Identification of Novel 5-Lipoxygenase-Activating Protein (FLAP) Inhibitors by an Integrated Method of Pharmacophore Virtual Screening, Docking, QSAR and ADMET Analyses

By: Rullah, K (Rullah, Kamal) [1] ; Roney, M (Roney, Miah) [2] ; Ibrahim, Z (Ibrahim, Zalikha) [1] ; Shamsudin, NF (Shamsudin, Nur Farisya) [1] ; Islami, D (Islami, Deri) [3] ; Ahmed, QU (Ahmed, Qamar Uddin) [1] ; Wai, LK (Wai, Lam Kok) [4] ; Aluwi, MFFM (Aluwi, Mohd Fadhlizil Fasihi Mohd) [2]

JOURNAL OF COMPUTATIONAL BIOPHYSICS AND CHEMISTRY

DOI: 10.1142/S2737416523500059

Early Access: NOV 2022

Indexed: 2022-12-09

Document Type: Article; Early Access

Abstract

This study explored a series of reported 5-lipoxygenase-activating protein (FLAP) inhibitors to understand their structural requirements and identify potential new inhibitor scaffolds through automated unbiased procedures. Docking studies have revealed that inhibitor binding affinity can be influenced by several key binding interactions with Phe114 and Lys116 from chain B and Val21, Phe25, His28 and Lys29 from chain C in the FLAP-binding site. A ligand-based alignment three-dimensional (3D)-quantitative structure-activity relationship (QSAR) was adopted, resulting in a robust model with a statistically significant noncross-validated coefficient (r(2) = 0.992), a cross-validated correlation coefficient (q(2) = 0.681) and a predictive squared correlation coefficient (r(2)pred = 0.736). Overall, the analysis revealed the important electrostatic and steric attributes responsible for the FLAP inhibitory activity, which appeared to correlate well with the docking results. In addition, two statistically significant two-dimensional (2D)-QSAR models (r(2) = 0.9369, q(2) = 0.889 and r(2) = 0.9679, q(2) = 0.655) were developed by a genetic function approximation (GFA). HypoGen 1, a proposed pharmacophore model, was used for database mining to identify potential new FLAP inhibitors. The bioactivity of the retrieved hits was then evaluated in silico based on the validated QSAR models, followed by pharmacokinetics and toxicity predictions.

Keywords

Author Keywords: Docking; 2D-and 3D-QSAR; pharmacophore; virtual screening; 5-lipoxygenase-activating protein (FLAP); inflammation

Keywords Plus: LEUKOTRIENE BIOSYNTHESIS INHIBITOR; QUANTITATIVE STRUCTURE; DRUG DISCOVERY; MODELS

Author Information

Corresponding Address: Rullah, Kamal (corresponding author)

Int Islamic Univ Malaysia, Dept Pharmaceut Chem, Drug Discovery & Synthet Chem Res Grp, Kulliyyah Pharm, Kuantan 25200, Pahang, Malaysia

Corresponding Address: Aluwi, Mohd Fadhlizil Fasihi Mohd (corresponding author)

Univ Malaysia Pahang, Fac Ind Sci & Technol, Lebuhraya Tun Razak, Gambang 26300, Pahang, Malaysia

Addresses:

1 Int Islamic Univ Malaysia, Dept Pharmaceut Chem, Drug Discovery & Synthet Chem Res Grp, Kulliyyah Pharm, Kuantan 25200, Pahang, Malaysia

2 Univ Malaysia Pahang, Fac Ind Sci & Technol, Lebuhraya Tun Razak, Gambang 26300, Pahang, Malaysia

3 Univ Abdurrab, Fac Pharm & Hlth Sci, Jalan Riau Ujung, Pekanbaru 28292, Riau, Indonesia

4 Univ Kebangsaan Malaysia, Fac Pharm, Drugs & Herbal Res Ctr, Jalan Raja Muda Abdul Aziz, Kuala Lumpur 50300, Malaysia

E-mail Addresses: kamalrullah@iium.edu.my; fasihi@ump.edu.my

Categories/Classification

Research Areas: Chemistry

Funding

Funding agency	Grant number
International Islamic University of Malaysia-IIUM through Research Management Centre Grant 2020	RMCG20008-0008
Universiti Kebangsaan Malaysia-UKM	

Close funding text

This research was financially supported by the International Islamic University of Malaysia-IIUM through Research Management Centre Grant 2020 (RMCG20008-0008) and Universiti Kebangsaan Malaysia-UKM for providing Discovery Studior software.

+ See more data fields

Journal information

JOURNAL OF COMPUTATIONAL BIOPHYSICS AND CHEMISTRY

ISSN: 2737-4165
eISSN: 2737-4173
Current Publisher: WORLD SCIENTIFIC PUBL CO PTE LTD, 5 TOH TUCK LINK, SINGAPORE 596224, SINGAPORE
Research Areas: Chemistry
Web of Science Categories: Chemistry, Multidisciplinary

THROUGHPUT SCREENING

Tong, JB; Wang, TH; Feng, Y; et al.
QSAR and Docking Studies of Thiazolidine-4-carboxylic Acid Derivatives as Neuraminidase Inhibitors
CHINESE JOURNAL OF STRUCTURAL CHEMISTRY

Zangeneh, J; Shirvani, P; Saghaie, L; et al.
In Silico Screening for Novel Tyrosine Kinase Inhibitors with Oxindole Scaffold as Anti-Cancer Agents: Design, QSAR Analysis, Molecular Docking and ADMET Studies
JOURNAL OF COMPUTATIONAL BIOPHYSICS AND CHEMISTRY

Yang, JS; Chun, K; Han, G; et al.
Structure based optimization of chromen-based TNF-alpha converting enzyme (TACE) inhibitors on S1 ' pocket and their quantitative structure-activity relationship (QSAR) study
BIOORGANIC & MEDICINAL CHEMISTRY

See all

Use in Web of Science

Web of Science Usage Count 17