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A possible potential COVID-19 drug candidate: Diethyl 2-(2-(2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetyl)hydrazono)malonate: Docking of disordered independent molecules of a novel crystal structure, HSA/DFT/XRD and cytotoxicity

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Abstract This study reports the synthesis, characterization and importance of a novel diethyl 2-(2-(2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetyl)hydrazono)malonate (MQOAHM). Two independent molecular structures of the disordered MQOAHM have been established by XRD single crystal analysis in a ratio of 0.596(3)/0.404(3), MQOAHM (a) and MQOAHM (b), respectively. MQOAHM was characterized by means of various spectroscopic tools ESI-MS, IR, $^{1}H$ & $^{13}C$ NMR analyses. Density Functional Theory (DFT) method, B3LYP, 6-311+ + G(d,p) basis set was used to optimize MQOAHM molecule. The obtained theoretical structure and experimental structure were superimposed on each other, and the correlation between them was calculated. The Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) were created, and the energy gap between these orbitals was calculated. For analyzing intermolecular interactions, Molecular Electrostatic Potential (MEP) and Hirshfeld Surface Analysis were studied. For a fair comparative study, the two forms of the title compound were
1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of Coronavirus Disease 2019 (COVID-19), is a novel beta-coronavirus first identified in December 2019 in Wuhan, China. As of 20 September 2021, there have been 219,113,953 confirmed cases of this disease, including 4,570,041 deaths in 216 countries, reported to the World Health Organization (WHO). The US Food and Drug Administration (FDA) approved only remdesivir for the treatment of COVID-19 (Parsey, 2020). However, several reports proposed agents to treat COVID-19 include direct antivirals (Cao et al., 2020), baricitinib (Cantini et al., 2020), hydroxychloroquine (Sogut et al., 2021), glucocorticoids (Russell et al., 2020) and anakinra (Pasin et al., 2021; Campochiaro et al., 2020). Quinoxaline as a wonder molecule structure’s binding scores against 7BQY were −7.0 and −6.9 kcal/mol for MQOAHM (a) and MQOAHM (b), respectively. Both the forms show almost identical superimposed structures and scores indicating that the disorder of the molecule, in this study, has no obvious effect. The high binding score of the molecule was attributed to the multi-hydrogen bond and hydrophobic interactions between the ligand and the receptor’s active amino acid residues. Worth pointing out here that the aim of using the free energy in Silico molecular docking approach is to rank the title molecule compared to the wide range of approved drugs and a well-established ligand N3. The binding scores of all the molecules used in this study are ranged from −9.9 to −4.5 kcal/mol. These results and the supporting statistical analyses suggest that this malonate-based ligand merits further research in the context of possible therapeutic agents for COVID-19. Cheap computational techniques, PASS, Way2drug and ADMET, online software tools, were used in this study to uncover the title compound’s potential biological activities and cytotoxicity.

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million (ppm); the IR spectrum was obtained using the Bruker-VERTEX 70 device and the associated software OPUS, an ATR (attenuated total reflectance) mode. Mass spectra were recorded on an API 3200 LC/MS/MS mass spectrometer using electrospray ionization (ESI) in positive polarity.

2.1.1. 3-Methyl-1H-quinoxalin-2-one (MQO)
Following a procedure similar to that of Hinsberg (Ramli and Essassi, 2015), we have successfully synthesized 3-methyl-1H-quinoxalin-2-one with a yield of 91% by condensation of O-phenylenediamine (10 mmol) with ethyl pyruvate (15 mmol) in HCl 4 N aqueous solution for 30 min at room temperature, Scheme 1.

2.1.2. Ethyl 2-(3-methyl-2-oxo-1,2-dihydroquinixalin-1-yl) acetate (EMQOA)
To a solution of 3-methylquinoxalin-2(1H)-one (3 g, 18.7 mmol) in N,N-dimethylformamide (15 mL) were added ethyl 2-bromoacetate (4.7 mL, 28.5 mmol), potassium carbonate (3.6 g, 28.5 mmol) and a catalytic quantity of tetranbutylammonium bromide. The reaction mixture was stirred at room temperature for 24 h. The solution was filtered, and the solvent was removed under reduced pressure. The solid obtained was recrystallized from ethanol solution to afford a white powder, ethyl 2- (3-methyl-2-oxoquinoxalin-1 (2H)-yl) acetate (EMQOA), with a yield of 72%.

2.1.3. 2-(3-methyl-2-oxoquinolin-1(2H)-yl)acetohydrazide (MQOAH)
To the formed residue (EMQOA) (1 g, 4 mmol) taken in ethanol (20 mL) was added hydrazine hydrate (0.3 mL, 6 mmol), then left stir for 24 h at room temperature. The target compound, 2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetohydrazide (MQOAH) precipitate and recrystallized from ethanol, the yield is around 77%, Scheme 1.

2.1.4. 2-(2-(2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetyl) hydrazono)malonate (MQOAHM)
In ethanol (15 mL), to this quinoxaline(0.5 g, 2.1 mmol) was added (0.7 mL, 4.2 mmol) of diethyl 2-oxomalonate, stirred for 2 h under reflux at 80 °C. The mixture then was filtered and the solvent evaporated under reduced pressure, and the residue was crystallized from its ethanol solution. The reaction yield is 65%. Scheme 1. The compound was dissolved in ethanol and left for slow evaporation to afford a colourless plate-like crystal, Fig. 1.

Scheme 1 Synthesis procedure for the preparation of (MQOAHM); Reagents: a) HCl 4 N; b) Bromoethylacetate, K₂CO₃, BTBA, DMF; c) NH₂NH₂·H₂O, EtOH; d) diethyl-2-oxomalonate, EtOH.
2.2. Crystal structure determination

A colourless plate-like specimen of $\text{C}_{18}\text{H}_{20}\text{N}_{4}\text{O}_{6}$, approximate dimensions $0.032 \text{ mm} \times 0.230 \text{ mm} \times 0.303 \text{ mm}$, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a Bruker Smart APEX CCD system equipped with a fine-focus sealed tube (Mo-K$_\alpha$, $\lambda = 0.71073 \text{ Å}$) and a graphite monochromator. The complete sphere of data was processed using SAINT (Bruker, 2016). The structure (Fig. 2) was solved by direct methods and refined by the full-matrix least-squares method on $F^2$ using SHELXT and SHELXL programs (Sheldrick, 2015a; Sheldrick, 2015b). The molecular and packing diagrams were generated using DIAMOND (Brandenburg and Putz, 2012). Crystal and refinement details are presented in Table 1.

CCDC 2062620 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033).

2.3. Computational procedure

2.3.1. Hirshfeld surface analysis (HAS)

HAS and the related 2D-fingerprint plots were calculated for diethyl-2-(2-(2-(3-methyl-2-oxoquinolin-1(2H)-yl)acetyl)hydrazono)malonate MQOAHM (a), using Crystal Explorer, Version 17, which reads CIF format as an X-ray input file (Turner et al., 2017). The cut-off for the hydrophobic interactions between the amino acid residues and the ligands is 3.9 Å (Tanoli et al., 2020).

2.3.2. Density Functional Theory (DFT)

Geometric optimization of the molecule was executed with Gaussian 09 W package program (Frisch et al., 2010) and was calculated by using Density Functional Theory (DFT) method by B3LYP (Becke’s three-parameter hybrid functional using the LYP correlation functional) with 6–311+ + G(d,p) basis set. For modeling, initial values were obtained X-ray diffraction. Molecular electrostatic potential map and molecular orbitals were plotted with Gauss-View 5 molecular visualization program (Dennington et al., 2009).

Table 1 Crystal data and structure refinement details for MQOAHM.

| Value                  | Parameter                        |
|------------------------|----------------------------------|
| Chemical formula       | $\text{C}_{18}\text{H}_{20}\text{N}_{4}\text{O}_{6}$ |
| $M_r$                  | 388.38                           |
| Crystal system, space group | Monoclinic, $P2_1/c$               |
| Temperature (K)        | 150                              |
| $a$, $b$, $c$ (Å)      | 4.7504 (3), 22.2791 (16), 17.3723 (12) |
| $\beta$ ($^\circ$)     | 90.076 (1)                       |
| $V$ (Å$^3$)            | 1838.6 (2)                       |
| $Z$                    | 4                                |
| Radiation type         | Mo $K\alpha$                     |
| $\mu$ (mm$^{-1}$)      | 0.11                             |
| Crystal size (mm)      | $0.30 \times 0.23 \times 0.03$   |
| Diffractometer         | Bruker Smart APEX CCD             |
| Absorption correction  | Multi-scan SADABS (Krause et al., 2015) |
| $T_{\text{min}}, T_{\text{max}}$ | 0.87, 1.00                      |
| No. of measured, independent and observed $|I > 2\sigma(I)$| reflections | 17274, 4563, 3100 |
| $R_{\text{int}}$      | 0.035                            |
| $(\sin \theta/\lambda)_{\text{max}}$ (Å$^{-1}$) | 0.669                        |
| $R[F^2 > 2\sigma(F^2)], wR[F^2], S$ | 0.051, 0.142, 1.05          |
| No. of reflections     | 4563                             |
| No. of parameters      | 265                              |
| H-atom treatment       | H-atom parameters constrained    |
| $\Delta \rho_{\text{max}}, \Delta \rho_{\text{min}}$ (e Å$^{-3}$) | 0.28, −0.17                |

Fig. 1 An image of MQOAHM crystals.

Fig. 2 ORTEP view of the title compound indicating the atom-numbering scheme. Displacement ellipsoids are illustrated at the 50% probability level.
2.4. Docking in silico studies

Docking calculations of MQOAHM (a) and 20 approved drugs were accomplished using the Autodock Vina wizard in PyRx 0.8 (Trott and Olson, 2009). The occupancies of the disordered ligand crystal are 0.593(2) MQOAHM (a), 0.404(3) MQOAHM (b). Settings are made the same in the program for all docked molecules in this study, which include: Grid box center_x = 6.99668717076, center_y = 0.922958951594, center_z = 22.8078934645, size_x = 19.4420049859, size_y = 129.31, size_z = 129.31. Our ligand's energy minimization, 20 approved drugs and protein, was performed using the default settings in the Autodock Vina-PyRx. The CIF files of the MQOAHM (a,b) (CCDC = 2062620). All drugs and ligands were converted to PDB file type using Mercury package (Macrae et al., 2006) and were used as input to Autodock vina in PyRx. The proteases (PDB code 7BQY) were saved in PDB format after deleting the water molecules and ligands using Discovery Studio Visualizer v17.2.0.16349. The PyMOL molecular viewer was used to present the output (DeLano, 2004). Schematic diagrams of protein–ligand interactions were generated using the LIGPLOT program (Wallace et al., 1995).

3. Results and discussion

3.1. Synthesis and crystallisation of diethyl 2-(2-(3-methyl-2-oxoquinolin-1(2H)-yl)acetamido) hydrazono)malonate (MQOAH)

3.1.1. 3-Methyl-1H-quinolin-2-one (MQO)

Yield 91%, mp = 219.3–220.5 °C, FT-IR (ATR, ν, cm⁻¹) 1568 ν (C=O, amide), 1213 ν (C=O amide), 1737 ν (C=O ester). 1H NMR (DMSO δ ppm: 2.40 (3H, s, CH₃), 7.27 (2H, m, Harom), 7.28 (1H, d, J = 8.86 Hz, H arom), 2.96 (1H, s, CH₂), 5.11 (2H, s, CH₂), 1H NMR (DMSO δ ppm: 2.48 (3H, s, CH₃), 7.21 (2H, m, Harom), 7.28 (1H, d, J = 8.6 Hz, H arom), 12.29 (1H, s, N-H). 13C NMR (DMSO δ ppm: 20.51 (CH₃), 115.22, 123.04, 127.86, 157.47 (C=O ester), 1H NMR (DMSO δ ppm: 2.00 (3H, s, CH₃), 7.27 (2H, m, Harom), 7.28 (1H, d, J = 8.6 Hz, H arom), 12.29 (1H, s, N-H). 13C NMR (DMSO δ ppm: 20.51 (CH₃), 115.22, 123.04, 127.86, 157.47 (C=O ester), 3.1.2. Ethyl 2-(3-methyl-2-oxo-1,2-dihydroquinolin-1-yl) acetate (EMQOA)

Yield 72%, color: white, mp = 140.5–142.3 °C, FT-IR (ATR, ν, cm⁻¹) 1568 ν (C=O, amide), 1600 ν (C=O amide), 2961 ν (C=H, CH₂), 1213 ν (C=O ester), 1737 ν (C=O ester). 1H NMR (DMSO δ ppm: 2.40 (3H, s, CH₃), 7.27 (2H, m, Harom), 7.28 (1H, d, J = 8.86 Hz, H arom), 2.96 (1H, s, CH₂), 5.11 (2H, s, CH₂), 4.19 (2H, q, J = 1.4 Hz, CH₂ ester), 7.39–7.82 (4H, m, J = 1.3 Hz, H arom). 13C NMR (DMSO δ ppm: 24.6 (CH₃), 131.65 (Carom-N), 131.91 (Carom-N), 159.22 (C=O). HRMS (ESI-MS) (m/z) calculated for C₉H₈N₂O 160.06, found 160.17.

3.1.3. 2-(3-methyl-2-oxoquinolin-1(2H)-yl)acetohydrazide (MQOAH)

Yield 77%, color: white, mp = 183.5–182.3 °C, FT-IR (ATR, ν, cm⁻¹) 1168 ν (N=C amide), 1600 ν (C=O amide), 2961 ν (C=H,CH₂), 1213 ν (C=O ester), 1737 ν (C=O ester). 1H NMR (DMSO δ ppm: 2.40 (3H, s, CH₃), 7.27 (2H, m, Harom), 7.28 (1H, d, J = 8.6 Hz, H arom), 2.96 (1H, s, CH₂), 5.11 (2H, s, CH₂), 4.19 (2H, q, J = 1.4 Hz, CH₂ ester), 7.39–7.82 (4H, m, J = 1.3 Hz, H arom). 13C NMR (DMSO δ ppm: 24.6 (CH₃), 131.65 (Carom-N), 131.91 (Carom-N), 159.22 (C=O). Its mass spectrum showed a molecular ion peak (MH⁺, m/z = 247.10739) which conforms to its molecular formula C₁₃H₁₂N₂O₃. 3.1.4. 2-(3-methyl-2-oxoquinolin-1(2H)-yl)acetohydrazide (MQOAH)

Yield 77%, color: white, mp = 183.5–182.3 °C, FT-IR (ATR, ν, cm⁻¹) 1168 ν (N=C amide), 1600 ν (C=O amide), 2961 ν (C=H,CH₂), 1213 ν (C=O ester), 1737 ν (C=O ester). 1H NMR (DMSO δ ppm: 2.40 (3H, s, CH₃), 7.27 (2H, m, Harom), 7.28 (1H, d, J = 8.6 Hz, H arom), 2.96 (1H, s, CH₂), 5.11 (2H, s, CH₂), 4.19 (2H, q, J = 1.4 Hz, CH₂ ester), 7.39–7.82 (4H, m, J = 1.3 Hz, H arom). 13C NMR (DMSO δ ppm: 24.6 (CH₃), 131.65 (Carom-N), 131.91 (Carom-N), 159.22 (C=O). Its mass spectrum showed a molecular ion peak (MH⁺, m/z = 247.10739) which conforms to its molecular formula C₁₃H₁₂N₂O₃.

Table 2 Hydrogen-bond geometry (Å, °).

| D—H···A | D—H | D···A | D—···A |
|---------|------|-------|--------|
| N3—H3A···O5 | 0.91 | 2.02 | 2.6865(18) | 128 |
| C2—H2···O2w | 0.95 | 2.40 | 3.213(2) | 144 |
| C9—H9A···Cglii | 0.99 | 2.72 | 3.473(2) | 134 |
| C10—H10B···O1i | 0.99 | 2.58 | 3.290(2) | 128 |
| C17—H17B···O2ii | 0.99 | 2.35 | 3.154(5) | 138 |

Symmetry codes: (i) x – 1, y, z; (ii) x + 1, y, z; (iii) – x + 2, – y + 1, – z + 1.

Fig. 3 A portion of one oblique stack projected onto (011). C–H···O hydrogen bonds are depicted by black dashed lines while π-stacking and C–H···π(ring) interactions are shown, respectively, by orange and green dashed lines.

Fig. 4 Packing viewed along the a-axis direction with intermolecular interactions depicted as in Fig. 3.
was elucidated based on spectral data. The structure of MQOAHM was determined by the condensation of EMQOA. This intermediate reacts with hydrazine to form the corresponding hydrazide MQOAH. The condensation of ethyl 2-bromoacetate to obtain the alkylated compound indicates that MQOAHM is very reactive, and so it was condensed with highly biologically active compounds. The lactam function of the heterocycle was proven to be a good synthon for different molecular ion peak (MH+, m/z = 232.10318) which conforms to its molecular formula C_{11}H_{12}N_{2}O_{2}.

3.1.4. 2-((2-(2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetyl)hydrazono)malonate (MQOAHM)

Yield 65%, color: Pale yellow, mp = 236.5 – 238.3 °C, FT-IR (ATR, v, cm⁻¹): 3215 ν(N-H amide), 1698 ν(C=O amide), 1604 ν(C=O ester), 1409 ν(C-H CH₂quin), 2973 ν(CH₃ stretching), 1733 ν(C=O ester), 1655 ν(C=O amide), 1162 ν(C=O ester). ¹H NMR (DMSO-d₆) δ ppm: 2.48 (s, 3H, CH₃quin), 5.41 (s, 2H, CH₂), 12.26 (s, 1H, NH), 1.29 (t, 3H, J = 8.1 Hz), 4.34 (q, 2H, J = 15.7 Hz, CH₂CH₂), 7.36–7.82 (m, 4H, 3.1.4. 2-(2-(2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetyl)hydrazono)malonate (MQOAHM)

The synthesis of the compound MQOAHM is depicted in Scheme1. The starting material, 3-methylquinoxalin-2(1H)-one was prepared through treatment of α-phenylenediamine with sodium pyruvate in acetic acid (Hinsberg, 1887). This heterocycle was proven to be a good synthon for different highly biologically active compounds. The lactam function of quinoxalinone is very reactive, and so it was condensed with ethyl 2-bromoacetate to obtain the alkylated compound EMQOA. This intermediate reacts with hydrazine to form the corresponding hydrazide MQOAH. The condensation of this hydrazide with diethyl-2-oxomalonate allowed us to isolate the title compound MQOAHM. The structure of MQOAHM was elucidated based on spectral data. The ¹H NMR spectrum revealed three signals at δ 2.48, 5.41 and 12.64 ppm due to the methyl group, CH₃ attached to the quinoxaline nitrogen and the NH of acetamide group, respectively. Also, ¹H NMR shows a triplet at δ 1.29 ppm and quadruplet at δ 4.34 ppm corresponding to two ethyls of the malonate. This confirms the reaction between MQOAH and diethyl-2-oxomalonate. ¹³C NMR spectrum showed signal at δ 13.61, 21.01, 62.04, 154.28 and 160.27 ppm referring to the methyl group and CH₂ attached to quinoxaline nitrogen group, C=N of quinoxaline group, C=O of quinoxaline group and carbon of acetamide group respectively (Missioui et al., 2021). The remaining signals are, δ 122.13 (C=N), 157.28 (C=O) and 13.87, 62.68 (CH₃-CH₂). The IR spectrum of MQOAHM showed bands at 3215, 1655 and 1733 cm⁻¹ for the NH, carbonyl and ester groups, respectively. The spectral data were in agreement with its structure.

3.2. Crystal description and optimized molecular structure

The quinoxaline moiety, except N2, is planar to within 0.0169 (15) Å (rms deviation = 0.0098). N2 is displaced by 0.0307(18) Å from the mean plane. The attached substituent to N2 is nearly perpendicular to the mean plane defined above as indicated by the dihedral angle of 83.34(6)° between this plane and that defined by N2/C11/C12/O2. The intramolecular N3=H3A...O5 hydrogen bond (Table 2) orients the two ester groups to be close to coplanarity with the N2/C11/C12/O2 unit (Fig. 3). Bond distances and interbond angles appear as expected for the given formulation. In the crystal, slipped π-stacking interactions between C1=C6 and C1/C6/N1/C7/C8/N2 rings (centroid–centroid = 3.6768(11)Å, dihedral

| Table 3 | Experimental and theoretical bond distances of the title compound (Å). |
|----------|--------------------------------------------------|
| **Bond Distances** | **Atoms** | **X-ray** | **DFT** | **Error** | **Atoms** | **X-ray** | **DFT** | **Error** |
| O1-C8 | 1.227(2) | 1.2241 | 0.0029 | N3-C11 | 1.379(2) | 1.3952 | –0.0162 |
| O2-C11 | 1.203(2) | 1.2068 | –0.0038 | N4-C12 | 1.284(2) | 1.2917 | –0.0077 |
| O3-C13 | 1.200(2) | 1.2068 | –0.0068 | C1-C2 | 1.391(3) | 1.4033 | –0.0123 |
| O4-C13 | 1.331(2) | 1.3381 | –0.0071 | C1-C6 | 1.409(2) | 1.4139 | –0.0049 |
| O4-C14 | 1.453(2) | 1.4538 | –0.0008 | C2-C3 | 1.367(3) | 1.3876 | –0.0206 |
| O5-C16 | 1.209(2) | 1.2191 | –0.0101 | C3-C4 | 1.394(3) | 1.3997 | –0.0057 |
| O6-C16 | 1.382(12) | 1.329 | 0.0530 | C4-C5 | 1.369(3) | 1.3837 | –0.0147 |
| O6-C17 | 1.458(3) | 1.4579 | 0.0001 | C5-C6 | 1.393(3) | 1.4036 | –0.0106 |
| O6A-C16 | 1.264(18) | – | – | C7-C8 | 1.482(2) | 1.4865 | –0.0045 |
| O6A-C17A | 1.458(3) | – | – | C7-C9 | 1.492(3) | 1.4973 | –0.0053 |
| N1-C6 | 1.386(2) | 1.3839 | 0.0021 | C10-C11 | 1.514(2) | 1.5296 | –0.0156 |
| N1-C7 | 1.288(2) | 1.2907 | –0.0027 | C12-C13 | 1.502(2) | 1.5062 | –0.0042 |
| N2-C1 | 1.392(2) | 1.3946 | –0.0026 | C12-C16 | 1.496(2) | 1.4949 | 0.0011 |
| N2-C8 | 1.374(2) | 1.3931 | –0.0191 | C14-C15 | 1.480(3) | 1.514 | –0.0340 |
| N2-C10 | 1.462(2) | 1.4532 | 0.0088 | C17-C18 | 1.403(4) | 1.5182 | –0.0352 |
| N3-N4 | 1.3437(19) | 1.3309 | 0.0128 | C17A-C18A | 1.483(4) | – | – |

Fig. 5 Supereposition of experimental structure (blue) and theoretical structure (red) (RMS = 0.254 Å).
## Table 4

The experimental and theoretical bond angles of the title compound (°).

| Atoms          | X-ray         | DFT          | Atoms          | X-ray         | DFT          |
|----------------|---------------|--------------|----------------|---------------|--------------|
| C13-O4-C14     | 115.92(14)    | 116.27(14)   | O1-C8-N2       | 122.30(16)    | 121.924      |
| C16-O6-C17     | 115.7(8)      | 117.83(8)    | O1-C8-C7       | 122.21(17)    | 122.7191     |
| C16-O6A-C17A   | 116.9(12)     | –            | N2-C8-C7       | 115.48(16)    | 115.3488     |
| C7-N1-C6       | 119.27(15)    | 119.52(15)   | N2-C10-C11     | 111.38(14)    | 111.596      |
| C8-N2-C1       | 122.25(14)    | 121.94(14)   | O2-C11-N3      | 120.32(15)    | 119.9901     |
| C1-N2-C10      | 120.19(15)    | 121.50(15)   | O2-C11-C10     | 123.93(15)    | 124.4707     |
| C8-N2-C10      | 117.53(15)    | 116.53(15)   | N2-C10-C11     | 115.74(14)    | 115.5345     |
| N4-N3-C11      | 117.11(13)    | 120.45(13)   | N4-C12-C13     | 114.03(14)    | 116.06       |
| C12-N4-N3      | 121.99(14)    | 122.09(14)   | N4-C12-C16     | 124.41(15)    | 123.9618     |
| C2-C1-N2       | 123.00(15)    | 122.90(15)   | C16-C12-C13    | 121.54(14)    | 119.9065     |
| C2-C1-C6       | 119.32(16)    | 119.33(16)   | O3-C13-O4      | 124.44(16)    | 124.9546     |
| N2-C1-C6       | 117.67(16)    | 117.67(16)   | O3-C13-C12     | 124.88(16)    | 122.9788     |
| C3-C2-C1       | 120.14(17)    | 119.99(17)   | O4-C13-C12     | 110.67(14)    | 112.0462     |
| C2-C3-C4       | 121.11(18)    | 120.95(18)   | O4-C14-C15     | 106.13(17)    | 107.5125     |
| C5-C4-C3       | 119.25(18)    | 119.39(18)   | O5-C16-O6A     | 122.9(5)      | –            |
| C4-C5-C6       | 121.02(17)    | 120.82(17)   | O5-C16-O6      | 126.6(4)      | 124.623      |
| N1-C6-C1       | 121.82(16)    | 122.11(16)   | O5-C16-C12     | 122.94(15)    | 122.8051     |
| N1-C6-C5       | 119.00(15)    | 118.39(15)   | O6A-C16-C12    | 112.9(5)      | –            |
| C5-C6-C1       | 119.15(16)    | 119.48(16)   | O6-C16-C12     | 110.4(3)      | 112.5148     |
| N1-C7-C8       | 123.41(16)    | 123.34(16)   | O6-C17-C18     | 108.6(5)      | 111.1413     |
| N1-C7-C9       | 120.31(16)    | 120.41(16)   | O6A-C17A-C18A  | 108.6(9)      | –            |
| C8-C7-C9       | 116.27(16)    | 116.24(16)   | –              | –             | –            |

**Fig. 6** The correlation values between experimental and theoretical geometrical parameters.

**Fig. 7** The Molecular Electrostatic Potential map of the molecule.
angle = 0.89(9)°, slippage = 1.53 Å), together with C2–H2⋯O2 and C10–H10B⋯O1 hydrogen bonds plus C9⋯H9A–Cg1 interactions (Table 2) form oblique stacks of molecules extending along the a-axis direction (Fig. 2). These stacks are connected in pairs by inversion-related C17⋯H17B⋯O2 hydrogen bonds (Table 2 and Fig. 4).

3.3. Computational studies

3.3.1. Geometric optimization of the compound

The optimized geometry of diethyl 2-[2-(2-(3-methyl-2-oxoquinolin-1(2H)-yl)acetyl)hydrazono]malonate molecule was obtained by DFT/B3LYP, 6–311++G(d,p) method. Due to disorder at one of methoxyethane groups, the theoretical structure was found by choosing O6-C17-C18 state of methoxyethane group. The superimposition of the theoretical and experimental structures can be seen in Fig. 5. Although the ethyl acetate groups of the molecule don’t overlap, theoretical and experimental structures almost overlap on each other for the other part. After calculation, the minimum energy of the molecule was calculated as −1368.7186 a.u.

Bond distances and bond angles in both X-ray results and theoretical results are given in Table 3 and Table 4, respectively. Linear correlations for all bond distances and all bond...
angles are shown in Fig. 6, too. In addition, the theoretical bond distances are close to the experimental bond distances. The most significant difference between theoretical and experimental bond distance was calculated for O6–A16 with 0.0530 Å error. The theoretical result of the O6–A17 is closest to the experimental result. RMSE and $R^2$ values were computed at 0.0162 Å, 0.9749 for all bond distances, respectively.

The most significant difference between theoretical and experimental bond angles is 3.3497° for N4–A17–N3 bond angle. RMSE and $R^2$ values for bond angles were found at 1.1314 Å and 0.955. If the bond angles were compared with the bond distances, the theoretical bond angles deviate further than the experimental bond angles with respect to bond distances.

The N2–C10–C11–N3, C10–C11–N3–N4 and C11–N3–N4–C12 torsion angles obtained X-ray diffraction are 173.10(15)°, 1.6(2)° and 174.97(15)°, respectively. Theoretical results of these torsion angles are 176.8909°, −1.8020° and 178.4503°, respectively.

3.3.2. Molecular Electrostatic map
Molecular Electrostatic Potential (MEP) map gives valuable information about intermolecular interactions. DFT method, B3LYP functional with 6-311++G (d,p) basis set, was set to create the MEP of this molecule. MEP contains blue and red areas, showing nucleophilic attack centres. Red regions show electrophilic attack centres. The most electrophilic attack centres for the molecule were calculated around the oxygen and N1 atoms. These regions can be seen in Fig. 7. Charge values for these regions are −0.05223 a.u. for O1, −0.04888 a.u. for O2, −0.04146 a.u. for O3, −0.02732 a.u. for O5 and −0.03642 a.u. for N1 atom. According to X-ray diffraction, the crystal structure has intermolecular C2–H2–O2, C10–H10–BO1 and C17–H17B–O2 hydrogen bonds. From these results, MEP is compatible with x-ray results.

3.3.3. Hirshfeld surface analysis
HSA is a successful tool in showing the inter-and intramolecular interactions in the crystal structure. The mesh drawing generated using Crystal Explorer shows the electron density around all of the molecule atoms and displays the short contacts, within 3.8 Å in red dashed lines, Fig. 8(A), (Trott and Olson, 2009). Many types of these interactions were detected (N–H...O, C–H...C, C–H...O and more) as red spots on the ligand surfaces Fig. 8(B), (C). This agrees with the bonding interactions found by X-ray structure analysis. The red spots represent the points of closest interactions, whereas the blue areas show weak interactions. Also, HSA was employed in this study to show the $d_e$ and $d_i$ for MQOAHM (a), Fig. 9. Because MQOAHM (a) has many heteroatoms (6O and 4N) and polar H atoms, it was expected to reveal several red spots on the computed surface, Fig. 8(B), (C) (Ozdemir Tar et al., 2018; Asadi et al., 2017). Combining the $d_e$ and $d_i$ on a fingerprint plot proposes helpful information about all the contacts in the molecule. The intermolecular interactions, N–H...O, C–H...H, C–H...C and C–H...N,
provide the stabilized molecular packing. These interactions are responsible for holding the molecules in layers in the crystal packing. The H⋯H contacts, in the fingerprint plots, show a high percentage of the interactions in MQOAHM (a), (44.5%). The second highest interaction is O⋯H (27.7%). The third is C⋯H, which displays 11.4%. The spikes due to the H⋯O contacts are apart on the fingerprint plots ($d_0 + d_1$) 2.3 Å, corresponding to 27.7% of all O⋯H interactions. The red dashed circle on $d_{norm}$ Hirshfeld surface shows the presence of π-π stacking, which corresponds to the phenyl–phenyl interaction. All 2D-finger plots and the percentage contributions of many interactions are shown in Fig. 9.

### 3.3.4. Frontier molecular orbitals

Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO), which are called Frontier Molecular Orbitals (FMOs) because of laying at the outermost boundaries, are very important to explain photostability and molecular transport properties (Prasad and Ojha, 2017). While Highest Occupied Molecular Orbital (HOMO) is related to ionization potential, and Lowest Unoccupied Molecular Orbital (LUMO) is related to electron affinity. The energy gap between HOMO and LUMO is related to charge transfer in molecules (Nataraj et al., 2012) and identifies the chemical stabilities of molecules (Gilman, 2007). Furthermore, a low energy gap indicates high biological activity due to transferring electrons efficiently from HOMO (Wu et al., 2020). Additionally, average energy values for HOMO and LUMO are connected to electronegativity (Prasad and Ojha, 2017). HOMO and LUMO of the molecule were plotted using the same level theory. These Frontier Molecular Orbitals

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**Table 5**  Main protease with various resolutions.

| Protease | Resolution | Inhibitor | PDB number |
|----------|------------|-----------|------------|
| 7BQY     | 1.70 Å     | N3        | [link](https://doi.org/10.2210/pdb7BQY/pdb) |
| 7C8U     | 2.35 Å     | MPI5      | [link](https://doi.org/10.2210/pdb7C8U/pdb) |
| 7JQ2     | 1.4 Å      | MPI5      | [link](https://doi.org/10.2210/pdb7JQ2/pdb) |
| 7BUY     | 1.6 Å      | carmofur  | [link](https://doi.org/10.2210/pdb7BUY/pdb) |
| 6M0K     | 1.50 Å     | 11b       | [link](https://doi.org/10.2210/pdb6M0K/pdb) |
| 5R81     | 1.95 Å     | Z1367324110 | [link](https://doi.org/10.2210/pdb5R81/pdb) |
| 5R82     | 1.31 Å     | Z219104216  | [link](https://doi.org/10.2210/pdb5R82/pdb) |
| 6LU7     | 2.16 Å     | inhibitorN3 | [link](https://doi.org/10.2210/pdb6LU7/pdb) |
| 5R7Y     | 1.65 Å     | Z45617795  | [link](https://doi.org/10.2210/pdb5R7Y/pdb) |
| 5R7Z     | 1.59 Å     | Z1220452176 | [link](https://doi.org/10.2210/pdb5R7Z/pdb) |
| 5R80     | 1.93 Å     | Z18197050  | [link](https://doi.org/10.2210/pdb5R80/pdb) |
and the energy gap between HOMO and LUMO can be seen in Fig. 10. While HOMO orbital is mainly localized on 3-methylquinoxalin-2(1H)-one molecule group, LUMO orbital is mainly localized on diethyl 2-(2-acetylhydrazono)malonate group. The energy gap between HOMO and LUMO is 3.6842 eV.

3.4. Docking analysis against 7BQY

The whole world is experiencing a tough time at many economic and social levels because of Covid-19. Hence, we have been motivated to study how a malonate ligand might behave in the main protease’s active site for Covid-19 (Mpro, Table 5, with different resolutions (Vraj Shah and Bhaliya, 2020). In this study, we preferred to use the 7BQY because it has been docked against the well-known inhibitor N3 that appeared recently in Nature journal (Jin et al., 2020). A representative example of a superposition of MQOAHM (a) (orange lines) and Oseltamivir (approved drug by FDA, grey lines) against 7BQY complex showing the hydrogen and hydrophobic interactions in (E) and only H-bonds in (F). A key to the symbols is given in our recent report (Alsafi et al., 2020). Schematic 2D LIGPLOT representations of all molecules are available in the SI.

(FMOs) and the energy gap between HOMO and LUMO can be seen in Fig. 10. While HOMO orbital is mainly localized on 3-methylquinoxalin-2(1H)-one molecule group, LUMO orbital is mainly localized on diethyl 2-(2-acetylhydrazono)malonate group. The energy gap between HOMO and LUMO is 3.6842 eV.
It is essential to mention that all the docked molecules against the target enzyme COVID-19 are ranked according to their binding energy, shown in ascending order and colour-coded molecules (Fig. 13). The binding affinity was attributed to many hydrogen bonds and hydrophobic interactions between the MQOAHM (a) and the receptor’s active amino acid residues, as shown in the Schematic 2D LIGPLOT, Fig. 11 (F). A similar full Schematic 2D LIGPLOT for Oseltamivir was presented for comparison, Fig. 11 (E). It could be seen that Arg188(A) and His 41(A) are the two common amino acids responsible for the hydrogen bond formation in both compounds. Docking of the disordered independent molecules MQOAHM (a) and MQOAHM (b) has been performed alongside the 18 drugs and N3 in one go and under the same conditions to make it a fair comparison. The docking result of MQOAHM (a) can be compared to MQOAHM (b) to show a slight difference in the layout of the aliphatic part of the ligand but a similar layout in the aromatic part in the binding site of the protease, Fig. 12, MQOAHM (a) + MQOAHM (b).

**Fig. 12** The superposition of 18 approved drugs, N3, and MQOAHM (a), (b) docked together into the binding pocket of 7BQY using the same parameters for a fair comparative study. The results are represented by PyMOL (DeLano, 2004) in the circle frame. Every docked drug is shown separately in a rectangular frame alongside our ligand MQOAHM (a) (orange stick). All are colour-coded. The top middle rectangular shows a superposition of our disordered independent molecules, MQOAHM (a) and MQOAHM (b).

**Fig. 13** Binding affinities of MQOAHM (a), MQOAHM (b), 18 approved drugs and the inhibitor N3 against COVID-19, 7BQY protease.
Essential roles in identifying effective drugs for COVID-19 are the protein-drug complexes and binding affinity; therefore, M\textsuperscript{pro} is well assigned to serve as the key drug target (Bhatia et al., 2020). Molecular docking computations in this study showed that MQOAHM (a) and MQOAHM (b) have a good binding affinity to the SARS-CoV-2 main protease (M\textsuperscript{pro}) in comparison to all the approved drugs. In fact, what is interesting about the data in Fig. 15 is that MQOAHM (a) and MQOAHM (b) were docked against 7BQY alongside 18 approved drugs and N3 inhibitor, in one run. The same parameters and conditions were used to rank our ligand compared to a large number of the approved drugs and N3 inhibitor used here. The range of the binding affinities of the 18 drugs in this study and N3 is from −4.5 to −9.0 kcal/mol, whereas the binding affinities of MQOAHM (a) and MQOAHM (b) are −7.0 and −6.9 kcal/mol, respectively. Thus the ligands are one unit less kcal/mol than the average value of all compounds, −8.0 7 ± 1.56 kcal/mol, Fig. 13. Besides, MQOAHM (a) and MQOAHM (b) demonstrated closer binding modes inside the active site of M\textsuperscript{pro}, establishing crucial hydrogen bonds and hydrophobic interactions with various amino acid residues, Fig. 11 and SI. The similar behavior of MQOAHM compared to the rest of the molecules in this study, suggest that our ligand merit considering in the context of a possible therapeutic agent for COVID-19, Fig. 12, Fig. 13. A quick check of each molecule’s total interactions with the binding site was performed by counting the total number of hydrogen and hydrophobic interactions. Interestingly, the statistical analysis supports that as the number of interactions increases, the binding energy gets lower (more negative, better) to a reasonable extent, Fig. 14. There are 47 Hydrogen bonds and 237 hydrophobic interactions for all the molecules involved in this study Fig. 15 (SI).

H-bonds and hydrophobic interactions emerged upon docking all the molecules used in this study to the substrate-binding pocket of COVID-19 (7BQY protease), summarised in Fig. 15. Amino acid E166 was responsible for creating the highest total number of H-bonds and hydrophobic interactions. Amino acid E166 forms an almost equal number of hydrophobic and hydrogen interactions. Amino acids T24 and S46 show only hydrogen bonds, whereas T25, F140, M165, L167, P168, H172 and D187 show only hydrophobic interactions.

The binding affinity to the protein target is usually considered in selecting a possible drug candidate. All docking poses demonstrated a good fit inside the substrate pocket. Therefore, the lowest-energy docking poses of all compounds were considered for the superposition in Fig. 12. Analysis results for all the nine poses of each molecule docked to 7BQY are presented in Table 6 to assess the predicted binding poses’ reasonability. Statistical analysis, using a statistical model (Minitab Statistical Software (Version 19) 2020. Available from: www.minitab.com), showed no significant differences between the nine-poses for each compound used, Table 5-SI. However, a highly significant variation between the nine-poses and compounds’ binding affinity means at p-value = 0.00, Table 6. The Pairwise comparison, Tukey, showed that Telaprevir with a mean of −9.20 ± 0.36 is the strongest significant binding affinity. The following medicines have no significant differences in their M\textsuperscript{pro} binding affinity; Faldaprevir (−9.06 ± 0.38), Indinavir (−8.94 ± 0.29), Remdesivir (−8.80 ± 0.39) and Telaprevir (−9.20 ± 0.36), Table 6, Table 7-SI. The drugs Boceprevir, Lopinavir, Vaniprevir, Amprenavir, Ritonavir, and Asunaprevir have a binding affinity (−8.50 to −8.1), Table 6, Table 7-SI. MQOAHM (a) and MQOAHM (b) have (−6.67 ± 0.22) and (−6.63 ± 0.18) binding affinity, respectively. MQOAHM (a) and MQOAHM (b) show no significant differences when compare to other drugs; Oseltamivir (−6.78 ± 0.42) and Arbidol (−6.43 ± 0.18). The lowest binding

**Fig. 14** Binding affinities against the total number of interactions for N3, MQOAHM (a), MQOAHM (b) and the 18 approved drugs.

**Fig. 15** Total number of H-bonds and hydrophobic interactions emerged upon docking all the molecules to 7BQY protease.
affinity means calculated for Chloroquine, Amantadine, and Favipiravir nine-poses have (−5.88 ± 0.22), (−4.22 ± 0.22), respectively Table 6, Table 7-SI.

3.5. PASS and Way2drug (Prediction of biological and cytotoxicity activities)

PASS (Prediction of Activity Spectra) (Lagunin et al., 2000) and Way2drug (Provides more information about the biological potential of new compounds, Way2Drug URL, http://way2drug.com) (Druzhilovskiy et al., 2017) are online software tools that predict various types of biological activities as shown in Table 7. They were both used at Pa > Pi (Pa represents the probability of being active, and Pi means inactive).

The aim mainly was to predict the cytotoxicity of our malonate-based ligand MQOAHM (a) against human tumours and non-tumours. The first predicted biological activity for MQOAHM (a) was Antieczematic, ranging from 0.079 to 0.616. Whereas, the second predicted activity was antiviral against a single-stranded RNA Picornavirus. This virus is considered a simple and positive-sense RNA vertebrate virus group. It comprises many small RNA viruses that cause significant pathogens in both humans and livestock (Abramo et al., 2012). The activity predicted, by PASS, was in the range of 0.041–0.524. The Picornaviruses (PV) and coronaviruses (Cov), to which COVID-19 belongs, are positive-stranded RNA viruses that infect humans worldwide. Around 6800 small molecules were tested to discover a novel inhibitor against viral protease for both viruses. Results showed a protease that inhibits SARS-CoV 3CLpro and 3Cpro from PV and CoV, respectively (Kuo et al., 2009). Therefore, in this study, MQOAHM (a) and MQOAHM (b) were biologically docked to COVID-19 Mpro alongside a range of approved antiviral drugs for comparison. Other inhibiting activities predicted by PASS are Mediator release, Trimethylamine-oxide aldolase, Proteasome ATPase, and Cyclic AMP phosphodiesterase inhibitors. Stimulant activity for MQOAHM (a) predicted by PASS as Platelet aggregation and ATPase, Table 7. Side negative effect was also predicted, such as Muscle twitching, oedema, splenomegaly, telangiectasia and Gastrointestinal Haemorrhage with Pa starting from 0.531 as a higher value and 0.277 as a lower value Pa, Table 8.

MQOAHM (a) was tested using Drug2Way for three cell lines from breast tissues; MDA-MB-453, MDA-MB-361 and Leukemic T-cells with Pa at 0.468, 0.274, respectively and Pi at 0.018, 0.056, and 0.135, respectively Table 9. Other cell lines also recorded YAPC from Pancreatic Carcinoma and Histiocytic Lymphoma, respectively Table 10. Predicted adverse toxicological activities found in two non-tumor, Fibroblast cell lines, CRL-7065 and AG1523, for skin and Fibroblast at lower Pa at 0.092 and 0.043, respectively.
3.6. Admet prediction

In silico assessment of absorption, distribution, metabolism, excretion and toxicity (ADMET) properties were also used. It is a fast method to screen compounds for their pharmacokinetics and pharmacodynamics properties. The toxicity risks and bioavailability of MQOAHM were predicted based on ADMET profile (Table 11). Results showed a good human intestinal absorption probability, a good Blood-Brain Barrier crossing and a high plasma protein binding percentage. In addition, it has a good excretion and optimal toxicity except for drug-induced liver injury. The prediction results also showed that no carcinogenic effects and no AMES toxicity were found.

4. Conclusion

The disordered structure of the novel diethyl 2-(2-(2-(3-methyl-2-oxoquinolin-1(2H)-yl)acetyl)hydrazono)malonate was established by XRD single crystal analysis in a ratio of 0.596 (3)/0.404 (3). Two strong types of hydrogen bond (C—H···O and C—H···C) interactions were detected in this molecule. Density Functional Theory (DFT) method, B3LYP, 6–311+ +G(d,p) basis set was used to optimize the molecule. The obtained results of bond distances are more compatible with the experimental results, whereas bond angles are less. MEP and HSA show that the vicinity of oxygen atoms are active regions for intermolecular interactions. Additionally, the energy gap is 3.6842 eV. A comparative study of the two forms of the title compound was docked together with a wide range of approved drugs and the ligand N3, against 7BQY, under the same conditions. The binding scores /C0 7.0 and /C0 6.9 kcal/mol[C0]1 suggest almost no difference. Also, both the forms show almost identical lay down of the structures, after docking, indicating that the disorder of the molecule, in this study, has no clear-cut effect. However, the multi-hydrogen bond and hydrophobic interactions between the ligand and the receptor’s active amino acid residues merits further research in the context of possible therapeutic agents for COVID-19. The binding scores of all the molecules used in this study ranged from /C0 9.9 to /C0 4.5 kcal/mol[C0]1. Preliminary toxicity properties of MQOAHM were predicted for its possible potential use as an inhibitory drug against COVID-19 using energy-free methods.

CRediT authorship contribution statement

Mohcine Missioui: Investigation. Musa A. Said: Investigation, Software, Writing – original draft. Günsel Demirtas: Investigation, Software. Joel T. Mague: Data curation, Formal analysis. Ahlam Al-Sulami: methodology. Nadia S. Al-Kaff: methodology. Youssef Ramli: Conceptualization, methodology, Supervision, Writing-Reviewing and Editing.

Declaration of Competing Interest

The authors of this manuscript declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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