IN SILICO SCREENING OF ISOLATED PHYTOCONSTITUENTS FROM HYDROALCOHOLIC EXTRACT OF CYPERUS ROTUNDUS USING CAD SOFTWARE SCHRODINGER VERSION 10.5

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Abstract

Application of Computational (in silico) methods are widely applied in drug discovery. In drug discovery process, recognition of the appropriate drug target is the first and leading task. These targets are biomolecules which mainly include DNA, RNA and proteins (such as receptors, transporters, enzymes and ion channels). Rationale of such targets is necessary to exhibit a sufficient level of 'confidence' and to get knowledge of their pharmacological relevance to the disease under investigation. Cyperus rotundus is one of the promising medicinal plant having anti-arthritic activity. This study is to illustrate some of the in silico methods applied for the validation of isolated molecules from the plant. This article aims to bring out the new technique in drug discovery.

Keyword: *In silico, Computational , Validation, Biomolecules*

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Introduction

At the present time, in silico methodologies have become a decisive part of the drug discovery development. This is mostly because they can force the entire drug development path, identifying and discovering new potential drugs with a significant reduction to cost and time. Moreover, computer-aided drug design (CADD) approaches are important for reducing the experimental use of animals for in vivo testing, for aiding the design of safer drugs, and for repositioning known drugs, assisting medicinal chemists at each step (design, discovery, development, and hit-optimization) during the drug discovery process.(1) On one hand, conventional methods for drug discovery involve the costly random screening of synthesized compounds or natural products.(2) On the other hand, computational procedures can be very multifarious, requiring interdisciplinary studies and the application of computer science to rationally design effective and commercially feasible drugs.

Method

The structures of the isolated phytoconstituents of Cyperus rotundus CR namely CR-1, CR-2 and CR-3 were converted to 3D structures using potential algorithms and application of high efficient force fields.(3) Initial geometrical optimization and energy minimization of molecules were performed by using Ligprep tool of Schrodinger suite 10.. Various ionization states were generated using a Ligprop module using a special program EPIK along with various possible conformers and tautomers(4). Molecular properties of the processed ligands were studied by using Qikprop module. Qikprop module also predicts the ADME profiles.(5)

Molecular Docking studies

Post Docking Calculations

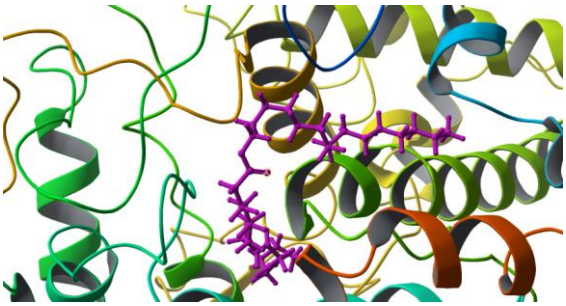

Figure 1: 3D Binding interactions of compound CR-1

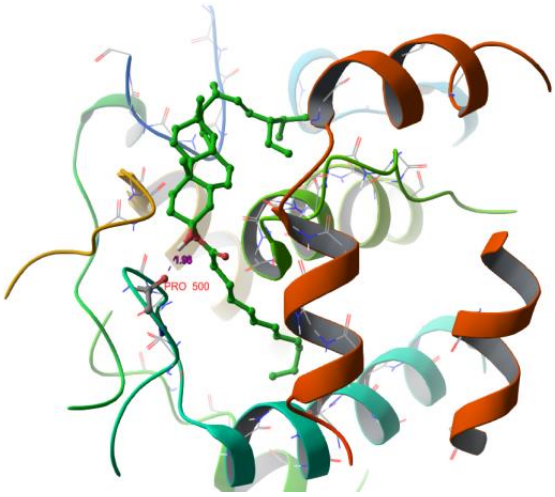

Figure 2: 3D Binding interactions of compound CR-2 with COX-2

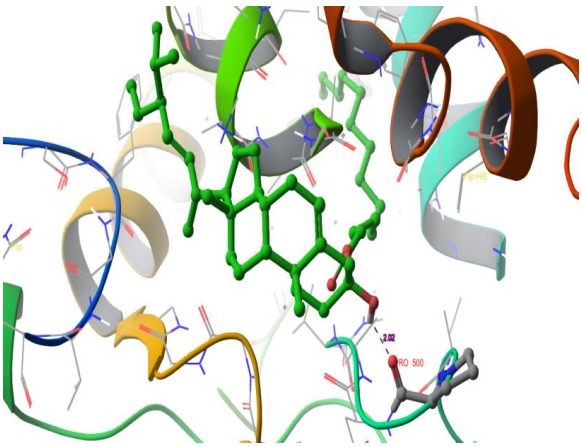

Figure3: 3D Binding interactions of compound CR-3 with COX-2

Table-1 Docking results and protein ligand binding interactions of isolated compounds

Molecule	No. of rotational bonds	Mol._MW	Donor HB	Acceptor HB	RuleOfFive	RuleOfThree
CR-03.mol	19	639.056	0	1.75	2	1
CR-02.mol	17	611.002	0	1.75	2	1
CR-01.mol	28	490.852	0	2	1	1

Results and Discussion

Table-2: Predicted molecular properties of the dataset ligands

ligand	GScore	DockScore	LipophilicEvdW	PhobEn	PhobEnHB	PhobEnPairHB	HBond	Electro	Sitemap	PiCat	ClBr	LowMW	Penalties	HBPenal	ExposPenal	RotPenal	EpikStatePenalty	Similarity	Activity
CR-03.mol	-5.89	-5.89	-5.89	-0.36	0	0	-0.61	-0.16	-0.4	0	0	0	1	0	0.23	0.29	0	--	-41
CR-03.mol-2	-4.8	-4.8	-6.79	-0.9	0	0	-1.33	-0.27	0	0	0	0	4	0	0.2	0.29	0	--	-51.95
CR-03.mol-3	-3.7	-3.7	-6.37	-0.84	0	0	-0.48	0.02	-0.39	0	0	0	4	0	0.07	0.29	0	--	-46.17
CR-02.mol	-2.85	-2.85	-5.13	-0.56	0	0	-0.96	-0.34	-0.4	0	0	0	4	0	0.26	0.28	0	--	-43.34
CR-01.mol	-2.83	-2.83	-6.64	-1.23	0	0	0	-0.04	0	0	0	0	4	0	0.11	0.98	0	--	-47.02
CR-02.mol-2	-2.75	-2.75	-4.95	-0.36	0	0	-1.59	-0.4	0	0	0	0	4	0	0.27	0.28	0	--	-44.48
CR-03.mol-4	-1.02	-1.02	-5.32	0	0	0	-0.48	-0.05	0	0	0	0	4	0	0.54	0.29	0	--	-45.49

Table 3: Predicted pharmacokinetic (ADME) profile of isolated compounds

Molecule	QPpolrz	QPlogPC16	QPlogPoct	QPlogPw	QPlogPo/w	QPlogS	CIQPlogS	QPlog HERG	QPPCaco	QPlogBB	QPPMDCK	QPlogKp
CR-03.mol	68.148	18.597	23.179	0.393	12.042	-11.798	-11.88	-5.201	2092.76	-1.361	1099.03	-0.92
CR-03.mol	73.624	21.02	24.606	0.776	12.976	-14.66	-11.88	-6.401	2412.255	-1.439	1281.458	-0.767
CR-03.mol	73.603	21.058	24.556	0.784	12.975	-14.716	-11.88	-6.434	2429.413	-1.439	1291.312	-0.759
CR-03.mol	74.336	21.424	24.738	0.816	13.095	-15.149	-11.88	-6.571	2428.459	-1.463	1290.764	-0.772
CR-02.mol	69.532	19.432	23.325	0.984	12.109	-13.57	-11.284	-6.074	2463.832	-1.264	1311.098	-0.965
CR-02.mol	69.889	19.576	23.436	1.016	12.168	-13.711	-11.284	-6.133	2477.138	-1.267	1318.753	-0.953
CR-02.mol	69.611	19.491	23.315	0.969	12.125	-13.689	-11.284	-6.109	2479.212	-1.268	1319.947	-0.975
CR-02.mol	69.878	19.629	23.416	1.009	12.166	-13.822	-11.284	-6.176	2468.684	-1.278	1313.889	-0.967
CR-01.mol	62.799	21.429	19.931	-0.878	12.099	-14.401	-8.569	-7.431	2968.76	-2.009	1603.791	0.262

Table-4. Predicted pharmacokinetic (ADME) profile of isolated compounds

Molecule	CNS	SASA	FOSA	FISA	PISA	WPSA	volume	Human Oral Absorption	% Human Oral Absorption	SA fluorine	SA amideO	PSA
CR-03.mol	-2	1033.806	937.716	71.199	24.891	0	2155.519	1	100	0	0	51.387
CR-03.mol	-2	1184.83	1085.977	64.692	34.161	0	2290.139	1	100	0	0	51.018
CR-03.mol	-2	1187.761	1088.685	64.368	34.709	0	2289.485	1	100	0	0	50.97
CR-03.mol	-2	1210.638	1115.065	64.386	31.188	0	2308.649	1	100	0	0	50.958
CR-02.mol	-2	1110.106	1019.011	63.723	27.371	0	2157.434	1	100	0	0	50.9
CR-02.mol	-2	1117.557	1024.362	63.477	29.719	0	2165.781	1	100	0	0	51.467
CR-02.mol	-2	1116.388	1029.772	63.438	23.177	0	2160.401	1	100	0	0	50.892
CR-02.mol	-2	1123.419	1033.468	63.633	26.318	0	2166.337	1	100	0	0	51.458
CR-01.mol	-2	1255.362	1168.864	55.186	31.312	0	2164.749	1	100	0	0	36.868

Results

Docking results and protein ligand binding interactions of isolated compounds are shown in Table-1. Predicted molecular properties of the dataset ligands are shown in Table-2.Various molecular properties such as molecular weight, dipole , volume, solvent accessible surface area(SASA), hydrophobic component of SASA (FOSA), hydrophilic component of SASA (FISA), π (carbon and attached hydrogen) component of SASA (PISA) and weakly polar component of the SASA of the halogens (P&S) (WPSA) have been derived by Qikprop module as in Table-3.Molecular weight of all the isolated compounds are in normal range of (130-700Daltons).Parameters such as dipole, volume, SASA, FISA, PISA and WPSA are all in normal range as per the suggested module.

Predicted ADME parameters include partition co-efficinet, predicted aqueous solubility (QPlogS), probability of CNS effects, blockage HERG K^+channels (QPlogHERG), apparent CaCO -2 cell permeability (QPPCaCO), blood brain partition co-efficient (QPlogBB), apparent MDCK cell permeability (QPPMDCK), skin permeability (QPlogKp), binding to human serum albumin(QPlogKhsa) and human oral absorption of the given data sets of ligands are given in Table-4.All the compounds that is CR-1, CR-2, CR-3 showed higher human oral absorption with the highest of 100%.

CONCLUSION

In the current investigation it can be hypothesized that the probable COX-2 inhibitory potential of isolated components of CR that is CR-1 , CR-2, CR-3 and docking simulations were performed in order to identify binding efficiency and binding s how energy towards COX-2 protein. Among all the dataset CR-3 showed highest dock score of G(-)5.89 with better ADME profile. Higher the negative side of G score and D score more efficient the ligand predicts. Binding energy in the protein ligand interaction explain how fit the ligand binds with target protein . Molecular docking studies of these isolated components provided deeper insight in understanding the probable confirmation of their tested ligand in the COX-2 protein environment.

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