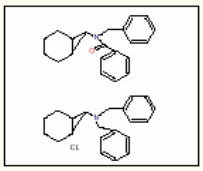
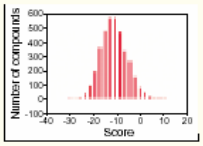
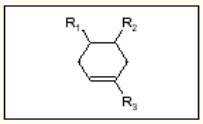
Proteins	Amino acids	Functions	Comments
C	102–126	Nucleoprotein. Forms the capsid	Cytoplasmic
PrM	166–183 (Glycoprotein)	Stabilizes E protein at acidic pH in the immature intracellular virion	Precursor of M. Forms heterodimers with E protein in the immature virion. N-glycosylation on one site
M	75	Membrane protein	Present on the mature extracellular virion
E	495 (Glycoprotein)	Binding to a cell receptor, fusion on the mature viron, induction of neutralizing antibodies	Dimeric envelope protein. N-glycosylation on one site
NS1	352 (Glycoprotein)	Functions in the viral RNA replication. Other functions (extracellular form)?	Forms intracellular dimers and extracellular hexamers. N-glycosylation on two sites
NS2A	348–354	Role in the cleavage of NS1–NS2A?	Hydrophobic protein
NS2B		Cofactor in NS3 protease activity	Hydrophobic protein
NS3	618–623	Protease, helicase, NTPase	Cytoplasmic protein
NS4A	395–405	RNA replication	Hydrophobic protein
NS4B		RNA replication	Hydrophobic protein
NS5	900–905	Polymerase, methyltransferase	Cytoplasmic protein

表一 Biological characteristics of flavivirus proteins.

Site	Lys-head		Arg-head	
	Residue	Binding pocket	Residue	Binding pocket
P5	Cys16	R157	Cys43	R157
P4	Asp17	No Contacts	Ile44	G153, V155
P3	Cys19	No Contacts	Cys45	G153, V155
P2	Thr19	**H51**, N152	Thr46	H51, G151, N152
P1	Lys20	L115, *S131*, P132 *G133*, *S135*, **Y150** *G151*, **S163**	Arg47	*S131*, P132, *G133*, T134, *S135*, *G151*
			$Arg47_A$	L115, **Y150** N152, A160 **S163**, I165
			$Arg47_B$	S127, L128, **D129**, A160
P1′	Ser21	I36, **H51**, **S135** V52	Ser48	I36, **H51**, V52, P132, G133, **S135**
P2′	Ile22	S34, Q35, *I36*, P132, G133	Met49	S34, Q35, *I36* P132, G133
P3′	Pro23	*S34*, Q35	Pro50	*S34*
P4′	Pro24	No contacts	Gly51	No contacts
P5′	Glu25	H51	Lys52	H51

表二 Residues in protease molecules that make interactions with MbBBI. (Murthy, 2000)

	Procedure	Goal	Alternatives	Pitfalls
				
1	**Receptor modeling**	Correct receptor pocket model(s).	Sources: X-ray, NMR, or homology modeling. Apo-form or liganded-form. Alternative conformations predicted by simulations.	Receptor model does not reflect the induced fit. Alternative conformations are missed.
				
2	**Library generation**	Sufficiently large and diverse set of relevant compounds.	In-house collection, HTS hits, commercially available compounds, virtual libraries computed from accessible scaffolds and sidechains.	The library is too restricted, molecules are not chemically feasible or not drug-like.
				
3	**Flexible docking**	Correct prediction of the binding geometry.	MC or GA, stochastic global optimization with gradient minimization, incremental construction, grid or explicit receptor representations, etc.	Inaccurate energy function, poor optimization algorithm. Wrong receptor model, inadequate ligand flexibility.
				
4	**Ligand scoring**	Maximal separation between binders and non-binders.	Weighted interaction terms, statistical potentials, combination of binding score with QSAR if binders are known.	Poorly predicted binding geometries, score over-training to a particular case/family, large number of false positives.
				
5	**Hit list post-processing**	The best task for the chemist, screener or compound vendor.	Clustering, diversity, selection of scaffolds and/or side-chains for a small combinatorial library or parallel synthesis.	Domination of one chemical family, lack of chemical availability, or ADME-tox and patent considerations.

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表三 Flow chart of flexible docking and VLS procedure.