

Proasis3

Rich Internet Application

Proasis3 is a new Rich Internet Application (RIA) built on top of DesertSci's Proasis2 database and visualization system and comes with many powerful new features

'Rich Internet applications (RIA) are Web applications that have the features and functionality of traditional desktop applications. RIAs typically transfer the processing necessary for the user interface to the Web client but keep the bulk of the data (i.e., maintaining the state of the program, the data etc) back on the application server.'

Wikipedia

Proasis3 is a browser application that works like a desktop application

Proasis3 Advantages



- Created with '*state of the art*' technology Proasis3 responds instantly for users and improves real time productivity.
- Built to be 'future proof' for the next decade
- Improved user experiences. Behaves like a desktop application by minimizing client-server communications and providing richer functionality. For example, Proasis3 sorts 'on the client' making data manipulation easier. It provides text completion for easy project identification and structure retrieval
- Linkages to ViewContacts - the highest quality protein-ligand interaction software available
- Engineered using 'best in class' techniques so that the system is:
 - robust
 - easy to understand
 - scalable
 - fast to implement
 - easy to maintain

Introducing Proasis3



A screenshot of the Proasis3 web application interface. The page has a blue header with the text "Proasis3". Below the header is a navigation menu with links: Search, HitList, StrucDetails, Overlay, SaveHitList, ViewContacts, TreeView, Settings, DataBase, and Help. The main content area is titled "Search Protein Structure Database" and features a large banner image with the Proasis3 logo and a molecular structure. Below the banner are two search sections: "Project, ID, Text or Sequence Search" and "Ligand Structure Search". The "Project, ID, Text or Sequence Search" section includes a text input field, a prompt "Enter project name(s), protein or ligand ID(s), text string, or a protein sequence", and buttons for "Project Lookup", "ID Lookup", "Text Search", and "Seq Search". The "Ligand Structure Search" section includes a toolbar with icons for smiley, CLR, DEL, D-R, +/-, UDO, and JME, a vertical list of element types (C, N, O, S, F, Cl, Br, I, P, X), a large empty search area, and buttons for "Structure Search" and "Combined Proj Lookup/Struc Search". At the bottom of the search area, it says "JME Molecular Editor®, Novartis Pharma AG".

Cutting-Edge Technology:

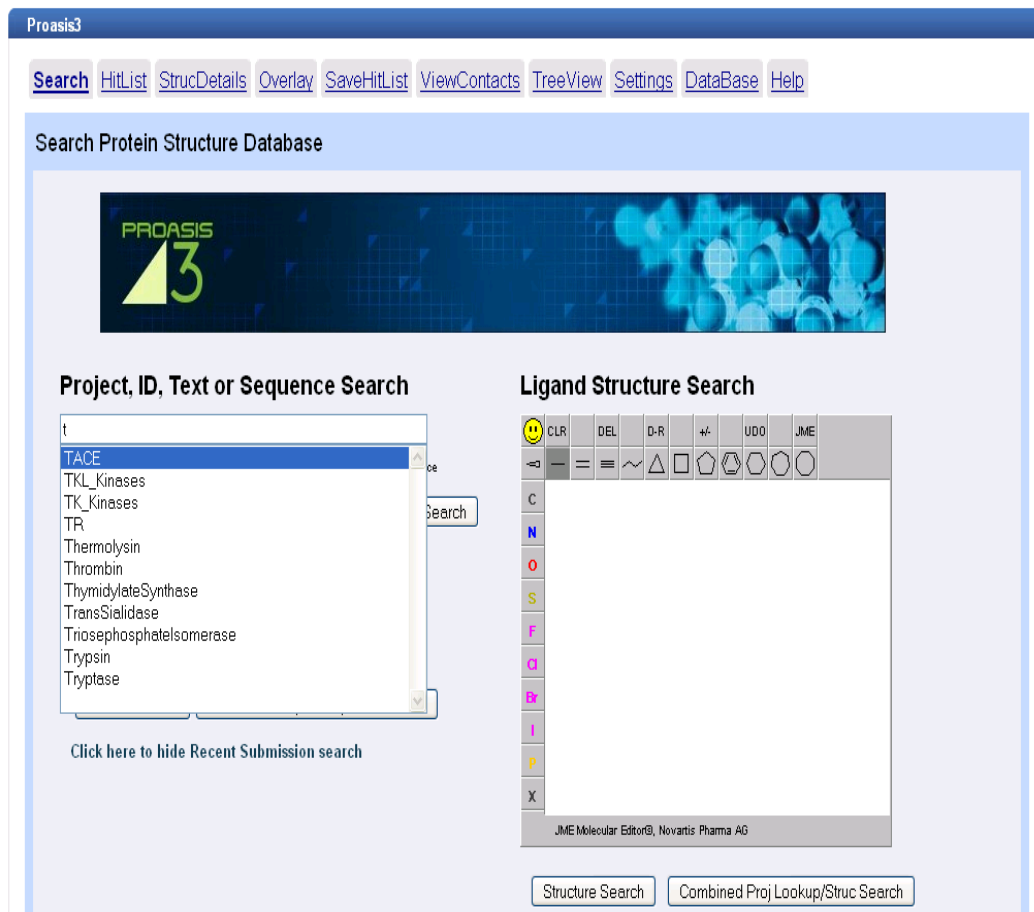
- GWT (Google web toolkit)
The most powerful toolkit for creating Ajax applications

- Pyjamas
The python version of the GWT

- PureMVC python
A powerful framework based on MVC

Proasis3 runs highly optimized javascript (compiled from python code!) so in all popular browsers it is **fast to load and fast to execute**

Easier Searching



The screenshot shows the Proasis3 web interface. At the top, there is a navigation bar with buttons for Search, HitList, StrucDetails, Overlay, SaveHitList, ViewContacts, TreeView, Settings, DataBase, and Help. Below this is a search bar labeled 'Search Protein Structure Database'. The main content area is divided into two sections: 'Project, ID, Text or Sequence Search' and 'Ligand Structure Search'. The first section has a search input field with 't' entered and a dropdown list of results including TACE, TKL_Kinases, TK_Kinases, TR, Thermolysin, Thrombin, ThymidylateSynthase, TransSialidase, Triosephosphatelsomerase, Trypsin, and Tryptase. The second section has a toolbar with various chemical structure drawing tools and a large empty area for the structure. At the bottom, there are buttons for 'Structure Search' and 'Combined Proj Lookup/Struc Search'.

- In-house project names are loaded automatically
- Simply typing a letter **lists all projects starting with that letter.**
- Select one and click 'Project Lookup' and all project structures are retrieved
- There is new, fast searching using ligand ID numbers or just the last few digits of a ligand ID
- A button for Combined Project/Structure searches makes these even easier

Many **different types of searches are easily available** from just one page of the interface, making Proasis3 even more user friendly

More like a Desktop Application

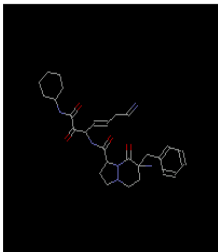
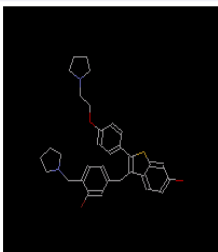
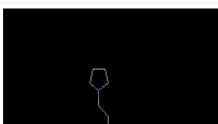


Proasis3

Search [HitList](#) [StrucDetails](#) [Overlay](#) [SaveHitList](#) [ViewContacts](#) [TreeView](#) [Settings](#) [DataBase](#) [Help](#)

Show HitList

<< First < Prev page 10 of 60 (299 hits, 299 strucs) Next > Last >> sort by: LIGANDSIZE Help: [i](#)

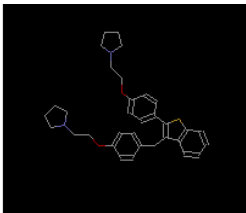
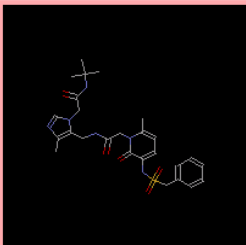
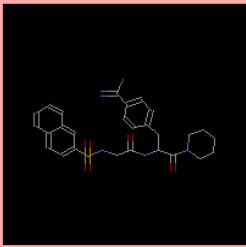
StrucId	Ligand	RegNo	Title	Links
46 1a46			THROMBIN COMPLEXED WITH HIRUGEN A MIMETIC INHIBITOR	Site Header Download
47 1d3d			CRYSTAL STRUCTURE OF HUMAN ALPHA THROMBIN IN COMPLEX WITH BENZOTHIOPHENE INHIBITOR 4	Site Header Download
			CRYSTAL STRUCTURE OF HUMAN ALPHA THROMBIN IN COMPLEX WITH	Site

- Hitlists can be re-sorted according to different properties and dynamically re-sized entirely on the client
- The desktop application retrieves data from the database more efficiently (using asynchronous javascript technology)
- Tooltips and PopUps link directly to helpful hints

More data can be stored on the client, making for **faster navigation**

New Hitlist Tools



48	1d3q		CRYSTAL STRUCTURE OF HUMAN ALPHA THROMBIN IN COMPLEX WITH BENZO[B]THIOPHENE INHIBITOR 2	Site Header DownLoad
49	3c1k		CRYSTAL STRUCTURE OF THROMBIN IN COMPLEX WITH INHIBITOR 15	Site Header DownLoad
50	1dwd		CRYSTALLOGRAPHIC ANALYSIS AT 3.0-ANGSTROMS RESOLUTION OF THE BINDING TO HUMAN THROMBIN OF FOUR ACTIVE SITE-DIRECTED INHIBITORS	Site Header DownLoad

Select All Select Page Select None Remove Selected Remove Unselected

- Individual and multiple rows can be selected and manipulated
- Hitlists can be pruned and/or extended
- Hitlist rows easy to customize
- Hyperlinks easy to extend to connect to other inhouse and external resources

Hitlists can be exported in multiple formats – in report style or as a set of pdb files

Updated Look and Feel



Proasis3

[Search](#) [HitList](#) [StrucDetails](#) [Overlay](#) [SaveHitList](#) [ViewContacts](#) [TreeView](#) [Settings](#) [DataBase](#) [Help](#)

View Structure Details

<<First <Prev 1d3p 1d3t 1g30 1sb1 1tbz 1a46 1d3d 1d3q 3c1k 1dwd Next> Last>> page 5 of 30 (299 hits, 299 strucs) ⓘ

Title CRYSTAL STRUCTURE OF HUMAN ALPHA THROMBIN IN COMPLEX WITH BENZOTHIOPHENE INHIBITOR 4
THROMBIN COMPLEXED WITH HIRUGEN AND A BETA-STRAND MIMETIC INHIBITOR

Summary

Reg.-No.:
Name:
Protein-Class: Thrombin,EC:3.4.21.5
Inhibition:
HET-Identifier: BIC H 372 :LYS H 375 :OHO H 377
Author: R.ST CHARLES, J.H.MATTHEWS, E.ZHANG, A.TULINSKY, M.KAHN
Source: PUBLIC **Date:** 11-FEB-98
Type: XRAY **Depositor:** admin
R-factor: 0 **Resolution [Å]:** 2.12
Comment:

Ligand

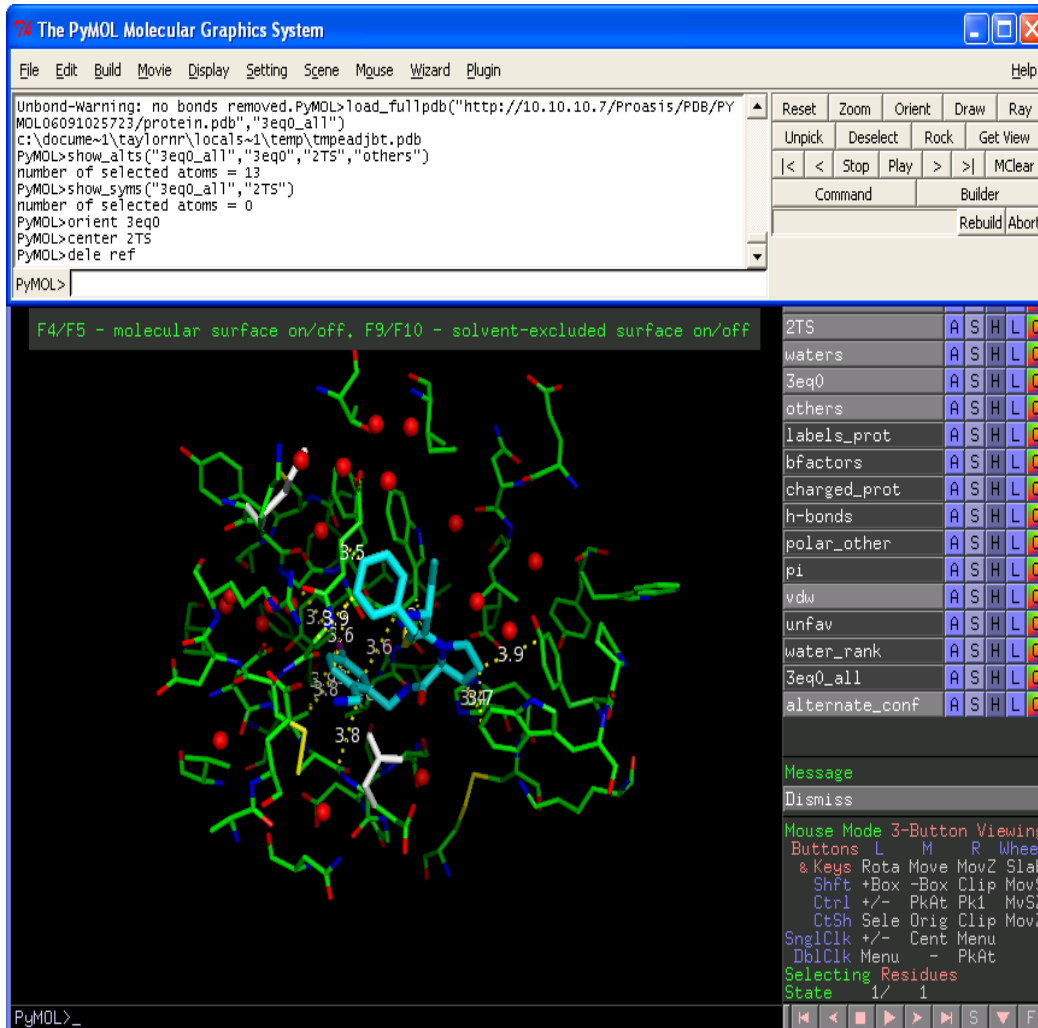
Links

[View Site](#) - Launch Viewer
[Header](#) - show full Header Section from pdb file
[Download](#) - go to Download from Database page (in Proasis2)
[RCSB](#) - go to PDB Databank for this structure (open a new window)
[Electron Density Maps](#) - go to page for Viewing Electron Density Maps (in Proasis2)
[Advanced Symmetry Module](#) - go to page for viewing symmetry related molecules (in Proasis2)
[Search for Similar Proteins](#)- blast search
[ViewContacts](#)- go to page to further explore protein-ligand interactions

- Structure information has a new improved look and layout, with all the familiar details and functionality
- Includes easy access to the Advanced Symmetry Module

Ajax facilitates **faster browsing** from one structure to the next

New PyMol Viewing Features



2TS	A	S	H	L	C
waters	A	S	H	L	C
3eq0	A	S	H	L	C
others	A	S	H	L	C
labels_prot	A	S	H	L	C
bfactors	A	S	H	L	C
changed_prot	A	S	H	L	C
h-bonds	A	S	H	L	C
polar_other	A	S	H	L	C
pi	A	S	H	L	C
vdw	A	S	H	L	C
unfav	A	S	H	L	C
water_rank	A	S	H	L	C
3eq0_all	A	S	H	L	C
alternate_conf	A	S	H	L	C

Message

Dismiss

Mouse Mode 3-Button Viewing
 Buttons L M R Wheel
 & Keys Rota Move MovZ Slab
 Shift +Box -Box Clip MovS
 Ctrl +/- PkAt Pk1 MovSZ
 CtSh Sele Orig Clip MovZ
 SnglClk +/- Cent Menu
 DblClk Menu - PkAt
 Selecting Residues
 State 1/ 1

Enhanced PyMol viewing all in one session:

- binding site views include both the binding site and the entire protein
- alternative conformations in the binding site are highlighted
- all symmetry molecules making contact with the binding site are shown
- fine-tuned protein-ligand interactions are illustrated, including unfavorable contacts, and water-mediated interactions

Additional Overlay Functionality



Proasis3

[Search](#) [HitList](#) [StrucDetails](#) **[Overlay](#)** [SaveHitList](#) [ViewContacts](#) [TreeView](#) [Settings](#) [DataBase](#) [Help](#)

Structure Overlays

Step 1. Select Structures
(Select rows from table on HitList page or use Select All or Select Page buttons)

Step 2. Select Reference
(All structures will be superimposed, with highlighted structure as the reference)

1a4b:H
1d3d:B
1d3q:B

Step 3. Select Overlay Method
PyMol optimized sequence alignment, binding site

Step 4. Size of Binding Site
8 ⓘ

Step 5. Prepare Structures

[Click here to launch PyMol](#)

- In addition to fast sequence and ligand based alignments, it is now possible to use PyMol's inbuilt optimized alignment algorithms
- Larger numbers of structures can be superimposed in one session
- Size of the binding site region can be fine-tuned
- Overlaid structures can be exported as pdb files

Protein-ligand interactions can now be viewed for overlaid structures ...

Linkages to ViewContacts™

Identification of Interactions

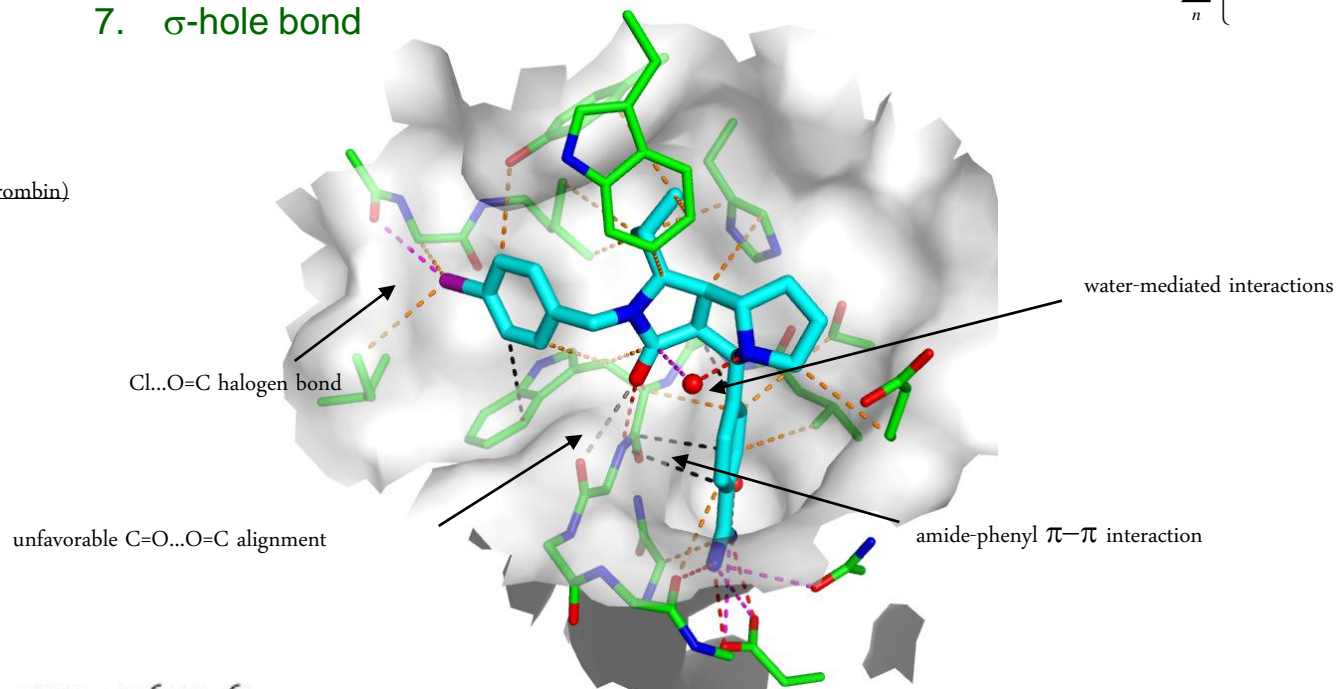
All of the important non-covalent interactions in a protein-ligand complex can be thoroughly explored using the link between Proasis3 and ViewContacts

- | | | |
|------------------------|---------------|---|
| 1. hydrogen bond | 8. h_donor-pi | 11. unfavorable of 1, 2, 3, 6 |
| 2. metal | 9. pi-pi | 12. polar and non-polar clashes |
| 3. ionic | 10. vdW | 13. polar-nonpolar contacts with likely desolvation penalties |
| 4. cation-dipole | | |
| 5. cation-pi | | |
| 6. dipolar | | |
| 7. σ -hole bond | | |

Water and rank score molecules:

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

Ex. 2cf8 (thrombin)



Additional Functionality for Interactions



A screenshot of the Proasis3 web application interface. The top navigation bar includes links for Search, HitList, StrucDetails, Overlay, SaveHitList, ViewContacts (highlighted), TreeView, Settings, DataBase, and Help. Below this is a section titled "Further Explore Non-Bonded Interactions" with several controls: "Display Interactions:" with radio buttons for "protein-ligand" (selected) and "all in binding site"; "Grouping of Interactions:" with a dropdown menu set to "Standard view - separated by type"; "Buried Interactions:" with radio buttons for "show buried and unburied" (selected) and "only show buried"; and "Size of Binding Site:" with a dropdown menu set to "8". A "Run ViewContacts" button is present, with a note below it stating "Calculation may take up to a minute". To the right of these controls is a window titled "Ligand" showing a 3D ball-and-stick model of a ligand structure on a black background, with the PDB ID "1a46" displayed at the bottom.

- Fine-grained representations of non-covalent interactions can be viewed easily
- All contacts in a binding site can be shown
- Contacts involving only those residues in very close proximity to the ligand can be displayed

The desktop application, **VCWeb**, for non-database structures such as docking results and structures generated from interactive modeling sessions, is also available

Project Views



Proasis3

[Search](#) [HitList](#) [StrucDetails](#) [Overlay](#) [SaveHitList](#) [ViewContacts](#) [TreeView](#) [Settings](#) [DataBase](#) [Help](#)

Tree View of Project Hierarchy

Summary for selected project: **PPAR_A**

Get all structures for selected project: **PPAR_A**

- + CycloOxygenases
- + Kinases
- NHR
 - AR
 - CAR
 - + ER
 - ERR
 - GR
 - + LXR
 - otherNHR
 - PPAR
 - PPAR_A**
 - PPAR_D
 - PPAR_G
 - PR
 - PXR
 - + RAR
 - + ROR

Project Summary

Structure Source - total, inhouse, public: 12, 0, 12

Number of complexes/unliganded: 12, 0

Multimeric: monomers, dimers, higher multimers: 4, 0, 8

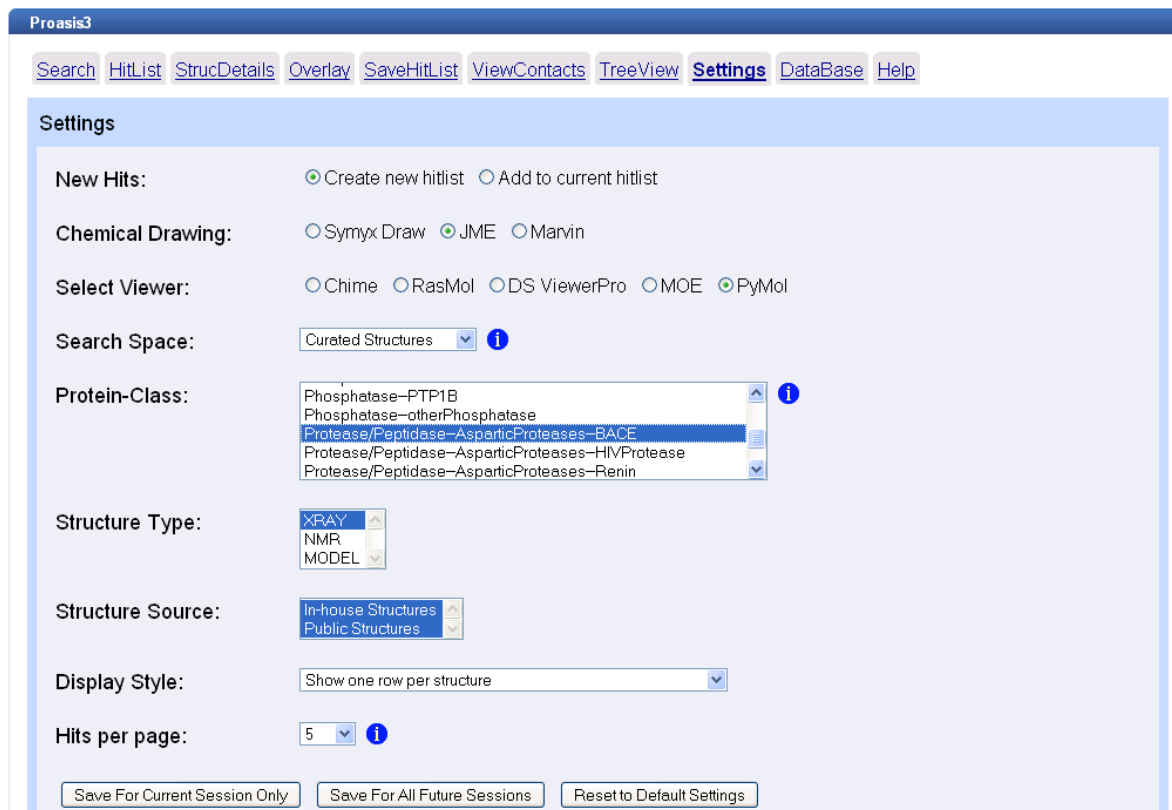
Most recent: 3kdu, 23-OCT-09

Highest resolution: 2p54, 1.79

All regnos:

- The Project Tree is fast to load, fast to navigate, and its state is maintained when leaving the page
- Project summaries can now be quickly retrieved and inspected
- Structures from any project, or set of projects, are easy to retrieve

More Options and Settings Saved



- Powerful new options, including the ability to extend hitlists

- Users can choose their preferred molecular drawing package

- Users can choose their preferred molecular viewing package

End-user **settings can now be saved** from one session to the next

Other Features



- GWT/pyjamas means **just one version of code** is needed to support each of Internet Explorer, Firefox, Safari, Opera, Chrome, ...
- Comprehensive test suite based on selenium
- Comprehensive on-line user manual
- Fine-tuned checking of input parameters
- Speed Tracer for Chrome (from Google) helps to achieve maximum performance



Future Enhancements

- Extend functionality for saving hitlists, eg:
 - Create reports with user defined columns
 - Export to Excel
- Session files maintained for each project
- Enable user structures not in the Proasis2 Database to be uploaded and compared and contrasted with experimental data
- Linking Proasis3 and PyMol on the desktop using PyMol's in-built web server functionality
- Providing hooks to DesertSci's '*Scorpion*' - **a new, innovative, state-of-the-art scoring function**
- Providing hooks to DesertSci's new **Ligand Design Tool** based on the '*Scorpion*' technology.