

ABSTRACT This study aims to predict BAM7 sensitivity using in silico approaches by analyzing binding patterns and structural features. Data collected from DepMap and GDSC databases were utilized to support the sensitivity prediction model and validate the computational analysis. There is currently no direct platform available for predicting BAM7 sensitivity across cancer cell lines. This web app addresses that gap by providing a rapid, data-integrated solution for researchers, enabling them to identify sensitive models based on existing genomic and drug response datasets — ultimately accelerating drug discovery and personalized cancer therapy research."

Background

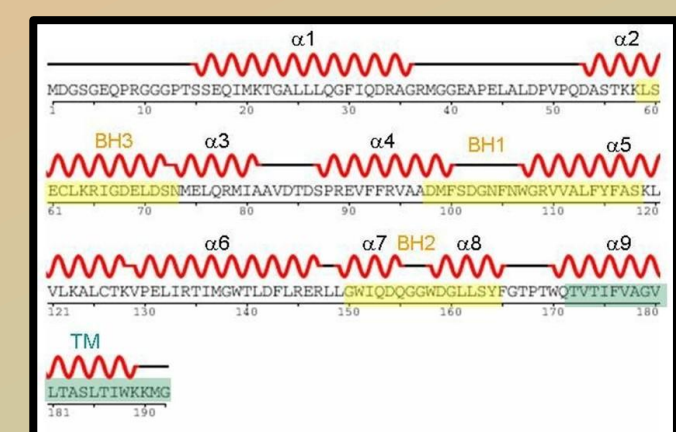


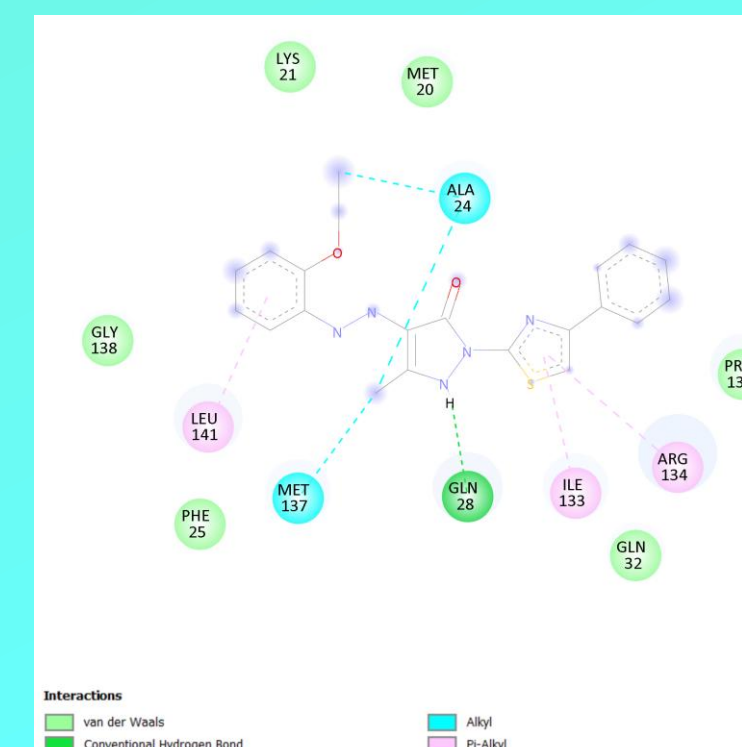
Fig 1: Structure of BaX, Naska et al, 2007.

- ❖ Common Chemotherapeutic drugs face resistance due to
 - Overexpression of P-gp, ABCB1, BCRP efflux pumps (Taxanes)
 - Missense mutation in T53 (Tumor Suppressor) (Cisplatin)
 - Mutation in Drug binding site of BCR-ABL (Imatinib)
 - Topoisomerase 2 mutation (Etoposide)
 - Enhanced transcription of gene encoding DHFR (Methotrexate)

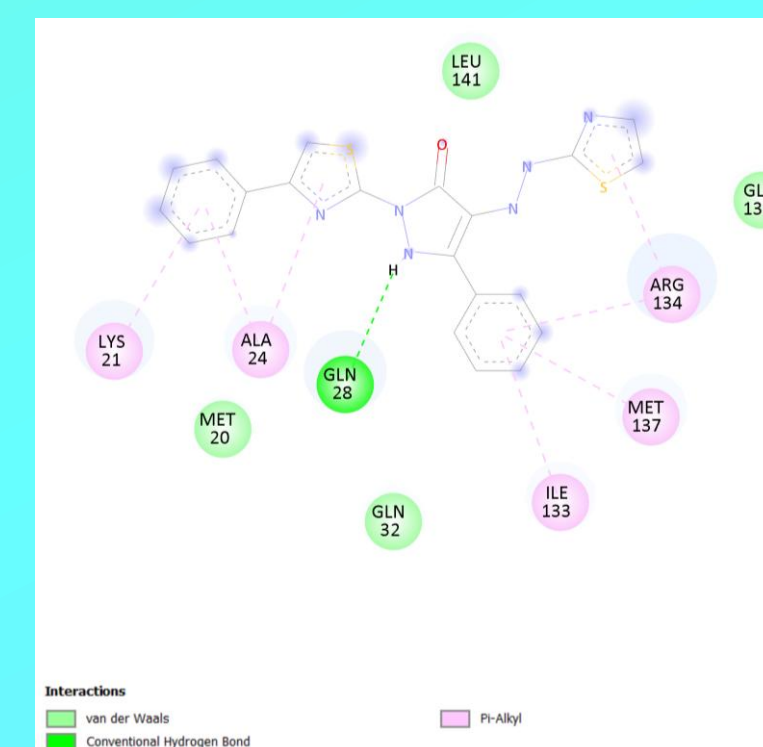
- ❖ *BaX, a protein remains in cytosol & on initiation of apoptosis move to mitochondria*
- ❖ *Forms channels by extracting lipid*
- ❖ *Releases Cytochrome C binding to it*
- ❖ *Cleavage and activation of caspase 9 and 3 leading to apoptosis.*
- ❖ *Agents like BAM7 and BTSA1 activates BaX directly, enhancing specificity*

Small Molecule Activators; Docking Analysis (2 clusters)

- ❖ BTSA1 and BAM7 affect Alpha 2 and Alpha 6 helices directly
- ❖ BAM7 relies on a strong, optimal alkyl bonds to anchor itself precisely, complemented by a broad set of interactions across the pocket, conferring stability
- ❖ The three strong alkyl bonds are at Ala 34 and Met 137
- ❖ BTSA1 serves as a characteristic activator creating a more powerful hydrophobic interaction network (dual engagement with ARG 134 and pi alkyl bond with lys21).



BAM7-BaX



BTSA1-BaX

Molecular Dynamics Simulation

❖ The BAM7-BAX (50ns) showed lower fluctuations than BTSA1-BaX complex that showed 2 states in RMSD, to confirm we extended to 100ns

❖ Binding at alpha 6 and alpha 8 residues lead to RMSF peaks (BTSA1 higher), showing strong rearrangements, with The activation being proved by peak at BH3 helix and alpha 5 loops.

❖ Interestingly, the peak at around residue 57 and 96 in BTSA1 starts very low but gradually grows and reaches peak at 50-55ns before decreasing

❖ BAM7 starts off with high flexibility and the peak suppresses a bit in the final frame. Proving that BTSA1 is more potent

• In BAM7 Diagonal line (self-correlation) is strong, rest are weak, Suggests a more localized and less cooperative residue motion

• BTSA1 Higher density of both pink (positive) and green (negative) regions → indicates greater cooperativity and inter-domain communication

In-Silico Toxicity Assay

❖ Both show hepatotoxicity & nephrotoxicity, BTSA1 has a higher probability (91.8 & 89.1% vs. 85.5 & 79.9%), showing respiratory toxicity, slightly higher clearance and bio-availability. (admetSAR)

❖ Bam7 and btsa1 both show good drug-likeness and no significant off-target interactions in SwissADME. (Complete 0 in BAM7 and 0.106% ADORA1 and ADORA2B in BTSA1)

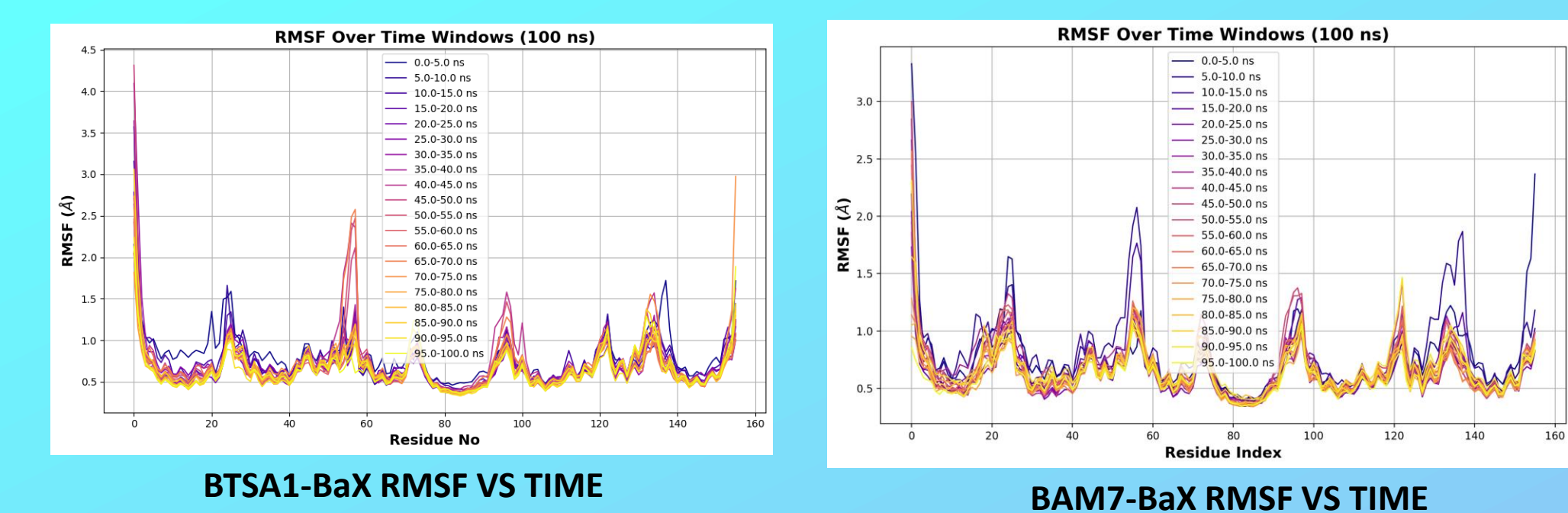
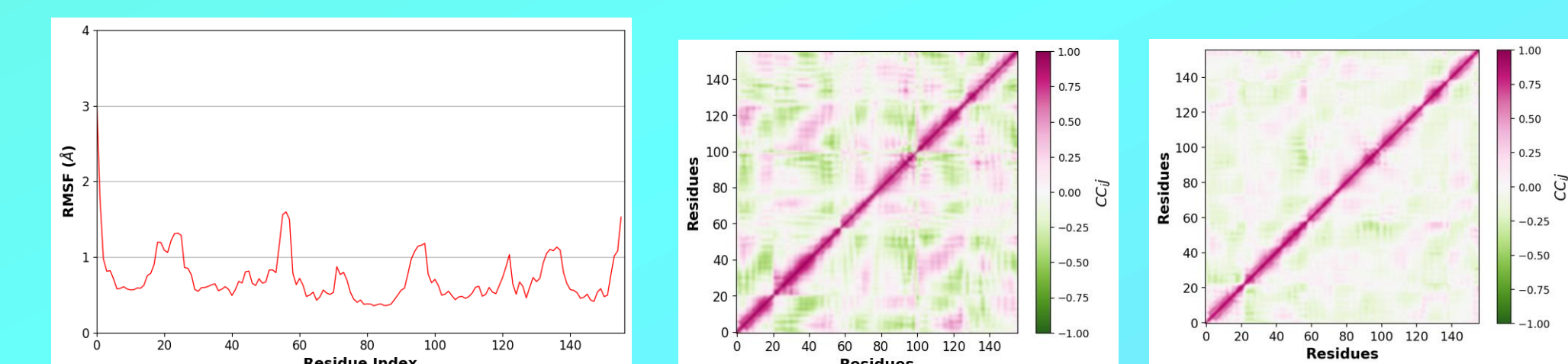
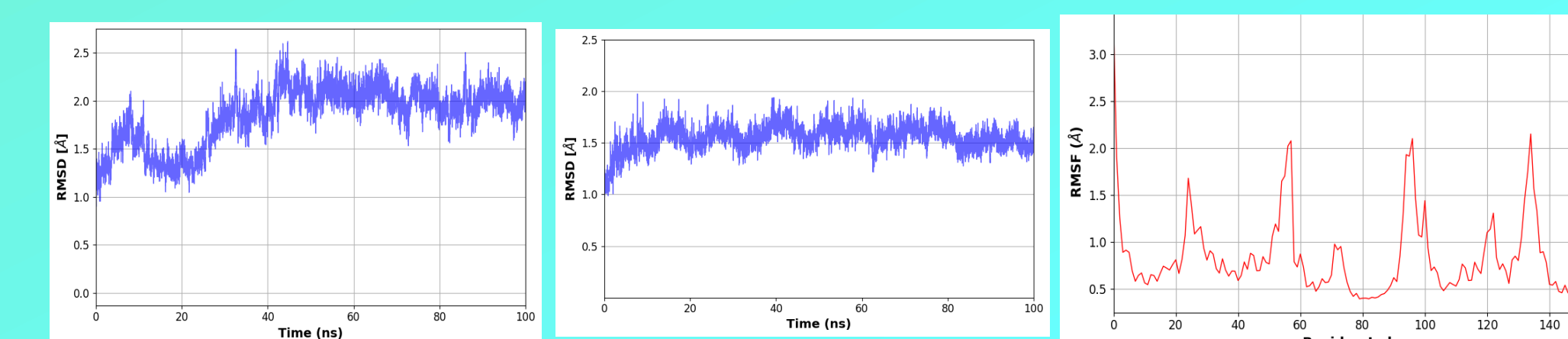
❖ One Problem Faced by BTSA1 is carcinogenicity as shown in admetSAR, but it needs clinal validation

❖ BTSA1 drives drastic conformational changes, with a higher toxicity profile

❖ It can be suitable for senescence-targeted therapies, hematologic malignancies or higher stages of metastasis where apoptosis induction is desirable.

❖ BAM7, while still inducing apoptosis, appears to be weak but controlled modulator of BAX, with fewer off-target effects and

❖ It can be used in long term therapies, pulsed therapies, synergistic treatment or in lower stages of cancer.



FUTURE PROSPECTS: Speculation of targeting Specific Biomarkers to make them viable & enhance specificity of BaX activators

- Higher Duration Molecular Dynamics Needed to further enhance the results
- *Wet-lab validation* of predicted BAM7 sensitivity across cancer cell lines using apoptosis assays and CRISPR-based gene knockouts.
- Antibody-Drug Conjugates (ADCs): Bax activators can be linked to monoclonal antibodies that recognize overexpressed surface markers (e.g., HER2 in breast cancer, EGFR in lung cancer).
- Synergistic treatment with Bcl2 inhibitors like Navitoclax

Sensitivity Model

❖ If BCL2_CRISPR < -0.5 → BAX/BCL2_Ratio = "Not Required"

❖ If MCL1_CRISPR < -0.5 → BAX/MCL1_Ratio = "Not Required"–Using BAX/MCL1 ratio without confirming MCL1 is active may lead to misclassification

❖ BaX/ BCL2 and BaX/MCL1 >1 Sensitive (IC50<100) <1 Resistant (If IC50<10)

❖ There is currently no direct platform available for predicting BAM7 sensitivity across cancer cell lines. This web app addresses that gap

❖ Across 450 cell lines the data on BAM7 sensitivity interpreted from DepMap and GDSC is provided.

❖ We need only to put a cell line, within seconds it will show the data



ACKNOWLEDGEMENT

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