

AN OVERVIEW ON HIV-1 REVERSE TRANSCRIPTASE INHIBITORS

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Human immunodeficiency virus type 1 reverse transcriptase (HIV-1 RT) is an essential enzyme for retroviral replication. Together with protease inhibitors, drugs inhibiting the RNA- and DNA-dependant DNA polymerase activity of RT are the major components of highly active antiretroviral therapy (HAART), which has dramatically reduced mortality and morbidity of people living with HIV-1/AIDS in developed countries. This article will focus on HIV-1 RT inhibitors (HIV-1 RTIs) approved by the US Food and Drugs Administration (FDA) and those are in phases II and III clinical trials. RT inhibitors belong to two main classes acting by distinct mechanisms. Nucleoside RT inhibitors (NRTIs) lack a 3' hydroxyl group on their ribose or ribose mimic moiety and thus act as chain terminators. Non-NRTIs bind into a hydrophobic pocket close to the polymerase active site and inhibit the chemical step of the polymerization reaction. For each class of inhibitors, we review the mechanism of action, the resistance mechanisms selected by the virus, and the side effects of the drugs. We also discussed about the new RT inhibitors under development and some QSAR studies on HIV-1 RTIs.

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1. Introduction

The human immunodeficiency virus type 1 (HIV-1) is the causative agent of acquired immunodeficiency syndrome (AIDS). AIDS continues to cause a serious toll throughout the world. The Centers for Disease Control and Prevention (CDC) estimated that 42 million people worldwide, 38.6 million adults and 3.2 million children younger than 15 years, were living with AIDS by the end of 2002. The World Health Organization (WHO) reported 5 million new infections in 2002. Nearly twenty thousand AIDS patients die each year. From 1981 to 2005, the U.S. alone spent \$170 billion on AIDS research and more than \$20 billion is still being invested per year. Despite these efforts, an effective solution is yet to be found. However, it is encouraging to note that important advances in its treatment have been made with the discovery of new drugs and the combination therapy.

HIV-1, the etiological agent of AIDS, has been identified in the beginning of the 1980s [1,2]. There is currently no cure for AIDS. Highly active antiretroviral therapy (HAART) is a powerful HIV treatment that was introduced in the mid-90s. The therapy consists of three or more different drugs that are used in combination to suppress the virus. The combination drugs consist of nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside RT inhibitors (NNRTIs), and protease inhibitors (PIs). NRTIs and NNRTIs get incorporated into newly synthesized DNA strands by HIV-1 reverse transcriptase resulting in chain termination and inhibition of genomic DNA synthesis. PIs specifically inhibit the virus-associated protease.

Twenty-three drugs targeting several stages of viral replication have been approved by FDA for treating AIDS. Eleven drugs are protease inhibitors that affect maturation of HIV particles by inhibiting processing of Gag and Gag-Pol precursors. A fusion inhibitor prevents viral

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particles from fusing with the cellular membrane. The 11 other drugs target viral reverse transcriptase (RT). HAART therapy resulted in decreased death rates due to AIDS-related infections. Recent studies suggested that if HAART is given early and used without interruption, a patient's chance of surviving 5 years is at least 90 percent.

HIV-1 RT is a key enzyme in the retroviral life cycle that catalyzes conversion of the single-stranded genomic RNA into double-stranded DNA with duplicated long terminal repeats, which is integrated into cellular DNA by the viral integrase. The mature p66/p51 heterodimeric HIV-1 RT is generated by the viral protease from a p66/p66 homodimer by cleavage of the C-terminal RNase H domain during maturation of the viral particle. The polymerase and RNase H catalytic sites are located on p66, while p51 plays a structural role [3].

Nucleoside Reverse Transcriptase Inhibitors

After penetrating the host cell, RT uses the viral genomic RNA as a template to replicate the RNA genome into DNA. The enzyme binds to one RNA strand and copies the RNA nucleotides using the corresponding DNA nucleotides. The infected host cell provides the nucleosides, which are made "active" nucleotides by adding three phosphate radicals. Nucleoside reverse transcriptase inhibitors (NRTI's) are nucleoside analogs that mimic cellular nucleosides.

These drugs inhibit the viral reverse transcriptase, thereby preventing the reverse transcription of viral RNA to DNA within the host cell. These agents inhibit viral replication in early stages of viral life cycle. They are metabolized into their active triphosphate form prior to reverse transcriptase inhibition. The currently approved NRTIs (Table 1) are Zidovudine (AZT), Lamivudine (3TC), Didanosine (ddI), Zalcitabine (ddC), Stavudine (d4T), Abacavir (ABC), and Emtricitabine (FTC) [4].

FDA-approved nucleoside reverse transcriptase inhibitors

Azidothymidine (AZT, Zidovudine) (Fig. 1) is the first FDA-approved NRTI in 1987 [5]. NRTIs interfere with HIV replication by competitively inhibiting RT, thus leading to the chain termination of HIV-1 proviral DNA [6]. Other AZT conjugates such as Fozivudine tidoxil and Tenofovir disoproxil fumarate have been approved for treatment of HIV-1 infections [7].

Lamivudine (also known as Epivir, 3TC) (Fig. 1) has been described as a potent NRTI and a relatively non-toxic selective inhibitor of HIV replication [8]. Lamivudine was well-tolerated and effectively improved prognostic virologic and immunologic markers during the treatment of HIV-infected patients [9]. When used in combination with AZT, 3TC had greater immunological benefits to patients than other drug combinations [10-12]. The major side effect is development of M184V mutation in HIV pol gene [13].

Stavudine (d4T) (Fig. 1) has been described as a potent antiviral activity when used alone in asymptomatic or advanced HIV-1 infection [14]. The drug showed potent antiviral and immunologic efficacy when used with ddI [15] or in combination with ddI and indinavir [16]. Prolonged treatment with d4T is not associated with the development of high levels of viral resistance [17]. Treatment with d4T was well tolerated and has been shown to delay the progression of AIDS in patients under AZT [18]. When used in combination with 3TC, d4T showed synergistic antiviral activity against both AZT sensitive as well as AZT-resistant HIV strains *in vitro* [19,20]. Combination therapy with d4T and ddI in HIV infected children resulted in durable suppression of viral replication [21]. Emtriva (FTC, Emtricitabine) (Fig. 1) is the most recent NRTI approved by FDA to be used in combination with other antiretroviral agents that inhibit HIV-1 infection [22-24].

The literature revealed that other NRTIs, alone or in combinations, to block replication of AZT-resistant isolates. For example, *in vitro* antiviral activity has been reported for ddI (Fig. 1) against viral isolates that showed high-level resistance to AZT [25]. The drug can have a persistent beneficial effect on surrogate markers of HIV infection, such as CD4 counts and p24 antigen levels [26]. Persons with advanced HIV disease have shown a significant improvement by switching from AZT to ddI [27].

It has been demonstrated that clinically stable HIV patients on AZT therapy, receiving ddI had a decreased rate of progression to AIDS, a sustained increase in CD4 counts and decrease in developing high-level resistance to AZT [28]. In symptomatic HIV infected children, treatment with either ddI alone or in combination with AZT was found to be more effective and less toxic than AZT alone [29].

Nucleoside reverse transcriptase inhibitors in development

In addition to the FDA-approved NRTI drugs, several modified nucleosides (Fig. 2) are in clinical and preclinical development. The main reasons for continuing the search for new NRTIs directed against HIV-1 are to decrease toxicity, augment efficiency against resistant viruses, and simplify anti-HIV-1 regimen. Several reviews have inventoried those new NRTIs [30-32]. Figure 2 represents eight of the most promising chain terminators in anti-HIV drug development.

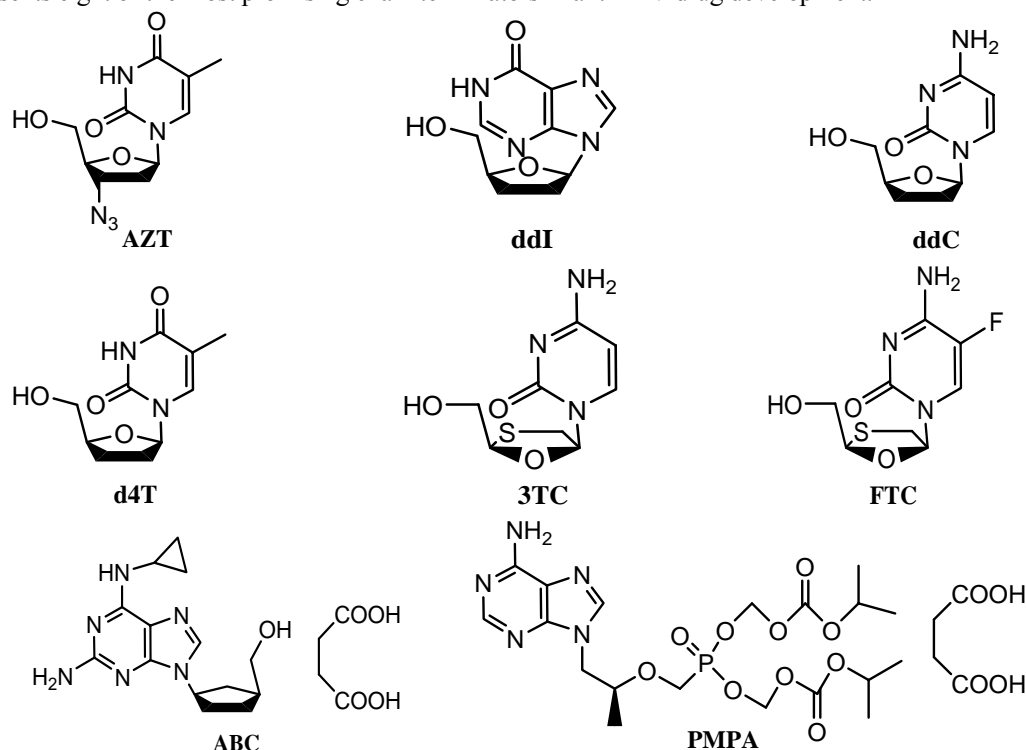


Fig. 1. FDA-Approved Nucleoside Reverse Transcriptase Inhibitors.

Apricitabine [(–)-2'-deoxy-3'-oxa-4'-thiocytidine and formerly AVX754 and SPD754] is a deoxycytidine analog undergoing phase II clinical tests. The structural originality of this molecule lies in its “oxa-thio” ribose structure. AVX754 showed *in vitro* activity against wild-type, AZT-, and 3TC-resistant HIV-1 strains [33,34]. It also showed additive antiviral activity in combination with AZT, d4T, or FTC, albeit having less potency than these NRTIs *in vitro* when used alone [35]. In fact, clinical trials of apricitabine showed much better results than the *in vitro* tests [36]. Apricitabine did not select any particular resistance mutation during a 10-day monotherapy and showed very low toxicity, causing no damage to mtDNA [35,36]. Racivir® [(+/-) 2',3'-dideoxy-3'-thia-5-fluorocytidine, RCV or (+/-)FTC] is a racemic mixture of the two β enantiomers of FTC and is in phase II clinical trials. It has shown significant anti-HIV (and anti-HBV) activity *in vitro* [37].

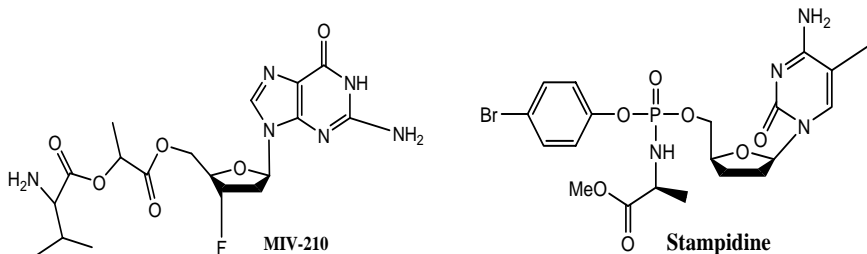
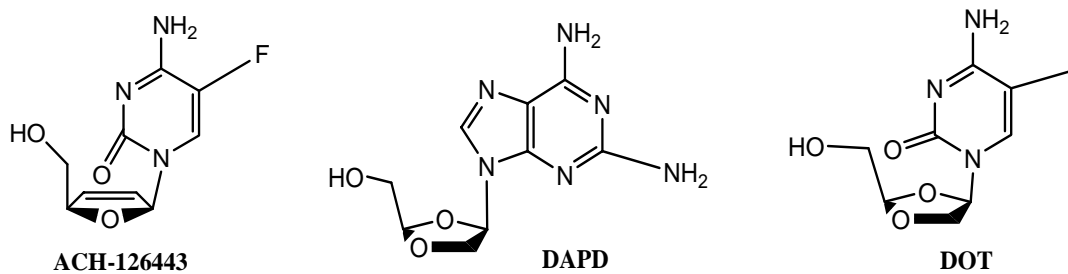
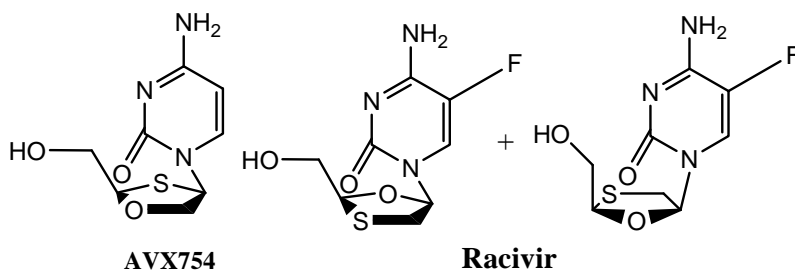
Racivir has an excellent bioavailability, and its pharmacokinetic profile supports once-a-day dosing and this NRTI has also shown promising antiviral activity when used in combination with d4T and Efavirenz [38]. Elvucitabine (ACH-126,443, L-d4FC, 2'-3'-didehydro-2',3'-dideoxy- β -L-5-fluorocytidine) is a deoxycytidine analog substituted with a fluorine atom on position 5 (Fig. 2). It has demonstrated potent *in vitro* activity against HIV [39,40]. *In vitro* studies showed that elvucitabine selected resistance mutations M184I and M184V [41]. In phase II trials, elvucitabine showed potent antiviral activity against 3TC and other NRTI resistant viruses [32]. However, clinical trials of elvucitabine are on hold, as it showed bone marrow suppression in several patients, with CD4+ cell numbers dropping.

Amdoxovir [diaminopurine dioxolane, (2R, 4R)-(2,6-diaminopurin-9-yl)-1,3-dioxolane-2-methanol, (–)- β -D-2,6-diaminopurine dioxolane or DAPD], reached phase II clinical trials. This

compound was designed to be a more soluble and bioavailable prodrug of (-)- β -D-dioxolane-guanine (DXG) [42-44]. In fact DAPD showed common patterns of resistance with some dideoxynucleosides and no cross-resistance with AZT [45,46].

Table 1. Anti-Viral (Reverse Transcriptase Inhibitors) Drugs Licensed by FDA.

Class	Drug	Generic Name	Date Approved by FDA
NRTIs/ NtRTIs	Retrovir	Zidovudine (AZT, ZDV)	March 1987
	Videx/Videx	Didanosine (ddI)	Oct 1991
	Hivid	Zalcitabine (ddc)	June 1992
	Zerit	Stavudine (d4T)	June 1994
	Epivir	Lamivudine (3TC)	November 1995
	Combivir	AZT & 3TC	September 1997
	Ziagen	Abacavir sulfate (ABC)	December 1998
	Trizvir	AZT + 3TC + Abacavir	November 2000
	Viread	Tenofovir disoproxil fumarate (PMPA)	October 2001
	Emtriva	Emtricitabine (FTC)	July 2003
	NNRTIs	Viramune	Nevirapine
Rescriptor		Delavirdine mesylate	April 1997
Sustiva		Efavirenz	September 1998



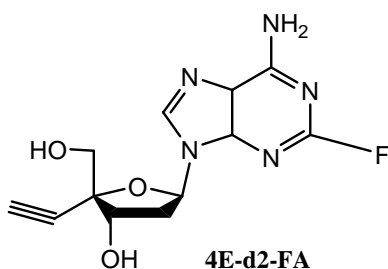


Fig. 2. Nucleoside Reverse Transcriptase Inhibitors in Development.

Dioxolane thymidine [(2R, 4R)-4-(thymidin-1-yl)-1,3-dioxolane-2-methanol or (-)- β -D-thymidine dioxolane or DOT] has made it into phase I clinical trials. It shows excellent bioavailability in monkeys and rats (close to 100%; [47]). It is the first thymidine-based nucleoside to show such activity [48]. A series of phosphates and phosphoramidates DOT prodrugs were prepared and showed enhanced antiviral activity [49]. MIV-210, a prodrug of β -D-2'-3'-dideoxy-3'-fluoroguanosine (FLG), is in phase I clinical trials [50]. Prodrugs designed to enhance cellular penetration or bioavailability or to liberate monophosphate analogs, thus bypassing the first phosphorylation step of nucleosides, constitute an important field in the search for novel NRTIs [51].

Tenofovir, the approved prodrug of PMPA-MP, nicely illustrates this last point. Stampidine (Fig. 2), a stavudine prodrug, also shunts the limiting first phosphorylation step and is highly effective [52-54]. Other promising NRTIs in development include the 4'-ethynyl nucleosides [55,56]. The presence of the ethynyl group inhibits the reactivity of the 3'OH by forming a neopentyle structure [57]. The lead compound of this new class of inhibitors is 4'-E-d2-FA (2'-deoxy-4'-C-ethynyl-2-fluoroadenosine (Fig. 2). Many of the 4'-ethynyl nucleosides appeared to be toxic, but 4'-E-d2-FA displayed highly potent activity against all HIV-1 strains [58].

Nucleotide Reverse Transcriptase Inhibitors

Unlike the nucleoside reverse transcriptase inhibitors (NRTIs), the nucleotide reverse transcriptase inhibitors (NtRTIs) contain a phosphate group and require only two phosphorylation steps to be converted to the active metabolites that serve as alternative substrates in the reverse transcriptase reaction. Once they (NtRTs) are incorporated into the newly transcribed DNA, chain termination occurs. The NtRTIs include adefovir and tenofovir with their officially approved forms adefovir diphosphonate (bis (pivaloyloxymethyl)-PMEA, Hepsara) and tenofovir disoproxil (bis(isopropoxyloxycarbonyloxymethyl)-PMPA-fumarate (Viread)) (Table 1) [59-61].

Non-Nucleoside Reverse Transcriptase Inhibitors

Unlike NRTIs, NNRTIs do not require cellular activation to inhibit HIV-1 RT. They are not incorporated into nascent viral DNA, are noncompetitive inhibitors, and bind into a hydrophobic "pocket" in the p66 subunit of HIV-1 RT located close to (but distinct from) the NRTI binding site [3,62]. NNRTI binding distorts the nearby RT polymerase active site, thus affecting the chemical step of polymerization [63,64].

The NNRTI binding pocket does not exist in the unliganded RT and is formed upon binding by the side chains of aromatic (including Y181 and Y188) and hydrophobic amino-acid residues [65,66]. NNRTIs are highly specific for HIV-1 and do not inhibit HIV-2 or any other retrovirus. NNRTI resistance mutations affect the binding of the inhibitors to their binding pocket. These mutations alter the size, shape, or polarity of the NNRTI binding pocket or affect the access of NNRTIs to this site [65].

FDA-approved non-nucleoside reverse transcriptase inhibitors

Nevirapine (Viramune) (Fig. 3) (Table 1) is an effective NNRTI that emerged as a key drug for the prevention of vertical transmission [67,68] 68- Marseille *et al.* 1999). Results from various studies suggest that nevirapine should be used in a triple-combination therapy regimen with two other anti-HIV drugs. Recent studies suggested that nevirapine was more effective than 3TC, d4T, AZT in crossing the blood-brain barrier [69].

Delaviridine (Fig. 3) (Table 1) is bulkier than nevirapine. Due to its size, it establishes more contacts with RT, in particular, hydrogen bonds with K103 and extended hydrophobic interactions with P236 [70]. The most frequent mutations in patients developing virologic failure while receiving delaviridine are K103N (in >50% of patients), Y181C, and P236L [71,72].

Efavirenz (Sustiva, Stocrin, EFV, DMP-266) (Fig. 3) (Table 1) is a potent NNRTI that binds to HIV-1 RT at a site distinct from the polymerase catalytic site. The combination of efavirenz, AZT, and 3TC had a greater antiviral activity and was better tolerated than the combination of indinavir, AZT, and 3TC [73]. Efavirenz has also been found effective when combined with nevirapine [74], nelfinavir [75] or indinavir [76].

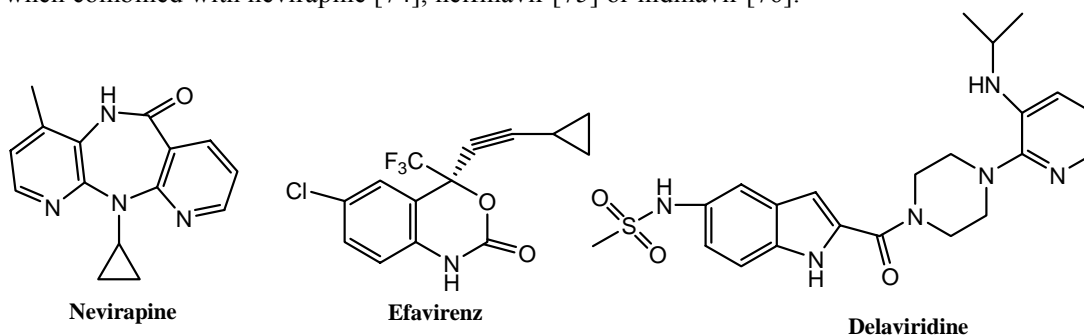


Fig. 3. FDA-Approved Non-Nucleoside Reverse Transcriptase Inhibitors.

Non-nucleoside reverse transcriptase inhibitors in development

The common inhibition mechanism causes problems of cross-resistance, and research on novel NNRTIs is focused on finding molecules that are active against RT resistant towards the FDA-approved drugs (Fig. 4).

The most advanced new NNRTI, etravirine [TMC 125, 4-((6-amino-5-bromo-2-((4-cyanophenyl)amino)-4-pyrimidinyl)oxy)-3,5-dimethylbenzotrile], is in phase III clinical trials [77,78]. Rilpivirine [TMC 278, 4-((4-5(4-((1E)-2-Cyanoethyl)-2,6-dimethylphenyl)amino)-2-pyrimidinyl)amino)benzotrile], also developed by Tibotec/Johnson&Johnson, is structurally related to TMC-125 and is in phase II clinical trials [79].

Calanolide A is an HIV inhibitor extracted from a tropical rainforest tree (*Calophyllum lanigerum*; [80]). Interestingly, calanolide A inhibits viruses bearing mutation Y181C, which are resistant to most NNRTIs, with tenfold enhanced potency as compared to wild-type virus [81,82]. Very few adverse effects were observed and correlated with treatment dosing [83]. Calanolide A can be chemically synthesized and extracted from different plants [84-86].

BILR 355-BS is a new drug developed by Boehringer Ingelheim. It shows potent activity against wild-type and NNRTI-resistant viruses. The effect of BILR 355-BS is boosted by co-administration of ritonavir [87]. Foscarnet has long been known for inhibiting HIV [88,89]. However, because of its very low bioavailability and due to nephrotoxicity, it was never approved for clinical use.

In fact, foscarnet inhibits several viral polymerases [90,91] including HIV-1 RT. This pyrophosphate analog interferes with the translocation of RT and therefore prevents deoxynucleotide to be added to the elongating DNA [92,93]. Thiovir is a foscarnet analog, with one sulfur atom replacing oxygen, and shows much improved oral bioavailability. Compared to foscarnet, it has a lower toxicity and a better efficiency.

NNRTIs are structurally diverse compounds that contain at least one aromatic ring. Based on their structures, NNRTIs reported to date can be divided into more than 30 classes (Fig. 5) including hydroxyethoxymethylphenylthiothymine (HEPT) derivatives [94], tetrahydroimidazobenzodiazepinone (TIBO, (Tivirapine)) derivatives [95], α -anilinophenylacetamide (α -APA, (Loviride)) derivatives [96], dihydropyridodiazepinone such as nevirapine derivatives (L-696339) [97], pyridinone derivatives

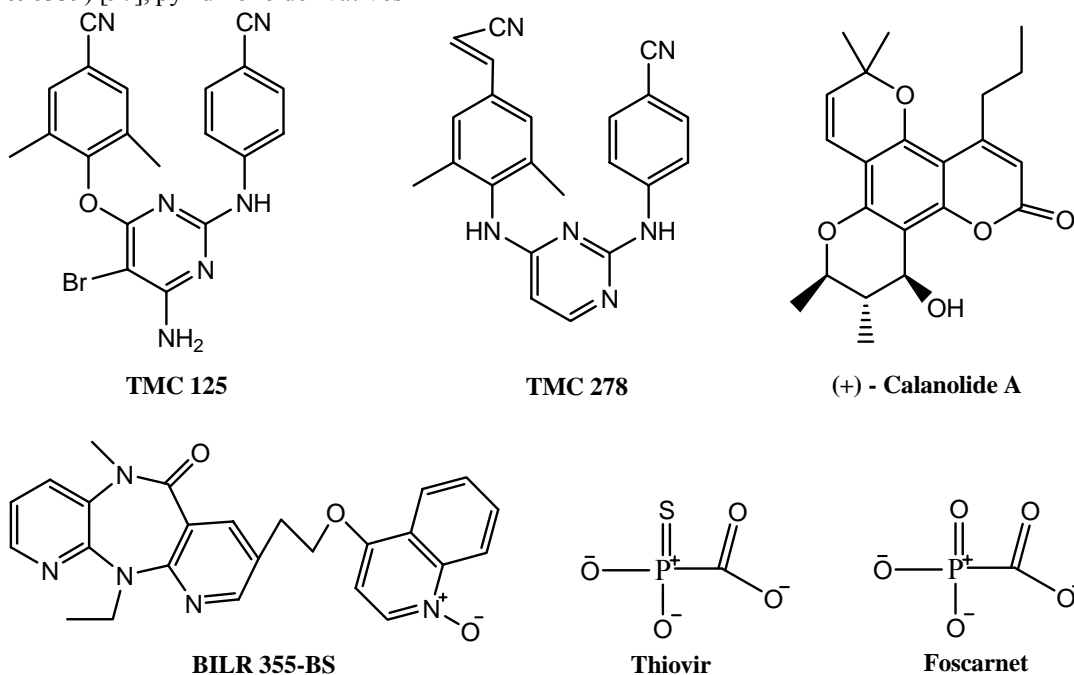
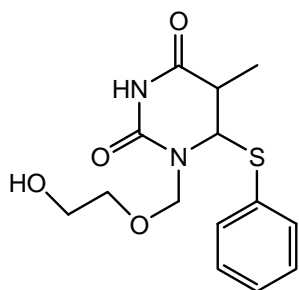
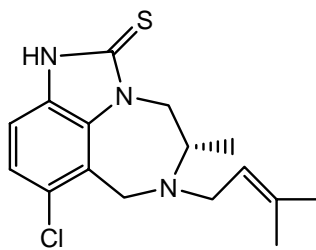
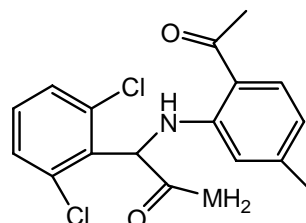
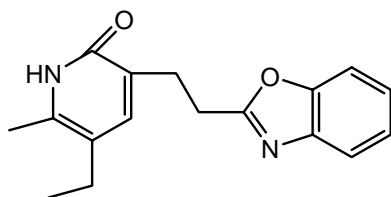
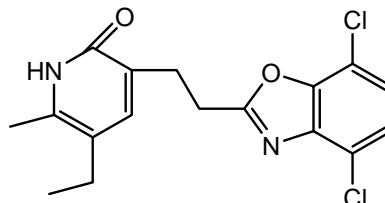
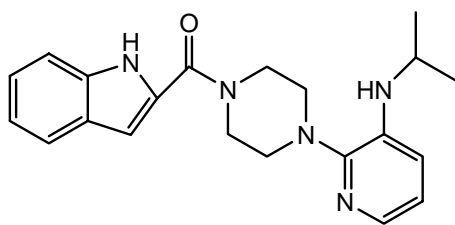
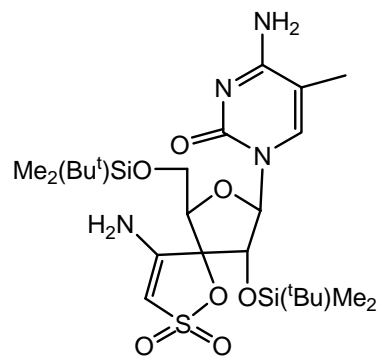
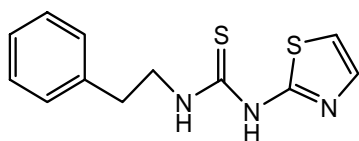
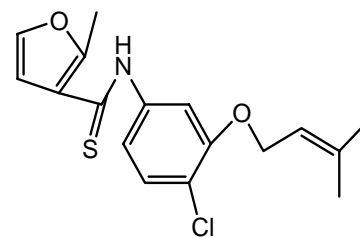
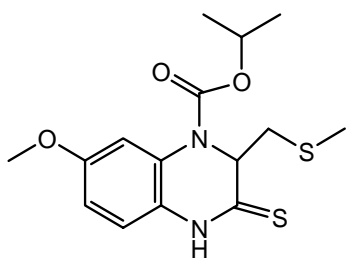
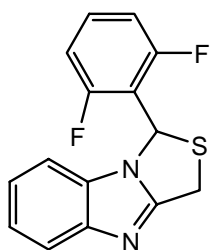


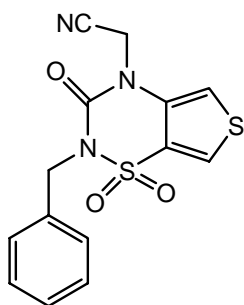
Fig. 4. Non-Nucleoside Reverse Transcriptase Inhibitors in Development.

(L-697661) [98], bis(heteroaryl) piperazine (BHAP, (U-88204)) derivatives [99], tertiarbutyldimethyl silylspiroaminoxathioledioxide (TSAO), pyrimidine nucleosides [100], phenethylthiazolylthiourea (PETT, LY 73487)) derivatives and analogs [101-103], the thiocarboxanilides (UC-781) [104], quinoxalines (HBY 097) [105], thiazolobenzimidazole (TBZ, NSC 625487) [106,107], benzoxazinones (i.e., efavirenz) and structurally related compounds [108-110], the thieno[3,4-*e*][1,2,4]thiadiazine derivatives such as QM96521 [111,112], the imidazole (e.g. capravirine) derivatives and analogues [113,114], (-)-6-chloro-2-{{1-(furo[2,3-*c*]pyridin-5-yl)ethyl}thio}pyrimidin-4-amine (PNU-142721) [115], N-[2-(5-bromopyridyl)-N'-[2-(2,5-dimethoxyphenyl)ethyl]thiourea (HI-236) [116], the pyrido[1,2-*a*]indole derivatives BCH-1 [117], the 4-(cyclopropylalkenyl)-3,4-dihydro-4-trifluoromethylquinazolin-2(1H)-ones DPC 082 and DPC 083 [118], the thiophene-ethylthiourea (TET) derivatives [119], the (cyclohexenyl)ethylthiourea derivatives [120], the cis-cyclopropyl urea-PETT derivatives [121], the (alkenyl)(diaryl)methane (ADAM) series of compounds [122], the pyrrolobenzoxazepinone (PBO) derivatives [123], the (quinoxalinyethyl)pyridylthioureas (QXPTs) [124,125], the 3,4-dihydro-2-alkoxy-6-benzyl-4-oxypyrimidine (DABO) derivatives [126], the imidoylthiourea (ITU, R 100943)) derivatives [127,128], the dianilinopyrimidine (DAPY) derivatives [129], 1-[2-(Diarylmethoxy)ethyl]-2-methyl-5-nitroimidazoles (DAMNIs) derivatives (RS 1478) [130,131], 4,4-disubstituted 1H,3H-2,1,3-benzothiadiazine 2,2-dioxides [132], N-(5-bromopyridin-2-yl)-N'-[2-(4-methylphenyl)ethyl]thiourea [133], 2,3-diaryl-1,3-thiazolidin-4-ones [134], 2-amino-6-(arylsulfanyl)benzonitriles [135], 6-substituted 2-(arylsulfanyl)benzonitriles [136], and 2-(methylsulfanyl)-1H-imidazoles [137].

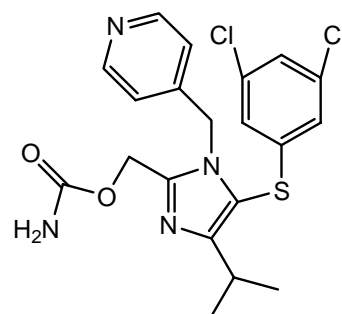
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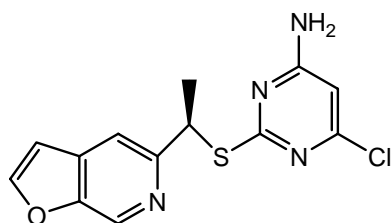
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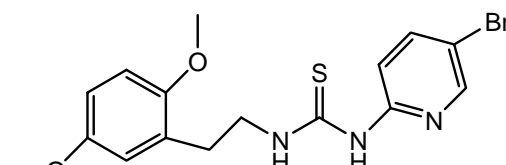
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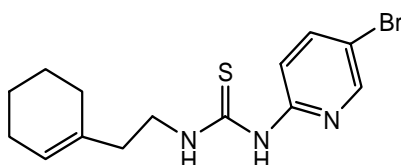
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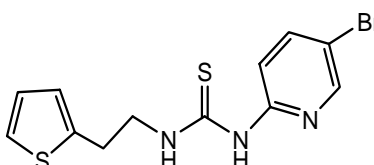
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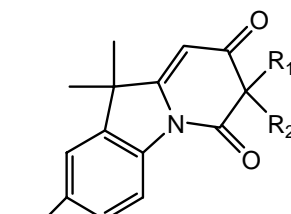
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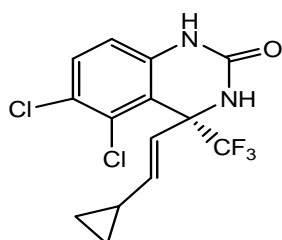
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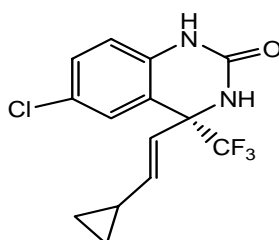
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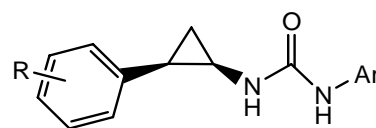
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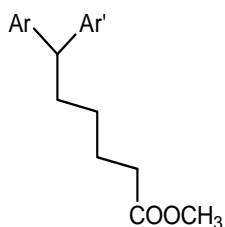
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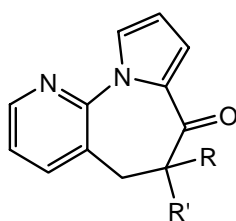
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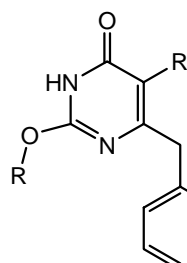
Cis-cyclopropylurea-PETT derivatives



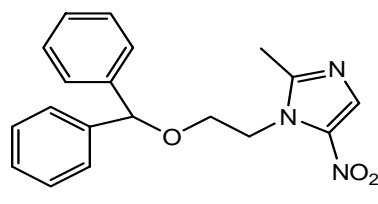
ADAMs



PBOs



DABOs



RS 1478

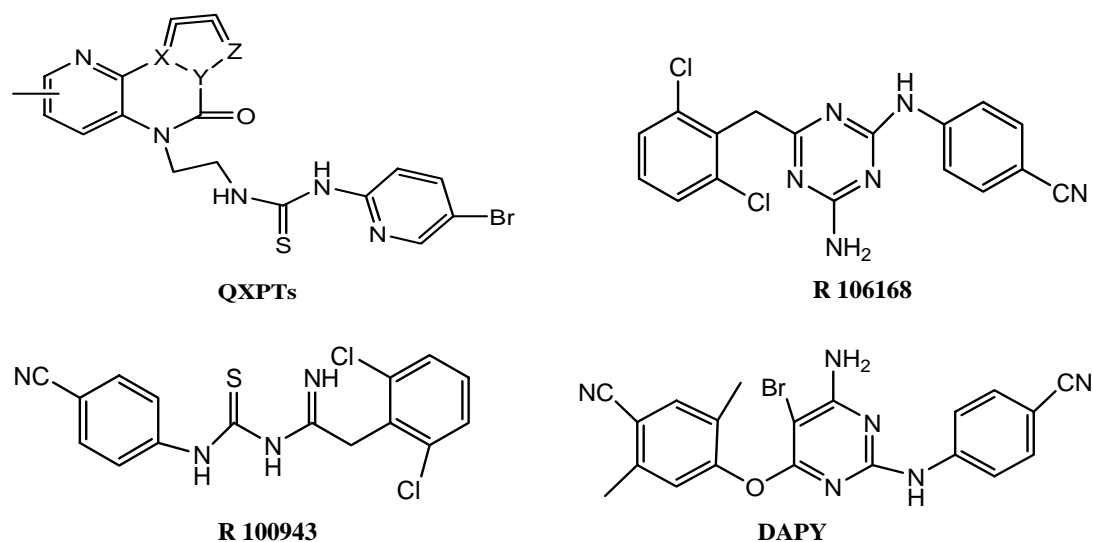


Fig. 5. Non-Nucleoside Reverse Transcriptase Inhibitors Reported to Date

QSAR Studies on HIV-1 RTIs

A quantitative structure activity relationship (QSAR) is an approach to build an activity model based on the structural and physicochemical properties of the known active compounds through multivariate analysis. CoMFA and CoMSIA are two of the most popular approaches to derivate 3D QSAR models. Traditional QSAR does not require receptor information and is a ligand-based computer-aided drug design (CADD) approach. Some important QSAR models have been established in the study of the HIV non-nucleoside inhibitor. The QSAR models have provided critical help to identification, screening, and design of new potent HIV inhibitors. There is no much QSAR has been reported for NRTIs.

Three dimensional QSAR models of two types of NNRTIs, HEPT and TIBO derivatives were built for HEPT, TIBO, and both of them. The results showed that the mixed model had the strongest predicted ability, which was validated by using a test set of 27 inhibitors [138]. Another QSAR of HEPT was established by Gaudio and coworkers [139]. The 3D QSAR models of a small set (12 compounds) of phthalimide derivatives were constructed using CoMFA and CoMSIA [140]. Also QSAR models of pyrrolbenzothiazepinones and pyrrolbenzoxazepinones were studied [141]. CoMFA and CoMSIA models for 71 PETT derivatives were established by Ravichandran and coworkers [142,143]. In addition to 3D descriptors from CoMFA and CoMSIA, varieties of physicochemical parameters were used as descriptors to build QSAR models.

The different physicochemical parameters like hydrophobicity, electronic, and steric terms along with other descriptors were used to construct classic QSAR models for a set of NNRTI 2-amino-6-arylsulfonylbenzotriazoles and congeners [144]. The connectivity indices were introduced to build QSAR models of 47 efavirenz derivatives by Zhong *et al.* The work showed that the structural descriptors were useful to model the activity of this set of NNRTIs [145]. A QSAR models for 44 NNRTIs of the pyridinone derivatives were constructed using the k nearest neighbor (kNN) variable selection approach and database mining. Multiple descriptors such as connectivity indexes have been utilized in the models. The best models demonstrated that the model had predictive power and could be used to identify potential hits from NCI libraries [146]. Another QSAR models were built for a set of 44 tricyclic oxazepinones and 76 tricyclic diazepinones using 15 physicochemical parameters which were obtained from Hyperchem program [147]. The present group of authors are also reported few classical QSAR studies on some NNRTIs like 36 benzoxazinones [148], 71 PETT [149], 33 TTDs [150], 113 1,3-thiazolidin-4-one [151], 26 pyridinyl amines [152] and 18 arylsulfonamides [153] using more than 50 physicochemical parameters which were obtained from WIN CAChe program along with some indicator

parameters. All constructed models had shown satisfactory internal and external predictive ability. QSAR models were also explored to try to correlate the cytotoxicity of a set of HEPT derivatives with molecular structural and physicochemical properties [154].

Another QSAR work used Hansch substituent constants as descriptors to build QSAR models for a set of HEPT and demonstrated that these constants improved the model quality [155]. The inhibitory activities of 55 NNRTIs against wild type and various mutants (Y181C, V106A, K103N, and L100I) of HIV-1 viruses were explored using multivariate analysis principal component analysis (PCA) [156]. All-atom models were also suggested for NNRTI QSAR [157]. In addition to multivariate regression and partial linear square regression, other approaches and methods were also used to derive QSAR models for NNRTIs. Artificial neural network (ANN) method was also used to derive QSAR models of NNRTIs [157-159].

Hologram quantity structure-activity relationships (HQSAR) were used to study the activity models of three sets of NNRTIs, 70 TIBO, 101 HEPT, and 125 dipyrindodiazeponone derivatives. All constructed models had satisfactory predictive ability. It was noticed that increase on the size of fragments enhanced the quality of the models. Comparison of HQSAR and other 2D QSAR models indicated that the HQSAR models produced superior predictive ability than others. In addition, the comparison of the HQSAR and CoMFA QSAR models revealed that the two models were comparable and the interpretations of both reinforced each other. It was suggested that the HQSAR could be a useful tool in QSAR study [160]. QSAR studies of NNRTIs have provided essential information to identification of the important structural features and properties what are responsible for the inhibitory activity of the variety of NNRTIs. These studies are critical to the design of new generation of NNRTIs that are effective to RT mutants.

Conclusions

Remarkable progress has been made since HIV-1 RT was recognized as a rational therapeutic target for treating HIV infection and preventing AIDS. The first line treatment usually combines one NNRTI or one protease inhibitor with a couple of NRTIs. Sometimes, several drugs are combined in a single pill. Drug resistant viruses, toxicity and bioavailability of current drugs also emphasize the need for continuing the search for novel anti-HIV-1 drugs. Prodrug design has definitely proven to be an essential research fields, as it can be applied to all NRTIs and can lead to dramatic activity enhancement by improving drug delivery and bioavailability. Twenty years ago the first RT inhibitor has been approved by FDA, even though it is still possible to target RT and inhibit HIV-1 replication by new mechanisms. Furthermore, we have discussed the development on computational ligand-based NNRTIs design through QSAR.

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