Synthesis of Cyclopentapyridine and Thienopyridine Derivatives as Potential Calcium Channel Modulators

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Key words
- 1,4-Dihydropyridine
- thienopyridine
- cyclopentapyridine
- calcium channel modulator

Abstract

In this study, novel condensed 1,4-dihydropyridines bearing cyclopentanone (1–21) or tetrahydrothiophene-1,1-dioxide ring (22–42) with various ester substituents were synthesized via a modified Hantzsch reaction and their calcium channel modulator activities were investigated on isolated rat ileum and rat thoracic aorta. The introduction of a cyclopentanone ring fused to the 1,4-dihydropyridine nucleus and methyl, ethyl and allyl moieties to the ester group led to more active calcium modulators.

Introduction

Calcium ions play a critical role in various biological functions such as muscle contraction, release of neurotransmitters and regulation of neuronal excitability [1]. Calcium entry into the cytosol is mediated by different types of calcium channels with distinct physiological roles [2]. L-type channels are confined to cell bodies and regulate contractions in muscle cells. Calcium channel antagonists reversibly block Ca^{2+} influx through L-type calcium channels [3]. 1,4-Dihydropyridines (DHP), of which nifedipine is the prototype (**Fig. 1**), are one of the known classes of calcium antagonists, which are frequently used for the treatment of cardiovascular diseases like angina, hypertension and supraventricular tachycardia [4–6].

Since the introduction of DHPs into clinical use, many DHP analogs have been synthesized in order to elucidate the structure-activity relationships and to enhance calcium-modulating effects [7]. It was reported that active derivatives could be obtained by introducing the DHP structure into condensed ring systems such as hexahydroquinolines, indenopyridines, acridines and furoquinolines [8–11]. C-3 and C-5 substituents modulate activity and tissue selectivity and different substituents in these positions alter the activity [12]. 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 [13]. The phenyl ring is preferred as the substituent at the C-4 position because of animal toxicity observed with heteroaromatic rings [14]. Phenyl groups which possess one or more electron-withdrawing substituents at the ortho- or meta-position are preferable to other groups such as alkyls or phenyl groups having a substituent at the para-position [15, 16].

The aim of this work is to evaluate the influence of cyclopentane or tetrahydrothiophene rings fused to the DHP ring and that of various ester groups in combination with 2 halogens attached to the phenyl ring in the 1,4-DHP nucleus. The compounds were synthesized and tested as racemates. The calcium modulator activities of the compounds were assayed on isolated rat ileum and rat thoracic aorta. Although compound 37 has been synthesized previously by Dodd and coworkers [17], there is no data about its calcium channel modulatory activity on ileum and aorta, so it was also synthesized in this study.

Material and Methods

Chemistry

General methods

All chemicals used in this study were purchased from Aldrich and Fluka. Melting points were determined on a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer FT-IR Spectrum BX. ^{1}H-NMR, ^{13}C-NMR DEPT and

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COSY spectra were obtained in dimethyl sulphoxide (DMSO) solutions on a Varian Mercury 400, 400 MHz High Performance Digital FT-NMR Spectrometer. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane. The X-ray crystallographic analysis was carried out on a Nonius Kappa CCD area-detector diffractometer. Mass spectra were obtained on an Agilent 5973 Network Mass Selective Detector by electron ionization. Elemental analyses were performed on a Leco CHNS-932 Elemental Analyzer. Purification by column chromatography was performed on Merck silica gel 60 (0.040–0.063 mm).

Synthesis

The synthesis of tetrahydrothiophene-3-one-1,1-dioxide is shown in (**Fig. 2**). Tetrahydrothiophen-3-one (0.1 mol), triethyl orthoformate (0.1 mol), p-toluensulfonic acid (0.26 mmol) and 2 mL ethanol was stirred for 20 h. The mixture was treated with anhydrous sodium acetate (4 mmol), sodium tungstate dehydrate (0.00085 mmol) and 28 mL water. 28 mL of a 35% solution of hydrogen peroxide in water was added dropwise while keeping the reaction cooled to 30 °C. After stirring overnight at room temperature, the resulting product was filtered and washed with water to achieve 3,3-diethoxytetrahydrothiephene-1,1-dione. The product was stirred in a mixture of HCl and water at 60 °C for 2 h. The mixture was extracted with dichloromethane (60 mL). The dichloromethane layer was isolated and dried with $MgSO_4$, filtered and concentrated. The residue was crystallized from ethanol to provide tetrahydrothiophene-3-one-1,1-dioxide [18].

The compounds 1–42 were prepared (**Fig. 3**) by heating 1,3-cyclopentanedione or tetrahydrothiophene-3-one-1,1-dioxide, the aromatic aldehyde, the appropriate acetoacetate compound and ammonium acetate in methanol, according to the Hantzsch reaction.

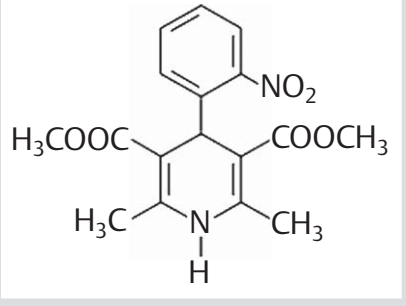


Fig. 1 Nifedipine.

Alkyl 2-methyl-4-(2,3-disubstituted phenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 1–21): 1,3-Cyclopentanedione (0.001 mol), 2,3-disubstituted benzaldehyde (0.001 mol), alkyl acetoacetate (0.001 mol) and ammonium acetate (0.005 mol) were refluxed for 8 h in 15 mL methanol. After the reaction was completed, either the reaction mixture was poored into ice-water, the obtained precipitate was filtered and crystallized from appropriate solvents or the solvent (methanol) was removed via a rotary evaporator and the crude product was then purified by column chromatography using silica gel as the solid phase and a 7:3 mixture of ethyl acetate: methanol as mobile phase.

Alkyl 5-methyl-7-(2,3-disubstituted phenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 22–42): Tetrahydrothiophene-3-on-1,1-dioxide (0.001 mol), 2,3-disubstituted benzaldehyde (0.001 mol), alkyl acetoacetate (0.001 mol) and ammonium acetate (0.005 mol) were refluxed for 8 h in 15 mL methanol. The precipitate, which was obtained after cooling the reaction mixture, was crystallized from methanol.

Pharmacology

The calcium antagonistic activities of the compounds were determined by the tests performed on isolated rat ileum and rat thoracic aorta. All procedures involving animals and their care were conducted in conformity with international laws and policies.

All data are expressed as mean ± standard error. The statistical comparison between groups was performed using general linear models, and p-values less than 0.005 were considered to be statistically significant.

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,

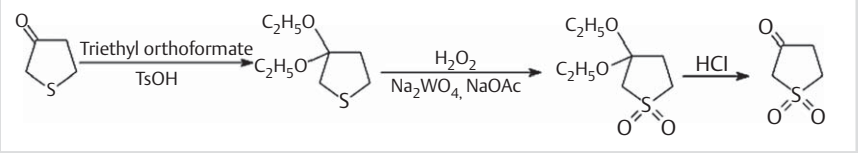
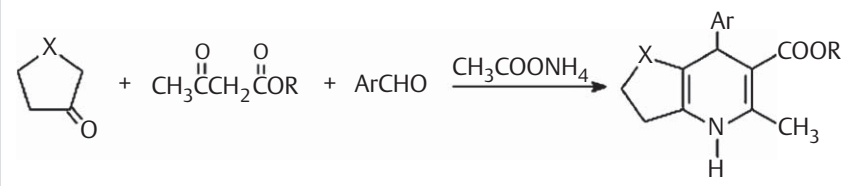


Fig. 2 Synthesis of tetrahydrothiophene-3-one-1,1-dioxide.



X: CO (Compound 1-21), SO_2 (Compound 22-42)
Ar: 2,3-Difluorophenyl, 2-Fluoro-3-chlorophenyl, 2,3-Dichlorophenyl
R: CH_3, C_2H_5, $CH_2CH_2OCH_3$, $CH_2CH=CH_2$, $CH_2CH(CH_3)_2$, $C(CH_3)_3$, $CH_2C_6H_5$

Fig. 3 Synthesis of the compounds 1–42.

the ileum (10–15 cm terminal portion) was immediately removed, discarding the 5–8 cm segment proximal to the ileocaecal 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, $CaCl_2$: 1.80, $MgSO_4$: 0.81, NaH_2PO_4: 4.16, $NaHCO_3$: 11.9, glucose: 5.55. 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 (FDT_{10}-A) 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 [19].

Studies on rat thoracic artery

Rat thoracic artery preparations were also obtained from the same animals, which were used for isolated rat ileum experiments. Rings (3 mm) were suspended in organ baths of 10 mL capacity which contained Tyrode solution. 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. The preparations were allowed to equilibrate for 60 min with regular washes every 15 min. In order to check calcium antagonistic effects, contractions were induced with 67 mmol/L potassium chloride. After washing out, this process was repeated until the amplitude of the contractions became constant. Investigations of the substances were performed using a single-dose technique. Potassium chloride contractions were induced after addition of the test substance and 10 min exposure time. During the administration of the individual substances, the preparation was washed until the initial situation had been re-established and the potassium chloride contractions were induced. The isometric contractions were recorded by an isometric transducer (FDT10-A) May TDA95 Transducer Data Acquisition System [20].

Results

Chemistry

Methyl 2-methyl-4-(2,3-difluorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 1): Purified via column chromatography. Yield: 45%. mp: 223 °C. IR (ν, cm^{-1}): 3288 (N-H), 1699 (C=O, ester), 1638 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.17–2.56 (4H; m; H-6, H-7), 2.27 (3H; s; 2-CH_3), 3.40 (3H; s; $COOCH_3$), 4.91 (1H; s; H-4), 6.89–7.15 (3H; m; Ar-H), 9.82 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 19.2, 24.2, 31.3, 33.8, 51.2, 102.8, 115.1, 124.7, 125.8, 136.7, 147.2, 148.6, 150.9, 151.1, 164.7, 167.3, 201.0. MS (m/z): 319 $[M]^+$. Anal. Calcd. for $C_{17}H_{15}F_2NO_3$: C, 63.95; H, 4.73; N, 4.39. Found: C, 63.49; H, 4.61; N, 4.43.

Ethyl 2-methyl-4-(2,3-difluorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 2): Purified via column chromatography. Yield: 60%. mp: 211 °C'dir. IR (ν, cm^{-1}): 3275 (N-H), 1698 (C=O, ester), 1634 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 0.99 (3H; t; $COOCH_2C\underline{H}_3$), 2.19–2.57 (4H; m; H-6, H-7), 2.31 (3H; s; 2-CH_3), 3.90 (2H; q; $COOC\underline{H}_2CH_3$), 4.95 (1H; s; H-4), 6.92–7.16 (3H; m; Ar-H), 9.83 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 13.6, 18.6, 23.7, 30.7, 33.3, 59.0, 102.4, 114.4, 114.9, 124.2, 125.3, 136.5, 136.6, 146.7, 148.0, 164.2, 166.2, 200.5. MS (m/z): 333 $[M]^+$. Anal. Calcd. for $C_{18}H_{17}F_2NO_3$: C, 64.86; H, 5.14; N, 4.20. Found: C, 64.67; H, 4.55; N, 4.38.

2-Methoxyethyl 2-methyl-4-(2,3-difluorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 3): Purified via column chromatography. Yield: 46%. mp: 156 °C. IR (ν, cm^{-1}): 3268 (N-H), 1680 (C=O, ester), 1642 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.19–2.57 (4H; m; H-6, H-7), 2.31 (3H, s, 2-CH_3), 3.15 (3H; s; OCH3), 3.31–3.38 (2H; m; $C\underline{H}_2OCH_3$), 3.90–4.02 (2H; m; $C\underline{H}_2CH_2OCH_3$), 4.95 (H; s; 4-H), 6.92–7.15 (3H; m; Ar-H), 9.85 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.7, 23.7, 30.7, 33.3, 57.8, 62.3, 69.6, 102.1, 114.4, 115.0, 124.1, 125.3, 136.3, 145.7, 148.1, 150.5, 164.1, 166.2, 200.5. MS (m/z): 363 $[M]^+$. Anal. Calcd. for $C_{19}H_{19}F_2NO_4$: C, 62.81; H, 5.27; N, 3.85. Found: C, 62.16; H, 4.98; N, 3.98.

Allyl 2-methyl-4-(2,3-difluorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 4): Crystallized from benzene/petroleum ether. Yield: 41%. mp: 183 °C. IR (ν, cm^{-1}): 3282 (N-H), 1686 (C=O, ester), 1640 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.14–2.57 (4H; m; H-6, H-7), 2.23 (3H; s; 2-CH_3), 4.37 (H; dd; $C\underline{H}_{2A}$-CH=CH_2), 4.43 (H; dd; $C\underline{H}_{2B}$-CH=CH_2), 4.97 (H; dd; $CH_2CH=C\underline{H}_{2A}$), 4.98 (H; s; 4-H), 5.04 (H; dd; $CH_2CH=CH_{2B}$) 5.66–5.75 (H; m; $C\underline{H}=CH_2$), 6.93–7.15 (3H; m; Ar-H), 9.86 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.8, 23.7, 30.7, 33.3, 63.7, 102.0, 114.7, 115.0, 116.8, 124.2, 125.2, 132.7, 136.3, 136.4, 145.4, 147.3, 164.1, 165.9, 200.5. MS (m/z): 345 $[M]^+$. Anal. Calcd. for $C_{19}H_{17}F_2NO_3$: C, 66.08; H, 4.96; N, 4.06. Found: C, 65.11; H, 4.60; N, 4.09.

Isobutyl 2-methyl-4-(2,3-difluorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 5): Crystallized from ethyl acetate/n-hexane. Yield: 52%. mp: 168 °C. IR (ν, cm^{-1}): 3314 (N-H), 1690 (C=O, ester), 1646 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 0.67 (3H, d, $COOCH_2CHC\underline{H}_3$), 0.73 (3H, d, COO $CH_2CHC\underline{H}_3$), 1.67–1.75 (H; m; $C\underline{H}(CH_3)_2$), 2.15–2.55 (4H; m; H-6, H-7), 2.33 (3H, s, 2-CH_3), 3.63 (H; dd; $C\underline{H}_ACH(CH_3)_2$), 3.71 (H; dd; $C\underline{H}_BCH(CH_3)_2$), 4.97 (H; s; 4-H), 6.93–7.17 (3H; m; Ar-H), 9.79 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.6, 18.8, 19.1, 23.6, 27.1, 30.6, 33.3, 69.3, 102.1, 114.4, 124.2, 125.1, 136.4, 145.3, 147.2, 148.2, 150.5, 164.0, 166.3, 200.4. MS (m/z): 360 $[M-1]^+$. Anal. Calcd. for $C_{20}H_{21}F_2NO_3$: C, 66.47; H, 5.86; N, 3.88. Found: C, 66.24; H, 5.86; N, 3.94.

Tert-butyl 2-methyl-4-(2,3-difluorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 6): Crystallized from ethyl acetate/n-hexane. Yield: 48%. mp: 196 °C. IR (ν, cm^{-1}): 3302 (N-H), 1696 (C=O, ester), 1632 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 1.16 (9H; s; $COOC(C\underline{H}_3)_3$), 2.12–2.52 (4H; m; H-6, H-7), 2.24 (3H; s; 2-CH_3), 4.88 (H; s; 4-H), 6.89–7.34 (3H; m; Ar-H), 9.67 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.9, 23.9, 24.0, 24.1, 28.0, 31.5, 33.7, 79.4, 104.3, 115.0, 124.6, 125.8, 136.9, 145.9, 146.1, 148.6, 150.9, 164.5, 166.2, 200.9. MS (m/z): 360 $[M-1]^+$. Anal. Calcd. for $C_{20}H_{21}F_2NO_3$: C, 66.47; H, 5.86; N, 3.88. Found: C, 66.40; H, 5.80; N, 3.85.

Benzyl 2-methyl-4-(2,3-difluorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 7): Crystallized from ethyl acetate/n-hexane. Yield: 54%. mp: 202 °C. IR (ν, cm^{-1}): 3260 (N-H), 1695 (C=O, ester), 1630 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.19–2.57 (4H; m; H-6, H-7), 2.33 (3H; s; 2-CH_3), 4.93, 5.02 (1H, AB system, J_{AB}=12.8Hz, COOC$\underline{H}_2$C$_6$H$_5$), 4.99 (1H; s; H-4), 6.90–7.27 (8H; m; Ar-H), 9.77 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.8, 23.7, 30.7, 33.3, 64.7, 101.8, 114.5, 115.0, 124.1, 125.2, 127.4, 127.6, 128.1, 136.2, 145.4, 145.6, 147.5, 147.9, 148.1, 150.5, 164.0, 166.1, 200.5. MS (m/z): 395 $[M]^+$. Anal. Calcd. for $C_{23}H_{19}F_2NO_3$: C, 69.87; H, 4.84; N, 3.54. Found: C, 69.25; H, 4.77; N, 3.61.

Methyl 2-methyl-4-(2-fluoro-3-chlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 8): Purified via column chromatography. Yield: 52%. mp: 245 °C. IR (ν, cm^{-1}): 3268 (N-H), 1709 (C=O, ester), 1634 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.20–2.59 (4H; m; H-6, H-7), 2.30 (3H; s; 2-CH_3), 3.44 (3H; s; $COOCH_3$), 4.93 (1H; s; H-4), 7.06–7.34 (3H; m; Ar-H), 9.85 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.7, 23.7, 31.5, 33.3, 50.6, 102.3, 114.8, 119.2, 124.9, 128.1, 129.2, 135.6, 146.8, 155.5, 164.3, 166.8, 200.5. MS (m/z): 334 $[M-1]^+$. Anal. Calcd. for $C_{17}H_{15}ClFNO_3$: C, 60.81; H, 4.50; N, 4.17. Found: C, 60.13; H, 4.66; N, 4.29.

Ethyl 2-methyl-4-(2-fluoro-3-chlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 9): Purified via column chromatography. Yield: 64%. mp: 239 °C. IR (ν, cm^{-1}): 3272 (N-H), 1698 (C=O, ester), 1632 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 0.98 (3H; t; $COOCH_2C\underline{H}_3$), 2.20–2.58 (4H; m; H-6, H-7), 2.30 (3H; s; 2-CH_3), 3.87 (2H; q; $COO\underline{H}_2CH_3$), 4.94 (1H; s; H-4), 7.06–7.34 (3H; m; Ar-H), 9.84 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 13.6, 18.6, 23.7, 31.2, 33.3, 59.0, 102.4, 114.9, 119.1, 124.9, 129.2, 135.9, 146.7, 152.9, 155.4, 164.2, 166.2, 200.5. MS (m/z): 349 $[M]^+$. Anal. Calcd. for $C_{18}H_{17}ClFNO_3$: C, 61.81; H, 4.90; N, 4.00. Found: C, 61.37; H, 5.10; N, 4.11.

2-Methoxyethyl 2-methyl-4-(2-fluoro-3-chlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 10): Purified via column chromatography. Yield: 51%. mp: 158 °C. IR (ν, cm^{-1}): 3319 (N-H), 1696 (C=O, ester), 1637 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.12–2.57 (4H; m; H-6, H-7), 2.31 (3H, s, 2-CH_3), 3.15 (3H; s; OCH3), 3.31–3.42 (2H; m; C$\underline{H}_2$OCH$_3$), 3.91–4.02 (2H; m; C$\underline{H}_2$CH$_2$OCH$_3$), 4.95 (H; s; 4-H), 6.92–7.17 (3H; m; Ar-H), 9.85 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 19.2, 24.2, 31.9, 36.4, 58.4, 64.8, 70.1, 102.6, 115.4, 125.3, 128.5, 129.7, 131.8, 136.1, 147.7, 153.6, 156.1,166.7, 200.5. MS (m/z): 379 $[M]^+$. Anal. Calcd. for $C_{19}H_{19}ClFNO_4$: C, 60.08; H, 5.04; N, 3.69. Found: C, 59.99; H, 4.99; N, 3.73.

Allyl 2-methyl-4-(2-fluoro-3-chlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 11): Purified via column chromatography. Yield: 49%. mp: 194 °C. IR (ν, cm^{-1}): 3265 (N-H), 1740 (C=O, ester), 1712 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.15–2.58 (4H; m; H-6, H-7), 2.32 (3H; s; 2-CH_3), 4.36 (H; dd; C$\underline{H}_{2A}$-CH=CH$_2$), 4.25 (H; dd; C$\underline{H}_{2B}$-CH=CH$_2$), 4.96 (H; s; 4-H), 4.99 (H; dd; CH$_2$CH=C$\underline{H}_{2A}$), 5.05 (H; dd; CH$_2$CH=C$\underline{H}_{2B}$), 5.65–5.76 (H; m; C$\underline{H}$=CH$_2$), 7.06–7.33 (3H; m; Ar-H), 9.85 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.8, 23.7, 31.3, 33.3, 63.7, 102.1, 117.0, 119.2, 124.9, 128.0, 129.1, 132.6, 135.7, 147.3, 153.0, 155.4, 164.2, 165.9, 200.5. MS (m/z): 361 $[M]^+$. Anal. Calcd. for $C_{19}H_{17}ClFNO_3$: C, 63.08; H, 4.74; N, 3.87. Found: C, 62.97; H, 4.89; N, 3.90.

Isobutyl 2-methyl-4-(2-fluoro-3-chlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 12): Purified via column chromatography. Yield: 56%. mp: 163 °C. IR (ν, cm^{-1}): 3254 (N-H), 1697 (C=O, ester), 1628 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 0.65 (3H; d; $COOCH_2CHC\underline{H}_3$), 0.72 (3H; d; COO $CH_2CHC\underline{H}_3$), 1.66–1.74 (H; m; C$\underline{H}$(CH$_3$)$_2$), 2.14–2.57 (4H; m; H-6, H-7), 2.33 (3H; s; 2-CH_3), 3.60 (H; dd; C$\underline{H}_{2A}$CH(CH$_3$)$_2$), 3.71 (H; dd; C$\underline{H}_{2B}$CH(CH$_3$)$_2$), 4.95 (H; s; 4-H), 7.07–7.33 (3H; m; Ar-H), 9.86 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.5, 18.6, 18.8, 23.7, 27.1, 31.1, 33.3, 69.4, 102.1, 115.0, 119.3, 125.0, 129.0, 135.9, 147.3, 152.8, 155.3, 164.1, 166.3, 200.4. MS (m/z): 377 $[M]^+$. Anal. Calcd. for $C_{20}H_{21}ClFNO_3$: C, 63.58; H, 5.60; N, 3.71. Found: C, 63.63; H, 5.41; N, 3.81.

Tert-butyl 2-methyl-4-(2-fluoro-3-chlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 13): Crystallized from ethyl acetate/n-hexane. Yield: 49%. mp: 207 °C. IR (ν, cm^{-1}): 3266 (N-H), 1696 (C=O, ester), 1631 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 1.16 (9H; s; COOC(C$\underline{H}_3$)$_3$), 2.12–2.52 (4H; m; H-6, H-7), 2.24 (3H; s; 2-CH_3), 4.88 (H; s; 4-H), 7.07–7.32 (3H; m; Ar-H), 9.63 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.9, 24.1, 24.3, 24.5, 28.0, 32.0, 33.7, 79.4, 104.4, 115.0, 119.5, 125.4, 128.3, 129.7, 136.4, 146.2, 153.3, 155.8, 166.2, 165.9, 200.7. MS (m/z): 377 $[M]^+$. Anal. Calcd. for $C_{20}H_{21}ClFNO_3$: C, 63.58; H, 5.60; N, 3.71. Found: C, 63.27; H, 5.22; N, 3.84.

Benzyl 2-methyl-4-(2-fluoro-3-chlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 14): Crystallized from ethyl acetate. Yield: 48%. mp: 172 °C. IR (ν, cm^{-1}): 3261 (N-H), 1699 (C=O, ester), 1633 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.19–2.56 (4H; m; H-6, H-7), 2.32 (3H; s; 2-CH_3), 4.89, 4.99 (1H, AB system, J_{AB}=13.2Hz, COOC$\underline{H}_2$C$_6$H$_5$), 4.95 (1H; s; H-4), 7.00–7.36 (8H; m; Ar-H), 9.88 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 19.3, 24.2, 31.9, 33.8, 65.3, 102.4, 115.5, 119.8, 125.4, 127.9, 128.1, 128.5, 128.6, 129.6, 135.9, 136.1, 136.8, 148.1, 153.5, 155.9, 164.7, 166.6, 200.1. MS (m/z): 411 $[M]^+$. Anal. Calcd. for $C_{23}H_{19}ClFNO_3$: C, 67.07; H, 4.65; N, 3.40. Found: C, 66.67; H, 4.67; N, 3.40.

Methyl 2-methyl-4-(2,3-dichlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 15): Crystallized from ethyl acetate/n-hexane. Yield: 62%. mp: 216 °C. IR (ν, cm^{-1}): 3294 (N-H), 1741 (C=O, ester), 1640 (C=O gerilim, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.10–2.57 (4H; m; H-6, H-7), 2.29 (3H; s; 2-CH_3), 3.41 (3H; s; $COOCH_3$), 5.17 (1H; s; H-4), 7.14–7.37 (3H; m; Ar-H), 9.76 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 19.0, 23.7, 33.2, 36.4, 51.0, 103.1, 115.6, 127.8, 128.3, 129.8, 130.5, 131.2, 146.5, 147.0, 164.0, 166.8, 200.4. DEPT-135 (δ, DMSO-d_6): 19.0 (CH_3), 23.7 (CH_2), 33.2 (CH_2), 36.4 (CH), 51.0 (CH_3), 128.3 (CH), 129.8 (CH), 130.5 (CH). MS (m/z): 351 $[M-1]^+$. Anal. Calcd. for $C_{17}H_{15}Cl_2NO_3$: C, 57.97; H, 4.29; N, 3.98. Found: C, 57.91; H, 4.24; N, 3.90.

Ethyl 2-methyl-4-(2,3-dichlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 16): Crystallized from ethyl acetate. Yield: 56%. mp: 206 °C. IR (ν, cm^{-1}): 3380 (N-H), 1675 (C=O, ester), 1639 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 0.93 (3H; t; $COOCH_2C\underline{H}_3$), 2.14–2.56 (4H; m; H-6,

H-7), 2.29 (3H; s; 2-CH_3), 3.85 (2H; q; $COOCH_2CH_3$), 5.71 (1H; s; H-4), 7.15–7.38 (3H; m; Ar-H), 9.80 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 14.2, 19.1, 24.2, 33.7, 36.5, 59.4, 103.8, 116.0, 128.3, 128.8, 129.8, 130.7, 131.7, 147.0, 147.6, 164.4, 166.8, 200.8. MS (m/z): 366 $[M]^+$. Anal. Calcd. for $C_{18}H_{17}Cl_2NO_3$: C, 59.03; H, 4.68; N, 3.82. Found: C, 59.87; H, 4.56; N, 3.74.

2-Methoxyethyl 2-methyl-4-(2,3-dichlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 17): Crystallized from benzene/petroleum ether. Yield: 58%. mp: 153 °C. IR (ν, cm^{-1}): 3263 (N-H), 1676 (C=O ester), 1637 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.12–2.56 (4H; m; H-6, H-7), 2.30 (3H, s, 2-CH_3), 3.12 (3H; s; OCH3), 3.26–3.34 (2H; m; CH_2OCH_3), 3.89–3.98 (2H; m; $CH_2CH_2OCH_3$), 5.16 (H; s; 4-H), 7.15–7.37 (3H; m; Ar-H), 9.90 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.7, 23.7, 33.3, 36.0, 57.8, 62.2, 69.5, 102.9, 115.5, 127.7, 127.9, 128.2, 129.4, 130.1, 131.3, 146.8, 147.0, 166.3, 200.3. MS (m/z): 396 $[M]^+$. Anal. Calcd. for $C_{19}H_{19}Cl_2NO_4$: C, 57.59; H, 4.83; N, 3.53. Found: C, 57.70; H, 4.68; N, 3.43.

Allyl 2-methyl-4-(2,3-dichlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 18): Crystallized from ethyl acetate/n-hexane. Yield: 44%. mp: 192 °C. IR (ν, cm^{-1}): 3315 (N-H), 1711 (C=O, ester), 1640 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.10–2.55 (4H; m; H-6, H-7), 2.29 (3H; s; 2-CH_3), 4.32 (H; dd; $CH_{2\,A}$-CH=CH_2), 4.39 (H; dd; CH_{2B}-CH=CH_2), 4.89 (H; dd; CH_2CH=$CH_{2\,A}$), 4.98 (H; dd; CH_2CH=CH_{2B}), 5.17 (H; s; 4-H), 5.60–5.69 (H; m; CH=CH_2), 7.14–7.35 (3H; m; Ar-H), 9.78 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.5, 23.7, 33.2, 36.7, 79.1, 104.8, 114.7, 127.6, 127.8, 128.2, 129.4, 130.3, 131.3, 132.1, 145.0, 146.6, 164.1, 165.9, 200.2. MS (m/z): 377 $[M-1]^+$. Anal. Calcd. for $C_{19}H_{17}Cl_2NO_3$: C, 60.33; H, 4.53; N, 3.70. Found: C, 60.13; H, 4.38; N, 3.83.

Isobutyl 2-methyl-4-(2,3-dichlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 19): Crystallized from ethyl acetate. Yield: 63%. mp: 234 °C. IR (ν, cm^{-1}): 3306 (N-H), 1699 (C=O, ester), 1638 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 0.58 (3H; d; $COOCH_2CHCH_3$), 0.69 (3H; d; $COOCH_2CHCH_3$), 1.68–1.76 (H; m; $CH(CH_3)_2$), 2.14–2.55 (4H; m; H-6, H-7), 2.32 (3H; s; 2-CH_3), 3.58 (H; dd; $CH_{2\,A}CH(CH_3)_2$), 3.70 (H; dd; $CH_{2B}CH(CH_3)_2$), 5.17 (H; s; 4-H), 7.16–7.37 (3H; m; Ar-H), 9.78 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.6, 18.8, 20.7, 23.7, 27.0, 33.3, 35.9, 69.3, 103.1, 115.7, 127.8, 127.9, 129.1, 130.1, 131.4, 147.0, 147.1, 163.9, 166.4, 200.3. MS (m/z): 393 $[M-1]^+$. Anal. Calcd. for $C_{20}H_{21}Cl_2NO_3$: C, 60.92; H, 5.37; N, 3.55. Found: C, 60.94; H, 5.07; N, 3.69.

Tert-butyl 2-methyl-4-(2,3-dichlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 20): Crystallized from ethyl acetate/n-hexane. Yield: 54%. mp: 193 °C. IR (ν, cm^{-1}): 3276 (N-H), 1697 (C=O, ester), 1634 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 1.14 (9H; s; $COOC(CH_3)_3$), 2.11–2.51 (4H; m; H-6, H-7), 2.21 (3H; s; 2-CH_3), 5.08 (H; s; 4-H), 7.14–7.39 (3H; m; Ar-H), 9.66 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.7, 23.5, 23.6, 23.7, 33.3, 35.9, 38.8, 63.7, 103.2, 115.6, 127.8, 127.9, 129.3, 130.2, 131.3, 132.7, 147.0, 163.9, 165.9, 200.4. MS (m/z): 394 $[M]^+$. Anal. Calcd. for $C_{20}H_{21}Cl_2NO_3$: C, 60.92; H, 5.37; N, 3.55. Found: C, 60.84; H, 5.47; N, 3.59.

Benzyl 2-methyl-4-(2,3-dichlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 21): Crystallized from benzene/petroleum ether. Yield: 58%. mp: 129 °C. IR (ν, cm^{-1}): 3257 (N-H), 1698 (C=O, ester), 1632 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.11–2.56 (4H; m; H-6, H-7), 2.30 (3H; s; 2-CH_3), 4.87, 4.99 (1H, AB system, J_{AB}=12.8Hz, $COOCH_2C_6H_5$), 5.20 (1H; s; H-4), 6.96–7.35 (8H; m; Ar-H), 9.79 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 19.3, 24.2, 33.7, 36.4, 65.1, 103.3, 116.2, 127.9, 128.0, 128.2, 128.4, 128.5, 128.7, 129.8, 130.7, 131.9, 132.8, 136.9, 147.4, 147.9. 165.4, 166.6, 200.8. MS (m/z): 427 $[M-1]^+$. Anal. Calcd. for $C_{23}H_{19}Cl_2NO_3$: C, 64.50; H, 4.47; N, 3.27. Found: C, 64.96; H, 4.27; N, 3.24.

Methyl 5-methyl-7-(2,3-difluorophenyl)-2,3,4,7-tetrahydrothieno-[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 22): Yield: 61%. mp: 264 °C. IR (ν, cm^{-1}): 3337 (N-H), 1683 (C=O), 1303, 1166 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.28 (3H; s; 5-CH_3), 2.78 (H; ddd; H-3_A), 2.85 (H; ddd; H-3_B), 3.26 (H; ddd; H-2_A), 3.31 (H; ddd; H-2_B), 3.44 (3H; s; $COOCH_3$), 5.14 (1H; s; H-7), 6.69–7.22 (3H; m; Ar-H), 9.50 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 19.2, 23.2, 30.2, 49.2, 51.3, 99.7, 112.0, 115.7, 124.9, 125.4, 135.8, 142.7, 145.9, 148.3, 151.1, 167.0. MS (m/z): 354 $[M-1]^+$. Anal. Calcd. for $C_{16}H_{15}F_2NO_4S$: C, 54.08; H, 4.25; N, 3.94; S, 9.02. Found: C, 53.89; H, 4.26; N, 4.43; S, 9.18.

Ethyl 5-methyl-7-(2,3-difluorophenyl)-2,3,4,7-tetrahydrothieno-[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 23): Yield: 75%. mp: 273 °C. IR (ν, cm^{-1}): 3333 (N-H), 1686 (C=O), 1252, 1135 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 0.99 (3H; t; $COOCH_2CH_3$), 2.28 (3H; s; 5-CH_3), 2.77 (H; ddd; H-3_A), 2.84 (H; ddd; H-3_B), 3.26 (H; ddd; H-2_A), 3.32 (H; ddd; H-2_B), 3.85 (H; dq; $COOCH_{2A}$-CH_3), 3.92 (H; dq; $COOCH_{2B}$-CH_3) 5.15 (H; s; H-7), 6.97–7.22 (3H; m; Ar-H), 9.48 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 14.2, 19.1, 23.2, 30.1, 49.1, 59.6, 99.9, 112.0, 115.6, 115.8, 125.0, 125.5, 135.9, 136.1, 142.6, 148.2, 166.4. MS (m/z): 368 $[M-1]^+$. Anal. Calcd. for $C_{17}H_{17}F_2NO_4S$: C, 55.28; H, 4.64; N, 3.79; S, 8.68. Found: C, 54.96; H, 4.26; N, 3.94; S, 8.65.

2-Methoxyethyl 5-methyl-7-(2,3-difluorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 24): Yield: 57. mp: 239 °C'dir. IR (ν, cm^{-1}): 3343 (N-H), 1665 (C=O), 1279, 1096 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.11 (H; ddd; H-3_A), 2.28 (3H; s; 5-CH_3), 2.43 (H; ddd; H-3_B), 3.02 (3H; s; OCH3), 3.08 (H; ddd; H-2_A), 3.21–3.35 (2H; m; CH_2OCH_3), 3.39 (H; ddd; H-2_B), 3.78 (H; ddd; $CH_{2\,A}CH_2OCH_3$), 3.93 (H; ddd; $CH_{2B}CH_2OCH_3$), 4.59 (H; s; 7-H), 5.89 (H; s; N-H), 6.96–7.44 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.2, 33.8, 34.2, 48.6, 57.8, 65.9, 70.0, 82.5, 99.3, 111.7, 115.9, 123.8, 126.8, 133.0, 142.1, 148.4, 153.6, 166.4. MS (m/z): 398 $[M-1]^+$. Anal. Calcd. for $C_{18}H_{19}F_2NO_5S$: C, 54.13; H, 4.79; N, 3.51; S, 8.03. Found: C, 54.40; H, 4.55; N, 3.55; S, 7.89.

Allyl 5-methyl-7-(2,3-difluorophenyl)-2,3,4,7-tetrahydrothieno-[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 25): Yield: 64%. mp: 240 °C. IR (ν, cm^{-1}): 3339 (N-H), 1666 (C=O), gerilim), 1288, 1132 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.12 (H; ddd; H-3_A), 2.29 (3H; s; 5-CH_3), 2.40 (H; ddd; H-3_B), 3.08 (H; ddd; H-2_A), 3.40 (H; ddd; H-2_B), 4.37 (H; dd; $CH_{2\,A}CH$=CH_2), 4.42 (H; dd; $CH_{2B}CH$=CH_2), 4.94 (H; dd; CH_2CH=CH_{2A}), 5.02 (H; dd; CH_2CH=CH_{2B}), 5.18 (H; s; 7-H), 5.66–5.73 (H; m; CH=CH_2), 6.69–7.49 (3H; m; Ar-H), 9.53 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 20.8, 30.1, 34.3, 49.2, 64.3, 83.0, 99.8, 115.7, 117.3, 124.2,

125.4, 127.3, 129.6, 135.8, 142.5, 148.6, 150.2, 166.0. MS (m/z): 381 $[M]^+$. Anal. Calcd. for $C_{18}H_{17}F_2NO_4S$: C, 56.69; H, 4.49; N, 3.67; S, 8.41. Found: C, 57.08; H, 4.45; N, 3.72; S, 8.45.

Isobutyl 5-methyl-7-(2,3-difluorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 26): Yield: 68%. mp: 264 °C. IR (ν, cm^{-1}): 3364 (N-H), 1683 (C=O), 1245, 1084 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 0.55 (3H; d; $COOCHC\underline{H}_3$), 0.58 (3H; d; $COOCHC\underline{H}_3$), 1.48–1.57 (H; m; $C\underline{H}(CH_3)_2$), 2.13 (H; ddd; H-3_A), 2.32 (3H; s; 5-CH_3), 2.46 (H; ddd; H-3_B), 3.03 (H; ddd; H-2_A), 3.37 (H; ddd; H-2_B), 3.49 (H; dd; $C\underline{H}_{2A}CH(CH_3)_2$), 3.65 (H; dd; $C\underline{H}_{2B}CH(CH_3)_2$), 4.62 (H; s; 7-H), 5.88 (H; s; N-H), 7.01–7.45 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 18.9, 19.0, 20.7, 27.6, 34.3, 34.7, 49.2, 69.9, 83.0, 99.9, 115.7, 124.0, 125.2, 127.3, 133.6, 142.5, 148.8, 154.1, 166.8. MS (m/z): 397 $[M]^+$. Anal. Calcd. for $C_{19}H_{21}F_2NO_4S$: C, 57.42; H, 5.33; N, 3.52; S, 8.07. Found: C, 57.06; H, 4.94; N, 3.57; S, 8.34.

Tert-butyl 5-methyl-7-(2,3-difluorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 27): Yield: 58%. mp: 259 °C. IR (ν, cm^{-1}): 3368 (N-H), 1684 (C=O), 1304, 1133 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 1.09 (9H; s; $COOC(C\underline{H}_3)_3$), 2.12 (H; ddd; H-3_A), 2.26 (3H; s; 5-CH_3), 2.44 (H; ddd; H-3_B), 3.06 (H; ddd; H-2_A), 3.39 (H; ddd; H-2_B), 4.53 (H; s; 7-H), 5.89 (H; s; N-H), 6.99–7.27 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.5, 28.2, 28.4, 28.7, 30.3, 34.5, 49.1, 80.9, 92.6, 101.2, 115.6, 124.9, 126.0, 134.3, 136.1, 142.4, 147.3, 153.0, 166.5. MS (m/z): 397 $[M]^+$. Anal. Calcd. for $C_{19}H_{21}F_2NO_4S$: C, 57.42; H, 5.33; N, 3.52; S, 8.07. Found: C, 57.16; H, 5.28; N, 3.77; S, 8.63.

Benzyl 5-methyl-7-(2,3-difluorophenyl)-2,3,4,7-tetrahydrothieno-[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 28): Yield: 67%. mp: 237 °C'dir. IR (ν, cm^{-1}): 3341 (N-H), aromatik), 1665 (C=O), 1288, 1131 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.14 (H; ddd; H-3_A), 2.33 (3H; s; 5-CH_3), 2.46 (H; ddd; H-3_B), 3.05 (H; ddd; H-2_A), 3.39 (H; ddd; H-2_B), 4.65 (H; s; 7-H), 4.77, 4.98 (1H, AB system, J_{AB}=13.2Hz, $COO\underline{H}_2C_6H_5$), 5.94 (H; s; N-H) 6.81–7.55 (8H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.8, 28.6, 34.7, 51.0, 66.4, 81.2, 90.1, 115.3, 115.5, 124.1, 125.8, 127.2, 127.7, 128.4, 128.6, 133.5, 133.6, 137.4, 143.6, 149.9, 154.6, 166.6. MS (m/z): 430 $[M-1]^+$. Anal. Calcd. for $C_{22}H_{19}F_2NO_4S$: C, 61.24; H, 4.44; N, 3.25; S, 7.43. Found: C, 61.52; H, 4.56; N, 3.29; S, 7.31.

Methyl 5-methyl-7-(2-fluoro-3-chlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 29): Yield: 59%. mp:245 °C. IR (ν, cm^{-1}): 3346 (N-H), 1663 (C=O), 1303, 1128 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.27 (3H; s; 5-CH_3), 2.78 (H; ddd; H-3_A), 2.85 (H; ddd; H-3_B), 3.25 (H; ddd; H-2_A), 3.33 (H; ddd; H-2_B), 3.43 (3H; s; $COOCH_3$), 5.13 (1H; s; H-7), 7.08–7.37 (3H; m; Ar-H), 9.51 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 19.2, 23.2, 30.9, 49.2, 51.3, 99.7, 112.0, 119.7, 125.6, 129.2, 134.9, 135.1, 142.7, 148.3, 156.0, 167.0. EI-MS (m/z): 370 $[M-1]^+$. Anal. Calcd. for $C_{16}H_{15}ClFNO_4S$: C, 51.69; H, 4.07; N, 3.77; S, 8.62. Found: C, 51.91; H, 3.74; N, 3.89; S, 8.45.

Ethyl 5-methyl-7-(2-fluoro-3-chlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 30): Yield: 56%. mp: 239 °C. IR (ν, cm^{-1}): 3348 (N-H), 1663 (C=O), 1287, 1127 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 0.97 (3H; t; $COOCH_2C\underline{H}_3$), 2.12 (H; ddd; H-3_A), 2.28 (3H; s; 5-CH_3), 2.45 (H; ddd; H-3_B), 3.03 (H; ddd; H-2_A), 3.37 (H; ddd; H-2_B), 3.74 (H; dq; $COOC\underline{H}_{2A}$-CH_3), 3.87 (H; dq; $COOC\underline{H}_{2B}$-CH_3) 5.12 (H; s; H-7), 7.04–7.43 (3H; m; Ar-H), 9.51 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 14.1, 20.7, 30.6, 34.6, 51.0, 59.6, 81.1, 90.8, 112.0, 129.4, 133.1, 135.4, 142.6, 148.2, 154.0, 156.5, 166.9. EI-MS (m/z): 385 $[M]^+$. Anal. Calcd. for $C_{17}H_{17}ClFNO_4S$: C, 52.92; H, 4.44; N, 3.63; S, 8.31. Found: C, 52.22; H, 4.61; N, 3.81; S, 8.42.

2-Methoxythyl 5-methyl-7-(2-fluoro-3-chlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 31): Yield: 64%. mp: 189 °C. IR (ν, cm^{-1}): 3332 (N-H), 1665 (C=O), 1284, 1125 (S=O gerilim). ^{1}H-NMR (δ, DMSO-d_6): 2.12 (H; ddd; H-3_A), 2.28 (3H; s; 5-CH_3), 2.42 (H; ddd; H-3_B), 3.01 (3H; s; OCH3), 3.08 (H; ddd; H-2_A), 3.21–3.27 (2H; m; $C\underline{H}_2OCH_3$), 3.38 (H; ddd; H-2_B), 3.78 (H; ddd; $C\underline{H}_{2A}CH_2OCH_3$), 3.93 (H; ddd; $C\underline{H}_{2B}CH_2OCH_3$), 4.57 (H; s; 7-H), 5.88 (H; s; N-H), 7.02–7.38 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.7, 29.0, 34.6, 51.2, 58.3, 66.3, 70.5, 81.1, 90.5, 119.5, 124.7, 128.6, 129.5, 129.8, 133.0, 150.3, 154.2,166.9. EI-MS (m/z): 415 $[M]^+$. Anal. Calcd. for $C_{18}H_{19}ClFNO_5S$: C, 51.99; H, 4.61; N, 3.37; S, 7.71. Found: C, 51.10; H, 4.54; N, 3.49; S, 7.89.

Allyl 5-methyl-7-(2-fluoro-3-chlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 32): Yield: 58%. mp: 232°C'dir. IR (ν, cm^{-1}): 3335 (N-H), 1699 (C=O), 1281, 1129 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.13 (H; ddd; H-3_A), 2.34 (3H; s; 5-CH_3), 2.44 (H; ddd; H-3_B), 3.03 (H; ddd; H-2_A), 3.39 (H; ddd; H-2_B), 4.27 (H; dd; $C\underline{H}_{2A}CH=CH_2$), 4.35 (H; dd; $C\underline{H}_{2B}CH=CH_2$), 4.75 (H; s; 7-H), 4.84 (H; dd; $CH_2CH=C\underline{H}_{2A}$), 4.93 (H; dd; $CH_2CH=C\underline{H}_{2B}$) 5.57–5.65 (H; m; $C\underline{H}=CH_2$), 5.86 (H; s; N-H) 7.22–7.57 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.8, 30.6, 34.2, 51.0, 66.3, 83.0, 99.6, 119.6, 124.8, 125.6, 128.7, 129.3, 132.7, 133.8, 148.8, 150.3, 154.5, 166.5. EI-MS (m/z): 397 $[M]^+$. Anal. Calcd. for $C_{18}H_{17}ClFNO_4S$: C, 54.34; H, 4.31; N, 3.52; S, 8.06. Found: C, 54.03; H, 4.53; N, 3.71; S, 8.55.

Isobutyl 5-methyl-7-(2-fluoro-3-chlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 33): Yield: 66%. mp: 243 °C'dir. IR (ν, cm^{-1}): 3339 (N-H), 1683 (C=O), 1304, 1132 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 0.52 (3H; d; $COOCHC\underline{H}_3$), 0.56 (3H; d; $COOCHC\underline{H}_3$), 1.48–1.55 (H; m; $C\underline{H}(CH_3)_2$), 2.11 (H; ddd; H-3_A), 2.31 (3H; s; 5-CH_3), 2.44 (H; ddd; H-3_B), 3.02 (H; ddd; H-2_A), 3.38 (H; ddd; H-2_B), 3.47 (H; dd; $C\underline{H}_{2A}CH(CH_3)_2$), 3.62 (H; dd; $C\underline{H}_{2B}CH(CH_3)_2$), 4.58 (H; s; 7-H), 5.86 (H; s; N-H), 7.05–7.44 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 18.9, 19.0, 20.7, 27.7, 34.2, 34.7, 49.2, 69.9, 83.0, 90.2, 112.2, 124.8, 125.7, 128.6, 129.5, 131.1, 142.5, 156.5, 166.8. MS (m/z): 413 $[M]^+$. Anal. Calcd. for $C_{19}H_{21}ClFNO_4S$: C, 55.14; H, 5.11; N, 3.38; S, 7.75. Found: C, 55.38; H, 4.51; N, 3.57; S, 7.27.

Tert-butyl 5-methyl-7-(2-fluoro-3-chlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 34): Yield: 70%. mp: 241 °C'dir. IR (ν, cm^{-1}): 3340 (N-H), 1689 (C=O), 1304, 1132 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 1.05 (9H; s; $COOC(CH_3)_3$), 2.10 (H; ddd; H-3_A), 2.23 (3H; s; 5-CH_3), 2.42 (H; ddd; H-3_B), 3.06 (H; ddd; H-2_A), 3.38 (H; ddd; H-2_B), 4.49 (H; s; 7-H), 5.86 (H; s; N-H), 7.05–7.40 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.0, 27.5, 27.6, 27.7, 30.3, 34.0, 48.5, 80.4, 92.1, 99.1, 124.4, 125.2, 128.4, 129.2, 130.6, 133.3, 149.8, 156.0, 166.0. MS (m/z): 413 $[M]^+$. Anal. Calcd. for $C_{19}H_{21}ClFNO_4S$: C, 55.14; H, 5.11; N, 3.38; S, 7.75. Found: C, 55.17; H, 4.95; N, 3.61; S, 7.05.

Benzyl 5-methyl-7-(2-fluoro-3-chlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 35): Yield: 72%. mp: 208°C. IR (ν, cm^{-1}): 3348 (N-H), 1664 (C=O), 1303, 1130 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.12 (H; ddd; H-3_A), 2.33 (3H; s; 5-CH_3), 2.43 (H; ddd; H-3_B), 3.04 (H; ddd; H-2_A), 3.38 (H; ddd; H-2_B), 4.61 (H; s; 7-H), 4.74, 4.94 (1H, AB system, J_{AB}=13.2Hz, $COO\underline{H}_2C_6H_5$), 5.90 (H; s; N-H), 6.77–7.54 (8H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.8, 29.0, 34.7, 49.2, 66.8, 83.0, 89.9, 124.9, 125.6, 127.7, 128.1, 128.6, 129.1, 129.6, 131.1, 132.8, 133.0, 136.7, 137.4, 142.5, 156.5, 166.6. EI-MS (m/z): 447 $[M]^+$. Anal. Calcd. for $C_{22}H_{19}ClFNO_4S$: C, 58.99; H, 4.28; N, 3.13; S, 7.16. Found: C, 58.12; H, 4.43; N, 3.34; S, 7.73.

Methyl 5-methyl-7-(2,3-dichlorophenyl)-2,3,4,7-tetrahydrothieno-[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 36): Yield: 48%. mp: 230 °C. IR (ν, cm^{-1}): 3373 (N-H), 1660 (C=O), 1299, 1127 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.11 (H, ddd, H-3_A), 2.32 (3H; s; 5-CH_3), 2.42 (H, ddd, H-3_B), 3.01 (H, ddd, H-2_A), 3.34 (3H; s; $COOCH_3$), 3.40 (H, ddd, H-2_B), 4.69 (1H; s; H-7), 5.82 (H; s; N-H), 7.18–7.46(3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.8, 34.2, 34.8, 50.7, 51.1, 81.5, 91.2, 127.7, 128.8, 129.4, 129.8, 130.5, 131.8, 143.2, 153.9, 167.6. DEPT-135 (δ, DMSO-d_6): 20.8 (CH_3), 34.2 (CH), 34.8 (CH_2), 50.7 (CH_2), 51.1 (CH_3), 127.7 (CH), 128.8 (CH),129.4 (CH). EI-MS (m/z): 388 $[M]^+$. Anal. Calcd. for $C_{16}H_{15}Cl_2NO_4S$: C, 49.50; H, 3.89; N, 3.61; S, 8.26. Found: C, 49.10; H, 4.15; N, 3.62; S, 8.01.

Ethyl 5-methyl-7-(2,3-dichlorophenyl)-2,3,4,7-tetrahydrothieno-[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 37): Yield: 53%. mp: 228 °C. IR (ν, cm^{-1}): 3369 (N-H), 1660 (C=O), 1299, 1093 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 0.81 (3H; t; $COOCH_2C\underline{H}_3$), 2.12 (H; ddd; H-3_A), 2.31 (3H; s; 5-CH_3), 2.44 (H; ddd; H-3_B), 3.03 (H; ddd; H-2_A), 3.36 (H; ddd; H-2_B), 3.71 (H; dq; $COOC\underline{H}_{2A}$-CH_3), 3.82 (H; dq; $COOC\underline{H}_{2B}$-CH_3) 4.72 (H; s; H-7), 5.86 (H; s; N-H), 7.22–7.47 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 14.3, 20.6, 30.5, 34.3, 51.1, 58.5, 81.3, 91.8, 127.6, 128.6, 129.5, 130.5, 131.6, 131.9, 143.7, 153.7, 167.0. EI-MS (m/z): 401 $[M-1]^+$. Anal. Calcd. for $C_{17}H_{17}Cl_2NO_4S$: C, 50.76; H, 4.26; N, 3.48; S, 7.97. Found: C, 50.98; H, 4.22; N, 3.53; S, 8.03.

2-Methoxythyl 5-methyl-7-(2,3-dichlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 38): Yield: 41%. mp: 196 °C. IR (ν, cm^{-1}): 3345 (N-H), 1663 (C=O), 1355, 1129 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.12 (H, ddd, H-3_A), 2.32 (3H, s, 5-CH_3), 2.44 (H, ddd, H-3_B), 3.02 (3H; s; OCH3), 3.08 (H, ddd, H-2_A), 3.21–3.29 (2H; m; $C\underline{H}_2OCH_3$), 3.40 (H, ddd, H-2_B), 3.78 (H; ddd; $C\underline{H}_{2A}CH_2OCH_3$), 3.92 (H; ddd; $C\underline{H}_{2B}CH_2OCH_3$), 4.73 (H; s; 7-H), 5.86 (H; s; N-H), 7.20–7.48 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.6, 34.3, 34.7, 48.9, 58.3, 65.6, 70.5, 91.4, 100.1, 127.5, 128.6, 129.8, 130.5, 131.6, 139.3, 143.5, 154.1, 166.9. EI-MS (m/z): 432 $[M]^+$. Anal. Calcd. for $C_{18}H_{19}Cl_2NO_5S$: C, 50.01; H, 4.43; N, 3.24; S, 7.42. Found: C, 50.22; H, 4.50; N, 3.31; S, 7.92.

Allyl 5-methyl-7-(2,3-dichlorophenyl)-2,3,4,7-tetrahydrothieno-[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 39): Yield: 47%. mp: 188 °C. IR (ν, cm^{-1}): 3342 (N-H), 1664 (C=O), 1303, 1129 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.13 (H; ddd; H-3_A), 2.34 (3H; s; 5-CH_3), 2.44 (H; ddd; H-3_B), 3.03 (H; ddd; H-2_A), 3.39 (H; ddd; H-2_B), 4.27 (H; dd; $C\underline{H}_{2A}CH=CH_2$), 4.35 (H; dd; $C\underline{H}_{2B}CH=CH_2$), 4.75 (H; s; 7-H), 4.84 (H; dd; $CH_2CH=C\underline{H}_{2A}$), 4.93 (H; dd; $CH_2CH=C\underline{H}_{2B}$) 5.57–5.65 (H; m; $C\underline{H}=CH_2$), 5.86 (H; s; N-H), 7.22–7.57 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.8, 30.5, 34.1, 51.0, 65.5, 91.0, 100.1, 115.7, 127.6, 128.8, 129.8, 130.5, 131.7, 133.7, 139.3, 150.4, 154.4, 166.5. EI-MS (m/z): 413 $[M-1]^+$. Anal. Calcd. for $C_{18}H_{17}Cl_2NO_4S$: C, 52.18; H, 4.14; N, 3.38; S, 7.74. Found: C, 52.29; H, 4.26; N, 3.43; S, 7.72.

Isobutyl 5-methyl-7-(2,3-dichlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 40): Yield: 58%. mp: 244 °C. IR (ν, cm^{-1}): 3345 (N-H), 1663 (C=O), 1302, 1128 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 0.52 (3H; d; $COOCHC\underline{H}_3$), 0.56 (3H; d; $COOCHC\underline{H}_3$), 1.47–1.54 (H; m; $C\underline{H}(CH_3)_2$), 2.12 (H; ddd; H-3_A), 2.30 (3H; s; 5-CH_3), 2.44 (H; ddd; H-3_B), 3.04 (H; ddd; H-2_A), 3.39 (H; ddd; H-2_B), 3.48 (H; dd; $C\underline{H}_{2A}CH(CH_3)_2$), 3.61 (H; dd; $C\underline{H}_{2B}CH(CH_3)_2$), 4.73 (H; s; 7-H), 5.84 (H; s; N-H), 7.22–7.47 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 18.9, 19.0, 20.6, 27.7, 34.1, 34.8, 51.1, 68.9, 81.3, 91.1, 127.6, 128.7, 129.5, 130.5, 131.8, 133.2, 143.5, 154.1, 166.9. EI-MS (m/z): 429 $[M-1]^+$. Anal. Calcd. for $C_{19}H_{21}Cl_2NO_4S$: C, 53.03; H, 4.92; N, 3.25; S, 7.45. Found: C, 53.19; H, 4.89; N, 3.35; S, 7.79.

Tert-butyl 5-methyl-(2,3-dichlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 41): Yield: 58%. mp: 248 °C. IR (ν, cm^{-1}): 3344 (N-H), 1689 (C=O), 1364, 1156 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 1.06 (9H; s; $COOC(C\underline{H}_3)_3$), 2.11 (H; ddd; H-3_A), 2.28 (3H; s; 5-CH_3), 2.44 (H; ddd; H-3_B), 3.06 (H; ddd; H-2_A), 3.37 (H; ddd; H-2_B), 4.65 (H; s; 7-H), 5.75 (H; s; N-H), 7.19–7.47 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 19.8, 27.5, 27.6, 27.7, 30.0, 34.1, 48.5, 80.6, 92.9, 101.9, 121.1, 128.0, 129.1, 130.8, 131.2, 131.4, 143.8, 152.6,166.1. EI-MS (m/z): 429 $[M-1]^+$. Anal. Calcd. for $C_{19}H_{21}Cl_2NO_4S$: C, 53.03; H, 4.92; N, 3.25; S, 7.45. Found: C, 53.38; H, 4.74; N, 3.35; S, 7.79.

Benzyl 5-methyl-7-(2,3-dichlorophenyl)-2,3,4,7-tetrahydrothieno-[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 42): Yield: 55%. mp: 214 °C. IR (ν, cm^{-1}): 3359 (N-H), 1661 (C=O), 1300, 1178 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.13 (H; ddd; H-3_A), 2.35 (3H; s; 5-CH_3), 2.44 (H; ddd; H-3_B), 3.04 (H,; ddd; H-2_A), 3.39 (H; ddd; H-2_B), 4.73, 4,94 (1H, AB system, J_{AB}=12.8Hz, $COO\underline{H}_2C_6H_5$), 4.75 (H; s; 7-H), 5.88 (H; s; N-H), 6.77–7.56 (8H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.7, 34.1, 34.7, 51.1, 64.3, 81.3, 90.9, 127.0, 127.7, 128.4, 128.8, 129.5, 129.9, 130.6, 130.8, 131.2, 131.9, 132.3, 137.3, 143.4, 154.7, 166.6. EI-MS (m/z): 464 $[M]^+$. Anal. Calcd. for $C_{22}H_{19}Cl_2NO_4S$: C, 56.90; H, 4.12; N, 3.02; S, 6.90. Found: C, 56.06; H, 4.43; N, 3.10; S, 6.95.

Pharmacology

The relaxant effects of the compounds and nicardipine on isolated rat ileum, on rat thoracic artery and the half maximal effective concentration (EC_{50}) of the selected compounds are given in ○ **Table 1, 2**.

Discussion

▼

In this work a series of condensed 1,4-dihydropyridines were prepared via modified Hantzsch reaction. The structures of the compounds were elucidated by IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, COSY 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 and thoracic aorta.

Table 1 Relaxant effects of the synthesized compounds and nicardipine (10^{-5} mol/L).

Compound	Inhibition % [a]	Inhibition % [b]	Compound	Inhibition % [a]	Inhibition % [b]
1	89.00 ± 13.05	4.18 ± 1.53*	**22**	78.67 ± 23.14	3.08 ± 1.74*
2	93.50 ± 8.67	3.77 ± 0.99*	**23**	88.00 ± 15.60	2.80 ± 1.82*
3	47.00 ± 23.07 *	–	**24**	0	–
4	58.50 ± 14.27*	3.42 ± 1.31*	**25**	80.12 ± 9.55	7.68 ± 2.38
5	48.83 ± 8.04 *	–	**26**	47.40 ± 16.00*	–
6	27.50 ± 10.75*	–	**27**	45.60 ± 14.66 *	–
7	99.17 ± 2.04	2.15 ± 1.42 *	**28**	65.83 ± 15.68 *	4.96 ± 1.39*
8	77.00 ± 21.37	3.42 ± 0.97*	**29**	91.40 ± 12.88	0
9	53.00 ± 17.58 *	2.12 ± 1.60 *	**30**	89.40 ± 11.22	0
10	47.80 ± 18.66 *	–	**31**	26.25 ± 19.92 *	–
11	100.00 ± 0	1.83 ± 1.13*	**32**	88.33 ± 16.26	3.82 ± 2.11*
12	100.00 ± 0	2.73 ± 1.19*	**33**	39.83 ± 11.90*	0
13	43.50 ± 11.90 *	–	**34**	52.20 ± 20.00*	3.30 ± 2.71*
14	61.60 ± 28.95*	3.08 ± 0.78*	**35**	40.60 ± 16.47*	–
15	96.83 ± 4.99	5.38 ± 1.78	**36**	82.67 ± 15.98	0
16	84.33 ± 23.35	4.62 ± 2.77*	**37**	75.83 ± 21.70	1.55 ± 0.9*
17	76.67 ± 19.79	1.72 ± 0.90*	**38**	48.67 ± 11.53 *	0
18	67.40 ± 27.29 *	3.10 ± 1.25*	**39**	60.33 ± 19.17 *	4.88 ± 2.89
19	88.00 ± 14.35	5.02 ± 1.36*	**40**	73.83 ± 16.20 *	0
20	54.50 ± 26.40*	2.60 ± 1.54*	**41**	37.83 ± 15.54 *	0
21	66.50 ± 22.00*	2.98 ± 0.74*	**42**	37.60 ± 10.79 *	3.21 ± 2.04*
Nicardipine	93.30 ± 7.42	9.13 ± 3.83	**Nicardipine**	93.30 ± 7.42	9.13 ± 3.83

[a] Studies on isolated rat ileum precontracted with barium chloride (4×10^{-3} M)

[b] Studies on rat thoracic artery precontracted with potassium chloride (67 mmol/L)

*$p < 0.05$, compared with control responses (n = 6)

Table 2. EC_{50} values of the synthesized compounds and nicardipine on isolated rat ileum.

Compound	EC_{50}
1	$0.34 \pm 0.17 \times 10^{-7}$ *
2	$2.66 \pm 1.53 \times 10^{-7}$
7	$0.14 \pm 0.08 \times 10^{-7}$ *
11	$1.32 \pm 0.35 \times 10^{-7}$
12	$2.88 \pm 1.67 \times 10^{-7}$
15	$4.63 \pm 2.98 \times 10^{-7}$
16	$6.22 \pm 4.78 \times 10^{-7}$
19	$0.85 \pm 0.68 \times 10^{-7}$
23	$0.55 \pm 0.33 \times 10^{-7}$*
25	$8.12 \pm 1.94 \times 10^{-7}$
28	$7.66 \pm 4.46 \times 10^{-7}$
29	$4.25 \pm 2.72 \times 10^{-7}$
30	$2.17 \pm 1.46 \times 10^{-7}$
32	$0.90 \pm 0.60 \times 10^{-7}$
36	$4.00 \pm 1.27 \times 10^{-6}$
39	$4.27 \pm 1.85 \times 10^{-7}$
Nicardipine	$1.33 \pm 0.34 \times 10^{-7}$

*$p < 0.05$, compared with control responses

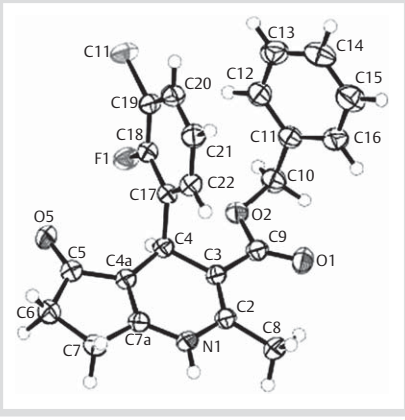


Fig. 4 The molecular structure of compound 14.

In the IR spectra, characteristic N-H, C=O (ester), C=O (ketone) and S=O stretching bonds were observed. In the ^{1}H-NMR, while the protons of the cyclohexanone ring were at 2.10–2.59 ppm as multiplet, each proton of the tetrahydrothiophene ring was observed at 2.10–3.40 ppm seperately and as doublet of doublet of doublets (ddd). The methyl and methine protons on the DHP ring were seen at 2.21–2.35 ppm and 4.69–5.71 ppm, respectively. The protons, which are on the aromatic rings, were seen at 6.69–7.57 ppm. The N-H signals were observed at either 5.75–5.94 ppm or 9.48–9.90 ppm as singlets. In the ^{13}C-NMR spectra the number of the signals fitted exactly the number of carbon atoms. The COSY spectrum of Compound 15 indicates that there is an interaction between the methylene groups of the cyclopentanone ring. 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 aromatisation of the DHP ring to the pyridine analogue were seen in the spectra of compounds. Cleavage of the ester groups and phenyl rings from the parent molecule are the next most observed fragmentations.

The structure of the compound 14 was also confirmed by an X-ray crystal structure analysis (**Fig. 4**). A detailed description of the structure has been presented in [21]. It was founded that, 1,4-DHP ring has very shallow boat conformation, whereas the oxocyclopentene ring is planar and there is an intermolecular N-H·····O hydrogen bond between the amine group and the carbonyl O atom of the oxocyclopentene ring of a neighbouring molecule.

On isolated rat ileum strips precontracted with barium chloride (4×10^{-3} M) compounds 2, 7, 11, 12 and 15 are more active than the standard compound, nicardipine, at 10^{-5} M concentration

(**Table 1**). The most potent calcium antagonists are compounds 11 and 12 with 100% inhibition. When the compounds are compared with respect to the fused rings, it has been observed that the compounds carrying a cyclopentanone ring have higher activities than the derivatives bearing a tetrahydrothiofen-1,1-dioxide ring. The compounds with methyl, ethyl and allyl esters increased the inhibition of the contraction more than the compounds having the other ester groups. Although there is no distinct relationship between calcium modulator activity and the substitution of the phenyl ring, it has been determined that the most active compounds (11 and 12) bear a 2-fluoro-3-chlorophenyl ring.

The half maximal effective concentration (EC_{50}) was also calculated for the compounds which exhibit more than 80% inhibition on isolated rat ileum (**Table 2**). Although there are some compounds having lower EC_{50} values compared to nicardipine, the EC_{50} values of compound 1, 7 and 23 have been found as the lowest ones in this series. The results indicated that most of the compounds which have a lower EC_{50} value than nicardipine have a cyclopentanone ring.

32 compounds that possessed calcium antagonist activity of more than 50% on isolated rat ileum were also investigated on rat thoracic artery precontracted with potassium chloride (67 mmol/L). It was determined that compounds 1, 15, 16, 19, 25, 28 and 39 are relatively active derivatives. The results indicate that 2,3-dichlorophenyl and 2,3-difluorophenyl rings, and methyl, ethyl and allyl esters enhance the activity positively. It was observed again that the compounds having a cyclopentanone ring were more active.

When the obtained data are analysed, it can be observed that most of the active compounds bear a cyclopentanone ring fused to the 1,4-DHP ring and methyl, ethyl and allyl groups in the ester moiety. While the compounds have high activities on isolated rat ileum, most of them show lower activities on rat thoracic aorta so it has to be emphasized that the synthesized compounds have spasmolytic activity rather than vasodilator activity.

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Conflict of Interest

All authors of the article declare no conflict of interest.

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