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Abstract

In the present study a microwave-assisted one-pot method was applied for the synthesis of 18 novel condensed 1,4-dihydropyridines carrying the indole moiety. The compounds were achieved by the reaction of appropriate 1,3-cyclohexanedione, substituted indole carboxaldehyde derivative, alkyl acetoacetate and ammonium acetate in methanol, according to a modified Hantzsch reaction. The structure elucidation of the compounds was carried out by spectral methods including X-ray studies. Their spasmolytic activities through calcium channel blockade were assayed on isolated rat ileum. The obtained results indicated that the introduction of the brom atom on the indole ring altered the mentioned activity positively.

Introduction

Calcium ions act as an intracellular signal and play an important role in variety of biological functions including muscle contraction, neurotransmitter release, neuronal excitability regulation and calcium dependent gene transcription [1]. Although several types of calcium channels have been identified, L-type channels are typically confined to cell bodies and are responsible for regulating contractility in muscle cells [2]. Calcium entry blockers are the class of drugs that inhibit selectively the calcium movement through voltage sensitive calcium channels [3,4]. They are structurally divided in 2 large groups: dihydropyridines (DHP), represented by nifedipine (Fig. 1), and non-dihydropyridines, represented by verapamil and diltiazem [5].

1,4-DHP nucleus serves as a scaffold for important commercially employed cardiovascular drugs particularly antihypertensive, antianginal and antiarrhythmic ones [6–8]. Since the discovery of the therapeutic benefits of 1,4-DHPs, many DHP analogs have been synthesized in order to elucidate the structure-activity relationships, to enhance calcium-modulating effects and to lead new active compounds [9].

Some studies indicated that racemic hexahydroquinolines, indenopyridines, acridines and furanquinolines, which are the condensed ring systems of the DHP structure, were active derivatives exhibiting calcium antagonistic effects [10–13]. Studies of fused 1,4-DHPs, in which one of the ester groups is immobilized, indicate that at least one ester group must be cis to the double bond of DHP for hydrogen bonding to the receptor [14]. Although the phenyl ring is generally preferred as the substituent at the C-4 position, also 1,4-DHPs bearing different rings have been synthesized to elucidate the structure-activity relationships in terms of substitution of o-nitrophenyl ring by aromatic or heteroaromatic ring [15]. The effect of the introduction of a heteroaromatic ring such as xanthone, coumarin, benzofurazan, benzofuroxan and pyrazol into 4-position of the 1,4-DHP nucleus was examined in many researches [16–19].

The indole nucleus is a ubiquitous nitrogen heterocyclic structure found in numerous natural and synthetic compounds with a wide variety of biological activities and considerable pharmaceutical importance [20]. It is an essential part of the amino acid tryptophan and the neurotransmitter serotonin. Several plant based alkaloids bearing indole as their basic ring are also found to be therapeutically active agents [21]. In recent years lots of indole derivatives have been synthesized exhibiting versatile pharmacological properties such as antitumor, anti viral, anti-inflammatory, antimicrobial, anti-tubercular, hypoglycemic and anticonvulsant activities [22–28].
It was also reported that 4-indoly-1,4-DHPs showed the same potency as nifedipine on rat aorta through calcium channel blockage [29].

Microwave (MW) assisted organic synthesis has been recently introduced to perform various chemical reactions and has attracted great interest because of its ability to reduce reaction times, to improve yields and to simplify the work-up processes [30]. Previously conventionally heated reactions to obtain 1,4-DHP derivatives could be also performed by applying this technique [31, 32].

The aim of this work is to describe an efficient and convenient method for the preparation of condensed 1,4-DHPs based on microwave irradiation and evaluate the influence of (substituted) cyclohexane ring fused to the DHP ring in combination with indole moiety on the 1,4-DHP backbone. The compounds were synthesized and tested as racemates. The spasmyloytic activities of the compounds were investigated on isolated rat ileum.

Material and Methods

Chemistry

General methods

All chemicals used in this study were purchased from Aldrich and Fluka (Steinheim, Germany). All reactions were carried out in Discover Microwave Apparatus (CEM). Thin layer chromatography (TLC) was run on Merck aluminium sheets (Darmstadt, Germany), Silica gel 60 F 254 (Merck, Darmstadt, Germany). All reactions were carried out according to the Hantzsch reaction.

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### Table 1: Structural data of the synthesized compounds.

<table>
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<th>Compound</th>
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<th>Melting Point (°C)</th>
<th>Empirical Formula</th>
<th>Molecular Weight</th>
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<td>C₂₃H₁₁BrN₂O₃</td>
<td>456</td>
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</table>

Studies on isolated rat ileum

Albino rats of either sex weighing 150–200 g were used in pharmacological studies. The animals were supplied from the Laboratory Animal Production Center in the Department of Pharmacology, School of Medicine, Osmangazi University, Eskişehir, Turkey. The animals used in the test were fasted overnight. After the animals were sacrificed 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, KCl: 2.68, CaCl₂: 1.80, MgSO₄: 0.81, NaH₂PO₄: 4.16, NaHCO₃: 11.9, glucose: 5.55. The bath contents were maintained at 37 °C and aerated by 95% O₂ and 5% CO₂. A tension of 2 g was applied and isometric recording was done by using an isometric transducer (FDT₁₀⁻₅) 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 the calcium antagonistic effects, contractions were induced with barium chloride (4·10⁻³ mol/L, bath concentration). After washing out, this process was repeated until the amplitude of the contraction became constant. Investigations of the substances were performed using the single-dose technique. Barium chloride contractions were induced after addition of the test substances dissolved in DMSO at 10⁻⁵ M concentration and 5 min exposure time. Only one compound was tested in each preparation [33].
Results

Chemistry

Methyl 2,6,6-trimethyl-4-(1-methyl-1H-indol-2-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (1)

Yield: 85%. IR (v, cm⁻¹): 3282 (N-H), 1697 (C=O, ester), 1642 (C=O, ketone). $\delta^{1}^{1}^H$-NMR (δ): 0.9–1.0 (6H; s; 2xCH₃), 1.1 (3H; t; CH₃CH₂), 1.6–1.8 (4H; m; quinoline H$^4$), 2.3 (3H; s; CH₃), 4.0 (2H; m; CH₂CH₃), 3.5 (3H; s; N-CH₃), 4.9 (1H; s; quinoline H$^6$), 6.5 (1H; s; indole H$^5$), 6.9–7.5 (4H; m; aromatic), 9.2 (1H; s; NH). $\delta^{13}^{C}$-NMR (δ): 14.5 (COOCH₂CH₃), 18.8 (2-CH₃), 21.0 (C$^4$), 24.2 (6-CH₃), 25.3 (6-CH₂), 28.5 (C$^3$), 30.4 (N-CH₃), 35.8 (C$^5$), 44.8 (C$^7$), 56.7 (COOCH₂CH₃), 99.1 (C$^1$), 102.3 (C$^6$), 104.5, 111.8, 118.7, 124.3, 127.2, 132.8, 135.5, 136.2 (indole carbons), 140.6, 145.0, 147.9 (C$^9$), 151.1 (C$^{10}$), 167.7 (COOCH₂CH₃), 198.3 (C$^8$), MS (m/z): 392 [M⁺]^+. Anal. Calcld. for C$_{23}$H$_{26}$NO$_{3}$: C, 72.99; H, 6.92; N, 7.41. Found: C, 72.95; H, 6.91; N, 7.47.

Ethyl 2,6,6-trimethyl-4-(1-methyl-1H-indol-2-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2)

Yield: 82%. IR (v, cm⁻¹): 3275 (N-H), 1702 (C=O, ester), 1641 (C=O, ketone). $\delta^{1}^{1}^H$-NMR (δ): 0.9–1.0 (6H; s; 2xCH₃), 1.1 (3H; t; CH₃CH₂), 2–2.2 (4H; m; quinoline H$^4$), 2.3 (3H; s; CH₃), 3.5 (3H; s; N-CH₃), 3.9 (2H; m; CH₂CH₃), 5.0 (1H; s; quinoline H$^6$), 6.5 (1H; s; indole H$^5$), 6.9–7.3 (4H; m; aromatic), 9.2 (1H; s; NH). $\delta^{13}^{C}$-NMR (δ): 14.1 (COOCH₂CH₃), 18.3 (2-CH₃), 20.6 (C$^4$), 26.1 (C$^7$), 27.9 (C$^9$), 29.4 (N-CH₃), 46.5 (C$^6$), 59.1 (COOCH₂CH₃), 98.8 (C$^5$), 103.3 (C$^8$), 109.4, 111.2, 116.6, 119.1, 119.9, 127.4, 135.8, 144.4 (indole carbons), 141.9 (C$^9$), 150.7 (C$^{10}$), 166.7 (COOCH₂CH₃), 194.9 (C$^8$), MS (m/z): 364 [M⁺]^+. Anal. Calcld. for C$_{23}$H$_{25}$NO$_{3}$: C, 72.51; H, 6.64; N, 7.69. Found: C, 72.54; H, 6.69; N, 7.62.

Methyl 2,6,6-trimethyl-4-(1-methyl-1H-indol-2-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (3)

Yield: 88%. IR (v, cm⁻¹): 3280 (N-H), 1691 (C=O, ester), 1645 (C=O, ketone). $\delta^{1}^{1}^H$-NMR (δ): 0.9–1.0 (6H; s; 2xCH₃), 1.1 (3H; t; CH₃CH₂), 1.7–2.2 (6H; m; quinoline H$^4$), 2.3 (3H; s; CH₃), 3.6 (3H; s; N-CH₃), 3.9 (2H; m; CH₂CH₃), 5.0 (1H; s; quinoline H$^6$), 6.5 (1H; s; indole H$^5$), 6.8–7.3 (4H; m; aromatic), 9.2 (1H; s; NH). $\delta^{13}^{C}$-NMR (δ): 14.1 (C$^3$), 146.7 (C$^{12}$), 146.2 (C$^{13}$), 146.3 (C$^{14}$), 151.8 (C$^{15}$), 166.3 (COOCH₂CH₃), 191.1 (C$^{11}$), 107.5, 110.3, 124.6, 124.9, 132.3, 135.8, 144.4 (indole carbons), 148.9 (C$^9$), 150.7 (C$^{10}$), 167.7 (COOCH₂CH₃), 194.9 (C$^8$), MS (m/z): 370 [M⁺]^+. Anal. Calcld. for C$_{22}$H$_{25}$NO$_{3}$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.95; H, 6.91; N, 7.47.
Ethyl 2,6,6-trimethyl-4-(1-methyl-1H-indol-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (10)

Yield: 88%. IR (ν, cm⁻¹): 3298 (N-H), 1696 (C=O, ester), 1631 (C=O, ketone). ¹H-NMR (δ): 0.9–1.0 (6H; s; 2CH₃), 1.1 (3H; t; CH₃CH₂), 1.6–1.8 (4H; m; quinoline H6,7,8), 2.3 (3H; s; CH₃), 3.9 (2H; m; CH₂CH₃), 3.1 (3H; s; N-CH₃), 5.1 (1H; s; quinoline H5), 6.8 (1H; s; indole H3), 6.9–7.6 (4H; m; aromatic), 9.13 (1H; s; NH). ¹³C-NMR (δ): 14.7 (COOCH₂CH₃), 18.6 (2-CH₃), 23.3 (C), 24.6 (6-CH₃), 25.7 (6-CH₃), 27.6 (C), 32.6 (N-CH₃), 34.6 (C), 38.2 (C), 59.4 (COOCH₂CH₃), 104.0 (C), 109.5 (C), 109.7, 118.4, 120.2, 120.8, 121.1, 126.5, 127.5, 135.6 (indole carbons), 144.1 (C), 149.6 (C₈H₉), 167.7 (COOCH₂CH₃), 199.9 (C). MS (m/z): 392 [M⁺]. Anal. Calc'd for C₂₃H₂₃BrN₂O₂: C, 57.85; H, 4.93; N, 6.53. Found: C, 57.88; H, 4.96; N, 6.54.

Ethyl 2,6,6-trimethyl-4-(1-methyl-1H-indol-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (15)

Yield: 87%. IR (ν, cm⁻¹): 3288 (N-H), 1695 (C=O, ester), 1640 (C=O, ketone). ¹H-NMR (δ): 0.9–1.0 (6H; s; 2CH₃), 1.6–1.8 (4H; m; quinoline H6,7,8), 2.2 (3H; s; CH₃), 3.5 (3H; s; COOCH₂), 5.0 (1H; s; quinoline H5), 6.8 (1H; s; indole H3), 7.1–7.7 (3H; m; aromatic), 9.2 (1H; s; quinoline NH), 10.8 (1H; s; indole NH). ¹³C-NMR (δ): 18.7 (2-CH₃), 20.6 (C), 23.8 (6-CH₃), 24.5 (6-CH₃), 28.7 (C), 35.2 (C), 37.8 (C), 53.4 (COOCH₂), 100.2 (C), 103.8 (C₈H₉), 112.3, 114.0, 114.5, 122.4, 126.5, 128.9, 130.2, 138.8 (indole carbons), 148.7 (C), 150.3 (C₈H₉), 168.9 (COOCH₂), 199.8 (C). MS (m/z): 441 [M⁺]. Anal. Calc'd for C₂₃H₂₃BrN₂O₂: C, 59.60; H, 5.23; N, 6.32. Found: C, 59.64; H, 5.21; N, 6.30.

Ethyl 2,6,6-trimethyl-4-(5-bromo-1H-indol-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16)

Yield: 86%. IR (ν, cm⁻¹): 3297 (N-H), 1712 (C=O, ester), 1638 (C=O, ketone). ¹H-NMR (δ): 0.9–1.0 (6H; s; 2CH₃), 1.1 (3H; t; CH₃CH₂), 1.6–1.8 (4H; m; quinoline H6,7,8), 2.2 (3H; s; CH₃), 3.5 (3H; s; COOCH₂), 5.0 (1H; s; quinoline H5), 6.8 (1H; s; indole H3), 7.1–7.7 (3H; m; aromatic), 9.2 (1H; s; quinoline NH), 10.8 (1H; s; indole NH). ¹³C-NMR (δ): 14.5 (COOCH₂CH₃), 18.6 (2-CH₃), 21.2 (C), 24.3 (6-CH₃), 25.2 (7-CH₃), 27.4 (C), 36.7 (C₈H₉), 43.5 (C), 56.9 (COOCH₂CH₃), 103.4 (C), 104.3 (C₈H₉), 1113, 114.5, 120.0, 123.5, 127.3, 128.9, 130.2, 135.6 (indole carbons), 145.6 (C), 148.7 (C), 167.6 (COOCH₂CH₃), 195.7 (C). MS (m/z): 456 [M⁺]. Anal. Calc'd for C₂₃H₂₃BrN₂O₂: C, 60.40; H, 5.51; N, 6.12. Found: C, 60.43; H, 5.53; N, 6.15.

Ethyl 2,7,7-trimethyl-4-(5-bromo-1H-indol-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (17)

Yield: 78%. IR (ν, cm⁻¹): 3299 (N-H), 1695 (C=O, ester), 1637 (C=O, ketone). ¹H-NMR (δ): 0.9–1.0 (6H; s; 2CH₃), 1.9–2.2 (4H; m; quinoline H6,7,8), 2.3 (3H; s; CH₃), 3.5 (3H; s; COOCH₂), 5.0 (1H; s; quinoline H5), 6.9 (1H; s; indole H3), 7.1–7.7 (3H; m; aromatic), 9.2 (1H; s; quinoline NH), 10.8 (1H; s; indole NH). ¹³C-NMR (δ): 19.4 (2-CH₃), 21.2 (C), 23.9 (7-CH₃), 24.3 (7-CH₃), 27.6 (C), 35.2 (C), 40.3 (C), 54.9 (COOCH₂), 99.2 (C), 102.8 (C₈H₉), 112.4, 115.6, 117.3, 122.4, 124.5, 127.1, 132.3, 135.8 (indole carbons), 149.3 (C), 151.3 (C₈H₉), 168.9 (COOCH₂), 200.2 (C). MS (m/z): 442 [M⁺]. Anal. Calc'd for C₂₃H₂₃BrN₂O₂: C, 59.60; H, 5.23; N, 6.32. Found: C, 59.59; H, 5.20; N, 6.29.

Ethyl 2,7,7-trimethyl-4-(5-bromo-1H-indol-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (18)

Yield: 83%. IR (ν, cm⁻¹): 3277 (N-H), 1688 (C=O, ester), 1639 (C=O, ketone). ¹H-NMR (δ): 0.9–1.0 (6H; s; 2CH₃), 1.1 (3H; t; CH₃CH₂), 2.0–2.2 (4H; m; quinoline H6,7,8), 2.3 (3H; s; CH₃), 4.0 (2H; m; CH₂CH₃) .
(2H; m; CH₃CH₃), 5.2 (1H; s; quinoline H¹), 6.9 (1H; s; indole H²), 7.1–7.7 (3H; m; aromatic), 9.2 (1H; s; quinoline NH), 10.8 (1H; s; indole NH). ¹³C-NMR (δ): 14.6 (COOCH₂CH₃), 18.6 (2-CH₃), 20.8 (C₁), 26.9 (7-CH₃), 27.4 (7-CH₃), 29.6 (C₆), 32.5 (C₅), 50.7 (C₆), 59.4 (COOCH₂CH₃), 104.3 (C₁), 110.1 (C⁴), 111.2, 113.6, 122.0, 122.4, 123.1, 124.9, 128.0, 135.1 (indole carbons), 144.3 (C⁸), 149.4 (C⁷), 167.6 (COOCH₂CH₃), 194.82 (C⁵). MS (m/z): 455 [M⁺]⁺. Anal. Calcd. for C₂₂H₂₃BrN₂O₃: C, 60.40; H, 5.51; N, 6.12. Found: C, 60.35; H, 5.53; N, 6.13.

X-Ray Studies
The X-ray crystallographic data of Compound 12 (Fig. 3) demonstrated that the cyclohexene ring is in a sofa conformation, while the 1,4-DHP ring has a slight boat conformation. In the crystal structure, the molecules are linked into chains by N-H···O hydrogen-bonding interactions. A weak intramolecular C-H···O hydrogen bond is also found.

For compound 16 (Fig. 4), it was found that the indole ring is planar, while the cyclohexene ring has a sofa conformation. In the crystal, molecules are linked by N-H···O hydrogen bonds, also a C-H···O contact occurs between independent molecules. Detailed descriptions of the structures have been presented in [34,35].

Pharmacology
The spasmolytic effects of the compounds and nicardipine on isolated rat ileum at 3 different concentrations are given in Table 2.

Discussion and Conclusion
In this work an easy, very rapid and convenient method is reported for the preparation of new condensed 1,4-dihydropyridines by the reaction of appropriate 1,3-cyclic diketone, substituted indole carboxaldehyde, alkyl acetocetate and ammonium bromide under microwave irradiation in methanol. This method also offers a reduction of solvent use and simplification of the work-up procedures in addition to higher yields. The structures of the compounds were elucidated by IR, ¹H-NMR, ¹³C-NMR and mass spectra. Elemental analysis results were within ±0.4 % of theoretical values for all compounds. Their calcium channel modulator activities were investigated on isolated rat ileum.

In the IR spectra, characteristic N-H and C=O (ketone) bonds were recorded via the electron ionization technique. The mass spectra of the compounds were obtained by the ionization technique. The molecular ion peak (M⁺) or the M-1 peak due to the aromatization of the DHP ring to the pyridine analogue were seen at about 9.2 ppm and 10.8 ppm, respectively. The protons, which are on the aromatic indole rings, were at 6.8–7.7 ppm. The N-H protons of the DHP ring and indole ring were seen at 9.2 ppm and 10.8 ppm, respectively.

In the ¹H-NMR spectra, the methylene groups of the hexahydroquinoline ring were at 1.6–2.2 ppm. The substituted methyl protons of the same ring were seen at 2.3 ppm and 4.9–5.2 ppm, respectively. The methyl and methine protons on the DHP ring were observed as singlets. The methyl protons on the DHP ring were observed at 2.3 ppm and 4.9–5.2 ppm, respectively. The protons, which are on the aromatic indole rings, were at 6.8–7.7 ppm. The N-H protons of the DHP ring and indole ring were seen at about 9.2 ppm and 10.8 ppm, respectively.

In the ¹³C-NMR spectra the number of the signals fitted exactly the number of carbon atoms. The mass spectra of the compounds were recorded via the electron ionization technique. The molecular ion peak (M⁺) or the M-1 peak due to the aromatization of the DHP ring to the pyridine analogue were seen in the spectra of all compounds. Cleavage of the ester group and indole rings from the parent molecule are the next most observed fragmentations.

Table 2 The spasmolytic effects of the compounds and nicardipine on isolated rat ileum (% inhibition ± SD, n = 6).

<table>
<thead>
<tr>
<th>Compound</th>
<th>10⁻³ M</th>
<th>10⁻⁶ M</th>
<th>10⁻⁹ M</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26.75 ± 14.01</td>
<td>28.75 ± 17.56</td>
<td>30.25 ± 18.66</td>
</tr>
<tr>
<td>2</td>
<td>11.80 ± 7.37</td>
<td>23.00 ± 10.31</td>
<td>31.40 ± 10.79</td>
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<tr>
<td>3</td>
<td>11.14 ± 6.77</td>
<td>20.27 ± 6.39</td>
<td>23.45 ± 10.07</td>
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<tr>
<td>4</td>
<td>23.16 ± 16.08</td>
<td>24.00 ± 18.29</td>
<td>25.60 ± 16.38</td>
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<tr>
<td>5</td>
<td>25.75 ± 8.45</td>
<td>27.00 ± 17.20</td>
<td>33.30 ± 9.81</td>
</tr>
<tr>
<td>6</td>
<td>16.33 ± 6.98</td>
<td>29.67 ± 18.82</td>
<td>32.33 ± 5.42</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>9.83 ± 3.93</td>
<td>23.17 ± 8.42</td>
</tr>
<tr>
<td>9</td>
<td>5.50 ± 3.54</td>
<td>19.00 ± 9.01</td>
<td>22.00 ± 9.40</td>
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<tr>
<td>10</td>
<td>16.67 ± 6.53</td>
<td>17.50 ± 9.90</td>
<td>19.67 ± 7.89</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>0</td>
<td>15.33 ± 8.71</td>
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<tr>
<td>12</td>
<td>21.83 ± 9.25</td>
<td>22.60 ± 7.79</td>
<td>29.80 ± 9.11</td>
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<tr>
<td>13</td>
<td>12.67 ± 7.04</td>
<td>18.33 ± 4.16</td>
<td>56.67 ± 19.14</td>
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<tr>
<td>14</td>
<td>30.17 ± 13.09</td>
<td>35.40 ± 12.34</td>
<td>49.33 ± 13.66</td>
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<tr>
<td>15</td>
<td>18.75 ± 7.54</td>
<td>35.00 ± 6.23</td>
<td>71.20 ± 25.57</td>
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<tr>
<td>16</td>
<td>8.00 ± 5.29</td>
<td>28.83 ± 9.97</td>
<td>45.00 ± 12.57</td>
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<tr>
<td>17</td>
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<td>0</td>
<td>23.66 ± 15.00</td>
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<tr>
<td>18</td>
<td>16.00 ± 6.91</td>
<td>34.00 ± 17.56</td>
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<tr>
<td>Nicardipine</td>
<td>90.50 ± 4.81</td>
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</table>
The results of the tests performed on with barium chloride (4 × 10\(^{-3}\) M) precontracted isolated rat ileum strips indicated that although all of the compounds except Compound 7, 8, 11 and 17 had concentration-dependent relaxation responses, none of the compounds are more active than nicardipine as a spasmolytic agent.

When the compounds are compared with respect to the ester groups, it has been observed that there is not a distinct correlation between the spasmolytic activity and methyl or ethyl esters for most of the compounds.

The introduction of the brom atom on the indole ring altered the mentioned activity positively with the activity order: 15 > 18 > 13 > 14 > 16 > 17. For these compounds it has been observed that compounds bearing methyl substituent instead of the ethyl group in ester function are more active analogs. It has been also determined that there is not a clear difference between the activities of the compounds with respect to the substitution of the cyclohexane ring.

The obtained results showed that most of the synthesized compounds have relaxing effects on ileum strips due to the blockade of Ca\(^{2+}\) channels similar to that of nicardipine. These results enhance the understanding of structure-activity relationships for these Ca\(^{2+}\) channel blockers.

**Conflict of Interest**

All authors of the article declare no conflict of interest.

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