

# ViewContacts<sup>TM</sup>

## Superior Understanding of Non-Covalent Interactions

**ViewContacts** is **state-of-the-art software** for improved understanding of favourable and unfavourable non-covalent interactions in protein-ligand complexes.

Non-covalent bonds, whilst weak by nature, help to maintain the three dimensional structure of a protein. They are critical in drug discovery because most drugs work by binding non-covalently with the target protein. By studying these non-covalent interactions, you gain sights into the processes in which proteins bind to one another and improve your targeted drug design. ViewContacts is the new leading tool in this area for your chemists, modelers and crystallographers.

## Advantages

**Data Driven** – created by industry experts, ViewContacts is accurate and comprehensive when finding the many different types of hydrogen bonds, polar interactions and lipophilic contacts in binding sites.

**Rule Based** – ViewContacts ensures interactions are correctly identified by using an extensive range of rigorously tested rules. These rules form the basis of a superior algorithm, developed from the latest findings in structural biology, molecular modeling, molecular recognition and database mining studies.

**Visualisation** – ViewContacts creates scripts that allow fast and easy exploration of the key protein-ligand interactions determining binding affinity.

**Handles Water Molecules** – Rank scores provide easy identification of bound water molecules for targeting in ligand design experiments.

**Identifies Unfavourable Interactions** – ViewContacts allows you to detect desolvation penalties that negatively affect target binding.

**Easy to Use** – all your scientists (expert crystallographers and modelers and non-expert medicinal chemists) can make the best use of protein crystallography in structure based drug design.

## Interaction Types

**ViewContacts** identifies all commonly occurring non-covalent interaction types such as:

- hydrogen bonding
- ionic pairs
- van der Waals

as well as many less well understood types:

- cation-pi
- hydrogen bonding to pi-systems
- $\sigma$ -hole bonding (halogen bonding)
- orthogonal dipolar alignment
- dipolar antiperiplaner interactions
- pi-stacking
- pi edge-to-face contacts
- hydrogen bonding involving CH groups

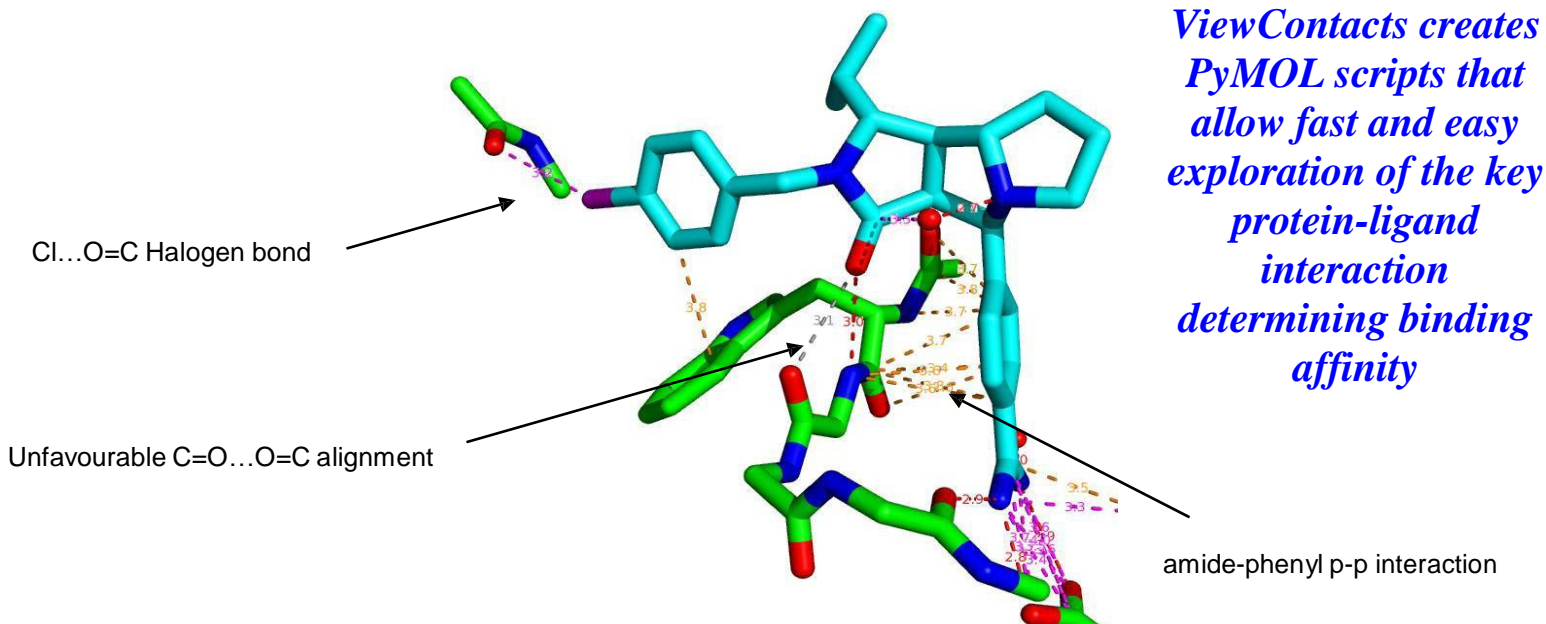
## Pair Interaction Definitions

ViewContacts automatically assigns SMARTS-based atom types and detects many different types of favourable and unfavourable interactions (with distance and angle constraints and pruning of redundant contacts).

### Classification of Interaction Types

1. hydrogen bonding
2. metal bonding
3. ionic
4. cation-dipole
5. cation-pi
6. dipolar
7.  $\sigma$ -hole bond
8. h\_donor-pi
9. pi-pi
10. van der Waals
11. unfavourable of 1, 2, 3, 6
12. polar and non-polar clashes
13. polar-nonpolar desolvation penalties

### Example: 2cf8 (Thrombin)



### ViewContacts – KEY FEATURES

- Any HET group in any domain of any pdb file can be explored
- Size of viewed binding site can be modified
- Interactions can be grouped into different schemes
- Interactions can be sub-divided into weak/strong
- All interactions in a binding site can be viewed
- Buried contacts can be viewed separately from solvated contacts
- Water mediated hydrogen bonds can be highlighted
- Results from docking studies can be read easily, with poses stored in sdf files(s)
- SMARTS definitions can handle tautomers
- PyMol script creates molecular surface, solvent excluded surface, shortcut for viewing temperature factors and more
- Bond orders from input sdf file, cif library or detected using automated methods
- SMARTS definitions and angle and distance constraints can be customized or extended
- Easily linked with our Proasis2 and Proasis3 protein structure database and visualization systems
- Available as both a web based system and a command line tool for Linux systems

## Handling of Water Molecules

ViewContacts includes a powerful method for scoring water replacement potential based on the deviation from the ideal tetrahedral coordination of the protein bound water molecules.

$$Rank = \sum_n \{ (2.80 A / r_n) + [\sum_m \cos(\Theta_{Td} - \Theta_{nm})] / 6 \}$$

The ranked scores are:

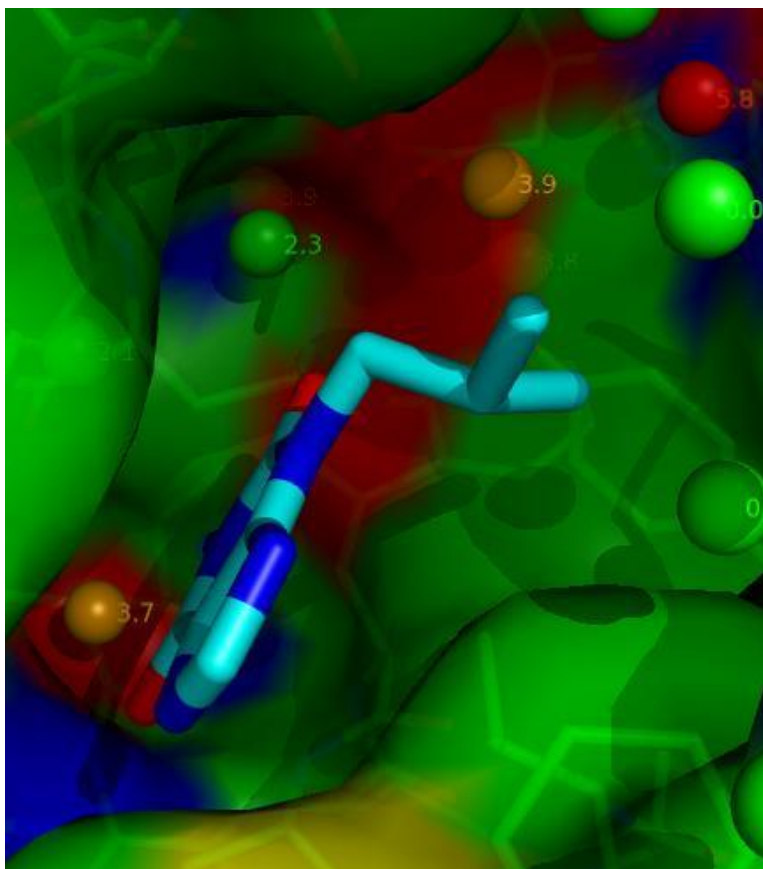
- 1 ideal H-bond: 1.0
- 2 ideal H-bonds: 2.3
- 3 ideal H-bonds: 4.0
- tetrahedral coordination: 6.0

A maximum of 4 protein contacts are counted ( $\leq 2$  donors and  $\leq 2$  acceptors), and any angle less  $60^\circ$  is rejected.

### Example: 2r8q (PDE-B1)

Colour-coding of rank score in PyMOL

1. green: 0 - 2.3 (easy to replace)
2. amber: 2.3 - 4.0 (possible to replace with suitable polar functionalities)
3. red: 4.0 - 6.0 (unlikely to replace)



*ViewContacts ranks scores to provide easy identification of bound water molecules that can be targeted in ligand design experiments*

## Identification of Unfavourable Interactions

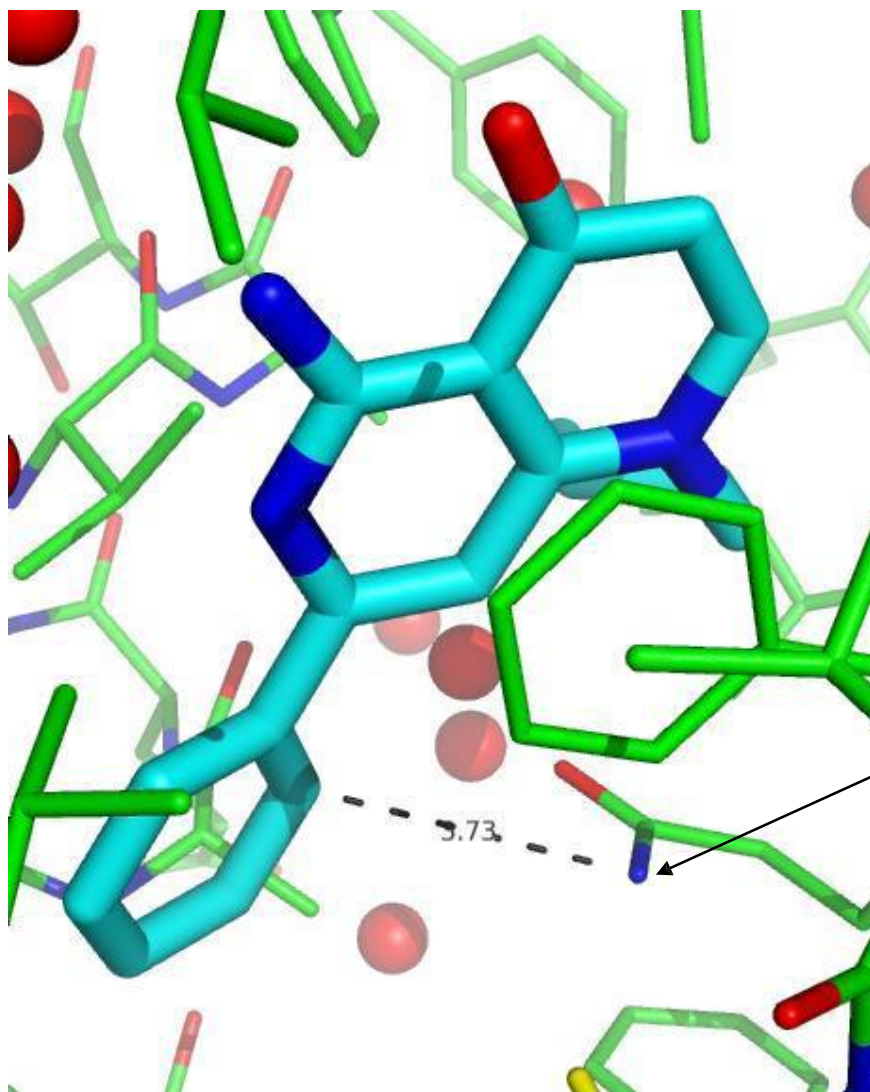
ViewContacts has been built to identify both unfavourable contact pairs and potential desolvation penalties.

Unfavourable contact pairs can arise due to very short contact distances or from repulsive electrostatic forces.

Desolvation penalties are detected by placing water molecules around the binding site to test whether a polar atom would be strongly preferred at the location of any apolar ligand atom.

Distances and angles are checked for all polar/apolar interactions and solvent exposure is taken into account when testing for desolvation penalties.

### Example: 3hdz (PDE-5)

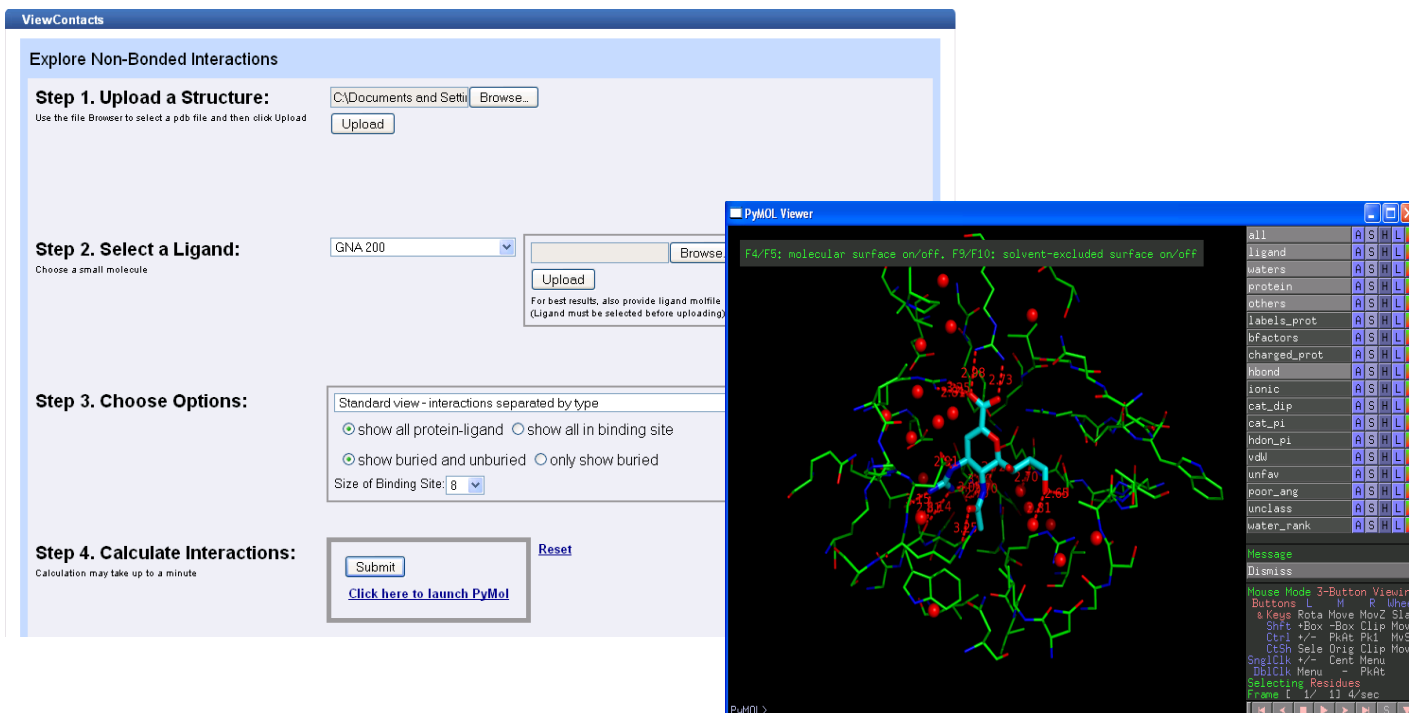


*ViewContacts allows for the detection of desolvation penalties that negatively affect the binding site*

No hydrogen bond partner for this buried N atom in the binding site so the contact is highlighted as an unfavourable interaction

## VCWeb

VCWeb is an easy to use web-based application for running ViewContacts. It runs highly optimized javascript which is fast to load and fast to execute in all popular browsers.



The screenshot displays the ViewContacts web application interface on the left and a PyMOL Viewer window on the right. The web application is titled "Explore Non-Bonded Interactions" and is divided into four steps:

- Step 1. Upload a Structure:** A file browser is open to "C:\Documents and Settings\...". An "Upload" button is visible.
- Step 2. Select a Ligand:** A dropdown menu shows "GNA 200". An "Upload" button is visible.
- Step 3. Choose Options:** Radio buttons for "show all protein-ligand" (selected) and "show all in binding site". Another set of radio buttons for "show buried and unburied" (selected) and "only show buried". A "Size of Binding Site" dropdown is set to "8".
- Step 4. Calculate Interactions:** A "Submit" button and a "Reset" link are visible.

The PyMOL Viewer window shows a 3D molecular model of a protein-ligand complex. The protein is shown as a green stick model, and the ligand is shown as a red stick model. The binding site is highlighted with a red surface. The PyMOL interface includes a command line at the bottom and a list of objects on the right side.

### Hardware and Software Requirements:

Industry standards:

- ViewContacts™ software runs on Linux, with Python 2.4 or above
- For visualization – support is provided for PyMOL (Incentive version recommended), MOE and Benchware 3D
- Openbabel (or OpenEye's Babel) needed for pdb to mol file format conversions
- clients using VCWeb can use MS Windows, Apple Mac, and Linux, and any of the major browsers

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