Journal of Mines, Metals and Fuels, *71(12C): 143-148; 2023. DOI: 10.18311/jmmf/2023/47249*

Print ISSN : 0022-2755

Journal of Mines, Metals and Fuels

Contents available at: *www.informaticsjournals.com/index.php/jmmf*

Effect of N-, S- and O-Substitutions of Isophthalic Acid Derivatives on their Binding Properties: An *In-Silico* Approach

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Abstract

The fuel industry, particularly the petroleum industry, uses organic compounds for different reasons to improve fuels to obtain the desired products. This review studies the binding of organic molecules with a protein. Binding studies of the N-, S- and O-substitutions of Isophthalic acid derivatives with COVID-19 protein were examined by molecular docking approach. In investigations using molecular docking, the ligand is attached to the protein's binding pocket in various ways, yielding crucial information regarding the binding site and method. Molecular docking experiments were performed to comprehend how Isophthalic acid derivatives and COVID-19 protein interactions take place. The docking research was conducted using Autodock 4.2.5. Auto Dock forecasts the binding conformations of flexible ligands to bio-macromolecular targets via the Lamarckian genetic technique. The technique involved adding Kollman charges and polar hydrogen to the ligand and protein molecules to produce the PDBQT files and combining non-polar bonds to produce molecular probes. To perform conformational search and docking simulation, the Lamarckian Genetic Algorithm (LGA) was chosen. PyMOL was used as a visualising tool. It was found that the principal binding forces in the interaction between Isophthalic acid derivatives and selected proteins were hydrophobic interactions and hydrogen bonding. The molecular probe's ideal form revealed the affinity as a release of free-binding energy. The current research report aims to highlight the approachable nature of derivatives of isophthalic acid and paves the way for focused biological interactions.

Keywords: *Binding Interaction, COVID-19 Protein, Isophthalic Acid Derivatives, Molecular Docking*

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1.0 Introduction

Petroleum products are being used in day-to-day life for different purposes and these petroleum products are converted into different products based on the applications. Organic compounds play a very important role in many industries for transforming into desired products. The heterocyclic compounds of organic molecules have importance in biological applications as they have different heteroatoms for interacting with the many molecules in biological systems. Isophthalic acids are the isomers of phthalic (some of which have been observed in natural water, sediments, soil, aquatic creatures, etc.[1,2]) and terephthalic acid, these are dicarboxylic acid compounds which are mainly used in the synthesis of varieties of polymers including drinking water bottles[3,4]. Early exposure to phthalates could considerably cause neuro-developmental harm, according to epidemiologic studies of phthalic acid esters[5]. Certain phthalic acid esters are poisonous to humans, animals and aquatic life throughout the reproductive and developmental stages[6-8]. Plants are shielded from insect consumption by phthalate esters' insecticidal properties[1,10]. Many phthalic acid derivatives significantly impede the germination of seeds and the growth of seedlings in a variety of plant species[11,12]. Plants harm the leaves affected by lipid peroxidation and damage the cell membrane[13]. No work has been done on *in-silico* activity studies for these isophthalic acid molecules and it is worth checking the functional group effect of these molecules.

The molecular docking technique is a theoretical method for researching protein-ligand interactions and recognition, predicts the binding type and binding strength of small molecule ligands and receptor bio-macromolecules to realise structure-based drug design that is important for molecular mechanisms of structure prediction of protein-ligand complexes, pharmacological activities and targeted drug screening[14-16]. Computer-Aided Drug Design (CADD) is a computational method which is employed for creating and optimising

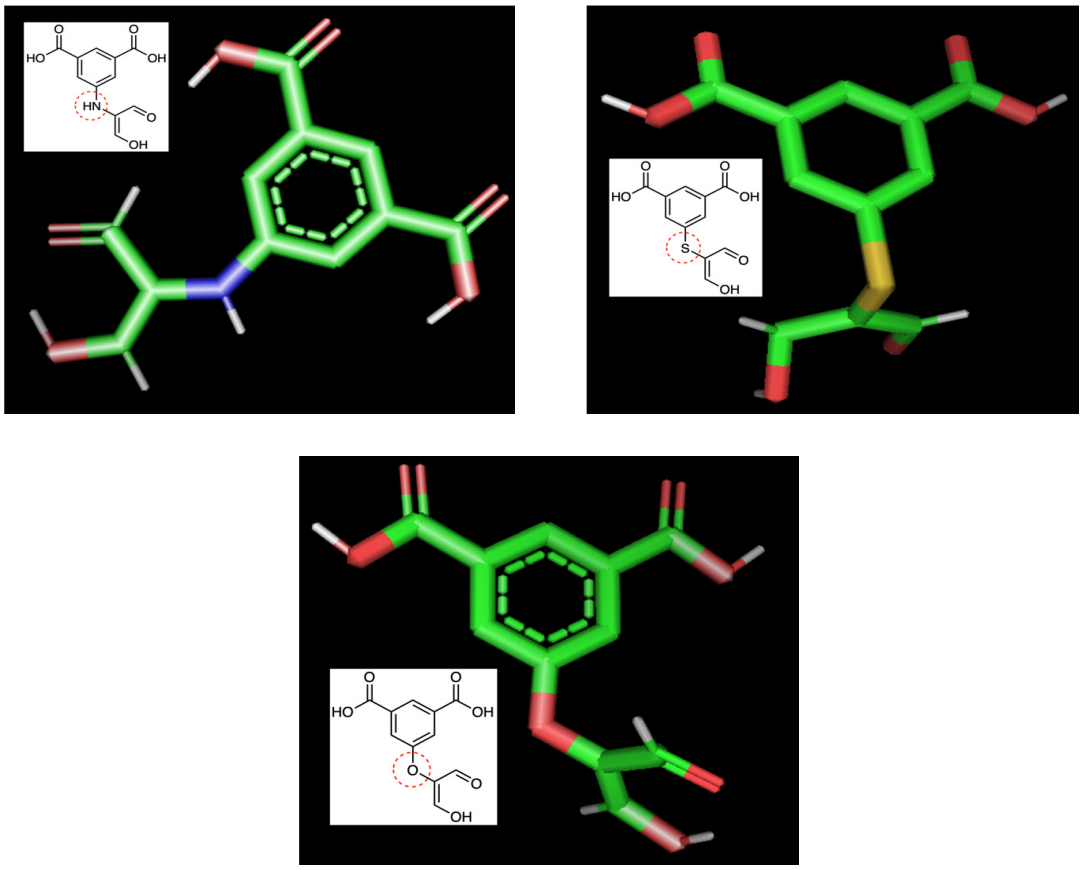


Figure 1. Structures of isophthalic acid derivatives.

pharmacological lead compounds using simulations, calculations and predictions of the drug-receptor connection. This method considerably enhances drug screening success rates, reduces research blindness, has inexpensive and short-cycle advantages, and is an important tool in drug research and development[17]. This is because of more user-friendly molecular docking operating processes and the increased interest in drug research over the past two decades. This technology has increased in popularity as a tool for the study of marine pharmaceuticals.

Serious and widespread illnesses like Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) are all brought on by the coronaviruses that infect people and other animals[18]. The SARS-CoV-2 replicase gene produces the overlapping polyproteins pp1a and pp1ab, which are required for viral transcription and replication. The genome of SARS-CoV-2 has about 30,000 nucleotides[19,20]. The polyproteins are extensively processed by proteolytic means to liberate the functional polypeptides, mostly by the 33.8-kDa M^{pro} (also known as 3C-like protease). The polyprotein is broken down by M^{pro} at least 11 conserved sites, beginning with the enzyme's autolytic cleavage from pp1a and pp1ab8. Due to M^{pro}'s functional significance in the viral life cycle and the lack of closely similar human homologues, it is an appealing target for the development of antiviral medicines[21]. Coronaviruses (CoVs) are known to be the root cause of several illnesses, such as MERS and SARS, which have serious negative effects on both health and the economy. The key structural protein Nucleocapsid (N), which is produced by CoVs, has several functions in the virus replication cycle and interacts with the viral RNA through its N-terminal domain to create a Ribonucleoprotein Complex (N-NTD). The study reports the interactions between the N-, S- and O-substitutions of Isophthalic acid derivatives with HCoV-OC43 N-NTD (4LM9) by molecular docking approach.

By combining structure-assisted drug design, virtual drug screening and high-throughput screening we have created a method that to repurpose current medications to target SARS-CoV-2 to speed up the discovery of antiviral medicines with therapeutic potential. For this purpose, the N-, S- and O-substitutions of Isophthalic acid derivatives were selected (Figure 1) and molecular docking studies were conducted with 4LM9 [22] (Figure 2), a COVID-19 protein and suitable conclusions were drawn.



Figure 2. Structure of 4LM9 protein.

2.0 Experimental

To anticipate the bound conformations of flexible ligands to bio-macromolecular targets using the Lamarckian genetic technique, docking investigations were conducted using Autodock 4.2.5 according to the literature[23,24]. In essence, the PDBQT files were made by adding Kollman charges and polar hydrogens to protein and ligand molecules and molecular probes were made by combining non-polar bonds. To perform conformational search and docking simulation, the LGA was chosen. The evaluation number was fixed to 25 in addition, and the other parameters were kept at their default settings. PyMOL was used as a visualising tool.

The 3D structures of N-, S- and O-substitutions of Isophthalic acid derivatives were taken from ChemDraw and the crystal structure of HCoV-OC43 N-NTD (PDB id: 4LM9) was obtained from Protein Data Bank. The LGA in conjunction with an adaptive local method search was used to eliminate the possibility that the isophthalic acid derivatives have a conformation that binds to the protein. The protein was given partial Kollman charges after the hydrogen atoms and water molecules were taken out. The

proteins were set to be stiff and their torsional connections were all expected to be free during the docking procedure. The proteins were set to be stiff and their torsional connections were all expected to be free while following the docking procedure. The solvent molecules were not taken into consideration during docking. To identify each binding site for isophthalic acid derivatives on 4LM9, blind docking was used with grid sizes of 92, 86 and 126 along the X, Y and Z axes, respectively, with a grid spacing of 0.452 A°. The parameters for the auto dock used a GA population size of 250, 50 GA runs and a maximum of 2,500,000 energy evolutions. The top 10 solutions were kept for further study based on docking score.

3.0 Results and Discussions

Molecular docking experiments were conducted to understand the interactions between 4LM9 and derivatives of isophthalic acid. In investigations using molecular docking, the ligand is attached to the protein's binding pocket in a variety of ways, yielding crucial information regarding the binding site and method. The outcomes of molecular docking show that 4LM9 interacts primarily with S-substituted isophthalic acid derivatives. Figure 3 displays the interaction of Isophthalic acid derivatives with 4LM9. The Isophthalic acid derivatives have ΔG value of -7.31 kcal.mol^{-1}, -8.05 kcal.mol^{-1} and -7.79 kcal.mol^{-1}, for N-, S- and O-substitutions, respectively. For

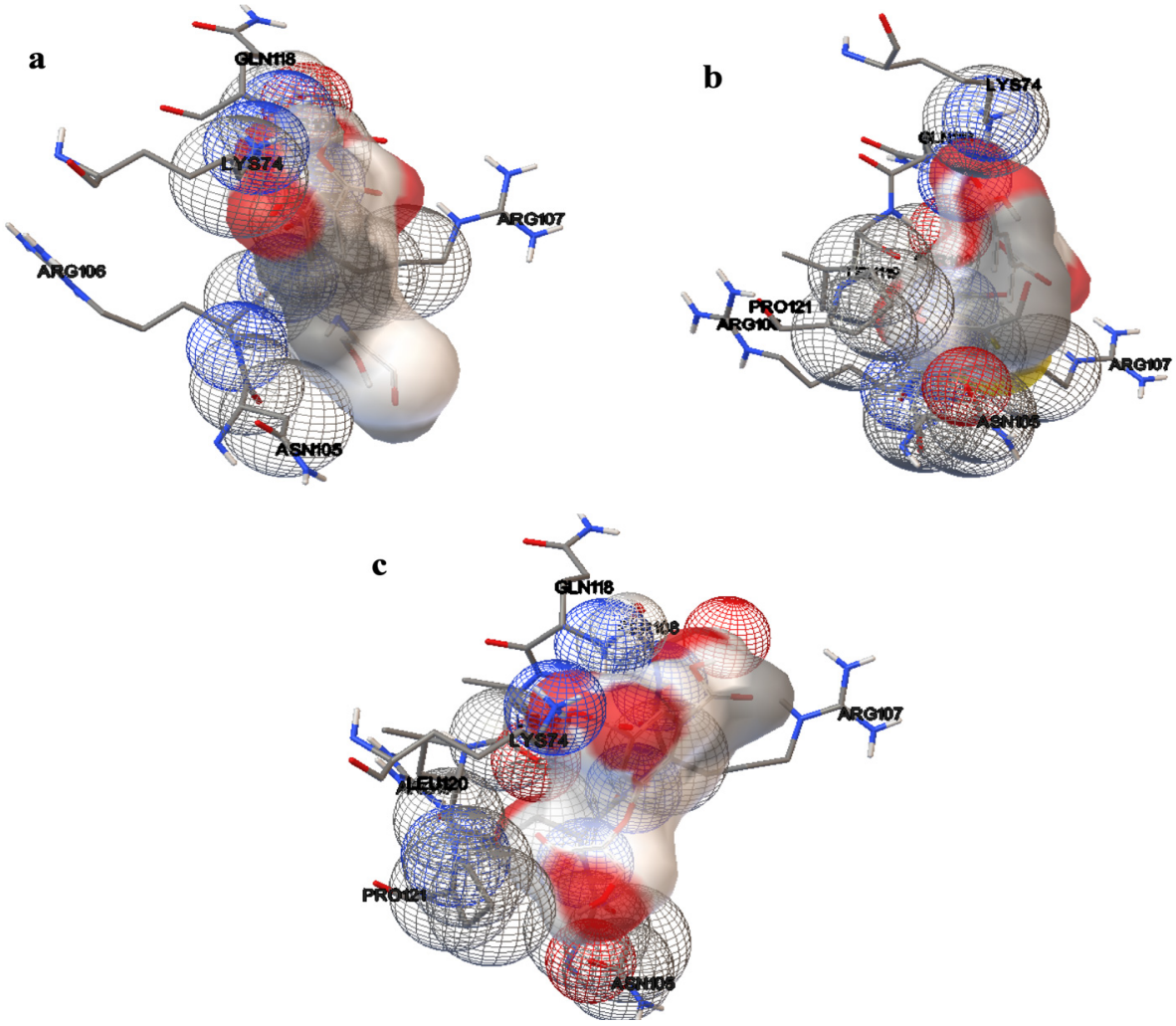


Figure 3. Molecular docking of isophthalic acid derivatives with 4LM9. **(a)** N-substituted isophthalic acid derivative with 4LM9 **(b)** S-substituted isophthalic acid derivative with 4LM9 **(c)** O-substituted isophthalic acid derivative with 4LM9.

Table 1. Binding parameters of isophthalic acid derivatives and 4LM9

Compound	ΔG in kcal. mol^{-1}	Amino acid residues involved in the interaction
N-substitution	-7.31	GLN118, SER108, ARG107, THR111 and LYS110
S-substitution	-8.05	LYS74, GLN118, SER108, LEU119, PRO121, ARG106, ASN105 and ARG107
O-substitution	-7.79	GLN118, SER108, PRO121, ARG106, LEU120, LYS74, LEU119, ARG107 and ASN105

N-substitution, residues GLN118, SER108, ARG107, THR111 and LYS110, for S-substitution, residues LYS74, GLN118, SER108, LEU119, PRO121, ARG106, ASN105 and ARG107, for O-substitution, residues GLN118, SER108, PRO121, ARG106, LEU120, LYS74, LEU119, ARG107 and ASN105 were involved in the interactions. Table 1 displays the binding energy and amino acids that were involved in the interactions.

These Results indicate that the S-substituted Isophthalic acid derivative has more potential than N- and O-substituted Isophthalic acid derivatives for the interaction with 4LM9.

4.0 Conclusion

The mechanisms that underlie the interactions between macromolecules and ligands have the potential to significantly affect the various drug pharmacokinetic phases and to compete with one another to affect the drugs' distribution, availability on the target, metabolism and excretion and ultimately their therapeutic efficacy and toxicity. This makes it extremely difficult to do research in any field of pharmacology. This work is helpful for further assessing the pharmacological characteristics of particular isophthalic acid derivatives and serves as a valuable resource for the development of new COVID-19 medications.

5.0 References

1. Roy RN. Bioactive natural derivatives of phthalate ester. Crit Rev Biotechnol. 2020; 40:913-29. https://doi.org/10.1080/07388551.2020.1789838
2. Net S, Sempere R, Delmont A, Paluselli A, Ouddane B. Occurrence, fate, behavior and ecotoxicological state of phthalates in different environmental matrices. Environ Sci Technol. 2015; 49:4019-35. https://doi.org/10.1021/es505233b
3. Brown, HC, *et al.*, in Baude EA, Nachod FC. Determination of organic structures by physical methods, Academic Press, New York, 1955.
4. Lorz PM. Towae FK, Enke W, Jäckh R, Bhargava N, Hillesheim W. Phthalic acid and derivatives. Ullmann's Encycl Ind Chem. https://doi.org/10.1002/14356007.a20_181.pub2
5. Miodovnik A, Edwards A, Bellinger DC, Hauser R. Developmental neurotoxicity of ortho-phthalate diesters: Review of human and experimental evidence. Neurotoxicology. 2014; 41:112-22. https://doi.org/10.1016/j.neuro.2014.01.007
6. Howdeshell KL, Wilson VS, Furr J, Lambright CR, Rider CV, Blystone CR. A mixture of five phthalate esters inhibits fetal testicular testosterone production in the sprague-dawley rat in a cumulative, dose-additive manner. Toxicologica Sciences. 2008; 105(1):153-65. http://doi.org/10.1093/toxsci/kfn077.
7. Hotchkiss AK, Gray LE, Jr. A mixture of five phthalate esters inhibits fetal testicular testosterone production in the sprague-dawley rat in a cumulative, dose-additive manner. Toxicol Sci. 2008; 105:153-65. https://doi.org/10.1093/toxsci/kfn077
8. Heudorf U, Mersch-Sundermann V, Angerer J. Phthalates: Toxicology and exposure. Int J Hyg Environ Health. 2007; 210:623-34. https://doi.org/10.1016/j.ijheh.2007.07.011
9. Wang Y, Zhang G, Wang L. Potential toxicity of phthalic acid esters plasticizer: Interaction of dimethyl phthalate with trypsin *in Vitro*. J Agric Food Chem. 2015; 63:75-84. https://doi.org/10.1021/jf5046359
10. Xu H, He XQ. Natural products-based insecticidal agents 6. Design, semisynthesis and insecticidal activity of novel monomethyl phthalate derivatives of podophyllotoxin against *Mythimna separata* walker *in vivo*. Bioorg Med Chem Lett. 2010; 20:4503-06. https://doi.org/10.1016/j.bmcl.2010.06.032

11. Callaway RM, Aschehoug ET. Invasive plants versus their new and old neighbors: A mechanism for exotic invasion. Science. 2000; 290:521-23. https://doi.org/10.1126/science.290.5491.521
12. Shao H, Huang X, Wei X, Zhang C. Phytotoxic effects and a phytotoxin from the invasive plant *Xanthium italicum* Moretti. Molecules. 2012; 17:4037-46. https://doi.org/10.3390/molecules17044037
13. Xuan TD, Chung IM, Khanh TD, Tawata S. Identification of phytotoxic substances from early growth of barnyard grass (*Echinochloa crusgalli*) root exudates. J Chem Ecol. 2006; 32:895-906. https://doi.org/10.1007/s10886-006-9035-x
14. Vakser IA. Protein-protein docking: From interaction to interactome. Biophysical Journal. 2014; 107(8):1785-93. https://doi.org/10.1016/j.bpj.2014.08.033
15. Eszter FN, Zelma F, Violetta M, Diána D, Beáta L, Tamás K, Cecília S, Balázs ZZ, Csaba H, Ádám IH, Zsuzsanna H, Ruth D, Dóra B, Andrea C, Péter M, Miklós P. Interaction of SZV 1287, a novel oxime analgesic drug candidate, and its metabolites with serum albumin. J Mol Liq. 2021; 333:115945. https://doi.org/10.1016/j.molliq.2021.115945
16. Xue LC, Dobbs D, Bonvin AM, Honavar V. Computational prediction of protein interfaces: A review of data-driven methods. FEBS Letters. 2015; 589(23):3516-26. https://doi.org/10.1016/j.febslet.2015.10.003
17. Pereira F, Aires-de-Sousa J. Computational methodologies in the exploration of marine natural product leads. Mar Drugs. 2018; 16(7):236. https://doi.org/10.3390/md16070236
18. de Wit, E, van Doremalen, N, Falzarano D, Munster VJ. SARS and MERS: Recent insights into emerging coronaviruses. Nat Rev Microbiol. 2016; 14:523-34. https://doi.org/10.1038/nrmicro.2016.81
19. Zhou P. *et al*. A pneumonia outbreak associated with a new coronavirus of probable batorigin. Nature. 2020; 579:270-3. https://doi.org/10.1038/s41586-020-2012-7
20. Wu, F. *et al*. A new coronavirus associated with human respiratory disease in China. Nature. 2020; 579:265-9. https://doi.org/10.1038/s41586-020-2008-3
21. Pillaiyar T, Manickam M, Namasivayam V, Hayashi Y, Jung SH. An overview of severe acute respiratory syndrome-coronavirus (SARS-CoV) 3CL protease inhibitors: peptidomimetics and small molecule chemotherapy. J Med Chem. 2016; 59:6595-628. https://doi.org/10.1021/acs.jmedchem.5b01461
22. Lin, SY, Liu CL, Hou MH. Crystal structure of HCoV-OC43 N-NTD complexed with GMP, structural basis for the identification of the N-terminal domain of coronavirus nucleocapsid protein as an antiviral target. J Med Chem. 2014; 57:2247-57. https://doi.org/10.2210/pdb4lm9/pdb
23. Morris GM, Goodsell DS, Halliday RS, Huey R, Hart WE, Belew RK, Olson AJ. Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. J Comput Chem. 1998; 19:1639-62. https://doi.org/10.1002/(SICI)1096-987X(19981115)19:14<1639::AID-JCC10>3.0.CO;2-B
24. Trott O, Olson AJ. AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading. J Comput Chem. 2010; 31:455-61. https://doi.org/10.1002/jcc.21334