A MODIFIED CDK12 INHIBITOR TARGETING TRASTUZUMAB RESISTANCE IN HER2-POSITIVE BREAST CANCER

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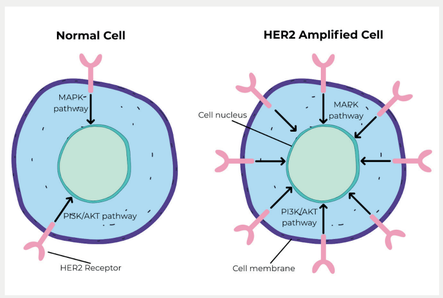
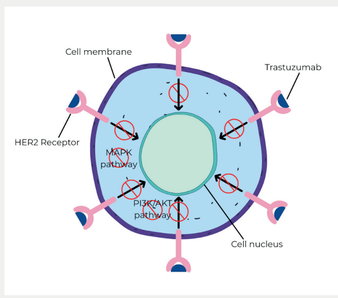
INTRODUCTION

Breast cancer alone was estimated to make up 15.5% of new cancers in 2025. A form of breast cancer, HER2 positive breast cancer is common and aggressive, characterized by the overexpression of HER2. **Although trastuzumab is the standard treatment, 50% of patients eventually develop resistance to it.** A common mechanism is by the overexpression of CDK12, which occurs in 90% of HER2 positive breast cancer. Specifically, it causes the amplification of the MAPK and PI3K/Akt pathways, the pathways that trastuzumab tries to suppress. Currently, no drugs targeting the overexpression of CDK12 are approved by the U.S. Food and Drug Administration (FDA).



HER2 Amplified Cell



Effects of Trastuzumab

OBJECTIVE

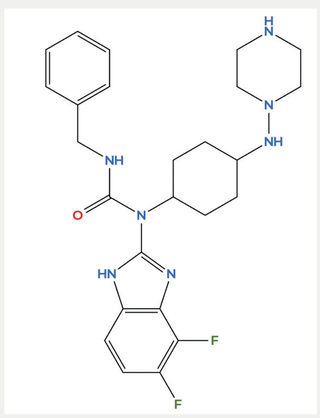
A novel, safe, and sustainable small-molecule drug targeting CDK12 will be produced, improving pharmacokinetic properties of existing drugs while ensuring the accuracy of the drug is unchanged.

METHODOLOGY

To begin, the main types of existing drugs were identified: reversible inhibitors, covalent inhibitors, proteolysis targeting chimeras (PROTACS), and molecular glue degraders. The pharmakokinetic properties of each were evaluated using the website SwissADME. A reversible inhibitor was chosen because it has strong pharmacokinetic properties and has limited side effects. Thus, CDK12-IN-2 and CDK12-IN-3, theoretical reversible inhibitors, will be modified. The main template will be CDK12-IN-2, which has higher selectivity, allowing for it to be a better baseline. This paper will also use SwissTargetPrediction, a website predicting the most likely targets of a drug.

RESULTS

By adding nitrogens, H-bond acceptors were added and the water solubility and GI absorption were improved. Moreover, adding a diflourobenzimidazole at the bottom improved LogS, LogP, and bioavailability scores while sustaining high GI absorption scores. Additionally, as shown in the table on the bottom, the novel drug was able to target molecules related to the PI3K/Akt and MAPK pathways.



Structure of the New Drug

Targeted Molecules	Relevance to PI3K/Akt or MAPK
Rho-associated protein kinases (ROCKs)	The PI3K/Akt pathway can regulate Rho protein activity, which regulates the activity of ROCKs
ADAM17	MAPK helps phosphorylate ADAM17
Serotonin receptors	MAPK regulates serotonin transporter (SERT) and Akt can regulate it as well
TNF-alpha	MAPK mediates TNF-alpha stabilization
HDACs	HDAC4 requires MAPK signaling
MAPK14	A member of MAPK

ANALYSIS

The major pharmacokinetic properties were improved, as shown in the table on the right. A limitation of the study is that this research was only conducted *in silico* using prediction models, making the need for chemical validation necessary. This is especially important as virtual simulation programs and predictive rules were used for the entire experiment, making no part of the experiment definitive. However, this still allows for opportunities to improve upon the work in clinical settings in the future.

	Optimal range	CDK12-IN-2	Novel drug
Chemical structure	N/A	CN1C=C(C=CC1=O)C2=CC=C(C=C2)N(C3CCC(CC3)NC4=NC=C(C=C4)C#N)C(=O)NCC5=CC=CC=C5	O=C(NCc1ccccc1)N(C(CC1)CCC1NN1CCNCC1)c1nc(c(F)c(cc2)F)c2[nH]1
Molecular weight (g/mol)	<500	532.64	483.56
Num. rotatable bonds	≤ 9	9	8
Num H-bond acceptors	≤ 10	4	7
Num. H-bond donors	≤ 5	2	4
Lipophilicity (LogP)	-0.7 to +5.0	4.13	3.35
Water solubility (LogS)	≥ −6	-5.67	-4.63
GI absorption	High	High	High
Lipinski druglikeness	Yes (≤ 1 violation)	Yes; 1 violation: MV>500	Yes; 0 violation
Veber druglikeness	Yes	Yes	Yes
Bioavailability score	≥ 0.55	0.55	0.55
Synthetic accessibility	< 6	4.7	4.51

CONCLUSION

This novel drug has the potential to be a sustainable treatment for a common, aggressive type of breast cancer. Specifically, after testing in more clinical settings, this drug provides the possibility of less toxic treatments due to more personalized treatments and less trial and error. Overall, it can address the issue that no drugs targeting the overexpression of CDK12 are currently approved by the FDA.

FULL PAPER AND REFERENCES