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Aziz, A.A.b.A.[a] , Aminudin, N.I.[a] , Hamid, S.A.[a] , Pungot, N.H.[b] , Hamzah, N.[a]

Molecular Docking and ADME Profiles of β-Carboline Analogues as Potential Antibiotic Agents Targeting DNA Gyrase

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[a] Department of Chemistry, Kulliyyah of Science, International Islamic University Malaysia (IIUM), Kuantan, Pahang, 25200, Malaysia
[b] Institute of Science (IOS), Universiti Teknologi MARA (UiTM), Shah Alam, Shah Alam, Selangor Darul Ehsan, 40450, Malaysia

Abstract
Antibiotic resistance remains a major threat to humans worldwide, owing to the ability of bacteria and fungi to mutate over time, as well as a dramatic decline in the antibiotic pipeline. Plants are widely recognised as sources for various bioactive secondary metabolites that can be developed as a hit compound for further antibiotic discoveries. β-Carboline has been recognised as one of the hit compounds exhibiting various biological activities including antibacterial properties. However, the optimisation and development of the hit compound always hampered by long and expensive procedures. The in-silico approaches involving molecular docking and ADME profiling can be expedite the process. Herein, an in-house library of β-carboline and its 19 analogues were virtually screened to evaluate their antibiotic activities and drug-likeness properties using molecular docking and ADME profiling respectively. Docking studies showed that all 19 β-carboline analogues strongly bound to the target protein (-6.8 to -9.4 kcal/mol) except 1o (-6.7 kcal/mol), which exhibited binding energy comparable to the reference drug, novobiocin (-6.8 kcal/mol). Of these, derivatives 1l bound the strongest (-9.4 kcal/mol) mainly due to the hydrogen bond interactions that occurred between the carboxylic acid moiety with Val71. ADME profiling showed that all β-carboline analogues demonstrated favourable drug-likeness properties and obey the Lipinski Rule of 5 (Ro5). The analogues 1l showed only one inhibition on CYP2D6 suggesting less toxicity properties. Thus, through this work, the derivatives of β-carboline, especially 1l, may serve as hit compound for future development of finding effective antibiotic agent.

Author Keywords
ADME Profile; antibiotic; DNA Gyrase; molecular docking; β-carboline

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Correspondence Address
Hamzah N.; Department of Chemistry, Kuantan, Malaysia; email: nurasyikinhamzah@iium.edu.my

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