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Preparation and Identification of Some New Heterocyclic Derivatives from Suberoyl Chloride and Their Study as Anti-bacterial

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Abstract

Some new derivatives of suberic chloride synthesized by reaction of suberoyl chloride with 4-amino acetophenone to prepare N¹,N⁸-bis(4-acetylcyclohex-2-en-1-yl)octanediamide, then react with 4-nitrobenzaldehyde in the presence of sodium hydroxide, the product reacted with (urea, thiourea, phenyl hydrazine, 2-amino aniline, 2-aminophenol, 2,4-dinitrophenyl hydrazine and 2-amino benzothiol) to prepare many heterocyclic derivatives. This reaction was checked by thin-layer chromatography (TLC) method. All new compounds were characterized by melting points, elemental analysis, FT-IR, ¹H & ¹³C-NMR. The antibacterial action of these derivatives was determined.

Keywords: Suberoyl Chloride, Chalcone, antibacterial, thiourea, urea.

1. Introduction

Suberic acid -it is also called Octanedioic acid- a dicarboxylic acid, chemical formula C₈H₁₄O₄, a solid white substance used in the manufacture of medicines and in the manufacture of plastics and plasticizers. It is obtained mainly from the suberin, Castor oil and Cork, whose name is derived from the Latin word Suber, which means Cork [1] Suberoyl chloride was synthesized from suberic acid by reacting with an excess of thionyl chloride [2].

A generic terminology for the 1,3-diaryl-2-propen-1-one is chalcone. The privileged scaffold chalcone remained a fascination among researchers in the 21st Century because they have a unique structural feature of having a >C=O functional group in conjugation with >C=C< ease of synthesis, diversity of substituents and wide range of biological properties spectrum of biological activities [3]. The presence of α, β-unsaturated carbonyl moiety as well as of substituted aromatic rings renders the

chalcones biologically active. Some substituted chalcones and their derivatives, including some of their heterocyclic analogues have been reported to possess a wide range of pharmacological activities such as cytotoxic, anti-retroviral, anti-malarial, anti-platelet, antitubercular, antimicrobial etc....[4] Cyclization of chalcone leading to benzodiazepine, pyrazoline, pyrimidine, isoxazole, 1,4-diketone, etc.... derivatives have been a developing field within the realm of heterocyclic chemistry for the past several years[5]. Pyrazole is a class of compounds, which has many applications in different field. One of the methods for the synthesis of such compound is from unsaturated carbonyls (chalcone) by the cyclization with hydrazine and substituted hydrazine. Pyrazole and their derivatives are considered to be important for drugs and agricultural chemicals. Some substituted pyrazoles and their derivatives have been reported to possess several interesting biological activities such as hypnotic properties, antimicrobial, antitumor and antifungal[6]. Many pyrazoles are used for the treatment of thyroid and leukemia. thiazine's derivatives that exhibit various biological activities such as anti-tubercular, anti-fungal, anti-bacterial, analgesic, anti-inflammatory, anti-mycobacterial activity etc[7]. The synthesis of 1,3-oxazines has attracted attention in the past because of their potential as antibiotics, antitumor agents, analgesics, and anticonvulsants. 1,3-Oxazines have generated great interest as antipsychotic agents and as possible effectors for serotonin and dopamine receptors. In addition, benzo-1,3-oxazines are known to be biologically active as anti-malarial, anti-anginal, anti-hypertensive and potent anti-rheumatic agents[8]. Oxazines are an important group of organic dyes which are generally π -conjugated systems, with interesting photo-physical and lasing properties. In this work synthesis new derivatives of suberoyl chloride by reactions suberoyl chloride with 4-amino acetophenone to prepare chalcone compound then prepare some heterocyclic derivatives and study biological activity[9].

2. EXPERIMENTAL

All materials were of highest purity and supplied by Merck, Sigma Aldrich and Fluka company. Melting points were measured on a Bauchi melting point device B-545 (Bauchi Laboratory Technik AG, Switzerland, France). Microanalytical data were obtained with a Vario, Elementary device (Shimadzu, Japan). The IR spectra were recorded on Shimadzu Fourier Transform Infra-red spectrophotometer (Model 270), used crystal KBr. NMR spectra were recorded on 400 MHz (^1H) and at 100 MHz and (^{13}C) spectrometers (Tehran, Iran) with TMS as the internal standard and on δ scale in ppm. (TLC) was performed on silica gel for (TLC) and spots were visualized by Iodine vapors. The reagents used were of analytical grade while the solvents were purified before use.

2.1. Preparation of N^1, N^8 -bis(4-acetylcyclohex-2-en-1-yl)octanediamide (1)

This derivative was obtained from mixing (0.001 mol, 0.21109 g) of suberoyl chloride with (0.002 mol, 0.27 g) of 4-aminoacetophenone with addition of 3 drops of triethylamine and using absolute ethanol as solvent and heated mixture with refluxed 5 hours[10]. The reaction was monitored by TLC (benzene: methanol) (1:4) the reaction is neutralized by glacial acetic acid and, the precipitate obtained was filtered, washed and recrystallized from ethanol. Yield (74%) as light yellow solid. $m.p = 158^\circ\text{C}$. $R_f = 0.68$. FT-IR (KBr, cm^{-1}): N-H (3145), C-H_{ali} (2954), C=O_{Ketone} (1718), C=O_{amide} (1688). $^1\text{H NMR}$: $\delta = 0.02$ -1.20 (s, 12H, $(\text{CH}_2)_6$), 1.27 (s, 1H, NH-CO), 6.36-7.23 (br., 10H, aromatic proton), 2.99 (s, 1H, -N=N-CH-). $^{13}\text{C NMR}$: $\delta = 12.3$ -19.5 ($(-\text{CH}_2)_6$), 149.6-153.4 (CO-N-), 105.3-129 (Aromatic Carbone), 191.5 (C=O)_{Ketone}. Anal. calc. for $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_4$ (412.53): C 69.611, H 6.007, N 6.189, S 0.000.

2.2. Preparation derivative (2)

This derivative was obtained from mixing of (0.01 mol) of the derivative (1) and (0.02 mol) of 4-nitro benzaldehyde in a 100 mL conical flask and added 30 ml of ethanol with continuous stirring on the stirring device To the reaction flask (5 ml) of sodium hydroxide (10%). The stirring process continued for 18 hours [11]. The reaction was monitored by TLC (benzene: methanol) (1:4) the reaction is neutralized by glacial acetic acid and, the precipitate obtained was filtered, washed and recrystallized from ethanol. Yield (68%) as yellow solid. *m.p*= 172 °C. *Rf*=0.62, **FT-IR** (KBr, cm⁻¹): N-H (3240), C-H_{ali.} (2987), C=O_{chalcone} (1719), C=O_{amide} (1686), CH=CH (3093), NO₂ (1404,1533). ¹H NMR: δ = 0.44-2.35 (s, 12H, (CH₂)₆), 9.67 (s, 1H, NH-CO), 6.98-7.89 (br., 10H, aromatic proton), 6.00-6.05 (s, 2H, -CH=CH-). ¹³C NMR: δ= 15.6-24.9 ((-CH₂)₆), 153.9-160.3 (CO-N-), 116.6-133.6 (Aromatic carbonyl), 100.7, 103 (CH=CH). Anal. calc. For C₃₈H₃₄N₄O₈ (674.71): C 66.771, H 4.642, N 8.090, S 0.000.

2.3.Preparation derivative (3-9)

These derivatives were obtained by dissolving (0.01 ml) of the derivative 2 in 50 ml of ethanol and then adding the compounds (urea, thiourea, phenylhydrazine, 2-aminoaniline, 2-aminobenzothiol, 2-aminophenol and 2, 4-dinitrophenylhydrazine in a quantity of (0.02 mol) respectively to prepare each derivative and then added to the reaction flask (5 ml) of sodium hydroxide (10%). the mixture refluxed (7-8 hours) [12-14] and reaction was monitored by TLC (benzene: methanol) (1:4) the reaction is neutralized by glacial acetic acid and, the precipitate obtained was filtered, washed and recrystallized from ethanol.

N¹-(4-(2-amino-6-(4-nitrophenyl)-6H-1,3-oxazin-4-yl)cyclohexyl)-N⁸-(4-(2-amino-6-(nitrophosphanyl)-4H-1,3-oxazin-4-yl)phenyl)octanediamide (3)

Yield (70%) as yellowish orange solid. *m.p*= 196°C. *Rf*=0.70 **FT-IR** (KBr, cm⁻¹): N-H_{amid} (3115), C-O-C (1199), C-H_{ali.} (2941), C=O_{chalcone} (1719), C=O_{amide} (1686), C=N (1624), NO₂ (1402,1504), NH₂ (3387,3431). ¹H NMR: δ = 0.20-1.20 (s, 12H, (CH₂)₆), 9.25 (s, 1H, NH-CO), 6.70-8.1 (br., aromatic proton), 3.04, 2.42 (s, 1H, -CH-CH=C), 8.96 (s, 2H, NH₂). ¹³C NMR: δ= 10.3-15.9 ((-CH₂)₆), 153.4 (CO-N-), 111.2-129.5 (Aromatic carbonyl), 55.1, 56.0 (O-CH-CH). Anal. calc. for C₄₀H₃₈N₈O₈ (758.79): C 65.563, H 4.870, N 15.151, S 0.000

N¹-(4-(2-amino-6-(3-nitrophenyl)-4H-1,3-thiazin-4-yl)phenyl)-N⁸-(4-(2-amino-6-(4-nitrophenyl)-6H-1,3-thiazin-4-yl)phenyl)octanediamide(4)

Yield (68%) as a yellowish orange color solid. *m.p*= 202 °C. *Rf*= 0.62, **FT-IR** N-H_{amid} (3207), C-S (775) C-H_{ali.} (2943), C=O_{chalcone} (1719), C=O_{amide} (1680), C=N (1641), NO₂ (1436,1546), NH₂ (3390,3423). ¹H NMR: δ = 0.36-1.10 (s, 12H, (CH₂)₆), 9.67 (s, 1H, NH-CO), 6.68-7.7 (br., aromatic proton), 2.99-3.02 (s, 1H, -CH-CH=C), 8.92 (s, 2H, NH₂). ¹³C NMR: δ= 16.6-24.7 ((-CH₂)₆), 165.3 (CO-N-), 116.6-132.6 (Aromatic Carbonyl), 67.8-77.5 (S-CH-CH), Anal. calc. for C₄₀H₃₈N₈O₆S₂ (790.91): C 60.327, H 4.129, N 14.008, S 7.885

N¹-(4-(5-(4-nitrophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-N⁸-(4-(3-(4-nitrophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl)phenyl)Octanediamide (5)

Yield (64%) as a yellowish brown color solid. *m.p*= 210 °C. *Rf*= 0.60, **FT-IR** N-H_{amid} (3271), C-H_{ali.} (2989), C=O_{amide} (1672), C=N (1620), NO₂ (1361,1512). 8.92 (s, 2H, NH₂). ¹H NMR: δ = 0.40-2.40 (s, 12H, (CH₂)₆), 9.71 (s, 1H, NH-CO), 6.05-7.97 (br., aromatic proton), 2.83-2.95 (s, 1H, -CH-CH=C). ¹³C NMR: δ= 12.4-18.3 ((-

$(CH_2)_6$, 157.5 (CO-N-), 111.3-132.3 (Aromatic Carbone), 55.1, 56.0 (N-CH-CH). Anal. calc. for $C_{50}H_{46}N_8O_6$ (854.97): C 70.148, H 4.175, N 13.001, S 0.000

N¹-(3-(4-(4-nitrophenyl)-1H-benzo[b][1,4]diazepin-2-yl)phenyl)-N⁸-(4-(2-(4-nitrophenyl)-1H-benzo[b][1,4]diazepin-4-yl)phenyl)octanediamide (6)

Yield (70%) as a the color is yellowish brown. *m.p* = 214 °C. *R_f* = 0.58, **FT-IR** N-H_{amid} (3300), C-H_{ali} (2910), N-H (3377), C=O_{amide} (1690), C=N (1625), NO₂ (1379, 1504). ¹H NMR: δ = 0.13-1.18 (s, 12H, (CH₂)₆), 9.58 (s, 1H, NH-CO), 7.16-7.57 (br., aromatic proton), 3.00 (s, 1H, CH-C), 8.20 (s, 1H, NH). ¹³C NMR: δ = 11.49-14.9 ((-CH₂)₆), 158.5 (CO-N-), 120.2-139.2 (Aromatic carbone), 72.2, 79.2 (N-CH-CH). Anal. calc. for $C_{50}H_{42}N_8O_6$ (850.94): C 69.718, H 4.549, N 13.087, S 0.000

N¹-(4-(4-(4-nitrophenyl)benzo[b][1,4]thiazepin-2-yl)phenyl)-N⁸-(4-(2-(4-nitrophenyl)benzo[b][1,4]thiazepin-4-yl)phenyl)octanediamide (7)

Yield (72%) as a dark Yellow color solid. *m.p* = 222 °C. *R_f* = 0.62 **FT-IR**: N-H (3261), C-H_{ali} (2987), C-S (785), C=O_{amide} (1669), NO₂ (1346, 1540). ¹H NMR: δ = 0.98-1.2 (s, 12H, (CH₂)₆), 9.74 (s, 1H, NH-CO), 6.92-7.40 (br., aromatic proton), 3.44 (s, 1H, -CH-C=). ¹³C NMR: δ = 20.2-23.4 ((-CH₂)₆), 163.9 (CO-N-), 120.2-141.5 (Aromatic carbone), 82.9, 85.9 (S-CH-CH). Anal. calc. for $C_{50}H_{40}N_6O_6S_2$ (885.03): C 69.531, H 4.162, N 9.273, S 0.000.

N¹-(4-(4-nitrophenyl)benzo[b][1,4]oxazepin-2-yl)phenyl)-N⁸-(4-(2-(4-nitrophenyl)benzo[b][1,4]oxazepin-4-yl)phenyl)octanediamide (8)

Yield (70%) as a dark yellow color solid. *m.p* = 202 °C. *R_f* = 0.60, **FT-IR**: N-H (3330), C-H_{ali} (2900), C-O-C (1170),

C=O_{amide} (1680), C=N (1668), NO₂ (1359, 1507). ¹H NMR: δ = 0.02-1.03 (s, 12H, (CH₂)₆), 9.45 (s, 1H, NH-CO), 6.47-7.69 (br., aromatic proton), 3.04 (s, 1H, CH-C=), 8.92 (s, 2H, NH₂). ¹³C NMR: δ = 11.2-27.5 ((-CH₂)₆), 153.4 (CO-N-), 105-129.5 (Aromatic carbone), 57.5, 67.9 (O-CH-CH). Anal. calc. for $C_{50}H_{40}N_6O_8$ (852.90): C 69.531, H 4.162, N 9.273, S 0.000

N¹-(4-(1-(2,4-dinitrophenyl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenyl)-N⁸-(4-(1-(2,4-dinitrophenyl)-5-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)octanediamide (9)

Yield (72%) as a yellowish orange color solid. *m.p* = 226 °C. *R_f* = 0.68, **FT-IR**: N-H (3425), C-H_{ali} (2924), C=O_{amide} (1690), C=N (1624), NO₂ (1356, 1543). ¹H NMR: δ = 0.40-1.30 (s, 12H, (CH₂)₆), 9.25 (s, 1H, NH-CO), 6.70-7.51 (br., aromatic proton), 3.04 (s, 1H, CH-C=). ¹³C NMR: δ = 11.5-14.8 ((-CH₂)₆), 160.3 (CO-N-), 116.6-132.4 (Aromatic carbone), 80.9, 83.4. (N-CH-CH). Anal. calc. for $C_{50}H_{42}N_{12}O_{14}$ (1034.96): C 57.215, H 3.648, N 16.100, S 0.000

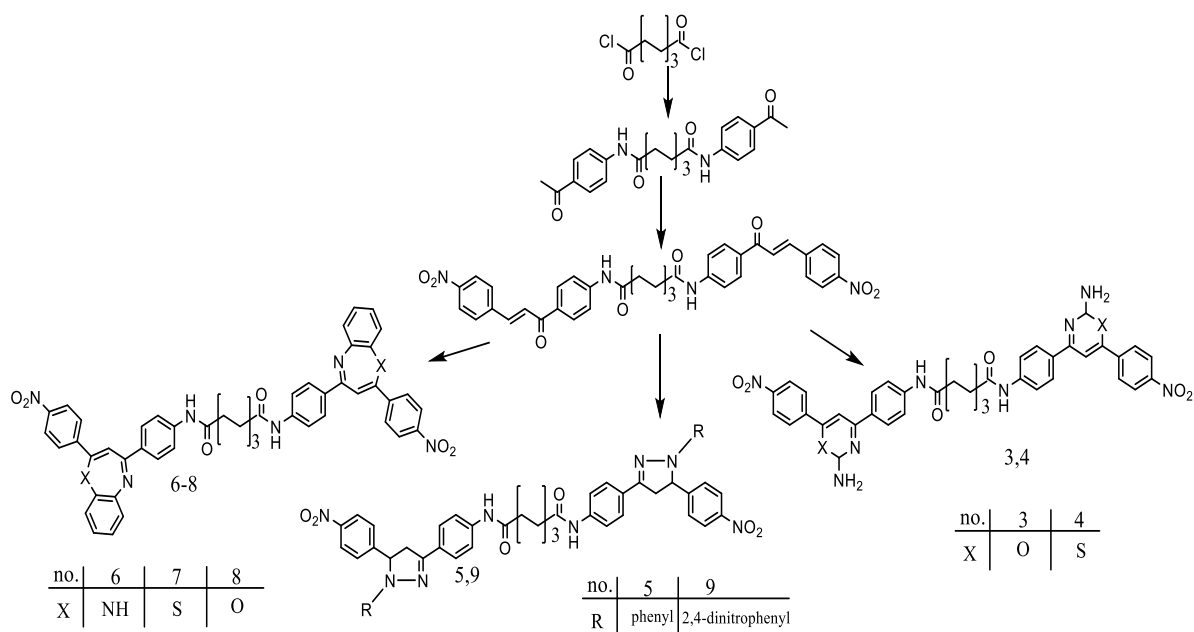
Antimicrobial Evolution

The newly synthesized compounds were selected for their antimicrobial activities against bacteria. The microorganisms used were *Staphylococcus aureus* (Gram positive), *Escherichia coli*, (Gram negative) by using the agar diffusion method to select the most potent compounds. 5 mg of each compound was dissolved in dimethylsulfoxide (DMSO, 1 mL) then complete up to 10 mL with distilled water to give a concentration of 1×10^{-3} M. The bacteria were maintained on Muller hinton agar media, the dishes incubated at 37 °C for 24 hr. The efficiency of the tested compounds was compared to the DMSO, zone of inhibition measured by ruler. [15,16].

3.Result and Dissection

Suberoyl Chloride was a starting material for the synthesis of new chalcone compound over a reaction with (4-amino acetophenone) then react with different amine to prepare different heterocyclic derivatives can be show in scheme [1]. For the prepared derivative **1** the appearance of stretching band of secondary amine (NH) at (3145) and disappearance of C-Cl of Suberoyl chloride at (760) cm^{-1} [17]. In other hand the $^1\text{H-NMR}$ spectrum for aromatic proton multi single at 6.36-7.23 are attributed to aromatic of N^1, N^8 -bis(4-acetylcyclohexa-2,4-dien-1-yl) octanediamide compound. $^{13}\text{C-NMR}$ spectrum appearance 149.6-153.4 attributed to carbonyl of amide group (CO-N-). For the prepared derivative **2** the appearance of stretching band of C=O of Chalcone at (1719) and (1686) cm^{-1} for (CH=CH). In other hand the $^1\text{H-NMR}$ spectrum for aromatic proton multi singles at 6.00-6.05 are attributed to the formation (-CH=CH-) of Chalcone compound. $^{13}\text{C-NMR}$ spectrum appearance 153.9-160.3 attributed to (CO-N-) carbonyl of amide group [19,20]. For the prepared derivative **3** the appearance of stretching band of C=N at (1624) and (1402,1504) cm^{-1} for (NO_2) and (3387,3431) for NH_2 . In other hand the $^1\text{H-NMR}$ spectrum for aromatic proton doublet single at 6.70-8.1 are attributed to the formation aromatic ring and 8.96 to (NH_2) of heterocyclic ring. C-NMR spectrum appearance (O-CH-CH) at 55.1,56.0. For the prepared derivative **4** the appearance of stretching band of C=N at (1641) and (1436,1546) cm^{-1} for (NO_2) and (3390,3423) for NH_2 . In other hand the $^1\text{H-NMR}$ spectrum for aromatic proton duplet single at 6.00-6.05

are attributed to the formation aromatic ring 8.92 to (NH_2) of heterocyclic ring. $^{13}\text{C-NMR}$ spectrum appearance (S-CH-CH) at 67.8-77.5. For the prepared derivative **5** the appearance of stretching band of C=N at (1620) and (1361,1512) cm^{-1} for (NO_2). In other hand the $^1\text{H-NMR}$ spectrum for aromatic proton doublet single at 9.71 (-NH-CO) of heterocyclic ring. C-NMR spectrum appearance (CO-N-) at 157.5 and (N-CH-CH) at 55.1,56.0. For the prepared derivative **6** the appearance of stretching band of C=O_{amide} at (1690) and (1379,1504) cm^{-1} for (NO_2). In other hand the $^1\text{H-NMR}$ spectrum for aromatic proton doublet single at 8.20 for (NH) of heterocyclic ring. $^{13}\text{C-NMR}$ spectrum appearance (N-CH-CH) at 72.2,79.2. For the prepared derivative **7** the appearance of stretching band of C-S at (785) and (1346,1540) cm^{-1} for (NO_2). In other hand the $^1\text{H-NMR}$ spectrum for aromatic proton duplet single at 3.44 (-CH-C=) of heterocyclic ring and 8.92 for (NH_2). $^{13}\text{C-NMR}$ spectrum appearance (S-CH-CH) at 82.9,85.9. For the prepared derivative **8** the appearance of stretching band of C=N at (1668) and (1359,1507) cm^{-1} for (NO_2). In other hand the $^1\text{H-NMR}$ spectrum for aromatic proton doublet single at 3.04 (-CH-C=) of heterocyclic ring and 8.92 for (NH_2). $^{13}\text{C-NMR}$ spectrum appearance (O-CH-CH) at 57.5,67.9. For the prepared derivative **9** the appearance of stretching band of C=N at (1624) and (1356,1543) cm^{-1} for (NO_2). In other hand the $^1\text{H-NMR}$ spectrum for aromatic proton doublet single at 3.04 (-CH-C=) of heterocyclic ring and 8.92 for (NH_2). $^{13}\text{C-NMR}$ spectrum appearance (N-CH-CH) at 80.9,83.4.



scheme [1]: Synthesis Derivatives of Suberoyl Chloride

9	+	+
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(+) Inhibition with diameter (9-6)mm ,

(-)There is no inhibition

Control of microbial population is necessary to prevent show of disease, infection, decomposition, spoilage and contamination and caused by them. The newly synthesized compounds were screened for their antimicrobial activity invitro against bacteria (*Staphylococcus aureus*, *Escherichia coli*) and fungal (*Candida albicans*) as show in Table 1. The antimicrobial activity results discovered that most of the tested compounds have moderate to strong activity. The most effective compounds are **5-9** and moderate **3,4** When these compounds were compared with the reference compounds (DMSO, distill water) we found that they have an antimicrobial activity higher or almost equal to them. While compound **1** and **2** not responsive for (*Staphylococcus aureus*, *Escherichia coli*).

3.1. Biological activity

Control of microbial population is necessary to prevent show of disease, infection, decomposition, spoilage and contamination and caused by them. The newly synthesized compounds were screened for the antimicrobial activity invitro against bacteria (*Staphylococcus aureus* and *Escherichia coli*). **Table 1:**

Zone of inhibition

Compounds	<i>Staphylococcus Aureus</i>	<i>Escherichia Coli</i>
1	-	-
2	-	-
3	+	-
4	+	-
5	+	+
6	+	+
7	+	+
8	+	+

4. Conclusion

In this study we are reported synthesis of many derivatives from Suberoyl Chloride by chalcone as intermediate to prepare different heterocyclic compound. These derivatives were found active against positive and negative bacterial and not response to DMSO. These derivatives

confirmed from spectral data analysis; FT-IR, ¹H-NMR and ¹³C-NMR. **Acknowledgment**

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