# MOLECULAR FIELD ANALYSIS AND DYNAMIC SIMULATION STUDIES OF 1,5-DISUBSTITUTED PYRAZOLINE-BASED MAO-A INHIBITORS FOR THE MANAGEMENT OF DEPRESSION

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**ABSTRACT**

Depression, along with grief and anxiety, is currently one of the most common mental illnesses. It was placed 25th among the major diseases. QSAR (CoMFA) of 37 compounds with MAO-A inhibitory activity yielded the most significant QSAR model, m.3, with $r^2$= 0.963, SDEC= 0.129, $q^2$ = 0.742, SDEP= 0.34. Using the lead likeness matrix, thirty-seven 1,5-disubstituted MAO-A inhibitors were developed and tested based on the QSAR models. The top 13 compounds were identified. Furthermore, compound 2B (ΔG: -10.3 kcal $mol^{-1}$, RMSD: 0.151 Å) was selected among the top 13 hits obtained from molecular docking experiments. Significant interactions were also observed, including π-π contacts with Phe208, Tyr444, Trp407, and hydrogen bond interactions with Ala68 and Tyr69. Furthermore, dynamic modelling demonstrated that compound **2B** (0.11 nm) has higher overall stability than clorgyline, with a lower RMSD value, and may reach equilibrium in the final 20-25 ns. In terms of RMSF, **2B** produced around 0.34 nm with less variation than clorgyline. Throughout the simulation, **2B** (No. of H-bond: 6) had more hydrogen bonding than clorgyline (No. of H-bond: 3) with the highest occupancy, i.e. 117.39% for GLU216, 29% for TYR444, and 49% for PRO72, and so on. Compound **2B** was proven to be the most essential throughout the experiments. These new chemicals will be optimized *in vitro* and *in vivo* in the future. This study will surely contribute to the development of novel MAO-A inhibitors for the treatment of depression.