*Available online www.jocpr.com*

**Journal of Chemical and Pharmaceutical Research, 2014, 6(11):753-756**

**Research Article**

**ISSN : 0975-7384**
**CODEN(USA) : JCPRC5**

# Synthesis of enone ester by conventional method for their possible use in anti-HIV chemotherapy

**Rachna Mishra**

*Banasthali-University, Rajasthan, India*

---

**ABSTRACT**

*The efficacy of delavirdine was found to be lower than other FDA approved NNRTIs, therefore, the US department of health and Human Services recommended its use not as a part of initial therapy but in combination with other drugs. The molecular assemblage of delavirdine was concurrently also altered by rearranging its vital fragments into altogether a different molecular setting and by synthesized enone ester formation of new delavirdine analogue could be possible.*

**Key words:** Anti-HIV activity, AIDS, Delavirdine, Isatin Mannich's base, Enone ester

---

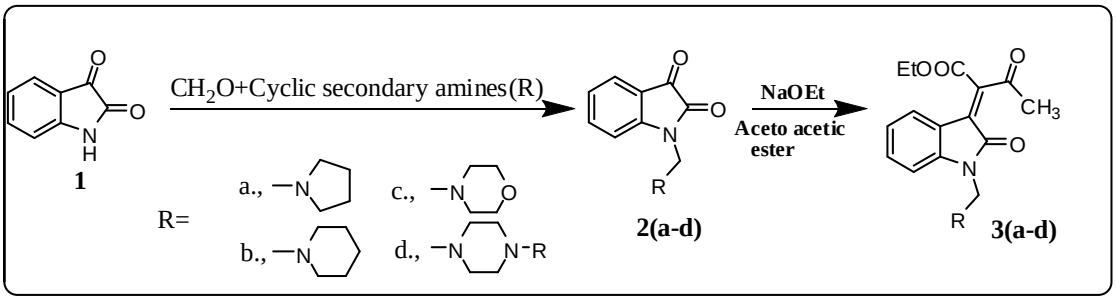
## INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is the result of the infection caused by the HIV-1**[1]**. The development of potential agents to combat the killer disease the 'AIDS', which is the greatest health threat for the human suffering and tragedy of this century is one of the highest aspirations of all AIDS research programmes. 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' or reverse 'transcriptase' enzymes. Reverse Transcriptase is an attractive target for the development of new anti-AIDS drugs because of its vital role in suppressing the replication cycle of HIV. Reverse transcriptase can be subdivided into NRTI (nucleoside reverse transcriptase inhibitors) and NNRTIS (Non nucleoside reverse transcriptase inhibitors). Inhibition of HIV-1 reverse transcriptase by nucleoside such as AZT (Zidovudine)**[2]**, 3tc (Lamivudine)[2], DDI (di-dioxyinosine)**[2]**, and D4T (Stavudine)**[2]** [fig.1.1] have emerged as a proven therapy for delaying the progression to AIDS**[3]**.

A major thrust of more recent research targets non-nucleoside HIV-1 reverse transcriptase inhibitors (NNRTIs) from this it became soon apparent that a viable treatment of AIDS would involve co-administration of drugs which inhibits RT via disparate mechanisms**[3]**. Efforts along these lines led to the identification of two clinical candidates of the bis-(heteroaryl) piperazine (BHAP) class of NNRTIs, atevirdine mesylate**[4]** and delavirdine mesylate**[5]**.The hypothesis for the successful treatment of AIDS by co-administration of drugs provided an optimism that sequential treatment with delavirdine followed by compounds with enhanced activity against delavirdine-resistant virus, might result in an effective anti-HIV therapy**[6-7]**. This invoked a global attention to embark upon the programs to identify compounds complimentary to delavirdine**[3, 8-9]**. These efforts resulted in the discovery of certain delavirdine analogues, namely those of the(alkylamino) piperidine (AAP-BHAP) variety, (Delavirdine **(1.001)** /Atevirdine**(1.002)**) which possessed better activity than delavirdine against the P236L mutant enzyme.

The incidence of bacterial infections has increased dramatically in recent years. The widespread use of antibacterial drugs and their resistance against bacterial infections has led to serious health hazards. The resistance of wide spectrum antibacterial agents has prompted discovery and modification towards new antifungal and antibacterial drugs. Enone derivatives have remarkable many biological, pharmaceutical and therapeutic activities. Here in this work enone ester synthesized as an intermediate compound having good biological activity.

**Chemistry:**
The synthetic pathways that led to the incorporation of enone ester has been outlined in scheme-**1.** The synthesis in its first step propelled forward with the preparation of Mannich bases **2(a-d)** of isatin, from **1.** Subsequent treatment of **2(a-d)** with ethyl acetoacetate afforded the enone ester **3(a-d).** The evaluation of the anti-HIV activity of **3(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. Antibacterial and anti-fungal activity (anti-microbial activity) were carried out by cup-plate agar diffusion method. The bacterial strains studied are identified strains.

**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:

**Table-1**

| S. No. | C. No. | Conc. In (µg/ml) | *B.cerus* | | *Pseudomonas* | | *Macrophomina* | | *Tricoderma* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Zone of inhibition(mm) | % Activity compared to the standard | Zone of inhibition (mm) | % Activity compared to the standard | Zone of inhibition (mm) | % Activity compared to the standard | Zone of inhibition (mm) | % Activity compared to the standard |
| 1. | 3a. | 300<br>200<br>100 | 9.90<br>9.80<br>9.31 | 58.00<br>57.00<br>54.76 | 9.01<br>8.59<br>7.76 | 60.06<br>57.26<br>51.73 | 11.12<br>09.02<br>08.03 | 46.33<br>37.58<br>33.45 | 9.11<br>8.91<br>7.10 | 47.94<br>46.89<br>37.36 |
| 2. | 3b. | 300<br>200<br>100 | 9.54<br>9.43<br>8.82 | 56.11<br>55.47<br>51.88 | 8.26<br>7.38<br>6.26 | 55.06<br>49.20<br>41.73 | 10.12<br>10.00<br>08.03 | 42.16<br>41.66<br>33.45 | 9.18<br>8.01<br>7.12 | 48.31<br>42.15<br>37.47 |
| 3. | 3c. | 300<br>200<br>100 | 9.71<br>9.70<br>9.33 | 57.11<br>57.05<br>54.88 | 8.86<br>8.66<br>8.24 | 59.06<br>57.73<br>54.93 | 10.12<br>10.02<br>08.07 | 42.16<br>41.75<br>33.62 | 9.11<br>8.00<br>7.09 | 47.94<br>42.10<br>37.31 |
| 4. | 3d. | 300<br>200<br>100 | 9.65<br>9.31<br>9.11 | 56.76<br>54.76<br>53.58 | 7.33<br>6.82<br>6.52 | 48.86<br>45.46<br>43.46 | 11.76<br>10.14<br>10.12 | 49.00<br>42.25<br>42.16 | 9.10<br>8.15<br>7.14 | 47.89<br>42.89<br>37.57 |
| ***Streptomycin*** | | 300 | 17<br>17<br>17 | 100.0<br>100.0<br>100.0 | 15<br>15<br>15 | 100.0<br>100.0<br>100.0 | | | - | - |
| ***Fluconazole*** | | 300 | - | - | - | - | 24 | 100.0<br>100.0<br>100.0 | 19 | 100.0<br>100.0<br>100.0 |

**Biological Evaluation:**
Newly synthesized compound 3(a-d) have been tested their antibacterial activity against gram positive and gram negative bacteria Pseudomoas aeruginosa and Bassilus cerus by the help of borer in agar medium and filled with 0.04ml (40µg) solution of sample in DMF and Streptomycin were used as a reference compound. The compound 3a, 3c, and 3d were shown significant activities and compound 3b have shown moderate activity. The plates were incubated at 37o C for 24 hours and the control was also maintained with 0.04 ml of DMF in a similar manner and the zones of inhibition of the bacterial growth were measured in millimeter and are recorded data in table-1.

**Anti Fungal activity:**
The same compounds were tested for their antifungal activity against Macrophomina phaseolina and Trichoderma candidum. The compound 3(a-d) were shown significant activities.

## RESULTS AND DISCUSSION

These synthesized compound having good biological activity and play a valuable role as a intermediate for various type of key intermediate compound The synthesis in its first step propelled forward with the preparation of Mannich bases **2(a-d)** of isatin, from **1.** Subsequent treatment of **2(a-d)** with ethyl acetoacetate afforded the enone ester **3(a-d).** The evaluation of the anti-HIV activity of **3(a-d)** is under study.

## CONCLUSION

Present study has sought to address the convenient preparation methods of the enone ester. It stimulated us to take an initiative to explore the possibility of developing an improved analogue of delavirdine.

**Acknowledgement**
The authors are thankful to Director SAIF, Punjab University Chandigarh (India) for providing spectral and analytical data of the compounds and to Department of Science and Technology New Delhi (India) for granting project to “Banasthali Centre of Education for Research in Basic Sciences” under their CURIE (Consolidation of University Research for Innovation and Excellence in Women Universities) programme.

## REFERENCES

[1] JE Kalplan; H Masur; HW Jaffe and KK Halmes; *J. Am. Med*. Assoc. **1997**, 278, 337-338.
[2] Scrip. US Panel Clears GW’s Epivir and Roche’s Invirase; Nov. 14, **1995**; P 22.
[3] DL Romero; RA Olmsted; TJ Poel; RA Morge; C Biles; BJ Keiser; LA Kopta; JM Friis; JD Hosley; KJ Stefanski; DG Wishka; DB Evans; j Morris; RG Stehle; SK Sharma; Y Yagi; RL Voorman; WJ Adams; WG Tarpley and RC Thomas; *J. Med. Chem*. **1996**. 39, 3769-3789.
[4] DL Romero; *Drugs Future* **1994**, 19(1), 9-12.
[5] DL Romero; *Drugs Future* **1994**, 19(3), 238-242.
[6] (a) E Clercq; *AIDS* 1994, 8(7), 1020-1021(b) *Med. Res. Rev*. **1996**, 16,125.
[7] TJ Dueweke; T Pushkarskaya; SM Poppe; SM Swaney, JQ Zhao; ISY Chen.; M Sttevenson.; and WGA Tarpley; *Proc. Natl, Acad. Sci. U.S.A.* **1993**, 90, 4813-1717.
[8] DG Wishka; DR Graber; L A Kopta; RA Olmsted; JM Friis; LA Dolak; Bj Keiser ; Y Yagi; J Azhwarsamy ; ST Schlachter; MJ Murphy ; GJ Cleck; RA Nugent; SM Pappe; SM Swaney; WHF Watt; WL White; TJ Poel; RC Thomas; RL Voorman; KJ Stefanski; RG Stehle; WG Tarpley; and J Morris; PNU-142721, *J .Med. Chem*.**1998**,41,1357-1360.
[9] RA Nugem; ST Schachter; MJ Murphy; GJ Cleek; TJ Poel; DG Wishka; DR Graber; Y Yagi; BJ Keiser; RA Almsted; LA Kopta; SM Swaney; SM Morris; WG Tarpley and RC Thomas ; *J. Med. Chem*. **1998**, 41, 3793-3803.