Synthesis of new derivate of 5-mercapto-3-phenyl-1,3,4-thiadiazol-2-thione, crystal structure, Hirshfeld surface analysis and estimation of its biological activity on PASS.

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The most important direction in the obtaining of new pharmaceuticals is synthesis of highly effective and low-toxic drugs. The researching and searching of new drugs with different biological activity implies the identification of new compounds with high efficacy and improved tolerability. Despite of the high selectivity pharmaceuticals and minimized their negative effects, it is very actually to create new pharmacological preparations.

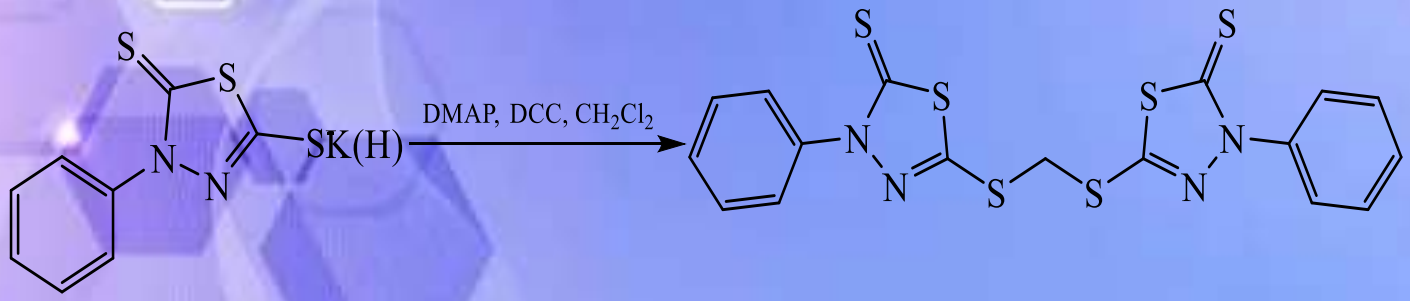
Heterocyclic compounds of 1,3,4-thiadiazole are the important class of substances with a wide spectrum of biological activity. The sulfur atom of thiadiazole gives these compounds lipophilic properties, which allow to better penetrate through biological membranes. Thiadiazole fragments have potential activity with G-receptors, through enzyme binding, at the active final cysteine (for example, bacterial enzymes are part of non-steroidal anti-inflammatory drugs.

Thiadiazole derivatives are versatile and promising compounds with wide spectrum of biological activity. The thiadiazole moiety acts as a hydrogen-binding dominant on the one hand and an electron donor on the other.
Derivatives of 1,3,4-thiadiazoles are characterized of variety pharmacological properties, such as fungicidal, insecticidal, bactericidal, herbicidal, antitumor, anti-inflammatory, CNS stimulating properties.

Synthesis of 5-mercapto-3-phenyl-1,3,4-thiadiazol-2-thione derivative.

For the synthesis of new heterocyclic derivativeswith a wide spectrum of biological activity, we study the formation of various derivatives based on 5-mercapto-3-phenyl-1,3,4-thiadiazol-2-thione. The experiment was carried out according to the general procedure.

Reaction scheme:



We supposed that, excess of methylene chloride as solvent for the reaction, and the other hand - promotes the binding of the potassium cation to the chloride ion. And the presence of a mixture of all of reagents, were promoted the formation of a methylene bridge in the structure of the resulting compound.

Investigation with PASS software

We studied the biological activity spectrum of obtained substance by PASS software. That screening let to describe biological activity properties of substance in a depending of its structure.

Such predictable analyses help to provide maximum information of biological activity of new structure substances whose molecular mechanism action is still unknown.

The structure of 5,5'-(methylenebis(sulfanediyl))bis(3-phenyl-1,3,4-thiadiazole-2(3H)-thione) was input in PASS software and predicted their biological activities.

Results of biological activities along with Pa and Pi predicted by PASS and described in the table:

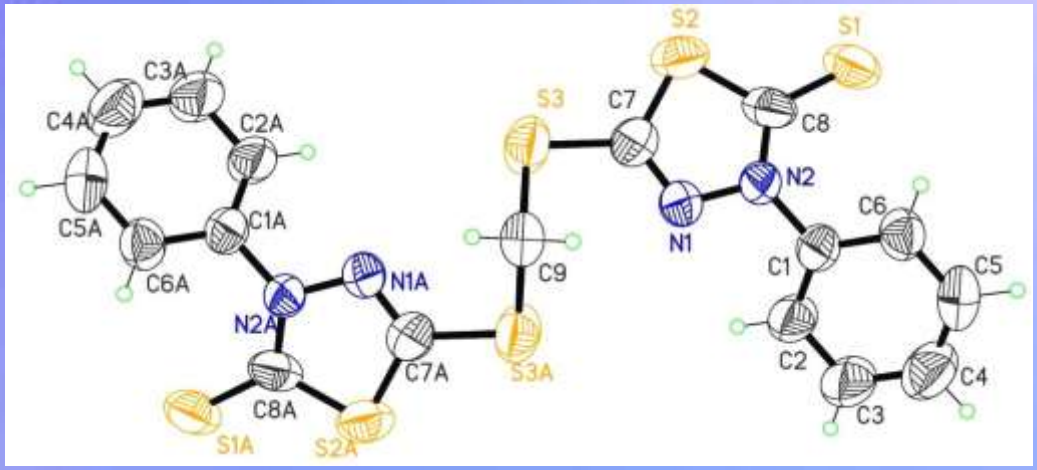
Pa	Pi	Activity
0,697	0,004	Amyloid beta precursor protein antagonist
0,699	0,023	5-O-(4-coumaroyl)-D-quinate 3'-monooxygenase inhibitor
0,588	0,068	Glycosylphosphatidylinositol phospholipase D inhibitor
0,509	0,003	Cyclin-dependent kinase 5 inhibitor
0,509	0,011	Taurine-2-oxoglutarate transaminase inhibitor
0,513	0,020	FMO1 substrate
0,518	0,030	CYP2A8 substrate
0,526	0,044	Chloride peroxidase inhibitor
0,488	0,008	Mcl-1 antagonist
0,536	0,057	Complement factor D inhibitor
0,453	0,004	Dual specificity phosphatase inhibitor
0,499	0,058	Thioredoxin inhibitor
0,437	0,003	Dual specificity phosphatase 1 inhibitor
0,548	0,117	Aspulvinone dimethylallyltransferase inhibitor

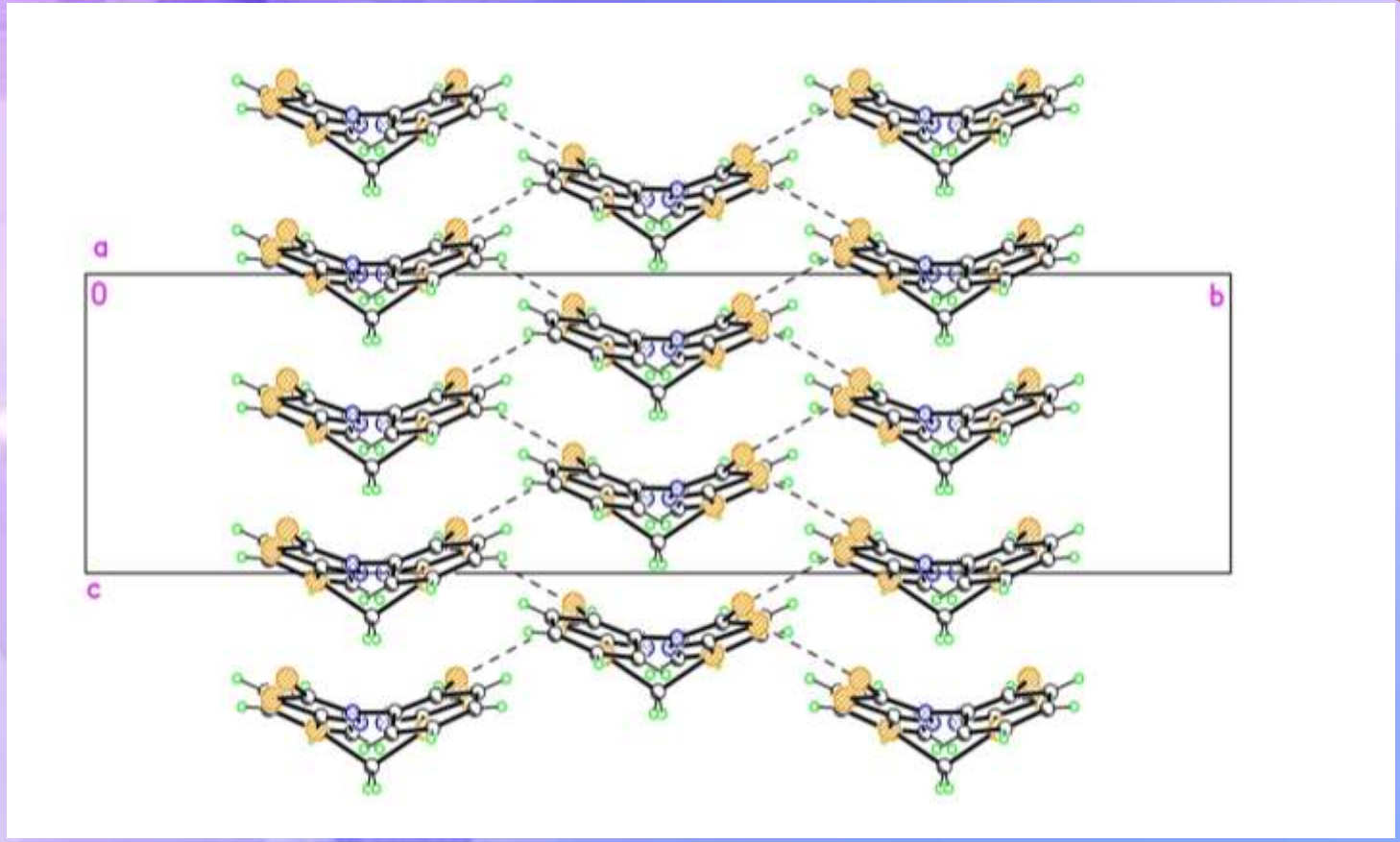
From PASS software we chose results with Pa > 0.5 activity, and predicted, that 5,5'-(methylenebis(sulfanediyl))bis(3-phenyl-1,3,4-thiadiazole-2(3H)-thione) was very likely to exhibit the activity in experiment with Pa = 0,7.

Molecular structure

5,5'-(methylenebis(sulfanediyl))bis(3-phenyl-1,3,4-thiadiazole-2(3H)-thione) crystallized in the non-centrosymmetric orthorhombic space group Fdd2 with half-molecule in the asymmetric unit; a twofold rotation axis, which passes through the C9 atom, generates the other half of the molecule.

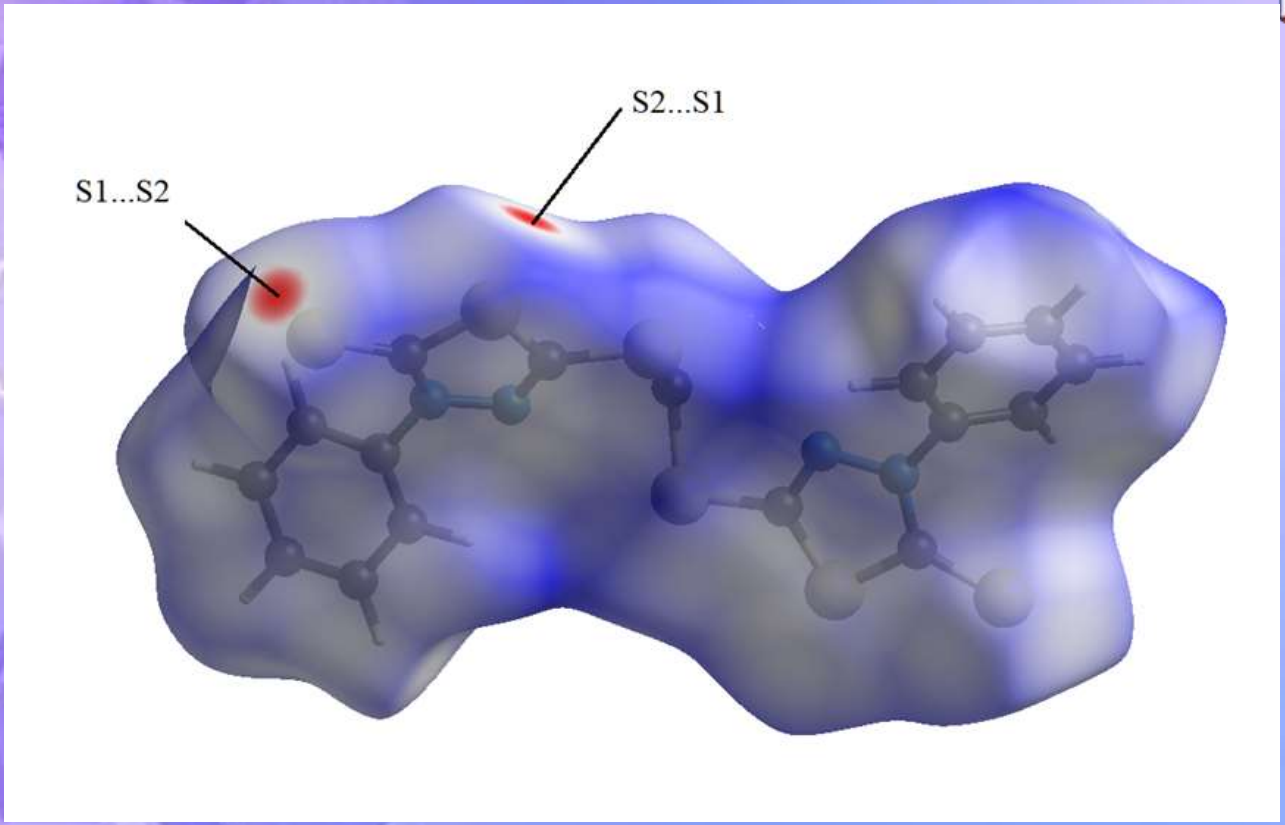
The 1,3,4-thiadiazole-2-thione unit is planar, with an r.m.s. deviation of 0.019 Å from the corresponding squares plane defined by the seven constituent atoms. Benzene and thiadiazole rings are not coplanar (corresponding C2-C1-N2-N1 torsion angles are 32.4 (12)°).





Crystal structure

The crystal packing is stabilized by intra- and intermolecular H-bonds, close intermolecular S…S contacts in the range of 3.416Å and by Van-der-Waals interactions. Molecule are combined into tree-dimensional construction.



Hirshfeld surface analysis

The Hirshfeld surface analysis indicates that the most important contributions to the crystal packing are from H…H (26.3%) and S…H/H…S (23.3%) – weak H-bonds and van-der-Waals interactions. S…S (13.1%), S…C/C…S (11%), C…C (9.9%) and C…H/H…C (5.5%) interactions contribute less and S…N/N…S (1.9%) and N…N (0.4%) interactions contribute minor significance to the overall HS.

Conclusion.

- In the result of our experiment were obtained new 1,3,4-thiadiazole derivative - 5,5'-(methylenebis(sulfanediyl))bis(3-phenyl-1,3,4-thiadiazole-2(3H)-thione). The presence of a mixture of all of reagents, were promoted the formation of a methylene bridge in the structure of the resulting compound.
- The crystal structure of (methylenebis(sulfanediyl))bis(3-phenyl-1,3,4-thiadiazole-2(3H)-thione) has been determined by X-ray diffraction and intermolecular interactions have been analyzed by HS.
- The biological activity spectrum of 5,5'-(methylenebis(sulfanediyl))bis(3-phenyl-1,3,4-thiadiazole-2(3H)-thione) were studied by PASS online software, and obtained data let to describe biological activity properties in a depending of its structure.
- On the base of structural features of the obtained compound, we suppose that on the molecular level, the 1,3,4-thiazole moieties of new derivative, will interact with protein's cysteine residues. Additionally, the presence of a disulfide bridge separated by a methylene fragment will facilitate easy penetration through the cell membrane, leading to subsequent exhibiting activity.
- Confirmation of the potential properties of the new compound and researching the interconnection between the structure of 1,3,4-thiadiazole derivative and its biological activity, as well as explanations of its action mechanism on the molecular level, are ongoing.