J. Chosun Natural Sci.
Vol.15, No.4 (2022) pp.179-186
https://doi.org/10.13160/ricns.2022.15.4.179

Virtual screening, molecular docking studies and DFT calculations on JNK3

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Abstract

The c-Jun N-terminal kinase (JNK3) play major role in neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, cerebral ischemia and other Central Nervous System disorders. Since JNK3 is primarily stated in the brain and stimulated by stress-stimuli, this situation is conceivable that inhibiting JNK3 could be a possible treatment for the mechanisms underlying neurodegenerative diseases. In this study drugs from Zinc15 database were screened to identify the JNK3 inhibitors by Molecular docking and Density functional theory approach. Molecular docking was done by Autodock vina and the ligands were selected based on the binding affinity. Our results identified top ten novel ligands as potential inhibitors against JNK3. Molecular docking revealed that Venetoclax, Fosaprepitant and Avapritinib exhibited better binding affinity and interacting with proposed binding site residues of JNK3. Density functional theory was used to compute the values for energy gap, lowest unoccupied molecular orbital (LUMO), and highest occupied molecular orbital (HOMO). The results of Density functional theory study showed that Venetoclax, Fosaprepitant and Avapritinib serves as a lead compound for the development of JNK3 small molecule inhibitors.

Keywords: JNK3, JNK3 inhibitors, Molecular docking, Density functional theory.

(**Recceived** November 25, 2022; **Revised** December 20, 2022; **Accepted** December 20, 2022)

1. Introduction

c-Jun N-terminal kinases belongs to mitogen-activated protein kinases (MAPKs) that play a significant partin stress signalling pathways involved in neuronal plasticity, gene expression, regulation of cellular senescence [1]. In humans three genes have been identified for encoding JNK, mainly jnk1 (MAPK8), jnk2 (MAPK9), and jnk3 (MAPK10) translate for ten different splice variants. C-Jun N-terminal kinase 3 (JNK3) is connected to neurological disorders like Alzheimer's disease, Parkinson's disease, cerebral ischemia and other CNS disorders and is widely studied for small drugs. JNK3 shares 92% and 87% amino acid profiles with JNK1 and JNK2 respectively [1]. JNK3 is primarily stated in the brain and stimulated by stress stimuli, this situation is conceivable that inhibiting JNK3 could be a possible treatment for the neurodegenerative processes linked to AD [1] [2]. The main key

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element for activation of JNK3 controls the regulation of apoptosis signals [2]. Alterations in JNK pathways are effectively associated with neurological disorders like Alzheimer's disease according to certain in vivo and in vitro research. Targeting JNK3 will be useful for developing a small molecule for the possible therapies of neurodegenerative diseases [2]. The typical drug research and development process can be considerably accelerated by computational or in silico drug repurposing by automatically integrating and assessing thousands of medications and ailments. Met149 and Glu147 are the reported active site residues which intricate in the binding of JNK3 protein. In this study we used computational approach to identify and validate the drugs from Zinc15 database utilising the JNK3 as a specific target [3][4].

2. Materials and methods

2.1 Preparation of protein

The crystal structure of JNK3 protein PDB ID: 1PMN) was retrieved from the protein data bank. The protein was prepared by removing the water molecules and co-crystal ligands using PyMol. Additionally the protein was prepared by adding polar hydrogen atoms, kollman and compute Gasteiger charges using autodock and converted into pdbqt format [5].

2.2 Ligand preparation

1600 drugs were downloaded from Zinc15 database in SDF format. OpenBabel software were used to prepare the ligands by adding charges and rotatable bonds. Further the ligands were saved in PDBQT format to perform docking [6].

2.3 Molecular docking

Molecular docking was used to investigate the affinity of binding between the receptor and small molecules. In the present study molecular docking was done with Autodock vina in PyRx virtual screening open-source software [7][8]. Met149 and Glu147 are the active site residues which intricatein the binding of JNK3 protein. The dimensions of the grid that appears on the protein are altered in accordance with the region around the binding site of JNK3 [3].

2.4 Conceptual Density Functional Theory (C-DFT) Analysis

Conceptual Density-functional theory is a quantum mechanical atomistic simulation technique (C-DFT). The global reactivity descriptors and their derivatives are the ten separate molecular descriptors used in the DFT technique. They are Total energy, molecular dipole moment, Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO), HOMO-LUMO gap, electrophilicity index, global softness, electronegativity and absolute hardness [9]. These descriptors can offer significant insights into the link between a molecule's structure and action. In this study the designated ligands were optimized by Becke-3-parameter, Lee-Yang-Parr (B3LYP) function with 311G (2d, p) basis set using Gaussian-16 software [9].

3. Results and Discussion

3.1 Molecular docking

Molecular docking was performed using the

drugs from Zinc15 database, in order to identify prospective therapeutic candidates for inhibiting the JNK3. In this study 1600 drugs from Zinc15 database were virtually screened and docked into the proposed binding site of JNK3 [7][8]. Drugs were selected based on binding affinity and the drugs intricate in forming bonds with active site residues. To evaluate and select the top candidates, the selected ten ligands were ranked based on the binding affinity and the best binding conformations were those with the highest binding affinity score [7][8]. In addition to their binding affinities, the hydrogen bonds & hydrophobic interactions between the ligands & protein have been tabulated in Table 1. Docked poses of selected top 10 compounds within the binding site of JNK3 protein was shown in Figure 1. As the result, three ligands Venetoclax, Fosaprepitant and Avapritinibwith highest binding affinity were selected. The binding site residues and hydrophobic interactions of Venetoclax, Fosaprepitant and Avapritinib were analysed using Pymoland shown in Figure 2, 3 and 4. The Gly71, Ile70, Ser72, Ala74, Val78, Ser96, Arg107, Met146, Glu147, Met149 and Leu206 residues were actively implicated in Venetoclax binding to JNK3 with a score of -11.9 kcal/mol. JNK3-fosaprepitant exhibited the binding score of -11.0 kcal/mol with binding site residues of Ile70, Gly71, Ser72, Val78, Ala91, Arg107, Met146, Glu147, Met149, Ser91 and Asn194. Furthermore JNK3-avapritinib exhibited -10.7 0 kcal/mol with binding site residues of Gly71, Ala74, Val78, Ala91, Ile92, Arg107, Leu126, Glu147, and Met149. According to a recent study, JNK3 must additionally bind hydrophobically with other amino acids like valine and glycine in order to be selectively inhibited. As previously reported, Met149 and Glu147 are the active site residues which intricatein the binding of JNK3 protein. Therefore Venetoclax, Fosaprepitant and Avapritinib binding to JNK3 exposed a significant influence of hydrophobic regions and residues of the active site regions, consistent with the binding pattern of earlier known inhibitors [3].

Table 1. Binding affinities of selected top 10 compounds with the JNK3 protein along with the H-bond interactions and hydrophobic interactions made with the amino acid residues

FDA drug Compounds	Binding affinity (kcal/mol)	H-bond interactions	Hydrophobic interactions
Venetoclax	-11.9	Ala74, Arg107, Lys191, Asn194	Ile70, Gly71, Ala74, Val78, Ala91, Ile124, Met146, Met149, Ala151, Val196, Leu206, Val225
Fosaprepitant	-11.0	Gla75, Ala107, Lys191, Ser193, Asn194	
Entrectinib	-11.0	Ala74, Arg107, Asn194, Leu206	
Lifitegrast	-10.7	Gln75, Arg107, Ser193, Asn194	
Exatecan	-10.7	Ala91, Asn152	
Avapritinib	-10.7	Lys191, Ser193	
Nilotinib	-10.6	Asn194	
Adapalene	-10.5	Lys93	
Capmatinib	-10.5	Ser72	
Ledipasvir	-10.4	Ala74, Arg107	

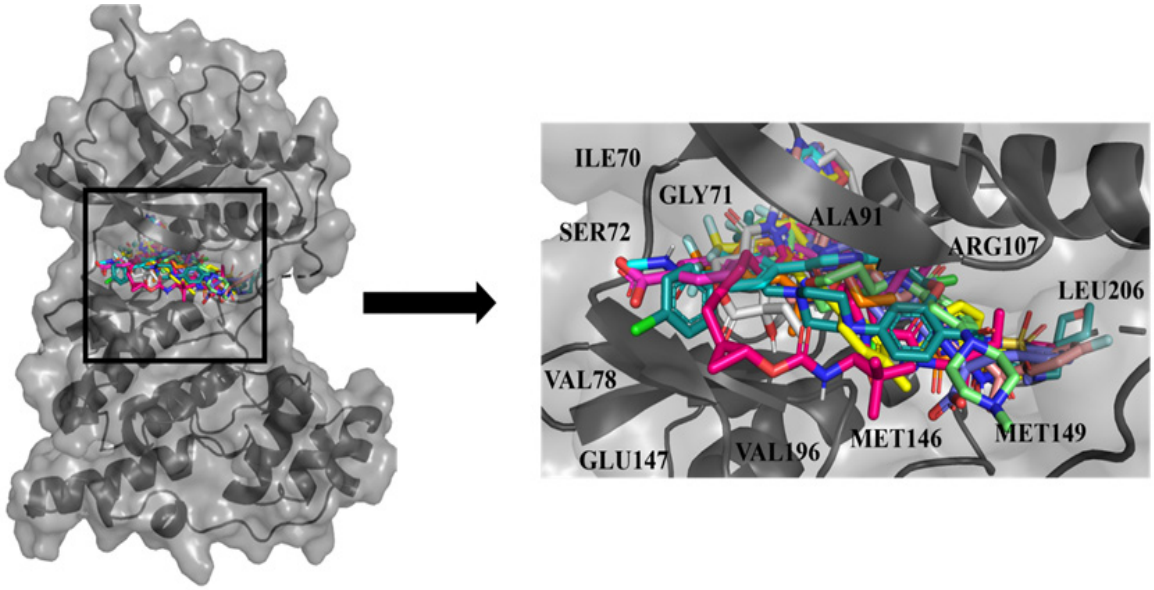


Fig.1. Docked poses of selected top 10 compounds (represented in different colours) within the binding site of JNK3 protein (PDB ID: 1PMN).

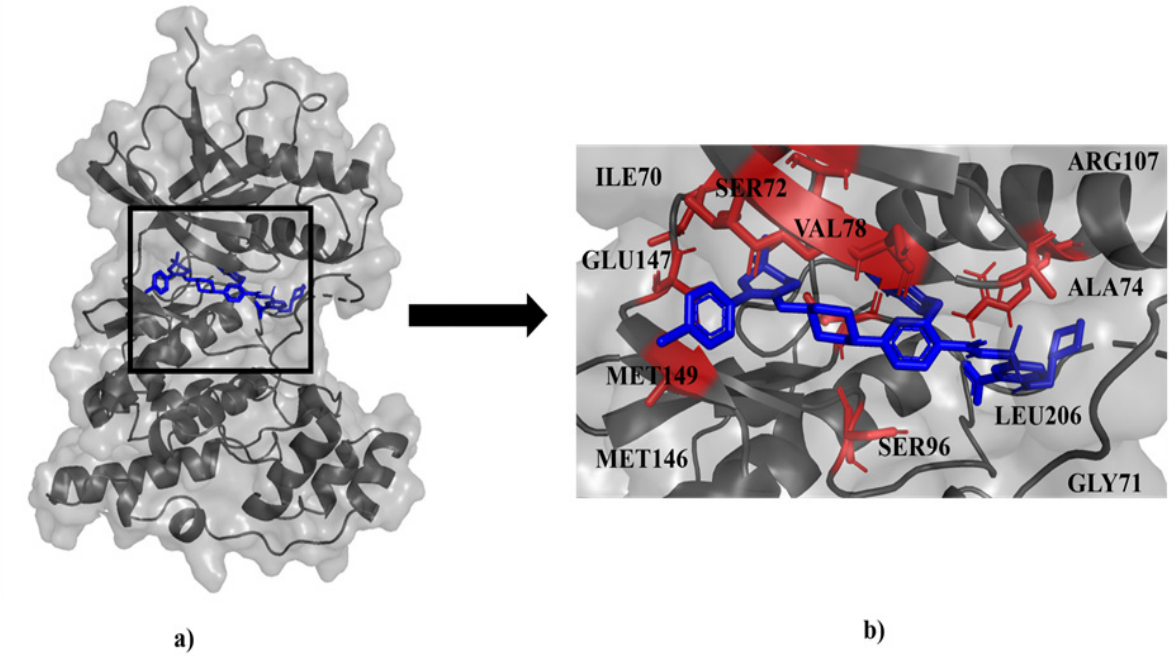


Fig. 2. (a) Binding pose of Venetoclax (blue) in JNK3protein.
(b) The active site residues involved in hydrophobic interaction has been depicted in red

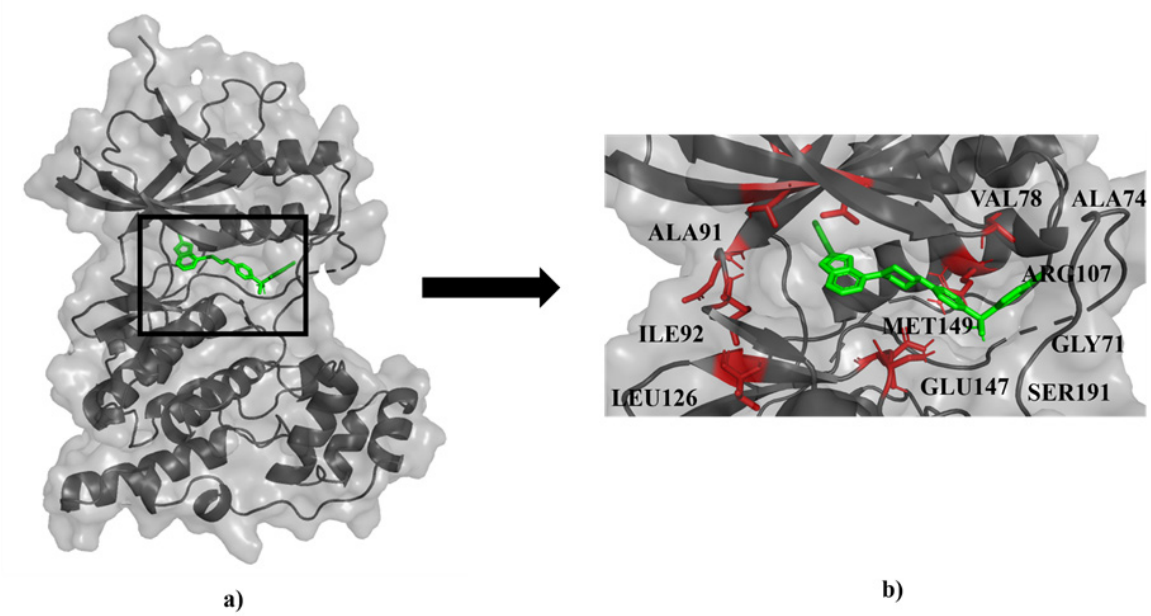


Fig. 4. (a) Binding pose of Avapritinib (green) in JNK3protein.
(b) The active site residues involved in hydrophobic interaction has been depicted in red

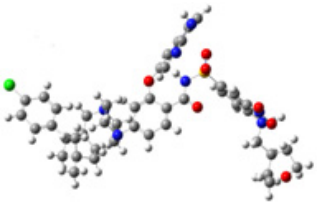
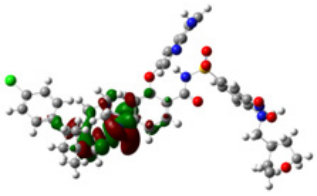
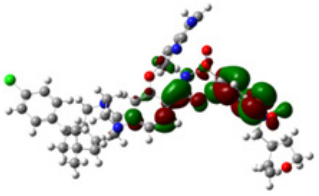
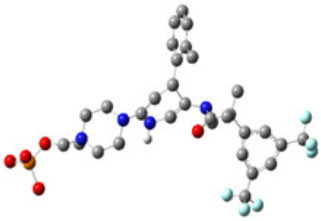
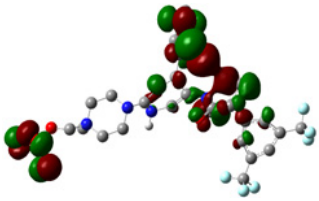
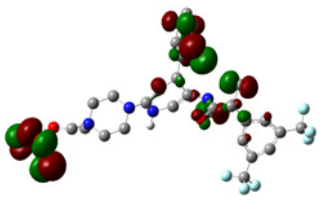
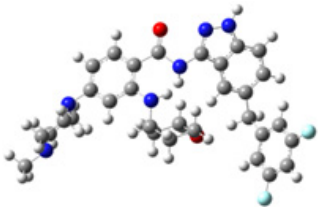
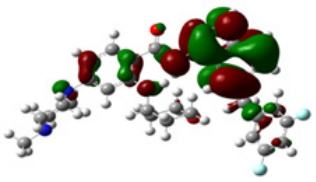
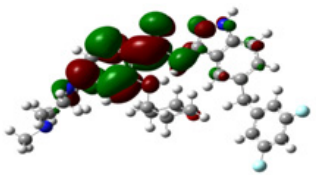
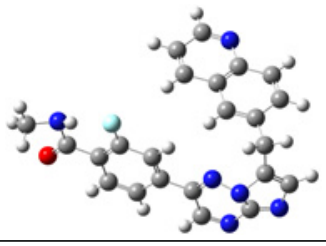
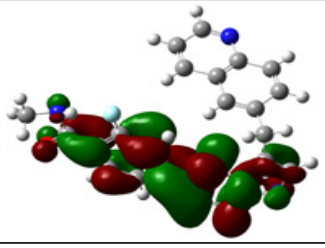
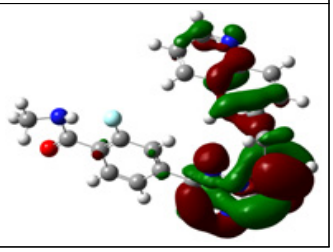
3.2 Conceptual DFT

In this study the designated ligands were optimized by the Becke-3-parameter, Lee-Yang-Parr (B3LYP) function with 311G (2d, p) basis set using Gaussian-16 software [9][10]. A stronger electron acceptor is implied by a lower HOMO value, whereas a larger value indicates a molecule with a good electron donor. Intermolecular charge distribution and molecular bioactivity are significantly influenced by a decreased energy gap among LUMO and HOMO energies [9][10]. Table 2

Table 2. Statistics of DFT based molecular descriptors of selected top 10 components

Compounds	Total Energy (E γ) (in eV)	Molecular dipole moment (Debye)	EHOMO	ELUMO	HOMO/ LUMO Gap (ΔE)	Absolute Hardness (η)	Global Softness (σ)	Electro-negativity (χ)	Chemical potential (μ)	Electrophilicity index (ω)
Venetoclax	-95529.10	6.23	-0.14	-0.07	0.07	0.03	12.86	-0.10	0.10	1.41
Fosaprepitant	-2714.84	29.39	-5.68	-5.47	0.21	0.10	4.76	-5.57	5.57	148.00
Entrectinib	-51166.65	3.86	-0.20	-0.04	0.16	0.08	6.13	-0.12	0.12	0.78
Lifitegrast	-1390.13	3.89	-6.41	-2.74	3.67	1.83	0.27	-4.57	4.57	5.70
Exatecan	-1480.63	10.98	-5.55	-5.10	0.45	0.22	2.22	-5.32	5.325	63.01
Avapritinib	-45014.70	7.10	-0.21	-0.57	-0.36	-0.18	-2.76	-0.39	0.39	-1.10
Nilotinib	-1826.61	6.43	-4.23	-3.88	0.35	0.175	2.85	-4.05	4.055	46.98
Adapalene	-35632.99	3.17	-5.71	-1.73	3.98	1.99	0.25	3.72	3.72	3.47
Capmatinib	-3073.94	3.26	-6.50	-1.71	4.79	2.39	0.20	- 4.10	4.10	3.15
Ledipasvir	-81337.27	10.39	-2.01	-1.68	0.33	0.16	2.98	-1.85	1.85	5.52

represents the E_{HOMO} and E_{LUMO} values of selected top ten ligands. The electron density maps of the selected ligands' molecular orbitals are shown in Figure 5. Thus, a smaller energy gap was observed among the compounds like Venetoclax, Fosaprepitant, Entrectinib, Ledipasvir and Avapritinib. The decrease in energy gap values increase the reactivity [10]. A molecule's molecular dipole moment will also increase the reactivity. Fosaprepitant, Exatecan and Ledipasvir scoredbetter dipole moment. Electronegativity is a significant characteristic of a compound; higher inhibitory efficiency is achieved by molecules with lower electronegativity. Compounds like Fosaprepitant, Exatecan, and Lifitegrast showed lower electronegativity values. Finally, by comparing the values of molecular docking and DFT, Venetoclax, Fosaprepitant and Avapritinib may be considered as a potential hit for JNK3 inhibition [9].

Compound	DFT optimized structure	HOMO	LUMO
Venetoclax			
Fosaprepitant			
Entrectinib			
Lifitegrast			

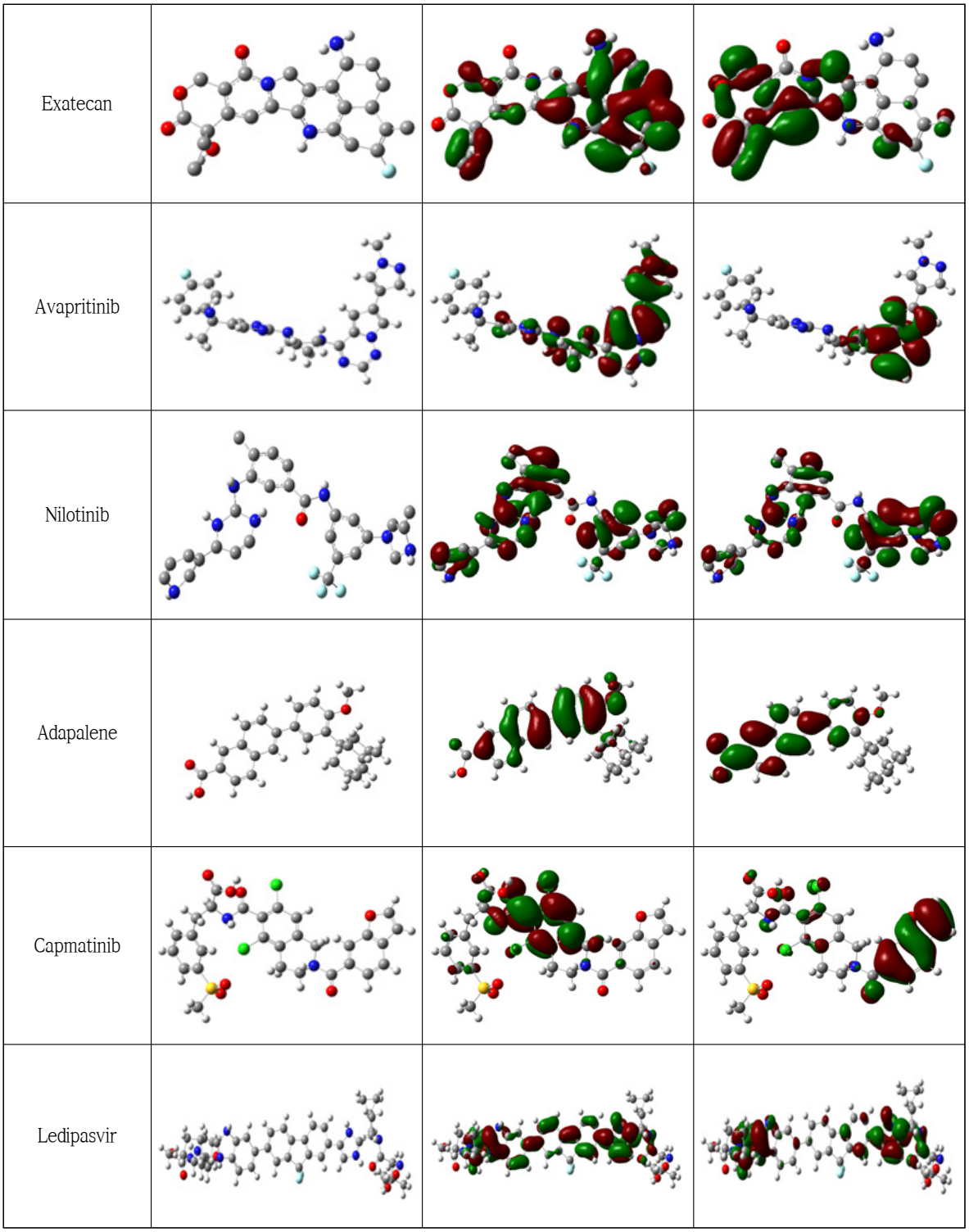


Fig. 5. Electron density maps of HOMO and LUMO of selected top 10 compounds

4. Conclusion

In silico techniques may also be employed to find the ligands that are acceptable for treatment. In this study we have performed molecular docking and conceptual DFT studyusing the drugs from Zinc15 database targeting JNK3. Our results showed that some potential ligands such as Venetoclax, Fosaprepitant and Avapritinib can inhibit the JNK3 by binding to the active site residues of JNK3 as reported in the literature and also have best docking score. Conceptual DFT analysis has provided greater insight into the chemical nature of the drugs from Zinc15 database. Molecular docking and DFT studies showed that Venetoclax, Fosaprepitant and Avapritinib may be considered as a potential hit for targeting JNK3.

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