Atom based 3D-QSAR of quinoline derivatives and pharmacophore based virtual screening for identification of selective Phosphodiesterase 4B inhibitors

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1. ABSTRACT

Phosphodiesterase 4B (PDE4B) hydrolyses cyclic adenosine monophosphate (cAMP) and thus regulates its intracellular levels. The enzyme has been proposed as a potential drug target against diseases like inflammation and chronic obstructive pulmonary disease. But use of current PDE4B inhibitors is limited due to dose-dependent nausea and vomiting. Adverse effects associated with current PDE4B inhibitors are possibly results of PDE4D inhibition, a highly similar homolog of PDE4B. Here we considered quinoline analogs and applied ligand-based pharmacophore and atom based 3D-QSAR modeling with structure-based docking and ADME approach. A 5-point pharmacophore model was developed and used to derive a predictive 3D-QSAR model for studied dataset. The obtained r^2 and q^2 values were 0.96 and 0.91 respectively. The result suggested that the generated 3D-QSAR model is reliable and can be considered for PDE4B activity prediction. Further, pharmacophore model was employed for virtual screening to identify potent PDE4B inhibitors. The selective ligands for PDE4B identified through docking and prime binding energy analysis of ligands in both PDE4B and PDE4D. ADME analysis was performed to confirm the drugeability of selective ligand.

2. OBJECTIVE

The aim of the present study is to analyze the pharmacophoric features for selective binding of the inhibitors to PDE4b. The study focuses on the analysis of presence and position of functional groups (hydrogen bonding, hydrophobic, electronegative etc.) necessary for PDE4B selectivity.

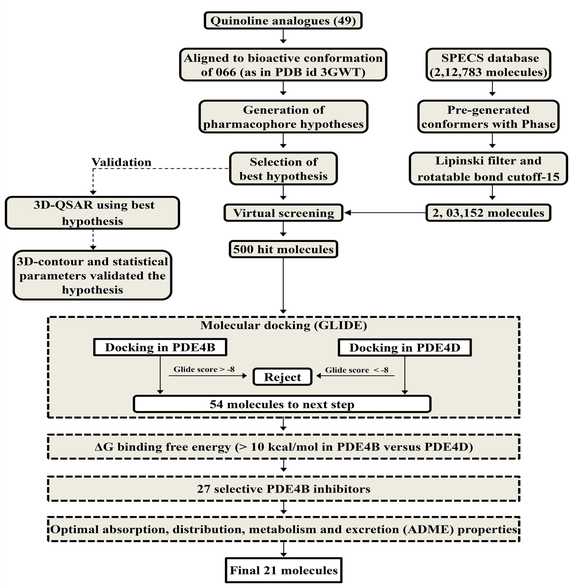
3. MATERIALS

- Workstation- Fujitsu linux workstation (xeon quad-core E3-1220 processor).
- Software- Phase 3.9, Glide 6.3, LigPrep 3.0, Prime 3.6, Impact 6.3, and QikProp 4.0 of Maestro 9.8 (Schrödinger, LLC, 2014).
- Crystal Structure- retrieved from RCSB Protein Data Bank (PDB)

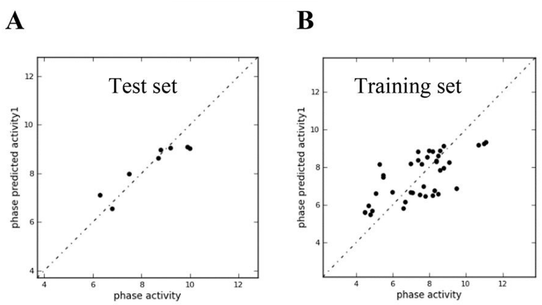
REFERENCES

- M. D. Woodrow, et. al. Bioorganic & medicinal chemistry letters, 2009, 19, 5261-5265.
- C. J. Lunniss, et al. Bioorganic & medicinal chemistry letters, 2009, 19, 1380-1385.

4. METHOD OVERVIEW

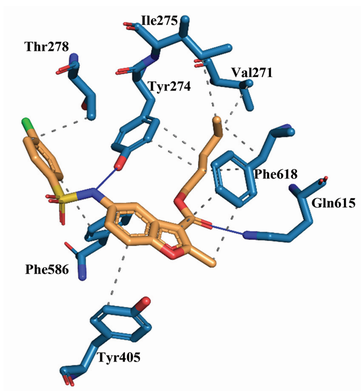


5. RESULTS

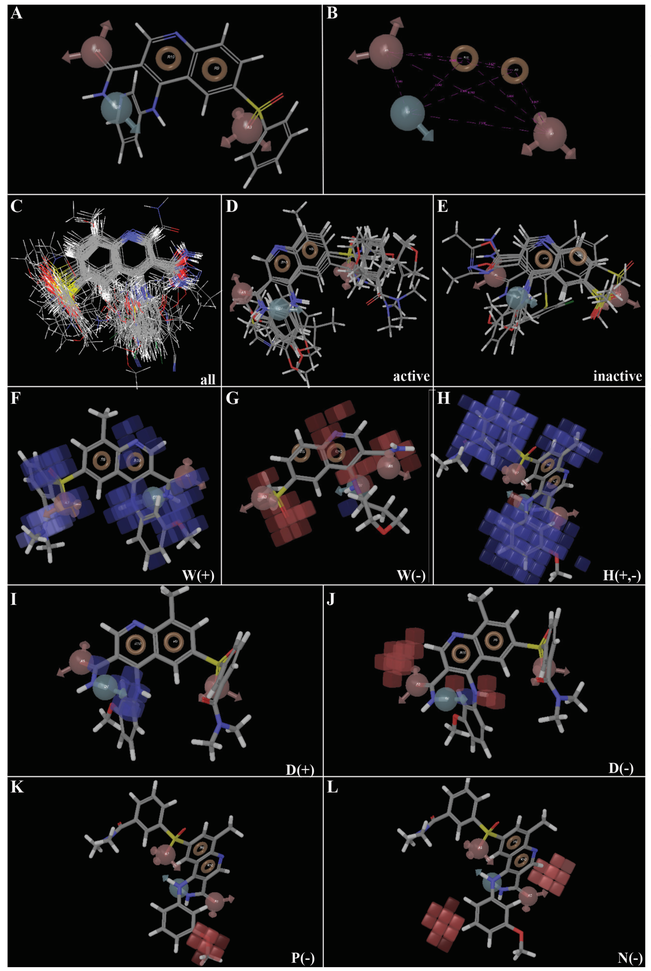


(A) Observed and predicted activities of test set compounds associated with PDE4B.

(B) Observed and predicted activities of training set compounds associated with PDE4B



Binding pose of top scoring ligand in PDE4B, PDBID: 3G45. The molecule showed H-bond with Tyr274 and Gln615 (blue solid line) and hydrophobic interaction with Phe618, Phe586, Tyr405, Val271, Thr278 and Ile275 (grey dotted lines)



(A) Pharmacophore model generated for PDE4B. (B) common pharmacophoric sites of active ligand with distance. (C) alignment of all ligands (quinoline analogues) to the bioactive conformation of crystal ligand 066 of PDBID: 3GWT. (D)Alignment of all active ligands to the pharmacophore. (E). Alignment of all inactive ligands to the pharmacophore.

Atom-based PDE4B 3D-QSAR models visualized (red cubes- negative effect, blue cubes- positive effect) for (F) electron withdrawing group/atom position (W+) (G) negative effect of electron withdrawing group/atom mapped position (W-), (H) negative effect and positive effect of position hydrophobic groups (H+,-), (I) positive effect of position H-bond donor (D+), (J) negative effect of position H-bond donor (D-), (K) negative effect of position of positive ionic groups (P-), (L) negative effect of position of negative ionic groups (N-)

6. CONCLUSIONS

- Five point pharmacophore was developed which explained the necessary features needed for PDE4B selective behavior of compounds, supported by literature.
- QSAR model was obtained r^2 and q^2 values were 0.96 and 0.91 respectively.
- Specs database was filtered and molecules were cross docked in PDE4B and PDE4D.
- The obtained molecules produced significant difference in docking score and prime binding energy for PDE4B and PDE4D. Also ADME properties were optimum for drugeable behaviour.

ACKNOWLEDGEMENT

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