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SYNTHESIS OF NOVEL DELAVIRDINE ANALOGUES CARRYING PYRAZOLE - ISOXAZOLE NUCLEUS IN THEIR MOLECULAR FRAMEWORK FOR POSSIBLE USE IN ANTI-HIV CHEMOTHERAPY

Rachna Mishra*[1] and Dharma Kishore[1]

*[1]Department of Chemistry, Banasthali University, Banasthali, Rajasthan-304022, India.

ABSTRACT

Delavirdine has been approved by the U.S. food and drug administration for its application in the treatment of AIDS and AIDS related opportunistic infections. As its efficacy is lower than other NNRTIs therefore, U.S. Department of Health and Human Services has recommended its use not as a part of initial therapy but in combination with other drugs. To circumvent this therapeutic difficulty a search for new delavirdine analogues with enhanced activity was needed to be perused. It has been observed that heterocycles that incorporates isoxazole and pyrazole in their molecules exhibit wide range of biological properties such as antibiotic, anticancer, antiviral, and anti-HIV activity. In view of this, it was considered of interest to incorporate isoxazole and pyrazole in the molecular framework of delavirdine. In this communication, we report the preliminary results of our study which was directed to incorporate these biologically active heterocyclic scaffolds in the molecular framework of delavirdine molecule.

KEY WORDS

AIDS, Delavirdine/ Isoxazole/ Pyrazole, Anti-HIV chemotherapy and Highly active anti-retroviral therapy [HAART].

Author of correspondence:
Rachna Mishra,
Department of Chemistry,
Banasthali University,
Banasthali, Rajasthan-304022, India.

Email: racshukla@gmail.com.

INTRODUCTION

HIV shows a special type of tropism for the helper T cells[1], leading to their depletion. The resultant profound immunosuppression predisposes patients to life threatening opportunistic infections. The monotherapeutic clinical trials of several non-nucleoside reverse transcriptase inhibitors (NNRTIs) have demonstrated rapid emergence of resistant mutants of the virus[2-6]. The successful treatment of AIDS by co-administration of drugs provided optimism that sequential treatment with drugs followed by treatment with delavirdine and their

analogues, might result in an effective anti-HIV chemotherapy. This invoked a global attention to embark upon the programs to identify compounds complimentary to delavirdine, namely those of the (alkylamino) piperidine (AAP-BHAP)[7] variety, which possessed better activity than delavirdine against the P236L mutant enzyme. This discovery stimulated the study on other structural analogues of delavirdine wherein their different constitution and biological activity, could allow them to be used as novel chemotherapeutic agents useful in anti-HIV chemotherapy.

Delavirdine (Figure No.1) ([N-[2-({4-[3-propane-2-ylamino) pyridine-2-yl] piperazine-1-yl} carbonyl)-1H-indol-5-yl] methanesulphonamide) (1) has been approved by the U.S. Foods and Drug Administration for its application in the treatment of AIDS and AIDS related opportunistic infections[1]. As its efficacy is lower than other NNRTIs therefore, U.S. Department of Health and Human Services has recommended its use not as a part of initial therapy[8] but in combination with other drugs.

To circumvent this therapeutic difficulty, a search for new delavirdine analogues with enhanced activity was needed to be pursued. A perusal of the structure of delavirdine reveals that its molecule consists of an indole, piperazine, pyridine nucleus and a sulphonamide motif in a distinct framework which allowed it to emerge as a potent anti-HIV agent. It was observed that heterocycles that incorporated pyrazole and isoxazole derivatives in their molecules exhibited a wide range of biological properties such as antibiotic[9], anticancer[10,11], anti-viral[12], and anti-HIV activities[13]. In view of this, it was considered of interest to replace the indole and pyridine nucleus of this molecule with more anti-HIV active pharmacophores of isatin Mannich's bases and isoxazole (and pyrazole) motifs on this assumption that their incorporation could produce favourable impact on the overall bioefficacy of its molecule. In this communication, we report the preliminary results of our study which was directed to incorporate the above biologically active heterocyclic scaffolds in the molecular framework of delavirdine and to concurrently also develop its novel analogues by allowing these to sit in its nucleus in altogether a different molecular setting.

Chemistry

The synthetic pathways that led to the incorporation of pyrazole and isoxazole has been outlined in scheme-1. This strategy envisaged the formation of compound **5(a-d)** from the key intermediate **4(a-d),** which in turn was realized in three steps from isatin **(1)** following the procedure reported for such reactions on other related substrates[14-16]. The synthesis in its first step propelled forward with the preparation of Mannich bases[17] **2(a-d)** of isatin, from **1.** Subsequent treatment of **2(a-d)** with ethyl acetoacetate afforded the enone ester **3(a-d)** from which **4(a-d)** was realized, on its reaction with CS_2 followed by treatment with CH_3I, in presence of NaOEt.

The enone derivative **5(a-d)** reacted smoothly with hydrazine hydrate and hydroxylamine hydrochloride to afford corresponding pyrazole and isoxazole[18] derivatives **6(a-d)** and **7(a-d)** respectively. The ester group of **6(a-d)** and **7(a-d)** allowed a very convenient entry of the sulphonamide motif in its molecule from its reaction with sulphacetamide to give **8(a-d)** and **9(a-d)** respectively. The evaluation of the anti-HIV activity of **8(a-d)** and **9(a-d)** is under study.

EXPERIMENTAL SECTION

Melting points were taken in open capillaries and are uncorrected. Purity of compounds was monitored on silica gel 'G' coated TLC plates. **IR** spectra were recorded on Schimadzu FTIR-8400S Spectrometer in **KBr**, **^{1}HNMR** spectra were taken in $CDCl_3$+$DMSOd_6$ on BRUKER AVANCE II 400 NMR Spectrometer using TMS as an internal standard and Mass spectra were recorded on a Joel SX-102 mass spectrometer.

Preparation of 1-(pyrrolidin-1-ylmethyl) indoline-2, 3-dione (2a):

To a suspension of isatin (2.94 g., 0.02 mol.) in ethanol was added pyrrolidine (1.42 g., 0.02 mol.) and 37% formaldehyde (0.5 ml). The mixture was irradiated in a microwave oven at an intensity of 80% with 30 s/cycle. The completion of the reaction was checked by TLC. The solution was kept at °C

for 30 min. and the resulting precipitate was recrystallized from a mixture of DMF and water to give 2a (3.22 g.): Same procedure was applied for the preparation of 2(b-d).

(2a. R=Pyrrolidine): Yield- 71%, m.p.116-118°C; IR(KBr)cm^{-1}: 3065[C-H], 1710[C=O, carbonyl], 1650[C=O, amide], 1455[C=C], 1371[C-H in CH_2]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 7.80-7.33[4H, m, Ar-H], 4.00[2H, s, CH_2], 2.51-1.68[8H, m, pyrrolidine-H]; MS: m/z: 230(75%) , Anal. Calcd. /found for $C_{13}H_{14}N_2O_2$: C: 67.51/67.81; H: 6.09/6.13; N: 12.10/12.17:

(2b. R=Piperidine): Yield- 69%, m.p.115-116°C; IR(KBr)cm^{-1}: 3068[C-H], 1715[C=O, carbonyl], 1665[C=O, amide], 1449[C=C], 1366[C-H in CH_2] ; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 7.89-7.38[4H, m, Ar-H], 4.03[2H, s, CH_2], 2.45-1.53[10H, m, piperidine-H]; MS: m/z: 244(64%) , Anal. Calcd./found for $C_{14}H_{16}N_2O_2$: C: 68.48/68.83; H: 6.56/6.60; N: 11.42/11.47:

(2c. R=Morpholine): Yield- 45%, m.p.100-101°C; IR(KBr)cm^{-1}: 1712[C=O], 1669[C=O, amide], 1450[C=C], 1371[C-H in CH_3]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 7.65-7.31[4H, m, Ar-H], 4.10[2H, s, CH_2], 3.65-2.50[8H, m, morpholine-H]; MS: m/z: 246(80%) , Anal. Calcd./found for $C_{13}H_{14}N_2O_3$: C: 63.20/63.40; H: 5.70/5.73; N: 11.32/11.38:

(2d. R=N-Methylpiperazine): Yield- 72%, m.p.110-112°C; IR(KBr)cm^{-1}: 1705[C=O], 1651[C=O, amide 1520[C=C], 1300[C-H in CH_3]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 7.77-7.38[4H, m, Ar-H], 4.03[2H, S, CH_2], 2.35[8H, m, piperazine-H], 2.26[3H, s, CH_3]; MS: m/z: 258(70%) , Anal. Calcd. /found for $C_{15}H_{18}N_2O_2$: C: 64.59/64.85; H: 6.58/6.61; N: 10.78/10.84:

Preparation of (Z)-ethyl 3-oxo-2-(2-oxo-1-(pyrrolidin-1-ylmethyl) indolin-3-ylidene) butanoate (3a):

A mixture of 2a (1.15 g., 0.005 mol.) and acetoacetic ester (0.65 g., 0.005 mol.) was dissolved in ethanol (20 ml) and piperidine (1ml) was added. The mixture was allowed to stand 15days at room temperature the yellow needles formed were recrystallized from ethanol to give 3a (1.19 g.): Same procedure was applied for the preparation of 3(b-d).

(3a. R=Pyrrolidine): Yield- 69%, m.p.130-135°C; IR(KBr)cm^{-1}: 3035[Ar-H], 1722[C=O, carbonyl], 1645[C=O, amide], 1467[C=C]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 8.71-7.14[4H, m, Ar-H], 4.20[2H, q, CH_2], 4.01[2H, s, CH_2], 2.27[3H, s, CH_2], 2.51-1.68[8H, m, pyrrolidine-H], 1.29[3H, m, CH_3]; MS: m/z: 342(18%) , Anal. Calcd./found for $C_{19}H_{22}N_2O_4$: C: 66.38/66.65; H: 6.44/6.48; N: 8.13/8.18:

(3b. R=Piperidine): Yield- 65%, m.p 115-116°C; IR(KBr)cm^{-1}: 3045[Ar-H], 1714[C=O], 1671[C=O, amide], 1477[C=C], 1378[C-H in CH_2]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 8.64-7.10[4H, m, Ar-H], 4.10[2H, q, CH_2], 4.05[2H, s, CH_2], 2.20[3H, s, CH_2], 2.45-1.53[10H, m, piperidine-H], 1.22[3H, m, CH_3]; MS: m/z: 356(65%) , Anal. Calcd./found for $C_{20}H_{24}N_2O_4$: C: 67.06/67.40; H: 6.75/6.79; N: 7.82/7.86:

(3c. R=Morpholine): Yield- 70 %, m.p.117-118°C ; IR(KBr)cm^{-1}: 3055[Ar-H], 1728[C=O, carbonyl], 1669[C=O, amide], 1566[C=C]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 8.74-7.14[4H, m, Ar-H], 4.20[2H, q, CH_2], 4.03[2H, s, CH_2], 3.65-2.50[8H, m, morpholine-H] 2.27[3H, s, CH_2], 1.29[3H, m, CH_3]; MS: m/z: 358(30%) , Anal. Calcd./found for $C_{19}H_{22}N_2O_5$: C:63.41/63.67; H: 6.16/6.19; N: 7.78/7.82:

(3d. R=N-Methylpiperazine): Yield- 67%, m.p.115-116 °C; IR(KBr)cm^{-1}: 3066[Ar-H], 1730[C=O, carbonyl], 1656[C=O, amide], 1480[C=C], 1210[C-C]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: : 8.61-7.14[4H, m, Ar-H], 4.12[2H, q, CH_2], 4.01[2H, s, CH_2], 2.25[8H, m, piperazine-H], 2.26[3H, s, CH_3], 2.27[3H, s, CH_2], 1.29[3H, m, CH_3]; MS: m/z: 371(45%) , Anal. Calcd./found for $C_{20}H_{25}N_3O_4$: C: 64.47/64.67; H: 6.74/6.78; N: 11.25/11.31:

Preparation of (Z)-ethyl-5, 5-bis (methylthio)-3-oxo-2-(2-oxo-1-(pyrrolidin-1-ylmethyl) indolin-3-ylidene) pent-4-enoate (4a):

A mixture of 3 (1.02g., 0.003 mol.) and CS_2 (0.684 g., 0.009 mol.) was added to a well stirred and cooled suspension of potassium-ter-butoxide (0.672

g., 0.006 moles) in dry benzene (15 ml) and DMF (10ml) and the reaction mixture was allowed to stand at room temperature for 4 h., then methyl iodide (0.45 g., 0.006 mol.) was gradually added with stirring and external cooling (exothermic reaction). The reaction mixture was allowed to stand for 2 h. at room temperature with occasional shaking and then refluxed on water bath for 3 h. The mixture was poured on crushed ice and the benzene layer was separated. The aqueous portion was extracted with benzene and was washed with water and dried over sodium sulphate and the solvent was removed by distillation. The product obtained was purified by crystallization to give 4a (1.17 g.): Same procedure was applied for the preparation of 4(b-d).

(4a. R=Pyrrolidine): Yield- 71%, m.p.121-123°C; IR(KBr)cm^{-1} : 3135[Ar-H], 1702[C=O, carbonyl], 1674[C=O, amide], 1537[C=C], 624[C-S]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 8.63-7.11[4H, m, Ar-H], 6.01[1H,s, CH], 4.20[2H, q, CH_2], 4.02[2H, s, CH_2], 2.80[3H, s, CH_3], 2.51-1.68[8H, m, pyrrolidine-H], 1.24[3H, t, CH_3]; MS: m/z: 446(16%), Anal. Calcd./found for $C_{22}H_{26}N_2O_4S_2$: C: 58.97/59.17; H: 5.84/5.87; N: 6.23/6.27; S: 14.29/14.36:

(4b. R=Piperidine): Yield-70 %, m.p. 122-124°C ; IR(KBr)cm^{-1} : 3035[Ar-H], 1711[C=O, carbonyl], 1668[C=O, amide], 1477[C=C], 1338[C-H in CH_2], 672[C-S]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 8.74-7.14[4H, m, Ar-H], 6.09[1H,s, CH], 4.20[2H, q, CH_2], 4.03[2H, s, CH_2], 2.80[3H, s, CH_3], 2.45-1.59[10H, m, piperidine-H], 1.29[3H, t, CH_3]; MS: m/z: 460(21%), Anal. Calcd./found for $C_{23}H_{28}N_2O_4S_2$: C: 59.77/59.97; H: 6.09/6.13; N: 6.04/6.08; S: 13.86/13.92:

(4c. R=Morpholine): Yield- 74%, m.p125-126°C; IR(KBr)cm^{-1} : 3005[Ar-H], 1724[C=O, carbonyl], 1658[C=O, amide], 1467[C=C], 1378[C-H in CH_2], 670[C-S]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 8.71-7.14[4H, m, Ar-H], 6.04[1H,s, CH], 4.16[2H, q, CH_2], 4.09[2H, s, CH_2], 2.85[3H, s, CH_3], 3.65-2.50[8H, m, morpholine-H], 1.29[3H, t, CH_3]; MS: m/z: 462(28%), Anal. Calcd./found for $C_{22}H_{26}N_2O_5S_2$: C: 56.84/57.12; H: 5.64/5.67; N: 6.02/6.06; S: 13.79/13.86:

(4d. R=N-Methylpiperazine): Yield- 72%, m.p.110-111°C ; IR(KBr)cm^{-1} : 3135[Ar-H], 1717[C=O], 1662[C=O, amide], 1477[C=C], 1300[C-H in CH_2], 652[C-S]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 8.77-7.24[4H, m, Ar-H], 6.03[1H,s, CH], 4.22[2H, q, CH_2], 4.03[2H, s, CH_2], 2.82[3H, s, CH_3], 2.35[8H, m, piperazine-H], 2.25[3H, s, CH_3], 1.29[3H, t, CH_3]; MS: m/z: 475(40%), Anal. Calcd./found for $C_{23}H_{29}N_3O_4S_2$: C: 57.80/58.08; H: 6.11/6.14; N: 8.79/8.83; S: 13.42/13.48:

Preparation of (2Z, 4Z)-ethyl 5-(4-methylpiperazin-1-yl)-5-(methylthio)-3-oxo-2-(2-oxo-1-(pyrrolidin-1-ylmethyl) indolin-3-ylidene) pent-4-enoate (5a):

A mixture of compound 4 (1.19 g., 0.0024 mol.) and 1-methyl piperazine (.073g., 0.0073 mol.) in toluene (10 ml) was heated to reflux for 2 h. Solvent and excess 1-methyl piperazine was removed under vacuum and the residue was triturated with a mixture of ethyl acetate and ether (1:3) to give 5a (0.75 g.) as yellow crystals: Same procedure was applied for the preparation of 5(b-d).

(5a. R=Pyrrolidine): Yield- 65%, m.p.120-121°C; IR(KBr)cm^{-1} : 1722 [C=O, carbonyl], 1650[C=O, amide], 1010[C-N], 634[C-S]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 8.76-7.10[4H, m, Ar-H], 5.20[1H, s, CH_2], 4.20[2H, q, CH_2], 4.08[2H, s, CH_2], 2.72-2.10[8H, m, piperazine-H], 2.51-1.68[8H, m, pyrrolidine-H], 2.41[3H, s, CH_3], 2.22[3H, s,CH_3], 1.29[3H, t, CH_3]; MS: m/z: 498(19%) [M^+], Anal. Calcd./found for $C_{26}H_{34}N_4O_4S$: C: 62.37/62.63; H: 6.84/6.87; N: 11.19/11.24; S:6.39/6.43:

(5b. R=Piperidine): Yield- 68%, m.p109-110°C; IR(KBr)cm^{-1} : 1743 [C=O, carbonyl] 1655[C=O, amide] 1002[C-N], 634[C-S],; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 8.74-7.14[4H, m, Ar-H], 5.24[1H, s, CH_2], 4.20[2H, q, CH_2], 4.03[2H, s, CH_2], 2.79-2.13[8H, m, piperazine-H], 2.45-1.53[10H, m, piperidine-H], 2.43[3H, s, CH_3], 2.26[3H, s,CH_3], 1.29[3H, t, CH_3]; MS: m/z: 512(12%) , Anal. Calcd./found for $C_{27}H_{36}N_4O_4S$: C: 61.98/62.26; H: 6.04/7.08; N: 10.87/10.93; S: 6.13/6.25:

(5c.R=Morpholine): Yield- 70%,m.p.116-117°C; IR(KBr)cm^{1}:1712[C=O, carbonyl],1622[C=O, amide],1450[C=C],1371[C-O], 1000[C-N], 634[C-S]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 8.74-7.14[4H, m, Ar-H], 5.24[1H, s, CH_2], 4.10[2H, q, CH_2], 4.06[2H, s, CH_2], 2.72-2.13[8H, m, piperazine-H], 3.65-2.50[8H, m, morpholine-H], 2.43[3H, s, CH_3], 2.26[3H, s,CH_3], 1.23[3H, t, CH_3]; MS: m/z: 514(15%), Anal. Calcd./found for $C_{26}H_{34}N_4O_5S$: C: 60.43/60.68; H: 6.62/6.66; N: 10.84/10.89; S: 6.19/6.23:

(5d. R=N-Methylpiperazine): Yield- 71%,m.p.112-114°C; IR(KBr)cm^{-1}: 1734[C=O, carbonyl], 1632[C=O, amide], 1650[C=C], 1010[C-N] 667[C-S]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 8.68-7.13[4H, m, Ar-H], 5.24[1H, s, CH_2], 4.19[2H, q, CH_2], 4.03[2H, s, CH_2], 2.79-2.11[8H, m, piperazine-H], 2.35[8H, m, piperazine-H], 2.43[3H, s, CH_3], 2.24[3H, s,CH_3], 1.29[3H, t, CH_3]; MS: m/z: 527(10%), Anal. Calcd./found for $C_{27}H_{37}N_5O_4S$: C: 61.15/61.46; H: 7.03/7.07; N: 13.20/13.27; S: 5.83/6.08:

Preparation of (E)-ethyl 2-(5-(4-methylpiperazin-1-yl)-1H-pyrazol-3-yl)-2-(2-oxo-1-(pyrrolidin-1-ylmethyl) indolin-3-ylidene) acetate (6a):

Hydrazine hydrate (5 ml, 1mol.) and compound 5a (1.54 g., 0.004 mol.) were taken in 25 -30 ml of ethanol and refluxed for 3 h. The solvent was removed and the residue was dissolved in 10 ml of chloroform. On removal of solvent the compound 6a (0.97g.) was obtained: Same procedure was applied for the preparation of 6(b-d).

(6a. R=Pyrrolidine): Yield- 69%, m.p.110-111°C; IR(KBr)cm^{-1} : 3210[NH], 1732[C=O, ester], 1723[C=O],1458 [C=N], 1048[C-N]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 12.66[1H, s, NH], 8.76-7.14[4H, m, Ar-H], 6.3[1H, s, CH], 4.20[2H,q, CH_2], 4.03[2H, s, CH_2], 3.62-2.36[8H, m, piperazine-H], 2.51-1.68[8H, m, pyrrolidine-H], 2.26[3H, s, CH_3], 1.29[3H, t, CH_3]; MS: m/z: 464(17%), Anal. Calcd. /found for $C_{25}H_{32}N_6O_3$: C: 64.36/64.63; H: 6.91/6.94; N: 17.99/18.09:

(6b. R=Piperidine): Yield- 73%, m.p 118-120°C; IR(KBr)cm^{-1} : 3253[NH], 1722[C=O, ester], 1720[C=O], 1482 [C=N], 1042[C-N]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 12.60[1H, s, NH], 8.74-7.10[4H, m, Ar-H], 6.3[1H, s, CH], 4.30[2H,q, CH_2], 4.10[2H, s, CH_2], 3.52-2.34[8H, m, piperazine-H], 2.35-1.53[10H, m, piperidine-H], 2.23[3H, s, CH_3], 1.25[3H, t, CH_3]; MS: m/z: 478(12%) , Anal. Calcd./found for $C_{26}H_{34}N_6O_3$: C: 64.99/65.25; H: 7.13/7.16; N: 17.48/17.56:

6(c. R=Morpholine) Yield- 71%, m.p. 127-128°C; IR(KBr)cm^{-1} : 3266[NH], 1733[C=O, ester], 1709[C=O], 1458 [C=N], 1128[C-N], 1124[C-O]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 12.62[1H, s, NH], 8.76-7.14[4H, m, Ar-H], 6.3[1H, s, CH], 4.28[2H,q, CH_2], 4.11[2H, s, CH_2], 3.62-2.36[8H, m, piperazine-H], 3.65-2.50[8H, m, morpholine-H], 2.24[3H, s, CH_3], 1.37[3H, t, CH_3]; MS: m/z: 480(20%), Anal. Calcd./found for $C_{25}H_{32}N_6O_4$: C: 62.18/62.48; H: 6.68/6.71; N: 17.41/17.49:

6(d. R=N-Methylpiperazine): Yield- 69%, m.p.120-121°C; IR(KBr)cm^{-1} : 3217[NH], 1742[C=O, ester], 1731[C=O], 1458 [C=N], 1022[C-N], 1002[C-H in CH_3]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 12.70[1H, s, NH], 8.66-7.10[4H, m, Ar-H], 6.1[1H, s, CH], 4.15[2H,q, CH_2], 4.03[2H, s, CH_2], 3.61-2.31[8H, m, piperazine-H], 2.35[8H, m, piperazine-H], 2.20[3H, s, CH_3], 1.23[3H, t, CH_3]; MS: m/z: 493(12%), Anal. Calcd./found for $C_{26}H_{35}N_7O_3$: C: 62.98/63.27; H: 7.11/7.15; N: 19.77/19.86:

Preparation of (E)-ethyl 2-(5-(4-methylpiperazin-1-yl) isoxazole-3-yl)-2-(2-oxo-1-(pyrrolidin-1-ylmethyl) indolin-3-ylidene) acetate (7a):

Hydroxyl amine hydrochloride (1.35 g., 0.02 mol.) was added to sodium methoxide (1.08 g., 0.03 mol.) in absolute methanol (35 ml) and stirred for 10 min., compound 5a (0.99g., 0.002 mol.) was added and the mixture was refluxed for 5 h. Most part of methanol was evaporated under reduced pressure and the mixture was poured into ice-cold water. The solid was filtered, washed with diethyl ether, dried and recrystallized from ethanol to give 7a (2.48 g.): Same procedure was applied for the preparation of 7(b-d).

(7a. R=Pyrrolidine): Yield- 70%, m.p.134-135°C; IR(KBr)cm^{-1} : 1742[C=O, ester], 1705[C=O], 1428

[C=N], 1159[C-O], 1008[C-N]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 12.66[1H, s, NH], 8.76-7.14[4H, m, Ar-H], 6.3[1H, s, CH], 4.20[2H,q, CH_2], 4.03[2H, s, CH_2], 3.15-2.36[8H, m, piperazine-H], 2.51-1.68[8H, m, pyrrolidine-H], 2.26[3H, s, CH_3], 1.29[3H, t, CH_3]; MS: m/z: 465(12%) , Anal. Calcd./found for $C_{25}H_{31}N_5O_4$: C: 64.20/64.50; H: 6.68/6.71; N: 14.97/15.04:

(7b. R=Piperidine): Yield- 72%, m.p.132-134°C; IR(KBr)cm^{-1}: 1722[C=O, ester], 1715[C=O],1432 [C=N], 1151 [C-O], 1050[C-N]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 12.66[1H, s, NH], 8.65-7.35[4H, m, Ar-H], 6.7[1H, s, CH], 4.31[2H,q, CH_2], 4.19[2H, s, CH_2], 3.11-2.34[8H, m, piperazine-H], 2.45-1.53[10H, m, piperidine-H], 2.26[3H, s, CH_3], 1.21[3H, t, CH_3]; MS: m/z: 479(12%), Anal. Calcd./found for $C_{26}H_{33}N_5O_4$: C: 61.90/65.12; H: 6.91/6.94; N: 14.53/14.60:

(7c. R=N-Morpholine): Yield- 68%, m.p.120-121°C; IR(KBr)cm^{-1}: 1754[C=O, ester], 1728[C=O],1431 [C=N], 1230[C-O],1102[C-N]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 12.66[1H, s, NH], 8.64-7.25[4H, m, Ar-H], 6.2[1H, s, CH], 4.15[2H,q, CH_2], 4.03[2H, s, CH_2], 3.10-2.26[8H, m, piperazine-H], 3.65-2.50[8H, m, morpholine-H], 2.22[3H, s, CH_3], 1.25[3H, t, CH_3]; MS: m/z: 481(12%) , Anal. Calcd./found for $C_{25}H_{31}N_5O_5$: C: 62.04/62.36; H: 6.45/6.49; N: 14.46/14.54:

(7d. R=N-Methylpiperazine): Yield- 71%, m.p.128-130°C; IR(KBr)cm^{-1}:1762[C=O, ester], 1734[C=O], 1358 [C=N], 1250[C-O], 1032[C-N], 1078[C-H, CH_3]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 12.60[1H, s, NH], 8.72-7.20[4H, m, Ar-H], 6.7[1H, s, CH], 4.39[2H,q, CH_2], 4.03[2H, s, CH_2], 3.25-2.56[8H, m, piperazine-H], 2.38[8H, m, piperazine-H], 2.34[3H, s, CH_3], 1.21[3H, t, CH_3]; MS: m/z: 494(12%) [M^+], Anal. Calcd. /found for $C_{26}H_{34}N_6O_4$: C: 62.79/63.05; H: 6.89/6.93; N: 16.92/16.99:

Preparation of (E)-2-(5-(4-methylpiperazin-1-yl)-1H-pyrazol-3-yl)-N-(4-(N-methylsulfamoyl) phenyl)-2-(2-oxo-1-(R-1-ylmethyl) indolin-3-ylidene) acetamide (8a):

A mixture of 6a (1.20 g., 0.002mol), sulphacetamide (1.3 g., 0.006mol) and ammonium chloride (1 g.) was taken in ethanol and refluxed for 36-40 h. Washed the cold reaction mixture with water. Stirred it with a little water containing a drop or two of dilute HCl. Collected the solid compound on a filter paper and recrystallized from a mixture of ethanol and ethyl acetate to give 8a (1.98 g.): Same procedure was applied for the preparation of 8(b-d).

(8a. R=Pyrrolidine): Yield-73 %, m.p.- 110-112°C; IR(KBr)cm^{-1} : 3568[NH], 3194[Ar C-H], 1645[C=O, amide] 1634[C=N], 1439[Ar, C=C], 1150[S=O]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 12.66[1H, s, NH], 12.60[1H, s, NH], 10.40[1H, s, NH], 8.74-7.14[4H, m, Ar-H], 7.84-7.64[4H, m, Ar-H], 6.3[1H, s, CH], 4.03[2H, s, CH_2], 3.62-2.36[8H, m, piperazine-H], 2.51-1.68[8H, m, pyrrolidine-H], 2.26[3H, s, CH_3], 2.04[3H, s, CH_3]; MS: m/z: 604(13%), Anal. Calcd./found for $C_{30}H_{36}N_8O_4S$: C: 59.40/59.58; H: 5.97/6.00; N: 18.45/18.53:

(8b. R=Piperidine): Yield- 71%, m.p.- 125-126°C; IR(KBr)cm^{-1} : 3378[NH], 3094[Ar C-H], 1685[C=O, amide] 1640[C=N], 1489[Ar, C=C], 1190[S=O]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 12.60[1H, s, NH], 12.74[1H, s, NH], 10.20[1H, s, NH], 8.64-7.20[4H, m, Ar-H], 7.74-7.54[4H, m, Ar-H], 6.2[1H, s, CH], 4.10[2H, s, CH_2], 3.51-2.30[8H, m, piperazine-H], 2.40-1.51[10H, m, piperidine-H], 2.20[3H, s, CH_3], 2.08[3H, s, CH_3]; MS: m/z: 618(13%), Anal. Calcd./found for $C_{31}H_{38}N_8O_4S$: C: 59.90/60.17; H: 6.16/6.19; N: 18.03/18.11; S: 5.15/5.18:

(8c. Morpholine): Yield- 70%, m.p.-120-122°C; IR(KBr)cm^{-1} : 3450[NH], 3004[Ar C-H], 1685[C=O, amide], 1640[C=N], 1489[Ar, C=C], 1230[S=O], 1090[C-O]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 12.64[1H, s, NH], 12.54[1H, s, NH], 10.40[1H, s, NH], 8.61-7.25[4H, m, Ar-H], 7.64-7.44[4H, m, Ar-H], 6.1[1H, s, CH], 4.05[2H, s, CH_2], 3.65-2.50[8H, m, morpholine-H], 2.42-1.51[8H, m, pyrrolidine-H], 2.21[3H, s, CH_3], 2.11[3H, s, CH_3]; MS: m/z: 620(12%), Anal. Calcd./found for $C_{30}H_{36}N_8O_5S$: C: 57.81/58.05; H: 5.82/5.85; N: 17.98/18.05; S: 5.14/5.17:

(8d. R= N-Methylpiperazine): Yield- 68%, m.p.-124-125°C; IR(KBr)cm^{-1} : 3474[NH], 3084[Ar C-H], 1655[C=O, amide], 1640[C=N], 1440[Ar, C=C], 1190[S=O], 1000[C-H in CH_3]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 12.58[1H, s, NH], 12.65[1H, s, NH], 10.35[1H, s, NH], 8.54-7.26[4H, m, Ar-H], 7.76-7.64[4H, m, Ar-H], 6.8[1H, s, CH], 4.09[2H, s, CH_2], 3.32-2.31[8H, m, piperazine-H], 2.35[8H, m, piperazine-H], 2.22[3H, s, CH_3], 2.11[3H, s, CH_3]; MS: m/z: 633(15%) , Anal. Calcd./found for $C_{23}H_{34}N_6S$: C: 58.45/58.75; H: 6.16/6.20; N: 19.79/19.89; S: 5.03/5.06:

Preparation of (E)-2-(5-(4-methylpiperazin-1-yl) isoxazol-3-yl)-N-(4-(N-methylsulfamoyl) phenyl)-2-(2-oxo-1-(R-1-ylmethyl) indolin-3-ylidene) acetamide 9(a):

The procedure described in 8a was used in the preparation of 9(a-d).

(9a. R=Pyrrolidine): Yield-70 %, m.p.- 135-136°C; IR(KBr)cm^{-1} : 3334[NH], 3064[Ar C-H], 1655[C=O, amide], 1644[C=N], 1459[Ar, C=C], 1120[S=O]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 12.60[1H, s, NH], 10.40[1H, s, NH], 8.74-7.14[4H, m, Ar-H], 7.84-7.64[4H, m, Ar-H], 6.3[1H, s, CH], 4.03[2H, s, CH_2], 3.15-2.36[8H, m, piperazine-H], 2.51-1.68[8H, m, pyrrolidine-H], 2.26[3H, s, CH_3], 2.04[3H, s, CH_3]; MS: m/z: 605(16%), Anal. Calcd./found for $C_{30}H_{35}N_7O_5S$: C: 59.19/59.49; H: 5.79/5.82; N: 16.10/16.19; S: 5.27/5.29:

(9b. R=Piperidine): Yield- 69%, m.p.- 120-122 °C; IR(KBr)cm^{-1} : 3276[NH], 3094[Ar C-H], 1685[C=O, amide], 1640[C=N], 1474[Ar, C=C], 1156[S=O]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 12.64[1H, s, NH], 10.28[1H, s, NH], 8.64-7.21[4H, m, Ar-H], 7.54-7.34[4H, m, Ar-H], 6.2[1H, s, CH], 4.02[2H, s, CH_2], 3.15-2.36[8H, m, piperazine-H], 2.45-1.53[10H, m, piperidine-H], 2.23[3H, s, CH_3], 2.04[3H, s, CH_3]; MS: m/z: 619(12%), Anal. Calcd./found for $C_{31}H_{37}N_7O_5S$: C: 59.78/60.08; H: 5.99/6.02; N: 15.76/15.82; S: 5.15/5.17:

(9c. R=Morpholine): Yield- 67%, m.p.-110-112°C; IR(KBr)cm^{-1} : 3393[NH], 3024[Ar C-H], 1688[C=O, amide], 1625[C=N], 1489[Ar, C=C], 1300[S=O],1067[C-O]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 12.53[1H, s, NH], 10.48[1H, s, NH], 8.68-7.56[4H, m, Ar-H], 7.77-7.34[4H, m, Ar-H], 6.7[1H, s, CH], 4.17[2H, s, CH_2], 3.11-2.23[8H, m, piperazine-H], 3.55-2.50[8H, m, morpholine-H], 2.31[3H, s, CH_3], 2.18[3H, s, CH_3]; MS: m/z: 621(14%), Anal. Calcd./found for $C_{30}H_{35}N_7O_6S$: C: 57.78/57.96; H: 5.65/5.67; N: 15.69/15.77; S: 5.14/5.16:

(9d. R=N-Methylpiperazine) : Yield-72 %, m.p.-115-116°C; IR(KBr)cm^{-1} : 3278[NH], 3014[Ar C-H], 1655[C=O, amide], 1640[C=N], 1471[Ar, C=C], 1250[S=O],1040[C-H in CH_3]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6)δppm: 12.68[1H, s, NH], 10.47[1H, s, NH], 8.70-7.19[4H, m, Ar-H], 7.74-7.69[4H, m, Ar-H], 6.7[1H, s, CH], 4.00[2H, s, CH_2], 3.15-2.36[8H, m, piperazine-H], 2.20[3H, s, CH_3], 2.12[3H, s, CH_3]; MS: m/z: 634(10%) , Anal. Calcd./found for $C_{31}H_{38}N_8O_5S$: C: 58.49/58.66; H: 6.00/6.03; N: 17.42/17.65; S: 5.03/5.05.

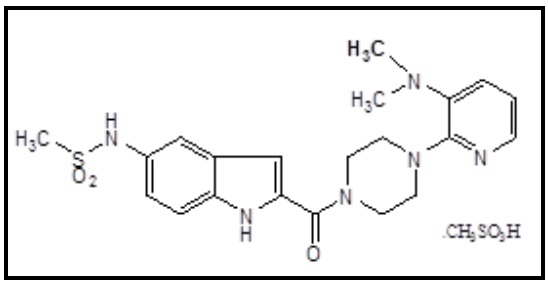
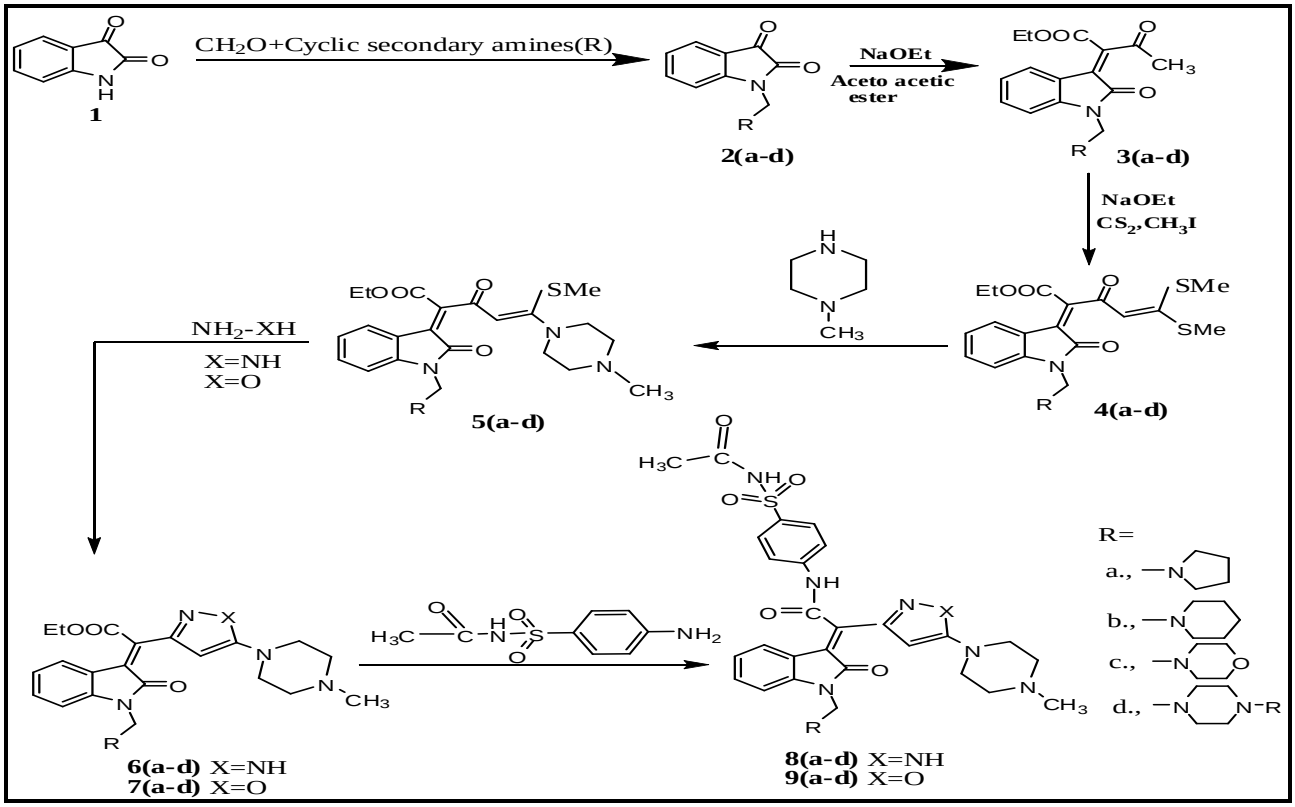


Figure No.1: Delavirdine mesylate



Scheme-1: The synthetic pathways that led to the incorporation of pyrazole and isoxazole

CONCLUSION

Present study has sought to address the problem arising in the application of the FDA approved anti-HIV agent 'Delavirdine' owing to its lower efficacy than other approved drugs. It stimulated us to take an initiative to explore the possibility of developing an improved analogue of delavirdine. The study in this direction proceeded on this assumption, that this problem could possibly be circumvented by amending its structure at different points. A programme was therefore, launched to replace its less anti-HIV active indole and pyridine nuclei, with the more anti-HIV prone isatin Mannich's bases and with the recently emerged anti-HIV motifs of isoxazole and pyrazole respectively. Besides this, the study also focused to alter the arrangements of the vital components of its molecule to allow it to emerge with altogether a new molecular setting. Biological screening results of the compounds were not available at the time when this manuscript was under preparation. The study will soon be published elsewhere.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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