Chaxines from the edible mushroom *Agrocybe chaxingu* engage the RORγt inverse-agonist pocket: an in silico docking and ADMET study

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Abstract

The retinoic acid receptor-related orphan receptor gamma t (RORγt) is the master transcription factor of Th17 differentiation and, through the Th17/IL-17 axis, a validated small-molecule target in autoimmune and inflammatory diseases including psoriasis, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease and rheumatoid arthritis; its ligand-binding domain (LBD) accommodates sterols, and natural products such as diosgenin act as RORγt inverse agonists. Chaxines are ergosterol-derived degraded sterols from the edible mushroom *Agrocybe chaxingu* with documented osteoclast-formation–suppressing activity, and because the RORγt-driven axis also promotes osteoclastogenesis and inflammatory bone loss, RORγt is a plausible but untested molecular target for these metabolites. Chaxines B–E were evaluated as candidate RORγt ligands by structure-based docking and consensus ADMET profiling. Verified structures were docked into the RORγt LBD inverse-agonist pocket (PDB 9N9L, 1.64 Å) using AutoDock Vina with triplicate seeds, benchmarked against the co-crystallized clinical inverse agonist A1BW2 and the fungal sterol ergosterol; the protocol was validated by redocking A1BW2 (RMSD 1.49 Å), and ADMET was assessed with SwissADME, ADMETlab 3.0 and ProTox 3.0. All chaxines occupied the same orthosteric pocket as A1BW2, contacting key residues His479, Trp317 and Phe377/378. Their binding affinities (−9.7 to −10.3 kcal/mol) were sterol-like, below the reference A1BW2 (−11.3) and comparable to ergosterol (−10.3), with chaxine B ranking highest. The chaxines showed favourable predicted acute toxicity (ProTox class 5; LD50 4216 to 6400 mg/kg), markedly safer than ergosterol (class 2), together with good intestinal absorption and low mutagenicity, while high lipophilicity remained the main liability. Overall, these mushroom-derived metabolites engage the validated RORγt inverse-agonist pocket with clinical-ligand-like contacts and a favourable safety profile, supporting them as starting scaffolds for Th17/IL-17-axis modulation; experimental and molecular-dynamics validation are warranted.

Keywords: RORγt, molecular docking, *Agrocybe chaxingu*, chaxines, Th17/IL-17 axis