ZANCO Journal of Pure and Applied Sciences
The official scientific journal of Salahaddin University-Erbil
https://zancojournals.su.edu.krd/index.php/JPAS

ISSN (print):2218-0230**, ISSN (online):** 2412-3986**, DOI: http://dx.doi.org/10.21271/zjpas**

RESEARCH PAPER

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A One-pot Multi-component Synthesis of some New Dihydropyrimidine Derivatives via Biginelli Condensations

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A B S T R A C T:

The Biginelli Reaction is a one-pot acid catalyzed cyclocondensation of -keto ester, urea and aromatic aldehyde which leads to the synthesis of functionalized 3,4-dihydro-2(H)-pyrimidinones (DHPMs). These DHPMs (synthetic and natural) possess a wide range of pharmacological activities. A simple, efficient, and cost-effective method for the synthesis of 3,4-dihydropyrimidin-2(1H)-one by a one-pot three-component cyclocondensation reaction of a 1,3-dicarbonyl compound, an aldehyde and urea using HCl as catalyst is reported. The three-component condensation of an aldehyde, a -keto ester and urea in the presence of a catalytic amount of HCl, 3,4-Dihydropyrimidin-2(1H)-ones were synthesized in high yields. Recently much attention has been devoted towards dihydropyrimidine derivatives due to their significant therapeutic and medicinal properties. All the products in reaction obtained in good to very good yields by proceeding through a simple and efficient procedure. All the synthesized compound's structure has been established by advanced spectroscopic data (FTIR, ^{1}HNMR, and ^{13}CNMR) and evaluated for their antibacterial activity against two types of bacteria (S. aureus and E.coli).

KEY WORDS: Dihydropyrimidine, Multicomponent reaction, Biginelli-Condensation, Acid-Catalyzed Reactions, Antibacterial Activity.DOI: http://dx.doi.org/10.21271/ZJPAS.35.4.15
ZJPAS (2023) , 35(4);151-159 .

1.INTRODUCTION :

The Biginelli reaction is considered as a common and classical easy approach to prepare dihydroprimidinones, through a process termed "Biginelli Condensation" equally dubbed the "Biginelli Dihydropyrimidine Synthesis"(Sweet and Fissekis, 1973). The process involves the reaction of aldehydes (aliphatic or aromatic), β-dicarbonyl compound (usually β-ketoester), and urea (or thiourea) in one-pot single step condensation reaction in which ethanol is used as a solvent and promoted using an acidic catalyst (Biginelli and Gazz, 1893, Peng and Deng, 2001). This type of reaction is suffering from low to acceptable yield (20-50%), harsh conditions, and long duration of time for the reaction (Ma et al., 2000).

The most common solvents utilized for Biginelli condensation are acetonitrile, dichloromethane, tetrahydrofuran, and dioxane (Ranu et al., 2002, Kappe, 2000).

Lately, diverse synthesis methodologies for the preparation of dihydropyrimidinones (DHPMs) have been devised and enhanced. Furthermore, numerous heterocyclic pyrimidinones have been synthesized apparently via multi-component reactions (MCRs). Nowadays, DHPMs have been prepared via multi-component reaction which is an important procedure that converts the multistep reactions to single step ones with easier operation, higher efficiency, molecular diversity, product complexity, and cost effectiveness (Ganem, 2009). Other techniques for the synthesis of these compounds have been developed such as catalyst-free, solvent-free and microwave irradiation procedures (Ranu et al., 2002).

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Article History:
Received: 20/07/2022
Accepted: 14/12/2022
Published: 30/08 /2023

3,4-dihydropyrimidin-2(1*H*)-ones are fascinating compounds owing to their participation as active constituents in bioorganic chemistry, therapeutics, and organic synthesis (Jauk et al., 2000), as well as their great role in pharmacy and medicine due to their vital pharmacological properties (Saha and Moorthy, 2011), including neuropeptide Y antagonists (Bruce et al., 1998), calcium channel blockers (Kappe, 2000), and antihypertensive agents (Atwal et al., 1991). Moreover, they possess some biological potentials ranging from antibacterial (Tale et al., 2011), to anticancer (Liu et al., 2019), anti-inflammatory potentials, and antiviral activities (Kappe, 2000, Hurst and Hull, 1960).

This research is aimed at using an acid-catalyzed procedure in an ethanolic medium for the synthesis of some 3,4-tetrahydropyrimidinones with medium to good yields followed by the experimental evaluation of antibacterial potentials of the synthesized products.

2. MATERIALS AND METHODS

2.1. General

The prerequisite chemicals were bought from Sigma Aldrich, Fluka, or Merk, and used in their present purchase state devoid of additional purification processes. The thin layer chromatographic technique (TLC) using Al plates pre-coated with silica gel having eluent system of (n-hexane: methanol: chloroform 5:2:3) was used to track the entire reaction process while ionic was employed for the visualization of the reaction process and product purity assessment (detection). The Stuart Scientific capillary melting point apparatus was utilized for the melting point determination. The infrared spectra was recorded with KBr disc on FTIR (Schimadzu IR Affinity-1) Spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on Varian Inova 400 MHz and 125 MHz, respectively, using TMS as internal standard; chemical shifts were assessed in units of parts per million (δ ppm); were s, d, t and m denote singlet, doublet, triplet and multiplet excitation states, respectively.

2.2. Synthesis of Dihydropyrimidine Derivatives (4a-h) (Folkers et al., 1932).

After setting up the reflux system for the procedure, aromatic aldehydes (0.1 mol), urea (1 g), and ethyl acetoacetate (3.19 mL) were poured into a round-bottomed flask while 0.5 mL of 95 % ethanol was added, and the entire mixture stirred thoroughly to ensure adequate miscibility of the reaction mixture. Concentrated hydrochloric acid (five drops) was added to the ethanolic mixture, and the temperature of the system was increased to reflux temperature and the entire system heated for 3 hrs. TLC was employed to monitor the reaction process by using (ethyl acetate: n-hexane 50:50) as an eluent to run the TLC system, until completion and product formation confirmed by the invisibility of the staring materials. After the completion of the condensation process the net system temperature had reduced to a magnitude of 0^{o}C and the products have precipitated. These were then separated and recovered using filtration with the ultimate step being the washing of the products using cold ethanol.

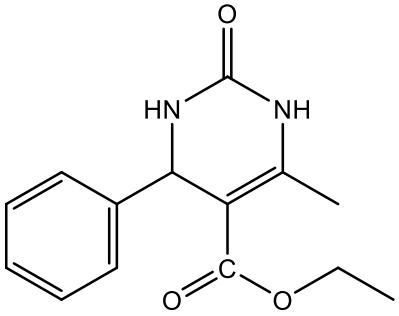
2.3. Antibacterial Evaluation

A standard agar (Moller Hinton) medium has prepared for antimicrobial evaluation plates and was inoculated with suspension of bacterial cell by swab cotton on a petri dish. Dimethyl sulfoxide (DMSO) was used as the solvent for dissolving the targeted compounds in order to prepare the solution with a concentration of 500 mg/L prior to the testing. Blank discs were put on the discs and 70 µL of the prepared compounds were added to the discs. Amikacin and dilute dimethyl sulfoxide (5%) served as positive and negative controls respectively. The plates were incubated for 24 hours at 37 ^{o}C after which the results were analyzed by measuring the diameter of the zones using a meter rule graduated in mm.

3. RESULTS

3.1. Synthesize of the Dihydropyrimidin-2-ones

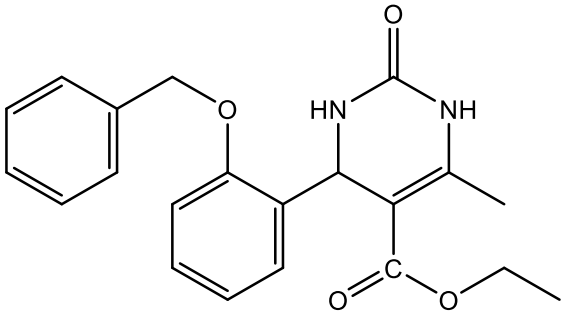
3.1.1. Ethyl 6-methyl-2-oxo-4-phenyl-3,4-dihydropyrimidine-5-carboxylate (4a)



Yield (69%); White, m.p. 200-202 ^{o}C, IRν_{max}cm^{-1} (KBr): 3244, 3116, 2980, 1724, 1701, 1649. ^{1}HNMR (400 MHz, DMSO-d_6) δ 1.16-1.20 (t, 3H,

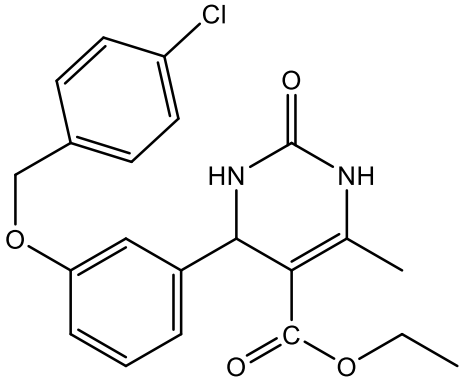
CH_3), 2.40 (s, 3H, CH_3), 4.06-4.12 (q, 2H, CH_2), 5.32-5.43 (s, 1H, CH), 7.28-7.34 (m, 5H, Ar-H), 8.05 (d, 1H, NH), 9.09 (s, 1H, NH). ^{13}CNMR (125 MHz, DMSO-d_6): δ 14.16 (CH_3), 18.64 (CH_3), 50.49 (C-NH), 59.89 (CH_2), 111.96 (C-C=O), 127.56-147.98 (Ar), 153.27 (=C-N), 156.03 (N-C=O), 165.80 (O=C-O).

3.1.2. Ethyl 4-(2-(benzyloxy)phenyl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (4b)



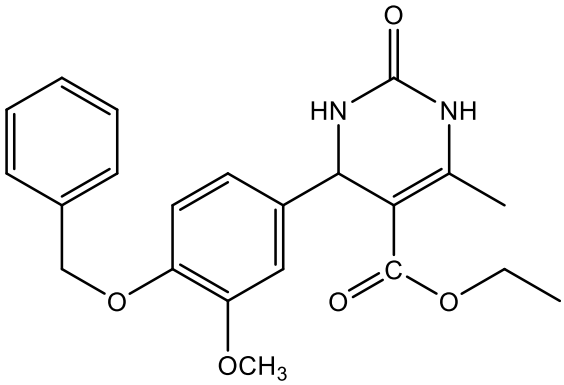
Yield (68%); White, m.p. 160-162^{o}C, IR$\nu_{max,}$ (KBr, cm^{-1}) 3205, 3107, 2941, 2929, 1693, 1635. ^{1}HNMR (400 MHz, DMSO-d_6) δ 1.17-1.20 (t, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.13-4.23 (d, 2H, CH_2), 5.11 (s, 1H, CH), 5.23 (s, 2H, CH_2), 6.80-7.44 (m, 9H, Ar-H), 7.88-7.92 (d, 1H, NH), 9.88 (s, 1H, NH). ^{13}CNMR (125 MHz, DMSO-d_6): δ 14.18 (CH_3), 18.70 (CH_3), 50.43, 60.00, 70.17, 98.42, 112.00, 120.85, 127.05- 148.00 (Ar), 153.12, 155.88, 166.01.

3.1.3. Ethyl 4-(3-((4-chlorobenzyl)oxy)phenyl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (4c)



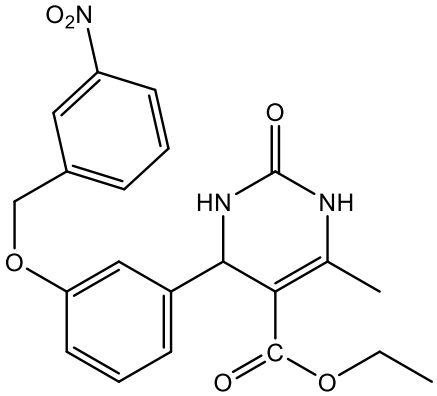
Yield (70%); White, m.p. 196-198^{o}C, IRν_{max}cm^{-1} (KBr): 3325, 3058, 2942, 1674, 1597, 1583, 1506. ^{1}HNMR (400 MHz, DMSO-d_6) δ 1.13-1.18 (t, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.07-4.17 (q, 2H, CH_2), 5.15 (s, 2H, CH_2), 5.20 (s, 1H, CH), 6.93-7.89 (m, 8H, Ar-H), 8.29 (d, 1H, NH), 9.53 (s, 1H, NH). ^{13}CNMR (125 MHz, DMSO-d_6): δ 14.20 (CH_3), 18.00 (CH_3), 55.13 (C-N), 61.97 (C-O), 72.00 (C-O), 108.26 (=C), 111.89-150.35 (Ar), 153.05 (C=O), 159.99 (=C-O), 162.25 (O=C-O).

3.1.4. Ethyl 4-(4-(benzyloxy)-3-methoxyphenyl)-6-methyl-2-oxo-,3,4-dihydropyrimidine-5-carboxylate (4d)



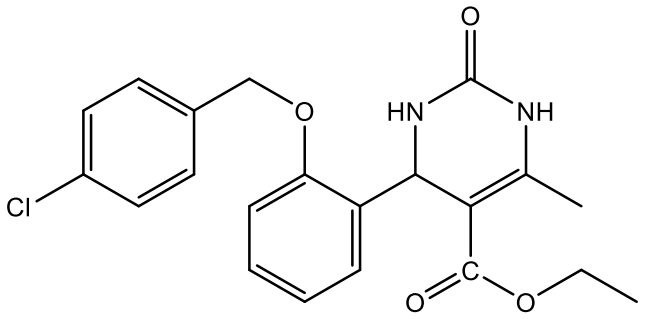
Yield (68%); White, m.p. 222-224^{o}C, IRν_{max}cm^{-1} (KBr): 3315, 3058, 2942, 1692, 1632, 1598. ^{1}HNMR (400 MHz, DMSO-d_6) δ 1.24-1.28 (t, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.58 (s, 3H, CH_3), 3.75-3.84 (q, 2H, CH_2), 5.39 (s, 3H, CH_2 and CH), 7.31-7.80 (m, 8H, Ar-H), 8.51 (d, 1H, NH), 9.42 (s, 1H, NH). ^{13}CNMR (125 MHz, DMSO-d_6): δ 14.20 (CH_3), 18.00 (CH_3), 55.13 (C-N), 61.97 (C-O), 72.00 (C-O), 108.26 (=C), 111.89-150.35 (Ar), 153.05 (C=O), 159.99 (=C-O), 162.18 (O=C-O).

3.1.5. Ethyl 6-methyl-4-(3-((3-nitrobenzyl)oxy)phenyl)-2-oxo-3,4-dihydropyrimidine-5-carboxylate (4e)



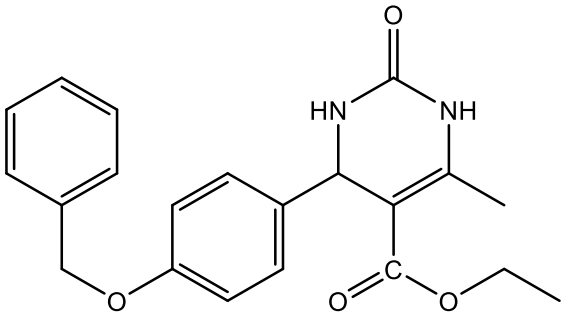
Yield (66%); White, m.p. 144-146^{o}C, IRν_{max}cm^{-1} (KBr): 3290, 3150, 2986, 1720, 1586 .^{1}HNMR (400 MHz, DMSO-d_6) δ 1.19-1.23 (t, 3H, CH_3), 2.36 (s, 3H, CH_3), 4.09-4.15 (q, 2H, CH_2), 5.14 (s, 2H, CH_2), 5.20 (s, 1H, CH), 6.89-8.32 (m, 8H, Ar-H), 7.28 (d, 1H, NH), 10.07 (s, 1H, NH). ^{13}CNMR (125 MHz, DMSO-d_6): δ 14.19 (CH_3), 18.87 (CH_3), 55.65 (C-N), 60.15 (C-O), 68.68 (C-O), 101.26 (=C), 113.38-146.21 (Ar), 148.45 (C=O), 158.49 (=C-O), 165.54 (O=C-O).

3.1.6. Ethyl 4-(2-((4-chlorobenzyl)oxy)phenyl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (4f)



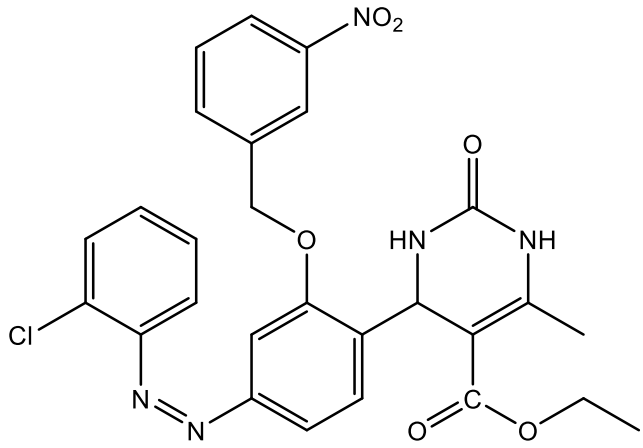
Yield (6%); White, m.p. 201-203^{o}C, IRν_{max}cm^{-1} (KBr): 3201, 3058, 2963, 1693, 1681, 1456. ^{1}HNMR (400 MHz, DMSO-d_6) δ 1.18-1.21 (t, 3H, CH_3), 2.39 (s, 3H, CH_3), 4.01-4.10 (q, 2H, CH_2), 5.08 (s, 1H, CH), 5.17-5.18 (d, 2H, CH_2), 7.15-7.48 (m, 8H, Ar-H), 7.85-7.87 (d, 1H, NH), 9.84 (s, 1H, NH). ^{13}CNMR (125 MHz, DMSO-d_6): δ 14.22 (CH_3), 18.25 (CH_3), 54.69 (C-N), 63.36 (CH_2-O), 73.85 (C-O), 109.58 (C-C=O), 114.25-143.76 (Ar), 149.18 (C=O), 152.43 (=C-O), 163.86 (O=C-O).

3.1.7. Ethyl 4-(4-(benzyloxy)phenyl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (4g)



Yield (78%); White, m.p. 186-188^{o}C, IRν_{max}cm^{-1} (KBr): 3296, 3102, 2953, 1695, 1674, 1632, 1586, 1532. ^{1}HNMR (400 MHz, DMSO-d_6) δ 1.24-1.27 (t, 3H, CH_3), 2.39 (s, 3H, CH_3), 4.12-4.19 (q, 2H, CH_2), 5.15 (s, 1H, CH), 5.21 (s, 2H, CH_2), 6.84-7.45 (m, 9H, Ar-H), 7.91-7.95 (d, 1H, NH), 9.21 (s, 1H, NH). ^{13}CNMR (125 MHz, DMSO-d_6): δ 13.98 (CH_3), 18.36 (CH_3), 55.12 (C-N), 64.28 (CH_2-O), 74.07 (C-O), 110.31 (C-C=O), 115.23-149.17 (Ar), 152.43 (C=O), 158.04 (=C-O), 164.25 (O=C-O**)**

3.1.8.Ethyl -4-(4-((2-chlorophenyl)diazenyl)-2-((3-nitrobenzyl)oxy)phenyl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (4h)



Yield (69%); White, m.p. 233-235^{o}C, IRν_{max}cm^{-1} (KBr): 3325, 3120, 2941, 1653, 1629, 1576, 1534. ^{1}HNMR (400 MHz, DMSO-d_6) δ 1.18-1.22 (t, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.12-4.19 (q, 2H, CH_2), 5.12-5.13 (d, 1H, CH), 5.18 (s, 2H, CH_2), 7.10-7.45 (m, 11H, Ar-H), 7.86-7.88 (d, 1H, NH), 9.91 (s, 1H, NH). ^{13}CNMR (125 MHz, DMSO-d_6): δ 14.20 (CH_3), 18.20 (CH_3), 48.19 (C-N), 63.58 (CH_2-O), 75.26 (C-O), 105.69 (C-C=O), 110.00-150.16 (Ar), 156.15 (C=O), 160.06 (=C-O), 169.24 (O=C-O).

3.2. Antibacterial Evaluation of the Dihydropyrimidin-2-ones

Table 1. Zone of Inhibition by products in mm against S. aureus and E. coli bacteria

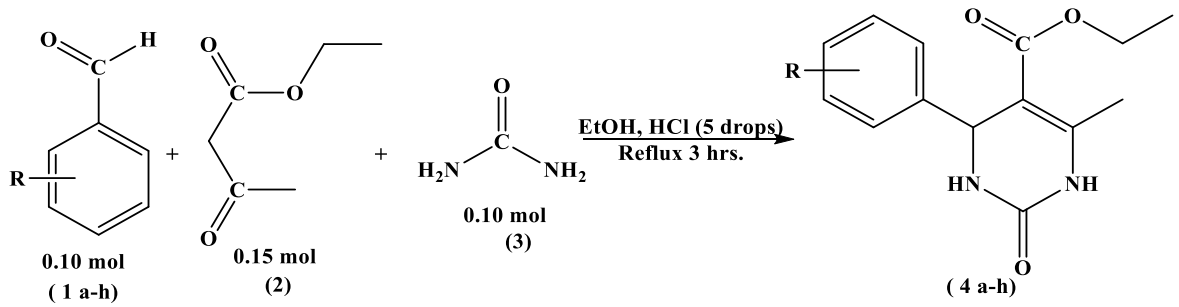
Compounds	Zone of Inhibition in mm	
	S. aureus	E. coli
4a	12	6
4b	13	7
4c	13.5	7.5
4d	13	7
4e	15	6.5
4f	14	8
4g	14.5	8
4h	15	7.5
AMK (Antibiotic)	6	6

4. DISCUSSION

4.1. Chemistry

Synthesis of DHPMs achieved by applying this eco-friendly procedure using ethanol which is a polar and protic solvent as opposed to other non-eco-friendly protocols which are toxic and pollutant in nature. Also, ethanol is effective to dissolve the catalyst thereby removing it easily from the final product.

The condensation reaction of aldehydes, ethyl acetoacetate, and urea in an ethanolic solution was performed successfully considering that HCl served as a positive catalyst thereby expediting the reaction rate to achieve the product in a shorter time because in the absence of the catalyst, although the reactions were heated at reflux temperature for about 10 hrs, no products were formed, for this reason the catalyst have been employed (Scheme 1).



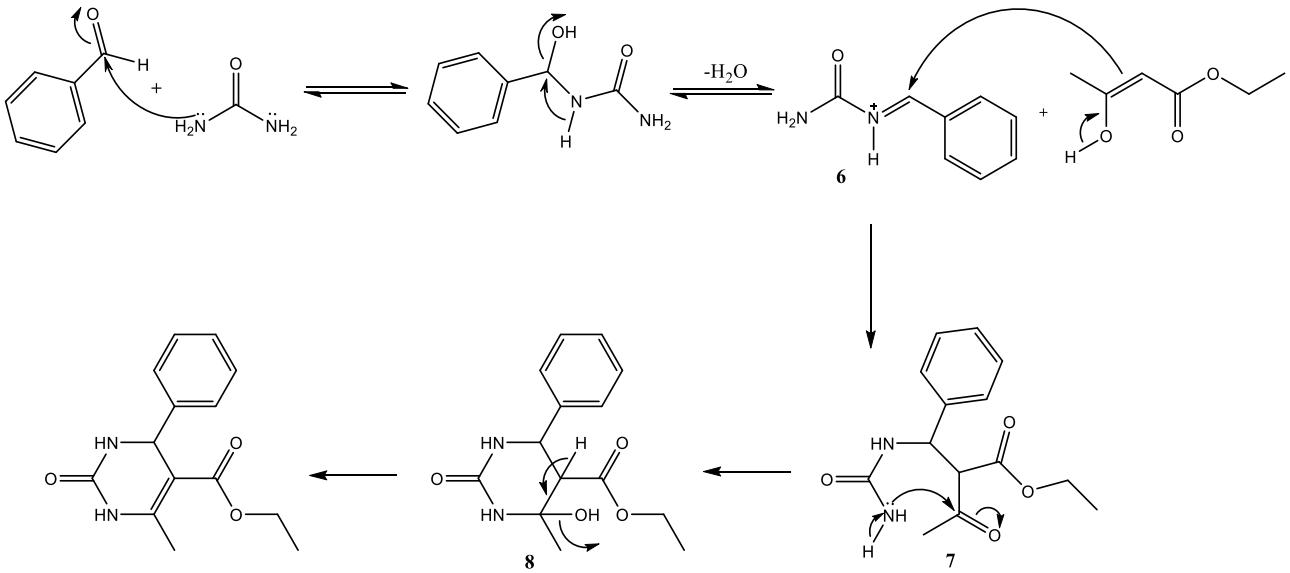
Scheme 1: Synthesis of the Dihydropyrmidine Derivatives

Spectroscopic analytical techniques namely: FT-IR, ^{1}H-NMR, and ^{13}C-NMR were employed in the structural elucidation of the products. In IR spectra of the compounds, appearance of a single shoulder peak instead of a two-shoulder peak in the range of (3500 cm^{-1} – 3200 cm^{-1}) is an acceptable confirmation for the conversion of the NH_2 group in the urea to NH of the product. On the other hand, peaks near 1700 cm^{-1} attributed to the ester group of the products.

In ^{1}H-NMR, aromatic signals appeared in the normal range (6.80 – 7.89 ppm), NH peak has showed in the range of (9.09 - 10.07 ppm), the deshielding effect of the peaks returns to the effect of high electronegativity of the nitrogen atom, to withdraw the electrons and reduce the electron density and moved to down field. As usual, two peaks with three protons have been appeared attributed to the methyl group's one form pyrimidinone part and the other one is the ethyl acetate.

On the other hand, ^{13}C-NMR has confirmed the production of the products via presenting the signals on the spectrum in the exact position and the number of carbons. Two peaks were appeared on 14.22-13.98 and 18.87-18.00 ppm attributed to the methyl group carbons, respectively. The peaks in the range of 110.00 – 150.13 ppm is the usual region for the aromatic carbons, and finally the most down filed peak 169.24-162.18 ppm is related to the carbon of the ester group, due to the anisotropic effect of the carbonyl group.

Recent accepted mechanism for the preparation of dihydropyrimidinones by means of Biginelli condensation basically involves the acid-catalyzed reaction of aldehyde and urea to form N-acyliminium ion intermediate (6), then the carbonyl group of ethylacetoacetate mostly in the tautomeric case of enol will intercept the iminium ion to form the product (7) which is readily cyclized to hexahydropyrimidine (8). Finally, elimination of water molecule by acid-catalyzed process leads to formation of the final product (PETERSEN, 1973, Hu et al., 1998).



Scheme 2: Proposed mechanism for the formation of Dihydropyrimidinones

4.2. Antibacterial Evaluation

The antibacterial efficacy of the products was evaluated using two catalase-producing bacteria namely: *Staphylococcus aureus* and *Escherichia coli* which are gram-positive and gram-negative respectively. At a constant concentration (500 mg/L), the produced compounds showed different activity against the bacteria based on the ability of their substituted functional groups and active sites to be attached with specific sites in the bacteria as well as their ability to penetrate the bacterial cell wall thereby halting the bacteria growth. The compounds were tested using amikacin and diluted DMSO as standard positive and negative control respectively. From the diameter (mm) of the inhibition zone as determined using a meter rule, the comparative efficacy of the product for inhibiting gram-positive bacteria as opposed to gram-negative bacteria is glaring. This observation can be accounted for by the predilection of the products for the thick peptidoglycan in the gram-positive bacteria hence the inhibition of a greater zone as pictorially illustrated in Table 1 and Figure 4.

5. CONCLUSION

The ever-growing global desideratum to synthesize more anti-microbial compounds to facilitate the fight to combat the prevalence of physiological disorders and numerous diseases due generally to bacterial pathogenicity has always persisted notwithstanding that some of such compounds are already existent. Basically, heterocyclic organic compounds such as the pyrimidine derivatives have proven to be highly resourceful towards this end. Therefore, in this work eight new dihydropyrimidine derivatives have been produced using substituted aromatic aldehydes, urea, and di-carbonyl compound via three component one pot protocol in the presence of an acidic catalyst. The products showed effectiveness against gram-positive and gram-negative bacteria, with a higher inhibition potential in gram-positive bacteria owing to their intrinsic morphological uniqueness conferred by their thick peptidoglycan cell wall. By this, the antimicrobial potency of the synthesized compounds is hereby verified.

Acknowledgements

We are grateful to thank Pavia University for recording the NMR spectra for the products and Tishk International University for their effort in biological evaluation of the targeted compounds. Also the support of Chemistry Department, College of Science, Salahaddin University is highly appreciated.

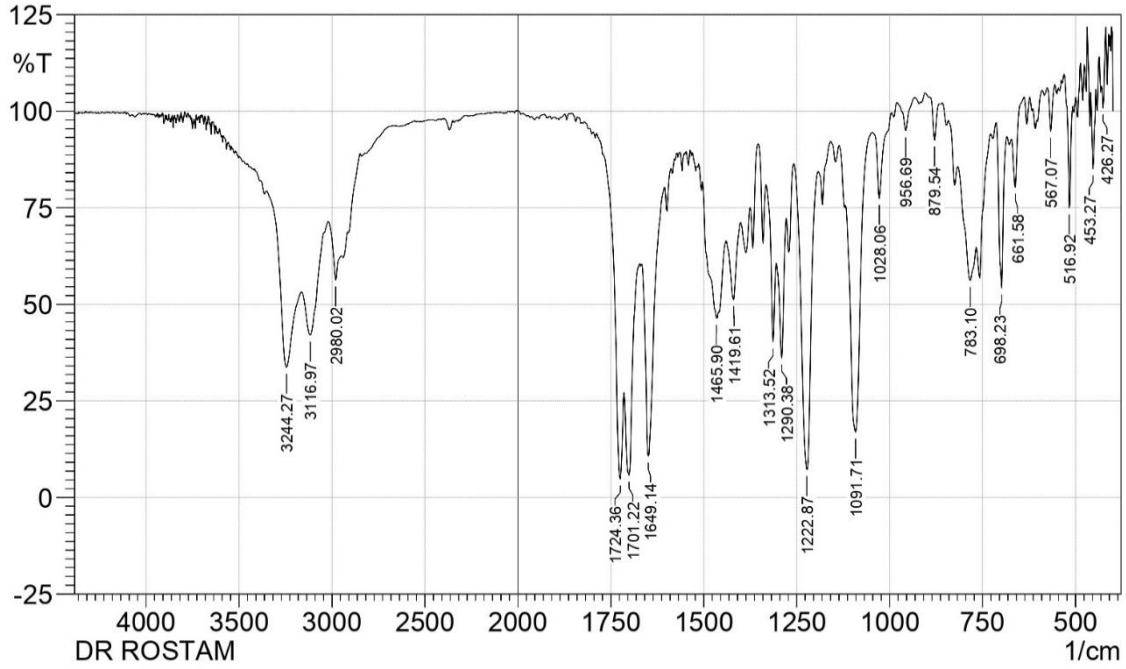


Figure 1. FTIR Spectrum of the targeted compound 4a

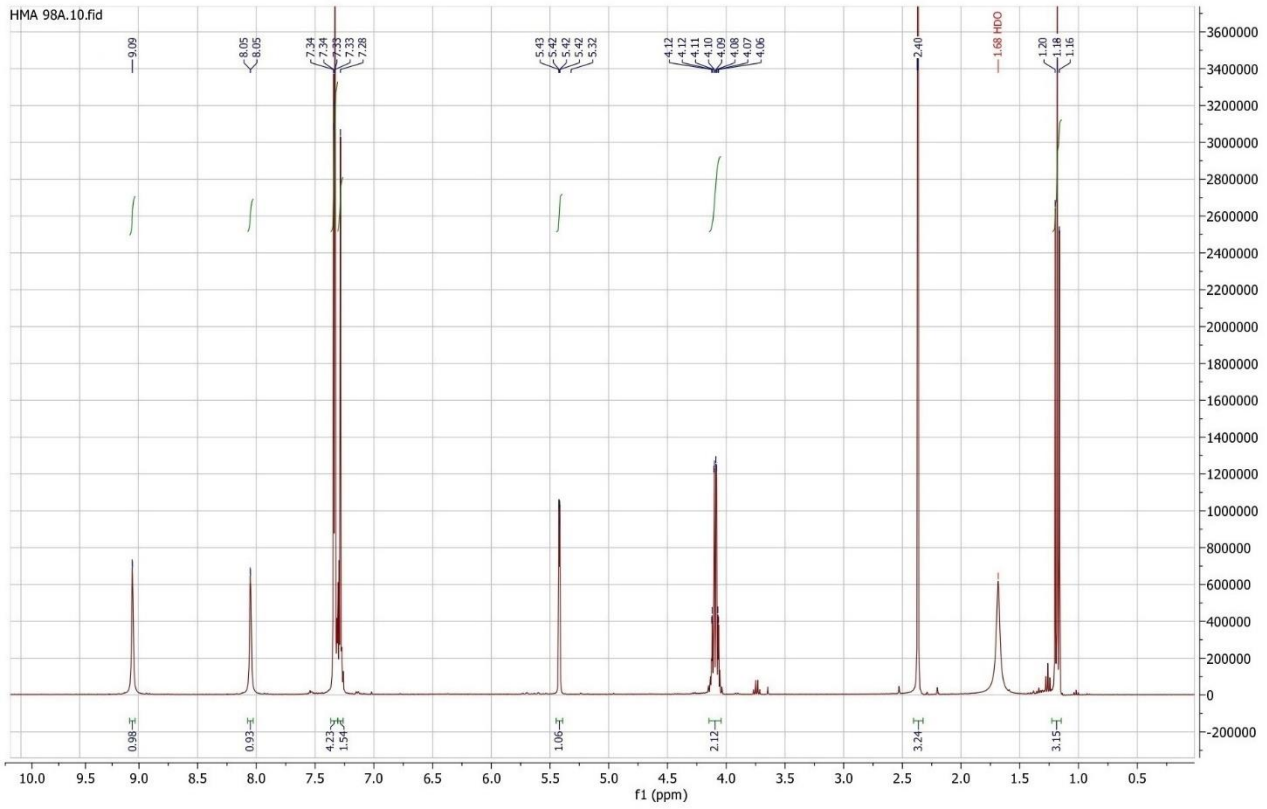


Figure 2. ^{1}HNMR Spectrum of the Furnished Product 4a

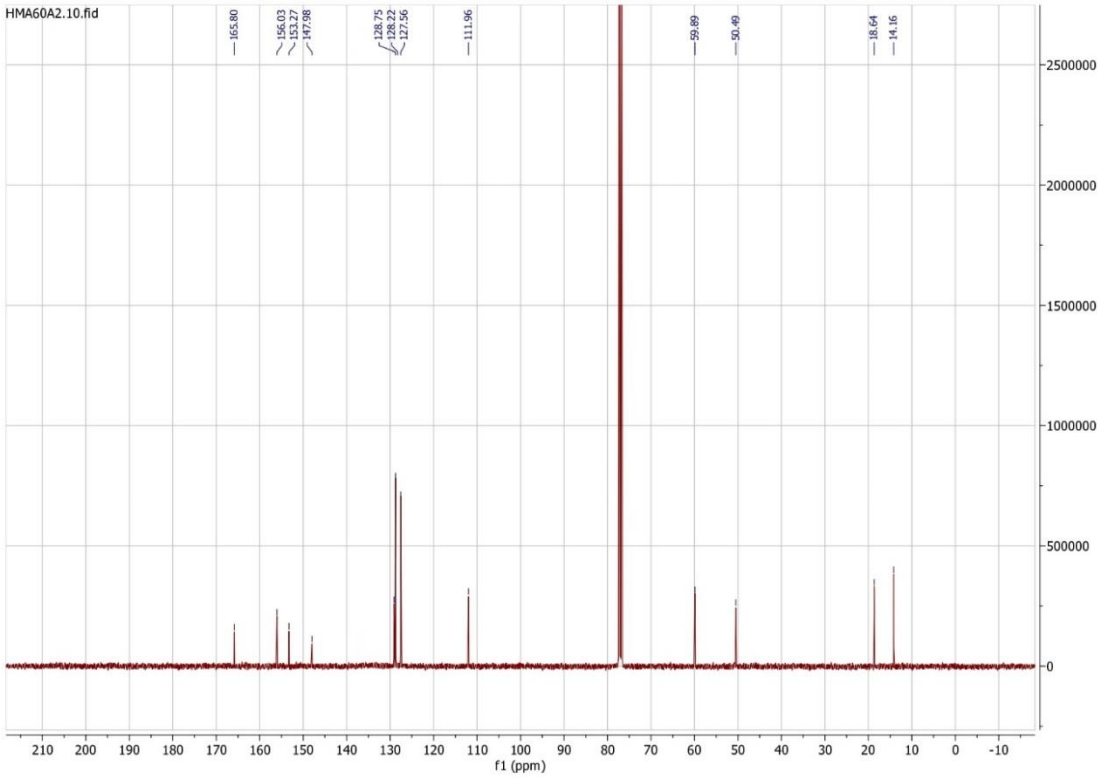


Figure 3. ^{13}CNMR Spectrum of the Product 4a

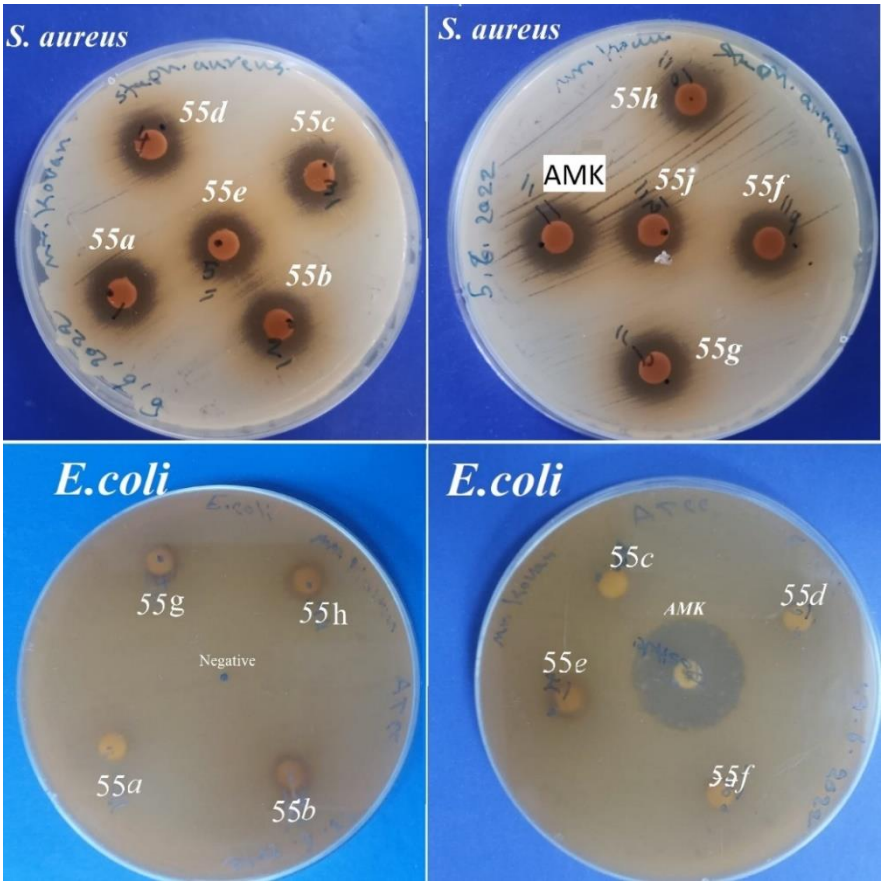


Figure 4. Zone of Inhibition by the targeted products against S. aureus and E. coli bacteria

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