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Application of group-based qsar and molecular docking in the design of insulin-like growth factor antagonists (Article)

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Abstract

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Purpose: To identify the structural requirements for designing a lead key for insulin-like growth factor (IGF-1R) inhibition using group-based quantitative structure activity relationship (GQSAR) and molecular docking. Methods: GQSAR method requires fragmentation of molecules. The molecules in the current dataset were fragmented into three (R1, R2 and R3) by applying common fragmentation pattern, and fragment-based 2D descriptors were then calculated. GQSAR models were derived by applying various methods including multiple linear regressions and partial least square or k-nearest neighbor. Results: Four generated GQSAR models were selected based on the statistical significance of the model. It was found that the presence of flexible and non-aromatic groups on fragment R1 was conducive for inhibition. Additionally, the existence of amino groups as hydrogen bond donors at fragments R2 and R3 was fruitful for inhibition. Docking studies revealed the binding orientation adopted by the active compounds at several amino acid residues, including Met 1126, Arg, 1128, Met 1052, GLU 1050, Met 1112, Leu 1051, Met 1049, Val 1033, and Val 983 at ATP binding sites of IGF-1R kinase domain. Conclusion: The generated models provide a site-specific insight into the structural requirements for IGF-1R inhibition which can be used to design and develop potent inhibitors.

Author keywords

Adenosine triphosphate Competitive inhib itors Electrotopological state index Insulin-like growth factor 1 (IGF-1) receptor Quantitative structure-activity relationship

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