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Molecular Docking Study of Some Nitro Diazo Dye Derivatives as Antiviral Candidates of COVID-19

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Authors' contributions

This work was carried out in collaboration by all authors. Author MHAD designed, managed the study and wrote the introduction section in the manuscript. Author EABS wrote the abstract, the chemistry and the molecular docking parts in the results and discussion section in the manuscript. Authors HHA and HYA managed and wrote the practical molecular docking in the results and discussion section of the study in the manuscript. Authors AKAB, DSAN, SMBM, KMY and FABH managed the chemistry experimental parts of the study in the manuscript. All authors wrote the first draft, read and approved the final manuscript.

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ABSTRACT

In this study, the computerized molecular docking method was used to investigate the interactions of five nitro diazo dye derivatives **1-5** with COVID-19, CLpro, RAF and PLpro as very important viral proteins to target the coronavirus SARS-CoV-2. Among the used diazo dyes, compound **5**

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showed the highest binding free energies and the lowest inhibition constants K_i with all studied proteins, and it exhibits a large effect to inhibit the activities of the RAF and COVID-19. Therefore, compound **5** may be useful as an antiviral candidate that worth more trials for COVID-19 disease. The binding sites of compound **5** with the tested viral proteins were evaluated.

Keywords: Molecular docking; SARS-CoV-2; COVID-19 protein; nitro functional group; diazo dyes; vanillin.

1. INTRODUCTION

Molecular docking is one of the most computational modelling method used to predict the biomolecular binding interactions between the ligand molecule and appropriate receptor target. It provides a virtual screen of drug molecule with a macromolecule library that simulates biological systems and it helpful in designing structure-based drugs [1-4].

Annually, over than 7 x 10^5 tons of more than 10,000 types of synthetic dyes were produced in worldwide [5]. The dyes which are stable during aerobic degradation [6], high stable to the light and temperature, low cost, easy to prepare, firmness, variety in colour and microbial attack are used in different fields [7-8]. They are found in our life as plastics, fabrics, cosmetics, papers, printing, drugs, and food. By the way, some dyes are toxic, teratogenic, mutagenic, and carcinogenic [9]. Azo dyes have been amongst widely studied synthetic organic dyes. They are the most important class of dyes due to their high degrees of thermal stability, property that recommend it for various applications [10-12]. Some azo dyes were studied to inhibit viral diseases [13-16], and DNA synthesis [17].

On the other hand, the viruses are submicroscopic infectious pathogens have either RNA or DNA nucleic acids. They are much smaller than bacteria, which are replicates only inside the living cells and infect all types of life forms. Influenza, one of these common viruses with negative sense and single-stranded RNA in four types, three types affect humans. While the forth type is not known to infect humans [18-19]. It is an air borne infection which spreads into the air as droplets from a cough and sneeze that attacks the respiratory system of human. Flu spreads around the world annually, causing approximately three to five million severe illness and about 290,000 to 650,000 deaths [20].

SARS-CoV-1 is a type of coronavirus identified in 2003. It spreads from animals, perhaps bats, to other animals such as civet cats, and the first known human infection was in southern China in 2002. It affected 26 countries with about more than 8,000 cases in 2003 [21]. In 2019, another strain type of SARS-CoV-1 was discovered in Wuhan, China and called SARS-CoV-2 [22], which becomes a pandemic in 2020. Until last week of Dec. 2020, there were more than 79 million confirmed cases and more than 1.7 million deaths of SARS-CoV-2 infections [23]. Both of SARS-CoV-1 and SARS-CoV-2 are positive- sense and single-stranded RNA viruses [24].

Our recent researches have concerned on studying of some nitro diazo dye derivatives, including their synthesis, biological activity, and molecular docking with human serum albumin HSA. In addition to, the study of their thermodynamic parameters, electronic structures, using computational DFT method [25-27]. During these investigations, the nitro diazo dye derivatives **1-5** have been synthesized and characterized [28-29], Fig. 1. As a part of our efforts to study some nitro diazo dye derivatives, in this study, we used the molecular docking method to test the ability of five nitro diazo dye compounds **1-5** for targeting the activities of four important viral proteins including COVID-19, CLpro, RAF, and PLpro, that are essential for the virus's lifecycle, viral replication, viral survival, and play the important role in the coronavirus infection especially, coronavirus SARS-CoV-2. Moreover, the binding sites of these nitro diazo dye derivatives with the studied viral proteins were investigated.

All five synthesized dyes have antibacterial activities [25,29]. Currently, COVID-19 is a pandemic threatens human life. It is a respiratory disease caused by a type of coronaviruses family which is known as coronavirus SARS-CoV-2. Up to now, there are no drugs have proven to treat the infection. On the other hand, molecular docking is one of the popular computational methods that can be used to study the protein-drug interactions and predicted the binding sites between them. Thus, it simulates biological systems and can be utilized to the rational drugs-design.

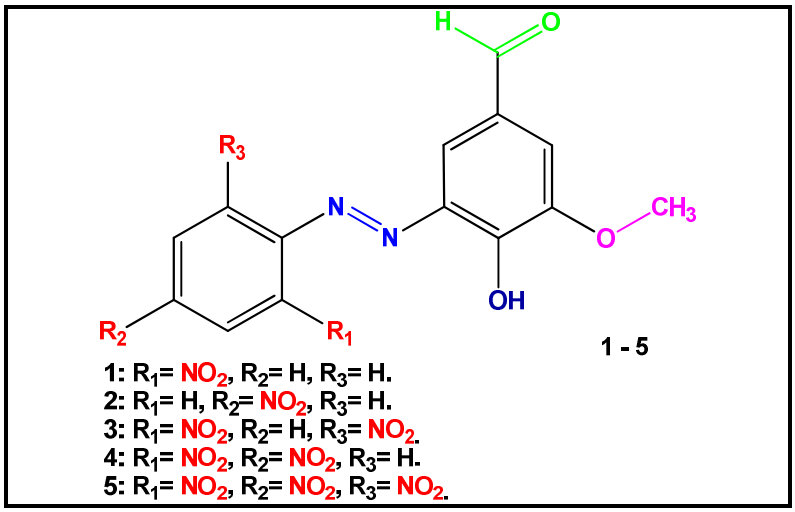

Fig. 1. The structure of nitro diazo dyes 1-5

2. MATERIALS AND METHODS

2.1 Synthesis of Nitro Diazo Dyes 1–5

The nitro diazo dyes **1-3** were synthesized and characterized as described previously [25], while diazo dyes **4-5** were synthesized by the same method [29].

2.2 Molecular Docking

Five synthesized nitro diazo dye compounds **1-5** were selected for the docking simulations. The 3D structures of these compounds were built using gaussview and the starting structures were relaxed and optimized to the minimum structure using AM1 semi-empirical method, which it is part of gaussian09 software [30]. The crystal structures of the studied proteins were downloaded from Protein Databank RCSB PDB. The COVID-19 crystal structure main protease, PDB ID:5R82 (resolution = 1.31 Å) were used for docking calculations while the crystal structures for the other proteins are as follows; PDB ID:1UK4 (resolution = 2.50 Å), 6CAD (resolution = 2.55 Å) and 5E6J (resolution = 2.85 Å) for the crystal structure of the CLpro, RAF and PLpro, respectively. All the water molecules and any co-crystalized hetero molecules were removed from the crystal structures and neutralized with Kollman united atom after adding polar hydrogen atoms using autodock tools platform. Autogrid4 was used to build the grid box with 60 x 60 x 60 dimensions and 0.375 Å distances between points. All the rotatable bonds were allowed and 250 conformations were evaluated using Lamarckian genetic algorithm implemented in Autodock4 software [31]. Autodock4 was used to calculate the K_i values. The docked conformations were grouped in clusters and ranked according to binding free energy. Discovery studio visualizer was used to view the docked conformations and elucidate the interactions between the five synthesized nitro diazo dye compounds **1-5** and the active site of the proteins.

3. RESULTS AND DISCUSSION

In this study, we use the molecular docking to test the ability of the nitro diazo dye compounds **1-5** to targeting the activities of four selectivity viral proteins, which are COVID-19, cathepsineL CLpro, the RAF, and the papain-like protease PLpro. The binding free energies and the inhibition constants K_i of the molecular docking of the diazo dyes **1-5** with the active sites of the studied viral proteins are tabulated in Table 1.

According to the Table 1, the 4-hydroxy-3-methoxy-5-((2,4,6-trinitrophenyl)diazenyl) benz-aldehyde **5** as compared to another four diazo dyes, has the highest binding free energy and lowest inhibition constant K_i in complex with all used viral proteins. Also, compound **5** shows lowest inhibitor constants K_i in the order: RAF > COVID-19 > CLpro > PLpro. Compound **4** has a higher binding free energy with the respective of the other three diazo dyes **2-3**, and has the lowest inhibition constant K_i with COVID-19. The more details about the interactions between the docked diazo dye **5** and the active sites of the viral proteins, are shown in Fig. 2 and Fig. 3.

Table 1. Docking free energy and inhibition constant of 1-5 against the four proteins

Comp.	COVID-19		CLpro		RAF		PLpro	
	Free Energy kcal/mol	K_i μM	Free Energy kcal/mol	K_i μM	Free Energy kcal/mol	K_i μM	Free Energy kcal/mol	K_i μM
1	-8.06	1.23	-7.30	4.42	-7.94	1.52	-5.63	75.26
2	-7.91	1.59	-7.07	6.53	-7.97	1.43	-4.92	249.27
3	-7.96	1.46	-7.09	6.40	-7.16	5.68	-5.53	88.92
4	-9.07	225.38*	-7.91	1.60	-9.03	239.53*	-5.60	78.80
5	-9.26	162.28*	-8.51	573.41*	-9.36	138.07*	-5.82	54.17

*μM: micro molar, *: nano molar*

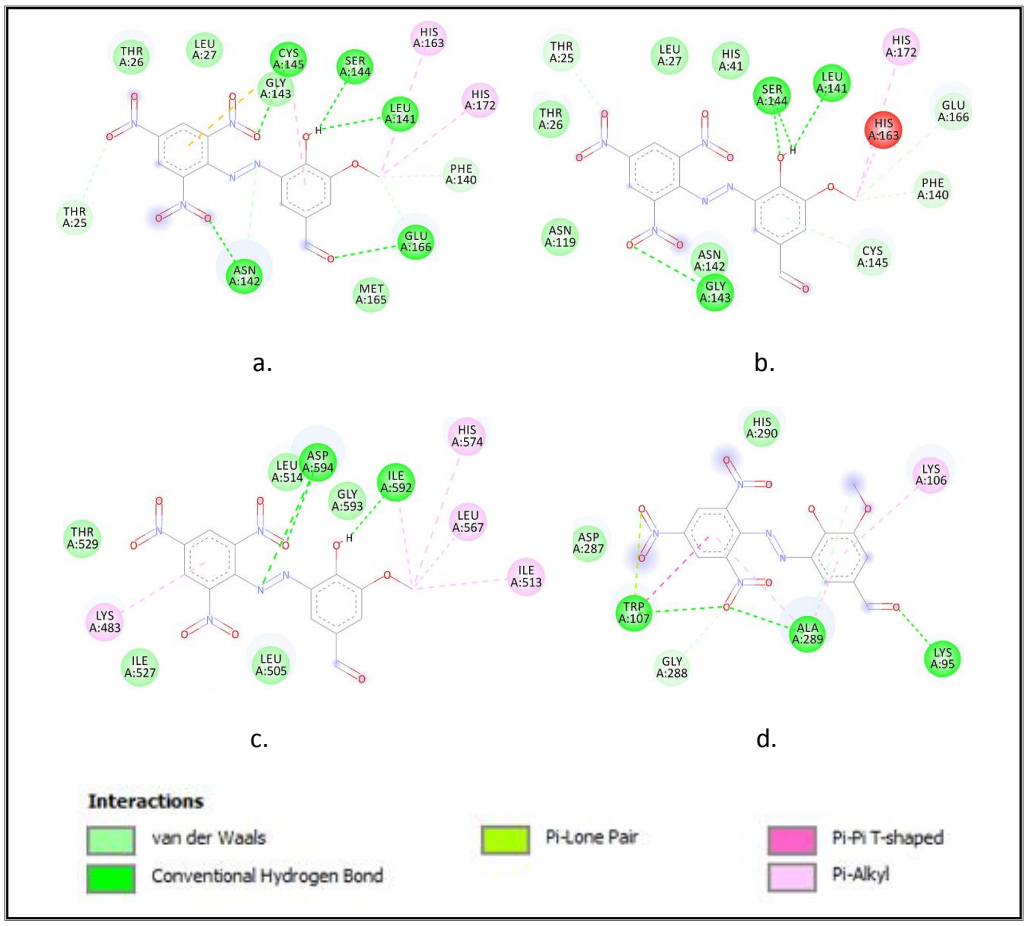

Fig. 2. Interactions of 5 with the active site of the studied proteins a. COVID-19, b. CLpro, c. RAF and d. PLpro

The main intermolecular interactions of the docked compound **5** at the active sites of the viral proteins are hydrogen bonding (hydrogen bond donors and/or acceptors) as the stronger intermolecular attractions with COVID-19, CLpro, RAF, and PLpro proteins. As shown in Fig. 2a, COVID-19 protein makes hydrogen bonding with the hydroxyl functional group of compound **5** through its LEU (A:141) and SER (A:144) residues. It also forms hydrogen bonds *via* its GLU (A:166) with the oxygen of aldehydic functional group, and another hydrogen bonds occur with the nitro functional groups that placed at the positions two and six of **5** *via* both ASN (A:142) and CYS (A:145) receptors of COVID-19. There are *π*-alkyl interactions between the HIS

(A:163), and HIS (A:172) of protein with the methyl methoxy functional group. Moreover, COVID-19 also forms through its GLY (A:143) receptor another *π*-alkyl interactions with the phenyl rings of the compound **5**. COVID-19 forms van der Waals interactions *via* ASN (A:142) with the azo functional group of compound **5**, and with the methyl methoxy functional group *via* PHE (A:140) and GLU (A:166) residues. In addition to, there are van der Waals intermolecular interactions between the oxygen of nitro functional group at position six of **5** and the THR (A:25) of COVID-19 protein, Fig. 2a.

It can be observed from Fig. 2b that compound **5** forms hydrogen bonding with SER (A:144) of CLpro through the oxygen and hydrogen of hydroxyl functional group as the hydrogen bond donor and acceptor, respectively. Another hydrogen bonds are formed between the hydrogen of hydroxyl functional group with the LEU (A:141) receptor, and between the nitro functional group at the position two with GLY (A:143) of CLpro. The *π*-Alkyl interactions are formed between the methyl methoxy functional group with both HIS (A:163) and HIS (A:172) residues. Compound **5** has also van der Waals interactions *via* methyl methoxy functional group with both GLU (A:166) and PHE (A:140), and *via* phenyl benzaldehyde ring through CYS (A:145) receptors of the CLpro.

According to the Fig. 2c, the RAF protein makes hydrogen bonding through ILE (A:592) with hydrogen of the hydroxyl functional group of the diazo dye **5**, and through the ASP(A:594) with both the azo functional group and the nitro functional group at position two. Compound **5** has *π*-alkyl interactions with the RAF protein through its methyl methoxy functional group with ILE (A:513), LEU (A:567), HIS (A:574), and ILE (A:592) of this viral protein. Another *π*-Alkyl interaction between the phenyl trinitro ring of compound **5** and LYS (A:483) of RAF protein.

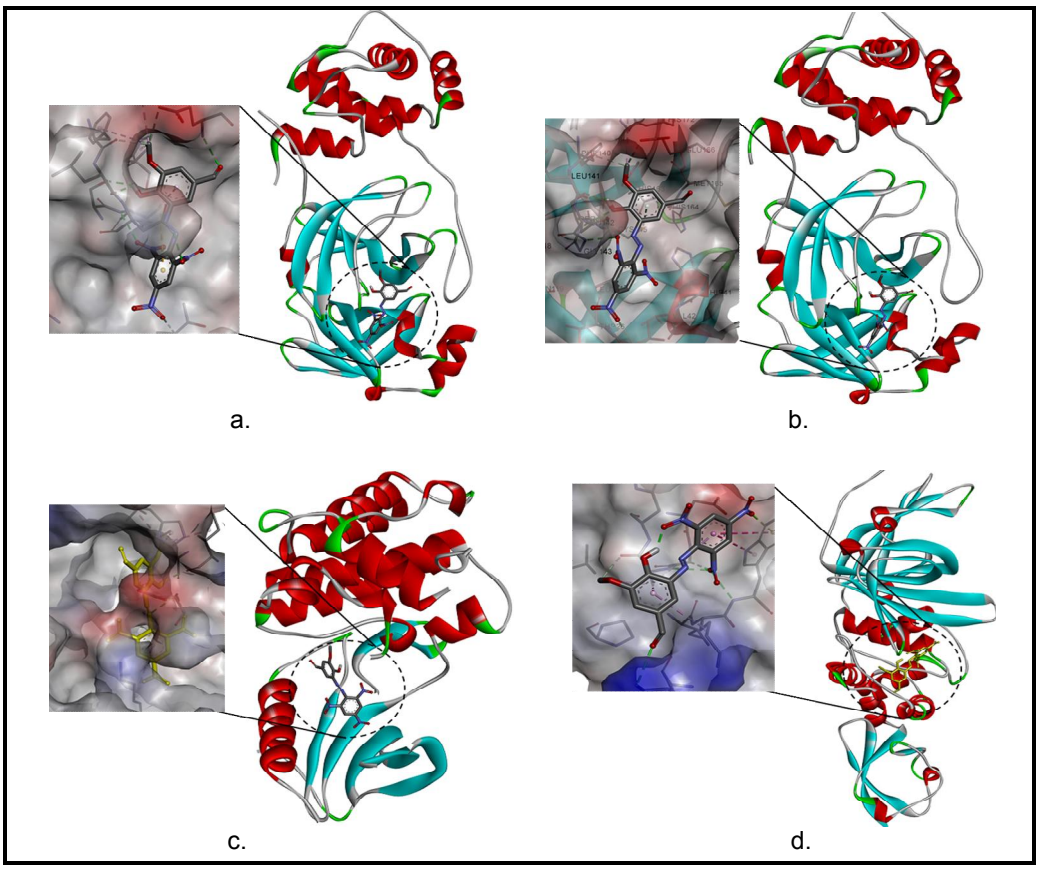

Fig. 3. The docked diazo dye 5 at the active site with a. COVID-19, b. CLpro, c. RAF and d. PLpro

The docked compound **5** at the PLpro shows that there are hydrogen bonding formed through the nitro functional group at position six with the TRP (A:107), Fig. 2d. The nitro functional group at position two with the TRP (A:107) and the ALA (A:289) residues of the PLpro. The oxygen aldehydic functional group of compound **5** forms hydrogen bonding as acceptor with the LYS (A:95) of the PLpro protein. There are *π*-Alkyl interactions of compound **5** through the phenyl benzaldehyde ring with the LYS (A:106) and the ALA (A:289). There are also *π*-Alkyl interactions of the phenyl trinitro ring with the TRP (A:107) and ALA (A:289) receptors of the PLpro as the viral protein, Fig. 2d.

4. CONCLUSION

As a result, 4-hydroxy-3-methoxy-5-((2,4,6-trinitrophenyl)diazenyl) benzaldehyde **5** shows the highest binding free energy and the lowest inhibition constant K_i with all studied viral proteins than other compounds **2-4**. Including, the lowest inhibition constant K_i occur with the RAF then with COVID-19 protein. For this reason, we suggest that compound **5** may be useful to inhibit the activities of the RAF and COVID-19 as the survival proteins of coronavirus 2 or SARS-CoV-2. Perhaps compound **5** as RAF and COVID-19 inhibitor could be considered a potentially promising candidate for COVID-19 disease, which worth more trials in the future.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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