Structural Analysis of Toxicophore Interaction with Biomolecules

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MOLECULAR MODELS

Introduction

A **toxicophore** is a feature or group within a chemical structure that is thought to be responsible for the toxic properties. A toxic substance exerts its toxicity through interaction with a biomolecule, such as a protein or DNA. This causes changes in the normal physiological state eliciting toxic effects. Sometimes the toxicophore requires bioactivation (modification by an enzyme), to produce a more reactive chemical species, that is able to covalently bind to cellular macromolecules. Generally, different chemical compounds that contain the same toxicophore elicit similar toxic effects within the same organ system or area of the body. Since the toxic properties of a compound are related to its chemical structure, a thorough molecular knowledge of toxicophore interactions with biomolecules can help predict the toxicity of a given compound. This study is designed to understand the structural and molecular basis of toxicophore interactions with biomolecules. A database of all these biomolecular interactions with various toxicophores will serve as a guide to efficiently design future drugs and pesticides and hence limit the release of harmful pollutants. A case study of the interactions of alkyl and aryl halides that are extensively used as pesticides, disinfectants and components of most drugs is presented. Although many halogenated compounds are very beneficial, they can also be harmful causing carcinogenic and mutagenic toxicity in the body. They are also known to cause genotoxicity based on the nature, number and position of the halogen substituent. Figure:1 describes a few examples of halogenated interactions with proteins that are known to be toxic in nature.
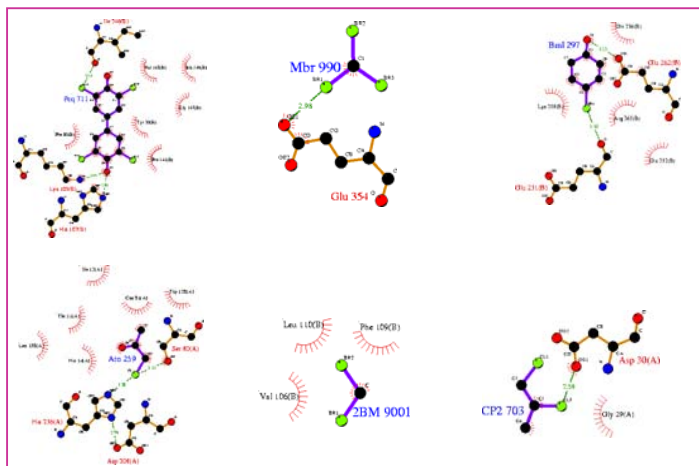

Figure-1: Schematic representation of the interaction of the toxicophores Alkyl halides and Aryl halides in biological systems. a) Polychlorinated biphenyl is bound to the estrogen binding site of human estrogen sulfotransferase b) interaction of bromoform with firefly luciferase enzyme c)4-bromophenol bound to tolune/o-xylene monooxygenase hydroxylase d) interaction of chloroacetone with hydroxynitrile lyase that has implications in cyanogenesis e) dibromomethane interaction with methane monooxygenase hydrolase f) interaction of dichloro propane with LINB – a haloalkane dehalogenase enzyme.

Methods:

- All halogenated ligands co-crystallized with proteins were chosen from PDB.
- Only those structures that had a resolution of 3Å or better resolution were considered, resulting in a set of 680 structures.
- All interactions between the halogenated atom of the ligand and any of the amino acid side-chain atoms less than 5Å in distance were included. Only the closest distance to an atom of an amino acid side chain was taken into account as an interaction.
- Since the interactions are likely to be influenced by the moiety to which the halogen is attached (e.g. alkyl or aryl groups), we classified the halogenated ligands into Alkyl-X and Aryl-X groups, where X is any halogen F, Cl, Br or I (see Figure-2).
- Ligands in which the halogen atom was covalently attached to any atoms other than C, O, N, S were not considered in this dataset, excluding interactions with molecules such as Berilyium Trifluoride or other metallic halides from the data set.
- The propensity of interaction of a halogen X with 19 amino acids in the entire data set was recorded as the observed frequency (OBS-Freq). Also, the expected frequency (EXP-Freq) for each such interacting pair was determined from a set of N(X,X) interactions and the results were normalized to get the Nor.Freq as described below:

$$P(A,X) = \frac{N(A,X)}{N(X,X)} \qquad P(B,X) = \frac{N(B,X)}{N(X,X)}$$

$$Exp.Freq = P(A,X) * P(B,X) * N(X,X)$$

$$Nor.Freq = \frac{Xi}{\sum_{i=1}^{i=19} Xi} * 100 \qquad C = 1.96 * \frac{\sigma}{\sqrt{n}}$$
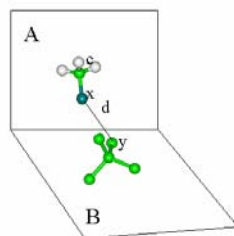

Figure-2: Schematic representation of halogenated ligand interaction. x represents the halogen atom, where x = F, Cl, Br or I. d is the distance of interaction, θ is the angle formed by atoms c, x and y and φ is the interplanar angle between planes A and B.

Results

- A total of 6854 interactions between the 19 amino acids and various halogenated ligands were found, of which 3565 interactions were with fluorinated, 899 with chlorinated, 1259 with brominated and 1131 with iodinated ligands.
- We found 1926 interactions involving Alkyl-F, and 1446 interactions with Aryl-F groups. Similarly, 400 interactions were found for Alkyl-Cl, 383 for Aryl-Cl, 690 for Alkyl-Br, 476 for Aryl-Br, 490 for Alkyl-I and 577 for Aryl-I groups.
- Fluorine and chlorine substitutions were found to have the highest propensities for interactions with Leu, while bromine interacts most often with Phe, and iodine with Ser. Fluorine has the lowest interaction preference for Cys, chlorine for Gln, bromine for Asp and iodine for Pro. Among the Alkyl-X groups interacting with alkyl amino acids, the highest propensity was observed for Ser and Leu, while the lowest preference was observed for the sulphur containing amino acids Cys or Met and the nitrogen containing Asp or Lys. For the Aryl-X ligands interacting with aromatic amino acids the highest preference of interaction was observed for Phe.

Table-1: Propensity of interaction between the various classes of ligands and the amino acids is shown. OBS-Freq represents the observed propensity, NOR-freq represents the normalized propensity and EXP-freq represents the expected propensity. The highest propensity is colored red and lowest blue.
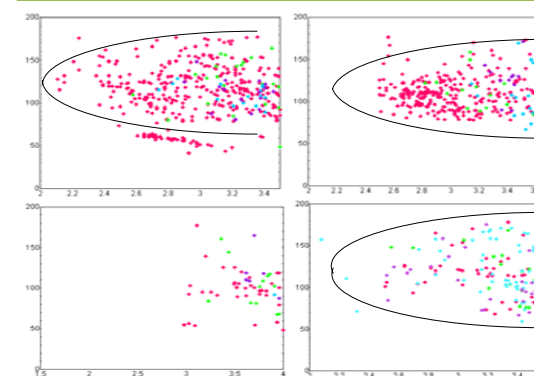

Figure-2: Illustration of the interactions of halogens with hydrogen bonding partners, X-axis represents distance and the Y-axis represents the corresponding angle A) with Oxygen B) with Nitrogen C) with Sulphur D) with Oxygen of water.
Fluorine is represented as red diamonds, Chlorine as green diamonds, Bromine as blue diamonds and Iodine as Purple diamonds.
The results illustrate the fact that bromine and iodine are better leaving groups.

Conclusions and future work

- Although the introduction of halogen atoms to potential drug compounds improves their affinity and lipophilicity, they can also be potentially toxic due to the number of halogens, nature of substitution and nature of interaction with other functional groups. Thus by understanding the nature and propensity of interactions of halogens with various amino acids, it is feasible to design drugs, pesticides and disinfectants so as to minimize these toxic effects.
- The present study shows the various structural parameters such as distance, angle and nature of interaction of two classes of toxicophores namely alkyl halides and aryl halides. These structural details serve as a guidelines for future design of molecules with reduced toxicity using halogens.
- Future goals for the project is to provide a complete database of molecular interactions of all known toxicophores with biomolecules.