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A SIMPLE AND NEW METHOD FOR THE SYNTHESIS OF 1,5-BENZODIAZEPINE AND ITS DERIVATIVES

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ABSTRACT

Delavirdine has been recently approved by FDA for its application in the treatment of AIDS. As its efficacy has been lower than other approved NNRTIs, therefore, its use was not recommended as a part of initial therapy but in combination of other drugs. To circumvent this therapeutic difficulty, a search of new delavirdine analogue with enhanced activity was pursued. A survey on the other recently FDA approved NNRTs revealed that a pyrimidine derivative 'etravirine' has emerged as one of the most potent and powerful anti-HIV agent. This discovery provided optimism that a better analogue of delavirdine could perhaps be developed by substituting pyrimidine nucleus in its molecule. We report in this communication, the preliminary results of the study focused in the direction of designing an amended analogue of delavirdine, in which the pyridine part of the delavirdine was replaced by pyrimidine nucleus.

Key words: Delavirdine, AIDS, NNRTIs, Etravirine, HAART.

INTRODUCTION

A variety of different compounds have been developed for the treatment of HIV, including nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PI), a viral fusion inhibitor (FI), a CCR-5 co-receptor inhibitor, and a viral integrase (IN) inhibitor[1,2].

However, an increasing number of patients with HIV infection /AIDS can no longer use such drugs as a result of drug resistance and serious adverse effects[3-5]. Therefore, it is essential to develop novel anti–HIV drugs targeting the suppression of drug resistant mutants of the virus. Inhibition of HIV-1 (human immunodeficiency virus type-1) reverse transcriptase by nucleoside such as AZT (Zidovudine), 3tc (lamivudine), D4T (Stavudine), DDI (di-dioxyinosine), and delavirdine have emerged as a proven therapy for delaying the

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progression to AIDS. Human immunodeficiency virus (HIV) belongs to the retrovirade family and causes the acquired immunodeficiency syndrome (AIDS)[1]. However, resistance to anti-HIV compounds develops rapidly, sometimes within a few days of initiating the treatment[6,7]. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are allosteric and non-competitive modulators of RT, one of the key enzyme in the life cycle of HIV-1[8,9]. The development of chemotherapeutically useful material from 'privileged heterocyclic scaffolds[10] is an emerging subject in medicinal chemistry. Recently, pyrimidine based drugs have been widely studied as this nucleus has also been recognized to belong to the class of privileged ligands for a number of functionally and structurally discrete biological receptors.

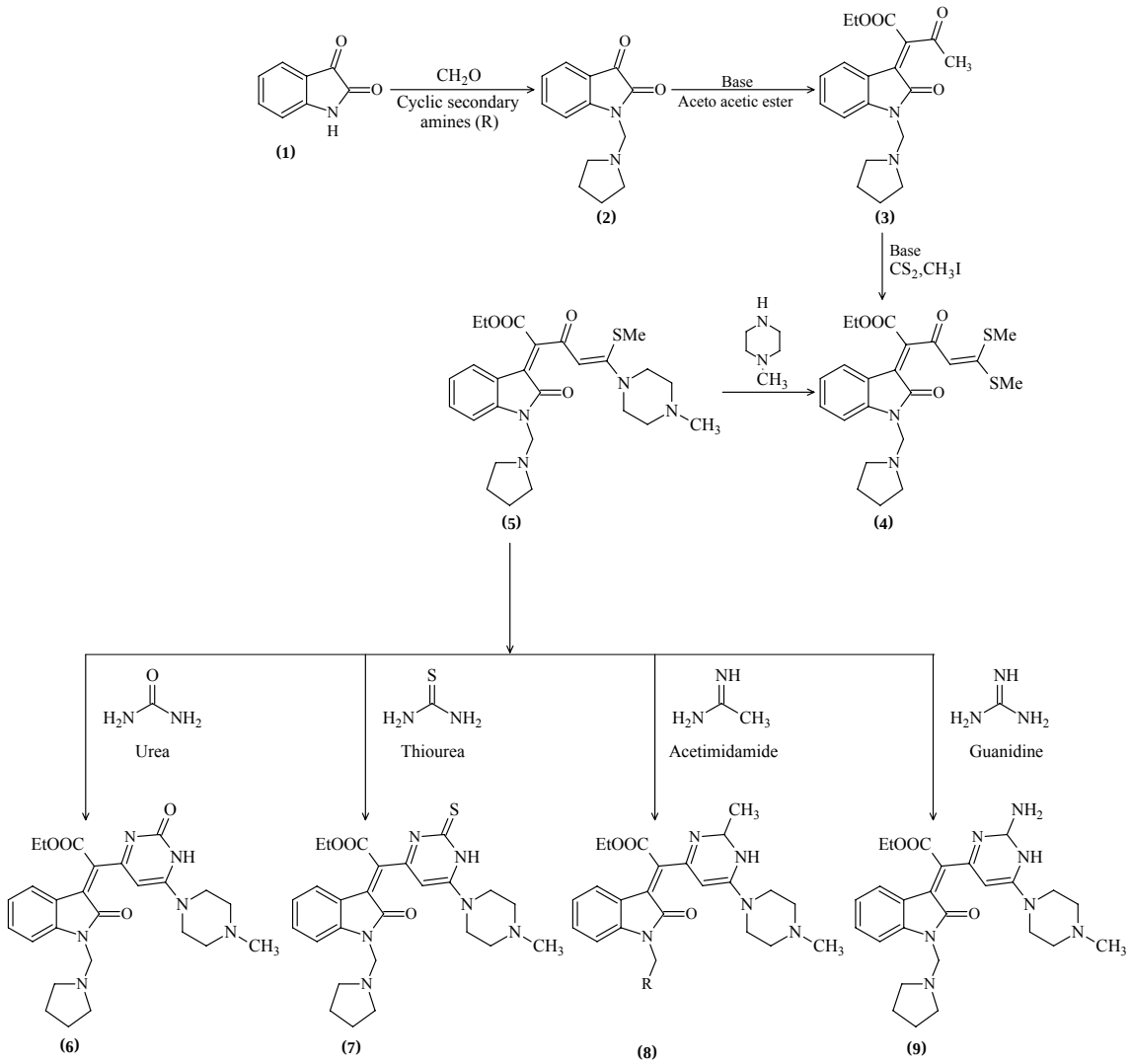
Non-nucleoside inhibitors of reverse transcriptase (NNRTIs) are part of certain multidrug regimens used in the treatment of HIV infection[11]. Three virus specific proteins, reverse transcriptase (RT), protease, and gp 41 are important targets for currently approved anti-HIV drugs. Additionally, a CCR5 virus co-receptor antagonist and an HIV intergase inhibitor have recently been approved for treatment of HIV infection[12].

The advent of FDA approved delavirdine molecule has been hailed as a major step forward in the battle against the AIDS[13].

One can easily discern the presence of two bioactive phrmacophores viz; the indole and the pyridine nucleus in its molecule has been identified recently as an important heterocyclic scaffolds exhibiting impressive anti-HIV activity. A pyrimidine nucleus, which has been known to belong to a class of privileged template, whose numerous derivatives have been identified for their selective activities against a diverse array of biological targets.

Chemistry

The synthetic pathways that led to the incorporation of pyrimidine nucleus has been outlined in **Scheme 1**. This strategy envisaged the formation of compound **(5)** from the key intermediate **(4)**, which in turn was realized in three steps from isatin **(1)** following the procedure reported for such reactions on other related substrates. The synthesis in its first step started with the preparation of Mannich bases **(2)** of isatin from **(1)**, Subsequent **(2)** on treatment with ethyl acetoacetate afforded the enone ester **(3)** from which **(4)** was realized, on the reaction with CS_2 followed by treatment with CH_3I, in the presence of NaOEt. Oxoketene dithioacetals and oxoketene N, S-aminals have been known to provide an easy access to the heterocyclic skeleton on their reaction with bidenate nucleophiles. In the present work, the chemistry of oxoketene N, S-aminal was explored to incorporate the pyrimidine ring making use of the aminal **(5)**, whose treatment with urea, thiourea, acetamidine and guanidine very smoothly provided a very convenient synthetic entry to the pyrimidine scaffolds in **(6-9)**, respectively.



Scheme 1

EXPERIMENTAL

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}H NMR spectra were taken in $CDCl_3$ + DMSO-d_6 on BRUKER AVANCE II 400 NMR Spectrometer using TMS as an internal standard and Mass spectra were recorded on a Joel SX-102 (EI/CI/FAB) mass spectrometer.

General procedure of the formation of compound (2-9)

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

To a suspension of indoline-2, 3-dione (2.94 g, 0.02 mol) in ethanol, pyrrolidine (1.42 g, 0.02 mol) and 37% formaldehyde (0.5 mL) was added. 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 obtained after the completion of the reaction (The reaction time varied from 1.5 -2 min.) was kept at °C for 30 min. and the resulting ppt. was recrystalized from a mixture of DMF and water, Yield- 72%, m.p. 115-117°C.

IR (KBr) cm^{-1} : 3065 [C-H (piperidine)] 1715 (C=O), 1650 (C=C), 1371 (C-H in CH_2); ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: 7.89-7.38 (4 H, m, Ar-H), 4.03 (2 H, s, CH_2), 2.51-1.68 (8 H, m, pyrrolidine-H); MS: m/z: 230 (75%), Anal. Calcd. /found for $C_{13}H_{14}N_2O_2$: C: 67.61/67.81; H: 6.09/6.13; N: 12.20/12.17; O: 13.83/13.90.

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

A mixture of isatin (1.47 g 0.01 mol) and substituted acetoacetic ester (1.30 g, 0.01) was dissolved in ethanol (100 mL) and diethylamine/piperidine (1 mL) was added. The mixture was allowed to stand overnight at room temperature. The yellow needles formed were recrystallised from ethanol: Compounds **(3 b-d)** were prepared by the same procedure.

Yield- 69%, m.p.118-119°C; IR (KBr) cm^{-1} : 3035 (Ar-H) 1722 (C=O) 1467 (C=C); ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: 8.74-7.14 (4 H, m, Ar-H), 4.20 (2 H, q, CH_2), 4.03 (2 H, s, CH_2), 2.27 (3 H, s, CH_2), 2.51-1.68 (8 H, m, pyrrolidine-H), 1.29 (3 H, m, CH_3); MS: m/z: 342 (60%), Anal. Calcd./found for $C_{19}H_{22}N_2O_4$: C: 66.31/66.65; H: 6.44/6.48; N: 8.13/8.18; O: 18.59/18.69.

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

A mixture of aryl acetone (1.02 g, 0.003 mole) and CS_2 (0.228 g, 0.003 mole) was added to a well stirred and cooled suspension of tert. Butyl oxide (0.672 g, 0.006 moles) in dry benzene (150 mL) and DMF (100 mL). The reaction mixture was allowed to stand at room temperature for 4 hrs. Then methyl iodide (0.45 g. 0.006 mole) was gradually added with stirring and external cooling (exothermic reaction) and the reaction mixture was allowed to stand for 4 hrs. at room temperature with occasional shaking and refluxed on a water bath for 3 hrs. The mixture was poured on crushed ice and the benzene layer was

separated. The aqueous portion was extracted with benzene. This layer was washed out with water and dried in sodium sulphate and the solvent was removed by distillation. The product obtained was purified before use, Yield- 71%, m.p.135-138°C;

IR (KBr) cm^{-1}: 3135 (Ar-H) 1702 (C=O) 1537 (C=C) 624 (C-S); ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: 8.74-7.14 (4 H, m, Ar-H), 6.09 (1 H,s, CH), 4.20 (2 H, q, CH_2), 4.03 (2 H, s, CH_2), 2.80 (3 H, s, CH_3), 2.51-1.68 (8 H, m, pyrrolidine-H), 1.29 (3 H, t, CH_3); MS: m/z: 446 (40%), Anal. Calcd./found for $C_{22}H_{26}N_2O_4S_2$: C: 58.87/59.17; H: 5.84/5.87; N: 6.23/6.27; O: 14.25/14.33; S: 14.28/14.36.

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 (5)

A mixture of compound **(4)** (1.19 g, 0.0024 mol) and 1-methyl piperazine (0.073 g, 0.0073 mol) in toluene (800 mL) was heated to reflux for 2 hrs. Solvent and excess 1-methyl piperazine was removed under vacuum and the residue was triturated with a mix of ethyl acetate and ether (1 : 3) to give the product as yellow crystals, Yield- 64%, m.p. 120-122°C.

IR (KBr) cm^{-1}: 1722 (C=O), 1650 (C=C), 1010 (C-N), 1000 (C-N), 634 (C-S); ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: 8.74-7.14 (4H, m, Ar-H), 5.24 (1H, s, CH_2), 4.20 (2H, q, CH_2), 4.03 (2 H, s, CH_2), 2.79-2.13 (8 H, m, piperazine-H), 2.51-1.68 (8 H, m, pyrrolidine-H), 2.43 (3 H, s, CH_3), 2.26 (3 H, s, CH_3), 1.29 (3 H, t, CH_3); MS: m/z: 498 (12%) [M^+], Anal. Calcd./found for $C_{26}H_{34}N_4O_4S$: C: 62.38/62.63; H: 6.83/6.87; N: 11.18/11.24; O: 12.76/12.83; S-6.22/6.43.

Preparation of (Z)-ethyl 2-(6-(4-methylpiperazin-1-yl)-2-oxo-1, 2-dihydropyrimidin-4-yl)- 2-(2-oxo-1-(pyrrolidin-1-ylmethyl) indolin-3-ylidene) acetate (6)

To a mixture of urea (2.58 g, 0.04 moles), sodium ethoxide (0.28 g, 0.004 mole) and ethanol (30-35 mL) was added to compound **(5)** (1.54 g, 0.004 mole) and the reaction mixture was refluxed for 10-18 hrs. The solvent was removed by distillation and the residue was treated with glacial acetic acid (4-5 mL) to dissolve sodium salt and refluxed for 15 min. The reaction mixture was poured on crushed ice and the ppt. was purified by chloroform, Yield-72%, m.p.90-92°C.

IR (KBr) cm^{-1}: 3140 (NH), 2965 (CH), 1719 (C=O), 1661 (C=O), 1447 (C=N); ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: MS: m/z: 492.57 (12%), Anal. Calcd./found for $C_{26}H_{32}N_6O_4$: C: 63.28/63.40; H: 6.51/6.55; N: 16.98/17.06; O: 12.93/12.99.

Preparation of (Z)-ethyl 2-(6-(4-methylpiperazin-1-yl)-2-thioxo-1,2-dihydropyrimidin-4-yl)-2-(2-oxo-1-(pyrrolidin-1-ylmethyl)indolin-3-ylidene)acetate (7)

Sodium ethoxide (2.8 g, 0.004 moles) and ethanol (20-25 mL) was added to compound **(5)** (1.54 g, 0.004) and refluxed for 10-16 hrs. The solvent was removed by distillation and treated with glacial acetic acid for 15 min. Reaction mixture was poured on crushed ice and ppt. was purified by recrystallization with ethanol, Yield-71%, m.p. 98-100°C.

IR (Kbr) cm^{-1}: 3222 (NH), 2965 (CH), 1708 (C=O), 1655 (C=O), 1440 (C=N), 1243 (C=S); ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: MS: m/z: 508.64 (12%), Anal. Calcd./found for $C_{26}H_{32}N_6O_3S$: C: 61.29/61.40; H: 6.30/6.34; N: 16.44/16.52; O: 9.40/9.44; S: 6.17/6.30.

Preparation of ethyl 2-(2-methyl-6-(4-methylpiperazin-1-yl)-1,2-dihydropyrimidin-4-yl)-2-(2-oxo-1-(pyrrolidin-1-ylmethyl)indolin-3-ylidene)acetate (8)

A solution of compound **(5)** (0.55 m mol) in ethanol (14 mL) was added to acetamidine hydrochloride (0.21 g, 2.57 m mol) and triethylamine (3.8 mol, 2.38 m mol). The solution was heated under reflux for 52 hrs and concentrated. The residue was extracted with ethyl acetate and washed with water. The organic layer was dried over anhydrous $MgSO_4$. The residue was purified by column chromatography eluting with hexane: ethyl acetate (1 : 2) to give brown powder**,** Yield-66%, m.p.125-127°C.

IR (KBr) cm^{-1}: 2955 (CH), 1711 (C=O), 1644 (C=O), 1431 (C=N); ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: MS: m/z: 492.61 (12%), Anal. Calcd./found for $C_{27}H_{36}N_6O_3$: C-65.78/65.83; H: 7.33/7.37; N: 16.97/17.06; O: 9.69/9.74.

Preparation of (E)-ethyl 2-(2-amino-6(4-methylpiperazin-1-yl)-1, 2-dihydropyrimidin-4yl)-2-(2-oxo-1-(pyrrolidin-1-ylmethyl) indolin-3-ylidene) acetate (9)

To a solution of compound **(5)** (0.90 g, 3.7 mol) in ethanol (20 mL) was added in guanidine nitrate (2.8 g, 15.1 m mol) and sodium acetate (2.4 g, 30.3 m mol) and the solution was refluxed for 48-60 h. Reaction mixture was filtered and extracted with chloroform and washed with water.Yield-68%, m.p.118-120°C.

IR(KBr) cm^{-1}: 3332 (NH), 2960 (CH), 1713 (C=O), 1643 (C=O), 1424 (C=N); ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: MS: m/z: 493.60 (12%), Anal. Calcd./found for $C_{26}H_{35}N_7O_3$: C: 63.16/63.27; H: 7.11/7.15; N: 19.76/19.86; O: 9.67/9.72:

CONCLUSION

Several novel pyrimidine analogues of indole condensed derivatives **(6-9)** displaying many important activities like antibacterial, anti-fungal etc. were synthesized from aminal**.** The study provided an elegant method for the synthesis of pyrimidine analogues of indole-condensed derivatives of biological interest from the corresponding oxoketene dithioacetal.

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