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Synthesis and in vitro calcium antagonist activity of 4-aryl-7,7-dimethyl/1,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione derivatives

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Abstract

In this study, a series of 4-aryl-7,7-dimethyl and 1,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-diones (**1**–**25**) were synthesized by condensing urea or *N*-methylurea with 5,5-dimethyl-1,3-cyclohexanedione and appropriate aromatic aldehydes according to the Biginelli reaction. The structures of the compounds were confirmed by spectral data and elementary analysis. The calcium antagonist activity of the compounds was tested in vitro on isolated rat ileum and lamb carotid artery. Compounds **16** and **19** were the most active derivatives on isolated rat ileum compared with the standard nicardipine. On isolated aortic strips of lamb the calcium antagonist activity of compound **16** (maximum relaxant effect: 38.83±5.84%) was found as high as that of nicardipine (maximum relaxant effect: 35.50±4.16%) used as a reference drug.
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Keywords: Condensed dihydropyrimidines; 1,2,3,4,5,6,7,8-Octahydroquinazoline-2,5-diones; Synthesis; Calcium antagonists

1. Introduction

Since the early 1980s, interest in 3,4-dihydropyrimidine-2(1*H*)-ones (DHPMs) has increased significantly due to the structural similarity of DHPMs to the well-known dihydropyridine calcium channel modulators of the Hantzsch type [1,2]. In recent years properly functionalized DHPMs have developed as calcium channel modulators, antihypertensive agents, α_{1a}-adrenergic antagonists, neuropeptide Y (NPY) antagonists and compounds that target the mammalian mitotic machinery [3–6]. In our previous studies, the synthesis and calcium antagonist activities of some new 4-aryl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline-2-one and 2-thione derivatives as condensed DHPMs have been described [7–10]. As a continuation of our program concerning condensed DHPMs we aimed to prepare a series of 4-aryl-7,7-dimethyl/1,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-diones in the hope of finding new and potent calcium antagonist agents and to identify the important functional groups in relation to calcium antagonist activity.

2. Chemistry

4-Aryl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione (**1**–**13**) and 4-aryl-1,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione derivatives (**14**–**25**) were prepared according to the Biginelli reaction [11] which involves one-pot condensation of urea, aromatic aldehyde and 5,5-dimethyl-1,3-cyclohexanedione under strongly acidic conditions (Fig. 1). Yields ranged from 19 to 69% (Table 1).

In our previous studies [12,13], the synthesis and molecular and crystal structure of the compounds **20** and **23** have been reported. In the present work, the calcium antagonist activity of these compounds is also included for comparison.

All compounds were characterized on the basis of their spectral data and elementary analysis (Tables 1 and

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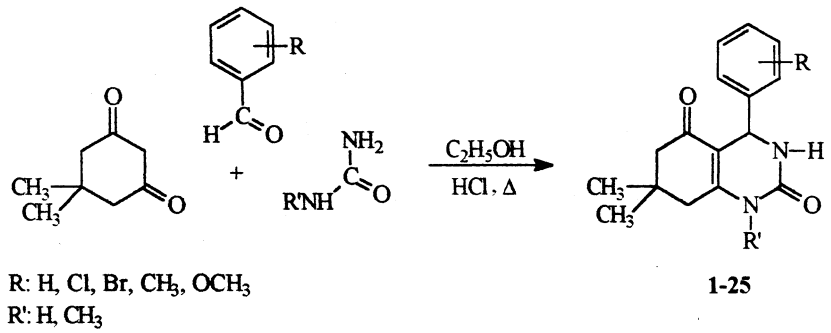
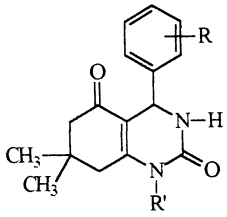


Fig. 1. Preparation of compounds **1**–**25**.

2). The UV spectra of the compounds showed two absorption bands at 295.2–310.0 and 210.6–224.0 nm regions. The IR spectra of the compounds displayed absorption bands characteristic for the N–H (3207–3290 cm^{-1}), 5-C=O (1674–1713 cm^{-1}) and 2-C=O (1594–1682 cm^{-1}) functions. Additionally disubstituted benzene deformation bands were observed in the expected wave number region.

In the ^{1}H NMR spectra, the formation of the octahydroquinazoline skeleton in this reaction was clearly demonstrated by the fact that the C-4 methine proton of compounds **1**–**25** appeared at δ 5.05–5.59

Table 1
Melting points, yields, molecular formula and elementary analysis of the compounds synthesized



Comp. No.	R	R′	M.p. (°C)	Yield (%)	Molecular formula	Elementary analysis (%)	
						Calc.	Found
1	-H		290–291	41.43	$C_{16}H_{18}N_2O_2$	C, 71.09; H, 6.71; N, 10.36	C, 71.67; H, 6.68; N, 10.66
2	**2**-Cl		282–283	55.78	$C_{16}H_{17}ClN_2O_2$	C, 63.05; H, 5.62; N, 9.19	C, 63.23; H, 5.49; N, 9.38
3	**3**-Cl		275–276	56.43	$C_{16}H_{17}ClN_2O_2$	C, 63.05; H, 5.62; N, 9.19	C, 63.19; H, 5.32; N, 9.09
4	**4**-Cl		> 300	49.21	$C_{16}H_{17}ClN_2O_2$	C, 63.05; H, 5.62; N, 9.19	C, 63.33; H, 5.08; N, 9.17
5	**2**-Br		263–264	51.55	$C_{16}H_{17}BrN_2O_2$	C, 55.03; H, 4.91; N, 8.02	C, 55.15; H, 5.47; N, 8.04
6	**3**-Br		274–275	41.81	$C_{16}H_{17}BrN_2O_2$	C, 55.03; H, 4.91; N, 8.02	C, 54.47; H, 5.01; N, 7.86
7	**4**-Br		> 300	44.10	$C_{16}H_{17}BrN_2O_2$	C, 55.03; H, 4.91; N, 8.02	C, 54.83, H, 4.63, N, 8.15
8	**2**-CH_3		240–241	36.57	$C_{17}H_{20}N_2O_2$	C, 71.81; H, 7.09; N, 9.85	C, 72.55; H, 6.92; N, 8.72
9	**3**-CH_3		266–267	23.21	$C_{17}H_{20}N_2O_2$	C, 71.81; H, 7.09; N, 9.85	C, 71.79; H, 6.98; N, 9.90
10	**4**-CH_3		> 300	39.38	$C_{17}H_{20}N_2O_2$	C, 71.81; H, 7.09; N, 9.85	C, 71.94; H, 7.26; N, 9.99
11	**2**-OCH_3		200–201	23.97	$C_{17}H_{20}N_2O_3$	C, 67.98; H, 6.71; N, 9.33	C, 67.52; H, 7.39; N, 8.86
12	**3**-OCH_3		247–248	33.96	$C_{17}H_{20}N_2O_3$	C, 67.98; H, 6.71; N, 9.33	C, 68.52; H, 6.33; N, 9.40
13	**4**-OCH_3		298–299	23.30	$C_{17}H_{20}N_2O_3$	C, 67.98; H, 6.71; N, 9.33	C, 68.53; H, 7.29; N, 9.55
14	H	CH_3	198–199	54.79	$C_{17}H_{20}N_2O_2$	C, 71.81; H, 7.09; N, 9.85	C, 71.51; H, 6.66; N, 9.68
15	**2**-Cl	CH_3	219–220	42.15	$C_{17}H_{19}ClN_2O_2$	C, 64.05; H, 6.01; N, 8.79	C, 63.92; H, 6.19; N, 8.55
16	**3**-Cl	CH_3	167–168	35.42	$C_{17}H_{19}ClN_2O_2$	C, 64.05; H, 6.01; N, 8.79	C, 64.16; H, 5.87; N, 8.52
17	**4**-Cl	CH_3	197–198	27.49	$C_{17}H_{19}ClN_2O_2$	C, 64.05; H, 6.01; N, 8.79	C, 63.45; H, 5.52; N, 8.52
18	**2**-Br	CH_3	236–237	56.29	$C_{17}H_{19}BrN_2O_2$	C, 56.21; H, 5.27; N, 7.71	C, 55.79; H, 4.80; N, 7.54
19	**3**-Br	CH_3	163–164	19.30	$C_{17}H_{19}BrN_2O_2$	C, 56.21; H, 5.27; N, 7.71	C, 55.85; H, 4.92; N, 7.48
20	**4**-Br	CH_3	174–175	62.19	$C_{17}H_{19}BrN_2O_2$	C, 56.21; H, 5.27; N, 7.71	C, 56.00; H, 5.18; N, 7.54
21	**2**-CH_3	CH_3	226–227	68.53	$C_{18}H_{22}N_2O_2$	C, 72.46; H, 7.43; N, 9.39	C, 72.20; H, 7.18; N, 9.15
22	**3**-CH_3	CH_3	165–166	31.33	$C_{18}H_{22}N_2O_2$	C, 72.46; H, 7.43; N, 9.39	C, 72.07; H, 7.07; N, 9.16
23	**4**-CH_3	CH_3	173–174	20.23	$C_{18}H_{22}N_2O_2$	C, 72.46; H, 7.43; N, 9.39	C, 72.00; H, 7.25; N, 9.12
24	**2**-OCH_3	CH_3	223–224	47.70	$C_{18}H_{22}N_2O_3$	C, 68.77; H, 7.05; N, 8.91	C, 67.73; H, 6.92; N, 8.61
25	**3**-OCH_3	CH_3	177–178	60.70	$C_{18}H_{22}N_2O_3$	C, 68.77; H, 7.05; N, 8.91	C, 68.56; H, 6.82, N, 8.72

Table 2
UV, IR and ^{1}H NMR spectral data of the compounds

Comp. No.	UV (MeOH) λ_{max} (log ε)	IR (KBr) υ (cm^{-1})	^{1}H NMR (DMSO-d_6) δ (ppm)
1	296.6 (3.81), 210.6 (3.81)	3259 (N–H), 1713 (C=O, ring), 1647 (C=O, urea)	0.90 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.11 (2H, q, CH_2-8), 2.35 (2H, q, CH_2-6), 5.16 (1H, d, $J = 2.80$ Hz, H-4), 7.19–7.36 (5H, m, hydrogens of the phenyl ring), 7.79 (1H, bs, N_3–H), 9.49 (1H, s, N_1–H)
2	296.4 (4.18), 215.6 (4.10)	3252 (N–H), 1703 (C=O, ring), 1645 (C=O, urea)	0.95 (3H, s, CH_3), 1.01 (3H, s, CH_3), 2.06 (2H, q, CH_2-8), 2.38 (2H, q, CH_2-6), 5.54 (1H, d, $J = 2.30$ Hz, H-4), 7.21–7.39 (4H, m, hydrogens of the phenyl ring), 7.69 (1H, d, $J = 2.20$ Hz, N_3–H), 9.53 (1H, s, N_1–H)
3	295.4 (3.94), 215.4 (4.04)	3247 (N–H), 1698 (C=O, ring), 1620 (C=O, urea)	0.90 (3H, s, CH_3), 1.05 (3H, s, CH_3), 2.11 (2H, q, CH_2-8), 2.40 (2H, q, CH_2-6), 5.16 (1H, d, $J = 2.90$ Hz, H-4), 7.17–7.39 (4H, m, hydrogens of the phenyl ring), 7.83 (1H, bs, N_3–H), 9.54 (1H, s, N_1–H)
4	296.0 (4.12), 220.2 (4.20)	3247 (N–H), 1709 (C=O, ring), 1645 (C=O, urea)	0.86 (3H, s, CH_3), 1.00 (3H, s, CH_3), 2.08 (2H, q, CH_2-8), 2.34 (2H, q, CH_2-6), 5.14 (1H, d, $J = 2.80$ Hz, H-4), 7.21–7.39 (4H, m, hydrogens of the phenyl ring), 7.80 (1H, d, $J = 2.80$ Hz, N_3–H), 9.52 (1H, s, N_1–H)
5	296.0 (4.07), 220.2 (4.15)	3260 (N–H), 1703 (C=O, ring), 1645 (C=O, urea)	0.90 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.05 (2H, q, CH_2-8), 2.38 (2H, q, CH_2-6), 5.55 (1H, d, $J = 2.44$ Hz, H-4), 7.10–7.50 (4H, m, hydrogens of the phenyl ring), 7.70 (1H, bs, N_3–H), 9.50 (1H, s, N_1–H)
6	295.2 (4.04), 215.4 (4.16)	3254 (N–H), 1698 (C=O, ring), 1620 (C=O, urea)	0.88 (3H, s, CH_3), 1.00 (3H, s, CH_3), 2.11 (2H, q, CH_2-8), 2.36 (2H, q, CH_2-6), 5.14 (1H, d, $J = 3.00$ Hz, H-4), 7.20–7.45 (4H, m, hydrogens of the phenyl ring), 7.82 (1H, bs, N_3–H), 9.54 (1H, s, N_1–H)
7	295.8 (4.06), 220.6 (4.15)	3250 (N–H), 1674 (C=O, ring), 1616 (C=O, urea)	0.86 (3H, s, CH_3), 1.00 (3H, s, CH_3), 2.08 (2H, q, CH_2-8), 2.34 (2H, q, CH_2-6), 5.12 (1H, d, $J = 2.90$ Hz, H-4), 7.14–7.54 (4H, m, hydrogens of the phenyl ring), 7.80 (1H, d, $J = 3.02$ Hz, N_3–H), 9.51 (1H, s, N_1–H)
8	298.6 (4.04), 214.6 (4.08)	3290 (N–H), 1699 (C=O, ring), 1594 (C=O, urea)	0.93 (3H, s, CH_3), 1.02 (3H, s, CH_3), 2.05 (2H, q, CH_2-8), 2.31 (2H, q, CH_2-6), 2.45 (3H, s, Ar–CH_3), 5.34 (1H, d, $J = 2.50$ Hz, H-4), 7.08–7.13 (4H, m, hydrogens of the phenyl ring), 7.64 (1H, bs, N_3–H), 9.43 (1H, s, N_1–H)
9	296.4 (4.03), 214.8 (4.07)	3254 (N–H), 1698 (C=O, ring), 1619 (C=O, urea)	0.85 (3H, s, CH_3), 1.00 (3H, s, CH_3), 1.95–2.40 (7H, m, CH_2-6, CH_2-8, Ar–CH_3), 5.10 (1H, d, $J = 3.01$ Hz, H-4), 6.90–7.25 (4H, m, hydrogens of the phenyl ring), 7.75 (1H, bs, N_3–H), 9.45 (1H, s, N_1–H)
10	296.0 (4.02), 216.4 (4.06)	3252 (N–H), 1712 (C=O, ring), 1682 (C=O, urea)	0.87 (3H, s, CH_3), 1.00 (3H, s, CH_3), 2.07 (2H, q, CH_2-8), 2.22–2.44 (5H, m, CH_2-6, Ar–CH_3), 5.09 (1H, d, $J = 2.80$ Hz, H-4), 7.10 (4H, s, hydrogens of the phenyl ring), 7.70 (1H, bs, N_3–H), 9.42 (1H, s, N_1–H)
11	297.6 (4.02), 220.6 (4.09)	3256 (N–H), 1708 (C=O, ring), 1681 (C=O, urea)	(3H, s, CH_3), 1.02 (3H, s, CH_3), 2.08 (2H, q, CH_2-8), 2.36 (2H, q, CH_2-6), 3.76 (3H, s, OCH_3), 5.39 (1H, d, $J = 2.50$ Hz, H-4), 6.80–7.21 (4H, m, hydrogens of the phenyl ring), 7.27 (1H, bs, N_3–H), 9.38 (1H, s, N_1–H)
12	296.2 (4.03), 219.8 (4.11)	3250 (N–H), 1698 (C=O, ring), 1620 (C=O, urea)	0.90 (3H, s, CH_3), 1.01 (3H, s, CH_3), 2.09 (2H, q, CH_2-8), 2.35 (2H, q, CH_2-6), 3.70 (3H, s, OCH_3), 5.11 (1H, d, $J = 3.10$ Hz, H-4), 6.77–7.26 (4H, m, hydrogens of the phenyl ring), 7.74 (1H, bs, N_3–H), 9.45 (1H, s, N_1–H)
13	296.8 (4.03), 224.0 (4.15)	3247 (N–H), 1712 (C=O, ring), 1615 (C=O, urea)	0.87 (3H, s, CH_3), 1.00 (3H, s, CH_3), 2.05 (2H, q, CH_2-8), 2.35 (2H, q, CH_2-6), 3.70 (3H, s, OCH_3), 5.05 (1H, d, $J = 2.80$ Hz, H-4), 6.85–7.15 (4H, m, hydrogens of the phenyl ring), 7.70 (1H, bs, N_3–H), 9.40 (1H, s, N_1–H)
14	305.8 (4.11), 210.6 (4.02)	3269 (N–H), 1689 (C=O, ring), 1606 (C=O, urea)	0.94 (3H, s, CH_3), 1.04 (3H, s, CH_3), 2.12 (2H, q, CH_2-6), 2.60 (2H, q, CH_2-8), 3.13 (3H, s, N–CH_3), 5.17 (1H, d, $J = 3.20$ Hz, H-4), 7.16–7.33 (5H, m, hydrogens of the phenyl ring), 8.01 (1H, d, $J = 3.20$ Hz, N_3–H)
15	307.8 (4.07), 215.4 (4.12)	3220 (N–H), 1687 (C=O, ring), 1620 (C=O, urea)	1.02 (3H, s, CH_3), 1.08 (3H, s, CH_3), 2.11 (2H, q, CH_2-6), 2.68 (2H, q, CH_2-8), 3.20 (3H, s, N–CH_3), 5.59 (1H, d, $J = 2.80$ Hz, H-4), 7.23–7.43 (4H, m, hydrogens of the phenyl ring), 7.95 (1H, d, $J = 3.10$ Hz, N_3–H)
16	305.6 (4.00), 215.4 (4.13)	3233 (N–H), 1683 (C=O, ring), 1626 (C=O, urea)	0.97 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.16 (2H, q, CH_2-6), 2.64 (2H, q, CH_2-8), 3.16 (3H, s, N–CH_3), 5.22 (1H, d, $J = 3.20$ Hz, H-4), 7.17–7.40 (4H, m, hydrogens of the phenyl ring), 8.10 (1H, d, $J = 3.40$ Hz, N_3–H)
17	305.6 (4.09), 220.4 (4.15)	3212 (N–H), 1694 (C=O, ring), 1630 (C=O, urea)	0.92 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.12 (2H, q, CH_2-6), 2.60 (2H, q, CH_2-8), 3.13 (3H, s, N–CH_3), 5.17 (1H, d, $J = 3.20$ Hz, H-4), 7.19–7.38 (4H, m, hydrogens of the phenyl ring), 8.05 (1H, d, $J = 3.50$ Hz, N_3–H)
18	307.8 (4.08), 215.6 (4.15)	3207 (N–H), 1695 (C=O, ring), 1626 (C=O, urea)	1.00 (3H, s, CH_3), 1.05 (3H, s, CH_3), 2.08 (2H, q, CH_2-6), 2.66 (2H, q, CH_2-8), 3.18 (3H, s, N–CH_3), 5.55 (1H, d, $J = 2.50$ Hz, H-4), 7.12–7.57 (4H, m, hydrogens of the phenyl ring), 7.92 (1H, d, $J = 2.80$ Hz, N_3–H)
19	305.8 (4.11), 215.8 (4.15)	3242 (N–H), 1685 (C=O, ring), 1631 (C=O, urea)	0.94 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.14 (2H, q, CH_2-6), 2.62 (2H, q, CH_2-8), 3.13 (3H, s, N–CH_3), 5.17 (1H, d, $J = 3.20$ Hz, H-4), 7.18–7.44 (4H, m, hydrogens of the phenyl ring), 8.06 (1H, d, $J = 3.40$ Hz, N_3–H)
20	305.8 (4.06), 220.4 (4.14)	3223 (N–H), 1692 (C=O, ring), 1632 (C=O, urea)	0.92 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.12 (2H, q, CH_2-6), 2.60 (2H, q, CH_2-8), 3.12 (3H, s, N–CH_3), 5.16 (1H, d, $J = 2.40$ Hz, H-4), 7.13–7.53 (4H, m, hydrogens of the phenyl ring), 8.05 (1H, d, $J = 3.50$ Hz, N_3–H)

Table 2 (*Continued*)

Comp. No.	UV (MeOH) λ_{max} (log ε)	IR (KBr) υ (cm^{-1})	^1H NMR (DMSO-d_6) δ (ppm)
21	310.0 (4.08), 214.6 (4.09)	3210 (N–H), 1694 (C=O, ring), 1626 (C=O, urea)	0.98 (3H, s, CH_3), 1.05 (3H, s, CH_3), 2.07 (2H, q, CH_2-6), 2.46 (3H, s, Ar–CH_3), 2.65 (2H, q, CH_2-8), 3.18 (3H, s, N–CH_3), 5.35 (1H, d, $J = 2.70$ Hz, H-4), 7.08 (4H, s, hydrogens of the phenyl ring), 7.88 (1H, d, $J = 2.80$ Hz, N_3–H)
22	307.2 (4.12), 214.8 (4.11)	3223 (N–H), 1685 (C=O, ring), 1631 (C=O, urea)	0.95 (3H, s, CH_3), 1.04 (3H, s, CH_3), 2.12 (2H, q, CH_2-6), 2.25 (3H, s, Ar–CH_3), 2.59 (2H, q, CH_2-8), 3.12 (3H, s, N–CH_3), 5.13 (1H, d, $J = 3.30$ Hz, H-4), 6.97–7.21 (4H, m, hydrogens of the phenyl ring), 7.97 (1H, d, $J = 2.80$ Hz, N_3–H)
23	307.8 (4.10), 216.0 (4.11)	3226 (N–H), 1686 (C=O, ring), 1633 (C=O, urea)	0.93 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.08 (2H, q, CH_2-6), 2.23 (3H, s, Ar–CH_3), 2.53 (2H, q, CH_2-8), 3.12 (3H, s, N–CH_3), 5.12 (1H, d, $J = 3.30$ Hz, H-4), 7.08 (4H, m hydrogens of the phenyl ring), 7.97 (1H, d, $J = 2.80$ Hz, N_3–H)
24	308.6 (4.11), 220.0 (4.14)	3217 (N–H), 1687 (C=O, ring), 1626 (C=O, urea)	0.95 (3H, s, CH_3), 1.05 (3H, s, CH_3), 2.10 (2H, q, CH_2-6), 2.65 (2H, q, CH_2-8), 3.15 (3H, s, N–CH_3), 3.75 (3H, s, Ar–OCH_3), 5.12 (1H, d, $J = 3.40$ Hz, H-4), 6.74–7.25 (4H, m, hydrogens of the phenyl ring), 7.50 (1H, d, $J = 3.04$ Hz, N_3–H)
25	305.8 (4.08), 219.6 (4.11)	3227 (N–H), 1685 (C=O, ring), 1645 (C=O, urea)	0.95 (3H, s, CH_3), 1.04 (3H, s, CH_3), 2.13 (2H, q, CH_2-6), 2.61 (2H, q, CH_2-8), 3.12 (3H, s, N–CH_3), 3.69 (3H, s, Ar–OCH_3), 5.15 (1H, d, $J = 3.40$ Hz, H-4), 6.74–7.25 (4H, m, hydrogens of the phenyl ring), 8.01 (1H, d, $J = 3.04$ Hz, N_3–H)

ppm as doublet. The signals of the N_3–H and N_1–H protons of compounds **1**–**13** appeared as one-proton singlets at δ 7.27–7.83 and δ 9.38–9.54 ppm, respectively. The proton on N_3-nitrogen atom might undergo slow exchange and the N_3–H signal was broadened in compounds **1**–**13** by the quadrupolar interaction with nitrogen. The coupling was observed in the signal due to hydrogen on C-4 atom and C-4 methine proton was split into a doublet by the N_3–H proton. These results are in accordance with the literature values [14,15]. ^1H NMR spectra of the compounds **14**–**25** revealed the absence of N_1–H signals; instead they exhibited three-proton singlets at δ 3.12–3.20 ppm assigned for the N_1–CH_3 protons of the octahydroquinazoline ring. The signals of the other protons were appeared at the expected chemical shifts and integral values.

NOE difference measurements of compound **23** has proved that methine proton H-4 has vicinal relationship with N_3–H and phenyl protons indicating the presence of a –CH(Ar)–NH– structure.

In the ^{13}C NMR spectra of the compounds **1**–**25** the most deshielded carbon atoms were C_5 (δ 192.45–193.27 ppm) and C_2 (δ 152.07–159.15 ppm) (Table 3). The chemical shifts of individual carbon atom were estimated using theoretical values given in literature [16] and all carbon atoms were seen at the expected chemical shift values. These assignments were further confirmed by means of a computer program (http://www.acdlabs.com/ChemSketch5.0Freeware).

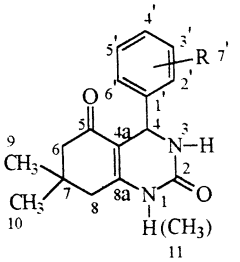
In the EI MS spectra of the compounds molecular ion peaks $[M]^{+\bullet}$ which appeared at different intensity confirmed the molecular weights of the compounds. The base peak was generally formed by the cleavage of the $R^\bullet$ or $C_6H_4R^\bullet$ radical from the molecular ion. In the cases of *o*-chlorophenyl or *o*-bromophenyl substitution, the $[M]^{+\bullet}$ peaks could not be seen in the spectra [17] (Scheme 1). The elementary analysis results of the compounds also supported the postulated structure.

All compounds have a chiral center and as stereoisomers may display quite different pharmacological behaviors [18], it seemed necessary to resolve the racemic mixtures to investigate the biological properties of each enantiomers. For example in DHPM series, it has been established that calcium modulation is dependent on the absolute configuration at C-4 aryl group [19]. Since DHPMs are readily available in racemic form through classical Biginelli dihydropyrimidine synthesis [1], we also examined the resolution of enantiomers on cellulose- and amylose-based chiral stationary phases. Chromatographic results have been published elsewhere [20].

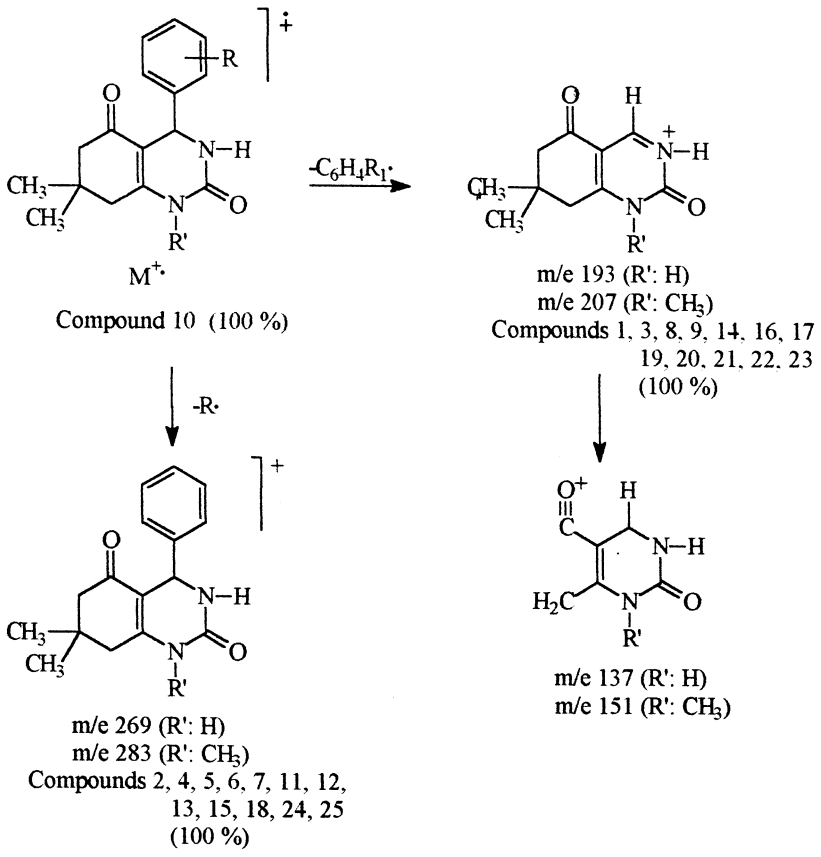
3. Experimental

Melting points were determined with a Thomas Hoover capillary melting point apparatus (Philadelphia, PA, USA) and are uncorrected. UV absorptions were measured on a Shimadzu UV-160A UV–Vis spectrophotometer (Shimadzu Co., Kyoto, Japan). The IR spectra were taken with a Perkin Elmer FT IR spectrophotometer 1720x (Beaconsfield, UK) (KBr disc). ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 MHz FT NMR spectrometer (Bruker, Karlsruhe, Germany) using tetramethylsilane as internal standard. All chemical shift values were recorded as δ (ppm). Mass spectra were taken with on a Finnigan MAT-GCQ mass spectrometer with electron ionization (EI) (Münster, Germany). The purity of the compounds were checked by thin-layer chromatography (Merck, silica gel, $HF_{254-361}$, Type 60, 0.25 mm). The elementary analysis of the compounds were performed on a Leco CHNS 932 analyzer (Leco Co., MI, USA) at the

Table 3
^{13}C NMR (DMSO-d_6) spectral data of the compounds **1**–**25**



Comp.	C_2	C_4	C_{4a}	C_5	C_6	C_7	C_8	C_{8a}	C_9	C_{10}	C_{11}	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	$C_{5'}$	$C_{6'}$	$C_{7'}$
1	152.32	51.93	107.39	192.81	49.80	32.24	40.34	151.87	26.82	28.69		144.56	126.17	127.06	128.25	127.06	126.17	
2	152.96	50.62	105.81	192.54	49.78	32.17	40.34	151.01	27.05	28.64		141.11	131.83	129.47	129.34	127.28	128.87	
3	152.71	51.58	106.78	192.83	49.72	32.20	39.50	151.65	26.78	28.58		144.88	124.77	132.78	126.12	130.23	126.99	
4	152.54	51.46	107.10	192.88	49.76	32.26	39.50	151.72	26.83	28.65		143.45	122.10	128.27	131.60	128.27	122.10	
5	152.87	51.80	106.21	192.45	49.78	32.15	39.52	150.90	27.12	28.54		142.81	132.63	129.14	129.10	122.21	127.96	
6	152.70	51.53	106.74	192.81	49.71	32.20	39.50	151.58	26.74	28.58		147.10	121.35	130.58	125.15	129.89	129.01	
7	152.45	51.49	106.94	192.76	49.73	32.16	39.50	151.61	26.80	28.56		143.92	120.02	128.39	131.09	128.39	120.02	
8	152.21	49.78	107.72	192.70	48.71	32.22	39.50	151.25	26.89	28.65		143.24	134.73	129.92	126.87	126.21	126.50	18.72
9	152.21	51.87	107.38	192.70	49.80	32.19	39.50	151.80	26.78	28.64		144.52	123.26	137.11	126.79	128.12	127.61	21.03
10	152.07	51.58	107.54	192.68	49.80	32.17	39.50	151.84	26.78	28.65		141.67	126.05	128.67	136.07	128.67	126.05	20.50
11	156.78	49.87	105.45	192.45	48.27	32.13	39.50	152.89	26.96	28.69		151.70	131.30	128.47	127.70	111.22	119.90	55.31
12	159.09	51.64	107.21	192.74	49.78	32.15	39.09	152.36	26.74	28.65		151.83	112.00	145.97	112.23	129.28	118.20	54.86
13	158.25	51.27	107.63	192.67	49.80	32.13	39.08	151.92	26.80	28.64		151.79	113.52	127.24	136.78	127.24	113.52	54.95
14	153.73	50.18	109.63	193.19	48.96	32.09	39.50	152.63	27.42	29.25	28.36	144.06	125.94	127.03	128.23	127.03	125.94	
15	154.45	49.09	107.87	192.79	48.84	32.02	39.50	151.61	27.62	29.15	29.15	140.64	131.91	129.43	128.99	127.28	128.88	
16	154.23	49.89	108.92	193.23	48.87	32.08	39.52	152.38	27.34	29.29	29.29	146.44	124.54	132.82	125.84	130.25	126.99	
17	153.94	49.73	109.20	193.14	48.87	32.04	39.50	151.40	27.36	29.25	29.25	143.02	127.81	128.17	131.56	128.17	127.81	
18	154.45	51.49	108.38	192.85	48.91	32.09	39.55	151.59	27.74	29.92	29.92	142.35	132.74	129.25	129.01	122.39	128.03	
19	154.27	49.87	108.90	193.27	48.87	32.08	39.50	152.36	27.33	29.31	29.31	146.66	121.44	130.60	124.92	129.92	128.87	
20	153.96	49.78	109.14	193.16	48.87	32.04	39.50	151.40	27.36	29.25	29.25	143.44	120.04	128.19	131.10	128.19	120.04	
21	153.71	48.93	109.76	193.07	47.32	32.13	39.50	151.87	27.53	29.11	29.11	142.66	134.82	129.98	126.94	126.25	126.25	18.72
22	153.72	50.13	109.61	193.16	48.96	32.09	39.50	152.60	27.38	29.24	29.24	144.01	122.97	137.15	126.61	128.16	127.63	21.03
23	153.56	49.82	109.78	193.10	48.94	32.06	39.50	152.63	27.36	29.20	29.20	141.13	125.79	128.70	136.07	128.70	125.79	20.48
24	156.94	48.94	107.45	192.81	47.20	32.08	39.50	152.47	27.60	29.15	29.15	152.34	130.69	128.54	127.67	111.20	119.86	55.37
25	159.15	49.89	109.49	193.21	48.96	32.08	39.09	153.89	27.36	29.24	29.24	152.67	111.98	145.52	112.03	129.34	117.98	54.86



Scheme 1. Fragmentation pathway of the compounds.

Scientific and Technical Research Council of Turkey, Instrumental Analyse Laboratory at Ankara.

*3.1. General procedure for the synthesis of 4-aryl-7,7-dimethyl/1,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-diones (**1**–**25**)*

A mixture of urea or *N*-methylurea (0.005 mol), benzaldehyde or substituted benzaldehyde (0.005 mol), 5,5-dimethyl-1,3-cyclohexanedione (1.107 g, 0.0075 mol) in abs. ethanol (20 ml) was treated with four drops of 37% HCl as catalyst and then refluxed for an appropriate period. The crude product, which precipitated on cooling, was filtered and washed with 50% ethanol. Then it was recrystallized several times from ethanol.

4. Pharmacology (calcium antagonist activity)

4.1. Studies on isolated rat ileum

Male and female albino rats weighing between 200 and 220 g were used in this study. Animals entered the test having fasted overnight. After the animals had been sacrificed by cervical dislocation, the ileum (10–15 cm terminal portion) was immediately removed, discarding the 5–8 cm segment proximal to the ilio-caecal junction. Segments 1.5–2 cm long were mounted vertically in a 10 ml organ bath containing Tyrode solution of the following composition (mM): NaCl: 136.87, KCl: 2.68, $CaCl_2$: 1.80, $MgSO_4$: 0.81, NaH_2PO_4: 4.16, $NaHCO_3$: 11.9, Glucose: 11.1. The bath contents were maintained at 37 °C and aerated by 95% O_2 and 5% CO_2.

A tension of 2 g was applied and isometric recording was done using an isometric transducer (T-FDT_{10}-A). Responses were recorded with a MAY TDA95 transducer data acquisition system.

The preparations were allowed to equilibrate for 60 min with regular washes every 15 min. In order to check for antagonistic effects, contractions were induced with barium chloride (4×10^{-3} mol/l, bath concentration). After thorough washing out, this process was repeated until the amplitude of the contraction became constant. The substances to be tested were investigated using the single-dose technique. Barium chloride contractions were induced after addition of the test substances at different concentrations (10^{-6}, 10^{-5} and 10^{-4} M) and 5 min exposure time. Only one compound was tested in each preparation. Because of solubility problems, the compounds were dissolved in dimethylsulfoxide (DMSO) and the control responses were taken after the addition of 0.1 ml DMSO.

Results were expressed as the percentage of the maximum relaxation of the contractions of the com-

pounds. The responses of the compounds were compared with the those of nicardipine. The data were expressed as mean ± SE Student's *t*-test was used for statistical analysis. *P* values < 0.05 were considered to be statistically significant.

4.2. Studies on lamb carotid artery

The carotid artery taken from lambs (Local Slaughter House, Eskişehir, Turkey) were cut in 3 mm ring preparations were fastened in an organ bath of 10 ml capacity which contains Tyrode solution in a gas of 95% O_2–5% 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 effects, contractions were induced with potassium chloride (67 mmol/l). After thorough washing out, this process was repeated until the amplitude of the contraction became constant. The substances to be tested were investigated using the single-dose technique. Potassium chloride contractions were induced after addition of the test substances at 10^{-4} M concentration and 10 min exposure time. Between administrations of the individual substances, the preparation was washed until the initial situation had been reestablished and the potassium chloride contractions were induced. The contractions were enrolled by 96 transducer data acquisition system.

5. Biological results and conclusions

Bioassay preparations such as isolated right (chronotropy) and left (inotropy) atria of guinea pig [21–23], rabbit portal vein, aortic strips of rabbit, isolated papillary muscle of guinea pig [24], guinea pig taenia coli in K^+-depolarizing Tyrode solution [25], isolated guinea pig ileum (Ba^{+2} stimulation) [24,26], isolated rat ileum (Ca^{+2} stimulation) [27], and radioligand binding method [28] are used for pharmacological screening tests of calcium antagonists. In the present preliminary assay, for determination of the effects of compounds **1**–**25** on smooth musculature, $BaCl_2$-stimulated ileum and KCl-stimulated arterial ring preparations were used. Nicardipine was included in all tests as the reference drug. The data obtained from these tests are shown in Table 4.

On $BaCl_2$-induced rat ileum, the maximum relaxation values of all compounds (**1**–**25**) were negligible when compared with those of nicardipine. Among the compounds tested, compounds **16** and **19**, carrying 3-Cl and

Table 4
The relaxant effects of nicardipine and the compounds for relaxant response on isolated rat ileum and lamb carotid artery ($n = 6$) [a]

Comp. No.	Relaxant effects on isolated rat ileum (%)			Relaxant effects on lamb carotid artery (%)
	10^{-6} M	10^{-5} M	10^{-4} M	10^{-4} M
1	0	0	14.83 ± 4.75	
2	0	20.40 ± 7.99	27.00 ± 6.20	
3	0	0	14.67 ± 3.82	
4	0	0	15.50 ± 2.04	
5	0	0	3.00 ± 1.43	
6	0	12.40 ± 5.05	34.83 ± 5.93	
7	0	0	19.50 ± 6.00	
8	0	0	8.33 ± 1.80	
9	0	0	8.33 ± 4.75	
10	0	22.33 ± 4.31	23.00 ± 4.47	
11	0	0	4.17 ± 2.04	
12	0	0	13.50 ± 4.18	
13	0	0	3.83 ± 1.79	
14	0	4.00 ± 1.99	11.00 ± 4.55	
15	0	7.17 ± 3.94	36.50 ± 6.72	
16	0	11.33 ± 3.94	68.67 ± 4.50	38.83 ± 5.84
17	0	0	45.50 ± 8.11	
18	0	0	11.00 ± 4.71	
19	0	12.83 ± 4.12	62.33 ± 6.77	0
20	0	12.83 ± 5.29	28.00 ± 6.04	
21	0	8.17 ± 4.01	15.67 ± 3.67	
22	0	0	34.50 ± 3.76	
23	0	11.67 ± 3.73	32.83 ± 5.37	
24	0	10.00 ± 3.71	20.17 ± 5.08	
25	0	0	11.17 ± 3.39	
Nicardipine [b]	100			35.50 ± 4.16

$P < 0.05$.
[a] *n* Refers to the number of heads used.
[b] Nicardipine showed a 71.50 ± 5.54% inhibition of $BaCl_2$-induced contractions at a concentration of 10^{-8} mol/l.

3-Br substituents on C-4 phenyl ring, are the most active derivatives on rat ileum at 10^{-4} M concentration with 68.67 ± 4.50 and $62.33 \pm 6.77\%$ of maximum relaxation, respectively. Both compounds were also tested on KCl-stimulated arterial ring preparations and compound **16** was found to be more potent (relaxant effect: $38.83 \pm 5.84\%$) than nicardipine (relaxant effect: $35.50 \pm 4.16\%$) (Table 4). But we could not observe any relaxant effect with compound **19**. Probably, compound **19** had only antispasmodic activity.

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