Target fishing of glycopentalone using integrated inverse docking and reverse pharmacophore mapping approach

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ABSTRACT. Glycopentalone isolated from *Glycosmis pentaphylla* (family Rutaceae) has cytotoxic and apoptosis inducing effects in various human cancer cell lines; however, its mode of action is not

known. Therefore, target fishing of glycopentalone using a combined approach of inverse docking and reverse pharmacophore mapping approach was used to identify potential targets of glycopentalone, and gain insight into its binding modes against the selected molecular targets, viz., CDK-2, CDK-6, Topoisomerase I, Bcl-2, VEGFR-2, Telomere:G-quadruplex and Topoisomerase II. These targets were chosen based on their key roles in the progression of cancer via regulation of cell cycle and DNA replication. Molecular docking analysis revealed that glycopentalone displayed binding energies ranging from -6.38 to -8.35 kcal/mol and inhibition constants ranging from 0.758 to 20.90 μM. Further, the binding affinities of glycopentalone to the targets were in the order: Telomere:G-quadruplex > VEGFR-2 > CDK-6 > CDK-2 > Topoisomerase II > Topoisomerase I > Bcl-2. Binding mode analysis revealed critical hydrogen bonds as well as hydrophobic interactions with the targets. The targets were validated by reverse pharmacophore mapping of glycopentalone against a set of 2241 known human target proteins which revealed CDK-2 and VEGFR-2 as the most favorable targets. The glycopentalone was well mapped to CDK-2 and VEGFR-2 which involve six pharmacophore features (two hydrophobic centers and four hydrogen bond acceptors) and nine pharmacophore features (five hydrophobic, two hydrogen bond acceptors and two hydrogen bond donors), respectively. The present computational approach may aid in rational identification of targets for small molecules against large set of candidate macromolecules before bioassays validation.

Key words: *Glycosmis pentaphylla*; Glycopentalone; Molecular docking; Reverse pharmacophore mapping; Anticancer; Cell cycle