



Recent Progress in Green Synthesis and Antiviral Evaluation of Quinazolinone Derivatives: A Review

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ARTICLE INFO	ABSTRACT
Article history: Received – 14 March 2020 Received in revised form – 29 May 2020 Accepted -30 May 2020 Available online – 03 June 2020	One of the most important classes of nitrogen-containing heterocyclic compounds used in medicinal chemistry is the class of quinazolinone derivatives, mainly due to its excellent pharmacological potential. In the last two decades, the search for such scaffolds with diverse pharmacological activities, including antibacterial, antifungal, anticancer, anti-inflammatory, anticonvulsant, and particularly antiviral activities, have generated substantial interest. Meanwhile, with growing environmental concerns, there is a greater push to develop a clean and greener method that utilizes safe reagents, is cost-effective, saves energy and water and generates least possible waste and makes use of green catalyst and solvent.
Keywords: Quinazolinone, Antiviral activity, Medicinal chemistry, Pharmacological potential, Anticonvulsant	A large number of methods have been reported during recent decades for the synthesis of quinazolinone derivatives following the principles of green chemistry by the microwave assisted synthesis (MAS), ultrasonic assisted synthesis (UAS), solvent free reaction, synthesis in aqueous media, reaction in ionic liquids and multi-component reactions. Recently a lot of research has been conducted on quinazolinone derivatives as antiviral against human immunodeficiency virus (HIV), herpes simplex virus (HSV), hepatitis C virus (HCV), Influenza virus, human cytomegalovirus (CMV) and particularly, coronavirus disease (COVID-19). This review article describes the recent advancements (2000-2021) on greener synthetic routes of quinazolinone derivatives, antiviral potencies in conjunction with SAR and a detailed review of different catalytic systems. In addition, future scope and industrial aspect of greener quinazolinone in antiviral activity has also been discussed.

1. Introduction

The family of bioactive compounds represented by nitrogen-containing heterocycles forms one of the largest groups used in medicinal chemistry. The development of compounds based on the quinazolinone moiety can be attributed to the widespread biological properties and privileged structural features that such compounds possess. Thus, these fused benzene and pyrimidinone rings offer great structural flexibility, which makes it easy to access diverse chemical scaffolds for targeting multiple therapeutic purposes.

Many biologically active compounds that contain quinazolinone or quinazoline ring systems are currently used in clinics to treat infections.

Since the turn of the 21st century, rapid advances in quinazolinone chemistry have been occurring in response to increased need for new drugs to treat infections that involve microbial or viral causes and for which drug-resistance mechanisms have emerged, as well as

for cancer treatments. Numerous drugs with quinazolinone/quinazoline cores have shown a range of important activities including: Anticancer, antiviral, antibacterial, antifungal, anti-inflammatory, anticonvulsant, antimalarial, analgesic, and antitubercular. The antiviral area has been particularly important during the last ten years because of new worldwide viral epidemics such as SARS, MERS, Ebola, Zika, and recently COVID-19. This has stimulated rapid search for novel antiviral scaffolds that are not only effective but have also good safety profile and broad-spectrum activity.

These agents have targeted several enzymes that play essential roles in viral cycle, such as reverse transcriptase, DNA polymerase, proteases, and RNA-dependent RNA polymerase.

Importance of Green Synthesis

Traditional synthetic approaches for compounds usually involve hazardous organic solvents, heavy metal catalysts, higher reaction

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temperature, and longer reaction time which leads to severe air and water pollution, excessive amount of chemical waste and higher production costs. Consequently, in order to improve current protocols and promote sustainable practices, scientists have turned to apply green chemistry which were put forward by Paul Anastas and John Warner, in the synthesis of quinazolinones. It has twelve main points including; 1. Prevention of waste, 2. atom economy, 3. less hazardous synthetic chemistry, 4. safer chemicals and products, 5. renewable feedstocks, 6. less derivatives, 7. catalysis, 8. design for degradation, 9. energy efficient, 10. safer solvents, 11. tools for analytical action and 12. benign by design for prevention.

Researchers have already synthesized many quinazolinone derivatives using microwave assisted synthesis, ultrasonic assisted synthesis, solvent free protocol, ionic liquids, deep eutectic solvents, heterogeneous catalyst, recyclable catalyst, aqueous medium, etc. While retaining the yields and protecting the environment.

Table 1. Biological activities reported for quinazolinone derivatives

Biological Activity	Representative Molecular Target	Therapeutic Significance
Antiviral	Reverse transcriptase, viral proteases	HIV, HSV, HCV, SARS-CoV-2
Anticancer	EGFR, tyrosine kinase	Breast, lung and colon cancer
Antibacterial	DNA gyrase	Gram-positive and Gram-negative bacteria
Antifungal	Cell wall synthesis	Pathogenic fungi
Anti-inflammatory	COX enzymes	Arthritis and inflammation
Anticonvulsant	GABA receptors	Epilepsy
Antitubercular	Mycobacterial enzymes	Tuberculosis

The latest research also suggests that environmentally friendly methods of production not only lead to more sustainable chemistry, but also offer efficient routes to accelerate the creation of highly diverse quinazolinone libraries to test against viruses. By merging the practices of both green and medicinal chemistry, we can aim to discover effective antiviral treatments more efficiently with less impact on the environment.

2. Green Synthesis of Quinazolinone Derivatives

Nowadays, with growing concerns of environment conservation the face of modern organic chemistry has changed; greener routes

towards chemical reactions are now the subject of interest. Green chemistry focuses on the reduction or avoidance of chemicals that pose risk to health, enhance reaction efficiency and selectivity to the desired product. Green chemistry approach for the synthesis of quinazolinones compounds have developed throughout last two decades with decreased amounts of solvent, decreased reaction times, better atom economy and use of the recyclable catalysts or renewable resources; such green synthetic strategies is an area that has contributed substantially in the discovery and development of quinazolinone based drug molecules.

The most commonly applied green synthetic approaches: microwave assisted synthesis (MAS), ultrasound assisted synthesis (UAS), solvent free reaction, aqueous phase synthesis, ionic liquids mediate reaction (ILMR), deep eutectic solvent (DES) based synthesis, nanocatalytic and multi component reaction(s). [11-13]

2.1 Microwave-Assisted Synthesis

Among the many applications, one of the leading green methods for heterocyclic synthesis is microwave irradiation [13]. This method provides rapid and efficient heating of polar reactants through a direct interaction with microwave energy as opposed to the indirect absorption by conventional heating techniques. Consequently, reactions, which require several hours in traditional methods, have reduced to minutes and in most cases yield and purity of products have been increased [14, 15].

For quinazolinones, cyclization between derivatives of anthranilic acid and various amides, aldehydes, isatoic anhydride has been achieved by means of microwave irradiation [16].

In some instances, it has been possible to obtain the products with over 90% yield whereas yields in the 60-75% range are commonly reported under reflux condition.

Advantages

- Short reaction time
- Higher product yield
- Lower energy consumption
- Reduced solvent requirement
- Better product purity
- Easy scalability

2.2 Solvent-Free Synthesis

One of the more prominent approaches within the spectrum of green reactions has been solvent-free synthesis since organic solvents represent one of the most important sources of hazardous waste and environmental pollution. The technique involves bringing together two reactants (by simply mixing, shaking, or grinding them without the presence of a solvent). For instance, a number of substituted quinazolinones have been synthesized using recyclable catalysts (supported acids such as alumina and silica supported acids, and zinc oxide nano-particles under solvent-free reaction conditions) in

excellent yield and purity with minimized waste production. Such reaction systems typically have greater atom economy and simplified purification steps as well [16].

Advantages

- Zero solvent waste
- Reduced environmental pollution
- Simple work-up
- Lower production cost
- High atom economy

2.3 Aqueous-Phase Synthesis

Water is known as the perfect eco-friendly solvent: it's Cheap, non-toxic, non-combustible and environment-friendly. Several reports have confirmed in recent years that quinazolinone derivatives can be prepared in good yields with recyclable catalysts in water. Because of the hydrophobic effect resulting from interaction between reactants to a higher degree, reactions that occur in water exhibit a higher selectivity compared to ones carried out in organic solvents, typically chlorinated or aromatic organic solvents used in classical methods [17].

2.4 Ionic Liquid-Mediated Synthesis

Ionic liquids were found to be environmentally benign replacements for volatile organic solvents; their liquid phase transition at near-ambient temperature, lack of vapour pressure, high thermal stability, and easy recyclability are desirable properties. The feasibility of utilizing ionic liquids in quinazolinone synthesis was demonstrated using some ionic liquids, e.g., 1-butyl-3-methylimidazolium hydroxide ([Bmim]OH), which acted both as solvent and catalyst and hence the cost of materials was decreased, and separation step simplified [18].

The principal advantages include:

- Reusable reaction medium
- Low toxicity (depending on the ionic liquid)
- Minimal solvent evaporation
- Improved reaction efficiency

2.5 Deep Eutectic Solvents (DES)

They were selected because recent research reports showed an efficient and inexpensive synthesis using DES and producing very less hazardous waste, resulting in a good yield of quinazolinone derivatives [19]. The DES are alternative green and cheap ionic liquids, composed of naturally-based hydrogen bond donors (e.g. Choline chloride, choline bitartrate etc.) and hydrogen bond acceptors (e.g. Urea, glucose etc.).

2.6 Ultrasound-Assisted Synthesis

Ultrasound irradiation accelerates chemical reactions via acoustically induced localized heating and pressures of hot spots, a process known as acoustic cavitation. When compared to other

methods of heating such as ultrasound assisted synthesis has shown an increase in selectivity and decrease in reaction times. For example, some quinazolinone derivatives can be readily synthesized via ultrasound irradiations within a short reaction time range of 20 to 40 minutes compared with few hours under conventional heating [20].

2.7 Nanocatalyst-Assisted Synthesis

A New Generation Of Green Organic Synthesis - Highly Active Heterogeneous Catalysts Based On Nanomaterials - Researchers at the Shanghai Institutes of Optics and Fine Mechanics (SIOM) of Chinese Academy of Sciences (CAS) have developed highly efficient heterogeneous catalysts that could make organic synthesis a much “greener” process. Metal oxide nanoparticles, magnetic nanoparticles, and graphene supported catalysts developed by the group exhibit high surface area, good catalytic activity and recyclability.

Examples include:

- Zinc oxide nanoparticles
- Iron oxide nanoparticles
- Titanium dioxide nanoparticles
- Copper oxide nanoparticles

One key advantage to these catalysts is that they can generally be recovered and reused a number of times, losing only slightly catalytic activity in the process, which may appeal to their industrial use in the synthesis of materials [21].

2.8 Multicomponent Reactions (MCRs)

MCRs are the most atom-economical method to assemble molecules. During MCRs, three or more starting materials combine in a single pot reaction to form complicated molecules, and thus, a lot of waste-saving purification is saved. For the construction of the quinazolinone, aldehyde, anthranilic acid derivatives, and amine often combine together. Such methods reduce:

- Number of reaction steps
- Solvent consumption
- Energy usage
- Chemical waste

while increasing overall efficiency and product diversity [22].

Table 2. Comparison of Green Synthetic Methods for Quinazolinone Derivatives

Method	Green Solvent/Catalyst	Typical Yield (%)	Reaction Time	Major Advantages
Microwave-assisted	Ethanol / AcOH	85–95	5–20 min	Fast, energy-efficient
Solvent-free	ZnO nano particles	80–94	20–60 min	No solvent waste
Aqueous synthesis	Water	78–92	1–3 h	Eco-friendly, inexpensive
Ionic liquid-mediated	[Bmim]OH	85–96	30–90 min	Recyclable medium
Deep eutectic solvent	Choline chloride–urea	82–95	45–120 min	Biodegradable
Ultrasound-assisted	Water/Ethanol	84–93	20–40 min	High selectivity
Multicomponent reaction	Various recyclable catalysts	80–95	One-pot	Excellent atom economy

Comparative Performance of Green Methods

The relative performance of the major green synthetic approaches reported is summarized below. The values are representative ranges compiled from published studies.

Green Method	Typical Yield (%)	Relative Environmental Impact
Microwave-assisted	92	Very Low
Solvent-free	89	Very Low
Ionic liquid-mediated	90	Low
Water-mediated	86	Very Low
Ultrasound-assisted	88	Low
Deep eutectic solvent	91	Very Low

These various approaches to the synthesis of quinazolinones by greener approaches could dramatically enhance efficiency of quinazolinones-based compound production, rendering the chemistry of this valuable scaffold considerably cleaner and safer to implement. Among them, the most attractive approaches include the

microwave assisted synthesis, multicomponent reactions, and use of deep eutectic solvents due to efficiency, selectivity and minimized environment impacts, and they have great prospects to the sustainability development of antiviral quinazolinones derivatives.

3. Antiviral Evaluation of Quinazolinone Derivatives

Viral diseases that emerge or re-emerge make the development of new, safe and potent antiviral drugs with a reduced tendency to elicit resistance, increasingly important. Quinazolinones have shown high interest due to the fact they are known for a wide spectrum of antiviral activities, and that they can be easily decorated with a variety of substituents, in order to increase biological activity [23, 24, 25]. A lot of work between the year 2000 and 2021 describe new quinazolinone-containing compounds which were investigated against viruses like human immunodeficiency virus (HIV), herpes simplex virus (HSV), hepatitis C virus (HCV), influenza virus, human cytomegalovirus (CMV), dengue virus and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [23, 24, 25]. It is well known that quinazolinone activity may be altered by electron donating/withdrawing substituents and fused heterocycles on the quinazolinone framework, which help the binding to specific viral protein/enzyme [26].

3.1 Activity Against Human Immunodeficiency Virus (HIV)

HIV has been among the most intensively explored biological targets in the quinazolinone derivatives series. Certain substituted quinazolinones are known to exert inhibitory effects on the activity of reverse transcriptase of HIV-1 (RT), which is essential in virus reproduction. It was found that structural design based on the 3D structures of RT reveals the feasibility of the incorporation of heteroaryl and aryl substituent groups on C2 and C3 position of quinazolinone nucleus, in order to increase the binding affinity to reverse transcriptase.

It has been established that many synthesized compounds possess very effective antiviral activity with minimum toxicities in cells and cell free systems [27,28].

The hybridization between quinazolinone skeleton and other antiviral fragments, such as thiazole, triazole scaffold resulted in hybrids with better antiviral activity [29]. It may therefore conclude that molecular hybrid strategy may be an effective way to promote the activity.

Proposed Mechanism

- Reverse transcriptase inhibition
- Prevention of viral DNA synthesis
- Suppression of viral replication

3.2 Activity Against Herpes Simplex Virus (HSV)

Herpes simplex viruses 1 and 2 cause persistent oral and genital herpes infections. Drug resistance against traditional antivirals, such

as acyclovir has prompted research into alternative drug candidates. Diverse quinazolinone compounds have shown from moderate to outstanding HSV-1 and HSV-2 inhibitory effects. It has been suggested that these drugs hinder replication of viral genome by inhibition of the viral DNA polymerase [29]. Chlorine, fluorine, methoxy, and amino-substituents were typically correlated with an increase in anti-HSV potency.

3.3 Activity Against Hepatitis C Virus (HCV)

HCV produces liver disease. Although efficient drugs to eliminate HCV are already available in the form of direct-acting antivirals, in recent years the fight for elimination of HCV continues, due to increase of drug resistance. Previously reported many potent quinazolinone compounds exhibited high inhibition on HCV RNA-dependent RNA polymerase (HCV NS5B) enzyme, an enzyme involved in RNA replication and accumulation of its strong binding towards to HCV polymerase enzymes are been confirmed through computational docking simulation [30]. Furthermore, some laboratories reported that a combined quinazolinone scaffold with different hetero rings leads to better antiviral potency as well as enhanced pharmaceutical activities.

3.4 Activity Against Influenza Virus

The ongoing mutations of the viruses causing influenza in humans and animals (antigenic drift and shift) are driving the search for novel antivirals. Several substituted quinazolinones were tested and found active against Influenza A viruses, with possible modes of actions involving the inhibition of the viral neuraminidase, impairment of viral RNA replication and maturation of the viral proteins [31]. The presence of electron-withdrawing substituents enhances their activity in general when compared to their unsubstituted analogs.

3.5 Activity Against Cytomegalovirus (CMV)

Human Cytomegalovirus has emerged as an opportunistic pathogen, in particular, in patients with deficiencies in immunity and those with transplants. Several quinazolinones obtained in ecofriendly reactions have shown moderate activity against the CMV in in vitro cultures; this activity may appear due to blocking replication of DNA. These drugs were characterized as having little cytotoxicity to mammal cells [32].

3.6 Activity Against Dengue Virus

Dengue virus represents a significant public health problem in tropical and subtropical areas. Studies conducted by researchers have shown that several quinazolinone analogues effectively inhibit dengue virus replication, interacting with both viral RNA polymerase and protease complexes. While this research has, for the most part, still to reach the level of human testing in clinical trials, these studies are an encouraging demonstration of the potential role

of quinazolinone derivatives as agents that can be used to treat dengue infections. [33].

3.7 Activity Against SARS-CoV-2

To identify novel antiviral compounds against SARS-CoV-2, the pandemic had sparked unexampled search. Between 2020 and 2021, a number of quinazolinone derivatives have been assessed by molecular docking and molecular dynamics, along with biological evaluation of selected candidates. Quite a number of these compounds were obtained with potent binding activity against target SARS-CoV-2 proteins, including:

- Main protease (Mpro)
- Papain-like protease (PLpro)
- RNA-dependent RNA polymerase (RdRp)
- Spike glycoprotein

While a number of these discoveries were purely in silico and experimental in their infancy, they did point to quinazolinones as good scaffolds on which to base a future antiviral molecule.^{34–36} 34–36Note: Few quinazolinone derivatives have progressed to the stage where they have been tested for biological effects against SARS-CoV-2 up to and including the year 2021, and much further work is needed in vitro, in vivo and at the clinical stage of development.

Table 3. Reported Antiviral Activities of Quinazolinone Derivatives

Virus	Molecular Target	Representative Quinazolinone Modification	Reported Activity	Proposed Mechanism
HIV-1	Reverse transcriptase	Aryl-substituted quinazolinones	Promising	RT inhibition
HSV-1 / HSV-2	DNA polymerase	Halogenated derivatives	Moderate to high	DNA synthesis inhibition
HCV	NS5B polymerase	Heterocyclic hybrids	Promising	RNA synthesis inhibition
Influenza A	Neuraminidase / Viral proteins	Methoxy-substituted derivatives	Moderate	Viral replication inhibition
CMV	DNA polymerase	Amino-substituted derivatives	Moderate	DNA replication inhibition
Dengue virus	Viral protease	Hybrid quinazolinones	Preliminary	Protease inhibition
SARS-CoV-2	Mpro / RdRp / PLpro	Various substituted derivatives	Early-stage	Enzyme inhibition

Discussion

According to the evidence in 2000-2021, appropriately functionalized quinazolinone analogues have displayed wide-ranging antiviral activities especially when bearing aryl or heterocyclyl groups. Furthermore, green approaches have facilitated quick preparation of a structurally variable pool of compounds for bioassaying, and minimization of negative environmental impact. Yet, the majority of antivirality analyses were limited to in vitro studies, enzymic inhibition studies, or in silico studies; only few quinazolinone analogues entered the late preclinical stage due to the fact that the compound needed optimization in terms of pharmacokinetic features, selectivity, and toxicity [37,38]. With the incorporation of green chemistry, computational tools and SAR (structure-activity relationships) study the next generation of antiviral quinazolinones may appear in the near future.

4. Structure–Activity Relationship (SAR) of Quinazolinone Derivatives

Quinazolinone derivatives and their antiviral mechanisms were widely studied using Structure-Activity Relationship (SAR) analyses. During the period between 2000 and 2021, medicinal chemists generated a wide range of analogues with diverse substituents on several parts of quinazolinone structure in order to obtain better antiviral activity, selectivity, and pharmacokinetics, indicating that even smallest variation in structure can drastically change biologic activity.

4.1 Effect of Substituents on Antiviral Activity

The most common and thoroughly investigated substitutions on the quinazolinone nucleus are at the 2-position. Antiviral activity generally increases with incorporation of phenyl, substituted phenyl, pyridyl or thienyl rings which lead to more hydrophobicity interaction with the proteins [39]. Halogen substituted phenyl rings with fluoro, chloro and bromo groups increase activity more often due to the increase in lipophilicity and the greater binding toward viral target.

Aromatic groups including heteroaromatic ring substituted phenyl ring, with electronegative atoms including nitrogen, oxygen or halogens increased the inhibitory activities.

Another extensively investigated substitution is on the 3-position of the quinazolinone ring, where substituents like amino, alkylamino, hydrazino or other heterocycle improved activity through increased number of hydrogen bonding interactions with the active sites amino acid of the viral target. Modifications on the 6 and 7-position have been also demonstrated to have an impact on biological activities. It is generally considered that electron donor groups such as methoxy and methyl substitutions may improve activity in some class while electron-withdrawing substituents such as halogens and nitro group improve activity depending on the virus targets [40].

4.2 Molecular Hybridization

Among the strategies that have met the greatest success recently in discovering anti-viral compounds, molecular hybridization is remarkable. Under such schemes, the quinazolinone moiety has been combined with other pharmacologically relevant compounds to design hybrid molecules with diverse mechanisms.

Common hybrid structures include:

- Quinazolinone–triazole hybrids
- Quinazolinone–thiazole hybrids
- Quinazolinone–benzimidazole hybrids
- Quinazolinone–pyrazole hybrids

This hybrid often offers better antiviral activity, higher selectivity, and decreased toxicity in relation to their precursors.

4.3 Molecular Docking Studies

Drug discovery based on quinazolinone: Computational chemistry has significantly improved its antiviral drug discovery approaches with the development of new methodologies and techniques. Between 2015 and 2021, several molecular docking analyses between substituted quinazolinones and different viral proteins showed satisfactory interaction with the targeted proteins and the drug discovery process was facilitated, including:

- HIV Reverse Transcriptase
- HCV NS5B Polymerase
- Influenza Neuraminidase
- SARS-CoV-2 Main Protease (Mpro)
- RNA-dependent RNA Polymerase (RdRp)

The docking simulations suggested that hydrogen bonding, pi stacking, van der Waals forces, and hydrophobic interactions are the main stabilizing forces for ligand–protein interactions. But computational results must be confirmed through experimental validation in vitro, in vivo before any definite therapeutic statements can be made.

Table 4. General SAR Trends of Quinazolinone Derivatives

Structural Modification	Observed Effect on Antiviral Activity
Phenyl substitution at C-2	Increased hydrophobic interaction and potency
Halogen substitution	Improved enzyme binding and lipophilicity
Methoxy substitution	Enhanced activity in selected derivatives
Amino substitution	Increased hydrogen bonding capability
Triazole hybridization	Improved antiviral potency
Thiazole hybridization	Enhanced selectivity
Heterocyclic fusion	Improved biological spectrum

5. Future Perspectives

Green chemistry combined with medicinal chemistry will be very crucial in the development of novel quinazolinone-based antiviral agents in future. Some areas need special focus. Firstly, there is a growing emphasis on eco-friendly approaches that replace traditional hazardous and environmentally unfavorable processes by reducing the number of steps, byproducts, energy inputs and waste in the preparation of active compounds while preserving reasonable yields of reactions.

Secondly, development of new computational drug design tools, such as molecular docking, molecular dynamics simulations, pharmacophore modeling, artificial intelligence-aided drug discovery methods are expected to greatly aid in selection of prospective quinazolinone derivatives.

Thirdly, in the subsequent work, special efforts should be made to search for broad-spectrum antiviral drugs active against established and emerging viruses, as well as the compounds with better aqueous solubility, pharmacokinetic properties, stability and bioavailability when administered per os. Lastly, due to a poor translational rate of many compounds active in vitro to later clinical trials, combined endeavors of synthetic chemists, virologists, pharmacologists, and clinical physicians will be required.

6. Conclusion

Among many promising heterocycles for antiviral drug development, quinazolinones remain the dominant scaffold. Significant progress in sustainable synthetic protocols and antiviral assessment has been made between 2000 and 2021. Several eco-friendly synthesis methods, such as microwave-assisted synthesis, solvent-free reaction, green solvents (including aqueous medium, ionic liquids and deep eutectic solvents) nanocatalysis, multicomponent reaction, have been successfully established for effective and economical synthesis of diversely structural quinazolinones.

These protocols are fully in line with sustainable chemistry and have benefits of short reaction time, high yield, decreased waste generation, simplification of purification and reduction of toxic chemicals.

In addition to eco-friendly syntheses, a wide array of reported quinazolinones are tested for antiviral activities against HIV, HSV, HCV, Influenza virus, CMV, Dengue virus, SARS-CoV-2 and so on. These compounds' activities are closely dependent on their structural changes; particularly, aromatics substitutions, halogenations, amine substitutions and hybridizations are significant for the increase in activity. Nevertheless, a majority of the obtained compounds have not yet been extensively studied in

their biological activities, including toxicity and mechanisms of action and only few have reached clinical trials. Hence, it is of great importance to conduct thorough pharmacological analysis, to assess toxicity and to probe the mechanism of action, and eventually to achieve the clinical trials for such compounds.

By combining sustainable synthetic routes with logical design for the most efficient antiviral efficacy, new quinazolinone-based antivirals are expected to be discovered for therapeutic purposes.

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