UNIVERSITI TEKNOLOGI MARA

INHIBITORY ACTIVITIES OF FLAVONOID DERIVATIVES ON CYCLOOXYGENASE-2 (COX-2): *IN SILICO* MODELLING AND CELL-BASED STUDY

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MSc

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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the results of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

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ABSTRACT

COX-2 inhibitors are introduced as a better alternative to replace the traditional NSAIDs. This is because it is associated with lower incidences of gastrotoxicity that commonly occurs among the users of the traditional NSAIDs. Therefore, this study aims to identify the lead compounds based on flavonoid scaffolds which can be further developed into drug(s) as treatment for inflammation. To achieve this, several pharmacophore hypotheses on COX-2 were developed. These pharmacophore hypotheses were then validated and the best pharmacophore was chosen and named as "phore1". The "phore1" was used in virtual screening of datasets (ASINEX and in-house datasets). The hit compounds with score of more than 45.00 were chosen for molecular docking. Then, the compounds with binding energy better than -8.00 kcal/mol at the COX-2 binding site were chosen as the final hit compounds. For the in-house virtual screening, additional methods were applied. The in-house dataset was prefiltered by Lipinski's Rule of Five and verified using COX peroxidase assay. Simultaneously, the filtered compounds were screened using virtual screening method mentioned before and both of the results were compared and validated. From the in-house dataset, five compounds were successfully predicted through *in silico* screening but only compound F3 was exhibited potency towards COX-2 with IC_{50} of 24.30 µM. For ASINEX dataset, fifteen (15) hit compounds successfully screened using *in silico* study and they are known as BAS00127074, BAS00384673, BAS00428711, BAS00547888, BAS00643043, BAS00643060, BAS00643061, BAS00654798, BAS00791751, BAS01121975, BAS01121978, BAS01316535, BAS01316573, BAS02332476, and BAS02557914. It is concluded from this study that the *in silico* COX-2 model has been successfully developed and is useful for the screening and identification of new potential COX-2 inhibitors. This model would allow researchers to screen more compounds without doing biological assay.

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