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Review on fluorinated nucleoside/non-nucleoside FDA-approved antiviral drugs

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FDA-approved antiviral agents represent an important class that has attracted attention in recent years to combat current and future threats of viral pandemics. Fluorine ameliorates the electronic, lipophilic and steric problems of drugs. Additionally, fluorine can prolong drug activity and improve metabolic stability, thereby, modifying their pharmacodynamic and pharmacokinetic character. Herein, we summarized the fluorinated FDA-approved antiviral agents, dealing with biological aspects, mechanisms of action, and synthetic pathways.

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1. Introduction

Viruses are amongst the dominant pathogenic organisms that cause a lot of severe diseases.[1] Advancing approaches for the treatment of viral infections focuses on either the viruses or the infected host cell. Some antiviral agents act directly as inhibitors of viral attachment, uncoating, entry, or fusion,[2] and some inhibit RNA polymerase,[3] protease,[4] integrase,[5] nucleoside, or nonnucleoside reverse transcriptase.[6,7]

During the 2010s, the protease viral DNA polymerase and integrase inhibitors were indexed among the top 200 marketed drugs. To date, there is no effectual antiviral agent for numerous viral diseases. Nevertheless, a pair of drugs has been discovered for herpes viruses, many drugs for influenza and a number of therapeutics for hepatitis C infection and human immunodeficiency virus type 1 (HIV-1).

Antiviral drugs are primarily transformed to their triphosphate then inhibit viral DNA synthesis. Mechanisms of famous antiviral drugs have been analyzed revealing their ability to improve the body's resistance to a virus,[8] repress adsorption or diffusion of the virus into the cell and denature viral protein. The inhibition of nucleic acid synthesis is another mechanism for antimetabolites.[9]

The modifications brought to the ribose or 2′-deoxyribose moiety of a nucleoside comprise changes in the sugar moiety, oxygen replacement with an isostere, ring size changes, or replacement with an open-chain moiety. These modifications may lead to astonishing discrepancies in toxicity and biological assets.[10]

It is well known that the high electronegativity of fluorine results in the polarization of adjacent bonds resulting in acidity enhancement and a decrease in the basicity of the substituents in close proximity. The electronegativity gives rise to a more polarizable C–F bond with increased electrostatic character. Conventionally, C–F bonds can bind with their receptors by either dipole or electrostatic interaction.[11,12] The pK_a is increased, which can affect the potency, selectivity, and toxicity.[13,14] The hydroxyl group is always replaced by fluorine,[15] which is characterized by the same polarity and ability to form a hydrogen bond.[16] The introduction of a fluorine atom or trifluoromethyl group ($-CF_3$) changes both the pharmacodynamics and pharmacokinetics (absorption, distribution, metabolism, and excretion) of the molecule.[17–30] Fluorine is a metabolic blocker; the blocking occurs when the C–H bond is replaced by a C–F bond which has a high impact on the biological half-life and bioavailability enhancement.[17] Fluorine is small compared to the hydrogen atom, therefore, replacing the hydrogen atom with fluorine can considerably increase the binding affinity of a drug with receptors *via* the formation of noncovalent bonds. On the other hand, cell penetration is increased due to less plasma protein binding and a higher free fraction of the drug. These outcomes lead to a greatly improved therapeutic activity.[31]

Among various antiviral drugs presently used, this review will address the mechanisms of action, synthetic pathways, and therapeutic uses of the fluorinated U.S. Food and Drug Administration (FDA)-approved antiviral agents over the last four decades. Furthermore, the biological value of the fluorine substituent will be clarified for the antiviral activity against HIV type-1, COVID-19, influenza, smallpox, acute asthma, and hepatitis C.

2. Treatment of smallpox

Tecovirimat (ST-246) has been endorsed in the United States and approved in 2018 as a therapy for smallpox, monkeypox, and orthopoxvirus diseases for which it showed potent antiviral

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activity. This drug blocks the viral escape from an infected cell, burdening the dissemination of the virus within the body. The *para*-trifluoromethyl group has an important role in the optimal metabolic stability and pharmacokinetic profile of this drug.[32] Tecovirimat (**7**) was synthesized in 2014 by Dai using versatile methods, starting from the reaction of maleic anhydride (**1**) with monoBoc hydrazine to afford the imide derivative **2**. Boc deprotection of **2** using 4 M HCl afforded *N*-amino maleimide hydrochloride **3** which can be acylated by *p*-trifluoromethyl benzoyl chloride **4** to give the hydrazide derivative **5**. Then, cyclo-addition of **5** was achieved with cycloheptatriene in xylene to produce tecovirimat, **7**, in excellent yield as shown in Scheme 1.[33]

Another modified protocol was employed to prepare tecovirimat starting from the cyclo-addition reaction of maleic anhydride, **1**, with cycloheptatriene, **6**, to yield the adduct **8**, which after reaction with $BocNHNH_2$ provided the fused imide derivative, **9**. Deprotection of **9** in 4 M HCl gave rise to the free hydrazine derivative, **10**, which is finally acylated by *p*-trifluoromethylbenzoyl chloride, **4**, to afford **7** (Scheme 2).[34]

3. Treatment of acute asthma

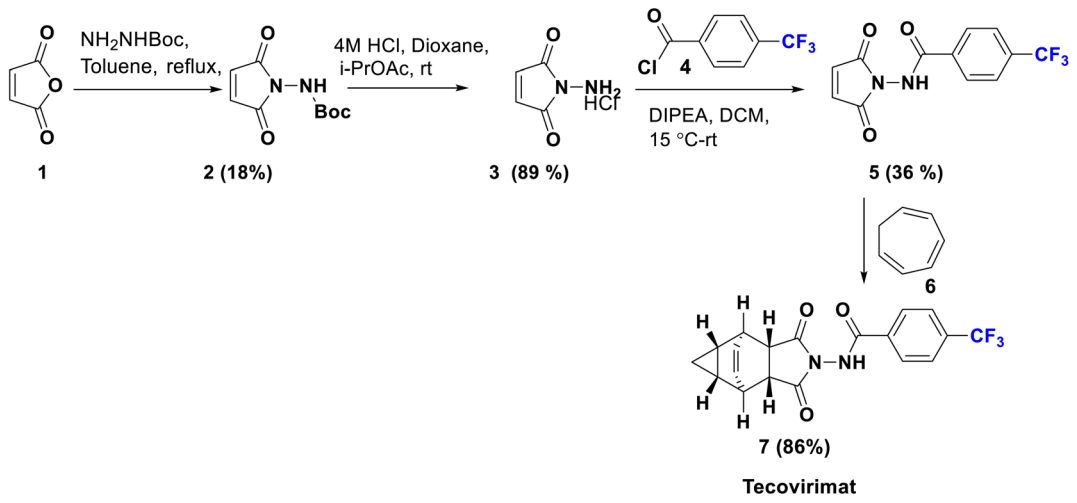
Pleconaril (Picovir) was originally manufactured by Schering-Plough, who made an agreement with ViroPharma in 2004 to license intranasal pleconaril for the treatment of the common cold in the US and Canada. Pleconaril is active against viruses in the picornavirus group; it is accommodated in a hydrophobic pocket of the virion, which leads to its rigidification and viral capsid compression in the capsid structural protein. Consequently, it prevents the viral attachment and uncoating process in the host cell, a crucial step in the life cycle of the virus.[35] Pleconaril is employed for the prevention of asthma exacerbation and currently, its intranasal spray formulation is in clinical stages for treatment of rhinovirus infections, while the oral medication is only formerly used due to reported aftereffects. A remarkable enhancement of its activity was observed due to the combination of two factors: the bulky trifluoromethyl group which interferes with the enzyme binding, and its effect as a metabolic blocker, especially against cytochrome P_{450} enzymes to protect the oxadiazole ring from hydroxylation.[35] The U.S. Food and Drug Administration rejected pleconaril in 2002 due to the fact that it has been found to induce CYP3A enzyme activity, therefore increasing the risk of serious drug interactions.

The synthesis of pleconaril (**18**) by Diana *et al.* in 1995 is shown in Scheme 3, starting from the reaction of dimethyl isoxazole, **11**, with oxirane (**12**) *via* carbon–carbon bond formation using BuLi to afford the primary alcohol, **13**, which provided the corresponding chloro derivative, **14**, upon treatment with thionyl chloride. Then, Williamson synthesis was carried out *via* reaction of **14** with the phenol **15** *via* S_N^2 reaction, to yield the ether **16** which upon addition of hydroxylamine to the nitrile functionality gave the corresponding amidoxime, **17**. Subsequently, the latter was cyclized using TFAA to afford pleconaril (**18**).[36–39]

4. Treatment of HIV type-1

When the immune system is attacked by HIV without treatment, severe acquired immunodeficiency syndrome (AIDS) will result, and unfortunately, there is no effective cure yet.[1,40] The presently accepted anti-HIV agents can be categorized as inhibitors of reverse transcriptase, integrase, protease, fusion, and co-receptor. Combination therapy using antiretroviral agents greatly suppresses viral growth and replenishes the immune system.[41,42] Development of drug resistance, in addition to their toxicity, limits the use of these drugs.[8,43,44]

Maraviroc (MVC) has commercial names such as Selzentry and Celsentri and was approved in 2007; it acts as a selective HIV entry and fusion inhibitor for C–C chemokine receptor type-5 (CCR5), and is accepted for the treatment of advanced patients infected with CCR5-tropic HIV-1. Much effort have been applied to decrease the affinity of these agents towards



Scheme 1 Synthesis of tecovirimat (**7**) from maleic anhydride.

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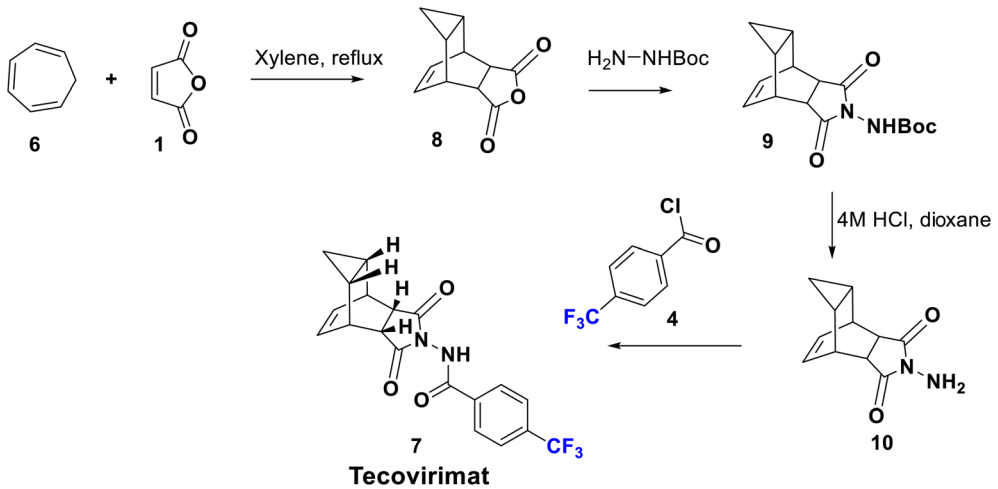
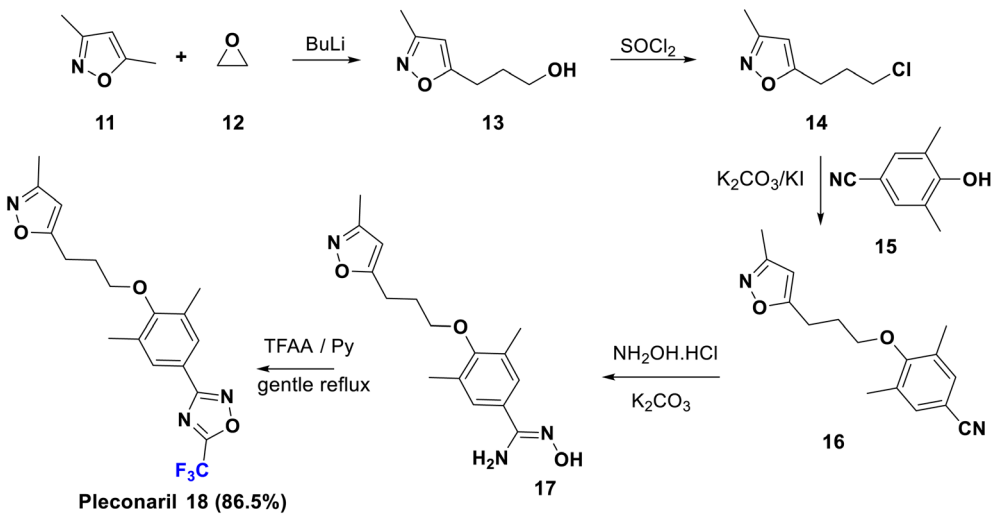


Scheme 2 Synthesis of tecovirimat (**7**) from heptatriene.

human receptors closely correlated with CCR5 *e.g.* the potassium channel HERG, responsible for the cardiotoxicity that appears with this type of medicament.[45] Combination therapy of MVC with other medications is advised to cure a certain type of human immunodeficiency virus (HIV) infection. The complete synthesis of maraviroc **33** was described in a US patent[46] by Igor *et al.* in 2014 *via* the formation of tropinone, **22**, by Robinson synthesis using benzylamine, 2-oxomalonic acid, and a furan derivative. Condensation of **22** with hydroxylamine affords the corresponding oxime **23**, which upon subsequent reduction *via* reflux with sodium in penthanol afforded the exo-amine **24**, which reacted with **25** to yield the corresponding amide, **26**. Cyclocondensation of **26** with acid hydrazide **27** afforded the 1,2,4-triazole derivative, **28**, which is then deprotected to **29** under transfer-hydrogenolysis conditions. Next, the addition of the tropane-triazole adduct **29** to the aldehyde **30** occurred followed by deprotection of the Boc group to yield **31**. Peptide coupling of **31** with the difluorinated acid, **32**, afforded the target antiviral drug maraviroc (**33**) (Scheme 4).[47,48]

Integration of the viral DNA into the host genome required an essential enzyme, HIV integrase, which is a well-executed target in combating HIV where there is no human homolog. Integrase inhibitors are composed of two distinctive constituents. The first is a diketo acid moiety, which is capable of forming covalent bonds with DNA, with the aid of integrase enzyme; then, the sealing of the viral DNA into the chromosome occurs by cellular repair activities. The second moiety is the benzyl group with lipophilic nature which permits binding to an important hydrophobic pocket of integrase.[49] The fluorine attached to the benzyl moiety results in a higher affinity between the drug and the protein *via* binding to numerous nonpolar residues within the hydrophobic pocket of the integrase enzyme. In the first generation of HIV integrase inhibitors, the *para*-fluorophenyl is in a favored position *e.g.* in raltegravir (RAL), or the *ortho*-fluorophenyl *e.g.* in elvitegravir,



Scheme 3 Synthesis of pleconaril (**18**) from dimethyl isoxazole **11** and oxirane **12**.

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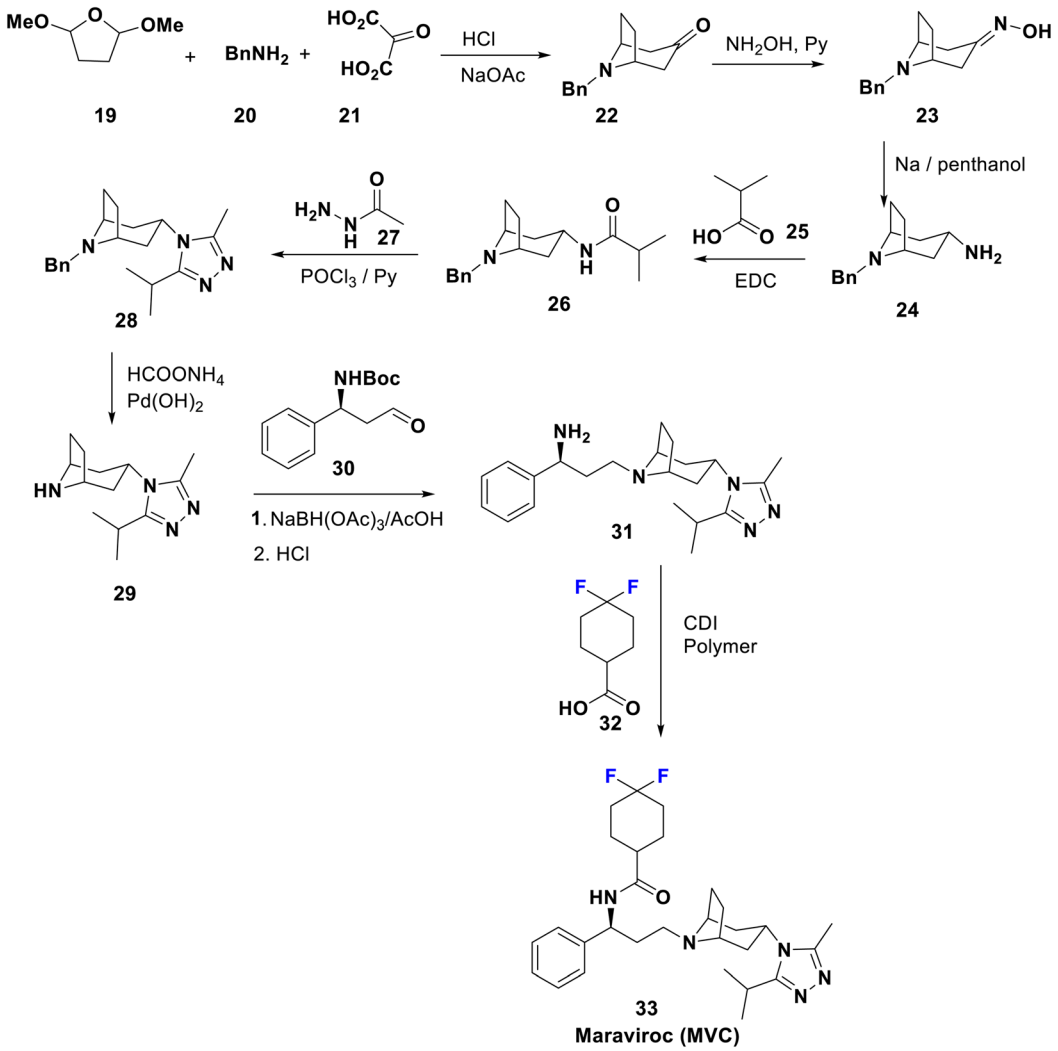

Scheme 4 Synthesis of maraviroc **33** from tropinone **22**.

while second-generation inhibitors like dolutegravir have the *ortho*/*para* bis-fluoro phenyl as an essential moiety.

Raltegravir is a first generation HIV integrase strand transfer inhibitor (INSTI), FDA-approved in 2007 and sold under the trade name Isentress. It inhibits the role of HIV integrase, required for viral reproduction. The *para*-fluoro group is capable of binding with the former viral nucleotide of the enzyme. RAL can be utilized as a prophylactic or as combined therapy with other drugs to treat HIV/AIDS. It is worth mentioning that RAL and other integrase strand transfer inhibitors are well-tolerated antiretroviral drugs (ARVs).[50] Raltegravir **44** was synthesized in 2013 by Gurjar *et al.*, starting from acylation of 2-amino-2-methyl propanenitrile, **35**, by oxadiazole acid chloride, **34**, in the presence of NMM, **36**, to afford the nitrile, **37**. Then, the addition of hydroxylamine to compound **37** yielded the corresponding amidoxime, **38**, which upon cyclization with dimethylacetylene-dicarboxylate, **39**, provided the dihydropyrimidine ester derivative, **40**. Amidation of the latter by *p*-fluorobenzylamine, **41**, gave the norraltegravir, **42**, which undergoes *N*-methylation using trimethylsulphoxide iodide, **43**, to afford raltegravir (**44**) (Scheme 5).[51]

Elvitegravir (EVG) **56** was first approved in 2012 and is utilized for HIV therapy; it acts *via* inhibition of the HIV-1 integrase enzyme and it also inhibits the integrase enzyme of HIV-2 to a lesser degree.[52] Phase II clinical trials showed that patients taking elvitegravir once a day enhanced by ritonavir (protease inhibitor, PI) had a more significant decline in viral burden when compared to patients receiving a ritonavir-boosted protease inhibitor after the same time period. Clearly, *ortho*-fluoro in EVG has a favorable role where it contributes to van der Waals interactions with glutamate residues in the enzymatic pocket. The synthetic procedure for EVG was achieved by Stanislav *et al.* in 2014 *via* the reaction of difluoro-iodobenzoic acid **45** with thionyl chloride to give the corresponding acid chloride **46**. Treatment of the latter with the ester **47** allowed the transformation to benzoyl acrylate **48**; then, a nucleophilic substitution reaction with *S*-(+)-valinol **49** provided the enamine **50**, which was then condensed to quinolin-4-one **51**. Activation of the primary alcohol of **51** was

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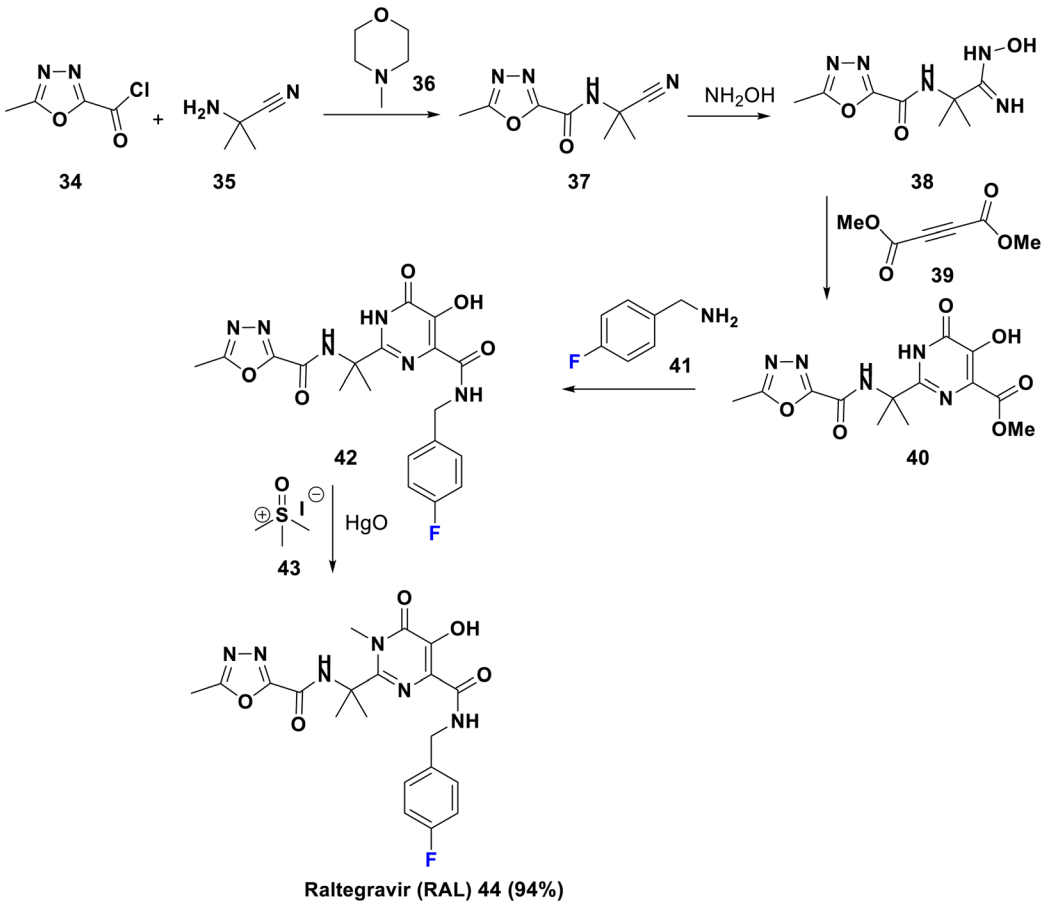

Scheme 5 Synthesis of raltegravir 44 from oxadiazole acid chloride 34.

carried out to produce the carbonate ester **52** using methyl chloroformate; then Negishi cross-coupling with an organo-zinc reagent **53** in the presence of a palladium catalyst provided the benzyl quinolone **54**. This was followed by alkaline deprotection to yield the corresponding free primary alcohol **55**, which was subjected to reaction with sodium methoxide to provide elvitegravir (**56**) (Scheme 6).[53]

Dolutegravir (DTG) **69** was FDA approved in 2013 and is marketed with the commercial name Tivicay; it is an antiretroviral therapy used, combined with other drugs, to treat HIV/AIDS. A combination of dolutegravir/abacavir/lamivudine is also available. Notably, DTG shows longer duration of action than raltegravir; this may be attributed to the amide linker attaching the diketo acid to the benzyl group which allows the difluorobenzyl moiety to interact more strongly with the lipophilic pocket of the integrase enzyme.[54] Since 2019, the WHO has advocated DTG as the first- and second-line treatment for everyone with HIV. The synthesis of DTG proceeds as mentioned in the US patent by Sumino *et al.* in 2012 and Maras *et al.* in 2016, starting from the condensation of ethyl chloroacetoacetate **57** with the acetal **58** to afford the enaminone **59** which was subsequently cyclized with chloro-oxalate **60** to give 4-pyrone derivative **61**. This was transformed to the corresponding 4-pyridone **63** *via* reaction with acetalamine, **62**. Then, acidic hydrolysis of **63** gave the corresponding aldehyde **64**; treatment of the latter with butanolamine **65** afforded the fused tricyclic ester **66**. Acidic hydrolysis of **66** gave **67** which underwent coupling with difluoro-benzylamine **68** to provide the target antiviral **69** (Scheme 7).[55,56]

Tipranavir (TPV) **78** was approved by the FDA in 2005 for pediatric use to treat HIV infection. Only combination therapy of tipranavir/ritonavir is allowed to be administered. Among protease inhibitors, tipranavir is capable of inhibiting viral replication which is resistant to other medications. Two mechanisms may elucidate the potency of tipranavir against C-resistant HIV. First, it may bind to protease's active site with a smaller number of hydrogen bonds than peptidic PIs, leading to more flexibility to tune amino acid substitutions at the active site.[57] Second, the presence of a trifluoromethyl pyridyl-sulfonamide moiety enhances the pharmacodynamic and pharmacokinetic profile.[58] Some side effects of tipranavir include intracranial hemorrhage, hepatitis, hyperglycemia and diabetes mellitus, in addition to an increase in total cholesterol and triglycerides.

Tipranavir (**78**) was prepared by Romines *et al.* in 1998 *via* an efficient and short enantio-selective synthesis starting with allylic alkylation of **70** with methyl sodiomalonate using molybdenum complex $Mo(CO)_3(C_3H_8)$ and the ligand **71** as a catalyst. The key compound **73** was obtained in an excellent yield from the malonate derivative **72**. Next, aldol coupling of

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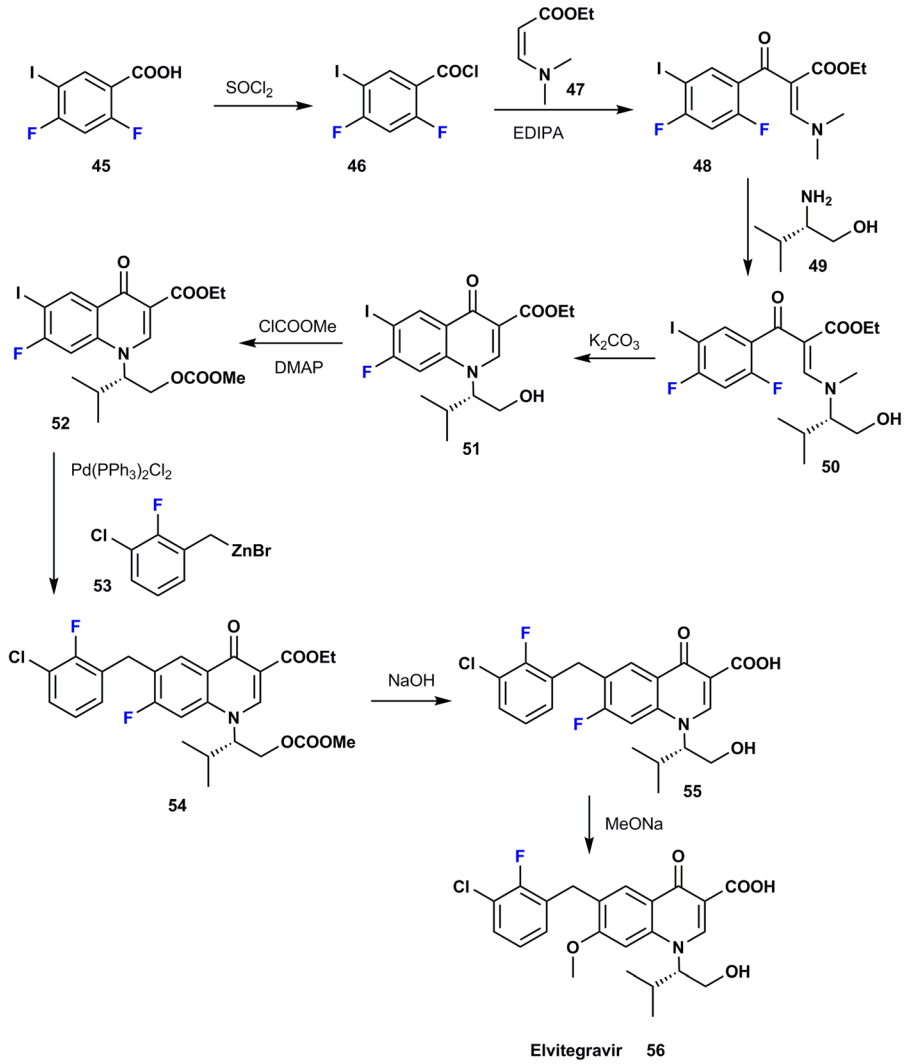

Scheme 6 Synthesis of elvitegravir (**56**) from difluoro-iodobenzoic acid **45**.

the ester derivative **73** with the aldehyde **74**, followed by Dess–Martin oxidation afforded β-ketoester **75** (1 : 1 mixture). The pyrone **76** was obtained after cleavage of the PMB group, and subsequent reduction of the NO_2 functionality followed by treatment of the resulting amine with trifluoromethyl pyridine sulfonyl chloride **77** to provide tipranavir (**78**) (Scheme 8).[59,60]

Viral infections are classified into three basic classes; the first one encompasses lethal viruses such as HIV, hepatitis B, and C viruses. The second class encompasses acute infections like influenza and the third class includes viral infections *e.g.* the common cold which is nonlethal.[61,62] Fluorinated nucleoside reverse transcriptase inhibitors (NRTI) such as emtricitabine (FTC) and racivir (RCV) are a notable category of FDA-approved medications for the treatment of HIV type-1.

Emtricitabine (**88**) is a 5-fluoro deoxycytidine approved in 2003 and is in the index of important drugs assembled by the WHO.[63] It is therapeutically employed for treatment of HIV infection in both adults and children *via* reverse transcriptase inhibition.[64,65] The FDA in 2006 accepted a three-drug combination (Atripla), emtricitabine, tenofovir and efavirenz. Additionally, the WHO registered two other combinations: emtricitabine/tenofovir and emtricitabine/efavirenz as indispensable drugs. Emtricitabine consists of a cytosine base with a fluorine atom at the C-5 position and an uncommon oxathiolane ring as a sugar moiety. It was realized that the activated form of FTC (triphosphate metabolite) was integrated faster into growing viral DNA than that of lamivudine. Furthermore, the introduction of fluorine improves its bio-accessibility parameters and duration compared to lamivudine.[66] A stereoselective synthetic route of emtricitabine (**88**) was accomplished by Mansour *et al.* in 1997, starting from the formation of *trans*-oxathiolane derivative **81** from the reaction of 2,5-dihydroxy-1,4-dithiane (**79**) and glyoxylic acid (**80**). Acetylation of **81** afforded **82** followed by esterification with a chiral auxiliary 1-menthol (**83**) which led to a mixture of diastereoisomers **84** and **85**. The desired diastereoisomer **84** was isolated by fractional crystallization and directly coupled with silylated 5-fluorocytosine (**86**), to provide the *N*-nucleoside derivative **87**. Finally, reductive removal of the chiral auxiliary from **87** gives emtricitabine **88**,

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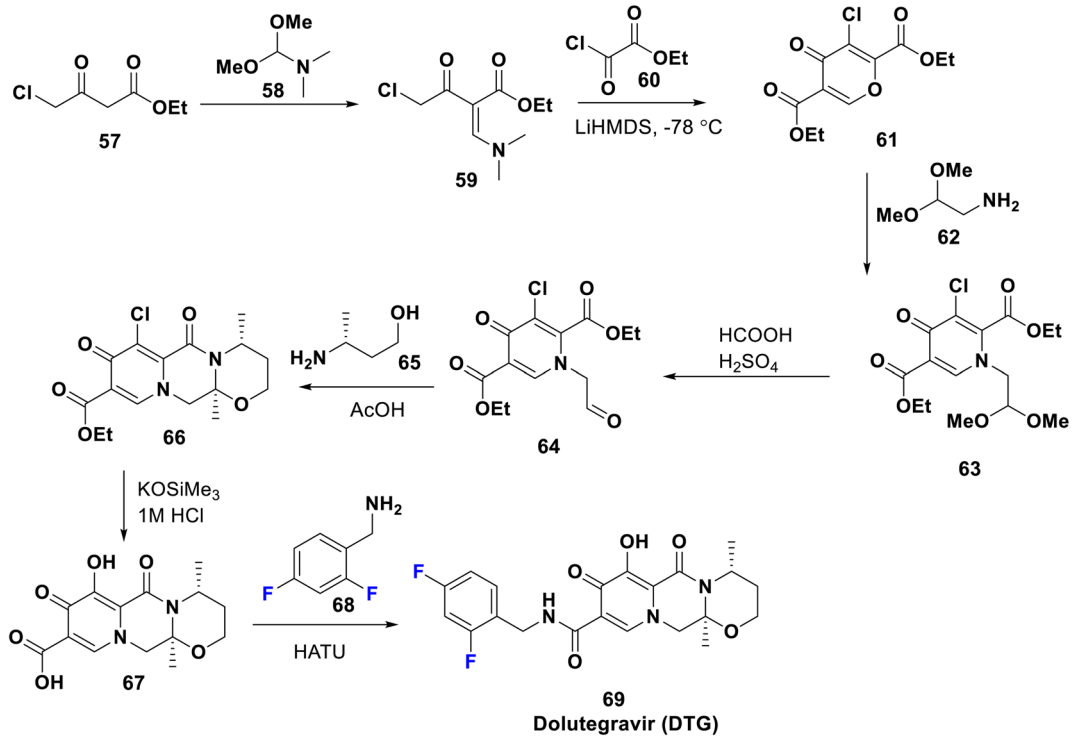
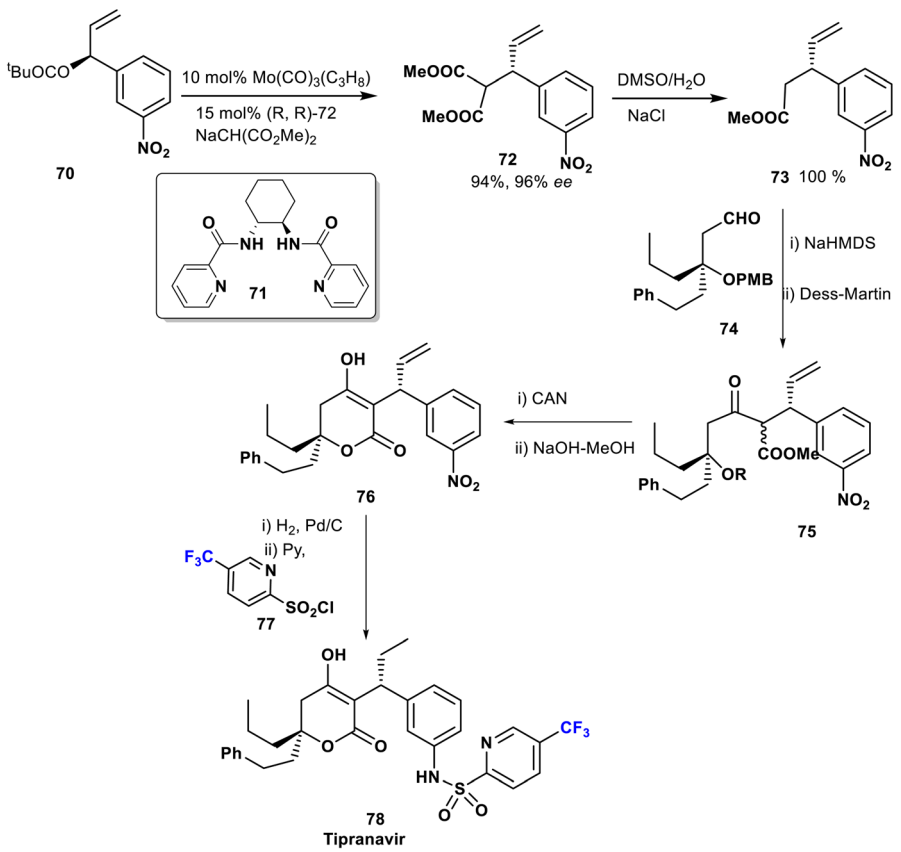


Scheme 7 Synthesis of dolutegravir **69** from ethyl chloroacetoacetate **57**.



Scheme 8 Synthesis of tipranavir (**78**) using molybdenum-catalyzed allylic alkylation.

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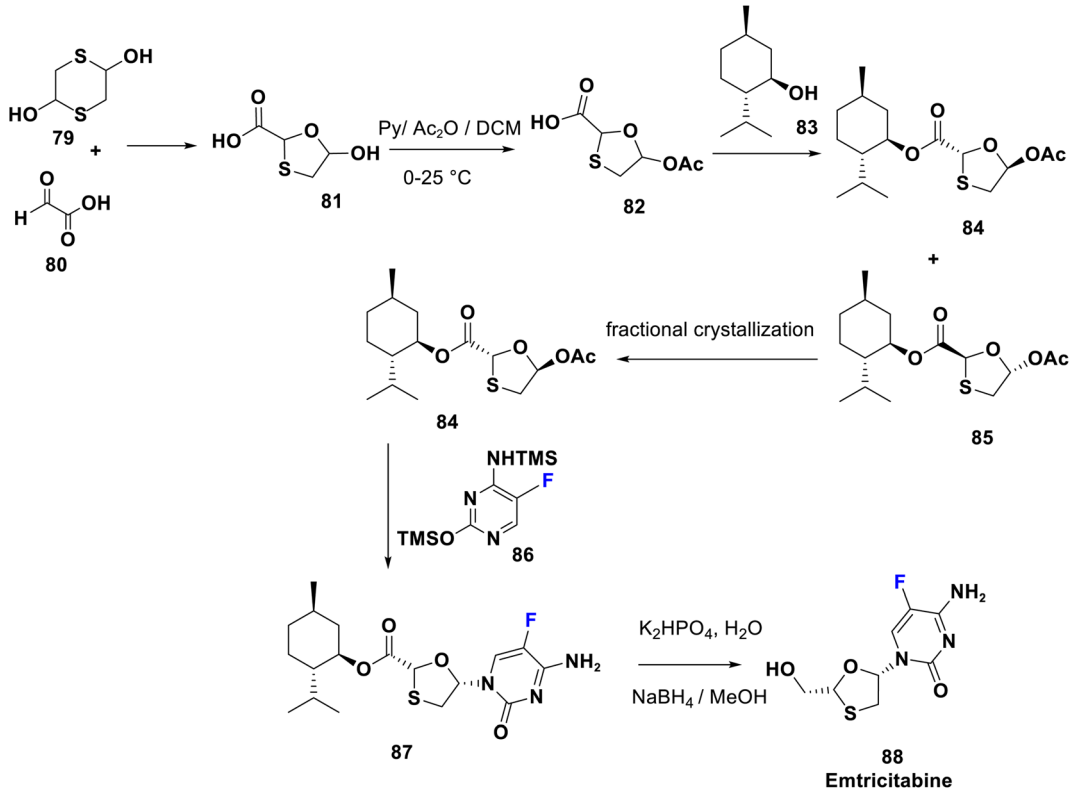
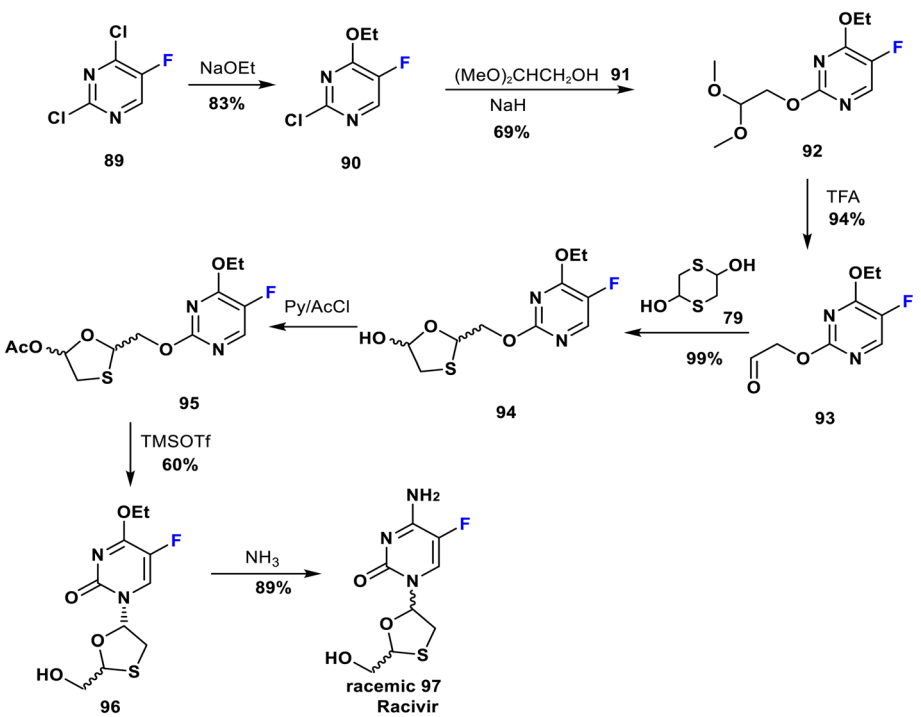


Scheme 9 Synthesis of emtricitabine (88) from *trans* oxathiolane derivative 81.

represented with inversion of configuration in position 5 of oxathiolane[67–70] (Scheme 9).

Racivir is an enantiomer of emtricitabine. It is a widely used nucleoside reverse transcriptase inhibitor advanced by Pharmasset Company for HIV treatment and is currently in phase 2b clinical trials; it blocks a further increase in the amount of HIV virus in the body.[71] Racivir is a racemic mixture of the two β-enantiomers of emtricitabine (88), and a neat



Scheme 10 Synthesis of racivir from 2,4-dichloro-5-fluoropyrimidine (89).

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synthetic method has been patented by Glaxo Wellcome Inc. Its synthesis was achieved by reaction of 2,4-dichloro-5-fluoropyrimidine (**89**) with NaOEt to yield **90**; which is then reacted with the anion of 2,2-dimethoxyethanol (**91**) to produce the pyrimidine derivative **92**. Deprotection of the latter gave the corresponding aldehyde **93**. Then, the formation of 1,3-oxathiolane **94** occurred *via* reaction of **93** and 2,5-dihydroxy-1,4-dithiane **79**. 1,3-Oxathiolane **94** was later acetylated to give **95** which upon treatment with TMSOTf afforded racemic **96**. Eventually, the reaction of **96** with ammonia led to the racemic mixture **97** (racivir) (Scheme 10).[72–74]

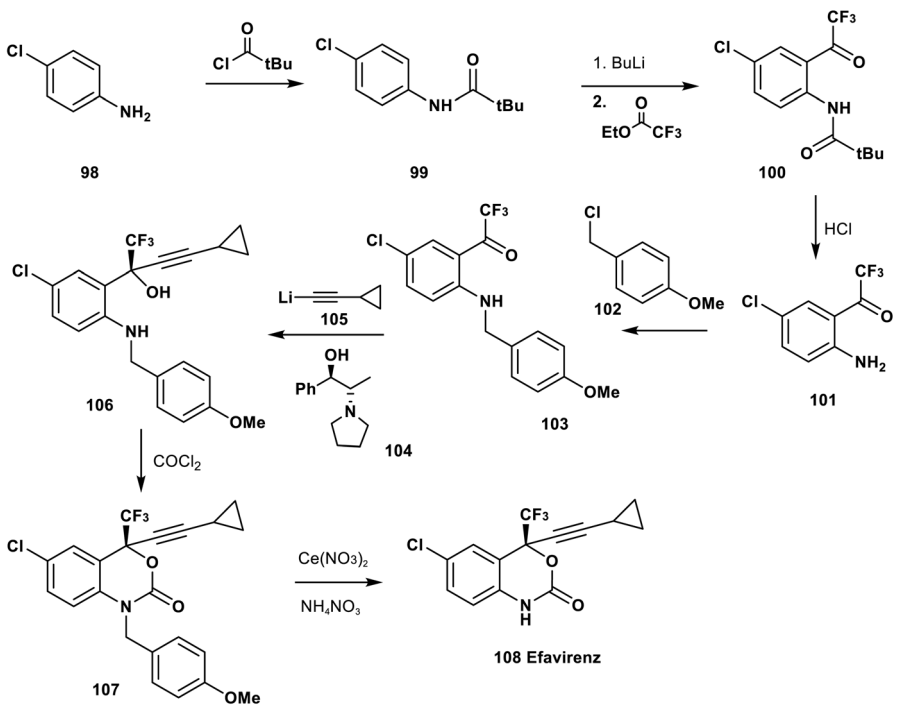
Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are dissimilar to NRTIs where metabolic activation is not required. Alternatively, they act as noncompetitive blockers targeting the nearby allosteric site of HIV-1 RT,[75–77] which leads to conformational changes and impairment of the viral replication.[78]

The FDA approved efavirenz (Sustiva, EFV) in 1998; it is considered one of the vital medicines by the WHO, and since 2016 it has been available as a generic medication. EFV is an essential antiretroviral drug for the prevention and therapy of HIV/AIDS. It is marketed as either a single drug or a combined form with other antiviral agents such as efavirenz, emtricitabine, and tenofovir for the treatment of HIV infection. Efavirenz is characterized by a trifluoromethyl group at the 4-position which reduces the pK_a of the cyclic carbamate. Therefore, the drug potency is improved by hydrogen bond formation between EFV and lysine residue inside the allosteric binding site of the enzyme.[79–81]

Udit *et al.* reported in 1999 the synthetic pathway of efavirenz **108**. The complete synthesis starts from the acylation of *p*-chloroaniline **98** by *t*-butylcarbonyl chloride to afford the amide **99**, followed by acylation of the aromatic ring using BuLi and trifluoroacetate to give the trifluoromethyl ketone derivative **100**. Acidic hydrolysis of **100** afforded the *O*-trifluoroacetyl aniline derivative **101**, and then *N*-alkylation of **101** using *p*-methoxybenzyl chloride (**102**) provided the corresponding *N*-PMB aniline derivative **103**. Asymmetric addition of the lithium salt of cyclopropyl acetylide, **105**, to the ketone group of **103** in the presence of the chiral catalyst **104** afforded the pure tertiary alcohol **106** in excellent enantiomeric excess. Cyclization of **106** was achieved by treatment with phosgene gas to afford the protected *N*-PMB efavirenz **107** which was deprotected by a cerium nitrate and ammonium nitrate protocol to provide efavirenz **108** (Scheme 11).[82,83]

5. Treatment of hepatitis C

Sofosbuvir (Sovaldi®, GS7977) **113** is an RNA-dependant RNA polymerase inhibitor approved by the FDA in 2013, manufactured by Gilead Sciences, Inc. It is a prodrug and has the advantage that the active phosphorylated nucleotide enhances both cell permeability and oral bioavailability. It is the nucleotide analog that interferes with the HCV lifecycle, curtailing viral replication. It can be integrated with HCV RNA by the NS5B polymerase which leads to chain termination. This prodrug is utilized along with ribavirin and sometimes another medication to treat certain types of chronic hepatitis C in adults. Sofosbuvir appears to have a high threshold to the development of resistance. Among sugar-fluorinated nucleosides, sofosbuvir is authorized by the FDA as a therapy for chronic HCV infections including for patients who suffer from hepatocellular



Scheme 11 Synthesis of efavirenz **108** from *p*-chloroaniline (**98**).

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carcinoma and others with HCV/HIV-1 co-infection.[84] Its preparation was accomplished by Kaushik *et al.* in 2015 *via* the reaction of fluorinated deoxynucleoside **110** with the phosphonate **109** which contains a good leaving group (X) such as tosylate, camphorsulfonate, mesylate, trifluoroacetate, trifluorosulfonate, an aryloxide, or heteroaryl oxide substituted with at least one electron-withdrawing group to afford the key compound phosphonucleoside **111**. Then, debenzoylation was carried out *via* reaction of the latter with aqueous acetic acid 70% to produce **112**. Subsequently, hydrolysis in the last step was performed using an aqueous acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, formic acid, acetic acid, fumaric acid, oxalic acid, or mixtures thereof to provide sofosbuvir **113** (Scheme 12).[85]

Ledipasvir was developed by Gilead Sciences. It inhibits an important hepatitis C virus protein (NS5A), which is incorporated into viral assembly, secretion, and replication.[86] Interestingly, patients with genotypes 1a or 1b recover upon using a combination of ledipasvir and sofosbuvir (approved in 2014 by the FDA), as a direct-acting antiviral agent without PEG-interferon or ribavirin.[87] Metabolism of sofosbuvir generates active uridine triphosphate which causes RNA chain termination, when integrated in RNA by NS5B polymerase. The addition of ribavirin to this combination will result in an effective therapy for chronic hepatitis C in both children and adults. Ledipasvir was prepared by Scott *et al.* in 2013 *via* acylation of 2-bromo-9,9-difluoro-7-iodo-9*H*-fluorene (**114**) with 2-chloro-*N*-methoxy-*N*-methylacetamide (**115**) in THF with a catalytic amount of i-PrMgCl at −10 to 0 °C to afford the chloroacetylfluorene derivative **116**. Then, the nucleophilic substitution of **116** was carried out with the potassium salt of the spiro compound **117** in acetone to produce the corresponding ester **118**. Subsequently, reflux of the latter in methoxyethanol with ammonium acetate was performed to provide the imidazole derivative **119** *via* a cyclization mechanism. New C–C bond formation occurred *via* the treatment of **119** with borono compound **120** using a palladium acetate, Mephos, and potassium acetate protocol to produce **121**. Then, Boc deprotection of **121** was achieved using HCl to give the tetrahydrochloride salt **122**. Ultimately, bis-peptide coupling of **122** with (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (Moc-valine) (**123**) using an EDC-HC1/NMM/HOBt/DMF protocol afforded the target ledipasvir (**124**) (Scheme 13).[88,89]

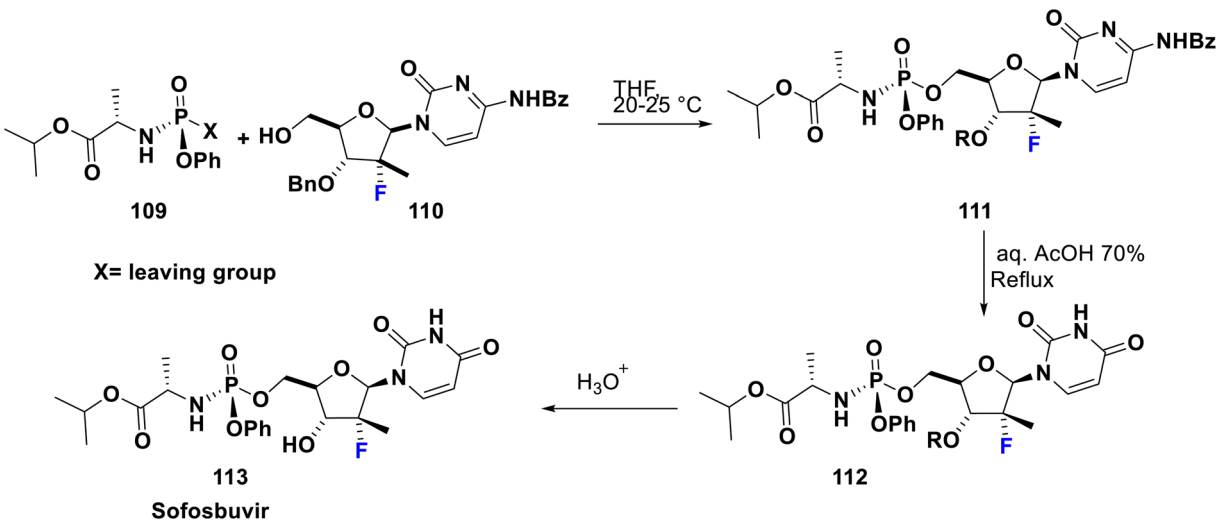
6. Treatment of eye infections

Trifluridine **127** (trifluorothymidine or TFT) was FDA approved in 1980. It was sold under the trade name Viroptic by Glaxo Wellcome; now it is merged into GlaxoSmithKline as an ophthalmic drug. It is utilized for viral eye infections caused by the herpes simplex virus in particular, and does not affect bacteria or fungi.[90] Furthermore, combined therapy of trifluridine and tipiracil is beneficial as an oral anticancer agent for colon or rectal cancers. Trifluridine is a thymidylate synthetase and DNA polymerase inhibitor. It is a suicide substrate that is converted to an irreversible inhibitor at the active site of the enzyme, preventing the conversion of deoxyuridine monophosphate (dUMP) into thymidine monophosphate (TMP), a crucial step in DNA biosynthesis. This will lead to apoptosis, and alter viral or cancer cell replication.[81]

The synthetic procedure of trifluridine, **127**, was achieved by Heidelberger *et al.* in 1962 *via* a free radical reaction of uridine (**125**) with Togni's reagent (**126**) in the presence of catalytic amounts of cuprous salt. Alternatively, trifluridine **127** could be prepared directly by reaction of 5-iodouridine (**128**) with CF_3Cu (that generated from the reaction *in situ* of CF_3I and copper powder)[91,92] as shown in Scheme 14.

7. Treatment of influenza and corona viruses

Favipiravir (T-705) (**134**) was approved for medical use in Japan by Toyama Chemical (a subsidiary of Fujifilm) in 2014. Then, in



Scheme 12 Synthesis of sofosbuvir (**113**) from fluorinated deoxynucleoside **110**.

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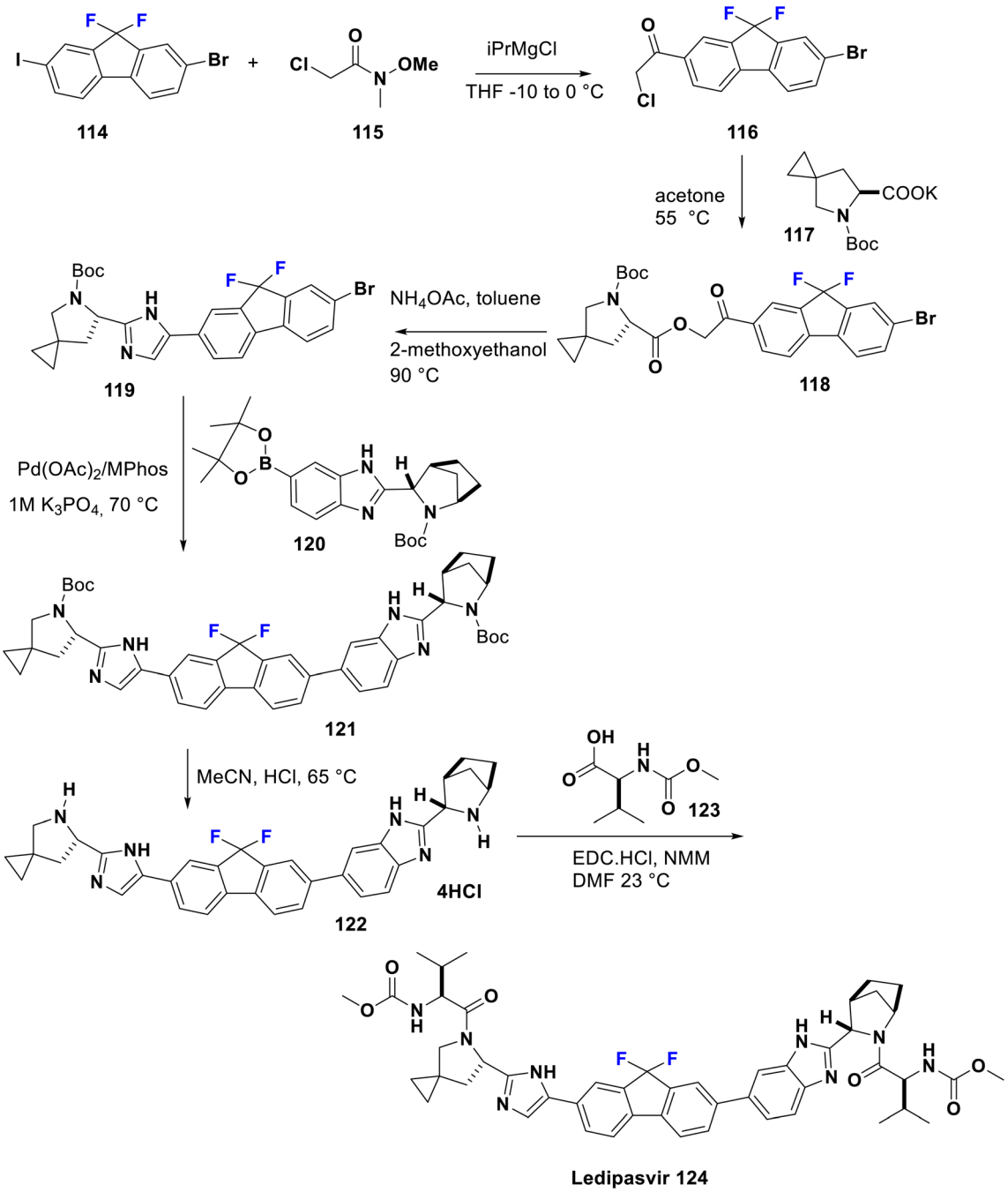
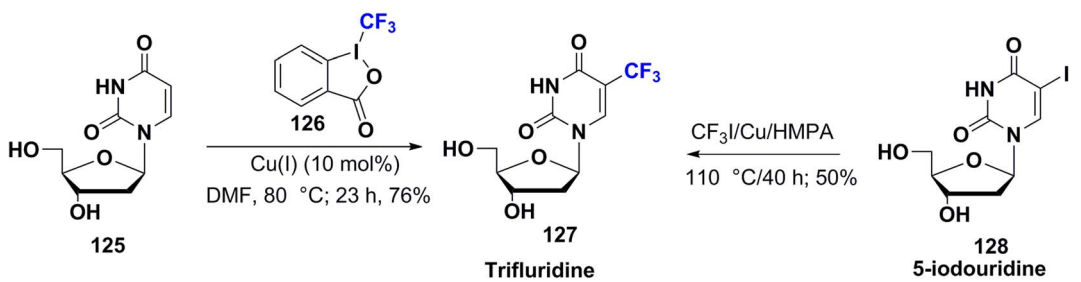


Scheme 13 Synthesis of ledipasvir (**124**) from 2-bromo-9,9-difluoro-7-iodo-9*H*-fluorene (**114**).



Scheme 14 Synthesis of trifluridine (**127**) from uridine.

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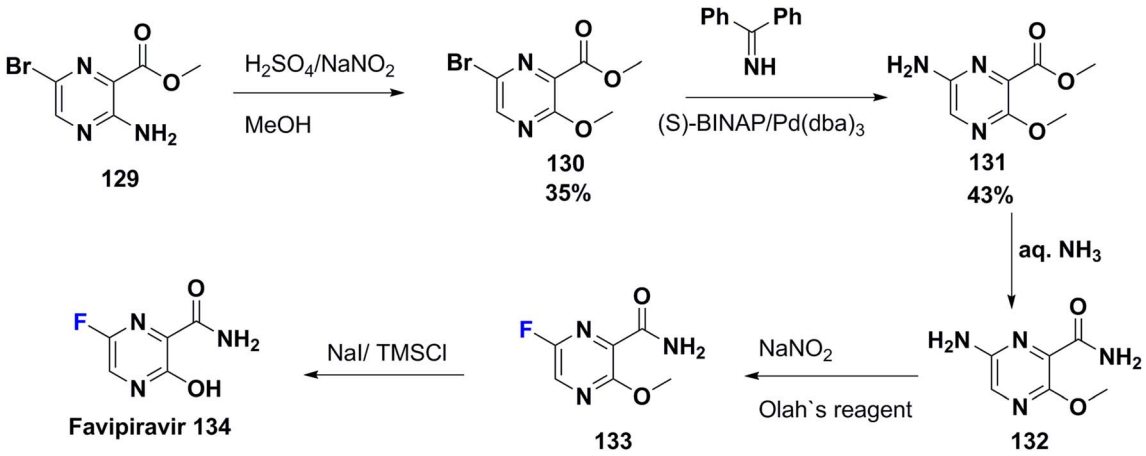

Scheme 15 Synthesis of favipiravir (**134**) from pyrazine-2-carboxylate derivative **129**.

2016, it became a generic drug and was sold under the brand name Avigan in 2019. T-705 has a selective and broad-spectrum antiviral effect towards the RNA-dependent RNA polymerase (RdRp) of RNA viruses.[93] It is a fluorinated pyrazine carboxamide derivative, used to treat influenza in Japan.[94] Concerning the oral formulation, the addition of a 6-fluoro group at the pyrazine ring enhanced both the biological potency and pharmacokinetic character of T-705 in comparison to other derivatives.[95] In addition, patients of COVID-19 suffering from a mild-to-moderate illness treated with T-705 show viral clearance and clinical improvement.[96] The synthesis of favipiravir (**135**) was achieved by Furuta *et al.* in 2000 as shown in Scheme 15,[97–99] starting from pyrazine-2-carboxylate derivative **129** which was transformed to its methoxy derivative **130** *via* diazotization in methanol. Next, **130** was subjected to Buchwald–Hartwig amination to give **131**; followed by amidation utilizing aq. ammonia to afford the corresponding amide **132**. Diazotization of **132** was carried out in the presence of pyridine hydrofluoride (Olah's reagent) to produce the fluorinated pyrazine derivative **133**. Then, deprotection of the methyl ether **133** occurred to give favipiravir (**134**).[97]

8. Conclusion

Most of the extraordinary potential of fluorine-containing molecules, as FDA-approved antiviral agents in medicinal chemistry and drug discovery, has been covered and clarified in this review. Clearly, the introduction of a fluorine atom or trifluoromethyl group to these drugs enhances both their pharmacodynamic and pharmacokinetic properties. Future directions must include larger clinical trials to assess the safety, tolerability, and resistance of the antiviral drugs. The antiviral combination strategy is highly beneficial to solve problems with these drugs.

Conflicts of interest

There are no conflicts of interest to declare.

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