Synthesis and Reactions of Some New Benzopyranone Derivatives With Potential Biological Activities

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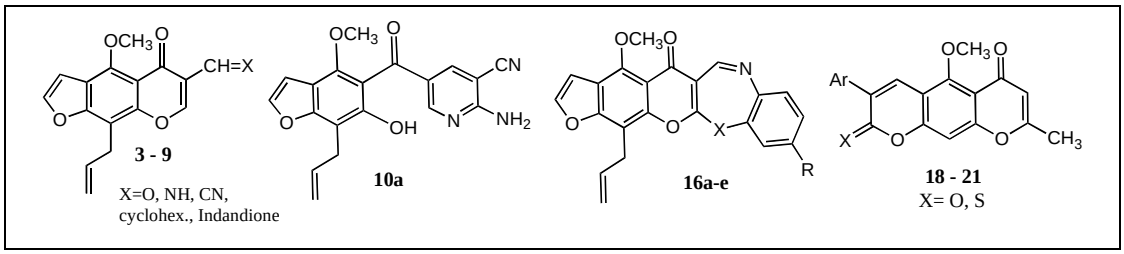

Reaction of visnaginone which derived from the naturally occurring compound "visnagine", with allyl bromide gave *O*-allyl visnaginone **1**, which underwent Claisen rearrangement to yield 7-allylbenzofuran **2** derivative. Vilsmeier Haack formylation of **2** afforded our versatile starting compound furochromene-6-carboxaldehyde **(3)** which was condensed with cyclohexane-1,3-dione, indandione, malononitrile or ethyl cyanoacetate to yield the ylidene nicotinonitrile and pyridone derivatives **4,7,10a-b**. Reaction of **3** with aniline or aniline acting on multiple function X-H (X = NH, O, S) at its *ortho* position afforded the corresponding anils, imidazolylfurochromene and azepines compounds **11-17**. On the other hand, oxidation of visnagin afforded chromene-6-carboxaldehyde derivative **18** which was condensed with different aryl or (heteroaryl) acetonitrile followed by hydrolysis to give pyrano[3,2-*g*]chromen-4,8-dione derivatives **20a-d** and **22**.

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INTRODUCTION

Visnagin is an active principle extracted from the fruits of *Ammi visnaga* [1] The fruit or its isolated active components have been used for the treatment of angina pectoris due to their peripheral and coronary vasodilator activity [2] In isolated *aorta*, *visnagin*, and other related active principles present in these fruits such as *visnadin* and *khellin* inhibited vascular smooth muscle contractility (VSNC) probably by acting or multiple sites to decrease the availability of Ca^{2+} required for activation [3-6], lipid altering activity for example decreasing the atherogenic cholesterol fraction, elevating antiatherogenic HDL cholestrol fraction and antiatherosclerotic activity [7-9].

Also, benzopyranones and furobenzopyranones are compounds of considerable significance as a result of their wide spread occurrence in plants and their potential as important pharmaceuticals in the treatment of renal colic, anginal syndromes, whopping cough, peptic ulcer, DNA stand breaking activity and mutagenicity, antiviral agent, antiproliferation agent, antitumor and central nervous system (CNS) activity, in photochemotherapy treatment of a variety of skin diseases such as psoriasis, vitiligo, mycosis fungicides [10-16]. In view of these facts and in continuation of our research program in this field [17-24], we present here the synthesis of some benzodipyranone and furobenzopyranones derivatives, the latter compounds are consider very interesting precursors to synthesis of antitumor agents brnzopyranone acetic acid analogues [25-28].

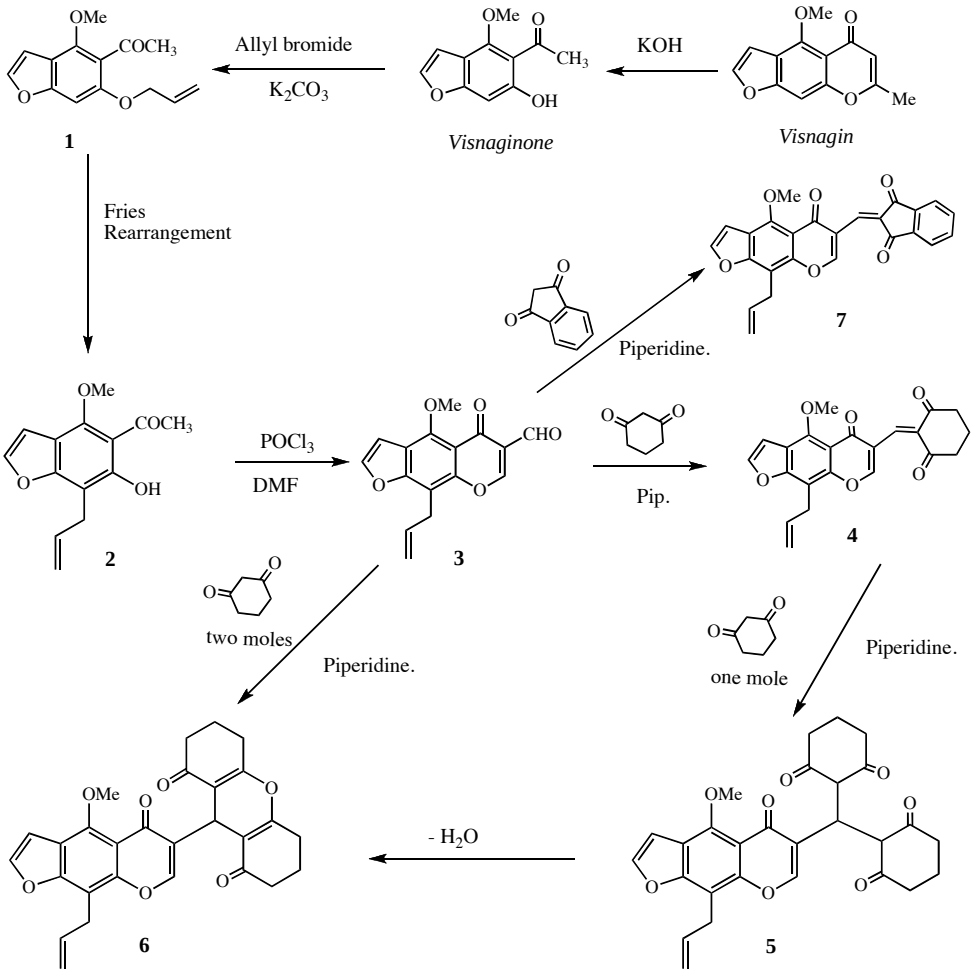
RESULTS AND DISCUSSION

Chromone-3-carboxaldehyde has been extensively used in the synthesis of various heterocyclic systems. The synthesis and reactivity of the versatile compound have been reviewed [29-31]. We present here the synthesis of new allylfurochromone-3-carboxaldehyde as starting material in the synthesis of condensed or isolated heterocyclic furobenzopyranones derivatives. O-allylation of 5-acetyl-6-hydroxy-4-methoxy-benzofuran "*visnaginone*" [32] which was previously prepared from hydrolysis of the naturally occurring compound *"visnagin"* gave the corresponding *O-allyl visnaginone* **(1)**. Compound **1** was refluxed in *N*,*N*-diethylaniline and underwent Claisen rearrangement to provide 5-acetyl-7-allyl-6-hydroxy-4-methoxybenzofuran **(2)** in quantitative yield [24] (Scheme 1).

The versatile starting compound, 9-allyl-4-methoxy-5-oxo-5*H*-furo[3,2-*g*]chromene-6-carbaldehyde **(3)** was obtained in good yield from Vilsmeier-Haack formylation of compound **2**. The ^{1}H NMR spectra of the latter product revealed disappearance the singlet CH_3 at 2.45, whereas two singlets appeared at δ 8.25 and 10.20 ppm.

Condensation of **3** with cyclohexane-1,3-dione or indandione provides the expected mono adducts **4** and **7**

Scheme 1



respectively. The mono adduct **4** was reacted again with another molecule of cyclohexane-1,3-dione to yield the 2:1 adduct **5** which underwent dehydration simultaneously to form 9-(9-allyl-4-methoxy-5-oxo-5*H*-furo[3,2-g]chromen-6-yl) methylene)-3,4,5,6,7,9-hexa-hydro-1*H*-xanthene-1,8-(2*H*)-dione **(6).** The same product **6** was prepared directly from reaction of the chromone-3-carboxaldehyde **3** with two moles of cyclohexane-1,3-dione [30b,d].

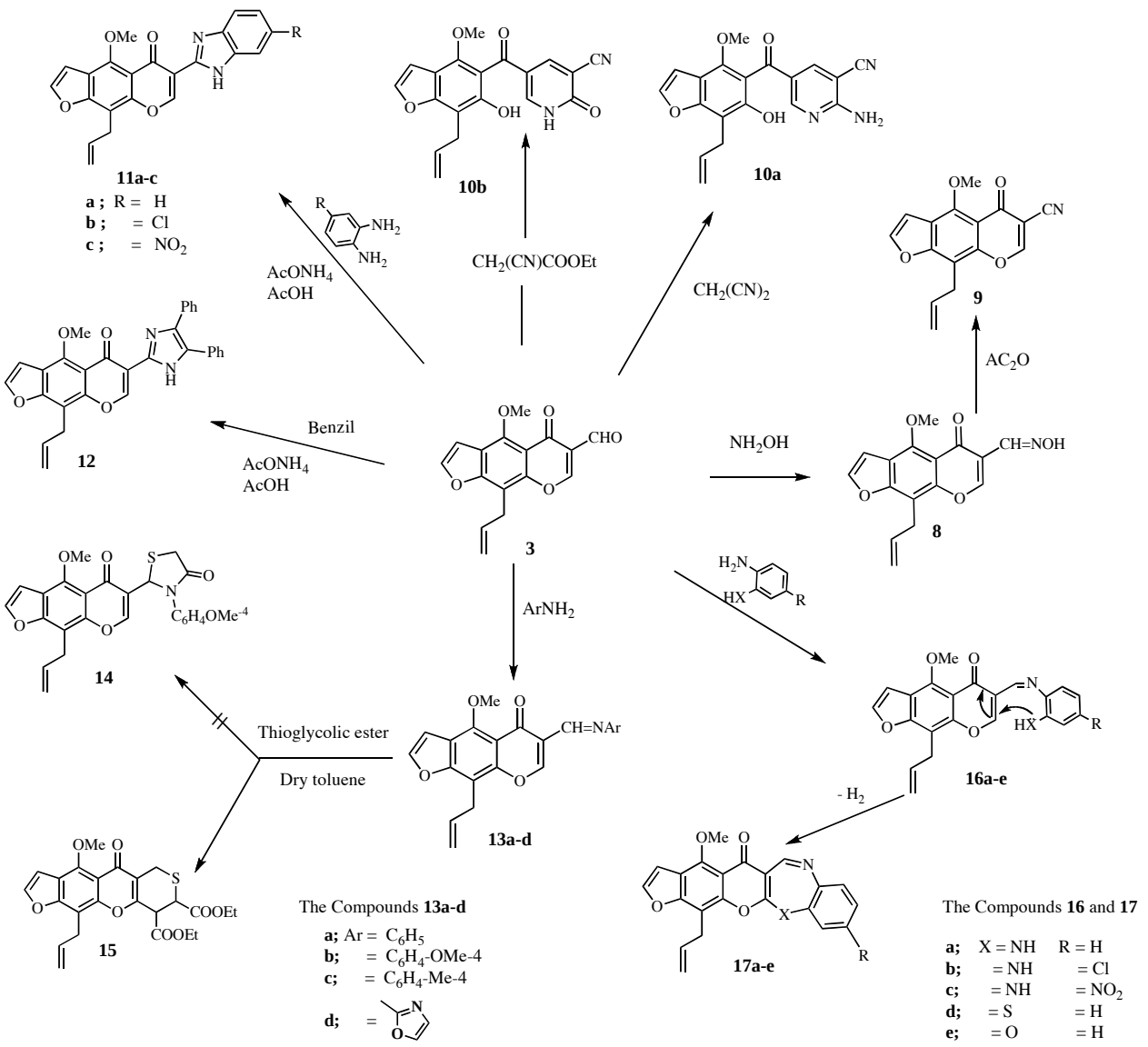
The latter products **4-7** have been characterized by elemental and spectroscopic analyses, the mass spectrum of **6** revealed in addition to the molecular ion peak, one daughter ion peak (M_1) at *m/z* 378 from extrusion cyclohexenone group and the base peak at *m/z* 294 due to extrusion oxirene and cyclopropene groups from the daughter ion M_1.

Compound **3** was condensed with hydroxylamine hydrochloride in ethanol to give a quantitative yield of the corresponding hydroxyiminomethyl chromone **8** which was refluxed in acetic anhydride to give 9-allyl-4-methoxy-5-oxo-5*H*-furo[3,2-*g*]-chromene-6-carbonitrile **(9)** [30b] The infra-red spectrum of **9** showed clearly disappearance of the imino absorption band at ν = 1620 cm^{-1} instead, a new band at ν = 2230 cm^{-1} for C≡N group was appeared.

Condensation of the chromene-6-carbaldehyde **3** with malononitrile or ethyl cyanoacetate in the presence of ammonium acetate afforded 5-(7-allyl-6-hydroxy-4-methoxybenzofuran-5-carbonyl)-2-aminonicotinonitrile **(10a)** and 5-(7-allyl-6-hydroxy-4-methoxybenzofuran-5-carbonyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**10b**) respectively (Scheme 2). The reaction mechanism involves an initial formation of the corresponding ylidene compounds followed by aminolysis of pyrone ring thereafter, nucleophilic attacking of the amino group to the cyano or the ester group simultaneously to form the products **10a,b**. Change of the reaction conditions in some analogue compounds gave different products as outlined in the literature [33]

The assigned structure of **10a** and **10b** were confirmed by spectral and the elemental analysis. The infra-red spectra revealed in addition to the hydroxyl and amino

Scheme 2



absorption bands, the characteristic (C≡N) band at ν = 2227 cm^{-1} as well as an amidic absorption band (compound **10b**) at ν = 1640 and 1576 cm^{-1} indicative of the amide form concerning compound **10b**. ^{1}H-NMR spectra of **10a** showed in addition to the allyl and aromatic protons, the amino and hydroxyl signals at δ 7.84 and 9.06 ppm.

When **3** is refluxed with 1,2-phenylenediamine, 4-chloro-1,2-phenylene diamine and 4-nitro-1,2-phenylene-diamine in glacial acetic acid/ammonium acetate, the corresponding benzoimidazolyl-benzopyranone derivatives **11a-c** were obtained (Scheme 2). The ^{1}H-NMR spectra of **11a-c** showed beside the allyl and aromatic protons, a broad NH signal at δ 12.68-13.12 ppm. By the same manner, when **3** was condensed with benzil under the same condition, 9-allyl-6-(4,5-diphenyl-1H-imidazol-2-yl)-4-methoxyfuro[3,2-*g*]chromen-5-one **(12)** was obtained in good yield.

The reaction of primary aromatic amines with different aromatic or heterocyclic aldehydes seemed to be unique route for the synthesis of several new Schiff bases which are known to possess diverse biological activities [34-36]. Also, highly promising for further chemical transfor–mations as well as a precursor for synthesis hetero-annulated chromones [37-39]. The reaction of furo-chromen-6-carbaldehyde **3** with different primary (hetero) aromatic amines (1:1) molar ratio such as aniline, *p*-anisidine, *p*-toluidine and 2-aminooxazole gave the corresponding anils **(13a-d)** as shown in scheme 2. The structure of compounds **13a-d** was confirmed through the corresponding elemental analyses and spectral data which were in accordance with the assigned structures (Tables 1

Table 1

Characterization data of the newly prepared compounds

No.	M.p. C°	Colour	Yield %	M. Formula (M. Weight)	Calcd. (Found) C	Elemental analysis H	N
3	148-150	Pale brown	95	$C_{16}H_{12}O_5$ (284.26	67.60 (67.43)	4.25 (4.20)	
4	215 (ch)	Dark brown	87	$C_{22}H_{18}O_6$ (378.37)	69.83 (69.77)	4.79 (4.58)	
6	260 (ch)	Dark bown	90	$C_{28}H_{24}O_7$ (472.49)	71.18 (71.03)	5.12 (5.33)	
7	224 (ch)	Pale brown	83	$C_{25}H_{16}O_6$ (412.39)	72.81 (72.66)	3.91 (4.09)	
8	165-166	Pale yellow	75	$C_{16}H_{13}NO_5$ (299.28)	64.21 (64.45)	4.38 (4.27)	4.68 (4.50)
9	193-196	Yellowish brown	80	$C_{16}H_{11}NO_4$ (281.28)	68.32 (68.51)	3.94 (3.79)	4.98 (4.77)
10a	210-213	Brown	73	$C_{19}H_{15}N_3O_4$ (349.34)	65.32 (65.63)	4.33 (4.52)	12.03 (12.44)
10b	204-206	Lustrous yellow	84	$C_{19}H_{14}N_2O_5$ (350.32)	65.14 (65.41)	4.03 (4.29)	8.00 (7.88)
11a	207-210	Yellowish brown	82	$C_{22}H_{16}N_2O_4$ (372.37)	70.96 (70.71)	4.33 (4.50)	7.52 (7.80)
11b	260-263	Dark brown	69	$C_{22}H_{15}ClN_2O_4$ (406.82)	64.95 (64.79)	3.72 (3.48)	6.89 (6.71)
11c	185-187	Reddish brown	70	$C_{22}H_{15}N_3O_6$ (417.37)	63.31 (63.54)	3.62 (3.80)	10.07 (10.27)
12	183-185	Pale yellow	92	$C_{30}H_{22}N_2O_4$ (474.51)	75.94 (75.81)	4.67 (4.88)	5.90 (5.76)
13a	165-167	Yellow	80	$C_{22}H_{17}NO_4$ (359.37)	73.53 (73.73)	4.77 (4.92)	3.90 (4.00)
13b	138-140	Dark yellow	85	$C_{23}H_{19}NO_5$ (389.4)	70.94 (71.11)	4.92 (4.73)	3.60 (3.44)
13c	140-143	Yellow	85	$C_{23}H_{19}NO_4$ (373.40)	73.98 (74.22)	5.13 (5.02)	3.75 (3.87)
13d	168-170	Yellow	70	$C_{19}H_{14}N_2O_5$ (350.32)	65.14 (65.31)	4.03 (4.21)	8.00 (8.27)
15	185-187	Yellow	65	$C_{24}H_{24}O_8S$ (472.51)	61.01 61.34	5.12 5.30	
16c	270-273	Pale brown	80	$C_{22}H_{17}N_3O_6$ (419.39)	63.01 (62.87)	4.09 (4.30)	10.02 (10.33)
16d	185-188	Yellow	90	$C_{22}H_{17}NO_4S$ (391.44)	67.50 (67.61)	4.38 (4.11)	3.58 (3.85)
17a	232-233	brownish red	90	$C_{22}H_{16}N_2O_4$ (372.37)	70.96 (71.20)	4.33 (4.50)	7.52 (7.81)
17b	175-179	Pale brown	77	$C_{22}H_{15}ClN_2O_4$ (406.82)	64.95 (64.69)	3.72 (3.90)	6.89 (7.07)
17c	167-170	Dark red	81	$C_{22}H_{15}N_3O_6$ (417.37)	63.31 (63.45)	3.62 (3.80)	10.07 (10.30)
17d	215-218	Dark yellow	70	$C_{22}H_{15}NO_4S$ (389.42)	67.85 (67.61)	3.88 (3.66)	3.60 (3.40)
17e	170-172	Brown	88	$C_{22}H_{15}NO_5$ (373.36)	70.77 (70.91)	4.05 (3.87)	3.75 (3.50)
19a	244-247	Yellow	85	$C_{20}H_{14}FNO_4$ (351.33)	68.37 (68.17)	4.02 (4.12)	3.99 (4.13)
19b	261-263	Pale yellow	90	$C_{20}H_{14}ClNO_4$ (367.78)	65.31 (65.50)	3.84 (4.01)	3.81 (3.99)
19c	280-282	Pale yellow	90	$C_{20}H_{14}N_2O_6$ (378.34)	63.49 (63.61)	3.73 (3.44)	7.40 (7.27)
19d	273-275	Pale yellow	80	$C_{20}H_{13}Cl_2NO_4$ (402.23)	59.72 (59.90)	3.26 (3.44)	3.48 (3.22)
20a	281-283	Yellow	85	$C_{20}H_{13}FO_5$ (352.31)	68.18 (68.36)	3.72 (3.82)	
20b	>300	Yellow	85	$C_{20}H_{13}ClO_5$ (368.77)	65.14 (65.30)	3.55 (3.27)	

Table 1. (Continued)

No.	M.p. C°	Colour	Yield %	M. Formula (M. Weight)	Calcd. (Found) Elemental analysis C	H	N
20c	>300	Pale yellow	80	$C_{20}H_{13}NO_7$ (379.32)	63.33 (63.09)	3.45 (3.71)	3.69 (3.85)
20d	>300	Yellow	95	$C_{20}H_{12}Cl_2O_5$ (403.21)	59.58 (59.71)	3.00 (3.19)	
21	244-247	Pale yellow	97	$C_{21}H_{14}N_2O_4S$ (390.41)	64.60 (64.88)	3.61 (3.47)	7.18 (7.00)
22	292-294	Pale yellow	95	$C_{21}H_{13}NO_5S$ (391.40)	64.44 (64.70)	3.35 (3.62)	3.58 (3.70)

Table 2

Spectral data of the newly prepared compounds

No	Spectral data
3	ir (cm^{-1}) ν = 1700 (CHO), 1650 (C=O), 1590 (C=C) . ^{1}H nmr ($CDCl_3$) δ : 3.40 (d, 2H, 2H-1`, J = 4.59 Hz), 4.01 (s, 3H, $OCH_3$), 5.06 (dd, 1H, H-3`, J_{gem}= 1.88 Hz, J_{cis}= 10.02 Hz), 5.08 (dd, 1H, H-3`, J_{gem}= 1.87 Hz, J_{trans}= 15.94 Hz), 6.01 (m, 1H, H-2'), 7.01 (d, 1H, H-3, J = 2.39 Hz), 7.79 (d, 1H, H-2, J = 2.39 Hz), 8.25 (s, 1H, H-7) and 10.20 ppm (s, 1H, CHO).
4	ir (cm^{-1}) ν = 1705, (C=O), 1684 (C=O, Chromone), 1605 (C=C). ^{1}H nmr (DMSO-d_6) δ : 1.7 (m, 2H, H-4 cyclohex.), 3.54 (m, 4H, H-3 and H-5 cyclohex.), 3.78 (d, 2H, 2H-1`, J = 4.61 Hz), 4.06 (s, 3H, $OCH_3$), 5.03 (m, 2H, 2H-3`), 6.01(m, 1H, H-2), 7.15 (m, 2H, furan H-3 and H-7), 7.82 (d,1H, H-2 furan, J = 2.41 Hz) and 8.08 ppm (s, 1H, C<u>H</u>=C).
6	^{1}H nmr ($CDCl_3$) δ : 1.52-2.01 (m, 8H, H-3,4.6,7 xanthene.), 3.18 (m, 4H, H-H-2,8 xanthene.), 3.42-3.56 (m, 3H, 2H-1', H-10 xanthene), 4.04 (s, 3H, OCH_3), 5.09 (dd, 1H, H-3`, $J_{gem}$= 1.83 Hz, $J_{cis}$= 10.15 Hz), 5.18 (dd, 1H, H-3`, J_{gem}= 1.83 Hz, J_{trans}= 16.09 Hz), 6.00 (m, 1H, H-2'), 7.56-7.77 (m, 2H, H-2 furan, H-7), 7.85 (d, 1H, H-2, J = 2.46 Hz). ms *m/z* (%) 473 $(M+1)^+$ (23), 472 (M^+)(30), 378 [M_1(M-cyclohexenone)$^+$](14), 294 [M_2 (M_1- oxirene &cyclopropene)](100).
7	ir (cm^{-1}) ν = 1710, (C=O), 1678 (C=O, Chromone), 1597 (C=C), 1594, (Ar.), ^{1}H nmr (DMSO-d_6) δ : 3.85 (d, 2H, 2H-1`, J = 4.55 Hz), 4.13 (s, 3H, $OCH_3$), 5.09 (m, 2H, 2H-3`), 5.91 (m, 1H, H-2), 7.28 (m, 2H, furan H-3 and H-7), 7.56-7.82 (m, 5H, Ar-H and H-2 furan, J = 2.36 Hz) and 8.75 ppm (s, 1H, C<u>H</u>=C). ms *m/z* (%) 414 $(M+2)^+$(33), 413 $(M+1)^+$(84), 412 $(M)^+$(10), 411$(M-1)^+$(6).
8	ir (cm^{-1}) ν = 3350-3220 (br., OH), 1655 (C=O), 1620 (C=N) and 1590 (C=C). ^{1}H nmr ($CDCl_3$) δ : 3.52 (d, 2H, 2H-1`, J = 5.71 Hz), 4.11 (s, 3H, $OCH_3$), 5.77 (m, 2H, H-3`), 6.18 (m, 1H, H-2'), 7.01 (d, 1H, H-3, J = 2.37 Hz), 7.86 (m, 1H, H-2, J = 2.38 Hz), 8.01 (s, 2H, H-7 and C<u>H</u>=N).and 12.70 ppm (s, br. OH).
9	ir (cm^{-1}) ν = 2230 (CN), 1659 (C=O), 1605 (C=C). ^{1}H nmr ($CDCl_3$) δ : 3.44 (d, 2H, 2H-1`, J = 5.46 Hz), 4.11 (s, 3H, $OCH_3$), 5.06-5.08 (m, 2H, H-3`), 6.05 (m, 1H, H-2'), 7.01 (d, 1H, H-3, J= 2.31 Hz), 7.79 (d, 1H, H-2, J = 2.31 Hz) and 8.10 ppm (s, 1H, H-7).
10a	ir (cm^{-1}) ν = 3385,3331 (Sym. NH_2) 3485 (OH), 2221 (CN) , 1676 (C=O), 1619 (C=C), 1586 (Ar.). ^{1}H nmr (DMSO-d_6) δ : 3.57 (d, 2H, 2H-1`, J = 5.86 Hz), 3.90 (s, 3H, $OCH_3$), 4.96 (dd, 1H, H-3`, J_{gem}= 1.72 Hz, J_{cis}= 10.32 Hz), 5.03 (dd, 1H, H-3`, J_{gem}= 1.73 Hz, J_{trans}= 16.81 Hz),6.02 (m, 1H, H-2'), 7.16 (d, 1H, H-3 furan, J = 2.24 Hz), 7.84 (s, br., 2H, NH_2) , 7.88 (d, 1H, H-2, furan, J = 2.28 Hz), 8.12 (s, 1H, H-6 pyridine) , 8.45 (s, 1H, H-4 pyridine) and 9.06 ppm (s, br,1H, OH).
10b	ir (cm^{-1}) ν = 3445(strong ,OH), 3030 (strong, NH), 2223 (CN), 1689 (C=O) 1620 (C=O , amide), 1610 (C=C) ^{1}H nmr (DMSO-d_6) δ : 3.58 (d, 2H, 2H-1`, J = 4.55 Hz), 3.98 (s, 3H, $OCH_3$) , 4.94 (dd, 1H, H-3` J_{gem}= 1.80 Hz, J_{cis}= 10.22 Hz) , 4.99 (dd, 1H, H-3, J_{gem}= 1.80 Hz, J_{trans}= 16.86 Hz), 6.00- (m, 1H, H-2'), 7.14 (d, 1H, H-3 furan, J= 2,40 Hz), 7.66 - 7.88 (m, 2H, H-2, furan, H-6 pyridine), 8.45 (s, 1H, H-4, pyridine), 11.60 (s, br., NH) and 13.20 ppm (s, br, OH).
11a	ir (cm^{-1}) ν = 3375(NH), 1640 (C=O), 1612-1605 (C=N and C=C). ^{1}H nmr (DMSO-d_6) δ 3.61 (d, 2H, 2H-1`), 4.08 (s, 3H, $OCH_3$), 5.02 (dd, 1H, H-3`), 5.11 (dd, 1H, H-3`), 5.97-6.11 (m, 1H, H-2'), 7.24 (d, 1H, H-3 furan), 7.88 - 9.12 (m, 6H, Ar.H) and 12.68 ppm (d, 1H, NH).
11b	ir (cm^{-1}) ν = 3390 (NH), 1650 (C=O), 1610-1590 (C=N and C=C). ^{1}H nmr (DMSO-d_6) δ : 3.63 (d, 2H, 2H-1`, J = 4.30 Hz), 4.09 (s, 3H, $OCH_3$), 5.01 (dd, 1H, H-3`, J_{gem}= 1.83 Hz, J_{cis}= 10.11 Hz), 5.08 (dd, 1H, H-3`, J_{gem}= 1.82 Hz, J_{trans}= 16.77 Hz), 6.00 (m, 1H, H-2'), 7.37 (d, 1H, H-3 furan, J = 2.37 Hz), 7.88-9.13 (m, 5H, Ar.H) and 12.56 ppm (s, 1H, NH). ms *m/z* (%) 408 $(M+2)^+$(32), 406$(M)^+$ (39), 377 $(M-C_2H_6)^+$(100).
11c	ir (Cm^{-1}) ν = 3390(NH), 1655 (C=O), 1620-1600 (C=N and C=C), 1560, 1395 (NO_2). ^{1}H nmr (DMSO-d_6) δ : 3.71 (d, 2H, 2H-1`, J = 4.33 Hz), 4.13 (s, 3H, $OCH_3$), 5.02 (dd, 1H, H-3`, J_{gem}= 1.73 Hz, J_{cis}= 10.23 Hz), 5.08 (dd, 1H, H-3`, J_{gem}= 1.73 Hz, J_{trans}= 16.62 Hz), 5.90-6.10 (m, 1H, H-2'), 7.37 (d, 1H, H-3 furan, J = 2.23 Hz), 7.88-9.13 (m, 5H, Ar.H) and 13.12 ppm (d, 1H, NH). ms *m/z* (%) 419 $(M+2)^+$ (28), 418$(M+1)^+$(87), 417 $(M)^+$(100), 371$(M-NO_2)^+$ (40)
12	ir (cm^{-1}) ν = 3390 (NH), 1655 (C=O), 1625-1615 (C=N and C=C). 1H nmr (DMSO-d_6) δ : 3.81 (d, 2H, 2H-1`, J = 5.01 Hz), 4.03 (s, 3H, OCH3), 5.13 (dd, 1H, H-3`, Jgem= 1.78 Hz, Jcis= 11.01 Hz), 5.21 (dd, 1H, H-3`, Jgem= 1.75 Hz, Jtrans= 15.81 Hz), 6.09 (m, 1H, H-2'), 7.37 (d, 1H, H-3 furan, J = 2.37 Hz), 7.45-8.88 (m, 12H, Ar.H) and 10.10 ppm (s, 1H, NH). ms m/z (%) 476 (M+2)+(43), 475 (M+1)+(100), 474 (M)+(88).

Table 2 (Continued)

No	Spectral data
13a	ir (cm^{-1}) ν = 1650 (C=O) , 1615-1590 (C=N and C=C). ^{1}H nmr ($CDCl_3$) δ : 3.66 (d, 2H, 2H-1`, J = 4.49 Hz), 3.90 (s, 3H, $OCH_3$), 4.96-5.08 (m, 2H, H-3`), 6.09-6.20 (m, 1H, H-2') and 6.92 -7.60 ppm (m, 8H, Ar-H, CH=N).
13b	ir (cm^{-1}) ν = 1648 (C=O) , 1612-1600 (C=N and C=C). ^{1}H nmr ($CDCl_3$) δ : 3.64 (d, 2H, 2H-1`, J = 4.53 Hz), 3.85 (s, 3H, $OCH_3$), 3.87 (s, 3H, $OCH_3$), 4.96-5.08 (m, 2H, H-3`), 6.00-6.20 (m, 1H, H-2') and 6.88-7.51ppm (m, 7H, Ar-H, CH=N) .ms *m/z* (%)390 $(M+1)^+$ (6), 389 $(M)^+$(11), 282 $(M-C_7H_7O)^+$(28).
13c	ir (cm^{-1}) ν = 1653 (C=O), 1618-1605 (C=N and C=C). ^{1}H nmr ($CDCl_3$) δ : 2.34 (s, 3H, CH_3) , 3.71 (d, 2H, 2H-1`, J = 4.49 Hz), 4.18 (s, 3H, $OCH_3$) , 4.98-5.08 (m, 2H, H-3`), 6.00-6.20 (m, 1H, H-2') and 6.80-7.54 ppm (m, 7H, Ar-H, CH=N). ms *m/z* (%) 374 (M+1) (2), 373 (M^+) (4).
13d	^{1}H nmr (DMSO-d_6) δ : 3.38(d, 2H, 2H-1`), 4.03 (s, 3H, $OCH_3$) , 4.96-5.08 (m, 2H, H-3`) , 5.90-6.10 (m, 1H, H-2') , 6,82 (s, 1H, H-7), 7.11 (d, 1H, H-3, J = 2.36 Hz), 7.90-8.40 (m, 2H, Ar-H) , 8.49 (s, 1H , CH=N) and 8.77ppm (s, 1H, H-7). ms *m/z* (%) 351 $(M+1)^+$(26), 350 (M^+) (42), 349 $(M-H)^+$ (29), and 282 (M- Oxazole ring)$^+$ (100).
15	IR(Cm^{-1}) ν = 1646 (br., C=O), 1614 (C=C). ^{1}H nmr ($CDCl_3$) δ : 1.97 (t. 6H, $C\underline{H}_3CH_2$, two groups), 3.60-3.78 (m, 4H, 2H-1`, =$C\underline{H}_2$-S-CH), 3.98-4.14 (m, 9H. OMe & –S-C<u>H</u>-C<u>H</u>-, & $CH_3C\underline{H}_2$ two groups), 5.03 (m, 2H, H-3`), 6.00 (m, 1H, H-2'), 6.97 (d, 1H, H-3, J = 2.48 Hz), and 7.59 ppm (d, 1H, H-2, J = 2.45 Hz)
16c	ir (cm^{-1}) ν = 3255 (br., NH_2), 1648 (C=O), 1605 (C=N, C=C), 1523,1343 (NO_2) ^{1}H nmr ($CDCl_3$) δ : 3.75 (d, 2H, 2H-1`, J = 6.0 Hz), 4.01 (s, 3H, $OCH_3$), 5.03 (dd, 1H, H-3`, J_{gem}= 1.73 Hz, J_{cis}= 10.23 Hz), 5.09 (dd, 1H, H-3`, J_{gem}= 1.73 Hz, J_{trans}= 16.62 Hz), 6.00-6.09 (m, 1H, H-2'), 7.32 (d, 1H, H-3 furan, J = 2.3 Hz), 7.75-8.40 (m, 5H, Ar.H and H-2 furan), 9.23 (s, br, 1H, CH=N) and 13.20 ppm (s, br., 2H, NH_2).
16d	ir (cm^{-1}) ν = 3446 (br., SH), 1646 (C=O), 1613 (C=N), 1605 (C=C). ^{1}H nmr ($CDCl_3$) δ : 3.69 (d, 2H, 2H-1`, J = 6.0 Hz), 3.91 (s, 3H, $OCH_3$), 5.12 (dd, 1H, H-3`, J_{gem}= 1.87 Hz, J_{cis}= 10.71 Hz), 5.18 (dd, 1H, H-3`, J_{gem}= 1.86 Hz, J_{trans}= 16.59 Hz), 6.11 (m, 1H, H-2'), 7.27 (d, 1H, H-3 furan, J = 2.6 Hz), 7.41-7.90 (m, 6H, Ar.H , 6H), 8.52 (s, br, 1H, CH=N) and 10.11 ppm (s, br., 1H, SH). ms *m/z* (%) 391 $(M)^+$ (7), 390 $(M-H)^+$(13), 360 (M-Sulfur atom)$^+$(27), 124 (100).
17a	ir (cm^{-1}) ν = 1650 (C=O) , 1590 (br., C=N and C=C). ^{1}H nmr ($CDCl_3$) δ : 3.61 (d, 2H, 2H-1`, J = 4.46 Hz), 3.98 (s, 3H, $OCH_3$), 4.95 (dd, 1H, 1H-3`, J_{gem}= 1.56 Hz, J_{cis}= 10.04 Hz), 5.03 (dd, 1H, H-3`, J_{gem}= 1.58 Hz, J_{trans}= 17.12 Hz) 6.00 (m, 1H, H-2'), 7.11-7.29 (m, 3H , H-3 and Ar-H), 7.88 (d, 1H , H-2, J = 2.7 Hz), 8.53 (d, 2H, Ar.H), 9.05 (s, br., 1H, N=CH) and 14.15 ppm (s, 1H, NH). ms *m/z* (%) 374 $(M+2)^+$(39), 373 $(M+1)^+$(66), 372 $(M)^+$(100), 371 $(M-H)^+$(48), 217 (49).
17b	^{1}H nmr (DMSO-d_6) δ : 3.58 (d, 2H, 2H-1`, J = 4.53 Hz), 3.95 (s, 3H, $OCH_3$), 4.96 (dd, 1H, H-3`, J_{gem}= 1.66 Hz, J_{cis}= 10.04 Hz) , 5.01 (dd, 1H, H-3`, J_{gem}= 1.67 Hz, J_{trans}= 16.80 Hz) ,5.99 (m, 1H, H-2'), 7.13 (d, 1H, H-3 furan, J = 2.35 Hz), 7.25-7.28 (m, 2H, Ar.H, H-8,11), 7.87 (d, 1H,H-2 furan, J = 2.35 Hz), 8.47 (d, 1H, Ar.H , H-10, J = 4.12 Hz), 9.48 (s, br, 1H, CH=N) and 14.09 ppm (s, 1H, NH).
17c	ir (cm^{-1}) ν = 3338 (NH), 1650 (C=O), 1612 (C=N), 1521,1331 (NO_2). ^{1}H nmr (DMSO-d_6) δ : 3.79 (d, 2H, 2H-1`, J = 4.71 Hz), 4.05 (s, 3H, OCH_3), 4.85-5.05(m, 2H, H-3'), 6.00-6.09 (m, 1H, H-2'), 7.34-8.46 (m, 5H, Ar.H) and 9.27 ppm (s, br, 1H, CH=N), 12.8 (s, br. NH)
17d	^{1}H nmr ($CDCl_3$) δ : 3.87 (d, 2H, 2H-1`), 4.27 (s, 3H, $OCH_3$), 5.11 (dd, 1H, H-3`), 5.16 (dd, 1H, H-3`), 6.02-6.18 (m, 1H, H-2'), 7.12 (d ,1H, H-3 furan), 7.20-7.40 (m, 2H, Ar.H), 7.69 (d, 1H, H-2 furan), 8.00-8.10 (m, 2H, Ar.H) and 9.23 ppm (s, 1H, CH=N).
17e	^{1}H nmr ($CDCl_3$) δ : 3.89 (d, 2H, 2H-1`), 4.18 (s, 3H, $OCH_3$), 5.15 (dd, 1H, H-3`), 5.19 (dd, 1H, H-3`), 6.01-6.18 (m, 1H, H-2'), 7.14 (d, 1H, H-3 furan), 7.20-7.40 (m, 2H, Ar.H), 7.69 (d, 1H, H-2 furan), 8.00-8.10 (m, 2H, Ar.H) and 9.01ppm (s, 1H, CH=N).
19a	ir (cm^{-1}) ν = 3425 (NH), 1654 (C=O), 1601 (Ar). ^{1}H nmr (DMSO-d_6) δ : 2.32(s, 3H, CH_3), 3.81 (s, br., NH), 4.0 (s, 3H, OMe), 6.21 (s, 1H, H-10), 7.36 (s, 1H, H-3), 7.32 (m, 2H, H-3',5'), 7.80 (m, 2H, H-2',6'), and 8.21 ppm (s, 1H, H-6).
19b	ir (cm^{-1}) ν = 3449 (NH), 1670 (C=O), 1604 (Ar.). ^{1}H nmr (DMSO-d_6) δ : 2.38 (s , 3H, CH_3), 3.15 (s, br., NH), 3.98 (s, 3H, OMe), 6.17 (s, 1H, H-10), 7.39 (s, 1H, H-3), 7.52 (d, 2H, H-3',5', J = 8.6 Hz), 7.80 (d, 2H, H-2',6', J = 8.6 Hz), and 8.21 ppm (s, 1H, H-6). ms *m/z* (%) 369 $(M+2)^+$(37), 368 $(M+1)^+$(50), 367 $(M)^+$(90), 366 $(M-1)^+$(35)
19c	ir (cm^{-1}) ν = 1655 (C=O), 1593 (C=N), 1508 and 1338 (NO_2). ^{1}H nmr (DMSO-d_6) δ : 2.35(s, 3H, CH_3), 3.77 (s, br., NH), 3.91 (s, 3H, OMe), 6.16 (s, 1H, H-10), 6.77 (s, 1H, H-3), 8.03 (d, 2H, H-2',6', J = 6.7 Hz), 8.36 (d, 2H, H-3',5', J = 6.7 Hz) and 9.03 ppm (s, 1H, H-6). ms *m/z* (%) 379 $(M+1)^+$(31), 378 $(M)^+$ (100), 217 (49).
19d	^{1}H nmr (DMSO-d_6) δ : 2.35 (s , 3H, CH_3), 3.81 (s, br. NH), 3.98 (s, 3H, OMe), 6.12 (s, 1H, H-10), 7.10 (s, 1H, H-3), 7.10 (s, 1H, H-6), 7.40-7.75 (m, 3H, Ar-H), and 8.77 ppm (s, 1H, H-6).
20a	ir (cm^{-1}) ν = 1739 (-O-C=O), 1654 (C=O), 1607 (Ar). ^{1}H nmr ($CDCl_3$) δ : 2.66 (s , 3H, CH_3), 4.11 (s, 3H, OMe), 6.12 (s, 1H, H-10), 6.80 (s, 1H, H-3), 7.41 (m, 2H, H-3',5'), 7.46 (m, 2H, H-2',6'), and 8.25 ppm (s, 1H, H-6).

Table 2 (Continued)

No	Spectral data
20b	ir (cm^{-1}) ν = 1735 (-O-C=O), 1674 (C=O), 1608 (Ar). ^{1}H nmr ($CDCl_3$) δ : 2.35 (s , 3H, CH_3), 3.99 (s, 3H, OMe), 6.12 (s, 1H, H-10), 6.92 (s, 1H, H-3), 7.41-7.46 (m, 4H, Ar-H), and 8.16 ppm (s, 1H, H-6). ms *m/z* (%) 370 (M+2)(29)), 369 $(M+1)^+$ (26), 368 $(M)^+$ (86).
20c	ir (cm^{-1}) ν = 1750 (-O-C=O), 1674 (C=O), 1600 (C=C) 1510 and 1345 (NO_2). ^{1}H nmr (DMSO-d_6) δ : 2.49 (s , 3H, CH_3), 4.03 (s, 3H, OMe), 6.31 (s, 1H, H-10), 7.05 (s, 1H, H-3), 7.50-8.03 (m, 4H, Ar-H), and 8.44 ppm (s, 1H, H-6). ms *m/z* (%) 381 $(M+2)^+$ (8)), 380 $(M+1)^+$, 379 $(M)^+$ (100), and 322 (M- HNO_2) (55).
20d	ir (cm^{-1}) ν = 1742 (-O-C=O), 1660 (C=O), 1600 (C=C). ^{1}H nmr (DMSO-d_6) δ : 2.33 (s, 3H, CH_3), 3.94 (s, 3H, OMe), 6.19 (s, 1H, H-10), 7.28 (s, 1H, H-3), 7.10 (s, 1H, H-6), 7.40-8.60 (m, 3H, Ar-H). and 8.34 ppm (s, 1H, H-6). ms *m/z* (%) 406 $(M+4)^+$(13), 405 $(M+3)^+$(22), 404 $(M+2)^+$(72), 403 $(M+1)^+$(35), 402 $(M)^+$ (100), 345 (60)
21	ir (cm^{-1}) ν = 3350 (NH), 1660 (C=O), 1609 (C=N), 1600 (Ar.). ^{1}H nmr ($CDCl_3$) δ : 2.35(s , 3H, CH_3), 4.11 (s, 3H, OMe), 6.07 (s, 1H, H-10), 7.00 (s, 1H, H-3), 8.12-8.44 (m , 4H, Ar.H) and 8.58 ppm (s, 1H , H-6).
22	ir (cm^{-1}) ν = 1725 (-O-C=O), 1655 (C=O), 1609 (C=N), 1600 (Ar.). ^{1}H nmr ($CDCl_3$) δ : 2.37 (s, 3H, CH_3), 4.18 (s, 3H, OMe), 6.10 (s, 1H, H-10), 7.15 (s, 1H, H-3), 8.16-8.42 (m, 4H, Ar.H) and 9.39 ppm, (s, 1H , H-6). ms *m/z* (%) 414 $(M)^+$ (90).

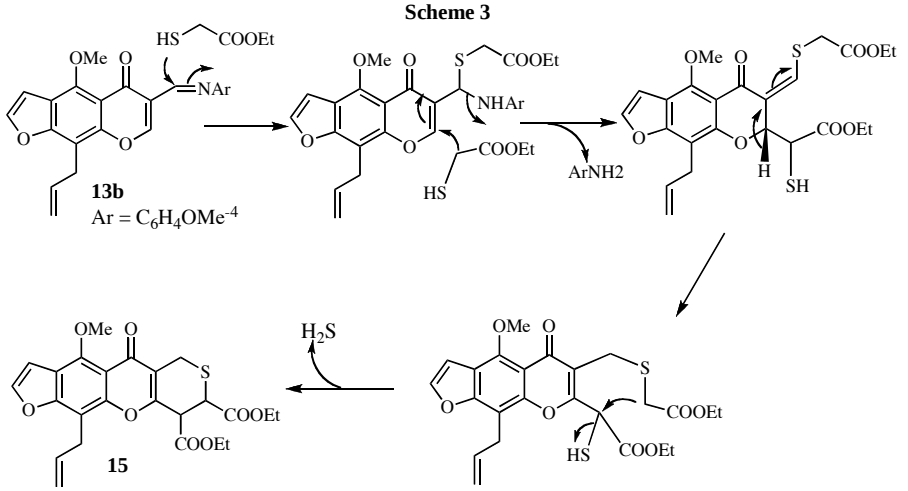
and 2). The base peak ion of the compounds **13a-d** have an *m/z* value (282) of the corresponding $[C_{16}H_{12}NO_4]$ showing that the most favoured point of rupture occurs between the ring residue of the aromatic amine and the imino group.

Heating of **13b** with ethyl glycolate under reflux in dry toluene, the product **15** could be isolated and not the expected thiazolidinone derivative **14** [40]. All the instrumental analyses which were performed on compound **15** confirmed the suggested structure, the mass spectrum gave the molecular ion M^+ at *m/z* = 472 which is in complete with its molecular weight $[C_{24}H_{24}O_8S]$, in addition to the base peak at *m/z* = 294 from extrusion of sulfur atom and two COOEt groups. The suggested mechanism of the formation the compound **15** is shown in Scheme 3.

6-Formylfurochromen-5-one contains three potential sites of nucleophilic attack C-7, C-5 and 6-formyl group [39], thus, condensation of a suitable reactant at two of these sites afforded new ring system. Reaction of **3** with aniline having a nucleophilic function X-H (X = NH, O, S) at ortho position such as 1,2-phenylenediamine, 4-chloro-1,2-phenylenediamine, 4-nitro-1,2-phenylenediamine, 2-aminothiophenol and 2-aminophenol afforded first the corresponding anils **16a-e**. The latter Schiff bases underwent nucleophilic addition of the X-H on the C-2, followed by dehydrogenation by air to form the cyclized azepine derivatives **17a-e** (Scheme 2). The latter compound **16a-e** and **17a-e** were established from their elemental analyses as well as spectral data which are in accordance with the assigned structures (Tables 1 and 2).

The interesting bioactivities of the naturally-occurring benzodipyranones as antibacterial, tuberculostatic and molluscicidal agents [41] promoted us to undertake a synthetic study of this nucleus to study their biological activities. Compound 7-hydroxy-5-methoxy-2-methyl-4-

Scheme 3



oxo-4*H*-chromene-6-carbaldehyde **(18)** was prepared from oxidation of the naturally occurring *visnagin* as outlined in the literature [42].

When an equimolar mixture of **18** and a number of phenylacetonitrile derivatives such as 4-fluoro-, 4-chloro-,4-nito- and 2,4-dichloro phenylacetonitrile was refluxed in ethanol and in a presence of a few drops of piperidine, the corresponding 7-aryl-8-imino pyrano[3,2-*g*]chromen-4(8*H*)-one derivatives **19a-d** were obtained quantitatively. The corresponding 7-aryl pyrano [3,2-g] chromen-4,8-dione derivatives **20a-d** were obtained by hydrolysis of **19a-d** in acetic acid (Scheme 4).

By the same manner, when **18** was condensed with benzothiazole-2-acetonitrile, 7-(benzo[*d*]thiazol-yl)-8-imino-5-methoxy-2-methylpyrano[3,2-g]chromen-4(8*H*)-one **(21)** was formed. Hydrolysis of **21** by using acetic acid, the corresponding pyranochromendione **22** was obtained. The corresponding open ylidene compounds not obtained as reported in the literature [43]. The infra-red spectra of the products **19a-d** and **21** showed absence of (C≡N) absorption peak, that is confirm the outlined suggested reaction pathway (Scheme 4)

EXPERIMENTAL

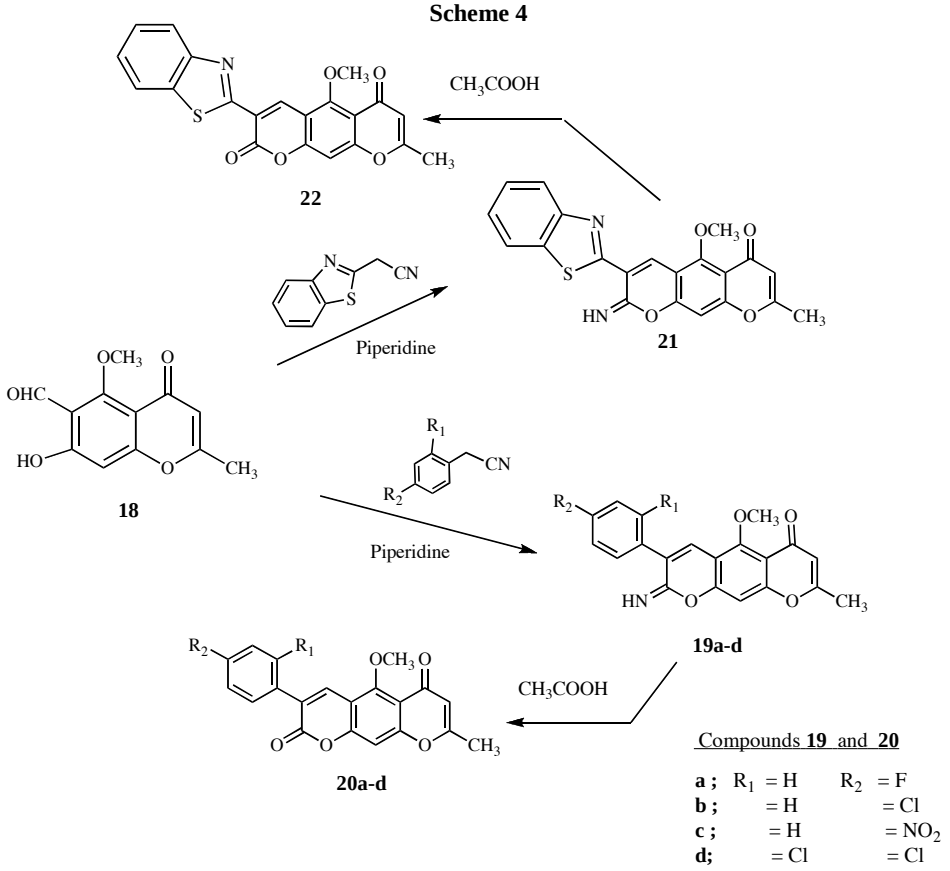
All melting points were determined on an electrothermal Gallenkamp apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. ^{1}H NMR spectra were carried out in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Mercurry V-300 MHz spectrometer and chemical shifts were expressed in δ units using TMS as internal reference, Mass spectra were recorded on a GC-MS-QP-1000EX mass spectrometer at 70 e.V.(Faculty of Science, Cairo university). Elemental analyses were carried out in the CHN Elementar Autoanalyzer unit, Faculty of Science, King Faisal University. Thin layer Chromatography Silica gel 60 F_{254}. Layer thickness 0.2 mm. Tables 1 and 2 show the characterization and spectral data of the newly prepared compounds.

The compounds *visnaginone*, 5-Acetyl-6-allyloxy-4-methoxy-benzofuran **(1)**, 5-Acetyl-7-allyl-6-hydroxy-4-methoxybenzo-furan **(2)** and 7-hydroxy-5-methoxy-2-methyl-4-oxo-4*H*-chromene-6-carbaldehyde **(18)** were prepared by the same procedures as outlined in the published literatures [24,32,42].

9-Allyl-4-methoxy-5-oxo-5*H*-furo[3,2-*g*]chromene-6-carboxaldehyde (3). To a stirred solution of compound **2** (2.46 g, 10 mmol) in dimethylformamide (30 ml), phosphorous oxychloride (15 ml) was added drop wise at 0-5℃ during about 10 min. The mixture was stirred at room temperature for 5 hrs, and hydrolysed by ice-water. The resulting precipitate was collected by filtration, washed with water and crystallized from ethanol to yield **3** as pale brown powder.

Condensation of compound 3 with cyclohexane-1,3-dione and indanedione. Synthesis of the compounds 4 and 7. To a solution of the aldehyde **3** (1.42 g, 5 mmol), and the appropriated active methylene compound (5 mmol) in absolute ethanol (20 mL), piperidine (0.5 mL) was added. The reaction mixture was

Scheme 4



refluxed for 3 hrs. The solid that was obtained was collected by filtration, washed with ethanol, dried and crystallized from ethanol to give the corresponding 1:1 adducts **4** and **7**.

9-(9-Allyl-4-methoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)-methylene)-3,4,5,6,7,9-hexahydro-1*H*-Xanthene-1,8-(2*H*)-dione (6) Method A. To a solution of the mono adduct ***4*** (0.38 g, 1 mmol), and cyclohexane-1,3-dione (1.1 mmol) in absolute ethanol (20 mL), piperidine (0.2 mL) was added. The reaction mixture was refluxed for 3 hrs. The solid that was obtained was collected by filtration, washed with ethanol, dried and crystallized from ethanol to give compound **6** directly without separation of the diadduct **5** (Table 1 and 2).

Method B. Compound **6** was also prepared directly upon treatment of compound **3** with cyclohexane-1,3-dione (1:2 moles), according to the procedure previously described for the synthesis of compound **4** (Tables 1 and 2).

9-Allyl-4-methoxy-5-oxo-5*H*-furo[3,2-*g*]chromene-6-carbaldehyde oxime (8). To a well-stirred solution of compound **3** (2.84 g, 10 mmol) in ethanol (30 mL), hydroxylamine hydrochloride (0.77 g, 11 mmol) was added. The solution was stirred vigorously for 5 hrs, and the reaction mixture was left overnight at room temperature. The solid that was obtained was collected by filtration, washed with water, dried and crystallized from ethanol to give compound **8** as pale yellow crystals.

9-Allyl-4-methoxy-5-oxo-5*H*-furo[3,2-*g*]chromene-6-carbonitrile (9). A solution of compound **8** (1.50 g, 5 mmol) in acetic anhydride (10 mL) was heated at 100°C for 2 hrs. The precipitate that formed after cooling, was collected by filtration, washed with water, dried and crystallized from ethanol to give compound **9** as yellowish brown crystals.

5-(7-Allyl-6-hydroxy-4-methoxybenzofuran-5-carbonyl)-2-aminonicotinonitrile (10a) and 5-(7-allyl-6-hydroxy-4-methoxybenzofuran-5-carbonyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (10b). A mixture of compound **3** (2.84 g, 10 mmol), malononitrile or ethyl cyanoacetate (10 mmol) and ammonium acetate (4 g) was refluxed in glacial acetic acid (25 mL) for 4 hrs. After cooling, the reaction mixture was poured on crushed ice and the solid that separated was collected by filtration, dried and crystallized from ethanol to give **10a** as brown crystals or **10b** as lustrous yellow solid.

Synthesis of imidazolyl furochromen-5-one derivatives 11a-c and 12. General procedure. A mixture of compound **3** (1.42 g, 5 mmol), ammonium acetate (2 g) and 1,2-phenylenediamine or 4-chloro-1,2-phenylenediamine or 4-nitro-1,2-phenylenediamine or benzil (5 mmol) as appropriate was refluxed in glacial acetic acid (15 mL) for 3 hrs, the reaction mixture was poured on crushed ice, the precipitate that was formed was collected by filtration, washed with water, dried and crystallized from ethanol to give the corresponding imidazolyl furochromen-5-one (Tables 1 and 2).

Condensation of 3 with aromatic amines; synthesis of Schiff bases 13a-d, 16a-e and 17a-e. General procedure. Equimolar amounts of the aldehyde **3** (1.42 g, 5 mmol), and the appropriated amine (5 mmol) in absolute ethanol (20 mL) were refluxed for 2-5 hrs (TLC control). The precipitated solid was collected by filtration, washed with hot ethanol, dried and crystallized from ethanol to give the corresponding anils **13a-d** and **16a-e.** Further reflux of the compounds **16a-e** under the same conditions afforded the corresponding azepines **17a-e.**

Reaction of 13b with ethyl thioglycolate; synthesis of the compound (15). A mixture of **13b** (2 g, 5 mmol) and ethyl thioglycolate (1.2 g, 10 mmol) in dry toluene was refluxed for 20 hrs the reaction mixture was left overnight at room temperature. The precipitate that was formed was collected by filtration, dried well and crystallized from ethanol to give the compound **15.**

Condensation of 18 with aryl and heteroaryl acetonitriles; synthesis of the compounds 19a-d and 21. General procedure. Equimolar amounts of the aldehyde **18** [42] (1.17 g, 5 mmol), the appropriated acetonitriles (5 mmol) and few drops of piperidine in absolute ethanol (20 mL) were refluxed for 5 hrs. The solid that separated during refluxing was collected by filtration, dissolved with hot ethanol, dried and crystallized from ethanol to give the corresponding 7-aryl (and heteroaryl)-8-imino pyrano[3,2-*g*]chromen-4(8*H*)-one derivatives **19a-d** and **21**. The products **19a-d** and **21** are sufficiently pure for using in the following step.

Synthesis of pyrano[3,2-*g*]chromen-4,8-dione derivatives 20a-d and 22. General procedure. The appropriate pyrano[3,2-*g*]chromen-2-imine-6-one **19a-d** or **21** (1 g) in glacial acetic acid (20 mL) was boiled for 1 h. After allowing it to cool to room temperature, fine crystals were formed that were collected by filtration, washed with hot ethanol, dried and then crystallized from acetone to give the corresponding pyrano[3,2-*g*]chromen-4,8-diones **20a-d** and **22** (Tables 1 and 2).

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