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Synthesis, structural characterization and myorelaxant activity of 4-naphthylhexahydroquinoline derivatives containing different ester groups

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Abstract: The present study reports the synthesis, structural characterization and myorelaxant activity evaluation of a series of 16 novel 4-naphthylhexahydroquinoline derivatives. The compounds were achieved by one-pot microwave-assisted method *via* a modified Hantzsch reaction. The structures of the compounds were confirmed by various spectral methods, such as IR, 1D and 2D NMR techniques and mass analysis. X-Ray studies of compound **10** provided further evidence for the proposed structure. To evaluate their myorelaxant activities, the E_{max} and pD_2 values of the compounds and nifedipine were determined on isolated rabbit gastric fundus smooth muscle strips. The obtained results indicated that the introduction of long chain alkyl groups, such as the 2-methoxyethyl or 2-(methacryloyloxy)ethyl moiety, to the ester group led to the most active compounds.

Keywords: 1,4-dihydropyridine; synthesis; myorelaxant activity; crystal structure, structure elucidation.

INTRODUCTION

Dihydropyridines (DHPs) represent low molecular weight heterocyclic compounds based on a pyridine core. Although theoretically five isomeric DHPs could exist, the most recognized ones have the 1,4-dihydro structure.[1] 1,4-Dihydropyridines are one of the most important chemical classes introduced into bio-

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logical sciences and are common in many commercialized drugs. These compounds mainly present a well-known capacity as calcium channel blockers, thus acting as vital drugs against cardiovascular diseases, particularly hypertension and angina pectoris.[2] Although DHPs were primarily developed as cardiovascular agents, medicinal chemists decorated the 1,4-DHP nucleus and achieved diverse activities at several receptors, channels and enzymes with different medical applications, such as antitubercular, antioxidant, antitumor, antithrombotic, antimicrobial, antidiabetic, antidyslipidemic and anticonvulsant.[3]

Since their introduction into clinical medicine, 1,4-DHPs have been one of the most studied class of drugs and many modifications have been performed on the structure of nifedipine, the prototype of DHPs, in order to enhance calcium modulating effects and obtain structure–activity relationships (SAR). According to SAR studies, a 1,4-DHP ring with an unsubstituted nitrogen and pseudoaxial oriented aryl ring substituent at C-4 are essential for activity.[4] Ester functionalities at C-3 and C-5 position are of utmost importance to modulate the activity and tissue selectivity. It was proved that modification of the ester moiety plays a key role in the ability of condensed 1,4-DHPs to block calcium currents.[5] Fused DHPs, such as hexahydroquinolines, that could be obtained by introducing the DHP ring into condensed ring systems, are active derivatives exhibiting calcium antagonistic effects.[6]

The classical method for the synthesis of 1,4-DHPs is a one-pot Hantzsch reaction, which proceeds effectively and involves dehydrative coupling of an aldehyde, two equivalents of a 1,3-dicarbonyl compound and ammonia.[7] Depending on the reagents and reaction conditions, long reaction times, unexpected products or low yields can be obtained.[8] Although most of the efforts focused on improving the reaction using various catalysts, such as Fe_3O_4, cobalt and ytterbium,[9–11] microwave (MW) irradiation has recently gained great popularity as an energy source for Hantzsch reactions because of its ability to reduce reaction times, to improve yields and to simplify the work-up processes.[12]

In the present study, sixteen DHP derivatives in which substituted cyclohexane rings were fused to the DHP ring under microwave irradiation were synthesized and how different ester groups and the naphthyl moiety attached to this backbone affected the myorelaxant activities of these compounds was investigated to obtain additional information to enrich the classical SAR studies.

EXPERIMENTAL

General

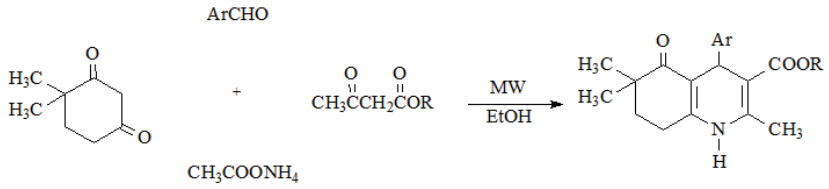
All chemicals used in this study were purchased from Aldrich and Fluka (Steinheim, Germany). The reactions were performed in a Discover microwave apparatus (CEM). Thin layer chromatography (TLC) was run on Merck aluminum sheets (Darmstadt, Germany), silica gel 60 F_{254}, mobile phase ethyl acetate–hexane: (1:1) and ultraviolet (UV) absorbing spots were detected by short wavelength (254 nm) UV light (Camag UV Cabinet, Wiesloch,

Germany). Melting points were determined on a Thomas Hoover capillary melting point apparatus (Philadelphia, PA, USA) and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Spectrum BX FT-IR instrument (Beaconsfield, UK) and are reported in cm^{-1}. The ^{1}H-NMR spectra were obtained in dimethyl sulfoxide (DMSO) solutions on a Varian Mercury 400, 400 MHz high performance digital FT-NMR spectrometer (Palo Alto, CA, USA). ^{13}C-NMR and COSY (2D-^{1}H–^{1}H homonuclear correlation spectrum) spectra were recorded on the same instrument. The chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane. The X-ray crystallographic analysis was realized on an Agilent Xcalibur (Ruby, Gemini) diffractometer. The ESI-MS spectra were measured on a micromass ZQ-4000 single quadruple mass spectrometer. Elemental analyses were performed on a Leco CHNS-932 Elemental Analyzer (Philadelphia, PA, USA).

Analytical, physical and spectral data of the synthesized compounds are given in Supplementary material to this paper.

Chemistry

The general procedure for the preparation of alkyl 2,6,6-trimethyl-4-(1-naphthyl/2-naphthyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylates (compounds **1**–**16**) was as follows: a one-pot four component mixture of 2 mmol 4,4-dimethyl-1,3-cyclohexanedione, 2 mmol of 1- or 2-naphthaldehyde, 2 mmol of an appropriate alkyl acetoacetate and 10 mmol of ammonium acetate was placed into a 35-mL microwave pressure vial and heated under microwave irradiation (power 50 W, maximum temperature 120 °C) for 5 min. in 5 mL ethanol. After completion of the reaction, monitored by TLC, the reaction mixture was poured into ice–water and the obtained precipitate was filtered and crystallized from ethanol–water. The synthetic route used to synthesize the target compounds is outlined in Fig. 1.



Ar: 1-Naphthyl (Compounds **1**-**8**), 2-Naphthyl(Compounds **9**-**16**)

R: CH_3 (Compounds **1**, **9**), C_2H_5 (Compounds **2, 10**), $CH(CH_3)_2$ (Compounds **3, 11**), $CH_2CH(CH_3)_2$ (Compounds **4, 12**), $C(CH_3)_3$ (Compounds **5, 13**), $CH_2CH_2OCH_3$ (Compounds **6, 14**), $CH_2CH_2OCOC(=CH_2)CH_3$ (Compounds **7, 15**), $CH_2C_6H_5$ (Compounds **8, 16**)

Fig. 1. Synthesis of compounds **1–16**.

X-Ray crystallography

Computing details. Data collection: CrysAlis PRO,[13] cell refinement: CrysAlis PRO,[13]; data reduction: CrysAlis PRO.[13] Program(s) used to solve and refine the structure: SHELXS97.[14] Program(s) used for molecular graphics and to prepare the material for publication: SHELXTL.[14]

Refinement. Carbon-bound H-atoms were placed in calculated positions (C–H, 0.93–0.98 Å) and were included in the refinement in the riding-model approximation, with U_{iso}(H) = = 1.2U_{eq}(C) or 1.5 U_{eq}(C-methyl). A rotating-group model was applied for the methyl groups.

The N-bound H-atoms were located in a difference Fourier map but were refined with a distance restraint: N–H = 0.83 (1) Å with $U_{iso}(H) = 1.2U_{eq}(N)$.

Pharmacology

New Zealand white rabbits, weighing 2.5–3 kg, were used in this study. The rabbits were sacrificed with i.v. injection of sodium pentobarbital (30–40 mg kg^{-1}), followed by removal of the stomach through abdominal incision. The fundal part of the stomach was then dissected parallel to the longitudinal muscle wall. One muscle strip about 15–20 mm length and 2 mm width was obtained and allowed to equilibrate for 60 min in 20 mL organ baths filled with calcium (Ca^{2+}) free Krebs–Henseleit solution (KHS). The composition of the Krebs solution was as follows (in mmol L^{-1}): NaCl 118; KCl 4.7; $NaHCO_3$ 25; $MgCl_2$ 0.54; $NaHPO_4$ 0.9; glucose 11. The solution was gassed with 95 % O_2 and 5 % CO_2 during the study and temperature was maintained at 37 °C by a thermoregulated water circuit. The pH of the saturated solution was 7.4. Each strip was connected to a force transducer (FDT 10-A, May IOBS 99, COMMAT Iletisim Co., Ankara, Turkey) for measurement of the isometric force, which was continuously displaced and recorded on an online computer *via* a four-channel transducer data acquisition system (MP30B-CE, BIOPAC Systems Inc., Santa Barbara, CA) using software (BSL PRO v. 3.6.7, BIOPAC Systems Inc.) which also had the capacity to analyze the data. After mounting, each strip was allowed to equilibrate with a basal tension of 1 g for 60 min. Ca^{2+} free KHS was replaced with fresh solution every 15 min during this time. N^{ω}-nitro-L--arginine methyl ester hydrochloride (L-NAME, a nitric oxide synthase inhibitor, 10^{-4} M), indomethacin (COX inhibitor, 10^{-5} M), tetraethylammonium chloride (Ca^{2+}-activated K^+ channel blocker, 10^{-4} M), glibenclamide (ATP-sensitive K^+ channel blocker, 10^{-6} M) and guanethidine (adrenergic nerve blocker, 10^{-6} M) were added into the organ bath 20 min before the compounds were added in order to eliminate the effects of nitric oxide, cyclooxygenase, Ca^{2+}-activated K^+ channel, ATP sensitive K^+ channel and adrenergic pathways, respectively.

After the smooth muscle strips of rabbit gastric fundus had been placed in a high K^+--containing (80 mM) solution, 2.5 mM Ca^{2+} was added to the organ bath to develop contraction. Concentration–relaxation responses for the compounds **1**–**16** (10^{-8}–3×10^{-4} M) and nifedipine (10^{-9}–10^{-6} M) were obtained by adding these into the bath in a cumulative manner. A cumulative concentration–response curve was constructed in a stepwise manner after the response to the previous concentration had reached a plateau. The relaxant effects of the compounds and nifedipine were expressed as percentage of the precontraction with 2.5 mM Ca^{2+} in the high K^+ containing solution. DMSO, used in activity studies as solvent, was also tested.

To evaluate the effects of the compounds, the maximum response (E_{max}) values of compounds and nifedipine were established at 3×10^{-4} M and 10^{-6} M concentrations, respectively and pD_2 values (the negative logarithm of the concentration for the half-maximal response (EC_{50})) were calculated, as predicted from the Scatchard equation for drug–receptor interaction. Agonist pD_2 values (apparent agonist affinity constants) were calculated from each agonist concentration–response curve by linear regression of the linear part of the curve and taken as a measure of the sensitivity of the tissues to each agonist. While E_{max} is the parameter for efficacy, pD_2 is the parameter for potency. All data are expressed as mean ± standard error. Statistical comparison between groups were performed using general linear models by the Scheffe *F*-test and *p* values less than 0.05 were considered to be statistically significant.

The study was approved by the Gazi University Ethics Committee. Procedures involving animals and their care were conducted in conformity with international laws and policies.

L-NAME hydrochloride, indomethacin, guanethidine, nifedipine, glibenclamide, and tetraethylammonium chloride were supplied by Sigma. While L-NAME, tetraethylammonium

chloride and guanethidine were dissolved in distilled water, indomethacin, glibenclamide, nifedipine and the compounds were dissolved in DMSO.

RESULTS AND DISCUSSION

Chemistry

A series of condensed 4-naphthyl-1,4-DHP derivatives were prepared *via* a modified Hantzsch reaction. In order to obtain the target compounds, 4,4--dimethyl-1,3-cyclohexanedione, 1-naphthaldehyde/2-naphthaldehyde, an appropriate alkyl acetoacetate were heated in the presence of excess ammonium acetate under microwave irradiation in ethanol, which was classified as an excellent microwave-absorbing solvent.[15,16]

The appearance of the products was monitored by TLC and the reaction time was determined as 5 min., which is quite a short time compared to conventional heating for the Hantzsch reaction.[17,18]

The structures and chemical characteristics of the synthesized compounds are reported in Table S-I of the Supplementary material.

The structures of the synthesized compounds were elucidated by spectral methods (IR, ^{1}H-NMR, ^{13}C-NMR, COSY, X-ray analysis and mass spectra) and confirmed by elemental analysis. In the IR spectra, characteristic N–H, C=O (ester) and C=O (ketone) stretching bonds were observed. In the ^{1}H-NMR spectra, the protons of the methyl substituents at the 6-position of the hexahydroquinoline ring were observed separately and as singlets at 0.73–0.99 ppm. The methylene groups of the same ring were at 1.57–2.57 ppm. The methine protons of the 1,4-DHP ring were seen as a singlet at 4.96–5.63 ppm. The aromatic protons of the naphthyl and phenyl rings were at 6.91–8.73 ppm, while the N–H protons of the DHP ring were seen at 9.02–9.21 ppm. In the ^{13}C-NMR spectra, the number of the signals fitted exactly the number of carbon atoms. The correlations between the interacting protons of compound **2** were determined by COSY. The correlations between H-7 and H-8, CH_2 and CH_3 protons in the ester side chain and H-4 and the aromatic protons were observed. These correlations are demonstrated in Fig. 2 and the COSY spectrum is provided as Supplementary material. Based on this information; the structure of compound **2** was conclusively identified as ethyl 2,6,6-trimethyl-4-(1-naphthyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate.

The mass spectra of the compounds were recorded *via* the electrospray ionization technique. The quasimolecular ions created by the addition of sodium ion $[M+Na]^+$ and also of a hydrogen cation $[M+1+Na]^+$ were observed in the spectra of all compounds. Cleavage of the ester group and the naphthyl ring from the parent molecule were the next most observed fragmentations.

Elemental analysis results were within ±0.4 % of the theoretical values for all compounds.

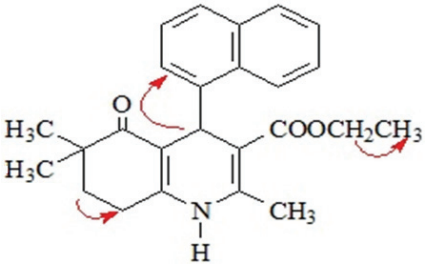


Fig. 2. COSY correlations of compound **2**.

*X-Ray analysis of compound **10***

The three-dimensional structure of ethyl 2,6,6-trimethyl-4-(2-naphthyl)-5--oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**10**) was evaluated by X-ray crystallography (Fig. 3).

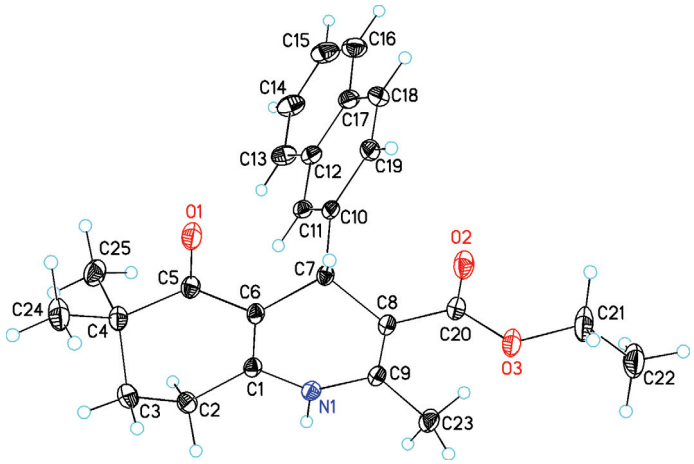


Fig. 3. X-Ray molecular structure of compound **10** with the atom-numbering scheme used in the crystallographic analysis.

The crystal data and a summary of intensity data collections and structural refinements, selected bond lengths, bond angles and torsion angles are given in the Supplementary material.

In compound **10** (Fig. 3), the naphthalene ring is almost planar with a maximum deviation from the mean plane of –0.029(2) Å for atom C(17). The cyclohexene rings adopt a sofa conformation and are puckered with puckering parameters[19] of Q_T = 0.4383(17) Å, θ = 50.6(2)°, φ = 127.6(3)°. The values of the bond lengths[20] and angles in the title compound are within the normal ranges and are comparable with those of related relationships.[21–23] The X-ray crystallographic data of the title compound demonstrated that there are intra- and intermolecular hydrogen bonds. In the crystal, molecules are linked by pairs of intermolecular N–H···O hydrogen bonds, forming dimers with $R_1^2(6)$ ring motifs,[24,25] and

these dimers are connected by N–H···O hydrogen bonds, generating one-dimensional chains along [011] (Supplementary material).

Pharmacology

The maximum relaxant effects (E_{max}) and pD_2 values of compounds **1**–**16**, DMSO and nifedipine on isolated strips of rabbit gastric fundus smooth muscle are given in Table I.

TABLE I. Maximum relaxant responses (E_{max}) and pD_2 values of the compounds, nifedipine and DMSO on strips of rabbit gastric fundus smooth muscle; the relaxation is expressed as the percentage of the precontraction induced by 2.5 mM Ca^{2+}. The negative logarithm of the concentration for the half-maximal response (pD_2) and E_{max} values represent mean value ± *SEM*; $p < 0.05$ compared with the control responses, $n = 6$

Compound	E_{max}	pD_2
1	81.20±10.26	5.42±0.71
2	82.78±8.98	5.53±0.65
3	77.42±4.71	4.63±0.37
4	45.52±9.10	4.92±0.66
5	53.32±7.53	5.00±0.57
6	93.54±9.31	5.56±0.67
7	91.83±5.29	4.95±0.42
8	43.17±5.97	5.39±0.47
9	63.93±5.90	4.52±0.47
10	42.30±4.67	5.31±0.37
11	50.42±10.01	4.37±0.70
12	36.88±5.96	6.09±0.47
13	48.90±10.41	5.37±0.71
14	92.68±8.15	4.67±0.61
15	91.50±5.94	5.07±0.47
16	21.94±3.68	6.34±0.26
Nifedipine	100.00±2.18	8.33±0.04
DMSO	11.35±2.25	6.31±0.05

Tissues were pretreated with indomethacin, guanethidine, L-NAME, tetraethylammonium chloride and glibenclamide to investigate whether the relaxation induced by the compounds occurred through cyclooxygenase, the adrenergic system, nitric oxide pathways, Ca^{2+}-activated K^+ channel and ATP-sensitive K^+ channel, respectively. Pretreatment of the strips with indomethacin, guanethidine, L-NAME, tetraethylammonium chloride and glibenclamide confirmed that cyclooxygenase, adrenergic and nitric oxide pathways, Ca^{2+}-activated K^+ channel and ATP-sensitive K^+ channel played no roles on the relaxations evoked by these substances.

The results of this study indicate that all of the compounds (10^{-8}–3×10^{-4} M) and nifedipine (10^{-9}–10^{-6} M) produced concentration-dependent relaxation on the rabbit gastric fundus smooth muscle strips that were statistically significant

from the control relaxations produced by DMSO. The compounds and nifedipine exerted concentration-dependent relaxation responses on the gastric fundus smooth muscle strips precontracted with Ca^{2+} (2.5 mM) with the efficacy order: nifedipine ≥ **6** ≥ **14** ≥ **7** = **15** > **2** ≥ **1** ≥ **3** > **9**≥ **5** ≥ **11** ≥ **13** ≥ **4** ≥ **8** ≥ **10** ≥ **12** > **16**.

The efficacy of compounds **6**, **7**, **14** and **15** were found to be the same as nifedipine. The obtained results suggested that myorelaxant effects of the compounds seem to exert their effects by blocking Ca^{2+} channels as does nifedipine.

Given that the main difference between these compounds is their ester groups, it follows that the ester moiety plays a key role in the ability of these compounds to block calcium channels.

Increasing the side chain length of the ester group mediated an increase whereas introducing a ring structure at the same locus did not lead to a significant improvement in blocking the activity. The introduction of a 2-(methacryloyloxy)ethyl or 2-methoxyethyl group as the side chain of the ester group resulted in a series of highly active compounds.

Two methyl groups at the 6-position of the hexahydroquinoline ring are present in all compounds and therefore they are not the most critical components for the preferential activity. When the obtained results are analyzed in terms of the substitution position of the naphthyl ring at the C-4 position of DHP, generally the 1-naphthyl derivatives possessed better activities. Although all compounds are potent myorelaxant agents on the gastric fundus smooth muscle strips, introduction of a naphthalene substituent into the 4-position of the 1,4-DHP nucleus decreased the myorelaxant effect of the compounds compared to nifedipine. This could suggest that the substitution of an *o*-nitrophenyl ring by a naphthyl ring increases the size of the molecules and may have a negative effect on the ability of these compounds to show their effects. As a result, the naphthyl ring could be a good choice as the aromatic substituent at the C-4 position of DHP only in combination with long chain alkyl esters.

CONCLUSIONS

An easy, very rapid and convenient method for the preparation of condensed 1,4-DHPs under MW irradiation was reported. The target compounds were achieved by the reaction of 4,4-dimethyl-1,3-cyclohexanedione, 1-naphthaldehyde/2-naphthaldehyde, an appropriate alkyl acetoacetate and ammonium acetate in ethanol. This method also offers a reduction of solvent use and reaction time in addition to higher yields.

The obtained pharmacological results showed that all the synthesized compounds had relaxing effects on isolated rabbit gastric fundus smooth muscle, possibly due to the blockade of the Ca^{2+} channels, similar to the action of nifedipine. The introduction of long chain alkyl groups, such as the 2-methoxyethyl or 2-(methacryloyloxy)ethyl moiety to the ester group led to the most active com-

pounds, suggesting that two hydrogen bond acceptor groups might be required for the calcium channel blocking activity. It was also proved that there is no contribution of cyclooxygenase, adrenergic and nitric oxide pathways, ATP-sensitive K^+ channels and Ca^{2+}-activated K^+ channels to the myorelaxant effects of the compounds. As a result, further investigations are required to ascertain the Ca^{2+} channel blockage effects of the compounds.

SUPPLEMENTARY MATERIAL

Data on the characterization of the synthesized compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

СИНТЕЗА, СТРУКТУРНА КАРАКТЕРИЗАЦИЈА И МИОРЕЛАКСНТНА АКТИВНОСТ ДЕРИВАТА 4-НАФТИЛХЕКСАХИДРОХИНОЛИНА КОЈИ САДРЖЕ РАЗЛИЧИТЕ ЕСТАРСКЕ ГРУПЕ

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Приказана је синтеза, структурна карактеризација и миорелаксантна активност серије од 16 нових деривата 4-нафтилхексахидрохинолина. Једињења су синтетисана у једном реакционом кораку под микроталсним озрачивањем, модификованом Ханчовом реакцијом. Структуре једињења одређене су на основу спектралних података ИЦ, 1D и 2D NMR спектроскопије и масене спектрометрије. Анализом рендгенске структуре монокристала деривата **10** додатно је потврђена предложена структура једињења. Током испитивања миорелаксантне активности одређене су E_{max} и pD_2 вредности испитиваних једињења и нифедипина, на исечцима глаткомишићних ћелија желудачног дна зеца. Добијени резултати указују на допринос алкил-група дугог ланца, као што су 2-метокси-етил или 2-(метакрилоилокси)етил-естара, доброј активности.

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