Synthesis and Characterization of New Conjugated Systems Derived from Piperazine-2,5-dione with antimicrobial screening

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Abstract:

The preparation of monoarylidene and unsymmetrical bisarylidene derivatives of 2,5- Piperazine dione is described. The use of 1,4-diacetylpiperazine٢,٥-dione make it possible to prepare unsymmetrical bisarylidenes.

Antibacterial activity of the prepared new compounds against five types of bacteria were evaluated and the results showed that the new compounds exhibit good to moderate antibacterial activity.

Keywords: Piperazine-2,5-dione, arylidene, bisarylidene, cyclic dipeptides, unsymmetrical

تحضير وتشخيص أنظمة متبادلة جديدة مشتقة من جزئي ٢,٥- ببرازين دايون واختبار الفعالية الميكروبية لها

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الخلاصة:

تم في هذا البحث الحصول على مشتقات جديدة من جزيئة 2,5- ببرازين دايون احادية التعويض وغير متناظرة عن طريق استلته ثم مفاعلته مع الفورفورال اولا للحصول على المشتق الاحادي التعويض .بعدها مفاعلة المشتق الاحادي التعويض مع الديهايدات اروماتية مختلفة للحصول على نظام حلقي متبادل .تم اختبار الفعالية الميكروبية للمركبات المحضرة مع خمس انواع من البكتريا وقد اظهر الاختبار نتائج اولية جيدة .

الكلمات المفتاحية:- ٢,٥ – ببرازين دايون ، الفورفورال ، نظام حلقي متبادل ،متناظر وغير متناظر

Introduction:

piperazines and their derivatives have been known for more than a century, only recently have 2,5- diketopiperazines attracted attention due to their biological properties.Thepiperazine-2,5-dione moiety occurs in a variety of drugs and natural products which span a wide spectrum of biological activities, *e.g.*, roquefortine,[1,2]bicyclomycin[3] dipodazine[4] neihumicin[5] phomamide[6] and dihydrodysamideC[7] Additionally, this heterocyclic system has found unique applications as an acceptor for organic anions or metal cations[8] and in material sciences[9] The chemistry of piperazine-2,5- dione attrate great interest, Recent studies showed that 3-salicylidenepiperazine-2,5-dione was sup- posed to be the most promising precursor for the synthesis of spiro[benzofuran-2(3H)-2'-piperzine]-
3',6'-dione as a main skeleton of aspirochlorine [10-11]. 2,5-diketopiperazines (DKPs, also known as cyclic dipeptides, 2,5-dioxopiperazines, cyclo(dipeptides), or anhydride dipeptides) are the small- est cyclopeptides. These peptides are most commonly found as natural products [12], showing antimicrobial [13], antitumoral and antiviral [14], cytotoxic [15], and neuroprotective effects [16], amongother activities. Some DKPs are stable to proteolysis (enzymatic degradation), an important feature for their high activity. All these properties make DKPs an interesting group of molecules for the development of new therapeutic agents. This paper deals with the synthesis of mono- and bisarylidene(unsymmetric)derivative

Expermental

Products were characterized by UV spectrophotometer (Table 1), ^{1}H-NMR Spectra (Table 2) and IR spectra (Tables 3). The melting points were determined on a Kofler Block apparatus and are un- corrected. Infrared spectra were recorded in 400 - 4000 cm^{-1} region by a Specord FT-IR Jusco 300
spectrometer using KBr disk. ^{1}H- NMR Spectra were measured on ambient Bruker DT-400 MHz spectrometer in deuterated $CDCl_3$, and UV-visible were determined with Shimadz190Aspectrometer. CHN analysis were determined on Elementer-vario Micro-CUBE. The magnetic stirrer and the other necessary laboratory equipment used. All fine chemicals and, reagents were purchased from Aldrich chemical Co. U.S.A. and microbial activity were done in the biology department la- boratories.

Synthesis of compound (II): 1, 4-Diacetylpiperazine-2, 5-Dione**:**

1,4-Diacetylpiperazine-2,5-dione(**II)**was prepared by treating compound(**I)** with Acetic anhydride under reflux for 6 hr. [17].

Synthesis of: III:

A mixture of 1,4-diacetylpiperazine-2,5-dione(**II)** (0.001 mole), furylaldehyde(**I**) (0.001 mole) and triethylamine (0.001 mole) ,in 5 ml DMF was stirred at room temperature for 12 hrs.(Table 1) The resulting yellow precipitate was filtered off and washed with water. Recrystallization from ethanol gave the pure monosubstituted derivative **III.** (Yield 75%),[18].

Synthesis of: IV, V, VI:

General procedure for the preparation of unsymmetrical bisarylidenes:

A solution of 1-acetyl-3-(3-furylmethylidene) piperazine-2, 5-dione **III** (0.01 moles), an aldehyde(Salicyldehyde ,anisaldehyde ,2,4-dihydroxybenzaldehyde) (0.01 moles) and triethylamine (0.01 moles) in DMF (25 ml) was stirred at 25ºC for 24 hrs. The precipitate was filtered off and washed with water and a small amount of cooled ethanol (10 ml). The pure samples were obtained after recrystallization from dimethyl formamide (see Tables 1 & 2).

Table 1.physcal properties, CHN analysis

Found% C H N	Calculated% C H N	λ_{max} ,nm	Time, (hr.)	Yield %	M.P C^0	Mr. Formula	Comp.
56.42,4.23,11.50	56.41; 4.30; 11.96	335	12	78	178-179	$C_{11}H_{10}N_2O_4$ 234.35	III
64.45, 4.16,9.35	64.86; 4.08; 9.46	411	24	68	279-280	$C_{16}H_{12}N_2O_4$ 296.36	IV
66.02,4.35,8.98	65.80; 4.55; 9.03	428	24	72	284-285	$C_{17}H_{14}N_2O_4$ 310.39	V
61,90,3.62,9.03	61.54; 3.87; 8.97	445	24	75	191-193	$C_{16}H_{21}N_2O_5$ 312.36	VI

Results and Discussion:

A four knoevenagel products(**III**,**IV,V,VI**) were obtained by condensation of active methylene heterocyclic compound Piperazine 2,5-dione with(some aryl aldehydes) 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).

^{1}H-NMR spectra of the compounds(**IV, V, VI)** , indicate disappearance of proton signals for the(methylene,and aldehyde groups) of the compounds(**IV, V, VI)**)at **δ** (4 ,10) ppm ,and appearance of a protons of olefins (H-α- protons) and(aromatic ring)at(6.4-8.6)ppm for all prepared compounds. Also^{1}H-NMR spectral analysis shows proton signals of NH group at **δ** (10.76, 10.61) ppm for all compounds except **III** at 9.1 ppm, where compound **III** appears to save a signal at **δ** (4.316)ppm belongs to methylene group as expected to be mono substituted product . While disappearance of this signal in spectra of the IV ,V , VI compounds (indicate unsymmetrical di substituted) aret shown in (Table 2)**.**

The resonance signals and their multiplicity confirmed the proposed structures, while study of this data (H-NMR) enable us to expected the configuration stereo structure (Z-S-Trans of com- pound III and (Z, Z^{-}-S, S^{-} -Trans) of IV,V,VI ,compounds fig.7,8.[18]

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

^{1}H NMR spectra (ppm)	SOLVENT	COMPS.
δ ;1.7 (S,3H, $COCH_3$);4.50 (S, 2H, CH_2);6.65.0-7.83(m,3H-Furan); ,7.82 (S,1H,=CH) ,9.12(S,1H,NH)	$CDCl_3$	III
δ ; 6.54-7.87 (m, 7H, Ar, Furan); 6,46 (S, 1H,=CH); 6.7(S,1H,=CH);10.76(S,2H,NH).	$CDCl_3$	IV
δ ; 1.45(S, 3H, CH_3O) 6.51-7.82 (m, 7H,Ar,Furan); 6.53,6.7 (S, 2H, =CH);10.61 (S, 2H, NH).	$CDCl_3$	V
δ ; 6.14-7.81 (m, 7H, Ar ,Furan); 6,56 (S, 1H,=CH); 6.79 (S,1H,=CH);10.76(S,2H,NH).	$CDCl_3$	IV

Where the infrared spectra of the prepared compounds III,IV,V,VI 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. (Table 3) .UV spectra showed red-shift phenomena for all prepared compounds attributed to furan ring as conjugation bridge with formed C=C bond [19] (table-1).

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

	v **(cm-1)**				
other	***v*** **C=C** ***olefenc***	***v*** **C=C Ar, furan**	***v*** **C=O heterocyclic**	***v*** **NH**	**Comps.**
	1625	**1463,1492,1575**	**1700**	**3218**	**III**
3380- OH	**1627**	**1448,1480,1571**	**1686**	**3278**	**IV**
2991,2944 CH_3 aliphatic	**1631**	**1417-1487,1558**	**1694**	**3276**	**V**
4030- OH	**1639**	**1434,1467,1585**	**1683**	**3255**	**VI**

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

Pseudomons **(sp)**	*S.aureus*	*K.Pneumonia*	*Strep. pneumonia*	*E.coli*	**Conc.**	**No**
++	**+++**	**++**	**-**	**-**	**50µg**	**III**
+++	**++**	**++**	**-**	**-**	**100 µg**	
++	**++**	**+**	**-**	**-**	**50µg**	**IV**
+++	**++**	**++**	**-**	**++**	**100 µg**	
++	**++**	**+**	**++**	**+**	**50µg**	**V**
+++	**++**	**++**	**-**	**-**	**100 µg**	
++	**-**	**+**	**-**	**+**	**50µg**	**VI**
+++	**++**	**+**	**-**	**++**	**100 µg**	

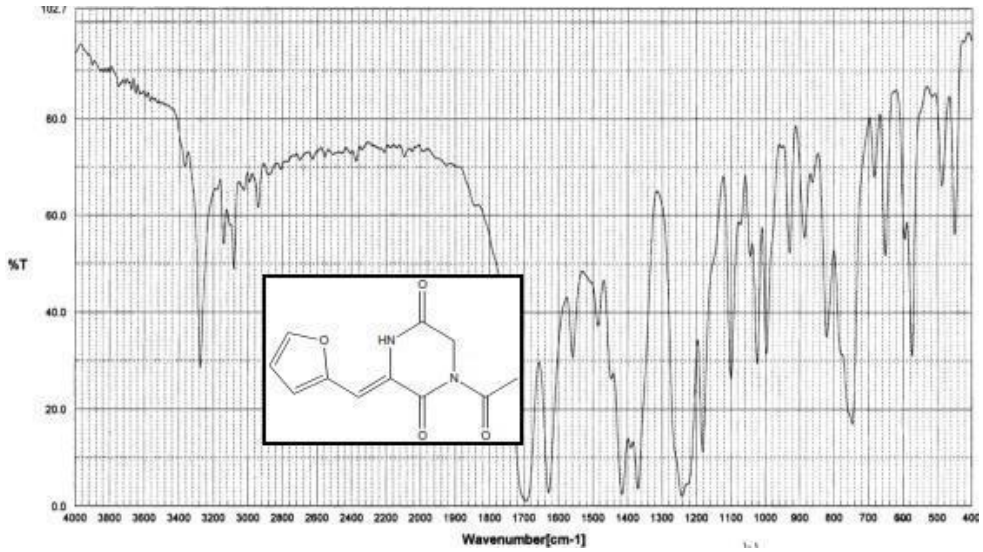

Fig .1. I.R spectrum of III

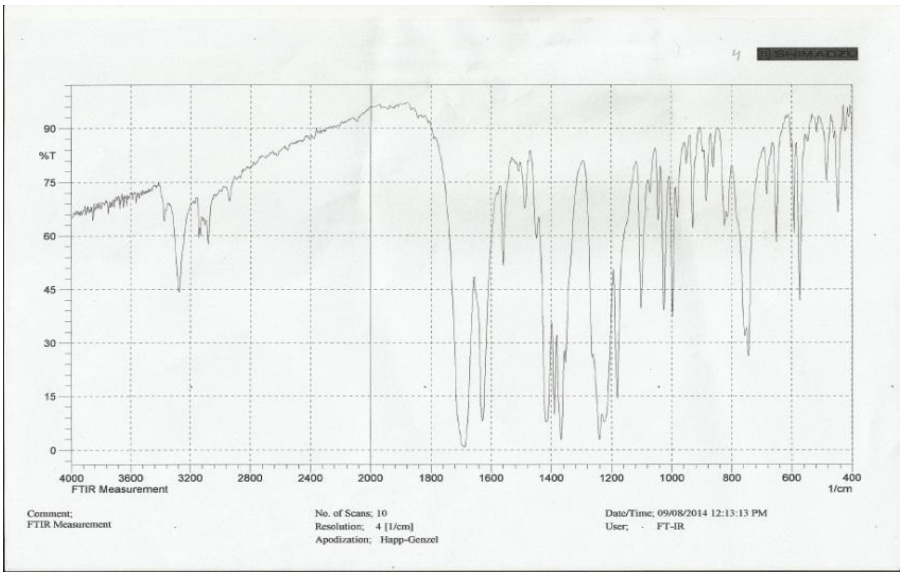

Fig. 2 . IR spectrum of IV

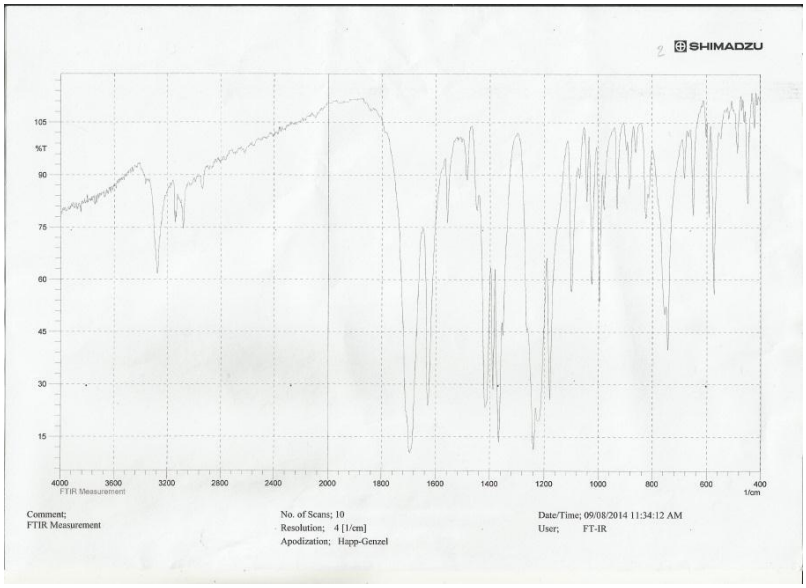

Fig. 3 . IR spectrum of V

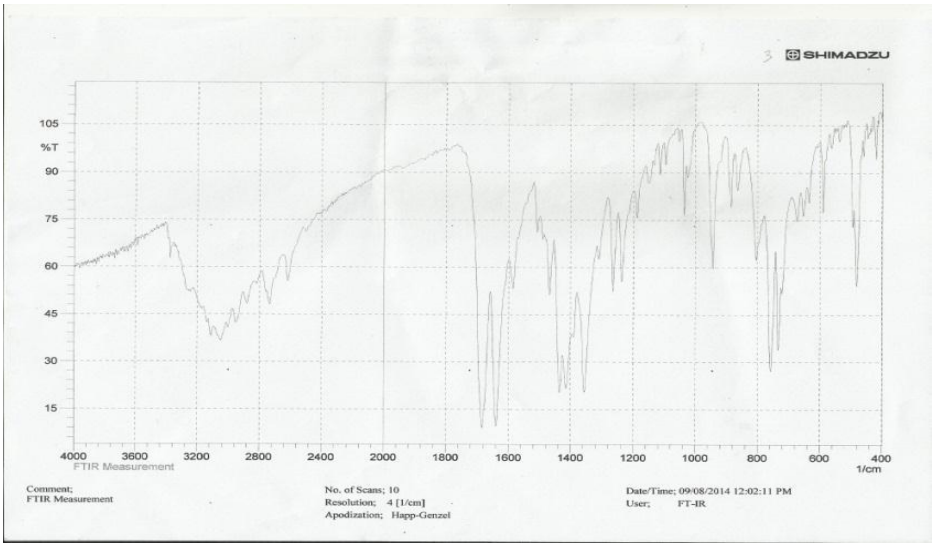

Fig. 4 . IR spectrum of VI

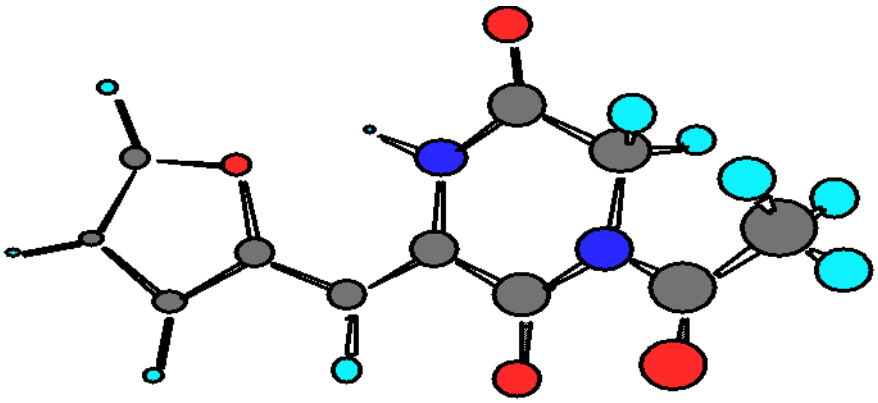

Fig .9. Expected stero configuration to compound III at lowest level energy as obtained from MM2 program

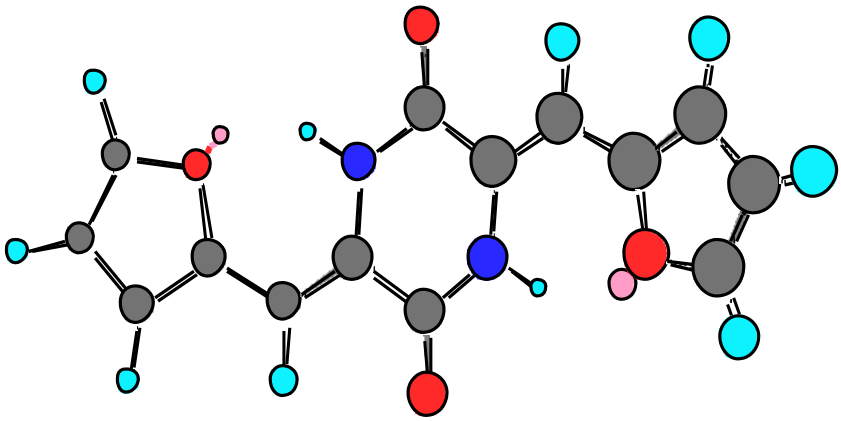

Fig .10. Expected stero configuration to compound IV-VI at lowest level energy as obtained from MM2 program

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