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Synthesis, structural elucidation and pharmacological properties of some 5-acetyl-3,4-dihydro-6-methyl-4-(substituted phenyl)-2(1*H*)-pyrimidinones

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Abstract

In this study, the synthesis of some new 5-acetyl-3,4-dihydro-6-methyl-4-(substituted phenyl)-2(1*H*)-pyrimidinones has been reported. The compounds were prepared by the Biginelli reaction of acetylacetone with aromatic aldehydes and urea. The structures of the compounds were characterized by UV, IR, ^{1}H NMR, ^{13}C NMR, mass spectra and elementary analysis. The calcium antagonistic activity of these compounds was tested in vitro on rat ileum precontracted with 4×10^{-3} M barium chloride.
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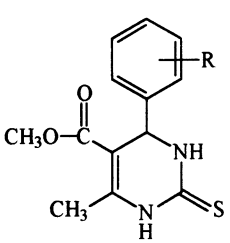
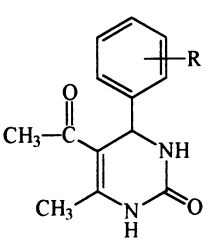
Keywords: Tetrahydropyrimidine-2-ones; Synthesis; UV, IR, ^{1}H and ^{13}C NMR, and mass spectra; Calcium antagonistic activity

1. Introduction

Calcium channel blockers have attained major significance in the therapy for cardiovascular diseases during the past few years [1,2]. It has been reported that some 1,2,3,4-tetrahydro-, 2-oxo- or 2-thioxo-1,2,3,4-tetrahydropyrimidine derivatives have vasodilator, antihypertensive and calcium channel blocker activities [3,4]. In our previous studies, the synthesis and calcium antagonistic activities of some 1,2,3,4-tetrahydro-6-methyl-4-(substituted phenyl)-2-thioxo-5-pyrimidinecarboxylic acid methyl esters (**I**) have been described [5,6]. In order to acquire further information on the structural characteristics enhancing calcium antagonistic activity in this series of compounds, we aimed to synthesize some new 5-acetyl-3,4-dihydro-6-methyl-4-(substituted phenyl)-2(1*H*)-pyrimidinone derivatives (**II**) and to test their calcium antagonistic activity.



(I)



(II)

2. Experimental

All chemicals used in this study were supplied by Merck (Darmstadt, Germany). Melting points were determined with a Thomas–Hoover capillary melting point apparatus and were uncorrected. UV absorptions were measured on a Shimadzu UV-160A UV–visible spectrophotometer. The IR spectra were taken with a Perkin–Elmer FT-IR spectrophotometer 1720x (KBr disc). ^{1}H NMR spectra were recorded on Bruker AC 80 and 200 MHz FT-NMR spectrometers using TMS as internal standard. ^{13}C NMR data were obtained with a Bruker DPX400, 400 MHz high performance digital ST-NMR spectrometer. All chemical shift values were

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recorded as δ (ppm). Mass spectra were taken on VG analytical 70-250 S and Finnigan MAT-GCQ mass spectrometers with electron ionization (EI) (Münster, Germany). The purity of the compounds was checked by thin-layer chromatography (Merck, silica gel, $HF_{254-361}$, type 60, 0.25 mm). Elemental analysis of the compounds was performed on a Leco CHNS 932 analyzer at the Scientific and Technical Research Council of Turkey, Instrumental Analysis Laboratory at Ankara.

2.1. Preparation of 5-acetyl-3,4-dihydro-6-methyl-4-(substituted phenyl)-2(1H)-pyrimidinones

A mixture of 1.50 g (0.015 mol) of acetylacetone, 0.60 g (0.01 mol) of urea and 0.01 mol of substituted benzaldehyde in 20 ml abs. ethanol was treated with four drops of 37% HCl as catalyst and then stirred at room temperature for a few hours. The crude product precipitated on cooling was filtered and washed with 50% ethanol, then it was recrystallized several times from ethanol.

The empirical formula of the compounds, melting points, reaction yields and elemental analysis data are shown in Table 1. Their structures were elucidated by spectral methods. UV, IR, and ^1H and ^{13}C NMR data of the compounds are shown in Tables 2 and 3.

2.2. Determination of calcium antagonist activity

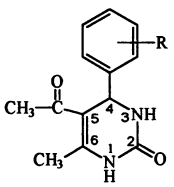
Male and female albino rats weighing between 200 and 220 g were used in this study. Animals entering the test fasted overnight. After the animals had been sacrificed by cervical dislocation, the ileum (10–15 cm terminal portion) was immediately removed, discarding the 5–8 cm segment proximal to the ilio–caecal 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 by using an isometric transducer (T-FDT_{10}-A). Responses were recorded through 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 activity, contractions were induced with barium chloride (4×10^{-3} M, bath concentration). After thorough washing, this process was repeated until the amplitude of the contraction became constant.

Investigation of the substances to be tested was performed using the single-dose technique. The barium

Table 1
Melting points, yields, empirical formula and elemental analyses of the synthesized compounds



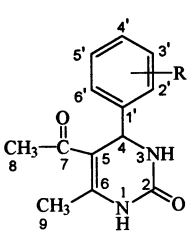
Comp.	R	M.p. (°C)	Yield (%)	Empirical formula	Elemental analysis					
					Calc. (%)			Found (%)		
					C	H	N	C	H	N
IIa [a]	–H	234–235	35.70	$C_{13}H_{14}N_2O_2$	72.87	6.59	13.07	72.95	6.46	12.93
IIb	2-Cl	257–258	32.11	$C_{13}H_{13}ClN_2O_2$	58.99	4.95	10.58	58.80	4.48	10.51
IIc	3-Cl	284–285	31.36	$C_{13}H_{13}ClN_2O_2$	58.99	4.95	10.58	58.99	4.02	10.54
IId [a]	4-Cl	215–216	36.64	$C_{13}H_{13}ClN_2O_2$	58.99	4.95	10.58	58.82	4.65	10.47
IIe	2-Br	222–223	24.58	$C_{13}H_{13}BrN_2O_2$	50.51	4.24	9.06	50.50	4.76	9.38
IIf	3-Br	220–221	28.46	$C_{13}H_{13}BrN_2O_2$	50.51	4.24	9.06	51.12	4.41	9.47
IIg	2-CH_3	218–219	33.57	$C_{14}H_{16}N_2O_2$	68.83	6.60	11.47	69.41	7.03	11.55
IIh	3-CH_3	253–254	39.30	$C_{14}H_{16}N_2O_2$	68.83	6.60	11.47	68.64	6.77	11.40
IIi	4-CH_3	228–229	37.66	$C_{14}H_{16}N_2O_2$	68.83	6.60	11.47	70.08	7.07	11.82
IIj [a]	2-OCH_3	251–252	29.58	$C_{14}H_{16}N_2O_3$	64.60	6.20	10.76	64.36	6.12	10.47
IIk	3-OCH_3	245–246	29.19	$C_{14}H_{16}N_2O_3$	64.60	6.20	10.76	64.27	5.59	10.66

[a] Compounds **IIa**, **IId** and **IIj** have been reported in the literature [7,8].

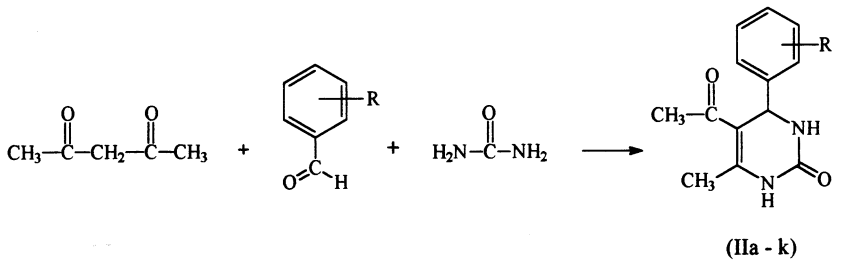
Table 2
UV, IR and ^{1}H NMR spectral data of the compounds

Comp.	UV_{max} (MeOH) (log ε)	IR (KBr) ν (cm^{-1})	^{1}H NMR (DMSO-d_6) δ (ppm)
IIa	300.5 (4.02), 218.0 (3.85)	3257 (N–H), 1703 (C=O, acetyl), 1675 (C=O, ring), 769, 706 (mono subst. benzene)	2.05 (3H, s, CH_3–CO), 2.28 (3H, s, CH_3), 5.26 (1H, d, *J* 3.41 Hz, H-4), 7.07–7.49 (5H, m, hydrogens of phenyl ring), 7.82 (1H, s, N_1–H), 9.16 (1H, s, N_3–H)
IIb	300.5 (3.87), 235.5 (3.69)	3247 (N–H), 1704 (C=O, acetyl), 1623 (C=O, ring), 757 (1,2-disubst. benzene)	2.18 (3H, s, CH_3–CO), 2.29 (3H, s, CH_3), 5.63 (1H, d, *J* 3.43 Hz, H-4), 7.06–7.55 (4H, m, hydrogens of phenyl ring), 7.74 (1H, s, N_1–H), 9.28 (1H, s, N_3–H)
IIc	300.5 (3.96), 234.5 (3.64)	3273 (N–H), 1703 (C=O, acetyl), 1615 (C=O, ring), 873, 800 (1,3-disubst. benzene)	2.07 (3H, s, CH_3–CO), 2.30 (3H, s, CH_3), 5.23 (1H, d, *J* 3.41 Hz, H-4), 6.99–7.54 (4H, m, hydrogens of phenyl ring), 7.89 (1H, s, N_1–H), 9.24 (1H, s, N_3–H)
IId	300.5 (4.03), 221.0 (4.04)	3288 (N–H), 1702 (C=O, acetyl), 1619 (C=O, ring), 839 (1,4-disubst. benzene)	2.15 (3H, s, CH_3–CO), 2.30 (3H, s, CH_3), 5.30 (1H, d, *J* 3.50 Hz, H-4), 7.10–7.50 (4H, m, hydrogens of phenyl ring), 7.85 (1H, s, N_1–H), 9.20 (1H, s, N_3–H)
IIe	300.2 (3.70), 235.0 (3.48)	3235 (N–H), 1704 (C=O, acetyl), 1624 (C=O, ring), 755 (1,2-disubst. benzene)	2.15 (3H, s, CH_3–CO), 2.30 (3H, s, CH_3), 5.25 (1H, d, *J* 3.50 Hz, H-4), 7.10–7.50 (4H, m, hydrogens of phenyl ring), 7.80 (1H, s, N_1–H), 9.20 (1H, s, N_3–H)
IIf	300.0 (3.66), 226.0 (3.51)	3281 (N–H), 1703 (C=O, acetyl), 1614 (C=O, ring), 876, 799 (1,3-disubst. benzene)	2.05 (3H, s, CH_3–CO), 2.30 (3H, s, CH_3), 5.60 (1H, d, *J* 3.40 Hz, H-4), 7.00–7.55 (4H, m, hydrogens of phenyl ring), 7.65 (1H, s, N_1–H), 9.20 (1H, s, N_3–H)
IIg	302.0 (3.96), 234.5 (3.73)	3241 (N–H), 1704 (C=O, acetyl), 1625 (C=O, ring), 752 (1,2-disubst. benzene)	2.10 (3H, s, CH_3–CO), 2.26 (3H, s, CH_3), 2.50 (3H, s, Ar–CH_3), 5.25 (1H, d, *J* 3.50 Hz, H-4), 6.80–7.50 (4H, m, hydrogens of phenyl ring), 7.80 (1H, s, N_1–H), 9.15 (1H, s, N_3–H)
IIh	300.5 (3.98), 233.5 (3.69)	3226 (N–H), 1702 (C=O, acetyl), 1594 (C=O, ring), 883, 785 (1,3-disubst. benzene)	2.08 (3H, s, CH_3–CO), 2.27 (6H, s, CH_3 and Ar–CH_3), 5.22 (1H, d, *J* 3.36 Hz, H-4), 6.81–7.38 (4H, m, hydrogens of phenyl ring), 7.77 (1H, s, N_1–H), 9.14 (1H, s, N_3–H)
IIi	299.0 (3.17), 218.4 (3.15)	3290 (N–H), 1700 (C=O, acetyl), 1619 (C=O, ring), 823 (1,4-disubst. benzene)	2.00 (3H, s, CH_3–CO), 2.26 (3H, s, CH_3), 2.55 (3H, s, Ar–CH_3), 5.21 (1H, d, *J* 3.51 Hz, H-4), 6.87–7.37 (4H, m, hydrogens of phenyl ring), 7.76 (1H, s, N_1–H), 9.15 (1H, s, N_3–H)
IIj	300.5 (3.98), 220.0 (4.00)	3274 (N–H), 1702 (C=O, acetyl), 1682 (C=O, ring), 762 (1,2-disubst. benzene)	2.01 (3H, s, CH_3–CO), 2.27 (3H, s, CH_3), 3.82 (3H, s, OCH_3), 5.57 (1H, d, *J* 3.30 Hz, H-4), 6.71–7.12 (4H, m, hydrogens of phenyl ring), 7.28 (1H, s, N_1–H), 9.13 (1H, s, N_3–H)
IIk	299.4 (3.36), 223.4 (3.39)	3273 (N–H), 1716 (C=O, acetyl), 1681 (C=O, ring), 757 (1,3-disubst. benzene)	2.04 (3H, s, CH_3–CO), 2.28 (3H, s, CH_3), 3.73 (3H, s, OCH_3), 5.22 (1H, d, *J* 3.39 Hz, H-4), 6.65–7.00 (3H, m, H-4, H-5 and H-6 of phenyl ring), 7.09–7.38 (1H, m, H-2 of phenyl ring), 7.76 (1H, s, N_1–H), 9.18 (1H, s, N_3–H)

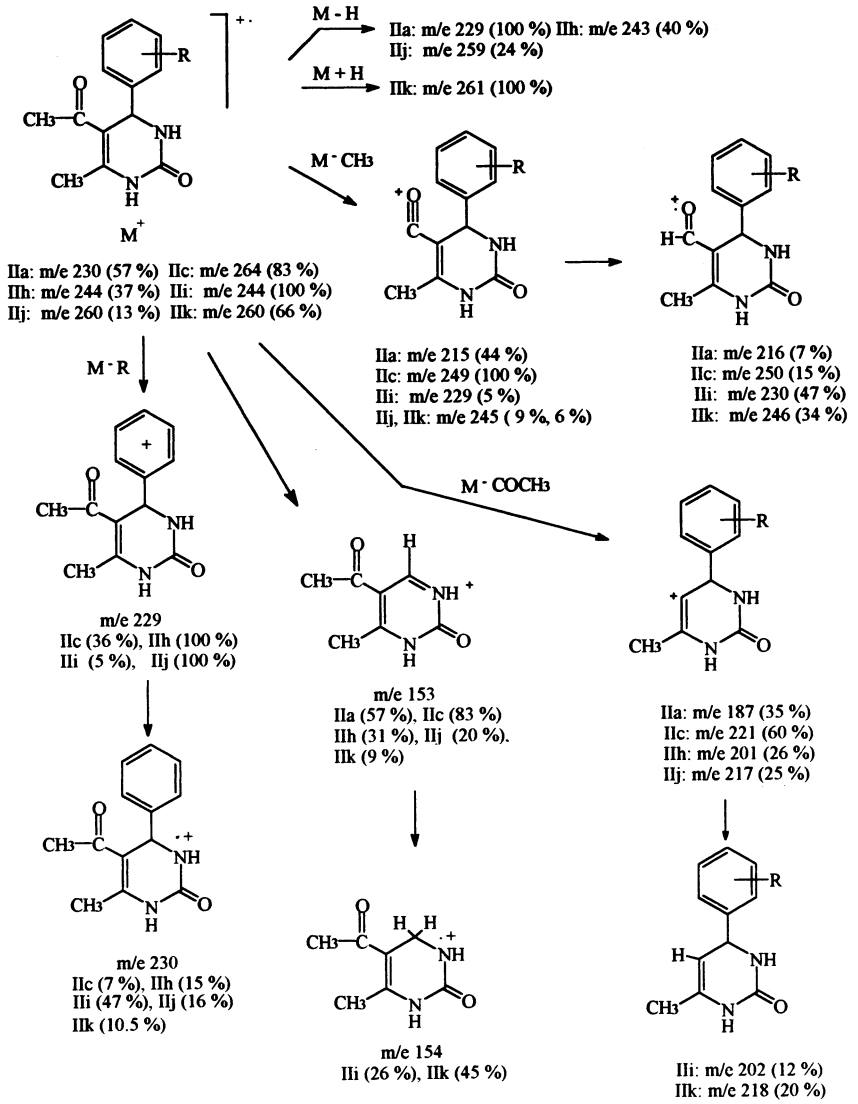
Table 3
^{13}C NMR (DMSO-d_6) spectral data of compounds **IIb** and **IIh**



Comp.	C_2	C_4	C_5	C_6	C_7	C_8	C_9	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	$C_{5'}$	$C_{6'}$	$C_{7'}$
IIb	149.55	49.64	106.50	125.92	192.03	16.90	28.13	138.88	146.80	129.89	127.36	126.57	127.69	–
IIh	152.94	54.76	110.40	124.36	195.18	19.73	22.02	145.10	129.30	148.81	128.85	138.40	127.89	31.11



Scheme 1.



Scheme 2. Fragmentation pathway of the compounds (**IIa**, **IIc**, **IIh–k**).

chloride contractions were induced after addition of the test substances at different concentrations (10^{-6}, 10^{-5} and 10^{-4} M) and 5 min of exposure time.

Only one compound was tested in each preparation. Because of the solubility problems, the compounds were dissolved in dimethylsulfoxide and the control responses were taken after the addition of 0.1 ml DMSO. Results are expressed as the percent of maximum relaxation of the contractions (Table 4).

Table 4
The relaxant effects of nicardipine and the compounds for relaxant response on isolated rat ileum (n = number of experiments)

Comp.	R	Concentration	Relaxant effects (%)
IIa	–H	10^{-4} ($n=6$)	16.17 ± 4.69
IIb	2-Cl	10^{-4} ($n=8$)	11.50 ± 2.97
IIc	3-Cl	10^{-4} ($n=8$)	13.88 ± 3.39
IId	4-Cl	10^{-4} ($n=8$)	19.75 ± 4.91
IIe	2-Br	10^{-4} ($n=8$)	23.75 ± 3.26
IIf	3-Br	10^{-4} ($n=8$)	16.38 ± 2.65
IIg	2-CH_3	10^{-4} ($n=8$)	17.50 ± 2.99
IIh	3-CH_3	10^{-4} ($n=8$)	11.50 ± 2.94
IIi	4-CH_3	10^{-4} ($n=8$)	19.13 ± 3.52
IIj	2-OCH_3	10^{-4} ($n=6$)	10.00 ± 4.26
IIk	3-OCH_3	10^{-4} ($n=8$)	11.13 ± 1.31
Nicardipine		10^{-8} ($n=6$)	71.50 ± 5.54

3. Results and discussion

The synthetic pathway employed in the preparation of 5-acetyl-3,4-dihydro-6-methyl-4-(substituted phenyl)-2(1*H*)-pyrimidinones is outlined in Scheme 1. The condensation of acetylacetone, substituted benzaldehyde and urea in abs. ethanol, catalyzed by HCl, proceeded according to the Biginelli reaction (Scheme 1) [9].

Compounds **IIa**, **IId** and **IIj** have been reported in the literature [7,8]. Since there were no pharmacological data available on these compounds, they have been synthesized to test their calcium antagonistic activity.

Although the compounds have an asymmetric center on the fourth position, their resolutions have not been done. The purity of the compounds was checked by thin-layer chromatography (silica gel $HF_{254+366}$, Merck). The structures of the compounds were confirmed by spectral data. All UV spectra showed two absorption maxima in the 218–235 and 299–302 nm regions, respectively. In the IR spectra all the compounds displayed strong absorption bands at 3290–3226 cm^{-1} (N–H), 1716–1700 cm^{-1} (C=O, acetyl) and 1682–1594 cm^{-1} (C=O, ring), respectively. Additionally, disubstituted benzene deformation bands were observed in the expected wave number regions. In the ^1H NMR spectra of the compounds the protons of the acetyl and methyl groups appeared as two singlets at about 2.00–2.18 and 2.26–2.30 ppm, respectively. The doublet appearing in the range 5.21–5.63 ppm confirmed the ring closure. The signals of the N_1–H and N_3–H protons appeared as a singlet at about 7.28–7.89 and 9.13–9.28 ppm. The phenyl protons were seen at the expected chemical shifts and integral values. In the ^{13}C NMR spectra of the compounds **IIb** and **IIh** the most shielded carbons are C_7 and C_2 (Table 3). The chemical shifts of C_7 and C_2 are 192.03 and 149.55 ppm for compound **IIb**, and 195.18 and 152.94 ppm for compound **IIh**, respectively.

The reported mass spectra data are in full agreement with the proposed structures (Scheme 2). The elemental analysis results of the compounds also supported the postulated structure.

The calcium antagonistic activity of the compounds **IIa–k** was evaluated in vitro by preventing $BaCl_2$-induced contractions in rat ileum [10,11] and then comparing with results of nicardipine activity under the same experimental conditions. As can be seen in Table 4, the maximum relaxation values of all these compounds were negligible when compared to those of nicardipine. Compound **IIe**, with a 2-bromo substituent, is the most active with $23.75 \pm 3.26\%$ of maximum relaxation. Compounds **IIi** and **IId**, carrying 4-methyl and 4-chloro substituents on the aromatic ring, respectively, have almost the same activity.

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