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Computational Design of New Teixobactin Analogues as Inhibitors of Lipid II Flippase MurJ

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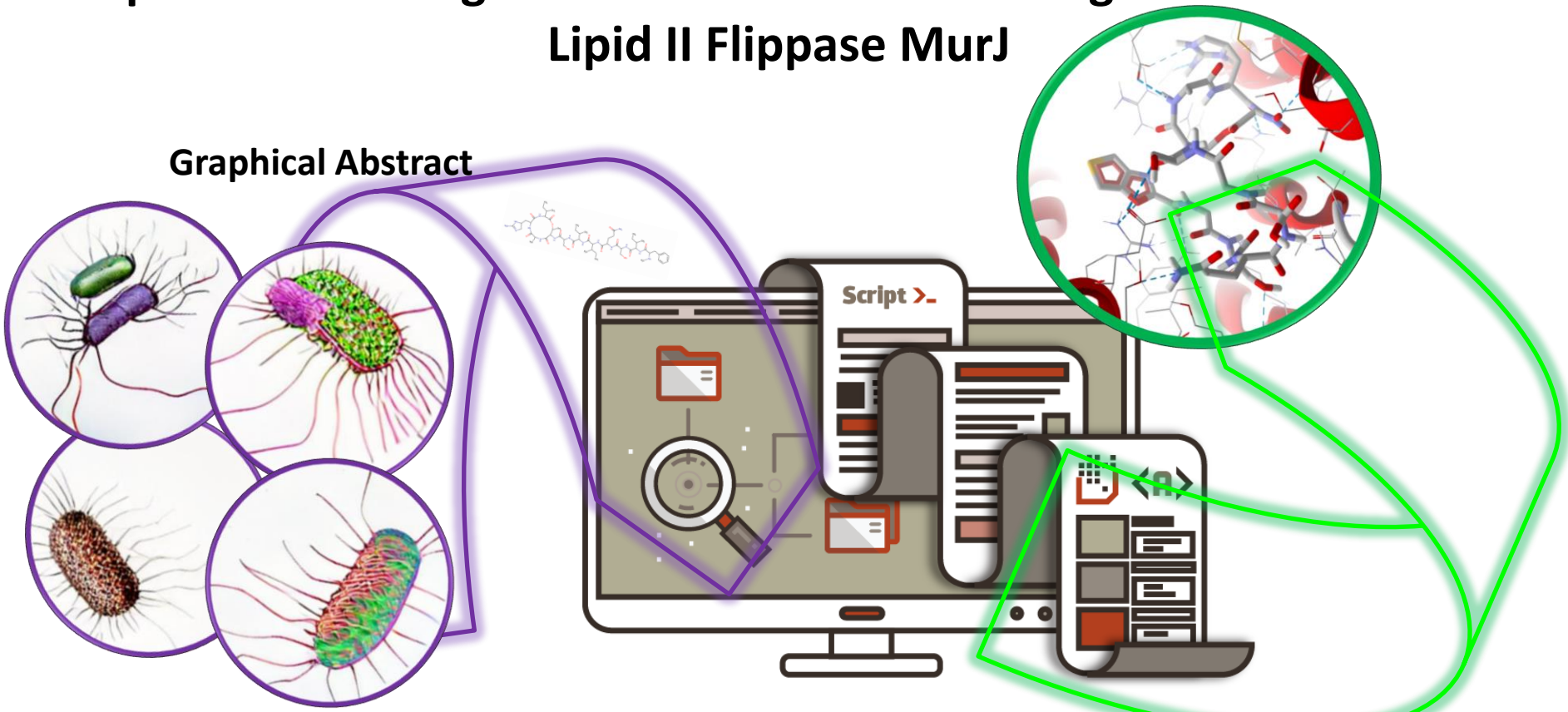
Graphical Abstract



Artistic depiction of mutant bacteria is generated with *Craiyon – AI model drawing images from any prompt!* (Craiyon LLC: https://www.craiyon.com)

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Abstract:

The peptidoglycan (PG) cell wall is an essential component of bacterial cell structure, and crippling its synthesis is one of the most successful strategies in the continuing war against pathogenic bacteria. MurJ is a member of MOP flippase superfamily critically required for the synthesis of PG from lipid II. Teixobactin (TXB) is a recently discovered promising natural antibiotic. This study focuses on the computational design of new TXB analogue prototypes. A combinatorial library was generated using a set of three scaffolds based on TXB structure and a selected list of building blocks in order to avoid the molecular obesity issue and minimalize the potential health risks. TXB and the combinatorial library were virtually screened with adequate drug-likeness filters, and PK/PD models. The safest drug candidates were docked against the crystal structure of MurJ. What was found was that 26 virtual analogues had better binding affinities than TXB against MurJ. Overall, the proposed computational drug design approach for novel antibiotics might be a useful asset for medicinal chemists and translational pharmacologists.

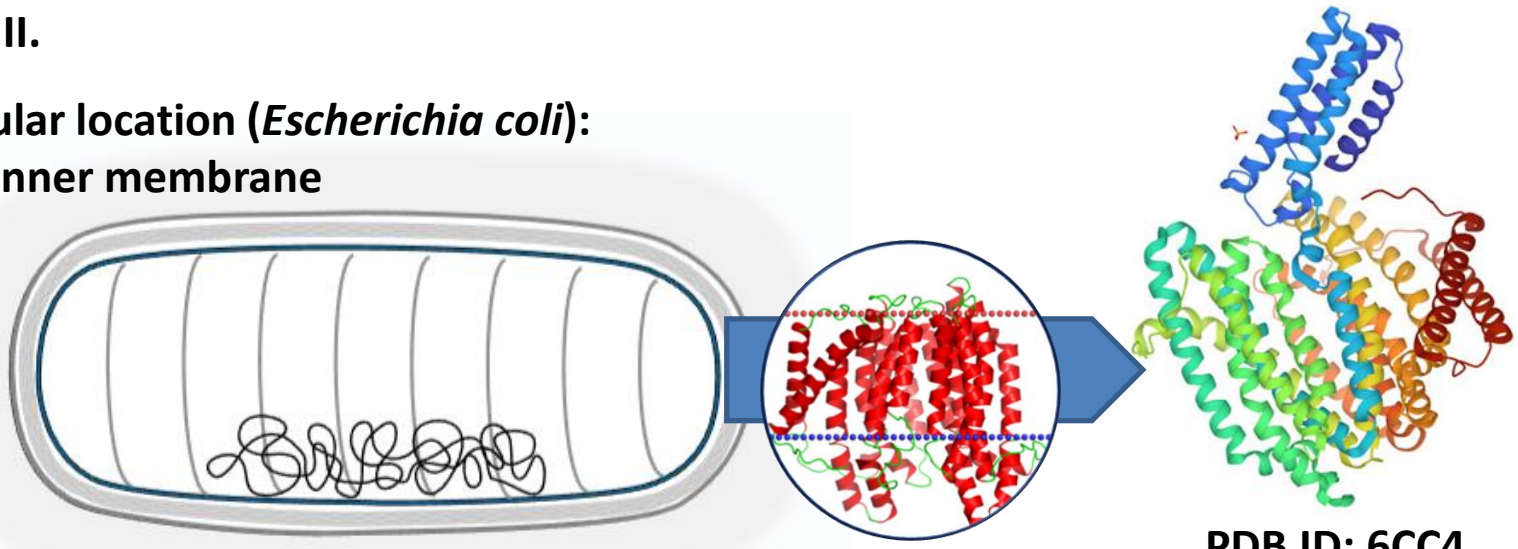
Keywords: antibacterials; *in silico*; molecular docking; PK/PD

Introduction [1/3]

- **PG cell wall is an essential component of bacterial cell structure, and crippling its synthesis is one of the most successful strategies in the continuing war against pathogenic bacteria.**
- **MurJ is a member of the multidrug/oligosaccharidyl-lipid/polysaccharide (MOP) flippase superfamily critically required for the synthesis of PG from lipid II.**

Subcellular location (*Escherichia coli*):

- **Cell inner membrane**

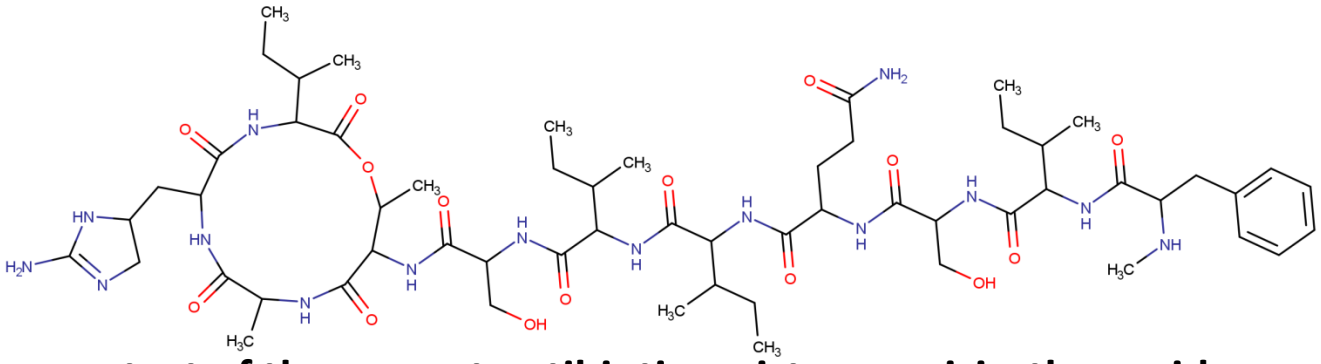


PDB ID: 6CC4

- **PDB DOI: [10.2210/pdb6CC4/pdb](10.2210/pdb6CC4/pdb)**

Introduction [2/3]

- **TXB is a recently discovered promising macrocyclic depsipeptide natural antibiotic. TXB is claimed to "kill pathogens without detectable resistance"[1] and considered a possible "paving stone toward a new class of antibiotics"[2].**



- **In the context of the current antibiotic resistance crisis, the rapid development of a plethora of TXB analogues with improved pharmacokinetics/pharmacodynamics (PK/PD) is a critical challenge.**

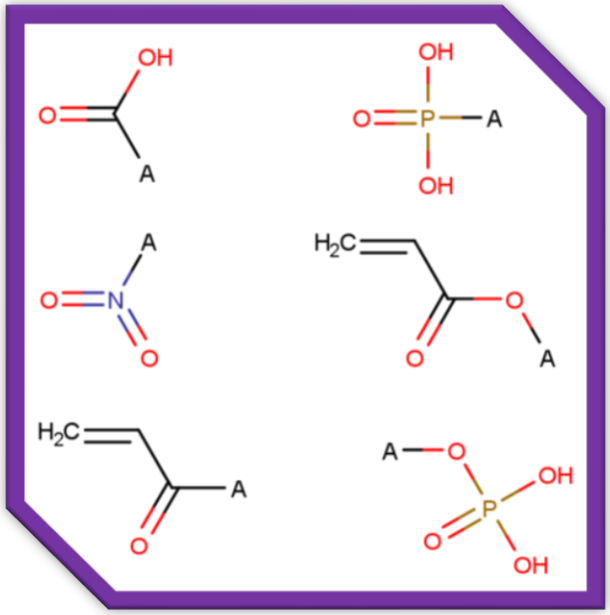
[1]. Ling, L. L. et all. A new antibiotic kills pathogens without detectable resistance. *Nature* 2015, 517, 455–459.

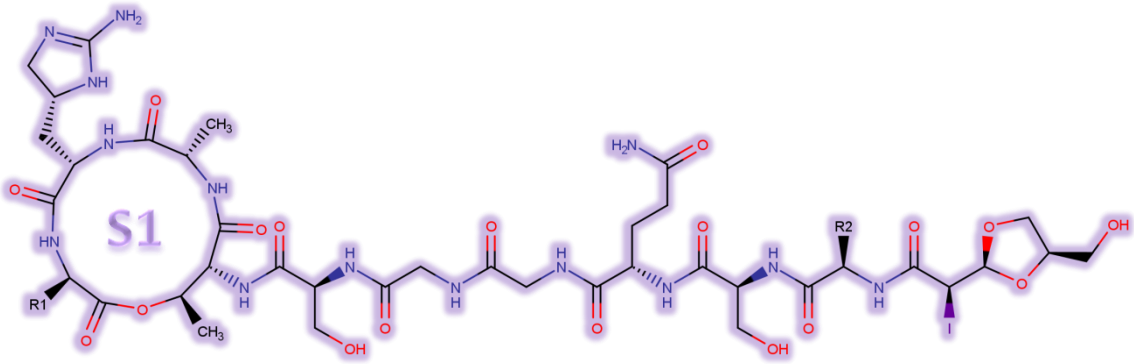
[2]. Gunjal, V. B.; Thakare, R.; Chopra, S.; Reddy, D. S. Teixobactin: A Paving Stone toward a New Class of Antibiotics? *J. Med. Chem.* 2020, 63, 12171–121

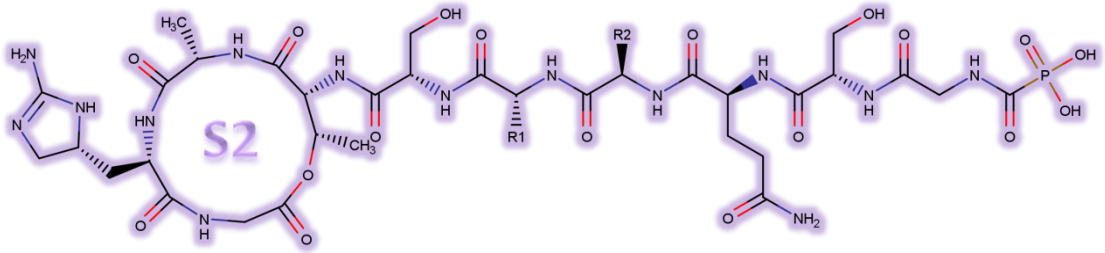
Introduction [3/3]

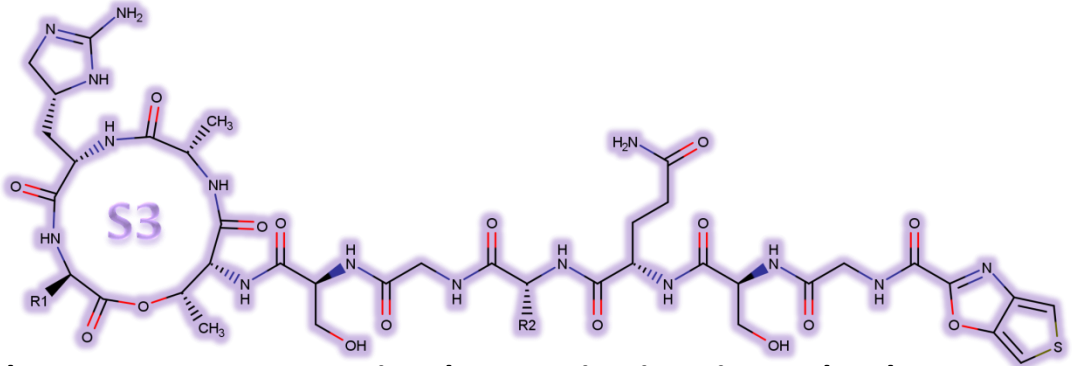
Virtual Library:

- **Designed scaffolds (S1-3)**
- **Building-blocks (BB1-6)[3]**







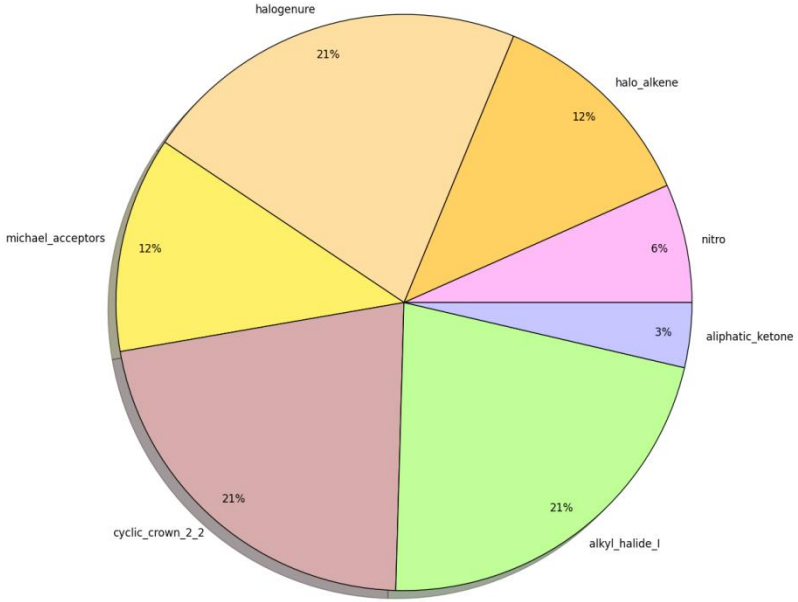


[3]. Ertl, P.; Altmann, E.; Mckenna, J. M. The Most Common Functional Groups in Bioactive Molecules and How Their Popularity Has Evolved over Time. *J. Med. Chem.* 2020, 63, 8408–8418.

Results and discussion [1/8]

S1 based virtual library – PK/PD filtering statistics

- **Accepted TXB analogues: 0**
- **PAINS (Pan Assays Interferences Compounds): 0**
- **Covalent inhibitors: 36**
- **Detected problematic moieties with an occurrence above 1%:**

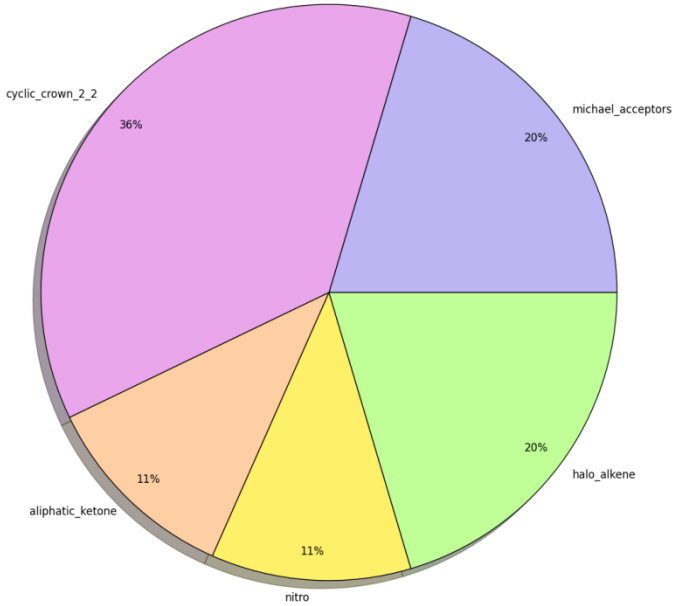


Software: *FAF-Drugs4*

Results and discussion [2/8]

S2 based virtual library – PK/PD filtering statistics

- **Accepted TXB analogues: 16**
- **PAINS (Pan Assays Interferences Compounds): 0**
- **Covalent inhibitors: 20**
- **Detected problematic moieties with an occurrence above 1%:**

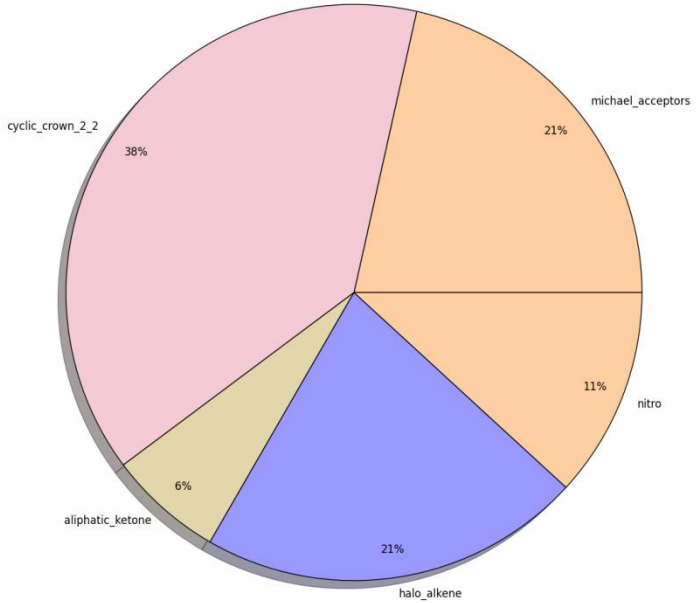


Software: *FAF-Drugs4*

Results and discussion [3/8]

S3 based virtual library – PK/PD filtering statistics

- **Accepted TXB analogues: 16**
- **PAINS (Pan Assays Interferences Compounds): 0**
- **Covalent inhibitors: 20**
- **Detected problematic moieties with an occurrence above 1%:**



Software: *FAF-Drugs4*

Results and discussion [4/8]

TXB *vs* accepted TXB analogues (S2 based virtual library)

Library	Compound ID	Solubility (mg/l)	Solubility Forecast Index	Oral Bioavailability (Veber Rule)	Oral Bioavailability (Egan Rule)	4/400 Rule	3/75 Rule	Phospholipidosis	PPI Friendly
N/A	TXB	5079.43	Good Solubility	Low	Low	good	good	NonInducer	Yes
S2	1.1_1.1_1_1_1	5597569.29	Good Solubility	Low	Low	good	good	NonInducer	Yes
S2	1.1_1.1_2_2_2	4609615.73	Good Solubility	Low	Low	good	good	NonInducer	Yes
S2	1.1_1.1_4_4_4	11841497.6	Good Solubility	Low	Low	good	good	NonInducer	Yes
S2	1.1_1.1_6_6_6	11262753.92	Good Solubility	Low	Low	good	good	NonInducer	Yes
S2	1.1_2.1_1_7_7	4609615.73	Good Solubility	Low	Low	good	good	NonInducer	Yes
S2	1.1_2.1_2_8_8	3796029.57	Good Solubility	Low	Low	good	good	NonInducer	Yes
S2	1.1_2.1_4_10_10	9751208.09	Good Solubility	Low	Low	good	good	NonInducer	Yes
S2	1.1_2.1_6_12_12	9274503.86	Good Solubility	Low	Low	good	good	NonInducer	Yes
S2	1.1_4.1_1_19_19	11841497.6	Good Solubility	Low	Low	good	good	NonInducer	Yes
S2	1.1_4.1_2_20_20	9751208.09	Good Solubility	Low	Low	good	good	NonInducer	Yes
S2	1.1_4.1_4_22_22	25023009.62	Good Solubility	Low	Low	good	good	NonInducer	Yes
S2	1.1_4.1_6_24_24	23939351.89	Good Solubility	Low	Low	good	good	NonInducer	Yes
S2	1.1_6.1_1_31_31	11262753.92	Good Solubility	Low	Low	good	good	NonInducer	Yes
S2	1.1_6.1_2_32_32	9274503.86	Good Solubility	Low	Low	good	good	NonInducer	Yes
S2	1.1_6.1_4_34_34	23939351.89	Good Solubility	Low	Low	good	good	NonInducer	Yes
S2	1.1_6.1_6_36_36	22754313.99	Good Solubility	Low	Low	good	good	NonInducer	Yes

Results and discussion [5/8]

TXB *vs* accepted TXB analogues (S3 based virtual library)

Library	Compound ID	Solubility (mg/l)	Solubility Forecast Index	Oral Bioavailability (Veber Rule)	Oral Bioavailability (Egan Rule)	4/400 Rule	3/75 Rule	Phospholipidosis	PPI Friendly
N/A	TXB	5079.43	Good Solubility	Low	Low	good	good	NonInducer	Yes
S3	1.1_1.1_1_1_1	443436.74	Good Solubility	Low	Low	good	good	NonInducer	Yes
S3	1.1_1.1_2_2_2	365043.52	Good Solubility	Low	Low	good	good	NonInducer	Yes
S3	1.1_1.1_4_4_4	937432.08	Good Solubility	Low	Low	good	good	NonInducer	Yes
S3	1.1_1.1_6_6_6	897024.09	Good Solubility	Low	Low	good	good	NonInducer	Yes
S3	1.1_2.1_1_7_7	516211.51	Good Solubility	Low	Low	good	good	NonInducer	Yes
S3	1.1_2.1_2_8_8	424950.32	Good Solubility	Low	Low	good	good	NonInducer	Yes
S3	1.1_2.1_4_10_10	1091258.23	Good Solubility	Low	Low	good	good	NonInducer	Yes
S3	1.1_2.1_6_12_12	1044211.69	Good Solubility	Low	Low	good	good	NonInducer	Yes
S3	1.1_4.1_1_19_19	937432.08	Good Solubility	Low	Low	good	good	NonInducer	Yes
S3	1.1_4.1_2_20_20	771692.88	Good Solubility	Low	Low	good	good	NonInducer	Yes
S3	1.1_4.1_4_22_22	1992219.73	Good Solubility	Low	Low	good	good	NonInducer	Yes
S3	1.1_4.1_6_24_24	1893542.92	Good Solubility	Low	Low	good	good	NonInducer	Yes
S3	1.1_6.1_1_31_31	1268490.28	Good Solubility	Low	Low	good	good	NonInducer	Yes
S3	1.1_6.1_2_32_32	1044211.69	Good Solubility	Low	Low	good	good	NonInducer	Yes
S3	1.1_6.1_4_34_34	2677677.02	Good Solubility	Low	Low	good	good	NonInducer	Yes
S3	1.1_6.1_6_36_36	2544573.04	Good Solubility	Low	Low	good	good	NonInducer	Yes

Results and discussion [6/8]

Molecular docking: TXB *vs* all accepted TXB analogues

- **26 virtual analogues had better binding affinities than TXB against MurJ**

Target – Ligand complex	Binding Affinity (kcal/mol)	RMSD/ub	RMSD/lb
6CC4-S3_1_1_6_1_6_36_36	-7.7	0	0
6CC4-S3_1_1_4_1_4_22_22	-7.8	0	0
6CC4-S3_1_1_1_1_4_4_4	-8.2	0	0
6CC4-S3_1_1_6_1_4_34_34	-8.3	0	0
6CC4-S2_1_1_4_1_2_20_20	-8.4	0	0
6CC4-TXB	-8.5	0	0
6CC4-S3_1_1_6_1_2_32_32	-8.5	0	0
6CC4-S3_1_1_1_1_2_2_2	-8.7	0	0
6CC4-S2_1_1_6_1_2_32_32	-8.7	0	0
6CC4-S3_1_1_4_1_6_24_24	-8.8	0	0
6CC4-S3_1_1_2_1_4_10_10	-8.8	0	0
6CC4-S3_1_1_1_1_1_1_1	-8.8	0	0
6CC4-S2_1_1_2_1_2_8_8	-8.8	0	0
6CC4-S2_1_1_6_1_1_31_31	-8.9	0	0
6CC4-S2_1_1_1_1_6_6_6	-8.9	0	0
6CC4-S2_1_1_1_1_1_1_1	-8.9	0	0
6CC4-S3_1_1_4_1_2_20_20	-9.0	0	0

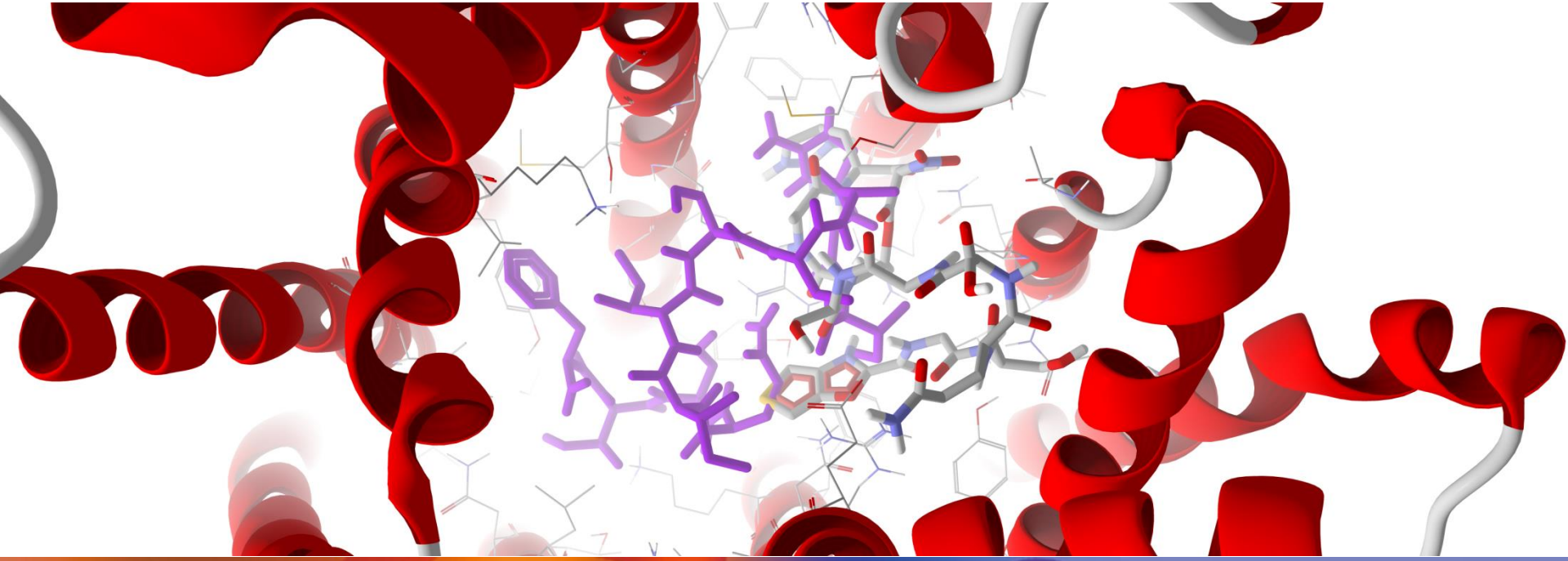
Target – Ligand complex	Binding Affinity (kcal/mol)	RMSD/ub	RMSD/lb
6CC4-S2_1_1_6_1_6_36_36	-9.0	0	0
6CC4-S2_1_1_4_1_1_19_19	-9.0	0	0
6CC4-S3_1_1_2_1_6_12_12	-9.1	0	0
6CC4-S2_1_1_2_1_1_7_7	-9.1	0	0
6CC4-S2_1_1_6_1_4_34_34	-9.2	0	0
6CC4-S2_1_1_1_1_4_4_4	-9.2	0	0
6CC4-S3_1_1_6_1_1_31_31	-9.3	0	0
6CC4-S3_1_1_4_1_1_19_19	-9.3	0	0
6CC4-S3_1_1_2_1_2_8_8	-9.4	0	0
6CC4-S2_1_1_4_1_6_24_24	-9.4	0	0
6CC4-S2_1_1_1_1_2_2_2	-9.5	0	0
6CC4-S2_1_1_4_1_4_22_22	-9.6	0	0
6CC4-S2_1_1_2_1_6_12_12	-9.6	0	0
6CC4-S2_1_1_2_1_4_10_10	-9.7	0	0
6CC4-S3_1_1_1_1_6_6_6	-9.8	0	0
6CC4-S3_1_1_2_1_1_7_7	-10.0	0	0

Software: *AutoDock Vina* run in *PyRx – Python Prescription 0.9.7* interface

Results and discussion [7/8]

Molecular docking

- **Target – Ligand complexes: TXB (purple) *vs* the best binder (S3_1_1_2_1_1_7_7, in CPK colors)**



Results and discussion [8/8]

Molecular docking

- **Target – Ligand complexes: TXB *vs* the best binder (S3_1_1_2_1_1_7_7)**
- **Re-ranking of the best poses (Software: Molegro Molecular Viewer 2.5)**

6CC4 - TXB Energy overview				
Descriptors	**Value**	**MolDock Score**	**Rerank Weight**	**Rerank Score**
[I] External Ligand interactions		-243.321		-218.605
• Protein - Ligand interactions		-243.321		-218.605
• Steric (by PLP)	-232.967	-232.967	0.686	-159.815
• Steric (by LJ12-6)	-94.913		0.533	-50.589
• Hydrogen bonds	-10.355	-10.355	0.792	-8.201
• Hydrogen bonds (no directionality)	-17.023			0
[II] Internal Ligand interactions		26.192		74.453
• Torsional strain	77.941	77.941	0.938	73.108
• Torsional strain (sp2-sp2)	0		0.636	0
• Hydrogen bonds	0			0
• Steric (by PLP)	-51.749	-51.749	0.172	-8.901
• Steric (by LJ12-6)	73.71		0.139	10.246
• Electrostatic	0	0	0.437	0
Total Energy: [I] + [II]		**-217.129**		**-144.152**

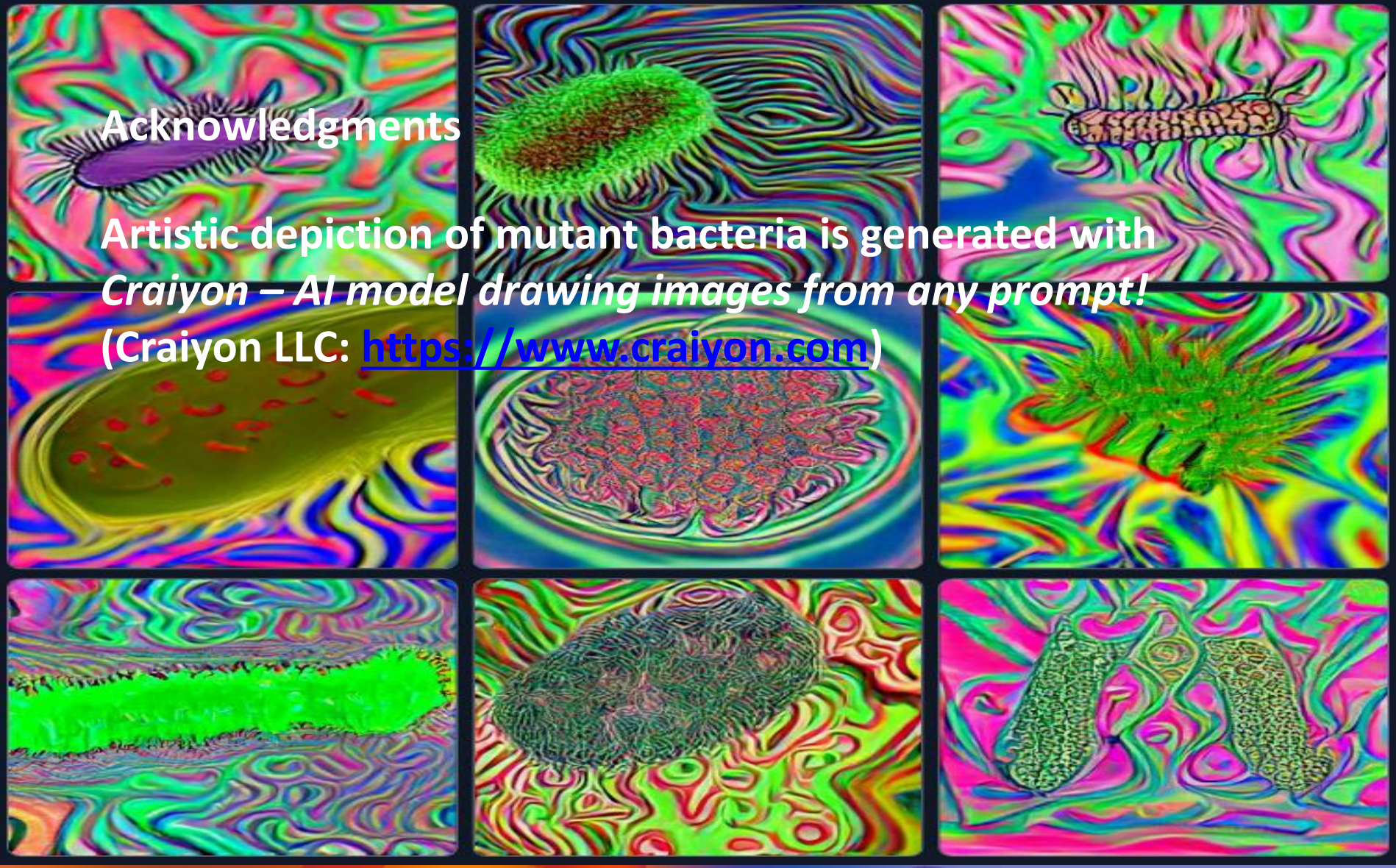
6CC4 - S3_1_1_2_1_1_7_7 Energy overview				
Descriptors	**Value**	**MolDock Score**	**Rerank Weight**	**Rerank Score**
[I] External Ligand interactions		-266.975		-235.481
• Protein - Ligand interactions		-266.975		-235.481
• Steric (by PLP)	-252.065	-252.065	0.686	-172.917
• Steric (by LJ12-6)	-95.226		0.533	-50.756
• Hydrogen bonds	-14.91	-14.91	0.792	-11.809
• Hydrogen bonds (no directionality)	-34.207			0
[II] Internal Ligand interactions		-12.17		27.684
• Torsional strain	36.165	36.165	0.938	33.922
• Torsional strain (sp2-sp2)	0		0.636	0
• Hydrogen bonds	0			0
• Steric (by PLP)	-48.334	-48.334	0.172	-8.314
• Steric (by LJ12-6)	14.93		0.139	2.075
• Electrostatic	0	0	0.437	0
Total Energy: [I] + [II]		**-279.145**		**-207.797**

Empty cells: data not applicable or not computed for respective descriptor; Value: the various terms which the MolDock Score and the Re-rank Score are based on; MolDock Score: this column shows how the MolDock score energy is composed (the sum of a subset of the Value terms in which all terms are given the same weight); Re-rank Weight: summations of coefficients for the weighted Rerank Score; Rerank Score: scoring function which uses a weighted combination of the terms used by the MolDock score mixed with additional terms: the Steric (by PLP) term which use an PLP to approximate the steric energy, respectively the Steric (by LJ12-6) term which is the LJ12-6 approximation of the steric energy.

Conclusions

- **Using rational design and virtual screening were found 26 promising drug prototypes based on structure of TXB:**
  - **improved binding affinity for MurJ;**
  - **similar PK/PD.**

- **The proposed rational drug design platform might be an indispensable tool to develop novel antibiotics against resistant bacteria.**



Acknowledgments

Artistic depiction of mutant bacteria is generated with *Craiyon – AI model drawing images from any prompt!* (Craiyon LLC: https://www.craiyon.com)