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COMBINATION AND MOLECULAR DOCKING STUDIES OF 1,2,3-TRIAZOLE, PYRIMIDIN-2-THIONE RINGS FOR POTENTIAL ANTI-COVID-19 ACTIVITY

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Abstract:
A combination of 1,2,3-triazole and pyrimidin-2-thione moieties in the same matrix was achieved via a multi-step synthetic pathway. The target novel 1,2,3-triaozle-pyrimidin-2-thione derivatives 4a-f were obtained via the condensation reaction of the synthesized chalcones 3a-f with thiourea in the presence of sodium hydroxide. Compounds 4a-f were characterized by FT-IR, ^{1}H-NMR and ^{13}C-NMR spectroscopies. The biological activity of the synthesized compounds 4a-f and their precursors 3a-f as antiviral was studied by molecular docking analysis against two selected enzymes (7dpp and 8cx9) which play an essential role in SARS-CoV-2 replication. Practically, the results revealed that all the synthesized compounds 4a-f and their precursors 3a-f displayed a promising binding affinity into the active site pocket through the target proteins compared to Remdesivir, X77 and N3 as standard antiviral drugs.

Keywords: Heterocyclic Compounds, 1,2,3-Triazole, Chalcones, Pyrimidines, SARS-COV2, COVID-19, Molecular docking, Antivirals.

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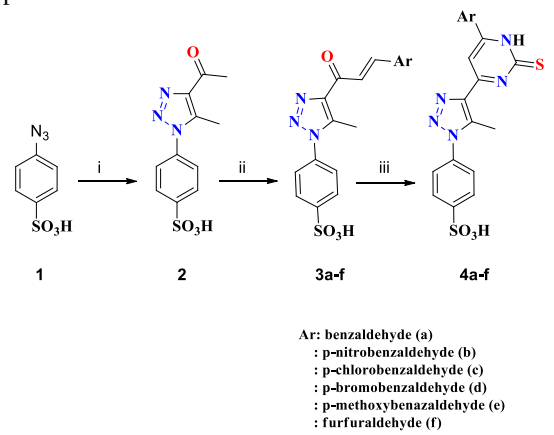
Introduction

Coronavirus disease (COVID-19) also known as the coronavirus pandemic caused by the virus severe acute respiratory syndrome SARS-CoV-2 [1][2]. It was first identified in the Chinese cities of Wuhan in December 2019 as spreadable and contagious disease [3]. On 11 March 2020, the World Health Organization recognized COVID-19 as a pandemic disease and it promptly spread worldwide [4]. Up to now, COVID-19 is still a global public health concern with no approved effective and safe drugs have been introduced despite continued attempts to discover new drugs to treat this disease. This has motivated researchers to continue in search to discover effective and non-toxic treatments for this fast spreading virus. As the field of heterocyclic chemistry offers a wide range of compounds having different biological activities [5][6][7], comprehensive review indicates that nitrogen-containing heterocycles including 1,2,3-triazole and pyrimidine moieties have shown an effective activity against coronaviruses [8][9][10][11]. Structurally, 1,2,3-triazole ring system is one of a pair of structural isomers of the chemical formula $C_2H_3N_3$ as an aromatic five-membered heterocycle with three neighboring nitrogen atoms located at 1-,2-,3-postions [12][13][14]. Characteristically, 1,2,3-triazole is as rigid link units mimic the electronic properties of amide bonds with bioisosteric effects [15]. Moreover, it is stable toward metabolic degradation and chemical hydrolysis [8]. In addition, 1,2,3-triazole structure display the ability for interplaying with biomolecular targets due to its high dipole moment and the adequacy for hydrogen bond formations and π–π stacking interactions [16]. Synthetically, the construction of 1,2,3-triazole ring system is currently achieved through 1,3-dipolar cycloaddition reactions of organic azides with alkynes or activated alkenes under different conditions to give regioselective 1,4-disubstitued-1,2,3-triazole derivatives [17][18][19]. On the other hand, pyrimidine structure is a heterocyclic aromatic organic similar to benzene and pyridine containing two nitrogen atoms at 1- and 3-positions to present m-diazine derivative [20][21]. Characteristically, pyrimidine ring is a weak base (pKa 1.1) and has a high dipole moment that subtends π-π stacking interactions with dual hydrogen-bonding capacity that are required to form drug-target interactions [22]. Compounds containing pyrimidine moiety are of great interest in medicinal field because pyrimidines constitute an important class of natural such as thymine, uracil and cytosine that are found as building units in nucleic acids [23]. In addition, many synthetic compounds containing pyrimidine moiety such as barbituric acid and veranal which are used as hypnotics, thus, it is based compounds exhibit diverse a wide range of therapeutic applications [24][25]. Synthetically, the reaction of α,β-unsaturated ketones (Chalcones) with thiourea under acidic or basic conditions is the common method used to incorporate 2-pyrimidin-2-thione ring to the target compounds [26]. An interesting addition, it is known that nitrogen containing heterocycles core can exhibit supramolecular assembly through hydrogen bonding formation and π-π stacking interactions [27]. Nowadays, possible biological applications are predicated by exploiting molecular docking analysis using computer-aided online software [28]. In view of the above, the current work is aimed to combine of 1,2,3-triazole and pyrimidin-2-thione motifs in the same matrix to examine the new compounds activity against active sites of SARS-COV2 proteases by molecular docking analysis.

Results and Discussion

Chemistry: Regarding to our interest in the synthesis and biological properties study of new 1,2,3-triazole derivatives [29][30][31][32], the novel 1,2,3-triazole-pyrimidin-2-thione derivatives were designed for antiviral investigations. As compounds **3a-f** have synthesized in our lab as reported in the literatures [33][34][35], thus, they were used as starting materials in an attempt to synthesize the target compounds **4a-f**. Practically, the synthesis involved refluxing of compounds **3a-f** with thiourea in ethanol for 6.0 hours in the presence of an aqueous solution of sodium hydroxide. This reaction resulted in constructing the target pyrmidin-2-thione ring system to give the target compounds **4a-f** as shown in Scheme 1.



Scheme 1: i) Acetylacetone, Et_3N, DMF; ii) an appropriate aldehyde, aq. NaOH, H^+; iii) Thiourea, aq. NaOH, H^+.

The reaction progress was monitored by TLC technique and by the first time, it was successful to give the target compounds **4a-f** as pure solids in high yields. Structure of the synthesized compounds **4a-f** was confirmed by FT-IR, ^{1}H-NMR and ^{13}C-NMR spectra. Mainly, FT-IR spectra indicate disappearing of the absorption band belong to the carbonyl group of chlacones **3a-f** at 1660-1668 cm^{-1} along with the appearance of new absorption bands at 3211-3299 cm^{-1}, 1660-1681 cm^{-1} and 1167-1116 cm^{-1} that could be imputed to NH, C=N and C=S groups which are incorporated into pyrimidin-2-thione ring system, respectively. Other functional group displayed their absorption band at their expected frequencies. ^{1}H-NMR spectra of compound **4a-f** indicated the absence of the signal of protons of α, β-unsaturated ketone group of compounds **3a-f**. This absence is associated with appearance of new singlet peak at 5.00-6.59 ppm which is attributed to proton of (=CH) group of pyrimidin-2-thione ring. On the other hand, protons of other groups were appeared at their expected chemical shifts with correct integral as mentioned experimental part. Moreover, ^{13}C-NMR spectra of compounds **4a-f** clearly indicated the disappearance of peak C=O of chalcones associated with the appearance of a new peak at δ=173.42-173.47 ppm and 95.8-114.4 ppm which belong to carbon atoms of C=S and CH= groups, which incorporated into pyrimidin-2-thione ring, respectively depending on its chemical structure. In addition, other carbon exhibited their peaks at their expected chemical shifts with correct integral. Synthesis of compounds **4a-f** takes advantage that these besides 1,2,3-trioalze ring and pyrmidin-2-thione ring are containing sulfonic acid group which possess the salt formation feature. Importantly, salt formation is a useful approach for optimizing the physicochemical, water solubility and biopharmaceutical or therapeutic properties of the target compounds as sulfa drugs [36].

Molecular Docking Analysis: The purpose of this docking study, at this critical time, is to examine how 1,2,3-triazole-pyrimidin-2-thione derivatives based ligands might approach the active site of the main protease for Covid-19. In a simple definition, docking is a molecular modeling technique that is used to predict how a protein (enzyme) interacts with small molecules (ligands) [37], molecular docking was primarily designed to predict the binding of small drug-like molecules to target proteins [38]. Molecular docking has become an important common component of the drug discovery toolbox, and its relative low-cost implications and perceived simplicity of use has stimulated an ever-increasing popularity within academic communities [39]. In the current research, binding affinity and docking interactions for the potential antiviral activity between the synthesized compounds **3a-f** and **4a-f** and two selected proteins (7dpp and 8cx9) were analyzed using PyRx software compared to three selected standard antivirals; Remdesivir [40], X77 [41] and N3 [42]. In general, all the synthesized compounds **3a-f** and **4a-f** showed a good binding affinities with the active sites of the target proteins. Interestingly, these binding affinities are higher than those recorded for the standard antivirals drugs as shown in Table 1. Furthermore, the data also showed that compounds **4a-f** displayed higher binding affinity values than their precursors **3a-f**, this can be imputed to the existence of the secondary amine group (NH) and thiocarbonyl group (C=S) of pyrimidin-2-thione ring, which facilitated more binding affinity with the key amino acids of the tested proteins through hydrogen bonding formation and hydrophobic interactions.

Table 1. Docking scores of the synthesized compounds **(3a-f** and **4a-f)** and three selected standard drugs with 7dpp and 8cx9 proteins.

No. Comp.	Docking Score (kcal/mol) with 7dpp	Docking Score (kcal/mol)with 8cx9
3a	**-7.2**	**-7.7**
3b	**-7.4**	**-8.8**
3c	**-7.3**	**-8.2**
3d	**-7.4**	**-8.3**
3e	**-7.2**	**-7.7**
3f	**-7.6**	**-7.8**
4a	**-8.1**	**-8.3**
4b	**-7.1**	**-8.4**
4c	**-7.1**	**-8.1**
4d	**-7.2**	**-8.2**
4e	**-6.8**	**-7.8**
4f	**-7.8**	**-7.9**
Remdesivir (Standard drug)	**-7.1**	**-7.4**
X77 (Standard drug)	**-5.7**	**-7.6**
N3 (Standard drug)	**-3.2**	**-7.8**

Among compounds **3a-f,** compound **3b** that is bearing nitro group (NO_2) displayed the best binding affinity by -8.8 kcal/mole with protein 8cx9. This result can be explained that this compound possess more active sites to

form conventional hydrogen bonding interactions with active sites of the amino acids; Glu307, Lys306, Asp164 and hydrophobic interactions with active sites of the amino acids; Tyr213, Gly256, Thr257, Phe258, Tyr171, Thr259, Glu167, Thr168, Cys155, Asp164, Gly163, Lys 157, Leu162, Glu161, Lys306, Glu307 as shown in Figure 1. While, for protein 7dpp, compound **4f** that containing furan moiety displayed the highest binding affinity by -7.6 kcal/mole, which can be assigned to the conventional hydrogen bonding interactions with active sites of amino acids; Gly143, Leu141, Ser144 and hydrophobic interactions with the amino acids; Asn142, Leu141, His164, Ser144, Phe140, Glu166, Gln189, Gln192, Thr190, Pro168, Met165, His 163, Cys145, Gly143 as shown in Figure 1. On the other hand, among compounds **4a-f**, compound **4b** displayed the best binding affinity by -8.4 kcal/mole with protein 8cx9, which can be imputed to higher degree of the conventional hydrogen bonding interactions at active sites of the amino acids Lys232 (2.86 A^o), Tyr207 (2.96 A^o), Met208 (2.93 A^o) and hydrophobic interactions at active sites of the amino acids; Ala141, Met208, Val202, Met206, Ser170, Glu203, Asn99, Tyr171, Lys 279, Glu167, Gly100, Gln97, Ile222, Gly209, Lys 232, Tyr207 as shown in Figure 2. With protein 7dpp, compound **4a** displayed the highest binding affinity value by -8.1 kcal/mole, which can have explained depending on the conventional hydrogen bonding interactions at active sites of the amino acids; Thr190 (2.94 A^o) and hydrophobic interactions at active sites of the amino acids; Gln192, Leu167, pro 168, Met 165, Asn142, Gly143, Leu141, Ser144, Cys145, Glu166, Gln189, Thr190 as shown in Figure 2 .

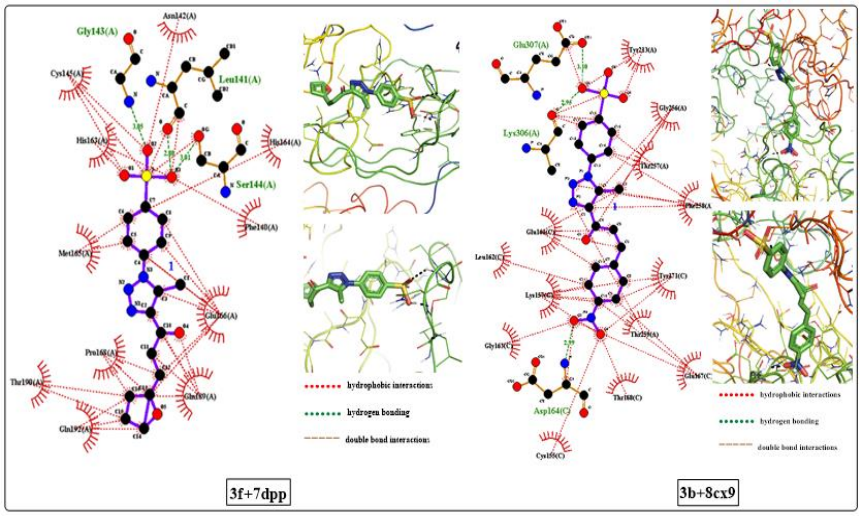


Figure 1: The best binding affinity of the newly synthesized compounds **3a-f** with the tested proteins.

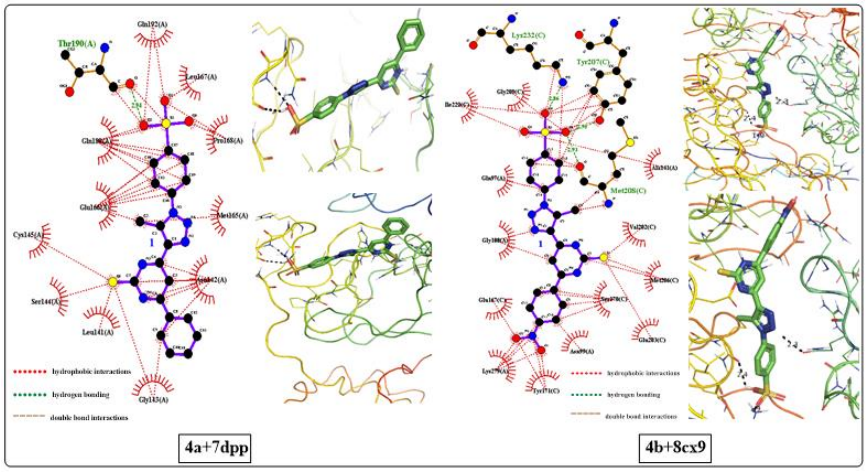


Figure 2. The best binding affinity of the newly synthesized compounds **4a-f** with the tested proteins.

Experimental Part

Chemicals and Instruments

All chemicals and solvents were supplied from available sources and used as received without further purification. The progress of all the reactions were monitored by TLC technique. The FT-IR spectra were recorded on a Shimadzu FT-IR 8400 spectrometer in KBr discs. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 400 MHz, 101 MHz, respectively on avance new spectrometer using DMSO-d_6 as a solvent and TMS as the internal standard.

Procedures:

General procedure for the synthesis of compounds 4a-f: An aqueous solution of sodium hydroxide (10.0 ml, 15.0 mmol) was added slowly to a mixture of an appropriate chalcone **3a-f** (5.0 mmol) and thiourea (0.38 g, 5.0 mmol) in ethanol (25 mL). The resulted mixture was then refluxed for 6.0 hours. The reaction mixture was then evaporated to a half before being neutralized with a diluted solution of hydrochloric acid. The resulted mixture concatenated to dryness and the residue was triturated in hot methanol and filtered. Methanol was removed on rotary evaporator and the solid product was collected to obtain the target compounds **4a-f**.

Synthesis of 4-(5-methyl-4-(6-phenyl-2-thioxo-1,2-dihydropyrimidin-4-yl)-1H-1,2,3-triazol-1-yl) benzene sulfonic acid 4a: It was prepared by using compound **3a** (1.85 g, 5.00 mmol); Yield (1.77 g, 83.09%) as a dark orange powder. FT-IR (KBr disc, cm^{-1}), 3439 (OH, SO_3H), 3299 (N-H), 3167 (Ar-H), 1670 (C=N), 1658 (C=C, pyrimidin-2-thione ring), 1599 (C=C, triazolyl), 1552 (Ar, C=C), 1500 (-N=N), 1228 (C-N), 1035 (C=S). ^{1}H-NMR (400 MHz, DMSO-d_6): δ(ppm)= 2.59 (s, 3H, CH_3), 6.57 (s, 1H, -CH= of pyrimidin-2-thione ring), 7.36-7.86 (m, 9H, Ar-H), 8.02 (s, 1H, NH).^{13}C-NMR (101 MHz, DMSO-d_6): δ(ppm)= 10.22, 95.90, 125.45, 127.31, 127.58, 131.21, 132.35, 135.65, 136.30, 137.06, 139.49, 143.96, 163.00, 166.23, 173.45.

Synthesis of 4-(5-methyl-4-(6-(4-nitrophenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl)-1H-1,2,3-triazol-1-yl) benzenesulfonic acid 4b: It was prepared by using compound **3b** (2.08 g, 5.00 mmol); Yield (2.15 g, 91.49 %) as a brown powder. FT-IR (KBr disc, cm^{-1}), 3417 (OH, SO_3H), 3215 (N-H), 2991 (C-H, Ar-H), 1660 (C=N), 1641 (C=C, pyrimidin-2-thione ring), 1626 (C=C, triazolyl), 1556 (Ar, C=C), 1510 (-N=N), 1222 (C-N), 1035.81 (C=S), 1523 and 1472 (NO_2). ^{1}H-NMR (400 MHz, DMSO-d_6): δ(ppm)= 2.59 (s, 3H, CH_3), 6.57 (s, 1H, -CH= of pyrimidinthione ring), 7.53-7.85 (m, 8H, Ar-H), 8.25 (s, 1H, NH).^{13}C-NMR (101 MHz, DMSO-d_6): δ(ppm)= 10.24, 95.92, 124.27, 125.47, 127.33, 131.23, 132.37, 135.67, 137.08, 139.51, 143.98, 149.21, 163.02, 166.25, 173.47.

Synthesis of 4-(4-(6-(4-chlorophenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl)-5-methyl-1H-1,2,3-triazol-1-yl) benzene sulfonic acid 4c: It was prepared by using compound **3c** (2.02 g, 5.00 mmol); Yield (1.92 g, 83.47 %) as a yellow powder. FT-IR (KBr disc, cm^{-1}), 3439.19, pyrimidin-2-thione ring), 1599 (C=C, triazolyl), 1552 (Ar, C=C), 1502 (-N=N), 1222 (C-N), 1072 (C=S), 840 (C-Cl). ^{1}H-NMR (400 MHz, DMSO-d_6): δ(ppm)= 2.59 (s, 3H, CH_3), 6.57 (s, 1H, -CH= of pyrimidin-2-thione ring), 7.36-7.86 (m, 8H, Ar-H), 8.01 (s, 1H, NH).^{13}C-NMR (101 MHz, DMSO-d_6): δ(ppm)= 10.24, 95.92, 118.45, 125.47, 127.33, 131.23, 132.37, 135.67, 136.32, 137.08, 139.51, 143.98, 163.02, 166.25, 173.47.

Synthesis of 4-(4-(6-(4-bromophenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl)-5-methyl-1H-1,2,3-triazol-1-yl) benzene sulfonic acid 4d: It was prepared by using compound **4d** (2.42 g, 5.00 mmol); Yield (2.4 g, 95.16 %) as a yellow powder. FT-IR (KBr disc, cm^{-1}), 3425 (OH, SO_3H), 3217 (N-H), 3014 (C-H, Ar-H), 1660 (C=N), 1637 (C=C, pyrimidin-2-thione ring), 1599 (C=C, triazolyl), 1552 (Ar, C=C), 1502 (-N=N), 1222 (C-N), 1035 (C=S), 578 (C-Cl). ^{1}H-NMR (400 MHz, DMSO-d_6): δ(ppm)= 2.59 (s, 3H, CH_3), 6.59 (s, 1H, -CH= of pyrimidin-2-thione ring), 7.35-7.86 (m, 8H, Ar-H), 8.13 (s, 1H, NH).^{13}C-NMR (101 MHz, DMSO-d_6): δ(ppm)= 10.21, 95.89, 124.24, 124.81, 125.44, 131.20, 132.34, 135.64, 136.29, 137.05, 139.48, 143.95, 162.99, 166.22, 173.44.

Synthesis of 4-(4-(6-(4-methoxyphenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl)-5-methyl-1H-1,2,3-triazol-1-yl) benzene sulfonic acid 4e: It was prepared by using compound **3e** (2.00 g, 5.00 mmol); Yield (1.98 g, 86.84 %) as a red-brown powder. FT-IR (KBr disc, cm^{-1}), 3423 (OH, SO_3H), 3277 (N-H), 2991 (C-H, Ar-H), 1680 (C=N), 1649 (C=C, pyrimidin-2-thione ring), 1604 (C=C, triazolyl), 1558 (Ar, C=C), 1506 (-N=N), 1222 (C-N), 1039 (C=S). ^{1}H-NMR (400 MHz, DMSO-d_6): δ(ppm)= 2.53 (s, 3H, CH_3), 3.45 (s, 3H, OCH_3), 5.00 (s, 1H, -CH= of pyrimidin-2-thione ring), 6.53 (s, 1H, NH), 6.57-7.71 (m, 8H, Ar-H), ^{13}C-NMR (101 MHz, DMSO-d_6): δ(ppm)= 10.19, 65.69, 95.87, 118.40, 124.22, 125.42, 127.28, 131.18, 132.32, 137.03, 139.46, 143.93, 150.44, 162.97, 166.20, 173.42.

Synthesis of 4-(4-(6-(furan-2-yl)-2-thioxo-1,2-dihydropyrimidin-4-yl)-5-methyl-1H-1,2,3-triazol-1-yl) benzene sulfonic acid 4f: It was prepared by using compound **3f** (1.80 g, 5.00 mmol); Yield (1.66 g, 79.80 %) as a black powder. FT-IR (KBr disc, cm^{-1}), 3414 (OH, SO_3H), 1656 (C=C, pyrimidin-2-thione ring), 1626 (C=C, triazolyl), 1556 (Ar, C=C), 1506 (-N=N), 1219 (C-N), 1124 (C-O), 1035 (C=S). ^{1}H-NMR (400 MHz, DMSO-d_6): δ(ppm)= 2.54 (s, 3H, CH_3), 5.00 (s, 1H, -CH= of pyrimidin-2-thione ring), 6.57-6.59 (t, J=10.4 Hz, 1H, C-CH= furan moiety), 7.39 (s, 1H, NH), 7.61-7.69 (m, 6H, Ar-H, C-CH= furan moiety, Ar-H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ(ppm)= 10.23, 114.42, 116.01, 116.79, 125.46, 131.22, 132.36, 137.07, 139.50, 143.98, 146.27, 149.76, 150.48, 163.01, 173.46.

Simulation Studies Using Molecular Docking: This method is used for predicting the best drug candidates based on the scoring. Firstly, the available Chem-draw software was utilized to generate the 3D structures of the synthesized compounds **(3a-f, 4a-f)**. The three-dimensional crystal structures of the SARS-CoV-2 3CL protease (PDB ID: 7dpp) and SARS-CoV-2 PLpro protease (PDB ID: 8cx9) were retrieved from the Protein Data bank (PDB) in PDB format [43] [44]. Unwanted molecules such as H_2O molecules or metal ions in the target proteins were removed [45]. The molecular docking was performed by using PyRx software version 0.8 which works based on the Auto Dock Vina configuration [46]. Both the protein and ligands (compounds **3a-f** and **4a-f**) were independently loaded to the PyRx virtual screening software. The protease proteins were put as fixed, however the synthesized compounds (ligands) had rotatable torsions. Furthermore, the size of the box was designed around the center of protease protein, with an exhaustiveness parameter of 20 A^o for all docking. The best binding affinity ligands were selected for the analysis of the inter-residue interaction. The ligand and protein intermolecular interactions were displayed by the PyMOL tool software.

Conclusions

The present study has effectively integrated 1,2,3-triazole, pyrimidinthione and sulfonic acid moieties into the same matrix using a multi-step synthetic route. The cyclization reaction of the chalcones **3a-f** with thiourea was effectively employed to construct the target pyrimidin-2-thione ring system, resulting in the formation of the desired compounds **4a-f**. Molecular docking analysis demonstrated that the synthesized derivatives **3a-f** and **4a-f** exhibited a high binding affinity to the active sites of the tested proteins. Furthermore, the binding affinities of the target compounds were shown to be superior to those of three commonly used antivirals. Notably, these compounds can promising drugs for antiviral activity.

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