

Міністерство охорони здоров'я України
Національний фармацевтичний університет
ДНТ «Львівський національний медичний університет імені Короля Данила»
Українське товариство медичної хімії

Міжнародна наукова конференція

Modern chemistry of medicines

15-17 жовтня 2026 р.
м. Харків, м. Львів, Україна

Посвідчення Державної наукової установи «Український інститут науково-технічної експертизи та інформації» № 828 від 17.11.2025 р.

Docking of 5,6-dihydrotetrazolo[1,5-*c*]quinazolines to serine palmitoyltransferase

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Introduction. Invasive fungal infections remain difficult to treat: few antifungal classes exist and resistance to all of them is documented in prevalent *Candida* pathogens. Serine palmitoyltransferase (SPT), catalysing the rate-limiting step of sphingolipid biosynthesis, was recently proposed as the target of the Z247611722, *N*-(1,3-dimethyl-2,4,7-trioxo-1,3,4,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-6-yl)-4-fluoro-benzamide [1]. 5,6-Dihydrotetrazolo[1,5-*c*]quinazolines are active against *Candida albicans* [2] and clinical *Nakaseomyces glabrata* isolates [3], yet the molecular basis of this activity remains uncertain. Whether SPT is a plausible target is examined here.

Materials and methods. Twenty previously reported 5,6-dihydrotetrazolo[1,5-*c*]quinazolines were studied, with the 4-fluorobenzamide as reference. Structures were drawn in ChemDraw Professional 15.0 and saved in mol format. The cryo-EM structure of the *Saccharomyces cerevisiae* SPT–Orm1 monomer complex (PDB 8C80) served as the receptor [4]. Blind docking used the curvature-based CB-Dock3 server [5]. Cavity volumes, contact residues and distances to the pyridoxal-5′-phosphate (PLP) cofactor were recorded, the poses of the reference and the strongest-scoring derivative examined, and compared with minimum inhibitory concentrations reported earlier [2,3].

Results and discussion. Five cavities of identical volume and position were returned in all twenty-one runs. The 4-fluorobenzamide attained its strongest affinity in cavity 1 (−9.2 kcal/mol; −7.2 to −8.7 elsewhere). This cavity encloses the PLP cofactor, its contact residues deriving chiefly from Lcb2 and Lcb1, at the catalytic interface of the subunits. The remaining cavities lie 19.8–39.2 Å from the cofactor; cavity 5, though giving the most negative mean affinities, lies at the Orm1–Lcb1 interface, so cavity 1 was selected.

Only two spiro[indoline-tetrazolo[1,5-*c*]quinazolin]-2-one 1-acetamides exceeded the reference, those bearing 2-(trifluoromethyl)benzyl (−10.3 kcal/mol) and 3-chlorophenyl, and the 5-(3-carboxyphenyl)-5-methyl derivative equalled it; the remaining seventeen fell between −8.7 and −7.2 kcal/mol. Neither the reference nor the trifluoromethylbenzyl acetamide approaches the cofactor within 11.5 Å, however; their centroids lie 18.5 Å apart with no shared contact residue within 4.0 Å, so the two occupy distinct peripheral subsites rather than the catalytic centre. No significant correlation with reported antifungal activity was found against *N. glabrata* [3] (Spearman ρ −0.43 to +0.43) or *C. albicans* [2] (−0.53 to +0.46; $p \geq 0.33$), and median affinities of active and inactive compounds did not differ: the 5-(4-bromophenyl)-5-methyl derivative, the most potent compound *in vitro* (0.37 μM), scored −7.5 kcal/mol, whereas the best-scoring trifluoromethylbenzyl acetamide was inactive.

Conclusions. The 4-fluorobenzamide binds preferentially in the cavity enclosing the PLP cofactor, yet neither its pose nor that of the best-scoring acetamide approaches the catalytic centre, and the calculated affinities bear no relationship to the antifungal activity measured earlier. SPT is therefore not supported as the target of this series; direct enzyme inhibition assays are required.

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