СЕКЦІЯ 7. ВПРОВАДЖЕННЯ ТЕХНОЛОГІЙ ШТУЧНОГО ІНТЕЛЕКТУ В ГАЛУЗІ ОХОРОНИ ЗДОРОВ'Я

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MACHINE LEARNING-DRIVEN IDENTIFICATION OF MULTI-TARGETED LEAD COMPOUNDS AMONG 5,6-DIHYDROTETRAZOLO[1,5-C]QUINAZOLINES FOR NEURODEGENERATIVE AND NEGLECTED TROPICAL DISEASES

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In the rapidly advancing field of drug discovery and development, computational methods have become indispensable tools for accelerating the identification and optimization of potential drug candidates. Among these methods, machine learning models have gained significant traction due to their ability to uncover intricate patterns and relationships within large datasets, thereby enabling accurate predictions of biological activity.

One such powerful tool is MolPredictX [1, 2], an online platform that leverages state-of-the-art machine learning algorithms to predict the biological activities of molecules against parasitic (*Trypanosoma* and *Leishmania*), viral (Dengue, Sars-CoV and hepatitis C), pathogenic yeast (*Candida albicans*), bacterial (*Salmonella enterica* and *Escherichia coli*), and Alzheimer disease enzymes. The comprehensive data integration from indexed scientific articles enables the models to capture a broad range of structure-activity relationships, enhancing their predictive power. It can rapidly evaluate vast chemical libraries, which saves considerable time and resources compared to traditional high-throughput screening methods. The models employed by MolPredictX are

regularly updated to incorporate the latest experimental data, ensuring that the predictions remain accurate and aligned with the current state of knowledge in the field. And it offers a user-friendly web interface, making it accessible to researchers with varying computational expertise, thereby democratizing the use of advanced machine learning techniques in drug discovery.

Hence, calculations on MolPredictX [2] with canonic SMILES of reported earlier antimicrobial 5,6-dihydrotetrazolo[1,5-*c*]quinazolines [3] (with additional **c11**, R = 3-NO_2, R^1 = Me, and **c12,** R = H, R^1 = Pr) yielded outcomes, illustrated in Fig. 1 and 2.

Alzheimer's Disease Targets: Substances **a1**, **a2**, **b1-3**, **c1**, **c2**, **c4-8**, **c11**, and **d1-3** (only substances with probability 1.0 are mentioned in the text) showed the highest potential for the NADPH (nicotinamide adenine dinucleotide phosphate), target related to Alzheimer's. And **a1**, **a2**, **b1**, **c3**, **c4**, **c7**, **c8**, **c10**, **c12**, and **d1-3** – for the iNOS (inducible nitric oxide synthase) target. The moderate probability (0.8) against COX2 (cyclooxygenase-2) was detected only for **d2**, while no activity was observed against JNK-3 (c-Jun *N*-terminal kinase 3), and PDE5 (phosphodiesterase type 5) by all.

Chagas Disease Targets: High potential was observed for many substances against the tripomastigote form of Chagas disease, including **a2, b1, c1, c3, c8-12**, and **d1**. However, only **c6** with probability of 0.8 was detected against its amastigote form. Regarding the amastigote of *Trypanosoma cruzi*, a smaller number of compounds, **b3**, **c4**, and **d1**, showed a probability of 1. Additionally, some activity was predicted against the *T. cruzi* epimastigote form, including **b2**, **c1**, **c2**, and **d2**.

Leishmania Targets. Notable activity potential against the *L. donovani* amastigote was observed by **c7, c8, c11**, and **d3**. Moderate probabilities are found against its promastigote form with **b2** and **b3** of highest potential.

Other Targets. Substantial activity against *Alphis gossypii* was predicted by most of substances (with **a1**, **a2**, **b3**, and **c12** of probability 1), some activity – against hepatitis C type 1 (**c1** and **b3**). Moderate to low activities against SARS-CoV, *E. coli*, and *Salmonella enterica* (**c10**). Low to negligible proper against *Dengue larvicida* (**c4**), *C. albicans* (**c12**), *L. amazonensis* amastigote and promastigote.

Summing up, 5-(R-phenyl)-5-methyl-5,6-dihydrotetrazolo[1,5-*c*]quinazolines, **c7**, **c4**, and **c10**, demonstrated the widest and highest total potential across multiple important targets like Alzheimer's (NADPH, and iNOS), Chagas disease (tripomastigote), *Leishmania* (*L. donovani* amastigote), and others (Fig. 2). While additionally other substituted **c6-c8**, **c11**, 6'*H*-spiro[indoline-3,5'-tetrazolo[1,5-*c*]quinazolin]-2-one's derivative **b3,** and 5-methyl-5-(pyridine-2-yl)-5,6-dihydrotetrazolo[1,5-*c*]quinazoline (**d1**) also demonstrated high probability to the above-mentioned targets.

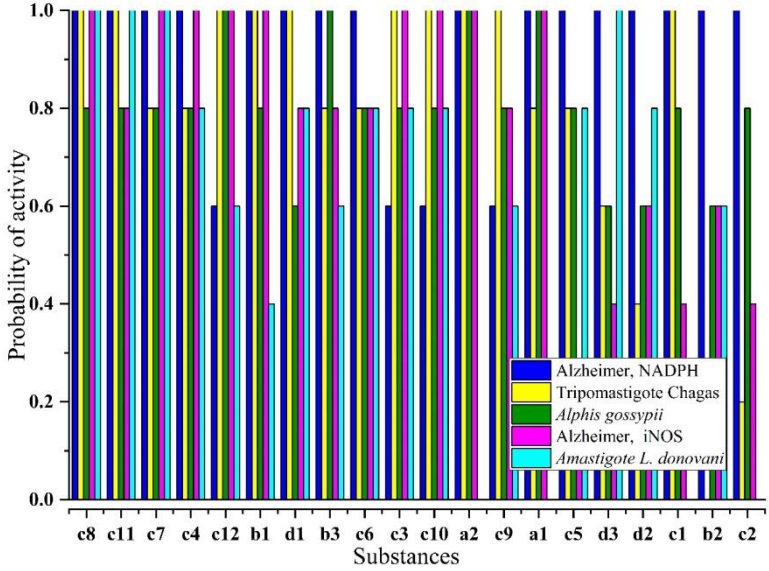

Fig. 1. Calculated highest activity probability of 5,6-dihydrotetrazolo [1,5-*c*]quinazolines [3] on website MolPredictX [1, 2] from the highest (c8) to lowest (c2) total values for the 5 best targets

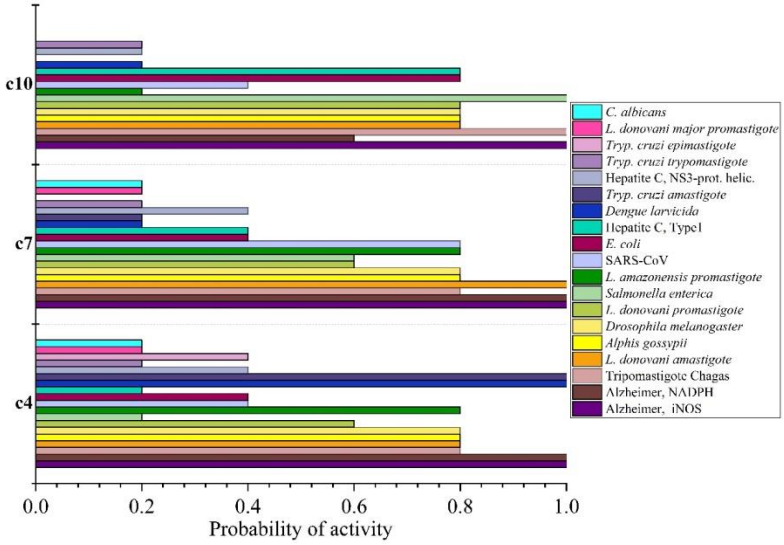

Fig. 2. Results of predicted activity probability of lead-compounds c4, c7, and c10

These compounds could serve as starting points for further optimization and development of potential therapeutic agents targeting neurodegenerative and neglected tropical diseases. It is important to note that these are preliminary predictions based on computational models, and further experimental validation would be necessary to confirm the actual biological activities and efficacies of these substances. Additionally, factors such as toxicity, bioavailability and potential off-target effects should be thoroughly evaluated.

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