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Synthesis, Characterization, ADMET Prediction and Molecular Docking Studies Against COVID-19 Proteins of Novel 2-(3-(4-substituted aryl)guanidine-1-yl)-4-phenyl-6-(thiophene-2-yl)pyrimidines

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Abstract:

Novel 2-(3-(4-substituted aryl)guanidine-1-yl)-4-phenyl-6-(thiophene-2-yl)pyrimidines (7) were synthesized by simple condensation between chalcones with therapeutic biguanide derivatives. The novel guanidinopyrimidine derivatives (7) were characterized by different spectral studies. Furthermore, subject to ADMET prediction using pkSCM software and molecular docking studies against different kinds of novel RNA proteins such as, spike (PDB ID: 6XC3), main protease (3CLpro - PDB ID: 6LU7), RNA-dependent RNA polymerase (RdRp – PDB ID: 6W9Q) and host protein ACE2 (PDB ID:1R42) spike protein

and also the activities are compared with FDA-approved few human trial drugs such as hydroxychloroquine (HQC), favipiravir and lopinavir.

Keywords: Pyrimidine, Biguanide, COVID-19, ADMET- pkSCM prediction, Molecular docking.

1. INTRODUCTION

As on 21st September 2020; COVID-19 (novel RNA virus) has infected >31 million individuals and caused approximately 1 million global deaths [1]. The novel human RNA virus is subjected to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which primarily gains entrance to cells via binding of SARS-CoV-2 Spike glycoprotein to angiotensin converting enzyme 2 (ACE-2) and subsequent endocytosis [2]-[4]. Current news has identified extra entry points, with neuropilin 1 (NRP-1) [5], [6]. Last two decades, the increasing resistances of microorganisms toward antimicrobial agents become severe health trouble so there is a need for a secure, high therapeutic and novel antimicrobial world [7].

Nitrogen & sulphur containing heterocyclic [8] compounds have significantly a lot of interest due to the wider application of pharmacological activity. Pyrimidine may perhaps be a basic nucleus in DNA & RNA; it is related with different biological activities like antibacterial [9], antifungal [10]-[13], antibiotics [14], anticancer [15], [16], anti-diabetic [17], anti-tubercular [18], anti-malarial [19], anti-HIV [20], antiviral [21]-[24], antioxidant [25] and anti-inflammatory [26]. The literature review reveals that mutual pyrimidine and biguanidine derivatives [27]-[30] are exhibits tremendous biological activities. Moving forward by this study, we synthesized a novel series of pyrimidine derivatives by incorporating the biguanidine moiety with the hope of superior therapeutic agents. The versatility of the infant generation of the novel pyrimidines will constitute a rewarding pharmacophore.

In-silico ADMET [31]-[33] predictions using pkSCM [34] software will further boost our aptitude to guess and representation the most significant pharmacokinetic, metabolic and toxicity endpoints, so accelerating the pills discovery route.

Gemcitabine is a pyrimidine anti-metabolite and has been approved to treat different types of (pancreatic, and lung) cancer [35]-[37]. Gemcitabine can also inhibit the different viruses, like Human immunodeficiency virus, hepatitis C virus and influenza A virus [38]-[40]. Gemcitabine is known to inhibit cancer and diverse viral infections by terminating sequence elongation through DNA/RNA synthesis, in this manner interrupting DNA/RNA synthesis [41],[42]. Specifically, gemcitabine is understood to possibly inhibit enteroviruses such as EV-A71 and Coxsackievirus B3 [43] with the contribution of pyrimidine inhibition-induced innate immune response [44]. Still, confecting that theory gemcitabine was also propagated as a 3Dpol inhibitor in enterovirus infections [45],[46].

Currently, there is no appropriate treatment for SARS-CoV-2 or vaccine alive to care for humans from such infections. It is extremely urgent to build up numerous therapeutic agents for SARS-CoV-2 virus because of its high infection, morbidity and its ability to cause epidemics universally. In addition, the primary drug discovery pipeline we introduced to the molecular docking studies against seven important target proteins like a spike, 3CLpro, PLpro, RdRp, N-protein, ACE2 protein and TMPRSS2protein, can be potential druggable targets. The docking study compared with currently used human trial drugs such as Hydroxychloroquine-212, Favipiravir-44, Ivermectin-39, Azithromycin-64, Chloroquine- 43, Methylprednisolone-31, Tocilizumab-58, Lopinavir/ritonavir-43 and Ascorbic acid-30. (http://www.redo-project.org/covid19db/). To accomplish the imperative requirement of drugs in the ground of chemotherapy for SARS-CoV-2 the title compounds viz., 2-(3-(4-methyl / 4-methoxy / 4-chlorophenyl)guanidine-1-yl)-4-phenyl-6-(thiophene-2-

yl)pyrimidine. (**7a-n**) were synthesized from its relevant chalcone and 1-(4-methyl / 4-methoxy and 4-chlorophenyl)biguanide hydrochloride in the presence of a base catalyst.

2. EXPERIMENTAL

All essential raw materials were purchase from Avra chemicals (p) ltd., Melting points were taken deep vision (230V) melting points apparatus by the open tube capillary and are uncorrected. IR spectra were taken on an Agilent Resolutions Pro Cary-630 spectrophotometer using the ATR method, ^{1}H and ^{13}C NMR spectra were recorded on Bruker Ultra shield TM 400 Advance-III spectrometer in chloroform-D ($CDCl_3$) with TMS as internal standard and the chemical shifts were reported in δ (ppm) scales.

*A General procedure for the synthesis of 1-(4-methyl / 4-methoxy and 4-chloro phenyl)biguanide hydrochloride**:*** Various p-substituted aniline (4-Me, 4-OMe, and 4-Cl,) (0.1mol) were dissolved in propan-1-ol (200 mL) at room temperature. To the above solution concentrated HCl (8.9mL, 0.1mol) was added at $0^{o}C$, the reaction mixture temperature slowly increased up to $50^{o}C$, cyanoguanidine (8.4g, 0.1mol) was added under the string and then refluxed for 3 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, it was allowed to cool at room temperature. A crude product separated was filtered, washed with acetone and then recrystallized from methanol to get white color solid with good yield (75-85%).

B General procedure for the synthesis of various chalcone: According to the literature procedure, a simple condensation reaction between various p-substituted acetophenone (4-H, 4-F, 4-Cl, 4-Br, and 4-Me) with thiophene-2-carboxaldehyde in basic ethanol solution afforded chalcone [47].

*C General procedure for synthesis 2-(3-(4-methyl / 4-methoxy / 4-chlorophenyl)guanidine-1-yl)-4-phenyl-6-(thiophene-2-yl)pyrimidine. (7a-7n)***:** A mixture of various chalcones

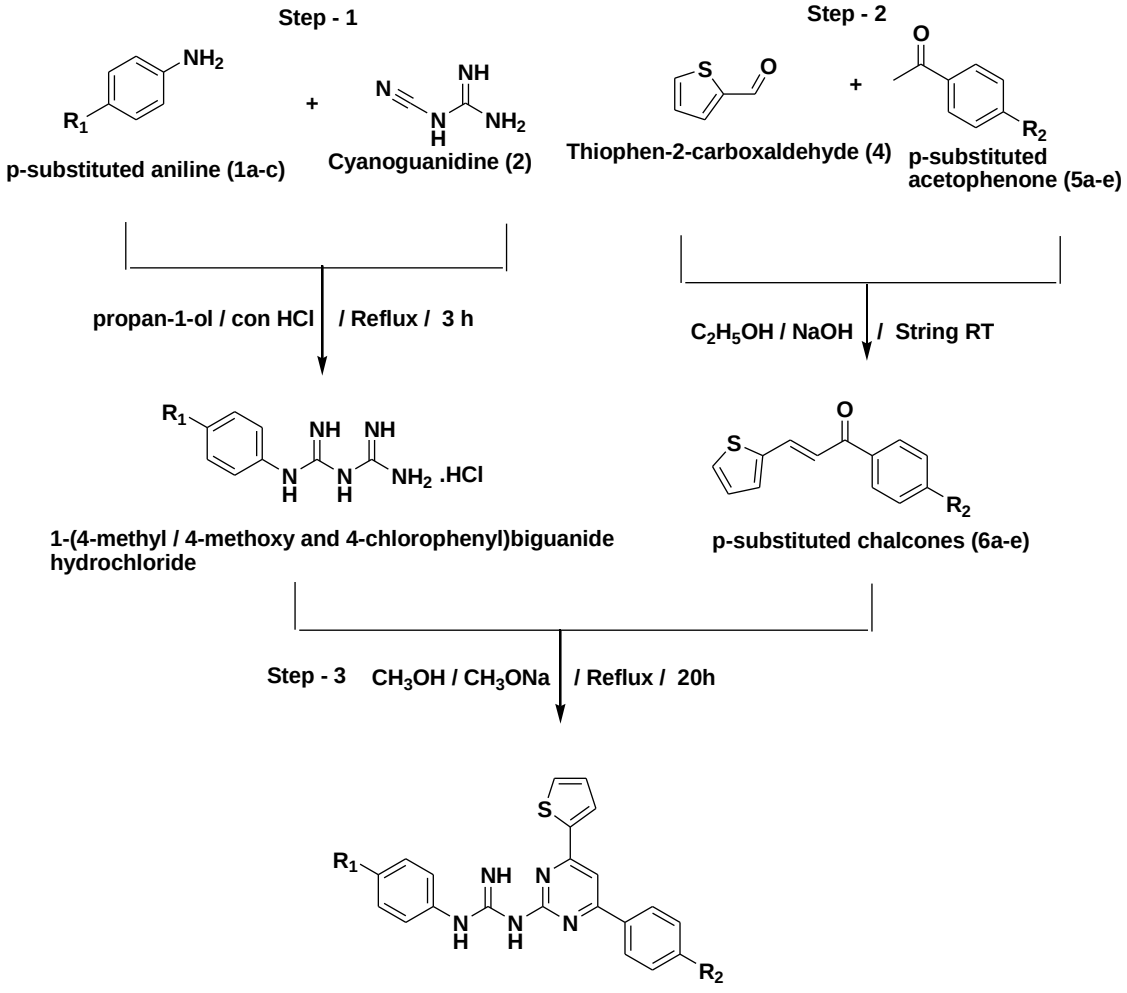
(0.001mol) and 1-(4-methyl / 4-methoxy and 4-chlorophenyl)biguanide hydrochloride (0.001mol) in presences of CH_3ONa catalyst in methanol (25ml) medium was refluxed for 20 hours and the reaction progress monitored by TLC. After completion of the reaction it was allowed to attain room temperature and poured into ice-cold water with stirring. The final product was filtered, dried and recrystallized using ethanol.

3. RESULT AND DISCUSSION

The novel guanidinopyrimidines (**7a-7n**) were synthesized as shown in **Scheme-1** by preparing 1-(4-methyl / 4-methoxy and 4-chlorophenyl)biguanide hydrochloride **(**prepared by an addition reaction between p-substituted aniline and cyanoguanidine) and chalcone (**6a-e**) (Preparation of various chalcone was carried out by the condensation of thiophene-2-carboxaldehyde and p-substituted acetophenone). The structure of the compound 7a was characterized by FT-IR and NMR (^1H &^{13}C) spectral analysis. In FT-IR spectra the incidence bands at **3307 and 1598** cm-1 indicate the presence of NH and C=N respectively in the newly synthesized compound. Then the disappearance of the sharp carbonyl group (C=O) band and these IR spectral data indicated the formation of compound **7a**.

From ^1H NMR spectra of compound **7a** revealed the following signals: a sharp singlet appeared in the region δ 7.372 ppm (due to HC=C confirmed the cyclization of the chalcone into pyrimidine ring.) was assigned to the H5 proton of the pyrimidine ring. A broad singlet at δ 5.418 ppm assigned to the imine NH protons, the aromatic methyl ($-CH_3$) three protons observed as a singlet at δ 2.245 ppm. A multiplet at δ 7.912 – 7.059 ppm characteristic for the aromatic protons. The NH proton appeared δ 7.041 ppm. In the ^{13}C NMR spectra of compound **7a**, the chemical shift values of carbon atoms appear between δ167.13 – 164.58 ppm due to pyrimidine ring ipso carbons, δ 167.79 ppm due to guanidine group ipso carbon, δ142.16 ppm due to thiophene ring ipso carbon, δ142.16– 120.9 ppm due to aromatic carbon atoms, δ 104.58 ppm due to the C5 carbon of the pyrimidine ring, δ20.84 ppm due to

aromatic ring methyl carbon atoms. All the above spectral data indicated the structure of the synthesized compound **7a**.



S.No	7a	7b	7c	7d	7e	7f	7g	7h	7i	7j	7k	7l	7m	7n
R_1 =	-4Me	-4Me	-4Me	-4Me	-4Me	-4OMe	-4OMe	-4OMe	-4OMe	-4Cl	-4Cl	-4Cl	-4Cl	-4Cl
R_2 =	H	-4F	-4Cl	-4Br	-4Me	-4F	-4Cl	-4Br	- 4Me	H	-4F	-4Cl	-4Br	-4Me

Scheme-I

*A hene-2-yl)pyrimidine. (**7a**):* Pale yellow solid, yield: 60%; mp 90-92°**C**; FT- IR (ATR) cm^{-1}: 3456.6- 3194.5 (NH), 3091.9, 3020.7 (Ar CH), 2917.9 (Ali CH), 1645.5, 1636.8 (C=N), 1592.6, 1559.8 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 2.245 (s, 3H, Ar-CH_3), 5.418 (s, 2H, imine N-H), 7.041 (s, 1H, N- H), 7.372 (s, 1H, pyrimidine ring C_5-H), 7.059-7.912 (m,

12H, Ar - H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.79 (imine C=NH), 167.13 (pyrimidine ring C_4 & C_6), 164.58 (pyrimidine ring C_2), 142.16 (thiophene ring C_{2ipso}), 136.88 - 120.90 (aromatic ring carbon atoms), 104.58 (pyrimidine ring C_5), 20.84 (aromatic ring methyl C), Elemental analysis for $C_{22}H_{19}N_5S$(%) ; C 68.55, H 4.97, N 18.17.

*B. 2-(3-(4-methylphenyl)guanidine-1-yl)-4-(4-fluorophenyl)-6-(thiophene-2-yl)pyrimidine. **(7b)**:* Pale yellow solid, yield: 76%; mp 84-86°**C**; FT- IR (ATR) cm^{-1}: 3406.8- 3182.8 (NH), 3101.9, 3021.6 (Ar CH), 2921.5 (Ali CH), 1653.0, 1636.5 (C=N), 1597.3, 1540.8 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 2.256 (s, 3H, Ar-CH_3), 5.267 (s, 2H, imine N-H), 7.044 (s, 1H, N-H), 7.398 (s, 1H, pyrimidine ring C_5-H), 7.057-8.011 (m, 11H, Ar - H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.83 (imine C=NH), 167.12 (pyrimidine ring C_4 & C_6), 164.57 (pyrimidine ring C_2), 142.15 (thiophene ring C_{2ipso}), 135.71 - 115.95 (aromatic ring carbon atoms), 105.60 (pyrimidine ring C_5), 20.85 (aromatic ring methyl C), Elemental analysis for $C_{22}H_{18}FN_5S$ (%) ; C 65.49, H 4.50, N 17.36.

*C. 2-(3-(4-methylphenyl)guanidine-1-yl)-4-(4-chlorophenyl)-6-(thiophene-2-yl)pyrimidine. **(7c)**:* Pale yellow solid, yield: 80%; mp 82-84°**C**; FT- IR (ATR) cm^{-1}: 3462.8- 3182.8 (NH), 3092.3, 3034.5 (Ar CH), 2919.8 (Ali CH), 1646.9, 1638.2 (C=N), 1592.0, 1560.3 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 2.254 (s, 3H, Ar-CH_3), 5.289 (s, 2H, imine N-H), 7.051 (s, 1H, N-H), 7.356 (s, 1H, pyrimidine ring C_5-H), 7.070-7.919 (m, 11H, Ar - H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.19 (imine C=NH), 164.76 (pyrimidine ring C_4 & C_6), 162.32 (pyrimidine ring C_2), 142.15 (thiophene ring C_{2ipso}), 135.71 - 120.91 (aromatic ring carbon atoms), 105.50 (pyrimidine ring C_5), 20.96 (aromatic ring methyl C), Elemental analysis for $C_{22}H_{18}ClN_5S$ (%) ; C 62.92, H 4.32, N 16.68.

*D. 2-(3-(4-methylphenyl)guanidine-1-yl)-4-(4-bromophenyl)-6-(thiophene-2-yl)pyrimidine. **(7d)**:* Pale yellow solid, yield: 82%; mp 88-90°**C**; FT- IR (ATR) cm^{-1}: 3457.3- 3177.4 (NH), 3092.6, 3025.8 (Ar CH), 2918.7 (Ali CH), 1646.6, 1615.1 (C=N), 1591.2, 1559.3 (C=C); ^{1}H

NMR (400 MHz,$CDCl_3$) δ, ppm: 2.251 (s, 3H, Ar-CH_3), 5.381 (s, 2H, imine N-H), 7.380 (s, 1H, pyrimidine ring C_5-H), 7.050-7.916 (m, 11H, Ar - H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.82 (imine C=NH), 167.16 (pyrimidine ring C4 & C_6), 164.60 (pyrimidine ring C_2), 142.19 (thiophene ring C_{2ipso}), 135.73 - 120.83 (aromatic ring carbon atoms), 103.81 (pyrimidine ring C_5), 20.84 (aromatic ring methyl C), Elemental analysis for $C_{22}H_{18}$ BrN_5S (%); C 56.90, H 34.91, N 15.08.

*E 2-(3-(4-methylphenyl)guanidine-1-yl)-4-(4-methylphenyl)-6-(thiophene-2-yl)pyrimidine. **(7e)**:* Pale yellow solid, yield: 75%; mp 92-94°**C**; FT- IR (ATR) cm^{-1}: 3447.5- 3194.5 (NH), 3090.0, 3026.1 (Ar CH), 2917.6, 2850.9 (Ali CH), 1650.3, 1614.9 (C=N), 1594.9, 1558.8 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 2.251, 2.284 (s, 3H, Ar-CH_3), 5.360 (s, 2H, imine N-H), 7.318 (s, 1H, pyrimidine ring C_5-H), 6.976-7.915 (m, 11H, Ar - H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.80 (imine C=NH), 167.14 (pyrimidine ring C_4 & C_6), 164.58 (pyrimidine ring C_2), 142.19 (thiophene ring C_{2ipso}), 135.74 - 120.84 (aromatic ring carbon atoms), 103.93 (pyrimidine ring C_5), 21.46, 20.85 (aromatic ring methyl C), Elemental analysis for $C_{23}H_{21}$ N_5S (%) ; C 69.15, H 5.30, N 17.53.

*F 2-(3-(4-methoxyphenyl)guanidine-1-yl)-4-(4-fluorophenyl)-6-(thiophene-2-yl)pyrimidine. **(7f)**:* Pale yellow solid, yield: 76%; mp 274-276°**C**; FT- IR (ATR) cm^{-1}: 3461.1- 3308.2 (NH), 3101.9, 2996.6 (Ar CH), 2933.1, 2834.6 (Ali CH), 1637.1 (C=N), 1599.2, 1540.5 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 3.827 (s, 3H, Ar-OCH_3), 5.426 (s, 2H, imine N-H), 7.438 (s, 1H, pyrimidine ring C_5-H), 6.887-8.075 (m, 11H, Ar - H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.75 (imine C=NH), 167.17 (pyrimidine ring C_4 & C_6), 164.66 (pyrimidine ring C_2), 142.22 (thiophene ring C_{2ipso}), 164.79 - 114.01 (aromatic ring carbon atoms), 103.29 (pyrimidine ring C_5), 55.51 (aromatic ring methoxy C), Elemental analysis for $C_{22}H_{18}$ FN_5OS (%) ; C 62.99, H 4.33, N 16.70.

*G 2-(3-(4-methoxyphenyl)guanidine-1-yl)-4-(4-chlorophenyl)-6-(thiophene-2-yl)pyrimidine. (**7g**):* Pale yellow solid, yield: 72%; mp 290-292°**C**; FT- IR (ATR) cm^{-1}: 3462.7- 3102.1 (NH), 3016.4 (Ar CH), 2933.0, 2834.5 (Ali CH), 1646.9, 1617.7 (C=N), 1567.3, 1540.9 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 3.725 (s, 3H, Ar-OCH_3), 5.447 (s, 2H, imine N- H), 7.340 (s, 1H, pyrimidine ring C_5-H), 6.773-7.901 (m, 11H, Ar - H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.73 (imine C=NH), 167.20 (pyrimidine ring C_4 & C_6), 164.58 (pyrimidine ring C_2), 142.75 (thiophene ring C_{2ipso}), 159.35 - 113.98 (aromatic ring carbon atoms), 103.22 (pyrimidine ring C_5), 55.50 (aromatic ring methoxy C), Elemental analysis for $C_{22}H_{18}ClN_5OS$ (%) ; C 60.61, H 4.16, N 16.07.

*H 2-(3-(4-methoxyphenyl)guanidine-1-yl)-4-(4-bromophenyl)-6-(thiophene-2-yl)pyrimidine. (**7h**):* Pale yellow solid, yield: 85%; mp 258-260°**C**; FT- IR (ATR) cm^{-1}: 3462.9- 3387.6 (NH), 3097.8, 2998.9 (Ar CH), 2931.2 , 2834.7 (Ali CH), 1641.7, 1614.8 (C=N), 1563.1 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 3.725 (s, 3H, Ar-OCH_3), 5.418 (s, 2H, imine N-H), 7.336 (s, 1H, pyrimidine ring C_5-H), 6.776-7.901 (m, 11H, Ar - H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.70 (imine C=NH), 167.16 (pyrimidine ring C_4 & C_6), 164.67 (pyrimidine ring C_2), 142.65 (thiophene ring C_{2ipso}), 156.36 - 113.96 (aromatic ring carbon atoms), 103.25 (pyrimidine ring C_5), 55.50 (aromatic ring methoxy C), Elemental analysis for $C_{22}H_{18}BrN_5OS$ (%) ; C 55.01, H 34.78, N 14.58.

*I 2-(3-(4-methoxyphenyl)guanidine-1-yl)-4-(4-methylphenyl)-6-(thiophene-2-yl)pyrimidine. (**7i**):* Pale yellow solid, yield: 62%; mp 230-232°**C**; FT- IR (ATR) cm^{-1}: 3399.1- 3196.4 (NH), 3055.3 (Ar CH), 2951.8, 2836.2 (Ali CH), 1640.9 (C=N), 1539.5 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 2.344 (s, 3H, Ar-CH_3), 3.731 (s, 3H, Ar-OCH_3), 5.366 (s, 2H, imine N-H), 7.383 (s, 1H, pyrimidine ring C_5-H), 6.790-7.909 (m, 11H, Ar - H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.67 (imine C=NH), 167.14, 165.92 (pyrimidine ring C_4 & C_6), 164.61 (pyrimidine ring C_2), 142.21 (thiophene ring C_{2ipso}), 159.30 - 113.97 (aromatic ring carbon atoms),

104.09 (pyrimidine ring C_5), 55.50 (aromatic ring methoxy C), 21.45(aromatic ring methyl C), Elemental analysis for $C_{23}H_{21}N_5OS$ (%) ; C 66.48, H 5.09, N 16.85.

*J 2-(3-(4-chlorophenyl)guanidine-1-yl)-4-phenyl-6-(thiophene-2-yl)pyrimidine. **(7j);*** Pale yellow solid, yield: 60%; mp 82-84°**C**; FT- IR (ATR) cm^{-1}: 3459.2- 3337.0 (NH), 3167.7, 3089.8 (Ar CH), 1646.6-1615.4 (C=N), 1591.8, 1543.9 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 5.656 (s, 2H, imine N-H), 7.375 (s, 1H, pyrimidine ring C_5-H), 7.054-8.010 (m, 12H, Ar - H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.88 (imine C=NH), 167.10, 166.15 (pyrimidine ring C_4 & C_6), 164.45 (pyrimidine ring C_2), 141.91 (thiophene ring C_{2ipso}), 137.08 - 121.75 (aromatic ring carbon atoms), 102.57 (pyrimidine ring C_5), Elemental analysis for $C_{21}H_{16}ClN_5S$ (%) ; C 62.14, H 3.97, N 17.25.

*K 2-(3-(4-chlorophenyl)guanidine-1-yl)-4-(4-fluorophenyl)-6-(thiophene-2-yl)pyrimidine. **(7k):*** Pale yellow solid, yield: 62%; mp 86-88°**C**; FT- IR (ATR) cm^{-1}: 3460.9- 3194.2 (NH), 3090.9 (Ar CH), 1647.8-1616.7 (C=N), 1593.6, 1559.1 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 5.402 (s, 2H, imine N-H), 7.364 (s, 1H, pyrimidine ring C_5-H), 6.954-7.921 (m, 11H, Ar - H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.90 (imine C=NH), 167.10 (pyrimidine ring C_4 & C_6), 164.46 (pyrimidine ring C_2), 141.93 (thiophene ring C_{2ipso}), 137.07 - 115.96 (aromatic ring carbon atoms), 104.19 (pyrimidine ring C_5), Elemental analysis for $C_{12}H_{15}FClN_5S$ (%) ; C 59.50, H 3.57, N 16.52.

*L 2-(3-(4-chlorophenyl)guanidine-1-yl)-4-(4-chlorophenyl)-6-(thiophene-2-yl)pyrimidine. **(7l):*** Pale yellow solid, yield: 68%; mp 80-82°**C**; FT- IR (ATR) cm^{-1}: 3464.9- 3177.3 (NH), 3093.2 (Ar CH), 1646.4-1616.5 (C=N), 1590.2, 1560.4 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 5.598 (s, 2H, imine N-H), 7.342 (s, 1H, pyrimidine ring C_5-H), 6.946-7.903 (m, 11H, Ar - H); ^{13}C NMR (100 MHz, $CDCl_3$): 165.22 (imine C=NH), 167.83 (pyrimidine ring C_6 & C_4), 167.83, 167.11 (pyrimidine ring C_2), 141.96 (thiophene ring C_{2ipso}), 137.11 -121.83

(aromatic ring carbon atoms), 104.43 (pyrimidine ring C_5), Elemental analysis for $C_{21}H_{15}Cl_2N_5S$ (%); C 57.28, H 3.43, N 15.90.

*M 2-(3-(4-chlorophenyl)guanidine-1-yl)-4-(4-bromophenyl)-6-(thiophene-2-yl)pyrimidine. **(7m)**:* Pale yellow solid, yield: 74%; mp 184-186°**C**; FT- IR (ATR) cm^{-1}: 3474.6- 3214.7 (NH), 3064.2 (Ar CH), 1646.7, 1619.5 (C=N), 1558.0, 1571.3 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 5.564 (s, 2H, imine N-H), 7.359 (s, 1H, pyrimidine ring C_5-H), 6.980-7.828 (m, 11H, Ar - H); ^{13}C NMR (100 MHz, $CDCl_3$): 164.97 (imine C=NH), 167.81, 167.18 (pyrimidine ring C_4 & C_6), 164.49 (pyrimidine ring C_2), 142.41 (thiophene ring C_{2ipso}), 159.71 - 121.91 (aromatic ring carbon atoms), 104.22 (pyrimidine ring C_5), Elemental analysis for $C_{21}H_{15}BrClN_5S$ (%) ; C 52.03, H 3.12, N 14.45.

*N 2-(3-(4-chlorophenyl)guanidine-1-yl)-4-(4-methylphenyl)-6-(thiophene-2-yl)pyrimidine. **(7n)**:* Pale yellow solid, yield: 60%; mp 70-72°**C**; FT- IR (ATR) cm^{-1}: 3465.6- 3181.4 (NH), 3071.0 (Ar CH), 2919.4 (Ali CH), 16463.8, 1638.2 (C=N), 1585.8, 1576 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 2.321 (s, 3H, Ar-CH_3), 5.540 (s, 2H, imine N-H), 6.928 (s, 1H, N-H), 7.368 (s, 1H, pyrimidine ring C_5-H), 7.037-7.912 (m, 11H, Ar - H); ^{13}C NMR (100 MHz, $CDCl_3$): 166.06 (imine C=NH), 167.88, 167.11 (pyrimidine ring C_4 & C_6), 164.45 (pyrimidine ring C_2), 141.92 (thiophene ring C_{2ipso}), 137.08 - 121.75 (aromatic ring carbon atoms), 102.24 (pyrimidine ring C_5), 20.24 (aromatic ring methyl C), Elemental analysis for $C_{22}H_{18}ClN_5S$ (%) ; C 62.92, H 4.32, N 16.68.

4. ADMET PREDICTION

Drug discovery and development is an extremely difficult and costly endeavour, which includes disease selection, target identification and validation, lead discovery and optimization, preclinical and clinical trials [48]. Recently, in-silico methods are used for new molecular entities approved by the FDA has risen obviously [49]. Nowadays in-silico

prediction are playing major role in the pharmaceutical research and development field. In 2018, the FDA permitted only fifty-nine (64%) new drugs to the next level among the screened using the ADMET properties. **(**https://doi.org/10.1016/j.drudis.2019.03.015**).**

The pkCSM software (http://structure.bioc.cam.ac.uk/pkcsm) is highly useful for determined the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) property and in the classification of drug discovery preliminary process. The above software saves money, time and reduced environmental pollution. The synthesized compounds (**7a-7n**) are analyzed and the few important results are shown in Table (1).

Table 1: Molecule Properties of Synthesized Compounds (7a-7n).

Ligand	**Molecule properties**					
	Molecular Weight	**LogP**	**Rotatable Bonds**	**H-Bond Acceptors**	**H-Bond Donors**	**Polar Surface Area**
7a	385.496	5.63929	4	4	3	167.197
7b	403.486	5.77839	4	4	3	171.363
7c	419.941	6.29269	4	4	3	177.501
7d	464.392	6.40179	4	4	3	181.065
7e	399.523	5.94771	4	4	3	173.562
7f	419.485	5.47857	5	5	3	176.476
7g	435.940	5.99287	5	5	3	182.614
7h	480.391	6.10197	5	5	3	186.178
7i	415.522	5.64789	5	5	3	178.676
7j	405.914	5.98427	4	4	3	171.136
7k	423.904	6.12337	4	4	3	175.301
7l	440.359	6.63767	4	4	3	181.439
7m	484.810	6.74677	4	4	3	185.003
7n	419.941	6.29269	4	4	3	177.501

Toxicity calculation has become essential in the drug discovery process because about 30% of drug molecules did not clear the clinical trials because of their toxicity. COVID-19 epitomic, in-silico studies also have been used for their process of drug discovery. It was concluded that the synthesized pyrimidine derivative (**7a-7n**) may be a promising hit molecule for the development of novel COVID therapeutics.

5. MOLECULAR DOCKING STUDIES

AutoDack Vina 1.1.2 (for window) is one of the freely existing software, crucially used to introductory molecular docking. The software offers multi-core capability, high performance, enhanced accuracy and ease of use. The target COVID-19 3D protein structures (6XC3, 6LU7, 6W9Q and 1R42) were downloaded from protein data bank (PDB) and then converted into pdbqt format. The newly synthesized ligands (**7a-7n**) were subjected to a molecular docking study against four important COVID-19 viral proteins. Protein and ligands preparations and their docking process are followed regular protocol and the discovery studio 4.5 (viewer) is used for the imaging process. Among the sequence of compounds, **7b** delivered outstanding binding energy against all the four (6XC3 [1a&1b], 6LU7 [2a&2b], 6W9Q and 1R42 [4a&4b]) proteins with binding energies -8.7, -8.7, -8.1 and -10.0 k.cal/mol respectively. Similarly, **7k** showed on greater dock score (-8.7 k.cal/mol) against 6LU7 protein; **7f-7i** showed on greater dock score (-8.4 k.cal/mol) against 6W9Q (7f-3a &3b) protein and **7b, 7e & 7n** showed on greater dock score (-10.0 k.cal/mol) against 1R42 protein. The docking results were compared with human trial drugs such as hydroxychloroquine (HQC), favipiravir and lopinavir. The outcome gives information to show an excellent result on COVID-19 proteins. The docking results were illustrated in T**able 2**. The docking images compounds**7b** and **7f** (2D & 3D) were given in **Figure 1.**

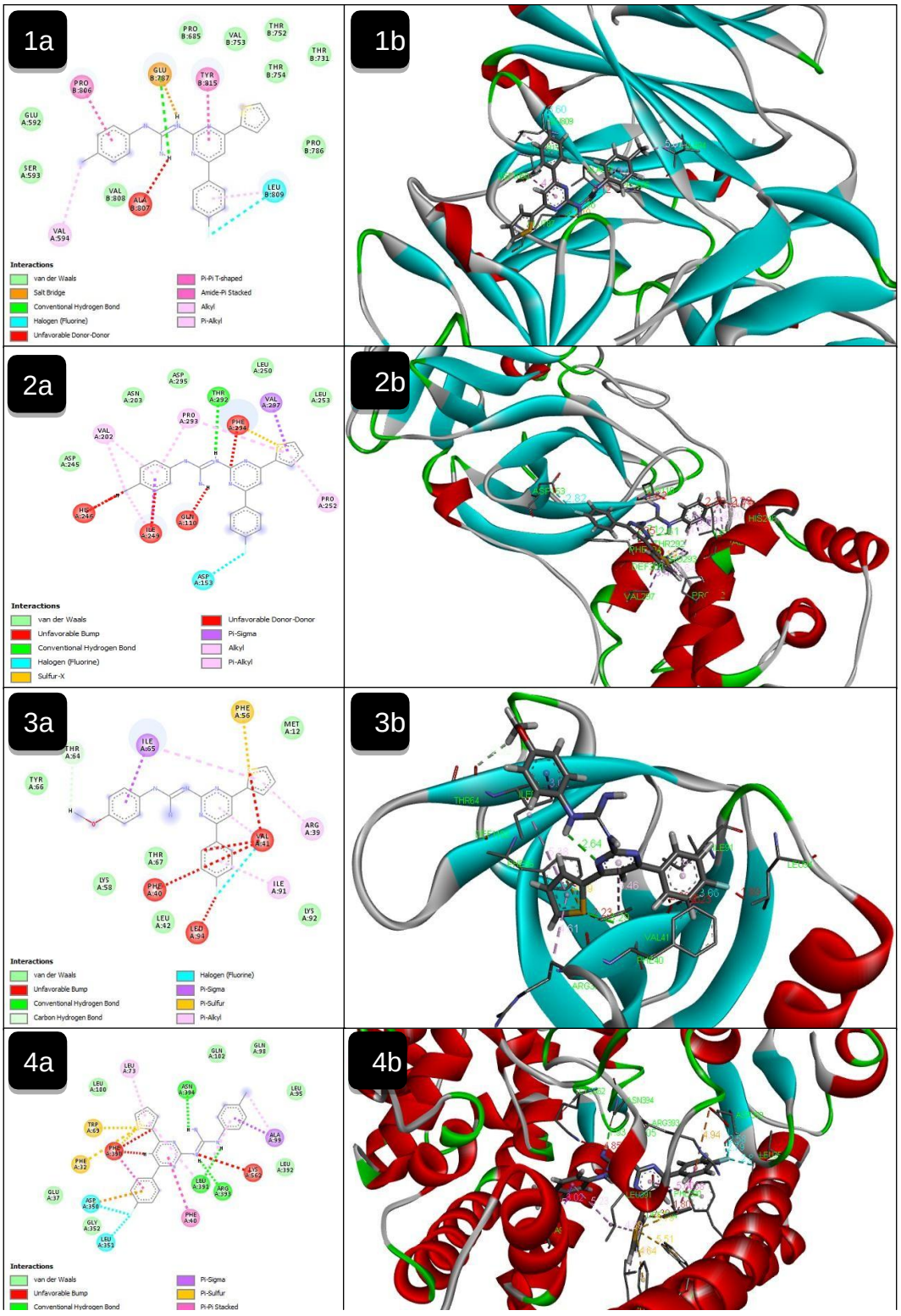


Fig. 1 2D and 3D images of compounds 7b (6XC3, 6LU7& IR42) and 7f (3a&b -6W9Q)

Table 2: Docking Results of the Designed Compounds (7a-7n) Towards COVID-19 Proteins.

Ligand	Binding Energy 6XC3 (k.cal/mol)	Binding Energy 6LU7 (k.cal/mol)	Binding Energy 6W9Q (k.cal/mol)	Binding Energy 1R42 (k.cal/mol)
7a	-8.5	-8.4	-8.0	-9.3
7b	**-8.7**	**-8.7**	-8.1	**-10.0**
7c	-8.4	-8.1	-8.1	-9.9
7d	-8.2	-8.1	-8.1	-9.5
7e	-8.6	-8.2	-8.0	**-10.0**
7f	-7.8	-8.4	**-8.4**	-9.6
7g	-7.8	-8.0	**-8.4**	-9.3
7h	-7.6	-8.0	**-8.4**	-9.3
7i	-8.0	-8.0	**-8.4**	-9.0
7j	-7.9	-8.4	-7.7	-9.9
7k	-8.4	**-8.7**	-8.1	-9.8
7l	-8.1	-8.1	-8.1	-9.9
7m	-8.2	-8.1	-8.2	-9.5
7n	-8.1	-8.1	-8.0	**-10.0**
Hydroxychloroquine	-4.9	-5.7	-4.5	-5.1
Favipiravir	-5.8	-6.0	-5.5	-6.6
Lopinavir	-8.1	-7.2	-7.0	-8.1

6. CONCLUSION

The novel guanidinopyrimidine derivatives were prepared in an efficient manner and characterized by FT-IR and NMR spectral studies. The recently synthesized compounds were subjected to pkSCM prediction highly useful for the pharmahopers. The molecular docking study results reviewed that compound **7b** shows excellent binding energy and other ligands also better than the FDA approved human trial drugs such as hydroxychloroquine, favipiravir and lopinavir. In total the newly synthesized ligands found to be with best results when compared to the above drugs.

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