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Machine learning approaches for the identification of ligands of the autophagy marker LC3

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ABSTRACT

The LC3 proteins play a crucial role in autophagy by participating to the formation of the autophagosome. Modulation of autophagy by molecular interference with LC3 proteins could help to understand this complex fundamental biological process and how it is involved in several pathologies. Identifying new LC3 ligands is a useful contribution to this aim. In the present study, we created a PubChem library of 749 compounds having a structure based on the central scaffold of novobiocin, a reported LC3A ligand. A robust, rapid and exhaustive algorithm was used for docking each compound of this database as ligands within the dihydronovobiocin binding site, providing a docking score. Remarkable reliability and consistency between docking scores and the reported binding efficiencies of known ligands was observed, validating the machine leaning protocol used in this study. Investigation of the binding mode of the ligands having the best docking score provides additional insights in possible mode of actions of the LC3 identified ligands.

1. Introduction

The autophagy is a vital intracellular mechanism that allows cells to degrade and recycle damaged, unwanted or obsolete organelle as well as cell constituents [1,2]. This natural process of self-digestion plays a determinant role in the state of health of the cell and in cellular homeostasis. It is an important process to prevent cancer by eliminating abnormal cells and suppressing the tumor growth. As a consequence, impaired autophagy may promote the development of cancer by allowing cancer cells to survive and grow. In addition to cancer, autophagy also plays a role in different pathologies in particular neurodegenerative diseases avoiding the accumulation of undesired proteins and cell constituents [3–7]. This process begins when signals activate the formation of a membrane in the cell, called phagophore. This latter sequesters the constituents of the cytoplasm and evolved through the interaction with the LC3 protein to an autophagosome which then merges with a lysosome allowing the degradation of the trapped compounds (Fig. 1). The LC3 protein is involved in the regulation of autophagy by initiating the process through the formation of the autophagic membrane [8–13].

Some studies have shown that LC3 ligands can modulate autophagy in certain cells [14–19]. For example stapled peptides with nanomolar affinities disrupt autophagy [15]. Finding new LC3 ligands is still useful as the overall understanding of how LC3 proteins are involved in the autophagy pathway is not fully understood [20]. The emergence of artificial intelligence as a tool for drug discovery [21–23] is particularly attractive and opens new opportunities in medicinal chemistry. The development of docking algorithms combined with scoring functions [24,25], together with the availability of compounds databases are indispensable tools towards machine learning and deep docking [26,27]. Taking advantages of the known X-ray structure of the complex of the LC3A protein with the antibiotic derivative dihydronovobiocin [16] (Fig. 2), the present work is a contribution towards machine learning perspectives aiming at retrieving LC3A ligands through original chemo-informatics approaches using docking simulations with an exhaustive and rapid search algorithm and a PubChem library based on the novobiocin substructure.

2. Material and methods

The construction of a Pubchem library based on the novobiocin substructure was achieved using the Pubchem database through the structural search tool using the novobiocin substructure smile template C1 =CC=CC2 =C1C(=C(C(=O)O2)NC=O)O. All the 749 3D-structures available were downloaded in a single SDF file.

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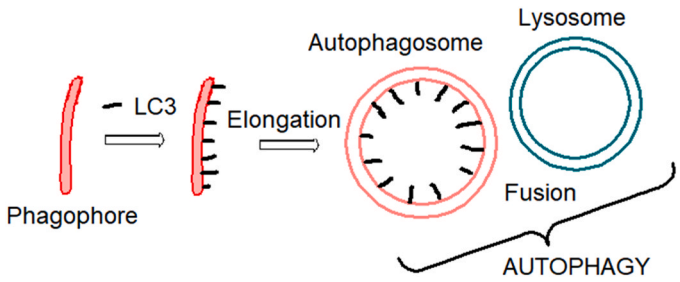


Fig. 1. Schematic representation of the autophagosome formation from a LC3-inserted phagophore membrane.

All collected compounds were then docked within the dihydronovobiocin binding site of the PDB structure (code 6tbe) [16] (Fig. 2). Prior to docking simulations using ArgusLab as software [28], the dihydronovobiocin ligand included in PDB structure was set as known ligand and residues interacting with the ligand were selected to define the binding site. A docking box 19.810 × 20.942 × 30 Å centered on this ligand was created with the docking module of the software. Docking simulations with ArgusDock as engine and Ascore as scoring function were then performed. All compounds were ranking according to their docking score. Compounds described in the study reported by Ewgenij Proschak and co-workers [16] were also found in the database and the docking scores were collected to be correlated with the pIC_{50} values.

Compounds in the top 10 were extracted from the SDF file and were then docked to analyze their binding mode using PyMol. 2D-representation with the H-bonds networks were generated with LigPlot + [29].

3. Theory/calculation

Docking simulations were conducted with the ArgusLab software allowing to perform docking simulations using two methods [30], a stochastic method with a genetic algorithm [31,32] and also a robust, exhaustive and rapid shape-based method leading to reproducible simulations (shape-based method probing shape matching with a flexible ligand defined as a torsion tree) [33–35]. The latter method implemented in ArgusLab and called "ArgusDock engine" was used and can be described as follow:

- The conformational space of the ligand is described as a torsion tree.
- Construction of binding site grids and search points inside the binding site.
- Conformational search within the binding site at the search points.
- Optimization and minimization / Pose candidates scoring ($\Delta G_{bind} = \Delta G_{vdw} + \Delta G_{H\text{-}bond} + \Delta G_{deformation} + \Delta G_{hydrophobic} + \Delta G_0$ as described by Wang and coworkers [36]).

Docking simulations are associated to the Ascore scoring function optimized from Xscore [25,36]. This function described above estimates the total protein–ligand binding free energy decomposed into several distinct terms such the contribution of van der interactions between the ligand and the protein, the hydrophobic effect, the hydrogen bonding between the ligand and the protein.

4. Results and discussion

4.1. Database construction and docking simulations

Due to the central role of the protein LC3 in autophagy, the search of ligand for this protein is still necessary for continuing the study of its role in autophagy [20]. The binding of dihydronovobiocin to the protein LC3 resolved by X-ray is a significant advance and a starting point for the search of ligand based on this structure (Fig. 2). Novobiocin is an antibiotic with an amino-coumarin central scaffold substituted with a benzamide and a sugar derivatives.

Dihydronovobiocin binds the LC3 protein through several interactions. Firstly hydrophobic interactions occur between the isopentyl chain of the ligand and the hydrophobic residues of the binding site forming the hydrophobic pocket HP2 Phe56, Ile39, Ile70 Leu67. With respect to the H-bond network, interactions between the carboxamide branched on the coumarine scaffold and the residue Leu57 and the carbonyl of the lactone with the residue Lys34 are obvserved. The terminal carboxamide functional group also develop a H-bond with the residue His31.

A Pubchem library based on the novobiocin substructure with the central aminocoumarin moiety with an amide functional group was drawn constructed using the Pubchem database through the structural search with drawing application tool using the molecular template depicted in Fig. 3. This resulted in a set of 749 compounds.

The 749 compounds with 3D structure available were downloaded in a single SDF file and docking simulations were achieved. Among all compounds, 722 out of the 749 were successfully docked and were ranked according to their docking score with docking energies ranging from – 14.92 to – 5.66 kcal/mol.

4.2. Correlation between docking score and biological activity

The compounds described in the Ewgenij Proschak and co-workers study were found in the database and their docking scores were thus available. These docking scores were plotted against the pIC_{50} values calculated from data (ability to induce the displacement of p62-LIR-sGFP from LC3A) reported in the Ewgenij Proschak study (Fig. 4).

First of all, the docking score were found to be favorable with a negative values ranging from − 14.92 to − 9.44 kcal/mol for all active compounds. Appropriated correlations between docking scores and biological activities were observed. For the compounds 164626676, 164620798, 164616275 and 164611734 displaying good activities, a remarkable docking score was obtained showing the robustness of the docking method. For the compound 1646131107 displaying a modest activity, a modest docking score was also obtained. The docking score of the compound 164609749 was overestimated in comparison with its activity. Overall a good reliability was observed for compounds in this series and suggest a potential prediction of active compounds with a favorable docking score.

Structure-activity relationships indicate that compounds bearing hydrophobic substituents in the meta-position of the benzamide moiety and also branched on the benzene ring of the coumarinyl scaffold are leading to favorable interactions with the two hydrophobic pocket HP1 and HP2.

4.3. Extension to the top20 compounds with best docking scores

Compounds were ranked and the ones in the top 20 among the 749 compounds were examined. For these compounds, docking energy values ranging from – 14.92 to – 12.41 kcal/mol were obtained. Their potential biological activity was searched in the PubChem database and is described in Table 1. Remarkably, five compounds reported to be LC3 binders using FRET experiments [16] (Fig. 3) were in this list showing the pertinence of the docking simulations. Hence, other compounds without any literature data as LC3 ligand but exhibiting high docking scores in this experiment appear as interesting possible LC3 ligand with a good affinity. Most of the compounds in Table 1 namely 139494545, 139494372, 155480556, 155480932, 139494534, 139494431, 139494507, 155480863, 139494582, 155481178 were in the PubChem database as antibiotics against gram negative bacteria, and other ones have been patented for their preparation in organic synthesis.

Among this collection of 20 compounds, the top 10 compounds were further examined with respect to their binding modes (Table 2). The binding modes clearly confirm the importance of the residues Lys34,

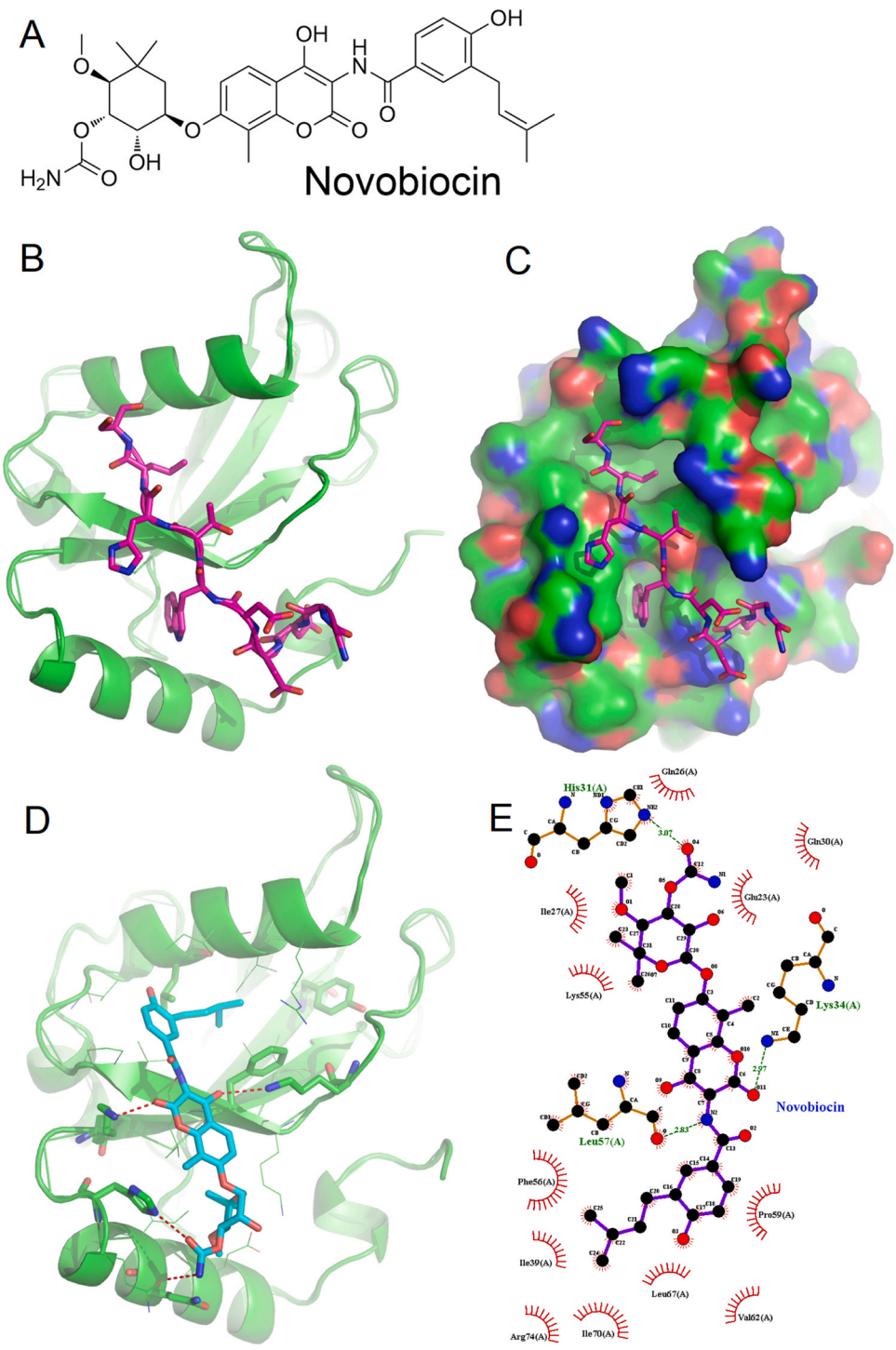


Fig. 2. A Structure of novobiocin; B, C Representation of LC3B in complex with the p62 LIR peptide (PDB code 2ZJD) [37]; D, E Binding mode of dihydronovobiocin [16] to the protein LC3A determined using X-ray (PDB code 6TBE) and hydrogen bonds networks.

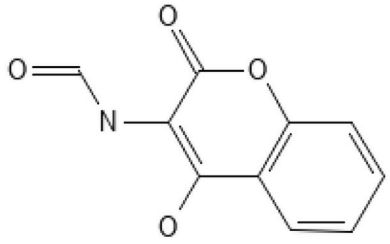


Fig. 3. Molecular template designed from the novobiocin substructure used for the construction of the database (smile C1 =CC=CC2 =C1C(=C(C(=O)O2) NC=O)O).

Leu57 frequently involved in H-bonds with the central 3-amino-4-hydroxycoumarine scaffold and His31 involed in the H-bonds with substituents of this pharmacophore. It is interesting to note that bis-substituted benzamide, compounds 159614606 and 162021392, fit particularly the hydrophobic pocket (HP2) with two arms i.e. the meta-isopentyl and para-benzyloxy substituents. Three sulfonamide derivatives known as LC3 ligands were also retrieved showing the importance of this functional group to provide a substituent able to interact in the corresponding hydrophobic pocket (HP1).

Further superimposition of the 10 complexes was performed to highlight the binding modes and the importance of the residues Lys34, Leu57 and His31 involved in the H-bonds network with the central 3-amino-4-hydroxy-coumarine pharmacophore and also to show the interactions of the ligands in the two hydrophobic pockets (HP1 and HP2) with diversely substituted benzamide (HP2) and also the other coumarinyl substituent especially with a sulfonamide functional group (HP1) (Fig. 5).

5. Conclusions

Taking advantages of the discovery of dihydronovobiocin as LC3A ligand along with the X-ray structure of the protein-ligand complex, a library based on the central scaffold of this antibiotic has been constructed from PubChem. Docking simulations of the 749 compounds with the ArgusDock engine, a robust shape-based method revealed several potential ligands in addition to ones already know. Examination of the different binding modes confirms the importance of the central coumarine scaffold and the residues involved in the H-bonds network and also the two hydrophobic part of the compounds interacting with the residues located in the two hydrophobic pockets HP1 (coumarinyl substituents especially with a sulfonamide functional group substituted with an hydrophobic substituent) and HP2 (benzamide substituents). The simulations also enable a good prediction of know ligands

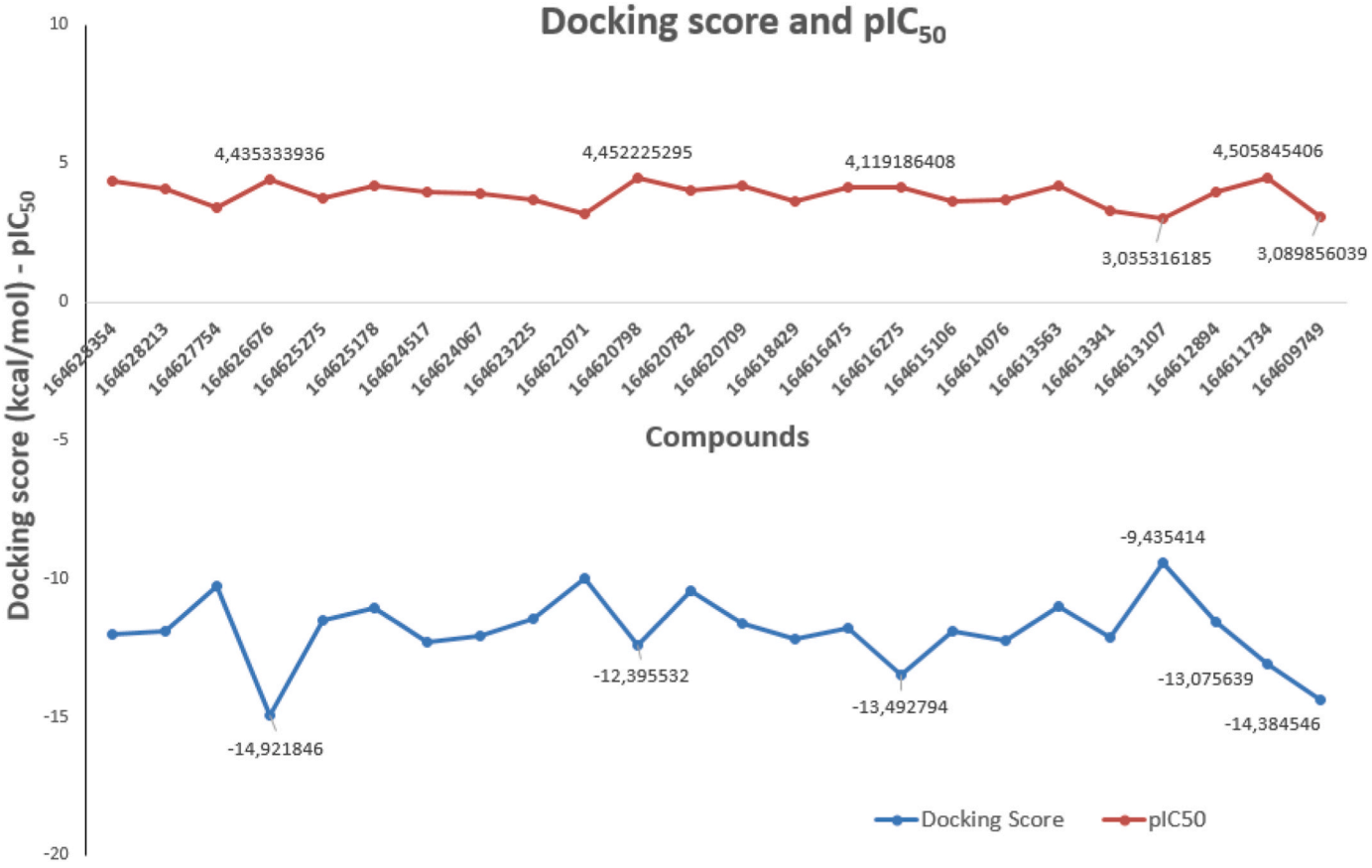


Fig. 4. Docking score and pIC_{50} for compounds able to induce the displacement of p62-LIR-sGFP from LC3A [16].

Table 1
Docking score and available data in the PubChem database for compounds in the top 20.

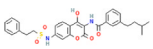
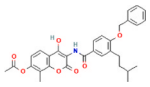
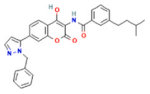
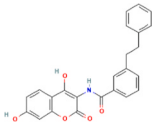
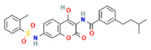
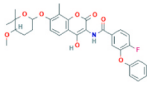
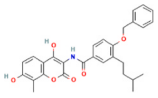
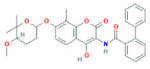
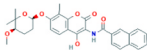
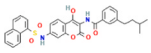
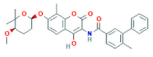
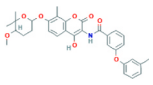
CID numbers	Docking score (kcal/mol) H-bonds donors/acceptors	PubChem Biological activity / patents
164626676 	-14.92 3/7	Displacement of sGFP-p62-LIR peptide from human N-terminal SNAP-fused LC3B by time-resolved FRET assay (Ki = 7.5 μM)
159614606 	-14.75 2/7	3-acylamino-7-glycosyloxycoumarins and their preparation
164609749 	-14.38 2/5	Displacement of sGFP-p62-LIR peptide from human N-terminal SNAP-fused LC3A by time-resolved FRET assay (Ki = 166.5 μM)
164618308 	-13.71 3/5	Displacement of sGFP-p62-LIR peptide from human N-terminal SNAP-fused LC3B by time-resolved FRET assay (Ki = 67 μM)
164616275 	-13.49 3/7	Displacement of sGFP-p62-LIR peptide from human N-terminal SNAP-fused LC3B by time-resolved FRET assay (Ki = 10.9 μM)
139494545 	-13.22 2/9	Aminocoumarin compounds and methods of their use in the treatment of a Gram- negative bacterial infection.
162021392 	-13.21 3/6	3-acylamino-7-glycosyloxycoumarins and their preparation
139494372 	-13.13 2/7	Aminocoumarin compounds and methods of their use in the treatment of a Gram- negative bacterial infection.
155480556 	-13.09 2/7	Aminocoumarin compounds and methods of their use in the treatment of a Gram- negative bacterial infection.
164611734 	-13.08 3/7	Displacement of sGFP-p62-LIR peptide from human N-terminal SNAP-fused LC3B by time-resolved FRET assay (Ki = 4.2 μM)
155480932 	-12.87 2/7	Aminocoumarin compounds and methods of their use in the treatment of a Gram- negative bacterial infection.
139494534 	-12.78 2/8	Aminocoumarin compounds and methods of their use in the treatment of a Gram- negative bacterial infection.

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Table 1 (*continued*)

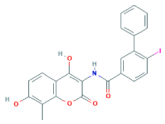
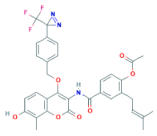
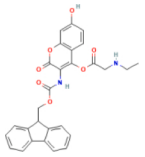
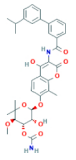
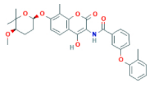
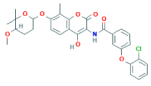
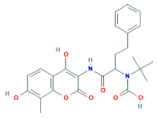
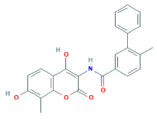
CID numbers	Docking score (kcal/mol) H-bonds donors/acceptors	PubChem Biological activity / patents
139494431 	-12.75 3/5	Aminocoumarin compounds and methods of their use in the treatment of a Gram- negative bacterial infection.
132849532 	-12.74 2/12	None
87195253 	-12.65 3/8	High-sensitive fluorescent energy transfer assay using fluorescent amino acids and fluorescent proteins
139494507 	-12.62 4/10	Aminocoumarin compounds and methods of their use in the treatment of a Gram- negative bacterial infection.
155480863 	-12.54 2/8	Aminocoumarin compounds and methods of their use in the treatment of a Gram- negative bacterial infection.
139494582 	-12.53 2/8	Aminocoumarin compounds and methods of their use in the treatment of a Gram- negative bacterial infection.
129275093 	-12.44 4/7	Autophagy inhibitors
155481178 	-12.41 3/5	Aminocoumarin compounds and methods of their use in the treatment of a Gram- negative bacterial infection.

Table 2
Binding of compounds in the top 10 and 2D representation with the H-bonds networks.

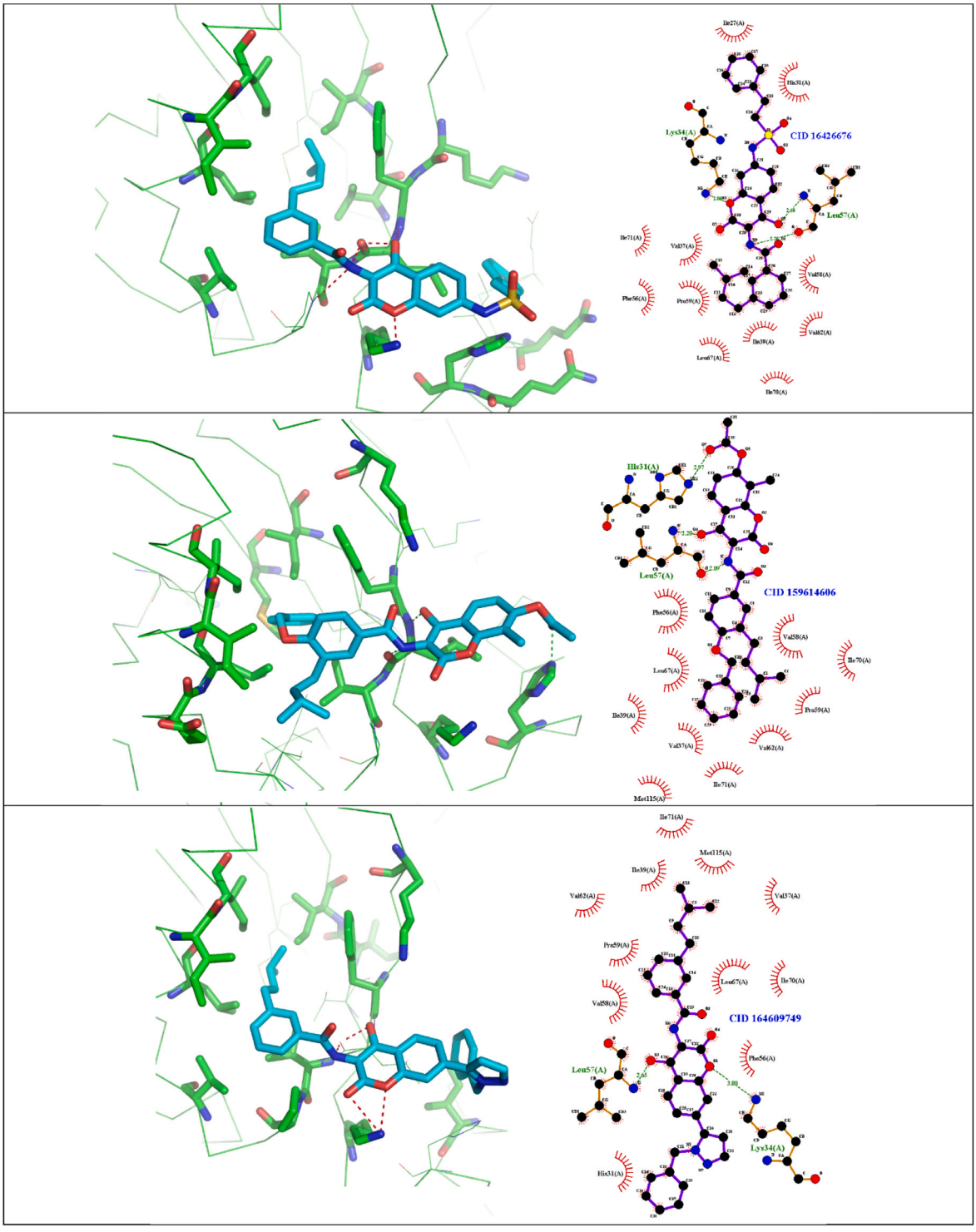


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Table 2 (*continued*)

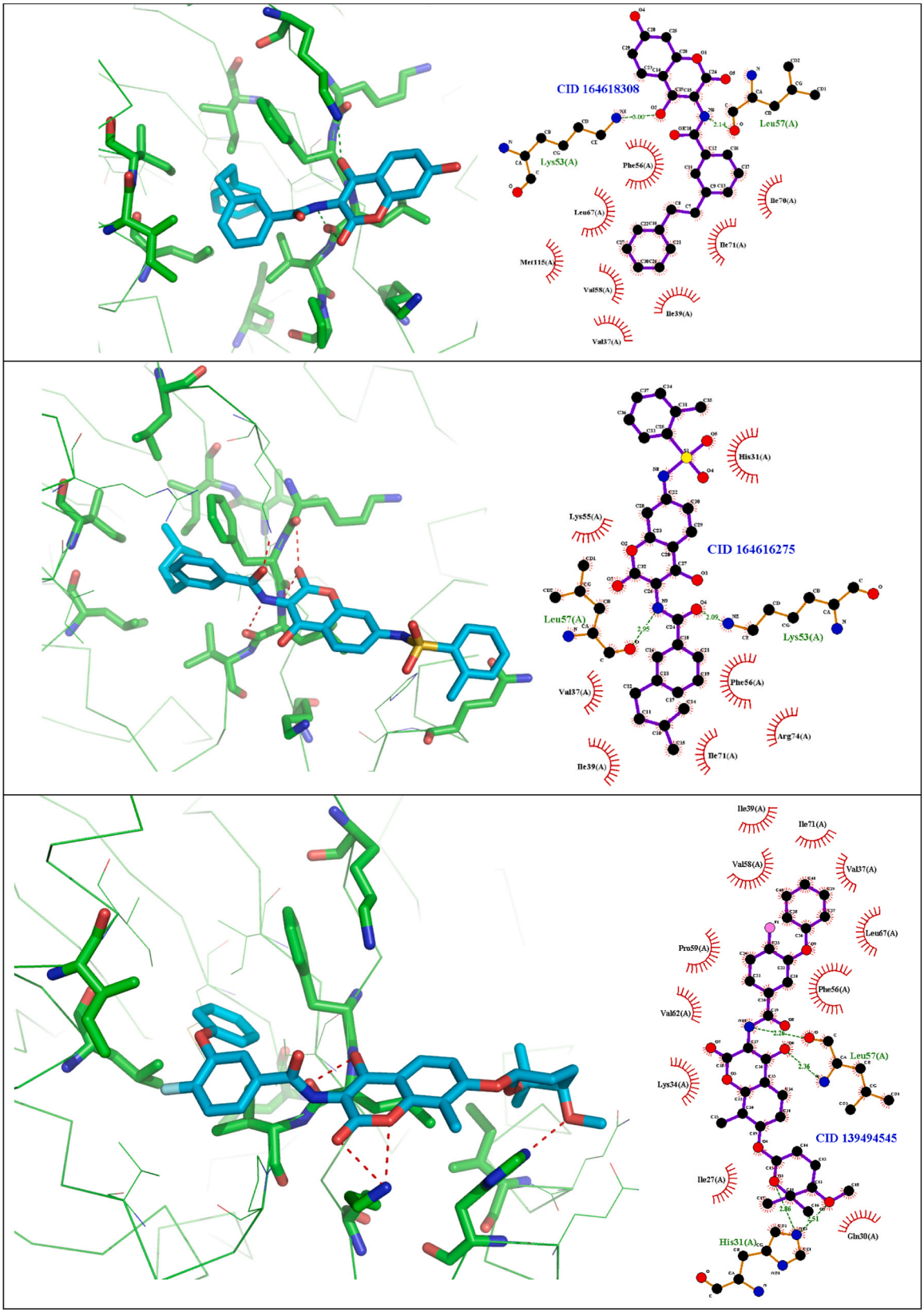

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Table 2 (*continued*)

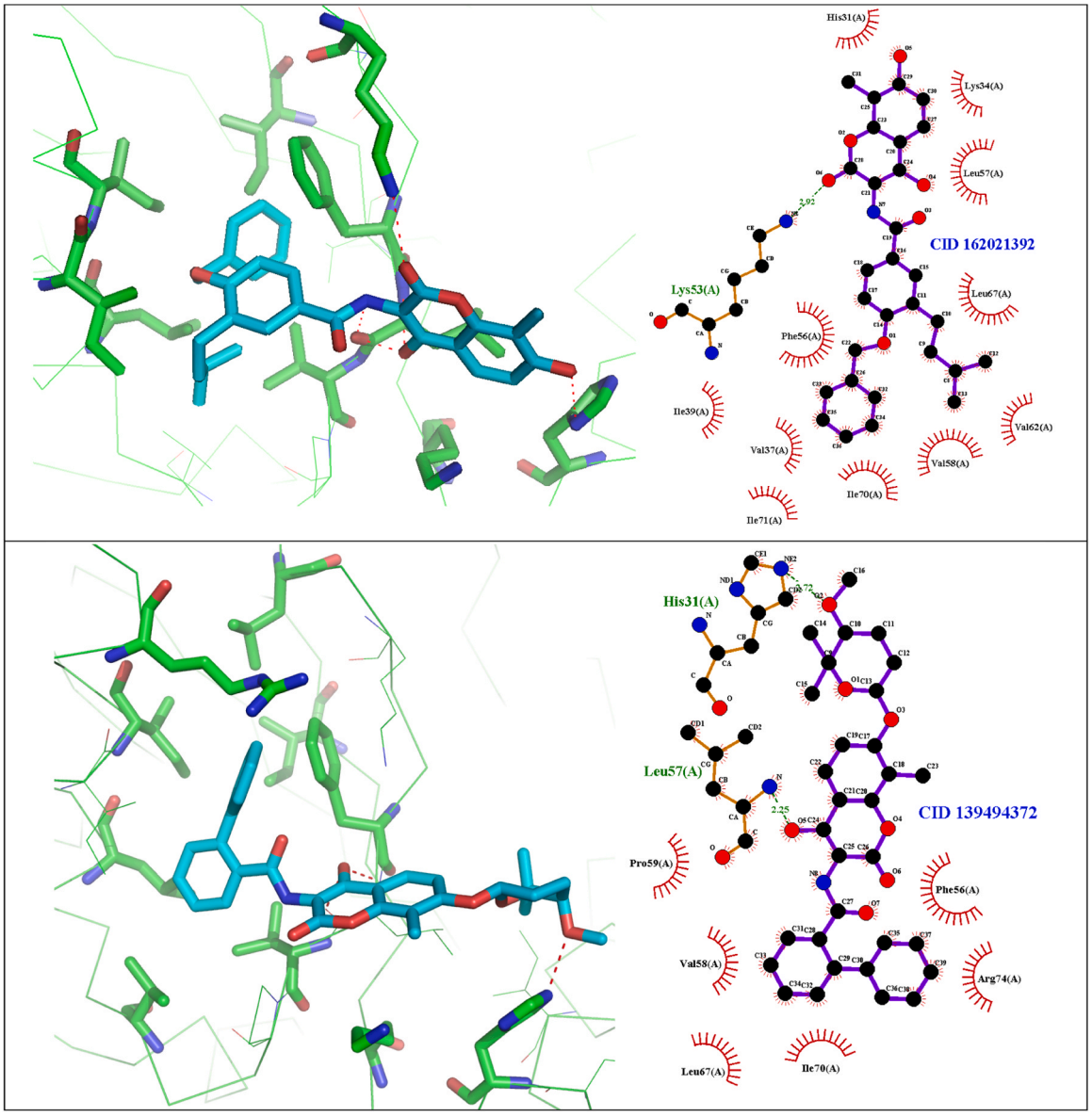

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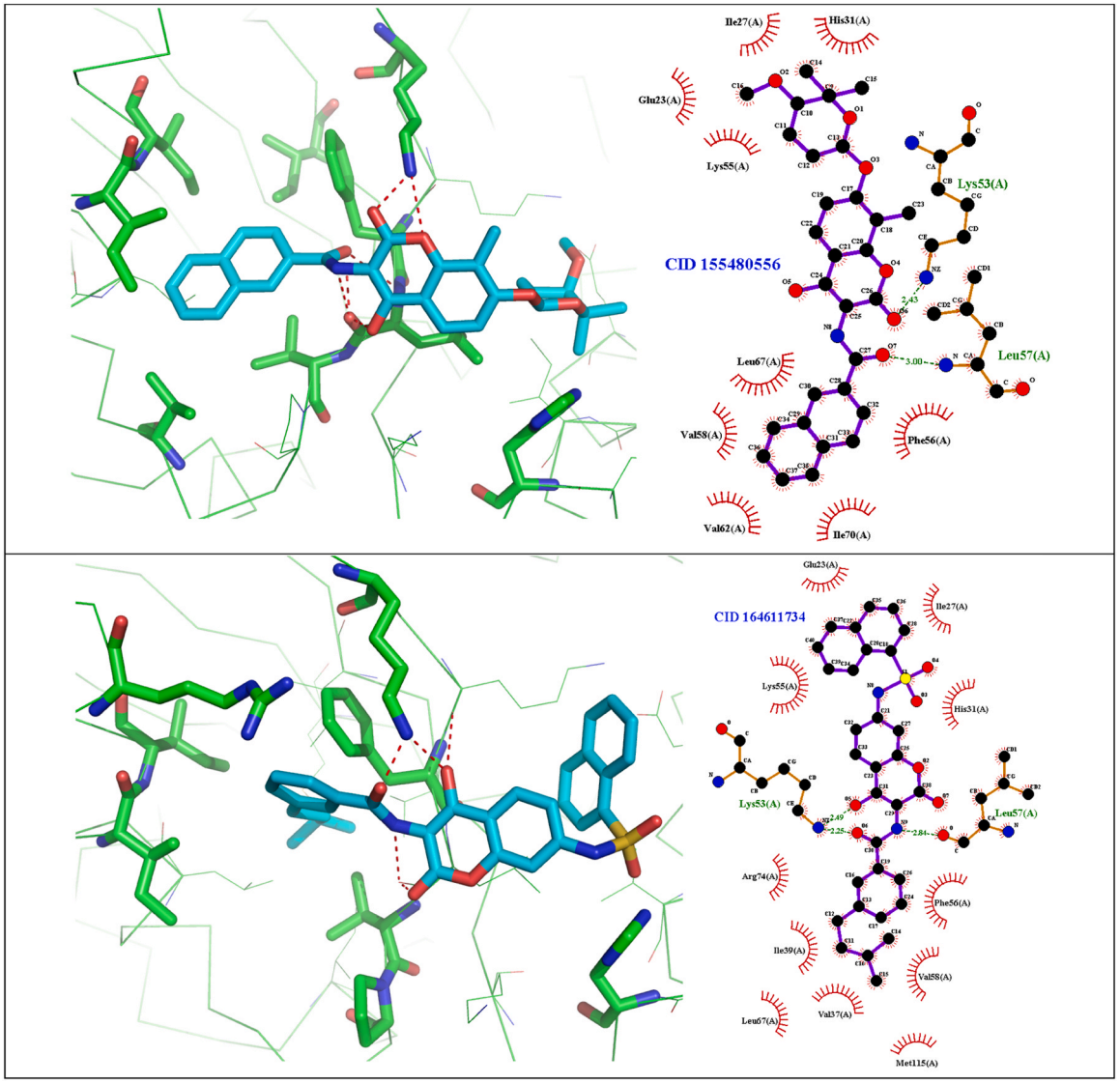
Table 2 (*continued*)



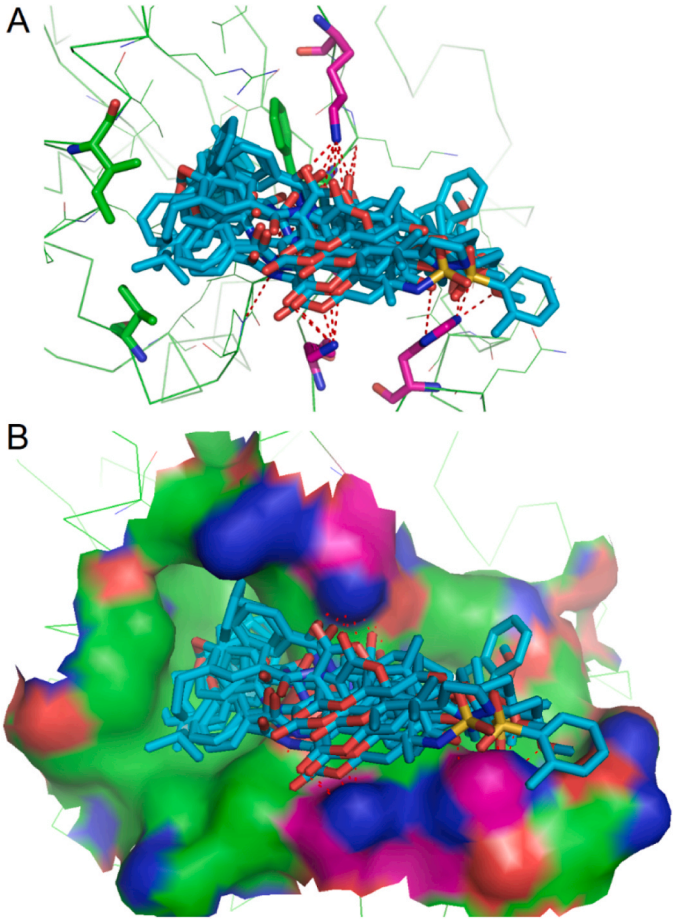


Fig. 5. Superimposition of the binding modes for the compounds (cyan) in top 10 within the binding site without surface (**A**) or with protein surface (**B**). Important residues involved in H-bonds are colored in magenta.

demonstrating the robustness of the docking method based on a robust and exhaustive search algorithm. This machine learning protocol can further be applied to the identification of LC3 ligands with original structure. This aspect is currently under investigation using larger compounds databases with structural diversity for the discovery of potential autophagy modulators.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.aichem.2023.100022.

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