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PREPARTION OF SOME NEW COUMARIN DERIVATIVES WITH MEASURING BIOLOGICAL ACTIVITY

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ABSTRACT

The present study was designed to be into stages. The first stage included preparing and dignosing four compounds of Schiff's-bases throught condensing be town 3-amino coumarin (1) with aldehyde aromatic. While, the second stage included the reaction the prepared Schiff's-bases (2a-d)with the compound 4-hydroxy coumarin and the compounds produced(3a-d). The biological effects of the prepared compounds towards some positive bacteria Gram and negative Gram studied Staphylococcus aureu, Bacillus subtilis, Bacillus cereus, Psedomonase aeruginosa,. Also towards some fungi including Aspergllus niger, penicillium italicum, fusarium oxysporum.

Introduction

Schff's base are compounds consisting of agroup of Azomethines (-CH=N-). Previously, they were known with other names suchas (imines) Azomethines)[1,2]. Many Schff's baseare were prepared after the years of discovering them and they are prepared through concentrating [1] Amino with Ethanol absolute and ketons[2] accelerating with in different periods: scheme (1). Some reaction need stimulating factors suchas HCl,CH3COOH.

The characteristics and stability of Schff's base are have a deep- rooted connection with the compounds of carbonil or aminos whether they were alphatic or aromatic. Aromatic aldyhade react easily with aminos to give stable azomethines and make easy form Imin if carboninal aromatic compound contains a drawing group of electrons in the (P) position. contrarily, the containing of the reactive Aromatic Imines of drawing group in the (P) position reduces the speed of reaction.

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Coumarin and its derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity [1-9]. Many of these compounds have proved to be active as antitumor [1-2], antibacterial [3-4], antifungal[5-7], anticoagulant[8] and anti-inflammatory[9]. In addition, these compounds are used as additives to food and cosmetics[10], dispersed Fluorescent and laser(11). Various analogues of 3- Substituted coumarins suchas 3-amino coumarins exhibit antimicrobial activity(12-13). From the above line of reasoning we directed this paper toward synthesis of various coumarin derivatives of biological interest using 3-amino coumarin(1) (14) as a key starting material.

Experimental

Materials and methods all melting points are uncorrected and were taken in open capillaries on a Gallenkamp apparatus. Infrared spectra were determined in KBr on a perkin Elmer Model-137 infracord. The N.M.R. spectra were measured in DMSO.d6 solutions using a JEOL EX=370 MHZ spectrometer. Spectroscopic and physical data is listed in tables (3) and (4).

Synthesis of Compounds:

Action of aromatic aldehydes on (1): Formation of Shiff- bases (2a-d). To solution of compound (1) (1.61 g: 0.01 mol) in absolute ethanol (50 ml). The reaction mixture was heated under reflux for (4 h.) and left to cool. The solid products (2a-d) Formed during time of reflux. The solid product was collected, dried and recrystallised from ethanol given compounds (2a-d), (See table (3)).

3-{(Substituted aryl)[coumarin- 3- yl amino] methyl}-4- hydroxyl coumarins }derivatives (3a-d).

A mixture of (2a-d) (0.01 mol for each) and 4-hydroxyl coumarin (1.62 g, 0.01 mol) in pyridine (20 ml) was refluxed for (5 h.). The reaction mixture was poured into H2O – HCl and the solid that separated was collected, washed thoroughly with water, dried and recrystallised from dilute dimethyl formamide to compounds (3a-d). (See table (3)).

Results and Discussion

The condensation of 3- amino coumarin (1) with aromatic aldehydes (Namely, m-nitrobenzaldehyde p-hydroxyobenzaldehyde, p-methoxyo benzaldehyde, obenzaldehyde) in absolute ethanol, containing a catalytic amount of Piperidine led to the formation of the Shiff-bases derivative (2a-d) (Scheme (2)). The 1H.NMR. spectrum (DMSO-d6) of compound (2a), as an example. Showed signals at δ 7.38-8.92 (m, 9H, Ar H+ olefinic H) and 9.15 ppm (s, 1H, CH-4). The IR. Spectrum (KBr) of (2a-d) showed bandes at 1615 (C=N) and at 1710 cm-1 (C=O).

Reaction of 4- hydroxyl coumarin and Shiff-bases (2a-d) condense in pyridine to afford 3-{(P-substituted aryl) coumarin- 3- yl amino] methyl}-4-hydroxyl coumarin }derivatives (3a-d). (Scheme (1)). The 1H.NMR. spectrum (DMSO-d6) of compound (3a), as an example. Showed signals at δ 5.02 (s, 1H,C3 –H in ketonic form_, 5.33 (s, 1H, -CH), 6.98 – 7.50 (m, 12H, ArH) and 1059 ppm (s, 2H, disappeared after D2O exchange,NH+ enolic OH). The IR. Spectrum (KBr) of (3a-d) showed characteristic bands at 3356 (NH), 1708-1732 (Lactonic C=O) and 1692 cm-1 (C=O).

Biological activity

All the prepared compounds were screened for their antimicrobial activity against the Gram-positive bacteria (1-Staphylococcus aureu, 2-Bacillus subtilis, 3- Bacillus cereus), Gram- negative bacteria (4-Psedomonase aeruginosa, 5- Esherichia Coli), as well as fugi :a) Aspergllus niger, b) Penicillium italicum, C) fusarium oxysporum. Standard antibiotic drug Amoxicillin for bacteria and Mycostatin for fungi were used at a concentration of (1000 ppm) for comparisons. The biological activity for these compound have been evaluated by filter paper disc method(16) after dissolved in N,N-dimethyl formamide to obtain a 1 mg/ ml solution (1000 ppm). The inhibition Zones of microbial growth surrounding the filter paper disc (5mm) were measured in millimeters at the end incubation period of 3 days at 37C0 for Esherichia Coli and 28C0 for other bacteria and fungi , N,N-dimethyl formamide alone showed on inhibition zone. The results are illustrated in Table (1) and (2).

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Table (1) Antibacterial activity of the synthesized compounds

Comp.	Organism*			
	1	2	3	4
2a	22	27	16	24
2b	28	22	19	18
2c	10	25	14	20
2d	26	16	22	13
3a	17	18	13	9

3b	25	20	12	6
3c	25	20	10	10
3d	20	12	23	11
Amoxicillin	29	20	12	26

Organism*: 1- *Staphylococcus aureu./* 2- *Bacillus subtilis./*3- *Bacillus cereus.*
4- *Psedomonase aeruginosa./*

Table (2) Antifungal activity of the synthesized compounds

Comp.	**Organism***		
	A	**B**	**C**
2a	14	17	22
2b	12	15	10
2c	14	18	20
2d	16	18	18
3a	15	16	22
3b	13	22	16

Mycostatin	12	19	25
3d	16	12	10
3c	13	17	16

Organism*: A- *Aspergllus niger./ B- penicillium italicum./ C- fusarium oxysporum.*

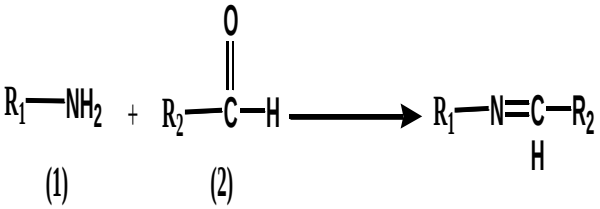
Table (3) Characterization data for the synthesized compounds

Comp.	**Mp./C^0**	**Yield(%) Colour**	**Formula (M.Wt.)**	**Analysis calc./Found**		
				C	**H**	**N**
2a	223	70 Yellow	$C_{16}H_{10}N_2O_4$ (294.27)	65.13 65.23	3.43 3.40	9.52 9.48
2b	160	50 Yellow	$C_{16}H_{11}NO_3$ (265.21)	72.45 72.40	4.15 4.18	5.28 5.25
2c	170	60 Yellow	$C_{17}H_{13}NO_3$ (279.12)	73.12 73.14	4.66 4.64	5.02 5.00
2d	138	80 Yellow	$C_{16}H_{10}NO_2$ (248)	77.42 77.39	4.03 4.06	5.65 5.69
3a	220	70 White	$C_{25}H_{14}N_2O_7$ (454.14)	66.06 66.00	3.10 3.15	6.16 6.13
3b	135	57 White	$C_{25}H_{17}NO_6$ (427)	70.26 70.24	3.98 3.95	3.28 3.23
3c	190	60 White	$C_{26}H_{19}NO_6$ (441.32)	70.74 70.70	4.31 4.34	3.17 3.19

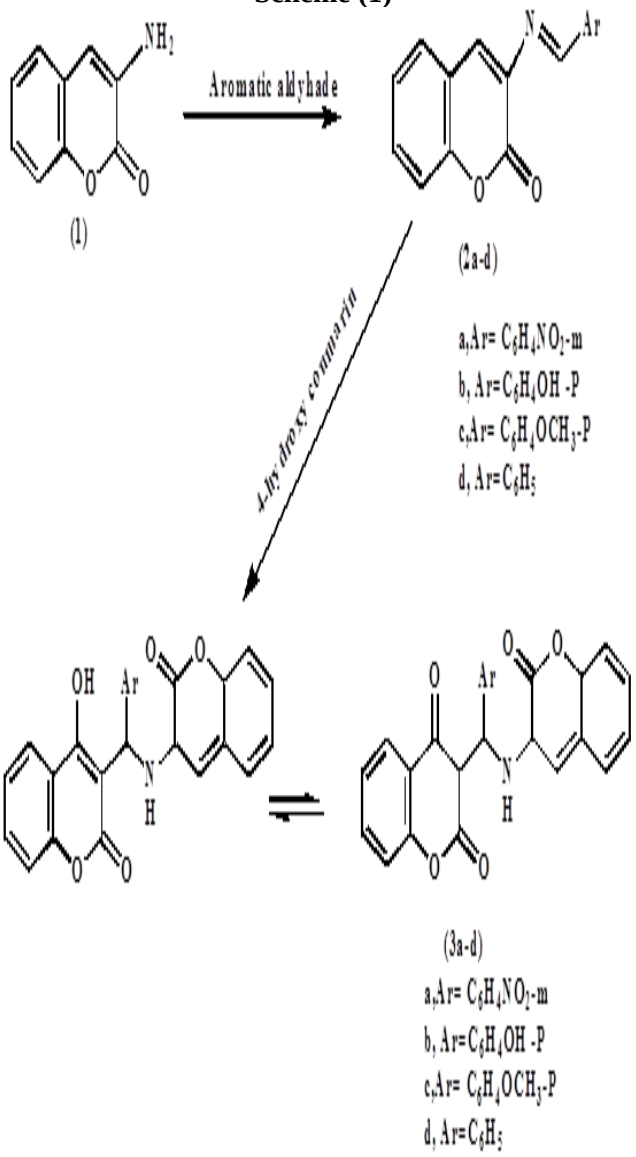
3d	250	40 Yellow	$C_{25}H_{17}NO_5$ (411.2)	72.9 72.7	4.14 4.12	3.41 3.44	

Table (4) IR. ,^{1}H. NMR. Spectra of products

Comp.	IR. Cm^{-1}	^{1}H. NMR. Δ ppm
2a	1615(C=N), 1710(C=O), 1353(NO_2)	7.38 -8.92(m, 9H,ArH^+ Olefinic H) and 9.15 pmm(s,1H, CH-4)
2b	1617(C=N), 1710(C=O), 3490(O-H)	7.35 -7.90(m, 9H,ArH^+ Olefinic H) and 8.95 pmm(s,1H, CH-4)
2c	1620(C=N), 1711(C=O),	7.25 -7.86(m, 9H,ArH^+ Olefinic H) and 8.9 pmm(s,1H, CH-4)
2d	1620(C=N), 1711(C=O),	7.44 -7.90(m, 9H,ArH^+ Olefinic H) and 8.9 pmm(s,1H, CH-4)
3a	3356(NH), 1708-1732(Lacton C=O) and 1692(C=O)	5.03 (s,1H, C_3–H in ketonic form), 5.33 (s,1H, -CH), 6.84 -7.60 (m, 13H,ArH^+NH, disappeared after D_2O exchange
3b	3356(NH), 1708-1732(Lacton C=O) and 1692(C=O)	5.63 (s,1H, C_3–H in ketonic form), 5.82 (s,1H, -CH), 7.32 -8.52 (m, 13H,ArH^+NH, disappeared after D_2O exchange
3c	3350(NH), 1708-1732(Lacton C=O) and 1692(C=O)	5.62 (s,1H, C_3–H in ketonic form), 5.80 (s,1H, -CH), 6.98 -5.50 (m, 13H,ArH^+NH, disappeared after D_2O exchange
3d	3356(NH), 1708-1732(Lacton C=O) and 1692(C=O)	2.05 (s,1H, C_3–H in ketonic form), 5.33 (s,1H, -CH), 7.30 -7.60 (m, 12H,ArH) and 10.59 ppm (m, 2H, disappeared after D_2O exchange NH^+ enolic OH)



Scheme (1)



Scheme (2)

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تحضير بعض مشتقات الكومارين الجديدة وقياس فعاليتها الحيوية

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الخلاصة

صممت الدراسة الحالية على ان تكون على مرحلتين تضمن المرحلة الاولى تحضير وتشخيص اربعة مركبات من قواعد شيف وذلك بالتكثيف بين ٣-امينوكومارين (١) مع الالديهدات الاروماتية في حين تضمنت المرحلة الثانية تفاعل قواعد شيف المحضرة (2a-d) مع المركب ٤-هيدروكسي كومارين وانتجت المركبات (3a-d). وتمت دراسة التأثير البايولوجي للمركبات المحضرة تجاه بعض البكتريا الموجبة لصبغة كرام وسالبة لصبغة كرام وهي: *Staphylococcus aureu, Bacillus subtilis, Bacillus cereus, Psedomonase aeruginosa* وكذلك تجاه بعض الفطريات وهي. *.spergllus niger, penicillium italicum, fusarium oxysporum*