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Microwave assisted solid phase catalyst-free Biginelli synthesis of 3,4-dihydropyrimidin-2(1H)-one and 3,4-dihydropyrimidin-2(1H)-thione: A green approach, characterization and molecular crystal structures

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ABSTRACT

Solid phase catalyst-free Biginelli synthesis of novel 5-carbethoxy-4-(3-bromo-4-hydroxy-5-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one ($C_{15}H_{17}BrN_2O_5$) and 5-carbethoxy-4-(3-bromo-4-hydroxy-5-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione ($C_{15}H_{17}BrN_2O_4S$) has been carried out under microwave irradiation at 400W. The structures of both compounds were confirmed by 1H NMR, ^{13}C NMR, Mass, FT-IR, Elemental analysis, and single crystal X-ray diffraction method. The single crystals of both compounds were obtained by crystallization in $0.35 \times 0.30 \times 0.25$ mm dimension for ($C_{15}H_{17}BrN_2O_5$) and $0.35 \times 0.32 \times 0.30$ mm dimension for ($C_{15}H_{17}BrN_2O_4S$). Both compounds, ($C_{15}H_{17}BrN_2O_5$) and ($C_{15}H_{17}BrN_2O_4S$) crystallizes in the monoclinic $P2_1/c$ space group and shows four and two intermolecular hydrogen bonds, respectively.

KEYWORDS

3,4-Dihydropyrimidin-2(1H)-one;
3,4-Dihydropyrimidin-2(1H)-thione; Microwave irradiation; solid phase catalyst-free biginelli synthesis; single crystal structure

Introduction

The Biginelli compounds, 4-substituted phenyl dihydropyrimidines (DHPMs) have set their position as pharmacological important compounds since they deport themselves as neuropeptide Y (NPY) antagonism, α_1 -1a-antagonists, calcium channel blockers and antihypertensive agents [1], also their use as an anticancer drug capable of inhibiting kinesin motor protein. In addition, DHPMs have been widely studied to develop their current Structure Activity Relation (SAR) to get an extra vision into the molecular interactions at the receptor level [2–4]. Many DHPMs and their derivatives are very much familiar for their extensive variety of biological properties, *viz.*, antibacterial, antitumor, antiviral, anti-inflammatory, etc. [5] and achieved a significant place in the empire of nature and synthetic organic chemistry. Many alkaloids holding the DHPM motif as a core unit in their structure unveil exciting biological belongings as well, which have been isolated from marine sources [6]. Precisely, batzelladine alkaloids, found as a potent HIV gp-120-CD4 inhibitors [7]. Merely, thioxo derivative of DHPM “monastrol” can be considered as a lead molecule for the development of new anticancer drugs because it is the only cell-permeable antagonist, which blocks normal bipolar spindle assembly in mammalian cells resulting in halt of the cell cycle [8,9].

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Classically DHPM was first synthesized by Biginelli using one-pot condensation reaction of benzaldehyde, ethyl acetoacetate, and urea under strong acidic conditions [5]. This conventional DHPM synthetic method always struggles with long reaction time and low yields throughout the entire reaction process with substituted aromatic and aliphatic aldehydes [10,11].

Moreover, various catalysts have been reported for the synthesis of DHPMs in past literature like triphenylphosphine [12], acidic ionic liquid [13], Tungstate Sulfuric Acid (TSA) [14], bioglycerol-based sulfonic acid functionalized carbon catalyst [15], hydrotalcite [16], chiral organocatalyst [17], Fe_3O_4 @ mesoporous SBA-15(mesoporous nanocatalyst) [18], 5% perchloric acid doped silica ($\text{HClO}_4/\text{SiO}_2$) [19], poly(1-vinyl-3-(3-sulfopropyl) imidazolium hydrogen sulfate) (poly(SIL)) [20], *t*-BuOK [21], SPINOL-phosphoric acid [22], 1-methylimidazolium hydrogen sulfate in the presence of catalytic amount of chlorotrimethylsilane ([Hmim]HSO₄/TMSCl) [23], [Gmim]Cl-Cu(II) complex in neat condition [24] and other general catalysts such as, triflates of lanthanide compounds [25], H_3BO_3 [26], CAN [27], NaCl [28], $[\text{Al}(\text{H}_2\text{O})_6](\text{BF}_4)_3$ [29], $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ [30], $\text{Fe}(\text{OTf})_3 \cdot 6\text{H}_2\text{O}$ [31], etc. along with microwave irradiation. All these catalytic approaches involves the use of organic solvents, harsh reaction conditions, challenging and costly catalysts preparation, protracted reaction time, inadequate and moderate yields and tiresome workup procedures.

That's why, with a vision of the inclusive pharmacological and therapeutically importance, plus drawbacks of catalytic synthetic methods of 3,4-DHPMs, two novel compounds 5-carbethoxy-4-(3-bromo-4-hydroxy-5-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one ($\text{C}_{15}\text{H}_{17}\text{BrN}_2\text{O}_5$) and 5-carbethoxy-4-(3-bromo-4-hydroxy-5-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione ($\text{C}_{15}\text{H}_{17}\text{BrN}_2\text{O}_4\text{S}$) have been synthesized without solvent and catalyst under microwave irradiation in 15 minutes and characterized by single crystal X-ray diffraction crystallography and several spectroscopic methods. In this paper, an efficient environment friendly procedure has been reported for the synthesis of two new DHPM molecules in microwave irradiation system without using any solvent and catalysts. There are very few reports on solvent- and catalyst-free synthesis of DHPMs [32,33].

Somehow, the crystal structure determination of the presented compounds is little bit difficult, because of very limited information on the DHPM crystal structures in their structural supports. The main approach of the present work is to discover these DHPMs under microwave irradiated synthesis by means of green approach and development of their single crystal structures because these compounds are extremely new and have not been reported in past literature. This both compounds are mean to be important because of very limited testimony on single crystal structures and very less medicinal accounts of the DHPMs as well. This effort is a pintsize contribution in the world of DHPM structural chemistry through the single crystal structure determination of innovative DHPM molecules.

The present research work is in prolongation of the previously published research involving two novel molecules of dihydropyridine (DHP) derivatives [34,35]. After successful solid phase catalyst free synthesis and structural characterization of both new DHPMs, the single crystal structure development of other DHPM and DHP derivatives is in progress.

Experimental

Materials and methods

All Reagents and solvents were commercially available from Spectrochem and Merck and was used as received without further purification. Synthesis of both compounds was carried out

in Whirlpool AKL260 microwave oven at 400 W. Analytical TLC was performed on silica gel-G using chloroform:methanol as solvent system. Melting points were determined in open capillaries on a melting point apparatus purchased from JSGW and is uncorrected. Both compounds were micro analyzed satisfactorily for C, H and N in EURO EA Elemental Analyzer, EA-3000, RS-232. The IR spectra were recorded on Shimadzu FT-IR 8400 spectrophotometer using KBr discs. The ESI mass spectra were recorded on Micromass Q-ToF Micro having mass Range of 4000 amu in quadruple and 20,000 amu in ToF. ^1H and ^{13}C NMR spectra were recorded in DMSO- d_6 on a Bruker Av 500 spectrophotometer using the TMS as an internal standard and the chemical shifts are reported in δ ppm scale. The single crystal X-Ray Diffraction studies were acquired on Enraf Nonius CAD4-MV₃₁ diffractometer.

Synthesis of 3-bromo-4-hydroxy-5-methoxybenzaldehyde

3-Bromo-4-hydroxy-5-methoxybenzaldehyde has been synthesized according to the previously published method [36]. To the continuous stirring solution of vanillin (15 g, 100 mmol) in glacial acetic acid (35 mL) at 0–5°C temperature, a solution of bromine (16 g, 100 mmol) in glacial acetic acid (10 mL) was added dropwise. A white colored product was separated immediately, which was treated with cold water and filtered through suction with 50 mL of water wash. Crude product was then dried in vacuum and crystallized from alcohol as cubic crystals. Yield 16 g (70.2%). M.p. 163–64°C. (Lit. m.p. 164°C) [37].

Synthesis of 5-carbethoxy-4-(3-bromo-4-hydroxy-5-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one/thione

A mixture of 3-bromo-4-hydroxy-5-methoxybenzaldehyde (2.301 g, 10 mmol), ethyl 3-oxobutanoate (1.301 g, 10 mmol), and urea (0.630 g, 10.5 mmol)/thiourea (0.799 g, 10.5 mmol) in 50 mL beaker was placed in a domestic microwave oven and irradiated at 400 W for 5 min. Reaction mixture was stirred with glass rod and again irradiated at 400W for 10 min and was monitored by TLC using chloroform:methanol (8.5:1.5) solvent system. After completion of reaction the resulting reaction mixture was cooled to room temperature and 15 mL methanol was added to soluble the solid which was then removed under reduced pressure to desired product.

5-Carbethoxy-4-(3-bromo-4-hydroxy-5-methoxyphenyl)-6-methyl-3,4-dihydro-pyrimidin-2(1H)-one (C₁₅H₁₇BrN₂O₅)

Yield 92% (3.55 g), m.p. 227°C, Elemental analysis: (C₁₅H₁₇BrN₂O₅) Calcd. C, 46.77; H, 4.45; N, 7.27; O, 20.77; Found C, 46.59; H, 4.32; N, 7.13; O, 20.61, Mass: $m/z = 385$, IR (KBr, ν cm⁻¹): 3575–3291 (N-H stretching), 3104 and 3010 (C-H stretching of aromatic), 2975 (C-H asymmetric stretching of -CH₃), 2941 (C-H symmetric stretching of -CH₃), 2848 (C-H asymmetric stretching of -CH₂), 2745 (C-H symmetric stretching of -CH₂), 1676 (C=O stretching of NH-CO-NH), 1586 (C=O stretching of ester), 1285 and 1042 (C-O-C stretching of -OCH₃). ^1H NMR (δ ppm, DMSO- d_6 + 500 MHz): 1.11–1.14 (t, 3H, -CH₃), 2.26 (s, 3H, -CH₃), 3.79 (s, 3H, -OCH₃), 3.98–4.05 (m, 2H, -CH₂), 5.09 (s, 1H, -CH), 6.83 (s, 1H, Ar-H), 6.87 (s, 1H, Ar-H), 7.72 (s, 1H -NH), 9.20 (s, 1H, -NH) and 9.44 (s, 1H, -OH). ^{13}C NMR (δ ppm, DMSO- d_6 + 500 MHz): 14.56, 18.22, 53.70, 56.49, 59.69, 99.39, 109.41 & 109.91, 121.96, 137.22, 143.39, 148.67, & 148.91, 152.50, 165.75.

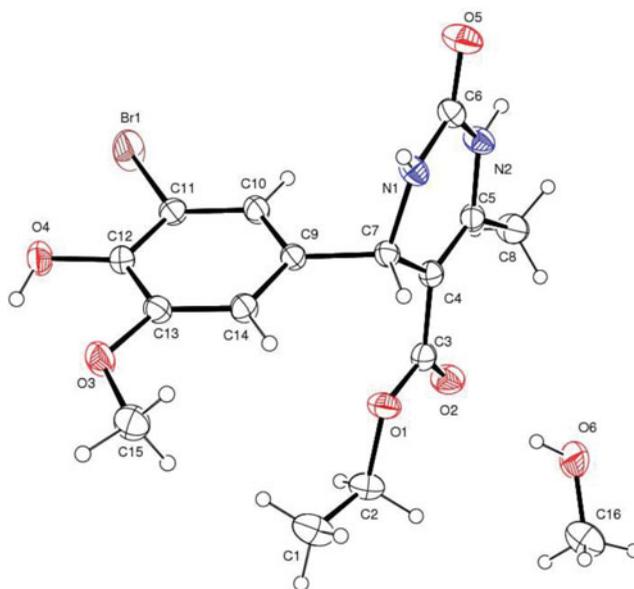


Figure 1. ORTEP diagram of 5-Carboxy-4-(3-bromo-4-hydroxy-5-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one ($C_{15}H_{17}BrN_2O_5$) using 50% probability level ellipsoids.

5-Carboxy-4-(3-bromo-4-hydroxy-5-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione ($C_{15}H_{17}BrN_2O_4S$)

Yield 87% (3.49 g), m.p. 210°C, Elemental analysis: ($C_{15}H_{17}BrN_2O_4S$) Calcd. C, 44.90; H, 4.27; N, 6.98; O, 15.95; Found C, 44.77; H, 4.11; N, 6.83; O, 15.78, Mass: $m/z = 401$, IR (KBr, ν cm^{-1}): 3576–3363 (N-H stretching), 3108 (C-H stretching of aromatic), 2967 (C-H asymmetric stretching of $-CH_3$), 2933 (C-H symmetric stretching of $-CH_3$), 2871 (C-H asymmetric stretching of $-CH_2$), 2733 (C-H symmetric stretching of $-CH_2$), 1683 (C=O stretching of NH-CO-NH), 1643 (C=O stretching of ester), 1228 and 1047 (C-O-C stretching of $-OCH_3$). 1H NMR (δ ppm, DMSO- d_6 + 500 MHz): 1.12–1.14 (t, 3H, $-CH_3$), 2.29 (s, 3H, $-CH_3$), 3.78 (s, 3H, $-OCH_3$), 4.00–4.07 (m, 2H, $-CH_2$), 3.98–4.01 (m, 2H, $-CH_2$), 5.10 (s, 1H, $-CH$), 6.81–6.84 (dd, 2H, Ar-H, $J = 15$ Hz), 9.54 (s, 1H, $-NH$), 9.61 (s, 1H, $-NH$), and 10.35 (s, 1H, $-OH$). ^{13}C NMR (δ ppm, DMSO- d_6 + 500 MHz): 14.03, 17.14, 53.24, 56.04, 59.62, 100.38, 109.06, & 109.47, 121.68, 135.35, 143.28, 145.12, 148.26, 156.06, 174.15.

Single crystal development method

In a 100 mL beaker 1 g quantity of dried pure product was taken along with sufficient amount of methanol for compound ($C_{15}H_{17}BrN_2O_5$) and binary mixture of methanol and acetonitrile for compound ($C_{15}H_{17}BrN_2O_4S$), which were then heated on hot plate till solid product gets dissolved, 1 g of activated charcoal was added and heated again then filtered the hot solution through whatmann 42 filter paper in 50 mL stopper conical flask and loosely cover the stopper for slow evaporation. The filtered solution was allowed to stand at room temperature for 2–4 weeks to form colorless and light yellow colored crystals of compound ($C_{15}H_{17}BrN_2O_5$) and ($C_{15}H_{17}BrN_2O_4S$), respectively. Obtained crystals were filtered and wash with very small quantity of methanol and analyzed by single crystal X-ray diffraction method. Both structures were successfully achieved by X-ray crystallographic analysis as displayed in Figures 1 and 2.

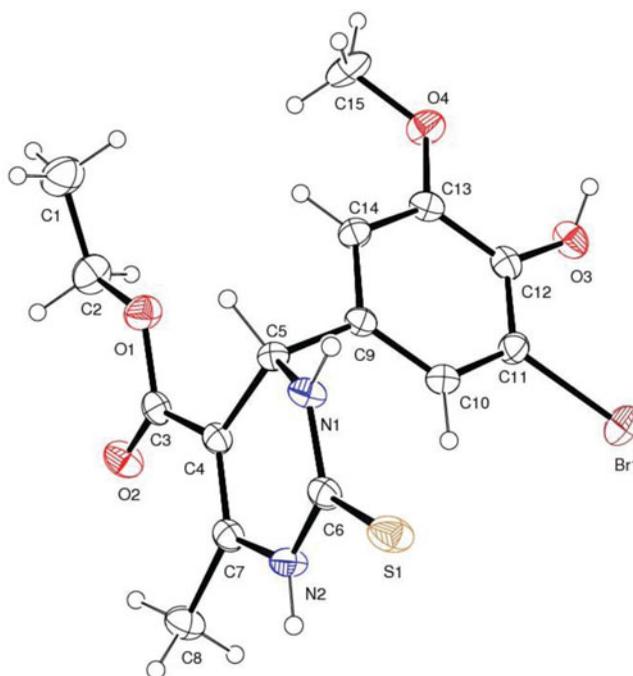
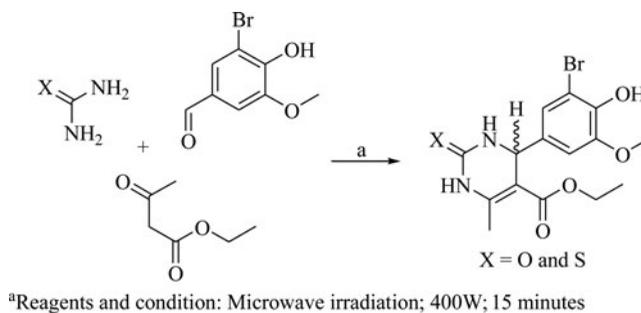


Figure 2. ORTEP diagram of 5-Carboxy-4-(3-bromo-4-hydroxy-5-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione ($C_{15}H_{17}BrN_2O_4S$) using 50% probability level ellipsoids.

Results and discussions

Both pioneering, 5-carboxy-4-(3-bromo-4-hydroxy-5-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one ($C_{15}H_{17}BrN_2O_5$) and 5-carboxy-4-(3-bromo-4-hydroxy-5-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione ($C_{15}H_{17}BrN_2O_4S$) compounds have been synthesized using Biginelli synthetic method under solvent- and catalyst-free microwave irradiation in excellent yield and purity. The synthetic route used for the synthesis of both compounds is given in Scheme 1. The reaction involves a one pot multicomponent cyclocondensation reaction of ethyl 3-oxobutanoate, 3-bromo-4-hydroxy-5-methoxybenzaldehyde and urea/thiourea without solvent and catalyst.

Both compounds were screened for selected solvents under microwave irradiation by using HCl as a catalyst to know the yield variation with and without use of solvents and catalyst, data are given in Table S1 (Supplementary material). The data obviously shows the best results in absence of solvent and catalyst under microwave irradiation at 400W for 15 min. Similarly,



Scheme 1. Reaction scheme for the synthesis of compounds ($C_{15}H_{17}BrN_2O_5$) and ($C_{15}H_{17}BrN_2O_4S$).

both compounds were conventionally synthesized under optimized reaction condition too, which takes 5 hours to give desired products with moderate yield formation when solvent and catalyst were used, however without catalyst the reaction time was double and the yield formations were very poor for both compounds.

The solid phase catalyst-free conventional Biginelly synthesis of both new compounds has been completed in an open beaker under optimized reaction conditions by taking known amounts of substrates and catalyst at 80°C temperature for 5 h with continuous stirring on oil bath, which were then treated with sufficient amount of methanol to get the yield in 57% and 48% of desired products ($C_{15}H_{17}BrN_2O_5$) and ($C_{15}H_{17}BrN_2O_4S$), respectively. While, without catalyst under reflux condition for 10 h the yield formation was in the range of 65–41% and 62–40% of both compounds, respectively.

The elemental analysis, FT-IR, ESI mass, 1H and ^{13}C NMR spectral data are in good agreement with the crystal structures of the both newly synthesized DHPM compounds. Formation of both compounds ($(C_{15}H_{17}BrN_2O_5)$ and $(C_{15}H_{17}BrN_2O_4S)$) was confirmed by the 1H NMR spectra with a presence of two NH peak at δ 7.72, 9.20, and 9.54, 9.61 ppm, respectively, and also by the ^{13}C NMR spectra, which shows the carbonyl carbon peak of ester, methoxy and the oxo groups at 156.75, 152.50, and 148.91 ppm, respectively in compound ($C_{15}H_{17}BrN_2O_5$), while in the compound ($C_{15}H_{17}BrN_2O_4S$) three characteristic carbon peak of ester, methoxy and the thioxo groups observed at 174.15, 165.05, and 148.26 ppm, respectively. The ESI mass spectra of both compounds show the molecular ion peaks at 389.28 m/z [$M+4$, 24%] and 407.27 m/z [$M+6$, 100%], also shows the fragmented molecular ion peaks with respect to their total molecular weight. The FT-IR spectrums of both compound displays a sharp band at 3291–3575 and 3327–3576 cm^{-1} corresponds to the $-NH$ groups present in DHPM compounds.

Crystal structure determination

The crystal structures of both compounds were cracked by direct method SHELXS-97 [38] and determined by full matrix least-squares on F^2 with program system SHELXL-97 [39]. The monoclinic single crystal system of the title compounds were obtained in $0.35 \times 0.30 \times 0.25$ and $0.35 \times 0.32 \times 0.30$ mm dimensional crystal size and analyzed at 296(2) K temperature for the collection of crystal data of the compound ($C_{15}H_{17}BrN_2O_5$) and ($C_{15}H_{17}BrN_2O_4S$) respectively. The intensity data of the both crystals of the compound ($C_{15}H_{17}BrN_2O_5$) and ($C_{15}H_{17}BrN_2O_4S$) having shelxl identification code were collected using graphite monochromated $MoK\alpha$ radiation is 0.71073 Å in the ω - 2θ scan mode. The compounds crystallizes in the monoclinic $P2_1/c$ space group with unit cell dimensions $a = 11.2902(5)$ Å, $b = 8.7197(4)$ Å, $c = 18.6642(7)$ Å and $\alpha = 90^\circ$, $\beta = 97.893(2)^\circ$, $\gamma = 90^\circ$ for ($C_{15}H_{17}BrN_2O_5$) and $a = 10.7986(4)$ Å, $b = 8.1241(3)$ Å, $c = 18.9091(8)$ Å, and $\alpha = 90^\circ$, $\beta = 92.0810(10)^\circ$, $\gamma = 90^\circ$ for ($C_{15}H_{17}BrN_2O_4S$). The crystal data and final refinement details of both DHPM compounds are given in Table 1.

The crystal structure of the compound ($C_{15}H_{17}BrN_2O_5$) shows the presence of methanol, because this crystal has a tendency to behave as opaque without solvent. In contrary, compound ($C_{15}H_{17}BrN_2O_4S$) doesn't show any solvent molecule in its crystal structure as it is translucent even without solvent (Figures 1 and 2). This difference may be because of the substitution change of atom O(5) and S(1) in both compounds on the atom C(6) of DHPM ring.

In both compound, ($C_{15}H_{17}BrN_2O_5$) and ($C_{15}H_{17}BrN_2O_4S$) the DHPM ring having atoms C(4), C(5), N(2), C(6), N(1), C(7), and C(4), C(5), N(1), C(6), N(2), C(7), respectively, are not planar, as indicated by the atomic coordinates and equivalent isotropic displacement

Table 1. Crystal data and structure refinement for (C₁₅H₁₇BrN₂O₅) and (C₁₅H₁₇BrN₂O₄S).

Identification code	Shelxl	Shelxl
Empirical formula	C ₁₅ H ₁₇ BrN ₂ O ₅	C ₁₅ H ₁₇ BrN ₂ O ₄ S
Formula weight	385.21	401.28
Crystal colour	White	Pale yellow
Temperature	296(2) K	296(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic
space group	P2 ₁ /c	P2 ₁ /c
Unit cell dimensions	a = 11.2902(5) Å α = 90° b = 8.7197(4) Å β = 97.893(2)° c = 18.6642(7) Å γ = 90°	a = 10.7986(4) Å α = 90° b = 8.1241(3) Å β = 92.0810(10)° c = 18.9091(8) Å γ = 90°
Volume	1820.03(13) Å ³	1657.78(11) Å ³
Z	4	4
Calculated density	1.523 mg/m ³	1.608 mg/m ³
Absorption coefficient	2.293 mm ⁻¹	2.626 mm ⁻¹
F(000)	856	816
Crystal size	0.35 × 0.30 × 0.25 mm	0.35 × 0.32 × 0.30 mm
Theta range for data collection	2.58 to 24.99°	2.16° to 26.00°
Limiting indices	13 ≤ h ≤ 13 10 ≤ k ≤ 10 16 ≤ l ≤ 22	-12 ≤ h ≤ 13 -10 ≤ k ≤ 10 -23 ≤ l ≤ 23
Reflections collected / unique	27145 / 3204 [R(int) = 0.0393]	26260 / 3250 [R(int) = 0.0269]
Completeness to theta = 26.00	99.8%	100.0%
Absorption correction	Semi empirical from equivalents	Semi empirical from equivalents
Max. and min. transmission	0.5990 and 0.5001	0.5184 and 0.4539
Refinement method	Full matrix least squares on F ²	Full matrix least squares on F ²
Data / restraints / parameters	3204 / 0 / 236	3250 / 2 / 220
Goodness of fit on F ²	1.079	1.035
Final R indices [I > 2σ(I)]	R ₁ = 0.0413, wR ₂ = 0.1213	R ₁ = 0.0288, wR ₂ = 0.0783
R indices (all data)	R ₁ = 0.0656, wR ₂ = 0.1404	R ₁ = 0.0369, wR ₂ = 0.0826
Largest diff. peak and hole	0.862 and 1.093 e.Å ⁻³	0.399 and 0.327 e.Å ⁻³

parameters of atoms C(7) [$x = 8207(3)$, $y = 5497(3)$, $z = 9649(2)$, $U_{eq} = 31(1) \text{ \AA}^2$] and C(5) [$x = 2297(2)$, $y = 5058(2)$, $z = 2184(1)$, $U_{eq} = 28(1) \text{ \AA}^2$] and by the torsion angle $17.9(4)^\circ$ of atoms C(4)-C(7)-N(1)-C(6) and $26.1(3)^\circ$ of atoms C(4)-C(5)-N(1)-C(6).

Torsion angle obtained from the compound (C₁₅H₁₇BrN₂O₅) is of the atoms C(7) and N(2) ($1.8(5)^\circ$) and from the compound (C₁₅H₁₇BrN₂O₄S) is of the atoms C(5) and N(2) ($4.6(3)^\circ$), which gives a good agreement of displacement from the ring in the same direction. On the other hand, opposite to those of pyrimidine ring, the substituted phenyl ring with methoxy, hydroxy and bromo groups has an axial orientation. This axial orientated substituted phenyl rings, C(9), C(10), C(11), C(12), C(13), C(14) being perpendicular to the DHPM ring in both compounds (Figures 1 and 2). The distance observed between the C(7) and N(2) atoms of compound (C₁₅H₁₇BrN₂O₅) and C(5) and N(2) atoms of compound (C₁₅H₁₇BrN₂O₄S) and the perpendicular orientation of phenyl ring on C(7) and C(5) atoms of both compounds gives clear evidence about the flattened boat-type confirmation of the DHPM ring having dihedral angles $110.1(2)^\circ$ and $113.8(2)^\circ$ of atoms N(1)-C(7)-C(9) and C(4)-C(7)-C(9) from (C₁₅H₁₇BrN₂O₅), whereas, angles $110.92(16)^\circ$ and $111.72(16)^\circ$ of atoms N(1)-C(5)-C(9) and C(4)-C(5)-C(9) from (C₁₅H₁₇BrN₂O₄S) with the substituted phenyl ring.

Hydrogen bonding determination

It is supposed to be for the DHPM compounds that hydrogen bonding existence in the crystal structure could be the major role during the calcium channel antagonist effect. According to the H-pack diagram of compound (C₁₅H₁₇BrN₂O₅), the carbonyl group substituted at

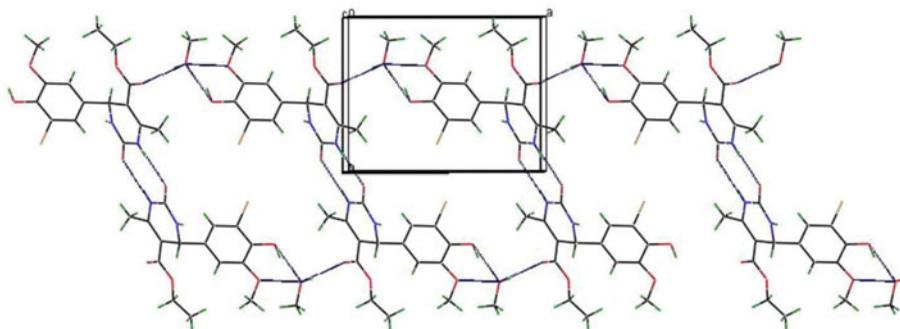
Table 2. Hydrogen bonds for the compound ($C_{15}H_{17}BrN_2O_5$) and ($C_{15}H_{17}BrN_2O_4S$) [Å and°].

$(C_{15}H_{17}BrN_2O_5)$				
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(16)-H(16C)...O(5) ^{#1}	0.96	2.57	3.409(5)	146.8
N(1)-H(1D)...O(3) ^{#2}	0.86	2.64	3.274(4)	131.4
N(1)-H(1D)...O(6) ^{#1}	0.86	2.62	3.409(6)	153.9
N(2)-H(2C)...O(5) ^{#3}	0.86	2.01	2.867(4)	171.8
O(4)-H(4)...O(6) ^{#4}	0.84(6)	1.85(6)	2.626(4)	153(6)
O(6)-H(6A)...O(2)	0.69(7)	2.05(7)	2.732(4)	170(7)
$(C_{15}H_{17}BrN_2O_4S)$				
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(2)-H(2A)...S(1) ^{#5}	0.97	2.97	3.740(3)	136.8
C(2)-H(2B)...Br(1) ^{#6}	0.97	3.08	3.901(3)	143.4
C(5)-H(5)...O(3) ^{#7}	0.98	2.51	3.245(3)	131.2
C(8)-H(8A)...O(2)	0.96	2.20	2.892(3)	128.3
C(15)-H(15B)...S(1) ^{#6}	0.96	3.00	3.810(2)	142.4
O(3)-H(3)...O(2) ^{#7}	0.82	1.90	2.702(2)	165.4
N(2)-H(2C)...S(1) ^{#8}	0.831(16)	2.571(16)	3.3956(18)	172(2)
N(1)-H(1D)...O(4) ^{#7}	0.817(15)	2.221(17)	3.017(2)	165(2)

Symmetry transformations used to generate equivalent atoms for ($C_{15}H_{17}BrN_2O_5$) ^{#1}-x + 2, -y + 1, -z + 2; ^{#2}-x + 1, -y + 1, -z + 2; ^{#3}-x + 2, -y + 2, -z + 2; ^{#4}x-1, y, z and for ($C_{15}H_{17}BrN_2O_4S$) ^{#5}-x, y + 1/2, -z + 1/2; ^{#6}-x + 1, y + 1/2, -z + 1/2; ^{#7}-x + 1, y-1/2, -z + 1/2; ^{#8}-x, -y + 1, -z.

C(4) in both compounds are involved in hydrogen bonding; thus, the structure of compound ($C_{15}H_{17}BrN_2O_5$) exhibits four intermolecular hydrogen bonds involving;

- An O(2) atom of C(4) substituted carbonyl group to the H(6A) hydrogen substituted at O(6) atom of methanol molecule [O(6)-H(6A)...O(2) having (x-1, y, z) symmetry code with 1.85(6) Å length and 153(6)° angle].
- An O(6) atom substituted at C(16) atom of methanol to the H(4) hydrogen of hydroxyl group substituted at C(12) atom [O(4)-H(4)...O(6) having (x-1, y, z) symmetry code with 1.85(6) Å length and 153(6)° angle].
- An O(3) atom of C(13) substituted methoxy group to the H(6) hydrogen of methanol.
- Hydrogen bonding between DHPM rings, an O(5) atom substituted at C(6) to the H(2C) hydrogen substituted at N(2) atom of DHPM ring [N(2)-H(2C)...O(5) having (-x + 2, -y + 2, -z + 2) symmetry code with 2.01 Å length and 171.8° angle] (Table 2, Figure 3).

**Figure 3.** The unit cell diagram of compound ($C_{15}H_{17}BrN_2O_5$) showing hydrogen bonding interactions.

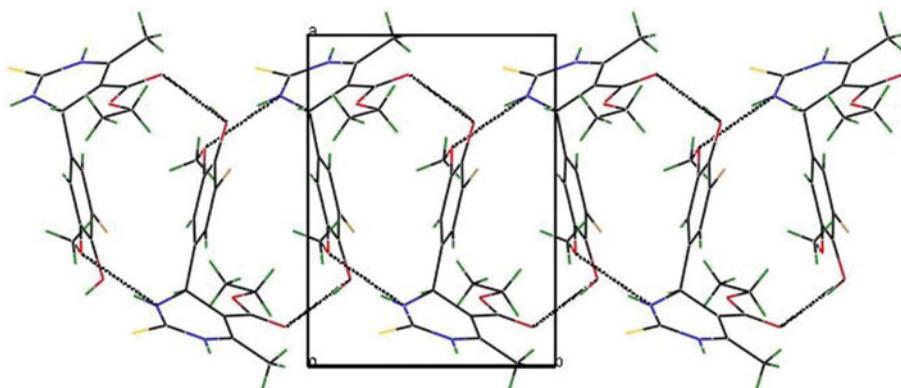


Figure 4. The unit cell diagram of compound ($C_{15}H_{17}BrN_2O_4S$) showing hydrogen bonding interactions.

However, in the compound ($C_{15}H_{17}BrN_2O_4S$), the H-pack diagram only shows two intermolecular hydrogen bonds having same symmetry code $(-x + 1, y - 1/2, -z + 1/2)$;

- An O(2) atom of C(2) substituted carbonyl group to the H(3) hydrogen of hydroxyl group substituted at C(12) [O(3)-H(3)⋯O(2) with 1.90 Å length and 165.4° angle].
- An O(4) atom of methoxy group substituted at C(13) to the H(1D) hydrogen of N(1) atom at DHPM ring [N(1)-H(1D)⋯O(4) with 2.221(17) Å length and 165(2)° angle] (Table 2, Figure 4).

The rest of intermolecular hydrogen bonds of both compounds are summarized in Table 2 which are not displayed in H-pack diagrams, among them for the compound ($C_{15}H_{17}BrN_2O_5$) are;

- H(16C) hydrogen of C(16) atom of methanol to the oxo O(5) atom [C(16)-H(16C)⋯O(5) with 2.57 Å length and 146.8° angle] and H(1D) hydrogen of N(1) atom to the O(6) atom of methanol [N(1)-H(1D)⋯O(6) with 2.62 Å length and 153.9° angle] having same symmetry code $(-x + 2, -y + 1, -z + 2)$.
- H(1D) hydrogen of N(1) atom to the O(3) atom of methoxy group having $(-x + 1, -y + 1, -z + 2)$ symmetry code [N(1)-H(1D)⋯O(3) with 2.64 Å length and 131.4° angle].

And for the compound ($C_{15}H_{17}BrN_2O_4S$) are;

- H(2A) hydrogen of C(2) atom to the thioxo S(1) atom [C(2)-H(2A)⋯S(1) with 2.97 Å length and 136.8° angle] having $(-x, y + 1/2, -z + 1/2)$ symmetry code.
- H(2B) hydrogen of C(2) atom to Br(1) atom substituted to the C(12) atom of phenyl ring [C(2)-H(2B)⋯Br(1) with 3.08 Å length and 143.4° angle] and H(15B) hydrogen of C(15) atom to the thioxo S(1) atom [C(15)-H(15B)⋯S(1) with 3.00 Å length and 142.4° angle] having $(-x + 1, y + 1/2, -z + 1/2)$ symmetry code.
- H(2C) hydrogen of N(2) atom to the thioxo S(1) atom having $(-x, -y + 1, -z)$ symmetry code [N(2)-H(2C)⋯S(1) with 2.571(16) Å length and 172(2)° angle].

Crystallographic data information

Crystallographic data for the structures reported in this paper have been deposited in the Cambridge Crystallographic Data Centre as supplementary information, which can be accessed on an application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk, www: <http://www.ccdc.cam.ac.uk>). The structure deposition number for 5-Carboethoxy-4-(3-bromo-4-hydroxy-5

-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (C₁₅H₁₇BrN₂O₅) is CCDC-1001977 and for 5-Carboxy-4-(3-bromo-4-hydroxy-5-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (C₁₅H₁₇BrN₂O₄S) is CCDC-1001970.

References

- [1] (a) Atwal, K. S., Rovnyak, G. C., O'Reilly, B. C., & Schartz, J. J. (1989). *J. Org. Chem.*, 54, 5898–5907. (b) Atwal, K. S. et al. (1990). *J. Med. Chem.*, 33, 2629–2635. (c) Rovnyak, G. C. et al. (1995). *J. Med. Chem.*, 38, 119–129.
- [2] Atwal, K. et al. (1990). *J. Med. Chem.*, 33, 1510–1515.
- [3] Rovnyak, G. C. et al. (1992). *J. Med. Chem.*, 35, 3254–3263.
- [4] (a) Kappe, C. O., (1993). *Tetrahedron*, 49, 6937–6963. (b) Kappe, C. O., Fabian, W. M. F., & Semones, M. A. (1997). *Tetrahedron*, 53, 2803–2816.
- [5] Biginelli, P., (1893). *Gazz. Chim. Ital.*, 23, 360–413.
- [6] Overman, L. E., Rabinowitz, M. H., & Renhowe, P. A. (1995). *J. Am. Chem. Soc.*, 117, 2657–2658.
- [7] Patil, A. D. et al. (1995). *J. Org. Chem.*, 60, 1182–1188.
- [8] Kappe, C. O., Shishkin, O. V., Uray, G., & Verdino, P. (2000). *Tetrahedron*, 56, 1859–1862.
- [9] Gartner, M. et al. (2005). *ChemBioChem*, 6, 1173–1177.
- [10] Folkers, K., & Johnson, T. B. (1934). *J. Am. Chem. Soc.*, 56, 1180–1185.
- [11] Wipf, P., & Cunningham, A. (1995). *Tetrahedron Lett.*, 36, 7819–7822.
- [12] Aswin, K., Sheik Mansoor, S., Logaiya, K., & Sudhan, S. P. N. (2014). *J. King Saud Univ. Sci.*, 26, 141–148.
- [13] Heidarzadeha, F., Rezaee Nezhada, E., & Sajjadifar, S. (2013). *Scientia Iranica C*, 20, 561–565.
- [14] Karami, B., Haghhighijou, Z., Farahi, M., & Khodabakhshi, S. (2012). *Phosphorus, Sulfur Silicon Relat. Elem.*, 187:6, 754–761.
- [15] Konkala, K. et al. (2012). *Tetrahedron Lett.*, 53, 1968–1973.
- [16] Lal, J., Sharma, M., Gupta, S., Parashara, P., Sahu, P., & Agarwala, D. D. (2012) *J. Mol. Catal. A. Chem.*, 352, 31–37.
- [17] Saha, S., & Moorthy, J. N. (2011). *J. Org. Chem.* 76, 396–402.
- [18] Mondal, J., Sen, T., & Bhaumik, A. (2012). *Dalton Trans.*, 41, 6173–6181.
- [19] Narahari, S. R., Reguri, B. R., Gudaparthi, O., & Mukkanti, K. (2012). *Tetrahedron Lett.*, 53, 1543–1545.
- [20] Pourjavadi, A., Hosseini, S. H., & Soleyman, R. (2012). *J. Mol. Catal. A. Chem.*, 365, 55–59.
- [21] Shen, Z. -L., Xu, X. -P., & Ji, S. -J. (2010). *J. Org. Chem.*, 75, 1162–1167.
- [22] Xu, F., Huang, D., Lin, X., & Wang, Y. (2012). *Org. Biomol. Chem.*, 10, 4467–4470.
- [23] Kefayati, H., Asghari, F., & Khanjanian, R. (2012). *J. Mol. Liq.*, 172, 147–151.
- [24] Parasuraman, K., Aswar, S. A., Muskawar, P. N., Bhagat, P. R., & Senthil Kumar, S. J. (2012). *Organomet. Chem.*, 723, 154–162.
- [25] Huang, Y., Yang, F., & Zhu, C. (2005). *J. Am. Chem. Soc.*, 127 (47), 16386–16387.
- [26] Ismaili, L. et al. (2008) *Eur. J. Med. Chem.*, 43, 1270–1275.
- [27] Karade, H. N., Acharya, J., & Kaushik, M. P. (2012). *Tetrahedron Lett.*, 53, 5541–5543.
- [28] Kolosov, M. A., Orlov, V. D., Beloborodov, D. A., & Dotsenko, V. V. (2009). *Mol. Div.*, 13, 5–25.
- [29] Litvic, M. et al. (2010). *Tetrahedron*, 66, 3463–3471.
- [30] Ashok, M., Holla, B. S., & Kumari, N. S. (2007). *Eur. J. Med. Chem.*, 42, 380–385.
- [31] Starcevic, J. T., Laughlin, T. J., & Mohan, R. S. (2013). *Tetrahedron Lett.*, 54, 983–985.
- [32] Wang, R., & Liu, Z. -Q. (2012). *J. Org. Chem.*, 77(8), 3952–3958.
- [33] Hari Krishnan, P. S., Rajesh, S. M., Abdulrahman, S. P., & Almansour I. (2013). *Tetrahedron Letters*, 54, 1076–1079.
- [34] Minaxi, S. M., & Manish, K. S. (2013). *Mol. Cryst. Liq. Cryst.*, 574(1), 117–128.
- [35] Minaxi S. M., & Manish K. S. (2015) *Mol. Cryst. Liq. Cryst.*, 623(1), 217–225.
- [36] Ahluwalia, V. K., Bhagat, P., Aggarwal, R., & Chandra, R. (2005). *Intermediates for organic synthesis*, I. K. international Pvt. Ltd., New Delhi, 44.
- [37] Dictionary of organic compounds by Chapman, & Hall, 5th Edition, B-02262.
- [38] Sheldrick, G. M. (1990). *Acta Crystallogr.*, A46, 467–473.
- [39] Sheldrick, G. M. (1997). *SHELXL-1997, Program for Refinement of Crystal Structures*, University of Göttingen: Germany.