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Investigating the binding affinity, molecular dynamics, and ADMET properties of 2,3-dihydrobenzofuran derivatives as an inhibitor of fungi, bacteria, and virus protein

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Abstract

Background: 2,3-Dihydrobenzofurans (DHB) have proposed as advantages structures, and used as chemical entresol to design small compound libraries. The present study illustrates to explore 2,3-dihydrobenzofurans(DHB) in comparison to selected some derivatives drugs by using molecular docking and molecular dynamics, as well as ADMET studies. The online database "Molinspiration online server" was used to detect the physicochemical pharmacokinetics and drug likeness score of DHB drugs. For estimation of molecular docking, six pathogens, such as *Aspergillus niger* (PDB id: 1kum), *Candida albicans* (3dra), *Escherichia coli* (6og7), *Salmonella typhi* (4k6l), *Influenza* (1ru7), and *Hepatitis C* (4tyd), were chosen due to close biological studies.

Results: From Molinspiration online server has showed that DHB did not violate the "Lipinski five rule" as drugs, leading compound for molecular docking exhibited the potential interaction to the active residue. The binding affinity of DHB2 (−7.00 kcal/mol) against 3dra was higher than DHB8 (−6.40 kcal/mol) and DHB (5.70 kcal/mol) for compounds. The results of molecular docking show that the compounds mentioned in this study are not equally effective against pathogens, such as fungi, viruses, and bacteria. However, DHB2, DHB3, and DHB 8 compounds can work against almost given pathogens which results are derived from auto dock vina in terms of binding affinity around 6.00 kcal/mol, and Fire Dock has values from about 38.0 to 42.0 kcal/mol. To explore the dynamic nature of the interaction, 50 ns molecular dynamics (MD) simulation was performed on the selected protein-DHB complexes. Thus, DHB 8 has greater potential to interact for further for fungi.

Conclusion: Finding from this study can play an effective role as a drug in any biological system. This study as well recommends to researchers to synthesize these DHBs for evaluation of its biological activity.

Keywords: 2,3-Dihydrobenzofuran, Molecular docking, Molecular dynamic simulation, Binding affinity

1 Background

Molecular modeling has been accelerating as guide to the chemist, biochemist, pharmacist, and scientist for drug design, as well as contributes to the comprehension of the biochemical operations of gene products [1, 2]. Secondly, molecular modeling techniques have used for the study of organic/inorganic/bio molecules for use of theoretical and computationally stationed process to model or player the role of molecules. Moreover, it has widely been applied for understanding and predicting the behavior of molecular systems [3], translocation of biomolecules in carbon nanotube [4], structural environments within proteins; the energy levels of ring-shaped molecular nanomagnets of different sizes and spin

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numbers [5] and reaction mechanism [6]. Due to vast applications, molecular modeling has become an essential part of concurrent drug discovery processes though new molecules [7, 8]. In current yeast, the charge of these methods has raised significantly and it takes over a decennia for too much short shred of compounds to pass the drug discovery pipeline from basic screening shocks or leads, chemical optimization, and clinical trials before launching into the market as a drug [9]. The pathway and methodologies used in drug design have changed over time, parasitic, and leading new technological advances to evolve the several bottlenecks found along the path [10].

There is various scope used for docking, including SURFLEX, FlexX, FRED, GLIDE, GOLD and DOCK-6, and has been evaluating and these programs verified to produce unfailing poses in numerous docking studies on drug molecules [11]. To 1990, the principal issues were operating to discovery and chemical synthesis of drug-like molecules [12], the emersion of combinatorial chemistry [13], gene technology [14], and high-throughput tests which has shifted the focus on various computational tools due to save the consumption of time, experimental cost and labor [15–18]. On the other hand, poor absorption, distribution, metabolism, and excretion (ADME) properties of new drugs have captured more attention [19], besides the lipophilicity plays an important role on drug discovery [20]. To predict the binding of protein with strong interaction partners as ligands or drugs, protein docking has performed by computational tools and selected the bind site of protein with binding affinity score. Rarey et al. reported on docking and its applications thought the all procedure that it is closely saying about how a drug molecule relative orientation to protein, interaction with protein, and position after interaction [21, 22]. Besides, molecular docking is the best methods in structure-based drug design, and it can foretell the binding-conformation of very small molecule ligands to the appropriate target binding site of protein [23]. Two characterization of the binding behavior plays an important role in rational design of drugs which are protein and the ligand as complementary surfaces [24, 25] and ligand-protein pairwise interaction energies [26].

2,3-Dihydrobenzofurans has been recognized as key pharmacophores in the field of many natural and synthetic bioactive molecules [27]. The most important place of dihydrobenzofuran and their derivatives are used as biological significance molecules, such as anti-cancer [28], anti-HIV [29], anti-inflammatory or antibiotic [30], antitubercular evaluations [31], leishmanicidal agents [32], and induce immunogenic cell death (ICD) of specific cancer cells [33]. Moreover, they have been found to induce the secretion of an endogenous anticancer factor, antileishmania drugs, and immunomodulatory activities [34]. Similarly, natural products and many organic compounds were obtained from synthetic methodologies from 2,3-dihydrobenzofuran moieties [35]. Due to enormous applications and biological significances, we have designed this study as new leading compounds as drug against some fungi, bacteria, and virus proteins. Following a successful strategy of repeated steps of molecular docking calculations, computational study, binding assessment, and ADMET studies have employed on this work.

2 Methods

2.1 2,3-Dihydrobenzofuran derivatives (DHB) optimization, protein preparation, and molecular docking

We selected twelve DHB considering their proved antiviral activities (Table S1). Optimization of the DHB and calculation of vibrational frequency were performed using Gaussian 16, Revision B.01 [36]. All DHB were optimized at semi-empirical PM6 method. Two fungi, two bacteria, and two virus crystal structure of proteins were taken for performing molecular docking from RSCB Protein Data Bank *Aspergillus niger* (PDB id: 1kum), *Candida albicans* (3dra), *E. coli* (6og7), *Salmonella Typhi* (4k6l), Influenza (1ru7), and Hepatitis C (4tyd) (PDB ID: 1kum, 3rda, 6og7, 4k6l, 1rub, 1rub).

PDB ID	Function
1kum	Polysaccharide metabolic process, glucan 1,4-alpha-glucosidase, glucan 1,4-alpha-glucosidase activity, starch binding, polysaccharide catabolic process [37].
3rda	Regulation of necrotic cell death, regulation of proton-transporting ATPase activity, rotational mechanism, mitochondrial outer membrane permeabilization involved in programmed cell death, negative regulation of oxidative phosphorylation uncoupler activity, regulation of mitochondrial membrane permeability involved in programmed necrotic cell death [38].
6og7	Translation release factor activity, codon specific, mRNA binding involved in posttranscriptional gene silencing, ornithine decarboxylase inhibitor activity, misfolded RNA binding, transcription antitermination factor activity, endoribonuclease inhibitor activity [39].
4k6l	Transferases; Glycosyltransferases; Pentosyltransferases, NAD+ ADP-ribosyltransferase activity, toxin activity, endonuclease activity [40].
1ru7	Intracellular transport of viral protein in host cell, receptor-mediated endocytosis of virus by host cell, viral genome packaging, viral protein processing [41].
4tyd	Transformation of host cell by virus, serine-type peptidase activity, ATP binding, metal ion binding [42].

Then, the crystal structure of the protease was optimized and checked by Swiss-PDB viewer software packages (version 4.1.0) [43] based on their least energy. Some significant factors, such as improper bond order, side chain geometry, and missing hydrogen, were observed in the crystal structure of the protease. PyMol

(version 1.1) [44] software package was used to erase all the hetero atoms, water molecules, and inhibitor present. Molecular docking by using AutodockVinawas done for molecular docking, and insights of these results PatchDock web server were used for ligand-receptor docking [45]. 1000 solutions with area, six-dimensional transformation space and score were gained from Patch-Dock server, and then all solutions were afterward shifted into FireDock to retouch the ten best solutions associated with global energy. The adopted complexes from FireDock were aligned according to minimum global binding energy. In the end, the Discovery Studio 4.1 Client was employed for the visualization of binding modes of the receptor and ligands [46]. The grid box in AutodockVina was generated targeting the active site of the protein, where the center was at X = 34.92, Y = 87.74, Z = 80.16, and the grid box was maximum different dimensions for six proteins (unit of the dimensions, Å). Finally, we docked total seventy-two of twelve ligand (DHB) against six proteins. ClusPro online Docking was performed on the best five selected docking result obtained from FireDock and AutoDockVina study.

2.2 Analysis of physicochemical pharmacokinetics of DHB

Some pharmacokinetic and toxicity parameters were taken from new version admetSAR- 2.0 online (http://lmmd.ecust.edu.cn/admetsar2/) [47]. In the current study, Molinspiration online server (Srivastava AK, et al. Interdiscip Sci. 2017;9:116.; https://www.molinspiration.com/cgi-bin/properties) was employed to analyze the drug like properties of lead compounds.

2.3 Molecular dynamic (MD) simulations of selected DHB

MD simulation was devoted to underpin the docking results gained for the best antiviral drugs. 100 ns MD simulation was performed for holo-form (drug-protein). YASARA dynamics [48] program was used for all simulation applying AMBER14 force field [49]. In the presence of a water solvent, the total system was equilibrated with 0.9% NaCl at 298 K temperature. By simulation, the atomy Mesh Ewald algorithm was discussed for radial electrostatic interactions. A cubic cell was propagate within 20 Å on every side of process and periodic boundary circumstance was proposed during the simulation. A time step of 1.25 fs was maintained to carry out 10 ns MD simulation and the snapshots were taken at every 100 ps.

3 Results

3.1 Drug-like properties

DHB membrane permeability, molecular properties, for instance, and bioavailability of guidance compounds relay on some basic properties of molecules which are molecular weight (MW), partition coefficient (logP), and number of hydrogen bond acceptors/donors, and those properties are developed by Lipinski et al. known as Lipinski “rule of five” shoes (Table S2) [50]. As a matter of principle, an orally active drug should have no more than one interruption of the following status: (1) no more than five hydrogen bond donors, (2) no more than ten hydrogen bond acceptor, (3) molecular mass of less than 500 daltons (Da), and (4) an octanol-water partition coefficient of not more than five. As all the numbers of these recommendations are multiple of 5, the rules are termed Lipinski's rule of five [50]. Table 1 represents all DHB compounds which followed the rule of five indicating the good bioavailability score of DHB. The drug-likeness score of command molecules is ascertained with a multitude of GPCR, ion channel modulator, a kinase inhibitor, nuclear receptor ligands, protease inhibitor, and enzyme inhibitor which has been applied to look into the efficiency of molecules to tether for drug

Table 1 Determination of drug likeness score of DHB through molinspiration online server

Drug	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
DHB 1	−0.03	−0.07	−0.53	0.28	-0.21	0.13
DHB 2	0.17	0.00	−0.33	0.49	0.05	0.24
DHB 3	0.17	0.00	−0.27	0.46	0.10	0.22
DHB 4	−0.54	−0.34	−0.96	−0.14	−0.79	−0.21
DHB 5	−0.51	−0.23	−0.83	0.08	−0.83	−0.13
DHB 6	−0.35	−0.18	−0.61	0.14	−0.56	0.00
DHB 7	−0.40	−0.25	−0.86	−0.06	−0.61	−0.11
DHB 8	−0.28	−0.26	−0.48	−0.10	−0.38	0.03
DHB 9	−0.27	−0.16	−0.71	0.28	−0.45	0.07
DHB 10	−0.46	−0.23	−0.83	−0.05	−0.71	−0.14
DHB 11	−0.55	−0.25	−0.86	−0.12	−0.74	−0.22
DHB 12	−0.41	−0.14	−0.83	0.11	−0.68	−0.02

development. Srivastava et al. [51] expatiated that the richer the bioactivity score has a higher likelihood of the specific molecule to be active as a drug.

It is well documented that, if bioactivity score is more than 0, the molecules have better biological activity. If the bioactivity score is −0.5 to 0, the molecules have moderate activity and less than −0.5, the molecules have no biological activity [52]. The results of bioactivity data indicated that DHB 1 and DHB 2 were highly active as enzyme inhibitor, nuclear receptor ligand, ion channel modulator, GPCR ligands, and protease inhibitor. Other compound (DHB 1, 6–10, 12) were predicted as moderately active as GPCR ligands and all.

3.2 ADMET properties

Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) properties of drug candidates or environmental chemicals play a key role in drug discovery and environmental hazard assessment. The admetSAR [47, 53] was developed as a comprehensive source and free tool for the prediction of chemical ADMET properties [54]. Total eight ADMET parameters including human intestinal absorption (HIA), blood–brain barrier (BBB), human oral bioavailability, water solubility, acute oral toxicity, *and Tetrahymenapyriformisp*, IGC50, were tested for the twelve DHB by AdmetSAR prediction [55]. The results are summarized in Table 2. The results provide the information for molecules that the DHB are safer to use, because twelve DHB are perceived to be non cancerogenic, and have good passive gastrointestinal absorption and blood–brain barrier.

The rationale of the blood–brain barrier has to reveal that it protects against circulating toxins or pathogens which are responsible for brain infections. Sometimes, it is accountable for allowing vital nutrients to reach the brain. From Table 2, it is observed that all DHBs show positive activity to their functions. The human oral bioavailability (HOB) represent the therapeutic variability or dose fraction of new chemical. Moreover, HOB indicates the positive when the logK(%F) is greater than zero [56]. Thus, DHB 4, 9, and 11 show the positive value and others are negative value. On the other hand, fish aquatic toxicity prediction illustrates that these compounds may harm aquatic ecology. Besides, DHB may also damage the acute ecology which is noticed from the data of acute oral toxicity, and it is found from 1.514 to 3.041 kg/mol with varying compounds. Finally, all DHBs are highly water soluble which indicates that it has high affinity to water, and easily dissociate with water when it will be taken in human body as drug.

3.3 Molecular docking

Molecular docking are usually expressed by the binding affinity of a drug with the protein of pathogen, besides it also mentions about the number of hydrogen bonds, hydrophobic bonds, polar and non-polar bond, and van dar Waal force interaction between drug and protein. There were some studies for development of anticancer drugs [57], antibiotics, and drug discovery by small molecules [58]. This study consists of two type molecular docking, such as auto dock score and FireDock score. The standard value of auto dock vina is 6.0 or more for

Table 2 Data for ADMET parameters

Drug candidate	Human intestinal absorption (+ve/−ve)	Blood–brain barrier (+ve/−ve)	Human oral bioavailability (+ve/−ve)	Water solubility logS	Acute oral toxicity (kg/mol)	Tetrahymenapyriformisp IGC_{50} (ug/L)
DHB 1	HIA+	BBB+	HOB −	−4.249	2.885	2.08
DHB 2	HIA +	BBB +	HOB −	−3.095	2.773	1.584
DHB 3	HIA +	BBB +	HOB −	−3.095	2.694	2.032
DHB 4	HIA +	BBB +	HOB +	−2.871	1.685	1.267
DHB 5	HIA +	BBB +	HOB −	−2.605	1.514	1.223
DHB 6	HIA +	BBB +	HOB −	−2.733	2.227	1.291
DHB 7	HIA +	BBB +	HOB −	−2.851	2.15	1.256
DHB 8	HIA +	BBB +	HOB −	−2.536	3.041	0.949
DHB 9	HIA +	BBB +	HOB +	−2.546	2.672	0.996
DHB 10	HIA +	BBB +	HOB −	−2.977	2.36	1.543
DHB 11	HIA +	BBB +	HOB +	−3.196	2.43	1.4
DHB 12	HIA +	BBB +	HOB −	−2.506	1.871	1.591

The BBB+ means that the compound can penetrate the BBB. If a compound with the HIA% is greater than 30%, it is labeled as HIA+. HOB Compounds with logK(%F) > 0 were regarded as positives. *T. pyriformis* toxicity (TPT)

Table 3 Molecular docking scores for DHB

Protein ID	1kum		1ru7		4k6l		4tyd		6og7		3dra	
Drug	Vina	Fire Dock	Vina	Fire Dock	Vina	FireDock	Vina	Fire Dock	Vina	Fire Dock	Vina	Fire Dock
DHB 1	−5.60	−35.87	−5.60	−44.54	−5.80	−34.65	−6.00	−37.70	−6.20	−36.35	−5.70	−39.71
DHB 2	**−6.00**	**−39.46**	**−6.00**	**−47.53**	**−5.70**	**−35.35**	**−6.00**	**−41.77**	**−5.80**	**−36.90**	**−7.00**	**−38.54**
DHB 3	**−6.10**	**−38.08**	**−5.90**	**−45.45**	**−5.40**	**−36.14**	**−6.30**	**−40.53**	**−5.90**	**−46.57**	**−5.70**	**−42.97**
DHB 4	−5.50	−30.94	−5.50	−34.64	−5.40	−28.87	−6.00	−32.90	−6.00	−33.32	−6.00	−34.64
DHB 5	−5.60	−33.56	−5.50	−37.49	−5.40	−33.52	−5.80	−35.32	−5.80	−32.34	−5.80	−32.80
DHB 6	−5.80	−32.87	−5.50	−38.10	−5.50	−29.42	−6.10	−35.25	−6.10	−35.61	−6.00	−35.64
DHB 7	−5.90	−34.57	−5.90	−36.14	−5.80	−29.72	−6.00	−39.48	−5.90	−31.24	−6.00	−35.32
DHB 8	**−6.00**	**−34.34**	**−6.00**	**−35.86**	**−5.70**	**−31.33**	**−6.10**	**−34.82**	**−6.00**	**−33.66**	**−6.00**	**−36.66**
DHB 9	−5.90	−36.05	−5.80	−38.14	−5.70	−30.72	−5.90	−35.44	−5.80	−32.51	−6.10	−35.69
DHB 10	−5.30	−31.19	−5.30	−33.19	−5.50	−30.66	−6.00	−28.68	−5.90	−30.93	−5.80	−30.97
DHB 11	−5.60	−33.61	−5.70	−31.22	−5.50	−29.69	−5.80	−36.26	−5.90	−31.19	−6.10	−31.35
DHB 12	−5.40	−35.37	−5.30	−35.03	−5.20	−30.11	−5.90	−32.21	−5.70	−32.75	−5.70	−33.05

becoming drug. It had been reported by Shityakov and Förster [59] that docking score has been considered as the Gibbs free energy of binding, and the Gibbs free energy of binding is more −6.0 kcal mol^{-1} indicates the active drug and inactive (Gibbs free energy of binding) is less −6.0 kcal mol^{-1}. Molecular docking by using PatchDock web server and refine 1000 solutions with FireDock web server molecular docking is performed to find out the best candidates among the 12 DHB based on their minimum global binding energy. FireDock were ranked according to minimum global binding energy. Global energy of the DHB is distributed within the range from −28.68 to −47.53 kcal/mol shown in Table 3 and Fig. 1. Selected DHB are screened primarily using PatchDock and FireDock web server to find out the best candidates, and then, the AutoDockVina was employed to understand their fitness. Six best molecular docking shown in Fig. 2. The binding affinity of AutoDockVina and FireDock score of all DHB are shown in Table 3.

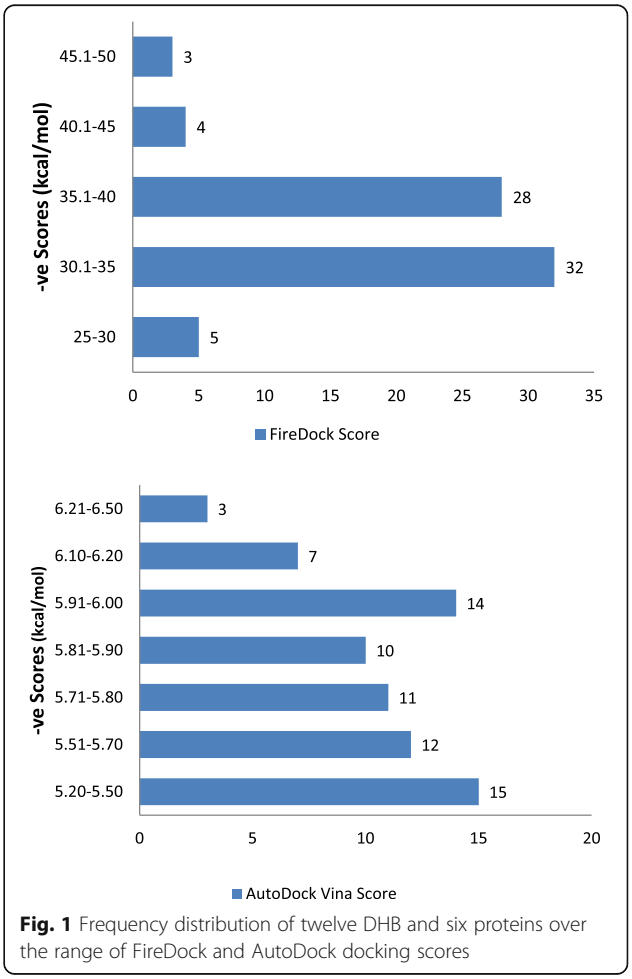

Fig. 1 Frequency distribution of twelve DHB and six proteins over the range of FireDock and AutoDock docking scores

3.4 Molecular dynamics simulation

MD simulation for each complex with three selected DHB derivatives like DHB 2, DHB 3, and DHB 8 has performed against two proteins (1kum and 6og7) for 10 ns and one protein complex (3dra) for 50ns, because the DHB 2, DHB 3, and DHB 8 derivatives are found as the highest binding affinity against these pathogens. The MD simulation of DHB3 against 6og7 protein demonstrates the lowest RMSD value than the other complexes which indicates its greater stability, and keeps in the pocket of proteins. As a result, DHB3 has to be considered as drug. Moreover, the lowest RMSF value of the DHB3 against 6og7 has also found after MD simulation. Secondly, the DHB2 against protein (3dra)

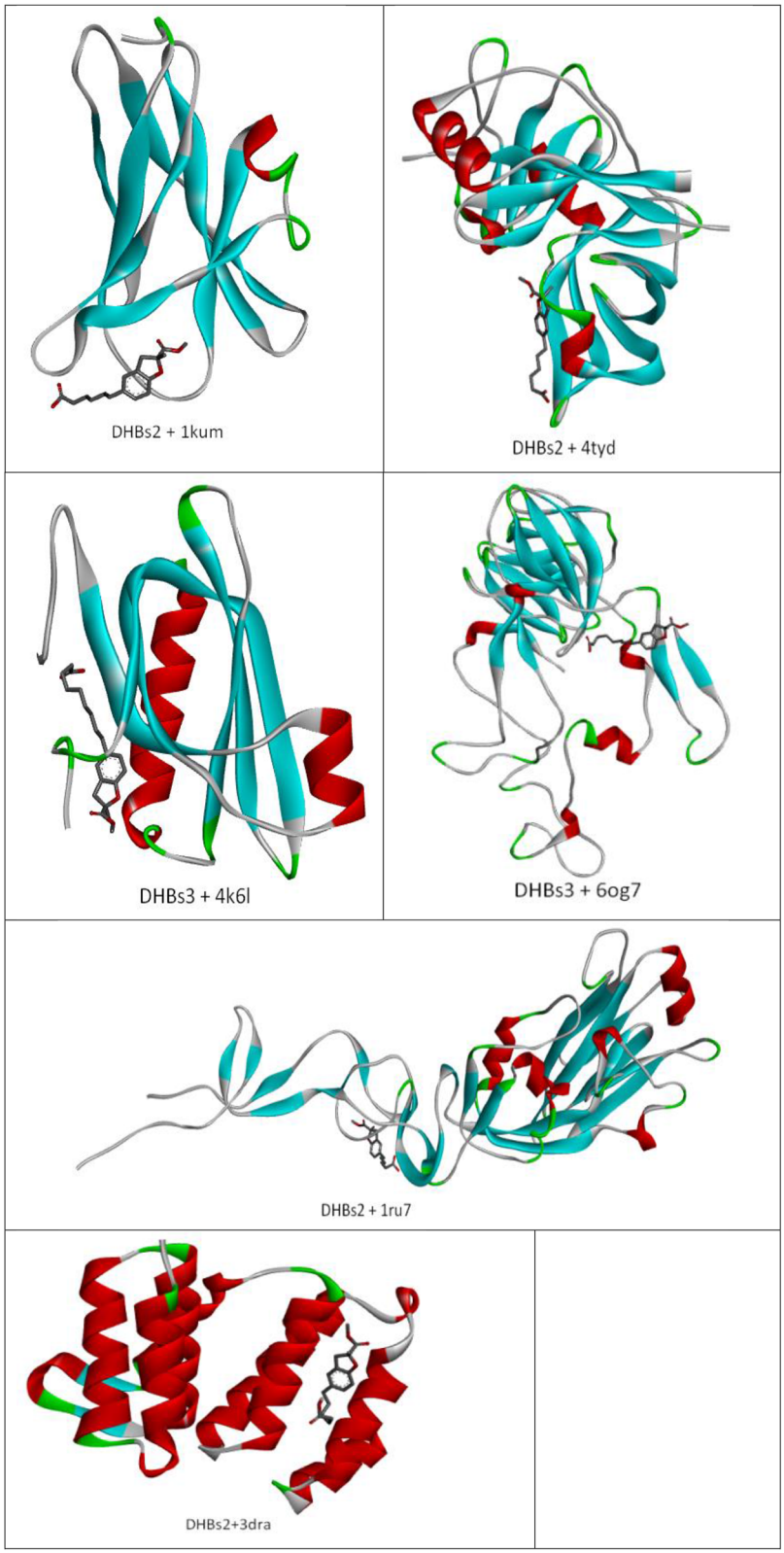

Fig. 2 Six best molecular docking

illustrates binding affinity (−7.00 kcal/mol); in this case, it was selected for MD simulation for fitting in the protein pocket. In general, the DHB2 against 1kum, DHB3 against 1kum, DHB8 against 1kum, DHB2 against 6og7, DHB3 against 6og7, and DHB8 against 6og7 schemes are chosen for MD simulation on based of binding affinity from molecular docking studies. Analysis of RMSD, RMSF and Backbone of selected three complexes (DHB2 against 1kum, DHB3 against 1kum, DHB8 against 1kum, DHB2 against 6og7, DHB3 against 6og7, DHB8 against 6og7) with protein at 10 ns MD simulations are presented in Fig. 3.

4 Discussions

If the oral bioactivity score (%F) of the molecule is greater than 0.00, has the important biological activities and scores between 0.50 and 0.00, will be considered to be fairly active, and if the value is less than 0.50, it is

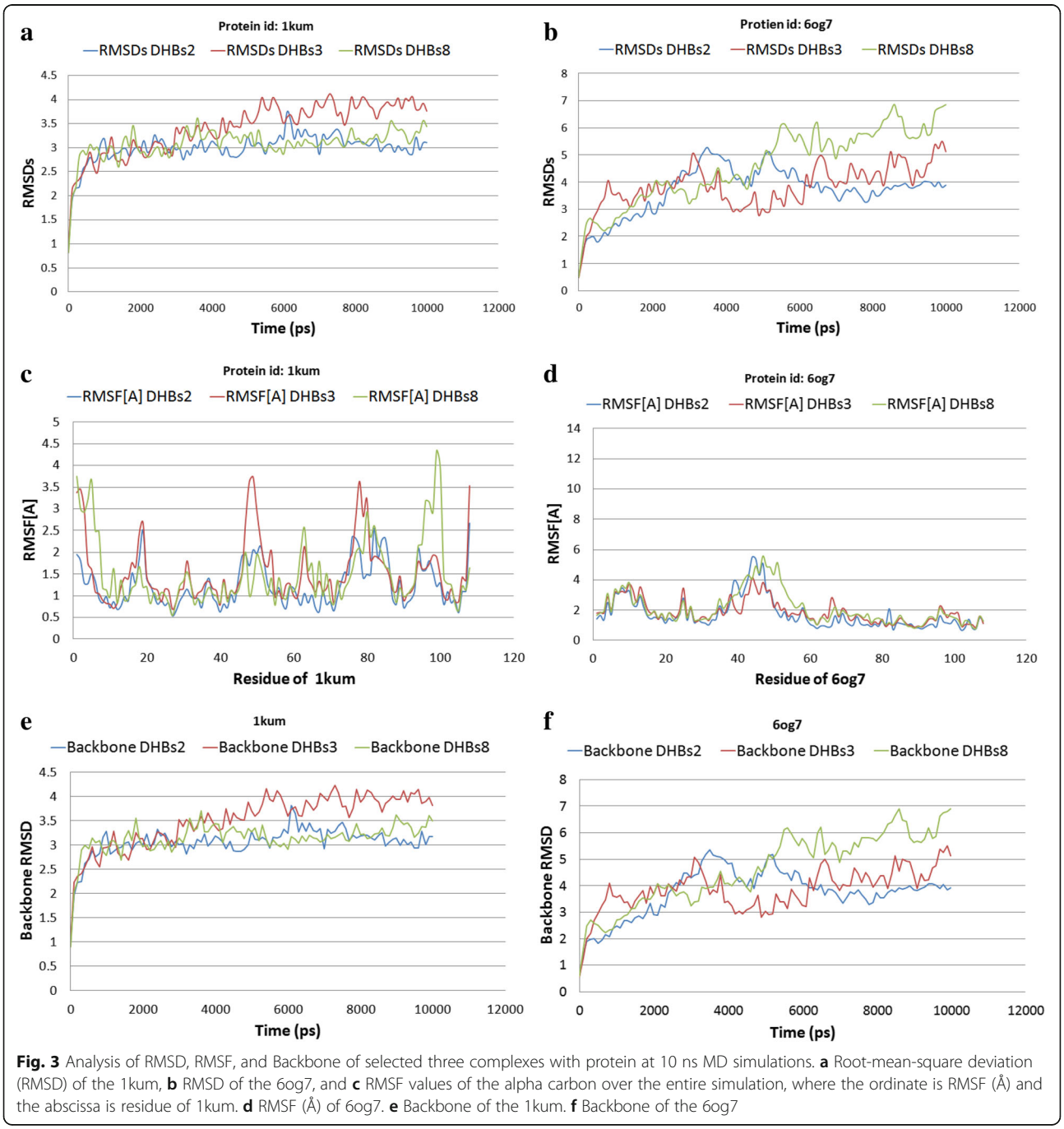

Fig. 3 Analysis of RMSD, RMSF, and Backbone of selected three complexes with protein at 10 ns MD simulations. **a** Root-mean-square deviation (RMSD) of the 1kum, **b** RMSD of the 6og7, and **c** RMSF values of the alpha carbon over the entire simulation, where the ordinate is RMSF (Å) and the abscissa is residue of 1kum. **d** RMSF (Å) of 6og7. **e** Backbone of the 1kum. **f** Backbone of the 6og7

guessed to be inactive. The gained values of drug-likeness score stated that DHB 2 followed the good drug-likeness along with other standard drugs, for instance DHB 3 and DHB 8 (Table 1).

Molecular docking is a computational tool that virtually seeks to predict a complex of two binding partners, such as drugs and protein or macromolecules. Withal, the molecular docking is equivalent the interaction of ligand and protein as a specific scoring function through the binding free energy which is the sum of intermolecular interaction between them after docking. The binding energy is also expressed by Gibbs free energy of binding from docking. Regarding a standard drugs, the binding affinity is equal to 6.00 kcal mol^{-1} or more [59, 60]. In general, the AutoDock approves a simultaneous sample process to arrangement with side chain flexibility, active site of protein and side chains of the receptor. Thus AutoDock evaluates the binding affinity of ligand and protein interaction which is the sum of the binding constant (K_d) and the Gibbs free energy (ΔG_L) [61], and 6.00 kcal mol^{-1} is the starting value for good drugs small structural molecules for theoretical value [62, 63].

Based on the best Auto Dock Vina score and binding affinities, DHB 2, DHB 3, and DHB 8 are selected for further analysis as best candidate having the score 6.00, −6.10 and −6.00, respectively. In this study, DHB 2, DHB 3, and DHB 8 are considered as a control ligand for six receptor protein, such as fungi [*Aspergillus niger* (1kum), *Candida albicans* (3rda)], bacteria [*E. coli* (6og7), *Salmonella typhi* (4k6l)], and virus [*Influenza* (1rub), *Hepatitis C* (4tyd)] proteins, because yet not used DHB skeleton for those receptor.

Analysis of RMSD, RMSF, and Backbone of DHB2 against 3dra complex is also listed in Fig. 4 and 5ns snapshot showing in Fig. 5. Finally, it has been found that the stability and protein interact with drug molecules are almost right to the height range of MD study, and it has provided information as a drug.

Analysis of the nonbonding interactions of the best two DHB (*2, 3 & 8*) with the six proteins reveals that the selected compounds interact with either both or at least one catalytic residue detected by FireDock shown in Table 4 and Fig. 1. For molecular docking for *DHB2+4tyd*, the eight hydrogen bonds and eight hydrophobic bonds are showed in Table 4. The result of *DHB3+6og7* docking is illustrated in Table 4 which are listed by five hydrogen bonds and eight hydrophobic bonds. In case of *DHB2+1kum* docking, there are found the three hydrogen bonds and seven hydrophobic bonds showing in Table 4. We observed maximum four interaction of TRP563 and three interaction of THR525 in *DHB2+1kum*. Maximum pi-alkyl interaction is observed in *DHB2 + 4tyd*. From these studies, the best binding affinity

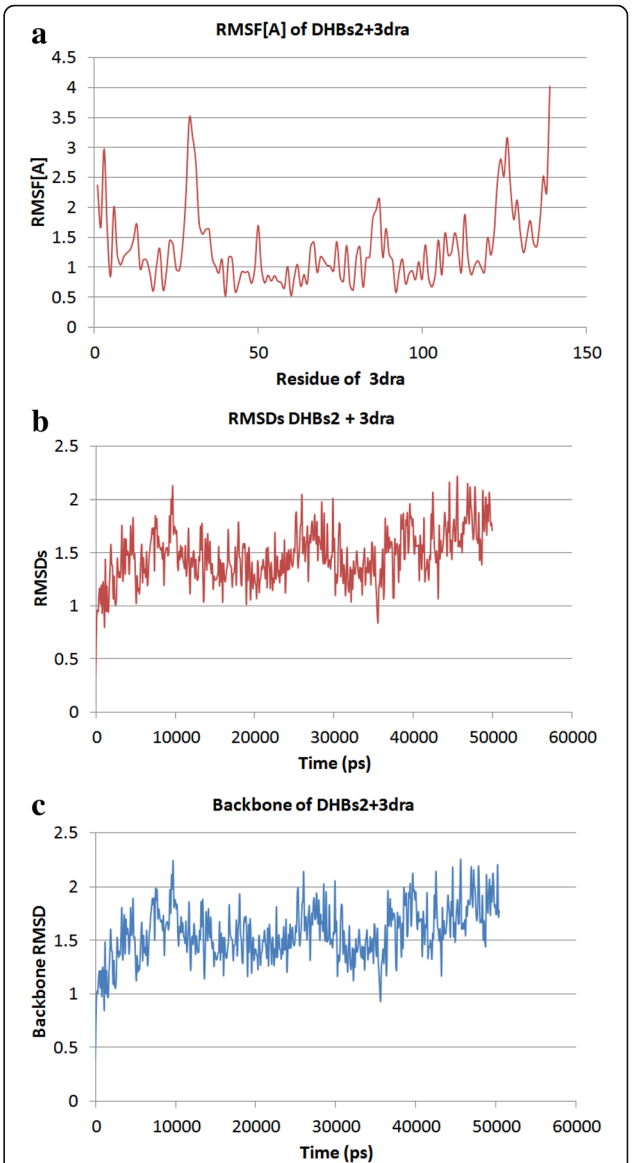

Fig. 4 Analysis of 50ns RMSD, RMSF, and Backbone of selected three complexes with protein at 50 ns MD simulations. **a** RMSD of the 3dra. **b** RMSF (Å) of 3dra. **c** Backbone of the 3dra

vote is going to *DHB2* against 3dra shown in Fig. 6, because it contains the maximum protein residue interactions with drugs or DHB2, as well as active sites. In addition, from Fig. 5, it is illustrated the evaluation of the distribution of drugs within the biological system through the MD simulation that DHB2 remains in protein pocket with wide range of dynamics which is other supporter information for the best drugs (Fig 1).

5 Conclusions

Summarizing from the above discussion, it is also found that the compounds used in the given work show great interest in biological activity. The first thing is that came

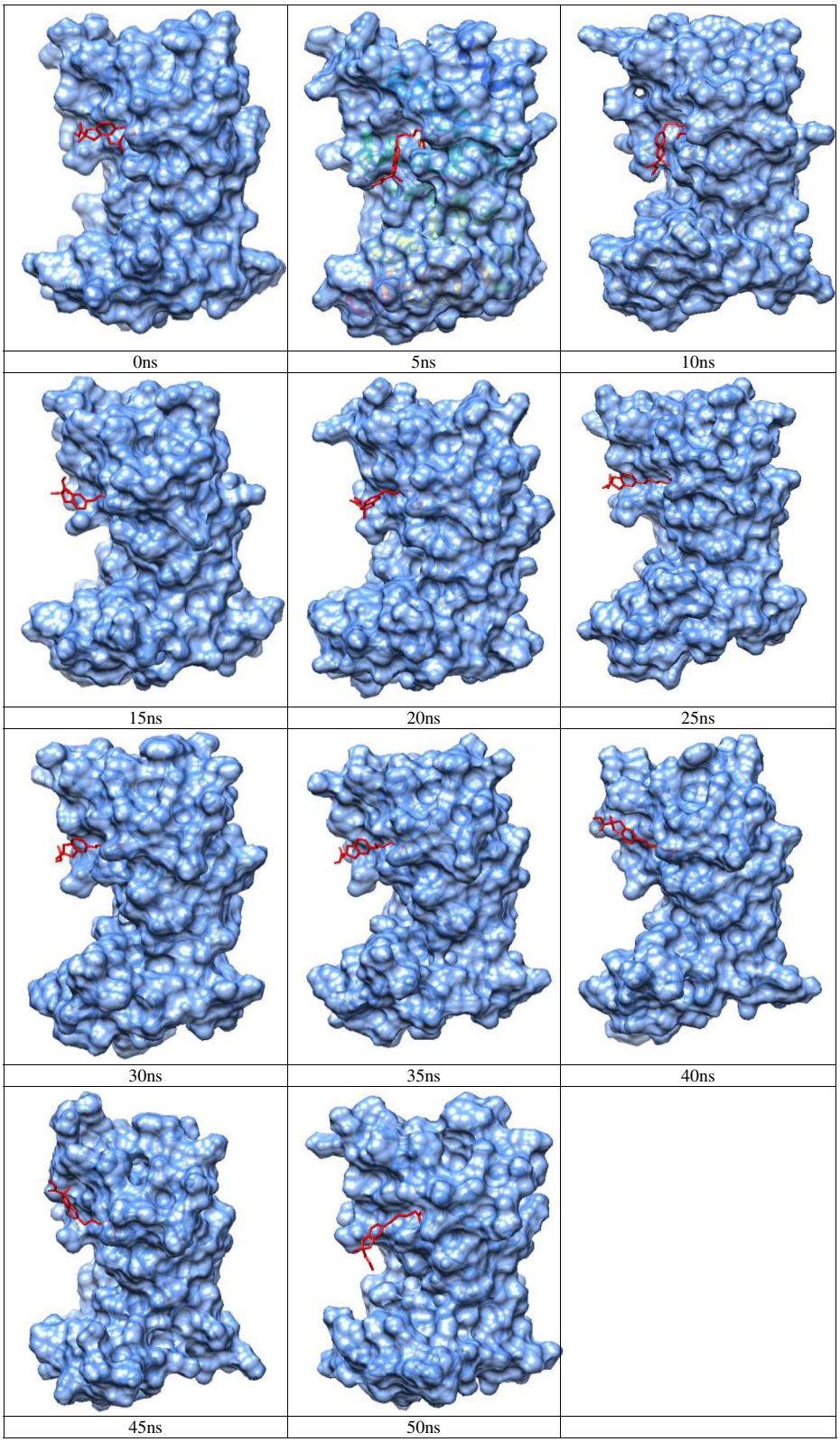

Fig. 5 5ns snapshot of DHB2+3dra complex

Table 4 Nonbonding interactions of selected two DHB with six proteins (pose predicted by FireDock). *CH* conventional hydrogen bond, *H* hydrogen bond, *C* carbon hydrogen bond

Interaction residue	Distance	Bond category	Bond type	Interaction residue	Distance	Bond category	Bond type
DHB 2 + 1kum					**DHB 3 + 4k6l**		
TRP563	2.215	H	CH	GLY135	2.522	H	C
THR525	2.407	H	C	PRO136	1.963	H	C
SER558	2.288	H	C	LEU125	2.407	H	Pi-D H
THR525	2.607	Other	Pi-Lone Pair	PRO136	4.231	Hydrophobic	Alkyl
THR524 THR525	4.930	Hydrophobic	Amide-Pi Stacked	LEU85	4.128	Hydrophobic	Alkyl
ALA553	5.087	Hydrophobic	Alkyl	LEU125	3.829	Hydrophobic	Alkyl
ALA553	4.238	Hydrophobic	Alkyl	TRP25	5.244	Hydrophobic	Pi-Alkyl
ILE531	4.933	Hydrophobic	Alkyl				
TYR556	4.083	Hydrophobic	Pi-Alkyl				
TRP563	5.086	Hydrophobic	Pi-Alkyl				
TRP563	4.961	Hydrophobic	Pi-Alkyl				
TRP563	4.139	Hydrophobic	Pi-Alkyl				
DHB 2 + 1ru7					**DHB 3 +3rda**		
SER291	2.564	H	C	LEU63	2.524	H	CH
PRO307	2.034	H	C	ASN143	2.333	H	CH
LEU293	1.966	H	C	LEU58	2.020	G	C
CYS278	2.522	Other	Sulfur-X	ASP98	3.335	Electrostatic	Pi-Anion
LYS281	3.333	Electrostatic	Pi-Cation	ALA96	4.587	Hydrophobic	Alkyl
SER291	3.091	H	Pi-Donor H	ALA96	3.843	Hydrophobic	Alkyl
LYS281	2.484	Hydrophobic	Pi-Sigma	TRP106	4.791	Hydrophobic	Pi-Alkyl
LYS281	5.284	Hydrophobic	Alkyl	ILE95	5.495	Hydrophobic	Pi-Alkyl
PRO307	3.699	Hydrophobic	Alkyl				
DHB 3 +6og7					**DHB 2 + 4tyd**		
ASP83	1.843	H	CH	GLY137	1.318	H	CH
ARG86	2.920	H	CH	SER139	2.840	H	CH
PRO21	2.956	H	C	VAL163	3.035	H	CH
PRO21	2.124	H	C	LYS136	2.351	H	C
ASN20	2.545	H	Pi-D H	LYS136	2.994	H	C
VAL18	4.884	Hydrophobic	Alkyl	SER139	2.135	H	C
VAL18	5.293	Hydrophobic	Alkyl	GLY162	1.365	H	C
VAL19	3.656	Hydrophobic	Alkyl	HIS57	2.729	H	C
LEU23	5.444	Hydrophobic	Alkyl	LYS136	4.992	Electrostatic	Pi-Cati
TYR82	4.897	Hydrophobic	Pi-Alkyl	CYS159	5.342	Other	Pi-Sulfur
TYR82	5.358	Hydrophobic	Pi-Alkyl	VAL132	4.192	Hydrophobic	Alkyl
HIS199	5.393	Hydrophobic	Pi-Alkyl	ALA157	4.471	Hydrophobic	Alkyl
VAL19	4.222	Hydrophobic	Pi-Alkyl	CYS159	3.009	Hydrophobic	Alkyl
				HIS57	4.399	Hydrophobic	Pi-Alkyl
				PHE154	3.796	Hydrophobic	Pi-Alkyl
				LYS136	5.418	Hydrophobic	Pi-Alkyl
				ALA156	5.132	Hydrophobic	Pi-Alkyl
				ALA157	3.578	Hydrophobic	Pi-Alkyl

Table 4 Nonbonding interactions of selected two DHB with six proteins (pose predicted by FireDock). *CH* conventional hydrogen bond, *H* hydrogen bond, *C* carbon hydrogen bond *(Continued)*

Interaction residue	Distance	Bond category	Bond type	Interaction residue	Distance	Bond category	Bond type
DHB 2 + 3rda				**DHB 8 + 3rda**			
ASN180	2.082	H	CH	ASN180	2.497	H	CH
ASN224	1.866	H	CH	PHE187	3.781	Hydrophobic	Pi-Pi Stacked
PHE187	3.674	Hydrophobic	Pi-Pi Stacked	PHE187	4.996	Hydrophobic	Pi-Alkyl
ARG232	4.106	Hydrophobic	Alkyl	TYR225	4.896	Hydrophobic	Pi-Alkyl
PHE187	5.312	Hydrophobic	Pi-Alkyl				
TYR225	5.360	Hydrophobic	Pi-Alkyl				

to light when designing the molecules was the replacement of the benzofuran and its derivatives using changing the site chain by the alkyl chain. First of all, the SAR was studied where it was shown that with the change of alkyl the biological properties will be the lightness, talking molecular docking studies and ADME T. Secondly, the twelve compounds used in this chapter are found to have more or less biological activity, of which DHB2, DHB3, and DHB8 may exhibit the most biological activity. The reason molecular docking has been used as the basis for determining their properties is because it makes it easier to understand how much value a drug can attach to a particular protein of pathogens. Since the value of talking is considered to be close to 6 in any of the previous standard cases, the value of DHB2, DHB3 and DHB8 is close to or above 6. On the other hand, to be used as a molecular drug, it is first confirmed by molecular screening, then it goes to the human body and a molecular dynamic study is done to find out what dynamics might be. Molecular dynamics shows that DHB2, DHB3, and DHB8 drugs are located in the pocket of the protein. As a result, it can play an effective role as a drug in any biological system. In addition, AMDET studies have been performed for their side effects, suggesting that not all drugs have anti-cancer activity and that they exhibit aquatic and fish toxicity.

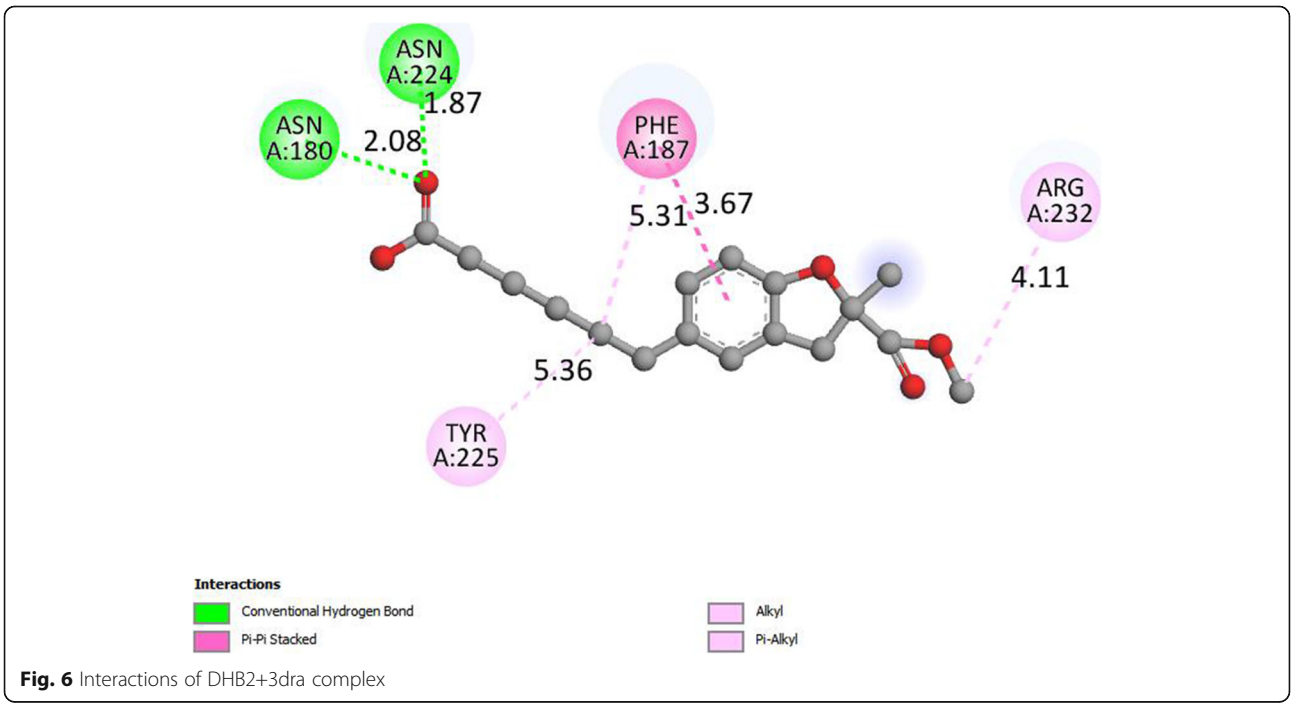

Fig. 6 Interactions of DHB2+3dra complex

Abbreviations
MD: Molecular dynamics; ADMET: Absorption, Distribution, Mechanism, Excretion, and Toxicity; PDB: Protein Data Bank; DHB: Dihydrobenzofuran derivatives; RMSD: Root mean square deviation; RMSF: Root mean square fluctuation; %F: Oral bioavailability

6 Supplementary Information

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Additional file 1: Table S1. Optimized Structures of the 12 DHBs. **Table S2.** Drug likeness properties of DHBs. **Table S3.** Docking Score.

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Authors' contributions
AN developed the concept, optimized the molecules, and was responsible for the analysis of the optimized data, molecular dynamics, and its data collection and writing draft manuscript; AK: writing—reviewing and editing manuscript; FZ: reviewing and editing; MWK: supervision, writing—reviewing and editing. All authors have read and approved the final manuscript

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