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Synthesis and Antidepressant Activity of Some New Coumarin Derivatives

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Abstract

The coumarin-3-cinnamoyl derivatives **2a-d** were prepared via Claisen-Schmidt condensation of 3-acetylcoumarin **1** with different aromatic aldehydes. Cycloaddition reaction of **2b,e** with guanidine and thiourea yielded the corresponding aminopyrmimidine **3a,b** and thioxypyrimidine derivatives **4a,b**, respectively. Compounds **4a,b** were condensed with chloroacetic acid or 3-bromopropionic acid to yield coumarin 3-thiazolo-pyrimidine **5a,b** and thiazinopyrimidine **6a,b** derivatives, respectively. Compounds **4a,b** were condensed with chloroacetic acid and aromatic aldehyde to yield the aryl methylene derivatives **7a,b** which could be prepared directly by condensation of compounds **5a,b** with aromatic aldehydes.

Compounds **2a-e** were condensed with malononitrile or ethyl cyano acetate in presence of ammonium acetate to yield cyanopyridine **8a,b** and cyanopyridone **9a-d** derivatives, respectively, which were prepared by condensation of 3-acetylcoumarin **1**, malononitrile or ethylcyanoacetate and aromatic aldehydes in presence of ammonium acetate.

Condensation of compounds **2a,b,e** with o-phenylenediamine in refluxing ethanol led to the formation of **10a-c** as intermediate, followed by cleavage by thermolysis to benzimidazole derivative **11** along with compounds **12a-c** as mixture, which were obtained directly by fusion of α,β-unsaturated ketones **2** with o-phenylene diamine at 200-220°C, while compound **11** could be prepared in pure form by fusion of **1** with o-phenylene diamine at the same temperature.

The pharmacological screening showed that many of these obtained

compounds have good antidepressant activity comparable to Tranylcypromine® as reference drugs.

Keywords:

3-Acetylcoumarin, pyrimidine, cyanopyridine, cyanopyridone, antidepressant activity.

Introduction

Coumarins have been found to be physiologically active in animals as well as in man [1]. Many biological properties for coumarins have been reported such as dermal photosensitizing activity [2-4], antimicrobial [5-7], diuretic [8,9], molluscicidal and anthelminitic [10,11], vasodilatory [12,13], estrogenic [14], anticoagulant [15-18] and antitumor [19-22] activities.

It has been reported that substituted pyridine derivatives showed antimicrobial [23,24], antitumor [25,26], analgesic and anticonvulsant [27] activities. Also pyrimidine derivatives showed anticancer [28,29], antimicrobial [30,31], antiviral [32], cytotoxic [33], antitumor [34] and antidepressant [35] activities.

Based on the previous findings, it is of interest to synthesize some new coumarin-3-derivatives starting with 3-acetylcoumarin and incorporating to biologically active moieties such as pyrimidine, cyanopyridine and cyanopyridone.

Experimental

All melting points are uncorrected and were taken on Electro-thermal IA 9000 series digital melting point apparatus. Analytical data were obtained from the microanalytical unit, *National Research Centre,* Cairo, Egypt. The IR spectra (KBr) were recorded on a Pye Unicam SP-1000 spectrophotometer. The ^{1}H-NMR spectra (δ, ppm) were recorded at 270 MHz on Varian EM-360 Spectrometer using TMS as an internal standard. The Central Services Laboratory, National Research Centre. The mass spectra were performed using VG 2AB-3F spectrometer (70eV). All

reactions were followed by TLC (silica gel, aluminum sheets 60 F_{254}, Merck). The physical and analytical data of the synthesized compounds are given in Table 1.

Synthesis of 3-cinnamoyl-coumarin derivatives 2a-e:

General procedure

A mixture of 3-acetylcoumarin **1** (2 mmol), the appropriate aldehyde (2 mmol), namely, benzaldehyde, p-fluorobenzldehyde, p-nitrobenzaldehyde, salicylaldehyde, 5-methyl furfural, and few drops triethylamine in 30 ml absolute ethanol was refluxed for 4-6 hr. The reaction mixture was cooled and the separated solid was filtered off, air-dried and crystallized from the proper solvent to afford compounds **2a-e** [36].

Formation of 3-(2-amino-4-aryl-3,4-dihydropyrimidine-6-yl) benzopyran-2-one 3a,b:

General procedure

To a solution of compounds **2b,e** (2 mmol), sodium hydroxide (0.2g in 1 ml water) in ethanol (30 ml), guanidine hydrochloride (0.2g, 2 mmol) was added. The reaction mixture was refluxed for 5-7 hr, allowed to cool, then poured onto cold water, the solid formed was collected by filtration and crystallized from the proper solvent to give compounds **3a,b**, respectively.

Synthesis of 3-(4-aryl-1,2,3,4-tetrahydropyrimidine-2-thioxo-6-yl)benzopyran-2-one 4a,b:

General procedure

To a mixture of **2b,e** (2 mmol), sodium hydroxide (0.2g in 1 ml water) in ethanol (30 ml), thiourea (0.15g, 2 mmol) was added. The reaction mixture was heated under reflux for 3-5 hr, allowed to cool. The solid formed was filtered off and crystallized from the proper solvent to give the corresponding thioxopyrimidine derivatives **4a,b**.

Preparation of compounds 5a,b and 6a,b:

General procedure

A mixture of compounds **4a,b** (2 mmol), chloroacetic acid or bromopropionic acid (2 mmol) in a mixture of glacial acetic acid (30 ml) and acetic anhydride (10 ml) in the presence of anhydrous sodium acetate (3g) was refluxed for 6-7 hr. The reaction mixture was cooled and poured onto cold water with stirring, the solid formed was filtered off and crystallized from the proper solvent to give the corresponding **5a,b** and **6a,b**, respectively.

Preparation of 3-[2-aryl-methylene-5`-aryl-2,3-dihydro-5H-thiazolo[3,2-a] pyrimidine-3-one-7-yl)benzopyran-2-one 7a,b:

Method A:

A mixture of compound **4a,b** (2 mmol), chloroacetic acid (0.19g, 2 mmol), sodium acetate anhydrous (3g) in glacial acetic acid (30 ml), acetic anhydride (10 ml) and the appropriate aldehydes (2 mmol) was refluxed for 5-6 hr. The reaction mixture was cooled and poured onto ice-water, the obtained solid was collected by filtration and crystallized from the proper solvent to give compounds **7a,b**.

Method B:

A mixture of compound **5a,b** (2 mmol), the appropriate aldehydes (2 mmol), acetic acid (30 ml) and acetic acid anhydride (10 ml) was refluxed for 2-3 hr., allowed to cool, then poured onto water the solid formed was collected by filtration and crystallized from the proper solvent to yield the title compounds **7a,b**.

The obtained products from method B were identified by m.p., mixed m. p.'s and TLC by comparison with authentic samples, but method (A) gives better yield than method (B).

Preparation of cyanoaminopyridine 8a-e and cyanopyridone 9a-e derivatives:

Method A:

A mixture of **2a,e** (2 mmol), malononitrile or ethyl cyanoacetate (2 mmol) and

ammonium acetate (0.3g, 4 mmol) in absolute ethanol (30 ml) was refluxed for 3-5 hr. After cooling, the formed product was collected by filtration, washed with ethanol, dried and crystallized from the proper solvent to give the corresponding cyanoaminopyridines **8a-e** and cyanopyridones **9a-e**, respectively.

Method B:

A mixture of 3-acetylcoumarin **1** (0.38g, 2 mmol), 1,1-dicyano-2-arylethylene or 1-cyano-1-ethyl ester-2-arylethylene (2 mmol) and ammonium acetate (0.30g, 4 mmol) in absolute ethanol (30 ml) was refluxed for 5-7 hr. The reaction mixture was concentrated and left to cool. The formed solid was filtered off and crystallized from the proper solvent to give the corresponding **8a-e** and **9a-e**, respectively.

Method C:

A mixture of 3-acetylcoumarin **1** (0.38g, 2 mmol), the appropriate aldehydes (2 mmol), namely, benzaldehyde, p-fluorobenzaldehyde, p-nitrobenzadehyde, salicyaldehyde, or 5-methyl furfural and malononitrile or ethylcyanoacetate (2 mmol) in the presence of ammonium acetate (0.3g, 4 mmol) in absolute ethanol (30 ml) was refluxed for 7-9 hr. The obtained solid was filtered off, washed with ethanol, and crystallized from the proper solvent to give the corresponding **8a-e** and **9a-e**, respectively.

The obtained products from methods B and C were identified by its m.p.; mixed m.p. and R_f values on TLC by comparison with authentic samples from method A.

Reaction of chalcones 2a,b,e with o-phenylenediamine:

Method A*: In butanol (Formation of diazipene derivatives)*

A mixture of compound **2a,b,e** (1 mmol) and o-phenylenediamine (0.11g, 1 mmol) in absolute butanol (30 ml) was heated under reflux for 10-12 hr. The solvent was evaporated under reduced pressure till dryness, the oily product was triturated with petroleum ether (40-60°C) and the separated solid was filtered off, washed

with petroleum ether (40-60°C), dried and crystallized from the proper solvent to give the corresponding benzodiazipine derivatives **10a-c**.

Method B: ***By fusion***

Equimolecular amounts of **2a,b,e** (1 mmol) and o-phenylenediamine (0.11g, 1 mmol) were fused together in an oil bath at 200-220°C for 4-6 hr. After cooling, the obtained solid was crushed and extracted with hot dioxane, evaporated under reduced pressure and the residue was solidified with methanol, the obtained solid was filtered off, and crystallized from ethanol to give **11**. The filtrate was evaporated under reduced pressure, the obtained residue was solidified with n-hexane to give compounds **12a-c**.

Thermolysis of benzodiazipine derivatives 10a-c:

Benzodiazipine derivatives **10a-c** (0.5 mmol) were heated in an oil bath at 200-220°C for 4-6 hr. After cooling, the dark mass was crushed and extracted with hot dioxane then evaporated under reduced pressure, the residue was solidified with methanol, the obtained solid was filtered off and crystallized from ethanol to give **11** in 35-40% yield. The filtrate was evaporated under reduced pressure, the obtained residue was solidified with n-hexane to give **12a-c**. The obtained products were identified by m.p. and R_f values in comparison with authentic samples from the above method (method B).

Reaction of 3-acetyl coumarin 1 with o-phenylene diamine.
Formation of compound 11

A mixture of 3-acetyl coumarin **1** (0.19g, 1 mmol) and o-phenylene diamine (0.11g, 1 mmol) was fused in an oil bath at 200-220°C for 6 hrs. The obtained residue was solidified with methanol. The obtained solid was collected by filtration and crystallized from the proper solvent to give benzimidazole derivative **11**, in 60% yield. The product was identified by its m.p. and R_f value in comparison with authentic sample.

Table 1: Physical and analytical data of newly synthesized compounds

Comp. No.	M.P. (°C) Solvent of cryst.	Yield (%)	Mol. formula (M.wt)	Analysis Found (Calcd)			
				C	H	N	S
2b	172-4 EtOH	75	$C_{18}H_{11}O_3F$ (294.27)	73.21 (73.46)	3.68 (3.77)		
2c	155-7 EtOH	76	$C_{18}H_{11}NO_5$ (309.27)	69.76 (69.90)	3.53 (3.59)	4.48 (4.53)	
2d	179-81 EtOH	79	$C_{18}H_{12}O_4$ (292.28)	73.88 (73.96)	4.05 (4.14)		
2e	183-5 EtOH	72	$C_{17}H_{12}O_4$ (280.27)	72.76 (72.85)	4.23 (4.32)		
3a	202-4 EtOH	80	$C_{19}H_{14}N_3O_2F$ (335.33)	67.95 (68.05)	4.15 (4.21)	12.45 (12.53)	
3b	215-17 EtOH	78	$C_{18}H_{15}N_3O_3$ (321.33)	67.15 (67.28)	4.62 (4.71)	12.95 (13.08)	
4a	209-11 AcOH/H_2O	80	$C_{19}H_{13}N_2O_2SF$ (352.38)	64.66 (64.76)	3.64 (3.72)	7.88 (7.95)	9.00 (9.10)
4b	239-41 AcOH/H_2O	82	$C_{18}H_{14}N_2O_3S$ (338.38)	63.78 (63.89)	4.08 (4.17)	8.20 (8.28)	9.39 (9.48)
5a	185-7 dioxane	77	$C_{21}H_{13}N_2O_3SF$ (392.40)	64.16 (64.27)	3.26 (3.34)	7.06 (7.14)	8.10 (8.17)
5b	202-4 dioxane	75	$C_{20}H_{14}N_2O_4S$ (378.40)	63.36 (63.48)	3.64 (3.73)	7.31 (7.40)	8.39 (8.47)
6a	200-1 EtOH/H_2O	68	$C_{22}H_{15}N_2O_3SF$ (406.43)	64.90 (65.01)	3.66 (3.72)	6.80 (6.89)	7.79 (7.89)
6b	186-8 EtOH/H_2O	65	$C_{21}H_{16}N_2O_4S$ (392.43)	64.16 (64.27)	4.04 (4.11)	7.08 (7.14)	8.09 (8.17)
7a	260-21 AcOH/H_2O	75(A) 60(B)	$C_{28}H_{16}N_2O_3SF_2$ (498.50)	67.35 (67.46)	3.15 (3.26)	5.55 (5.62)	6.34 (6.43)
7b	230-2 AcOH/H_2O	64(A) 62(B)	$C_{26}H_{18}N_2O_5S$ (470.49)	66.28 (66.37)	3.78 (3.86)	5.88 (5.96)	6.75 (6.82)

8a	202-4 EtOH	62(A) 60(B) 60(C)	$C_{21}H_{13}N_3O_2$ (339.35)	74.21 (74.32)	3.75 (3.86)	12.31 (12.38)	
8b	251-3 EtOH	65(A) 60(B) 58(C)	$C_{21}H_{12}N_3O_2F$ (357.34)	70.49 (70.58)	3.32 (3.39)	11.70 (11.76)	
8c	227-9 EtOH	66(A) 61(B) 60(C)	$C_{21}H_{12}N_4O_4$ (384.35)	62.55 (65.62)	3.10 (3.15)	14.52 (14.58)	
8d	263-5 EtOH	60(A) 58(B) 65(C)	$C_{21}H_{13}N_3O_3$ (355.35)	70.90 (70.98)	3.62 (3.69)	11.75 (11.83)	
8e	280-2 EtOH	61(A) 60(B) 60(C)	$C_{20}H_{13}N_3O_3$ (343.34)	69.88 (69.96)	3.76 (3.82)	12.18 (12.24)	
9a	261-3 AcOH/H_2O	63(A) 61(B) 62(C)	$C_{21}H_{12}N_2O_3$ (340.33)	74.00 (74.11)	3.48 (3.56)	8.16 (8.23)	
9b	273-5 AcOH/H_2O	64(A) 60(B) 63(C)	$C_{21}H_{11}N_2O_3F$ (358.32)	70.30 (70.39)	3.00 (3.09)	7.75 (7.82)	
9c	285-7 AcOH	65(A) 62(B) 60(C)	$C_{21}H_{11}N_3O_5$ (385.33)	65.34 (65.45)	2.80 (2.88)	10.16 (10.90)	
9d	255-7 AcOH/H_2O	66(A) 64(B) 60(C)	$C_{21}H_{12}N_2O_4$ (356.33)	70.70 (70.78)	3.32 (3.40)	7.78 (7.86)	
9e	295-7 AcOH/H_2O	70(A) 66(B) 64(C)	$C_{20}H_{12}N_2O_4$ (344.32)	69.67 (69.76)	3.45 (3.51)	8.05 (8.14)	
10a	240-2 EtOH	70	$C_{24}H_{18}N_2O_2$ (366.40)	78.58 (78.67)	4.88 (4.95)	7.57 (7.65)	
10b	247-9 EtOH	70	$C_{24}H_{17}N_2O_2F$ (384.40)	74.90 (74.98)	4.38 (4.46)	7.22 (7.29)	

10c	251-3 EtOH	72	$C_{23}H_{18}N_2O_3$ (370.40)	74.50 (74.58)	4.84 (4.90)	7.50 (7.56)	
11	263-5 EtOH	52	$C_{16}H_{10}N_2O_2$ (262.26)	73.16 (73.27)	3.76 (3.84)	10.60 (10.68)	
12a	261-3 AcOH	25	$C_{13}H_{10}N_2$ (194.23)	80.30 (80.38)	5.10 (5.19)	14.35 (14.43)	
12b	233-5 AcOH	27	$C_{13}H_{19}N_2F$ (212.22)	73.48 (73.57)	4.20 (4.27)	13.10 (13.20)	
12c	241-3 AcOH	30	$C_{12}H_{10}N_2O$ (198.22)	72.62 (72.71)	5.00 (5.09)	14.08 (14.14)	

Pharmacological screening

MAOI Antidepressant activity

Purpose and rationale:

Monoamino seizures in rats caused by an intravenous infusion of tryptamine HCl. This procedure can be used to elucidate the in vivo MAO inhibiting properties of compounds.

Procedure:

Group of 5 male Webster rats weighing 150-200g are used test compounds, standard or vehicle controls are administered intraperitoneally 0.5, 1, 2 and 4 hours prior testing. At the time of testing 5mg/kg tryptamine HCl Freshly dissolved in saline are injected intravenously. Immediately after tryptamine HCl administration, the animals are observed individually for three minutes for the appearance of clonic pedaling movements of the forepaws, which is considered a positive response. Frequently, these clonic seizures are preceded by akyphotic curvature of the spine but this sign does not constitute a positive response. In addition to the vehicle control group a series of five positive control animals receiving Tranylcypromine® at 5 mg/ kg i. p. with a 0.5 hours pretreatment time are subjected to the test in order to check the effectiveness of the tryptamine HCl solution which is relatively unstable. A 100% response is expected fresh tryptamine HCl solution should be prepared hourly as needed [37,38].

Evaluation:

The normalized percent potentiation is calculated as follows:

$$100 \text{ X } \frac{\text{\% animals potent in drug group-\% animals potent in vehicle}}{\text{1-\% animals potent in vehicle group}}$$

A dose-response was obtained in the same manner at the peak time of drug effect expect that a group size of 10 animals is used and four different doses are tested in addition to the vehicle and the Tranylcypromine® groups.

All the tested compounds showed potent antidepressant activities via MAOI mechanism than Tranylcypromine®. Compounds **6a, 7b** and **9b** showed 12.8, 12.15, 12.06 more activities than that of Tranylcypromine® respectively, these compounds exhibit good therapeutic windows & high safety margins.

Compounds **3b, 5a, 5b** and **10b** showed also potent MAOI activities but less than that previously mentioned, their relative potencies of 10.14, 10.11, 10.51 and 11.66 of that of the standard drug. Compounds **2b, 3a, 4a, 8c, 8b, 8e, 9d** and **10c** showed from 7-8 folds more activities than that of standard, while compounds **2d, 2e, 4b, 6b, 8d, 9c** and **11** showed from 4-6 folds of the activities of Tranylcypromine®. The rest of compounds showed less than 4 folds of the activities of reference drug.

Table 2: Antidepressant activity of the new compounds

Comp. No.	LD_{50}	LD_{90}	Relative Antidepressant Potency to Tranylcypromine®
2a	115	223	3.44
2b	225	518	8.56
2c	127	226	2.11
2d	212	416	4.11
2e	313	898	6.18
3a	275	603	8.11
3b	250	661	10.14
4a	215	556	8.16
4b	418	930	6.30

5a	204	427	11.66
5b	216	513	10.11
6a	206	425	12.06
6b	213	541	4.66
7a	130	227	2.03
7b	205	512	12.8
8a	103	190	1.18
8b	211	490	7.44
8c	407	813	7.44
8d	404	891	5.22
8e	316	818	8.52
9a	116	215	2.16
9b	204	475	12.15
9c	450	1000	5.21
9d	403	843	8.31
9e	318	676	6.21
10a	110	220	1.80
10b	203	423	10.51
10c	399	741	8.41
11	206	533	6.50
12a	117	225	1.98
12b	110	201	2.05
12c	105	205	2.33
Tranylcypromine®	117	207	1

Results and Discussion

Condensation of 3-acetylcoumarin **1** with aromatic aldehydes, namely, benzaldehyde, p-fluorobenzaldehyde, p-nitrobenzaldehyde, salicylaldehyde and 5-methylfurfural in presence of triethyl amine yielded the corresponding 3-cinnamoyl derivatives **2a-e**. Compound **2a** was previously reported [36] (Scheme 1).

The IR spectra of compounds **2b-e** exhibited absorption bands at 1679-1662 cm^{-1} regions, characteristic for α,β-unsaturated ketones and at 1618-1607 region attributed to (C=C). The ^{1}H-NMR spectrum of compound **2b** [DMSO-d_6] showed

signals at (δ, ppm) 8.65 (1H, s, H-4 pyrone), 7.95 (2H, d, Ph-$H_{3,5}$), 7.75 (2H, d, Ph-$H_{2,6}$) and 7.6-7.35 (6H, m, 4 Ar-H + olefinic system).

The ^{1}H-NMR spectrum of compound **2e** [DMSO-d_6] showed signals at 8.65 (1H, s, H-4 pyrone), 7.95 (1H, d, H-3 furan), 7.7 (1H, d, H-4 furan), 7.6-7.3 (4H, m, coumarin protons), 6.95 (1H, d, COCH=*CH*), 6.35 (1H, d, CO*CH*=CH) and 2.45 (3H, s, CH_3). Mass spectrum of **2e** showed peaks at m/z = 280 (M^+, 100%, base peak), 265 (98%), 237 (14.9%), 210 (14%), 181 (32%).

The cycloaddition reaction of compounds **2b,e** with guanidine hydrochloride in the presence of a pellet of sodium hydroxide yielded 3-(2-amino-4-aryl-3,4-dihydropyrimidin-6-yl)benzopyran-2-one **3a,b** (Scheme 1).

It is worth mentioning that the previous reaction did not cause α-pyrane ring fission, which indicated by the negative ferric chloride test for the obtained products. The IR spectra of compounds **3a,b** showed absorption bands at 3470, 3365 (NH_2), 3320, 3315 (NH). The ^{1}H-NMR spectrum of **3a** [DMSO-d_6] showed signals at 5.50 (2H, s, NH_2 which exchangeable with D_2O), 10.5 (1H, s, NH which exchangeable with D_2O), 8.65 (1H, s, H-4 pyrone), 7.00-7.50 (9H, m, Ar-H and Hb for pyrimidine ring) and 5.25 (1H, d, Ha for pyrimidine ring). The mass spectrum of compound **3b** exhibited peaks at m/z 321 (M^+, 92%), 306 (80%), 226 (79%), 211 (62%) and base peak at 267 (100%).

Also, reaction of **2b,e** with thiourea in ethanolic sodium hydroxide yielded 3-(4-aryl-1,2,3,4-tetrahydropyrimidine-2-thioxo-6-yl)benzopyran-2-one **4a,b** (Scheme 1). The IR spectra of compounds **4a,b** showed two absorption bands at 3445-3430 (NH) and 1195, 1190 characteristic for the C-O-C system and at 1275, 1280 (C=S). The ^{1}H-NMR spectrum of compound **4b** [DMSO-d_6] showed signals at 5.10 (1H, dd, Ha pyrimidine), 9.50 (2H, s, 2NH which exchangeable with D_2O), 7.25-7.75 (5H, m, 4 Ar-H and Hb pyrimidine) besides the other characteristic signals for the compound. The mass spectrum of compound **4b** exhibited peaks at m/z, 338 (M^+, 2. 38%), 312 (50.7%), 237 (64.3%) and base peak at 267 (100%).

The reaction of α,β-unsaturated ketones **2** with thiourea can proceed by addition on carbonyl group of **2** followed by cyclization and dehydrogenation to yield

the final products **4.** The force for such elimination reactions is the resonance stabilization energy in **4**. We were not able to isolate any intermediate [23,39].

Compounds **4a,b** were condensed with chloroacetic acid or 3-bromopropanoic acid in a mixture of acetic acid/acetic anhydride in the presence of sodium acetate anhydrous to yield 3-(5-aryl-2,3-dihydro-5H-thiazolo[3,2-a]-pyrimidin-3-one-7-yl)benzopyran-2-one **5a,b** and 3-(6-aryl-2,3-dihydro-6H-thiazino[3,2-a]-pyrimidine-4-one-8-yl)benzopyran-2-one **6a,b**, respectively (Scheme 1). The formation of the cyclized product **5** and **6** was proved by the pyrimidine proton Ha which was deshielded by about 0.60 ppm relative to the thioxopyrimidine proton of compound **4** [40,41].

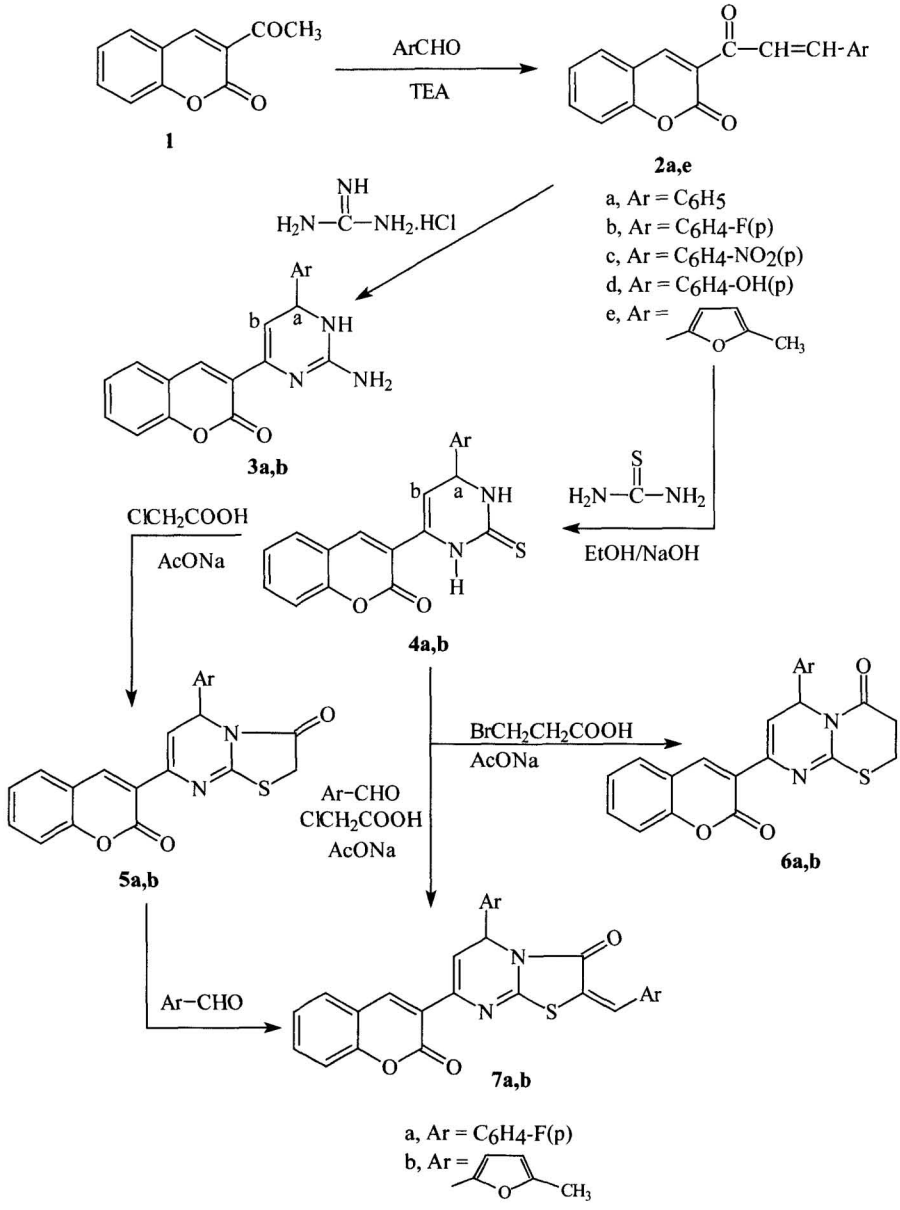
The IR spectra of compounds **5a,b** showed new bands for C=O in the thiazol ring at 1735, 1732 beside the pyrone C=O and disappear of bands characteristic for C=S.

The ^{1}H-NMR spectrum of **5a** [DMSO-d_6] showed signals at 8.65 (1H, s, H-4 pyrone), 6.75-7.75 (9H, m, 8 Ar-H and Hb pyrimidine), 5.75 (1H, s, Ha for pyrimidine ring) and 3.75 (2H, s, CH_2 thiazole protons). The mass spectrum of compound **5b** showed peaks at m/z 378 (81%), 361 (65%), 245 (82%) and base peak at 146 (100%).

Also, the IR spectra of compounds **6a,b** showed bands at 1725 cm^{-1} and 1720 cm^{-1} for the new (C=O) in thiazine rings beside the C=O for pyrone rings. The ^{1}H-NMR spectrum of compound **6b** [DMSO-d_6] showed signals at 8.65 (1H, s, H-4 pyrone), 7.25-8.10 (7H, m, Ar-H and Hb pyrimidine), 5.7 (1H, d, Ha pyrimidine), 3.4-3.55 (4H, m, $2CH_2$ thiazine ring) and 2.75 (3H, s, CH_3 furan).

Condensation of thiazolopyrimidine **5a,b** with aromatic aldehydes in the presence of anhydrous sodium acetate in a mixture of glacial acetic acid/acetic anhydride yielded 3-(2-aryl methylene-5-aryl-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidin-3-one-7-yl)benzopyran-2-one **7a,b**. However, compounds **7a,b** were prepared directly from **4a,b** by its reaction with chloroacetic acid, aromatic aldehyde and sodium acetate anhydrous in acetic acid/acetic anhydride mixture (Scheme 1). The IR spectra of compounds **7a,b** showed peaks at 1706 and 1707 for (C=O) in

thiazole which are shifted to lower frequency due to conjugation with exocyclic double bond [41].



(Scheme 1)

Compounds **2a-e** were reacted with malononitrile in the presence of

ammonium acetate to give the cyanoaminopyridine derivatives **8a-e**. One-step synthesis of compounds **8a-e** could be prepared by condensation of 3-acetylcoumarin **1** with 1,1-dicyano-2-arylethylene or malononitrile and aromatic aldehydes in the presence of ammonium acetate (Scheme 2). The IR spectra of compounds **8a-e** showed peaks at 3450-3375 (NH_2), 2220-2210 (C≡N) beside peak at 1710-1702 for (C=O) α-pyrone ring. The ^{1}H-NMR of compound **8a** [DMSO-d_6] showed signals at 5.25 (2H, s, NH_2 exchangeable with D_2O), 8.7 (1H, s, H-4 pyrone) and 8.2-7.3 (10H, m, Ar-H). The mass spectrum of compound **8d** showed molecular ion peak at m/z 355 (M^+, 82.6%), 328 (22.9%), 327 (100%, base peak), 299 (10.8%), 270 (14.8%).

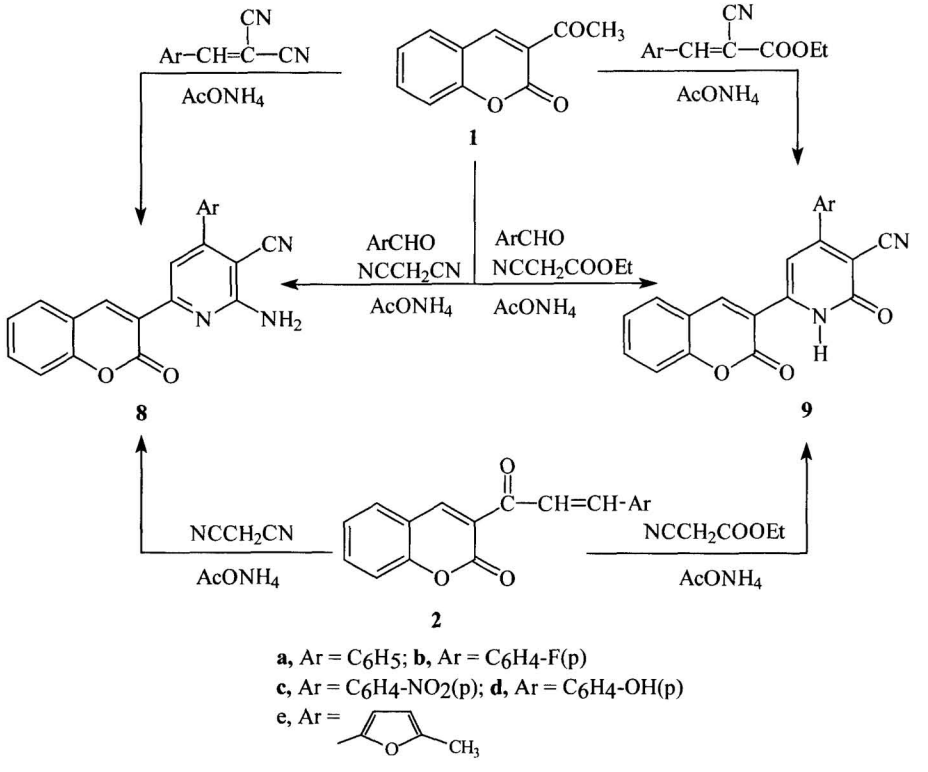
Cyanopyridone derivatives **9a-e** were obtained by the reaction of compounds **2a-e** with ethylcyanoacetate in the presence of ammonium acetate. One step synthesis of compounds **9a-e** could be prepared by condensation of **1** with 1-cyano-1-carboethoxy-2-aryl ethylene or ethylcyanoacetate and aromatic aldehydes in the presence of ammonium acetate (Scheme 2).

The IR spectra of compounds **9a-e** showed peaks at 3430-3370 (NH), 2220-2210 (C≡N) and new peaks at 1700-1725 (C=O in pyridine) beside the C=O for α-pyrone ring. The ^{1}H-NMR spectrum of compound **9e** [DMSO-d_6] showed signals at 9.1 (1H, s, NH), 8.7 (1H, s, H-4 pyrone), 8.2 (1H, d, H-3 furan), 7.9 (1H, d, H-4 furan), 7.25-7.75 (5H, m, Ar-H) and 2.95 (3H, s, CH_3). The mass spectrum of compound **9c** showed the molecular ion peak at m/z 385 (21.3%), 364 (23.23%), 363 (100%, base peak), 336 (13.49%), 335 (53.46%).

Several publications [42-44] reported that the reaction of 1,2-diamines with α,β-unsaturated ketones gave products depend on the experimental conditions. In the present work 3-styryl coumarin **2a,b,e** reacted with 1,2-phenylene diamine under different conditions. The uncatalyzed reaction in refluxing butanol afforded the substituted diazepino derivatives **10a-c** (Scheme 3).

The IR spectra of **10a-c** showed bands at 3385-3340 (NH) and at 1612-1608 (C=N), while bands corresponding to (C=O) of α,β-unsaturated ketones and NH_2 of the diamine were not observed. The ^{1}H-NMR spectrum of **10c** [DMSO-d_6] showed

signals at 11.2 (1H, s, NH which exchangeable with D_2O), 8.65 (1H, s, H-4 pyrone), 7.9 (1H, d, H-3 furan), 7.75 (1H, t, CH diazepine ring), 7.55-7.35 (8H, m, Ar-H), 7 (1H, d, H-4 furan), 6.35 (1H, d, CH_2 diazepine) and 2.35 (3H, s, CH_3).



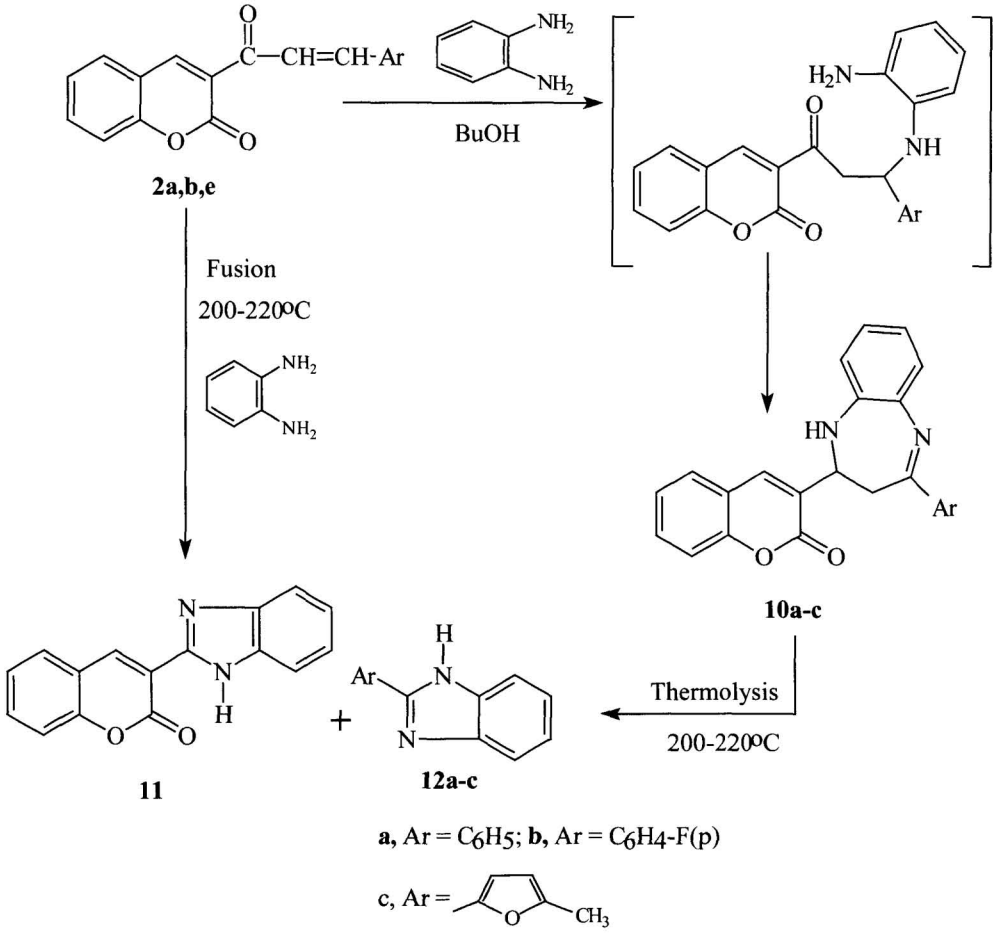
Scheme (2)

The Mass spectrum of compound **10c** exhibited peaks at m/z 370 (M^+, 63%), 280 (98.17%), 265 (100%, base peak), 237 (15.55%), 209 (21.67%).

Formation of **10** was believed to take place with the addition of the diamine ethylenic double bond of **2**, followed by interamolecular condensation of the amino group with the carbonyl function, affording **10** as final products (Scheme 3).

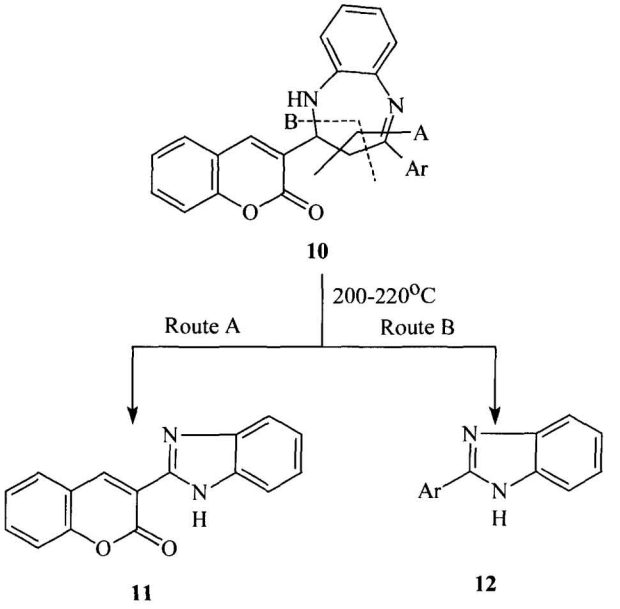
On the other hand, compounds **2a,b,e** were fused with o-phenylenediamine at 200-220°C to afford benzimidazole derivative **11** as the main product along with the benzimidazole derivatives **12a-c** (Scheme 3). The IR spectrum of **11** showed peak

at 3345 (NH). The ^{1}H-NMR spectrum of **11** [DMSO-d_6] showed signals at 10.5 (1H, s, NH which exchangeable with D_2O), 8.65 (1H, s, H-4 pyrone) and 7.50-8.25 (8H, m, Ar-H), its mass spectrum exhibited peaks at m/z 262 (M^+, 26%), 245 (65%), 230 (30%), 201 (61%) and base peak at 146 (100%).

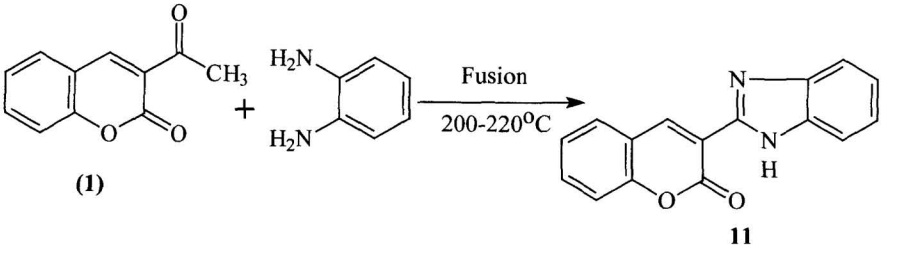


Scheme (3)

Formation of benzimidazoles **11** and **12** are presumed to proceed through the intermediate formation of the corresponding diazepine derivatives **10**, followed its cleavage to give mixture of **11** and **12** depending on the mode of cleavage as follows:



However, compound **11** could be prepared in pure form by fusion of 3-acetyl coumarin **1** with o-phenylenediamine at the same conditions.



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