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A Novel Analogue of Delavirdine Developed by Replacing Its Indole Nucleus with Isatin's Mannich's Base and Pyridine Nucleus with Pyrimidine Ring

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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 with 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 the 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.

1. 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' or 'reverse transcriptase' [1] 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. Inhibition of HIV-1 (human immunodeficiency virus type-1) reverse transcriptase by nucleoside such as AZT [2] (Zidovudine), 3tc [2] (lamivudine), D4T [2] (Stavudine), DDI [2] (di-dioxyinosine), and Delavirdine [2] (shown in Fig. 1) have emerged as a proven therapy for delaying the progression to AIDS.

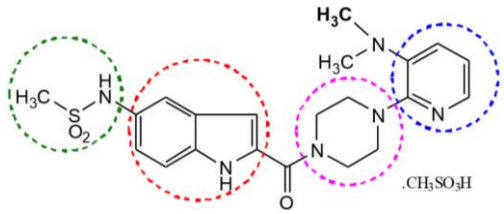

Fig. 1 Structure of Delavirdine

The advent of FDA approved delavirdine molecule has been hailed as a major step forward in the battle against the AIDS. But serious limitations have been imposed on its use [3], the most concerning of which has been the emergence of viral strains resistant to this drug. This calls to the development of new generation anti-HIV agents that exhibit improved pharmacokinetic properties and drug resistant profiles.

One can easily discern the presence of two bioactive phrmacophores viz; the indole and the pyridine nucleus [4] in its molecule has been identified recently as an important heterocyclic scaffolds exhibiting impressive anti-HIV activity [5] and on that basis one can reason that the problem associated with the emergence of the viral strain resistant to delavirdine can possibly be circumvented by replacing any one of the two nucleus by such medicinally useful heterocyclic scaffolds which have the proven record of the bioactivity profile in the literature. One such nucleus is pyrimidine 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 [6-7].

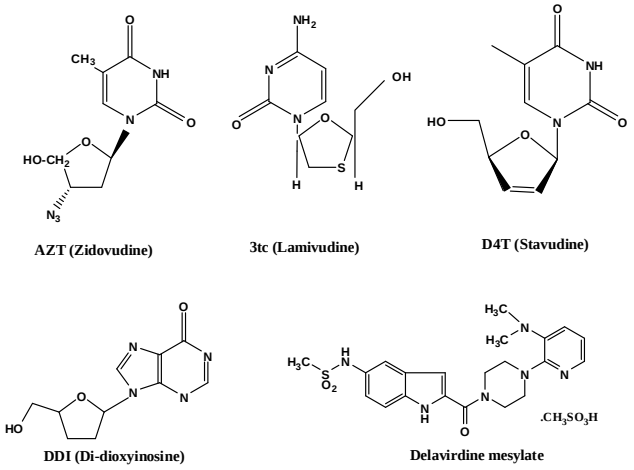

Fig. 2 Anti-HIV agents

2. Results and discussion

Greatly encouraged by the broad spectrum of biological activities of pyrimidine and pyridine derivatives, it was considered of interest in the present work to construct a system, which contained pyrimidine and pyridine nucleus in the molecular framework of delavirdine. The synthesis of the molecules **6-9 (a-d)** carrying the above bioactive pharmacophores was conceived in the present work from oxoketene N, S-aminal following the strategy shown in Scheme 1. This synthesis consisted of treating oxoketene N, S-aminal **5 (a-d)** with urea, thiourea, acetamidine and guanidine in presence of a base in boiling ethanol to give corresponding pyrimidine analogues **6-9 (a-d).**

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(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. The synthesis in its first step started with the preparation of Mannich bases [8] **2(a-d)** of

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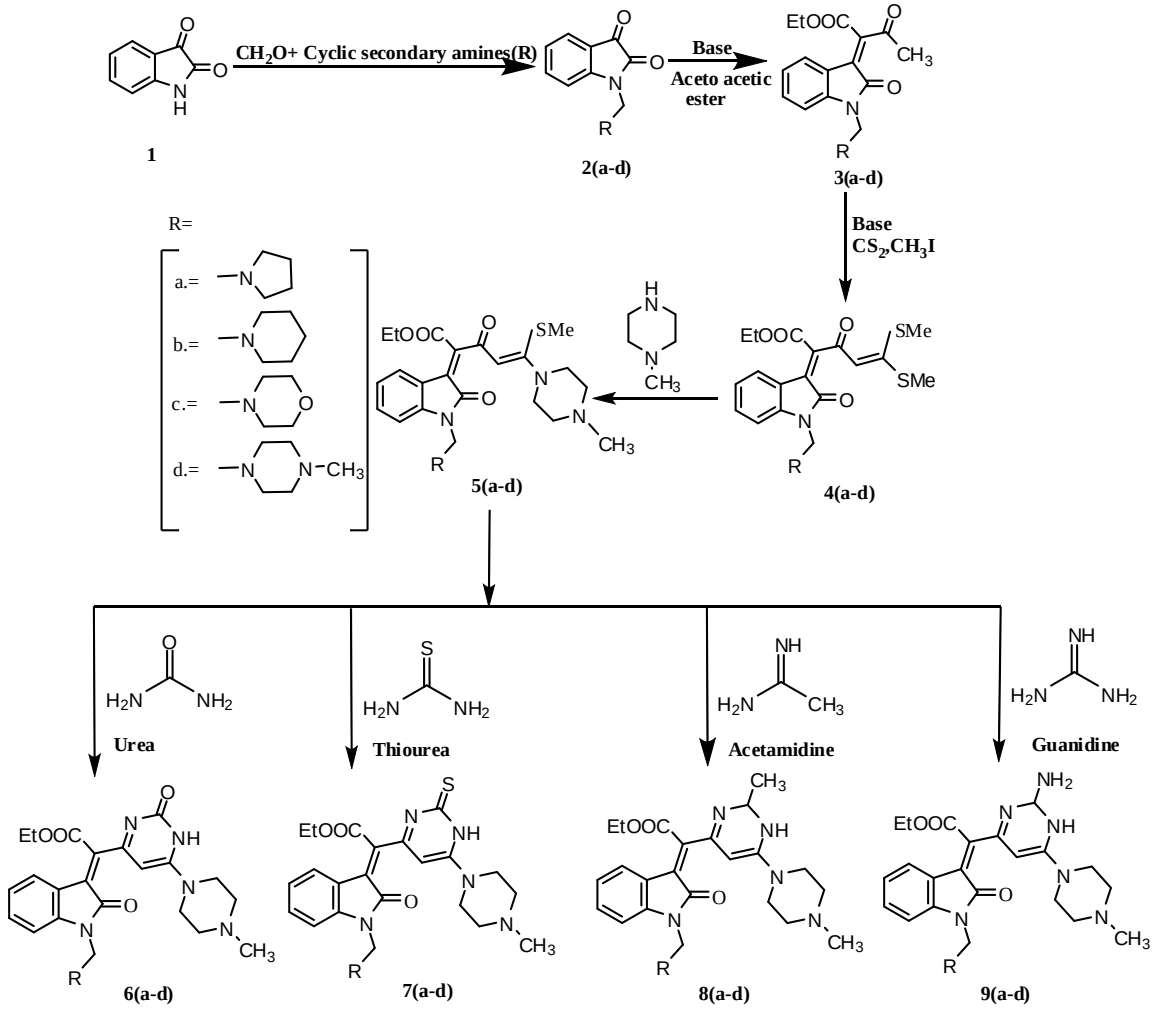
isatin from **1,** Subsequent **2(a-d)** treatment with ethyl acetoacetate afforded the enone ester **3(a-d)** from which **4(a-d)** was realized, on the reaction with CS_2 followed by treatment with CH_3I, in the presence of NaOEt. Oxoketene dithioacetals and oxoketene N, S-aminals have been known to provide an easy access to the heterocyclic skeleton on their reaction with bidenate nucleophiles [9-11]. In the present work the chemistry of oxoketene N,S-aminal was explored to incorporate the pyrimidine ring making use of the aminal **5(a-d),** whose treatment with urea, thiourea, acetamidine, and guanidine very smoothly provided a very convenient synthetic entry to the pyrimidine scaffolds in **6-9(a-d)** respectively.



Scheme 1 Synthesis of compounds 6-9 (a-d)

3. Experimental Methods

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 $CDCl_3$+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 (EI/CI/FAB) mass spectrometer.

*3.1 General Procedure of the Formation of Compound **2(a-d)**:*

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

To a suspension of indoline-2, 3-dione (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 obtained after the completion of the reaction (The reaction time varied from 1.5 – 2 min.) was kept at 180 °C for 30 min. and the resulting precipitate was recrystallized from a mixture of DMF and water. Compounds **2(b-d)** were prepared by the same procedure.

***[2a**. R=Pyrrolidine]:* Yield- 72%, m.p. 116 °C; IR(KBr)cm^{-1}: 3065[C-H(piperidine)] 1715[C=O], 1650[C=C], 1371[C-H in CH_2]; ^{1}HNMR(300 MHz, $CDCl_3$+DMSO-d_6)δppm: 7.89-7.38[4H, m, Ar-H], 4.03[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: 67.61/67.81; H: 6.09/6.13; N: 12.20/12.17; O: 13.83/13.90.

*Preparation of 1-(piperidin-1-ylmethyl) indoline-2,3-dione: **(2b)***

***[2b**. R=Piperidine]:* Yield- 71%, m.p. 100 °C; IR(KBr)cm^{-1}: 3065[C-H(piperidine)] 1710[C=O], 1665[C=C], 1489[C=C] ,1380[C-H in CH_2], 1489[C=C] ; ^{1}HNMR(300 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(80%), Anal. Calcd./found for $C_{14}H_{16}N_2O_2$: C: 68.58/68.83; H: 656/6.60; N: 11.41/11.47; O: 13.03/13.10.

*Preparation of 1-(morpholinomethyl) indoline-2, 3-dione: **(2c)***

***[2c**. R=morpholine]:* Yield- 71%, m.p. 105 °C; IR(KBr)cm^{-1} : 1712[C=O], 1450[C=C], 1371[C-H in CH_3]; ^{1}HNMR(300 MHz, $CDCl_3$+DMSO-d_6)δppm: 7.89-7.38[4H, m, Ar-H], 4.03[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: 63.10/63.40; H: 5.70/5.73; N: 11.32/11.38; O: 19.39/19.49.

*Preparation of 1-((4-methylpiperazin-1-yl) methyl) indoline-2, 3-dione:**(2d)***

***[2d**. R=Methyl piperazine]* Yield- 70%, m.p. 116 °C; IR(KBr)cm^{-1}: 1705[C=O], 1520[C=C], 1300[C-H in CH_3]; ^{1}HNMR(300 MHz, $CDCl_3$+DMSO-d_6)δppm: 7.89-7.38[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: 64.56/64.85; H: 6.57/6.61; N: 10.78/10.84; O: 12.27/12.34.

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*3.2 General procedure of the formation of compound **3(a-d)***

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

A mixture of isatin (1.47 g, 0.01 mol) and substituted acetoacetic ester (1.30 g, 0.01 mol) was dissolved in ethanol (100 mL) and di ethyl amine/piperidine (1 mL) was added. The mixture was allowed to stand overnight at room temperature (36 °C) the yellow needles formed were recrystallized from ethanol: Compounds **3(b-d)** were prepared by the same procedure.

***[3a**. R=Pyrrolidine]:* Yield- 69%, m.p. 118 °C; IR(KBr)cm^{-1}: 3035[Ar-H], 1722[C=O], 1467[C=C]; ^{1}HNMR(300 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], 2.27[3H, s, CH_2], 2.51-1.68[8H, m, pyrrolidine-H], 1.29[3H, 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 3-oxo-2-(2-oxo-1-(piperidin-1-ylmethyl) indolin-3-ylidene) butanoate: **(3b)***

***[3b**. R=Piperidine]:* Yield-65 %, m.p 121 °C; IR(KBr)cm^{-1}: 3055[Ar-H], 1714[C=O], 1477[C=C], 1378[C-H in CH_2]; ^{1}HNMR(300 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], 2.27[3H, s, CH_2], 2.45-1.53[10H, m, piperidine-H], 1.29[3H, m, CH_3]; MS: m/z: 356(65%) , Anal. Calcd./found for $C_{20}H_{24}N_2O_4$: C: 67.22/67.40; H: 6.75/6.79; N: 7.82/7.86; O: 17.87/17.96.

*Preparation of (Z)-ethyl 2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)-3-oxobutanoate: **(3c)***

***[3c**. R=morpholine]:* Yield-65 %, m.p. 125 °C ; IR(KBr)cm^{-1}: 3055[Ar-H], 1728[C=O], 1566[C=C]; ^{1}HNMR(300 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(55%) , Anal. Calcd./found for $C_{19}H_{22}N_2O_5$: C:63.52/63.67; H: 6.15/6.19; N: 7.78/7.82; O: 22.20/22.32.

*Preparation of (Z)-ethyl 2-(1-((4-methylpiperazin-1-yl) methyl)-2-oxoindolin-3-ylidene)-3-oxobutanoate: **(3d)***

***[3d**. R=Methyl piperazine]:* Yield- 67%, m.p. 133 °C ; IR(KBr)cm^{-1}: 3065[Ar-H], 1730[C=O], 1480[C=C], 1210[C-C]; ^{1}HNMR(300 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], 2.35[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(60%), Anal. Calcd./found for $C_{20}H_{25}N_3O_4$: C: 64.34/64.67; H: 6.59/6.78; N: 11.25/11.31; O: 17.14/17.23.

*3.3 General procedure of the formation of compound **4(a-d)***

*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 mix of aryl acetone (1.02 g, 0.003 mol) and CS_2 (0.228 g, 0.003 mol) was added to a well stirred and cooled suspension of ter. Buteroxide (0.672 g, 0.006 mol) in dry benzene (150 mL) and DMF (100 mL) and the reaction mixture was allowed to stand at Rt for 4 hrs, then methyl iodide (0.45 g, 0.006 mol) was gradually added with stirring and external cooling (exothermic reaction) and the reaction mixture was allowed to stand for 4 hrs at RT with occasional shaking and then refluxed on water bath for 3 hrs. The mix was poured on crushed ice and the benzene layer was separated. The aq. portion was extracted with benzene and this layer was washed out with water and dried in sodium sulphate and the solvent was removed by distillation. The product obtained purified before use: Compounds **4(b-d)** were prepared by the same procedure.

***[4a**. R=Pyrrolidine]:* Yield- 71%, m.p. 137 °C; IR(KBr)cm^{-1} : 3135[Ar-H], 1702[C=O], 1537[C=C], 624[C-S]; ^{1}HNMR(300 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], 2.51-1.68[8H, m, pyrrolidine-H], 1.29[3H, 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 (Z)-ethyl 5, 5-bis (methylthio)-3-oxo-2-(2-oxo-1-(piperidin-1-ylmethyl) indolin-3-ylidene) pent-4-enoate: **(4b)***

***[4b**. R=Piperidine]:* Yield-71 %, m.p. 143 °C ; IR(KBr)cm^{-1} : 3035[Ar-H], 1711[C=O], 1477[C=C], 1338[C-H in CH_2], 672[C-S]; ^{1}HNMR(300 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(40%) , Anal. Calcd./found for $C_{23}H_{28}N_2O_4S_2$: C: 59.67/59.97; H: 6.09/6.13; N: 6.04/6.08; O: 13.82/13.89; S: 13.85/13.92.

*Preparation of (2Z, 4E)-ethyl 5-(methylthio)-2-(1-morpholinomethyl)-2-oxoindolin-3-ylidene) pent-4-enoate: **(4c)***

***[4c**. R=morpholine]:* Yield- 79%, m.p. 121 °C; IR(KBr)cm^{-1} : 3005[Ar-H], 1724[C=O], 1467[C=C], 1378[C-H in CH_2], 670[C-S]; ^{1}HNMR(300 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], 3.65-2.50[8H, m, morpholine-H], 1.29[3H, t, CH_3]; MS: m/z: 462(38%) , Anal. Calcd./found for $C_{22}H_{26}N_2O_5S_2$: C: 56.89/57.12; H: 5.64/5.67; N: 6.02/6.06; O: 17.20/17.29; S: 13.79/13.86.

*Preparation of (2Z, 4E)-ethyl 2-(1-((4-methylpiperazin-1-yl) methyl) - 2-oxoindolin-3-ylidene) 5, 5-bis (methylthio)-3-oxopent-4-enoate: **(4d)***

***[4d**. R=Methyl piperazine]* Yield- 74%, m.p. 112 °C ; IR(KBr)cm^{-1} : 3135[Ar-H], 1717[C=O], 1477[C=C], 1300[C-H in CH_2]652[C-S]; ^{1}HNMR(300 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], 2.35[8H, m, piperazine-H], 2.26[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: 57.62/58.08; H: 6.10/6.14; N: 8.78/8.83; O: 13.39/13.46; S: 13.41/13.48.

*3.4 General procedure of the formation of compound **5(a-d)***

*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 mix of compound (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: Compounds 5(b-d) were prepared by the same procedure.

***[5a**. R=Pyrrolidine]* Yield- 64%, m.p. 122 °C ; IR(KBr)cm^{-1} : 1722 [C=O], 1650[C=C], 1010[C-N], 1000[C-N], 634[C-S]; ^{1}HNMR(300 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], 2.51-1.68[8H, m, pyrrolidine-H], 2.43[3H, s, CH_3], 2.26[3H, s,CH_3], 1.29[3H, 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 (2Z, 4Z)-ethyl 5-(4-methylpiperazin-1-yl)-5-(methylthio)-3-oxo-2-(2-oxo-1-(piperidin-1-ylmethyl) indolin-3-ylidene) pent-4-enoate: **(5b)***

***[5b**. R=Piperidine]:* Yield- 68%, m.p 115 °C; IR(KBr)cm^{-1} : 1743 [C=O] 1650[C=C] 1002[C-N], 634[C-S],; ^{1}HNMR(300 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: 7.04/7.08; N: 10.87/10.93; O: 12.41/12.48; S: 6.21/6.25.

*Preparation of (2Z, 4Z)-ethyl 5-(4-methylpiperazin-1-yl)-5-(methylthio)-2-(1-morpholinomethyl)-2-oxoindolin -3-ylidene)-3-oxopent-4-enoate: **(5c)***

***[5c**. R=morpholine]:* Yield-68%, m.p. 121 °C; IR(KBr)cm^1: 1712[C=O], 1622[C=O], 1450[C=C], 1371[C-O], 1000[C-N] 634[C-S]; ^{1}HNMR(300 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], 3.65-2.50[8H, m, morpholine-H], 2.43[3H, s, CH_3], 2.26[3H, s,CH_3], 1.29[3H, t, CH_3]; MS: m/z: 514(15%), Anal. Calcd./found for $C_{26}H_{34}N_4O_5S$: C: 60.47/60.68; H: 6.62/6.66; N: 10.83/10.89; O: 15.46/15.54; S: 6.19/6.23.

*Preparation of (2Z, 4Z)-ethyl 5-(4-methylpiperazin-1-yl)-2-(1-((4-methylpiperazin-1-yl) methyl-2-oxoindolin-3-ylidene)-5-(methylthio)-3-oxopent-4-enoate: **(5d)***

***[5d**. R=Methyl piperazine]:* Yield-71%, m.p.120 °C; IR(KBr)cm^{-1}: 1734[C=O], 1632[C=O], 1650[C=C], 1331[C-O], 1010[C-N], 667[C-S]; ^{1}HNMR(300 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], 2.35[8H, m, piperazine-H], 2.43[3H, s, CH_3], 2.26[3H, s,CH_3], 1.29[3H, t, CH_3]; MS: m/z: 527(12%), Anal. Calcd./found for $C_{27}H_{37}N_5O_4S$: C: 61.35/61.46; H: 7.03/7.07; N: 13.20/13.27; O: 12.09/12.12; S: 6.04/6.08.

3.5 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: ***(6a)***

To a mixture of urea (2.58 g, 0.04 mol) , sodium ethoxide (0.28 g, 0.004 mol) and ethanol (30-35 mL) was added to compound (1.54 g, 0.004 mol) 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 precipitate was purified by chloroform. Compounds **6(b-d)** were prepared by the same procedure.

[6a*. R=Pyrrolidine]:* Yield-72%, m.p. 92 °C; IR(Kbr)cm^{-1}: 3140[NH], 2965[CH], 1719[C=O], 1661[C=O], 1447[C=N]; ^{1}HNMR(300 MHz, $CDCl_3$+DMSO-d_6)δppm: 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-oxo-1,2-dihydropyrimidin-4-yl)-2-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)acetate: ***(6b)***

[6b*. R=Piperidine]:* Yield-74%, m.p. 120 °C; IR(Kbr)cm^{-1}: 3143[NH], 2975[CH], 1719[C=O], 1661[C=O], 1447[C=N]; ^{1}HNMR(300 MHz, $CDCl_3$+DMSO-d_6)δppm: MS: m/z: 506.60(12%), Anal. Calcd./found for $C_{27}H_{34}N_6O_4$: C: 63.96/64.01; H: 6.72/6.76; N: 16.52/16.59; O: 12.56/12.63.

Preparation of (Z)-ethyl 2-(6-(4-methylpiperazin-1-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)acetate: ***(6c)***

[6c*. R=morpholine]:* Yield-70%, m.p. 156 °C; IR(Kbr)cm^{-1}: 3143[NH], 2968[CH], 1720[C=O], 1645[C=O], 1437[C=N] 1168[C-O-C]; ^{1}HNMR(300 MHz, $CDCl_3$+DMSO-d_6)δppm: MS: m/z: 508.57(12%), Anal. Calcd./found for $C_{26}H_{32}N_6O_5$: C: 61.49/61.60; H: 6.30/6.34; N: 16.43/16.52; O: 15.58/15.73.

Preparation of (Z)-ethyl 2-(6-(4-methylpiperazin-1-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-(1-((4-methylpiperazin-1-yl)methyl)-2-oxoindolin-3-ylidene)acetate: ***(6d)***

[6d*. R=Methyl piperazine]:* Yield-70%, m.p. 137 °C; IR(Kbr)cm^{-1}: 3133[NH], 2963[CH], 1713[C=O], 1643[C=O], 1437[C=N]; ^{1}HNMR(300 MHz, $CDCl_3$+DMSO-d_6)δppm: MS: m/z: 521.61(12%), Anal. Calcd./found for $C_{27}H_{35}N_7O_4$: C: 61.94/62.17; H: 6.72/6.76; N: 18.74/18.80; O: 12.20/12.27.

3.6 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: ***(7a)***

Sodium ethoxide (2.8g, 0.004 mol) and ethanol (20-25 mL) was added to compound (1.54g, 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. Compounds **7(b-d)** were prepared by the same procedure.

[7a*. R=Pyrrolidine]:* Yield-71%, m.p. 100 °C; IR(Kbr)cm^{-1}: 3222[NH], 2965[CH], 1708[C=O], 1655[C=O], 1440[C=N], 1243[C=S]; ^{1}HNMR(300 MHz, $CDCl_3$+DMSO-d_6)δppm: 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 (Z)-ethyl 2-(6-(4-methylpiperazin-1-yl)-2-thioxo-1,2-dihydropyrimidin-4-yl)-2-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)acetate: ***(7b)***

[**7b**. R=Piperidine]: Yield-69%, m.p. 103 °C; IR(Kbr)cm^{-1}: 3243[NH], 2971[CH], 1719[C=O], 1661[C=O], 1447[C=N], 1241[C=S]; ^{1}HNMR(300 MHz, $CDCl_3$+DMSO-d_6)δppm: MS: m/z: 522.66(12%), Anal. Calcd./found for $C_{27}H_{34}N_6O_3S$: C-61.98/62.05; H: 6.52/6.56; N: 16.06/16.08; O: 9.15/9.18; S: 6.09/6.13.

Preparation of (Z)-ethyl 2-(6-(4-methylpiperazin-1-yl)-2-thioxo-1,2-dihydropyrimidin-4-yl)-2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)acetate: ***(7c)***

[7c*. R=morpholine]:* Yield-65%, m.p. 117 °C; IR (Kbr) cm^{-1}: 3272[NH], 2964[CH], 1717[C=O], 1640[C=O], 1463[C=N], 1237[C=S]; ^{1}HNMR(300 MHz, $CDCl_3$+DMSO-d_6)δppm: MS: m/z: 524.64(12%), Anal. Calcd./found for $C_{26}H_{32}N_6O_4S$: C: 59.45/59.52; H: 6.11/6.15; N: 15.99/16.02; O: 12.13/12.20; S: 6.08/6.11.

Preparation of (Z)-ethyl 2-(6-(4-methylpiperazin-1-yl)-2-thioxo-1,2-dihydropyrimidin-4-yl)-2-(1-((4-methylpiperazin-1-yl)methyl)-2-oxoindolin-3-ylidene)acetate: ***(7d)***

[7d*. R=Methyl piperazine]:* Yield-71%, m.p. 141 °C; IR(Kbr)cm^{-1}: 3250[NH], 2968[CH], 1725[C=O], 1643[C=O], 1460[C=N], 1243[C=S]; ^{1}HNMR(300 MHz, $CDCl_3$+DMSO-d_6)δppm: MS: m/z: 537.68(12%), Anal. Calcd./found for $C_{27}H_{35}N_7O_3S$: C: 60.27/60.31; H: 6.52/6.56; N: 18.17/18.24; O: 8.85/8.93; S: 5.93/5.96.

3.7 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: ***(8a)***

A solution of compound (0.55 mmol) in ethanol (14 mL) were added acetamidine hydrochloride (0.21g, 2.57 mmol) and tri ethyl amine (3.8 g, 2.38 mmol) and 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. Compounds **8(b-d)** were prepared by the same procedure.

[8a*. R=Pyrrolidine]:* Yield-66%, m.p. 126 °C; IR(Kbr)cm^{-1}: 2955[CH], 1711[C=O], 1644[C=O], 1431[C=N]; ^{1}HNMR(300 MHz, $CDCl_3$+DMSO-d_6)δppm: 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 ethyl 2-(2-methyl-6-(4-methylpiperazin-1-yl)-1,2-dihydropyrimidin-4-yl)-2-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)acetate: ***(8b)***

[8b*. R=Piperidine]:* Yield-72%, m.p. 136 °C; IR(Kbr)cm^{-1}: 2963[CH], 1716[C=O], 1633[C=O], 1454[C=N]; ^{1}HNMR(300 MHz, $CDCl_3$+DMSO-d_6)δppm: MS: m/z: 506.64(12%), Anal. Calcd./found for $C_{28}H_{38}N_6O_3$: C: 66.25/66.38; H: 7.52/7.56; N: 16.51/16.59; O: 9.43/9.47.

Preparation of ethyl 2-(2-methyl-6-(4-methylpiperazin-1-yl)-1,2-dihydropyrimidin-4-yl)-2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)acetate: ***(8c)***

[8c*. R=morpholine]:* Yield-69%, m.p. 124 °C; IR(Kbr)cm^{-1}: 2970[CH], 1716[C=O], 1615[C=O], 1463[C=N], 1237[C-O-C]; ^{1}HNMR(300 MHz, $CDCl_3$+DMSO-d_6)δppm: MS: m/z: 508.61(12%), Anal. Calcd./found for $C_{27}H_{36}N_6O_4$: C: 63.67/63.76; H: 7.12/7.13; N: 16.45/16.52; O: 12.52/12.58.

Preparation of ethyl 2-(2-methyl-6-(4-methylpiperazin-1-yl)-1,2-dihydropyrimidin-4-yl)-2-(1-((4-methylpiperazin-1-yl)methyl)-2-oxoindolin-3-ylidene)acetate: ***(8d)***

[8d*. R=Methyl piperazine]:* Yield-71%, m.p. 141 °C; IR(Kbr)cm^{-1} : 2964[CH], 1710[C=O], 1620[C=O], 1414[C=N] ; ^{1}HNMR(300 MHz, $CDCl_3$+DMSO-d_6)δppm: MS: m/z: 521.65(12%) , Anal. Calcd./found for $C_{28}H_{39}N_7O_3$: C: 64.39/64.47; H: 7.50/7.54; N: 18.70/18.80; O: 9.15/9.20.

3.8 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: ***(9a)***

To a solution of compound (0.90 g, 3.7 mol) in ethanol (20 mL) were add in guanidine nitrate (2.8 g, 15.1 mmol) and sodium acetate (2.4 g, 30.3 mmol) and the solution was refluxed for 48-60 h. Reaction mixture was filtered and extracted with chloroform and washed with water. Compounds **9(b-d)** were prepared by the same procedure.

[9a*. R=Pyrrolidine]:* Yield-68%, m.p. 120 °C; IR(Kbr)cm^{-1}: 3332[NH], 2960[CH], 1713[C=O], 1643[C=O], 1424[C=N]; ^{1}HNMR(300 MHz, $CDCl_3$+DMSO-d_6)δppm: 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:

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

[9b*. R=Piperidine]:* Yield-72%, m.p. 124. °C; IR(Kbr)cm^{-1}: 3313[NH], 2961[CH], 1722[C=O], 1677[C=O], 1456[C=N]; ^{1}HNMR(300 MHz, $CDCl_3$+DMSO-d_6)δppm: MS: m/z: 507.63(12%), Anal. Calcd./found for $C_{27}H_{37}N_7O_3$: C: 63.59/63.88; H: 7.31/7.35; N: 19.21/19.31; O: 9.41/9.46.

Preparation of (E)-ethyl 2-(2-amino-6-(4-methylpiperazin-1-yl)-1,2-dihydropyrimidin-4-yl)-2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)acetate: ***(9c)***

[9c*. R=morpholine]:* Yield-71%, m.p. 135 °C; IR(Kbr)cm^{-1}: 3344[NH], 2933[CH], 1717[C=O], 1673[C=O], 1444[C=N], 1233[C-O-C]; ^{1}HNMR(300 MHz, $CDCl_3$+DMSO-d_6)δppm: MS: m/z: 509.60(12%), Anal. Calcd./found for $C_{26}H_{35}N_7O_4$; C: 61.18/61.28; H: 6.88/6.92; N: 19.21/19.24; O: 12.49/12.56.

Preparation of (E)-ethyl 2-(2-amino-6-(4-methylpiperazin-1-yl)-1,2-dihydropyrimidin-4-yl)-2-(1-((4-methylpiperazin-1-yl)methyl)-2-oxoindolin-3ylidene)acetate: ***(9d)***

[9d*. R=Methyl piperazine]:* Yield-70%, m.p. 125 °C; IR(Kbr)cm^{-1}: 3341[NH], 2954[CH], 1714[C=O], 1652[C=O], 1436[C=N]; ^{1}HNMR(300 MHz, $CDCl_3$+DMSO-d_6)δppm: MS: m/z: 522.64(12%), Anal. Calcd./found for $C_{27}H_{38}N_8O_3$; C: 61.94/62.05; H: 7.28/7.33; N: 21.33/21.44; O-10.0/9.18.

4. Conclusion

In conclusion, several novel pyrimidine analogues of indole condensed derivatives **6-9(a-d)** displaying many important activities as antibacterial, anti-fungal were synthesized from aminal **5(a-d).** 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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