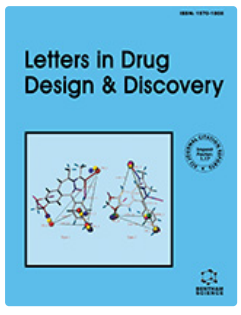

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Research Article

A Rational Approach to Anticancer Drug Design: 2D and 3D- QSAR, Molecular Docking and Prediction of ADME Properties using Silico Studies of Thymidine Phosphorylase Inhibitors

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Abstract

Background: Cancer is the most prevalent disease seen nowadays. Thymidine phosphorylase (TP) is an angiogenic enzyme that is overexpressed in many solid tumors. Over the years, Thymidine phosphorylase has emerged as a novel target for anticancer drug development as an inhibitor.

Objective: To design novel oxadiazole-isatin pharmacophore-containing molecules and explore their structural requirements related to the anticancer activity.

Methods: Pharmacophore optimisation was carried out for oxadiazole-isatin hybrid molecules using molecular modeling studies (2D and 3D QSAR). Further, the new chemical entities were designed using the combilib tool of V life software. To have a better understanding of the binding interactions, the newly designed molecules were docked. To achieve a drug-like pharmacokinetic profile, molecules were also tested for ADME prediction.

Results: Two-Dimensional Quantitative Structure-Activity Relationship (2D-QSAR) model was generated using the multiple regression method with r^2 = 0.84 and q^2 = 0.76. Three-Dimensional Quantitative Structure-Activity Relationship (3D-QSAR) model was obtained by simulated annealing k nearest near (SA kNN) method with q^2 = 0.8099. Molecular docking studies showed promising results. Compound 5 was found to be with the best dock score and the best fit to the active site pocket of the thymidylate phosphorylase enzyme. The compounds have notable absorption, distribution, metabolism, and excretion (ADME) properties that can be predicted to assure a drug-like pharmacokinetic profile.

Conclusion: One of the most successful and fast-increasing methodologies is molecular modeling. It not only aids in the prediction of specific target compounds but also aids in the cost reduction of valuable substances. The successful use of molecular modeling was done in this study, with caution taken to avoid any chance co-relation. Optimised pharmacophore was obtained and new chemical entities were designed. Docking studies revealed that Compound 5 has shown better H-bond interaction with Lys 221 and Thr 151 with bond distances 2.0 A° and 1.8 A° which is the most active molecule. ADME tests discovered that the majority of the newly designed compounds were within a reasonable range as required in a druglike pharmacokinetic profile. Molecules 2, 4, 5, 6 can be considered as a lead for future synthesis and biological screening.

Keywords: Phosphorylase inhibitions, structure-activity relationship, oxadiazole-isatin hybrid, docking, ADME, anticancer.

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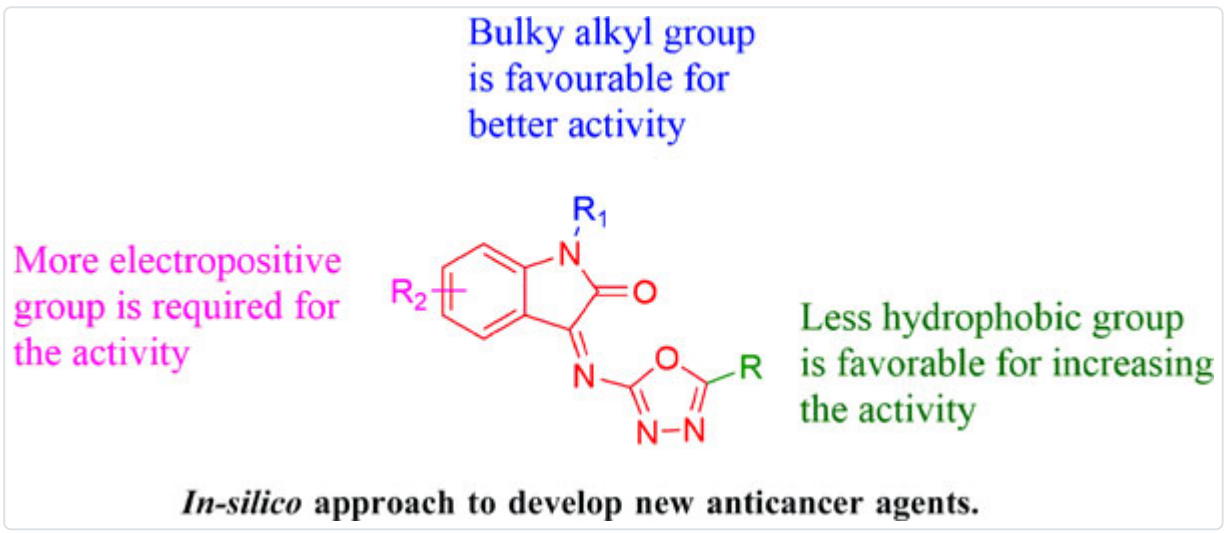
Graphical Abstract



***In-silico* approach to develop new anticancer agents.**

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