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Research Article

Potential Inhibition of Human Neutrophil Elastase Enzyme to Attenuate Emphysema; A Molecular Docking Study

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Abstract

Chronic Obstructive Pulmonary Disease (COPD), also referred to as chronic bronchitis and emphysema, is a major threat to global health. It is an essential part of the Rehabilitation 2030 initiative of the World Health Organization (WHO). It is more common in nations with enhanced smoking habits. The latter is associated with the damage of the elastin protein of the lung parenchyma as a result of the enhanced protease activity of human neutrophil elastase (HNE). This leads to impaired gaseous exchange and air entrapment in the lungs. Among symptomatic pharmacotherapy, anti-proteases such as alpha-1 antitrypsin could be used to counter the effect of proteases, but the treatment costs too much and is not easily available. This study aims to explore and discover potential drug compounds for lessening the progression of protease-induced lung parenchymal damage in emphysema. Molecular docking and ADMET analysis investigated the anti-HNE activity of several compounds and newly designed analogs of Sivelestat, a drug molecule that has been approved as Sivelestat Sodium Hydrate in Japan as well as in the Republic of Korea for the management of acute lung injury. The software used in this study were PyRx, BIOVIA Discovery Studio Visualizer v17.2.0.16349, and DataWarrior V5.5.0. All the potential drug molecules demonstrated binding with the active residues of HNE, i.e., Ser 195, His 57, and Ser 214, and showed potentially promising results in terms of their binding energies and poses. Subsequent *in vitro* and *in vivo* studies are recommended to support the findings of this study.

Keywords: Human Neutrophil Elastase (HNE); Emphysema; alpha-1 antitrypsin; anti-protease; Sivelestat; molecular docking.

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is one of the most devastating ailments of the respiratory system affecting millions of lives worldwide (Sullivan et al. 2018). It progresses gradually leading to progressive parenchymal damage to the lungs. Homeostatic disturbances and impaired repair may cause alveolar damage, leading to emphysema. The literature reveals that the subsequent stimuli, especially smoking, impair the maintenance of the lung parenchyma and alveolar tissue, which leads to low lung compliance by limiting the expiratory flow, preceded by inflammation (Nevzorova, Brodskaya, and Gilifanov 2019). Cigarette smoke causes oxidative stress, leading to the generation of pro-inflammatory immune responses (Caliri, Tommasi, and Besaratinia 2021). One of the main etiologies is the imbalance between proteases and anti-proteases. The enhanced protease activity in the lungs may lead to injury to the respiratory membrane in the alveoli. Alpha-1 antitrypsin is an anti-protease whose hereditary deficiency may give rise to emphysema (Cazzola et al. 2020). Some studies have revealed that inhibition of proteases such as elastases, matrix

metalloproteinases (MMPs), cathepsins, etc. reduced the risk of developing emphysema (Sasank 2019, Subbarao 2018). Macrophage and neutrophil infiltration in alveolar sacs as a response to the chemotaxis and proinflammatory cascades leads to the necrosis of the alveolar elastic tissue through the release of elastases, among which the most common is human neutrophil elastase (HNE) (Janssen et al. 2019).

Different elastases cleave elastin, a structural protein in the human body present in the vascular system, lungs, integumentary, and other body systems (Le Page et al. 2019). HNE (molecular weight approximately 33 kDa), also termed human leukocyte elastase, has several physiological roles, such as the breakdown of foreign entities and gram-negative bacteria when phagocytized by neutrophils. It also shows activity against pathogenic bacterial proteins such as flagellin by cleaving them and preventing their pro-inflammatory response in the host body. It is inhibited by some endogenous anti-proteases that deform the active sites of elastases (Jakimiuk et al. 2021). The disturbed balance between both leads to pathological scenarios, such as emphysema.

The inhibition of HNE is an avenue of research for finding out molecules that may act as potential inhibitors for this enzyme that may prevent the tissue damage caused in the alveolar membrane, thus preventing ailments such as emphysema. Many phytochemicals, such as polyphenols and flavonoids, potentially cause inhibition of elastases (Jakimiuk, Gesek, and Atanasov 2021). Further research is also underway for the exploration of synthetic compounds as potential inhibitors of elastases, as augmentation therapy with anti-proteases such as Alpha-1 antitrypsin that is quite costly and less accessible for emphysema patients. In order to cope with this research gap, the aim of this study is to discover the drug molecules having potential inhibitory activity for HNE, using the molecular docking and *in silico* absorption, distribution, metabolism, elimination, and toxicity profile (ADMET) analysis of the compounds retrieved from literature as well as their designed potential analogs. The findings of our study may assist drug discovery scientists and molecular pharmacologists to test and devise new therapies for emphysema. The mechanism of pathogenesis of emphysema is provided in **Figure 1**.

2. Materials and Methods

2.1. Macromolecule (Protein) Preparation

The three-dimensional structure of HNE (PDB ID: 1HNE) was acquired from the RCSB Protein Data Bank (PDB) database in PDB format (Nayak and Sundararajan 2023). The retrieved PDB structure was characterized using the X-ray diffraction method with a resolution of 1.84 Å as mentioned in the RCSB PDB database. The protein preparation was done by removing unnecessary molecules such as ligands, heteroatoms, water molecules, etc. using the BIOVIA Discovery Studio Visualizer v17.2.0.16349. This step is performed to prevent any distortion or interference in protein and ligand interactions during virtual analysis (de la Vega de Leon 2015).

2.2. Ligand Retrieval and Preparation

The literature was searched, and several ligands were revealed to be potential candidates for having inhibitory activity for human elastases. Sivelestat (**Ligand 01),** is well known for its therapeutic utility in case of acute lung injury (Lucas et al. 2013, Zhang et al. 2023). Some other compounds studied for their affinity for human elastases were Nigranoic Acid (**Ligand 02)** (Huang et al. 2015), Midesteine (Ligand 03) (Lucas et al. 2013), Cholesterol Sulfate (Ligand 04) (Le et al. 2022), Cephalothin (Ligand 05) (Fayad, Morin, and Nehmé 2017), Chondroitin 4'

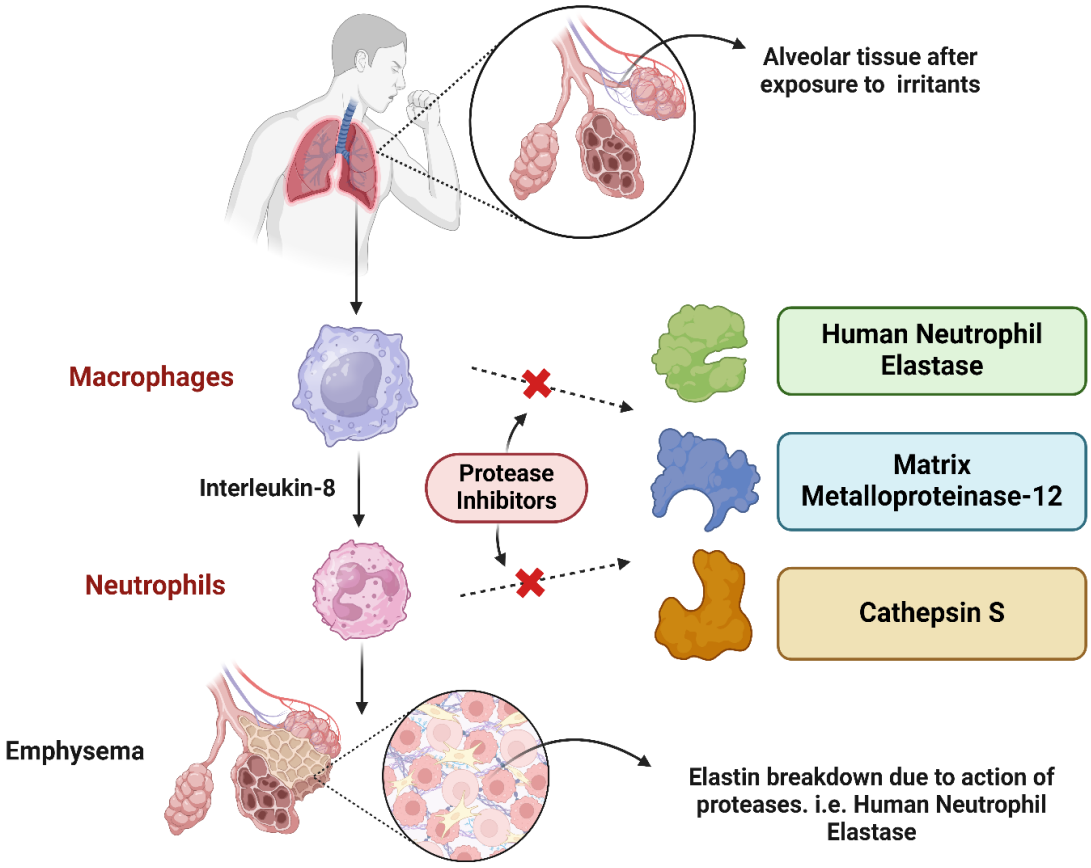


Figure 1: Mechanism of the pathogenesis of emphysema and subsequent destruction of elastin tissue of lung parenchyma

Sulfate (Ligand 06) (Teshigahara et al. 2020b), 2,3-dihydro-6-[3-(2-hydroxymethyl)-phenyl-2-propenyl]5-benzofuranol (Ligand 07) (Pacholok et al. 1995, Zhang 2020) and 1,2,5-thiadiazolidin-3-one 1,1-dioxide (Ligand 08) (Huang et al. 2008). The IUPAC names of these ligands were retrieved from the PubChem database. PerkinElmer ChemDraw Professional 16.0 and Chem3D 16.0 software were utilized to draw and convert the structure of ligands into PDB format, respectively. The same steps were also performed to design four analogs of the particular ligand with the best binding energies rendered by molecular docking. As HNE is a serine protease; hence, it is assumed that the serine residues, along with a few other amino acid residues, may be a valuable target for the inhibition of HNE. The details of the ligands are provided in **Table 1**, while the chemical structures of these ligands are shown in **Figure 2**.

2.3. Molecular Docking

Molecular docking is the computational technique employed in order to find the most suitable drug candidate for a potential drug target based on the best pose (Rahman et al. 2021, Vidal-Limon, Aguilar-Toala, and Liceaga 2022). For the purpose of probing the best drug candidates in our study, the PyRx Virtual Screening Tool was used for molecular docking analysis, which works on the configuration of

Table 1: Details of the ligands studied for their potential inhibition of HNE in this study

Sr. No.	Ligands	Pubchem ID	Chemical Formula	Source
01.	Sivelestat	107706	$C_{20}H_{22}N_2O_7S$	PubChem
02	Nigranoic acid	10814237	$C_{30}H_{46}O_4$	PubChem
03	Midesteine	65837	$C_{12}H_{13}NO_3S_3$	PubChem
04	Cholesterol Sulfate	65076	$C_{27}H_{46}O_4S$	PubChem
05	Cephalothin	6024	$C_{16}H_{16}N_2O_6S_2$	PubChem
06	Chondroitin 4' Sulfate	70678574	$C_{14}H_{21}NO_{15}S^{-2}$	PubChem
07	2,3-dihydro-6-[3-(2-hydroxymethyl)-phenyl-2-propenyl]5-benzofuranol	6438824	$C_{18}H_{18}O_3$	PubChem
08	1,2,5-thiadiazolidin-3-one 1,1-dioxide	372649	$C_2H_4N_2O_3S$	PubChem

the Auto Dock Vina molecular docking tool (Jain et al. 2022, Dey et al. 2022).

BIOVIA Discovery Studio Visualizer v17.2.0.16349 was employed to visualize the protein-ligand interactions including the 2D and 3D interactions, hydrogen bonds, hydrophobicity, bond lengths, and other parameters (Jejurikar and Rohane 2021). The ligands being employed in this study were selected on the basis of previously reported potential inhibitory activities against elastases. The protein macromolecule and ligand files were loaded on PyRx in PDB format. In PyRx, the grid dimensions for HNE were set as 46.38, 41.85, and 38.56 Angstrom for X, Y, and Z axes respectively, after maximizing the grid. Molecular docking (blind) was performed for the ligands (Ligand 01 – Ligand 08), while four analogs were also designed and subsequently subjected to the same *in silico* analysis. After the molecular docking, the scoring was performed based on their binding energies.

2.4. *In silico* ADMET Analysis

Absorption, distribution, metabolism, elimination, and toxicity (ADMET) analysis is necessary for the pharmacokinetic and toxicity profile prediction of any compound. SwissADME, an authentic online tool used for the purpose of pharmacokinetic profiling of potential drug molecules, was utilized for the absorption, distribution, metabolism, and elimination (ADME) analysis of the potential drug candidates in our study (Daina, Michielin, and Zoete 2017). Whereas DataWarrior V5.5.0 was used for the toxicity profiling (Sander et al. 2015). These predictions are necessary to make as they may assist in the drug discovery and development process along with the drug formulation in a wet laboratory.

3. Results

The ligands subjected to this molecular docking analysis demonstrated notable binding energies as well as bond lengths. The promising interactions of the ligands with the HNE active site are indicated in Table 2.

3.1. Molecular Docking Findings for Ligand 01-Ligand 08

Most of the ligands showed affinities for Serine 195, Serine 214, and Histidine 57 residues of the active site of HNE. The best binding energies were displayed by Sivelestat (**Ligand 01**). In ascending order, the binding energies of -7.7, -6.6, -6.5, -6.3, -5.2, -5.0, -4.5, and -4.2 kcal/mol were expressed by Sivelestat (Ligand 01), Nigranoic Acid (**Ligand 02),** 2,3-dihydro-6-[3-(2-hydroxymethyl)-phenyl-2-propenyl], 5-benzofuranol (**Ligand 07**), chondroitin 4' sulfate (**Ligand 06**), Midesteine (**Ligand 03**), Cephalothin (**Ligand 05**), Cholesterol Sulphate (**Ligand 04),** and 1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Ligand 08),** respectively.

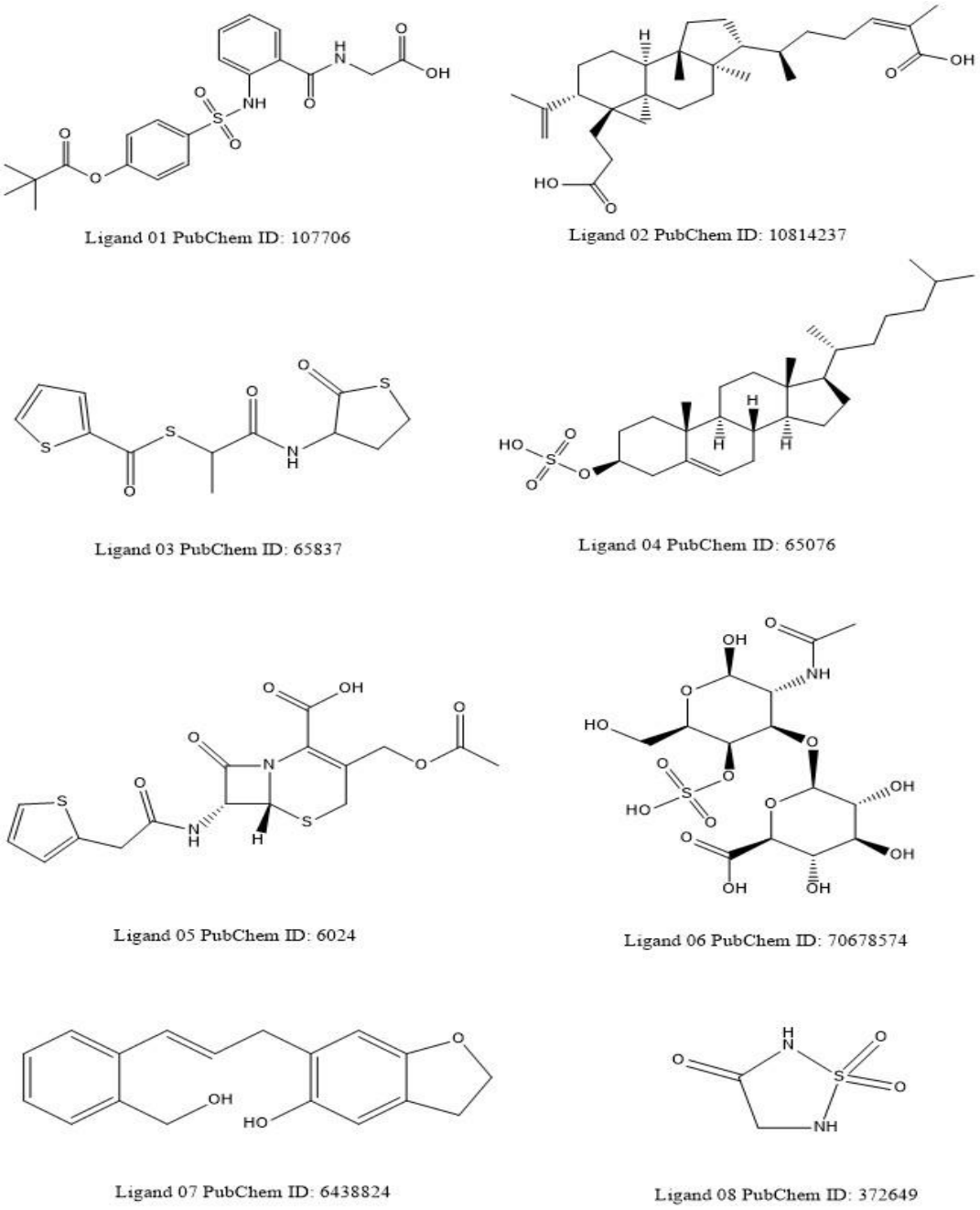


Figure 2: 2D representation of the chemical structures of the potential drug candidates (Ligands 01-08)

Ligand **01** showed a really promising binding affinity with the active site residues of HNE, i.e., Ser 195 and His 57. Ligand **02** exhibited an encouraging binding affinity with His 57 and Phe 192 amino acid residues of the catalytic site of HNE. Ligand **03** also manifested potentially strong interactions towards the active site residues Ser 195, His 57, and Phe 192. **Ligand 04** showed binding interactions with Ser 195 and His 57 with a hydrogen bond and an alkyl bond, respectively. **Ligand 05** and **Ligand 06** also exhibited interactions with protein active site

Table 2: Interpretation of molecular docking study done for Ligand 01- Ligand 08 and their interactions with HNE residues

Ligand Protein Interaction	Binding energy (kcal/mol)	Bonding Residues	Type of bond	Bond Length (Å)	No. of H bonds	Other Residues
Ligand 01	-7.7	Ser 195	H bond	2.16, 2.68	4	Gly 193, Val 216
		His 57	Pi bond	4.84		
Ligand 02	-6.6	His 57	H bond, Alkyl	2.88, 3.91	2	Asn 61, Leu 99B
		Phe 192	Alkyl	4.85,5.08, 5.40		
Ligand 03	-5.2	Ser 195	H bond	2.74	1	----------
		His 57	Pi- Pi	4.82		
		Phe 192	Pi	3.73		
Ligand 04	-4.5	Ser 195	H bond	2.74	1	Phe 192, Leu 143
		His 57	Alkyl	2.22		
Ligand 05	-5.0	Ser 195	H bond	2.94	1	Phe 41, Ile 151
		Phe 192	Alkyl	5.08		
Ligand 06	-6.3	Ser 195	H bond	2.70, 2.56, 3.04	5	----------
		Ser 214	H bond	2.33, 3.66		
		His 57	H bond, Alkyl	2.64, 3.66		
Ligand 07	-6.5	Ser 195	H bond	2.93	2	Val 62, Phe 41, Cys 42, Cys 58
		Ser 214	H bond	2.11		
		Phe 192	Pi-Pi	4.98		
Ligand 08	-4.2	Ser 195	H bond	2.80, 3.05	4	Cys 191, Phe 192
		Ser 214	H bond	3.12		
		His 57	Pi-Sigma	3.79		

residues Ser 195, His 57, Ser 214, and Phe 192 with considerable binding energies. Ligand **07** rendered interactions with Ser 195, Ser 214, and Phe 192, while **Ligand 08** formed a complex with catalytic serine residues, Ser 195 and Ser 214 with reasonable bond lengths. The two- and three-dimensional interactions are illustrated in **figure 3**.

3.1.1. Designed Analogues of Sivelestat (Ligand 01)

Sivelestat (**Ligand 01**) expressed the best binding affinity with the active site residues of HNE in this study. Hence, about four potential analogues of Sivelestat were designed using Perkin Elmer ChemDraw Professional 16.0, and their IUPAC names were retrieved using the same tool. The molecular docking analysis was conducted for these analogues to determine their tendency to become potential lead compounds. The list includes 4-(N-(2-((2-amino-2-oxoethyl)carbamoyl)phenyl)sulfamoyl)phenyl pivalate (**Analogue 01**), 4-(N-(2-((2-oxo-2-(tetrahydrothiophen-2-yl)ethyl)carbamoyl)phenyl)sulfamoyl)phenyl pivalate (**Analogue 02**), 4-(N-(2-((2-oxo-2-(thiazolidin-5-yl)ethyl)carbamoyl)phenyl)sulfamoyl)phenyl pivalate (**Analogue 03),** and 4-(N-(2-((2-oxo-2-(pyrrolidin-2-yl)ethyl)carbamoyl)phenyl)sulfamoylphenyl pivalate (**Analogue 04**). Some functional group modifications were done on position 01 in the Sivelestat (**Ligand 01**) molecule to design these analogues, as shown in **table 3,** and the chemical structures of the designed analogues are displayed in **figure 4**.

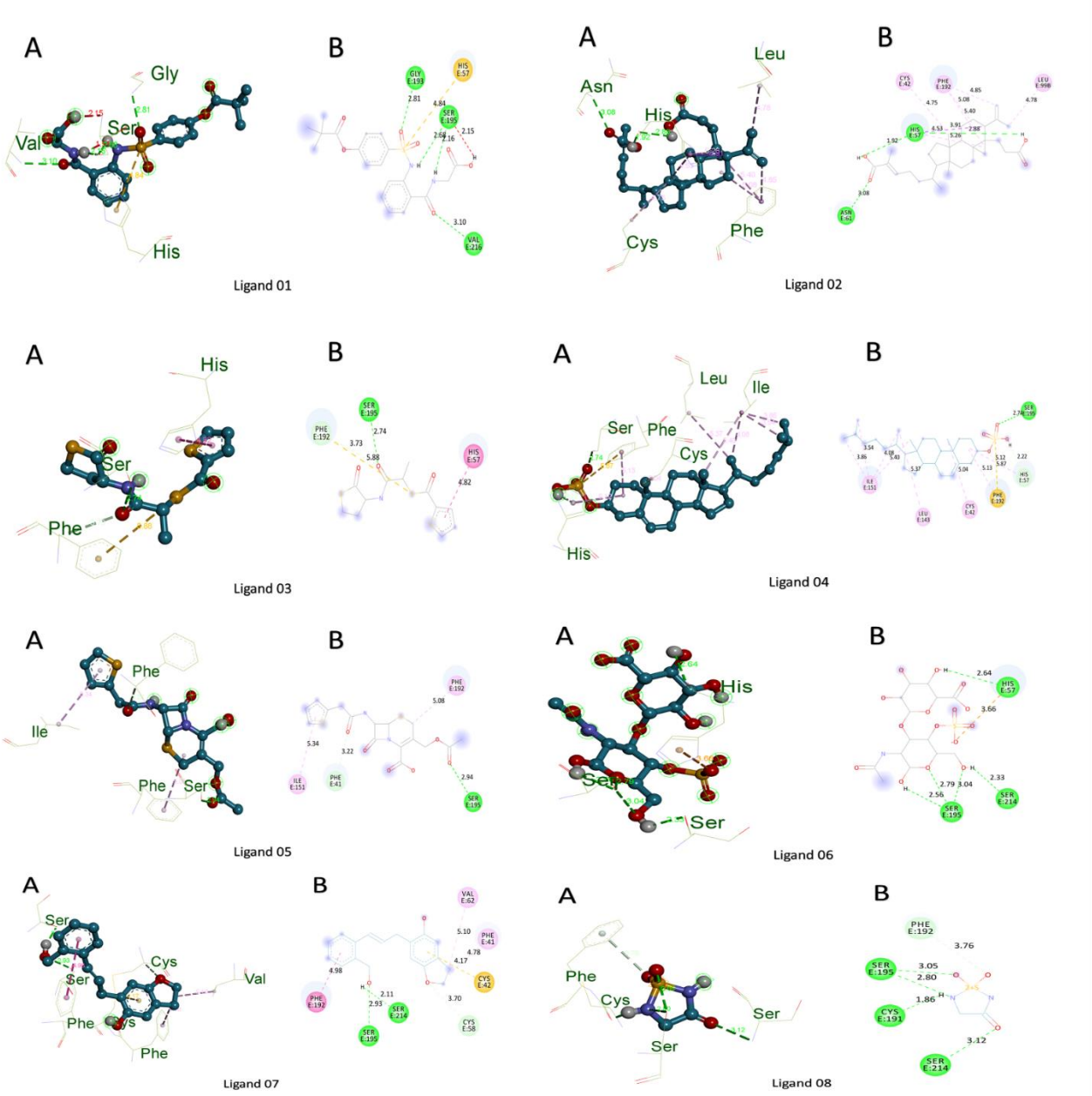


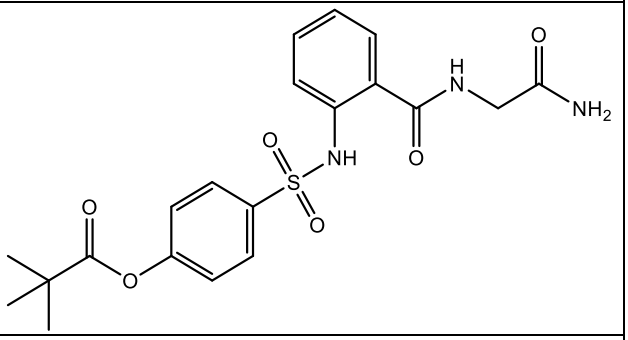
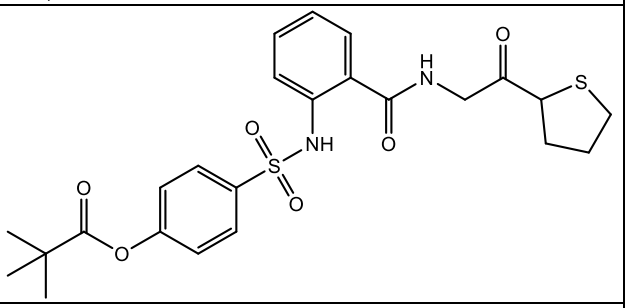
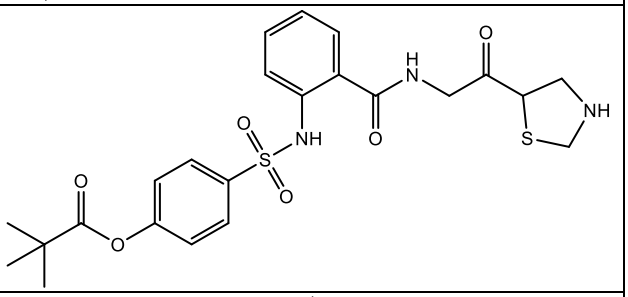
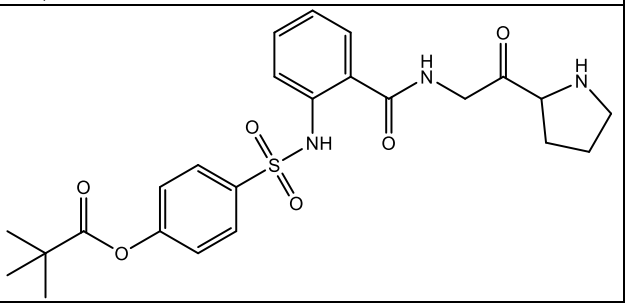
Figure 3: (A) 3D and (B) 2D docking poses showing interactions of ligands (01-08) with the binding sites of HNE protein

3.1.2. Molecular Docking Analysis for Sivelestat Analogues

The molecular docking and scoring analysis for the analogs (Analogue 01- Analogue 04) were performed using the same methodology and tools as executed for Ligand **01- Ligand 08** in this study. These analogs rendered encouraging binding energies with the target protein, HNE (PDB ID: 1HNE), as shown in **Table 4**.

Analogue **01**, Analogue **02,** Analogue **03,** and Analogue **04** have provided potentially

Table 3: Details of the designed analogs of Ligand 01 Sivelestat (Analogues 01- 04) in this study

Sr. No.	Derivatization	Analogues (IUPAC Name)	Molecular Formula	Structure
Analogue 01	Amine Derivative	4-(N-(2-((2-amino-2-oxoethyl)carbamoyl)phenyl)sulfamoyl)phenyl pivalate	$C_{20}H_{23}N_3O_6S$	
Analogue 02	Tetrahydrothiophene Derivative	4-(N-(2-((2-oxo-2-(tetrahydrothiophen-2-yl)ethyl)carbamoyl)phenyl)sulfamoyl)phenyl pivalate	$C_{24}H_{28}N_2O_6S_2$	
Analogue 03	Thiazolidine Derivative	4-(N-(2-((2-oxo-2-(thiazolidin-5-yl)ethyl)carbamoyl)phenyl)sulfamoyl)phenyl pivalate	$C_{23}H_{27}N_3O_6S_2$	
Analogue 04	Pyrrolidine Derivative	4-(N-(2-((2-oxo-2-(pyrrolidin-2-yl)ethyl)carbamoyl)phenyl)sulfamoyl)phenyl pivalate	$C_{24}H_{29}N_3O_6S$	

auspicious binding energies and poses with the active residues of HNE, i.e., -6.8, -7.0, -7.1, and -6.4 kcal/mol, respectively. 4-(N-(2-((2-amino-2-oxoethyl)carbamoyl)phenyl)sulfamoyl)phenyl pivalate (Analogue **01)** showed potentially strong affinity for Ser 195, Ser 214, and His 57 active residues of HNE, while 4-(N-(2-((2-oxo-2-(tetrahydrothiophen-2 yl)ethyl)carbamoyl)phenyl)sulfamoyl)phenyl pivalate (Analogue **02**) indicated notably favorable binding energies and complexed with Gly 193, Phe 41, and Phe 192 residues. 4-(N-(2-((2-oxo-2-(thiazolidin-5-yl)ethyl)carbamoyl)phenyl)sulfamoyl)phenyl pivalate (Analogue **03**) demonstrated interactions with serine residues of the HNE

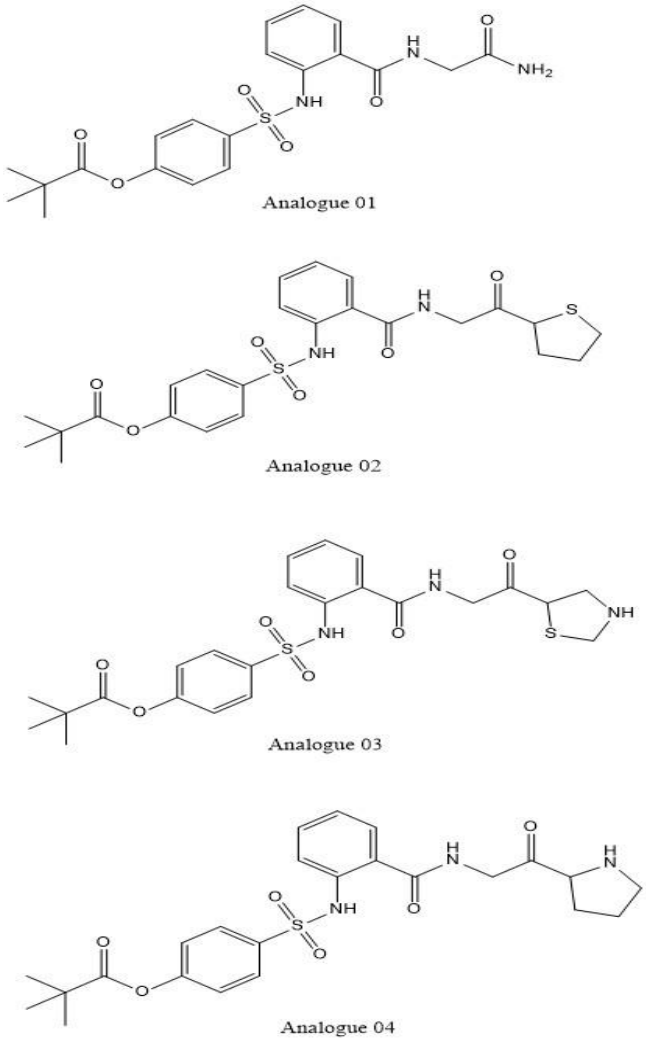


Figure 4: Chemical structures of analog 01- 04, Sivelestat (Ligand 01) analogs.

active site, i.e., Ser 195 and Phe 192, and 4-(N-(2-((2-oxo-2-(pyrrolidin-2-yl)ethyl)carbamoyl)phenyl)sulfamoyl)phenyl pivalate (Analogue **04**) manifested its affinity for the active residues, i.e., Ser 195 and His 57 residues, with shorter bond lengths. The interactions of these analogs with HNE protein are exhibited in **Figure 5**.

3.2. In *silico* ADMET Profiling

The drug candidates in this study were subjected to ADMET analysis. The **Ligand 01**, **Ligand 02**, **Ligand 03**, **Ligand 04**, **Ligand 05**, **Ligand 06**, **Ligand 07**, **Ligand 08**, Analogue **01,** Analogue **02,** Analogue **03,** and Analogue **04** had molecular weights equal to 434.46, 470.68, 315.43, 466.72, 396.44, 477.40, 282.33, 136.13, 433.48, 504.62, 505.61, and 487.57 grams per mole (g/mol), respectively. **Ligand 02 and Ligand 04 provided the** highest bioavailability score of about 0.85. **Ligand 01** attained a bioavailability score of 0.56, while **Ligand 03, Ligand 07, Ligand 08,** Analogue **01,** Analogue **02,** Analogue

Table 4: Tabular presentation of molecular docking parameters and interactions of Analogue 01-Analogue 02 with HNE

Ligand Protein Interaction	Binding energy (kcal/mol)	Bonding Residues	Type of bond	Bond Length (Å)	No. of H bonds	Other Residues
Analogue 01	-6.8	Ser 195	H bond	2.53, 3.04	4	Phe 192, Cys 42
		Ser214	H bond	2.85		
		His 57	Pi-Pi	3.6		
Analogue 02	-7.0	Gly 193	H bond	3.19	2	Cys 58
		Phe 41	H bond	2.78		
		Phe 192	Pi-Pi	5.0		
Analogue 03	-7.1	Ser 195	H bond	3.19	2	Phe 41
		Phe 192	Pi-Pi	5.0		
Analogue 04	-6.4	Ser 195	H bond	2.96	1	Phe 41
		His 57	Pi-Sigma	3.79		

03, and Analogue **04** demonstrated the same bioavailability score of 0.55. **Ligand 06** showed two, while **Ligand 2**, **Ligand 4,** Analogue **01,** and Analogue **02** manifested a single violation of Lipinski's rule, while all other drug candidates displayed no violations. The toxicity profiling reflected that all the drug candidates had no tumorigenic, mutagenic, irritant, or reproductive effects, except **Ligand 07,** which showed low reproductive effects. The conduction of further studies is recommended to explore and maneuver its structure-activity relationship to eradicate these features. The drug-likeness score for all potential drug candidates was predicted using OSIRIS Property Explorer, a widely used *in silico* tool (Buryi et al. 2019). The complete pharmacokinetic and toxicity profiling for all the potential drug candidates analyzed in this study is provided in Table **5**. The bioavailability radars of the **Ligands 01– 08 and Analogues 01–04,** acquired from SwissADME are exhibited in **figures 6** and **7**, respectively.

4. Discussion

Chronic Obstructive Pulmonary Disease (COPD) is a challenge for physicians and clinicians all over the world due to its high mortality rate (López-Campos, Tan, and Soriano 2016). Emphysema is a progressive form of COPD that occurs as a result of increased neutrophil protease activity in the alveolar sac that leads to the destruction of the elastic lung tissue (Sharafkhaneh, Hanania, and Kim 2008). In order to protect the lungs from excessive protease activity, we need to discover agents that can inhibit proteases, especially HNE, in order to prevent protease-induced elastin damage in lung parenchyma.

Sivelestat (**Ligand 01**) is a HNE inhibitor that has been used in Japan for the management of acute lung injuries and acute respiratory distress syndrome (Aikawa and Kawasaki 2014). A post-marketing study conducted in Japan has also reinforced the efficacy and safety of Sivelestat. (Aikawa et al. 2011), but still, it has not been approved by the FDA. In our molecular docking study, Sivelestat (**Ligand 01**) has a binding

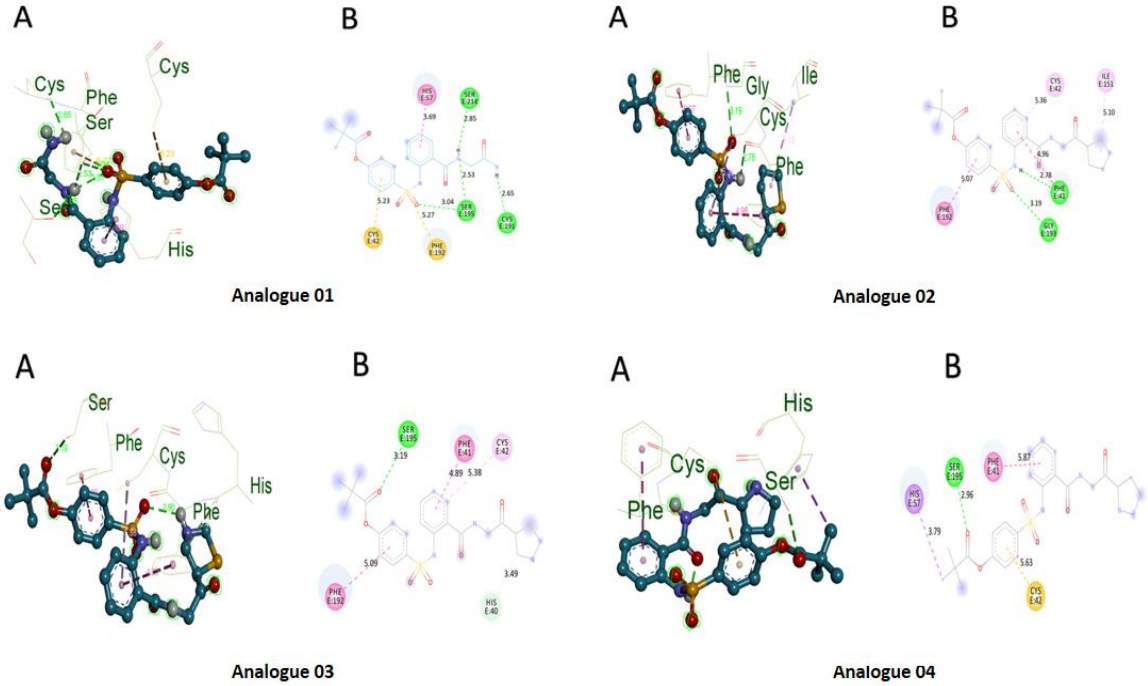


Figure 5: (A) 3D and (B) 2D docking poses showing interactions of analogs of Sivelestat (Analogue 1 to Analogue 4), with the active site residues of HNE protein

energy of -7.7 kcal/mol, which is highly significant to consider as a powerful agent to potentially inhibit serine proteases such as HNE. Many studies have proposed the bioactivity of Sivelestat (Vidhya et al. 2022). Nigranoic acid (**Ligand 02**) derived from the stems of *Schisandra sphaerandra* has been studied for numerous therapeutic effects, such as attenuation of human immunodeficiency virus infection (Wu et al. 2020). Nigranoic Acid has also shown considerable inhibition of HNE with IC_{50} value of 3.77 μM, while the ester salts of nigranoic acid also exhibited a commendable inhibition of HNE, hence supporting the findings of our study (Huang et al. 2015). Here, nigranoic acid has demonstrated a binding energy of -6.6 kcal/mol and short bond length with active site residues of HNE. Midesteine (Ligand 03), is a HNE inhibitor approved in Italy after phase III studies, which causes an effective inhibition of HNE by its interaction with serine residues of the HNE active site (Lucas et al. 2013). In our study, midesteine showed decent interactions with HNE residues with a binding energy of -5.2 kcal/mol and could be considered a candidate to be an inhibitor of HNE. Cholesterol Sulfate (Ligand 04) has exhibited its binding with catalytic residues of HNE in our study and could be considered as a potential inhibitor. The inhibitory potential of cholesterol sulfate for pancreatic elastases is also well-known (Le et al. 2022). Cephalothin (Ligand 05), a cephalosporin antibiotic has been reported to be a good potential inhibitor of HNE and hence may halt the pathogenesis of emphysema. Other cephalosporin antibiotics could also be modified

Table 5: ADMET profiling of Ligand 01– Ligand 08 and Analogue 01- Analogue 04

Drug Candidates	M.W (g/mol)	H-Ac	H-Do	N.Rot.B	TPSA	Log P	B.S	D.L	N.L.V	Enzyme Inhibitor					Toxicity Profile			
										CYP 1A2	CYP 2C19	CYP 2C9	CYP 2D6	CYP 3A4	Tum	Mut	Irr	R.E
Ligand 01	434.46	7	3	10	147.35	2.34	0.56	-2.3	0	No	No	Yes	Yes	No	No	No	No	No
Ligand 02	470.68	4	2	9	74.60	6.49	0.85	-19	1	No	No	Yes	No	No	No	No	No	No
Ligand 03	315.43	3	1	6	142.08	2.18	0.55	3.8	0	Yes	Yes	Yes	No	No	No	No	No	No
Ligand 04	466.72	4	1	7	71.98	6.14	0.85	-2.3	1	No	No	Yes	No	No	No	No	No	No
Ligand 05	396.44	6	2	8	166.55	0.77	0.11	12.15	0	No	No	No	No	No	No	No	No	No
Ligand 06	477.40	15	8	8	267.22	-4.2	0.11	-0.7	2	No	No	No	No	No	No	No	No	No
Ligand 07	282.33	3	2	4	49.69	3.18	0.55	-5.4	0	Yes	No	No	Yes	No	No	No	No	Low
Ligand 08	136.13	4	2	0	83.65	-1.0	0.55	3.04	0	No	No	No	No	No	No	No	No	No
Analogue 01	433.48	6	3	10	153.04	1.93	0.55	4.1	0	No	Yes	Yes	Yes	No	No	No	No	No
Analogue 02	504.62	6	2	11	152.32	3.51	0.55	3.99	1	No	Yes	Yes	Yes	Yes	No	No	No	No
Analogue 03	505.61	7	3	11	164.35	2	0.55	4.7	1	No	Yes	Yes	Yes	Yes	No	No	No	No
Analogue 04	487.57	7	3	11	139.05	2.54	0.55	0.88	0	No	Yes	Yes	Yes	Yes	No	No	No	No

M.W; Molecular Weight, *H-Ac*; Hydrogen bond Acceptors, *H-Do*; Hydrogen bond Donors, *N.Rot .B*; Number of Rotatable Bonds, *TPSA*; Topological Polar Surface Area, *Log P*; prediction of octanol/water partition coefficient, *BS*; Bioavailability Score, *D.L*; Drug-likeness, *Tum*; Tumorigenesis, *Mut*; Mutagenesis, *Irr*; Irritation, *R.E*; Reproductive effects.

to find the same effects (Fayad, Morin, and Nehmé 2017). In our study, Cephalothin exhibited a binding energy of -5.0 kcal/mol and short bond length with catalytic serine residues that predict it as a potent inhibitor of HNE. Chondroitin 4' Sulfate (Ligand 06) has been reported as a urinary trypsin inhibitor in many studies. It also inhibits the serine proteases such as HNE and our study reinforces this idea (Teshigahara et al. 2020a, Voynow, Zheng, and Kummarapurugu 2020). It manifested binding energy of -6.3 kcal/mol with shorter bond lengths with serine residues, making it a potential drug candidate for HNE inhibition. 2, 3-dihydro-6-[3-(2-hydroxymethyl)-phenyl-2-propenyl]5-benzofuranol (Ligand 07) is a polymorphonuclear leukocyte elastase inhibitor (Pacholok et al. 1995, Zhang 2020). In our *in silico* study, its potential for inhibition of serine protease such as HNE was testified computationally through molecular docking and the findings suggest that with a binding energy of -6.5 kcal/mol, it could be a potent inhibitor of HNE. 1,2,5-thiadiazolidin-3-one 1,1-dioxide (Ligand 08) and its derivatives are potent HNE inhibitors (Huang et al. 2008). Our *in silico* analysis has determined that 1,2,5-thiadiazolidin-3-one 1,1-dioxide exhibits potentially strong binding with active site serine residues and Phe 192, leading to its potential inhibitory activity for HNE.

The designed Sivelestat (Ligand 01) analogues i.e. Analogue 01– Analogue 04 have exhibited marvelous molecular docking results with a range of binding affinities -7.1 to -6.4 kcal/mol. Their ADME profile has also unveiled a potentially optimistic picture to consider them as powerful candidates to be developed as drug molecules for emphysema, after the conduction of subsequent *in vitro* and *in vivo* studies in the future. The *in silico* toxicity studies have established that the drug candidates in our study are non-toxic, safe, and could be consumed by humans in specified doses.

5. Conclusion and Future Aspects

Emphysema is one of the highly prevailing conditions in a large portion of the global population, especially among smokers. Pharmacotherapies need to be devised for the purpose of preventing the damage caused to the elastin tissue of the lung parenchyma. Our study may prove helpful in addressing this matter productively. Generally, it has been observed that most of the compounds that tend to bind in the oxyanion hole in the structure of enzymes have a good affinity to bind with the active residues of serine proteases such as HNE. In our study, all the potential drug molecules, including the Ligands 01-08 and **Analogues 01–04,** bound with the active serine and other residues with highly favorable and considerable binding energies, along with an incredible *in silico* pharmacokinetics and toxicity profile. Hence, all of them, especially the Sivelestat (**Ligand 01**) analogs, could be considered potential therapeutic molecules for drug development and subsequent pharmacotherapy for attenuation of emphysema. Our *in silico* study may facilitate the researchers in preclinical and clinical inquiries regarding these potential drug candidates.

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Author Contribution

Main idea and conceptualization, and initial draft by A.I., literature collection, and review by A.I. & M.A., graphics, language, and grammar by A.I. & M.H., analysis and proofreading by M.A., review editing and final draft by A.I. & M.H. All authors read and approved the final manuscript.

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All the data related to this manuscript including research papers that were analyzed for this research study are available with the authors.

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The authors declare no competing interests.

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