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Research Article

DOCKING STUDIES OF SUBSTITUTED CHROMAN ANALOGS AT ESTROGEN RECEPTOR

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ABSTRACT

Objective: The objective of the present study is to perform the molecular docking studies of some newly designed chroman analogs on estrogen receptor (ER) (PDB: 1YIM) by Glide v5.0.

Methods: The docking studies of designed chroman analogs were performed on the active site of ER (PDB: 1YIM) for anti-breast cancer activity using Schrodinger Glide v5.0. Absorption, distribution, metabolism, excretion properties of all designed compounds were also calculated by Qik Prop v3. 0.

Results: Among all compounds, compound 38 showed highest docking score (−8.17) in the series. Docking scores were compared with standard drugs tamoxifene (−11.08) and anastrazole (−7.86). All compounds were found to be within expectable range for percent human oral absorption, octanol/water partition coefficient (QP log Po/w), brain/blood partition coefficient (QP log BB), total solvent accessible surface area, and rule of five predicted by Qikprop.

Conclusion: Most of the compounds in the series showed good molecular docking score on the ER (PDB: 1YIM). Compound 38 (−8.16) exhibited better docking score than standard drug anastrazole (−7.86). Most of the pharmacokinetic properties conducted by Qikprop were found to be within the permissible range.

Keywords: Chroman, Docking, Estrogen receptor, Lipinski's rule of five.

INTRODUCTION

Among all cancers, breast cancer is one of the most common diagnosed cancers in the world. It creates a major health problem among women and consider as the second leading deaths in women [1]. The main cause includes age, personal health history, family health history, diet, exercise, and obesity. Although various forms of treatment available but the treatment is limited due to the resistant to chemotherapy and endocrine therapy [2]. Therefore, it is an urgent need to develop new effective drug for the treatment of breast cancer.

Estrogen receptor (ER) is found to be overexpressed in more than 60% cases of human breast cancers [3]. Designing drug-like molecules that can fit to the alpha ligand-binding domain of ER will be a promising starting point in developing anti-breast cancer drugs [4]. Recently, chroman molecules have received great attention in this field [5-8]. Chroman is an important class of oxygen containing heterocyclic compounds having many interesting activities, such as insulin release process inhibitors [9], human rhinovirus capsid-binding inhibitors [10], neuroprotective [11], antiestrogens [12], antioxidant [13], selective serotonin reuptake inhibitors [14], anti-HIV [15], antiarrythmic [16], and potassium channel activators [17], and well-tolerated in human subjects.

Therefore herein, we have designed some new chroman analogs by replacing nitrogen from chroman hydrazide with different substituted isatin and anhydride molecules and evaluated their binding ability to ER by molecular docking. As per the available literature, various chroman analogs had been designed and docked on ER, but chroman hydrazides containing isatin and anhydride molecules are new compounds and have not been docked.

METHODS

Structure selection and preparation for docking studies

The interactions and selectivity of the designed compounds were observed for alpha ligand-binding domain of ER. The X-ray crystallographic structures of the ER (PDB: 1YIM) were obtained from Protein Data Bank (www.rcsb.org) and prepared for molecular modeling [4]. Ligands were prepared using Maestro (v8.5) and minimized. An extensive set of conformations were generated using a liquid simulations-2005 (OPLS 2005) force field in solvent water conditions. Ligpreps were generated for three-dimensional co-ordinates of the conformers, their stereochemical, ionization, and tautomeric variations. The docking procedure was validated by extracting ligand CM4 from the binding site and re-docking it to the ER (PDB: 1YIM). Glide had successfully reproduced the experimental binding conformations of CM4 in ER with an acceptable root-mean-square deviation of 1.87 Å.

Docking studies

All ligands were docked with the obtained ligprep conformers into the active site of ER using the extra precision settings of the docking panel with default settings.

Absorption, distribution, metabolism, excretion (ADME) studies

In silico, ADME properties of the compounds (1-40) were calculated using QikProp (v3.1) module of Schrodinger [18]. It helps in predicting both the physically significant descriptors and pharmaceutically relevant properties. Different parameters such as predicted aqueous solubility (Log S), predicted apparent MDCK cell permeability (PMDCK), percent human oral absorption, octanol/water partition coefficient (QP log Po/w), brain/blood partition coefficient (QP log BB), and total solvent accessible surface area (SASA) were calculated. All compounds were neutralized before being used by QikProp. Compounds were also evaluated for acceptability of the inhibitors based on the Lipinski's rule of 5, which is necessary for rational drug design.

RESULTS AND DISCUSSION

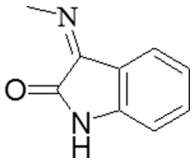
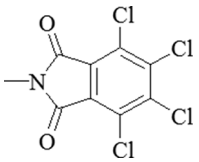
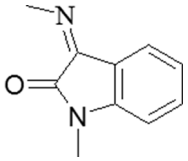
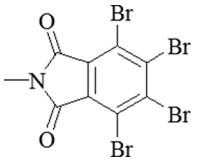
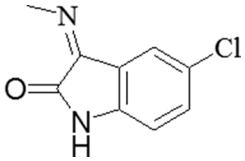
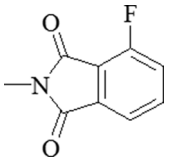
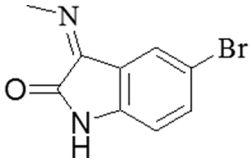
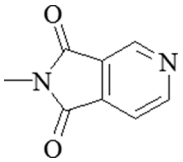
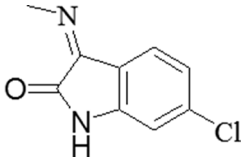
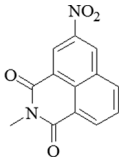
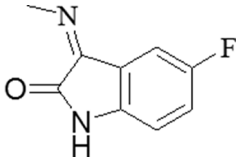
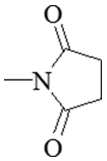
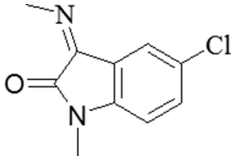
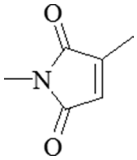
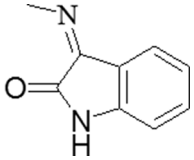
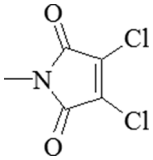
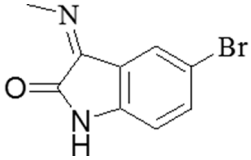
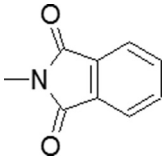
Design and molecular docking

Various compounds were designed by doing the substitution of chroman hydrazides by different isatin and anhydride molecules using chemoffice 2004 software and docking studies were performed by

Glide v5.0 [19] (Schrodinger-Maestro) for all the designed compounds against ER. Table 1 showed the docking scores of designed compounds (1-40) along with standard drugs. Docking score of compounds ranges between −4.00 and −8.17. All compounds showed less docking score than tamoxifene (−11.08). Compound 38 having citraconic anhydride possessed better docking score (−8.17) than standard drug, anastrazole (−7.86). Compounds 38, 36, 35, 26, 39, 11, 18, 5, and 27 exhibited good score (−8.17, −7.83, −7.66, −7.64, −7.50, −7.40, −7.34, −7.34, and −7.05, respectively). Compounds 14 showed lowest docking score (−4.00).

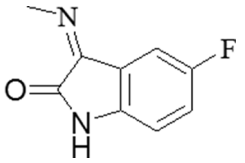
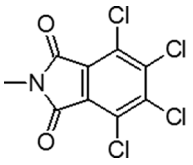
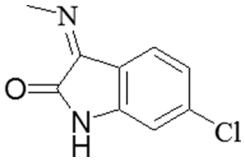
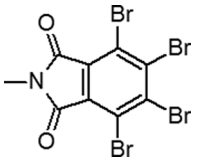
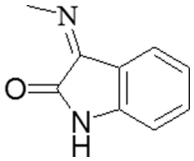
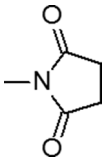
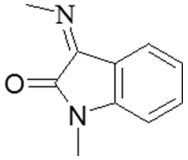
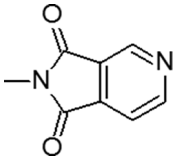
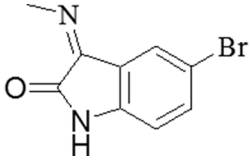
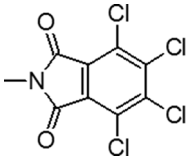
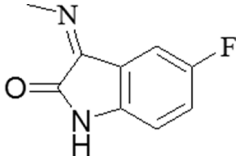
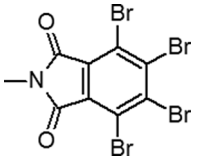
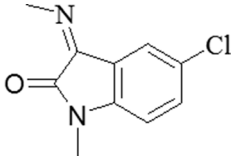
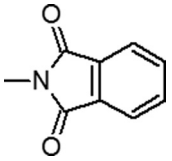
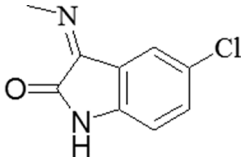
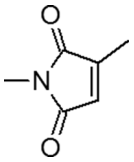
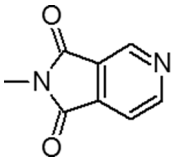
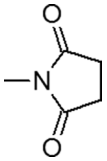
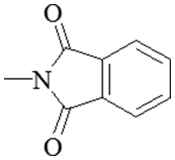
Ligand-receptor interactions for all docked compounds were analyzed on the basis of hydrogen bonding because H-bond plays a significant role in the structure and function of biological molecules. The carbonyl group (-COC<) of anhydrides of compounds 21, 26, 27, 29, 30, and carbonyl group (-CONHNH-) of compounds 2, 5, 8, 10, 11, 22, 23, 31, 32, interacted with CYS530 through their carbonyl oxygen atoms. While this carbonyl oxygen atom in highest docking scored compound 38, on other hand, involved in hydrogen bonding interaction with LYS531 (Fig. 1). The hydroxyl oxygen atom formed H-bond with LEU387 in compound 3, 18, 26, 27, and with GLU353 in compounds 21, 28, 29.

Table 1: Docking scores of designed chroman analogs (1-40) and standard drugs

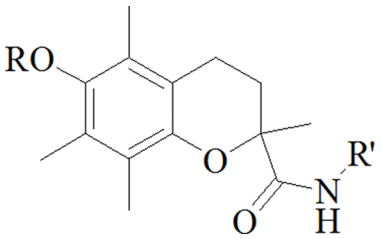
Entry	R	R'	Docking score	Entry	R	R'	Docking score
1	H		−6.50	22	H		−6.38
2	H		−6.80	23	H		−6.92
3	H		−6.24	24	H		−6.50
4	H		−5.59	25	H		−5.53
5	H		−7.34	26	H		−7.64
6	H		−5.87	27	H		−7.05
7	H		−4.83	28	H		−4.51
8	CH3		−6.95	29	H		−6.32
9	CH3		−5.65	30	CH3		−5.42

(*Contd*...)

Table 1: (*Continued*)

Entry	R	R'	Docking score	Entry	R	R'	Docking score
10	CH3		−6.32	31	CH3		−5.67
11	CH3		−7.40	32	CH3		−4.88
12	C6H5		−6.04	33	CH3		−6.00
13	C6H5		−6.79	34	CH3		−5.94
14	C6H5		−4.00	35	C6H5		−7.66
15	C6H5		−5.00	36	C6H5		−7.83
16	C6H5		−6.91	37	C6H5		−5.34
17	C6H5		−6.95	38	C6H5		−8.17
18	H	-NH2	−7.34	39	C6H5		−7.50
19	CH3	-NH2	−6.74	40	C6H5		−6.94
20	C6H5	-NH2	−5.25	Tamoxifene			−11.08
21	H		−6.92	Anastrazole			−7.86

Compounds containing anhydride groups showed better docking score as compare to compounds with isatin. R substitution by benzyl group seems to increase its binding profile. It had been observed that the top docking scored compounds interacted within the active site of the enzyme in a similar way. Interaction diagrams of best docked compound 38 showed in Fig. 2.



ADME studies

ADME properties of titled compounds (1-40) such as predicted aqueous solubility (Log S), predicted apparent MDCK cell permeability (PMDCK), percent human oral absorption, octanol/water partition coefficient (QP log Po/w), brain/blood partition coefficient (QP log BB), SASA, and rule of five were predicted by Qikprop v3.0 (Table 2). The human oral absorption percentage of all compounds was in the appropriate range of 81 to 100%. Compounds 2, 7-10, 12, 13, 20, 30, 33, 38, 39, and 40 showed 100% oral absorption. For selected lead compounds, the partition coefficient (QP log Po/w) was within the permissible range of −2.0-6.5 except for compounds 16, 35 and 37 (6.560, 6.747, and 7.030, respectively). Brain/blood partition coefficient (QP log BB) and SASA were also found to be within satisfactory range. Violations of Lipinski's rule of five were also calculated [20]. All compounds followed Lipinski's rule, thereby indicating their potential as a drug-like molecule. Most of the compounds do not follow the acceptable range for predicted aqueous solubility (Log S) and predicted apparent MDCK cell permeability (PMDCK). Table 2 showed some pharmacokinetic properties calculated for chroman analogs (1-40) by Qikprop simulation.

CONCLUSION

Various chroman analogs were designed and examined for its binding ability by molecular docking studies. From the docking studies conducted on the alpha ligand-binding domain of ER (PDB: 1YIM), it can be concluded that compound 38 (−8.16) showed better docking score than standard drug anastrazole (−7.86). Most of the pharmacokinetic properties conducted by Qikprop were within the permissible range. Therefore, the present work suggests these molecules as promising leads for the development of new anti-breast cancer agents.

Table 2: Pharmacokinetic properties (ADME) of titled compounds (1-40)

Comp	Log S	PMDCK	Percentage oral absorption	QP log Po/w	QP log BB	SASA	Rule of five
1	−5.379	99.717	89	3.463	−1.289	640	0
2	−6.470	196.011	100	4.158	−0.884	707	0
3	−5.864	196.145	92	3.904	−1.155	654	0
4	−6.701	258.248	95	4.245	−1.321	698	0
5	−5.983	192.493	81	3.890	−1.215	664	0
6	−5.626	152.632	91	3.668	−1.207	645	0
7	−6.990	439.954	100	4.669	−0.998	720	0
8	−5.970	290.597	100	4.305	−0.887	668	0
9	−6.222	429.852	100	4.563	−0.832	672	0
10	−6.007	347.939	100	4.336	−0.902	662	0
11	−6.789	697.295	91	4.810	−0.774	697	0
12	−6.717	370.173	100	5.643	−1.276	758	1
13	−7.550	442.614	100	6.231	−0.938	801	1
14	−6.751	659.196	87	6.035	−0.754	716	2
15	−6.866	663.180	87	5.822	−1.215	726	2
16	−7.704	1111.1	94	6.560	−0.681	796	2
17	−7.407	366.883	83	5.966	−0.695	742	2
18	−3.138	159.633	81	1.413	−0.941	736	0
19	−3.546	361.199	91	2.108	−0.635	521	0
20	−4.846	351.993	100	3.588	−0.835	619	0
21	−5.786	143.891	92	3.410	−1.194	639	0
22	−7.512	2546.7	88	4.884	−0.360	675	2
23	−7.252	2796.1	88	4.910	−0.517	703	1
24	−6.041	267.400	92	3.650	−1.044	680	0
25	−4.512	79.574	81	2.342	−1.279	631	0
26	−5.307	17.520	74	3.044	−1.906	677	0
27	−4.441	218.664	90	2.526	−0.892	597	0
28	−5.147	137.684	88	2.769	−1.173	638	0
29	−5.668	−5.812	95	3.468	−0.744	634	0
30	−5.873	320.661	100	3.718	−0.853	689	0
31	−7.086	10000	87	5.552	−0.031	706	2
32	−7.577	6796.3	86	5.587	−0.182	728	2
33	−4.412	510.221	100	3.68	−0.551	698	0
34	−5.151	172.409	93	3.016	−1.109	686	0
35	−8.625	4490.1	91	6.747	−0.499	805	0
36	−8.387	6574.5	95	7.030	−0.282	792	2
37	−6.820	268.314	93	5.145	−0.940	718	1
38	−6.864	312.057	100	4.968	−1.039	761	0
39	−6.599	229.964	100	4.662	−1.184	784	0
40	−6.423	320.420	100	4.635	−1.002	737	0

Log S: Predicted aqueous solubility (acceptable range: −6.5-0.5), MDCK cell permeability in nm/second (acceptable range: <25 poor, >500 great), percentage of human oral absorption (<25% is poor and >80% is high), predicted octanol/water partition co-efficient (acceptable range: −2.0-6.5), predicted blood brain barrier permeability (acceptable range: −3.0-1.2), total solvent accessible surface area (acceptable range: 300.0-1000.0), Lipinski's rule of five (maximum 4), ADME: Absorption, distribution, metabolism, excretion

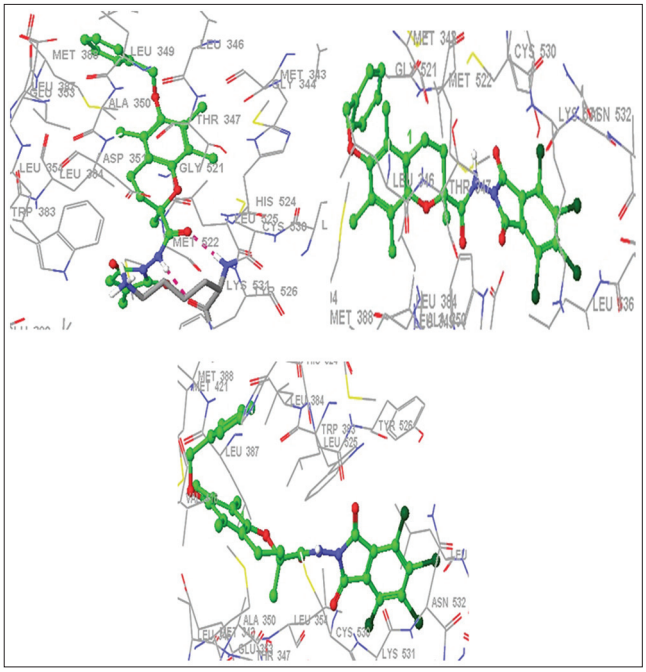


Fig. 1: Docked conformations of compounds 38 (a), 36 (b), and 35 (c) important amino acid residues of alpha ligand-binding domain of estrogen receptor. Ligands are shown as ball and stick, and interacting amino acids are shown as sticks. H-bonds are displayed in red dotted line

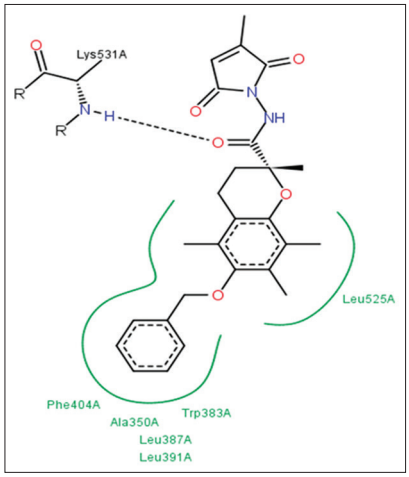


Fig. 2: Interaction diagram for compound 38. Hydrogen bond interaction represented by dotted lines. The hydrophobic residues located at the opening of the active site were represented as green lines

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