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Studies on 2-Ethyl-3-carbmethoxy-4-aryl-5-oxo-1,4,5,6,7,8-hexahydroquinoline Derivatives and Calcium Modulatory Activities

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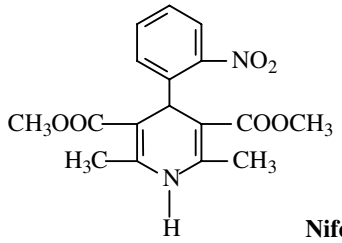
Twelve new compounds having a 2-ethyl-3-carbmethoxy-4-aryl-5-oxo-1,4,5,6,7,8-hexahydroquinoline structure were synthesized, characterized and screened for their calcium modulatory activities. The calcium antagonistic activities of the compounds were investigated by tests performed on isolated rat ileum and lamb carotid artery. Compounds **1, 4, 8** and **9** showed considerable activity.

Key Words: Dihydropyridine, hexahydroquinoline, antihypertensive activity, calcium antagonist.

Introduction

Calcium channel antagonists inhibit muscle contraction by blocking the influx of Ca^{2+} through calcium channels and are used as antianginal and antihypertensive drugs [1–5]. Nifedipine, with 1,4-dihydropyridine (DHP) moiety in its structure, is the prototype of this group.



Nifedipine

Many 1,4-DHP derivatives have been synthesized by making various modifications to the nifedipine molecule. These derivatives can be agonist or antagonist. Although agonist and antagonist compounds have similar structural properties, they interact with different regions of the same receptor [1,2,6–10]. Many active

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compounds have also been obtained by the introduction of 1,4-DHP moiety into condensed systems [11−25]. Active antagonists have an aromatic ring in the 4 position of the dihydropyridine ring, which tends both to restrict the aromatic ring to the DHP vertical plane and to flatten the DHP ring.

The aim of this study was to synthesize novel hexahydroquinoline derivatives and investigate their calcium modulatory activity.

Experimental

Chemistry

All the chemicals used in this study were purchased from Aldrich (Germany) and Fluka (Switzerland).

Melting point: Thomas Hoover Capillary Melting Point Apparatus; the values are uncorrected. UV spectra: Shimadzu UV-160A UV-Visible Spectrophotometer. IR spectra: Perkin Elmer FT-IR Spectrophotometer 1720 X (KBr disc) (γ, cm^{-1}). ^{1}H-NMR spectra: Bruker DPX-400 MHz Digital FT NMR and H^{1}AMX 600 MHz FT NMR Spectrophotometer (DMSO-d_6; tetramethylsilane as internal standard). ^{13}C-NMR Spectra: ^{13}C AMX 150 MHz FT NMR Spectrophotometer. Chemical shift values are given as ppm. Mass spectra: Hewlett Packard Series II plus 5890 Gas Chromatograph- Hewlett Packard 5972 Series mass selective detector (Philadelphia, USA). Elemental analysis was carried out an a Leco 932 CHNS-O Elemental Analyzer (Philadelphia, USA) (TUBITAK, Ankara, Turkey). Elemental analysis results were within 0.4% of theoretical values.

Synthesis of methyl 4-aryl-2-ethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylates (1-12)

A mixture of equimolar amounts (0.001 mol) of appropriate 1,3-cyclohexanedione derivative (I) aromatic aldehyde (II), methyl 3-oxopentanoate and 1 mL ammonia was refluxed in 20 mL methanol for 4 h. The mixture was poured into ice-water. The precipitate formed was filtered and crystallized from alcohol.

Methyl 4-(2-chloro-5-nitrophenyl)-2-ethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (1)

M.p. 103 °C. IR (cm^{-1}) 3286, 1703, 1608. ^{1}H-NMR (ppm) 1.06 (3H; t; $CH_2C\underline{H}_3$, J: 7.2 Hz), 1.44 (2H; m; H-7), 1.96-2.84 (6H; m; $C\underline{H}_2CH_3$, H-6 and H-8), 3.76 (3H; s; $COOCH_3$), 5.05 (1H; s; H-4), 7.40-7.95 (3H; m; Ar-H), 8.80 (1H; s; NH). ^{13}C-NMR (ppm) 10, 21, 24, 30, 32, 37, 53, 103, 112, 120, 126, 130, 140, 144, 150, 167, 198. Mass (m/z): 390, 388, 355, 347, 234, 193, 44, 43. Analysis for $C_{19}H_{19}ClN_2O_5$ (M.W.: 390.82) calculated (CHN): 58.39, 4.90, 7.17; found 58.58, 4.73, 7.41.

Methyl 4-(4-chloro-6-nitrophenyl)-2-ethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2)

M.p. 98 °C. IR (cm^{-1}) 3290, 1705,1610. ^{1}H-NMR (ppm) 1.10 (3H; t; $CH_2C\underline{H}_3$, J: 7.2 Hz), 1.42 (2H; m; H-7), 2.00-2.86 (6H; m; $C\underline{H}_2CH_3$, H-6 and H-8), 3.80 (3H; s; $COOCH_3$), 5.00 (1H; s; H-4), 7.20-7.95 (3H; m; Ar-H), 8.75 (1H; s; NH). ^{13}C-NMR (ppm) 10, 20, 24, 31, 32, 37, 52, 103, 110, 121, 125, 130, 140, 143, 151, 167, 197. Mass (m/z): 390, 388, 355, 347, 234, 193, 44, 43. Analysis for $C_{19}H_{19}ClN_2O_5$ (M.W.: 390.82) calculated (CHN): 58.39, 4.90, 7.17; found 58.44, 5.03, 7.01.

Methyl 4-(4-chloro-3-nitrophenyl)-2-ethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (3)

M.p. 98 °C. IR (cm^{-1}) 3266, 1710, 1605. ^{1}H-NMR (ppm) 1.10 (3H; t; $CH_2C\underline{H}_3$, J: 7.2 Hz), 1.40 (2H; m; H-7), 1.98-2.75 (6H; m; $C\underline{H}_2CH_3$,H-6 and H-8), 3.70 (3H; s; $COOCH_3$), 5.10 (1H; s; H-4), 7.10-7.85 (3H; m; Ar-H), 8.40 (1H; s; NH). ^{13}C-NMR (ppm) 10, 20, 23, 30, 31, 37, 53, 102, 109, 120, 127, 131, 139, 144, 149, 167, 197. Mass (m/z): 390, 388, 355, 347, 234, 193, 44, 43. Analysis for $C_{19}H_{19}ClN_2O_5$ (M.W.: 390.82) calculated (CHN): 58.39, 4.90, 7.17; found 58.17, 4.77, 7.11.

Methyl 4-(5-chloro-2-nitrophenyl)-2-ethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4)

M.p. 200 °C. IR (cm^{-1}) 3280, 1700, 1625. ^{1}H-NMR (ppm) 1.05 (3H; t; $CH_2C\underline{H}_3$, J: 7.2 Hz), 1.45 (2H; m; H-7), 2.05-2.90 (6H; m; $C\underline{H}_2CH_3$,H-6 and H-8), 3.75 (3H; s; $COOCH_3$), 5.055 (1H; s; H-4), 7.00-7.85 (3H; m; Ar-H), 8.80 (1H; s; NH). ^{13}C-NMR (ppm) 10, 21, 23, 32, 34, 38, 53, 102, 109, 122, 126, 132, 140, 144, 150, 150, 168, 198. Mass (m/z): 390, 388, 355, 347, 234, 193, 44, 43. Analysis for $C_{19}H_{19}ClN_2O_5$ (M.W.: 390.82) calculated (CHN): 58.39, 4.90, 7.17; found 58.70, 5.14, 7.32.

Methyl 4-(2-chloro-5-nitrophenyl)-6,6-dimethyl-2-ethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5)

M.p. 194 °C. IR (cm^{-1}) 3290, 1710, 1640. ^{1}H-NMR (ppm) 0.80 (6H; s; 6-CH_3), 1.10 (3H; t; $CH_2C\underline{H}_3$, J: 7.2 Hz), 1.75 (2H; m; H-7), 2.40-2.80 (4H; m; $C\underline{H}_2CH_3$ and H-8), 3.76 (3H; s; $COOCH_3$), 5.10 (1H; s; H-4), 7.40-7.95 (3H; m; Ar-H), 8.80 (1H; s; NH). ^{13}C-NMR (ppm) 10, 24, 25, 32, 38, 39, 52, 103, 111, 119, 125, 129, 140, 145, 146, 149, 152, 167, 204. Mass (m/z): 418, 416, 383, 375, 262, 193, 44, 43. Analysis for $C_{21}H_{23}ClN_2O_5$ (M.W.: 418.87) calculated (CHN) 60.22, 5.53, 6.69; found 59.89, 5.33, 6.81.

Methyl 4-(2-chloro-6-nitrophenyl)-6,6-dimethyl-2-ethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate(6)

M.p. 90 °C. IR (cm^{-1}) 3277, 1700, 1615. ^{1}H-NMR (ppm) 0.80 (6H; s; 6-CH_3), 1.06 (3H; t; $CH_2C\underline{H}_3$, J: 7.2 Hz), 1.70 (2H; m; H-7), 2.35-2.80 (4H; m; $C\underline{H}_2CH_3$ andH-8), 3.65 (3H; s; $COOCH_3$), 5.05 (1H; s; H-4), 7.10-7.85 (3H; m; Ar-H), 8.60 (1H; s; NH). ^{13}C-NMR (ppm) 9, 23, 24, 25, 33, 38, 40, 51, 101, 109, 118, 124, 130, 139, 145, 147, 150, 153, 167, 203. Mass (m/z): 418, 416, 383, 375, 262, 193, 44, 43. Analysis for $C_{21}H_{23}ClN_2O_5$ (M.W.: 418.87) calculated (CHN) 60.22, 5.53, 6.69; found 59.63, 5.47, 6.74.

Methyl 4-(4-chloro-3-nitrophenyl)-6,6-dimethyl-2-ethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (7)

M.p. 87 °C. IR (cm^{-1}) 3266, 1701, 1618. ^{1}H-NMR (ppm) 0.85 (6H; s; 6-CH_3), 1.00 (3H; t; $CH_2C\underline{H}_3$, J: 7.2 Hz), 1.64 (2H; m; H-7), 2.25-2.60 (4H; m; $C\underline{H}_2CH_3$ andH-8), 3.60 (3H; s; $COOCH_3$), 5.00 (1H; s; H-4), 7.00-7.90 (3H; m; Ar-H), 8.55 (1H; s; NH). ^{13}C-NMR (ppm) 10, 23, 24, 25, 33, 38, 40, 51, 101, 109, 118,

124, 130, 139, 145, 147, 150, 153, 167, 203. Mass (m/z): 418, 416, 383, 375, 262, 193, 44, 43. Analysis for $C_{21}H_{23}ClN_2O_5$ (M.W.: 418.87) calculated (CHN) 60.22, 5.53, 6.69; found 60.36, 5.80, 6.84.

Methyl 4-(5-chloro-2-nitrophenyl)-6,6-dimethyl-2-ethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (8)

M.p. 88 °C. IR (cm^{-1}) 3255, 1690, 1598. ^{1}H-NMR (ppm) 0.80 (6H; s; 6-CH_3), 1.05 (3H; t; $CH_2C\underline{H}_3$, J: 7.2 Hz), 1.65 (2H; m; H-7), 2.20-2.60 (4H; m; $C\underline{H}_2CH_3$ andH-8), 3.65 (3H; s; $COOCH_3$), 5.00 (1H; s; H-4), 7.40-7.95 (3H; m; Ar-H), 8.60 (1H; s; NH). ^{13}C-NMR (ppm) 10, 24, 25, 26, 32, 38, 40, 51, 102, 109, 119, 124, 131, 140, 145, 146, 150, 152, 167, 203. Mass (m/z): 418, 416, 383, 375, 262, 193, 44, 43. Analysis for $C_{21}H_{23}ClN_2O_5$ (M.W.: 418.87) calculated (CHN) 60.22, 5.53, 6.69; found 60.44, 5.61, 6.82.

Methyl 4-(2-chloro-5-nitrophenyl)-7,7-dimethyl-2-ethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9)

M.p. 97 °C. IR (cm^{-1}) 3280, 1710, 1600. ^{1}H-NMR (ppm) 0.75 (6H; s; 7-CH_3), 1.10 (3H; t; $CH_2C\underline{H}_3$, J: 7.2 Hz), 1.95 (2H; s; H-6), 2.25-2.45 (4H;m; $C\underline{H}_2CH_3$ and H-8), 3.80 (3H; s; $COOCH_3$), 5.20 (1H; s; H-4), 7.40-8.20 (3H; m; Ar-H), 9.20 (1H; s; NH). ^{13}C-NMR (ppm) 10, 24, 27, 31, 32, 43, 51, 52, 103, 111, 120, 125, 130, 140, 145, 146, 150, 150, 167, 199. Mass (m/z): 418, 416, 383, 375, 262, 193, 44, 43. Analysis for $C_{21}H_{23}ClN_2O_5$ (M.W.: 418.87) calculated (CHN) 60.22, 5.53, 6.69; found 60.62, 5.87, 7.00.

Methyl 4-(2-chloro-6-nitrophenyl)-7,7-dimethyl-2-ethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (10)

M.p. 86 °C. IR (cm^{-1}) 3273, 1688, 1593. ^{1}H-NMR (ppm) 0.75 (6H; s; 7-CH_3), 1.00 (3H; t; $CH_2C\underline{H}_3$, J: 7.2 Hz), 1.85 (2H; m; H-6), 2.15-2.50 (4H; m; $C\underline{H}_2CH_3$ and H-8), 3.60 (3H; s; $COOCH_3$), 5.15 (1H; s; H-4), 7.40-7.95 (3H; m; Ar-H), 8.95 (1H; s; NH). ^{13}C-NMR (ppm) 10, 25, 28, 30, 32, 44, 50, 52, 104, 112, 120, 126, 131, 141, 145, 147, 151, 167, 198. Mass (m/z): 418, 416, 383, 375, 262, 193, 44, 43. Analysis for $C_{21}H_{23}ClN_2O_5$ (M.W.: 418.87) calculated (CHN) 60.22, 5.53, 6.69; found 60.51, 5.33, 6.29.

Methyl 4-(4-chloro-3-nitrophenyl)-7,7-dimethyl-2-ethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (11)

M.p. 91 °C. IR (cm^{-1}) 3240, 1685, 1578. ^{1}H-NMR (ppm) 0.75 (6H; s; 7-CH_3), 1.05 (3H; t; $CH_2C\underline{H}_3$, J: 7.2 Hz), 1.90 (2H; m; H-6), 2.05-2.50 (4H; m; $C\underline{H}_2CH_3$ and H-8), 3.70 (3H; s; $COOCH_3$), 4.90 (1H; s; H-4), 7.40-7.95 (3H; m; Ar-H), 8.70 (1H; s; NH). ^{13}C-NMR (ppm) 10, 25, 27, 31, 33, 43, 50, 53, 102, 109, 119, 125, 130, 140, 145, 147, 150, 168, 197. Mass (m/z): 418, 416, 383, 375, 262, 193, 44, 43. Analysis for $C_{21}H_{23}ClN_2O_5$ (M.W.: 418.87) calculated (CHN) 60.22, 5.53, 6.69; found 60.44, 5.40, 6.45.

Methyl 4-(5-chloro-2-nitrophenyl)-7,7-dimethyl-2-ethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (12)

M.p. 87 °C. IR (cm^{-1}) 3286, 1703, 1608. ^{1}H-NMR (ppm) 0.85 (6H; s; 7-CH_3), 1.10 (3H; t; $CH_2C\underline{H}_3$, J: 7.2 Hz), 1.85 (2H; m; H-7), 2.20-2.60 (4H; m; $C\underline{H}_2CH_3$ and H-8), 3.60 (3H; s; $COOCH_3$), 5.05 (1H; s; H-4), 7.40-7.95 (3H; m; Ar-H), 8.65 (1H; s; NH). ^{13}C-NMR (ppm) 10, 26, 27, 41, 45, 48, 50, 110, 117, 122, 125, 130, 140, 141, 143, 144, 146, 165, 197. Mass (m/z): 418, 416, 383, 375, 262, 193, 44, 43. Analysis for $C_{21}H_{23}ClN_2O_5$ (M.W.. 418.87) calculated (CHN) 60.22, 5.53, 6.69; found 60.18, 5.19, 6.94.

Pharmacology

The calcium antagonistic activities of the compounds were determined by tests performed on isolated rat ileum and lamb carotid artery. All procedures involving animals and their care were conducted in conformity with international laws and policies.

Studies on isolated rat ileum[26]

Albino rats of either sex (150-200 g) were used in the present study. Six experimental animals were used per experiment. They were supplied by the Laboratory Animal Production Center in the Department of Pharmacology, School of Medicine, Osmangazi University, Eskişehir (Turkey). The animals were fasted overnight. After the animals were sacrificied by cervical dislocation, the ileum (10-15 cm terminal portion) was immediately removed, discarding the 5-8 cm segment proximal to the ileocecal junction. Segments 1.5-2 cm long were mounted vertically in a 10 ml organ bath containing Tyrode solution of the following composition (mmol/L): NaCl: 136.87; KC1: 2.68; $CaCl_2$: 1.80; $MgSO_4$ 0.81; NaH_2PO_4: 4.16; $NaHCO_3$: 11.9; glucose: 5.55. The bath contents were maintained at 37 °C and aerated by 95% O_2 and 5% $C0_2$. A tension of 2 g was applied and isometric recording was done using an isometric transducer (FDT_{l0}-A) MAY TDA95 Transducer Data Acquisition System (MAY, Commat, Ankara, Turkey). The preparations were allowed to equilibrate for 60 min. with regular washes every 15 min in order to check for antagonistic effects and contractions were induced with barium chloride (3.10^{-3} mol/L, bath concentration). After washing out, this process was repeated until the amplitude of the contraction become constant. Investigations of the substances were performed using the single dose technique. Barium chloride contractions were induced after the addition of the test substances dissolved in dimethylsulphoxide at different concentrations (10^{-6} mol/L) and 5 min exposure. Only one compound was tested in each preparation. In order to check for calcium antagonistic effects, contractions of isolated ileum were induced with barium chloride.

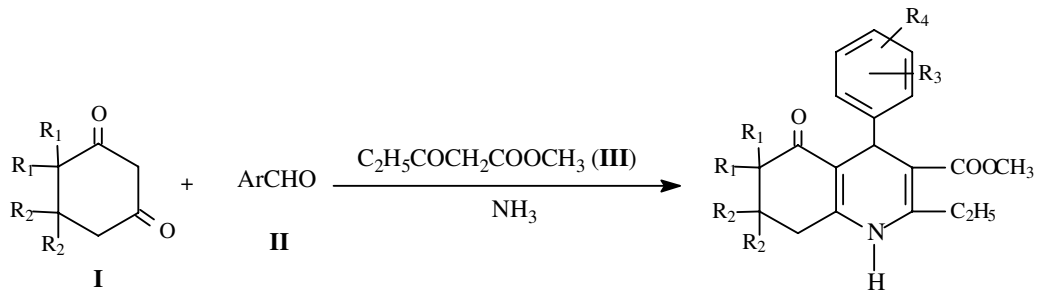
Studies on lamb carotid artery [25]

Sheep (*Ovis aries*) carotid artery preparations were obtained from the local slaughterhouse. Rings (3 mm) were suspended in organ baths of 10 mL capacity containing Tyrode solution of the following composition (mmol/L): NaCl: 136.87; KC1: 2.68; $CaCl_2$: 1.80; $MgSO_4$: 0.81; NaH_2PO_4: 4.16; $NaHCO_3$: 11.9; glucose: 5.55. The bath contents were maintained at 37 °C and aerated by 95% O_2 and 5% CO_2 and a tension of 2 g was applied. The preparations were allowed to equilibrate for 60 min with regular washes every 15 min in order to check for antagonistic effectsand contractions were induced with 67 mmol/L potassium chloride. After washing out, this process was repeated until the amplitude of the contraction become

constant. Investigations of the substances were performed using the single dose technique. Potassium chloride contractions were induced after the addition of the test substance and 10 min exposure. During the administration of the individual substances, the preparation was washed until the initial situation had been re-established and potassium chloride contractions were induced. The isometric contractions were recorded by an isometric transducer (FDT_{10}-A) May TDA95 Transducer Data Acquisition System (May, Commat, Ankara, Turkey).

Results and Discussion

The hexahydroquinoline derivatives were prepared by modified Hantzsch synthesis [27]. In this reaction, benzylidene derivatives form by the reaction appropriate 1,3-cyclohexanedione compound and appropriate aldehyde derivative. Then 2-benzylidene-1,3-cyclohexanedione derivative reacts in methyl 3-oxopentanoate to give corresponding hexahydroquinoline derivatives.

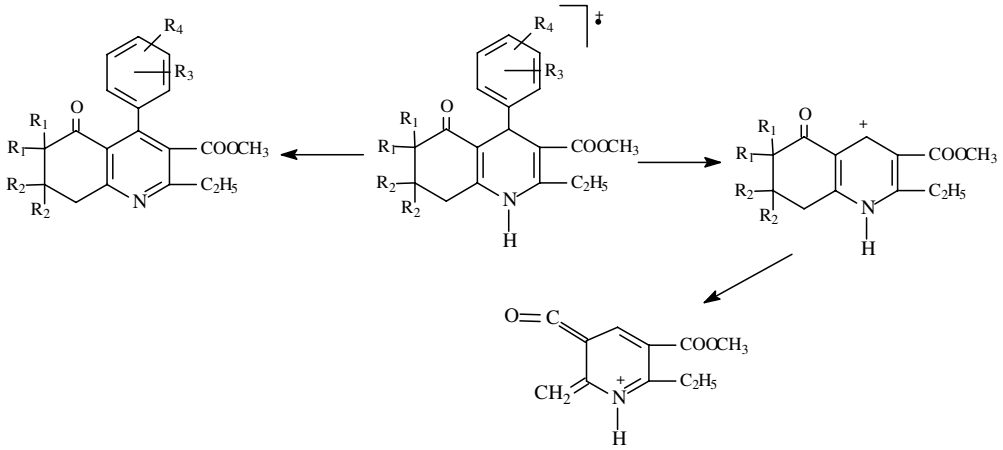


1-12

Compound	R_1	R_2	R_3, R_4	Compound	R_1	R_2	R_3, R_4	Compound	R_1	R_2	R_3, R_4
1	**H**	**H**	**2-Cl 5-NO_2**	**5**	**CH_3**	**H**	**2-Cl 5-NO_2**	**9**	**H**	**CH_3**	**2-Cl 5-NO_2**
2	**H**	**H**	**2-Cl 6-NO_2**	**6**	**CH_3**	**H**	**2-Cl 6-NO_2**	**10**	**H**	**CH_3**	**2-Cl 6-NO_2**
3	**H**	**H**	**4-Cl 3-NO_2**	**7**	**CH_3**	**H**	**4-Cl 3-NO_2**	**11**	**H**	**CH_3**	**4-Cl 3-NO_2**
4	**H**	**H**	**5-Cl 2-NO_2**	**8**	**CH_3**	**H**	**5-Cl 2-NO_2**	**12**	**H**	**CH_3**	**5-Cl 2-NO_2**

Scheme 1

The structures of the compounds were elucidated by IR, ^{1}H-NMR, ^{13}C–NMR and mass spectra. All spectra data of the compounds are in accordance with their structures. The mass spectra of the compounds were recorded using the electron impact technique. Molecular ion peaks were seen in the mass spectra of the compounds. The base peak forms by cleavage of the aryl ring from the parent molecule. In further fragmentation, the ions are formed by the rupture of the cyclohexene ring and acylium ions are formed by the cleavage of the ester group. Aromatization of the DHP ring to the pyridine analogue was also realized. These findings are in accordance with the literature [16−18,25,28,29]. The results of elemental analyses are also consistent with the postulated structures.



Scheme 2

Calcium antagonistic activities of the compounds were determined by tests performed on isolated rat ileum and lamb carotid artery. In these studies, nicardipine was used as standard. The results of activity studies of the compounds on isolated rat ileum and lamb carotid artery are given in the Table.

Table. Relaxant effects of the compounds and nicardipine (10^{-5} mol/L) on isolated rat ileum precontracted with barium chloride (4.10^{-3} mol/L) and on lamb carotid artery precontracted with barium chloride (67 mmol/L) (% ± SD) (n = 7).

	% Inhibition	
	Isolated rat ileum	Lamb carotid artery
1	59.24 ± 11.48	0
2	33.14 ± 3.44	
3	23.73 ± 8.08	
4	79.80 ± 7.31	15.85 ± 1.66
5	33.44 ± 10.62	
6	41.51 ± 8.10	
7	29.69 ± 17.66	
8	79.11 ± 3.11	13.02 ± 3.63
9	58.09 ± 7.77	2.59 ± 2.65
10	26.41 ± 5.14	
11	43.10 ± 14.16	
12	40.02 ± 8.92	
Nicardipine	69.57 ± 5.72	15.94 ± 7.72

On isolated rat ileum strips precontracted with barium chloride (4.10^{-3} mol/L), compounds **4** and **8** were more active than nicardipine in 10^{-5} M concentration. Furthermore compounds **1** and **9** showed meaningfull activity compared with nicardipine. It can be said that introduction of the methyl groups into the hexahydroquinoline ring increases the mentioned activity. When the activity results were investigated with respect to the position of methyl groups in the hexahydroquinoline ring, no activity differences were found.

To investigate the activities on lamb carotid artery, the compounds possessing relaxant activity higher than 50% in isolated rat ileum were taken.

In lamb carotid artery preparations precontracted with barium chloride (67 mmol/L) studies, the activity of compounds **4, 8** and **9** was investigated in 10^{-5} M concentration. In this concentration,

compounds **4** and **8** were almost equipotent to nicardipine. These findings are in accordance with the results obtained from rat ileum. The activity results obtained are in accordance with the structure-activity relationships of these derivatives.

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