In silico quest of selective naphthyl-based CREBBP bromodomain inhibitor

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Abstract

The reader proteins like bromodomains have recently gained increased attentions in the area of epigenetic drug discovery, as they are the potent regulators in gene transcription process. Among the other bromodomains, cAMP response element-binding protein (CREB) binding protein or CREBBP bromodomain involved in various cancer progressions and therefore, efforts to develop specific inhibitors of CREBBP bromodomain are of clinical value. In this study, we tried to identify selective CREBBP bromodomain inhibitor, which was accomplished by using molecular docking, free energy calculation and molecular dynamics (MD) simulation studies, considering a series of naphthyl based compounds. The docking procedure was validated by comparing root mean square deviations (RMSDs) of crystallographic complex to docked complex. Favorable electrostatic interactions with the Arg1173 side chain were considered to attain selectivity for CREBBP bromodomain over other human bromodomain subfamilies. We found that naphthyl-based compounds have greater binding affinities towards the CREBBP bromodomain, and formed non-bonded interactions with various side chain residues that are important for bromodomain inhibition. From detailed investigation by induced fit docking, compound 31 was found to have favorable electrostatic interactions with the Arg1173 side chain by forming conventional hydrogen bonds. This result was further confirmed by analyzing hydrogen bond occupancy and bonding distance during the molecular dynamics simulation. We believe that these findings offer useful insight for the designing of target specific new bromodomain inhibitor and also promote further structure guided synthesis of analogues for identification of potent CREBBP bromodomain inhibitors as well as detailed in vitro and in vivo analyses.

Keywords Bromodomain · CREBBP · Selectivity · In silico

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Abbreviations

BET	Bromo and extra terminal
cAMP	Cyclic adenosine monophosphate
CREB	Cyclic-AMP response element-binding protein
CHARMm	Chemistry at HARvard macromolecular mechanics
CREBBP	cAMP response element-binding protein (CREB) binding protein
EMM	Molecular mechanics energies
EP300	Adenoviral E1A binding protein of 300 kDa
GNP	Non-polar solvation (GNP)
GSGB	Solvation model for polar solvation
HTVS	High throughput virtual screening
Kcal/mol	Kilocalorie per mol
MD	Molecular dynamics
MM	Molecular mechanics
MM-GBSA	Molecular mechanics-generalised born and surface area

NAMD	Nanoscale molecular dynamics
PME	Particle mesh Ewald
Rg	Radius of gyration
RMSD	Root mean square deviation
RMSF	Root mean square fluctuation
SAR	Structure activity relationship
SGB	Surface generalized born
TIP3P	The transferable intermolecular potential3 points
XP	Extra precision

Introduction

Gene transcriptional expression or repression in the eukaryotic cell is a highly sophisticated mechanism, occurs via post-transcriptional modifications of histone tails in the chromatin (Poplawski et al. 2014). The acylation of lysine residues in histone tails is an important event (Jacobson et al. 2000) in this process, maintained highly by some epigenetic proteins, categorized by ‘writers’, ‘readers’ and ‘erasers’. The reader proteins put post translational marker on the lysine residue of histone tail like acetyl, methyl and phosphate groups, while eraser proteins remove these (Unzue et al. 2016). The proteins containing bromodomains, chromodomains and tudor domains act as reader, bind selectively to the marker (Hewings et al. 2011), and thereby participate in decoding the histone code (Strahl and Allis 2000), activate downstream signaling pathway. Bromodomains are comprised with ~ 110 amino acid modules that have been further classified into several distinct subgroups by their different functions (Florence and Faller 2001). These proteins play various cellular processes, especially in gene regulation and have recently gained an increased interest in the drug discovery area, as they are the key drivers in several human diseases caused by epigenetic dysregulation. Till to date, 61 bromodomains have been solved by spectroscopy and crystallography techniques, among them the bromo and extra terminal (BET) family of bromodomains has been found to be the most druggable (Vidler et al. 2012) and their inhibitors are now in clinical trials (Romero et al. 2015). The strategy of inhibition of these bromodomains has recently been increased, due to their directly connection to inflammation, aggressive types of squamous cell carcinomas and haematological malignancies such as acute myeloid leukaemia (Filippakopoulos and Knapp 2014; Muller et al. 2011; Müller and Knapp 2014).

Among the other bromodomains, cAMP response element-binding protein (CREB) binding protein (CREBBP or CBP) bromodomain is one of the primary transcriptional regulators, plays important key roles in the transcriptional activation of human cells. The architecture of CREBBP

protein comprises with a HAT domain, a CREB binding domain, several zinc finger domains, a plant homology domain (PHD) and a bromodomain (BRD). The CREBBP protein shares 96% sequence identity with same subfamily protein called, adenoviral E1A binding protein of 300 kDa (EP300), and its bromodomain binds to the acetylated lysine 382 of p53 (Mujtaba et al. 2004). And thus, CREBBP bromodomain participates in major biological functions like genomic stability, cell cycle regulation, DNA replication and repair, and cell growth. In recent decades, CREBBP bromodomain has been regarded as potential drug target in cancer, as it modulates a number of oncology-relevant transcription factors, including p53, c-MYC and cMYB (Das et al. 2009; Hammitzsch et al. 2015; Ito et al. 2001; Jin et al. 2011; Taylor et al. 2016). The mechanisms of CREBBP are not only involved in the regulation of cell survival mechanisms (Goodman and Smolik 2000) but also in other oncogenic activity of additional fusion protein (Giles et al. 1998). Both CREBBP and EP300 suppress apoptosis and promote cell proliferation and tissue growth, and also their overexpressions have been directly correlated with tumor aggressiveness (Li et al. 2011a, b). It was appeared from recent reports by Conery et al. (2016) and Picaud et al. (2015) that inhibition of CREBBP bromodomain by small molecules improved the traditional chemotherapy by controlling intractable expression of oncogenic transcriptional factors, and also it was predicted to have better druggability than the other domains (Vidler et al. 2012). Hence, development of CREBBP bromodomain inhibitors represents a promising direction for future therapeutics.

In the quest for potent CREBBP bromodomain inhibitor, various researches have been conducted currently, where first nanomolar CREBBP inhibitor was reported by Rooney et al. (2014), based on dihydroquinoxalinone scaffold. Hay et al. (2014) reported selective CREBBP bromodomain inhibitors starting from a non-selective 3,5-dimethylisoxazole ligand. More recently, Taylor et al. (2016) reported fragment based selective CREBBP bromodomain inhibitor CPI-637, derived from benzodiazepinone. In a similar manner, Unzue et al. (2015) and Xu et al. (2015) demonstrated selective inhibitor, using in silico model followed by taking account of polar interactions of ARG1173 side chain at the rim of binding site.

In this study, we have focused to a series of naphthyl-based compounds and started CREBBP ligand-identification by docking and free-energy calculations (Dash et al. 2015). Here we have presented the outcome of in silico structure based approach, compound 31, a selective naphthyl based CREBBP bromodomain inhibitor, validated by molecular dynamics simulation.

Materials and methods

Dataset and ligand preparation

A dataset of 39 naphthyl-based compounds was taken from the previously published KDR inhibitors (Table S1, See Supplementary File) (Harmange et al. 2008). The structures were drawn by Accelrys symyx drawer 4.1 (Symyx Technologies, Inc) and then, 3D structures were built by using Ligprep2.5 in Schrödinger Suite 2013 with an OPLS_2005 force field. Their ionization states were generated at pH 7.0 ± 2.0 using Epik2.2 in Schrödinger Suite. Up to 32 possible stereoisomers for per ligand were retained. In which, only the lowest energy conformer was kept for analysis.

Protein preparation

Three dimensional crystal structure of the bromodomain of human CREBBP (PDB id 5I86) was downloaded in pdb format from the protein data bank (Berman et al. 2000). After that, the structure was prepared and refined using the Protein Preparation Wizard of Schrödinger-Maestro v9.4. Charges and bond orders were assigned, hydrogens were added to the heavy atoms, and all waters were deleted. Reorientation of certain hydroxyl and thiol groups, amide groups of asparagines, glutamines and imidazole ring of histidines, protonation states of histidines, aspartic acids, and glutamic acids were done by optimizing the protein at neutral pH. Using force field OPLS_2005, minimization was carried out setting maximum heavy atom RMSD to 0.30 Å.

Docking analysis

Prior of docking, receptor grid was calculated for the prepared protein within the predicted active site during docking. In Glide, grids were generated to $14 \text{ Å} \times 14 \text{ Å} \times 14 \text{ Å}$ by keeping the default parameters of van der Waals scaling factor 1.00 and charge cutoff 0.25 subjected to OPLS_2005 force field. After that, extra precision (XP) flexible ligand docking were carried out in Glide of Schrödinger-Maestro v9.4 (Friesner et al. 2004, 2006) within which penalties were applied to non-*cis/trans* amide bonds. Van der Waals scaling factor and partial charge cutoff was selected to be 0.80 and 0.15, respectively for ligand atoms. Final scoring was performed on energy-minimized poses and displayed as Glide score. The best docked pose with lowest Glide score value was recorded for each ligand.

Prime MM-GBSA

To evaluate the actual binding energy of the compounds, the complexes generated from the docking simulation were subjected to MM-GBSA analysis of prime module. Using, OPLS_AA molecular mechanics force field, MM-GBSA (Rastelli et al. 2010) calculate relative binding energy by combining molecular mechanics energies (EMM), an SGB solvation model for polar solvation (GSGB), and a non-polar solvation term (GNP) composed of the non-polar solvent accessible surface area and van der Waals interactions. The total free energy of binding:

$$\Delta G_{\text{bind}} = G_{\text{complex}} - (G_{\text{protein}} + G_{\text{ligand}}),$$

where $G = \text{EMM} + \text{GSGB} + \text{GNP}$

Induced fit docking

Induced fit docking (IFD) was performed using the module Induced Fit Docking of Schrödinger-Maestro v9.4 (Doman et al. 2002). In this docking procedure, the ligand was docked into the target protein (PDB ID 5I86) with a constrained minimization process, and 0.18 Å was selected for generation of centroid of the residues, and the box size was generated automatically. After that, a soften potential glide docking was performed; in which, side chains were trimmed automatically based on B-factor, with receptor and ligand van der Waals scaling of 0.70 and 0.50, respectively; and the number of poses generated were set to be 20. In the docking simulation, residues closed to the ligand (within 5 Å of ligand pose) were kept flexible in prime refinement and during the process the side chains were further optimized. Glide redocking process was further introduced for the ligand having the best pose with in 30.0 kcal/mol. The ligand was rigorously docked into the induced-fit receptor structure and the results yielded an IFD score for each output pose. The pose having the lowest IFD score of the ligand was selected for further consideration (Schrödinger 2012).

Molecular dynamics simulation

To validate the prediction from docking study, molecular dynamics simulation was performed using the NAMD (Phillips et al. 2005) software, ver 2.9. In this study, the CHARMM force (Vanommeslaeghe et al. 2010) field was utilized, as it is widely applied to describe macromolecular system. The transferable intermolecular potential3 points (TIP3P) water model was used by adding Cl[−] and/or Na⁺ ions, where the total solvent molecules, 4663, having density of 1.012 gm/cm³. The periodic boundary condition was employed to perform the simulation, where the box size $61.4 \times 56.6 \times 46.5 \text{ Å}^3$. Following the steepest descent energy

minimization, equilibration of 100 steps was done with NPT ensemble. Using Langevin dynamics for constant temperature, full-system periodic electrostatics was maintained by using Particle Mesh Ewald (PME). Consistently Nose–Hoover Langevin piston was used for constant pressure dynamics and SHAKE was used to keep all bonds involving hydrogen atoms at their equilibrium values. Finally, the full system was subjected to MD production run at 300 K temperature for 25 ns in NVT ensemble. The MD trajectories were saved every 5 ps for analysis.

In order to analyze the stability of the complex, the binding free energy was calculated by using the generalized born/volume integral (GB/VI) implicit solvent method. The MM/GBVI calculates the binding energy of the given pose of the ligand in protein complex, where more negative values indicates more favorable binding. Trajectories of 100 step interval have been taken out for the analysis, therefore a total of 250 snapshots have been subjected to MM/GBVI analysis, using the force field of Amber10:EHT with R-Field solvation (Labute 2008). The following calculation has been done through MOE 2015 package.

Results and discussions

Extra precision docking and free energy calculations

A total of 39 naphthamides docked in the active site of CREBBP bromodomain in complex with the synthetic ligand, benzodiazepinone. Notably, the compounds were selected and classified on the basis of their different SAR

modifications. Briefly, compounds numbering from 1 to 13 represent the variation of the nitrogen containing heterocycle binding the hinge region, compounds 14–16 correspond to the variation of the naphthyl region, compound 17 and 18 represent the variation of linker atom, while compounds 19–39 demonstrate the variations of the naphthamide moiety.

To determine the probable binding conformations of these compounds, glide docking with extra precision mode was selected, because it helps in removing the false positives and the scoring function is much stricter than the HTVS (Jatana et al. 2013). Prior of docking, it is necessary to validate the accuracy of docking protocol for better prediction and reliability (Talele and McLaughlin 2008). For that we applied docking methodology to the known X-ray structure of CREBBP bromodomain in complex with a small benzodiazepinone. The compound benzodiazepinone was re-docked to the active site of protein and the docked conformation having the lowest free energies was selected as the most possible binding conformation. The value of the root mean square deviation (RMSD) of the docked conformation with respect to experimental conformation was 0.963 Å, signifying the high reliability of docking protocol. As shown in Fig. 1a, the position of docked compound was found to be similar with co-crystallized. Henceforth, the remaining compounds were docked following the same docking protocol.

From the docking analysis, similar binding confirmations of all compounds were observed and represented in Fig. 1b. Experimentally, previously published reports on CREBBP bromodomain inhibition demonstrated that electrostatic attractions between the conserved Asn1168,

Fig. 1 Predicted pose from extra precision glide docking. Here, **a** superimposed view of docked (pink) and co-crystallized ligand (green), and **b** docked confirmation of 39 structures at inhibitor bounding site of CREBBP

Tyr1125, Pro1110 side chain, and hydrophobic interactions with Ile1122, Leu1120 and Val1174 are critical for inhibitor binding and inhibition (Taylor et al. 2016; Unzue et al. 2015; Xu et al. 2015).

As shown in Fig. S1 and Table S2, the docking results of the compounds from 1 to 13 revealed that 4-chloro phenyl containing naphthamide moiety of the compounds act as a head group in the binding cleft, and formed halogen bond between the chlorine atom and MET1163 side chain. At this position, the oxygen atom of carboxamide was involved in the hydrogen-bond interaction with conserved Asn1168 (Table S2). Furthermore, hydrophobic interactions with Ile1122, Leu1120, Val1174 were also observed with naphthyl region, where Val1174 formed pi-alkyl bonds with the aromatic rings of naphthyl and phenyl regions. The variations in the hinge region of the compounds were placed at the outside of the cleft, which influenced the non-bonded interactions with Pro1110 side chain. Similar binding confirmations were observed for the remaining compounds, however compound 15 resulted different confirmation due to having methyl group on the amine that may disrupting the coplanarity of the quinoline and naphthyl rings by generating a steric clash between the *N*-methyl group and the C5 hydrogen on the quinoline (Harmange et al. 2008).

Along with docking simulation, we used MM-GBSA approach to rescore and estimate binding energies of the compounds under this study. It is noteworthy that, all the docking process is not free from false positive and also a more precise computational method is vital for lead hit identification (Aparna et al. 2014). Using Molecular Mechanics (MM) force fields and implicit solvation, MM-GBSA calculates binding free energies to find the best hits, which is very useful in computing the relative binding affinities that each hit requires for the target protein, several reports indicated that (Hou et al. 2010; Kuhn et al. 2005; Weis et al. 2006). The binding energy of all of the compounds resulted from MM-GBSA are enlisted in Table 1. According to Table 1, compound 13, 33 and 37 showed the least binding energy of -90.38 , -90.19 , -90.99 kcal/mol respectively. The least binding energy of -59.72 kcal/mol was observed for compound 5. In the mean while, we calculated the binding energy of co crystallized ligand, which was -70.25 kcal/mol. This result indicates the compounds having binding energy higher than 70 kcal/mol are the active inhibitors of CREBBP bromodomain (Wichapong et al. 2014).

Induced fit docking

As described in introduction section, the search of selective inhibitor was carried out by doing further investigation on the docked complexes, the strategy of selective inhibitor identification was based on the approach described in previously published reports (Hewings et al.

Table 1 Extra precision Glide docking results of the compounds with binding energy

Compound name	Docking score	Glide energy	Glide emodel	ΔG_{bind}
1	-7.034	-47.991	-73.111	-83.578
2	-5.718	-42.335	-62.157	-73.479
3	-5.119	-43.395	-68.961	-70.882
4	-7.151	-47.4	-70.728	-74.233
5	-3.777	-44.101	-61.957	-59.725
6	-7.945	-48.662	-76.299	-84.562
7	-7.124	-47.678	-70.403	-87.090
8	-7.453	-48.213	-69.148	-83.527
9	-6.517	-44.543	-71.666	-81.156
10	-6.911	-50.553	-72.437	-84.180
11	-5.388	-43.308	-71.948	-81.000
12	-6.099	-52.05	-78.767	-80.799
13	-6.39	-51.708	-73.317	-90.389
14	-6.034	-51.047	-74.988	-81.708
15	-7.365	-49.255	-70.159	-82.213
16	-6.435	-51.79	-77.381	-83.814
17	-3.821	-38.596	-62.456	-72.156
18	-1.321	-51.074	-73.584	-84.257
19	-7.703	-35.867	-52.95	-88.292
20	-7.305	-52.159	-74.553	-81.123
21	-7.147	-39.785	-66.762	-86.448
22	-6.738	-45.257	-59.722	-73.428
23	-6.71	-50.886	-76.138	-72.961
24	-6.672	-51.458	-67.442	-74.962
25	-7.508	-49.506	-68.395	-81.244
26	-6.612	-52.885	-80.445	-79.702
27	-6.601	-51.268	-72.235	-84.022
28	-6.411	-44.891	-55.926	-72.234
29	-6.204	-38.783	-57.014	-70.425
30	-7.733	-55.725	-76.789	-81.629
31	-6.202	-49.834	-66.742	-74.428
32	-5.937	-52.752	-74.45	-81.833
33	-5.811	-52.773	-76.792	-90.196
34	-5.731	-43.6	-59.711	-72.406
35	-6.306	-50.73	-71.173	-77.595
36	-5.086	-44.019	-60.389	-86.077
37	-4.828	-47.283	-74.588	-90.997
38	-4.523	-34.419	-57.088	-78.130
39	-2.528	-49.99	-77.085	-74.139

Results are represented in Kcal/mol unit

2011; Unzue et al. 2015; Xu et al. 2015), i.e. electrostatic interaction with Arg1173, a residue located at the entrance of the binding site that is considered to be key for attaining selectivity towards CREBBP. As the docking results from Glide XP indicated the polar interaction of compound 31 with Arg1173, we performed induced

fit docking to find accurate binding conformation of protein–ligand complex.

Induced fit docking is a mix methodology of molecular docking and molecular dynamics simulations, predicts more accurate bioactive conformation than glide docking procedure. From the docking result, we found that compound 31, having two hydrogen bonds with the Arg1173. Both of these two bonds formed between the guanidinium of the Arg1173 side chain and the acceptor oxygen of carboxamide group of the compound, where the distances were 2.634 and 1.889 Å, respectively. According to the per residue contribution from the glide docking, the contribution of electrostatic interaction was −6.131 kcal/mol. Besides, it formed another hydrogen bond with conserved ASN1168 side chain and also a halogen bond was seen with Leu1109 residue. The aromatic rings of naphthyl and hinge region were involved with the hydrophobic interactions with side chains of Leu1120 on the ZA loop and Val1174, by forming pi-alkyl and pi-sigma bonds. The side chain Tyr1125 was also involved with the nonbonded hydrophobic interaction, shown in Fig. 2.

Molecular dynamics simulation

Concurrent with the investigation on compound 31, we performed molecular dynamics (MD) simulations with explicit solvent of apo and protein ligand complex to authenticate the binding mode resulted from the docking study. The timescale considered in this study is enough to facilitate various conformations by the side chain rearrangements in protein's native state, while recent studies demonstrated that the dynamic motions of a single protein molecule are

self-similar and look the same, how long you look at them for, from picoseconds to hundreds of seconds (Hu et al. 2015). In biomolecular system, the stability of the protein–ligand interactions plays an important key role and therefore, root mean square deviation (RMSD), root mean square fluctuation (RMSF) and radius of gyration (Rg) of both apo and protein–ligand complex were calculated and depicted in Figs. 3 and 4. The RMSD calculation is a global measurement protein and ligand fluctuations, indicates the thermodynamic stability within the system.

As shown in Fig. 3a, the RMSD values of the protein backbone of both apo and protein ligand were calculated, where ligand-free protein obtained equilibrium state after 2 ns, while the complex obtained 4 ns. Despite of several magnitudes, the RMSD of both systems remained stable afterwards. As high RMSD values represented the higher flexibility of the protein, the binding of the compound 31 influenced the CREBBP bromodomain to be more rigid thereby the complex can be regarded as more stable than the free protein. Furthermore, RMSF of the protein in two systems were also calculated and plotted in Fig. 3b. It is clearly seen that from the Fig. 3b, the binding of the ligand decreased the local fluctuation of the protein, while the ligand free protein showed high fluctuation. Moreover, certain residues of the protein in both systems highly fluctuated to 8 Å in MD simulations; however, we carefully observed the local fluctuations of the interacting residues of the active site, where we found that the binding site residues were less fluctuated during the simulation in binding with the ligand (Fig. 4a). Only Tyr 1175 and Met1113 residues were seen to fluctuate more, nevertheless in all case, the RMSF

Fig. 2 Binding orientation and 2D interaction map of important amino acids for compound 31, showing hydrogen bond interaction including π – π stacking

Fig. 3 Confirmation stability of CREBBP bromodomain by means of **a** RMSD, **b** RMSF and **c** radius of gyration of backbone atom calculated during 25 ns simulation for both ligand free and protein–ligand complex systems. Here red color indicates the protein–ligand complex, where black color denotes free protein

eventually indicates that the ligand formed stable complex with CREBBP bromodomain, hence the interacting residues produced lower fluctuations in the simulation. The conformational changes of the protein due to binding with ligands were also observed by the calculation of radius of gyration. As can be seen in Fig. 3c, the ligand-free CREBBP bromodomain undergoes the conformational change, where its holo form remains stable over the time. The significant changes in overall structural dimension of the apo-CREBBP protein was observed from 4 to 9 ns, having Rg values ranging from 15.70 to 14.7 Å, and remained stable afterward with several large fluctuations. The radius of gyration is an indicator of compactness of protein structure, where lower values denote higher compactness (Priya Doss et al. 2014; Tanwar et al. 2017), and thus it can be concluded that the CREBBP–Compound 31 complex is more stable than the free protein.

In addition, MM-GBVI approach was accumulated to assess the binding free energy of the trajectory snapshots produced from the complex during the simulations. As a result, binding energies of 250 snapshots for 25 ns were calculated and the results were plotted in Fig. 4b, where more negative values represent the better binding. According to

Fig. 4 Comparative **a** root mean square fluctuations (RMSF) active site residues of ligand free and protein–ligand complex of CREBBP bromodomain during the simulations. Red bar represents the protein–ligand complex, where black indicates ligand free protein. **b** MM/GBVI binding free energy of the complex during the MD simulation. More negative energy denotes higher binding

the Fig. 4b, the compound 31 produced binding free energy ranging from -77 to -95 kcal/mol, while the average binding free energy was -86.88 kcal/mol. This result further concludes that compound 31 has the strong affinity towards the CREBBP bromodomain, which is also in agreement with the results from MM-GBSA analysis.

Again, the RMSD of heavy atoms of compound 31 over the time was also calculated, which were found to ranging from 1 to 3 Å. Highest fluctuation was seen in 5–20 ns, where lower fluctuations were observed in 0–5 and 21–25 ns, concluded that the ligand within the protein is more flexible and stable (Fig. 5). Since our attention towards the polar interactions with Arg1173 side chain, and the resulted

Fig. 5 The time series of the RMSD of the heavy atoms of compound 31 during 25 ns MD simulation

docked compound 31 formed polar interactions by forming hydrogen bond, we calculated the number of hydrogen bond and bonding distance between the guanidinium of the Arg1173 side chain and the carboxamide group of the compound. We found 37% of the MD snapshots having bonding distance shorter than 3.5 Å (Fig. 6a), while hydrogen bond occupancy was retrieved more than 20% of simulation time (Fig. 6b). We also calculated the hydrogen bond occupancy and distance for ASN1168 side chain, as it is found critical for CREBBP inhibition. As rendered in Fig. 6c, 96% of the MD snapshots having bonding distance shorter than 3.5 Å between the nitrogen atom of aromatic part at hinge region of compound 31 and the hydrogen of ASN1168 residue, emerging over 90% hydrogen bond occupancy (Fig. 6d). As a corollary, it can be concluded the CREBBP inhibition mechanism of compound 31 by selective manner.

Conclusion

In conclusion, the anticancer roles of naphthyl-based compounds have been previously explored and well established, since they have good pharmacokinetic profile and robust pharmacological action. Guiding from molecular docking and molecular dynamics simulation studies, this work represents the potentiality of naphthyl-based compounds in CREBBP bromodomain inhibition. Among them, compound 31 was found encouraging the selectivity to CREBBP bromodomain. We believe that these findings offer useful insight for the designing of target specific new CREBBP bromodomain inhibitor and provide a suitable starting point for further development as well as detailed in vitro and in vivo analyses.

Fig. 6 Time series of the distance (a) and hydrogen bond occupancy (b) between the carboxamide oxygen of compound 31 and the ARG1173 side chain, and the distance (c) and hydrogen bond occupancy (d) between the nitrogen atom of compound 31 and ASN1168 side chain along the trajectory

Author contributions RD and SMZH conceived and designed the study. RD and SM preformed the experiments, prepared the figures, and wrote the initial draft. MA and SMZH analyzed the data, guided and supported in the preparation of manuscript. All authors have read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest All authors declare that they have no competing interests.

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