Identification of novel 5-lipoxygenase-activating protein (FLAP) inhibitors by an integrated method of pharmacophore virtual screening, docking, QSAR and ADMET analyses

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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 (r2=0.992), a cross-validated correlation coefficient (q2=0.681) and a predictive squared correlation coefficient (rpred2=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 (r2=0.9369, q2=0.889 and r2=0.9679, q2=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

2D- and 3D-QSAR; 5-lipoxygenase-activating protein (FLAP); Docking; inflammation; Pharmacophore; Virtual screening

REFERENCES

1. Jo-Watanabe, A., Okuno, T., Yokomizo, T.
   The role of leukotrienes as potential therapeutic targets in allergic disorders
   (2019) *International Journal of Molecular Sciences*, 20 (14), art. no.
   3580. https://www.mdpi.com/1422-0067/20/14/3580/pdf
   doi: 10.3390/ijms20143580

2. Peters-Golden, M., Brock, T.G.
5-Lipoxygenase and FLAP (Open Access)
(2003) *Prostaglandins Leukotrienes and Essential Fatty Acids*, 69 (2-3), pp. 99-109. http://www.elsevier-international.com/journals/plef/
doi: 10.1016/S0952-3278(03)00070-X

3. Vickers, P.J.
5-Lipoxygenase-activating protein (FLAP) (Open Access)
(1995) *Journal of Lipid Mediators and Cell Signalling*, 12 (2-3), pp. 185-194.
doi: 10.1016/0929-7855(95)00018-L

4. Evans, J.F., Ferguson, A.D., Mosley, R.T., Hutchinson, J.H.
What's all the FLAP about?: 5-lipoxygenase-activating protein inhibitors for inflammatory diseases
(2008) *Trends in Pharmacological Sciences*, 29 (2), pp. 72-7
doi: 10.1016/j.tips.2007.11.006

5. Ferguson, A.D., McKeever, B.M., Xu, S., Wisniewski, D., Miller, D.K., Yamin, T.-T., Spencer, R.H., (...), Becker, J.W.
Crystal structure of inhibitor-bound human 5-lipoxygenase-activating protein
(2007) *Science*, 317 (5837), pp. 510-512.
doi: 10.1126/science.1144346