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SYNTHESIS AND TUBERCULOSTATIC ACTIVITY OF NOVEL DIVERSE HETEROCYCLIC COMPOUNDS DERIVED FROM HETEROCYCLIC CARBOHYDRAZIDES AND METHYL 2-HETEROAROYLHYDRAZINECARBODITHIOATES

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Abstract – A series of 1,3,4-oxadiazole-2-thiones (**4**, **5**), 2-methylthio-1,3,4-thiadiazoles (**15**, **16**) and 1,2,4-triazole-3-thiones (**17-32**) have been synthesized using high reactivity of various methyl 2-heteroaroylhydrazinecarbodithioates, that underwent cyclization in alkaline or acidic solution. Reaction of 4-(2-(methylthiocarbonothioyl)hydrazine) carbonyl)pyridine 1-oxide with morpholine led to 4-(5-morpholino-1,3,4-oxadiazol-2-yl)pyridine 1-oxide (**11**). 2-Methylthio- 1,3,4-oxadiazoles (**12-14**) were obtained by the methylation of 1,3,4-oxadiazole-2-thiones (**1**, **4**, **5**) in alkaline solution. 1,2,4-Triazole-3-thiones (**21-23**, **31**) obtained in reaction with aminoalcohols gave 1,2,4-triazolo[3,4-*b*][1,3]thiazines when refluxed in conc. HCl. The obtained compounds were tested *in vitro* towards *Mycobacterium tuberculosis* standard strain ($H_{37}Rv$) and two "wild" strains, susceptible (Spec. 192) and resistant (Spec. 210).

INTRODUCTION

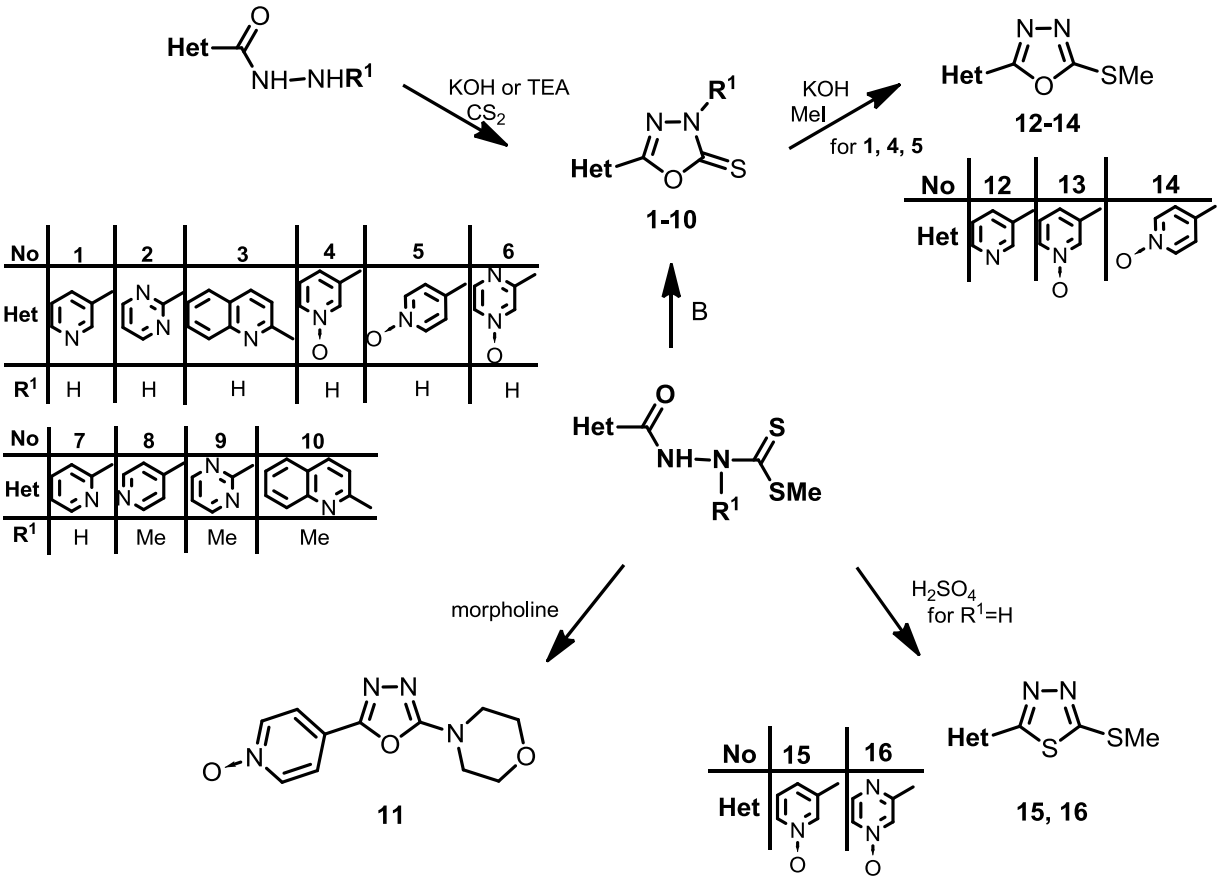
Tuberculosis (TB) seems to be one of the deadliest infectious disease.[1] The increasing emergence of multidrug-resistant TB (MDR-TB),[2] especially among HIV-positive patients,[3] toxicity of administrated chemotherapeutics[4] and lack of the new effective drugs in TB treatment[5] caused an urgent need for novel

MDR-TB active and less toxic chemotherapeutic agents. Most of the administrated drugs belong to the group of nitrogen heterocyclic compounds.[6] Isoniazid (INH) and pyrazinamide (PZA) containing pyridine and pyrazine rings are the most commonly applied agents.[7] That is why potential antituberculous drugs are searched for in this chemical group. Chemical literature[8-10] as well as our previous research works[11,12] demonstrated that nitrogen heterocyclic five-membered systems like 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles also exhibit antituberculous activity. One strategy of drug development is to combine different active structural fragments with each other in one molecule, each of which acts in an independent manner with the relevant molecular target.[13] In this way it is possible to get double or even synergistic effect of the drug. These findings prompt us to extend our studies on the development of novel tuberculostatic agents. We have demonstrated earlier that methyl hydrazine-carbodithioates are perfect starting material for the synthesis of those heterocyclic systems.[14,15] The main goal of this work is the synthesis of 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles fused with heterocyclic systems of 2-, 3-, 4-pyridine, 2-pyrimidine, 2-quinoline, 3- and 4-pyridine 1-oxide and 3-pyrazine 1-oxide using corresponding 2-hetroaroyl-hydrazinecarbodithioates.

RESULTS AND DISCUSSION

The respective carbohydrazides were the starting materials for syntheses carried out. These compounds were reflux with potassium hydroxide to carbon disulfide in an aqueous-ethanol solution giving the potassium salts of 1,3,4-oxadiazoles, and finally 1,3,4-oxadiazole-2(3*H*)-thiones (**1**-**6**) after acidification of the reaction mixture (Scheme 1). *N*′-Methylcarbohydrazides refluxed with an equimolar amount of CS_2 in an ethanol solution of triethylamine (TEA) also cyclized to corresponding 3-methyl-1,3,4-oxadiazole-2(3*H*)-thiones (**9**, **10**). In contrast, 1,3,4-oxadiazole-2(3*H*)-thiones (**7**, **8**) were obtained from respective methyl 2-hetroaroyl-hydrazinecarbodithioates when refluxed with *N*-aminomorpholine in pyridine (**7**) or with morpholine alone (**8**). 1,3,4-Oxadiazole-2(3*H*)-thiones (**4**, **5**) that are derivatives of 3- and 4-pyridine 1-oxides have been also synthesized by an alternative method from the corresponding carbonyl-hydrazinecarbodithioates that synthesis we described in the previous article.[16] Refluxing of these compounds with morpholine in EtOH led to the formation of mentioned 1,3,4-oxadiazole-2(3*H*)-thiones (**4**, **5**). Neither of two presented method of synthesis was significantly more efficient. Derivatives of 2- and 3-pyridine (**1**, **7**) have been previously obtained and described by Pancechowska-Ksepko and co-workers.[11] Methyl carbonyl-hydrazinecarbodithioate, derived from 4-pyridine 1-oxide, when refluxed with morpholine alone underwent substitution and cyclization to 1,3,4-oxadiazole (**11**) with morpholine substituent in C-2 position, however the yield of this reaction was negligible (9%). 1,3,4-Oxadiazole-2(3*H*)-thiones (**1**, **4**, **5**) were then methylated with methyl iodide in a water-ethanol solution of KOH to give the corresponding 2-methylsulfides (**12**-**14**).

3-Pyridine 1-oxide- and 3-pyrazine 1-oxide-derived methyl 2-heteroaroylhydrazinecarbodithioates under the influence of conc. H_2SO_4 cyclized giving the corresponding 2-methylthio-1,3,4-thiadiazole-2(3*H*)-thiones (**15**, **16**).

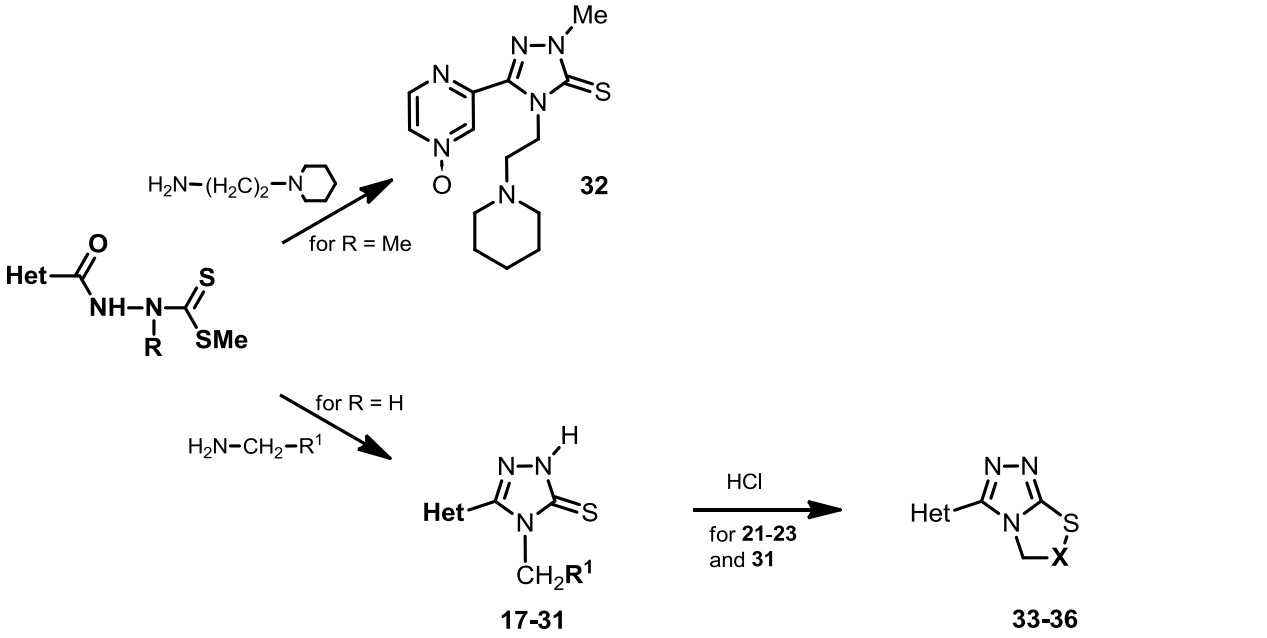


B (basic solution): *N*-aminomorpholine in pyridine or TEA in Et OH or morpholine in EtOH or morpholine alone

Scheme 1

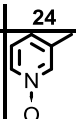
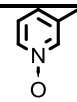
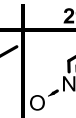
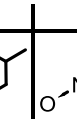
Methyl carbonyl-hydrazinecarbodithioates, 3-pyridine, 4-pyridine, 3-pyridine 1-oxide, 4-pyridine 1-oxide and 3-pyrazine 1-oxide derivatives, were used for the synthesis of 1,2,4-triazole-5(4*H*)-thiones (**17**-**31**) (Scheme 2). The compounds were treated with aminoalcohols (2-aminoethanol, 3-aminopropan-1-ol, 1-aminopropan-2-ol, 3-aminopropane-1,2-diol) or 2-cycloalkylaminoalkylamines (2-(pyrrolidin-1-yl)-ethanamine, 2-morpholinoethanamine, 2-(piperidin-1-yl)ethanamine) to yield corresponding 4-hydroksyalkyl- (**17**-**19**, **21**-**24**, **28**-**31**) and 4-cycloalkylaminoalkyl-1,2,4-triazole-5-(4*H*)-thiones (**20**, **25**-**27**). Analogical reaction for 3-pyrazine 1-oxide derivative with 2-(piperidin-1-yl)ethanamine was carried to result in 1-methyl-1,2,4-triazole-5(4*H*)-thione (**32**). Reactions occurred as a result of direct thioester refluxing in an excess of the corresponding amines with methyl mercaptan liberation. Only the reaction with 2-aminoethanol completed successfully for the 3-pyrazine 1-oxide derivative (product **31**).

The reaction with the other aminoalcohols, conducted in similar conditions, proceeded with the hydrolytic decomposition of an amide bond. 3-Carboxypyrazine 1-oxide was the reaction product (mp 212-213 °C, according to the literature).[17] The resulting 1,2,4-triazole-5(4*H*)-thiones (**21**-**23**, **31**) were then subjected to cyclization in conc. HCl to result the respective triazolo[3,4-*b*][1,3]thiazines (**33**-**36**).



No	17	18	19	20	21	22	23
Het							
R^1	CH_2OH	$(CH_2)_2OH$	CH(OH)Me		$(CH_2)_2OH$	CH(OH)Me	$CH(OH)CH_2OH$

No	33	34	35	36
Het				
X	$(CH_2)_2$	CHMe	$CH(OH)CH_2$	CH_2

No	24	25	26	27	28	29	30	31
Het								
R^1	CH_2OH				CH_2OH	$(CH_2)_2OH$	CH(OH)Me	CH_2OH

Scheme 2

Described reactions proceeded with moderate yields. The syntheses of 1,2,4-triazole-5(4*H*)-thiones (**17**-**21**) were the most efficient (74-99%). Extremely low yields were obtained for the synthesis of products (**11**, **27**, **36**) (9, 6 and 7% respectively). Thin-layer chromatography analysis of those crude compounds indicated presence of some impurities perhaps products of side reactions or decomposition. Those impurities have not been isolated and analyzed. Purification of main products resulted in considerable loss of those impurities and very low reaction yields.

The newly synthesized compounds were characterized by the IR and NMR spectra as well as the elemental analysis listed in experimental section. The spectral analyses were in accordance with the assigned structures.

Tuberculostatic activity

The newly synthesized 1,3,4-oxadiazole-2(3*H*)-thiones (**2**-**5**, **7**, **9**, **10**), 2-substituted 1,3,4-oxadiazoles (**11**-**14**), 2-methylthio-1,3,4-thiadiazole (**15**), 1,2,4-triazole-5(4*H*)-thiones (**17**-**30**) and triazolo[3,4-*b*][1,3]-thiazines (**33**-**35**) were examined *in vitro* for their tuberculostatic activity against *Mycobacterium tuberculosis* H_{37}Rv strain and two "wild" strains isolated from tuberculosis patients: one (Spec. 210) resistant to *p*-aminosalicylic acid (PAS), isonicotinic acid hydrazide (INH), etambutol (ETB) and rifampicine (RMP) and the another (Spec. 192) fully sensitive to the administered tuberculostatics. Investigations were performed by a classical test-tube method of a successive dilution in Youmans modification of Proskauer and Beck's liquid medium containing 10% of bovine serum.[18,19] Bacterial suspensions were prepared from 14-days-old cultures of slowly growing strains and from 48-hours-old cultures of saprophytic strains.[20,21] Solutions of compounds in ethylene glycol were tested. Stock solutions contained 10 mg of compounds in one millilitre. Dilutions (in a geometric progression) were prepared in Youmans' medium. The medium containing no investigated substances and containing isoniazid (INH) or pyrazinamide (PZA) as reference drug were used for comparison.

The results of tuberculostatic activity indicated that most of the title compounds showed rather low activity against tested strains *in vitro* and were definitely less active than isoniazid (INH) and pyrazinamide (PZA) used as reference drugs (Table 1). The MIC values for the majority of the tested compounds were ranged from 50 to 100 μg/mL, from 0.5 to 1.1 μg/mL for INH and from 25 to 40 μg/mL for PZA. There were no differences in sensitivity to tested compounds between sensitive 192 and resistant 210 strain. Six compounds, 1,3,4-oxadiazole-5(4*H*)-thione (**4**) with 3-pyridine 1-oxide in C-2 position, 2-morpholine-1,3,4-oxadiazole (**11**) and 1,2,4-triazole-5(4*H*)-thiones (**17**, **18**, **21**, **29**) with hydroxyalkyl substituents in N-4 position, exhibited a little bit higher tuberculostatic activity *in vitro*. The MIC values for these compounds were 25-50 μg/mL. Interestingly, in the case of 1,2,4-triazole-5(4*H*)-thiones (**21**, **29**), that are 4-pyridine and 4-pyridine 1-oxide derivatives, obtained MIC values indicated higher compounds' activity towards resistant strain 210 (25 μg/mL) than sensitive one 192 (50 μg/mL). 1,3,4-Oxadiazole-2(3*H*)-thiones (**5**, **7**) with 2-pyridine or 4-pyridine 1-oxide systems in C-5 position showed the highest activity in the group of tested compounds. The MIC values determined for these compounds were 12.5-25 μg/mL against sensitive strain 192, 12.5-50 μg/mL against the standard H_{37}Rv strain, and 25-50 μg/mL against resistant 210 strain. These results confirmed antimycobacterial activity of

1,3,4-oxadiazoles *in vitro* as described in literature.[8,9] Therefore, further studies of this group of compounds appear to be interesting.

In summary, a series of 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles have been synthesized successfully using high reactivity of various heterocyclic methyl carbonylhydrazinecatrbodithioates, that underwent cyclization in alkaline or acidic solution. 1,2,4-Triazole-3-thiones obtained in reaction with aminoalcohols gave 1,2,4-triazolo[3,4-*b*][1,3]thiazines when refluxed in conc. HCl. The obtained compounds exhibited low activity *in vitro* towards *M. tuberculosis*. The most active compound was 4-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)pyridine 1-oxide (**5**) that inhibited growth of mycobacterial strains in the concentration range 12.5-25 μg/mL.

Table 1. *In vitro* tuberculostatic activity of the newly synthesized compounds [a, b, c]

No	MIC *[μg/mL]*			No	MIC *[μg/mL]*		
	$H_{37}Rv$	Spec. 192	Spec. 210		$H_{37}Rv$	Spec. 192	Spec. 210
2	100	100	100	**21**	**50**	**50**	**25**
4	**50**	**50**	**25**	**22**	50	50	50
5	**12.5**	**25**	**25**	**23**	50	50	50
7	**50**	**12.5**	**50**	**24**	50	50	50
9	50	100	100	**25**	50	50	50
10	50	50	50	**26**	50	100	50
11	**25**	**50**	**50**	**27**	50	50	50
12	50	50	50	**28**	50	50	50
13	100	100	100	**29**	**50**	**50**	**25**
14	50	50	50	**30**	50	50	50
15	100	100	50	**33**	50	50	50
17	25	50	50	**34**	100	100	50
18	25	50	50	**35**	50	100	25
19	50	50	50	**INH**	0.5	0.5	1.1
20	50	50	50	**PZA**	25	25	40

[a]Minimum inhibitory concentrations for bacterial strains were determined by two-fold serial dilution method for microdilution plates and for mycobacterial strains by two-fold classical test-tube method of successive dilution.
[b]**INH** isoniazid, **PZA** pyrazinmide.
[c]*M. tuberculosis* $H_{37}Rv$, Spec. 192, Spec. 210.

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 the 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 Gemini (200 MHz) instrument (Varian, Palo Alto, CA). IR Spectra were determined as KBr pellets of the solids on a Satellite FT-IR spectrophotometer (Mattson

Instruments, Madison, WI). Mass spectrum for compound (**16**) was taken on Finningan MAT 95 spectrometer (ThermoFisher Scientific, Waltham, MA) (15 eV). Melting points were determined with Boethius apparatus (Franz Küstner Nachf. KG, Dresden, Germany) and were uncorrected. Methyl 2-carbonylhydrazinecarbodithioates required for further syntheses were obtained according to the method described earlier by Gobis and co-workers.[18] 5-(Pyridine-3-yl)-1,3,4-oxadiazole-2(3*H*)-thione (**1**) was synthesized by the method described earlier.[11] The reaction yield and compound characteristics were found to be identical with those described (mp 234-236 °C).

General method for the synthesis of 1,3,4-oxadiazole-2(3*H*)-thiones (2-6). The respective carbohydrazide (10 mmol) was dissolved in 30 mL of EtOH and 0.56 g (10 mmol) of KOH in 2 mL of water was added. Then 1.2 mL (20 mmol) of CS_2 was added drop-wise to the stirred solution. The mixture was refluxed for 4 h and concentrated under vacuum. The residue was dissolved in 20 mL of water, the impurities were filtered off and filtrate was acidified with conc. HCl. The precipitate was filtered off, washed with cold water, dried and recrystallized from suitable solvent.

5-(Pyrimidin-2-yl)-1,3,4-oxadiazole-2(3*H*)-thione (2). This product was recrystallized from MeOH afforded 1.29 g (72%) **1**. Mp 229-231 °C; IR (KBr): 3390, 3067, 2899, 2741, 1568, 1484, 1357, 1126, 947 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.71 (t, 1H, pyrimidine, J = 5 Hz), 9.02 (d, 2H, pyrimidine, J = 5 Hz), 14.7 (brs, 1H, NH) ppm. Anal. Calcd for $C_6H_4N_4OS$ (180.19): C, 39.99; H, 2.24; N, 31.09. Found: C, 39.89; H, 2.25; N, 30.99.

5-(Quinolin-2-yl)-1,3,4-oxadiazole-2(3*H*)-thione (3). This product was recrystallized from dioxane afforded 1.60 g (70%) **3**. Mp 226-228 °C; IR (KBr): 3057, 2973, 2930, 2857, 2770, 1520, 1456, 1368, 1317, 1125, 1114, 1075, 954 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.70-8.63 (m, 6H, quinoline), 14.21 (brs, 1H, NH) ppm. Anal. Calcd for $C_{11}H_7N_3OS$ (229.26): C, 57.63; H, 3.08; N, 18.33. Found: C, 57.75; H, 3.07; N, 18.37.

An alternative method for the synthesis of 1,3,4-oxadiazole-2(3*H*)-thiones (4, 5). The respective methyl carbonylhydrazinecarbodithioate (2.43 g, 10 mmol) was dissolved in 10 mL of EtOH and morpholine (4 mL, 46 mmol) was added. The mixture was refluxed for 4 h and cooled down. The precipitate was filtered off and dissolved in 20 mL of water. The solution was acidified with AcOH and precipitate was filtered off, washed with cold water, dried and recrystallized from the suitable solvent.

3-(5-Thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)pyridine 1-oxide (4). This product was recrystallized from DMF afforded 1.28 g (65% - method from carbohydrazide) or 0.85 g (43% - method from methyl carbonylhydrazinecarbodithioate) **4**. Mp 227-228 °C; IR (KBr): 3261, 3073, 1482, 1366, 1216, 1149, 1063, 821, 706, 556 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.19-7.24 (m, 2H, pyridine 1-oxide), 8.34 (dd, 1H, pyridine 1-oxide, J_1 = 8.0 Hz, J_2 = 4.6 Hz), 8.74 (d, 1H, pyridine 1-oxide, J = 4.8 Hz), 14.35 (brs, 1H, NH) ppm. Anal. Calcd for $C_7H_5N_3O_2S$ (195.20): C, 43.07; H, 2.58; N, 21.53. Found: C, 42.98; H, 2.59; N, 21.49.

4-(5-Thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)pyridine 1-oxide (5). This product was recrystallized from EtOH afforded 0.539 g (28% - method from carbohydrazide) or 1.05 g (53% - method from methyl carbonylhydrazinecarbodithioate) **5**. Mp 204-205 °C; IR (KBr): 3258, 3092, 1535, 1479, 1447, 1364, 1238, 927, 842, 550 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.82 (d, 2H, pyridine 1-oxide, J = 5.4 Hz), 8.35 (d, 2H, pyridine 1-oxide, J = 5.6 Hz), 14.70 (brs, 1H, NH) ppm. Anal. Calcd for $C_7H_5N_3O_2S$ (195.20): C, 43.07; H, 2.58; N, 21.53. Found: C, 43.19; H, 2.57; N, 21.56.

3-(5-Thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)pyrazine 1-oxide (6). This product was recrystallized from DMF-water mixture (1:1) afforded 1.14 g (58%) **6**. Mp 214-216 °C; IR (KBr): 3262, 3077, 2875, 2722, 1591, 1428, 1352, 1011, 936, 727 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.66 (d, 1H, pyrazine 1-oxide J = 7.1 Hz), 9.79 (t, 2H, pyrazine 1-oxide, J = 7.2 Hz), 14.60 (brs, 1H, NH) ppm. Anal. Calcd for $C_6H_4N_4O_2S$ (196.19): C, 36.73; H, 2.06; N, 28.56. Found: C, 36.81; H, 2.05; N, 28.49.

5-(Pyridin-4-yl)-1,3,4-oxadiazole-2(3*H*)-thione (7). Methyl 2-isonicotinoylhydrazinecarbodithioate (2.27 g, 10 mmol) and 4-aminomorpholine (1.44 mL, 15 mmol) were refluxed in 5 mL of pyridine for 1 h. Then the solvent was evaporated and the residue was diluted with 5 mL of water. The resulting solution was acidified with acetic acid. The precipitate was filtered off, washed with cold water, dried and recrystallized from EtOH afforded 89.6 mg (5%) **7**. Compounds characteristics were found to be identical with those reported earlier by Pancechowska-Ksepko and co-workers (mp 217-219 °C).[11]

3-Methyl-5-(pyridin-2-yl)-1,3,4-oxadiazole-2(3*H*)-thione (8). Methyl 2-isonicotinoylhydrazine-carbodithioate (0.964 g, 4 mmol) was refluxed with 3.5 mL of morpholine for 2 h. Then the mixture was poured on 50 g of ice. The precipitate was filtered off, washed with water, dried and recrystallized from MeOH afforded 0.178 g (23%) **8**. Mp 152-155 °C; IR (KBr): 3071, 1561, 1480, 1388, 1343, 1297, 1177, 1050, 795, 695 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.81 (s, 3H, NMe), 7.45-7.52 (m, 1H, pyridine), 7.89-7.97 (m, 2H, pyridine), 8.77 (d, 1H, pyridine, J = 4.8 Hz) ppm; Anal. Calcd for $C_8H_7N_3OS$ (193.23): C, 49.73; H, 3.65; N, 21.75. Found: C, 49.61; H, 3.64; N, 21.69.

General method for the synthesis of 3-methyl-1,3,4-oxadiazole-2(3*H*)-thiones (9, 10). The respective methyl carbonylhydrazinecarbodithioate (1.5 mmol) was refluxed with the mixture consisted of 10 mL of EtOH and 0.5 mL of TEA for 5 h. Then the mixture was concentrated under vacuum and cooled in ice-bath. The precipitate was filtered, dried and recrystallized.

3-Methyl-5-(pyrimidin-2-yl)-1,3,4-oxadiazole-2(3*H*)-thione (9). This product was recrystallized from MeOH afforded 55.3 g (19%) **9**. Mp 254-255 °C; IR (KBr): 3068, 1565, 1477, 1426, 1394, 1353, 1300, 1155, 1051, 836, 757, 692 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.85 (s, 3H, NMe), 7.49 (t, 1H, pyrimidine, J = 4.9 Hz), 8.94 (d, 2H, pyrimidine, J = 5.1 Hz) ppm; Anal. Calcd for $C_7H_6N_4OS$ (194.21): C, 43.29; H, 3.11; N, 28.85. Found: C, 43.18; H, 3.10; N, 28.88.

3-Methyl-5-(quinolin-2-yl)-1,3,4-oxadiazole-2-(3*H*)-thione (10). This product was recrystallized from EtOH afforded 0.102 g (28%) 10. Mp 198-200 °C. IR (KBr): 3089, 2927, 1698, 1571, 1507, 1473, 1423, 1392, 1360, 1123, 1108, 997, 837, 765 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.87 (s, 3H, NMe), 7.62-8.37 (m, 6H, quinoline) ppm. Anal. Calcd for $C_{12}H_9N_3OS$ (243.28): C, 59.24; H, 3.73; N, 17.27. Found: C, 59.36; H, 3.74; N, 17.22.

4-(5-Morpholino-1,3,4-oxadiazol-2-yl)pyridine 1-oxide (11). 4-(2-(Methylthiocarbonothioyl)-hydrazine)carbonyl)pyridine 1-oxide (2.43 g, 10 mmol) was refluxed with 2 mL of morpholine for 2 h. Then the mixture was concentrated under vacumand 20 mL of water was added. The water solution was extracted with CH_2Cl_2 (4 x 10 mL). The organic fractions were combined, dried with $MgSO_4$ and the solvent was removed under vacuum. The residue was treated with ice-cold methanol. The precipitate was filtered off, dried and recrystallized from MeOH afforded 0.223 g (9%) 11. Mp 211-212 °C; IR (KBr): 3078, 1596, 1561, 1495, 1275, 1256, 1111, 909, 845, 742, 646 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.55-3.65 (m, 4H, $2NCH_2$), 3.70-3.80 (m, 4H, $2OCH_2$), 7.80 (d, 2H, pyridine 1-oxide, J = 5.6 Hz), 8.32 (d, 2H, pyridine 1-oxide, J = 5.7 Hz) ppm; Anal. Calcd for $C_{11}H_{12}N_4O_3$ (248.24): C, 53.22; H, 4.87; N, 22.57. Found: C, 53.31; H, 4.86; N, 22.51.

General method for the synthesis of 2-methylthio-1,3,4-oxadiazoles (12-14). The respective 1,3,4-oxadiazole-2(3*H*)-thione (**1**, **4**, **5**) (3 mmol) was dissolved in a solution of 0.2 g (3.5 mmol) of KOH in 10 mL of EtOH-water mixture (1:1). Then 0.22 mL (3.5 mmol) of MeI was added. The mixture was stirred at 50 °C for 0.5 h. The solvent was evaporated under vacuum and the residue was cooled down. The precipitate was filtered off, dried and recrystallized from the suitable solvent.

2-(Methylthio)-5-(pyridine-3-yl)-1,3,4-oxadiazole (12). This product was recrystallized from water afforded 0.151 g (26%) **12**. Mp 81-83 °C; IR (KBr): 3087, 1602, 1470, 1412, 1195, 1080, 952, 813, 702, 620 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.81 (s, 3H, SMe), 7.51 (t, 1H, pyridine, J = 8.0 Hz), 8.38 (d, 1H, pyridine, J = 8.1 Hz), 8.80 (d, 1H, pyridine, J = 4.5 Hz), 9.27 (s, 1H, pyridine) ppm; Anal. Calcd for $C_8H_7N_3OS$ (193.23): C, 49.73; H, 3.63; N, 21.75. Found: C, 49.63; H, 3.62; N, 21.69.

3-(5-Methylthio)-1,3,4-oxadiazol-2-yl)pyridine 1-oxide (13). This product was recrystallized from toluene-petroleum ether mixture (1:1) afforded 0.176 g (28%) **13**. Mp 138-139 °C; IR (KBr): 3075, 1468, 1299, 1238, 1184, 1013, 889, 716, 669, 557 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.79 (s, 3H, SMe), 7.45 (dd, 1H, pyridine 1-oxide, J_1= 8.0 Hz, J_2 = 4.4 Hz), 7.90 (d, 1H, pyridine 1-oxide, J = 8.1 Hz), 8.35 (d, 1H, pyridine 1-oxide, J 4.5 Hz), 8.80 (s, 1H, pyridine 1-oxide) ppm; Anal. Calcd for $C_8H_7N_3O_2S$ (209.23): C, 45.92; H, 3.37; N, 20.08. Found: C, 46.04; H, 3.38; N, 20.03.

4-(5-(Methylthio)-1,3,4-oxadiazol-2-yl)pyridine 1-oxide (14). This product was recrystallized from EtOH afforded 0.257 g (41%) 14. Mp 207-208 °C; IR (KBr): 3068, 1618, 1573, 1459, 1436, 1267, 1195,

1167, 859, 650, 532 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.80 (s, 3H, SMe), 7.85 (d, 2H, pyridine 1-oxide, *J* = 5.5 Hz), 8.30 (d, 2H, pyridine 1-oxide, *J* = 5.6 Hz) ppm; Anal. Calcd for $C_8H_7N_3O_2S$ (209.23): C, 45.92; H, 3.37; N, 20.08. Found: C, 45.83; H, 3.36; N, 20.12.

General method for the synthesis of 3-(5-(methylthio)-1,3,4-thiadiazol-2-yl)azine 1-oxides (15, 16). Methyl carbonylhydrazinecarbodithioate (2 mmol) was dissolved in 3 mL of conc. H_2SO_4 and stirred at 90 °C for 1 h. Then clear solution was poured on 10 g of ice and the precipitate of product 16 was filtered off and recrystallized from EtOH. The solution of 1,3,4-thiadiazole (**15**) was additionally alkalized with NH_4OH. White precipitate was filtered off and recrystallized from water.

3-(5-(Methylthio)-1,3,4-thiadiazol-2-yl)pyridine 1-oxide (15). This product was recrystallized from water afforded 0.162 g (36%) **15**. Mp 169-170 °C; IR (KBr): 2913, 1451, 1412, 1363, 1201, 1014, 884, 801, 675, 551 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.82 (s, 3H, SMe), 7.36 (t, 1H, pyridine 1-oxide, *J* = 8.0 Hz), 7.86 (d, 1H, pyridine 1-oxide, *J* = 8.1 Hz), 8.39 (d, 1H, pyridine 1-oxide, *J* = 4.4 Hz), 8.74 (s, 1H, pyridine 1-oxide) ppm; Anal. Calcd for $C_8H_7N_3OS_2$ (225.29): C, 42.65; H, 3.13; N, 18.65. Found: C, 42.57; H, 3.12; N, 18.69.

3-(5-(Methylthio)-1,3,4-thiadiazol-2-yl)pyrazine 1-oxide (16). This product was recrystallized from EtOH afforded 0.235 g (52%) **16**. Mp 199-201 °C; IR (KBr): 3062, 1589, 1504, 1424, 1354, 997, 887 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.85 (s, 3H, SMe), 8.45 (s, 1H, pyrazine 1-oxide), 8.95 (s, 2H, pyrazine 1-oxide) ppm; MS (15 eV): 226 (100), 105 (8.33), 228 (7.52); Anal. Calcd for $C_7H_6N_4OS_2$ (226.28): C, 37.16; H, 2.67; N, 24.76. Found: C, 37.08; H, 2.68; N, 24.81.

General method for the synthesis of 1,2,4-triazole-5(4*H*)-thiones (17-31). Methyl 2-nicotinoylhydrazinecarbodithioate (2.27 g, 10 mmol) and respective primary amine (50 mmol) were refluxed for 1 h. Then the mixture was cooled in ice bath and 10 mL of water and 3.5 mL (61 mmol) of AcOH were added. The precipitates of products (**17-20**) were filtered off and recrystallized from MeOH. The neutralized solutions of compounds (**21-31**) were refrigerated for 24 h. Precipitates were filtered off and recrystallized from water.

4-(2-Hydroxyethyl)-3-(pyridin-3-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (17). This product was recrystallized from MeOH afforded 1.64 g (74%) **17**. Mp 194-195 °C; IR (KBr): 3361, 1545, 1501, 1342, 1180, 1055, 1022, 961, 712, 634 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.72 (t, 2H, NCH_2, *J* = 7.0 Hz), 4.03 (t, 2H, OCH_2, *J* = 6.9 Hz), 4.38 (s, 1H, OH), 7.58 (dd, 1H, pyridine, J_1 = 8.1 Hz, J_2 = 4.3 Hz), 8.25 (d, 1H, pyridine, *J*= 8.0 Hz), 8.75 (d, 1H, pyridine, *J* = 4.5 Hz), 8.30 (s, 1H, pyridine), 13.90 (brs, 1H, NH) ppm; Anal. Calcd for $C_9H_{10}N_4OS$ (222.27): C, 48.63; H, 4.53; N, 25.21. Found: C, 48.52; H, 4.54; N, 25.26.

4-(3-Hydroxypropyl)-3-(pyridin-3-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (18). This product was recrystallized from MeOH afforded 1.94 g (82%) **18**. Mp 147-148 °C; IR (KBr): 3370, 2910, 1551, 1486, 1426, 1308, 1267, 1029, 823, 710 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.27-1.58 (m, 2H, CH_2), 3.17-3.39 (m, 2H,

NCH_2), 3.91-4.18 (m, 2H, OCH_2), 4.36 (s, 1H, OH), 7.61 (dd, 1H, pyridine, J_1 = 8.0 Hz, J_2 = 4.3 Hz), 8.16 (d, 1H, pyridine, J = 8.1 Hz), 8.79 (d, 1H, pyridine, J = 4.4 Hz), 8.87 (s, 1H, pyridine), 14.07 (brs, 1H, NH) ppm; Anal. Calcd for $C_{10}H_{12}N_4OS$ (236.29): C, 50.83; H, 5.12; N, 23.71. Found: C, 50.74; H, 5.11; N, 23.75.

4-(2-Hydroxypropyl)-3-(pyridin-3-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (19). This product was recrystallized from MeOH afforded 2.03 g (86%) **19**. Mp 220-221 °C; IR (KBr): 3266, 1546, 1428, 1349, 1271, 1034, 962, 813, 706, 594 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.05 (d, 3H, Me, J = 6.8 Hz), 3.72-4.00 (m, 2H, CH2), 4.08-4.20 (m, 1H, CH), 5.00 (s, 1H, OH), 7.56 (dd, 1H, pyridine, J_1 = 8.0 Hz, J_2 = 4.2 Hz), 8.28 (d, 1H, pyridine, J =8.1 Hz), 8.74 (d, 1H, pyridine, J = 4.5 Hz), 8.93 (s, 1H, pyridine), 14.00 (brs, 1H, NH) ppm; Anal. Calcd for $C_{10}H_{12}N_4OS$ (236.29): C, 50.83; H, 5.12; N, 23.71. Found: C, 50.89; H, 5.13; N, 23.68.

3-(Pyridin-3-yl)-4-(2-(pyrrolidin-1-yl)ethyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (20). This product was recrystallized from MeOH afforded 1.70 g (88%) **20**. Mp 145-146 °C; IR (KBr): 2955, 2825, 1558, 1450, 1401, 1319, 1109, 1028, 957, 704, 631 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.73 (s, 4H, $2CH_2$), 2.86-2.95 (t, 2H, NCH_2, J = 4.8 Hz), 3.54 (s, 4H, $2NCH_2$), 4.32 (t, 2H, NCH_2, J = 4.8 Hz), 7.46 (dd, 1H, pyridine, J_1 = 8.0 Hz, J_2 = 4.5 Hz), 8.06 (d, 1H, pyridine, J = 8.1 Hz), 8.78 (d, 1H, pyridine, J = 4.5 Hz), 8.93 (s, 1H, pyridine), 14.02 (brs, 1H, NH) ppm; Anal. Calcd for $C_{13}H_{17}N_5S$ (193.23): C, 56.70; H, 6.22; N, 25.43. Found: C, 56.83; H, 6.20; N, 25.37.

4-(3-Hydroxypropyl)-3-(pyridine-4-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (21). This product was recrystallized from water afforded 2.34 g (99%) **21**. Mp 178-180 °C; IR (KBr): 3360, 1605, 1478, 1432, 1424, 1345, 1303, 1065, 842, 599, 541 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.71-1.77 (m, 2H, CH_2), 3.50 (t, 2H, CH_2, J = 7.1 Hz), 3.65 (s, 1H, OH), 4.37 (t, 2H, NCH_2, J = 7.2 Hz), 7.98 (d, 2H, pyridine, J = 5.5 Hz), 8.66 (d, 2H, pyridine, J = 5.7 Hz), 14.10 (brs, 1H, NH) ppm; Anal. Calcd for $C_{10}H_{12}N_4OS$ (236.29): C, 50.83; H, 5.12; N, 23.71. Found: C, 50.71; H, 5.10; N, 23.69.

4-(2-Hydroxypropyl)-3-(pyridine-4-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (22). This product was recrystallized from water afforded 1.18 g (50%) **22**. Mp 224-225 °C; IR (KBr): 3363, 1613, 1571, 1440, 1410, 1347, 1259, 1061, 971, 594, 542 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.03 (d, 3H, Me, J = 6.9 Hz), 3.70-4.15 (m, 3H, CH_2CH), 5.07 (s, 1H, OH), 7.83 (d, 2H, pyridine, J = 5.1 Hz), 8.74 (d, 2H, pyridine, J = 5 Hz), 14.12 (brs, 1H, NH) ppm; Anal. Calcd for $C_{10}H_{12}N_4OS$ (236.29): C, 50.83; H, 5.12; N, 23.71. Found: C, 50.95; H, 5.13; N, 23.65.

4-(2,3-Dihydroxypropyl)-3-(pyridine-4-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (23). This product was recrystallized from water afforded 0.656 g (26%) **23**. Mp 171-172 °C; IR (KBr): 3366, 1609, 1515, 1446, 1430, 1301, 1182, 1002, 830 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.48-3.75 (m, 7H, $2CH_2$, CH, 2OH), 7.98 (d, 2H,

pyridine, *J* = 5.4 Hz), 8.66 (d, 2H, pyridine, *J* = 5.6 Hz), 14.08 (brs, 1H, NH) ppm; Anal. Calcd for $C_{10}H_{12}N_4O_2S$ (252.29): C, 47.61; H, 4.79; N, 22.21. Found: C, 47.48; H, 4.77; N, 22.26.

3-(4-(2-Hydroxyethyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridine 1-oxide (24). This product was recrystallized from MeOH afforded 0.548 g (23%) **24**. Mp 199-200 °C; IR (KBr): 3395, 3088, 1521, 1287, 1210, 1063, 972, 895, 797, 669, 621 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.74 (t, 2H, NCH_2, *J* = 6.8 Hz), 4.06 (t, 2H, OCH_2, *J* = 6.7 Hz), 4.57 (s, 1H, OH), 7.57 (t, 1H, pyridine 1-oxide, *J* = 8.2 Hz), 7.72 (d, 1H, pyridine 1-oxide, *J* = 8.1 Hz), 8.40 (d, 1H, pyridine 1-oxide, *J* =4.4 Hz), 8.68 (s, 1H, pyridine 1-oxide), 14.15 (brs, 1H, NH) ppm; Anal. Calcd for $C_9H_{10}N_4O_2S$ (238.27): C, 45.37; H, 4.23; N, 23.51. Found: C, 45.29; H, 4.24; N, 23.46.

3-(4-(2-(Pyrrolidin-1-yl)ethyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridine 1-oxide (25). This product was recrystallized from MeOH afforded 0.583 g (20%) **25**. Mp 163-165 °C; IR (KBr): 3063, 2962, 1442, 1302, 1279, 1125, 1016, 812, 669 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.57-1.73 (m, 4H, $2CH_2$), 2.41-2.52 (m, 6H, $3NCH_2$), 3.54 (t, 2H, NCH_2, *J* = 7.1 Hz), 7.22 (dd, 2H, pyridine 1-oxide, J_1 = 8.2 Hz, J_2 = 4.5 Hz), 7.82 (d, 1H, pyridine 1-oxide, *J* = 8.0Hz), 8.34 (d, 1H, pyridine 1-oxide, *J* = 4.4 Hz), 8.74 (s, 1H, pyridine 1-oxide), 14.10 (brs, 1H, NH) ppm; Anal. Calcd for $C_{13}H_{17}N_5OS$ (291.37): C, 53.59; H, 5.88; N, 24.04. Found: C, 53.45; H, 5.86; N, 24.09.

3-(4-(2-(Piperidin-1-yl)ethyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridine 1-oxide (26). This product was recrystallized from MeOH afforded 1.77 g (58%) **26**. Mp 220-221 °C; IR (KBr): 3073, 2937, 1502, 1480, 1287, 1119, 891, 805, 710, 667 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.19-1.26 (m, CH_2), 2.04-2.19 (m, 4H, $2CH_2$), 2.31-2.48 (m, 4H, $2NCH_2$), 4.07-4.19 (m, 4H, $2NCH_2$), 7.60 (t, 1H, pyridine 1-oxide, *J* = 8.5 Hz), 7.70 (d, 1H, pyridine 1-oxide, *J* = 8.1 Hz), 8.40 (d, 1H, pyridine 1-oxide, *J* = 4.6 Hz), 8.64 (s, 1H, pyridine 1-oxide) 14.03 (brs, 1H, NH) ppm; Anal. Calcd for $C_{14}H_{19}N_5OS$ (305.40): C, 55.06; H, 6.27; N, 22.93. Found: C, 55.17; H, 6.29; N, 22.98.

3-(4-(2-Morpholinoethyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridine 1-oxide (27). This product was recrystallized from MeOH afforded 0.184 g (6%) **27**. Mp 81-83 °C; IR (KBr): 3067, 1450, 1289, 1223, 1116, 1020, 944, 892, 797, 667 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.36 (t, 4H, $2NCH_2$, *J* = 4.8 Hz), 2.53 (t, 2H, NCH_2, *J* = 7.1 Hz), 3.54 (t, 2H, NCH_2, *J* = 4.8 Hz), 3.65 (t, 4H, $2OCH_2$, *J* = 4.6 Hz), 7.62 (t, 1H, pyridine 1-oxide, *J* = 8.3 Hz), 7.67 (d, 1H, pyridine 1-oxide, *J* = 8.0 Hz), 8.42 (d, 1H, pyridine 1-oxide, *J* = 4.5 Hz), 8.69 (s, 1H, pyridine 1-oxide) 14.10 (brs, 1H, NH) ppm; Anal. Calcd for $C_{13}H_{17}N_5O_2S$ (307.37): C, 50.80; H, 5.57; N, 22.78. Found: C, 50.71; H, 5.58; N, 22.73.

4-(4-(2-Hydroxyethyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridine 1-oxide (28). This product was recrystallized from water afforded 1.31 g (55%) **28**. Mp 254-256 °C; IR (KBr): 3361, 1542, 1509, 1480, 1451, 1414, 1338, 1294, 1238, 1194, 1061, 957, 846, 575 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.65-3.78 (m, 2H,

NCH_2), 4.01-4.26 (m, 2H, OCH_2), 4.52 (s, 1H, OH), 7.85 (d, 2H, pyridine 1-oxide, J = 5.7 Hz), 8.35 (d, 2H, pyridine 1-oxide, J =5 7 Hz), 14.09 (brs, 1H, NH) ppm; Anal. Calcd for $C_9H_{10}N_4O_2S$ (238.27): C, 45.37; H, 4.23; N, 23.51. Found: C, 45.28; H, 4.21; N, 23.48.

4-(4-(3-Hydroxypropyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridine 1-oxide (29). This product was recrystallized from water afforded 1.51 g (60%) **29**. Mp 227-228 °C; IR (KBr): 3261, 1617, 1508, 1482, 1451, 1413, 1248, 1239, 1192, 846, 572 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.61-1.78 (m, 2H, CH_2), 3.87 (s, 1H, OH), 4.02-4.18 (m, 2H, NCH_2), 4.38-4.52 (m, 2H, OCH_2), 7.75 (d, 2H, pyridine 1-oxide, J = 5.8 Hz), 8.35 (d, 2H, pyridine 1-oxide, J = 5.6 Hz), 14.06 (brs, 1H, NH) ppm; Anal. Calcd for $C_{10}H_{12}N_4O_2S$ (252.29): C, 47.61; H, 4.79; N, 22.21. Found: C, 47.72; H, 4.78; N, 22.24.

4-(4-(2-Hydroxypropyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridine 1-oxide (30). This product was recrystallized from water afforded 0.479 g (19%) **30**. Mp 221-222 °C; IR (KBr): 3362, 1617, 1569, 1514, 1481, 1241, 1193, 967, 845, 580 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.09 (d, 3H, Me, J = 6.8 Hz), 3.65-4.10 (m, 2H, CH_2), 4.20 (m, 1H, CH), 8.15 (d, 2H, pyridine 1-oxide, J = 5.8 Hz), 8.42 (d, 2H, pyridine 1-oxide, J = 5.8 Hz), 14.07 (brs, 1H, NH) ppm; Anal. Calcd for $C_{10}H_{12}N_4O_2S$ (252.29): C, 47.61; H, 4.79; N, 22.21. Found: C, 47.53; H, 4.80; N, 22.17.

3-(4-(2-Hydroxypropyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyrazine 1-oxide (31). This product was recrystallized from water afforded 0.813 g (34%) **31**. Mp 194-195 °C; IR (KBr): 3380, 1584, 1504, 1321, 1003, 957 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.35 (t, 2H, NCH_2, J = 7.0 Hz), 3.50 (t, 2H, OCH_2, J = 7.1 Hz), 4.80 (brs, 1H, OH), 6.40-6.60 (m, 3H, pyrazine 1-oxide), 10.20 (brs, 1H, NH) ppm; Anal. Calcd for $C_8H_9N_5O_2S$ (239.25): C, 40.16; H, 3.79; N, 29.27. Found: C, 40.26; H, 3.78; N, 29.21.

3-(1-Methyl-4-(2-(piperidin-1-yl)ethyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyrazine 1-oxide (32). 3-(2-((Methylthio)carbonothioyl)hydrazinecarbonyl)pyrazine 1-oxide (1.29 g, 5 mmol) was refluxed with *N*-(2-aminoethyl)piperidine (3g, 25 mmol) for 1 h. Then 20 g of ice was added and precipitate was filtered off, washed with cold water and recrystallized from EtOH-water mixture (1:1) afforded 1.06 g (66%) **32**. Mp 96-98 °C; IR (KBr): 2933, 1468, 1381, 1184, 861, 558 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.40-1.57 (m, 6H, $3CH_2$), 2.35-2.54 (m, 9H, $3NCH_2$ and NCH_3) 3.54 (t, 2H, NCH_2, J = 7.1 Hz), 9.66 (s, 1H, pyrazine 1-oxide), 9.79 (s, 2H, pyrazine 1-oxide), ppm; Anal. Calcd for $C_{14}H_{20}N_6OS$ (320.41): C, 52.48; H, 6.29; N, 26.23. Found: C, 52.39; H, 6.27; N, 26.18.

General method for the synthesis of triazolo[3,4-*b*][1,3]thiazines (33-36). Respective 1,2,4-triazole-5(4*H*)thione (**21**-**23**, **31**) (3 mmol) was suspended in the mixture of 3 mL of EtOH and 5 mL of conc. HCl. The suspension was refluxed for 2 h, EtOH was removed under vacuum and 5 g of ice was added to the residue. The solution was alkalized with NH_4OH and refrigerated for 24 h. The precipitate was filtered off and recrystallized from water.

3-(Pyridin-4-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3]thiazine (33). Yield 0.426 g (65%). Mp 193-194 °C; IR (KBr): 2980, 1600, 1473, 1436, 1406, 829, 699, 603 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.17-2.20 (m, 2H, CH_2), 3.20 (t, 2H, SCH_2, J = 7.1 Hz), 4.22 (t, 2H, NCH_2, J = 7.0 Hz), 7.72 (d, 2H, pyridine, J = 5.2 Hz), 8.84 (d, 2H, pyridine, J = 2.1 Hz) ppm; Anal. Calcd for $C_{10}H_{10}N_4S$ (218.28): C, 55.02; H, 4.62; N, 25.67. Found: C, 54.87; H, 4.61;N, 25.72.

6-Methyl-3-(pyridine-4-yl)-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazole (34). Yield 0.177 g (27%). Mp 230-231 °C; IR (KBr): 2976, 2926, 1604, 1457, 1435, 1144, 1071, 839, 694 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.28 (d, 3H, Me, J = 6.8 Hz), 2.91-3.13 (m, 1H, SCH), 4.15-4.26 (m, 2H, NCH_2), 7.57 (d, 2H, pyridine, J = 5.3 Hz), 8.75 (d, 2H, pyrazine, J =5.4 Hz) ppm; Anal. Calcd for $C_{10}H_{10}N_4S$ (218.28): C, 55.02; H, 4.62; N, 25.67. Found: C, 55.13; H, 4.63; N, 25.61.

3-(Pyridin-4-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3]thiazin-6-ol (35). Yield 0.246 g (35%). Mp 158-160 °C; IR (KBr): 3223, 2960, 1605, 1481, 1439, 1407, 1092, 1040, 833, 718, 703, 565 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.00-3.30 (m, 2H, SCH_2), 4.00-4.30 (m, 2H, NCH_2), 4.35-4.45 (m, 1H, CH), 5.85 (brs, 1H, OH), 7.70 (d, 2H, pyridine, J = 5.1 Hz), 8.73 (d, 2H, pyridine, J = 5.0 Hz) ppm; Anal. Calcd for $C_{10}H_{10}N_4OS$ (234.28): C, 51.27; H, 4.30; N, 23.91. Found: C, 51.13; H, 4.28; N, 23.95.

3-(5,6-Dihydrothiazolo[2,3-*c*][1,2,4]triazol-3-yl)pyrazine 1-oxide (36). Yield 46.5 mg (7%). Mp 234-236 °C; IR (KBr): 3046, 1588, 1482, 1451, 1403, 1312, 1215, 913 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.96 (t, 2H, SCH_2, J = 7.1 Hz), 4.31 (t, 2H, NCH_2, J = 7.1 Hz), 9.66 (s, 1H, pyridine 1-oxide), 9.79 (s, 2H, pyrazine 1-oxide) ppm; Anal. Calcd for $C_8H_7N_5OS$ (221.24): C, 43.43; H, 3.19; N, 31.66. Found: C, 43.34; H, 3.18; N, 31.73.

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