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Computational Studies on Human CDK9 Inhibitors

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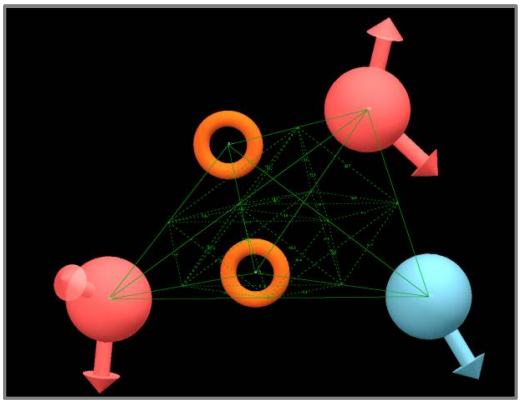
ABSTRACT

CDK9 (cyclin dependent kinase) is a protein used as a target in the treatment of cancer. CDK9 is a component of the multi-protein complex TAK/P-TEFb, an elongation factor for RNA polymerase II-directed transcription and functions by phosphorylating the C-terminal domain of the largest subunit of RNA polymerase II. It forms a complex with regulatory subunit of cyclin-T or cyclin-K. CDK9 is also known to associate with other proteins such as TRAF2, and is involved in differentiation of skeletal muscle. A 5-Point AADRR.63 pharmacophore model was developed using wogonin derivatives as CDK9 inhibitors. The generated pharmacophore model was used to derive a predictive–atom based 3D Quantitative structure activity relationship analysis (3D QSAR) model for the studied dataset. The obtained 3D-QSAR model has an excellent correlation coefficient value (r^2 =0.9332) along with good statistical significance as shown by higher fischer ratio (F=130.4). The model also exhibited good predictive power confirmed by the high value of cross validated correlation coefficient (q^2=0.6843).Virtual screening was carried out further to identify potential CDK9 inhibitors. The QSAR model suggests the electron withdrawing character is crucial for the CDK9 inhibitory activity. In addition to the electron-withdrawing character, hydrogen bond donating groups, hydrophobic and negatively charged groups contribute to the CDK9 inhibition. These findings provide promising guidelines for designing compounds with better CDK9 inhibitory potential.

Graphical Abstract



Geometry of best pharmacophore hypothesis AADRR.63 with (a) angles.

Keywords: Kinase, RNA polymerase II, CDK9, Wogonin derivatives.