Oral Presentation

Targeting Acute Myeloid Leukemia via FLT3 Kinase Inhibition: Structural Optimization and MD Simulation Study of Benzimidazole-Based Derivatives

Eman M. E. Dokla

Pharmaceutical Chemistry Department, Faculty of Pharmacy, Ain Shams University, Abbassia, Cairo 11566, Egypt, E-mail: emanelawady@pharma.asu.edu.eg.

ABSTRACT: Acute myeloid leukemia (AML) is an aggressive blood cancer with poor survival rates in adults, posing a significant economic burden. FMS-like tyrosine kinase 3 (FLT3) mutations are linked to poor prognosis and resistance to current FLT3 inhibitors, underscoring the need for new treatments. We previously identified a benzimidazole-based FLT3 inhibitor, **4ACP**, with nanomolar activity against FLT3-WT and FLT3-ITD and FLT3-TKD mutants, showing selective cytotoxicity in FLT3-ITD$^+$ AML cell lines. In our recent study, a detailed structure-activity relationship (SAR) analysis of **4ACP** led to the identification of compound **22b** which exhibited sub-nanomolar activity against FLT3-TKD(D835Y) (IC_{50} = 0.48 nM) and potent antiproliferative effects on FLT3-ITD$^+$ AML cell lines, with IC_{50} values of 16.1 nM and 10.5 nM against MOLM-14 and MV4-11, respectively. It also showed strong activity against MOLM-14-D835Y and MOLM-14-F691L mutant cell lines, with IC_{50} values of 26.5 nM and 160.3 nM. Compound **22b** induced dose-dependent inhibition of ERK, STAT5, and S6 phosphorylation, G0/G1 cell cycle arrest, and apoptosis at low nanomolar concentrations in MOLM-14 and MOLM-14-D835Y cells. Additionally, **22b** was more selective for FLT3-driven cell lines, showing reduced activity against FLT3-WT cell lines K-562 and HL-60, and exhibited around 80-fold selectivity for FLT3-TKD(D835Y) over KIT, indicating lower myelosuppression potential. Molecular dynamics studies of **4ACP** and **22b** explained the significant activity changes due to structural alterations. These findings establish **22b** as a potent mutant FLT3 inhibitor, warranting further investigation and optimization to target resistant AML.

Alexandria Journal of Science and Technology, 2025, **3**(2), 127–127
Online ISSN: 2974-3273
DOI: 10.21608/AJST.2025.452265