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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NEW PYRIMIDINE DERIVATIVES

Kamelia M. El-mahdy and Azza M. El-Kazak*

Department of Chemistry, Faculty of Education, Ain Shams University, Roxy, 11711, Cairo, Egypt

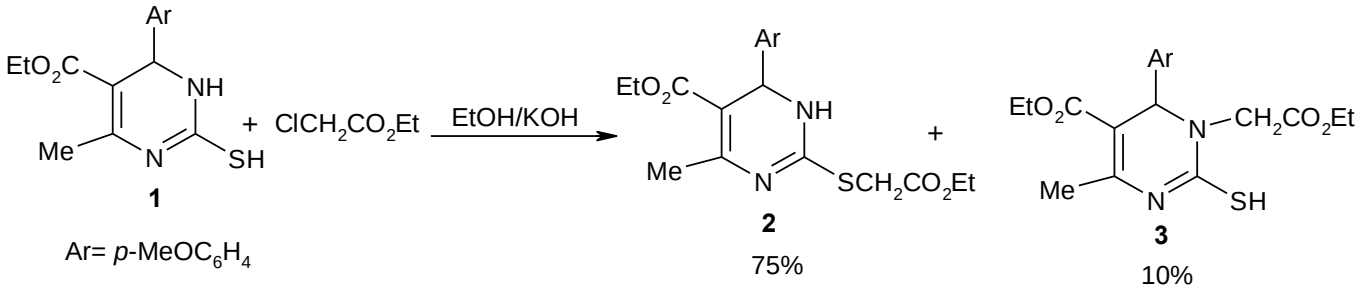
*Corresponding Author: Email: az_azelkazak@yahoo.com

Abstract – Reaction of 2-mercaptopyrimidine **1** with ethyl chloroacetate afforded isomeric pyrimidines **2** and **3**. Interaction of **3** with bifunctional nitrogen nucleophiles yielded pyrimidotriazine **5** and **7**. Hydrazinolysis of **2** by hydrazine hydrate afforded hydrazinopyrimidine **8**. Treatment of **8** with acetophenone gave **9**. Cyclization of **9** with Vilsmeier reagent afforded the pyrazole carbaldehyde **10**. Interaction of **8** with benzylidenemalononitrile and/or ethyl ethoxymethylene-cyanoacetate afforded the pyrazoles **11** and **12**. The reaction of **8** with *p*-chlorobenzaldehyde yielded **13**, which was cyclized with thioglycolic acid to give thiazolidinone **14**. The biological activity of selected compounds was investigated.

The synthesis of dihydropyrimidine derivatives have been attracting extensive attention as a wide range of such compounds played an important role in the field of medicinal chemistry as antiviral,[1] antibacterial,[2] antimalarial,[3] antihypertensive[4] and anti-inflammatory agents.[5] In addition, pyrimidine derivatives form the basis of a large number of pharmacological products with anticancer and protein kinase inhibitory activity.[6,7] The Biginelli reaction[8] is a simple one-pot condensation of an aldehyde, keto ester, and urea or thiourea in the presence of catalytic amount of acid to produce 3,4-dihydropyrimidin-2(1*H*)-ones. Dihydropyrimidinones (DHPMs) and their derivatives exhibit wide range of biological activities such as antibacterial, antiviral, antitumour, and anti-inflamatory actions.[9] Biginelli compounds exhibit pharmacological activities as calcium channel blockers, antihypertensive agents, α-1a–antagonists, and neuro peptide Y(NPY) antagonists.[10-12] Biological activities of some marine alkaloids isolated were also found to contain the dihydropyrimidinone-5-carboxylate core.[13-16]

The versatile biological properties of pyrimidine derivatives prompted us to synthesize some novel pyrimidine and fused heterocyclic pyrimidine derivatives for biological screening.

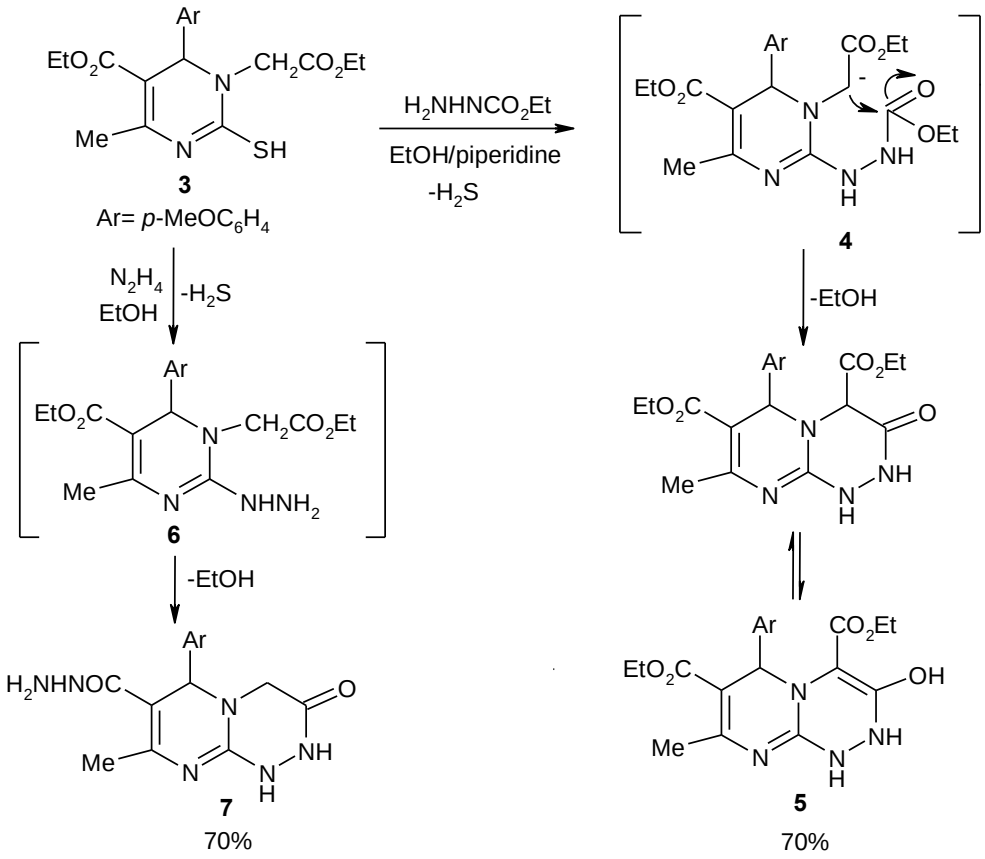
On heating of ethyl 2-mercapto-6-(*p*-methoxyphenyl)-4-methyl-1,6-dihydropyrimidine-5-carboxylate (**1**)[17] under reflux with ethyl chloroacetate in ethanolic potassium hydroxide solution, ethyl 2-(2-ethoxy-2-oxoethyl)-2-mercapto-6-(*p*-methoxyphenyl)-4-methyl-1,6-dihydropyrimidine-5-carboxylate (**2**) and ethyl 1-(2-ethoxy-2-oxoethyl)-2-mercapto-6-(*p*-methoxyphenyl)-4-methyl-1,6-dihydropyrimidine-5-carboxylate (**3**) were obtained (Scheme 1).



Scheme 1

As depicted in Scheme 1, the reaction proceeded through *S*-alkylation[18] to give *S*-alkylated product **2** as the major reaction product in 75% yield. In addition, this reaction was accompanied by a second, minor product, **3**, which was obtained in 10% yield. The structures of compounds **2** and **3** were confirmed on the basis of their elemental analysis, IR, ^{1}H NMR and mass spectral analysis.

Treatment of compound **3** with ethyl carbazate, in refluxing ethanol in the presence of a catalytic amount of piperidine, furnished a single product identified as diethyl pyrimido[2,1-*c*][1,2,4]triazine-4,7-dicarboxylate **5**. The formation of **5** may be attributed to the intermediacy of the non-isolable transamination adduct **4**, which underwent cyclization *via* loss of ethanol molecule. Also, compound **3** was allowed to react with hydrazine hydrate in boiling ethanol, it yielded the respective pyrimido[2,1-*c*]-[1,2,4]triazine-7-carbohydrazide **7**. The direct formation of **7** indicates that the initially formed product namely ethyl 1-(2-ethoxy-2-oxoethyl)-2-hydrazino-6-(*p*-methoxyphenyl)-4-methyl-1,6-dihydropyrimidine-5-carboxylate (**6**) underwent *in situ* cyclization *via* loss of ethanol molecule to give pyrimido[2,1-*c*][1,2,4]triazine **7** (Scheme 2).

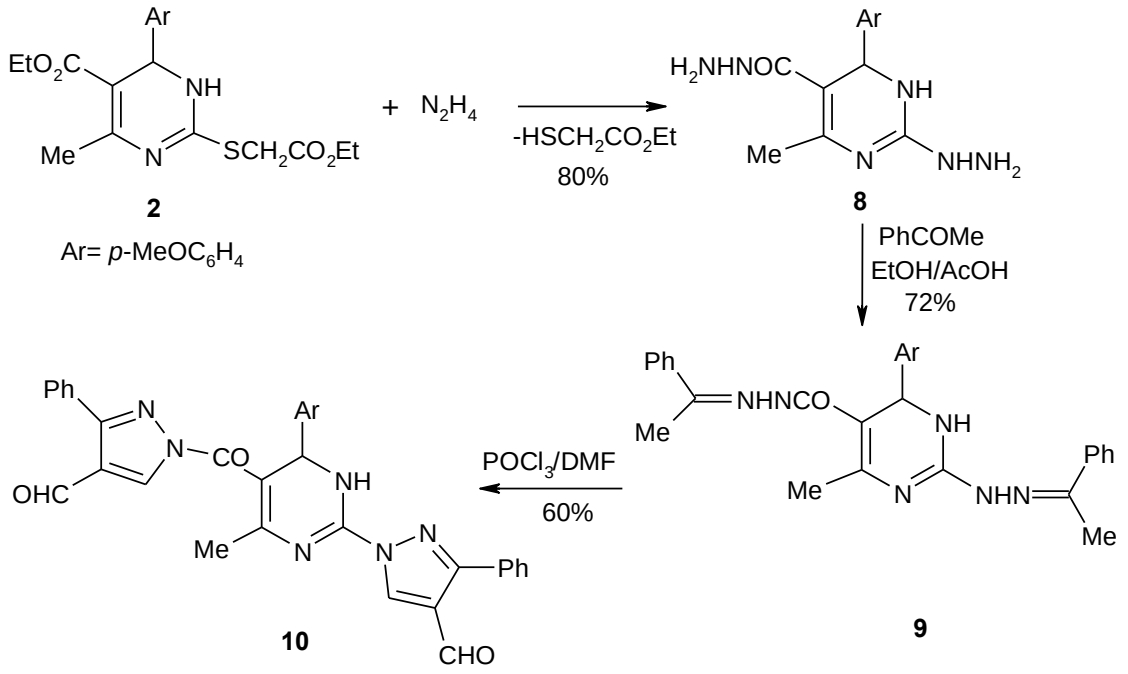


Scheme 2

The structures of compounds **5** and **7** were characterized from their spectroscopic as well as elemental analytical data. Thus, compound **5** showed absorption bands at 3243, 1704 and 1648 cm^{-1} corresponding to NH and two C=O functions, respectively. Its ^1H NMR spectrum revealed a triplet signal at δ 1.09 ppm with coupling constant (J = 6.6 Hz) due to CH_3 protons, a quartet signal at δ 3.99 ppm with coupling constant (J = 6.9 Hz) due to CH_2 protons, two D_2O-exchangeable signals at δ 6.88 and 7.15 due two NH protons in addition to D_2O-exchangeable signal at δ 9.13 corresponding to OH proton. The IR spectrum of compound **6** revealed bands at 3431, 3250 and 1632 cm^{-1} corresponding to NH_2, NH and C=O groups, respectively. Its ^1H NMR spectrum showed the absence of CH_3 and CH_2 protons of ethoxycarbonyl group and showed D_2O-exchangeable signal at δ 3.39 ppm due to NH_2 protons. It showed also three D_2O-exchangeable signals at δ 7.65, 7.81 and 7.82 ppm corresponding to three NH protons, in addition to aromatic protons.

When the thioglycolate **2** was treated with hydrazine hydrate, it afforded 2-hydrazino-6-(*p*-methoxyphenyl)-4-methyl-1,6-dihydropyrimidine-5-carbohydrazide (**8**). 2-hydrazinopyrimidine carbohydrazide **8** could be used as versatile building blocks in the synthesis of new heterocyclic systems.

Thus, condensation of 2-hydrazinopyrimidine **8** with acetophenone in boiling ethanol and few drops of acetic acid were added, it gave *N*-[(1-phenylethylidene)-2-[2-(1-phenylethylidene)hydrazino]-1,6-dihydropyrimidine **9**, which on treatment with $POCl_3$/DMF under Vilsmeier reaction condition yielded the final product 1-{5-[(4-formyl-3-phenyl-1*H*-pyrazol-1-yl)carbonyl]-6-(*p*-methoxyphenyl)-4-methyl-1,6-dihydro pyrimidin-2-yl}-3-phenyl-1*H*-pyrazole-4-carbaldehyde (**10**) (Scheme 3).

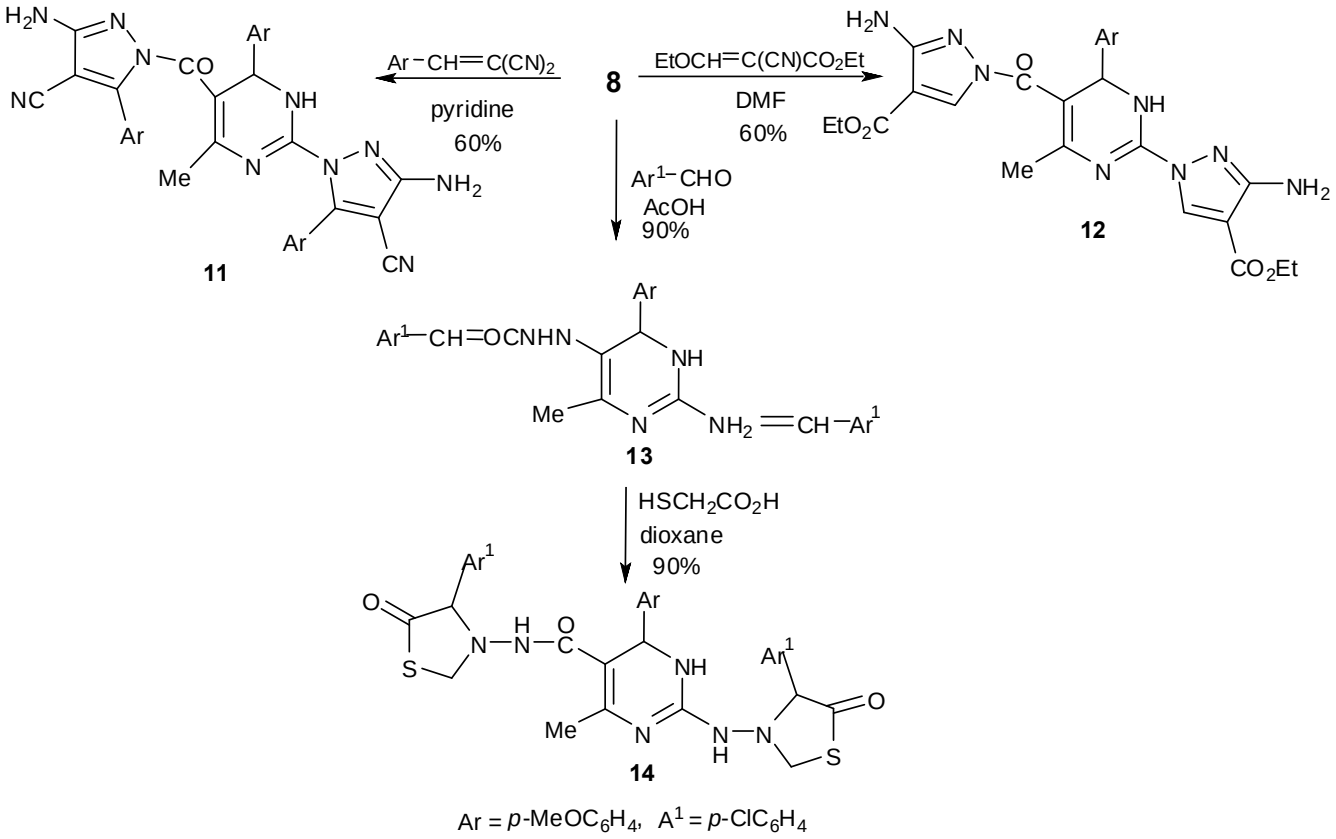


Scheme 3

The structures of compounds **9** and **10** were characterized from their spectroscopic as well as elemental analytical data. The IR and ^{1}H NMR spectrum of compound **9** lacked an absorption band and protons corresponding to NH_2 groups. While, the IR spectrum of compound **10** showed bands at 1717 and 1680 due to formyl and exocyclic C=O groups, its ^{1}H NMR spectrum were characterized by the appearance of single broad signal at 13 ppm attributed to formyl proton.

Furthermore, cyclocondensation of 2-hydrazinopyrimidine **8** with (*p*-methoxybenzylidene)malononitrile in pyridine gave the corresponding aminopyrazolecarbonitrile **11**. Also, interaction of **8** with ethyl ethoxymethylenecyanoacetate in DMF led to the formation of the ethyl pyrazolecarboxylate **12**. Finally, the amino functionality of 2-hydrazinopyrimidine carbohydrazide **8** was reacted with carbon electrophiles such *p*-chlorobenzaldehyde to afford 2-[2-(*p*-chlorobenzylidene)hydrazine]-*N*-[1-(*p*-chlorophenyl)-methylene]-6-(*p*-methoxyphenyl)-4-methyl-1,6-dihydropyrimidine-5-carbohydrazide (**13**). Compound **13** was formed by nucleophilic attack of the amino group on the electronically deficient carbonyl carbon atom of the aldehyde followed by dehydration. It is of interest to investigate the behavior of **13** which

contain an activated C=N bond towards aliphatic mercaptan. Thus, cyclocondensation of **13** with thioglycolic acid in dioxane gave the thiazolidinone derivative **14** (Scheme 4).



11 **12** **13** **14**

Scheme 4

The structures of compounds **11** and **12** were confirmed on the basis of their elemental analysis, IR, ^{1}H NMR, and the mass spectral data. The IR spectrum of compound **11** showed characteristic bands at 2208 attributed to C≡N group. While, the IR spectrum of compound **12** revealed absorption peaks at 1721 and 1693 cm^{-1} due to ester and exocyclic C=O group. The ^{1}H NMR spectrum of compound **11** was characterized by the appearance of douplet douplet signals at δ 6.95 ppm with coupling constant (J = 8.7 Hz), 7 ppm with coupling constant (J = 8.4 Hz), 7.08 ppm with coupling constant (J = 6.9 Hz), 7.13 ppm with coupling constant (J = 6.9 Hz), 7.42 ppm with coupling constant (J = 8.4 Hz), and 7.75 ppm with coupling constant (J = 8.7 Hz), assignable to aromatic protons. While, the ^{1}H NMR spectrum of compound **12** was characterized by the appearance of CH_3 and CH_2 protons of ethoxycarbonyl groups. The mass spectrum of compound **12** showed a molecular ion peak (M^+) at m/z = 536 which is in an agreement with the molecular formula $C_{25}H_{28}N_8O_6$.

Also, the structures of compounds **13** and **14** were confirmed on the basis of their elemental analysis, IR, ^{1}H NMR and mass spectral analysis. The IR and ^{1}H NMR spectrum of compounds **13** and **14** lacked an

absorption band and protons corresponding to NH_2 group. ^{1}H NMR spectrum of compound **13** revealed singlet signal at δ 8.71 assigned to the **CH**=N. The mass spectrum of **14** showed a molecular ion peak (M^+) at *m/z* = 683 corresponding to a molecular formula $C_{31}H_{28}Cl_2N_6O_4S_2$.

EXPERIMENTAL

Melting points are uncorrected and were recorded in open capillary tubes on a Stuart SMP3 melting point apparatus. Infrared spectra were recorded on FT-IR Bruker Vector 22 spectrophotometer using KBr wafer technique. The ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ on Gemini spectrometer (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) and the chemical shift in δ downfield from TMS as an internal standard. Elemental microanalyses were performed at the Main Laboratories of the War Chemical. Mass spectra were obtained using gas chromatography GCMS qp-2010 plus Schimadzu instrument mass spectrometer (70 eV) were performed at the Cairo University Microanalytical Center.

Ethyl 2-mercapto-6-(*p*-methoxyphenyl)-4-methyl-1,6-dihydropyrimidine-5-carboxylate (1). This compound was prepared according to the reported method.[17]

Ethyl 2-(2-ethoxy-2-oxoethyl)-2-mercapto-6-(*p*-methoxyphenyl)-4-methyl-1,6-dihydropyrimidine-5-carboxylate (2) and ethyl 1-(2-ethoxy-2-oxoethyl)-2-mercapto-6-(*p*-methoxyphenyl)-4-methyl-1,6-dihydropyrimidine-5-carboxylate (3). A mixture of compound **1** (3 g, 0.01 mol) and ethyl chloroacetate (1.6 mL, 0.015 mol) in ethanolic potassium hydroxide solution (prepared by dissolving 0.56 g, 0.01 mol of KOH in 50 mL EtOH) was heated under reflux for 3 h and cooled. The solid obtained was filtered off and recrystallized from dilute dioxane to give compound **3** as yellow crystals (0.3 g, yield 10%): mp >300 °C; IR (ν cm^{-1}) 3114 (CH aromatic), 2979, 2956 (CH aliphatic), 1704 (C=O), 1648 (C=O), 1611 (C=N); ^{1}H NMR (DMSO-d_6) δ 1.09 (t, 6H, CH_2 **CH_3**, *J* = 6.9 Hz), 2.23 (s, 3H, CH_3), 3.35 (s, 2H, NCH_2), 3.71 (s, 3H, OCH_3), 3.96 (q, 4H, **CH_2** CH_3, *J* = 6.9 Hz), 5.09 (s, 1H, pyrimidine-H-6), 6.86 (d, 2H, ArH's, *J* = 9 Hz), 7.14 (d, 2H, ArH's, *J* = 9 Hz), 9.16 (s, 1H, D2O-exchangeable, SH); MS *m/z* (%): [M^+-CH_2] 378 (5.8), 351 (21.8), 328 (28.8), 302 (25.3), 234 (20.2), 232 (4.2), 218 (18.9), 195 (19.9), 155 (100), 151 (20.8), 123 (9.3), 97 (8.9); *Anal*. Calcd for $C_{19}H_{24}N_2O_5S$ (%): C, 58.15; H, 6.16; N, 7.14. Found C, 58.18; H, 6.16; N, 7.10%.

On the other hand, the filtrate of the above reaction was poured gradually onto crushed ice. The solid was filtered off and recrystallized from EtOH to give compound **2** as yellow crystals (2.25 g, yield 75%): mp 180-182 °C; IR (ν cm^{-1}) 3114 (CH aromatic), 2979, 2956 (CH aliphatic), 1704 (C=O), 1648 (C=O), 1611 (C=N); ^{1}H NMR (DMSO-d_6) δ 1.09 (t, 6H, CH_2**CH_3**, *J* = 6.9 Hz), 2.23 (s, 3H, CH_3), 3.35 (s, 2H, NCH_2), 3.71 (s, 3H, OCH_3), 3.96 (q, 4H, **CH_2**CH_3, *J* = 6.9 Hz), 5.09 (s, 1H, pyrimidine-H-6), 6.86 (d, 2H, ArH's, *J* = 9 Hz), 7.14 (d, 2H, ArH's, *J* = 9 Hz), 9.16 (s, 1H, D_2O-exchangeable, NH); MS *m/z* (%): [M^+-CH_2]

378 (22.4), 348 (5.5), 290 (21.2), 275 (11.8), 261 (100), 244 (20.2), 217 (63.5), 183 (42.1), 155 (39.1), 137 (43.1), 77 (42.6); *Anal*. Calcd for $C_{19}H_{24}N_2O_5S$ (%): C, 58.15; H, 6.16; N, 7.14. Found C, 58.20; H, 6.14; N, 7.18%.

Diethyl 3-hydroxy-6-(*p*-methoxyphenyl)-8-methyl-1,6-dihydro-2*H*-pyrimido[2,1-*c*][1,2,4]triazine-4,7-dicarboxylate (5). A mixture of compound **3** (0.392 g, 0.001 mol) and ethyl carbazate (0.104 g, 0.001 mol) in EtOH (10 mL) and few drops of piperidine was refluxed for 2 h. The solid thus obtained was filtered off and recrystallized from EtOH to give compound **5** as yellow crystals (0.274 g, yield 70%): mp 248-250 °C; IR (ν cm^{-1}) 3243 (NH), 3113 (CH aromatic), 2979, 2955 (CH aliphatic), 1704, 1648 (C=O), 1612 (C=N); ^{1}H NMR (DMSO-d_6) δ 1.09 (t, 6H, CH_2**CH_3**, *J* = 6.6 Hz), 2.23 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 3.99 (q, 4H, **CH_2**CH_3, *J* = 6.9 Hz), 5.08 (s, 1H, pyrimidine-H-6), 6.85 (d, 2H, ArH's, *J* = 8.1 Hz), 7.12 (d, 2H, ArH's, *J* = 9 Hz), 6.88, 7.15 (s, 2H, D_2O-exchangeable, NH), 9.13 (s, 1H, D_2O-exchangeable, OH); MS *m/z* (%): [M^+] 416 (34.3), 415 (32.5), 403 (32.5), 373 (38.5), 340 (34.3), 308 (36.7), 284 (51.5), 274 (42), 183 (45), 137 (100), 84 (88.7), 58 (52.6); *Anal*. Calcd for $C_{20}H_{24}N_4O_6$ (%): C, 57.68; H, 5.81; N, 13.45. Found C, 57.70; H, 5.80; N, 13.50%.

6-(*p*-Methoxyphenyl)-8-methyl-3-oxo-1,3,4,6-tetrahydro-2*H*-pyrimido[2,1-*c*][1,2,4]triazine-7-carbohydrazide (7). A suspension of compound **3** (0.392 g, 0.001 mol) and hydrazine hydrate (4 mL, 99%) in EtOH (10 mL) was refluxed for 2 h and cooled. The solid separated was filtered off and recrystallized from dioxane to give compound **7** as yellow crystals (0.274 g, yield 70%): mp 258-260 °C; IR (ν cm^{-1}) 3431, 3250 (NH_2, NH), 3050 (CH aromatic), 2925 (CH aliphatic), 1632 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.28 (s, 3H, CH_3), 3.39 (brs, 2H, D_2O-exchangeable, NH_2), 3.77 (s, 3H, OCH_3), 3.79 (s, 2H, CH_2), 6.82 (s, 1H, pyrimidine-H-6), 7.03 (d, 2H, ArH's, *J* = 8.7 Hz), 7.79 (d, 2H, ArH's, *J* = 8.7 Hz), 7.65, 7.81, 7.82 (s, 3H, D_2O-exchangeable, NH); MS *m/z* (%): [M^+] 330 (55.3), [M^++1] 331 (82.9), 302 (61.7), 286 (61.7), 274 (15), 252 (70.2), 206 (61.7), 172 (74.5), 92 (100), 78 (80), 58 (46.8); *Anal*. Calcd for $C_{15}H_{18}N_6O_3$ (%): C, 54.54; H, 5.49; N, 25.44. Found C, 54.60; H, 5.50; N, 25.40%.

2-Hydrazino-6-(*p*-methoxyphenyl)-4-methyl-1,6-dihydropyrimidine-5-carbohydrazide (8).

A mixture of compound **2** (0.392 g, 0.001 mol) and hydrazine hydrate (5 mL, 99%) was heated under reflux for 2 h. The reaction mixture was cooled and poured gradually onto crushed ice. The solid obtained was filtered off and recrystallized from EtOH to give compound **8** as yellow crystals (0.31 g, yield 80%): mp 168-170 °C; IR (ν cm^{-1}) 3243, 3139 (NH_2, NH), 3034 (CH aromatic), 2981 (CH aliphatic), 1625 (C=O), 1602 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.24 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 4.71 (s, 4H, D_2O-exchangeable, NH_2), 6.83 (s, 1H, pyrimidine-H-6), 7.02 (d, 2H, ArH's, *J* = 8.4 Hz), 7.56 (s, 1H, D_2O-exchangeable, NH), 7.59 (s, 1H, D_2O-exchangeable, NH), 7.77 (d, 2H, ArH's, *J* = 8.4 Hz), 8.20 (s, 1H, D_2O-exchangeable, NH); MS *m/z* (%): [M^++1] 291 (16.1), [M^+] 290 (17.8), 275 (19.2), 264 (20.9), 234 (25.1), 219 (21.4), 172 (24.2), 135 (29.9), 134 (22), 75 (100), 60 (9.6), 52(8.4); *Anal*. Calcd for

$C_{13}H_{18}N_6O_2$ (%): C, 53.78; H, 6.25; N, 28.95. Found C, 53.72; H, 6.20; N, 28.90%.

6-(*p*-Methoxyphenyl)-4-methyl-*N*-[(1-phenylethylidene)-2-[2-(1-phenylethylidene)hydrazino]-1,6-dihydropyrimidine-5-carbohydrazide (9). To a solution of **8** (0.29 g, 0.001 mol) in hot EtOH, acetophenone (0.22 mL, 0.002 mol) and few drops of acetic acid were added. The solid that separated on warming for 30 min on a water-bath was filtered off and recrystallized from MeOH to give compound **9** as yellow crystals (0.2 g, yield 72%): mp 128-129 °C; IR (ν cm^{-1}) 3350 (NH), 3056 (CH aromatic), 2958 (CH aliphatic), 1679 (C=O), 1602 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.22 (s, 3H, CH_3), 2.27 (s, 6H, CH_3C=N), 3.62 (s, 3H, OCH_3), 7.45-7.91 (m, 15H, ArH's and pyrimidine-H-6), 7.92, 7.93 (s, 3H, D_2O-exchangeable, NH); MS *m/z* (%): [M^+] 494 (28.7), [M^+-1] 493 (3.9), 412 (44), 387 (31.1), 334 (18.8), 320 (41.5), 214 (42.5), 187 (28.7), 174 (36.1), 131 (83.6), 101 (100), 73 (29.7), 66 (34.1); *Anal*. Calcd for $C_{29}H_{30}N_6O_2$ (%): C, 70.42; H, 6.11; N, 16.99. Found C, 70.40; H, 6.10; N, 16.70%.

1-{5-[(4-Formyl-3-phenyl-1*H*-pyrazol-1-yl)carbonyl]-6-(*p*-methoxyphenyl)-4-methyl-1,6-dihydropyrimidin-2-yl}-3-phenyl-1*H*-pyrazole-4-carbaldehyde (10). To the Vilsmeier reagent [prepared from DMF (10 mL) and $POCl_3$ (1.1 mL, 0.012 mol)], compound **9** (1.1 g, 0.004 mol) in DMF was added and then the reaction mixture stirred at 60-65 °C for 2 h. The reaction mixture was cooled and poured gradually onto crushed ice. The solid obtained was filtered off and recrystallized from dilute dioxane to give compound **10** as yellow crystals (0.66 g, yield 60%): mp 288-290 °C; IR (ν cm^{-1}) 3430 (NH), 3057 (CH aromatic), 2926 (CH aliphatic), 1717, 1680 (C=O), 1628 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.23 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 6.68 (s, 1H, pyrimidine-H-6), 7.03-8.57 (m, 16H, ArH's and pyrazole-H-5), 8.21 (s, 1H, D_2O-exchangeable, NH), 13 (s, br, 2H, CHO); MS *m/z* (%): [M^++1] 571 (0.71), [M^+] 570 (0.20), 549 (6.50), 537 (8.87), 532 (6.63), 509 (5.57), 492 (2.72), 480 (3.09), 423 (3.97), 313 (14.62), 236 (21.37), 150 (100), 64 (43.14), 55 (38.83); *Anal*. Calcd for $C_{33}H_{26}N_6O_4$ (%): C, 69.46; H, 4.59; N, 14.73. Found C, 69.40; H, 4.54; N, 14.70%.

3-Amino-1-{(5-[(3-amino-4-cyano-5-(*p*-methoxyphenyl)-1*H*-pyrazol-1-yl)carbonyl]}-6-(*p*-methoxyphenyl)-4-methyl-1,6-dihydropyrimidin-2-yl)-5-(*p*-methoxyphenyl)-1*H*-pyrazole-4-carbonitrile (11). A mixture of **8** (0.29 g, 0.001 mol) and (*p*-methoxybenzylidene)malononitrile (0.368 g, 0.002 mol) in pyridine (10 mL) was heated under reflux for 3h. The reaction mixture was cooled, poured gradually onto crushed ice and neutralized with diluted HCl. The solid obtained was filtered off and recrystallized from MeOH to give compound **11** as brown crystals (0.17 g, yield 60%): mp 130-132 °C; IR (ν cm^{-1}) 3320, 3205 (NH_2, NH), 3006 (CH aromatic), 2930 (CH aliphatic), 2208 (C≡N), 1670 (C=O), 1603 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.48 (s, 3H, CH_3), 3.32 (s, br, 4H, NH_2), 3.82 (s, 9H, OCH_3), 6.75 (s, 1H, pyrimidine-H-6), 6.95 (d, 2H, ArH's, *J* = 8.7 Hz), 7 (d, 2H, ArH's, *J* = 8.4 Hz), 7.08 (d, 2H, ArH's, *J* = 6.9 Hz), 7.13 (d, 2H, ArH's, *J* = 6.9 Hz), 7.42 (d, 2H, ArH's, *J* = 8.4 Hz), 7.75 (d, 2H, ArH's, *J* = 8.7 Hz), 9.10 (s, 1H, D_2O-exchangeable, NH); MS *m/z* (%): [M^++1] 655 (56.7), [M^+] 654 (61.2), 518 (80.1), 490 (73.8), 401

(75.6), 398 (72.9), 345 (66.6), 321 (100), 318 (59.4), 297 (70.2), 271 (81), 260 (88.2), 229 (65.7), 191 (63), 145 (70.2), 73 (63.9); *Anal*. Calcd for $C_{35}H_{30}N_{10}O_4$ (%): C, 64.21; H, 4.62; N, 21.39. Found C, 64.20; H, 4.60; N, 21.36%.

Ethyl 3-amino-1-(5-{[(3-amino-4-(ethoxycarbonyl)-1*H*-pyrazol-1-yl)carbonyl]}-6-(*p*-methoxyphenyl)-4-methyl-1,6-dihydropyrimidin-2-yl)-1*H*-pyrazole-4-carboxylate (12). Equimolar mixture of compound **8** (0.29 g, 0.001 mol) and ethyl ethoxymethylenecyanoacetate (0.338 g, 0.002 mol) in DMF (10 mL) was refluxed for 4 h then cooled and diluted with cooled water. The solid obtained was filtered off and recrystallized from EtOH to give compound **12** as yellow crystals (0.17 g, yield 60%): mp 185-186 °C; IR (ν cm^{-1}) ν 3392, 3279, 3124 (NH_2, NH), 3090 (CH aromatic), 2933, 2904 (CH aliphatic), 1721, 1693 (C=O), 1635 (C=N); ^{1}H NMR (DMSO-d_6) δ 1.32 (t, 6H, $CH_2\mathbf{CH_3}$, *J* = 6.9 Hz), 2.49 (s, 3H, CH_3), 3.31 (s, 3H, OCH_3), 4.24 (s, 2H, D_2O-exchangeable, NH_2), 4.31 (q, 4H, $\mathbf{CH_2}CH_3$, *J* = 6.9 Hz), 4.39 (s, 2H, D_2O-exchangeable, NH_2), 5.20 (s, 1H, pyrimidine-H-6), 8.57-8.79 (m, 6H, ArH's and pyrazole-H-5), 9 (s, 1H, D_2O-exchangeable, NH); MS *m/z* (%): [M^+] 536 (59.7), [M^+-1] 535 (77.1), 515 (93.4), 499 (89.1), 465 (85.8), 429 (61,9), 381 (59.7), 355 (88), 307 (77.1), 284 (76), 241 (100), 201 (93.4), 155 (13), 101(80.4), 81 (46.7), 56 (28.2); *Anal*. Calcd for $C_{25}H_{28}N_8O_6$ (%): C, 55.96; H, 5.26; N, 20.88. Found C, 55.90; H, 5.24; N, 20.90%.

2-[2-(*p*-Chlorobenzylidene)hydrazine]-*N*-[1-(*p*-chlorophenyl)methylene]-6-(*p*-methoxyphenyl)-4-methyl-1,6-dihydropyrimidine-5-carbohydrazide (13). A mixture of **8** (0.29 g, 0.001 mol) and *p*-chlorobenzaldehyde (0.28 g, 0.002 mol) in glacial acetic acid (10 mL) was heated under reflux for 2 h. The reaction mixture was cooled and poured gradually onto crushed ice. The solid obtained was filtered off and recrystallized from EtOH to give compound **13** as yellow crystals (0.26 g, yield 90%): mp 208-210 °C; IR (ν cm^{-1}) 3429 (NH), 3027 (CH aromatic), 2931 (CH aliphatic), 1664 (C=O), 1624 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.49 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 6.90 (s, 1H, pyrimidine-H-6), 7.56-7.89 (m, 12H, ArH's), 7.91 (s, 3H, D_2O-exchangeable, NH), 8.71 (s, 2H, **CH**=N); MS *m/z* (%): [M^++2] 537 (62), [M^+] 535 (21), 446 (86), 427 (73), 413 (54), 364 (78), 319 (86.), 309 (57), 294 (78), 226 (73), 157 (92), 117 (100), 68 (58), 55 (79); *Anal*. Calcd for $C_{27}H_{24}Cl_2N_6O_2$ (%): C, 60.57; H, 4.52; N, 15.70. Found C, 60.54; H, 4.50; N, 15.78%.

***N*-[(4-(*p*-Chlorophenyl)-5-oxo-1,3-thiazolidin-3-yl)-2-[(4-(*p*-chlorophenyl)-5-oxo-1,3-thiazolidin-3-yl)amino]-6-(*p*-methoxyphenyl)-4-methyl-1,6-dihydropyrimidine-5-carboxamide (14)**. A mixture of **13** (0.535 g, 0.001 mol) and thioglycolic acid (0.69 mL, 0.01 mol) in dioxane (10 mL) was refluxed for 10 h. The solid obtained was filtered off and recrystallized from EtOH to give compound **14** as yellow crystals (0.48 g, yield 90%): mp 197-199 °C; IR (ν cm^{-1}) 3434 (NH), 3090 (CH aromatic), 2981, 2925 (CH aliphatic), 1670, 1654 (C=O), 1624 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.08 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 3.83 (s, 2H, N$\mathbf{CH_2}$S), 3.97 (s, 2H, N$\mathbf{CH_2}$S), 6.48 (s, 1H, pyrimidine-H-6), 7.38-7.89 (m, 14H,

ArH's and thiazolidinone-H-4), 7.92 (s, 3H, D_2O-exchangeable, NH); MS *m/z* (%): [M^++2] 685 (29.5), [M^++1] 684 (39.5), [M^+] 683 (28.6), 667 (25.9), 655 (30), 627 (35.4), 586 (42.7), 534 (35.4), 454 (44), 405 (46.3), 364 (45.4), 289 (40.9), 258 (14.1), 195 (46.8), 72 (100), 58 (14.5); *Anal*. Calcd for $C_{31}H_{28}Cl_2N_6O_4S_2$ (%): C, 54.46; H, 4.13; N, 12.29. Found C, 54.40; H, 4.10; N, 12.20%.

BIOLOGICAL ACTIVITIES

The results depicted in Table 1, showed various activities against all species of microorganisms which suggest that the variations in the structures affect on the growth of the microorganisms. Thus, we can conclude from these results that, some of the prepared compounds showed a low to high antimicrobial activity towards Gram positive bacteria, Gram negative bacteria and the fungal strain (Table 1).

Table 1. The antimicrobial activity of the newly synthesized compounds

Compound No.	Diameter of inhibition zone[a] (mm), Conc. (100 µg mL^{-1})			
	S. aureus (Gram +ve)	*B. subtilis (Gram +ve)*	*E. coli (Gram –ve)*	*C. albicans (Fungal strain)*
2	-	-	-	-
3	-	-	-	-
5	10	-	8	12
7	18	21	22	16
8	11	20	28	20
9	-	-	-	-
11	-	-	-	21
12	-	-	-	-
13	-	-	-	16
14	-	15	-	19
Control[b]	3	3	38	35

[a]12 mm or less: resistant or no inhibition, 13–19 mm: moderate inhibition, 20 mm or more: strong inhibition.
[b]Chloramphencol in the case of Gram-positive bacteria, Cephalothin in the case of Gram-negative bacteria and Cycloheximide in the case of fungi.

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