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Synthesis and potential antimycotic activity of 4-substituted-3-(thiophene-2-yl-methyl)-Δ^2--1,2,4-triazoline-5-thiones

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In the reaction of hydrazide of thiophene-2-acetic acid (**1**) with isothiocyanates, the respective thiosemicarbazides **2a-g** were obtained. Further cyclization with 2% NaOH led to formation of 4-substituted-3-(thiophene-2-yl-methyl)-Δ^2-1,2,4-triazoline-5-thiones (**3a-g**). These compounds showed promising antimycotic activity.

Keywords: 4-substituted-3-(thiophene-2-yl-methyl)-Δ^2-1,2,4-triazoline-5-thiones, synthesis, spectral analysis, antimycotic activity

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1,2,4-Triazole system is a structural element of many drugs that have antimycotic activity such as fluconazol, itraconazol, voriconazol (1, 2). One of the methods of preparing derivatives of 1,2,4-triazole is the cyclization reaction of acyl derivatives of thiosemicarbazide in alkaline medium (3–13). Using the cyclization reactions of thiosemicarbazide derivatives of 1,2,4-triazole-1-acetic acid and 1,2,4-triazole-4-acetic acid compounds composed of two 1,2,4-triazole systems connected by a methylene group were prepared (3, 4).

As a continuation of investigations of compounds of a similar structure, a series of new 1,2,4-triazoline-5-thione derivatives with potential pharmacological activity on the central nervous system were prepared (14). When investigated on mice, these compounds did not produce neurotoxic activity, but acted on the central nervous system calmatively, and prolonged the hexobarbital sleeping time significantly and depressed the locomotor activity (14). Derivatives of 1,2,4-triazoline-5-thione show different biological activities: analgesis (15), antiinflamatory (16), bacteriostatic (17, 18), antifungal (19).

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This work is a continuation of our search for 1,2,4-triazole derivatives with antimycotic and antibacterial activity.

EXPERIMENTAL

Melting points were determined in Fisher-Johns blocs (Sanyo, Japan) and are presented without corrections. IR spectra were recorded in KBr using a Specord IR-75 spectrophotometer (Perkin Elmer, UK). The ^{1}H NMR spectra were recorded on a Bruker Avance 300 (Bruker, Germany) in DMSO-d_6 with TMS as internal standard.

Chemicals were purchased from Merck (Germany) or Fluka (Switzerland) and were used without purification. Purity of all compounds was checked by TLC on aluminium oxide 60 F_{254} plates (Merck), in a $CHCl_3/C_2H_5OH$ (10:2) solvent system with UV visualization (λ = 254 nm).

Syntheses

Thiophene-2-acetic acid hydrazide (***1***). – Ethyl thiophene-2-acetate (0.01 mol, 1.7 g), dry ethanol (5 mL) and hydrazine hydrate (0.02 mol) were boiled for 3 h under reflux. After cooling, the precipitate was filtered off, dried and recrystallized from 95% ethanol. m.p. 89–90 °C; Yield 1.28 g (89%). Analysis for $C_5H_8N_2OS$ (M_r 144.31): calcd. C 41.65%, H 5.59%, N 19.43%; found: C 41.52%, H 5.09%, N 19.37%. Spectral data were as follows: IR (ν_{max}): 3240 (NH), 3047 (CH arom.), 1427 (CH aliph.), 1678 (C=O) cm^{-1}.

^{1}H NMR (δ ppm): 3.57 (s, 2H, CH_2), 4.28 (s, 2H, NH_2), 6.89–6.95 (m, 2H, 2CH), 7.32–7.34 (m, 1H, CH), 9.23 (s, 1H, NH).

Thiosemicarbazide derivatives of thiophene-2-acetic acids (***2a-g***). – Hydrazide **1** (0.01 mol) and isothiocyanates (0.01 mol) were mixed carefully and then placed in a round-bottom flask, and heated on oil bath at 90 °C for 10 h. The reaction product was washed with diethyl ether in order to remove the unreacted isothiocyanate and then with water to remove unreacted hydrazide. Next, the product was filtered, dried and crystallized from 95% ethanol.

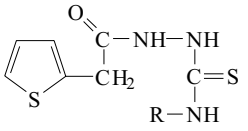
4-Substituted-3-(thiophene-2-yl-methyl)-Δ^2-1,2,4-triazoline-5-thiones (***3a-g***). – Thiosemicarbazide **2a-g** (0.01 mol) and sodium hydroxide (2%, 40 mL) were boiled for 2 h. After cooling, the solution was neutralized with diluted hydrochloric acid. The precipitate was filtered off and then crystallized from 95% ethanol.

The data relating to compounds **2a-g** and **3a-g** are listed in Table I.

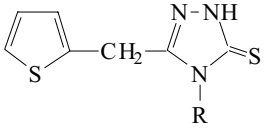
Microbiological tests

Compounds **2a**, **2c-e**, **3a** and **3c-e** were assayed for their antimicrobial activity *in vitro* against 11 strains of aerobic bacteria – 3 strains of Gram-positive bacteria (*Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis*), 8 strains of Gram-negative bacteria (*Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris, Proteus mirabilis, Salmonella enteritidis, Salmonella agonae, Yersinia enterocolitica, Pseudomonas aeruginosa*) and 12

Table I. Physical and analytical data for compounds ***2a-g*** *and* ***3a-g***



2a–g



3a–g

Compd. No.	R	Molecular formula (M_r)	Yield (%) M.p. (°C)	Elemental analysis Calc./found (%)			IR (KBr, cm^{-1})	^1H NMR (DMSO–d_6, δ ppm)
				C	H	N		
2a	C_2H_5	$C_9H_{13}N_3OS_2$ (243.34)	80 138–140	44.41 44.52	5.38 5.43	17.26 17.30	3312 (NH) 3142 (CH arom.) 2971, 1432 (CH aliph.) 1695 (C=O) 1375 (C=S)	1.03–1.08 (t, 3H, CH_3) J = 7.1 Hz 3.41–3.48 (q, 2H, CH_2) J = 6.9 Hz 3.68 (s, 2H, CH_2) 6.88–6.97 (m, 2H, 2CH) 7.36–7.38 (m, 1H, CH) 7.93, 9.24, 9.92 (3s, 3H, 3NH)
2b	$CH_2C_6H_5$	$C_{14}H_{15}N_3OS_2$ (305.41)	85 154–156	55.04 54.96	4.95 5.02	13.75 13.67	3285 (NH) 3128 (CH arom.) 2931, 1423 (CH aliph.) 1690 (C=O) 1342 (C=S)	3.72 (s, 2H, CH_2) 4.73 (s, 2H, CH_2) 6.94–6.97 (m, 2H, 2CH) 7.22–7.31 (m, 5H, arom. benz.) 7.33–7.38 (m, 1H, CH) 8.52, 9.46, 10.04 (3s, 3H, 3NH)
2c	C_6H_5	$C_{13}H_{13}N_3OS_2$ (291.38)	82 145–147	53.58 53.60	4.50 4.62	14.42 14.57	3243 (NH) 3051 (CH arom.) 2921, 1496 (CH aliph.) 1687 (C=O) 1358 (C=S)	3.76 (s, 2H, CH_2) 6.94–6.97 (m, 2H, 2CH) 7.14–7.19 (m, 1H, CH) 7.31–7.44 (m, 5H, arom. benz.) 9.63 (s, 2H, 2NH) 10.19 (s, 1H, NH)
2d	4-CH_3-C_6H_4	$C_{14}H_{15}N_3OS_2$ (305.41)	84 140–142	55.04 55.21	4.95 4.94	13.75 13.82	3232 (NH) 3130 (CH arom.) 2956, 1406 (CH aliph.) 1680 (C=O) 1336 (C=S)	2.28 (s, 3H, CH_3) 3.75 (s, 2H, CH_2) 6.93–6.97 (m, 2H, 2CH) 7.12–7.36 (m, 4H, arom. benz.) 7.37–7.39 (m, 1H, CH) 9.56 (s, 2H, 2NH) 10.15 (s, 1H, NH)

2e	4-OCH_3-C_6H_4	$C_{14}H_{15}N_3O_2S_2$ (321.41)	87 155–157	52.30 52.42	4.70 4.81	13.07 13.06	3133 (NH) 3053 (CH arom.) 2958, 1435 (CH aliph.) 1668 (C=O) 1336 (C=S)	3.32 (s, 3H, CH_3) 3.75 (s, 2H, CH_2) 6.88–6.93 (m, 2H, 2CH) 6.95–7.27 (m, 4H, arom. benz.) 7.37–7.39 (m, 1H, CH) 9.52 (s, 2H, 2NH) 10.14 (s, 1H, NH)
2f	4-Br-C_6H_4	$C_{13}H_{12}BrN_3OS_2$ (370.28)	85 168–170	42.16 42.15	3.27 3.28	11.35 11.34	3211 (NH) 3028 (CH arom.) 1699 (C=O) 1487 (CH aliph.) 1353 (C=S)	3.77 (s, 2H, CH_2) 6.94–6.98 (m, 2H, 2CH) 7.35–7.51 (m, 4H, arom. benz.) 7.53–7.54 (m, 1H, CH) 9.74 (s, 2H, 2NH) 10.20 (s, 1H, NH)
2g	4-Cl-C_6H_4	$C_{13}H_{12}ClN_3OS_2$ (325.83)	88 150–152	48.07 48.10	3.73 3.86	12.94 12.89	3219 (NH) 3027 (CH arom.) 1678 (C=O) 1492 (CH aliph.) 1341 (C=S)	3.78 (s, 2H, CH_2) 6.94–6.98 (m, 2H, 2CH) 7.32–7.37, 7.47–7.50 (m, 4H, arom. benz.) 7.38–7.41 (m, 1H, CH) 9.73 (s, 2H, 2NH) 10.21 (s, 1H, NH)
3a	C_2H_5	$C_9H_{11}N_3S_2$ (225.33)	70 146–147	47.95 47.86	4.92 4.90	18.64 18.62	3094 (CH arom.) 2953,1418 (CH aliph.) 1568 (C=N) 1496 (C-N) 1354 (C=S)	0.97–1.02 (t, 3H, CH_3) J = 7.1 Hz 3.89–3.96 (q, 2H, CH_2) J = 7.1 Hz 4.37 (s, 2H, CH_2) 6.98–7.05 (m, 2H, 2CH) 7.44–7.46 (m, 1H, CH) 13.62 (s, 1H, NH)
3b	$CH_2C_6H_5$	$C_{14}H_{13}N_3S_2$ (287.39)	69 158–160	58.50 58.57	4.56 4.59	14.62 14.61	3087 (CH arom.) 2919,1437 (CH aliph.) 1574 (C=N) 1499 (C-N) 1358 (C=S)	4.17 (s, 2H, CH_2) 5.23 (s, 2H, CH_2) 6.81–6.82 (m, 1H, CH) 6.87–6.89, 7.30–7.37 (m, 5H, arom. benz.) 7.18–7.21 (m, 2H, 2CH) 13.83 (s, 1H, NH)

3c	C_6H_5	$C_{13}H_{11}N_3S_2$ (273.37)	68 160–162	57.11 57.17	4.06 4.09	15.37 15.34	3079 (CH arom.) 2907,1494 (CH aliph.) 1590 (C=N) 1494 (C-N) 1338 (C=S)	4.10 (s, 2H, CH_2) 6.57–6.58 (m, 1H, CH) 6.82–6.85, 7.30–7.52 (m, 5H, arom. benz.) 7.27–7.29 (m, 2H, 2CH) 13.84 (s, 1H, NH)
3d	4-CH_3-C_6H_4	$C_{14}H_{13}N_3S_2$ (287.39)	71 154–156	58.50 58.62	4.56 4.59	14.62 14.54	3075 (CH arom.) 2918,1492 (CH aliph.) 1564 (C=N) 1492 (C-N) 1338 (C=S)	2.37 (s, 3H, CH_3) 4.07 (s, 2H, CH_2) 6.61–6.63 (m, 1H, CH) 6.85–6.87, 7.30–7.40 (m, 4H, arom. benz.) 7.14–7.17 (m, 2H, 2CH) 13.80 (s, 1H, NH)
3e	4-OCH_3-C_6H_4	$C_{14}H_{13}N_3OS_2$ (303.39)	73 164–165	55.42 55.49	4.32 4.38	13.85 13.74	3040 (CH arom.) 2928,1438 (CH aliph.) 1569 (C=N) 1468 (C-N) 1335 (C=S)	3.81 (s, 3H, CH_3) 4.05 (s, 2H, CH_2) 6.81–6.82 (m, 1H, CH) 6.87–6.89, 7.30–7.37 (m, 4H, arom. benz.) 7.18–7.21 (m, 2H, 2CH) 13.83 (s, 1H, NH)
3f	4-Br-C_6H_4	$C_{13}H_{10}BrN_3S_2$ (352.26)	67 134–136	44.32 44.38	2.86 2.83	11.93 11.91	3040 (CH arom.) 2921,1491 (CH aliph.) 1572 (C=N) 1413 (C-N) 1332 (C=S)	3.77 (s, 2H, CH_2) 6.63–6.65 (m, 1H, CH) 6.84–6.87 (m, 1H, CH) 7.25–7.30, 7.69–7.74 (m, 4H, arom. benz.) 7.34–7.36 (m, 1H, CH) 13.88 (s, 1H, NH)
3g	4-Cl-C_6H_4	$C_{13}H_{10}ClN_3S_2$ (307.81)	65 143–145	50.72 50.78	3.27 3.29	13.65 13.69	3042 (CH arom.) 2921,1493 (CH aliph.) 1574 (C=N) 1438 (C-N) 1333 (C=S)	4.13 (s, 2H, CH_2) 6.63–6.64 (m, 1H, CH) 6.84–7.59 (m, 4H, arom. benz.) 7.50–7.59 (m, 2H, 2CH) 13.89 (s, 1H, NH)

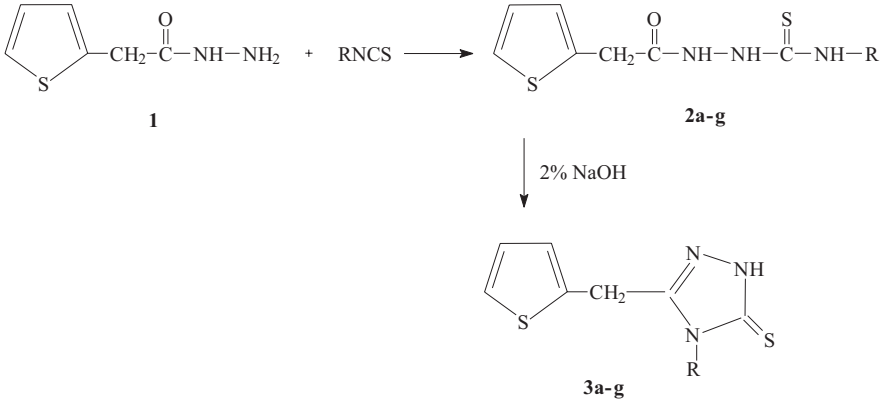
strains of fungi – yeast-like fungi (*Candida albicans, Candida famata, Geotrichum candidum*), moulds (*Aspergillus fumigatus, Aspergillus niger, Penicillium* spp., *Scopulariopsis* spp.) and dermatophytes (*Trichophyton granulosum, Trichophyton galinae, Trichophyton interdigitale, Trichophyton mentagrophytes, Trichophyton rubrum*). Tested microorganisms were isolated from clinical specimens. In addition, two reference strains of dermatophytes – *Trichophyton mentagrophytes* ATCC9533 and *Trichophyton rubrum* ATCC28188 were included in the studies.

The minimal inhibitory concentration (*MIC*) defined as the lowest concentration of the compound preventing visible growth, was estimated for all compounds, by agar dilution method, using Mueller-Hinton medium without or with 4% glucose for the growth of bacteria and fungi, respectively (20).

The compounds were dissolved in mixture of acetone and DMSO (1:1). The final concentration of each solvent in the medium (2%) had no influence on the growth of tested microorganisms. Microbial cultures (optical density of 0.5 McFarland standard, 0.025 mL) were put into Petri dishes with 20 mL medium containing several concentrations of the compounds (500, 250, 125, 62.5, 31.25 mg L^{-1}). The media were incubated for 18 h at 37 °C for bacteria or for 5 days at 30 °C for fungi. The medium with no synthesized compounds added served as the control.

RESULTS AND DISCUSSION

Hydrazide of thiophene-2-acetate (**1**) was obtained in the reaction of ethyl thiophene-2-acetate with hydrazine hydrate. The new thiosemicarbazide derivatives (**2**) were obtained in the reaction of hydrazide with isothiocyanates. These compounds were subjected to cyclization in a 2% solution of sodium hydroxide, giving suitable, 4-substituted-3-(thiophene-2-yl-methyl)-Δ^2-1,2,4-triazoline-5-thiones (**3**). The reaction was performed according to Scheme 1.



1 **2a-g** **3a-g**

R = C_2H_5, $CH_2C_6H_5$, C_6H_5, 4-CH_3-C_6H_4, 4-OCH_3-C_6H_4, 4-BrC_6H_4, 4-Cl-C_6H_4

Scheme 1

The structure of the new compounds was confirmed by elemental analysis as well as the IR and ^{1}H NMR spectra. ^{1}H NMR spectra of thiosemicarbazide derivatives (**2**) gave proton signals typical of the NH group in the range δ (ppm) 7.93–10.21. In ^{1}H NMR spectra of 4-substituted-3-(thiophene-2-yl-methyl)-Δ^2-1,2,4-triazoline-5-thiones (**3**), proton signals for –NH group in the δ (ppm) 13.62–13.89 range were observed. The above observations suggest that the compounds exist mainly in the thione form.

According to the results from Table II, none of the compounds tested (**2a**, **2c**-**e**, **3a**, **3c**-**e**) inhibited the growth of Gram-positive and Gram-negative bacterial strains, not

Table II. Antibacterial activity of the tested compounds

	Species	*MIC* (mg L^{-1})							
		2a	**2c**	**2d**	**2e**	**3a**	**3c**	**3d**	**3e**
Gram-positive bacteria	*Staphylococcus aureus*	> 500	> 500	> 500[a]	> 500	> 500	> 500	> 500[a]	> 500
	Staphylococcus epidermidis			> 500			> 500[a]	> 500	
	Enterococcus faecalis			> 500			> 500	> 500	
Gram-negative bacteria	*Escherichia coli*	> 500	> 500	> 500	> 500	> 500	> 500	> 500	> 500
	Klebsiella pneumoniae								
	Proteus vulgaris								
	Proteus mirabilis								
	Salmonella enteritidis								
	Salmonella agonae								
	Yersinia enterocolitica								
	Pseudomonas aeruginosa								
Yeast-like fungi	*Candida albicans*	> 500	> 500	> 500	> 500	> 500	> 500	> 500	> 500
	Candida famata								
	Geotrichum candidum								
Moulds	*Aspergillus fumigatus*	> 500	> 500	> 500	> 500	> 500	> 500	> 500	> 500
	Aspergillus niger		> 500[a]						
	Penicillium spp.		> 500						
	Scopulariopsis spp.		> 500						
Dermato-Phytes	*Trichophyton granulosum*	> 500	> 500	> 500[b]	> 500[a]	> 500[a]	> 500	> 500[b]	> 500[a]
	Trichophyton galinae			500	500	> 500		250	500
	Trichophyton interdigitale			500	> 500[b]	> 500		> 500	> 500[a]
	Trichophyton mentagrophytes								
	Trichophyton mentagrophytes ATCC9533			> 500[b]	> 500[a]	> 500[a]		> 500[b]	500
	Trichophyton rubrum			> 500[b]	> 500[a]	> 500		> 500[b]	500
	Trichophyton rubrum ATCC28188			> 500[b]	500	250		250	500
				> 500[b]	500	250		250	500

[a] Growth inhibition by about 50–70% at a concentration of 500 mg L^{-1} compared to growth intensity on the medium without the tested compound (visual assessment).
[b] Growth inhibition by about 80–90% at a concentration of 125, 250 or 500 mg L^{-1} compared to growth intensity on the medium without the tested compound (visual assessment).

even at a concentration > 500 mg L^{-1}. However, compounds **2d**, **3c**, **3d** affected the growth of some *Staphylococci* by about 50–70%.

As shown in Table II, none of the compounds except compound **2d**, inhibits the growth of yeast-like fungi and moulds even at a high concentration of 500 mg L^{-1}. Only compound **2d** affected the growth of *Aspergillus niger* by 50–70% at 500 mg L^{-1}.

Likewise, compounds **2a**, **2c** and **3c** showed no inhibitory effect on the growth of dermatophytes (*MIC* > 500 mg L^{-1}). In contrast, compounds **2d**, **2e**, **3a**, **3d**, **3e** showed total or partial inhibitory effect on the growth of some clinical and reference species of *Trichophyton* spp. at concentrations of 250 or 500 mg L^{-1}. Besides, some of them affected the growth of dermatophytes by 80–90% at a concentration of 125 mg L^{-1}. It is worth noting that even *MICs* of some triazoles currently used in the treatment of mycoses, including dermatophytoses, showed high variability in activity against different species of *Trichophyton* (*e.g.*, for itraconazole *MIC* range from 0.015 to 8 mg L^{-1}, for fluconazole from 0.5 to 64 mg L^{-1}).

CONCLUSIONS

In this report, an easy method of synthesizing 4-substituted-3-(thiophene-2-yl-methyl)-Δ^2-1,2,4-triazoline-5-thione in good yield is presented. Eight new compounds were tested for their antibacterial and antifungal activity. Our preliminary data indicate that the assessed, newly synthesized compounds had no significant antibacterial activity but some of them (compounds **2d**, **2e**, **3a**, **3d**, **3e**) showed promising antifungal activity against some species belonging to *Trichophyton* spp. known as the causative agents of superficial mycoses. The most effective derivatives have the carbon ring substituted with a methyl or methoxy group. Although *MICs* values for the newly synthesized compounds were higher than those for currently available triazoles (*e.g.*, fluconazole, itraconazole), we found them as a good basis for further research.

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S A Ž E T A K

Sinteza i antimikotsko djelovanje 4-supstituiranih 3-(tiofen-2-il-metil)-Δ^2-1,2,4-triazolin-5-tiona

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Rekacijom hidrazida tiofen-2-octene kiseline (**1**) s izotiocijanatima sintetizirani su odgovarajući tiosemikarbazidi (**2a-g**), a njihovom ciklizacijom u 2% NaOH 4-supstituirani 3-(tiofen-2-il-metil)-Δ^2-1,2,4-triazolin-5-tioni (**3a-g**). Sintetizirani spojevi su potencijalni antimikotici.

Ključne riječi: 4-supstituirani 3-(tiofen-2-il-metil)-Δ^2-1,2,4-triazolin-5-tioni, sinteza, spektralna analiza, antimikotsko djelovanje

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