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Original research article

Design, synthesis and Docking Based Studies of Combretastatin analog as anti-cancer activity

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Abstract

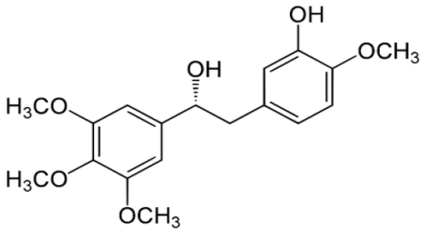
series of substituted 6-bromo-3-(3-chloro-2-oxo-4-arylazetidin-1-yl)-2-methylquinazolin-4(3H)-onehas been synthesized and evaluated for their biological activity. The title compounds (G_1-G_{10}) were prepared by the reaction of 5-bromo anthranilic acid with acetic anhydride to form 6-bromo-2-methyl-4H-benzo[1,3]oxazin-4-one which upon treatment with hydrazine hydrate in the presence of anhydrous pyridine form 3-amino-6-bromo-2-methylquinazolin-4(3H)-one. This resulting intermediate undergoes Schiff reaction with different aromatic aldehyde followed by reflux with chloroacetylchlorideand triethylamine. Ten different quinazoline derivatives (G_1-G_{10}) were synthesized. Structural assignments of these compounds have been made by elemental analysis, FTIR, ^{1}HNMR and Mass spectral data and the purity of the compounds was determined by TLC. All synthesized compounds have been tested for their anti-inflammatory activity by using diclofenac sodium as a standard drug. Most of the compounds showed a moderate degree of potent anti-inflammatory activity. The study concluded that the compound G_3& G_8were found to exhibit significant anti-inflammatory activity when compared to standard drug.

Keywords: Anti-inflammatory activity, Azetidine, 5-bromo anthranilic acid, Diclofenac sodium, Schiff base

Introduction

Cancer is one of the major causes of death throughout the world. In the U.S., the number of deaths caused by cancer is second highest and next to that from the cardiovascular diseases[1]. Tubulin, a validated target in cancer chemotherapy plays an important role in the formation of

the mitotic spindle, which provides the structural framework for the physical segregation of the chromosomes during the mitosis [2]. Combretastatin, binds to b-tubulin and strongly inhibit tubulin polymerization by binding to the colchicinee site [3,4,5] and disrupts the normal mitotic spindle function [6], and its action may be through endothelial cadherin signaling pathway [7]. Combretastatin was first isolated from the bark of African willow tree Combretum caffrum [8]. Two synthetic combretastatin analogs viz., D-24851 and ABT-75 are in advanced phased clinical trials [9]. Plenty of combretastatin analogs (Fig. 1) have been synthesized [10,11] till date with different substituents on aryl rings. The structure– activity relationship of these analogs reveals that methoxy substituents in ring B are required for biological activity. Furthermore, free hydroxyl group or other equivalent hydrogen bonding donors at ring B are also essential for activity [12]. Combretastatin has low aqueous solubility and Z-configured C–C double bond prone to isomerization to E-form during storage and administration, which results in dramatic reduction of activity [13]. To overcome this isomerization problem when heterocyclic rings viz., isoxazole, imidazole, triazole, azetidinones, etc. were introduced in place of the ethene bridge, however this also reduces activity because molecule becomes planar, as molecular modeling study confirms that combretastatin with ethene bridge has twisted geometries preferred for binding to the colchicines binding site [14,15]. The structure-based modeling studies have been reported to address important structure–activity relationship for the combretastatins[16,17,18] described a docking model for tubulin–combretastatin interactions and compared with colchicine. These studies suggested that the combretastatins show similar binding mode as colchicine and fit well at the colchicine-binding site of tubulin and interaction energies of the compounds with colchicine-binding sites were also calculated. The structure-based modeling studies have been reported to address important structure–activity relationship for the combretastatins[19,20,21,22]. A key structural feature is the presence of double bond forcing the two aromatic rings to stay within an appropriate distance is therefore responsible for tubulin affinity [23].



Structure of Combretastatin

A growing solid tumor relies on a developing vasculature to meet its needs in terms of oxygen, nutrients, depuration, etc. This implies that if the vascular bed that has developed within the tumoral mass can be made to collapse, tumoral growth can be significantly hampered. Indeed, the first proof of principle that this could be achieved was provided more than 10 years ago when a ricin-conjugated antibody directed against an endothelial protein was able to eradicate the tumoral mass in mice.1-4 Therapeutically, two pharmacological strategies can be foreseen that stand on this observation: [24] the development of the growing tumoral vasculature can be arrested by drugs; [25] the established vasculature perfusing the tumoral mass can be destroyed by drugs. Among the crucial questions in the field is how to specifically target the endothelial cells participating in the tumoral neo vasculature without causing damage to vasculature elsewhere. A wide body of data has emerged over this issue.3 It has now been shown that the developing vasculature and the tumoral vasculature express unique proteins and that this uniqueness can be used for selective pharmacological targeting. Indeed, if we consider a plasma membrane protein expressed solely on the undesired vasculature, we could envisage the use of specific antibodies conjugated with toxins, vaccines, etc.[26] Yet it is also possible that the neo vasculature is more sensitive over normal tissues to more traditional small-molecule drugs. Indeed, this strategy has also been exploited, and a number of compounds have entered or are entering clinical trials (these drugs are cumulatively referred to as low molecular weight vasculature-disrupting agents).[27]For example, the growth of the neo vasculature is dependent on activation of the vascular endothelial growth factor receptor, and therefore, a number of receptor antagonists have been devised and are currently tested or employed[28]. Disruption of tubulin polymerization also disrupts the formation of tumoral vasculature, and it is therefore no surprise that a number of agents have been brought forward into the drug pipeline that share this mechanism of action. The present review will concentrate primarily on the medicinal chemistry of one of these drugs, combretastatin A4 (CA-4a (1), Figure 1), because of space constraints and the presence of excellent reviews dealing with other aspects of this drug elsewhere.4-9 Yet it is difficult to limit the discussion to derivatives of one product when other products from a variety of natural sources share their capacity to inhibit tubulin polymerization binding at the same protein domain and are structurally related. Indeed, alongside CA-4, which displays a 1,2-diarylethene scaffold, other natural agents bear two polyoxygenated aromatic rings with a different molecular scaffold (e.g., biaryl for colchicine and steganacine or 1,1-diarylmethane for podophyllotoxin; Figure 2) and act on the same binding site. All these molecules have been shown to destroy neovasculature, but except for CA4, this effect is

observed close to the maximum tolerated dose. Although the reason for this is unknown, it can be hypothesized that their mode of interaction with tubulin is different.

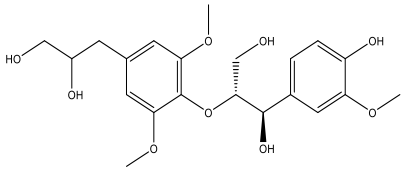
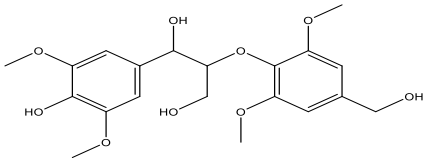
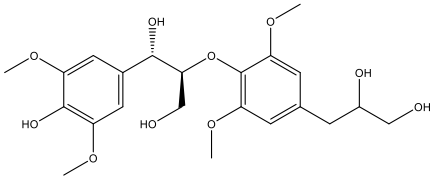
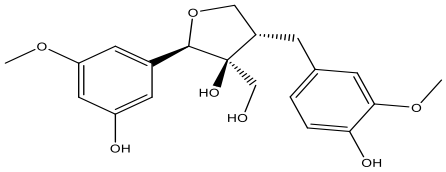
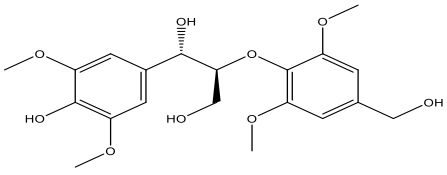
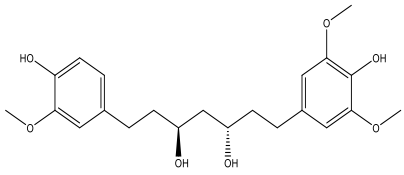
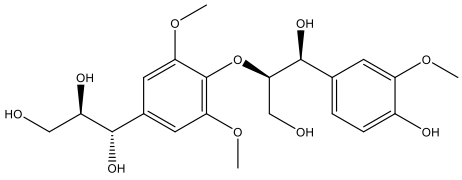
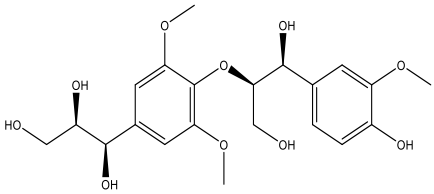
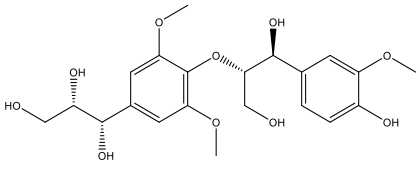
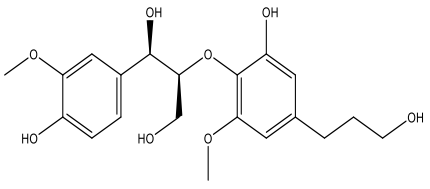
Materials and methods

An entire computational calculation was performed on Windows 10 (64-bit) operating systems with 64 GB RAM and 11th Gen Intel(R) Core (TM) i7-11800H @ 2.30GHz 2.30 GHz except molecular docking. Molecular docking, and binding energy calculations were carried out by Maestro, v10.4, Schrödinger software.

Data set collection

The 27 carbamate and aryl ether substituted Combretastatin derivatives with antagonistic activity oftheanti-cancer receptor were selected for the study [29]. Chemical structures and activity of the compounds were described in Table 1.

Table 1: 2D structure,

Com. Code	2D Structure	Com.	2D Structure
1		2	
3		4	
5		6	
7		8	
9		10	

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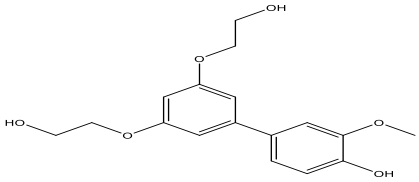

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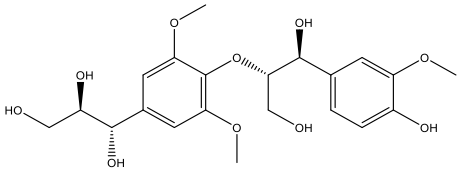

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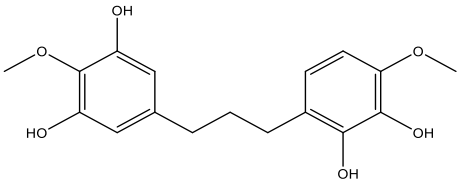

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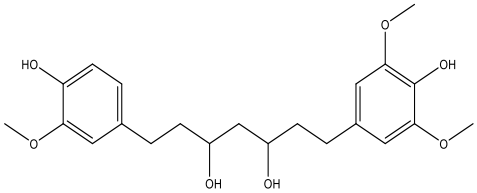

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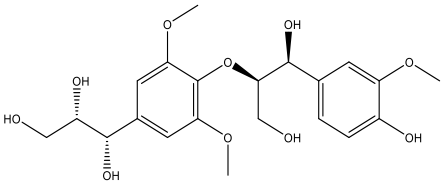

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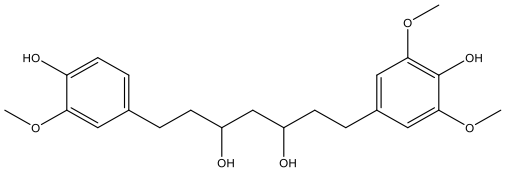

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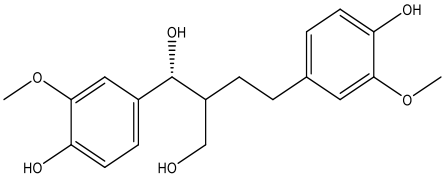

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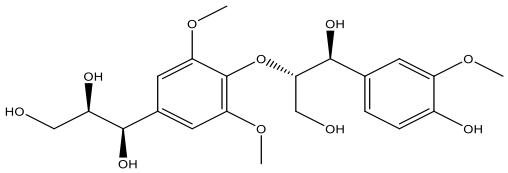

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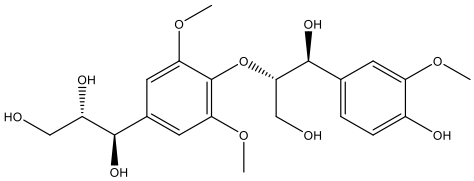


Moleculardocking

Selection of reference compounds

Various reported antagonists of the CRF-1 receptor were downloaded [30] and save as SDF format. Antalarmin is a potential drug that blocks the CRF-1 receptor [31]. Pexacerfont, Verucerfont, Emicerfont, CP-316,311, NBI-34041 and R121919 are other discovered molecules which have potential for the treatment of stress related disorders. Docking analysis has been done with a CRF-1 protein (1SA0) in the same grid byGlide.

Ligandpreparation

Ligands were prepare dusing LigPrep application (Schrödinger). In this process, OPLS 2005 force field was used for energy optimization for all ligands until 0.01 Å RMSD cut off not obtained. Tautomers and all possible ionizations tates were generate dusing Epic at target pH of 7±2 and low energy ring conformation for each ligand was also generated [32]. Prepared ligands were saved as a maestro out put format.

Preparation of target protein

In this study, the crystal structure of the tubulin-colchicine: stathmin-like domain complex protein (PDBID:1SA0) was retrieved from Protein Data Bank. The downloaded protein was in complex with the small molecule with 3.58 Å resolution [33]. The protein was pre-processed using a Protein Preparation Wizard by assigning bond orders, adding missing hydrogen atoms, adding missing atoms and loops. Following the generation of ionization and tautomeric states of hetgroups, finally restrained minimization till RMSD constraint value of 0.3Å was done using OPLS-2005 as force field after optimization no f hydrogen bonds, to refine the structure. Glide-grid generation for performing molecular docking, the grid generation is essential for more than one conformation on binding to ensure possible active sites. There fore, to perform docking, a rectangular receptor grid box was generated din 20Å size using grid generation module of Glide, in to the active site of the receptor by removing the ligand molecule. In order to default settings, the van der Waals radius scaling factor was set as 1 with partial charge cut off as 0.25, positional constraints were also selected additionally along with hydrophobic region [34].

XP glide docking

Docking is a powerful tool to screen large data set to locate compounds that appear to have the atomic structure and conformation to dock readily at the receptor. All compounds were docked into the binding site of target protein followed by grid generation process using the Glidepanelin extra precision (XP) mode. Prior to docking, ligands were set as flexible to generate conformations while protein was set as rigid.

Advanced settings were utilized with generation of 5000 poses per ligand, none constraints were chosen. Best 100poses were selected and energy minimized, finally, ligands were identified based on docking score which showed best interactions with active site of the target protein. Extra precision mode is coupled with force field-based parameters with default van der Waals radii scaling of ligand atoms. Glide Score includes a steric clash term, adds other terms, hydrophobic enclosure terms and penalties such as buried polar terms, amidetwist penalties, excluded volume penalties and given as-

Gscore = 0.05∗vdW + 0.15 ∗Coul + Lieo + Hbond + Metal + Reward + RotB+ Site

Where, vdW is Vander Waal senergy, Coulis Coulombenergy, Lipo for favourable hydrophobic interactions, Hbond for number of hydrogen bonds, Metal for metal binding, Rewards for various penalties, Rot Bispenalty for freezing rotablebonds and site for polar interactions in the active site of protein.

Pharmacokineticanalysis

Insilicopharmacokinetic parameters calculation of all compounds were carried out by using Qik Proppanel of Maestro [38]. Qik Propisan accurate, powerful tool for prediction of physically significant descriptors along with pharmaceutically appropriate properties [39] such as molecular weight, volume, donor and acceptor Hbond, human oral absorption, blood/ brain partition coefficient, human serum albumin binding. All compounds were also screened for drug-likenes sability [40]to follow the Lipinski's rule of five [41] which needs to be taken into account to consider design a good drug.

Physiochemical properties analysis

Physicochemical parameters calculation of all compounds was performed using a QikProp module of Maestro [41]. In this module, all compounds were also analyzed for drug likeness ability which essential to be taken into account to consider designing an ideal drug.

Result and discussion

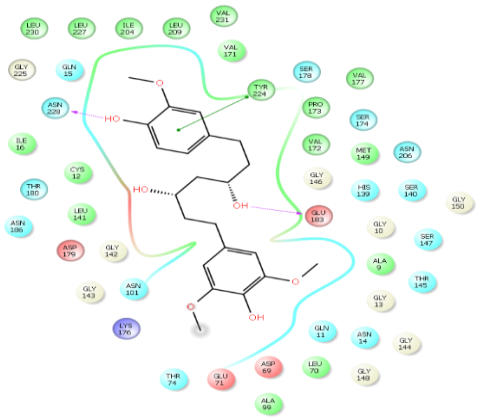
Molecular docking studies

To explore the investigation, we performed molecular docking analysis of all compounds with reference compounds. The receptor protein (PDB ID: 1SA0) has been selected for performing docking. The grid was generated around the binding site of protein, prior to docking. The docking results with binding energy calculation were revealed in the Table 1.

Com. Code	Glide Gscore	DockScore	dG Bind Rotpenal	dG Bind Lipo	dG Bind Hbond	dG Bind Low MW
1	-9.1	-9.1	0.4	-3.6	-4.7	-0.1
2	-8.7	-8.7	0.3	-3.0	-3.8	-0.1
3	-9.0	-9.0	0.3	-4.6	-3.6	0.0
4	-8.7	-8.7	0.2	-3.4	-3.8	-0.2
5	-8.7	-8.7	0.3	-3.0	-3.8	-0.1
6	-10.1	-10.1	0.4	-4.5	-3.6	-0.1
7	-9.8	-9.8	0.3	-2.6	-5.0	-0.0

8	-8.7	-8.7	0.3	-3.1	-4.3	-0.0
9	-9.8	-9.8	0.3	-3.0	-5.2	-0.0
10	-8.6	-8.6	0.4	-2.6	-4.9	0.2
11	-9.4	-9.4	0.6	-3.2	-4.8	-0.4
12	-9.3	-9.3	0.3	-4.3	-3.9	-0.0
13	-8.6	-8.6	0.3	-3.1	-3.3	-0.4
14	-10.1	-10.1	0.4	-4.5	-3.6	-0.1
15	-9.2	-9.2	0.3	-3.5	-4.5	-0.0
16	-10.1	-10.1	0.4	-4.5	-3.6	-0.1
17	-8.6	-8.6	0.4	-2.6	-4.9	-0.2
18	-8.9	-8.9	0.3	-3.9	-4.0	-0.0
19	-8.9	-8.9	0.3	-3.5	-4.1	-0.0

6



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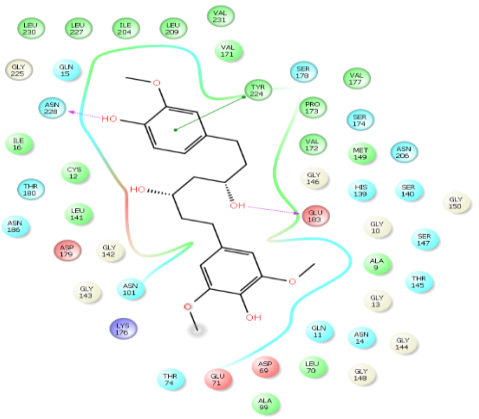

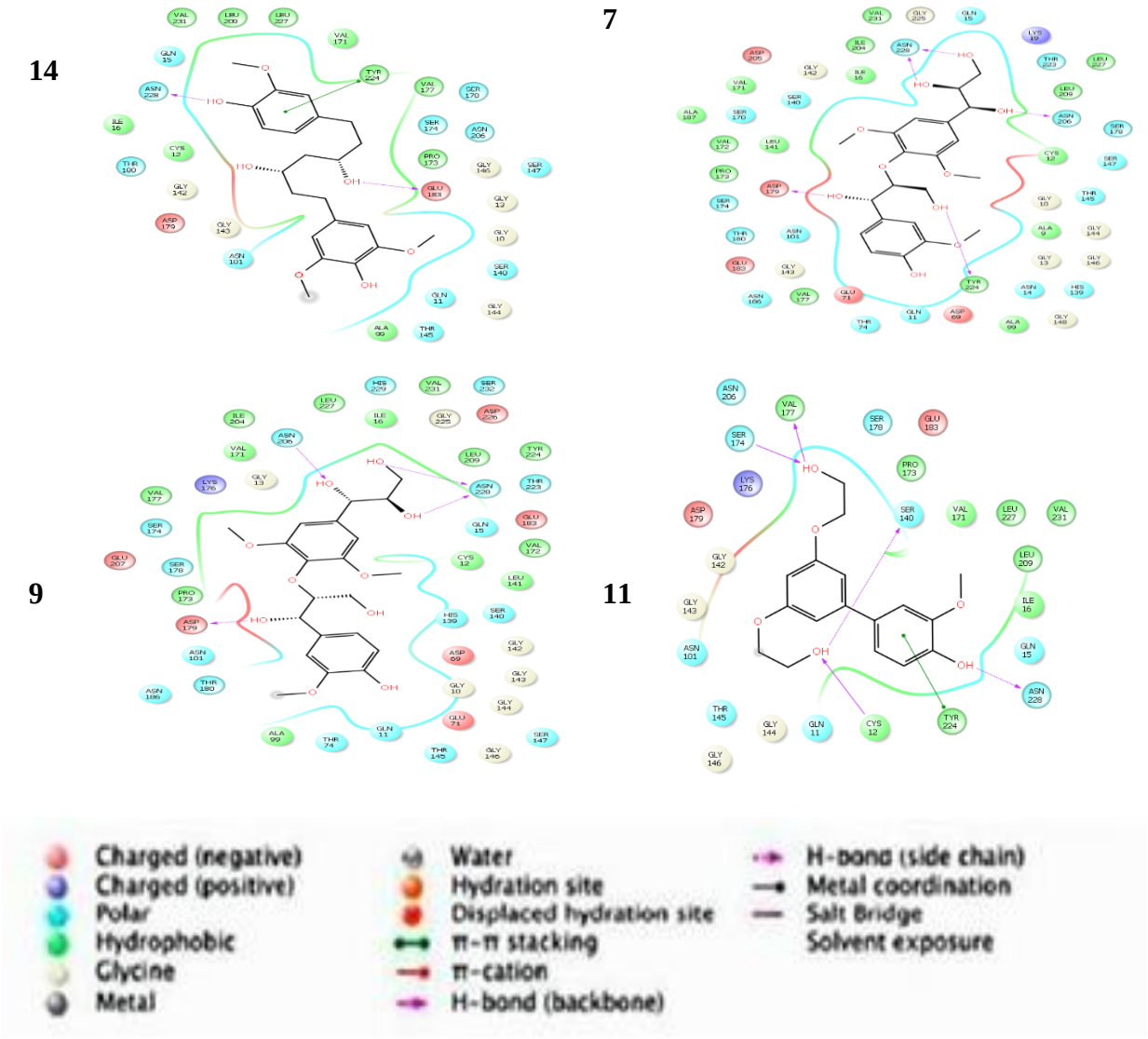

Figure 8: Target protein-ligand interaction diagram (A) Compound **6**(B) Compound **16**(C) Compound **14**(D) Compound 7 Compound **9**(F) Compound **11**

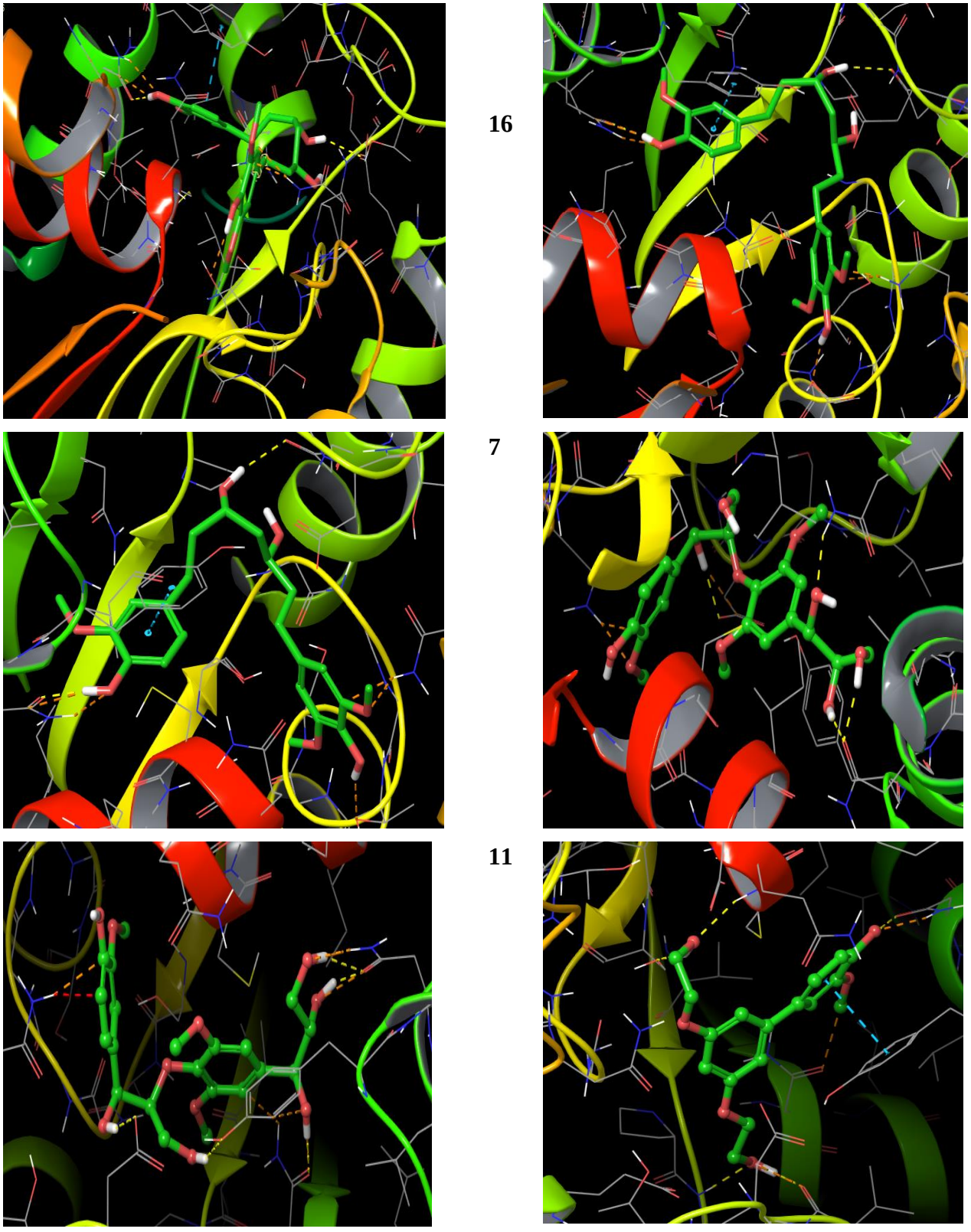

Figure 9: (A) Binding view of reference compound **6**(B) Hydrogen bond interaction of compound **16** (C) Binding view of compound **14**(D) Binding view of compound **7** (E) Binding view of compound 9 (F) Binding view of compound **11** with hydrogen bondsOverall, Compound **6** has highest binding affinity towards target protein. The docking results revealed that the binding residue ASN228,ASN101, Tyr224, Glu183, consists hydrophobic region of the protein and

responsible for hydrophobic interaction with compounds. More hydrophobic interactions enhance the binding affinity [43]. Therefore, comparison of synthesized compounds with reference molecules suggests that aromatic substitution at carbamate nitrogen shows excellent binding due to π-π stacking interaction. Large bulky groups do not contribute in binding as well as activity. According to the ligand interaction diagram, the binding pocket consists of ten hydrophobic (Phe193, Tyr74, Cys12, Gln15, Asp105, Pro173, Thr145, Glu31, Gly142, Asn101,Asp69, and Ala9), two hydrogen bonding (ASN228,Glu183) and one π-π stacking (Tyr224) amino acid residues.

Physiochemical properties

All synthesized compounds with reference compounds were subjected to evaluate their physicochemical parameters by using Qikprop tool of the maestro. Principle and therapeutic significant parameters are given in table 2 and 3 respectively. The QPlogPo/w value is used to calculate the lipophilic efficiency that measures the potency of drug. Therefore Octanol- water partition coefficient logP value is essential in rational drug design and QSAR studies. Polar surface area (PSA) is the sum of all polar atoms mainly oxygen and nitrogen including attached hydrogen. A molecule which have more number of rotatable bond (rotor) become more flexible and have good binding affinity with binding pocket [43].

Table 6: Principle pharmacokinetic parameters of selected compounds

Com.	MW	Dipole	donorHB	acceptHB	QPlogPC16	Volum	PSA
1	424.447	6.494	5	10.55	13.747	1289.653	137.396
2	410.42	8.171	4	9.6	12.157	1224.802	117.038
3	454.473	4.753	5	11.3	13.733	1337.706	143.455
4	376.405	5.034	4	7.15	11.837	1126.159	105.063
5	410.42	8.171	4	9.6	12.157	1224.802	117.038
6	406.475	5.775	4	7.15	14.042	1356.909	108.593
7	440.446	9.119	6	12.25	13.616	1262.548	148.485
8	440.446	8.355	6	12.25	13.528	1237.869	145.224

9	440.446	6.102	6	12.25	13.95	1283.187	150.131
10	394.421	3.448	5	8.85	13.208	1226.432	125.703
11	320.341	2.486	3	6.4	10.734	1037.568	89.354
12	440.446	4.884	6	12.25	13.886	1278.452	154.729
13	394.421	3.448	5	8.85	13.208	1054.207	125.703
14	406.475	5.775	4	7.15	14.042	1356.909	108.593
15	440.446	7.262	6	12.25	13.79	1270.693	145.98
16	406.475	5.775	4	7.15	14.042	1356.909	108.593
17	348.395	3.081	4	6.4	12.113	1131.855	101.574
18	440.446	6.547	6	12.25	14.083	1281.656	151.11
19	440.446	5.362	6	12.25	13.945	1272.326	147.845

Table 7: Therapeutic significant parameters of all selected compounds

Com. Code	CNS	QPlogPo/w	QPlogS	QPPCaco	QPlogBB	QPPMDCK	metab	QPlogKhsa	Percent HOA
1	-2	1.108	-2.708	65.619	-2.684	26.044	10	-0.601	65.956
2	-2	1.777	-2.813	402.709	-1.697	185.094	9	-0.478	83.974
3	-2	1.202	-2.485	92.196	-2.527	37.612	11	-0.615	69.149
4	-2	2.086	-3.377	316.319	-1.429	142.576	10	-0.138	83.909
5	-2	1.777	-2.813	402.709	-1.697	185.094	9	-0.478	83.974
6	-2	3.208	-4.703	194.734	-2.311	84.396	9	0.085	86.703
7	-2	0.211	-1.817	55.258	-2.699	21.629	10	-0.886	46.411
8	-2	0.096	-1.45	46.001	-2.628	17.74	10	-0.865	44.309
9	-2	0.211	-2	40.332	-2.887	15.389	10	-0.867	43.958
10	-2	1.458	-3.124	101.159	-2.532	41.579	9	-0.512	71.366
11	-2	2.03	-3.179	385.311	-1.58	176.466	6	-0.31	85.113
12	-2	0.302	-1.951	54.847	-2.737	21.455	10	-0.87	46.88
13	-2	2.197	-3.281	206.413	-1.742	89.88	8	-0.133	81.238
14	-2	3.208	-4.703	194.734	-2.311	84.396	9	0.085	86.703
15	-2	0.363	-1.942	74.734	-2.614	29.975	10	-0.891	49.645

16	-2	3.208	-4.703	194.734	-2.311	84.396	9	0.085	86.703
17	-2	2.291	-3.37	241.096	-1.823	106.309	7	-0.184	82.996
18	-2	0.244	-2.028	43.263	-2.876	16.602	10	-0.878	44.699
19	-2	0.294	-1.898	54.971	-2.722	21.507	10	-0.876	46.852

Conclusion

Cancer are the disorders caused severe harmful effect on human beings. Due to the role of CRF in stress vulnerability and hyper-secretion in stress disorders, it makes an attractive target for anti-depressant drug development programme. In summary, we have obtained 2D and 3D-QSAR model using 27 substituted pyrazinone derivatives with different training sets. Both models were found to be robust, predictive and significant. In both models, a high r^2, q^2 and low standard value were found that indicated the robustness of the generated model. There were various 2D and 3D-descriptors calculated and their positive and negative contribution was evaluated. The results suggest that nitrogen substituted carbamate with an aromatic ring enhance the activity. Presence of the less bulky group and highly electronegative substituent at the R' position increases the antagonistic activity. The presence of sp^2 hybridized nitrogen, core heterocyclic ring involved the hydrophobic and hydrogen bond interaction with binding site. Docking results revealed that compound **11i** (2-(5-chloro-3-((6-methoxy-2,5-dimethylpyridin-3-yl)amino)-2-oxopyrazin- 1(2*H*)-yl)-2-cyclopropylethyl (2,4-dichlorophenyl)carbamate) has binding affinity towards the binding pocket of target protein in comparison to all reference compounds. The residue of the CRF-1 protein involved in binding mechanism are Phe193, Tyr194, Trp119, Tyr139, Pro195, Tyr8, Trp287, Met19, Phe288, and Ala286 (hydrophobic), Asp284, Glu305 (hydrogen bonding) and Trp9 (π-π stacking). Simulation studies revealed that compound **11i** has better binding as compared to reference compound **2** (3-(6-(dimethylamino)-4- methylpyridin-3-yl)-2,5-dimethyl-*N*,*N*-dipropylpyrazolo[1,5-a]pyrimidin-7-amine). The presence of the NH group makes the compound lipophilic. Synthesized pyrazinone substituted compounds showed an excellent binding affinity and antagonistic activity as compared to reference compounds, thus design new antagonists of CRF-1 using observed information gained more potent and efficacious compounds. Relative binding energy and physicochemical parameters were also evaluated for all compounds. Most of the compounds including reference compounds shown excellent pharmacokinetic and therapeutic profile. Therefore, substituted pyrazinones could be potent and efficacious class for treatment of depression, anxiety and post-traumatic stress disorders.

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