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SYNTHESIS AND TUBERCULOSTATIC ACTIVITY OF NOVEL 1,2,4-TRIAZOLES OBTAINED FROM HETEROCYCLIC CARBOHYDRAZIDES

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Abstract – The novel 1,2,4-triazole derivatives have been synthesized by a few different pathways. Heterocyclic carbohydrazides were used to obtain monoesters of hydrazine acids (**1**-**6**), thiosemicarbazide derivatives (**7**-**17**), and finaly 1,2,4-triazole-5-thiones (**18**-**38**). Carbohydrazides were also cyclized with methyl carbamodithioates in the presence of DBU giving 1,2,4-triazole-5-thiones (**18**, **19**, **39**-**47**). Two of final products (**39**, **40**) were undergone alkylation in alkaline solution to appropriate sulfides (**48**-**53**). Then methylsulfides (**48**, **49**) were oxidized with peroxyacetic acid to sulfoxides (**54**, **55**). The obtained compounds were tested in vitro towards *Mycobacterium tuberculosis*.

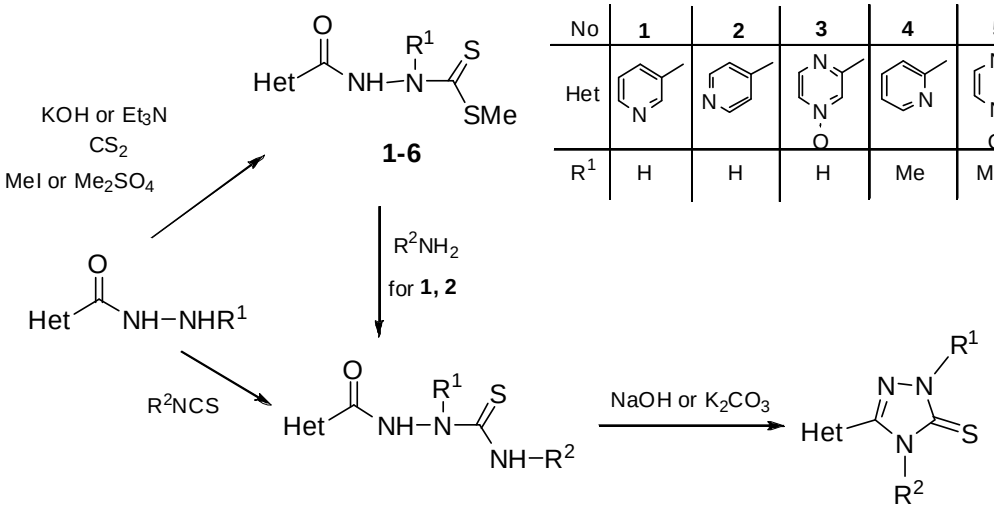
INTRODUCTION

Tuberculosis (TB) caused by Mycobacterium tuberculosis is one of the major global health issues.[1] The increasing emergence of drug-resistant TB, especially multidrug-resistant TB (MDR-TB and XDR-TB) are particularly alarming. MDR-TB and XDR-TB are highly lethal in people living with HIV, with case of fatality rates of over 90%. At the same time, there are not many drugs effective in TB chemotherapy. Among others isoniazide (INH), pyrazinamide (PZA), and morinamide (MZA) are the most popular frontline agents recommended in TB treatment.[2] Unfortunately, the most active therapeutics rapidly induce MDR and caused serious side effects such as hepatotoxicity, neurotoxicity, acute pancreatitis and hypersensitivity reactions.[3,4] Therefore, there is an urgent need for novel MDR-TB active and less toxic TB chemotherapeutic drugs. Our previous research works[5,6] as well as chemical literature[7,8] have

indicated that 1,2,4-triazole derivatives exhibit wide range of biological activity, inclusive tuberculostatic action. These observations prompted us to synthesize some new 1,2,4-triazole-5-thiones substituted in C-3 position with heterocyclic rings of 2-, 3-, 4-pyridine, 3-, 4-pyridine-*N*-oxide, 3-pyrazine-*N*-oxide, 2-pyrimidine, and 2-quinoline. Additionally, performed syntheses led to gain derivatives bearing among others cycloalkylamine substituents in N-4 position. Only two reports on that class of compounds have appeared up till now.[9,10]

RESULTS AND DISCUSSION

In this work, we investigate and compare few pathways of 1,2,4-triazole-5-thiones synthesis. The starting heterocyclic carbohydrazides and carbomethylhydrazides were obtained from methyl esters of carboxylic acids in a result of typical reactions described in the literature.[11,12] Carbohydrazides under treatment of CS_2 and dimethyl sulfate in ethanol – aqueous solution and of lye excess gave hydrazinecarbodithioic acid methyl esters (**1**-**3**) (Scheme 1).



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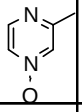
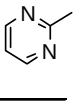
Het						
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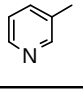
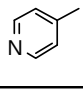
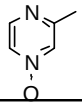
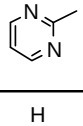
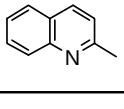
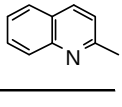
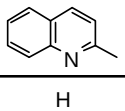
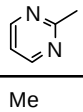
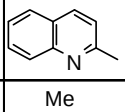
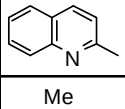
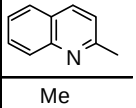
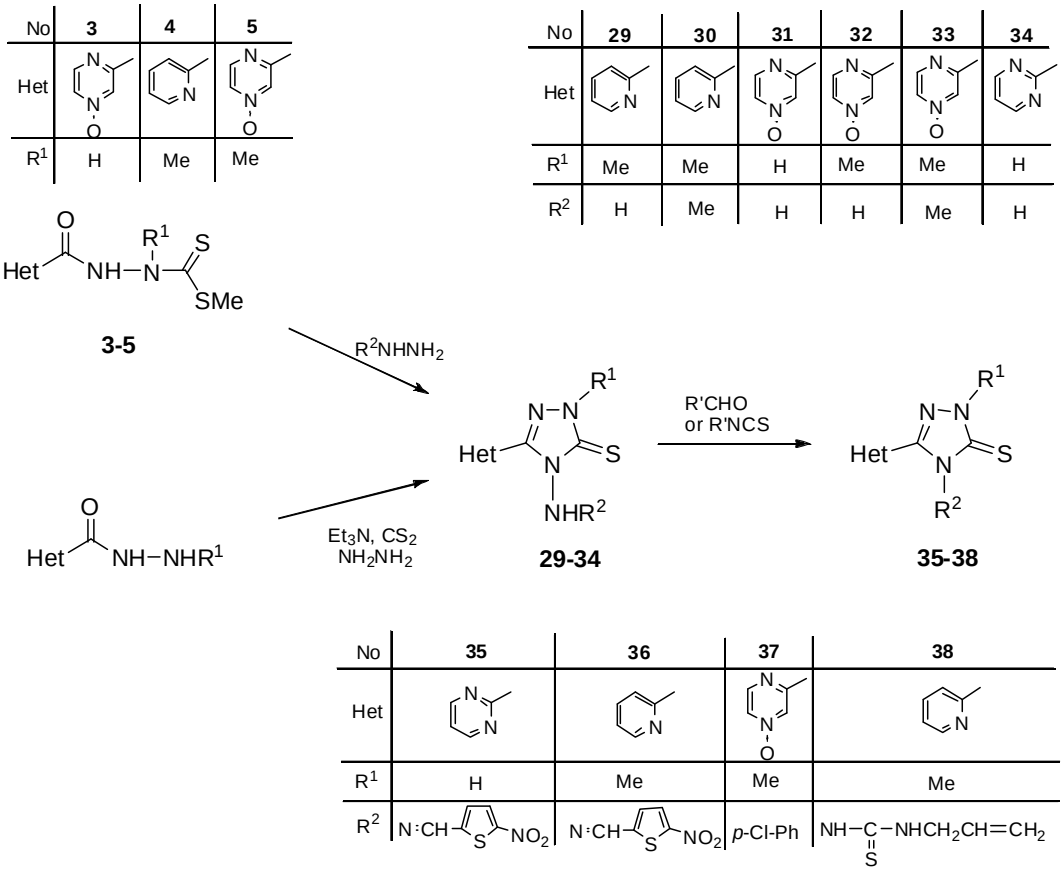
Het						
R^1	H	H	H	H	H	H
R^2				$CH_2CH{=}CH_2$	Me	$CH_2CH{=}CH_2$

No	13, 24	14, 25	15, 26	16, 27	17, 28
Het					
R^1	H	Me	Me	Me	Me
R^2	*p*-Cl-Ph	$CH_2CH{=}CH_2$	Me	$CH_2CH{=}CH_2$	*p*-Cl-Ph

Scheme 1

Those reactions occurred with good yields at room temperature. Because of acidic properties of unsubstituted sulfur atom products were isolated from alkaline solution by acidification with acetic acid. Usage of dimethyl sulfate protected that sulfur atom from methylation which occurred faster under influence of methyl iodide. That efficient reactant was used in the case of methylhydrazinecarbodithioates (**4**-**6**). Those reactions were performed in ethanol solution of triethylamine. In a reaction of methyl carbodithioates (**1**, **2**) with *N*-aminopiperidine in dry pyridine methyl mercaptane was eliminated and hydrazinecarbothioamides (**7**, **8**) of thiosemicarbazide structure were formed. That class of compounds was also obtained in direct reaction of started hydrazides with appropriate isothiocyanates: methyl, allyl, cyclohexyl, and 4-chlorophenyl. Those reactions occurred in 15 minutes with better yields than hydrazinecarbothioamides (**7**, **8**) synthesis. Condensations to thiosemicarbazides (**9**-**17**) were carried in neutral solvent like dioxane or DMF. The heating of thiosemicarbazide derivatives (**7**-**17**) in weak basic solution of 10% K_2CO_3 or 10% NaOH resulted cyclization and 1,2,4-triazole-5-thiones (**18**-**28**) were obtained. Because of weak acidic properties of the products isolation of derivatives (**20**-**24**) required acidification of reaction mixture with concentrated hydrochloric acid. Those syntheses enable to gain new class of 1,2,4-triazole-5-thiones bearing cycloalkylamine substituent in N-4 position.

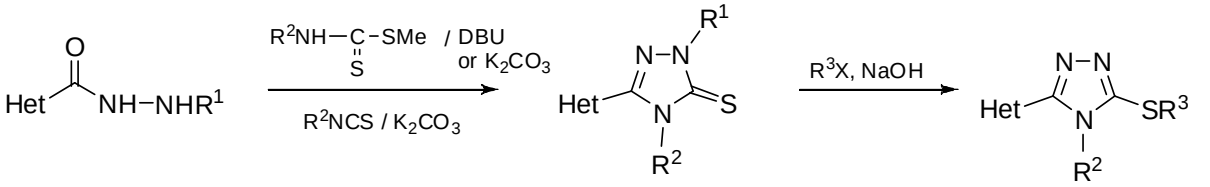
1,2,4-Triazole-5-thione structures (**29**-**33**) substituted with amine or methylamine group in N-4 position were synthesized by refluxing methyl carbodithioates (**3**-**5**) with hydrazine hydrate or methylhydrazine (Scheme 2).

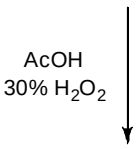


Scheme 2

Reactions required triple excess of appropriate hydrazine and were performed in various solvents: dioxane, ethanol, and water. The kind of the solvent had no distinct influence for reactions yield which was moderate and depended rather on the substrate structure. The best yield was gained for derivative (**31**) with pyrazine 1-oxide ring in C-3 position. Pyrimidine derivative (**34**) formed while refluxing of carbohydrazide with CS_2 and hydrazine hydrate in ethanol-aqueous solution of triethylamine. The yield of that direct reaction seemed to be a little better than acquired for compounds (**29**-**33**). Obtained 1,2,4-triazole-5-thione (**29**) was condensed with 5-nitro-2-thiophenecarboxaldehyde giving product (**36**). Analogical reaction for 1,2,4-triazole-5-thione (**34**) led to derivative (**35**). For 1,2,4-triazole-5-thione (**32**) condensation with 4-chlorobenzaldehyde result hydrazone derivative (**37**). All condensation reactions were ran fast with good yields in alcohol solution while few drops of acetic acid were added as a catalyst. 1,2,4-Triazole-5-thione (**29**) was also condensed with allyl isothiocyanate and hydrazinecarbothioamide (**38**) was obtained.

An alternative method of 1,2,4-triazole-5-thiones (**18**, **19** and also **39**-**44**, **46**) synthesis was cyclization of starting carbohydrazides with *N*-amino substituted carbamodithioic acid methyl esters in the presence of equimolar amount of DBU in dry pyridine (Scheme 3).





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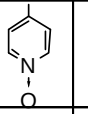
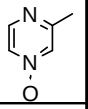
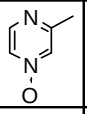
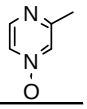
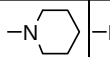
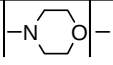
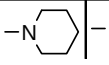
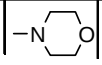
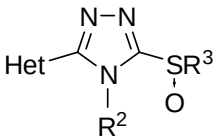
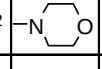
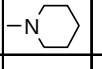
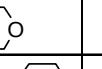
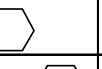
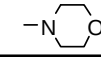
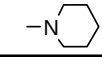
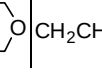
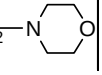
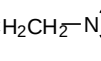
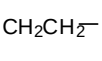
Het									
R^1	H	H	Me	Me	H	H	H	Me	H
R^2									CH_2-Ph

54, 55



No	48, 54	49, 55	50	51	52	53
Het						
R^2						
R^3	Me	Me				

Scheme 3

In spite of our expectation the yields of that reaction for compounds (**18**, **19**) were lower than for cyclization of appropriate thiosemicarbazides (**7**, **8**). Additionally they seem to be less comfortable because of pyridine usage.

It was also possible to carry cyclization of hydrazides with carbamodithioates using other basic environment. In the case of derivative (**45**) aqueous solution of K_2CO_3 and dioxane mixture was used. It had no influence on reaction yield which was also moderate. At the similar conditions 1,2,4-triazole-5-thione (**47**) was obtained with better yield in a result of condensation reaction between 3-(hydrazinecarbonyl)pyrazine 1-oxide and benzyl isothiocyanate. While lack of basic environment led to thiosemicarbazide structures of earlier described compounds (**9**-**17**).

Next, 1,2,4-triazole-5-thiones (**39**, **40**) were undergone an alkylation to appropriate sulfides with methyl iodide (**48**, **49**), 4-(2-chloroethyl)morpholine hydrochloride (**50**, **51**), and 1-(2-chloroethyl)pyrrolidine (**52**, **53**) in NaOH aqueous solution. Subsequent oxidation of methylsulfides (**48**, **49**) using an excess of 30% hydrogen peroxide and glacial acetic acid gave methylsulfoxides (**54**, **55**).

Some reactions described above such as formation of products (**8**, **27**, **30**, **33** and **42**) had rather low yields. Thin-layer chromatography analysis of those crude compounds indicated presence of some impurities perhaps products of side reactions. Those impurities have not been isolated and analyzed. Purification of main products by crystallization resulted in considerable loss of those compounds and low reaction yields.

The characteristics of newly synthesized compounds are given in Table1.

Table 1 Characteristics of the newly synthesized compounds

No	mp [ºC] Solvent	Yield [%]	Molecular formula MW	Elemental Analysis [%] Calcd/Found		
				C	H	N
1	159-160 MeOH/H_2O	69	$C_8H_9N_3OS_2$ 227.31	42.27 42.16	3.99 3.98	18.49 18.45
2	192-193 EtOH	85	$C_8H_9N_3OS_2$ 227.31	42.27 42.31	3.99 4.00	18.49 18.47
3	252-254 *decomp.* H_2O	73	$C_7H_8N_4O_2S_2$ 244.29	34.42 34.53	3.30 3.30	22.93 22.97
4	155-157 EtOH	60	$C_9H_{11}N_3OS_2$ 241.33	44.79 44.82	4.59 4.57	17.41 17.42
5	200-203 EtOH	80	$C_8H_{10}N_4O_2S_2$ 258.32	37.20 37.12	3.90 3.89	21.69 21.65
6	254-255 MeOH	25	$C_8H_{10}N_4OS_2$ 242.32	39.65 39.51	4.16 4.17	23.12 23.13
7	105-107 MeOH	45	$C_{12}H_{17}N_5OS$ 279.36	51.59 51.71	6.13 6.11	25.07 25.06
8	176-177 H_2O	9	$C_{12}H_{17}N_5OS$ 279.36	51.59 51.48	6.13 6.15	25.07 25.09

9	214-216 DMF/H_2O	88	$C_{12}H_{17}N_5O_2S$ 295.36	48.80 48.89	5.80 5.81	23.71 23.75
10	177-199 MeOH	88	$C_9H_{11}N_5OS$ 237.28	45.56 45.45	4.67 4.68	29.51 29.57
11	218-219 dioxane/MeOH	58	$C_{12}H_{12}N_4OS$ 260.31	55.37 55.48	4.65 4.66	21.52 21.57
12	187-188 EtOH	70	$C_{14}H_{14}N_4OS$ 286.35	58.72 58.51	4.93 4.94	19.57 19.56
13	177-179 dioxane/H_2O	66	$C_{17}H_{13}ClN_4OS$ 356.83	57.22 57.03	3.67 3.66	15.70 15.79
14	157-159 H_2O	75	$C_{10}H_{13}N_5OS$ 251.31	47.79 47.90	5.21 5.19	27.87 27.84
15	212-214 dioxane/MeOH	88	$C_{13}H_{14}N_4OS$ 274.34	56.91 57.05	5.14 5.13	20.42 20.45
16	187-188 MeOH	89	$C_{15}H_{16}N_4OS$ 300.38	59.98 60.10	5.37 5.39	18.65 18.69
17	179-180 dioxane/MeOH	93	$C_{18}H_{15}ClN_4OS$ 370.86	58.30 58.45	4.08 4.08	15.11 15.09
18	265-267 DMF/EtOH	A: 75 B: 45	$C_{12}H_{15}N_5S$ 261.35	55.15 54.99	5.79 5.77	26.80 26.87
19	263-264 EtOH	A: 69 B: 42	$C_{12}H_{15}N_5S$ 261.35	55.15 55.08	5.79 5.78	26.80 26.78
20	224-226 DMF/H_2O	43	$C_{12}H_{15}N_5OS$ 277.35	51.97 52.03	5.45 5.43	25.25 25.17
21	83-84 MeOH/H_2O	84	$C_9H_9N_5S$ 219.27	49.30 49.37	4.14 4.15	31.94 31.99
22	289-290 DMF/H_2O	88	$C_{12}H_{10}N_4S$ 242.30	59.48 59.43	4.16 4.16	23.12 23.08
23	237-239 dioxane/H_2O	90	$C_{14}H_{12}N_4S$ 268.34	62.66 62.48	4.51 4.52	20.88 20.92
24	105-106 H_2O	86	$C_{10}H_{11}N_5S$ 233.29	51.48 51.47	4.75 4.76	30.02 30.05
25	241-243 dioxane/H_2O	82	$C_{17}H_{11}ClN_4S$ 338.81	60.26 60.13	3.27 3.28	16.54 16.52
26	237-239 dioxane/MeOH	93	$C_{13}H_{12}N_4S$ 256.33	60.91 60.87	4.72 4.71	21.86 21.91
27	125-127 dioxane/H_2O	25	$C_{15}H_{14}N_4S$ 282.36	63.80 63.85	5.00 5.01	19.84 19.87
28	208-210 dioxane/MeOH	93	$C_{18}H_{13}ClN_4S$ 352.84	61.27 61.11	3.71 3.70	15.88 15.84
29	162-164 EtOH	34	$C_8H_9N_5S$ 207.26	46.36 46.51	4.38 4.37	33.79 33.78
30	85-87 H_2O	19	$C_9H_{11}N_5S$ 221.28	48.85 48.95	5.01 5.02	31.65 31.68
31	191-193 H_2O	44	$C_6H_6N_6OS$ 210.22	34.28 34.19	2.88 2.87	39.98 39.91
32	166-167 H_2O	43	$C_7H_8N_6OS$ 224.24	37.49 37.51	3.60 3.61	37.48 37.52
33	100-102 cyclohexane	16	$C_8H_{10}N_6OS$ 238.27	40.33 40.21	4.23 4.24	35.27 35.25
34	167-169 H_2O	53	$C_6H_6N_6S$ 194.22	37.10 37.18	3.11 3.10	43.27 43.21

35	196-199 EtOH	64	$C_{13}H_9ClN_6S$ 316.77	49.29 49.34	2.86 2.86	26.53 26.51
36	188-190 EtOH	65	$C_{13}H_{10}N_6O_2S_2$ 346.39	45.08 45.12	2.91 2.90	24.26 24.28
37	195-198 DMF/H_2O	71	$C_{12}H_9N_7O_3S_2$ 363.37	39.66 39.72	2.50 2.49	26.98 26.91
38	182-185 MeOH	87	$C_{12}H_{14}N_6S_2$ 306.41	47.04 47.08	4.61 4.60	27.43 27.48
39	243-245 H_2O	67	$C_{11}H_{13}N_5OS$ 263.32	50.14 50.09	4.98 4.99	26.60 26.63
40	105-108 MeOH/H_2O	33	$C_{12}H_{15}N_5S$ 261.35	55.15 55.08	5.79 5.43	26.80 26.77
41	179-180 MeOH	52	$C_{12}H_{15}N_5OS$ 277.35	51.97 52.02	5.45 5.43	25.25 25.28
42	123-125 MeOH	25	$C_{13}H_{17}N_5S$ 275.37	56.70 56.77	6.22 6.21	25.43 25.41
43	273-275 EtOH	80	$C_{11}H_{13}N_5OS$ 263.32	50.17 50.07	4.98 4.99	26.60 26.58
44	290-292 EtOH	65	$C_{11}H_{13}N_5O_2S$ 279.32	47.30 47.34	4.69 4.68	25.07 25.09
45	218-220 H_2O	46	$C_{10}H_{12}N_6O_2S$ 280.31	42.85 42.89	4.32 4.34	29.98 29.96
46	219-221 EtOH	39	$C_{11}H_{14}N_6O_2S$ 294.33	44.89 44.85	4.79 4.77	28.55 28.53
47	157-159 EtOH	71	$C_{13}H_{11}N_5OS$ 285.32	54.72 54.68	3.89 3.90	24.55 24.57
48	172-175 MeOH/H_2O	37	$C_{12}H_{15}N_5OS$ 277.35	51.97 51.89	5.45 5.47	25.25 25.27
49	95-98 H_2O	55	$C_{13}H_{17}N_5S$ 275.37	56.70 56.74	6.22 6.20	25.43 25.41
50	118-120 H_2O	60	$C_{17}H_{24}N_6O_2S$ 376.48	54.23 54.28	6.43 6.44	22.32 22.29
51	108-110 H_2O	62	$C_{18}H_{26}N_6OS$ 374.50	57.73 57.70	7.00 7.02	22.44 22.46
52	95-98 H_2O	40	$C_{14}H_{24}N_6OS$ 360.48	56.64 56.67	6.71 6.70	23.31 23.35
53	88-90 H_2O	62	$C_{18}H_{26}N_6S$ 358.50	60.30 60.32	7.31 7.33	23.44 23.41
54	188-190 H_2O	32	$C_{12}H_{15}N_5O_2S$ 293.34	49.13 49.07	5.15 5.16	23.87 23.80
55	120-122 H_2O	31	$C_{13}H_{17}N_5OS$ 291.37	53.59 53.49	5.88 5.88	24.04 24.10

Tuberculostatic activity

The new synthesized derivatives were examined for their tuberculostatic activity towards the *Mycobacterium tuberculosis* $H_{37}Rv$ strain and two "wild" strains from tubeculotic patients: one (Spec. 210) resistant to p-aminosalicilic acid (PAS), isonicotinic acid hydrazide (INH), etambutol (ETB), and rifampicine (RFP); another (Spec. 192) fully sensitive to the administrated drugs. In vitro investigations

were performed by a classical test-tube method of successive dilution with Youman's liquid medium containing 10% of bovine serum.[13]

The determined minimum concentrations (MIC) inhibiting the growth of tuberculous strains for all the tested 1,2,4-triazole derivatives were within the limits 50-100 μg/mL, which indicates low antituberculosis activity. Although obtained 1,2,4-triazoles exhibited low tuberculostatic activity might be useful for further syntheses of tuberculostatic drugs. They are also planed to be tested with regard to other biological action.

Unexpectedly the most active compound appeared intermediate methyl hydrazinecarbodithioate (**3**). The MICs for that compound were 15.6 μg/mL ($H_{37}Rv$) and 31.2 μg/mL (Spec. 192). Compound (**3**) exhibited low activity against resistant strain (Spec. 210), MIC 100 μg/mL. Those interesting results demands farther syntheses and structure – activity relationship analysis for that class of chemical compounds.

EXPERIMENTAL

All materials and solvents were of analytical reagent grade. Thin-layer chromatography was performed on Merck silica gel $60F_{254}$ plates and visualized with UV. The results of elemental analyses (% C, H, N) for all of obtained compounds were in agreement with calculated values within ± 0.3% range. ^{1}H NMR spectra in $CDCl_3$ or DMSO-d_6 were recorded on Varian Unity Plus (500 MHz) and Varian Gemini (200 MHz) instruments. IR Spectra (KBr) were determined as KBr pellets of the solids on a Satellite FT-IR spectrophotometer. Mass spectra for compound **31** was taken on Finingan MAT 95 (15 eV). Melting points were determined on BOETIUS apparatus and were uncorrected.

Methyl carbamodithiates required for further syntheses were obtained by the method described earlier[10] and followed after Podgornaya and co-workers.[12]

Methyl 2-carbonylhydrazinecarbodithioates (1-3). In the solution of 12.3 g (0.22 mole) of KOH in water (40 mL) and EtOH (40 mL) 0.1 mole of appropriate carbohydrazide was dissolved. Then 7.2 mL (0.12 mole) of CS_2 was added. The mixture was stirred at room temperature for 15 min and 4.7 mL (0.05 mole) of dimethyl sulfate was added. The solution was stirred for 30 min and 150 g of ice was added. Then mixture was acidified with AcOH. Precipitate was filtered, washed with water and dried.

Methyl 2-nicotinoylhydrazinecarbodithioate (1). IR: 3156, 2961, 1644, 1595, 1521, 1303, 1047, 1025, 694, 559 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.55 (s, 3H, SCH_3), 7.59 (m, 1H, pyridine), 8.30 (m, 1H, pyridine), 8.76 (m, 1H, pyridine), 8.87 (m, 1H, pyridine), 10.08 (s, 1H, NH), 10.85 (s, 1H, NH) ppm.

Methyl 2-isonicotinoylhydrazinecarbodithioate (2). IR: 3225, 2954, 1693, 1463, 1361, 1271, 1063, 1032, 755, 694, 591, 499 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.58 (s, 3H, SCH_3), 7.86 (d, 2H, pyridine, J = 6.5 Hz), 8.82(d, 2H, pyridine, J = 6.5 Hz), 9.52 (s, 1H, NH), 10.26 (s, 1H, NH) ppm.

3-[2-(Methylthiocarbonothioyl)hydrazinecarbonyl]pyrazine 1-oxide (3). IR: 3302, 3078, 1676, 1590,

1450, 1008, 855, 576 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6 + TFA) δ: 3.25 (s, 3H, SCH_3), 8.20 - 8.80 (m, 3H, pyrazine 1-oxide), 10.15 (s, 1H, NH), 11.25 (s, 1H, NH) ppm.

Methyl 1-methyl-2-carbonylhydrazinecarbodithioates (4-6). Appropriate *N′*-methylcarbohydrazide (0.1 mole) was dissolved in 80 mL of EtOH. Then 17 mL (0.12 mole) of Et_3N and 7.2 mL (0.12 mole) of CS_2 were added. The solution was stirred at room temperature for 15 min and 7.5 mL (0.12 mole) of methyl iodide was added. Then mixture was stirred for 1 h and 150 g of ice was added. Precipitate was filtered, washed with cold water and dried.

Methyl 1-methyl-2-picolinoylhydrazinecarbodithioate (4). IR: 3302, 2925, 1686, 1462, 1420, 1357, 1101, 746, 605 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.56 (s, 3H, SCH_3), 3.82 (s, 3H, NCH3), 7.52 - 7.58 (m, 1H, pyridine), 7.89-7.97 (m, 1H, pyridine), 8.22 (d, 1H, pyridine, J = 7.9 Hz), 8.62 (m, 1H, pyridine), 10.11 (s, 1H, NH) ppm.

3-(2-Methyl-2-(methylthiocarbonothioyl)hydrazinecarbonyl)pyrazine 1-oxide (5). IR: 3264, 3073, 1698, 1497, 1336, 1123, 1011, 850, 569 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6 + TFA) δ: 3.11 (s, 3H,SCH_3), 3.95 (s, 3H, NCH_3), 8.60 - 8.90 (m, 3H, pyrazine 1-oxide), 10.08 (s, 1H, NH) ppm.

Methyl 1-methyl-2-(pyrimidine-2-carbonyl)hydrazinecarbodithioate (6). IR: 3172, 2913, 1704, 1568, 1505, 1410, 1361, 1096, 958, 634 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.58 (s, 3H, SCH_3), 3.85 (s, 3H, NCH_3), 7.56 (t, 1H, pyrimidine, J = 5 Hz), 8.97 (d, 2H, pyrimidine, J = 5 Hz), 10.03 (s, 1H, NH) ppm.

Hydrazinecarbothioamides (7, 8). In 5 mL of pyridine 2.3 g (0.01 mole) of methyl hydrazinecarbodithioate (**1**, **2**) was dissolved and 1.6 mL (0.01 mole) of 1-aminopiperidine was added. The mixture was refluxed for 1 h. Then solvent was evaporated and 5 g of ice was added. The mixture was acidified with AcOH and precipitate was filtered, washed with water and dried.

2-Nicotinoyl-*N*-(piperidin-1-yl)hydrazinecarbothioamide (7). IR: 2938, 2827, 1680, 1530, 1320, 1249, 1034, 908, 781, 704 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.18 (m, 2H, CH_2), 1.58 (m, 4H, $2CH_2$), 3.15 (m, 4H, $2NCH_2$), 7.62 (m, 1H, pyridine), 8.25 (s, 1H, NH), 8.75 (m, 1H, pyridine), 8.99 (m, 1H, pyridine), 9.90 (s, 1H, NH), 11.20 (s, 1H, NH) ppm.

2-Isonicotinoyl-*N*-(piperidin-1-yl)hydrazinecarbothiamide (8). IR: 1698, 1677, 1520, 1485, 1311, 1244, 994, 754 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.15 (m, 2H, CH_2), 1.59 (m, 4H, $2CH_2$), 2.93 (m, 4H, $2NCH_2$), 7.85 (d, 2H, pyridine, J = 6.5 Hz), 8.40 (s, 1H, NH), 8.84 (d, 2H, pyridine, J = 6.5 Hz), 9.20 (s, 1H, NH), 10.00 (s, 1H, NH) ppm.

3-(2-(Cyclohexylcarbamothioyl)hydrazinecarbonyl)pyrazine 1-oxide (9).

3-(Hydrazinecarbonyl)pyrazine 1-oxide (0.39 g, 2.5 mmole) and cyclohexyl isothiocyanate (0.35 mL, 2.5 mmole) were refluxed in 5 mL of DMF for 15 min. The mixture was cooled and 40 mL of water was added. Precipitate was filtered, washed with water and dried. IR: 3280, 2923, 1703, 1600, 1524, 1323,

1003, 864, 550 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6 + TFA) δ: 0.85-2.50 (m, 11 H, cyclohexyl), 8.48 (s, 1H, NH), 8.53 - 8.82 (m, 1H, pyrazine 1-oxide), 9.55 (m, 2H, pyrazine 1-oxide), 9.81 (s, 1H, NH), 11.10 (s, 1H, NH) ppm.

Thiosemicarbazides (10, 14). Appropriate carbohydrazide or *N*'-methylcarbohydrazide (5 mmole) was added to 5 mL of dioxane. Suspension was heated until substrate was dissolved and 0.44 mL (5 mmole) of allyl isothiocyanate was added. The mixture was refluxed for 15 min, then cooled. Precipitate was filtered and dried. In the case of compound **10** the mixture of 5 mL of dioxane and 5 mL of MeOH was used as a solvent. Precipitation of product **14** was induced by 30 mL of petroleum ether addition.

***N*-Allyl-2-(pyrimidine-2-carbonyl)hydrazinecarbothioamide (10).** IR: 3333, 3272, 1704, 1541, 1409, 1295, 1177, 634 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 4.10 (s, 2H, CH_2), 5.10 (2H, m, CH_2), 5.80 (m, 1H, CH), 7.71 (t, 1H, pyrimidine, J = 5 Hz), 8.20 (s, 1H, NH), 8.99 (d, 2H, pyrimidine, 9.49 (s, 1H, NH), 10.72 (s, 1H, NH) ppm.

***N*-Allyl-1-methyl-2-(pyrimidine-2-carbonyl)hydrazinecarbothioamide (14).** IR: 3297, 3056, 2918, 1704, 1534, 1487, 1411, 1341, 1171, 1096, 944 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 3.48 (s, 3H, NCH_3), 4.07 (s, 2H, CH_2), 5.06 (m, 2H, CH_2), 5.80 (m, 1H, CH), 7.75 (t, 1H, pyrimidine, J = 5 Hz), 8.30 (s, 1H, NH), 9.01 (d, 2H, pyrimidine, J = 5 Hz), 11.15 (s, 1H, NH) ppm.

Thiosemicarbazides (11-13, 15-17). Quinoline-2-carbohydrazide (0.47 g, 2.5 mmole) and appropriate isothiocyanate were dissolved in 5 mL of dioxane. Mixture was heated to boiling and left at room temperature for 1 h. Then 30 mL of Et_2O was added, precipitate was filtered, washed with Et_2O and dried.

***N*-Methyl-2-(quinoline-2-carbonyl)hydrazinecarbothioamide (11).** IR: 3336, 3204, 1676, 1548, 1494, 1423, 1264, 1078, 841, 774 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 2.86 (s, 3H, CH_3), 7.65 – 8.63 (m, 7H, 6H quinoline and 1H NH), 9.44 (s, 1H, NH), 10.33 (s, 1H, NH) ppm.

***N*-Allyl-2-(quinoline-2-carbonyl)hydrazinecarbothioamide (12).** IR: 3335, 3269, 3165, 1693, 1555, 1476, 1306, 1142, 780 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 4.30 (m, 2H, CH_2), 5.20 (m, 2H, CH2), 5.90 (m, 1H, CH), 6.85 (s, 1H, NH), 7.40 – 8.40 (m, 7H, 6H quinoline and 1H NH), 10.03 (s, 1H, NH) ppm.

***N*-(4-Chlorophenyl)-2-(quinoline-2-carbonyl)hydrazinecarbothioamide (13).** IR: 3322, 3217, 3161, 1688, 1534, 1493, 1351, 1092, 925, 837, 772 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 7.30 - 8.60 (m, 10H, 6H quinoline and 4H Ph), 9.86 (s, 1H, NH), 9.95 (s, 1H, NH), 10.95 (s, 1H, NH) ppm.

***N*,1-Dimethyl-2-(quinoline-2-carbonyl)hydrazinecarbothioamide (15).** IR 3322, 3162, 2936, 1687, 1540, 1491, 1427, 1343, 1292, 1075, 840, 777, 681, 623 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.14 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 6.73 (s, 1H, NH), 7.54 – 8.50 (m, 6H, quinoline), 10.04 (s, 1H, NH) ppm.

***N*-Allyl-1-methyl-2-(quinoline-2-carbonyl)hydrazinecarbothioamide (16).** IR: 3327, 3193, 3056, 2975, 2918, 1690, 1528, 1490, 1381, 1333, 1162, 1093, 926, 841, 777, 678 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$)

δ: 3.77 (s, 3H, CH_3), 4.32 (m, 2H, CH_2), 5.10 – 5.26 (m, 2H, CH_2), 5.85 (m, 1H, CH), 6.69 (s, 1H, NH), 7.65 – 8.45 (m, 6H, quinoline), 9.93 (s, 1H, NH) ppm.

***N*-(4-Chlorophenyl)-1-methyl-2-(quinoline-2-carbonyl)hydrazinecarbothioamide (17).** IR: 3292, 2925, 2854, 1686, 1507, 1427, 1339, 1086, 1024, 830, 775, 729 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.83 (s, 3H, CH_3), 6.83 (s, 1H, NH), 7.30 – 8.46 (m, 10H, 6H quinoline and 4H Ph), 10.00 (s, 1H, NH) ppm.

1,2,4-Triazole-5-thiones (18, 19). *Method A.* Appropriate thiosemicarbazide (**7**, **8**) (0.2 g, 0.7 mmole) was refluxed with K_2CO_3 (1 g, 7 mmole) in 5 mL of water for 3 h. Mixture was cooled and acidified with AcOH. Precipitate was filtered, washed with water and dried.

Method B. Appropriate pyridinecarbohydrazide (1.4 g, 10 mmole) and methyl piperidin-1-ylcarbamodithioate (1.9 g, 10 mmole) were dissolved in 6 mL of dry pyridine. Then 1.5 mL (10 mmole) of DBU was added. Mixture was refluxed for 3h. Then solvent was evaporated and 5 g of ice was added to residue. Water solution was acidified with AcOH, precipitate was filtered, washed with water and dried.

4-(Piperidin-1-yl)-3-(pyridin-3-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (18). IR: 2938,2855, 1555, 1415, 1188, 1029, 947, 801, 742, 695 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 1.72 (m, 2H, CH_2), 3.05 (m, 4H, $2CH_2$), 4.36 (m, 4H, $2NCH_2$), 7.50 (q, 1H, pyridine, J_1 = 7.5 Hz, J_2 = 4.5 Hz), 8.22 (d, 1H, pyridine, J = 7.5), 8.71 (d, 1H, pyridine, J = 4.5 Hz), 8.93 (s, 1H, pyridine), 13.90 (s, 1H, NH) ppm.

4-(Piperidin-1-yl)-3-(pyridin-4-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (19). IR: 2855, 1611, 1574, 1426, 1314, 1292, 1216, 1007, 954, 827, 625, 538 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 1.10 – 1.75 (m, 2H, CH_2), 3.05 (m, 4H, $2CH_2$), 4.37 (m, 4H, $2NCH_2$), 7.85 (d, 2H, pyridine, J = 6.6 Hz), 8.76 (d, 2H, J = 6.5 Hz), 13.60 (s, 1H, NH) ppm.

1,2,4-Triazole-5-thiones (20-24). Appropriate thiosemicarbazide (**9**, **10**, **12-14**) (1 mmole) was refluxed in 10 mL of 10% aqueous NaOH for 2 h. Then solution was cooled and acidified with concentrated HCl. Precipitate was filtered, washed with cold water and dried.

3-(4-Cyclohexyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyrazine 1-oxide (20). IR: 2923, 1583, 1440, 1183, 912 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6 + TFA) δ: 0.95-2.60 (m, 11H, cyclohexyl), 8.80 (m, 3H, pyrazine 1-oxide), 14.08 (s, 1H, NH) ppm.

4-Allyl-3-(pyrimidin-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (21). IR: 3407, 3160, 2925, 2735, 1569, 1447, 1388, 1273, 1197 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 5.16 (m, 2H, CH_2), 5.41 (d, 2H, NCH_2, J = 4.5 Hz), 5.98 (m, 1H, CH), 7.44 (t, 1H, pyrimidine, J = 5 Hz), 8.97 (d, 2H, pyrimidine, J = 5 Hz), 12.62 (s, 1H, NH) ppm.

4-Methyl-3-(quinolin-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (22). IR: 3448, 3015, 2927, 1600, 1493,

1341, 1278, 965, 833,761 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 4.04 (s, 3H, CH3), 7.60 – 8.60 (m, 6H, quinoline), 14.21 (s, 1H, NH) ppm.

4-Allyl-3-(quinolin-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (23). IR: 3095, 3010, 2925, 1597, 1459, 1360, 1271, 997, 832, 757 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 5.10 (m, 2H, CH_2), 5.40 (d, 2H, CH_2, J = 5.4 Hz), 6.00 (m, 1H, CH), 7.65 – 8.56 (m, 6H, quinoline), 14.31 (s, 1H, NH) ppm.

4-(4-Chlorophenyl)-3-(quinolin-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (24). IR: 3099, 2922, 1596, 1497, 1342, 1280, 1096, 833, 760 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 7.28 (d, 1H, quinoline, J = 8.3 Hz), 7.37 (d, 2H, Ph, J = 8.7 Hz), 7.53 (d, 2H, Ph, J = 8.7 Hz), 7.58 (t, 1H, quinoline, J = 6.8 Hz), 7.69 (t, 1H, quinoline, J = 6.8 Hz), 7.95 (d, 1H, quinoline, J = 8.3 Hz), 8.08 (d, 1H, quinoline, J = 8.8 Hz), 8.43 (d, 1H, quinoline, J = 8.8 Hz), 14.24 (s, 1H, NH) ppm.

4-Allyl-1-methyl-3-(pyrimidin-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (25). Thiosemicarbazide (**11**) (0.25 g, 1 mmole) was refluxed in the mixture of 5 mL of 10% aqueous K_2CO_3 and 3 mL of EtOH for 30 min. Then mixture was concentrated and 5 g of ice was added. Precipitate was filtered, washed with water and dried. IR: 3446, 2941, 1562, 1465, 1349, 1296, 1209, 931, 814 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.98 (s, 3H, NCH_3), 5.19 (m, 2H, CH_2), 5.42 (d, 2H, NCH_2, J = 5 Hz), 5.98 (m, 1H, CH), 7.43 (t, 1H, pyrimidine, J = 5 Hz), 8.91 (d, 2H, pyrimidine, J = 5 Hz) ppm.

1,2,4-Triazole-5-thiones (26-28). Appropriate thiosemicarbazide (**15-17**) (1 mmole) was refluxed in 10 mL of 2M aqueous NaOH for 15 min. Ten mixture was cooled and precipitate was filtered, washed with water and dried.

1,4-Dimethyl-3-(quinolin-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (26). IR: 3051, 2935, 1476, 1452, 1405, 1358, 1171, 1065, 876, 763 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.96 (s, 3H, CH_3), 4.28 (s, 3H, CH_3), 7.62 – 8.32 (m, 6H, quinoline) ppm.

4-Allyl-1-methyl-3-(quinolin-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (27). IR: 3103, 2929, 1600, 1470, 1423, 1341, 1063, 965, 833, 762 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.96 (s, 3H, NCH_3), 5.18 – 5.30 (m, 2H, CH_2), 5.60 (d, 2H, CH_2, J = 5.8 Hz), 6.1 (m, 1H, CH), 7.60 – 8.30 (m, 6H, quinoline) ppm.

4-(4-Chlorophenyl)-1-methyl-3-(quinolin-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (28). IR: 3034, 2925, 1595, 1407, 1345, 1099, 1088, 834, 760 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 4.01 (s, 3H, NCH_3), 7.30 – 8.26 (m, 10H, 6 H quinoline and 4H Ph) ppm.

4-Amino-1-methyl-3-(pyridine)-1*H*-1,2,4-triazole-5(4*H*)-thione (29). In the mixture of 6 mL of dioxane and 4 mL of EtOH 2.1 g (9 mmole) of methyl hydrazinecarbodithioate (**3**) was dissolved. Then 1 mL (0.02 mole) of hydrazine hydrate was added. Reaction mixture was refluxed for 2 h, then cooled. Precipitate was filtered, washed with cooled EtOH and dried. IR: 3212, 1682, 1611, 1466, 1317, 1122, 941, 790 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 3.89 (s, 3H, NCH_3), 6.19 (s, 2H, NH_2), 7.41 – 7.47 (m, 1H,

pyridine), 7.88 (q, 1H, pyridine, J_1 = 7.8 Hz, J_2 = 6.4 Hz), 8.08 (d, 1H, pyridine, J = 7.9 Hz), 8.71 (t, 1H, pyridine, J = 4.9 Hz) ppm.

1-Methyl-4-(methylamino)3-(pyridine-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (30). Methyl hydrazinecarbodithioate (**3**) (2.2 g, 9 mmole) was dissolved in 10 mL of dioxane and 2.1 g (0.04 mole) of methylhydrazine was added. The mixture refluxed for 2 h, then cooled and 5 mL of water was added. Precipitate was filtered after cooling, washed with water and dried. IR: 3224, 2963, 1462, 1446, 1397, 1337, 789 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.87 (s, 3H, NCH_3), 3.88 (s, 3H, $NHC\underline{H}_3$), 6.03 (s, 1H, NH), 7.44 (t, 1H, pyridine, J = 6.2 Hz), 7.87 (t, 1H, pyridine, J = 7.7 Hz), 8.16 (d, 1H, pyridine, J = 7.7 Hz), 8.74 (d, 1H, pyridine, J = 4.1 Hz) ppm.

3-(4-Amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyrazine 1-oxide (31). Methyl hydrazinecarbodithioate (**4**) (1.2 g, 5 mmole) was suspended in 5 mL of water and 1 mL (0.032 mole) of hydrazine hydrate was added. Mixture was refluxed for 6 h, then cooled and acidified with concentrated HCl. Precipitate was filtered, washed with cold water and dried. IR: 3276, 1584, 1504, 1453, 1325, 1020, 960 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 6.25 (s, 2H, NH_2), 8.80 (m, 2H, pyrazine 1-oxide), 9.45 (s, 1H, pyrazine 1-oxide), 14.05 (s, 1H, NH) ppm. MS (15 eV): 210 (100), 194 (75.72), 106 (14.82).

1,2,4-Triazole-5-thiones (32, 33): 1.3 g (5 mmole) of methyl hydrazinecarbodithioate (**5**) was suspended in 5 mL of water and 0.31 mL (10 mmole) of hydrazine hydrate or 0.53 mL (10 mmole) of methylhydrazine was added. Mixture was refluxed for 5 h, then cooled. Precipitate was filtered, washed with water and dried.

3-(4-Amino-1-methyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyrazine 1-oxide (32). IR: 3143, 1601, 1463, 1325, 1015, 857 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 2.88 (s, 3H, NCH_3), 6.28 (s, 2H, NH_2), 8.75 (m, 2H, pyrazine 1-oxide), 9.43 (d, 1H, pyrazine 1-oxide, J = 7.6 Hz) ppm.

3-(1-Methyl-4-(methylamino)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyrazine 1-oxide (33). IR: 3234, 1510, 1457, 1342, 1015, 880 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 2.90 (s, 3H, NCH_3), 3.91 (s, 3H, $NHC\underline{H}_3$), 6.05 (s, 1H, NH), 8.73 (d, 1H, pyrazine 1-oxide, J = 7.7 Hz), 9.41 (m, 1H, pyrazine 1-oxide) ppm.

4-Amino-1-methyl-3-(pyrimidin-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (34).

Pyrimidine-2-carbohydrazide (0.7 g, 5 mmole) was added to the mixture consisted of EtOH (15 mL), water (2 mL), Et_3N (1.8 mL, 12 mmole) and CS_2 (0.5 mL, 8 mmole). Then 0.5 mL (15 mmole) of hydrazine hydrate was added. Mixture was refluxed for 4 h, then concentrated. Residue was diluted with water (20 mL) and acidified with AcOH. IR: 3273, 3181, 1567, 1484, 1286, 1143, 1014 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 6.29 (s, 2H, NH_2), 7.69 (t, 1H, pyrimidine, J = 5 Hz), 9.02 (d, 2H, pyrimidine, J = 5 Hz), 12.03 (s, 1H, NH) ppm.

Hydrazones (35-37). Appropriate 1,2,4-triazole-5-thione (**29**, **32**, **34**) (2 mmole) was dissolved in 20 mL of MeOH, 2.5 mmole of aldehyde and 3 drops of acetic acid were added. Mixture was refluxed for 1 h, then cooled. Precipitate was filtered, washed with cold MeOH and dried.

4-[(Nitrothiphen-2-yl)methyleneamino]-3-(pyrimidin-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (35). IR: 3184, 2963, 1488, 1240, 1084, 1010, 823, 787 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 7.50 - 8.90 (m, 7H, 3H pyrimidine and 4H Ph), 10.15 (s, 1H, CH), 12.65 (s, 1H, NH) ppm.

1-Methyl-4-((nitrothiophen-2-yl)methyleneamino)-3-(pyridin-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (36). IR: 1533, 1504, 1465, 1344, 1321, 1215 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 3.84 (s, 3H, NCH_3), 6.32 (s, 1H, thiophene), 7.59 (q, 1H, thiophene, J = 6.3 Hz, J = 4.9 Hz), 7.93 (t, 1H, pyridine, J = 4.4 Hz), 8.04 (m, 1H, pyridine), 8.21 (m, 1H, pyridine), 8.73 (q, 1H, pyridine, J = 4.9 Hz), 10.11 (s, 1H, CH) ppm.

3-(4-(4-Chlorophenyl)-1-methyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyrazine 1-oxide (37). IR: 1507, 1344, 1208, 816, 731 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 3.84 (s, 3H, CH_3), 7.95 (d, 1H, thiophene, J = 4 Hz), 8.20 (d, 1H, thiophene, J = 4 Hz), 8.84 (s, 1H, pyrazine), 9.13 (s, 2H, pyrazine), 10.26 (s, 1H, CH) ppm.

1-Allyl-3-(1-methyl-3-(pyridine-2-yl)-5-thioxo-1*H*-1,2,4-triazol-4(5*H*)-yl)thiourea (38).

1,2,4-Triazole-5-thione (**30**) (0.5 g, 2.4 mmole) and allyl isothiocyanate (0.53 mL, 5 mmole) dissolved in 5 mL of EtOH were refluxed for 1.5 h, then cooled. Precipitate was filtered, washed with cooled EtOH and dried. IR: 3114, 2985, 2895, 1571, 1525, 1450, 1342, 1286, 1182 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 3.92 (s, 3H, NCH_3), 5.15 - 5.22 (m, 2H, NCH_2), 5.49 (d, 2H, CH_2, J = 6 Hz), 5.76 – 5.92 (m, 1H, CH), 7.49-7.55 (m, 1H, pyridine), 7.90-8.15 (m, 3H, 2H pyridine and 1H NH), 8.73 (d, 1H, pyridine, J = 4.1 Hz) ppm.

1,2,4-Triazole-5-thiones (39, 40). Picolinohydrazide (1.4 g, 10 mmole) and appropriate methyl carbamodithioate (10 mmole) were dissolved in 6 mL of dry pyridine and 1.5 mL (10mmole) of DBU was added. The mixture was refluxed for 48 h and concentrated. Then 20 mL of water was added and solution was acidified with AcOH. Precipitate was filtered, washed with cold water and dried.

4-Morpholino-3-(pyridine-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (39). IR: 3090, 3048, 2924, 2857, 1560, 1499, 1460, 1448, 1322, 1291, 1277, 1108, 915, 799 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.06 (s, 2H, NCH_2), 3.63 (s, 2H, NCH_2), 3.93 (d, 2H, OCH_2, J = 12.7 Hz), 4.69 (s, 2H, OCH_2), 7.45 (t, 1H, pyridine, J = 4.4 Hz), 7.88 (m, 2H, pyridine), 8.81 (s, 1H, pyridine), 11.58 (s, 1H, NH) ppm.

4-(Piperidin-1-yl)-3-(pyridine-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (40). IR: 2934, 2855, 1546, 1501, 1451, 1412, 1300, 1283, 1252, 966, 786 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.40 - 1.79 (m, 6H, $3CH_2$), 3.10 (s, 2H, NCH_2), 4.50 (s, 2H, NCH_2), 7.27 – 7.44 (m, 2H, pyridine), 7.85- 8.02 (m, 1H, pyridine), 8.83

(s, 1H, pyridine), 11.89 (s, 1H, NH) ppm.

1,2,4-Triazole-5-thiones (41, 42). *N*'-Methylpicolinohydrazide (1.5 g, 10 mmole) and appropriate methyl carbamodithioate (10 mmole) were dissolved in 6 mL of dry pyridine. Then 1.5 mL (10 mmole) of DBU was added and mixture was refluxed for 2.5 h. Solvent was evaporated and 20 mL of water was added to the residue. Precipitate was filtered, washed with water and dried.

1-Methyl-4-morpholino-3-(pyridine-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (41). IR: 3004, 2967, 2838, 1587, 1472, 1447, 1380, 1330, 1265, 1207, 1107, 845, 791 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.97 (d, 2H, NCH_2, J = 10.4 Hz), 3.48 – 3.67 (m, 2H, NCH_2), 3.83 (s, 3H, NCH_3), 3.96 (d, 2H, OCH_2, J = 11.2 Hz), 4.75 - 4.86 (m, 2H, OCH_2), 7.44-7.51 (m, 1H, pyridine), 7.88 – 7.98 (m, 2H, pyridine), 880 (d, 1H, pyridine, J = 4.5 Hz) ppm.

1-Methyl-4-(piperidin-1-yl)-3-(pyridine-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (42). IR: 3098, 3054, 2930, 2865, 1646, 1587, 1482, 1431, 1407, 1330, 1208, 1091, 788 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.33 - 1.80 (m, 6H, $3CH_2$), 3.05 (d, 2H, NCH_2, J = 9.3), 3.84 (s, 3H, NCH_3), 4.57 (t, 2H, NCH_2, J = 11 Hz), 7.48 (m, 1H, pyridine), 7.90 (m, 1H, pyridine), 8.10 (d, 1H, pyridine, J = 7.8 Hz), 8.82 (d, 1H, pyridine, J = 4.4 Hz) ppm.

1,2,4-Triazole-5-thiones (43, 44). These compounds were obtained according to *method B* described for derivatives (**18**, **19**) from 10 mmole of appropriate hydrazide and 1.9 g (10 mmole) of methyl morpholinocarbamodithioate. In the case of compound (**44**) refluxing time was extended to 6 h.

4-Morpholino-3-(pyridine-4-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (43). IR: 2850, 2361, 1607, 1575, 1423, 1295, 1113, 832 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 3.03 (m, 2H, NCH_2), 3.45 (m, 2H, NCH_2), 3.85 (m, 2H, OCH_2), 4.76 (m, 2H, OCH_2), 7.85 (d, 2H, pyridine, J = 6.6 Hz), 8.76 (d, 2H, pyridine, J = 6.5 Hz), 14.12 (s, 1H, NH) ppm.

4-(4-Morpholino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridine 1-oxide (44). IR: 1517, 1452, 1404, 1322, 1236, 1182, 1107, 952, 842 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6 + TFA) δ: 3.03 (m, 2H, NCH_2), 3.54 (m, 2H, CH_2), 3.86 (m, 2H, OCH_2), 4.60 (m, 2H, OCH_2), 7.94 (d, 2H, pyridine 1-oxide, J = 6.1 Hz), 8.30 (d, 2H, pyridine 1-oxide, J = 6.1 Hz), 14.08 (s, 1H, NH) ppm.

4-(4-Morpholino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyrazine 1-oxide (45). The mixture of 0.77 g (5 mmole) of 3-(hydrazinecarbonyl)pyrazine 1-oxide, 0.96 g (5 mmole) of methyl morpholinocarbamodithiate, 10 mL of 10% aqueous K_2CO_3 and 10 mL of dioxane was refluxed for 12 h. Then solvent was evaporated and the residue was diluted with 20 mL of water. Solution was acidified with acetic acid and product precipitated. Solid was filtered, washed with cold water and dried. IR: 3134, 2977, 2855, 1687, 1592, 1450, 1105, 976 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6 + TFA) δ: 3.02 (s, 2H, NCH_2), 3.65 (s, 2H, NCH_2), 3.95 (d, 2H, OCH_2, J = 11.5 Hz), 4.65 (s, 2H, OCH_2), 8.30 - 8.70 (m, 3H,

pyrazine 1-oxide), 14.02 (s, 1H, NH) ppm.

4-(1-Methyl-4-morpholino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyrazine 1-oxide (46). Synthesis was performed according to method described for derivatives (**41**, **42**) from 1.7 g (10 mmole) of 3-(2-methylhydrazinecarbonyl)pyrazine 1-oxide and 1.9 g (10 mmole) of methyl morpholinocarbamodithioate. Refluxing time was extended to 6 h. IR: 2853, 1444, 1384, 1325, 1107, 846 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 3.09 (s, 2H, NCH_2), 3.62 (s, 2H, NCH_2), 3.82 (s, 3H, NCH_3), 3.95 (d, 2H, OCH_2, J = 12.7 Hz), 4.62 (s, 2H, OCH_2), 8.20 - 8.80 (m, 3H, pyrazine 1-oxide) ppm.

3-(4-Benzyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyrazine 1-oxide (47).
3-(Hydrazinecarbonyl)pyrazine 1-oxide (0.38 g, 2.5 mmole) was dissolved in 15 mL of 5% aqueous K_2CO_3 and 0.31 mL (2.5 mmole) of benzyl isothiocyanate was added. Mixture was refluxed for 3 h, then cooled and acidified with AcOH. Precipitate was filtered, washed with water and dried. IR: 3079, 1591, 1477, 1264, 916, 722 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6 + TFA) δ: 5.12 (s, 2H, $NC\underline{H}_2Ph$), 7.21-7.40 (m, 5H, Ph), 8.32-8.75 (m, 3H, pyrazine 1-oxide), 14.03 (s, 1H, NH) ppm.

Methylsulfides (48, 49). In 10 mL of 1M NaOH appropriate 1,2,4-triazole-5-thione (**41**, **42**) (1 g, 3.6 mmole) was dissolved. Then 0.31 mL (5 mmole) of methyl iodide in 2 mL of EtOH was added. Mixture was stirred at room temperature for 2 h. Precipitate was filtered, washed with water and dried. IR: 3079, 1591, 1477, 1264, 916, 722 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 5.12 (s, 2H, $NC\underline{H}_2Ph$), 7.21 - 7.40 (m, 5H, Ph), 8.32-8.75 (m, 3H, pyrazine 1-oxide), 14.03 (s, 1H, NH) ppm.

4-(3-(Methylthio)-5-(pyridin-2-yl)-4*H*-1,2,4-triazol-4-yl)morpholine (48). IR: 2966, 2923, 1579, 1448, 1434, 1270, 1104, 919, 790 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.74 (s, 3H, SCH_3), 2.89 (d, 2H, NCH_2, J = 10 Hz), 3.76 - 4.10 (m, 6H, 2H NCH_2 and 4H OCH_2), 7.37 (q, 1H, pyridine, J_1 = 7.3 Hz, J_2 = 5.4 Hz), 7.84 (t, 1H, pyridine, J = 7.8 Hz), 8.25 (d, 1H, pyridine, J = 7.8 Hz), 8.74 (d, 1H, pyridine, J = 3.9 Hz) ppm.

2-(5-(Methylthio)-4-(piperidin-1-yl)-4*H*-1,2,4-triazol-3-yl)pyridine (49). IR: 2942, 2924, 2861, 1586, 1439, 1425, 1104, 1026, 795 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 1.62 (d, 6H, CH_2, J = 8.6 Hz), 2.61 (s, 3H, NCH_3), 2.95 (d, 2H, NCH_2, J = 7.8 Hz), 3.54 (t, 2H, NCH_2, J = 9.3 Hz), 7.53 (t, 1H, pyridine, J = 5.9 Hz), 8.00 (m, 2H, pyridine), 8.76 (d, 1H, pyridine, J = 3.9 Hz) ppm.

Sulfides (50-53). In 5 mL of 2M NaOH appropriate 1,2,4-triazole-5-thione (**41**, **42**) (0.55 g, 2 mmole) was dissolved. Then 2 mmole of 4-(2-chloroethyl)morpholine hydrochloride or 1-(2-chloroethyl)-pyrrolidine hydrochloride was added. The mixture was stirred at room temperature for 12 h. Precipitate was filtered, washed with water and dried.

4-(2-(4-Morpholino-5-(pyridine-2-yl)-4*H*-1,2,4-triazol-3-ylthio)ethyl)morpholine (50). IR: 2958, 2931, 2855, 1584, 1443, 1426, 1267, 1113, 1003, 791 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.64 (s, 4H, $2NCH_2$),

2.88 (s, 4H, $2OCH_2$), 3.48 (t, 2H, SCH_2, J = 6.9 Hz), 3.78-4.11 (m, 10H, $4NCH_2$ and $2OCH_2$), 7.35 (q, 1H, pyridine,J_1 = 5.2 Hz, J_2 = 6.9 Hz), 7.80 (m, 1H, pyridine), 8.20 (d, 1H, pyridine, J = 7.8 Hz), 8.72 (d, 1H, pyridine, J = 4.4 Hz) ppm.

4-(2-(4-(Piperidin-1-yl)-5-(pyridine-2-yl)-4*H*-1,2,4-triazol-3-ylthio)ethyl)morpholine (51). IR: 2941, 2856, 1586, 1441, 1420, 1305, 1265, 1141, 1115 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.31-1.71 (m, 6H, $3CH_2$), 2.62 (s, 4H, $2OCH_2$), 2.84-3.01 (m, 4H, CH_2 and NCH_2), 3.45 (t, 2H, NCH_2, J = 6.9 Hz), 3.71 (m, 6H, $3CH_2$), 7.30 (m, 1H, pyridine), 7.79 (m, 1H, pyridine), 8.15 (d, 1H, pyridine, J = 7.9 Hz), 8.68 (d, 1H, J = 4.3 Hz) ppm.

4-(3-(Pyridine-2-yl)-5-(2-(pyrrolidin-1-yl)ethylthio)-4*H*-1,2,4-triazol-4-yl)morpholine (52). IR: 2953, 2921, 2855, 2790, 1585, 1442, 1426, 1111, 914, 979 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.87 (s, 4H, $2CH_2$), 2.90 (m, 8H, $3NCH_2$ and SCH_2), 3.50 (t, 2H, NCH_2, J = 6.3 Hz), 3.85 (m, 4H, OCH_2), 4.07 (s, 2H, NCH_2), 7.36 (t, 1H, pyridine, J = 4.9 Hz), 7.81 (t, 1H, pyridine, J = 7.3 Hz), 8.22 (d, 1H, pyridine, J = 7.8 Hz), 8.73 (d, 1H, pyridine, J = 3.9 Hz) ppm.

2-(4-(Piperidin-1-yl)-5-(2-(pyrrolidin-1-yl)ethylthio)-4*H*-1,2,4-triazol-3-yl)pyridine (53). IR: 2935, 2855, 2793, 1585, 1439, 11420, 1289, 794 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.30-1.84 (m, 10H, $5CH_2$), 2.72 (s, 4H, NCH_2), 3.00 (m, 4H, NCH_2 and SCH_2), 3.52 (m, 4H, $2NCH_2$), 7.30 (t, 1H, pyridine, J = 5.7 Hz), 7.78 (t, 1H, pyridine, J = 7.1 Hz), 8.14 (d, 1H, pyridine, J = 7.7 Hz), 8.67 (d, 1H, pyridine, J = 2.8 Hz) ppm.

Methylsulfoxides (54, 55). Appropriate 1,2,4-triazole (**48**, **49)** (1 mmole) was dissolved in 3 mL of glacial acetic acid. Then 3 mL of 30% H_2O_2 was added. Mixture was heated at 50 °C for 3 h. Then solution was cooled and alkalized with saturated aqueous solution of $NaHCO_3$ and extracted with $CHCl_3$. Organic fractions were collected and dried with $MgSO_4$. Then solvent was evaporated and residue was washed with dry Et_2O and dried.

4-(3-(Methylsulfinyl)-5-(pyridine-2-yl)-4*H*-1,2,4-triazol-4-yl)morpholine (54). 2962, 2927, 2869, 1586, 1439, 1103, 1046, 916, 792 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.45 (s, 2H, NCH_2), 2.91 (d, 2H, NCH_2, J = 5.5 Hz), 3.28 (s, 3H, SCH_3), 3.88 (t, 4H, OCH_2, J = 5.9 Hz), 7.45 (m, 1H, pyridine), 7.89 (m, 1H, pyridine), 8.32 (m, 1H, pyridine), 8.80 (m, 1H, pyridine) ppm.

2-(5-(Methylsulfinyl)-4-(piperidin-1-yl)-4*H*-1,2,4-triazol-3-yl)pyridine (55). IR: 2943, 2881, 2855, 1585, 1439, 1330, 1157, 1108, 952, 793, 555, 503 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.34-1.85 (m, 6H, $2NCH_2$), 3.17-3.50 (m, 2H, NCH_2), 3.52 (s, 3H, SCH_3), 3.73 (t, 2H, NCH_2, J = 10 Hz), 7.48 (m, 1H, pyridine), 7.87-7.95 (m, 1H, pyridine), 8.27 (d, 1H, pyridine, J = 8.0 Hz), 8.79 (d, 1H, pyridine, J = 4.8 Hz) ppm.

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