

SYNTHESIS OF SOME NEW SUBSTITUTED PYRIMIDINES AND FUSED PYRIMIDINES

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a.khames@yahoo.com**Abstract**

4-(4-Chlorophenyl)-3,4-dihydro-6-methyl-5-(4-tolyl)carbamoyl-2(1H)-pyrimidinethione (**1**) was reacted with benzylidenemalononitrile or ethyl cyanocinnamate to afford the pyrimidothiazine derivatives **2** and **4**. Treatment of **1** with N,N-dimethylformamide-dimethylacetal (DMF-DMA) afforded **5**. Acetylpyrimidine derivative **7** was produced upon treatment of **1** with mixture of acetic anhydride and acetic acid. Compound **1** was treated with chloroacetic acid to give the 5-(4-Chlorophenyl)-7-methyl-3-oxo-6-(4-tolyl)-carbamoyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidine (**8**), thione **1** was cyclized to 2-benzylidenethiazolopyrimidine derivatives **9a,b** upon reaction with chloroacetic acid and aldehydes, also compound **1** was treated with 1,2-dichloroethane to give 5-(4-chlorophenyl)-7-methyl-6-(4-tolyl)carbamoyl-2,3-dihydro-5-H-[1,3]thiazolo[3,2-a]pyrimidine (**10**). The hydrazine derivative **11** was prepared by boiling **1** with hydrazine. Reaction of **11** with ethyl acetoacetate, DMF-DMA, acetic anhydride and 4-chlorobenzaldehyde gave 2-pyrazolopyrimidine **12**, 4-(4-Chlorophenyl)-2-(N,N-dimethylaminomethylene)hydrazino-6-methyl-5-(4-tolyl)carbamoylpyrimidine (**13**), acetylhydrazinyl derivative **15** and 4-(4-Chlorophenyl)-2-(4-chlorophenylmethylenehydrazono)-6-methyl-5-(4-tolyl)carbamoylpyrimidine (**16**), respectively.

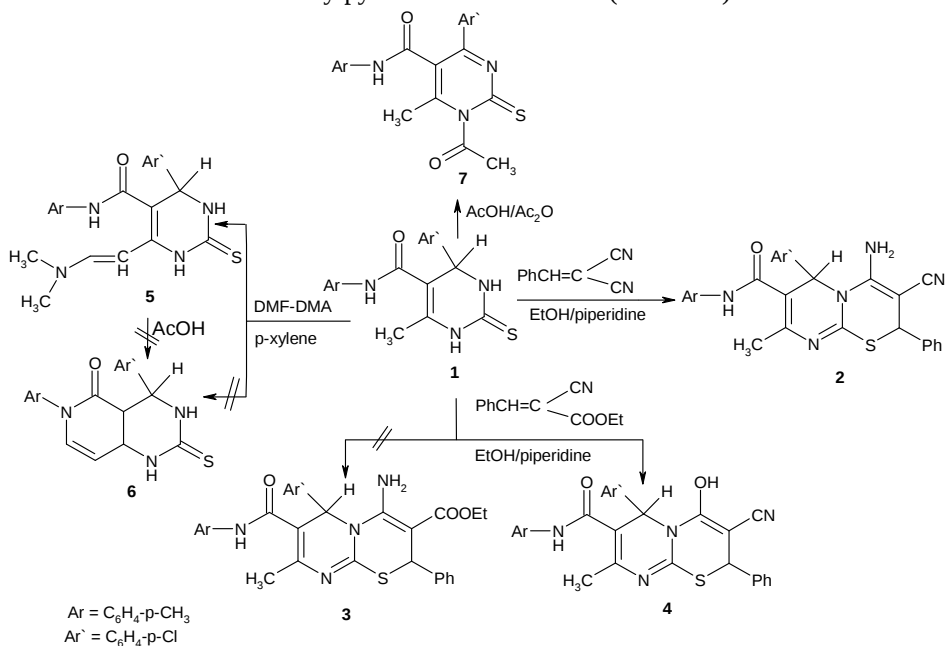
Introduction

The reported biological activity of pyrimidine derivatives¹⁻¹¹, especially 2-hydrazinopyrimidines as antifungal, antiviral and antibacterial¹²⁻¹⁵, agents as well as the leishmanicidal activity¹⁶⁻¹⁷ of the annulated pyrimidine derivatives, stimulated my interest in the synthesis of several new heterocyclic derivatives of these ring system. 4-(4-Chlorophenyl)-3,4-dihydro-6-methyl-5-(4-tolyl)carbamoyl-2(1H)-pyrimidinethione (**1**) was prepared according to literature procedure¹⁸ and used as good starting material for the present study.

Results and Discussion

Thus it has been found that compound **1**¹⁸ reacted with benzylidenemalononitrile to afford pyrimido[2,1-*b*][1,3]thiazine derivative **2**. The structure of the latter compound was confirmed on the basis of elemental analysis and spectral data. Similarly, treatment of thione **1** with ethyl cyanocinnamate gave 6-(4-chlorophenyl)-3-cyano-4-hydroxy-8-methyl-2-phenyl-2H,6H-7-(4-tolyl)carbamoylpyrimido[2,1-*b*][1,3]thiazine (**4**) of the molecular formula C₂₉H₂₃ClN₄O₂S formed via the elimination

of ethanol based on the presence of CN absorption band in the IR spectrum. The other possible structure **3** was ruled out on the basis of analytical and spectral data. Compound **1** was treatment with *N,N*-dimethylformamide-dimethylacetal to give enamine derivative **5**, the ^1H NMR spectrum showed singlet signal (6H) at $\delta = 3.09$ assigned for $\text{N}(\text{CH}_3)_2$ protons. The latter compound was refluxed in acetic acid for a long time period in an attempt to cyclize **5** into pyrido[2,3-*d*]pyrimidine derivative **6** was unsuccessful, however the ^1H NMR spectrum of the product have signals at 3.09 of $\text{N}(\text{CH}_3)_2$. Treatment of compound **1** with a mixture of acetic anhydride and acetic acid afforded the acetylpyrimidine derivative **7**. (Scheme 1).

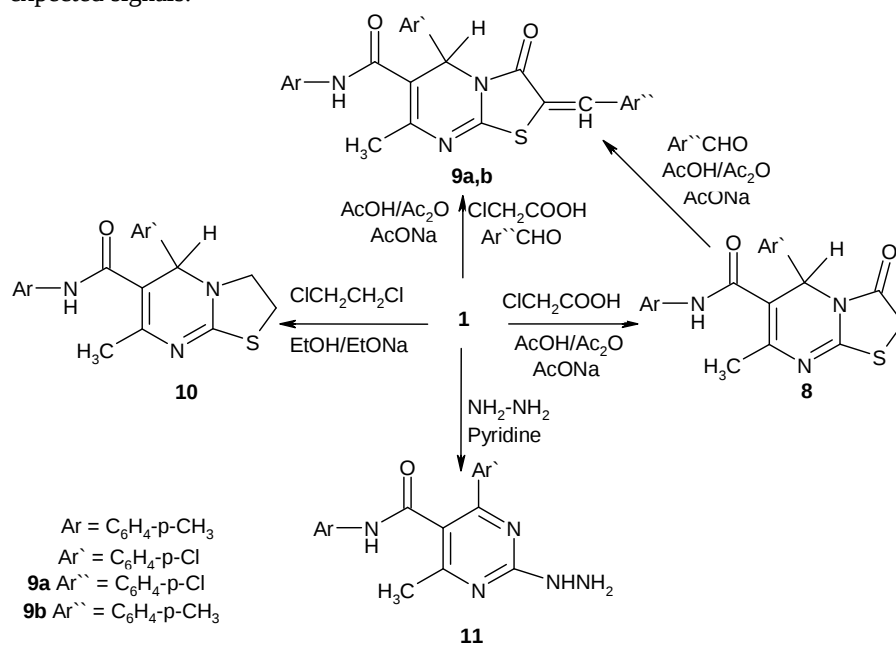


Scheme 1

Condensation of compound **1** with chloroacetic acid in presence of anhydrous sodium acetate furnished the corresponding thiazolopyrimidine **8** which was condensed with aromatic aldehydes in the presence of anhydrous sodium acetate and glacial acetic acid/acetic anhydride mixture yielded benzylidene derivatives **9a,b**. However, the latter compounds were also prepared directly from **1** by the action of chloroacetic acid, aromatic aldehydes and anhydrous sodium acetate in presence of a glacial acetic acid/acetic anhydride mixture. Also, the reaction of **1** with 1,2-dichloroethane in sodium ethoxide afforded 5-(4-chlorophenyl)-7-methyl-6-(4-

tolyl)carbamoyl-2,3-dihydro-5-*H*-[1,3] thiazolo[3,2-*a*]pyrimidine (**10**). The ^1H NMR spectrum of compound **10** showed triplet signal at $\delta = 2.05$ ppm for CH_2 protons, singlet signals at $\delta = 2.33, 2.34$ ppm assigned for 2 CH_3 protons, triplet signal at $\delta = 2.71$ ppm for SCH_2 protons, singlet signal at $\delta = 5.52$ ppm for CH pyrimidine, multiplet at $\delta = 6.90\text{--}7.85$ ppm assigned for CH aromatic and singlet signal at $\delta = 9.14$ assigned for NH, exchangeable with D_2O . (Scheme 2)

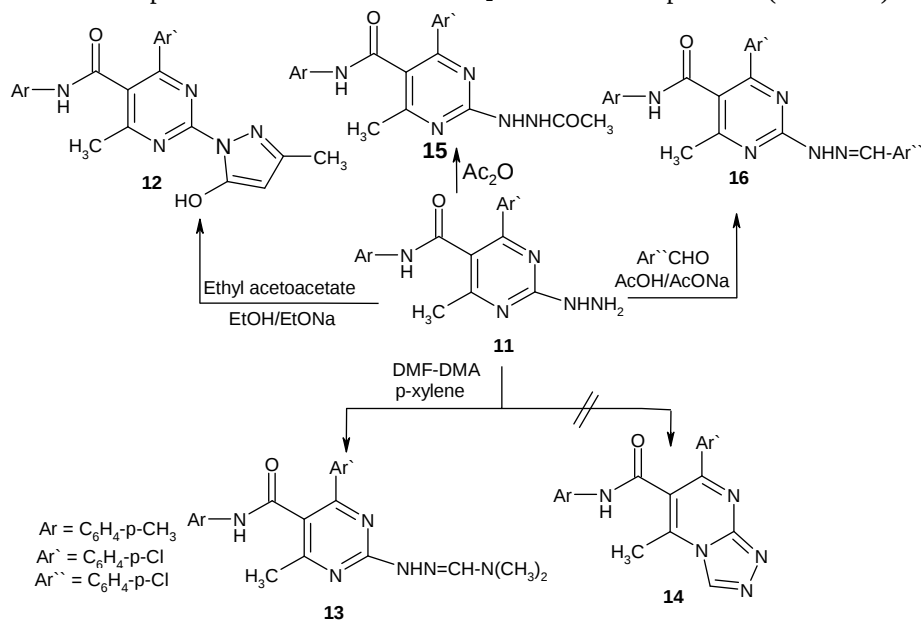
The formation of hydrazinopyrimidine **11** was achieved by heating **1** with hydrazine hydrate in pyridine under reflux for 12h¹⁹. The structure **11** was confirmed on the basis of its elemental analysis and spectral data. The ^1H NMR spectrum of compound **11** showed absorption peaks at $\delta = 1.85$ ppm (CH_3) protons, at $\delta = 1.96$ ppm assigned for (CH_3) protons, at $\delta = 7.26, 10.01$ ppm for 2 NH protons, exchangeable with D_2O , and at $\delta = 8.62$ ppm assumed for (NH_2) protons beside the expected signals.



Scheme 2

The synthetic potency of the hydrazine group of **11** was examined with some reagents in mind to synthesize new 2-pyrazolyl-pyrimidine, dimethylaminomethylenehydrazino derivative, acetylhydrazinyl derivative,

benzylidene derivative. Thus, treatment of **11** with ethyl acetoacetate in sodium ethoxide solution afforded the 4-(4-chlorophenyl)-2-(4-hydroxy-3*H*-pyrazol-3-yl)-6-methyl-5-(4-tolyl)carbamoylpyrimidine (**12**). The IR spectrum of this compound displayed absorption bands at ν 3300 cm^{-1} (br, OH), 3174 cm^{-1} (NH), 1640 cm^{-1} (CONH). When compound **11** was reacted with *N,N*-dimethylformamide-dimethylacetal afforded the dimethylaminomethylenehydrazino derivative **13**. Compound **14** was ruled out based on spectral data and the compound **13** is the sole product. So, the ^1H NMR spectrum of **13** revealed singlet signal (6H) at $\delta = 3.05$ assigned for $\text{N}(\text{CH}_3)_2$ protons. Reaction of **11** with acetic anhydride at refluxing temperature gave 2-(2-acetylhydrazinyl)-4-(4-chlorophenyl)-6-methyl-5-(4-tolyl)carbamoylpyrimidine (**15**). Further demonstration for the activity of compound **11** was achieved through their condensation with aldehyde; Thus it has been found that **11** reacted with 4-chlorobenzaldehyde in glacial acetic acid to give the Schiff's base **16**. The product showed no band of NH_2 function in IR spectrum. (Scheme 3)



Scheme 3

Experimental:

All melting points are uncorrected. IR spectra (KBr) were recorded on a FTIR 480 spectrometer (ν cm^{-1}). The ^1H NMR spectra were recorded in DMSO-d_6 and CDCl_3 200 MHz on a Varian Gemini NMR spectrometer (δ ppm) using TMS as an internal standard. Elemental analysis were carried out by the Microanalytical Research Center, Faculty of Science, Cairo University and Al-Azhar University, Faculty of Science, Department of Chemistry, Assiut branched.

General procedure for preparation of compounds 2 and 4.

A mixture of **1** (0.01 mole) and benzylidinemalononitrile (0.01 mole) or ethyl cyanocinnamate (0.01 mole) in (30 mL) ethanol in the presence of piperidine was refluxed for 6h. The reaction mixture was poured into water and few drops of HCl, the separated solid was collected and crystallized from ethanol to give **2** and **4**.

4-Amino-6-(4-chlorophenyl)-3-cyano-8-methyl-2-phenyl-2H,6H-7-(4-tolyl)carbamoylpyrimido[2,1-b][1,3]thiazine (2).

IR spectrum (KBr) cm^{-1} : 3310, 3206 (NH_2 , NH), 2923 (CH-aliphatic), 2210 (CN), 1645 (CONH). ^1H NMR (CDCl_3) δ ppm: 1.29 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 3.95 (s, 1H, CH thiazine), 4.05 (s, 2H, NH_2), 5.43 (s, 1H, CH pyrimidine), 7.05-7.53 (m, 13H, Ar-H), 8.08 (s, 1H, NH). See **table (1)**.

6-(4-Chlorophenyl)-3-cyano-4-hydroxy-8-methyl-2-phenyl-2H,6H-7-(4-tolyl)carbamoylpyrimido[2,1-b][1,3]thiazine (4).

IR spectrum (KBr) cm^{-1} : 3300, 3200 (OH+NH), 2950 (CH-aliphatic), 2223 (CN), 1670 (CONH). ^1H NMR (CDCl_3) δ ppm: 2.16 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.80 (s, 1H, OH) 3.95 (s, 1H, CH thiazine), 5.44 (s, 1H, CH pyrimidine), 6.92-7.47 (m, 13H, Ar-H), 8.22 (s, 1H, NH). See **table (1)**.

4-(4-Chlorophenyl)-3,4-dihydro-6-(N,N-dimethylamino)ethylene-5-(4-tolyl)carbamoyl-2(1H)-pyrimidinethione (5).

A mixture of compound **1** (0.01 mole) and *N,N*-dimethylformamide-dimethylacetal (0.01 mole) in *p*-xylene (20 mL) was refluxed for 5h, then allowed to cool and poured into ether (40 mL). The solid product was collected and recrystallized from benzene/petroleum ether (40-60) to give **5** as brown crystals. IR spectrum (KBr) cm^{-1} : 3261, 3108 (3NH), 3044 (CH aromatic), 2927 (CH aliphatic), 1651 (CONH). ^1H NMR (CDCl_3) δ ppm: 2.19 (s, 3H, CH_3), 3.09 (s, 6H, $\text{N}(\text{CH}_3)_2$),

5.42 (s, 1H, CH pyrimidine), 7.04-7.85 (m, 12H, Ar-H+ CH=CH+2NH), 9.99 (s, 1H, NH). See **table (1)**.

1-Acetyl-4-(4-chlorophenyl)-6-methyl-5-(4-tolyl)carbamoyl-2-thioxo-1,2-dihydropyrimidine (7).

Compound **1** was heated under reflux with acetic acid (10 mL) and acetic anhydride (5 mL) for 5h. The reaction mixture was cooled and diluted with water. The solid product was filtered off and crystallized from ethanol to produce **7** as brown crystals. IR spectrum (KBr) cm^{-1} : 3259 (NH), 2956 (CH aliphatic), 1700 (CO), 1645 (CONH). ^1H NMR (CDCl_3) δ ppm: 2.09 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 7.10-7.36 (m, 9H, Ar-H+NH). See **table (1)**.

5-(4-Chlorophenyl)-7-methyl-3-oxo-6-(4-tolyl)-carbamoyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidine (8).

A mixture of **1** (0.01 mole), chloroacetic acid (0.01 mole) and fused sodium acetate (1 g) in acetic acid (30 mL) and acetic anhydride (15 mL) was heated under reflux for 8 h. The reaction mixture was left to stand and acidified with dilute HCl, shaken well. The solid product was filtered off and recrystallized from ethanol to give **8** as yellow crystals. IR spectrum (KBr) cm^{-1} : 3284 (NH), 2921 (CH aliphatic), 1710 (CO), 1655 (CONH). ^1H NMR (CDCl_3) δ ppm: 1.44 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.83 (s, 2H, CH_2), 6.00 (s, 1H, CH pyrimidine), 6.98-7.44 (m, 8H, Ar-H), 7.66 (s, 1H, NH). See **table (1)**.

2-Benzylidene-5-(4-chlorophenyl)-7-methyl-6-(4-tolyl)carbamoyl-2,3-dihydro-5H-[1,3] thiazolo[3,2-*a*]pyrimidine derivatives 9a,b.

General procedure

Method A. A mixture of compound **1** (0.01 mole), chloroacetic acid (0.01 mole), appropriate aromatic aldehydes (0.01 mole), and anhydrous sodium acetate (1 g) was refluxed in 30 mL of glacial acetic acid and 15 mL of acetic anhydride for 6h. The reaction mixture was cooled and poured into water. The deposited precipitate was filtered-off and recrystallized from ethanol/DMF to produce **9a,b**.

Method B. Compound **8** was heated under reflux with the proper aldehydes in acetic acid (30 mL) and acetic anhydride (15 mL), in presence of anhydrous sodium

acetate (1 g) for 5h. The reaction mixture was cooled and poured into water. The solid product was filtered and crystallized to give **9a,b**.

2-(4-chlorobenzylidene)-5-(4-Chlorophenyl)-7-methyl-6-(4-tolyl)carbamoyl-2,3-dihydro-5-H-[1,3] thiazolo[3,2-a]pyrimidine (9a).

IR spectrum (KBr) cm^{-1} : 3430 (NH), 1700 (CO) this shift to lower frequency is due to conjugation with the exocyclic double bond, 1639 (CONH). ^1H NMR (CDCl_3) δ ppm: 2.10 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 6.19 (s, 1H, CH pyrimidine), 7.09-7.44 (m, 13H, Ar-H+benzylic proton), 7.68 (s, 1H, NH). See **table (1)**.

5-(4-Chlorophenyl)-2-(4-methylbenzylidene)-7-methyl-6-(4-tolyl)carbamoyl-2,3-dihydro-5-H-[1,3] thiazolo[3,2-a]pyrimidine (9b).

IR spectrum (KBr) cm^{-1} : 3440 (NH), 1695 (CO) this shift to lower frequency is due to conjugation with the exocyclic double bond, 1638 (CONH). ^1H NMR (CDCl_3) δ ppm: 1.66 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 6.17 (s, 1H, CH pyrimidine), 6.90 (s, 1H, CH benzylic), 6.93-7.44 (m, 12H, Ar-H), 7.71 (s, 1H, NH). See **table (1)**.

5-(4-Chlorophenyl)-7-methyl-6-(4-tolyl)carbamoyl-2,3-dihydro-5-H-[1,3]thiazolo[3,2-a]pyrimidine (10).

A mixture of compound **1** (0.01 mole), 1,2-dichloroethane (0.01 mole) in ethanolic solution of sodium ethoxide was refluxed for 5h. The solid product produced on cold was collected and recrystallized from ethanol to give **10** as brown crystals. IR spectrum (KBr) cm^{-1} : 3271 (NH), 2928 (CH aliphatic), 1652 (CONH). ^1H NMR (CDCl_3) δ ppm: 2.05 (t, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.71 (t, 2H, SCH_2), 5.52 (s, 1H, CH pyrimidine), 6.90-7.85 (m, 8H, Ar-H), 9.14 (s, 1H, NH). See **table (1)**.

4-(4-Chlorophenyl)-2-hydrazinyl-6-methyl-5-(4-tolyl)carbamoylpyrimidine (11).

A mixture of compound **1** (0.01 mole) and hydrazine hydrate (1ml; excess) was heated under reflux in pyridine (15 mL) for 12h¹⁹. The reaction mixture was cooled, poured into water. The solid product was filtered and crystallized from ethanol to produce **11** as pale green crystals. IR spectrum (KBr) cm^{-1} : 3406, 3368 (NH_2), 3310, 3250 (2NH), 2938 (CH aliphatic), 1660 (CONH). ^1H NMR (CDCl_3) δ ppm: 1.85 (s,

3H, CH₃), 1.96 (s, 3H, CH₃), 7.26 (s, 1H, NH), 7.27-7.81 (m, 8H, Ar-H), 8.62 (s, 2H, NH₂), 10.01 (s, 1H, NH). See **table (1)**.

4-(4-Chlorophenyl)-2-(4-hydroxy-3H-pyrazol-3-yl)-6-methyl-5-(4-tolyl)carbamoylpyrimidine (12).

A mixture of compound **11** (0.01 mole) and ethyl acetoacetate (0.01 mole) in sodium ethoxide solution (prepared by dissolving 0.23 g, 10 mmol of sodium metal in absolute ethanol 30 mL) was heated under reflux for 6h. The reaction mixture was allowed to cool, poured into cold water (100 ml) and neutralized by hydrochloric acid, where by a solid precipitated which was filtered off and recrystallized from ethanol to give **12** as brown crystals. IR spectrum (KBr) cm⁻¹: 3300 (br, OH), 3174 (NH), 3047 (CH aromatic), 2933 (CH aliphatic), 1640 (CONH). ¹H NMR (CDCl₃) δ ppm: 1.25 (s, 3H, CH₃), 2.22 (s, 3H, CH₃), 2.38 (s, 3H, CH₃), 7.27 (s, 1H, OH), 7.42-7.80 (m, 9H, Ar-H+ pyrazole H-4 proton), 8.61 (s, 1H, NH). See **table (1)**.

4-(4-Chlorophenyl)-2-(N,N-dimethylaminomethylene)hydrazino-6-methyl-5-(4-tolyl)carbamoylpyrimidine (13).

A mixture of compound **11** (0.01 mole) and *N,N*-dimethylformamide-dimethylacetal (0.012 mole) in *p*-xylene (20 mL) was refluxed for 5h, then allowed to cool and poured into ether (40 mL). The solid product was collected and recrystallized from benzene/petroleum ether (40-60) to give **13** as brown crystals. IR spectrum (KBr) cm⁻¹: 3403, 3247 (2NH), 3046 (CH aromatic), 2929 (CH aliphatic), 1628 (C=N). ¹H NMR (CDCl₃) δ ppm: 2.02 (s, 3H, CH₃), 2.57 (s, 3H, CH₃), 3.05 (s, 6H, N(CH₃)₂), 6.95-7.80 (m, 10H, Ar-H+ NH+ N=CH), 8.61 (s, 1H, NH). See **table (1)**.

2-(2-Acetylhydrazinyl)-4-(4-chlorophenyl)-6-methyl-5-(4-tolyl)carbamoylpyrimidine (15).

A suspension of compound **11** (0.01 mole) in acetic anhydride (10 mL) was refluxed for 5h. The reaction mixture was cooled and diluted with water. The solid thus obtained was filtered off and crystallized from ethanol to produce **15** as pale brown crystals. IR spectrum (KBr) cm⁻¹: 3216 (NH), 3050 (CH aromatic), 2930 (CH aliphatic), 1640 (CO). ¹H NMR (DMSO-d₆) δ ppm: 1.39 (s, 3H, CH₃), 2.03 (s, 3H, CH₃), 2.41 (s, 3H, CH₃), 6.58-7.81 (m, 8H, Ar-H), 8.80 (s, 1H, NH), 10.00 (s, 1H, NH), 11.26 (s, 1H, NH). See **table (1)**.

4-(4-Chlorophenyl)-2-(4-chlorophenylmethylenehydrazone)-6-methyl-5-(4-tolyl)carbamoylpyrimidine (16).

A mixture from compound **11** (0.01 mole), 4-chlorobenzaldehyde (0.01 mole), and anhydrous sodium acetate (1 g) was refluxed in glacial acetic acid (20 mL) for 5h. The reaction mixture was allowed to cool and poured into water (100 mL). Where by a solid was filtered off and crystallized from benzene/petroleum ether to produce **16** as brown crystals. IR spectrum (KBr) cm^{-1} : 3189 (2NH), 3041 (CH aromatic), 2934 (CH aliphatic), 1650 (CONH). ^1H NMR (CDCl_3) δ ppm: 1.65 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 5.07 (s, 1H, $\text{CH}=\text{N}$), 6.91-7.84 (m, 13H, Ar-H+NH), 8.61 (s, 1H, NH). See **table (1)**.

.Table (1): Characterization data of the newly synthesized compounds

Comp. NO	M.P $^{\circ}\text{C}$	Yield % Color	/Mol. Formula M. Wt	Elemental analysis Calcd. /Found %		
				C	H	N
2	110-112	80 Yellow	$\text{C}_{29}\text{H}_{24}\text{ClN}_5\text{OS}$ (526.05)	66.21	4.60	13.31
				66.15	4.70	13.30
4	105-106	80 Brown	$\text{C}_{29}\text{H}_{23}\text{ClN}_4\text{O}_2\text{S}$ (527.03)	66.09	4.40	10.63
				66.00	4.45	10.70
5	145-147	63 Brown	$\text{C}_{22}\text{H}_{23}\text{ClN}_4\text{OS}$ (426.96)	61.89	5.43	13.12
				61.80	5.40	13.00
7	210-212	70 Brown	$\text{C}_{21}\text{H}_{18}\text{ClN}_3\text{O}_2\text{S}$ (411.90)	61.23	4.40	10.20
				61.30	4.46	10.24
8	230-231	61 Yellow	$\text{C}_{21}\text{H}_{18}\text{ClN}_3\text{O}_2\text{S}$ (411.90)	61.23	4.40	10.20
				61.30	4.50	10.30
9a	250-251	70 Yellow	$\text{C}_{28}\text{H}_{21}\text{Cl}_2\text{N}_3\text{O}_2\text{S}$ (534.47)	62.92	3.96	7.86
				62.90	4.00	7.80
9b	260-262	71 Yellow	$\text{C}_{29}\text{H}_{24}\text{ClN}_3\text{O}_2\text{S}$ (514.05)	67.76	4.71	8.17
				67.60	4.80	8.20
10	125-126	56 Brown	$\text{C}_{21}\text{H}_{20}\text{ClN}_3\text{OS}$ (397.92)	63.39	5.07	10.56
				63.30	5.20	10.60
11	196-198	66 pale green	$\text{C}_{19}\text{H}_{18}\text{ClN}_5\text{O}$ (367.84)	62.04	4.93	19.04
				62.10	5.00	19.00
12	150-152	60 Brown	$\text{C}_{23}\text{H}_{20}\text{ClN}_5\text{O}_2$ (433.90)	63.67	4.65	16.14
				63.50	4.60	16.20
13	115-117	68 Brown	$\text{C}_{22}\text{H}_{23}\text{ClN}_6\text{O}$ (422.92)	62.48	5.48	19.87
				62.60	5.55	20.00
15	160-162	65 Brown	$\text{C}_{21}\text{H}_{20}\text{ClN}_5\text{O}_2$ (409.86)	61.54	4.92	17.09
				61.40	5.00	17.00
16	130-132	75 Brown	$\text{C}_{26}\text{H}_{21}\text{Cl}_2\text{N}_5\text{O}$ (490.40)	63.68	4.32	14.28
				63.50	4.30	14.30

References

1. Ram, V. J.; Goel, A.; Nath, M.; Srivastava, P. *Bioorg. Med. Chem. Lett.* **1994**, 22, 2653.
2. Kluchko, S. V.; Khutova, B. M.; Rozhenko, A. V.; Romanenko, E. A.; Vdovenko, S. I.; Ribchenko, L. I.; Rrikazchikova, L. P.; Drach, B. S. *Khim. Geterotiski. Soedin.* **1992**, 1, 95.
3. Attaby, F. A.; Eidin, S. M.; Hanafi E. Z. *Arch. Pharm. Res.* **1997**, 20, 620.
4. Ram, V. J. *Arch. Pharm.* **1990**, 323, 895.
5. Ram, V. J.; Hague, N.; Guru, P. Y. *Eur. J. Med. Chem.* **1992**, 27, 851.
6. Fawzy, A. A.; Sanaa, M.; Eldin, Z. *Naturforsch* **1999**, 54b, 788.
7. Bakhite, E. A.; Geiese, A. A.; Elkashef, H. S. *Phosphorus, Sulfur and Silicon* **2002**, 177, 303.
8. Geies, A. A.; El-Dean, A. M. K.; Abd El-Hafes, A. A.; Gaber, A. M. *Phosphorus, Sulfur and Silicon* **1991**, 56, 87.
9. El-Gazzar, A. B. A.; Hassan, N. A. *Molecules* **2000**, 5, 835.
10. Ho, Y. W.; Yao, C. T. *J. Chin. Chem. Soc.* **2003**, 50(2).
11. Abdullah, A. A. *J. Chin. Chem. Soc.* **2004**, 51, 547-552.
12. Koksharova, T. G.; Volkava, N. V.; Dianova, V.; Tlenko, V. I.; Plantov, V. G.; Shcherbakova, I. R. *Khim. Farm. Zh.* **1992**, 27, 57.
13. Leven, M.; Vlielinck, A. J.; Vanden-Berghe, D. A.; Totle, M.; Domisse, R.; Esmans, E.; Alderwreldt, E. *J. Nat. prod.* **1982**, 45, 564.
14. Vanden-Berghe, D. A.; Leven, M.; Mertens F.; Vlietinck, A. J.; Lammens, E. *Lloydia* **1978**, 41, 463.
15. Vanden-Berghe, D. A.; Vlietinck, A. J.; Vanlloof, L. *Bull. Inst. Pasteur* **1986**, 84, 101.
16. Vishnu, Ram. J.; Haqne, N.; Ginru, P. Y. *Eur. J. Med. Chem.* **1992**, 27(8), 8.
17. Vishnu, Ram. *J. Arch. Pharm.* **1990**, 323, 895.
18. Ahmed A. A. Khames. *Ph. D. Thesis*, Al-Azhar University, **2006**.
19. El-Emary, T. I.; Abdel-Mohsen, Sh. A. *Phosphorus, Sulfur and Silicon* **2006**, 181, 2459.