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In silico identification of a potent arsenic based lead drug di-phenyl phenoxy roxarsone against SARS-CoV-2

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In this article we have tried to address the plausible identification of a novel lead drug molecule against COVID-19. Nine different arsenic (As) based molecules, roxarsone derivatives were designed and optimized for computational analysis to determine its binding affinity against SARS-CoV-2. The molecules were screened based on their chemical reactivity with respect to conceptual density functional theory (CDFT) and global reactivity descriptors. The screened molecules were docked blindly against RNA dependent RNA polymerase (RdRp) using molecular docking software iGEMDOCK v2.1. On the basis of idock score in their respective catalytic domain, di-phenyl phenoxy roxarsone identified as promising inhibitor against SARS-CoV-2 with binding free energy calculated as –86.8 kcal/mol. Site specific docking was also executed with target site, receptor binding domain (RDB) of spike glycoprotein of SARS-CoV-2 whose structure was computationally designed using Phyre2 server. The interaction study of RDB with di-phenyl phenoxy roxarsone revealed a binding energy –133.3 kcal/mol. Thus it can be concluded from the above *in silico* experiment that screening of potential arsenic based roxarsone derivative would help in development of new therapeutic drug for COVID-19.

Keywords: Drug molecule design, di-phenyl phenoxy roxarsone, COVID-19, *in silico* experiment.

Introduction

The novel corona virus COVID-19 is pushing the world into a precariously unpredictable new phase. It has already created its own roadmap to make a pandemic worldwide, after the official announcement by Director-General of WHO (World Health Organization) on 30th January 2020, that '2019-nCoV outbreak is a Public Health Emergency of International Concern'[1]. From its first reporting on November 2019 at Wuhan, China[2,3], till 13th July 2020, the virus has already killed 566,654 along with 12,768,307 confirmed cases as reported to WHO[4]. Novel corona virus disease is a respiratory trouble and it causes fever, fatigue, dry cough, muscle aches, shortness of breath and in some instances lead to pneumonia[2,5,6]. Patients are unable to get the test of food and any odour or scent. In harsh situation, it causes ARDS (Acute Respiratory Distress Syndrome) where a severe inflammation occurs in patient's lungs, fluid builds up within and around the lungs[5]. It can cause 'septic shock' due to sudden fall in blood pressure and different organs of patient's body cry for oxygen. Symptoms and severity may differ for different patient[5]. Aged people, children (age up to 6 years), and patients who have medical history of heart disease, asthma, diabetes, kidney problems, are more in danger to CORONA disease, as they are immune compromised[5]. The contributory mediator for CORONA disease is COVID-19, a virus from the family of SARS-CoV-2 (*Severe acute respiratory syndrome coronavirus -2*). MERS-CoV and SARS-CoV[6,7] are similar virus agents known previously. SARS-CoV-2 belongs to *Coronaviridae* family of enveloped single-stranded, positive-strand ribonucleic acid (RNA) structure. This SARS family have 14 (fourteen) binding residues and among them 8 (eight) amino acids are distinctively conserved for SARS-CoV-2. Importantly, the binding residues of this family interact with the ACE-2 (*Angiotensin converting enzyme-2*) directly[2,8]. Currently, no specific drug or vaccine is available to combat this disease. As per experts report, the swift transmission of corona virus is mainly due to 'person to person', and if it run in community transmission mode, it can be ca-

lamitous for the entire world. So, with the directives of WHO, the healthcare authorities have recommended certain defensive methods, like quarantining the infected patients, vigorous testing and swift diagnosis, use of appropriate masks, regular hand washing with soap, using hand sanitizer, to counter and control the progress of this disease[9]. When researchers are trying their best day and night to find out suitable drug, doctors and clinical experts are trying with the strategy to fight with existing drugs available in market. They are recommending the usage of some known broad-spectrum antiviral drugs to use, like Nucleoside analogues and HIV-protease inhibitors as promise treatment approach. '*RNA-dependent RNA polymerase*' (RdRp) and '*Angiotensin-converting enzyme-2*' (ACE-2) are also used as effective drug targets for COVID-19 treatment. Favinapir, Umifenovir, Ritoavir, Oseltamivir, Lopinavir, Ganciclovir, Remdesivir, Dexamethazone which are known as established antiviral drug, are now clinically tested against COVID-19 infection, and doctors are applying these drugs on their patients[2,9]. Chloroquine (CQ), an antimalarial drug, has been used in treatment of COVID-19 cases in some countries[10]. In this connection, the polysyllabic word hydroxychloroquine (HCQ) has been more familiar to people than most other drugs these days, because of a request from the USA President to the Indian Prime Minister to supply the medicine in an ample quantity to USA to control COVID-19. Thus India is now in the global picture as a huge producer and supplier of hydroxychloroquine to the rest of the world. The hypothesis that, together with zinc ion, prophylactic hydroxychloroquine which is also a zinc ionophore can combat with COVID-19 through an 'open and shoot' mechanism, (HCQ to open the gate of the lipid membrane of infected cells and zinc to shoot down the virus) was neither proved nor disproved and human trials were apparently ongoing at many places. But on advocacy of Solidarity Trial's International Steering Committee, WHO has stopped the trial of HCQ, lopinavir and ritonavir for COVID-19 treatment on hospitalized patients[11]. FDA also made caution against the use of CQ or HCQ outside hospital, or clinical trial due to threat of heart rhythm problems[12]. Several organizations are trying to launch an effective vaccine against COVID-19, to scissor the life cycle of SARS-CoV-2 which is an urgent need for the mankind. Implicit study with *in silico* is a helpful technique to meet the special challenges of searching effective antiviral drug. Large no. of compounds from chemical libraries are screened by different artificial intelligence methods, such as molecular docking, pharmacore-based screening, for squeezing the number of lead molecules to a smaller set of promising candidates to be tested in fast biological and clinical study. This rational approach will save resources in terms of time, manpower and money[13]. But to find out the best possible drug candidate it is also necessary to design new molecule and optimize their energetically favourable geometry. Molecular docking, a well accepted *in silico* technique, has been objectively used in pharmaceutical chemistry for the identification of best potential inhibitor molecule among its derivatives, for target specific drug design. In search of SARS-CoV-2 inhibitor, in our recent study[14]. Arsenic (As) derivative darinaparsin is identified as significant lead molecule to prevent the replication of SARS-CoV-2. Regardless of some adverse effects of Arsenic (As) on human body, different organo-As compounds or their derivatives have been used for medical purposes for more than 2000 years[15]. Arsenic, which is a non-essential trace element for human body have been reported as the inhibitor of viral replication in *in vitro* study[16]. Among our screened As-derivatives, roxarsone[14] created curiosity to study further due to its high chemical reactivity. In this paper we have designed nine derivatives of roxarsone, optimized their geometry, and screened them for *in silico* study against SARS-CoV-2.

Materials and methods

Geometry optimization and theoretical calculations:

Geometry of the Roxarsone derivatives (methoxy roxarsone, phenoxy roxarsone, mono-phenyl roxarsone, mono-phenyl phenoxy roxarsone, mono-methyl roxarsone, mono-methyl methoxy roxarsone, di-phenyl roxarsone, di-phenyl-phenoxy roxarsone, di-methyl roxarsone) was optimized using B3LYP/LANL2Dz level of theory[17] with Gaussian 09 suit[18]. The imaginary frequency of all the molecules attended to be 'zero', imply to energy minima on their potential energy surface. The computations were carried out using the GAUSSIAN 09 program package and the optimized structures were spawned through the GAUSSVIEW 6 package[18]. The optimized geometries (Fig. 1) were used further for docking study. The stability and reactivity of any molecule can be assessed quantitatively by conceptual density functional theory (CDFT) approach, by calculating its ionization potential (I), electron affinity (A), electronegativity (χ), hardness (η), electrophilicity (ω). These CDFT based reactivity de-

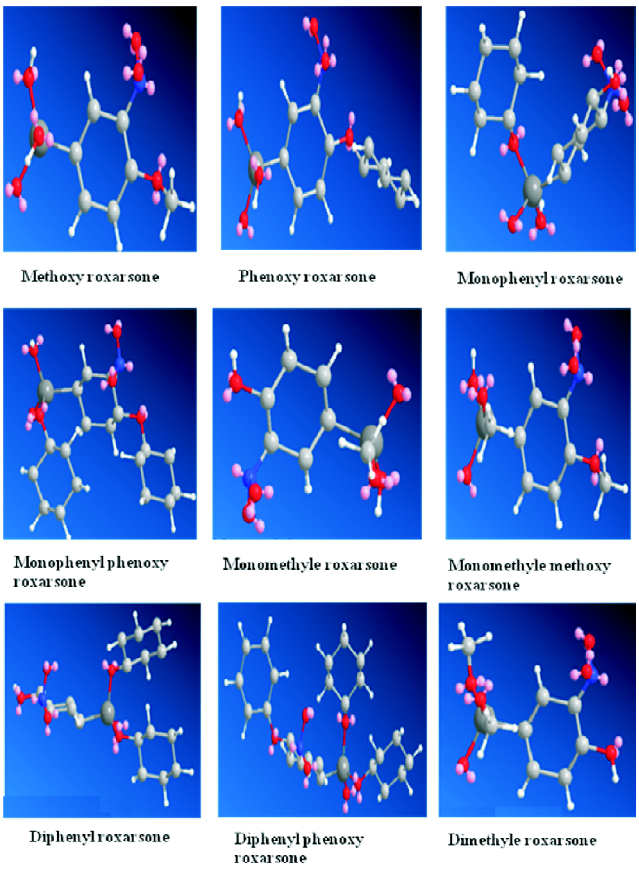

Fig. 1. Optimzed geometry of different roxarsone derivatives.

scriptors can be determined with the help of Koopmans' theorem[19]. According to this theorem ionization potential (*I*) and electron affinity (*A*) of a molecular system can be expressed in terms of the energies of the frontier molecular orbital's (FMOs) as:

$I = -E_{HOMO}$ and $A = -E_{LUMO}$. The hardness is calculated using the equation [$\eta = I - A$], the global electrophilicity index [$\omega = \chi^2/2\eta$], involving electronegativity [$\chi = (I + A)/2$][20–24]. The thermodynamic stability and reactivity of molecular system may be meaningfully justified from the scrutiny of their chemical hardness (η) and electrophilicity (ω) values. This has been further validated by the principle of maximum hardness[25,26] with minimum electrophilicity principle[27,28]. In another way, higher the band gap ($E_{HOMO} - E_{LUMO}$) higher the stability and lower the band gap more reactive species is to be considered[24]. These electronic structure principles act as major determinants towards assessing the stability and reactivity trends of different chemical system.

Virtual screening:

In this study, different arsenical compounds of roxarsone derivatives (methoxy roxarsone, phenoxy roxarsone, mono-phenyl roxarsone, mono-phenyl phenoxy roxarsone, mono-methyl roxarsone, mono-methyl methoxy roxarsone, di-phenyl roxarsone, di-phenyl phenoxy roxarsone, di-methyl roxarsone) were chosen to analyze the *in silico* interaction between each of these derivatives with RdRp of SARS-CoV-2 (PDB: 6NUR) and at the same time with the Receptor Binding Domain (RBD) of S-Glycoprotein[29] of SARS-CoV-2 (GenBank Accession No. QHR63250.1). The target receptor RdRp was chosen as it is the site where viral RNA synthesis starts, and RBD is the receptor binding domain of spike[30] glycoprotein where ligand used to bind and stops the viral replication. Each arsenical compound was undergone energy minimization using ChemBio3DUltra 13.0 software, a high quality workstation where MM2 energy minimization of each molecule was identified with stable molecular conformation (Fig. 1). Minimum RMS gradient was taken as 0.010. The iGEMDOCK v2.1 software was used for the docking studies of different arsenical roxarsone derivative with RdRp of SARS-CoV-2 as well as RBD of SARS-CoV-2. The iGEMDOCK software was implemented with generic evolutionary algorithm (GA) carry out automated molecular dockings. AutoDock Vina software was also used for the docking analysis. The software can work through AutoDock Tools (ADT) or Pyrex tools[31]. The macromolecules were cleaned from water residues and Gasteiger charges were calculated. The ligands and macromolecules were uploaded in the Pyrex tool[32]. Thereafter, the files were converted into pdbqt format. The RBD region present in the spike glycoprotein was first selected and executed for modelling the 3-D structure of the receptor. The receptor binding motif present within the RDB is the main active/catalytic site where the ligand comes and binds with it thus acts as inhibitor in viral entry to the host cell. The modelling was done using Phyre2 server[33,34] and viewed in PyMOL software.

Results and discussion

From the primary screening by *in silico* study of optimized roxasone derivatives, di-phenyl phenoxy roxarsone is one of the efficient molecules to mitigate the corona virus infection.

While optimizing all roxarsone derivatives (arsenical compounds), the conceptual density functional theory (CDFT) based reactivity descriptors are widely used to calculate the stability and reactivity of molecules. In relation to the Koopmans' theorem[19], the ionization potential (*I*) and electron affinity (*A*) of a molecular system can be articulated in terms of the energies of the frontier molecular orbital's (FMOs). In another way, higher the band gap ($\Delta E = E_{HOMO} - E_{LUMO}$) higher the stability and lower the band gap more reactive species is to be considered[21–25]. These electronic structure principles act as major determinants towards assessing the stability and reactivity trends of different chemical system.

It is found that among these roxarsone derivatives, four molecules are potent reactive towards lead drug i.e. mono-phenyl roxarsone, mono-phenyl phenoxy roxarsone, di-phenyl roxarsone, and di-phenyl phenoxy roxarsone. They are the less stable, more reactive among all and the reactivity order is di-phenyl roxarsone > di-phenyl phenoxy roxarsone > mono-phenyl roxarsone > mono-phenyl phenoxy roxarsone (Table 1). While the data are calculated from the optimized geometry of the compounds in gas phase and individual molecular reactivity was considered, the trend may slightly varied in solvent phase or within biological environment. This is exactly happened in our docking study. The chemical reactivity of di-phenyl roxarsone and di-phenyl phenoxy roxarsone are nearly same, docking study shows that di-phenyl phenoxy roxarsone show more efficacy among all screened molecules. Di-phenyl phenoxy roxarsone shows a very strong binding affinity with bacterial cell with strong electrostatic force of attraction. The presence of phenoxy group make the molecule energetically more favourable in its ground state configuration having a good electron mobility making di-phenyl phenoxy roxarsone towards strong binding agent with RdRp of corona virus with strong electrostatic interaction.

The RNA-dependent RNA polymerase (RdRp) (Fig. 2A), catalyzes the viral RNA synthesis by actively participating in the replication and transcription cycle of corona virus, with the association of nsp7 and nsp8. The structure of RdRp of SARS-CoV-2 comprises seven conserved polymerase motifs (A, B, C, D, E, F, G) in RdRp. The catalytic residues which are mainly the target site present in Motif A comprised residues 611-TPHLMGWDYPKCDRAM-626; and Motif C comprising residues 753-FMSSILSDDAVVCFN-767. Some hydrophobic residues including K545, R553 and R555 in F motif helps in the formation of nucleosite triphosphase entry channel. The entry of RNA template is the site of Motif A and Motif C through which a groove was clamped by Motif F and Motif G. The primer strand was supported by Motif E and the thumb subdomain. The product-template hybrid exits the active site through the RNA exit tunnel which is situated at the front side of polymerase[35]. Similarly another target receptor was chosen, spike glycoprotein of SARS-CoV-2 which causes disaster in Wuhan city. The overall topology of SARS-CoV-2 spike glycoprotein monomer consist of fusion peptides such as heptad repeat 1, heptad repeat 2, intracellular domain, N-terminal domain, receptor binding domain, subdomain 1,

Table 1. CDFT based reactivity parameters of studied compounds

Com. No.	Compd.	Energy (au)	(HOMO-LUMO) (au)	IP (*I*) (au)	EA (*A*) (au)	Electronegativity (χ) (au)	Hardness (η) (au)	Electrophilicity (ω) (au)
1.	Methoxy roxarsone	–783.544	0.160	0.2768	0.1169	0.1969	0.1599	0.0031
2.	Phenoxy roxarsone	–975.252	0.159	0.2767	0.1178	0.1971	0.1591	0.00309
3.	Mono-phenyl roxarsone	–975.254	0.127	0.2490	0.1221	0.1856	0.1268	0.00218
4.	Mono-phenyl phenoxy roxarsone	–1206.259	0.128	0.2464	0.1184	0.1824	0.1280	0.00213
5.	Mono-methyl roxarsone	–783.541	0.164	0.2842	0.1199	0.2021	0.1642	0.00335
6.	Mono-methyl methoxy roxarsone	–822.838	0.159	0.2744	0.1156	0.1950	0.1588	0.00302
7.	Di-phenyl roxarsone	–1206.262	0.119	0.2406	0.1212	0.1809	0.1193	0.00195
8.	Di-phenyl phenoxy roxarsone	–1437.267	0.120	0.2389	0.1187	0.1788	0.1202	0.00192
9.	Di-methyl roxarsone	–1102.269	0.163	0.2806	0.1178	0.1992	0.1628	0.00320

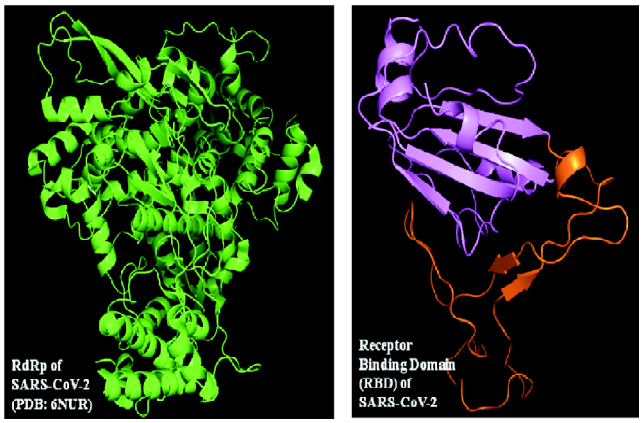

Fig. 2. RNA dependent RNA polymerase (RdRp) structure of SARS-CoV-2 viewed in PyMOL **(A)** Modelling of receptor binding domain of spike glycoprotein of SARS-CoV-2 using Phyre 2 server viewed in PyMOL **(B)**.

the same time with the residues R553, R555, V557 and K545 which is the entry channel of RNA template. Thus by blocking the active site the inhibitor di-phenyl phenoxy roxarsone helps to stop the further synthesis of RNA (Fig. 3A and 3B). *In silico* docking study of all roxarsone derivative with receptor binding domain present in spike protein of SARS-CoV-2 clearly depicts, di-phenyl phenoxy roxarsone to have greater binding free energy (–113.3 kcal/mol) in all respect. All interaction study including binding free energy and site of interaction are summarized in Table 3. The amino acid sequence of the modelled structure of receptor binding domain showed in Fig. 4A. In the interaction of di-phenyl phenoxy roxarsone with receptor binding domain present in spike glycoprotein of SARS-CoV-2, the residues involved are R136, R139, K140, D149, S151 and D153 (Fig. 4B).

Table 2. Interaction of different roxarsone derivative with RdRp of SARS-CoV-2

Receptor	Ligand	Binding free energy (kcal/mol)	Binding site
RdRp (6NUR)	Methoxy roxarsone	–67.17	Ala383, PRO328, Val330, Val398
RdRp (6NUR)	Phenoxy roxarsone	–73.72	Leu207, Asp208, His133, Thr206, Leu240
RdRp (6NUR)	Mono-phenyl roxarsone	–79.6	Asp452, Arg553, Lys621, Arg624, Tyr455, Asp623
RdRp (6NUR)	Mono-phenyl phenoxy roxarsone	–74.87	Asp235, Asn734, Arg735, Ile233, Arg733
RdRp (6NUR)	Mono-methyl roxarsone	–84.66	Asp452, Arg553, Arg555, Thr556, Arg624, Asp623
RdRp (6NUR)	Mono-methyl methoxy roxarsone	–74.31	Asp235, Asp291, Asn734, Arg735, Ile233
RdRp (6NUR)	Di-phenyl roxarsone	–80.9	Asp390, Lys391, Arg392, Val405, Phe407
RdRp (6NUR)	Di-phenyl phenoxy roxarsone	–86.8	Arg553, Arg555, Lys545, Val557, Asp623, Arg624, Ser682
RdRp (6NUR)	Di-methyl roxarsone	–80.2	Asp452, Arg553, Lys621, Asp623, Arg624, Tyr455

subdomain 2 and transmembrane region[36]. Receptor binding domain is the main target site of any ligand that binds to the spike protein. Here the target motif is present within the receptor binding domain where di-phenyl phenoxy roxarsone comes and binds. The modelling of receptor binding domain (RBD) was done using Phyre 2 server and viewed in PyMOL (Fig. 2B). From the docking study, it clearly reveals that out of all roxarsone derivatives, di-phenyl phenoxy roxarsone has higher binding affinity (–86.8 kcal/mol) in respect to other compounds when interacting with RdRp of SARS-CoV-2. The binding free energy of all roxarsone derivatives with RdRp was enlisted in Table 2. The ligand binds with the residues D623, R624 which is present in the Motif A of RdRp and at

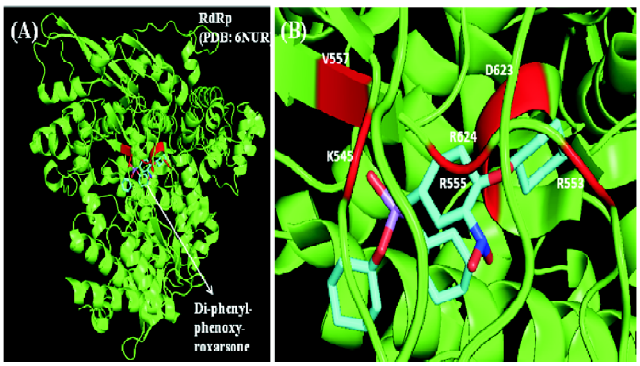

Fig. 3. Interaction of RNA dependent RNA polymerase (RdRp) with di-phenyl phenoxy roxarsone viewed in PyMOL **(A)** Zoomed image of ligand binding site viewed in PyMOL **(B)**.

Table 3. Interaction of different roxarsone derivative with receptor binding domain of spike glycoprotein of SARS-CoV-2

Receptor	Ligand	Binding free energy (kcal/mol)	Binding site
Receptor binding domain of SARS-CoV-2	Methoxy roxarsone	–74.3	Arg136, Asp149, Ser151, Glu153, Tyr155
Receptor binding domain of SARS-CoV-2	Phenoxy roxarsone	–92.14	Arg136, Arg139, Asp149, Ser151, Lys140, Glu153, Tyr155
Receptor binding domain of SARS-CoV-2	Mono-phenyl roxarsone	–85.3	Gln156, Ser159, Arg139, Lys140, Ser159.
Receptor binding domain of SARS-CoV-2	Mono-phenyl phenoxy roxarsone	–96.71	Arg136, Arg139, Asp149, Ser151, Lys140, Glu153, Tyr155
Receptor binding domain of SARS-CoV-2	Mono-methyl roxarsone	–75.79	Gln156, Ser159, Thr160, Lys140, Glu153, Tyr155
Receptor binding domain of SARS-CoV-2	Mono-methyl methoxy roxarsone	–73.02	Lys140, Ser159, Thr160, Pro161, Glu153, Tyr155
Receptor binding domain of SARS-CoV-2	Di-phenyl roxarsone	–80.3	Ser151, Ile154, Gln156, Arg139, Lys140, Asp149, Glu153, Tyr155
Receptor binding domain of SARS-CoV-2	Di-phenyl phenoxy roxarsone	–113.3	Arg136, Arg139, Asp149, Ser151, Lys140, Glu153
Receptor binding domain of SARS-CoV-2	Di-methyl roxarsone	–77.08	Gln156, Ser159, Thr160, Lys140, Glu153, Tyr155

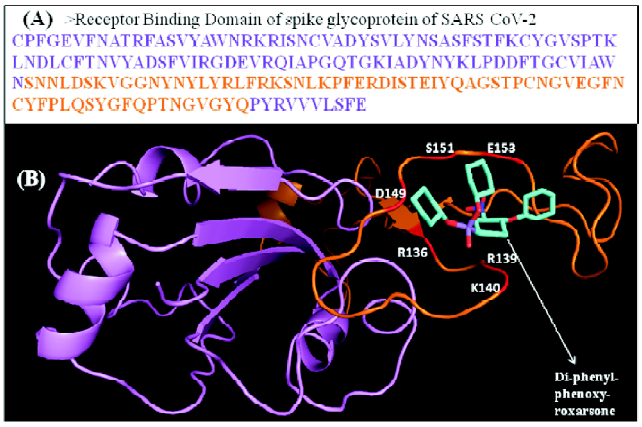

Fig. 4. Amino acid sequence of Receptor Binding Domain of spike glycoprotein of SARS-CoV-2 (A). Interaction of Receptor Binding Domain (RBD) with di-phenyl phenoxy roxarsone viewed in PyMOL (B). Violet highlighted portion depicts the receptor binding domain, whereas orange highlighted portion depicts the receptor binding motif of spike glycoprotein of SARS-CoV-2.

Conclusions

From the *in silico* analysis including DFT calculations, it is confirmed that di-phenyl phenoxy roxarsone have greater binding affinity to RdRp and RBD of SARS-CoV-2, among all other roxarsone optimized derivatives. This study seems to believe that it stop the replication of virus as it binds to RdRp. Simultaneously, the affinity to Spike protein may also inhibit the entry of virus particle into the cell. This effective drug needs to pass through different trials in patients for the need of developing therapeutic drugs against COVID-19. Thus di-phenyl phenoxy roxarsone may be a potential and promising antiviral agent for COVID-19.

Dedication and Acknowledgement

The author GR dedicates this article to the loving memory of Late Smt. Tamalika Panda Seth, Co-founder of Haldia Institute of Technology (HIT), on the occasion of her 64th Birth Anniversary on August 06, 2020. All of the authors sincerely acknowledge the infrastructure support provided by HIT Haldia and IIT Kharagpur, India, for this research.

References

1. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen
2. C. Liu, Q. Zhou, Y. Li, L. V. Garner, S. P. Watkins, L. J. Carter, J. Smoot, A. C. Gregg, A. D. Daniels, S. Jervey and D. Albaiu, *ACS Central Science*, 2020, **6(3)**, 315.
3. I. I. Bogoch, A. Watts, A. Thomas-Bachli, C. Huber, M. U. G. Kraemer and K. Khan, *J. Trav. Med.*, 2020, **27(2)**, taaa008. doi:10.1093/jtm/taaa008.
4. https://covid19.who.int/?gclid=CjwKCAjwjLD4BRAiEiwAg5NBFIrddIZ-GgC4Ti_uFp0BOovrvZ9F0 zkzMSnrjdgrmSmjGKfmGrfeeBoCXj4QAvD_BwE.

5. B. Shah, P. Modi and S. R. Sagar, *Life Sciences*, 2020, **252**, 117652.
6. A. A. Elfiky, *Life Sciences*, 2020, **248**, 117477.
7. D. Wrapp, W. NianShuang, K. S. Corbett, J. A. Goldsmith, C.-L. Hsieh, O. Abiona, B. S. Graham and J. S. McLellan, *Science*, 2020, **367(6483)**, 1260.
8. A. M. Baig, A. Khaleeq, U. Ali and H. Syeda, *ACS Chem. Neurosci*., 2020, **11 (7)**, 995.
9. C. Sohrabi, Z. Alsafi, N. O'Neill, M. Khan, A. Kerwan, A. Al-Jabir, C. Iosifidis and R. Agha, *Int. J. Surg*., 2020, **76**, 71.
10. C. A. Devaux, J.-M. Rolain, P. Colson and D. Raoult, *Int. J. Antimicrob. Agents*, 2020, **55(5)**, 105938.
11. https://www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19.
12. https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or.
13. M. S. Murgueitio, M. Bermudez, J. Mortier and G. Wolber, *Drug Discov. Today Technol.*, 2012, **9(3)**, e-219.
14. T. Chowdhury, G. Roymahapatra and S. M. Mandal, *Infectious Disorders-Drug Targets,* 2020 DOI: 10.2174/1871526520666200727153643 (In Press).
15. L. M. Del Razo, B. Quintanilla-Vega, E. Brambila-Colombres, E. S. Calderón-Aranda, M. Manno and A. Albores, *Toxicol. Appl. Pharmacol.,* 2001, **177**, 132.
16. M. Kuroki, Y. Ariumi, M. Ikeda, H. Dansako, T. Wakita and N. Kato, *J. Virol.,* 2009, **83**, 2338.
17. T. Samanta, G. Roymahapatra, W. F. Porto, S. Seth, S. Ghorai, S. Saha, J. Sengupta, O. L. Franco, J. Dinda and S. M. Mandal, *PLoS One*, 2013, **8(3)**, e58346.
18. Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford CT, 2013. (b) Gaussian 16, Revision C.01, Gaussian, Inc., Wallingford CT, 2016.
19. T. A. Koopmans, *Physica,* 1933, **1**, 104.
20. R. G. Parr, Lv. Szentpaly and S. Liu, *J. Am. Chem. Soc.,* 1999, **121**, 1922.
21. P. K. Chattaraj, U. Sarkar and D. R. Roy, *Chem. Rev.,* 2006, **106(6)**, 2065.
22. S. Das Adhikary, T. Samanta, G. Roymahapatra, F. Loiseau, D. Jouvenot, S. Giri, P. K. Chattaraj and J. Dinda, *New J. Chem.*, 2010, **34**, 1974.
23. G. Roymahapatra, S. M. Mandal, W. F. Porto, T. Samanta, S. Giri, J. Dinda, O. L. Franco and P. K. Chattaraj, *Current Med. Chem.,* 2012, **19**, 4184.
24. G. Roymahapatra, T. Samanta, S. K. Seth, A. Mahapatra, S. K. Chattopadhyay and J. Dinda, *J. Chem. Sci.,* 2015, **127(6)**, 1057.
25. R. G. Parr, *Ann. Rev. Phys. Chem.*, 1983, **34**, 631.
26. D. Becke, *J. Chem. Phys.*, 1993, **98(7)**, 5648.
27. S.-m. Gao and Y.-h. Ding, *RSC Adv.*, 2012, **2**, 11764.
28. J.-D. Chai and M. Head-Gordon, *Phys. Chem. Chem. Phys*., 2008, **10**, 6615.
29. A. Spinello, A. Saltalamacchia and A. Magistrato, *J. Phys. Chem. Lett.,* 2020, **11(12)**, 4785.
30. S. L. Rath and K. Kumar, Cold Spring Harbor Laboratory, *bioRxiv*, 2020, doi: https://doi.org/10.1101/2020.06.10.145086.
31. R. B. Jacob, T. Andersen and O. M. McDougal, *PLoS Comput. Biol.,* 2012, **8(5)**, e1002499.
32. K. Yellamma, S. Nagaraju, K. Peera and K. Praveen, *Int. J. Pharm. Sci. Rev. Res.,* 2013, **22(2)**, 296.
33. L. A. Kelly, S. Mezulis, C. M. Yates, M. N. Wass and M. J. E. Sternberg, *Nature Protocols*, 2015, **10(6)**, 845.
34. T. Chowdhury, M. Sarkar, B. Chaudhuri, B. Chattopadhyay and U. C. Halder, *J. Biol. Inorg. Chem.*, 2015, **20(5)**, 791.
35. Y. Gao, L. Yan, Y. Huang, F. Liu, Y. Zhao, L. Cao, T. Wang, Q. Sun, *et al.,* 2020, 368, 6492, 779 DOI: 296 10.1126/science.abb7498.
36. J. Lan, J. Ge, J. Yu, S. Shan, H. Zhou, S. Fan, Q. Zhang, X. Shi, Q. Wang, L. Zhang and X. Wang, *Nature*, 2020, **581(7807)**, 215.