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Design, Synthesis, and Calcium Channel Antagonist Activity of New 1,4-Dihydropyridines Containing 4-(5)-Chloro-2-ethyl-5-(4)-imidazolyl Substituent

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A series of dialkyl, dicycloalkyl, and diaryl ester analogues of nifedipine, in which the *ortho*-nitro phenyl group at position 4 is replaced by the 4-(5)-chloro-2-ethyl-5-(4)-imidazolyl substituent, were synthesized and evaluated as calcium channel antagonists using the high K^+ contraction of guinea pig ileal longitudinal smooth muscle. The results for the symmetrical ester series showed that increasing the length of the chain in C_3- and C_5-ester substituents increased the activity and the most active compound was the diphenylethyl ester derivative, so it was more active than the reference drug nifedipine. In unsymmetrical diester series, when R^1 is methyl or ethyl, increasing lipophilic properties in the R substituent, increased the activity. The most active compounds were methyl/phenethyl and ethyl/phenethyl ester derivatives, being slightly more active than nifedipine.

Keywords: Calcium channel blockers / Dihydropyridines / Chloroimidazole / Nifedipine analogues

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Introduction

The development of 4-aryl-1,4-dihydropyridines (DHPs), related to the first generation calcium antagonist nifedipine, as therapeutic agents for the treatment of cardiovascular disorders [1, 2] has stimulated many structure-activity relationship studies [3]. Changes in the substitution pattern at the C-3, C-4, and C-5 positions of nifedipine alter potency [3], tissue selectivity [4, 5], and the conformation of the DHP ring [6]. One of the structural requirements is that the substituted aromatic ring occupies an axial position perpendicularly bisecting the boat-like DHP ring with the substituent in a *syn*-periplanar orientation. A *syn-cis*-carbonyl ester orientation with respect to the olefinic double bond is also needed for a high activity [7, 8]. It is possible to replace the phenyl ring on the C-4 position with some heterocyclic rings [9 – 11]. In previous studies we showed that a C-4 imidazolyl substituent was isosteric with a nitrophenyl substituent and they were potent calcium channel blocker [12 – 15]. We now describe the synthesis and calcium channel antagonist activity for DHPs containing a 4-[4-(5)-chloro-2-ethyl-5-(4)-imidazolyl] moiety. For the selection of this moiety in the 4 positions, the following reasons were considered:

a) substitution of chlorine instead of NO_2 in the 4-aryl ring produces active compounds [8]; b) a bulky substitu-

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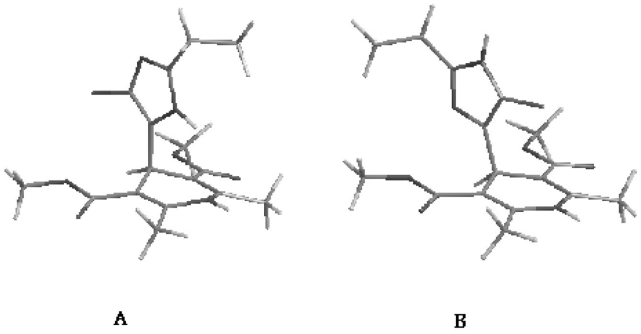


Figure 1. COSMIC optimized geometric for lowest energy tautomeric forms (**A**, **B**) of compound **4a**.

ent in the 2- and 5-position of imidazole was tolerated by the receptor [13–15]; c) considering the tautomeric forms of the 2-ethyl-4-(5)-chloro-5-(4)-imidazolyl moiety, both of the nitrogen atoms probably can interact with the receptor via hydrogen bonding (donor, acceptor) and, therefore, both tautomeric forms should be pharmacologically active. Our molecular modeling studies indicate that the 4-chloro tautomer is the main form and is more stable than the 5-chloro tautomer (Fig. 1). 4-H is *syn*-perpendicular and has good compatibility with the reference drug nifedipine. In addition, it has been shown that 4-aryl in DHPs have a lipophilic pocket in the DHP receptor [16]. In order to adjust the lipophilic property of the imidazole ring, ethyl and chloro groups were inserted in the 2- and 4-(5) position of the imidazole ring, respectively.

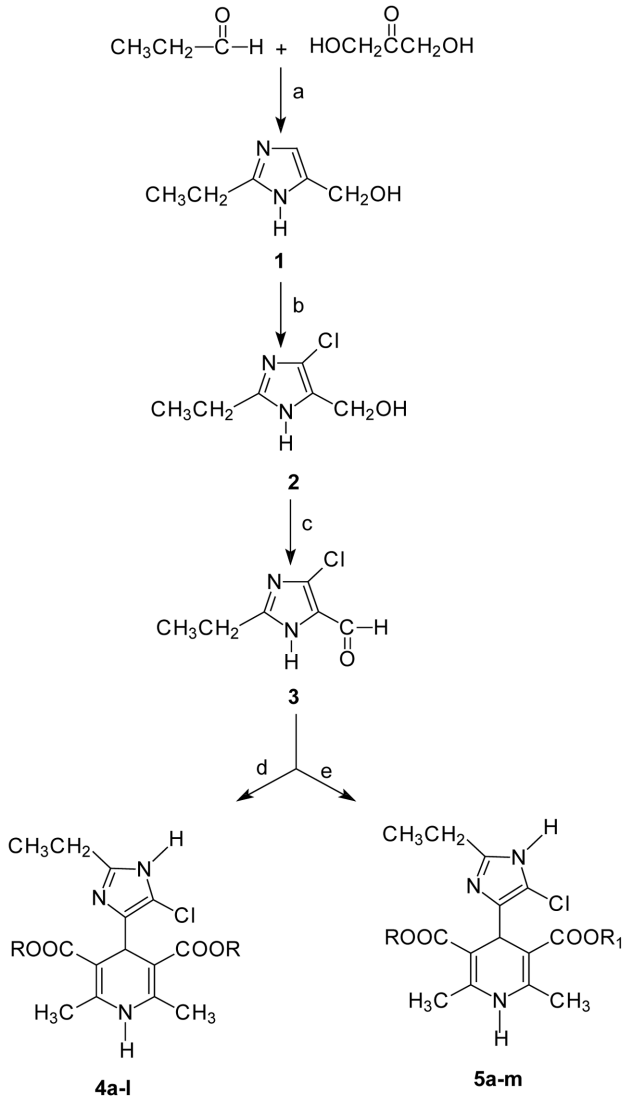
Results and discussion

The synthesis method used is represented in Scheme 1. The compounds (**1**–**5**) were readily characterized by conventional spectral and analytical data.

The conformational study of compound **4a** was done by COSMIC molecular mechanics calculations and two favored tautomers were found for this compound. They were labeled as A when the imidazole substituent at C-4 lies in a 4-chloro tautomeric form and B when the imidazole substituent lies in a 5-chloro tautomeric form (Fig. 1).

In both cases the DHP ring showed a twisted boat conformation and the imidazole ring occupies an axial position perpendicularly bisecting the boat-like DHP ring. The carbonyl ester orientation is *syn-cis* with respect to the olefinic double bond. In the A-form 4-H is *syn*-perpendicular (sp) but in B-form 4-H is *anti*-perpendicular (ap).

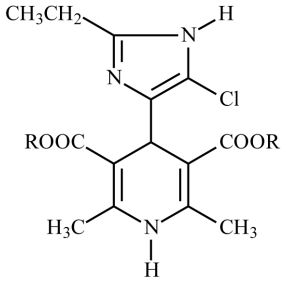
The energy of formation for the two possible tautomers A and B was calculated. Tautomer A (10.101 kcal/mol) was found to be about 1.1 kcal more stable than tautomer B (11.221 kcal/mol). 4-H is *syn*-perpendicular and had good compatibility with nifedipine. In addition, *ab initio* calcalution at 298 K gives 1.73 kcal/mol for the interconversion of tautomers A and B. Therefore, the two possible tautomers are converted into each other at room temperature.



Scheme 1. Synthesis of new 1,4-dihydropyridines containing 4-(5)-chloro- 2-ethyl-5-(4)-imidazolyl substituent.

The Ca^{2+} channel antagonist activities of **4a**–**l** and **5a**–**m** determined as the contraction needed to produce 50% inhibition of the guinea pig ileal longitudinal smooth muscle contractility, are summarized in Table 1 (symmetrical compounds) and Table 2 (unsymmetrical compounds).

Table 1. Physical properties and calcium channel antagonist activity of symmetrical esters.



N°	R	M. p. (0°C)	Yield (%)	Formula[a)]	Calcium channel antagonist activity: IC_{50}[b)]
4a	CH_3	263 – 266	67	$C_{16}H_{20}ClN_3O_4$	0.596 ± 0.112
4b	CH_2CH_3	245 – 249	54	$C_{18}H_{24}ClN_3O_4$	0.158 ± 0.026
4c	$CH_2CH_2CH_3$	204 – 207	52	$C_{20}H_{28}ClN_3O_4$	0.130 ± 0.018
4d	$CH(CH_3)_2$	212 – 216	72	$C_{20}H_{28}ClN_3O_4$	0.749 ± 0.010
4e	$CH_2CH(CH_3)CH_3$	179 – 183	71	$C_{22}H_{32}ClN_3O_4$	2.64 ± 0.55
4f	$C(CH_3)_3$	214 – 216	54	$C_{22}H_{32}ClN_3O_4$	34.2 ± 10.5
4g	Cyclopentyl	212 – 217	84	$C_{24}H_{32}ClN_3O_4$	0.212 ± 0.045
4h	Cyclohexyl	189 – 191	60	$C_{26}H_{36}ClN_3O_4$	0.132 ± 0.013
4i	Cyclohexylmethyl	147 – 150	70	$C_{28}H_{40}ClN_3O_4$	not tested
4j	Benzyl	160 – 171	76	$C_{28}H_{28}ClN_3O_4$	0.905 ± 0.108
4k	Phenethyl	186 – 189	88	$C_{30}H_{32}ClN_3O_4$	0.0437 ± 0.0070
4l	Phenpropyl	162 – 164	49	$C_{32}H_{36}ClN_3O_4$	0.0668 ± 0.0069
Nif[c)]					0.0582 ± 0.0106

[a)] Microanalytical analyses were within ± 0.4% of theoretical values.

[b)] The nanomolar concentration of antagonist test compound causing a 50% rise in the tonic contractile response (IC_{50} ± SEM) in guinea pig ileal smooth muscle by KCl (80 mM) was determined graphically from the dose-response curve. The number of experiment was six for all compounds.

[c)] Nifedipine.

The results reveal that the test compounds show a significant calcium cannel antagonist activity in comparison to the reference drug nifedipine. Comparison of the activities of symmetrical esters in the alkyl ester series (Table 1, **4a – d**) indicates that increasing the length of the chain in C_3- and C_5- ester substituents increase the activity (**4c** > **4b** > **4a**). When increasing of the length accompanied by increasing the hindrance, the activity decreases (**4d – 4f**). In addition, the *t*-butyl ester (**4f**) is the weakest compound in the dialkyl ester series. In the cycloalkyl ester series **4g – i**, cyclohexyl is more potent than cyclopentyl. Comparison of the activity of phenyl relative to the cycloalkyl substituent, namely **4g, 4h** with **4j**, **4k, 4l,** shows that phenethyl and phenpropyl derivatives are more active than cycloalkyl derivatives. Finally, the results show that compound **4k** is the most active compound. The latter is more active than the reference drug nifedipine. In addition, the activity of compound **4l** is comparable to nifedipine.

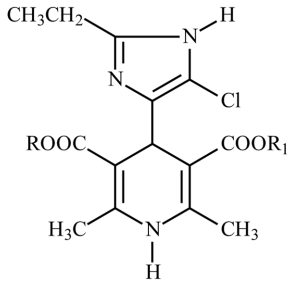
A comparison of the activity of the unsymmetrical series of esters (Table 2) shows that, when R_1 is methyl or ethyl and when the lipophilic property in the R substituent is increased, this leads to increased activity if no steric hindrance occurs. Here again, *t*-butyl derivatives **5d** and **5j** have weak activities. In the unsymmetrical series of esters, the results show that compound **5g** and **5m** are the most active compounds. They are slightly more active than the reference drug nifedipine.

Experimental

General

Reagents and solvents were obtained from Merck (Darmstadt, Germany). Melting points were determined using a Thomas Hoover capillary apparatus (Philadelphia, PA, USA) and were uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker FT-500 spectrometer (Bruker) and TMS was used as an internal standard. Infrared spectra were acquired on a Nicolet 550-FT spectrometer (Nicolet, Madison, WI, USA). Mass spectra were measured with a Finnigan TSQ-70 spectrometer (Thermo Electron Company) at 70 eV. Elemental analysis was carried out with a Perkin-Elmer model 240-C apparatus (Perkin-Elmer). The

Table 2. Physical properties and calcium channel antagonist activity of symmetrical esters.



N°	R_1	R	M. p. (0C)	Yield (%)	Formula[a)]	Calcium channel antagonist activity: IC_{50}[b)]
5a	CH_3	CH_2CH_3	236 – 239	61	$C_{17}H_{22}ClN_3O_4$	2.02 ± 0.40
5b	CH_3	$CH_2CH_2CH_3$	211 – 214	52	$C_{18}H_{24}ClN_3O_4$	0.146 ± 0.035
5c	CH_3	$CH(CH_3)_2$	233 – 238	42	$C_{18}H_{24}ClN_3O_4$	0.487 ± 0.12
5d	CH_3	$C(CH_3)_3$	238 – 242	46	$C_{19}H_{26}ClN_3O_4$	50.8 ± 21.0
5e	CH_3	Cyclohexylmethyl	147 – 152	24	$C_{22}H_{30}ClN_3O_4$	not tested
5f	CH_3	Benzyl	127 – 130	52	$C_{22}H_{24}ClN_3O_4$	1.75 ± 0.49
5g	CH_3	Phenethyl	177 – 180	50	$C_{23}H_{26}ClN_3O_4$	0.0309 ± 0.0034
5h	CH_2CH_3	$CH_2CH_2CH_3$	227 – 231	50	$C_{19}H_{26}ClN_3O_4$	0.543 ± 0.115
5i	CH_2CH_3	$CH(CH_3)_2$	217 – 221	48	$C_{19}H_{26}ClN_3O_4$	0.564 ± 0.105
5j	CH_2CH_3	$C(CH_3)_3$	207 – 210	50	$C_{20}H_{28}ClN_3O_4$	99.7 ± 1.2
5k	CH_2CH_3	Cyclohexylmethyl	204 – 206	12	$C_{23}H_{32}ClN_3O_4$	1.07 ± 0.28
5l	CH_2CH_3	Benzyl	207 – 209	18	$C_{23}H_{26}ClN_3O_4$	2.66 ± 0.30
5m	CH_2CH_3	Phenethyl	153 – 157	26	$C_{24}H_{28}ClN_3O_4$	0.0457 ± 0.0074
Nif[c]						0.0582 ± 0.0106

[a)] Microanalytical analyses were within ± 0.4% of theoretical values.

[b)] The nanomolar concentration of antagonist test compound causing a 50% rise in the tonic contractile response (IC_{50} ± SEM) in guinea pig ileal smooth muscle by KCl (80 mM) was determined graphically from the dose-response curve. The number of experiment was six for all compounds.

[c)] Nifedipine.

results of elemental analysis (C, H, N) were within ± 0.4% of the calculated amounts.

Chemistry

Symmetrical **4a** – **l** (Table 1) and unsymmetrical diesters **5a** – **m** (Table 2), analogues of nifedipine, were synthesized according to Scheme 1. The symmetrical analogues were prepared by classical Hantzsch condensation [17], in which 4-(5)-chloro-2-ethylimidazole-5-(4)-carboxaldehyde **3** was reacted with 3-oxobutanoic acid ester and ammonium acetate. The unsymmetrical diesters were synthesized according to a modified procedure reported by Meyer *et al.* [18]. The compound **3** could be prepared in three steps from propionaldehyde, dihydroxyacetone, and ammonia [19, 20]. Methyl and ethyl 3-aminocrotonates [21] and some of the 3-oxobuthanoic acid esters [21] were prepared according to the literature.

*2-Ethyl-4-(5)-hydroxymethylimidazole (**1**)*

To a stirred solution of copper acetate(II)monohydrate (177.28 g, 0.88 mol) and propionaldehyde (63.7 mL, 0.87 mol) in concentrated ammonia (25%, 1.3 L), a solution of dihydroxyacetone (40 g, 0.44 mol) in 25 mL water was added dropwise during 15 min and heated with stirring for 5 h. The mixture was cooled in an ice bath, filtered, and washed with water three times. The cake was boiled in acetone, filtered, and dried in the oven to give a green copper complex of imidazole (45 g). A suspension of this complex in 1.3 L water was treated with H_2S gas for 3 h. The mixture was filtered, washed with water, and decolorized with charcoal to give a pale yellow solution. The solvent was removed under reduced pressure and the oily residue (29 g, 52%) was crystallized from acetone to give the title compound (25 g) as a white crystals: m. p. 86 – 87°C. IR (KBr): ν cm^{-1} 3160 (OH). ^{1}H-NMR (DMSO-d_6): δ = 1.18 (t, *J*= 7.4 Hz, 3H, CH_3), 2.61 (q, *J* = 7.4 Hz, 2H, CH_2), 4.34 (s, 2H, CH_2OH), 4.54 (s, 1H, OH), 6.75 (s, 1H, imidazole). Anal. Calcd. for $C_6H_{10}N_2O$: C, 57.12; H, 7.99; N, 22.21, found C, 57.33; H, 7.75; N, 22.40.

*5-(4)-Chloro-2-ethyl-4(5)hydroxymethylimidazole (**2**)*

To a stirred solution of **1** (29.9 g, 0.237 mol) in 2-methoxyethanol (133 mL) and 1,4-dioxane (133 mL) a solution of *N*-chlorosuccinimide (32.28 g, 0.237 mol) in 2-methoxyethanol (133 mL) and 1,4-dioxane (133 mL) was added dropwise during 2 h. The mixture was stirred in the dark at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in water (300 mL) and filtered. To the filtrate brine (200 mL) was added and extracted with ethyl acetate (3 × 200 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and evaporated under reduced

pressure to give a yellow solid. This was triturated twice with CH_2Cl_2 to give the title compound as a white solid (21 g, 56%), m.p. 130 – 131°C. IR (KBr): ν cm^{-1} 3100 (OH). ^{1}H-NMR (DMSO-d_6): δ = 1.2 (t, 3H, CH_3), 2.6 (q, 2H, CH_2), 4.35 (d, 2H, *CH_2*OH), 5.1 (t, 1H, *OH*), 11.05 (s, 1H, NH). Anal. Calcd. for $C_6H_9Cl\ N_2O$: C, 44.87; H, 5.65; N, 17.44, found C, 44.68; H, 5.80; N, 17.63.

*5-(4)-Chloro-2-ethylimidazole-4(5)-carboxaldehyde (**3**)*

A suspension of **2** (12.79 g, 0.079 mol) and manganese dioxide (21.5 g, 0.24 mol) in CH_2Cl_2 (175 mL) and 1,4-dioxane (175 mL) was heated at reflux for 9 h. The hot mixture was filtered and washed with warm $CHCl_3$. The solvent was removed under reduced pressure. The residue was crystallized from CCl_4 to give the title compound (12.4 g, 98%) as white crystals: m.p. 107 – 110°C. IR (KBr): ν cm^{-1} 1670 (CO). ^{1}H-NMR ($CDCl_3$): δ = 1.4 (t, 3H, CH_3), 2.9 (q, 2H, CH_2), 9.65 (s, 1H, CHO), 11.45 (s, 1H, NH). Anal. Calcd. for $C_6H_7ClN_2O$: C, 45.44; H, 4.45; N, 17.66, found C, 45.29; H, 4.27; N, 17.49.

*General procedure for the preparation of dialkyl-1,4-dihydro-2,6-dimethyl-4-[-4(5)-chloro-2-ethyl-5-(4)-imidazolyl]-3,5-pyridinedicarboxylate (**4a – 4l**)*

A solution of compound **3** (0.3 g, 1.893 mmol), ammonium acetate (0.14 g, 1.89 mmol) and alkyl 3-oxobutanoate (3.78 mmol) in methanol (3 mL) was refluxed for several hours. The solvent was removed under reduced pressure and the residue was crystallized from ethyl acetate to give the title compound.

*Diphenethyl-1,4-dihydro-2,6-dimethyl-4-[4-(5)-chloro-2-ethyl-5-(4)-imidazolyl]-3,5-pyridinedicarboxylate (**4k**)*

Using the general procedure and phenethyl 3-oxobutanoate provides the title compound after 31 h reflux: White crystals, yield 88%; m.p. 186 – 189°C (ethyl acetate). IR (KBr): ν cm^{-1} 3411, 3263 (NH), 1690 (CO). ^{1}H-NMR ($CDCl_3$): δ = 1.22 (t, *J* = 7.5 Hz, 3H, CH_3, imidazole), 2.17 (s, 6H, C_2, C_6-CH_3), 2.50 (q, *J* = 7.55 Hz, 2H, CH_2-imidazole), 2.91 (t, *J* = 6.83 Hz, 4H, CH_2-Ph), 4.26 (m, 2H, -O-CH_2), 4.41 (m, 2H, -O-CH_2), 4.95 (s, 1H, H_4-DHP), 6.75 (s, 1H, NH, DHP), 7.28 (m, 6H, phenyl), 7.37 (m, 4H, phenyl), 9.05 (s, 1H, NH-imidazole). ^{13}C-NMR ($CDCl_3$): δ = 168.67 (CO), 146.39 (C_2, imidazole), 146.31 (C_2, C_6-DHP), 138.85 (C_1, phenyl), 129.33 (C_3, C_5, phenyl), 129.27 (C_4, imidazole), 128.99 (C_2, C_6, phenyl), 126.93 (C_4, phenyl), 125.07 (C_5, imidazole), 99.93 (C_3, C_5, DHP), 64.86 (OCH_2), 35.72 (CH_2-Ph), 31.53 (CH_2-imidazole), 22.23 (C_4, DHP), 19.67 (C_2, C_6-CH_3, DHP), 12.54 (CH_3, imidazole). MS: *m/z* (%) 533 [M^+] (3), 498 (87), 426 (15), 384 (30), 376 (10), 318 (30), 262 (35), 255 (10), 196 (45), 130 (10), 104 (100), 79 (17). Anal. Calcd. for $C_{30}H_{32}ClN_3O_4$: C, 67.47; H, 6.04; N, 7.87, found C, 67.59; H, 6.25; N, 7.71.

*Diphenpropyl-1,4-dihydro-2,6-dimethyl-4-[4-(5)-chloro-2-ethyl-5-(4)-imidazolyl]-3,5-pyridinedicarboxylate (**4l**)*

Using the general procedure and phenpropyl 3-oxobutanoate provides the title compound after 30 h reflux: White crystals, yield 49%; m.p. 162 – 164°C (ethyl acetate). IR (KBr): ν cm^{-1} 3411, 3263 (NH), 1696 (CO). ^{1}H-NMR ($CDCl_3$ + DMSO-d_6): δ = 1.20 (t, *J* = 7.62 Hz, 3H, CH_3, imidazole), 2.01 (m, 4H, CH_2–CH_2–Ph), 2.29 (s, 6H, C_2, C_6-CH_3, DHP), 2.58 (q, *J* = 7.6 Hz, 2H, CH_2-imidazole), 2.68 (t, *J* = 7.4 Hz, 4H, CH_2-Ph), 4.17 (m, 4H, –O–CH_2), 5.13 (s, 1H, H_4-DHP), 7.17 (d, *J* = 7.28 Hz, 4H, $H_{2,6}$-phenyl), 7.21 (m, 3H, 4-H, phenyl, NH-DHP), 7.30 (t, *J* = 7.28 Hz, 4H, $H_{3,5}$), 9.77 (s, 1H, NH-imidazole). ^{13}C-NMR ($CDCl_3$): δ = 168.34 (C=O), 146.61 (C_2, imidazole), 146.57 (C_2, C_6, DHP), 141 (C_1, phenyl), 128.85 (C_4, imidazole and C_3, C_5, phenyl), 128.76 (C_2, C_6, phenyl), 126.41 (C_4, phenyl), 124.68 (C_5, imidazole), 100.06 (C_3, C_5, DHP), 63.98 (–O–CH_2), 32.71 (–CH_2–Ph), 31.69 (CH_2, imidazole), 30.85 (–CH_2–CH_2–Ph), 22.24 (C_4, DHP), 19.76 (C_2, C_6-CH_3, DHP), 12.43 (CH_3, imidazole). MS: *m/z* (%) 561 [M^+] (4), 526 (72), 398 (22), 261 (15), 195 (10), 119 (10), 118 (100), 50 (25). Anal. Calcd. for $C_{32}H_{36}ClN_3O_4$: C, 68.38; H, 6.46; N, 7.48; found C, 68.49; H, 6.62; N, 7.61.

Compounds **4a-4j** was prepared similarly (Table 1).

*General procedure for the preparation unsymmetrical dialkyl-1,4-dihydro-2,6-dimethyl-4-[4-(5)-chloro-2-ethyl-5-(4)-imidazolyl]-3,5-pyridinedicarboxylate (**5a – 5m**)*

A solution of compound **3** (0.2 g, 1.26 mmol), alkyl 3-aminocrotonate (0.16 g, 1.24 mmol) and alkyl 3-oxobutanoate (1.29 mmol) in methanol (3 mL) was reflux for several hours. The reaction mixture was purified with preparative TLC (silica gel, chloroform : methanol 20 : 1). The crude product was crystallized from ether to give the desired compound.

*Methyl-phenethyl-1,4-dihydro-2,6-dimethyl-4-[4-(5)-chloro-2-ethyl-5-(4)-imidazolyl]-3,5-pyridinedicarboxylate (**5g**)*

Using the general procedure, methyl 3-aminocrotonate and phenethyl 3-oxobutanoate afford the title compound after 35 h reflux: White crystals, yield 50%; m.p. 177 – 180°C (ether). IR (KBr): ν cm^{-1} 3339 (NH), 1711 (CO). ^{1}H-NMR ($CDCl_3$): δ = 1.21 (t, *J* = 7.6 Hz, 3H, CH_3-imidazole), 2.21 and 2.28 (2s, 6H, C_2, C_6-CH_3, DHP), 2.54 (q, *J* = 7.6 Hz, 2H, CH_2-imidazole), 2.98 (m, 2H, CH_2–Ph), 3.72 (s, 3H, –O–CH_3), 4.27 (m, 1H, –O–*CH_2*–CH_2–Ph), 4.38 (m, 1H, O*CH_2*–CH_2–Ph), 5.00 (s, 1H, H_4–DHP), 6.80 (s, 1H, NH, DHP), 7.27 (m, 3H, phenyl), 7.35 (m, 2H, phenyl), 9.06 (s, 1H, NH-imidazole). ^{13}C-NMR ($CDCl_3$): δ = 168.91 (C=O) 167.90 (CO), 146.38 and 146.31 (C_2, C_6, DHP), 146.12 (C_2-imidazole), 138.84 (C_1, phenyl), 129.33 (C_4, imidazole), 129.26 (C_3, C_5, phenyl), 128.98 (C_2, C_6, phenyl), 126.91 (C_4, phenyl), 125.06 (C_5, imidazole), 99.92 (C_3, C_5, DHP), 64.86 (–O-CH_2–), 51.55 (–O–CH_3), 35.70 (–CH_2–Ph), 31.53 (CH_2-imidazole), 22.23 (C_4-DHP), 19.66 and 19.61 (C_2, C_6, CH_3-DHP), 12.53 (CH_3, imidazole). – MS: *m/z* (%), 443 (4), 408 (64), 294 (50), 210 (30), 165 (44), 104 (100), 91 (67), 77 (40), 56 (25), 42 (10). Anal. Calcd. for $C_{23}H_{26}ClN_3O_4$: C, 62.23; H, 5.90; N, 9.47, found C, 62.47; H, 5.71; N, 9.21.

*Ethyl-phenethyl-1,4-dihydro-2,6-dimethyl-4-[4-(5)-chloro-2-ethyl-5-(4)-imidazolyl]-3,5-pyridinedicarboxylate (**5m**)*

Using the general procedure, ethyl 3-aminocrotonate and phenethyl 3-oxobutanoate afford the title compound after 36 h reflux: White crystals, yield 26%; m.p. 153 – 157°C (ether). IR (KBr): ν cm^{-1} 3345 (NH), 1701 (CO). ^{1}H-NMR ($CDCl_3$): δ = 1.17 (m, 6H, CH_3-imidazole-O–CH_2–*CH_3*), 2.19 and 2.24 (2s, 6H, C_2, C_6-CH_3,DHP), 2.55 (q, *J* = 7.55 Hz, 2H, CH_3-*CH_2*-imidazole), 2.96 (m, 2H, CH_2-Ph), 4.14 (m, 2H, O-*CH_2*-CH_3), 4.26 (m, 1H, O–*CH_2*–CH_2–Ph), 4.38 (m, 1H, –O–*CH_2*–CH_2–Ph), 5.00 (s, 1H, H_4-DHP), 6.80 (s, 1H, NH-DHP), 7.27 (m, 3H, phenyl), 7.35 (m, 2H, phenyl), 9.10 (s, 1H, NH-imidazole). ^{13}C-NMR ($CDCl_3$): δ = 168.40 (C=O), 167.89 (CO), 146.51 and 146.46 (C_2, C_6-DHP), 146.21 (C_2-imidazole), 139.01 (C_1, phenyl), 129.35 (C_4-imidazole), 129.20 (C_3, C_5 phenyl), 128.98 (C_2, C_6 phenyl), 126.89 (C_4, phenyl), 125.12 (C_5-imidazole), 99.89 and 99.72 (C_3, C_4, DHP), 64.59 (-O-CH_2-) 59.75 (–O–*CH_2*–CH_3), 35.73 (O–CH_2–*CH_2*–Ph) 31.43 (CH_2-imidazole), 22.19 (C_4-DHP),

19.59 and 19.39 (C_2, C_6–CH_3–DHP), 12.36 (O–CH_2–*CH_3*), 12.49 (CH_3-imidazole). MS: *m/z* (%) 457 [M^+] (4), 408 (64), 294 (50), 210 (30), 165 (44), 104 (100), 91 (67), 77(40), 56 (25), 42 (10). Anal. Calcd. for $C_{24}H_{28}ClN_3O_4$: C, 62.95; H, 6.16; N, 9.18, found C, 62.63; H, 6.47; N, 9.50.

Compounds **5a–5f** and **5h–5l** were prepared similarly (Table 2).

Molecular modeling

The molecular geometry was optimized by using molecular mechanics with the Nemesis program. The COSMIC force field is used in energy calculations and structure optimization. Conformation of the two favored tautomers of compound **4a** (Fig. 1) and nifedipine were optimized. Among all energy minima conformers, the global minimum of the two favored tautomers of compound **4a** was compared with the global minimum of nifedipine as a reference drug.

Pharmacology

Male albino guinea pigs (300–450 g) were killed by a blow to the head. The intestine was removed above the ileocecal junction and longitudinal smooth muscle segments of 2 cm length were mounted under a resting tension of 0.5 g. The segments were maintained at 37°C in a 20 mL jacketed organ bath containing oxygenated physiological saline solution of the following (mM) composition:

NaCl, 137; $CaCl_2$, 1.8; KCl, 2.7; $MgSO_4$, 1.1; NaH_2PO_4, 0.4; $NaHCO_3$, 12; and glucose, 5. The muscles were equilibrated for 1 h with solution changes every 15 min. The contraction was recorded with a force displacement transducer (F-50) on a NARCO physiograph. Test agents were prepared at 10^{-2} M stock solutions in dimethyl sulfoxide (DMSO) and stored protected from light. Dilutions were made into DMSO. The contractile response was taken as the 100% value for the tonic (slow) component of the response. The contraction was elicited with 80 mM KCl. Test compounds were cumulatively added and compound-induced relaxation of contracted muscle was expressed as percent of control. The IC_{50} values (concentration needed to produce 50% relaxation on contracted ileal smooth muscle) were graphically determined from the concentration-response curves [23, 24]. The research protocol and experimental animals have been approved by the ethics committee of Tehran University of Medical Sciences.

Statistical analysis

The results are presented as mean ±SEM., and the statistical significance between the groups was analyzed by means of variance followed by one-way ANOVA test. P values less than 0.05 were considered significant.

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