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Design, docking study and ADME prediction of Chalcone derivatives as potent Tubulin inhibitors

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ABSTRACT

A series of piperonal chacones bearing schiff base moiety were designed and docked in to colchicine binding site of tubulin using the podophyllotoxin-tubulin complex (PDB 1SA1) as template. Docking study reveals that few of the designed derivatives were found to have significant interaction with active site of the receptor. The derivatives with trimethoxyphenyl ring, amino phenyl & nitro phenyl ring were found to have maximum docking score. In silico ADME predictions of most promising derivatives were also performed and compared.

INTRODUCTION

Drugs that target cellular microtubules can be divided into two groups, microtubule stabilizers and microtubule destabilizers, on the basis of their effects on tubulin polymerization and cellular microtubules. Colchicine is a microtubule depolymerizer that binds to tubulin at a site distinct from that of the vinca alkaloids. Although colchicine has not proven to be useful in the treatment of cancer, multiple compounds that bind within the colchicine site are advancing in clinical trials for anticancer indications. Chalcones represent an essential group of natural as well as synthetic products and some of them possess wide range of pharmacological activity.The previous research finding revealed that chalcone molecules have been extensively structurally modified and tested for their role in tubulin inhibition as potential anticancer compounds. Methylenedioxy moiety of benzodioxol is found to be present in some of currently used antitumor agents such as etoposide and teniposide which are glycosides of natural tubulin inhibitor called podophyllotoxin. Literature study revealed that this particular ring plays a key role in interacting with receptor. So the aim of the study was to design some chalcone derivatives of piperonal containing benzodioxol ring.

MATERIALS AND METHODS

Molecular docking

The designed compounds were subjected to *in silico* screening .A number of structures of piperonal chalcones and Schiff base derivatives of piperonal chacones were drawn on drawing window of chemsketch and further explored for gross biological activity, which is comprised of Lipinski rules of 5, drug likeness, drug score. *In silico* docking experiments were performed using Schrodinger suite 2012 update1 and modules like Ligprep, quick prop, and glide were used in the study. The protein structure podophyllotoxin-tubulin complex (PDB 1SA1) was obtained from the RCSB PDB and was used for docking. Major possible mechanism and site of metabolism of most potent derivatives were also performed by MetaPrin2D software**.**

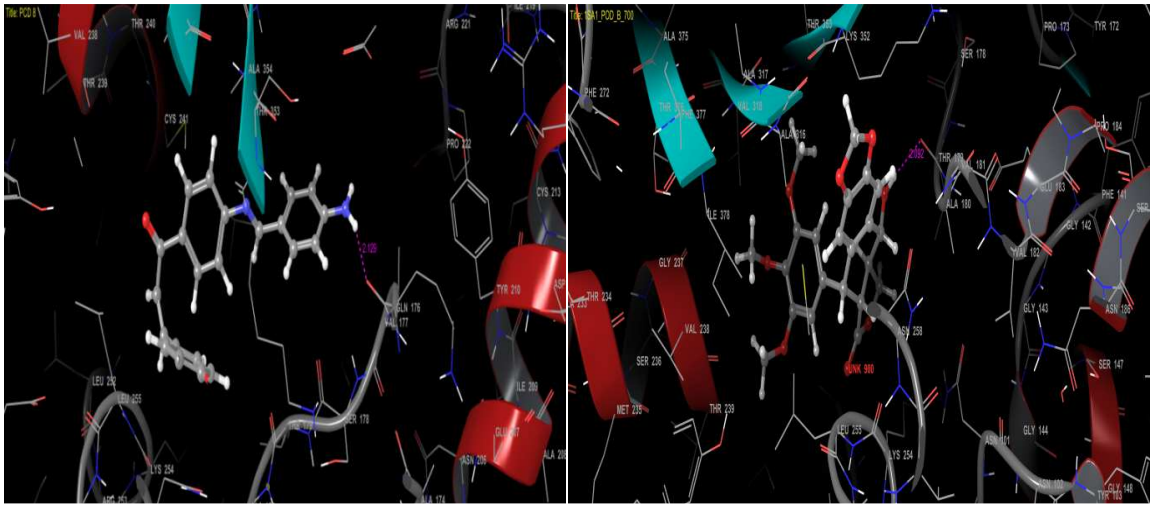

Figure 1 showing docking window of schrodinger software

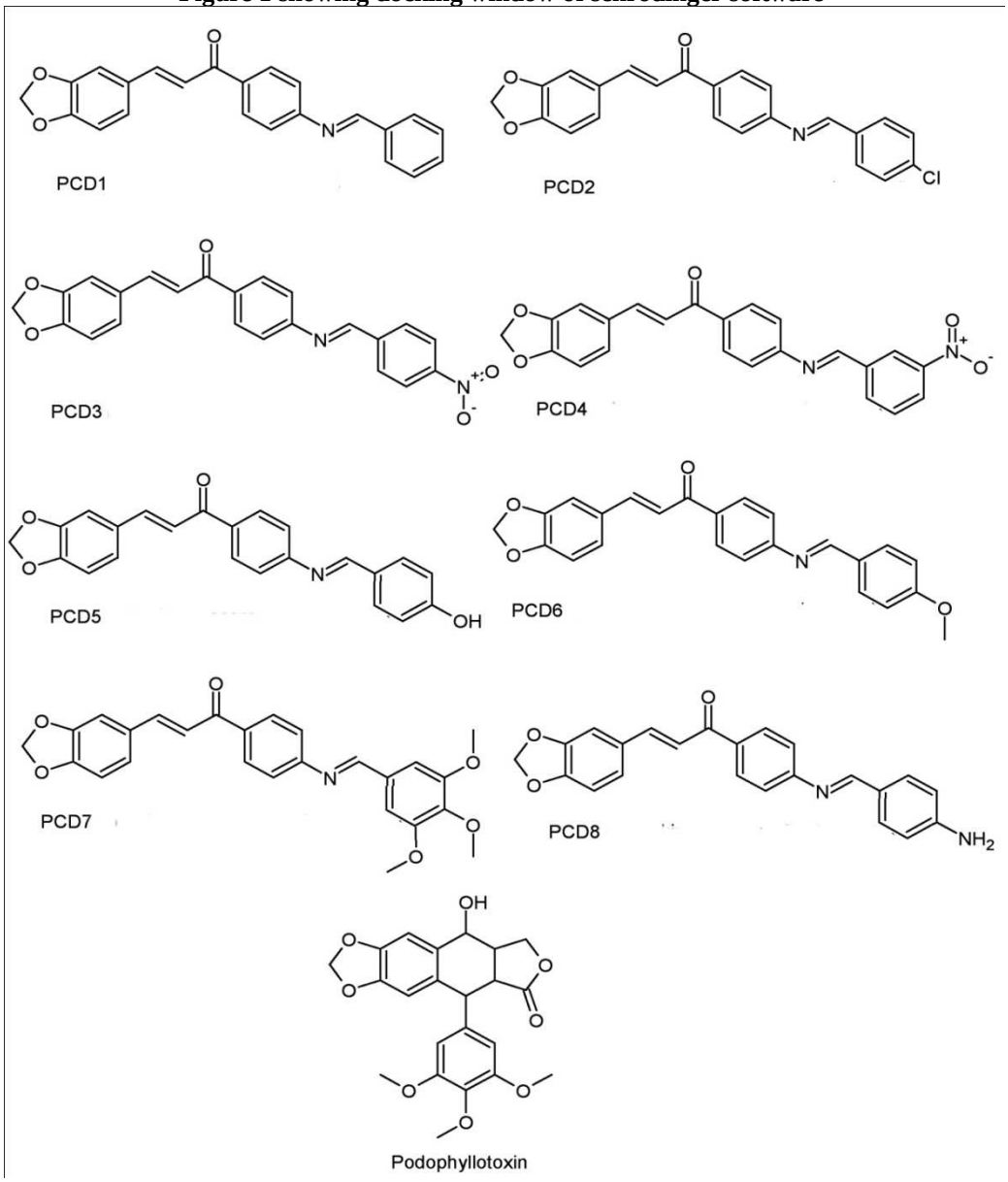

Figure 2 showing structures of potent derivatives

Prediction of Metabolism using MetaPrint2D

MetaPrint2D is a a new software tool implementing a data-mining approach for predicting sites of xenobiotic metabolism. The algorithm is based on a statistical analysis of the occurrences of atom centred circular fingerprints in both substrates and metabolites.

RESULTS

In silico docking study showed that eight designed derivatives were having excellent affinity towards active site of tubulin.

Ligand interaction diagram of most promising derivatives

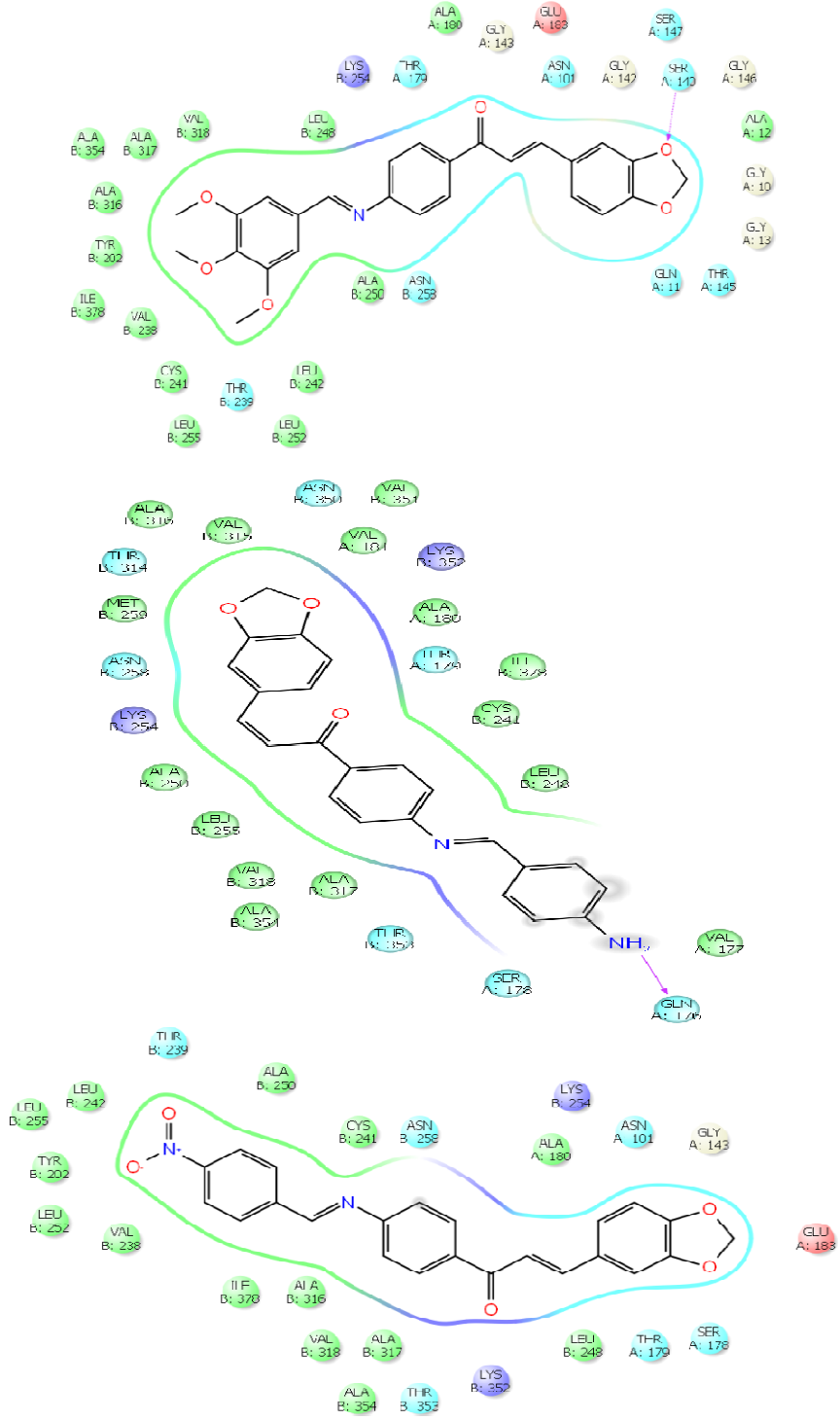

Figure 3 showing interaction of most potent ligands with amino acids of receptor

Docking scores of most potent derivatives

SAMPLE CODE	DOCKING SCORE (kcal/mol)
PCD1	-6.11
PCD7	-7.34
PCD8	-7.13
PCD3	-6.43
Podophyllotoxin (POD)	-8.21

***In silico* ADME prediction using quick prop module of schrodinger**

SAMPLE	QPlogPo/w	QPlogS	QPPCaco	QPPMDCK	% Oral Absorption
PCD1	2.34	-2.741	1751.74	906.801	100
PCD7	3.845	-4.672	680.25	326.224	100
PCD8	4.735	-5.088	2891.90	1558.44	100
PCD3	5.285	-5.889	2837.13	3766.38	100
POD	2.29	-2.711	1759.831	911.329	100

QPlogPo/w : Predicted octanol/water partition co-e_cient log p (acceptable range: −2.0 to 6.5
QPlogS : Predicted aqueous solubility; S in mol/L (acceptable range: −6.5 to 0.5).
QPPCaco : Predicted Caco-2 cell permeability in nm/s (acceptable range , <25 is poor and >500 is great).

QPPMDCK : Predicted apparent MDCK cell permeability for the blood-brain barrier,(acceptable range , < 25 is poor and >500 is great)

Percentage of human oral absorption (< 25% is poor and >80% is high)

Prediction of Metabolism using MetaPrint2D

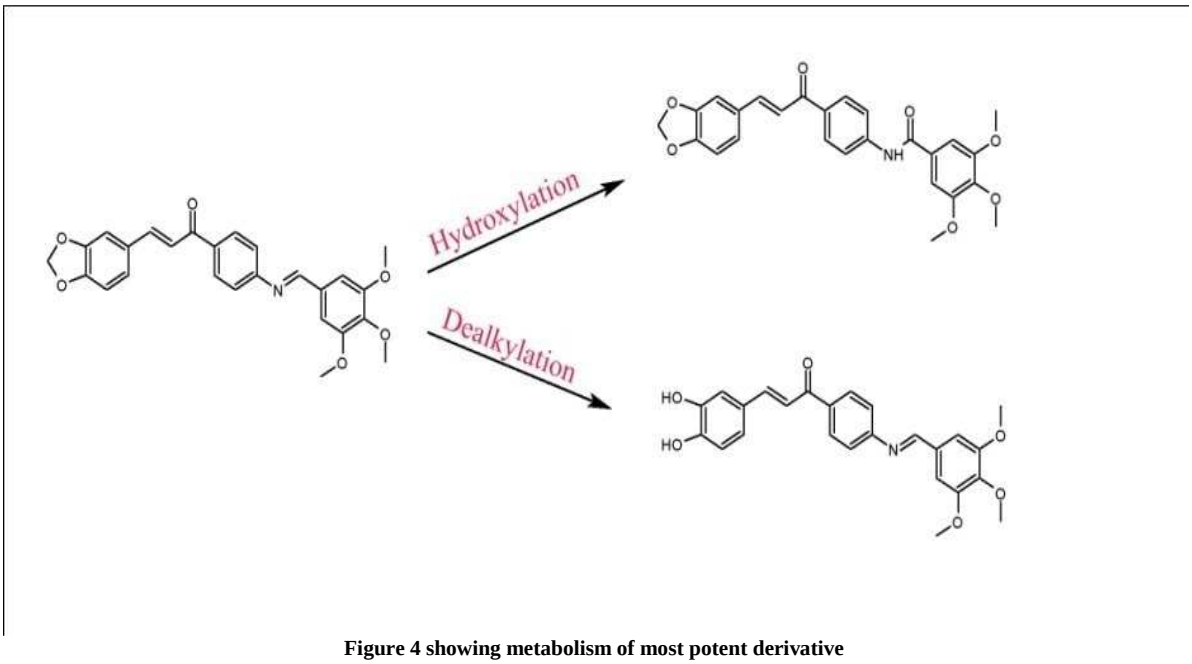

Figure 4 showing metabolism of most potent derivative

DISCUSSION

Design and docking of chalcone derivatives were carried out and it was found that proposed compounds were having good affinity to receptor. PCD7 showed maximum docking score as its benzodioxole moiety was buried well inside the hydrophobic pocket containing Ser140 , Asn101, Thr 145 of tubulin. The trimethoxyphenyl moiety of PCD2 was oriented so that favorable hydrophobic interactions formed with the side chains of tubulin residues Val238, Leu242, Leu248, Ala250, Leu255, Ala317, Val318, and Ala354.The amino group of PCD3 showed good interaction with Gln176.

CONCLUSION

Insilco designing and molecular docking of various proposed tubulin inhibitors were performed. Few promising derivatives showed comparable interaction pattern as that of podophyllotoxin. The most potent derivatives resulted in this study can be subjected to synthesis and pharmacological evaluations to develop highly potent tubulin inhibitors.

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