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Synthesis of some New Pyrimidine Compounds Derived from *biginelli reaction* and Study their Biological activity

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Abstract:

Biginelli reaction of malononitrile, thiourea and the appropriate aromatic aldehyde was used to produce ethyl 4-aryl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates (M1-5) that reacted with 1,3-Dibromopropane. All the new compounds have been characterized using infrared spectroscopy (IR), Proton nuclear magnetic resonance (H1-NMR) and Carbon-13 nuclear magnetic resonance (C13NMR) data and physical methods. The antibacterial activity has been tested in vitro by the disk diffusion assay method against two kinds of bacteria gram positive and gram negative. The minimum inhibitory concentration [MIC] have been determined with the reference of stander drugs, the results showed that the hydroquinone derivatives are better than growth of both types of bacteria (gram-positive and germ-negative compared to drug.

Key words: *biginelli reaction, malononitrile , thioura, and aldehyde* .

تخليق بعض مركبات بيريميدين الجديدة المشتقة من تفاعل البيجينيلي ودراسة نشاطها البيولوجي

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الخلاصة:

تم استخدام تفاعل Biginelli من malononitrile و thiourea والألدهيد العطري المناسب لإنتاج ethyl 4-aryl-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylates (M1-5) الذي تفاعل مع 1، 3-ديبروموبروبان. تم توصيف جميع المركبات الجديدة باستخدام التحليل الطيفي بالأشعة تحت الحمراء(IR), الرنين المغناطيسي النووي البروتون (H^1-NMR) والرنين المغناطيسي النووي للكربون -13 (C^{13}NMR) والطرق الفيزيائية. تم اختبار النشاط المضاد للبكتيريا في المختبر بواسطة طريقة اختبار الانتشار القرصي ضد نوعين من البكتيريا موجبة الجرام والجرام. تم تحديد الحد الأدنى للتركيز المثبط MIC بالإشارة إلى الأدوية المعيارية ، وأظهرت النتائج أن مشتقات الهيدروكينون أفضل من نمو كلا النوعين من البكتيريا (موجبة الجرام وسالبة الجرثومية مقارنة بالدواء.

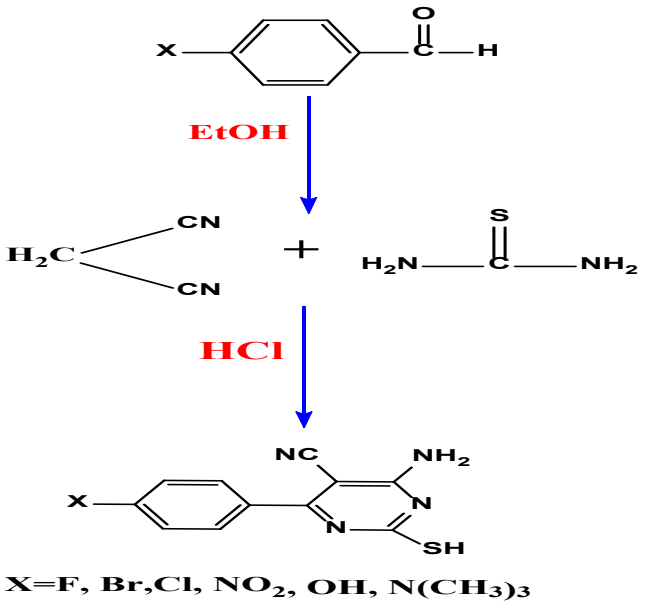
الكلمات المفتاحية: تفاعل البيجينيللي ، مالونونتريل أثايويوربا ، وألدهيد.

Introduction:

Pyrimidine is a heterocyclic aromatic organic compound similar to benzene and pyridine, containing two nitrogen atoms at positions 1 and 3 of the six-member ring. It is isomeric with two other forms of diazine.[1] According to the literature, pyrimidine derivatives exhibit various pharmacological activities as antibacterial,[2] antifungal,[3] antiviral,[4,5] anticancer,[6,7] analgesic and anti-inflammatory drugs.[8] In addition,thienopyrimidine derivatives show many biological activities, such as anticancer,[9] antiviral,[10] antitumor,[11] anti-inflammatory,[12] antimicrobial,[13] and antimalarial,.[14] Despite the high toxicity of many selenium compounds, they show antiviral, anti-microbial, anti-tumor[15,16] and anticancer activity. Organoselenium compounds have been tested as agents against bacteria, viruses, fungi, parasites, as antihistamines, as well as anti-cancer drugs.

2. Experimental:

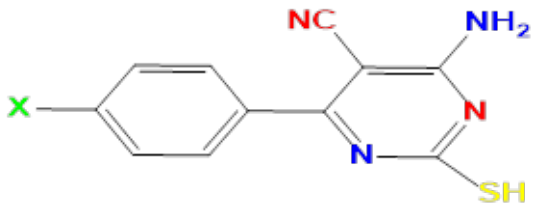
All the chemicals and the solvents used were of Aldrich and Fluka products and were used without further purification. Melting points are uncorrected and were recorded in an open capillary tube on Stuart melting point apparatus. Infrared spectra have been recorded on a Shimadzo FTIR-8100 spectrophotometer using KBr discs-and ^{1}H NMR Spectra have been measured on a MH_Z spectrometer using (DMSO-d_6) as solvent. reaction monitoring and verification of the purity of the compounds was done by TLC on silica gel-percolated alumni sheets (type 60 F254 Merck, Darmstadt, Germany).



X=F, Br,Cl, NO_2, OH, $N(CH_3)_3$

Synthesis of pyrimidine [18] (M_1-M_7)

Mix 0.006 mole of malononitrile, in (10ml) of ethanol mixed 0.006 mole of thiourea, then (3-4) drops from HCl was added to the mixture, the reaction was in the manner of escalation for 6 hours, deposits were obtained in different colors and proportions, filtered, dried, purified and measured their melting degree and percentage percentage. The physical properties are shown in table (1) .



X=F, Br,Cl, NO_2, OH, $N(CH_3)_3$, and trans cinnmaldyhede

Evaluation of biological activity:

The antimicrobial activities of the synthesized compounds were determined in vitro against several pathogenic representative microorganism (Staph and Bacillus pumilus), using Agar well-diffusion method [14], holes were prepared for each dish using a Cork Porer and a diameter of (5) mm per hole (0.1) ml of the prepared solutions of the fourth hole using (DMSO) as a control, sample and incubated the dishes for (24) hours at 37 . The inhibition zone diameters around each holes has been measured in milmeter, depending on the method of Prescott

3. Result and Discussion:

A- Characterization of pyrimidine (M_2):

The structure of compounds (M_1-M_7) are confirmed by (IR) spectrum showing band at (1573-1580)cm^{-1} ,belonging to the C=N group and band at (1413-1423 cm^{-1}) belong to the (CH=CH) group, Significant bands in the region (3035- 3045) cm^{-1} attributed to the stretching vibration of the v (Ar-H), which belongs to the aromatic (Ar-H) stretch[1] , HNMR chemical shifts for compound M1 shows that the resonances at (7.94-7.49) ppm due to singlet of HC=CH group of aromatic ring, δ=7.42 ppm can be ascribed to the presence of NH_2 group, and the signal shown at (ppm 4.46) belongs to the (CH) for aromatic ring.

B-Evaluation of Biological activity:

Some of the synthesized compounds (M_1-M_7) were tested against various strains of bacteria: gram positive bacteria, staphylococcus, aureus, and gram native bacteria, Escherichia, coli by cup plate agar diffusion method. The microbial cultures were incubated at (37 C° for 8 hur.) and diluted with 0.8% sterile saline. The concentration of solution for used drugs in DMSO, were kept at 100µg/mL. Ampicillin as standard, streptomycin as a

reference drug, and DMSO. as a negative control were used. The biological activity was measured by measuring the inhibition diameter of growth of bacteria around the disk in use.

Table (1): Physical properties and elemental analysis of prepared compounds (M_1-M_7)

Comp No.	X	Molecular formula	MP (°C)	Yield %	Powder Color
M_1	4-F	$C_{11}H_7FN_4S$	142-144	82	Dark Yellow
M_2	4-Cl	$C_{11}H_7ClN_4S$	161-163	78	Light Yellow
M_3	4-NO_2	$C_{11}H_7N_5O_2S$	156-158	81	Dark Yellow
M_4	4-Br	$C_{11}H_7BrN_4S$	125-127	72	Dark Red
M_5	4-OH	$C_{12}H_{10}N_4O_2S$	119-121	79	Yellow
M_6	4-$N(CH_3)_2$	$C_{13}H_{13}N_5S$	182-184	86	Light Red
M_7	Trans- cinnma	$C_{13}H_{10}N_4S$	152-154	74	Yellow

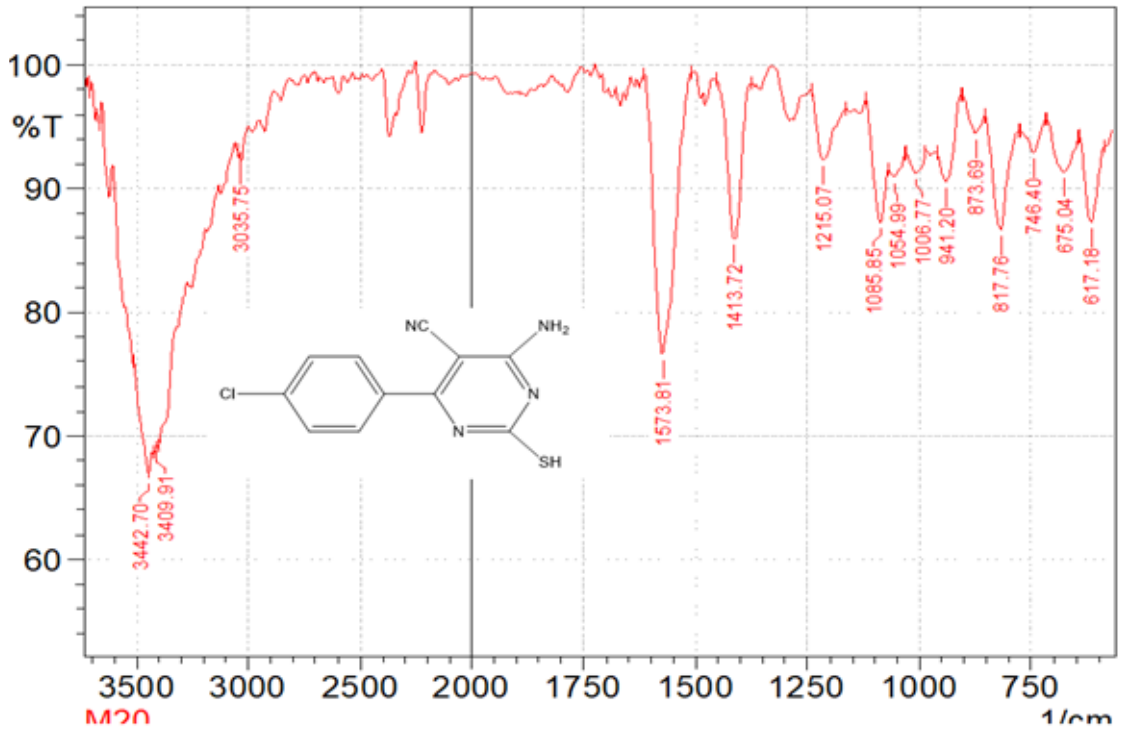
Table (2): IR spectra of compounds (M1-M7)

IR(KBr) cm^{-1}					
Comp. No	**X**	**ν Ar (C-H) cm^{-1}**	**ν C=N cm^{-1}**	**ν (C=C) Ar cm^{-1}**	**Others cm^{-1}**
M_1	**F**	**3015**	**1598**	**15231483-**	**F 1270**
M_2	**Cl**	**3035**	**1573**	**1413-1540**	**746 ν C-Cl**
M_3	**NO_2**	**3041**	**1596**	**1585 1487 -**	**1310 v NO2**
M_4	**Br**	**3060**	**1602**	**1440 1541 -**	**2553 v SH**
M_5	**-OCH_3**	**3078**	**1662**	**1541 1508 -**	**CH_3 2935**
M_6	**$N(CH_3)_2$**	**3043**	**1664**	**15251587-**	**3391 v NH2**
M_7	**H**	**3041**	**1591**	**1585 1487 -**	**2547 v SH**

Table (3): Antibacterial activity of the prepared compounds [M_1-M_7] and control antibiotic

Comp. No.	Staph			Bacillus pumilus. mg/ml		
	0.01	**0.001**	**0.0001**	**0.01**	**0.001**	**0.0001**
M_1	21	25	15	23	18	28
M_2	23	27	31	21	24	22
M_3	17	24	19	15	27	24
M_4	26	22	30	21	19	25
M_5	21	30	23	17	21	27
M_6	20	32	18	21	24	16
M_7	16	23	29	17	30	26
Ciprofloxa-cin	2	3	3	2	2	4
Blank disk	0	0	0	0	0	0

Slight activity 15-18 mm, moderate activity 18-20 mm and high activity 21-25 mm; MIC: minimum inhibition concentration (µ g / mL).



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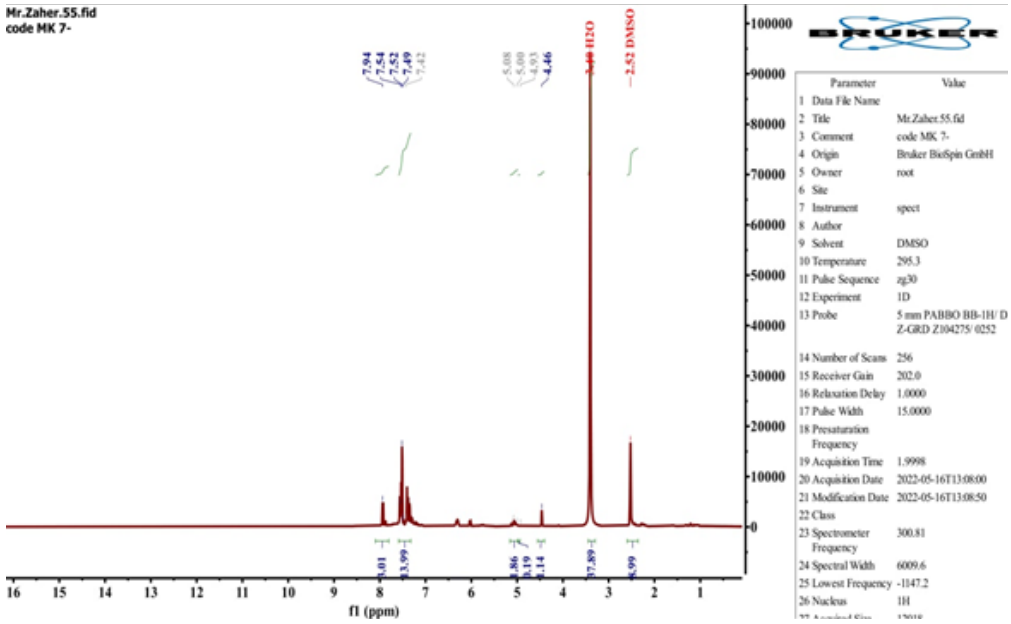

Fig. (2): (^{1}H-NMR) for (M_2)

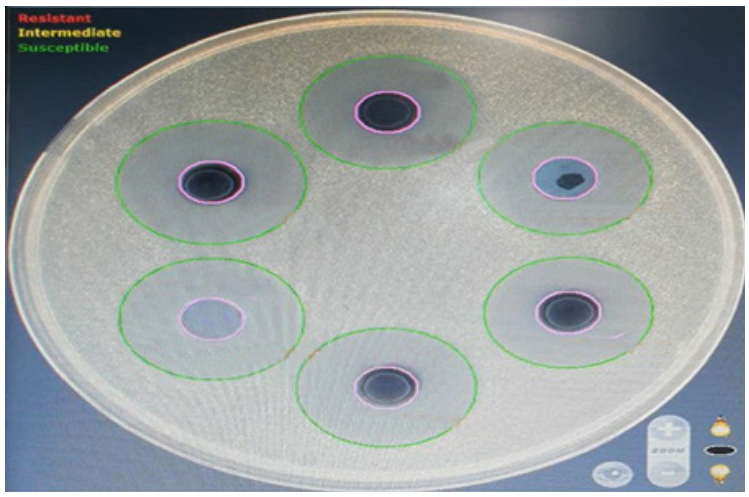

Figure (3) Compound (M_1) inhibits growth of bacteria Staph

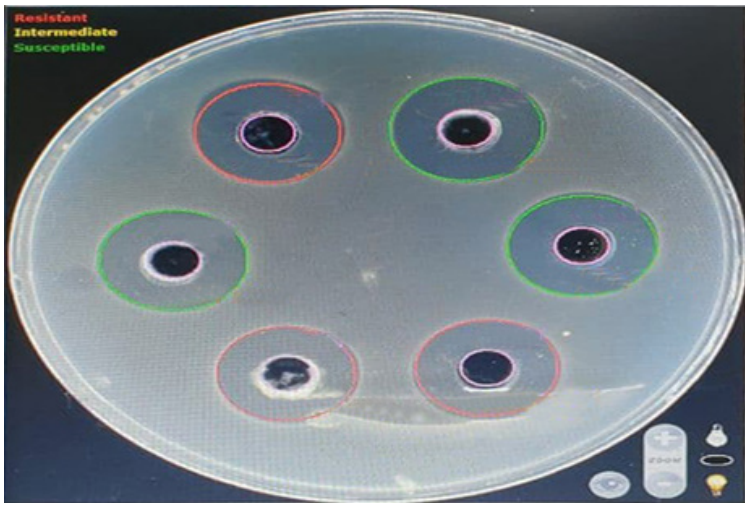

Figure (4): Compound (M_1) inhibits growth of bacteria bacteria Bacillus pumilus

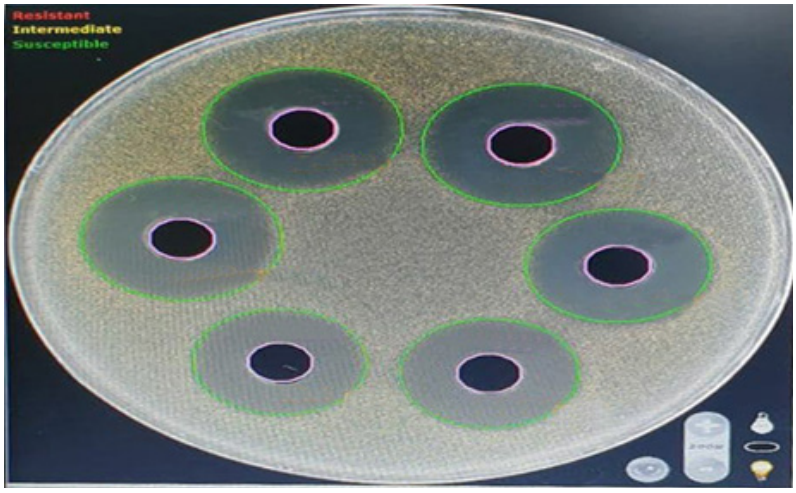

Figure (5) Compound (M6) inhibits growth of bacteria Staph

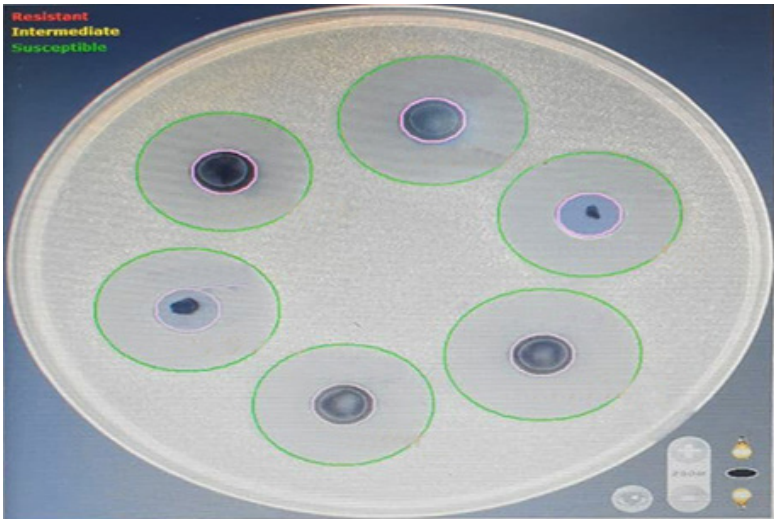

Figure (6): Compound (M6) inhibits growth of bacteria Bacillus

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