PŘEHLEDY A ODBORNÁ SDĚLENÍ

# Ingavirin might be a promising agent to combat Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2)

## Ingavirín môže byť sľubnou zlúčeninou v boji proti koronavírusu 2 vyvolávajúcemu ťažký akútny respiračný syndróm (SARS-CoV-2)

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**Summary**

The Severe Acute Respiratory Coronavirus 2 (SARS--CoV-2) and Coronavirus Disease-19 (COVID-19) pandemic, caused by the virus, have changed the world in just half a year. Lack of effective treatment, coupled with etiology of COVID-19, has resulted in more than 500,000 confirmed deaths at the time of writing, and the global economy is at an unseen unprecedented low level with unknown near- and long-term consequences. Ingavirin has been considered a non-toxic broad-spectrum antiviral with a complex mechanism of action. The molecule was originally designed for the prophylaxis and treatment of flu caused by both Influenza A and B viruses and for the treatment of viral causes of acute respiratory illness. The article hypothesized that the efficiency of given 1*H*-imidazol-4-yl heterocyclic scaffold-containing compound against SARS-CoV-2 might be connected with its ability to interfere with specific heterogeneous nuclear ribonucleoproteins (A1, for example). These specific cellular RNA-binding proteins showed affinity to Severe Acute Respiratory Coronavirus (SARS-CoV) nucleocapsid (N) protein, which shared high homology with the N protein of SARS-CoV-2 and the fact was expressed by a sequence identity of 90.52%. Impairing of the interactions between nuclear ribonucleoproteins and nucleocapsid (N) protein of SARS-CoV-2 might result in the inhibition of a viral replication cycle. Additional immunomodulating properties of ingavirin could be favorable for induction of adaptive immunity of host cells.

**Key words:** SARS-CoV-2 • COVID-19 • ingavirin • heterogeneous nuclear ribonucleoproteins • nucleocapsid (N) protein

**Súhrn**

Koronavírus 2 vyvolávajúci ťažký akútny respiračný syndróm (SARS-CoV-2) a pandémia ochorenia COVID-19 (COrona VIrus Disease-19), ktoré je týmto vírusom zapríčinené, v priebehu polroka zmenili svet. Deficit efektívnej terapie COVID-19, spolu s jeho etiológiou, rezultovali v čase písania tejto publikácie do viac ako 500 000 potvrdených úmrtí a globálna ekonomika je na nevídanej, bezprecedentne nízkej úrovni s neznámymi krátkodobými a dlhodobými dôsledkami. Ingavirín je považovaný za netoxické širokospektrálne antivirotikum s komplexným mechanizmom pôsobenia. Zlúčenina bola pôvodne projektovaná pre profylaxiu a liečbu chrípky, ktorá je zapríčinená vírusmi chrípky antigénnych typov A a B a pre liečbu ďalších akútnych respiračných ochorení vyvolaných inými vírusmi. V publikácii je formulovaná hypotéza o účinnosti tejto molekuly obsahujúcej 1*H*-imidazol-4-ylový heterocyklus proti SARS-CoV-2. Aktivita by mohla súvisieť so schopnosťou derivátu interferovať so špecifickými heterogénnymi nukleárnymi ribonukleoproteínmi (napríklad s typom A1). Tieto špecifické RNA-viažuce proteíny vykazovali afinitu k nukleokapsidovému proteínu (N-proteínu) koronavírusu vyvolávajúceho ťažký akútny respiračný syndróm (SARS-CoV), ktorý sa vyznačuje vysokou homológiou s N-proteínom SARS-CoV-2 vyjadrenou sekvenčnou zhodou 90,25 %. Narušenie optimálnych interakcií medzi nukleárnymi ribonukleoproteínmi a nukleokapsidovým proteínom SARS-CoV-2 by mohli rezultovať do inhibície rep-

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likačného cyklu tohto vírusu. Aditívne imunomodulačné vlastnosti ingavirínu by mohli byť výhodné pre indukciu adaptívnej imunity hostiteľských buniek.

**Kľúčové slová:** SARS-CoV-2 • COVID-19 • ingavirín • heterogénne jadrové ribonukleoproteíny • nukleokapsidový proteín (N-proteín)

## Introduction

Coronavirus Disease-2019 (COVID-19) is an infectious illness caused by a novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), formerly known as novel Coronavirus (2019-nCoV) or Wuhan Coronavirus. The virus first originated in Wuhan, the capital of Hubei Province (China), spreading globally and affecting more than 200 countries till now. The disease has rapidly become a global health pandemic[1].

Coronaviruses (CoVs) are a large family of pathogenic enveloped viruses with a positive-sense single-stranded RNA genome. CoVs belong to the *Coronaviridae* family of the *Nidovirales* order. The viruses have been classified into four genera that include α-, β-, γ-, and δ-CoVs. Among them, α- and β-CoVs infect mammals, γ-CoVs infect avian species, and δ-CoVs are able to infect both mammals and aves[2].

The whole genome of a zoonotic SARS-CoV-2 (β-CoV, subfamily *Coronavirinae*, family *Coronaviridae*, order *Nidovirales*) is composed of approximately 30,000 nucleotides, which encodes many structural proteins (SPs) as well as non-structural proteins (NSPs).

The SPs include transmembrane spike (S), envelope (E), membrane (M) and highly immunogenic nucleocapsid (N) proteins, which are needed to produce a structurally complete viral particle. Their specific structural organizations and functions were described comprehensively in previous research[3, 4].

Design and development of SARS-CoV-2 specific direct-acting antiviral drugs can be made possible by focusing on not to the SPs only but conserved enzymes (NSPs), such as main protease or 3C-like protease (Mpro or 3CLpro), papain-like protease (PLpro), helicase (non-structural protein 13; nsp13), non-structural protein 12 (nsp12) or RNA-dependent RNA polymerase (RdRp), are very promising viral targets as well[5, 6].

The SARS-CoV-2 genome shared about 82% sequence identity with Severe Acute Respiratory Coronavirus (SARS-CoV) reported earlier and more than 92% sequence identity for SPs and essential enzymes[3, 7].

Many drugs (or their combinations) from various pharmacotherapeutic groups that could potentially target specific viral proteins (targets) or critical host cell processes have been evaluated *in vitro* against SARS-CoV-2 or as treatment interventions for COVID-19 in clinical trials[8], however, minimal attention[8–10] has been paid to **ingavirin** (Fig. 1) as a promising therapeutic modality.

## Ingavirin acts as a powerful weapon against Influenza viruses and other viral causes of acute respiratory illness

**Ingavirin** (Fig. 1), a well-tolerated and safe 6-[2-(1*H*-imidazol-4-yl)ethylamino]-5-oxohexanoic acid (CAS Registry Number: 219694-63-0), was developed in the Russian Federation. The drug was recently added to a list of Influenza-limiting antivirals because of its direct interference with transportation of a newly synthesized viral nucleocapsid protein (nucleoprotein or N protein)[11].

The molecule, also known as **ingaviruin**, was approved recently in the Russian Federation for the prophylaxis and treatment of flu caused by Influenza A (species *Influenza A virus*; genus *Influenzavirus A*; family *Orthomyxoviridae*) and B (*Influenza B virus*; *Influenzavirus B*; *Orthomyxoviridae*) virus as well as other acute respiratory viral infections (ARVI)[12, 13]. This compound was also efficient against both pandemic A/California/04/2009 and A/California/07/2009 strains and other strains of Influenza viruses, i.e., H3N2 or H5N1[14].

**Ingavirin** interacted with the N protein of Influenza A and B Virus, thus preventing oligomerization of the protein, a process essentially required for viral replication[15]. The compound was found to impair the biogenesis of concerned protein, lower efficiency of formation of mature conformationally compact N protein oligomers and retard the migration of newly synthesized N proteins from cytoplasm to a nucleus[16–18].

Besides, non-steroidal anti-inflammatory drug **naproxen** (Fig. 2) competed with RNA for binding to the N protein binding groove[19] stabilizing protein monomers by altering the groove, in which an oligomerization loop interacted with RNA.

**Ingavirin** has been very efficient *in vivo* and *in vitro* against other RNA viruses, including Human Metapneumovirus (*Metapneumovirus*; *Pneumovirinae*; *Paramyxoviridae*)[20], Human Respiratory Syncytial Virus

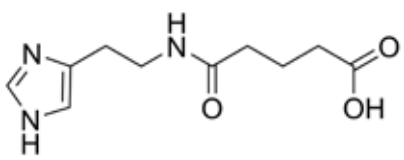


*Fig. 1. Ingavirin*

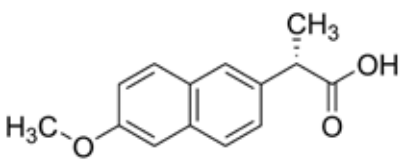


*Fig. 2. Naproxen*

(*Paramyxovirus*; *Paramyxoviridae*), Human Parainfluenza viruses (*Paramyxovirus*; *Paramyxoviridae*), the viruses, which can be found in *Picornaviridae* or *Coronaviridae* family as well as some DNA viruses (*Adenoviridae*)[21].

## Might be ingavirin effective against Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2)?

The N protein, an important antigen for SARS-CoV-2, is located within the virions in a complex with genomic RNA participating in RNA package and virus particle release. The nucleocapsid protein plays an essential role in enhancing the efficiency of subgenomic viral RNA transcription as well as viral replication. It was observed that this highly charged basic protein was full of coils, highly disordered, formed a dimer by the interaction of its both *C*-terminal domains and could interact with non-specific nucleic acids with high affinity, i.e., the dimeric form might act as a fundamental functional unit *in vivo*. Very notable finding was that the SARS-CoV-2 N protein shared high homology with SARS-CoV N protein, which was defined by sequence identity of 90.52%[22, 23].

The N protein of SARS-CoV has been regarded as one of the most crucial structural components of the virus being responsible for recognition of RNA stretch that served as a packaging signal leading to the formation of ribonucleoprotein. On the other hand, this protein shared 20–30% sequence identity (quite low homology) with N proteins of other CoVs[24, 25].

Luo et al. discovered that the N protein of SARS-CoV showed high binding affinity to human heterogeneous nuclear ribonucleoproteins (hnRNPs), especially to the A1 type (hnRNP A1), which was related to pre-mRNA splicing in a nucleus and translation regulation in cytoplasm[26].

**Ingavirin** interacted efficiently with the N protein of particular Influenza viruses and administration of concerned 1*H*-imidazol-4-yl cycle-containing small molecule in patients with asthma exacerbation associated with ARVI, including the one caused by SARS-CoV, increased effectiveness of the treatment. After being treated, fever periods were reduced, systemic manifestations were suppressed and, in addition, the number of bacterial complications was decreased by 15%[11, 27].

Tsai et al. concluded that specific cellular RNA-binding proteins, including NS1-binding protein (NS1-BP) and specific heterogeneous nuclear ribonucleoproteins (hnRNPs), regulated Influenza A Virus RNA splicing[28]. The hnRNPs assisted in controlling the maturation of newly formed heterogeneous nuclear RNAs (hnRNAs/pre-mRNAs) into messenger RNAs (mRNAs), stabilized mRNA during their cellular transport and regulated their translation. Considering their functional diversity and complexity, hnRNPs acted as the key proteins in cellular nucleic acid modifications[29].

Following the mentioned, the efficiency of **ingavirin** against SARS-CoV-2 might relate to its ability to interfere with hnRNP A1 and thus affecting the interactions between specific hnRNP A1 and viral N protein.

Additional beneficial immunomodulating properties of the drug were associated with the activation of a group of Toll-like and RIG-I-like receptor signalling pathways of innate and adaptive immunity and differentiation of hematopoietic cell precursors[30]. The receptors play a dominant role in first-line defence and in the induction of subsequent adaptive immunity[31, 32].

**Ingavirin**, although not being interferon (INF) inducer itself, enhanced synthesis of both INF-α and INF-β receptors to INF and cell sensitivity to INF signaling[33].

## Conclusion

**Ingavirin** might be considered a promising anti-SARS-CoV-2 drug due to probable interactions with specific heterogeneous nuclear ribonucleoproteins of the virus. The interferences would result in the inhibition of viral replication. Moreover, the compound provided additional beneficial immunomodulating properties. On the other hand, the indisputable fact is that **ingavirin** was not originally designed or structurally optimized as the anti-SARS-CoV-2 agent for the treatment of COVID-19 but was repurposed. Continuous intensive systematic *in silico* investigation employing relevant computational techniques, *in vitro* and *in vivo* evaluations of specifically designed compounds, which affect selectively very key proteins (targets) of SARS-CoV-2 responsible for its attachment and replication within host cells, might open the window for efficient, highly specific and safe therapy of COVID-19.

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