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AZOLES AS NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs): MINI REVIEW

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ABSTRACT: Non-nucleoside reverse transcriptase inhibitors (NNRTIs) in addition with Nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) used in the treatment of HIV-1 infection. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) gained exact place in the treatment of HIV-1 infections. Starting from the HEPT and TIBO derivatives, different classes of compounds have been identified as NNRTIs, that is compounds that are specifically inhibitory to HIV-1 replication and targeted at the HIV-1 reverse transcriptase (RT). Two NNRTIs (nevirapine and delavirdine) have been formally licensed for clinical use and several others are (or have been) in preclinical and/or clinical development [tivrapipe (TIBO R-86183), loviride (a-APA R89439), thiocarboxanilide UC-781, HEPT derivative MKC-442, quinoxaline HBY 097, DMP 266 (efavirenz), PETT derivatives (troviridine, PETT-4, PETT-5) and the dichlorophenylthio (pyridyl) imidazole derivative [S-1153]. Several compounds acting as Reverse transcriptase inhibitors was proved to be highly valuable against HIV-1 replication with minimal toxicity. NNRTIs interact with a specific 'pocket' site of HIV-1 RT and thus inhibiting the translocation and further elongation of DNA strand. The major drawbacks of NNRTIs are their resistance and pharmacokinetic problems. HIV is no exception as it is a retrovirus, which means that it has capacity to insert its genetic material into the host cells and infect it. In this review, we focus on the several moiety used against HIV-1 infection.

INTRODUCTION: Human immunodeficiency virus was found to be a causative agent for development of AIDS ¹. Human immunodeficiency virus, also called retrovirus, has two subtypes i.e. HIV-1 (occurs worldwide) and HIV-2 (found mainly in Africa), consist of a single stranded RNA genome which is converted into double stranded DNA. This conversion occurs in the cytoplasm of newly HIV infected cell in the presence of a viral enzyme named as reverse transcriptase.

Anti HIV-1 drugs act on the reverse transcriptase enzyme and decrease the viral load and increase CD4 lymphocytes. There are three classes of Anti-Reverse Transcriptase Drugs- 1. Nucleoside Reverse Transcriptase Inhibitors (Zidovudine, Stavudine, Zalcitabine, Lamivudine, Didanosine and Abacavir etc). 2. Non- Nucleoside Reverse Transcriptase Inhibitors (Nevirapine, Efavirenz, Delavirdine etc). 3. HIV Protease Inhibitors (Saquinavir, Nelfinavir, Indinavir etc) ²⁻⁴.

Through X-Ray crystallographic analysis inhibitor action of NNRTIs on HIV-1 mainly three mechanisms have given- 1. *Esnouf et al* proposed that NNRTIs change the conformation of DNA polymerase active site to an inactive site, thus inhibit DNA polymerase 2. *Hsiou et al* proposed that NNRTIs deform the structural element of

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polymerase active site that consist of the “Primer grip” which is a region of reverse transcriptase that is involved in the precise positioning of primer DNA strand. This deformation of primer grip may change the position of Template/Primer (T/P) substrate 3. *Kohlstaedit et al* observed that NNRTI-binding pocket act as a joint between palm and thumb, and movement of thumb help in translocation of Template/Primer. NNRTIs bind and inhibit the movement of thumb domain thus preventing the translocation and further elongation of DNA strand⁵⁻⁷.

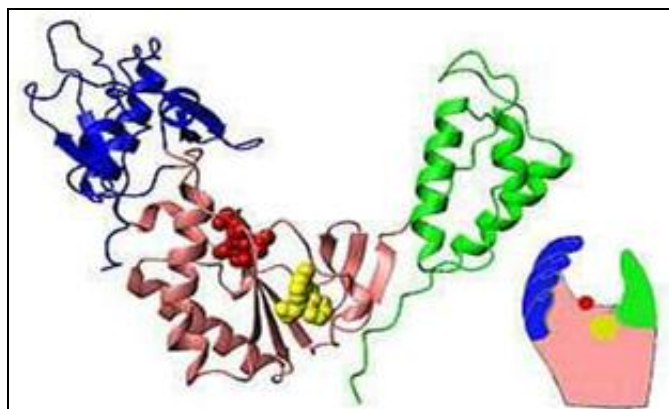


FIG.1: THIS RIBBON REPRESENTATION OF RT ACTIVE DOMAIN (i.e P66 SUBUNIT) DESCRIBES ITS HAND- LIKE STRUCTURE, SHOWING FINGERS (BLUE), PALM (PINK), AND THUMB (GREEN). THE ACTIVE SITE (RED ATOMS), WHERE DNA IS ELONGATED, IS IN THE PALM REGION. ALSO SHOWS IN AN NNRTI DRUG (YELLOW) IN THE POCKET WHERE IT BINDS.

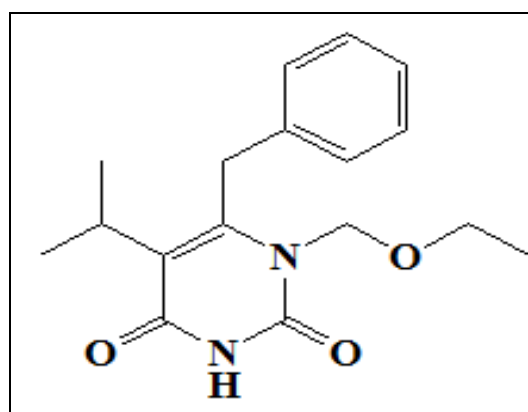
Chemistry of NNRTIs: For producing a large number of physiologically active compounds, the significance of heterocyclic and bicyclic compounds as intermediates have been reviewed by Avila and Jeyaraman⁸. In therapy of HIV infections NNRTIs, the class of anti-reverse transcriptase inhibitors, are significantly used. The epoch of NNRTIs began about a decade with the identification of two classes of compounds i.e. 1-(2-hydroxyethoxymethyl)-6-(phenylthio)thymine [HEPT] (a) (Baba et al., 1989, Miyasaka et al., 1989) and tetrahydroimidazo[4,5,1-jk][1,4] benzodiazepin-2(1*H*)-one and-thione [TIBO] (b) (Pauwels et al., 1990, Debyser et al., 1991) which have specific HIV-1 reverse transcriptase inhibitors activity (Pauwels et al., 1990, Baba et al., 1991a,b, Debyser et al., 1991).

Recently, it has been shown that 4-thiazolidinonederivatives have become a promising area of research because a large no. of activities

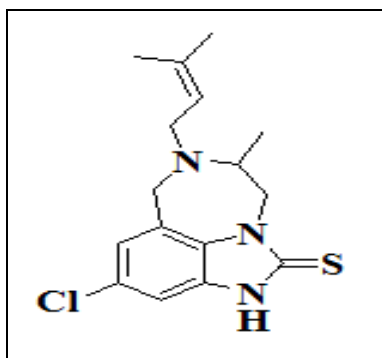
such as- anticancer activity on leukemia (blood-cancer), ovarian, renal, breast cancer, CNS, colon, lung, melanoma are found in this nucleus. The growth on this scaffold from time-to-time have been reviewed by various researchers such as Newkome et al. in 1977⁹, Singh et al. in 1981¹⁰, Abdel-Rahman et al. in 2001¹¹, Verma et al. in 2008¹², Hamama et al. in 2008¹³ and Jain et al. in 2012¹⁴.

The continuous/discontinuous use of NNRTIs in AIDS patients finally cause resistance of virus strains against the drug. So, it is promising to discover new chemical molecule with a broad-spectrum activity against viral reverse transcriptase enzymes¹⁵.

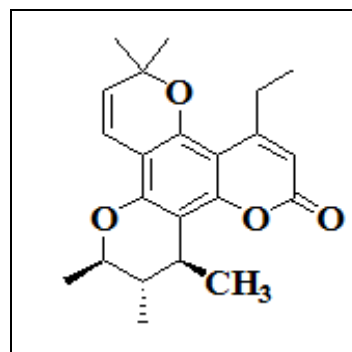
The term first generation NNRTIs related to nevirapine (c) and delavirdine (d) is strongly established in the literature, and the term second generation NNRTIs has an improved activity spectrm against the most common NNRTI – resistant HIV variants. Recently approved NNRTI is efavirenz which shows activity against various NNRTI mutants^{16,17}. Various new NNRTIs, which have various potencies, have been depicted¹⁸⁻²⁰. Some of them such as emivirine (e) also called MKC-442²¹, HBYO97²² (f), Calanolide A²³ (g), the phenylethylthiazolythiourea (PETT) derivatives also called MIV-150²⁴ and the quinazolinone derivatives also called DPC083 and DPC961²⁵ are undergoing to various clinical phases. But due to toxicity, unfavourable pharmacokinetic activities, poor in-vivo efficacy and potency against NNRTI-resistant viruses, most of these drugs has been removed. The thiocarboxanilide (h) also known as UC781 is still in progress due to potent microbicidal activity²⁶.



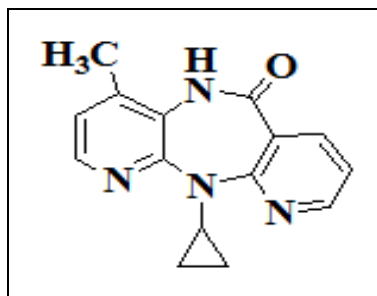
(A) HEPT



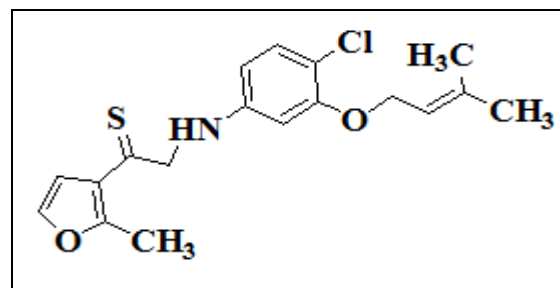
(B) TIBO



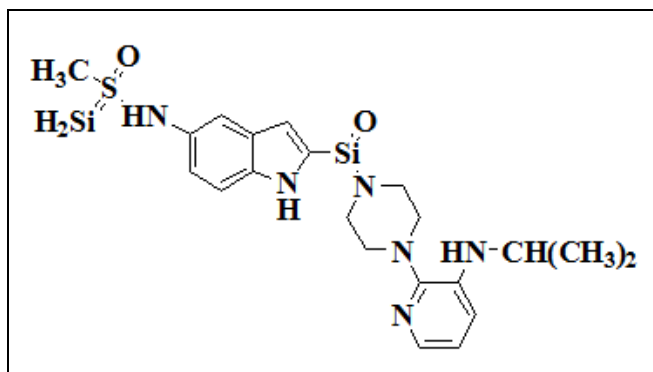
(G) CALANOLIDE A



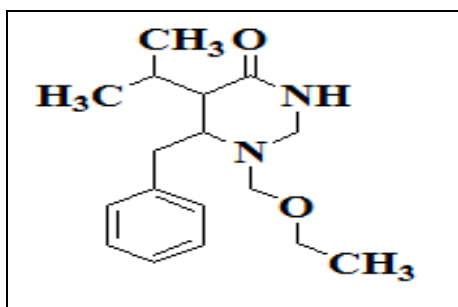
(C) NEVIRAPINE



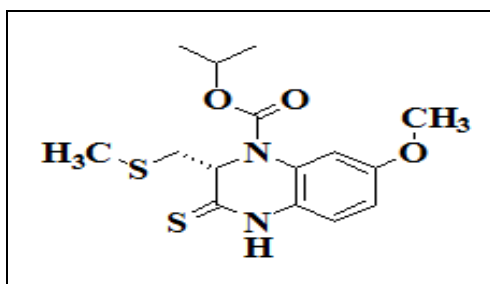
(H) THIOCARBOXANILIDE



(D) DELAVIRDINE



(E) EMIVIRINE (MKC442)



(F) HBY097

Biological Activity:

Antiviral activity: Uncontrolled viral replication in CD4⁺⁺T cells cause HIV-1 disease²⁷. In this situation, for synthesizing inhibitors, HIV-1 RT has been identified as a prime target for treatment of HIV/AIDS^{28,29}.

Thiazolidinone derivative: Several 2,3-diaryl-1,3-thiazolidin-4-ones have reported to be particularly effective non-nucleoside HIV reverse transcriptase inhibitors (NNRTIs)³⁰. A number of thiazolidin-4-one having adamantane moiety at position-2 and another substituent at N-atom of ring have been synthesized such as (±)-2-adamantan-1-yl-3-(4,6-dimethyl-pyridin-2-yl)-thiazolidin-4-one showed modest anti HIV activity. Adamantine moiety have capable to provide antiviral activity. A new series of thiazolidinone compound having an adamantane moiety at 3rd position also exhibit anti HIV activity as well as cytostatic activity³¹.

Benzimidazole derivative: Benzimidazole and their derivatives shows antiviral activity through interaction with different enzymes such as human cytomegalovirus (HCMV), human herpes simplex virus (HSV-1), human immunodeficiency virus (HIV), and hepatitis B and C virus (HBV and HCV).

Luo et al. explored the hepatitis B virus (HBV) activity and cytotoxicity of novel benzimidazole derivatives in the HepG2.2.15 cell line. Its cytotoxicity ($CC_{50} \approx 33.3$ mM) was over six times less than lamivudine ($CC_{50} \approx 5$ mM), it had nearly three times higher selectivity than lamivudine³².

Monforte et al. synthesized N-1-aryl-benzimidazoles 2-substituted analogs and screened them as novel HIV-1 nonnucleoside reverse

transcriptase inhibitors (NNRTIs). Some of the compounds were effective in inhibiting the replication of human immunodeficiency virus (HIV) at nanomolar concentration and also possessed low cytotoxicity. Among the series, compounds 13 and 14 surfaced out as the most promising candidates having potent activity and as well as no toxicity³³.

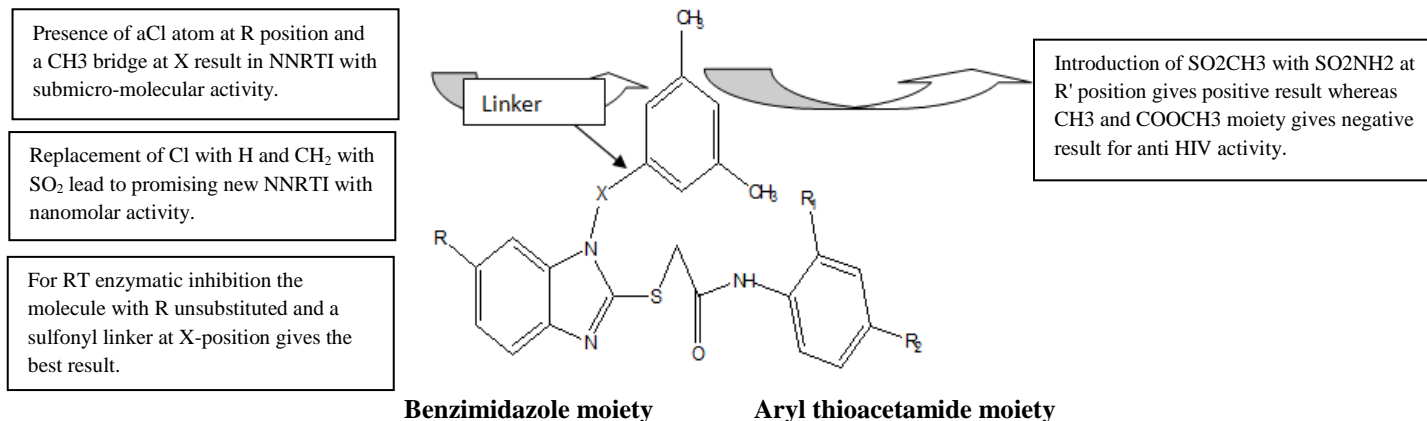


FIG.2: STRUCTURAL ACTIVITY RELATIONSHIP OF ARYL THIOACETAMIDE MOIETY

Cmpd.	R	X	R ₁	R ₂	IC ₅₀	EC ₅₀	CC ₅₀
1.	H	SO ₂	Br	H	0.18±0.018	0.06±0.02	≥235.64
2.	H	SO ₂	Cl	SO ₂ CH ₃	0.12±0.035	0.04±0.07	>221.59

Thiocarboxanilide derivatives: The selective anti-HIV-1 activity of oxathin (thio) carboxanilides was given in 1991³⁴. These drugs are represented as second generation NNRTIs. The lead compound of this class is designated UC-84 (39), contains an oxathiin moiety connect by a carboxamide group to the isopropyl ester of 2-chlorobenzoic acid. These compounds have EC₅₀ values from 0.015 to 0.07 μM against the mutant virus strains³⁵. The first NNRTIs having strong binding in the NNIBP, which is an important feature for NNRTIs use as microbicides. NNRTIs are in general having hydrophobic nature and should readily cross membranes such as the HIV envelope. The hydrophobic nature of this compound would allow inflow and outflow of the NNRTIs from the virion. The hydrophobic UC781 penetrate by the virion membrane envelope and capsid core would allow binding to RT. The tight-binding property of the compound lowest the dissociation of the NNRTI from RT, and grabbing the NNRTI within the virion particle shows a prolonged inhibition of RT activity.

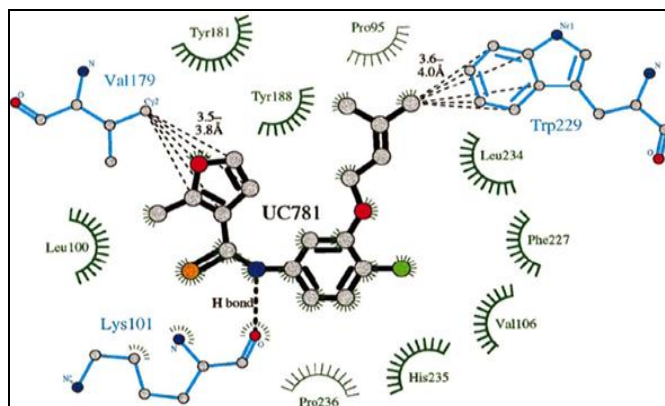


FIG.3: THIOCARBOXANILIDE UC-781 POSITIONED IN THE NNRTI-BINDING POCKET OF HIV-1 RT³⁶.

2-Aminopyrimidines derivative: The development of pyrimidines as NNRTIs was the effect of 18 years of research of its prototype 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-ones (TIBO) (b), derivative³⁷. The structure-based lead discovery started with this find. This group of non nucleoside RT inhibitors (NNRTI's) interferes with the function of viral polymerase through interaction at a common

“allosteric” binding site which is in close proximity to the catalytic site of DNA synthesis.

Imidazole derivative: A series of imidazole were synthesized with the aim to develop novel imidazole analogue with broad spectrum anti HIV activity³⁸. Imidazole have been known as antiviral drug, one of the example being capravirine. Capravirine was one of the most promising NNRTI because it has a favorable profile to many drug resistance mutations³⁹. The use of Capravirine has newlybeen prohibited due to vasculitis (an inflammation of the blood vessels) in animals that taken high doses of Capravirine⁴⁰. In, the synthesis of novel Capravirineanalogues was achieved by synthesis of 2-(aminocarbonylmethylthio)-1H-imidazoles and they were tested for their biological activity against HIV-1.

Arylazolythioacetanilide derivative: Currently, arylazolythioacetanilides, a particular series of five membered heterocyclic derivatives, given more attention to the discovery of new NNRTIs because it having more potency against wild-type and resistant HIV-1 strains, maximum bioavailability and low toxicity⁴¹⁻⁴⁸. The newly synthesized imidazopyridinylthioacetanilide derivatives were tested for anti-HIV activity by determining their ability to inhibit the replication of the HIV-1 IIB strain, HIV-1 mutant strain RES056 (K103 N/Y181C double RT mutant), and HIV-2 ROD strain in MT-4 cells in comparison with other NNRTs such as nevirapine, delavirdine etc.

CONCLUSION: Concerted efforts are being made worldwide by medicinal chemists, biologists and clinicians to wipe out most advanced HIV strains. The combination therapy to date involving synthetic drugs has been successful for partial cure of patients ailing from AIDS. Although extensive efforts have been made in developing efficient molecules for the management of AIDS, search is still on as the virus undergoes rapid mutation making the existing drugs active only for a short span. A variety of anti-HIV agents with diverse chemical structures are presented in this review and these have shown heartening activities but with some drawbacks or the other.

The present review summarises recent advances made in anti-HIV/AIDS research.

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