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Research Article

Visible Light Promoted Catalyst Free, the Sustainable Synthesis of Dihydropyrano [2,3-C] Pyrazoles and Docking Studies with COVID-19 M^{pro}

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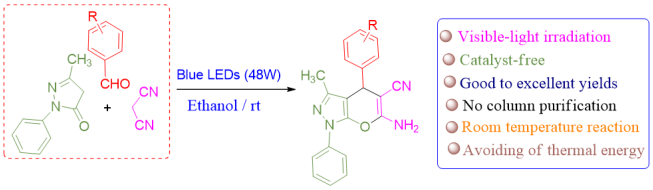
ABSTRACT

A highly efficient, simple, cost-effective, and environmentally benign method has been described for the synthesis of dihydropyrano[2,3-c]pyrazoles via one-pot, three-component condensation of 3-methyl-1-phenyl-2-pyrazoline-5-one, malononitrile, substituted aromatic aldehydes under visible light irradiation in catalyst-free condition at room temperature. This methodology's main advantage is good to excellent yield, simple work-up procedure, mild and clean reaction conditions, no chromatographic separation, and catalyst-free condition. All synthesized compounds are screened *in silico* with 6LU7, which is a COVID-19 M^{pro}. These computational studies were performed on AutoDock Vina, BIOVIA Discovery Studio 2017 R2, Auto Dock Tools-1.5.6 software. From screening results, we found that compound 4i and nitro group compounds 4d, 4e, 4f are showing a strong correlation at the active center of 6LU7. So, it is predicted that these compounds may be useful for COVID-19 patients.

GRAPHICAL ABSTRACT



INTRODUCTION

In recent times, safe, simple, high efficiency, high selectivity, green, and sustainable synthetic procedures have been developed in moderrn drug discovery. Green technologies, which were developed in modern chemistry, in which reduced hazardous substance, energy uses, cost, waste, toxicity and improvement in selectivity, efficiency of reactant, milder condition.[1] Worldwide, green methodologies, which are progressing day by day on the basis of environmentally benign transformation.[2-10] Green solvent combined with light, which is used to create one-pot (MCRs) i.e multicomponent reactions, has high potential for environmental approaches.[11-12] Visible light has a source of energy for performing green reactions in field of organic chemistry.[13] This methodology is non-toxic, cleaner, safer, nonpolluting, sustainable, eco-friendly, and have renewable characteristics.[14-16] The MCRs are an amazing tool for developing complex molecules with maximum simplicity in modern synthetic chemistry in which more than three available components react to form a single product. Worldwide, MCR methodology is a

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short-time reaction, easy, efficient, and plays a vital role in synthesizing many biologically active drugs.[17-24] In heterocycles chemistry, several synthetic and natural drugs were designed successfully through MCRs.[25-27] N-Phenyl-3-substituted 5-pyrazolone derivatives are an important class of oxygen-containing heterocyclic moieties. N-Phenyl-3-substituted 5-pyrazolone derivatives play a key role in the building block of many natural compounds[28-30] and show various biological activities such as anti-cancer[31-32], anti-allergic,[33] anti-microbial [34], anti-inflammatory,[35] and inhibitors of human Chk1 kinase.[36] Pyrano[2,3-c] pyrazole ring in their core structure were exhibited a different kind of biological activities in Fig. 1.

Several methodologies have been used for improved of dihydropyrano[2,3-c]pyrazoles via three-component reaction of 3-methyl-1-phenyl-2-pyrazoline-5-one, malononitrile, and aldehyde by using different conditions and catalysts such as ultrasound irradiation [44], ionic liquid[45], DABCO[46], nanosized magnesium oxide [47], basic catalysts,[48] CuO/ZrO_2,[49] brovine serum albumin[50], imidazole[51], $H_{14}[NaP_5W_{30}O_{110}]$[52], trichloroacetic acid [53], D,L-proline,[54] and cupreine.[55] This activiry of these compounds are predicted with COVID-19 M^{pro}. This study's prediction will give more detail that these compounds can be utilized *in vitro*, *in vivo*, and clinical trials.

Materials and Methods

General Experimental Procedures

3-methyl-1-phenyl-5-pyrazolone, all the aldehydes along with malononitrile were procured from Sigma-Aldrich and all solvents were purchased from Otto Chemie and Merck. Stuart digital melting point apparatus (SPM 10) was used to measure melting points and are uncorrected. Silica gel (GF_{254}) plates were used for TLC analysis. Infrared spectra analysis was measured using KBr pellets on a Perkin-Elmer 10.4.00 IR spectrophotometer. NMR spectra (500 MHz for ^{1}H-NMR, 125 MHz for ^{13}C-NMR, ^{1}H-^{1}H COSY, HSQC, and HMBC) of products were recorded on Bruker Avance Neo spectrometer using DMSO as a solvent and TMS as an internal reference. Mass spectra of synthesized compounds were analyzed on XEVO G2-XS QTOF instrument.

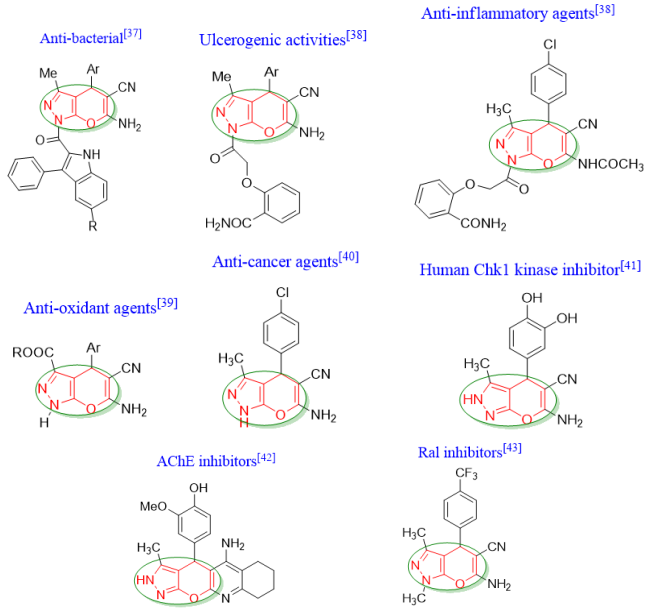


Fig. 1: Some biologically active molecules containing pyrano[2,3-c] pyrazole moiety.

Synthesis of Dihydropyrano[2,3-c]pyrazoles derivatives (4a-l)

A combination of substituted aldehyde (aromatic) (1 mmol) and malononitrile (1 mmol) were added in 5 ml ethanol with a magnetic stirrer in a 50 ml round-bottom flask under visible light irradiation using 48W blue LED strip at room temperature. 3-methyl-1-phenyl-2-pyrazoline-5-one was added to the reaction mixture when intermediate was formed and monitored by TLC. The monitoring of the stirring reaction mixture was done by TLC for 6h at room temperature. After completion of the reaction, white solid mass was precipitated, which filtered and washed with cold EtOH. Finally, the product was further purified by recrystallization using a solvent mixture of CH_3CN and chloroform.

Spectral Data of Synthesized Compounds

6-amino-4-(2,4-dichlorophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4a): Obtained as white solid; yield: 88%; mp 190 °C; IR (KBr, cm^{-1}): 3457, 3324, 2197, 1659, 1589, 1519, 1393, 1268, 1126, 1068, 1029, 815, 757, 690; ^{1}H-NMR (500 MHz, DMSO-d6) δ 1.78 (s, 3H, CH_3), 5.15 (s, 1H, CH), 7.33 (m, 3H, ArH + NH_2), 7.38 (m, 1H, ArH), 7.43 (dd, *J* = 8.4, 2.1 Hz, 1H, ArH), 7.49 (m, 2H, ArH), 7.62 (d, *J* = 2.15 Hz, 1H, Ar), 7.79 (d, J = 7.6, 2H, ArH); ^{13}C-NMR (125 MHz, DMSO-d6) δ 12.21, 33.47, 56.10, 97.17, 119.37, 119.92, 126.15, 127.98, 128.81, 129.20, 132.37, 132.40, 132.97, 137.33, 139.14, 144.16, 144.70, 1259.82. EI-MS: Anal. Calcd for [$C_{20}H_{15}Cl_2N_4O + H^+$]: 397.07; found, 397.06.

6-Amino-4-(3,4,5-trimethoxy-phenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4i): Isolated as white solid; yield: 91%; mp 190 °C; IR (KBr, cm^{-1}): 3461, 3323, 2197, 1662, 1592, 1521, 1459, 1425, 1390, 1325, 1235, 1128, 1069, 766; ^{1}H-NMR (500 MHz, DMSO-d6) δ 1.87 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 3.74 (s, 3H, 2 × OCH_3), 4.66 (s, 1H, CH), 6.56 (s, 2H, ArH), 7.21 (s, 2H, NH_2), 7.31 (t, *J* = 7.4 Hz, 1H, ArH), 7.48 (t, *J* = 7.6 Hz, 2H, ArH), 7.80 (d, *J* = 7.7 Hz, 2H, ArH); ^{13}C-NMR (125 MHz, DMSO-d6) δ 12.70, 36.91, 55.78, 57.73, 59.87, 98.25, 104.87, 119.75, 119.99, 125.98, 129.20, 136.27, 137.48, 139.13, 143.70, 145.26, 152.76, 159.45.

6-Amino-4-(thiophen-2-yl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4k): Isolated as white solid in colour; yield: 86%; mp 180 °C; IR (KBr, cm^{-1}): 3453, 3319, 2198, 1659, 1592, 1516, 1389, 1125, 1066, 753, 705; ^{1}H-NMR (500 MHz, DMSO-d6) δ 1.92 (s,

3H, CH_3), 5.09 (s, 1H, CH), 6.98 (m, 1H, ArH), 7.0 (d, J = 3.4 Hz, 1H, ArH), 7.29 (s, 2H, NH_2), 7.34 (t, J = 7.45 Hz, 1H, ArH), 7.43 (d, *J* = 5.05 Hz, 1H, ArH), 7.49 (t, J = 8.5 Hz, 2H, ArH), 7.78 (d, J = 7.65 Hz, 2H, ArH); ^{13}C-NMR (125 MHz, DMSO-d6) δ 12.40, 31.82, 58.43, 98.53, 119.68, 119.82, 124.89, 125.33, 126.16, 126.59, 129.28, 137.31, 143.32, 145.31, 148.68, 159.12. EI-MS: Anal. Calcd for [$C_{18}H_{14}N_4OS + H^+$]: 335.11; found, 335.09.

Molecular Docking Studies

Crystal structure of ligands (N-Phenyl-3-substituted 5-pyrazolone derivatives) were carried out using software Chem 3D Pro 12.0. The energy minimization of all synthesized derivatives were done. The computer gasteiger charge was added and non-polar hydrogen was merged in all ligands by Auto Dock Tool software. At last, ligands were saved as in pdbqt file. The structure of COVID-19 M^{pro} was used for the target, which was retrieved from the RCSB website. PDB ID of this protein is 6LU7 and resolution 2.16 A°. Downloaded protein was opened on BIOVIA Discovery Studio software and water molecules, ligand from protein was removed. Next, the protein was loaded on Auto Dock Tools software, and polar hydrogen, gasteiger charge was added. The grid was generated with dimensions and center at the active center of the protein with ligand interaction point. Finally, docking of all synthesized products was completed by Auto Vina.

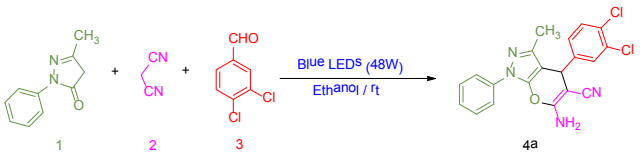
Results and Discussion

Initially, we studied a series of the three-component reactions of 3-methyl-1-phenyl-2-pyrazoline-5-one, malononitrile, and aromatic aldehyde in 5 mL ethanol using 48 W blue LED strips under catalyst-free condition at room temperature. TLC monitored progress of reaction and consumption of starting materials. Reaction was successfully completed and give 88% yield of product **4a** in 6 hours. Structure of product **4a,** was confirmed by melting point and spectroscopic studies, like IR, ^{1}H-NMR, ^{13}C-NMR, and MASS (Table 3, entry 1). Next, we performed the reaction in different solvents such as dichloromethane, ethyl acetate, water, acetonitrile, ethanol, DMF, glycerol, methanol and ethanol/water 1:1 (Table 1, entries 1-9). In the case of dichloromethane, ethyl acetate, water, giving yield in trace in 12 h at room temperature. The yield of product was improved when the reaction was performed in acetonitrile (48%), DMF (65%), glycerol (68%), methanol (82%), respectively. It was found that a better yield (88%) was offered in ethanol solvent (Table 1, entry 5).

Next, we investigated reaction using blue LED of different intensities such as 12 W, 24 W, 36 W, and 48 W. When we used 12 W blue LED for this reaction, it provides desired product **4a** in lower yields (Table 2, entry 4). Yields of products were increased in same when used blue LED of 24 W and 36 W (Table 2, entries 2-3). Better yields 88% of product **4a** was offered when 48 W blue LED was used for 6 hours at room temperature (Table 2, entry 1).

After determining the optimized conditions, we started our reactions with benzaldehyde, malononitrile, and 3-methyl-1-phenyl-2-pyrazoline-5-one under optimized reaction conditions and obtained the desired dihydropyrano[2,3-c]pyrazoles derivative **4b** in 87% yield within 6 hours (Table 3, entry 2). Next, we performed of reactions with substituted aromatic aldehydes such as 4-NO_2, 3-NO_2, 2-NO_2, 4-OMe, 4-Cl, 3,4-di-OMe, 3,4,5-tri-OMe, 4-Et with 3-methyl-1-phenyl-2-pyrazoline-5-one, and malononitrile under optimized reaction conditions, affording the corresponding dihydropyrano[2,3-c] pyrazoles derivatives (**4c-4j**) in good to excellent yields (Table 3, entries 3-10). Similarly, this reaction was also performed under the same reaction condition with hetero-aldehydes such as thiophene-2-carboxaldehyde and pyridine-3-carboxaldehyde, afforded products (**4k-4l**) in 86-87% yields (Table 3, entries 11-12). Excitingly, It has been observed that aromatic substituted benzaldehyde afforded products smoothly with electron-withdrawing groups as well as electron-donating groups.

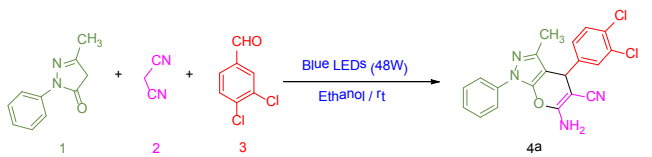
Table 1: Optimization of the Reaction Conditions for the synthesis of compound 4a[a]



Entry	*Solvent*	*Time (h)*	*1:2:3 (mmol)*	*Yield of 4[b] (%)*
1	CH_2Cl_2	12	1:1:1	Trace
2	EtOAc	12	1:1:1	Trace
3	H_2O	12	1:1:1	Trace
4	CH_3CN	10	1:1:1	48
5	**EtOH**	**6**	**1:1:1**	**88**
6	DMF	10	1:1:1	65
7	Glycerol	10	1:1:1	68
8	Methanol	6	1:1:1	82
9	EtOH/H_2O (1:1)	8	1:1:1	72

[a]Reaction conditions: 3-methyl-1-phenyl-2-pyrazoline-5-one (1 mmol), malononitrile (1 mmol), 2,4-dichloro benzaldehyde, under blue LED (48 W) at room temperature. [b]Isolated yields.

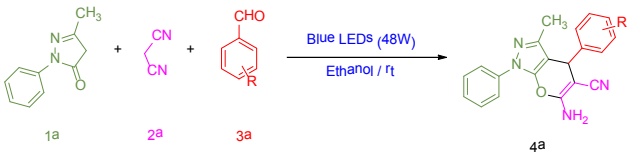
Table 2: Optimization of visible light intensity for synthesis of compound 4a[a]

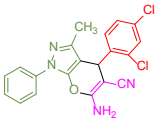
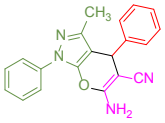
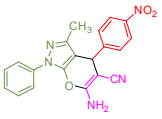
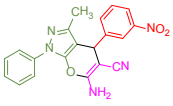
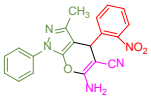
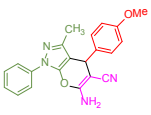
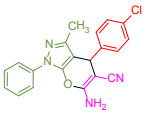
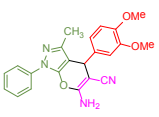
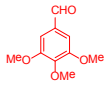
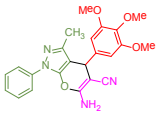
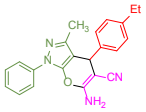
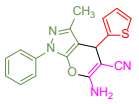
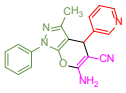


Entry	*Visible light intensity*	*Time (h)*	*Yield %*
1	48 W (Blue LED)	6	88
2	36 W (Blue LED)	7	82
3	24 W (Blue LED)	7	80
4	12 W (Blue LED)	8	74

[a]All reactions were carried out using visible light at room temperature. [b]Isolated yields.

Table 3: Substrate scope for the synthesis of dihydropyrano[2,3-c]pyrazoles derivatives[a]



Entry	*R^1*	*Product[a]*	*Time (h)*	*Yield[b] (%)*	*MP (°C)*	*Reported MP (°C)*
1		 4a	6	88	190	184-185[56]
2		 4b	6	87	174	170-172[56]
3		 4c	5	92	197	195-196[56]
4		 4d	5	85	190	188-190[56]
5		 4e	6	82	175	174-177[60]
6		 4f	6	88	178	176-178[56]
7		 4g	6	87	174	175-177[61]
8		 4h	5	89	194	193-195[57]
9		 4i	5	91	190	194-196[58]
10		 4j	7	83	181	----
11		 4k	8	86	180	172-174[56]
12		 4l	6	87	216	213-215[59]

[a]Reactions were performed with 3-methyl-1-phenyl-2-pyrazoline-5-one (1 mmol), malononitrile (1 mmol), and substituted aromatic aldehydes (1 mmol) under visible light irradiation (48 W) at room temperature.

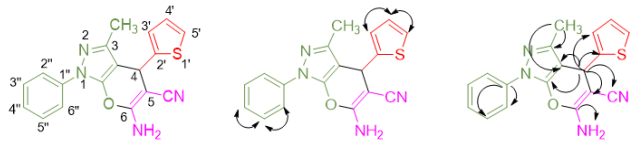


Fig. 2: (A) Structure **(B)** COSY **(c)** HMBC correlation of product (4r).

All the synthesized products were characterized by melting point and spectroscopic techniques such as IR, ^{1}H-NMR, ^{13}C-NMR, COSY, HSQC, HMBC and MASS. From the IR spectrum of compound 4k (Table 3, entry 11), frequencies of strong absorption bands appeared at 3453, 3319, and 2198 cm-1 due to NH2 and CN. ^{1}H-NMR spectrum of **4k** showed the singlet peaks at δ_H 1.92 (s, 3H), 5.09 (s, 1H), and 7.29 (broad s, 2H) which corresponds to the –CH_3, -CH, and -NH_2 groups, respectively. The ^{1}H-NMR decoupled ^{13}C-NMR experiments showed the presence of 16 distinct signals with characteristic peaks at δ_C = 12.4, 31.82, 119.68, 159.12, 145.31 ppm due to –**CH_3**, **CH**-thiophene, -**CN**, **CH**-NH_2, **C**=N-N carbons, respectively. COSY data of compound **4k** showed a correlation between δ_H 7.77 (H-2") and δ_H 7.49 (H-3") as well as δ_H 7.49 (H-3") and 7.32 (H-4") in N-phenyl ring. COSY correlation in the 4-thiophene ring were observed between δ_H 7.0 (H-3') and δ_H 6.97 (H-4') as well as δ_H 6.97 (H-4') and δ_H 7.43 (H-5'). In HMBC experiment, H-4 (δ_H 5.09) correlated to C-5 (δc 58.43), C-8 (δc 148.68), C-9 (δc 98.53), C-2' (δc 143.32), C-3' (δc 124.89), CN (δc 119.68). Similarly, methyl proton (δ_H 1.92) showed connectivity to C-3 (δc 145.31), C-9 (δc 98.53). HMBC correlation of NH_2 proton (δ_H 7.29) was observed from C-6 (δc 159.12). The structure of 4k, COSY correlation, and HMBC correlation were summarized in Fig. 2 and 3.

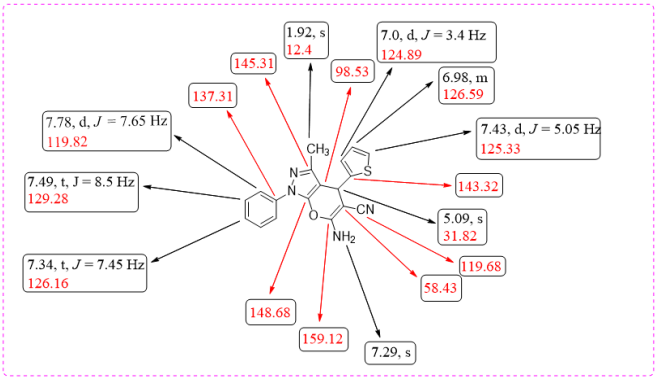


Fig.3: ^{1}H-NMR and ^{13}C-NMR assignment of product 4r.

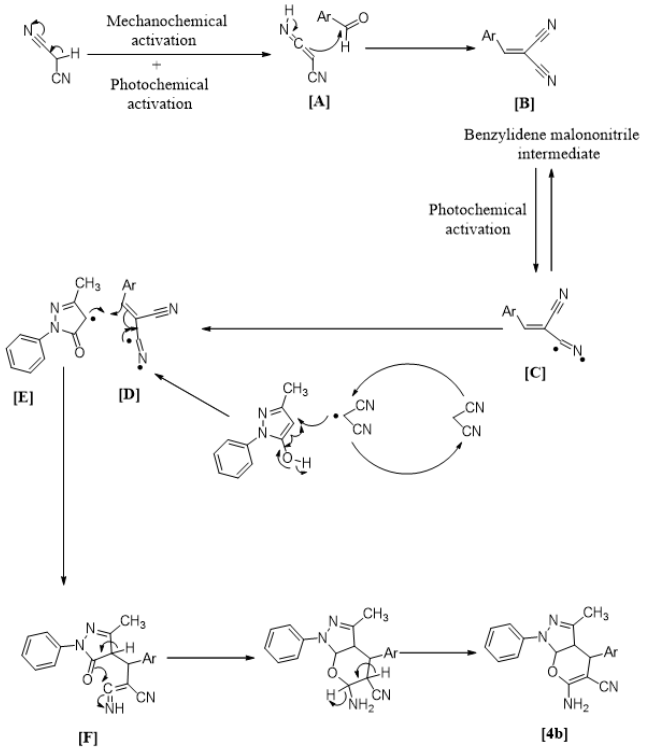


Fig. 4: Synthesis of the dihydropyrano[2,3-c]pyrazoles showing plausible reaction mechanism.

Finally, a plausible mechanistic pathway was proposed for dihydropyrano[2,3-c]pyrazoles derivatives synthesis in blue LED is illustrated in Fig. 4. We consider that the initial step involves the condensation reaction of malononitrile with aromatic aldehydes through mechanochemical activation under irradiation with visible light to produce intermediate **A**. Photochemical activation seems in the second step, which has a definite role. Then, visible light activates the benzylidene malononitrile intermediate **B** to form free radical intermediate **C**. Then, Intermediate C play a role in abstract a methylenic hydrogen from malononitrile, generating malononitrile radical, which in turn abstracting hydrogen from 3-methyl-1-phenyl-2-pyrazoline-5-one, generating intermediate **E**. Then, **E** further reacts with intermediate **D,** which generating intermediate **F**. Then, intramolecular

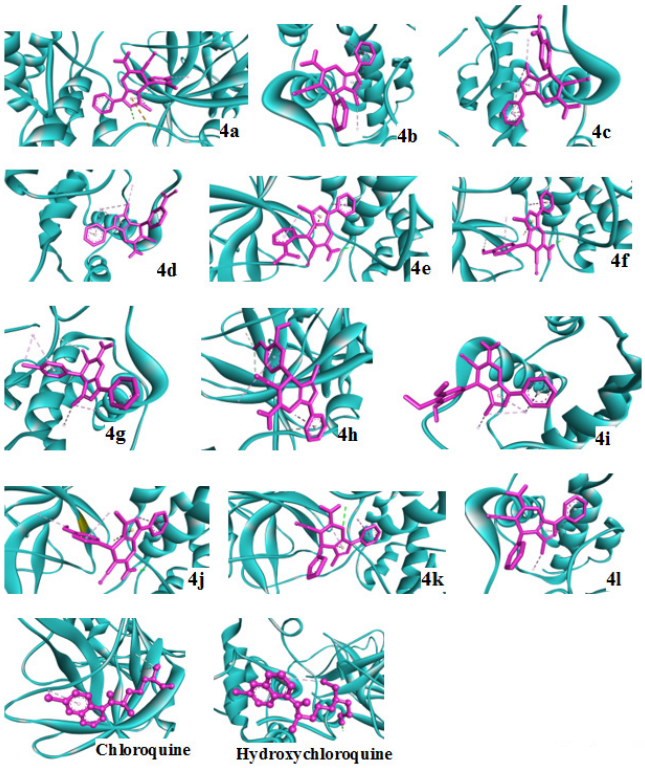


Fig. 5: Visulization of molecular docking of 6LU7 with compounds (ball and stick)

cyclization of intermediate **F** provides the desired product **4b**.

Docking Prediction With COVID-19 M^{pro}

Prediction of binding energy between all synthesized ligands and COVID-19 M^{pro} are calculated (*in silico*). The binding energy of all ligands is compared with chloroquine (-5.6 Kcal/mole) and hydroxychloroquine (-4.6 Kcal/mole). At present, these drugs are highly effective in clinical practice for COVID-19 patients and after ethical approval as a trial as stated by the WHO.[62] These are used as a standard.

6LU7 is the main protease (M^{pro}), which is present in COVID-19. These proteases were demonstrated by Chinese researchers, which is a potential drug target. Screening of all synthesized compounds are performed with these M^{pro}. Compound **4i** shows high binding energy -7.6 Kcal/mole with 6LU7 protein, as summarized in Figs 5-7. The conventional hydrogen binding, pi-donar hydrogen binding, and alkyl/pi-alkyl hydrophobic binding are displayed with amino acid Leu, Tyr, Met, at the active site of 6LU7. Interaction of compound **4i** is completed with 6LU7 by the formation of classical hydrogen binding interaction of –NH2 group with amino acid Leu-272 at a distance 3.02, pi-donar hydrogen binding interaction of benzene ring with amino acid Tyr-239 at a distance 3.44, and alkyl and pi-alkyl hydrophobic interaction with amino acid Leu-287 at a distance 4.63, 4.76, 5.16, and Met-276 at a distance 3.59. Compound **4d** shows binding energy -7.5 Kcal/mole

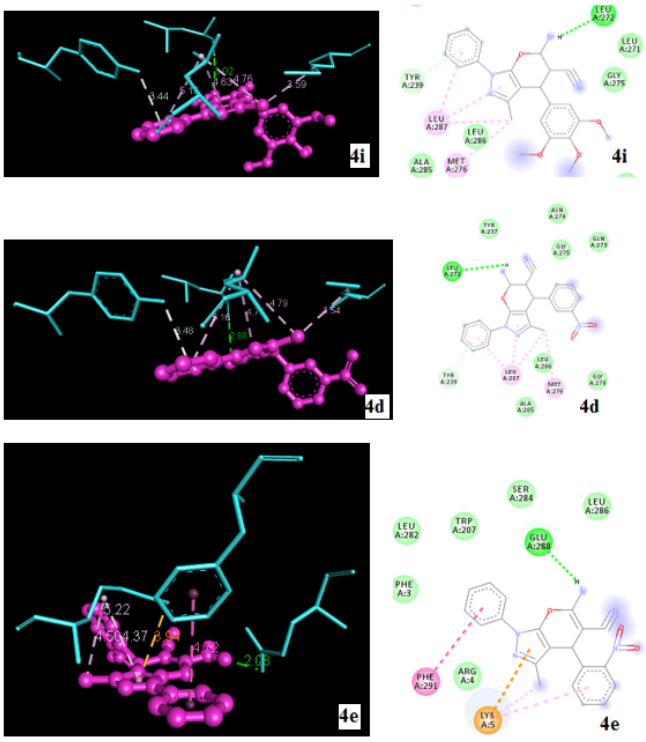


Fig. 6: 3D and 2D interaction of synthesized compounds at active site of 6LU7.

(Figs 5-7). Conventional hydrogen bond, pi-donar hydrogen bond, and alkyl/pi-alkyl hydrophobic bond are found with amino acid Leu, Tyr at active center of 6LU7. Binding interaction of compound **4d** is successfully completed with 6LU7 by hydrogen binding interaction of NH2 group with amino acid Leu-272 at a distance 2.88, benzene ring with amino acid Tyr-239 at distance 3.48, and hydrophobic interaction with amino acid Leu-287 at distance 4.75, 4.79, 5.16 and Met-276 at a distance 3.54. Compound **4e** has interacted with binding energy -7.3 Kcal/mole (Fig. 5,6,7). Compound **4e** is interacted with 6LU7 protein by conventional hydrogen binding of NH2 with amino acid Glu-288 at a distance 2.08, pi-cation binding of benzene ring with amino acid Phe-291 at a distance 3.49, pi-pi T-shaped binding of hetero ring with amino acid Lys-5 4.72, and alkyl/pi-alkyl hydrophobic binding with amino acid Lys-5 at a distance 4.37, 4.50, 5.22. Binding energies of compounds 4a, 4b, 4c, 4f, 4g, 4h, 4j, 4k, 4l are showed in renge from -6.2 Kcal/mole to -7.1 Kcal/mole. Structures of these compounds are visualized (Fig. 5).

The structure activity relationship (SAR) of all compounds are shown in Fig. 7. Compound 4i is more active because strong correlation with binding energies 7.6 Kcal/mole. Nitro group compounds such as **4d-f** are showed high activity with binding energies 7.1 Kcal/mole, 7.5 Kcal/mole, and 7.3 Kcal/mole, in which a strong correlation is found of compound **4e**. 4-ethyl and 3-methoxy group compounds **4j** and **4g** are showed moderate activity with binding energy -7.1 Kcal/mole and -7.0 Kcal/mole. Hetero compounds **4k** and **4l** are showed weak activity because

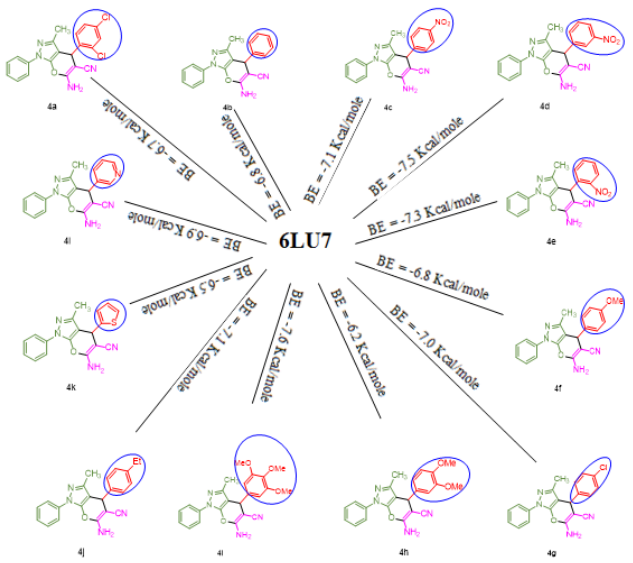


Fig. 7: Structure activity relationship (SAR) of all synthesized compounds with 6LU7 M^{pro}.

of weak correlation with binding energies -6.5 Kcal/mole and -6.9 Kcal/mole. From SAR, it is predicted that nitro group compounds **4d, 4e, 4f** are high active and maybe useful in the treatment of COVID-19.

Conclusion

In summary, we have successfully developed a highly efficient, cost-effective, visible light activated one pot multicomponent component reaction of 3-methyl-1-phenyl-2-pyrazoline-5-one, malononitrile, substituted aromatic aldehydes for the synthesis of dihydropyrano[2,3-c] pyrazoles derivatives under catalyst-free conditions at room temperature. The noteworthy point of these protocol are environmentally benign reaction conditions, high atom economy, good to fantastic yields, easy workup procedure. The synthesized compounds are tested in silico with COVID-19 M^{pro}. All compounds (**4a–l**) are successfully docked with 6LU7 protein, in which **4i** compound shows high inhibitory activity with strong correlation. This prediction may be useful for experimental work *in vitro*, and *in vivo*.

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