Current Research in Green and Sustainable Chemistry 4 (2021) 100097

Contents lists available at ScienceDirect

Current Research in Green and Sustainable Chemistry

journal homepage: www.elsevier.com/journals/current-research-in-green-and-sustainable-chemistry/2666-0865

Recent advances made in the synthesis of small drug molecules for clinical applications: An insight

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ARTICLE INFO

Keywords:
Remdesivir
Galidesivir
Favipiravir
Baricitinib
Baloxavir
Small drug molecules
Drug repurposing
Clinical applications
COVID-19

ABSTRACT

Over decades dependency of humans on the drugs has become indispensable and irreplaceable. Thus, each year many new drugs are licensed. Nonetheless, drugs undergo rigorous testing and analysis to be available globally in economic price for the suitability of patients with different age and physiological conditions. The testing of drugs include phase I clinical trial using small group of 20–100 healthy volunteers for safety, pharmacology and efficacy; phase II clinical trial using 100–500 volunteer patients to optimize effective dose, dose interval, safety analysis and mode of delivery such as oral or intravenous; phase III clinical trial using 1000–5000 in a larger population of patients globally at different international places to collect sufficient safety and efficacy data for patenting and licencing. Moreover, thousands of drugs fail to achieve these objectives. Therefore, this mini-review intends to critically examine and assimilate the clinical applications of selected complex repurposed small drug molecules which are in different phase of trials for treating viral infection including complications due to COVID-19: (a) Remdesivir, (b) Galidesivir, (c) Favipiravir, (d) Baricitinib, and (e) Baloxavir.

1. Introduction

Currently coronavirus disease 2019 (COVID-19) has become a global pandemic. The number of people being infected by this highly contagious virus is increasing rapidly and continuously [1–3]. However, to date no drug, vaccine or monoclonal antibodies have been approved for the treatment of COVID-19 except few for emergency use. Therefore, development of effective vaccines remains a vital importance. However, scientists and researchers across the globe have been investigating pre-existing anti-viral drugs that might be repurposed to fight COVID-19. Moreover, some small drug molecules such as Remdesivir, Galidesivir, Favipiravir, Baricitinib, and Baloxavir are currently under clinical trials for their application to treat viral infection including complications due to COVID-19. Therefore, this mini-review aims to survey small drug molecules Remdesivir, Galidesivir, Favipiravir, Baricitinib and Baloxavir for their applications to combat viral diseases including COVID-19.

First drug which has been considered for the review is Remdesivir, showed promising in vitro activity against several strains of coronavirus, including SAR-CoV-2 in Vero E6 cells with EC_{50} and EC_{90} values of 0.77 μM and 1.76 μM, respectively [4]. Thus, it can be a potential drug for coronavirus. Clinical trials are ongoing to assess both the safety and anti-viral activity in patients with mild- moderate- and severe- COVID-19 symptoms. The second drug Galidesivir exhibits broad-spectrum antiviral activity against more than 20 RNA viruses and is extremely important in the treatment of nine different virus families i.e., Flavivirus, Togavirus, Bunyavirus, Arenavirus, Paramyxovirus, Coronavirus, Phylovirus,

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https://doi.org/10.1016/j.crgsc.2021.100097
Received 31 October 2020; Received in revised form 21 February 2021; Accepted 24 March 2021
Available online xxxx

Orthomyxovirus and Picornavirus [5–8]. The drug is currently under clinical investigation for the treatment of Ebola virus disease and yellow fever [9,10], and has also been reported to be effective in Zika virus [11–14]. Considering the outbreak of novel coronavirus infection, recent studies are focusing on repurposing Galidesivir for the treatment of SARS-CoV-2 [15–18]. The third drug discussed in the line is Favipiravir. The effective and potent activity of Favipiravir against RNA influenza viruses makes it a promising drug that could be used for specifically untreatable RNA viral infections. Recently, Favipiravir showed promising in-vitro results against SARCoV-2 in early clinical studies [19]. The fourth drug Baricitinib, is an approved drug in the treatment of rheumatoid arthritis. The drug's anti-inflammatory activity is expected to act on the inflammatory cascade associated with COVID-19 [20,21]. Its mode of action and green synthetic routes have been discussed in detail. The last one Baloxavir, a newly discovered drug to treat influenza A or B, has been included with its relevant available data. Compared to other drugs which block release of virus from the infected cell such as neuraminidase inhibitor, Baloxavir inhibits influenza virus replication by stopping synthesis of mRNA [22]. Fig. 1 depict these small drugs molecules and their currently reported clinical significance.

2. Remdesivir

Remdesivir (Fig. 2), formally known as GS-5734, is an investigational broad-spectrum antiviral agent developed and introduced by Gilead Sciences [23,24]. It is a prodrug of its parent adenosine analog, GS-441524. Being a viral RNA-dependent RNA polymerase (RdRP) inhibitor, it can be used to treat a variety of RNA virus infections. It has demonstrated activity against Coronaviridae family (eg. severe acute respiratory syndrome coronavirus SARSCoV), Paramyxoviridae family (eg. Nipah virus and Hendra) and Filoviridae family (eg. Ebola virus). Remdesivir was primarily designed to treat Ebola virus infection, however, the drug showed poor efficacy in phase III clinical trials and hence, remained in the research and development (R & D) stage. Recently, the drug is gaining much attention and is anticipated to be effective for treating SARS-CoV-2 infection [24–28].

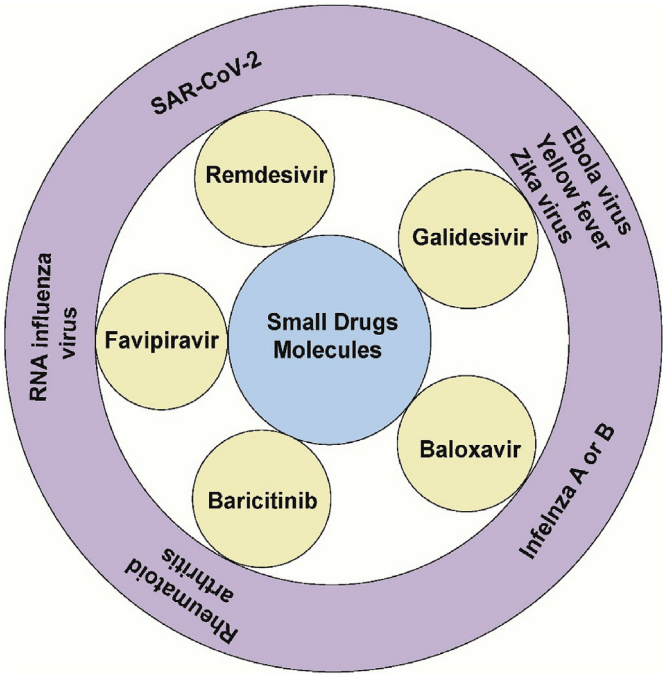


Fig. 1. Schematic representation of small drug molecules and their currently reported clinical significance.

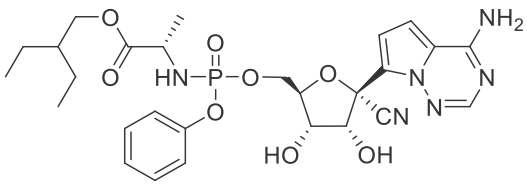


Fig. 2. Structure of remdesivir.

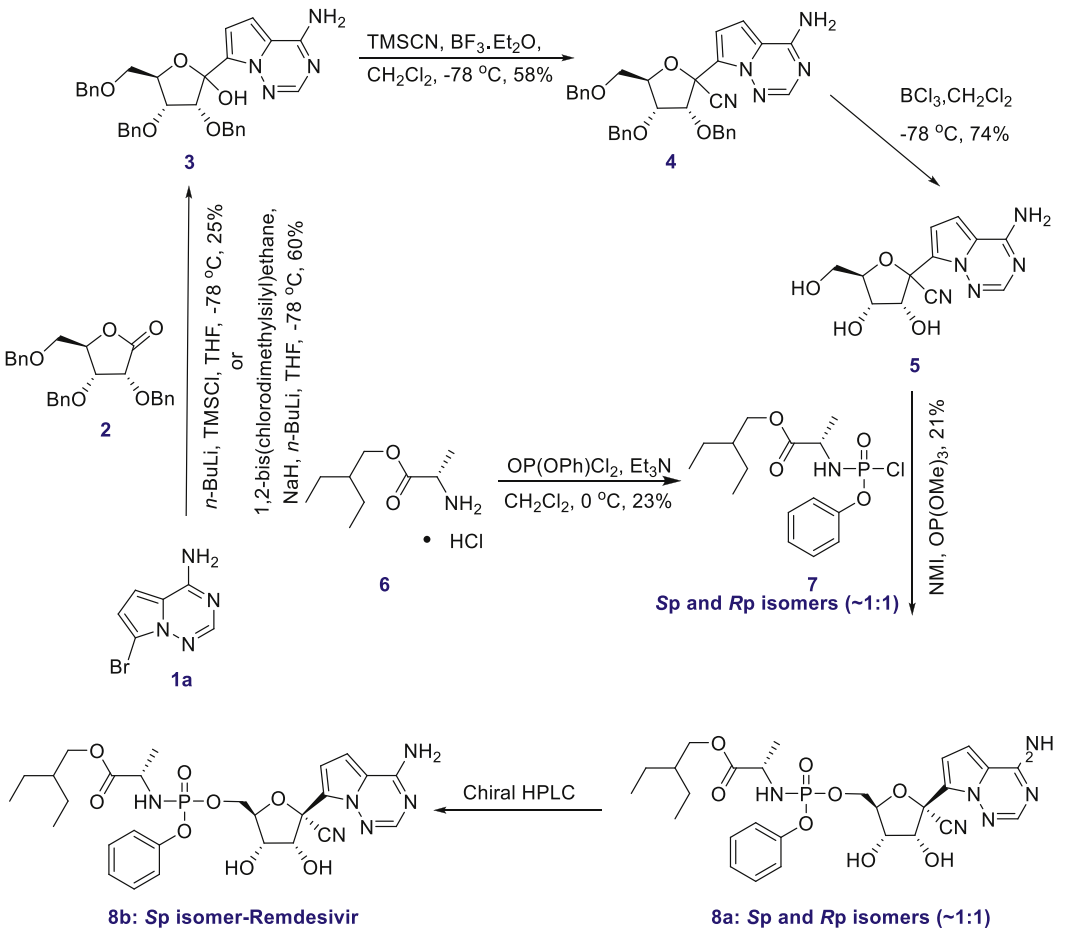
2.1. History of remdesivir

Remdesivir was invented by Gilead Sciences. It has emerged from a collaboration between Gilead, the U.S. Centers for Disease Control and Prevention (CDC) and the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), that was established to identify [29] family [30]. Initially, a library consisting of approximately 1000 small molecules was developed that focused on nucleoside analogues. Owing to poor cell permeability of nucleosides, major attention was given to modified nucleosides such as monophosphate, ester and phosphoramidate prodrugs. These modified nucleosides are more permeable and metabolized to release phosphorylated or non-phosphorylated nucleoside within the cells [31,32]. One such nucleoside was 1′-CN modified adenosine C-nucleoside (GS-441524) and its prodrug GS-5734 was found quite effective [33]. The study conducted in 2012 reported that GS-441524 and its S-acyl-2-thioethyl monophosphate prodrug showed broad activity against a range of RNA viruses including influenza A, dengue virus type 2, yellow fever virus and SARS [34]. Further, GS-5734 was found active against SARS strain Toronto 2 (IC_{50} = 2.2 μM) without showing cytotoxicity toward the host Vero African green monkey kidney epithelial cells used in the CPE assay. During Ebola outbreak, it was reported that GS-441524 was inactive while GS-5734 successfully reduced EBOV replication in HeLa cells [35]. With many such studies, scientific community gained interest in Remdesivir, and it was validated that it possesses wide antiviral activity against SARS, MERS zoonotic coronaviruses, circulating human coronaviruses HCoV-OC43 and HCoV-229E, common agents of the common cold [29,36,37].

Recently, a novel pneumonia caused by an unknown pathogen has outbreak in Wuhan, China. The pathogen was identified as a strain of coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to close similarities with severe acute respiratory syndrome coronavirus [38]. Currently, coronavirus disease 2019 (COVID-19) has become a global pandemic [39]. The number of people being infected by this highly contagious virus is still increasing quickly [1–3]. In this scenario, physicians are considering "repurposing" several existing antiviral drugs that are effective in treating related viral infections. Therefore, clinical trials are being accelerated for the various antiviral medications known for SARS, MERS, HIV/AIDS, malaria etc. [4,15,40–44] Clinical trials of some small molecule drugs are also being conducted for the treatment of COVID-19, including Remdesivir. Remdesivir, showed promising in vitro activity against several strains of coronavirus, including SAR-CoV-2 in Vero E6 cells with EC_{50} and EC_{90} values of 0.77 μM and 1.76 μM, respectively [4]. Thus, it can be a potential drug. Clinical trials are ongoing to assess both the safety and anti-viral activity in patients with mild-moderate-severe COVID-19.

2.2. Synthesis of Remdesivir

The chemical formula of Remdesivir is $C_{27}H_{35}N_6O_8P$. It is a *Sp* isomer of compound 8a (*Sp* and *Rp* isomers ~1:1, Scheme 1). Stereochemically, 8a can have two configurations; *Sp*-isomer (8b) and *Rp*-isomer. The difference in both isomers lies in the spatial configuration of 2-ethylbutyl-2-aminopropanoate and anisole. Among both, 8b possesses greater selectivity and therapeutic window desirable for antiviral activity [45].



Scheme 1. Route 1 for the Synthesis of Remdesivir.

After an extensive literature survey, three synthesis route maps were identified for its development which have been discussed below.

Route 1

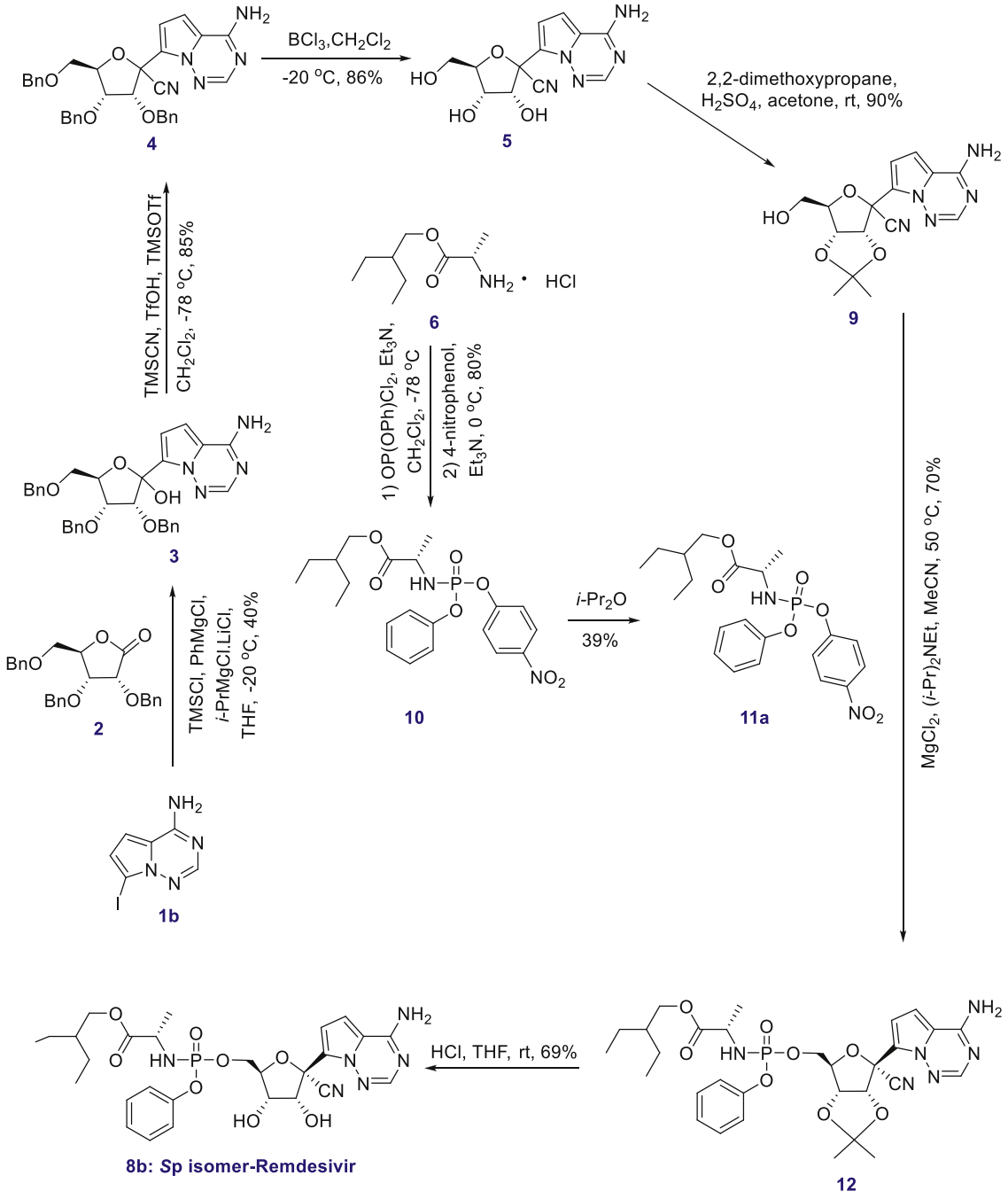
The first synthetic route to Remdesivir was proposed by Richard L. Mackman (Scheme 1) [35,45–49]. The scheme was initiated with the glycosylation reaction of 2,3,5-tri-O-benzyl-D-ribono-1,4-lactone (2) with 7-bromopyrrolo[2,1-f][1,2,4]triazine-4-amine (1a), followed by the addition of trimethylsilyl chloride (TMSCl) and *n*-BuLi or NaH and 1, 2-bis(chlorodimethylsilyl)ethane for the *N*-protection of 1a. Compound (3) was obtained after metal-halogen exchange in tetrahydrofuran (THF) at −78 °C. Next, hydroxyl nucleoside 3 was cynated using trimethylsilyl cyanide (TMSCN) mediated by $BF_3 \bullet Et_2O$ in dichoromethane at −78 °C to afford cyano nucleoside, and the desired product (*R*)-isomer (4) is separated after chromatography in 58% yield. Next, deprotection of benzyl protecting groups was carried out in CH_2Cl_2 and BCl_3 to form compound 5, which was combined with 7 (a diastereomer mixture of the phosphoramidyl chloride hydrochloride prodrug portion) to obtain compound 8a in 21% yield as ~1:1 mixture of diastereomers. The targeted drug Remdesivir (8b) was finally obtained after chiral HPLC of compound 8a [44,45].

Route 2

Later, Richard L. Mackman and Warren, T. K. reported a modified route for the synthesis of Remdesivir (Scheme 2) [35,46–49]. This method provides a diastereoselective synthesis through selective crystallization of phosphorus coupling partner 11a-*S*p, hence, eliminating preparative scale chiral chromatography. In this method, 7-iodopyrrolo [2,1-f][1,2,4]triazin-4-amine (1b) was treated with TMSCl, PhMgCl and isopropylmagnesium chloride lithium chloride (*i*-PrMgCl·LiCl) in THF at −20 °C and then condensed with lactone (2) to obtain adduct 3. Cyano group was introduced using TMSCN, trifluoromethanesulfonate (TMSOTf) and trifluoromethanesulfonic acid (TfOH) at −78 °C in dichloromethane to produce corresponding epimeric cyanide. This was followed by the chromatographic separation of desired (*R*)-isomer (4). Next, triol (5) was generated through benzylation in presence of BCl_3 in CH_2Cl_2 at −20 °C. The diol moiety of (5) was protected with 2,2-dimethoxypropane using H_2SO_4 in acetone to produce the isopropylidene derivative (9). Finally, (9) was condensed with amidophosphate (11a) in presence of $MgCl_2$ and *N,N*-diisopropylethylamine in acetonitrile to give protected Remdesivir (12), which is deprotected with aqueous HCl in THF to yield the target drug Remdesivir (8b) [4,45].

Route 3

Gilead Sciences introduced another synthetic route to form Remdesivir (Scheme 3) [35,46–50]. Firstly, *N*-protection of 7-iodopyrrolo[2,1-f] [1,2,4]triazin-4-amine (1b) was done using TMSCl and PhMgCl followed by metal-halogen exchange with *i*-PrMgCl·LiCl in THF at −15 °C. Subsequently, persilylated lactone (13) was added along with $LaCl_3{\cdot}2LiCl$ in THF at −15 °C produces lactol intermediate (14). The cyanation and selective desilylation of lactol (14) with TMSCN using TMSOTf and trifluoroacetic acid in CH_2Cl_2 at −40 °C yields the corresponding epimeric cyanide. Next, preparative HPLC was done to separate the desired (*R*)-isomer (15). Next, (15) is condensed with either amidophosphate (11a) in presence of $MgCl_2$ and $(i\text{-}Pr)_2NEt$ in THF or with pentafluorophenyl protected derivative (11b) in the presence of tert-butylmagnesium chloride (*t*BuMgCl) in THF to give silylated



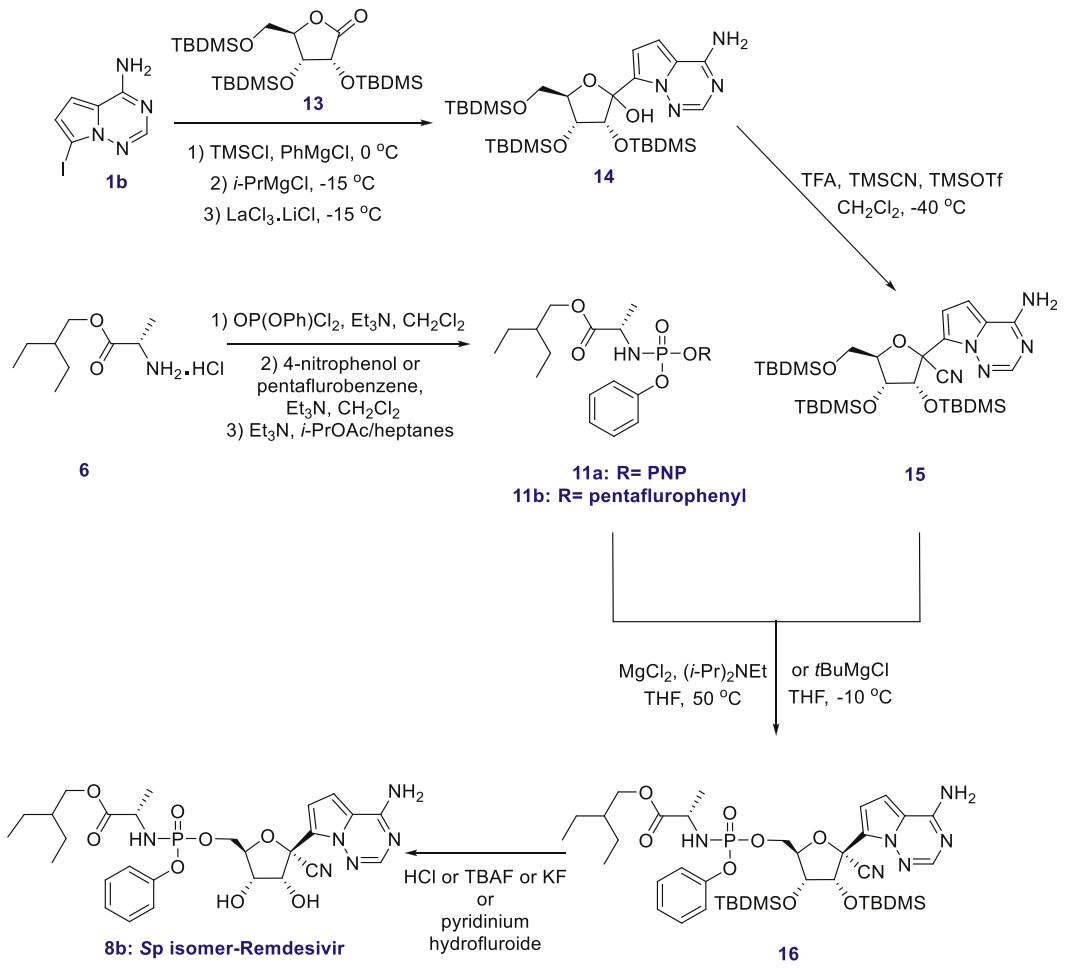
Scheme 2. Route 2 for the synthesis of Remdesivir.

compound (16). Finally, the target Remdesivir (8b) was obtained after deprotection of (16) using HCl, tetrabutylammonium fluoride (TBAF), KF or pyridinium hydrofluoride [4,44].

2.3. Mode of action

Within the host, an antiviral chemotherapeutic intervention generally attacks either specific viral enzymes or weak point of virus replication, such as RdRp. Remdesivir is a monophosphoramidate prodrug of an adenosine nucleoside analogue. Nucleoside analogues often classified into three classes, i.e., mutagenic nucleosides, obligate chain terminators and delayed chain terminators [51]. Mutagenic nucleosides are those that attacks the viral reliance over RdRp to catalyze the replication of the RNA genome from the native RNA template. Obligate chain terminators include nucleotides that once incorporated, directly inhibits further DNA primer extension. Remdesivir is a delayed chain terminator, that block transcription and its 3′-hydroxyl group can still form phosphodiester bond with further incorporated nucleotide [52].

Remdesivir enters the host cell as a prodrug. Within the cell, it metabolizes into alanine metabolite, GS-704277, further converted into nucleotide monophosphate (NMP) and finally dephosphorylated to active nucleoside triphosphate (NTP), Fig. 3 [35]. This conversion to NMP takes place through a series of hydrolytic steps that begins with esterase-mediated hydrolysis of the amino acid ester to form carboxylate that undergoes internal cyclization to phosphonate and eliminate phenoxide. Cyclic anhydride thus formed, being unstable, gets hydrolyzed to alanine metabolite GS-704277 whose P–N bond is hydrolyzed by phosphoramidase-type enzymes to give highly polar NMP. Highly polar



Scheme 3. Route 3 for the synthesis of Remdesivir.

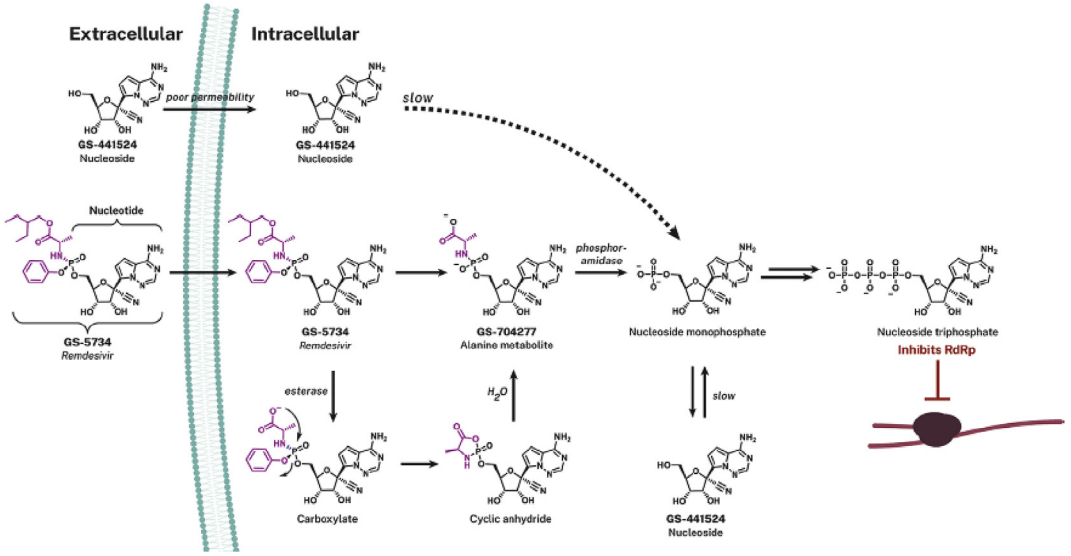


Fig. 3. Intracellular processing of the prodrug Remdesivir (GS-5734). Reproduced with permissions from (ref [35]) Nature 508, 402–405 (2014). Copyright: Springer Nature, 2014.

nature of NMP restricts its reverse diffusion across the cell membrane. Now, NMP is converted to active NTP analogue *via* phosphorylation events by host cell kinases [30]. NTP and adenosine triphosphate (ATP) have a similar structure and competes with each other to bind to the viral RdRp with nearly same efficiencies, therefore NTP is used by the viral RdRp which results in premature termination of RNA synthesis, halting the growth of the RNA strand after a few more nucleotides are added [45]. Götte et al. reported that, in case of EBOV RdRp, NTP incorporated into the RNA synthesis chain at position i does not affect the incorporation of subsequent nucleotide at position i+1 [53]. However, RNA

chain termination takes place at a position few bases downstream of position i (predominantly at position i+5). This process is called "delayed chain termination".

3. Galidesivir

Galidesivir (BCX4430) is an adenosine analog in which nitrogen at position 7 on the base is substituted by carbon and oxygen on position 1 on ribose ring is substituted by nitrogen (Fig. 4) [9]. Galidesivir exhibits broad-spectrum antiviral activity against more than 20 RNA viruses and is extremely important in the treatment of nine different virus families i.e., flavivirus, togavirus, bunyavirus, arenavirus, paramyxovirus, coronavirus, phylovirus, orthomyxovirus and picornavirus [5–8]. The drug is currently under clinical investigation for the treatment of Ebola virus disease and yellow fever [9,10]. Recently, Galidesivir has also been reported to be effective in Zika and tick-borne flavivirus infection models [11–14].

3.1. History of galidesivir

Galidesivir was developed by BioCryst under broad-spectrum antiviral (BSAV) research program which aims to synthesize broad-spectrum parenteral and oral therapeutics for viruses that are hazardous to human health and national security. BioCryst developed this drug in collaboration with US Government Agencies. In 2013, National Institute of Allergy and Infectious Diseases (NIAID) and BioCryst agreed on a contract to develop Galidesivir as a treatment for Marburg virus disease and for other filoviruses, such as Ebola virus. Later in March 2015, Biomedical Advanced Research and Development Authority (BARDA) within the U.S. Department of Health & Human Services' Office of the Assistant Secretary for Preparedness and Response (ASPR) awarded BioCryst a contract for the continued development of Galidesivir as a potential treatment for diseases caused by RNA pathogens [46]. Recently, Galidesivir has been approved in Phase I clinical safety and pharmacokinetics trials in which it was administered in healthy subjects through intravenous as well as intramuscular manner. During animal studies, there are confirmed survival benefits associated with the drug against a variety of serious pathogens, including Ebola, Marburg, Yellow Fever and Zika viruses [54].

Considering the outbreak of novel coronavirus 2019 infection, recent studies are focusing on repurposing Galidesivir for the treatment of SARS-CoV-2 [15–18]. In this regard, BioCryst has initiated enrolment of a randomized, double-blind, placebo-controlled clinical trial to evaluate the safety, clinical impact and antiviral effects of Galidesivir in patients infected with COVID-19. This trial (NCT03891420) has been funded by NIAID as a part of the National Institutes of Health.

3.2. Synthesis of galidesivir

Warren et al. synthesized BCX4430 as part of a small-molecule library designed to prevent viral RNA polymerase activity [5]. The synthetic route has been depicted in Scheme 4 that comprises total seven synthetic steps starting from BCX1777 in 22–25% overall isolated yield. The synthetic of BCX1777 was reported by Evans et al. [55].

This method involved the condensation in the basic conditions of 5-methylol-3,4-pyrrolidine glycol and base. Further, the method requires the protection and deprotection of various functional groups using blocking agents which makes the process tedious and time consuming.

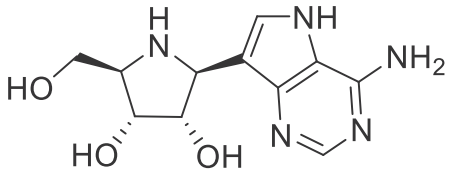


Fig. 4. Structure of galidesivir.

Lately, US Patent No. 6458799 also reported a synthetic route for direct transformation of nucleoside analog (Scheme 5) [56]. In this route the starting material, BCX1777 was acetylated using acetic anhydride in pyridine to give tri-O-acetate (7) which was later chlorinated using dimethylchloromethyleneammonium chloride to give 8. Ammonolysis of 8 yields BCX4430 by cleaving the acetate protecting groups. In 2017 a patent was published describing the synthetic methods for the preparation of Galidesivir [57].

3.3. Mode of action

As mentioned earlier, in Galidesivir there is a structural change in furanose moiety of adenosine to an azasugar ring. This change causes alteration in steric and electrostatic interactions which affect the conformation of the sugar. The conformational changes influence the incorporation of nucleotide and chain extension by the viral RNA-dependent RNA polymerases resulting in non-obligate chain termination of viral RNA synthesis [5,9,58].

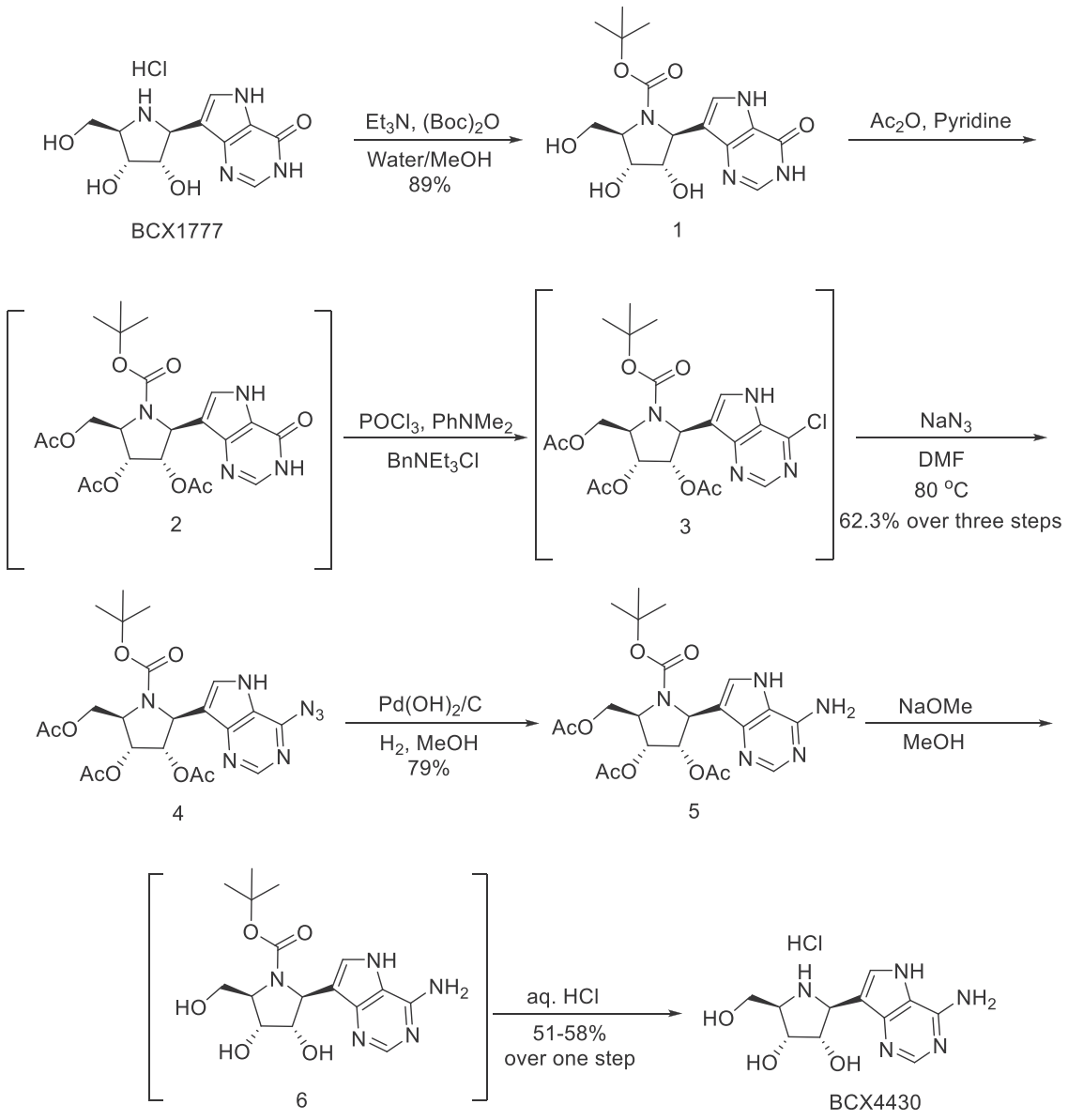
The mechanism of chain termination requires phosphorylation of parent BCX4430 to BCX4430-triphosphate (BCX4430-TP) through cellular kinases phosphorylate. Then, after pyrophosphate cleavage, BCX4430-monophosphate (BCX4430-MP) is incorporated into a growing viral RNA chain leading to premature termination of transcription and replication of viral RNA. It has been reported that the chain termination takes place two bases after insertion of BCX4430-MP probably due to inhibitory stereochemical distortions of the growing RNA chain. This mechanism has been demonstrated in vitro using a hepatitis C RNA polymerase assay by Warren et al. (Fig. 5) [5].

4. Favipiravir

Favipiravir (chemical name: 6-fluoro-3-hydroxypyrazine-2-carboxamide) (Fig. 6) is a pyrazine based antiviral drug discovered by Japanese company Toyama Chemical Co., Ltd for the treatment of influenza virus. This drug was firstly synthesized in 2000 by Toyama Chemical (Fujifilm group) and approved for medical use in 2014. After two year in 2016 this drug was licensed to Chinese company Zhejiang Hisun Pharmaceuticals Co. and in 2019 it became a generic drug. Favipiravir was found to be effective against various types, subtypes and strains of influenza viruses including the strains which are resistant to existing marketed anti-influenza drugs. This drug is found to be a selective inhibitor of RND-dependent RNA polymerase, various other RNA viruses such as Ebola virus, West Nile virus, Norwalk virus, and RNA viruses which are responsible for fatal haemorrhagic fever. Therefore, the effective and potent activity of Favipiravir against RNA influenza viruses makes it a promising drug that could be used for specifically untreatable RNA viral infections. Recently, Favipiravir showed promising in-vitro results against SARCoV-2 in early clinical studies [19], although high concentration (EC_{50} = 61.88 μM) of drug dose was required in comparison with chloroquine or remedisivir [59]. In a study Favipiravir exhibited in-vitro antiviral activity against Covid-19 by less than 50% at concentration up to 100 mM and at 21 mM concentration clinically in patients who has given the dose of Favipiravir [60]. Very recently, Glenmark pharmaceuticals has come up with top-line results of Favipiravir against mild to moderate Covid-19 patients from phase-3 clinical trial conducted across seven clinical sites in India. The results of phase-3 clinical trial displayed numerical developments for the primary efficiency endpoint with 28.6% rapid viral clearance in the overall population [61].

4.1. Synthesis of Favipiravir

The first synthesis of Favipiravir was carried out by Furuta and Egawa in 2000 in seven steps [62]. The synthesis was started by the methylation



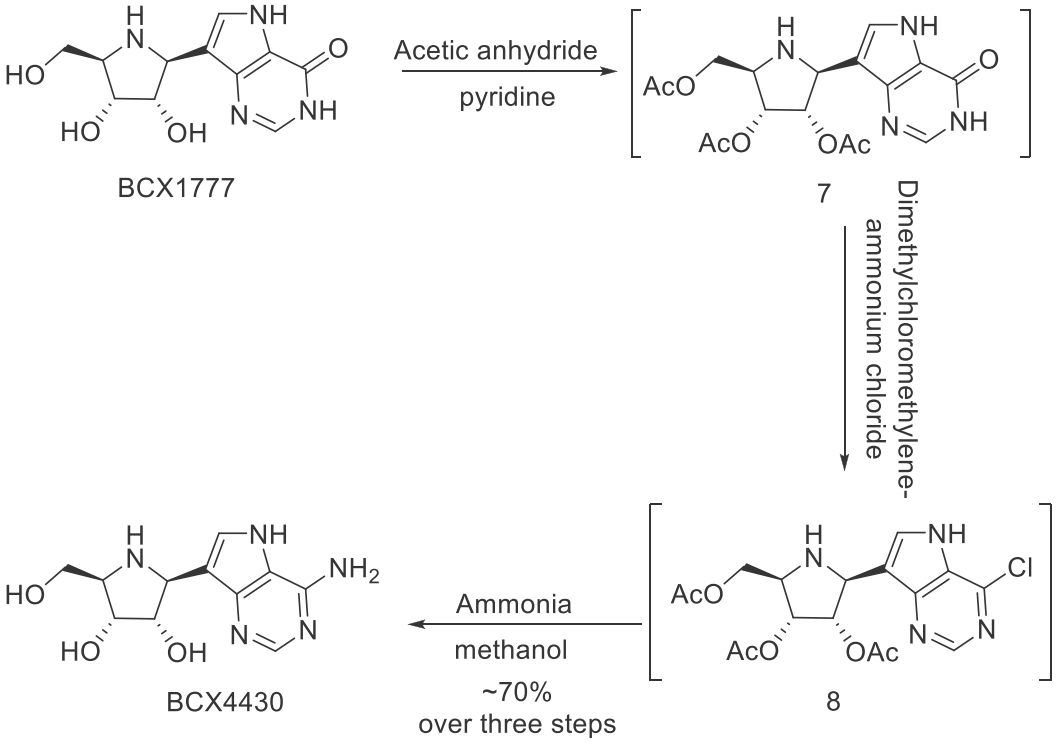
Scheme 4. Synthetic route of BCX4430 (ref [2]).

of 3-aminopyrazine-2-carboxylic acid using methanol and sulphuric acid. Then pyrazine moiety was brominated at 6-position followed by conversion of amino group into methoxy group. Afterwards Pd-catalyzed amination was carried out using diphenylmethanimine in presence of (*S*)-BINAP. The amino group was converted into a fluoro group in presence of Olah reagent and finally favipiarvir was obtained by treating 6-fluoro-3-methoxypyrazine-2-carboxamide with sodium iodide and trimethylsilyl chloride (TMSCl) (Scheme 6).

After fourteen years of Furuta and Egawa report in 2014 Shi et al. reported a highly improved protocol for the preparation of Favipiravir which involves only four steps [63]. This group started the synthesis of Favipiravir using 3-hydroxypyrazine-2-carboxylic acid as starting material. Initially, the amidation of 3-hydroxypyrazine-2-carboxylic acid was done to form 3-hydroxypyrazine-2-carboxamide. The reaction of 3-hydroxypyrazine-2-carboxamide with potassium nitrite in presence of H_2SO_4 delivered 3-hydroxy-6-nitropyrazine-2-carboxamide. Reduction of 3-hydroxy-6-nitropyrazine-2-carboxamide using Raney Ni and hydrazine followed by fluorination in presence of Olah reagent delivered the Favipiravir (Scheme 7).

Watanabe and co-workers in 0215 patented a nontrivial method for the synthesis of Favipiravir [64]. They have used ethyl 2, 2-diethoxyacetate as starting material which was initially converted into isoxazole derivative which was converted into isoxazolo[4,5-*b*] pyrazine compound in presence of PTSA and then subsequent treatment of isoxazolo[4,5-*b*]pyrazine derivative with sodium hydroxide and DOWEX delivered 6-fluoro-3-hydroxypyrazine-2-carbonitril. Finally, oxidative amidation of 6-fluoro-3-hydroxypyrazine-2-carbonitrile in presence of alkaline hydrogen peroxide furnished Favipiravir (Scheme 8).

In 2017 Liu et al. disclosed the synthesis of favipravir starting from 3-aminopyrazine-2-carboxylic acid [65]. Initial few steps of this protocol were similar to that of Furuta et al. till the formation of key intermediate methyl 2-amino-5-bromobenzoate. This intermediate was then subjected to a sequence of reactions such as conversion of amino group into hydroxyl group followed by methylation to obtain methyl 5-bromo-2-methoxybenzoate. Reaction of methyl 5-bromo-2-methoxybenzoate with $POCl_3$ in presence of DIEA delivered 3,6-dichloropyrazine-2-carbonitrile. Finally, one-pot treatment of 3,6-dichloropyrazine-2-carbonitrile with potassium fluoride in presence of Bu_4NBr followed by reaction with hydrogen peroxide using potassium carbonate base and then with sodium bicarbonate resulted in the targeted Favipiravir (Scheme 9).



Scheme 5. Direct synthetic route to BCX4430.

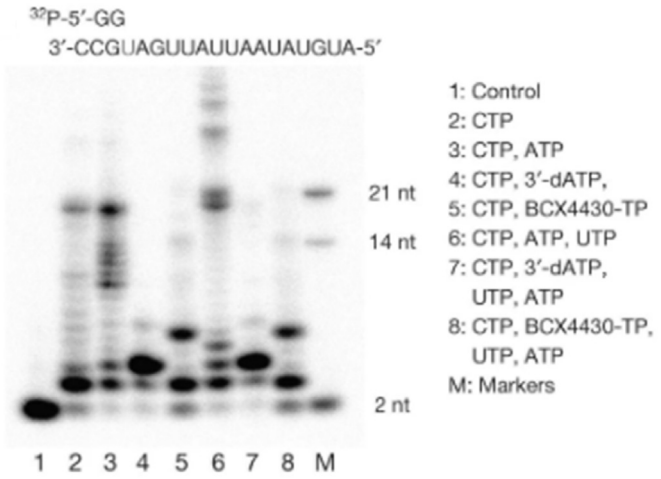


Fig. 5. Non-obligate chain termination of hepatitis C *via* in vitro RNA-dependent, template-directed RNA synthesis by incubation with BCX4430-TP. Lane 5 and 8 depicts chain termination due to incorporation of BCX4430. Lanes 4 and 7 show 3′-deoxyATP, an acknowledged obligate chain terminator positive control. The pattern of RNA oligomers shown in absence of inhibitors or in presence of normal nucleotides is represented in lane 6. Reproduced with permissions from (ref [5]) Nature 508, 402–405 (2014). Copyright: Springer Nature, 2014.

In 2019 Guo et al. developed a new approach [66] which involved the conversion of pyrazin-2-amine into Favipiravir through a number a reactions such as regioselective chlorination, bromination, Pd-catalyzed cyanantion, Sandmeyer reaction for conversion of amine group into chlorine *via* diazotization, replacement of chlorine group with fluorine through aromatic nucleophilic substitution reaction followed by hydrolysis reaction, etc. Finally, thus obtained 3,6-difluoropyrazine-2-carboxamide was converted into Favipiravir in presence of sodium bicarbonate and 1,4-dioxane-water system (Scheme 10).

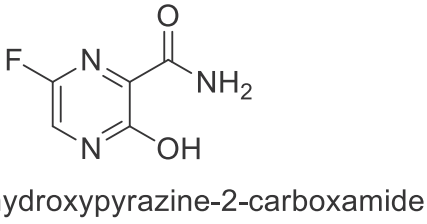


Fig. 6. Structure of favipiravir.

4.2. Mode of action

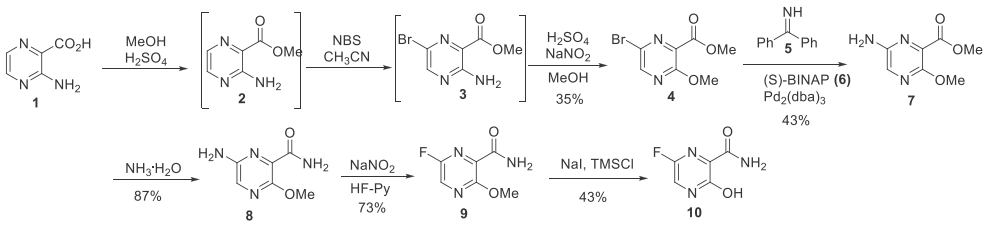
Favipiravir showed different mechanisms of action compared to existing antiviral drugs. Studies exposed that active Favipiravir-RTP selectively binds to RNA-dependent RNA-polymerase (RdRp) thereby precludes replication of viral genome [67]. Favipiravir-RTP assimilation to newly developed RNA blocks the RNA strand elongation and viral proliferation. It has also found in studies that the existence of purine analogues can reduce antiviral activity of Favipiravir, revealing competition of favipravir-RTP with purine nucleotide for RdRp binding [68,69].

5. Baricitinib

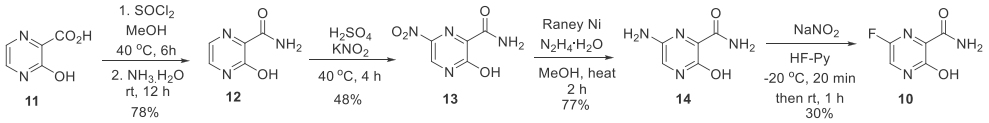
Baricitinib ($C_{16}H_{17}N_7O_2S$) (Fig. 7), is a drug for the treatment of rheumatoid arthritis (RA) [69] in adults whose disease was not well controlled using RA medications called tumor necrosis factor (TNF) antagonists [71–73]. Its brand name is Olumiant. It has been tested for phase III trial for treatment of COVID-19 [20,21].

5.1. History of baricitinib

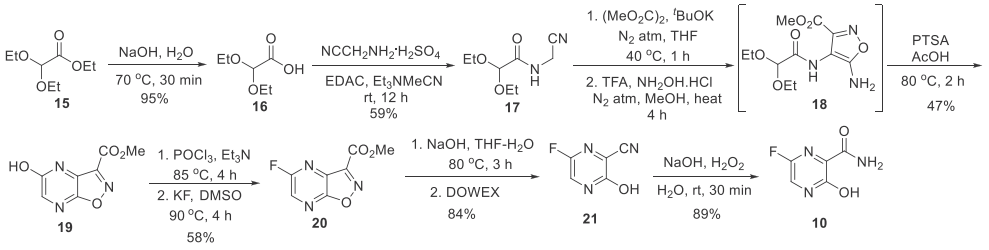
European Committee for Medicinal Products for Human Use (CHMP) approved for using Baricitinib in the treatment of RA in February 2017. Baricitinib was approved in the United States for the treatment of rheumatoid arthritis in May 2018 [74]. In April 2020 Eli Lilly announced they



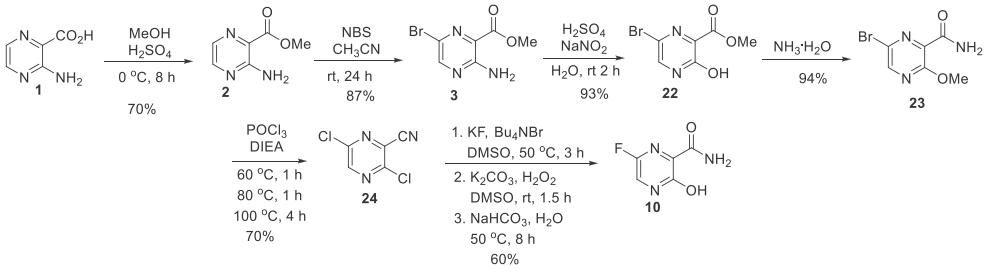
Scheme 6. Synthesis of Favipiravir.



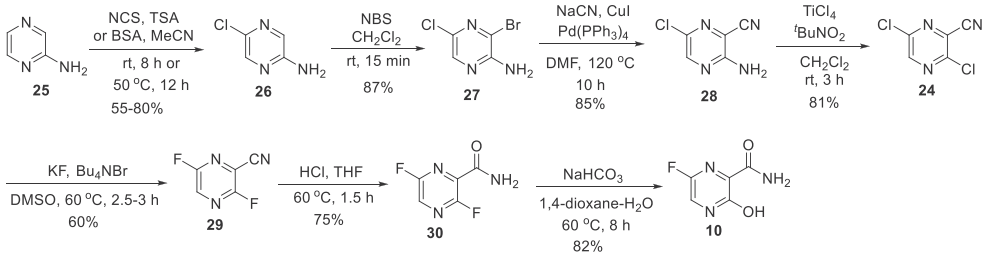
Scheme 7. Synthesis of Favipiravir.



Scheme 8. Synthesis of Favipiravir.



Scheme 9. Synthesis of Favipiravir.



Scheme 10. Synthesis of Favipiravir.

were investigating the use of Baricitinib for treating COVID-19 patients. The drug's anti-inflammatory activity is expected to act on the inflammatory cascade associated with COVID-19 [20,21].

5.2. Synthesis of baricitinib

Almost all the synthetic methods reported for the preparation of Baricitinib employed important intermediates 2-(1-(ethylsulfonyl) azetidin-3-ylidene)acetonitrile(**1**) and *tert*-butyl 3-(cyanomethylene) azetidine-1-carboxylate(**2**). Eco-friendly synthetic routes are in demand for intermediate 1 and 2. The synthesis of intermediates **1** and **2** was associated with various drawbacks. For example, starting materials used, harmful reagents, poor yields, production of a large amount of mixed salt wastewater, hazardous to environment as well as not suitable for industrial production and produce inseparable by products.

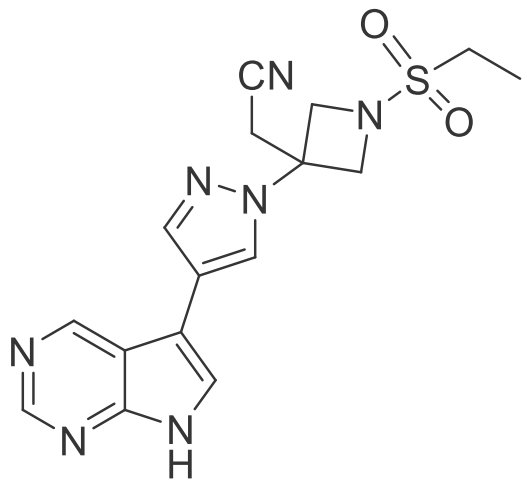


Fig. 7. Structure of baricitinib.

5.3. Development of green and eco-friendly synthetic route

Alternate greener routes were tried to synthesize the intermediates **1** and **2**. The cheaper material benzylamine was used as the starting material instead of unstable reagent benzhydrylamine as benzhydrylamine will be partly converted to dibenzophenone, to produce the intermediate 2 (Scheme 11) [75].

The cheaper and commercially available 2-(chloromethyl)oxirane (V-1) and benzylamine (V-2), which was converted to 1-benzylazetidin-3-ol (V-3). Compound V-3 was then converted via reduction reaction and N-Boc protection to afford compound V-4, which was reacted with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) to obtain intermediate V-5 by two different methods. Then intermediate V-5 was employed to afforded key intermediates *tert*-butyl 3-(cyanomethylene)azetidine-1-carboxylate (V-6, 2) and 2-(1-(ethylsulfonyl)azetidin-3-ylidene)acetonitrile (V-8, 3) successively underwent wittig reaction, deprotection, and hinsber reactions [75].

5.4. Clinical importance

Baricitinib was approved in February of 2017 to treat adult patients suffering from moderate to severe active rheumatoid arthritis [71]. Rheumatoid arthritis is a progressive autoimmune disease commonly associated with pain, disability, and damage of joints. As the disease progresses it leads to swelling in joints, deformations and may lead to impairment in functioning [70,71]. It reduces quality of life [76,77]. While there are other anti-rheumatic drugs (DMARDs) available for treatment, patients have not received adequate therapeutic responses to these drugs. Baricitinib was shown to have significant anti-inflammatory effects in animal models of inflammatory arthritis [76]. Trials are under process if Baricitinib could help treat the complications of Covid-19 in patients [21].

6. Baloxavir

Baloxavir (Fig. 8B) is an active form of the prodrug baloxavir marboxil (7A). It is completely converted into the active metabolite Baloxavir from the hydrolysis of prodrug baloxavir marboxil. Baloxavir inhibits influenza virus replication by inhibiting the activity of endonuclease protein (polymerase acidic protein) essential for the replication of the virus. Recently, Baloxavir has been also tested in one phase 2 clinical trial and two phase 3 clinical trials for their clinical efficacy and safety to treat acute uncomplicated influenza. However, headaches, nauseas, nasopharyngitis, bronchitis and diarrhoea were observed as the most common side-effect of the Baloxavir during clinical trials. Volume distribution (Vd) of Baloxavir is 1, 180 L and it has about 93% binding of affinity to the proteins. Half-life and clearance of Baloxavir is 79.1h and 10.3 L/h respectively. Metabolism of Baloxavir takes place through UGT1A3 with a little participation of CYP3A4. Moreover, administration of radiolabelled Baloxavir maraboxil shown to be excreted mainly through faeces (80.1%) and 14.7% through urine. Whilst, 3.3% excreted as Baloxavir [78].

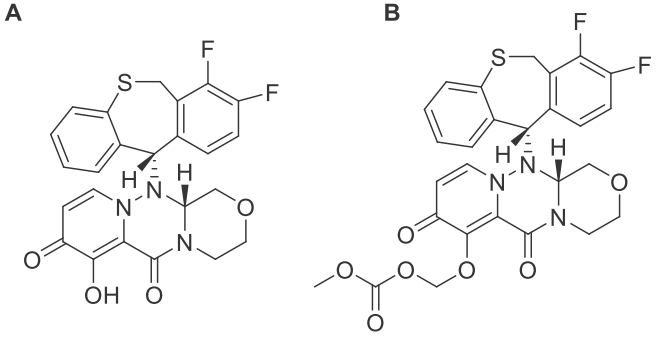
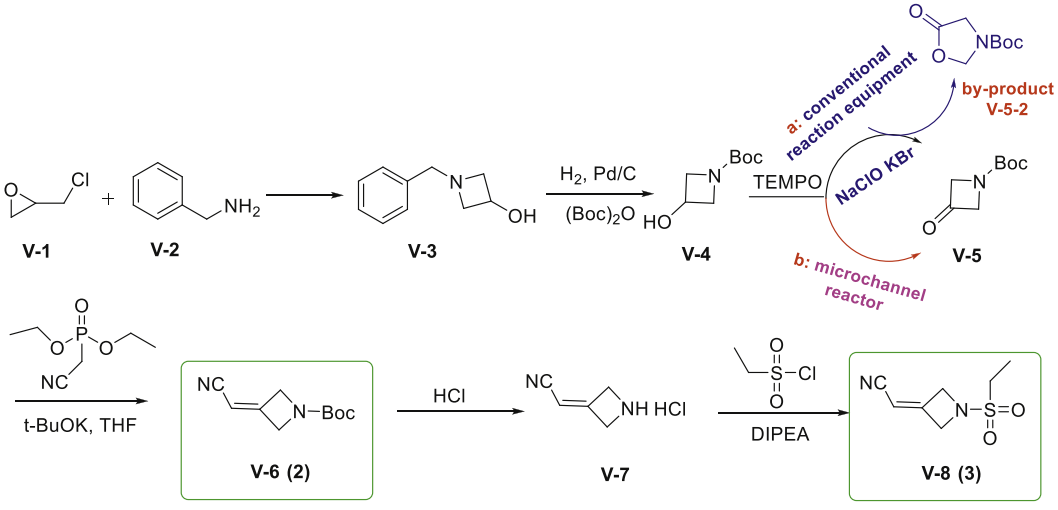


Fig. 8. Chemical structure of **(A)** Baloxavir marboxil and **(B)** Baloxavir.



Scheme 11. Green and eco-friendly synthetic route for intermediate 3. Reproduced from Ref. [74] under Creative Commons Attribution License 4.0.

6.1. History of baloxavir

Currently new antiviral drugs are going under different phases of clinical trials to cope with the increasing resistance of the drugs to the influenza versus. Among them Baloxavir is a newly developed novel drug developed to treat influenza A or B. Compared to other drugs which block release of virus from the infected cell such as neuraminidase inhibitor, Baloxavir inhibits influenza virus replication by stopping synthesis of mRNA. Therefore, Shionogi and Roche made a memorandum of understanding in February 2016 for the development and global commercialization of Baloxavir. As per this agreement Shionogi receives advance payment from Roche with the condition to receive future payments received from the development and commercialization as well as royalties from Baloxavir sale. Moreover, Shionogi holds full commercialization rights of Baloxavir in Japan and Taiwan with few co-promotion rights in the USA. Whilst, Roche hold global commercialize right of Baloxavir except Japan and Taiwan [22].

Furthermore, Shionogi began recruitment for a randomised, multinational and double-blind phase III trial (CAPSTONE-2; NCT02949011) in December 2016. The objective of this trial was to study the efficacy of Baloxavir for the treatment of both adult and children (more than 12 year) patients of influenza A and B compared to placebo and oseltamivir. Patients recruited for trials have compromised immune systems having different diseases or disorders such as chronic lung diseases, heart diseases, asthma or metabolic, blood, endocrine and neurological disorders. Besides, patients of age more than 65 years were also recruited for the clinical trials. Additionally, Shionogi started an open-label phase III trial (JapicCTI-173811) on healthy children of age less than 12 years with influenza A or B for studying the efficacy and safety. Children having influenza A or B was given one dose of Baloxavir 2% [22]. Recently, due to its novel significance to treat influenza A or B, Baloxavir was granted first global approval on 23 February 2018 in Japan to treat paediatric and adult patients suffering from influenza A or B. It is prescribed to take one dose of Baloxavir as the symptoms become evident. However, dosages strength could be optimised both in children and adults based on their body weight. It is recommended 40 mg as a single dose for the patient weighing between 40 and 80 Kg, and 80 mg as a single dose for the patient weighing more than 80 Kg [22].

6.2. Mode of action

Mode of action of Baloxavir is unique compared to other available drugs for treating the influenza virus. Furthermore, single dose regimen together with its orally administrable property is an important advantage of the Baloxavir [79]. Baloxavir, inhibits influenza virus replication by inhibiting the activity of enzyme “polymerase acidic protein”. This enzyme is essential to acts on capped 5′ RNA primers for the transcription of the viral genetic material (RNA) [80]. Therefore, Baloxavir inhibit the action of “polymerase acidic protein” which prevent transcription and consequently stop replication of the virus [81].

7. Conclusions and future outlooks

In this article five promising complex small drug molecules Remdesivir, Galidesivir, Favipiravir, Baricitinib, and Baloxavir of clinical importance have been reviewed. As per the current available literature a detailed outlook of each drug has been presented in terms of history, synthesis methods and mode of action. Study shows that all the described drugs have been considered to repurpose for the treatment of COVID-19 disease. Especially Remdesivir and Favipiravir have shown good efficacy in clinical trials. These drugs bind to the RdRp of the SARS-CoV-2 strain and thus inhibit the viral action. Hence, these drugs may be useful for its treatment. Further, no toxicity measures are required as these drugs have been tested previously for other diseases.

However, Remdesivir was mainly developed to treat Ebola virus infection. Furthermore, early in-vitro clinical results show that high concentration of Favipiravir required compared to Remedisivir to treat SARCoV-2. Moreover, Trials are under process for repurposing Galidesivir and Baricitinib to treat the complications of Covid-19 in patients. Whereas, Baloxavir has been developed to treat different types of influenza. The described drugs have shown interesting antiviral activities, yet the scope for the further modification still remains required to improve the potency of the drugs so that one drug can be used against multiple targets. Also, the reported methods for the construction of the described drugs can be modified because these protocols involve the multistep conventional approaches, use of expensive and toxic reagents, etc. Therefore, there is a significant room for the incorporation of strategies following green chemistry principles in the productions of such highly valuable drug molecules. Applications of green chemistry principles may result in use of (a) least chemical and reagents, (b) lesser solvents, and (c) least or no production of toxic and product harmful for the environment and having adverse effects on human health. Also, there is substantial scope for the use of visible light mediated synthesis and continuous flow synthesis as well as alternative energy sources such as microwaves and ultrasound radiations for the fabrication of these drugs. We anticipate that in due course of time the research community will work to improve the potency of these drugs by modifying the various functional groups present or by introducing the new functionalities through post-functionalization approaches.

Funding

Fund Researcher Links workshop grant, ID 2018-RLWK10-10480. The grant was funded by the UK Department for Business, Energy and Industrial Strategy and the Royal Society of Chemistry and delivered by the British Council.

CRediT authorship contribution statement

Gunjan Arora: Conceptualization, Writing - original draft, Formal analysis, Resources, Data curation, Writing - review & editing. **Ruchi Shrivastava:** Conceptualization, Writing - original draft, Formal analysis, Resources, Data curation, Writing - review & editing. **Prashant Kumar:** Conceptualization, Writing - original draft, Formal analysis, Resources, Data curation, Writing - review & editing. **Rakeshwar Bandichhor:** Conceptualization, Writing - review & editing, Supervision, Validation. **Dhileep Krishnamurthy:** Writing - review & editing, Supervision. **Rakesh Kumar Sharma:** Writing - review & editing. **Avtar S. Matharu:** Writing - review & editing. **Jaya Pandey:** Writing - review & editing. **Mohammad Rizwan:** Conceptualization, Writing - original draft, Formal analysis, Resources, Data curation, Writing - review & editing, Project administration, Methodology, Validation. We confirm that the manuscript has been read and approved by all named authors. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The Authors would like to acknowledge that this work is the direct output of a Newton Fund Researcher Links Workshop grant, ID 2018-RLWK10-10480, between the United Kingdom and India, which allowing researchers to collaborate. The grant is funded by the UK Department for Business, Energy and Industrial Strategy and The Royal Society of Chemistry and delivered by the British Council. For further information, please visit www.newtonfund.ac.uk.

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