Comprehensive In Silico Evaluation of Physicochemical and Pharmacokinetic Profiles of Novel Thienopyrimidine Derivatives for Potential Neuropharmacological Use

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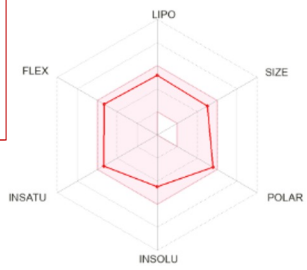
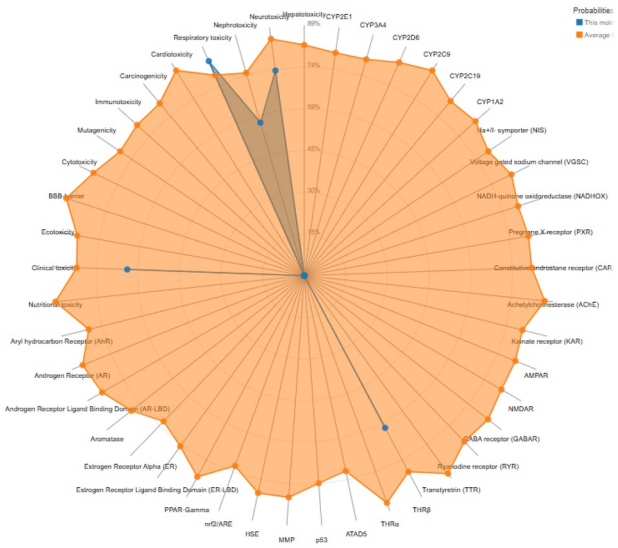
Introduction. The search for novel compounds with neuroprotective potential remains a key focus of modern neuropharmacology and medicinal chemistry. Thienopyrimidine derivatives are of particular interest due to their broad pharmacological spectrum, including anti-inflammatory, antioxidant, antibacterial, and enzyme-inhibitory properties relevant to neurodegenerative diseases such as Alzheimer's and Parkinson's. At the preclinical stage, in silico prediction of ADMET parameters enables early assessment of drug-likeness, bioavailability, and safety, thereby optimizing the development of promising neuropharmacological agents.

Materials and methods. In silico ADMET modeling of seven novel 4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylate derivatives was performed using the SwissADME platform. Potential toxicity was further evaluated with ProTox-3.0, which utilizes machine learning and QSAR-based predictive models.





Results and discussion. All investigated compounds exhibited acceptable physicochemical parameters: molecular weight ranged from 385 to 459 Da, TPSA from 118 to 137 Å², and consensus LogP from 2.82 to 3.91. According to the Lipinski, Ghose, Veber, and Muegge criteria, all derivatives satisfied the requirements of drug-likeness. High gastrointestinal absorption was predicted for all compounds, while blood–brain barrier (BBB) permeability was observed for most derivatives except 4d, which had a higher polarity (TPSA > 131 Å²).

The predicted toxicity index for all compounds was 4 (LD_{50} ≈ 1000 mg/kg, class IV – "harmful if swallowed"), remaining acceptable for preclinical evaluation. ProTox-3.0 results showed an overall favorable toxicological profile: compounds were inactive toward hepatotoxicity and cardiotoxicity, with only moderate neuro- and respiratory toxicity, likely reflecting their neuronal activity. Major endpoints (carcinogenicity, mutagenicity, cytotoxicity, immunotoxicity, ecotoxicity) were inactive, indicating low genotoxic and oncogenic risks. No interactions were predicted with key nuclear receptors or stress-response pathways, suggesting minimal oxidative or DNA damage potential. Weak activity toward thyroid receptor β was not toxicologically significant. The compounds were predicted inactive toward major CYP450 isoforms, implying good metabolic stability and low risk of drug–drug interactions.

Conclusions. The obtained in silico data demonstrate that the synthesized 4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylate derivatives possess favorable physicochemical, pharmacokinetic, and toxicological properties. They exhibit good predicted bioavailability, BBB permeability, and low toxicity, supporting their potential as promising candidates for further preclinical studies in the field of neuropharmacology.