Studies on the Synthesis of Some Dihydropyridine Derivatives Possessing Calcium Antagonistic Activity

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In this study, it is aimed to investigate the synthesis and the calcium antagonistic activity of some flavone derivatives which contain the 1,4-dihydropyridine ring system at the A ring of the flavone nucleus. For this purpose we first synthesized 6-formylflavone and then twelve 1,4-dihydropyridine derivatives were synthesized by the reaction of 6-formylflavone with alkylacetoacetates, acetoacetanilide and methyl or ethyl aminocrotonate. Conformational analysis was performed for compound **3a**. The calcium antagonistic activity of compound **2a** was examined using nifedipine as the reference compound.

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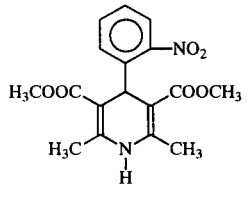
4-Aryl-1,4-dihydropyridine derivatives, such as nifedipine (**I**) [1] and nicardipine (**II**) [2] are highly potent calcium antagonists and are widely used clinically for the treatment of hypertension, angina pectoris, peripheral and vascular diseases. Although nifedipine and nicardipine have been proven to be clinically useful, the rather short duration of action of this class of drugs is disadvantageous [1,2].

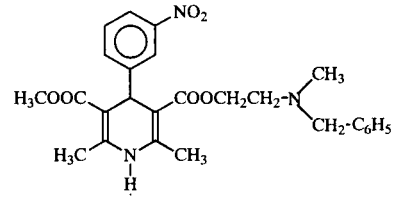
Some derivatives which have a heterocylic group instead of *o*- or *m*-substituted phenyl ring at the 4 position of 1,4-dihydropyridine ring, were synthesized with the concept that long acting derivatives by introducing substituents that are expected to have both high lipophilicity and high affinity for vascular tissues [3]. In this class of compounds, Isradipine (**III**) has shown long-acting and selective calcium antagonist action on the heart as well as peripheral vasodilator activity [4,5]. The replacement of the *o*-nitrophenyl ring of nifedipine with a heterocyclic moiety shown in **IV** determines potent selective bradycardic effects [6-8].

When the *o*-nitrophenyl moiety of nifedipine is substituted by the flourenone system **V**, cardiac potency and selectivity were increased [9].

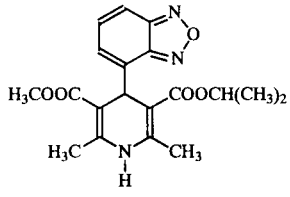
In this paper, we report the synthesis of some 1,4-dihydropyridine derivatives (Table 1) containing the flavone ring system, that already is known to have spasmolytic,



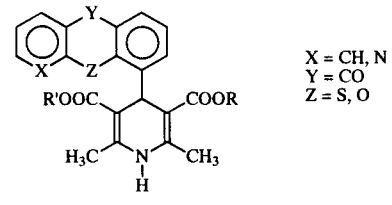
I



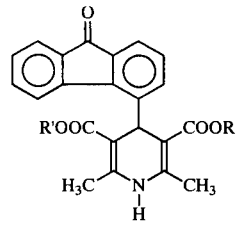
II



III



IV

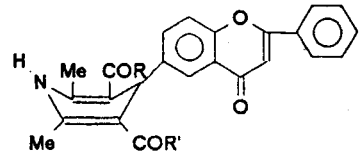


V

In the uv spectra, all compounds show three absorption bands between 204-209, 259-262 and 291-299 nm. In the ir spectra carbonyl absorption was observed between 1620-1710 cm^{-1}. In the ^1H nmr spectra characteristic protons belonging to the flavone and the dihydropyridine moieties are evident. The H-5' proton of the A ring of **VI** was observed at 7.82-8.10 ppm with the effect of CO group of the γ-pyron ring. The NH proton was observed at 5.70-6.60 ppm, except for the compounds **10a-12a**, due to the deshielding effect of the neighbouring amide group. Other protons were observed at the expected δ values in ppm (Table 2).

Table 1

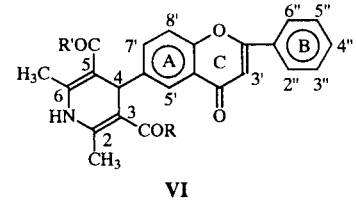
Synthetic Routes and Physicochemical Data for the Compounds Prepared



Compound	R	R'	Method	Yield (%)	mp (°C)	R_f (tlc)	Formula
1a	OCH_3	OCH_3	A	25	254	0.45 [a]	$C_{26}H_{23}NO_6 0.3H_2O$
2a	OC_2H_5	OC_2H_5	A	58	200	0.46 [a]	$C_{28}H_{27}NO_6 0.3H_2O$
3a	$OCH_2CH=CH_2$	$OCH_2CH=CH_2$	A	25	199	0.52 [a]	$C_{30}H_{27}NO_6 0.6H_2O$
4a	$OC(CH_3)_3$	$OC(CH_3)_3$	A	24	238	0.58 [a]	$C_{32}H_{35}NO_6 0.6H_2O$
5a	OCH_3	OC_2H_5	B	27	197	0.51 [bl	$C_{27}H_{25}NO_6$
6a	OCH_3	$OCH_2CH=CH_2$	B	40	177	0.46 [a]	$C_{28}H_{25}NO_6$
7a	OCH_3	$OC(CH_3)_3$	B	31	194	0.51 [b]	$C_{29}H_{29}NO_6$
8a	OC_2H_5	$OCH_2CH=CH_2$	B	23	199	0.51 [b]	$C_{29}H_{27}NO_6$
9a	OC_2H_5	$OC(CH_3)_3$	B	25	206	0.49 [a]	$C_{30}H_{31}NO_6$
10a	NHC_6H_5	NHC_6H_5	C	30	267	0.37 [b]	$C_{36}H_{29}N_3O_4$
11a	NHC_6H_5	OCH_3	D	12	208	0.69 [a]	$C_{31}H_{26}N_2O_5$
12a	NHC_6H_5	OC_2H_5	D	13	219	0.64 [a]	$C_{32}H_{28}N_2O_5$

[a] Dichloromethan:ethyl acetate (1:1); [b] Methanol:water:ammonia (9:1:0.1).

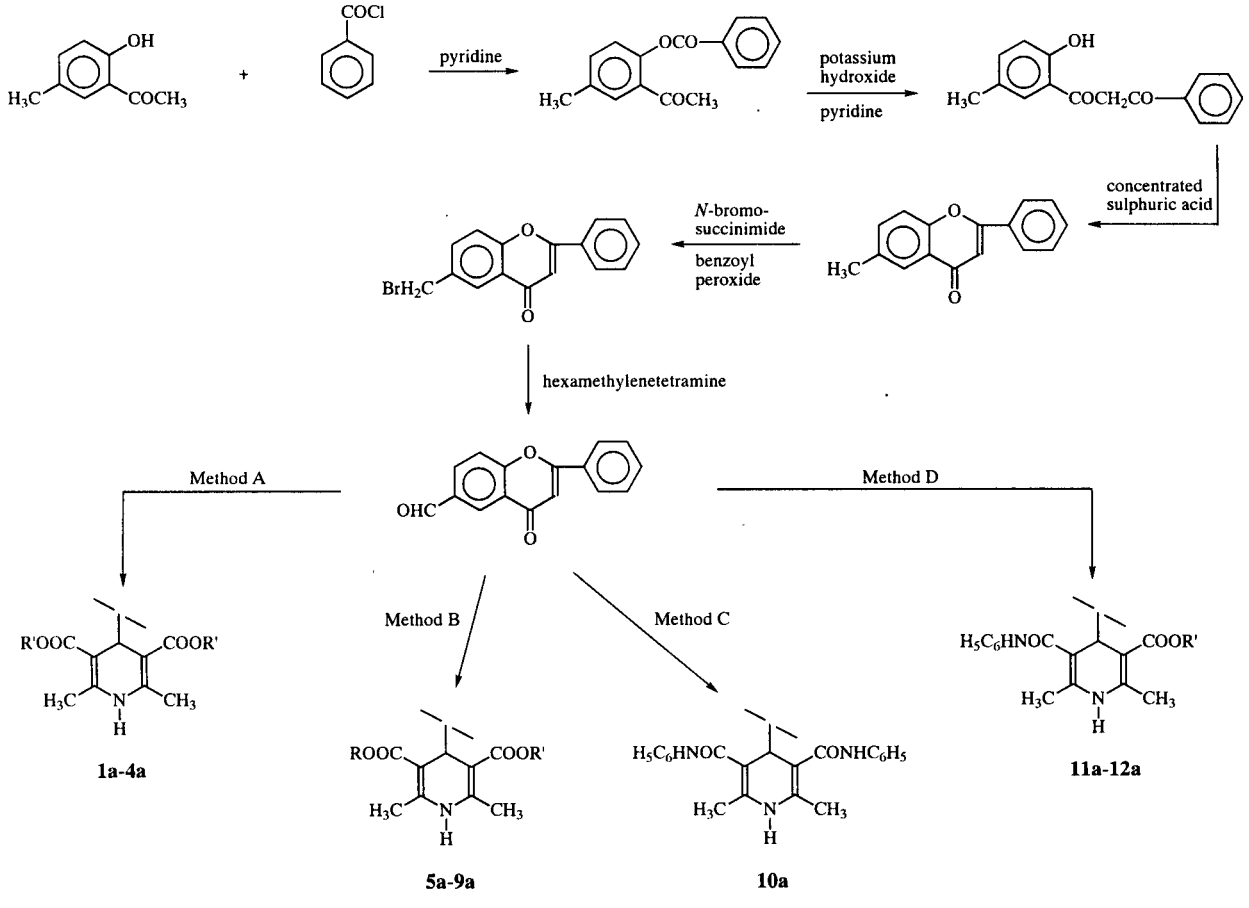
capillary resistance activity and a coronary dilation effect when at the 4 position of the 1,4-dihydropyridine ring [10-13]. A flavone containing a methyl group at the 6 position of the flavone A ring was prepared using the classical Baker-Venkataraman method [14,15]. The bromination of the benzylic methyl group of the flavone was afforded by bromination with *N*-bromosuccinimide [16]. 6-Formylflavone (flavone-6-carboxaldehyde) was prepared from the 6-bromomethyl derivatives by reaction with hexamethylentetramine [17]. Compounds **1a-12a** were prepared using the modified Hantzsch reaction [18] (Scheme 1).



VI

Scheme 1

Synthesis of the 1,4-Dihydropyridine Derivatives



The structural features of the 1,4-dihydropyridine ring are associated with calcium antagonistic activity [19,20]. The X-ray structure analysis (Tables 3-6) of **3a** also revealed that this feature is preserved in **3a**. The 1,4-dihydropyridine ring adopts a boat configuration with N and C4 at 0.118 and 0.274Å, respectively, above the four atom plane through C2, C3, C5 and C6. For C2-C3-C4-C5 the torsion angle is 22.5° in **3a**, compared to 22.0° in nifedipine [19] and 22.85° in allyl ethyl 1,4-dihydro-2,6-dimethyl-4-[4'(4*H*-4-oxo-1-benzopyran-2-yl)phenyl)]-3,5-pyridinedicarboxylate [21]. For C3-C4-C5-C6 the torsion angle is 21.8° in **3a**, compared to 17.9° in nifedipine and 21.64° in allyl ethyl 1,4-dihydro-2,6-dimethyl-4-[4'(4*H*-4-oxo-1-benzopyran-2-yl)phenyl)]-3,5-pyridinedicarboxylate. The torsion angles about the bonds to N in **3a** are 12.4° [C2-N-C6-C5] and -11.9° for [C6-N-C2-C3]. The corresponding angles in nifedipine are -11.3° and 7.4°. Two allyl groups are slightly twisted in opposite directions as shown in Figure 1. Strong elongations of the thermal ellipsoids of C35, C36, C55 and C56 indicate that these atoms are disordered. The flavone molecule is planar and the benzopyran ring system of the molecule is approximately perpendicular to the dihydropyridine ring. The dihedral angle between the plane of the benzopyran ring system and the plane through the four carbon atoms C2, C3, C5 and C6 is 91.39°. The two allyl groups are slightly twisted in opposite directions.

The calcium antagonistic activity of **2a** was also examined using nifedipine as the reference compound and preliminary biological findings show that this compound was comparable with nifedipine (Table 7).

Table 2

^{1}H-NMR Spectral Data for Compounds **1a-12a** (δ ppm)

Compound	NH	2-CH_3	6-CH_3	H-4	H-3'	H-5'	H-7'	H-8'	H-2" H-6"	H-3" H-4" H-5"	OCH_3	OCH_2	CH_3	OCH_2	CH	$=CH_2$	$OC(CH_3)_3$	NHC_6H_5	NHC_6H_5
1a	6.50	2.35		5.10	6.78	8.08	7.75	7.45	7.90	7.50	3.65								
2a	6.35	2.35		5.10	6.80	8.10	7.75	7.45	7.90	7.55		4.10	1.20						
3a	6.55	2.40		5.25	6.78	8.08	7.75	7.42	7.92	7.53		4.55			5.85	5.15			
4a	5.85	2.35		5.05	6.80	8.10	7.75	7.45	7.95	7.55							1.40		
5a	6.45	2.35		5.10	6.78	8.08	7.75	7.45	7.90	7.50	3.60	4.05	1.25						
6a	6.60	2.35		5.20	6.80	8.08	7.75	7.45	7.90	7.50	3.65			4.55	5.90	5.15			
7a	5.70	2.30	2.35	5.05	6.80	8.08	7.70	7.45	7.90	7.50	3.65						1.40		
8a	6.35	2.35		5.20	6.78	8.08	7.75	7.45	7.90	7.50		4.05	1.20	4.55	5.85	5.15			
9a	5.70	2.30	2.35	5.05	6.80	8.05	7.75	7.45	7.90	7.50		4.05	1.20				1.40		
10a	8.20	2.15		5.30	6.95	7.95	7.70	7.65	8.05	7.55								9.40	6.95-7.55
11a	8.62	2.05	2.25	5.05	7.00	7.82	7.68	7.62	8.08	7.55	3.50							9.60	7.00-7.60
12a	8.60	2.05	2.30	5.05	6.95	7.85	7.65	7.60	8.05	7.55		3.95	1.20					9.60	6.95-7.55

Table 3

Experimental Data for the Crystallographic Analysis

Molecular formula	$C_{30}H_{27}NO_6$
Molecular weight	497
Crystal system	Triclinic
Space group	P1
a, Å	10.194(1)
b, Å	10.898(1)
c, Å	13.617(1)
α, deg	102.81(1)
β, deg	105.49(1)
γ, deg	106.55(1)
V, Å^3	1322.8 (2)
Z	2
ρ calcd., g.cm^{-3}	1.22
F(000)	512
μ cm^{-1}	0.8
Temperature, °C	23
Crystal size, mm	0.56 x 0.60 x 0.64
Scan type	ω-2θ
2θ range, deg	2.0 to 56
Reflections measured	5672
Reflections observed	3055(F>3σ(F))
Min-max height in final Δρ-eÅ^{-3}	-0.089, 0.502
GOF	0.93
R	0.071
ωR	0.068
Δ/σ	0.01
w	unit weight

Table 4

Fractional Atomic Coordinates for Non-hydrogen Atoms

Atom	x	y	z	B(Å^2)
O1	0.3054(3)	0.3428(3)	0.4872(2)	4.58(7)
O2	0.5370(3)	0.4084(4)	0.7995(2)	7.4(1)
O32	-0.0173(4)	0.6747(3)	0.7325(2)	6.63(9)
O33	0.1584(4)	0.8391(3)	0.8731(3)	7.8(1)
O52	-0.0780(4)	0.1390(3)	0.8434(3)	8.3(1)
O53	-0.1660(4)	0.2219(3)	0.7148(3)	7.4(1)
N	0.2327(4)	0.5437(4)	1.0075(3)	5.5(1)
C2	0.2200(4)	0.6468(4)	0.9671(3)	4.9(1)
C2'	0.4408(4)	0.3377(4)	0.5161(3)	4.2(1)
C3	0.1219(4)	0.6133(4)	0.8669(3)	4.18(9)
C3'	0.5213(4)	0.3624(4)	0.6189(3)	4.9(1)
C4'	0.4672(4)	0.3920(4)	0.7056(3)	4.9(1)
C4	0.0422(4)	0.4684(4)	0.7969(3)	4.15(9)
C5	0.0373(4)	0.3720(4)	0.8625(3)	4.6(1)
C5'	0.2531(4)	0.4282(4)	0.7465(3)	4.17(9)
C6	0.1363(4)	0.4122(4)	0.9620(3)	5.2(1)
C6'	0.1170(4)	0.4329(4)	0.7141(3)	3.94(9)
C7'	0.0448(4)	0.4064(4)	0.6041(3)	4.9(1)
C8'	0.1077(4)	0.3763(4)	0.5297(3)	5.0(1)
C9'	0.2458(4)	0.3725(4)	0.5654(3)	4.07(9)
C10'	0.3222(4)	0.3977(4)	0.6730(3)	3.99(9)
C20	0.4819(4)	0.2987(4)	0.4207(3)	4.5(1)
C21	0.3196(5)	0.7842(5)	1.0433(4)	7.0(2)
C30	0.3825(5)	0.2635(5)	0.3184(3)	6.0(1)
C31	0.0805(4)	0.7088(4)	0.8171(3)	4.9(1)
C34	0.1019(7)	0.9367(5)	0.8346(6)	10.5(2)
C35	0.166(2)	0.979(2)	0.777(1)	9.1(4)*

(continued)

Table 4 (continued)

Atom	x	y	z	B(Å^2)
C36	0.293(2)	1.157(2)	0.842(1)	10.9(5)*
C40	0.4213(5)	0.2212(5)	0.2298(4)	7.5(2)
C50	0.5560(5)	0.2165(5)	0.2433(4)	7.4(1)
C51	-0.0700(5)	0.2343(5)	0.8101(4)	6.0(1)
C54	-0.2752(8)	0.0854(6)	0.6528(5)	10.6(2)
C55	-0.211 (1)	0.018(1)	0.5804(9)	8.0(3)*
C56	-0.256(2)	-0.013(1)	0.477(1)	10.8(4)*
C60	0.6552(5)	0.2536(6)	0.3434(4)	7.9(2)
C61	0.1575(5)	0.3290(5)	1.0350(3)	7.5(1)
C70	0.6193(5)	0.2958(5)	0.4332(4)	6.8(1)

Starred atoms were refined isotropically.

Table 5

Bond Lengths (Å) and Angles (°)

O1	C2'	1.352(5)	C4	C6'	1.561(6)
O1	C9'	1.382(5)	C5	C6	1.342(5)
O2	C4'	1.230(5)	C5	C51	1.459(5)
O32	C31	1.202(5)	C5'	C6'	1.359(6)
O33	C31	1.335(5)	C5'	C10'	1.404(6)
O33	C34	1.475(8)	C6	C61	1.502(7)
O52	C51	1.213(7)	C6'	C7'	1.402(5)
O53	C51	1.351(6)	C7'	C8'	1.365(6)
O53	C54	1.471(6)	C8'	C9'	1.377(6)
N	C2	1.379(7)	C9'	C10'	1.385(5)
N	C6	1.372(5)	C20	C30	1.380(5)
C2	C3	1.355(5)	C20	C70	1.375(7)
C2	C21	1.494(5)	C30	C40	1.390(8)
C2'	C3'	1.341(5)	C34	C35	1.24(2)
C2'	C20	1.481(6)	C40	C50	1.354(8)
C3	C4	1.500(5)	C50	C60	1.354(6)
C3	C31	1.460(7)	C54	C55	1.49(2)
C3'	C4'	1.444(7)	C55	C56	1.29(2)
C4'	C10'	1.450(6)	C60	C70	1.387(8)
C4	C5	1.522(6)			

C2'	O1	C9'	119.4(3)	C4	C6'	C5'	121.1(3)
C31	O33	C34	115.9(4)	C4	C6'	C7'	120.3(4)
C51	O53	C54	116.0(5)	C5'	C6'	C7'	118.5(4)
C2	N	C6	124.3(3)	C6'	C7'	C8'	121.7(4)
N	C2	C3	118.0(3)	C7'	C8'	C9'	118.2(3)
N	C2	C21	113.4(4)	O1	C9'	C8'	116.0(3)
C3	C2	C21	128.6(5)	O1	C9'	C10'	121.4(4)
O1	C2'	C3'	122.3(4)	C8'	C9'	C10'	122.5(4)
O1	C2'	C20	111.1(3)	C4'	C10'	C5'	122.7(3)
C3'	C2'	C20	126.6(4)	C4'	C10'	C9'	120.1(4)
C2	C3	C4	121.1(4)	C5'	C10'	C9'	117.3(4)
C2	C3	C31	125.3(3)	C2'	C20	C30	120.4(4)
C4	C3	C31	113.5(3)	C2'	C20	C70	120.3(4)
C2'	C3'	C4'	122.1(4)	C30	C20	C70	119.3(4)
O2	C4'	C3'	122.8(4)	C20	C30	C40	119.4(5)
O2	C4'	C10'	122.5(4)	O32	C31	O33	121.5(5)
C3'	C4'	C10'	114.6(3)	O32	C31	C3	123.4(4)
C3	C4	C5	112.0(3)	O33	C31	C3	115.1(3)
C3	C4	C6'	109.8(3)	O33	C34	C35	110.0(1)
C5	C4	C6'	109.7(4)	C30	C40	C50	120.7(4)
C4	C5	C6	119.7(3)	C40	C50	C60	120.3(5)
C4	C5	C51	117.5(3)	O52	C51	O53	121.4(3)
C6	C5	C51	122.6(4)	O52	C51	C5	127.1(4)
C6'	C5'	C10'	121.7(3)	O53	C51	C5	111.5(4)
N	C6	C5	119.7(4)	O53	C54	C55	106.9(7)
N	C6	C61	112.7(3)	C50	C60	C70	120.3(5)
C5	C6	C61	127.6(4)	C20	C70	C60	120.0(4)

Table 6

Selected Torsion Angles

C6	N	C2	C3	-11.91	(0.65)
C6	N	C2	C21	167.74	(0.42)
C2	N	C6	C5	12.44	(0.67)
C2	N	C6	C61	-167.33	(0.42)
N	C2	C3	C4	-7.08	(0.63)
N	C2	C3	C31	171.62	(0.41)
C21	C2	C3	C4	173.33	(0.45)
C21	C2	C3	C31	-7.97	(0.77)
C2	C3	C4	C5	22.47	(0.57)
C2	C3	C4	C6'	-99.63	(0.44)
C31	C3	C4	C5	-156.38	(0.37)
C31	C3	C4	C6'	81.52	(0.43)
C2	C3	C31	O32	-172.30	(0.46)
C2	C3	C31	O33	6.90	(0.66)
C4	C3	C31	O32	6.49	(0.63)
C4	C3	C31	O33	-174.31	(0.38)
C3	C4	C5	C6	-21.79	(0.57)
C3	C4	C5	C51	162.83	(0.39)
C6'	C4	C5	C6	100.35	(0.44)
C6'	C4	C5	C51	-75.02	(0.47)
C3	C4	C6'	C5'	67.90	(0.48)
C3	C4	C6'	C7'	-111.53	(0.42)
C5	C4	C6'	C5'	-55.55	(0.49)
C5	C4	C6'	C7'	125.02	(0.41)
C4	C5	C6	N	5.95	(0.64)
C4	C5	C6	C61	-174.32	(0.44)
C51	C5	C6	N	-178.92	(0.42)
C51	C5	C6	C61	0.81	(0.76)
C4	C5	C51	O53	-10.50	(0.59)
C6	C5	C51	O52	-5.68	(0.81)
C6	C5	C51	O53	174.27	(0.43)

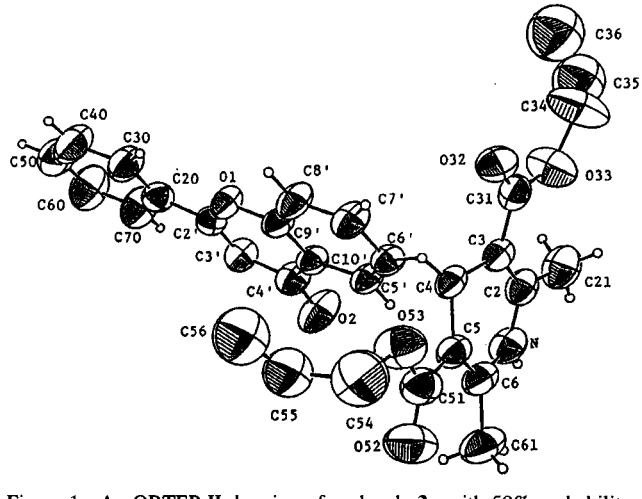


Figure 1. An ORTEP-II drawing of molecule **3a** with 50% probability ellipsoids. The H atoms are shown as circles of a small arbitrary diameter.

Table 7

Calcium Channel Blocker Activity of Nifedipine and Compound **2a**

Receptor	Ligand	Reference	**2a**
Ca^{+2} channel	[^{3}H] PN 200-110	Nifedipine	
		$K_{0.5}$:2.5 x 10^{-8}	6.9 x 10^{-7}
		K_1:1.5 x 10^{-8}	2.5 x 10^{-7}

EXPERIMENTAL

Instrumentation.

Melting points were determined with a Buchi SMP-20 capillary melting point apparatus and are uncorrected. The ir spectra were recorded on a Pye Unicam SP 1025 spectrometer as potassium bromide pellets. The ^{1}H nmr spectra were recorded with Bruker AC 200 and 400 spectrometers in deuteriochloroform and dimethyl-d_6 sulfoxide on the δ scale from the internal standard, tetramethylsilane. The mass spectra were determined with a VG Analytical 70-250S spectrometer in the electron impact mode at 70eV. Elemental analyses were determined with a Perkin-Elmer 240B analyser. All chemicals were obtained from Aldrich Chemical Company. Column chromatograpy was performed using silica gel (Merck Art. 9385). 6-Formylflavone was synthesized by the literature method [17].

Method A.

General Procedure.

6-Formylflavone (0.25 g, 0.001 mole), 0.002 mole of alkylacetoacetate and 0.25 ml of ammonia (25% w/v) were refluxed in 10 ml of 2-propanol for 12 hours for **1a** and **2a** and 10 hours for **3a** and **4a**. The solvent was removed and the residue was purified by column chromatography using hexane:ethyl acetate (1:1, v/v) as the eluent.

Dimethyl 1,4-Dihydro-2,6-dimethyl-4-(2-phenyl-4*H*-1-benzopyran-4-oxo-6-yl)-3,5-pyridinedicarboxylate (**1a**).

This compound had ir (potassium bromide): 1620 (γ-pyrone C=O), 1690 (ester C=O), 3300 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform): Table 2; ms: m/z (%): 445 (M^+) (2.4), 386 (3.0), 224 (100), 192 (5.4), 149 (4.2), 102 (3.3).

Anal. Calcd. for $C_{26}H_{23}NO_6 \cdot 0.3H_2O$: C, 69.27; H, 5.24; N, 3.11. Found: C, 69.22; H, 4.78; N, 2.78.

Diethyl 1,4-Dihydro-2,6-dimethyl-4-(2-phenyl-4*H*-1-benzopyran-4-oxo-6-yl)-3,5-pyridinedicarboxylate (**2a**).

This compound had ir (potassium bromide): 1625 (γ-pyrone C=O), 1680 (ester C=O), 3300 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform): Table 2; ms: m/z (%) 473 (M^+) (2.9), 400 (5.0), 252 (100), 196 (16.7), 150 (4.7), 102 (2.7), 77 (2.3).

Anal. Calcd. for $C_{28}H_{27}NO_6 \cdot 0.3H_2O$: C, 70.23; H, 5.77; N, 2.93. Found: C, 69.71; H, 5.80; N, 2.90.

Diallyl 1,4-Dihydro-2,6-dimethyl-4-(2-phenyl-4*H*-1-benzopyran-4-oxo-6-yl)-3,5-pyridinedicarboxylate (**3a**).

This compound had ir (potassium bromide): 1625 (γ-pyrone C=O), 1700 (ester C=O), 3320 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform): Table 2; ms: m/z (%) 497 (M^+) (2.3), 412 (5.2), 276 (100), 178 (3.5), 150 (5.5), 102 (3.2).

Anal. Calcd. for $C_{30}H_{27}NO_6 \cdot 0.6H_2O$: C, 70.89; H, 5.55; N, 2.76. Found: C, 70.45; H, 5.28; N, 2.75.

Di-*t*-butyl 1,4-dihydro-2,6-dimethyl-4-(2-phenyl-4*H*-1-benzopyran-4-oxo-6-yl)-3,5-pyridinedicarboxylate (**4a**).

This compound had ir (potassium bromide): 1630 (γ-pyrone C=O), 1690 (ester C=O), 3320 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform): Table 2; ms: m/z (%) 529 (M^+) (1.4), 472 (1.2), 354 (3.0), 327 (3.7), 308 (17.3), 196 (100), 178 (4.3), 150 (6.0), 102 (2.7).

Anal. Calcd. for $C_{32}H_{35}NO_6 \cdot 0.6H_2O$: C, 71.14; H, 6.71; N, 2.59. Found: C, 70.89; H, 6.21; N, 2.38.

Method B.

General Procedure.

6-Formylflavone (0.25 g, 0.001 mole) and 0.001 mole of alkyl acetoacetate were suspended in 10 ml of 2-propanol and 0.001 mole methyl or ethyl aminocrotonate was added. The mixture was refluxed 8 hours for **5a**, **7a** and **9a**, 10 hours for **6a** and **8a**. After removal of the solvent the residue was purified by elusion from column chromatography with hexane:ethyl acetate (1:1, v/v) as the eluent.

Ethyl Methyl 1, 4-Dihydro-2,6-dimethyl-4-(2-phenyl-4*H*-1-benzopyran-4-oxo-6-yl)-3,5-pyridinedicarboxylate (**5a**).

This compound had ir (potassium bromide):1630 (γ-pyrone C=O), 1690 and 1700 (ester C=O), 3340 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform): Table 2; ms: m/z (%): 459 (M^+) (4.1), 400 (4.9), 386 (7.0), 354 (4.6), 238 (100), 178 (11.9), 150 (13.1), 102 (10.6).

Anal. Calcd. for $C_{27}H_{25}NO_6$: C, 70.59; H, 5.45; N, 3.05. Found: C, 70.86; H, 5.85; N, 2.77.

Allyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(2-phenyl-4*H*-1-benzopyran-4-oxo-6-yl)-3,5-pyridinedicarboxylate (**6a**).

This compound had ir (potassium bromide): 1640 (γ-pyrone C=O), 1710 (ester C=O), 3320 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform): Table 2; ms: m/z (%) 471 (M^+) (2.6), 414 (2.5), 412 (2.5), 354 (3.2), 326 (1.2), 250 (100), 192 (5.9), 178 (5.4), 150 (8.1), 102 (6.9), 77 (6.5).

Anal. Calcd. for $C_{28}H_{25}NO_6$: C, 71.34; H, 5.31; N, 2.97. Found: C, 72.18; H, 5.53; N, 3.06.

Methyl *t*-Butyl 1,4-Dihydro-2,6-dimethyl-4-(2-phenyl-4*H*-1-benzopyran-4-oxo-6-yl)-3,5-pyridinedicarboxylate (**7a**).

This compound had ir (potassium bromide): 1630 (γ-pyrone C=O), 1680 and 1700 (ester C=O), 3320 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform): Table 2; ms: m/z (%): 487 (M^+) 430 (1.1), 414 (2.0), 386 (9.0), 372 (3.1), 354 (4.8), 328 (2.0), 266 (10.1), 252 (44.6), 238 (6.3), 224 (73.4), 210 (100), 196 (13.0), 178 (13.0), 150 (18.5).

Anal. Calcd. for $C_{29}H_{29}NO_6$: C, 71.46; H, 5.95; N, 2.87. Found: C, 71.60; H, 6.35; N, 3.36.

Allyl Ethyl-1,4-Dihydro-2,6-dimethyl-4-(2-phenyl-4*H*-1-benzopyran-4-oxo-6-yl)-3,5-pyridinedicarboxylate (**8a**).

This compound had ir (potassium bromide): 1640 (γ-pyrone C=O), 1680 and 1705 (ester C=O), 3330 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform): Table 2; ms: m/z (%) 485 (M^+) (7.9), 440 (3.4), 428 (4.3), 412 (7.3), 400 (9.6), 354 (4.0), 327 (1.9), 264 (100), 196 (11.5), 178 (2.6), 150 (6.1), 102 (4.2), 77 (3.9).

Anal. Calcd. for $C_{29}H_{27}NO_6$: C, 71.75; H, 5.57; N, 2.89. Found: C, 72.41; H, 5.70; N, 2.76.

Ethyl *t*-Butyl 1,4-Dihydro-2,6-dimethyl-4-(2-phenyl-4*H*-1-benzopyran-4-oxo-6-yl)-3,5-pyridinedicarboxylate (**9a**).

This compound had ir (potassium bromide): 1620 (γ-pyrone C=O), 1685 and 1700 (ester C=O), 3300 (NH) cm^{-1}; ^1H nmr (deuteriochloroform): Table 2; ms: m/z (%): 501 (M^+) (1.4), 487 (2.3), 428 (3.2), 400 (11.8), 372 (8.0), 354 (5.3), 328 (2.6), 280 (17.6), 252 (60.7), 224 (100), 196 (54.0), 178 (12.7), 150 (16.5), 102 (11.7), 77 (8.3).

Anal. Calcd. for $C_{30}H_{31}NO_6$: C, 71.86; H, 6.19; N, 2.79. Found: C, 71.91; H, 6.19; N, 3.05.

Method C.

N,N'-Diphenyl-[1,4-dihydro-2,6-dimethyl-4-(2-phenyl-4*H*-1-benzopyran-4-oxo-6-yl]-3,5-pyridinedicarboxamide (**10a**).

A solution of 0.25 g (0.001 mole) of 6-formylflavone, 0.354 g (0.002 mole) of acetoacetanilide and 0.25 ml of ammonia (25% w/v) was heated under reflux in 10 ml of 2-propanol for 13 hours. The solvent was evaporated and the residue was dissolved in hot tetrahydrofuran and filtered. The filtrate was cooled and the precipitate separated.

This compound had ir (potassium bromide): 1630 (γ-pyrone C=O), 1620 (CONH), 3300 (NH) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): Table 2; ms: m/z (%) 567 (M^+) (1.3), 475 (1.2), 447 (5.2), 354 (64.0), 326 (60.2), 118 (63.1), 93 (100), 77 (8.5).

Anal. Calcd. for $C_{36}H_{29}N_3O_4$: C, 76.19; H, 5.11; N, 7.41. Found: C, 75.74; H, 4.97; N, 7.22.

Method D.

General Procedure.

A solution of 0.25 g (0.001 mole) of 6-formylflavone, 0.001 mole of methyl or ethyl amino crotonate and 0.177 g (0.001 mole) of acetoacetanilide was heated under reflux in 10 ml 2-propanol 15 hours for **11a**, 13 hours for **12a**. After removal of the solvent, the residue was purified by column chromatography using hexane:ethyl acetate (1:1, v/v) as the eluent.

Methyl 5-(*N*-Phenylcarboxamido)-1,4-dihydro-2,6-dimethyl-4-(2-phenyl-4*H*-1-benzopyran-4-oxo-6-yl)-3-pyridinecarboxylate (**11a**).

This compound had ir (potassium bromide): 1620 (γ-pyrone C=O), 1635 (CONH), 3330 (NH) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): Table 2; ms: m/z (%) 506 (M^+) (11.2), 491 (2.2), 473 (1.1), 447 (3.9), 414 (22.3), 386 (11.2), 354 (15.6), 285 (100), 192 (58.1), 166 (27.1), 149 (10.0), 102 (7.2), 93 (13.7), 77 (17.5).

Anal. Calcd. for $C_{31}H_{26}N_2O_5$: C, 73.52; H, 5.14; N, 5.53. Found: C, 73.72; H, 5.64; N, 5.63.

Ethyl 5-(*N*-Phenylcarboxamido)-1,4-dihydro-2,6-dimethyl-4-(2-phenyl-4*H*-1-benzopyran-4-oxo-6-yl)-3-pyridinecarboxylate (**12a**).

This compound had ir (potassium bromide): 1620 (γ-pyrone, C=O), 1635 (HN-C=O), 1685 (C=O ester), 3300 (NH) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): Table 2; ms: m/z (%) 520 (M^+) (11.4), 428 (19.7), 400 (10.8), 354 (19.0), 299 (100), 271 (17.8), 206 (12.2), 178 (46.8), 150 (24.7), 119 (19.3), 93 (28.5), 77 (38.4).

Anal. Calcd. for $C_{32}H_{28}N_2O_5$: C, 73.85; H, 5.38; N, 5.38. Found: C, 74.09; H, 5.56; N, 5.05.

X-Ray Crystallography of Compound **3a**.

Crystallographic and refinement parameters are summarized in Table 3. The data were collected on a Nonius CAD 4 diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71073Å). Three standard reflections were measured every two hours. The structure was solved by direct methods. The refinement was made with anisotropic temperature factors for all non-hydrogen atoms except for the C35, C36, C35', C36', C55, C56, C55' and C56'. The hydrogen atoms were generated geometrically and refined riding on the C atoms. An empirical ψ scan absorption correction was applied from the MolEN [22] which has been used to carry out all calculations. The final atomic parameters for non-hydrogen atoms are reported in Table 4. Bond lengths and angles and some selected torsion angles are listed Tables 5 and 6. The view of the molecule was performed using ORTEP [23].

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