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Effective biological properties of nitrogen-containing compounds

J. Lesy Josephine[a,b], G. Sujatha[c], K. Thanigaimani[a*], P. Ramanathan[c]

[a*]Department of Chemistry, Government Arts College, (Affiliated to Bharathidasan University, Trichirappalli), Tiruchirappalli – 620 022, Tamilnadu, India

[b]Department of Chemistry, Immaculate College for Women, (Affiliated to Annamalai University), Manjakuppam, Cuddalore – 607 001, Tamilnadu, India

[c]PG & Research Department of Chemistry, Thanthai Hans Roever College (Autonomous), (Affiliated to Bharathidasan University, Trichirappalli), Perambalur - 621220, Tamilnadu, India.

(Corresponding Author Email Id: thanigaimani81@gmail.com)

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Abstract

Understanding drug-receptor interaction is frequently achieved through the use of molecular docking, a recent drug designs technique. Imidazole compounds with substituted moieties were created for this investigation. Molecular docking tests were conducted on all substances to determine their ability to inhibit the 7K3N virus, NSP1 crystal structure. The findings of the molecular docking investigation indicated that every synthetic drug had a low binding energy and a strong affinity for the active pocket, making them potential effective inhibitors of the 7K3N virus.

Keywords: Drug design**,** Imidazole, Molecular Docking, NMR

1. Introduction

The majority of interesting cases in molecular docking investigations involve protein-ligand interactions because of their potential medical implications. A ligand is a little molecule that binds with locations needed by proteins. There are a wide range of likely reciprocal conformations where binding may occur. It's common to refer to these as necessary modes.[1,2] Molecular docking is a commonly used method for drug-receptor interface consideration in modern drug manipulation. Molecular docking is often used to predict the direction in which small molecule medication candidates will bind to their protein targets in order to estimate the size and motion of the small molecule. It offers useful information about the relationships between medicine receptors.

Because of its wide-ranging natural behaviour and use in synthetic chemistry, imidazole and its moieties have become extremely important. A broad range of pharmacological actions are exhibited by imidazole derivatives, including anti-inflammatory,[3,4] antitubercular,[5] antibacterial,[6] anti-pain, anti-convulsant, anti-inflammatory, anti-Parkinson,[7] and anti-inflammatory actions. Due to their important roles in natural systems, particularly in enzymes as proton donors and acceptors, ligand coordination categorization, and bases for charge transfer activities, imidazole and its moieties are extremely important.

Important natural behaviours such as anti-microbial,[8,9] anti-inflammatory,[10,11] anti-cancer,[12] and analgesic properties were demonstrated by pyrazole moieties. This greatly accelerated the development of potentially potent pharmacological medicines that carry pyrazole substituents. The enzyme known by the trivial name glucosamine-6-phosphate synthase (also known as GlmS, GlcN-6-P synthase, or L-glutamine:D-fructose-6P amidotransferase) is a novel target for antifungals.[13] GlcN-6-P synthase catalyses the conversion of fructose 6-phosphate (Fru6P) into glucosamine 6-phosphate in the presence of glutamine, which is the initial step in the metabolism of hexosamine. Prokaryotic and human enzymes differ structurally from one another, which might be used to design specific inhibitors that could act as models for anti-fungal and anti-bacterial medications.[14,15] It is widely acknowledged that even minor adjustments to the targets organisation can have a significant impact on their physiochemical activity and inherent personality.[16–19] A thorough analysis of the literature on the antimicrobial movement of a range of substances shows that ornamental mobility is significantly influenced by the presence of specific pharmacophores, such as imidazole or pyrazole, in many molecules.

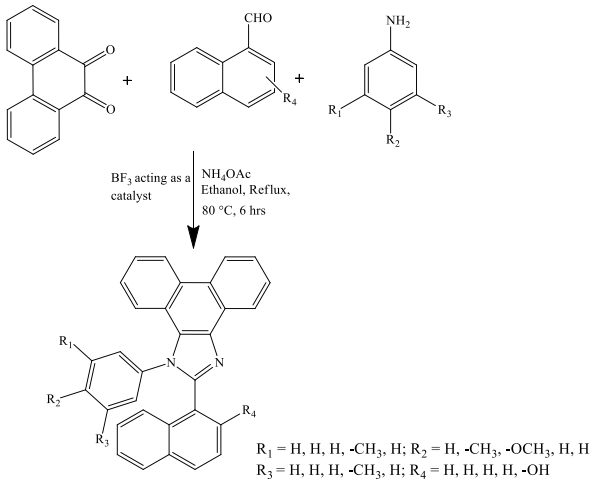
2. Experimental

2.1. Materials and methods

A JASCO FT/IR-4100 spectrophotometer was used to record the IR spectra (in KBr pellets). On a Bruker (400 MHz) NMR spectra of ^{1}H and ^{13}C were obtained (DMSO-d6) with TMS serving as the internal standard. At 70 eV, the mass spectra were captured using a JEOL JMS-D 300 spectrometer.

2.2. General procedure for the synthesis of new derivatives (1-5)

One millimol of diketone, one millimol of aldehyde, one millimol of substituted aryl amine, one millimol of NH_4OAc, and one millimol of BF3 were refluxed for five to six hours at 80 °C. The reaction mixture was allowed to cool once the reaction was finished, and any precipitate was removed by filtering. After adding 300 millilitres of ice water to the filtrate, the precipitated product was filtered and collected. The ethanol–DMF mixture was used to recrystallize the crude product (Scheme 1).



Scheme 1. Synthetic route of nitrogen containing compounds

2.3. Spectral data for synthesized compounds

2-(Naphthalen-1-yl)-1-phenyl-1H-phenanthro[9,10-d]imidazole (1)

^{1}H NMR: δ 8.88 (d, J = 7.6 Hz, 1H), 8.81 (d, J = 8.3 Hz, 1H), 8.76 (d, J = 7.7 Hz, 1H), 7.98 (d, J = 5.6 Hz, 1H),7.84 (d, J = 7.5 Hz, 2H), 7.73 (t, 1H), 7.68 (t, 1H), 7.54 (t, 1H), 7.48-7.43 (m, 3H), 7.35-7.29 (m, 6H). ^{13}C NMR: δ 121.06, 122.89, 123.01, 123.18, 124.16, 124.48, 125.02, 125.64, 126.02, 126.17, 126.34, 126.88, 127.37, 127.44, 128.05, 128.14, 128.34, 128.49, 129.28, 129.48, 129.55, 129.72, 133.22, 133.47, 137.38, 138.04, 150.48. MS: m/z. 420.80 [M^+]

2-(Naphthalen-1-yl)-1-p-tolyl-1H-phenanthro[9,10-d]imidazole (2)

^{1}H NMR: δ 2.32 (s, 3H), 8.87 (d, J = 7.7 Hz, 1H), 8.78 (d, J = 8.3 Hz, 1H), 8.74 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 7.3 Hz, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 7.6 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 7.72 (t, 1H), 7.65 (t, 1H), 7.54 (t, 1H), 7.42 (q, 3H) 7.35-7.24 (m, 4H). ^{13}C NMR: δ 21.31, 121.11, 122.87, 123.12, 123.20, 124.14, 124.51, 124.70, 125.00, 125.10, 125.62, 126.04, 126.14, 126.35, 126.83, 127.39, 127.53, 127.77, 128.15, 128.34, 128.39, 129.28, 129.47, 129.67, 130.21, 133.23, 133.44, 133.76, 135.32, 137.27, 139.28, 150.63. MS: m/z. 434.10 [M^+]

1-(4-Methoxyphenyl)-2-(naphthalen-1-yl)-1H-phenanthro[9,10-d] imidazole (3)

^{1}H NMR: δ 3.72 (s, 3H), 8.97 (d, J = 8.5 Hz, 1H), 8.92 (d, J = 8.3 Hz, 1H), 8.65 (d, J = 7.5 Hz, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.39 (t, 1H), 7.21 (d, J = 8.1 Hz, 1H), 6.95 (d, J = 8.4 Hz, 2H), 7.97 (t, 2H), 7.68 (t, 2H), 7.55-7.42 (m, 5H). ^{13}C NMR: δ 55.28, 114.62, 120.27, 121.98, 122.59, 123.67, 124.42, 124.67, 125.19, 125.60, 125.78, 126.21, 126.69, 126.82, 126.86, 127.24, 127.42, 127.65, 128.04, 128.09, 128.29, 128.41, 129.50, 129.52, 129.72, 129.96, 132.35, 132.76, 136.28, 150.47, 159.47. m/z. 450.50 [M^+].

1-(3,5-Dimethylphenyl)-2-(naphthalen-1-yl)-1H-phenanthro[9,10-d] imidazole (4)

^{1}H NMR: δ 2.17 (s, 6H), 8.96 (d, J = 8.3 Hz, 1H), 8.92 (d, J = 8.1 Hz, 1H), 8.65 (d, J = 7.5 Hz, 1H), 7.98 (t, 2H), 7.92 (d, J = 7.3 Hz, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.73 (d, J = 6.4 Hz, 2H), 7.07 (s, 1H), 7.17 (t, 2H), 7.36-7.40 (m, 3H),7.60-7.48 (m, 3H). ^{13}C NMR: δ 20.54, 120.36, 121.99, 122.45, 123.66, 124.41, 124.66, 125.22, 125.44, 125.66, 125.83, 126.06, 126.22, 126.33, 126.72,

126.76, 127.00, 127.23, 127.45, 127.62, 127.90, 128.03, 128.29, 128.40, 129.54, 131.01, 132.29, 132.75, 136.27, 137.28, 138.90, 150.06. MS: m/z. 448.60 [M^+]

1-(1-phenyl-1H-phenanthro[9,10-d]imidazol-2-yl)naphthalen-2-ol (5)

^{1}H NMR: δ, 13.99 (s, 1H), 8.93 (d, J = 8.5 Hz, 1H), 8.88 (d, J = 9.3 Hz, 1H), 8.77 (d, J = 8.7 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 7.2 Hz, 2H), 7.78 (t, J = 8.8 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.50 (q, J = 8.0 Hz, 3H), 7.40 – 7.38 (m, 6H), ^{13}C NMR: δ 121.07, 122.89, 123.01,123.18, 124.15, 124.48, 125.02, 125.65, 126.03, 126.17, 126.34, 126.88, 127.39, 127.44, 128.05, 128.15, 128.34, 128.49, 129.28, 129.47, 129.55, 129.73, 133.21, 133.48, 137.38, 138.04, 150.48. MS: m/z. 436 [M^+]

2.4. DPPH radical scavenging assay

Using 1,1-diphenyl-2-picrylhydrazil (DPPH), the produced compounds capacity to scavenge free radicals was assessed using a previously described methodology. In summary, 10 mL of a 0.0001M DPPH in DMSO solution was made and mixed with 100 mL of DMSO solutions containing all chemicals at varying concentrations (200, 400, 600, 800, and 1000 µL). After giving the combinations a good shake, they were left to stand for thirty minutes at room temperature. They were then tested for absorbance at 517 nm with a UV-VIS spectrophotometer. The reference utilised was ascorbic acid. Higher free radical scavenging activity is shown by reaction mixture absorbance values that are lower. The following formula was used to determine the capacity to scavenge the DPPH radical:

DPPH scavenging effect (% inhibition) = [A_0-A_t/ A_0] x100, Where A_0 is the absorbance of control and A_t is the absorbance of tested samples at particular time. The concentration of a substance needed to prevent 50% of DPPH• formation is known as its IC50 value.

2.5. Anti- inflammatory activity

The reaction contained 1% bovine albumin fraction solution and test extracts. A small amount of HCl was added to the reaction pH at 37 °C. Aspirin was utilised as a standard medication and the extracts were incubated for 20 minutes at 37 °C, followed by 20 minutes at 51 °C. After cooling, the turbidity was measured spectrophotometrically at 660 nm.

% of inhibition = (OD of Control - OD of Sample / OD of Control) X 100.

2.6. Molecular docking Studies

Replication of molecular docking was done using the Argus Lab 4.0. The 3D structures that were ready were obtained from the protein data bank (http://www.rcsb.org/pdb), and the option "Making binding site for this protein" was selected to prepare the binding site. The ligand was added, and the shape-based search method and A Score scoring function allowed the docking computation to proceed. The evaluation of the energy between the ligand and protein target is the responsibility of the scoring purpose. By building grids larger than the protein's binding locations and establishing energy-based alternation for the ligand cluster of atoms without rotatable links, flexible docking was made possible. The docking development generates torsions and produced poses (conformation) for each rotation. The majority appropriate binding conformation was selected based on the hydrogen bond contact between the protein and ligand near the substrate binding site, and the optimal docking model was selected based on the lowest

binding energy determined by arguslab. While elevated energy results in imbalanced conformations, lowest energy poses indicate the maximum binding similarity. The subsequent receptor representation was stored in the Brookhaven PDB file from the file that Discovery Studio 4.5 versions used to view the 2D and 3D interactions.

3. Result and Discussion

3.1. Anti-Oxidant activity by DPPH scavenging assay method

The percentage activity of imidazole derivatives **1–5** in DMSO solution was measured and contrasted with ascorbic acid, the internal standard. When compared to ascorbic acid, compounds **3** and **5** in the result exhibit the highest levels of antioxidant activity; their respective IC50 values are 141.23 and 92.63 mg/ml. The strongest molecules have methoxy and hydroxyl groups as substituents, and even at extremely low concentrations, they exhibit good antioxidant action. Cytotoxicity of compound **3** for 200 mg/ml as 50%, 400 mg/ml as 65%, 600 mg/ml as 75%, 800 mg/ml as 85% and 1000 mg/ml as 95% whereas **5** for 200 mg/ml as 55%, 400 mg/ml as 66%, 600 mg/ml as 76%, 800 mg/ml as 85% and 1000 mg/ml as 90%, respectively. Ascorbic acid at doses of 200, 400, 600, 800, and 1000 mg/ml is used to compare all of the inhibitory values. As a result, the assay offered sequential information on the materials reactivity with a steady free radical. In the process of examining the anti-oxidant activity technique, the compounds ability to inhibit the DPPH scavenging assay was investigated. Compounds **3** and **5** have the highest level of antioxidant activity out of all the five. Figure 1 displays the graphical representation of the % inhibition at various doses (Table 1) of compounds **1–5**.

Table 1. Compounds **1–5** antioxidant properties as determined by the DPPH scavenging test method

S.No.	**Concentration of the Sample (**mg **/ml)**	**% of Inhibition**					
		1	**2**	**3**	**4**	**5**	**Ascorbic acid**
1	200	23	30	50	15	55	40
2	400	46	40	65	26	66	50
3	600	55	55	75	35	76	60
4	800	66	68	85	49	85	75
5	1000	70	70	95	59	90	80
IC_{50} value		564.91	551.85	141.23	837.83	92.63	391.30

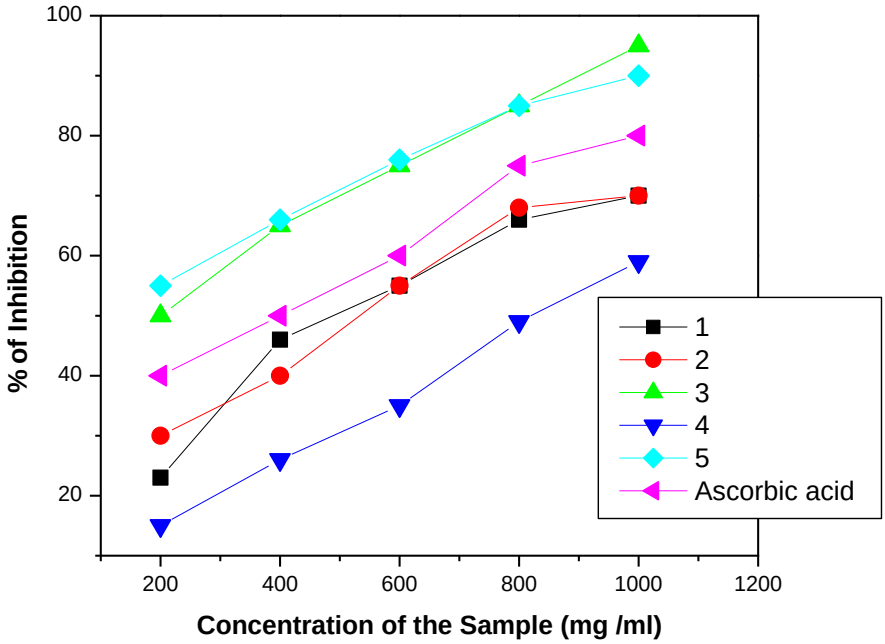


Figure 1. The percentage of inhibition for moieties **1–5** at various doses

3.2. Anti- inflammatory activity

Denaturation of protein is responsible for the production of autoantigen in certain cases of arthritic illness. Denaturation is achieved via altering hydrophobic, disulfide, and electrostatic hydrogen bonds. As can be shown in Table 2 and Figure 2, aspirin was utilised as a common anti-inflammatory medication. There was agreement on the protein denaturation technique at 100, 200, 300, 400, and 500 µg/ml. Comparing the synthetic molecules 3, 4, and 5 to regular aspirin, the former exhibits more action. Compound **3** the % of cytotoxicity for 100 µg/ml as 50 %, 200 µg/ml as 60%, 300 µg/ml as 70.3%, 400 µg/ml as 80.6 and 500 µg/ml as 95% and compound **4** and **5** % of cytotoxicity for 100 µg/ml as 45 %, 200 µg/ml as 56%, 300 µg/ml as 66%, 400 µg/ml as 78 % and 500 µg/ml as 85 %; cytotoxicity for 100 µg/ml as 50%, 200 µg/ml as 60%, 300 µg/ml as 75%, 400 µg/ml as 80% and 500 µg/ml as 98%. For all other drugs with lesser activity, these inhibition values are compared to those of aspirin. When the isolated compound's concentrations are 100, 200, 300, 400, and 500 µg/ml and its percentage of cytotoxicity values are compared with aspirin, albumen denaturation significantly changes. According to in-vitro investigations on anti-inflammatory effect, the compound's inhibition % using the albumen denaturation method is indicated. Moieties **3, 4,** and **5** have larger inhibition percentages than the other compounds.

Table 2. Compounds **1–5** anti-inflammatory properties

S.No.	**Concentration of the Sample (µg /ml)**	**% of Protein Denaturation**					
		1	**2**	**3**	**4**	**5**	**Aspirin**
1	100	12	18	50	45	50	40
2	200	24	28	60	56	60	52

3	300	36	39	70.3	66	75	64
4	400	45	46	80.6	78	80	70
5	500	55	59	95	85	98	85
	IC_{50} value	445.79	420.19	108.49	145.28	113.79	172.72

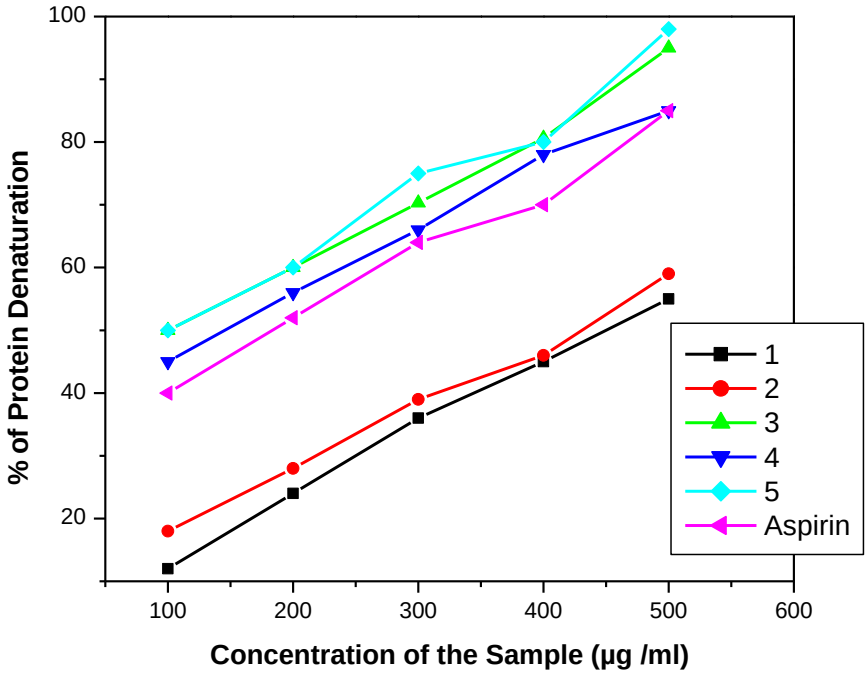


Figure 2. Compounds **1–5** ability to reduce inflammation

3.3. Molecular docking studies compounds 1-5

Score for docking energy

Compounds **1** - **5** were examined using insilico molecular docking in respect to the NSP1 crystal structure from SARS-CoV-2 (PDB ID: 7K3N). The crystal structure of NSP1 from the SARS-CoV-2 optimisation (PDB ID: 7K3N) has binding affinities of -3.48, -4.60, -4.85, -3.43, and -5.17 kcal, in that order (Figure 3). Compound 4 with a methoxy substitution has superior potential inhibitory effects against the corresponding virus. From the docking visualization of Crystal Structure of NSP1 from SARS-CoV-2 (PDB ID: 7K3N), the docked ligands **1-5** is bound within the Vander Waals interaction consisting of amino acids viz. ARG A 110, TYR A 109, LEU A 12, VAL A 45, GLN A13 (**1**); LEU A 52, GLU A 93, THR A 94, GLY A 92, LYS A 63, GLN A 87, GLY A 85 (**2**); TYR A 109, ARG A 64, GLU A 46, VAL A 75, GLU A 48, VAL A 47 (**3**); TYR A 109, ARG A 64, GLU A 93, LEA A 95, THR A 94, GLU A 48, VAL A47 (**4**) and GLN A 13, LEU A 12, VAL A 14, VAL A 45, TYR A 109 (**5**). The ring shows Pi-bond interaction of compounds **1-5** are GLU A 46 (**1**); GLU A 82 (**2**); ARG A 110, GLU A 93 (**3**); ARG A 110, GLU A 46 (**4**); GLU A 46 (**5**). The ring compounds **1** and **5** shows the better Pi-sigma bond interaction protein of VAL A 107 (Figure 4) (Table 3).

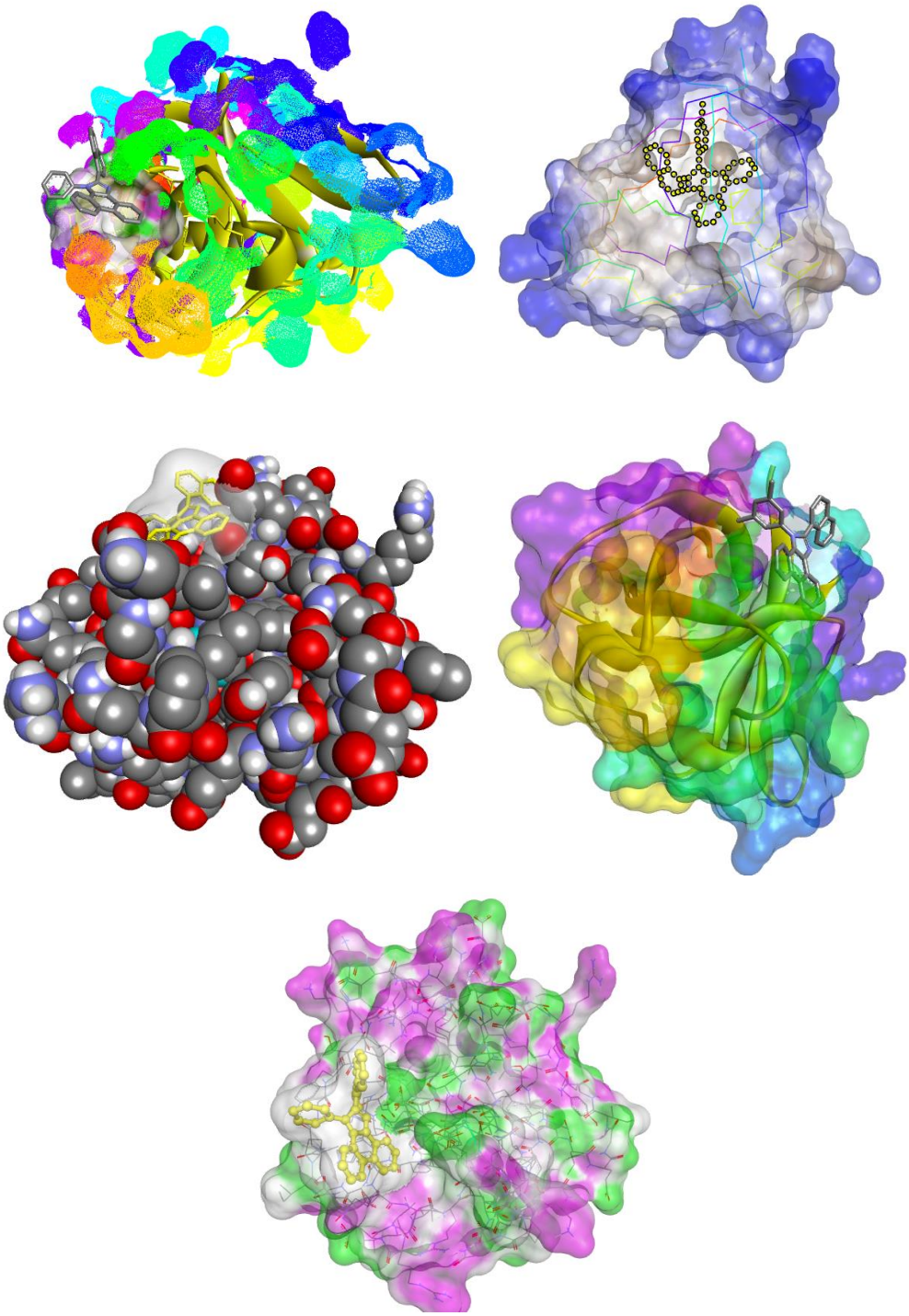


Figure 3. 3D binding interactions between **1–5** and the 7K3N receptor's active site residues

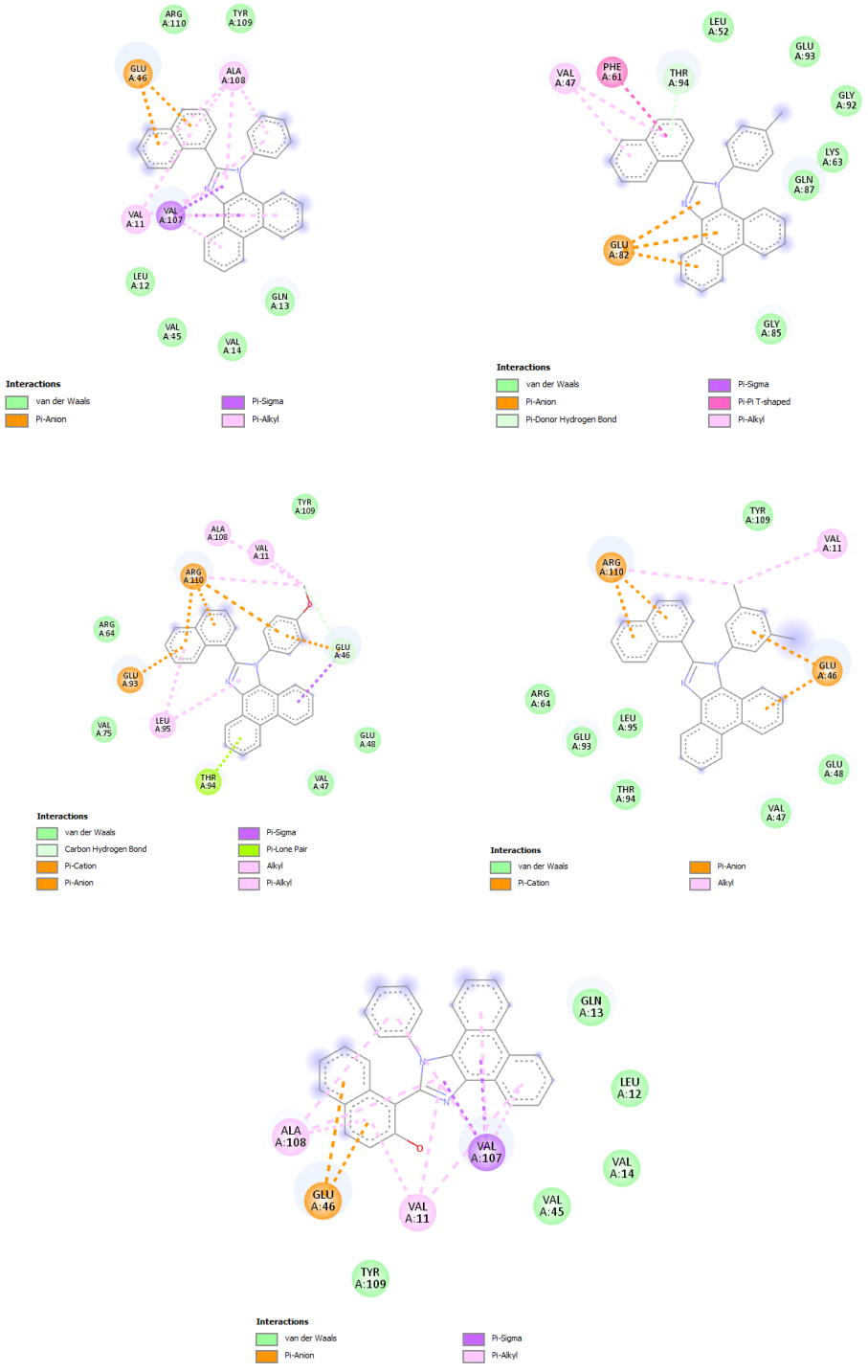


Figure 4. Potential interactions between substances **1–5**

Table 3. Docking score, bonding energy of hydrogen, combining energy, Van der Waals, Pi-bond and Pi-sigma bond interactions of moieties **1-5**

Compds.	Docking	H –	Binding	Vander Waals	Pi-bond	Pi-sigma

	score	bonding energy (kcal/mol)	energy (kcal/mol)	interaction	interaction	bond interaction
1	-5.59	-3.51	-3.48	ARG A 110, TYR A 109, LEU A 12, VAL A 45, GLN A13	GLU A 46	VAL A 107
2	-6.25	-5.28	-4.60	LEU A 52, GLU A 93, THR A 94, GLY A 92, LYS A 63, GLN A 87, GLY A 85	GLU A 82	-
3	-5.69	-4.72	-4.85	TYR A 109, ARG A 64, GLU A 46, VAL A 75, GLU A 48, VAL A 47	ARG A 110, GLU A 93	-
4	-5.99	-3.80	-3.43	TYR A 109, ARG A 64, GLU A 93, LEA A 95, THR A 94, GLU A 48, VAL A47	ARG A 110, GLU A 46	-
5	-5.47	-5.15	-5.17	GLN A 13, LEU A 12, VAL A 14, VAL A 45, TYR A 109	GLU A 46	VAL A 107

4. Conclusion

The strongest molecules have methoxy and hydroxyl groups as substituents, and even at extremely low concentrations, they exhibit good antioxidant action. Cytotoxicity of compound **3** for 200 mg/ml as 50%, 400 mg/ml as 65%, 600 mg/ml as 75%, 800 mg/ml as 85% and 1000 mg/ml as 95% whereas **5** for 200 mg/ml as 55%, 400 mg/ml as 66%, 600 mg/ml as 76%, 800 mg/ml as 85% and 1000 mg/ml as 90%, respectively. According to in-vitro investigations on anti-inflammatory effect, the compounds inhibition % using the albumen denaturation method is indicated. Moieties **3, 4**, and **5** have larger inhibition percentages than the other moieties. The Crystal Structure of NSP1 from SARS-CoV-2 (PDB ID: 7K3N) optimisation has binding affinities of -3.48, -4.60, -4.85, -3.43, and -5.17 kcal, in that order. Compound 4 with a methoxy substitution has superior potential inhibitory effects against the corresponding virus.

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Conflict of interests

The authors declare that there is no conflict of interests.

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