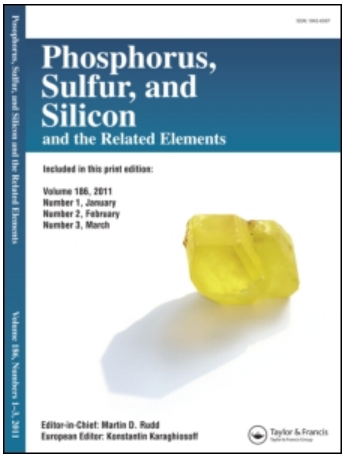

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis and Tuberculostatic Activity of 2-(4,5-Disubstituted-[1,2,4] triazol-3-ylsulphanyl)-*N*-phenyl-acetamides

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Synthesis and Tuberculostatic Activity of 2-(4,5-Disubstituted-[1,2,4] triazol-3-ylsulphanyl)-*N*-phenyl-acetamides

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The activity of the SH group of the new 4,5-disubstituted 1,2,4-triazol-3-thiole derivatives obtained earlier[1] was used in the reactions with 2-chloro-N-phenyl-acetamides. The structures of the products obtained were determined by means of ^1H NMR spectroscopy and X-ray diffraction. Tuberculostatic activity of the starting triazolothioles and of their S-substituted derivatives was tested in vitro, and the minimum growth inhibiting concentration values obtained were within 12.5–100 $\mu g/mL$.

Keywords 1,2,4-Triazole-3-thiones; 1,2,4-triazole-3-thioles; 1,2,4-triazole-3-ylsulphanyl-*N*-phenyl-acetamides; X-ray structure; tuberculostatic activity

INTRODUCTION

The manifold biological activity of [1,2,4]-triazolo-3-thioles was emphasized in many relevant reports. This activity can be influenced by introducing specific substituents into the 4- and 5- positions of the

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[1,2,4]-triazolo-3-thiole ring. The antibacterial, including tuberculostatic, activity of these compounds was repeatedly reported.[2–4] The influence of similar derivatives on the circulatory system was tested as well,[5–8] and a positive effect of a pyridyl substituent in the 5 position of the triazole ring was found. The diuretic action[9] of such compounds, as well as some blood pressure reduction activity, particularly in the case of substitution products at the SH group from reactions with halogenoesters and halogenoalkanes[8,10–12] were also reported.

Strong antiphlogistic activity of 4,5-diaryl-1,2,4-triazolo-3-thiole *S*-methyl derivatives and their lower toxicity[13,14] compared with that of acetylsalicylic acid and 2-[4-(2-methylpropyl)phenyl]propanoic acid (ibuprofen) were observed as well. The investigation of the activity of *S*-substituted derivatives toward hepatitis B virus also gave positive results.[15]

RESULTS AND DISCUSSION

The syntheses of 4,5-disubstituted 1,2,4-triazolo-3-thioles from aryldithiocarbazoic acid methyl esters and the corresponding β-substituted ethyl amines were reported earlier.[1] The syntheses of their *S*-substituted derivatives are described in this article (Table I).

The reactions with *N*-substituted chloroacetic acid amides were conducted in a methanolic solution of KOH by stirring equimolar amounts of the starting materials for 8 days or refluxing for a few hours. The course of the reaction was controlled by means of thin layer chromatography. The derivatives **1d–n** and **2g–i** were obtained by this procedure.

Due to the low yields of the products under the conditions previously described, the syntheses of the other derivatives were accomplished in an alcoholic sodium ethanolate solution.

The structures of new products resulted from their elemental analysis and ^{1}H NMR spectra. In addition, the structures of products **6n** and **6t** were unequivocally confirmed by single crystal X-ray diffraction.

CRYSTAL STRUCTURES

Due to chemical similarity of the two molecules (**6n** and **6t**) studied by X-ray diffraction, their conformations (Figure 1), packing, and hydrogen bonding network (Table II) are similar in the solid state. Resulting is the same space group, similar unit cells (Table III), and coordinates of corresponding atoms in the two structures. The differences in bond lengths and angles in the molecules **6n** and **6t** are within the sum of their standard deviations and agree well with the average bond lengths and angles found in compounds with similar fragments.[19] There are

TABLE I Characteristics of the New Synthesized 1,2,4-Triazole-3-Thioles Derivatives

	R	R^1	R^2	Formula Molecular weight	M.P. (°C) Solvent for Crystallization	Reaction Yield (%)	^{1}H NMR δ (ppm) 80 MHz–**A**, 200 MHz–**B** Solvent: (**C**–$CDCl_3$, **D**–d_6-DMSO, **E**–CD_3OD)
1d	C_6H_5	$CH_2OC_2H_5$	H	$C_{21}H_{24}N_4O_2S$ 396.51	63–66 Methanol	41	**A**, **C**: 1.08 (t,J = 7.0 Hz, 3H, CH_3); 1.92 (m, 2H, CH_2); 3.22 (m, 4H, CH_2OCH_2); 4.07 (m, 4H, SCH_2+ NCH_2); 7.12–7.65 (m, 10H, Ar); 10.51 (s, 1H, CONH)
1e	C_6H_5	$CH_2OC_2H_5$	2-CH_3	$C_{22}H_{26}N_4O_2S$ 410.53	80–82 Benzene + Petr.	68	**B**, **C**: 1.08 (t, J = 7.0 Hz, 3H, CH_3); 1.93 (m, 2H, CH_2); 2.35 (s, 3H, CH_3); 3.27 (m, 4H, CH_2OCH_2); 4.08 (m, 4H, SCH_2+ NCH_2); 7.04–7.65 (m, 8H, Ar); 8.00 (d, J = 8.0 Hz, 1H, Ar); 9.98 (s, 1H, CONH)
1f	C_6H_5	$CH_2OC_2H_5$	4-CH_3	$C_{22}H_{26}N_4O_2S$ 410.53	116–119 Methanol + H_2O	65	**B**, **E**: 1.01 (t, J = 7.0 Hz, 3H, CH_3); 1.89 (m, 2H, CH_2); 2.28 (s 3H, CH_3); 3.25 (m, 4H, CH_2OCH_2); 4.08 (s, 2H, SCH_2); 4.24 (t, J = 6.0 Hz, 2H, NCH_2); 7.09–7.64 (m, 9H, Ar); 10.10 (s, 1H, CONH)
1g	C_6H_5	$CH_2OC_2H_5$	4-Cl	$C_{21}H_{23}ClN_4O_2S$ 430.95	130–131 Methanol + H_2O	46	**A**, **C**: 1.01 (t, J = 7.0 Hz, 3H, CH_3); 1.90 (m, 2H, CH_2); 3.25 (m, 4H, CH_2OCH_2); 4.15 (m, 4H, SCH_2+ NCH_2); 7.20–7.71 (m, 9H, Ar); 10.68 (s, 1H, CONH)
1h	C_6H_5	$CH_2OC_2H_5$	2,6-Cl_2	$C_{21}H_{22}Cl_2N_4O_2S$ 465.40	148–149 Methanol	53	**B**, **C**: 1.08 (t, J = 7.0 Hz, 3H, CH_3); 1.95 (m, 2H, CH_2); 3.28 (m, 4H, CH_2OCH_2); 4.15 (m, 4H, SCH_2+ NCH_2); 7.10–7.66 (m, 8H, Ar); 10.24 (s, 1H, CONH)
1i	C_6H_5	1-piperidinyl	2,6-Cl_2	$C_{23}H_{25}Cl_2N_5OS$ 490.45	163–166 Dioxane + H_2O	65	**B**, **E**: 1.43 (m, 6H, $(CH_2)_3$); 2.28 (m, 4H, CH_2NCH_2); 2.49 (t, J = 6.1 Hz, 2H, CH_2N); 4.26 (m, 4H, SCH_2+ NCH_2); 7.25–7.69 (m, 8H, Ar); 9.98; (s, 1H, CONH)

(Continued on next page)

TABLE I Characteristics of the New Synthesized 1,2,4-Triazole-3-Thioles Derivatives *(Continued)*

	R	R^1	R^2	Formula Molecular weight	M.P. (°C) Solvent for Crystallization	Reaction Yield (%)	^{1}H NMR δ (ppm) 80 MHz–**A**, 200 MHz–**B** Solvent: (**C**–$CDCl_3$, **D**–d_6-DMSO, **E**–CD_3OD)
1j	C_6H_5	4-morpholinyl	H	$C_{22}H_{25}N_2O_2S$ 423.53	178–179 Methanol	71	**A**, **C**: 2.30 (m, 4H, CH_2NCH_2); 2.55 (t, $J = 6.1$ Hz, 2H, CH_2N); 3.51 (m, 4H, CH_2OCH_2); 4.10 (m, 4H, SCH_2+NCH_2); 7.08–7.65 (m, 10H, Ar); 10.50 (s, 1H, CONH)
1k	C_6H_5	4-morpholinyl	2-CH_3	$C_{23}H_{27}N_5O_2S$ 437.56	171–172 Benzene + Petr.	34	**B**, **C**: 2.34 (s, 3H, CH_3); 2.52 (t, $J = 4.6$ Hz, 4H, CH_2NCH_2); 2.75 (t, $J = 6.1$ Hz, 2H, CH_2N); 3.68 (t,$J = 4.6$ Hz, 4H, CH_2OCH_2) 3.99 (t, $J = 6.1$Hz, 2H, NCH_2); 4.10 (s, 2H, SCH_2); 7.02–7.74 (m, 9H, Ar); 9.93 (s, 1H, CONH)
1l	C_6H_5	4-morpholinyl	4-CH_3	$C_{23}H_{27}N_5O_2S$ 437.56	193–196 Benzene + Petr.	64	**B**, **C**: 2.32 (s, 3H, CH_3); 2.68 (t, $J = 4.7$ Hz, 4H, CH_2NCH_2); 2.85 (m, 2H, CH_2N); 3.87 (t, $J = 4.6$ Hz, 4H, CH_2OCH_2); 3.96 (m, 4H, SCH_2+ NCH_2); 7.12–7.57 (m, 9H, Ar); 9.33 (s, 1H, CONH)
1m	C_6H_5	4-morpholinyl	4-Cl	$C_{22}H_{24}ClN_5O_2S$ 457.98	184–186 Methanol + H_2O	37	**A**, **D**: 2.16 (m, 4H, CH_2NCH_2); 2.48 (m, 2H, CH_2N); 3.33 (m, 4H, CH_2OCH_2); 4.11 (m, 4H, SCH_2+ NCH_2); 7.32–7.68 (m, 9H, Ar); 9.10 (s, 1H, CONH)
1n	C_6H_5	4-morpholinyl	2,6-Cl_2	$C_{22}H_{23}Cl_2N_5O_2S$ 492.42	142–146 Methanol + H_2O	20	**B**, **E**: 2.26 (m, 4H, CH_2NCH_2); 2.51 (t,$J = 6.0$ Hz, 2H, CH_2N); 3.48 (m, 4H, CH_2OCH_2); 4.27 (m, 4H, SCH_2+ NCH_2); 7.14–7.69 (m, 8H, Ar); 10.01 (s, 1H, CONH)
2g	2-ClC_6H_4	OH	2,6-Cl_2	$C_{18}H_{15}Cl_3N_4O_2S$ 457.76	196–198 Methanol + H_2O	70	**B**, **E**:3.63 (m, 2H, CH_2); 4.03 (m, 2H, CH_2); 4.21 (s, 2H, SCH_2); 7.25–7.65 (m, 7H, Ar); 10.20 (s, 1H, CONH)
2h	2-ClC_6H_4	CH_2OH	2,6-Cl_2	$C_{19}H_{17}Cl_3N_4O_2S$ 471.79	221–222 Methanol + H_2O	95	**A**, **D**: 1.61 (m, 2H, CH_2); 3.25 (m, 2H, CH_2N); 3.85 (t, 2H, $J = 6.9$ Hz, CH_2); 4.15 (s, 2H, SCH_2); 4.51 (s, 1H, OH); 7.21–7.71 (m, 7H, Ar); 9.91 (s, 1H, CONH)

2i	2-ClC_6H_4	CH_2CH_2OH	2,6-Cl_2	$C_{20}H_{19}Cl_3N_4O_2S$ 485.81	137–139 Methanol + H_2O	85	**A**, **E**: 1.55 (m, 4H, $(CH_2)_2$); 3.41 (m, 2H, CH_2); 4.02 (t, $J = 6.9$ Hz, 2H, CH_2O); 4.15 (s, 2H, SCH_2); 7.21–7.65 (m, 7H, Ar); 10.30 (s, 1H, CONH)
3b	3-ClC_6H_4	$CH_2OC_2H_5$	H	$C_{21}H_{23}ClN_4O_2S$ 430.95	86–91 Methanol + H_2O	46	**B**, **C**: 1.09 (t, $J = 7.0$ Hz, 3H, CH_3); 1.95 (m, 2H, CH_2); 3.29 (m, 4H, CH_2OCH_2); 4.02 (s, 2H, SCH_2); 4.13 (t, $J = 7.3$ Hz, 2H, NCH_2); 7.05–7.68 (m, 9H, Ar) 10.46 (s, 1H, CONH)
3c	3-ClC_6H_4	$CH_2OC_2H_5$	4-CH3	$C_{22}H_{25}ClN_4O_2S$ 444.98	60–66 Methanol + H_2O	67	**B**, **C**: 1.09 (t, $J = 7.0$ Hz, 3H, CH_3); 1.98 (m, 2H, CH_2); 2.30 (s, 3H, CH_3); 3.30 (m, 4H, CH_2OCH_2); 4.03 (s, 2H, SCH_2); 4.14 (t, $J =$ 7.3 Hz, 2H, NCH_2); 7.12–7.67 (m, Ar); 8H, 10.33 (s, 1H, CONH)
3d	3-ClC_6H_4	$CH_2OC_2H_5$	3-Cl	$C_{21}H_{22}Cl_2N_4O_2S$ 465.40	51–57 Methanol + H_2O	87	**B**, **C**: 1.09 (t,$J = 7.0$ Hz, 3H, CH_3); 1.95 (m, 2H, CH_2); 3.30 (m, 4H, CH_2OCH_2); 4.02 (s, 2H, SCH_2); 4.14 (t, $J = 7.3$ Hz, 2H, NCH_2); 7.08–7.79 (m, 8H, Ar); 10.70 (s, 1H, CONH)
3e	3-ClC_6H_4	$CH_2OC_2H_5$	4-Cl	$C_{21}H_{22}Cl_2N_4O_2S$ 465.40	144–146 Methanol + H_2O	80	**B**, **C**: 1.09 (t,$J = 7.0$ Hz, 3H, CH_3); 1.95 (m, 2H, CH_2); 3.33 (m, 4H, CH_2OCH_2); 4.03 (s, 2H, SCH_2); 4.15 (t, $J =$7.3 Hz, 2H, NCH_2); 7.23–7.68 (m, 8H, Ar); 10.72 (s, 1H, CONH)
3f	3-ClC_6H_4	$CH_2OC_2H_5$	2,6-Cl_2	$C_{21}H_{21}Cl_3N_4O_2S$ 499.84	110–112 Methanol	60	**B**, **C**: 1.09 (t, $J = 7.0$ Hz, 3H, CH_3); 1.96 (m, 2H, CH_2); 3.34 (m, 4H, CH_2OCH_2); 4.15 (m, 4H, SCH_2+ NCH_2); 7.15–7.67 (m, 7H, Ar); 10.09 (s, 1H, CONH)
4d	4-ClC_6H_4	$CH_2OC_2H_5$	H	$C_{21}H_{23}ClN_4O_2S$ 430.95	115–116 Methanol	60	**B**, **C**: 1.10 (t, $J = 7.0$ Hz, 3H, CH_3); 1.98 (m, 2H, CH_2); 3.29 (m, 4H, CH_2OCH_2); 4.03 (s, 2H, SCH_2); 4.12 (t, $J = 7.3$ Hz, 2H, CH_2); 7.08–7.64 (m, 9H, Ar); 10.49 (s, 1H, CONH)
4e	4-ClC_6H_4	$CH_2OC_2H_5$	4-CH_3	$C_{22}H_{25}ClN_4O_2S$ 444.98	134–136 Methanol	58	**B**, **C**: 1.09 (t,$J = 7.0$ Hz, 3H, CH_3); 1.95 (m, 2H, CH_2); 2.29 (s, 3H, CH_3); 3.29 (m, 4H, CH_2OCH_2); 4.00 (s, 2H, SCH_2); 4.11 (t, $J =$7.2 Hz, 2H, NCH_2); 7.11–7.64 (m, 8H, Ar); 10.33 (s, 1H, CONH)

(Continued on next page)

TABLE I Characteristics of the New Synthesized 1,2,4-Triazole-3-Thioles Derivatives *(Continued)*

	R	R^1	R^2	Formula Molecular weight	M.P. (°C) Solvent for Crystallization	Reaction Yield (%)	^{1}H NMR δ (ppm) 80 MHz–**A**, 200 MHz–**B** Solvent: (**C**–$CDCl_3$, **D**–d_6-DMSO, **E**–CD_3OD)
4f	4-ClC_6H_4	$CH_2OC_2H_5$	2-Cl	$C_{21}H_{22}Cl_2N_4O_2S$ 465.40	70–77 Methanol + H_2O	39	**B**, **C**: 1.10 (t, J = 7.0 Hz, 3H, CH_3); 1.99 (m, 2H, CH_2); 3.29 (m, 4H, CH_2OCH_2); 4.18 (m, 4H, SCH_2+ NCH_2); 7.01–7.64 (m, 7H, Ar) 8.27 (dd, J = 8.2, 1.6 Hz, 1H, Ar); 10.00 (s, 1H, CONH)
4g	4-ClC_6H_4	$CH_2OC_2H_5$	3-Cl	$C_{21}H_{22}Cl_2N_4O_2S$ 465.40	123–125 Methanol	52	**B**, **C**: 1.10 (t,J = 7.0 Hz, 3H, CH_3); 1.95 (m, 2H, CH_2); 3.33 (m, 4H, CH_2OCH_2); 3.99 (s, 2H, SCH_2); 4.12 (t, J = 7.3 Hz, 2H, NCH_2); 7.07–7.78 (m, 8H, Ar); 10.72 (s, 1H, CONH)
4h	4-Cl C_6H_4	$CH_2OC_2H_5$	4-Cl	$C_{21}H_{22}Cl_2N_4O_2S$ 465.40	138–141 Methanol + H_2O	95	**B**, **C**: 1.13 (t, J = 7.0 Hz, 3H, CH_3); 1.95 (m, 2H, CH_2); 3.30 (m, 4H, CH_2OCH_2); 3.99 (s, 2H, SCH_2); 4.12 (t, J = 7.3 Hz, 2H, NCH_2); 7.22–7.64 (m, 8H, Ar); 10.71 (s, 1H, CONH)
4i	4-ClC_6H_4	$CH_2OC_2H_5$	2,5-Cl_2	$C_{21}H_{21}Cl_3N_4O_2S$ 499.84	55–60 Benzene + Petr.	44	**B**, **C**: 1.10 (t, J = 7.0 Hz, 3H, CH_3); 1.94 (m, 2H, CH_2); 3.33 (m, 4H, CH_2OCH_2); 4.16 (m, 4H, SCH_2+ NCH_2); 7.00–7.63 (m, 6H, Ar); 8.41 (d, J = 2.4 Hz, 1H, Ar); 10.23 (s, 1H, CONH)
4j	4-ClC_6H_4	$CH_2OC_2H_5$	2,6-Cl_2	$C_{21}H_{21}Cl_3N_4O_2S$ 499.84	158–162 Methanol + H_2O	40	**B**, **C**: 1.10 (t,J = 7.1Hz, 3H, CH_3); 1.99 (m, 2H, CH_2); 3.30 (m, 4H, CH_2OCH_2); 4.15 (m, 4H, SCH_2+ NCH_2); 7.19–7.63 (m, 7H, Ar); 10.15 (s, 1H, CONH)
4k	4-ClC_6H_4	1-piperidinyl	4-Cl	$C_{23}H_{25}Cl_2N_5OS$ 490.45	133–135 Acetone + H_2O	82	**B**, **C**: 1.49 (m, 6H, $(CH_2)_3$); 2.35 (m, 4H, CH_2NCH_2); 2.57 (t, J = 6.4 Hz, 2H, CH_2); 4.05 (m, 4H, SCH_2+ NCH_2); 7.23–7.68 (m, 8H, Ar); 10.72 (s, 1H, CONH)
4l	4-ClC_6H_4	1-piperidinyl	2,6-Cl_2	$C_{23}H_{24}Cl_3N_5OS$ 524.89	187–188 Methanol	57	**B**, **C**: 1.49 (m, 6H, $(CH_2)_3$); 2.33 (m, 4H, CH_2NCH_2); 2.55 (t, J = 6.4 Hz, 2H, CH_2N); 4.09 (m, 4H, SCH_2+ NCH_2); 7.15–7.68 (m, 7H, Ar); 10.19 (s, 1H, CONH)

4m	4-ClC_6H_4	4-morpholinyl	4-CH_3	$C_{23}H_{26}ClN_5O_2S$ 472.00	205–206 Acetone + Methanol	78	**B**, **C**: 2.30 (m, 7H, CH_2NCH_2+ CH_3); 2.59 (m, 2H, CH_2N); 3.57 (m, 4H, CH_2OCH_2); 4.05 (m, 4H, SCH_2+ NCH_2); 7.27–7.64 (m, 8H, Ar); 10.21 (s, 1H, CONH)
4n	4-ClC_6H_4	4-morpholinyl	4-Cl	$C_{22}H_{23}Cl_2N_5O_2S$ 492.42	160–164 Acetone + Methanol	91	**B**, **C**: 2.71 (m, 4H, CH_2NCH_2); 2.87 (t, $J = 6.3$ Hz, 2H, CH_2N); 3.87 (m, 4H, CH_2OCH_2); 3.93 (m, 4H, SCH_2+ NCH_2); 7.26-7.58 (m, 8H, Ar); 9.65 (s, 1H, CONH)
4o	4-ClC_6H_4	4-morpholinyl	2,6-Cl_2	$C_{22}H_{22}Cl_3N_5O_2S$ 526.87	183–185 Methanol	77	**B**, **C**: 2.32 (m, 4H, CH_2NCH_2); 2.57 (t, $J = 6.3$ Hz, 2H, CH_2N); 3.56 (m, 4H, CH_2OCH_2); 4.15 (m, 4H, SCH_2+ NCH_2); 7.23–7.63 (m, 7H, Ar); 10.64 (s, 1H, CONH)
5f	3-pyridyl	OCH_3	4-CH_3	$C_{19}H_{21}N_5O_2S$ 383.47	127–129 Benzene + Petr.	84	**B**, **C**: 2.33 (s, 3H, CH_3); 3.31 (s, 3H, OCH_3); 3.68 (t, 2H, $J = 5.1$ Hz, CH_2O); 4.02 (s, 2H, CH_2); 4.15 (t, $J = 5.1$ Hz, 2H, NCH_2); 7.11–7.51 (m, 4H, Ar + 1H, Py); 8.16 (dt, $J = 8.0$, 1.9 Hz, 1H, Py); (dd, $J = 4.9$, 1.7 Hz, 1H, Py); 9.03 (d, $J = 1.7$ Hz, 1H, Py; 10.31 (s, 1H, CONH)
5g	3-pyridyl	OCH_3	4-Cl	$C_{18}H_{18}ClN_5O_2S$ 403.89	132–135 Methanol + H_2O	88	**B**, **C**: 3.30 (s, 3H, CH_3); 3.71 (t, $J = 5.1$Hz, 2H, CH_2O); 4.05 (s, 2H, CH_2); 4.20 (t, $J =$ 5.1 Hz, 2H, NCH_2); 7.30–7.64 (m, 4H, Ar + 1H, Py); 8.13 (dt, $J =$ 8.0, 1.9 Hz, 1H, Py); 8.80–9.04 (m, 2H, Py) 10.70 (s, 1H, CONH)
5h	3-pyridyl	OCH_3	2,6-Cl_2	$C_{18}H_{17}Cl_2N_5O_2S$ 438.33	147–149 Acetone	45	**B**, **C**: 3.32 (s, 3H, CH_3); 3.71 (t, $J = 5.1$Hz, 2H, OCH_2); 4.17 (m, 4H, SCH_2+ NCH_2); 7.17–7.51 (m, 3H Ar + 1H, Py); 8.13 (dt, $J = 8.1$, 1.9 Hz, 1H, Py); 8.80 (dd, $J = 4.9$, 1.7 Hz, 1H, Py) 9.03 (d, $J = 1.8$ Hz, 1H, Py); 10.00 (s, 1H, CONH)

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TABLE I Characteristics of the New Synthesized 1,2,4-Triazole-3-Thioles Derivatives *(Continued)*

	R	R^1	R^2	Formula Molecular weight	M.P. (°C) Solvent for Crystallization	Reaction Yield (%)	^{1}H NMR δ (ppm) 80 MHz–**A**, 200 MHz–**B** Solvent: (**C**–$CDCl_3$, **D**–d_6-DMSO, **E**–CD_3OD)
5i	3-pyridyl	CH_2OCH_3	4-CH_3	$C_{20}H_{23}N_5O_2S$ 397.50	120–123 Benzene + Petr.	62	**B**, **C**: 2.01 (m, 2H, CH_2); 2.32 (s, 3H, OCH_3); 3.27 (s, 3H, CH_3); 3.30 (t, J = 5.6 Hz, 2H, CH_2O); 4.04 (s, 2H, SCH_2); 4.14 (t, J = 7.2 Hz, 2H, NCH_2); 7.14–7.54 (m, 4H, Ar + 1H, Py); 8.03 (dt, J = 7.9, 1.9 Hz, 1H, Py); 8.82 (dd, J = 4.9, 1.7 Hz, 1H, Py); (d, J = 1.7 Hz, 1H, Py) 10.30 (s, 1H, CONH)
5j	3-pyridyl	CH_2OCH_3	3-Cl	$C_{19}H_{20}ClN_5O_2S$ 417.91	49–54 Benzene + Petr.	80	**B**, **C**: 1.79 (s, 3H, CH_3); 2.01 (m, 2H, CH_2); 3.31 (t, J = 5.6 Hz, 2H, CH_2O); 4.04 (s, 2H, SCH_2); 4.15 (t, J = 7.2 Hz, 2H, NCH_2); 7.10–7.55, 7.79 (m, 4H, Ar + 1H, Py); 8.04 (dt, J = 8.0, 1.9 Hz, 1H, Py); 8.81 (dd, J = 4.9, 1.7 Hz, 1H, Py); 8.95 (d, J = 1.7 Hz, 1H, Py); 10.62 (s, 1H, CONH)
5k	3-pyridyl	CH_2OCH_3	4-Cl	$C_{19}H_{20}ClN_5O_2S$ 417.91	130–131 Acetone + H_2O	85	**B**, **C**: 1.97 (m, 2H, CH_2); 3.20 (s, 3H, CH_3); 3.30 (t, J = 5.7 Hz, 2H, CH_2); 4.03 (s, 2H, SCH_2); 4.15 (t, J = 7.3 Hz, 2H, NCH_2); 7.25–7.62 (m, 4H, Ar + 1H, Py) 8.00 (dt, J = 8.0, 1.9 Hz, 1H, Py); 8.82 (dd, J = 4.9, 1.7 Hz, 1H, Py); 8.94 (d, J= 1.7 Hz, 1H, Py); 10.51 (s, 1H, CONH)
5l	3-pyridyl	CH_2OCH_3	2,6-Cl_2	$C_{19}H_{19}Cl_2N_5O_2S$ 452.36	156–157 Benzene + Petr.	55	**B**, **C**: 2.00 (m, 2H, CH_2); 3.20 (s, 3H, CH_3); 3.30 (t, J = 5.7 Hz, 2H, CH_2O); 4.18 (m, 4H, SCH_2+ NCH_2); 7.14–7.53 (m, 3H, Ar + 1H, Py); 8.03 (dt, J = 7.9, 1.8 Hz, 1H, Py); 8.81 (dd, J = 4.9, 1.8 Hz, 1H, Py); 8.94 (d, J = 1.7, 1H, Py); 10.02 (s, 1H, CONH)

5m	3-pyridyl	$CH_2OC_2H_5$	4-CH_3	$C_{21}H_{25}N_5O_2S$ 411.52	113–116 Benzene + Petr.	95	**B**, **C**: 1.09 (t, $J = 7.0$ Hz, 3H, CH_3); 2.02 (m, 2H, CH_2); 2.31 (s, 3H, CH_3); 3.33 (m, 4H, CH_2OCH_2); 4.05 (s, 2H, SCH_2); 4.15 (t, $J =$ 7.2 Hz, 2H, NCH_2); 7.14–7.53 (m, 4H, Ar + 1H, Py); 8.02 (dt, $J = 8.0$, 1.8 Hz, 1H, Py); 8.81 (dd, $J = 4.9$, 1.7 Hz, 1H, Py); 8,95 (d, $J = 1.7$ Hz, 1H, Py); 10.27 (s, 1H, CONH)
5n	3-pyridyl	$CH_2OC_2H_5$	3-Cl	$C_{20}H_{22}ClN_5O_2S$ 431.94	114–116 Methanol + H_2O	66	**B**, **C**: 1.08 (t, $J = 7.0$ Hz, 3H, CH_3); 2.01 (m, 2H, CH_2); 3.33 (m, 4H, CH_2OCH_2); 4.01 (s, 2H, SCH_2); 4.15 (t, $J = 7.2$ Hz, 2H, NCH_2); 7.08–7.77 (m, 4H, Ar + 1H, Py); 8.01 (dt, $J = 7.9$, 1.9 Hz, 1H, Py); 8.81 (dd, $J = 4.9$, 1.7 Hz, 1H, Py); 8.94 (d, $J = 1.7$ Hz, 1H, Py); 10.62 (s, 1H, CONH)
5o	3-pyridyl	$CH_2OC_2H_5$	4-Cl	$C_{20}H_{22}ClN_5O_2S$ 431.94	127–129 Methanol + H_2O	90	**B**, **C**: 1.09 (t, $J = 7.1$ Hz, 3H, CH_3); 1.99 (m, 2H, CH_2); 3.33 (m, 4H, CH_2OCH_2); 4.04 (s, 2H, SCH_2); 4.16 (t, $J = 7.2$ Hz, 2H, CH_2); 7.26–7.62 (m, 4H, Ar, + 1H, Py); 8.04 (dt, $J = 8.0$, 1,8 Hz, 1H, Py); 8.81 (dd, $J = 4.9$, 1.7 Hz, 1H, Py); 8.95 (d, $J = 1.7$ Hz, 1H, Py); 10.62 (s, 1H, CONH)
5p	3-pyridyl	$CH_2OC_2H_5$	2,6-Cl_2	$C_{20}H_{21}Cl_2N_5O_2S$ 466.38	120–121 Methanol + H_2O	57	**B**, **C**: 1.11 (t, $J = 7.0$ Hz, 3H, CH_3); 2.01 (m, 2H, CH_2); 3.32 (m, 4H, CH_2OCH_2); 4.15 (m, 4H, SCH_2+ NCH_2); 7.14–7.39 (m, 3H, Ar); 7.50 (m, 1H, Py); 8.03 (dt, $J = 7.9$, 1.8 Hz, 1H, Py); 8.81 (dd, $J = 4.9$, 1.7 Hz, 1H, Py); 8.95 (d, $J = 1.7$ Hz, 1H, Py); 10.02 (s, 1H, CONH)
5r	3-pyridyl	1-piperidiny	4-CH_3	$C_{23}H_{28}N_6OS$ 436.57	131–133 Acetone	73	**B**, **C**: 1.45 (m, 6H, $(CH_2)_3$); 2.31 (m, 7H, CH_2NCH_2+ CH_3); 2.57 (t, $J = 6.4$, 2H, CH_2N); 4.05 (m, 4H, SCH_2+ NCH_2); 7.10–7.54 (m, 4H, Ar + 1H, Py); 8.10 (dt, $J = 7.9$, 1.9 Hz, 1H, Py); 8.81 (dd, $J = 4.9$, 1.7 Hz, 1H, Py); 8.99 (d, $J = 1.7$ Hz, 1H, Py); 10.30 (s, 1H, CONH)

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TABLE I Characteristics of the New Synthesized 1,2,4-Triazole-3-Thioles Derivatives *(Continued)*

	R	R^1	R^2	Formula Molecular weight	M.P. (°C) Solvent for Crystallization	Reaction Yield (%)	^{1}H NMR δ (ppm) 80 MHz–**A**, 200 MHz–**B** Solvent: (**C**–$CDCl_3$, **D**–d_6-DMSO, **E**–CD_3OD)
5s	3-pyridyl	1-piperidinyl	3-Cl	$C_{22}H_{25}ClN_6OS$ 456, 99	133–135 Acetone + H_2O	50	**B**, **C**: 1.44 (m, 6H, $(CH_2)_3$); 2.31 (m, 4H, $(CH_2)_2$); 2.58 (t, $J = 6.4$ Hz, 2H, CH_2N); 4.06 (m, 4H, SCH_2+ NCH_2); 7.08–7.80 (m, 4H, Ar + 1H, Py); 8.09 (dt, $J = 8.0$, 1.9 Hz, 1H, Py); 8.82 (dd, $J = 4.9$, 1.7 Hz, 1H); 9.00 (d, $J = 1.7$ Hz, 1H, Py); 10.72 (s, 1H, CONH)
5t	3-pyridyl	1-piperidinyl	4-Cl	$C_{22}H_{25}ClN_6OS$ 456.99	170–172 Acetone + H_2O	68	**B**, **C**: 1.41 (m, 6H, $(CH_2)_3$); 2.30 (m, 4H, CH_2NCH_2); 2.57 (t, $J = 6.3$ Hz, 2H, CH_2N); 4.00 (s, 2H, SCH_2); 4.06 (t, $J = 6.3$ Hz, 2H, NCH_2); 7.25–7.63 (m, 4H, Ar + 1H, Py); 8.07 (dt, $J = 8.0$, 1.9 Hz, 1H, Py); 8.82 (dd, $J = 4.9$, 1,7 Hz, 1H, Py); 8.99 (d, $J = 1.7$ Hz, 1H, Py); 10.70 (s, 1H, CONH)
5u	3-pyridyl	1-piperidinyl	2,6-Cl_2	$C_{22}H_{24}Cl_2N_6OS$ 491.44	158–159 Acetone	36	**B**, **C**: 1.43 (m, 6H, $(CH_2)_3$); 2.31 (m, 4H, $(CH_2)_2$); 2.60 (t, $J = 6.3$ Hz, 2H, CH_2N); 4.09 (m, 4H, NCH_2+ SCH_2) 7.18–7.39 (m, 3H, Ar); 7.50 (m, 1H, Py); 8.12 (dt, $J = 7.9$, 1.9 Hz, 1H, Py); 8.80 (dd, $J = 4.9$, 1.7 Hz, 1H, Py); 9.00 (d, $J = 1.7$ Hz, 1H, Py); 10.13 (s, 1H, CONH)
5w	3-pyridyl	4-morpholinyl	4-CH_3	$C_{22}H_{26}N_6O_2S$ 438.55	172–174 Benzene + Petr.	61	**B**, **C**: 2.32 (m, 7H, CH_2NCH_2+ CH_3); 2.61 (t, $J = 6.1$ Hz, 2H, CH_2N); 3.54 (m, 4H, CH_2OCH_2); 4.02 (s, 2H, SCH_2); 4.12 (t, $J = 6.1$ Hz, 2H, NCH_2); 7.11–7.55 (m, 4H, Ar + 1H, Py); 8.04 (dt, $J = 8.0$, 1.9 Hz, 1H, Py); 8.81 (dd, $J = 4.9$, 1.7 Hz, 1H, Py); 8.96 (d, $J = 1.7$ Hz, 1H, Py); 10.20 (s, 1H, CONH)

5z	3-pyridyl	4-morpholinyl	3-Cl	$C_{21}H_{23}ClN_6O_2S$ 458.97	155–156 Acetone	82	**B**, **C**: 2.35 (t, $J = 4.6$ Hz, 4H, CH_2NCH_2); 2.62 (t,$J = 6.1$ Hz, 2H, CH_2N); 3.56 (t, $J = 4.6$ Hz, 4H, CH_2OCH_2); 4.01 (s, 2H, SCH_2); 4.10 (t, $J = 6.1$ Hz, 2H, NCH_2); 7.10–7.79 (m, 4H, Ar + 1H, Py); 8.06 (dt, $J = 8.0$, 1.9 Hz, 1H, Py); 8.83 (dd, $J = 4.9$, 1.7 Hz, 1H, Py); 8.96 (d, $J = 1.7$ Hz, 1H, Py); 10.61 (s, 1H, CONH)
5x	3-pyridyl	4-morpholinyl	4-Cl	$C_{21}H_{23}ClN_6O_2S$ 458.97	172–174 Benzene + Petr.	89	**B**, **C**: 2.34 (t, $J = 4.7$ Hz, 4H, CH_2NCH_2); 2.62 (t,$J = 6.1$ Hz, 2H, CH_2N); 3.56 (t, $J = 4,7$ Hz, 4H, CH_2OCH_2); 4.01 (s, 2H, SCH_2); 4.10 (t, $J = 6.1$ Hz, 2H, NCH_2); 7.26–7.59 (m, 4H, Ar + 1H, Py); 8.04 (dt, $J = 8.0$, 1.9 Hz, 1H, Py); 8.81 (dd, $J = 4.9$, 1.7 Hz, 1H, Py); 8.96 (d, $J = 1.7$ Hz, 1H, Py); 10.60 (s, 1H, CONH)
5y	3-pyridyl	4-morpholinyl	2,6-Cl_2	$C_{21}H_{22}Cl_2N_6O_2S$ 493.41	147–149 Benzene + Petr.	80	**B**, **C**: 2.35 (m, 4H, CH_2NCH_2); 2.63 (t, $J = 6.1$ Hz, 2H, CH_2N); 3.60 (m, 4H, CH_2OCH_2); 4.12 (m, 4H, SCH_2+ NCH_2); 7.22–7.39 (m, 3H, Ar); 7.51 (m, 1H, Py); 8.08 (dt, $J = 8.0$, 1.9 Hz, 1H, Py); 8.81 (dd, $J = 4.9$, 1.7 Hz, 1H, Py); 8.96 (d, $J = 1.7$ Hz, 1H, Py);10.02 (s, 1H, CONH)
6f	4-pyridyl	$CH_2OC_2H_5$	4-CH_3	$C_{21}H_{25}N_5O_2S$ 411.52	127–129 Methanol + H_2O.	71	**B**, **C**: 1.12 (t, $J = 7.0$ Hz, 3H, CH_3); 2.03 (m, 2H, CH_2); 2.33 (s, 3H, CH_3); 3.36 (m, 4H, CH_2OCH_2); 4.05 (s, 2H, SCH_2); 4.21 (t, $J =$ 7.3 Hz, 2H, NCH_2); 7.14–7.52 (m, 4H, Ar); 7.69, (dd, $J = 4.5$, 1.7 Hz, 2H, Py); 8.81 (dd, $J = 4.5$, 1.6 Hz, 2H, Py); 10.18 (s, 1H, CONH)

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TABLE I Characteristics of the New Synthesized 1,2,4-Triazole-3-Thioles Derivatives *(Continued)*

	R	R^1	R^2	Formula Molecular weight	M.P. (°C) Solvent for Crystallization	Reaction Yield (%)	^{1}H NMR δ (ppm) 80 MHz–**A**, 200 MHz–**B** Solvent: (**C**–$CDCl_3$, **D**–d_6-DMSO, **E**–CD_3OD)
6g	4-pyridyl	$CH_2OC_2H_5$	3-Cl	$C_{20}H_{22}ClN_5O_2S$ 431.94	85–90 Methanol + H_2O	67	**B**, **C**: 1.15 (t, $J = 7.0$ Hz, 3H, CH_3); 2.05 (m, 2H, CH_2); 3.40 (m, 4H, CH_2OCH_2); 4.07 (s, 2H, SCH_2); 4.24 (t, $J = 7.3$ Hz, 2H, NCH_2); 7.06–7.77 (m, 4H, Ar); 7.86 (m, 2H, Py); 8.84 (d, $J = 5.1$ Hz, 2H, Py); 10.47 (s, 1H, CONH)
6h	4-pyridyl	$CH_2OC_2H_5$	4-Cl	$C_{20}H_{22}ClN_5O_2S$ 431.94	138–139 Methanol + H_2O	53	**B**, **C**: 1.13 (t, $J = 7.0$ Hz, 3H, CH_3); 2.04 (m, 2H, CH_2); 3.34 (m, 4H, CH_2OCH_2); 4.03 (s, 2H, SCH_2); 4.22 (t, $J = 7.3$ Hz, 2H, NCH_2); 7.26–7.62 (m, 4H, Ar); 7.73 (dd, $J = 4.5$, 1.6 Hz, 2H, Py); 8.83 (dd, $J = 4.5$, 1.6 Hz, 2H, Py) 10.53 (s, 1H, CONH)
6i	4-pyridyl	$CH_2OC_2H_5$	2,6-Cl_2	$C_{20}H_{21}Cl_2N_5O_2S$ 466.38	156–159 Methanol + H_2O	51	**B**, **C**: 1.15 (t, $J = 7.0$ Hz, 3H, CH_3); 2.09 (m, 2H, CH_2); 3.35 (m, 4H, CH_2OCH_2); 4.17 (s, 2H, SCH_2); 4.28 (t, $J = 7.3$ Hz, 2H, NCH_2); 7.18–7.39 (m, 3H, Ar); 7,69 (dd, $J = 4.5$, 1.65 Hz, 2H, Py); 8.82 (dd, $J = 4.5$, 1.65 Hz, 2H, Py) 9.76 (s, 1H, CONH)
6j	4-pyridyl	1-piperidinyl	4-CH_3	$C_{23}H_{28}N_6OS$ 436.57	175–178 Methanol + H_2O	77	**B**, **C**: 1.43 (m, 6H, $(CH_2)_3$); 2.32 (m, 7H, $(CH_2)_2$+ CH_3); 2.61 (t, $J = 6.2$ Hz, 2H, CH_2N); 4.12 (m, 4H, SCH_2+ NCH_2); 7.14–7.68 (m, 4H, Ar); 7.72 (dd, $J = 4.4$, 1.6 Hz, 2H, Py); 8.85 (dd, $J = 4.4$, 1.7 Hz, 2H, Py); 10.19 (s, 1H, CONH)
6k	4-pyridyl	1-piperidinyl	3-Cl	$C_{22}H_{25}ClN_6OS$ 456.99	136–138 Benzene	62	**B**, **C**: 1.42 (m, 6H, $(CH_2)_3$); 2.32 (m, 4H, $(CH_2)_2$); 2.59 (t, $J = 6.2$ Hz, 2H, CH_2N); 4.08 (s, 2H, SCH_2); 4.11 (t, $J = 6.1$Hz, 2H, NCH_2); 7.10–7.80 (m, 4H, Ar); 7.72 (dd, $J =$ 4.5, 1.6 Hz, 2H, Py); 8.86 (dd, $J = 4.5$, 1.6 Hz, 2H, Py); 10.64 (s, 1H, CONH)

6l	4-pyridyl	1-piperidinyl	4-Cl	$C_{22}H_{25}ClN_6OS$ 456.99	184–185 Methanol	50	**B**, **C**: 1.53 (m, 6H, $(CH_2)_3$); 2.40 (m, 4H, $(CH_2)_2$); 2.68 (m, 2H, CH_2N); 4.02 (s, 2H, SCH_2); 4.22 (m, 2H, NCH_2); 7.25–7.62 (m, 4H, Ar); 7.72 (dd, $J = 4.5$, 1.6 Hz, 2H, Py); 8.86 (dd, $J = 4.5$, 1.6 Hz, 2H, Py); 10.53 (s, 1H, CONH)
6m	4-pyridyl	1-piperidinyl	2,6-Cl_2	$C_{22}H_{24}Cl_2N_6OS$ 491.44	154–155 Acetone	54	**B**, **C**: 1.45 (m, 6H, $(CH_2)_3$); 2.33 (m, 4H, $(CH_2)_2$); 2.61 (t, $J = 6.0$ Hz, 2H, CH_2N); 4.13 (m, 4H, SCH_2+ NCH_2); 7.13–7.39 (m, 3H, Ar); 7.72 (dd, $J =$ 4.5, 1.6 Hz, 2H, Py); 8.84 (dd, $J =$ 4.5, 1.6 Hz, 2H, Py); 10.05 (s, 1H, CONH)
6n	4-pyridyl	1-piperidinyl	2,5-Cl_2	$C_{22}H_{24}Cl_2N_6OS$ 491.44	63–66 Methanol + H_2O	20	**B**, **C**: 1.42 (m, 6H, $(CH_2)_3$); 2.31 (m, 4H, $(CH_2)_2$); 2.59 (t, $J = 6.2$ Hz, 2H, CH_2N); 4.09 (t, $J = 6.1$ Hz, 2H, NCH_2); 4.15 (s, 2H, SCH_2); 7.02–7.32 (m, 2H, Ar); 7.71 (dd, $J =$ 4.4, 1.6 Hz, 2H, Py); 8.45 (d, $J = 2.5$ Hz, 1H, Ar); 8.83 (dd, $J = 4.4$, 1.6 Hz, 2H, Py); 10.17 (s, 1H, CONH)
6o	4-pyridyl	4-morpholinyl	4-CH_3	$C_{22}H_{26}N_6O_2S$ 438.55	195–199 Acetone + H_2O	61	**B**, **C**: 2.31 (m, 7H, CH_2NCH_2+ CH_3); 2.61 (t, $J = 6.1$ Hz, 2H, CH_2O); 3.52 (m, 4H, CH_2OCH_2); 4.04 (s, 2H, SCH_2); 4.13 (t, $J = 6.1$ Hz, 2H, NCH_2); 7.13–7.51(m, 4H, Ar); 7.65 (dd, $J = 4.4$, 1.7 Hz, 2H, Py); 8.84 (dd, $J = 4.4$, 1.7 Hz, 2H, Py); 10.10 (s, 1H, CONH)

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TABLE I Characteristics of the New Synthesized 1,2,4-Triazole-3-Thioles Derivatives *(Continued)*

	R	R^1	R^2	Formula Molecular weight	M.P. (°C) Solvent for Crystallization	Reaction Yield (%)	^{1}H NMR δ (ppm) 80 MHz–**A**, 200 MHz–**B** Solvent: (**C**–$CDCl_3$, **D**–d_6-DMSO, **E**–CD_3OD)
6p	4-pyridyl	4-morpholinyl	3-Cl	$C_{21}H_{23}ClN_6O_2S$ 458.97	200–201 Methanol	93	**B**, **C**: 2.36 (m, 4H, CH_2NCH_2); 2.63 (t, J = 6.1 Hz, 2H, CH_2N); 3.55 (m, 4H, CH_2OCH_2); 4.01 (s, 2H, SCH_2); 4.14 (t, J = 6.1 Hz, 2H, NCH_2); 7.26–7.62 (m, 4H, Ar); 7.66 (dd, J = 4.4, 1.6 Hz, 2H, Py); 8.86 (dd, J = 4.4, 1.6 Hz, 2H, Py); 10.52 (s, 1H, CONH)
6r	4-pyridyl	4-morpholinyl	4-Cl	$C_{21}H_{23}ClN_6O_2S$ 458.97	198–201 Methanol + H_2O	70	**B**, **C**: 2.35 (t, J = 4.6 Hz, 4H, CH_2NCH_2); 2.63 (t, J = 6.1 Hz, 2H, CH_2N); 3.55 (t, J = 4.6 Hz, 4H, CH_2OCH_2); 4.01 (s, 2H, SCH_2); 4.14 (t,J = 6.1 Hz, 2H, NCH_2); 7.26–7.61 (m, 4H, Ar); 7.66 (dd, J = 4.5, 1.6 Hz, 2H, Py); 8.86 (dd, J = 4.5, 1.6 Hz, 2H, Py); 10.49 (s, 1H, CONH)
6s	4-pyridyl	4-morpholinyl	2,6-Cl_2	$C_{21}H_{22}Cl_2N_6O_2S$ 493.41	142–144 Benzene + Petr.	43	**B**, **C**: 2.39 (m, 4H, CH_2NCH_2); 2.64 (t, J = 6.0 Hz, 2H, CH_2N); 3.57 (m, 4H, CH_2OCH_2); 4.16 (m, 4H, SCH_2+ NCH_2); 7.19–7.39 (m, 3H, Ar); 7.67 (dd, J = 4.4, 1.7 Hz, 2H, Py); 8.85 (dd, J = 4.4, 1.7 Hz, 2H, Py); 9.95 (s, 1H, CONH)
6t	4-pyridyl	4-morpholinyl	2,5-Cl_2	$C_{21}H_{22}Cl_2N_6O_2S$ 493.41	130–133 Methanol + H_2O	19	**B**, **C**: 2.31 (t, J = 4.6 Hz, 4H, CH_2NCH_2); 2.60 (t, J = 6.1 Hz, 2H, CH_2N); 3.51 (t, J = 4.6 Hz, 4H, CH_2OCH_2); 4.09 (t, J = 6.1 Hz, 2H, NCH_2); 4.14 (s, 2H, SCH_2); 7.04–7.28 (m, 2H, Ar); 8.41 (d, J = 2.4 Hz, 1H, Ar) 7.63 (dd, J = 4.4, 1.6 Hz, 2H, Py); 8.81 (dd, J = 4.5, 1.6 Hz, 2H, Py); 10.06 (s, 1H, CONH)

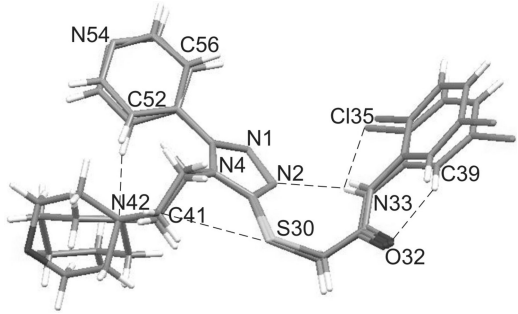


FIGURE 1 Superposition of **6n** and **6t** showing important intramolecular contacts.

several unexpected features of the structures that are worthy to be mentioned.

Despite the brunched structure and significant freedom of movements present in the molecules (there are at least three single bonds

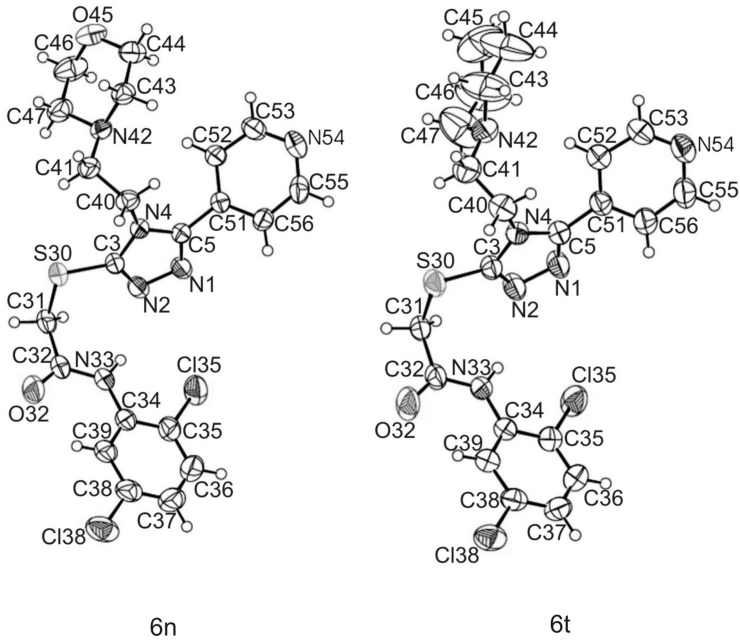


FIGURE 2 ORTEP views of the molecular structures in the crystal and labelling of the atom in **6n** and **6t**. Displacement ellipsoids are shown at the 50% probability level (PLATON).[28]

TABLE II Selected Geometrical Parameters (Å, °) for Compounds 6n and 6t[a]

				6n		**6t**
Bond lengths						
S30–C3				1.7522(17)		1.748(2)
S30–C31				1.816(2)		1.811(2)
C31–C32				1.513(3)		1.508(3)
C32–N33				1.359(2)		1.350(3)
N33–C34				1.401(2)		1.397(3)
C51–C5				1.473(2)		1.472(3)
Bond angles						
C3–S30–C31				98.74(10)		99.69(11)
C32–N33–C34				127.20(16)		127.36(18)
Torsion angles						
C35–C34–N33–C32				172.0(2)		168.9(2)
	D–H···A	D–H	H···A	D···A	D–H···A	Symmetry operations
Intra molecular hydrogen bonds						
6n	N33–H33···N2	0.86	2.21	2.938(2)	143	
6ts		0.86	2.35	3.062(3)	141	
6n	N33–H33···Cl35	0.86	2.49	2.947(1)	114	
6t		0.86	2.51	2.959(2)	113	
6n	C39–H39···O32	0.93	2.22	2.823(3)	122	
6t		0.93	2.24	2.818(3)	120	
6n	C41–H41A···S30	0.97	2.71	3.400(2)	128	
6t	C52–H52···N42	0.93	2.43	3.311(3)	158	
Inter molecular hydrogen bonds						
6n	C31–H31A···N54	0.97	2.57	3.514(3)	165	[x,y,−1+z]
6t		0.97	2.55	3.482(3)	160	[x,y,1+z]
6t	C31–H31B···N1	0.97	2.59	3.237(3)	124	[1−x,1−y,1−z]
6t	C31–H31B···N2	0.97	2.50	3.378(3)	151	[1−x,1−y,1−z]
6n	C56–H56···O45	0.93	2.57	3.364(2)	144	[x,1+y,z]
6t	C41–H41B···O32	0.97	2.45	3.204(5)	135	[2−x,1−y,1−z]

[a]Symmetry operations indicated for *inter*molecular contacts refer to the acceptors. Due to refinement of H atoms in the "riding" positions, their standard uncertainties have been omitted.

joining two cyclic systems at N4 and C3 with the central phenyltriazole ring), the molecules adopt a compact structure due to numerous intramolecular hydrogen contacts (Table II and Figure 2). Some of the contacts are rather weak but obviously important. The *intra*molecular hydrogen bond N33-H···Cl35, with a H···Cl distance of 2.51 Å (Table II), requires coplanarity of the benzene ring and the adjacent amide group (Figure 2). Thus the torsion angle C35-C34-N33-C32 is 172.0(2)° and 168.9(2)°, respectively, in **6n** and **6t** (Table II). Similar values of

TABLE III Crystal Data and Structure Refinement for 6n and 6t

	6n	6t
Empirical formula	$C_{21}H_{22}C_{12}N_6O_2S$	$C_{22}H_{24}C_{12}N_6OS$
Formula weight	493.42	491.44
Crystal system, space group, and Z	triclinic, P-1 (2)	triclinic, P-1 (2)
Unit cell dimensions a, b, c (Å) α, β, γ(°)	a = 9.134(2) α = 77.95(3) b = 10.754(2) β = 79.03(3) c = 12.300(3) γ = 77.64(3)	a = 10.476(2) α = 76.69(3) b = 10.775(2) β = 74.25(3) c = 12.278(3) γ = 66.01(3)
Volume (Å^3)	1140.7(5)	1207.3(5)
Density (calculated) (Mg/mm^3)	1.437	1.352
Absorption coefficient (mm^{-1})	3.682	3.443
F(000)	512	512
Crystal size (mm)	0.40 × 0.50 × 0.70	0.35 × 0.30 × 0.08
Theta range (°)	3.7 to 70.03	3.78 to 70.08
Index ranges	$-11 \le h \le 11$ $-13 \le k \le 13$ $-14 \le l \le 14$	$-12 \le h \le 12$ $-12 \le k \le 11$ $-14 \le l \le 14$
Reflections collected	12810	13665
Independent reflections	4131 [R(int) = 0.025]	4388 [R(int) = 0.0217]
Data completeness	95.8	95.9
Ratio of min. to max. apparent transmission	0.468	0.457
Data/restraints/ parameters	4131/0/378	4175/0/289
Goodness-of-fit on F^2	1.05	1.03
Final R indices [I>2sigma(I)]	R_1 = 0.0422 [4025]	R_1 = 0.0454 [4175]
R indices (all data)	R_1 = 0.0428, wR2 = 0.1186	R_1 = 0.0466, wR2 = 0.1380
w^{-1} where P = $(Fo^2+2Fc^2)/3$	$\sigma^2(Fo^2)+(0.0700P)^2+0.3546P$	$\sigma^2(Fo^2)+(0.0860P)^2+0.4045P$
Extinction coefficient	0.0087(7)	
Largest diff. peak and hole (eÅ^3)	−0.36, 0.38	−0.313, 0.523

*R1 = $\Sigma \; \|F_o\}-\}F_c\| / \Sigma |F_o\|$ and wR2 = $[\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^2)^2]^{1/2}$
Goof = $[\Sigma w(F_o^2 - F_c^2)^2 / (N_d - N_p)]^{1/2}$.
Rint = $\Sigma \; |F_o^2 - F_c^2 \text{ (mean)}| / \Sigma w F_o^2$.

179° and 168° have been found in only two other *ortho*-monosubstituted benzanilides,[16,17] while more often the angle is within the narrow range between 135° and 141°.[18–21] It is not surprising, that the angle C35-C34-N33-C32 is correlated with the N33-C34 bond length. The torsion angles below 141° correspond to longer N33-C34 distances (1.407 Å[21] and 1.426 Å,[19]) while the torsion angles above 168° correspond to the

shorter bonds (1.400 Å or less) indicating a partial conjugation of the π systems of the amide and the benzene ring. The only exceptions are the values found in the structure of piperidinoacetic acid *o*-chloroanilide[19] (1.409 Å and 167.7°). However, this structure has been refined only to R_1 of 11.2%.

Another interesting phenomenon is that in the crystal the molecules of the two compounds do not form *inter*molecular hydrogen bonds through their amide functions (Table II). Typically, amides (peptides) in *trans* configuration form strong *inter*molecular N-H···O=C hydrogen bonds, building a chain of hydrogen bonded molecules. However, a CSD search showed that among 16 crystal structures comprising the 2-chloro- or 2-methylacetanilide fragment similar to that present in **6n** and **6t**, the amide group in the majority of the cases (10) does not participate in hydrogen bonding,[22] contrary to the common conviction and in accord with our observation. A similar situation is observed in *ortho*-unsubstitutet anilides: among 240 known structures, in 101 of them the amide group does not participate in hydrogen bonding, and only 109 compounds form typical chain-like arrangements. In this study the NH donor group undergoes two weak *intra*molecular hydrogen bonds with the Cl substituent in *ortho* position of the phenyl ring and with N2 of the triazole ring (Figure 2, Table II). As a result, an access to the N-H group by a potential acceptor of another molecule is difficult, and the carbonyl group has to seek another donor. This role is taken over by H39, the acidic character of which is enhanced by two electron-withdrawing Cl substituents present in the aromatic ring (Figure 2).

The third interesting observation is a deformation of the C-S-C group (Figure 2). The values of S30–C(*alkyl*) bond length are about 1.81–1.82 Å as compared with the S30–C(*triazole*) bond length of about 1.75 Å (Table II), indicating the possibility of an easy S–CH_2 bond cleavage with a formation of the acetanilide and 1,2,4-triazoline-5-thione. Also the C3-S30-C31 angle (98.7° in **6n** and 99.7° in **6t**) differs significantly from the values found in the only two other crystal structures known containing an aryl-S-CH2-C(O)-NH-Ph fragment.[22] In *N*, *N*′-diphenyl-2,2'-(1,3,4-thiadiazolyl-2,5-dithio)diacetamide,[23] this angle is 100.6° and 101.4°, and in *N*-(2-hydroxy-5-chlorophenyl)thiophenylacetamide,[24] it is 103.2°. Obviously the smaller C—S—C values in the structures of **6n** and **6t** result from the N33-H..N2 *intra*molecular hydrogen bond (Figure 2).

MICROBIOLOGY

The triazolothione derivatives obtained were supposed to display a variety of biological activities, as previously mentioned. Tuberculostatic

activity was the only one tested at this stage. Tests were done in vitro with the classical test tube method on Youman's liquid medium containing 10% of bovine serum toward the standard *Mycobacterium tuberculosis* $H_{37}Rv$ strain, as well as toward two strains isolated from tuberculotic patients. One of them, Myc. species 210, was resistant to *p*-aminosalicylic acid (PAS), isonicotinic acid hydrazides (INH), ethambutol (EMB), and rifampycine (RFP); the other, Myc. species 192, was fully susceptible to the drugs administered.

The Minimum Growth Inhibiting Concentration (MIC) values obtained showed that the compounds tested were of only inconsiderable tuberculostatic activity. For the majority of the compounds tested, MIC values were within the limits 50–100 μg/mL, except for compounds **1b**, **4d**, and **5k**, having MIC values of 12.5–25 μg/mL as compared with 30–60 μg/mL for pyrazinamide, which was tested with the same method.

EXPERIMENTAL

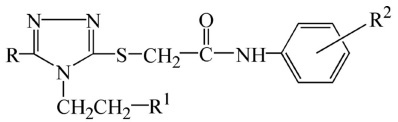
All melting points were obtained with a Boëtius apparatus and are uncorrected. The IR spectra were recorded with a Satellite spectrophotometer, and ^1H NMR spectra were recorded with a Tesla BS-487 spectrometer at 80 MHz in $CDCl_3$, CD_3OD, or DMSO-d_6, or with a Varian Gemini 200 spectrometer at 200 MHz in $CDCl_3$ or CD_3OD. The results of the elemental analyses (% C, H, and N) for all compounds obtained were in good agreement with the data calculated. Reaction yields and physical constants of the new compounds are given in Table I.

The syntheses of compounds **1a–c**, **2a–f**, **4a–c, 5a–e**, and **6a–e** were described elsewhere.[1]

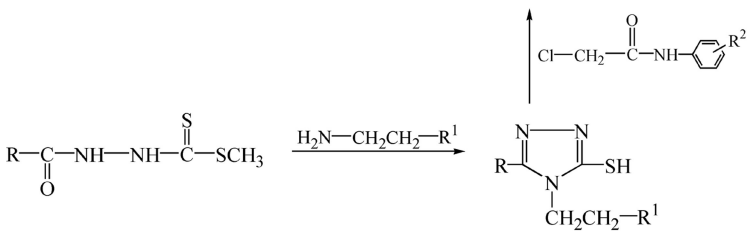
General Method for the Synthesis of 2-(4,5-Disubstituted-[1,2,4]-triazol-3-ylsulphanyl)-*N*-substituted Acetamides

Method A (1d–n, 2g–i)

The corresponding [1,2,4]-triazolo-3-thiol (1 mmol) was added to a solution of KOH (1.5 mmole, 84 mg) in methanol (6 mL). The respective *N*-substituted chloroacetamide (1 mmol) was added, and the mixture was refluxed for 7 h (**2a–c**) or stirred at ambient temperature for 8 days (**1a–c**). The end of the reaction was checked by TLC. The solvent was removed under reduced pressure, and the residue was treated with water (3–4 mL). The precipitated product was filtered and recrystallized (Table I).



For R, R^1, R^2: see Table I



1a–c, 2a–f, 3a, 4a–c, 5a–e, 6a–e,

R^1 \ R	Ph	2-Cl C_6H_4	3-Cl C_6H_4	4-Cl C_6H_4		
OH		**2a**				
CH_2OH		**2b**				
CH_2CH_2OH		**2c**				
OCH_3					**5a**	**6a**
CH_2OCH_3					**5b**	**6b**
$CH_2OC_2H_5$	**1a**	**2d**	**3a**	**4a**	**5c**	**6c**
piperidin	**1b**	**2e**		**4b**	**5d**	**6d**
morpholin	**1c**	**2f**		**4c**	**5e**	**6e**

SCHEME 1

Method B (3b–f, 4d–c, 5f–y, 6f–t)

Compound **3a**, **4a–c**, **5a–e** or **6a–e** (5 mmol) was dissolved in ethanol (7 mL) containing sodium ethanolate (5 mmol) and was treated with the corresponding chloroacetic acid *N*-arylamide (5 mmol). The reaction mixture was refluxed for 3 h; the end of the reaction was checked with TLC. The solvent was removed under reduced pressure, and the residue was treated with water (5 mL). The resulting precipitate was collected and recrystallized (Table I).

X-Ray Crystallography

Single crystals suitable for X-ray diffraction were obtained by slow evaporation of a methanolic solution. The diffraction data were collected on a Bruker SMART CCD diffractometer with Cu radiation at r.t. (ω scan) and corrected for absorption.[25] The structures were solved by direct methods[26] and refined by full-matrix least-squares.[27] Hydrogen atoms, although clearly visible on Fourier maps, were refined in riding positions with free isotropic thermal parameters. Details of data collection and refinement are summarized in Table III. Table II contains important geometric parameters.

Crystallographic data for the structures of **6n** and **6t** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 623525 and CCDC 623524. Copies of the data can be obtained free of charge by quoting the respective CCDC code numbers on application to Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk; http://www.ccdc.cam.ac.uk).

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