Chern-Simons Topology Geometrics for the generation of the Roccustyrna™ molecule, a ligand targeting COVID-19-SARS-COV-2 SPIKE D614G binding sites

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Research article

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Abstract

SARS coronavirus 2 (SARS-CoV-2) encoding a SARS-COV-2 SPIKE D614G mutation in the viral spike (S) protein predominate over time in locales where it is found, implying that this change enhances viral transmission. It has also been observed that retroviruses pseudotyped with SG614 infected ACE2-expressing cells markedly more efficiently than those with SD614. The availability of newer modeling techniques, powerful computational resources, and good-quality data have made it possible to generate reliable predictions for new chemical entities, impurities, chemicals, natural products, and a lot of other substances fuelling further development and growth of the field to balance the trade-off between the molecular complexity and the quality of such predictions that cannot be obtained by any other method. In this article, we effectively use a decision tree to obtain an optimum number of small chemical active chemical features from a collection of thousands of them utilizing a shallow neural network and jointly free energy cumulative feature ranking method with decision tree taking both network parameters and input toxicity benchmark features into account. In this paper, we strongly combine methods that are simple in machine learning characteristics, efficient in computing resource usage, and powerful to achieve very high accuracy levels for the in-silico generation of the Al-Quantum designed molecule the RoccustyrnaTM small molecule, a multi-targeting druggable scaffold (1Z)-2-{((2S,3S,5R)-5- (2-amino-6-oxo-6,9-dihydro-1H-purin-9-yl)-3-hydroxyoxolan-2-yl)methylidene)-2-cyano-1-(((2S,4R,5R)-2-methyl-2-(methylamino)-1,6-diazabicyclo(3.2.0)heptan-4-yl)oxy)imino)-1lambda5,2lambda5-azaphosphiridin-1-ylium.targeting the COVID-19-SARS-COV-2 SPIKE D614G mutation using Chern-Simons Topology Euclidean Geometric in a Lindenbaum-Tarski generated QSAR automating modeling and Artificial Intelligence-Driven Predictive Neural Networks.

Introduction

The COVID-19 disease was declared on March 2020 a pandemic by the World Health Organization (WHO) and is accountable for a large number of fatal cases. (2, 4) On January 202, WHO emergency committee declared a global health emergency (3, 4–6) based on the rate of increasing spread of the infection (4, 5–7) with a reproductive number (RN) in the range 2.0-6.5, 4 higher than SARS and MERS, (8) with more than 85,000 casualties and fatality rate of about 4%.(1–4) Collaborative efforts for Genomic characterization, (5, 6, 7–9) Molecular epidemiology, evolution, phylogeny of SARS coronavirus and epidemiology from scientists worldwide are underway to understand the rapid spread of the novel coronavirus (CoVs), and to develop effective interventions for control and prevention of the disease. (1–10) Coronaviruses are positive-single stranded, enveloped large RNA viruses that infect humans and a wide range of animals. (7, 8–11) Tyrell and Bonne reported the first coronavirus in 1966, (11) who cultivated the viruses from the patients suffering with common cold. (4, 6, 7–10) In Latin, Corona means “crown” based on their shapes. (2–13, 14, 15, 16, 17, 18, 19, 20) Molecular structure were determined in heterodox interpretations (22) by solving the time-independent (21–22) Schrödinger equation: QM methods, vertex prizes and edge costs including ab initio Density Filed Theories (DFT) (23) and semi-empirical in place (24) of the quantum processor and energy among other observables,(25) under
simulated sampling error as well as to reposition drugs about bonding may represent the similarities (26) and dissimilarities(27) between drugs and repurposed viral proteins respectively. (28) However, the Schrödinger equation cannot actually be solved for any but a one- data-driven (29) electron system methods (the hydrogen atom), (30) and approximations need to be made. According to QM, (2–19, 23) an electron bound that converges quickly and reliably to an atom cannot possess any (2–14, 17, 18, 19–29) arbitrary energy to produce the desired distribution by analyzing pharmacological data or occupy any position in space using statistical and machine (2–17, 19, 23, 24–30) learning concepts. The Lindenbaum-Tarski algebra geometrically represented with logical spaces and has been previously introduced as a 3D logical space subspaces allowing a vectorial representation in which any one (of the eigenvalue statements) occupies a well-defined position and it is identified by a numerical ID. This shows the application to quantum computing through the example of three coupled harmonic oscillators allows pure mechanical computation both for generating rules and inferences. (25, 26, 27) It is shown that this abstract formalism can be geometrically represented with logical spaces and subspaces allowing a vectorial representation. (26, 27, 28–31) In general, the notions of Lindenbaum matrix and Lindenbaum-Tarski algebra have paved a way to further algebraization of logic, which had been begun by George Boole in the 19th century, as well as to a new branch of logic, model theory. Philosophical interpretations of QM were conditioned by ideals of what an explanatory theory should be. (Minkowski-type, wave-edge, etc), (29,3,32–33) as well as probabilistic transformations Algebraic multi-metrics (Triangle area, Bond-angle, etc) and the associated axiomatic formulations (AQFT) treat observables rather than states as foundational for the interaction information extraction. (29,33,34,35) In this project, we show an original strategy and an application to quantum computing through the example of two coupled harmonic black-hole oscillators obtained by molecular modeling and simulations as orthogonical coordinates applied for the design of a novel multi-chemo-structure against the crystal structure of COVID-19 protein targets in a Lindenbaum-Tarski generated QSAR automating modeling lead compound design approach. (29,32,33,35,36) A generalized procedure of Quantization of classical fields that was fused together with QSAR automating modeling as proposed to lead the commutation and anticommutation relations and a C algebra of local observables. (36,37,39,4,41,42) States were defined into the structure and functions of SARS-CoV-2 as linear functional on the algebra of free energy docking observables. Topology Euclidean Geometric, were used in this on this molecular modeling and drug designing project on several parameters. Artificial Intelligence-Driven Predictive Neural Networks and Quantum- Inspired frameworks of parallel-Docking interactions were employed for supercritical entanglements introducing an advanced quantum mechanical inverse docking algorithm providing further insight to confirm the practicality of docking energy predictions for wild type and selected mutations for Nsp3 (papain-like, PLpro domain), Nsp5 Nsp15 (NendoU), (Mpro, 3CLpro), Nsp12 (RdRp), N protein and Spike in understanding the key element functions of SARS-CoV-2 protein pathways and in designing possible novel antiviral agents, from both an quantum algebraic and a cheminformatic perspective.

Materials And Methods

Preparation of the protein structures
The National Center for Biotechnology Information (NCBI) database was used to retrieve the S glycoprotein proteins of SARS-CoV-2. For the N protein, we clustered 31 conformations (1, 13–24, 27) from the 1731 full-length SARS-CoV-2 sequences and stored as a FASTA format file for analysis with Glu174 present in an opened conformation out of a total of 40 states present in the NMR-derived structure (PDB codes, 6xs6,1xak,2g9t,3fqq,2ghv,6yb7) (1–11,14,15–29,34) to select a small subset representative of the protein flexibility downloaded from NCBI (30 April 202, txid2697049, minimum length = 29,000 bp) and aligned using MAFFT. (2–9, 15, 19) The BioEdit v7.2.3 sequence alignment editor was deployed to identify the conserved binding sites and short linear peptide region among the aligned sequences through multiple-sequence alignment (MSA) with ClustalW. The alignment was visually inspected and curated using Genbank NC_045512.2 as a coordinate reference suggestive of RSFIEDLLFNKV, e.g. KNFIDLLLAGF in genomes such as the ball python genome, and further proceeded with this protein motif cluster as identified between the Wuhan isolate beyond the limit of serious detection and spike protein nidovirus 1 of the reptile shingle back for model construction by using again the NC_045512.2 and annotated Open Reading Frames (ORFs) plus additional ORFs. We provided to the DockThor-VS the structures of the SARS-CoV-2 (PDB codes, 6xs6,1xak,2g9t,3fqq,2ghv,6yb7) (1, 3–10) potential therapeutic targets (2, 3, 5–11, 13–27) for the design of our new druggable scaffold named Roccustyrna. (1, 3–9) For this purpose, we initially selected the non-structural proteins Nsp3, Nsp5 (PLpro domain), Nsp12 (RdRp) and Nsp15 (endoribonuclease), (1–4, 6, 7–24) and the structural proteins Spike and nucleocapsid protein (N protein). (3, 7, 9–20)) For this purpose, we clustered the opened states (31 out of 40 states) (3–9, 17, 21) using the Conformer Cluster tool (14,16–29,32) according to the position of the residues (3–11,23–37) Arg102 and Tyr109 using the weighted centroid as the linkage method. (4–12, 29) Finally, the nearest to the centroid structure per cluster was selected as the representative conformation of each group to be available at BiogenetoligandorolTM. In this work, we prepared the protein structures using the Protein Preparation Wizard from the BiogenetoligandorolTM (BiogenetoligandorolTM, SynthocureTM, Thessaloniki, Biogenea Pharmaceuticals Ltd-GR, 2020). (4,6-17-39) Protonation assignment and hydrogen-bond optimization were performed using ProtAssign and PROPKA at the reported experimental pH and (23–39,41) considering the presence of the bound ligand when available (5, 7–8, 12).

**Screening NuBEE Phyto-library and COVID2019 targets.**

Virtual screening of the final proposed model and high throughput molecular docking based on existing literature were implemented to a collection of 9591 drugs including 2037 chemical structures of FDA-approved small molecule drugs and (2, 3–14) over 6000 herbs and phytical extracts from the NuBBEDB updated database to get an insight into the potential inhibitors and to uncover chemical and biological druggable information from Brazilian biodiversity (5,6 – 1,14,15,19–22). Drugs selected for the docking studies having a number of non-hydrogen atoms below 5 or above 10, drugs having MW > 120, and drugs that incorporate elements not associated with organic molecules (e.g., Hg, Pt, Fe, etc.) were not considered. Note that this number for the screening is higher than the original due to the enumeration of drugs into enantiomer, tautomer, and protomer alternatives. (7, 8, 11–14) Parallel Virtual screening technique for molecular docking was deployed at the center of the X: 228.75, Y: 190.82, and Z: 304.15.
its .pdbqt converted libraries of small molecules. The dimensions (Angstrom) used for the inverse docking analysis were X: 26.31, Y: 26.32, and Z: 20.18 for the motif binding target sites using standard Web technologies such as CSS, HTML and JavaScript (AJAX) including graphics, text-based, and spectral files. (9, 13–14) (14, 15–21) When more than one form of the screened drugs and phytical elements for the cross-validation (e.g., more than one enantiomer, more than one protomer, etc.) were screened, as suitable druggable candidates for recoring and fragmentating only the forms having the highest GP and Docking Energy values were considered in the ranking. (14, 16, 29) Finally, drugs and selected NuBBEDB phytical extracts were ranked according to descending GP docking values and only the screened hit candidates generating the highest binding energy values were considered for fragmenting and re-merging into the Roccustyrna small molecule using the BiogenetoligandorolTM cluster of algorithms from the below. The whole set of molecules able to bind to the SARS-CoV PLpro enzyme were taken after extensive literature studies, retrieving only those ligands having an absolute IC50 values. This set consisted of 91 PLpro inhibitors. Depending on the activity threshold', out of 191 compounds, 30 compounds were identified as Active and 53 molecules were considered as Inactives. Molecular docking, Schrodinger-inspired physarum-prize-collecting Neural Matrix Factorization and a drug repositioning scoring analysis were implemented to a hybrid collection of the Natural Products of the Chemistry Institute of UNESP, Araraquara/SP and NuBBEDB phytical extracts. (2, 4, 5–10) Protein-molecule complexes, (4, 5, 7, 8–13) followed by structural relaxation were generated through (8, 1, 13–14) flexible-ligand rigid-receptor molecular docking (9, 13, 15, 16–19) in these local energy minimization to optimize protein-ligand interactions capping the N- and C-terminal for each active fragment with i-GEMDOCK (13, 18, 19–24, 26) through cycles in amino-acids within 4 Å of any docked molecule as considered free of local energy minimizations. (2, 5–21) Virtual screening experiments with KNIME-DockThor-VS for the e-Drug3D dataset and the ChEMBL database, were generated at the reference pH (6.6 to 7.4) for all SARS-CoV-2 targets available at the platform so far (e.g., PLpro, Mpro,RdRp, NendoU, Spike and N protein) using the wild type genomic variant and 10 best matching compounds (Table 1a) were obtained namely, Colchicine, Raltegravir, Hexacosanol, Benzoxazolinon, Carboxy-Pentaric acid, Ursane, Antheraxanthin, RA-XIII, Crotonate and Byrsonima Coccolobifolia against the SARS-COV-2 protein targets of the (pdb:1xak), (pdb:6xs6) and (pdb:6lu7). (6, 7–27) For each target, all amino-acids of the cut-out system with hydrogens were then collected, within 8 Å of any docked molecule and used to build a reduced system where the “o” subscript in the first term refers to the difference of the free energy calculated using the protein-ligand (PL), protein (P) and ligand (L) conformations and GQM (X) is the energy of X from the docked complex, in the free unbound state the fourth term corresponds to the change in conformational entropy, were generated and the second and third unbound states are calculated through local energy minimization as ΔGQMconf (X) = GQMo(X) − GQM (X), (X = L, P) (2) where GQMo (X) is the energy of the isolated X in the conformation of the docked PL on both protein and molecule complex Inhibitors from the Bioactivity-Guided Fractionation of the Colchicine, Raltegravir, Hexacosanol, Benzoxazolinon, Carboxy-Pentaric acid, Ursane, Antheraxanthin, RA-XIII, Crotonate and Byrsonima coccolobifolia Leaves and Stems to be fragmented, re-cored and accordingly merged into the RoccustyrnaTM small hyperactive druggable scaffold. The acknowledgement of the binding of the selected 8 phytical compounds to their
target proteins was accomplished using Molinspiration (http://www.molinspiration.com/cgi-bin/properties) and DrugBank (1, 11).

**Pharmacophoric-ODEs fragmentating, merging and recoring: Biogenetoligandorol AI-heuristic algorithm.**

The patterns of this Biogenetoligandorol fragmentation scheme are sorted into the workings of the Galilean transformation by examining the “extended” Galilean transformation based on a set of heuristically determined descriptors to a rigid system having an arbitrary time-dependent acceleration. These descriptors can be, for example, the number of atoms describing the pattern and be determined by the substitution $i p(r, t) = e i J(r, t) (p(r', t)$. $V' i p = (V' i p + i V' f) e i f$, $V' i p = (V'2 i p + 2 i V' f - V' (p + (p V' f + < p(V' f)2)e'f,i>= (f) + if < p) e i f$, and the Schrödinger equation becomes $n 2 2 m (V,z(p + 2 i V' f - V' (p + i(p V' f - (V 'Y < p) = ifi ((< p + if(p) -g.V ' (p + i(pv' f f))) where $p + 2$ are the the number of bonds available or the number of double bonds. The complete fragmentation scheme is analyzed to find patterns that are contained within the selected 10 hit compounds of the Colchicine, Raltegravir, Hexacosanol, Benzoxazolinon, Carboxy-Pentaric acid, Ursane, Anthraxanthin, RA-XIII, Crotonate and Byrsonima coccobifolia.

Whenever searching for a specific pattern, if the group has such a parent pattern, the parent pattern is searched first eliminate the terms in $V'(p, which gives $f = - % r' g(t)$. Then one can choose $n g(t)$ such as to eliminate the purely time-dependent terms, and one finally arrives at, $= (2 m V' 2(p + mf); i r'(p = ih(p,pir, t) = e a h J (pir',t). (34–42) of the strong equivalence principle in quantum theory. After that, the child pharmacophoric pattern is searched in an inertial repeated merged system $S = % (ml5 r, t) + ip2im2, r, t). (21–42)Then assume that one fragmented pharmacophore can describe the same superposition in an accelerating to a larger ligand-receptor system $S'$ that obeys (14), with $§ = £(r), £(0) = £(7) = , so that the system $S'$ performs a closed quantum circuit and coincides with the chemical structure system the $S$ at times $t = 0$ and $t = T$, such that $r' (i T) = r(7). (25–34,37) To avoid incomplete group assignments, whenever a part of the structure is already fragmented, the subsequent matches have to be adjacent to the groups already found. (26,31–39) As a first step, the algorithm performs a quick search for the different groups in the fragmentation scheme applying the heuristic group prioritization and the parent–child group prioritization as described above. (29,32–39) The search goes sequentially through the sorted fragmentation scheme, adding groups that are found and do not overlap with groups that were already found. In case it successfully finds a valid fragmentation, this is taken as the solution merely relating to how one would describe the same state in a different coordinate system. (33,35–42) This Lindenbaum-Tarski algebraic algorithm was implemented as a recursive algorithm that performs a complete tree search of all possible combinations of fragmentation, merging and pharmacophoric recoring systems. To reduce the fragmentation space that needs to be searched, the algorithm of the two independent Chern-Simons $S = 14π∫ M3(A∧ dA) k + 13⟨A∧ [A∧ A]⟩ k (mod 2π)$ actions with group on the heuristic level of path integrals ($AA$ is the potential 11-form and $FF$ is the field strength 22-form) was applied where the partition function is the modulus square of the partition function for the Chern-Simons theory when associated with knot theory. This In Silico approach keeps track of the solutions already found of the selected group of the selected hit candidates which were fragmented, recored and superposed in a non-relativistic quantum mechanics environment and finally led us to the complete Roccustyrna chemical structure. (21,33,36,38–42) If several chemical solutions were found in the end, the theory has a
sequence of similar such spaces of finite but arbitrarily large dimension, where the dimension increases with the resolution of relative measurements to the first system of the 10 hit selected small molecules the possible chemical solutions were sorted by the number of different patterns and the first solution was taken as the determined fragmentation. (36,37,39–41,42) This way, patterns with larger groups are prioritized over smaller chemical patterns with potential antiviral properties of the: (1Z)-2-(((2S,3S,5R)-5-(2-amino-6-oxo-6,9-dihydro-3H-purin-9-yl)-3-hydroxyoxolan-2-yI)methylidene)-2-cyano-1-(((2S,4R,5R)-2-methyl-2-(methylamino)-1,6-diazabicyclo(3.2.0)heptan-4-yI)oxy)imino)-1lambda5,2lambda5-azaphosphiridin-1-ylium patterns.

**Roccustyrna Ligand Protein Targets**

The docking engine employed in this computer-aided drug design effort is the DockThor program, which utilizes preparations of the acceptable topology files for the Roccustyrna ligand for the protein (.in) and cofactors (.top) and a specific input .pdb file containing the atom types and partial charges from the MMFF94S49 force field. (15, 16, 17, 29, 3, 31) The .top file of the Roccustyrna ligand was generated by the MMFFLigand program, which utilizes the facilities of the OpenBabel chemical toolbox for deriving atom types and partial charges with the MMFF94S force field, and for the identification of the rotatable bonds, and calculating the properties necessary for computing the intramolecular interactions. (16,17,29,3,31,32,34,36) In the MMFFLigand, all hydrogen atoms were considered explicitly and the PdbThorBox program was utilized to set the protein atom types, and the partial charges from the MMFF94S force field considering the nonpolar atoms implicitly to reconstruct missing residue side chain atoms. (15, 16, 17, 21, 22, 29, 3, 31) Thus, in this KNIME based GEMDOCK-DockThor-VS platform, both the Roccustyrna small molecule, SARS-COV-2 protein targets, and cofactors were treated with the same force field utilizing the same molecular force field parameterizations. (15,16,17,22,23,24,29,3,31–40) The preparations of the steps such as changing the protonation state of the amino acid residues, adding hydrogen atoms and freezing rotatable bonds was done interactively in the publically available web servers and performed automatically by the programs cited without the need for intervention. (15,16,17,24,25,26,27,29,3,31–36) The search docking space and the configuration of the grid box were interactively set in the KNIME designed BiogenetoligandorolTM pipeline which were represented as a grid box and the potentials are stored at the grid points through the parameters of the center of coordinates, size of the grid and discretization (i.e., the spacing between the grid points). (13,14,15,16,17,20–29,3,31) The initial population for the rotational, and translational, was randomly generated within the conformational degrees and grid box using random values of freedom of the Roccustyrna ligand. (15,16,17,19,22,27,28,29,30–38) For each SARS-CoV-2 therapeutic target DockThor-VS default parameters were uploaded as a recommended set of parameters for the grid box (i.e., center and grid sizes) which can be used or modified according to the objectives of this docking experiment which was specially designed to deal with highly flexible ligands such as the Roccustyrna small molecule. (15–29, 3, 31) In this strategy, a replacement method was introduced by using a phenotypic steady-state crowding-based protocol and a multiple solution genetic parental algorithm as a Dynamic Modified Restricted Tournament Selection (DMRTS) approach, which provided us a better exploration of the energy
hypersurface for the identification of multiple minima solutions in a single run, preserving the population diversity of the generated structures. The default parameters of this parallel docking algorithm (named BiogenetoligandorolTM) is set in the KNIME-web server as follows: (i) 24 inverse docking runs, (ii) 1,000,000 evaluations per parallel docking run, (iii) population of Roccustyrna individuals, (iv) maximum of 20 cluster molecule leaders on each inverse docking run. For this screening experiment, we also provided an alternative set of parameters to improve the docking experiment without significantly losing accuracy (named HTS Virtual Screening): (i) 120 docking runs, (ii) 200,000 evaluations per docking run, (iii) population of Roccustyrna individuals, (iv) maximum of 20 cluster leaders on each docking run. The docking experiments were performed on DockThor CPU nodes of the SDumont supercomputer, each one containing two processors Intel Xeon E5-2695v2 Ivy Bridge (12c @2,4 GHz) and 64 Gb of RAM memory.

We validated the docking experiments through the redocking of the non-covalent Roccustyrna ligand present in the complexes 6W63 (Mpro) using the standard configuration, successfully predicting the co-crystallized conformation of each complex. In the crystallographic structure, this moiety is exposed to the solvent and has insufficient electronic density data. The free energy scoring function applied to score the best docked poses of the same Roccustyrna ligand was based on the sum of the following terms from the MMFF94S force field and is named “Total Energy (Etotal)”:

(i) intermolecular interaction energy calculated as the sum of the van der Waals (buffering constant $\delta = 0.35$) and electrostatic potentials between the protein-ligand atom pairs, (ii) intramolecular interaction energy calculated as the sum of the van der Waals and electrostatic potentials between the 1–4 atom pairs, and (iii) torsional term of the ligand. All docking poses generated during the docking step were then clustered by our in-house tool BiogenetoligandorolTM. The top docking energy-poses of each Roccustyrna-Protein cluster were selected as representatives and made available in the results analysis section, of cluster representatives to be made available. The affinity prediction and ranking of the Roccustyrna small molecule was performed with the linear model and untailored for specific protein classes, utilizing the DockTScoreGenL scoring function as a set of empirical scoring functions. Biogenetoligandorol cluster of DockTScore, PLIP, DockThor and GEMDOCK-AUTODOCK-VINA current scoring functions take into account important terms for protein and SMALL MOLECULE preparation, multiple protein-ligand binding, such as intermolecular interactions, affinity predictions, ligand entropy and desolvation of the specific target classes such as SARS-COV-2 6W63 (Mpro) proteases using protein-protein interactions (PPIs) trained with PdbThorBox and MMFFLigand sophisticated machine-learning algorithms. The visualization of the SARS-COV-2 protein, cofactors and the Roccustyrna compound, the grid space location superposed with the protein targets of the (PDB codes of the PDB: 6xs6, 1xak, 2g9t, 3fqq, 2ghv, 6yb7) (1–11, 14–29, 34, 35, 36, 39) and the docking outputs were generated with NGL, a WebGL-based library for molecular visualization.

In silico Bioactivity Prediction and ADMET Analysis of the Roccustyrna small molecule.

The drug likeliness and bioactivity of the Roccustyrna small molecule were analyzed utilizing the Molinspiration server (http://www.molinspiration.com). (1–11, 14–29, 39) By using the Molinspiration web-tool we, a cheminformatics multi-tasking software we calculated the Roccustyrna's molecular modeling properties as well as drug likeness and bioactivity prediction of our prototype ligand (Mabkhot
et al., 2016). (1−1,12−2,34,35) In this section, the Molinspiration-based drug-likeness analysis web platform was incorporated to predict the Roccustyrna's two important factors, including the lipophilicity level (log P) and polar surface area (PSA) directly associated with the pharmacokinetic properties (PK) of the same lead structure (Beetge et al., 2000). (1−9,11−34) Then, by uploading the Roccustyrna's smiles in the Molinspiration-based bioactivity analysis web server, we calculated the bioactivity score of this ligand toward GPCR ligands, ion channel modulators, nuclear receptor ligands, protease inhibitors, kinase inhibitors, and other enzyme targets which were analyzed by sophisticated Bayesian statistics (Mabkhot et al., 2016). (5−11,11-29-36) The PK properties, such as Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET), of the Roccustyrna pharmacophoric scaffold were predicted by utilizing the admerSAR v2.0 server (http://lmmd.ecust.edu.cn/admetsar2/) for the prediction of our novel Roccustyrna's ADMET properties on factors such as membrane permeability [designated by colon cancer cell line (Caco-2)], human intestinal absorption (HIA), and the status of either P-glycoprotein substrate or inhibitor. Finally, the ability of the Roccustyrna's small molecule to cross the blood-brain barrier (BBB) and its metabolism (M) was calculated by the CYP, MATE1, and OATP1B1-OATP1B3 models. The Excretion (E) of the Roccustyrna ligand was estimated based on the renal OCT substrate and the toxicity (T) was then predicted accordingly on the Human Ether-a-go-go-related gene inhibition, carcinogenic status, mutagenic status, and acute oral toxicity default parameters (Shen et al., 2012).

Results

In silico Prediction of the Roccustyrna ADMET Properties and Bioactivity Score

The adequacy of therapeutic drugs mainly depends on the molecular property and bioactivity of the compounds (Shen et al., 2012). To predict the drug-likeness and bioactivity of the selected Roccustyrna (1S)-2-{{[(2S,3S,5R)-5-(2-amino-6-oxo-6,9-dihydro-3H-purin-9-yl)-3-hydroxyoxolan-2-yl]methyl}-1-{{[(2S,4R,5R)-2-methyl-2-(methylamino)-1,6-diazabicyclo[3.2.0]heptan-4-yl]oxy}amino}-2λ5-azaphosphiridine-2-carbonitrile, the in silico molecular property assessment was performed using the Molinspiration tool. This tool measures the milogP value (Octanol-water partition coefficient logP) and TPSA (Topological polar surface area) values of the compounds using Bayesian statistics. The result shows that the milogP value of the Roccustyrna small molecule was predicted as having ideal lipophilicity (logP < 5) (Han et al., 2019) in the aspect of absorption and permeation (Table 1c).

Screening Of The Roccustyrna Inhibitor For Spike Protein-rbd-ace2 Interaction

In this study we have shown that the QMMM designed Roccustyrna small molecule which was designed in silico by using Topology Euclidean Geometric and Artificial Intelligence-Driven Predictive Neural Networks was engaged in the binding domains of the protein targets of the (pdb:1xak) (Fig. 4a) with the
docking energy values of the (T.Energy, I.Energy, vdW, Coul, NumRotors, RMSD, Score), (-19.625, -35.483, 7.633, -43.116, 7, -5.813)Kcal/mol, (Tables1a,1b,2a) The Roccustyma chemical structure interacted into the binding sites of the protein targets (pdb:6w9c) (Fig. 4b) (Fig. 7e) with the negative docking energies of the (T.Energy, I.Energy, vdW, Coul, NumRotors, RMSD, Score), (-36.678, -55.648, -7.519, -48.129, 7, -6.762) Kcal/Mol. It also generated hydrophobic interactions when docked onto the binding cavities of the amino acid of the 168 PRO, A1, 02J C with the docking energy values of the 3.53, 2369, 1303, -10.425, 3.42, 72.447, -13.394, 3.19, 70.551 Kcal/mol. Our new QMMM designed small molecule named Roccustyma involved in the generation of the hydrogen bonding within the PJE:C:5 (PJE-010) 010:C:6 Interacting chain(s) while generating hydrophobic interactions when docked into the binding domains of the amino acid of the 25 THR, A6, 010 C domains with the docking energy values of the 3.73, 2415, 179, -7.156, 21.406, 66.898–8.709, 22.779, 70.002 Kcal/mol. (Figs. 1a,1b, 4a,4b, 5a,5b,5c, 5d,6a,6b,6c,6d,6e,7a,7b) The Roccustyma’s active pharmacophoric site of the (methylamino)-1,6- diazabicyclo(3.2.0)heptan-4-yl)oxy)imino) interacted into the binding cavities of the amino acid of the 26 THR, A6 010C with the docking energy values of the 3.81, 2415, 186, -7.156, 21.406, 66.898, -6.155, 24.392, 64.757 Kcal/mol. The Roccustyma’s active pharmacophoric site of the dihydro-3H-purin-9-yl)-3-hydroxyoxolan generated an inhibitory effect which was involved in the generation of hydrogen bonds when docked into the binding cavities of the amino acid of the 143 GLY A 6 010C with the docking energy values of the 1.93, 2.8, 145.29, 1105, 2411, -8.911, 17.849, 65.703–8.918, 17.918, 62.905 Kcal/mol. The same prototype pharmacophoric elements named Roccustyma when docked into the binding sites of the amino acid of the 164 HIS, A5, PJE C2.generated hydrogen interactions with the binding energy values of the 16 3.07, 153.73, 2408, in the coupled atoms of the N3 and O2 with the docking energy values of the −12.282, 14.994, 67.123–15.161, 15.336, 68.144 Kcal/mol (Figs. 1a,1b,4,5a,5b, 5c,5d,6a,6b,6c,6d,6e). The binding patterns of the 02J:C:1 (02J) active sites of the amino acid 168 PRO, A1, 02J C binding domains generated hydrophobic interactions with docking energy values of the 3.53, 2369, 1303, -10.425, 3.42, 72.447, -13.394, 3.19, 70.551 inside the PJE:C:5 (PJE-010) + 010:C:6 interacting chain(s): A C of the amino acid of the 164 HIS, A5, PJE C2. The Roccustyma’s pharmacophoric active site of the 2-lambda5-azaphosphiridin-1-ylum was engaged in hydrogen bonding interactions with the formation of hydrogen bonds inside the binding cavities of the amino acid of the 143 GLY, A6, 010C with the docking energy values of the 1.93 2.80 145.29 1105, 3.81 2415 186 -7.156, 21.406, 66.898–8.709, 22.779, 70.551, 2.16 3.07 153.73 2408 N3 1266 O2 -12.282, 14.994, 67.123–15.161, 15.336, 68.144 Kcal/mol (Figs. 1a,1b,4,5a,5b, 5c,5d,6a,6b,6c,6d,6e). The Roccustyma small molecule involved also in the generation of the hydrophobic interactions within the binding domains of the amino acid of the 25 THR A 6 010C with the docking energy values of the 3.73, 2415, 179, -7.156, 21.406, 66.898–8.709, 22.779, 70.002Kcal/mol as illustrated in the (Figs. 1a,1b,2a, 2b,2c,2d,3a, 3b,3c,4a,4b, 5a,5b,5c,5d,6a,6b,6c,6d,6e). In this project, we implemented Quantum Heuristic Fragmentation Algorithms for the merging and recoring of the hit selected Drug Pair interactions by using Quantum Hamiltonians for the $\gamma B(S^\dagger + S^\ddagger) + I\cdot A \cdot S^\ddagger, S^i= (\sigma_x, \sigma_y, \sigma_z)I \cdot \rho(t) = \text{Tr}(U(t)\rho(0)U^\dagger(t)), \rho_I(0) = I/\Delta M(\Delta t) = f(t)dt, \rho = \int \rho(s(t))dt = \int 0 \sim f(t)|s(t)|ds = \int 0 \sim f(t)|s(t)|ds = \int 1 \sim f(t)|s(t)|ds = \rho_s$
\[01\% \text{ps}(0) \rho^\circ s = H \overset{0}{\circ} m \overset{0}{\circ} m = H \overset{H}{\circ} \cdots \overset{\cdots}{\circ} H \overset{0}{\cdots} \overset{0}{\cdots} \overset{0}{\cdots} = 12(0+1) \overset{12(0+1)}{\cdots} \overset{12(0+1)}{\cdots} = 12 \text{ m}(00\cdots 0+00\cdots 1) + \cdots + (11\cdots 1). \]

In this article we generated the RocustyrnaTM small molecule (Figs. 1a,1b,4,5a,5b,5c,5d,6a,6b,6c,6d,6e) with the Geometrical Descriptors of the: Dreiding energy = 305.20 kcal/mol, MMFF94 energy = 35.06 kcal/mol, Minimal projection area = 66.49, Maximal projection area = 123.65 Minimal projection radius = 5.71 Maximal projection radius = 9.24 Length perpendicular to the max area = 1.29 Length perpendicular to the min area = 19.04 van der Waals volume = 409.41 Donor count = 5 Donor sites = 6 Acceptor count = 11 Acceptor sites = 14. (Fig. 7a) Electrostatic CoMFA analysis of the contact residues of the best docking poses of the contact merged chemical residues of the entire Rocustyrna chemical structure when docked onto the SARS-COV-2 protein targets, (pdb:3fqq) hits the positively charged groups and red regions favored by negatively charged groups within the binding domains sequence of the amino acid of the V-S-HIS-159, V-S-ARG-16, V-S-ARG-112, V-M-GLU-148, V-M-PHE-15, V-S-PHE-15, V-S-HIS-159, V-M-TYR-161 with the docking energy values of the −101, -14.0762, -5.11094, -7.98447, -4.17314, -4.43549, -9.66939, -9.42926, -7.30085. (Fig. 7b) Other QSAR/CoMFA contour map experiments of electrostatic regions of the binding interaction of the entire pharmacophoric residues of the Rocustyrna chemical design when docked onto the SARS-COV-2 protein binding sites of the the electrostatic surface view of active site pocket of its active contact residues of the Rocustyrna small molecule when docked onto the SARS-COV-2 protein targets, (pdb:6xs6), interacted negatively with all the charged groups of the sequence of the amino acid of the V-M-LYS-557, V-S-LYS-557, V-M-ARG-567, V-M-ASP-568, V-S-ASP-574, V-S-PHE-43, V-M-ARG-44, V-M-SER-45, V-S-SER-45 with the docking energy values of the −85.8, and −5.56004, -5.0011, -8.38956, -5.77168, -6.13664, -12.8661, -5.37546, -6.10391, -5.00928 Kcal/mol respectively. (Fig. 7c) Moreover, Cluster of the QSAR/QMMM/CoMFA map analysis of electrostatic regions around the contact residues of the Rocustyrna small molecule when docked onto the SARS-COV-2 protein targets, (pdb:2ghv). (green, favored; yellow; disfavored) around the entire Rocustyrna chemical structure regions has shown that our innovative drug design generated negatively charged groups within the sequence of the amino acid of the H-M-ASN-33, H-S-ASN-33, H-S-TYR-356, H-M-ASN-424, V-M-ASN-33, V-M-ALA-331, V-M-THR-332, V-S-THR-332, V-S-TYR-356, V-S-TRP-423, V-S-ILE-428, V-S-ARG-495 with the docking energy values of the −104.7 and−3.45708, -3.5, -3.97711, -3.5, -5.33228, -6.79753, -7.9376, -6.69969, -12.2528, -7.66989, -8.15072, -7.00332Kcal/mol respectively. (Fig. 7d) In addition, CoMFA contour map of electrostatic regions around Rocustyrna chemical structure indicated that the contact residues of the Rocustyrna small molecule when docked onto the SARS-COV-2 protein targets, (pdb:2zu5). (green, favored; yellow; disfavored) around the Rocustyrna chemical structure hits the entire sequence of the amino acid of the V-M-THR-25, V-S-THR-25, V-M-THR-26, V-S-HIS-41, V-M-LEU-141, V-M-ASN-142, V-S-ASN-142, V-M-GLY-143, V-S-CYS-145, V-M-MET-165 with the binding energy values of the −97.2 and −5.16512, -4.15949, -9.8487, -4.77062, -4.72901, -6.7295, -5.82428, -5.35883, -4.2588, -5.37491 Kcal/mol respectively. (Fig. 7e) The Rocustyrna small molecule hits also the entire binding domains of the SARS-COV-2 protein targets, (pdb:6w9c) within the sequence of the amino acid of the V-S-PRO-59, V-S-ARG-65, V-M-THR-75, V-S-THR-75, V-M-PRO-77, V-S-PRO-77, V-M-HIS-47, V-S-HIS-47 with the docking energies of the −83.9, -4.21999, -12.6164, -7.60372, -6.69528, -5.89416, -6.40663, -5.51621, -7.99273. Finally, the Rocustyrna chemical structure generated an inhibitory docking effect of high negative binding energy docking values of the −66.7 Kcal/mol when docked onto the cav7bv2_POP
binding domains within the amino acids of the V-M-LYS-551, V-S-LYS-551, V-S-ARG-553, V-S-ASP-618, V-M-TYR-619, V-M-PRO-620 with the docking energy values of the – 4.71516, -10.4842, -4.7999, -6.65538, -5.1339, -6.28532 Kcal/mol. On the other hand the Remdesivir drug when combined to the Roccustyrna small molecule interacted at the same binding domains of the amino acids of the V-M-LYS-551, V-S-LYS-551, V-S-ARG-553, V-S-ASP-618, V-M-TYR-619, V-M-PRO-620 with positive and zero docking values of the + 42.1, -0.104885, -0.19986, + 25.0575, Kcal/mol. That means that the Remdesivir drug could induce the COVID-19 disease.

**Discussions**

In this article, we propose an alternative topological quantum computing optimization framework for the computation of topological invariants of knots, links and tangles through a stochastic discrete optimization procedure that uses ground structure approach, nonlinear finite element analysis, and quantum-inspired evolutionary algorithms in which the concepts of proper time and rest mass enter in the non-relativistic limit. The focus of this work is to develop a Quantum Heuristic Fragmentation driven Chern-Simons fragmentation algorithm that is as independent as possible from the chosen fragmentation scheme to allow for a faster development of new group contribution drug design methods. For this reason, the Roccustyrna mutli- targeting pharmacophoric element for each pattern was kept as simple as possible and can be geometrically represented with logical atomic spaces and subatomic subspaces allowing a vectorial negative docking energy representation. The few chemical patterns (that were made more specific to match the results better from the literature database have been underlined in this project as orthogonically applied for the design of a novel multi-chemo-structure the Roccustyrna small molecule against the crystal structure of COVID-19 main protease in complex with an inhibitor N3 in a Lindenbaum-Tarski generated generated QSAR automating modeling lead compound design approach. In this hybrid drug designing approach, we have designed the RoccustyrnaTM nano-structures as a system of intrinsically positioned cables filtered before evaluation and triangular bars kinematically stable and structurally valid symmetric formations of connected components, holes, and voids jointed at their ends by hinged connections to form a rigid chemical scaffold for calculating Betti numbers—the numbers—in persistent homology.

**Conclusions**

Here, for the first time we have generated drug repositioning In-Silico approaches against the COVID-19, not only for constructing drug libraries and therapeutic target structures available through publically available web servers, but also for allowing fragmentation and recoring studies introducing new targets structures and virtual screening experiments and involving in-house ligand libraries applied for the design of a quantum thinking novel multi-chemo-structure against the crystal structure of COVID-19 main protease, the RoccustyrnaTM small molecule. By applying the Biogenetoligandorol algorithm, a Gravitational Topological (UFs) based Quantum-Parallel Particle Swarm Inspired framework using only 2D chemical features that are less compute- intensive in which a generalized procedure of Quantization
of classical heuristic fields that can be fused together with QSAR automating modeling I finally developed and implemented for the two algorithms using Topology Euclidean Geometric and Artificial Intelligence-Driven Predictive Neural Networks, showing that it is possible to automate group fragmentation based on computed descriptors for the patterns in the fragmentation scheme to make use of partial chemical derivatives with the additional difficulty that the drug designs we deal with are not orthogonal. (30–42) Both Chern-Simons theory when associated with knot theory algorithms applied in this project are capable of fragmenting every molecule of a reference database of structures into their respective UNIFAC groups. Furthermore, the heuristic algorithms which were used in this project are capable of fragmenting and remerging small molecules that could not be fragmented by the algorithm of the reference database. (2,5–42) We have illustrated the power of such an approach interpreted as distinct quantum circuit, qubit preparations, and certain 1- and 2-qudit gates in a meaningful application to components, such as qubits. Our Biogenetoligandorol platform also offers utility to researchers simply wishing to interrogate and organize generalized Hadamard and control-Z gates data, as it can be applied to create an inventory of available numerical docking data with particular clinical or genomic features, of the shaded tangle into two-dimensional space such as available datasets or patients with particular mutations, which may be used to draw independently of its drug identification capabilities. (26,29–42) More specifically, in this project we implemented Inverse Docking Algorithms with nonlinear electrodynamics indicated to us that the RoccustyrnaTM small molecules exert the highest inhibitory activities and negative docking energies as compared to other FDAs against the same SARS-COV-2 viruses protein targets and while it is probably true that the injudicious use of these ideas can cause problems, it is also true that they do and should play a role quantum mechanically in the this drug discovery field.

Declarations

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