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Synthesis , characterization and antimicrobial activity of shiff and mannich bases of uracil derivatives

Hala M . Gareeb Alzahawi
College of science / Chemistry Department / Kirkuk university, Iraq
halamohammmud@yahoo.com

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ABSTRACT

In the present work some Shiff bases ($1_{a,b,c,d}$)were syuthesized using phenyl alanine with aniline by microwave irradiation. Aseries of mannich base ($2_{a,b,c,d}$) were prepared by the reaction of ($1_{a,b,c,d}$) with uracil in the presence of formaldehyde.The newly synthesized compounds were characterized on the basis of elemental analysis,I.R and H^1NMR. All the synthesized compounds were tested for their antibacterial activites and antifungal activities.

Keyword: *antimicrobial activity , shiff, mannich bases and uracil derivatives*

تحضير وتشخيص ودراسة الفعالية البايولوجية لبعض قواعد شف ومانخ المشتقة من يوراسيل

هالة محمد غريب الزهاوي
جامعة كركوك / كلية العلوم / قسم الكيمياء
halamohammmud@yahoo.com

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الملخص

تم تحضير سلسلة من قواعد شف وقواعد مانخ المشتقة من اليوراسيل والتي من المتوقع ان تكون لها فعالية بايولوجية باستخدام التشعيع بالمايكروويوف . تم تشخيص المركبات المحضرة بالطرق الفيزياوية والطيفية(I.R , H.N.M.R , C.H.N) وتم متابعتها بواسطة كروماتوغرافيا الطبقة الرقيقة (TLC) كما تمت دراسة الفعالية البايولوجية للمركبات المحضرة على عدة انواع من البكتريا والفطريات.

الكلمات الدالة : يوراسيل ، قواعد شف ، قواعد مانخ ، فعالية البايلوجية.

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1. Introduction

The application of microwave irradiation to organic synthesis has been the focus of considerable attention in recent years and is becoming an increasingly popular technology[1].Microwave assisted organic reaction methods are superior to conventional method because it occur more rapidly, safely and with the highest chemicals yields[2,3]. Last few decades, increasing the number of publications in microwave – assisted synthesis includes almost all types of reactions[4,5].

In the Mannich reaction , ammonia or primary or secondary amines are employed for the activation of formaldhyde . Tertiary amines lack an N – H proton to form the intermediate imine . α – H acidic compounds (nucleophiles) include carbonyl compounds , nitriles , acetylenes , aliphatic nitro compounds , α – alkyl – pyridines or imines[6].It is also possible to use activated phenyl groups and electron – rich heterocycles such as furan , pyrrole , and thiophene . Indole is a particularly active substrate ; the reaction provides gramine derivatives[7]. Mannich reaction is also used in the synthesis of medicinal compounds e.g. rolitetracycline , fluoxetine , tramadol and tolmetin[8].

Mannich bases of isatin derivatives are reported to show variety of biological activities like antibacterial[9], antifungal[10] , anticonvulsant[11] , anti HIV[12] , antidepressant[13], and antiiflammatory [14] activities.

2- Experimental

Techniques :- Melting points were determined using an open – ended capillary method and are uncorrected . The purity of synthesized compounds was checked by TLC.Infra-red spectra (Ft-IR) were recorded on Shimadzu FT-IR-8300 spectrophotometer and H^1NMR spectra were recorded on a BRUKER-400 MHz operating at 300 MHz with tetra methyl silane as internal standard in $CDCI_3$and DMSO-d_6 as solvent.

General synthesis of shiff base :- Phenyl alanine was allowed to react with different aromatic primary amines like 4- hydroxyl aniline ,4-amino benzoic acid ,2- amino benzoic acid and 4-chloro aniline respectively, in the presence of absolute alcohol and the pH was adjusted to 4-5 with glacial acetic acid to get 2,3-dihydro-2-oxo-3-substituted indoles (1a,b,c,d).These compounds were directly used for the next step.

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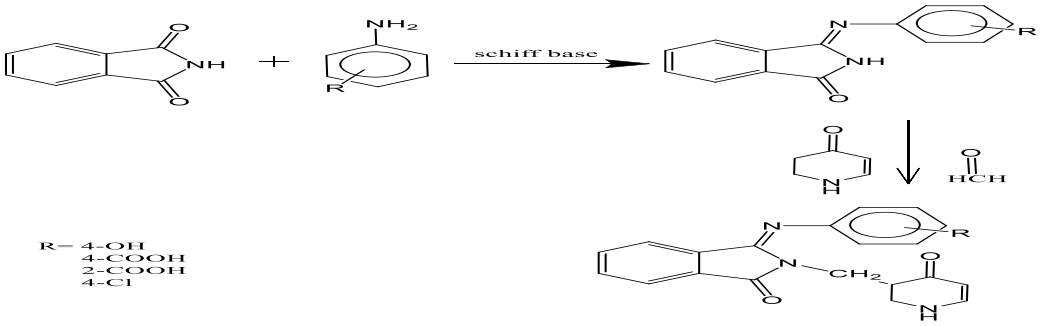
General synthesis of mannich base:- The mannichreaction of 2,3-dihydro-2-oxo-3-substituted indoles (1a,b,c,d) with uracil in the presence of formaldehyde were carried out at 0-5 C^{o} by stirring the reaction mixture with magnetic stirre. The reaction yielded 2,3-dihydro-2-oxo-3-substituted indoles scheme (1).The synthesized compounds were recrystallized from hot ethanol . The physical characteristics of synthesized compounds are listed in Table (1).



Scheme (1): Synthesis of phenyl alanine derivatives

Table (1) : physical properties of the prepared compounds

No. Comp.	Name of compounds	Melting point	Yield %	M.Wt.	Color
1a	2-(p-phenol) – imino phenyl alanine	زيتي	40	239 237	أحمر
1b	2-(p-benzoic acid) – imino phenyl alanine	زيتي	52	267	بني
1c	2-(2- benzoic acid -) – imino phenyl alanine	زيتي	50	281 279	بني غامق
1d	2-(p- chloro phenyl) – imino phenyl alanine	زيتي	45	280	بني
2a	1-uracil methyl-2-(p-phenol) – imino phenyl alanine	زيتي	43	279	بني
2b	1-uracil methyl-2-(p-benzoic acid) – imino phenyl alanine	190	85	202 200	أصفر
2c	1-uracil methyl-2-(2--benzoic acid) – imino phenyl alanine	زيتي	40	240 238	بني
2d	1-uracil methyl-2-(p- chloro phenyl) – imino phenyl alanine	زيتي	42	287 285	أصفر

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3. Results and Discussion

FT-IR spectrum of compound (1a) as example , confirmed the appearance of carbonyl group band at (1662cm^{-1})also , (C-H) aromatic band appeared at (3062 cm^{-1}) and (C-H) aliphatic band at (2800 cm^{-1}) . All the spectral data for other compounds are listed in Table (2). H^{1}NMR spectrum of compound (2a) shows the following characteristic chemical shifts , (DMSO-d_6) ppm .(N-H) proton appeared at (б 3.4) , olefinic protons appeared at (б 6.5) ,and aromatic ring protons appeared at the rang (б 7.3 – 7.8).Table 3 shows the spectral data.

All the synthesized compounds were tested for in vitro antimicrobial activity. The MIC values of the compounds against pathogenic bacteria and fungi are presented in Table (4).All compounds have shown moderate activity

Table (2) : FT-IR spectral data of compounds

Comp. No.	R	υO-H	υN-H	υC=N	C---C υ	υ others(cm^{-1})
1a	4 - OH	3600	3250	1600	1500 1600	υ(C=C-H)3260
1b	4 - COOH	3550	3280	1570	1530	υC-N(1250)
1c	2 - COOH	3600	3200	1510	1500	υC-N(1220)
1d	4 - Cl	3610	3210	1550	1510	υC-N(210)
2a	4 - OH	3500	3290	1620	1580	υC-N(1220)
2b	4 - COOH	3600	3250	1650	1500	υ(C=O) acid 1710 υ(C-O) acid 1240
2c	2 - COOH	3500	3200	1600	1550	υ(C≡C-H)3250
2d	4 - Cl	3600	3250	1600	1500	υ(C-N) 1200

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Table (3) : ^{1}H-NMR spectral data ppm (б) of compounds

رقم المركب	جزيئة اليوراسيل		ملاحظات
	C-H	O-H	
1a	**(2.4 s , 1H)**	**8.7 s - 8.75 s**	**8.1 m for (NH-NH_2)**
1b	**(2.45 s , 1H)**	**8.9 d**	**(2.37 s , 3H) for CH_3 ,(2.2 s , 3H) for CH_3**
2a	**(2.4 s , 1H)**	**8.5 s - 8.7 s**	**(2.55 s , 2H) for CH_2**
2b	**(2.35 s , 1H)**	**8.6 s - 8.8 s**	**(2.5 s , 2H) for CH_2 ,(7.85-795)d for H-aromatic**

Table (4) : antibacterial activity of the tested compounds .

Compound No.	Escherichia Coli	Klebsiella Pneumonia	Proteus Vulgaris
1a	+	+	-
1b	+	+	-
1c	+	++	-
2a	-	+	+
2b	++	++	-
2c	-	+	-

Note:-

-- = No inhibition = inactive

+ = (5 – 10)mm = slightly active

++ = (11 – 20) mm = moderately active

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AUTHOR

Hala. Mohammad.G . Al- Zahawi : Postal address : College of science , University of kirkuk. Occupation : Assist. Prof. Academic degree : A- B.Sc. , Chemist , 1992 . B - M.Sc. , Bio organic chemist, 2000.C- Ph.D. ,Carbohydrate ,Chemist , 2007 , college of science ,University of Mustansiriya. Scientific specialization :-Organic synthesis , Carbohydrate , nucleoside analoge , Carrier polymer with drug , Stereochemistry and Study of effect some compounds on the enzyme activity.