Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ankara University, Tandoğan, Ankara, Turkey

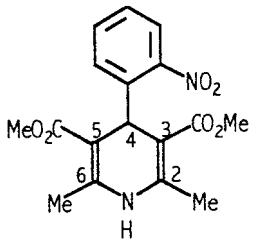
Synthesis of some 4-[3′ or 4′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]-1,4-dihydropyridine derivatives as potential calcium channel antagonists

M. TUNÇBİLEK and R. ERTAN

In this study, the synthesis of new flavonoid derivatives, which possess a 1,4-dihydropyridine (1,4-DHP) moiety on the phenyl ring of flavone were realized. 3′ or 4′-Formyl-flavones were synthesized, then the aldehyde groups of these compounds were converted to the 1,4-DHP moiety by the Hantzsch method. A series of 23 new derivatives having different substituents at C-3 and C-5 of the 1,4-DHP ring were prepared. Two compounds (**8a**, **8b**) were tested for their calcium channel blocker activity and **8b** exhibited the best result.

1. Introduction

One of the most important classes of cardiovascular drugs is represented by the calcium channel antagonistic 4-aryl-1,4-dihydropyridine (DHP) derivatives [1]. Nifedipine (4-(2′-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-DHP) (**1**) is the prototype of this class and in order to develop more selective and long acting analogues several molecular modifications have been realized on this molecule [2–9]. It was reported that, rather high calcium antagonistic activity was obtained by replacing the o-nitrophenyl residue of nifedipine with a heterobicyclic system [10–14] and the replacement of the same group with a heterotricyclic group exhibited potent selective bradycardic effects [15, 16] and cardiodepressant activities [17, 18].
Flavonoids have been shown to have a wide range of effects on biological systems [19]. In particular, flavonoids possess spasmolytic [20] and coronary dilating effects [21, 22]. In addition, their inhibitor activity of platelet aggregation [23] have received considerable attention.
These findings encouraged us to synthesize a new series of 1,4-DHP derivatives having the 2-phenyl-4H-1-benzopyran-4-one (= flavone) moiety at C-4 in stead of the nitrophenyl ring of nifedipine. The targeted compounds are represented by the general formula in Table 1.

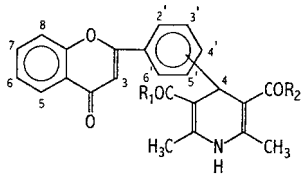


(1)

2. Investigations, results and discussion

3′- or 4′-Methylflavone (**I**, **II**) was prepared by the Baker-Venkataraman method. The methyl group of the flavones was converted to bromomethyl (**1a**, **1b**) with *N*-bromosuccinimide and benzoyl peroxide. Then these groups were oxidized to the carboxaldehydes **2a**, **2b** using hexamethylentetramine (HMTA). The carboxaldehyde groups were cyclized to the 1,4-DHP moities by the classical Hantzsch reaction [25]. The symmetric (**3a**, **8a–b**, **12a–b**, **13a–b**) and asymmetric (**4a–b**, **5a–b**, **6a–b**, **9a–b**, **10a–b**) ester compounds were synthesized by substituted acetoacetate and ammonium hydroxide (Method A) or acetoacetates and substituted aminocrotonate (Method B), respectively.
In a similar manner, acetoacetanilide was used instead of acetoacetates in method C (**14a–b**) and method D (**7a–b**, **11a–b**) (Scheme).
All the synthesized compounds were fully characterized analytically (Table 2). Calcium channel antagonist activity of the isomers **8a** and **8b** were investigated using nifedi-

Table 1: 4-[3′ or 4′-(4 H-4-Oxo-1-benzopyran-2-yl)phenyl]-1,4-dihydropyridine derivatives



m-Substituted Compd.	R_1	R_2	p-Substituted Compd.	R_1	R_2
3a	OCH_3	OCH_3	**4b**	OCH_3	OCH_2CH_3
4a	OCH_3	OCH_2CH_3	**5b**	OCH_3	$OCH_2CH{=}CH_2$
5a	OCH_3	$OCH_2CH{=}CH_2$	**6b**	OCH_3	$OC(CH_3)_3$
6a	OCH_3	$OC(CH_3)_3$	**7b**	OCH_3	NHC_6H_5
7a	OCH_3	NHC_6H_5	**8b**	OCH_2CH_3	OCH_2CH_3
8a	OCH_2CH_3	OCH_2CH_3	**9b**	OCH_2CH_3	$OCH_2CH{=}CH_2$ [24]
9a	OCH_2CH_3	$OCH_2CH{=}CH_2$	**10b**	OCH_2CH_3	$OC(CH_3)_3$
10a	OCH_2CH_3	$OC(CH_3)_3$	**11b**	OCH_2CH_3	NHC_6H_5
11a	OCH_2CH_3	NHC_6H_5	**12b**	$OCH_2CH{=}CH_2$	$OCH_3CH{=}CH_2$
12a	$OCH_2CH{=}CH_2$	$OCH_2CH{=}CH_2$	**13b**	$OC(CH_3)_3$	$OC(CH_3)_3$
13a	$OC(CH_3)_3$	$OC(CH_3)_3$	**14b**	NHC_6H_5	NHC_6H_5
14a	NHC_6H_5	NHC_6H_5			

Scheme

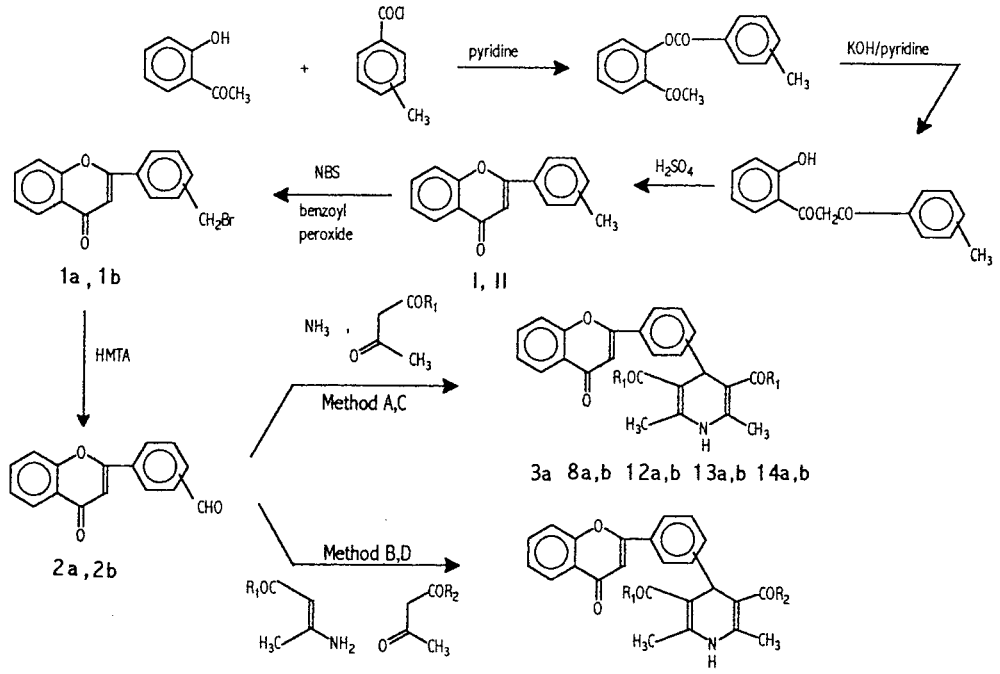


Table 2: Synthetic routes and physicochemical data of 4-[3′ or 4′-(4 H-4-oxo-1-benzopyran-2-yl)phenyl]-1,4-dihydropyridine derivatives

Compd.	Method	Starting material	Reaction time (h)	Yield (%)	Eluent*	M.p. (°C)	Recryst. solvent	Formula**
3a	A	**2a**	9	16.3	EtAc-Hx (1 : 1)	239	EtAc	$C_{26}H_{23}NO_6$
4a	B	**2a**	12	21.8	EtAc-Hx (0.5 : 1)	165	Toluene	$C_{27}H_{25}NO_6$
5a	B	**2a**	15	23.5	EtAc-Hx (1 : 1)	180	EtAc-Petrol	$C_{28}H_{25}NO_6$
6a	B	**2a**	22	16.2	EtAc-Hx (0.5 : 1)	147	–	$C_{29}H_{29}NO_6$
7a	D	**2a**	23	21.0	EtAc-Hx (0.5 : 1)	175	–	$C_{31}H_{26}N_2O_5$
8a	A	**2a**	12	63.4	–	185	Toluene	$C_{28}H_{27}NO_6$
9a	B	**2a**	20	35.6	EtAc-Hx (0.5 : 1)	182	EtAc-Hx	$C_{29}H_{27}NO_6$
10a	B	**2a**	20	31.2	EtAc-Hx (0.5 : 1)	136	–	$C_{30}H_{31}NO_6$
11a	D	**2a**	20	36.5	EtAc-Hx (0.5 : 1)	125	EtAc-Hx	$C_{32}H_{28}NO_6$
12a	A	**2a**	12	46.9	EtAc-Hx (1 : 1)	197	EtAc-Petrol	$C_{30}H_{27}NO_6$
13a	A	**2a**	23	38.0	EtAc-Hx (1 : 1)	203	EtAc-Petrol	$C_{32}H_{35}NO_6$
14a	C	**2a**	8	28.0	–	230	EtOH	$C_{36}H_{29}N_3O_4$
4b	B	**2b**	2	54.5	EtAc-Hx (1 : 1)	219	Toluene	$C_{27}H_{25}NO_6$
5b	B	**2b**	16	37.6	EtAc-Hx (0.5 : 1)	160	–	$C_{28}H_{25}NO_6$
6b	B	**2b**	28	41.1	EtAc-Hx (0.5 : 1)	230	–	$C_{29}H_{29}NO_6$
7b	D	**2b**	15	22.2	EtAc-Hx (0.5 : 1)	278	EtAc-Hx	$C_{31}H_{26}N_2O_5$
8b	A	**2b**	6	52.9	–	225	Toluene	$C_{28}H_{27}NO_6$
9b	Ref. [24]							
10b	B	**2b**	21	33.9	EtAc-Hx (0.5 : 1)	228	EtAc-Hx	$C_{30}H_{31}NO_6$
11b	D	**2b**	21	41.7	EtAc-Hx (1 : 0.5)	205	–	$C_{32}H_{28}NO_6$
12b	A	**2b**	13	52.3	EtAc-Hx (0.5 : 1)	198	EtAc-Hx	$C_{30}H_{27}NO_6$
13b	A	**2b**	23	32.0	EtAc-Hx (0.5 : 1)	269	EtAc-Hx	$C_{32}H_{35}NO_6$
14b	C	**2b**	14	53.4	–	273	EtOH	$C_{36}H_{29}N_3O_4$

* Hx: Hexane, EtAc: Ethyl acetate, Petrol: 40–60 °C Petroleum ether, EtOH: Ethanol.
** All the new compounds gave satisfactory C, H, N analyses

Table 3: Calcium channel blocker activity of nifedipine and compounds 8a, 8b

Receptor	Ligand	Nifedipine	8a	8b
Ca^{+2} Channel	[^{3}H] PN 200-110	$K_{0.5}$: 2.5×10^{-8}	7.9×10^{-7}	7.5×10^{-8}
		K_1: 1.5×10^{-8}	4.6×10^{-7}	8.7×10^{-8}

pine as the reference compound. Pre-experiment results show that these compounds have activity comparable with nifedipine. The results are presented in the Table 3.

3. Experimental

3.1. Apparatus

Melting points were determined with a Büchi SMP-20 apparatus and are uncorrected. IR Spectra were recorded on a Pye-Unicam SP-1025 Spectrophotometer as KBr pellets. The ^{1}H NMR spectra were determined with Bruker AC 80 (80.13 MHz), Bruker AC 200 (199.975 MHz) and Bruker AM 300 (300 MHz) spectrometer using $CDCl_3$, or DMSO-d_6 as solvents and TMS as an internal standard (chemical shifts in δ, ppm). MS were determined on a Jeol-JMS 01SG-2, VG Analytical 70-250S and KRATOS MS 890 Spectrometer by using Electron Ionisation (EI): Ionisation Energy 70 eV and Chemical Ionisation (CI): Reagent gase NH_3. Microanalyses were performed on a Perkin-Elmer 240 analyzer and satisfactory results ±0.4% of calculated values (C, H, N) were obtained for the new compounds. Chromatography was carried out using the flash method and Merck silica gel 60 (230–400 mesh ASTM).
3′-Methyl flavone and 4′-methyl flavone [26] were prepared in our laboratory.

3.2. Synthesis of flavone derivatives

3.2.1. 2-(3′-Bromomethyl-phenyl)-4 H-1-benzopyran-4-one (3′-bromomethyl flavone) **(1a)**

A mixture of 2-(3′-methyl-phenyl)-4 *H*-1-benzopyran-4-one 3.0 g (0.012 mol), *N*-bromosuccinimide 2.14 g (0.012 mol) and a catalytic amount of benzoyl peroxide in 150 ml of CCl_4, was refluxed for 7 h, concentrated to dryness and the residue on crystallizing from toluene gave 1.9 g (48.1%) dirty-white crystals; m.p. 137 °C. IR (KBr) cm^{-1}: 1655 (C=O, γ-pyrone). ^{1}H NMR ($CDCl_3$): δ = 4.7 (s, 2 H, bromomethyl CH_2), 6.9 (s, 1 H, 3-H), 7.5–8.0 (m, 7 H, 6,7,8,2′,4′,5′,6′-H), 8.3 (dd, $J_{5,6}$ = 8 Hz, $J_{5,7}$ = 2 Hz, 1 H, 5-H). MS (EI): m/z (%) = 314 (100) $[M]^{+\cdot}$, 316 (90.6) $[M+2)^{+\cdot}$, 235 (9.2), 221 (1.3), 120 (1.2), 92 (5.3).

3.2.2. 2-(4′-Bromomethyl-phenyl)-4 H-1-benzopyran-4-one (4′-bromomethyl flavone) **(1b)**

With the same procedure starting from 2-(4′-methyl-phenyl)-4 *H*-1-benzopyran-4-one, reaction time: 6 h, light cream crystals, yield: 2.6 g, 67.5%, m.p. 139 °C. IR (KBr) cm^{-1}: 1644 (C=O, γ-pyrone). ^{1}H NMR ($CDCl_3$): δ = 4.7 (s, 2 H, bromomethyl CH_2), 7.0 (s, 1 H, 3-H), 7.4–8.1 (m, 7 H, 6,7,8,2′,3′,5′,6′-H), 8.4 (dd, $J_{5,6}$ = 8 Hz, $J_{5,7}$ = 2 Hz, 1 H, 5-H). MS (CI) NH_3: m/z (%) = 315 ($(M+1)^+$, 44.3), 317 ($(M+1+2)^+$, 39.2), 235 (100), 236 (45.7), 221 (1.5), 120 (3.7), 121 (1.8), 92 (8.2).

3.2.3. 2-(3′-Formyl-phenyl)-4 H-1-benzopyran-4-one (3′-flavone carboxaldehyde) **(2a)**

A solution of 2.7 g (0.0086 mol) **1a** and 2.41 g (0.0172 mol) of hexamethylenetetramine in 35 ml of 50% CH_3COOH was refluxed for 5 h. Conc. HCl (15 ml) was added and the mixture was refluxed for 30 min. After cooling the mixture was extracted with $CHCl_3$. The organic layer was washed with H_2O, dried (Na_2SO_4) and then evaporated to dryness. The residue on crystallizing from toluene, gave 1.1 g (51.2%) white crystals. IR (KBr) cm^{-1}: 1715 (C=O, aldehyde carbonyl), 1665 (C=O, γ-pyrone). ^{1}H NMR ($CDCl_3$): δ = 7.1 (s, 1 H, 3-H), 7.5–8.2 (m, 7 H, 6,7,8,2′,4′,5′,6′-H), 8.4 (dd, $J_{5,6}$ = 8 Hz, $J_{5,7}$ = 2 Hz, 1 H, 5-H), 10.2 (s, 1 H, CHO). MS (EI): m/z (%) = 250 (100) $[M]^{+\cdot}$, 249 (11.4) $[M-1]^+$, 222 (39.5), 221 (11.9), 120 (11.3), 121 (1.2), 92 (53.4), 64 (16.2).

3.2.4. 2-(4′-Formyl-phenyl)-4 H-1-benzopyran-4-one (4′-flavone carboxaldehyde) **(2b)**

With the same procedure starting from **1b**, reaction time: 4 h, white crystals, yield: 1.14 g, 53.27%, m.p. 165 °C. IR (KBr) cm^{-1}: 1715 (C=O, aldehyde carbonyl), 1655 (C=O, γ-pyrone). ^{1}H NMR ($CDCl_3$): δ = 7.1 (s, 1 H, 3-H), 7.5–8.2 (m, 7 H, 6,7,8,2′,3′,5′,6′-H), 8.3 (dd, $J_{5,6}$ = 8 Hz, $J_{5,7}$ = 2 Hz, 1 H, 5-H), 10.15 (s, 1 H, CHO). MS (CI) NH_3: m/z (%) = 251 (100) $[M+1]^{+\cdot}$, 249 (9.2) $[M-1]^{+\cdot}$, 222 (13.8), 221 (8.3), 120 (14.0), 121 (1.7), 92 (13.0), 64 (1.1).

3.3. Synthesis of 1,4-DHP derivatives

3.3.1. Method A (general procedure)

3′- or 4′-Flavone carboxaldehyde (0.001 mol), alkylacetoacetate (0.002 mol) and 0.4 ml NH_3 (25% w/v) were refluxed in 4 ml isopropyl alcohol for 9–41 h. The solvent was removed and the residue was purified by CC. Reaction conditions are given in Table 2.

3.3.1.1. Dimethyl 1,4-dihydro-2,6-dimethyl-4-[3′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]-3,5-pyridine dicarboxylate (**3a**)

Light yellow crystals. IR (KBr) cm^{-1}: 3360 (NH), 1700 (C=O, ester), 1630 (C=O, γ-pyrone). ^{1}H NMR ($CDCl_3$): δ = 2.40 (s, 6 H, 2,6-CH_3), 3.65 (s, 6 H, $COOCH_3$), 5.10 (s, 1 H, DHP 4-H), 6.30 (s, 1 H, NH), 6.75 (s, 1 H, 3-H), 7.38–7.76 (m, 6 H, 6,7,8,4′,5′,6′-H), 7.79 (s, 1 H, 2′-H), 8.25 (dd, $J_{5,6}$ = 8 Hz, $J_{5,7}$ = 2 Hz, 1 H, 5-H). MS (EI): m/z (%) = 445 (6.2) $[M]^{+\cdot}$, 414 (3.4), 386 (4.6), 370 (1.3), 354 (1.2), 224 (100), 210 (4.0), 165 (3.4), 149 (1.4), 121 (4.9), 120 (9.8), 92 (32.6), 63 (3.8), 51 (3.0), 44 (8.5).

3.3.1.2. Diethyl 1,4-dihydro-2,6-dimethyl-4-[3′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]-3,5-pyridine dicarboxylate (**8a**)

White crystals. IR (KBr) cm^{-1}: 3340 (NH), 1695 (C=O, ester), 1640 (C=O, γ-pyrone). ^{1}H NMR ($CDCl_3$): δ = 1.22 (t, 6 H, $CH_2C\underline{H}_3$), 2.38 (s, 6 H, 2,6-CH_3), 4.10 (q, 4 H, $C\underline{H}_2CH_3$), 5.08 (s, 1 H, DHP 4-H), 6.28 (s, 1 H, NH), 6.78 (s, 1 H, 3-H), 7.26–7.76 (m, 6 H, 6,7,8,4′,5′,6′-H), 7.83 (s, 1 H, 2′-H), 8.24 (dd, $J_{5,6}$ = 8 Hz, $J_{5,7}$ = 2 Hz, 1 H, 5-H). MS (EI): m/z (%) = 473 (7.1) $[M]^{+\cdot}$, 444 (2.6), 428 (5.9), 400 (7.5), 370 (2.7), 356 (2.5), 354 (4.2), 328 (1.2), 252 (100), 224 (10.9), 196 (28.6), 178 (8.0), 165 (10.6), 150 (8.5), 134 (2.9), 121 (7.6), 120 (6.4), 92 (23.2), 65 (3.4).

3.3.1.3. Diethyl 1,4-dihydro-2,6-dimethyl-4-[4′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]-3,5-pyridine dicarboxylate (**8b**)

Light yellow crystals. IR (KBr) cm^{-1}: 3317 (NH), 1680 (C=O, ester), 1630 (C=O, γ-pyrone). ^{1}H NMR ($CDCl_3$): δ = 1.22 (t, 6 H, $CH_2C\underline{H}_3$), 2.38 (s, 6 H, 2,6-CH_3), 4.10 (q, 4 H, $C\underline{H}_2CH_3$), 5.06 (s, 1 H, DHP 4-H), 6.02 (s, 1 H, NH), 6.77 (s, 1 H, 3-H), 7.40 (ddd, 1 H, 6-H), 7.45 (d, $J_{2',3'} = J_{5',6'}$ = 9 Hz, 2 H, 3′,5′-H), 7.53 (dd, 1 H, 8-H), 7.70 (ddd, 1 H, 7-H), 7.80 (d, $J_{2',3'} = J_{5',6'}$ = 9 Hz, 2 H, 2′,6′-H), 8.20 (dd, $J_{5,6}$ = 8 Hz, $J_{5,7}$ = 2 Hz, 1 H, 5-H). MS (EI): m/z (%) = 473 (3.3) $[M]^{+\cdot}$, 445 (1.2), 444 (4.1), 428 (2.3), 400 (7.9), 398 (0.4), 372 (3.8), 356 (2.9), 354 (1.6), 328 (1.5), 252 (100), 224 (18.2), 196 (38.7), 178 (6.7), 150 (10,2), 134 (2.0), 121 (10.0), 120 (6.7), 92 (48.4), 65 (12.8).

3.3.1.4. Diallyl 1,4-dihydro-2,6-dimethyl-4-[3′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]-3,5-pyridine dicarboxylate (**12a**)

White crystals. IR (KBr) cm^{-1}: 3320 (NH), 1710 (C=O, ester), 1630 (C=O, γ-pyrone). ^{1}H NMR ($CDCl_3$): δ = 2.35 (s, 6 H, 2,6-CH_3), 4.45 (d, 4 H, $OC\underline{H}_2CH=CH_2$), 5.05 (d, 4 H, $OCH_2CH=C\underline{H}_2$), 5.15 (s, 1 H, DHP 4-H), 5.80 (m, 2 H, $OCH_2C\underline{H}=CH_2$), 6.30 (s, 1 H, NH), 6.70 (s, 1 H, 3-H), 7.30–7.70 (m, 6 H, 6,7,8,4′,5′,6′-H), 7.75 (s, 1 H, 2′-H), 8.15 (dd, $J_{5,6}$ = 8 Hz, $J_{5,7}$ = 2 Hz, 1 H, 5-H). MS (EI): m/z (%) = 497 (6.4) $[M]^{+\cdot}$, 456 (2.5), 440 (3.3), 412 (5.5), 370 (1.7), 354 (3.0), 327 (2.0), 277 (17.8), 276 (100.0), 236 (6.6), 222 (4.8), 191 (4.4), 165 (2.0), 150 (2.7), 121 (3.0), 120 (1.2), 92 (1.9), 44 (3.4), 41 (7.5).

3.3.1.5. Diallyl 1,4-dihydro-2,6-dimethyl-4-[4′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]-3,5-pyridine dicarboxylate (**12b**)

Light yellow crystals. IR (KBr) cm^{-1}: 3340 (NH), 1680 (C=O, ester), 1630 (C=O, γ-pyrone). ^{1}H NMR ($CDCl_3$): δ = 2.25 (s, 6 H, 2,6-CH_3), 4.50 (d, 4 H, $OC\underline{H}_2CH=CH_2$), 5.10 (d, 4 H, $OCH_2CH=C\underline{H}_2$), 5.15 (s, 1 H, DHP 4-H), 5.80 (m, 2 H, $OCH_2C\underline{H}=CH_2$), 5.90 (s, 1 H, NH), 6.70 (s, 1 H, 3-H), 7.35 (ddd, 1 H, 6-H), 7.45 (d, $J_{2',3'} = J_{5',6'}$ = 9 Hz, 2 H, 3′,5′-H), 7.55 (dd, 1 H, 8-H), 7.65 (ddd, 1 H, 7-H), 7.75 (d, $J_{2',3'} = J_{5',6'}$ = 9 Hz, 2 H, 2′,6′-H), 8.15 (dd, $J_{5,6}$ = 8 Hz, $J_{5,7}$ = 2 Hz, 1 H, 5-H). MS (EI): m/z (%) = 497 (8.0) $[M]^{+\cdot}$, 456 (6.6), 440 (3.8), 412 (8.2), 354 (2.1), 329 (3.3), 276 (100.0), 236 (5.7), 222 (3.9), 192 (3.4), 191 (2.9), 165 (1.7), 151 (1.6), 150 (2.3), 121 (4.8), 120 (2.2), 92 (2.4), 67 (1.6), 57 (5.6), 41 (10.8).

3.3.1.6. Di-*t*-butyl 1,4-dihydro-2,6-dimethyl-4-[3′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]-3,5-pyridine dicarboxylate (**13a**)

Light yellow crystals. IR (KBr) cm^{-1}: 3310 (NH), 1705 (C=O, ester), 1635 (C=O, γ-pyrone). ^{1}H NMR ($CDCl_3$): δ = 1.35 (s, 18 H, $OC(CH_3)_3$), 2.35 (s, 6 H, 2,6-CH_3), 5.05 (s, 1 H, DHP 4-H), 6.15 (s, 1 H, NH), 6.75 (s, 1 H, 3-H), 7.30–7.75 (m, 6 H, 6,7,8,4′,5′,6′-H), 7.85 (s, 1 H, 2′-H), 8.25 (dd, $J_{5,6}$ = 8 Hz, $J_{5,7}$ = 2 Hz, 1 H, 5-H). MS (EI): m/z (%) = 529 (6.1) $[M]^{+\cdot}$, 515 (4.8), 501 (1.0), 472 (2.8), 456 (4.0), 442 (2.1), 429 (1.5), 417 (1.6), 416 (4.9), 400 (3.4), 372 (26.9), 328 (11.5), 327 (9.0), 308 (23.2), 294 (21.4), 280 (10.0), 252 (13.2), 238 (33.5), 222 (8.2), 208 (6.5), 196

(100.0), 165 (4.3), 152 (26.7), 121 (6.4), 120 (3.5), 92 (4.4), 57 (14.8), 41 (28.4).

3.3.1.7. Di-*t*-butyl 1,4-dihydro-2,6-dimethyl-4-[4′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]-3,5-pyridine dicarboxylate (**13b**)

Light yellow crystals. IR (KBr) cm^{-1}: 3300 (NH), 1700 (C=O, ester), 1635 (C=O, γ-pyrone). ^1H NMR ($CDCl_3$): δ = 1.40 (s, 18 H, $OC(CH_3)_3$), 2.30 (s, 6 H, 2,6-CH_3), 5.05 (s, 1 H, DHP 4-H), 5.80 (s, 1 H, NH), 6.75 (s, 1 H, 3-H), 7.40 (ddd, 1 H, 6-H), 7.45 (d, $J_{2',3'} = J_{5',6'} = 9$ Hz, 2 H, 3′,5′-H), 7.55 (dd, 1 H, 8-H), 7.65 (ddd, 1 H, 7-H), 7.80 (d, $J_{2',3'} = J_{5',6'} = 9$ Hz, 2 H, 2′,6′-H), 8.25 (dd, $J_{5,6} = 8$ Hz, $J_{5,7} = 2$ Hz, 1 H, 5-H). MS (EI): m/z (%) = 529 (9.8) $[M]^{+\cdot}$, 515 (6.5), 458 (6.2), 416 (15.7), 372 (45.6), 328 (8.5), 308 (26.8), 294 (19.9), 252 (15.8), 238 (31.7), 222 (5.6), 208 (5.0), 196 (100.0), 194 (6.3), 165 (2.6), 152 (29.7), 121 (4.9), 120 (3.1), 56 (19.0), 41 (34.1).

3.3.2. Method B (general procedure)

3′- or 4′-Flavone carboxaldehyde (0.001 mol) and alkylacetoacetate (0.001 mol) were suspended in 5 ml of isopropyl alcohol and 0.001 mol methyl/ethylaminocrotonate were added. The mixture was refluxed for 3–28 h. After removal of the solvent, the residue was purified by CC. Reaction conditions are given in Table 2.

3.3.2.1. Ethyl methyl 1,4-dihydro-2,6-dimethyl-4-[3′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]-3,5-pyridine dicarboxylate (**4a**)

White crystals. IR (KBr) cm^{-1}: 3360 (NH), 1700 (C=O, ester), 1655 (C=O, γ-pyrone). ^1H NMR ($CDCl_3$): δ = 1.20 (t, 3 H, $OCH_2C\underline{H}_3$), 2.35 (s, 6 H, 2,6-CH_3), 3.65 (s, 3 H, $COOCH_3$), 4.05 (q, 2 H, $OC\underline{H}_2CH_3$), 5.10 (s, 1 H, DHP 4-H), 6.35 (s, 1 H, NH), 6.75 (s, 1 H, 3-H), 7.35–7.75 (m, 6 H, 6,7,8,4′,5′,6′-H), 7.80 (s, 1 H, 2′-H), 8.20 (dd, $J_{5,6} = 8$ Hz, $J_{5,7} = 2$ Hz, 1 H, 5-H). MS (EI): m/z (%) = 459 (8.0) $[M]^{+\cdot}$, 444 (4.0), 428 (4.9), 400 (6.1), 386 (2.6), 238 (100), 222 (9.5), 210 (6.3), 196 (9.5), 150 (2.2), 121 (8.2), 120 (14.7), 92 (9.1), 67 (1.5).

3.3.2.2. Ethyl methyl 1,4-dihydro-2,6-dimethyl-4-[4′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]-3,5-pyridine dicarboxylate (**4b**)

Light yellow crystals. IR (KBr) cm^{-1}: 3330 (NH), 1680 (C=O, ester), 1630 (C=O, γ-pyrone). ^1H NMR ($CDCl_3$): δ = 1.24 (t, 3 H, $OCH_2C\underline{H}_3$), 2.37 (s, 6 H, 2,6-CH_3), 3.66 (s, 3 H, $COOCH_3$), 4.12 (q, 2 H, $OC\underline{H}_2CH_3$), 5.07 (s, 1 H, DHP 4-H), 5.83 (widespread s, 1 H, NH), 6.79 (s, 1 H, 3-H), 7.42 (ddd, 1 H, 6-H), 7.47 (d, $J_{2',3'} = J_{5',6'} = 9$ Hz, 2 H, 3′,5′-H), 7.55 (dd, 1 H, 8-H), 7.70 (ddd, $J_{5,7} = 2$ Hz, 1 H, 7-H), 7.81 (d, $J_{2',3'} = J_{5',6'} = 9$ Hz, 2 H, 2′,6′-H), 8.23 (dd, $J_{5,6} = 8$ Hz, $J_{5,7} = 2$ Hz, 1 H, 5-H). MS (EI): m/z (%) = 459 (7.0) $[M]^{+\cdot}$, 444 (6.9), 428 (5.5), 400 (10.9), 386 (3.5), 238 (100.0), 222 (4.9), 210 (6.5), 196 (11.4), 150 (2.6), 121 (3.4), 120 (1.6), 92 (5.2), 67 (1.6).

3.3.2.3. Allyl methyl 1,4-dihydro-2,6-dimethyl-4-[3′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]-3,5-pyridine dicarboxylate (**5a**)

Light yellow crystals. IR (KBr) cm^{-1}: 3320 (NH), 1710 (C=O, ester), 1630 (C=O, γ-pyrone). ^1H NMR ($CDCl_3$): δ = 2.35 (s, 6 H, 2,6-CH_3), 3.65 (s, 3 H, $COOCH_3$), 4.55 (d, 2 H, $OC\underline{H}_2CH{=}CH_2$), 5.10 (d, 2 H, $OCH_2CH{=}C\underline{H}_2$), 5.15 (s, 1 H, DHP 4-H), 5.85 (m, 1 H, $OCH_2C\underline{H}{=}CH_2$), 6.35 (s, 1 H, NH), 6.75 (s, 1 H, 3-H), 7.38–7.75 (m, 6 H, 6,7,8,4′,5′,6′-H), 7.80 (s, 1 H, 2′-H), 8.20 (dd, $J_{5,6} = 8$ Hz, $J_{5,7} = 2$ Hz, 1 H, 5-H). MS (EI): m/z (%) = 471 (5.8) $[M]^{+\cdot}$, 456 (1.9), 443 (6.8), 440 (3.7), 414 (3.7), 412 (10.0), 386 (4.8), 354 (6.5), 250 (100), 210 (7.7), 191 (3.7), 150 (1.9), 121 (17.2), 120 (10.1), 92 (9.4).

3.3.2.4. Allyl methyl 1,4-dihydro-2,6-dimethyl-4-[4′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]-3,5-pyridine dicarboxylate (**5b**)

Light yellow crystals. IR (KBr) cm^{-1}: 3340 (NH), 1685 (C=O, ester), 1630 (C=O, γ-pyrone). ^1H NMR ($CDCl_3$): δ = 2.35 (s, 6 H, 2,6-CH_3), 3.65 (s, 3 H, $COOCH_3$), 4.55 (d, 2 H, $OC\underline{H}_2CH{=}CH_2$), 5.10 (s, 1 H, DHP 4-H), 5.20 (d, 2 H, $OCH_2CH{=}C\underline{H}_2$), 5.90 (m, 1 H, $OCH_2C\underline{H}{=}CH_2$), 6.15 (s, 1 H, NH), 6.75 (s, 1 H, 3-H), 7.43 (ddd, 1 H, 6-H), 7.48 (d, $J_{2',3'} = J_{5',6'} = 9$ Hz, 2 H, 3′,5′-H), 7.55 (dd, 1 H, 8-H), 7.70 (ddd, 1 H, 7-H), 7.80 (d, $J_{2',3'} = J_{5',6'} = 9$ Hz, 2 H, 2′,6′-H), 8.25 (dd, $J_{5,6} = 8$ Hz, $J_{5,7} = 2$ Hz, 1 H, 5-H). MS (EI): m/z (%) = 471 (9.3) $[M]^{+\cdot}$, 456 (2.5), 430 (4.7), 414 (4.1), 386 (8.8), 354 (3.2), 250 (100.0), 210 (6.7), 191 (2.1), 150 (2.4), 121 (6.9), 120 (4.7), 92 (7.1), 67 (1.7), 57 (2.9).

3.3.2.5. Methyl-*t*-butyl 1,4-dihydro-2,6-dimethyl-4-[3′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]-3,5-pyridine dicarboxylate (**6a**)

Light yellow crystals. IR (KBr) cm^{-1}: 3350 (NH), 1700 (C=O, ester), 1640 (C=O, γ-pyrone). ^1H NMR ($CDCl_3$): δ = 1.45 (s, 9 H, $C(CH_3)_3$), 2.37 (s, 6 H, 2,6-CH_3), 3.65 (s, 3 H, $COOCH_3$), 5.06 (s, 1 H, DHP 4-H), 5.87 (s, 1 H, NH), 6.78 (s, 1 H, 3-H), 7.37–7.76 (m, 6 H, 6,7,8,4′,5′,6′-H), 7.81 (s, 1 H, 2′-H), 8.25 (dd, $J_{5,6} = 8$ Hz, $J_{5,7} = 2$ Hz, 1 H, 5-H). MS (EI): m/z (%) = 487 (1.7) $[M]^{+\cdot}$, 473 (10.8), 430 (5.5), 414 (6.9), 386 (11.6), 372 (3.4), 266 (9.4), 252 (100.0), 224 (11.9), 222 (8.2), 210 (71.8), 193 (1.4), 178 (3.4), 165 (3.9), 150 (3.2), 121 (5.9), 120 (3.8), 92 (3.4), 67 (1.7), 57 (2.0).

3.3.2.6. Methyl-*t*-butyl 1,4-dihydro-2,6-dimethyl-4-[4′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]-3,5-pyridine dicarboxylate (**6b**)

Light yellow crystals. IR (KBr) cm^{-1}: 3350 (NH), 1690 (C=O, ester), 1640 (C=O, γ-pyrone). ^1H NMR ($CDCl_3$): δ = 1.40 (s, 9 H, $OC(CH_3)_3$), 2.35 (s, 6 H, 2,6-CH_3), 3.65 (s, 3 H, $COOCH_3$), 5.05 (s, 1 H, DHP 4-H), 6.10 (s, 1 H, NH), 6.80 (s, 1 H, 3-H), 7.40 (ddd, 1 H, 6-H), 7.45 (d, 2 H, $J_{2',3'} = J_{5',6'} = 9$ Hz, 3′,5′-H), 7.55 (dd, 1 H, 8-H), 7.70 (ddd, 1 H, 7-H), 7.80 (d, 2 H, $J_{2',3'} = J_{5',6'} = 9$ Hz, 2′,6′-H), 8.25 (dd, $J_{5,6} = 8$ Hz, $J_{5,7} = 2$ Hz, 1 H, 5-H). MS (EI): m/z (%) = 487 (1.9) $[M]^{+\cdot}$, 473 (14.4), 430 (13.8), 414 (9.5), 386 (20.5), 372 (9.9), 266 (7.1), 252 (100.0), 224 (41.6), 222 (8.2), 210 (66.1), 193 (3.3), 178 (3.2), 166 (10.8), 165 (4.7), 150 (4.1), 121 (5.3), 120 (3.7), 92 (3.5), 67 (2.4), 57 (2.1).

3.3.2.7. Allyl ethyl 1,4-dihydro-2,6-dimethyl-4-[3′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]-3,5-pyridine dicarboxylate (**9a**)

White crystals. IR (KBr) cm^{-1}: 3360 (NH), 1710 (C=O, ester), 1635 (C=O, γ-pyrone). ^1H NMR ($CDCl_3$): δ = 1.25 (t, 3 H, $CH_2C\underline{H}_3$), 2.40 (s, 6 H, 2,6-CH_3), 4.11 (q, 2 H, $C\underline{H}_2CH_3$), 4.55 (d, 2 H, $OC\underline{H}_2CH{=}CH_2$), 5.15 (d, 2 H, $OCH_2CH{=}C\underline{H}_2$), 5.25 (s, 1 H, DHP 4-H), 5.85 (m, 1 H, $OCH_2C\underline{H}{=}CH_2$), 6.20 (s, 1 H, NH), 6.80 (s, 1 H, 3-H), 7.34–7.77 (m, 6 H, 6,7,8,4′,5′,6′-H), 7.82 (s, 1 H, 2′-H), 8.25 (dd, $J_{5,6} = 8$ Hz, $J_{5,7} = 2$ Hz, 1 H, 5-H). MS (EI): m/z (%) = 485 (7.3) $[M]^{+\cdot}$, 456 (1.6), 440 (3.6), 428 (3.7), 412 (4.7), 400 (5.0), 372 (1.2), 370 (2.3), 354 (3.8), 326 (1.0), 264 (100), 236 (11.0), 222 (7.8), 206 (1.0), 191 (2.0), 178 (1.9), 150 (3.0), 121 (3.2), 120 (1.7), 92 (0.8), 67 (1.5).

3.3.2.8. Ethyl-*t*-butyl 1,4-dihydro-2,6-dimethyl-4-[3′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]-3,5-pyridine dicarboxylate (**10a**)

White crystals. IR (KBr) cm^{-1}: 3370 (NH), 1700 (C=O, ester), 1655 (C=O, γ-pyrone). ^1H NMR ($CDCl_3$): δ = 1.25–1.40 (m, 12 H, $OCH_2C\underline{H}_3$, $OC(CH_3)_3$), 2.40 (s, 6 H, 2,6-CH_3), 4.05 (q, 2 H, $OC\underline{H}_2CH_3$), 5.05 (s, 1 H, DHP 4-H), 6.15 (s, 1 H, NH), 6.75 (s, 1 H, 3-H), 7.30–7.75 (m, 6 H, 6,7,8,4′,5′,6′-H), 7.80 (s, 1 H, 2′-H), 8.25 (dd, $J_{5,6} = 8$ Hz, $J_{5,7} = 2$ Hz, 1 H, 5-H). MS (EI): m/z (%) = 501 (2.3) $[M]^{+\cdot}$, 487 (9.9), 473 (1.1), 444 (4.7), 428 (4.6), 400 (8.7), 372 (6.9), 354 (4.8), 280 (19.8), 266 (100.0), 252 (15.7), 224 (41.1), 222 (6.6), 196 (40.6), 165 (4.1), 150 (3.9), 121 (5.4), 120 (2.3), 92 (3.8), 67 (2.3).

3.3.2.9. Ethyl-*t*-butyl 1,4-dihydro-2,6-dimethyl-4-[4′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]-3,5-pyridine dicarboxylate (**10b**)

Light yellow crystals. IR (KBr) cm^{-1}: 3380 (NH), 1685 (C=O, ester), 1640 (C=O, γ-pyrone). ^1H NMR ($CDCl_3$): δ = 1.24 (t, 3 H, $OCH_2C\underline{H}_3$), 1.41 (s, 9 H, $OC(CH_3)_3$), 2.34 (s, 6 H, 2,6-CH_3), 4.11 (q, 2 H, $OC\underline{H}_2CH_3$), 5.03 (s, 1 H, DHP 4-H), 5.83 (s, 1 H, NH), 6.79 (s, 1 H, 3-H), 7.35 (ddd, 1 H, 6-H), 7.45 (d, $J_{2',3'} = J_{5',6'} = 9$ Hz, 2 H, 3′,5′-H), 7.55 (dd, 1 H, 8-H), 7.70 (ddd, 1 H, 7-H), 7.78 (d, 2 H, $J_{2',3'} = J_{5',6'} = 9$ Hz, 2′,6′-H), 8.20 (dd, $J_{5,6} = 8$ Hz, $J_{5,7} = 2$ Hz, 1 H, 5-H). MS (EI): m/z (%) = 501 (0.9) $[M]^{+\cdot}$, 444 (3.6), 428 (1.2), 400 (4.3), 372 (6.4), 355 (1.8), 280 (22.7), 252 (9.2), 224 (100.0), 222 (3.9), 196 (36.2), 165 (6.0), 150 (7.7), 121 (6.4), 120 (3.7), 92 (22.1), 67 (8.3).

3.3.3. Method C (general procedure)

3′- or 4′-Flavone carboxaldehyde (0.001 mol), acetoacetanilide (0.002 mol) and 0.4 ml NH_3 (25% w/v) were refluxed in 5 ml isopropyl alcohol for 8–14 h, cooled and then evaporated to dryness. The residue was crystallized from EtOH. Reaction conditions are given in Table 2.

3.3.3.1. 1,4-Dihydro-2,6-dimethyl-4-[3′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]pyridine-3,5-diphenyl carboxamide (**14a**)

Light cream crystals. IR (KBr) cm^{-1}: 3400–3310 (amid-NH, DHP-NH), 1690 (C=O, CONH), 1640 (C=O, γ-pyrone). ^1H NMR ([D_6]DMSO): δ = 2.15 (s, 6 H, 2,6-CH_3), 5.25 (s, 1 H, DHP 4-H), 6.90 (s, 1 H, 3-H), 7.00 (t, 2 H, c-H), 7.25–7.80 (m, 14 H, a,b,6,7,8,4′,5′,6′-H), 7.90 (s, 1 H, 2′-H), 8.05 (dd, 1 H, 5-H), 8.20 (s, 1 H, N–H), 9.45 (s, 2 H, CONH). MS (EI): m/z (%) = 565 (0.9) $[M\text{-}2]^{+\cdot}$, 473 (0.7), 354 (0.9), 221 (0.8), 207 (1.5), 191 (1.2), 165 (5.1), 138 (2.7), 121 (7.9), 120 (22.3), 108 (12.2), 93 (22.3), 92 (100), 77 (25.8), 66 (5.9), 65 (67.2).

3.3.3.2. 1,4-Dihydro-2,6-dimethyl-4-[4′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]pyridine-3,5-diphenylcarboxamide (**14b**)

Yellow crystals. IR (KBr) cm^{-1}: 3400–3300 (amid-NH, DHP-NH), 1690 (C=O, CONH), 1640 (C=O, γ-pyrone). ^1H NMR ($CDCl_3$): δ = 2.15 (s,

6 H, 2,6-CH_3), 5.25 (s, 1 H, DHP 4-H), 6.95 (s, 1 H, 3-H), 7.00 (t, 2 H, c-H), 7.25 (t, 4 H, b-H), 7.43 (ddd, 1 H, 6-H), 7.47 (d, 2 H, $J_{2',3'} = J_{5',6'} = 9$ Hz, 3′,5′-H), 7.60 (d, 4 H, a-H), 7.75 (dd, 1 H, 8-H), 7.80 (ddd, 1 H, 7-H), 8.00 (d, 2 H, $J_{2',3'} = J_{5',6'} = 9$ Hz, 2′,6′-H), 8.05 (dd, 1 H, 5-H), 8.15 (s, 1 H, N−H), 9.45 (s, 2 H, CONH). MS (EI): m/z (%) = 566 (0.01) $[M-1]^{+\cdot}$, 565 (0.02) $[M-2]^{+\cdot}$, 447 (4.0), 446 (10.0), 434 (3.4), 355 (8.9), 354 (33.9), 328 (44.4), 327 (80.9), 326 (8.8), 208 (6.8), 207 (22.2), 121 (22.4), 120 (22.4), 119 (100.0), 108 (66.2), 107 (8.6), 93 (30.8), 92 (20.1), 91 (42.6), 77 (8.6), 65 (11.9), 64 (28.3).

3.3.4. Method D (general procedure)

A solution of 3′- or 4′-Flavone carboxaldehyde (0.001 mol), methyl/ethyl-aminocrotonate (0.001 mol) and acetoacetanilid (0.001 mol) was heated under reflux in 5 ml isopropyl alcohol for 15–23 h. After removal of the solvent, the residue was purified by CC. Reaction conditions are given in Table 2.

3.3.4.1. Methyl 1,4-dihydro-2,6-dimethyl-3-phenyl carbamoyl-4-[3′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]-5-pyridine carboxylate (**7a**)

Light yellow crystals. IR (KBr) cm^{-1}: 3400–3310 (amid-NH, DHP-NH), 1705 (C=O, CONH), 1640 (C=O, γ-pyrone). ^1H NMR ($CDCl_3$): δ = 2.25 and 2.30 ppm (s, 6 H, 2,6-CH_3), 3.60 (s, 3 H, $COOCH_3$), 4.90 (s, 1 H, DHP 4-H), 6.45 (s, 1 H, NH), 6.70 (s, 1 H, 3-H), 6.95 (t, 1 H, c), 7.15–7.75 (m, 11 H, a,b,6,7,8,4′,5′,6′-H, CONH), 7.85 (s, 1 H, 2′-H), 8.15 (dd, $J_{5,6} = 8$ Hz, $J_{5,7} = 2$ Hz, 1 H, 5-H). MS (EI): m/z (%) = 506 (7.1) $[M]^{+\cdot}$, 504 (9.3) $[M-2]^{+\cdot}$, 413 (8.1), 412 (29.3), 387 (9.2), 386 (18.6), 385 (57.2), 370 (11.0), 368 (18.2), 354 (31.5), 328 (10.5), 327 (25.3), 292 (21.0), 285 (12.9), 250 (13.0), 249 (51.7), 222 (7.6), 177 (8.2), 166 (52.3), 165 (7.5), 121 (30.5), 120 (19.6), 119 (78.8), 93 (100), 92 (24.7), 77 (7.7), 66 (18.1), 65 (17.9), 64 (19.4), 43 (27.8).

3.3.4.2. Methyl 1,4-dihydro-2,6-dimethyl-3-phenyl carbamoyl-4-[4′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]-5-pyridine carboxylate (**7b**)

Light yellow crystals. IR (KBr) cm^{-1}: 3400–3320 (amid-NH, DHP-NH), 1705 (C=O, CONH), 1640 (C=O, γ-pyrone). ^1H NMR ([D_6]DMSO): δ = 2.05 and 2.35 (s, 6 H, 2,6-CH_3), 3.55 (s, 3 H, $COOCH_3$), 5.05 (s, 1 H, DHP 4-H), 6.95 (s, 1 H, 3-H), 7.05 (t, 1 H, c-H), 7.25 (t, 2 H, b-H), 7.35 (d, 2 H, $J_{2',3'} = J_{5',6'} = 9$ Hz, 3′,5′-H), 7.50 (ddd, 1 H, 6-H), 7.60 (d, 2 H, a-H), 7.75 (dd, 1 H, 8-H), 7.85 (ddd, 1 H, 7-H), 8.00 (d, 2 H, $J_{2',3'} = J_{5',6'} = 9$ Hz, 2′,6′-H), 8.05 (dd, 1 H, $J_{5,6} = 8$ Hz, $J_{5,7} = 2$ Hz, 5-H), 8.60 (s, 1 H, NH), 9.60 (s, 1 H, NHCO). MS (EI): m/z (%) = 506 (3.0) $[M]^{+\cdot}$, 504 (32.1) $[M-2]^{+\cdot}$, 413 (14.3), 412 (50.1), 386 (6.4), 385 (17.3), 354 (11.9), 292 (6.3), 252 (8.7), 166 (13.5), 121 (15.2), 120 (11.1), 119 (29.3), 93 (62.8), 92 (18.0), 77 (5.5), 66 (11.3), 43 (100.0).

3.3.4.3. Ethyl 1,4-dihydro-2,6-dimethyl-3-phenyl carbamoyl-4-[3′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]-5-pyridine carboxylate (**11a**)

Light yellow crystals. IR (KBr) cm^{-1}: 3390–3315 (amid-NH, DHP-NH), 1700 (C=O, CONH), 1635 (C=O, γ-pyrone). ^1H NMR ($CDCl_3$): δ = 1.25 (t, 3 H, $OCH_2C\underline{H}_3$), 2.35 (s, 6 H, 2,6-CH_3), 4.10 (q, 2 H, $OC\underline{H}_2CH_3$), 5.00 (s, 1 H, DHP 4-H), 6.35 (s, 1 H, NH), 6.75 (s, 1 H, 3-H), 7.00 (t, 1 H, c), 7.25–7.80 (m, 11 H, a,b,6,7,8,4′,5′,6′-H, NH), 7.95 (s, 1 H, 2′-H), 8.20 (dd, $J_{5,6} = 8$ Hz, $J_{5,7} = 2$ Hz, 1 H, 5-H). MS (EI): m/z (%) = 520 (6.6) $[M]^{+\cdot}$, 518 (6.6) $[M-2]^{+\cdot}$, 428 (3.9), 426 (15.4), 401 (14.8), 399 (6.2), 356 (4.8), 354 (9.1), 328 (18.8), 327 (12.3), 299 (10.3), 222 (3.9), 181 (11.4), 180 (100.0), 152 (29.7), 121 (12.7), 119 (12.1), 93 (26.0), 92 (11.6), 77 (3.8), 65 (7.3), 64 (5.6).

3.3.4.4. Ethyl 1,4-dihydro-2,6-dimethyl-3-phenyl carbamoyl-4-[4′-(4 *H*-4-oxo-1-benzopyran-2-yl)phenyl]-5-pyridine carboxylate (**11b**)

Light yellow crystals. IR (KBr) cm^{-1}: 3390–3320 (amid-NH, DHP-NH), 1700 (C=O, CONH), 1635 (C=O, γ-pyrone). ^1H NMR ($CDCl_3$): δ = 1.25 (t, 3 H, $OCH_2C\underline{H}_3$), 2.35 (s, 6 H, 2,6-CH_3), 4.15 (q, 2 H, $OC\underline{H}_2CH_3$), 5.00 (s, 1 H, DHP 4-H), 5.90 (s, 1 H, NH), 6.80 (s, 1 H, 3-H), 7.05 (t, 1 H, c-H), 7.25 (t, 2 H, b-H), 7.30 (d, 2 H, a-H), 7.35 (ddd, 1 H, 6-H), 7.45 (d, 2 H, $J_{2',3'} = J_{5',6'} = 9$ Hz, 3′,5′-H), 7.55 (dd, 1 H, 8-H), 7.70 (ddd, 1 H, 7-H), 7.90 (d, 2 H, $J_{2',3'} = J_{5',6'} = 9$ Hz, 2′,6′-H), 7.91 (s, 1 H, CONH), 8.20 (dd, 1 H, $J_{5,6} = 8$ Hz, $J_{5,7} = 2$ Hz, 5-H). MS (EI): m/z (%) = 520 (2.1) $[M]^{+\cdot}$, 518 (7.6) $[M-2]^{+\cdot}$, 444 (2.5), 426 (11.6), 401 (20.9), 399 (15.5), 372 (12.9), 356 (6.8), 354 (13.7), 328 (19.8), 327 (8.9), 299 (4.4), 253 (2.3), 222 (4.1), 181 (11.8), 180 (100.0), 152 (19.1), 121 (11.8), 119 (47.3), 93 (13.7), 91 (12.6), 65 (4.4), 64 (9.2).

3.4. Binding assay

The binding assay was performed at 20 °C on microsomal fractions by using [^3H] PN 200–110 as radioligand. Increasing concentrations of the compounds tested were added into the incubation medium containing [^3H] PN 200–110. Activities were determined by displacement of [^3H] PN 200–110 from its specific binding sites. K_i values given in the text represent the concentrations of the compounds required to cause 50% inhibition of [^3H] PN 200–110 binding. The incubations were performed in dublicate in at least two independent experiments. Nifedipine was used as the reference antagonist.

Acknowledgement: We would like to thank Prof. Dr. W. Wiegrebe from Regensburg University/Germany for the elemental analysis and Mass spectra, Dr. Y. Rolland from Servier Research Center/France for the preliminary biological activity and NMR spectra.

References

1 Nayler, W. G.: Calcium Antagonists, Academic Press, London 1988
2 Vater, W.; Kroneberg, G.; Hoffmeister, F.; Kaller, H.; Meng, K.; Oberdorf, A.; Puls, W.; Schlossmann, K.; Stoepel, K.: Arzneim.-Forsch./Drug Res **22**, 1 (1972)
3 Auterhoff, B. H.; Knabe, J.; Höltje, H. D.: Lehrbuch der Pharmazeutischen Chemie. 12. Aufl. Wissenschaftliche Verlagsges. Stuttgart 1991
4 Meguro, K.; Aizawa, M.; Sohda, T.; Kawamatsu, Y.; Nagaoka, A.: Chem. Pharm. Bull. **33**, 3787 (1985)
5 Arrowsmith, J. E.; Campbell, S. F.; Cross, P. E.; Stubba, J. K.; Burges, R. A.; Gardiner, D. G.; Blackburn, K. J.: J. Med. Chem. **29**, 1696 (1986)
6 Arrowsmith, J. E.; Campbell, S. F.; Cross, P. E.; Burges, R. A.; Gardiner, D. G.: J. Med. Chem. **32**, 562 (1989)
7 Alker, D.; Campbell, S. F.; Cross, P. E.; Burges, R. A.; Carter, A. J.; Gardiner, D. G.: J. Med. Chem. **32**, 2381 (1989)
8 Alker, D.; Campbell, S. F.; Cross, P. E.; Burges, R. A.; Carter, A. J.; Gardiner, D. G.: J. Med. Chem. **33**, 585 (1990)
9 Alker, D.; Campbell, S. F.; Cross, P. E.: J. Med. Chem. **34**, 19 (1991)
10 Hof, R. P.; Hof, A.; Neumann, P.: J. Cardiovasc. Pharmacol. **4**, 352 (1982)
11 Hof, R. P.; Scholtysik, G.; Loutzenhiser, R.; Vuorela, H. J.; Neumann, P.: J. Cardiovasc. Pharmacol. **6**, 399 (1984)
12 Hof, R. P.; Salzmann, R.; Siegl, H.: Am. J. Cardiol. **59**, 30B (1987)
13 Tamargo, J.; Lopez-Sendon, J.; Delpon, E.; Gonzalez-Morales, M.; Miguel, E.: Arzneim.-Forsch./Drug Res. **41**, 895 (1991)
14 Cozzi, P.; Carganico, G.; Fusar, D.; Grossoni, M.; Menichincheri, M.; Pinciroli, V.; Tonani, R.; Vaghi, F.; Salvati, P.: J. Med. Chem. **36**, 2964 (1993)
15 Valenti, P.; Chiarini, A.; Gasperi, F.; Budriesi, R.: Arzneim.-Forsch./Drug Res. **40**, 122 (1990)
16 Rampa, A.; Chiarini, A.; Bisi, A.; Budriesi, R.; Valenti, P.: Arzneim.-Forsch./Drug Res. **41**, 705 (1991)
17 Chiarini, A.; Rampa, A.; Bisi, A.; Budriesi, R.; Valenti, P.: Arzneim.-Forsch./Drug Res. **42**, 797 (1992)
18 Rampa, A.; Budriesi, R.; Bisi, A.; Chiarini, A.; Valenti, P.: Arzneim.-Forsch./Drug Res. **42**, 1284 (1992)
19 Gabor, M.: The Pharmacology of Benzopyrone derivatives and Related Compounds, Akademiai Kiado, Budapest 1986
20 Nardi, D.; Leonardi, A.; Pennini, R.; Tajana, A.; Cazzulani, P.; Testa, R.: Arzneim.-Forsch./Drug Res. **43**, 28 (1993)
21 Colleoni, D. R.; Setnikar, D. R.: Brit. Pat. 803,372, 824,547 (1958 and 1959 to Dr. Recoedati-Laboratorio Farmacol. S.P.A.)
22 Chen, C. C.; Chen, Y. P.; Hsu, H. Y.; Chen, Y. L.: Chem. Pharm. Bull. **32**, 166 (1984)
23 Cazenave, J. P.; Beretz, A. In: L. Farkas, M. Gabor, F. Kallay (eds.): Flavonoids and Bioflavonoids, Stud Org Chem., Elsevier Sci Publ. Amsterdam, 373 1986
24 Kendi, E.; Özbey, S.; Tunçbilek, M.; Ertan, R.; Fun, H. K.; Yip, B. C.: J. Chem. Crystallogr. **24**, 747 (1994)
25 Hantzsch, A.: Liebigs Ann. Chem. **215**, 1 (1882)
26 Cramer, F.; Elsching, G. H.: Chem. Ber. **89**, 1 (1956)

Received February 17, 1998
Accepted July 15, 1998

Prof. Dr. R. Ertan
University of Ankara
Faculty of Pharmacy
06100 Tandogan
Ankara
Turkey