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Anti-cancer potential of natural products containing (6*H*-dibenzo[*b,d*]pyran-6-one) framework using docking tools

Ishtiaq Jeelani[1], Hitoshi Abe[2], Allah Nawaz[3], Mrinalini Bhosale[4], Saeed Ahmad[5], Abeda Jamadar[6], Khursheed Ahmed[4], Tanzeela Qadir[7], Andleeb Amin[7], Praveen Kumar Sharma[7] and Safia Abidi[8]*

[1]Graduate School of Innovative Life Science, University of Toyama, Gofuku, Japan
[2]Faculty of Engineering, University of Toyama, Gofuku, Japan
[3]Department of Molecular and Medical Pharmacology, Faculty of Medicine, University of Toyama, Toyama, Sugitani, Japan
[4]Department of Chemistry, Abeda Inamdar Senior College, K.B Hidayatullah Rd., Camp, Pune, India
[5]Rawalpindi Medical University, Rawalpindi, Pakistan
[6]University of Kansas Medical Centre, Kansas USA
[7]Department of Chemistry, School of Chemical Engineering and Physical Sciences, Lovely Professional University, Phagwara, Punjab, India
[8]Department of Phamacognosy, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi, Pakistan

Abstract: To explore complex biological and chemical systems, pharmaceutical research has effectively included several molecular modeling tools into a range of drug development initiatives. Molecular docking methods are widely employed in current drug design to investigate ligand conformations within macromolecular targets' binding sites. This method also estimates the ligand-receptor binding free energy by assessing critical phenomena involved in the intermolecular recognition process. In an attempt, several natural products have been synthesized in our laboratory. All the synthesized compounds containing (6*H*-Dibenzo[*b,d*]pyran-6-one) framework were subjected to molecular docking studies for the inhibition of CYP1B1 and BCL2 proteins using Auto Dock Vina software and the interacting amino acid residues were visualized using Discovery Studio, to look into the binding modalities that might influence their anticancer properties. The in silico molecular docking study outcomes showed that all the synthesized compounds having optimum binding energy and have a decent affinity to the active pocket, thus, they may be considered as a respectable inhibitor of CYP1B1 and BCL2 proteins.

Keywords: Anticancer, docking, palladium, protein-ligand, lactone, coupling reaction.

INTRODUCTION

Cancer is the most lethal disease, and researchers are working to find potential anticancer treatments. The fact that cancer acts in the human body through multiple routes involving many cancer macromolecules make it extremely difficult for a single medicine to block all of these macromolecules at the same time (Taleb B, 2019). To evaluate the anticancer potential of medications or chemicals, researchers used a variety of *in vitro*, *in vivo*, and computational methodologies. Docking is one of these strategies that has been frequently employed in the development of cancer drugs (Wilcken *et al*., 2013, Fischer *et al*., 2021). Natural products have the potential to deliver the drugs at the stipulated site with the highest efficacy. Phytochemicals derived from curcumin, plumbagin, and resveratrol are reported to show target-specific anticancer activity (Zubair *et al.,* 2017, Lohning *et al.,* 2017).

Because of their distinctive biological actions, a range of natural compounds with the highly oxygenated 6H-dibenzo[*b,d*]pyran-6-one core have grabbed our interest. Using the Pd-mediated intramolecular biaryl coupling reaction with phenyl benzoate derivatives to generate the 6H-dibenzo[*b,d*]pyran-6-one ring system, we have reported several natural product syntheses. (Abe *et al*., 2014). Utilizing this transformation, we planned the efficient syntheses of hyalodendriol C (1), palmariol A (2) and B (3), urolithin C 3-glucuronide (4), and graphislactone A (5), B (6) and G (7) (Abe *et al*., 2021, Itaya *et al*., 2021, Jeelani *et al*., 2021). We also aim at synthesizing urolithin M 7-glucuronide (8) which has shown significant molecular docking results, therefore, making it our next favorite target compound for synthesis. Reportedly, graphislactone G has exhibited strong anticancer activities against SW111 cancer cell lines (Abe *et al*., 2010). However, no other compounds have been tested against any cancer cell lines. Since all these compounds have closely related structural frameworks hence, we hypothesize that other compounds can also exhibit strong anti-cancer properties. To prove this hypothesis, we have performed molecular docking studies of all the compounds with CYP1B1 (Li *et al*., 2017, Murray *et al*., 1997) and BCL2 (Youle and Strasser, 2008) protein and we have found amazing results for all the synthesized compounds. Molecular docking is an

**Corresponding author:* e-mail: safiaabidi@yahoo.com

optimization problem that predicts the structure of an intermolecular complex created by two or more molecules by describing the "best-fit" orientation of a ligand that binds to a certain protein of interest (Salmaso and Moro, 2018, Chen *et al*., 2020). Because of its applications in medicine, the protein-ligand interaction is the most interesting instance. A ligand is a small molecule that interacts with the binding sites of proteins. Binding can take place in several different mutual conformations known as binding modalities. Molecular docking is commonly utilized in modern drug design to investigate drug-receptor interactions. Molecular docking is widely used to anticipate the binding orientation of small molecule therapeutic candidates to their protein targets in order to anticipate the small molecule's affinity and activity (Pereira and Aires-de-Sousa, 2018).

Especially hyalodendriol C, urolithin M 7-glucuronide, and graphislactone G have higher binding energy in the protein cavity revealing higher activity in the protein pocket. The hydrophobic interactions of all the reported molecules affect their binding and hence the molecules with higher binding energy and hydrogen bond are said to show more inhibition than others. All the synthesized compounds show optimum hydrogen bond distance and are well fitted in the protein cavity. Among the above-mentioned compounds, graphislactone G (7) was isolated from *Cephalosporium acremonium* IFB-E007 in 2005 (Zhang *et al*., 2005). In addition, palmariol A (2) and B (3) were found from *Lachnum palmae* in 2010, hyalodendriol C (1) was isolated from an endophytic fungus associated with the hybrid 'Neva of Populus deltoides' P. nigra L (Mao *et al*., 2017). Whereas, graphislactone A-B were isolated from the cultured lichen mycobiont of *Graphis scripta var. pulverulenta*. Recently we reported the total synthesis of compounds, 1, 2, 3, 4, and 7 by making use of Pd catalyzed intramolecular biaryl coupling reactions of phenyl benzoate derivatives. However, the total synthesis of compounds 5 and 6 was reported by our research group long back. Among the various provisions of this type of ring structure, the Pd catalyzed biaryl coupling reaction is one of the most convenient procedures for forming carbon-carbon bonds between two aromatic rings. The intramolecular biaryl coupling reaction of phenyl benzoate derivatives with the Pd reagent has been shown to be beneficial in the production of several of these natural compounds. The outstanding structural feature of compounds 1, 2, 3 and 7 is that these compounds commonly possess a chlorine atom on the 6*H*-dibenzo[*b,d*]pyran-6-one ring (fig. 2). Natural products with a halogen atom on their aromatic ring have caused a great deal of attention due to their intriguing biological properties. As a result, total syntheses of such compounds have attracted the interest of synthetic chemists.

In fig. 1, our simple synthetic plan is shown in which the sequential transformation of esterification between the corresponding benzoic acid and phenol, followed by the Pd-mediated coupling reaction is involved (Harayama *et al*., 2000, Ahmed *et al*., 2019).

MATERIALS AND METHODS

Molecular docking experiments were performed using Auto Dock Vina software (Trott and Olson, 2010). All the chemical structures were drawn in Chem Draw and their 3D structures were procured from 3D corona software. A protein pdb file was obtained from the online depository of RCSPBD for CYP1B1 [6OYU] and BCl2 [1K3K] (Berman *et al*., 2003, ww, 2019). The proteins were cleaned to remove water, heteroatoms and ligand molecules, and the cleaned proteins were used for docking. The cleaned protein was converted into pdbqt file using MGL tools software. Docking experiments were performed by keeping protein rigid and allowing the ligand to occupy any place in the cavity. The grid size for the proteins were BCL2 [106,126,120] and CYP1B1 [94, 66, 124] in X, Y and Z axis respectively. The two reported proteins and the synthesized ligands were docked into each other using Auto Dock Vina software. The best-fitted conformation amongst the ten confirmations was visualized using Pymol software. The number of hydrogen bonds and amino acid residues involved in stabilizing the ligand in the protein pocket were obtained from Pymol software. Docking images showing the protein in cartoon and surface view shown in the results are procured from Pymol visualization tool.

RESULTS

The docking results of the reported molecules with CYP1B1 protein are tabulated in table 1 and the docking images can be seen in fig. 2. All the reported molecules show high binding in CYP1B1 protein and the binding energy ranges from -7.3 to -10.6 Kcal/mole. The high values of binding energy attribute to higher inhibition of the protein and thus all these molecules can act as a potent inhibitor of CYP1B1 protein. Amongst the reported molecules urolithin M 7-glucuronide shows the highest binding of -10.6Kcal/mol in the protein cavity. Ligand molecules are stabilized in the protein cavity by hydrophobic interactions and hydrogen bonds. The number of hydrogen bonds explains the stable binding between ligand and protein and during the transport process, the ligand gets least released due to external pressure. On average one hydrogen bond is formed by this series in the protein pocket and the hydrogen bond with glycine is most prominently visible. CYP1B1 protein has a reported inhibitor and the energy of all the molecules is greater than the inhibitor reported.

The docking images are shown in three different styles to better understanding the ligand-protein binding. The first

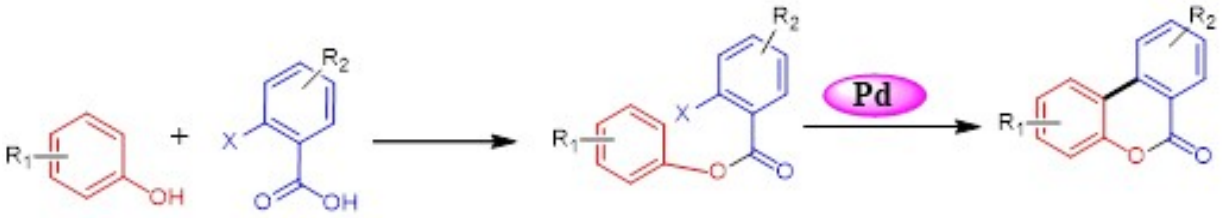


Fig. 1: General synthetic scheme

Table 1: Docking results of synthesized compounds in CYP1B1 cavity.

S. no.	Name	Binding energy [Kcal/mol]	Number of hydrogen bond/bonds	Bond distance [Å]	Amino acid residues involved in bonding
1.	Hyalodendriol C	-9.3	3	2.0,2.6,2.4	SER-127,HIS-227
2.	Graphislactone G	-9.2	1	2.7	HIS-227
3.	Graphislactone A	-7.5	1	2.2	ASN-228
4.	Graphislactone B	-7.1	1	2.5	SER-239
5.	Urolithin 3-C glucuronide	-7.7	5	2.1,2.3,2.2,2.1,2.3	ARG-161,SER-150,SER-150
6.	Urolithin M 7-glucuronide	-10.6	2	2.3,2.6	HIS-227,GLN-332
7.	Palmariol A	-8.2	2	2.2,2.1	ARG-117,ILE-399
8.	Palmariol B	-7.3	2	2.1,2.7	LEU-309,HIS-71
9.	Standard inhibitor	-4.8	1	2.3	ILE-399

Table 2: Docking results of synthesized compounds in BCL2 cavity.

S. no.	Name	Binding energy [Kcal/mol]	Number of hydrogen bond/bonds	Bond distance[Å]	Amino acid residue involved in bonding
10.	Hyalodendriol C	-7.1	2	2.1,2.3	GLN80, MET82
11.	Graphislactone G	-6.6	1	2.1	GLN85
12.	Graphislactone A	-6.6	1	2.3	GLN87
13.	Graphislactone B	-6.5	1	2.3	GLN85
14.	Urolithin 3-C glucuronide	-4.8	1	2.6	ASP67
15.	Urolithin M 7-glucuronide	-7.6	7	2.2,2.3,2.6,2.3,2.1,2.6,2.2	GLY126, GLY80, SEB77, GLY78, ARG31
16.	Palmariol A	-8.2	4	2.1,2.5,2.1,2.6	ASN82, MET83, SER77
17.	Palmariol B	-5.3	2	2.8,2.3	ARG131
18.	Standard inhibitor	-4.8	1	2.4	HIS-30

image shows only the ligand and the amino-acid involved in hydrogen bonding with it, the second image shows a cartoon view of protein showing the coiling of protein and the third image shows the protein in mesh form helping us understand the penetration of the ligand in the protein. On visualizing the protein in the surface, the ligand was completely encapsulated in the cavity and hence mesh visualization is preferred. The entire series of molecules show similar behavior and hence all the images were visualized in mesh view. In ribbon view the protein primary and secondary coiling are visible and how well the ligands occupy the cavity is seen. Thus, all the molecules reported in this paper show significant affinity towards CYP1B1 protein and they can prominently act on inhibition of its activity.

Docking results of a series of reported compounds in BCL2 protein are shown in table 2 and the docking images are shown in fig. 3. The series shows binding energy ranging from -4.8 to -8.2Kcal/mole. The negative sign of the binding energy attributes to the bound state and hence the values of binding energy are seen for commenting on results.

DISCUSSION

Structurally related eight molecules synthesis is reported in our earlier papers. In this paper, we have explored the docking studies of these molecules in two proteins i.e., CYP1B1 and BCL2.

The activity of cytochrome P450 is required for the metabolism of both endogenous and foreign substances (Nebert and Russell, 2002). The CYP protein was previously known as "cytochrome P450" after the discovery of a colorful pigment in the cell with a 450 nm wavelength spectrum when reduced and linked with carbon monoxide. Because these proteins are not real cytochromes, the word continues to be overused. They're more properly referred to as heme-thiolate

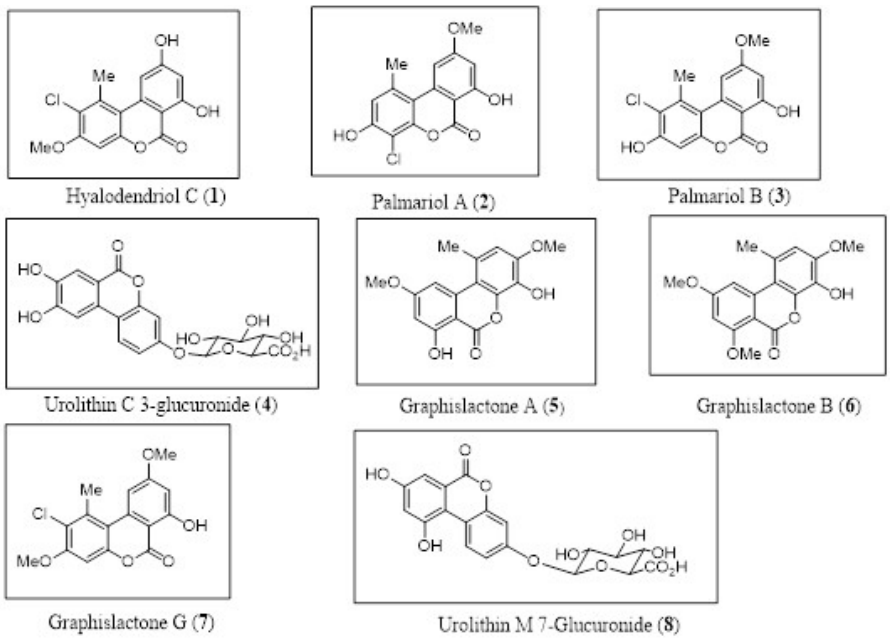


Fig. 2: Structures of the compounds used for molecular docking.

monooxygenases (Guengerich, 2008). Aromatic hydrocarbon receptors (AhRs) trigger CYP enzymes, which are made up of a huge number of proteins. They take part in the metabolism of xenobiotics as well as endogenous substances such as oestradiol. They're also in charge of most foreign substance biotransformation and drug detoxification (Liu *et al*., 2013, Bartuzi *et al*., 2017). Many factors influence CYP expression, including gender, age, and genetic variants. Xenobiotic stimulation, cytokine, and hormone modulation, and disease states can all alter expression (Cui and Li, 2014, Wang *et al*., 2021).

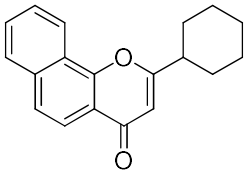
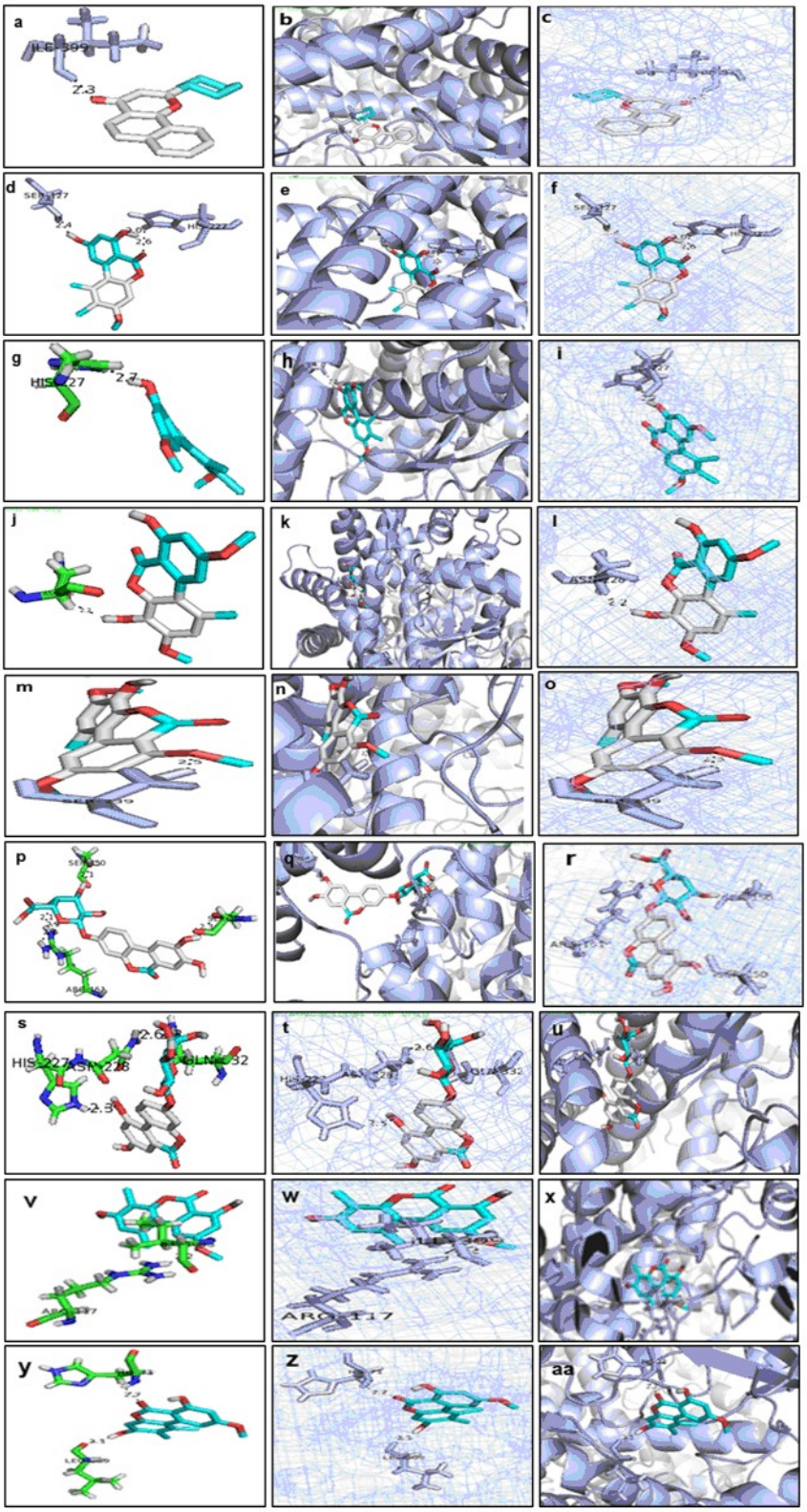


Fig. 3: Standard inhibitor structure

In estrogen-dependent malignancies such as breast and ovarian cancer, the CYP1 family plays a critical role. CYP1A1, CYP1B1 and CYP1A2 are proteins involved in the bioactivation of procarcinogenic substances. Cytochromes P450 (CYPs) are a superfamily of heme-containing enzymes that catalyze oxidative biotransformations of both endogenous and exogenous substances such steroidal hormones, bile acids, various types of xenobiotics and medicines and are thus vital for biological drug discovery. CYP1B1, CYP1A1 and CYP1A2 are members of the CYP1 family, which is responsible for the bioactivation of procarcinogenic substances. CYP1 family substrates include polycyclic aromatic hydrocarbons (e.g., benzo[α]pyrene and 7,12-dimethylbenz[α]anthracene) (Conney, 1982, Androutsopoulos *et al*., 2009, Xu *et al*., 2021). These are procarcinogens that the CYP1 family activates. As a result, the CYP1 family has been identified as a potential target for chemoprevention of these carcinogens. The CYP1 family is also involved in the metabolism of endogenous estrogens, such as 17-estradiol (E2) and estrone (E1), which are responsible for estrogen-dependent malignancies such as breast cancer and ovarian cancer. 2-Hydroxylation of E2, which is regulated by CYP1A1 and CYP1A2, has been identified as a primary inactivation mechanism of E2, yielding 2-hydroxy-E2 (2OHE2) as a metabolite and methylation by catechol-O-methyltransferase (COMT), which yields an inactivated metabolite. CYP1B1, on the other hand, creates 4-hydroxy-E2 (4OHE2), because they are rapidly converted to oxidized products with resistance to COMT-mediated inactivation, 4OHE2 retains substantial estrogenic activity and is gradually oxidized to quinone compounds (Cavalieri *et al*., 1997) which are tumor initiators, in contrast to 2OHE2. Under normal circumstances, the average adult person creates and eliminates B60 billion cells each day, with new cells created by cell division and old cells removed primarily by apoptosis, resulting in a balance. The capacity to adjust cell counts at both entry and exit locations allow for greater flexibility in responding to stress, damage and physiological stimuli. However, it poses a risk in terms of neoplasia, as genes responding to stress, damage and physiological stimuli. However, it poses a risk in terms of neoplasia, as genes that usually repress or trigger physiological cell death are frequently dysregulated in malignancies, with faulty cell death processes now recognized as one of cancer's six hallmarks (Hanahan and Weinberg, 2000). BCL-2 family



(a,b,c) standard inhibitor; (d,e,f) Hyalodendriol C; (g,h,i) Graphislactone G, (j,k,l) Graphislactone A; (m,n,o) Graphislactone B; (p,q,r) Urolithin 3-C glucuronide; (s,t,u) Urolithin M 7-glucuronide; (v,w,x) Palmariol A; (y,z,aa) Palmariol B

Fig. 4: Best docked poses for respective compounds in CYP1B1 protein.

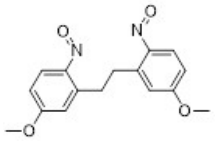
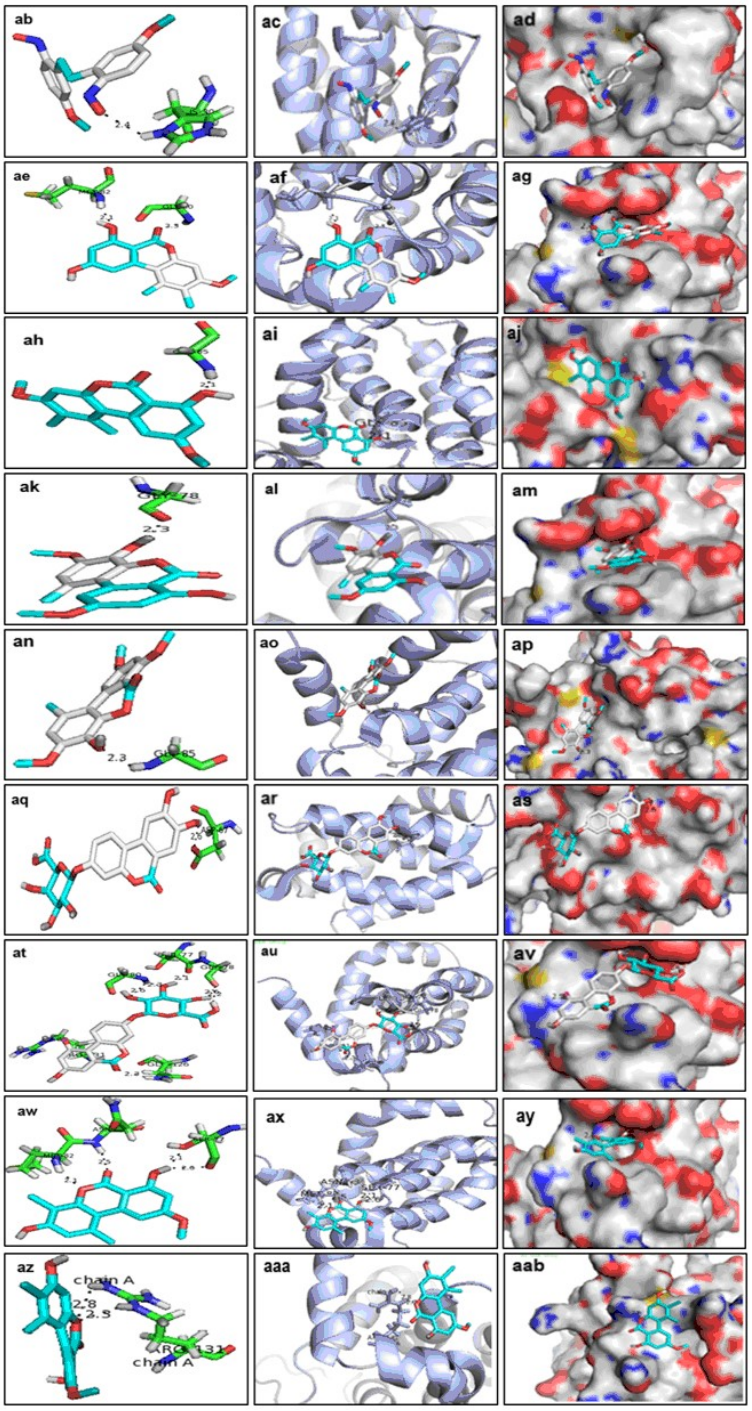


Fig. 5: Standard inhibitor structure



(ab, ac, ad) standard inhibitor; (ae, af, ag) Hyalodendriol C; (ah, ai, aj) Graphislactone G, (ak, al, am) Graphislactone A; (an, ao, ap) Graphislactone B; (aq, ar, as) Urolithin 3-C glucuronide; (at, au, av) Urolithin M 7-glucuronide; (aw, ax, ay) Palmariol A; (az, aaa. aab) Palmariol B

Fig. 6: Best docked poses for respective compounds in BCL2 protein.

proteins are involved in cell death regulation and can regulate a variety of cell death pathways, including apoptosis, necrosis, and autophagy (Levine and Kroemer, 2008, Pinzi and Rastelli, 2019). Changes in their expression and function play a role in the development and progression of human malignancies, making them potential therapeutic targets now being tested in human clinical trials.

Amongst the series, palmariol A shows the highest binding energy -8.2Kcal/mole. The reported inhibitor of BCl2 shows -4.8Kcal/mole binding energy and one hydrogen bond with histidine molecule. The reported series of molecules show binding with glycine molecules. All the molecules show at least one hydrogen bond with amino acids in the cavity of the protein. Urolithin M 7-glucuronide shows the highest number of hydrogen bonds i.e., 7 which means it is occupying the protein volume completely. Palmariol A with the highest binding energy shows 4 hydrogen bonds showing hydrophobic interactions with the protein and sitting the pocket correctly. Docking images are shown in three ways, the first one shows ligand and amino acid residue involved in binding, the second one shows protein in cartoon view and the third one shows the ligand occupying the pocket in the protein. This series shows high occupancy in the cavity of the protein. The ligands penetrate the protein cavity and are stabilized by hydrogen bonds and hydrophobic interactions. BCl2 protein shows a well-defined pocket and the entire series occupies this pocket effectively. This can be seen from the docking images in the surface view. Thus, the entire series of reported molecules can act as a good inhibitor of BCl2 protein.

CONCLUSION

We achieved the total synthesis of several natural products containing 6*H*-dibenzo[*b*,*d*]pyran-6-one structural framework. In the synthesis, the palladium-mediated intramolecular aryl–aryl coupling reaction was found to be very useful for the synthesis of these types of natural products. The series of molecules mentioned in this paper have high efficiency of binding with CYP1B1 and BCl2 protein. The series shows high penetration in CYP1B1 and BCl2. The docking images of BCl2 show a predefined pocket and thus all the ligands are seen to occupy the pocket. CYP1B1 pocket is embedded inside and ligands are seen to occupy this pocket. The reported molecules show binding energies higher than the standard inhibitors and hence they can act as promising inhibitors of CYP1B1 and BCl2 proteins. Urolithin M 7-glucuronide shows the highest inhibition in CYP1B1 whereas, palmariol A shows the highest inhibition in BCl2 protein. Natural products have the potential to deliver the drugs at the stipulated site with the highest efficacy.

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