

Synthesis of Some New 1-[2-(alkylthio-1-benzyl-5-imidazolyl) carbonyl]-4-[3-(isopropylamino)-2-pyridyl] piperazines as Anti-HIV

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Abstract

A few analogues of atevirdine or 1-[(5-methoxyindol-2-yl) carbonyl]-4-[3-(ethylamino)-2-pyridyl] piperazine – an anti-HIV belonging to non-nucleoside reverse transcriptase inhibitors were synthesized and evaluated for anti-HIV activity. Replacement of indolyl moiety with 2-alkylthio-1-benzyl-5-imidazolyl substituent afforded 1-[2-(alkylthio-1-benzyl-5-imidazolyl) carbonyl]-4-[3-(isopropylamino)-2-pyridyl] piperazines. The title compounds were tested for anti-HIV activity and had maximum percent of protection 14.6% at concentration of 2×10^{-5} M.

Keywords: Imidazole; Arylpiperazine; Anti-HIV

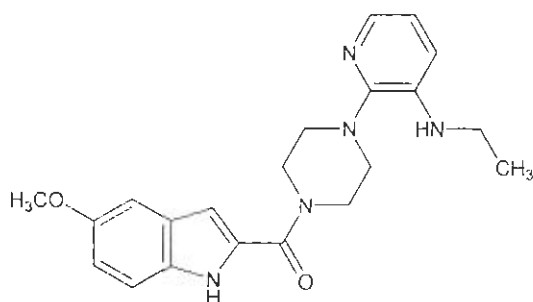
1. Introduction

The human immunodeficiency virus type-1 (HIV-1) is a member of a class of viruses known as retroviruses, wherein the normal flow of genetic information is reversed during viral replication. This process is accomplished by a unique enzyme responsible for converting the information encoded in viral genomic RNA into double-stranded DNA. This enzyme, reverse transcriptase (RT), possesses an RNA-dependent DNA polymerase, a DNA dependent DNA polymerase and a ribonuclease H functions. These functions are essential for retroviral replication [1]. The uniqueness of RT causes it to be an especially advantageous target for therapeutic intervention.

Since no closely related cellular homologues have been identified, the possibility of developing drugs selective for HIV-1 RT exists.

There are two classes of RT inhibitors; nucleoside and non-nucleoside inhibitors. Among nucleoside inhibitors we can mention azidothymidine (AZT), dideoxyinosine (ddI) and diethylthiocarbamate (ddC) [2,3]. These drugs act by mimicking the normal deoxyribonucleoside triphosphate substrates of the enzyme eventually resulting in chain termination. Such nucleoside drugs require phosphorylation by cellular enzymes in order to act as inhibitors. Although these drugs appear to provide some clinical benefit for AIDS victims, their utility is limited by serious side effects [4] and the emergence of resistant strains [5,6]. So, non-

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1 (Ateviridine)

nucleoside RT inhibitors (NNRTIs), which inhibit the RT in a manner distinct from the nucleoside drugs, have been developed. Several unique classes of non-nucleoside RT inhibitors have been identified such as 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one (TIBO) [7], 5- or 6-substituted analogues of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) [8], pyridinone [9], bis-O-(*tert*-butyldimethylsilyl)-3'-spiro-5''-(4''-amino-1',2'-oxathiole-2'',2''-dioxide)pyrimidine (TSAO) [10], dipyrrodoiazepinone [11], and bis(heteroaryl) piperazine (BHAP) [12] classes. We selected atevirdine (U-87201E) **1** which belongs to the latter class as a lead template. According to previous structure and activity relationship studies on atevirdine [13] 1-(3-alkylamino-2-pyridyl)piperazine part of the molecule should remain unchanged and 5-alkoxy-2-indolylcarbonyl part of molecule can be replaced by other moieties, so in this work replacing this part of the molecule with novel 1-benzyl-2-alkylthio-5-imidazolylcarbonyl moiety was investigated and the title compounds 4-(2-alkylthio-1-benzyl-5-imidazolylcarbonyl)-1-(3-alkylamino-2-pyridyl)piperazines **9a, b** (Scheme 2) were synthesized. 1-(4-Chlorobenzoyl)-4-(2-pyridyl)piperazine (**10**) was also synthesized.

2. Investigations and Results

2.1. Synthesis of Compounds

The desired compounds were synthesized by the reactions outlined in Schemes 1 and 2. Scheme 1 illustrates method of preparing 2-alkylthio-1-benzyl-5-imidazolecarboxylic acid [14]. In brief alkylation of readily available 1-benzyl-2-mercapto-5-hydroxymethylimidazole (**2**), which was obtained from the reaction of benzylamine hydrochloride, potassium thiocyanate and dihydroxyacetone [14], afforded 1-benzyl-2-alkylthio-5-hydroxymethyl imidazole **3**. Oxidation of **3** with manganese dioxide gave 1-benzyl-2-alkylthio-5-

formylimidazole **4**. Further oxidation of **4** with silver oxide gave 1-benzyl-2-alkylthio-5-imidazolecarboxylic acid **5**.

Pyridylpiperazine part of the molecule was synthesized as illustrated in Scheme 2 [13]. Nucleophilic aromatic substitution of the 2-chloro-3-nitropyridine with excess piperazine afforded 1-(3-nitro-2-pyridyl)piperazine. Protection of the remaining free nitrogen of piperazine as *tert*-butylcarbamate **6** and subsequent manipulation of 3-nitro group (hydrogenation and reductive alkylation) afforded **7**. Removal of BOC protecting group with trifluoroacetic acid afforded 1-(3-alkylamino-2-pyridyl)piperazine **8**. Coupling of **8** with **5** was accomplished utilizing 1,1'-sulfinyldiimidazole to afford the title compounds 4-(2-alkylthio-1-benzyl-5-imidazolylcarbonyl)-1-(3-alkylamino-2-pyridyl)piperazines **9**. Also, coupling of commercially available 4-chlorobenzoic acid and 1-phenylpiperazine at the same manner as described for **9** afforded 1-(4-chlorobenzoyl)-4-phenylpiperazine **10** (Scheme 2).

2.2. In vitro Anti-HIV-1 Screening

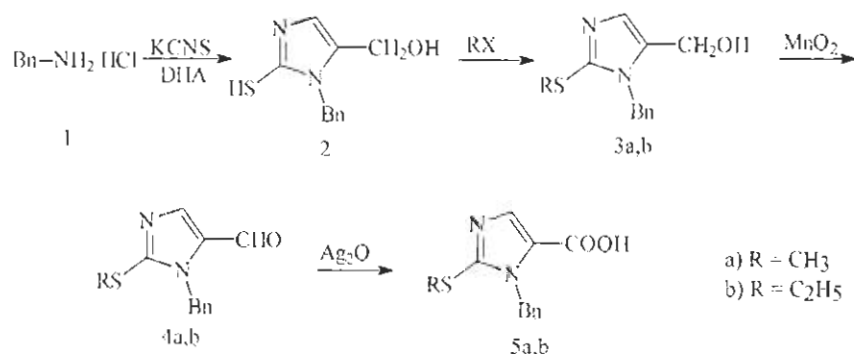
Title compounds **9a, 10** were sent for National Cancer Institute in U.S. and tested for their *in vitro* anti-HIV-1 activity according to their protocol [15]. Although compounds **9a** and **10** were considered inactive in this screen, it was noted that they gave percent of protection values of 14.60 and 15.65 at molar concentrations of 2.00×10^{-5} and 6.33×10^{-5} , respectively.

3. Experimental

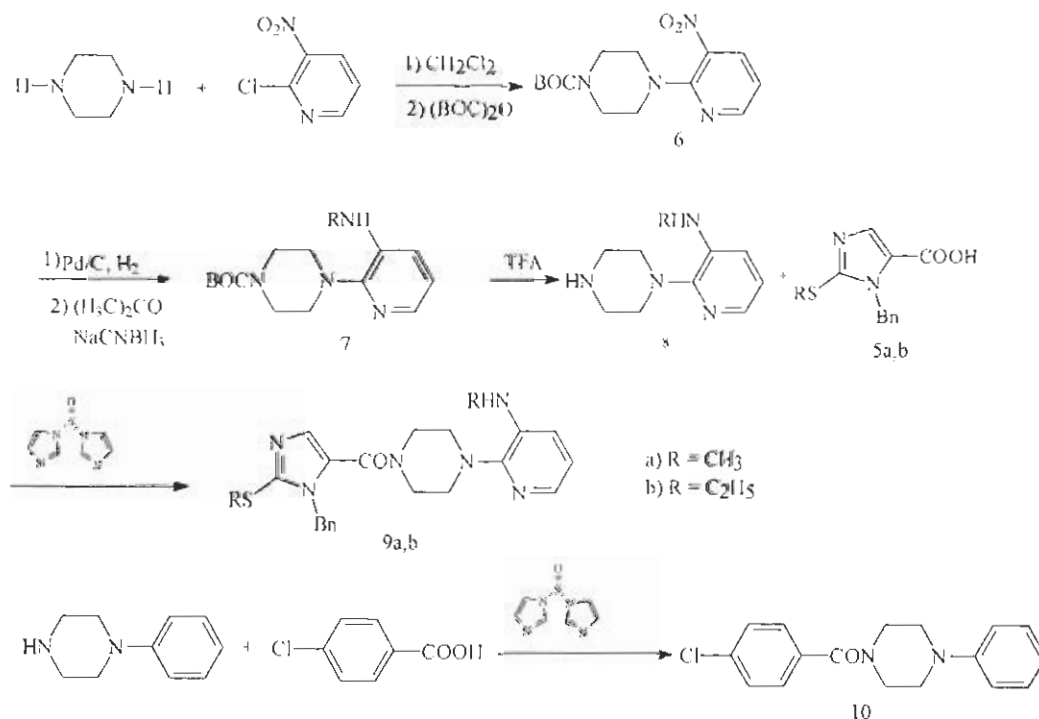
Melting points were determined on Electrothermal Capillary apparatus and are uncorrected. The IR spectra were obtained using a Perkin-Elmer Model Paragon 1000. ^1H NMR were obtained on Bruker Ac-80 spectrophotometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Anti-HIV screening was conducted by the National Cancer Institute, Bethesda, M.D., U.S.A.

3.1. General Procedure for Coupling of Arylpiperazines with Carboxylic Acids

Compounds **2** to **8** were synthesized according to the literature [14,15]. Arylpiperazine and 4-chlorobenzoic acid were commercially available. Carboxylic acid was added to a solution of 1,1'-sulfinyldiimidazole (13.2 mmol) in dry tetrahydrofuran (15 ml) at room temperature. After 1h of stirring the reaction was cooled to 0°C . Arylpiperazine (5.35 mmol) was dissolved in



Scheme 1



Scheme 2

dry tetrahydrofuran (15 ml) and added dropwise to the stirring solution of 5. Then the reaction was solely warmed to room temperature and stirred a further 20 h. A saturated solution of sodium bicarbonate (100 ml) was added to the reaction mixture and then it was extracted with dichloromethane (3×50 ml). The organic phase was evaporated in vacuum to afford the title compounds **9a, b** & **10**.

3.1.1. 1-(1-Benzyl-2-methylthio-5-imidazolyl)-4-[3-[(1-methylethyl)amino]-2-pyridyl] piperazine **9a**

This compound was obtained in 89% yield, m.p. 89-91°C; $^1\text{H NMR}$ (CDCl_3): δ 7.85 (s, 1H, H-C₄ imidazole), 7.65 (dd, 1H, H-pyridine), 7.15 (m, 5H, arom), 6.85 (m, 2H, H-pyridine), 5.37 (s, 2H, CH₂N), 4.20 (br, 1H, NH), 3.80-3.40 (m, 5H, CH-iso-propyl, CH₂-piperazine), 2.88 (m, 4H, CH₂ piperazine), 2.64 (s,

3H, CH₃), 1.22 (d, 6H, CH₃). IR (KBr): ν 1622 cm⁻¹ (C=O).

3.1.2 1-(1-Benzyl-2-ethylthio-5-imidazolyl)-4-f3-[(1-methylethyl)amino]-2-pyridyl] piperazine 9b

This compound was obtained in 93% yield, m.p. 81-83°C; ¹H NMR (CDCl₃): δ 7.90 (s, 1H, H-C₄ imidazole), 7.70 (dd, 1H, H-pyridine), 7.25 (m, 5H, arom), 6.85 (m, 2H, H-pyridine), 5.40 (s, 2H, CH₂N), 4.25 (br, 1H, NH), 3.90-3.40 (m, 5H, CH-iso-propyl, CH₂-piperazine), 3.20 (q, 2H, CH₂S), 2.85 (m, 4H, CH₂ piperazine), 1.50-1.10 (m, 9H, CH₃). IR (KBr): ν 1622 cm⁻¹ (C=O).

3.1.3 1-(4-Chlorobenzoyl)-4-(2-pyridyl) piperazine (10)

This compound was obtained in 54% yield, m.p. 91-93°C; ¹H NMR (CDCl₃): δ 7.43 (s, 5H, arom), 7.40-6.90 (m, 4H, arom), 3.85 (m, 4H, CH₂ piperazine), 3.20 (m, 4H, CH₂ piperazine). IR (KBr): ν 1636 cm⁻¹ (C=O).

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