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Synthesis and Biological Activities of Some Oxazolo- and Oxothiazolo Pyrimidines

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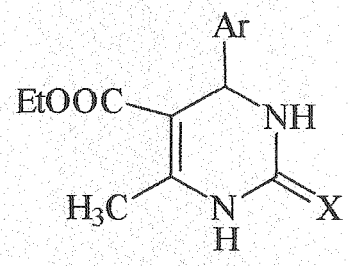
A series of pyrimidine derivatives **2a–i** and **3–5** were synthesized and their antimicrobial activities determined. These synthesized compounds were tested *in vitro* against *Escherichia Coli* (PTCC 1338), *Pseudomonas aeruginosa* (PTCC 1074), *Enterococcus faecalis* (PTCC 1237) and *Staphylococcus aureus* (PTCC 1119) bacteria. Microbiological results showed that only compound **5** containing an oxazepino ring was the active pyrimidine derivative against the *E. faecalis* and *S. aureus* bacteria with a MIC value of 128 μg/mL and 64 μg/mL respectively. However, the pyrimidines fused to a thiazole or ozazole ring; **2, 3** and **4** were not active against these bacteria.

Key Words: Oxazolo, Thiazolo. Pyrimidine, Microbiological, Bacteria.

INTRODUCTION

Pyrimidine derivatives are an important chemical class of heterocyclic compounds because of their diverse biological activities[1–13]. They show various interesting pharmacological properties including antiviral[1], antibacterial[2, 5], antihypertensive[4], antitumor[6] and antinflammatory effects[7]. Recently, the synthesis and microbiological activities of ethyl-4-aryl-6-methyl-2-oxo (or thioxo)-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives (**1**, X = O or S) with different aryl groups has been reported[11].



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In the present study, some pyrimidines countering oxazolo and thiazolo ring

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were synthesized in order to examine their *in vitro* antimicrobial activities against different Gram-positive and Gram-negative bacteria.

EXPERIMENTAL

Pyrimidine derivative **1** was prepared following a procedure in our earlier reports[14–16]. Compounds **2a–i, 3** and **4** were synthesized according to literature[17, 18]. The melting points were determined using an electrothermal digital melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker (500 MHz) spectrometer. TMS was used as an internal standard. The IR spectra were recorded on Galaxy FT-IR 500 spectrometer. Reaction courses and product mixtures were monitored by thin layer chromatography. All synthesized compounds were characterized. **2a–f, 3** and **5** as known compounds were characterized by comparison of their spectral data (IR, ^{1}H NMR) with those of authentic samples.

General preparation for 2a–i

A mixture of appropriate thiazolopyrimidine derivative **1** (0.002 mol), chloroacetylchloride (0.002 mol) and 10 mg silver acetate in dioxan (7 mL) was refluxed for 30 min. The mixture was filtered and the filtrate cooled at room temperature for 2 h. The precipitate was filtered off and washed with ethanol. The crude product was recrystallized from ethanol.

5-(2-Chloro-6-fluorophenyl)-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]-pyrimidine-6-carboxylic acid ethyl ester (2g): Yield: 65%; m.p. 152–154°C. IR (KBr, cm^{-1}) ν: 3080, 2940, 1724, 1703; ^{1}H NMR (DMSO-d_6): δ (ppm): 1.00 (t, 3H, J = 7.2 Hz, $CH_{3\text{-ester}}$), 2.20 (s, 3H, $CH_{3\text{-pyrimidine}}$), 4.00 (s, 2H, $CH_{2\text{-thiazole}}$), 4.50 (q, 2H, J = 7.2, $CH_{2\text{-ester}}$), 6.40 (s, 1H, $H_{pyrimidine}$), 7.40 (m, 3H, H_{arom}). Anal. (%) Calcd. for $C_{16}H_{14}N_2SO_3ClF$: C, 52.10; H, 3.80; N, 7.60; Found: C, 52.41; H, 3.55; N, 7.45.

5-(4-Acetamidophenyl)-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]-pyrimidine-6-carboxylic acid ethyl ester (2h): Yield: 60%, m.p. 148–150°C. IR (KBr; cm^{-1}) ν: 3700, 1691, 1685, 1514. ^{1}H NMR (DMSO-d_6): δ (ppm): 1.20 (t, 3H, J = 7.2 Hz, $CH_{3\text{-ester}}$), 2.10 (s, 3H, $CH_{3\text{-pyrimidine}}$), 2.40 (s, 3H, $COCH_3$), 4.00 (S, 2H, $CH_{2\text{-thiazole}}$), 4.22 (q, 2H, J = 7.2, $CH_{2\text{-ester}}$), 6.00 (s, 1H, $H_{pyrimidine}$), 7.50 (m, 4H, H_{arom}), 10.00 (bs, 1H, NH). Anal. (%) Calcd. for $C_{18}H_{19}N_3SO_4$: C, 57.91; H, 5.09; N, 11.26; Found: C, 57.75; H, 5.00; N, 11.46.

5-(4-N,N-dimethylaminophenyl)-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo-[3,2-a]pyrimidine-6-carboxylic acid ethyl ester(2i): Yield: 68%, m.p. 128–130°C; IR (KBr, cm^{-1}) ν: 3000, 2829, 1714, 1682; ^{1}H NMR (DMSO-d_6): δ (ppm): 1.46 (t, 3H, J = 7.2 Hz, $CH_{3\text{-ester}}$), 2.72 (s, 3H, $CH_{3\text{-pyrimidine}}$), 3.50 (s, 6H, 2 × NCH_3), 4.01 (s, 2H, $CH_{2\text{-thiazoie}}$), 4.40 (q, 2H, J = 7.2, $CH_{2\text{-ester}}$), 6.10 (s, 1H, $H_{pyrimidine}$), 7.50 (m, 4H, H_{arom}). Anal. (%) Calcd. for $C_{18}H_{21}N_3SO_3$: C, 60.10; H, 5.84; N, 11.69; Found: C, 60.30; H, 5.65; N, 11.50.

5-Phenyl-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-methyl-ketone (4): Yield: 90%, m.p. 195–196°C; IR (KBr, cm^{-1}) ν: 3000, 2940, 1760, 1660; ^1H NMR (DMSO-d_6): δ (ppm) : 2.20 (s, 3H, $CH_{3\text{-pirimidine}}$), 2.40 (s, 3H, $COCH_3$), 4.20 (s, 2H, $CH_{2\text{-thiazole}}$), 6.00 (s, 1H, $H_{pyrimidine}$), 7.36 (m, 5H, H_{arom}). Anal. (%) Calcd. for $C_{15}H_{14}N_2SO_2$: C, 62.93; H, 4.90; N, 9,79; Found: C, 62.50; H, 4.70; N, 9.60.

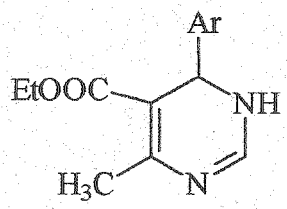
Biological activities

Antibacterial effects were studied through applying broth dilution method, which is the most precise and reliable one for determining the sensitivity degree of microbes towards antibiotics[19]. All compounds were dissolved in DMSO (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 was Muller-Hinton Broth (21 g/L). A set of tubes containing only inoculated broth was kept as control. It was determined that the solvent had no antimicrobial activity against any of the test microorganisms. All compounds were tested for their *in vitro* growth inhibitory activity against different bacteria. The origins of bacterial structures were *Escherichia coli* (PTCC 1338), *Pseudomonas aeruginosa* (PTCC 1074), *Enterococcus 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 growth of microorganism was recorded to represent the minimum inhibitory concentrations (MIC) in terms of μg/mL. Every experiment in the antibacterial assay was replicated twice in order to define the MC values

RESULTS AND DISCUSSION

Reaction of appropriate pyrimidine derivative **1** and chloroacetylchloride in dioxane as a solvent under reflux afforded **2a–i** in high yield. These compounds were obtained as a result of nucleophilic attack on N-3 position of the pyrimidine **1**, which is a well-documented reaction[17, 18, 20]. Compounds **2a–f, 3** and **5** are known. The structural elucidation of the synthesized compounds was assigned on the basis of their IR and ^1H NMR spectral data. As an example, in the IR spectra of **2g** absence of the absorption at 3400–3200 cm^{-1}, the characteristic absorption of NH group of starting material is in support of the expected reactions.

^1H NMR spectra of **2g** shows a singlet signal at 2.20 ppm due to CH_3 resonance of the pyrimidine ring. The multiplet signal at 7.40 ppm and the sharp singlet signal at 6.40 ppm are assigned to resonance of the aryl and pyrimidine ring protons, respectively. Two protons of one CH_2 group of the thiazole ring resonate as a singlet signal at 4.00 ppm. The CH_3 of the ester group resonates as a triplet at 1.00 ppm.



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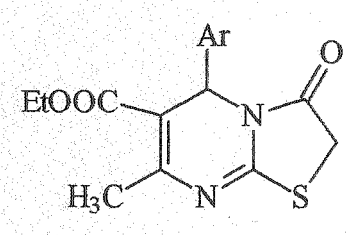
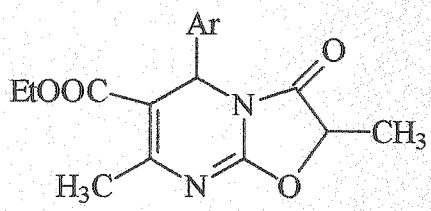
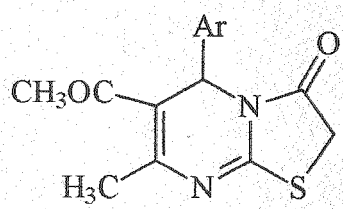


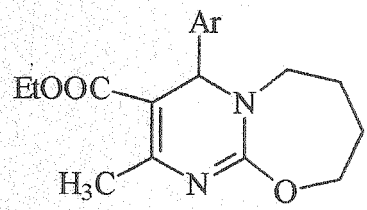
2a) Ar: 4-methylphenyl
2b) Ar: 2,5-dimethoxyphenyl
2c) Ar: 3-nitrophenyl
2d) Ar: 4-metthoxyphenyl
2e) Ar: 2-thienyl (C_4H_3S)
2f) Ar: 3-nitrophenyl
2g) Ar: 2-chloro-6-fluorophenyl
2h) Ar: 4-acetamidophenyl
2i) Ar: 4-(N,N-dimethyaminophenyl)



3) Ar: 4-methoxyphenyl



4) Ar: phenyl



5) Ar: 4-chlorophenyl

All synthesized compounds were tested against *Escherichia coli* (PTCC 1338), *Pseudomonas aeruginosa* (PTCC 1074), *Entrococcus faecalis* (PTCC 1237) and *Staphylococcus aureus* (PTCC 1119) bacteria. Ethyl 4-(4-chlorophenyl)-2-methyl-6,7,8,9-tetrahydro-4H-pyrimido[2,1-b][1,3]oxazepine-3-carboxylate **(5),** containing an oxazepino ring, showed antibacterial activity against the *E. farcalis* and *S. aureus* bacteria with an MIC value of 128 μg/mL and 64 μg/mL respectively. However other pyrimidine compounds containing an oxazolo or thiazolo ring were not effective against all four chosen bacteria compared to pyrimidine derivatives without these two rings[11, 20]. Therefore, the oxazol or thiazol ring may have negative effect on the antibacterial activity of the original pyrimidine derivatives **1**.

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