Preparation of Some New Coumarin Derivatives with Biological Activity

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Abstract:

The reaction of 3-aminocoumarin(1) with benzoyl isothiocyanate gave 3-(3`-coumarinyl)-*N*-benzoyl thiourea (2).Compound (2) was cyclised into either 2-thioxo-1,3,5-trihydropyrimidine-4,6-dione derivative (3) or thiazolidin-4-one derivative (4). Alkylation of (1) using excess of benzyl chloride afforded *N*,*N*,*N*-tribenzyl-*N*-(coumarin-3-yl) ammonium chloride (5), also, treatment of (1) with 2-alkylthio-4-chloro-6-phenyl pyrimidine (6a,b) gave 3-[(2-alkylthio-6-phenylpyrimidin4`-yl) amino] -*2H*-benzopyran-2-ones (7a,b). Condensation of (1) with aromatic aldehydes produced the Shiff-bases (8a-d). Each of compounds (8a-d) reacted with 4-hydroxycoumarin to give 3-{(substituted aryl)[coumarin-3`-yl amino] methyl}-4-hydroxycoumarin derivatives (9a-d). Reaction of (8a) with phenylmagnesium bromide afforded 2,2,4-triphenyl chroman derivative (10). Reaction of each compounds (8a-d) with maleic anhydride gave 3-[*N*-(coumarin-3`-yl)carbamoyl]prop-2-enoic acid (11) as the same product. Treatment of (11) with hydrazine hydrate and phenyl hydrazine in ethanol at room tempreature afforded the ring opening products (12a,b) respectively. The antimicrobial activity of the synthesized compounds was tested against Gram positive and Gram negative bacteria as well as fungi.

Introduction:

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 antiinflammatory[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 such as 3-aminocoumarins 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-aminocoumarin (1) [14] as a key starting material.

Experimental

General Methods

Melting points were determined with Kofler apparatus and are uncorrected. The microanalyses were done at faculty of Science, King Khalid University. Nuclear magnetic resonance spectra were recorded on JEOL Ex-270 MHz NMR spectrometer. Infrared spectra were recorded, for potassium bromide disks, with a Jasco FT/IR 460 spectrometer. Mass spectra were recorded on a Finnigan Mat SSQ- 7000 mass spectrometer.

3-(3`-Coumarinyl)-*N*-benzoyl thiourea (2)

A mixture of 3-aminocoumarin (1) (1.61g; 0.01 mole) and benzoyl isothiocyanate (1.4 ml; 0.01 mole) in absolute ethanol (20 ml) was refluxed for 2h. The solid that separated during reflux was filtered after cooling, dried and recrystallised from dimethylformamide to yield compound (2) (*cf*. Tables 3,4&5).

3-Benzoyl-1-(3`-coumarinyl)-2-thioxo-1,3,5-trihydropyrimidin-4,6-dione (3).

A mixture of (2) (3.24g; 0.01 mole) and diethyl malonate (1.4 ml;0.01 mole) was added to a solution of sodium (0.27 g; 0.012 atom) in absolute ethanol (20 ml) . The reaction mixture was heated under reflux for 6h, concentrated, cooled and poured into ice-HCl. The yellow solid product was filtered off, washed thoroughly with water, dried and recrystallised from diluted ethanol to produce (3) (*cf*. Tables 3,4&5).

2-(*N*-Benzoylimino)-1-*N*-(coumarin-3`-yl)-1,3-thiazolidin-4-one (4).

To a solution of (2) (3.24g ; 0.01 mole) in acetic acid (15 ml), monochloroacetic acid (0.94g ; 0.01 mole) and fused sodium acetate (1.39 gm; 0.017 mole) were added. The reaction mixture was refluxed for 8h and then left to cool. The solid that obtained on diluting with water (50 ml) was filtered off, dried and recrystallised from ethanol to yield (4) (*cf*. Tables 3,4&5).

_N_,_N_,_N_-Tribenzyl-_N_-(coumarin-3-yl) ammonium chloride (5)

A mixture of (1) (1.6g ; 0.01 mole) and benzyl chloride (4.6 ml; 0.04 mole) in acetic acid (20 ml) containing fused sodium acetate (1gm) was refluxed for 2h. The solid product was isolated during reflux. The product was poured into water, filtered off, dried and recrystallised from dilute dimethylformamide to give (5) (*cf*. Tables 3,4&5).

3-[(2-Alkylthio-6-phenyl pyrimidin-4`-yl)amino]-*2H*-benzopyran - 2 -ones (7a,b).

A mixture of (1) (1.6gm; 0.01 mole) and 2-alkylthio-4-chloro-6-phenyl pyrimidine (6a,b) (0.01 mole for each) in glacial acetic acid (20 ml) was heated under reflux for 4h. During time of reflux, a white solid product was precipitated, cooled , filtered off and recrystallised from dimethylformamide to produce (7a,b) (*cf*. Tables 3,4&5).

Action of aromatic aldehydes on (1): Formation of Schiff-Bases (8a-d).

To a solution of compound (1) (1.61g; 0.01 mole) in absolute ethanol (50 ml), containing a catalytic amount of piperidine, equimolecular amount of the appropriate aldehyde was added. The reaction mixture was heated under reflux for 4h and left to cool. The solid products (8a,b,c) formed during time of reflux, whearase (8d) formed after cooling. The solid product was collected, dried and recrystallised from dimethylformamide to give compounds (8a,b,c) or ethanol to form (8d) (*cf*. Tables 3,4&5).

3-{(*p*-Substituted aryl)[coumarin-3`-yl amino] methyl}-4-hydroxy-coumarins (9a-d).

A mixture of (8a-d) (0.01 mole for each) and 4-hydroxycoumarin (1.62g; 0.01 mole) in pyridine (20 ml) was refluxed for 5h. The reaction mixture was poured into H_2O-HCl and the solid that separated was collected, washed throughly with water, dried and recrystallised from dilute dimethylformamide to yield compounds (9a,c,d) or dimethylform- amide to give (9b) (*cf*. Tables 3,4&5).

[(*p*-Nitrophenyl)phenyl methyl](2,2,4-triphenyl chroman-3-yl)amine (10) .

To the Grignard solution (prepared from 1.6g Mg and phenyl bromide (11g; 0.06 mole) in 200 ml dry ether) was added a suspension of compound (8a) (2.9g; 0.01 mole) in dry ether (50ml). The reaction mixture was heated under reflux for 2h and decomposed with saturated aq. ammonium chloride solution. The organic layer was separated, the solvent removed and the residue washed several times with petroleum ether (40-60^{o}C) and crystallised from benzene-pet.-ether (40-60^{o}C) to give (10) (*cf*. Tables 3,4&5).

3-[*N*-(3`-Coumarinyl) carbamoyl] prop-2-enoic acid (11).

A mixture of (8a-d) (0.01 mole for each) and maleic anhydride (0.99g; 0.01 mole) in p-xylene (50 ml) was heated under reflux for 20h. The reaction mixture was allowed to cool. The solid that separated was filtered off, dried and recrystallised from xylene to produce (11), m.p. and m.m.p determinations (*cf*. Tables 3,4&5).

3-{*N*-[(1-*N*-Substituted carbamoyl)-2-substituted hydrazino-2- (2`-hydroxyphenyl) ethyl] carbamoyl} prop-2-enoic acid derivatives (12a,b).

A mixture of (11) (2.5 g; 0.01 mole) and hydrazine hydrate or phenyl hydrazine (0.02 mole for each) in ethanol (50 ml) was stirred at room temperature for 4h. The reaction mixture was dissolved then precipitated. The product was filtered off, dried and recrystallised from dimethylformamide to produce (12a,b) (*cf*. Tables 3,4&5).

Results and Discussion

The condensation of 3-aminocoumarin(1)[14] with benzoyl isothiocyanate in absolute ethanol gave 3-(3`-coumarinyl)-*N*-benzoyl thiourea (2) (scheme 1). The ^{1}H-NMR (DMSO-d_6) of compound (2) showed signals at δ 6.81-7.99 (m,9H, ArH), 9.6 (s,1H,CH-4), 11.85 (s,1H, disappeared after D_2O exchange, NH), and 13.47 ppm (s,1H, disappeared after D_2O exchange, NH). The IR (KBr) of (2) showed characteristic

bands at 3273 (NH), 1709 (lactone C = O), 1672 (amide C = O) and 1486 cm-1 (C = S). Also, the mass spectrum of (2) showed a molecular ion peak (M+) at m/z 324 (63.41%) , 3-coumarinyl isothiocyanate 203 (40.98), 3-aminocoumarin 161 (39.54) and unknown C7H6O,105 (100).

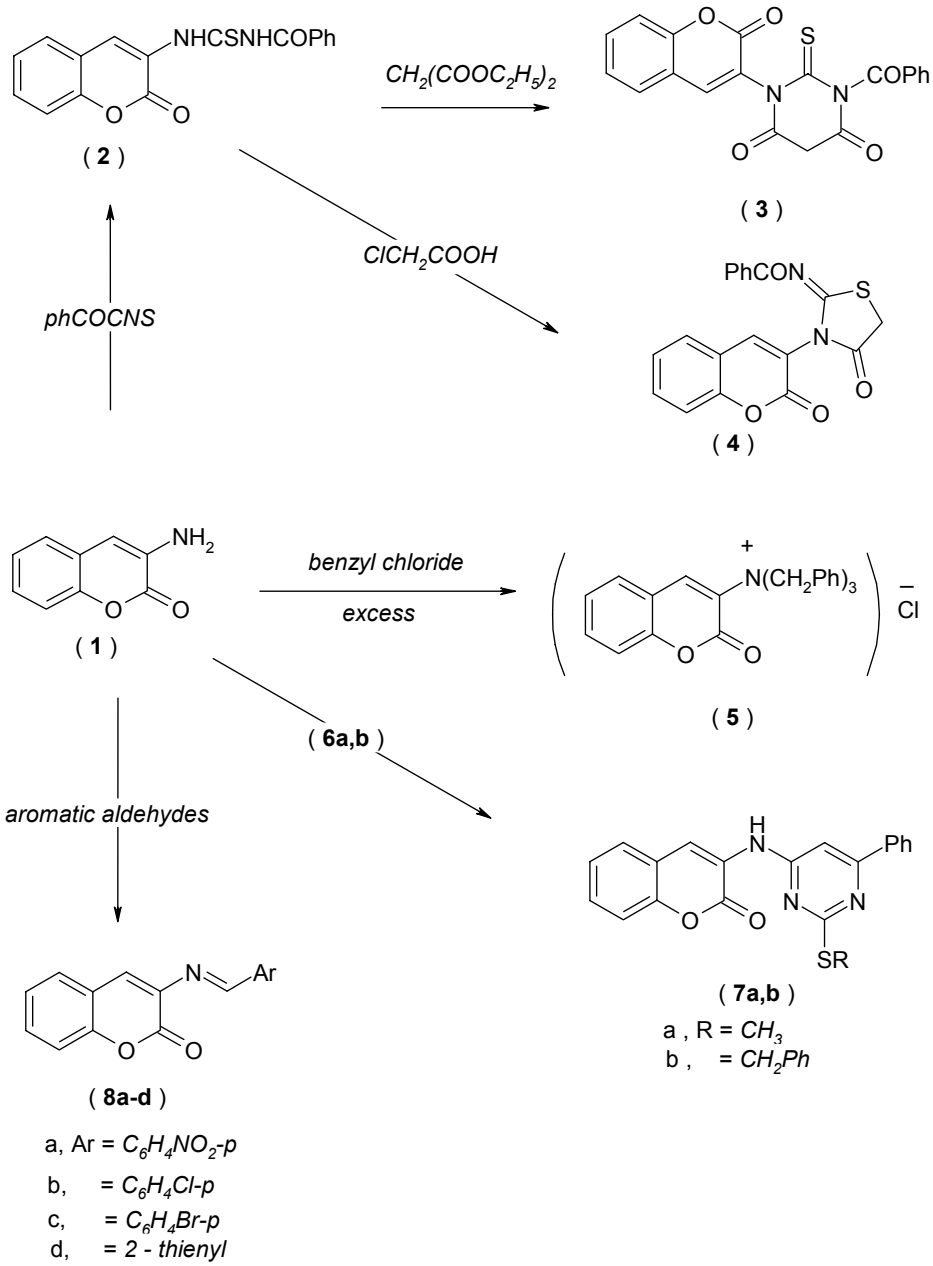
Compound (2) was cyclised by treatment with diethyl malonate in presence of sodium ethoxide to give 3-benzoyl-1-(3`-coumarinyl)-2-thioxo-1,3,5-trihydropyrimidin-4.6-dione (3) (scheme 1). The 1H-NMR spectrum (DMSO-d_6) of compound (3) showed signals at δ 4.1 (s,2H,CH_2), 6.87-7.7 (m,9H, ArH), 10.3(s, 1H, CH-4), 11.88 and 12.31 ppm (s, 1H, disappeared after D2O exchange, 2 enolic OH). The infrared spectrum (KBr) of (3) displayed absorption bands at 3413-3344 (enolic OH), 1723 (lactone C = O), and 1646 cm-1 (C = O). Mass spectrum of (3) showed the less stability of the molecular ion peak (M+) at m/z 392 (zero%) and exhibited 3-coumarinyl thiourea 220 (100%), 3-coumarinyl isothiocyanate 203 (16.81) and 3-aminocoumarin 161 (15.92).

Also, cyclisation of (2) with monochloroacetic acid in the presence of acetic acid and fused sodium acetate gave 2-(N-benzoylimino) -1-N-(coumarin-3`-yl)-1,3-thiazolidin-4-one (4) (scheme 1). The 1H-NMR spectrum (DMSO-d6) of (4) showed signals at δ 7.30-8.41 (m,9H, ArH), 9.72 (s, 1H, CH-4) and 10.23 ppm (s, 1H, disappeared after D2O exchange, enolic OH) and its infrared spectrum (KBr) showed bands at 3336 (enolic OH), 1710 (lactone C = O) and 1679 cm-1 (amide C = O). The mass spectrum of compound (4) exhibited absence of the molecular ion peak (M+) at 364 (zero %), and appeared 3-coumarinyl isothiocyanate 203 (18%) and the same fragments like to nucleus of coumarin.

Alkylation of 3-aminocoumarin (1) using excess of benzyl chloride afforded N,N,N-tribenzyl-N-(coumarin-3-yl) ammonium chloride (5) (scheme 1). The ^{1}H-NMR of compound (5) showed signals at δ 4.45 (s,6H, 3CH2), 7.01 (s, 1H, CH-4) and 7.31-7.33 ppm (m, 19 H, ArH). The IR spectrum (KBr) of compound (5) revealed no absorption in the NH2 region, furthermore , it displayed absorption band at 1708 cm-1 (lactone C=O) and its mass spectrum showed molecular ion peak (M^+) at m/z 467 (zero%), 432 (30.43%), 342 (100), 250 (100), 222 (50), 181 (37.55), 146 (8.94), 91 (91.29) and 65 (46.32).

Also, treatment of compound (1) with 2-methylthio (or 2-benzylthio)-4-chloro-6-phenyl pyrimidine (6a,b)[15] gave 3-[(2-alkylthio-6-phenylpyrimidin-4`-yl)amino]-2H-benzopyran-2-one derivatives (7a,b) (scheme 1). The 1H-NMR spectrum (DMSO-d6) of compounds (7a,b) exhibited signals at δ 7.54-8.02 (m,10H, ArH+ pyrimidine protone), 8.87 (s, 1H, NH) and 9.56 ppm (s, 1H, CH-4), furthermore, compound (7a) showed signal at 2.66 ppm (s, 3H,-SCH3) and (7b) showed signal at 4.57 (s,2H,-SCH2Ph). The IR spectrum (kBr) of compounds (7a,b) displayed absorption bands at 3341 (NH) and 1699 cm-1 (lactone C = O). The mass spectrum of (7a,b) showed molecular ion peak (M+) at m/z at (361) (100%) and 437 (100 %), respectively. Other peaks displayed due to lack of alkylthiol and fragments like to the coumarin nucleus : 314 (8.82-18.44%), 286 (20.58-26.30), 128 (62.95-25.69) and at 77 (43.89-30.82).

Condensation of (1) with aromatic aldehydes (Namely, p-nitrobenzaldehyde, p-chlorobenzaldehyde, p-bromobenzaldehyde and 2-thiophene carboxaldehyde) in absolute ethanol, containing a catalytic amount of piperidine led to the formation of the Shiff-base derivatives (8a-d) (scheme 1). The ^{1}H-NMR spectrum (DMSO-d_6) of compound (8a) , as an example , showed signals at 7.38-8.92 (m, 9H, ArH+ olefinic H) and 9.15ppm (s, 1H, CH-4). The IR spectrum (KBr) of (8a-d) showed bands at 1711 (lactone C=O) and at 1620 cm-1 (C=N). The mass spectrum of compounds (8a-d) exhibited a molecular ion peak (M+) at m/z 294 (100%) (8a), 283 (29.61%) (8b), 328 (64.27%) (8c) and at 255 (100%) (8d) in addition to the same fragments like to nucleus of coumarin.


NHCSNHCOPh
(2)
CH2(COOC2H5)2
(3)
ClCH2COOH
phCOCNS
PhCON
(4)
NH2
(1)
benzyl chloride
excess
(5)
(6a,b)
aromatic aldehydes
(7a,b)
a , R = CH3
b , = CH2Ph
(8a-d)
a, Ar = C6H4NO2-p
b, = C6H4Cl-p
c, = C6H4Br-p
d, = 2 - thienyl

Scheme (1)

4-Hydroxycoumarin and Schiff-bases (8a-d) condense in pyridine to afford 3-{(p-substituted aryl)[coumarin-3`-yl amino] methyl}-4-hydroxycoumarin derivatives (9a-d) (scheme 2). The 1H-NMR spectrum (DMSO-d_6) of compound (9d), 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 10.59 ppm (s,2H, disappeared after D2O exchange, NH+ enolic OH). The IR spectrum (KBr) of (9a-d) showed characteristic bands at 3356 (NH), 1708-1732 (lactone C=O) and 1692 cm-1 (C = O) .

The mass spectrum of compounds (9a-c) exhibited absence of the molecular ion peaks (M+) m/z at 456 (zero %), 445 (zero %) and 490 (zero %), respectively, whereas (9d) showed molecular ion peak (M+) m/z at 417 (3.7%). Also, compounds (9a-c) showed peaks at m/z 316 (12.99% for)9a), (100% for 9b) and (100% for 9c) due to lake -OH in addition to nitro-, chloro-, bromophenyl, respectively.

Reaction of (8a) with phenylmagnesium bromide gave [(p-nitrophenyl) phenylmethyl](2,2,4-triphenylchroman-3-yl) amine (10) (scheme 2). Four moles of phenylmagnesium bromide are incorporated in the reaction with the formation of intermediate which easily undergo cyclodehydration to give (10). The ^{1}H-NMR spectrum (DMSO-d_6) of (10) showed signals at δ 1.30(d,1H,CH), 1.47(s,1H,NH), 4.03(s,1H,CH), 5.60(s,1H,CH) and 6.76 – 8.00 ppm (m,28H,ArH) .

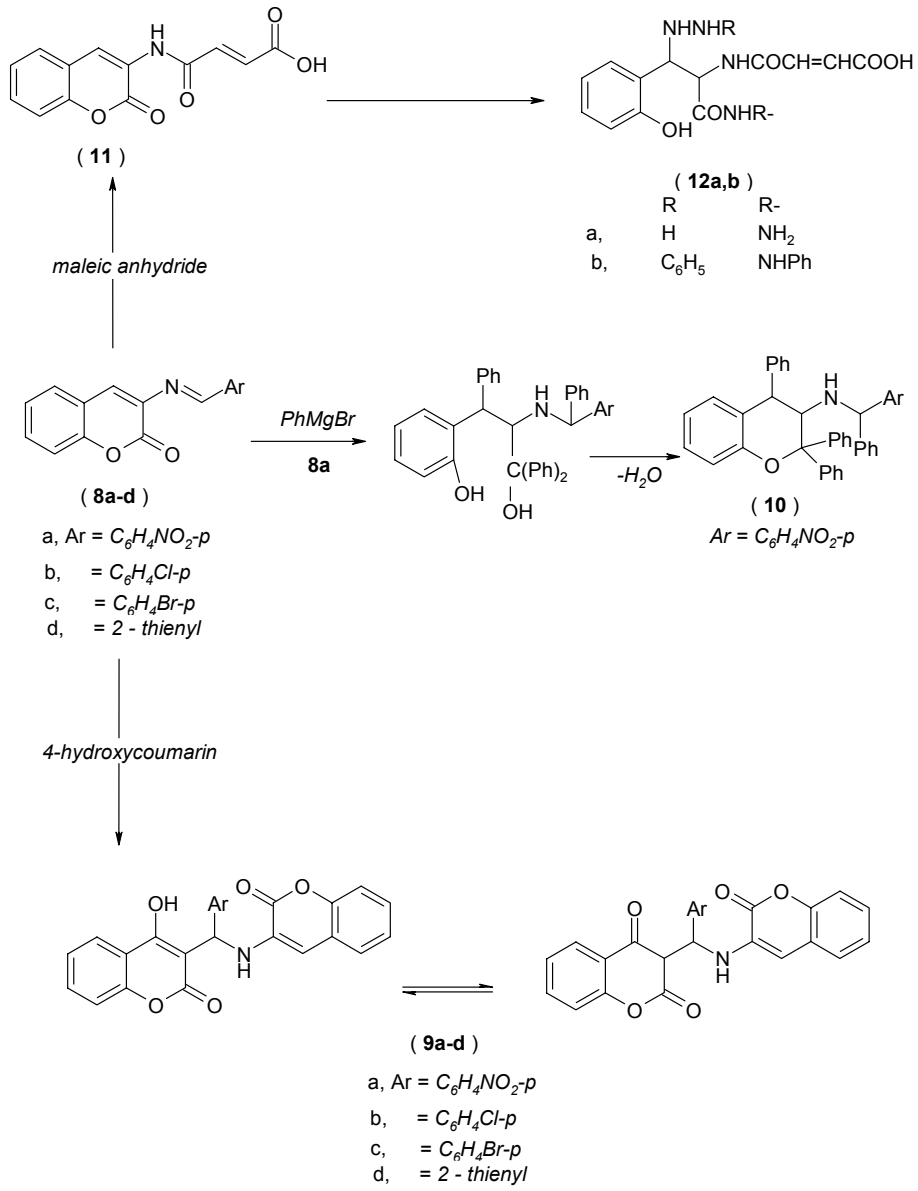
The infrared spectrum (KBr) of (10) revealed no absorption in the carbonyl of the δ-lactone region, furthermore, it displayed absorption band at 3404 cm^{-1} (NH). Mass spectrum of (10) showed a molecular ion peak (M^+) at m/z 587 (1.27%), 586 (2.06), 466 (1.58), 465 (3.21), 390 (3.30), 389 (7.40), 314 (4.07), 313 (4.11), 238 (6.50), 182 (16.63), 165 (32.63), 77 (100%).

On the other hand, the reaction of each compounds (8a-d) with maleic anhydride in refluxing p-xylene afforded the same product which formulated as 3-[N-(coumarin-3`-yl)carbamoyl]prop-2-enoic acid (11) (scheme 2). The 1H-NMR spectrum (DMSO-d6) of compound (11) showed signals at δ 6.43 (d,1H, = CHCO-), 6.63(d,1H, COCH=), 7.35-7.41 (m,4H,ArH) and 10.33 ppm (s,2H,NH+COOH). The infrared spectrum

(KBr) of (11) displayed absorption bands at 3281-2904 (broad NH and OH), 1732 (carboxylic C= O) and 1710 cm-1 (lactone C = O) and its mass spectrum showed a molecular ion peak (M+) at m/z 259 (28.07%), 242 (1.88), 241 (1.28), 162 (14.65), 161 (100), 133 (34.22), 132 (7.49), 99 (18.45).

Treatment of compound (11) with hydrazine hydrate and phenyl hydrazine in ethanol at room temperature gave 3-{N-[1-aminocarbamoyl)-2-(2-hydroxyphenyl) ethyl] carbamoyl} prop-2-enoic acid (12a) and 3-(N-{2-(2`-hydroxyphenyl)-1-[N-(phenylamino) carbamoyl] -2-(2`-phenylhydrazino) ethyl } carbamoyl) prop-2-enoic acid (12b), respectively (scheme 2). The 1H-NMR (DMSO-d6) of (12a) showed signals at δ 4.06 (d, ^{1}H, C-1`), 4.96 (d,1H, C-2`), 5.9 (d, 1H, = CHCO and 7.37-8.6 ppm (m,13H, ArH+3NH+ 2NH2+COOH). Also, compound (12b) showed in its ^{1}H-NMR (DMSO-d6) the same signals, but for aromatic protones appear at 6.57-7.48 (m, 15H, 14 ArH+ COCH =), 8.00 (d,2H, disappeared after D2O exchange , NH+ phenolic OH), 9.12 (s, 1H, disappeared after D2O exchange, NH), 9.66 (d, 3H, disappeared after D2O exchange, 3NH) and 10.22 ppm (s,1H, COOH).

The infrared spectrum (KBr) of compounds (12a,b) revealed absorption bands at 3426, 3347-3073, 3049 (broad NH_2, NH, OH), 1723-1710 (carboxylic C=O) and 1688-1663 cm^{-1} (C=O). Mass spectrum of compound (12a) showed a molecular ion peak (M^+) at m/z 323 (zero%), 229 (2.64), 162 (10.84), 161 (100%), 133 (38.71), 106 (9.63), 85 (13.14), 78 (33.92), mass spectrum of (12b) showed a molecular ion peak (M^+) at m/z 474 (1.37%), 473 (8.80), 471 (20.73), 444 (11.29), 353 (18.73), 310 (39.70), 308 (100%), 197 (34.58), 125 (18.80), 107 (20.23), 93 (80.63).


(11)
maleic anhydride
(12a,b)
R R-
a, H NH2
b, C6H5 NHPh
(8a-d)
a, Ar = C6H4NO2-p
b, = C6H4Cl-p
c, = C6H4Br-p
d, = 2 - thienyl
PhMgBr
8a
-H2O
(10)
Ar = C6H4NO2-p
4-hydroxycoumarin
(9a-d)
a, Ar = C6H4NO2-p
b, = C6H4Cl-p
c, = C6H4Br-p
d, = 2 - thienyl

Scheme (2)

Biological Activity

All the prepared compounds were screened for their antimicrobial activity against the Gram-positive bacteria : (*1-Staphylococcus aureus*, 2-*Bacillus Subtilis*, 3-*Bacillus cereus*), Gram-negative bacteria (4-*Pseudomonas aurignosa, 5-Echerichia coli*,6-*Enterobacter aerogenes*), as well as fungi : a) *Aspergillus 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 of these compounds have been evaluated by filter paper disc method [16] after dissolved in *N*,*N*-dimethylformamide to abtain a 1mg/ml solution (1000 ppm). The inhibition zones of microbial growth surrounding the filter paper disc (5 mm) were measured in millimeters at the end of an incubation period of 3 days at 37^{o}C for *Echerichia coli* and at 28^{o}C for other bacteria and fungi, *N*,*N*-dimethylformamide alone showed no inhibation zone. The results are illustrated in Tables 1 and 2.

Table (1)
Antibacterial activity of the synthesized compounds

Compd.	Organism*					
	1	**2**	**3**	**4**	**5**	**6**
2	24	12	14	11	14	16
3	26	10	18	12	25	14
4	22	16	20	10	20	14
5	10	9	9	11	-	16
7a	28	16	13	19	13	13
7b	20	15	22	14	18	12
8a	26	10	18	12	10	10
8b	25	11	18	7	14	11
8c	22	11	12	6	12	13
8d	28	12	19	10	13	14
9a	22	12	13	10	20	12
9b	20	15	13	11	7	12
9c	28	14	22	23	19	17
9d	26	1	15	10	11	12
10	27	17	15	10	13	10
11	22	10	14	10	11	12
12a	25	10	13	10	12	15
12b	22	13	13	11	9	12
Amoxicillin	29	12	20	11	36	10

Table (2)

Antifungal activity of the synthesized compounds

Compd.	Organism*		
	A	B	C
2	16	18	22
3	12	18	22
4	14	12	14
5	13	12	10
7a	14	18	20
7b	14	15	18
8a	10	18	20
8b	10	16	18
8c	12	22	20
8d	10	12	22
9a	11	16	18
9b	15	18	18
9c	10	12	18
9d	15	18	12
10	12	15	10
11	15	17	16
12a	13	18	16
12b	13	18	8
Mycostatin	12	20	26

***Organism** *1-Staphylococcus aureus, 2-Bacillus Subtilis,3-Bacillus cereus,4-Pseudomonas aurignosa, 5-Echerichia coli and 6-Enterobacter aerogenes.*

*** Organism** : A) *Aspergillus niger,* B) *Penicillium italicum* and c) *Fusarium Oxysporum*.

Table (3)
Characterization data of the synthesized compounds

Compd.	M.P. (°C)	Yield (%) / Colour	Formula (M.W.)	Analysis Calcd./ Found			
				C	H	N	S
2	226	60 Yellow	$C_{17}H_{12}N_2O_3S$ (324.35)	62.95 62.88	3.72 3.80	8.63 8.71	9.88 9.78
3	242	60 Yellow	$C_{20}H_{12}N_2O_5S$ (392.38)	61.22 61.01	3.08 3.14	7.13 7.22	8.17 8.04
4	150	40 Yellow	$C_{19}H_{12}N_2O_4S$ (364.37)	62.63 62.70	3.31 3.39	7.68 7.57	8.79 8.68
5	138	60 White	$C_{30}H_{26}ClNO_2$ (467.99)	76.99 76.95	2.60 2.51	2.99 2.96	- -
7a	284	71 White	$C_{20}H_{15}N_3O_2S$ (361.41)	66.46 66.48	4.18 4.21	11.62 11.66	8.87 8.84
7b	276	60 White	$C_{26}H_{19}N_3O_2S$ (437.51)	71.37 71.30	4.37 4.39	9.60 9.58	7.32 7.39
8a	223	60 Yellow	$C_{16}H_{10}N_2O_4$ (294.27)	65.31 65.23	3.43 3.40	9.52 9.48	- -
8b	174	54 Yellow	$C_{16}H_{10}ClNO_2$ (283.72)	67.74 67.70	3.55 3.57	4.94 4.90	- -
8c	170	57 Yellow	$C_{16}H_{10}BrNO_2$ (328.17)	58.56 58.58	3.07 3.12	4.27 4.20	- -
8d	144	50 Yellow	$C_{14}H_9NO_2S$ (255.30)	65.87 65.71	3.55 3.60	5.49 5.40	12.56 12.59
9a	>300	38 Yellow	$C_{25}H_{14}N_2O_7$ (454.14)	66.06 66.00	3.10 3.15	6.16 6.13	- -
9b	>300	35 Yellow	$C_{25}H_{16}ClNO_5$ (445.85)	67.34 67.29	3.61 3.70	3.14 2.95	- -
9c	>300	39 Yellow	$C_{25}H_{16}BrNO_5$ (490.31)	61.24 61.28	3.28 3.23	2.85 2.80	- -
9d	250	33 Pale Yellow	$C_{23}H_{15}NO_5S$ (417.43)	66.17 66.21	3.62 3.70	3.35 3.36	7.68 7.62
10	130	40 Yellow	$C_{40}H_{32}N_2O_3$ (588.70)	81.60 81.58	5.47 5.44	4.75 4.80	- -
11	192	55 Yellow	$C_{13}H_9NO_5$ (259.21)	60.23 60.18	3.49 3.40	5.40 5.35	- -
12a	172	40 White	$C_{13}H_{17}N_5O_5$ (323.30)	48.29 48.18	5.30 5.28	21.66 21.52	- -
12b	160	38 Yellow	$C_{25}H_{25}N_5O_5$ (475.50)	63.14 63.10	5.29 5.22	14.72 14.68	- -

Table (4)

IR and ^{1}H NMR spectra of products in table

Compd.	IR cm^{-1}	^{1}H NMR δ ppm
2	3273 (NH), 1709 (lactone C = O), 1672 (amide C = O) and 1486 cm^{-1} (C = S).	6.81-7.99 (m,9H, ArH), 9.6 (s,1H,CH-4), 11.85 (s,1H, disappeared after D_2O exchange, NH), and 13.47 ppm (s,1H, disappeared after D_2O exchange, NH).
3	3413-3344 (enolic OH), 1723 (lactone C = O), and 1646 cm^{-1} (C = O).	4.1 (s,2H,CH_2), 6.87-7.7 (m,9H, ArH), 10.3(s, 1H, CH-4), 11.88 and 12.31 ppm (s, 1H, disappeared after D_2O exchange, 2 enolic OH).
4	3336 (enolic OH), 1710 (lactone C = O) and 1679 cm^{-1} (amide C= O).	7.30-8.41 (m,9H, ArH), 9.72 (s, 1H, CH-4) and 10.23 ppm (s, 1H, disappeared after D_2O exchange, enolic OH)
5	1708 cm^{-1} (lactone C= O)	4.45 (s,6H, 3CH_2), 7.01 (s, 1H, CH-4) and 7.31-7.33 ppm (m, 19 H, ArH).
7a	3341 (NH) and 1699 cm^{-1} (lactone C = O)	2.66 ppm (s, 3H,SCH_3) , 7.54-8.02 (m,10H, ArH+ pyrimidine protone), 8.87 (s, 1H, NH) and 9.56 ppm (s, 1H, CH-4)
7b	3341 (NH) and 1699 cm^{-1} (lactone C = O)	4.57ppm(s,2H,SCH_2Ph) , 7.32-8.03 (m,10H, ArH+pyrimidineprotone), 8.77 (s, 1H, NH) and 9.59ppm (s, 1H, CH-4)
8a	1711 (lactone C=O) and at 1620 cm^{-1} (C=N).	7.38-8.92 (m, 9H, ArH+ olefinic H) and 9.15 ppm (s, 1H, CH-4).
8b	1711 (lactone C=O) and at 1620 cm^{-1} (C=N).	7.35-7.90 (m, 9H,ArH+ olefinic H) and 8.95 ppm (s, 1H, CH-4).
8c	1711 (lactone C=O) and at 1620 cm^{-1} (C=N).	7.25-7.86 (m,9H, ArH+ olefinic H) and 8.9 ppm (s, 1H, CH-4).
8d	1711 (lactone C=O) and at 1620 cm^{-1} (C=N).	7.44-7.90 (m, 8H,ArH+ olefinic H) and8.94ppm (s, 1H, CH-4)
9a	3356 (NH), 1708-1732 (lactone C=O) and 1692 cm^{-1} (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.
9b	3356 (NH), 1708-1732 (lactone C=O) and 1692 cm^{-1} (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.

Table (4)
IR and ^{1}H NMR spectra of products in table

Compd.	IR cm^{-1}	^{1}H NMR δ ppm
9c	3356 (NH), 1708-1732 (lactone C=O) , 1692 cm^{-1}(C = O)	5.62 (s,1H,C_3-H in ketonic form), 5.80 (s,1H,-CH), 7.30-8.55 (m,13H,ArH+NH disappeared after D_2O exchange.
9d	5.02 (s,1H,C_3-H in ketonic form), 5.33 (s,1H,-CH), 6.98-7.50 (m,12H, ArH) and 10.59 ppm (s,2H, disappeared after D_2O exchange, NH+ enolic OH).	3356 (NH), 1708-1732 (lactone C=O) and 1692 cm^{-1} (C = O) .
10	1.30(d,1H,CH),1.47(s,1H,NH), 4.03(s,1H,CH), 5.60(s,1H,CH) and 6.76 – 8.00 ppm (m,28H , ArH).	3404 cm^{-1} (NH).
11	6.43 (d,1H, = CHCO-) , 6.63(d,1H, COCH=), 7.35-7.41 (m,4H,ArH) and 10.33 ppm (s,2H,NH+COOH).	3281-2904 (broad NH and OH), 1732 (carboxylic C= O) and 1710 cm^{-1} (lactone C = O)
12a	4.06 (d, 1H, C-1`), 4.96 (d,1H, C-2`), 5.9 (d, 1H, = CHCO and 7.37-8.6 ppm (m,13H, ArH+3NH+ 2NH_2+COOH).	3418, 3340-3078, 3052 (broad NH_2, NH, OH), 1723-1710 (carboxylic C=O) and 1688-1663 cm^{-1} (C=O).
12b	4.06 (d, 1H, C-1`), 4.96 (d,1H, C-2`), 5.9 (d, 1H, = CHCO 6.57-7.48 (m, 15H, 14 ArH+ COCH =), 8.00 (d,2H, disappeared after D_2O exchange , NH+ phenolic OH), 9.12 (s, 1H, disappeared after D_2O exchange, NH), 9.66 (d, 3H, disappeared after D_2Oexchange, 3NH) and 10.22 ppm (s,1H, COOH).	3426, 3347-3073, 3049 (broad NH_2, NH, OH), 1723-1710 (carboxylic C=O) and 1688-1663 cm^{-1} (C=O).

Table (5)

Mass spectra of products in table 3

Compd.	MS m/z
2	324 (63.41%), 203 (40.98), 161 (39.54) , C_7H_6O,105 (100).
3	392 (zero%) ,220 (100%), 203 (16.81) , 161 (15.92).
4	364(zero%),203(18),189(21.94),161 (100%),133(46.95),78(29.10),51(32.37).
5	467 (zero%), 432 (30.43), 342 (100),250(100), 222 (50), 181 (37.55), 146 (8.94),91 (91.29), 65 (46.32).
7a	(361) (100%),314 (8.82), 286 (20.58), 128 (62.95), 77 (43.89).
7b	437 (100 %),314(18.44),286(26.30), 128(25.69), 77(30.82).
8a	294 (100%),247(1.27),220(5.30),190(8.41), 165(16.65),146(99.44),118(46.46),89(29.29)
8b	283(29.61),213(5.60),161(13.15),149(41.94) 146(91.48),129(22.66),85(28.12),69(100%)
8c	328(64.27),182(6.12),165(10.56),146(100%) 89(44.01).
8d	255(100%),241(13.74),226(67.91),146(93.35) 118(59.54),96(51.21)89(32.03)
9a	456(zero%),332(26.78),316(12.99),196(72.17) 168(100%),139(59.72),69(19.31).
9b	445 (zero%),427(19.77),316(100%),57(25.11)
9c	490 (zero %),473(10.06),316(100%),174(5.80) 75(1.28).
9d	417 (3.7%),296(100%),213(3.64),121(24.86), 93(5.85),65(6.58).
10	587 (1.27%), 586 (2.06), 466 (1.58), 465 (3.21), 390 (3.30), 389 (7.40), 314 (4.07), 313 (4.11), 238 (6.50), 182 (16.63), 165 (32.63), 77(100%).
11	259 (28.07%), 242 (1.88), 241 (1.28), 162 (14.65), 161 (100), 133 (34.22), 132 (7.49), 99 (18.45)
12a	323 (zero%), 229 (2.64), 162 (10.84), 161 (100%), 133 (38.71), 106 (9.63), 85 (13.14), 78 (33.92)
12b	474 (1.37%), 473 (8.80), 471 (20.73), 444 (11.29), 353 (18.73), 310(39.70), 308 (100%), 197(34.58) 125(18.80), 107 (20.23), 93 (80.63).

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تحضير مشتقات كومارين جديدة لها نشاط بيولوجي

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الملخص :

تفاعل ٣- أمينوكومارين (1) مع بنزويل أيزوثيوسيانات وأعطي مشتق الثيويوريا (2) ٠ تم حلوقة المركب (2) إلى كل من مشتقات ٢- ثيوأوكسو- ١،٣،٥- ثلاثي هيدروبيريميدين- ٤،٦- ثنائي أون (3) والثيازولدين- ٤- أون (4)٠ ألكلة المركب (١) أعطي المركبات (5) ، (7a,b)٠ تكاثف المركب(1) مع بعض الألدهيدات الأروماتية وأنتج قواعد شيف (8a-d)٠ تفاعلت المركبات (8a-d) مع ٤- هيدروكسي كومارين وأنتجت المركبات (9a-d)٠ تفاعل كاشف جيرينارد مع (8a) وانتج مشتق الكورمان (10)٠ وقد تفاعلت المشتقات (8a-d) مع أنهيدريد حامض الماليك وأعطت المركب (11) كناتج واحد لهذا التفاعل٠ معالجة المركب (11) مع الهيدرازين و الفينيل هيدرازين عند درجة حرارة الغرفة أدى إلى فتح حلقة الكومارين ونتج المركبات (12a,b) على التوالي٠

تم دراسة التأثير البيولوجي للمركبات المحضرة تجاه بعض البكتريا موجبة الجرام وسالبة الجرام وكذلك تجاه بعض الفطريات٠