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Knoevenagel condensation of some 5-substituted furan-2-carboxaldehyde with creatinine and their antimicrobial Screening

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Abstract: A series of heterocyclic compounds of 5-(5-R-furfurylidene)- creatinine were prepared and screened for their antimicrobial activity, these compounds were identified by their melting points, Infrared,Ultraviolate, and Nuclear magnetic resonance spectra.
Key wards: Knoevenagel condensation, furfurylidene creatinine.

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 cumarins and its derivatives, which are important intermediates in the preparation of cosmetics , perfumes, and pharmaceuticals [14,15]. Furfural and its 5-substituted derivatives were chosen as being synthetically versatile molecules with a reactive carbonyl group they have considerable significance for their biological activities [16-19], and for their reactivity toward Nucleophiles which allows the synthesis of a wide variety of heterocyclic such as nifuroxazide (NF) (condensation of 5-nitro furfural with p-hydroxy benzhydrazide) [20], which is used for the treatment of acute bacterial diarrhea [21]. The aim of this work is the preparation of some new five –member nitrogen heterocyclic derivatives of furfural 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**) ,^{1}H-NMR Spectra (Table 3) and IR spectra (Tables 4) ,CHN analysis (Table 2). The melting points were determined on a Kofler Block apparatus and are uncorrected. Infrared spectra of nujol suspensions were recorded in 400 - 4000 cm-1 region by a Specord FT-IR Jusco 300 spectrometer using KBr tablet. ^{1}H- NMR Spectra were measured on ambient Broker DT-400 MHz spectrometer in deuterated DMSO and $CDCl_3$, and UV-visible were determined with Shimadzu 190 A spectrometer, CHN analysis were determined on Elementer-vario Micro-CUBE. The magnetic stirrer and the other necessary laboratory equipments used and microbial activity were done in the plant biology laboratory.

Synthesis of 3a-3d

In a round bottom flask (50ml), put (5 mmol),of creatinine (**2**) with dry acetic anhydride (5cm3) and (10cm3) aceticacid, the solution stirred with heating until the solid dissolved, then 5-R-furafural (**1a-1d**) (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 solid precipitate was filtered washed with a little amount of acetic acid. The products were recrystallized from ethanol or acetic acid.

Table 1. Characterization of the prepared compounds

Comps.	**R**	***M*r. Formula**	**m.p. °C**	**Yield %**	***T*ime, min or (hr)**	**λ_{max} ,nm**
3a	H	$C_{11}H_{11}N_3O_3$ 233.22	248 dec.	80	45 min	366,410
3b	C_2H_5	$C_{13}H_{15}N_3O_3$ 261.28	175-176	55	10min	393,412
3c	I	$C_{11}H_{10}N_3IO_3$ 359.12	226-227	73	1.5hr	330,410
3d	Cl	$C_{11}H_{10}N_3ClO_3$ 267.67	194-196	60	1hr	390,410

Table 2. **CHN analysis of prepared compounds**

ComPs.	**Calculated%**				**Founded%**			
	C	**H**	**N**	**O**	**C**	**H**	**N**	**O**
3a	56.59	4.72	18.00	20.68	56.77	4.32	17.97	20.94
3b	59.58	5.72	16.04	18.66	59.81	5.56	16.01	18.62
3c	36.79	2.81	11.07	13.37	36.97	2.65	10.92	13.28
3d	49.36	3.77	15.70	17.93	49.61	3.37	15.62	17.79

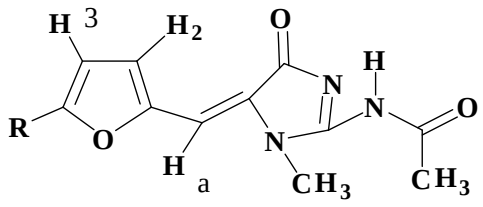


Table 3. ^{1}H NMR spectra data of prepared compounds.

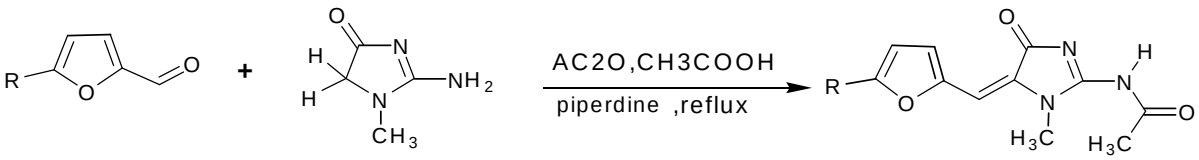
COMPS.	SOLVENT	^{1}H NMR spectrum (ppm)	Figs.
3a	**$CDCl_3$**	**δ ;2.25 (s, 3H, $COCH_3$),3.36 (s, 3H, CH_3-N),6.25-6.36 (d d,1H, H-3);6.44 (s, 1H, H-a);7.5(dd,1H-H5);7.9 (d,1H,H2) 10.84 (s, 1H, NH-broad).**	**FIG.1**
3b	**$CDCl_3$**	**δ ;1.24(t,3H-CH_3-C_2H_5),2.69 (q, 2H, CH_2);2.25(s,3H CH_3CO) 3.35 (s, 3H, CH_3-N); 6.41 (s, 1H, Ha); 6,21(d, 1H,H-3); 6.76(1H,d H-2);10.86(s,1H,NH).**	**FIG2**
3c	**$CDCl_3$**	**δ ; 2.26(s, 3H, CH_3O)3.34(s, 3H, CH_3-N), 6.41 (S, 1H,Ha); 6.73 (d, 1H, H-3); 7.82 (d, 1H, H-2); 10.84 (s, 1H, NH).**	**FIG3**
3d	**$CDCl_3$**	**δ ;2.26 (s, 3H, $COCH_3$); 3.34 (s, 3H, CH_3-N); 6.42 (s, 1H, H-a); 6.53 (d, 1H, H-3),7.9(d , 1H,H-2) 10.9 (s, 1H, NH-br).**	**FIG4**

Table 4. IR spectral data of synthesized compounds 3a-d

	***v* (cm-1)**			
Comps.	***v* NH**	***v* C=O heterocyclic**	***v* C=C furan**	***v* C=C**
3a	**3316**	**1733**	**1463,1492,1575**	**1632**
3b	**3198**	**1758**	**1483-1515**	**1640**
3c	**3216**	**1731**	**1475,1513,1573**	**1624**
3d	**3299**	**1739**	**1455,1563**	**1631**

Results and Discussion

2-Acetamido-1-methyl-5-(5-R-furfurylidene) imidazol-4-ones (**3a-3d**) were obtained by condensations of (1a-1d)with creatinine (2) in acetic anhydride, and acetic acid and piperidineas catalyst, in normal conditions. The yields of prepared compounds were (55-80%).



Where R =a:H ,b: C_2H_5 ,c:I ,d :Cl

In the ^{1}H- NMR spectra of compounds, no proton signals for the(methylene and aldehyde groups) of the compounds (1 and 2) were observed at (4,10) ppm chemical shifts, also the data show signals at (6.40-6.44) ppm low field belong to α-proton for all prepared compounds, the data show low field chemical shift value(6.2-7.9) ppm with 3c,3d attributed to (H-2,H-3) protons, and less value(6.1-6.68)ppm high field with 3b compounds as expected (**Table 2).**All condensation products are stable solid compounds, rather insoluble in common solvents, with high melting points. The resonance signals and their multiplicity confirmed the proposed structures. The infrared spectra of the prepared compounds 3a-3d showed strong absorption bands of the C=C and C=O stretching vibrations in two very well distinguished regions 1620 - 1668 cm-¹ and 1730 - 1755 cm-¹ (Table 2). The absorption bands in the lower region of the spectra (1500-1600) cm-¹ belong to the (C=C) of the furan ring. The higher region of spectrum was attributed to the heterocyclic part (-NH) of the prepared compounds. The compound 3c showed the (C=C) band at 1619 cm-¹ Strong band due to the presence of withdrawing effect iodo group and its conjugation effect with furan ring (**Table 3)** .UV spectra showed red-shift phenomena for all prepared compounds attributed to furan ring as the conjugated with formed C=C bond (**table1).**

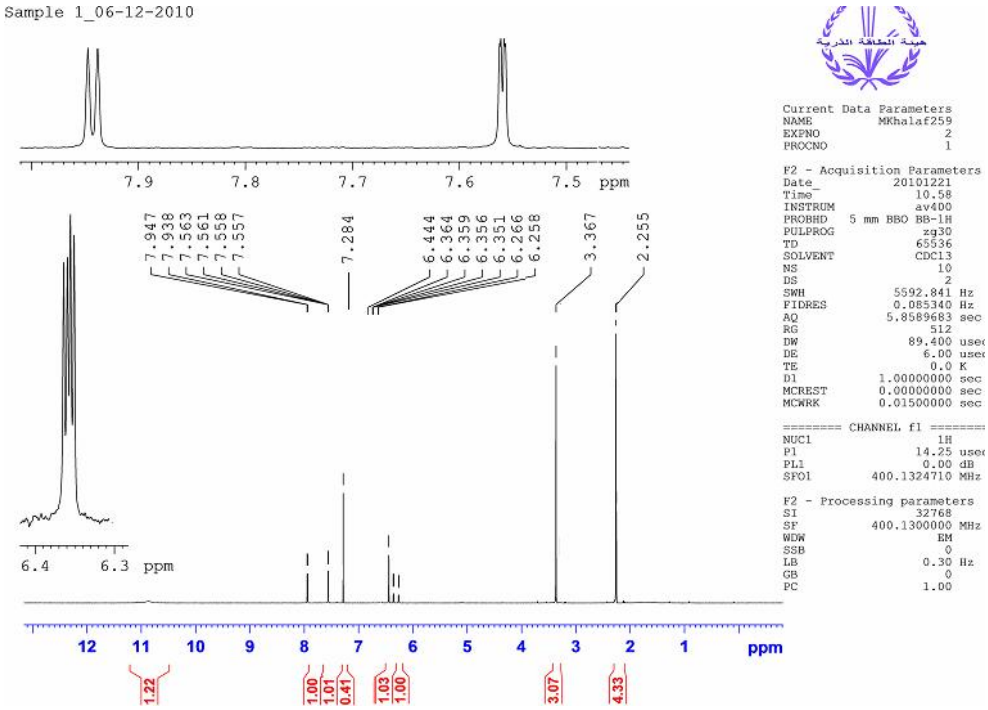


FIG.1: ^{1}H NMR spectra of compound 3a

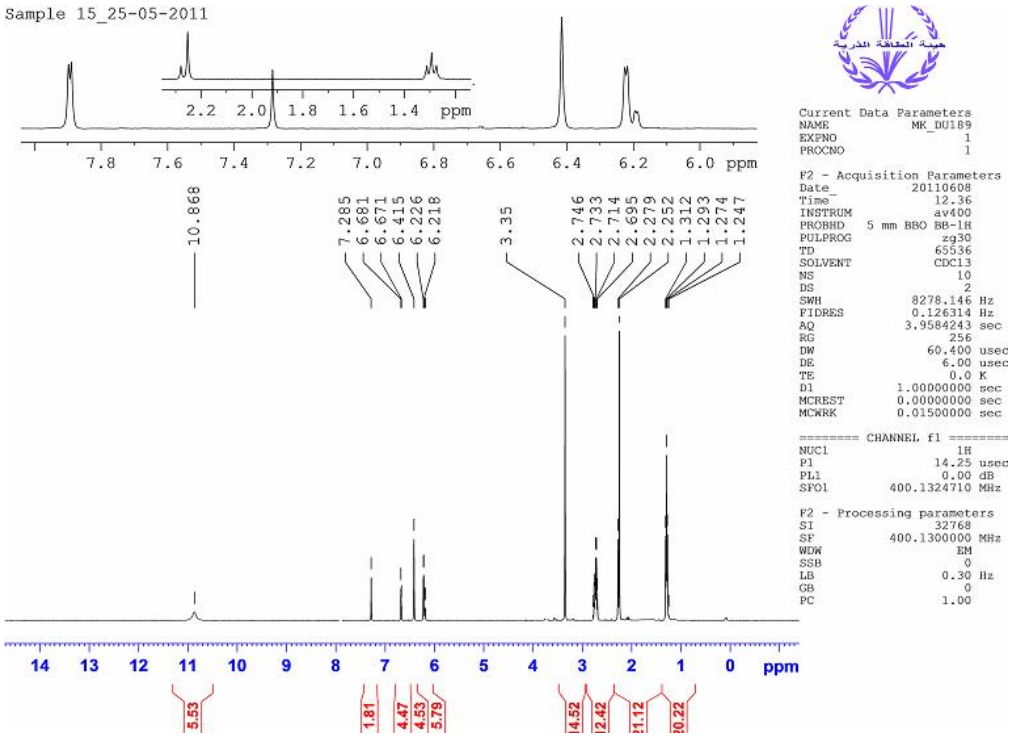


FIG.2: ^{1}H NMR spectra of compound 3b

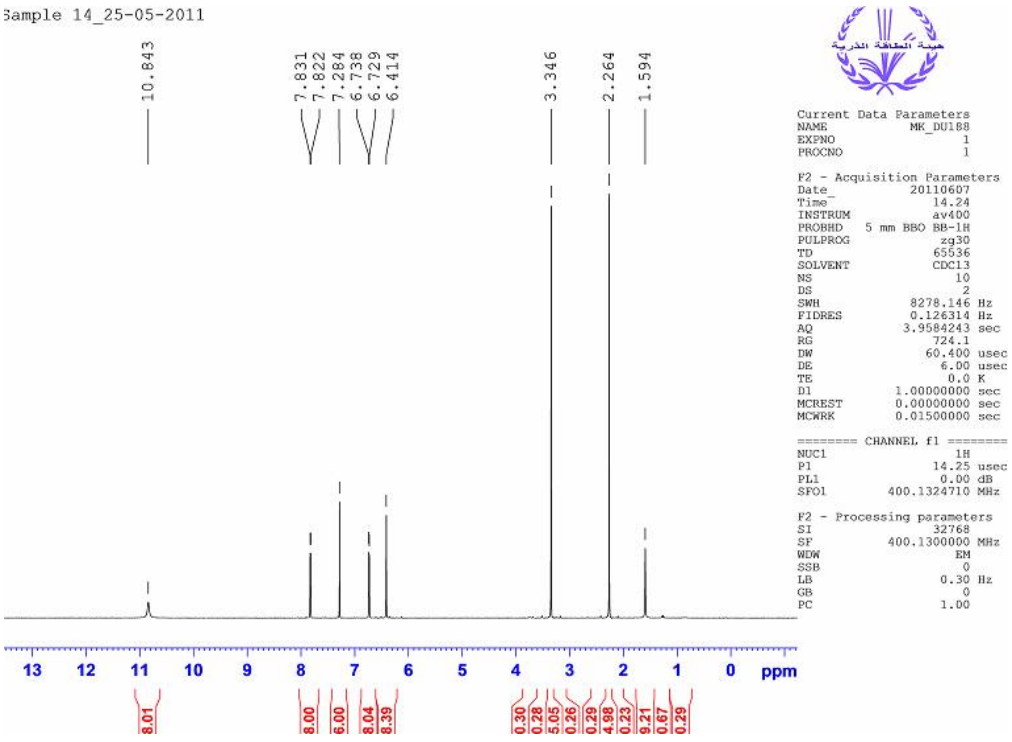


FIG.3: ^{1}H NMR spectra of compound 3c

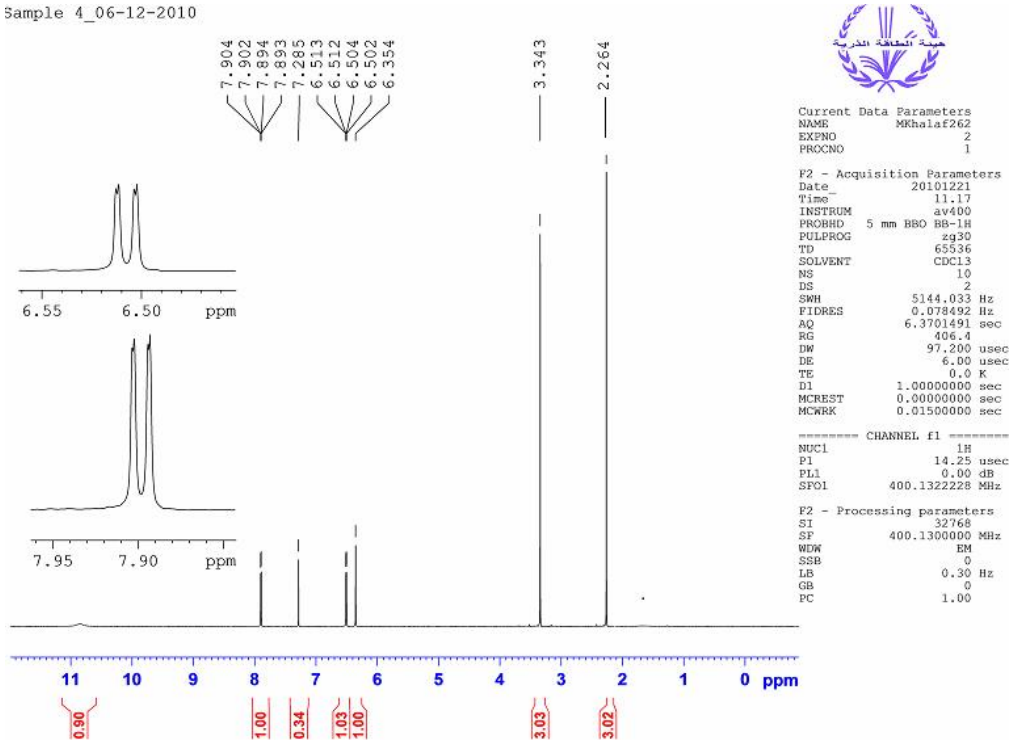


FIG.4: ^{1}H NMR spectra of compound 3d

Antibacterial studies:-

Condensation products of some active methylene compounds with furan-2-carboxaldehydes or their 5-sustituted derivatives (Rabarova *et al*., 2004; Lacova *et al.* 2000, [16,17]) found to Possess antimicrobial activity**.** Compounds 3a ,3b, 3c ,and 3d were tested in vitro against Pseudomonas aeruginosa, Escherichia coli, as Gram-negative bacteria and Staphylococcus aureus,Serratia,Enterobacter,Acetobacter, 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 (1mg/mlDMSO) 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 ofinhibition zone in mm.

All the newly synthesized compounds were subjected to antimicrobial screening by in vitro cupplate technique((Mahamoud *etal.* 2011(21)),withaout using any positive controls. Compounds **3a**,**3c**, showed remarkable activity towards the gram positive bacteria Staphylococcus where Enterobacter not yet effect with any compoundes . The Gram negative bacteria Pseudomonas aeruginosa, Escherichia proved to be sensitive toward compounds **3a**, **3d**,

Compounds **3a,3b** showed very weak activity toward the tested strains Acetobacter and **3d** toward staphylococcus.

This study (Table 5),in conclusion revealed that the heterocyclic system bearing either furfural or creatinine moieties could be useful as template for future,development through modification or derivatization to design a more potent antimicrobial agents.

Table 5: Antimicrobial screening results of the tested compounds at 1mg/ml concentration.

No	Comps.	E.coli	S.aureus	Serratia	Eenterobacter,	Pseudomons	Acetobacter
1[3]	3a	5	6	6	4	-	2
2	3b	4	4	5	4	4	2
3	3d	5	2	-	-	5	4
4	3c	4	6	3	4	-	-

[3]; published previously without screening activity.
Note:(-) inactive.
the largest note: activity not large as we expected.
(increasing the concentration or replace solvent may increase activity).

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