CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://doi.org/10.5281/zenodo.17409031

Available online at: http://www.iajps.com Review Article

GALIDESIVIR'S POTENTIAL AS A BROAD SPECTRUM ANTIVIRAL: A REVIEW

Ramya Nagabathula*[1], A.V.R.Aparajitha[1], K.Lalitha Sundari[2], CH.Vineela[2]
Department of Pharmaceutical Analysis, Koringa College of Pharmacy

Abstract:
Galidesivir (BCX4430) is an adenosine nucleoside analogue that has gained considerable attention as a promising broad-spectrum antiviral candidate.Originally developed against filoviruses, such as Ebola and Marburg, Galidesivir has subsequently demonstrated activity against a wide range of RNA viruses, including flaviviruses, arenaviruses, and coronaviruses. Its mechanism of action involves intracellular phosphorylation to the active triphosphate metabolite, which competes with adenosine triphosphate for incorporation into viral RNA by RNA-dependent RNA polymerase (RdRp), ultimately leading to premature chain termination. Despite this potent mechanism, its conversion to the triphosphate form is cell-dependent, influencing efficacy across different host systems. Significant progress has been made in understanding both the synthetic pathway of Galidesivir and its preclinical pharmacology. Chemical modification strategies have been explored to optimize nucleoside analog activity, while recent research highlights sustainable approaches such as utilizing bio-based intermediates, including compounds derived from corn husk, as potential raw material sources. These innovations aim to improve cost-effectiveness and accessibility for large-scale production. Clinically, Galidesivir has advanced to phase II trials in the treatment of COVID-19 and other viral infections. Intravenous and intramuscular routes have been investigated, with pharmacokinetic studies confirming dose-dependent distribution and elimination. Although early trials established favorable safety and tolerability profiles, clinical efficacy outcomes remain variable, and further evidence is needed to establish its therapeutic position against emerging viral threats. This review provides a consolidated overview of Galidesivir, focusing on its chemistry, synthesis strategies, pharmacological mechanisms, and clinical progress. By critically analyzing its strengths and limitations, the article underscores Galidesivir's potential as an important antiviral candidate while also highlighting future research directions required for translation into effective therapeutic application.

Keywords: *Galidesivir (BCX-4430),C-nucleoside analogues, Antiviral drug development, RNA-dependent RNA polymerase (RdRp) inhibitor, Broad-spectrum antivirals, Pharmacokinetics (PK) and ADME, Clinical trials of Galidesivir, Synthetic strategies of nucleoside analogues, Triphosphate metabolite (BCX-4430-TP),Ebola and emerging viral infections.*

Corresponding author:
Ramya Nagabathula,
Department of Pharmaceutical Analysis,
Koringa College of Pharmacy

QR CODE

Please cite this article in press ***Ramya Nagabathula*** *et al.,* ***Galidesivir's potential as a broad spectrum Antiviral: a review****, Indo Am. J. P. Sci, 2025; 12(10).*

INTRODUCTION:

Galidesivir(BCX4430, Immucillin-A) is an investigational adenosine nucleoside developed by BioCryst Pharmaceuticals, Birmingham, AL, USA and manufactured by Millipore Sigma, Madison, WI, USA and this developed as a broad-spectrum antiviral candidate with activity against multiple RNA virus families[1].The molecule was first highlighted for its ability to protect animals from lethal filovirus infections and since then has been evaluated across numerous preclinical models for pathogens such as Ebola, Marburg, yellow fever, Zika, Rift Valley fever, and others, which established its potential as a countermeasure against emerging and re-emerging RNA viruses[2].Structurally, Galidesivir is an imino-C-nucleoside in which the sugar oxygen is replaced by nitrogen and the heterobase is a substituted pyrrolo[2,3-d]pyrimidine; this C-glycosidic linkage provides enhanced metabolic stability compared with many O-glycosidic nucleosides and demands specialized synthetic approaches [3,4].Mechanistically, Galidesivir functions as a nucleoside analogue prodrug, it enters host cells and is phosphorylated stepwise by host kinases to the active triphosphate species (BCX-4430-TP), which can be incorporated by viral RNA-dependent RNA polymerases (RdRps) and cause delayed chain termination or stalling of RNA synthesis, thereby inhibiting viralreplication [5].Biochemical and polymerase-assay studies have demonstrated that BCX-4430-TP is accepted to varying extents by diverse viral polymerases, explaining the compound's broad in vitro spectrum but also accounting for differences in potency between virus families and polymerase contexts[6].Chemical synthesis of BCX-4430 and its triphosphate has therefore been essential: access to the nucleoside and especially to BCX-4430-TP enabled polymerase biochemistry, ADME characterization, and efficacy testing across in vitro and in vivo models[7].Preclinical efficacy studies revealed that parenteral administration intramuscular or intravenous of Galidesivir can provide therapeutic benefit when dosed after virus exposure in small animals and nonhuman primates, with several studies showing reduced morbidity and mortality in high-consequence infection models and an extended post-exposure therapeutic window[8].Clinically,Galidesivir's development has followed a cautious translational path—moving from robust animal efficacy to Phase-1 safety and PK characterization in humans, and subsequently to targeted exploratory use and stockpiling considerations for outbreak response[9].Regulatory communications and industry updates emphasize that while Galidesivir is investigational, its broad-spectrum profile and favorable preclinical safety/efficacy data make it a candidate for strategic development against priority pathogens such as filoviruses and emerging flaviviruses [10].The present article aims to summarize the current state of knowledge on Galidesivir, including its unique mechanism of action and pharmacokinetic characteristics, a detailed assessment of its antiviral spectrum and preclinical efficacy across diverse models, and an overview of emerging data from clinical studies. This synthesis will also contextualize ongoing challenges and opportunities in optimizing Galidesivir for therapeutic application.

ANTIVIRAL ACTIVITY OF GALIDESIVIR

- The antiviral potential of Galidesivir has been demonstrated to be specific, with activity not attributable to general cytotoxic or anti-proliferative effects. In cell-based assays, the compound showed low cytotoxicity, with the 50% cytotoxic concentration (CC_{50}) exceeding 500 µm in HeLa cells and consistently above 100 µm in other models [4].
- Infected human macrophages, including those derived from normal peripheral blood monocytes, confirmed the antiviral activity of Galidesivir against Ebola virus (EBOV), suggesting its effectiveness extends beyond immortalized cell lines. Interestingly, studies have shown that immortalized cells often display a reduced ability to convert Galidesivir (BCX4430) into its active triphosphate form compared to primary hepatocytes. As a result, in vitro assays using such cells may underestimate the true antiviral potency that is observed in vivo during experimental or clinical infections [9].
- Galidesivir has demonstrated broad-spectrum activity across a wide range of RNA viruses by targeting the viral RNA-dependent RNA polymerase (RdRp). However, its antiviral efficacy varies across viral families, with some studies indicating stronger potency against particular groups. In vitro, Galidesivir consistently exhibits more promising activity against specific RNA viruses than others [10].
- Quantitative assays such as the cytopathic effect (CPE) reduction assay further support its antiviral profile, with EC_{50} values typically in the micromolar range and favorable selectivity indices [11]. Although the EC_{50} and EC_{90} values do not always fully capture the compound's therapeutic potential, they highlight its consistent ability to inhibit viral replication in cell-based systems.Together, these findings reinforce Galidesivir's promise as a broad-spectrum antiviral

candidate worthy of continued preclinical and clinical evaluation [12].

MECHANISM OF ACTION

- Galidesivir is classified as an adenosine nucleoside analogue that specifically interferes with the RNA-dependent RNA polymerase (RdRp), a key enzyme required for the replication of RNA viruses. For the compound to exert its antiviral activity, it must undergo intracellular phosphorylation by host kinases, resulting in the formation of its active triphosphate metabolite (BCX4430-TP or BCX6870)[1]. This metabolite functions as a structural mimic of adenosine triphosphate (ATP), thereby competing with natural nucleotides during viral RNA synthesis and ultimately leading to premature termination of RNA chain elongation. However, the efficiency of this metabolic activation can vary between different cell types. For instance, Vero cells exhibit limited capacity to phosphorylate the parent compound into its triphosphate form, which explains their comparatively lower antiviral response, whereas other cell lines with higher kinase activity show enhanced conversion and more potent antiviral effects[13-14].

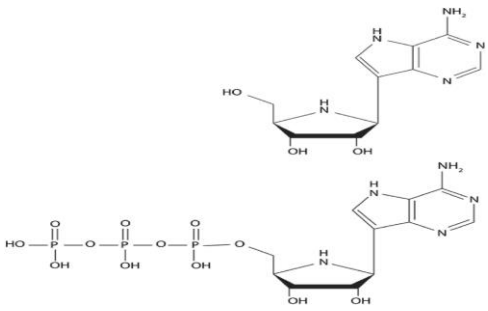

Fig1:Structure of Galidesivir, an adenosine nucleoside analogue (upperpanel),and its active triphosphate form (lower panel) [14]

- Once intracellular phosphorylation takes place, the active metabolite BCX4430-TP becomes incorporated into the viral RNA chain, where it interferes with elongation and ultimately induces premature chain termination. Experimental data suggest that BCX4430-TP shows a stronger affinity for viral RNA polymerase than for host cell polymerases, which explains its selective antiviral action [15].
- The mechanism of action of Galidesivir has also been validated in studies using tick-borne encephalitis virus (TBEV), where resistance was observed in a mutant strain specifically adapted to Galidesivir exposure. This resistance was associated with a single amino acid substitution within the catalytic site of the viral RdRp, clearly reflecting viral adaptation under drug pressure [16].
- Interestingly, the mutant TBEV strain displayed nearly seven-fold reduced sensitivity to Galidesivir compared with the wild-type strain. However, this mutation also resulted in a significant decrease in viral fitness when tested in vivo, underscoring the evolutionary trade-off between resistance and replication efficiency [17].
- Structurally, Galidesivir is an adenosine-like compound with a nitrogen-modified sugar moiety, a unique feature that requires phosphorylation by host kinases for conversion into its triphosphate form [18,19].
- Importantly, this activation process is cell-type dependent. For example, Vero cells possess limited kinase activity and therefore show reduced capacity to metabolize Galidesivir into its triphosphate form. Consequently, antiviral potency in these cells is diminished compared with primary or other cell lines capable of more efficient phosphorylation [15].

PHARMACOKINETICS

- The pharmacokinetic profile of BCX4430 in non-clinical species,Phase 1 clinical safety and pharmacokinetic studies of Galidesivir, administered both intravenously and intramuscularly have been completed in healthy volunteers. At present, Galidesivir is being evaluated in Phase II clinical trials for the treatment of coronavirus infections, with ongoing studies conducted in Brazil as well as in other parts of the world. Galidesivir has demonstrated broad-spectrum activity in vitro with EC50ranging from ~ 3 to ~ 68 μm in preclinical studies against more than 20 RNA viruses in ninedifferent families filoviruses, togaviruses, bunyavirus, arenaviruses, paramyxoviruses, flaviviruses, coronaviruses[26-27].
- An adenosine-based nucleoside analogue that blocks viral RNA polymerase by converting into a triphosphate form, which resembles the natural cellular kinase substrate ATP. Viral RNA polymerases incorporate the drug's monophosphate nucleotide into the growing RNA chain, resulting in early chain termination, thereby disrupting the activity of viral RNA-dependent RNA polymerase [9],[28-29].

- After IM injection in rats, Galidesivir is systemically distributed in plasma where the parent compound is rapidly cleared (with a half life<5 minutes), with clearance occuring concomitant with accumulation of the active BSX4430-TP form in the liver (with a half life of 6.2 hours)[30].

Absorption / Routes & early PK

Galidesivir has been evaluated in humans in first-in-human Phase-1 trials using intramuscular (IM) injections and intravenous (IV) 60-min infusions; oral clinical formulations were not reported in the published human PK trials. IM administration produced rapid absorption, with median $T_{max} \approx$ 0.25–0.375 h (~15 min) after injection, and the IM formulation showed ~84% bioavailability relative to IV at the 10 mg/kg comparison. IV dosing (60-min infusion) reached C_{max} at the end of infusion, and AUC and C_{max} increased approximately dose-proportionally over the tested IV dose range. [31]

Distribution (plasma ↔ tissues / intracellular)

The plasma concentration–time profile is biphasic (initial rapid distribution/clearance followed by a prolonged terminal elimination phase), consistent with rapid tissue uptake and delayed release. Human IV studies reported very long terminal half-lives estimated in extended sampling (examples ~104–175 h), indicating prolonged terminal elimination likely driven by tissue/tightly-bound pools[31].Preclinical tissue distribution documents widespread tissue uptake but limited CNS penetration in healthy animals (brain, plasma ratio ≤ 0.10 in rats), implying the intact blood-brain barrier restricts parent drug entry under normal conditions[32].Animal PK/tissue data show a very large apparent volume of distribution (extensive tissue partitioning in small-animal models), supporting the human observations of rapid plasma disappearance and long terminal phase[33].Importantly, intracellular concentrations of the active triphosphate metabolite (BCX4430-TP) exceedplasma parent levels within minutes and are substantially higher in target tissues (for example, in liver), leading to prolonged intracellular exposure despite low circulating parent drug[34].

Metabolism / Bioactivation

Galidesivir is not primarily cleared by complex oxidative metabolism in extracellular fractions; instead it requires intracellular phosphorylation by host kinases to form BCX4430-MP → BCX4430-DP → BCX4430-TP, the pharmacologically active nucleotide that inhibits viral RdRp [34].The rate and efficiency of intracellular phosphorylation vary by cell type and species, but preclinical and in vitro hepatocyte data show rapid formation of BCX4430-TP, consistent with liver being a major site of activation and retention. Measured tissue half-lives of BCX4430-TP (preclinical) demonstrate substantive persistence (example: ~6 h in rat liver), which helps explain sustained antiviral activity after transient plasma exposures [32].Several preclinical studies observed intracellular catabolism of BCX4430-TP and slow reappearance of parent drug in plasma (a delayed secondary plasma peak), consistent with slow release of parent from tissue/intracellular stores[33].Mechanistic biochemical work shows BCX4430-TP can be incorporated by viral RNA polymerases and promote premature chain termination (non-obligate chain terminator), linking intracellular TP levels directly to antiviral effect[35].

Excretion / Clearance

Human urine collections show a meaningful fraction of the dose is recovered unchanged in urine: cumulative recovery after IM dosing (48 h) was roughly 25–35%, and after IV dosing (96 h) roughly 33–46%, indicating renal elimination of parent contributes substantially to overall clearance measured plasma clearance and renal clearance in the Phase 1 data indicate renal elimination is a significant route, but the prolonged terminal plasma phase is dominated by slow release from tissues rather than instantaneous renal removal. Across species, excretion and elimination show biphasic behavior an early rapid plasma decline followed by slow terminal elimination which is consistent with parent release from tissue/intracellular stores and subsequent renal removal[31].

In Study 1, healthy participants received single intramuscular doses of Galidesivir (n=6 per dose). The doses were delivered through 1 to 4 intramuscular injections. A total of fourteen individuals were administered Galidesivir alone and again in combination with 20 mg of lidocaine, with a one-week interval between the two treatments.

Dose(mg/kg)	Cmax,ng/mlmeanSD	$T_{max,h}$ Median(range)	$AUC_{0-t,ng.h/ml}$Mean(SD)	%Dose excreted inurineMean(SD)
Single dose,intramuscular dosing of Galidesivir(Study 1, Part 1)				
0.3	167 (30.5)	0.75(0.25, 1.05)	518 (18.6)	27.7 (2.6)*
0.75	562 (37.0)	0.25(0.25, 0.50)	1340 (7.0)	27.8 (7.1)
1.8	1000 (28.6)	0.25(0.08, 0.25)	3890 (8.0)	31.2 (5.9)
4.0	2760 (31.2)	0.25(0.25, 0.50)	10100 (12.1)	33.0 (32.9)
7.0	5760 (25.7)	0.25(0.25, 0.25)	18900 (12.0)	34.7 (5.4)

10	7980 (30.6)	0.375(0.25,0.50)	27100 (17.7)	25.2 (8.4)
Single-dose intramuscular dosing of Galidesivir with and without lidocaine (Study 1, Part 2).				
4	2930 (33.7)	0.25(0.25, 0.50)	10200(12.3)	N/C**
4+lidocaine	3000 (22.7)	0.25(0.08, 0.50)	10400(11.1)	N/C**

* after administration of 0.3 mg/kg, urinary excretion was measured over a 48-hour period. For the remaining dose levels, excretion was assessed up to 96 hours. ** Urine samples were not obtained in Part 2.

Table 1.Pharmacokinetic parameters observed following a single intramuscular dose of Galidesivir[31]

In Study 2, healthy volunteers were administered single 60-minute intravenous infusions of Galidesivir (n=6 per dose).

Dose mg/kg	Cmax, ng/mL Mean(SD)	Tmax,h Median (range)	AUC0-t, ng.h/m* Mean(SD)	t1/2 (h) Mean (SD)	CL(L/) Mean (SD)	Vz (L) Mean (SD)	Clr(L/h) Mean(SD)	%Dose excreted in Urine Mean(SD)
Single dose, 60-minute IV infusions of Galidesivir (Study 2).								
5	5560 (425)	1.00 (1.00,10)	17840 (4116)	116.3 (45.6)	116.3 (45.6)	2775 (611)	2775 (611)	27.7 (2.6)**
10	10500 (2250)	1.00 (0.50,12)	32730 (5103)	103.9 (21.0)	20.9 (2.5)	3107 (678)	11.8 (2.2)	27.8 (7.1)
15	17950 (2942)	1.00 (1.00,13)	60730 (12569)	174.8 (36.3)	16.8 (2.2)	4198 (797)	11.6 (1.6)	31.2 (5.9)
20	20720 (3389)	1.00 (1.00,12)	73940 (10540)	161.5 (54.0)	18.1 (2.5)	4083 (873)	8.6 (4.7)	33.0 (32.9)

* AUC_{0}–t for Study 2: After administration of the 5 and 10 mg/kg doses, AUC_{0}–t was evaluated over 168 hours; for the 15 mg/kg dose, it was assessed up to 480 hours; and for the 20 mg/kg dose, it was determined through 312 hours.

Table 2. Pharmacokinetic parameters after single intravenous doses of Galidesivir [31]

Clinical Development Status of Galidesivir (BCX4430)

Galidesivir is currently classified as an experimental antiviral agent in the early clinical (Phase 1) development stage. A randomized, placebo-controlled first-in-human Phase 1 study in healthy volunteers evaluated both intramuscular (IM) and intravenous (IV) administration, demonstrating acceptable tolerability and characterizing the pharmacokinetic profile, including bioavailability, peak concentration, half-life, volume of distribution, clearance, and urinary excretion of intact drug[31].Peer-reviewed overviews and development-status reviews published more recently continue to describe Galidesivir as clinical-stage but still predominantly within Phase 1, noting that while it has entered early interventional evaluations for emerging infections (such as yellow fever and COVID-19), there are no published peer-reviewed Phase 2 or Phase 3 clinical efficacy trials to date[32].

Synthetic Strategies of Galidesivir

Galidesivir (BCX-4430) is a C-nucleoside analogue structurally related to Immucillin-A, in which the ribofuranose oxygen is replaced by a nitrogen atom and the heterobase is a pyrrolo[2,3-d]pyrimidine ring system [36]. This unusual architecture confers enhanced metabolic stability but also demands non-classical synthetic approaches [37].

Legacy Seven-Step Synthesis

The first synthetic route to Galidesivir was a linear seven-step process starting from BCX1777, an immucillin analogue [38]. In this method, a protected azasugar fragment was condensed with a functionalized pyrrolo[2,3-d]pyrimidine ring system. Sequential protection and deprotection steps were employed to reveal hydroxyl and amino functionalities necessary for bioactivity [39]. The overall isolated yield of this legacy synthesis was approximately 22–25%, which limited its practicality for large-scale preparation.

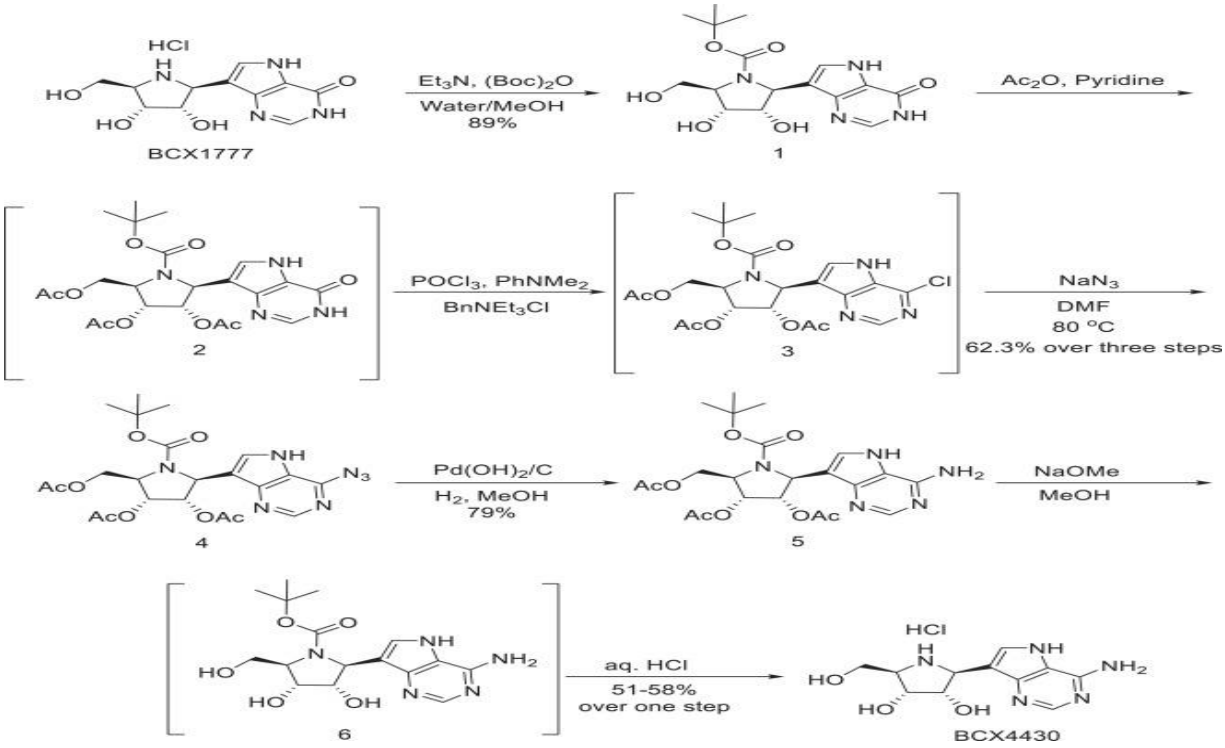

Fig2: Seven-step synthesis of Galidesivir from BCX-1777 [40]

Convergent Nitrone Approach

To overcome inefficiencies of the legacy route, a convergent nitrone-based synthesis was later developed [41]. In this approach, a tri-O-benzyl cyclic nitrone derived from D-ribose was coupled with a lithiated 9-deazapurine derivative, forming the imino-C-nucleoside skeleton of Galidesivir in a single step [42]. The protecting groups were subsequently removed through deprotection and hydrogenolysis, yielding the free nucleoside. Importantly, the C-7 amino substituent of the heteroaryl ring was introduced by a copper-catalyzed Ullmann-type amination, which improved regioselectivity and reduced the number of synthetic steps compared with the earlier linear route.

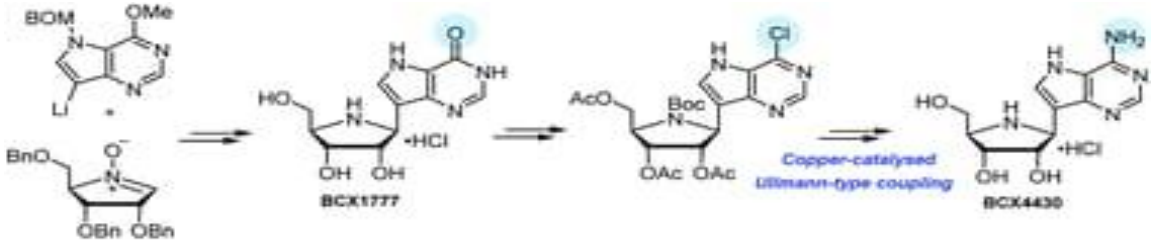

Fig3: Convergent nitrone based synthesis of Galidesivir [43].

Common Precursor Strategy

A further improvement was achieved through a divergent synthesis starting from a common precursor. In this method, a Boc-protected pyrrolidinone intermediate was prepared from tri-O-benzyl-D-ribonolactone and used as a central scaffold [44]. This scaffold was selectively coupled to a dihalogenated pyrrolo[2,3-d]pyrimidine derivative via chemoselective cross-coupling, achieving 79% yield in the key step [45]. Additional transformations including Luche reduction, mesylation, and global deprotection yielded analytically pure Galidesivir [46]. This common precursor strategy enabled access to both BCX-1777 and BCX-4430 in a more scalable and practical manner.

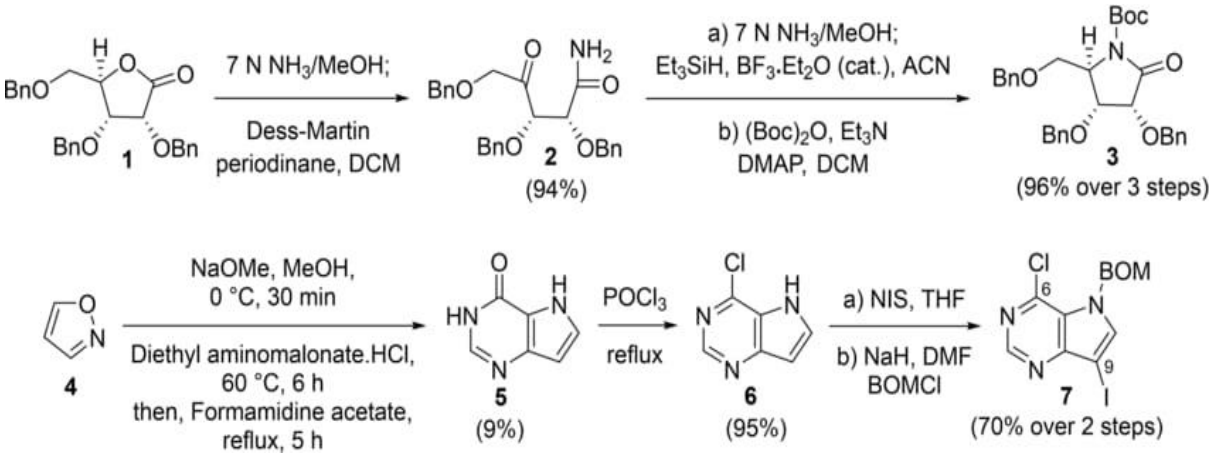

Fig4: Synthesis of Boc-protected γ-lactam 3 and dihalogenated pyrrolo[3,2-d]pyrimidine 7 [47].

Triphosphate Metabolite Synthesis

The pharmacologically active form of Galidesivir is its intracellular triphosphate metabolite (BCX-4430-TP), which directly inhibits viral RNA polymerases [48]. To enable biochemical testing, a solution-phase phosphorylation method was optimized for azasugars, providing access to BCX-4430-TP in sufficient yield and purity [49]. This protocol allowed preparation of triphosphate standards necessary for enzyme assays and drug–target interaction studies.

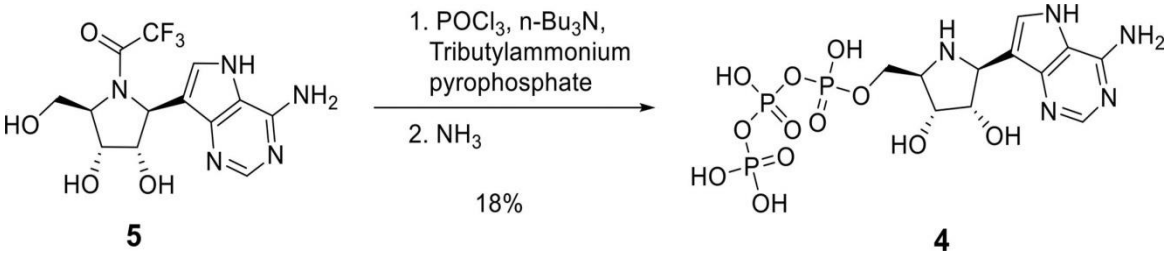

Fig5: Chemical synthesis of BCX-4430 triphosphate [50]

Current Status

Collectively, synthetic strategies for Galidesivir have evolved from a seven-step linear route to highly efficient convergent and divergent methods[51].These approaches emphasize direct C–C bond construction of the imino-C-nucleoside skeleton, late-stage amination for step economy, and the use of common precursors for scalability[52]. In addition, triphosphorylation protocols have enabled preparation of the pharmacologically relevant triphosphate metabolite for preclinical assays. Together, these synthetic advances provide a foundation for further medicinal chemistry optimization and support ongoing drug development efforts[53].

GALIDESIVIR FROM CORN HUSK

According to recent press report, an innovative synthetic approach to Galidesivir proposed by Adam Kovalcik, a 19-year-old Slovakian student. His method begins with furfuryl alcohol obtained from corn husks as the starting material, representing a sustainable and low-cost feedstock. The strategy reportedly reduces the number of synthetic steps required to produce Galidesivir from 15 to 10 steps, while simultaneously shortening the overall production time from nine days to five days. Furthermore, the estimated cost of production decreases significantly, from approximately $75 per gram to $12.50 per gram, suggesting substantial economic advantages for large-scale manufacturing. This approach utilizes an aza-sugar intermediate to assemble the nucleoside analogue scaffold, aligning with previously established methodologies while offering notable improvements in efficiency. In addition, Kovalcik has proposed a novel structural analogue of Galidesivir, which demonstrated potentially enhanced antiviral activity in computational docking models against SARS-CoV-2. A preliminary patent application has been filed,

and collaborative efforts with researchers at the Slovak University of Technology have been initiated to further evaluate this process[54].

CONCLUSION:

Clinical Trials of Galidesivir

Galidesivir (BCX-4430) demonstrated robust in vivo efficacy in multiple animal models of filovirus infection, providing the preclinical basis for clinical development.Comprehensive reviews of BCX-4430 summarize its broad antiviral activity across RNA virus families and note that efficacy in animal models is frequently greater than cell-culture potency would predict, emphasizing translational potential[55].First-in-human evaluations (single ascending IV and IM doses) established an acceptable safety and tolerability profile in healthy volunteers, supporting further clinical study.Phase-1 pharmacokinetic studies reported dose-proportional exposure, rapid absorption after IM dosing, and a biphasic plasma profile consistent with rapid distribution and a slower terminal elimination phase[56].Clinical PK and preclinical ADME data together emphasize that the pharmacologically relevant species is the intracellular triphosphate (BCX-4430-TP), and plasma parent concentrations alone are an imperfect predictor of antiviral exposure[57].Available human data show measurable renal elimination of parent drug and a small fraction recovered unchanged in urine, but full human tissue measurements of intracellular TP remain limited.Polymerase biochemistry studies using chemically synthesized BCX-4430-TP corroborate the proposed mechanism incorporation by viral RdRp and delayed chain termination and these mechanistic data inform PK/PD modeling for clinical dosing[58].Regulatory and industry communications indicate clinical development to date has prioritized safety, PK characterization, and readiness for outbreak-responsive deployment rather than large randomized efficacy trials.Resistance mapping in vitro has identified polymerase substitutions that reduce susceptibility to BCX-4430, but available work suggests many such substitutions carry fitness costs, which mitigates immediate clinical resistance concerns[59].Important translational gaps remain before definitive clinical utility can be established: validated surrogate markers of intracellular TP in humans, tissue-level TP exposure data (lung/liver/CNS) under disease conditions, and efficacy evidence from indication-specific trials.Taken together, clinical trial results to date position Galidesivir as a well-tolerated investigational antiviral with clear mechanistic rationale and strongpreclinicalsupport, but further targeted human PK/PD and efficacy studies are required to define its therapeutic role[60].

Current Status of Synthesis

Early preparative chemistry for BCX-4430 relied on multi-step, protection-intensive conversions from Immucillin precursors, which were adequate for discovery quantities but suboptimal for scaled production[61].Practical, convergent laboratory routes now build the imino-C-nucleoside core by addition of lithiated heteroaromatics to protected cyclic nitrones, which forms the C–C bond in a single key step and reduces overall step count. Late-stage installation of the heteroaryl amino substituent by copper-catalyzed Ullmann-type amination has been shown to be an efficient strategy that preserves step economy and region selectivity in modern BCX-4430 routes[62].Modular, common-precursor approaches using Boc-protected pyrrolidinone sugar fragments allow divergent access to BCX-1777 and BCX-4430 and report high yields for the central cross-coupling step, improving flexibility for analogue synthesis and scale-up[64].Chemists have developed reliable chemical phosphorylation methods to produce BCX-4430-TP as a reference standard, which is essential for polymerase biochemistry and ADME studies that underpin translational development. Process-chemistry and patent summaries describe scale-up modifications—e.g., acetylation, selective sugar chlorination, and ammonolysis sequences that aim to reduce manipulations and improve throughput for manufacture[65].Recent reports also document triphosphate synthesis and analytical methods that make BCX-4430-TP broadly available to the research community, enabling standardized mechanistic comparisons across viral polymerases[66].Collectively, these synthetic advances have transformed BCX-4430 production from discovery-scale routes to more step-economic, convergent strategies that are compatible with preparative and process chemistry goals[67].Remaining synthetic priorities include further lowering step count, improving overall yields, implementing greener reagents/flow methods for scale, and developing cost-effective GMP manufacturing routes to support wider clinical deployment if efficacy is confirmed[68].In sum, the synthetic state-of-the-art for Galidesivir is sufficiently advanced to supply material for continued translational work, and ongoing process optimization will be a critical enabler for future large-scale use should clinical efficacy be demonstrated[69].

REFERENCES:

1. Ataei, M., &Hosseinjani, H. (2020). Molecular mechanisms of galidesivir as a potential antiviral treatment for COVID-19. *Journal of Pharmaceutical Care*, 150-151

2. Arora, G., Shrivastava, R., Kumar, P., Bandichhor, R., Krishnamurthy, D., Sharma, R. K., ... &Rizwan, M. (2021). Recent advances made in the synthesis of small drug molecules for clinical applications: An insight. *Current Research in Green and Sustainable Chemistry*, *4*, 100097.
3. Siegel, D., Hui, H. C., Doerffler, E., Clarke, M. O., Chun, K., Zhang, L., ... &Mackman, R. L. (2017). Discovery and Synthesis of a Phosphoramidate Prodrug of a Pyrrolo [2, 1-f][triazin-4-amino] Adenine C-Nucleoside (GS-5734) for the Treatment of Ebola and Emerging Viruses.
4. Celik, I., Erol, M., &Duzgun, Z. (2021). In silico evaluation of potential inhibitory activity of remdesivir, favipiravir, ribavirin and galidesivir active forms on SARS-CoV-2 RNA polymerase. *Molecular Diversity*, 1-14.
5. Zhao, L., Li, S., &Zhong, W. (2022). Mechanism of action of small-molecule agents in ongoing clinical trials for SARS-CoV-2: a review. Frontiers in Pharmacology, 13, 840639.
6. Xu, X., Chen, Y., Lu, X., Zhang, W., Fang, W., Yuan, L., & Wang, X. (2022). An update on inhibitors targeting RNA-dependent RNA polymerase for COVID-19 treatment: promises and challenges. Biochemical pharmacology, 205, 115279.
7. Duan, M., Wang, Y., & Zhu, S. (2023). Nickel-catalyzed asymmetric 1, 2-alkynylboration of vinylarenes. Tetrahedron Letters, 114, 154247.
8. Taylor, R., Bowen, R., Demarest, J. F., DeSpirito, M., Hartwig, A., Bielefeldt-Ohmann, H., ... &Babu, Y. S. (2021). Activity of galidesivir in a hamster model of SARS-CoV-2. Viruses, 14(1), 8.
9. Warren, T. K., Wells, J., Panchal, R. G., Stuthman, K. S., Garza, N. L., Van Tongeren, S. A., ... &Bavari, S. (2014). Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue BCX4430. Nature, 508(7496), 402-405.
10. Zhou, S., Yang, Q., & Wang, L. (2023). Phosphorylation methods for nucleoside analogues: Application to antiviral triphosphates. Tetrahedron Letters, 118, 154377.
11. Stuyver, L. J., Whitaker, T., Raboisson, P., &Schinazi, R. F. (2017). C-nucleosides for the treatment of RNA virus infections. Antiviral Research, 144, 63–74.
12. Julander, Justin G., James F. Demarest, Ray Taylor, Brian B. Gowen, Dennis M. Walling, Amanda Mathis, and Y. S. Babu. "An update on the progress of galidesivir (BCX4430), a broad-spectrum antiviral." Antiviral research 195 (2021): 105180.
13. Julander, J. G., Siddharthan, V., Evans, J., Taylor, R., Tolbert, K., Apuli, C., ... &Babu, Y. S. (2017). Efficacy of the broad-spectrum antiviral compound BCX4430 against Zika virus in cell culture and in a mouse model. Antiviral research, 137, 14-22.
14. Julander, J. G., Demarest, J. F., Taylor, R., Gowen, B. B., Walling, D. M., Mathis, A., &Babu, Y. S. (2021). An update on the progress of galidesivir (BCX4430), a broad-spectrum antiviral. Antiviral research, 195, 105180.
15. Warren, T. K., Wells, J., Panchal, R. G., Stuthman, K. S., Garza, N. L., Van Tongeren, S. A., ... &Bavari, S. (2014). Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue BCX4430. Nature, 508(7496), 402-405.
16. Tisdale, M. (2023). Development of antiviral nucleoside analogues: From discovery to clinical application. Current Opinion in Virology, 58, 101311.
17. Eyer, L., Nougairède, A., Uhlířová, M., Driouich, J. S., Zouharová, D., Valdés, J. J., ... &Ruzek, D. (2019). An E460D substitution in the NS5 protein of tick-borne encephalitis virus confers resistance to the inhibitor galidesivir (BCX4430) and also attenuates the virus for mice. Journal of Virology, 93(16), 10-1128.
18. Tchesnokov, E. P., Feng, J. Y., Porter, D. P., &Götte, M. (2019). Mechanism of inhibition of Ebola virus RNA-dependent RNA polymerase by remdesivir. Viruses, 11(4), 326.
19. Elfiky, A. A. (2020). Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): A molecular docking study. Life sciences, 253, 117592.
20. Ruzek, D., Županc, T. A., Borde, J., Chrdle, A., Eyer, L., Karganova, G., ... &Zajkowska, J. (2019). Tick-borne encephalitis in Europe and Russia: Review of pathogenesis, clinical features, therapy, and vaccines. Antiviral research, 164, 23-51.
21. Pizzorno, A., Padey, B., Terrier, O., & Rosa-Calatrava, M. (2019). Drug development against RNA viruses: Advances and perspectives. Nature Reviews Drug Discovery, 18(7), 447–467.
22. Deshpande, S., Huo, W., Shrestha, R., Sparrow, K., Evans, G. B., Harris, L. D., ... &Bulloch, E. M. (2022). Inhibition of the DENV2 and ZIKV RNA polymerases by Galidesivir triphosphate measured using a continuous fluorescence assay. bioRxiv, 2022-12.

23. Torres, D. (2025). Synthesis of Nucleoside Analogues and Elucidation of their Antiviral Mechanisms (Doctoral dissertation, Open Access TeHerenga Waka-Victoria University of Wellington).
24. Bui, T. Q., Hai, N. T. T., My, T. T. A., Phong, N. H. V., Nhan, N. T., Quy, P. T., ... &Nhung, N. T. A. (2022). An in silico study on inhibitability of Baloxavirmarboxil, Baricitinib, Galidesivir, Nitazoxanide, and Oseltamivir against SARS-CoV-2. Vietnam Journal of Chemistry, 60(3), 333-345.
25. Mawazi, S. M., Fathima, N., Mahmood, S., & Al-Mahmood, S. M. A. (2024). Antiviral therapy for COVID-19 virus: A narrative review and bibliometric analysis. The American Journal of Emergency Medicine.
26. Ju, J., Kumar, S., Li, X., Jockusch, S., & Russo, J. J. (2020). Nucleotide analogues as inhibitors of viral polymerases. *BioRxiv*, 2020-01.
27. Dömling, A., & Gao, L. (2020). Chemistry and biology of SARS-CoV-2. *Chem*, *6*(6), 1283-1295.
28. Abuo-Rahma, G. E. D. A., Mohamed, M. F., Ibrahim, T. S., Shoman, M. E., Samir, E., &Abd El-Baky, R. M. (2020). Potential repurposed SARS-CoV-2 (COVID-19) infection drugs. *RSC advances*, *10*(45), 26895-26916.
29. Julander, J. G., Bantia, S., Taubenheim, B. R., Minning, D. M., Kotian, P., Morrey, J. D., ... &Babu, Y. S. (2014). BCX4430, a novel nucleoside analog, effectively treats yellow fever in a Hamster model. *Antimicrobial agents and chemotherapy*, *58*(11), 6607-6614.
30. Iversena, P., Bixlera, S., Kanea, C. D., &Warrena, T. K. (2021). Small-molecule and Synthetically Derived Antivirals for Ebola Virus and Other Filoviruses1. *Antiviral Discovery for Highly Pathogenic Emerging Viruses*, *80*.
31. Mathis, A., Collins, D., Dobo, S., Walling, D. M., Sheridan, W. P., & Taylor, R. (2022). Pharmacokinetics and safety of the nucleoside analog antiviral drug galidesivir administered to healthy adult subjects. Clinical pharmacology in drug development, 11(4), 467-474.
32. Julander, J. G., Demarest, J. F., Taylor, R., Gowen, B. B., Walling, D. M., Mathis, A., &Babu, Y. S. (2021). An update on the progress of galidesivir (BCX4430), a broad-spectrum antiviral. Antiviral research, 195, 105180.
33. Westover, J. B., Mathis, A., Taylor, R., Wandersee, L., Bailey, K. W., Sefing, E. J., ... &Gowen, B. B. (2018). Galidesivir limits Rift Valley fever virus infection and disease in Syrian golden hamsters. Antiviral research, 156, 38-45.
34. Taylor, R., Kotian, P., Warren, T., Panchal, R., Bavari, S., Julander, J., ... & Sheridan, W. P. (2016). BCX4430–a broad-spectrum antiviral adenosine nucleoside analog under development for the treatment of Ebola virus disease. Journal of infection and public health, 9(3), 220-226.
35. Warren, T. K., Wells, J., Panchal, R. G., Stuthman, K. S., Garza, N. L., Van Tongeren, S. A., ... &Bavari, S. (2014). Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue BCX4430. Nature, 508(7496), 402-405.
36. Pfeiffer, M., &Nidetzky, B. (2020). Reverse C-glycosidase reaction provides C-nucleotide building blocks of xenobiotic nucleic acids. Nature Communications, 11(1), 6270.
37. Santos, G. C. D., Martins, L. M., Bregadiolli, B. A., Moreno, V. F., Silva-Filho, L. C. D., & Silva, B. S. T. D. (2021). Heterocyclic compounds as antiviral drugs: synthesis, structure-activity relationship and traditional applications.
38. Nie, P. (2019). Synthesis and biological evaluation of C-nucleoside analogues.
39. Rashid, M. H. O., Ezzikouri, S., Soliman, A. M., Akter, L., Momohara, K., Hifumi, T., ... &Tsukiyama-Kohara, K. (2025). Drug repositioning: Identification of potent inhibitors of NS3 protease and NS5 RdRp for control of DENV infection. Biomedicine & Pharmacotherapy, 187, 118104.
40. Dang, Z., Wu, M., Chintareddy, V., Polach, K. J., Babu, Y. S., &Kotian, P. (2023). An efficient triphosphate synthesis of a novel broad-spectrum antiviral nucleoside BCX4430. Tetrahedron Letters, 114, 154219.
41. Deshpande, S., Huo, W., Shrestha, R., Sparrow, K., Wood, J. M., Evans, G. B., ... &Bulloch, E. M. (2023). Galidesivir triphosphate promotes stalling of dengue-2 virus polymerase immediately prior to incorporation. ACS Infectious Diseases, 9(8), 1658-1673.
42. De Fenza, M., Esposito, A., D'Alonzo, D., &Guaragna, A. (2021). Synthesis of piperidine nucleosides as conformationally restricted immucillin mimics. Molecules, 26(6), 1652.
43. Zhang, M., Xue, F., Ou, J., Huang, Y., Lu, F., Zhou, B., ... & Qin, Y. (2020). Practical synthesis of immucillins BCX-1777 and BCX-4430. Organic Chemistry Frontiers, 7(22), 3675-3680.
44. Guinan, M., Benckendorff, C., Smith, M., & Miller, G. J. (2020). Recent advances in the chemical synthesis and evaluation of

anticancer nucleoside analogues. Molecules, 25(9), 2050.
45. Mukhin, E. M., Savateev, K. V., &Rusinov, V. L. (2023). Approaches to the synthesis of heterocyclic C-nucleosides. Russian Chemical Bulletin, 72(2), 425-481.
46. Torres, D. (2025). Synthesis of Nucleoside Analogues and Elucidation of their Antiviral Mechanisms (Doctoral dissertation, Open Access TeHerenga Waka-Victoria University of Wellington).
47. Krishnakumar, K. A., &Lankalapalli, R. S. (2022). Synthesis of Immucillins BCX-1777 and BCX-4430 from a Common Precursor. European Journal of Organic Chemistry, 2022(25), e202200428.
48. dos Santos, G. C., Martins, L. M., Bregadiolli, B. A., Moreno, V. F., da Silva-Filho, L. C., & da Silva, B. H. S. T. (2021). Heterocyclic compounds as antiviral drugs: Synthesis, structure–activity relationship and traditional applications. Journal of Heterocyclic Chemistry, 58(12), 2226-2260.
49. Sparrow, K. J., Shrestha, R., Wood, J. M., Clinch, K., Hurst, B. L., Wang, H., ... & Harris, L. D. (2023). An Isomer of Galidesivir That Potently Inhibits Influenza Viruses and Members of the Bunyavirales Order. ACS medicinal chemistry letters, 14(4), 506-513.
50. Saillard, E., Brouillard, M., Roy, V., &Agrofoglio, L. A. (2025). Synthesis of Selected Nucleoside Analogues against RNA Viruses. In Synthesis and Applications of Carbohydrates, Lipids, and Steroids (pp. 199-226). CRC Press.
51. Darwish, I. A., Alzoman, N. Z., &Abuhejail, R. M. (2024). Development of Green and High-Throughput Microwell Spectrophotometric Methods for Determination of Galidesivir in Bulk Drug and Dosage Forms Based on Simple Oxidimetric Reactions With Inorganic Agents. Journal of AOAC International, 107(4), 529-537.
52. Huang, S. (2021). Interfering with Nucleic Acid Synthesis: Recent Progress of Nucleoside and Nucleotide Analogues in Anti-viral Treatment. Annals of the Romanian Society for Cell Biology, 25(4), 12982-12996.
53. Wong, C. A., Hubert, J. G., Sparrow, K. J., Harris, L. D., Tyler, P. C., & Brimble, M. A. (2023). Expedient synthesis of imino-C-nucleoside fleximers featuring a one-pot procedure to prepare aryl triazoles. Organic &Biomolecular Chemistry, 21(30), 6134-6140.
54. https://www.businessinsider.com/teenager-invents-cheaper-faster-antiviral-drug-manufacturing-method-wins-award-2025-5
55. Silva Arouche, T. D., Reis, A. F., Martins, A. Y., S Costa, J. F., Carvalho Junior, R. N., & JC Neto, A. M. (2020). Interactions between remdesivir, ribavirin, favipiravir, galidesivir, hydroxychloroquine and chloroquine with fragment molecular of the COVID-19 main protease with inhibitor N3 complex (PDB ID: 6LU7) using molecular docking. Journal of Nanoscience and Nanotechnology, 20(12), 7311-7323.
56. Lim, S. Y., Osuna, C., Lakritz, J., Chen, E., Yoon, G., Taylor, R., ... & Whitney, J. (2017, October). Galidesivir, a direct-acting antiviral drug, abrogates viremia in rhesus macaques challenged with Zika virus. In Open Forum Infectious Diseases (Vol. 4, No. Suppl 1, p. S55).
57. Hassan, H. A., Abdelwahab, S. F., Al-Khdhairawi, A., Al Zrkani, M. K., Rehman, H. M., Abdel-Rahman, I. M., ... &Abdelhamid, M. M. (2024). Exploring the therapeutic potential of galidesiviranalogs against zaire ebolavirus protein 24 (V24): database screening, molecular docking, drug-relevant property evaluation and molecular dynamics simulations. Journal of Biomolecular Structure and Dynamics, 42(13), 6761-6771.
58. Darwish, I. A., &Alzoman, N. Z. (2024). Green and Versatile High-Throughput Microwell Oxidation-Based Spectrophotometric Methods for Determination of Galidesivir in Capsules. Journal of AOAC International, 107(5), 727-734.
59. Haviernik, J., Eyer, L., Nougairède, A., Uhlířová, M., Driouich, J. S., Zouharová, D., ... &Ruzek, D. (2020, June). An E460D substitution in the NS5 protein of tick-borne encephalitis virus confers resistance to the inhibitor Galidesivir (BCX4430) and also attenuates the virus in mice. In Proceedings (Vol. 50, No. 1, p. 12). MDPI.
60. Mishra, A., &Rathore, A. S. (2022). RNA dependent RNA polymerase (RdRp) as a drug target for SARS-CoV2. Journal of Biomolecular Structure and Dynamics, 40(13), 6039-6051.
61. De Clercq, E. (2019). New nucleoside analogues for the treatment of hemorrhagic fever virus infections. Chemistry–An Asian Journal, 14(22), 3962-3968.
62. Prajapat, R., & Jain, S. (2023). Analysis the Effectiveness of Remdesivir, Galidesivir, Sofosbuvir, Tenofovir and Ribavirin as Potential Therapeutic Drug target against SARS-Cov-2 RNA-Dependent RNA Polymerase (RdRp): An in Silico Docking Study. Journal of Research in Applied and Basic Medical Sciences, 9(3), 143-153.
63. Sahoo, P. R., Sahoo, J. R., &UsharaniSahoo, A. (2023). Insilco discovery of promising

antiviral drug Galidesivir against SARS-CoV2 RNA dependant RNA polymerase (RdRp) through molecular docking.

64. Ribavirin, E. A., &Remdesivir, S. (2020). Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): A molecular docking study. Life Sci, 253(117592), 10-1016.
65. Kwal, J., Bartlett, M., Crane, A., Greissman, S., Gunaratne, N., Lardy, M., ... & Curry, C. (2017). Challenges of Zika Virus Testing in Pregnancy in the Setting of Local Mosquito-Borne Transmission. In Open Forum Infectious Diseases (Vol. 4, No. suppl_1, pp. S302-S302). US: Oxford University Press.
66. Abers, M., & Vyas, J. (2017). Corticosteroid Use Following the Onset of Invasive Aspergillosis is Associated with Increased Mortality: A Propensity Score-Matched Study. In Open Forum Infectious Diseases (Vol. 4, No. suppl_1, pp. S55-S55). US: Oxford University Press.
67. George, I., Rajasingham, R., Powderly, W., &Boulware, D. (2017, October). Routine cryptococcal antigen screening in solid organ transplant recipients: is it time to save lives and money?. In Open Forum Infectious Diseases (Vol. 4, No. Suppl 1, p. S55).
68. Yuan, X. I. E., Xiao-Yan, T. A. O., Peng-Cheng, Y. U., Qian, L. I. U., Shu-Qing, L. I. U., & Wu-Yang, Z. H. U. (2023). Inhibitory effects of Galidesivir (BCX4430) on rabies virus in vitro. Chinese Journal of Zoonoses, 1151-1157.
69. CN, H. (2020). Reimposing of marketed drugs in treatment of COVID 19 by insilicomethods. International Journal of Pharmaceutical Research (09752366)