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Review Article

COVID-19 Main Protease Molecular Docking Simulation against Synthesised Bis Imidazo [4,5-b] Indole using Nano Au-Zeolite

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Abstract

Novel compounds prepared by one-pot, multicomponent hantzsch reaction of 1, 1'-(butane-1,4-diyl)bis(indoline-2,3-dione), aromatic aldehydes and ammonium acetate, in presence of ethanol/nano Au-zeolite catalyst under mild condition. This research study the effect of novel synthesised 1,3-bis(2-arylimidazo[4,5-b] indol-4(3H)-yl)propane derivatives against COVID-19 main protease. Molecular docking simulation study was done using PDB:ID (7BUY) of COVID-19 main protease against the syntheised compounds revealed that compound 6d was strongly fit into the active sites of the target protein through five bindings, and hence, it was considered as promising inhibitor for COV-19 proliferation.

Keywords: Viral protein; Imidazo[4,5-b]indole; Nano Au-zeolite; COVID-19 main protease

Introduction

Coronavirus Disease (COVID-19) pandemic is a respiratory tract disease. The first report was in December 2019 in Wuhan, China [1]. On March 11, 2020 World Health Organization (WHO) declares (COV-19) a pandemic [2]. A serial viral load analysis in COVID-19 patients was observed during the first week of symptom [3-5]. Antibody production starts approximately 10 days after symptom onset. Following the COVID-19 pandemic outbreak, several repository drugs have been tested for activity against CoV-2 [4-17]. Protein 3C-like proteinase severe acute respiratory syndrome corona virus 2 and it has been identified as an important drug target due to its role in viral replication [9,18,19]. The lack of a potent 3C inhibitor and the availability of the X-ray crystal structure of 3C-like (PDB-ID 7BUY) [20] to perform computational studies to identify commercially available potential inhibitors.

Results and Discussion

Molecular docking

Docking simulation was performed in this study using Molecular Operating Environment (MOE) 2008.10 [21]. The crystal structure of COVID-19 main protease was reported for (pdb code: 7BUY). All the interaction energies and different calculations were calculated. 1,3-bis(2-arylimidazo[4,5-*b*]indol-4(3*H*)-yl)propane derivatives 6a-e were docked to the binding pocket of (pdb: 7BUY). Compounds were docked into the validated binding site and their ability to interact with the binding site rationalizes their activity as indicated by their docking pattern and docking scores (Figures 1-3) (Table 1). The theoretical binding mode between 6a and (pdb: 7BUY) in which the phenyl ring formed arene-arene bond with the residues Phe 8, and solvent contact between imidazole nitrogen atom and Gln 99 (Figure 1). Compound 6b where the phenyl group of 6a were substituted by methoxy group in its para position where it interacts with Gln 127 (bond length: 2.4 Å) (Figure 1). In order to increase the activity of 6a, two methoxy groups were added to the aromatic ring to give 6c as they interact with a residue, one of them interact with Ser 46 (bond length: 1.95 Å) and the other interact with His 161 (bond length: 1.95 Å), while the nitrogen atom of imidazole ring interact with Thr 25 (bond length: 2.99 Å). The theoretical binding mode between 6c and (7BUY) pocket is shown in (Figure 2). By increasing methoxy groups the interaction with (pdb: 7BUY) increase. So, compound 6d which have three methoxyes group form five bonds with Ser 158 (bond length: 2.96 Å), Asn 151 (bond length: 2.69 Å), Thr 243 (bond length: 2.59 Å), Gln 110 (bond length: 1.95 Å), Asn 151 (bond length: 1.71 Å) (Figure 3). Detailed analysis showed that **6e** has a nitro group in its *para* aryl position interact with Pro 108 (bond length: 1.28 Å) (Figure 2). VIRAL PROTEIN of COVID-19 main protease screening assay promoted that compounds 6d showed promising inhibitory activity.

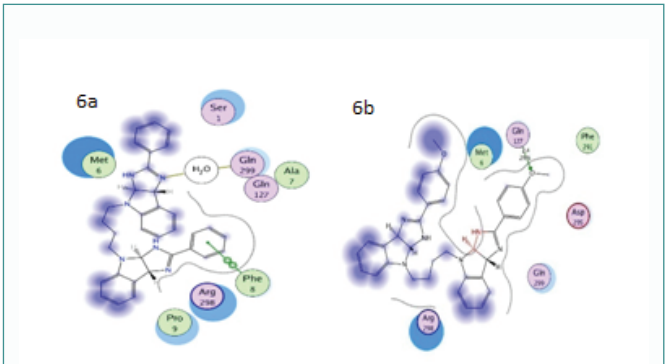

Figure 1: 2D interaction of Compound 6a, 6b was docked into the binding pocket of pdb: 7BUY.

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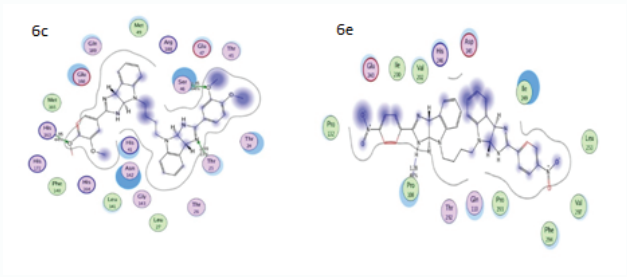


Figure 2: 2D interaction of Compound 6c, 6e was docked into the binding pocket of pdb: 7BUY.

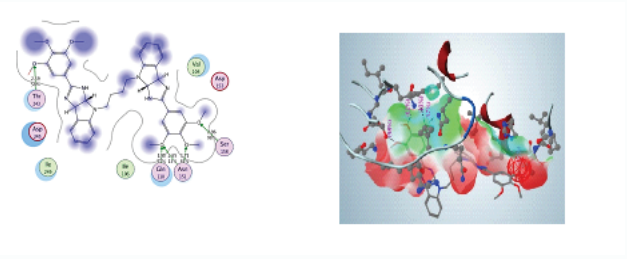


Figure 3: 2D, 3D interaction of Compound 6d was docked into the binding pocket of pdb: 7BUY.

Table 1: Molecular docking simulation of 6a-e.

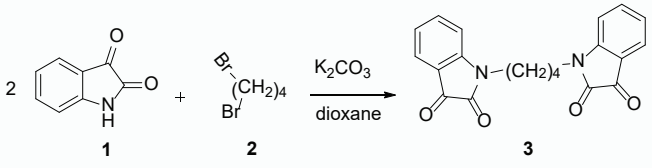
compound	S (score)
6a	-10.79
6b	-9.88
6c	-9.33
6d	-10.11
6e	-10.98

Chemistry

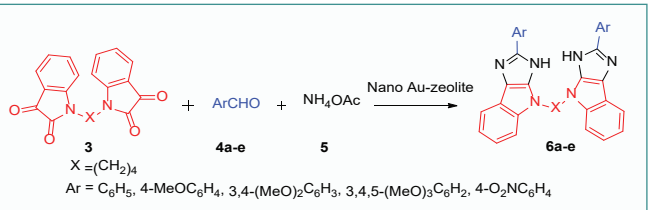
The 1,1'-(butane-1,4-diyl)bis(indoline-2,3-dione) 3 were chosen as precursors. It was prepared by reaction of 1*H*-indol-2,3-dione 1 with the appropriate 1,4-dibromobutane 2 in the presence of anhydrous K_2CO_3 and dioxane (Scheme 1) [22-24].

The three-component reaction of bis(indoline-2,3-diones) 3 with aldehyde derivatives 4a-e and ammonium acetate 5 in ethanol using nano Au-zeolite as a catalyst under convential heating for 120 min afforded the corresponding 1,3-bis(2-arylimidazo[4,5-*b*]indol-4(3*H*)-yl)propane derivatives 6a-e (Scheme 2).

To optimum the reaction conditions using several parameters, such as screening of different solvents and catalysts, effect of time and temperature on the model reaction 6a (Table 2). It was clear that high yield and low time of reaction reported in using nano Au-zeolite catalyst and ethanol solvent under reflux for 120 min at 80°C to give 93% yield. Noted that nano Au-zeolite were prepared as in literature [25]. The yield of different derivatives was shown in (Table 3).



Scheme 1: Synthesis of bis(indoline-2,3-diones) 3.



Scheme 2: Synthesis of 1,3-bis(2-arylimidazo[4,5-b]indol-4(3H)-yl)propane derivatives 6a-e.

Table 2: Optimization of the reaction conditions for 6a under conventional condition.

Entry	Solvent/catalyst[a]	Temperature (°C)	Time (min)	Yield (%)[b]
1	EtOH/ No catalyst	80	240	trace
2	Acetic acid/ No catalyst	120	420	50
3	EtOH/ L-proline	80	420	80
4	EtOH/ nano Au-zeolite	80	120	93
5	EtOH/ Piperidine	80	120	82
6	EtOH/nanoZnO	80	180	85
7	H2O/nano Au-zeolite	80	300	84
8	Acetic acid/nano Au-zeolite	120	180	90

[a]The amount of catalyst 0.18 mmol/mmol of substrate 3; [b]Isolated yield.

Table 3: The structure of 6a-e was confirmed by their spectral data (IR, MS and ^1H, ^{13}C-NMR) and elemental analyses.

Entry	Product	Ar	Classical	
			Time (min)	Yield%[a]
1	6a	C_6H_5	120	93
2	6b	4-$MeOC_6H_4$	120	92
3	6c	3,4-$(MeO)_2C_6H_3$	120	90
4	6d	3,4,5-$(MeO)_3C_6H_2$	120	89
5	6e	4-$O_2NC_6H_4$	120	90

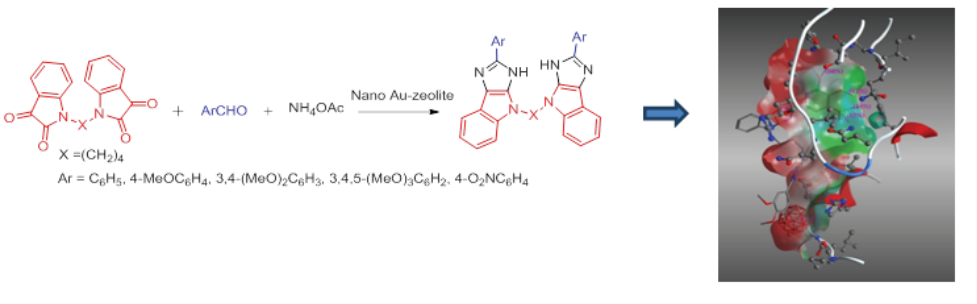
[a]Isolated yield

Conclusion

Molecular docking simulation can be used effectively to accelerate the process of developing therapeutic agents for the treatment of Covid-19 disease. In this study, analysis of the binding interactions of bisimidazo[4,5-*b*]indole against pdb (7BUY) revealed that compound 6d (Scheme 3) has high activity for the inhibition of 3C-like proteinase. Bisimidazo[4,5-*b*]indole were prepared under convential method using nano Au-zeolite in hantzsch reaction of 1,1'-(butane-1,4-diyl) bis(indoline-2,3-dione), aromatic aldehydes and ammonium acetate, high yields were obtained.

Experimental

Molecular modeling study: All the molecular modeling calculations and docking simulation studies were performed utilizing Molecular Operating Environment (MOE) 2008.10 [21]. The three-dimensional X-ray structures of COVID-19 main protease (PDB code: 7BUY) were obtained from the Protein Data Bank through the internet. The prepared compounds were built using the MOE builder interface and subjected to energy minimization using the included MOPAC. The produced model was subjected to Systematic Conformational Search where all items were set as default with RMS gradient of 0.01 kcal/mole and RMS distance of 0.1A°. Protein was selected and downloaded from the Protein Data Bank (PDB ID: 7BUY). The proteins were prepared for docking studies where the bound ligand molecule was removed from the protein active site, and then hydrogen atoms were added to the isolated target with their



Scheme 3: Synthesis of bisimidazo[4,5-b]indole against pdb (7BUY) revealed that compound 6d.

standard geometry. MOE alpha site finder was used for specifying the active sites in the protein structure and then dummy atoms were created from the obtained alpha spheres. The obtained model was then used in predicting the target diligent- protein interactions at the active site.

Chemistry

Melting points were measured on an electrothermal 9100 apparatus. IR spectra were determined on a Shimadzo IR-470 spectrometer. ^{1}HNMR and ^{13}CNMR spectra were recorded on a 400MHz Bruker DRX-400 in DMSO-d_6 as solvent and TMS as an internal standard. All the chemicals were purchased from Merck and used without further purification. All solvents used were dried and distilled according to standard procedures.

General Procedure for the Synthesis of 1,1'-(butane-1,4-diyl) bis(indoline-2,3-dione) 3: A reaction mixture of isatin 1 (0.3 mmol) and 1,4-dibromobutane 2 (0.8 mmol) in presence of K_2CO_3 (30 mmol) was refluxed in dioxane (10 mL) for 30 min, to give Yields: 80% [24].

General Procedure for the Synthesis of 1,3-bis(2-Arylimidazo[4,5-*b*]indol-4(3*H*)-yl)propane derivatives 6a-e: A mixture of 1,1'-(butane-1,4-diyl)bis(indoline-2,3-dione) (0.3 mmol) (3), aromatic aldehyde (0.6 mmol) (4), and ammonium acetate (1 mmol) (5) in ethanol /zeolite-nano Au particles was heated under reflux conditions for 120 min. Reaction progress was monitored through TLC. The product acidified with HCl (1N) to get precipitate then add ethyl acetate, wash the yield with distilled water. Filtrate and recrystallization with ethanol and dried [26-29].

1,4-Bis(2-phenylimidazo[4,5-*b*]indol-4(3*H*)-yl)butane 6a: IR (KBr): υ_{max} 3450, 1650, 1560 cm^{-1}. ^{1}HNMR (400MHz, DMSO-d_6): δ=2.12 (m, 4H, CH_2), 3.39 (t, 4H, CH_2), 7.30-8.18 (m, 18H, Ar), 11.42 (br s, 2H, NH) ppm, Mass m/z: 520 (M^+, 38%), Anal. Cald. For $C_{34}H_{28}N_6$ (520.) C, 78.44; H, 5.42; N, 16.14%; Found: C, 78.32; H, 5.40; N, 16.09%.

1,4-Bis(2-(4-methoxyphenyl)imidazo[4,5-*b*]indol-4(3*H*)-yl) butane 6b: IR (KBr): υ_{max} 3445, 1650, 1562 cm^{-1}. ^{1}HNMR (400MHz, DMSO-d_6): δ=2.10 (m, 4H, CH_2), 3.33 (s, 6H, 2OCH_3), 3.40 (t, 4H, CH_2), 7.35-7.78 (m, 16H, Ar), 11.32 (br s, 2H, NH) ppm, Mass m/z: 580 (M^+, 39%), Anal. Cald. For $C_{36}H_{32}N_6O_2$ (580) C, 74.46; H, 5.55; N, 14.47%; Found: C, 74.43; H, 5.50; N, 14.39%.

1,4-bis(2-(3,4-dimethoxyphenyl)imidazo[4,5-*b*]indol-4(3*H*)-yl)butane 6c: IR (KBr): υ_{max} 3444, 1650, 1565 cm^{-1}. ^{1}HNMR (400MHz, DMSO-d_6): δ=2.10 (m, 4H, CH_2), 3.33 (s, 6H, 4 OCH_3), 3.35 (s, 6H, 2OCH_3), 3.55 (t, 4H, CH_2), 7.25-7.88 (m, 14H, Ar), 11.30 (br s, 2H, NH) ppm, Mass m/z: 640 (M^+, 41%), Anal. Cald. for $C_{38}H_{36}N_6O_4$ (640) C, 71.23; H, 5.66; N, 13.12%; Found: C, 71.20; H, 5.60; N,13.09%.

1,4-bis(2-(3,4,5-trimethoxyphenyl)imidazo[4,5-*b*]indol-4(3*H*)-yl)butane 6d: IR (KBr): υ_{max} 3444, 1650, 1565 cm^{-1}. ^{1}HNMR (400MHz, DMSO-d_6): δ=2.12 (m, 4H, CH_2), 3.35 (s, 6H, 4 OCH_3), 3.42 (s, 12H, 4OCH_3), 3.97 (t, 4H, CH_2), 7.32-8.08 (m, 12H, Ar), 11.30 (br s, 2H, NH) ppm, Mass m/z: 700 (M^+, 43%), Anal. Cald. for $C_{40}H_{40}N_6O_6$ (700) C, 68.56; H, 5.75; N, 11.99%; Found: C, 68.50; H, 5.72; N,11.89%.

1,4-bis(2-(4-nitrophenyl)imidazo[4,5-*b*]indol-4(3*H*)-yl) butane 6e: IR (KBr): υ_{max} 3435, 1650, 1585 cm^{-1}. ^{1}HNMR (400MHz, DMSO-d_6): δ=2.12 (m, 4H, CH_2), 3.39 (t, 4H, CH_2), 7.10-8.01 (m, 16H, Ar), 11.36 (br s, 2H, NH) ppm, Mass m/z: 610 (M^+, 36%), Anal. Cald. for $C_{34}H_{26}N_8O_4$ (610) C, 66.88; H, 4.29; N, 18.35%; Found: C, 66.82; H, 4.20; N, 18.32%.

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