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COMPUTER AIDED COMPARISON OF THE NEW ORAL DRUG MOLNUPIRAVIR AND INDEPENDENTLY DESIGNED AND PREVIOUSLY REPORTED DRUG LIKE MOLECULE (HAD-08)

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ABSTRACT

The medicinal scientists and drug researchers around the world are facing various complicated challenges always but particularly in this pandemic period. They are constantly trying to overcome the hurdles of the puzzles given by the COVID-19. In this research work a computer aided comparison of the newly introduced oral drug Molnupiravir and an independently designed and previously reported drug like molecule (HAD-08) are compared without any prejudices.

KEYWORDS: Molnupiravir, designed molecule (HAD-08), Drug discovery, COVID-19, SARS CoV-2, Docking, ArgusLab 4.0.1, T.E.S.T.

INTRODUCTION

The pandemic COVID-19 caused by the SARS CoV-2 virus and its various reported variants are perplexing the scientific community since December 2019. Many of the microbes and especially otherwise facultative pathogens get new pathogenicity or higher drug-resistance capacities as a result of blind academic and industry researches. Various chemicals or synthesized compounds that cannot be even called drugs or near drugs are found screening against many pathogens to observe their antimicrobial activities by researchers. Such blind research studies result the Drug Resistances in the highest possible manner so that the pathogens are found even resistant to multiple drug therapy.[1] The present pandemic COVID-19 might also be a result of the destructive researches for biological weapons to get superiority over others. Now the scientists are contributing to help the community to overcome the hurdles of this present pandemic by dedicating their entire time, studies, knowledge and researches. The computational scientists and drug researchers are also tirelessly trying to identify the leads, designing the drug like molecules, predicting the

efficacies and *in silico* QSAR studies etc. The discovery and development of a new chemical entity with demonstrated therapeutic utility is usually a long and arduous process. Industry statistics suggest that up to 10000 compounds are synthesized and tested, up to 100 compounds are assessed for safety, and up to 10 compounds are tested clinically in humans for every drug that is finally approved for medical use. Even when a drug is approved for marketing, the final success is not assured or guaranteed due to the lack of its sufficient efficacious in practice or because of its undesirable side effects. This long process of finding the possible leads, identifying and screening to get proposed plausible ones and one could be a successful drug finally can be correlated to the words of Lord Krishna in Bhagavad Gita.[2] The lead molecule is the molecule showing a desired pharmacological property that could be used to initiate a medicinal chemistry drug design and development research project. Generally natural products and their derivatives could be selected as lead molecules. Most of the successful drugs of the present market are either obtained from natural source or were developed from a lead molecule originally obtained from natural source. The choice and selection of lead structures is very important for success in drug development.[3] This work becomes very challenging to identify and discover new leads to many diseases for which effective therapeutic agents are still not available and the same is also applicable in the case of COVID-19 pandemic. The majority of the drugs on the present market to treat various diseases and syndromes were discovered by chance observations or by systematic screening of large series of synthetic and natural substances or their derivatives. The computer assisted designing of the drug like molecules within a short span of time to identify suitable one that is effective for the treatment of the COVID-19 was started with screening of the leading antiviral drugs. That helped to design a protocol for the compassionate therapy of a less researched disease using the present known antivirals.[4] The research studies for finding suitable leads from the natural products including vitamins were conducted systematically.[5,6] Based on the previous studies suitable drug like molecules were designed and screened to suggest the most suitable serieses.[7] Recently a new oral drug for treating COVID-19 was introduced to the market called Molnupiravir in 2021 by Merck & Co., Inc., Kenilworth, N.J., USA. This new molecule Molnupiravir is the orally administered form of a potent ribonucleoside analogue that inhibits the replication of SARS-CoV-2, the causative agent of COVID-19.[8,9] The present research paper compares one of those previously reported independently designed drug like molecules (HAD-008) with the newly approved oral drug Molnupiravir by applying the same methodologies adopted in the previously reported works.

The results obtained from the computer aided drug designing processes were reported and compared without any prejudices.

MATERIALS AND METHODS

The present research being purely theoretical and computational in nature it requires neither chemicals nor sophisticated instruments for analysis but only computers and interdisciplinary knowledge, an essential skill for the computer assisted drug designing. The reported 6yb7.pdb was downloaded from the website and assigned the binding sites.[10] The structure drawing of the molecules was achieved using ACD/ChemSketch (Freeware) 2019.2.2 version.[11] The work was carried out using free docking software like ArgusLab 4.0.1 and a laptop with Intel(R) Core (TM) i3 1.20GHz processor working on Windows 10, 64bit operating system with 4GB RAM having an internet connection [12]. The toxicity predicting free software T.E.S.T. developed by EPA, US was also used to predict the toxic study endpoints or parameters.[13]

Experimental

In this research paper the comparison of the newly suggested drug for treating COVID-19 namely Molnupiravir and independently designed and a previously reported drug like molecule (HAD-08) was carried out without any prejudices or presumptions. The structures of the molecules understudy were optimized geometrically. The reported protein databank file (6yb7.pdb) was used for docking studies in ArgusLab. The structures of the molecules were also screened with free toxicity estimation software for estimating various toxicity endpoints like Fathead minnow (LC50; 96 Hour), *Daphnia magna* (LC50; 48 Hour), *Tetrahymena pyriformis* (IGC50; 48 Hour), Oral rat (LD50), Bioaccumulation factor, Developmental toxicity and Ames mutagenicity by adopting available methods like Hierarchical Method (HM), FDA method, Single Model Method (SMM), Group Contribution Method (GCM), Nearest Neighbour Method (NNM), Consensus Method (CM), Random Forest Method (RFM) and Mode of action method. The ACD/ChemSketch (Freeware) 2019.2.2 was used to predict various properties like Composition, Molar Refractivity, Molar Volume, Parachor, Index of Refraction, Surface Tension, Density, Dielectric Constant, Polarizability, Ring Double Bond Equivalent (RDBE) etc. as well as to draw, optimize and name the molecules. The results obtained from the studies are tabulated, compared and discussed (Figure 01 and Figure 02).

Molecule Name: Molnupiravir

SMILES Notation

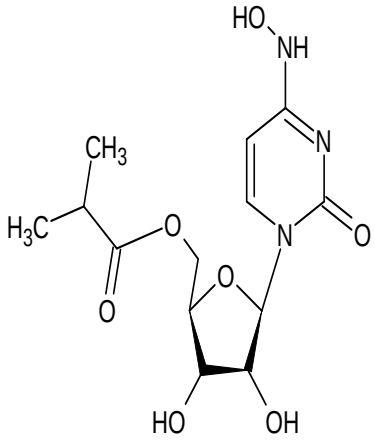
CC(C)C(=O)OC[C@H]1O[C@@H](N2C=CC(=NC2=O)NO)C(O)C1O

Chemical Name (IUPAC)

{(2*R*,3*S*,4*R*,5*R*)-3,4-dihydroxy-5-[4-(hydroxyamino)-2-oxopyrimidin-1(2*H*)-yl]oxolan-2-yl}methyl 2-methylpropanoate

Log P (Calculated): -0.80+/- 0.80

Chemical Structure



Predicted properties

Molecular Formula:	$C_{13}H_{19}N_3O_7$
Formula Weight:	329.30586
Composition:	C(47.41%) H(5.82%) N(12.76%) O(34.01%)
Molar Refractivity:	74.09 ± 0.5 cm^3
Molar Volume:	202.7 ± 7.0 cm^3
Parachor:	571.9 ± 8.0 cm^3
Index of Refraction:	1.651 ± 0.05
Surface Tension:	63.3 ± 7.0 dyne/cm
Density:	1.62 ± 0.1 g/cm^3
Dielectric Constant:	Not available
Polarizability:	29.37 ± 0.5 $10^{-24}cm^3$
RDBE:	6
Monoisotopic Mass:	329.1223 Da
Nominal Mass:	329 Da
Average Mass:	329.3059 Da
M+:	329.121751 Da
M-:	329.122849 Da
[M+H]+:	330.129576 Da
[M+H]-:	330.130674 Da
[M-H]+:	328.113926 Da
[M-H]-:	328.115024 Da

Figure 01: The predicted properties of the Molnupiravir.

Molecule Name: HAD-008

SMILES Notation

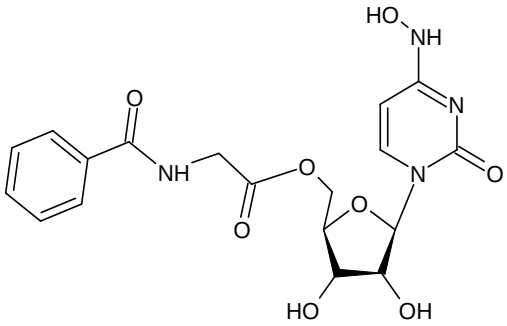
O=C(NCC(=O)OC[C@H]1O[C@@H](N2C=CC(=NC2=O)NO)C(O)C1O)c1ccccc1

Chemical Name (IUPAC)

{(2*R*,3*S*,4*R*,5*R*)-3,4-dihydroxy-5-[4-(hydroxyamino)-2-oxopyrimidin-1(2*H*)-yl]oxolan-2-yl}methyl benzamidoacetate

Log P (Calculated): -1.04+/- 0.87

Chemical Structure



Predicted properties

Molecular Formula:	$C_{18}H_{20}N_4O_8$
Formula Weight:	420.3734
Composition:	C(51.43%) H(4.80%) N(13.33%) O(30.45%)
Molar Refractivity:	98.86 ± 0.5 cm^3
Molar Volume:	258.2 ± 7.0 cm^3
Parachor:	750.6 ± 8.0 cm^3
Index of Refraction:	1.691 ± 0.05
Surface Tension:	71.4 ± 7.0 dyne/cm
Density:	1.62 ± 0.1 g/cm^3
Dielectric Constant:	Not available
Polarizability:	39.19 ± 0.5 $10^{-24}cm^3$
RDBE:	11
Monoisotopic Mass:	420.128114 Da
Nominal Mass:	420 Da
Average Mass:	420.3734 Da
M+:	420.127565 Da
M-:	420.128662 Da
[M+H]+:	421.13539 Da
[M+H]-:	421.136487 Da
[M-H]+:	419.11974 Da
[M-H]-:	419.120837 Da

Figure 02: The predicted properties of the designed drug like molecule HAD-008.

Docking and Toxicity studies

The Molnupiravir on docking has showed a BLPE of -5.44599 k cal mol^{-1} and UPC 661. Similarly, the second molecule HAAD-008 on docking has showed a BLPE of -5.4945 k cal mol^{-1} and UPC 552. The results of predicted and computed Toxicological studies by applying Nearest Neighbour Method (NNM) where the predicted toxicity is estimated by taking an average of the 3 chemicals in the training set that are most similar to the test chemical. Various fundamental toxicological end points like Fathead minnow (LC_{50}; 96 Hour), *Daphnia magna* (LC_{50}; 48 Hour), *Tetrahymena pyriformis* (IGC_{50}; 48 Hour), Oral rat (LD_{50}), Bioaccumulation factor, Developmental toxicity and Ames mutagenicity were estimated

using NNM. The estimated toxicity results are tabulated for general comparison (Table 01). Some end points were not computable based on NNM as the insufficient nearest neighbours in the training set were available to make a prediction.

Table 01: The toxicological end points with estimated/computed values.

End point	Molnupiravir	HAD-008
Fathead minnow (LC_{50} ; 96 Hour) mg/L	0.31	1.10E-02
D. magna (LC_{50} ; 48 Hour) mg/L	2.80	112.72
T. pyriformis (IGC_{50} ; 48 Hour) mg/L	21.69	10.97
Oral rat (LD_{50}) mg/kg	3313.49	4152.89
Bioaccumulation factor	N/A (Not computable)	4.27
Developmental toxicity	N/A (Not computable)	N/A (Not computable)
Ames mutagenicity	Mutagenicity Negative (Value: 0.00)	Mutagenicity Negative (Value: 0.33)

All the other methods except NNM were found not able to make a prediction or estimation of the proposed toxicity endpoints. From the predicted Oral rat (LD50) results the safe doses for humans could be computed as all know.

RESULTS AND DISCUSSION

The Molnupiravir has secured a BLPE of -5.44599 k cal mol^{-1} and UPC 661 while the second molecule HAAD-008 has also showed a BLPE of -5.4945 k cal mol^{-1} and UPC 552. Both the molecules passed the threshold values of BLPE and UPC set by the previous research studies based on Chloroquine and Hydroxychloroquine (-5.0000 k cal mol^{-} & 500). The docking results were found comparable and based on BLPE the HAD-008 is found more effective while based on the UPC values the Molnupiravir is found more effective. The estimated values of toxicological end points were found comparable and based on the computed values HAD-008 has many advantages as evident from the table. The predicted log P values of the Molnupiravir and HAD-008 were -0.80 +/-0.80 and -1.04 +/-0.87 respectively. The molecular weights of both the molecules were found below 500 g mol^{-1}. All these were in support to the drug likeness of both the molecules understudy.

CONCLUSION

The newly discovered oral drug Molnupiravir and one of the previously reported independently designed drug like molecules (HAD-008) from the two different series (AAD and HAD series) were compared. The results were found comparable and, in some parameters, the designed drug molecule (HAD-008) was found more preferable while in some other parameters the Molnupiravir showed advantages. Some of the previously designed and reported series of drug like molecules (AAD and HAD series) have more advantages over both these molecules. Even though certain vaccines were developed by many research organizations within a short span of time and were implemented and supported by Government agencies, the pandemic is still pervading without any border limitations. Similarly certain medicaments developed by some leading alternative systems of medicine organisations (both private and government) have also got introduced for controlling the pandemic.[14] This supports the urgent need of implementing wholistic treatment approaches to control the pandemic fruitfully. That indicates the possibilities of the alternative systems of medicines and naturopathic methodologies that could be adopted in a complimentary manner in the treatment protocols for the present pandemic. The present research not only shows the importance of the Computer Aided Drug Designing (CADD) but also points to the need of urgent attention of the authorities and scientific communities to overcome the barriers and borders of narrow mindedness by taking necessary deeds without any prejudices. Each and every branch of knowledge systems can play important and crucial roles whenever suitably and logically adopted wherever required during the processes of drug research. This alone can lead the scientific community to the universal goal of finding the best solution for protecting the life in the planet.

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