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ЗАПОРІЗЬКИЙ ДЕРЖАВНИЙ МЕДИКО-ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

МАТЕРІАЛИ

ВСЕУКРАЇНСЬКОЇ НАУКОВО- ПРАКТИЧНОЇ КОНФЕРЕНЦІЇ З МІЖНАРОДНОЮ УЧАСТЮ

«ЗАПОРІЗЬКИЙ ФАРМАЦЕВТИЧНИЙ ФОРУМ - 2024»

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HIF-1a/p300). Hence, by assessing how strongly different substances bind to these proteins, it's possible to identify the potential drug candidates, anticipate side effects, and gain insights into the molecular mechanisms of various diseases and biological processes.

So, Matthews correlation coefficients and inhibitory potency predictions (IC_{50}, 0.11-8.65 μM) were calculated for 43 derivatives of triazolo[1,5-*c*]quinazoline: carboxylic acids and esters (Fig. 1).

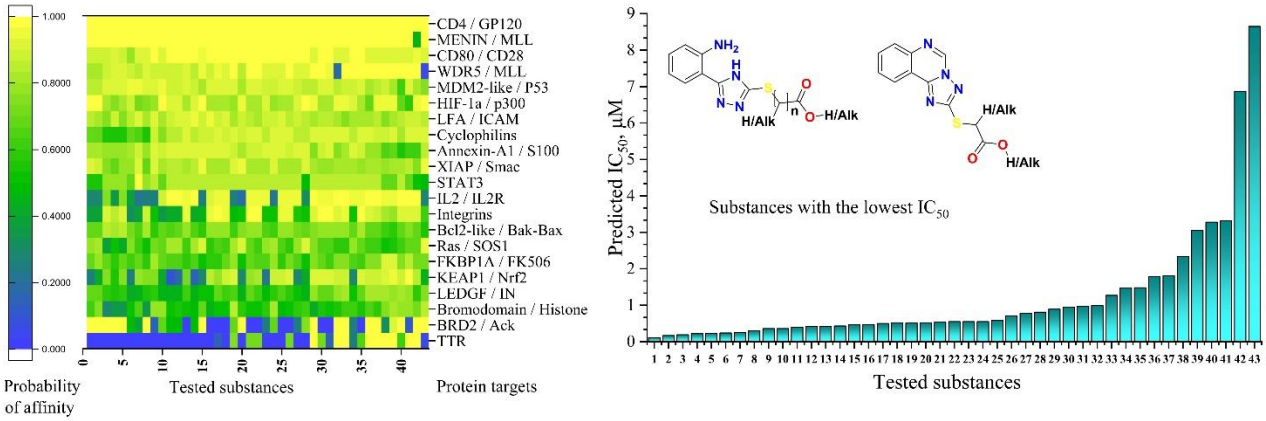

Fig. 1. Calculated Matthews correlation coefficients and average IC_{50} (μM) *via* pdCSM-PPI.

For some proteins, such as MENIN/MLL (involved in transcriptional regulation and leukemogenesis) and CD4/GP120 (their interaction is critical for HIV entry into cells), all tested substances consistently showed high affinity (MCC ≥ 0.9), while to TTR (transport thyroid hormones and retinol) had the lowest values. Besides, variable affinity patterns were observed for proteins like IL2/IL2R (cytokine signaling important for T cell proliferation and immune response), KEAP1/Nrl2 (cellular response to oxidative stress), and BRD2/Ack (transcriptional regulation), indicating that certain substances may have selectivity towards them.

Thus, these findings highlight the importance of a broad affinity profile early in drug development to predict both expected and the possibility of off-target effects. The data also offer a strong foundation for further research into the molecular mechanisms of leading substance-protein interactions and their potential therapeutic applications.

References:

1. pdCSM-PPI. Biosig. URL: https://biosig.lab.uq.edu.au/pdcsm_ppi/ (date of access: 13.09.2024).

PREDICTING CARDIOTOXICITY OF 6-(1-(R-PHENOXY)ETHYL)-3-METHYL/PHENYL-2*H*-[1,2,4]TRIAZINO[2,3-*C*]QUINAZOLIN-2-ONES

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Introduction. Nowadays, predicting cardiotoxicity of novel synthesized compounds is crucial, especially in light of COVID-19's cardiovascular impacts: ischemic heart disease, heart failure, arrhythmias, myocarditis, etc. [1]. That's why there is a need to avoid additional cardiac stress from any medications.

Aim. To identify the potentially cardiotoxic novel synthesized compounds early, in order to reduce late-stage drug development failures, and to make the drug development process cost-effective.

Materials and Methods. The cardioToxCSM tool of Biosig Lab [2] was used to predict six types of cardiac toxicity of methyl, methoxy, chloro, fluoro, and trifluoromethyl derivatives of 6-(1-(R-phenoxy)ethyl)-3-methyl/phenyl-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones (Fig. 1).

Results. All substances were found to be safe for arrhythmia, cardiac failure, heart block, and hERG toxicity. Interesting, that the only substance without any cardiotoxicity appeared to be **158**, bearing CF_3 as R, when R^1 = Me, while its analogue **148** with R^1 = Ph was predicted to cause myocardial infarction (Fig. 1).

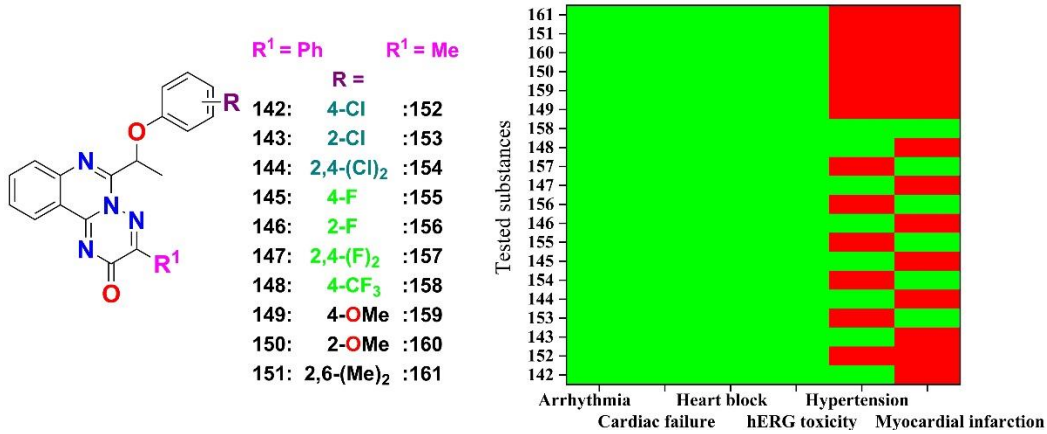

Fig. 1. The structural formulas of novel compounds and their predicted cardiotoxicity, where green indicates safe compounds and red indicates toxic ones.

Furthermore, it was found that all phenyl substituted series **142-151** would result in myocardial infarction, but their methylated series **152-161** would produce hypertension. Additionally, it appears that **152** and all methyl and methoxy derivatives (**149**–**151**, **159**–**161**) are the least tolerated, resulting in both forms of toxicity.

Conclusions. The results suggest that modifications to the R^1 and R^2 substituents can have a significant impact on the cardiotoxicity profile of these compounds. Substances might influence hypertension or myocardial infarction, so have several significant implications, and the following measures should be taken into consideration: further safety research, additional structure modifications, evaluation of drug delivery methods, dose adjustments, and individual risk assessment.

References:

1. Cardiac Manifestations of Coronavirus (COVID-19) - StatPearls - NCBI Bookshelf. *National Center for Biotechnology Information*. URL: https://www.ncbi.nlm.nih.gov/books/NBK556152 (date of access: 05.11.2024).

2. cardioToxCSM | Home. *Biosig | Home*. URL: https://biosig.lab.uq.edu.au/cardiotoxcsm (date of access: 05.11.2024).

PREDICTING CARDIOTOXICITY OF HETARYL/CYCLOALKYL/SPIRO [1,2,4]TRIAZOLO[1,5-*C*]QUINAZOLINE CARBOXYLIC ACIDS' SALTS BY MACHINE LEARNING

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Introduction. Machine learning (ML) to predict cardiotoxicity can be effectively used for the prediction, diagnosis, and treatment of cardiotoxicity [1]. ML models can integrate different types of data to provide a more comprehensive assessment of toxicity, than traditional methods.

Aim. To use ML tools to identify potentially cardiotoxic compounds among novel synthesized ones in the early stages of development, saving time and resources.

Materials and Methods. CardioToxCSM tool of Biosig Lab [2] was used to predict six types of cardiac toxicity outcomes, including arrhythmia, cardiac failure, heart block, hERG toxicity, hypertension, and myocardial infarction of 2-(hetaryl/cycloalkyl)-[1,2,4]triazolo[1,5-*c*]quinazolin-5-