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Chapter

Biological Evaluation and Molecular Docking Studies of Benzalkonium Ibuprofenate

Kodakkat Parambil Safna Hussan, Mohamed Shahin Thayyil, Thaikadan Shameera Ahamed and Karuvanthodi Muraleedharan

Abstract

The third-generation ionic liquids (ILs), which are being used to produce double active pharmaceutical ingredients (d-APIs) with tunable biological activity along with novel performance, enhancement, and delivery options, have been revolutionizing the area of drug discovery since the past few decades. Herein we report the in vitro antibacterial and anti-inflammatory activity of benzalkonium ibuprofenate (BaIb) that are being used as in-house d-API, with a particular focus on its interaction with respective protein target through molecular docking study. The evaluation of the biological activity of BaIb with the antibacterial and anti-inflammatory target at the molecular level revealed that the synthesized BaIb could be designed as a potential double active drug since it retains the antibacterial and anti-inflammatory activity of its parent drugs, benzalkonium chloride (BaCl) and sodium ibuprofenate (NaIb), respectively.

Keywords: benzalkonium ibuprofenate, double active pharmaceutical ingredient, molecular docking studies, anti-inflammatory, antibacterial activities

1. Introduction

In the pharmaceutical field, ionic liquids (ILs) by salification of drugs were widely applied to improve the performance of drugs on its oral administration, especially, their solubility, bioavailability, and stability. The research on the antimicrobial activity of ILs is a growing field because of its unprecedented flexibility for chemical diversity in a severely drained arsenal of antimicrobial. The third-generation ionic liquids give us the freedom to tune the biological properties in addition to its physical and chemical properties. The proper selection of ions with synergetic effects may result in the formation of double active pharmaceutical ingredient (d-API). Thus the d-APIs are composed of asymmetric organic ions, which prevent the formation of the stable crystal lattice and are liquid at unusually low temperatures. Such d-APIs can be used for the ailment situations where the two activities are required. This strategy will reduce the excess in taking of unwanted chemicals and will enhance the solubility and bioavailability [1, 2].

Benzalkonium ibuprofenate (BaIb) is a double active pharmaceutical ingredient designed by combining benzalkonium cations with ibuprofen. Benzalkonium chloride

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(BaCl) is a potential antibacterial drug and sodium ibuprofen is a prospective anti-inflammatory drug [3]. It is important to evaluate the pharmaceutical profiles of the d-API to confirm the retainity of the biological activities of the parent drugs. We have synthesized a d-API, benzalkonium ibuprofenate, carried out its quantum mechanical calculations using density functional theory, characterized different experimental techniques, and reported glass-forming ability in earlier works [4, 5]. Now, in this work, the biological evaluations, in particular, the antibacterial and anti-inflammatory activities, were performed and the results with the activity of parent drugs, BaCl and sodium ibuprofenate (NaIb), compared. The molecular docking of all the samples was done to get a better understanding of the mode of interaction between the drugs and respective targeted proteins and to trace their binding pores and cites.

2. Materials and method

2.1 Materials

The benzalkonium chloride and sodium ibuprofenate were purchased from Sigma-Aldrich (USA). Cell culture plastic flasks, test tubes, and culture plates were purchased from Borosil (India).

2.2 Experimental

2.2.1 Synthesis

The double active pharmaceutical ingredient, benzalkonium ibuprofenate, was synthesized using stoichiometric metathesis reaction. Solid (1 mmol) BaCl and NaIb were dissolved in 50 mL distilled water, each taken in two beakers and stirred separately with gentle heating (40–60°C). Then the two solutions were mixed together and again stirred for another 30 min with heating (around 80°C) and then cooled to room temperature. 60 mL of chloroform was added to separate the organic and inorganic part; then the chloroform phase was washed with cold distilled water until it removes the inorganic salt completely. $AgNO_3$ test was used to confirm the absence of chloride anions in the product. This is followed by continuous washing of the chloroform phase with deionized (DI) water until the water washings tested negative for NaCl or NaBr via $AgNO_3$ test. The chloroform was then evaporated using rotary evaporator, and the BaIb was dried under high vacuum for 12 h with gentle heating (50–60°C) [4, 6].

The double active pharmaceutical ingredient, BaIb was characterized well using Nuclear Magnetic Resonance using Bruker Avance III, 400MHzwith a 9.4 Tesla super-conducting magnet in an operating temperature at 309 K, Fourier transform infrared spectroscopy JASCO FTIR-4100 spectrophotometer, Fourier Transform-Raman spectroscopy and UV–visible spectroscopy using Jasco UV–Visible Spectrophotometer model V-550 (USA) and are reported in earlier works [4, 5].

2.2.2 Biological evaluation

2.2.2.1 Antibacterial activity

The synthesized double active pharmaceutical ingredient BaIb was screened against Gram-negative bacteria to confirm the retainity of the biological activity of its parent drug BaCl, which is a potential germicide. For this study, we have chosen *Pseudomonas aeruginosa* and *E. coli* as Gram-positive, while DMSO is considered as

Gram-negative. Paper disk method was used for the in vitro analysis. The experiment was started with the preparation of nutrient agar (28 g in 100 mL) and was sterilized by autoclaving. This nutrient agar media was cooled without solidifying and incubated overnight. *P. aeruginosa* and *E. coli* were prepared. 15–20 mL of this media was poured into sterilized Petri plate and allowed to solidify. Then sterilized disks were placed in this solidified agar plate; each plate contains three disks. 10 μL negative controls on to one disk, 10 μL standard parent drugs on to the second disk, and 10 μL samples on to the third disk were added and appropriately labeled. After incubating the Petri dishes in 310 K for 24 h, the plates were checked for the zone of inhibition, and the zone diameter was measured using a scale [4, 7].

$$Formula\ for\ ABA = \frac{sample\ diameter}{+ve\ control} \times 100 \quad (1)$$

2.2.2.2 Anti-inflammatory activity

2.2.2.2.1 In chick albumin

The anti-inflammatory activity of BaIb and NaIb was done using an egg albumin. For this, a reaction mixture of 5 mL was made with fresh hen's egg (0.2 mL) and phosphate buffer saline with pH = 6.4 of 2 mL with varying concentrations of extract for preparing the concentrations of 100, 200, 300, 400, and 500 μg/mL. The same steps were repeated for the preparation of double distilled water, which served as control. Then the prepared mixtures were incubated in BOD incubator (Labline Technologies, India) at 210 ± 2 K for 15 min; after that, it is heated to 343 K and was hold for 5 min. The absorbance was measured after incubating using Shimadzu (Japan), UV 1800 at 660 nm. At the final concentration of 100, 200, 300, 400, and 500 μg/mL, acetyl salicylic acid was used as reference drug. The protein denaturation inhibition percentage was calculated using the following formulae:

$$\%inhibition = \frac{Abs_{control} - Abs_{test}}{Abs_{control}} \times 100 \quad (2)$$

2.2.2.2.2 In human serum albumin

In addition, the synthesized drug BaIb was screened for its anti-inflammatory activity, and its efficiency with the parent drug NaIb and drug diclofenac was compared. For this, blood samples from a healthy donor (male) were collected and mixed with sterilized Alsever's solution before centrifuging it at 3000 rpm. The suspension of packed cells was made with isoline. This suspension with phosphate buffer, hyposaline, was mixed with diclofenac at varying concentration, where the distilled water is taken as control while diclofenac as standard. Then the mixtures were incubated for 30 min at 303 K and centrifuged. Spectrophotometric analysis was used for hemolysis at 560 nm and its percentage recorded [4, 8, 9].

2.3 Computational

The input structures of BaCl (PubChem: 2330), NaIb (PubChem: 5338317), and BaIb (PubChem: 86612072) were taken from the PubChem database [9] and optimized using density functional theory with B3LYP level of theory and 631-G+(d,p) [10] basis sets using Gaussian software packages [11]. Further, the molecular docking was also conducted using Schrodinger Maestro software package [10]. The optimized structures and downloaded Protein Data Bank (PDB) files [12] of proteins were used for molecular docking studies.

The Schrodinger's Glide module was used for docking analysis of the present work. Glide offers the full range of speed vs. accuracy options, from the HTVS (high-throughput virtual screening) mode for efficiently enriching million compound libraries, to the SP (standard precision) mode for reliably docking tens to hundreds of thousands of ligand with high accuracy, and to the extra precision (XP) mode where further elimination of false positives is accomplished by more extensive sampling and advanced scoring, resulting in even higher enrichment. Many researchers carried out extensive comparisons of several docking programs and scoring functions using an extensive data set of pharmaceutically attractive targets and active compounds [13–18]. All the study leads to the same result that Glide XP methodology was shown to yield enrichments superior to the alternative methods consistently. Glide SP scoring also shows improvement as compared to the scoring in GOLD and DOCK. The drawbacks of Glide come from the fact that it's increasing computational time. From computational efficiency, the CPU time required on average for Glide XP calculations (7.0 min per ligand) is larger than other methods except for the most accurate version of Goldscore (8.5 min per ligand). This extra cost for Glide XP is the trade-off for the higher enrichment factors obtained. Glide SP delivers the second best overall enrichment performance while providing a considerable speedup (0.42 min per ligand) as compared to all approaches except for the fast version of GOLD Chemscore setting.

2.3.1 Molecular docking studies

The structure-based drug design always promotes the in silico method for molecular docking before going to lab screening. In silico methods can site the binding pores and predict the mechanism of protein-ligand interactions as well as target binding.

Moreover, the analysis and interpretation of the binding behavior play a crucial role in rational drug designs and in elucidating fundamentals of biochemical processes. The antibacterial activity of BaCl and BaIb was studied using LpxC enzymes since the enzyme LpxC places an important role in the lipid A biosynthesis. Lipid A acts as a hydrophobic membrane of lipopolysaccharide (LPS) in the outer leaflet of the outer membrane of Gram-negative bacteria; however, the bacteria is with a defective lipid. A synthesis reduces its hydrophobicity and shows increased membrane permeability, which in turn increase the sensitivity to the antibiotics, and hence, it results in cell death. For this work, we have selected LpxC from *Escherichia coli* and *P. aeruginosa*. In the same way, the targeted protein for the anti-inflammatory activity of NaIb and BaIb were studied using human serum albumin (HSA).

Thus the structures of proteins used in this work were downloaded from the Protein Data Bank [12]. The detailed information of the selected proteins, their PDB IDs, inbuilt inhibitor, X-ray resolution, etc., were given in **Table 1**. Molecular docking study has been carried out by the Glide docking program [19–21] provided by Schrodinger suite. Protein preparation is done by using the Protein Preparation Wizard module of Glide [22, 23]. Initially, all the protein structures must be preprocessed to be used as a receptor for docking. Some of the typical operations in preprocessing include (i) addition of hydrogen atoms, (ii) assignment of atomic charges, and (iii) elimination of water molecules that are not involved in ligand binding. Missing chains and loops can also be added if necessary. Preprocessed protein was optimized with PROPKA and then minimized with OPSL3 force field function, which is followed by a convergence of heavy atoms of RMSD 0.3 Å.

Then, the Glide's receptor grid generation wizard was used to generate a three-dimensional (3D) grid with a maximal size of 20 × 20 × 20 Å with 0.5 Å spacing.

Sl. no.	Protein	Organism	PDB-ID	Inbuilt inhibitor	X-ray resolution	Ligands	Activity
1	LpxC	*Escherichia coli*	3P3G	3p3	1.65 Å	BaCl, BaIb	Antibacterial
2	LpxC	*Pseudomonas aeruginosa*	5U3B	NVS	2.00 Å	BaCl, BaIb	Antibacterial
3	HSA	*Homo sapiens*	2BXG	Ibuprofen	2.70 Å	NaIb, BaIb	Anti-inflammatory

Table 1.
Detailed information regarding the proteins under study.

There is enough option to apply any constraints such as precision constraints, H-bond constraint, etc., in the receptor grid generation wizard. At last, flexible docking was performed with extra precision docking mode in Glide docking module.

3. Results and discussions

3.1 Antibacterial activities of BaCl and BaIb

3.1.1 In vitro studies

As we know, benzalkonium chloride is a prominent germicide widely used in medicinal chemistry [24]. It is mandatory to confirm the retainity of BaCl's antibacterial effect in the synthesized d-API, BaIb. The inhibition zone method using agar diffusion was used to screen the antibacterial activity of the prepared as well as parent drug against *P. aeruginosa* and *E. coli* bacterial strains [25]. The percentage of inhibition and its diameter are listed in **Table 2**. The results emphasized that BaIb retains the antibacterial activity of parent drug BaCl, though it had less inhibitory action against *E. coli* and *P. aeruginosa* than the parent drug [25].

3.1.2 Molecular docking studies with LpxC (E. coli)

Here, molecular docking of the parent and daughter drugs, BaCl and BaIb with *Escherichia coli* LpxC/LPC-009 complex, has been employed to trace its binding pore and binding affinity. The docking scores and binding free energies of lowest energy pose of its inbuilt inhibitor, 3p3 and the samples under study, BaCl, and BaIb in active sites on chain A of the LpxC/LPC-009 X-ray crystal structures have been computed after deleting the unwanted ligands and amino acids (So4 at 501, 502, 504, 505, 506; dimethyl sulfide (DMS) at 701; and UKW) using Schrodinger Glide module and are given in **Table 3**. The docking result points out that the drugs BaCl and BaIb show considerable binding affinity scores compared to the inbuilt ligand. However, interestingly the d-API BaIb exhibits high docking score compared to the parent drug BaCl, which emphasize that the interaction between the ligand and protein increases on double active formation with ibuprofen.

Figure 1 demonstrates the three-dimensional protein-ligand interaction of the three samples under study in the dynamic site of LpxC/LPC-009 obtained from graphical interface Maestro. All the ligands are found to be buried in the deep binding pocket of LpxC/LPC-009 in the same way. The d-API BaIb interacts with the active site's amino acids of the protein by H-bonding, which is depicted in red and dotted lines.

The diameter of zone of inhibition (mm)			Percentage of inhibition (%)		
	E. coli	*P. aeruginosa*		*E. coli*	*P. aeruginosa*
Standard BaCl	19	38	Standard BaCl	21.11	42.22
Sample BaIb	14	31	Sample BaIb	15.55	34.44
Negative (DMSO)	0	0	Negative (DMSO)	0	0

Table 2.
Preliminary in vitro antibacterial screening activity of BaIb.

Compound	Schrodinger software	
	Glide docking score (kcal/mol)	Glide ligand efficiency
3P3	−13.682	−0.507
BaCl	−3.234	−0.147
BaIb	−6.315	−0.175

Table 3.
Docking scores and binding free energies of inbuilt inhibitor 3P3, BaCl, and BaIb to the LpxC/LPC-009 using Schrodinger Maestro software.

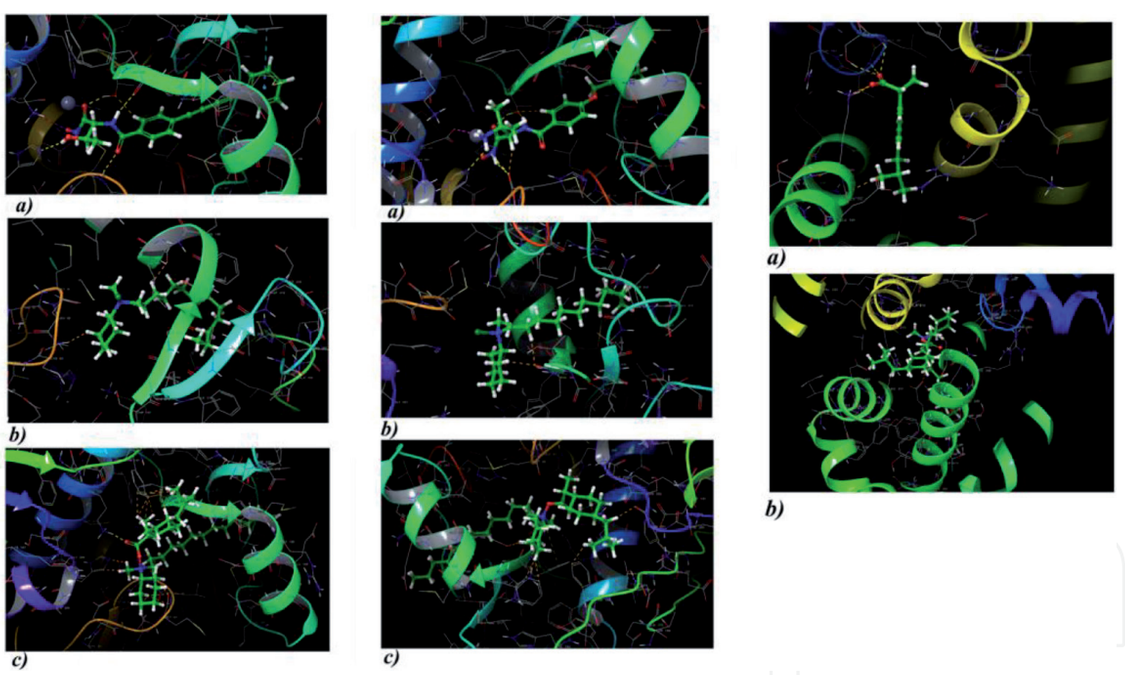


Figure 1.
Three-dimensional (3D) protein-ligand interactions diagram using Schrodinger software (I) with LpxC protein of E. coli *using (a) inbuilt ligand 3P3, (b) parent ligand BaCl, and (c) double active pharmaceutical ingredient BaIb; (II) with LpxC (*P. aeruginosa*) using (a) inbuilt ligand 3P3, (b) parent ligand BaCl, and (c) double active pharmaceutical ingredient BaIb; and (III) with human serum albumin using (a) inbuilt ligand ibuprofen and (b) double active pharmaceutical ingredient BaIb.*

In addition to the 3D binding orientations of the ligands in the protein, the docking results provide further insights into selective interactions of the ligands with the *E. coli* LpxC in the 2D image, as shown in **Figure 2**. The ligands were encompassed by active site amino acids THR191, PHE192, SER211, PHE212, CYS214, LYS239, HIS238, HIS265, etc., of LpxC. The co-crystallized ligand 3P3 occupied the deep cavity by forming three hydrogen bonds and one π-π interaction with active site amino acid PHE212. Though the parent ligand BaCl occupied the deep cavity of

LpxC with the support of salt bridges between them, the daughter ligand BaIb formed one hydrogen bond with the active amino acid LYS239.

Despite the binding energy and docking score difference between parent and daughter drugs, BaCl and BaIb were well occupied in the binding site of the LpxC protein as similar to the native ligand 3P3 by forming a hydrogen bond with active site amino acids. Besides, the binding energy and docking score emphasize that the d-API has a higher binding affinity with LpxC than the parent drug BaCl. This indicates that BaIb can be considered as a potential inhibitor of LpxC protein with antibacterial activity.

3.1.3 Molecular docking studies with LpxC (P. aeruginosa)

Here, molecular docking of the parent and daughter drugs, BaCl and BaIb with LpxC protein of *Pseudomonas aeruginosa*, has been employed to trace the nature of its binding interaction and binding affinity value. The docking scores and binding free energies of lowest energy pose of its inbuilt inhibitor, NVS-LpxC-01 and the samples under study, BaCl, and BaIb in active sites on chain B of the NVS-LpxC X-ray crystal structures, have been computed after deleting the unwanted ligands and amino acids and including the Zn^{2+} using Schrodinger Maestro software and are given in **Table 4**. The docking result points out that the drugs BaCl and BaIb show considerable binding affinity scores compared to the inbuilt ligand. However,

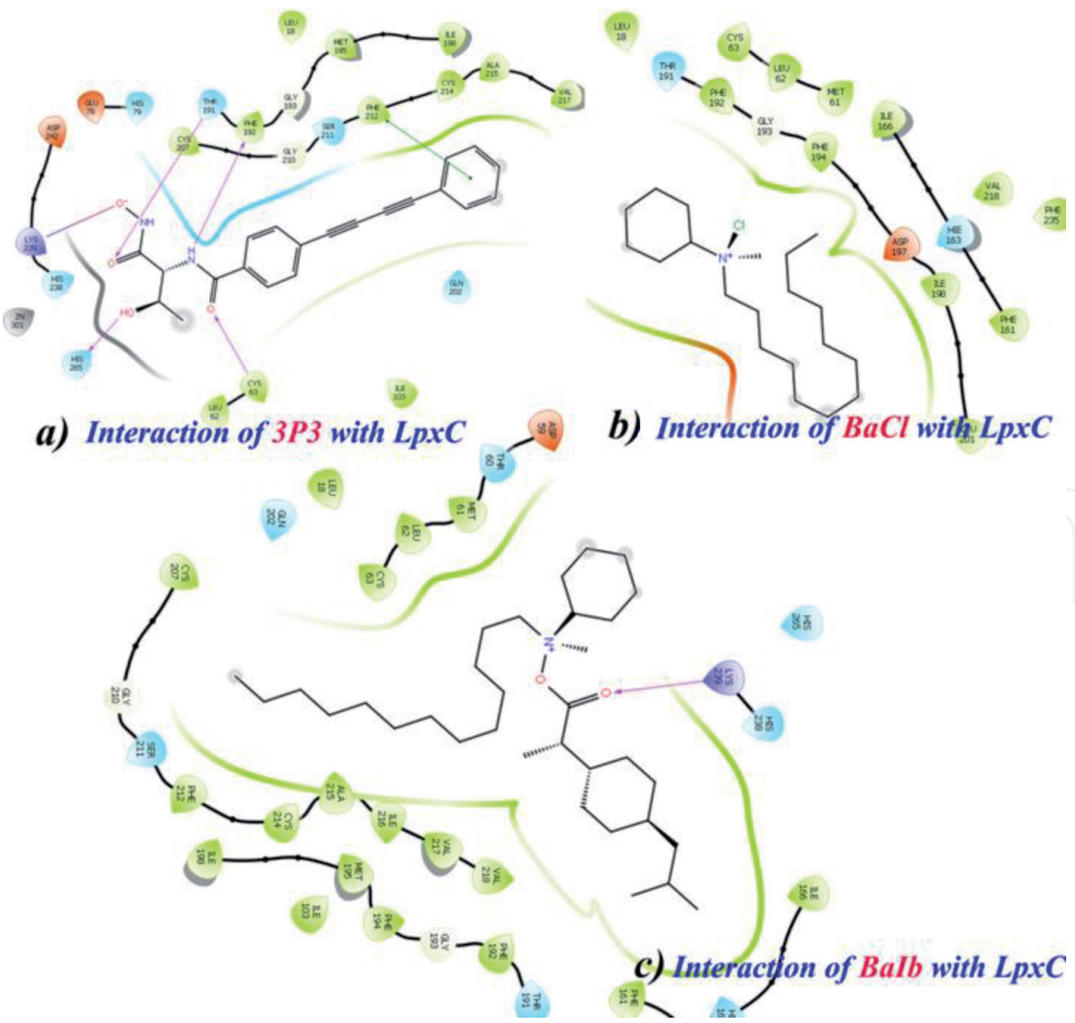


Figure 2.
Schematic representations of ligand-protein interaction and binding interaction using stick mode. (a) 3P3 with LpxC, (b) BaCl with LpxC, and (c) BaIb with LpxC.

Compound	Schrodinger software	
	Glide docking score (kcal/mol)	Glide ligand efficiency
NVS	−11.095	−0.482
BaCl	−4.540	−0.206
BaIb	−5.494	−0.153

Table 4.
Docking scores and binding free energies of inbuilt inhibitor NVS, BaCl, and BaIb to the LpxC/LPC-009 using Schrodinger Maestro software.

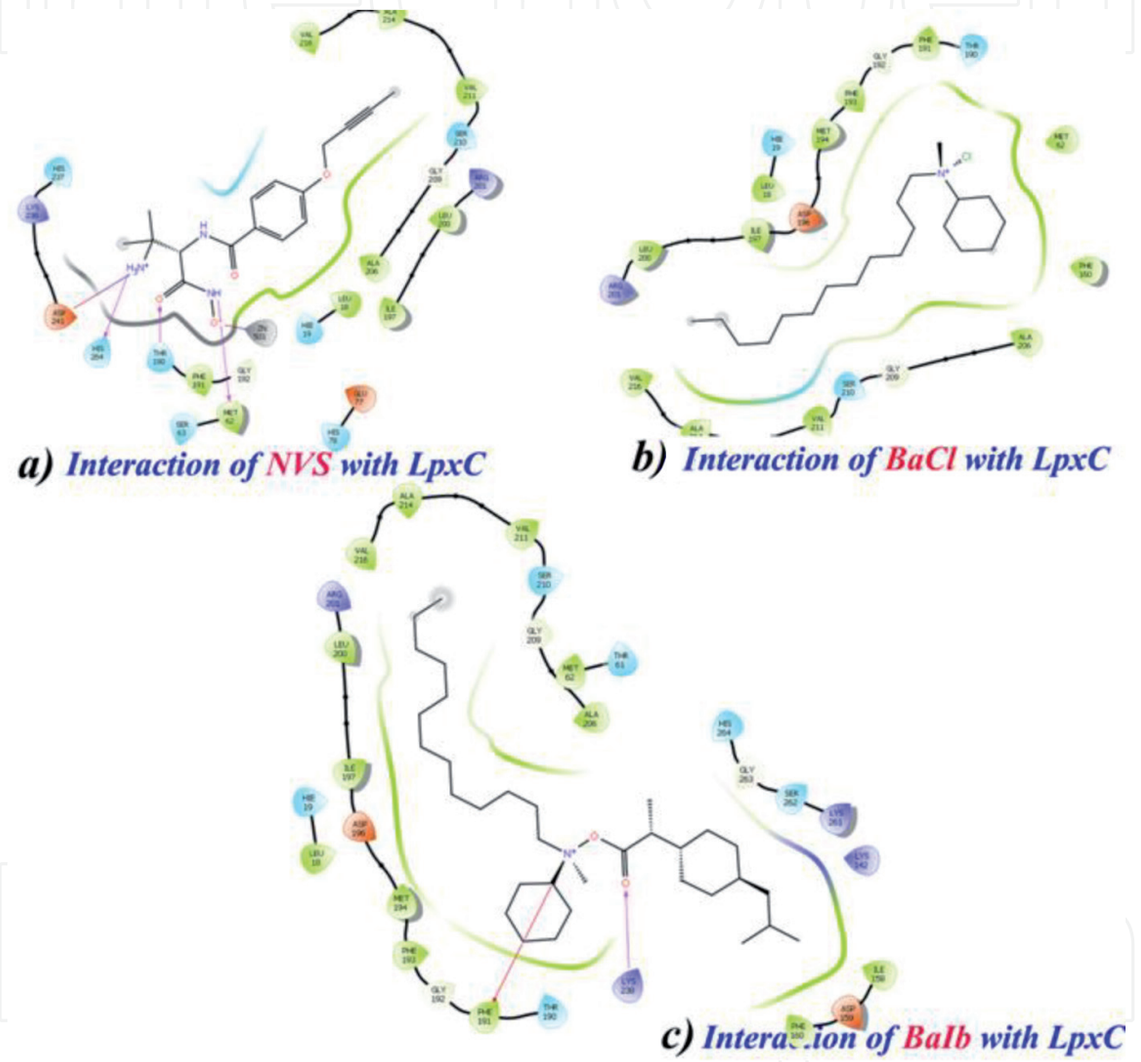


Figure 3.
Schematic representations of ligand-protein interaction and binding interaction using stick mode. (a) 3P3 with LpxC, (b) BaCl with LpxC, and (c) BaIb with LpxC using Schrodinger software.

interestingly the d-API BaIb exhibits high docking score compared to the parent drug BaCl, which emphasizes that the interaction between the ligand and protein increased on double active formation with ibuprofen.

Figure 1 demonstrates the three-dimensional protein-ligand interaction of three samples under study in the active site of LpxC in complex obtained from graphical interface Maestro. All the ligands are found to be buried in the deep binding pocket of LpxC in the complex in an indistinguishable way. The d-API BaIb interact with the active site's amino acids of the protein by H-bonding, which is depicted in red and dotted lines.

In addition to the 3D binding orientations of the ligands in the protein, the docking results provide further insights into selective interactions of the ligands with the *Pseudomonas aeruginosa* LpxC in the 2D image as shown in **Figure 3**. The ligands were surrounded by active site amino acids THR190, GLY192, PHE191, SER211, PHE193, MET194, ASP196, DLE197, LEU200, ARG201, VAL216, etc., of LpxC. The co-crystallized ligand NVS occupied the deep cavity by forming five hydrogen bonds in addition to its salt bridge. Though the parent ligand BaCl occupied the deep cavity of LpxC with the support of salt bridges between them, the daughter ligand BaIb formed one hydrogen bond with the active amino acid LYS238 and a π-cation interaction with active site amino acid PHE191.

Despite the binding energy and docking score difference of parent as well as the daughter drugs, BaCl and BaIb were well occupied in the binding site of the LpxC protein as similar to the native ligand NVS with hydrogen bonding with active site amino acids. Also, the binding energy and docking score emphasize that the d-API has a higher binding affinity with LpxC than the parent drug BaCl. This indicates the BaIb can be considered as a potential inhibitor of LpxC protein with antibacterial activity.

3.2 Anti-inflammatory activities of NaIb and BaIb

3.2.1 In vitro studies using chick albumin

The anti-inflammatory properties of the synthesized drug BaIb and parent drug NaIb were studied in chick albumin membrane. **Figure 4** depicts the bar diagram of the percentage inhibition of inflammation against the concentration of NaIb and BaIb. Sample NaIb and BaIb have almost the same inhibitory activity in all concentration, which is around 95%. Thus from this analysis, one can confirm that BaIb retains the anti-inflammatory activity of NaIb and states.

3.2.2 In vitro studies using human serum albumin

The anti-inflammatory properties of the synthesized drug BaIb, parent drug NaIb, and drug diclofenac as standard samples were given in **Table 5**. Among samples provided, diclofenac shows maximum inhibitory activity, whereas the NaIb and BaIb are less active than the reference compound, but still, its activity is significant as an inflammatory agent. This fact suggests that the anti-inflammatory activity of NaIb was retained in the double active pharmaceutical ingredient. Thus the in vitro study confirms that the synthesized BaIb is a double active pharmaceutical ingredient by retaining the biological activities of the parent drugs.

3.2.3 Molecular docking studies of NaIb and BaIb with HSA

Here, molecular docking of the parent and daughter drugs, NaIb and BaIb, respectively, with human serum albumin complex has been employed to analyze its binding mode and binding affinity value. The docking scores and binding free energies of lowest energy pose of its inbuilt inhibitor, ibuprofen and the BaIb in active sites on chain A of the 2BXG X-ray crystal structures, have been computed after deleting the unwanted ligands and amino acids using Schrodinger Maestro software and are given in **Table 6**. The docking result points out that the drugs ibuprofen and BaIb show considerable binding affinity scores compared to the inbuilt ligand. However, interestingly the d-API BaIb exhibited almost similar docking score to the parent drug Ib, which emphasizes that the interaction between the ligand and protein is still functional on double active formation with ibuprofen.

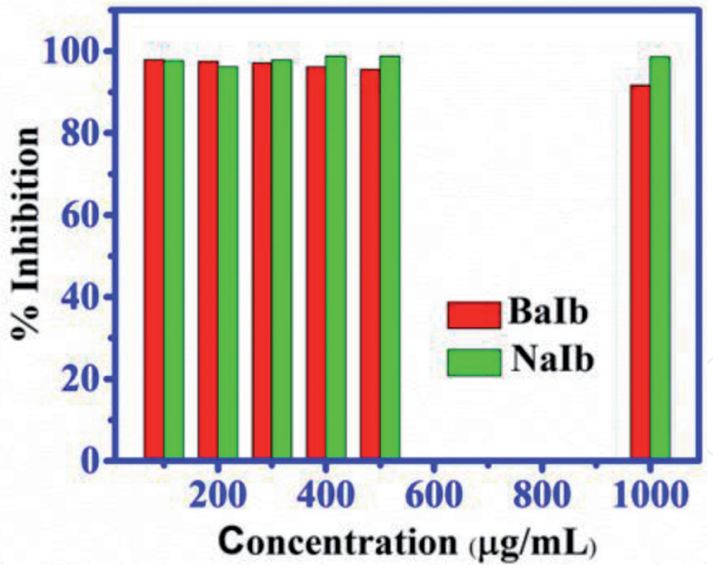


Figure 4.
Plot of percentage inhibition of inflammation against the concentration of NaIb and BaIb studied in chick albumin membrane.

Percentage of inhibition of hemolysis (%)	
Diclofenac	92.16
Standard sample NaIb	88.47
Sample BaIb	88.59

Table 5.
Preliminary in vitro anti-inflammatory properties of BaIb.

Compound	**Schrodinger software**	
	Glide docking score (kcal/mol)	**Glide ligand efficiency**
Ibuprofen	−5.435	−0.362
BaIb	−3.554	−0.099

Table 6.
Docking scores and binding free energies of inbuilt inhibitor ibuprofen and BaIb to the 2BXG using Schrodinger Maestro software.

Figure 1 demonstrates the three-dimensional protein-ligand interaction of three samples under study in the dynamic site of 2BXG obtained from graphical interface Maestro. All the ligands are found to be well occupied in the deep binding pocket of 2BXG in the same way. The d-API BaIb interact with the active site's amino acids of the protein by H-bonding, which is depicted in red and dotted lines. Interaction of amino acids at the active site of HAS with the studied compound is displayed in the 2D image (**Figure 5**). The ligands were encircled by amino acids like SER480, LBU481, VAL482, ASN483, PHE205, ARG209, ALA210, ALA213, etc., of HSA. The co-crystallized ligand ibuprofen occupies the deep cavity by forming three hydrogen bonds with active sites of amino acids SER480, LBU481, VAL482, and one π-anion interaction with active site amino acid LYS351. The daughter ligand BaIb forms only one hydrogen bond with the amino acid LYS239.

Despite the binding energy and docking score difference of parent as well as the daughter drug, the daughter drug, BaIb, was well occupied in the binding site of the

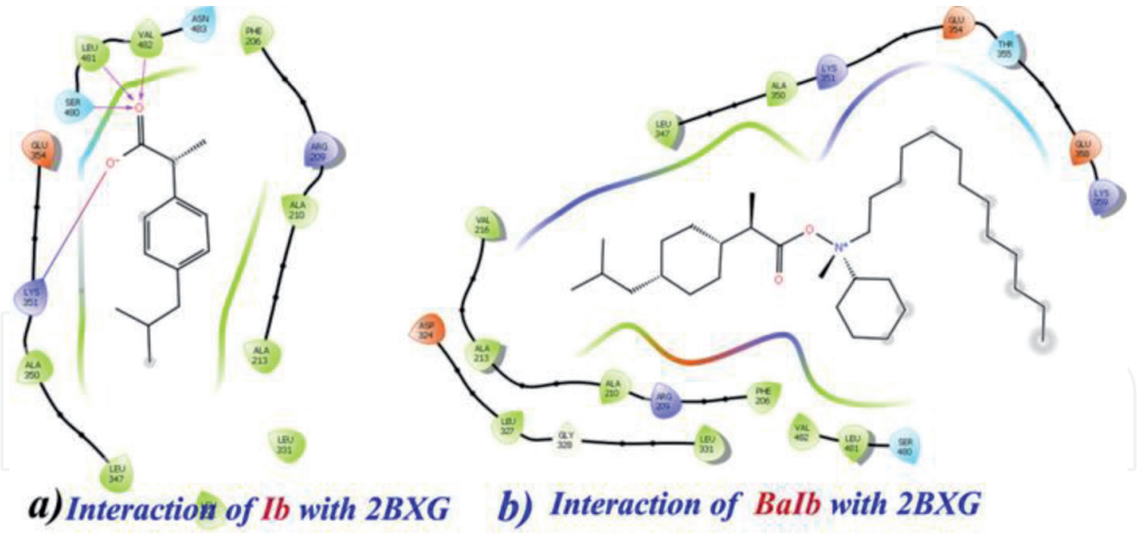


Figure 5.
Schematic representations of ligand-protein interaction and binding interaction using stick mode. (a) Ibuprofen with 2BXG and (b) BaIb with 2BXG using Schrodinger software.

HSA protein as similar to the native ligand ibuprofen by forming a hydrogen bond with active site amino acid.

4. Conclusions

In this work, the biological evaluations of a synthesized double active pharmaceutical ingredient BaIb were done to confirm the retainity of the biological activities of its parent drugs and to elucidate information regarding its potential activities against their respective ailments. Further molecular docking studies were done to get a better understanding about the mode of interaction of the parent as well as daughter drugs with the targeted proteins and trace out the binding pore and cites in the targeted proteins.

The in vitro studies revealed that the synthesized BaIb could be designed as a potential double active drug since it retained the antibacterial activity of its parent BaCl with considerable inhibitory action against *E. coli* and *P. aeruginosa* compared to the parent drug. The binding energy and docking score of BaCl and BaIb again confirm that the prepared d-API BaIb docks well into the LpxC proteins of *E. coli* and *P. aeruginosa* with high docking and Glide score compared to the parent drug BaCl.

Similarly, the results from both in vitro and in silico method emphasize that the prepared d-API retained the anti-inflammatory action of its parent NaIb and bound well to the deep pocket of the active site in the human serum albumin. Thus, in total, one can conclude that the prepared BaIb can be used as a potential double active drug with antibacterial and anti-inflammatory actions.

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Author details

Kodakkat Parambil Safna Hussan[1], Mohamed Shahin Thayyil[1], Thaikadan Shameera Ahamed[2] and Karuvanthodi Muraleedharan[2*]

1 Department of Physics, University of Calicut, Malappuram, Kerala, India

2 Department of Chemistry, University of Calicut, Malappuram, Kerala, India

*Address all correspondence to: kmuralika@gmail.com

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