Insight parameter drug design for human beta-tryptase inhibition integrated molecular docking, QSAR, molecular dynamics simulation, and pharmacophore modelling studies of alpha-keto-[1,2,4]-oxadiazoles

By: Yu, CX (Yu, Chai Xin) [1] ; Tan, JW (Tan, Jian Wei) [1] ; Rullah, K (Rullah, Kamal) [2] ; Imran, S (Imran, Syahrul) [3] , [4] ; Tham, CL (Tham, Chau Ling) [1]

JOURNAL OF BIOMOLECULAR STRUCTURE & DYNAMICS

DOI: 10.1080/07391102.2023.2171131
Early Access: JAN 2023
Indexed: 2023-02-17
Document Type: Article; Early Access

Abstract:

Dengue hemorrhagic fever (DHF) is severe dengue with a hallmark of vascular leakage. beta-tryptase has been found to promote vascular leakage in DHF patients, which could be a potential target for DHF treatment. This study aims to develop a theoretical background for designing and selecting human beta-tryptase inhibitors through computational studies. Thirty-four alpha-keto-[1,2,3]-oxadiazoles scaffold based compounds were used to generate 2D-QSAR models and for molecular docking studies with beta-tryptase (PDB Code 4A6L). In addition, molecular dynamics (MD) simulation and molecular mechanics generalised born surface area (MM-GBSA) analysis on the binding of the reported most active compound, compound 11e, towards beta-tryptase were performed. Finally, a structure-based pharmacophore model was generated. The selected 2D-QSAR models have statistically proven good models by internal and external validation as well as the y-randomization test. The docking results of compound 11e showed lower CDOCKER energy than the 4A6L co-crystallised ligand and a similar binding pattern as the 4A6L co-crystallised ligand. From molecular dynamics simulation, 4A6L in compound 11e bound state has RMSD below 2 angstrom throughout the 500 ns simulation, indicating the docked complex is stable. Besides, MM-GBSA analysis suggested the 4A6L-compound 11e docked complex (-66.04 Kcal/mol) is structurally as stable as the 4A6L-native ligand co-crystallized structure (-66.84 Kcal/mol). The best pharmacophore model identified features included hydrogen bond acceptor, ionic interaction, hydrophobic interaction, and aromatic ring, which contribute to the inhibitory potency of a compound. This study supplied insight and knowledge for developing novel chemical compounds with improved inhibition of beta-tryptase.

Keywords

Author Keywords: beta-tryptase inhibitors; QSAR; docking; molecular dynamics; pharmacophore
Keywords Plus: MAST-CELL TRYPTASE; EDGE ADJACENCY RELATIONSHIPS; POTENT; DISCOVERY; DENGUE; TETRAMER; SAR; IDENTIFICATION; REQUIREMENTS; DERIVATIVES

Author Information

Corresponding Address: Tham, Chau Ling (corresponding author)

Univ Putra Malaysia, Fac Med & Hlth Sci, Dept Biomed Sci, Serdang, Selangor, Malaysia

Corresponding Address: Rullah, Kamal (corresponding author)

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

Addresses:

1 Univ Putra Malaysia, Fac Med & Hlth Sci, Dept Biomed Sci, Serdang, Selangor, Malaysia

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

3 Univ Teknol MARA, Atta Ur Rahman Inst Nat Prod Discovery AuRIns, Cawangan Selangor, Kampus Puncak Alam, Puncak Alam, Selangor, Malaysia

4 Univ Teknol MARA UiTM, Fac Appl Sci, Shah Alam, Selangor, Malaysia

E-mail Addresses: kamalrullah@iium.edu.my; chauling@upm.edu.my

Categories/ Classification

Research Areas: Biochemistry & Molecular Biology; Biophysics

Citation Topics: 1 Clinical & Life Sciences › 1.65 Allergy › 1.65.936 Mast Cells

Funding

Funding agency	Grant number	
		Hide All Details
Ministry of Education, Malaysia	FRGS/1/2018/SKK10/UPM/02/2	Hide details

Appeared in source as: Ministry of Higher Education Malaysia

View funding text

+ See more data fields

New

Journal information

JOURNAL OF BIOMOLECULAR STRUCTURE & DYNAMICS

ISSN: 0739-1102
eISSN: 1538-0254
Current Publisher: TAYLOR & FRANCIS INC, 530 WALNUT STREET, STE 850, PHILADELPHIA, PA 19106
Journal Impact Factor: Journal Citation Reports ™
Research Areas: Biochemistry & Molecular Biology; Biophysics
Web of Science Categories: Biochemistry & Molecular Biology; Biophysics

5.235
Journal Impact Factor ™ (2021)

1.1
Journal Citation Indicator ™ (2021)

104 Cited References

Showing 30 of 104 View as set of results

(from All Databases)