IJBPAS, January, Special Issue 2, 2022, 11(1): 317-327
ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)
'A Bridge Between Laboratory and Reader'

www.ijbpas.com

BRINGING HOPE FOR COVID-19 – REMDESIVIR DRUG

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Received 15th June 2021; Revised 10th July 2021; Accepted 24th Aug. 2021; Available online 25th Jan. 2022

https://doi.org/10.31032/ijbpas/2022/11.1.2029

ABSTRACT

According to global pandemic of novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has created an urgent need for effective[1] .Its unique structural features allow high concentrations of the active triphosphate metabolite to be delivered intracellularly and it evades proofreading to successfully inhibit viral RNA synthesis. [1]In pre-clinical models, remdesivir has demonstrated potent antiviral activity against diverse human and zoonotic β-coronaviruses, including SARS-CoV-2. In this article, we critically review available data on remdesivir with an emphasis on biochemistry, pharmacology, pharmacokinetics, Remdesivir (formerly GS-5734) is a nucleoside analogue pro-drug currently being evaluated in COVID-19 clinical trials. Remdesviris an investigational nucleotide analogue with broad-spectrum antiviral activity [1].currently it is not approved anywhere globally for any use. Remdesivir has demonstrated in vitro and in vivo activity in various animal models against the viral activity of pathogens MERS and SARS, which are also coronaviruses and are structurally similar to COVID-19[1.] The limited preclinical data is available on remdesivir in MERS and SARS indicate that remdesivir may have potential activity against CORONA virus. Remdesivir is an experimental medicine and it doesn't have any safety and efficacy . This Prodrug having demostrated ability to inhibit SARS-CoV-2 replication, which support its clinical evaluation for COVID-19 treatment.[2]

INTRODUCTION:

COVID-19 has resulted in huge numbers of infections and deaths worldwide and brought the most severe disruptions to societies and economies since the Great Depression.

Massive experimental andresearch effort to understand and characterize the disease and rapidly develop diagnostics, vaccines, and drugs has emerged in response to this devastating pandemic and more than 130[thin space (1/6-em)]COVID-19.[1]With almost 180 million cases and 4 million deaths worldwide (June 2021),1 the COVID-19 pandemic generated a need for a rapid, massive and effective therapeutic response. Since the emergence of COVID-19 in late December 2019, both its causative agent, SARS-CoV-2 virus, and the host response to the virus have been extensively studied to understand the disease pathogenesis. Corona virus are family of enveloped viruses with a positive sense single strandard RNA genome that infects animals species and humans. Among the coronavirus member are these responsible for the common cold, severe, acute respiratory syndrome[2]. Coronavirus middle fast respiratory syndrome related coronavirus and the recently emerged severe acute respiratory syndrome coronavirus- the causative pathogen of disease. Remedesivir sold under the brand name Veklury. Remedesivir is a broad spectrum antiviral medication development by the biopharmaceutical company grilled sciencs, it's administration via injection into vein.[2]

MATERIAL AND METHODS:

Description: Remdesivir is an antiviral nucleotide analogue used for therapy of severe novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome (SARS) coronavirus 2 (CoV-2) infection.[2]

Remdesiviris a carboxylic ester resulting from the formal condensation of the carboxy group of N-[(S)-{[(2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl]methoxy}(phenoxy)phosphoryl]-L-alanine with the hydroxy group of 2-ethylbutan-1-ol.A prodrug and an anticoronaviral agent. It is a carboxylic ester, a pyrrolotriazine, a nitrile, a phosphoramidate ester, a C-nucleoside and an aromatic amine. It derives from a GS-441524.Remdesivir is a prodrug of an adenosine triphosphate (ATP).[2]

2.1.1IUPAC Name :

2-ethylbutyl (2S)-2-[[[(2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxyoxolan-2-yl]methoxy-phenoxyphosphoryl]amino]propanoate[2]

Computed by Lexichem TK 2.7.0 (PubChem release 2021.05.07)

2.1.2InChI

InChI=1S/C27H35N6O8P/c1-4-18(5-2)13-38-26(36)17(3)32-42(37,41-19-9-7-6-8-10-19)39-14-21-23(34)24(35)27(15-28,40-21)22-12-11-20-25(29)30-16-31-

33(20)22/h6-12,16-18,21,23-24,34-35H,4-5,13-14H2,1-3H3,(H,32,37)(H2,29,30,31)/t17-,21+,23+,24+,27-,42-/m0/s1

Computed by InChI 1.0.6 (PubChem release 2021.05.07)

2.2: Molecular Formula

C27H35N6O8P

Computed by PubChem 2.1 (PubChem release 2021.05.07)[3]

2.4: Synonyms

2.4.1MeSH Entry Terms

2-ethylbutyl (2S)-2-(((2R, 3S, 4R, 5R)-5-(4-aminopyrrolo(2,1-f) (1,2,4)triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl) methoxy)(phenoxy) phosphoryl) amino) propanoate

GS 5734GS-5734

l-alanine, N-((S)-hydroxyphenoxyphosphinyl)-, 2-ethylbutyl ester, 6-ester with 2-C-(4-aminopyrrolo(2,1-f)(1,2,4)triazin-7-yl)-2,5-anhydro-d-altrononitrile

remdesivir

2.4.2 Depositor-Supplied Synonyms

1809249-37-33QKI37EEHEGS 5734GS 5734 [WHO-DD]GS-5734GS5734Remdesivir

REMDESIVIR [INN]

Remdesivir [USAN]

REMDESIVIR [WHO-DD]

Remdesivirum

UNII-3QKI37EEHE

Veklury

2-ethylbutyl (2S)-2-[[[(2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxyoxolan-2-yl]methoxy-phenoxyphosphoryl]amino]propanoate[2]

2-Ethylbutyl (2S)-2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo(2,1-f)(1,2,4)triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate

2-ethylbutyl (2S)-2-{[(S)-{[(2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl]methoxy}(phenoxy)phosphoryl]amino}propanoate

Veklury (TN) Remdesivir (JAN/USAN) Remdesivir (GS-5734)

CHEMBL4065616SCHEMBL17712225

GTPL10715Med.21724, Compound 178[3]

CHEBI:145994BDBM429505EX-A326NSC825151S8932AT11308BCP24975

DB14761DT-0049NSC-825151Compound 4b [PMID: 28124907]

NCGC00686694-01

2-ethylbutyl (2S)-2-(((2R, 3S, 4R, 5R)-5-(4-aminopyrrolo(2,1-f) (1,2,4)triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl) methoxy)(phenoxy) phosphoryl) amino) propanoate

AC-31297

L-Alanine, N-((S)-hydroxyphenoxyphosphinyl)-, 2-ethylbutyl ester, 6-ester with 2-C-(4-aminopyrrolo(2,1-f)(1,2,4)triazin-7-yl)-2,5-anhydro-D-altrononitrile

HY-104077CS-0028115D11472

(2S)-2-{(2R,3S,4R,5R)-[5-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxy-tetrahydro-furan-2-ylmethoxy]phenoxy-(S)-phosphorylamino}propionic acid 2-ethyl-butyl ester

(S)-2-ethylbutyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate

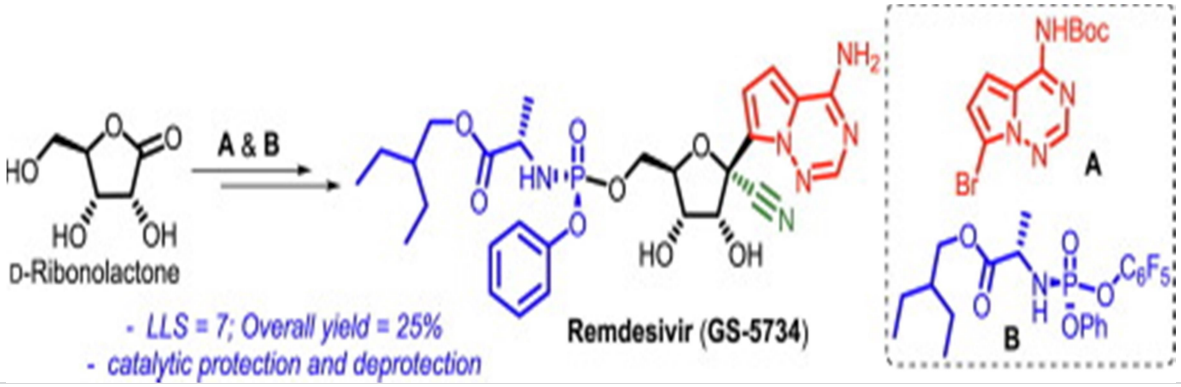
(S)-2-Ethylbutyl 2-((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate

2-ethylbutyl (2S)-2-{[(S)-{[(2R,3S,4R,5R)-5-{4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl}-5-cyano-3,4-dihydroxyoxolan-2-yl]methoxy}(phenoxy)phosphoryl]amino}propanoate[2]

HISTORY AND DEVELOPMENT OF REMDESIVIR

In the quest towards finding a potent drug against the Ebola virus (EBOV), scientists from Gilead Sciences and the United States Army Medical Research Institute of Infectious Diseases screened more than 1000 nucleoside analogues focused towards cyclic ribose or ribose like core that could target RNA viruses in 2014.

This led to the identification of the parent nucleoside 6 and its potent phosphoramidate prodrug diastereoisomer 9a (GS-5734). Structure activity relationship studies pointed towards the criticality of 1'-CN functional group as it provided lower toxicity and selectivity towards viral polymerase as compared to the unmodified nucleoside. The prodrug diastereoisomer 9a had potent in vitro activity against HCV (Hepatitis C virus[3]human and zoonotic coronaviruses like RCV (Rat Coronavirus), SARS-CoV, MERS- CoV (Middle east respiratory syndrome) in addition to anti-EBOV activity found in 6. This broad-spectrum antiviral activity of 9a (GS-5734) has led it to being tested against the 2020 pandemic Covid-19 caused by SARS-Cov-2.



Synthesis[3]

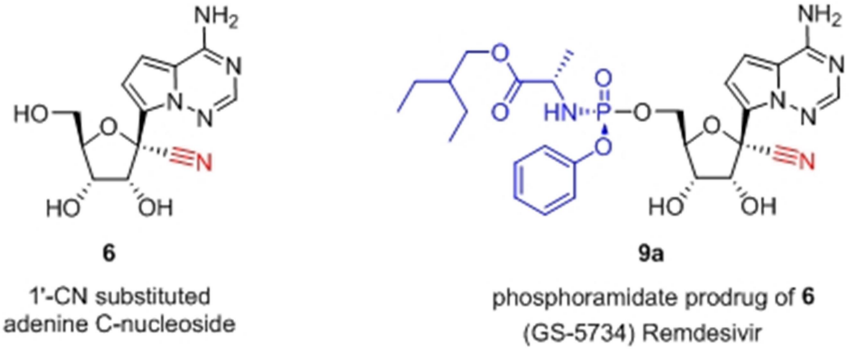
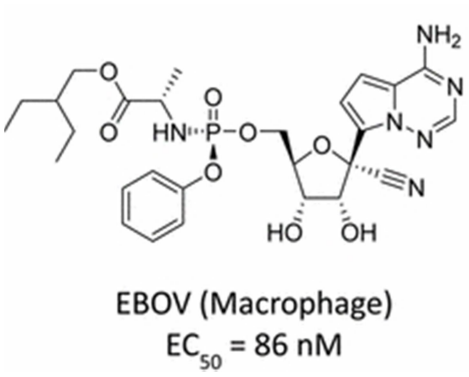
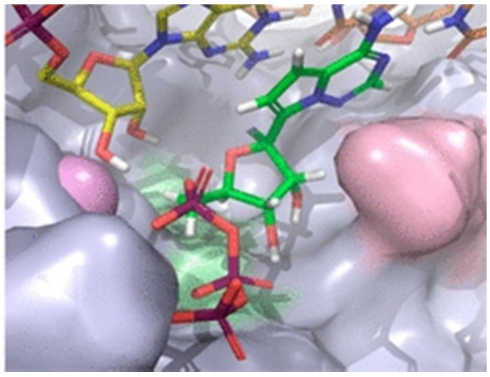
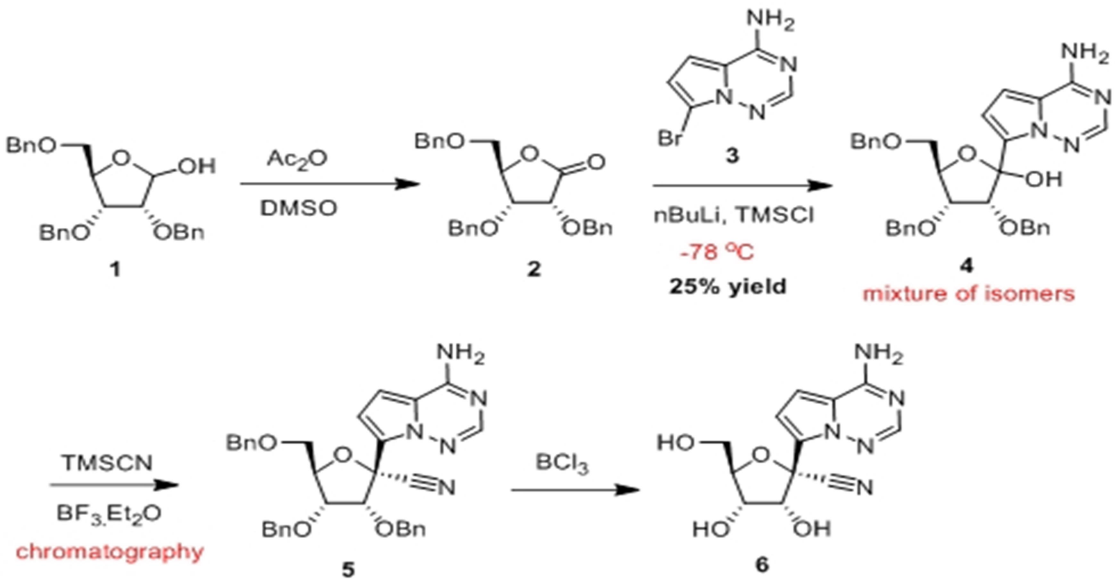


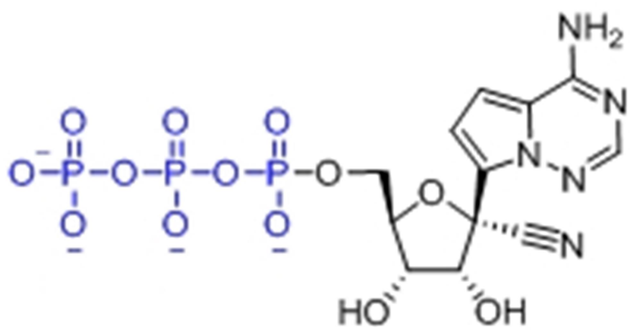
Fig. 1 Structures of remdesivir and other related antiviral drugs







GS-5734 (9a) – also called Remdesivir – is an RNA polymerase inhibitor with promising efficacy data in non-human primate models against EBOV, RCV, MERS, etc. Remdesivir converts into its triphosphate metabolites 9tp in human cells which is taken up in place of adenosine triphosphate by the viral RNA polymerase, thereby crippling the virus replication.

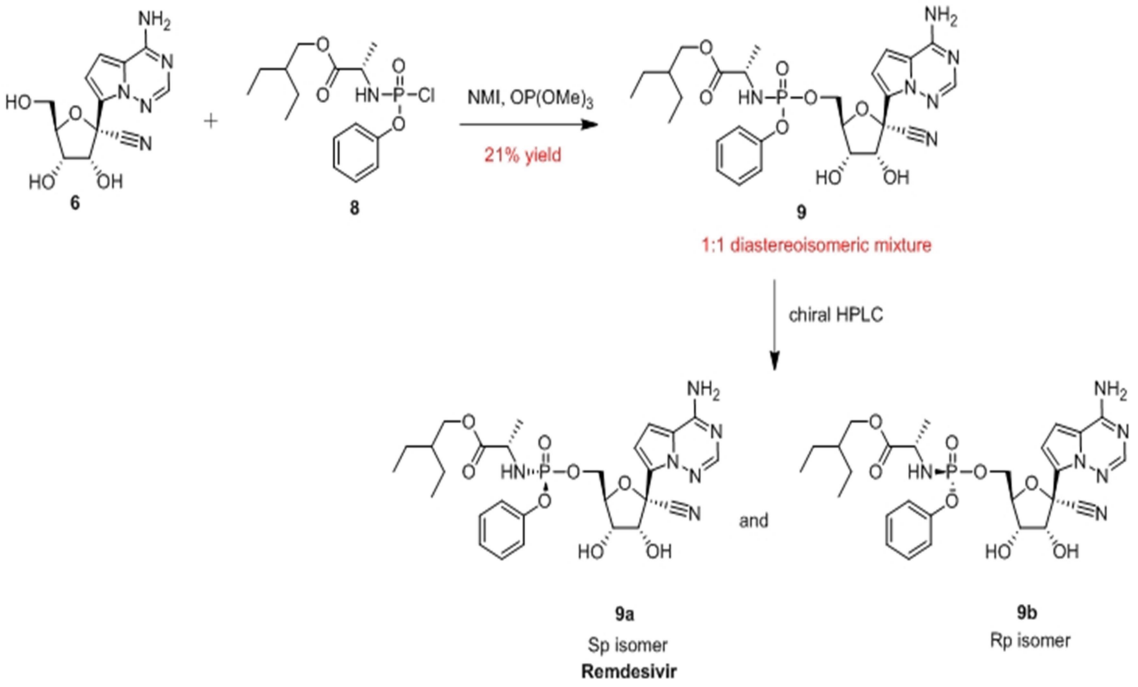


9tp

FIRST GENERATION SYNTHESIS OF REMDESIVIR

The scientists at Gilead started with the synthesis of Btheir best lead and the single Spphosphoramidate prodrug with a commercially available tribenzyl protected lactol 1 followed by oxidation to its corresponding lactone 2. The next key step was the C-C bond forming glycosylation reaction of the ribolactone 2 with a bromopyrrolotriazine nucleus 3. This was facilitated by the N-silyl protection in 3, followed by a lithium-halogen exchange using excess BuLi at -78°C. The lithiatedpyrrolotriazine was coupled with ribolactone 2 to provide a mixture of 1’

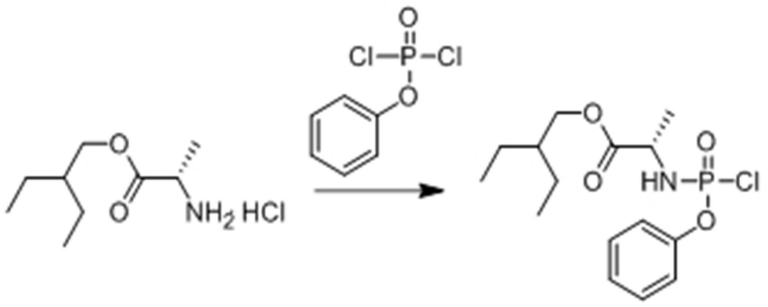
isomers of nucleoside 4 followed by 1'-cyanation to give the β-anomer 5 after chromatographic purification. Tribenzyldeprotection gave the 1-cyano modified adenine nucleoside 6.The diastereomeric mixture of the phosphoramidoylchloridate prodrug moiety 8 was prepared from the L-alanine analogue 7.[4]



Finally, coupling of nucleoside **6** and chloridate **8** provided the phosphoramidate prodrug mixture **9** in ~ 1:1 diastereomeric ratio. The two diastereomers were resolved using chiral HPLC to afford the Sp isomer **9a** and Rp isomer **9b**, respectively.[4]

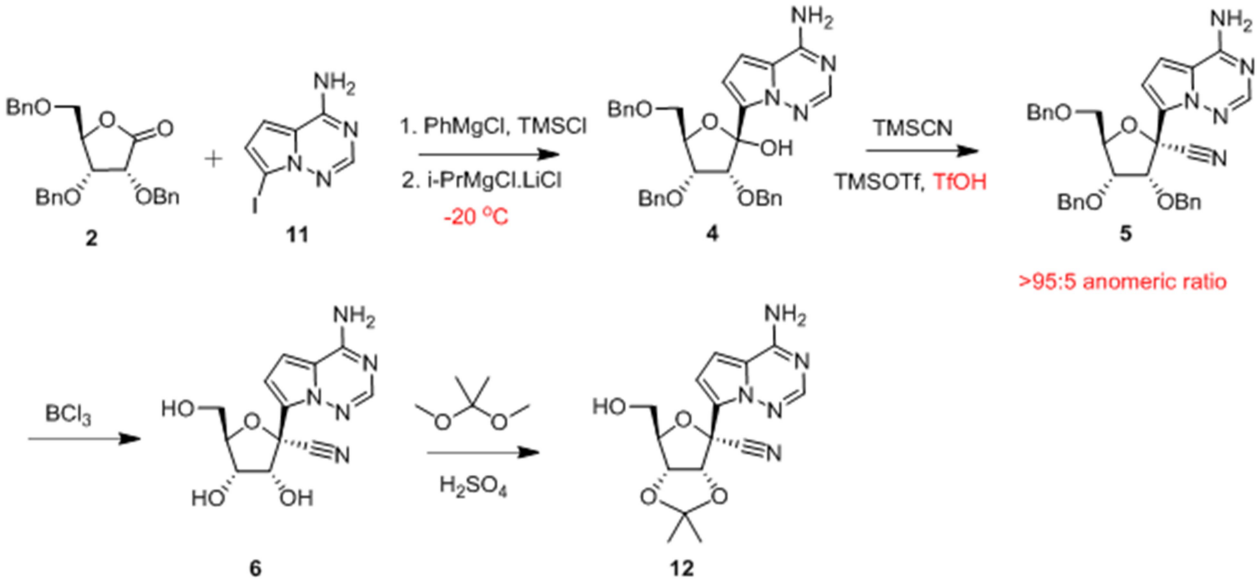
SECOND GENERATION SYNTHESIS OF REMDESIVIR

The use of cryogenic temperatures, dependency on rate of addition of *n*-BuLi, unpredictable yields and need for chiral chromatography deemed the first-generation synthetic route unscalable. Efforts were directed towards using milder reagents and temperature and obtaining enhanced selectivity.



7 **8**
diastereoisomeric mixture

The foremost changes in the method proceeded with replacement of the inconsistent *n*-BuLi method for the glycosylation reaction towards a coupling accelerated by the Turbo Grignard reagent *i*-PrMgCl·LiCl. The use of PhMgCl and TMSCl led to better control in the amino protection, and the iodo base **11** enabled a more facile metal-halogen exchange than its bromo equivalent. This method of the nucleoside synthesis allowed for consistent yields at milder temperatures, hence making it scale-up friendly.[4]



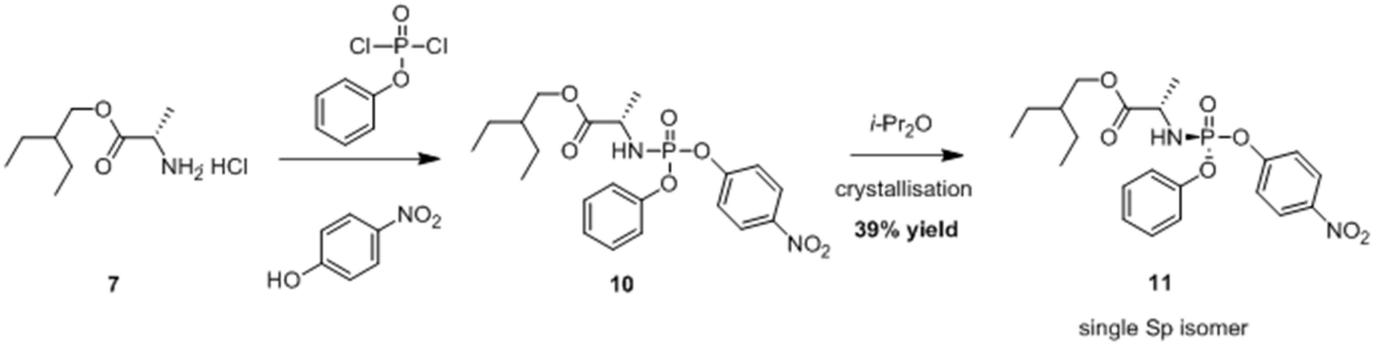
2 **11** **4** **5**

6 **12**

The 1'-cyanation of C-nucleoside **4** gave the product **5** in >95:5 anomeric ratio favoring the desired β-anomer. The inclusion of TfOH was found to be responsible for the high yield and high selectivity, thereby bypassing the need for chiral separation. Henceforth, a crucial change in the protection-deprotection strategy was undertaken whereby after the initial debenzylation, 2',3'-acetonide protection of the hydroxyl moieties was

carried out to give **12**. It was found that the coupling of nucleoside **12** with the prodrug counterpart **11** provided far better yields as compared to the unprotected glycoside [6].

Opting for a *p*-nitrophenolate prodrug precursor **10** instead of chloridate **8** afforded a single Sp isomer **11** after resolution through solvent crystallization, which proved to be the key step towards the stereoselective synthesis of the final product.[4]



The final reaction of the p-nitrophenolate 2-ethylbutyl-L-alaninate prodrug coupling partner **11** with the acetonide protected nucleoside **12** proceeded in the presence of $MgCl_2$ to give a diastereoselective product (exclusive Sp isomer) through S_N2 type inversion of the phosphorus stereocenter. In both cases, the Sp isomer was establishedthrough single X-raycrystallography. Final deprotection of the acetonide yielded Remdesivir (**9a**) in 69% yield.[4]

The second-generation synthesis of Remdesivir thus was a far better improvement in terms of scalability, yields and stereoselectivity bypassing the bottleneck of inconsistent yields and chiral separation.

Activity of Remdesivir: It is an adenosine nucleoside triphosphate analog (GS-443902). the active metabolite of remdesivir interferes with the action of viral RNA-dependent RNA polymerase and evades proofreading by viral exoribonuclease (ExoN), causing a decrease in viral RNA production. In some viruses,

such as the respiratory syncytial virus, it causes the RNA-dependent RNA polymerases to pause, but its predominant effect (as in Ebola) is to induce an irreversible chain termination. Unlike with many other chain terminators, this is not mediated by preventing addition of the immediately subsequent nucleotide, but is instead delayed, occurring after five additional bases have been added to the growing RNA chain.For the RNA-Dependent RNA Polymerase of MERS-CoV, SARS-CoV-1, and SARS-CoV-arrest osynthesis occurs after incorporation of three additional nucleotides. Hence, remdesivir is classified as a direct-acting antiviral agent that works as a delayed chain terminator. Remedesivir is protide (prodrug of nucleotide) able to diffuse into cell. Where it is converted to GS-441524 monophosphate via the action of esterase (CES1 and CTSA) and a phosphoamidase this is turn it further phosphorylated to its active metabolite triphosphate by nuclioside triphosphate kinases.this pathway of bioactivation means to occur intracellularly but a substantial amount of Remedesivir is prematurely hydrolysed in plasma with GS-441524 being the major metabolite in plasma and the only metabolite remaining two hours after dosing.[5]

RESULT AND DISCUSSION:

Remedesivir inhibits SARS-CoV-2 replication, reduces viral load and exerts protective effects in SARS-CoV-2 infected animals. Remedesivir has been used as a compassionate drug for treating COVID-19 patient. Remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with covid-19 and had evidence of lower respiratory tract infection [1].

Patient who received remdesivir had a shorter time to recovery than those who received placebo recovery, 1.29 and were more likely to have improvement in the ordinal scale score at 15 days.

CONCLUSION:

Although Remdesivir has shown potent Antiviral activities more efficacy assessment are urgently warrented in clinical trial.[2]

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