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Synthesis and electronic aspects of tetrahydrobenzothienopyrimidine derivatives

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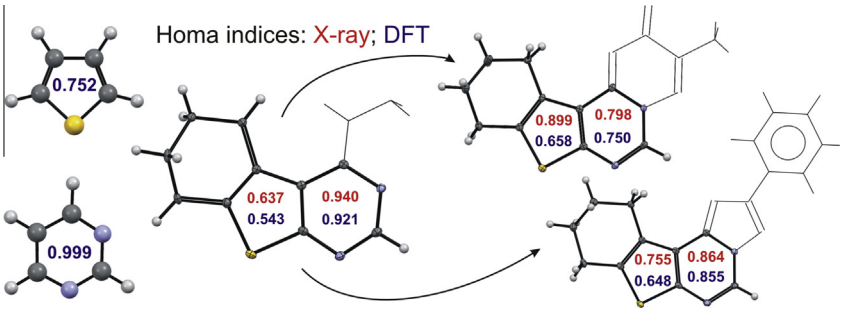
HIGHLIGHTS

- Compound (I) can react in different centres so is a promising substrate for new drugs.
- The geometry of common core in all structures is typical for this class of compounds.
- Side groups show different ability to influence the aromaticity of the core.
- When the rings are fused in the larger heterocyclic systems aromaticity is disturbed.
- The T-complex in (I) between thiophene rings influence its aromaticity.

GRAPHICAL ABSTRACT



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ABSTRACT

The chemistry of thiophenes, pyrimidines, triazolopyrimidines and benzothiophenes has drawn much attention because of their biological activities. Their interesting properties are connected with their complex π-electron delocalisation effects. Herein the synthesis, crystal and molecular structures at 100 K and DFT calculated structures of three tetrahydrobenzothienopyrimidine derivatives are reported i.e. 4-hydrazino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine which was a substrate for 2-phenyl-8,9,10,11-tetrahydro[1]benzothieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine and 3-methyl-9,10,11,12-tetrahydro-2*H*-[1]benzothieno[2′,3′:4,5]pyrimido[1,6-*b*][1,2,4]triazin-2-one. Moreover the influence of the substituents, polycyclic structure and crystal packing and on the aromaticity of the fused heterocyclic rings have been also discussed. The 4-hydrazino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine is a promising substrate for a number of different reactions and discovering novel biologically active heterocycles. All three molecules are planar except of the tetrahydrobenzene part, which shows normal conformation. In crystals the molecules are connected to each other by C–H···N, N–H···N, C–H···S and S···π contacts. The geometry of common core in all structures is similar and typical for this class of compounds. The aromaticity of the fused heteroaromatic systems has been investigated by means of the HOMA indices. The discrepancy between values of HOMA for isolated monocyclic compounds and studied molecules from crystal structure shows destabilization of aromaticity when the rings are fused in a larger heterocyclic systems. The thiophene part of the molecule is far more sensitive on the influence of both mesomeric effects in polycyclic system and molecular environment in solid-state than pyrimidine ring. The presence of intermolecular interactions was confirmed by Hirshfeld area analysis.

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Introduction

Fused pyrimidines along with heterocyclic compounds play an important role in designing new classes of structural entities of medical importance with potentially new mechanisms of action and their great practical usefulness, primarily, due to a very wide spectrum of their biological activities [1]. The organic molecules are of great importance due to possible promising biological applications [2–8]. Purines, pteridines, quinazolines, pyridopyrimidines, triazolopyrimidines, pyrazolopyrimidines, pyrimidoazepines, furopyrimidines and pyrrolopyrimidines are the most important pyrimidine derivatives [9–18]. Thienopyrimidines occupy a special position among them [19,20]. Compounds containing fused pyrimidine ring make up a broad class of heterocycles that has attracted attention in the past few years owing to its medical activities such as anticancer [21], antiviral [22,23], antitumor [24], anti-inflammatory and analgesic [25–28], antiallergic [29], antibacterial [30,31], antihypertensive [32], antidepressant [33] and antidiabetic [34]. The appearance of qualitatively new properties of an annelated molecule, enlargement of the possibility of varying pharmacophore groups in different positions of the molecule, and the ability of the latter to interact with a wider spectrum of receptors adopting various conformations are apparently of crucial importance. In addition, the structure of the molecule can be varied due to annelation at different positions of individual heterocyclic fragments. Along with some other pyrimidine systems containing an annelated five-membered heteroaromatic ring, thienopyrimidines are structural analogues of biogenic purines and can be considered as potential nucleic acid antimetabolites.

The rapid growth in the literature dealing with the synthesis and biological activity of the thienopyrimidine derivatives [35] prompted us to undertake the synthesis of novel fused thienopyridine derivatives with common 5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine core, i.e. 4-hydrazino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (I) which was a substrate for 2-phenyl-8,9,10,11-tetrahydro[1]benzothieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (II) and3-methyl-9,10,11,12-tetrahydro-2*H*-[1]benzothieno[2′,3′:4,5]pyrimido[1,6-*b*][1,2,4]triazin-2-one (III). As the crystal and molecular structure of (II) have been determined previously at room temperature [36], to obtain comparable geometry parameters for all studied structures, herein we have redone the X-ray experiment at 100 K.

Experimental

Synthesis and crystallization

(I) Ethylpyruvate (4.23 ml, 0.0386 mol) and 4-hydrazino-5,6,7,8-tetrahydro(1)benzothieno(2,3-*d*)pyrimidine (8.5 g, 0.0386 mol) in acetic acid (10 ml) were heated under reflux for 4 h. The crystalline product formed after cooling was filtered, washed with water and dried. The product (m.p. 235–237 °C) was recrystallized from propanol-2 and the single crystal used for analysis was obtained from acetonitrile by slow evaporation.

^{1}H NMR (200 MHz, DMSO): δ 1.81 (br. s, 4 H), 2.85 (br. s, 2 H), 3.03 (br. s, 2 H), 2.48 (s, 3 H, CH_3), 8.92 (s, 1 H).

(II) To the solution of 4-hydrazino-5,6,7,8-tetrahydro(1)benzothieno(2,3-*d*)pyrimidine (0.5 g, 2.27 mmol) in dry acetonitrile (15 ml) triethylamine (0.29 ml, 2.27 mmol) and benzoyl chloride (0.26 ml, 2.27 mmol) was added. The mixture was heated under reflux for 1 h and evaporated under vacuum. The residue was washed with water, dried and crystallized from acetonitrile. The solution of *N*′-(5,6,7,8-tetrahydro(1)benzothieno(2,3-*d*)pyrimidin-4-yl)benzohydrazide (m.p. 160–162 °C) (0.5 g, 1.54 mmol) obtained in acetic acid (10 ml) was heated under reflux for 4 h then poured into water. The separated solid was filtered and dried. The product (m.p. 196–198 °C) was recrystallized from propanol-2 and the single crystal used for analysis was obtained from ethanol by slow evaporation.

^{1}H NMR (200 MHz, DMSO): δ 1.88 (br. s, 4 H), 2.86 (br. s, 2 H), 3.07 (br. s, 2 H), 1.53 (t, 3 H, Ph), 8.20 (m, 2 H, Ph), 9.56 (s, 1 H).

(III) The mixture of 5,6,7,8-tetrahydro(1)benzothieno(2,3-d)pyrimidin-4(3H)-one (2.4 g, 0.0116 mol), dimethylaniline (7 ml) in $POC1_3$ (30 ml) was refluxed for 4.5 h. Excess of $POCl_3$ and dimethylaniline was evaporated under reduced pressure. The residue was poured on ice cautiously and neutralized with sodium carbonate solution. A precipitate formed was filtered, washed with water and crystallized from ethanol (96%), m.p. 99–l00 °C). Then the solution of 4-chloro-5,6,7,8-tetrahydro(1)benzothieno(2,3-d)pyrimidine (2 g, 0.0089 mol) obtained and hydrazine hydrate (98%, 1.33 ml) in ethanol (20 ml) was heated under reflux for 2 h. The crystalline product formed after cooling was filtered and dried. The product (m.p. 184–186 °C) was recrystallized from ethanol and the single crystal used for analysis was obtained from acetonitrile by slow evaporation.

^{1}H NMR (200 MHz, DMSO): δ 1.75 (br. s, 4 H), 2.72 (br. s, 2 H), 2.89 (br. s, 2 H), 4.55 (s, 2 H, $NHNH_2$), 7.86 (s, 1 H, $NHNH_2$), 8.30 (s, 1 H).

XRD data collection and refinement

The (I), (II) and (III) single-crystal X-ray diffraction experiment were performed at 100.0(1) K on the Xcalibur diffractometer, equipped with a CCD area detector and a graphite monochromator for the Mo Kα radiation, with an Oxford Cryosystem N_2 gas stream device. The reciprocal space was explored by ω-scans. The reflections were measured with a radiation exposure time from 4 to 20 s, according to diffraction intensities. The detector was positioned at 60 mm distance from the crystal. The diffraction data of studied compounds was performed using the CrysAlis CCD [37]. Further details on the crystal data collection, processing and experimental conditions are given in Table 1. The structure of (I), (II) and (III) was solved by direct methods and refined by a full-matrix least-squares method using SHELXL14 program [38]. Lorentz and polarization corrections were applied. All hydrogen atoms were located from difference Fourier synthesis. Non-hydrogen atoms were refined anisotropically. In structures, H atoms refined using a riding model. The structure drawings were prepared using SHELXTL, SHELXS14 and SHELXL14 programs [30]. The packing drawings were prepared using Mercury 3.1.1 [39]. Supplementary crystallographic data can be found in the CCDC deposit CCDC 995332 for (I), CCDC 995342 and (II) and CCDC 995360 for (III). Data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif/.

Theoretical calculations

Based on the solid-state geometry, the molecular structures of (I), (II) and (III) were optimized using the B3LYP hybrid functional [40–42] with the 6-311++G(d,p) level of theory. All species correspond to the minima at the B3LYP/6-311++G(d,p) level with no imaginary frequencies. All calculations were performed using the GAUSSIAN09 program package [43].

Results and discussion

Synthesis

The synthesis of 1,2,4-triazolothieno[2,3-d]pyrimidine system has been reported in a number of publications [44–46].

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