Indian Journal of Chemistry
Vol. 37B, January 1998, pp. 68 - 72

Synthesis and biological activities of 5*H*-furo [3,2-*g*] [1] benzopyran-5-one derivatives

Jehan A A Miky & Hammouda H Sharaf*
Chemistry Department, Faculty of Science (Girls)
*Pharmacology Department, Faculty of Medicine, Al-Azhar University, Nasr City, Cairo, Egypt

Received 30 September 1996; accepted (revised) 31 May 1997

The acetylation of 4-methoxy and 4,9-dimethoxy-7-methyl-5*H*-furo-[3,2-*g*] [1] benzopyran-5-one (visnagin and khellin) **1 a-b** with acetic anhydride gives 3-acetyl-visnagin and khellin **2a-b** which on reaction with cyanoacetamide, α-cyanothioacetamide, malononitriles or ethyl cyanoacetate yield furobenzopyranyl pyridone derivatives **3 a-h** or the possible isomer **4 a-h**. When 3-acetyl-visnagin or khellin is treated with bromine 6-(ω-bromoacetyl) visnagin or khellin **5 a-b** is obtained. The latter compound on treatment with thiourea and amines forms the 2-substituted-4-(3-furobenzopyranyl) thiazole **6 a-b** and 6-(ω-aminoacetyl) furochromone derivatives **8 a-g** respectively. The 2-amino-4-(3-furobenzopyranyl) thiazole on condensation with aldehyde yields the iminosubstituted thiazole derivatives **7 a-e**. Results of the biological effect of compounds **1a, 6b, 3a, 8a** and **3d** on blood pressure in experimental animals have been reported.

Benzopyran derivatives are known to have wide variety of pharmacological activities[1-5]. This prompted us to modify this ring and to explore new activities associated with this nucleus. Herein we report the synthesis and biological activity of hitherto unknown derivatives of 3-acetyl-visnagin and khellin.

When 4-methoxy-7-methyl-5*H*-furo[3,2-*g*][1] benzopyran-5-one **1a** (visnagin) or 4,9-dimethoxy-7-methyl-5*H*-furo[3,2-*g*][1] benzopyran-5-one **1b** (khellin) was refluxed with acetic anhydride, 6-acetyl-visnagin **2a** and khellin **2b** respectively were obtained (cf. Table I). Compounds **2a-b** separately on reaction with cyanoacetamide, α-cyanothioacetamide, malononitrile and ethyl cyanoacetate in the presence of ammonium acetate yielded furochromones **3a-h** or the possible isomers **4a-h** respectively (cf. Table I). Bromination of 6-acetyl-visnagin **2a** and 6-acetyl-khellin **2b** with bromine in chloroform yielded 6-(ω-bromoacetyl)visnagin and khellin **5a-b**[6] respectively (Scheme 1, cf. Table I). Further, **5a-b** on treatment with thiourea and amines (i.e. benzylamine, *p*-aminobenzoic acid, *p*-toluidine or morpholine) in ethanol yielded the compounds **6a-b** and **8a-g** respectively (cf. Table I). When **6a-b** were condensed with the appropriate aldehyde (i.e. benzaldehyde, 4-chlorobenzaldehyde or *p-N,N*-dimethylaminobenzaldehyde) iminosubstituted thiazole derivatives **7a-e** were obtained (cf. Table I). Analytical and spectroscopic results for all the compounds were in conformity with the assigned structures.

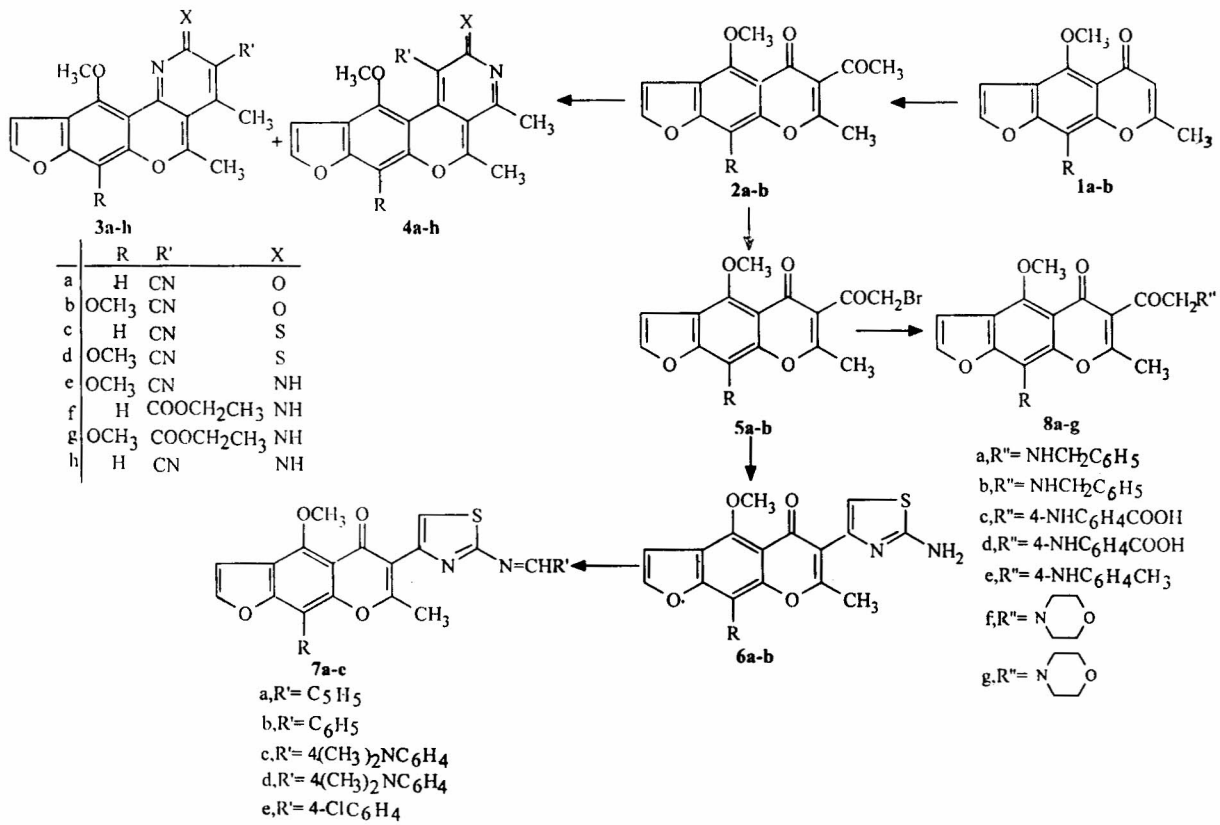
Biological activity

Blood pressure recording procedure. Under general anaesthesia induced by pentobarbitone (40 mg/kg i.p.) blood pressure in rats was recorded through canula inserted in the carotid artery. After freshly prepared drugs in gradually increasing doses were injected into jugular vein through a polyethylene canula. Compounds **1a, 6b, 3a, 8a** and **3d** were screened for their effects on blood pressure.

Results and conclusions

Compounds **1a, 6b** and **8a** produced dose dependent drop in blood pressure. The lowering effect on blood pressure of the three compounds was of short duration.

As regards compound **3a**, in a dose of 1 mg, it produced a drop of blood pressure and in a dose of



	R	R'	X
a	H	CN	O
b	OCH_3	CN	O
c	H	CN	S
d	OCH_3	CN	S
e	OCH_3	CN	NH
f	H	$COOCH_2CH_3$	NH
g	OCH_3	$COOCH_2CH_3$	NH
h	H	CN	NH

Scheme I

2mg it produced a biphasic response, at first drop and then rise in blood pressure followed by return to the basal value, while in a dose of 4mg/kg it produced a triphasic response at first drop then rise and lastly a gradual and persistent decrease in blood pressure till it ended with shock and death of animal. Compound **3d** produced prolonged drop in blood pressure, an effect which was lethal after injecting 4mg/kg. From these results, it can be concluded that compound **1a** has a potent depressing but reversible effect on blood pressure. Compounds **3a** and **3d** have both potent and lethal depressing effect on blood pressure and this may be attributed to the presence of cyano group in **3a** and thione group in **3d**. This observation might throw light on the harmful effect of cyano and thione groups on blood pressure. On the other hand the moderate hypotensive effect of compounds **6b** and **8a** may be due to the presence of amino group. Although it is early to say much, these results are encouraging to investigate the effect of these compounds on other organs and systems.

Experimental Section

All melting points are uncorrected. The IR spectra were run in KBr on a Pye-Unicam sp11000 spectrophotometer, ^{1}H NMR spectra in $CDCl_3$ or DMSO-d_6 on a Varian 1M-3901 spectrometer at 90, 200 or 270 MHz using TMS as internal standard (chemical shifts in δ, ppm) and mass spectra on a Varian Mat CH-4B spectrometer.

3-Acetyl-visnagin or khellin 2 a-b. A mixture of **1 a-b** (0.03 mole) was refluxed in acetic anhydride (10mL) and zinc dust (0.2g) for 10 hr. The reaction mixture was left to cool and then treated with cold water while stirring. The solid so obtained was filtered and crystallized from the suitable solvent to yield compounds **2a-b** (cf. Table I). Compounds **2a** and **2b** did not give colour reaction with aq. ferric chloride solution.

2a: IR (KBr) : 1657(C=O of γ-pyrone), 1621(C=O).

2b: IR (KBr) : 1659(C=O of γ-pyrone), 1632(C=O); PMR ($CDCl_3$):2.35 (s, 3H, CH_3), 3.39 (s, 3H, $COCH_3$), 3.91 (S, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 7.15 (d, J=2.5 Hz, 1H, H-3 of furan) and 8.07 (d, J = 2.5Hz, 1H, H-2 of furan).

Preparation of derivatives of 11-methoxy-4,5-dimethyl-2*H*-oxo-furo [3,2-*g*] [1] benzopyran

Table I—Analytical and physical data of compounds

Compd.	m.p. (°C)	Yield (%)	Mol. formula (Mol.wt.)	Found(Calcd) % C	H	N	S	X
2a	120-21	65[n]	$C_{15}H_{12}O_5$	66.2	4.1	—	—	—
			(272.25)	(66.17	4.40	—	—	—)
2b	159-60	80[t]	$C_{16}H_{14}O_6$	63.7	4.6	—	—	—
			(302.21)	(63.58	4.63	—	—)	—
3a	180-81	50[m]	$C_{18}H_{12}O_4N_2$	67.6	4.0	8.8	—	—
			(320.21)	(67.52	3.75	8.75	—	—)
3b	209-210	70[t]	$C_{191}H_{14}O_5N_2$	65.0	4.0	8.1	—	—
			(412.27)	(65.16	3.99	7.99	—	—)
3c	190-91	60[m]	$C_{18}H_{12}O_3N_2S$	64.3	3.7	8.4	9.0	—
			(336.27)	(64.29	3.75	8.33	9.53	—)
3d	220-21	65[t]	$C_{19}H_{14}O_2N_2S$	62.0	4.0	7.7	9.0	—
			(366.28)	(62.30	3.82	7.65	8.75	—)
3e	120-21	60[u]	$C_{19}H_{15}O_4N_3$	65.2	4.3	12.0	—	—
			(349.23)	(65.35	4.29	12.03	—	—)
3f	138-39	70[n]	$C_{20}H_{18}O_5N_2$	65.7	5.0	7.5	—	—
			(366.23)	(65.59	4.91	7.65	—	—)
3g	205-206	75[t]	$C_{21}H_{20}O_5N_2$	63.7	5.1	6.9	—	—
			(396.24)	(63.66	5.05	7.07	—	—)
3h	135-36	55[p]	$C_{18}H_{13}O_3N_3$	67.9	4.0	13.0	-	—
			(319.22)	(67.73	4.07	13.16	—	—)
5a	150-51	65[t]	$C_{15}H_{11}O_5Br$	51.0	3.0	—	—	22.8
			(351.06)	(51.32	3.13	—	—	22.76)
5b	177-78	70[n]	$C_{16}H_{13}O_6Br$	50.5	3.5	—	—	21.0
			(381.07)	(50.43	3.41	—	—	22.76)
6a	180-81	75[m]	$C_{16}H_{12}O_4N_2S$	58.8	3.8	8.7	10.0	—
			(328.25)	(58.55	3.66	8.53	9.77	—)
6b	140-41	60[p]	$C_{17}H_{14}O_5NS$	57.0	4.0	8.0	9.1	—
			(358.26)	(56.99	3.91	7.82	8.95	—)
7a	220	50[t]	$C_{23}H_{16}O_4N_2S$	66.6	4.0	6.9	8.0	—
			(416.32)	(66.36	3.84	6.73	7.70	—)
7b	190-91	65[t]	$C_{24}H_{18}O_5N_2S$	64.8	4.2	6.0	7.0	—
			(446.33)	(64.59	4.03	6.28	7.18	—)
7c	220	50[t]	$C_{25}H_{21}O_4N_3S$	65.5	4.8	9.0	7.0	—
			(459.35)	(65.37	4.57	9.15	6.98	—)
7d	200-201	50[m]	$C_{26}H_{23}O_5N_3S$	64.0	4.8	8.7	6.8	—
			(489.36)	(63.82	4.70	8.59	6.55	—)
7e	130-31	75[n]	$C_{24}H_{17}O_5N_2SCl$	60.0	3.7	6.0	6.5	7.0
			(480.79)	(59.96	3.53	5.83	6.67	7.37)
8a	179-80	75[m]	$C_{22}H_{17}O_5N$	70.2	4.3	3.6	—	—
			(375.25)	(70.42	4.53	3.73	—	—)
8b	220-21	50[t]	$C_{23}H_{19}O_6N$	68.0	4.8	3.6	—	—
			(405.26)	68.17	4.69	3.46	—	—)
8c	110-11	60[u]	$C_{22}H_{17}O_7N$	65.05	4.0	3.6	—	—
			(440.24)	(64.89	4.17	3.44	—	—)
8d	139-40	55[t]	$C_{23}H_{19}O_8N$	63.0	4.5	3.4	—	—
			(437.25)	(63.18)	4.35	3.20	—	—)
8e	199-200	70[m]	$C_{23}H_{21}O_6N$	68.0	5.2	3.5	—	—
			(407.25)	(67.83	5.16	3.52	—	—)
8f	110-11	50[u]	$C_{19}H_{19}O_6N$	63.8	5.0	4.0	—	—
			(357.21)	(63.89	5.32	3.92	—	—)
8g	145-46	40[n]	$C_{20}H_{21}O_7N$	62.0	5.6	3.4	—	—
			(387.22)	(62.04	5.42	3.62	—	—)

Solvent: m = methanol, t = ethanol; n = *n*-hexane
p = pet. ether (80-110°C); u = pet. ether (40-60°C)

[3,4-c] pyridine-1-carbonitrile 3a: Compounds 3a-h and 4a-h. To a solution of **2a-b** (0.03 mole) in ethanol 30mL was added cyanoacetamide (0.03 mole), α-cyanothioacetamide, malononitrile or ethyl cyanoacetate (0.03 mole) in the presence of ammonium acetate (0.01 mole). The reaction mixture was refluxed for 8 hr and the hot solution was filtered. The solvents were removed under reduced pressure, and the residue was crystallized from appropriate solvent (cf. Table I).

All compounds did not give colour reaction with aq. ferric chloride solution.

3b: IR(KBr):2223(C≡N), 1700(C=O of pyridone), 1602 (C=N); MS: m/z 350 (M^+, 31%). The IR spectra of **3c-f** showed absorption bands at 3329-3399 and 2206-2220 cm^{-1} for NH and C≡N respectively.

PMR ($CDCl_3$) of **3f**: 2.96(s, 6H, 2×CH_3), 3.8(s, 6H, 2×OCH_3), 7.25(d., *J*=2.2 Hz, 1H, H-3 of furan), MS: m/z 349 (M^+, 19%).

3h:IR(KBr), 3313 (NH), 1777 (C=O of ester), 1614 (C=N); PMR (DMSO-d_6): 1.32(t,*J*=7.1 Hz, 3H, CH_3 of $COOCH_2CH_3$), 2.39 (s, 3H, OCH_3), 3.45 (s, 3H, CH_3), 4.05 (s, 3H, OCH_3), 4.15 (s, 3H, OCH_3), 4.37 (q, *J*=7.1 Hz, 2H, CH_2 of $COOCH_2CH_3$), 5.02 (broad s, 1H, NH, exchangeable with D_2O), 7.01 (d, *J*=2.5 Hz, 1H, H-3 of furan) and 7.62 (d, *J*=2.5H, 1H, H-2 of furan).

6-ω-bromoacetyl-4-methoxy- and 4,9-dimethoxy-7-methyl-5*H*-furo[3,2-γ] [1] benzopyran-5-one 5a-b.To a solution of **2a-b** (0.008 mole) was added chloroform (10mL) while shaking for half an hour. The solid so obtained was filtered and crystallized from a suitable solvent to give **5a-b** which gave no colour reaction with aq. ferric chloride solution (cf. Table I).

The IR spectra of **5a** and **5b** showed absorption bands at 1694 and 1688 cm^{-1} (C=O of $COCH_2Br$), 1657 and 1659 for (C=O of γ-pyrone) and 798 and 797 (C-Br).

PMR of **5a** (DMSO-d_6): 2.01 (s, 3H, CH_3), 4.16 (s, 3H, OCH_3), 5.4 (s, 2H, $COCH_2Br$), 7.02 (d, *J*=2.2 Hz, 1H, H-3 of furan), 7.4 (s, 1H, benzofuran) and 7.59 (d, *J*=2.2 Hz, 1H, H-2 of furan).

2-amino-4-(4-methoxy-7-methyl-5*H*-furo [3,2-*g*] [1] benzopyranyl) thiazoles 6 a-b. When a suspension of **5a-b** (0.008 mole) in hot ethanol (15mL) was treated with thiourea (0.02 mole), a smooth exothermic reaction took place giving a clear solution that soon deposited crystals. The crystals were filtered, washed with ethanol and then boiled with water containing sodium acetate. The bright yellow crystals were crystallized from a suitable solvent to yield **6a-b** (cf. Table I).

6a: IR (KBr) : 3256 and 3202 cm^{-1} (NH_2), 1656 (C=O of γ-pyrone) and 1603 cm^{-1} (C=N); MS (m/z) : 328 (M^+, 48%), 329 (M^+ + 1, 27%), 313(M^+–NH_2), 213 (M^+ - C_3HNS, 51%).

2-imino-4-(4-methoxy-7-methyl-5*H*-furo[3,2-*g*] [1] benzopyranyl) thiazoles 7a-d. To a solution of **6a-b** (0.03 mole) in ethanol (30mL) was added aldehyde (0.03 mole) (i.e. benzaldehyde, 4-chlorobenzaldehyde or *p-N,N*-dimethylamino-benzaldehyde) in the presence of ammonium acetate (0.01 mole). The reaction mixture was refluxed for 8hr, filtered and crystallized from the appropriate solvent to give **7a-d** (cf. Table I).

7c: PMR ($CDCl_3$/TMS): 2.3 (s, 3H, CH_3), 4.05 (s, 3H, OCH_3), 4.35 (s, 3H, OCH_3), 6.5 (d, *J*=2.5 Hz, 1H, H-3 of furan), 6.9 (s, 1H, = CH of thiole), 7.2 (d, *J* = 8.5 Hz, 2H, phenyl), 7.7-7.9 (m, 3H, 2H of phenyl and 1H of H-2 of furan), and 8.5 (s, 1H, N=CH); MS: m/z 481 (M^+, 39%).

6-ω-aminoacetyl-4-methoxy-7-methyl-5*H*-furo-3,2-*g*] [1]benzopyrany-5-one 8 a-g. A solution of **5a-b** (0.03 mole) and the appropriate amine (0.05 mole) (i.e. benzylamine, 4-aminobenzoic acid, 4-toluidine or morpholine) in ethanol (30 mL) was refluxed for 2hr, cooled and the solid separated was crystallized from the suitable solvent to furnish **8a-g** (cf. Table I). All compounds gave no colour reaction with aq. ferric chloride solution.

8c: IR (KBr): 3214 (NH), 1663 (C=O of γ-pyrone), 1644 (C=O), 2750-3250 cm^{-1} (br, OH of COOH).

PMR ($CDCl_3$) : 217 (s, 3H, CH_3), 4.22 (s, 3H, OCH_3), 4.72 (s, 2H, $COCH_2$), 6.9 (d, *J*=2.4 Hz, 1H, H-3 of furan), 7.4 (d, *J*=8.7 Hz, 2H, aromatic), 7.5 (s, 1H, benzofuran), 7.7 (d, *J*=2.4 Hz, 1H, H-2 of furan), 8.45 (d, *J*=8.7 Hz, 2H, aromatic) and 13.18 (br, 1H, OH, exchangeable with D_2O); MS: m/z of **8d** at 437 (M^+, 55%).

References

1 Ellis G P, Becket G I P, Shaw & H K, *J Med Chem*, 21, **1978**, 1120.

2 Hudson J B, Gaham E A, Hudon L L & Towers H N,

Planta Med, 54, **1988**, 131.
3 Ybeda A & Villan A, *J pharm Pharmacol*, 41, **1989**, 236.
4 Jordan R & Allen L, PCT Int Appl W003, 800, **1988**, *Chem Abstr*, 110, **1989**, 147, 880k.
5 Abdel-Hafez O M & El-Bazza, *Bull NRC Egypt*, 18, **1993**, 71.
6 Hishmat O H, Miky J A A, Farrag A A & Fadl-Allah E M, *Arch Pharm Res*, 12, **1989**, 181