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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NITROGEN HETEROCYCLES INCORPORATION INTO COUMARIN

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Abstract

3-Carbethoxycoumarin derivatives were reacted with some neucleophilic reagents such as amines, hydrazines, urea derivatives and amino acids in order to study their effect on coumarin nucleus especially carbonyl coumarin and synthesis of new derivatives which have biological effects on microorganisms such as bacteria and fungi. The structural assignments of the new compounds were based on analytical and spectral data.

Results and discussion:

3-Carbethoxycoumarin **(Ia)** and 5-bromo-3-carbethoxy coumarin **(Ib)** reacted with aromatic primary amines e.g. aniline and o-toludine to give N-substituted carboxamides (**IIa,b)**[1,2], respectively

Also, when 3-carbethoxycoumarin derivatives **(Ia-c)** were reacted with aromatic heterocyclic amines such as 2-aminopyridine, 2-aminothiazole, 2-minobenzothiazole and 3-methyl-5-ethoxypyroyle the products were N-substituded carboxamidocoumarins, **(IIIa-e)** and **(IV)**, respectively**.**

The mass spectrum of the compound **(IIId)** shows ion peaks fragmentation at m/z 400/402 (5.3%) and other peaks at m/z 251/252 (1.1%) m/z 172 and m/z 74 (5.6%).

Alcoholic ferric chloride test didn't give any definite colour of phenol[3] i.e. the α-pyrone ring is not cleavage.

The previous studies[4] reported that when coumarin derivatives reacted with secondary amines the α-pyrone ring may be opened. In the present investigation[5] when 3-carbethoxycoumarin derivatives are reacted with diethyl amine in the presence of ethanol it give N-diethyl coumarin carboxamide **(V)** which does not give any phenolic colour with alcoholic ferric chloride[3].

3-Carbethoxycoumarin condensed with ethyl acetoacetate in the presence of ammonium acetate to give chemoselective products according to the conditions of the reaction[6]. Thus, when 5-bromo-3-carbethoxycoumarin **(Ib)** is reacted with ethyl acetoacetate and ammonium acetate in boiling ethanol it gave 5-bromo-3(6-ethoxy-4'-methyl pyridozine-3'-yl)-2H-chromen-2-one **(VI).**

A previous studies[2] proved that coumarin derivatives react with hydrazine hydrate through opening of α-pyrone ring to give different phenolic derivatives. Then it was reported[3] that 3-carbethoxycoumarin derivatives react the with hydrazine hydrate to give different hydrazide derivatives, the reaction of 3-carbethoxy coumarin derivatives **(Ia-c)** with phenylhydrazine, 4-nitrophenyl-hydrazine and 2,4-dinitrophenyl hydrazine gave the hydrazide derivatives **(VIIa-f)**, respectively without α-pyrone ring opening products.

Previous studies[7,8] showed that when 3-bromoacetyl coumarin derivative was condensed with aryl thiourea derivatives, the thiazolylcoumarin derivatives were obtained.

Now the reaction of the 3-carbethoxycoumarin **(Ib)** with thiourea in presence of boiling acetic acid gave 3-(6'-amino-4'-thioxo-4',5'-dihydro1',3',5'-triazin-2'-yl)-5-bromo-2H-chromen-2-one **(VIII)**.

The previous studies[9] proved that 3-aminocoumarin derivatives react with phthalic anhydride to give benzopyrano-benzoxazines.

In this study 3-carbethoxycoumarin **(Ia)** reacted with aliphatic amides such as formamide to give [1] benzopyran [3,2-d] chroman 2,4-dione **(IX)**.

Also, 3-carbethoxycoumarins **(Ia-c)** react with succinimide and/or phthalimide in basic medium to give N-[3-2H-(1) benzopyran-2-one] carbonylsuccinamide **(Xa-c)** and benzopyran-3-carbonyl phthalimide **(Xd),** respectively.

3- Carbethoxycoumarin **(Ib)** reacted with anthranilic acid in the presence of sodium ethoxide in boiling ethanol to give 2-(5-bromo-2-oxo-2H-chromen-3-yl)-4H-3,1-benzoxazine-4- one **(XI**).

The reaction of **(IIId)** with chlorosulphonic acid gave the corresponding 6-sulphonyl chloride derivative[10] **(XII),** which is used for preparing dyes especially

flourscence dye[10]. Compound **(XII)** is reacted with secondary aliphatic amine such as diethylamine to give N-alkyl sulphonamide derivative **(XIII).**

Biological screening

The prepared compounds were tested against different types of Gram positive, Gram negative bacteria, Unicellular yeast and Film entous fungi using agar-diffusion technique and/or agar plate diffusion techniques[11], as shown in table (1)

Table (1) : Antimicrobial Activity of Some Newly (1) benzopyran derivatives

Tested organism	***Staphylococcus aureus***			***Bacillus subtilis***			***Salmonella typhi***			***Aspergillus flavus***			***Aspergillus niger***			***Candida albicans***		
concentration	**1**	**2.5**	**5**	**1**	**2.5**	**5**	**1**	**2.5**	**5**	**1**	**2.5**	**5**	**1**	**2.5**	**5**	**1**	**2.5**	**5**
compd. No.	**(mg/ml)**			**(mg/ml)**			**(mg/ml)**			**(mg/ml)**			**(mg/ml)**			**(mg/ml)**		
IId	0	0	0	+	+	+	+	+	+	+	+	+	++	++	++	++	++	++
IIe	0	+	+	+	+	+	+	+	+	++	++	++	0	0	0	0	0	0
V	++	++	++	0	+	+	+	+	+	+	+	+	+	+	++	0	0	0
VII	0	0	0	++	++	++	+	+	+	+	+	+	0	0	0	+	+	+
IXb	0	+	+	+	+	+	+	+	+	+	+	+	0	0	0	+	+	++
IXc	+	+	+	+	+	+	+	+	++	+	+	+	+	+	+	0	0	0
X	0	+	+	+	+	+	0	+	+	++	++	++	+	+	+	+	+	++
XIII	0	+	+	++	++	++	0	+	+	++	++	++	+	+	+	+	+	+

Well diameter : 1 cm (100 μl of each conc. was tested).
Inhibition values = 0.1-05 cm beyond control = + ;
Inhibition values = 0.6-1.0 cm beyond control = ++
Inhibition values = 1.1-1.5 cm beyond control = +++ ;
0 = not detected.

Experimental

All melting points are uncorrected. The IR spectra were detected on a Shimadzu FT-IR 8201 PC spectrophotometer, Wafer technique in KBr discs and $\overline{\upsilon}$ in cm^{-1}. The ^{1}H-NMR spectra were run on a Bruker proton NMR Avance (300 Mz) using DMSO-d_6 as solvent and TMS as internal standard. The mass spectra were measured on a Varian Mat 112 spectrophotometer (70 eV).

Compounds **I, II , III** and **V** were prepared according to Sammour *et al.*[2]

3-[(3'-Ethoxy-5'-methyl-1H-pyrazol-yl)carbonyl[-2H-chromen-2-one (IV):

To 3-carbethoxycoumarin **(Ia)** (0.01 mole) in (30 ml) of absolute alcohol was added 3-methyl-5-ethoxypyrazol (0.01 mole) and the mixture was refluxed for 6 hours, then filtered while hot, left to cool, yellow crystals were separated which were crystallized from ethanol (Table 2).

5-Bromo-3-(6-ethoxy-4-methyl pyridazin-3-yl)-2H-chromen-2-one (VI).

Heating a mixture of of 3-carbethoxy coumarin **(Ib)**, (0.01 mole), ethyl acetoacetate(0.01 mole) and ammonium acetate (0.04 mole) in 30 ml of absolute ethanol until clear solution. The reaction mixture was left at room temperature for 72 hours, then concentrated and the solid product that separated out was filter and wash with acetone, then recrystallized from the proper solvent (Table 2).

***Reaction of 3-carbethoxycoumarin (Ia-c) derivatives with hydrzines*. Formation of the hydrazide *derivatives* (VIIa-f):**

To 3-carbethoxycoumarin derivatives (0.01 mole) **(Ia-c)** was added phenylhydrazine (0.01 mole), 4-nitrophenylhydrazine or 2,4-dinitriophenyl hydrazine in absolute ethanol (30 ml). The mixture was refluxed for 6 hours, then filtered off on hot, cooled to room temp and filter. The precipitates obtained were filtrated off and recrystallized from the proper solvent (Table 2).

3-(6-Amine-4-thioxo-4,5-dihydro-1,3,5-triazin-2-yl)-5-bromo-2H-chromen-2-one (VIII).

Heating a mixture of 3-carbethoxycoumarin derivative **(Ib)** (0.005 mole) and thiourea (0.005 mole) in (10 ml) of acetic acid and (5 ml) of absolute ethyl alcohol under reflux for 6 hours. The mixture was filtered off while hot and then cooled. The solid product obtained was filtered off, washed with cold water and then recrystallized from ethanol (c.f. Table 2).

[1] benzopyran [3,2-d] Chroman 2,4-dione (IX)

A mixture of of 3-carbethoxy coumarin **(Ia)** (0.01 mole) in (50 ml) of ethanol of formamide solution (0.01 mole) and 5 drops of dry pyridine was heated under reflux for 6 hours. The mixture was filtered off while hot and poured onto ice/HCl (99%).

The product obtained was filtered off and then recrystallized of from ethanol (c.f. Table 2).

Reaction of 3-carbethoxycoumarin derivatives (Ia-c) with succinimide. Formation of (1) benzopyran-2-carbonylsuccinamide (Xa-c).

Heating a mixture of 3-carbethoxycoumarin **(Ia-c)** (0.01 mole) and succinimide (0.01 mole) in (25 ml) of ethanol and 5 drops of pyridine under reflux for 6 hours. The mixture was filtered off and add ice/HCl. The, separated solid was filtered off, washed well with water and recrystallized from ethanol (Table 2).

2-[2-oxo-2H-chromen-3-yl) carbonyl]-1H-isoindole-1,3(2H) dione (Xd):

(0.01 mol) at 3-carbethoxycoumarin derivative **(Ia)** was dissolved in (50 ml) of hot ethanol, then (0.01 mole) of phthalimide was added and (0.03 mole) of anhydrous potassium carbonate, then the mixture was heated under reflux for 6 hours. The mixture was filtered as and ice/HCl was added. The product obtained was filtered off and washed with water, then recrystallized from ethanol (Table 2).

2-(5-Bromo-2-oxo-2H-chromen-3-yl)-4H-3,1-benzoxazine-4-one (XI)

A mixture of 3-carbethoxycoumarin **(Ib)** (0.01 mole) in (30 ml) of absolute ethanol, sodium ethoxide (0.01 mol), and (0.01 mol) of anthranilic acid under reflux for 6 hours after cooling ice/HCl was added. The product filtered off and washed with water, then recrystallized from ethanol (Table 2).

2-{(5-Bromo-2-oxo-2H-chromen-3-yl) carbonyl) amino}-1,3-benzo-thiazole 6-sulfonyl chloride (XII).

A mixture of **(IIId)** (0.01 mol) and (0.25 mol) of chlorosulphonic acid was heated was at 130˚C while stirring for 3 hours. The mixture was cooled to 10˚C and poured into cold water and filtered. The precipitate obtained was filtered off, washed with water (the pH is 5).

5-BromoN-[(6-diethylsulfamoyl-benzothiazol-2-yl) amide]-2-oxo-2H- chromene-3-carboxamide (XIII).

To the solution mixture from step (1) **(XII)** add (5 ml) of water as a solvent, then, (0.02 mol) of diethylamine stirring. The mixture was left at room temperature

for 2 hours, the wash the product with water and recrystallized with ethanol (Table 2)

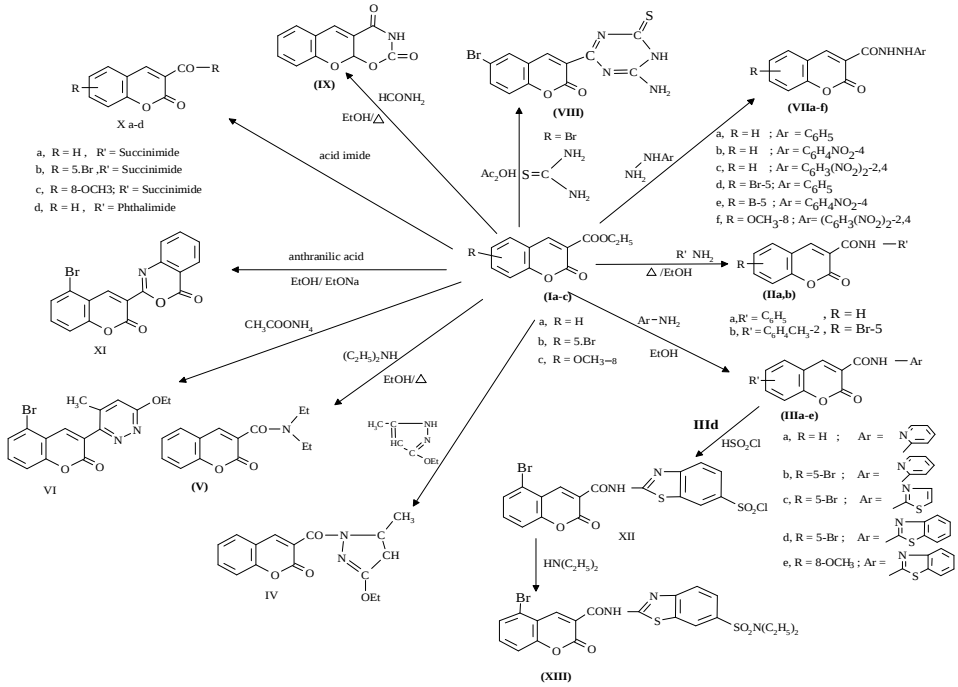

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Table (2): Analytical and spectral data of the newly prepared compounds

Comp. No.	M.P. °C yield %	Solvent of crystallization colour crystals	molecular formula (Mol.wt.)	IR	^{1}HNMR- (δ ppm)
IIa	128°C 70	EtOH Dusty powder	$C_{16}H_{11}NO_3$ (265)	υNH at 3220 cm^{-1}, υC–H at 2916.2, 2846.7 cm^{-1}, υC=O of lactone at 1705 cm^{-1} and υCONH carboxamide at 1635.5 cm^{-1}.	4.12 (s, 1H, NH) ; 6.25 (s, 1H, olefinic H); 6.39-6.37 (m, 9H, Ar–H) .
IIb	150 60	EtOH beige crystals	$C_{17}H_{12}BrNO_3$ (358)	υNH at 3120cm^{-1}, υC–H at 2846.7, 2916 cm^{-1}, υcm^{-1}, υC=O at 1705 cm^{-1} and υC=N at 1651 cm^{-1}.	
IIIa	114 40	EtOH Dusty reddish powder	$C_{15}H_{10}N_2O_3$ (266)	υNH at 3240cm^{-1}, υC–H at 3031, 2916.2, 2846.7 cm^{-1} υC=O for δ lactone at 1743.5 cm^{-1}, υC=O carboxamide at 1681.8 cm^{-1} and υC=N at 1630 cm^{-1}	7.39 (m, 9H, Ar–H and olefinic proton) at 8.73 .
IIIb	245 55	EtOH light beige crystals	$C_{15}H_9BrN_2O_3$ (345)	υNH at 3140 cm^{-1}, υC–H at 2916.2, 2846.7 cm^{-1}, υC=O for δ lactone at 1720.0 cm^{-1}, υC=O carboxamide at 1643.2 cm^{-1}.	
IIIc	215 50	EtOH dark beige crystals	$C_{13}H_7BrN_2O_3S$ (351)	υNH at 3140, 3240 cm^{-1}, υC–H at 3039.6, 2916.2, 2816.7 cm, υC=O δ lactone at 1735.8 cm^{-1} υC=O carboxamide at 1674.1 and υC=N at 1630 cm^{-1}.	
IIId	217 40	EtOH light beige powder	$C_{17}H_9BrN_2O_3S$ (401)	υNH at 3225.5 cm^{-1}, υC–H at 2916.2, 2846.7 cm^{-1}, υC=O δ lactone at 1743.5 cm^{-1}, υC=O carboxamide at 1681.8 cm^{-1} and υC=N at 1640 cm^{-1}.	
IIIe	125 40	EtOH Beige yellowish powder	$C_{18}H_{12}N_2O_4S$ (352)	υNH at 3240cm^{-1}, υC–H at 2918, 2848 cm^{-1}, υC=O δ lactone at 1710.0 cm^{-1}, υC=O carboxamide at 1670 cm^{-1} and υC=N at 1610 cm^{-1}.	
IV	146 65	EtOH yellow crystals	$C_{16}H_{14}N_2O_4$ (298)	υC–H at 2846.7, 2916.2 cm^{-1}, υC=O at 1705 cm^{-1} and υC=N at 1635,5 cm^{-1}	0.98(s,3H, CH_3) (t, 3H, CH_2CH_3) 1.1 (q, 2H, CH_2CH_3) 4.1 (m, 4H, Ar–H) at 7.69–6.g
V	152 60	EtOH Dusty flakes	$C_{14}H_{15}NO_3$ (245)	C–H at 2846.7, 2916.2 cm^{-1}, υC=O at 1705 cm^{-1} and υC–N at 1635.5 cm^{-1}.	
VI	277 35	EtOH yellow crystals	$C_{14}H_{11}BrN_2O_3$ (335)	υC=O δ lactone at 1710 cm^{-1}, υC=N at 1620cm^{-1}, υC–H at 2940, 2918, 2850 cm^{-1} and υNH at 3420, 3268, 3143 cm^{-1}	
VIIa	180 75	EtOH Light orange crystals	$C_{16}H_{12}N_2O_3$ (280)	υNH at 3301.9 cm^{-1}, υC–H at 3055, 2916.2, 2846.7 cm^{-1}, υC=O hydrazide at 1697.2 cm^{-1} , υC=C at 1596.9 and υC=O lactone at 1720cm^{-1}	9.43 (s,  NH) at 9.43, 8.31-7.17 (m, 9H, Ar–H) 6.79 (s, 1H, CH=C) at 6.79 ppm.

Table (2) : Continued

VIIb	222	EtOH	$C_{16}H_{11}N_3O_5$	υNH at 3268.5, υC–H at 3050, 2916.2, 2846.7 cm^{-1}, υCO δ lactone at	

	80	yellow crystals	(325)	1720 cm^{-1}, υC=O at 1697.2 cm^{-1} and υC=C at 1604.2 cm^{-1}	
VIIc	175 90	EtOH yellow white crystals	$C_{16}H_{10}N_4O_7$ (370)	υNH at 2380 cm^{-1}, υC–H at 3030, 2916.2, 2846.7 cm^{-1}, υC=O δ lactone at 1743.5 cm^{-1}, υC=O hydrazide at 1697.2 cm^{-1} and υC=C 1605 cm^{-1}	
VIId	192 20	EtOH light yellow crystal	$C_{16}H_{11}$ BrN_2O_3 (359)	υNH 3450 cm^{-1}, υC–H at 3010, 2918, 2848 cm^{-1}, υC=O δ lactone at 1686 cm^{-1} and C=C at 1602cm^{-1}	
VIIe	241 20	EtOH light yellow crystal	$C_{16}H_{10}$ BrN_3O_5 (404)	υNH at 3440 cm^{-1}, υC–H at 3010, 2956, 2918, 2848 cm^{-1} υC=O δ lactone at 1710 cm^{-1}, υC=O hydrazide at 1680 cm^{-1} and υC=C at 1598 cm^{-1}	
VIIf	148 50	EtOH Orange powder	$C_{17}H_{12}N_4O_8$ (400)		3.35 (s, OCH_3), 4.99 (d, NH-NH) and 8.98-6.6 (m, 8H, Ar–H and olefinic proton)
VIII	211 50	EtOH pale brown dusty powder	$C_{12}H_7$ BrN_4OS (351)	υC=S at 1280 cm^{-1} υC=N at 1676 cm^{-1} , C=O δ lactone at 1738 cm^{-1} and υCH, υNH_2 at 3042, 3250, 2850, 2918, 3310 and 3390 cm^{-1}	
IX	149 50	EtOH pale brown light dusty powder	$C_{11}H_7NO_4$ (217)	υNH/OH at 3417.6 cm^{-1}, stretching absorption band for C=H at 2846.7, 2916.2cm^{-1}υC=O δ lactone at 1705 cm^{-1} and υC=O carbooxamid at 1635.5 cm^{-1}	7.05-8.97 (4H, Aromatic protons), 6.61 (olefinic protons, 4.11 (NH-proton) 9.0 and 11.21 (s.20H groups) .
Xa	165 60	EtOH brown crystals	$C_{14}H_9NO_5$ (271)	υC–H at 2846.7, 2916.2, 3040 cm^{-1} υC=O δ lactone at 1705 cm^{-1} and υC=O imide at 1643.2, 1680 cm^{-1}.	7.09-8.31 (4H-Aromatic protons) , 2.57 (d,7Hz) and 6.92 (s, 1H, olefinic) .
Xb	215 30	EtOH dusty crystalline	$C_{14}H_8BrNO_5$ (350)	υC–H at 2850, 2918, 3042 cm^{-1} υC=O δ lactone at 1736cm^{-1} and υC=O imide at 1676, 1680cm^{-1}	7.4-8.6 (3H–Aromatic protons), 13 (d, 2H of methylene) and 2.45 (t, 2H of the second methylene group) .
Xd	133 40	EtOH dusty powder	$C_{15}H_{11}NO_6$ (301)	υN–H at 2848, 2918, 3020cm^{-1}, υC=O δ lactone at 1718 cm^{-1}, υC=O imide at 1670, 1680 cm^{-1}.	
XI	190 70	EtOH dark yellow crystals	$C_{17}H_8$ $BrNO_4$ (370)	υC–H at 2850, 2920, 3050cm^{-1}, υC=O δ lactone at 1692 cm^{-1} and υC=N at 1628 cm^{-1}	6.65-7.9 (m, 8H–Aromatic protons) .
XII	134 70	EtOH light brown crystal	($C_{17}H_8BrN_2O_5S_2Cl$) ()	υC–H at 3050, 2920, 2850 cm^{-1} υC=O δ lactone at 1692cm^{-1}, υC=N at 1628 cm^{-1}	79-6.65 (8H-Aromatic protons)
XIII	209 50	EtOH grey circle crystals	$C_{21}H_{18}BrN_3O_5S_2$ (536)	υOH/NH at 3146, 3296 cm^{-1} υC–H at 2860, 2980, 3020cm^{-1} υC=O δ lactone at 1710cm^{-1} υC=S at 1638 cm^{-1} and υC–S–C at 1284 cm^{-1}	1.2 (t, 6H) 2.99 (q, 4H) 7.91-71.7 (m, 6H-Aromatic protons) .

It is satisfactory for microanalysis C, H, N, S and Br.