

# CHEMINFORMATIC BIOPROSPECTION UNVEILS P.AERUGINOSA LASR QUORUM SENSING SYSTEM MODULATORS FROM THE METABOLOMIC MILIEU INSOUTH AFRICAN PLANTS

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South African plants with antimicrobial activity consist of bioactive molecules that could be explored in novel antimicrobials discovery and development. These plants may be targeted against the key quorum sensing (QS) system (LasR transcription regulatory protein) of a critical priority pathogen like *Pseudomonas aeruginosa*. Hence, this study compiled 1211 metabolites reported from South African plants with antimicrobial action, assessed binding affinities for LasR using advanced computational methods. Molecular docking identified 5 lead metabolites (oxyavicine, mamegakinone, elliptinone, diospyrol, benzo- $\alpha$ -pyrene) with best binding poses against the *P. aeruginosa* LasR target, with docking scores ranging from -13.9 to -12.5 kcal/mol, relative to the azithromycin standard (-3.7 kcal/mol). Pharmacokinetics predictions showed all leads conformed to the Lipinski rule of 5 (Ro5), with only oxyavicine able to cross the blood-brain barrier. All leads had synthetic accessibility scores of  $\leq 5$ , and molecular fingerprinting revealed highest substructural similarity scores of 0.6 (elliptinone and mamegakinone), and 0.9 (diospyrol, non-conformer) relative to the standards (0.2). MD simulation showed closest  $\Delta G_{bind}$  for diospyrol and elliptinone at -46.86 kcal/mol and  $-45.84 \pm 4.45$  kcal/mol, respectively, compared to the standard (-48.38 kcal/mol). All lead interacted with key residues (Trp55, Tyr56, Trp60, Asp73, Thr75, Ser129). A high number of total, hydrogen, and hydrophobic bonds were key to ensuring the thermodynamic compactness and stability of ligand at the LasR active site. The identified plant-based lead products could be the key mechanistic contributors to the antimicrobial activity reported for the plants they are found in. These South African plants'-based bioactives could be further explored as novel antibacterials for LasR QS system modulation following added in vitro and in vivo validations.

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