Synthesis, spectroscopic and crystal structure analysis of two dihydropyrimidines

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The preparation of two reduced pyrimidine derivatives, ethyl 3-acetyl-4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate and ethyl 4-(3,4-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, is described, along with details of their crystal structure analysis.

Keywords: dihydropyrimidines, calcium channel blockers, crystal structure

Dihydropyridines (DHPs) are the most studied class of organic calcium channel modulators and have become almost indispensable for the treatment of cardiovascular diseases such as hypertension, cardiac arrhythmias, and angina.[1] In recent years, interest has also been focused on their aza-analogs such as dihydropyrimidines (DHPMs), which exhibit a pharmacological profile similar to classical dihydropyridine calcium channel modulators. These inherently asymmetric dihydropyrimidine derivatives are better calcium channel blockers, and they have been extensively studied to expand the existing structure-activity relationships and to gain further insight into molecular interactions at the receptor level.[2-10] The DHPMs can be easily synthesised by the so-called Biginelli dihydropyrimidine synthesis,[11,12] which is a simple, one-pot, acid-catalysed condensation reaction.

The present work is part of our research involving a series of novel dihydropyrimidine derivatives which can be potent mimics of the dihydropyridines.[13,14] A knowledge of the molecular geometry and the probable bioactive structure of a compound is a prerequisite for any understanding of its pharmacological properties. We report here the structures of two dihydropyrimidine derivatives, **1** and **2**, both of them potential calcium channel blockers.

Results and discussion

The DHPM compounds **2** and **3** were prepared by the standard three-component condensation reaction.[15] Compound **3** was acetylated at N(3) using acetic anhydride, forming **1** (Scheme 1).

Figures 1 and 4 show the ORTEP diagrams of the molecules **1** and **2.** Figures 2, 3 and 5 show the crystal packing of the two compounds. Selected bond distances and angles are given in Table 1 and Table 2 for compounds **1** and **2**, and Tables 3 and 4 show the hydrogen-bond interactions for compounds **1** and **2** respectively**.** In the following two subsections of this discussion, except for the compound names, the atoms are numbered using the crystallographic numbering scheme as shown in Figs 1 and 4.

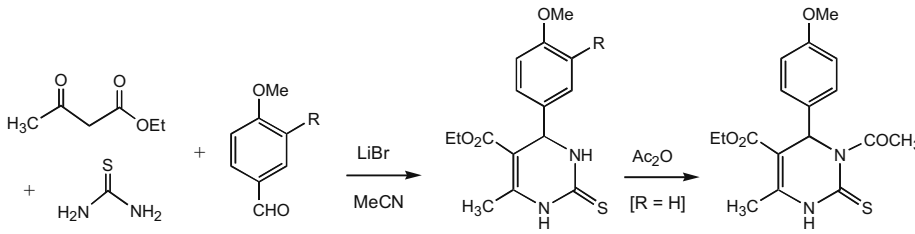
Table 1 Selected bond lengths [Å] and angles [°] for compound **1**

Bond	Length/Å	Bonds	Angle/°
C3–O3	1.369(4)	C2–C3–O3	124.4(3)
C7–C10	1.513(3)	C4–C3–O3	116.4(3)
C8–N1	1.373(3)	N1–C8–N2	113.7(2)
C8–N2	1.363(3)	N1–C8–S1	125.07(19)
C8–S1	1.644(3)	N2–C8–S1	121.08(19)
C9–C10	1.343(4)	C10–C9–C14	129.3(2)
C9–C14	1.498(4)	C10–C9–N2	116.6(2)
C9–N2	1.401(3)	C14–C9–N2	114.2(3)
C10–C11	1.470(4)	C7–C10–C11	121.7(2)
C11–O1	1.199(3)	C9–C10–C11	122.2(2)
C11–O2	1.334(4)	C10–C11–O1	125.5(3)
C12–C13	1.427(7)	C10–C11–O2	111.7(2)
C15–C16	1.493(4)	O1–C11–O2	122.7(3)
C15–N1	1.431(3)	C16–C15–N1	119.6(3)
C15–O4	1.193(4)	C16–C15–O4	122.2(3)
C17–O3	1.419(4)	N1–C15–O4	118.1(3)
		C8–N1–C15	126.9(2)
		C8–N2–C9	125.1(2)
		C3–O3–C17	117.8(3)

Ethyl 3-acetyl-4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1**)

In this molecule, the aryl ring is essentially planar, positioned axially, perpendicular to and bisecting the boat-like dihydropyrimidine ring (Fig. 1). The dihedral angle between the planes of the aryl and dihydropyrimidine rings is 86.462(5)°, indicating the extent of orthogonality between the two ring systems. This 'aryl-group up' configuration is considered crucial for enhanced calcium antagonist activity in these compounds. The methoxy substituent on the phenyl ring adopts a configuration which is almost normal to the C7–H7 bond. The carbonyl group of the ester at C10 is *cis* to the dihydropyrimidine double bond (C9–C10).

All bond lengths and angles are within the normal ranges. The molecular packing shows the presence of the less frequent N–H···S hydrogen bonds. These N2–H2N···S1 interactions



Scheme 1

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Table 2 Selected bond lengths [Å] and angles [°] for compound **2**

Bond	Length/Å	Bonds	Angle/°
S1–C5	1.685(3)	C2–C3–O3	119.6(2)
N2–C5	1.328(3)	C6–C2–C8	122.7(2)
O3–C3	1.326(3)	O3–C3–O4	114.9(2)
O4–C3	1.210(3)	O3–C3–C2	122.4(2)
C2–C3	1.468(4)	O4–C3–C2	124.2(2)
C2–C6	1.517(3)	C5–N1–C8	123.90(19)
C2–C8	1.353(3)	S1–C5–N2	120.67(18)
N1–C5	1.364(3)	S1–C5–N1	115.4(2)
N1–C8	1.394(3)	N2–C5–N1	114.5(3)
C4–C6	1.528(4)	C10–O2–C17	118.4(2)
O2–C10	1.380(3)	C2–C8–N1	128.7(2)
O2–C17	1.425(4)	C2–C8–C7	112.9(2)
C11–C15	1.498(4)	N1–C8–C7	119.0(2)
O1–C14	1.369(4)	O2–C10–C9	120.9(3)
O1–C16	1.408(4)	O2–C10–C14	120.1(3)
C12–C14	1.380(4)	C9–C10–C14	118.1(3)

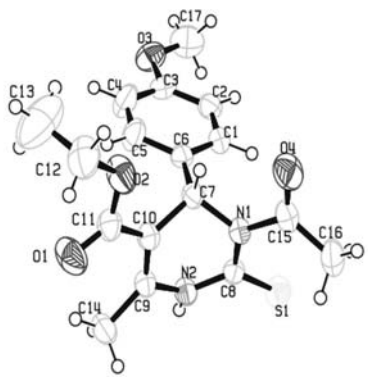

Fig. 1 ORTEP view of compound **1**, showing 50% probability ellipsoids and the atom numbering scheme.

give rise to centrosymmetric dimers of graph set $R_2^2(8)$ (Fig. 2). This observation is in accord with the general tendency of the dihydropyrimidines to form dimers through intermolecular hydrogen bonds. The crystal cohesion is further enhanced by C-H···O short contacts [C16–H16B···O1].

Ethyl 4-(3,4-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2**)

The classical dihydropyrimidine structural features are emphasised further in this molecule, due to the effect of the second methoxy substituent on the aryl ring (Fig.**4**).

Disubstitution by bulky methoxy groups bring about enhanced conformational restriction resulting in the aryl group having an enhanced axial position, perpendicular to and bisecting the

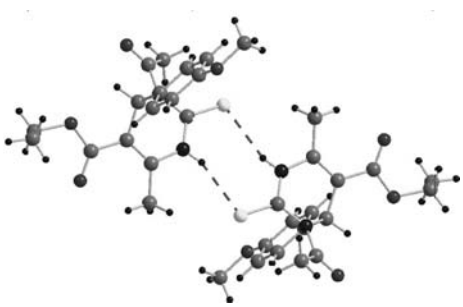

Fig. 2 The NH···S interactions in **1** viewed along the *c* axis.

Table 3 Non-bonded interactions and possible hydrogen bonds (Å,°) for compound **1** (D – donor; A – acceptor; H – hydrogen)

D–H···A	D–H	H···A	D···A	angle D–H···A
C16–H16B···O1^{i}	0.96(3)	2.429(3)	3.284(4)	148(2)
N2–H2N···S1^{ii}	0.86(2)	2.546(1)	3.356(3)	157(2)

Symmetry codes: (i) $-x+1, -y+1, -z+1$; (ii) $-x, -y+1, -z+1$.

Table 4 Non-bonded interactions and possible hydrogen bonds (Å,°) for compound **2** (D – donor; A – acceptor; H – hydrogen)

D–H···A	D–H	H···A	D···A	angle D–H···A
N2–H2N···S1^{i}	0.85(7)	2.511(5)	3.340(3)	165(6)
N1–HN1···O4^{ii}	0.80(2)	2.175(2)	2.937(3)	158(2)

Symmetry codes: (i) $-x, -y+1, -z$; (ii) $-x+1, +y, +z$.

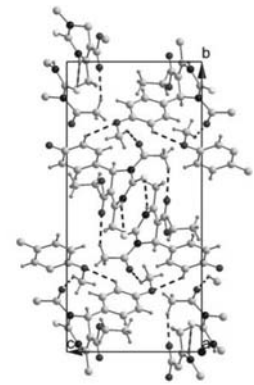

Fig. 3 View of the molecular packing in **1**, showing CH···O and NH···S interactions, down the *a* axis.

boat-like dihydropyrimidine ring. The dihedral angle between the planes of aryl and dihydropyrimidine rings in this case is 88.767(2)°, which predisposes the molecule towards excellent receptor-binding properties. Additionally, it can be seen that both the substituents are added to the biologically less important 'right hand side' of the molecule, thereby not interfering with the receptor-sensitive groups of the 'left hand side'.[9]

The ester group is, in contrast to compound **1**, considered to be in the *trans* conformation because the carbonyl group is facing away from the C2–C8 double bond and does not eclipse it. The 1,4-dihydropyrimidine ring, as before, adopts a 'boat' conformation. The deviations from the least-squares

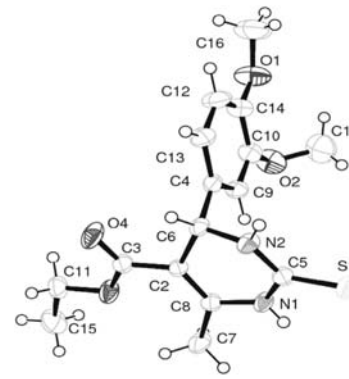

Fig. 4 ORTEP diagram of compound **2**, showing 50% probability displacement ellipsoids and the atom numbering scheme.

plane through the dihydropyrimidine ring atoms suggest that the greatest displacement from zero occurs about the bonds from N1 and C6 (carbon with aryl substituent), indicating that the greatest degree of ring puckering occurs at these positions, the distortion being greatest at the C6 position. The magnitudes of ring torsion angles indicate that both C6 and N1 are displaced from the ring in the same direction, which imparts the boat-type conformation to the dihydropyrimidine ring

Due to the aryl group axially bisecting this boat like dihydropyrimidine ring, the second methoxy group, being an additional aryl substituent, is forced into the synperiplanar orientation relative to C6–H.

The molecular packing of compound **2** reveals N–H···S interactions with N2–HN2···S1 hydrogen bonds generating a centrosymmetric dimer of graph set R_2^2 (8) (Fig. 5). In addition to these interactions there are also N–H···O interactions linking the molecules into a chain along the crystallographic *a* axis The N–H···S hydrogen bonds link the molecules in dimers about centres of symmetry, and the dimers are linked in chains, in a ladder formation, parallel to the *a* axis.

Conclusion

In conclusion, the authors consider that, given the intense interest generated by the therapeutic activities of the dihydropyrimidines and subsequent studies conducted on their structural aspects, the two compounds discussed here are analogues possessing the special structural requirements for calcium channel modulation. They are therefore highly relevant to the design of new cardiovascular drugs and are, therefore, suitable for further pharmacological testing.

The crystal structure analyses of the two compounds revealed several structural aspects which are prerequisites for calcium antagonist activity as suggested by the well-documented structure-activity studies carried out on both DHPs and DHPMs. These include the latent structural asymmetry, the substituted phenyl ring at C4, the resultant perpendicular conformation of the aromatic ring at C4 with respect to the dihydropyrimidine ring, the non-identical substitution at positions 3 and 5, methyl substitution at C6 and the sulfur group at C2. Further, it is interesting to note the influence of an additional substituent on the phenyl ring in compound **2**, which causes an enhancement of these desirable features, suggesting optimum calcium antagonist activity.

Inspection of the extended crystal structures also showed the less common N–H···S interactions along with C–H···O and N–H···O hydrogen bonds in the packing of both compounds.

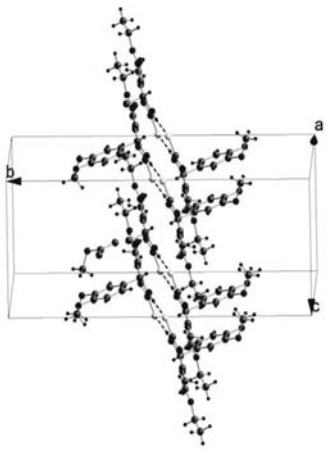

Fig. 5 Packing in **2** due to N-H···S dimers viewed along the *a* axis.

Experimental

Synthesis and characterisation

Melting points were determined in open capillaries. The IR spectra of samples as KBr pellets were recorded on a Shimadzu FTIR 8400 instrument. NMR spectra of the samples in $CDCl_3$ were recorded on an AMX 400 NMR spectrometer.

Ethyl 3-acetyl-4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1**): Ethyl acetoacetate (3.12 g, 24 mol), anisaldehyde (2.72 g, 20 mmol), thiourea (1.83 g, 24 mmol), and LiBr (0.175 g, 2 mmol) were refluxed together for 5 h in acetonitrile (25 mL)**.** The reaction mixture was cooled, poured onto crushed ice, and stirred for several minutes. The ethyl 4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3**) was filtered off, washed with cold water, dried and recrystallised from ethanol, from which it separated as a white solid (5.02 g, 82%), m.p. 172 °C (lit.[16] m.p. 150–152 °C).

Compound **3** (2.0 g) was mixed with acetic anhydride (10 mL) and refluxed for 4 hours. The reaction mixture was cooled and diluted by addition of water (20 mL). The acetyl derivative separated as an oil, which solidified on prolonged stirring. The solid was washed with more water. White crystals of this solid (**1,** 1.95 g, 86%) were obtained by slow evaporation from a solution in chloroform.

IR: ν_{max} 3186, 3132, 2993, 1705, 1643, 1227, 1026 cm^{-1}. NMR: δ_H 8.5 (s, 1H), 6.82–7.22 (m, 4H), 6.60 (s, 1H), 4.21 (q, J = 7 Hz, 2H), 3.77 (s, 3H), 2.77 (s, 3H), 2.41 (s, 3H), 1.27 (t, J = 7 Hz, 3H).

Ethyl 4-(3,4-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2**): A solution of ethyl acetoacetate (3.12 g, 24 mM), veratraldehyde (3.32 g, 20 mM), thiourea (1.83 g, 24 mM) and LiBr (0.175 g, 2 mM) in acetonitrile (25 mL) was refluxed for 5 h**.** After cooling, the reaction mixture was poured onto crushed ice and stirred for a few minutes. The solid product was filtered off, washed with cold water, dried and recrystallised from ethanol. Yield: 5.24 g (78%), m.p. 152 °C (lit.[17] m.p. 149–150 °C). Pale brown crystals suitable for crystallography were obtained by slow evaporation from a mixture of ethanol and ethyl acetate.

IR: ν_{max} 3209, 3155, 2962, 1705, 1643, 1227, 1026, 1589 cm^{-1}. NMR: δ_H 8.83 (s, 1H), 6.73–6.90 (3H), 6.58 (s, 1H), 4.21 (q, J = 7 Hz, 2H), 3.81 (s, 6H), 2.39 (s, 3H), 1.26 (t, J = 7 Hz, 3H).

Crystal structure determination

The X-ray diffraction data for compounds **1** and **2** were collected on a Bruker Smart CCD Area Detector System using MoKa (0.71073Å) radiation. The data were processed using SAINTPLUS.[18] The structures were solved by direct methods and difference Fourier synthesis using SHELXS97.[19] The positions and anisotropic displacement parameters of all non-hydrogen atoms were included in the full matrix least-square refinement using SHELXL97.[20] Molecular diagrams were generated using ORTEP.[21]

Ethyl 3-acetyl-4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1**)

Intensity data were collected up to a maximum of 28.13° for the compound in the ω–ϕ scan mode. A total of 15,060 reflections were collected, resulting in 4130 (R_{int} = 0.024) independent reflections of which the number of reflections satisfying $I > 2\sigma(I)$ criteria were 3175. These were treated as observed. The hydrogen atoms were fixed geometrically and were refined isotropically. The R indices for all data were R_1 = 0.0903 and wR_2 = 0.2026. The R factor for 'observed' data finally converged to 0.0707 with wR_2 = 0.1880. The maximum and minimum values of residual electron density were 0.630 and –0.416 $eÅ^{-3}$.

Crystal data for **1**: $C_{17}H_{20}N_2O_4S$, formula weight = 348.41, monoclinic, $P2_1/c$, a = 9.092(4)Å, b = 20.483(10)Å, c = 9.867(5)Å, β = 106.573(7)^0, V = 1761.3(14)$Å^3$, Z = 4, μ = 0.206 mm^{-1}, D_x = 1.314 Mg m^{-3}, T = 293(2)K.

Ethyl 4-(3,4-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2**)

Intensity data were collected up to a maximum of 28.33° for the compound in the ω–ϕ scan mode. A total of 14,314 reflections were collected, resulting in 3967 (R_{int} = 0.024) independent reflections of which the number of reflections satisfying $I > 2\sigma(I)$ criteria were 2983. These were treated as observed. The hydrogen atoms (a few located in ΔF maps and a few geometrically fixed) were refined isotropically. The R indices for all data were R_1 = 0.1043 and wR_2 = 0. 1459. The R factor for 'observed' data finally converged to 0.0740 with wR_2 = 0.1344. The maximum and minimum values of residual electron density were 0.33 and –0.22$eÅ^{-3}$.

Crystal data for **2**: $C_{16}H_{20}N_2O_4S$, formula weight = 336.40, monoclinic, $P2_1/c$, $a = 7.2181(9)$Å, $b = 24.592(3)$Å, $c = 10.1024(13)$Å, $\beta = 107.845(2)^0$, $V = 1707.0(4)$Å^3, $Z = 4$, $\mu = 0.210$ mm^{-1}, $D_x = 1.309$ Mg m^{-3}, T = 293(2)K.

Supplementary material

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. The deposition numbers are CCDC 686220 (compound **1**) and CCDC 686219 (compound **2**).

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