ISSN (online): 2250-141X
Vol. 4 Issue 2, September 2014

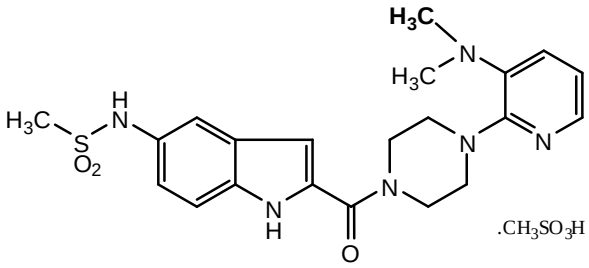
SYNTHESIS OF AN AMMENDED ANALOGUE OF DELAVIRDINE PART-I : A NOVEL DELAVIRDINE ANALOGUE DEVELOPED BY REPLACING ITS INDOLE NUCLEUS WITH ISATIN MANNICH'S BASE AND CONCURRENTLY REARRANGING ITS VITAL FRAGMENTS INTO AN ALTERNATE MOLECULAR SETTING

Rachna Mishra and Dharma Kishore*
Department of chemistry, Banasthali-University, Banasthali (Raj. 304022) India
e.mail: racshukla@rediffmail.com

Abstract-: *The efficacy of delavirdine is lower than other FDA approved NNRTIs, therefore, the US 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 of delavirdine, we amended its structure to develop a novel analogue by replacing its less active indole fragment with a more active anti-HIV prone isatin's Mannich bases. The molecular assemblage of delavirdine was concurrently also altered by rearranging its vital fragments to allow it to emerge with altogether a different molecular setting.*

Key words-: Delavirdine, anti-HIV activity, AIDS, isatin Mannich's base.

Introduction-: The quest to develop effective therapies for treatment of HIV infection has demonstrated that clinical benefits can be achieved with drugs that target the 'protease'[1] or 'reverse transcriptase'[2] enzymes. Reverse transcriptase (RT) is an attractive target for the development of new anti-AIDS drugs because of its vital role in suppressing the replication cycle of HIV[3]. In the last decade a number of anti-HIV agents have been discovered and have been introduced in the clinical practice .These include: Zidovudine (AZT), Delavirdine, Etravirine, Efavirenz[4,5], Nevirapine[6] etc. The therapeutic effectiveness of these inhibitors is limited by relatively rapid emergence of drug resistant mutants of HIV-1 strain. The advent of the highly active antiretroviral therapy [HAART] regimens comprising of three or four USFDA approved antiretroviral drugs in a cocktail has been highly encouraging as it suppressed the viral load on patients. But rapidly emerging multidrug resistant viral strains and severe adverse effects from long term HAART medication imposed restriction on its long use. To overcome the problems associated with the development of the drug resistant mutants of the virus, there is a continuing need to identify the improved agents within each class of RT inhibitors. Delavirdine (1) which has been approved recently by FDA for its application in the treatment of AIDS[7] has



Delavirdine mesylate

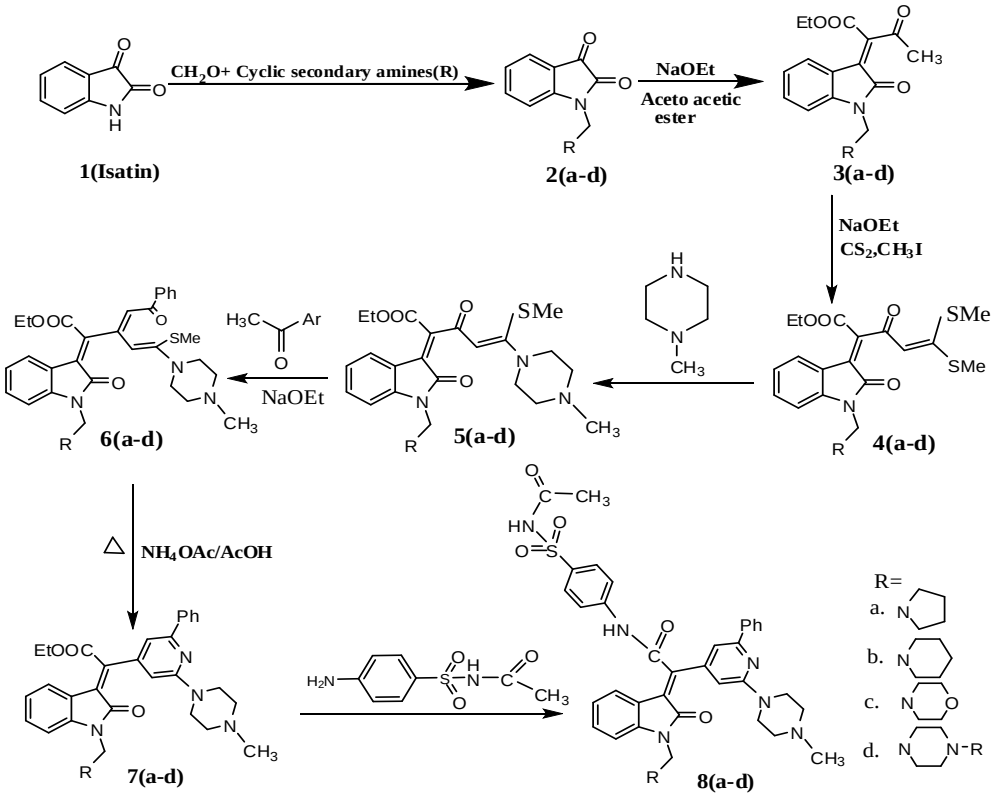
lower efficacy than other NNRTIs therefore U.S. Development of Health and Human Services has recommended its use not as a part of initial therapy but in combination with other drugs. To circumvent this therapeutic difficulty a search of new delavirdine analogues with enhanced activity was pursued. Herein, in this communication, we report the preliminary results of our study focused in the direction of developing novel substitutes to delavirdine. A perusal of the structure of delavirdine revealed that its molecule contained an indole, piperazine, pyridine nucleus and a sulphonamide motif in a distinct framework which allowed it to emerge as a potent anti-HIV agent. Recent reports on isatins have demonstrated that imino isatin Mannich's base analogues exhibited a very promising anti-HIV activity. Encouraged by the impressive anti-HIV profiles of isatin derivatives, we considered it of interest to explore the possibility of incorporating isatin in the amended structure of delavirdine through the

ISSN (online): 2250-141X
Vol. 4 Issue 2, September 2014

strategy outlined in **Scheme-1**. The aim behind undertaking this study was to bring together isatin (with its Mannich's base), along with pyridine, piperazine and sulphonamide moieties to allow it to become the part of the same molecule, on this premise that their presence in tandem in the same molecular framework could contribute significantly in providing an additive effect on the overall bioefficacy in the resulting molecules. It was envisioned that an easily accessible molecule that could fulfil this structural requirement was **8 (a-d)[Scheme-1].**

Chemistry-: An innovative protocol to the synthesis of compound **8 (a-d)** emerged on exploring the potential of the oxoketenedithioacetal functionality present in compound **4 (a-d) (Scheme-1)**. The thioacetal group of the oxoketenedithioacetal species was highly activated for nucleophilic attack. This feature of oxoketenedithioacetal function of **4 (a-d)**, was very elegantly exploited in the present work in the replacement of one of its thiomethyl ether group with N-methyl piperazine to give **5 (a-d)**[8]. Treatment of **5 (a-d)** with acetophenone under the conditions of Claisen-Schmidt condensation afforded **6(a-d)**.An examination of the structure of compound **6 (a-d)** revealed that it carried the basic structural requirement of the presence of a carbonyl group and enolic thioether function on 1 and 5 positions respectively in its molecule, to allow its elaboration to a pyridine ring through its reaction with NH_3 (produced from NH_4OAc in AcOH). The application of this strategy on **6 (a-d)** formed **7 (a-d) i**n good yield. The carboxylic acid ester group present in **7 (a-d)** reacted smoothly in subsequent step with the sulpha drug (sulphacetamide) to give **8 (a-d)**.

The most recorded method for the preparation of Mannich's bases of isatin was applied on **1** to give **2 (a-d).** The reaction of **2(a-d)** with ethylacetoacetate 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. One can easily discern the existence of the vital fragments of delavirdine in **8(a-d)** but incorporated in an altered setup in its molecule.



Scheme-1

ISSN (online): 2250-141X
Vol. 4 Issue 2, September 2014

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]

[2a. R=pyrrolidine]: 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 mass was recrystallized from a mixture of DMF and water to give 2a (3.22 g.): 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: Same procedure was applied for the preparation of 2(b-d).

[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: 68.68/68.83; 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 $C_{15}H_{17}N_2O_2$: C: 64.59/64.85; H: 6.58/6.61; N: 10.78/10.84:

Preparation of Ethyl 3-oxo-2-(2-oxo-1-(1-ylmethyl) indolin-3-ylidene) butanoate:[3a]

[3a. R=pyrrolidine]: A mixture of isatin (1.47 g., 0.01 mol.) and acetoacetic ester (1.30 g., 0.01 mol.) was dissolved in ethanol (20 ml) and piperidine (1ml) was added. The mixture was allowed to stand overnight at room temperature the yellow needles formed were recrystallized from ethanol to give 3a (2.38 g.): 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: Same procedure was applied for the preparation of 3(b-d).

[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:

ISSN (online): 2250-141X
Vol. 4 Issue 2, September 2014

[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 Ethyl 5, 5-bis (methylthio)-3-oxo-2-(2-oxo-1-(1-ylmethyl) indolin-3-ylidene) pent-4-enoate:[4a]

[4a. R=pyrrolidine]: 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). 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 , was washed with water, dried over sodium sulphate and the solvent was removed by distillation. The product obtained was purified by crystallization to give 4a (1.17 g.): 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: Same procedure was applied for the preparation of 4(b-d).

[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 Ethyl 5-(4-methylpiperazin-1-yl)-5-(methylthio)-3-oxo-2-(2-oxo-1-1-ylmethyl) indolin-3-ylidene) pent-4-enoate:[5a]

[5a. R=pyrrolidine]: 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: 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: Same procedure was applied for the preparation of 5(b-d).

ISSN (online): 2250-141X
Vol. 4 Issue 2, September 2014

[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],1331[C-O], 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 Ethyl 3-2-(4-methylpiperazin-1yl)-2-(methylthio)vinyl)-5-oxo-2 - (2-oxo-1-(pyrrolidi-1-ylmethyl)indolin-3-ylidene)-5-phenylpent-3-enoate :[6a]

[6a. R= pyrrolidine]: A mixture of 5a (2.49 g., 0.05 mol.) and substituted acetophenone (0.60 g., 0.05 mol.) was taken in ethanol (25 ml) and piperidine (1 ml) was added. The mixture was allowed to stand overnight at room temperature. The yellow needles formed were recrystallized from ethanol to give 6a (2.12 g.)**.** Yield- 73%, m.p. 145-146 °C; IR(KBr)cm^{-1}: 3014[CH-Ar],1634 [C=O, amide], 612[C-S], 1405[C-N, indole]; ^{1}HNMR (400 MHz, $CDCl_3$+DMSO-d_6) δppm: 8.74-7.14[4H, m, ArH], 7.89-7.64[10H, m, ArH], 7.17[1H, s, CH],6.08[1H, s, CH], 4.20[2H, q, CH_2], 4.03[2H, s, CH_2],2.79-2.13[8H, m, piperazin-H], 2.51-1.68[8H, m, pyrrolidin-H], 2.43[3H, s, CH_3], 2.26[3H, s, CH_3], 1.29[3H, s, CH_3] ; MS: m/z: 600(19%) , Anal. Calcd./found for $C_{34}H_{40}N_4O_4S$: C: 67.90/67.97; H: 6.67/6.71; N: 9.28/9.33; S: 5.31/5.34: Same procedure was applied in the preparation of 6(b-d).

[6b. R= piperidine]: Yield- 69%,m.p. 125-127 °C; IR(KBr)$cm^{-1:}$: 3010[CH-Ar], 1642 [C=O, amide], 643[C-S], 1408[C-N, indole]; ^{1}HNMR (400 MHz, $CDCl_3$+DMSO-d_6) δppm: 8.74-7.14[4H, m, ArH], 7.89-7.64[10H, m, ArH], 7.17[1H, s, CH],6.08[1H, s, CH], 4.20[2H, q, CH_2], 4.03[2H, s, CH_2], 2.79-2.13[8H, m, piperazin-H], 2.45-1.53[10H, m, piperidin-H], 2.43[3H, s, CH_3], 2.26[3H, s, CH_3], 1.29[3H, s, CH_3] ; MS: m/z: 614(25%) , Anal. Calcd./found for $C_{35}H_{42}N_4O_4S$: C: 67.94/68.38; H: 6.85/6.89; N: 9.06/9.11; S: 5.19/5.22 :

[6c. R= morpholine]: Yield-67 %,m.p. 122-124 °C; IR(KBr)cm^{-1}: 3045[CH-Ar], 1632 [C=O, amide], 618[C-S], 1400[C-N, indole]; ^{1}HNMR(400 MHz, $CDCl_3$+DMSO-d_6) δppm: 8.74-7.14[4H, m, ArH], 7.89-7.64[10H, m, ArH], 7.17[1H, s, CH],6.08[1H, s, CH], 4.20[2H, q, CH_2], 4.03[2H, s, CH_2], 2.79-2.13[8H, m, piperazin-H], 3.65-2.50[8H, m, morpholin-H], 2.43[3H, s, CH_3], 2.26[3H, s, CH_3], 1.29[3H, s, CH_3] ; MS: m/z: 616(21%) , Anal. Calcd./found for $C_{34}H_{40}N_4O_5S$: C: 65.99/66.21; H: 6.50/6.54; N: 9.03/9.08; S: 5.17/5.20 :

[6d. R= N-methyl piperazine]: Yield- 74%,m.p. 129-131 °C; IR(KBr)cm^{-1}: 3051[CH-Ar], 1639 [C=O, amide], 634[C-S], 1410[C-N, indole]; ^{1}HNMR (400 MHz, $CDCl_3$+DMSO-d_6) δppm: 8.74-7.14[4H, m, ArH], 7.89-7.64[10H, m, ArH], 7.17[1H, s, CH],6.08[1H, s, CH], 4.20[2H, q, CH_2], 4.03[2H, s, CH_2], 2.79-2.13[8H, m, piperazin-H], 2.35[8H, m, piperazin-H], 2.43[3H, s, CH_3], 2.26[3H, s, CH_3], 1.29[3H, s, CH_3] ; MS: m/z: 629(18%) , Anal. Calcd./found for $C_{35}H_{43}N_5O_4S$: C: 66.41/66.75; H: 6.84/6.88; N: 11.06/11.12; S: 5.06/5.09 :

ISSN (online): 2250-141X
Vol. 4 Issue 2, September 2014

Preparation of Ethyl 2-(2-(4-methylpiperazin-1-yl)-6-phenylpyridin-4-yl)-2-(2-oxo-1-(pyrrolidin-1-ylmethyl)indolin-3-ylidene)acetate :[7a]

[7a. R= pyrrolidine]: Compound 6a (1.20 g., 002 mol) taken in acetic acid (5 ml) and heated with ammonium acetate (0.15 ml, .002 mol.) in low temperature and the resulting precipitate was recrystallized from ethanol to give 7a (0.98 g.). Yield- 70 %, m.p 146-147. °C; IR(KBr)cm^{-1}: 3017 [CH-Ar], 1716[C=O, ester], 1625[C=O, amide],1520 [C=N, pyridine] ; ^{1}HNMR (400 MHz, $CDCl_3$+DMSO-d_6) δppm: 8.74-7.14[8H, m, ArH], 8.30-7.47[10H, m, ArH], 6.47[1H, s, CH],6.43[1H, s, CH], 4.20[2H, q, CH_3], 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] ; MS: m/z: 551(24%) , Anal. Calcd./found for $C_{33}H_{37}N_5O_3$: C: 71.50/71.84; H: 6.72/6.76; N: 12.62/12.69: Same procedure was applied in the preparation of 7(b-d).

[7b. R= piperidine]: Yield- 68%, m.p. 115-117 °C; IR(KBr)cm^{-1}: 3034[CH-Ar], 1717 [C=O, ester], 1635[C=O, amide],1530 [C=N, pyridine] ; ^{1}HNMR (400 MHz, $CDCl_3$+DMSO-d_6) δppm: 8.74-7.14[8H, m, ArH], 8.30-7.47[10H, m, ArH], 6.47[1H, s, CH],6.43[1H, s, CH], 4.20[2H, q, CH_3], 4.03[2H, s, CH_2], 3.62-2.36[8H, m, piperazine-H], 2.45-1.53[10H, m, Piperidine-H], 2.26[3H, s, CH_3] ; MS: m/z: 565(17%) , Anal. Calcd./found for $C_{34}H_{39}N_5O_3$: C: 72.04/72.19; H: 6.92/6.95; N: 12.32/12.38:

[7c. R= morpholine]: Yield- 72%, m.p. 125-126 °C; IR(KBr)cm^{-1}:3022 [CH-Ar],1712[C=O, ester], 1632[C=O, amide], 1590[C=N, pyridine], [C-O-C]; ^{1}HNMR (400 MHz, $CDCl_3$+DMSO-d_6) δppm: 8.74-7.14[8H, m, ArH], 8.30-7.47[10H, m, ArH], 6.47[1H, s, CH],6.43[1H, s, CH], 4.20[2H, q, CH_3], 4.03[2H, s, CH_2], 3.62-2.36[8H, m, piperazine-H], 3.65-2.50[8H, m, morpholine-H], 2.26[3H, s, CH_3] ; MS: m/z: 567(24%) , Anal. Calcd./found for $C_{33}H_{37}N_5O_4$: C: 69.58/69.82; H:6.53/6.57 ; N:12.29/12.34 :

[7d. R= N-methyl piperazine]: Yield- 70%, m.p.124-126 °C; IR(KBr)cm^{-1}:3041 [CH-Ar], 1710[C=O, ester], 1645[C=O, amide],1576[C=N, pyridine]; ^{1}HNMR (400 MHz, $CDCl_3$+DMSO-d_6) δppm: 8.74-7.14[8H, m, ArH], 8.30-7.47[10H, m, ArH], 6.47[1H, s, CH],6.43[1H, s, CH], 4.20[2H, q, CH_3], 4.03[2H, s, CH_2], 3.62-2.36[8H, m, piperazine-H],2.35[8H, m, piperazine-H], 2.26[3H, s, CH_3] ; MS: m/z: 580(20%) , Anal. Calcd./found for $C_{34}H_{40}N_6O_3$: C: 70.08/70.32; H: 6.90/6.94 ; N: 14.40/14.47 :

Preparation of N-(4-(N-acetylsulfamoyl)phenyl)-2-(2-(4-methylpiperazin-1-yl)-6-phenylpyridin-4-yl)-2-(2-oxo-1-(pyrrolidin-1-ylmethyl)indolin-3-ylidene)acetamide :[8a]

[8a. R= pyrrolidine]: A mixture of 7a (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.): Yield- 70 %,m.p. 154-155 °C; IR(KBr)cm^{-1}: 3422, 3331[NH], 1681, 1673[C=O, amide],1472[C=N], 1335[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, ArH], 8.30-7.32[4H, m, ArH], 4.03[2H, s, CH_2], 2.51-1.68[8H, m, pyrrolidine-H], 2.26[3H, s, CH_3], 2.04[3H, s, CH_3] ; MS: m/z: 719.85 (10%) , Anal. Calcd./found for $C_{39}H_{41}N_7O_5S$: C: 64.89/65.07 ; H: 5.71/5.74 ; N: 13.59/13.62 ; S: 4.43/4.45 : Same procedure was applied for the preparation of 8(b-d).

[8b. R= piperidine]: Yield- 69 %,m.p 120-121. °C; IR(KBr)cm^{-1}: 3462, 3355[NH], 1666, 1642[C=O, amide],1460[C=N], 1320[S=O]; ^{1}HNMR (400 MHz, $CDCl_3$+DMSO-d_6) δppm: 12.52[1H, s, NH], 10.22[1H, s, NH], 8.50-7.02[4H, m, ArH], 8.35-7.40[4H, m, ArH], 7.80[4H, m, ArH], 2.45-1.54[10H, m, piperidin-H], 4.00[2H, s, CH_2], 3.86-3.26.[8H, m, piperazine-H], 2.54[3H, s, CH_3], 2.08[3H, s, CH_3] ; MS: 733.88 m/z: (18%) , Anal. Calcd./found for $C_{40}H_{43}N_7O_5S$: C: 65.35/65.46 ; H: 5.90/5.91 ; N: 13.24/13.30 ; S: 4.34/4.37 :

[8c. R= morpholine]: Yield- 71 %,m.p. 145-147 °C; IR(KBr)cm^{-1}: 3470, 3379[NH], 1686, 1640[C=O, amide],1469[C=N], 1245[C-O-C], 1322[S=O] ; ^{1}HNMR (400 MHz, $CDCl_3$+DMSO-

ISSN (online): 2250-141X
Vol. 4 Issue 2, September 2014

d_6) δppm: 12.45[1H, s, NH], 10.30[1H, s, NH], 8.90-7.01[4H, m, ArH], 8.30-7.67[4H, m, ArH], 7.44[4H, m, ArH], 2.50-3.65[8H, m, morpholin-H], 4.01[2H, s, CH_2], 3.82-3.21.[8H, m, piperazine-H], 2.50[3H, s, CH_3], 2.04[3H, s, CH_3] ; MS: m/z: 735.85(12%) , Anal. Calcd. /found for $C_{39}H_{41}N_7O_6S$: C: 63.42/63.66; H: 5.59/5.62; N:13.29/13.32; S: 4.33/4.36:

[8d. R= N-methyl piperazine]: Yield- 73%,m.p. 160-162 °C; IR(KBr)cm^{-1}: 3455, 3332[NH], 1656,1648[C=O, amide], 1450[C=N], 1322[S=O] ; ^{1}HNMR (400 MHz, $CDCl_3$+DMSO-d_6)
δppm: 12.57[1H, s, NH], 10.42[1H, s, NH], 8.69-7.11[4H, m, ArH], 8.27-7.30[4H, m, ArH], 4.00[2H, s, CH_2], 2.26[3H, s, CH_3], 2.35[8H, m, piperazine-H] 2.01[3H, s, CH_3], 2.26[3H, s, CH_3]; MS: m/z: 748.89 (15%) , Anal. Calcd./found for $C_{40}H_{44}N_8O_5S$: C: 63.94/64.15; H: 5.89/5.92 ; N: 14.90/14.96 ; S: 4.21/4.28:

Results and Discussion: Oxoketene dithioacetals and oxoketene N,S-aminals are useful synthons that have been extensively employed in the literature in the preparation of five, six and seven membered heterocyclic rings from its reaction with bidentate nucleophiles.Application of this strategy on oxoketene dithioacetals **4(a-d)** and N,S-aminal derivatives **5(a-d)** with acetophenone (shown in **scheme-1)** resulted 2-phenyl pyridine substituted derivatives **7(a-d)** in high yield and purity. The structures of these compounds were established on the basis of their microanalysis **IR, ^{1}HNMR, and MS** spectral data. The IR spectrum of 2 and 3 showed the presence of a strong absorption band near 1700 cm^{-1} for [C=O] group. The formation of corresponding oxoketene dithioacetals **4** and **5** was confirmed by the appearance of the band near 600 cm^{-1} for [C-S].The disappearance of the C-S absorption band and appearance of [C=N of pyridine] in IR spectrum in compound **7** provided a strong evidence in favour of the formation of **7(a-d).** The IR spectrum of **8(a-d)** showed the presence of a strong absorption band near 1325 cm^{-1} for [S=O] group and the conversion of [C=O, ester] with [C=O, amide] provided a strong evidence in the favour of formation of **8(a-d).** The appearance of the [M^+] peak corresponding to their molecular mass in MS spectrum substantiated further the formation of the compounds.

Conclusion-: The study aimed to address the problem associated with the application of the FDA approved anti-HIV agent Delavirdine owing to its lower efficacy than other approved drugs. To overcome this difficulty a programme was launched to explore the possibility of developing an improved analogue of delavirdine by amending its structure at different points.
The first amended structure reported in this communication resulted by replacing its less anti-HIV active indole nucleus with the more anti-HIV prone isatin's Mannich's bases. Besides this, the study also focused towards altering the arrangement of the vital components of delavirdine to allow this molecule to
emerge with altogether a different molecular setting. The biological potential of this amended structure is under study.

Acknowledgement-: The authors thank to the Director SAIF, Punjab University Chandigarh (India) for providing spectral and analytical data of compounds and to the Department of Science and Technology (DST), New Delhi (India) for providing the financial assistance to 'Banasthali Center for Education and Research in Basic Sciences' under their CURIE (Consolidation of University Research for Innovation and Excellence in Women Universities) Programme.

References-:

I. Paul A. J. Jansen, Paul J. Lewi, Eddy Arnold, Frits Daeyaert, Mare de Jonge, Jan Heers, Luc Koymans, Maarten Vinkers, Jerome Guillemont, Elisabeth Pasquier, Mike Kukla, Don Ludovici, Koen Andries, Marie-Pierre de Bethune, Rudi Pauwels, Kalyan Das, Art D. Clark, Jr., Yulia Voloik Frankel, Stephan H. Hughes, Bart Meder, Fons De Knaep, Hilde Bohets, Fred De Clerk, Ann Lampo, Peter Williams and Paul Stoffels, In Search of a Novel Anti-HIV Drug: Multidisciplinary Coordination in the Discovery of 4-[[4-[[4-(1E)-2-Cyanoetheynyl]-2,6-Dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile (R278474, Rilpivirine), *J.Med. Chem*., 2005, 48, 1901-1909.

ISSN (online): 2250-141X
Vol. 4 Issue 2, September 2014

Transcriptase -1-tricyclic pyridobenzo and Dipyridodiazepinone *J. Med.Chem*.**1991**, 34, 2231-2241.

II. Andreas Blum, Jark Bottcher, Andreas Heine, Gerhard Klebe, and Wibke E. Diederich, Structure-Guided Design of C_2-Symmetric HIV-1 Protease Inhibitors Based on a pyrrolidine Scaffolds, *J.Med.Chem*., 2005, 51, 2078-2087.

III. Mertuzzi. V.J.; Hargrave, K.D.; Labadia, M.; Grozinger, K.; Skoog, M.; Wu, Jc.; Shih, C.K.; Eckner, K.; Hottox, S.; Adams, J.; Rosenthal, A.S.; Fannes, R.; Eckner. R.J.; Koup, R.A.; and Sullivan, J.L. Inhibition of HIV-1 Replication by a Non – nucleoside Reverse Transcriptase Inhibitor. *Science* **1990**, 250, 1411-1413.

IV. Ren, J.; Milton, J.; Weaver, K.L.; Short, S.A.; Stuart, D.I. and Stammers, D.K.; Structural basis for the resilience of efavirenz (DMP-266) to drug resistance mutations in HIV-1 Reverse Transcriptase. *Struct. Fold. Des*. **2000,** 8, 1089-1094.

V. Lindberg, J.; Sigurdsson, S.; Lowgren, S.; Andersson, H.O.; Sahlberg, C.; Nareen, R.; Fridborg, K; Zhang, H. and Unge, T.; Structural basis for the inhibitory efficacy of efavirenz (DMP-266), MSC194 and PNU142721 towards the HIV-1 RT K103N mutant; *Eur. J. Biochem*. **2002**, 269, 1670-1677.

VI. Hargrave K.D.; Proudfoot, J.R.; Grozinger .K.G. Kapadia. S.R.; Patel, U.R.; Fuchs, V.U.; Mauldin, S.C.; Vitous. J.; Behnke M.L. Klunder, J.M.; Pal. K. Skiles, J.W. Mc, Neil , D.W.; Rose J.M.; Chow, Gc.; Skoog, M.T.; Wu, J.C. Schmidt, G. Engel W.; Eberlein, W.G.; Saboe, T.D. ; Camphell. S.J.; Rosenthal, AS.; and Adams, J. Novel Non-nucleoside Inhibitors of HIV-1 Reverse

VII. Romero, D.L.; Olmsted, R.A.; Poel, T.J.; Morge , R.A.; Biles, C.; Keiser, B.J.; Kopta, L.A.; Friis. J.M.; Hosley, J.D.; Stefanski, K.J., Wishka, D.G.; Evans. D.B, Morris, j. Stehle, R.G.; Sharma, S.K.; Yagi, Y.; Voorman. R.L. Adams, W.J. Tarpley, W.G. and Thomas R.C. Targeting delaviradine/ateviradine Resistant HIV-1: Identification of (alkyl aminopiperadine containing bis-heteroaryl) piperazines as Broad spectrum. HIV-1 Reverse Transcriptase Inhibitors *J. Med. Chem*. **1996**. 39, 3769-3789.

VIII. Rao, H.S.P.; and Sivakumar, S.; Aroylketene dithioacetal chemistry: Facile synthesis of 4-aroyl-3-methylsulfanyl-2-tosylpyrroles from aroylketene dithioacetals and TosMIC; *J. Org. Chem.* **2007,** 3 ,31.