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Research Article

Anti-HIV Drugs Study: Study of NNRTIs Function and Overview Synthesis of Specific and Rare Aryloxy Tetrazoles Derivatives as NNRTIs and Anti-HIV Drug

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Abstract

Design and use of enzyme inhibitors against viral enzymes is one of the new and effective ways to control viruses and treat viral infections, Enzyme inhibitors inactivate these enzymes by binding to the nucleotides functional groups of the virus vital enzymes, thus can directly disrupt the virus replication cycle and indirectly prevent the spread of viral infections by reducing and controlling the population and number of viruses, these inhibitors, on the one hand, inhibit the virus by filling and Occupying the active sites of the enzyme and on the other hand, they change the stereochemistry of the enzyme by binding to the structure of the enzyme, for this reasons, they are used as an effective and complementary drug in the treatment of infections and viral diseases. Human Immunodeficiency Virus (HIV) is a retrovirus because it has the reverse transcriptase enzyme. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) are a class of Antiretroviral HIV drugs. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) block HIV reverse transcriptase enzymes by connecting to it. Tetrazole derivatives have strong antiviral activity against efavirenz and nevirapine-resistance viruses that have different genetic mutations. In this research, we study NNRTIs function and overview synthesis of 5-aryloxy-tetrazole derivatives in the development path of NNRTIs.

Keywords: Anti-HIV Drugs; NNRTIs; Tetrazole; HAART; Retrovirus; Reverse Transcriptase Enzyme

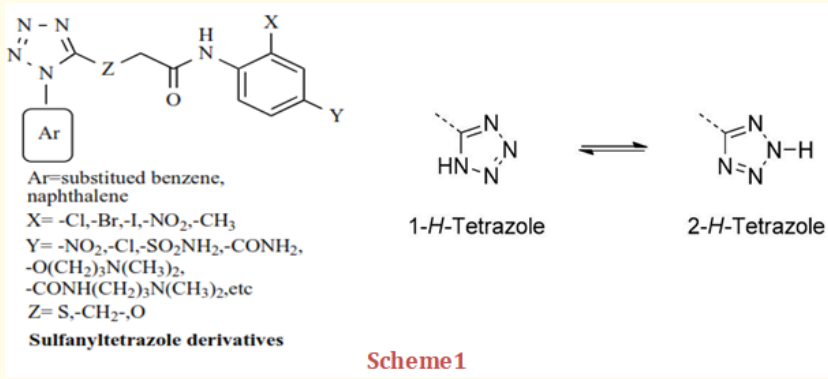
Abbreviations

HIV: Human Immunodeficiency Virus.
AIDS: Acquired Immune Deficiency Syndrome.
NNRTIs: Non-Nucleoside Reverse Transcriptase Inhibitors.
HAART: Highly Active Antiretroviral Therapy.
NRTIs: Nucleoside Reverse Transcriptase Inhibitors.

Introduction

Acquired Immune Deficiency Syndrome (AIDS) is a chronic disease in which the Human Immunodeficiency Virus (HIV) threatens a patient's life by attacking the immune system for life. The HIV virus, which causes AIDS, destroys the body's ability to defend itself against infections. Acquired Immune Deficiency Syndrome (AIDS) remains a major health problem worldwide, with approximately 37.7 million people infected with the Human Immunodeficiency Virus (HIV) [1]. Although the introduction of highly active antiretroviral therapy (HAART) has greatly reduced the morbidity and mortality of HIV infection, the rate of mortality from the disease has

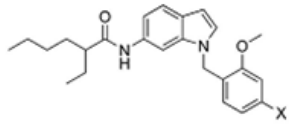
not slowed down enough to eradicate it [2]. Despite decades of scientific research. It is one of the most important and fundamental problems of international health. In scientific research on the treatment of AIDS, NNRTIs have an important place and rank due to their antiviral properties [3, 4]. Among these inhibitors, tetrazole and their derivatives have a more important place because viruses that have become resistant to other drugs due to their genetic mutations are still sensitive to tetrazole derivatives, this susceptibility of viruses to tetrazole derivatives is due to the special structure of the heterocyclic ring of tetrazoles [5]. The tetrazole ring, as shown in Scheme 1, is a five-membered ring with two unsaturations that consist of four nitrogen atoms and one carbon atom [6, 7]. The tetrazole ring proton due to unsaturated resonance is Non-deployed and has an acidic property equivalent to carboxylic acids, the tetrazole ring is considered as Bioisosteres of amides and carboxylic acids Table 1 [8, 9].

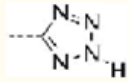


Scheme1

The aryl linked to the tetrazole core fits into the important hydrophobic pocket, where many key resistant mutations take place, which include Y188L, Y181C, and F227C. Tautomers of 5-substituted tetrazoles [9-11].

Recently, the tetrazole ring system [12-15], particularly among pharmacological chemists, has attracted much consideration for the binding of cis-peptides and carboxylic acids as a possible alternative. In fact, the number of patent claims and publications related to the pharmaceutical applications of tetrazoles is growing rapidly and covers a wide range of applications. Tetrazoles have been shown to have antihypertensive, anti-allergic, and antibiotic activities and are currently used as activators, anticonvulsants, and in the treatment of cancer and AIDS. In addition, tetrazole derivatives have been reported for muscle relaxation, anti-inflammatory, anti-arthritis, analgesic, wound healing and coccidiostatic properties. Also tetrazoles are used in agronomy as growth regulators for plants, Pesticides, the process of emergence in photography and explosives and explosive detonators in rocket propellant fuel. Another important application of tetrazoles is the preparation of azides and Nucleoside Reverse Transcriptase Inhibitor (NRTIs) [16]. Addition of azide anion to nitriles, cyanates and cyanamides most commonly used for the preparation of 5-substituted tetrazoles and 5-aryl/alkyl oxytetrazoles. Mostly, the reaction actually occurs in hydrazoic acid (HN_3) solutions,so as example solvents of xylene, benzene, chloroform and toluene. When using hydrazoic acid, care should be taken to monitor hydrazoic acid concentration to prevent explosion in the reaction mixture [5]. A mixture of ammonium chloride and sodium azide salt in dimethylformamide (DMF) solvent is a suitable option for hydrazoic acid. In dimethylformamide, the required temperature is 150°C and the duration is more than 12 hours. But the problem of DMF is its high solubility in organic solvents and water, and therefore the process of separating this substance from the reaction mixture is very difficult, to remove this problem, the reaction was performed in different solutions and the temperature was increased to increase the reaction efficiency. The old system reported for the synthesis of 5-aryloxytetrazole derivatives was the addition of NaN_3 to aryl cyanates with the aid of HCl and acetone under thermal conditions, Restrictions and obstacles in the preparation of raw materials and the difficulty of this method and the use of expensive reagents and toxic and acidic and explosive caused for safety and health reasons [6, 12, 13], We needed a method that did not use HN3,so, a suitable and efficient method for the synthesis of aryloxy tetrazole was essential.

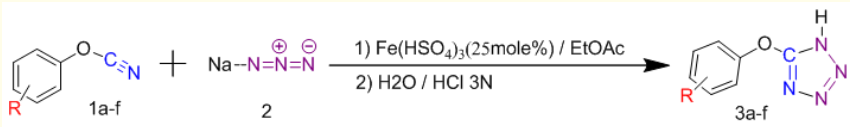


Compd	X	Concn [μM]	Inhibition [a] [%]	pK_d [b]
24	COOH	3.3	100	6.6
25		1	50	6.6
22	$CONHSO_2Ph$	0.1	100	8.6
23	$CONHSO_2nBu$	1.0	100	–

[a]Inhibition of LTE4. [b]pK_d determined in guinea pig tracheal spirals using LTE4 as an agonist

Table 1: Comparison of Bioisosteric property of carboxylic acid and amides with tetrazole group:Antagonists of the cysteinyl leukotriene (LTE_4) receptor(9).

Recently, organic reactions on solid acids and silica-supported reagents have received many considerations in the synthetic reactions because of their ease of handling, enhanced reaction rates, greater selectivity, simple work-up, and recoverability of the catalysts From the standpoint of 'green chemistry', significant efforts have been made to find an alternative to organic solvents (industrially important due to reduced pollution, low cost, and simplicity in process and handling) [17-20]. In view of the importance of aryloxy tetrazoles and aryloxy imidoyl azides, our aim was to find an easy and low-risk method for the synthesis of 5-aryloxytetrazole (3a-f) from aryl cyanates (1a-f) with efficiency appropriate in the presence of $Fe(HSO_4)_3$ as an effective green acidic catalyst, (Scheme 2).



Scheme 2

Materials and Methods

Caution: Aryloxytetrazoles are almost kinetically stable and almost insensitive to electron transfer, friction, and mechanical shocks, but they are also high-energy materials, so appropriate safety precautions should be considered, especially when on a large scale. These compounds are prepared. HN_3 is not a stable component, and is highly degradable to hydrogen and nitrogen, and can form an explosive gas mixture in air or nitrogen with a concentration of more than 8-15%, All products and compounds used are known, and can be identified and proven by comparing some of their spectral data such as IR and 1H-NMR spectral data and their physical properties such as color and melting and boiling temperatures with valid recorded samples, with proper purification methods, all raw materials and solvents were purified before use, if necessary [5]. $Fe(HSO_4)_3$, according to the literature [21] was prepared from $FeCl_3$ and H_2SO_4.

Typical experimental procedure for the preparation of 5-aryloxy tetrazoles 3 with using $Fe(HSO_4)_3$

Ferric hydrogen sulfate ($Fe(HSO_4)_3$) (0.2 g, 0.5 mmol) was add to cyanate (2 mmol) and NaN_3 (0.2 g, 3 mmol) and distilled ethyl acetate (8 mL) and the mixture was stirred at 70°C for (2-4) h (Table 2). After completion of the reaction (as indicated by TLC), the reaction mixture was treated with H_2O (20 mL) and 3 N HCl (20 mL) and stirred vigorously. The resultant organic layer was separated

and the aqueous layer was extracted with ethyl acetate (25 mL). The combined organic layer was washed with water (8 mL) and drying and concentrated to give a crude product. The obtained crude product is recrystallized in chloroform and petroleum ether to give pure product in high yields. The pure product was characterized and identified by their melting point, IR, 1H-NMR and compared with those reported.

Entry	*Cyanate*	*Ar*	*Product (tetrazole)*	*Reaction time (h)*	*Yield (%)[a]*	*Mp°C*	*Mp(lit, ref)° C (6)*
1	1a	4-$CH_3C_6H_4$	3a	2.5	95	139-140	140-142
2	1b	2,6-$(CH_3)_2C_6H_3$	3b	2.5	94	171-173	173-174
3	1c	4-$CH_3OC_6H_4$	3c	2	97	150-151	149-150
4	1d	C_6H_5	3d	3	85	136-138	137-138
5	1e	4-ClC_6H_4	3e	3.5	78	166-168	166-167
6	1f	4-$NO_2C_6H_4$	3f	4	52	161-163	162-163

[a]Reported yields returns to isolated net products.

Table 2: Synthesis of aryloxytetrazoles (3a-f) in the presence of $Fe(HSO_4)_3$ reagent.

Results and Discussion

Similar to literature [22] the cyanates 1a-f were synthesized. The nature of substitutions seems to play a significant role in reaction yield and time and guiding the reaction process. According Table 2, between the different cyanides experimented, electron-rich aromatic cyanides are perfected since (2-4) hours and whilst electron-poor aromatic types require some longer times (consider entry1-4 with 5-6 on Table 2).There is a great relation among benzene ring substitution and the reaction time. Scheme 2 and Table 2. The following significant conclusions are summarized from data in Table 2. Generally, when the electron-donating group is substitution, the reaction is performed at a shorter time (cyanates 1a-c consumption faster) toward since the electron with-drawing group is substitution (checking entries 5 and 6 with 1, 2, 3 and 4 in Table 2). The entries 5 (3.5h) and 6 (4h) verifications this result. Be decreased the reaction rate with increasing the atom or group electro negativity that substituted on the aryl group. These inverse results are what have been reported for nitriles. When the branch on the aryl ring in the aryl cyanates 1 is electron donor, the oxygen attached to the aryl ring is more alkaline power. In other words, the electron-donating branch causes to increase the electron cloud located on the oxygen atom attached to the aryl ring, and It thus aids to cyclization of imidoyl azide (imidoyl azide rearrangement) for the produce of 5-aryloxy tetrazole In any case, the time taken to complete the reactions (listed in Table 2) is a good confirmation, The first step, the addition of H^+ to aryl cyanates 1a-f (Binding of Lewis acid or catalyst to the nitrogen atom of the cyanate group), is the most significant step and is rate determine step of reaction (RDS of reaction) Because when have electron donor substitutes on aryl ring of cyanates, the reaction is completed in a shorter time, As a result, the factors influencing this stage of the reaction directly affect the whole reaction. In all cases, the obtained products with elemental analysis (CHN), melting points andspectral data (IR, ^{1}H-NMR and ^{13}C-NMR) were identified. The missing of one sharp and strong pike (stretching band of CN) and the advent of a CO and NH stretching bands in the IR spectra verify the formation of aryloxy tetrazoles (Fig. 1).The signals that appear at δ=154–157.5 ppm in^{13}C-NMR spectra is belong of the tetrazole ring C atom. The free and delocalized N–H bond (NH of tetrazoles ring) has made the tetrazoles to acidic molecules, and it is not amazing that pKa values like to those of the related carboxylic acids have been reported for the aliphatic and aromatic derivatives of tetrazoles due to their ability to stabilize negatively charged with resonance. Generally, tetrazoles display physical properties same to those carboxylic acids. Thus, the proton (H^+) of tetrazole ring (NH) pike moved to downfield (see Fig. 1 and Fig. 2, IR and ^{1}H-NMR data of 3a–f). Among the types of tetrazole derivatives, type 5, on the one hand, because unlike other types of tetrazole, no synthesis of this type of tetrazole has been reported from a path other than cyanate, and on the other hand, due to the special role of oxygen atoms in the group. Cyanate Synthetic methods of this group of tetrazoles through cyanate are very important, so the synthetic method presented in this report becomes particularly important. The role of tetrazole in inhibiting reverse transcription enzyme Figure 3 is important in several ways:1. Suitable pH for activity in the human body 2. Stable composition and structure (non-stationary proton)

that makes it successful in binding to reverse transcription enzyme in competition with RNA3. The spatial structure of tetrazoles, which binds to the reverse transcription enzyme, changes the spatial orientation of the enzyme, which in addition to filling the active sites of the enzyme (involving enzyme functional groups with acidic tetrazole NH) prevents the enzyme from approaching RNA, which in turn prevents Enzyme binding to RNA and 3, 5-phosphodiester bonds and reverse transcription and virus DNA are made from RNA.

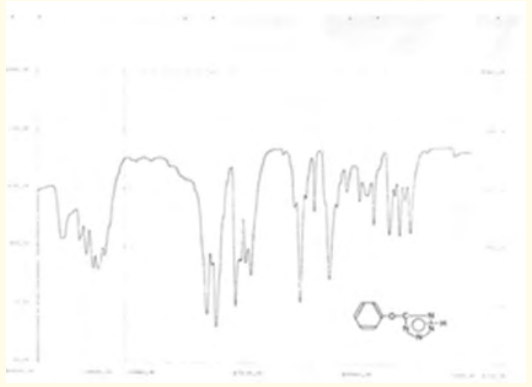


Figure 1: IR spectrum (KBr) 5-phenoxy tetrazole (3d).

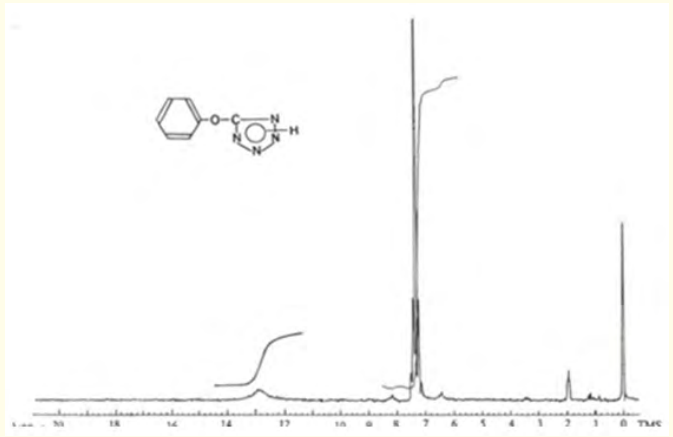


Figure 2: ^{1}H-NMR spectrum 5-phenoxy tetrazole (3d).

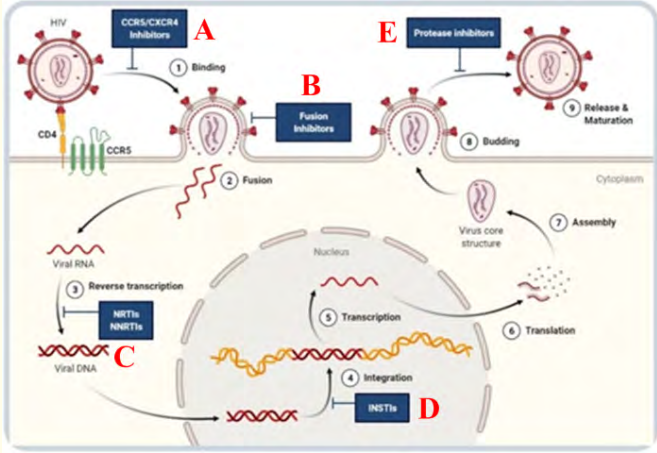


Figure 3: Stages [A-E] of Highly Active Antiretroviral Therapy (HAART), Created With Biorender.Com.

Conclusions

A facile, convenient and less hazard synthetic method for 5-aryloxy tetrazoles 3 from arylcyanates in ethyl acetate as solvent and in the presence of Ferric hydrogen sulfate ($Fe(HSO_4)_3$) as catalyst achieved with quantitative yields high purity without involvement of expensive reagents or the formation of undesirable side products. Enzyme inhibitors inactivate these enzymes by binding to the nucleotides functional groups of the virus vital enzymes, thus can directly disrupt the virus replication cycle and indirectly prevent the spread of viral infections by reducing and controlling the population and number of viruses, these inhibitors, on the one hand, inhibit the virus by filling and Occupying the active sites of the enzyme and on the other hand, they change the stereochemistry of the enzyme by binding to the structure of the enzyme, for this reasons, they are used as an effective and complementary drug in the treatment of infections and viral diseases (stage C in Figure 3)., Even tetrazole derivatives have potent antiviral activity against viruses that have become resistant to efavirenz and nevirapine drugs due to different genetic mutations, and inhibit and inactivate these viruses. Tetrazoles interact and bond faster with the reverse transcriptase enzyme in competition to the substrate (RNA) and the reverse transcriptase process is stopped.

Acknowledgements

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Volume 2 Issue 3 April 2022