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Proceeding Paper

Synthesis and Structural Investigation of New Derivate of 5-Mercapto-3-Phenyl-1,3,4-Thiadiazol-2-Thione †

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Abstract: Heterocyclic compounds of 1,3,4-thiadiazole are the important class of substances with a wide spectrum of biological activity. The synthesis of new derivate 5-mercapto-3-phenyl-1,3,4-thiadiazol-2-thione have been made in the presence of excess methylene chloride and mixture of catalysts. The crystal structure of new derivate of 5-mercapto-3-phenyl-1,3,4-thiadiazol-2-thione has been determined by X-ray analysis and intermolecular interactions were studied using Hirschfeld surface analysis. The biological activity spectrum of new compound have been studied by PASS software.

Keywords: 5-mercapto-3-phenyl-1,3,4-thiadiazol-2-thione; 5,5′-(methylenedi(sulfanediyl))bis(3-phenyl-1,3,4-thiadiazole-2(3H)-thione); synthesis, X-ray analysis; biological activity spectrum; PASS software

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1. Introduction

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. It is very actually to create new pharmacological active compounds with high selectivity pharmaceuticals and minimized their negative effects.

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. According to the mechanisms of biochemical reactions involving the thiadiazole fragments, potentially should connected with G-receptors, through enzyme binding, at the active final cysteine [1].

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 [2], such as fungicidal, insecticidal, bactericidal, herbicidal, antitumor, anti-inflammatory, CNS stimulating properties.

On the other hand, big interest for scientists were cause sulfur-containing compounds which characterized by a wide range of antibacterial properties and many other types of biological activity with less harm to the organism [3].

Heterocyclic derivatives of 1,3,4-thiadiazoles can be involved in certain biochemical processes of organism, therefore it is important and timely to identify the action mechanism of heterocycles as electrophilic "target sites" [4].

The purpose of this study was synthesis a new 1,3,4-thiadiazole derivative—5,5′-(methylenebis(sulfanediyl))bis(3-phenyl-1,3,4-thiadiazole-2(3H)-thione) and estimation

the structural features of the synthesized compound, as well as analysis of its potential biological activity.

2. Methods

Chemicals and solvents were purified by standard techniques by distillation or recrystallization. For thin-layer chromatography (TLC), silica gel plates Silufol, eluents (ethyl acetate:hexane/1:5), compound were visualized by irradiation with iodine vapor.

Data for the crystal structure determinations were collected on an 'XtaLAB Synergy, HyPix3000' CCD diffractometer (CuKa-radiation, λ = 1.54184 A, ω-scan mode, graphite monochromator (at 293 K) [5]. The structure was solved and refined using program packages SHELXS-97 and SHELXL-2018 [6]. The molecular drawings were plotted by MERCURY program package [7].

Crystallographic data have been deposited with Cambridge Crystallographic Data Centre (Deposite Number 2255753). The data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

Biological activity spectrum have been obtained by PASS on line software.

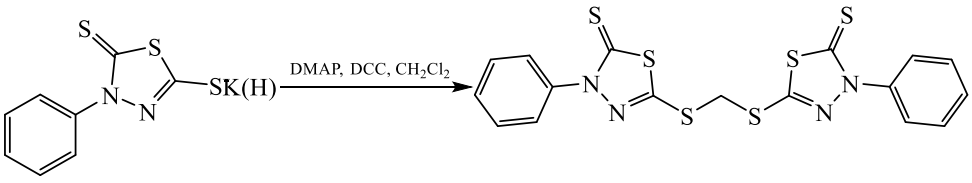
Synthesis and Crystallization

5-Mercapto-3-phenyl-1,3,4-thiadiazol-2-thione 0,95 mmol was treated with a mixture of catalysts (0.95 mmol—DCC (dicyclohexylcarbodiimide) and 0.95 mmol—DMAP (4-dimethylaminopyridine) in methylene chloride. The mixture was boiled with stirring for 8 h. The first 4 h, the reaction was carried out under an inert gas–nitrogen. And at the end, the reaction solution was diluted with 10 mL of methylene chloride, after, the solution of 30% acetic acid was added, till about the pH = 5–6. The organic layer was separated. The organic extracts were washed with saturated NaCl solution. Dried under Na_2SO_4. The solvent was removed under reduced pressure. Yield of crude product: 85%.The residue was recrystallized. A good quality single crystal was obtained by slow evaporation of a solution of the compound in methylene chloride.

3. Results and Discussion

3.1. Synthesis of 5-Mercapto-3-Phenyl-1,3,4-Thiadiazol-2-Thione Derivative

For the synthesis of new heterocyclic derivatives with 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 in the presence of excess methylene chloride and mixture of DMAP and DCC catalysts according to the general procedure [9].



Scheme 1.

The 5,5'-(methylenebis(sulfanediyl))bis(3-phenyl-1,3,4-thiadiazole-2(3H)-thione) was obtained from the 5-mercapto-3-phenyl-1,3,4-thiadiazol-2-thione potassium salt under the treatment of excess methylene chloride in the presence of mixture of DMAP and DCC. 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.

3.2. X-Ray Structure Analysis and Refinement

Data for the crystal structure determinations were collected on an 'XtaLAB Synergy, HyPix3000' CCD diffractometer (CuKa-radiation, λ = 1.54184 A, ω-scan mode, graphite monochromator (at 293 K) [5]. The structure was solved and refined using program packages SHELXS-97 and SHELXL-2018 [6]. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were inserted at calculated positions and constrained with isotropic thermal parameters.

The molecular drawings were plotted by MERCURY program package [8].

The crystallographic data and details of the structure refinement are given in Table 1. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre (Deposite Number 2255753). The data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/ retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

Crystal data: $C_{17}H_{12}N_4S_6$, orthorhombic, Fdd2 (No.43): a = 16.457(2), b = 32.008(5), c = 7.6778(12) Å, V = 4044.3(10) Å^3, Z = 8, M = 464.67, d_{calc} = 1.526 g/cm^3, 2519 reflections were collected at 273 K, 1387 independent reflections [R_{int} = 0.064] were used in the refinement procedure that was converged to wR2 = 0.2592 calculated on F2hkl (GOF = 1.056, R1 = 0.0907 calculated on F_{hkl} using 1152 reflections with I > 2σ(I)). Flack x = −0.01(11).

3.3. Description of Molecular Crystal 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 (Figure 1). 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)°).

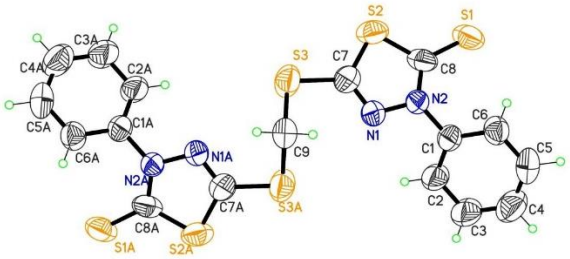


Figure 1. Structure of molecule 5,5′-(methylenebis(sulfanediyl))bis(3-phenyl-1,3,4-thiadiazole-2(3H)-thione) with numbering of the nonhydrogen atoms and the thermal ellipsoids drawn at 50% probability.

The crystal packing is stabilized by intramolecular H-bond C6-H6A …S1 (2.86, 3.241(14) Å, 106.00°), close intermolecular S…S contacts in the range of 3.416 Å and by Van-der-Waals interactions. Molecules are combined into tree-dimensional construction (Figure 2).

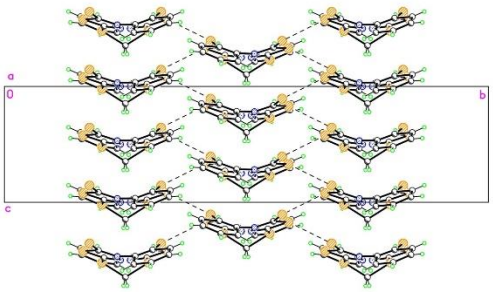


Figure 2. Crystal structure of 5,5′-(methylenebis(sulfanediyl))bis(3-phenyl-1,3,4-thiadiazole-2(3H)-thione). Dots show close intermolecular S…S contacts.

3.4. Hirshfeld Surface Analysis

Additional insight into the intermolecular interactions was obtained from analysis of the Hirshfeld surface (HS) [10] and the two-dimensional fingerprint plots [11].

The program CrystalExplorer [12] was used to generate Hirshfeld surfaces mapped over d_{norm} and the electrostatic potential for the title compound**.** The function d_{norm} is a ratio enclosing the distances of any surface point to the nearest interior (d_i) and exterior (d_e) atom and the van der Waals (vdW) radii of the atoms. Figure 3 shows the Hirshfeld surfaces mapped over d_{norm} in the range −0.2247 (red) to 1.3787 (blue) a.u.

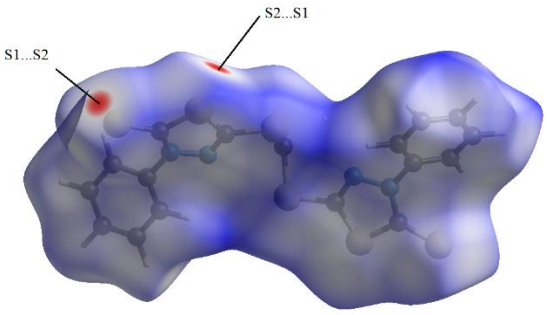


Figure 3. A view of the Hirshfeld surface of 5,5′-(methylenebis(sulfanediyl))bis(3-phenyl-1,3,4-thiadiazole-2(3H)-thione) mapped over d_{norm}.

The overall two-dimensional fingerprint plot, Figure 4 and those delineated into H…H, S…H/H…S, S…S, S…C/C…S, C…C, C…H/H…C, N…S/S…N, N…N contacts are illustrated together with their relative contributions to the Hirshfeld surface.

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.

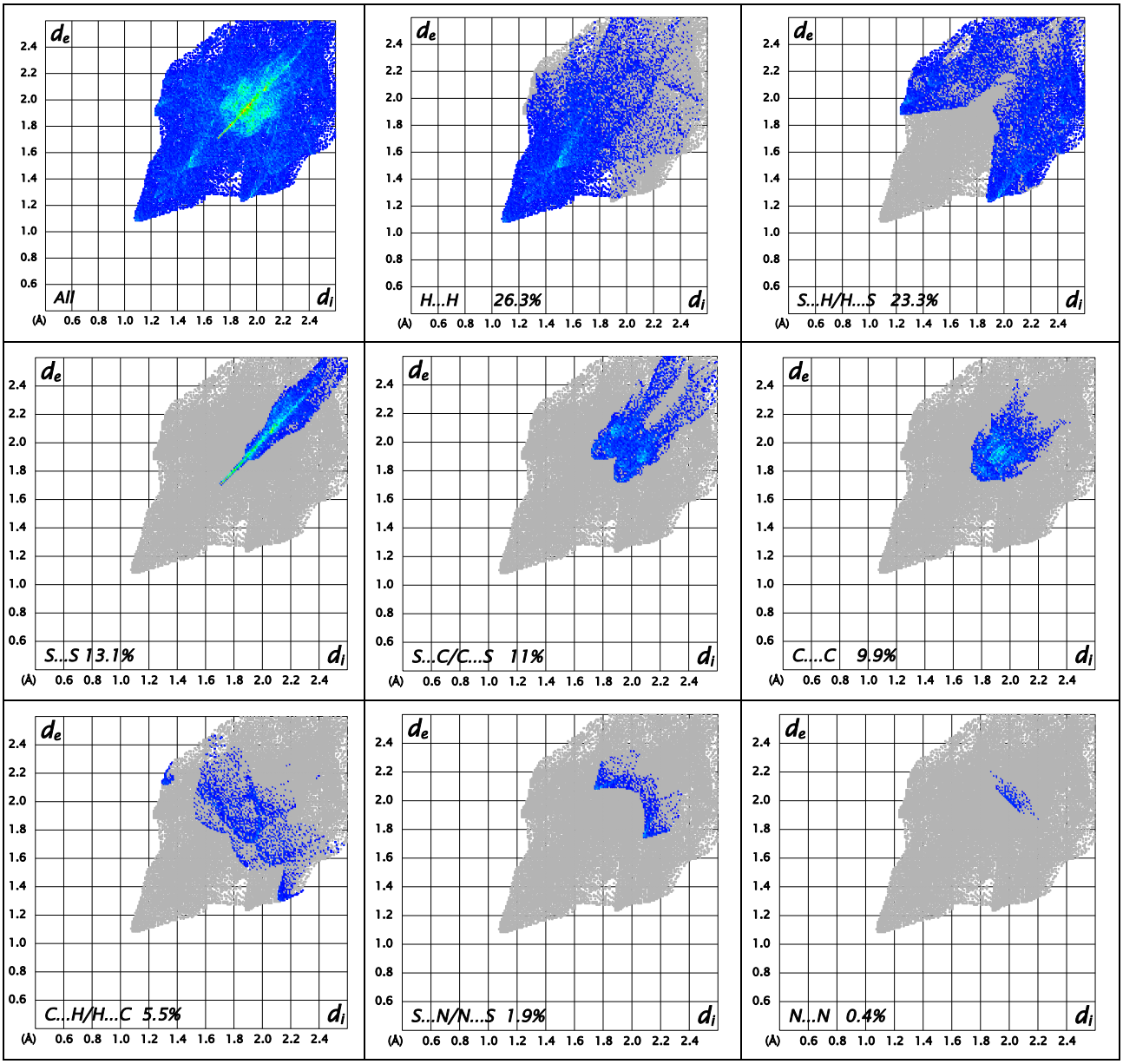


Figure 4. Full two-dimensional fingerprint plots for the title compound.

3.5. Investigation with PASS Software

We studied the biological activity spectrum of obtained substance by PASS software [13].

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. The Pa characterizes probability to be active and Pi—be inactive. The Pa and Pi values vary from 0,000 to 1,000.

Results of biological activities along with Pa and Pi predicted by PASS and presented in the Table 1.

Table 2. From PASS software we chose results with the most significant values of 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.

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

4. Conclusions

In the field of medical chemistry, the obtaining and researching of new pharmaceuticals is a actual task. The researching and synthesis of new drugs with different biological activity supposes the investigation of new compounds with high efficacy and improved tolerability. One of the promising groups for such substances are 1,3,4-thiadiazole derivatives.

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.

Author Contributions: Conceptualization, O.K.X. and B.N.B.; methodology, B.T.I.; synthesis G.S.S. and O.K.X.; X-ray analysis L.Y.I.; G.S.S. and L.Y.I. writing, supervision B.N.B. All authors have read and agreed to the published version of the manuscript.

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References

1. Song, Y.; Connor, D.T.; Doubleday, R.R.; Sorenson, J.; Sercel, A.D.; Unangst, P.C.; Roth, B.D.; Gilbertsen, R.B.; Chan, K.; Schrier, D.J.; et al. Synthesis, structure-activity relationships, and in vivo evaluations of substituted di-tert-butylphenols as a novel class of potent, selective, and orally active cyclooxygenase-2 inhibitors. 2. 1,3,4- and 1,2,4-thiadiazole series. *J. Med. Chem.* **1999**, *42*, 1161–1169. https://doi.org/10.1021/jm9805081.
2. Dahmani, R.; Grubišić, S.; Yaghlane, S.B.; Boughdiri, S.; Hochlaf, M. New bis-aminomercaptotriazoles and bis-triazolothiadiazoles as possible anticancer agents. *Eur. J. Med. Chem.* **2002**, *37*, 511–517. https://doi.org/10.1016/s0223-5234(02)01358-2.
3. Kulikov, M.A.; Vorobyov, Y.G.; Berezina, G.R.; Stepanenko, V.A. Macroheterocyclic compounds with fragments of 2,3-pyridino(pyrazino)pyrrole and 1,3,4-thiadiazole. *J. Gen. Chem.* **2004**, *74*, 1031–1034.
4. Sharma, B.; Verma, A.; Prajapati, S.; Sharma, U.K. Synthetic Methods, Chemistry, and the Anticonvulsant Activity of Thiadiazoles. *Int. J. Med. Chem.* **2013**, *2013*, 348948. https://doi.org/10.1155/2013/348948.
5. Rigaku, O.D. *CrysAlis PRO*; Rigaku Corporation: Wroclaw, Poland, 2020.
6. Sheldrick, G.M. *Acta Cryst.* **2018**, *A71*, 3–8. https://doi.org/10.1107/S2053229614024218.
7. Macrae, C.F.; Bruno, I.J.; Chisholm, J.A.; Edington, P.R.; McCabe, P.; Pidcock, E.; Rodriguez-Monge, L.R.; Taylor, J.; van de Streek, J.; Wood, P.A. Mercury programme. *J. Appl. Crystallogr.* **2008**, *41*, 466–470. https://doi.org/10.1107/S0021889807067908.
8. Sheikh, M.C.; Takagi, S.; Yoshimura, T.; Morita, H. Mechanistic studies of DCC/HOBt-mediated reaction of 3-phenylpropionic acid with benzyl alcohol and studies on the reactivities of 'active ester' and the related derivatives with nucleophiles. *Tetrahedron* **2010**, *66*, 7272–7278. https://doi.org/10.1016/j.tet.2010.07.011.
9. Spackman, M.A.; Jayatilaka, D. Hirshfeld surface analysis, *CrystEngComm*. **2009**, *11*, 19–32. https://doi.org/10.1039/B818330A.
10. McKinnon, J.J.; Jayatilaka, D.; Spackman, M.A. Towards quantitative analysis of intermolecular interactions with Hirshfeld surfaces, *Chem. Commun.* **2007**, *37*, 3814–3816. https://doi.org/10.1039/B704980C.
11. Turner, M.J.; MacKinnon, J.J.; Wolff, S.K.; Grimwood, D.J.; Spackman, P.R.; Jayatilaka, D.; Spackman, M.A. *CrystalExplorer17.5*; University of Western Australia: Perth, Australia, 2017.
12. Tidke, K.J.; Solanki, P.R. Microwave assisted synthesis of (substitutedbenzilidene)-4-amino dihydrothiophen-3(2H)-one (IA-IH) and their biological activities on PASS. *JETIR* **2020**, *7*, 1185–1196.