Synthesis and Characterization of Some Pyrimidine Derivatives from Dimethyl Malonate and Evaluation their Biological Activity

Sajed Khalil Mahmood* and Malath Khalaf Rasheed

Department of Chemistry – College of Education – University of Samarra

*sajid.dore3@gmail.com

Received: 21 October 2018 Accepted: 19 February 2019

Abstract

In this research of some new pyrimidine derivatives were synthesized by reaction of dimethyl malonate with different aldehydes (Cinnamaldehyde, Vanilline, Naphthaldehyde or Furfural) and urea, Thiourea or Thiosemicarbazide in three-component Biginelli reaction with good yield and signed as (A1-A10). These compounds were synthesized via microwave irradiation by using modified domestic microwave oven. Some of the newly synthesized compounds exhibited antibacterial and antifungal activity. The structure of the synthesized compounds were confirmed by physical and spectra $^{13}C/^{1}H$-NMR and FTIR.

Keywords: Pyrimidine, Diethyl malonate, Biginelli reactions, modified domestic microwave oven.

Synthesis and Characterization of Some Pyrimidine Derivatives from Dimethyl Malonate and Evaluation their Biological Activity

Sajed Khalil Mahmood and Malath Khalaf Rasheed

تحضير وتشخيص بعض مشتقات البيرميدين المشتقة من ثنائي مثيل مالونيت وتقييم فعاليتها الحيوية

ساجد خليل محمود و ملاذ خلف رشيد

قسم الكيمياء – كلية التربية – جامعة سامراء

الخلاصة

البحث تضـــمن تحضـــير بعض من المشـــتقات الجديدة للبيرميدين من تفاعل ثنائي مثيل مالونيت مع الألديهايدات المختلفة (الفانلين، أو السينملديهايد، أو فورفورال، أو نفثلديهايد) واليوريا، أو الثايويوريا، أو الثايوسميكاربازايد بتفاعل بجنيلي ثلاثي المكونات وبنسب منتوج جيدة (A1-A10) حضرت المركبات تحت التشعيع بالأمواج الدقيقة وباستخدام فرن المايكروويف المنزلي المحور، وأظهرت بعض المركبات المحضـــرة فعالية ضـــد البكتريا وضـــد الفطريات كما شـــخصـــت المركبات المحضرة بواسطة البيانات الفيزيائية والطيفية $^{13}C/^{1}H$-NMR and FT-IR.

الكلمات المفتاحية: بيرميدين، ثنائي مثيل مالونيت، تفاعلات بجنيلي، فرن المايكروويف المنزلي المحور.

Introduction

Pyrimidines are 6-membered heterocyclic ring compounds composed of nitrogen and carbon. They are present throughout nature in various forms and are the building blocks of numerous natural compounds from antibiotics to vitamins and liposaccharides. The most commonly recognized pyrimidines are the bases of RNA and DNA, the most abundant being cytosine, thymine or uracil. The origin of the term pyrimidine dates back to 1884 when Pinner coined the term from a combination of the word's pyridine and amidine because of the structural similarity to those compounds [1].

Pyrimidine and their derivatives as an integral part of nucleic acid DNA and RNA in it, play an important role in several biological processes [2] Pyrimidine substituted at 4,5-position is commonly found in biologically active and naturally occurring compounds such as voriconazole and avitriptan [3]. A literature survey shows that pyrimidine derivatives possess a broad spectrum of biological activities, such as antifungal, [4-6] anticancer, [7] antimicrobial, [8, 9] and antiviral [10].

Antiviral and antimicrobial agents are among the most commonly prescribed pharmaceuticals worldwide. Efforts to improve the therapeutic significance of these agents have resulted in identification of more potent compounds [11, 12]. They show dihydrofolate reductase inhibition and antitumor [13, 14] as well as diuretic properties [15]. In the last two decades, Biginelli 3,4-dihydropyrimidin-2(1H) one (DHPM) scaffolds have received considerable attention due to a wide range of pharmaceutical properties such as antibacterial, antitumor, anti-inflammatory, calcium channel blockers, antihypertensive agents, antagonists, and neuropeptide antagonists [16]. In addition, several marine alkaloids containing the dihydropyrimidinone-5-carboxylate motifs also showed interesting biological properties [17] also called Biginelli compounds are important synthetic targets in organic and medicinal.

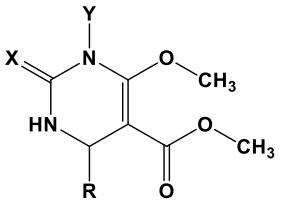
Experimental part

1. Instrumentation and chemicals

All the chemical was purchased from CDH and Aldrich. The melting point was recorded by Digital Advanced electro thermal SMP30. IR spectra were recorded via Infrared spectrophotometer model Shimadzu (FTIR-8400S) by using KBr disc. Proton-NMR spectra were recorded on nucleic magnetic resonance model (600MHz, Jeol ECA), using TMS as internal reference and DMSO-d6 as solvent.

2. Synthesis the compounds (A_1-A_{10}) from the dimethyl malonate

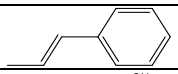
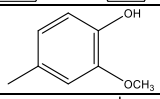
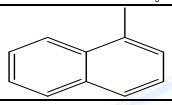
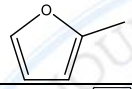
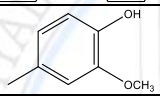
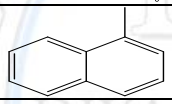
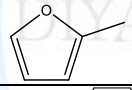
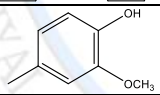
A mixture of dimethyl malonate (0.005 mol, 0.57 ml), with different aldehydes compounds Cinnamaldehyde, Vanilline, Naphthaldehyde or Furfural (0.005 mol) and Urea, Thiourea or Thiosemicarbazide (0.005 mol) was dissolved in ethanol absolute (10 ml) and refluxed with catalytic hydrochloride (2 drops) in a modified domestic microwave oven for 4-10 minutes (425 Watt). It was filtrated and recrystallized in ethanol to give compounds (A1-A10), table 1.



Synthesis and Characterization of Some Pyrimidine Derivatives from Dimethyl Malonate and Evaluation their Biological Activity

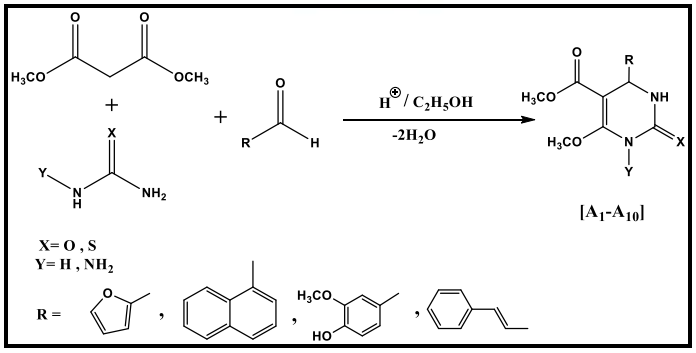
Sajed Khalil Mahmood and Malath Khalaf Rasheed

Table 1: physical properties data of prepared compounds (A_1-A_{10})

Comp. No	X	Y	R	Molecular Formula	Color	M.P(°C)	Yield %
A_1	O	H		$C_{15}H_{16}N_2O_4$	White	202-204	73
A_2	O	H		$C_{14}H_{16}N_2O_6$	White	122-124	81
A_3	O	H		$C_{17}H_{16}N_2O_4$	Light Brown	199-201	80
A_4	O	H		$C_{11}H_{12}N_2O_5$	Dark Brown	166-168	86
A_5	S	H		$C_{15}H_{16}N_2O_3S$	Dark Brown	187-189	77
A_6	S	H		$C_{14}H_{16}N_2O_5S$	Dark Yellow	Oily	72
A_7	S	H		$C_{17}H_{16}N_2O_3S$	Yellow	205-207	85
A_8	S	H		$C_{11}H_{12}N_2O_4S$	Dark Brown	Oily	89
A_9	S	NH_2		$C_{15}H_{17}N_3O_3S$	Yellow	119-121	83
A_{10}	S	NH_2		$C_{14}H_{17}N_3O_5S$	Light Yellow	149-151	85

Results and discussion

The pyrimidine derivatives were synthesized by biginelli method, as shown in scheme A



Scheme A: Synthesis of compounds (A_1-A_{10})

The FTIR spectra of compounds (A_2, A_6, A_{10}) showed absorption at the range (3447-3525) cm^{-1} for (OH), the (NH_2) absorption (3527,3436) cm^{-1} for asymmetrical and symmetrical stretching in compounds (A_9, A_{10}). The compounds (A_1-A_{10}) showed absorption at (3382,3155) cm^{-1} for (NH) and (CH) aromatic at the range (3016-3085) cm^{-1} and (CH) aliphatic at range (2991-2844) cm^{-1}, strong stretching absorption at about (1733-1653) cm^{-1} for (C=O) ester and amidine. All of these are presented in the table 2 and figures (1, 2 and 3).

Table 2: (FT-IR) data of compounds (A_1-A_{10})

Comp. No.	Characteristic bands of FT-IR Spectra (cm^{-1})						
	O-H	NH_2 asy sy	N-H	C-H Ar.	C-H Al.	C=O ester C=O amidine	C=C Ar.
A_1	-	-	3230	3085	2974 2939	1733 1691	1523
A_2	3471	-	3321	3024	2972 2844	1708 1674	1583
A_3	-	-	3294	3049	2974	1722 1664	1600
A_4	-	-	3336	3029	2902	1733 1658	1610
A_5	-	-	3280	3022	2991	1701 -	1569
A_6	3447	-	3287	3018	2983	1653 -	1552
A_7	-	-	3382	3016	2948	1681 -	1535
A_8	-	-	3345	3031	2912	1715 -	1589
A_9	-	3527 3436	3278	3035	2995	1703 -	1591
A_{10}	3525	3443 3276	3155	3031	2974	1689 -	1591

Synthesis and Characterization of Some Pyrimidine Derivatives from Dimethyl Malonate and Evaluation their Biological Activity

Sajed Khalil Mahmood and Malath Khalaf Rasheed

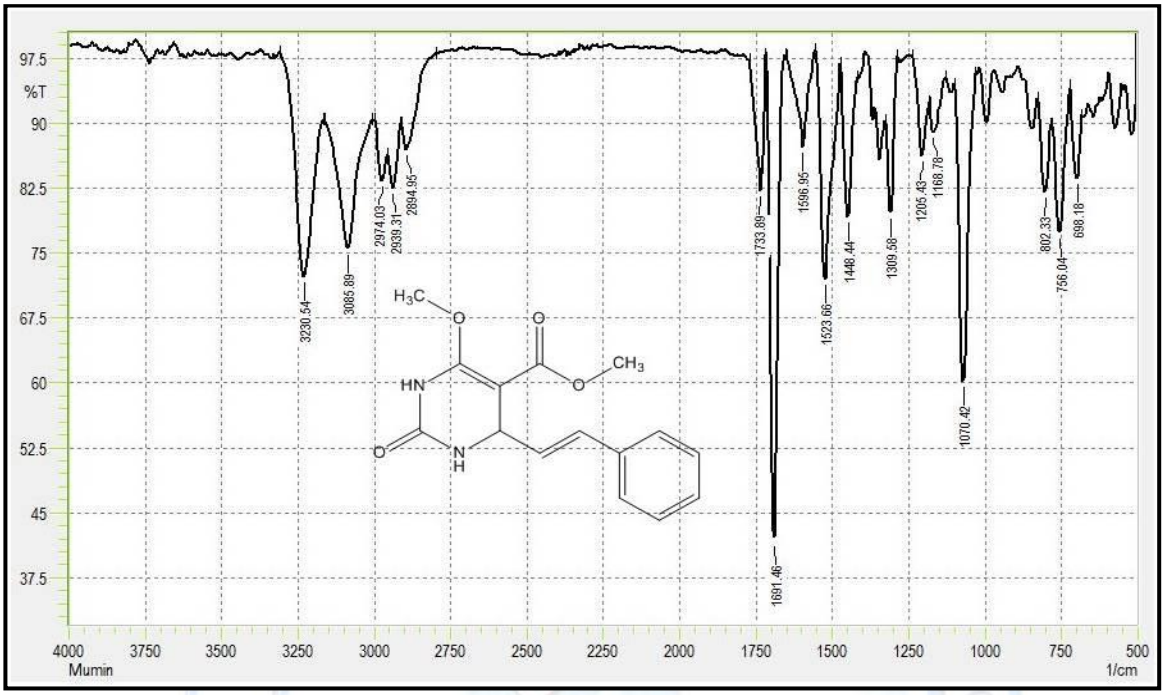


Figure 1: FT-IR spectrum for compound (A_1)

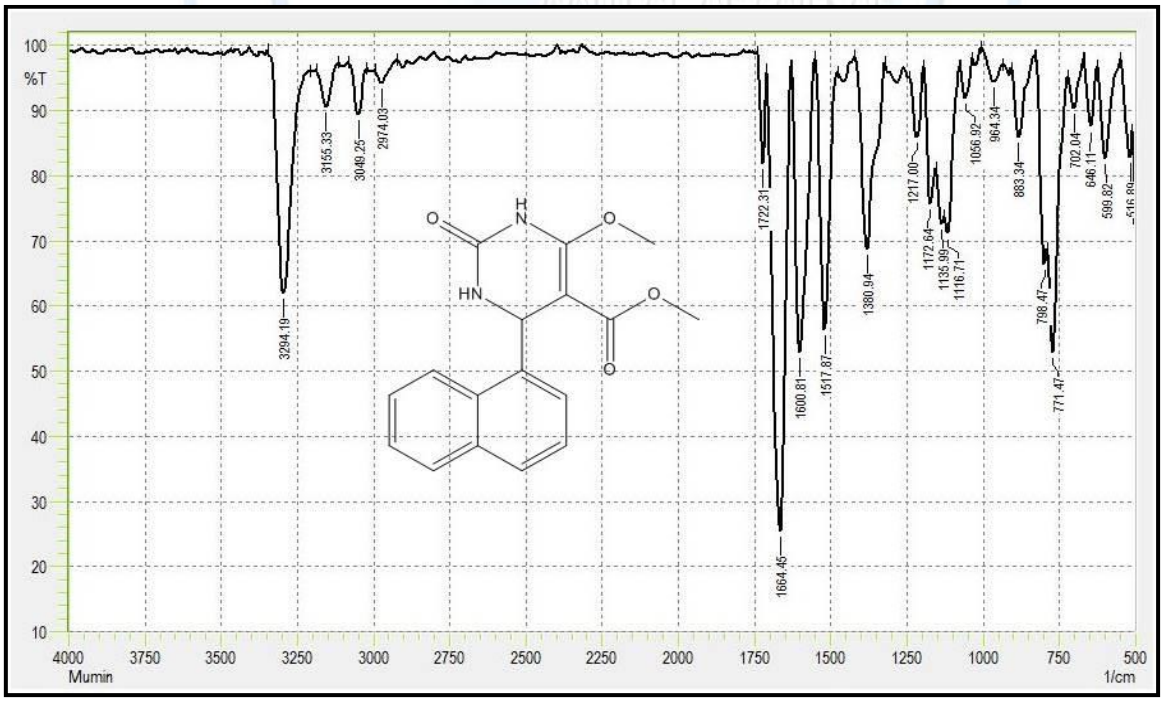


Figure 2: FT-IR spectrum for compound (A_7)

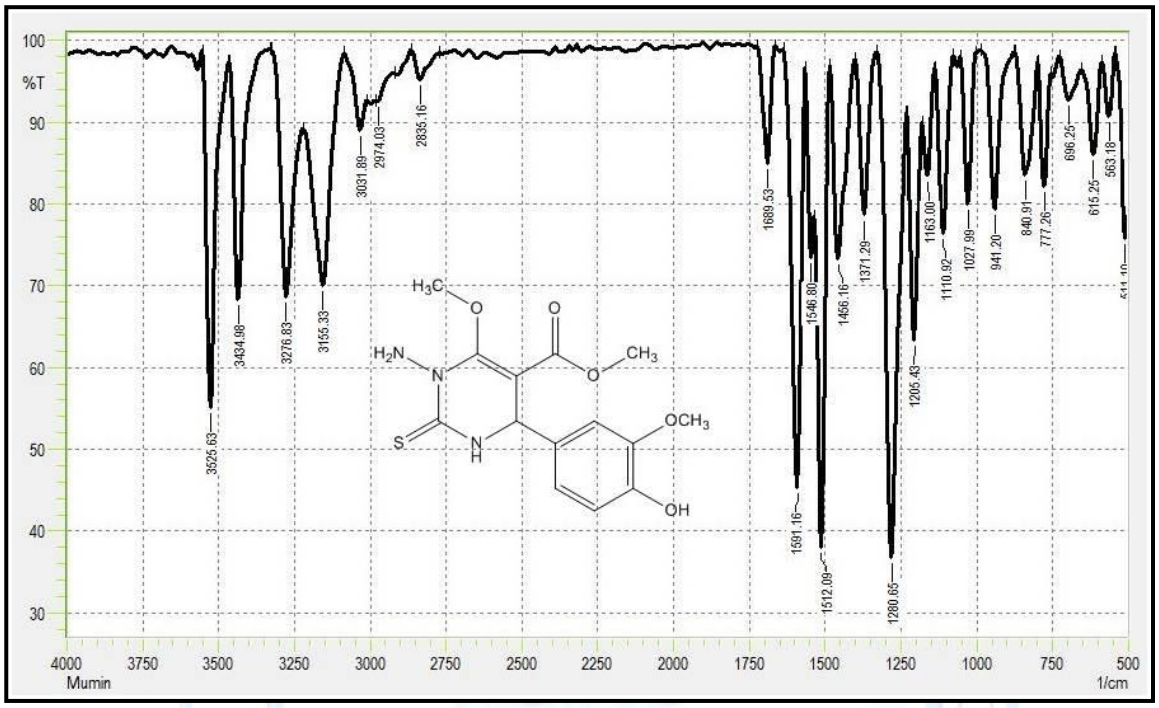


Figure 3: FT-IR spectrum for compound (A_{10})

The ^{1}H.NMR Spectrum of compound (A_7) showed signal at (10.37 δ) back to (NH) labeled (1), single sign at (9.12 δ) back to (NH) labeled (2) and showed sign of multi-at (8.26-6.97 δ) back to 7 protons aromatic, single sign (3.60 δ) back to (CH) labeled (3), single sign (3.33) back to (CH_3) group labeled (4) and single sign (2.94 δ) back to (CH_3) group labeled (5), the sign at (2.46 δ) back to (DMSO) protons figure 4.

The ^{1}H.NMR Spectrum of compound (A_{10}) showed single sign (11.22 δ) back to (OH) labeled (1), single sign (9.41 δ) back to (NH) labeled (2) and multi-sign at (7.36-6.74 δ) back to 3 protons of aromatic, single sign (5.00 δ) back to (NH_2) labeled (3), single sign (4.75 δ) back to (CH) labeled (4), two signs at (4.31 δ) and (3.78 δ) back to (CH_3) group labeled (5), (6) respectively, and single sign (3.32 δ) back to (CH_3) group labeled (7), the sign at (2.46 δ) back to (DMSO) protons figure 5.

Synthesis and Characterization of Some Pyrimidine Derivatives from Dimethyl Malonate and Evaluation their Biological Activity

Sajed Khalil Mahmood and Malath Khalaf Rasheed

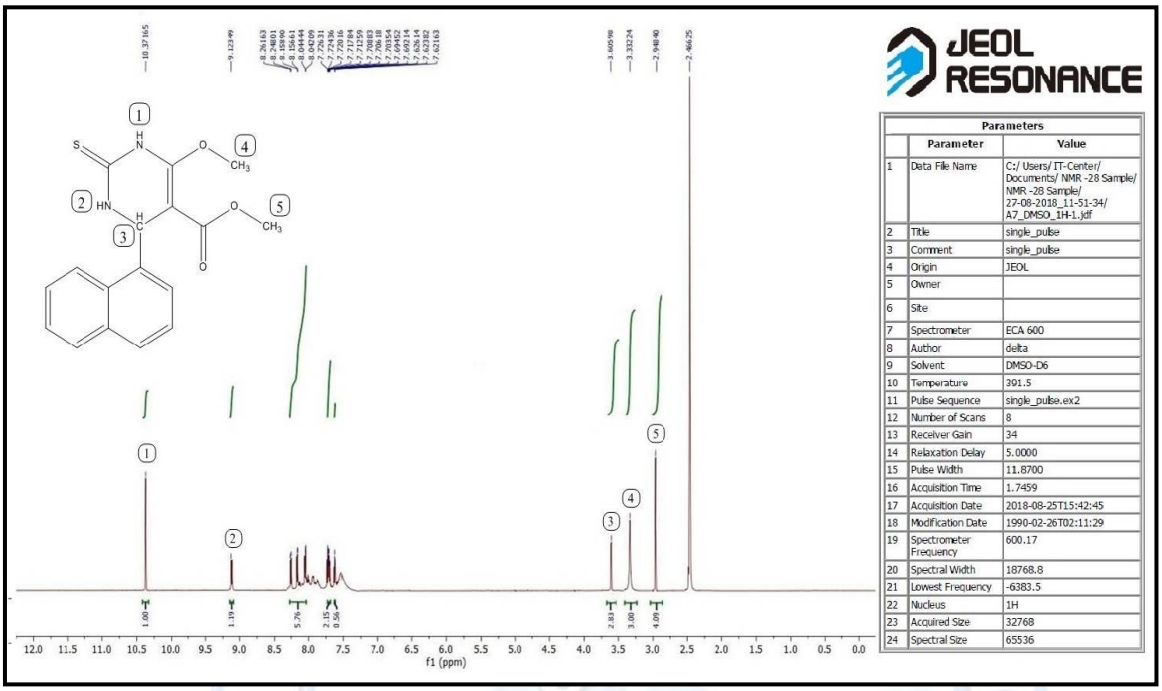


Figure 4: ^{1}H.NMR spectrum for compound (A_7)

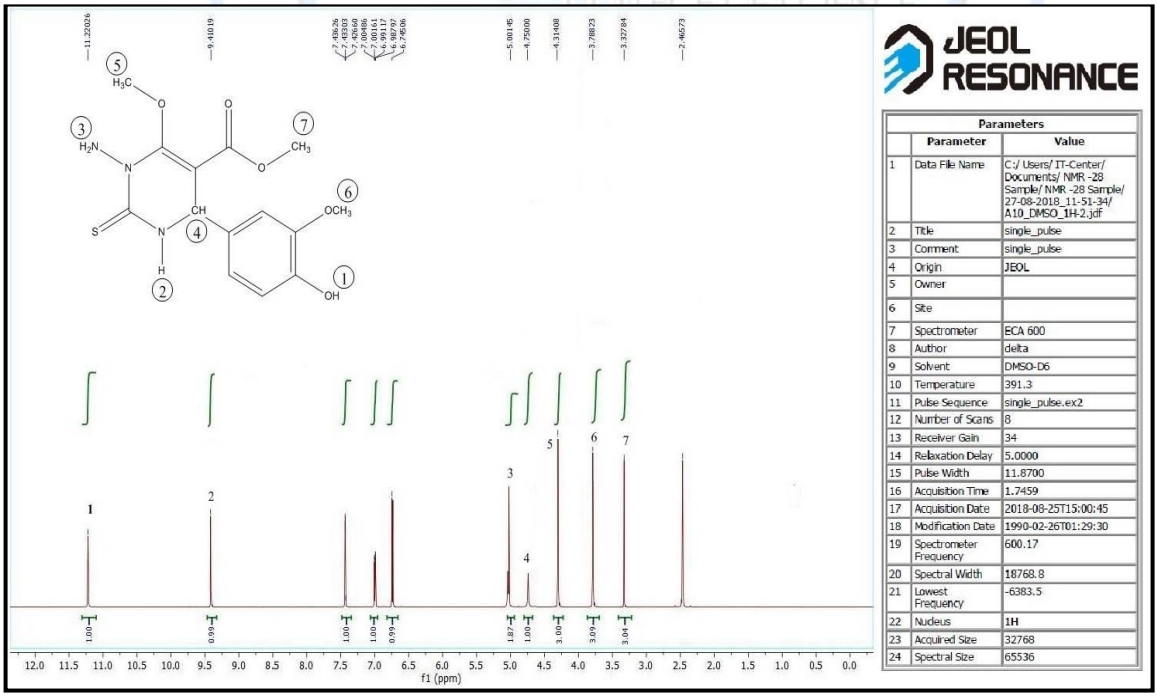
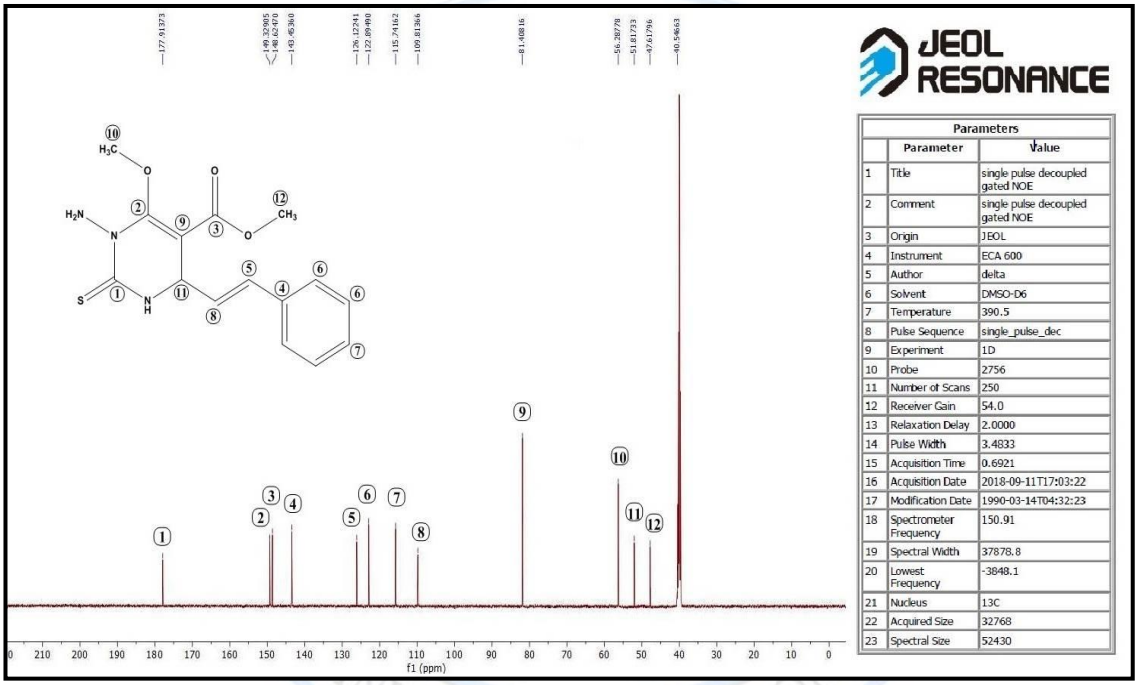


Figure 5: ^{1}H.NMR spectrum for compound (A_{10})

The ^{13}C.NMR spectrum for compound (A_{10}), figure 6 showed chemical shift at (177.91 δ) back to carbonyl (C=O) labeled (1), (149.32 δ) back to carbon atom labeled (2), (148.62 δ) back to carbonyl (C=O) ester labeled (3), (143.45 δ), (126.12 δ) back to carbon atom labeled (4, 5), and two signal (122.89 δ ,115.74 δ) back to carbon atom benzene labeled (6,7), (109.81 δ), (81.40 δ), (56.28 δ), (51.81 δ), (47.61 δ) back to other carbon atoms labeled (8,9,10,11,12). And showed chemical shift at (40.54 δ) back to (DMSO) carbon.



Parameters		
	Parameter	Value
1	Title	single pulse decoupled gated NOE
2	Comment	single pulse decoupled gated NOE
3	Origin	JEOL
4	Instrument	ECA 600
5	Author	delta
6	Solvent	DMSO-D6
7	Temperature	390.5
8	Pulse Sequence	single_pulse_dec
9	Experiment	1D
10	Probe	2756
11	Number of Scans	250
12	Receiver Gain	54.0
13	Relaxation Delay	2.0000
14	Pulse Width	3.4833
15	Acquisition Time	0.6921
16	Acquisition Date	2018-09-11T17:03:22
17	Modification Date	1990-03-14T04:32:23
18	Spectrometer Frequency	150.91
19	Spectral Width	37878.8
20	Lowest Frequency	-3848.1
21	Nucleus	13C
22	Acquired Size	32768
23	Spectral Size	52430

Figure 6: ^{13}C.NMR spectrum for compound (A_{10})

Biological activity

The biological activity of some prepared compounds (A_1, A_3, A_9, A_{10}) were evaluated against bacteria (*Escherichia coli* and *Staphylococcus aureus*) and against fungus (*Candida fungus*) figures (7, 8 and 9). The results showed that these compounds (A_1, A_3, A_9, A_{10}) have higher activity against *Escherichia coli* compounds with standard control (Neomycin sulfate). Compound A_1 showed higher activity against *Staphylococcus aureus* compared with standard control (Neomycin sulfate) at concentration 10 mg/ml Fig G, H. Compound A_9 was tested against *Candida fungus* showed a good activity in comparison with standard control (Nystatin) at concentration 10 mg/ml fig I.

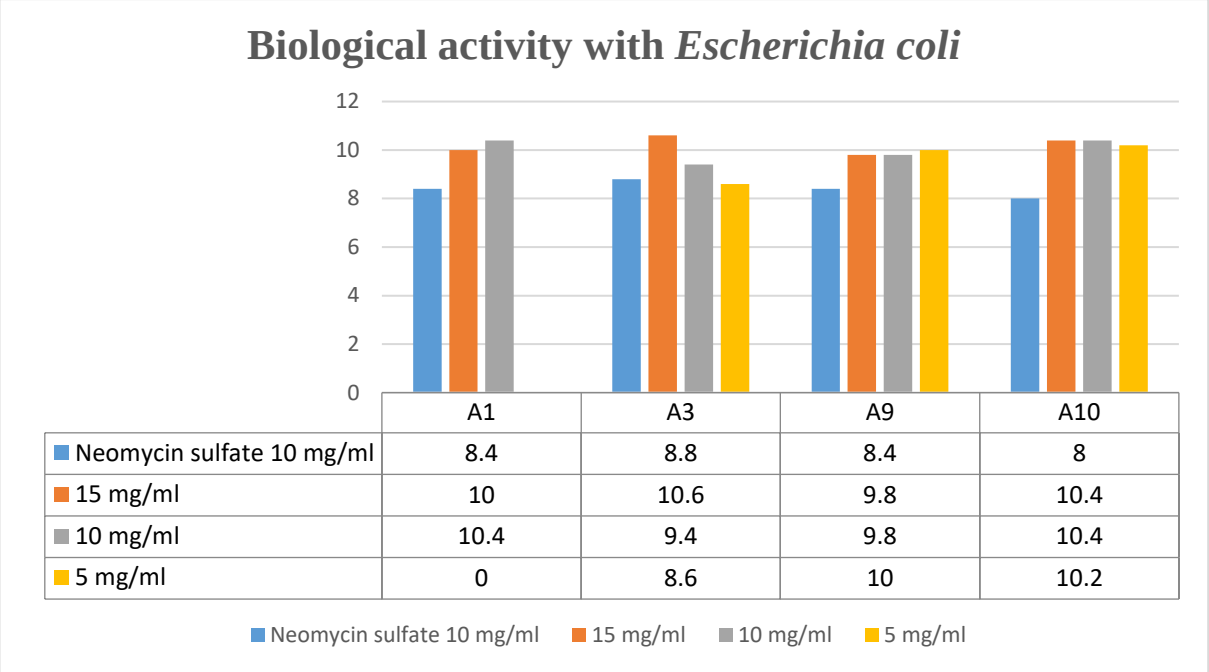


Figure 7: Biological activity with *Escherichia coli*

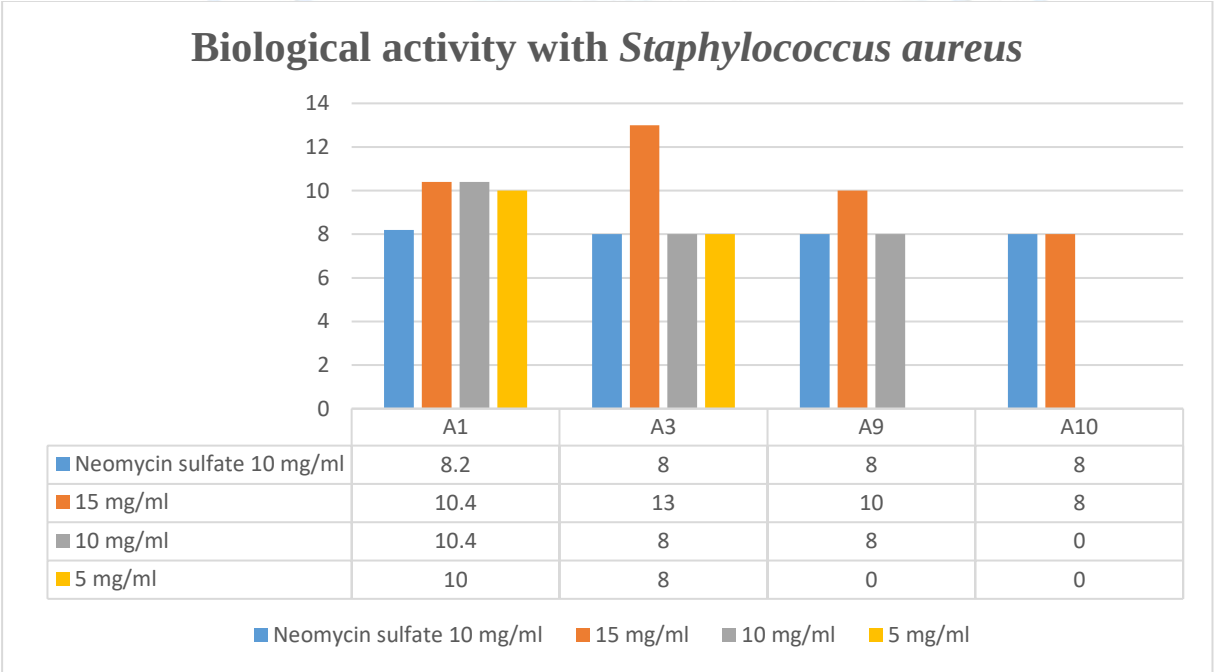
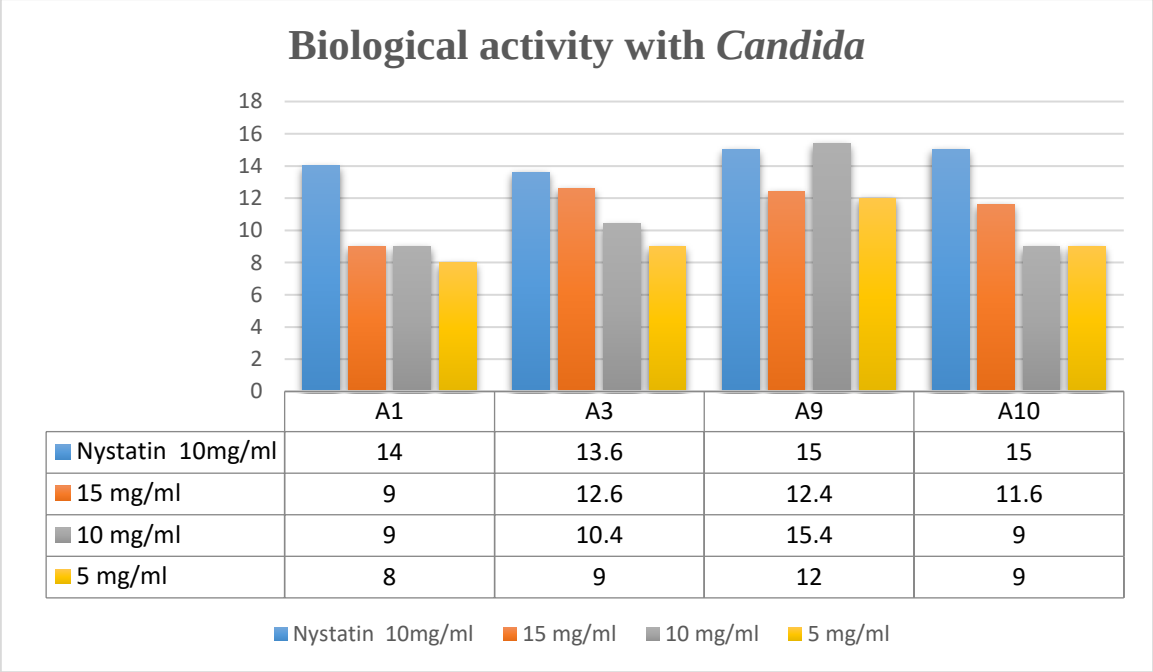


Figure 8: Biological activity with *Staphylococcus aureus*



	A1	A3	A9	A10
Nystatin 10mg/ml	14	13.6	15	15
15 mg/ml	9	12.6	12.4	11.6
10 mg/ml	9	10.4	15.4	9
5 mg/ml	8	9	12	9

Figure 9: Biological activity with *candida albicans*

Conclusions

I have seen possible synthesis pyrimidines derivatives by biginelli method from dimethyl malonate and the reaction time can be shortened by using modified domestic microwave oven. It can be concluded that the dihydropyrimidines compounds series has good biological activity against the bacteria (Escherichia coli and Staphylococcus aureus) and fungus (candida albicans).

References

1. Krakow, G.; Vennesland, B. Journal of Biological Chemistry 1961, 236(1),142-144.
2. Neumann, D. M.; Cammarata, A.; Backes, G.; Palmer, G. E.; Jursic, B. S. *Bioorganic & medicinal chemistry* 2014, *22*(2), 813-826.
3. Wang, B. L.; Shi, Y. X.; Zhang, S. J.; Ma, Y.; Wang, H. X.; Zhang, L. Y.; Wei, W.; Liu, X. H.; Li, Y. H.; Li, Z. M.; Li, B. J. *European journal of medicinal chemistry* 2016, *117*, 167-178.

4. Wang, S. C.; Gao, J. G.; Zhang, S.; Liu, S.; Jiang, L. *Phosphorus, Sulfur, and Silicon and the Related Elements* 2018, *193*(4), 245-248.

5. Tănase, C. I.; Drăghici, C.; Cojocaru, A.; Galochkina, A. V.; Orshanskaya, J. R.; Zarubaev, V. V.; Shova, S.; Enache, C.; Maganu, M. *Bioorganic & medicinal chemistry* 2015, *23*(19),6346-6354.

6. Yi, Y.; Xu, X.; Liu, Y.; Xu, S.; Huang, X.; Liang, J.; Shang, R. *European journal of medicinal chemistry* 2017, *126*, 687-695.

7. Chen, P. J.; Yang, A.; Gu, Y. F.; Zhang, X. S.; Shao, K. P.; Xue, D. Q.; He, P.; Jiang, T. F.; Zhang, Q.R.; Liu, H. M. *Bioorganic & medicinal chemistry letters* 2014, *24*(12), 2741-2743.

8. Li, T.; Zhang, J.; Pan, J.; Wu, Z.; Hu, D.; Song, B. *European journal of medicinal chemistry* 2017, *125*, 657-662.

9. Prakash, L.; Malik, S. E. E. M. A.; Mital, R. L. *Die Pharmazie* 1989, *44*(7), 490.

10. Rahman, L. K.; Chhabra, S. R. *Medicinal research reviews* 1988, *8*(1), 95-155.

11. Grivsky, E. M.; Lee, S.; singel, C. W.; Duch, D. S.; Nichol, C. A. Journal of Medicinal Chemistry1980,23,327.

12. Gangjee, A.; Vasudevan, A.; Queener, S. F.; Kisliuk, R.L. *Journal of medicinal chemistry* 1996, *39*(7),1438-1446.

13. Monge, A.; Martinez, V.; San Martín, C.; Simon, M. A. Spanish Patent ES 2,056,742 (1994). Chemical Abstracts.1995, (122),105912q.

14. Xia, S.; Yin, S.; Tao, S.; Shi, Y.; Rong, L.; Wei, X.; Zong, Z. *Research on Chemical Intermediates* 2012, *38*(9), 2435-2442

15. Sasada, T.; Kobayashi, F.; Sakai, N.; Konakahara, T. *Organic letters* 2009, *11*(10), 2161-2164.

16. Kappe, C. O.;100 years of the Biginelli dihydropyrimidine synthesis. *Tetrahedron* 1993, *49*(32), pp.6937-6963.

17. Aron, Z. D.; Overman, L. E. Chemical Communications. 2004, (3), 253-265.