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ASAD U Khan
Professor and Coordinator
Int Biotechnology Unit AMU Aligarh 202002 India

Biography

Dr. Asad U Khan has received his PhD from Aligarh M University in collaboration with ICGEB, New Delhi during the period of 1998. Currently, he is working as Associate Professor in Aligarh M University. He has successfully completed his Administrative responsibilities as Editorial members of **Scientific Domain of Global Science Book, Gene, Molecular & Cell Therapy, Medical & Pharma Board, Gene Genomes & Genomics**, **Biochemistry Processes Biotechnology & Molecular Biology**. He /she is serving as an editorial member of several reputed journals like **PlOS ONE, *Bioinformation (Biomedical Information), Genomics proteomics and Bioinformatics (Elsevere), Asian Pacific Journal of Tropical Medicine (Elsevier), Journal of Mol. Genetic Medicine (Oxford), Journal of Industrial Research and Toxicology***. He has authored over 135 research articles, 3 books. He is a member of (1) Life member of International Society of Genomics and Evolutionary Microbiology, (2) Life member of AMI (3) Member of New York Academy of Science. He has honoured as **BOYSCAST Fellow** of DST, Government of India to work as Visiting Scientist in one of the lab in University of Napoli, Italy in 2004. He is recipient of **INSA Fellowship** of 2005 for Indian lab. He is recipient of **Young Scientist Award** and **Alembic Award** of Association of Microbiologist of India in Medical Microbiology in 2006 and 2009 respectively. In year 2010 Dr. Khan has been given "**Most Active Teachers Award of AMU**" and **DBT-CREST** award of Department of Biotechnology and **National Bioscience Award for Career Development**" of Government of India, Department of Biotechnology for the year 2012

Characterization of some important resistant mutants of Class A β-lactamases

- Beta-lactamases confer resistance to a broad range of antibiotics and inhibitors by accumulating mutations.
- The number of betalactamase and their variants are steadily increasing.
- However, the information about these betalactamase classes and their variants was scattered.
- Categorizing all these classes and associated variants along with their relevant information on one platform could be helpful to the researcher working on multidrug resistant bacteria.
- Thus, the BLAD (Betalactamase database) has been developed to provide comprehensive information on betalactamases.

DATABASE CONTENT

This database includes

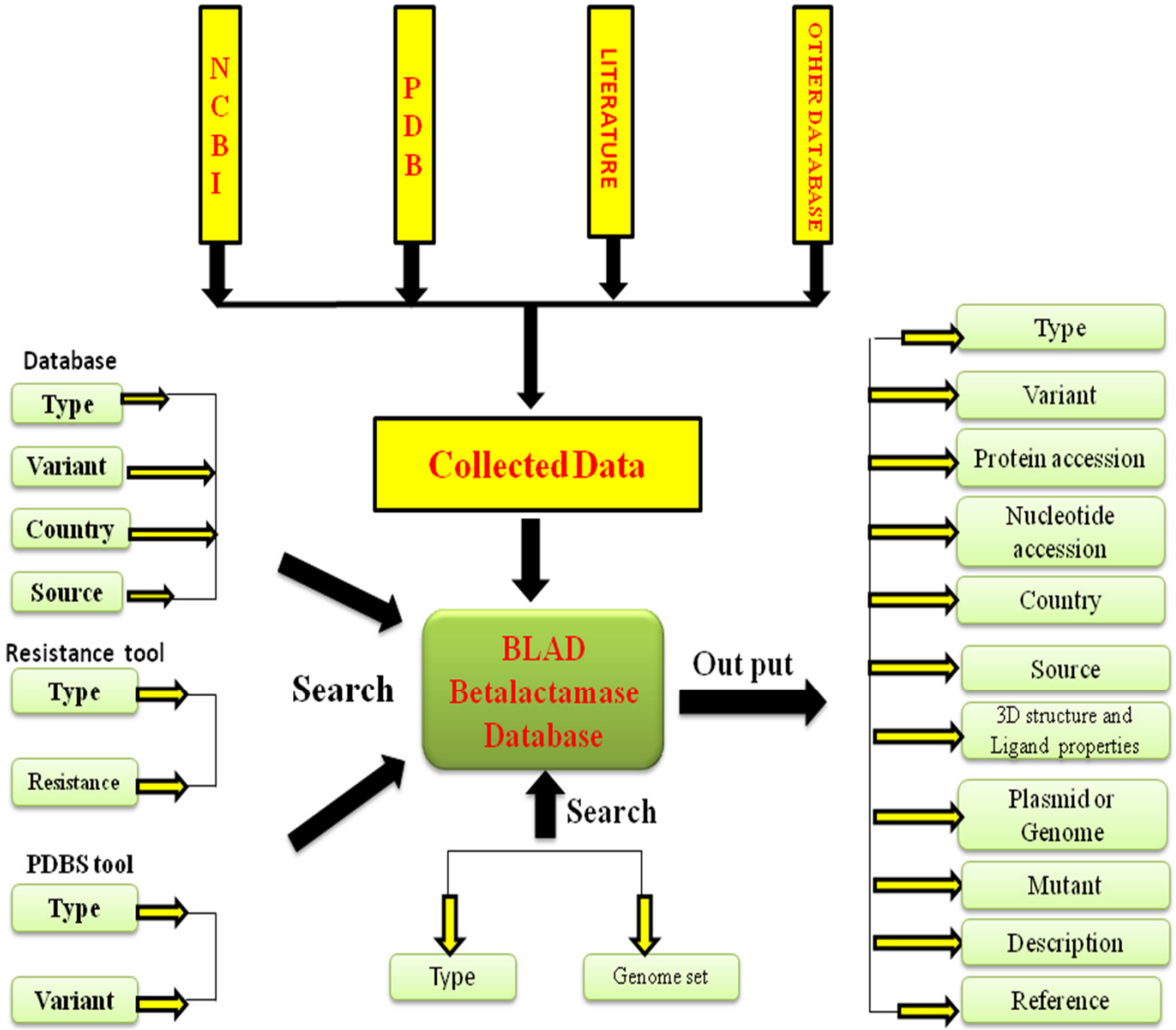
•Information about the sequences (nucleotide and protein)

•Resistance: It includes information about the resistance type.

•PDBS: This dataset includes information about the three dimensional structure of enzymes and their variants along with the description of physiochemical properties of bounds ligand.

• Genome: Iincludes the information of the plasmids. These information included as type, variant, organism, resistance type, mutant, protein and nucleotide sequences with NCBI links and literature reference with the PubMed links. Cross-reference to the UniProt protein sequence database is also provided.

•The current version of BLAD holds ~4000 gene sequences which includes all classes betalactamase. Moreover, ~200 crystal structures for all types of betalactamase were also included. All the data were collected from literatures, NCBI, protein data bank (Sussman et al., 1998) and other authentic resources



A schematic representation of architecture of BLAD database.

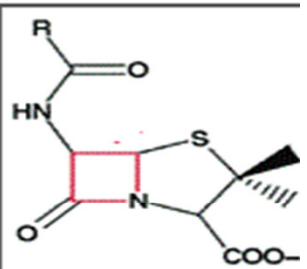
BLAD ß-Lactamase Database

A comprehensive database of widely circulated ß-Lactamase

Home | Database | Resistance | PDBS | Genome | Contact Us | Feedback

Welcome to ß-Lactamase

Beta-lactamases are enzymes produced by some bacteria and are responsible for their resistance to beta-lactam antibiotics like penicillins, cephamycins, and carbapenems (ertapenem) (Cephalosporins are relatively resistant to beta-lactamase). These antibiotics have a common element in their molecular structure: a four-atom ring known as a beta-lactam. The lactamase enzyme breaks that ring open, deactivating the molecule's antibacterial properties.



Betalactam antibiotics and inhibitors inhibit the growth of sensitive bacteria by inactivating enzymes. Beta-lactams inhibit not just a single enzyme involved in cell wall synthesis, but a family of related enzymes aspects of cell wall synthesis. These enzymes can be detected by their covalent binding of radioactively-labeled penicillin or other beta-lactams

Define search set:

○ Metallo ◉ Non-Metallo

Type	Sub Type	Resistance Type	Name
Class A	TEM	Any	Any
Class C	CTXM	Inhibitor	Clavulanate
Class D	SHV	Antibiotic	Sulbactum
	GES		Tazobactum
	KPC		Penem1

Reset Search | Show Results

BLAD ß-Lactmase Database

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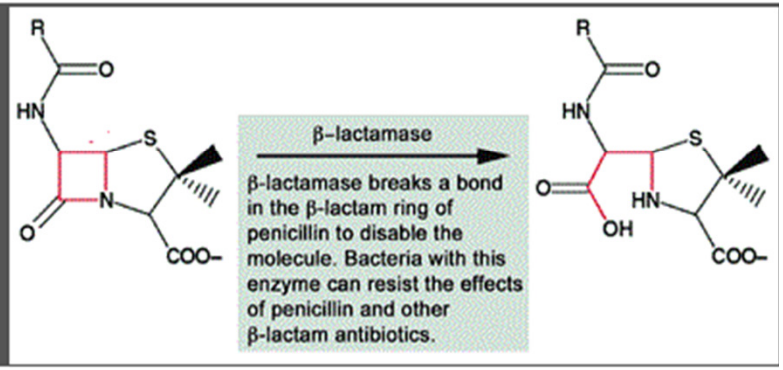
Welcome to ß-Lactmase

Beta-lactamases are enzymes produced by some bacteria and are responsible for their resistance to beta-lactam antibiotics like penicillins, cephamycins, and carbapenems (ertapenem) (Cephalosporins are relatively resistant to beta-lactamase). These antibiotics have a common element in their molecular structure: a four-atom ring known as a beta-lactam. The lactamase enzyme breaks that ring open, deactivating the molecule's antibacterial properties.



Protein or nucleotide sequences can be retrieved from the database using GenBank accession numbers or search terms Sequences can be downloaded, and it is possible to analyze them using the multiple sequence alignment or tree building tool integrated to the database.

Class : **A**, SubType:**SHV**, Resistance:**Inhibitor** ,Name: **Clavulanate**

Modify Search

Total 3 Sequences Found

Showing 0 - 20 out of 3

Class	SubType	Variant	Mutation	Resistance Type	Name	Description	Reference
A	SHV	49	Met69Ile	Inhibitor	Clavulanate	View	article
A	SHV	48	NA	Inhibitor	Clavulanate	View	article
A	SHV	72	Lys234Arg	Inhibitor	Clavulanate	View	article

BLAD ß-Lactamase Database

A comprehensive database of widely circulated ß-Lactamase

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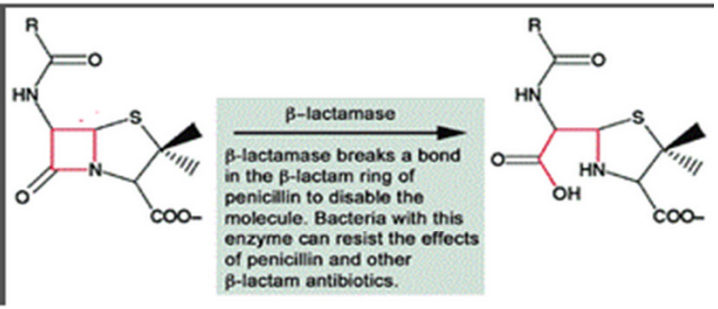
Welcome to ß-Lactamase

Beta-lactamases are enzymes produced by some bacteria and are responsible for their resistance to beta-lactam antibiotics like penicillins, cephamycins, and carbapenems (ertapenem) (Cephalosporins are relatively resistant to beta-lactamase). These antibiotics have a common element in their molecular structure: a four-atom ring known as a beta-lactam. The lactamase enzyme breaks that ring open, deactivating the molecule's antibacterial properties.



Mutation Lys234Arg

Substitution at position 234(Lys to Arg) stabilized the conformation of the serine residue at 130 position. The O atom of serine 130 acquire the distance of 3.5Å from the O atom of serine residues at 70, which prevents the cross-linking between Ser130 and Ser70, thus decreases the susceptibility to clavulanic acid

Important Links

http://hwmaint.jbc.org/cgi/content/abstract/280/42/35528

FUTURE PROSPECTS

- This is the is the first time one have developed such a comprehensive database, especially for all the widely circulated β-lactamases which catalog, categorize, the resistance pattern about all the four different classes of β-lactamases identified by experimental studies.

- These informations were scattered and we have tried to bring them on a common platform.

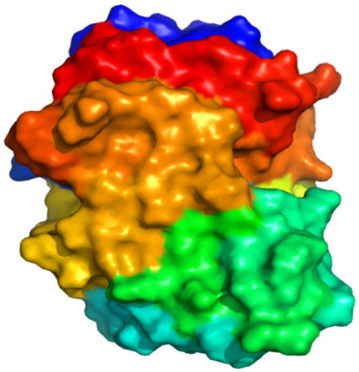
- This database also provides information about the available three dimensional structures along with the physio-chemical properties of ligand bound within each structure.

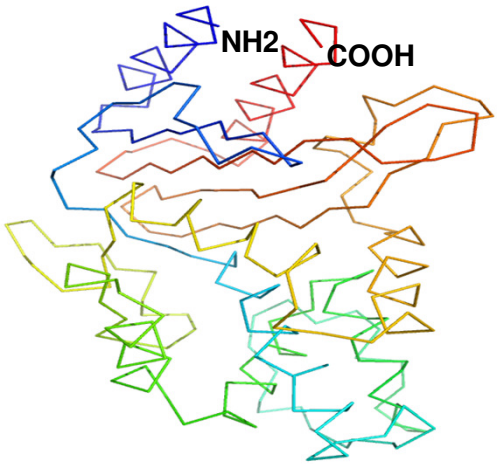
- BLAD is equipped with highly flexible search features which includes a user-friendly browse interface and hypertext link-outs to nucleotide and protein sequence databases.

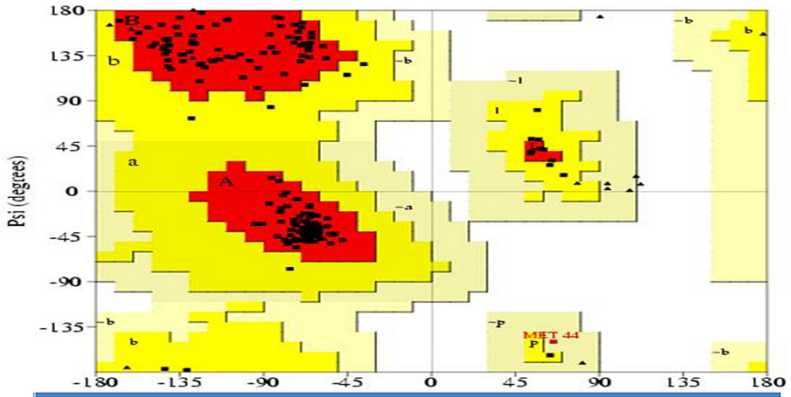
- We believe that this database will provide a very useful platform for future experimental and computational analyses of β-lactamases.

Homology Modelling Process

- Template recognition
- Alignment
- Determining structurally conserved regions
- Backbone generation
- Building loops or variable regions
- Conformational search for side chains
- Refinement of structure
- Validating structures







Plot Statistics	
Residues	**Percentage (%)**
Most favoured regions [A,B,L]	93.1%
Additional allowed regions [a,b,l,p]	6.5%
Generously allowed regions [-a,-b-l-p]	0.4%
Disallowed regions	0.0%
Total	100%

```
SHV-1       SPQPLEQIKLSESQLSGRVGMIEMDLASGRTLTAWRADERFPMMSTFKVVLCGAVLARVDAGDEQLERKI
SHV-S130G   SPQPLEQIKLSESQLSGRVGMIEMDLASGRTLTAWRADERFPMMSTFKVVLCGAVLARVDAGDEQLERKI
SHV-72      SPQPLEQIKLSESQLSGRVGMIEMDLASGRTLTAWRADERFPMMSTFKVVLCGAVLARVDAGDEQLERKI

SHV-1       HYRQQDLVDYSPVSEKHLADGMTVGELCAAAITMSDNSAANLLLATVGGPAGLTAFLRQIGDNVTRLDRW
SHV-S130G   HYRQQDLVDYSPVSEKHLADGMTVGELCAAAITMGDNSAANLLLATVGGPAGLTAFLRQIGDNVTRLDRW
SHV-72      HYRQQDLVDYSPVSEKHLADGMTVGELCAAAITMSDNSAANLLLATVGGPVGLTAFLRQIGDNVTRLDRW

SHV-1       ETELNEALPGDARDTTTPASMAATLRKLLTSQRLSARSQRQLLQWMVDDRVAGPLIRSVLPAGWFIADKT
SHV-S130G   ETELNEALPGDARDTTTPASMAATLRKLLTSQRLSARSQRQLLQWMVDDRVAGPLIRSVLPAGWFIADKT
SHV-72      ETELNEALPGDARDTTTPASMAATLRKLLTSQRLSARSQRQLLQWMVDDRVAGPLIRSVLPAGWFIADRT

SHV-1       GAGERGARGIVALLGPNNKAERIVVIYLRDTPASMAERNQQIAGIGAALIEHWQR
SHV-S130G   GAGERGARGIVALLGPNNKAERIVVIYLRDTPASMAERNQQIAGIGAALIEHWQR
SHV-72      GAGERGARGIVALLGPNNKAERIVVIYLRDTPASMAERNQQIAGIGAALIEHWQR
```

Modelled structure of SHV-72 along with its Ramachandran plot and sequence alignment with its wild type.

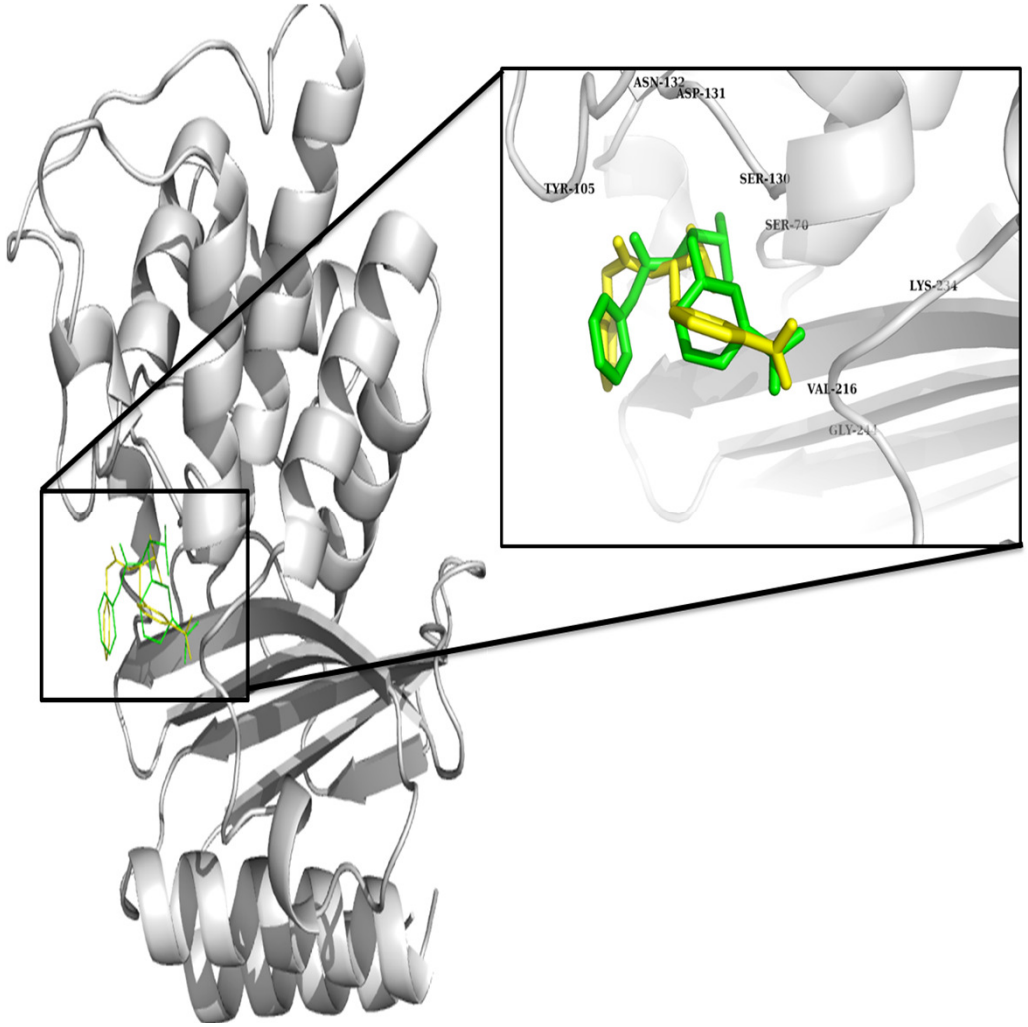
VALIDATION OF THE DOCKING PROTOCOL

• Docking methods are typically validated by ‘redocking’ experiments,where a known crystal complex is separated and then redocked, ensuring that the docking algorithm can reproduce the observed binding mode.

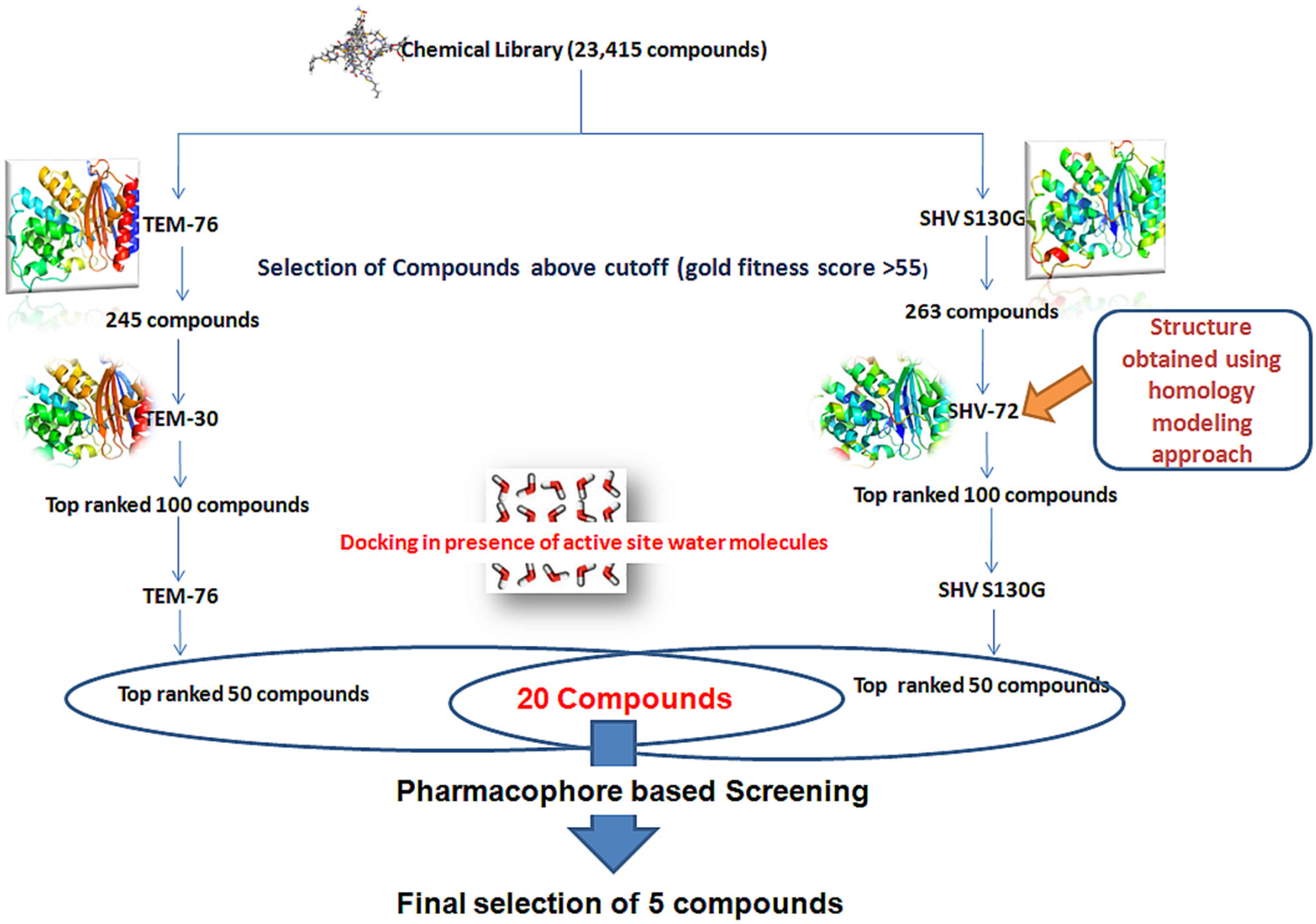
• The structure of TEM-1 β-lactamase in complex with a designed boronic acid inhibitor (1R)-2-phenylacetamido-2-(3-carboxyphenyl) ethyl boronic acid (pdb id: 1ERO) was selected.

• Protein and ligands were separated, hydrogen atoms were added and minimized using the CHarMm force field.

• Finally the ligand was docked back into the active site of TEM-1 using GOLD.



Binding orientation of the original (green) and redocked (yellow) conformation of the ligand.


Chemical Library (23,415 compounds)
TEM-76
SHV S130G
Selection of Compounds above cutoff (gold fitness score >55)
245 compounds
263 compounds
Structure obtained using homology modeling approach
TEM-30
SHV-72
Top ranked 100 compounds
Top ranked 100 compounds
Docking in presence of active site water molecules
TEM-76
SHV S130G
Top ranked 50 compounds
20 Compounds
Top ranked 50 compounds
Pharmacophore based Screening
Final selection of 5 compounds

Mutants Selected: SHV S130G, SHV-72, TEM-30 and TEM-76

Library Design

4.5 millions compounds from zinc database were scanned on the properties of the known β-lactamase inhibitors (Xlogp, MW, Rotatable bonds, HBD, HBA) to screen out the compounds . A total of 23,415 compounds were screened out for further analysis of their efficacies against the resistant mutants.

Docking-based virtual screening

- GOLD (Genetic Optimization for Ligand Docking)
- AUTODOCK
- X-SCORE

Compounds	Pubchem id	Fit Value
LN-1255	25147490	2.94547
Tazobactam	123630	1.99978
Penam-1	21941339	1.99911
Penam-2	21941375	1.96089
Clavulanic acid	5280980	1.55216
Sulbactam	130313	1

The fit values of the external test set of known β-lactamase inhibitors

Compounds	Fit value
ZINC00959167	3.96904
ZINC01234548	3.93984
ZINC01301026	3.93677
ZINC14671560	3.93437
ZINC02775438	3.82992
ZINC03830398	3.67902
ZINC06143162	3.65642
ZINC01738195	3.63313
ZINC00627649	3.28382
ZINC09212678	2.99403

The fit values of the test set of compounds on Hypo-1.

Compounds	Gold Fitness Score			
	SHV S130G	SHV-72	TEM-76	TEM-30
ZINC00959167	62.56	63.23	60.89	61.44
ZINC14671560	60.20	60.03	60.25	62.02
ZINC02775438	61.95	61.25	64.05	63.46
ZINC01301026	60.28	63.16	61.16	67.99
ZINC01234548	63.15	62.79	60.93	64.24

Goldfitness score of the selected inhibitors against all the selected mutants

Compounds	ΔG(Kcal/mol) (autodock)	X-score	ΔG(Kcal/mol) (autodock)	X-score
	SHV S130G		SHV-72	
ZINC00959167	-8.14	-8.23	-6.93	-7.20
ZINC14671560	-7.59	-7.14	-7.02	-6.98
ZINC02775438	-7.54	-7.85	-7.38	-7.94
ZINC01301026	-7.67	-7.93	-8.54	-8.44
ZINC01234548	-8.53	-8.24	-6.95	-7.36

Binding affinity obtained by autodock and x-score of the selected inhibitors against SHV S130G and SHV-72.

Compounds	ΔG(Kcal/mol) (autodock)	X-score	ΔG(Kcal/mol) (autodock)	X-score
	TEM-76		TEM-30	
ZINC00959167	-6.84	-6.96	-7.56	-7.20
ZINC14671560	-6.98	-7.44	-7.73	-7.18
ZINC02775438	-7.86	-7.94	-7.46	-6.94
ZINC01301026	-7.24	-6.98	-8.42	-8.23
ZINC01234548	-6.48	-7.02	-7.94	-6.97

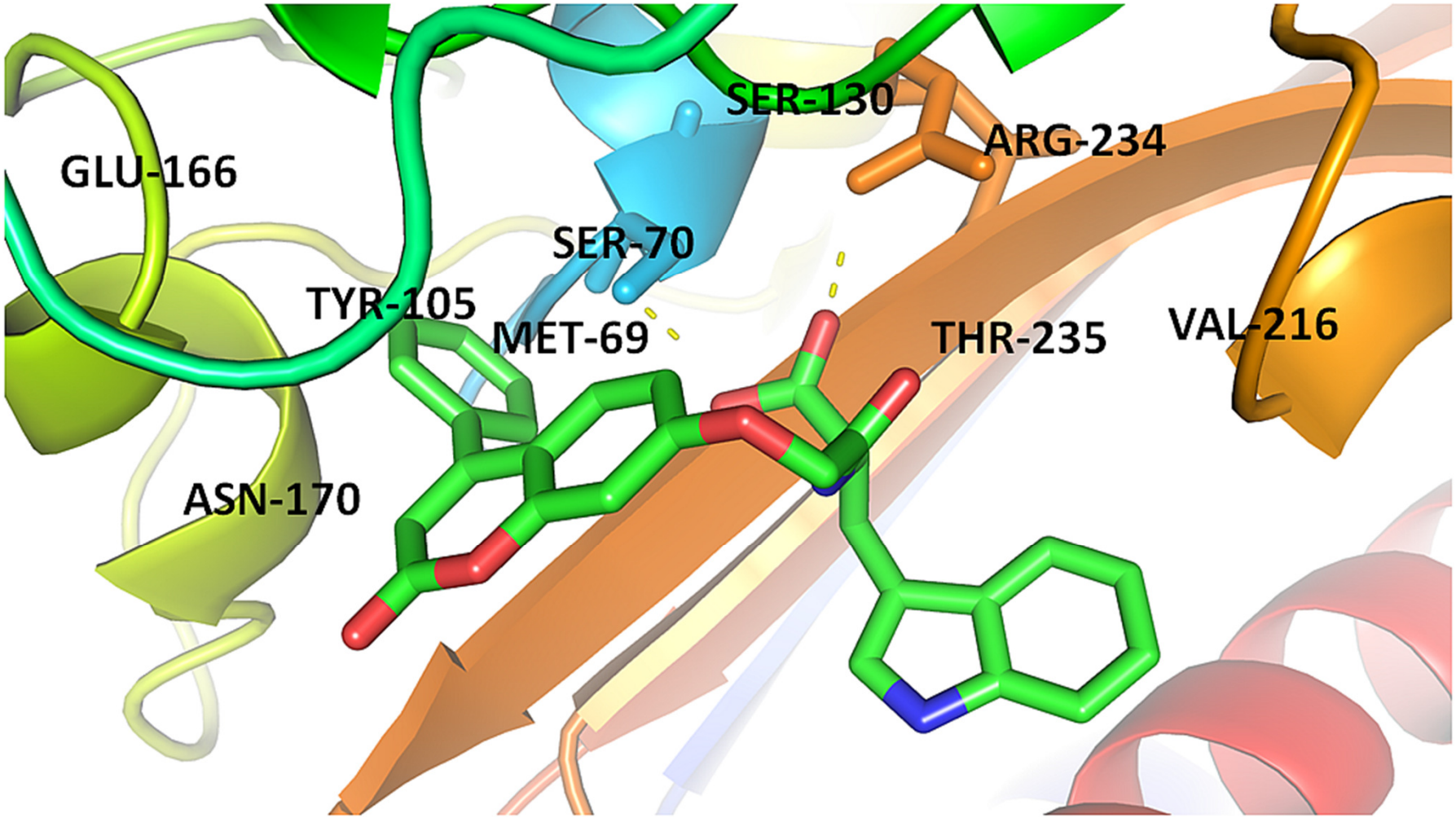
Binding affinity obtained by autodock and x-score of the selected inhibitors against TEM-76 and TEM-30.

Compounds	Residues involved	
	Hydrogen bond	**Hydrophobic interactions**
ZINC00959167	K73, K234, T235	S70, Y105, G130, T167, N170, E171, G238, E240
ZINC14671560	N132	Y105, T167, E168, N170, E171, V216, A237, G238, E240, R244, M272
ZINC02775438	N132, N170	S70, Y105, G130, T167, E168, E171, V216, T235
ZINC01301026	N132	S70, T167, E168, N170, E171, V216, T235, G236, A237, G238, E240, R244, M272
ZINC01234548	N132, K234, T235	S70, G130, N132, T167, N170, T235, A237, G238

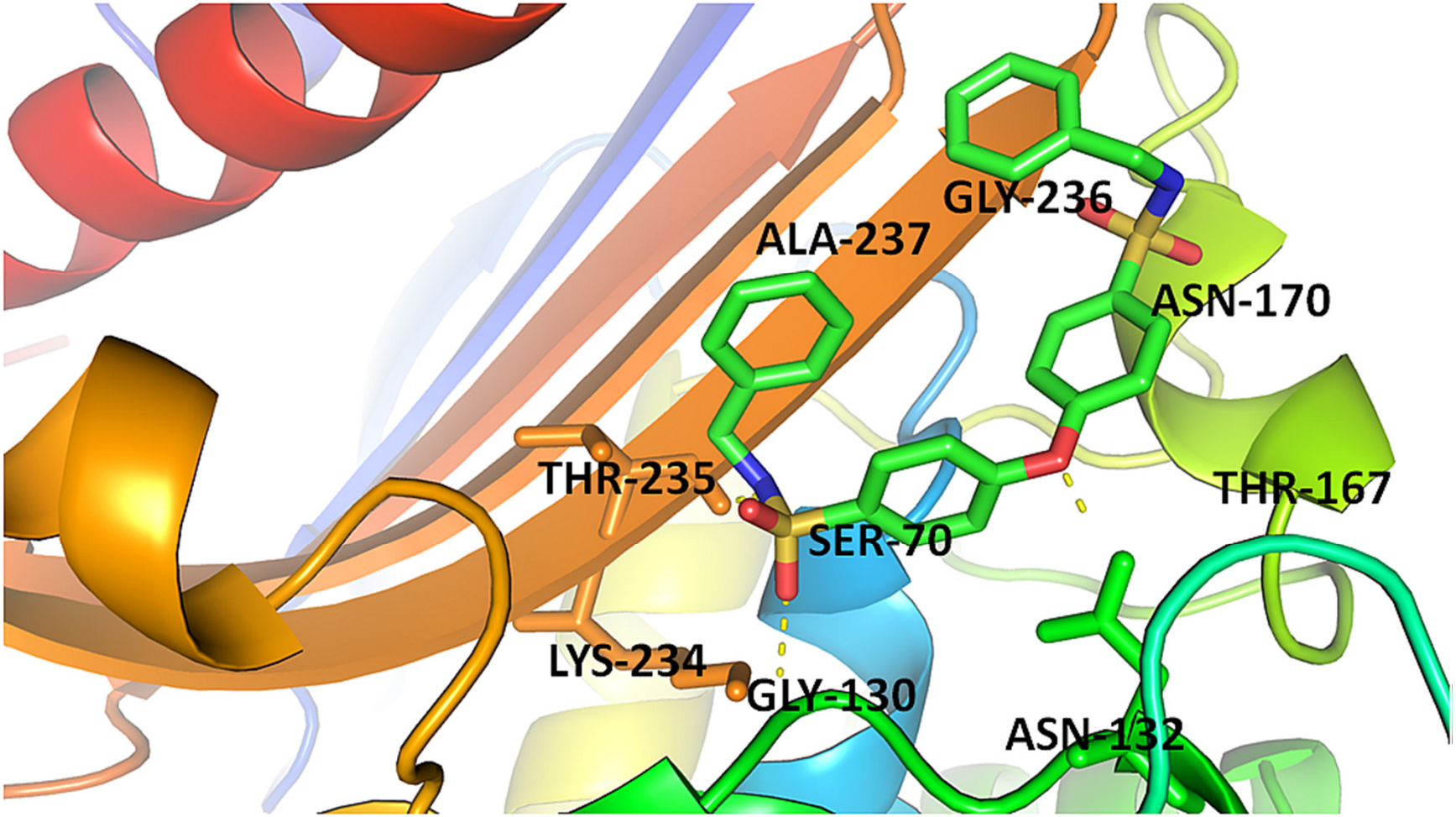
Detail description of the amino acid residues involved in interaction of the selected inhibitors against SHV S130G

Compounds	Residues involved	
	Hydrogen bond	**Hydrophobic interactions**
ZINC00959167	N170, A237	S70, Y105, G130, N170, V216, P219, A237, G238, M272
ZINC14671560	No Hydrogen bond	S70, Y105, G130, N132, P167, N170, V216, P219, G238, R244, M272
ZINC02775438	K73, G238	S70, Y105, G130, N132, E166, N170, V216, A237, G238, R244
ZINC01301026	Y105	S70, Y105, S106, P107, G130, V216, K234, A237
ZINC01234548	S70, N132, N170, A237	S70, E104, G130, P167, N170, V216, G236, R244, M272

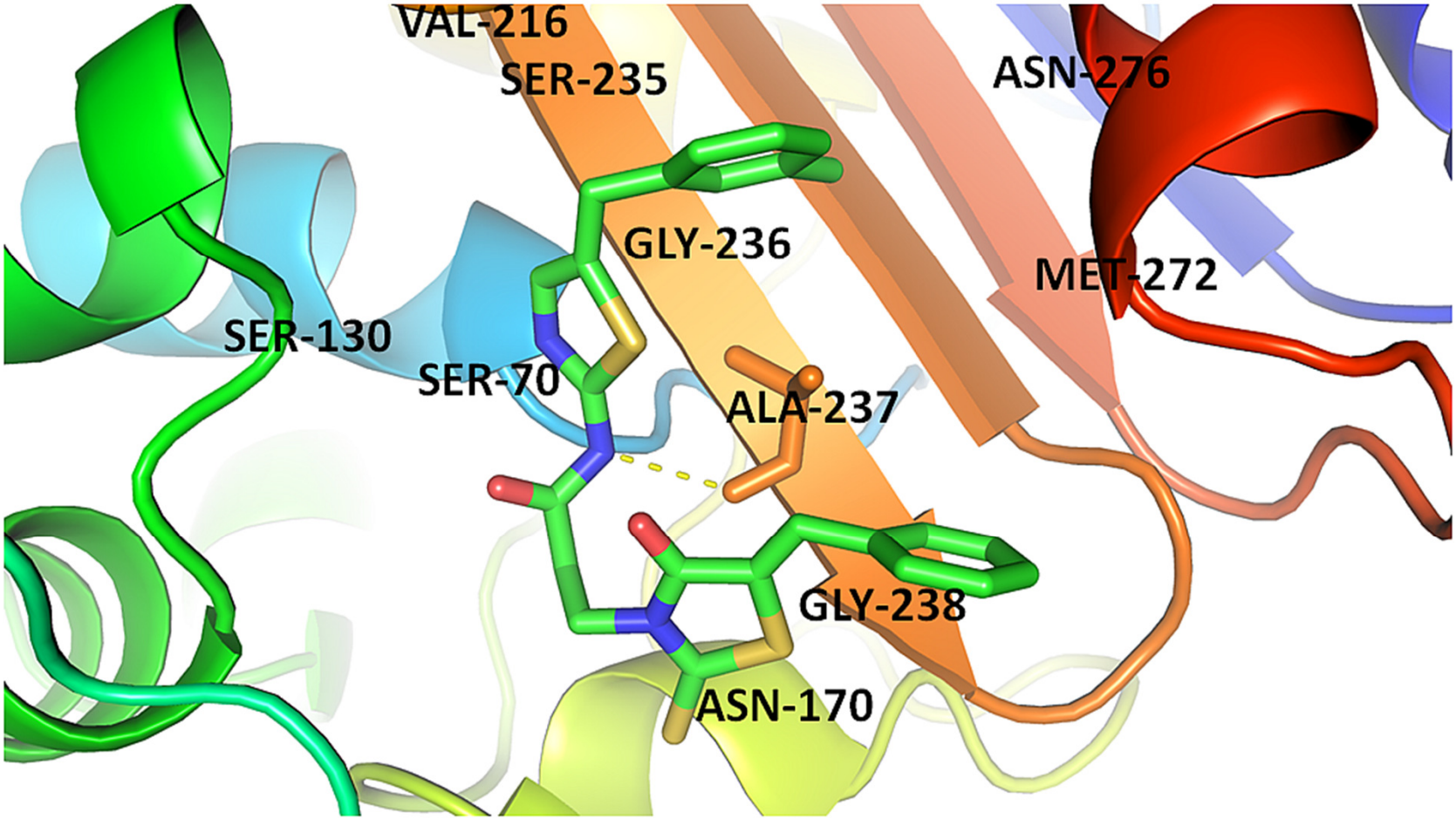
Detail description of the amino acid residues involved in interaction of the selected inhibitors against TEM-76



The binding mode of compound ZINC00959167 within the active site of SHV-72



The binding mode of compound ZINC01234548 within the active site of SHV-S130G



The binding mode of compound ZINC01301026 within the active site of TEM-30

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