

# Psssst. Are you looking for ligands for your protein?

# DOCK Blaster

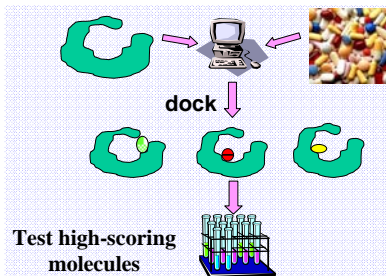
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## Have you got a 3D model of your protein? Are you set up to test compounds?

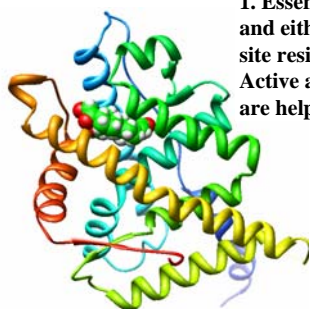
Virtual screening is the most practical way to use structure for ligand discovery. Yet docking continues to be challenging to use for the very biologists and medicinal chemists who could most benefit from it. The programs are difficult to use even by an expert, and there are many pitfalls for the unwary. To help lower the barriers to entry to virtual screening we are developing tools to make docking easier to use, particularly for non-specialists. First, we developed ZINC, a public access database of ready-to-dock molecules for virtual screening, which we give away at <http://zinc.docking.org>. We created DUD, a directory of useful decoys, which can be used to assess docking performance, publicly accessible at <http://dud.docking.org>. Here we present DOCK Blaster, a free virtual screening service. DOCK Blaster is ready to use now, so please go to <http://blaster.docking.org> and register to beta test it against your target.

## Virtual Screening for Ligands

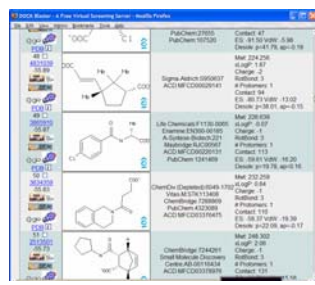


## From protein target to ligands to test in a few easy steps with DOCK Blaster

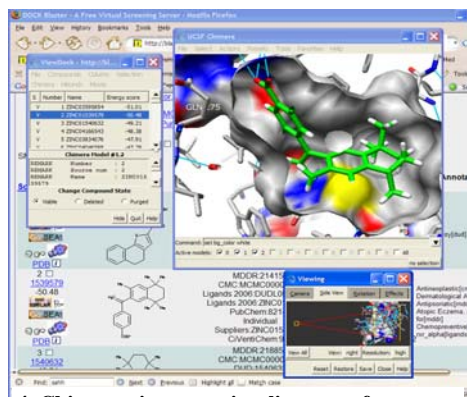
1. Essential input is a target structure and either a docked ligand or binding site residues to define the binding site. Active and inactive control molecules are helpful, but optional.



2. Prepare docking job by uploading target, ligand, and (optionally) other controls.



3. DOCK Blaster results browser, showing purchasing information.



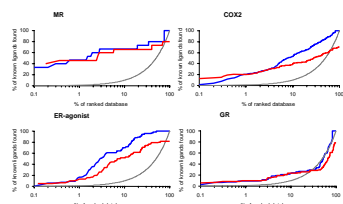
4. Chimera viewer to visualize poses from DOCK Blaster overlaid on the results browser.

### Docking step by step

### Points to consider

|                                     |  |
|-------------------------------------|--|
| <b>Acquire target structure</b>     | A good structure is essential for successful docking. If you do not have a structure of your target, you cannot use DOCK Blaster. Sorry.                   |
| <b>Prepare Input Files</b>          | Consider ionizable residues, cofactors, protein flexibility, other models. Active and inactive controls help calibrate the model.                          |
| <b>Prepare and Submit Job</b>       | Upload locally edited files to the DOCK Blaster website. Interface checks for many simple formatting errors.   |
| <b>Computer: Scrutinize Input</b>   | Computer checks for problems in files, including unrecognized atoms, format problems, problems in the specification of the binding site                    |
| <b>Computer: Target Preparation</b> | Computer prepares "hot spots", assigns parameters, calculates scoring grids, and prepares and uploads control ligands.                                     |
| <b>Computer: Model Calibration</b>  | Computer test docks and scores control molecules. Produces enrichment plots, depending on information supplied.  |
| <b>Review Preliminary Results</b>   | Did docking work on your target? You decide based on reports prepared by the computer. Enrichment. Poses. This is why control ligands are so helpful.      |
| <b>Select Database to Dock</b>      | Choose from: "lead-like", "fragment-like", "FDA", "metabolites", "kinase-inhibitor like" or "CNS permeable", or other ZINC subsets.                        |
| <b>Computer: Docking</b>            | Docking can take days. As the calculation progresses, you can see results available so far, and take corrective action (e.g. cancel the job) if warranted. |
| <b>Analysis and Interpretation</b>  | Browse top 500 docking hits. Cluster and browse top hits by similarity. Examine enrichment plots. View in Chimera, PyMol or Jmol.                          |
| <b>Purchase Compounds to Test</b>   | Check price and availability directly from your browser. Prioritize and order compounds for experimental testing.  |

## Does DOCK Blaster really work?



Enrichment plots for 4 targets comparing an expert (blue) to DOCK Blaster (automatic). Fully automatic docking is often comparable to an expert.

Receiver Operator Characteristic Area Under the Curve (ROC AUC) enrichment values comparing an expert to DOCK Blaster (auto). 50 is random, 100 is perfect. Results in **bold** indicate automated performance that is very close to the expert, *italicized* values indicate satisfactory enrichments for the automated screens. Target abbreviations below.

| Target | Expert    | Auto      | Target     | Expert    | Auto      | Target | Expert | Auto | Target | Expert    | Auto      |
|--------|-----------|-----------|------------|-----------|-----------|--------|--------|------|--------|-----------|-----------|
| AR     | 86        | 69        | ER-agonist | 91        | 74        | CDK2   | 60     | 32   | DHFR   | 81        | 39        |
| GR     | 53        | 43        | ER-antag   | 65        | 47        | EGFR   | 65     | 50   | GART   | 85        | 43        |
| MR     | <b>80</b> | <b>75</b> | PPARg      | 20        | 31        | FGF1   | 32     | 40   | ACE    | <b>61</b> | <b>57</b> |
| PR     | <b>70</b> | <b>65</b> | RXRa       | 62        | 60        | HSP90  | 73     | 41   | ALR2   | <b>67</b> | <b>64</b> |
| SRC    | <b>57</b> | <b>52</b> | Thrombin   | 68        | 58        | HIVRT  | 69     | 49   | AmpC   | <b>91</b> | <b>95</b> |
| TK     | 97        | 77        | Trypsin    | <b>64</b> | <b>63</b> | HMGa   | 66     | 56   | COX1   | <b>57</b> | <b>53</b> |
| FXa    | 83        | 75        | PSMAP      | 70        | 13        | InhA   | 35     | 31   | COX2   | 80        | 67        |
| ACE    | <b>80</b> | <b>82</b> | PDGFRb     | 52        | 51        | PDE5   | 65     | 32   | GPB    | 89        | 76        |
| ADA    | <b>71</b> | <b>66</b> | VEGF2      | 58        | 53        | PARP   | 79     | 71   | PNP    | 91        | 32        |
| NA     | 71        | 61        | HIVPR      | 56        | 52        | SAHH   | 98     | 86   | COMT   | 72        | 66        |

Abbreviations: DUD, directory of useful decoys; EF, enrichment factor; MDDR, MDL Drug Data Report; Tc, Tanimoto coefficient; ROC, receiver operating characteristic; ACE, angiotensin-converting enzyme; AChE, acetylcholinesterase; ADA, adenosine deaminase; ALR2, aldose reductase; AmpC, AmpC beta-lactamase; AR, androgen receptor; CDK2, cyclin-dependent kinase 2; COMT, catechol O-methyltransferase; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; DHFR, dihydrofolate reductase; EGFR, epidermal growth factor receptor; ER, estrogen receptor; FGF1, fibroblast growth factor receptor kinase; FXa, factor Xa; GART, glycineamide ribonucleotide transformylase; GPB, glycogen phosphorylase beta; GR, glucocorticoid receptor; HIVPR, HIV protease; HIVRT, HIV reverse transcriptase; HMGa, hydroxymethylglutaryl-CoA reductase; HSP90, human heat shock protein 90; InhA, enoyl ACP reductase; MR, mineralocorticoid receptor; NA, neuraminidase; PSM MAP, P38 mitogen activated protein; PARP, poly(ADP-ribose) polymerase; PDE5, phosphodiesterase 5; PDGFRb, platelet derived growth factor receptor kinase; PNP, purine nucleoside phosphorylase; PPARg, peroxisome proliferator activated receptor gamma; PR, progesterone receptor; RXRa, retinoic X receptor alpha; SAHH, S-adenosyl-homocysteine hydrolase; SRC, tyrosine kinase SRC; TK, thymidine kinase; VEGF2, vascular endothelial growth factor receptor; ATP, adenosine-5'-triphosphate; -GAR, beta-glycineamide ribonucleotide; NAD(P)-(H), nicotinamide adenine dinucleotide (phosphate)-(reduced); PLP, pyridoxal-5'-phosphate.30

## Web sites and more information

DOCK Blaster: <http://blaster.docking.org/> - free docking for non-specialists. Now in beta test.

ZINC: <http://zinc.docking.org/> - a public access database for virtual screening. New version in Jan 2008.

DUD: <http://dud.docking.org/> - a directory of useful decoys for benchmarking virtual screening.

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