A Novel Drug Design Approach: Quantitative Structure-Interaction Activity Relationship (QSIAR) in Anti-Tubercular Agents

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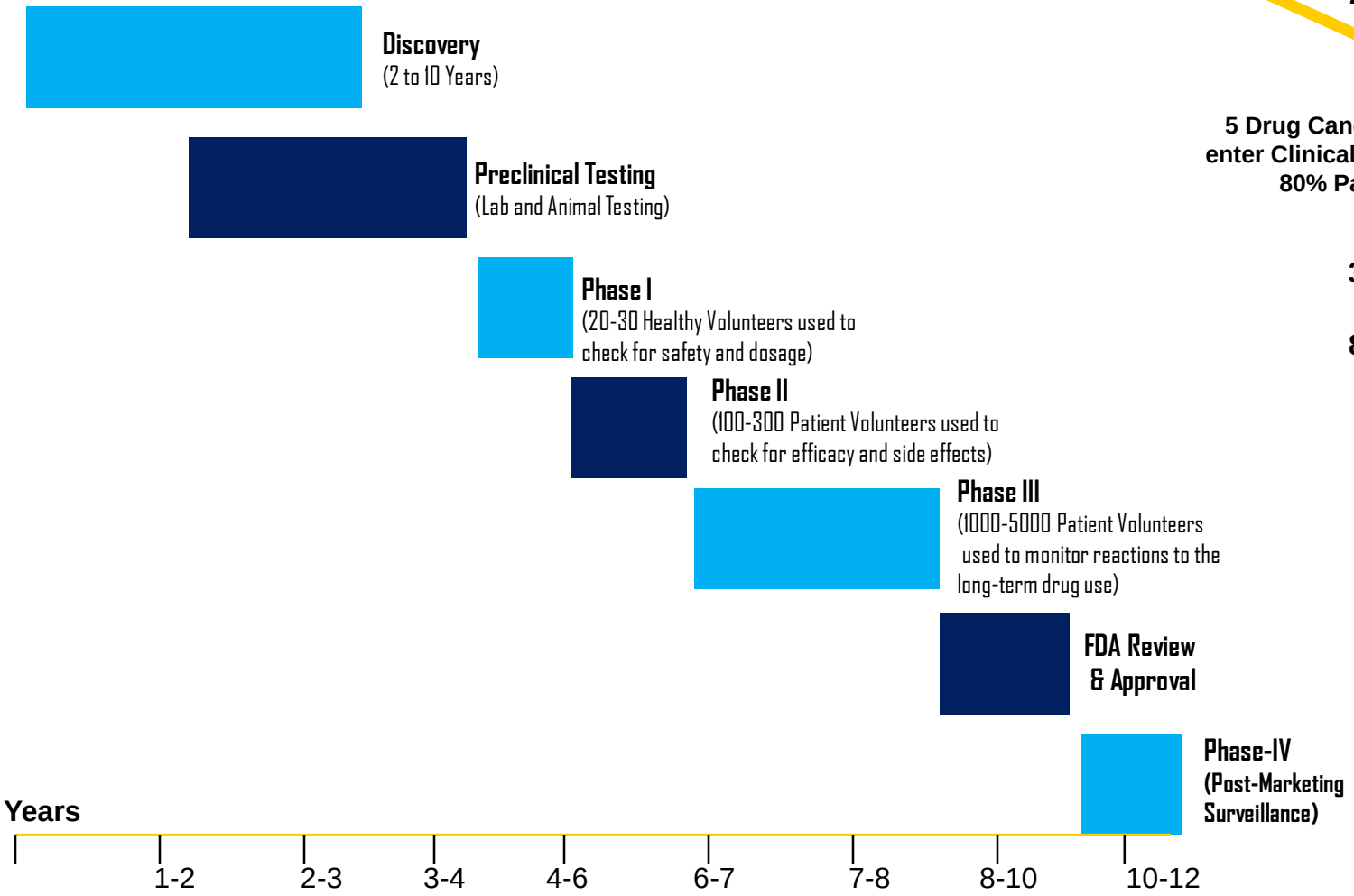
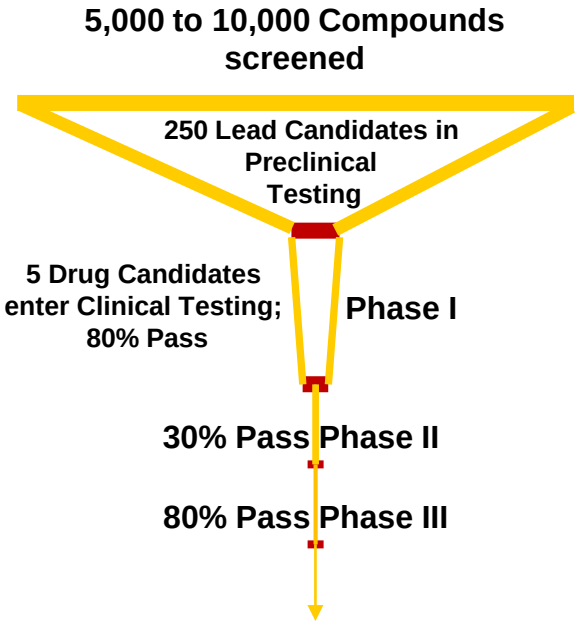
Overview of the Drug Discovery and Development Process





DRUG DISCOVERY & DEVELOPMENT

Pre-genomics (Time 6-7 years, US$ ~200 M)

1.Lead Generation

Plant Origin

Random Screening / HTS

Biochemical Origin

Combinatorial Chemistry

2. Lead Optimization

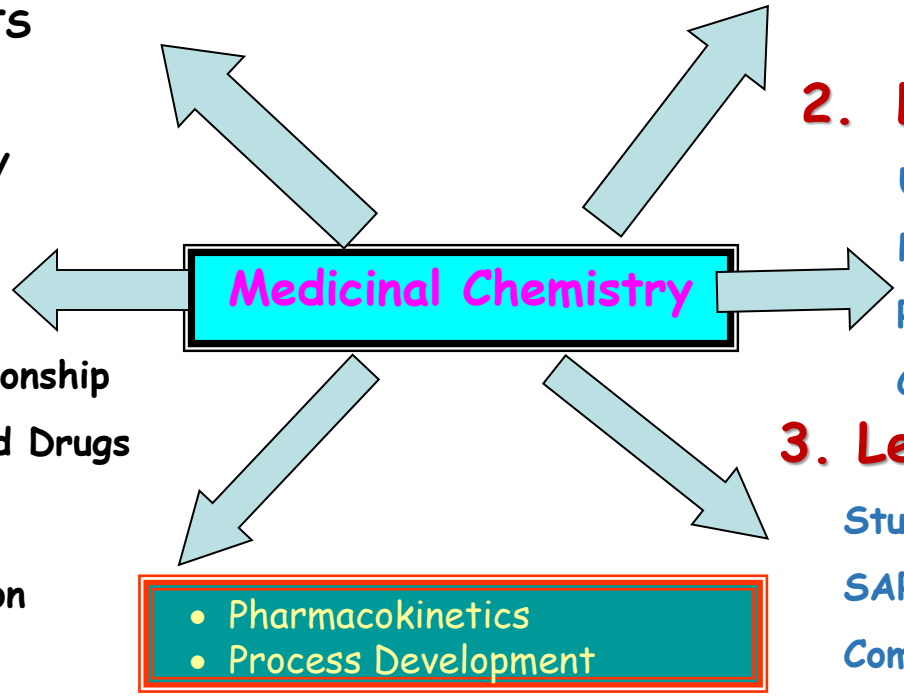
Study of analogs

Structure-Activity Relationship

Comparison with Standard Drugs

3. Molecular Targets

identification and validation
(Chemo-genomics)



Post-genomics (Time 4-5 years, US$ ~800 M)

1. Molecular Targets

identification and validation
(Chemo-genomics)

2. Lead Generation

Under standing disease process

Plant Origin

Random Screening / Virtual screening

Combinatorial Chemistry/HTS/ CADD

3. Lead Optimization

Study of analogs

SAR, QSAR and CADD

Comparison with Standard Drugs

DEVELOPMENT PHASE

(Time 10-12 years, US$ ~ 800M)

(Time 8-9 years, US$ ~1800 M)

Candidate Drug for development
Toxicity Studies
Phase I Clinical Trials
Phase II Clinical Trials
Phase III Clinical Trials
Approval for Marketing

https://www.biostock.se/en/2023/01/drug-development-the-four-phases

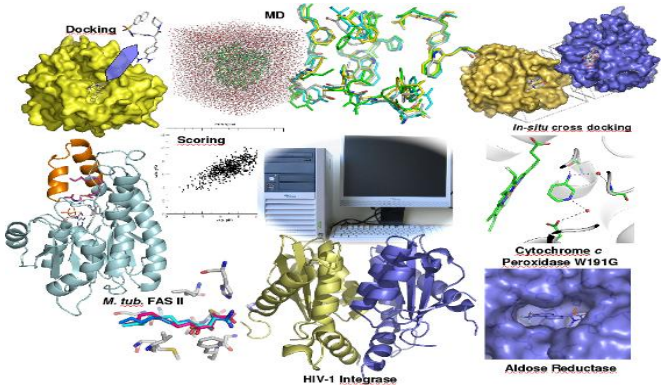
Computer-aided drug design (CADD)

CADD

Direct design

Used where target structure is known (structure-based design)

X-ray, NMR, Homology based 3D structures are used to design novel molecules

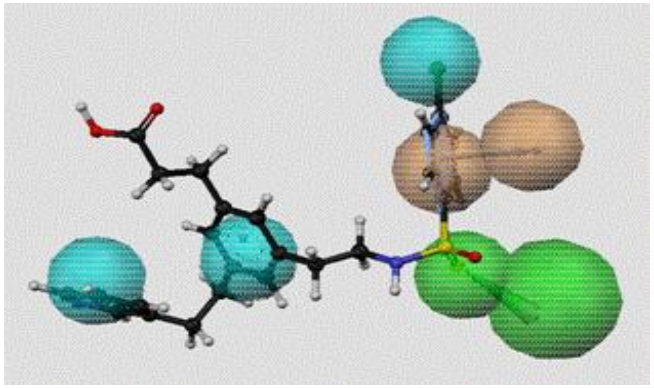


Indirect design

Used in cases where target structure is not known

Structure activity relationship studies

2D/3D QSARs



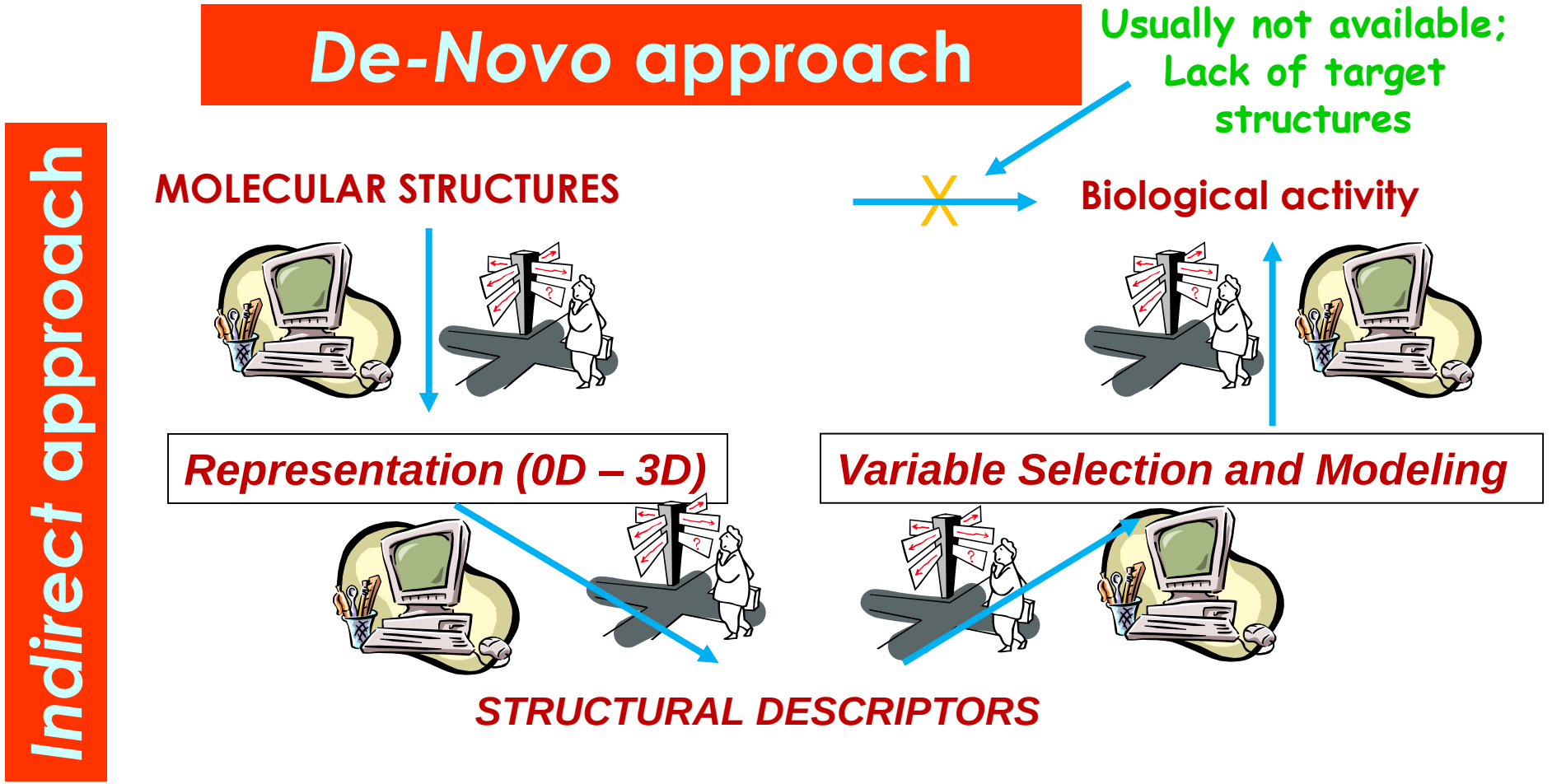
A comparison of structure based and ligand-based methods for virtual screening

	Direct design	Indirect design
Requirement	Requires availability of 3D structures of ligand macromolecule complex or target macromolecule (Today less than 10% of drug targets are crystallized, some important targets like membrane proteins and others are still to be crystallized).	Requires ligand structures only.
Implementation/ Complexity	Highly complex and very high computational cost	Less complex and low computational cost. Implementation is relatively simple.
Information	Abstract	Minimum and simple
Predictivity	Requires multiple scoring functions, less predictive	Highly predictive (within the SSS)
Concerns	Pose versus score correlation	Variable selection, consistency with the active site
Reliability	De Novo, more reliable when screening against diverse molecules	As good as the training set, limitations to the diversity of the database to be used.

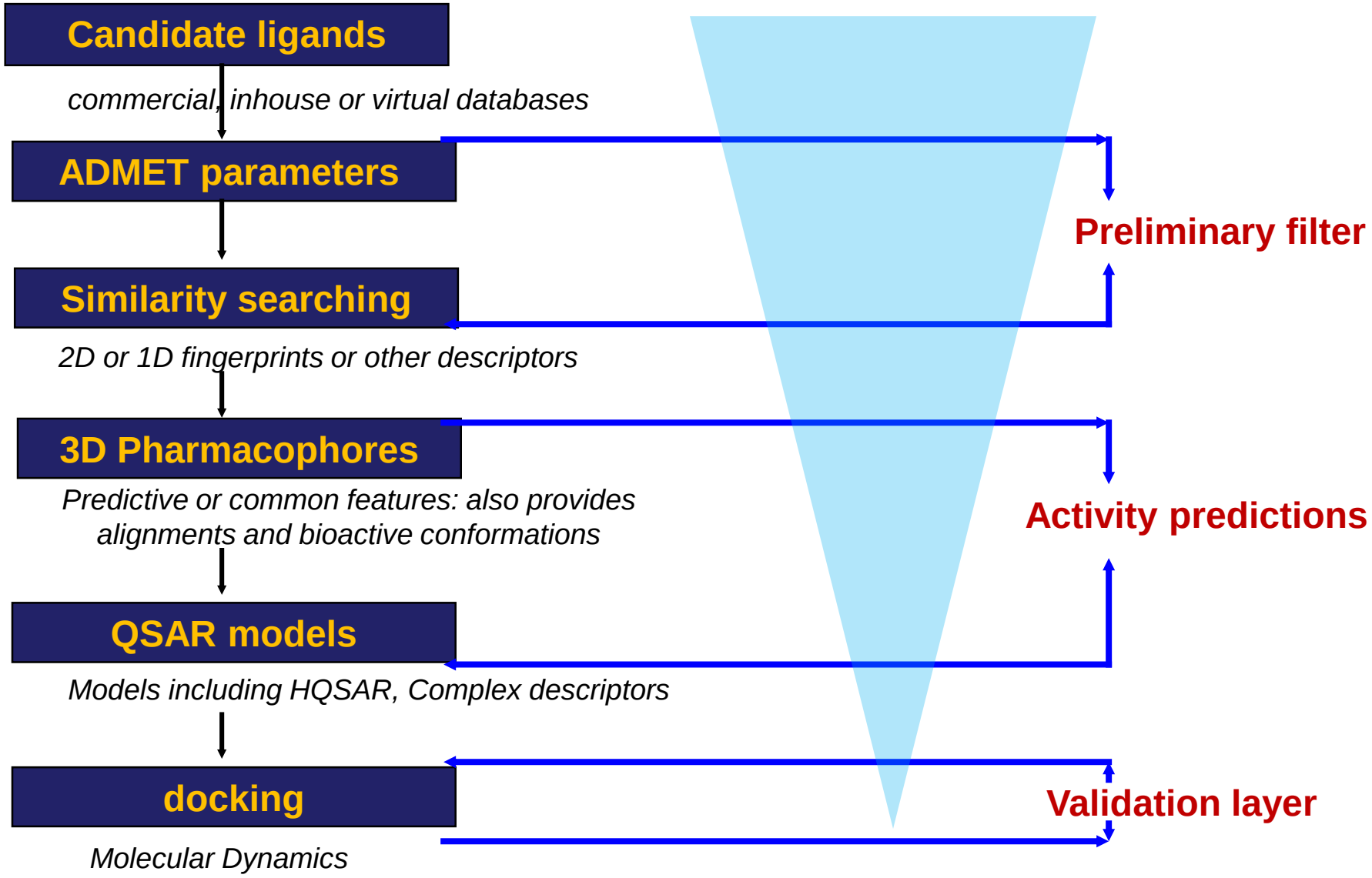
Virtual screening: Ligand-based approaches

Structure-function relationship

Basic Assumption: Molecular structure determines its property



Virtual screening (VS) paradigm
A multi-layer hybrid prediction protocol



Structure-Based Drug Design (SBDD)

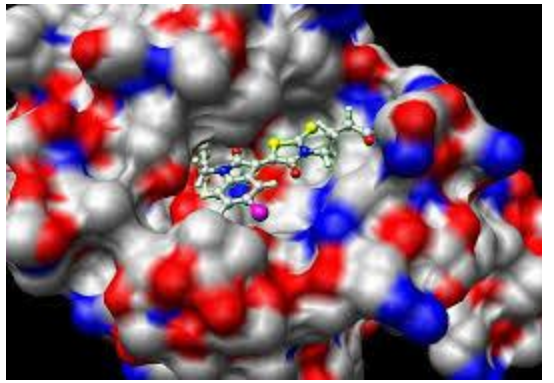
Structure-Based Drug Design (SBDD) uses the 3D structure of biological targets (usually proteins) to design molecules that bind specifically and modulate their activity.

Key Steps

1. **Target Identification & Structure Determination** – Obtain 3D structure using X-ray crystallography, NMR, or Cryo-EM.
2. **Binding Site Analysis** – Identify active or allosteric sites for ligand binding.
3. **Ligand Design / Docking** – Use computer-aided modeling to design or screen ligands that fit the target site.
4. **Scoring & Optimization** – Evaluate binding affinity and optimize structure for potency, and selectivity.

Advantages:

- Rational, faster, and cost-effective drug discovery
- Reduces experimental trial-and-error



Limitation of Structure based approaches in development of predictive models for virtual screening

- The major drawback of docking approach in the Structure-based drug design is **poor correlation of biological activity with docking scores** and hence non-availability of reliable predictive models for virtual screening.

- It may be due to the major limitation of docking scores to accurately predict binding energies interactions due to factors such as the algorithm’s inability to predict interactions like entropy change and solvation effect and sometimes ignorance of useful interactions.

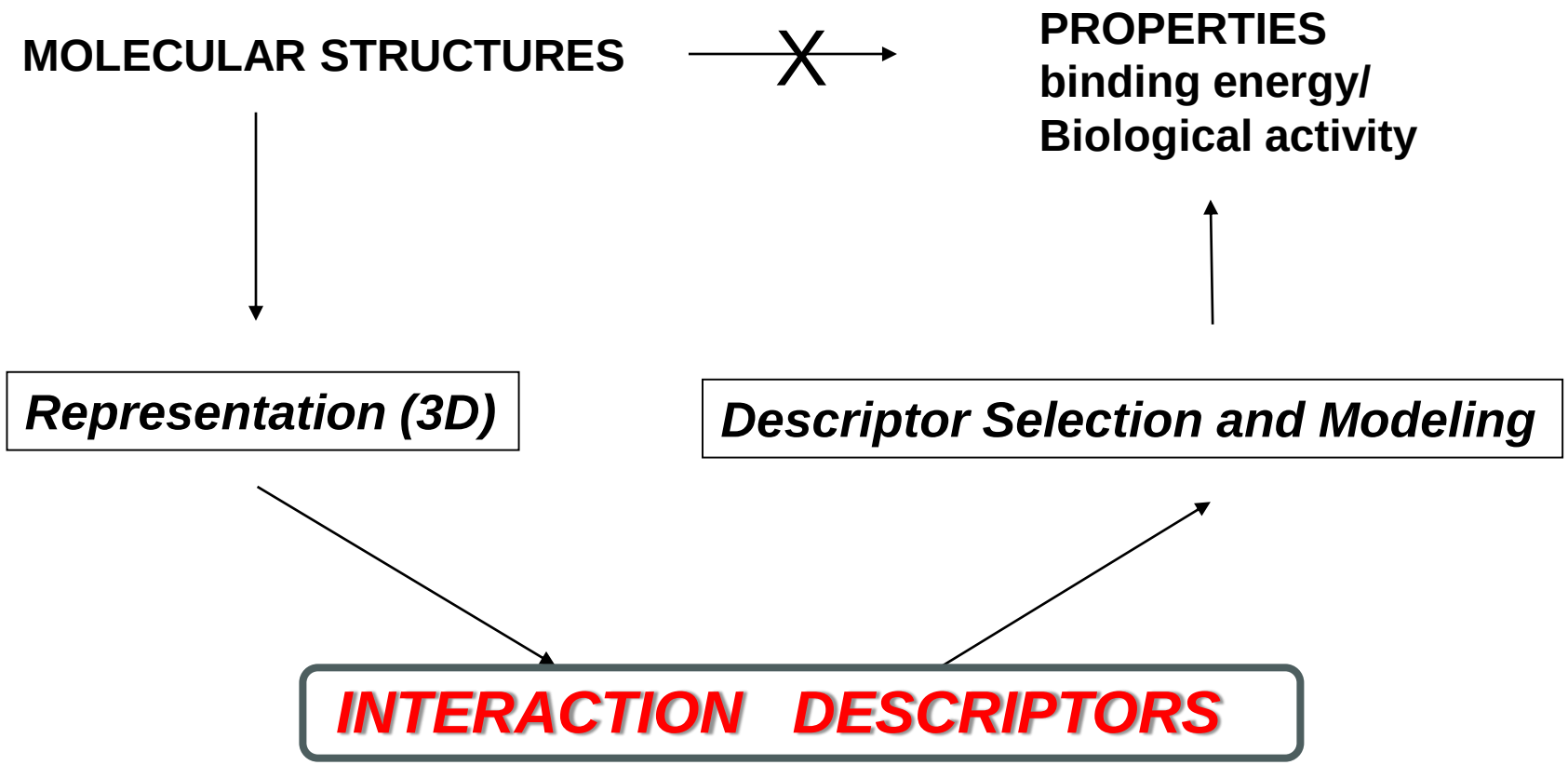
- Complication due to the presence of water molecules in the binding pocket.

- The scoring function limitations incorporated in different docking programs.

Quantitative Structure Interaction Activity Relationship (QSIAR): a novel approach to drug design

Basic Assumption: Interactions of the molecule at the binding site determines its binding energy which is related to biological activity

Integrated approach



Quantitative Structure Interaction Activity Relationship (QSIAR)
A novel approach to drug design

A novel approach where the interactions of the ligand molecule with the amino acid residues of the target protein are given weightage and are considered as independent parameters while the binding energy/affinity, docking scores/biological activity as dependent parameter was used in the development of the QSAR model.
This QSIAR model(s) are developed using MLR or other statistical/ analysis used in QSAR *which also provide the weightage to the interactions in describing the biological response*.

BA= Const.+ a1AR1+ a2AR2+.....anARn

BA = binding energy/affinity, docking scores/biological activity
AR= interaction with amino acid residue

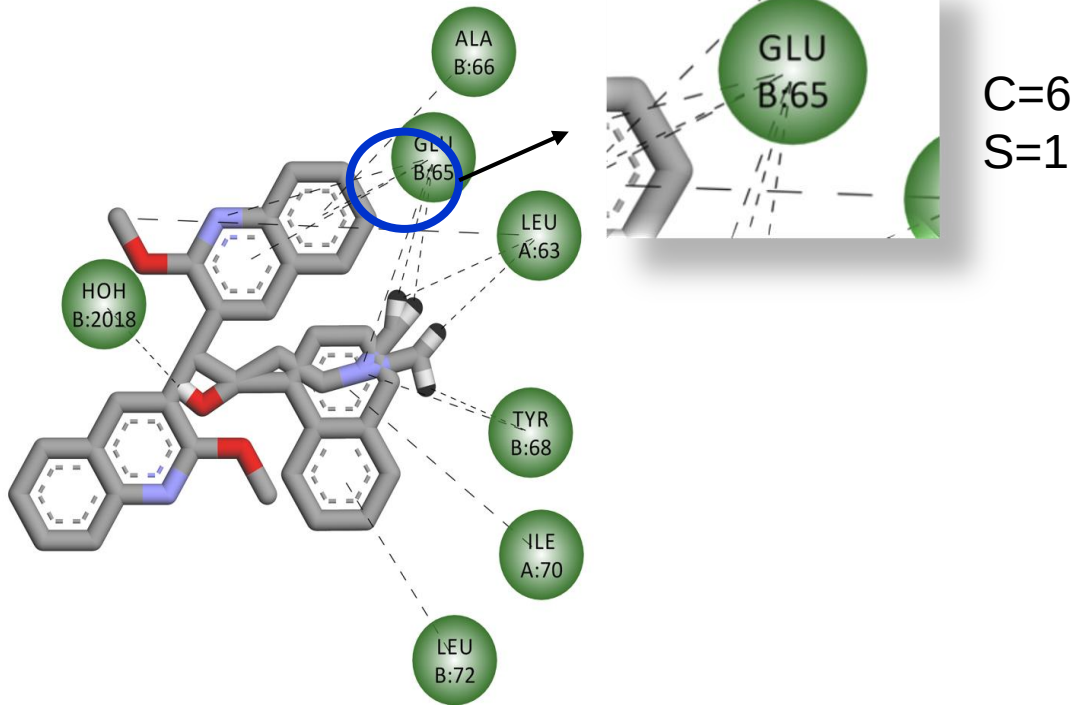
Saxena, A. K. (2024, March). In *GTHTM* (pp. 1-20). Cham: Springer Nature Switzerland.

Quantitative Structure Interaction Activity Relationship (QSIAR)

A novel approach to drug design

Comp. No.	Glu65b		HOHb		Tyr68b		Ala66b		Phe69b		Asp32b		Leu72b		Ile70b		Val61b		Gly62b		Phe57b		Phe58b		Phe74b		Leu63a		Ile70a		Ala66a		Phe74a		Ile59a		Gly62a		Glu65c		Phe69c		Leu72c	
	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C
1	1	3	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	1	1	1	2	0	0	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	1	2	0	0	0	0	1	1	1	2	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	1	1	0	0	0	0	1	2	0	0
3	1	4	1	1	0	0	1	1	0	0	0	0	0	0	0	0	1	2	1	1	0	0	1	1	0	0	1	2	0	0	1	1	0	0	1	1	1	1	0	0	0	0
4	1	4	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	1	1	0	0	1	1	0	0	0	0	0	0	0	0	1	1	0	0	0	0

Comp. No.	Glu65b		HOHb		Tyr68b	
	S	C	S	C	S	C
1	1	3	1	1	0	0
2	1	2	0	0	0	0
3	1	4	1	1	0	0
4	1	4	0	0	1	1



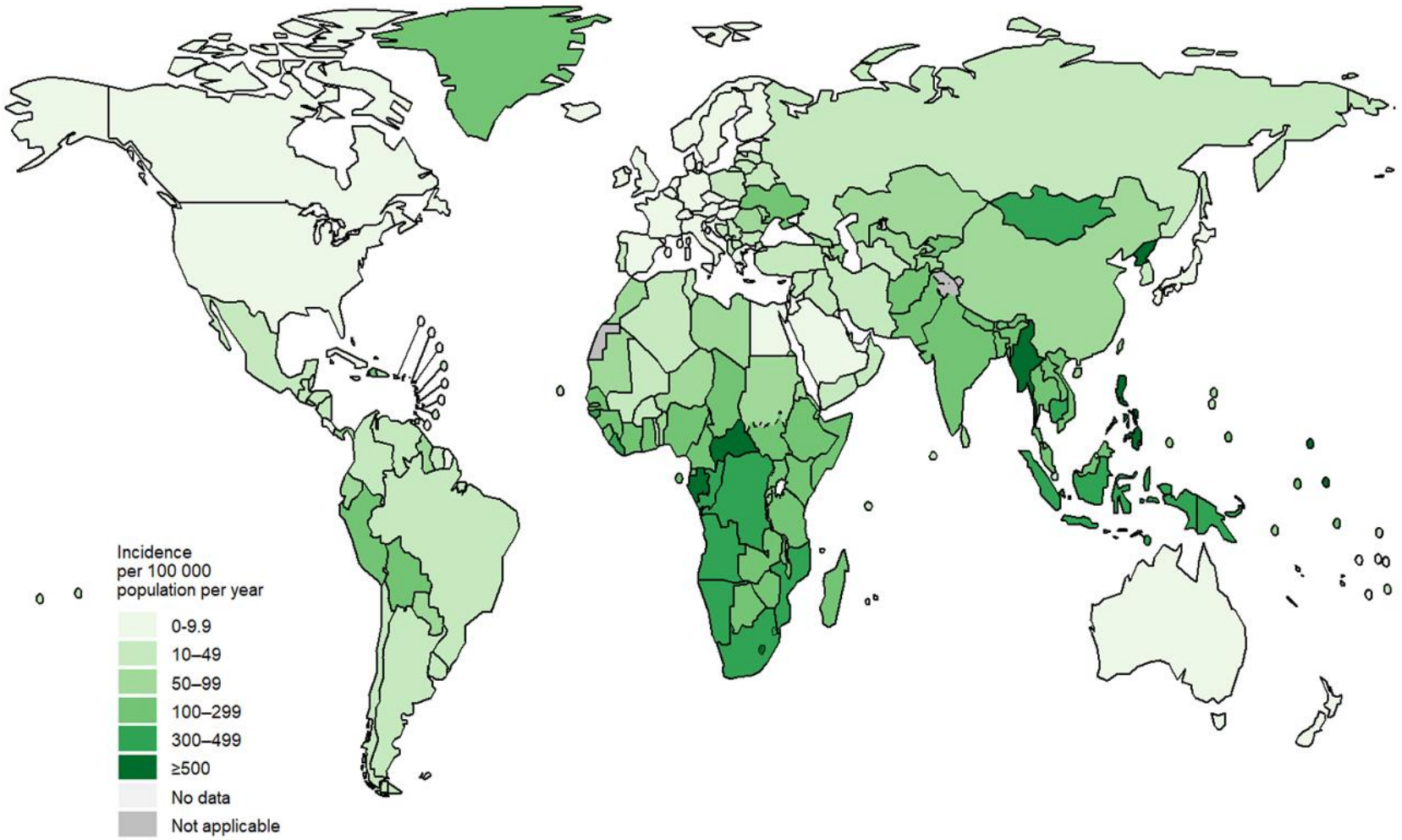
C=6
S=1

Emerging challenges in TB treatment

- *Mycobacterium tuberculosis* is the pathogen responsible for TB which uses diverse strategies to survive in a variety of host injury and to evade immune systems.
- A total of 1.25 million people died from TB in 2023 (including 161,000 people with HIV). Worldwide, TB is the second leading infectious killer after COVID-19 (above HIV and AIDS).
- In 2023, an estimated 10.8 million people fell ill with tuberculosis (TB) worldwide, which included 55% men, 33% women and 12% children. TB is present in almost all countries and age groups and is curable.

WHO Report 2024

Global estimated TB incidence



WHO global tuberculosis report 2024

Desired profile for a new TB drug

Desired profile	Characteristics
Treatment of MDR-TB and XDR-TB	▪ New chemical class with a new mechanism of action or cheaper and better drug than Bedaquiline
Reduction in duration of treatment	▪ Strongly bactericidal activity ▪ Good activity on latent or dormant populations ▪ More potent and safer regimens of a novel drug and its combinations
Lowering of dosing frequency	▪ Good pharmacokinetics including longer half-life and target tissue levels ▪ Novel fixed-dose formulations and delivery technologies
Reduction of pills burden	▪ Combinations of more efficacious drugs to reduce number of pills taken ▪ Child-friendly formulation of newer drugs
Drug–drug interactions	▪ No cytochrome P450 induction liabilities ▪ Minimal drug–drug interaction

Current drug and drug targets for TB treatment

FIRST LINE DRUGS

- **Isoniazid (INH)**
- **Rifampin (RIF)**
- **Pyrazinamide (PZA)**
- **Ethambutol (EMB)**

SECOND LINE DRUGS

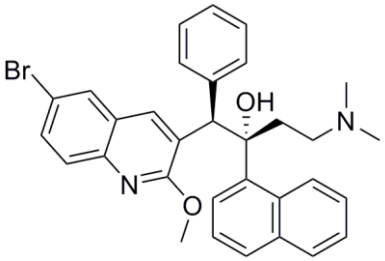
- **Para-amino salicylate**
- **Kanamycin**
- **Cycloserine**
- **Ethionamide**
- **Amikacin**
- **Capreomycin**
- **Thiacetazone**
- **Fluoroquinolones**
- **Rifabutin**
- **Bedaquiline**

Drugs	Targets
Isoniazid (INH)	Mycolic acid synthesis inhibition
Pyrazinamide (PZA)	Cell membrane Interference
Rifampin	RNA synthesis inhibition
Ethambutol (EMB)	Arabinogalactan biosynthesis inhibition
Streptomycin	RNA and protein synthesis inhibition
Kanamycin and Capreomycin	Inhibition of protein synthesis through modification of ribosomal structures at the 16S rRNA
Cycloserine	Peptidoglycan synthesis inhibition
Thiolactomycin	β-keto ACP synthase inhibitor
Cerulenin	Fatty acid synthase (FAS) inhibitor
Bedaquiline	***M.Tb ATP Synthase***
Delamanid	***inhibits mycolic acid synthesis***
Pretomanid	***inhibits cell wall biosynthesis***

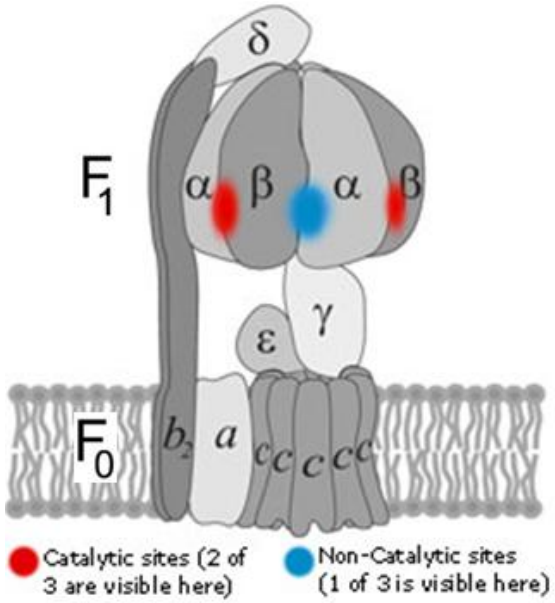
A.K. Saxena et.al, CURR TOP MED CHEM., 2019, 19, 1-19

Mycobacterium F_0F_1-ATPase

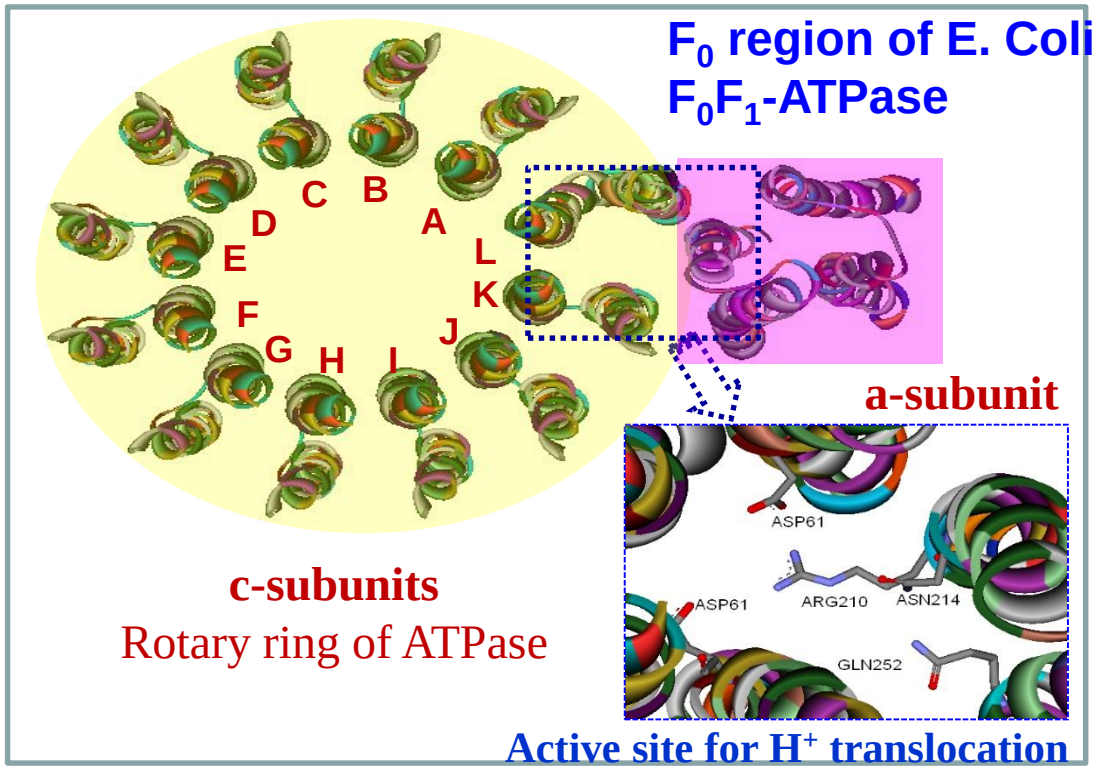
F-type ATPases have a lipophilic intramembrane portion (F_0) and a more polar ATP-binding region (F_1) that extends into the cytoplasm. For the functioning of the enzyme, the **a-** and **c-subunits** move relative to each other on a contact area that spans the membrane



Bedaquiline

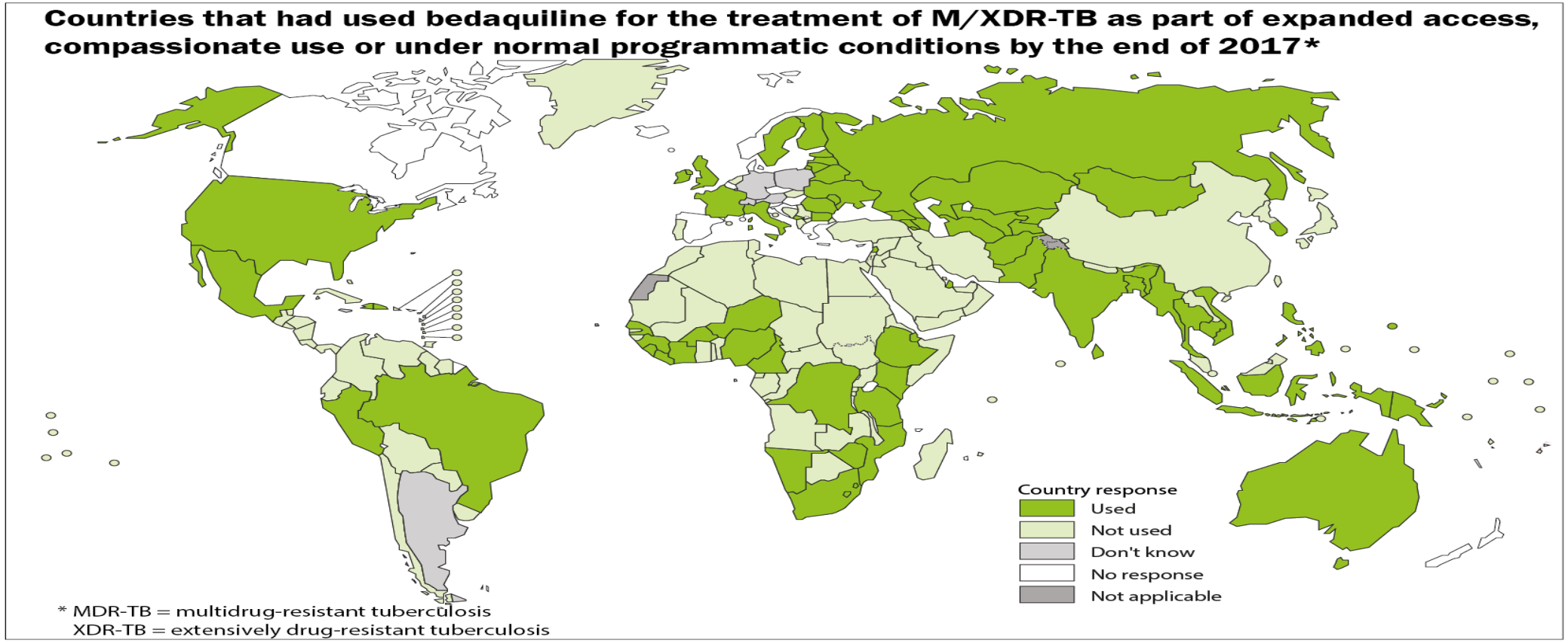


Cartoon depiction of F_0F_1-ATPase



Nature 1999, 402, 263–268

Bedaquiline: Clinical use worldwide



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: *Global Tuberculosis Report 2018*. WHO, 2018.

World Health Organization

However, some reports of resistance threaten its effectiveness in MDR-TB control programs worldwide.

The Lancet Microbe, 2023, Volume 4, Issue 12, e964 - e965
The Lancet Microbe, 2023, Volume 4, Issue 5, e358 – e368

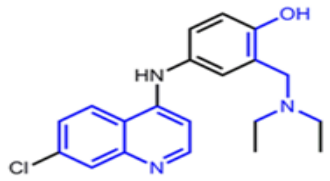
Novel potent orally bio available and selective Mtb ATP synthase inhibitors

AsinexDB

Database searching

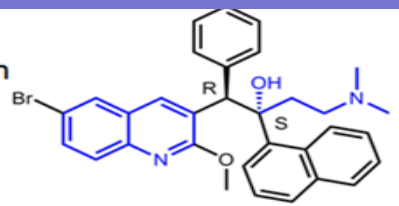
Queries

(1) Quinoline substructure
(2) Tertiary nitrogen
(3) Hydroxy function



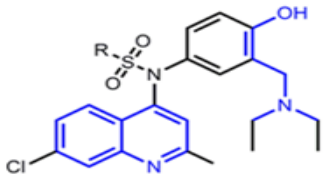
Hit
(BAS 00327385)

Comparison

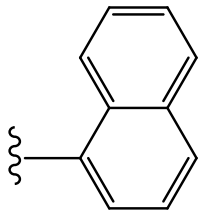


Bedaquiline
(TMC207)

Structure-based Design

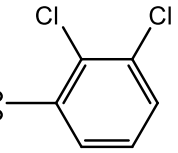


Novel Series of Compounds
(1-14)

12, R= 

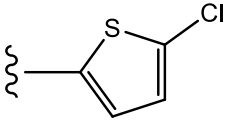
IC50= 1.00 ± 0.031

MIC=12.5

4, R= 

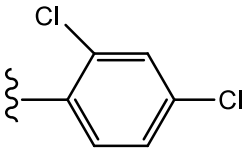
IC50=0.51 ± 0.030

MIC=3.12

16, R= 

IC50=0.36 ± 0.303

MIC=6.25

5, R= 

IC50=0.51 ± 0.030

MIC=3.12

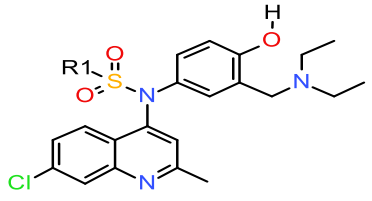
A. K. Saxena et. al, patent WO2013102936,September 12, 2013.,
A.K. Saxena et.al, BMC,2015,742-752

A case study on mycobacterium ATP synthase inhibitors as anti-tubercular agents

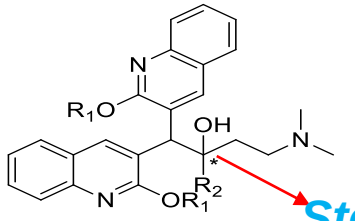
Quantitative structure-activity relationship (QSAR) studies were conducted to analyze physicochemical factors influencing antitubercular activity against mycobacterium ATPase comprising of **4-substituted amino sulphonyl-2-methyl-7-chloroquinolines and bis-quinoline core** (Table 1).

Saxena, Anil K.; Alam, Muneer *Curr. Top. Med. Chem.*, 20, 2020, 2723-2734

Table 1

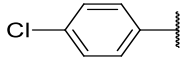
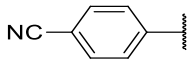
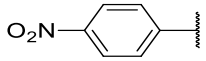
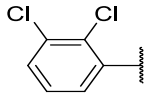
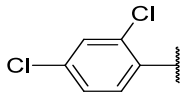
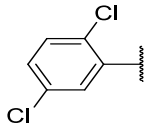
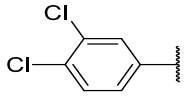
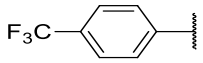
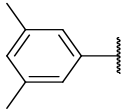
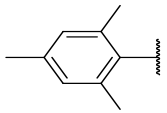
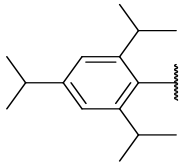
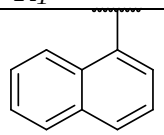
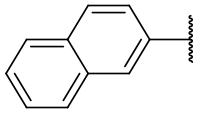
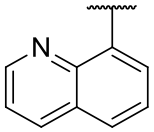
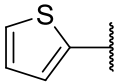
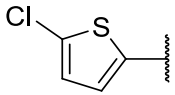


1-16



17-25

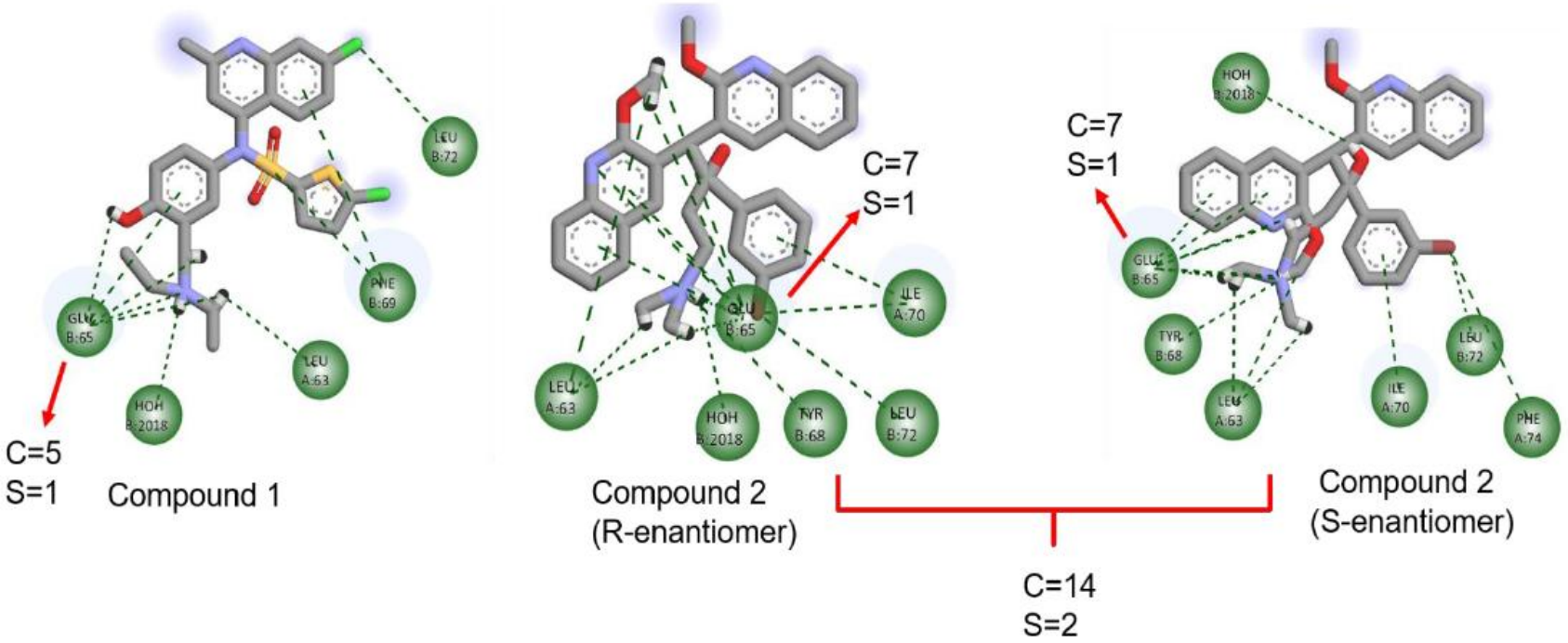
Stereocenter

Comp. No.	Compound structure R_1	R_2	pIC50 (μM)
1		-	0.275
2		-	0.13
3		-	0.408
4		-	0.292
5		-	0.2
6		-	-0.127
7		-	-0.1
8		-	-0.133
9		-	-0.262
10		-	-0.017
11		-	-0.517
12		-	0
13		-	0.036
14		-	-0.267
15		-	-0.195
16		-	0.443
17 *(RS)*	Me	Phenyl	1.154
18 *(RS)*	Me	3-bromophenyl	1.301
19 *(RS)*	CH_2-CH=CH_2	Phenyl	1.397
20 *(RS)*	CH_2-CH=CH_2	3-bromophenyl	1.522
21 *(RS)*	CH_2-CH=CH_2	4-bromophenyl	0.522
22 *(RS)*	CH_2-CH_2-CH =CH_2	4-bromophenyl	1.096
23 *(RS)*	Me	2-naphthyl	1.522
24 *(RS)*	Me	4-bromophenyl	2
25 *(RS)*	Me	3-bromophenyl	3

1. Bioorg. Med. Chem. 23 (2015), pp. 742-752
2. Med. Chem. Commun. 6 (2015), pp. 1554-1563

Quantitative Structure Interaction Activity Relationship (QSIAR) methodology

Comp. No.	R/S	Activity	Glu65b	HOHb	Tyr68b	Ala66b	Phe69b	Asp32b	Leu72b	Ile70b	Val61b	Gly62b	Phe57b	Phe58b	Phe74b	Leu63a	Ile70a	Ala66a	Phe74a	Ile59a	Gly62a	Glu65c	Phe69c	Leu72c	Docking score
01	-	0.443	5	1	0	0	2	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	-4.767
02	R	1.301	7	1	1	0	0	0	1	0	0	0	0	0	0	3	2	0	0	0	0	0	0	0	-6.778
	S	1.301	7	1	1	0	0	0	1	0	0	0	0	0	0	3	1	0	1	0	0	0	0	0	-7.332



Saxena, A. K. (2024, March). In *GTHTM* (pp. 1-20). Cham: Springer Nature Switzerland.

The single ‘S’ and the combined ‘C’ interaction parameters for the compounds 1-25 used in the QSAR analysis

Comp. No.	Glu65b		HOHb		Tyr68b		Ala66b		Phe69b		Asp32b		Leu72b		Phe58b		Val61b		Ile70bb		Phe57b		Phe74b		Gly62b		Ile70aa		Ile59aa		Gly62aa		Leu63aa		Phe74aa		Ala66aa		Leu72cc		Phe69cc		Glu65cc	
	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C
1	1	3	1	1	0	0	0	0	0	0	0	0	0	0	1	2	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0
2	1	2	0	0	0	0	1	1	1	2	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	2	0	0	1	2	0	0	0	0	1	1	0	0	0	0
3	1	4	1	1	0	0	1	1	0	0	0	0	0	0	1	1	1	2	0	0	0	0	0	0	1	1	0	0	1	1	1	1	1	2	0	0	1	1	0	0	0	0
4	1	4	0	0	1	1	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0
5	1	5	1	2	0	0	0	0	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0
6	1	3	1	1	1	1	1	1	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	1	1	0	0	0	0	1	1	1	2	0	0	1	1	0	0	0	0	0	0	1	1	0	0	1	1	0	0	0	0	0	0	0	0
8	1	2	0	0	0	0	0	0	1	1	0	0	1	1	1	1	1	2	0	0	1	1	0	0	0	0	0	0	0	0	1	1	1	3	0	0	0	0	0	0	0	0
9	1	3	0	0	1	1	0	0	1	1	0	0	0	0	1	2	1	2	0	0	1	1	0	0	0	0	0	0	1	1	1	1	1	2	0	0	1	1	0	0	0	0
10	1	4	0	0	0	0	1	1	1	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
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18	2	14	2	2	2	2	0	0	0	0	0	0	2	2	0	0	0	0	0	0	0	0	0	0	0	0	2	3	0	0	0	0	2	6	1	1	0	0	0	0	0	0
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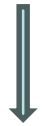
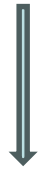
23	2	10	2	3	2	2	2	2	1	1	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	2	0	0	0	0	2	5	0	0	0	0	0	0	0	0
24	2	10	2	2	2	3	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	3	0	0	0	0	2	5	0	0	0	0	0	0	0	0
25	2	10	2	2	1	2	1	1	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	1	1	2	4	0	0	0	1	0	0	0	0

QSIAR model development on the dataset

pIC_{50} = - 0.847 + 0.882(±0.8577)Glu65b + 0.432(±0.3774) HOHb - 0.316(±0.3174) Phe69b - 1.17(±0.9920) Gly62b + 0.044(±0.1898) Ala66b - 0.223(±0.4260) Val61b + 0.117(±0.3556) Leu72b - 0.287(±0.2976) Tyr68b - 0.059(±0.8266) Asp32b - 0.083(±0.4658) Phe58b + 0.286(±0.7943) Ile74b - 0.467(±0.4381) Phe57b - 0.750(±0.4875) Ala66a - 1.25(±1.135) Phe74a + 0.285(±0.2891) Ile70a + 0.270(±0.5042) Leu63a + 0.575(±0.4052) Gly62a + 1.28(±0.9337) Ile59a



pIC_{50} = - 0.881 + 0.659(±0.1999) Glu65b + 0.595(±0.1738) HOHb - 0.468(±0.2444) Ala66a + 0.569(±0.2083) Gly62a



pIC_{50}= -0.428+0.161(±0.01582) Glu65b .....(Eq. 1)

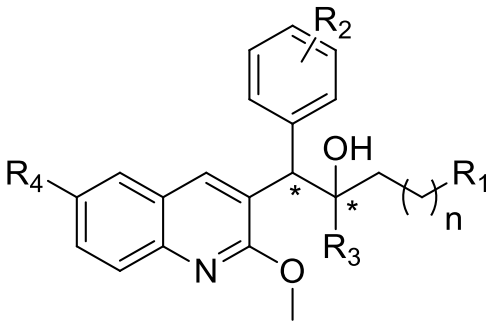
N=24; R^2= 82.5%; R^2 (adj)= 81.7%; S=0.301; R-Sq(pred)= 77.71%

The Eq.1 was also validated with an external dataset which displayed a high correlation (R=0.8518) between the pIC50 and pIC90 values.

S Ahmed, AE Prabahar, AK Saxena, SAR QSAR Environ. Res. , 33:4, 289-305

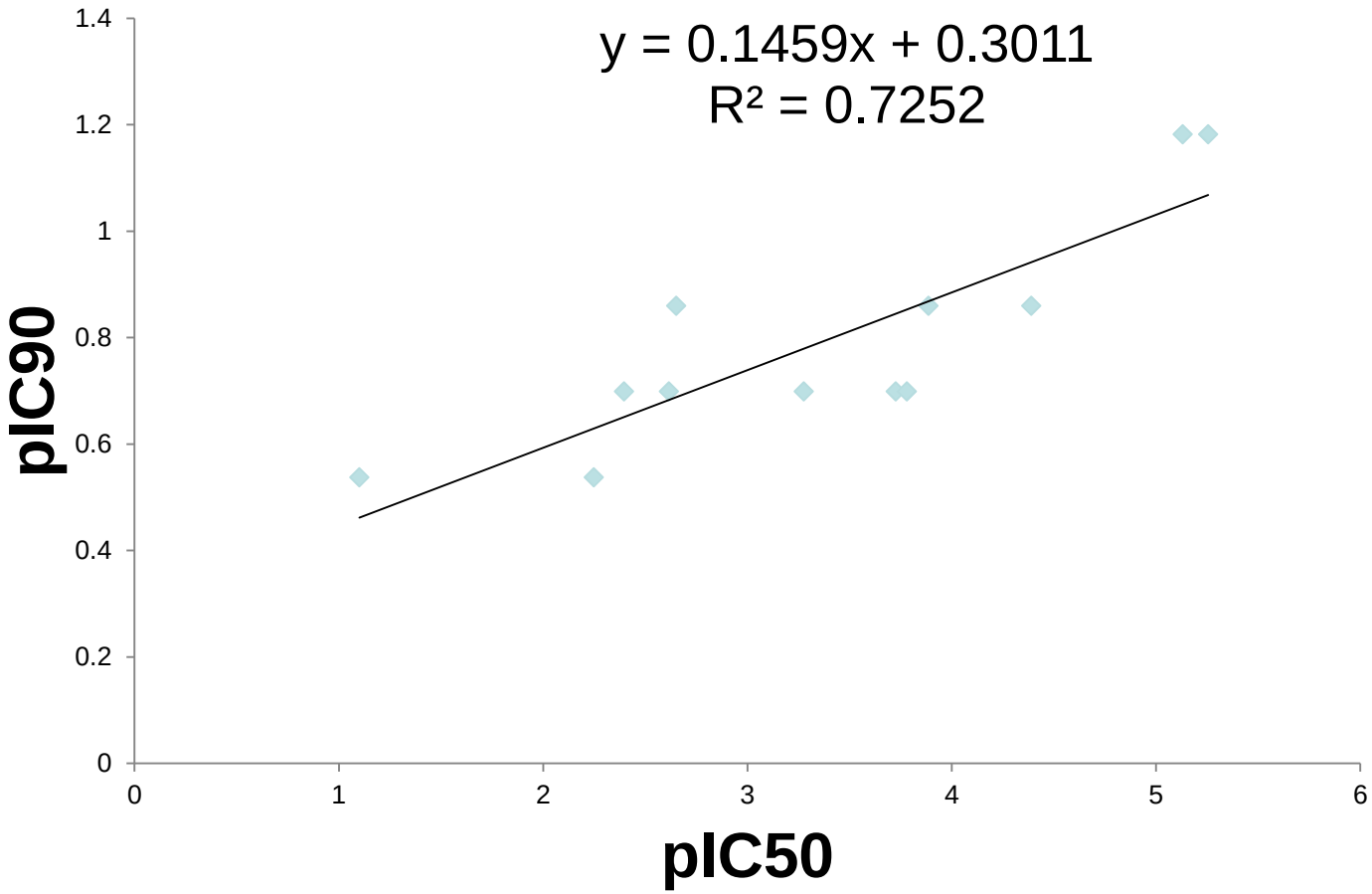
Validation of the developed model

Table 2: Compounds of the external dataset (Future med. Chem., 2011, 3, 1345-1360) with their activity



Comp. No.	Compound structure					pIC_{90} (μM)
	n	R_1	R_2	R_3	R_4	
1	2	$N(Me)_2$	-	Phenyl	Br	3.2757
2	4	$N(Me)_2$	-	Phenyl	Br	2.6161
3	1	NHMe	-	Phenyl	Br	4.389
4	1	Morpholinyl	-	Phenyl	Br	2.3968
5	1	Imidazolyl	-	Phenyl	Br	2.2479
6	1	$N(Me)_2$	3-Cl	Phenyl	Br	5.1302
7	1	$N(Me)_2$	4-Cl	Phenyl	Br	3.7798
8	1	$N(Me)_2$	-	p-cyanophenyl	Br	3.7258
9	1	$N(Me)_2$	-	2,5-difluorophenyl	Br	5.256
10	1	$N(Me)_2$	-	Phenyl	Br	2.652
11	1	$N(Me)_2$	-	Phenyl	6-Cl	3.886
12	1	$N(Me)_2$	-	Phenyl	6-NMepiperazinyl	1.1001

Validation of the developed model

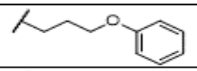
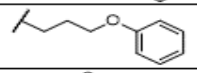
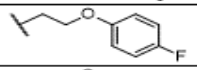
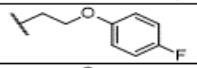
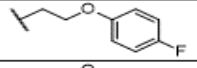
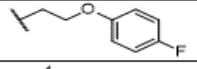
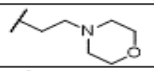
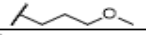
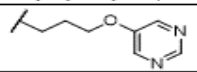
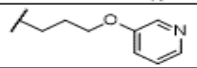
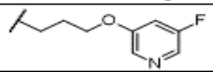
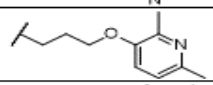
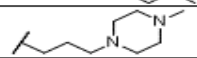
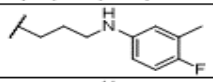
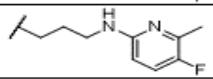


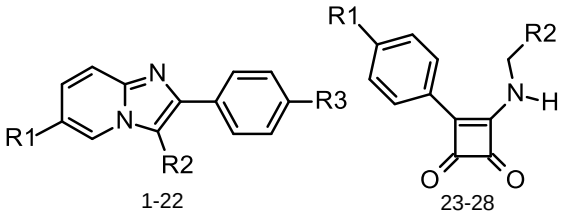
The Eq.1 was also validated with an external dataset which displayed a high correlation (R=0.8518) between the pIC50 and pIC90 values.

S Ahmed, AE Prabahar, AK Saxena, SAR QSAR Environ. Res. , 33:4, 289-305

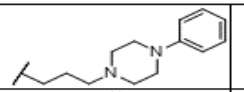
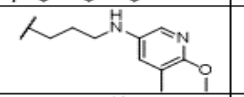
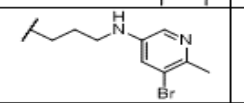
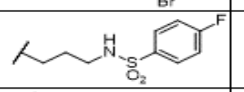
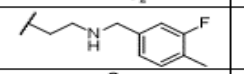
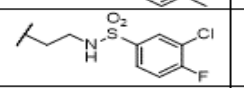
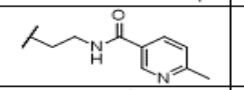
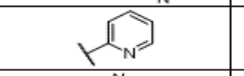
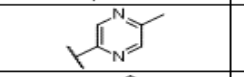
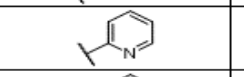
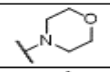
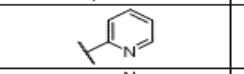
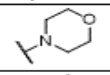
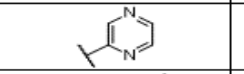
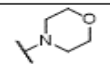
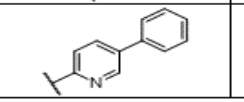
ATP synthase inhibitory activity of a dataset comprising of diverse set of compounds with imidazo[1,2-a] pyridine ethers and squaramides nucleus

Table 4

Comp. No	R_1	R_2	R_3	Observed activity in pIC50 (μM)
1*	H		H	0.886
2*	CH_3		H	1.522
3	H		H	1.097
4	Cl		H	1.398
5*	CH_3		H	1.301
6*	CH_3		F	1.699
7*	Cl		H	-1.557
8	H		H	-1.276
9*	H		H	-0.748
10	CH_3		F	0.796
11	CH_3		F	1.222
12	CH_3		F	1.046
13	CH_3		H	-0.806
14*	CH_3		F	2.301
15*	CH_3		F	1.222



1-22 23-28

16	CH_3		F	1.301
17*	CH_3		F	1.097
18*	CH_3		F	0.678
19	CH_3		F	0.155
20*	CH_3		F	1.155
21	CH_3		F	0.398
22*	CH_3		F	-0.857
23	CF_3		-	0.523
24	CF_3		-	-0.924
25*	CN		-	-1.823
26			-	1.523
27			-	0.113
28*			-	-0.978

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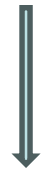
QSIAR model development on the dataset (imidazo[1,2-a] pyridine ethers and squaramides nucleus)

pIC_{50} =-0.361 + 0.813(±0.167) Glu65b - 0.727(±0.220) HOHb - 0.508(±0.421) Tyr68b + 0.562(±0.160) Ala66b - 0.548(±0.157) Phe69b - 0.068(±0.293) Leu72b + 0.734(±0.568) Ile70b - 0.308(±0.222) Val61b + 0.271(±0.204) Gly62b - 0.437(±0.570) Phe57b + 0.234(±0.327) Phe58b + 0.245(±0.149) Leu63a - 0.439(±0.246) Ile70a + 0.070(±0.157) Ala66a + 0.141(±0.629) Gly62a

pIC_{50}= -0.763 + 0.964(±0.112) Glu65b - 0.304(±0.154) HOHb + 0.437(±0.118) Ala66b - 0.334(±0.111) Phe69b



pIC_{50}=-0.845 + 1.094(±0.137) Glu65b ….(Eq.2)

n=28, r^2=71.00%, r-Sq(adj)=69.88%, F=63.65, S=0.615, R-Sq(pred)= 67.75%

Equation 2 is similar to equation 1 in terms of the positively correlating parameter Glu65b as the independent variable emphasizing the dependence of activity on this interaction which alone was capable to predict the activities.

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QSAR model development on the combined dataset of 4-substituted amino sulphonyl-2-methyl-7-chloroquinolines, bis-quinoline core, imidazo[1,2-a] pyridine ethers and squaramides nucleus

pIC_{50} =0.396 + 0.3348(±0.0736) Glu65b - 0.931(±0.176) HOHb - 0.385(±0.189) Tyr68b + 0.377(±0.129) Ala66b - 0.507(±0.132) Phe69b - 0.861(±0.530) Asp32b - 0.004(±0.241) Leu72b - 0.645(±0.354) Ile74b - 0.458(±0.200) Val61b + 0.135(±0.205) Gly62b - 0.203(±0.373) Phe57b + 0.158(±0.242) Phe58b + 0.310(±0.140) Leu63a - 0.069(±0.188) Ile70a + 0.255(±0.166) Ala66a - 2.800(±0.931) Phe74a + 0.228(±0.417) Ile59a - 0.550(±0.229) Gly62a + 0.446(±0.694) Ile70b

pIC_{50}= 0.165 + 0.2352(±0.0365) Glu65b - 0.610(±0.153) HOHb + 0.307(±0.128) Ala66b - 0.3359(±0.0986) Phe69b

n=52, R^2=50.83%, R-Sq(adj)=46.65%, F=12.15, S=0.688, R-Sq(pred)=39.63%

pIC_{50}= 0.319 + 0.3080(±0.0393) Glu65b - 0.649(±0.138) HOHb + 0.230(±0.118) Ala66b - 0.2371(±0.0936) Phe69b -0.800(±0.234) I **…(Eq.3)**

[Indicator variable]

n=52, R^2=60.80%, R-Sq(adj)=56.54%, F=14.27, S=0.621, R-Sq(pred)= 48.13%

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QSAR model development on the combined dataset of 4-substituted amino sulphonyl-2-methyl-7-chloroquinolines, bis-quinoline core, imidazo[1,2-a] pyridine ethers and squaramides nucleus

The dataset of 52 molecules was divided equally into training and test set.
Criteria: All the 52 molecules were first arranged in decreasing order of activity and divided two sets **[training set (27 molecules)** included the most and the least active molecules along with every alternate molecule while the **test set (25 molecules)** included the rest of the molecules.

$$pIC50 = 0.259 + 0.3802(\pm 0.0655)\ Glu65b - 0.793(\pm 0.191)\ HOHb + 0.287(\pm 0.176)\ Ala66b - 0.353(\pm 0.125)\ Phe69b - 0.870(\pm 0.348)\ I \quad \textbf{(Eq.4)}$$

n=27, R^2=67.74%, R-Sq(adj)=60.06%, F=8.82, S=0.647, R-Sq(pred)= 48.60%

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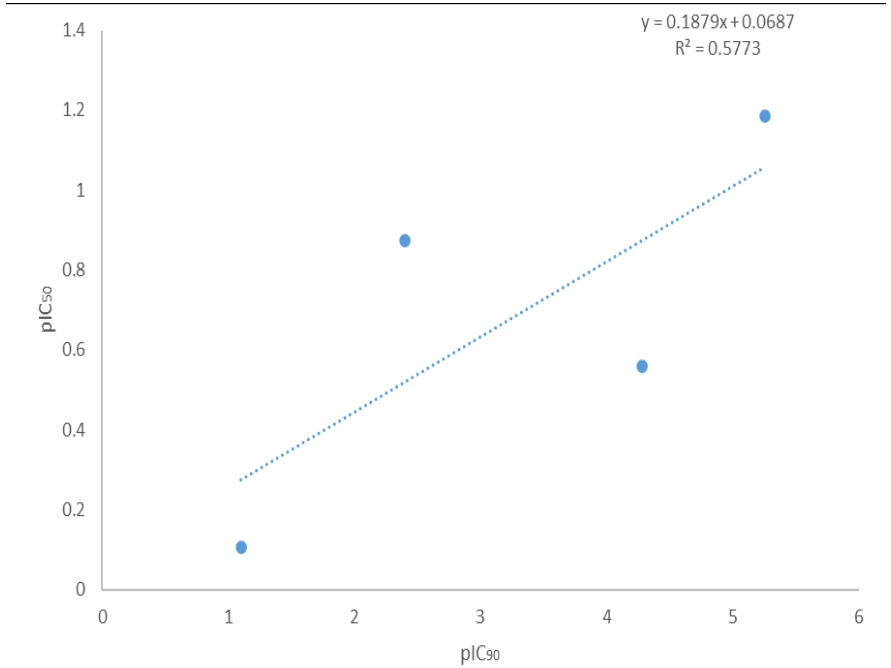
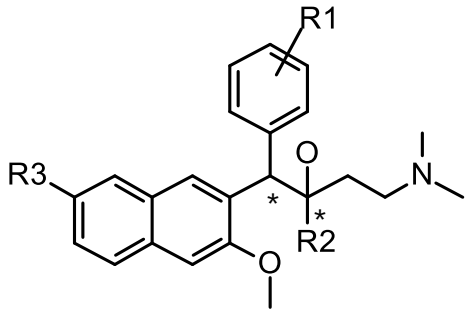
Validation of the developed model by dataset-1

The model (Eq. 4) was validated by an external dataset (diarylquinolines) (Future med. Chem., 2011, 3, 1345-1360). Four compounds comprising of the most, the least and two more compounds with in between activity were taken for the validation of the model. A correlation analysis showing a a good correlation (**R=0.76**) between the predicted pIC_{50} values and the pIC_{90} further validates this model and points towards its robustness.





Comp. No.	Compound structure				Pred. pIC_{50}(μM)
	R_1	R_2	R_3	Obs. pIC_{90}(μM)	
1	-	Phenyl	Br	2.398	0.8738
2	3,4-diCl	Phenyl	Br	4.282	0.5596
3	-	2,5-difluorophenyl	Br	5.256	1.186
4	-	Phenyl	6-NMepiperazinyl	1.1001	0.1052

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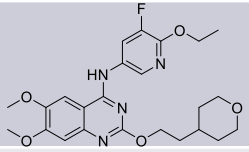
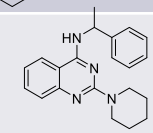
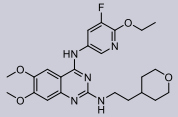
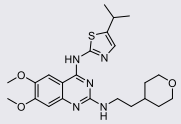
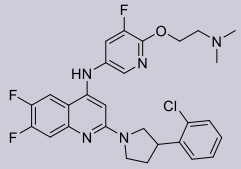
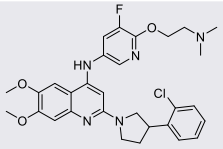
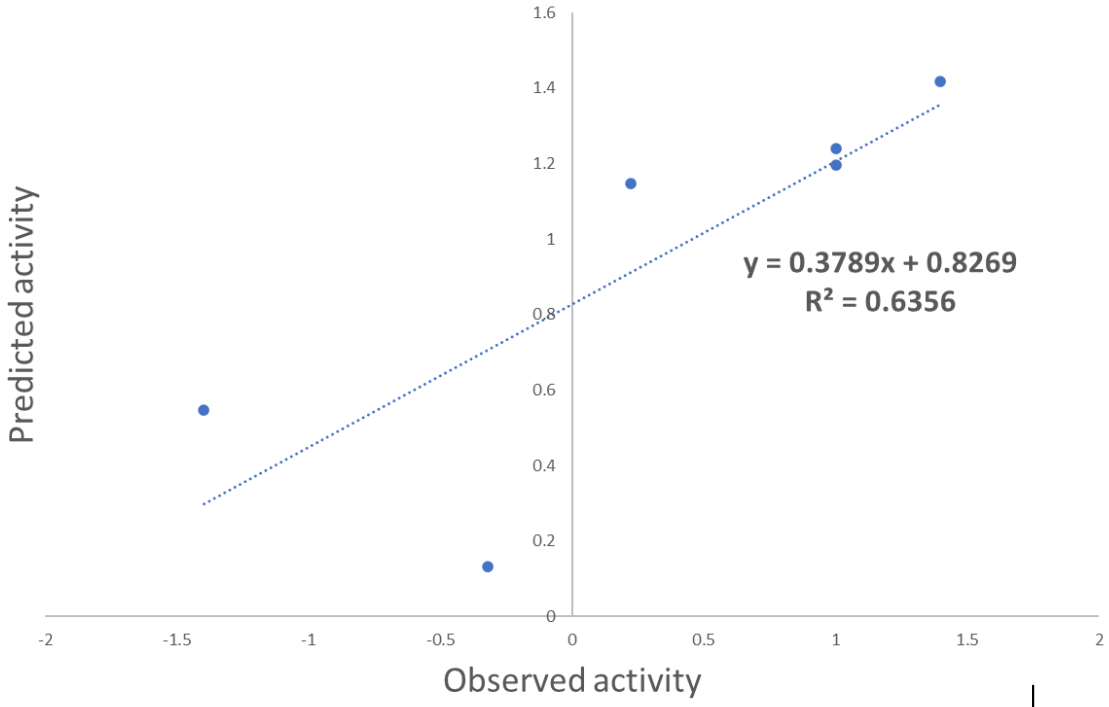
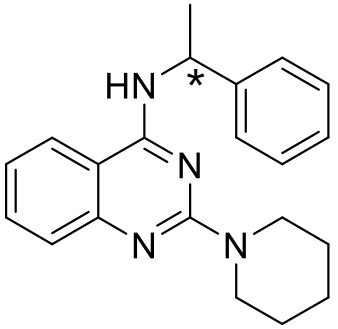
Validation of the developed model by dataset-2

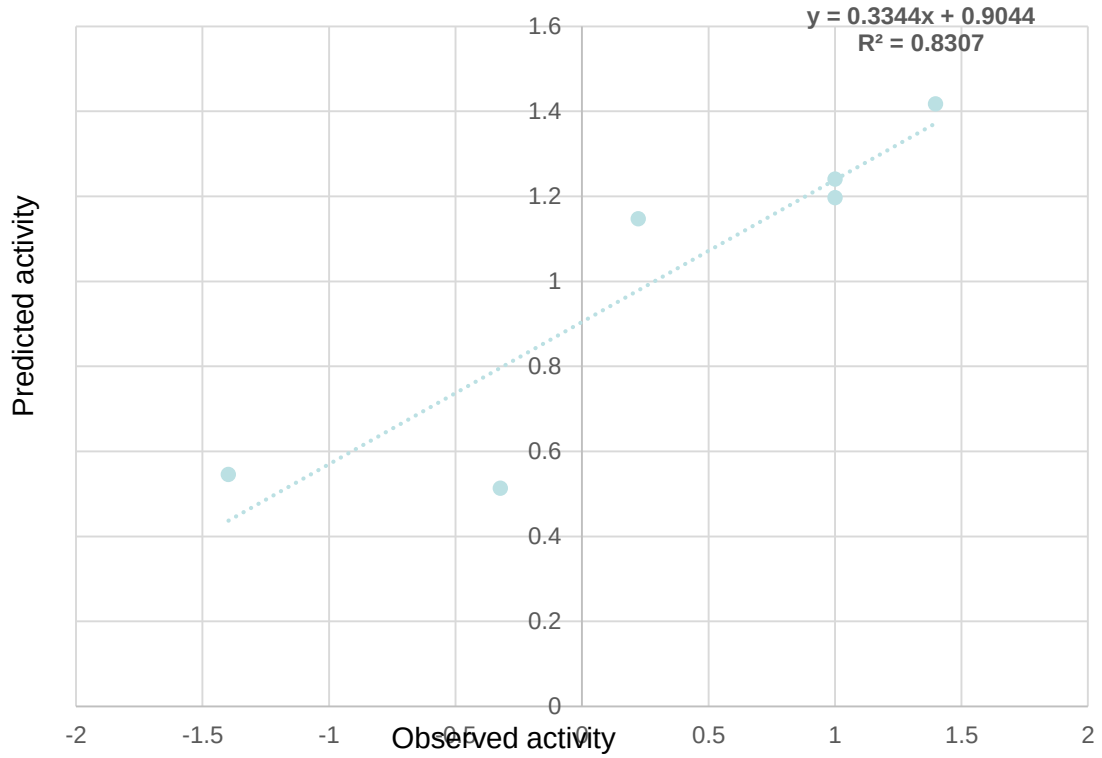
S.No	Structure (MedChemComm 2016, 7(5):1022-1032)	Mycobacterial ATP synthase activity IC_{50} (μM)	Mycobacterial ATP synthase activity pIC_{50} (μM)	Predicted ATP synthase activity pIC_{50} (μM)
1		25	-1.39794	0.546
2		2.1	-0.32222	0.1332
3		0.6	0.221849	1.1472
4		0.1	1	1.2404
5		0.1	1	1.1968
6		0.04	1.39794	1.4178

Validation of the developed model by dataset-2



R=0.79

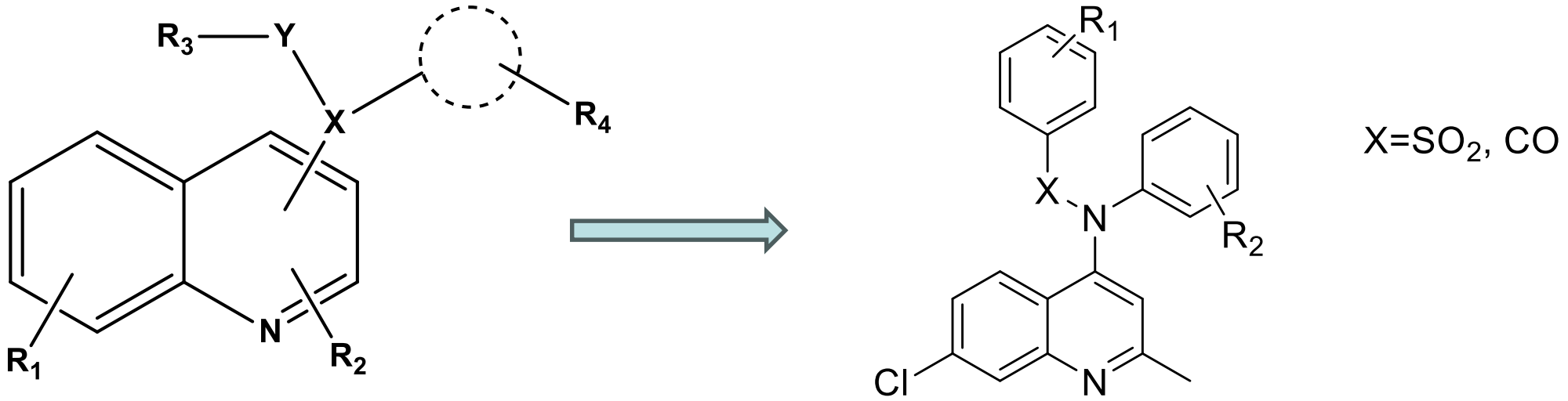


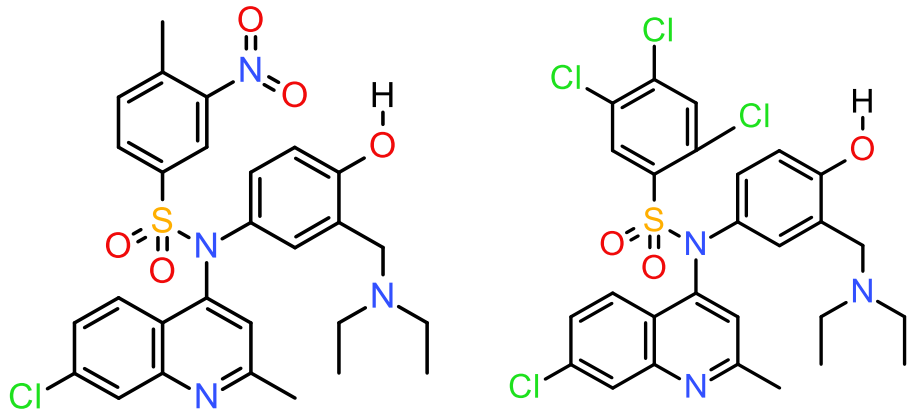


R=0.91

A plot between the observed and predicted values of the external dataset-2**.**

Generation of the focussed library and prediction of selected molecules for validation





Predicted pIC_{50} =0.1168μM Predicted pIC_{50} =0.1494μM

Predicted compounds

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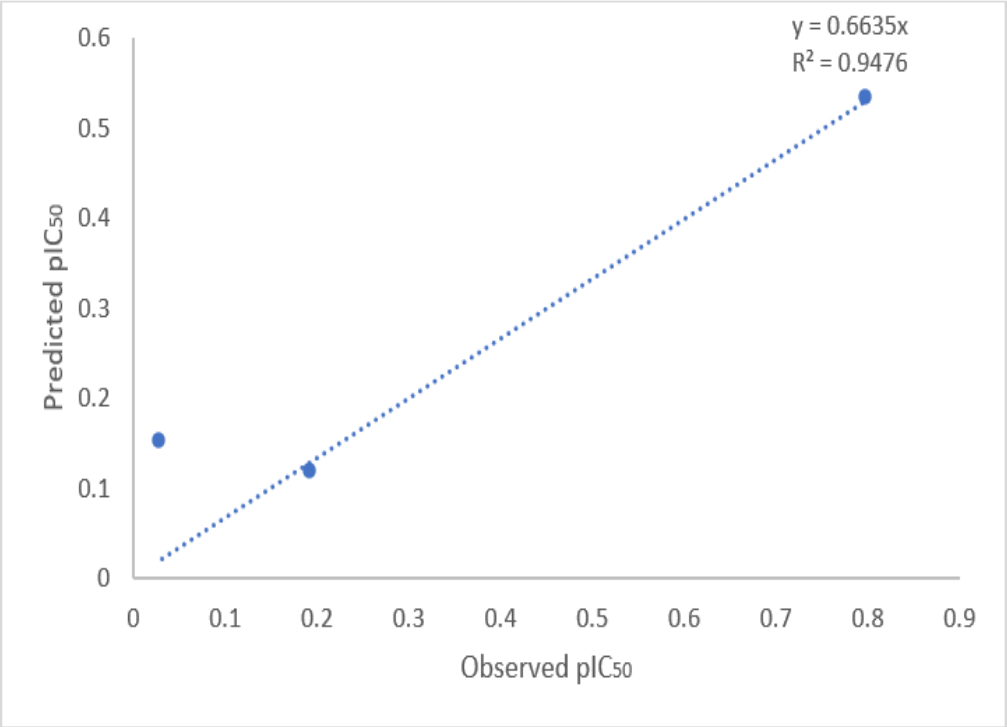
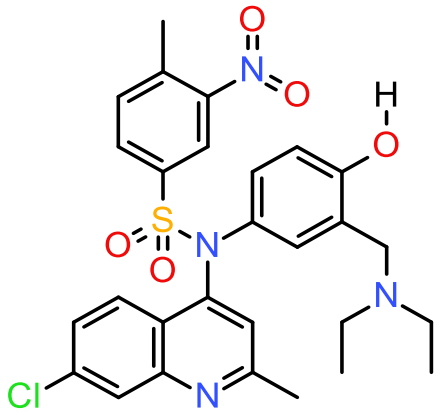
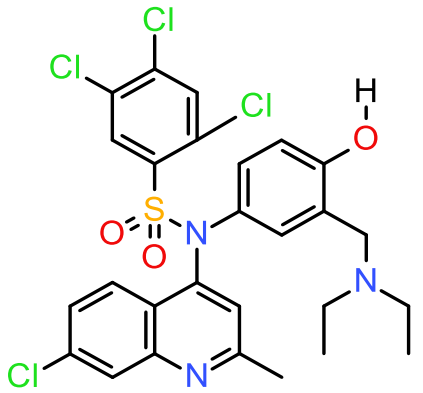
Prediction and Evaluation of the selected novel compounds

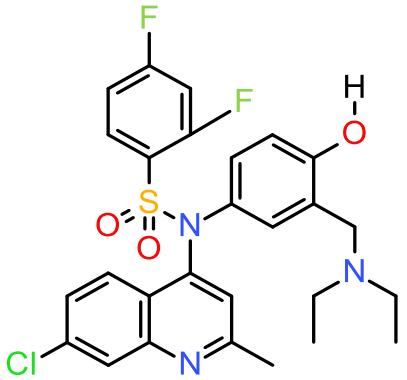




Predicted pIC_{50} =0.1168μM
Obs pIC_{50}= 0.195μM



Predicted pIC_{50} =0.1494μM
Obs pIC_{50}= 0.032μM



Predicted pIC_{50} =0.5296μM
Obs. pIC_{50}= 0.8013μM

Conclusions

- The docking scores always do not correlate with the biological activity.
- To address this issue, a novel approach (Quantitative Structure Interaction Activity Relationship-**QSIAR**) has been developed where the observed interactions of the ligand molecule with the amino acid residues of the target protein were used as an independent parameters and the binding energy/affinity, docking scores/biological activity as dependent parameter.
- This approach was used to develop predictive models for Mycobacterium ATP synthase inhibitory activity in diverse class of 4-substituted amino sulphonyl-2-methyl-7-chloroquinolines, bis-quinoline core, imidazo[1,2-a] pyridine ethers and squaramides nucleus.
- The developed models were validated on diverse set of compounds and well explained the variation in ATP synthase inhibitory activity.
- The studies led to the design of novel compounds which showed high activity and well correlated with the predicted activity.
- Thus, the QSIAR approach has a high potential in the development of predictive models using structure-based drug design which was hitherto not possible. Such models may thus result in novel lead molecules for drug design and development.

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Mr. Sarfaraz Ahmed

Let’s make the World TB Safe!

THANK YOU