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SYNTHETIC AND BIOLOGICAL STUDIES ON COUMARIN HYDRAZONE DERIVATIVES

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SYNTHETIC AND BIOLOGICAL STUDIES ON COUMARIN HYDRAZONE DERIVATIVES

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The reaction of both of coumarin and 6-nitrocoumarin hydrazones (**1,4**) with alkyl(aryl)isothiocyanate afforded the corresponding 3-N[alkyl(aryl)thioamido] coumarins $\mathbf{3_{a-d}}$ or benzopyrano[2,3-c]pyrazole-3-thione derivatives $\mathbf{6_{a-d}}$, respectively. Compounds ($\mathbf{3_{a-d}}$) were used as key intermediates for the preparation of benzopyrano-pyridine derivatives ($\mathbf{7_{a-d}}$ & $\mathbf{10_a}$) or benzopyranoazepine derivatives $\mathbf{8_{a,c}}$ & $\mathbf{12_{a-d}}$ through the reaction with different acyl halides or ethoxymethylenemalononitriles and subsequent cyclization. Biological activity of some new compounds against Gram +ve and Gram -ve were given.

Keywords: Coumarin hydrazone; Isothiocyanate; Ylidenenitriles; Biological activity

INTRODUCTION

A considerable attention has been directed towards the synthesis of coumarin derivatives and their uses as antibacterial and antibiotic agents[1–8]. In a new extention of our recent lab. Work[6,8,9] on the synthesis of heterocyclic compounds containing benzopyran moiety, a new series of heterocyclic compounds containing this nucleus were prepared. Also, their antibacterial activities against some Gram +ve and Gram -ve bacteria were recorded.

RESULTS AND DISCUSSION

The reaction of coumarin hydrazone **1** with alkyl(aryl) isothiocyanates at room temperature afforded the corresponding ω-alkyl(aryl)coumarin thiosemicarbazone derivatives[8] $\mathbf{2_{a-d}}$, but when the reaction was performed in

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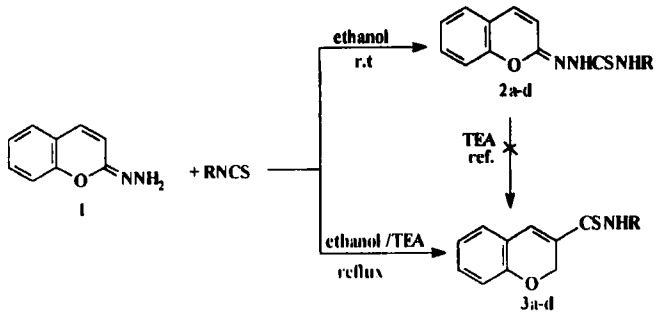
refluxing ethanol and in presence of triethylamine as a catalyst, it gave 3-N [alkyl(aryl)thioamido]coumarins $\mathbf{3_{a-d}}$ in good yields. The IR spectra of these compounds showed the absence of the characteristic bands corresponding to NH_2 group while exhibited bands referring to NH at 3300 – 3250. ^{1}HNMR showed the disappearance of NH_2 and vinylic CH (at position 3) signals and the appearance of a new signal for -CH_2 groups. The MS showed M^+ 217 and M^+268 for compounds $\mathbf{3_b}$ and $\mathbf{3_c}$ respectively. Refluxing of compounds $\mathbf{2_{a-d}}$ with a catalytic amount of triethylamine in ethanol for several hours led to its separation without change.



a,R =CH_3; b,R=C_2H_5

c,R=C_6H_5; d,R=3-CLC_6H_4

The formation pathway of compounds $\mathbf{3_{a-d}}$ was assumed to proceed via the addition of acidic hydrogen of coumarin hydrazone[10] on isothiocyanates to form 3-N[alkyl(aryl)thioamido]coumarin hydrazone followed by catalytic decomposition of hydrazone group through the intermediate L under the effect of triethylamine catalyst.

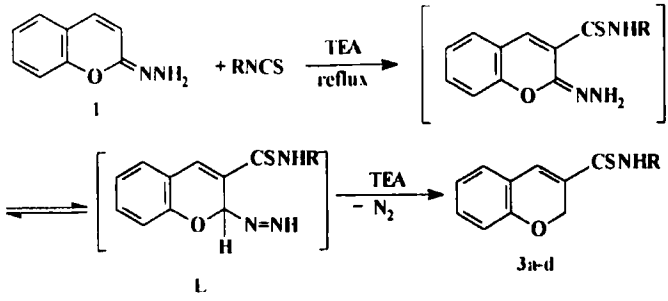


TABLE I Analytical and spectral data of the prepared compounds

Comp No	M.P.[a] (Cryst solvent)	Yield %	$M_F(M_w)$	Analytical data[b] calc (Found) %				IR(Kbr)[c] ν (cm^{-1})	^{1}H-NMR (DMSO-d_6)[d] (δppm)
				C	H	N	S		
3_a	183 ethanol	70	$C_{11}H_{11}NOS$ (205.28)	67.36 (67.72)	5.40 (5.50)	6.82 (6.67)	15.62 (15.80)	3325 (NH), 3127 (CH), 2962 (CH), 1180 (C=S)	9.7 (s, 1H, NH), 8.6–6.9 (m. 5H. arom + vinylic), 3.7 (S. 3H. CH_3), 3.2, (s. 2H,CH_2).
3_b	210 (dioxan)	79	$C_{12}H_{13}NOS$ (219.31)	65.72 (65.63)	5.97 (5.88)	6.39 (6.50)	14.62 (14.44)	3150 (NH), 3050 (CH), 2950 (CH), 1100 (C=S)	9.2 (NH), 8.5–7 (m. 5H, arom + vinylic). 4.3 (S, 2H, CH_2), 4–3 (Q, 2H,CH_2), 1.4–1.0 (t, 3H, CH_3).
3_c	246 (dioxan)	81	$C_{16}H_{13}NOS$ (267.35)	71.88 71.58	4.90 (4.82)	5.24 (5.40)	11.99 (11.80)	3200 (NH), 3050 (CH), 2950 (CH), 1200 (C=S).	9.3 (NH), 8.7–6.8 (m, 10H, arom + vinylic), 3.0 (s, 2H, CH_2).
3_d	197 ($CHCl_3$)	68	$C_{16}H_{12}NOSCl$ (301.80)	63.68 (63.60)	4.00 (4.05)	4.64 (4.42)	10.62 (10.79)	3210 (NH), 3040 (CH), 2950 (CH), 1190 (C=S).	9.5 (s, 1H, NH), 8.5–7.0 (m, 9H, arom + vinylic), 3.1, (s. 2H. CH_2).
6_a	240 (DMF)	72	$C_{11}H_7N_3O_3S$ (261.26)	50.57 (50.62)	2.70 2.73	16.08 (16.18)	12.27 (12.09)	3426 (CH), 2990 (CH), 1610 (C=N), 1587, 1253 (NO_2).	8.5–6.9 (m, 4H, arom + vinylic), 2.3 (s, 3H, CH_3).
6_b	210 (Acetone)	76	$C_{12}H_9N_3O_3S$ (275.29)	52.36 (52.21)	3.30 (3.24)	15.26 (15.41)	11.65 (11.51)	3200 (CH), 2950 (CH), 1620 (C=N), 1520, 1220 (NO_2).	8.5–7.0 (m. 4H. arom + vinylic), 4.1–3.3 (Q. 2H. CH_2), 1.6–1.0 (t, 3H. CH_3).
6_c	298 (DMF)	74	$C_{16}H_9N_3O_3S$ (323.33)	59.44 (59.64)	2.81 (2.90)	13.00 (13.18	9.92 (9.76)	3100 (CH), 2900 (CH), 1608 (C=N), 1585, 1263 (NO_2).	8.5–7.0 (m. 9H. arom + vinylic).

Comp No	M.P.[a] (Cryst solvent)	Yield %	$M_F(M_w)$	Analytical data[b] calc (Found) %				IR(Kbr)[c] ν (cm^{-1})	^{1}H-NMR (DMSO-d_6)[d] (δppm)
				C	H	N	S		
6_d	285 (Acetone)	77	$C_{16}H_8N_3O_3SCl$ (357.78)	53.71 53.61	2.25 (2.20)	11.74 (11.62)	8.96 (8.12)	3150 (CH), 2930 (CH), 1600 (C=N), 1580, 1270 (NO_2)	8.5–7.0 (m. 8H. arom + vinylic)
7_a	165 (dioxan)	78	$C_{13}H_9NO_3S$ (259.29)	60.22 (60.40)	3.50 (3.59)	5.40 (5.66)	12.37 (12.20)	3415 (OH), 3150 (CH), 2990 (CH), 1700, (C=O).	8.5–6.9 (m, 5H. arom + vinylic), 4.3 (br. 1H, OH), 1.5 (s, 3H, CH_3).
7_b	220 (ethanol)	80	$C_{14}H_{11}NO_3S$ (273.31)	61.52 (61.43)	4.06 (4.01)	5.12 (5.30)	11.73 (11.64)	3410 (OH), 3159 (CH), 2982 (CH), 1699 (C=O).	8.5–6.9 (m, 5H. arom + vinylic), 4.5 (br, 1H, OH), 2.9–2.0 (Q, 2H, CH_2), 1.3 (t, 3H, CH_3).
7_c	270 (dioxan)	80	$C_{18}H_{11}NO_3S$ (321.36)	67.28 (67.38)	3.45 (3.51)	4.36 (4.50)	9.98 (9.79)	3416 (OH), 2960 (CH), 1714 (C=O), 1110 (C=S).	8.6–6.6 (m, 10H, arom + vinylic), 3.3 (br. 1H, OH).
7_d	240 (chloroform)	73	$C_{18}H_{10}NO_3SCl$ (355.79)	60.77 (60.61)	2.83 (2.77)	3.94 (3.68)	9.01 (9.20)	3435 (OH), 3073 (CH), 1753 (C=O), 1134 (C=S).	8.2–6.2 (m. 9H, arom + vinylic), 4.8–4.0 (br. 1H, OH).
8_a	180 (benzene)	68	$C_{14}H_{11}NO_3S$ (273.31)	61.52 (61.42)	4.06 (4.11)	5.42 (5.28)	11.73 (11.54)	3433 (OH), 3291 (CH_3), 2920 (CH, 1700 (C=O), 1103 (C=S).	8.5–7.0 (m, 5H, arom + vinylic), 4.2 (s, 1H, CH), 4 (s, 2H, CH_2), 2.0 (s. 3H, CH_3).
8_c	190 (ethanol)	69	$C_{19}H_{13}NO_3S$ (335.38)	68.05 (68.35)	3.91 (3.99)	4.18 (4.39)	9.56 (9.40)	3429 (OH), 3246 (CH), 2990 (CH).	8.5–7.0 (m, 10H, arom + vinylic), 4.2 (s, 1H, CH), 3.9 (s, 2H, CH_2).
9_a	225 (dioxan)	71	$C_{14}H_{11}N_3OS$ (269.33)	62.43 (62.68)	4.12 (4.20)	15.60 (15.47)	11.90 (12.05)	2937 (CH), 2760 (N-CH_3), 2200 (CN), 1170. (C=S).	8.6–7.0 (m, 5H, arom + vinylic), 4.5–3.9 (br, 2H, CH_2), 3.5 (s, 1H, CH), 2.9 (s, 1H, CH), 2.6–2.0 (br. 3H, CH_3).

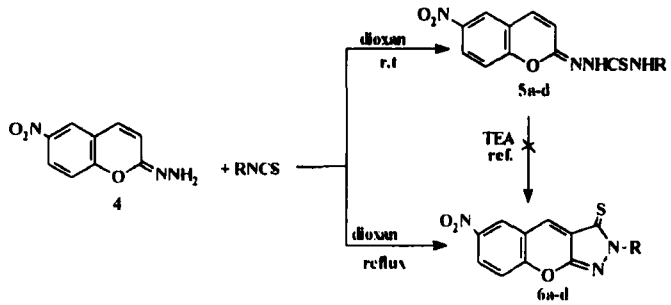
Comp No	M.P.[a] (Cryst solvent)	Yield %	$M_F(M_w)$	Analytical data[b] calc (Found) %				IR(Kbr)[c] ν (cm^{-1})	^{1}H-NMR (DMSO-d_6)[d] (δppm)
				C	H	N	S		
10$_a$	270 (dec benzene)	67	$C_{14}H_{11}N_3OS$ (269.33)	62.43 (62.49)	4.12 (4.18)	15.60 (15.72)	11.90 (11.79)	3165, 3065 (NH_2), 2963 (CH), 2195 (CN), 1109 (C=S)	8.5–7.0 (m, 5H, arom + vinylic), 4.6–4.0 (br, 2H. NH_2), 3.0 (s, 1H, CH), 0.5 (s, 3H, CH_3).
11$_a$	139 (ethanol)	69	$C_{16}H_{13}N_3OS$ (295.37)	65.06 (65.16)	4.44 (4.50)	14.27 (14.48)	10.86 (10.65)	3200 (CH), 2940 (CH), 2190 (CN), 1110 (C=S).	8.3 (s, 1H, vinylic CH), 8.0–6.9 (m, 4H, arom), 6.3–6.0 (s, 1H, CH), 4.3–4.0 (Q, 4H, $2CH_2$), 1.7–1.0 (t, 3H, CH_3).
11$_b$	140 (dioxan)	70	$C_{18}H_{18}N_2O_3S$ (342.42)	63.14 (63.34)	5.30 (5.38)	8.18 (8.39)	9.36 (9.18)	3050 (CH), 2978 (CH), 2204 (CN), 1700 (C=O), 1101 (C=S).	8.3 (s, 1H, CH vinylic), 8.0–6.8 (m, 5H, arom), 5.9–5.0 (s, 1H, CH), 4.6–4.0 (m, 6H, $3CH_2$), 1.7–1.0 (t, 6H, $2CH_3$).
11$_c$	155 (dioxan)	72	$C_{20}H_{13}N_3OS$ (343.41)	69.95 (69.76)	3.82 (3.74)	12.24 (10.02)	9.34 (9.46)	3052 (CH), 2989 (CH), 2200 (CN)	8.5–7.0 (m, 10H, arom + vinylic), 5.5 (s, 1H, CH), 4 (s. 2H. CH_2).
11$_d$	160 (DMF)	68	$C_{22}H_{18}N_2O_3S$ (390.46)	67.68 (67.89)	4.65 (4.73)	7.17 (7.29)	8.21 (8.11)	3061 (CH), 2980 (CH), 2201 (CN), 1700 (C=O).	8.3–6.9 (m, 10H, arom + vinylic), 4.3–4.0 (Q, 2H, CH_2), 5.6 (s, 1H, CH), 3.2 (s, 2H, CH_2), 1.6–1.0 (t, 3H, CH_3).
12$_a$	150 (ethanol)	80	$C_{16}H_{13}N_3OS$ (295.37)	65.06 (65.31)	4.44 (4.52)	14.27 (14.39)	10.86 (10.74)	3219, 3110 (NH_2), 2932 (CH), 2191 (CN), 1105 (C=S).	8.0–6.9 (m. 4H, arom), 4.5–3.5 (br, 4H. NH_2 + 2CH), 2.6–2.3 (Q, 2H, CH_2), 1.6–1.0 (t, 3H, CH_3).

Comp No	M.P.[a] (Cryst solvent)	Yield %	$M_F(M_w)$	Analytical data[b] calc (Found) %				IR(Kbr)[c] ν (cm^{-1})	^{1}H-NMR (DMSO-d_6)[d] (δppm)
				C	H	N	S		
12b	180 (DMF)	77	$C_{18}H_{18}N_2O_3S$ (342.42)	63.14 (63.02)	5.30 (5.20)	8.18 (8.38)	9.36 (9.27)	3198, 3090 (NH_2), 3020 (CH), 2934 (CH), 1700 (C=O), 1100 (C=S).	8.0–6.9 (m, 6H, arom + vinylic), 5-4.5 (br, 2H, NH_2), 4.6–2.9 (m, 5H, 2CH + CH), 1.6–1.0 (t, 6H, $2CH_3$).
12c	> 310	69	$C_{20}H_{13}N_3OS$ (343.41)	69.95 (69.75)	3.82 (3.71)	12 24 (12.40)	9.34 (9.18)	3210, 3130 (NH_2) 3127 (CH), 2950 (CH) 2190 (CN), 1084 (C=S).	8.6 (s, 1H, vinylic). 8.1–7.6 (s, 5H, arom), 7.6–6.8 (m, 4H, arom), 46-4 (br, 2H, NH_2), 2.6 (s, 1H. CH).
12d	310 (dioxan)	70	$C_{22}H_{18}N_2O_3S$ (390.46)	67.68 (67.60)	4.65 (4.61)	7.17 (7.25)	8.21 (8.08)	3205, 3105 (NH_2), 3069 (CH), 2910 (CH), 1700 (C=O), 1105 (C=S)	8.2–6.7 (m, 10H, arom + vinylic), 4.5 (s, 1H, CH), 3.2 (s,2H,CH_2), 1.5 (s, 1H, CH_3).

The MS were recorded on a Micromass 7070 E spectrometer operating at 70 ev, using direct inlet.

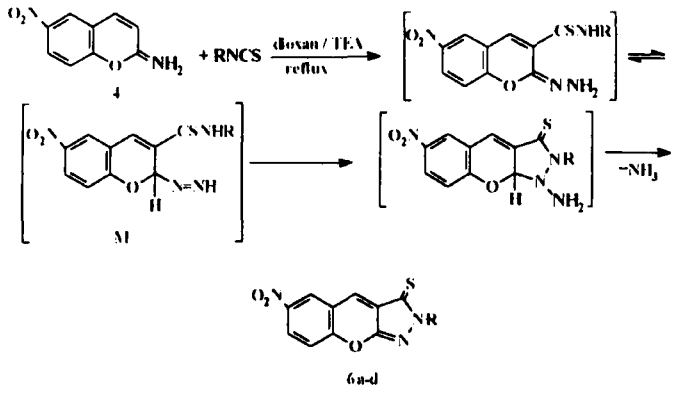
a. Uncorrected.
b. Satisfactory microanalyses; obtained; C ± 0.35%; H. ± 0.11%; N ± 0.40%; S ± 0.21%.
c. Measured on Nicolet 710 FT-IR spectrophotometer.
d. Measured with a Varian EM 360L using TMS as internal standard.

Also, 6-nitrocoumarin hydrazone[8] **4** was reacted with alkyl(aryl)isothiocyanate at room temperature to give ω-alkyl(aryl)thiosemicarbazone derivatives[8] $\mathbf{5_{a-c}}$, while on refluxing the compound **4** with the same reagents in dioxan and triethylamine as a catalyst, afforded the corresponding pyrazolobenzopyran derivatives $\mathbf{6_{a-d}}$ with pronounced NH_3 gas evolution. The MS of compounds $\mathbf{6_b}$ and $\mathbf{6_c}$ showed M^+ 276, and M^+ 323, respectively. The elemental and spectral analyses of these compounds were in agreement with their structures (cf. Table I).

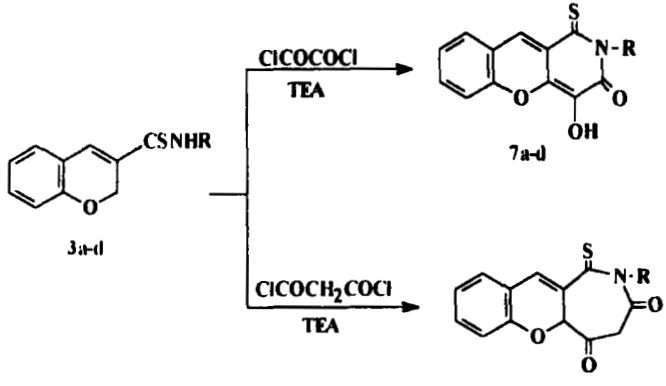


5&6: a.R=CH_3 b.R=C_2H_5 c.R=C_6H_5 d.R=3-ClC_6H_4

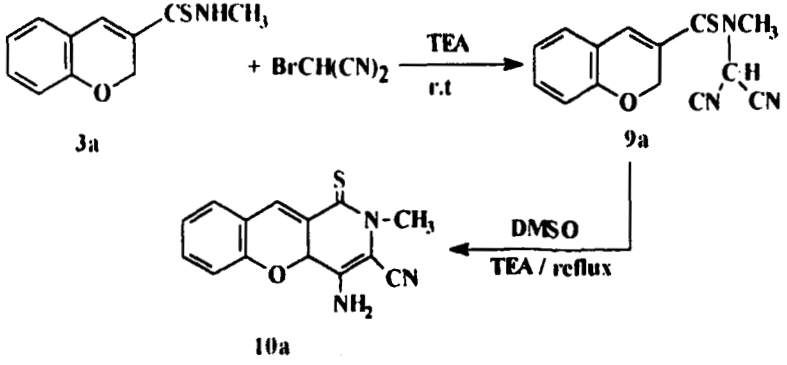
The postulated mechanism for the formation of $\mathbf{6_{a-d}}$ implies, firstly formation of 3-N[alkyl(aryl)thioamido]-6-nitrocoumarin-2-hydrazone which tatumerized to intermediate M. The cyclization step occurs through the addition of highly acidic NH of 3-thioamido group (due to the presence of NO_2 in conjugation with it) on N=N bond in hydrazone group followed by elimination of NH_3 molecule to give pyrazolobenzopyran derivatives $\mathbf{6_{a-d}}$.



The reaction of compounds $\mathbf{3}_{a\text{-}d}$ with oxalyl chloride or malonyl chloride and triethylamine in 1:1:2 molar ratio in dioxan at room temperature afforded the corresponding pyridinocoumarins $\mathbf{7}_{a\text{-}d}$ or azapinocoumarins $\mathbf{8}_{a,c}$ respectively. The structures of the products were confirmed by elemental, IR and ^{1}HNMR analyses (cf. Table I).

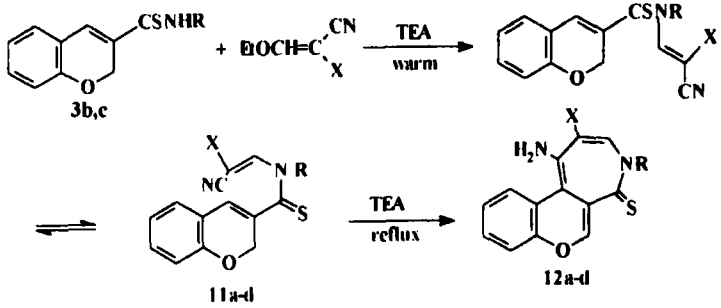


Also, 3-[N-methylthioamido]coumarin $\mathbf{3}_a$, was allowed to react with bromomalononitrile and TEA in 1:1:1 molar ratio at room temperature to give the intermediate $\mathbf{9}_a$, which cyclized to pyridinobenzapyran derivative $\mathbf{10}_a$by refluxing in DMSO containing catalytic amount of TEA. The elemental and spectral analyses of these compounds proved their structures (cf. Table I).



On warming equimolar ratio of compounds $\mathbf{3_{a,c}}$ and ethoxymethylene-malononitrile or ethyl exthoxymethylenecyanoacetate in presence of triethylamine as a catalyst afforded the corresponding 3-[N-alkyl(aryl)N-(1,1-disubstituted ethenyl) thioamido] (4H) benzopyran $\mathbf{11_{a-d}}$.

By refluxing compounds $\mathbf{11_{a-d}}$ in DMSO containing a catalytic amount of triethylamine, a more stable azepinobenzopyran derivatives $\mathbf{12_{a-d}}$ were obtained. The elemental and spectral analyses of these compounds were in agreement with their structures (cf. Table I).



11&12 : a.R=C_2H_5 X=CN b,R=C_2H_5 X=$COOC_2H_5$

c.R=C_6H_5 X=CN d.R=C_6H_5 X=$COOC_2H_5$

Biological screening

Pseudomonas aeruginosa -ve pathogenic bacteria and *Micrococcus lotus* Gram +ve pathogenic bacteria were used (Kindly provided by Bahig El-Deeb, Faculty of Science, Mol. Gen. Lab., Sohag, Egypt). Nutrient agar (NA) medium consisted of (g/L) beef extract, 1g; yeast extract, 2g; peptone, 5g; Sodium Chloride 5g and agar 15g for soft agar 2g/L was used. The medium was adjusted to pH 7.2 (Spear and Sussmuch, 1987). A 10g-phase bacteria suspension (0.05 ml in 3 ml soft agar) was poured onto the surface of the hard agar plate (NA) and the soft agar was left to solidify. A disc of filter paper (Whatman No.1), 1cm in diameter was saturated with a dose of 20μg/ml of the appropriate compound (dissolved in Methanol). After evaporation of (Methanol), the disc was placed in the center of the NA plate and incubated for 24 h at 30°C, after which the time the diameter

of the growth inhibition zone was measured, A control disc (Methanol only) was also performed. The experiment was carried out twice for each compound. The results in Table II indicate that compound $\mathbf{7_c}$ exhibits high effect on both Gram -ve and Gram +ve bacteria. Compound $\mathbf{12_d}$ has sever effect on *Pseudomonas aureginosa* and has no effect on the Gram +ve bacteria. In contrast compounds $\mathbf{12_b}$, $\mathbf{7_b}$ have no effect on -ve bacteria but exhibit high effect on Gram +ve bacteria. Compounds $\mathbf{7_d}$ and $\mathbf{8_a}$, have low effect on Gram -ve pathogenic bacteria but exhibit high effect on the Gram +ve bacteria.

TABLE II

Comp. No.	*Gram -ve Pseudomones aeruginosa*	*Gram +ve Micrococcus Letus*
$\mathbf{7_c}$	++	++
$\mathbf{12_d}$	++	–
$\mathbf{12_b}$	–	++
$\mathbf{7_b}$	+	++
$\mathbf{7_d}$	+	++
$\mathbf{8_a}$	–	++

Summary: – No effect, + Low effect, ++ High effect.

EXPERIMENTAL

Synthesis of 3-N[alkyl(aryl)thioamido] coumarin $\mathbf{3_{a-d}}$

An equimolar mixture of compound **1**, (methyl, ethyl, phenyl or m-chlorophenyl) isothiocyanate (0.01 mol) and 3 drops of triethylamine in dry ethanol (30 ml) was refluxed for 10 h. The reaction mixture was concentrated and cooled. The separated solid was filtered and crystallized from the proper solvent (cf. Table I).

MS of compound $\mathbf{3_b}$: m/z (relative intensity): 217(3), 202(19.5), 172(100), 146(72.96), 132(41.07), 102(37.19).

MS of compound $\mathbf{3_c}$: m/z (relative intensity): 268(100), 150(41), 104(35), 77(85.5), 51(55.8).

Reaction of 6-nitrocoumarinhydrazone 4 with isothiocyantes 6_{a-d}

A solution of compound **4** (0.01 mol) in dioxan (30 ml) was treated with methyl, ethyl. phenyl or m-chlorophenyl isothiocyanate (0.01 mol) and 3 drops of triethylamine. The reaction mixture was refluxed for 10 h, concentrated and cooled. The separated solid was filtered and crystallized from the proper solvent (cf. Table I).

MS of compound 6_b: m/z (relative intensity): 292(42.5), 276(55.9), 191(62.6), 159(33.8), 60(72), 44(100),

MS of compound 6_c: m/z (relative intensity): 322(22.61), 205(19.63), 172 (55.17), 135(56.88), 86(100), 58(49.77).

Reaction of 3-[N-alkyl(aryl)thioamido] coumarin with oxalyl chloride or malonyl chloride: 7_{a-d}, $8_{a,c}$

General procedure

To a solution of compounds 3_{a-d} (0.01 mol) in P-xylene (20 ml) was added (0.01 mol) of oxalyl chloride or malonyl chloride and triethylamine (0.02 mol). The reaction mixture was stirred at room temperature (20–25°C) for 6 h. The solid product was filtered, washed with water and crystallized from the proper solvent (cf. Table I).

Reaction of compound 3_a with bromomalononitrile: 9_a

Bromomalononitrile (0.01 mol) was added to a solution of compound 3_a (0.01 mol) and 2 drops of triethylamine in dioxan (30 ml) with stirring for 4 h at room temperature. The solid product 9_a was filtered, washed with water and crystallized from ethanol (cf. Table I).

Synthesis of pyridinobenzopyrano derivative: 10_a

A solution of compound 9_a (0.01 mol) and few drops of triethylamine in DMSO (30 ml) was refluxed for 1 h. The solution was concentrated, cooled, filtered and crystallized from DMSO (cf. Table I).

Synthesis of compounds $\mathbf{11_{a-d}}$

General procedure

Ethoxymethylenemalononitrile or ethyl ethoxymethylenecyanoacetate (0.01 mol) was added to a solution of compounds $\mathbf{3_{a-d}}$ (0.01 mol) in dioxan (40 ml) in presence of three drops of triethylamine. The reaction mixture was stirred with warming (40–45°C) for 4 h. After cooling, the formed precipitate compounds $\mathbf{11_{a-d}}$ was filtered and crystallized from suitable solvent (cf. Table I).

Synthesis of azepinobenzopyrano $\mathbf{12_{a-d}}$

The solution of compound $\mathbf{11_{a-d}}$ (0.005 mol) in DMSO (30 ml) containing two drops of triethylamine was refluxed for 2 h. The solution was concentrated, cooled and filtered. The solid product was crystallized from the suitable solvent (cf. Table I).

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