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NAHED ABD EL-GHAFFAR
Chemistry Department, Faculty of Science, Al-Azhar University, Nasr City, Cairo

NADIA DAWOOD
Chemistry Department, Faculty of Science, Al-Azhar University, Nasr City, Cairo

FATMA ABD EL-SALAM
Chemistry Department, Faculty of Science, Al-Azhar University, Nasr City, Cairo

AWTIF FARRAG
Chemistry Department, Faculty of Science, Al-Azhar University, Nasr City, Cairo

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SYNTHESIS OF 4-HYDROXY-3-SUBSTITUTED COUMARINS OF EXPECTED BIOLOGICAL ACTIVITY AND THEIR REACTIONS WITH SOME NUCLEOPHILES

NAHED F. ABD EL-GHAFFAR, NADIA. T. DAWOOD, , FATMA,H. ABD EL-SALAM AND AWTIF E.FARRAG

Chemistry Department, Faculty of Science, Al-Azhar University, Nasr City, Cairo

Abstract

3-Acetyl-4-hydroxy substituted coumarins **(II_{a-c})** were prepared. Their reactions with hydrazines in DMF gave the corresponding 4-hydroxy -(3-substituted pyrazolin-3-yl)coumarins **(IV_{a-f})** via the intermediate hydrazone **(III)**. Their reaction with hydroxylamine hydrochloride gave the corresponding isoxazol-3-yl coumarin **(VI_{a-c})** and **($VII_{a,b}$)** via the oxime intermediate **(V)**. Reaction of **II** with aromatic aldehydes gave the corresponding chalcone derivatives **($VIII_{a-k}$)** which were reacted with hydrazines and hydroxyl amine hydrochloride and gave **(IX_a)** and **(X_{a-c})**. Condensation of **(II_{a-c})** with aromatic aldehydes, malononitrile in the presence ammonium acetate yielded the corresponding 3-cyano-4-aryl nictoinamido-6-yl-coumarin **(XI_{a-f}).**

4-Hydroxy comumarin **(1_{a-c})** on treatment with $POCl_3$ in DMF give the corresponding 4-Chloro-3-formyl coumarin **(XII_{a-c})** which on treatment with sod azide gave the corresponding 4-azido-3-formyl coumarin **($XIII_{a-c}$)**. 4-chloro-3-formyl coumarine (XII)on treatment with hydrazine gave pyrazolo coumarin derivatives **(XIV_{a-d})** and on treatment with hydroxylamine hydrochloride gave 4-chloro-3-aldo oxime coumarin derivatives **($XV_{a,b}$)**. On treatment of 4-azido-3-formyl coumarin with active methylene compounds such as malononitrile and ethyl cyanocetate derivatives gave **(XVI_{a-d})** respectively.

The antibacterial and antifungal activities of some compounds have been described.

Results and Discussion :

Coumarins are versatile reagents and their utility in heterocyclic synthesis has recently received a considerable attention. They possess significant biological activities[1-3], anti-bacterial[4], anti-tumoral[5], and anti-HIv[6-9]. Due to those varied biological activities, we have synthesized several 4-substituted, 4,3-substituted-2H-1-benzopyran-2-one derivatives in order to investigate the structure activity relationships of coumarin derivatives. In the present investigation, we report here the synthetic procedures for compounds **(I-IV)** and the anti-microbial activity of the products. Thus 4-hydroxycoumarins **(I_{a-c})** under suitable procedures yielded 3-

acetyl-4-hydroxycoumarin **(II_{a-c})**, which reacted with hydrazines, namely hydrazines hydrate, phenyl hydrazine and 4-nitrophenyl hydrazine in boiling DMF containing few drops of piperidine to give the pyrazole derivative **(IV_{a-f})**. The reaction of **(II)** with hydroxylamine hydrochloride in boiling ethanol containing sodium acetate yielded the oximes **(V)** which on reaction with DMF/piperidine in boiling xylene gave the corresponding isoxazol-3-yl coumrains **(VI_{a-c})** and **($VII_{a,b}$)** respectively. It is believed that compounds **(VI_{a-c})** are formed via nucleophilic attack of nitrogen of the hydroxylamine moiety the carbonyl of compounds **(II)** and the formyl groups of DMF affected cyclization to the desired isoxazole derivatives **(VI)** and may be a little of **($VII_{a,b}$)**.

Structure **(VI)** was established on the basis of ^{1}H-NMR spectrum as the 4-hydroxy proton was observed at δ 12.8 pmm and the absence of the methyl protons.

The base catalyzed reaction of **(II)** with aromatic aldehydes[10,11] in chloroform in the presence of piperidine with azostropic removal of water afforded the corresponding 4-hydroxy-3-cinnamoyl coumarin derivatives **($VIII_{a-k}$)**[12]. The ^{1}H-NMR spectrum of **($VIII_a$)** showed the coupling of the olefinic protons at δ 5.95 and δ 8.55 ppm (J=15Hz, AB system). The reaction of **VIII** with malononitrile in refluxing ethanol containing ammonium acetate yielded the corresponding 4-hydroxy-3 (3-cyano-4-aryl-2(1H)-pyridine)-yl coumarins **(XI_{a-f})**. The formation of **XI**-might proceed via an intermediate reaction between β-aminoenones and malononitrile to give 2(1H)-pyridone **(XI)** and considered to begin with a conjugated addition of the nitrile to the enone followed by elimination of water and cyclization to **(XI)**. This was further proved by the reaction of (**II)** with aromatic aldehydes namely 4-nitrobenzaldehyde, 2,4-dimethylamino benzaldehyde, furfural and/or isonicotinaldehyde to give **XI.** This was in agreement with the previous findings[13].

The reaction of 3-cinnamoyl coumarins **VIII** with hydrazines namely, hydrazine hydrate, phenyl hydrazine and/or 4-nitro phenyl-hydraine in boiling ethanol afforded the corresponding pyrazoline derivatives **IX_{a-h}**; while the reaction of compounds **VIII** with hydrazine hydrate in refluxing glacial acetic acid, it affected acetylation of NH of the pyrazoline ring and gave the corresponding 4-hydroxy-3-[(N-acetyl) pyrazoline]-3-yl coumarin **IX**i,j. Similarly, the reaction of **VIII** with hydroxylamine hydrochloride in boiling pyridine gave the corresponding 3-(isoxazol)-5-yl coumarin **(X_{a-c})**.

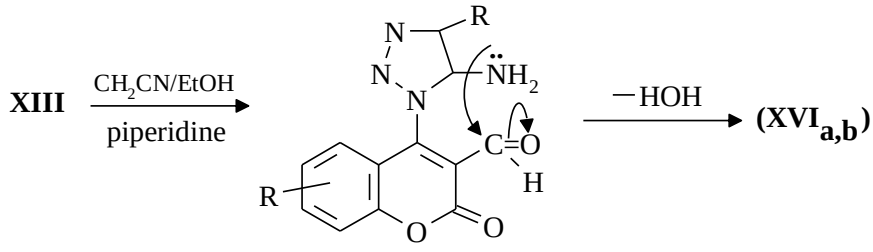
The formation of **IX** and **X** were assumed to proceed via initial nucleophilic attack of the amino group to the carbonyl of the cinnamoyl moiety without attack at the carbonyl of the α-pyrone ring followed by cyclization.

The present investigation also deals with the action of halogen nucleophiles on the α,β-unsaturated α-pyrone ring in coumarin derivatives. Thus, the reaction of **(I)** with phosphoryl chloride in DMF afforded 4-chloro-3-formyl-(2-H)-1-benzopyran-2-one derivatives **(XII_{a-c})**. The hydroxyl group at positon-4-in the α-pyrone ring seemed to be a good leaving group towards the halogen nucleophile and the behavior of the α-pyrone ring as a nucleophile was established by the reaction with DMF afforded the correspondtng 4-chloro-3-formyl coumarin **(XII_{a-c})**. It has been reported[14] that ammonia causes ring opening of the α-pyrone moiety in coumarin.

Similarly, the reaction of 4-azidocoumarins with nitrogen nucleophiles affected α-pyrone ring fission[15]. Thus, the reaction of 4-chloro-3-formyl coumarin **(XII_{a-c})** with sodium azide in DMF afforded the corresponding 4-azido-3-formyl-1-benzopyran-2-one **(XIII)**.

The reaction of **XIII** with active methylene compounds such as, malononitrile and/or ethylcyanoacetate in boiling ethanol containing a few drops of piperidine afforded nitrogen bridge head derivatives, which were defined as 3-cyano-6-oxo-[1] benzopyrano[4,3-d] pyrimidino [3,2-c] triazole **(XVI_{a-d})**

The reaction was believed to proceed via the formation of 3-formyl-4-aminotriazolyl coumarin intermediate which underwent intramolecular cyclo condensation gave the desired products.



a, R = CN , b, R = COOEt

Hydrazinolysis of compound **(XII)** with hydrazine hydrate in boiling ethanol afforded 1-aryl-4-oxo-[1] benzopyrano[4,3-c] pyrazole **(XIV_{a-d})**.

On the other hand the reaction of hydroxylamine hydrochloride with **(XII)** in boiling ethanol containing few drops of piperidine yielded the corresponding oxime via a nucleophilic attack at the position-3 **($XV_{a,b}$)**.

Experimental

All melting points were measured in capillary tubes on a GK apparatus and are uncorrected. The IR spectra were recorded in KBr disks (Wafer technique) on a Shimadzu IR-740 spectrophotometer. The ^{1}H-NMR spectra were measured on a Perkin-Elmer 360L 60 MHz spectrometer with DMSO-d_6 as a solvent, TMS as internal standard and chemical shifts expressed in δ ppm. The mass spectra were measured on a Finnigan GC/MS INCOS XL spectrometer at 70eV.

Synthesis of 3- Acetyl-4-hydroxy coumarin (II_{a-c}).

They were prepared according to a previous publication[16,17], c.f. Table 1.

Synthesis of 4-Hydroxy-3-(coumarin-3-yl) pyrazoles (IV_{a-f})

To a solution of **II_{a-c}**(0.01 mol) in 15 ml of DMF hydrazine hydrate, phenyl hydrazine and/or 4-nitrophenylhydrazine (0.01 mol) in 10 ml of absolute ethanol containing a few drops of piperidine was added. The reaction mixture was kept at room temperature overnight, then filtered off, washed with ethanol and dried to give the hydrazone **(III_{a-f})**. Compounds **(III_{a-f})** each was taken in 15 ml of DMF and 15 ml of ethanol containing few drops of piperidine was heated under reflux for 6 hours, then left to cool. The product was collected and recrystallised from the ethanol as **IV_{a-f}**, c.f. Table 1.

Synthesis of 4-Hydroxy-3-(coumarin-3-yl) isoxazol ($VI_{a,c}$), ($VII_{a,b}$)

A mixture of **II_{a-c}** (0.01 mol) and hydroxylamine hydrochloride (0.01 mol) in 30 ml of absolute ethanol containing anhydrous sodium acetate (0.01 mol, 0.82g) was refluxed for 6 hours, then filtered while hot and left to cool. The product that obtained was collected, washed well with water and recrystalized from the proper solvent to give (**V_{a-c}**). A mixture of **(V_{a-c})** (0.01 mol) in 20 ml of DMF and 10 ml of ethanol containing few drops of piperidine was heated under reflux for 6 hours, then left to cool. The products VIa-c were separated by filtration recrystallised from the proper solvent in a yield 45-60%, while the filtrate contained VIIa,b recrystallised from the proper solvent recrystallised from the proper solvent in yield 20-25% c.f. Table 1.

Synthesis of 3- Cinnamoyl-4-Hydroxycoumarin ($VIII_{a-k}$)

To a solution $\mathbf{II_{a-c}}$ (0.01 mol) in 30 ml of absolute ethanol containing few drops of piperidine add a solution of the aromatic aldehyde namely, 4-nitrobenzaldehyde, 4-dimethylamineobenzaldehdye, 2-furaldehyde, isonicotinaldehyde, 4-chlorobenzaldehyde, 4-methoxy benzaldehyde, and/or 4-methylbenzaldehyde (0.01 mol) in 10 ml of absolute ethanol while stirring. Stirring was continued for 2 hours and the solution was rendered alkaline to litmus, then left to cool overnight. It was then acidified with dil. Hcl and the precipitate was collected, washed well with light petrol, dried and recrystallised from the proper solvents $\mathbf{VIII_{a-k}}$ **c.f.** Table 1.

Synthesis of 3- (1-Substituted)-5'-arylpyrazo-3'yl-4-hydroxycoumarin (IX_{a-h}).

To a solution of $\mathbf{VIII_{a-k}}$ (0.01 mol) in 50 ml of ethanol-butanol (1:1 involume), add hydrazines namely hydrazine hydrate and/or phenyl hydrazine (0.01 mol). The mixture was heated under reflux for 6 hours, then cooled and the product was collected and washed well with light petrol and recrystallized from the proper solvent as $\mathbf{(IX_{a-h})}$ c.f. Table 1.

Synthesis of 3-(1'-acetyl)-5'-arylpyrazol-3'-yl-4-hydrazol-3'yl-4-hydroxycoumarin (IXi,j**)**.

To a solution of $\mathbf{VIII_a}$, $\mathbf{VIII_c}$, (0.01 mol) in 25 of glacial acetic acid add hydrazine hydrate (0.01 mol) and the reaction mixture was heated under reflux for 6 hours, then cooled and the product was collected washed with little ethanol, dried and recrystallized from the proper solvent as **IX**i,j; c.f. Table 1.

Synthesis of 6-(4'-hydroxy substituted coumarin-3'yl)-1,2-dihydro-2-oxo-4-aryl nicotinonitrile (XI_{a-f}).

To a solution of $\mathbf{VIII_{a-f}}$ (0 .01 mol) in 20 ml of ethanol add a solution of malononitrile (0.01 mol) in 20 mol of ethanol and ammounium acetate (0.04 mol) and the mixture was heated under reflux for 4 hours. After cooling, the product was poured into H_2O(50 ml), stirred well and the solid obtained was collected, dried and recrystallized from the proper solvent as $\mathbf{XI_{a-f}}$**;** c.f. Table 1.

Reaction of VIII with hydroxyl amine hydrochloride. Formation of 3-(isoxazole-5') yl coumarine (X_{a-c}).

To a solution of (0.01mol of **VIII a,g,j**) in 50 ml pyridine, add 0.01mol of hydroxyl amine hydrochloride. the mixture was Refluxed for 3 hrs. Cool the mixture

, then add cold dil Hcl. The solid obtained was collected, dried and recrystallzied from the proper solvent as **(Xa-c)**; c.f. table 1.

Reaction of (I_{a-c}) with phosphoryl chloride . Formation of 4-chloro-3-formyl coumarin (XII_{a-c}).

To 0.01, mole of **I** in 50 ml DMF added 5ml of phosphoryl chloride then refluxed the mixture for 3 hours on water bath. Cool the mixture and add 1:1 mixture of ice a conc. Hcl. The solid obtained was collected, dried and crystallized from the proper solvent as **(XII_{a-c})**; c.f. table (1).

Reaction of 4-chloro-3-formyl coumarine (XII_{a-c}) with sodium azide. Formation of 4-azido-3-formyl-2H-1benzopyran-2-one ($XIII_{a-c}$).

To (0.01 mole) of **XII** in 50 ml of DMF add (0.01 mole) of sod azide. the mixture was refluxed for 3 hrs. The solid obtained was collected after cooling dried and recrysallized from the proper solvent as **(XII_{a-c})**; c.f. table 1.

Reaction of XIII with active methylene compounds . Formation of 3-cyano-6-oxo [1] benzopyrano [4,3-d] pyrimidino [3,2-c] triazole (XVI_{a-d}).

To (0.01 mole) of XIII in 50 ml EtOH added (0.01 mole) of active methylene compounds such as, malononitrile and/ or ethylcyanoacetate in the presence of a few drops of piperidine. the mixture was refluxed for 6 hours. The solid obtained was collected after cooling and recrystallized from the proper solvent as **(XVI_{a-d})**; c.f. table (1).

Reaction of 4-chloro-3-formyl coumarin XII with hydrazine hydrate. Formation of 1-aryl-4-oxo-[1] benzopyrano [4,3-c] pyrazole (XIV_{a-d})

To (0.01 mol) of **XII** in 50 ml dioxan add (0.01 mole) of hydrazines namely hydrazine hydrate, phenyl hydrazine and/or 4-nitrophenylhydrazine. the mixture was Refluxed for 6 hours. The solid obtained was collected after cooling and recrystallized from the proper solvent as **(XIV_{a-d})** c.f. table (1).

R**eaction of 4-chloro-3-formyl coumarin XII with hydroxyl amine. Formation of 4-chloro-3-oximo coumarin $XV_{a,b}$.**

To (0.01 mole) of **XII** in 50 ml ethanol in presence of sodium ethoxide add (0.01 mol) of hydroxylamine hydrochloride. the mixture was Refluxed for 6 hours. The solid obtained was collected and recrystallized from the proper solvent as **$XV_{a,b}$;** c.f. table (1).

Table I. Physical data of the prepared compounds

Compd. No.	M.P.°C solvent of crystallization	Molecular formula (Mol. wt.)	Analysis calcd./Found %			
			C	H	N	X
I_a	101 E	$C_{10}H_8O_3$ (176)	68.19 68.45	4.55 4.57	-- --	-- --
I_b	112 E	$C_{10}H_8O_4$ (192)	62.50 62.72	4.17 4.25	-- --	
I_c	132 E	$C_9H_5O_3Br$ (240)	45.00 45.23	2.08 2.22	-- --	32.92 33..19
II_a	152 E	$C_{12}H_{10}O_4$ (218)	66.06 66.24	4.59 4.75	-- --	-- --
II_b	161 E	$C_{12}H_{10}O_5$ (234)	61.54 61.75	4.27 4.35	-- --	
II_c	168 E	$C_{11}H_7O_4Br$ (274)	48.18 48.44	2.55 2.60	-- --	28.83 28.95
III_a	138 P.E.	$C_{18}H_{16}N_2O_3$ (308)	70.13 70.35	5.19 5.35	9.09 9.33	-- --
III_b	149 P.F.	$C_{18}H_{15}N_3O_5$ (353)	61.19 61.20	4.25 4.12	11.89 11.98	-- --
III_c	115 P.E.	$C_{18}H_{14}N_4O_7$ (398)	54.27 54.45	3.52 3.50	14.07 14.25	-- --
III_d	162 E	$C_{12}H_{12}N_2O_4$ (248)	58.06 58.28	4.83 4.95	11.29 11.43	-- --
III_e	157 E	$C_{18}H_{16}N_2O_4$ (324)	66.67 66.75	4.94 4.73	8.64 8.60	
III_f	168 E	$C_{18}H_{14}N_4O_8$ (414)	52.17 52.36	3.38 3.42	13.53 13.62	
III_g	111 P.E.	$C_{11}H_9N_2O_3Br$ (296)	44.59 44.68	3.04 3.20	9.46 9.50	26.69 26.70
III_h	139 E	$C_{17}H_{13}N_2O_3Br$ (372)	54.84 55.13	3.49 3.30	7.53 7.57	21.24 21.20
IV_a	163 E	$C_{19}H_{14}N_2O$ (318)	71.70 71.88	4.40 4.42	8.81 8.79	-- --
IV_b	172 E	$C_{19}H_{13}N_3O_5$ (363)	62.81 62.89	3.58 3.60	11.57 11.60	-- --
IV_c	159 E	$C_{13}H_{10}N_2O_4$ (258)	60.47 60.65	3.88 3.67	10.85 10.90	-- --
IV_d	168 E	$C_{19}H_{14}N_2O_4$ (334)	68.26 68.34	4.20 4.21	8.40 8.38	-- --
IV_e	131 E	$C_{12}H_7N_2O_3Br$ (306)	47.06 47.31	2.29 2.38	9.15 9.13	25.81 25.82
IV_f	188 E	$C_{18}H_{11}N_2O_3Br$ (382)	56.54 56.62	2.88 2.95	7.33 7.32	20.68 20.70
VI_a	128 P.E.	$C_{13}H_9NO_4$ (243)	64.20 64.38	3.70 3.68	5.76 5.73	-- --
VI_b	159 E	$C_{13}H_9NO_5$ (259)	60.23 60.40	3.50 3.37	5.41 5.40	-- --
VI_c	83 P.E.	$C_{12}H_6NO_4Br$ (307)	46.91 47.06	2.93 2.90	4.56 4.58	25.73 25.70
VII_a	67 P.E.	$C_{12}H_9NO_3$ (215)	66.98 67.17	4.19 4.37	6.51 6.50	-- --
VII_b	101 P.E.	$C_{12}H_9NO_4$ (231)	62.34 62.56	3.90 4.18	6.06 6.10	-- --
IX_a	154 E	$C_{19}H_{13}N_3O_5$ (363)	62.81 63.18	3.58 3.60	11.57 11.54	
IX_b	162 E	$C_{25}H_{17}N_3O_5$ (439)	68.34 68.53	3.87 3.93	9.57 9.60	-- --
		$C_{21}H_{19}N_3O_3$	69.81	5.26	11.63	--

Compd. No.	M.P.°C solvent of crystallization	Molecular formula (Mol. wt.)	Analysis calcd./Found %			
			C	H	N	X
IX_c	157 E	(361)	69.98	5.33	11.65	--
IX_d	169 E	$C_{29}H_{23}N_3O_3$ (461)	75.49 75.60	4.50 4.42	9.11 9.00	-- --
IX_e	170 E	$C_{19}H_{13}N_3O_6$ (379)	60.16 60.35	3.43 3.40	11.08 11.21	-- --
IX_f	162 E	$C_{25}H_{17}N_3O_6$ (455)	65.93 66.12	3.74 3.70	9.23 9.33	-- --
IX_g	144 E	$C_{19}H_{13}N_2O_4Br$ (412)	55.34 55.53	3.16 3.21	6.80 6.99	19.17 19.20
IX_h	150 E	$C_{14}H_{14}N_3O_5Br$ (503)	57.26 57.45	3.70 3.78	8.35 8.34	12.71 12.70
IX_i	203 E	$C_{21}H_{13}N_3O_6$ (405)	62.22 62.49	3.70 3.73	10.37 10.40	-- --
IX_j	222 E	$C_{19}H_{14}N_2O_5$ (350)	65.14 64.85	4.00 4.11	8.00 8.11	-- --
X_a	115 P.E.	$C_{17}H_{13}NO_5$ (309)	66.02 66.21	3.56 3.55	4.53 4.50	-- --
X_b	124 P.E.	$C_{19}H_{12}N_2O_7$ (380)	60.00 60.22	3.20 3.15	7.37 7.35	-- --
X_c	136 E	$C_{19}H_{12}NO_5Br$ (413)	55.21 54.95	2.91 2.90	3.39 3.40	19.13 19.12
XI_a	187 E	$C_{22}H_{13}N_3O_6$ (415)	63.61 63.78	3.13 3.10	10.12 10.00	-- --
XI_b	189 E	$C_{24}H_{18}N_3O_4$ (412)	69.91 70.4	4.37 4.36	10.19 10.17	-- --
XI_c	192 E	$C_{22}H_{13}N_3O_7$ (431)	61.25 61.17	3.02 3.01	9.74 9.76	-- --
XI_d	193 E	$C_{24}H_{19}N_3O_5$ (429)	67.13 67.30	4.43 4.42	9.79 9.80	-- --
XI_e	201 E	$C_{19}H_9N_2O_5$ (345)	66.17 66.08	2.61 2.60	8.12 8.10	-- --
XI_f	202 E	$C_{20}H_{10}N_3O_4Br$ (435)	55.17 54.95	2.30 2.29	9.66 9.70	18.16 18.20
XII_a	221 E	$C_{11}H_7O_3Cl$ (222.5)	59.33 59.52	3.15 3.14	-- --	15.96 15.95
XII_b	176 E	$C_{11}H_7O_4Cl$ (238.5)	55.35 55.54	2.94 2.93	-- --	14.88 14.86
XII_c	174 E	$C_{10}H_4O_3BrCl$ (286.5)	41.88 42.13	1.39 1.40	-- --	27.57Br 27.60Br 12.39Cl

Compd. No.	M.P.°C solvent of crystallization	Molecular formula (Mol. wt.)	Analysis calcd./Found %			
			C	H	N	X
						12.40 Cl
$XIII_a$	182 E	$C_{11}H_7N_3O_3$ (229)	57.64 57.88	3.06 3.05	18.34 18.32	-- --
$XIII_b$	179 E	$C_{11}H_7N_3O_4$ (245)	53.88 54.17	2.86 2.85	17.14 17.12	-- --
$XIII_c$	180 E	$C_{10}H_4N_3O_3Br$ (309)	38.83 39.09	1.29 1.30	13.59 13.60	25.57 25.60
XIV_a	133 P.E.	$C_{11}H_8O_2N_2$ (200)	66.00 66.23	4.00 4.02	14.00 14.03	-- --
XIV_b	129 E	$C_{17}H_{12}N_2O_2$ (264)	77.27 77.35	4.55 4.53	10.61 10.63	-- --
XIV_c	130 E	$C_{17}H_{11}N_3O_4$ (321)	63.55 63.60	3.43 3.42	13.08 13.20	-- --
XIV_d	121 P.E.	$C_{17}H_{12}N_2O_3$ (292)	69.86 70.09	4.11 4.10	9.59 9.60	-- --
XV_a	111 P.E.	$C_{11}H_8NO_3Cl$ (237.5)	55.58 55.57	3.37 3.36	5.89 5.90	14.95 14.97
XV_b	122 P.E.	$C_{11}H_8NO_4Cl$ (253.5)	52.07 52.22	3.20 3.16	5.52 5.50	14.00 14.03
XVI_a	66 P.E.	$C_{14}H_7N_5O_2$ (277)	60.65 60.84	2.53 2.50	25.27 25.30	-- --
XVI_b	89 P.E.	$C_{16}H_{11}N_4O_4$ (323)	59.44 59.63	3.41 3.40	17.34 17.33	-- --
XVI_c	78 P.E.	$C_{14}H_7N_5O_3$ (293)	57.34 57.38	2.39 2.38	23.89 23.90	-- --
XVI_d	80 P.E	$C_{16}H_{11}N_4O_5$ (339)	56.64 56.43	3.24 3.22	16.52 16.50	-- --

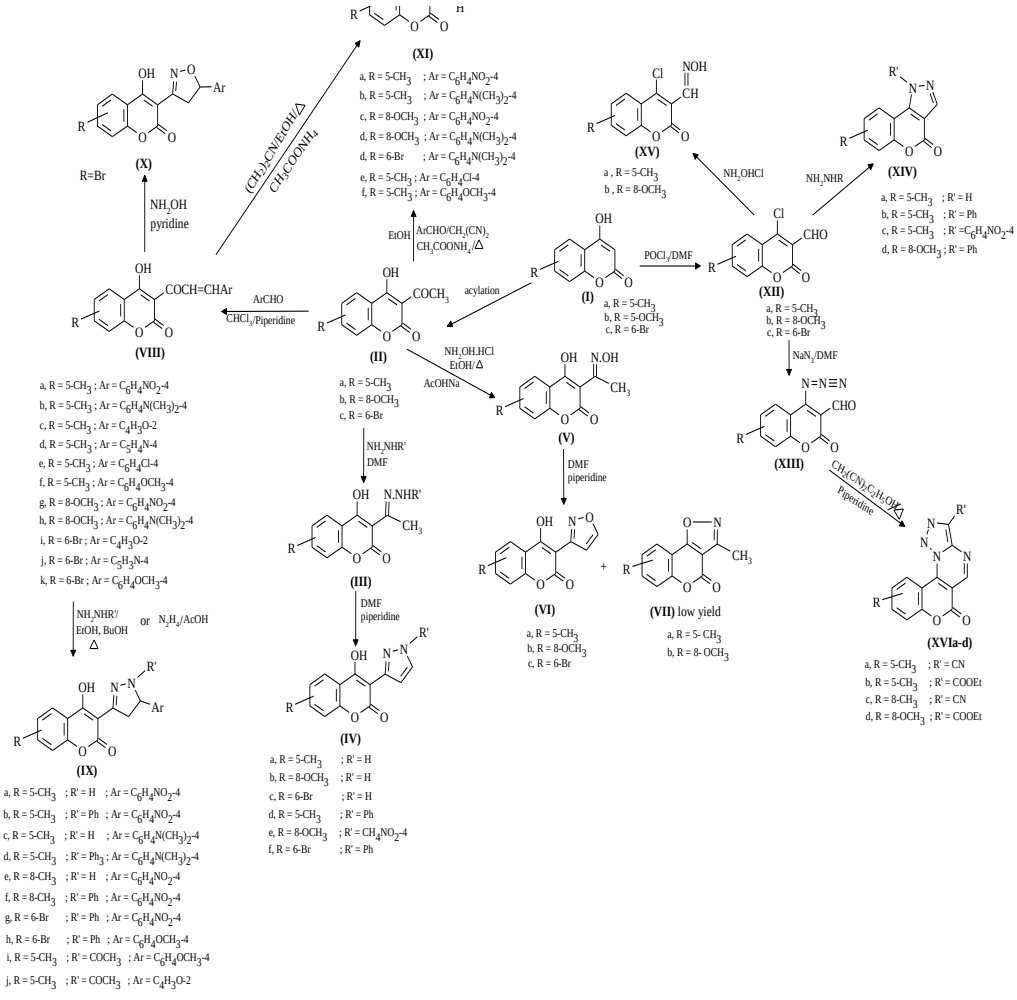
Pharmacological activity

All the compounds **III_b, $IV_{a-c,e}$, VI_b, VII_b, $VIII_{a,b,e,f,h}$, IX_e and $XIV_{c,d}$** were screened for their *in vitro* antibacterial activity against *E.coli* and *Xanthomonas citri* by cup plate method[15,], Summarized in table II. Nutrient agar was melted in a water bath and cooled to 45°C with gentle shaking to bring about uniform cooling. It was with 0.5-0.6 ml of culture and mixed well by pouring gentle shaking before onto the sterilized Petri dishes. The poured materials were allowed to set and thereafter the "CUPS" were made by punching into the agar surface with sterile cork borer and scooping out the punched part of the agar. Into these cups were added 0.1 ml. portion of the tested compound in the solvent with the help of sterile syringe. The drug solution was allowed to diffuse for about an hour into the medium. The plates were incubated at 37°C and the results noted. The standard is (streptomycin)

Table II. Antibacterial activity data of the tested compounds

Comp. No.	*E.coli** (Zone in mm)	*X.Citri** (zone in mm)
III_b	8	13
IV_a	12	15
IV_b	10	11
IV_c	8	10
IV_e	11	8
VI_b	9	10
VII_b	13	12
$VIII_a$	10	13
$VIII_b$	12	14
$VIII_e$	9	9
$VIII_f$	12	8
$VIII_h$	7	13
IX_e	10	11
XIV_c	11	10
XIV_d	12	14

* Standard (Streptomycin)


(XI)
a, R = 5-CH3 ; Ar = C6H4NO2-4
b, R = 5-CH3 ; Ar = C6H4N(CH3)2-4
c, R = 8-OCH3 ; Ar = C6H4NO2-4
d, R = 8-OCH3 ; Ar = C6H4N(CH3)2-4
d, R = 6-Br ; Ar = C6H4N(CH3)2-4
e, R = 5-CH3 ; Ar = C6H4Cl-4
f, R = 5-CH3 ; Ar = C6H4OCH3-4
(CH3)2CN/EtOH/Δ
CH3CCONH4
R=Br
(X)
NH2OH
pyridine
(VIII)
ArCHO
CHCl3/Piperidine
EtOH
ArCHO/CH2(CN)2
CH3COONH4/Δ
(II)
acylation
(I)
a, R = 5-CH3
b, R = 5-OCH3
c, R = 6-Br
POCl3/DMF
(XII)
a, R = 5-CH3
b, R = 8-OCH3
c, R = 6-Br
NH2OHCl
NH2NHR
(XV)
a , R = 5-CH3
b , R = 8-OCH3
(XIV)
a, R = 5-CH3 ; R' = H
b, R = 5-CH3 ; R' = Ph
c, R = 5-CH3 ; R' =C6H4NO2-4
d, R = 8-OCH3 ; R' = Ph
NaN3/DMF
(XIII)
CH2(CN)C6H4OH
Piperidine
(XVIa-d)
a, R = 5-CH3 ; R' = CN
b, R = 5-CH3 ; R' = COOEt
c, R = 8-CH3 ; R' = CN
d, R = 8-OCH3 ; R' = COOEt
NH2OH.HCl
EtOH/ Δ
AcOHNa
(V)
DMF
piperidine
(VI)
a, R = 5-CH3
b, R = 8-OCH3
c, R = 6-Br
(VII) low yield
a, R = 5- CH3
b, R = 8- OCH3
NH2NHR'
DMF
(III)
DMF
piperidine
(IV)
a, R = 5-CH3 ; R' = H
b, R = 8-OCH3 ; R' = H
c, R = 6-Br ; R' = H
d, R = 5-CH3 ; R' = Ph
e, R = 8-OCH3 ; R' = CH4NO2-4
f, R = 6-Br ; R' = Ph
a, R = 5-CH3 ; Ar = C6H4NO2-4
b, R = 5-CH3 ; Ar = C6H4N(CH3)2-4
c, R = 5-CH3 ; Ar = C4H3O-2
d, R = 5-CH3 ; Ar = C5H4N-4
e, R = 5-CH3 ; Ar = C6H4Cl-4
f, R = 5-CH3 ; Ar = C6H4OCH3-4
g, R = 8-OCH3 ; Ar = C6H4NO2-4
h, R = 8-OCH3 ; Ar = C6H4N(CH3)2-4
i, R = 6-Br ; Ar = C4H3O-2
j, R = 6-Br ; Ar = C5H3N-4
k, R = 6-Br ; Ar = C6H4OCH3-4
NH2NHR'/
EtOH, BuOH
Δ
or N2H4/AcOH
(IX)
a, R = 5-CH3 ; R' = H ; Ar = C6H4NO2-4
b, R = 5-CH3 ; R' = Ph ; Ar = C6H4NO2-4
c, R = 5-CH3 ; R' = H ; Ar = C6H4N(CH3)2-4
d, R = 5-CH3 ; R' = Ph3 ; Ar = C6H4N(CH3)2-4
e, R = 8-CH3 ; R' = H ; Ar = C6H4NO2-4
f, R = 8-CH3 ; R' = Ph ; Ar = C6H4NO2-4
g, R = 6-Br ; R' = Ph ; Ar = C6H4NO2-4
h, R = 6-Br ; R' = Ph ; Ar = C6H4OCH3-4
i, R = 5-CH3 ; R' = COCH3 ; Ar = C6H4OCH3-4
j, R = 5-CH3 ; R' = COCH3 ; Ar = C4H3O-2

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