RESEARCH ARTICLE

Synthesis and Molecular Docking Studies of New Pyrimidinone ring Containing 1,2,3-Triazole Derivatives

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ABSTRACT

The current work describes the design, synthesis and molecular mocking studies of a series of new 1,4-disubstituted-1,2,3-triazole linked 2-pyrimidinone derivatives. Firstly, 4-(4-acetyl-5-methyl-1H-1,2,3-triazol-1-yl)benzene sulfonic acid **1** was synthesized as a key starting material. This compound was reacted with a series of aromatic aldehydes under-investigated conditions to give a new series of chalcones 2a-f. Reaction of compounds 2a-f with urea in the presence of an aqueous solution of sodium hydroxide led to the construct 2-pyrimidinone ring system to obtain a series of new compounds containing 1,2,3-triaozle ring and pyrimidinone ring 3a-f. The newly synthesized compounds 2a-f and 3a-f were characterized by FT-IR, ^{1}H-NMR and ^{13}C-NMR spectra. *In-silico* molecular docking simulations, compounds 3a-f and their precursors 2a-f were conducted on two selected proteins: 7dpp and 8cx9. The results revealed that all of the newly synthesized compounds 2a-f and 3a-f displayed have a good binding affinity with the target proteins and higher than values recorded for the selected three standard antiviral drugs.

Keywords: 1,2,3-Triazole, Antivirals, Chalcones, Heterocyclic compounds, Molecular docking, Pyrimidines, Pyrimidinone, SARS-COV2.

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INTRODUCTION

The research in the field of therapeutics is of great importance for reducing human diseases and for the improvement of the quality of human life. Among a wide range of nitrogen-containing heterocycles, 1,2,3-triazole and pyrimidine rings are the most common structural motifs in synthetic and natural bio-active compounds.[1,2] 1,2,3-Triazole ring is an aromatic five-membered heterocycle containing two carbon atoms and three nitrogen atoms located at 1-,2-,3-positions.[3,4] Synthetically, 1,2,3-triazole ring system is easily constructed via 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.[5-8] Characteristically, 1,2,3-triazole ring system is amide bond isosteres to be resistance *the biological* degradation,[9] stable towards chemical hydrolysis, oxidative and reductive conditions.[4] Moreover, 1,2,3-triazole ring system can form interactions via hydrogen bonding Vander-Waals forces, π-π stacking interactions and dipole–dipole bonds with a variety of receptors such as enzymes, proteins and nucleic acids.[10,11] Thus, compounds contain 1,2,3-triazole ring system showing a broad range of pharmaceutical applications such as antioxidant,[12] anticancer,[13] antimicrobial,[14] antiviral,[15] antibacterial[16] and antidiabetic agents.[17,18] On the other hand, pyrimidine ring (1,3-diazine) is an aromatic six-membered heterocycle with two nitrogen atoms located at 1- and 3-positions and alloxan (5,5-dihydroxypyrimidine-2,4,6(1H,3H,5H)-trione) is the first pyrimidine derivative was isolated in 1818 via oxidizing of uric acid with nitric acid.[19] Characteristically, pyrimidine ring is a weak base (pKa 1.31) and has a high dipole moment that subtends π-π stacking interactions with dual hydrogen-bonding capacity that can be of importance in drug-target interactions and is normally stable towards ring-opening reactions.[20] Many efficient synthetic approaches for synthesizing compounds containing pyrimidine ring or its derivatives have been developed and reported.[21,22] However, the reaction of α, β-unsaturated ketones (Chalcones) with urea under acidic or basic conditions is an excellent illustrative method to produce the corresponding 2-pyrimidinone ring.[23,24] Pyrimidine motif and its derivatives are privileged fragments in drug discovery with a wide range of medical applications for example; antioxidant [25] anticancer,[26] antiviral,[27] and anti-inflammatory.[28] Given the above, combining 1,2,3-triazole and pyrimidine motifs in the same matrix was interesting to introduce new compounds with two active sites for potential antiviral applications.

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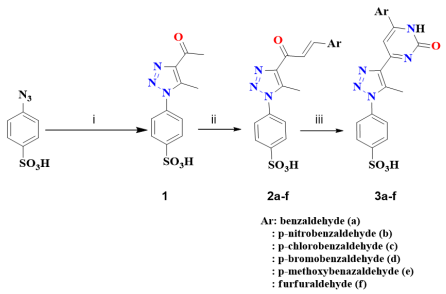
RESULTS AND DISCUSSION

Chemistry

A series of new 1*H*-1,2,3-triazole derivatives containing pyrimidinone ring system were prepared efficiently using a multi-step synthetic pathway as shown in Scheme 1. The key starting material 4-(4-acetyl-5-methyl-1H-1,2,3-triazol-1-yl)benzene sulfonic acid 1 is already synthesized in our lab via reaction of 4-azido benzene sulfonic acid with acetyl acetone in the presence of triethyl amine as described in the literature.[29] Synthesis of compound 1 takes advantage that this compound is containing sulfonic acid group (-SO_3H) that is important to improve water solubility of the synthesized compounds. By the same time, it introduces the bioactive 1,2,3-triazole ring system linked to the methyl ketonic group (-$COCH_3$). Thus, we first focused on checking the chemical reactivity of compound 1 under conditions of the Claisen-Schmidt reaction. The procedure involved treating compound 1 with a series of different aromatic aldehydes in the presence of an aqueous sodium hydroxide towards synthesizing the corresponding chalcones. To achieve this aim, we investigated some parameters such as the concertation of base used as a catalyst, reaction time and reaction temperature.

The reaction progress was monitored by TLC technique. After a few attempts, it was able to choose the best conditions to obtain the target chalcones 2a-f in a simple work-up with a good yield and high purity. The structures of 2a-f were confirmed based on FTIR, ^{1}H-NMR and ^{13}C-NMR spectra analysis. Mainly, their FTIR spectra showed shifting of the absorption band of the carbonyl group (C=O) from 1685 cm^{-1} to 1656 to 1668 cm^{-1} as a result of conjugating with a double bond that be seen at 1556 to 1574 cm^{-1} to indicate that the chalcone structure (-CH=CH-C=O) has been formed. Their ^{1}H-NMR spectra showed the disappearing of the signal peak of protons of methyl ketonic group ($COCH_3$) that seen in spectra of compound 1 at 2.61 along with appearances of new doublet-doublet peaks at 7.39 to 7.86 and 7.56 to 8.08 ppm belong to protons of H-C(α) and H-C(β) of chalcone structure, respectively. Moreover, all the other protons such as protons of methyl group attached 1,2,3-triazole ring, aromatic protons and furfural moiety protons appeared at their expected chemical shifts with a correct integral. In addition, the structure of compounds 2a-f was supported by ^{13}C-NMR spectra that are mainly showed the disappearance the single peak belong to the carbon atom of methyl group that is attached to carbonyl group. As chalcone are starting materials for constructing the pyrimidinone ring, compounds 2a-f were reacted with urea under basic conditions to obtain the target pyrimidinone derivatives 3a-f. The reaction progress was monitored by TLC technique. By the first time, giving the target compounds 3a-f in good yields was successful. FTIR, ^{1}H-NMR and ^{13}C-NMR spectra confirmed the structure of compounds 3a-f. Mainly, FTIR spectra indicate the disappearing of the absorption bands belong to the carbonyl group of chlacones (O=C-C=C) at 1660 to 1668 cm^{-1} along with the appearance of new absorption bands at 3277 to 3356 cm^{-1} and 1701 to 1707 cm^{-1} which can be imputed to amino and carbonyl groups of the functional group (NHCO) that is incorporated into pyrimidinone ring. ^{1}H-NMR spectra of compound 3a-f indicated disappearing signal protons of α, β-unsaturated ketone group associated with new singlet single peak at 4.44 to 6.57 ppm attributed to proton of pyrimidinone ring (-CH=). Moreover, ^{13}C-NMR spectra of compounds 3a-f showed the appearance of new peak at range 95.90 to 114.75 ppm belonging to carbon atom of -CH= incorporated into the pyrimidinone ring depending on the compound structure.



Scheme 1: (i) aectylacetone, Et,N, DMF ii) an appropriate aldehyde, ethanol, NaOH(aq), HCl; (iii) Urea, NaOH(aq), HCl.

Molecular Docking Analysis

Molecular docking is a fundamental tool and computational procedure aims to predict the best orientation of a drug molecules to the target macromolecular (receptor), when these are bound to each other to form a stable complex thereby assisting in drug design and discovery.[30] Nowadays, molecular docking an integral part of drug discovery research, imparting knowledge on binding affinities, binding modes, and the associated thermodynamic interactions with the target enzyme that governs the inhibition of the pathogen.[31] In the present work, binding affinity and docking interactions for the potential antiviral activity between the synthesized compounds (2a-f, 3a-f) and two selected proteins (7dpp and 8cx9) were analyzed using PyRx software against three selected standard antivirals; Remdesivir,[32] X77 [33] and N3.[34] In general, all the synthesized compounds 2a-f and 3a-f showed a promising binding affinity with the active site of the target proteins. This was higher than this was recorded for the standard antivirals drugs as shown in Table 1. Interestingly, the data also showed that compounds 3a-f displayed higher binding affinity values than their precursors 2a-f, this can be imputed to the existence of carbonyl group (C=O) and amine group (NH) in the pyrimidinone ring which facilitated more binding affinity with the key amino acids of the tested proteins through hydrogen bonding and hydrophobic interactions. Table 1 and Figures 1 and 2 discussed details the best binding affinity and interactions for these compounds with the target proteins.

Among compounds 2a-f, compound 2b showed the best binding affinity (-8.8 kcal/mole) with protein 8cx9, which can be explained as a result to the 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,

Table 1: Docking scores (in kcal/mol) of the synthesis compounds (2a-f, 3a-f) and three selected standard drugs with 7 dpp and 8cx9 proteins.

No. Comp.	*Docking Score (kcal/mol) with 7dpp*	*Docking Score (kcal/mol)with 8cx9*
2a	-7.2	-7.7
2b	-7.4	-8.8
2c	-7.3	-8.2
2d	-7.4	-8.3
2e	-7.2	-7.7
2f	-7.6	-7.8
3a	-8.1	-8.4
3b	-8.0	-8.7
3c	-7.9	-8.5
3d	-7.8	-8.4
3e	-7.6	-8.1
3f	-8.2	-8.0
Remdesivir (Standard drug)	-7.1	-7.4
X77 (Standard drug)	-5.7	-7.6
N3 (Standard drug)	-3.2	-7.8

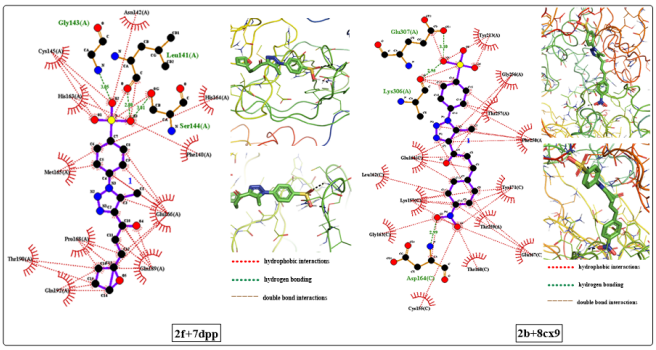


Figure 1: The best binding affinity of the newly synthesized compounds 2a-f with the tested proteins.

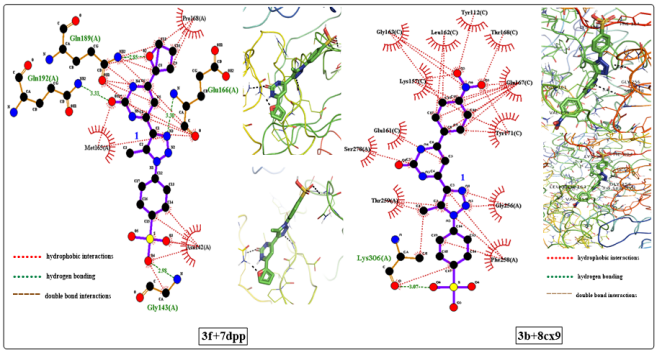


Figure 2: The best binding affinity of the newly synthesized compounds 3a-f with the tested proteins.

Thr259, Glu167, Thr168, Cys155, Asp164, Gly163, Lys 157, Leu162, Glu161, Lys306, Glu307. While, for protein 7dpp, compound 2f displayed the highest binding affinity (-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. For compounds 3a-f, compound 3b have the best binding affinity (8.7 kcal/mole) with protein 8cx9, which can be imputed to the conventional hydrogen bonding interactions with active sites of the amino acid Lys306 and hydrophobic interactions with active sites of the amino acids; Phe258, Gly256, Tyr171, Glu167, Thr168, Tyr112, Leu162, Gly163, Lys157, Glu161, Ser278, Thr259, Lys306. For protein 7dpp, compound 3f displayed the highest binding affinity value with -8.2 kcal/mole, which can have explained depending on the conventional hydrogen bonding interactions with active sites of the amino acids Glu189, Gln192, Glu166, Gly143 and hydrophobic interactions with active sites of the amino acids; Pro168, Glu166, Asn142, Gly143, Met 165.

Chemicals and Instruments

All chemicals and solvents were supplied from available sources and used as received. The progress of all the reactions were monitored by TLC technique using TLC aluminum sheets. The FTIR spectra were recorded on a Shimadzu FTIR 8400 spectrometer in KBr discs. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 400 MHz and 101 MHz on advance new spectrometer using DMSO-d_6 as a solvent and TMS as the internal standard.

Procedures

The key starting material 4-(4-acetyl-5-methyl-1H-1,2,3-triazol-1-yl)benzenesulfonic acid 1 was prepared according to the procedures that were described in the literature.[29]

General procedure for the synthesis of chalcones 2a-f

A mixture of a 4-(4-acetyl-5-methyl-1H-1,2,3-triazol-1-yl) benzenesulfonic acid 1 (2.81 g, 10.0 mmol), an appropriate aldehyde (10.0 mmol) were dissolved in a mixture of aqueous solution of sodium hydroxide (5.0 mL, 40% w/v) and ethanol (25 mL). The mixture was stirred for 2.0 hours at 50°C before being acidified with a diluted hydrochloric acid solution. The formed solid product was filtered under vacuum, washed with diethyl ether and dried to give the target products 2a-f.

4-(4-cinnamoyl-5-methyl-1H-1,2,3-triazol-1-yl)benzene sulfonic acid 2a

It was prepared using benzaldehyde (1.02 mL, 10 mmol); Yield (3.1 g, 84%). FTIR (KBr disc, cm^{-1}), 3477 (OH, SO_3H), 3059 (Ar-H), 2922 (C-H, sp^3-aliphatic), 1660 (C=O, CH=CHC=O), 1597 (C=C-triazolyl), 1572 (C=C, C=C-C=O), 1448 (-N=N). ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm)= 2.61 (s, 3H, CH_3), 7.47 -7.88 (m, 9H, Ar-H, H-C(α)), 8.02 (d, *J*= 12.8 Hz, 1H, H-C(β)).^{13}C-NMR (101 MHz, DMSO-d_6): δ (ppm)= 10.4, 123.2, 125.4, 127.3, 129.2, 129.6, 131.3, 134.8, 135.3, 139.5, 143.5, 143.6, 150.1, 183.8.

4-(5-methyl-4-(3-(4-nitrophenyl)acryloyl)-1H-1,2,3-triazol-1-yl)benzene sulfonic acid 2b

It was prepared using *p*-nitro benzaldehyde (1.51 g, 10 mmol); Yield (3.7 g, 89.3%). FTIR (KBr disc, cm^{-1}), 3450 (OH, SO_3H),

3111 (Ar-H), 2937 (C-H, sp^3-aliphatic), 1668 (C=O), 1608 (C=C-triazolyl), 1556 (C=C, C=C-C=O), 1514 (Ar, C=C), 1425 (-N=N). ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm)= 2.61 (s, 3H, CH_3), 7.65 (d, *J*= 8.4 Hz, 1H, H-C(α)), 7.87-8.08 (m, 6H, Ar-H), 8.13 (d, *J*=8.4, 1H, H-C(β)), 8.25-8.27 (d, *J* = 8.6 Hz, 2H, Ar-H). ^{13}C-NMR (101 MHz, DMSO-d_6): δ (ppm)= 10.1, 124.2, 125.1, 126.6, 127.0, 129.9, 134.9, 139.5, 140.4, 140.9, 143.0, 148.2, 149.7, 183.1.

4-(4-(3-(4-chlorophenyl)acryloyl)-5-methyl-1H-1,2,3-triazol-1-yl)benzene sulfonic acid 2c

It was prepared using p-chloro benzaldehyde (1.41 g, 10 mmol); Yield (3.63 g, 90.01%), as a shine white powder. FT-IR (KBr disc, cm^{-1}), 3456 (OH, SO_3H), 3068 (Ar-H), 2982 (C-H, sp^3-aliphatic), 1666 (C=O), 1606 (C=C-triazolyl), 1566 (C=C, C=C-C=O), 1508 (Ar, C=C), 1489 (-N=N), 667 (C-Cl). ^{1}H-NMR (400 MHz, DMSO-d_6): δ= 2.61 (s, 3H, CH_3), 7.53-7.66 (m, 4H, Ar-H), 7.8 (d, *J*= 11.8 Hz, 1H, H-C(α)), 8.0-8.01 (m, 4H, Ar-H), 8.04 (d, *J*= 11.8 Hz, 1H, H-C(β)).^{13}C-NMR (101 MHz, DMSO-d_6): δ= 10.1, 123.7, 125.1, 127.1, 129.39, 130.7, 133.6, 135.0, 135.5, 139.3, 141.9, 143.3, 149.9, 183.4.

4-(4-(3-(4-bromophenyl)acryloyl)-5-methyl-1H-1,2,3-triazol-1-yl)benzene sulfonic acid 2d

It was prepared using p-bromobenzaldehyde (1.85 g, 10 mmol); Yield (4.1 g, 91.5%), as a white solid. FTIR (KBr disc, cm^{-1}), 3450 (OH, SO_3H), 3064 (Ar-H), 2978 (C-H, sp^3-aliphatic), 1666 (C=O), 1604 (C=C-triazolyl), 1558 (C=C, C=C-C=O), 1506 (Ar, C=C), 1485 (-N=N), 626 (C-Br). ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm)= 2.61 (s, 3H, CH_3), 7.64-7.81 (m,6H, Ar-H), 7.84-8.02 (m, 3H, Ar-H, H-C(α)), 8.05 (d, *J*= 15.9 Hz, 1H, H-C(β)). ^{13}C-NMR (101 MHz, DMSO-d_6): δ (ppm)= 10.3, 123.84, 124.5, 125.2, 127.2, 131.0, 132.4, 134.0, 135.1, 139.4, 142.1, 143.4, 150.0, 183.5.

4-(4-(3-(4-methoxyphenyl) acryloyl)-5-methyl-1H-1,2,3-triazol-1-yl)benzene sulfonic acid 2e

It was prepared using p-methoxy benzaldehyde (1.30 mL, 10 mmol); Yield (3.3 g, 82.7%). FTIR (KBr disc, cm^{-1}), 3454 (OH, SO_3H), 3059 (Ar-H), 2918 (C-H, sp^3-aliphatic), 1656 (C=O), 1583 (C=C-triazolyl), 1574 (C=C, C=C-C=O), 1506 (Ar, C=C), 1460 (-N=N). ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm)= 2.55 (s, 3H, CH_3), 3.45 (s, 3H, OCH_3), 7.04-7.05 (d, *J* = 12.3 Hz, 1H, H-C(α)), 7.37-7.41 (m, 4H, Ar-H), 7.56 (d, *J*= 12.3 Hz, 1H, H-C(β)), 7.57-7.72 (m, 4H, Ar-H).^{13}C-NMR (101 MHz, DMSO-d_6): δ (ppm)= 10.1, 53.2, 123.0, 124.1, 125.3, 127.32, 129.4, 131.20, 135.57, 137.0, 138.2, 143.3, 150.2, 163.0, 183.6.

4-(4-(3-(furan-2-yl)acryloyl)-5-methyl-1H-1,2,3-triazol-1-yl) benzene sulfonic acid 2f

It was prepared using furfuraldehyde (0.83 mL, 10 mmol); Yield (2.4 g, 66.85%). FTIR (KBr disc, cm^{-1}): 3460 (OH, SO_3H), 3117 (Ar-H), 2978 (C-H, sp^3-aliphatic), 1666 (C=O), 1589 (C=C-triazolyl), 1556 (C=C, C=C-C=O), 1506 (Ar, C=C), 1473 (-N=N). ^{1}H-NMR (400 MHz, DMSO-d_6): δ= 2.60 (s, 3H, CH_3), 6.70 (t, *J* = 2.24 Hz, 1H, Furan moiety), 7.12-7.86 (m, 7H, Ar-H, H-C(α), Furan moiety), 7.92 (d, *J*= 12.3 Hz, 1H, H-C(β)). ^{13}C-NMR (101 MHz, DMSO-d_6): δ= 10.24, 113.5, 117.9, 119.9, 125.2, 127.2, 129.7, 135.2, 139.2, 143.3, 146.8, 149.9, 151.2, 183.1

General procedure for the synthesis of 1,2,3-trizole linked pyrimidinone derivatives 3a-f

An aqueous solution of sodium hydroxide (10.0 mL, 15.0 mmol) was added slowly to a mixture of an appropriate derivative of chalcones 2a-f (5.0 mmol) and urea (0.3 g, 5.0 mmol) in ethanol (25 mL). The resulted mixture was then refluxed for overnight. The reaction mixture was evaporated to a half before being neutralized with a diluted solution of hydrochloric acid. The resulting mixture was concatenated and the residue was dissolved in hot methanol and filtered. Methanol was removed on rotary evaporator and the solid product was collected to obtain the target compounds 3a-f.

4-(5-methyl-4-(2-oxo-6-phenyl-1,2-dihydropyrimidin-4-yl)-1H-1,2,3-triazol-1-yl)benzene sulfonic acid 3a

It was prepared using compound 2a (1.85 g); Yield (1.70 g, 82.93%). FTIR (KBr disc, cm^{-1}), 3406 (OH, SO_3H), 3215 (NH), 3047 (Ar-H), 2931 (C-H, sp^3-aliphatic), 1701 (C=O), 1681 (C=N), 1675 (C=C), 1599 (C=C), 1554 (Ar, C=C), 1504 (-N=N), 1224 (C-N). ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm)= 2.59 (s, 3H, CH_3), 5.37 (s, 1H, -CH= of pyrimidinone ring), 7.37-7.84 (m, 9H, Ar-H), 8.02 (s, 1H, NH).^{13}C-NMR (101 MHz, DMSO-d_6): δ (ppm)= 10.2, 95.9, 124.2, 125.4, 127.3, 131.2, 132.3, 135.6, 136.3, 137.0, 139.4, 143.9, 149.7, 161.7, 163.0.

4-(5-methyl-4-(6-(4-nitrophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-1H-1,2,3-triazol-1-yl) benzene sulfonic acid 3b

It was prepared using compound 2b (2.08 g); Yield (2.00 g, 87.6%). FT-IR (KBr disc, cm^{-1}), 3431 (OH, SO_3H), 3228. (NH), 3018 (Ar-H), 2978 (C-H, sp^3-aliphatic), 1701 (C=O), 1678 (C=N), 1639 (C=C), 1597 (C=C), 1573 (Ar, C=C), 1504 (-N=N), 1224 (C-N). ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm)= 2.59 (s, 3H, CH_3), 6.57 (s, 1H, -CH= of pyrimidinone ring), 7.54 -8.23 (m, 9H, NH, Ar-H).^{13}C-NMR (101 MHz, DMSO-d_6): δ (ppm)= 10.2, 95.9, 124.2, 125.4, 127.3, 131.2, 132.3, 136.3, 137.0, 139.4, 143.9, 149.1, 149.7, 161.7, 163.0.

4-(4-(6-(4-chlorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-5-methyl-1H-1,2,3-triazol-1-yl) benzene sulfonic acid 3c

It was prepared using compound 2c (2.02 g); Yield (2.10 g, 94.59%). FTIR (KBr disc, cm^{-1}), 3456 (OH, SO_3H), 3244 (NH), 3138 (Ar-H), 2972 (C-H, sp^3-aliphatic), 1701 (C=O), 1680 (C=N), 1639 (C=C), 1595 (C=C), 1552 (Ar, C=C), 1500 (-N=N), 1228 (C-N), 694 (C-Cl). ^{1}H-NMR (400 MHz, DMSO-d6): δ (ppm)= 2.59 (s, 3H, CH_3), 5.37 (s, 1H, CH= of pyrimidinone ring), 7.36-7.85 (m, 8H, Ar-H), 8.01 (s, 1H, NH).^{13}C-NMR (101 MHz, DMSO-d_6): δ (ppm)= 10.2, 95.9, 118.4, 125.4, 127.3, 131.2, 132.3, 135.6, 136.3, 137.0, 139.4, 143.9, 150.4, 161.7, 163.0.

4-(4-(6-(4-bromophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-5-methyl-1H-1,2,3-triazol-1-yl)benzene sulfonic acid 3d

It was prepared using compound 2d (2.24 g); Yield (2.20 g, 90%). FTIR (KBr disc, cm^{-1}), 3456 (OH, SO_3H), 3269 (NH),

3109 (Ar-H), 2955 (C-H, sp^3-aliphatic), 1707 (C=O), 1674 (C=N), 1639 (C=C), 1595 (C=C), 1552 (Ar- C=C), 1502 (-N=N), 1226 (C-N), 536 (C-Br). ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm)= 2.62 (s, 3H, CH_3), 4.44 (s, 1H, CH= pyrimidinone ring), 7.20-7.82 (m, 9H, Ar-H, NH).^{13}C-NMR (101 MHz, DMSO-d_6): δ (ppm)= 10.2, 95.9, 124.2, 125.4, 127.3, 131.2, 132.3, 135.6, 136.3, 137.0, 139.5, 143.9, 149.7, 161.8, 163.0.

4-(4-(6-(4-methoxyphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-5-methyl-1H-1,2,3-triazol-1-yl)benzene sulfonic acid 3e

It was prepared by using compound 2e (1.99 g); Yield (1.95 g, 88.74%). FTIR (KBr disc, cm^{-1}), 3419.90 (OH, SO_3H), 3213 (NH), 3064 (Ar-H), 2933 (C-H, sp^3-aliphatic), 1703 (C=O), 1656 (C=N), 1629 (C=C), 1599 (C=C), 1552 (Ar-C=C), 1502 (-N=N), 1220 (C-N). ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm)= 2.53 (s, 3H, CH_3), 3.45 (s, 3H, OCH_3), 5.0 (s, 1H, CH= pyrimidinone ring, Ar-H), 6.57-7.70 (m, 9H, Ar-H and NH). ^{13}C-NMR (101 MHz, DMSO-d_6): δ (ppm)= 10.2, 65.7, 95.9, 124.2, 124.8, 125.4, 131.0, 135.5, 136.0, 137.0, 139.5, 143.9, 149.7, 150.4, 161.7, 163.0.

4-(4-(6-(furan-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-5-methyl-1H-1,2,3-triazol-1-yl)benzene sulfonic acid 3f

It was prepared by using compound 2f (1.80 g); Yield (1.60 g, 80%). FTIR (KBr disc, cm^{-1}), 3439.19 (OH, SO_3H), 3227 (NH), 3080 (Ar-H), 2935 (C-H, sp^3-aliphatic), 1701 (C=O), 1689 (C=N), 1631 (C=C), 1599 (C=C), 1554 (Ar-C=C), 1504 (-N=N), 1220 (C-N). ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm)= 2.59 (s, 3H, CH_3), 5.01 (s, 1H, CH= pyrimidinone ring), 6.58 (t, *J*=8.6, 1H, C-CH= furan moiety), 7.39-7.85 (m, 7H, furan ring, Ar-H, NH).^{13}C-NMR (101 MHz, DMSO-d_6): δ (ppm)= 10.2, 114.4, 114.7, 116.7, 125.4, 131.2, 132.3, 136.3, 137.0, 139.5, 143.9, 149.2, 149.7, 150.4, 163.0.

Computational Methodology

Simulation studies using molecular docking

This method is used for predicting the best drug candidates based on the scoring. Firstly, the available Chemdraw software was utilized to generate the 3D structures of the synthesized compounds (2a-f, 3a-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.[35,36] Unwanted molecules such as H_2O molecules or metal ions in the target proteins were removed.[37] The molecular docking was performed by using PyRx version 0.8 which works based on the Auto Dock Vina configuration.[38] Both the protein and ligands (compounds 2a-f and 3a-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 PyMOL tool application software displayed the ligand and protein intermolecular interactions interaction.

CONCLUSION

In conclusion, we have successfully combined 1,2,3-triazole, pyrimidinone rings and sulfonic acid group in the same matrix via a multi-step synthetic approach established in this work. Firstly, 4-(4-acetyl-5-methyl-1H-1,2,3-triazol-1-yl) benzenesulfonic acid 1 was synthesized as a key starting material. This compound displayed a high chemical activity with a series of aromatic aldehydes towards the Claisen-Schmidt reaction to give the corresponding chalcones 2a-f in high yields. Cyclization reaction of chalcone structure with urea was successful to construct pyrimidinone ring system to give the target compounds 3a-f. Molecular docking study showed that the synthesized derivatives 2a-f and 3a-f displayed a good binding affinity towards the active sites of the tested proteins. Moreover, their binding affinities were higher than those reworded for three selected standard antivirals and compounds containing furan moiety (2f, 3f) and nitro group (2b, 3b) have the best binding affinity. Thus, the docking approach facilitates the prediction of activity profile for future experimental findings.

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