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REGULAR ARTICLE

QSAR Study and Molecular Docking of 23-hydroxybetulinic Acid Derivatives as RMGPa and HeLa Cells Inhibitors

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Abstract: A number of 23-hydroxybetulinic acid derivatives were found to be potent glycogen phosphorylase a (GPa) inhibitors. Some derivatives of these triterpenes exhibit anti-tumor activities against a variety of tumor cell lines. In this study, we have constructed two different sets of QSAR equations. One set of QSAR equations predicts inhibitory activity of rabbit muscle glycogen phosphorylase a (RMGPa), which shares considerable sequence similarity with human liver GPa. The other set of equations predicts the antiproliferative activities against HeLa cells. This QSAR study has shown that topological indices and quantum chemical descriptors are the important parameters for determining the activity of 23-hydroxybetulinic acid derivatives. We have also performed Docking study with a number of 23-hydroxybetulinic acid derivatives with RMGPa and it has been found that the important interacting amino acids present in the active site cavity are ILE68, GLN71, GLN72, TYR75, ARG81, TYR155, ARG193, ARG242, ARG310 and SER313. Most of the compounds can form hydrogen bonds with ARG193 and/or ARG310. The unfavorable steric clashes between ligand and the protein and decrease of number of hydrogen bonds lower the inhibitory activity of the ligand.

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Introduction

The breakdown of glycogen into glucose is mediated by glycogen phosphorylase (GP) with the help of a debranching enzyme and plays an important role for controlling hepatic glucose production [1]. GP has three isoforms which are brain, liver, and muscle according to their expression patterns. The muscle isoform supplies energy for muscle contraction. The brain isoform provides glucose during the periods of severe hypoglycemia. In glycogenolysis, liver enzyme plays a rate limiting role and hence it is an attractive target for the treatment of type 2 diabetes [2-5]. GP exists in two interconvertible forms: the phosphorylated high activity glycogen phosphorylase a (GPa) and the dephosphorylated low activity glycogen phosphorylase b (GPb). Allosteric effectors can promote equilibrium between a less active GPb and an active GPa. The active conformation is stabilized by phosphorylation of Ser 14 and binding of AMP [6, 7]. GP contains at least six regulatory sites: glucose analogues at the catalytic site, azasugar inhibitors, lactones at the allosteric site (AMP), caffeine at the purine inhibitor site, indole-2-carboxamide at the indole binding site and cyclodextrins at the glycogen storage site [8,9]. The X-ray analysis indicates that pentacyclic triterpenes bind at the allosteric site [10].

A number of 23-hydroxybetulinic acid derivatives were reported as potent GPa inhibitors [11]. Furthermore, some derivatives of these triterpenes display anti-tumor activities against a variety of tumor cell lines and the mechanism of action may be associated to its effects on the proliferation, migration, cell cycle and apoptosis of tumor cells [12, 13].

Apoptosis or programmed cell death plays an important role in regulating development and homeostasis. In many diseases including cancer, apoptosis is suppressed. Telomerase, a ribonucleoprotein, maintains chromosome lengths by adding telomeres to the chromosome ends repeatedly. Telomerase activation is found in about 90% of tumor tissues, but with very low, almost undetectable activity in somatic cells. Apoptosis is regulated by a number of cellular genes including B cell leukemia/lymphoma 2 (bcl-2). The stable expression of bcl-2 in human cancer cells increases telomerase activity and resistance to apoptosis. The 23-hydroxybetulinic acid induces apoptosis through concurrent inhibition of bcl-2 expression and telomerase activity [14- 17].

Furthermore, 23-hydroxybetulinic acid enhances anti-tumor activity of doxorubicin in vitro and in vivo. The synergism is associated with increase in the doxorubicin concentration in tumor tissue brought about by 23-hydroxybetulinic acid. Hence 23-hydroxybetulinic acid has the prospect to be developed as a novel chemosensitizer [18].