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 advantageous 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...
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 shrift 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, 3dra, 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]. |
| 3dra   | 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) software package was used to erase all the hetero atoms, water molecules, and inhibitor present. Molecular docking by using AutodockVina was 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 PatchDock 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 atomic 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

DH B 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 ascertainment 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

| 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                     | -0.33           | 0.49                   | 0.05              | 0.24             |
| DHB 3 | 0.17        | 0                     | -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 Tetrahymenapryiformisp, 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 der 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

| Drug candidate | Human intestinal absorption (+ve/−ve) | Blood–brain barrier (+ve/−ve) | Human oral bioavailability (+ve/−ve) | Water solubility log5 | Acute oral toxicity (kg/mol) | Tetrahymenapryiformisp IGC50 (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. pyriformisp toxicity (TPT)
Table 3: Molecular docking scores for DHB

| Protein ID | Drug | 1kum | 1ru7 | 4k6l | 4tyd | 6og7 | 3dra |
|------------|------|------|------|------|------|------|------|
|            | Vina | Fire Dock | Vina | Fire Dock | Vina | Fire Dock | Vina | Fire Dock | 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 | -36.64 |
| 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.

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, and 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
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 to 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 ($\Delta G_d$) [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 3rda 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 vote is going to DHB2 against 3rda 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 DH82+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              | 4.930    | Hydrophobic Amide-Pi Stacked | LEU85 | 4.128 | Hydrophobic | Alkyl |
| THR525              |          |               |           |                     |          |               |           |
| 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  | ASP08               | 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 | CYS139 | 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 Alkyl | |
| LYS136              | 5.418    | Hydrophobic Pi-Alkyl | ALA156 | 5.132 | Hydrophobic Pi-Alkyl | |
| ALA157              | 3.578    | 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.

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  |

Fig. 6 Interactions of DHB2+3rda complex
Abbreviations: MD: Molecular dynamics; ADMET: Absorption, Distribution, Mechanism, Excretion, and Toxicity; POB: Protein Data Bank; DHB: Dihydrobenzofuran derivatives; RMSD: Root mean square deviation; RMSF: Root mean square fluctuation; %F: Oral bioavailability

6 Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43088-021-00117-8.

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; MWK: supervision, writing—reviewing and editing, all authors have read and approved the final manuscript.

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References

1. Andrew RL (2001) Molecular modelling principles and applications, 2nd edn. Pearson Education Limited. https://doi.org/10.1021/c98040441

2. Mark JGV (1994) Molecular modelling and drug design. Macmillan International Higher Education.

3. Régis EEVK, Gazzali Amirah M, Muriel BH, Cédric B, Céline F, Omar S, André A, Wahab Habibah A (2017) Molecular modelling, synthesis and biological evaluation of peptide inhibitors as anti-angiogenic agent targeting neuropilin-1 for anticancer application. J Biomol Struct Dyn 35:36–45. https://doi.org/10.1080/07391102.2015.1131196

4. Er-Yu LCL, Jia-Wei S, Qi W (2016) Molecular modelling of translocation of biomolecules in carbon nanotubes: method, mechanism and application. Mol Simul 42(10):827–835. https://doi.org/10.1080/07391102.2015.1107184

5. Antkowia M (2017) Parallel exact Diagonalization approach to large molecular Nanomagnets Modelling. In: International conference on parallel processing and applied mathematics, pp 351–358

6. Martinez MTGMAA, David H, Neill M, Moomey Kathleen M, Morgan Amy E, Proctor Carole J (2017) Modelling the molecular mechanisms of aging. Biosci Rep 37:BSR20160177. https://doi.org/10.1042/BSR20160177

7. Sandeepkumar GKS, Jens M, Lowie Edward W (2014) Computational methods in drug discovery. Pharmacol Rev 66(1):334–395. https://doi.org/10.1124/pr.112.0117336

8. Xian MLZ, Yuan X, Honglin L, Cheng L, Hualiang J (2013) Computational methods for drug design and discovery: focus on China. Trends Pharmacol Sci 34:549–559. https://doi.org/10.1016/j.tips.2013.08.004

9. Divya SSV (2018) Drug discovery and development: an overview. In: Pharmaceutical medicine and translational clinical research. Elsevier, pp 19–32

10. Tang YD, Fei JG (2020) The computational models of drug-target interaction prediction. Protein Pept Lett 27:348–358. https://doi.org/10.2174/09298652666190140121410

11. Gschwend DAG, Andrew C, Kunz ID (1996) Molecular docking towards drug discovery. J Mol Recognit Intedicp 9:175–186. https://doi.org/10.1016/S0887-831X(96)80123-0

12. Walters WPM, Ajay A, Murcko MA (1999) Recognizing molecules with drug-like properties. Curr Opin Chem Biol 3:384–387. https://doi.org/10.1016/S1367-5931(99)80058-7

13. Kolb HCS, Barry K (2003) The growing impact of click chemistry on drug discovery. Drug Discov Today 8:1128–1137. https://doi.org/10.1016/S1359-6446(03)02933-7

14. Naylor LH (1999) Reporter gene technology: the future looks bright. Biochem Pharmacol 58:749–757. https://doi.org/10.1016/S0006-2952(99)00096-9

15. Paul KSA, Sarker MN, Islam MJ (2019) The prediction of thermo physical, vibrational spectroscopy, chemical reactivity, biological properties of morpholinum borate, phosphate, chloride and bromide ionic liquid: a DFT study. Int J New Chem 6:236–253. https://doi.org/10.20320/ijnc.2019.01042.1053

16. Jahidul IM, Nuruzzaman SM, Kumer A, Paul S (2019) The evaluation and comparison of thermo-physical, chemical and biological properties of palladium(II) complexes on binuclear amine ligands with different anions by DFT study. Int J Adv Biol Biomed Res 7:318–337

17. Jahidul IM, Kumer A, Sarker MN, Paul S, Zannat A (2019) The prediction and theoretical study for chemical reactivity, thermophysical and biological activity of morpholinum nitride and nitrite ionic liquid crystals: a DFT study. Adv J Chem-Soc A 2:316–326. https://doi.org/10.33945/SAM/JAICA.2019.4.5

18. Islam MJ, Kumer A, Paul S, Sarker MN (2020) The activity of alkyl groups in morpholinum cation on chemical reactivity, and biological properties of morpholinium tetrafluoroborate ionic liquid using the DFT method. Chemical Methodol 4:130–142. https://doi.org/10.3945/SAM/CHEMM.2020.2.3

19. Eric HGJN (2003) ADMET in silico modelling: towards prediction paradise? Nat Rev Drug Discov 2:192–204. https://doi.org/10.1038/nrd1032

20. Amott JAP, Lobo S (2012) The influence of lipophilicity in drug discovery and design. Expert Opin Drug Discovery 7:863–875. https://doi.org/10.1517/717460441.2012.141463

21. Matthias TRL (1996) Computational methods for biomolecular docking. Curr Opin Struct Biol 6:402–406. https://doi.org/10.1016/0959-440X(96)80061-3

22. Bernd MKR, Lengauer T, Klebe G (1996) A fast flexible docking method using an incremental construction algorithm. J Mol Biol 261:470–489. https://doi.org/10.1006/jmbi.1996.0477

23. Hélène DBOK, Furr JR, Bajorath J (2004) Docking and scoring in virtual screening for drug discovery: methods and applications. Nat Rev Drug Discov 3:935–949. https://doi.org/10.1038/nrd1549

24. Morris GMS, David S, Halliday RS, Huey R, Hart WE, Belew RK, Olson AJ (1998) Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. J Comput Chem 19:1620–1622. https://doi.org/10.1002/(SICI)1096-987X(19981015)19:2%3C175::AID-JMC1%3E3.0.CO;2-D

25. Meng ECS, Brian K, Kunz ID (1992) Automated docking with grid based energy evaluation. J Comput Chem 13:505–524. https://doi.org/10.1002/jcc.10378

26. Morris GMS, David S, Halliday RS, Huey R, Hart WE, Belew RK, Olson AJ (1998) Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. J Comput Chem 19:1620–1622. https://doi.org/10.1002/(SICI)1096-987X(19981015)19:2%3C175::AID-JMC1%3E3.0.CO;2-D

27. Matthews III, Eric H (2003) ADMET in silico modelling: towards prediction paradise? Nat Rev Drug Discov 2:192–204. https://doi.org/10.1038/nrd1032

28. Morris GMS, David S, Halliday RS, Huey R, Hart WE, Belew RK, Olson AJ (1998) Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. J Comput Chem 19:1620–1622. https://doi.org/10.1002/(SICI)1096-987X(19981015)19:2%3C175::AID-JMC1%3E3.0.CO;2-D

29. Badra UNF, Shams A, Raza Y, Ahmed A, Rashid U, Sadiq A (2019) Isolation of dihydrobenzofuran derivatives from ethnomedicinal species Polygonum barbatum as anticancer compounds. Biol Res 52:1. https://doi.org/10.1186/s43088-021-00117-8.

30. Liu Q-BH, Xiao-Xiao, Bai M, Chang X-B, Yan X-J, Zhu T, Zhao W, Peng Y, Song S-J (2014) Antioxidant and anti-inflammatory active dihydrobenzofuran derivatives from the seeds of Prunus tomentosa. J Agric Food Chem 62:7796–7803. https://doi.org/10.1021/acs.jafc.1j05217z
