicity. It is more common to find QSAR studies being carried out on compounds of the same general structure, where substituents on aromatic rings or accessible functional groups are varied. The QSAR study then considers how the hydrophobic, electronic, and steric properties of the substituents affect biological activity. The three most studied physicochemical properties are now considered in some detail.

Hydrophobicity

The partition coefficient (*P*)

$$P = \frac{\text{Concentration of drug in octanol}}{\text{Concentration of drug in aqueous solution}}$$

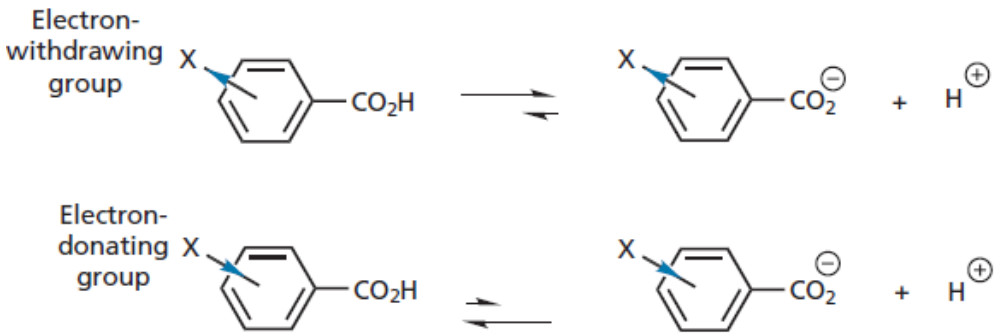


Altering log *P* to remove central nervous system side effects The cardiotonic agent (I) was found to produce 'bright visions' in some patients, which implied that it was entering the central nervous system (CNS). This was supported by the fact that the log *P* value of the drug was 2.59. In order to prevent the drug entering the CNS, the 4-Ome group was replaced by a 4-S(O)Me group. This particular group is approximately the same size as the methoxy group, but more hydrophilic. The log *P* value of the new drug (**sulmazole**) was found to be 1.17. The drug was now too hydrophilic to enter the CNS and was free of CNS side effects.

Electronic effects

The electronic effects of various substituents will clearly have an effect on a drug's ionization or polarity. This, in turn, may have an effect on how easily a drug can pass through cell membranes or how strongly it can interact with a binding site. It is, therefore, useful to measure the electronic effect of a substituent.

When a substituent is present on the aromatic ring, this equilibrium is affected. Electron-withdrawing groups, such as a nitro group, result in the aromatic ring having a stronger electron-withdrawing and stabilizing influence on the carboxylate anion, and so the equilibrium will shift more to the ionized form. Th erefore, the substituted benzoic acid is a stronger acid and has a larger *K* X alue (X represents the substituent on the aromatic ring) (Fig.). f the substituent X is an electron-donating group such as an alkyl group, then the aromatic ring is less able to stabilize the carboxylate ion. The equilibrium shift s to the left indicating a weaker acid with a smaller K_x value



Steric factors

The bulk, size, and shape of a drug will influence ho easily it can approach and interact with a binding site.

A bulky substituent may act like a shield and hinder the ideal interaction between a drug and its binding site.

Alternatively, a bulky substituent may help to orientate a drug properly for maximum binding and increase activity.

Steric properties are more difficult to quantify than

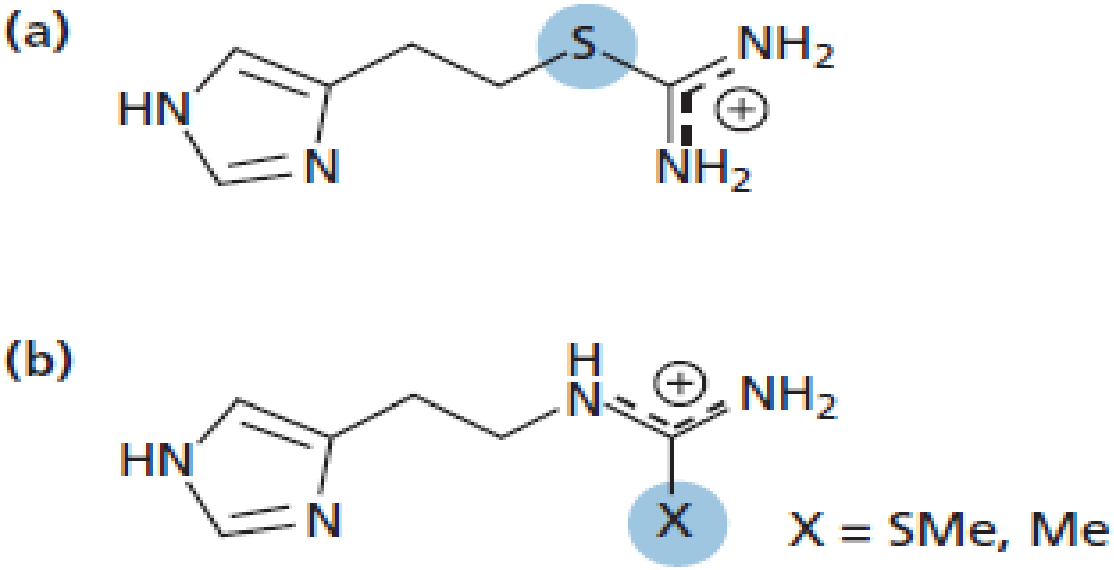
hydrophobic or electronic properties It is highly unlikely that a drug's biological activity will be affected by steric factors alone

Bioisosteres

Tables of substituent constants are available for various physicochemical properties. A knowledge of these constants allows the medicinal chemist to identify substituents which may be potential bioisosteres. Thus, the substituents CN, NO 2 , and COMe have similar hydrophobic, electronic, and steric factors, and might be interchangeable.

Such interchangeability was observed in the development of cimetidine and cimetidine analogues

The task was now to find an analogue which would
bind to the antagonist region only. The isothiourea (Fig.a) was synthesized as the positive charge would be restricted to the terminal portion of the chain and should interact more strongly with the more distant antagonist binding region. Antagonist activity did increase, but the compound was still a partial agonist, showing that binding was still possible to the agonist region. other analogues were synthesized where one of the terminal amino groups in the guanidine group was
replaced by a methylthio group or a methyl group (b in Fig.). Both these structures were partial agonists, but with poorer antagonist activity
From these results, it was concluded that both terminal amino groups were required for binding to the antagonist binding site.



THREE-DIMENSIONAL (3D) QSAR

comparative molecular field analysis (CoMFA)

favourable and unfavourable interactions are represented graphically by 3D contours around a representative molecule. A graphical picture such as this is easier

to visualize than a mathematical formula;

• in CoMFA, the properties of the test molecules are calculated individually by computer programs. There is no reliance on experimental or tabulated factors. There is no need to confine the study to molecules of similar structure. As long as one is confident that all the compounds in the study share the same pharmacophore and interact in the same way with the target, they can all be analysed in a CoMFA study;

• the graphical representation of beneficial and non beneficial interactions allows medicinal chemists to design new structures. For example, if a contour map shows a favourable steric effect at one particular location,

this implies that the target binding site has space for further extension at that location. This may lead to further favourable receptor–drug interactions

Advantages of CoMFA over traditional QSAR

problems involved with a traditional QSAR

- only molecules of similar structure can be studied;
- However, separating on property from another is not always possible in experimental

measurement. For example, the Taft steric factor is not purely a measure of the steric factor, because the measured reaction rates used to define it are also affected by electronic factors. Also, the n -octanol/water partition coefficients which are used to measure log P are known to be affected by the hydrogen bonding character of molecules;

- the tabulated descriptors may not include entries for

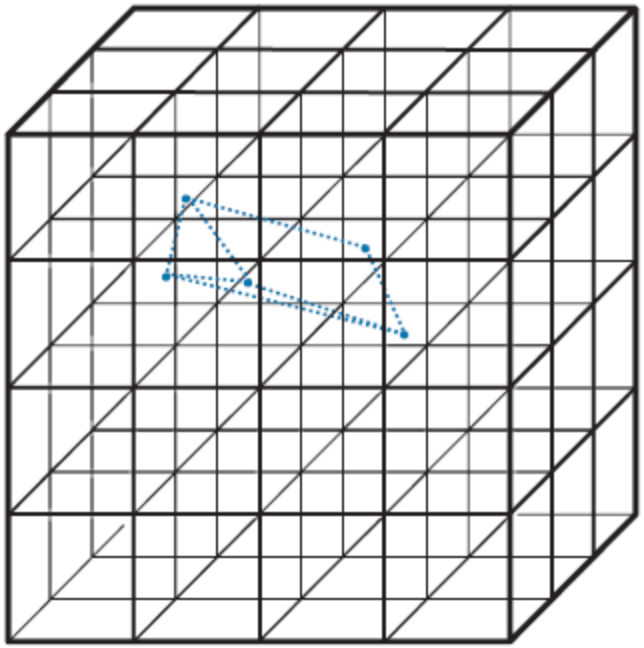
unusual substituents;

- it is necessary to synthesize a range of molecules

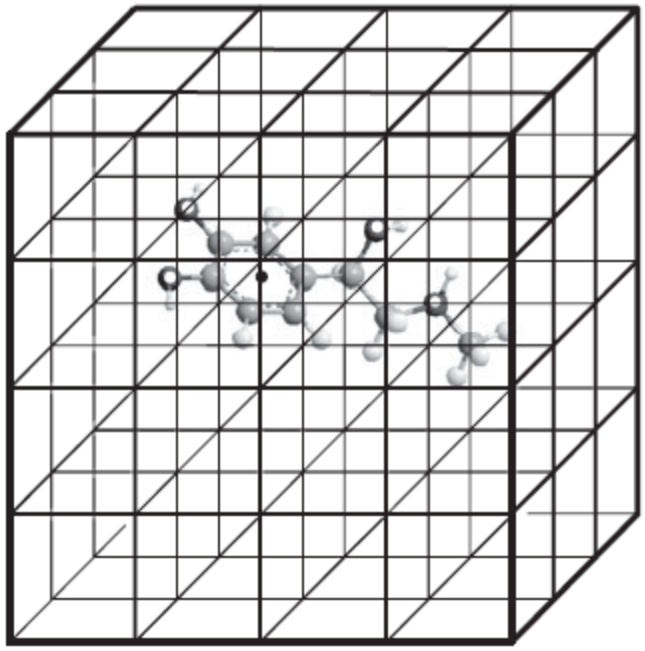
where substituents are varied in order to test a particular property

CoMFA methodology is based on

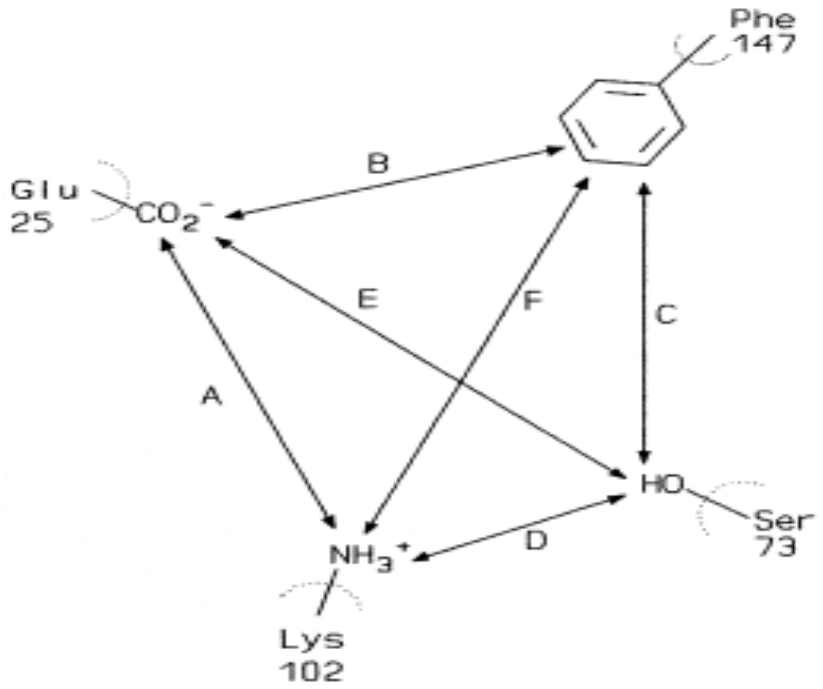
the assumption that drug–receptor interactions are noncovalent and that changes in biological activity correlate with the changes in the steric and/or electrostatic fields of the drug molecules.



Position pharmacophore in lattice



Position molecule to pharmacophore


Phe
147
B
Glu
25
CO_2^-
E
F
C
A
HO
Ser
73
D
NH_3^+
Lys
102

MOLCULAR DOCKING

Molecular docking is a kind of bioinformatic modelling which involves the interaction of two or more molecules to give the stable adduct

TYPES OF DOCKING

-Rigid docking

Assuming the compounds are inflexible, we are seeking a rearrangement of one of the compounds in three-dimensional space that results in the best match to the other compounds in parameters of a scoring system. The ligand's conformation can be formed with or without receptor binding activity

–FLEXIBLE DOCKING

In conjunction with transformation, we evaluate molecular flexibility to identify confirmations for the receptor and ligand molecules as they exist in the complex in.

QSAR / in silico Tools

VEGA platform. ...
CAESAR software (version 2) ...
CAESAR software (version 1)
The CAESAR Application is a JAVA™ web application that allows the access to all the toxicity predictive models developed within the CAESAR Project. ...
DEMETRA. ...
T.E.S.T.

protein-ligand docking programs:

Auto dick vina extended

Beta dock

Glide

THANK YOU