Mini-Review Article

Synthetic Advances against Coronaviruses: A Short Review of the Recent Literature on Various Synthetic Methods and Recently Developed Strategies

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 antivirals on the novel coronavirus were tested, but none of these antivirals was found to have any significant effect on mortality. This short review summarizes the synthesis of new antiviral derivatives that target coronaviruses and describes 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), 2019 novel coronavirus (2019-nCoV), World Health Organization (WHO), severe acute respiratory syndrome (SARS), Middle East Respiratory Syndrome (MERS), non-structural protein 13 (nsp13), sulfuric acid (H2SO4), half-maximal effective concentration (EC50), human coronavirus 229E (HCoV-229E), Venezuelan equine encephalitis (VEE), tetra-n-butylammonium iodide (n-Bu)4NI), boron tribromide (BBr3), half-maximal inhibitory concentration (IC50), dimethylformamide (DMF), human immunodeficiency virus (HIV), β-hydroxy β-methylglutaryl-CoA (HMG-CoA), hepatitis C virus (HCV).

1. Introduction

Infection with a novel zoonotic betacoronavirus entitled “2019 novel coronavirus” (2019-nCoV) has become a worldwide danger. The knowledge regarding 2019-nCoV 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. In addition to 2019-nCoV, two coronaviruses have caused significant outbreaks of infection: severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). While 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 2019-nCoV [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 utilised 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 heartrate variations, especially when the two medications are mixed. Therefore, the 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. Remdesivir 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.

2. New Synthetic Derivatives to Treat Coronavirus Infections

Zhang et al. (2020) 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). Fig. 1 shows the structures of the most active derivatives [5].

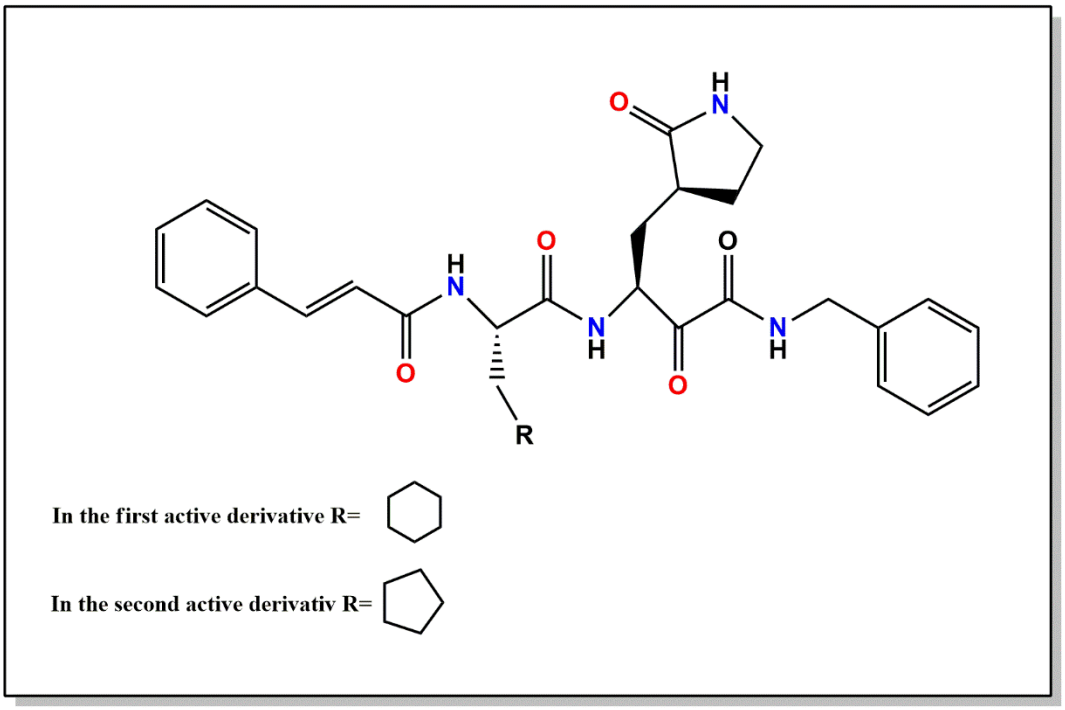

Figure 1. The structures of the most active derivatives from the newly synthesized derivatives.

Zaher et al. (Zaher 2020) 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 (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].

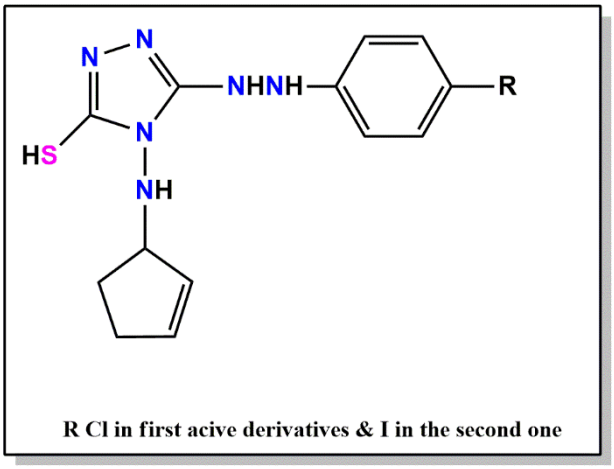

Figure 2. The structures of the most influential compounds synthesized in the article.

Çağla et al. (2019) 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 strongest compound was N- (2- methyl- 8- tert- butyl- 3- oxo- 1- thia- 4- azaspiro[4.5]decan- 4- yl)- 3- phe nylpropanamide (Fig. 3), which had an EC50 value of 5.5 μM [7].

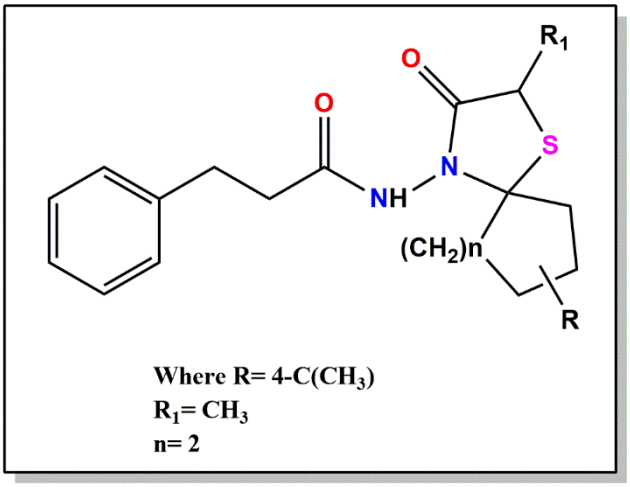

Figure 3. The most active derivative synthesized in the article.

Konstantina et al. (Karypidou et al., 2018) 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^{o} amines and phenyl-azide. Five compounds showed promising antiviral properties against human coronavirus 229E (HCoV-229E; Fig. 4) [8].

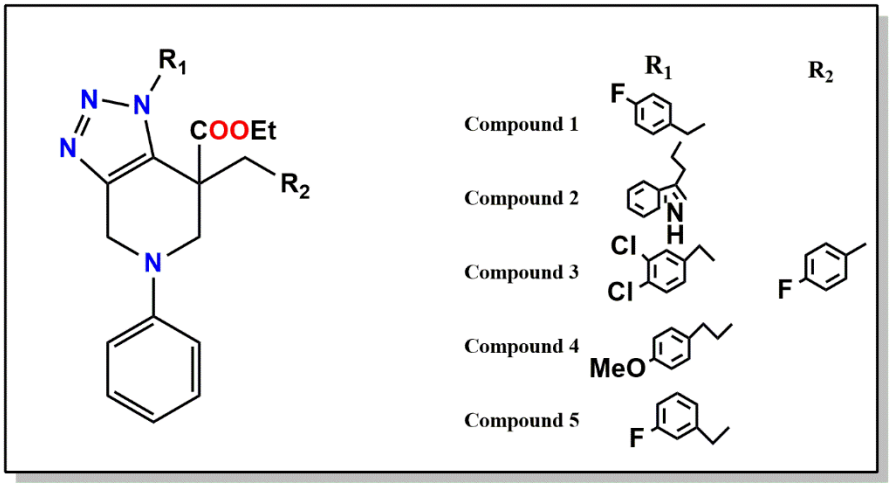

Figure 4. Promising antiviral derivatives against human coronavirus.

Peters et al. (2015) designed a series of nucleoside analogues based on the acyclic sugar scaffold of the acyclovir drug and the flex-base of the fleximers. The obtained compounds were evaluated for their antiviral activity and found to inhibit many types of coronaviruses (Fig. 5) [9].

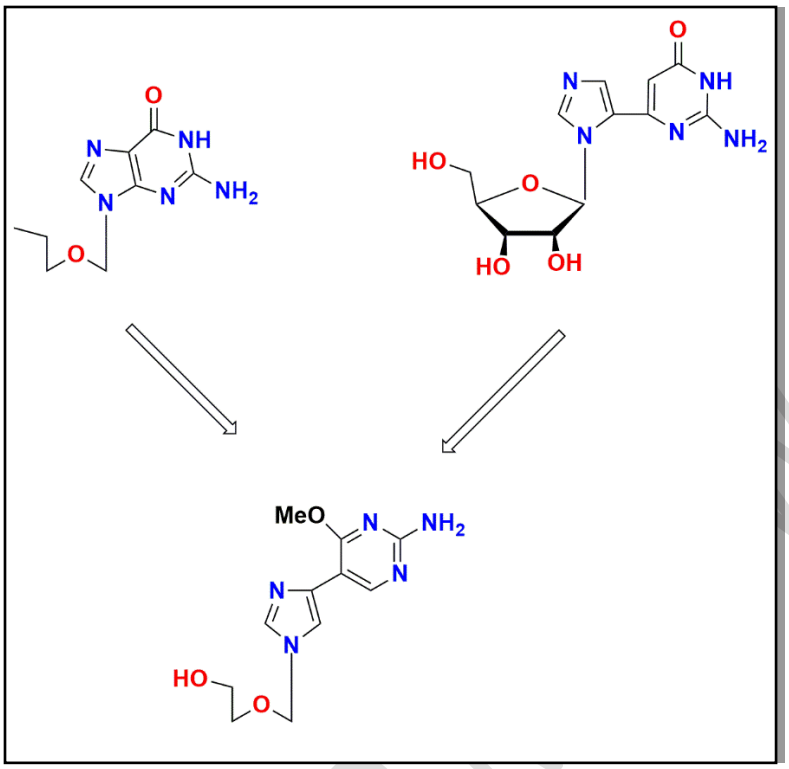

Figure 5. Doubly flexible nucleoside analogues.

Periyasamy (2007) designed and synthesized novel disubstituted quinazolin-4(3H)-ones 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-2yl) benzenesulphonamide showed promising activity (Fig. 6) [10].

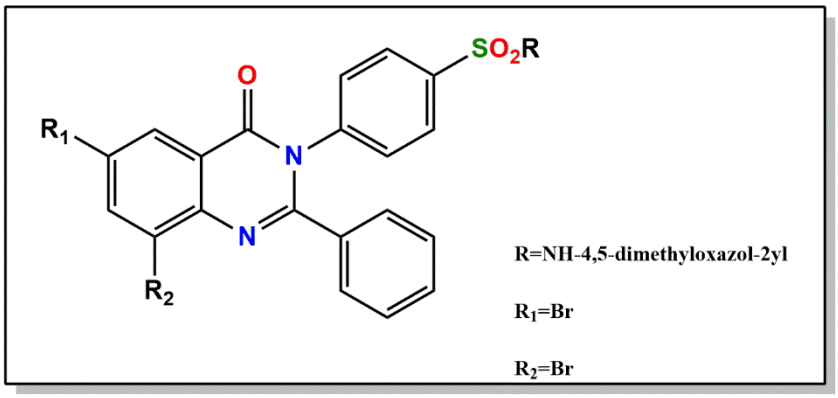

Figure 6. The promising derivative synthesized in the article.

Yueqing et al. (Li et al., 2006) synthesized novel stilbene derivatives. 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 (BBr3) in dichloromethane. The results showed that the SARS virus was inhibited by tetrthydroxystilbene and tetrahyroxystilbene-2-nitrogen derivatives (≤ 0.5 mg ml–1; Fig. 7). However, no remarkable cytotoxic effects were observed in vitro [11].

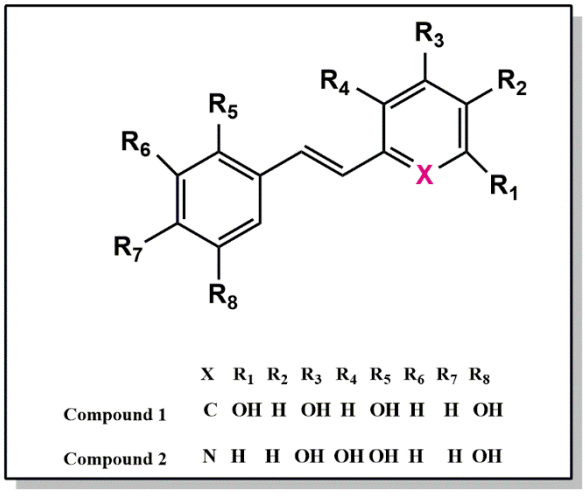

Figure 7. Tetrthydroxystilbene and tetrahyroxystilbene-2-nitrogen derivatives.

Biot et al. (2006) synthesized a new derivative of organometallic compounds (hydroxyferroquine) 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 with minimal side effects [12].

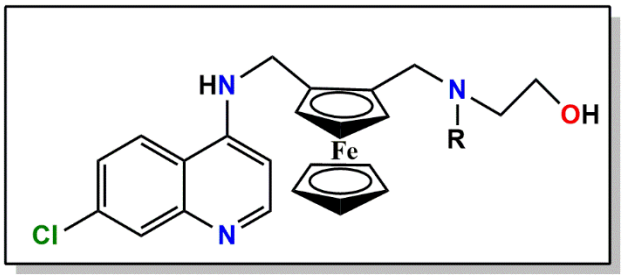

Figure 8. Bioorganometallic compounds which showed a good effect against virus growth with some sensitivity toward SARS.

Chen et al. (2005) developed new N substituted isatin derivatives, 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_{50}) 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) [13].

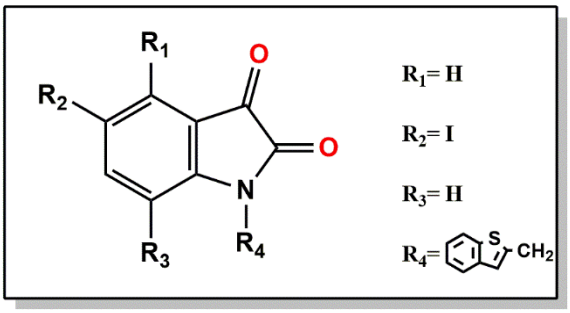

Figure 9. The most potent inhibitor against SARS which the article mentioned.

3. 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 [14, 15, 16].

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 derivativs in the target site of the proteins just as to explain major biochemical pathways [17] . 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 [18].

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 β-hydroxy β-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 [19]. Hydroxychloroquine, a drug for malaria, has gained attention for its potential to combat 2019-nCoV.

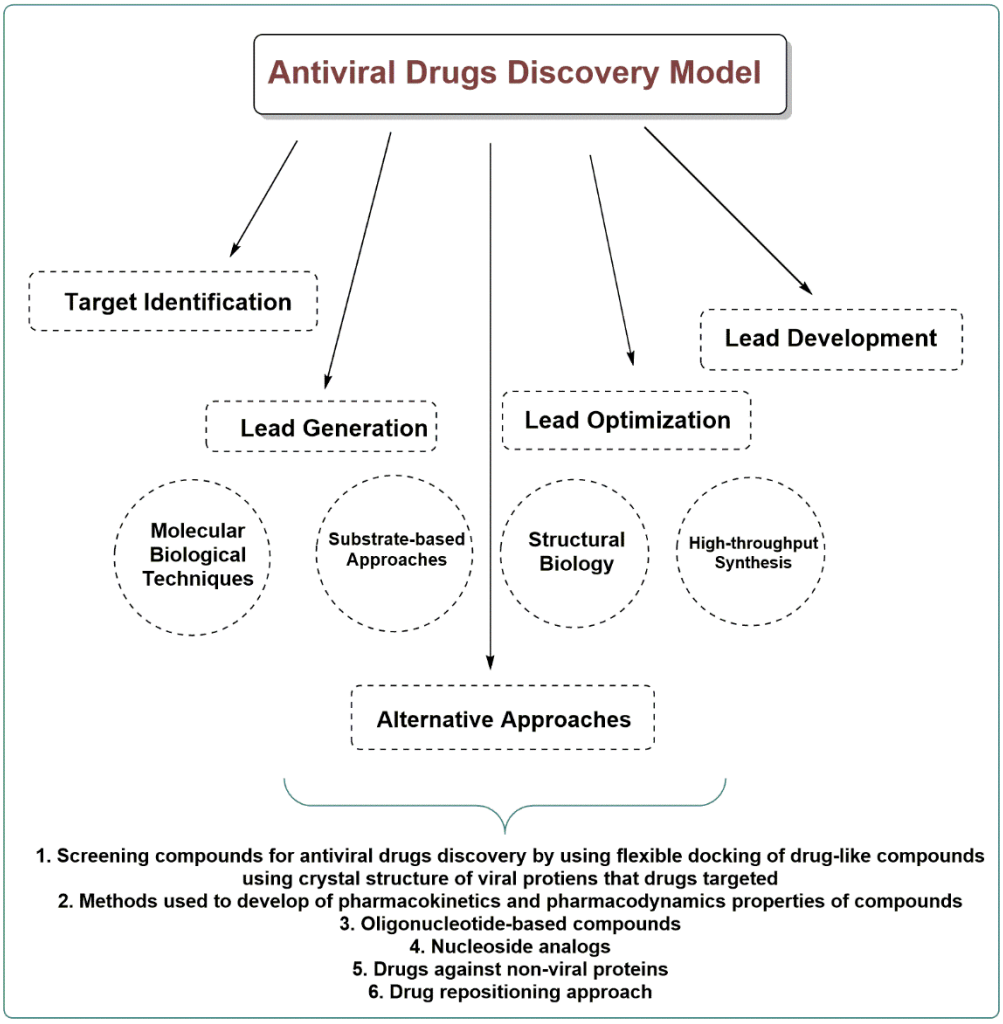

Figure 10. Antiviral drugs discovery model.

4. Conclusion

Antiviral drugs need to be developed urgently because of the development of viruses and their permanent risk to human health. Therefore, antivirals are one of the most important medications for mankind. The techniques used to deliver antiviral remedial specialists have grown quickly and viably. By focusing on the derivatives that have shown great outcomes in the synthetic methods, a proper treatment can be achieved in a brief timeframe. 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 these procedures, numerous antivirals should be developed throughout the next few years; this is necessary for guaranteeing people's wellbeing and prosperity.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. 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.

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