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Toward Fighting COVID-19 Pandemic: Drug Candidates and synthetic strategies for triazines with potential anti-viral activities against human coronaviruses

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Abstract

The COVID-19 pandemic, caused by SARS-CoV-2, has had a profound global impact, resulting in widespread infections and fatalities. Despite extensive research, no antiviral drugs have been clinically approved to specifically target the virus, highlighting the urgent need for innovative therapeutic approaches. Triazine-based compounds have gained attention as potential antiviral agents due to their broad-spectrum activity and ability to inhibit crucial viral enzymes, including the main protease (3CLpro) and RNA-dependent RNA polymerase (RdRp). Their synthetic versatility allows for structural modifications that enhance potency, selectivity, and pharmacokinetics, making them valuable candidates for drug development. Drug candidates for treating COVID-19 were reported. Crucial routes and novel synthetic strategies for many up-to-date triazine analogues were demonstrated for further drug development to overcome this outbreak.
This review explores the antiviral potential of triazine-based compounds and synthetic strategies for optimization. By highlighting their role in antiviral drug discovery, this work provides insights into their therapeutic potential for combating current and future coronavirus outbreaks.

1. Introduction

The COVID-19 pandemic, triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a devastating global impact, posing a serious public health threat [1]. Initially detected in Wuhan, China, in December 2019, the outbreak quickly escalated, prompting the World Health Organization (WHO) to classify it as the sixth Public Health Emergency of International Concern (PHEIC) [2-5]. Since then, the virus has spread across the globe, causing millions of infections and fatalities.

Coronaviruses (CoVs), members of the Coronaviridae family within the order Nidovirales, are distinguished by their

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crown-like spikes (Latin: *corona*) visible under electron microscopy [7-9]. Similar to other coronaviruses, SARS-CoV-2 is an enveloped, positive-sense single-stranded RNA (+ssRNA) virus with a genome size of 27–32 kb, making it the largest known RNA virus [10-12]. Its genome encodes 16 non-structural proteins (nsp1–nsp16) within the open reading frame (ORF) 1a/b at the 5′ end, followed by structural proteins—including nucleocapsid (N), spike (S), envelope (E), and membrane (M)—that are essential for viral entry, replication, and pathogenesis [4,6].

The spike (S) protein enables viral entry by recognizing and binding to the host cell receptor, angiotensin-converting enzyme 2 (ACE2), while the membrane (M) protein plays a crucial role in viral assembly and budding. Additionally, the envelope (E) protein contributes to morphogenesis and pathogenesis, further enhancing viral infectivity. Despite significant research efforts, no clinically approved antiviral drugs specifically target SARS-CoV-2, underscoring the critical need for innovative therapeutic strategies [7].

Among the diverse antiviral drug candidates, triazine-based compounds have garnered significant interest due to their broad-spectrum activity and favorable pharmacological profile. These heterocyclic compounds are recognized for their potent inhibitory effects on essential viral enzymes, including the main protease (3CLpro) and RNA-dependent RNA polymerase (RdRp), positioning them as promising candidates for antiviral drug development. Their synthetic versatility allows structural modifications to enhance potency, selectivity, and pharmacokinetics, further expanding their therapeutic potential.

Beyond their antiviral properties, triazines have been widely studied for their diverse biological activities. Numerous naturally occurring and synthetic triazine derivatives exhibit potent inhibitory effects against various biological targets [13], including tubulin [14], metalloproteinases [15], histone deacetylases [16], urease, and tyrosinase [17]. Moreover, some triazine-based compounds act as inhibitors of key protein kinases involved in critical signaling pathways associated with cancer cell proliferation, such as glycogen synthase kinase 3 [18], cyclin-dependent kinases [19], ABL kinase [20], and casein kinase 2 [21]. Their broad pharmacological relevance highlights their versatility in drug discovery and therapeutic applications [22-25]. To combat human disease-causing pathogens, extensive research has focused on the synthesis of diverse triazine derivatives, Structural variations, such as thiazole-triazines, quinoline-triazine hybrids, and s-triazine nucleobases, have been explored for their potential in treating several diseases [26- 39].

This review examines the antiviral potential of triazine-based compounds against coronaviruses, highlighting key drug candidates, and the synthetic strategies of triazine based compounds aimed at optimizing their therapeutic efficacy. Since triazine derivatives are being explored for their potential in antiviral drug discovery, a review of established and investigational antiviral agents helps to highlight key structural and mechanistic features that can inform the rational design of triazine-based antivirals and bridge the gap between existing and novel therapeutics. By providing insights into their role in antiviral drug discovery, this work aims to contribute to the development of effective treatments against current and future coronavirus outbreaks.

2. Drug candidates

2.1. Remdesivir

Remdesivir (GS- 5734) (Fig.1), is an adenosine triphosphate analog as an effective treatment for Ebola. Its potency against coronaviruses was also investigations in 2017. Remdesivir is moreover being studied as a compound that can be utilized for treating SARS-CoV-2.

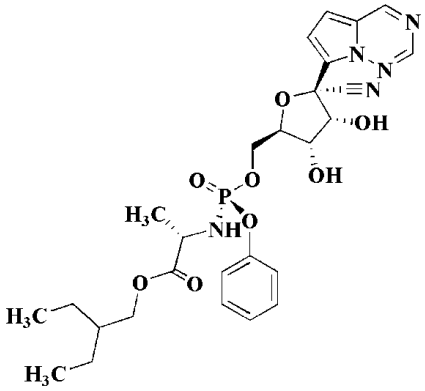


Fig. 1. Remdesivir

Remdesivir, a mono-phosphoramidate prodrug of the C-adenosine nucleoside analog GS-441524, inhibits the replication of the model β-coronavirus murine hepatitis virus and suppresses RNA synthesis in the wild-type virus. In contrast, an nsp14 ExoN (-) mutant, which lacks proofreading ability, exhibits increased susceptibility to remdesivir. Additionally, remdesivir effectively inhibits MERS-CoV infection in human amniotic epithelial cells, with an EC50 of 0.074±0.023 μM and a CC50 of 10 μM [40].

Remdesivir is an experimental anti-viral drug, designed for treating Ebola virus disease can potentially fight Nipah virus. Four African green monkeys completely were protected by using remdesivir from a lethal dose of Nipah virus. It is being developed by Gileald Sciences, INC. in cooperation with the centers for disease control and prevention [41].

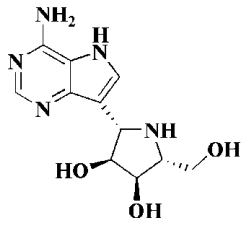


Fig. 2. BCX4430 (Immucillin-A)

In multiple in vitro systems, comprising primary human airway epithelial cell cultures with submicromolar EC_{50} values.

Remdesivir (GS-5734), a drug with anti-Ebola characteristics, has been indicated to inhibit MERS-CoV and SARS-CoV replication. Remdesivir's prophylactic and early therapeutic dosing lowered lung viral load and enhanced respiratory function with other clinical symptoms, according to experimental evaluation in a mouse model of SARS-CoV infection. Remdesivir's exact mode of action is yet unknown, but it is hypothesized that the molecule targets the viral polymerase's RdRP function.

2.2. Galidesivir

Galidesivir (BCX4430) (Fig.3) is nucleoside analogue that similar to other representatives of this group inhibit viral RNA polymerase function and result in chain termination. When it was adminstred intramuscularly after virus exposure in animal experiments, those drugs protected against EBOV infection. It is significant that remdesivir and galidesivir did not incorporate into human DNA or RNA underling the drug‘s potential for approval as the drug safety perspective showed, if clinical trials affirm animal experiments. Monentarily, utility of remdesivir and galidesivir might be a choice for compassionate utility for potentially exposed individuals [26, 28]. Remdesivir has recently also been observed to reveal reasonable antiviral potency against Lassa virus and Junin virus, both mammarena viruses resulting in high consequence disease and possessing the potential for misuse [42].

Galidesivir is classified as an adenosine analog and has been shown to inhibit Zaire Ebolavirus [43]. In vitro, it has demonstrated broad-spectrum antiviral activity against various negative- and positive-sense RNA viruses [44]. Additionally, this drug has exhibited antiviral efficacy against other coronaviruses [45]. Phase I clinical trials have been initiated to evaluate its safety in humans [46]. Given its potency against emerging coronaviruses, it may be explored as a potential therapeutic option for COVID-19.

2.3. Favipiravir

A new antiviral drug, favipiravir, T-705 (Fig.4), is a pyrazine carboxamide analog, its discovery was arisen in Japan as a candidate antiviral drug by Toyama chemical Co. It is potent against different viruses such as influenza viruses, west Nile virus, yellow fever virus, foot- and mouth disease virus, arenaviruses, flaviviruses, alphaviruses, bunyaviruses, norovirus and picornavirus. Favipiravir was affirmed in japan in 2014 for treating influenza virus disease [47].

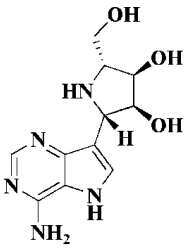


Fig. 3. Galidesivir

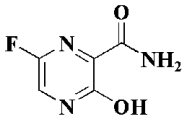


Fig. 4. Favipiravir

The effect of T-705 on NSP4 was also studied. The features of these virus variants in cell culture proposed that the target of T-705 is the highly preserved portion of the viral polymerase of positive-strand RNA viruses. Favipiravir & the ribofuranosyl triphosphate (Fig. 5) have indicated binding affinity for NSP4 protease domain. Metabolic experimentation affirmed a direct impact of favipiravir on CHIKV RNA synthesis [48].

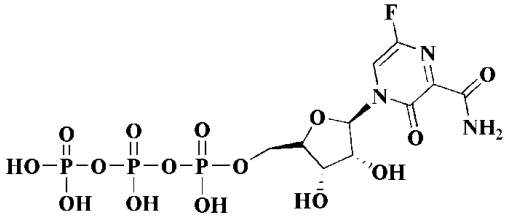


Fig. 5. T-705 ribofuranosyl triphosphate

Inhibition of the viral RNA-dependent RNA polymerase without inbition of cellular RNA and DNA synthesis is involved. Investigations with T-705 revealed inhibition of 2009 H1N1 influenza virus and H5 virus in vitro and animal model [49]. T-705 is undergoing clinical investigation for treating influenza A & B virus [50]. It is used experimentally in both China & Japan for treating SARS-CoV-2 [51]. The antiviral revealed effectiveness in treating SARS-CoV-2 through clinical trials [51, 52]. The approval of the drug Marketing affirmed in 2020 [51, 52].

2.4. Ribavirin & BILN 2061

Ribavirin (Fig.6), a nucleoside inhibitor, interacted with the catalytic site with remarkable binding energy [48]. Non-nucleoside inhibitors, as diketo acid analogs & BILN 2061

(**7**) (Fig.7), indicated well interactions with the thumb & palm allosteric sites. There is selective anti-viral potency of favipiravir on the replication of alphaviruses, CHIKV, and favipiravir-resistant CHIKV variants, which all bear a K291R mutation in the RdRp NSP4.

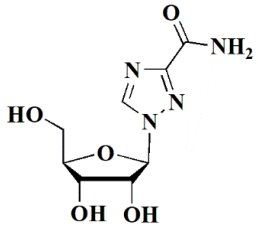


Fig. 6. Ribavirin

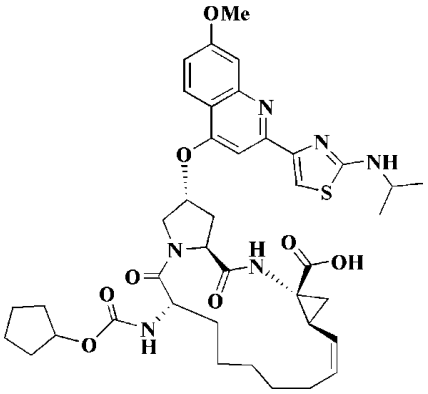


Fig. 7. BILN 2061

2.5. Umifenovir

The antiviral drug umifenovir (Fig.8) is considered as an indole-based analogue (arbidol), hydrophobic, and dual acting direct antiviral and host-targeting agent [49]. It was initially developed at the research institute of pharmaceutical chemistry in Russia. This drug has been utilized for the intervention of prophylaxis and acute respiratory infections such as influenza since 1990. Umifenovir shows inhibitory potency against CHIKV. The remarkable anti-viral potency of this drug might be ascribed to the varied mechanisms of action, counting interference with the first stages of CHIKV attachment or entry or the replication cycle, as well as changes of cellular membranes. A synthetic approach resulting in umifenovir comprises main steps which are the Fridel-Crafts alkylation, reductive cyclization, and the mannich condensation. Also, it can be furinshed via Nenitzescu indole synthesis, S-alkylation, acylation/bromination, and the mannich condensation [47].

Umifenovir's capacity to exert antiviral effects via multiple of pathways prompted research into the drug's applicability for different enveloped and non-enveloped DNA and RNA viruses. Due to the slow emergence of umifenovir resistance, its dual potency may also provide extra defence against viral resistance. Currently, umifenovir is being demonstrated as an effective therapeutic and prophylactic agent for the pandemic COVID-19 resulted from 2019-nCoV infections combining with investigational antiviral therapies [49].

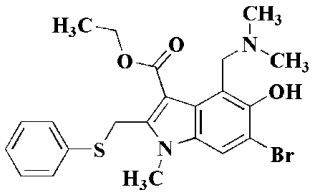


Fig. 8. Umifenovir

2.6. Lopinavir/ritonavir

Lopinavir/ritonavir (Fig.9, 10), Kaletra as a brand name, is an HIV-1 protease inhibitor. In 2000, that was first approved for the treatment of HIV-1 infection in the United States, often in combination with other anti-retrovirals [53, 54]. Low-level proof has proposed that the combination showed utility in treating earlier coronavirus outbreaks, as MERS-CoV & SARS-CoV, and it may be utilized in treating early SARS-CoV-2 infections [55].

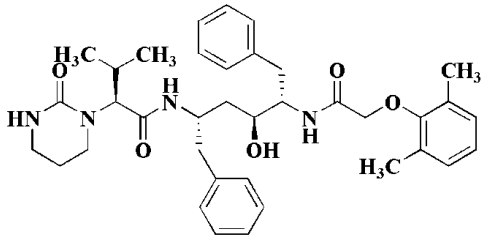


Fig. 9. Lopinavir DB01601

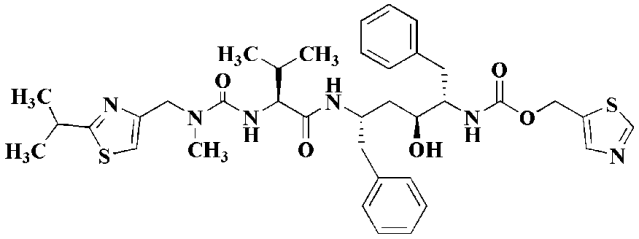


Fig. 10. Ritonavir DB00503

2.7. Triazavirin

Triazavirin (Fig.11) is an anti-viral agent developed in Russia that has demonstrated efficiency against influenza A & B, comprising the H5N1 strain [56, 57]. Triazavirin has indicated ability in eliminating influenza disease and its complications [58]. Because of the resemblances between H5N1 and 2019-nCoV, Triazavirin is demonstrated as a choice to combat SARS-CoV-2 [57].

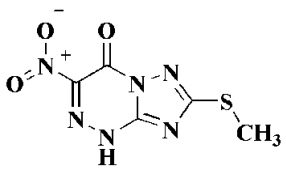


Fig. 11. Triazavirin

2.8. Darunavir

Darunavir (Fig.12) is a protease inhibitor utilized with other HIV protease inhibitor drugs for managing the infection of HIV-1. As a 2nd generation protease inhibitor, darunavir is designed and synthesized to challenge resistance to the standard HIV therapy. In 2006, the FDA approved it. Primary consequences from *in vitro* studies show that darunavir combined with umifenovir, an anti-viral utilized in treating the flu in China and Russia is potential in suppressing 2019-nCoV [49]. One more *in vitro* investigation also supports the utility of darunavir in COVID 19 treatment [59]. Clinical trials in humans are ongoing that combine cobicistat and darunavir, and identify the efficiency of this combination towards SARS-CoV-2 [60]. Currently, it is indistinct if the *in vitro* effects of darunavir combined with boosting agents will interpret to clinical effects in humans [61], but clinical trials may offer advance vision [62].

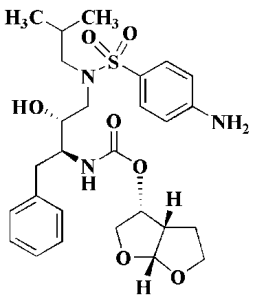


Fig. 12. Darunavir

2.9. TMC-310911

TMC-310911 (ASC-09) (Fig.13) is a new investigational protease inhibitor that is structurally close to the drug darunavir [63]. It has been demonstrated for utility in HIV-1 infections. It might provide benefits over currently available HIV therapies, for instance a broader *in vitro* resistance profile comparable to other currently used protease inhibitors.

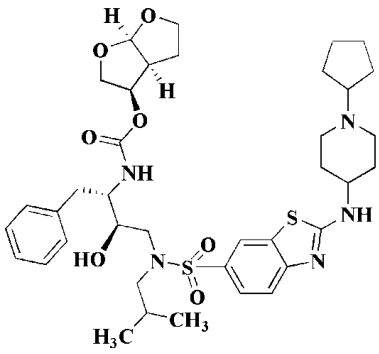


Fig. 13. TMC-310911

2.10. Chloroquine

Currently, chloroquine (Fig.14) is enduring clinical trials in China as an effective therapy for COVID-19 . CQ has been investigated to prevent viral entry into cells through increasing the pH of endosomes and inhibition of the glycosylation of ACE2. *In vitro* investigations have indicated the inhibition of infections at concs. seen in patients treated with CQ [64].

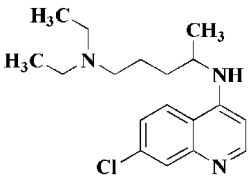


Fig. 14. Chloroquine

Using these medications for treating COVID-19 is still experimental, and they should not be used during these trials without medical supervision.

3. Chloroquine against coronavirus

In vitro, chloroquine is a bioactive agent possesses antiviral potency against RNA viruses as HIV [65-68], hepatitis C virus [69], hepatitis A virus [70, 71], hepatitis B virus [72], influenza A H5N1 virus [73], influenza A & B viruses [74-77] , Dengue virus [78, 79], Chikungunya virus [80-82], Zika virus [83], poliovirus [84], rabies virus [85], Lassa virus [86], Crimean–Congo hemorrhagic fever virus [87], Hendra and Nipah viruses [88, 89], herpes simplex virus [90] and Ebola virus [91].

Chloroquine (CQ) has been demonstrated to inhibit the in vitro coronaviruses' replication. Up-to-date researches lend credence to the idea that CQ can enhance the clinical outcome for SARS-CoV-2-infected patients. It is yet unknown how chloroquine achieves these outcomes at the molecular level [92-97]. Remarkably, it could be concluded that 2019-nCoV molecular crosstalk with its target cell can be changed via CQ through inhibiting kinases like MAPK.

CQ could also interfere with the M protein's proteolytic processing and cause alteration of virion assembly & budding.

Indirectly, this drug could act through eliminating the formation of pro-inflammatory cytokines and/or via the activation anti-SARS-CoV-2 CD8 + T-cells in COVID-19 disease. In 2007, the possibility of utilizing CQ to oppose orphan viral infections was demonstrated [98]. The clinical trials [99] will confirm if the hopes of utilizing CQ in treating COVID-19 can be vertified [100]. Chloroquine has side effects it affects vision and cause retinal toxicity [101], so we should search for the other analogs of chloroquine which may have not those serious side effects.

Herein there are the novel synthetic strategies of the triazine-based antivirals which should be a focusing spot on the methods of synthesizing various analogues that should be taken in concern to facilitate developing novel effective drugs is to begin from the chemical strategies outlined in this review.

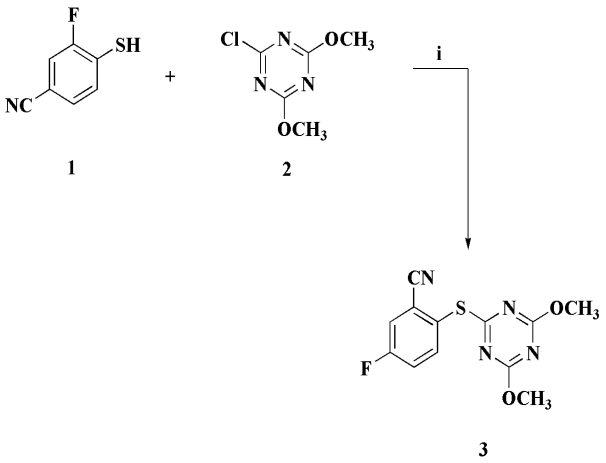
4. Synthetic Strategies for Triazine-Based Antivirals

4.1. Traditional S-Triazine Synthesis and Functionalization

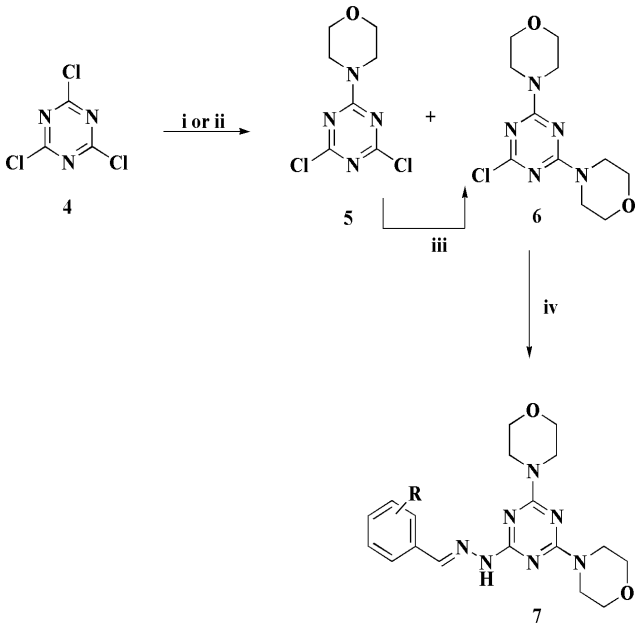
Compound **3** was synthesized from compound **1** and 2-chloro-4,6-dimethoxy-1,3,5-triazine **2** in the presence of triethylamine, using acetonitrile as the solvent (Scheme 1). The novel pyrithiobac (PTB) derivatives were systematically assessed across various biological platforms to determine their potential as antiviral agents. Notably, compound **3** demonstrated promising inhibitory activity against SARS-CoV Mpro, with an IC_{50} of 4.471 mM, while exhibiting low cytotoxicity in mammalian 293T cells. However, while its inhibitory potency is encouraging, the relatively high IC_{50} value suggests a need for further structural optimization to enhance efficacy. Molecular modeling results indicated that HOMO-1 plays a role in AHAS inhibition, and a potential binding mode of **3** with SARS-CoV Mpro was predicted [102], providing valuable insight into structure-activity relationships (SAR) for future modifications.

4.2 Morpholine-Assisted Functionalization of Triazines

A synthetic pathway was employed to obtain highly functionalized triazines. Compound **7** were synthesized from 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride, compound **4**) using the synthetic route outlined in Scheme 2. The s-triazine privileged scaffold was utilized to synthesize a series of derivatives, among which compound **7** emerged as the lead candidate, exhibiting micromolar activity against SARS-CoV-2. The low cytotoxicity observed in Caco-2 cells further supports its potential as a viable drug candidate. Preliminary mechanistic investigations revealed that **7** (R= 2-OH) inhibits the human DEAD-box RNA helicase DDX3X, a host factor critical for viral replication. Given that helicase inhibitors have been implicated in broad-spectrum antiviral activity, these findings suggest that compound **7** could be further explored for pan-coronaviral therapeutic potential [103].



Scheme 1. Reagents and Conditions:i) TEA,CH_3CN.



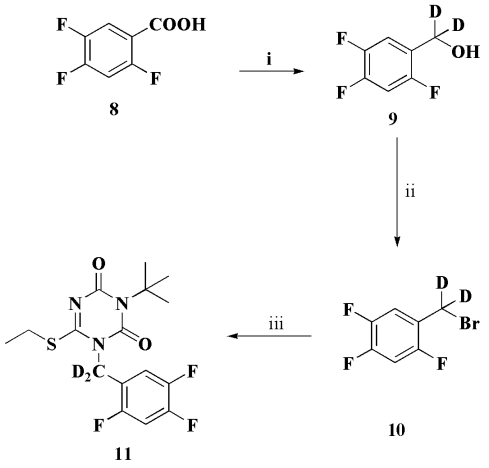
Scheme 2. **Reagents and Conditions: i)** CH_3OCH_3, -60 °C, $O(CH_2CH_2)_2NH$, 5 h; **ii)** Hünig′s base, $O(CH_2CH_2)_2NH$, EtOH, 25 °C, 18 h; **iii)** DCM, 25 °C, $O(CH_2CH_2)_2NH$, 18 h; **iv)** 1. DCM, NH_2NH_2, reflux 12 h, 2. $C_6H_5CH_3$, 2-hydroxybenzaldehyde, 3 h, reflux, Dean–Stark.

4.3 Cyclization Strategies with Carbonyldiimidazole (CDI)

The synthesis of compound **15** began with the reduction of 2,4,5-trifluorobenzoic acid (**8**) using $LiAlD_4$. Bromination of the resulting product (**9**) afforded the key deuterated intermediate **10**. Subsequent alkylation with 3-tert-butyl-6-(ethylthio)-1,3,5-triazine-2,4(1*H*,3*H*)-dione, followed by removal of the tert-butyl group and installation of the triazole moiety, yielded intermediate **14**. Final substitution of the

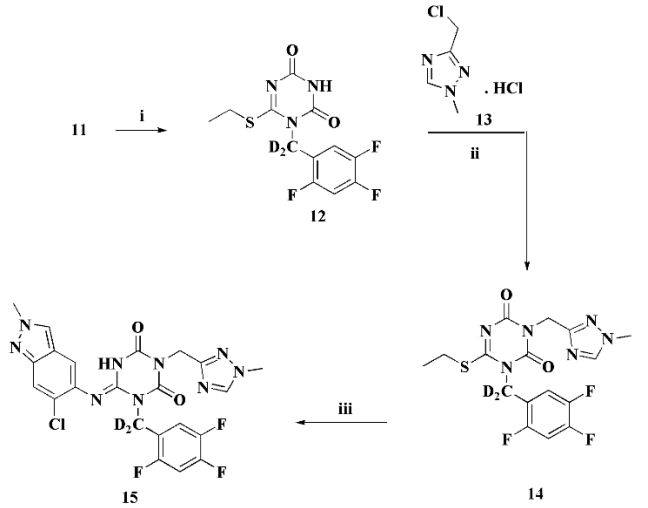
ethylthio group with the indazole unit furnished the C11-d_2 compound **15** (Scheme 3 & 4).

Compound **15** exhibited potent in vitro activity against SARS-CoV-2 3CLpro, with X-ray crystallographic analysis confirming key binding interactions. Its favorable pharmacokinetic profile, including bioavailability and plasma exposure, highlights its translational potential. Additionally, its broad-spectrum activity against other coronaviruses, particularly MHV-A59, reinforces its therapeutic relevance. However, its reduced efficacy against alphacoronaviruses underscores the need to fine-tune molecular features to achieve broader antiviral coverage [104].



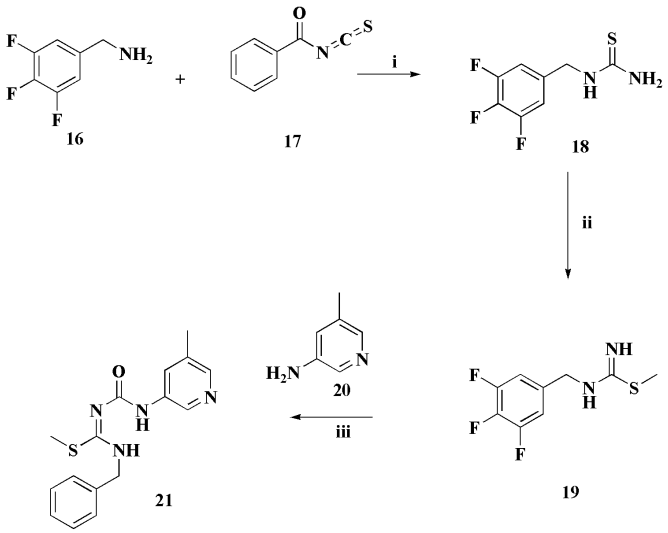
Scheme 3. Reagents and Conditions: i) $LiAlH_4$, $(CH_2)_4O$, 0 ◦C to rt; **ii)** Phosphorus tribromide, rt; **iii)** 3-tert-butyl-6-(ethylthio)-1,3,5-triazine-2,4(1H,3H)-dione, K_2CO_3, CH_3CN, 80 ◦C.

A new class of compounds is described as shown in schemes 5-8 that inhibit the coronavirus 3CL protease, along with their pharmaceutically acceptable salts and related pharmaceutical compositions. Additionally, the synthesis of these compounds and their efficacy based on in vitro and cell-based assays were performed [105].

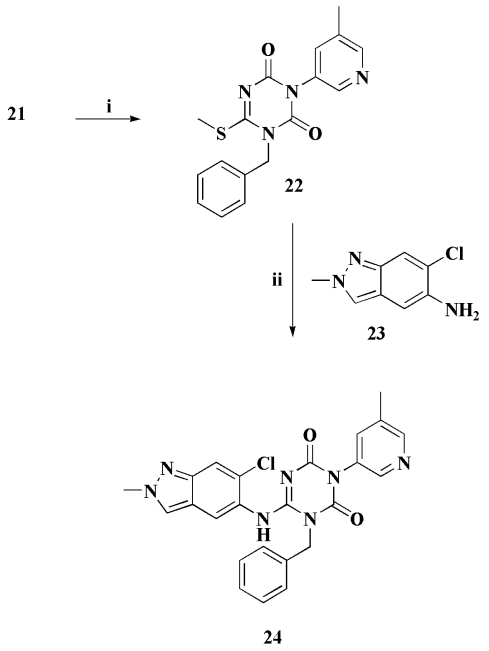


Scheme 4. Reagents and Conditions: i) TFA, rt; **ii)** K_2CO_3, DMF, 60 ◦C; **iii)** 5-amino-6-chloro-2-methyl-2*H*-indazole, Li(HMDS), $(CH_2)_4O$, 0 ◦C to rt.

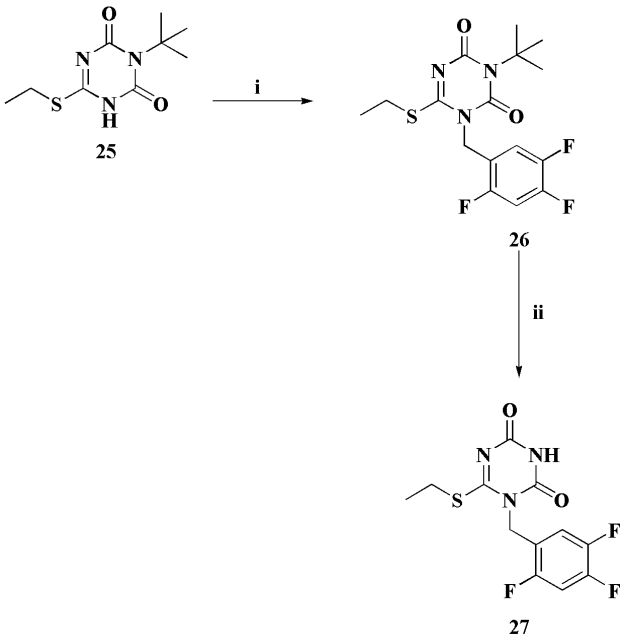
The synthetic process begins with the coupling of compound **16** and compound **17** to form an intermediate, which is then hydrolyzed using aqueous sodium hydroxide and subsequently acidified to yield compound **18** in quantitative yield. Methylation of the thiol group with methyl iodide in dimethylformmide at 50°C results in compound **19** with an 80% yield. Compound **19** is then coupled with compound **20** utilizing triphosgene and triethylamine, producing compound **21** in quantitative yield. Cyclization of compound **21** with carbonyldiimidazole (CDI) in the presence of *N*,*N*-diisopropylethylamine (DIEA) yields compound **22** at 35%. Finally, nucleophilic substitution of the thiomethyl group in compound **22** with compound **23** leads to the formation of compound **24** in 57% yield, as illustrated in Scheme 5 [105].



Scheme 5. Reagents and Conditions: i) 1. CH_2Cl_2, rt. 2. NaOH, CH_3OH. 3. HCl. **ii)** CH_3I, DMF, 50°C. **iii)** Triphosgene, THF, Et_3N.



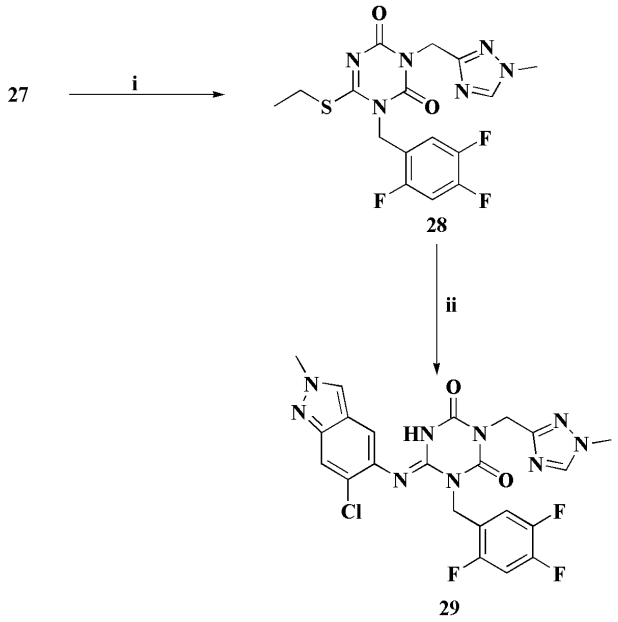
Scheme 6. Reagents and Conditions: i) DIEA, DMF. **ii)** LHMDS, THF.



Scheme 7. Reagents and Conditions: i) *α*-Bromo-2,4,5-trifluorotoluene, K_2CO_3, ACN, 80 °C; **ii)** CF_3CO_2H, rt.

The discovery of S-217622 (**29**), the first oral noncovalent, nonpeptidic SARS-CoV-2 3CLpro inhibitor, represents a significant advancement in COVID-19 therapeutics. Identified through a structure-based drug design approach, S-217622 demonstrated potent in vitro antiviral activity against circulating SARS-CoV-2 variants and exhibited favorable pharmacokinetic properties in vivo, supporting once-daily oral dosing. Its dose-dependent suppression of intrapulmonary viral replication in mice underscores its therapeutic promise. Nevertheless, further clinical validation is required to confirm its long-term efficacy and resistance profile against emerging variants [105,106].

The synthesis of S-217622 (**29**) is outlined in Scheme 8. Beginning with the known compound **25**, alkylation with 1-(bromomethyl)-2,4,5-trifluorobenzene produced compound **26** in 93% yield. Subsequent removal of the 3-*t*-Bu group, introduction of the triazole unit, and substitution of the SEt moiety with an indazole unit ultimately yielded S-217622 (**29**) [106].



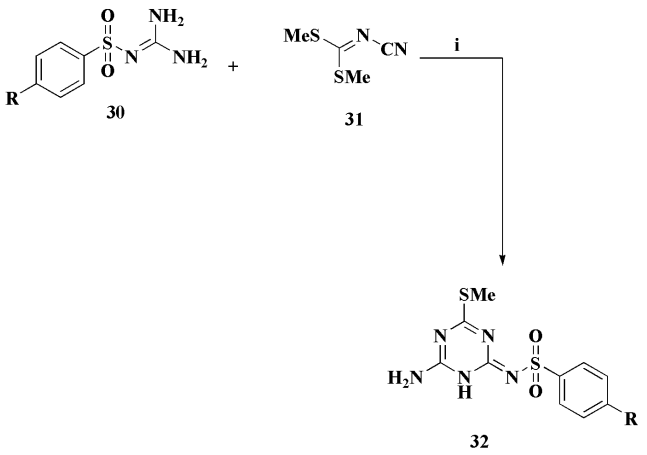
Scheme 8. Reagents and Conditions: i) 3-Chloromethyl-1-methyl-1*H*-[1,2,4]triazole hydrochloride, K_2CO_3, $HCON(CH_3)_2$, 60 °C; **ii)** 5-amino-6-chloro-2-methyl-2*H*-indazole, $LiN(Si(CH_3)_3)_2$, $(CH_2)_4O$, 0 °C to rt.

4.4. Synthesis of Triazine Sulfonamides via Cyanodithioiminocarbonate

Triazine sulfonamide derivatives emerged as another promising antiviral class. Notably, compound **32** exhibited superior antiviral activity against SARS-CoV-2 (IC_{50} = 2.378 μM) compared to remdesivir (IC_{50} = 10.11 μM), suggesting strong potential for further development. However, a

comprehensive pharmacokinetic and toxicity assessment is necessary to determine its clinical viability. Structural modifications may be required to optimize its drug-like properties while maintaining potency [107].

A novel approach for synthesizing triazine sulfonamide derivatives **32** involves the reaction of sulfaguanidine derivatives **30** with *N*-cyanodithioiminocarbonate **31** (Scheme 9). Subsequent modifications with several secondary amines and anilines produced substituted triazine sulfonamide analogs, which exhibited promising broad-spectrum biological activities, comprising antimicrobial, antitumor, and antiviral properties. The antiviral potential against SARS-CoV-2 was evaluated using the MTT cytotoxicity assay to determine the half-maximal cytotoxic concentration (CC_{50}) and inhibitory concentration 50 (IC_{50}) of a representative compound. Notably, compound **32** (R =H) demonstrated potent antiviral activity against SARS-CoV-2, with an IC_{50} of 2.378 µM, surpassing the efficacy of remdesivir (IC_{50} = 10.11 µM). These findings indicate that, with further optimization, triazine sulfonamides could be promising candidates for antiviral drug development [107].



Scheme 9. Reagents and Conditions: i) Diethylene dioxide, KOH, reflux, 2 h.

Novel substituted 1,3,5-triazine sulfonamide thioglycosides have been designed and synthesized through an efficient direct approach, starting from potassium cyanocarbonimidodithioate. This highly reactive intermediate was reacted with substituted sulfonyl guanidines to yield the corresponding 1,3,5-triazine sulfonamides. The final triazine sulfonamide thioglycosides were then obtained by coupling these sulfonamides with peracylated α-D-gluco- & galacto-pyranosyl bromides. The novel synthesized compounds were characterized via spectroscopic techniques and elemental analysis.

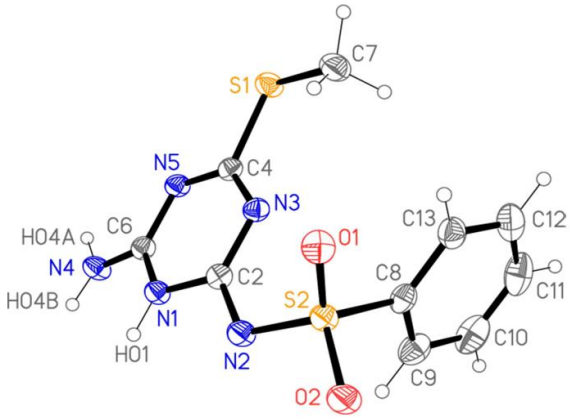
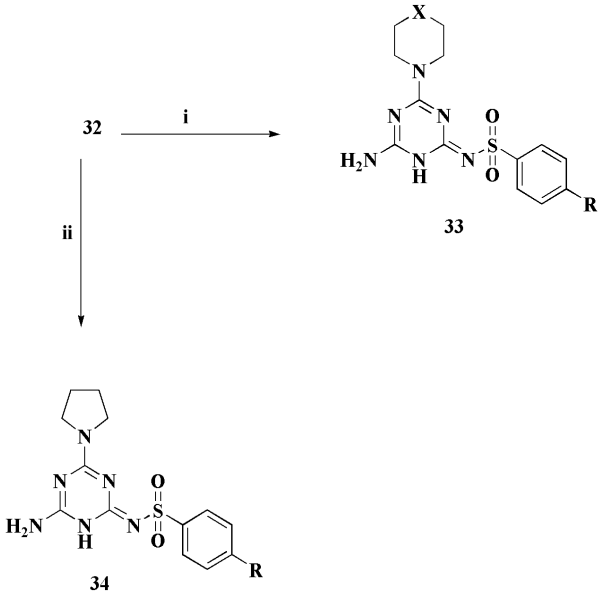


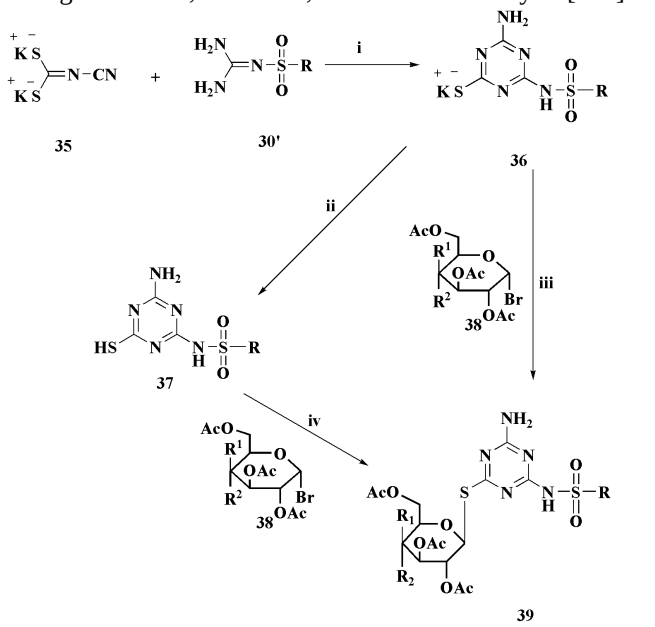
Fig.15. The molecule of Structure **32** in the crystal. The figure is reproduced with permission from the International Union of Crystallography under an open-access license." [108]



Scheme 10. Reagents and Conditions: i) Diethylene dioxide, amine, K_2CO_3, reflux, 2 h. **ii)** Diethylene dioxide, pyrrolidine, K_2CO_3, reflux, 2 h

The synthesis of novel triazine sulfonamides was achieved using the cyanocarbonimidodithioate **35**, which was prepared by reacting carbon disulfide with aminomethanenitrile in the presence of potassium hydroxide in ethylalchol. Compound **35** was then refluxed with substituted sulfonyl guanidines in the presence of sodium ethoxide in dimethylformamide, yielding potassium triazine sulfonamide thiolates **36**. Subsequent treatment with hydrochloric acid afforded the corresponding sulfanyl triazine sulfonamide derivatives **37** in high yields. The structures of compounds **37a-d** were confirmed utilizing spectral data. Compounds **36a-d** were further reacted with halosugars **38** in dimethylformamide at room temperature, resulting in the formation of the corresponding *S*-glycosides **39a–e**, as outlined in Scheme 11. The reaction of substituted 1,3,5-triazine-4-thiolate salts **36** and halosugars **38** followed an SN2 mechanism, producing β-glycosides from the cis-(α)

sugars. At room temperature, compounds **36a-d** were successfully coupled with activated sugars, leading to the formation of substituted 1,3,5-triazine sulfonamide thioglycosides **39a-e**. The structures of **39a-e** were confirmed through ^{1}H-NMR, ^{13}C-NMR, and elemental analysis [109].



36, 37	R	39	R	R^1	R^2
a	CH_3	a	CH_3	H	OAc
b	C_6H_5	b	C_6H_5	H	OAc
c	4-CH_3.C_6H_4	c	4-CH_3.C_6H_4	H	OAc
d	4-Cl.C_6H_4	d	C_6H_5	OAc	H
		e	4-CH_3.C_6H_4	OAc	H

Scheme 11. Reagents and conditions: i) Sodium ethoxide, DMF, reflux, 0.5-1h. **ii)** Hydrochloric acid, H_2O, RT, 5 min. **iii)** DMF, RT, 24h. **iv)** KOH, DMF, RT, 24h.

The in vitro antiviral evaluation of the compounds against the HCoV-229E virus revealed that some exhibited promising activity. Compounds **37a**, **37b**, **37d**, **39d**, and **39e** demonstrated moderate to low antiviral activity (27.65%, 24.41%, 24.17%, and 29.7%, respectively) against the low-pathogenic HCoV-229E virus, compared to remdesivir (67.2%) at a concentration of 100 µg/mL**.**

Additionally, there in vitro antiproliferative effects were assessed against the NCI-60 cancer cell lines**.** Among them, compound **37a** emerged as the most potent, exhibiting the lowest cell growth promotion against CNS cancer SNB-75 (GP = 65.22%) and renal cancer UO-31 (GP = 67.34%) [82].

4.5. Fatty Acyl Conjugation of Triazine Derivatives

Fatty acyl conjugation was explored as a strategy to enhance remdesivir's pharmacokinetic properties. While monofatty acyl derivatives such as **43b** showed improved metabolic stability (77.9% intact after 4 hours in human plasma compared to 47% for RDV at 2 hours), their antiviral potency was lower than that of RDV. In contrast, difatty acylation significantly reduced activity against SARS-CoV-2, indicating that careful structural tuning is necessary to balance stability and efficacy. These findings highlight the potential of fatty acylation as a prodrug strategy, albeit with the need for further refinement to achieve optimal antiviral performance [110].

This study presents the synthesis and characterization of mono- and di-fatty acyl conjugates of remdesivir (RDV) and evaluates there in vitro antiviral activity against SARS-CoV-2, an Ebola virus transcription- and replication-competent virus-like particle (trVLP) system, and infectious Ebola virus [110].

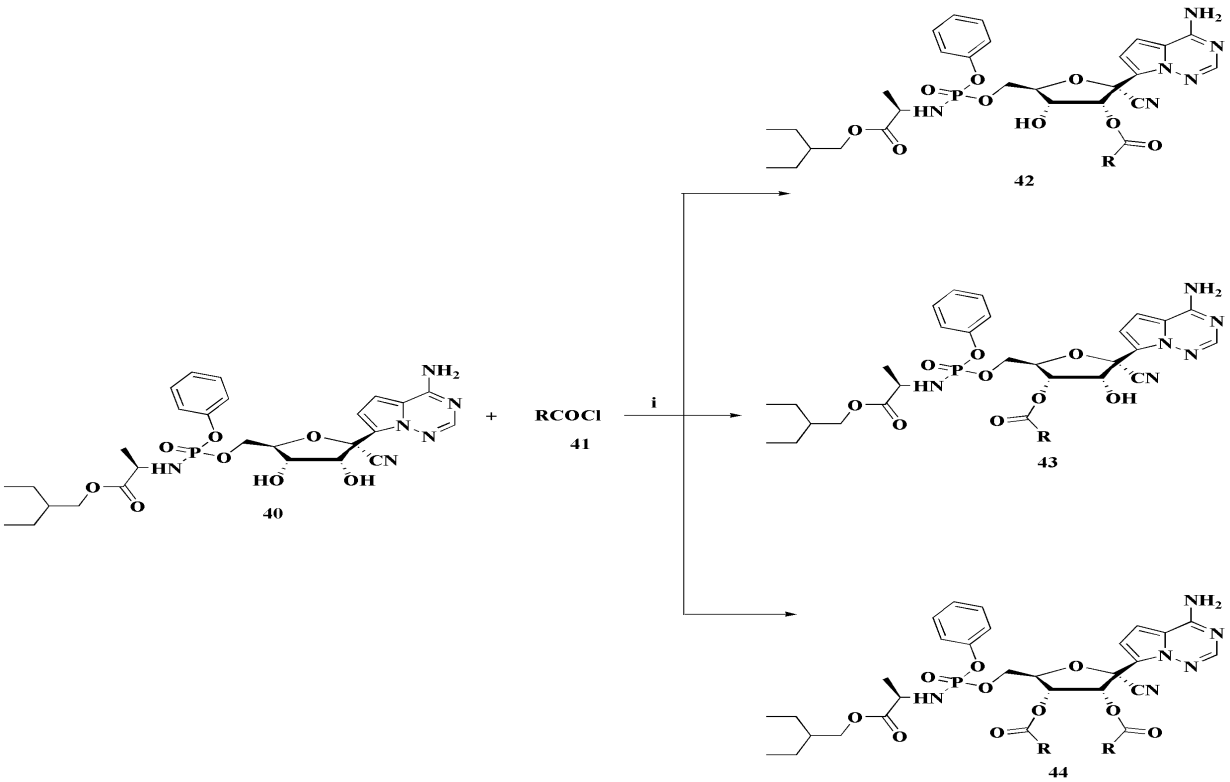
Among the synthesized compounds, the most potent monofatty acyl conjugate was **43b**, which contains a 4-oxatetradecanolyl modification at the 3′ position. Monofatty acyl conjugates, including 3′-O-tetradecanoyl **43a** (IC_{50}: 2.3 µM in VeroE6, 0.24 µM in Calu3), 3′-O-4-oxatetradodecanoyl **43b** (IC_{50}: 2.0 µM in VeroE6, 0.18 µM in Calu3), and 3′-O-(12-ethylthiododecanoyl) **43e** (IC_{50}: 2.4 µM in VeroE6, 0.25 µM in Calu3), exhibited lower activity than RDV (IC_{50}: 0.85 µM in VeroE6, 0.06 µM in Calu3). However, difatty acylation significantly reduced RDV's antiviral activity against SARS-CoV-2, as observed in conjugates **44a** and **44b**, when compared to monofatty acyl derivatives **42a-e** and **43a-e** [110].

Metabolic stability studies revealed that 77.9% of compound **43c** remained unchanged after 4 hours of incubation in human plasma, whereas only 47% of the parent RDV was detected at the 2-hour time point. These findings highlight the potential of fatty acylation to enhance RDV's half-life. Additionally, several monofatty acyl conjugates, including **42b, 42e**, and **43b**, demonstrated antiviral activity comparable to RDV in the Ebola trVLP system.

A remarkable reduction in viral RNA synthesis was observed for selected compounds **42a** and **43b**, aligning with their IC_{50} values. These results suggest that monofatty acyl conjugates of RDV could serve as long-acting antiviral agents or prodrugs with improved pharmacokinetic properties [110].

5. The Selection of Specific Triazine Analogs and Their Potential Advantages Over Other Antiviral Compounds

Triazine-based compounds have emerged as promising antiviral agents due to their diverse functionalization potential, favorable pharmacokinetic properties, and broad-



Scheme 12. Reagents and Conditions: i) DIPEA, DCM, CH_3CN, 40°C, 5-9h.

spectrum activity against various viral targets. The selection of specific triazine analogs for antiviral drug development is justified based on multiple factors, including their structure-activity relationship (SAR), efficacy against viral proteases and helicases, and their ability to achieve favorable bioavailability and metabolic stability.

5.1. Advantages of Triazine Analogs Compared to Other Antivirals

5.1.1. Target-Specific Inhibition

Novel pyrithiobac (PTB) derivatives, particularly compound **3**, exhibit selective inhibition of SARS-CoV Mpro, an essential protease for viral replication. While the IC_{50} value (4.471 mM) necessitates optimization, molecular modeling insights into the binding interactions offer a foundation for rational drug design.

Morpholine-assisted functionalization of triazines resulted in compound **7**, which inhibits the human DEAD-box RNA helicase DDX3X, a host factor essential for viral replication. This broad-spectrum mechanism suggests potential application beyond SARS-CoV-2.

5.1.2. Enhanced Bioavailability and Pharmacokinetics

Cyclization strategies with carbonyldiimidazole (CDI) led to compound **15**, which demonstrated favorable bioavailability, plasma exposure, and potent activity against SARS-CoV-2 3CLpro. X-ray crystallography confirmed key binding interactions, reinforcing its suitability for further clinical development.

The synthesis of S-217622, a noncovalent, nonpeptidic SARS-CoV-2 3CLpro inhibitor, highlights the application of structure-based drug design in achieving potent antiviral activity with a once-daily oral dosing regimen.

5.1.3. Superior Potency Compared to Existing Antivirals

Triazine sulfonamide derivatives, particularly compound **32**, displayed an IC_{50} of 2.378 μM against SARS-CoV-2, significantly outperforming remdesivir (IC_{50} = 10.11 μM). This suggests a potential for triazine sulfonamides to serve as more effective therapeutic options.

In vitro evaluation of triazine sulfonamide thioglycosides revealed that certain derivatives demonstrated moderate antiviral activity against HCoV-229E, suggesting further refinement could yield broad-spectrum inhibitors.

5.1.4. Synthetic Versatility and Functionalization

Various synthetic strategies, including traditional *s*-triazine synthesis, morpholine-assisted functionalization, CDI-mediated cyclization, and cyanodithioiminocarbonate-based synthesis, enable structural diversity and optimization for enhanced antiviral efficacy.

The fatty acyl conjugation approach improved metabolic stability, as demonstrated by compound **43b**, which retained 77.9% integrity after 4 hours in human plasma compared to remdesivir's 47% at 2 hours. This suggests the potential for

developing long-acting antiviral prodrugs.

The selection of triazine-based antivirals is strongly supported by their target-specific inhibition, superior potency compared to existing drugs, and synthetic versatility. These properties provide a compelling rationale for further optimization and development of triazine derivatives as potential therapeutic candidates for combating SARS-CoV-2 and other coronaviruses. Future research should focus on structural refinements to enhance potency, reduce cytotoxicity, and broaden antiviral coverage to ensure the clinical success of these novel compounds.

6. Comparison of Synthetic Strategies for Triazine-Based Antivirals:

6.1. Traditional S-Triazine Synthesis and Functionalization

The traditional synthesis of *s*-triazine-based antivirals employs the privileged s-triazine scaffold as a core structure, leveraging well-established synthetic routes that typically yield high product efficiency. This method allows for extensive modifications at multiple positions, facilitating the enhancement of bioactivity against viral targets. However, its primary limitation lies in the restricted scope for introducing novel functionalities, which may hinder further optimization for emerging viral threats. Additionally, certain derivatives have demonstrated moderate cytotoxicity, necessitating careful evaluation in drug development.

6.2. Morpholine-Assisted Functionalization of Triazines

Morpholine-assisted functionalization of triazines involves regioselective modifications using morpholine and related reagents, offering improved solubility and bioavailability of the resulting antiviral compounds. This strategy enables precise fine-tuning of electronic and steric properties to optimize biological activity. However, it requires stringent reaction conditions to ensure selectivity and efficiency. Additionally, compared to other functionalization methods, it often involves longer reaction times, potentially impacting its practicality for large-scale synthesis.

6.3. Cyclization Strategies with Carbonyldiimidazole (CDI)

CDI-mediated cyclization is employed to enhance molecular rigidity and improve receptor binding affinity in antiviral compounds. This approach results in highly stable bioactive molecules and strengthens interactions with viral proteases such as 3CLpro. However, it often leads to low yields, approximately 35%, and requires extensive purification steps, making large-scale synthesis challenging.

6.4. Synthesis of Triazine Sulfonamides via Cyanodithioiminocarbonate

The reaction of sulfaguanidine derivatives with cyanodithioiminocarbonate yields sulfonamide-triazine hybrids with broad-spectrum antimicrobial and antiviral activity. This method offers high yields and allows for facile structural modifications, making it highly versatile. However, it necessitates the use of specialized reagents, and some derivatives exhibit reduced efficacy against specific viral strains, requiring further optimization.

6.5. Fatty Acyl Conjugation of Triazine Derivatives

Fatty acylation of triazine-based antivirals enhances metabolic stability and pharmacokinetics, prolonging plasma half-life and improving bioavailability. This strategy has been shown to enhance antiviral potency against SARS-CoV-2 and Ebola. However, certain derivatives may experience a reduction in intrinsic antiviral activity, and comprehensive metabolic studies are required to confirm long-term efficacy and stability.

7. Novel Insights into Triazine-Based Antivirals

7.1. Structural Optimization and Rational Drug Design

While traditional triazine-based antivirals exhibit promising inhibitory activity, their relatively high IC_{50} values indicate that further structural refinement is necessary. For instance, compound **3** demonstrated an IC_{50} of 4.471 mM against SARS-CoV Mpro, highlighting the need for enhanced binding efficiency. Molecular modeling insights suggest that modifying the electronic properties of the triazine core—particularly through targeted substitutions at key reactive sites—could improve ligand-receptor interactions. Future research should explore bioisosteric replacements or hybridized scaffolds integrating triazine with heterocyclic moieties to optimize antiviral efficacy. Additionally, fragment-based drug design (FBDD) can be employed to systematically improve ligand efficiency by identifying minimal pharmacophores that enhance binding interactions.

7.2. Morpholine-Assisted Functionalization: Potential for Enhanced Bioavailability

Morpholine-assisted functionalization has emerged as a key synthetic strategy, conferring favorable solubility and cell permeability. Notably, compound **7** demonstrated inhibition of DDX3X helicase, a critical host factor in viral replication. However, the regioselectivity challenges associated with morpholine substitution necessitate further exploration of alternative heterocyclic analogs, such as piperazine or thiomorpholine, to enhance selectivity and therapeutic index. Additionally, comparative studies on metabolic stability and intracellular retention of morpholine-functionalized triazines could provide deeper insights into their pharmacokinetic advantages. Introducing polyethylene glycol (PEG) linkers or dendritic architectures could further improve systemic circulation times and reduce renal clearance.

7.3. CDI-Mediated Cyclization: Efficiency vs. Yield Limitations

Carbonyldiimidazole (CDI)-mediated cyclization has been instrumental in developing triazine-based inhibitors targeting SARS-CoV-2 3CLpro. Despite its structural benefits, the method suffers from low yields (35%) and complex purification steps. To overcome these challenges, microwave-assisted cyclization or alternative coupling reagents, such as triphosgene or EDCI, could be investigated to improve reaction efficiency. Furthermore, a comparative mechanistic study of CDI-based cyclization versus classical amidation strategies may help identify cost-effective alternatives for large-scale drug synthesis. Incorporating flow chemistry techniques into CDI-mediated reactions may enhance yield reproducibility and scalability for industrial production.

7.4. Triazine Sulfonamides: A Potential Paradigm Shift in Antiviral Development

The cyanodithioiminocarbonate-mediated synthesis of triazine sulfonamides has yielded derivatives with superior potency over established antivirals like remdesivir. Compound **32**, for example, exhibited an IC_{50} of 2.378 μM against SARS-CoV-2, significantly outperforming remdesivir. However, to fully harness the therapeutic potential of triazine sulfonamides, a deeper understanding of their pharmacokinetics, off-target effects, and resistance mechanisms is required. Strategies such as fluorination or incorporation of lipophilic side chains may further enhance membrane permeability and target specificity. Additionally, designing covalent inhibitors that form irreversible interactions with viral proteases may lead to prolonged therapeutic activity and reduced dosing frequency.

7.5. Fatty Acyl Conjugation: A Double-Edged Sword?

Fatty acyl conjugation has been explored to extend the plasma half-life of triazine derivatives. While monofatty acyl derivatives such as **43b** exhibited improved metabolic stability, they displayed reduced antiviral potency compared to RDV. This suggests that fatty acyl conjugation may enhance drug pharmacokinetics at the cost of intrinsic activity. To address this trade-off, hybrid strategies combining fatty acylation with prodrug modifications (e.g., phosphoramidate derivatives) should be considered. Additionally, in vivo metabolism studies are crucial to determine whether fatty acyl derivatives exhibit favorable tissue distribution and reduced immunogenicity. Lipid nanoparticle formulations could also be explored to improve targeted delivery and bioavailability.

7.6. Emerging Directions for Next-Generation Triazine Antivirals

The future of triazine-based antivirals lies in integrating computational approaches, such as AI-driven molecular docking and QSAR modeling, to predict optimal substitution patterns. Additionally, dual-target inhibitors that combine triazine derivatives with allosteric modulators of viral proteases may offer enhanced antiviral coverage. Further exploration of triazine-based conjugates with polymeric carriers or nanoparticle formulations could revolutionize drug delivery strategies, improving bioavailability and targeted release. Investigating the synergistic potential of triazine antivirals with host-targeted therapies (e.g., immune modulators or autophagy inducers) could provide broader-spectrum antiviral activity and reduce the risk of resistance development.

Conclusion

The ongoing COVID-19 pandemic remains a critical global health crisis, necessitating continuous efforts in drug discovery and development. The exploration of triazine-based compounds and their novel synthetic strategies presents promising avenues for effective antiviral treatments. The synthesis of triazine-based antiviral compounds involves diverse methodologies, each with distinct advantages and limitations. Traditional functionalization techniques provide robust platforms, while advanced strategies such as fatty acyl conjugation and structure-based drug design offer enhanced pharmacokinetics and efficacy. A combination of these approaches may be key to developing next-generation antiviral therapeutics targeting SARS-CoV-2 and other coronaviruses. Future research should focus on optimizing synthetic routes and evaluating long-term clinical viability. By advancing these synthetic approaches, researchers can contribute to the development of potent therapeutics, ultimately aiding in the fight against COVID-19 and future viral outbreaks. The insights provided in this review serve as a valuable foundation for further innovation in medicinal chemistry, fostering collaboration and progress in drug discovery.

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