Journal of Biomolecular Structure and Dynamics ›
Volume 39, 2021 - Issue 15

Research Articles

Development of triple mutant T790M/C797S allosteric EGFR inhibitors: a computational approach

Kshipra S. Karnik, Aniket P. Sarkate, Deepak K. Lokwani, Ishudeep S. Narula, Prasad V. L. S. Burra & **Pravin S. Wakte**

Pages 5376-5398 | Received 30 May 2020, Accepted 18 Jun 2020, Published online: 01 Jul 2020

Cite this article https://doi.org/10.1080/07391102.2020.1786460 Check for updates

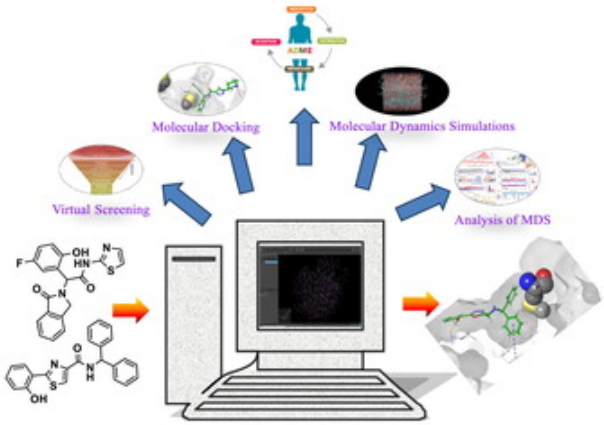
Abstract

The mutations concerned with non-small cell lung cancer involving epidermal growth factor receptor of tyrosine kinase family have primarily targeted. EGFR inhibitors binding allosterically to C797S mutant EGFR enzyme have been developed. Here, database building, library screening performing R-group enumeration and scaffold hopping technique for increasing the EGFR binding affinity of compounds have been carried out. Virtual screening was performed subjecting to HTVS, SP and XP docking protocol along with its relative binding free energy calculations. Molecular docking studies provided the information about binding pockets and interactions of molecules on mutant (PDB: 5D41) as well as wild type (PDB: 4I23) EGFR enzyme. This was supported with ADMET and molecular simulation studies. On the basis of glide score and protein-ligand interactions, highest scoring molecule was selected for molecular dynamic

simulation providing a complete insight into the conformational stability. The virtually screened molecules can act as potential EGFR inhibitors in the management of drug resistance.

Communicated by Ramaswamy H. Sarma

Graphical Abstract



Keywords: Non-small cell lung cancer EGFR allosteric library generation virtual screening molecular docking molecular dynamics simulations

Acknowledgements

The authors are thankful to The Head, Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431 004 (MS), India, for providing the laboratory facility. The authors are also thankful to The Head, Department of Biotechnology, KLEF University, Vaddeswaram 522502 (AP), India for the computational support.

Disclosure statement

The authors declare no competing financial interest.

Funding

The authors K. S. K and P. S. W are thankful to Indian Council of Medical Research (ICMR) for

providing funding in support of Senior Research Fellowship with Ref No: 3/2/2/33/2018/Online OncoFship/NCD-III. The author P. V. L. S. B is thankful to Indian Council of Medical Research (ICMR) [ISRM/12(07)/2019] and DST-SERB [CRG/2018/003276] for providing financial support.

Table 1. Comparison of docking score with relative binding free energy score along with interacting residues of top 50 hits.

Display Table

Additional information

Funding

The authors K. S. K and P. S. W are thankful to Indian Council of Medical Research (ICMR) for providing funding in support of Senior Research Fellowship with Ref No: 3/2/2/33/2018/Online OncoFship/NCD-III. The author P. V. L. S. B is thankful to Indian Council of Medical Research (ICMR) [ISRM/12(07)/2019] and DST-SERB [CRG/2018/003276] for providing financial support.

Log in via your institution

Access through your institution

Log in to Taylor & Francis Online

Log in

Restore content access

Restore content access for purchases made as guest

Purchase options *

Save for later

PDF download + Online access

- 48 hours access to article PDF & online version
- Article PDF can be downloaded
- Article PDF can be printed

USD 61.00

Add to cart

Issue Purchase

- 30 days online access to complete issue
- Article PDFs can be downloaded
- Article PDFs can be printed

USD 1,074.00

Add to cart

* Local tax will be added as applicable

Related Research

People also read | Recommended articles | Cited by 6