Title: Leveraging GABA and Muscimol Binding Mechanisms to Enhance the Treatment Landscape for Neurodegenerative Disorders.

Presenting author name: Abdul Rashid Issahaku

Affiliation details of Presenting author:

Department of Chemistry, University of the Free State, 205 Nelson Mandela Avenue, Bloemfontein 9301, South Africa

Co-authors' details: Anke Wilhelm[a], Marietjie Schutte-Smith[a], Elizabeth Erasmus[a] Anwar Noreljaleel[a], Az-Eddine El Mansouri[a], Sophia Khom-Steinkellner[b] and HendrikVisser[a]

[a]Department of Chemistry, University of the Free State, 205 Nelson Mandela Avenue, Bloemfontein 9301, South Africa.

[b]Department of Pharmaceutical Sciences, University of Vienna, Josef-Holaubek-Platz 2 UZA2 2E360 A-1090 Vienna, Austria.

Abstract:

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the mammalian central nervous system, modulating neuronal excitability and playing a key role in maintaining neural homeostasis. The $GABA_A$ receptor, a ligand-gated ion channel, is the main target for GABA and related agonists. One of the most well-studied GABA analogs is muscimol, a naturally occurring isoxazole derivative in certain mushrooms. Muscimol exhibits potent agonistic properties at $GABA_A$ receptors and has been instrumental in advancing our understanding of GABAergic signaling. Despite decades of research, the molecular mechanisms governing the binding and activation of $GABA_A$ receptors by GABA and muscimol remain incompletely understood. This knowledge gap presents a barrier to the rational design of GABA-mimetic drugs for therapeutic applications.

In this study, we employed integrated computational techniques to elucidate GABA and muscimol binding mechanisms at the $GABA_A$ receptor. Molecular docking studies, and extensive molecular dynamics (MD) simulations, were used to characterize the ligand-receptor interactions at the atomic level. Our analysis highlighted critical differences in the binding modes of GABA and muscimol, identifying key interactions with residues in the $GABA_A$ receptor's orthosteric site that may be leveraged to design novel GABA-mimetic compounds. These insights were then applied to predict and model novel GABA-mimetic compounds which were validated through in vivo GABA activity testing and Zebra fish toxicity studies.

This work provides valuable insights into the receptor's pharmacology by dissecting the structural and functional aspects of $GABA_A$ receptor-ligand interactions. We further identified several druggable hotspots within the receptor's binding pocket that can also be targeted for developing novel small-molecule agonists or modulators with improved specificity and

pharmacokinetic properties. These GABA-mimetic compounds have the potential to serve as therapeutic agents for a variety of neurological and psychiatric disorders, including Alzheimer's disease, and possibly other neurodegenerative conditions, where dysregulation of GABAergic neurotransmission is implicated.

The results of this study not only contribute to a deeper understanding of $GABA_A$ receptor function but also lay the foundation for the rational design of new therapeutic agents. The identification of novel GABA-mimetic small molecules could ultimately enhance the treatment landscape for disorders rooted in GABAergic dysfunction, offering more targeted and effective therapeutic options.

Biography

Abdul Rashid Issahaku is a postdoctoral research fellow at the Department of Chemistry at the University of the Free State in South Africa. His research is focused on protein-protein interactions, ligand-protein interactions, and the discovery of novel small molecules from natural products against neurodegenerative diseases and cancer through computational models. Abdul Rashid has over 30 research publications in peer-reviewed journals in this area of study. Abdul Rashid holds a PhD and master's in pharmaceutical Chemistry from the University of Kwazulu-Natal in South Africa in 2023 and 2020 respectively and Honors in Medical Laboratory Science from the University of Cape Coast, Ghana in 2015.