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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NEW 3, 4- DIHYDROPYRIMIDINONES

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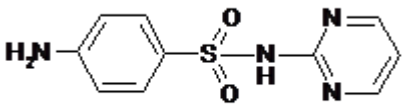
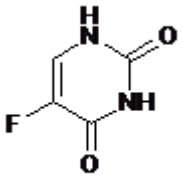
ABSTRACT

A number of aldehydes were reacted with acetyl acetone or ethyl acetoacetate and urea under Biginelli reaction conditions to give the corresponding 5-acyl-4-(substituted-aryl)-6-methyl-3,4-dihydropyrimidin-2-one. The 5-acetyl-derivatives were converted into pyrimido-oxazoles, pyrimido-pyrazoles, and chalcones. Some Mannich bases were also synthesized. Some selected compounds were tested for their antimicrobial activities.

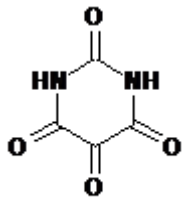
INTRODUCTION: The presence of pyrimidine ring in nucleic acid, uric acid, several vitamins, some purines, and their importance in many biological processes may explain the biological significance of such molecule in the drugs containing them. Examples of synthetic drugs containing this group include. Sulfadiazines [1] and fluorouracil [2] as antimicrobials, alloxan [3] for its diabetogenic action, trimethoprim [4] as antibacterial and others.



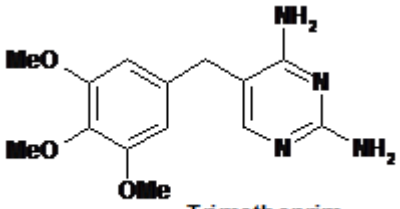
Sulfadiazine



Fluorouracil



Alloxan

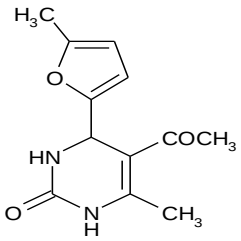


Trimethoprim

Other interesting pyrimidine containing compounds are those derived from dihdropyrimidinones (the so called Biginelli compounds) [5] which draw the attention of many synthetic workers in the last few decades. These compounds even those having small molecules, are known by their antihypertensive properties [6] in addition to their diverse range of biological activities such as antiviral [7], antimicrobial [8], antitumor [9], anti-inflammatory [10] and especially as antifungal activities [11]. The most familiar examples of Biginelli compounds are those obtained by condensation of a β- keto- ester with urea (or thiourea) and an aldehyde. On this basis, several dihydropyrimidinones have been synthesized by using the art of combinatorial chemistry [6-11]. Using acetyl acetone or its derivatives in this reaction has not taken the same attention as for the use of β-keto-esters, in spite the fact that the acetyl group in position-5 is chemically reactive and thus giving an access to new derivatives, while that of the ester group in the same position has been proven in most cases not reactive.

In this work we report the synthesis and antimicrobial activity of some new dihydropyrimidinones of the Biginelli type, using mainly acetyl acetone with urea and an aldehyde followed by using the acetyl group in building other derivatives. Derivatives such as chalcones, oxazoles and pyrazoles constitute a major subgroup of naturally occurring compounds of pharmaceutical interest, e.g., chalcone synthase (CHS) catalyzes the first committed step in the biosynthesis of flavonoids and anthocyanin pigments. Anthocyanins play roles as pigments of flowers and fruits to attract insects for pollination and act as protectants against UV-B irradiation. They also exhibit anti-oxidant activities and therefore may serve as potential anticancer compounds [16].

Chemistry: The aldehydes used in this work include 5-methyfurfural, 4- hydroxy- and 4- methoxy benzaldehyde and 3-methyl benzaldehyde. The reaction was carried out by refluxing a mixture of the given aldehyde, acetyl acetone and urea in ethanol as solvent with few milliliters of acetic acid (conventional Biginelli method) by which the dihydropyrimidinones **1**-**4** were obtained. .



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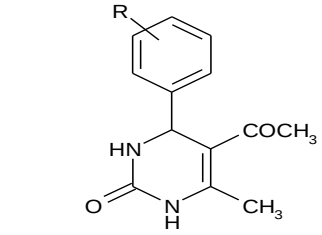
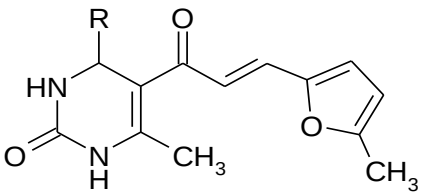


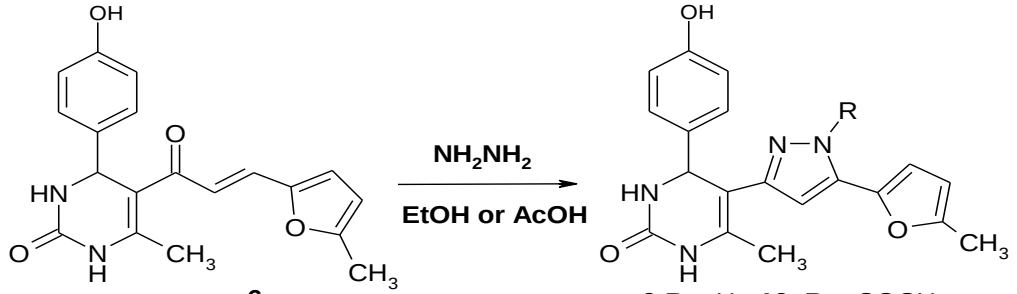
2, R= 4-OH, **3,** R= 4-OMe,
4, R= 3-Me

Reaction of any of the compounds **1**-**4** with 5-methyl-furfural gave the corresponding chalcones, 1-[6-methyl-4-(5-methyl-furan-2-yl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidin-5-yl]- 3- (5- methyl- furan- 2-yl)-prop-2-en-1-one **(5)** 1- [6- methyl- 4- (4- hydroxy-phenyl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidin-5-yl]-3- (5- methyl- furan- 2- yl)- prop- 2- en- 1- one (**6**), 1-[6- methyl- 4- (4- methoxy- phenyl)- 2- oxo- 1, 2, 3, 4-tetrahydropyrimidin-5-yl]-3-(5-methyl-furan-2-yl)-prop-2-en-1-one (**7**) and 1-[6-methyl-4-(3-methyl-phenyl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidin-5-yl]-3-(5- methyl- furan- 2- yl)- prop- 2- en- 1- one (**8**), respectively.



5 R = 5-methyl furan-2-yl, **6** R = 4-hydroxyphenyl.
7 R = 4-methoxyphenyl, 8 R = 3-methylphenyl

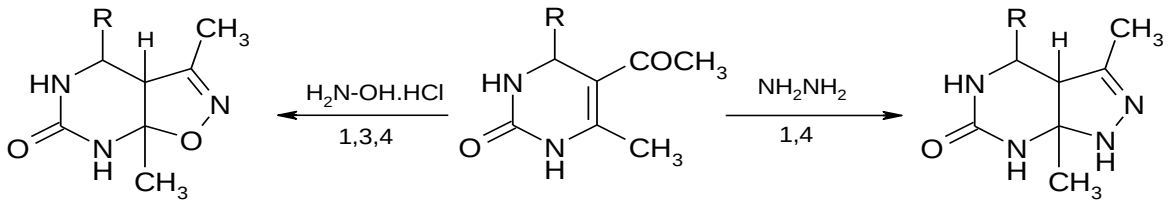
Reaction of the chalcone **6** with hydrazine hydrate in ethanol gave the corresponding 4- (4- hydroxy-phenyl)- 6- methyl- 5- [5- (5- methyl- furan- 2- yl)-1H- pyrazol- 3- yl]- 3, 4- dihydro- 1H- pyrimidin- 2-one (**9**), while with hydrazine hydrate in acetic acid gave the N-acetyl derivative (**10**).



6

9 R = H; **10**, R = $COCH_3$

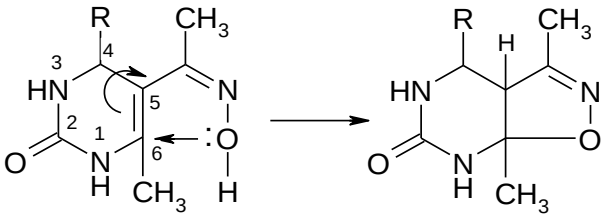
Reaction of each of the compounds **1**,**3** and **4** with hydroxyl amine hydrochloride in the presence of sodium acetate gave the corresponding 3,7a-dimethyl-4-(aryl)-4,5,7,7a-tetrahydro-3aH-isoxazolo-[5, 4-d]-pyrimidin-6-one (**11-13)** via intramolecular cyclization. Hydrazine hydrate behaved similarly upon its reaction with **1** and **3** and gave the corresponding 3, 7a- dimethyl-4- (aryl) - 1, 3a, 4, 5, 7, 7a- hexahydro-pyrazolo-[3, 4- d]- pyrimidin- 6-one (**14** and **15**).



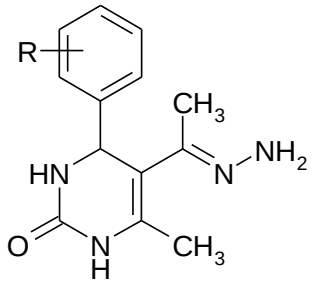
11 R = 5-methyfuranyl
12 R = 4-methoxyphenyl
13 R = 3-methylphenyl

14 R = 5-methyfuranyl
15 R = 4-methoxyphenyl

Cyclization was formed by a Michael-type addition of the oxime (or hydrazone) proton to C_5 with linking of the oxygen (or nitrogen) atom to C_6 of the pyrimidine ring; both types of reactions have been described in one of our previous publications [12].

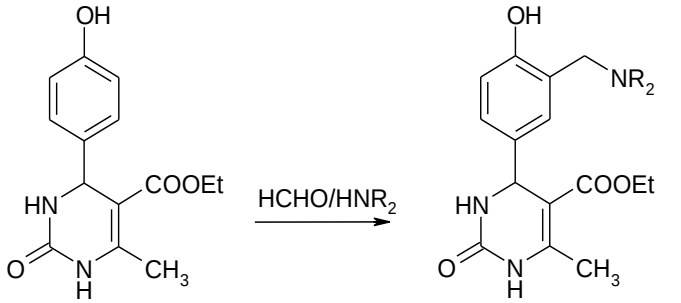


Reaction of hydroxyl amine with compound **2** gave a mixture of hardly separable products, Compounds **2** and **4** reacted with hydrazine hydrate to give the corresponding hydrazones, 5-(1-hydrazonoethyl)-4-(4-aryl)-6-methyl-3, 4-dihydro-1H-pyrimidin-2-ones (**16** and **17)**, respectively without cyclization, the reason is not clear and needs further study..



16 R = 4-OH, **17** R = 3-Me,

Because the Mannich [13] bases play some role in the biological activity of compounds containing them, it was of interest to prepare some of their pyrimidinone derivatives. Thus, reaction of ethyl acetoacetate with urea and 4-hydroxy-benzaldehyde gave the corresponding ester **18**, which was subjected to react with formaldehyde and some secondary amines mainly, piperidine, morpholine and methyl piperazine to give the Mannich bases 4- (4- hydroxy- 3- N-substituted-methyl-phenyl)- 6- methyl- 2- oxo- 1, 2, 3, 4- tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (**19-21**).



18

19 $R_2 = C_5H_{10}$, **20** $R_2 = C_4H_8O$
21 R = $C_5H_{11}N_2$

Antimicrobial activity: The antimicrobial activity of twelve representative examples from the synthesized compounds was examined. Antibacterial activity was carried out against *Bacillus subtilis, Bacillus cereus* and *Staphylococcus aureus* (gram positive bacteria), and two of gram negative bacteria, *Escherichia coli* and *Pseudomonas aeruginose* in addition to the fungus *Candida albicans*. The obtained results were compared with reference antibiotics

Experimental: Melting points were measured using Electro-thermal IA 9100 melting point apparatus, (Shimadzu, Tokyo, Japan). IR spectra were recorded on Perkin-Elmer 1650 spectrophotometer (Perkin-Elmer, Norwalk, CT, USA) using potassium bromide pellets and measured. in wave number cm^{-1} ^{1}H-NMR was determined on a Jeol-Ex-300 NMR spectrometer (JEOL, Tokyo, Japan) and chemical shifts were expressed as part per million (ppm) against TMS as internal reference; measurement of all the compounds was performed in Deuterated dimethyl sulfoxide (DMSO-d_6).

Mass spectra were recorded on VG 2AM-3F mass spectrometer. Microanalyses were measured by the Organic Microanalysis Unit at Cairo University, Egypt. Purity of the compounds was checked by thin layer chromatographic technique

Synthesis of 5- acyl- 4- aryl- 6- methyl- 3, 4- dihydropyrimidinones (1- 4 and 18):

General procedure: A mixture of the selected aldehyde (10 mmol), urea (1.5 g, 25 mmol) and acetylacetone or ethyl acetoacetate (15 mmol) in absolute ethanol (50 mL) acidified with glacial acetic acid (2 mL) or *p*-toluene sulphonic acid (2.0 g, 12 mmol) was heated under reflux for 5-12 h. The solvent was removed under reduced pressure and the residue was treated with water, filtered off, washed with water, dried and crystallized from methanol to give the desired compounds.

5- Acetyl- 4- (5- methylfuranyl) - 6- methyl- 3, 4- dihydro-1H-pyrimidin-2-one (1): Yield**,** 78%, m.p. 208-210^{o}C, IR: 3345 (NH), 3268 (NH), 1706 (CO), 1679 (CO). ^{1}H-NMR: 2.13 (s, 3H, CH_3), 2.19 (s, 3H, $COCH_3$), 2.22 (s, 3H, CH_3), 5.22 (s, 1H, C^4-H), 5.82 (d, 1H, furan), 5.94 (d, 1H, furan), 7.80 (s, 1H, N^3H, D_2O exchangeable), 9.18 (s, 1H, N^1H, D_2O exchangeable). Analysis: for $C_{12}H_{14}N_2O_3$ (234.25) Calcd.: C, 61.53; H:6.02; N:11.96; Found: C, 61.76; H, 5.87; N, 11.91.

5-Acetyl- 4- (4- hydroxyphenyl) - 6- methyl- 3, 4- dihydro-1H-pyrimidin-2-one (2). Yield**,** 75%, m.p. 206-208^{o}C (as reported) [14].

5- Acetyl- 4- (4- methoxyphenyl) - 6- methyl- 3, 4- dihydro-1H-pyrimidin-2-one (3). Yield**,** 88%, m.p. 178-180^{o}C (as reported) [14].

5- Acetyl- 4- (3- methylphenyl)- 6- methyl- 3, 4- dihydro-1H-pyrimidin-2-one (4). Yield**,** 70%, m.p. 255-258^{o}C (as reported) [15].

Synthesis of the chalcone derivatives (5-8):

General procedure: To a solution of any of the acetyl derivatives (**1-4**) (10 mmol) in ethanol (30 mL), was added 5-methylfurfural (1.1 mL,10 mmol) followed by addition of 30% solution of sodium hydroxide (12 ml). The mixture was stirred at room temperature for 24 h. The reaction product was then diluted with water (250 mL), acidified with dilute HCl and the formed precipitate was filtered, air dried and crystallized from dil. ethanol to give the desired compounds **5-8.**

1-[6-Methyl-4-(5-methylfuran-2-yl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidin-5-yl]-3-(5-methylfuran-2-yl)-prop-2-en-1-one (5): Yield, 75%, m.p. 110-113^{o}C. IR: 3226 (NH), 3108 (NH), 1689 (CO), 1620 (CO), 1563 (CH=CH). ^{1}H-NMR (d_6-DMSO, δ ppm): 2.23 (s, 3H, CH_3), 2.28 (s, 6H, 2 overlapped CH_3), 5.34 (s, 1H, C^4-H), 6.02 (d, 1H, furan), 6.25 (d,1H, furan), 6.56 (d, 1H, furan), 6.85 (d, 1H, furan), 7.19 (d, 1H, =CHCO), 7.35 (d, 1H, =CH-Ar), 7.90 (s, 1H, N^3H), 9.27 (s, 1H, N^1H). Ms: m/z (%): 327 (M^++1, 35), 283 (26), 216 (37), 177 (63), 166 (51), 159 (100%), 149 (73), 81(49); Analysis: for $C_{18}H_{18}N_2O_4$ (326.36) Calcd: C, 66.25; H, 5.56; N, 8.58; Found: C, 66.38; H, 5.79; N, 8.36.

1-[6-Methyl-4-(4-hydroxyphenyl)-2-oxo- 1, 2, 3, 4-tetrahydropyrimidin-5-yl]- 3-(5-methylfuran-2-yl)-prop-2-en-1-one (6): Yield, 85%, m.p.100-103^{o}C. IR: 3226 (NH), 3108 (NH), 1689 (CO), 1620 (CO), 1563 (CH=CH). ^{1}H-NMR: 2.18 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 5.23 (s, 1H, C^4-H), 6.24 (d, 1H, furan), 6.25 (d, 1H, furan), 6.52 (s, 1H, N^3H), 6.78 (d, 1H, COCH=), 7.05 (d, 2H, Ar-Hs), 7.13 (d, 2H, Ar-Hs), 7.82 (d, 1H, =CH-Ar), 9.16 (s, 1H, N^1H), 9.37 (s, 1H, OH). Ms, m/z (%): 338, M^+ (25), 323 (12), 243 (17), 229 (10), 201 (62), 135 (46), 94 (65), 82 (20), 78 (100%). Analysis: for $C_{19}H_{18}N_2O_4$. (338.36), Calcd: C, 67.45; H: 5.36; N, 8.28; found: C, 67.31; H, 5.28; N, 8.02

1-[6-Methyl-4-(4-methoxyphenyl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidin-5-yl]- 3-(5-methylfuran-2-yl)-prop-2-en-1-one (7): Yield, 88%, m.p. 112-114^{o}C. IR: 3228 (NH), 3114 (NH), 1696 (CO), 1626 (CO), 1603 (CH=CH). ^{1}H-NMR: 2.15 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 5.31 (s, 1H, C^4-H), 6.24 (d, 1H, furan), 6.25(d, 1H, furan), 6.56 (s, 1H, N^3-H, D_2O exchangeable), 6.75 (d, 1H, COCH=), 6.89 (d, 2H, Ar-Hs), 7.22 (d, 2H, Ar-Hs), 7.76 (d, 1H, =CH-Ar), 9.21 (s,

1H, N^1H). Ms, m/z (%): 352, M^+ (23), 239 (25), 226 (18), 201 (20), 171 (42), 136 (27), 108 (35), 78 (100%). Analysis: for $C_{20}H_{20}N_2O_4$. (352.38), Calcd: C, 68.17; H, 5.72; N, 7.95; found: C, 68.43; H, 5.78; N, 7.87,

1-[6-Methyl-4-(3-methylphenyl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidin-5-yl] - 3-(5-methylfuran-2-yl)-prop-2-en-1-one (8): Yield, 90%, m.p.124-125, IR: 3228 (NH), 3114 (NH), 1696 (CO), 1626 (CO), 1603 (CH=CH). Ms, m/z (%): 335, M^+-1 (15), 320 (9), 292 (22), 243 (43), 229 (74), 201 (65), 153 (100%), 91 (28). Analysis: for $C_{20}H_{20}N_2O_3$ (336.38) C, 71.41; H, 5.99; N, 8.33; found: C, 71.39; H, 5.90; N, 8.16%.

4- (4- Hydroxyphenyl) - 6- methyl- 5- [1- (5-methylfuran- 2- yl) - 1H-pyrazol- 3- yl]-3, 4-dihydro- 1H- pyrimidin- 2-one (9): A solution of compound **6** (0.67 g, 2 mmol) in absolute ethanol (25 mL) was refluxed with hydrazine hydrate (2 mL) for 12 h. The reaction product was diluted with water (50 mL) and the solid formed was filtered off and recrystallized from ethyl alcohol to give compound **9**. Yield 60%; m.p**.** 138-139 °C. Ms: m/z (%): 352 M^+, (31), 320 (18), 261 (100%), 202 (30), 149 (20), 93 (21). Analysis: $C_{19}H_{20}N_4O_3$ (352.39) Calcd: C, 64.76; H, 5.72; N; 15.90%; found: C: 64.92; H: 5.63 N: 15.78, found.

5-[1-Acetyl-5-(5-methylfuran-2-yl)-1H-pyrazol-3-yl]-4- (4- hydroxy- phenyl)- 6- methyl- 3, 4- dihydro-1H-pyrimidin-2-one (10): The molar ratios of the reactants and the method used are similar to that described above except that ethanol was replaced by acetic acid (10 mL). Yield, was 72%, m.p.152-154°C. IR: 3354 (OH), 3175 (NH), 3118 (NH), 1731 (CO), 1679 (CO). Ms m/z (%) 396, M^++2, (16), 320 (9), 279 (36), 187 (75), 178 (16), 163 (22), 94 (100%). Analysis: For $C_{21}H_{22}N_4O_4$ (394.42) Calcd: C, 63.95; H, 5.62; N, 14.20%; found: C, 63.85; H: 5.70; N: 14.39.

Synthesis of 3aH-isoxazolo-[5, 4-d]-pyrimidin-6-ones (11-13):

General procedure: A mixture of any of the acetyl derivatives **1**,**3** or **4** (10 mmol), hydroxylamine hydrochloride (1.0 g, 15 mmol) and anhydrous sodium acetate (1.5g) in absolute ethyl alcohol (30 mL) was heated under reflux for several hours until completion of the reaction (4-12 h, monitored by TLC). The solvent was removed under reduced pressure and the residual product was treated with water, filtered,washed with water and crystallized from methanol to give the title compounds **11-13**

3, 7a-Dimethyl-4-(5-methylfuran-2-yl)- 4, 5, 7, 7a-tetrahydro-3aH-isoxazolo-[5,4-d]-pyrimidin-6-one (11): Yield 75%, m.p. 248-250˚C, IR: 3324 (NH), 3217 (NH), 1690 (CO). ^{1}H-NMR (d_6-DMSO,δ ppm): 1.21 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 3.69 (s, 1H, C^5-H), 4.63 (s, 1H, C^4-H), 5.94 (d, 1H, furan), 6.04 (d, 1H, furan), 7.00 (s, 1H, N^3-H), 7.25(s, 1H, N^1-H). Ms m/z (%): 249 M^+, (40), 190 (35), 176 (47), 151 (100%). Analysis, for $C_{12}H_{15}N_3O_3$ (249.27), Calcd. C:57.82; H, 6.07; N, 16.86 found: C, 57.70; H, 6.17; N, 16.65.

3, 7a-Dimethyl- 4- (4- methoxyphenyl) - 4, 5, 7, 7a-tetrahydro-3aH-isoxazolo-[5, 4-d]-pyrimidin-6-one (12): Yield 78%, m.p. 222-225˚C, IR: 3356 (NH), 3215 (NH), 1686 (CO). ^{1}H-NMR: (δ ppm)1.06 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 3.68 (s, 1H, C^5-H), 3.75 (s, 3H, OCH_3), 4.63 (s, 1H, C^4-H), 6.93 (d, 2H, Ar-Hs), 7.08 (s, 2H, 2NHs), 7.26 (d, 2H, Ar-Hs). Ms m/z (%): 274, M^+-1, (15), 257 (5), 201 (31), 186 (10), 177 (94), 134 (100%), 97 (16). Analysis: for $C_{14}H_{17}N_3O_3$ (275.30), Calcd. C: 61.08; H: 6.22 N, 15.26; found: C, 61.00; H, 6.23; N, 15.16.

3, 7a- Dimethyl- 4- (3- methylphenyl) - 4, 5, 7, 7a-tetrahydro-3aH-isoxazolo-[5, 4-d]-pyrimidin-6-one (13): Yield 80%, m.p. 280-282˚C, IR: 3329 (NH), 3230 (NH), 1693 (CO). ^{1}H-NMR (δ ppm): 1.04 (s, 3H, CH_3), 1.97 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.71 (s, 1H, C^5-H),

4.64 (s, 1H, C^4-H), 7.08-7.29 (m, 6H, 4Ar-Hs and 2NHs). Ms m/z (%): 260, M^++1, (15), 211 (8), 197 (7), 169 (11), 111 (37), 97 (100%). Analysis: for $C_{14}H_{17}N_3O_2$ (259.30), calcd.: C, 64.85; H, 6.61; N, 16.20; found: C, 64.70; H: 6.42; N, 16.38.

Synthesis of pyrazolo-pyrimidinones (14 and **15):**

General procedure: To a solution of the appropriate acetyl derivative **1** or **4** (10 mmol) in dioxane (30 mL), was added hydrazine hydrate (2 mL), the mixture was then heated under reflux for several hours until completion of the reaction (monitored by TLC). The solvent was removed under reduced pressure and the residual product was treated with water, filtered, washed with water and dried. Crystallization from methanol gave the title compounds **14** and **15**

3, 7a-Dimethyl-4-(5-methylfuran-2-yl)-1, 3a, 4, 5, 7, 7a- hexahydro- pyrazolo-[3, 4-d] - pyrimidin- 6- one (14): Yield 75%, m.p. 231-233°C, IR: 3351(NH), 3282 (NH), 3211 (NH), 1649 (CO). ^{1}H-NMR. (δ ppm): 1.03 (s, 3H, CH_3), 1.83 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 3.15 (s,1H, C^5-H), 4.63 (s, 1H, C^4-H), 5.95(d, 1H, furan), 6.08 (d, 1H, furan), 6.19 (s,1H, N^3-H), 6.83 (s, 1H, N^1-H), 11.94 (s, 1H, NH) Analysis: for $C_{12}H_{16}N_4O_2$ (248.28); Calcd. C, 58.05; H, 6.50; N: 22.57; found: C, 58.37; H, 6.28; N, 22.39.

3, 7a-Dimethyl-4-(3-methyphenyl)-1, 3a, 4, 5, 7, 7a-hexahydro-pyrazolo-[3, 4-d]-pyrimidin-6-one (15): Yield 65%, m.p. 240-242°C ^{1}H-NMR (d_6-DMSO,δ ppm): 0.85 (s,3H, CH_3), 1.86 (s, 3H,CH_3), 3.11(s, 1H, C5-H), 3.73(s, 3H, OCH_3), 4.65(s, 1H, C4-H), 6.05(s, 1H, N^3H), 6.14(s, 1H, N^1H), 6.84(s,1H, NH), 6.93(d, 2H, Ar-Hs), 7.23 (d, 2H, Ar-Hs). Analysis: for $C_{14}H_{18}N_4O$ (258.33); Calcd.: C, 65.09; H, 7.02; N,: 21.69; found: C, 65.12: H, 7.31: N, 21.60%.

Synthesis of the hydrazonoethyl derivatives 16 and 17: A mixture consisting of any of the acetyl derivatives **2** or **4** (10 mmol), dioxane (30 mL) and hydrazine hydrate (2 mL) was heated under reflux for 6 h. The solvent was removed under reduced pressure and the residual product was treated with water, filtered, washed with water, dried and crystallized from ethanol to give the title compounds **16** and **17.**

5- (1- Hydrazonoethyl) - 4- (4- hydroxyphenyl) - 6-methyl- 3, 4- dihydro- 1H- pyrimidin- 2-ones (16): Yield 76%, m.p. 243-245°C; IR: 3473 (NH_2), 3267 (NH), 3221 (NH), 1643 (CO). ^{1}H-NMR (δ ppm): 1.95 (s, 6H, $2CH_3$), 5.51 (s, 2H, NH_2), 5.73 (d, 1H, C^4-H), 6.40 (d, 1H, N^3-H), 6.69 (d, 2H, Ar-Hs), 6.97 (d, 2H, Ar-Hs), 9.27 (s, 1H, N^1-H), 12.00 (s, 1H, OH). Analysis: for $C_{13}H_{16}N_4O_2$ (260.29) Calcd.: C, 59.99; H, 6.20; N, 21.52; found: C, 60.25; H, 6.40 N, 21.48%.

5- (1- Hydrazonoethyl) - 4 - (3- methylphenyl) - 6-methyl-3, 4- dihydro- 1H- pyrimidin- 2- ones (17): Yield 80%, m.p. 285-287°C; IR: 3467& 3465 (NH_2), 3260 (NH), 3225 (NH), 1650 (CO); ^{1}H-NMR (δ ppm): 1.93 (s, 6H, $2CH_3$), 2.25 (s, 3H, CH_3), 5.51 (s, 2H, NH_2), 5.75 (d, 1H, C^4-H), 6.47 (d, 1H, N^3-H), 7.00 - 7.23 (m, 4H, Ar-Hs), 11.99 (s, 1H, N^1-H). Analysis:for $C_{14}H_{18}N_4O$ (258.32) Calcd.: C, 65.09; H, 7.02; N, 21.69 %; found: C, 65.00; H, 7.00; N, 21.50%

Synthesis of the Mannich bases 19-21:

General method: A mixture of compound **10** (2.76 g, 10 mmol) and the appropriate secondary amine, namely, piperidine, morpholine or methyl piperazine (10 mmol) and paraformaldehyde (0.99 g, 33 mmol) in absolute ethyl alcohol (50 mL) was heated under reflux for 12 h. (monitored by TLC). The solvent was then evaporated under vacuum and the residue obtained was treated with water, filtered then washed with water, dried and crystallized from methanol to give compounds **(19-21)**

4- (4- Hydroxy- 3- piperidinomethyl- phenyl) - 6-methyl- 2- oxo- 1, 2, 3, 4- tetrahydro- pyrimidine-5-carboxylic acid ethyl ester (19): Yield 74%, m.p. 108-110; IR (υ cm^{-1}): 3560, (OH); 3260 (NH), 3215

(NH), 1739 (CO ester); 1650 (CO);. ^{1}H-NMR (δ ppm): 1.05 (t, 3H, CH_3 ester) 1.54 (m, 2H, CH_2-piper-H); 1.66 (m, 4H, CH_2-piper-H).; 2.22 (s, 3H, CH_3-C_5); 2.35 (t, 4H, - 2CH_2-piper.); 3.46 (s, 2H, CH_2-N); 4.12 (q, 2H, CH_2-ester), 4.87 (s, 1H, C4-H); 6,72 (d, 2H, Ar-H); 7.12 (s, 1H, Ar-H); 7.35 (s, 1H, NH); 9.22 (s, 1H, N^1-H), 12.00 (s, 1H, OH); Ms: m/z (%): 373 (M^+, 15), 183 (21), 98 (32), 84 (100%). Analysis: for $C_{20}H_{27}N_3O_4$ (373.45) Calcd.: C, 64.32; H; 7.29; N, 11.25; found: C, 64.20; H, 7.32; N, 11.10

4- (4- Hydroxy- 3- morpholinomethyl- phenyl) - 6- methyl- 2- oxo- 1, 2, 3, 4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (20); Yield 74%, m.p. 102-104; Ms: m/z (%): 375(M^+, 16%), 358 (7%), 302 (10%), 289 (13), 183 (36), 100 (60), 87(100%) Analysis: for $C_{19}H_{25}N_3O_5$ (375.42) Calcd.: C, 60.79; H:6.71; N:11.19; found: C: 60.77; H: 6.59; N: 11.31

4- [4- Hydroxy- 3- (4- methyl- piperazin- 1- ylmethyl) - phenyl]- 6- methyl- 2- oxo- 1, 2, 3, 4-tetrahydro-pyrimidine-5-carboxylic acid ethyl este (21): Yield 70%, m.p. 99-102; IR (υ cm^{-1}): 3556, (OH); 3266 (NH), 3210 (NH), 1746 (CO ester); 1650 (CO);. Ms: m/z (%): 389 (M^++1, 21), 315 (45), 99 (100%). Analysis: for $C_{20}H_{28}N_4O_4$ (388.47) Calcd. C, 61.84; H, 7.27; N, 14.42; found: C, 61.66; H, 7.40; N, 14.32.

Antibacterial and Antifungal Activities of the Synthesized Compounds:

MATERIALS AND METHODS: Measuring of antimicrobial activities was carried out by using the plate method [21-24]. A filter paper sterilized disc saturated with (1ml, mg/ml) of the sample is placed on a plate (9cm diameter) containing a solid bacterial medium (nutrient agar broth) or a fungal medium (Dox's medium) which has been seeded with the spore suspension of the test organism. After incubation at 37^{o}C for 24 h for bacteria and at 25^{o}C for 72 h in case of fungi, the diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism;

(% inhibition = sample inhibition zone (cm)/plate diameter × 100).

All measurements were done in chloroform as a solvent which has zero inhibition activity. The antimicrobial activity of the tested compounds were examined with gram positive bacteria, Bacillus *subtilis,* Bacillus *cereus* and Staphylococcus *aureus* and gram negative bacteria Escherichia *coli,* Pseudomonas *aeruginose* and the fungus Candida *albicans*. The obtained results are compared with a reference antibiotics that were purchased from Egyptian markets.

RESULTS: As seen from the **table 1**, the tested compounds showed variable antimicrobial activities which range from non to moderate. With respect to this class of compounds, it is characterized by their antifungal activity towards the pathogen, *Candida albicans*, yet compounds No. 5, 6 (examples of chalcones) 15, and 21 showed the highest clear zone reaching 14 and 15 mm, which has a valuable medical trend.

ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF THE SYNTHESIZED COMPOUNDS

Organism	Inhibition zone diameter mm/ mg sample												
	Compound Number												
	1	2	3	4	5	6	11	12	15	16	18	21	Ref.
B. subtilis	11	8	8	3	12	9	10	4	2	10	7	8	40
B. cereus	9	2	4	0	0	0	0	0	9	7	4	8	30
E. coli	2	2	7	0	0	0	6	0	0	3	0	3	20
P. aeruginose	5	0	3	0	0	0	5	2	0	0	5	0	35
Staph aureus	0	0	5	0	0	4	3	3	0	3	0	3	50
C. albicans	12	11	10	10	14	15	12	14	15	12	13	15	44

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