Perspective

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Two-Sided RdRp SARS-CoV-2 and SARS-CoV-2 M^{pro} Selective Targeting Approach for COVID-19 Pandemic Therapy

Sameh A Mohammed[1]* and Esraa Ibrahim A Shaaban[2]

[1]*Faculty of Pharmacy, Department of Pharmacology and Toxicology, Beni-Suef University, Egypt*

[2]*Graduate School of Medical Sciences, Department of Biochemistry, Nagoya City University, Japan*

ABSTRACT

Since the emergence of coronavirus disease (COVID-19) pandemic induced by SARS-CoV-2, the world is being suffered from a serious threat to public health through several hospitalizations and thousands of deaths leading to boosting global concern and intensive precautionary measurements. Exploring the key targets of SARS-CoV-2 for the evolution of efficient therapeutics has become dire of need. Our viewpoint provides current therapeutic targets and insights for advanced COVID-19 therapies to date and discusses new structural design of a potential therapeutic drug (Coronavir SJ) posing an innovative modality and framework for COVID-19 therapy, which, in turn, mediates different pattern for curbing greater SARS-CoV-2 virulence. Coronavir SJ is a prodrug providing two bioactive metabolites once administered in the blood for targeting definite RdRp SARS-CoV-2 and SARS-CoV-2 M^{pro} binding pockets, thereby displaying versatile curative functions. Although this design might be evidenced insufficient, we hypothesise that this therapeutic approach can open up pharmacological direction and guided avenues for basic experiments and research on COVID-19 infection and superspreading at this moment.

INTRODUCTION

SARS-CoV-2 was first identified in December 2019, belongs to Coronaviridae family, which encompasses a massive variety of regularly widespread viruses in animals and humans. The major manifestations in humans are mild respiratory or digestive disturbances [1]. Otherwise, minor coronaviruses, for instance, MERS-CoV, SARS-CoV-1, and SARS-CoV-2 have dense and serious respiratory disorders leading to lethal outbreaks [2,3]. Comparable to MERS-CoV and SARS-CoV-1 outbreaks, the current SARS-CoV-2 outbreak has characteristic features of rapid transmission among human beings to be classified as the largest global public health menacing to humanity in this century. The World Health Organization (WHO) had declared on March 2020 the COVID-19 outbreak a pandemic owing to the wide number of infectious cases with an accelerated mortality rate. High SARS-CoV-2 mutations and the appearance of several variants in different countries readily result in several challenges for the existing vaccines. The unprecedented swift outbreak of the COVID-19 pandemic urges the detection and development of innovative vaccines, antiviral agents with a high degree of safety and efficiency.

Overview on COVID-19 Therapeutic Options

However, plenty of therapeutic agents have been estimated for COVID-19 treatment, no antiviral drug has yet been demonstrated to be effective [4]. Recently, the Food and Drug Administration (FDA) has approved only one drug, remdesivir, to treat COVID-19 [5]. Remdesivir is a broad-spectrum antiviral of RNA-dependent RNA polymerase with in vitro suppressive activity against MERS-CoV and SARS-CoV-1 [6-9]. Recent studies have been reported the potency of remdesivir to inhibit SARS-CoV-2 [10,11]. Furthermore, monoclonal antibodies such as casirivimab, imdevimab, and

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Address for correspondence: Sameh Abdelmoneem Mohammed Ali, Faculty of Pharmacy, Department of Pharmacology and Toxicology, Beni-Suef University, Egypt

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bamlanivimab have been authorized for emergency use by the FDA, assisting the immune system in SARS-CoV-2 recognition and attachment to respond more effectively to the virus [12,13]. Since publishing a detailed SARS-CoV-2 genome, several studies shed new light on innovative targets to support researchers and pharmaceutical industries in developing and producing potent SARS-CoV-2 therapies [14,15].

Current Approaches for covid-19 Therapy

There are two fundamental strategies for COVID-19 therapy relying on handling a single therapeutic agent for only one target or indicating conventional drug combinations for two or more targets of SARS-CoV-2. The first one is no longer propitious particularly in the case of SARS-CoV-2 infection because of massive variations and mutations in the viral genome as well as the entire evolutionary virulent factors of SARS-CoV-2 are still unknown along with the overwhelming number of patients and deaths. The second, exhibiting numerous serious complications and toxicities due to non-selectivity. Therefore, both of them are yet to be satisfactory for pandemic control.

The evolution of antiviral structural design based on RdRp SARS-CoV-2 and SARS-CoV-2 Mpro selective targeting

We discuss designing a prospective antiviral structure (Figure 1,2) that blocks the main biological processes of SARS-CoV-2, encounters viral resistance mechanisms, and ensures the safety of patients. Coronavir SJ could cleave once passed into the blood by esterase enzyme into adenosine-mimic analog and α-ketoamide inhibitor exerting robust SARS-CoV-2 inhibitory effects (Table 1); (Figure 3).

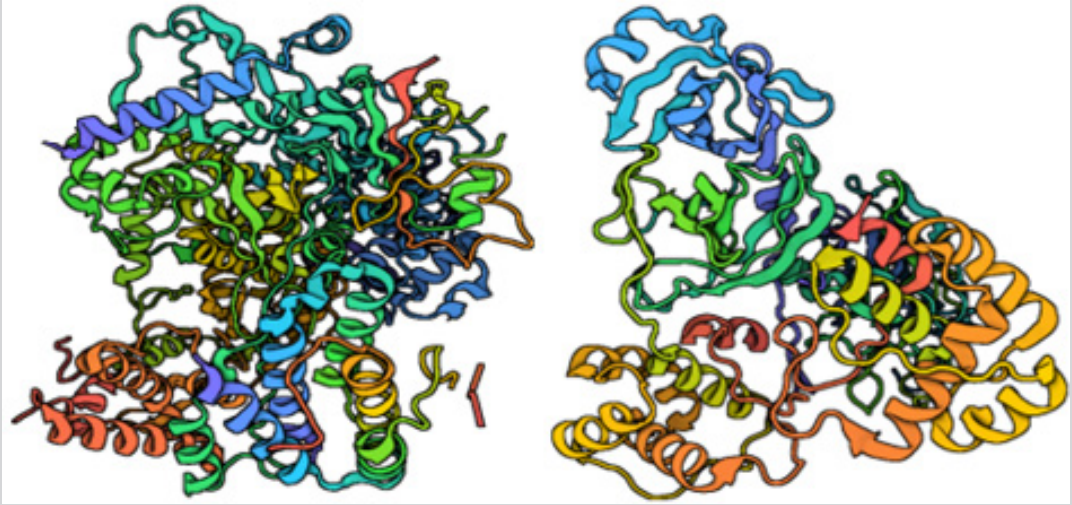


Figure 1: Three-dimensional structures of RdRp SARS-CoV-2 and SARS-CoV-2 M^{pro} (left to right).

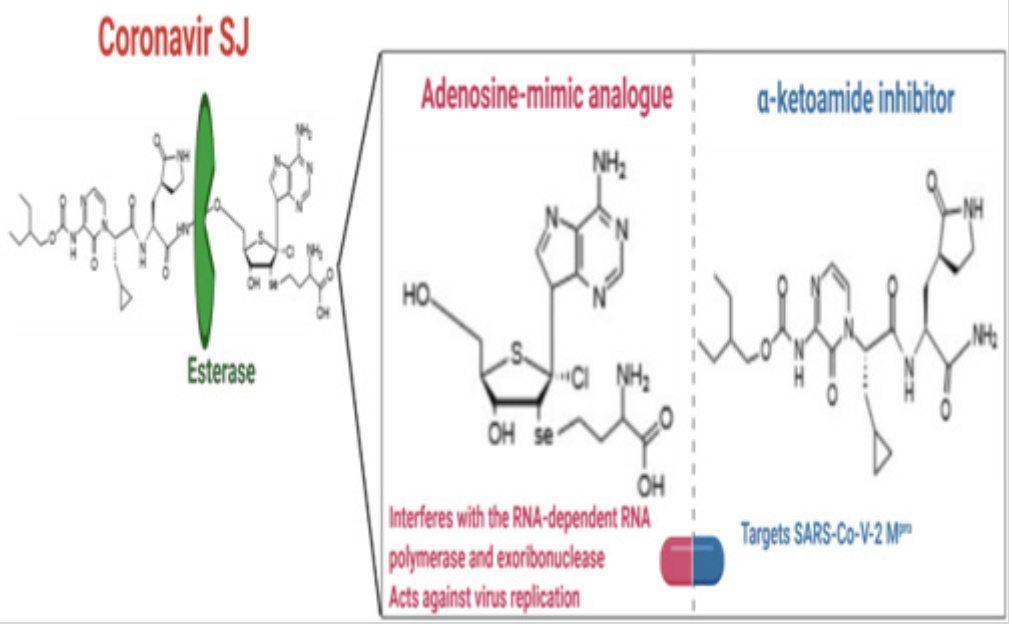
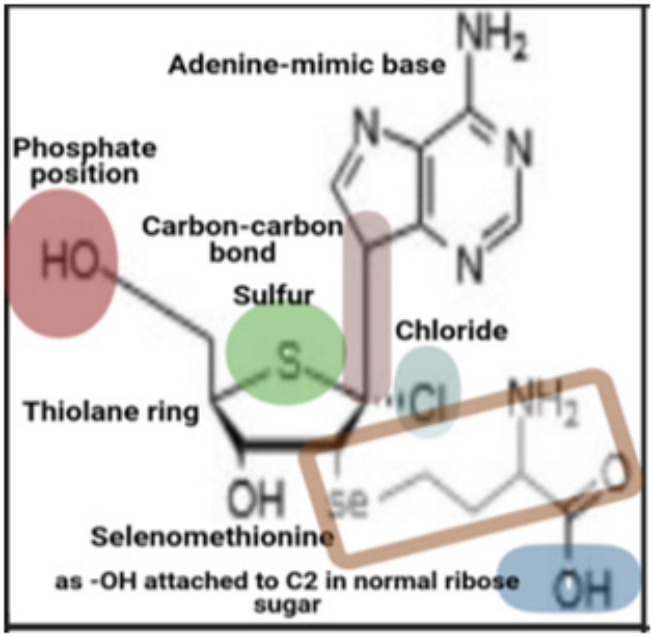
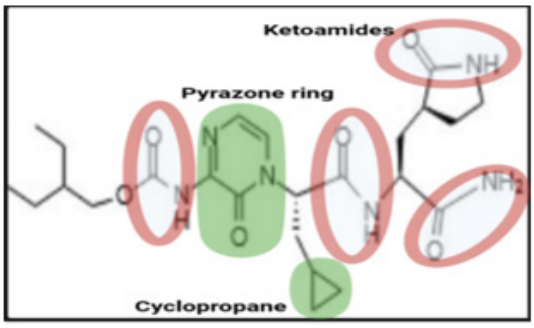


Figure 2: Proposed Coronavirus SJ structural design as a potential antiviral for SARS-Co-V-2. Coronavirus SJ prodrug converts into its active metabolites (adenosine-mimic analog and a-ketoamide inhibitor) in the blood for molecular two-sided targeting of RdRp SARS-CoV-2 and SARS-CoV-2 M^{pro} in SARS-CoV-2 RNA genome.

Table 1: Key features of designed adenosine-mimic analog and a-ketoamide inhibitor against SARS-CoV-2.

Structure	Characteristics
	1. Adenosine-mimic molecule Interferes with RdRp SARS-CoV-2. 2. Cl attached to the sugar causes crinkling of sugar shape once the drug Incorporated into the RNA growing chain, which, in turn, distorts the shape of RNA strand while the addition of 3-4 nucleotides. This terminates the production of RNA strand leading to ultimately sabotages the SARS CoV 2 replication. 3.Change of C-N bond in adenosine into C-C bond Is critical to drug effectiveness. This chemical bond Is stronger enough to hinder exoribonuclease In coronaviruses to recognize unnatural nucleotides and clips them out after the proofreading process, allowing the drug to sustain In the growing chain and block the replication. 4.Thlolane ring looks like a ribose ring that augments distortion of RNA shape. 5.Selenomethlonlne moiety regards as a hidden weapon against the virus via its powerful antioxidant effect and further protection of cellular damage resulting from free radicals of existing viral Infection or later. There Is no fear of attacking It because methionine Is a regular protein in the body and also the end-OH group resembles a normal ribose -OH.
	1. α-ketoamide inhibitor interferes with SARS CoV·2 main protease (M^{pro} or $3CL^{pro}$) leading to preventing proteolytic cleavage of pp1a and pp 1ab polyproteins and blocking the translation of SARS-CoV-2 RNA. 2. Ketoamide groups are intriguing keys facilitating a robust binding owing to the relative similarity of 3CLpro structure. 3. Addition of pyrazone plus cyclopropane rings ameliorates the compound half-life in plasma. 4.There is no fear of high mutation or variation rates.

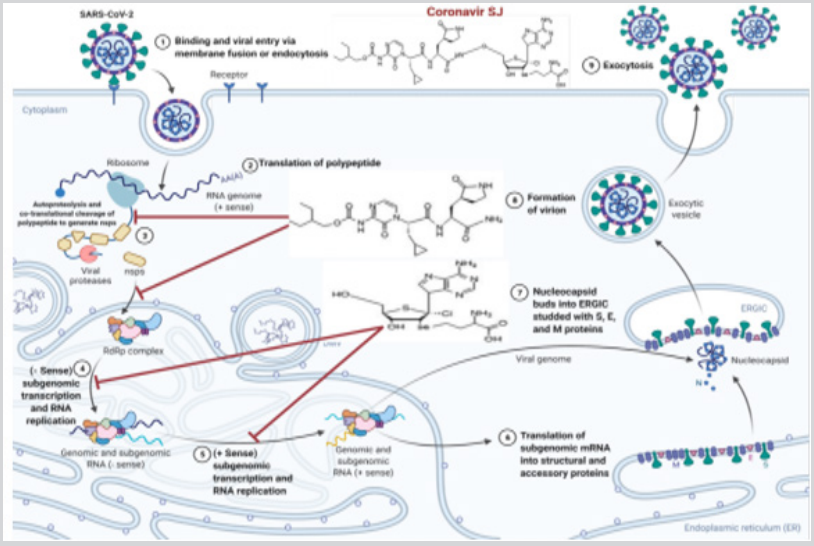


Figure 3: Proposed Coronavir SJ mechanisms of action across the infected cell as a potential antiviral for SARS-Co-V-2. Coronavir SJ prodrug converts into its active metabolites (adenosine-mimic analog and a-ketoamide inhibitor) in the blood for molecular two-sided targeting of RdRp SARS-CoV-2 and SARS-CoV-2 M^{pro} in SARS-CoV-2 RNA genome. Adenosine-mimic analog blocks genomic replication and sub genomic transcription of main structural proteins of SARS-CoV-2. a-ketoamide inhibitor inhibits autoproteolysis process blocking polypeptide cleavage to produce different non-structural proteins (NSPs). Both thus could hinder SARS-CoV-2 to invade excessive human cells leading to curb SARS-CoV-2 progression.

The formula of adenosine-mimic analog is C16H23N5O4SSeCl. Mechanistically, the main adenosine-mimic analog activity is relied on compromising the viral RNA-dependent RNA polymerase in infected cells, whereas it interferes with the proofreading function of exoribonuclease of newly synthesized RNA to excise nucleotide-based therapeutics that should not be integrated into the RNA leading to a reduction in SARS-CoV-2 RNA replication and production [16]. This compound is similar to adenosine nucleotide which is bioactivated within cells via kinases by the triphosphate's addition for compromising RNA synthesis (not DNA synthesis), thus it is active against SARS-CoV-2 RNA. The most significant activity of this active metabolite triphosphate is being the interference with RNA-dependent RNA polymerase (RdRp) and exoribonuclease enzymes. This compound suppresses active sites in both SARS-CoV-2 enzymes (RdRp and exonuclease). This leads to a rising integration; retarded chain ends, and reduced excision (Figure 4).

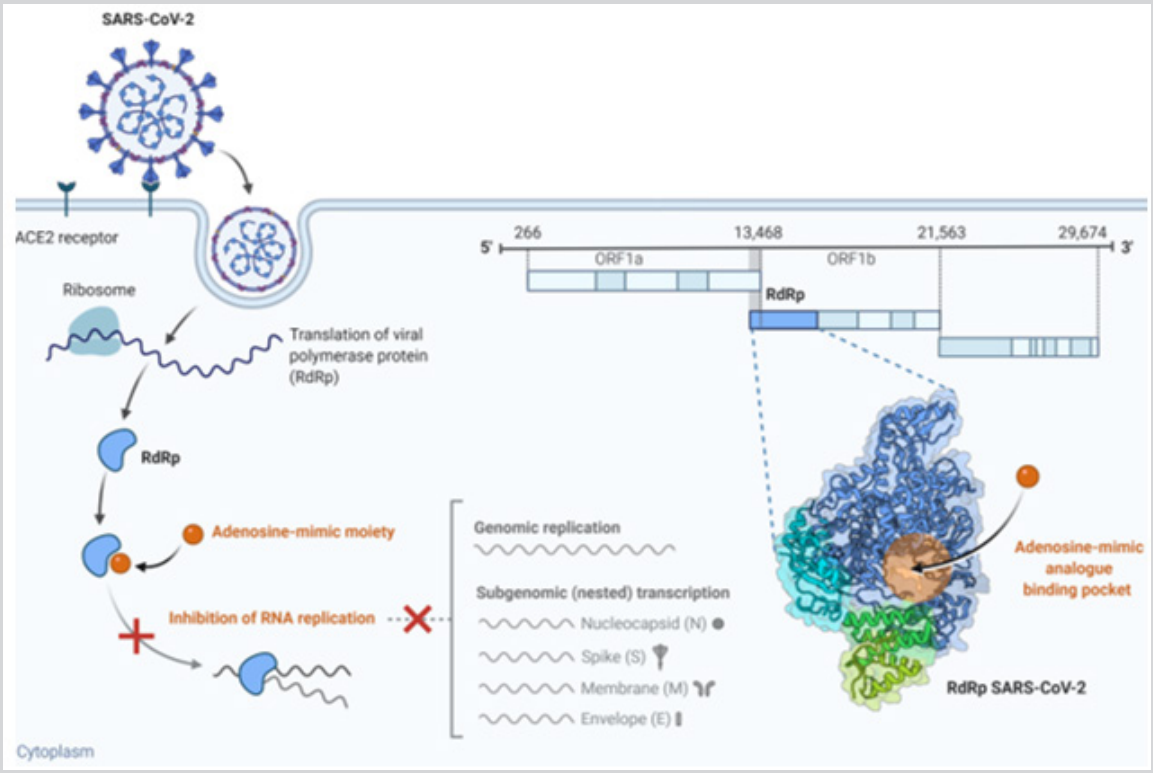


Figure 4: Proposed mechanism of action of adenosine-mimic analog against SARS-CoV-2 progression. adenosine-mimic analog attaches to its binding pocket of RdRp-SARS-CoV-2, it initially inhibit RNA replication blocking genome replication and subgenomic transcription of nucleocaspid, spike, membrane, and envelope proteins, thereby control SARS-CoV-2 cellular invasion and progression.

On the other hand, an α-ketoamide inhibitor with the formula C24H35N6O6 overlaps with SARS-CoV-2 M^{pro} (also called 3CL), is the substantial protease characterizing with cleavage specificity that totally different to all human proteases, responsible for processing polyproteins pp1a and pp1ab that are translated from the viral RNA into different putative non-structural proteins (NSPS). Zhang and co-authors reported a recent study in science indicating the crystal structure of SARS-CoV-2 M^{pro} prompting researchers for creating and synthesizing innovative inhibitors for SARS-CoV-2 M^{pro} targeting [17]. Downregulation this main target would prohibit viral RNA replication and block the formation of structural proteins (Spike protein, Nucleocapsid protein, Membrane protein, and Envelope protein). This leads to the viral assembly via polyproteins cleavage preventing COVID-19 progression (Figure 4).

A two-sided therapeutic platform has been planned to reveal a promising therapeutic candidate with a state-of-the-art manner exerting the probability of potent and efficient inhibition of SARS-CoV-2. Coronavir SJ could provide a selectively favorable therapeutic inhibitor for SARS-CoV-2. This hypothesis displays new analogs of essential molecules targeting SARS-CoV-2 that could be incorporated into one chemical structure to provide us tremendous advantages for SARS-CoV-2 therapy (Figure 5). These scientific and technical merits encompass that Coronavir SJ is a prodrug thus it must be modified once administered in the body before it becomes an active drug. Prodrugs are regularly utilized for many reasons, including protecting a drug till reaching its location of action. This prodrug would provide two active drugs targeting two different sites of action with versatile functions. It is administered directly into the blood, accelerating its action and preserving it from major absorption and metabolic barriers. In addition, there is no fear of rapid mutation of SARS-COV-2 because this drug targets the backbone of the virus with a minor possibility of variation comparable with targets that regulate spike proteins production. Eventually, the existence of selenomethionine could represent a powerful antioxidant as a hidden weapon for extra protection from cellular damage resulting from the release of endogenous free radicals once viral infection incidence.

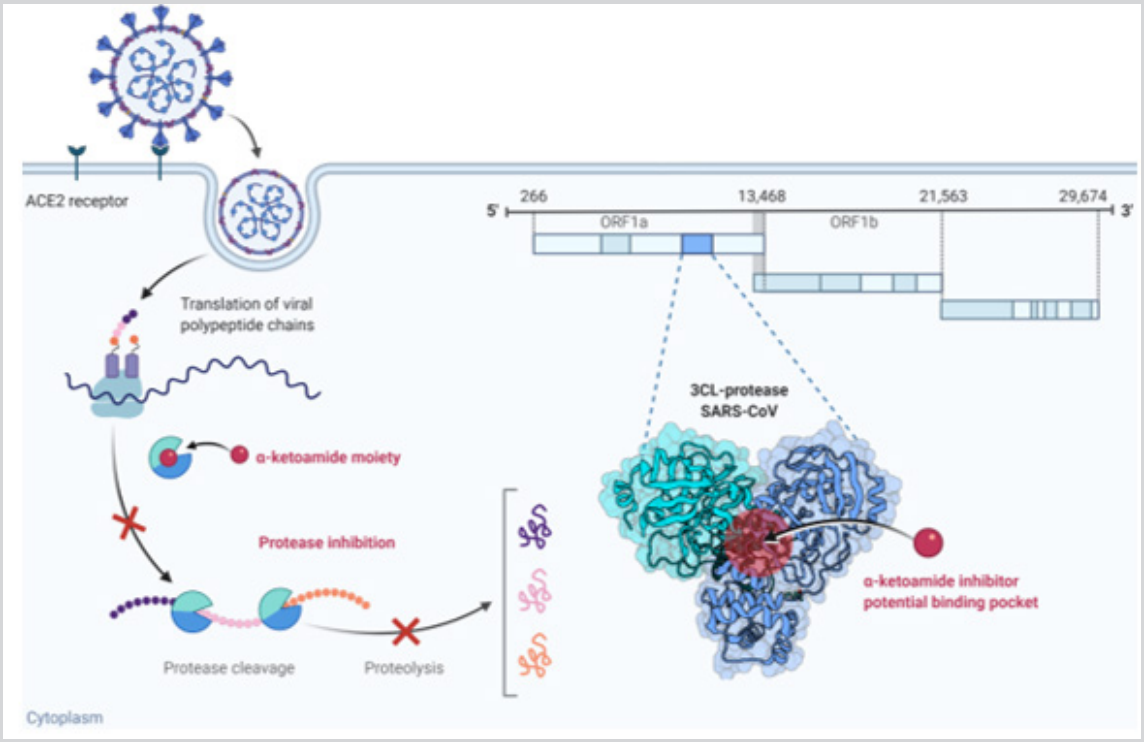


Figure 5: Proposed mechanism of action of a-ketoamide inhibitor against SARS-CoV-2 progression. a-ketoamide inhibitor attaches to its binding pocket of SARS-CoV-2 M^{pro}, it could cause protease inhibition blocking polyproteins pp1a and pp1ab cleavage that are translated from the viral RNA into different putative non-structural proteins (nsps), thus preventing moving to genomic replication and subgenomic transcription of nucleocaspid, spike, membrane, and envelope proteins for control SARS-CoV-2 cellular invasion and progression.

CONCLUSION

On the basis of SARS-Co-V2 pathogenesis and virulence, we hypothesise that two-sided targeting of both RdRp SARS-CoV-2 and SARS-CoV-2 M^{pro} harnessing new antiviral structural design to be a potent and selective inhibitor for SARS-CoV-2 without interference with animal or human enzymes or DNA, hence it is unlikely to be pharmacologically toxic. Although this design might be evidenced insufficient, we discuss that this therapeutic insight boosts several questions for upcoming research. Future scientific research is urgently needed to evaluate the potential therapeutic activity of Coronavir SJ on SARS-CoV-2.

Animal experiments and clinical trials should be performed to examine the in vivo effects of both adenosine-mimic analog and α-ketoamide inhibitor on SARS-CoV-2. Such beneficial frameworks could be exploited for further therapeutic studies and research purposes in the future. We believe that dense research efforts from scientists and researchers should be recommended to guarantee COVID-19 pandemic control and termination.

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AUTHORS CONTRIBUTION

SAM and EIAS -conceived and designed the study, were responsible for the data acquisition, analysis, and interpretation. EIAS -responsible for the manuscript drafting. SAM – responsible for critical revision for important intellectual content. All the authors approved the manuscript final version submitted and all of the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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