Synthesis and Biological activity of Some PyrroloPyrimidine Compounds.

Suliman Mohamed Mussa*

Chemistry Department, Faculty of Science, Misurata University, Misurata - Libya.

Abstract

The present work was planned to synthesize some heterocyclic compounds containing pyrrolo[2,3-d]pyrimidines.

Our approach to the synthesis of the target compounds started through the hydrolysis of 6-ethylthio-4-methyl-2-(p-methoxyphenyl)pyrimidine-5-carbonitrile by refluxing in ethanol containing sodium hydroxide to give the corresponding sodium salt derivative which in turn was acidified to give 5-cyano-4-methyl-2-(p-methoxyphenyl)pyrimidin-6(H)one**.** Chlorination of the 5-Cyano-4-methyl-2-(p-methoxyphenyl)pyrimidin-6(1H)-one afforded 6-Chloro-4-methyl-2-(p-methoxyphenyl)pyrimidin-5-carbonitrile**,** which reacted with ethyl glycinate hydrochloride to give Ethyl (5-cyano-4-methyl-2-(p-methoxyphenyl)yrimidin-6-yloxy)acetate**,** which underwent cyclization to give the ethyl 5-amino-4-methyl-2-(p-methoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate**.** The reaction of 5-Cyano-6-chloro-4-methyl-2-(p-methoxyphenyl)pyrimidine with piperidine, and morpholine, gave the 4-Methyl-6-(morpholin-4-yl)-2-(p-methoxyphenyl)pyrimidine-carbonitrile and 4-Methyl-6-(morpholin-4-yl)-2-(p-methoxyphenyl)pyrimidine-5-carbonitrile respectively .

The Ethyl 5-amino-4-methyl-2-(p-methoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate was used as key intermediates in the synthesis of other pyrrolo[2,3-d]pyrimidine derivatives**,** pyrimido[4\',5\':4,5]pyrrolo[2,3-d]pyrimidines and triazolopyrro lopyrimidines by reaction with different reagents **.**

Seven compounds were selected and screened *in vitro* for their antimicrobial activity against four strains of bacteria and two fungal species .

Key words : pyrrolopyrimidines, Pyrimidopyrimidines, synthesis , Biological activity

Introduction:

Five positional isomers of pyrrolopyrimidines are known as aresult of fusion of pyrrole to the pyrimidine nucleous: pyrrolo[2.3-d]pyrimidine, pyrrolo[3.2-d]pyrimidine, pyrrolo[3.4-d]pyrimidine, pyrrolo[1.2-a]pyrimidine and pyrrolo[1.2-c]pyrimidine . two synthetic route have been used for the synthesis of pyrrolo[2.3-d]pyrimidine either starting with the pyrrole moiety or the pyrimidine one. The literature survey reveals that the most important one is ttat starting from the appropriate ortho-substituted aminopyrroles . pyrimidine derivatives have occupied a unique position in medicinal chemistry, the pyrimidine ring is present in a large number of biological important compounds such as alkaloids. Condensed pyrimidines have received much attention over the years because of their interesting biological and medicinal importance such as antiviral [1], antitumors [2 , 3], anti cancer [4 , 5], competitive inhibitors

[6, 7], antimicrobial [8, 9] , antiplasmodial activities [10] as well as antiproliferactive activity [11] . in view of the above observation and as a continuation of our previous work about the synthesis of fused pyrimidine compounds [12-14], which are expected to be of biological and medicinal importance. we became interested in the synthesis of some heterocyclic compounds containing pyrrolo[2,3-d]pyrimidines.

Experimental:

All melting points are uncorrected and measured on a Gallan-Kamp apparatus. IR spectra were recorded on a Shimadzu-470 IR-spectrophotometer (KBr; υ_{max} in cm^{-1}). ^{1}HNMR spectra were measured on a Varian EM-390, 90 MHz spectrometer or on a Jeol LA 400 MHz FT-NMR spectrometer with TMS as internal standard (δ in ppm); MS on a Jeol JMS-600 mass spectrometer. Elemental analyses were determined on a Perkin-Elmer 240C elemental analyzer or on an Elemental Analyses system GmbH VARIOEL $V_{2,3}$ CHNS Mode.

5-Cyano-4-methyl-2-(p-methoxyphenyl) pyrimidin-6(1H)-thione (1):

Prepared as previously reported in literature procedure [14] .

The synthesized compounds (2-19) were Prepared with some modification of reported methods in literature procedures [12-14] .

6-Ethylthio-4-methyl-2-(p-methoxyphenyl) pyrimidin-5-carbonitrile (2):

A mixture of **1** (2.57 g, 0.01 mol.) and ethyl bromide (0.015 mol) in ethanol (50 ml) was refluxed for 3 hrs., in the presence of anhydrous potassium carbonate (0.5g). The solid product separated from the hot mixture was filtered off, washed with water and recrystallized from ethanol as pale yellow crystals .

Sodium 5-cyano-4-methyl-2-(p-methoxy phenyl)-6-pyrimidinate (3):

A mixture of **2** (2.85 g, 0.01 mol.) , sodium hydroxide (0.02 mol) in water (1 ml) and ethanol (20 ml), was refluxed for 4 hrs, then allowed to cool. The solid product was filtered off, washed with ethanol as white crystals.

5-Cyano-4-methyl-2-(p-methoxyphenyl) pyrimidin-6(1H)-one (4):

To a solution of **3** (2.63 g, 0.01 mol.) in water, 50 ml of HCl was added. The white precipitate which separated was collected by filtration and air dried. Recrystallization from DMF gave white crystals.

5-Cyano-6-chloro-4-methyl-2-(p-methoxy phenyl)pyrimidine (5):

A sample of **3** (2.63 g, 0.01 mol.) in phosphorus oxychloride (15 ml) was heated under reflux for 4 hrs. After cooling the reaction mixture was poured into ice/water mixture (200g) drop wise with stirring. The solid product was filtered off and recrystallized from ethanol as pale yellow crystals.

Ethyl (5-cyano-4-methyl-2-(p-methoxy phenyl)pyrimidin-6-yloxy)acetate (6):

A mixture of **3** (2.63 g, 0.01 mol.) and ethyl chloroacetate in pure acetone (20 ml) was refluxed for 6 hrs, then allowed to cool and poured into cold water with stirring. The solid product was collected and recrystallized from ethanol as white crystals.

4-Methyl-2-(p-methoxyphenyl)-6-(piperi din-1-yl)pyrimidine-5-carbonitrile (7):

A sample of compound **5** (1.30 g, 0.005 mol.) in pipyridine (2 ml) was fused for 15 min, then ethanol (20 ml) was added and the mixture was refluxed for 2 hrs. The solid product obtained after cooling was filtered off and recrystallized from ethanol as pale yellow crystals.

4-Methyl-6-(morpholin-4-yl)-2-(p-methoxy phenyl)pyrimidine-5-carbonitrile (8):

A sample of compound **5** (1.3 g, 0.005 mol.) and morpholine (2 ml) was fused for 15 min, then ethanol (20 ml) was added and the mixture was refluxed for 2 hrs. The solid product obtained after cooling was filtered off and recrystallized from ethanol as pale yellow crystals.

Ethyl N-(5-cyano-4-metheyl-2-(p-methoxy phenyl)pyrimidin-6-yl)glycinate (9):

A mixture of **5** (2.6 g, 0.01 mol.), ethyl glycinate hydrochloride (2.1 g, 0.015 mol) and K_2CO_3 (0.02 mol.) in DMF (30 ml) was heated on steam bath at (70-80^oC) for 8 hrs. After cooling the reaction mixture was poured into ice-water mixture (50 gm) slowly with stirring. The solid product was filtered off and recrystallized from ethanol as white crystals.

Ethyl 5-amino-4-methyl-2-(p-methoxy phenyl)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate (10):

A sample of **9** (1.63 g, 0.005 mol.) in absolute ethanol (50 ml) containing sodium metal (0.5 g) was refluxed for 1 hr. The solid product was collected by filtration, washed thoroughly with water and recrystallized from ethanol as yellow crystals.

Sodium 5-amino-4-methyl-2-(p-methoxy phenyl)-7H-pyrrolo[2,3-d]pyramid-ine-6-carboxylate (11):

A mixture of **10** (3.26 g, 0.01 mol.) in ethanolic sodium hyroxide solution (0.6g) in ethanol (30 ml) was heated under reflux for 5 hrs. The solid product was collected, washed with ethanol and air dried. The yellowish white solid was subjected to the next step without further purification.

4-Methyl-2-(p-methoxyphenyl)-5,6-dihydro -7H-pyrrolo[2,3-d]pyrimidin-5-one (12):

A sample of **11** (1.6 g, 0.005 mol.) in orthophosphoric acid (10 ml) was stirred at room temperature for 3 hrs then poured into ice-water mixture (200 g) and neutralized by ammonium hydroxide. The white precipitate was collected and recrystallized from ethanol as white crystals.

5-Amino-4-methyl-2-(p-methoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine-6-carbo hydrazide (13):

A mixture of **10** (1.63 g, 0.005 mol.) and hydrazine hydrate 99% (3 ml) in ethanol (50 ml) was refluxed for 2 hrs. The solid product which formed on hot was filtered off and recrystallized from dioxan as yellow crystals.

9-Methyl-7-(p-methoxyphenyl)pyrimido [4\',5\':4,5]-5H-pyrrolo[2,3d]pyramidin-4(3H) -one (14):

A sample of **10** (1.63 g, 0.005 mol.) in formamide (15 ml) was refluxed for 3 hrs. The solid product which formed on hot was filtered off and recrystallized from dioxan as yellow crystals.

4-Cloro-9-methyl-7-(p-methoxyphenyl)-5H pyrimido[4\',5\':4,5]pyrrolo[2,3-d] pyramidine (15):

A sample of **14** (3.07 g, 0.01 mol.) in phosphorus oxychloride (15 ml) was heated under reflux for 4 hrs. After cooling the reaction mixture was poured into ice/water mixture dropwise with stirring. The solid product was filtered off and recrystallized from ethanol as pale yellow crystals.

4-Hydrazino-9-methyl-7-(p-methoxyphenyl)-5H-pyrimido[4\',5\':4,5]pyrrolo[2,3-d]pyri midine (16):

A mixture of **15** (3.25 g, 0.01 mol.) and hydrazine hydrate 99% (0.015 mol.) in ethanol (50 ml) was refluxed for 3 hrs. The solid product which separated from the hot mixture was filtered off and recrystallized from dioxan as pale yellow crystals.

9-Methyl-4-(p—substitutedbenzylidene hydrazono)-7-(p-methoxyphenyl)-5H-pyrimido[4\',5\':4,5]pyrrolo[2,3-d]pyrimidine (17a-c):

General procedure:

A mixture of **16** (1.60 g, 0.005 mol.) and appropriate aromatic aldehyde (0.005 mol.) in 10 ml acetic acid was refluxed for 3 hrs, then allowed to cool. The solid product was collected and recrystallized from acetic acid as yellow crystals.

9-Methyl-7-(p-methoxyphenyl)-5H-[1,2,4] triazolo[4,3:1,6]pyrimido[4\',5\':4,5]pyrrolo[2,3-d]pyr imidine (18):

A mixture of hydrazine derivative16 (0.01 mol) and triethyl orthoformate (2 ml) in ethanol (30 ml) in the presence of a few drops of acetic acid was refluxed for 3 hrs The. solid crystals separated from the hot mixture

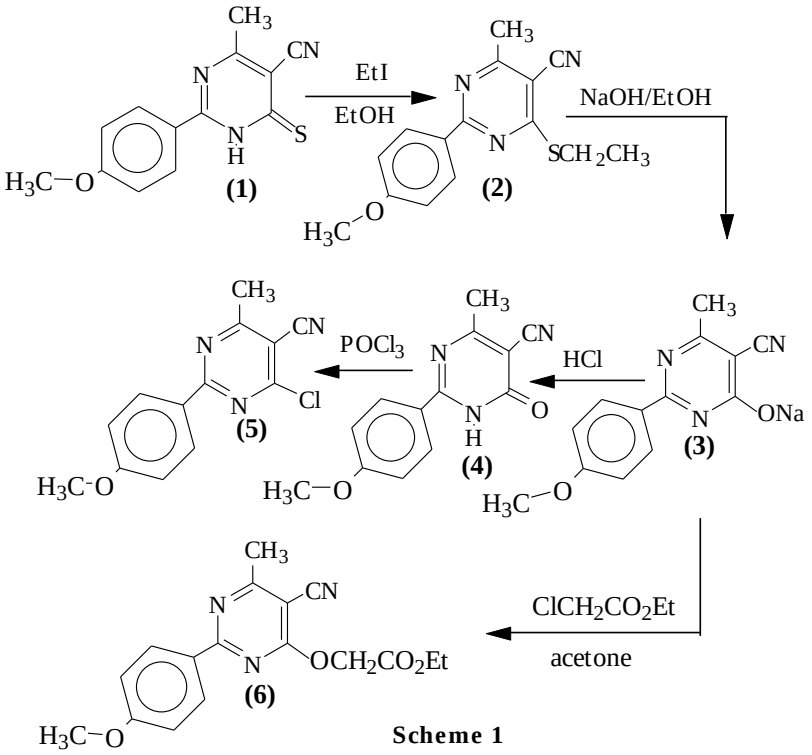
were filtered off and recrystallized from dioxane as yellow crystals .

9-Methyl-7-(p-methoxyphenyl)-5H-2-methyl-[1,2,4]triazolo[4,3:1,6]pyrimido[4\, 5\ : 4,5]pyrrolo[2,3-d]pyrimidine (19):

A mixture of hydrazine derivative**16** (0.01 mol) and acetic anhydride (20 ml) was refluxed for 4 hrs. The solid crystals separated from the hot mixture were filtered off and recrystallized from DMF as yellow crystals .

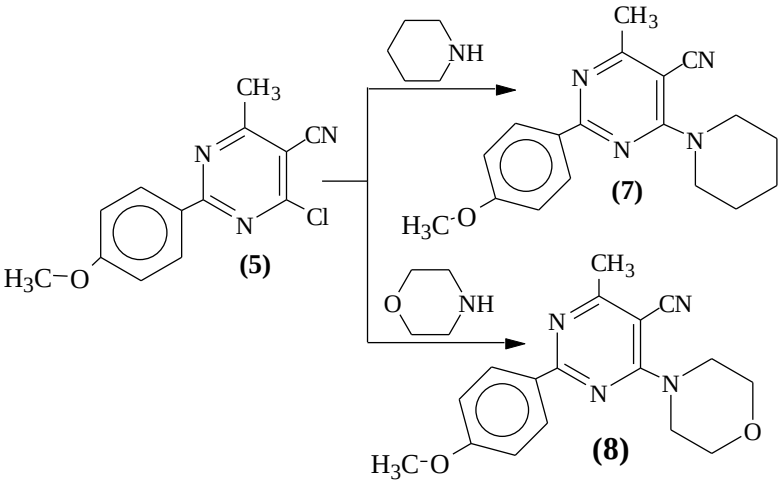
Results and discussion :

The approach to the synthesis of the target compounds started from the hydrolysis of 6-ethylthio-4-methyl-2-(4-methoxyphenyl) pyrimidine-5-carbonitrile **(2)** by refluxing in ethanol containing sodium hydroxide to give the corresponding sodium salt derivative **(3)** which in turn was acidified to give the hydroxy derivative **(4).** Chlorination of (4) with phosphorus oxychloride afforded 6-chloropyrimidine derivative **(5)** . Also the reaction of (3) with ethyl chloroacetate, by refluxing in ethanol or acetone gave the corresponding O-substituted oxopyrimidine **(6)** (Scheme 1).



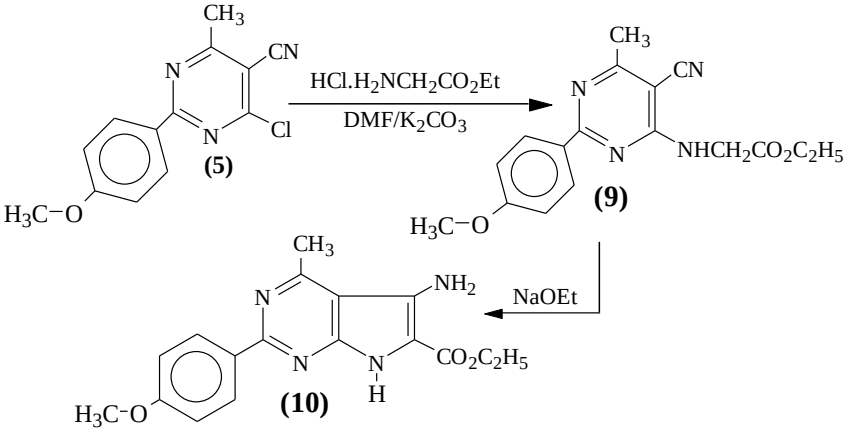
Scheme 1

On treatment of compound **(5)** with piperidine, and morpholine, nucleophilic displacement took place to give the piperidino- and morphilino- derivatives **(7)** and **(8)** respectively (Scheme 2)**.**



Scheme2

6-Chloro-4-methyl-2-(p-methoxyphenyl)-pyrimidine-5-carbonitrile **(5)** was employed as starting material for the target compound pyrrolopyrimidine**.** The reaction of compound **(5)** with ethyl glycinate hydrochloride by heating in DMF in the presence of anhydrous K_2CO_3 gave the corresponding glycinate derivative **(9)** which underwent intramolecular *Thorpe-Ziegler* cyclization upon treatment with sodium ethoxide to give ethyl 5-amino-4-methyl-2-(p-methoxy phenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-carboxylate **(10)** (Scheme 3)**.**



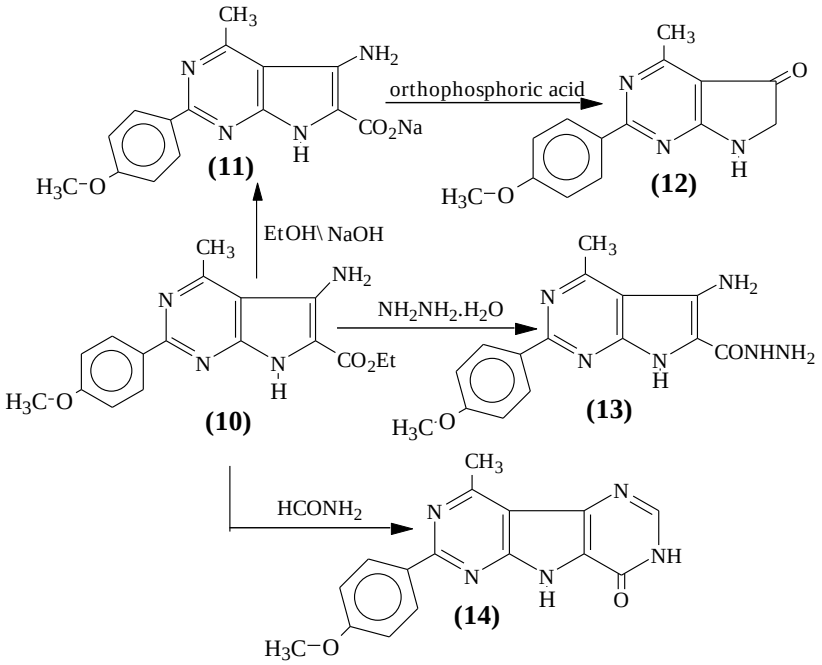
Scheme3

The *o*-amino ester **(10)** was used as a key intermediate in the synthesis of other new pyrrolo[2,3-d]pyrimidines and pyrimido[4\',5\' :4,5]pyrrolo[2,3-d]pyrimidine (Scheme 3)**.**

Thus saponification of compound **(10)** with an ethanolic sodium hydroxide solution afforded (**11**) which on treatment with orthophosphoric acid gave 4-methyl-2-(4-methoxyphenyl)-5,6-dihydro-7H-pyrrolo[2,3-d]pyrimidin-5-one **(12).**

The reaction of compound **(10)** with an excess amount of hydrazine hydrate (99%) in refluxing ethanol produced 5-amino-4-methyl-2-(4-methoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine-6-carbohydrazide **(13)**

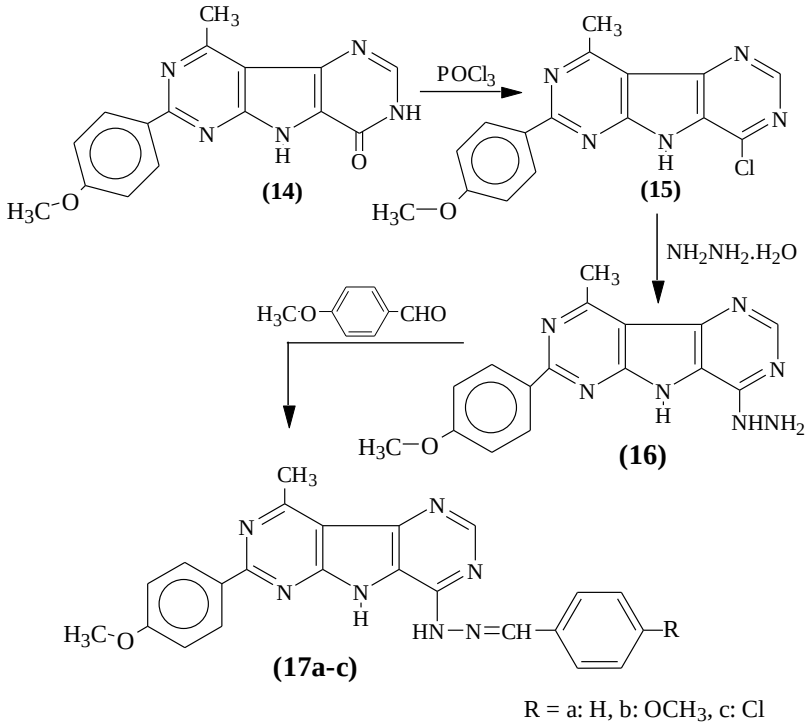
Also compound **(10)** underwent ring closure reaction upon treatment with formamide to afford the 9-Methyl-7-(4-methoxyphenyl)pyrimido[4\', 5\' : 4, 5]-5H-pyrrolo[2,3-d]pyrimidin-4(3H)-one **(14)** (Scheme 4)**.**



Scheme 4

phenyl)-5H-pyrimido[4\',5\':4,5]pyrrolo[2,3-d] pyrimidine **(16) .**The latter compound was used as precursor for synthesizing 9-Methyl-4-(4\'-methoxybenzylidenehydrazono)-7-(4-methoxyphenyl)-5H-pyrimido[4\',5\':4,5]pyrr olo[2,3-d]pyrimidine **(17a-c)** by reaction with a variety of aromatic aldehydes in acetic acid (Scheme 5).

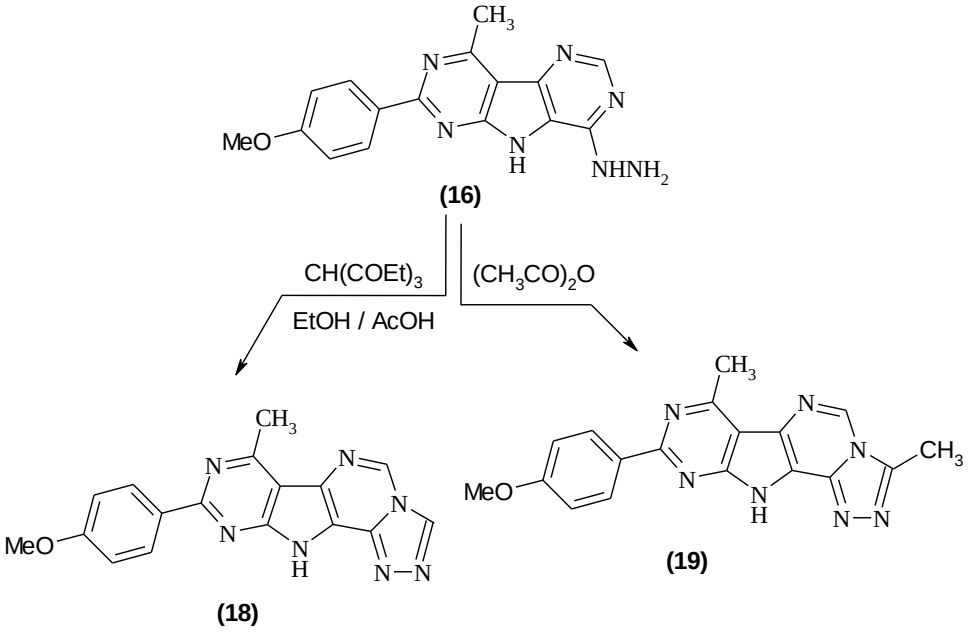
Chlorination of compound **(14)** by refluxing with an excess amount of phosphorus oxychloride gave 4-Cloro-9-methyl-7-(4-methoxyphenyl)-5H-pyrimido[4\', 5\':4,5]pyrrolo[2,3-d]pyrimidine **(15),** which reacted with an equimolar amount of hydrazine hydrate (99%) in refluxing ethanol produced 4-hydrazino-9-methyl-7-(4-methoxy



Scheme 5

reagents such as triethyl orthoformate and acetic anhydride to give compounds **(18)** and **(19**) respectively (Scheme 6).

The hydrazino derivative (**16)** was used as a key intermediate to synthesize a new ring system, namely triazolopyrrolo pyrimidine, through the reaction with



Scheme 6

The structural formulae of the synthesized compounds (2-19) were confirmed by elemental and spectral analyses as shown in tables (2&3) .

Biological Activity :

Seven of the synthesized compounds have been tested against two pathogenic gram positive bacteria, Bacillus cereus and Staphylococcus aureus and two gram negative bacteria : Serratia marcescens and Pseudomonas aeruginosa. Also three fungal species were used in the present investigation : Aspergillus, Penicillium chrysogenium and Fusarium monolifofme . The biological activity as expressed by the growth inhibition zone of the tested microorganism listed in table **1** It is obvious that some of the tested compounds exhibit the moderate activity (inhibition zone 6-10 mm) against the mentioned species of bacteria and fungi as shown in table 1.

Table 1: Results of the antimicrobial screening

Comp.No	B. cereus	S. aureus	S. marcescens	P. aeruginosa	A. terreus	P. chrysogenum	F. moniliforme
5	10	8	-	-	7	8	8
8	-	-	-	-	-	-	-
10	10	8	-	-	7	8	8
11	8	-		-	-	-	-
13	10	8	-	-	8	-	10
16	10	8	-	-	8	8	-
17a	8	6	-	-	7	6	-

Table2: Physical Properties and Analytical Data of Compounds (2-19)

.No	m.p°C	Yield %	Formula/mol.wt	Calculated / Found C	H	N
2	125-127	70	$C_{15}H_{15}N_3OS$ 285.37	63.13 63.15	5.30 5.27	14.72 14.70
3	----------	61	$C_{13}H_{10}N_3O_2$ Na 263.20	59.32 59.18	3.83 3.76	15.96 16.02
4	285-287	76	$C_{13}H_{11}N_3O_2$ 241.25	64.72 65.01	4.60 4.58	17.42 17.33
5	184-186	71	$C_{13}H_{10}ClN_3O$ 259.70	60.13 60.07	3.88 3.90	16.18 16.30
6	123-125	73	$C_{17}H_{17}N_3O_4$ 327.34	62.38 62.26	5,23 5.19	12.84 13.01
7	102-104	68	$C_{18}H_{20}N_4O$ 308.39	70.11 70.32	6.54 6,50	18.17 18.09
8	175-177	90	$C_{17}H_{18}N_4O_2$ 310.36	65.79 65.70	5.85 6.00	18.05 18.10
9	142-144	90	$C_{17}H_{18}N_4O_3$ 326.36	62.57 62.58	5.56 5.54	17.17 17.21
10	163-165	75	$C_{17}H_{18}N_4O_3$ 326.36	62.57 62.60	5.56 5.51	17.17 17.25
12	143-145	65	$C_{14}H_{13}N_3O_2$ 255.28	65.87 66.01	5.13 5.08	16.46 16.37
13	310-315	68	$C_{15}H_{16}N_6O_2$ 312.33	57.68 57.60	5.16 5.10	26.91 27.03
14	>350 decompose	76	$C_{16}H_{13}N_5O_2$ 307.31	62.53 62.45	4.26 4.35	22.79 22.82
15	315-317	69	$C_{16}H_{12}ClN_5O$ 325.76	58.99 59.05	3.71 3.68	21.50 21.51
16	285-287	65	$C_{16}H_{15}N_7O$ 321.34	59,80 60.00	4.71 4.65	30.51 30.49
17a	295-297	68	$C_{23}H_{19}N_7O$ 409.44	67.47 67.58	4.68 4.65	23.95 24.06
17b	310-312	69	$C_{24}H_{21}N_7O_2$ 439.48	65.59 65.60	4.82 4.90	22.31 22.20
17c	>300 decompose	72	$C_{23}H_{18}ClN_7O$ 443.90	62.23 62.15	4.09 4.00	22.09 22.10
18	>320 decompose	75	$C_{17}H_{13}N_7O$ 331.34	61.63 61.55	3.95 4.00	29.59 29.54
19	>320 decompose	63	$C_{18}H_{15}N_7O$ 345.37	62.60 62.75	4.38 4.31	28.39 28.42

5 Cl (Cal. 13.65, Found 13.50).
15 Cl (Cal. 10.88, Found 11.00).
17c Cl (Cal. 7.99, Found 8.05).

Table 3 Spectroscopic Data of Compounds (2-17)

2	IR: υ = 2200cm^{-1} (C≡N). ^{1}HNMR(DMSO-d_6) : δ = 1.3-1.5 (t, 3H, CH_3), 2.8 (s,3H, CH_3 , pyrimidine), 3.3-3.5 (q, 2H, CH_2), 3.9 (s, 3H, OCH_3) 7.3, 7.4 (d, 2H, Ar-H) and 7.9, 8.0 (d, 2H, Ar-H .
4	IR: υ = IR: υ = 3450 cm^{-1}(NH), 2200 cm^{-1} (C≡N) and 1680cm^{-1} (C=O). m/z = 241
5	IR: υ = 2200cm^{-1} (C≡N) and no bands characteristic for (NH, C=O) . ^{1}HNMR(DMSO-d_6) : δ = 2.8 (s,3H, CH_3 , pyrimidine), 3.85 (s, 3H, OCH_3), 7.3, 7.4 (d, 2H, Ar-H) and 7.9, 8.0 (d, 2H, Ar-H . m/z = 259 (98%), 261(31.8%), 224(M^+-Cl).
6	IR: υ = IR: υ = 2200 cm^{-1} (C≡N) and 1730 cm^{-1} (C=O). ^{1}HNMR($CDCl_3$) : δ = 1.15-1.3 (t, 3H, CH_3, ester), 2.8 (s,3H, CH_3, pyrimidine), 3.85 (s, 3H, OCH_3), 4.05-4.30 (q, 2H, CH_2, ester), 5.0 (s, 2H, CH_2), 7.3, 7.4 (d, 2H, Ar-H) and 7.9, 8.0 (d, 2H, Ar-H .
7	IR: υ = IR: υ = 2200 cm^{-1} (C≡N) . ^{1}HNMR(DMSO-d_6) : δ =1.6 (s,6H, 3CH_2), 2.6 (s,3H, CH_3, pyrimidine), 3.2(s,4H, CH_2-N-CH_2), 3.85 (s, 3H, OCH_3),7.3, 7.4 (d, 2H, Ar-H) and 7.9, 8.0 (d, 2H, Ar-H .
8	IR: υ = IR: υ = 2200 cm^{-1} (C≡N) . ^{1}HNMR(DMSO-d_6) : δ = 2.7 (s,3H, CH_3, pyrimidine), 3.4 (s, 4H, CH_2-N-CH_2), 3.9 (s, 4H, CH_2-O-CH_2), 4.1 (s, 3H, OCH_3), 7.3, 7.4 (d, 2H, Ar-H) and 7.9, 8.0 (d, 2H, Ar-H .
9	IR: υ = 3400 cm^{-1}(NH), 2200 cm^{-1} (C≡N) and 1700 cm^{-1} (C=O). ^{1}HNMR($CDCl_3$) : δ =1.3-1.5 (t, 3H, CH_3, ester), 2.7 (s, 3H, CH_3, pyrimidine), 4.1 (s, 3H, OCH_3), 4.2- 4.5 (m, 4H, 2CH_2), 6.0 (s,1H, NH), 7.3, 7.4 (d, 2H, Ar-H) and 7.9, 8.0 (d, 2H, Ar-H .
10	IR: υ = 3450, 3350 cm^{-1}(NH_2), 3100 cm^{-1}(NH) and 1680 cm^{-1} (C=O). ^{1}HNMR($CDCl_3$) : δ =1.9-132 (J = 7.0 Hz, t, 3H, CH_3, ester), 2.87 (s,3H, CH_3, pyrimidine), 4.1 (s, 3H, OCH_3), 4.8 (broad signal, 2H, NH_2), 4.25-4.31 (J = 7.0 Hz, q, 2H, CH_2, ester), 7.3, 7.4 (d, 2H, Ar-H) , 7.9, 8.0 (d, 2H, Ar-H and 11.0 (s,1H, NH) .
12	IR: υ = 3250 cm^{-1}(NH) and 1730 cm^{-1} (C=O). ^{1}HNMR(DMSO-d_6) : δ = 2.6 (s, 3H, CH_3, pyrimidine), 4.1 (s, 3H, OCH_3), 4.5, 4.6 (d, 2H, CH_2), 6.5 (broad signal,1H, NH), 7.3, 7.4 (d, 2H, Ar-H) and 7.9, 8.0 (d, 2H, Ar-H .
13	IR: υ = 3400-3200 cm^{-1}(NH, NH, NH_2 , NH_2) and 1650 cm^{-1}(C=O) . ^{1}HNMR(DMSO-d_6) : δ = 2.81(s,3H, CH_3, pyrimidine), 4.44 (s. 2H, NH_2, hydrazide group), 4.1 (s, 3H, OCH_3), 5.82 (s. 2H, NH_2, pyrrole), 7.3, 7.4 (d, 2H, Ar-H) and 7.9, 8.0 (d, 2H, Ar-H , 8.79 (s, 1H, NH) and 11.40 (s. 1H, NH, pyrrole),
14	IR: υ = 3150-3400 cm^{-1}(2NH) and 1680 cm^{-1}(C=O) . ^{1}HNMR(DMSO-d_6) : δ = 3.0 (s, 3H, CH_3, pyrimidine), 4.1 (s, 3H, OCH_3), 7.3, 7.4 (d, 2H, Ar-H), 7.9, 8.0 (d, 2H, Ar-H), 8.11 (s, 1H, CH), 9.83(s, 1H, NH), and 12.92 (s. 1H, NH, pyrrole) .
15	IR: υ = 3100 cm^{-1}(NH) . Mass spectrum showed M^+ and M+2 peaks at m/z = 325 (100%), 327 (32.7%).
16	IR: υ = 3400-3300 cm^{-1}(NH, NH, NH_2 , NH_2). ^{1}HNMR(DMSO-d_6) : δ = 3.0 (s,3H, CH_3, pyrimidine), 3.54 (s,2H, NH_2, hydrazino), 4.1 (s, 3H, OCH_3), 7.3, 7.4 (d, 2H, Ar-H), 7.9, 8.0 (d, 2H, Ar-H), 8.13(s,1H,NH, hydrazino), 8.45(s,1H,CH),10.13 (s,1H, NH, pyrrole) .

17a	IR: υ = 3200-3000 cm^{-1}(2NH). ^{1}HNMR(DMSO-d_6) : δ = 3.0 (s, 3H, CH_3, pyrimidine), 3.9 (s, 3H, OCH_3), 7.01 (s.1H, HN-N=C), 8.18 (s, 1H, HC=N), 7.51-8.55 (m,9H, Ar-H), 8.59 (s,1H, CH, pyrimidine) and 9.84 (s, 1H, NH, pyrrole) .
17b	IR: υ = 3200-3000 cm^{-1}(2NH). ^{1}HNMR(DMSO-d_6) : δ = 3.0 (s, 3H, CH_3, pyrimidine), 3.9 (s, 6H, 2 OCH_3), 7.01 (s.1H, HN-N=C), 8.18 (s, 1H, HC=N), 7.40-8.35 (m,8H, Ar-H), 8.59 (s,1H, CH, pyrimidine) and 9.84 (s, 1H, NH, pyrrole) .
17c	IR: υ = 3200-3000 cm^{-1}(2NH). ^{1}HNMR(CF_3COOD) : δ = 3.0 (s, 3H, CH_3, pyrimidine), 4.1 (s, 3H, OCH_3), 8.3 (s, 1H, HC=N), 7.40-8.4 (m,8H, Ar-H) and 8.6 (s,1H, CH, pyrimidine) .
18	IR: υ = 2950 cm^{-1}(CH aliph.), and 1600 cm^{-1} (C=N). ^{1}HNMR(CF_3COOD) : δ = 2.9 (s,3H, CH_3, pyrimidine), 4.1 (s, 3H, OCH_3), 7.3, 7.4 (d, 2H, Ar-H), 7.9, 8.0 (d, 2H, Ar-H) and 8.6, 9.1(2s,2H,2CH triazole, pyrimidine),.
19	IR: υ = 2950 cm^{-1}(CH aliph.), and 1620 cm^{-1} (C=N). ^{1}HNMR(CF_3COOD) : δ = 2.9 (s,6H, 2CH_3, pyrimidine and triazole), 4.1 (s, 3H, OCH_3), 7.3, 7.4 (d, 2H, Ar-H), 7.9, 8.0 (d, 2H, Ar-H) and 9.2 (s, H, CH, pyrimidine),.

Low ester carbonyl stretching frequencies around 1680 cm^{-1} was found in the IR spectrum as a result of intramolecular. hydrogen bonding with the ortho-amino group [15].

Conclusion :

Synthesis of some heterocyclic compounds related to pyrimidine moiety and confirmation of their structural formulae on the basis of elemental and spectral analyses . The synthesized compounds posses biological activity against some species of bacteria and fungi .

تخليق وتفاعلات بعض مركبات بيرولوبيريميدين.

سليمان محمد موسى

قسم الكيمياء – كلية العلوم – جامعة مصراته

الملخص

أستهدف هذا البحث تحضير بعض المركبات الحلقية غير المتجانسة الجديدة المتضمنة بيرولو[2،3-د]بيريميدينات التي من المتوقع أن يكون لها أهمية بيولوجية وطبية. وقد تضمن هذا البحث ايضاً تفاعل هذه المركبات مع بعض الكواشف لتعطى أنظمه غير متجانسة الحلقة ملتحمة معها.

طريقنا لتحضير المركبات المستهدفة بدء من التحلل المائي للمركب 6- ايثيل ثيو- 4- ميثيل- 2-بارا-فينيل بيريميدين -5- كربونتريل بغليانه في الايثانول المحتوي على هيدروكسيد الصوديوم ليعطي مشتق الملح الصوديومي المقابل والذي تم تحميضه ليعطي مشتق الهيدروكسيل المقابل . كلورة المركب 5-سيانو-4-ميثيل-2-(بارا مبثوكسي فينيل)بيريميدين-6(1يد)ون بواسطة أكسي كلوريد الفوسفور أعطى المشتق 4-

كلوروبيريميدين. تفاعل الملح الصديومي مع أسيتات كلوريد الايثيل أعطى المركب ايثايل(5-سيانو-4-ميثيل-2-(بارا مبثوكسي فينيل)بيريميدين-6-يل اوكسى)اسيتيت (6). معالجة المشتق 4- كلوروبيريميدين بالبيبيريدين و المورفولين أعطى المركبان 4-ميثيل-2-(بارا مبثوكسي فينيل)-6-(بايبيريدين-1-يل)بيريدين-5-كربونتريل و 4-ميثيل-6-(مورفولين-4-يل)-2-(بارا مبثوكسي فينيل)-بيريدين-5-كربونتريل على التوالي .

تفاعل المركب 5-سيانو-6-كلورو-4- ميثيل-2-(بارا مبثوكسي فينيل)بيريميدين مع هيدروكلوريد ايثيل جلايسينات أعطى مشتق الجلايسينات المقابلة الذي خضع لعملية تحولق ليعطي المركب إيثيل 5- أمينو- 4-ميثيل- 2-بارا- فينيل-7يد- بيرولو[2،3- د]بيريميدين-6- كربوكسيلات . وهذا الأخير استخدم في تحضير بعض مشتقات بيرولو[2،3- د]بيريميدينات ، بيريميدينو[4،5/:5،4]بيرولو[2،3- د]بيريميدينات و ترايزولوبيريميدينوبيريميدينات بتفاعله مع كواشف مختلفة . تم دراسة عدد سبعة مركبات ضد أنواع مختلفة من البكتريا والميكروبات .

خلاصة هذا البحث تتمثل في تحضير عدد من المركبات الحلقية الغير متجانسة المنتمية إلي نواة البيرولو[2،3- د]بيريميدين واثبات تركيبها بأطياف الأشعة تحت الحمراء ، الرنين النووي المغناطيسي والتحليل الكمي للعناصر، بالإضافة إلى معرفة تأثير بعضها على أنواع مختلفة من البكتريا والميكروبات .

References:

1. Kristjan, S.G., Zhichen, W., Suzan, M. D., Lance, C. J., Lynn, D. C. and Chistopher, M. (2004) "Phosphoramidate Protides of carboxylic-2,3-Dideoxy-7- Deaza adenosine with potential activity against HIV" **Nucleos.,Nucleot. & Nucleic Acids**, Vol. **23**, pp 1929.

2. Atonino, L., Partizia, D., Paola, B., Alessandra, M., Gaetano, D., Girolamo, C. And Anna, M. A. (2004) "Docking of Indolo and Pyrrolopyrimidines to DNA" **Arkivoc**, Vol **5**, pp 263.

3. Alexanderova, L. A., Lvanov, M. A., Victorova, L. S. and Kukhanova, M. K. (2007) " Furano and pyrrolo[2,3-d]pyrimidine nucleosides : Synthesis and enzymatic activity " **Nucleos.,Nucleot. & Nucleic Acids**, Vol. **26** pp. 1083.

4. Delphine, E., Francoise, E., Bertrand, M., Jean-Marc, L., Patrick,D. and Tean-Emmanvel; K: (2003) "Multitargeted Antifolate and Future Prospects" **Cancer therapy,** Vol**. 1,** pp 315.

5. Nadia, R., Maria, S. and Anna, T. (2008) " Ihibition of protin Kinase c-Src as Therapeutic approach for cancer and bone Metastases" **Anticancer agents in Med.Chem**.Vol. **8** pp. 342 .

6. Helmut, R., Martina, A. and Frank, S. (2007) "Synthesis of dimeric Potential Anti-Gout Drugs " **Molecules,** Vol. **12**, pp. 563.

7. Varaprasad, C., Ramasamy, K., Girardet, J., Gunic, E., Lai, V., Zhony, W. and Hong, Z. (2007) " Synthesis of pyrrolo[2,3-d]pyrimidine nucleoside derivatives" **Bioorg. Chem**. Vol. **35** pp. 25.

8. Makara, G. M., Ewing, W., Ma, Y. and Makara, E. (2001) "Synthesis of Bicyclic Pyrimidine Derivatives as ATP Analogues" **J. Org. Chem**., Vol. **66,** pp.5783.

9. Moosad S. M., Ramadan A. A. and Rania H. A. (2009) " Synthesis of certain

pyrrolo derivatives and antimicrobial agents ″ **Acta Pharm.,** Vol. **59** pp. 145 .

10. Marce4l, K., Sergio, W., Angela, N., Yuxiang, D., Andrew, H., Hugues, M. And Jonathan, L. V. (2007) "Peroxide Bond-Dependent Anti-plasmodic Specificity of Artemisinin ″ **Antimicrobial Agent and Chemotherapy,** Vol. **51**, pp. 2991.

11. Myung-Ho, J. and Chang-Hyun, O. (2008) ″ Synthesis and antiproliferactive activityof pyrrolo[2,3-d]pyrimidine derivativesfor melanoma cell ″ **Bull. Korean Chem. Soc**. Vol. **29** pp. 2231.

12. Abdel Moneam, M. I., Geies, A. A. El-Naggar, G. M. and Mussa, S. M. (2003) "Synthesis and Reactions of Some New Thienopyrimidines″ **Phosphorus, Sulfur and Silicon**, Vol, **178** pp. 737.

13. Abdel Moneam, M. I., Geies, A. A. El-Naggar, G. M. and Mussa, S. M. (2004) "Synthesis of New Furo[2,3-d]pyrimidines and Pyrimido[4\,5\:4,5]furo[2,3-d]pyrimidines″ **J. Chin. Chem. Soc**., Vol, **51**, pp.1357.

14. Mussa S. M. (2007) "Synthesis of Some New Fused Pyrimidothienopyrimidines Derivatives″ **Al-Satil,** Vol. **1**, pp 53.

15. Cuodrado, F. J., Perez, M. A. and Soto, J. L. (1984), **J. Chem. Soc. (Perkin Tarans.),** Vol.**1,** pp.2247 .