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Full Length Research Paper

SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME OXO- AND THIOXOPYRIMIDINES

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ABSTRACT

Some oxo and thioxotetrahydropyrimidines 4(a-j) were prepared using multicomponent reaction of β-keeto ester, arylaldehyde and urea/thiourea in the presence of the NaY zeolite. The microbiological activity of these compounds was tested in vitro against Escherichia Coli (PTCC 1338), Pseudomonas aeruginosa (PTCC 1074), Entrococcus faecalis (PTCC 1237) and Staphylococcus aureus (PTCC 1119) bacteria.

Keywords: *Pyrimidine, catalyst, zeolite, biological activity, carboxylate*

Introduction

It is well known that a large number of 3,4-dihidropyrimidines, DHPMs, exhibit wide range of pharmacological activities such as antitumor[1], antiviral[2], antifolate[3], anti-inflammatory[4], anticancer[4], antitubercular[5], antiproliferative[6] and antifungal[7] activities. Many pyrimidine derivatives with appropriate functional groups have emerged as antihypertensive agents[8-11] and potent calcium channel blockers[12,13]. In addition, several marine alkaloids containing the dihydropyrimidine core have been found to be potent HIV gp-120 to CD4 inhibitors[14]. There are numerous modified preparative methods for the synthesis of pyrimidines which known as Biginelli compounds[14-20]. Some of these methods need expensive reagent, toxic reagent or force reaction conditions. In view of these points and continuation of our interest in the synthesis of pyrimidines[15-20], we wish to report the synthesis and biological activity of some pyrimidines which prepared in the presence of NaY zeolite as a friendly catalyst.

Material and Methods

Compounds **4(a-j)** were prepared according to our published method[21]. ^{1}H NMR spectra were recorded on a Bruker (300 MHz) Spectrometer. The IR spectra were recorded on Glaxy FT-IR 5000 Spectrometer. Reactions were monitored by thin layer chromatography. All materials were used as they received. NaY zeolite was prepared and activated according to the literature procedure[22].

For preparation of 3,4-dihidropyrimidines, to a mixture of urea/thiourea (0.01 mol), ethylacetoacetate (0.01 mol) and corresponding aromatic aldehyde (0.01 mol) in 25 ml of ethanol, NaY zeolite (0.25g) was added and refluxed for 19-40 h. The NaY zeolite was filtered off and the solution allowed cooling to -5 ^{o}C. The precipitate was separated by filtration and recrystallized from ethanol to give the pure product.

Antibacterial effects were studied through applying broth dilution method[23]. Compound **4** was dissolved in dimethyl sulfoxide (25.6 mg/ml) and diluted with acetonitrile (256 μg/ml). Further dilution of the compounds in the test medium was carried out at the required concentration of a 128, 64, 32, 16, 8, 4, 2, 1, 0.5 μg/ml with Muller-Hinton broth. The base medium used is Muller Hinton Broth (21 g/lit). A set of tubes

containing only inoculated broth was kept as controls. It was determined that the solvent had no antimicrobial activity against any of the test microorganism. All compounds were tested for their in vitro grow inhibitory activity against different bacteria. The origins of bacterial structures were Escherichia Coli (PTCC 1338), Pseudomonas aeruginosa (PTCC 1074), Entrococcus faecalis (PTCC 1237) and Staphylococcus aureus (PTCC 1119). The cultures were obtained in Muller Hilton Broth for all bacteria after 18-24 h of incubation at 37 °C. After incubation for 18-24 h, the last tube with no grow of microorganism was recorded to represent the minimum inhibitory concentrations (MIC) in term of µg/ml.

Ethyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a)

Yield 62%. IR (KBr): ν = 3223, 3126, 2931, 1730, 1649, 1465 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 1.08 (t, 3H, J= 7 Hz, CH_3), 2.23 (s, 3H, CH_3), 3.80 (q, 2H, J= 7 Hz, CH_2), 5.13 (d, 1H, J= 3 Hz, H-4), 7.23-7.31 (m, 5H, H_{arom}), 7.75 (s, 1H, NH), 9.19 (s, 1H, NH). Anal cald for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.70%. Found: C, 64.20; H, 6.10; N, 10.80%.

Ethyl-6-methyl-2-oxo-4-(4-nitrophenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b)

Yield 61%. IR (KBr): ν = 3394, 3219, 3099, 1730, 1707, 1647, 1521 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 1.06 (t, 3H, J= 7 Hz, CH_3), 2.26 (s, 3H, CH_3), 3.97 (q, 2H, J= 7 Hz, CH_2), 5.26 (d, 1H, J= 3 Hz, H-4), 7.49-8.24 (m, 4H, H_{arom}), 7.90 (d, 1H, NH), 9.36 (s, 1H, NH).

Anal cald for $C_{14}H_{15}N_3O_5$: C, 55.08; H, 4.95; N, 13.76%. Found: C, 55.38; H, 5.20; N, 13.50%.

Ethyl-6-methyl-2-oxo-4-(4-methylyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c)

Yield 61%. IR (KBr): ν = 3330, 3150, 1690, 1655, 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 1.11 (t, 3H, J= 7 Hz, CH_3), 2.25 (s, 3H, CH_3), 4.07 (q, 2H, J= 7 Hz, CH_2), 5.20 (d, 1H, J= 3 Hz, H-4), 6.90-7.51 (m, 4H, H_{arom}), 7.76 (s, 1H, NH), 9.70 (s, 1H, NH). Anal cald for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21%. Found: C, 65.50; H, 6.54; N, 10.31%.

Ethyl-4-(2-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d)

Yield 65%. IR (KBr): ν = 3360, 3220, 1690, 1640 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 1.10 (t, J = 7.2 Hz, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.90 (q, J = 7.2 Hz, 2H, CH_2), 5.65 (bs, 1H, H-4), 7.20-7.50 (m, 4H, H_{arom}), 7.70 (bs, 1H, NH), 9.29 (bs, 1H, NH). Anal cald for $C_{14}H_{15}ClN_2O_3$: C, 57.05; H, 5.13; N, 9.50%. Found: C, 57.23; H, 5.21; N, 9.78%.

Ethyl-4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e)

Yield 58%. IR (KBr): IR (KBr): ν = 3248, 3119, 3080-2900, 1722, 1700 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 1.01 (t, 3H, J= 7.1 Hz, CH_3), 2.10 (s, 3H, CH_3), 3.61 (6H, $2OCH_3$), 3.90 (q, 2H, J= 7.2 Hz, CH_2), 5.01 (d, 1H, J= 3.6 Hz, H-4), 6.60-6.80 (m, 3H, H_{arom}), 7.50 (bs, 1H, NH), 9.0 (bs, 1H, NH). Anal cald for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.74%. Found: C, 59.72; H, 6.34; N, 8.83%.

Ethyl-6-methyl-2thioxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f)

Yield 55%. IR (KBr): ν = 3223, 3126, 2931, 1730, 1649, 1465 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 1.08 (t, 3H, J= 7 Hz, CH_3), 2.23 (s, 3H, CH_3), 3.80 (q, 2H, J= 7 Hz, CH_2), 5.13 (d, 1H, J= 3 Hz, H-4), 7.23-7.31 (m, 5H, H_{arom}), 7.73 (s, 1H, NH), 9.19 (s, 1H, NH). Anal cald for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14%. Found: C, 61.04; H, 5.91; N, 10.21%.

Ethyl-6-methyl-2-thioxo-4-(3-hydroxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g)

Yield 72%. IR (KBr): ν = 3300, 3185, 1680, 1650, 1570 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 1.11 (t, 3H, J= 7 Hz, CH_3), 2.34 (s, 3H, CH_3), 4.02 (q, 2H, J= 7 Hz, CH_2), 5.20 (d, 1H, J= 3 Hz, H-4), 6.66-7.20 (m, 4H, H_{arom}), 8.90 (d, 1H, OH), 9.20 (s, 1H, NH), 9.80 (s, 1H, NH). Anal cald for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58%. Found: C, 57.36; H, 5.64; N, 9.84%.

Ethyl-4-(4-methoxyhenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4h)

Yield 61%. IR (KBr): ν = 3220, 3100-2900, 1680 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 1.14 (t, J = 7.3 Hz, 3H, CH_3), 2.35 (s, 3H, CH_3), 4.03 (q, J = 7.2 Hz, 2H, CH_2), 5.31 (bs, 1H, H-4), 6.84-7.20 (m, 4H, H_{arom}), 7.74 (bs, 1H, NH), 8.60 (bs, 1H, NH). Anal cald for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.14%. Found: C, 58.96; H, 6.05; N, 8.97%.

Ethyl-4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4i)

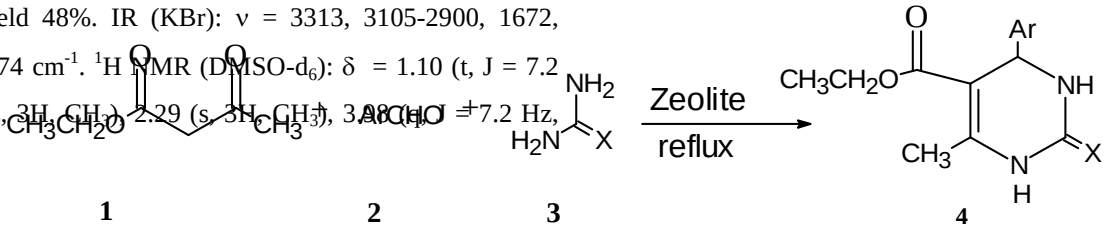
Yield 48%. IR (KBr): ν = 3313, 3105-2900, 1672, 1574 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 1.10 (t, J = 7.2 Hz, 3H, CH_3), 2.29 (s, 3H, CH_3), 3.98 (q, J = 7.2 Hz, 2H, CH_2), 5.16 (bs, 1H, H-4), 7.20-7.44 (m, 4H, H_{arom}), 9.70 (bs, 1H, NH), 10.42 (bs, 1H, NH). Anal cald for $C_{14}H_{15}ClN_2O_2S$: C, 54.10; H, 4.86; N, 9.01%. Found: C, 53.86; H, 4.98; N, 9.27%.

Ethyl-4-(4-methylphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4j)

Yield 65%. IR (KBr): ν = 3325, 3177, 1674, 1655 cm^{-1}. ^{1}H NMR (DMSO-d_6) : δ = 1.10 (t, J = 7.2 Hz, 3H, CH_3), 2.31 (s, 6H, $2CH_3$), 4.00 (q, J = 7.2 Hz, 2H, OCH_2), 5.20 (bs, 1H, H-4), 6.92-7.50 (m, 4H, H_{arom}), 9.50 (bs, 1H, NH), 10.20 (bs, 1H, NH). Anal cald for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25; N, 9.65%. Found: C, 62.24; H, 6.30; N, 9.51%.

Results and Discussion

The reaction was carried out by heating of three components, β-keto ester **1**, aldehyde **2** and urea/thiourea **3** in the presence of catalyst to give oxo- and thioxopyrimidines **4(a-j)** as shown in **Scheme 1**.



1 **2** **3** **4**

4a) Ar=phenyl, X=O
4b) Ar=4-nitrophenyl, X=O
4c) Ar=4-methylphenyl, X=O
4d) Ar=2-chlorophenyl, X=O
4e) Ar=3,4-dimethoxyphenyl, X=O
4f) Ar=phenyl, X=S
4g) Ar=3-hydroxyphenyl, X=S
4h) Ar=4-methoxyyphenyl, X=S
4i) Ar=4-chlorophenyl, X=S
4j) Ar=4-methylphenyl, X=S

Scheme 1

The ^{1}H and IR spectra of all synthesized compounds confirm the expected structures. In the ^{1}H-NMR spectra the two NH protons give two broad signals at down field shift, which is in support of the expected reaction. This is also confirmed by IR spectra, which included signals in the region of 3223-3394 cm^{-1}.

Antibacterial activity results of pyrimidines **4** against the Escherichia Coli (PTCC 1338), Pseudomonas aeruginosa (PTCC 1074), Entrococcus faecalis (PTCC 1237) and

Staphylococcus aureus (PTCC 1119) bacteria are shown in Table **1**. While compounds **4(a-j)** were not active against the Staphylococcus aureus, but these compounds found to be very active against the Escherichia Coli.

Table 1: Antibacterial activity of pyrimidines against four bacterials

Entry	Escherichia Coli (PTCC 1338)	Pseudomonas aeruginosa (PTCC 1074)	Entrococcus faecalis (PTCC 1237)	Staphylococcus aureus (PTCC 1119)
4a	+++	++	+	-
4b	++	+	+	-
4c	+++	++	-	-
4d	++	-	+	-
4e	+++	++	+	-
4f	+++	-	-	-
4g	+++	++	+	-
4h	+++	+	++	+
4i	+++	+	-	-
4j	+++	+	++	-

Weak activity = + (3-5) No activity= - (1-3)

Strong activity= +++ (10-15) Moderate activity= ++ (5-10)

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