



# **Synthetic Advances against Coronaviruses: A Short Review of the Recent Literature on Newly Synthetized Derivatives and Recently Developed Strategies**

**Weiam Hussein<sup>1,2\*</sup>, Fawaz Alheibshy<sup>3,4</sup> and Farhan Alshammari<sup>3</sup>**

<sup>1</sup>Department of Pharmaceutical Chemistry, College of Pharmacy, University of Hail, 2240/Hail, KSA.

<sup>2</sup>Department of Pharmaceutical Chemistry, College of Pharmacy, Aden University, 6075/Aden, Yemen.

<sup>3</sup>Department of Pharmaceutics, College of Pharmacy, University of Hail, 2240/ Hail, KSA.

<sup>4</sup>Department of Pharmaceutics College of Pharmacy, Aden University, 6075/Aden, Yemen.

## **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

## **Article Information**

DOI: 10.9734/JPRI/2021/v33i34B31861

### Editor(s):

(1) Dr. Takashi Ikeno, National Center of Neurology and Psychiatry, Japan.

(2) Prof. Mohamed Fawzy Ramadan Hassanien, Zagazig University, Egypt.

(3) Dr. Alyautdin Renad N, Scientific Centre for Expert Evaluation of Medicinal Products, Russia.

### Reviewers:

(1) Robert Suslo, Wroclaw Medical University, Poland.

(2) Senthilraja M, J. K. K. Nattraja College of Pharmacy, India.

(3) Yohannes Markos Woldesenbet, Wolaita Sodo University, Ethiopia.

(4) Amit Sharma, National Institute of Tuberculosis and Respiratory Medicine (NITRD), India.

(5) Monika Kniolek, Medical University of Warsaw, Poland.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/69684>

**Mini-Review Article**

**Received 25 April 2021**

**Accepted 30 June 2021**

**Published 03 July 2021**

## **ABSTRACT**

The coronavirus pandemic is a modern social emergency and the biggest global challenge since the Second World War. Since the pandemic began in China at the end of 2019, the disease spread to every landmass except Antarctica. The effect of antiviral drugs on the new corona virus has been tested, but no basic and complete cure has been found, although there are many drugs such as interleukin-6 inhibitor, monoclonal antibody and corticosteroid which remarkably reduced mortality of critically ill COVID-19 patients in a major clinical trial. Although not enough experimental data has

\*Corresponding author: E-mail: [white.wf.rose@gmail.com](mailto:white.wf.rose@gmail.com);

been released yet, many researchers have hailed the result as a step in the right direction. In this review, a series of the newly chemical derivatives were synthesized and evaluated against human coronavirus. Many derivatives found to be active in inhibiting the cellular infection of human coronavirus which causes the SARS-CoV-2 pandemic. This mini- review summarizes the synthesis of these new antiviral derivatives that target coronaviruses and describes general current strategies and models for developing antiviral drugs. The review aims to provide a starting point for medicinal chemists to synthesize necessary and effective drugs against coronaviruses.

**Keywords:** *Anti-coronavirus; Recent synthetic methods; Recent development strategies.*

**Abbreviations:** Coronavirus infection 2019 (COVID-19), Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), The Food and Drug Administration (FDA), World Health Organization (WHO), severe acute respiratory syndrome (SARS), Middle East Respiratory Syndrome (MERS), non-structural protein 13 (nsp13), sulfuric acid (H<sub>2</sub>SO<sub>4</sub>), half-maximal effective concentration (EC<sub>50</sub>), human coronavirus 229E (HCoV-229E), Venezuelan equine encephalitis (VEE), tetra-n-butylammonium iodide (n-Bu)<sub>4</sub>NI, boron tribromide (BBr<sub>3</sub>), half-maximal inhibitory concentration (IC<sub>50</sub>), dimethylformamide (DMF),  $\beta$ -hydroxy  $\beta$ -methylglutaryl-CoA (HMG-CoA), hepatitis C virus (HCV).

## 1. INTRODUCTION

Infection with a novel zoonotic betacoronavirus entitled "Severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) has become a worldwide danger. The knowledge regarding SARS-CoV-2 and infection with this coronavirus (COVID-19) should be exhaustively summarized to upgrade control measures and settle on remedial choices like prevention and available therapies.

As indicated by the World Health Organization (WHO), coronaviruses create a wide spectrum of infections, from a mild cold to considerably more severe illnesses. Previously, two coronaviruses: severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) have caused significant outbreaks of infection. Now COVID-19 is similar to infections caused by other coronaviruses in that it presents with cold-like symptoms, it spreads more easily than SARS. More than 170,900,293 people have died from COVID-19 (30 May 2021), but the disease may be more widespread than current testing numbers suggest [1]. No drug has yet been identified that treats COVID-19. More than 150 different drugs, most of which were pre-existing treatments, are being tested worldwide. These

drugs comprise two different groups: antiviral drugs and drugs that create an antibody response (whether derived from survivors' blood or made in a lab; Gallagher, 2020). Included in these drugs are medications recently created to treat other viral infections, as they may likewise be successful against SARS-CoV-2 [2]. Early reports from China and France found that patients with extreme manifestations of COVID-19 improved more quickly when given chloroquine or hydroxychloroquine. A few doctors utilized a mix of hydroxychloroquine and azithromycin with some constructive outcomes. However, the latest studies on these treatments have found no advantage of hydroxychloroquine or azithromycin and potentially a higher risk of mortality due to heart rate variations, especially when the two medications are mixed. Therefore, the Food and Drug Administration (FDA) currently advises against the use of chloroquine or hydroxychloroquine for COVID-19 infection unless their use is supported in the medical clinic or as a major aspect of a clinical trial. Another medication that has received significant attention is the antiviral medication remdesivir. This drug helps limit the multiplication and spread of SARS and MERS infections and thus may also be effective against COVID-19 due to the similarity amongst coronaviruses. Furthermore, many studies found that, remdesivir was better than placebo treatment in shortening the opportunity to recuperation in grown-ups who were hospitalized with Covid-19 and had proof of lower respiratory tract infection. [3,4].

Nevertheless, no specific treatment for COVID-19 is currently available, and little evidence exists showing that the disease can be treated permanently with the above-mentioned drugs. Therefore, safe and effective treatment for COVID-19 is still needed. Medicinal chemists must try to find new synthetic methods either for developing existing drugs or making new, effective drugs that treat this disease. To accomplish this, the previous attempts to synthesize drugs that combat coronaviruses

must be understood to achieve quicker results. This short review mainly focuses on the recent research reported in the literature on the development of new synthetic derivatives to treat viruses in general and coronaviruses in particular to help researchers to discover therapies and prevent future crises.

## 2. METHODS (SEARCH STRATEGY)

The literature study was conducted using different well-known databases: PubMed, Science Direct, Web of Science, Scopus and Google Scholar. The articles were evaluated in detail and the summary information about the synthetic methods, test system, results, discussion and conclusion was also made. The main exclusion criteria were:

- Articles containing a method of synthesizing derivatives effective against viruses other than the corona virus (or of the same class of virus).
- Non-English-language articles.

## 3. RESULTS AND DISCUSSION

### 3.1 New Synthetic Derivatives to Treat Coronavirus Infections

Zhang et al. synthesized new amides as wide-spectrum inhibitors of coronavirus. Dimethyl ester derivatives were alkylated with bromoacetonitrile and then hydrogenated. After the cyclization reaction, the resulting intermediate produced lactam. The pivotal derivatives were obtained using the condensation of the lactam derivative and the amino acids. A Dess–Martin periodinane reagent was used to obtain the aldehydes, and then a nucleophilic addition with isocyanides was performed. The oxidation of the exposed alcohol

group generated the required amides. The best inhibitors were found to be cyclopentylmethyl and cyclohexylmethyl derivatives; these showed low micromolar half-maximal effective concentration ( $EC_{50}$ ) values against three types of coronavirus (enteroviruses, alphacoronaviruses, and betacoronaviruses) [5]. The major proteases of coronaviruses share a similar active site structure and unique requirements for glutamine. Due to the specificity of these proteases and their essential role in the processing of viral proteins, they are suitable targets for antiviral drug development. Therefore, the author tried to approximate the design of this compound to make it chemically similar to the design of peptidomimetic as major inhibitors of proteases. Fig. 1 shows the structures of the most active derivatives.

Zaher et al. [5] described the synthesis of new thiazole derivatives using hydrazine derivatives as a starting material. An equimolar quantity of 3-chlorocyclopent-1-ene and different phenyl hydrazine derivatives were continuously stirred at 150 °C for 5 min; this mixture produced good yields (75–91%) of a variety of hydrazinyl derivatives. The biological results showed that the most influential compounds were the chlorine and iodine derivatives as a result of all new compounds subjected to justification for their target structures by microanalytical and spectral data. The biological results showed that the most influential compounds were the chlorine and iodine derivatives (Fig. 2).

*In silico* molecular modelling of the most potent compounds was performed using an effective binding site of the coronavirus causing MERS (MERS-CoV) [6].

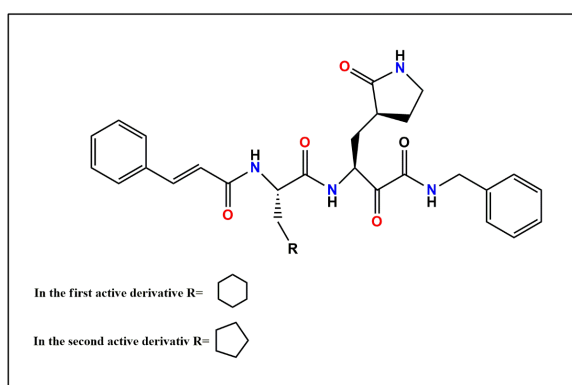
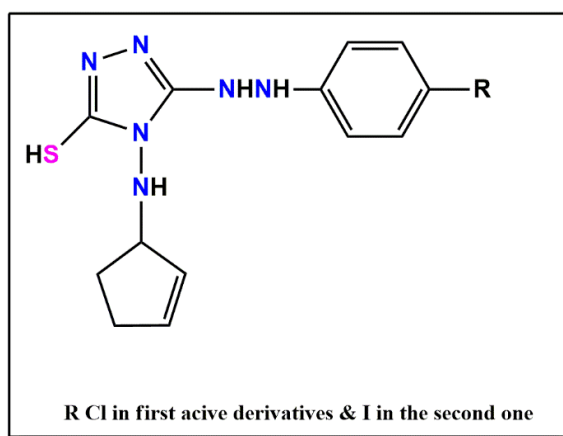


Fig. 1. The structures of the cyclopentylmethyl and cyclohexylmethyl derivatives



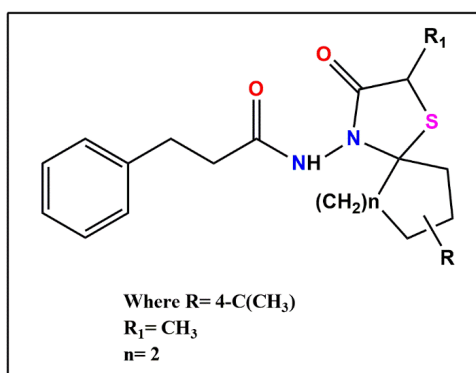
**Fig. 2. The structures of the most influential compounds synthesized in the article (Chlorine and Iodine derivatives)**

Çağla et al. described the synthesis of a series of compounds bearing an amide group to develop treatments for human coronaviruses and the influenza virus. First, hydrazides were obtained through acid esterification in methanol. Then, hydrazinolysis of esters was performed to produce the target derivatives. The structures of these derivatives were shared with already discovered class of hemagglutinin-specific influenza virus fusion inhibitors, which were found to be active. The strongest compound was N-(2-methyl-8-tert-butyl-3-oxo-1-thia-4-azaspiro[4.5]decan-4-yl)-3-phenylpropanamide (Fig. 3), which had an EC<sub>50</sub> value of 5.5 μM [7].

Konstantina et al. described the synthesis of a novel fused 1,2,3-triazole derivative. The use of Michael's addition of aniline onto ethyl acrylate was followed by Dieckmann condensation. The subsequent nucleophilic substitution with benzyl-bromide provided the starting material at a 65%

overall yield. Once the starting material was obtained, fused triazole formation began using a series of 1° amines and phenyl-azide. Five compounds showed promising antiviral properties against human coronavirus 229E (HCoV-229E; Fig. 4). Moreover, in silico studies of the main molecular interactions between these compounds and proteases, which is essential for the intracellular replication of the virus, reinforcing the hypothesis that the protease is the target protein of the effective antiviral derivatives. [8].

Peters et al. designed a series of nucleoside analogues based on the acyclic sugar scaffold of the acyclovir drug (Acyclovir is a FDA approved antivirals) and the flex-base of the fleximers. The obtained compounds were evaluated for their antiviral activity and found to be active against many types of coronaviruses (Fig. 5) [9].



**Fig. 3. The most active derivative synthesized in the article**

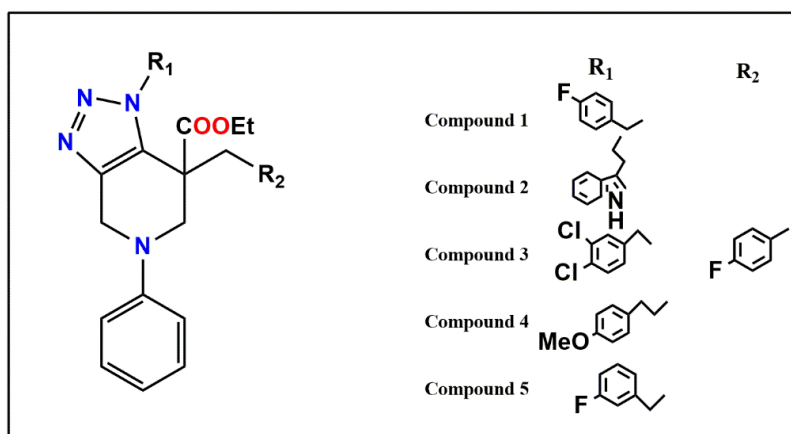


Fig. 4. Promising antiviral derivatives against human coronavirus

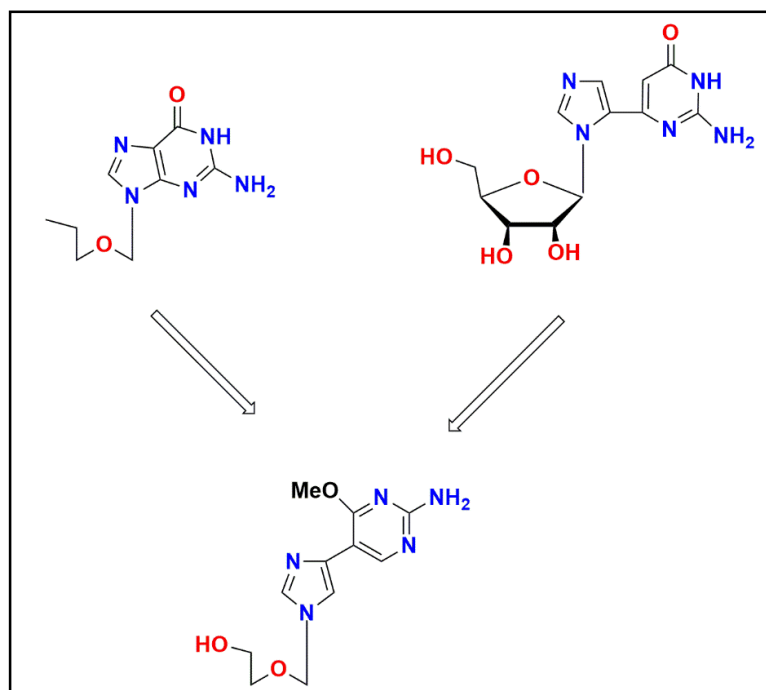


Fig. 5. Doubly flexible nucleoside analogs

Periyasamy designed and synthesized novel disubstituted quinazolin-4(3H)-ones (A large number of quinazolines have been synthesized and studied for wide range of antiviral activity) and evaluated their antiviral activity against influenza A, SARS, dengue, yellow fever, Venezuelan equine encephalitis (VEE), Rift Valley fever, and Tacaribe viruses in cell cultures. Equimolar mixtures of benzoxazine and sulphonamides were dissolved in acid. The reaction was performed using microwave irradiation from a microwave oven, and the

resultant solid was dried and recrystallized from an ethanol–chloroform mixture. The compound 4-(6,8-dibromo-4-oxo-2-phenyl quinazolin-3(4H)-yl)-N-(4,5-dimethyloxazol-2-yl) benzenesulphonamide showed promising activity (Fig. 6) [10].

Yueqing et al. (Li et al.) synthesized novel stilbene derivatives [The author designed these substituted structures to resemble phytoalexins (Annual plants can be systemically immunized against viruses by phytoalexins)]. First, different

pyridine derivatives were heated with tri-ethyl phosphite according to the Michaelis–Arbuzov reaction. The reaction (i.e., the Wittig–Horner reaction) between aldehyde and the phosphate anion in the presence of a strong base at room temperature produced stilbene derivatives and water-soluble diethyl phosphate. However, the yield of pyridine containing derivatives was weak. Methoxy derivatives were demethylated using boron tribromide (BBr<sub>3</sub>) in dichloromethane. The results showed that the SARS virus was suppressed by tetrhydroxystilbene and tetrahydroxystilbene-2-nitrogen derivatives ( $\leq 0.5$  mg ml<sup>-1</sup>; Fig. 7). However, no remarkable cytotoxic effects were observed in vitro [11].

Biot et al. synthesized a new derivative of organometallic compounds (hydroxyferroquine, closely mimicking the antimalarial drug hydroxychloroquine. These new drugs may offer a good choice for SARS and malaria has remained endemic) that showed antiviral effects with near-sensitivity toward SARS. Alcohol and ferrocenylmethylamine iodide were mixed, after which excess potassium carbonate was added and the mixture was refluxed. After drying, the resulting final residue was purified by silica gel chromatography. The results inhibited the growth of *P. falciparum* much better than chloroquine (Fig. 8). Moreover, this class of bio-organic minerals showed good effects against virus growth with some sensitivity toward SARS. These novel derivatives may provide an amazing alternative to chloroquine and hydroxychloroquine (Hydroxychloroquine, after a treatment that received a significant amount of support but was found in trials to be ineffective against COVID-19 because of side effects) with minimal side effects [12].

Chen et al. developed new N substituted isatin derivatives (Isatin pharmacophore responsible for the synthesis of effective antivirals) [13], which were prepared from the reaction of isatin and different bromides in two steps. The results of the laboratory tests showed that some of these compounds were strong inhibitors against selective SARS at very low half-maximal inhibitory concentration (IC<sub>50</sub>) values. The N-alkylation of the corresponding isatin was achieved through its reaction with sodium hydride and various types of bromide derivatives in dimethylformamide (DMF). Laboratory test results showed that some of these compounds were strong, selective inhibitors against SARS, and one of them exhibited more potent inhibition against SARS (Fig. 9) [14].

### 3.2 Recent Strategies for the Development of Antiviral Drugs

Viral infections are a significant worldwide health threat. In the past 50 years, critical endeavours have been given to develop antiviral medications, and incredible achievement has been accomplished for some infections. Nevertheless, other infectious diseases, such as COVID-19, continue to spread, while new dangers continue emerging from developing and reappearing infections and drug-resistant viruses. Effective therapies are not available for various viral infections, and additional improvement of antiviral medication structure is needed. This section describes the reasoning behind present and future medication-based synthetic techniques for battling viral infections.

The model used to develop antiviral drugs has varied (Fig. 10), but it can now be classified into distinct processes, including target disclosure, production of candidate drugs (lead compounds), lead optimization and lead advancement. The generation of lead compounds is one of the crucial steps in this process, and methods used to generate novel leads include substrate-based methodologies and molecular biological techniques. Structural biology also directs lead discovery, as well as lead optimization, which includes high-throughput synthesis as well. This synthesis, which has been developed recently can be used for the fast discovery of the required effective drugs, places great significance on microwave-based synthesis using techniques such as polymer-supported purification and frosted reagents and catalysts [15,16,17].

Many alternative approaches to discovering antiviral therapies also exist. For example, the designs of protein substrates can be used as a beginning stage for drug development. Using X-beam crystallographic and sub-atomic docking information regarding target–inhibitor edifices to enhance lead constructions is also popular, and the techniques for preparing libraries of mixtures to make and streamline leads are extraordinary, which permit us to describe the behavior of newly synthesized derivatives in the target site of the proteins just as to explain major biochemical pathways [18]. Likewise, the strategies used to develop the pharmacokinetic and pharmacodynamics properties of mixtures are advancing quickly. Furthermore, novel ways to develop antiviral treatments utilizing oligonucleotide-based mixtures or regulating the host resistant reaction are being investigated [19].

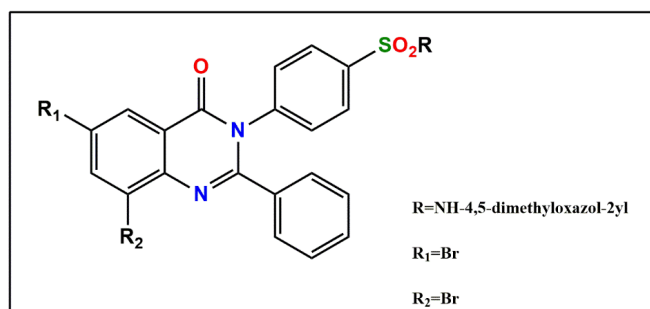


Fig. 6. The promising derivative synthesized in the article

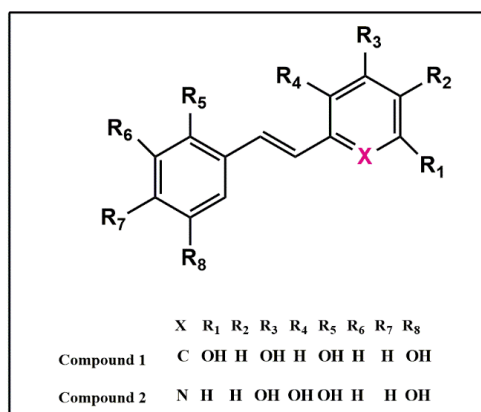


Fig. 7. Tetrhydroxystilbene and tetrahydroxystilbene-2-nitrogen derivatives

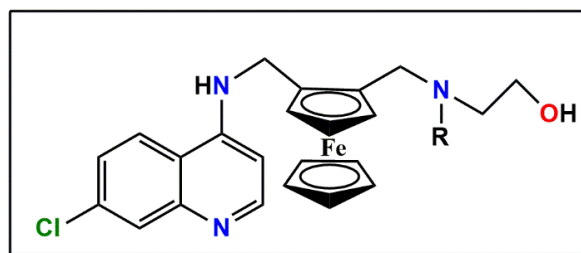


Fig. 8. Bioorganometallic compounds showed a good effect against virus growth with some sensitivity toward SARS

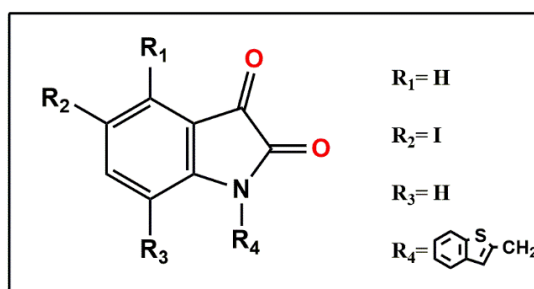


Fig. 9. The most potent inhibitor against SARS which the article mentioned

Nucleoside-like derivatives are other alternatives for broad-spectrum antiviral drugs, and ribavirin is an antiviral drug used frequently to treat recently developed infectious diseases. Drugs against non-viral proteins are also examples of broad-spectrum antiviral drugs. Viruses use a very soft cellular mechanism to get in and out of host cells. Inhibitors against this cellular mechanism can prevent viral spread, and more research studies on this mechanism are in progress. Moreover, nucleic acid (RNA) viruses use host membrane parts for reproduction and survival. Thus, fat metabolism is the selected target for antiviral drugs, and lipid-lowering medications have been reported as having an effect against many viral infections, including HIV

and influenza. The antiviral activity of  $\beta$ -hydroxy  $\beta$ -methylglutaryl-CoA (HMG-CoA) reductase inhibitors may be due to the disruption of the membrane components used by viruses.

Finally, drug repositioning has become more popular as an option to reduce the time and cost related to drug developments. Cyclosporine A is an authorized immunosuppressive drug that is also effective against viruses such as HIV, influenza, hepatitis C virus (HCV), coronaviruses, and human cyto-megalovirus [20]. Hydroxychloroquine, a drug for malaria, has gained attention for its potential to combat SARS-CoV-2.

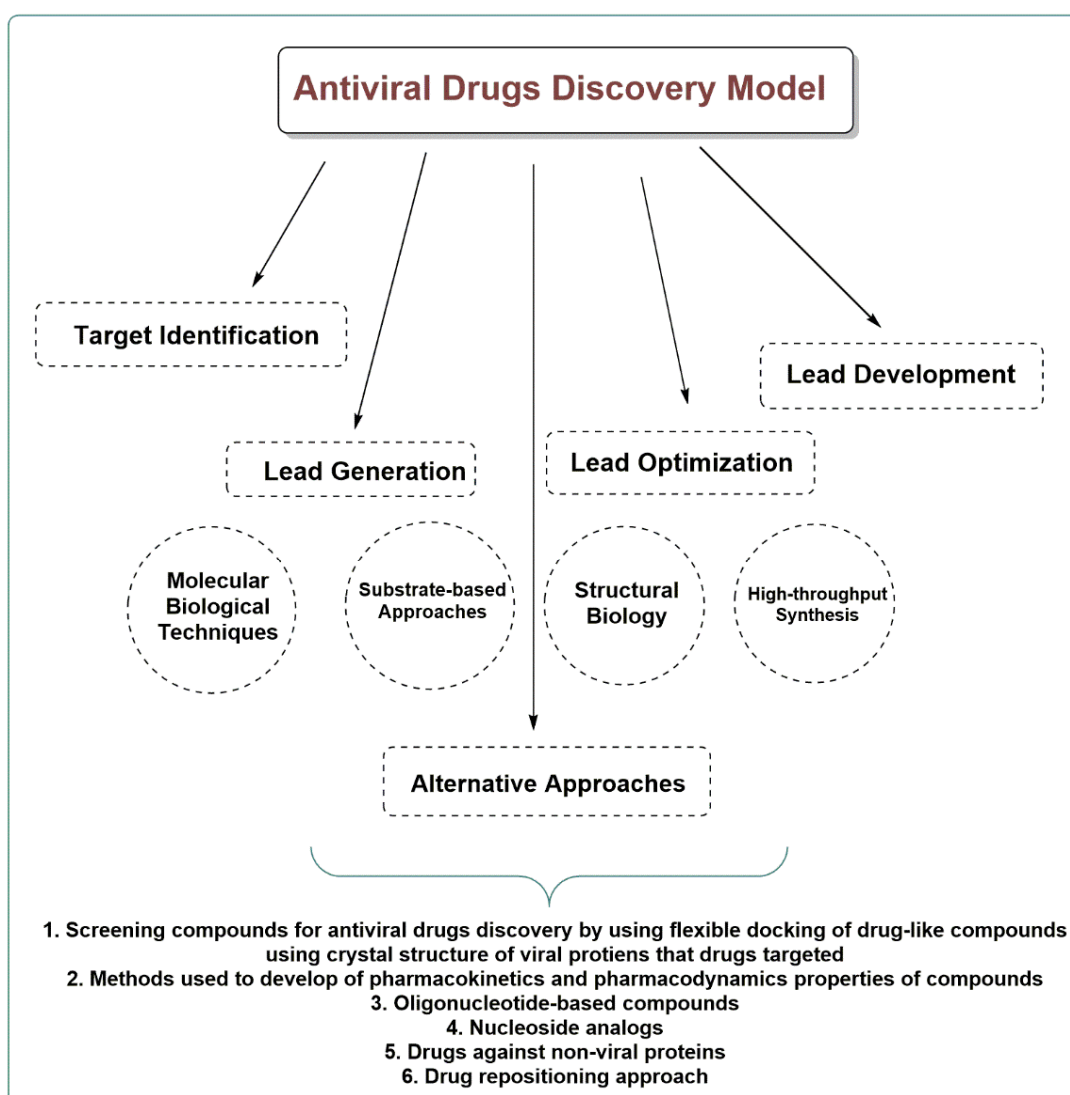


Fig. 10. Antiviral drugs discovery model



#### 4. CONCLUSION

Part of viral infections can be relieved by approved antiviral drugs, but for other viral infections there are no drugs available, yet. Therefore, antiviral medications should be developed urgently due to the advancement of infections and their lasting danger to human wellbeing. The previous mini-review clearly indicates those many new chemical derivatives easily to synthesize based on a variety of starting materials. Most of them were active against the coronaviruses, and this makes them important scaffolds for developing new drugs against coronaviruses in the nearest future. By focusing on the derivatives that have shown great outcomes in the synthetic methods, a proper treatment can be achieved in a brief timeframe. As the techniques used to deliver antiviral remedial specialists have grown quickly and viably. Moreover, high-throughput screening advancements and construction-based medication configuration will be reinforced by productivity chemistry that relies upon creating basic and viable combination techniques and understanding the infection system. Because of all these procedures, numerous antivirals should be developed throughout the next few years; this is necessary for guaranteeing people's wellbeing and prosperity.

#### DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

#### CONSENT

It's not applicable.

#### ETHICAL APPROVAL

It's not applicable.

#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

#### REFERENCES

1. Available:<https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf>. (Accessed: May 2021).
2. <https://www.scientificamerican.com/article/these-drugs-might-prevent-severe-covid-1/>.
3. Harvard Health Publishing. [citad 2020 Sep. 20] Available:<https://www.health.harvard.edu/diseases-and-conditions/treatments-for-covid-19>. (Accessed: May 2021).
4. Madsen LW. Remdesivir for the Treatment of Covid-19-Final Report. *The New England Journal of Medicine*. 2020;338(19):1813-1826.
5. Zhang L, Lin D, Kusov Y, et al.  $\alpha$ -Ketoamides as broad-spectrum inhibitors of coronavirus and enterovirus replication: Structure-based design, synthesis, and activity assessment. *J. Med. Chem.* 2020; 63: 4562-4578. Available:<https://doi.org/10.1021/acs.jmedchem.9b01828>.
6. Zaher NH, Mostafa MI, Altaher AY. Design, synthesis, and molecular docking of novel triazole derivatives as potential CoV helicase inhibitors. *Acta Pharm.*2020; 70: 145-59. Available:<https://doi.org/10.2478/acph-2020-0024>.
7. Apaydın ÇB, Cesur N, Stevaert A, et al. Synthesis and anti-coronavirus activity of a series of 1-thia-4-azaspiro [4.5] decan-3-one derivatives. *Archiv der Pharmazie*. 2019;352(6):1800330. <https://doi.org/10.1002/ardp.201800330>.
8. Karypidou K, Ribone SR, Quevedo MA, et al. Synthesis, biological evaluation, and molecular modeling of a novel series of fused 1, 2, 3-triazoles as potential anti-coronavirus agents. *Bioorganic & medicinal chemistry letters*. 2018;15;28(21):3472-6. Available:<https://doi.org/10.1016/j.bmcl.2018.09.019>.
9. Peters HL, Jochmans D, De Wilde AH, et al. Design, synthesis and evaluation of a series of acyclic fleximer nucleoside analogues with anti-coronavirus activity. *Bioorganic & medicinal chemistry letters*. 2015; ;25(15):2923-6. Available:<https://doi.org/10.1016/j.bmcl.2015.05.039>.
10. Selvam P, Vijayalakshimi P, Smee DF, et al. Novel 3-sulphonamido-quinazolin-4 (3

- H)-One Derivatives: Microwave-Assisted Synthesis and Evaluation of Antiviral Activities against Respiratory and Biodefense Viruses. *Antiviral Chemistry and Chemotherapy*. 2007;18(5):301-5. Available: <https://doi.org/10.1177%2F095632020701800506>.
11. Li YQ, Li ZL, Zhao WJ, et al. Synthesis of stilbene derivatives with inhibition of SARS coronavirus replication. *European journal of medicinal chemistry*. 2006;41(9):1084-9. Available: <https://doi.org/10.1016/j.ejmech.2006.03.024>.
  12. Biot C, Daher W, Chavain N, et al. Design and synthesis of hydroxyferroquine derivatives with antimalarial and antiviral activities. *Journal of medicinal chemistry*. 2006;49(9):2845-9. Available: <https://doi.org/10.1021/jm0601856>.
  13. Jarrahpour A, Sheikh J, El Mounsi I, et al. Computational evaluation and experimental in vitro antibacterial, antifungal and antiviral activity of bis-Schiff bases of isatin and its derivatives. *Medicinal Chemistry Research*. 2013;22(3):1203-1211.
  14. Chen LR, Wang YC, Lin YW, et al. Synthesis, and evaluation of isatin derivatives as effective SARS coronavirus 3CL protease inhibitors. *Bioorganic & medicinal chemistry letters*. 2005; 15(12):3058-62. Available: <https://doi.org/10.1016/j.bmcl.2005.04.027>.
  15. Chighine A, Sechi G, Bradley M. Tools for efficient high-throughput synthesis. *Drug discovery today*. 2007;12(11-12):459-64. Available: <https://doi.org/10.1016/j.drudis.2007.04.004>.
  16. Ghorpade A, Xia MQ, Hyman BT, et al. Role of the  $\beta$ -chemokine receptors CCR3 and CCR5 in human immunodeficiency virus type 1 infection of monocytes and microglia. *Journal of Virology*. 1998;72(4):3351-61. DOI: 10.1128/JVI.72.4.3351-3361.1998.
  17. Baba M, Tanaka H, De Clercq E, et al. Highly specific inhibition of human immunodeficiency virus type 1 by a novel 6-substituted acyclouridine derivative. *Biochemical and biophysical research communications*. 1989 ;165(3):1375-81. Available: [https://doi.org/10.1016/0006-291X\(89\)92756-3](https://doi.org/10.1016/0006-291X(89)92756-3).
  18. Mc Conkey BJ, Sobolev V, Edelman M. The performance of current methods in ligand-protein docking. *Current Science*. 2002;83:845–855.
  19. Jones PS. Strategies for antiviral drug discovery. *Antiviral Chemistry & Chemotherapy*. 1998;9: 123-333. Doi/pdf/10.1177/095632029800900401.
  20. Takizawa N, Yamasaki M. Current landscape and future prospects of antiviral drugs derived from microbial products. *The Journal of Antibiotics*. 2018;71(1):45-52 Available: <https://doi.org/10.1038/ja.2017.115>.

© 2021 Hussein et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

The peer review history for this paper can be accessed here:  
<http://www.sdiarticle4.com/review-history/69684>