Electronic Supplementary Material (ESI) for New Journal of Chemistry.


# ELECTRONIC SUPPLEMENTARY DATA

# Toward an efficient and eco-friendly route for the synthesis of dimeric 2,4-diacylphloroglucinol and its potential as a SARS-CoV-2 main protease antagonist insight from in silico studies

Triana Kusumaningsih,* Wahyu E Prasetyo, Fajar R Wibowo, and Maulidan Firdaus

Department of Chemistry, Faculty of Mathematics and Natural Sciences, Sebelas Maret University, Jl. Ir. Sutami No.36A, Surakarta, 57126, Indonesia

**corresponding author: triana_kusumaningsih@staff.uns.ac.id*

ORCID: http://orcid.org/0000-0002-5795-0125

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## S1: EXPERIMENTAL

### Materials and instrumentations

All of reagents and solvents were purchased from Merck or Sigma-Aldrich and utilised without additional purification. Branson B1510R-DTH Ultrasonic Cleaner was used to perform any reactions under sonication condition. Silica gel with pore size 60 Å, 230-400 mesh was used to perform column chromatography. Thin Layer Chromatography (TLC), which performed on gel 60 $F_{254}$ (Merck) plate was used to monitor the progress of the reactions. UV light at λ=254 and 365 nm was used for visualisation of TLC spot. Agilent DD2 Nuclear magnetic resonance (NMR) Spectrometer was used to record NMR spectra, 500 MHz for $^{1}H$ and 125 MHz for $^{13}C$ using $CDCl_3$ as the solvent, operated at 25 °C and using tetramethyl silane as the internal standard. Melting Point Apparatus SMP10 Stuart was used to measure melting points of the isolated product.

### Preparation of SAA catalyst

The catalyst was prepared following the previous work[1]. A 12.375 g of silica gel was soaked in 50 mL of diethyl ether ($Et_2O$) and 6.25 mmol of concentrated $H_2SO_4$. The obtained mixture was stirred for 15 min at ambient temperature and pressure under the atmospheric nitrogen ($N_2$) and dried at 60 °C for 18 h. The solvent in the resulted residue was then removed by heating at 120 °C for 6 h. Finally, before further use, the resulted **SSA** catalyst was placed in a desiccator for storage.

### General procedure for the synthesis of 2,4-diacylphloroglucinols (2a-2c)

The synthesis of monomeric diacylphloroglucinols was performed by following the previous work[1]. To the round bottom flask, phloroglucinol **1** (1 mmol) and acetic anhydride or acyl chlorides (2 mmol) were stirred at ambient temperature and pressure for 5 min. Then, into the mixture, 20% (w/w) **SSA** as a catalyst was added and sonicated at 60 °C for 15-20 min. Upon reaction completion, the mixture was cooled, diluted with 15 mL of water, and extracted with ethyl acetate (EtOAc) (3 x 15 mL). Finally, the solvent was evaporated and the crude product was subjected for further purification through short flash column chromatography using n-hexane/EtOAc (95/5 → 70/30 gradient) in silica gel. All of the $^{1}H$ NMR and $^{13}C$ NMR spectra of monomers are given in **ESI S2**.

**General procedure for the synthesis of 4a *via* a condensation reaction.** In a vial was placed monomer **2a** (0.1 mmol), formaldehyde (0.5 mmol) and **SSA**. The resulted mixture was reacted under ultrasound irradiation. The reaction typically took 10-15 min which monitored by TLC. Upon completion of the reaction, 4 M hydrogen chloride (HCl) was used to neutralise the crude solution. EtOAc (3 x 10 mL) was then used to extract the aqueous layer. The combined organic layers were dried over sodium sulphate anhydrous ($Na_2SO_4$). Finally, the solvent was removed and the crude product was collected and used without using further purification.

**General procedure for the synthesis of 4a *via* one-pot synthesis using Eschenmoser's salt**

To the round bottom flask, a solution of the monomer of diacylphloroglucinol **2a** (0.1 mmol) and the suspension of Eschenmoser's salt (0.5 eq.) was heated at 60 °C in the small amount of chloroform ($CHCl_3$) under the US method in $N_2$ atmosphere. The obtained mixture was refluxed until most of diacylphloroglucinol converted to the desired product. To the obtained mixture, 5 mL dichloromethane ($CH_2Cl_2$) was then added and gently washed with 5 mL of 1 N aqueous HCl and brine solution. $CH_2Cl_2$ (3 x 5 mL) was used to extract the resulted aqueous layer. The combined organic layers were dried over magnesium sulphate anhydrous ($MgSO_4$), filtered with filter paper and evaporated using a rotary evaporator. The obtained crude residue was purified by short flash chromatography using n-hexane/EtOAc (95/5 → 80/20 gradient) in silica gel.

**Synthesis of arylation of dimethylammonium Salt 3**

A solution of the desired acylated phloroglucinol **2a** (1.0 eq.) was reacted with the corresponding dimethylaminomethylated monomer (1.0 eq.) using small amount of toluene under US method at room temperature until most of the acylated phloroglucinol converted to the expected product. Upon completion of the reaction, the solvent was removed. Finally, before further used, $CH_2Cl_2$ was used to wash the crude product.

**1-(3,5-diacetyl-2,4,6-trihydroxyphenyl)-N,N-dimethylmethanaminium (3).** Yield: 98%; white coloured solid; $^1$H NMR (500 MHz, $CDCl_3$): δ 9.31 (tt, *J* =

6.6, 2.9 Hz), 4.45 (d, *J* = 6.6 Hz), 2.67 (t, *J* = 1.5 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 206.09, 165.70, 104.31, 103.11, 48.75, 40.60, 32.63.

**General Synthesis of Dimeric Acylphloroglucinol *via* Arylation of Dimethylammonium Salt.** A solution of diacylphloroglucinol monomer **2a** (1.0 eq.) with the activated dimethylammonium salts from monomer **3** (1.0 eq.) was heated at 80 °C in a small amount of toluene for the designated time. The solvent was then removed and the crude product was collected and used without using further purification.

**Methylene-bis-(3,5-diacetyl-2,4,6-trihydroxybenzene) (4a):** Yield: 94%; cream coloured solid; mp 279-281 °C; $^1$H NMR ($CDCl_3$, 500 MHz) δ ppm: 4.03 (s, 2H, -C**H$_2$**-), 2.76 (s, 12H, 4 x -C**H$_3$**). $^{13}$C NMR ($CD_3Cl_3$, 125 MHz) δ ppm: 205.7, 166, 164.42, 106, 107.31, 32.63, 16.40.

**Methylene-bis-(3,5-di-isobutanoyl-2,4,6-trihydroxybenzene) (4b):** Yield: 90%; light orange coloured solid; mp 200–202 °C;$^1$H NMR ($CDCl_3$, 500 MHz) δ ppm: 3.98 (s, 2H, -C**H$_2$**-), 3.51 (m, 2H, *J* = 5.4 Hz, 2 x -C**H**$(CH_3)_2$), 1.2 (d, *J* = 5.4 Hz, 24H, 4 x C**H**$_3$). $^{13}$C NMR ($CDCl_3$, 125 MHz) δ ppm: 212, 171.03, 167.56, 163.37, 108.13, 106.12, 39.74, 18.78, 17.17.

**Methylene-bis-(3,5-di-isopentanoyl-2,4,6-trihydroxybenzene) (4c):** Yield: 88%; yellow coloured solid; mp158–160 °C; $^1$H NMR ($CDCl_3$, 500 MHz) δ ppm: 4.00 (s, 2H, -C**H$_2$**-), 3.01 (d, *J* = 5.6 Hz, 8H, 4 x -C**H$_2$**-CH$(CH_3)_2$, 2.27 (dt, *J* = 11.0, 5.5 Hz, 4H, 4 x $CH_2$-C**H**$(CH_3)_2$), 1.00 (d, *J* = 5.4 Hz, 24H, 8 x C**H$_3$**). $^{13}$C NMR ($CDCl_3$, 125 MHz) δ ppm: 208.00, 171.3, 165.78, 162.82, 108.39, 105.50, 53.50, 25.91, 23.10, 16.89.

**Methyl-methylene-bis-(3,5-diacetyl-2,4,6-trihydroxybenzene) (4d):** Yield: 82%; yellow coloured solid; mp 206–208 °C. $^1$H NMR ($CDCl_3$, 500 MHz) δ ppm: 4.78 (d, *J* = 5.5 Hz, 1H, >C**H**-$CH_3$), 2.76 (s, 12H, 4 x -C**H$_3$**), 1.56 (d, *J* = 5.4 Hz, 3H, >C**H**-$CH_3$). $^{13}$C NMR ($CDCl_3$, 125 MHz) δ ppm: 206.10, 171.2, 166.37, 164.51, 112.59, 107.08, 33.06, 26.48, 21.37.

**Phenyl-methylene-bis-(3,5-diacetyl-2,4,6-trihydroxybenzene) (4e)**: Yield: 64%; cream coloured solid; mp 109–111 °C. $^1$H NMR ($CDCl_3$, 500 MHz) δ ppm: 7.33 – 7.21 (m, 3H, Ar**H**), 7.20 (d, *J* = 0.6 Hz, 2H, Ar**H**), 5.32 (s, 1H, >C**H**-phenyl), 2.70 (s, 12H, 4 x C**H**$_3$). $^{13}$C NMR ($CDCl_3$, 125 MHz) δ ppm: δ 206.00, 166.27, 171.6, 164.36, 140.87, 128.9, 128.47, 127.21, 109.78, 107.16, 36.34, 32.67.

**Reusability and heterogeneity of SSA catalyst**

After the completion of the reaction, the collected **SSA** catalyst was stirred in 10 mL of EtOAc for 5-10 min. Then, it was filtered and washed with 5 mL of EtOAc and acetone, respectively. After that, before further used, the filtered catalyst was dried at 120 °C for 3 h. Additionally, a hot filtration technique was performed following the previous methods[1] to observe the possible leaching of **SSA** active sites.

**Environmental assessment**

To assess the environmental assessment of the present method, the combination between the Environmental Assessment Tool for Organic Syntheses (EATOS) software established by Eissen and Metzger[2] and the algorithm by Andraos[3] were performed. The necessitated data related to their detail of stochiometric data was attained from the recent literatures[4–7] both for EATOS and Andraos algorithm. For further detail about energy efficiency profile, the energy calculation measurement established by Clark and co-workers[8] was accomplished. As a note, the details of workup and purification stages were not included in this assessment due to the lack of procedures information.

**Preparation of protein targets $3CL^{pro}$ and ligands**

The X-ray crystallographic structures of **$3CL^{pro}$** in complex with an inhibitor N3 was retrieved from the Protein Data Bank database with PDB ID: 6LU7 **(htttp://www.rscb.org/)**, then, chain A was loaded into the AutoDock Tools (version 1.5.6) software. Through this software, the ligand N3, water, and ions molecules were removed. PrankWeb **(http://prankweb.cz/)** was used to identify the active sites of selected receptors. Finally, before the docking studies were performed, polar hydrogen atoms and Gasteiger charges were added.

**Density-functional theory (DFT) studies**

All of the studied compounds will be sketched with PerkinElmer Informatics ChemDraw (version 17.1). The quantum chemical calculation for all the investigated molecular structures will be carried out in GAUSSIAN 09 suit of program. The optimisation of all the stationary points of desired molecules was calculated using 6-31G (d, p) basis set with the Lee-Yang–Parr exchange-correlation (B3LYP) density functional in the gas phase. It allows calculating the values of orbital energy HOMO and LUMO, total energy, gap energies ($\Delta E_{gap}$).

Then, based on the calculated orbital energy (HOMO and LUMO), it can be used to calculate several other molecular electronic properties including electronegativity ($\chi$) = -($E_{HOMO}$-$E_{LUMO}$)/2, electron affinity (A) = -$E_{LUMO}$, ionisation energy (I) = -$E_{HOMO}$, chemical potential($\mu$) = 1/2 ($E_{LUMO}$ + $E_{HOMO}$), chemical softness (S) = 1/2 $\eta$, chemical hardness ($\eta$) = 1/2 ($E_{LUMO}$ - $E_{HOMO}$) and electrophilicity index ($\omega$) = $\mu^2$/2 $\eta$[9,10]. Additionally, Molecular electrostatic potential (MEP) calculation derived from Mulliken charge was performed to access the detail information of nucleophilic and electrophilic sites.

**Molecular docking studies**

Molecular docking has extensively used in structure-based drug design[11]. To assess the binding difference between the synthesised dimeric 2,4-diacetyl phloroglucinol and its derivatives along with N3, Chloroquine, and Remdesivir as a reference with the **3CL$^{pro}$**, a comparative molecular docking analysis was performed using PyRx software by AutoDock wizard[12], which generated using Grid box centre_x= -14.1744035865, centre_y= 13.2322187073, centre_z= 68.9220623083, size_x= 20.4592380327, size_y= 23.6792741601, size_z= 26.2300864435 and exhaustiveness = 8. The interactions between the receptor and the result of the concerned ligands were compiled, visualised and analysed using PyMol (version 1.7.4) and BIOVIA Discovery Studio Visualizer 2020.

**Molecular target prediction**

The synthesised **4a** and its derivatives may interact with several numbers of protein bind to proteins or other macro-molecular targets. Accordingly, it is essential to predict the molecular targets for these investigated molecules. It can be easily investigated using an accessible free of charge Swiss Target Prediction **(http://www.swisstargetprediction.ch/index.php)**[13].

**Drug likeness prediction and ADMET analysis**

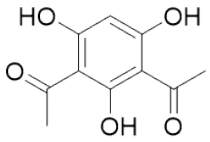
Drug-likeliness properties of ligands were assessed using SwissADME (**http://www.swissadme.ch/**). The ADMET ((*i.e.,* absorption, distribution, metabolism, excretion, and toxicity) analysis was accessed using admetSAR **(http://lmmd.ecust.edu.cn/admetsar1)** and pKCSM approach **(http://biosig.unimelb.edu.au/pkcsm/)**[14].

**Prediction of activity spectra for substances (PASS)**

The prediction of activity, particularly antiviral activities of the **4a** and its derivatives were assessed using PASS **(http://www.way2drug.com/).** This is an accessible free of charge a computer program, which can estimate the activity of molecules[15]. Through the basic structural formula, it could predict about 4,000 types of biological activity with an average accuracy of about 90%[16], therefore, the use of PASS to discover and optimize new lead compounds is very reasonable.

## S2: $^{1}$H NMR AND $^{13}$C NMR SPECTRA

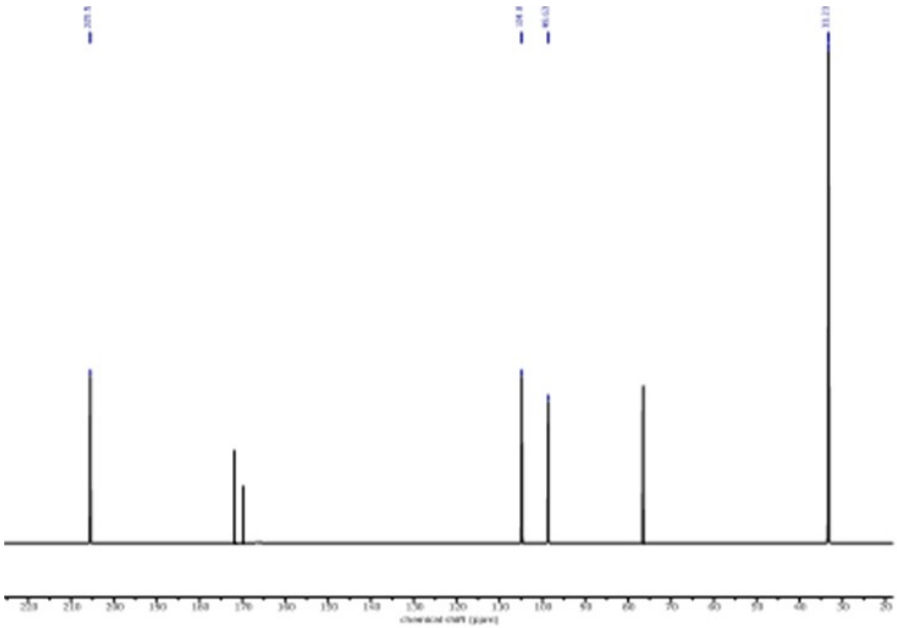
After purification and characterization, all of the products were characterized using NMR and the spectral data of $^{1}$H NMR and $^{13}$C NMR were compared with the relevant literature[4,17].




**1,1'-(2,4,6-trihydroxy-1,3-phenylene)bis(ethan-1-one) (2a).** $^{1}$H NMR ($CD_3Cl_3$, 500 MHz) δ ppm: 6.19 (s, 1H, Ar**H**), 2.64 (s, 6H, 2 x C**H**$_3$).$^{13}$C NMR ($CD_3Cl_3$, 125 MHz) δ ppm: 205.56, 173.56, 170.65, 104.83, 98.63, 33.23.

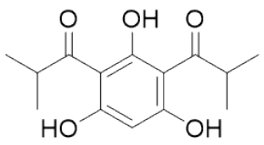



**$^{1}$H NMR spectrum of 2a**



**$^{13}$C NMR spectrum of 2a**

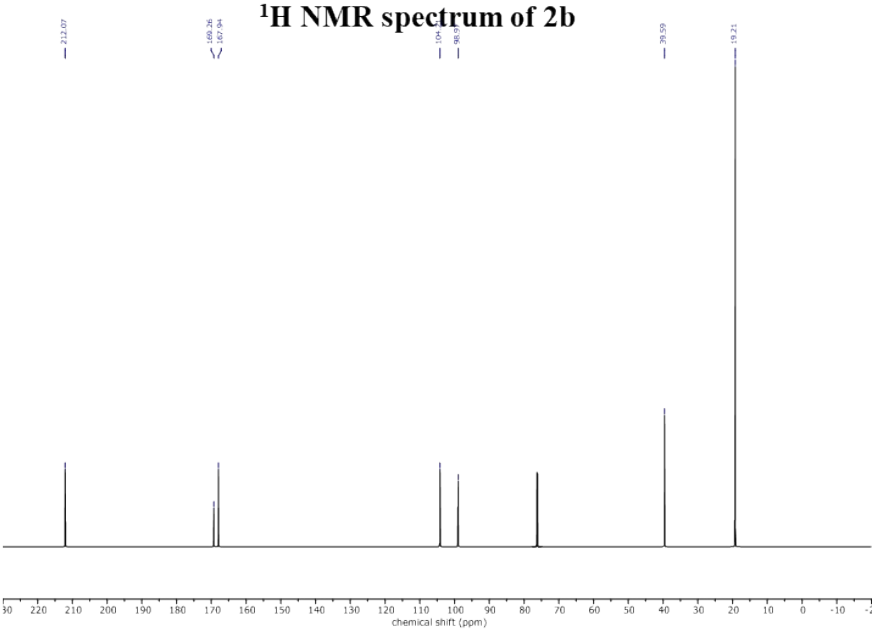
**Yield: 95%**




**1,1'-(2,4,6-trihydroxy-1,3-phenylene)bis(2-methylpropan-1-one) (2b).** $^{1}$H NMR ($CD_3Cl_3$, 500 MHz) δ ppm: 6.19 (s, 1H, Ar**H**), 3.52 (p, J = 5.4 Hz, 2H, 2 x -C**H**$(CH_3)_2$), 1.15 (d, J = 5.4 Hz, 12H, 4 x C**H**$_3$).$^{13}$C NMR ($CD_3Cl_3$, 125) δ ppm: 212.07, 170, 168, 104.21, 98.97, 39.59, 19.21.

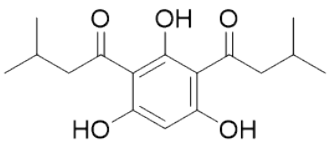



**$^{1}$H NMR spectrum of 2b**




**$^{13}$C NMR spectrum of 2b**

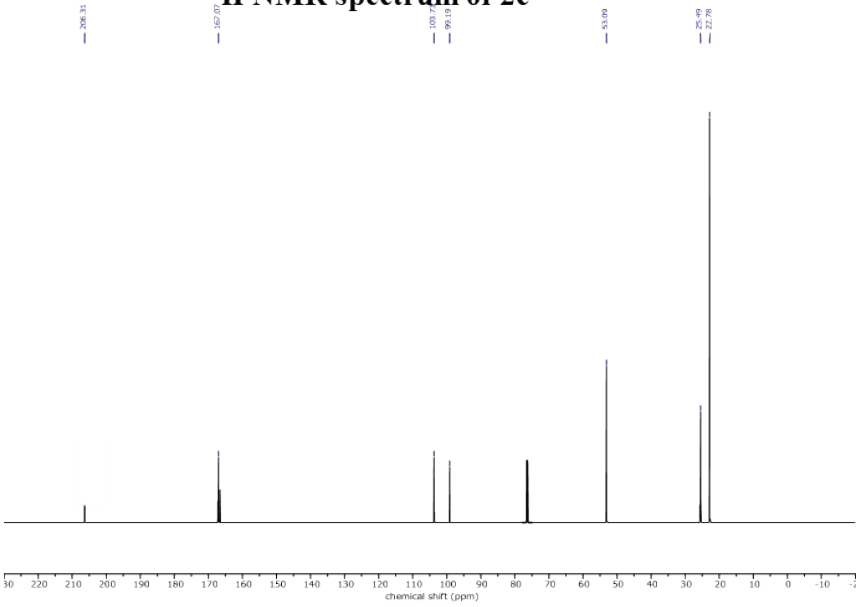
**Yield: 89%**




**1,1'-(2,4,6-trihydroxy-1,3-phenylene)bis(3-methylbutan-1-one) (2c).** $^{1}$H NMR ($CD_3Cl_3$, 500 MHz) δ ppm: : 6.20 (s, 1H, Ar**H**), 2.9 (d, J = 5.6 Hz, 4H, 2 x -C**H$_2$**-CH$(CH_3)_2$), 2.26 (dh, J = 11.0, 5.5 Hz, 2H, 2 x $CH_2$-C**H**$(CH_3)_2$), 0.97 (d, J = 5.4 Hz, 12H, 4x C**H$_3$**). $^{13}$C NMR ($CD_3Cl_3$, 125 MHz) δ ppm: 205.98, 167.07, 103.73, 99.19, 53.09, 24.94, 22.81.



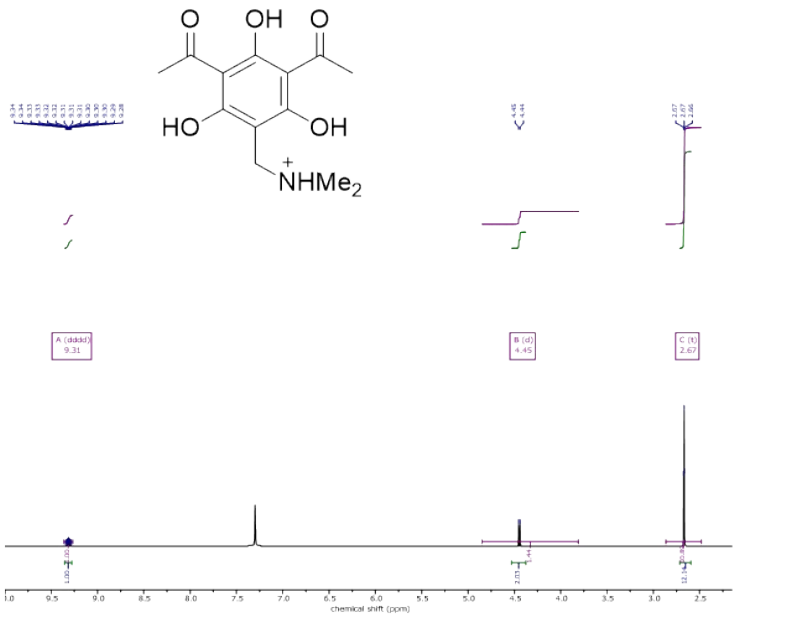

**$^{1}$H NMR spectrum of 2c**



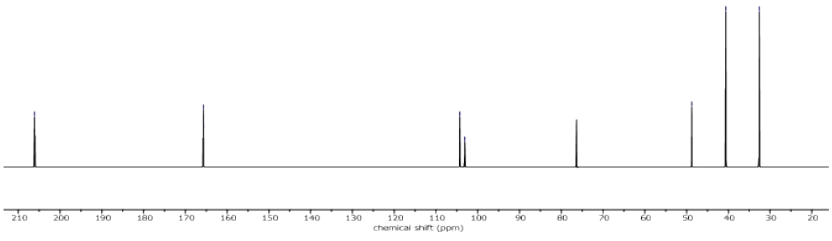

**$^{13}$C NMR spectrum of 2c**

**Yield: 88%**

**1-(3,5-diacetyl-2,4,6-trihydroxyphenyl)-N,N-dimethylmethanaminium (3).** $^{1}$H NMR ($CD_3Cl_3$, 500 MHz) δ ppm: 9.31 (dddd, $J$ = 9.5, 6.6, 5.9, 3.0 Hz), 4.45 (d, $J$ = 6.6 Hz), 2.67 (t, $J$ = 1.5 Hz). $^{13}$C NMR ($CD_3Cl_3$, 125 MHz) δ ppm: 206.09, 165.70, 165.69, 104.31, 103.11, 48.75, 40.60, 32.63.



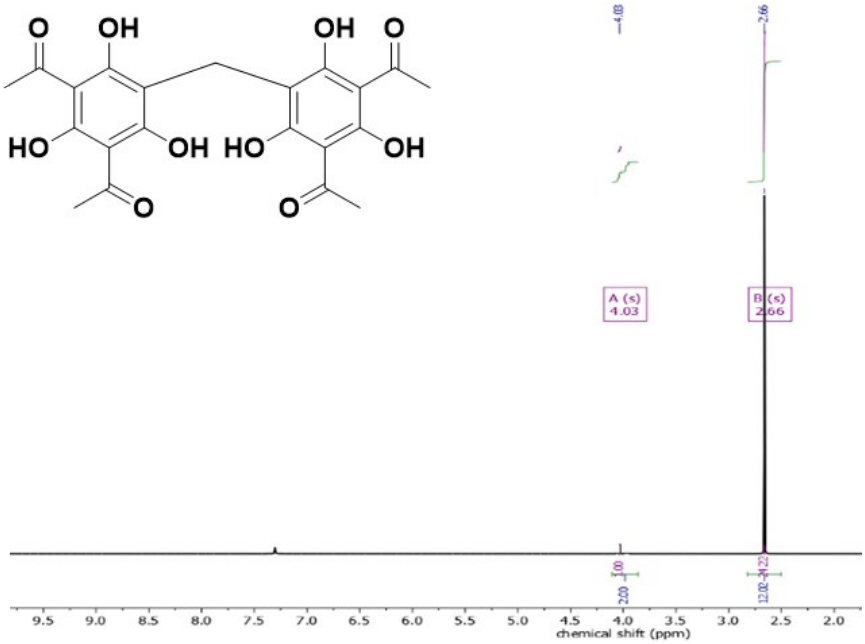

**$^{1}$H NMR spectrum of 3**



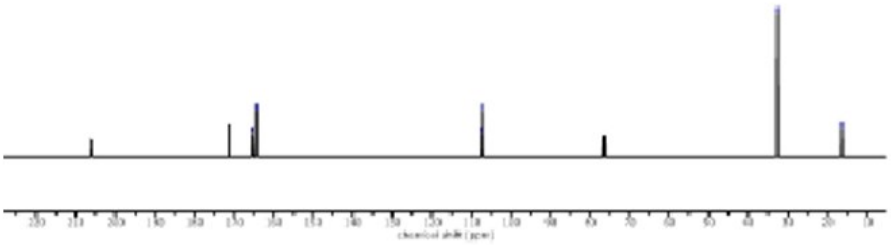

**$^{13}$C NMR spectrum of 3**

**Yield: 98%**

**Methylene-bis-(3,5-diacetyl-2,4,6-trihydroxybenzene) (4a):** $^{1}H$ NMR ($CD_3Cl_3$, 500 MHz) δ ppm: 4.03 (s, 2H, -C**H**$_2$-), 2.76 (s, 12H, 4 x -C**H**$_3$). $^{13}C$ NMR ($CD_3Cl_3$, 125 MHz) δ ppm: 205.7, 166, 164.42, 106, 107.31, 32.63, 16.40.



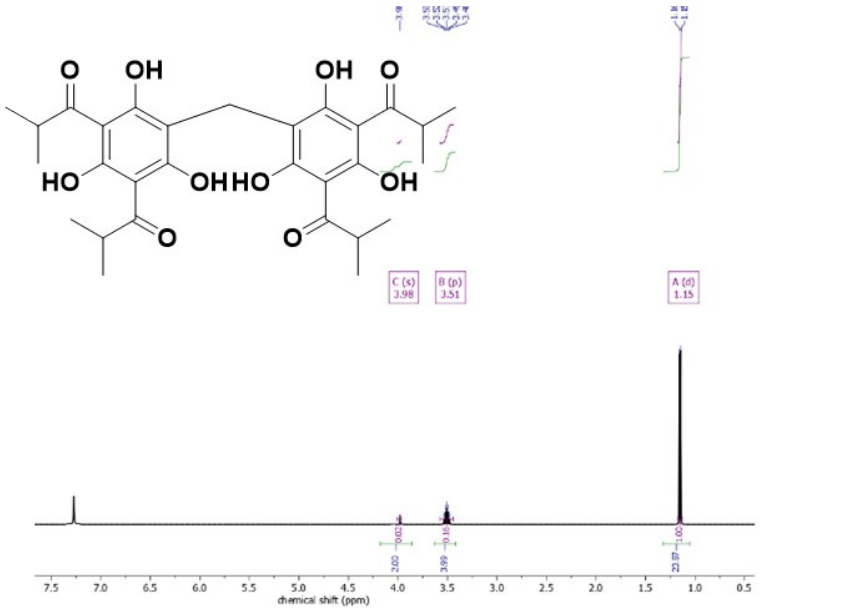

**$^{1}H$ NMR spectrum of 4a**



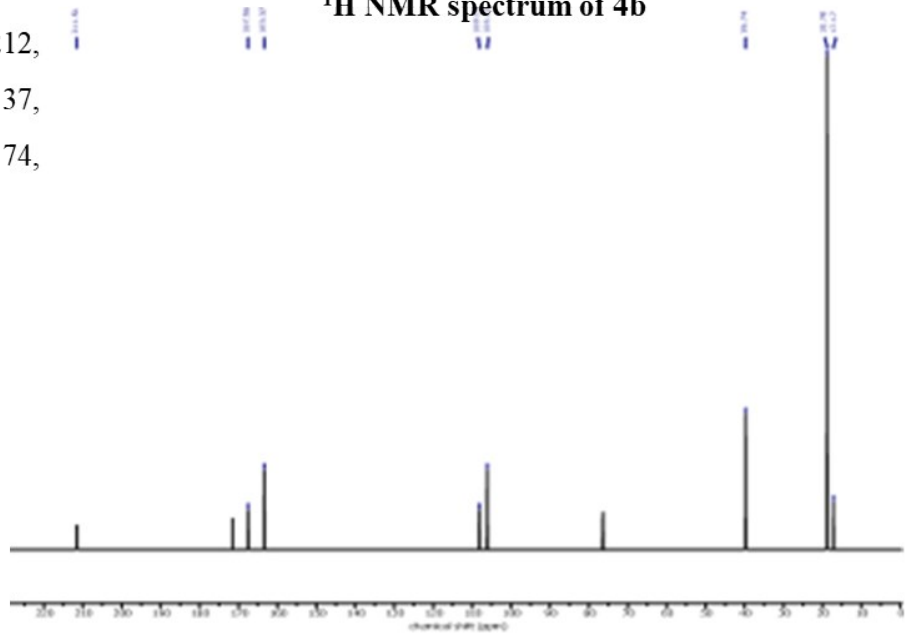
**$^{13}C$ NMR spectrum of 4a**

**Yield: 94%**

**Methylene-bis-(3,5-di-isobutanoyl-2,4,6-trihydroxybenzene) (4b):** $^{1}$H NMR ($CD_3Cl_3$, 500 MHz) δ ppm: 3.98 (s, 2H, -C**H**$_2$-), 3.51 (m, 2H, *J* = 5.4 Hz, 2 x -C**H**$(CH_3)_2$), 1.2 (d, *J* = 5.4 Hz, 24H, 4 x C**H**$_3$). $^{13}$C NMR ($CD_3Cl_3$, 125 MHz) δ ppm: 212, 171.03, 167.56, 163.37, 108.13, 106.12, 39.74, 18.78, 17.17.



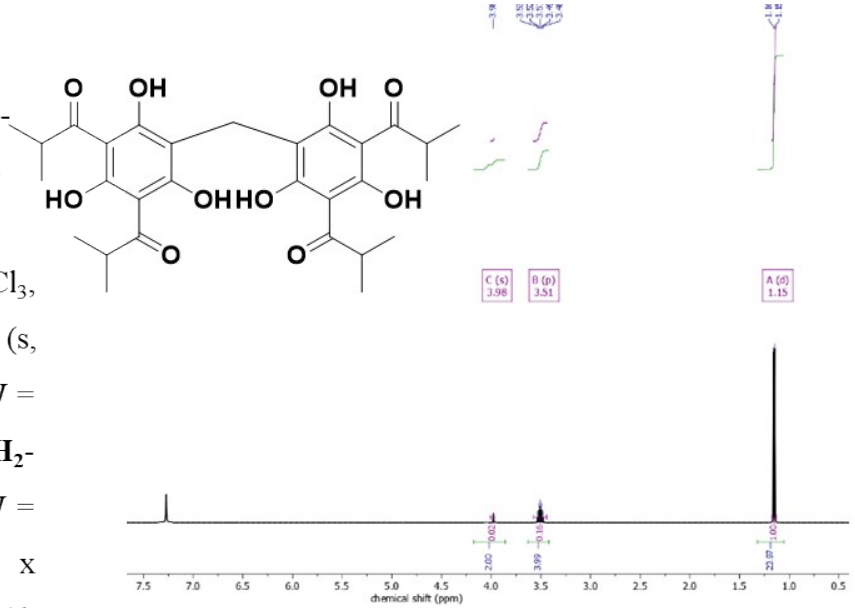

**$^{1}$H NMR spectrum of 4b**



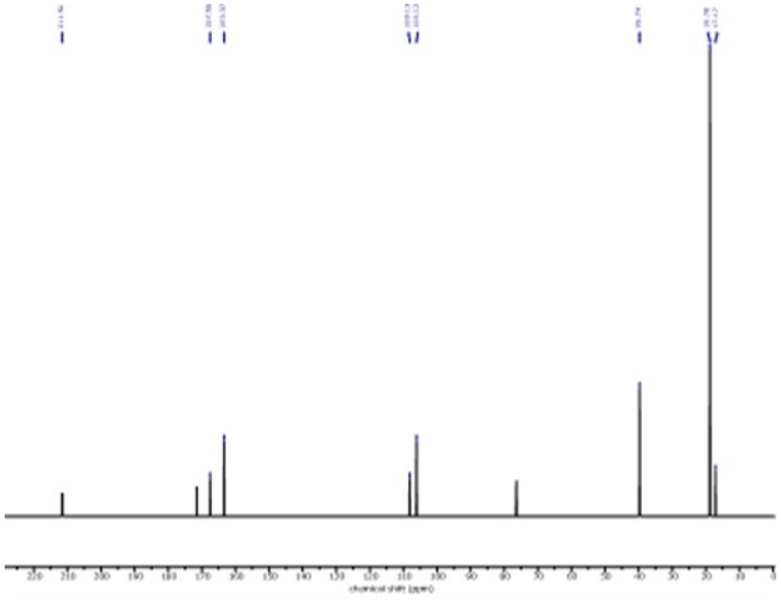
**$^{13}$C NMR spectrum of 4b**

**Yield: 90%**

**Methylene-bis-(3,5-di-isopentanoyl-2,4,6-trihydroxybenzene) (4c):** $^{1}$H NMR ($CD_3Cl_3$, 500 MHz) δ ppm: 4.00 (s, 2H, -C**H**$_2$-), 3.01 (d, *J* = 5.6 Hz, 8H, 4 x -C**H**$_2$-CH($CH_3$)$_2$, 2.27 (dt, *J* = 11.0, 5.5 Hz, 4H, 4 x $CH_2$-C**H**($CH_3$)$_2$), 1.00 (d, *J* = 5.4 Hz, 24H, 8 x C**H**$_3$). $^{13}$C NMR ($CD_3Cl_3$, 125 MHz) δ ppm: 208.00, 171.3, 165.78, 162.82, 108.39, 105.50, 53.50, 25.91, 23.10, 16.89.



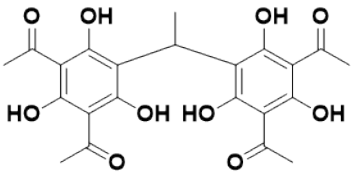

**$^{1}$H NMR spectrum of 4c**



**$^{13}$C NMR spectrum of 4c**

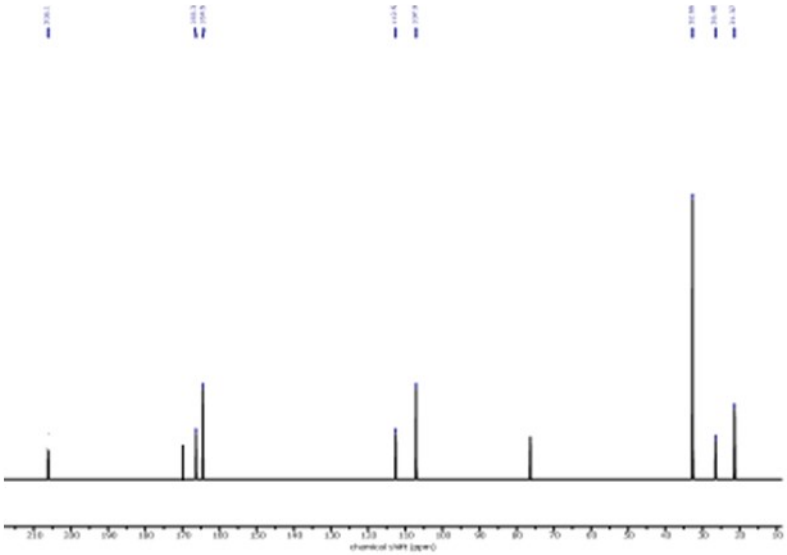
**Yield: 88%**

**Methyl-methylene-bis-(3,5-diacetyl-2,4,6-trihydroxybenzene) (4d):** $^{1}$H NMR ($CD_3Cl_3$, 500 MHz) δ ppm: 4.78 (d, $J$ = 5.5 Hz, 1H, >C**H**-$CH_3$), 2.76 (s, 12H, 4 x -C**H$_3$**), 1.56 (d, $J$ = 5.4 Hz, 3H, >C**H**-$CH_3$). $^{13}$C NMR ($CD_3Cl_3$, 125 MHz) δ ppm: 206.10, 171.2, 166.37, 164.51, 112.59, 107.08, 33.06, 26.48, 21.37.





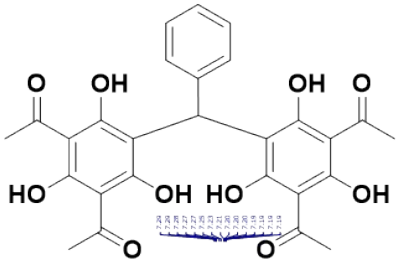

**$^{1}$H NMR spectrum of 4d**

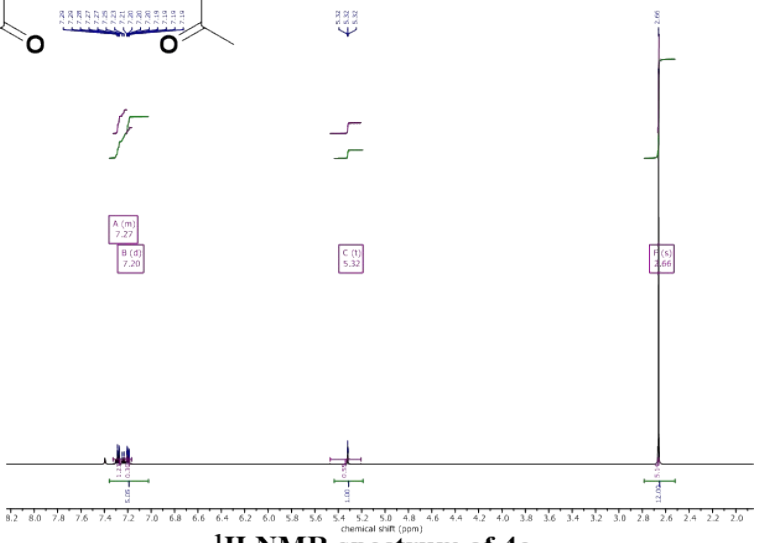


**$^{13}$C NMR spectrum of 4d**

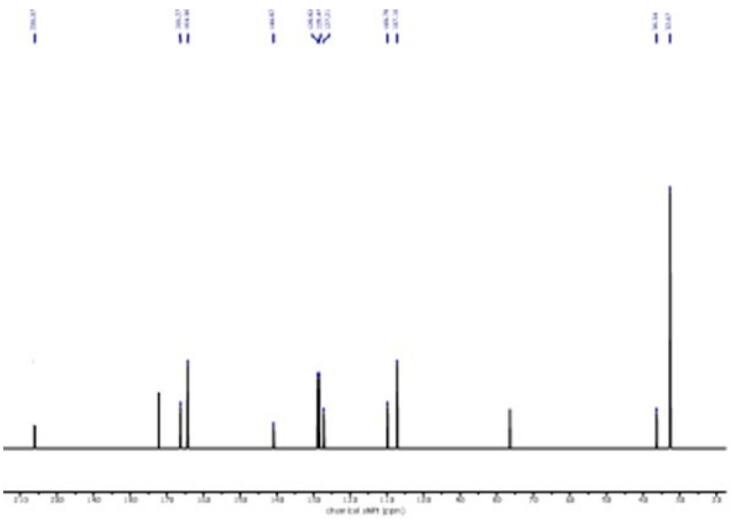
**Yield: 82%**

**Phenyl-methylene-bis-(3,5-diacetyl-2,4,6-trihydroxybenzene) (4e)**: 109–111 °C. $^1$H NMR ($CD_3Cl_3$, 500 MHz) δ ppm: 7.33 – 7.21 (m, 3H, Ar**H**), 7.20 (d, *J* = 0.6 Hz, 2H, Ar**H**), 5.32 (s, 1H, >C**H**-phenyl), 2.70 (s, 12H, 4 x C**H**$_3$). $^{13}$C NMR ($CD_3Cl_3$, 125 MHz) δ ppm: δ 206.00, 166.27, 171.6, 164.36, 140.87, 128.9, 128.47, 127.21, 109.78, 107.16, 36.34, 32.67



**$^1$H NMR spectrum of 4e**



**$^{13}$C NMR spectrum of 4e**

**Yield: 64%**

## S3: ENVIRONMENTAL ASSESSMENT

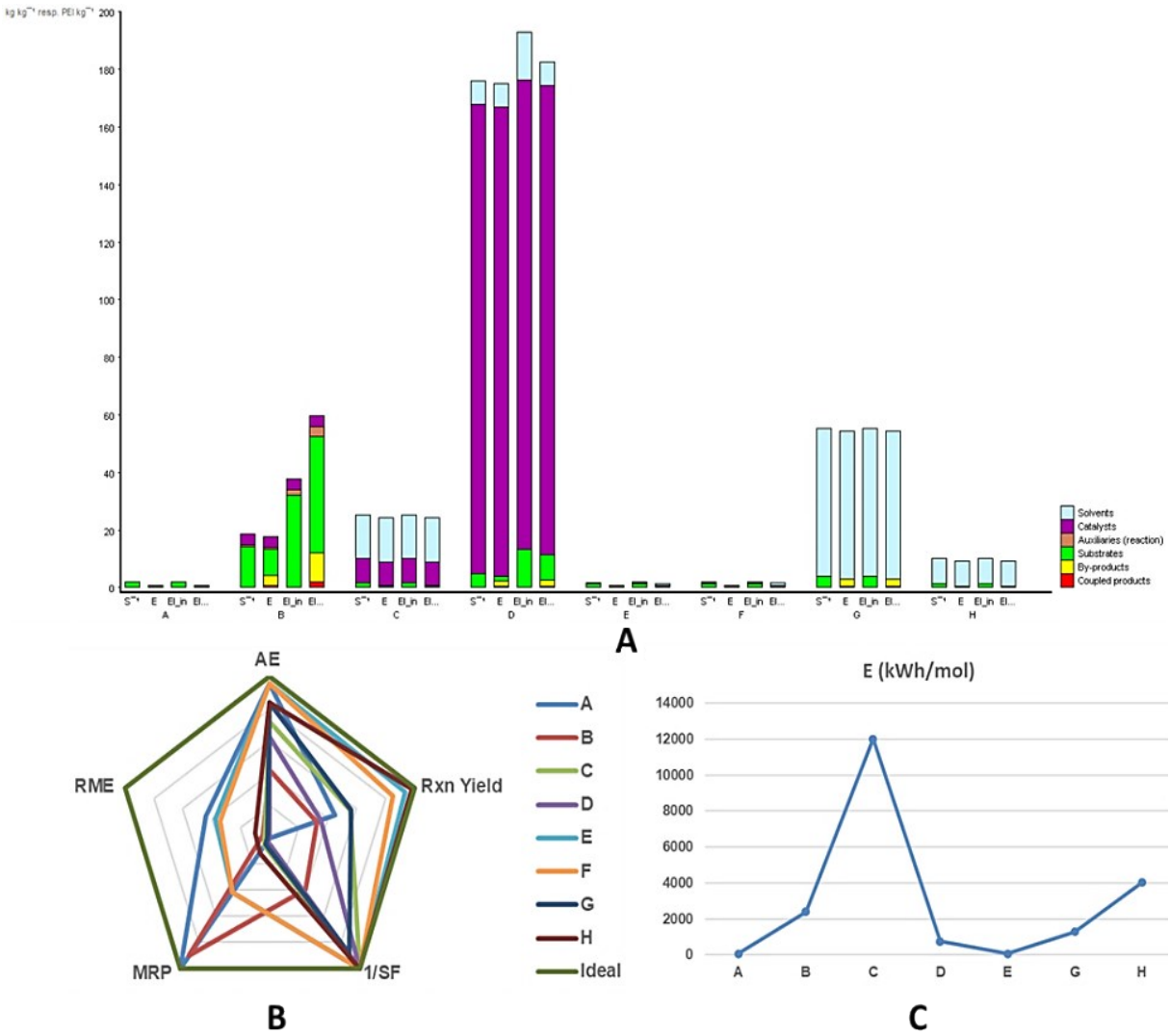


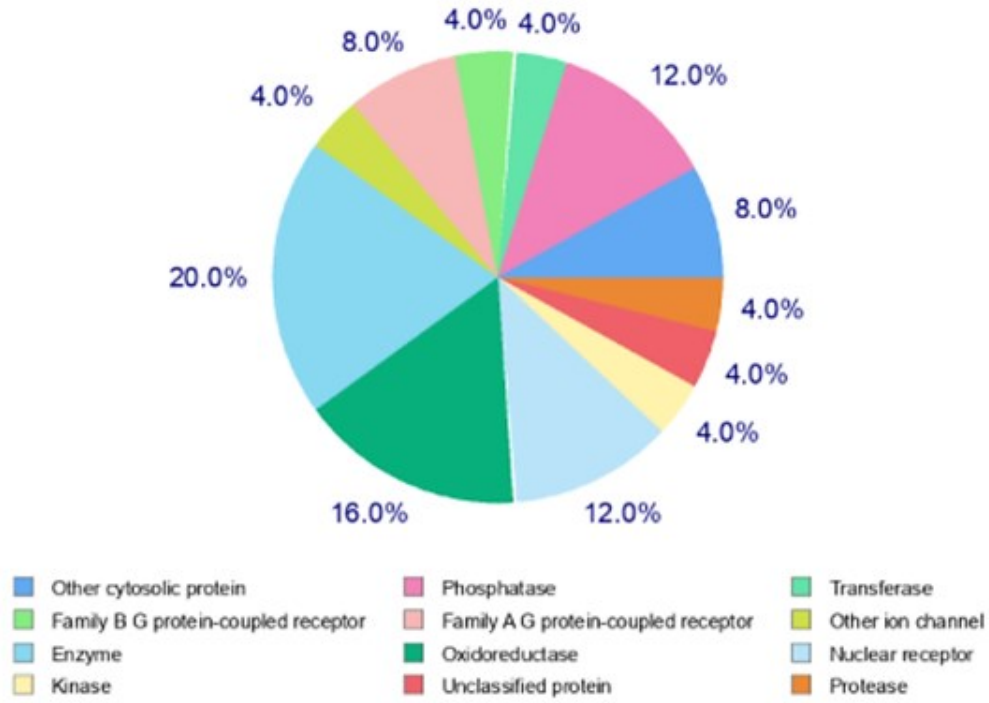

**Figure S1**. Environmental assessment results investigated by EATOS software (**A**), Andraos's algorithm (**B**), and energy intake requirement (**C**). Method A: MW[6], Method B: Oil-bath[7], Method C: Oil-bath [7], Method D: Oil-bath [5], Method E: present US, Method F: present LAG, Method G: Eschenmoser's salt, Method H: Dimethylammonium salt.

## S4: ENERGY REQUIREMENTS CALCULATION RESULTS

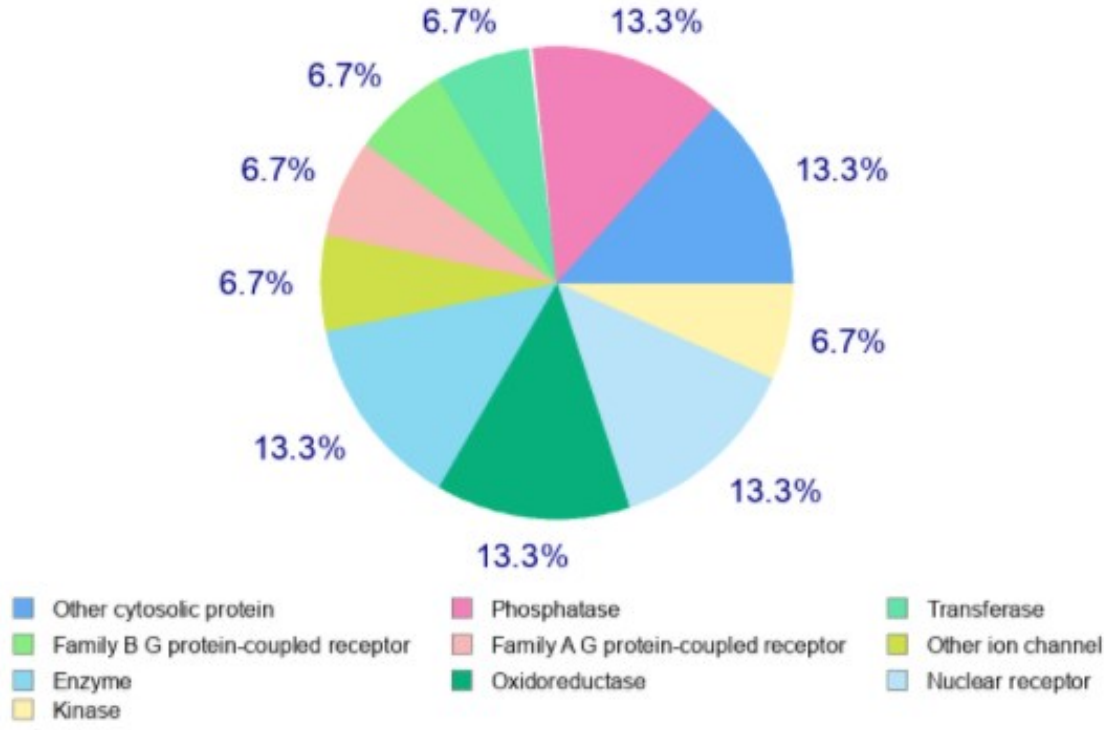
**Table S1.** Energy requirements calculation results for the synthesis of **4a**

| Method | Heating method | mmol | Yield (%) | P (kW) | t (h) | E (kWh) | Reference |
|---|---|---|---|---|---|---|---|
| **A** | MW | 1.00 | 88.00 | 0.70 | 0.08 | 0.06 | [6] |
| **B** | Oil bath | 1.00 | 30.00 | 1.44 | 0.50 | 0.72 | [7] |
| **C** | Oil bath | 2.50 | 60.00 | 1.44 | 2.00 | 2.88 | [7] |
| **D** | Oil bath | 1.00 | 95.00 | 1.44 | 0.50 | 0.72 | [5] |
| **E** | US | 1.00 | 95.00 | 0.16 | 0.33 | 0.05 | Present: US |
| **G** | Oil bath | 1.00 | 56.00 | 1.44 | 0.50 | 0.72 | Present: Eschenmoscher's salt |
| **H** | Oil bath | 1.00 | 98.00 | 3.16 | 1.25 | 3.95 | Present: Dimethylammonium salt |

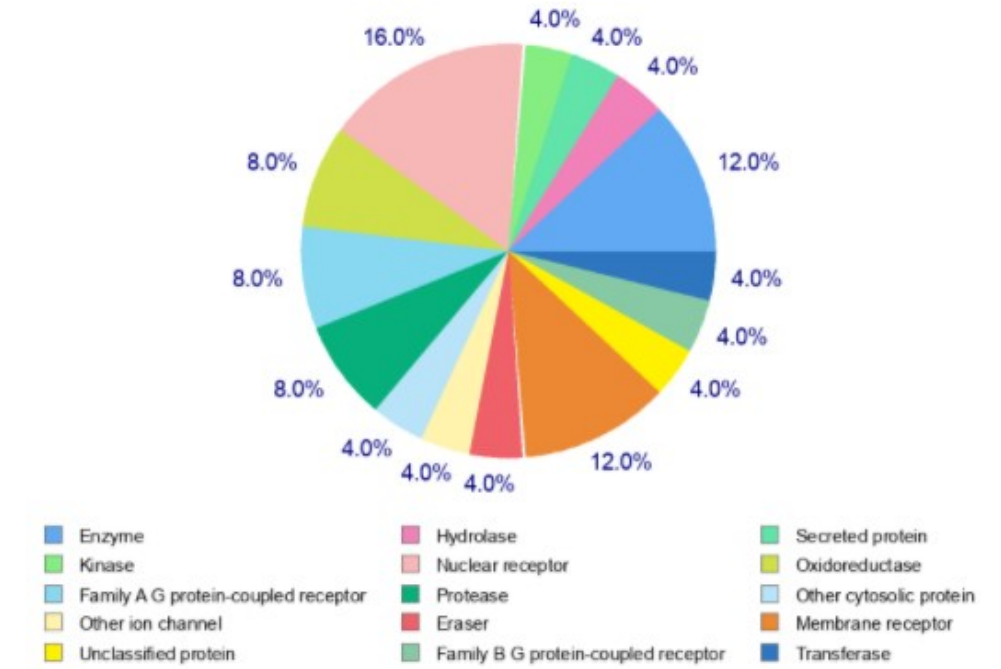
## S5: MOLECULAR TARGET PREDICTION



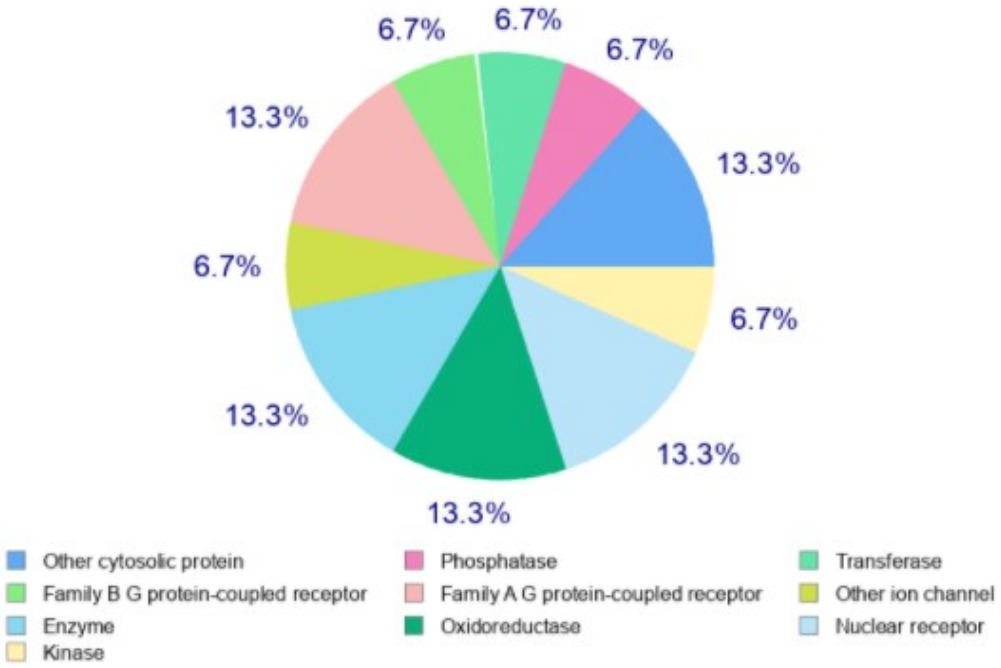

**Molecular target prediction of 4a**




**Molecular target prediction of 4b**




**Molecular target prediction of 4c**




**Molecular target prediction of 4d**

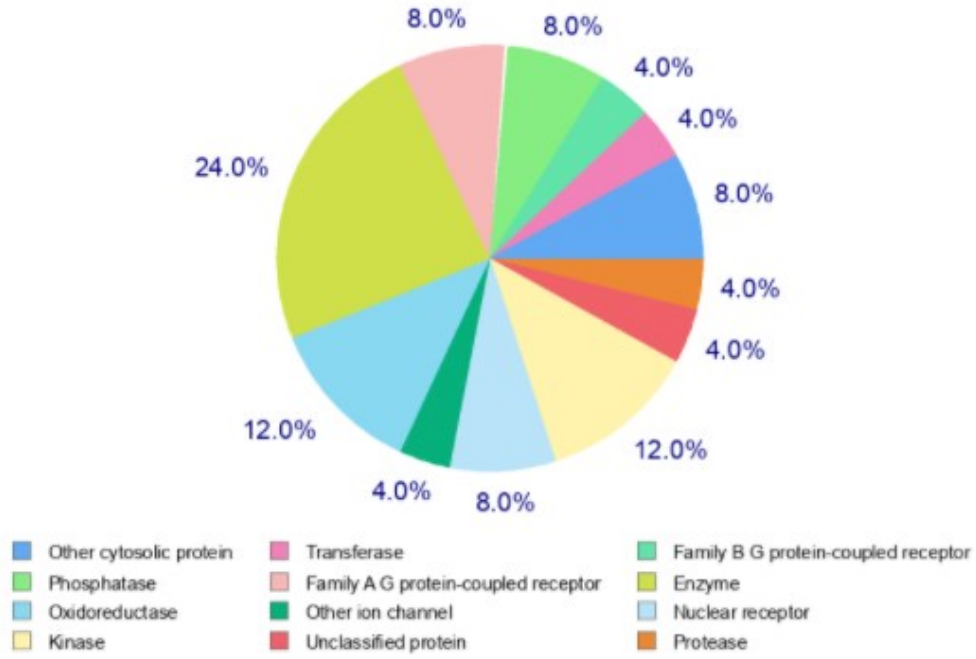



**Figure S2**. Molecular target prediction of **4a-e**

## S6: SURFACE REPRESENTATION

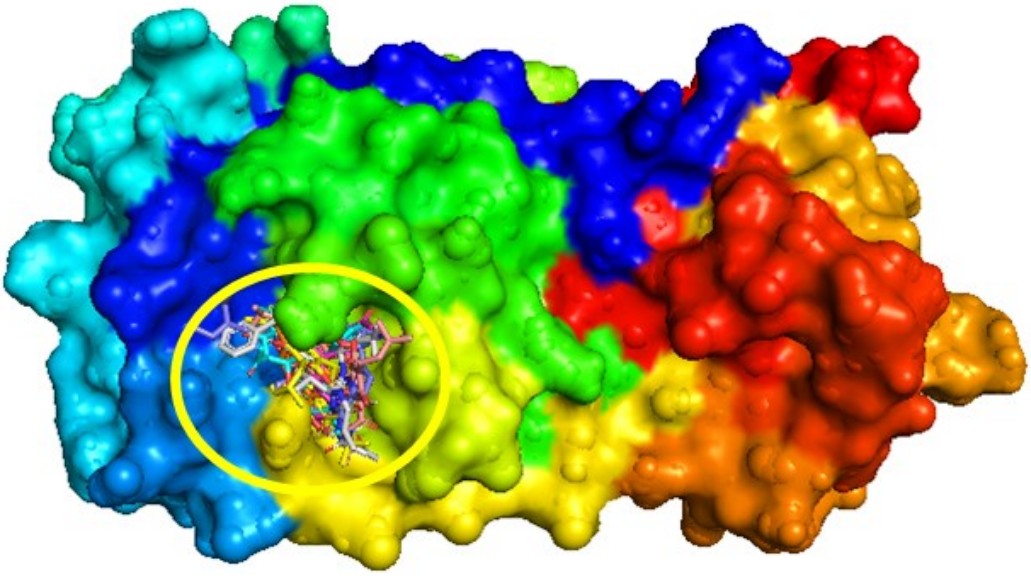
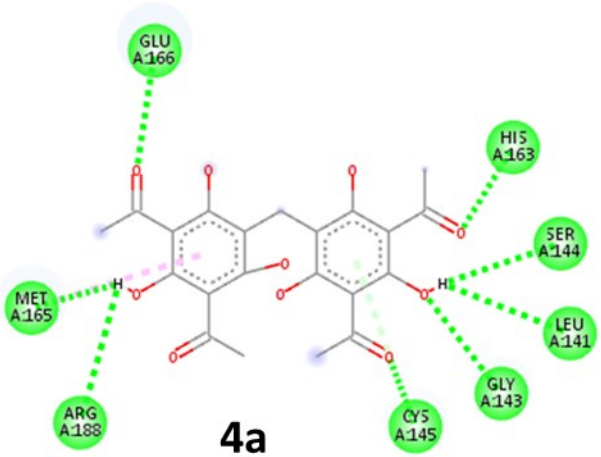
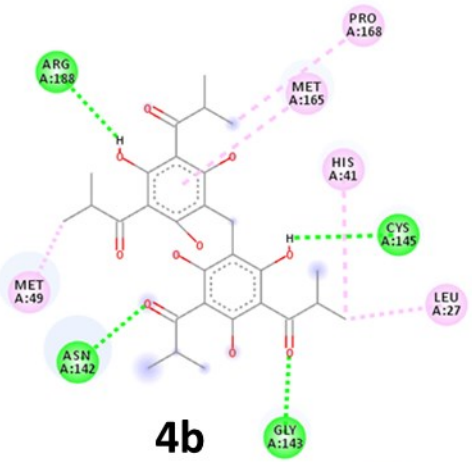


**Figure S3**. Surface representation showing the interaction of compound **4a-e**, N3, Chloroquine and Remdesivir at the substrate-binding region of $3CL^{pro}$ of SARS-CoV-2 (**A**),

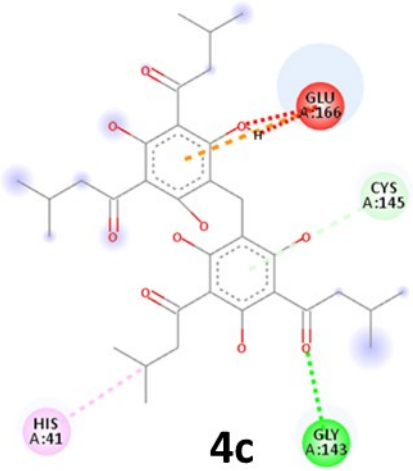
## S7: 2D STRUCTURE DEMONSTRATING THE BINDING INTERACTIONS



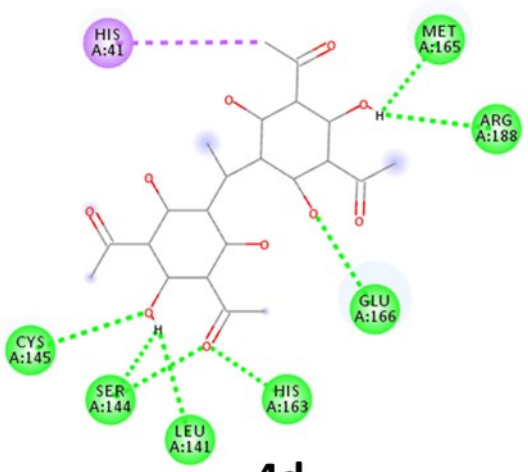

4a



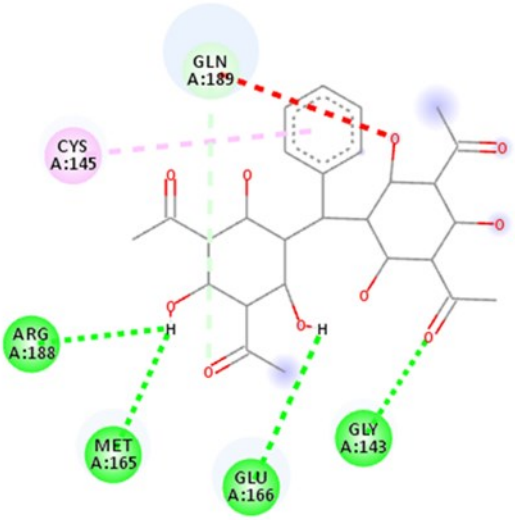

4b



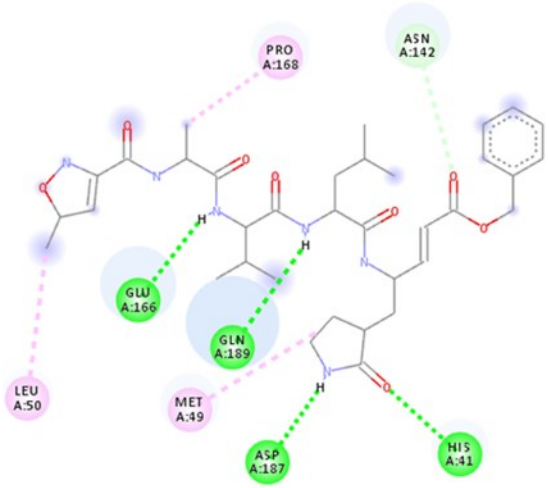

4c




4d




4e




N3

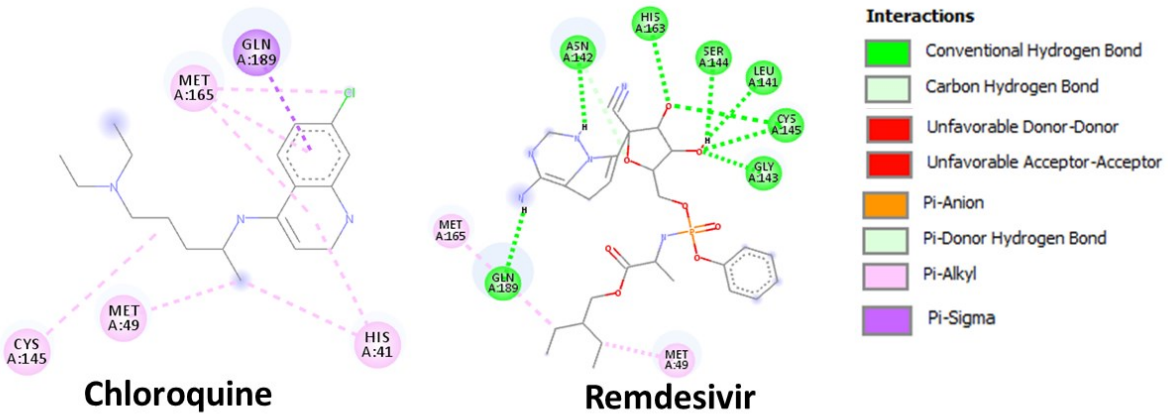
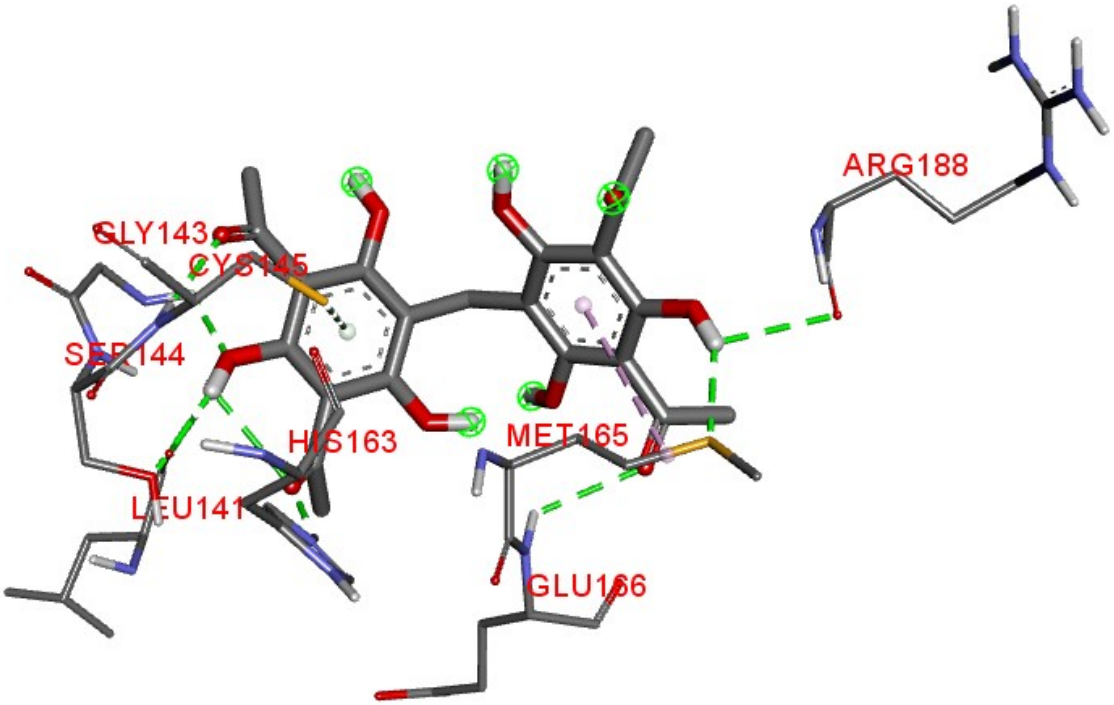
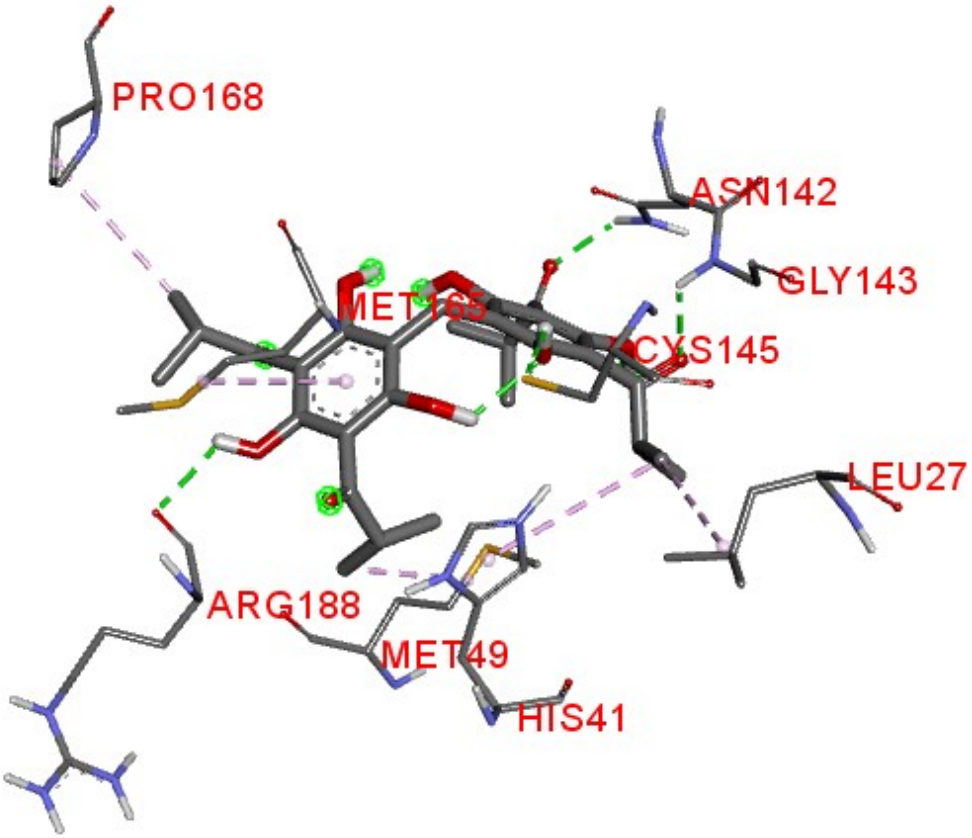



**Figure S4**. A 2D structure demonstrating the binding interactions between synthesised compounds along with N3, Chloroquine, and Remdesivir against $3CL^{pro}$.

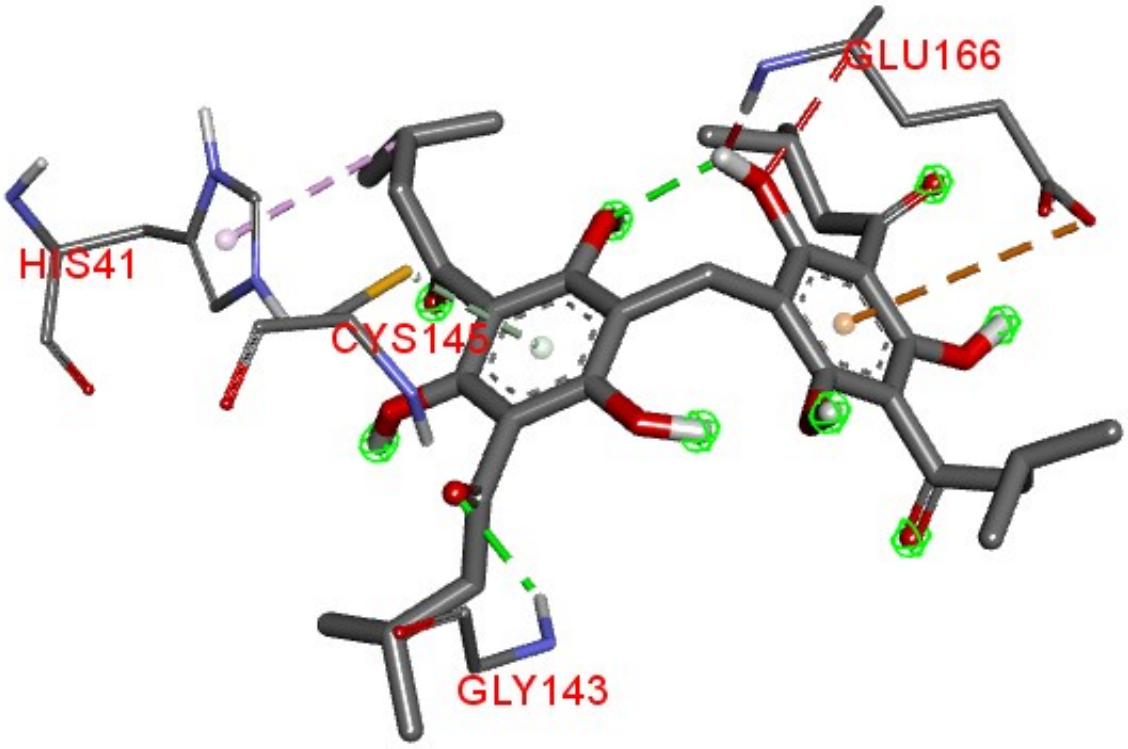
## S8: 3D REPRESENTATION OF COMPOUND 4A-D DOCKED INTO THE ACTIVE POCKET OF 3CL$^{pro}$



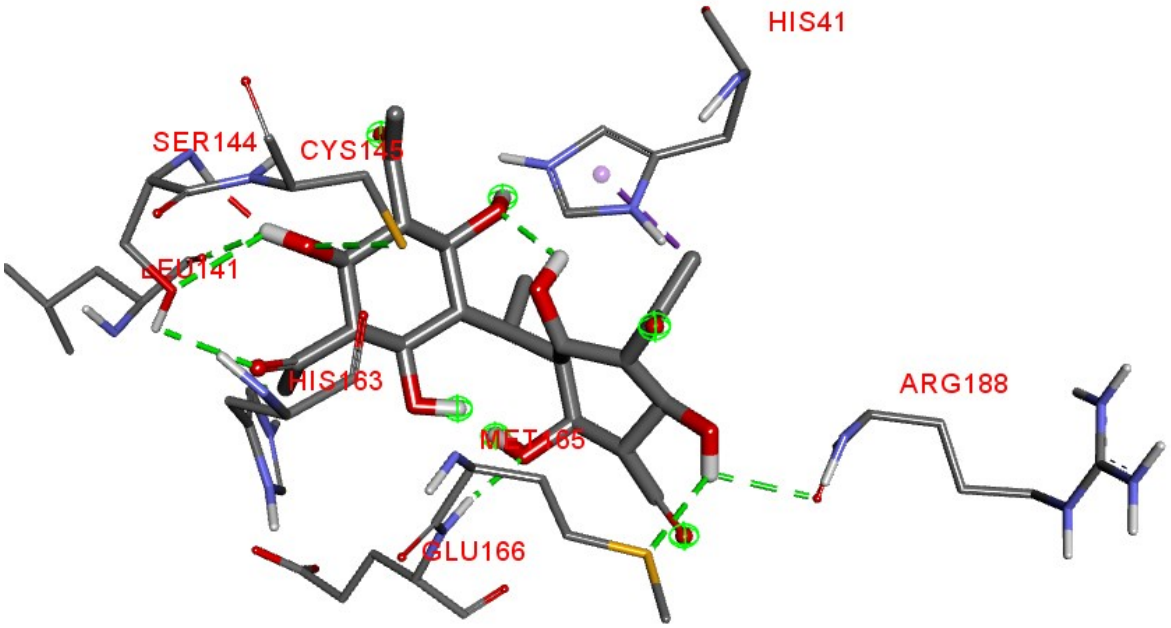

**4a**



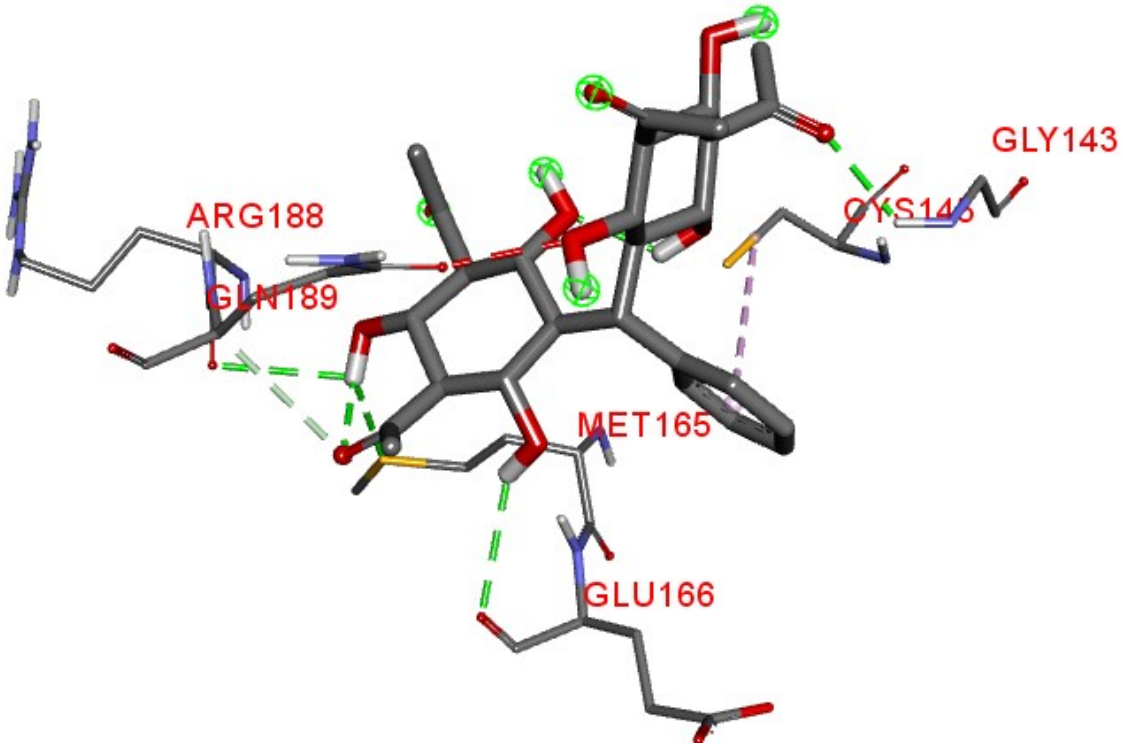

**4b**


GLU166
HIS41
CYS145
GLY143

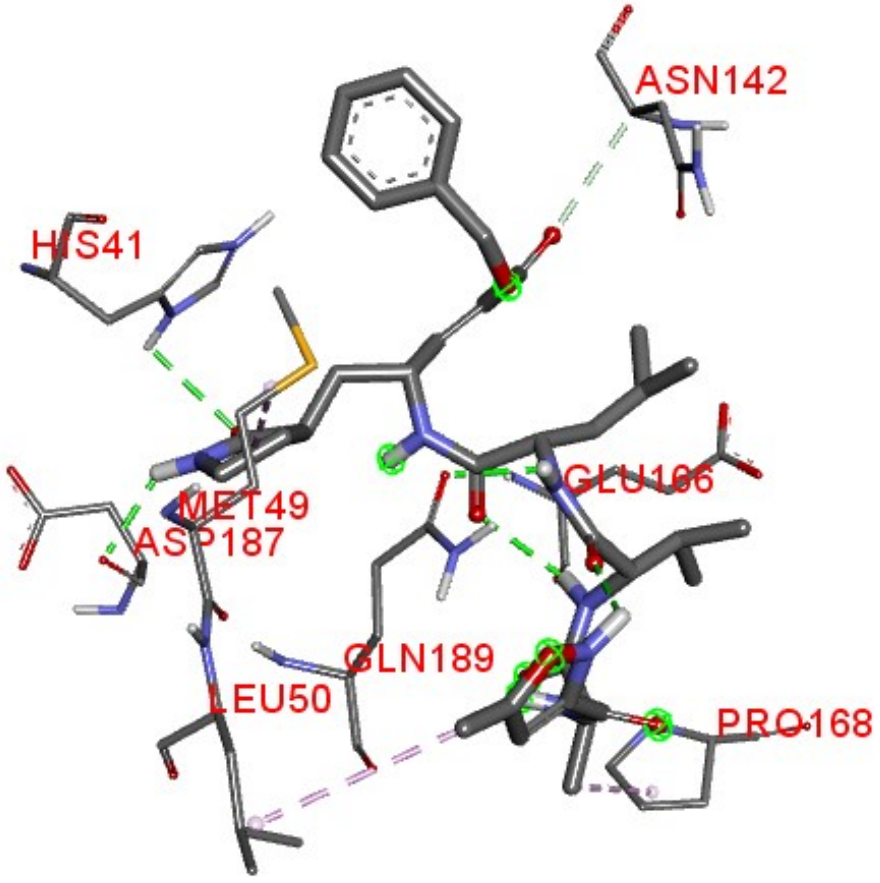
**4c**


HIS41
SER144
CYS145
LEU141
HIS163
ARG188
MET165
GLU166

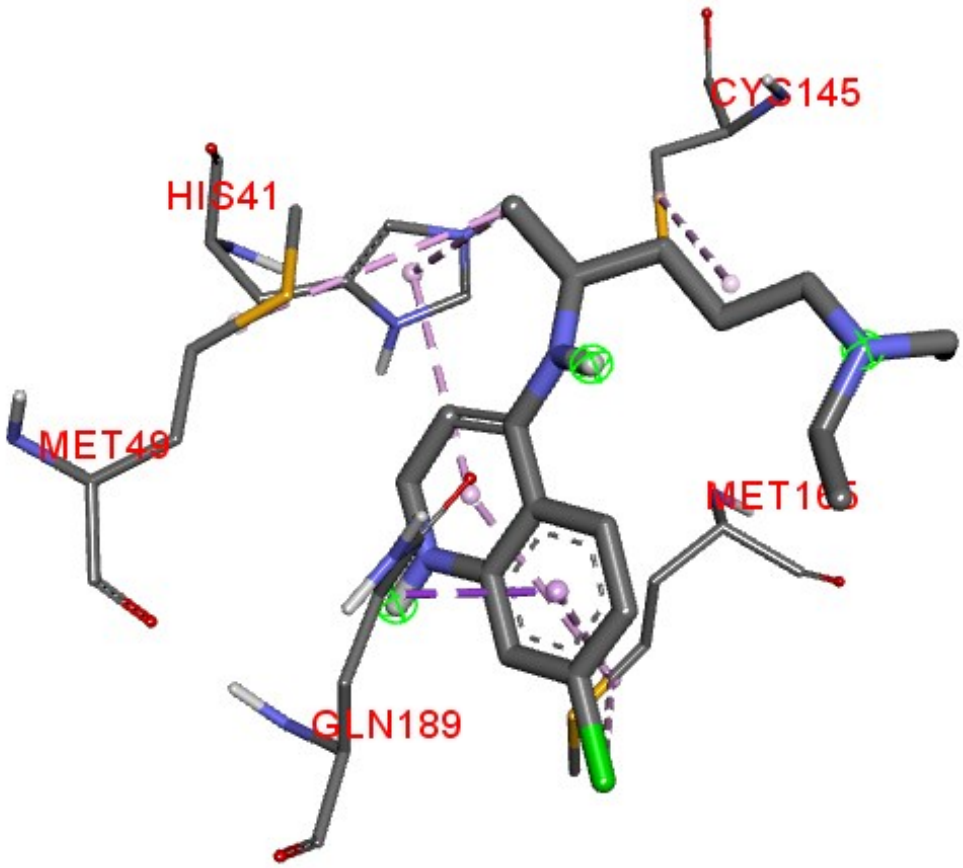
**4d**


GLY143
ARG188
GLN189
MET165
GLU166

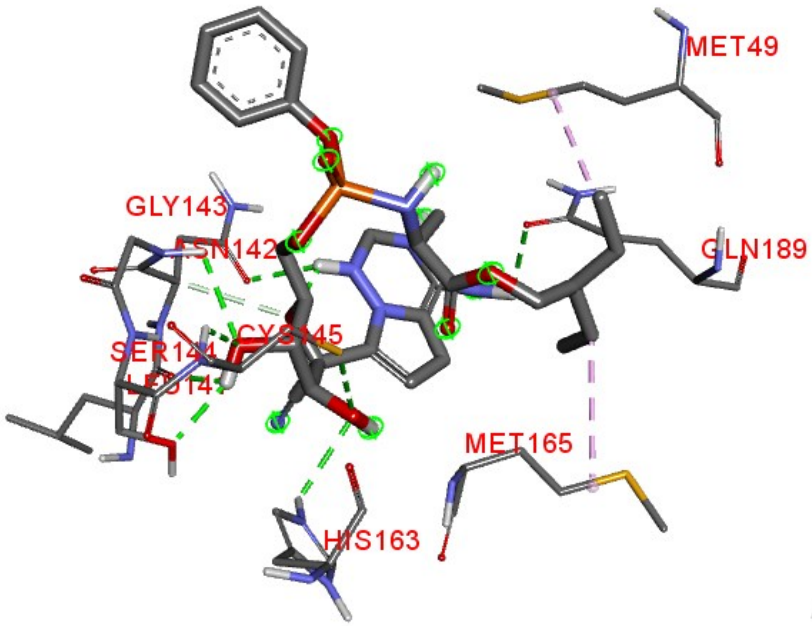
**4e**


ASN142
HIS41
GLU166
MET49
ASP187
GLN189
LEU50
PRO168

**N3**




**Chloroquine**




**Remdesivir**

**Figure S5.** 3D representation of compound **4a-d** docked into the active pocket of $3CL^{pro}$

## S9: PHARMACOKINETIC PARAMETERS

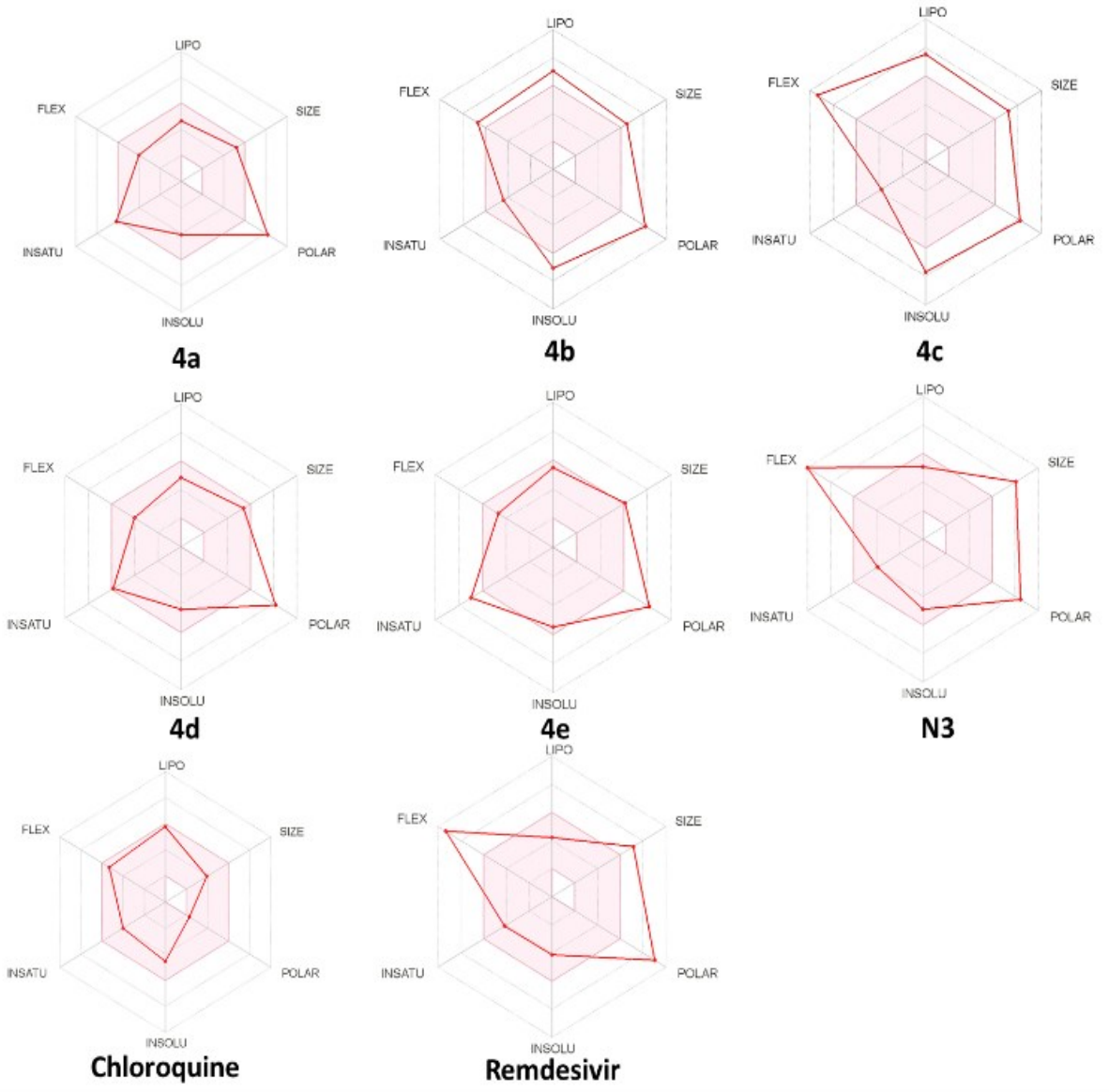


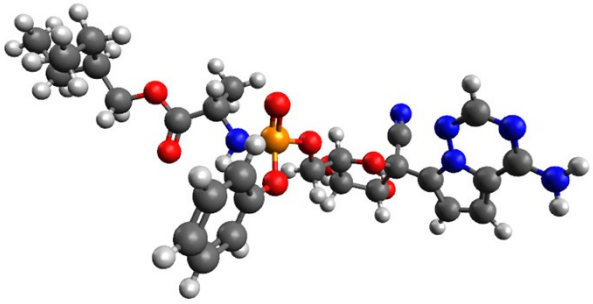

**Figure S6**. The analysis of pharmacokinetic parameters of the 5 synthesised compounds along with N3, Chloroquine, and Remdesivir using SwissADME server (http://www.swissadme.ch/). The colour space is the suitable physiochemical space for oral bioavailability. LIPO Lipophility: -0.7 < XLOGP3 < þ5.0. SIZE: 150g/mol: < MW<500g/mol. POLAR (Polarity): 20Å2 < TPSA < 130 Å2. INSOLU (insolubility): 0 < Log S (ESOL) < 6. INSATU (insaturation): 0.25 < Fraction Csp3<1. FLEX (Flexibity): 0 < Num. rotatable bonds < 9.

## S10: PART OF THE PREDICTED ANTIVIRAL ACTIVITY SPECTRA

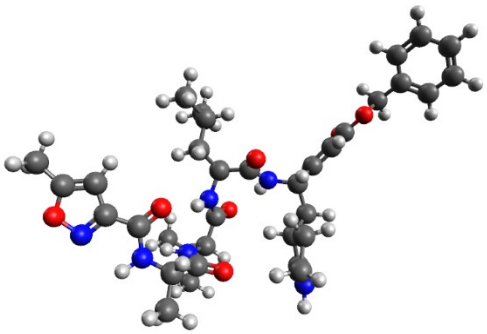
**Table S2**. Part of the predicted antiviral activity spectra for the synthesised compounds **4a-e** along with N3, Chloroquine, and Remdesivir

| **Ligands** | **4a** | | **4b** | | **4c** | | **4d** | | **4e** | | **N3** | | **Chloroquine** | | **Remdesivir** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Activity name | Pa | Pi | Pa | Pi | Pa | Pi | Pa | Pi | Pa | Pi | Pa | Pi | Pa | Pi | Pa | Pi |
| Antiviral (Adenovirus) | 0.341 | 0.059 | 0.342 | 0.059 | 0.352 | 0.053 | 0.314 | 0.078 | 0.289 | 0.099 | - | - | - | - | - | - |
| Antiviral (CMV) | 0.281 | 0.042 | 0.277 | 0.046 | 0.265 | 0.058 | 0.236 | 0.098 | 0.228 | 0.114 | - | - | - | - | - | - |
| Antiviral (HIV) | 0.229 | 0.020 | 0.249 | 0.016 | 0.262 | 0.013 | 0.205 | 0.028 | 0.554 | 0.004 | 0.121 | 0.113 | - | - | 0.272 | 0.012 |
| Antiviral (Herpes) | 0.303 | 0.090 | 0.311 | 0.084 | 0.335 | 0.068 | 0.251 | 0.129 | 0.221 | 0.155 | - | - | - | - | 0.466 | 0.015 |
| Antiviral (Herpesvirus 3) | 0.011 | 0.008 | - | - | - | - | - | - | - | - | - | - | - | - | | |
| Antiviral (Influenza A) | 0.243 | 0.111 | 0.217 | 0.172 | 0.232 | 0.133 | 0.235 | 0.126 | 0.225 | 0.150 | 0.234 | 0.129 | - | - | 0.216 | 0.174 |
| Antiviral (Influenza) | 0.317 | 0.079 | 0.242 | 0.141 | 0.230 | 0.155 | 0.412 | 0.043 | 0.259 | 0.122 | - | - | - | - | - | - |
| Antiviral (Parainfluenza) | 0.042 | 0.032 | 0.047 | 0.025 | 0.040 | 0.034 | 0.039 | 0.037 | - | - | - | - | - | - | - | - |
| Antiviral (Picornavirus) | 0.429 | 0.088 | 0.425 | 0.091 | 0.388 | 0.120 | 0.482 | 0.059 | 0.347 | 0.162 | - | - | - | - | - | - |
| Antiviral (Poxvirus) | 0.240 | 0.105 | 0.192 | 0.171 | - | - | 0.216 | 0.135 | 0.189 | 0.176 | - | - | - | - | - | - |
| Antiviral (Rhinovirus) | 0.453 | 0.047 | 0.385 | 0.108 | 0.426 | 0.066 | 0.427 | 0.065 | 0.417 | 0.074 | 0.337 | 0.181 | - | - | - | - |
| Antiviral (Hepatitis C) | - | - | 0.104 | 0.054 | 0.116 | 0.039 | - | - | - | - | 0.119 | 0.036 | - | - | 0.509 | 0.003 |
| Antiviral (Hepatitis) | - | - | 0.110 | 0.086 | 0.125 | 0.062 | - | - | - | - | 0.136 | 0.047 | - | - | 0.544 | 0.003 |
| Antiviral (Hepatitis B) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 0.344 | 0.024 |

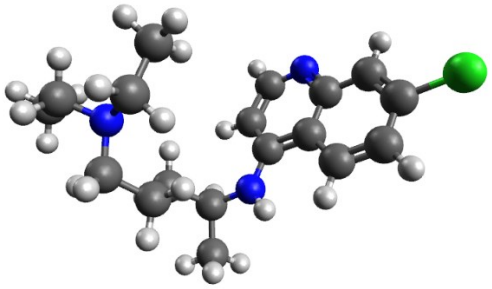
## S11: DFT GEOMETRY OPTIMISATION



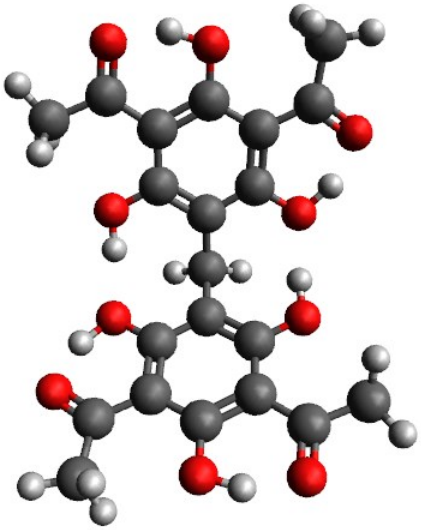
Chloroquine
CQ_TD_chelpg B3LYP/6-31+G(d,p)
E=-2321.7550354 H TD DFT
(-1456923.59220691 kcal/mol )
E=-2321.7551045 H DFT
(-1456923.6355678 kcal/mol)



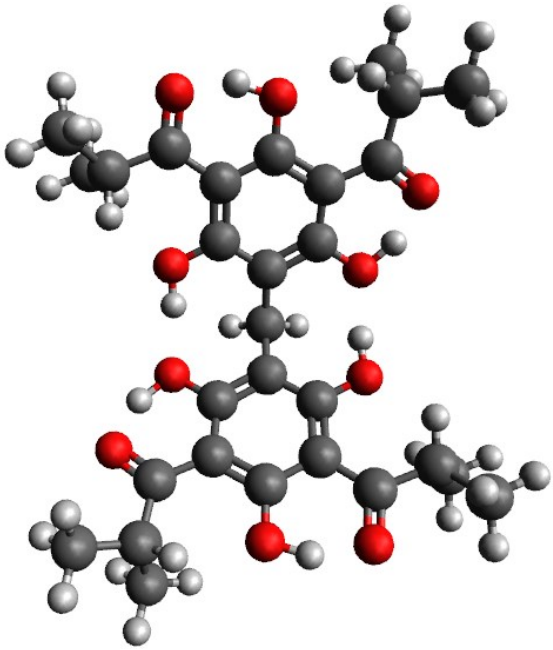
N3
N3_TD_chelpg B3LYP/6-31+G(d,p)
E=-2293.1680254 TD DFT
(-1438984.968767 kcal/mol)
E=-2293.1680945 DFT
(-1438985.01212796 kcal/mol)



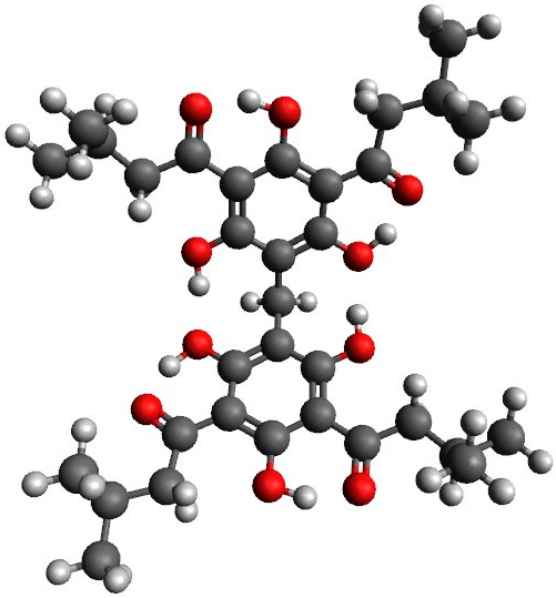
Remdesivir
RDS_TD_chelpg B3LYP/6-31+G(d,p)
E=-1326.1005639 TD DFT
(-832140.845062037 kcal/mol)
E= -1326.1006115 DFT
(-832140.874931494 kcal/mol)



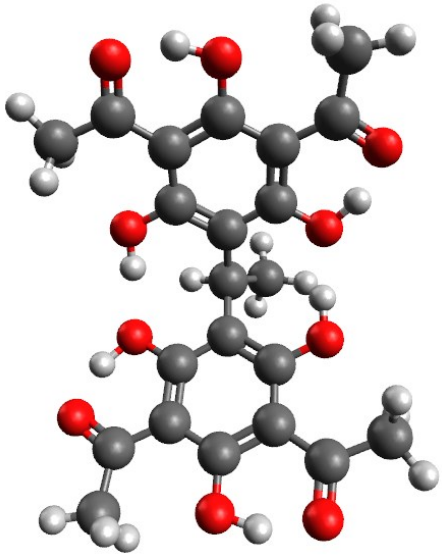
**4a**
4a_TD_chelpg B3LYP/6-31+G(d,p)
E= -1564.7022105 TD DFT
(-981865.670795457 kcal/mol)
E= -1564.7021775 DFT
(-981865.65008764 kcal/mol)



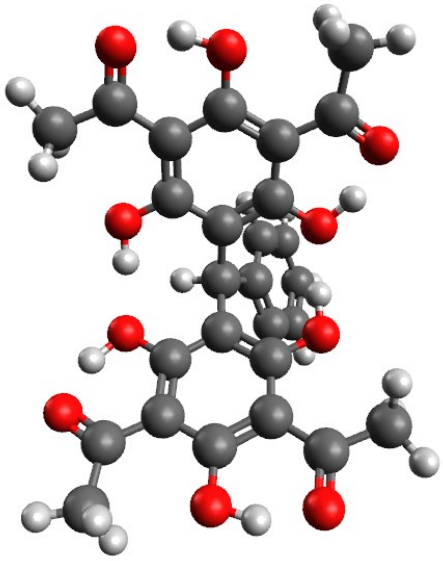
**4b**
4b_TD_chelpg B3LYP/6-31+G(d,p)
E= -1879.2276558 TD DFT
(-1179233.40969131 kcal/mol)
E= -1879.2276558 DFT
(-1179233.40969131 kcal/mol)



**4c**
4c_TD_chelpg B3LYP/6-31+G(d,p)
E= -2036.5032204 TD DFT
(-1277925.33758624 kcal/mol)
E= -2036.5032204 DFT
(-1277925.33758624 kcal/mol)



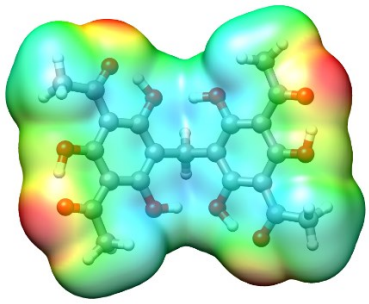
**4d**
4d_TD_chelpg B3LYP/6-31+G(d,p)
E= -1604.007756 TD DFT
(-1006530.2782456 kcal/mol)
E= -1604.0077461 DFT
(-1006530.27203325 kcal/mol)



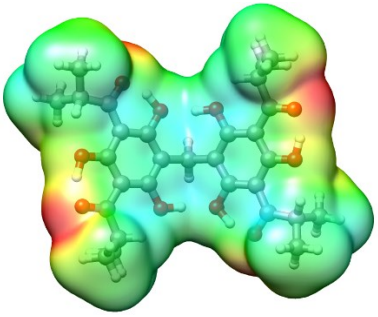
**4e**
4e_TD_chelpg B3LYP/6-31+G(d,p)
E= -1795.7512622 TD DFT
(-1126851.1706636 kcal/mol)
E= -1795.7512666 DFT
(-1126851.17342461 kcal/mol)

**Figure S7.** DFT geometry optimisation of compound **4a-d**

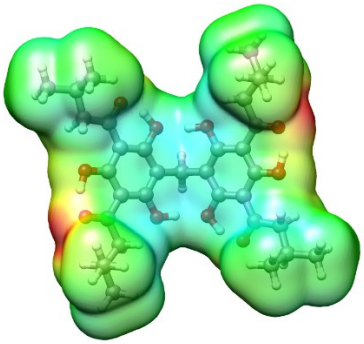
## S12: MOLECULAR ELECTROSTATIC POTENTIAL (MEP) MAPS



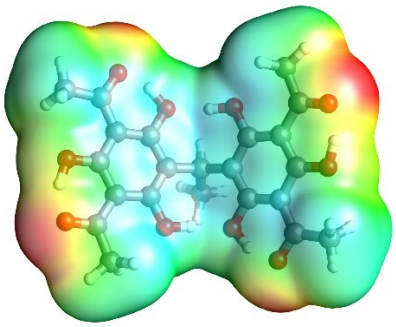
**4a**



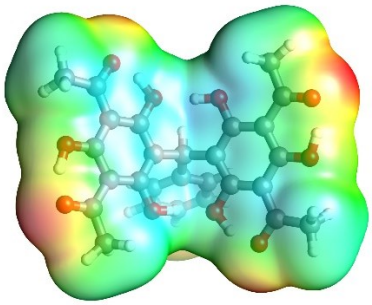
**4b**



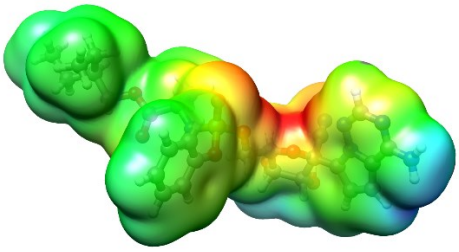
**4c**



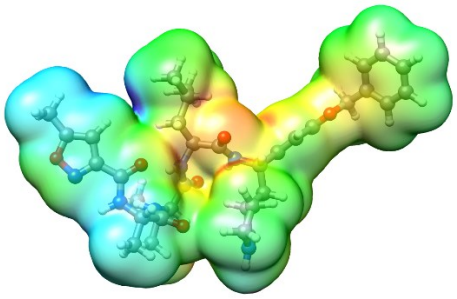
**4d**

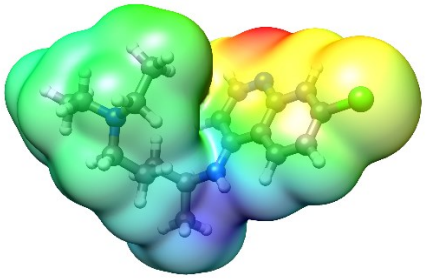


**4e**



**Chloroquine**





**Remdesivir**

**N3**

**Figure S8.** MEP maps of compound **4a-d**

## S13: CALCULATED QUANTUM CHEMICAL PARAMETERS

**Table S3**. Calculated quantum chemical parameters for the synthesised compounds **4a**-**e** along with N3, Chloroquine, and Remdesivir

| Chemical reactivity indices | **4a** | **4b** | **4c** | **4d** | **4e** | **N3** | **Chloroquine** | **Remdesivir** |
|---|---|---|---|---|---|---|---|---|
| $E_{HOMO}$ (eV) | -6.63 | -6.54 | -6.55 | -6.56 | -6.58 | -6.50 | -6.24 | -5.87 |
| $E_{LUMO}$ (eV) | -2.25 | -2.21 | -2.16 | -2.25 | -2.27 | -2.23 | -1.41 | -1.50 |
| Energy gap ($\Delta E$) = ($E_{LUMO}$ - $E_{HOMO}$) (eV) | 4.38 | 4.33 | 4.39 | 4.31 | 4.31 | 4.27 | 4.84 | 4.37 |
| Ionisation potential (I) = -$E_{HOMO}$ (eV) | 6.63 | 6.54 | 6.55 | 6.56 | 6.58 | 6.50 | 6.24 | 5.87 |
| Electron affinity (A) = -$E_{LUMO}$ (eV) | 2.25 | 2.21 | 2.16 | 2.25 | 2.27 | 2.23 | 1.41 | 1.50 |
| Electronegativity ($\chi$) = -($E_{HOMO}$-$E_{LUMO}$)/2 (eV) | 2.19 | 2.17 | 2.19 | 2.16 | 2.15 | 2.14 | 2.42 | 2.19 |
| Chemical potential ($\mu$) = 1/2 ($E_{LUMO}$ + $E_{HOMO}$) (eV) | -4.44 | -4.38 | -4.35 | -4.40 | -4.42 | -4.36 | -3.83 | -3.68 |
| Global hardness ($\eta$) = 1/2 ($E_{LUMO}$ - $E_{HOMO}$) (eV) | 2.19 | 2.17 | 2.19 | 2.16 | 2.15 | 2.14 | 2.42 | 2.19 |
| Softness chemical softness (S) = 1/2 $\eta$ $(eV)^{-1}$ | 1.10 | 1.08 | 1.10 | 1.08 | 1.08 | 1.07 | 1.21 | 1.09 |
| Electrophilicity index electrophilicity index ($\omega$) = $\mu^2$/2 $\eta$ ($\psi$) | 4.50 | 4.42 | 4.31 | 4.49 | 4.55 | 4.46 | 3.02 | 3.10 |

## S14: COORDINATES OF THE OPTIMISED STRUCTURES

Chloroquine DFT TD chelpg

```
P
O       1       B1
O       2       B2    1       A1
O       3       B3    2       A2    1       D1    0
O       1       B4    2       A3    4       D2    0
O       1       B5    5       A4    2       D3    0
O       1       B6    5       A5    6       D4    0
O       1       B7    7       A6    5       D5    0
O       8       B8    1       A7    7       D6    0
N       2       B9    1       A8    7       D7    0
N       10      B10   2       A9    1       D8    0
N       1       B11   7       A10   5       D9    0
N       3       B12   2       A11   1       D10   0
N       11      B13   10      A12   2       D11   0
N       14      B14   11      A13   10      D12   0
C       2       B15   1       A14   7       D13   0
C       3       B16   2       A15   1       D14   0
C       4       B17   3       A16   2       D15   0
C       2       B18   1       A17   7       D16   0
C       10      B19   2       A18   1       D17   0
C       5       B20   1       A19   7       D18   0
C       13      B21   3       A20   2       D19   0
C       20      B22   10      A21   2       D20   0
C       10      B23   2       A22   1       D21   0
C       24      B24   10      A23   2       D22   0
C       14      B25   11      A24   10      D23   0
C       12      B26   1       A25   7       D24   0
C       11      B27   10      A26   2       D25   0
C       8       B28   1       A27   7       D26   0
C       8       B29   1       A28   7       D27   0
C       29      B30   8       A29   1       D28   0
C       29      B31   8       A30   1       D29   0
C       9       B32   8       A31   1       D30   0
C       27      B33   12      A32   1       D31   0
C       6       B34   1       A33   7       D32   0
C       31      B35   29      A34   8       D33   0
C       32      B36   29      A35   8       D34   0
C       35      B37   6       A36   1       D35   0
C       35      B38   6       A37   1       D36   0
C       38      B39   35      A38   6       D37   0
C       39      B40   35      A39   6       D38   0
C       40      B41   38      A40   35      D39   0
H       17      B42   3       A41   2       D40   0
H       18      B43   4       A42   3       D41   0
H       19      B44   2       A43   1       D42   0
H       21      B45   5       A44   1       D43   0
H       21      B46   5       A45   1       D44   0
H       3       B47   2       A46   1       D45   0
```

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| H | 23 | B48 | 20 | A47 | 10 | D46 | 0 |
| H | 4 | B49 | 3 | A48 | 2 | D47 | 0 |
| H | 25 | B50 | 24 | A49 | 10 | D48 | 0 |
| H | 12 | B51 | 1 | A50 | 7 | D49 | 0 |
| H | 27 | B52 | 12 | A51 | 1 | D50 | 0 |
| H | 29 | B53 | 8 | A52 | 1 | D51 | 0 |
| H | 28 | B54 | 11 | A53 | 10 | D52 | 0 |
| H | 30 | B55 | 8 | A54 | 1 | D53 | 0 |
| H | 30 | B56 | 8 | A55 | 1 | D54 | 0 |
| H | 32 | B57 | 29 | A56 | 8 | D55 | 0 |
| H | 31 | B58 | 29 | A57 | 8 | D56 | 0 |
| H | 32 | B59 | 29 | A58 | 8 | D57 | 0 |
| H | 31 | B60 | 29 | A59 | 8 | D58 | 0 |
| H | 15 | B61 | 14 | A60 | 11 | D59 | 0 |
| H | 15 | B62 | 14 | A61 | 11 | D60 | 0 |
| H | 34 | B63 | 27 | A62 | 12 | D61 | 0 |
| H | 34 | B64 | 27 | A63 | 12 | D62 | 0 |
| H | 34 | B65 | 27 | A64 | 12 | D63 | 0 |
| H | 37 | B66 | 32 | A65 | 29 | D64 | 0 |
| H | 36 | B67 | 31 | A66 | 29 | D65 | 0 |
| H | 37 | B68 | 32 | A67 | 29 | D66 | 0 |
| H | 37 | B69 | 32 | A68 | 29 | D67 | 0 |
| H | 36 | B70 | 31 | A69 | 29 | D68 | 0 |
| H | 36 | B71 | 31 | A70 | 29 | D69 | 0 |
| H | 38 | B72 | 35 | A71 | 6 | D70 | 0 |
| H | 39 | B73 | 35 | A72 | 6 | D71 | 0 |
| H | 40 | B74 | 38 | A73 | 35 | D72 | 0 |
| H | 41 | B75 | 39 | A74 | 35 | D73 | 0 |
| H | 42 | B76 | 40 | A75 | 38 | D74 | 0 |

| | |
|---|---|
| B1 | 4.46157339 |
| B2 | 3.61097956 |
| B3 | 2.73586475 |
| B4 | 1.60906964 |
| B5 | 1.63495435 |
| B6 | 1.48112331 |
| B7 | 4.99001303 |
| B8 | 2.26148093 |
| B9 | 3.02755247 |
| B10 | 1.36190702 |
| B11 | 1.66603993 |
| B12 | 3.44101461 |
| B13 | 2.40697271 |
| B14 | 2.30624533 |
| B15 | 1.42674806 |
| B16 | 1.40193278 |
| B17 | 1.41891439 |
| B18 | 1.43853854 |
| B19 | 1.36901011 |
| B20 | 1.43422509 |
| B21 | 1.16160140 |
| B22 | 1.39738935 |
| B23 | 1.39422091 |
| B24 | 1.39624714 |
| B25 | 1.32568118 |

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| B26 | 1.46545151 |
| B27 | 1.31050921 |
| B28 | 2.41965901 |
| B29 | 1.45477877 |
| B30 | 1.54675022 |
| B31 | 1.54504098 |
| B32 | 1.21783630 |
| B33 | 1.54013769 |
| B34 | 1.39755477 |
| B35 | 1.53533564 |
| B36 | 1.53358628 |
| B37 | 1.39648113 |
| B38 | 1.39516713 |
| B39 | 1.39772155 |
| B40 | 1.39667350 |
| B41 | 1.39767079 |
| B42 | 1.09134448 |
| B43 | 1.09837694 |
| B44 | 1.09816061 |
| B45 | 1.09566614 |
| B46 | 1.09728520 |
| B47 | 0.97089589 |
| B48 | 1.08011855 |
| B49 | 0.96717367 |
| B50 | 1.08072375 |
| B51 | 1.01624882 |
| B52 | 1.09649108 |
| B53 | 1.10022816 |
| B54 | 1.08512619 |
| B55 | 1.09451677 |
| B56 | 1.09372322 |
| B57 | 1.09828958 |
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| B59 | 1.09809866 |
| B60 | 1.09564383 |
| B61 | 1.00688174 |
| B62 | 1.00953104 |
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| B64 | 1.09317757 |
| B65 | 1.09472690 |
| B66 | 1.09454927 |
| B67 | 1.09554713 |
| B68 | 1.09497142 |
| B69 | 1.09643879 |
| B70 | 1.09551956 |
| B71 | 1.09501955 |
| B72 | 1.08414797 |
| B73 | 1.08525118 |
| B74 | 1.08610217 |
| B75 | 1.08601914 |
| B76 | 1.08571822 |
| A1 | 137.23086642 |
| A2 | 64.27641946 |
| A3 | 10.72155051 |
| A4 | 99.07527313 |

| | |
|---|---|
| A5 | 111.27422239 |
| A6 | 86.65952948 |
| A7 | 57.99019077 |
| A8 | 136.07453735 |
| A9 | 80.40796965 |
| A10 | 114.37559394 |
| A11 | 58.64986320 |
| A12 | 87.13286290 |
| A13 | 123.01987182 |
| A14 | 166.66344859 |
| A15 | 19.46938664 |
| A16 | 65.01302021 |
| A17 | 59.63276026 |
| A18 | 50.53645318 |
| A19 | 122.47069913 |
| A20 | 50.09954737 |
| A21 | 107.16729078 |
| A22 | 146.93665276 |
| A23 | 107.58466657 |
| A24 | 91.81997787 |
| A25 | 121.66961911 |
| A26 | 113.27877173 |
| A27 | 164.68555627 |
| A28 | 146.13645240 |
| A29 | 92.57311214 |
| A30 | 143.15191666 |
| A31 | 29.25899489 |
| A32 | 112.52702495 |
| A33 | 124.08663988 |
| A34 | 116.07964017 |
| A35 | 114.32932552 |
| A36 | 121.78542339 |
| A37 | 116.77907517 |
| A38 | 118.65582828 |
| A39 | 119.25809358 |
| A40 | 120.80632844 |
| A41 | 106.38410012 |
| A42 | 110.15810827 |
| A43 | 109.86569236 |
| A44 | 109.38517859 |
| A45 | 109.73346315 |
| A46 | 92.49206439 |
| A47 | 125.39595695 |
| A48 | 74.29605317 |
| A49 | 126.67014736 |
| A50 | 119.32940787 |
| A51 | 109.51977480 |
| A52 | 86.89655044 |
| A53 | 114.79588190 |
| A54 | 108.10594567 |
| A55 | 108.39298167 |
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| A57 | 108.31677190 |
| A58 | 109.84530697 |
| A59 | 108.01349618 |

| | |
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| A60 | 149.95097260 |
| A61 | 87.04668740 |
| A62 | 109.33766871 |
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| A64 | 110.72598105 |
| A65 | 112.01398033 |
| A66 | 112.16181757 |
| A67 | 110.65770972 |
| A68 | 111.15361761 |
| A69 | 112.27315985 |
| A70 | 110.16033707 |
| A71 | 119.87116894 |
| A72 | 119.42487214 |
| A73 | 119.11501792 |
| A74 | 119.47624848 |
| A75 | 120.19782032 |
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| D2 | -47.58642130 |
| D3 | -24.74388333 |
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| D15 | -34.15469897 |
| D16 | -130.53399658 |
| D17 | 155.25188605 |
| D18 | -179.22322779 |
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| D20 | -149.85508474 |
| D21 | 92.94940172 |
| D22 | 47.14303001 |
| D23 | 0.50419110 |
| D24 | 16.95321183 |
| D25 | 155.73061025 |
| D26 | -37.04234446 |
| D27 | -127.15088661 |
| D28 | 15.99897063 |
| D29 | -122.16778641 |
| D30 | -13.63703060 |
| D31 | 89.48028651 |
| D32 | 52.93361161 |
| D33 | -94.56400469 |
| D34 | -167.74695262 |
| D35 | -47.18111925 |
| D36 | 135.89858466 |
| D37 | -177.39942990 |
| D38 | 177.19025494 |
| D39 | 0.53260040 |

| | |
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| D40 | -144.22071154 |
| D41 | -111.81108137 |
| D42 | 94.00137217 |
| D43 | -71.09722446 |
| D44 | 49.30350396 |
| D45 | 82.47937102 |
| D46 | -177.74016710 |
| D47 | -154.25507898 |
| D48 | 178.95915913 |
| D49 | -134.49416537 |
| D50 | -31.26102885 |
| D51 | 122.72863319 |
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| D53 | -85.28797056 |
| D54 | 31.38352270 |
| D55 | -46.36375240 |
| D56 | 142.38535349 |
| D57 | 68.86040855 |
| D58 | 28.26879863 |
| D59 | -23.99427785 |
| D60 | -173.50912852 |
| D61 | -59.66936020 |
| D62 | -179.09046869 |
| D63 | 59.75559725 |
| D64 | -65.12234796 |
| D65 | 59.96997277 |
| D66 | 175.01303203 |
| D67 | 55.41501773 |
| D68 | -61.40722272 |
| D69 | 179.09645530 |
| D70 | 2.82050537 |
| D71 | -2.42740255 |
| D72 | -179.89154082 |
| D73 | -179.96997766 |
| D74 | 179.71041620 |

N3 TD chelpg

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| O | | | | | | | |
| O | 1 | B1 | | | | | |
| O | 2 | B2 | 1 | A1 | | | |
| O | 1 | B3 | 3 | A2 | 2 | D1 | 0 |
| O | 1 | B4 | 3 | A3 | 2 | D2 | 0 |
| O | 4 | B5 | 1 | A4 | 5 | D3 | 0 |
| O | 5 | B6 | 1 | A5 | 3 | D4 | 0 |
| O | 7 | B7 | 5 | A6 | 1 | D5 | 0 |
| N | 1 | B8 | 5 | A7 | 7 | D6 | 0 |
| N | 2 | B9 | 1 | A8 | 9 | D7 | 0 |
| N | 3 | B10 | 2 | A9 | 1 | D8 | 0 |
| N | 5 | B11 | 1 | A10 | 9 | D9 | 0 |
| N | 7 | B12 | 5 | A11 | 1 | D10 | 0 |
| N | 8 | B13 | 7 | A12 | 5 | D11 | 0 |
| C | 9 | B14 | 1 | A13 | 5 | D12 | 0 |
| C | 15 | B15 | 9 | A14 | 1 | D13 | 0 |
| C | 15 | B16 | 9 | A15 | 1 | D14 | 0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| C | 10 | B17 | 2 | A16 | 1 | D15 | 0 |
| C | 9 | B18 | 1 | A17 | 15 | D16 | 0 |
| C | 1 | B19 | 9 | A18 | 19 | D17 | 0 |
| C | 11 | B20 | 3 | A19 | 2 | D18 | 0 |
| C | 21 | B21 | 11 | A20 | 3 | D19 | 0 |
| C | 2 | B22 | 1 | A21 | 20 | D20 | 0 |
| C | 22 | B23 | 21 | A22 | 11 | D21 | 0 |
| C | 18 | B24 | 10 | A23 | 2 | D22 | 0 |
| C | 12 | B25 | 5 | A24 | 1 | D23 | 0 |
| C | 26 | B26 | 12 | A25 | 5 | D24 | 0 |
| C | 3 | B27 | 2 | A26 | 1 | D25 | 0 |
| C | 24 | B28 | 22 | A27 | 21 | D26 | 0 |
| C | 24 | B29 | 22 | A28 | 21 | D27 | 0 |
| C | 25 | B30 | 18 | A29 | 10 | D28 | 0 |
| C | 27 | B31 | 26 | A30 | 12 | D29 | 0 |
| C | 27 | B32 | 26 | A31 | 12 | D30 | 0 |
| C | 5 | B33 | 1 | A32 | 20 | D31 | 0 |
| C | 13 | B34 | 7 | A33 | 5 | D32 | 0 |
| C | 6 | B35 | 4 | A34 | 1 | D33 | 0 |
| C | 35 | B36 | 13 | A35 | 7 | D34 | 0 |
| C | 7 | B37 | 5 | A36 | 1 | D35 | 0 |
| C | 4 | B38 | 1 | A37 | 20 | D36 | 0 |
| C | 14 | B39 | 8 | A38 | 7 | D37 | 0 |
| C | 39 | B40 | 4 | A39 | 1 | D38 | 0 |
| C | 40 | B41 | 14 | A40 | 8 | D39 | 0 |
| C | 41 | B42 | 39 | A41 | 4 | D40 | 0 |
| C | 41 | B43 | 39 | A42 | 4 | D41 | 0 |
| C | 8 | B44 | 7 | A43 | 5 | D42 | 0 |
| C | 43 | B45 | 41 | A44 | 39 | D43 | 0 |
| C | 44 | B46 | 41 | A45 | 39 | D44 | 0 |
| C | 47 | B47 | 44 | A46 | 41 | D45 | 0 |
| C | 45 | B48 | 8 | A47 | 7 | D46 | 0 |
| H | 15 | B49 | 9 | A48 | 1 | D47 | 0 |
| H | 16 | B50 | 15 | A49 | 9 | D48 | 0 |
| H | 16 | B51 | 15 | A50 | 9 | D49 | 0 |
| H | 17 | B52 | 15 | A51 | 9 | D50 | 0 |
| H | 17 | B53 | 15 | A52 | 9 | D51 | 0 |
| H | 18 | B54 | 10 | A53 | 2 | D52 | 0 |
| H | 19 | B55 | 9 | A54 | 1 | D53 | 0 |
| H | 19 | B56 | 9 | A55 | 1 | D54 | 0 |
| H | 9 | B57 | 1 | A56 | 20 | D55 | 0 |
| H | 21 | B58 | 11 | A57 | 3 | D56 | 0 |
| H | 22 | B59 | 21 | A58 | 11 | D57 | 0 |
| H | 22 | B60 | 21 | A59 | 11 | D58 | 0 |
| H | 10 | B61 | 2 | A60 | 1 | D59 | 0 |
| H | 24 | B62 | 22 | A61 | 21 | D60 | 0 |
| H | 25 | B63 | 18 | A62 | 10 | D61 | 0 |
| H | 26 | B64 | 12 | A63 | 5 | D62 | 0 |
| H | 11 | B65 | 3 | A64 | 2 | D63 | 0 |
| H | 27 | B66 | 26 | A65 | 12 | D64 | 0 |
| H | 29 | B67 | 24 | A66 | 22 | D65 | 0 |
| H | 29 | B68 | 24 | A67 | 22 | D66 | 0 |
| H | 29 | B69 | 24 | A68 | 22 | D67 | 0 |
| H | 30 | B70 | 24 | A69 | 22 | D68 | 0 |
| H | 30 | B71 | 24 | A70 | 22 | D69 | 0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| H | 30 | B72 | 24 | A71 | 22 | D70 | 0 |
| H | 12 | B73 | 5 | A72 | 1 | D71 | 0 |
| H | 31 | B74 | 25 | A73 | 18 | D72 | 0 |
| H | 32 | B75 | 27 | A74 | 26 | D73 | 0 |
| H | 32 | B76 | 27 | A75 | 26 | D74 | 0 |
| H | 32 | B77 | 27 | A76 | 26 | D75 | 0 |
| H | 33 | B78 | 27 | A77 | 26 | D76 | 0 |
| H | 33 | B79 | 27 | A78 | 26 | D77 | 0 |
| H | 33 | B80 | 27 | A79 | 26 | D78 | 0 |
| H | 35 | B81 | 13 | A80 | 7 | D79 | 0 |
| H | 37 | B82 | 35 | A81 | 13 | D80 | 0 |
| H | 37 | B83 | 35 | A82 | 13 | D81 | 0 |
| H | 37 | B84 | 35 | A83 | 13 | D82 | 0 |
| H | 13 | B85 | 7 | A84 | 5 | D83 | 0 |
| H | 39 | B86 | 4 | A85 | 1 | D84 | 0 |
| H | 39 | B87 | 4 | A86 | 1 | D85 | 0 |
| H | 42 | B88 | 40 | A87 | 14 | D86 | 0 |
| H | 43 | B89 | 41 | A88 | 39 | D87 | 0 |
| H | 44 | B90 | 41 | A89 | 39 | D88 | 0 |
| H | 46 | B91 | 43 | A90 | 41 | D89 | 0 |
| H | 47 | B92 | 44 | A91 | 41 | D90 | 0 |
| H | 48 | B93 | 47 | A92 | 44 | D91 | 0 |
| H | 49 | B94 | 45 | A93 | 8 | D92 | 0 |
| H | 49 | B95 | 45 | A94 | 8 | D93 | 0 |
| H | 49 | B96 | 45 | A95 | 8 | D94 | 0 |

| | |
|---|---|
| B1 | 6.33770998 |
| B2 | 4.54323430 |
| B3 | 8.50541517 |
| B4 | 4.37641337 |
| B5 | 2.26685390 |
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Remdesivir TD chelpg

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| N | 2 | B2 | 1 | A1 | | | | | |
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| C | 5 | B5 | 3 | A4 | 2 | D3 | 0 | | |
| C | 3 | B6 | 2 | A5 | 1 | D4 | 0 | | |
| C | 2 | B7 | 1 | A6 | 4 | D5 | 0 | | |
| C | 7 | B8 | 3 | A7 | 2 | D6 | 0 | | |
| C | 2 | B9 | 1 | A8 | 4 | D7 | 0 | | |
| C | 2 | B10 | 1 | A9 | 4 | D8 | 0 | | |
| C | 3 | B11 | 2 | A10 | 1 | D9 | 0 | | |
| C | 12 | B12 | 3 | A11 | 2 | D10 | 0 | | |
| C | 10 | B13 | 2 | A12 | 1 | D11 | 0 | | |
| C | 11 | B14 | 2 | A13 | 1 | D12 | 0 | | |
| C | 12 | B15 | 3 | A14 | 2 | D13 | 0 | | |

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| C | 13 | B17 | 12 | A16 | 3 | D15 | 0 |
| C | 4 | B18 | 3 | A17 | 2 | D16 | 0 |
| C | 17 | B19 | 4 | A18 | 3 | D17 | 0 |
| C | 18 | B20 | 13 | A19 | 12 | D18 | 0 |
| C | 20 | B21 | 17 | A20 | 4 | D19 | 0 |
| H | 5 | B22 | 3 | A21 | 2 | D20 | 0 |
| H | 5 | B23 | 3 | A22 | 2 | D21 | 0 |
| H | 6 | B24 | 5 | A23 | 3 | D22 | 0 |
| H | 6 | B25 | 5 | A24 | 3 | D23 | 0 |
| H | 7 | B26 | 3 | A25 | 2 | D24 | 0 |
| H | 8 | B27 | 2 | A26 | 1 | D25 | 0 |
| H | 8 | B28 | 2 | A27 | 1 | D26 | 0 |
| H | 3 | B29 | 2 | A28 | 1 | D27 | 0 |
| H | 9 | B30 | 7 | A29 | 3 | D28 | 0 |
| H | 9 | B31 | 7 | A30 | 3 | D29 | 0 |
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| H | 14 | B37 | 10 | A36 | 2 | D35 | 0 |
| H | 14 | B38 | 10 | A37 | 2 | D36 | 0 |
| H | 14 | B39 | 10 | A38 | 2 | D37 | 0 |
| H | 15 | B40 | 11 | A39 | 2 | D38 | 0 |
| H | 15 | B41 | 11 | A40 | 2 | D39 | 0 |
| H | 15 | B42 | 11 | A41 | 2 | D40 | 0 |
| H | 16 | B43 | 12 | A42 | 3 | D41 | 0 |
| H | 18 | B44 | 13 | A43 | 12 | D42 | 0 |
| H | 19 | B45 | 4 | A44 | 3 | D43 | 0 |
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4a TD chelpg

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O             4    1.32534293    3  118.56003550    2 -179.34647173    0
H             7    1.02641269    4  105.67247045    3 -179.48983715    0
O             6    1.34137374    1  120.87362465    2 -178.98727545    0
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O            12    1.25544934    5  119.45012658    4    0.68653316    0
C            12    1.50802513    5  124.03668882    4 -179.36441670    0
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C            28    1.46320422   26  118.55756362   25  179.82029273    0
C            29    1.46973681   27  124.09390597   25  179.30072471    0
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O            26    1.34480257   25  117.39028866   24   -4.48970060    0
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| H | 44 | 1.04227879 | 26 | 105.19751820 | 25 | -179.83634326 | 0 |
| H | 43 | 0.98617897 | 27 | 113.70827721 | 25 | 15.18994434 | 0 |
| H | 9 | 0.98608649 | 6 | 113.69434696 | 1 | 15.14746166 | 0 |

4b TD chelpg

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
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| C | 1 | B1 | | | | | | | |
| C | 2 | B2 | 1 | A1 | | | | | |
| C | 3 | B3 | 2 | A2 | 1 | D1 | 0 | | |
| C | 4 | B4 | 3 | A3 | 2 | D2 | 0 | | |
| C | 1 | B5 | 2 | A4 | 3 | D3 | 0 | | |
| O | 4 | B6 | 3 | A5 | 2 | D4 | 0 | | |
| H | 7 | B7 | 4 | A6 | 3 | D5 | 0 | | |
| O | 6 | B8 | 1 | A7 | 2 | D6 | 0 | | |
| O | 2 | B9 | 1 | A8 | 6 | D7 | 0 | | |
| C | 5 | B10 | 4 | A9 | 3 | D8 | 0 | | |
| C | 3 | B11 | 2 | A10 | 1 | D9 | 0 | | |
| O | 12 | B12 | 3 | A11 | 2 | D10 | 0 | | |
| O | 11 | B13 | 5 | A12 | 4 | D11 | 0 | | |
| C | 11 | B14 | 5 | A13 | 4 | D12 | 0 | | |
| C | 12 | B15 | 3 | A14 | 2 | D13 | 0 | | |
| H | 16 | B16 | 12 | A15 | 3 | D14 | 0 | | |
| C | 1 | B17 | 2 | A16 | 10 | D15 | 0 | | |
| C | 18 | B18 | 1 | A17 | 2 | D16 | 0 | | |
| C | 19 | B19 | 18 | A18 | 1 | D17 | 0 | | |
| C | 19 | B20 | 18 | A19 | 1 | D18 | 0 | | |
| C | 20 | B21 | 19 | A20 | 18 | D19 | 0 | | |
| C | 21 | B22 | 19 | A21 | 18 | D20 | 0 | | |
| C | 22 | B23 | 20 | A22 | 19 | D21 | 0 | | |
| C | 22 | B24 | 20 | A23 | 19 | D22 | 0 | | |
| C | 23 | B25 | 21 | A24 | 19 | D23 | 0 | | |
| C | 26 | B26 | 23 | A25 | 21 | D24 | 0 | | |
| C | 25 | B27 | 22 | A26 | 20 | D25 | 0 | | |
| O | 25 | B28 | 22 | A27 | 20 | D26 | 0 | | |
| O | 26 | B29 | 23 | A28 | 21 | D27 | 0 | | |
| O | 21 | B30 | 19 | A29 | 18 | D28 | 0 | | |
| O | 20 | B31 | 19 | A30 | 18 | D29 | 0 | | |
| O | 24 | B32 | 22 | A31 | 20 | D30 | 0 | | |
| H | 18 | B33 | 1 | A32 | 2 | D31 | 0 | | |
| H | 18 | B34 | 1 | A33 | 2 | D32 | 0 | | |
| H | 33 | B35 | 24 | A34 | 22 | D33 | 0 | | |
| H | 32 | B36 | 20 | A35 | 19 | D34 | 0 | | |
| H | 9 | B37 | 6 | A36 | 1 | D35 | 0 | | |
| H | 31 | B38 | 21 | A37 | 19 | D36 | 0 | | |
| H | 10 | B39 | 2 | A38 | 1 | D37 | 0 | | |
| C | 16 | B40 | 12 | A39 | 3 | D38 | 0 | | |
| H | 41 | B41 | 16 | A40 | 12 | D39 | 0 | | |
| H | 41 | B42 | 16 | A41 | 12 | D40 | 0 | | |
| H | 41 | B43 | 16 | A42 | 12 | D41 | 0 | | |
| C | 16 | B44 | 12 | A43 | 3 | D42 | 0 | | |
| H | 45 | B45 | 16 | A44 | 12 | D43 | 0 | | |
| H | 45 | B46 | 16 | A45 | 12 | D44 | 0 | | |

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| H | 15 | B48 | 11 | A47 | 5 | D46 | 0 |
| C | 15 | B49 | 11 | A48 | 5 | D47 | 0 |
| H | 50 | B50 | 15 | A49 | 11 | D48 | 0 |
| H | 50 | B51 | 15 | A50 | 11 | D49 | 0 |
| H | 50 | B52 | 15 | A51 | 11 | D50 | 0 |
| C | 15 | B53 | 11 | A52 | 5 | D51 | 0 |
| H | 54 | B54 | 15 | A53 | 11 | D52 | 0 |
| H | 54 | B55 | 15 | A54 | 11 | D53 | 0 |
| H | 54 | B56 | 15 | A55 | 11 | D54 | 0 |
| H | 28 | B57 | 25 | A56 | 22 | D55 | 0 |
| C | 28 | B58 | 25 | A57 | 22 | D56 | 0 |
| H | 59 | B59 | 28 | A58 | 25 | D57 | 0 |
| H | 59 | B60 | 28 | A59 | 25 | D58 | 0 |
| H | 59 | B61 | 28 | A60 | 25 | D59 | 0 |
| C | 28 | B62 | 25 | A61 | 22 | D60 | 0 |
| H | 63 | B63 | 28 | A62 | 25 | D61 | 0 |
| H | 63 | B64 | 28 | A63 | 25 | D62 | 0 |
| H | 63 | B65 | 28 | A64 | 25 | D63 | 0 |
| H | 27 | B66 | 26 | A65 | 23 | D64 | 0 |
| C | 27 | B67 | 26 | A66 | 23 | D65 | 0 |
| H | 68 | B68 | 27 | A67 | 26 | D66 | 0 |
| H | 68 | B69 | 27 | A68 | 26 | D67 | 0 |
| H | 68 | B70 | 27 | A69 | 26 | D68 | 0 |
| C | 27 | B71 | 26 | A70 | 23 | D69 | 0 |
| H | 72 | B72 | 27 | A71 | 26 | D70 | 0 |
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| H | 72 | B74 | 27 | A73 | 26 | D72 | 0 |

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| B11 | 1.46841195 |
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| B14 | 1.52556648 |
| B15 | 1.52140062 |
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| B18 | 1.52427119 |
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| B73 | 1.09472436 |
| B74 | 1.09266012 |
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| A15 | 108.47510356 |
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| D47 | 151.63267124 |
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| D53 | 179.53248294 |
| D54 | -61.52992841 |
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4c TD chelpg

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| C | | | | | | | | |
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| C | 2 | 1.42943724 | 1 | 123.52904091 | | | | |
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| O | 4 | 1.32586431 | 3 | 118.41611506 | 2 | -177.20712410 | 0 | |
| H | 7 | 1.02567054 | 4 | 105.65643959 | 3 | -179.94574031 | 0 | |
| O | 6 | 1.34168243 | 1 | 120.62325717 | 2 | -179.55318083 | 0 | |
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| O | 12 | 1.25831803 | 3 | 118.83003294 | 2 | 2.32622126 | 0 | |
| O | 11 | 1.25496795 | 5 | 119.04578499 | 4 | 3.77090756 | 0 | |
| C | 11 | 1.51729770 | 5 | 123.52609541 | 4 | -176.60417795 | 0 | |
| H | 15 | 1.09790543 | 11 | 106.93633803 | 5 | -63.63367501 | 0 | |
| H | 15 | 1.09548196 | 11 | 109.03927534 | 5 | 48.41901184 | 0 | |
| C | 12 | 1.51351962 | 3 | 123.17470767 | 2 | -178.02182150 | 0 | |
| H | 18 | 1.09856030 | 12 | 106.65810205 | 3 | -63.86775861 | 0 | |
| H | 18 | 1.09590600 | 12 | 108.90953554 | 3 | 47.60790965 | 0 | |
| C | 1 | 1.52385997 | 2 | 119.22389414 | 10 | -4.64152664 | 0 | |
| C | 21 | 1.52386027 | 1 | 117.67450995 | 2 | 95.75818282 | 0 | |
| C | 22 | 1.40441485 | 21 | 122.65985461 | 1 | -88.18948806 | 0 | |
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| C | 23 | 1.43033916 | 22 | 122.20757016 | 21 | -173.83053889 | 0 |
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| C | 26 | 1.42326378 | 24 | 116.72021428 | 22 | -1.21998967 | 0 |
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| C | 28 | 1.51729896 | 25 | 123.52594020 | 23 | 3.12224412 | 0 |
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| O | 23 | 1.34168344 | 22 | 120.62328577 | 21 | 4.34919415 | 0 |
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| H | 39 | 0.98626512 | 23 | 113.68577275 | 22 | 15.67270228 | 0 |
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| C | 18 | 1.53859300 | 12 | 115.26483369 | 3 | 172.81421503 | 0 |
| H | 48 | 1.09651385 | 18 | 108.16615610 | 12 | 46.79680257 | 0 |
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| C | 48 | 1.53713413 | 18 | 109.61248120 | 12 | 164.75537850 | 0 |
| H | 54 | 1.09607455 | 48 | 111.60039067 | 18 | -59.48345377 | 0 |
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| H | 60 | 1.09553583 | 58 | 110.80816251 | 15 | -179.48359024 | 0 |
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| H | 84 | 1.09341293 | 68 | 111.57765218 | 30 | 59.46680809 | 0 |
| H | 84 | 1.09571797 | 68 | 110.70832217 | 30 | 179.46532858 | 0 |

4d TD chelpg

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| C | | | | | | | | | | | | |
| C | 1 | B1 | | | | | | | | | | |
| C | 2 | B2 | 1 | A1 | | | | | | | | |
| C | 3 | B3 | 2 | A2 | 1 | D1 | 0 | | | | | |
| C | 4 | B4 | 3 | A3 | 2 | D2 | 0 | | | | | |
| C | 1 | B5 | 2 | A4 | 3 | D3 | 0 | | | | | |
| O | 4 | B6 | 3 | A5 | 2 | D4 | 0 | | | | | |
| H | 7 | B7 | 4 | A6 | 3 | D5 | 0 | | | | | |
| O | 6 | B8 | 1 | A7 | 2 | D6 | 0 | | | | | |
| O | 2 | B9 | 1 | A8 | 6 | D7 | 0 | | | | | |
| H | 10 | B10 | 2 | A9 | 1 | D8 | 0 | | | | | |
| C | 5 | B11 | 4 | A10 | 3 | D9 | 0 | | | | | |
| C | 3 | B12 | 2 | A11 | 1 | D10 | 0 | | | | | |
| O | 13 | B13 | 3 | A12 | 2 | D11 | 0 | | | | | |
| O | 12 | B14 | 5 | A13 | 4 | D12 | 0 | | | | | |
| C | 12 | B15 | 5 | A14 | 4 | D13 | 0 | | | | | |
| H | 16 | B16 | 12 | A15 | 5 | D14 | 0 | | | | | |
| H | 16 | B17 | 12 | A16 | 5 | D15 | 0 | | | | | |
| H | 16 | B18 | 12 | A17 | 5 | D16 | 0 | | | | | |
| C | 13 | B19 | 3 | A18 | 2 | D17 | 0 | | | | | |
| H | 20 | B20 | 13 | A19 | 3 | D18 | 0 | | | | | |
| H | 20 | B21 | 13 | A20 | 3 | D19 | 0 | | | | | |
| H | 20 | B22 | 13 | A21 | 3 | D20 | 0 | | | | | |
| C | 1 | B23 | 2 | A22 | 10 | D21 | 0 | | | | | |
| C | 24 | B24 | 1 | A23 | 2 | D22 | 0 | | | | | |
| C | 25 | B25 | 24 | A24 | 1 | D23 | 0 | | | | | |
| C | 25 | B26 | 24 | A25 | 1 | D24 | 0 | | | | | |
| C | 26 | B27 | 25 | A26 | 24 | D25 | 0 | | | | | |
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| H | 37 | B37 | 31 | A36 | 28 | D35 | 0 | | | | | |
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| O | 27 | B42 | 25 | A41 | 24 | D40 | 0 | | | | | |
| O | 26 | B43 | 25 | A42 | 24 | D41 | 0 | | | | | |

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|---|---|---|---|---|---|---|---|---|---|
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| C | 1 | B1 | | | | | | | |
| C | 2 | B2 | 1 | A1 | | | | | |
| C | 3 | B3 | 2 | A2 | 1 | D1 | 0 | | |
| C | 4 | B4 | 3 | A3 | 2 | D2 | 0 | | |
| C | 1 | B5 | 2 | A4 | 3 | D3 | 0 | | |
| O | 4 | B6 | 3 | A5 | 2 | D4 | 0 | | |
| H | 7 | B7 | 4 | A6 | 3 | D5 | 0 | | |
| O | 6 | B8 | 1 | A7 | 2 | D6 | 0 | | |
| O | 2 | B9 | 1 | A8 | 6 | D7 | 0 | | |
| H | 10 | B10 | 2 | A9 | 1 | D8 | 0 | | |
| C | 5 | B11 | 4 | A10 | 3 | D9 | 0 | | |
| C | 3 | B12 | 2 | A11 | 1 | D10 | 0 | | |
| O | 13 | B13 | 3 | A12 | 2 | D11 | 0 | | |
| O | 12 | B14 | 5 | A13 | 4 | D12 | 0 | | |
| C | 12 | B15 | 5 | A14 | 4 | D13 | 0 | | |
| H | 16 | B16 | 12 | A15 | 5 | D14 | 0 | | |
| H | 16 | B17 | 12 | A16 | 5 | D15 | 0 | | |
| H | 16 | B18 | 12 | A17 | 5 | D16 | 0 | | |
| C | 13 | B19 | 3 | A18 | 2 | D17 | 0 | | |
| H | 20 | B20 | 13 | A19 | 3 | D18 | 0 | | |
| H | 20 | B21 | 13 | A20 | 3 | D19 | 0 | | |
| H | 20 | B22 | 13 | A21 | 3 | D20 | 0 | | |
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| C | 25 | B26 | 24 | A25 | 1 | D24 | 0 | | |
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| H | 33 | B35 | 32 | A34 | 29 | D33 | 0 | | |
| C | 31 | B36 | 28 | A35 | 26 | D34 | 0 | | |
| H | 37 | B37 | 31 | A36 | 28 | D35 | 0 | | |
| H | 37 | B38 | 31 | A37 | 28 | D36 | 0 | | |
| H | 37 | B39 | 31 | A38 | 28 | D37 | 0 | | |
| O | 31 | B40 | 28 | A39 | 26 | D38 | 0 | | |
| O | 32 | B41 | 29 | A40 | 27 | D39 | 0 | | |
| O | 27 | B42 | 25 | A41 | 24 | D40 | 0 | | |
| O | 26 | B43 | 25 | A42 | 24 | D41 | 0 | | |
| O | 30 | B44 | 28 | A43 | 26 | D42 | 0 | | |
| H | 24 | B45 | 1 | A44 | 2 | D43 | 0 | | |
| H | 45 | B46 | 30 | A45 | 28 | D44 | 0 | | |
| H | 44 | B47 | 26 | A46 | 25 | D45 | 0 | | |
| H | 43 | B48 | 27 | A47 | 25 | D46 | 0 | | |
| H | 9 | B49 | 6 | A48 | 1 | D47 | 0 | | |

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| C | 52 | B53 | 51 | A52 | 24 | D51 | 0 |
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| C | 53 | B55 | 51 | A54 | 24 | D53 | 0 |
| H | 53 | B56 | 51 | A55 | 24 | D54 | 0 |
| C | 56 | B57 | 53 | A56 | 51 | D55 | 0 |
| H | 54 | B58 | 52 | A57 | 51 | D56 | 0 |
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| H | 58 | B60 | 56 | A59 | 53 | D58 | 0 |

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