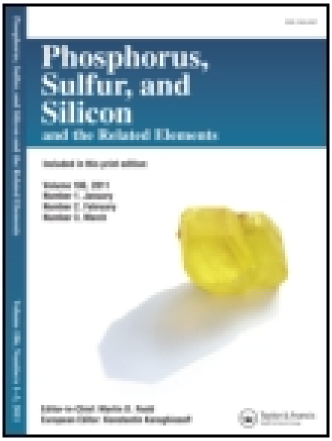

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Synthesis and Tuberculostatic Activity of Some 2-Piperazinmethylene Derivatives 1,2,4-Triazole-3-Thiones

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Published online: 21 Dec 2010.

Phosphorus, Sulfur, and Silicon, 180:537–543, 2005

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/104265090517280

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The Mannich reaction's products of 1,2,4-triazole-3-thiones, substituted in position 4 (with ethyl, allyl, phenyl, Ph-4-Br) or 5 (with phenyl, Ph-4-OH, Ph-3,4,5-(OMe)$_3$, 2-phenyl) were obtained. Their amino-components were 1-phenylpiperazine, 1-(4-fluorophenyl)-piperazine, 1-benzylpiperazine, 1-(2-pyridyl)-piperazine and 1-piperonyl-piperazine. Tuberculostatic activity of the compounds obtained was tested in vitro *and their MIC values within 25–100 mcg/mL.*

Keywords 1,2,4-Triazole-3-thiones; Mannich reactions; tuberculostatic

INTRODUCTION

Many examples of Mannich compounds' officinal use may be found in therapeutics. These compounds gave evidence of more advantageous physiological effect, than the parent ones—disposessed of the aminomethylene arrangement. The Mannich bases of tetracyclines[1] medicinal use, as well as the morpholinomethylene-pyrazinamide derivative (Morfazinamid) application to tuberculosis treatment could be given for instance.

Some aminomethylation products of 1,2,4-triazole-3-thiones, already reported, showed the antibacterial activity as well.[2–6]

Received July 6, 2004; in final form July 20, 2004.
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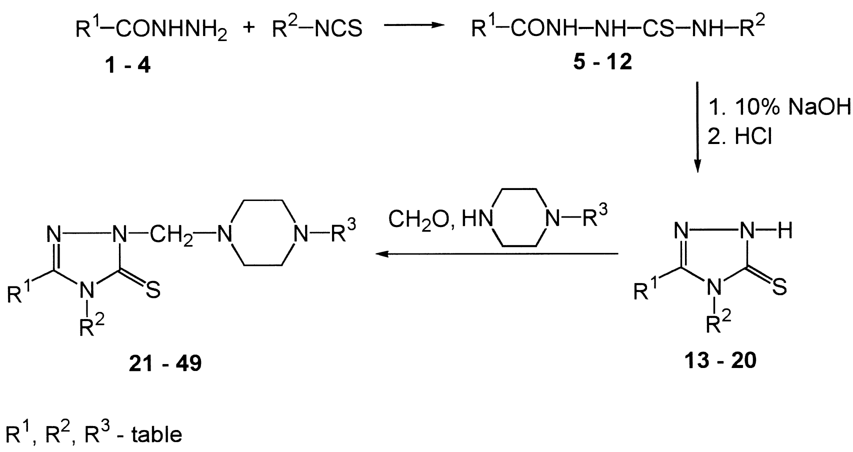
RESULTS AND DISCUSSION

With regard to the reasons, for 4,5-disubstituted-1,2,4-triazole-3-thiones the aminomethylation products with the piperazine arrangement were synthesised. Our previous works (unpublished) showed that the presence of this arrangement in the compounds tested often used to increase the tuberculostatic activity, while checked *in vitro*.

In accordance with the methods commonly used, acid hydrazides **1–4** (benzoic, 4-hydroxy-benzoic, 3,4,5-trimethoxybenzoic and 2-furylocarboxylic hydrazides) in the reactions with ethyl-, allyl-, phenyl-, and p-bromophenyl isothiocyanates gave the corresponding thiosemicarbazide derivatives (**5–12**), which subsequently underwent the cyclization (in 10% NaOH) to triazolothiones (**13–20**). The last-mentioned compounds were exposed to the Mannich reaction, in which formalin and the substituted piperazines [1-phenyl-, 1-benzyl-, 1-(4-fluorophenyl)-, 1-piperonyl- and 1-(2-pyridyl)-piperazine] were used (Scheme 1).



SCHEME 1

MICROBIOLOGY

The compounds obtained were tested for their tuberculostatic activity towards the Mycobacterium tuberculosis $H_{37}Rv$ strain and two wild strains isolated from the tuberculotic patients: one—resistant to p-aminosalicylic acid (PAS), isonicotinic acid hydrazide (INH), ethambutol (ETB) and rifampycine (RFP)—and the other fully susceptible to the drugs administered.

Tuberculostatic activity was tested *in vitro* by classical test tube method with Youman's liquid medium containing 10% of bovine serum.[6] On the ground of the minimum inhibiting concentration (MIC) values obtained it may be concluded, that the group of the compounds tested exhibited low tuberculostatic activity. MIC values for the most of the compounds was within 25—100 mcg/mL.12

EXPERIMENTAL

Melting points were determined with a Boetius apparatus and are uncorrected. The IR spectra were taken with Satellite spectrophotometer. The ^{1}H NMR spectra were taken with Varian Gemini (200 MHz) spectrometer at the NMR Laboratory, Technical University of Gdansk.

The results of the elemental analyses (% C, H, N) for all the compounds obtained were in good agreement with the data calculated.

Thiosemicarbazides (5–12)

Acid hydrazided (benzoic, p-hydroxybenzoic, 3,4,5-trimethoxybenzoic, or 2-furylcarboxylic (10 mmole), ethanol (30 mL) and the corresponding isothiocyanate (ethyl-, allyl-, or p-bromo-phenyl (10 mmole)) were refluxed for 0.5 h. On cooling the precipitated thiosemicarbazides were filtered off and crystallized.

4,5-Disubstituted-1,2,4-triazole-3-thiones (13–20)

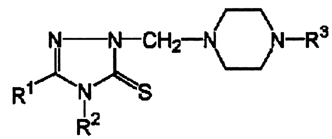
The corresponding thiosemicarbazide (**5–12**) (10 mmole) was refluxed in 10% aqueous NaOH solution (30 mL) for 2 h. On cooling, the mixture was acidified with diluted (1:1) HCl. The precipitates were washed with water, dried, and purified by crystallization.

Mannich Compounds (21–49)

Triazolothione (**13–20**) (5 mmole) dissolved in methanol or dioxane (20 mL) was treated with the corresponding piperazine (1-phenyl-, 1-benzyl-, 1-(4-fluorophenyl)-, 1-piperonyl-, or 1-(2-pyridyl)-piperazine (6 mmole)) and then with 40% formalin (1 mL). The mixture was refluxed for 1 h. On cooling with ice the precipitates were filtered off, dried, and purified by crystallization. When oils were obtained the solvent was distilled under reduced pressure and the residue allowed to stand for crystallization.

The physical characteristics of the compounds obtained are given in Table I.

TABLE I Characteristics of Synthesized Compounds



Compound	R^1	R^2	R^3	M.p. [°C] solvent for crystallization	Yield [%]	Formula	IR [cm^{-1}], 1H-NMR δ [ppm]
21	Ph	Et	Ph	107–110 EtOH	77	$C_{21}H_{25}N_5S$	683, 1003, 1096, 1163, 1280, 1328, 1424 1.3 (t, 3H, CH_3); 2.9–3.4 (m, 8H piperazin); 4.2 (m, 2H, CH2); 5.2 (s, 2H, CH_2); 6.7–7.4 (m, 5H, Ph); 7.6 (s, 5H, Ph)
22	Ph	Et	—CH_2-Ph	110–113 EtOH	52	$C_{22}H_{27}N_5S$	704, 784, 1008, 1104, 1168, 1376, 1428, 1488
23	Ph	Et	Pyridin-2-yl	130–133 EtOH	92	$C_{20}H_{24}N_6S$	775, 975, 1003, 1096, 1164, 1243, 1283, 1312, 1435, 1483, 1600
24	Ph	Et	p-F-Ph	85–88 EtOH	80	$C_{21}H_{24}FN_5S$	816, 1012, 1100, 1163, 1232, 1280, 1223, 1423, 1504
25	Ph	Ph	Ph	177–180 EtOH	37	$C_{25}H_{25}N_5S$	695, 763, 824, 1008, 1143, 1232, 1295, 1352, 1456, 1483, 1600 3.03–3.4 (m, 8H piperain); 5.4 (s, 2H, CH_2); 6.7–7.6 (m, 15H, Ph)
26	Ph	Ph	—CH_2-Ph	147–151 EtOH	60	$C_{26}H_{27}N_5S$	696, 768, 1008, 1232, 1328, 1456, 1488, 1600
27	Ph	Ph	Pyridin-2yl	170–173 MeOH	34	$C_{24}H_{24}N_6S$	768, 976, 1152, 1216, 1248, 1320, 1424, 1483, 1600
28	Ph	Ph	p-F-Ph	178–181 MeOH	60	$C_{25}H_{24}FN_5S$	776, 832, 1008, 1072, 1168, 1220, 1280, 1324, 1408, 1456, 1504

29	Ph	Ph-4-Br	Ph	165–168 MeOH	63	$C_{25}H_{24}BrN_5S$	768, 1008, 1072, 1152, 1232, 1324, 1424, 1483, 1600 3.0–3.4 (m, 8H piperazin); 5.4 (s, 2H, CH_2); 6.8–7.8 (m, 13H Ph)
30	Ph	Ph-4-Br	—CH_2-Ph	164–167 EtOH	82	$C_{26}H_{26}BrN_5S$	704, 768, 1008, 1163, 1324, 1456, 1488
31	Ph	Ph-4-Br	Pyridin-2-yl	163–165 Acetone	72	$C_{24}H_{23}BrN_6S$	784, 1003, 1072, 1163, 1243, 1324, 1424, 1472, 1592
32	Ph	Ph-4-Br	p-F-Ph	168–171 MeOH	57	$C_{25}H_{23}BrFN_5S$	784, 832, 1072, 1168, 1220, 1328, 1408, 1500
33	Ph-4-OH	Et	Ph	175–179 MeOH/H_2O	71	$C_{21}H_{25}N_5OS$	768, 1104, 1168, 1232, 1280, 1368, 1432, 1604 1.3 (t, 3H, CH_3); 2.9–3.4 (m, 8H piperazin); 4.1 (q, 2H, CH_2); 6.7–7.6 (m, 9H, Ph)
34	Ph-4-OH	Et	Piperonyl	178–183 MeOH	54	$C_{23}H_{27}N_5OS$	848, 928, 1136, 1244, 1360, 1448, 1488, 1616
35	Ph-4-OH	Et	Pyridin-2-yl	80–82 MeOH/H_2O	57	$C_{20}H_{24}N_6OS$	772, 1003, 1104, 1163, 1280, 1328, 1436, 1488, 1600
36	Ph-4-OH	Ph	Ph	208–212 MeOH	73	$C_{25}H_{25}N_5OS$	768, 1008, 1168, 1232, 1296, 1328, 1408, 1504, 1600 2.9–3.4 (m, 8H piperazin); 3.65 (s, OH); 5.3 (s, 2H, CH_2); 6.5–7.6 (m, 14H, Ph)
37	Ph-4-OH	Ph	Piperonyl	107–110 DMF/H_2O	85	$C_{27}H_{27}N_5O_3S$	800, 928, 1040, 1168, 1248, 1348, 1440, 1488, 1600, 1664
38	Ph-4-OH	Ph	Pyridin-2-yl	85–90	30	$C_{24}H_{24}N_6OS$	772, 944, 1008, 1120, 1248, 1320, 1440, 1600
39	Ph-4-OH	Ph	p-F-Ph	190–193 DMF/H_2O	77	$C_{25}H_{24}FN_5OS$	704, 820, 928, 1008, 1168, 1228, 1328, 1500, 1664
40	Ph-4-OH	Ph-4-Br	Ph	93–96	44	$C_{25}H_{24}BrN_5OS$	764, 832, 1008, 1232, 1328, 1356, 1488, 1600

(Continued on next page)

TABLE I Characteristics of Synthesized Compounds *(Continued)*

Compound	R^1	R^2	R^3	M.P. [°C] solvent for crystallization	Yield [%]	Formula	IR [cm^{-1}], 1H-NMR δ [ppm]
41	Ph-4-OH	Ph-4-Br	Piperonyl	90–93	33	$C_{27}H_{26}BrN_5O_3S$	832, 1008, 1040, 1120, 1168, 1248, 1328, 1440, 1488
42	Ph-4-OH	Ph-4-Br	Pyridin-2-yl	136–139 Dioxane	42	$C_{24}H_{23}BrN_6OS$	832, 1003, 1120, 1243, 1323, 1440, 1483, 1600
43	Ph-4-OH	Ph-4-Br	p-F-Ph	124–127 Acetone	35	$C_{25}H_{23}BrFN_5OS$	823, 1163, 1232, 1280, 1323, 1424, 1496, 1616
44	3,4,5-$(Ome)_3$-Ph	$-CH_2-CH=CH_2$	Ph	115–117 MeOH	66	$C_{25}H_{31}N_5O_3S$	683, 880, 923, 1000, 1120, 1232, 1312, 1424, 1596 2.9–3.4 (m, 8H piperazin); 3.9 (s, 9H, OCH_3); 4.6–4.8 (d, 2H, CH_2); 5.0–5.4 (m, 2H, CH_2); 5.2 (s, 2H, CH_2); 5.8–6.3 (m, 1H, CH); 6.7–7.4 (m, 7H, Ph)
45	3,4,5-$(Ome)_3$-Ph	$-CH_2-CH=CH_2$	Piperonyl	76–79 MeOH	74	$C_{27}H_{33}N_5O_5S$	800, 923, 1132, 1243, 1320, 1423, 1504, 1584
46	3,4,5-$(Ome)_3$-Ph	$-CH_2-CH=CH_2$	Pyridin-2-yl	122–125 MeOH	57	$C_{24}H_{30}N_6O_3S$	780, 848, 912, 1008, 1132, 1244, 1312, 1436, 1588
47	3,4,5-$(Ome)_3$-Ph	$-CH_2-CH=CH_2$	p-F-Ph	128–130 EtOH	93	$C_{25}H_{30}FN_5O_3S$	672, 784, 816, 912, 1008, 1120, 1232, 1312, 1420, 1504, 1584
48	Ph	$-CH_2-CH=CH_2$	Ph	78–82 MeOH	72	$C_{20}H_{23}N_5OS$	752, 800, 912, 1008, 1168, 1200, 1232, 1312, 1436, 1504, 1600 2.9–3.3 (m, 8H piperazin); 5.0 (d, 2H, CH_2); 5.3 (s, 2H, CH_2); 5.1–5.4 (m, 2H, $=CH_2$); 5.7–6.2 (m, 1H, =CH); 6.5–7.7 (m, 8H, Ph)
49	Ph	$-CH_2-CH=CH_2$	p-F-Ph	75–77 MeOH	43	$C_{20}H_{22}FN_5OS$	776, 832, 923, 1220, 1280, 1312, 1344, 1432, 1452, 1504, 1606

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