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# SYNTHESIS AND CRYSTAL STRUCTURE ANALYSIS OF TWO THIAZOLO[3,2-*a*]PYRIMIDINE DERIVATIVES

**H. Nagarajaiah[1], M.I.A. Khazi[2], A.Y. Khan[2], N. Fathima[1], I.A.M. Khazi[2], N.S. Begum[1]**

[1]*Department of Chemistry, Bangalore University, Bangalore-560001, India*
E-mail: noorsb05@gmail.com, noorsb@rediffmail.com (N.S. Begum)
[2]*Department of Chemistry, Karnatak University, Dharwad-580003, India*

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Synthesis of 5R*-(3-methoxy-phenyl)-3,7-dimethyl-5*H*-thiazolo[3,2-*a*]pyrimidine-2,6-dicarboxylic acid diethyl ester (**2a**) and 3,7-dimethyl-5S*-thiophen-2-yl-5*H*-thiazolo[3,2-*a*]pyrimidine-2,6-dicarboxylic acid diethyl ester (**2b**) are achieved by the cyclocondensation of 3,4-dihydropyrimidine-2-thione derivative with α-haloester. Preliminary analysis was done spectroscopically by means of $^1$H NMR spectra, mass spectra and elemental analyses. Further the structures were confirmed by X-ray crystal structure analysis. The two molecules are not identical in configuration. In both the compounds the central pyrimidine ring adopts a conformation which is best described as an intermediate between a boat and screw boat form. The crystal structure is stabilized by intermolecular C—H…O and C—H…π weak interactions.

**K e y w o r d s:** thiazolo[3,2-*a*]pyrimidine derivative, crystal structure, C—H…O and C—H…π weak interactions.

## INTRODUCTION

Dihydropyrimidines represent a heterocyclic system with remarkable pharmacological efficiency and are described as potent mimics of dihydropyridine calcium channel blockers [ 1—5 ]. In recent years, several biological activities including antiviral, antitumor, antibacterial, and antiinflammatory activities has been ascribed to these partly reduced pyrimidine derivatives. More recently, appropriately functionalized DHPMs have emerged as orally active antihypertensive agents [ 6—8 ]. By performing pharmacological studies with uniquely designed single-enantiomer DHPMs, it was established that calcium channel modulation (antagonist *versus* agonist activity ) is dependent on the absolute configuration at chiral carbon atom, whereby the orientation of the aryl group substituted to chiral carbon atom acts as a ″molecular switch″ between antagonist (aryl-group up) and agonist (aryl-group down) activity [ 9 ]. Furthermore, in the receptor-bound conformation the substituted aryl ring should be positioned axially, perpendicular to, and bisecting the boat-like dihydropyridine/pyrimidine ring, with the 4-aryl substituent preferring the synperiplanar orientation [ 10 ]. A cis-carbonyl ester orientation was also found mandatory for optimum calcium channel modulators activity. Thus, pyrimidines have been subjected to a large variety of structural modifications in order to synthesize derivatives with different biological properties.

In the course of our structural studies of the family of thiazolopyrimidine derivatives, we report here the structures of two such compounds, namely 5R*-(3-methoxy-phenyl)-3,7-dimethyl-5*H*-thiazolo[3,2-*a*]pyrimidine-2,6-dicarboxylic acid diethyl ester (**2a**) and 3,7-dimethyl-5S*-thiophen-2-yl-5*H*-thiazolo[3,2-*a*]pyrimidine-2,6-dicarboxylic acid diethyl ester (**2b**). The synthesis of similar derivatives has been reported earlier [ 11 ]. The syntheses of these compounds were followed by acquisi-

tion of their analytical data and subsequent spectroscopic analyses using $^1$H NMR, mass spectra and elemental analysis techniques to confirm the presence of the supposed ring systems, as well as the signals for the existence of various protons. Single crystal X-ray diffraction analysis has been carried out for the two compounds in order to establish the crystal as well as molecular structure and to understand the self-aggregation in terms of possible intermolecular interactions. Molecular packing is controlled by various intermolecular interactions. In the present work we report the synthesis and spectroscopic analysis of the two compounds with more emphasis laid on weak interactions.

## EXPERIMENTAL

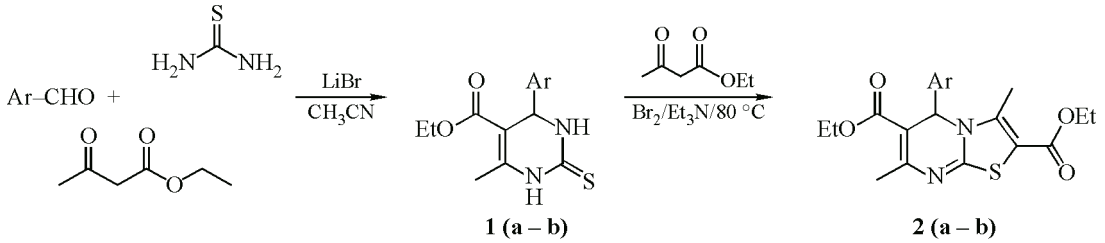
All reagents were obtained from commercial sources. Solvents were dried and purified with known conventional methods.

**Analytical methods.** The melting point was determined in open capillary using Guna melting point apparatus and is uncorrected. The IR spectra were recorded as KBr discs using Nicolet FT-IR 410 spectrophotometer. $^1$H NMR spectra were recorded on Varian RXZ-300 MHz spectrometer using TMS as internal reference compound. C, H, N and S were estimated in CHNS elementar vario micro cube. Mass spectra were recorded on Finnigan MAT (Model MAT8200) spectrometer. Synthesis of the two compounds is as shown in Scheme.

**Procedure for the preparation of 5R*-(3-methoxy-phenyl)-3,7-dimethyl-5*H*-thiazolo[3,2-*a*]pyrimidine-2,6-dicarboxylic acid diethyl ester (2a) and 3,7-Dimethyl-5S*-thiophen-2-yl-5*H*-thiazolo[3,2-*a*]pyrimidine-2,6-dicarboxylic acid diethyl ester (2b).** To a solution of ethylacetoacetate (0.72 mmol) in 2 ml of 1,2 dichloroethane, bromine (0.72 mmol) was added slowly with constant stirring, and the mixture was allowed to stir till the solution became colorless. To the above colorless solution the compound **1** and triethylamine (0.72 mmol) were added. The reaction mixture was heated to 80 °C with vigorous shaking, and heating was continued for 2 hrs. The solvent was removed under reduced pressure and the residue was treated with aqueous sodium bicarbonate solution followed by extraction with ethyl acetate and water, the ethyl acetate layer was dried over anhydrous sodium sulphate [ 12 ]. Recrystallization from a mixture of methanol and ethyl acetate in 1:1 ratio yielded pale yellow crystals of **2a** and **2b.** Yield 77—81 %. IR showed the absence of a sharp band NH stretching frequency in the region of 3200—3400 cm$^{-1}$. The absence of peak corresponding to two NH groups in $^1$HNMR spectrum of compounds **2(a—b)** showed the formation of expected product.

**Compound 2a.** Yield: 81 %. M.p: 118—119 °C. IR (KBr $\nu_{max}$, cm$^{-1}$): 2977(CH), 1703(C=O), 1600(C=C), 1496(C=N). $^1$H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, $J$ = 7.2 Hz, 3H, —$CH_2CH_3$), 1.35 (t, $J$ = 7.2 Hz, 3H, —$CH_2CH_3$), 2.34 (s, 3H, $CH_3$), 2.41 (s, 3H, $CH_3$), 3.78 (s, 3H, —$OCH_3$), 4.15 (q, $J$ = 7.2 Hz, 2H, $CH_2CH_3$), 4.25 (q, $J$ = 7.2 Hz, 2H, $CH_2CH_3$), 6.10 (s, 1H, CH), 6.81—7.26 (m, 4H, ArH). %CHNS found (calc): C 60.56(60.32), H 5.81(5.46), N 6.73(7.03), S 7.70 (7.59). *m*/*z*: 416 (m+), 309 (m-107).

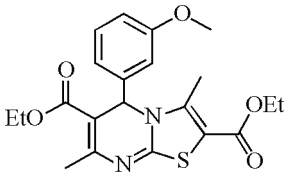
**Compound 2b.** Yield: 77 %. M.p: 113—114 °C. IR (KBr $\nu_{max}$, cm$^{-1}$): 2976(CH), 1705, 1610(C=O), 1506(C=N). $^1$H NMR (300 MHz, $CDCl_3$): δ 1.30 (t, $J$ = 7.2 Hz, 3H, —$CH_2CH_3$), 1.35 (t, $J$ = 7.2 Hz, 3H, —$CH_2CH_3$), 2.43(s, 3H, $CH_3$), 2.60 (s, 3H, $CH_3$), 4.21 (q, $J$ = 7.2 Hz, 2H, $CH_2CH_3$), 4.29 (q, $J$ = 7.2 Hz, 2H, $CH_2CH_3$), 6.56 (s, 1H, CH), 6.88–7.26 (m, 3H, ArH). %CHNS found (calc): C 55.08 (55.21), H 5.14 (4.97), N 7.14 (7.22), S 16.34 (16.23) *m*/*z*: 392 (m+), 319 (m-73).



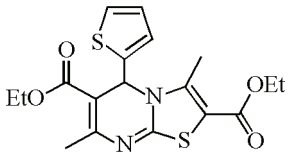

**1 (a – b)** **2 (a – b)**

**2a/1a** (Ar = 3-$OCH_3C_6H_4$) and **2b/1b** (Ar = $C_4H_3S$)

Scheme. Syntheses of compounds **2a** and **2b**




**2a**




**2b**

**X-Ray diffraction analysis.** Good quality yellow colored single-crystals of compounds **2a** and **2b** were obtained by slow evaporation from a methanol — ethyl acetate (1:1) mixture. The X-ray diffraction data were collected on a Bruker Smart CCD Area Detector System using Mo$K_\alpha$ (0.71073 Å) radiation for the crystal. The data were reduced using SAINT-Plus [ 13 ]. The structure was solved by direct methods using SHELXS97 [ 14 ] and difference Fourier synthesis using SHELXL97 [ 14 ]. The positions and anisotropic displacement parameters of all non-hydrogen atoms were included in the full-matrix least-square refinement using SHELXL97 [ 14 ] (Sheldrick, 1997) and the procedures were carried out for a few cycles until convergence was reached. The H atoms were placed at calculated positions in the riding model approximation; their temperature factors were set to 1.2 times those of the equivalent isotropic temperature factors of the parent atoms. All other non-H atoms were refined anisotropically. Molecular diagrams were generated using ORTEP [ 15 ]. The mean plane calculation was done using the program PARST [ 16 ].

For the compound **2a**, intensity data were collected up to a maximum of 27.00° for the compound in the ω—φ scan mode. A total of 6245 reflections were collected, resulting in 4347 independent reflections of which the number of reflections satisfying $I > 2\sigma(I)$ criteria were 3083. These were treated as observed. The $R$ factor after final convergence was 0.0693 and the maximum and minimum values of residual electron density were 0.438 and –0.574 e/Å$^{-3}$. For the compound **2b**, intensity data were collected up to a maximum of 27.00° for the compound in the ω—φ scan mode. A total of 17963 reflections were collected, resulting in 4066 independent reflections of which the number of reflections satisfying $I > 2\sigma(I)$ criteria were 2899. These were treated as observed. The R factor after final convergence was 0.0603 and the maximum and minimum values of residual electron density were 0.501 and –0.508 e/Å$^{-3}$.

Crystallographic data for the structure **2a** and **2b** reported in this paper have been deposited with the Cambridge data centre. The deposition numbers are CCDC 847174 and CCDC 866232. CIF file containing complete information on the above structures are

Freely available upon request from the following web site: www.ccdc.cam.ac.uk/data_request/cif.

## RESULTS AND DISCUSSION

**Crystallography.** The details of crystal data and refinements for **2a** and **2b** are given in Table 1. Table 2 gives their respective hydrogen bond interactions. The ORTEP diagrams of the molecules **2a** and **2b** are shown in Fig. 1, *a* and *b* respectively. Fig. 2, *a* and *b* show the hydrogen bond interactions in crystal structure of compounds **2a** and **2b** respectively.

The compound **2a** crystallizes in triclinic $P\bar{1}$ space group with one molecule in the asymmetric unit. All bond distances and angles fall within the normal limits. In this compound the substituted aryl group at C5 chiral carbon atom of the thiazolopyrimidine ring is positioned axially [ 17 ], bisecting the dihydropyrimidine ring. The carboxylic acid ethyl ester and the methyl groups are attached on the either sides of the ring with *trans* configuration to the thiazolopyrimidine ring. All the atoms of the ethyl ester group at C6 is in the plane of the thiazolopyrimidine ring, whereas one of the atom (C13) of the ethyl ester group at C2 is deviating from the plane. The aryl ring is positioned almost orthogonal to thiazolopyrimidine ring with a dihedral angle of 88.64°, similar to those reported in the earlier structure [ 18 ]. The methoxy group on the aryl ring adopts anti-periplanar conformation with respect to C5—H5 bond. These features have been found mandatory for optimum calcium channel modulation activity from the recently proposed new binding-site model for this class of cardiovascular drugs [ 19 ]. In compound **2a**, the central pyrimidine ring with a chiral C5 atom is significantly puckered and

Table 1

*Crystal data and structure refinement of* **2a** *and* **2b**

| Compound | **2a** | **2b** |
|---|---|---|
| Empirical formula | $C_{21}H_{24}N_2O_5S$ | $C_{18}H_{20}N_2O_4S_2$ |
| Formula weight | 416.48 | 392.48 |
| Temperature, K | 296(2) | 296 (2) |
| Crystal system, space group | Triclinic, $P\bar{1}$ | Triclinic, $P\bar{1}$ |
| Unit cell dimensions | | |
| *a*, *b*, *c*, Å | 7.747(3), 12.116(4), 12.533(4) | 10.1202(8), 10.2565(7), 11.0240(9) |
| α, β, γ, deg. | 64.903(6), 87.789(6), 75.878(6) | 107.368(7), 113.290(7), 101.598(6) |
| Volume, Å$^3$ | 1030.3(6) | 934.30(12) |
| *Z* | 2 | 2 |
| Calculated density, mg/cm$^3$ | 1.343 | 1.395 |
| Absorption coefficient, mm$^{-1}$ | 0.192 | 0.311 |
| *F*(000) | 440 | 412 |
| θ range for data collection, deg. | 2.72 to 27.00 | 2.35 to 27.00 |
| Limiting indices | $-9 \le h \le 9$, $-14 \le k \le 15$, $-15 \le l \le 15$ | $-12 \le h \le 12$, $-13 \le k \le 13$, $-14 \le l \le 14$ |
| Reflections collected / unique | 6245 / 4347 [*R*(int) = 0.0244] | 17963 / 4066 [*R*(int) = 0.0645] |
| Completeness to θ, % | 27.00 97.0 | 27.00 99.9 |
| Max. and min. transmission | 0.9699 and 0.9662 | 0.9519 and 0.9462 |
| Data / restraints / parameters | 4347 / 0 / 267 | 4066 / 0 / 239 |
| Goodness-of-fit on $F^2$ | 1.218 | 1.052 |
| $wR_2$ [$I > 2\sigma(I)$] | 0.1809 | 0.1698 |
| *R* indices (all data) | $R_1 = 0.0940$, $wR_2 = 0.2374$ | $R_1 = 0.0850$, $wR_2 = 0.1922$ |

adopts a conformation which is best described as an intermediate between a boat and screw boat form similar to those reported earlier [ 20 ]. The plane calculation shows that the atoms C5 and N2 deviate from the mean plane N1/C7/C6/C21 constituting the ring by –0.331 and 0.026 Å respectively. The ring puckering parameters [ 21 ] for the pyrimidine ring are Q(2) = 0.246(3) Å, φ(2) = 7.5(7)° and θ = 114.3(7)° respectively.

The crystal structure of compound **2a** is stabilized by intermolecular C—H…O interactions. The C—H…O interactions forms two sets of centrosymmetric head to head and head to tail dimers with graph set motif $R_2^2(6)$ and $R_2^2(18)$ respectively along *b* axis. The molecular packing is further stabi-

Table 2

C—H…π *interactions and possible hydrogen bonds* (Å, deg.) *for* **2a** *and* **2b**
(D — *donor*; A — *acceptor*; H — *hydrogen*)

| D—H···A | D—H | H···A | D···A | D—H···A | D—H···A | D—H | H···A | D···A | D—H···A |
|---|---|---|---|---|---|---|---|---|---|
| **2a** | | | | | **2b** | | | | |
| C4—H4C···O3$^{i}$ | 0.960 | 2.718 | 3.671(5) | 172 | C4—H4A···O3$^{i}$ | 0.960 | 2.733 | 3.644(5) | 158 |
| C9—H9A···O1$^{ii}$ | 0.970 | 2.872 | 3.699(5) | 143 | C11—H11C···O2$^{ii}$ | 0.960 | 2.765 | 3.682(5) | 160 |
| C20—H20C···$C_{g1}$ | 0.960 | 3.157 | 3.797(4) | 125 | C10—H10A···$C_{g2}$ | 0.969 | 2.872 | 3.729(4) | 147 |

Symmetry code for **2a**: $^{i}$ $-x+1, -y, -z+1$; $^{ii}$ $-x+1, -y, -z+2$; $^{iii}$ $1-x, 1-y, 1-z$.
Symmetry code for **2b**: $^{i}$ $-x, -y+2, -z$; $^{ii}$ $-x, -y+1, -z-1$; $^{iii}$ $-x, -y, -z$.

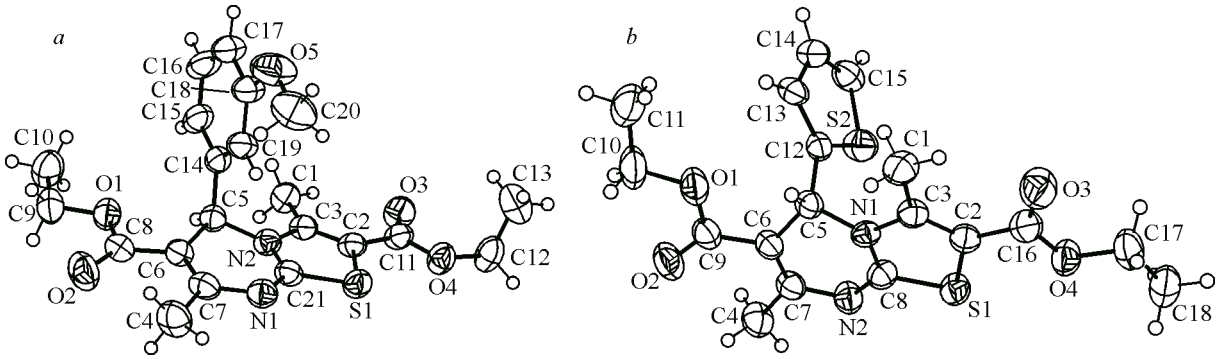



*Fig. 1.* ORTEP view of **2a** (*a*) and **2b** (*b*) showing 50 % probability ellipsoids, and the atom numbering scheme

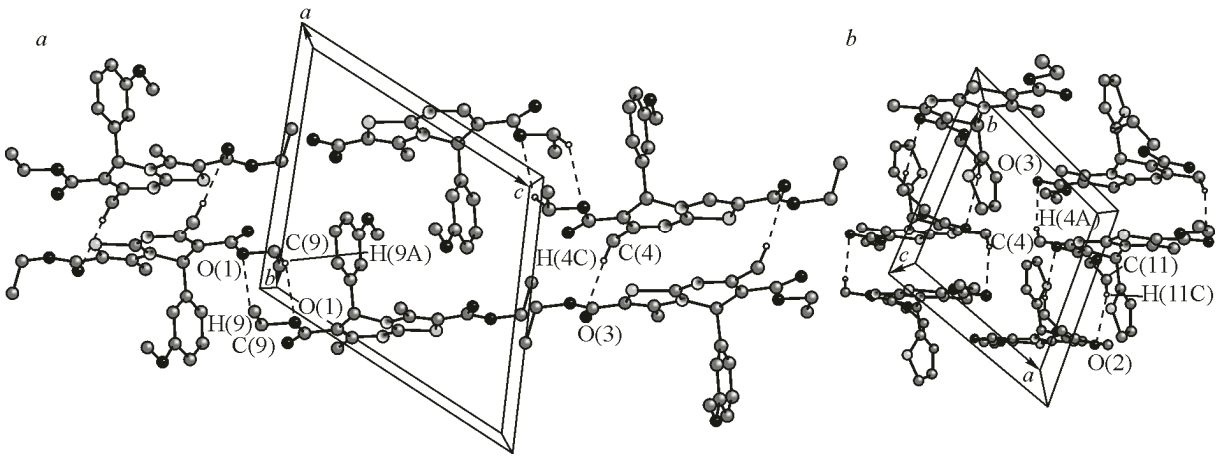



*Fig. 2.* View along the *a* axis of **2a** (*a*) and *c* axis of **2b** (*b*) showing C—H…O intermolecular interactions with dashed lines. H-atoms not involved in hydrogen bonding have been excluded

lized by π-ring interactions of the type C—H…$C_{g1}$ ($C_{g1}$ being the centroid of the ring C14—C19) are also observed in the crystal structure; details are given the Table 2.

In compound **2b** the substituted aryl group at C5 chiral carbon atom of the thiazolopyrimidine ring is positioned pseudo axially to the dihydropyrimidine ring. The carboxylic acid ethyl ester and the methyl groups are attached on the either sides of the ring with *trans* configuration to the thiazolopyrimidine ring. The structural studies reveal that in contrast to **2a** the C11 atom of the ethyl ester group at C6 is out of the plane of the thiazolopyrimidine ring, whereas the C18 atom of the ethyl ester group at C2 is slightly deviating from the plane. The aryl ring is almost orthogonal to thiazolopyrimidine ring with a dihedral angle of 84.88°. The survey of the structure at a molecular level reveals usual geometrical parameters for the S—C bond of 1.732(3) Å in the thiazolopyrimidine ring (aryl ring). In **2b**, the central pyrimidine ring with a chiral C5 atom is significantly puckered and adopts the same conformation as described in case of **2a**. The plane calculation shows that the atoms C5 and N2 deviate from the mean plane C8/N1/C6/C7 constituting the ring by 0.359 and 0.071 Å respectively. The ring puckering parameters [ 19 ] for the pyrimidine ring are Q(2) = 0.248(3) Å, φ(2) = 110.3(8)° and θ = 65.5(6)° respectively.

The crystal structure of **2b** is also stabilized by intermolecular C—H…O interactions. The C—H…O interactions forms centrosymmetric head-to-head and head-to-tail dimers with graph set motif $R_2^2(12)$ and $R_2^2(18)$, respectively, along *c* axis. In addition, π-ring interactions of the type C—H…$C_{g2}$ ($C_{g2}$ being the centroid of the ring C12/C13/C14/C15/S2) are also observed in the crystal structure; details are given the Table 2.

## CONCLUSIONS

Present work describes the synthesis of diester of thiazolopyrimidine derivatives which is a one step cyclocondensation reaction. The structural modifications in the pyrimidine moiety lead to improved biological properties. Crystals of the two compounds **2a** and **2b** were subjected to X-ray diffraction in order to get the blueprint of the molecules as well as the molecular structures. Additionally, the single crystal X-ray diffraction analysis revealed certain interesting features such as the aryl substitution at the C5 chiral carbon atom resulting in two different configurations. The crystal structures of both compounds are stabilized by C—H…O interactions resulting in formation of centrosymmetric dimers. Apart from this other weak interaction such as C—H…π further stabilize the crystal structure.

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