Research Article

Molecular design and docking analysis of the inhibitory activities of some α_substituted acetamido-*N*-benzylacetamide as anticonvulsant agents

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Abstract
The concentrations of Gama aminobutyric acid (GABA) in the brain have been shown to be a major factor in the determinations of convulsions. Computational molecular docking study was carried out on the α_substituted acetamido-*N*-benzylacetamide (anticonvulsant agents) to complement our previous QSAR work with the help of Autodock vina version 4.0 of Pyrx software. Docking analysis revealed that all the compounds have better binding scores (with the highest binding score of − 13.8 kcal/mol) than the commercially sold antiepileptic drug vigabatrin (− 4.4 kcal/mol) but with the exception of ligands 2-acetamido-*N*-benzyl-2-hydroxyacetamide and 2-acetamido-*N*-benzyl-*N*-methyl-2-(pyrimidin-2-yl)acetamide which were revealed to have unpromising binding affinities. The most potent derivatives of α_substituted acetamido-*N*-benzylacetamide (2-acetamido-2-((3-aminophenyl)amino)-*N*-benzyl-*N*-methylacetamide with the experimental activity (pED$_{50}$) of 1.99) from our previous QSAR research was in agreement with this present work as the same compound was revealed to be having the highest binding affinity (− 13.8 kcal/mol). Moreover, three anticonvulsant compounds were designed and one of the compounds (2-acetamido-2-((3-amino-4-vinylphenyl)amino)-*N*-benzyl-*N*-methylacetamide) with best binding score of − 14.15 kcal/mol was found to have excellently docked with GABAAT enzyme through amino acid residues of Lys203, Pro347, Arg430, Thr353, Arg192 and Ala346 than the commercially sold vigabatrin (− 4.4 kcal/mol). This study provides a valuable approach for pharmaceutical as well as medicinal chemists to synthesis these newly designed anticonvulsant drugs from α_substituted acetamido-*N*-benzylacetamide that will be more efficient in managing convulsion.

Keywords Docking study · GABAAT enzyme · α_Substituted acetamido-*N*-benzylacetamide

1 Introduction

Epilepsy is one of the most commonly occurring central nervous system disorders that affect approximately 69-72 Millions people globally [1, 2]. More than 80% of people with epilepsy are found in developing countries, where epilepsy remains a major public health problem, not only because of its health implications but also for its social, cultural and economic effects [1, 3]. However, the global prevalence of epilepsy ranges from 2 to 20 per 1000 of the general population [4]. Epilepsy causes a seizure to occur and these seizures can cause a variety of symptoms depending on the areas of the brain affected. Symptoms can vary from mild to severe and can include complete or partial loss of consciousness, loss of speech, uncontrollable motor behaviour, and unusual sensory experiences [5]. The concentrations of Gama aminobutyric acid (GABA) in the brain have been shown to be a major factor in determining the level of convulsions [5–7]. Gamma-aminobutyric acid aminotransferase (GABAAT enzyme) is a validated target for anti-epileptic drugs because of its selective inhibition raises GABA

concentration in the brain [8]. This knowledge of Gama aminobutyric acid neurotransmitter made ready for future examination and a percentage of the turmoil's first compelling medications. New compounds such as vigabatrin and gabapentin have emerged following the globally used antiepileptic [9, 10]

The modern antiepileptic drugs is mostly associated with dose-related side effects and chronic toxicity effects. [9]. Therefore, the search for safe and more potent anticonvulsant drug remains a drug design priority for medicinal chemists and the continued search for the safer and more effective antiepileptic drugs. Computational docking based drug design remains one of the most logical and pleasing rational in-silico technique in drug discovery [10]. The knowledge of the binding site residues to specific groups of inhibitor as lead to proposals for the synthesis of very specific agents with a high probability of biological action [11]. The application of docking software is mostly the used of the virtual screening method. Virtual screening selects the most interesting and promising molecules from an existing database for advanced research. This place demands on the use of the computational method for drug productions, which must be fast, accurate and reliable.

In this work, efforts were geared towards complementing our previously performed research on quantitative structure–activity relationship (QSAR) of acetamido-*N*-benzylacetamide derivatives against Gama aminobutyric acid aminotransferase (GABAAT enzyme), a validated target for anti-epileptic drugs [12] via a comprehensive molecular docking and designing approaches.

2 Materials and methods

2.1 Ligand dataset

2D structures of the ten most potent acetamido-*N*-benzylacetamide derivatives (Table 1) as anticonvulsant compounds were selected from our previous work and used as the ligand for this present study [12, 13]. The compounds were converted to 3D structures, optimized and converted to PDB format by utilizing Spartan'14 version 1.1.2 [14]. The molecular docking studies of active anticonvulsant compounds were performed using AutoDock Vina of PyRx virtual screening software [15] running on Toshiba Satellite, Dual-core processor window eight (8) operating system. The 3D model of GABAAT enzyme (PDB ID = 1OHV) was downloaded from PDB (http://www.rcsb.org/pdb/). Discovery Studio 4.5 version (DS, Accelrys Software Inc., USA) was used to perform the energy minimization of GABAAT enzyme.

2.2 Receptor and ligands preparation procedure

The preparation of acetamido-*N*-benzylacetamide derivatives (Table 1) as ligands were performed as follows: (i) molecular structures were drawn with the help of ACD Chemsketch (ii) conversions of 2D to 3D, (iii) correcting structures, (iv) generating variations of these structures, (v) validating and optimizing the structures. All of these tasks were performed using Spartan'14 version 1.1.2 (for geometric optimization) and autodock 4.2 software [14]. The prepared ligands are shown in Fig. 1. The structures of GABAAT enzyme were retrieved from Protein Databank (PDB: 1OHV). The 3D structure of GABAAT enzyme was prepared for molecular docking by removing bound water molecules, adding hydrogen and cofactors using Autodock version 4.2 software. The prepared receptor is shown in Fig. 1.

2.3 Molecular docking's computational procedure

PyRx was used to dock GABAAT enzyme and acetamido-*N*-benzylacetamide derivatives (Ligands) into the X/Y/Z grid with the flexible docking option turned on. The search efficiency was set at 100% so as to examine the docking conformational space comprehensively. The highest binding affinity (the lowest docking energy) score was chosen to explore the binding mode of the docked compound in the GABAAT enzyme using PyRx program. For the analysis of the docking calculations, 9 conformers were considered for each ligand-target complex, and the resulting docking clusters were calculated with a 2.0 Å root mean squared deviation (RMSD) tolerance on the heavy atoms [16]. The 3D molecular interaction models of the complex (involving hydrogen bonding and hydrophobic interactions) were displayed using the pymol visualization software.

3 Structure validation

Native ligands present in the protein structure were removed. In order to check the confirmation, root mean square deviation (RMSD) value was calculated between the original structure and the ligand deleted structure [17].

3.1 Template based virtual screening method

Molecular docking is an in silico computational screening technique which predicts the strength of chemical compounds. This virtual screening method could determine whether the bonded drug candidate with the receptor of interest can predict a better compound with

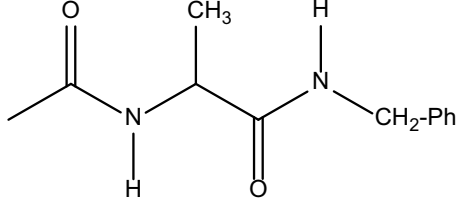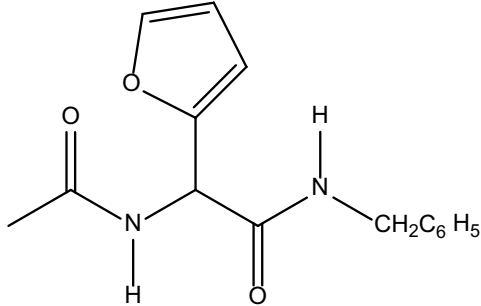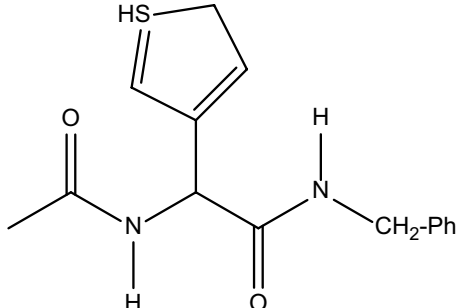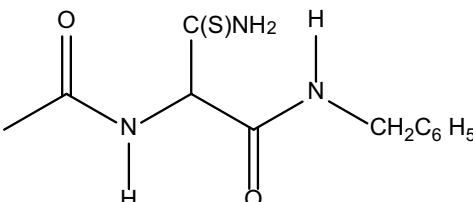**Table 1** Biological activities of α_substituted acetamido-*N*-benzylacetamide derivatives
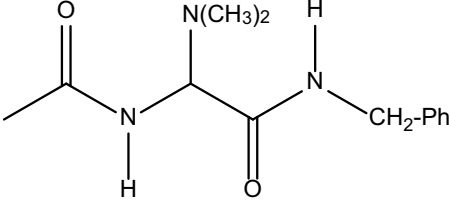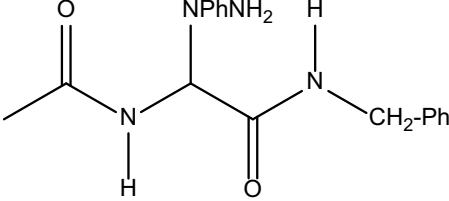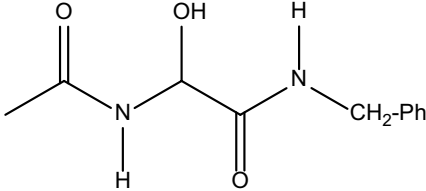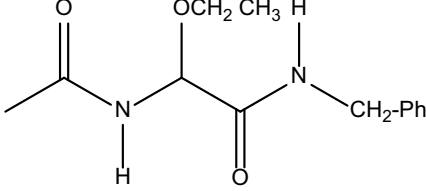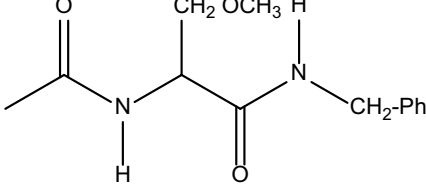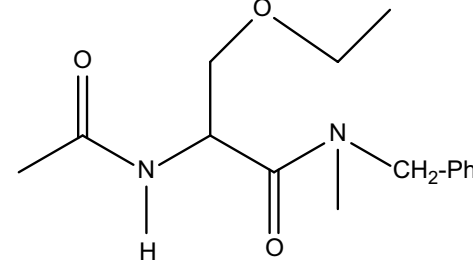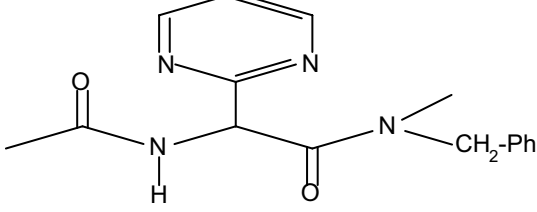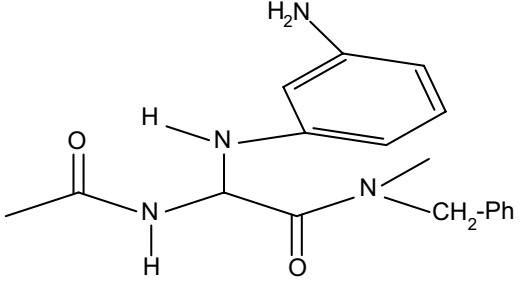
S.NO	Structures	$IC_{50}(\mu M)$
1[a]		1.88
7[t]		1.80
16[t]		1.94
20[t]		1.94
22[t]		1.66
24[t]		1.63

Table 1 (continued)

S.NO	Structures	$IC_{50}(\mu M)$
25[a]		1.90
26[t]		1.79
27[t]		0.92
28[a]		1.23
30[a]		0.91
33[t]		1.99

Fig. 1 Prepared 3D structures of Gama aminobutyric acid aminotransferase (Receptor) and its inhibitor (Ligand 33)

a very high binding strength or not. Moreover, it can also be used to identify which structural modifications could be permitted using the domain of applicability to design better novel chemical compound of desirable activities of interest.

4 Results and discussion

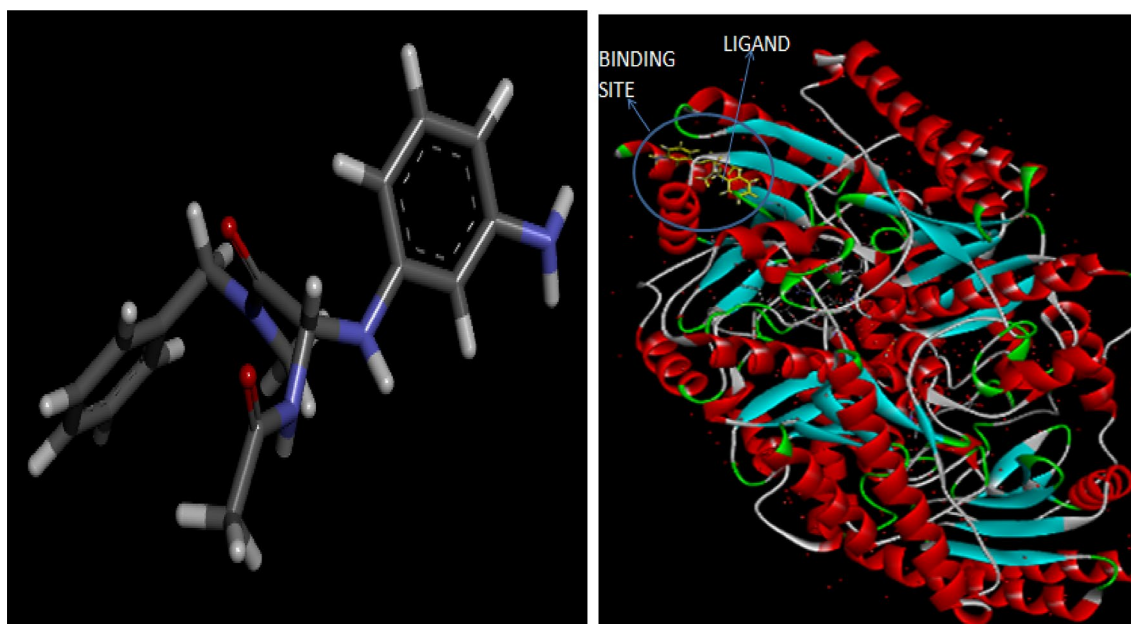Molecular docking of all the 12 ligands (Table 2) was performed on GABAAT enzyme (PDB code 1OHV). All the inhibitors (ligands) were found to strongly inhibit by completely occupying the active sites in the target protein. In Table 2, the interactions profile and binding affinity of all the docked ligands showed better binding affinities to the target than vigabatrin (− 4.4 kcal/mol) the commercially sold drug for epilepsy but with the exception of ligands 25[a] and 30[a] which were revealed to have unpromising binding affinities.

Docking studies revealed clearly that the amino α_substituted acetamido-N-benzylacetamide ring of ligand number 33[t] (− 13.8 kcal/mol) was found to be surrounded by interacting residues. Ligand number 33[t] (Table 2) ring was found to be bound by interacting residues such as Phe401, Ile402, Arg422, Asp415, Thy416, and Lys442. Moreover, we realized that the binding scores generated were found to be better than one proposed by Abdulfatai and co-workers [18, 19].

4.1 Designed anticonvulsant compounds analysis

In this current research, a ligand-based chemical compound design method was used to design a novel anticonvulsant compound with improved activities starting with chemical compound 33t (with binding affinity value of − 13.8 kcal/mol) as the template ligand and therefore offers reliable anticonvulsant activities and looked promising as a useful scaffold. The ligand 33t compound was chosen as the best synthetically viable structure at which further structural modifications were made. The three novel designed derivatives such as (A) 2-acetamido-2-((3-amino-4-vinylphenyl)amino)-N-benzyl-N-methylacetamide, (B) 2-acetamido-N-benzyl-2-((2,3-diamino-4-isopropylphenyl) amino)-N-methylacetamide and (C) 2-acetamido-N-benzyl-2-((2,3-diamino-4-isopropyl-5-(pentan-3-yl)phenyl) amino)-N-methylacetamide (Table 2) with their binding energies of − 13.89, − 13.91 and − 14.15 kcal/mol (Table 3) were designed and found to be more superior and better in term of binding strength than the one reported by Abdulfatai and co-workers [18, 19].

5 Conclusion

In this investigation, the selected most potent α_substituted acetamido-N-benzylacetamide derivatives have better binding scores than vigabatrin (− 4.4 kcal/mol), the widely used antiepileptic drug. This research (molecular

**Table 2** Structures of the newly designed anticonvulsant compounds
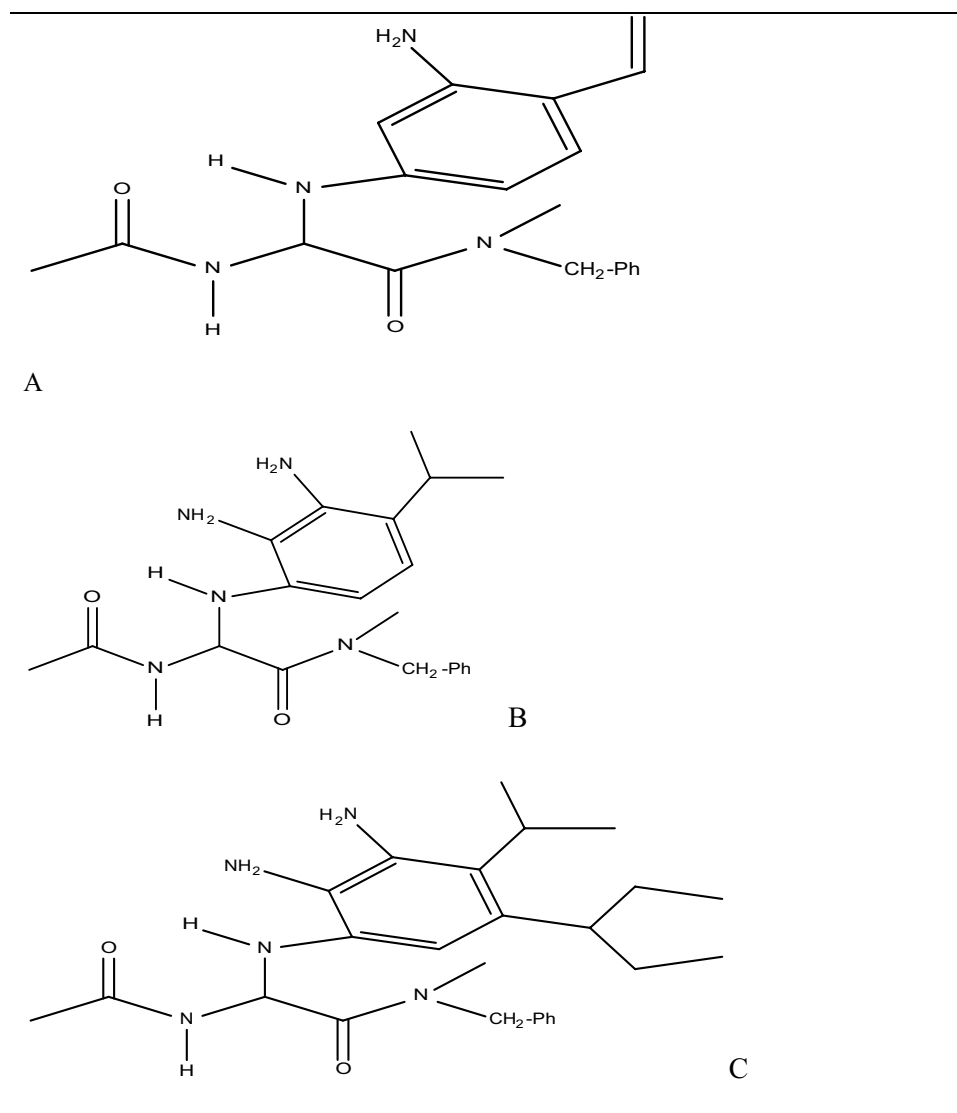
docking) and our previously conducted quantitative structure–activity relationships [12] were found to be in agreement with each other as the anticonvulsant activity (pED_{50}) values of α_substituted acetamido-*N*-benzylacetamide derivatives were found to be directly proportional to its binding affinities. The interacting residues such as Phe401, Ile402, Arg422, Asp415, Thy416, and Lys442 were the amino acids found in the active site, and they are responsible for protein action.

Moreover, the most potent derivatives of α_substituted acetamido-*N*-benzylacetamide (compound 33[t] with the experimental activity (pED_{50}) of 1.99) from our previous QSAR research was in agreement with this present work as the same compound was revealed to be having the highest binding affinity (− 13.8 kcal/mol). Also, all the three

designed anticonvulsant compounds (Table 2) were found to have better docking scores than all the studied anticonvulsant compounds in Table 3. Specifically, the molecular docking simulation study revealed that anticonvulsant compound 2-acetamido-2-((3-amino-4-vinylphenyl) amino)-*N*-benzyl-*N*-methylacetamide (Fig. 2) with best binding score of − 14.15 kcal/mol (Table 3) was found to have excellently docked with GABAAT enzyme through amino acid residues of Lys203, Pro347, Arg430, Thr353, Arg192 and Ala346 than the commercially sold vigabatrin (− 4.4 kcal/mol) (Table 3). This study provides a valuable approach for pharmaceutical as well as medicinal chemists to synthesis these newly designed anticonvulsant drugs from α_substituted acetamido-*N*-benzylacetamide that will be more efficient in managing convulsion.

Table 3 GABA$_{AT}$ active site residues involved in docking interactions with the inhibitors and docking scores

S/N	Receptor	Binding affinity (Kcal/mol)	Amino acid residues	Hydrogen bonding residues and bond length (Å)
1[a]	GABA$_{AT}$	−4.6	TYRC69, ARG430, SER401, ASN423, HIS, TYR348, HIS44	ARG192 3.22
7[t]	GABA$_{AT}$	−5.7	ASN423, ILE426, SER427, ARG430, TYR69, ILE72, HIS44, ILE105, PHE342, TYR450, GLU270	
16[t]	GABA$_{AT}$	−7.1	ILE426, LYS203, ILE205, GLY38, GLY437, TYR348	HIS44, 3.14
20[t]	GABA$_{AT}$	−7.3	PHE189, THR353, ARG192, ASN352, PHE351	PHE189 2.77
22[t]	GABA$_{AT}$	−4.9	GLY438, ARG430, SER427, ASN423, ARG422, TYR348,	HIS24, 3.09
24[t]	GABA$_{AT}$	−5.2	PHE351, ARG192, ASN352, THR353	PHE189 2.81, 2.77
25[a]	GABA$_{AT}$	−3.0	HIS44, TYR69, LYS203, ILE203, ILE205, PHE161, ALA346	
26[t]	GABA$_{AT}$	−5.6	ILE72, GLU270, HIS206, TYR34, PRO347, LYS203,	TYR69, 2.69
27[t]	GABA$_{AT}$	−6.2	ALA346, PRO347, TYR348, LYS203, ILE72, TYR69, HIS206, GLU270	
28[t]	GABA$_{AT}$	−5.9	PHE161, ILE205, LYS203, ALA346, TYR348, HIS44, TYR69	
30[a]	GABA$_{AT}$	−3.7	GLY438, ARG422, ASN423, SER427, ARG426, PRO23, HIS44, TYR348	
33[t]	GABA$_{AT}$	−13.8	PHE401, ILE402, ARG422, ASP415, THY416, LYS442	
A	GABA$_{AT}$	−13.89	ILE212, HIS116, TYR348, GLY437, TYR348	Ser403, 2.56
B	GABA$_{AT}$	−13.91	ARG422, ASP415, THY416, HIS206, TYR34, GLY432.	TYR348, SER427 4.32 and 3.16
C	GABA$_{AT}$	−14.15	LYS203, PRO347, ARG430, TYR348, ARG192, HIS206, ASN423	ALA346, 3.31 and 4.16
Vigabatrin	GABA$_{AT}$	−4.4	Phe401, Lys442, Phe414	Asp418, Ser403, Asp415, and Pro417, 2.67, 3.31, 2.88, and 2.79

Fig. 2 2D structure of GABA$_{AT}$–Ligand C Complex
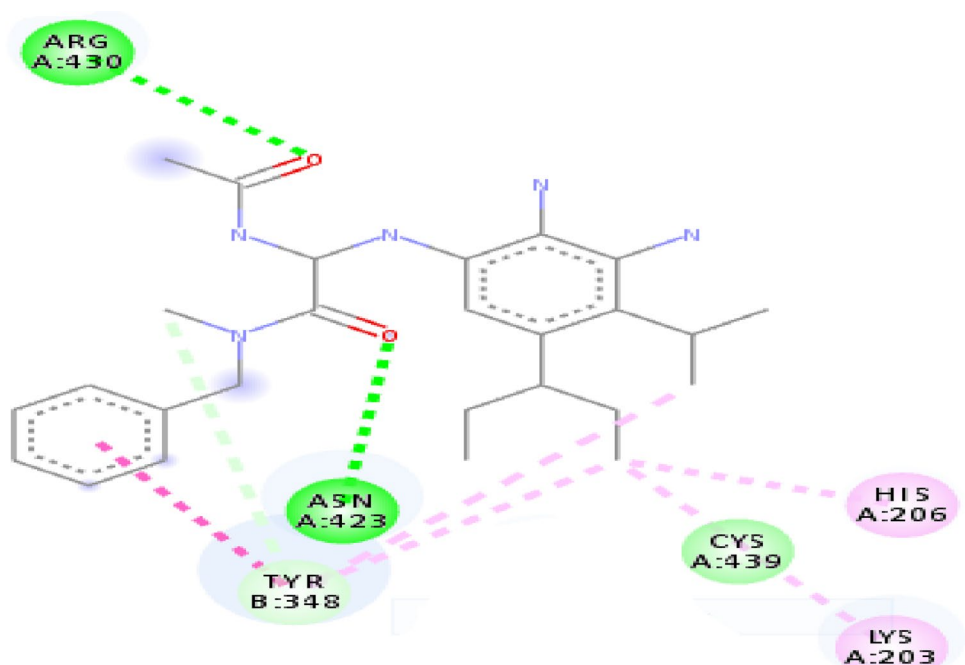
Compliance with ethical standards

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

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