Національна академія наук України
Фізико-хімічний інститут ім. О.В. Богатського НАН України
Південний науковий центр НАН та МОН України
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XXIII Наукова молодіжна конференція «Проблеми та досягнення сучасної хімії», присвячена 165-річчю з дня народження М.Д. Зелінського

ЗБІРНИК ТЕЗ ДОПОВІДЕЙ

11-13 травня 2026

ОДЕСА

TETRAZOLO[1,5-*c*]QUINAZOLINE DERIVATIVES AGAINST *TRITRICHOMONAS SUIS* IMPDH ACTIVE SITE AS A SURROGATE MODEL FOR ANTI-*NAEGLERIA* DRUG DISCOVERY

ANTYPENKO L.[1], ANTYPENKO O.[2]

[1]*Independent Researcher, Zaporizhzhia, Ukraine*

[2]*Zaporizhzhia State Medical and Pharmaceutical University, Zaporizhzhia, Ukraine*

e-mail: antypenkol@gmail.com

Primary amoebic meningoencephalitis (PAM), caused by the free-living thermophilic amoeba *Naegleria fowleri*, represents one of the most lethal infectious diseases known, with a fatality rate of about 97–98% [1, 2]. Because of the rarity of the disease, pharmaceutical companies do not pursue new drug discovery, yet the infection is possibly underreported, and identifying a more effective drug would have a direct impact on those suffering from this condition [3]. Current standard of care involves a combination of amphotericin B, azithromycin, fluconazole, rifampin, miltefosine, and dexamethasone; however, development of efficacious and safe drugs for PAM treatment remains an unmet medical need [4].

Inosine 5′-monophosphate dehydrogenase (IMPDH) is a tractable drug target in protozoan parasitology, catalyzing the NAD^+-dependent oxidation of IMP to xanthosine 5′-monophosphate (XMP) — the committed, rate-limiting step governing guanine nucleotide supply, cellular proliferation, and immune signaling [5]. The crystal structure deposited under PDB entry 1PVN resolves the *Tritrichomonas suis* IMPDH catalytic domain in complex with the transition state analogue mizoribine 5′-monophosphate (MZP) at 2.0 Å, with MZP, Cys319, and a water molecule arranged in closed-flap, transition-state-like geometry [6]. Although *T. suis* (Parabasalia) and *N. fowleri* (Percolozoa) occupy distinct phyla within Excavata, shared dependence on *de novo* purine biosynthesis provides structural justification for 1PVN as a surrogate docking target. *T. foetus* illustrates this dependency: its sole phosphoribosyltransferase preferentially salvages hypoxanthine, sustaining IMPDH reliance despite nominal xanthine/guanine salvage capacity, and IMPDH inhibitor resistance requires two discrete loss-of-function mutations [7].

To evaluate inhibitory potential of novel compounds, blind structure-based docking at CB-Dock2 website was performed for a series of tetrazolo[1,5-*c*]quinazoline-5-thio derivatives (halogenated benzyls (lab.# 99–104, 106–111); benzothiazole-substituted acetamides (96, 97, 112); esters (56, 65); thiol (63sh); thioether (60); and 5,6-

dihydrotetrazoles (313, 316)) [8] against the 1PVN structure, with MZP serving as the reference. Template docking yielded an RMSD of 0.02 Å, confirming reliable reproduction of the native binding pose.

The MZP pocket affinity scores at cavities 3 and 4 (the two crystallographically observed binding sites among five determined by blind docking) were −8.6 and −8.3 kcal/mol, respectively, serving as the primary benchmark. At cavity 3, compounds 101, 109, and 112 achieved the most favorable scores (−9.2 kcal/mol each), surpassing MZP by 0.6 kcal/mol, while compound 96 produced the highest affinity across the entire dataset at cavity 4 (−10.7 kcal/mol), exceeding the reference by 2.4 kcal/mol. Compound 109 also performed well at cavity 4 (−8.9 kcal/mol). These compounds may warrant further docking analysis or experimental investigation, whereas 5,6-dihydrotetrazoloquinazoline derivatives 313 and 316 underperformed at all sites and would likely be deprioritized.

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