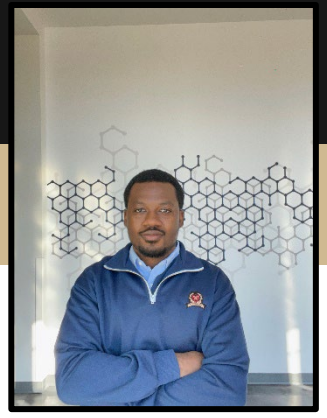

ORGANIC SEMINAR

Desmond Akwata

Graduate student | Sintim group | Purdue University

"Design and Development of Small Molecule Kinase Inhibitors Targeting TAK1 for Multiple Myeloma Therapy"

Multiple myeloma (MM) is a hematologic malignancy characterized by the abnormal proliferation of plasma cells, which contribute to extensive bone destruction and enhanced angiogenesis. MM cells suppress osteoblast differentiation while promoting osteoclastic activity, creating an imbalance that facilitates disease progression. Among the key molecular drivers of MM, the transforming growth factor-β activated kinase (TAK1) has been found to be constitutively upregulated and phosphorylated in MM cells and patient samples. TAK1 plays a critical role in cellular processes such as immune response, inflammation, survival, and differentiation. Its activation is mediated by receptor-associated proteins such as TGF-β receptors and interleukin-1 receptors, leading to downstream signaling cascades involving NF-κB, p38, MAPK, ERK, and STAT3, which regulate key oncogenic factors. Studies have shown that the inhibition of TAK1 suppresses these signaling pathways, leading to reduced MM cell proliferation and angiogenesis.

Despite the potential of TAK1 as a therapeutic target, currently available TAK1 inhibitors, such as OTS964, 5Z-7-Oxozeaenol, Ponatinib, and Takinib, exhibit limited potency, with GI50 values in the micromolar range, making effective clinical application challenging due to dose-limiting toxicities. To address this, we have designed and synthesized novel imidazo [1,2-b] pyridazine derivatives with appropriate aryl substitutions at position-3 and morpholine substitutions at position-6. Our lead compound demonstrates potent TAK1 inhibition with an IC50 of 55 nM, outperforming Takinib (IC50 = 187 nM). Furthermore, the lead compound and its analogs effectively inhibit the growth of MM cell lines MPC-11, RPMI-8226 and H929, with GI50 values as low as 30 nM. In vivo efficacy results show that our compounds significantly reduce tumor growth inhibition suggesting strong anti-tumor activity.

Given the need for targeted therapies in MM, particularly for patients who progress beyond proteasome inhibitors, anti-CD38 antibodies, and immunomodulatory agents, our findings provide a promising avenue for the development of potent TAK1 inhibitors as anti-MM therapeutics.