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ANTIMICROBIAL SCREENING OF SOME KNOEVENAGEL CONDENSATION POLYENE PRODUCTS DERIVED FROM- TRANS 3-(2-FURYL ACROLINE)

Abdel-Wahab Abdo[1]*, Farouk Kandil[1], Muna.I.Khalaf[3], Ali Nizam Adnan[2]

[1]Chemistry Department, Faculty of Science, Damascus University, Syria.
[2]Plant Biology Department, Faculty of Science, Damascus University, Syria.
[3]PhD Student, Chemistry Department, Faculty of Science, Baghdad University, Iraq.

ABSTRACT

A series of heterocyclic compounds of trans- 3-(2-furyl acroline) derivatives were prepared and screened for their antimicrobial activity against Pseudomonas (sp-local strain), Escherichia coli, as Gram negative bacteria and *Staphylococcus aureus, Treptococcus pneumonia* and *Klebsila pneumonia*, as Gram-positive bacteria(the strains isolated from the children hospital in Damascus).These compounds were identified by their melting points, Infrared, Ultraviolate, Nuclear magnetic resonance spectra and CHN analysis.

Keywords: Knoevenagel condensation, Trans 3-(2-furyl acroline), Antimicrobial activity.

INTRODUCTION

One of the most important properties of knovenagel condensation from a synthetic perspective is that they offer a rout to the formation of C=C bond, by which the arylidene compounds are obtained from carbonyl compounds and active methylene compounds [1-3], in the presence of basic catalyst or Lewis acid catalyst, such as piperedine , diethyl amine , or corresponding ammonium salt [4-8]. In recent years there has been a growing interest in knoevenagel condensation products because many of them have significant biological activity [9-13], this reaction has been widely used in organic synthesis to prepare Polyenes, which are poly-unsaturated organic compounds that contain one or more sequences of 2 alternating double and single carbon-carbon bonds. Organic compounds with two carbon-carbon double bonds are dienes, Many fatty acids are polyenes, and many dyes contain linear polyenes. Other examples of polyene compounds include beta -carotine, which is yellow to orange colored depending on concentration, and polyene antimycotics agent, some of which Amphotericin B, nystatin, and pimaricin (polyene antifungal drugs) [14-16], some of which like Amphotericin B are yellow coloured [17]. The aim of this work is the preparation of some new five, six –member nitrogen heterocyclic derivatives of furyl acroline as potentially useful intermediates in synthesis, study of their structures physical and chemical properties. as well as motivated by the aforementioned biological and pharmacological importance of the title compounds, we wish to report herein the expectation that the synthesized products will be of significant biological activity.

Experimental Products were characterized by UV spectrophotometer (Table 1),

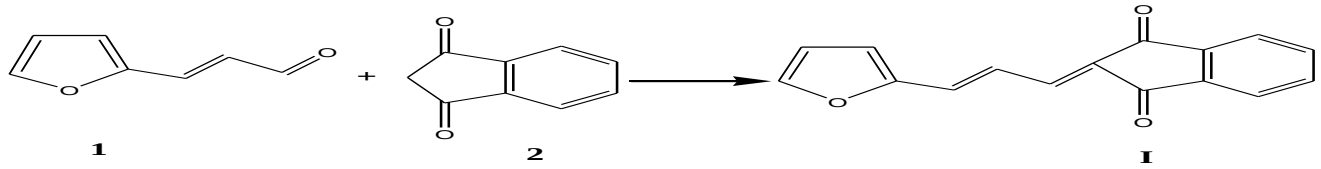
1H-NMR Spectra (Table 2) and IR spectra (Tables 3). The melting points were determined on a Kofler Block apparatus and are uncorrected. Infrared spectra were recorded in 400 - 4000 cm-1 region by a Specord FT-IR Jusco 300 spectrometer using KBr tablet.
1H- NMR Spectra were measured on ambient Broker DT-400 MHz spectrometer in deuterated DMSO and CDCl3, and UV-visible were determined with Shimadzu 190 A spectrometer.CHN analysis were determined on

Corresponding Author: - **Abdel-Wahab Abdo** Email: abdulwahababdo60@yahoo.com

Elementer-vario Micro-CUBE. The magnetic stirrer and the other necessary laboratory equipments used. All fine chemicals and reagents were purchased from Aldrich chemical Co. U.S.A. and microbial activity were done in the plant biology department laboratories.

Synthesis of: I 2-(3-F uran-2-y l-ally lidene)-indan-1,3-dione

A mixture of trans 3-(2-furyl acroline) (5 mmol)(1), Indan-1,3-dione (2) (5 mmol) in ethanol (10 cm3) , was stirred with simple heating until the solid was dissolved then stirred at room temperature for the time given in Table(1). The orange solid precipitate was filtered. The product (I) was recrystallized from ethanol (yield 62%).

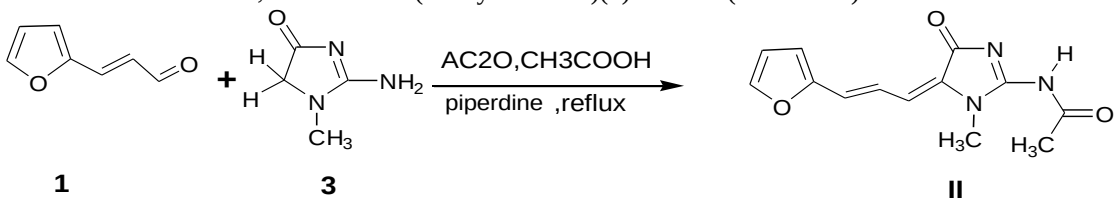


1 2 I

2-(3-Furan-2-yl-allylidene)-indan-1,3-dione

Synthesis of: II: N-[5-(3-Furan-2-yl-allylidine)-1-methyl-4-oxo-4,5-dihydro-1H-imidazol-2-yl]-acetamide

In a round bottom flask (50ml), was put (5 mmol),of creatinine (3) with dry acetic anhydride (5cm3) and (10cm3) acetic acid, the solution stirred with heating until the solid dissolved, then trans 3-(2-furyl acroline)(1) (5 mmol), a catalytic amount of piperidine (5 drops) was added, stirred and refluxed for the time given in Table(1). The solution was cold and greenish yellow solid precipitate was filtered and washed with a little amount of acetic acid. The product (II) was recrystallized from DMF. (Yield 78%).



1 3 II

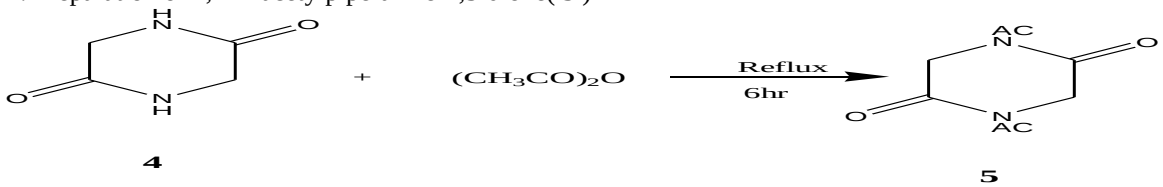
N-[5-(3-Furan-2-yl-allylidene)-1-methyl-4-oxo-4,5-dihydro-1*H*-imidazol-2-yl]-acetamide

Synthesis of: III:

1-Acety l-3-(3-furan-2-y l-ally lidene)-piperazine-2,5-dione

A: Preparation of 1,4-Diacetylpiperazine-2,5-dione(5)

1,4-Diacetylpiperazine-2,5-dione(5)was prepared by treating compound(4)with Acetic anhydride under reflux for 6hr [18].

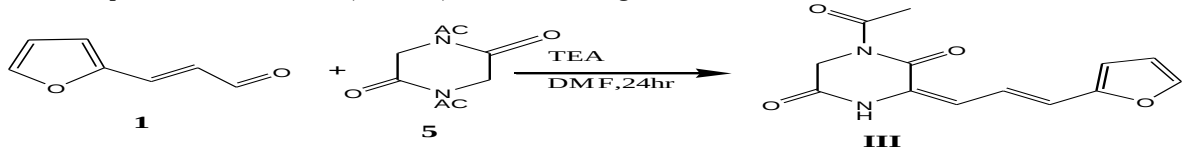


4 5

B: Preparation of compound (III)

A mixture of 1,4-diacetylpiperazine-2,5-dione 5 (0.001 mole), the appropriate aldehyde (0.001 mole) and triethylamine (0.001 mole) ,in 5 ml DMF was stirred at room temperature for 12 Hrs (Table 1). The resulting orange precipitate was filtered off and washed with water.

Recrystallization from ethanol gave the pure monosubstituted derivative III. (Yield 75%).



1 5 III

1-Acetyl-3-(3-furan-2-yl-allylidene)-piperazine-2,5-dione

RESULTS AND DISCUSSION

A three knoevenagel products (I,II,III) were obtained by condensations of some-active methylene heterocyclic compounds with (trans 3-(2-furyl acroline) in the chosen solvent, in normal conditions. All condensation products are stable solid compounds, rather

insoluble in common solvents, with high melting points. (Table 1). 1H-NMR spectra, indicate disappearance of proton signals for the (methylene and aldehyde groups) of the compounds(1 , 2, 3)at δ (4 ,10) ppm ,and appearance of a protons 5 of olefins (H-α,β,γ-protons) and(furan ring)at(6.4-8.6)ppm for all prepared compounds. Also 1H-NMR spectral analysis shows proton signals of NH group at δ (10.76,10.61) ppm for compounds II,III respectively ,where compound III appears to saved a signal at δ (4.316) ppm belongs to methylene group as expected to be mono substituted product .as it shown in (Table 2).example structure IV.

The resonance signals and their multiplicity confirmed the proposed structures. The infrared spectra of the prepared compounds I-III showed strong absorption bands of the C=C and C=O stretching vibrations in two very well distinguished regions 1620 - 1624 cm-¹ and 1698 - 1733 cm-¹ (Table 2). The absorption bands in the lower region of the spectra (1400-1600) cm-¹ belong to the (C=C) of the furan ring and aromatic ring. The higher region of spectrum was attributed to the heterocyclic part (-NH) of the compounds II, III. The compound I showed the (C=C) band at 1620 cm-¹ Strong band due to the presence of withdrawing effect diketo group and its conjugation effect with C=C formed (Table 3) .UV spectra showed red-shift phenomena for all prepared compounds attributed to furan ring as conjugation bridge with formed C=C bond[18] (table1).

Antibacterial studies

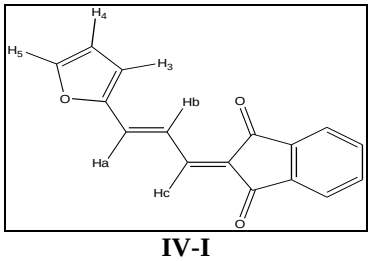
Condensation products of some active methylene compound with furan-derivatives, (Rabarova et al, Lacova et al [19,20] found to possess antimicrobial activity. Compounds I, II, and III, were tested invitro against Pseudomonas (sp-local strain), Escherichia coli as Gram-negative bacteria and Staphylococcus aureus,Streptococcus pneumonia and Klebsilla pneumonia , as Gram-positive bacteria(the strains isolated from the children hospital in Damascus). Nutrient agar plates were seeded using 0.1 of overnight cultures. Cylindrical plugs were removed from the agar plates using a sterile cork borer and 100 µL of the tested compound (50µg/ml, 100µg/mlEtOH) were added to the well in triplicates. Blank solvent was used as control. Plates inoculated with tested bacteria were incubated at 37˚c, while those of Fungi were incubated at30˚c. Results were taken after 24 h of incubation and were recorded as average diameter of inhibition zone in mm.

All the newly synthesized compounds were subjected to antimicrobial screening by in vitro Cup plate technique [21], using positive controls Nystatine. Compounds I, III showed remarkable activity towards the gram positive bacteria *Staphylococcus* and gram negative Pseudomonas where E.Coli not yet effect with thiscomps while compound II(100µg) appear to have remarkable activity towards E.Coli. The Gram positive bacteria Streptococcus pneumonia proved to be sensitive toward compound III(50µg).

All prepared Compounds showed very good activity toward the tested strains Klebsilla pneumonia, Compound I proved to be the most active broad spectrum antimicrobial agents in this study (Table 4). In conclusion this study revealed that the heterocyclic system bearing furan ring moiety could be useful as template for future, development through modification or derivatization to design a more potent antimicrobial agents.

Table 1. Characterization of the prepared compounds

Comps	*M*r. Formula	M.P.°C	Yield %	*T*ime, min or (hr)	λ_{max} ,nm	Calculated% C H N O	Found% C H N O
I	$C_{16}H_{10}O_3$ 250.25	179-180	62	45mn	442	76.79 , 4.03, - , 19.18	77.12, 4.23, - ,18.65
II	$C_{13}H_{13}N_3O_3$ 259.26	279-280	78	30mn	428	60.22, 5.05, 16.21, 18.51	60.55, 5.06,16.25,18.14
III	$C_{13}H_{12}N_2O_4$ 260.25	284-285	75	12 hr	411	60.0, 4.65, 10.76, 24.59	60.22,4.75,10.88,24.24



IV-I

Table 2. ^{1}H NMR spectra data of prepared compounds I-III

COMPS.	SOLVENT	^{1}H NMR spectrum (ppm)	Fig
I	$CDCl_3$	δ ;6. 5-6.7 (dd,1H, H-4);6.80-6.81 (d, 1H, H-a);7.0-7.13(d,1H-Hc);7.5-7.62(m,2H,H5,H3) ,7.77-7.99(m,4H,Ar) ,8.2(t,1H,Hb)	1
II	$CDCl_3$	δ ;2.25(S,3H-CH3CO),3.31 (S, 3H, CH_3N); 6.24-6.271 (d, 1H, Ha); 6,46,6.47(d, 1H,H-4); 6.52-6.53(1H,d H-c);6.65-7.4(m,2H,H5,H3),7.99-8.05(t,1H,Hb);10.76(s,1H,NH).	2
III	DMSO	δ ; 2.85(s, 3H, CH_3O)4.31(s, 2H, CH_2-)6.41 (d, 1H, H4); 6.53 (d, 1H, H-a); 6.7 (d, 1H, Hc); 7.22-7.29(t,1H.HB):7.39-7.49 (m,2H,H3,H5);10.61 (s, 1H, NH).	3

Table 3. IR spectral data of synthesized compounds I-III

	v (cm-1)			
Comps.	*v* NH	*v* C=O heterocyclic	*v* C=C furan	*v* C=C
I	-	1733	1463,1492,1575	1620
II	3227	1727	1448,1480,1571	1623
III	3275	1698	1415-1484,1558	1627

Table 4: Antimicrobial screening results of the tested compounds at (50,100) µg /ml concentration.

No	Conc	E.coli	Strep.pneumonia	K.pneumoni	S.aureus	Pseudomons (sp)
I	50µg	-	-	++	+++	++
	100 µg	-	-	+	+++	+++
II	50µg	-	-	+	++	++
	100 µg	++	-	++	++	++
III	50µg	-	++	++	+++	++
	100 µg	-	-	++	++	+++
Nystatin	50µg	+	-	+	-	++
	100 µg	+	-	-	+++	++

Fig 1. ^{1}H NMR spectra of compound I

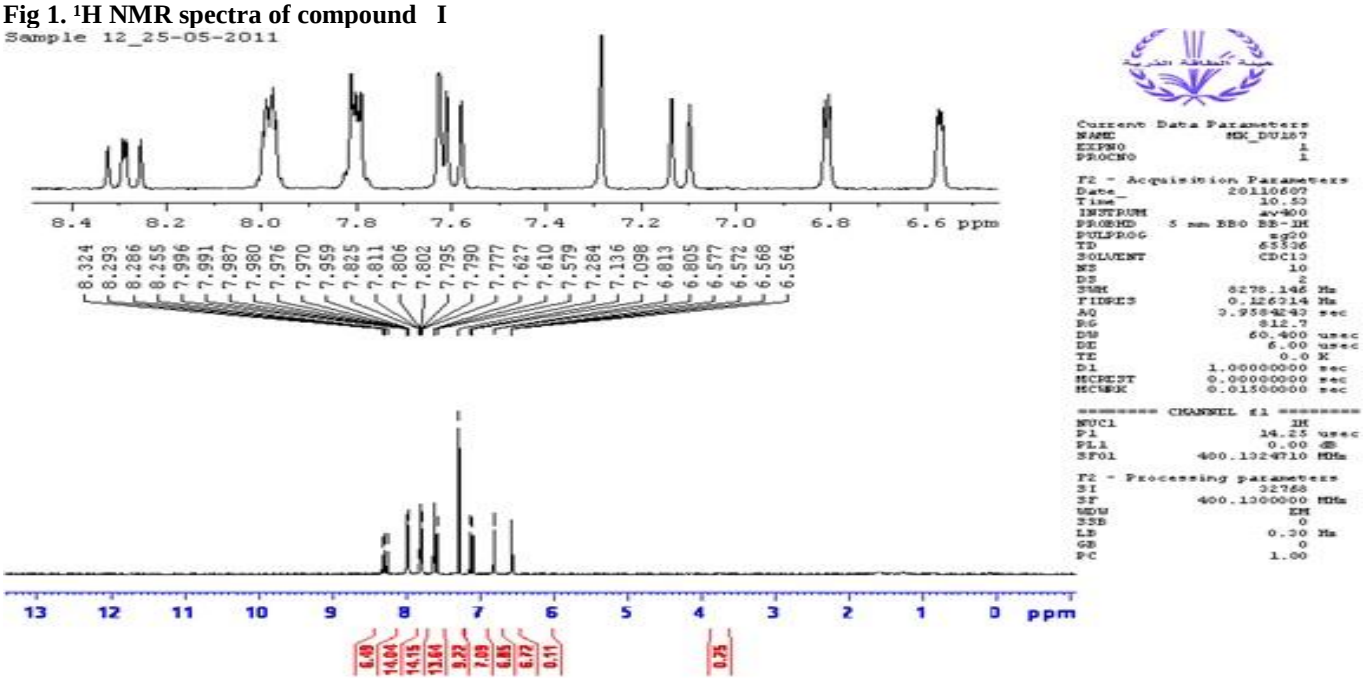


Fig 2. ^{1}H NMR spectra of compound II

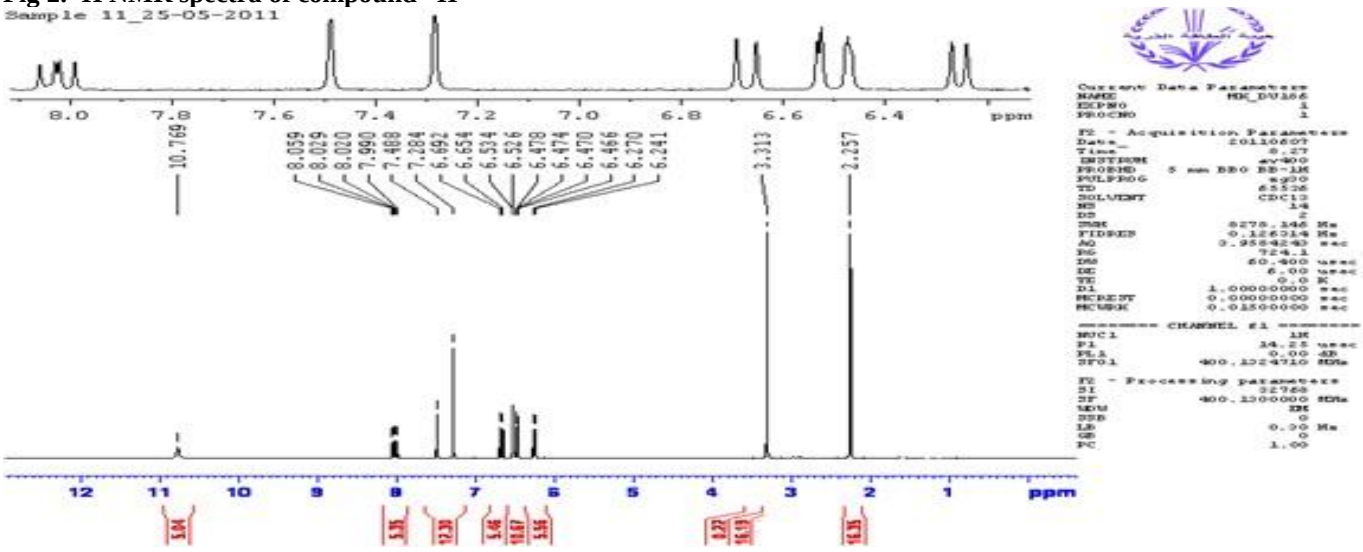
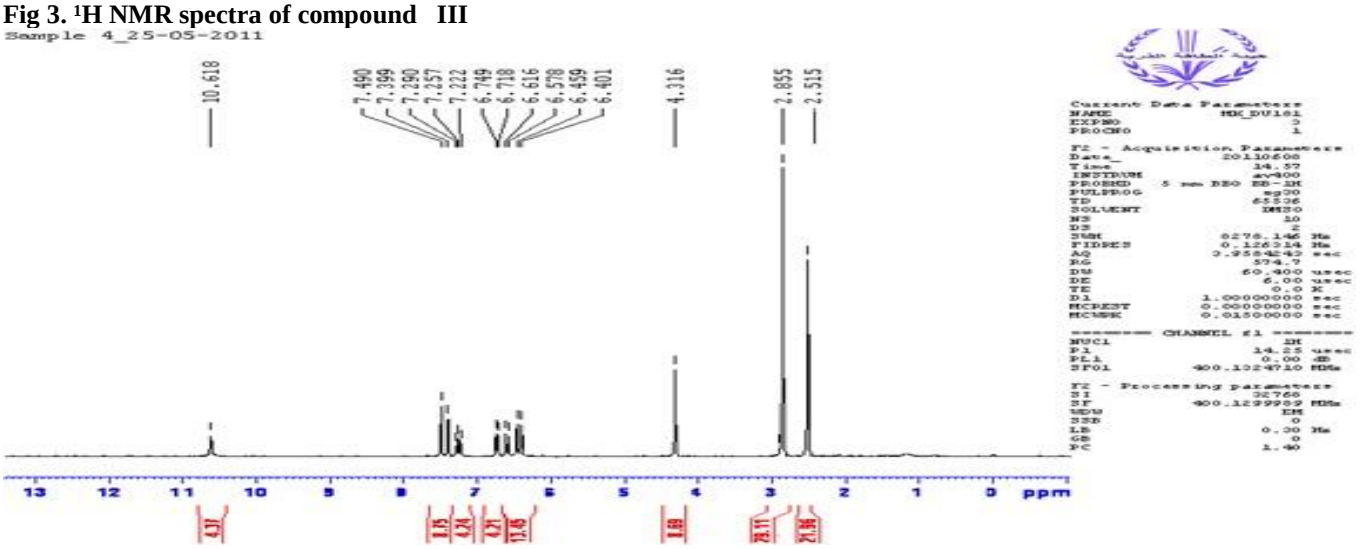


Fig 3. ^{1}H NMR spectra of compound III



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