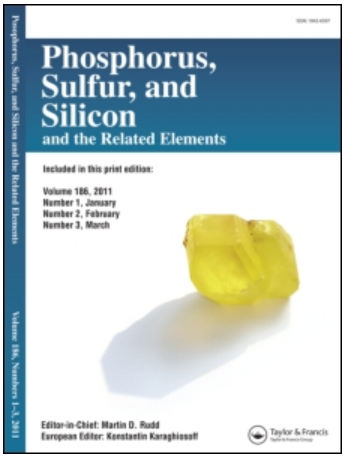

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Antimicrobial Properties of 4-Aryl-3-(2-methyl-furan-3-yl)-Δ²-1,2,4-triazoline-5-thiones

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Antimicrobial Properties of 4-Aryl-3-(2-methyl-furan-3-yl)-Δ^2-1,2,4-triazoline-5-thiones

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Four 4-aryl-3-(2-methyl-furan-3-yl)-Δ^2-1,2,4-triazole-5-thiones were synthesized by intramolecular cyclization of 4-aryl-1-[(2-methyl-furan-3-yl)carbonyl]thiosemicarbazides in alkaline medium. The antimicrobial activity of the synthesized triazoles was evaluated. Semiempirical calculations of geometries, energies, and QSAR parameters have been determined in the hope of gaining insight into different biological activities of closely related isomers. New RM1 parameterization has been shown to perform very well for this class of compounds.

Keywords Δ^2-1,2,4-triazoline-5-thione; antimicrobial activity; QSAR

INTRODUCTION

The biological activities of 1,2,4-triazoles have been extensively studied. In particular, their antimicrobial and central nervous system (CNS) activities have been extensively documented.[1] Although limited, there are also examples of the antibacterial, antinociceptive, anti-inflammatory properties of furan derivatives.[2] In a previous article,[3] we presented the synthesis of compounds containing the furan moiety at the position 3 of 4-substituted-1,2,4-triazoline-5-thione and examined their activity on the CNS in mice. Pharmacological results have shown strong antinociceptive properties of tested triazoles. Moreover, none of the compounds was found to show neurotoxic

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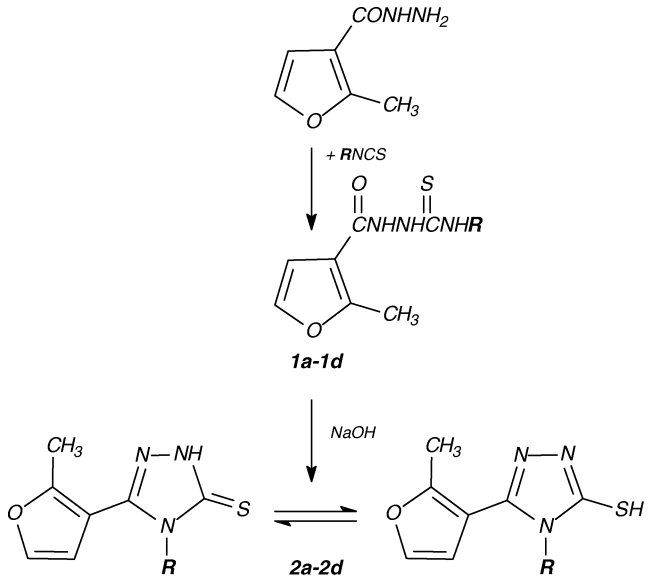
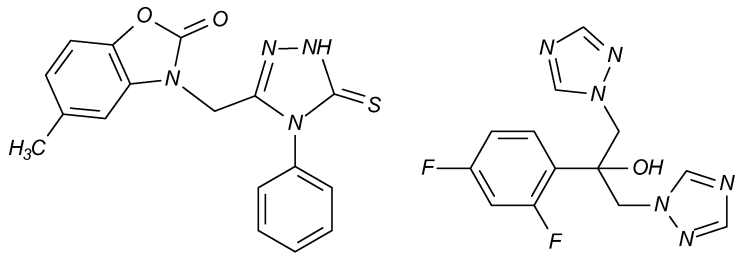


SCHEME 1 Synthesis of the 4-aryl-1-[(2-methyl-furan-3-yl)carbonyl] thiosemicarbazides **1a–1d** and 4-aryl-3-(2-methyl-furan-3-yl)-Δ^2-1,2,4-triazoline-5-thiones **2a–2d**.

activity. We have also hypothesized that 3-(2-methyl-furan-3-yl)-4-substituted-Δ^2-1,2,4-triazoline-5-thiones might show antibacterial and antifungal activity. To test this hypothesis we have synthesized four new analogues, **2a–2d**, presented in Scheme 1. Unfortunately, except for **2a**, the minimal inhibitory concentration (MIC) values of these compounds against tested microorganisms were higher than 500 μg/mL.

In order to understand why the tested triazoles **2b–2d** are inactive, in particular **2b**, while **2a** shows activity against Gram-positive bacteria, the structural and physicochemical properties of 4-aryl-3-(2-methyl-furan-3-yl)-Δ^2-1,2,4-triazoline-5-thiones were compared to pharmacokinetic properties of Fluconazole, which was used as standard antifungal powder, and 3-[(5-methyl-2-benzoxazolinone-3-yl)methyl]-4-phenyl-1H-1,2,4-triazole-5(4H)-thione, which is structurally similar to the tested compounds and exhibits moderate inhibitory activities at 128 μg/mL (see Figure 1) against *Candida crusei*, *Candida albicans*, and *Candida parapsilosis*.



a b

FIGURE 1 Structures of 3-[(5-methyl-2-benzoxazolinone-3-yl)methyl]-4-phenyl-1H-1,2,4-triazole-5(4H)-thione (*a*) and Fluconazole (*b*).

RESULTS AND DISCUSSION

Chemistry

The synthesis of the title compounds **2a–2d** is illustrated in Scheme 1. The preparation of the intermediate thiosemicarbazides **1a–1d** was carried out by the reaction of 2-methyl-furan-3-carboxylic acid hydrazide with aryl isothiocyanates. The 4-aryl-1-[(2-methyl-furan-3-yl)carbonyl]thiosemicarbazides **1a–1d**, when subjected to a reaction with 2% NaOH, underwent intramolecular cyclization to furnish the corresponding 4-aryl-3-(2-methyl-furan-3-yl)-Δ^2-1,2,4-triazole-5-thiones **2a–2d**.

The structures of all compounds were confirmed by the results of elemental analysis, as well as by IR and ^{1}H-NMR. The ^{1}H NMR spectra of **2a–2d** show a sharp singlet at 13.98–14.09 ppm typical for the proton linked to N1, indicating the presence of the thione tautomer. Domination of the thione form was observed also in the IR spectra of **2a–2d**, which showed absorption in the region 3400–3482 cm^{-1} attributed to NH and at 1323–1332 cm^{-1} attributed to C=S, in agreement with our earlier calculations for both tautomers.[4] The spectral data of **1a–1d** and **2a**, **2c**, and **2d** are presented in Table I.

The pharmacokinetic properties of 4-aryl-3-(2-methyl-furan-3-yl)-Δ^2-1,2,4-triazole-5-thiones **2a–2d** were determined and compared with structural and physicochemical properties of Fluconazole and 3-[(5-methyl-2-benzoxazolinone-3-yl)methyl]-4-phenyl-1H-1,2,4-triazole-5(4H)-thione. All triazoles **2a–2d**, Fluconazole, and the reference triazole obey Lipinski's "rule of five" and complementary criteria as shown in Table II. Except for lipophilicity, no major differences between the pharmacokinetic and QSAR properties of Fluconazole and **2a–2d** were observed.

TABLE I Spectral Data of Compounds 1a–1d and 2a, 2c, and 2d

Compound No.	Spectral data
1a	**IR** (KBr): 3348, 3156, 1605, 732, 2965, 1411, 1682, 1364, 1180, 804; **^{1}H-NMR** (DMSO): 2.28 s, 3H (CH_3); 2.53 s, 3H (CH_3); 6.92 d, 1H, J = 1.9 (CH); 7.11–7.32 m, 4H (4×CH); 7.55–7.56 d, 1H, J = 2.0 (CH); 9.53 s, 1H (NH); 9.69 s, 1H (NH); 10.03 s, 1H (NH).
1b	**IR** (KBr): 3382, 3236, 3154, 1603, 1500, 737, 2963, 1461, 1404, 1666, 1355, 1185, 750; **^{1}H-NMR** (DMSO): 2.27 s, 3H (CH_3); 2.53 s, 3H (CH_3), 6.91 d, 1H, J = 1.9 (CH); 7.13–7.21 m, 4H (4×CH); 7.54 d, 1H, J = 1.9 (CH); 9.50 s, 2H (2×NH); 10.05 s, 1H (NH).
1c	**IR** (KBr): 3353, 3232, 2961, 1602, 828, 2834, 1406, 1666, 1365, 1180, 795; **^{1}H-NMR** (DMSO): 2.53 s, 3H (CH_3); 3.74 s, 3H (CH_3); 6.87–6.90 dd, 2H, J = 2.0, J = 7.0 (2×CH); 6.92 d, 1H, J = 1.9 (CH); 7.27–7.30 d, 2H, J = 8.7 (2×CH); 7.55–7.56 d, 1H, J = 2.0 (CH); 9.50 s, 1H (NH); 9.64 s, 1H (NH); 10.02 s, 1H (NH).
1d	**IR** (KBr): 3347, 3162, 1601, 826, 2966, 1483, 1398, 1679, 1357; 1181, 796; **^{1}H-NMR** (DMSO): 2.53 s, 3H (CH_3); 6.80–6.81 d, 1H, J = 1.7 (CH); 7.49 d, 1H, J = 1.8 (CH); 7.53–7.67 m, 4H (4×CH); 9.22 s, 1H (NH); 9.27 s, 1H (NH); 10.06 s, 1H (NH).
2a	**IR** (KBr): 3409, 3058, 1557, 1515, 1480, 820, 2919, 1412, 1384, 1230, 1607, 1329; **^{1}H-NMR** (DMSO): 2.38 s, 3H (CH_3); 2.39 s, 3H (CH_3); 5.63–5.64 d, 1H, J = 2.0 (CH); 7.21–7.34 m, 4H (4×CH); 7.43–7.44 d, 1H, J = 2.0 (CH); 13.99 s, 1H (NH).
2c	**IR** (KBr): 3400, 3088, 1587, 1514, 833, 3041, 1230, 2928, 2836, 1466, 1454, 1442, 1386, 1610, 1332; **^{1}H-NMR** (DMSO): 2.40 s, 3H (CH_3); 3.82 s, 3H (CH_3); 5.65–5.66 d, 1H, J = 1.9 (CH); 7.03–7.08 m, 2H (2×CH); 7.25–7.30 m, 2H (2×CH); 7.44–7.45 d, 1H, J = 2.0 (CH); 13.98 s, 1H (NH).
2d	**IR** (KBr): 3410, 3090, 1562, 825, 3048, 1233, 2930, 1488, 1383, 1606, 1327; **^{1}H-NMR** (DMSO) *δ:* 2.38 s, 3H (CH_3); 5.72 d, 1H, J = 2.0 (CH); 7.17–7.21 m, 2H (2×CH), 7.46–7.47 d, 1H, J = 2.0 (CH); 7.87–7.92 m, 2H (2×CH); 14.06 s, 1H (NH).

Microbiology

The antimicrobial activities of the synthesized triazoles **2a–2d** were tested against a series of Gram-positive bacteria, Gram-negative bacteria, and yeasts. At first we performed tests using the disc-diffusion method. Compounds that showed activity in these tests were then examined using the broth dilution method in order to determine their MICs. Microbial susceptibility testing was performed according to the CLSI guidelines.[5]

The results revealed that compounds **2b–2d** were inactive against all tested bacteria and yeasts. Only triazole **2a** exhibited activity against

TABLE II Pharmacological and QSAR Properties[a] of Fluconazole, the Reference Triazole, 3-[(5-Methyl-2-benzoxazolinone-3-yl)methyl]-4-phenyl-1H-1,2,4-triazole-5(4H)-thione, and Compounds 2a–2d

Compound	Mw	logP	Hydration Energy	Volume	$\Delta H_{SH\text{-}NH}$	HOF	H-bond acceptors	H-bond donors	Rotable bonds	Polarizability	Polar surface area	Surface area	Dipole moment	Molar refractivity
Fluconazole	306.3	−0.118	−9.8	778.83	–	269.8	1	7	5	28.62	178.78	468.44	4.45	75.53
Reference triazole	338.4	2.151	−9.2	917.22	8.6	951.2	1	6	3	36.68	150.53	552.91	4.54	91.31
2a	271.3	2.452	−8.9	762.21	8.5	781.6	1	4	2	30.70	102.36	457.37	4.83	81.67
2b	271.3	2.616	−8.9	772.46	8.7	780.2	1	4	2	30.70	102.36	471.59	4.96	81.67
2c	287.3	2.060	−11.7	800.22	8.3	842.7	1	5	3	31.34	122.58	484.62	5.84	83.09
2d	383.2	3.087	−9.7	800.51	8.9	3040	1	4	2	33.89	102.36	489.19	4.79	89.03

[a]Energies in kcal/mol, surfaces in $Å^2$, volumes in $Å^3$.

TABLE III Antimicrobial Activity of 2a Expressed as the Growth Inhibition Zone [giz, mm] and Minimal Inhibitory Concentration (MIC, μg/mL)

	2a		Ciprofloxacin		Fluconazole	
Tested strain	giz	MIC	giz	MIC	giz	MIC
S. aureus NCTC 4163	11	200	26	0.500	nt**	
S. aureus ATCC 25923	12	100	26	0.500	nt	
S. aureus ATCC 6538	—	200	28	0.500	nt	
S. aureus ATCC 29213	—	200	22	0.500	nt	
S. epidermidis ATCC 12228	—	200	30	0.500	nt	
B. subtilis ATCC 6633	12	100	40	< 0.125	nt	
B. cereus ATCC 11778	—	100	20	1.000	nt	
E. hirae ATCC 10541	—	> 400	—	4.000	nt	
M. luteus ATCC 9341	11	50	22	4.000	nt	
M. luteus ATCC 10240	11	100	24	2.000	nt	
E. coli ATCC 10538	na*		34	< 0.125	nt	
E. coli ATCC 25922	na		35	< 0.125	nt	
E. coli NCTC 8196	na		35	< 0.125	nt	
P. vulgaris NCTC 4635	na		36	< 0.125	nt	
P. aeruginosa ATCC 15442	na		25	0.500	nt	
P. aeruginosa NCTC 6749	na		26	0.500	nt	
P. aeruginosa ATCC 27853	na		23	1.000	nt	
B. bronchiseptica ATCC 4617	na		31	1.000	nt	
C. albicans ATCC 10231	na		nt		22	1.000
C. albicans ATCC 90028	na		nt		32	1.000
C. parapsilosis ATCC 22019	na		nt		22	2.000

*__na –__ no activity in disc diffusion test- denotes lack of the growth inhibition zone.
**__nt__—not tested.
Ciprofloxacin (5 μg per disc); Fluconazole (25 μg per disc).

Gram-positive bacteria, especially against *M. luteus* ATCC 9341 (MIC 50 μg/mL), as illustrated in Table III.

Computational Methods

Geometries of Fluconazole, the reference triazole, and compounds **2a–2d** were fully optimized at the semiempirical level using new RM1 parameterization.[6] We have shown recently (Wujec, Siwek, and Paneth, unpublished results) that this method yields correct relative energies of thiol/thione tautomers and geometries in which bond lengths and valence angles are in excellent agreement with DTF results. Observed deviation in dihedral angles does not introduce significant contribution to the energy. This finding enabled us to use this much faster theory

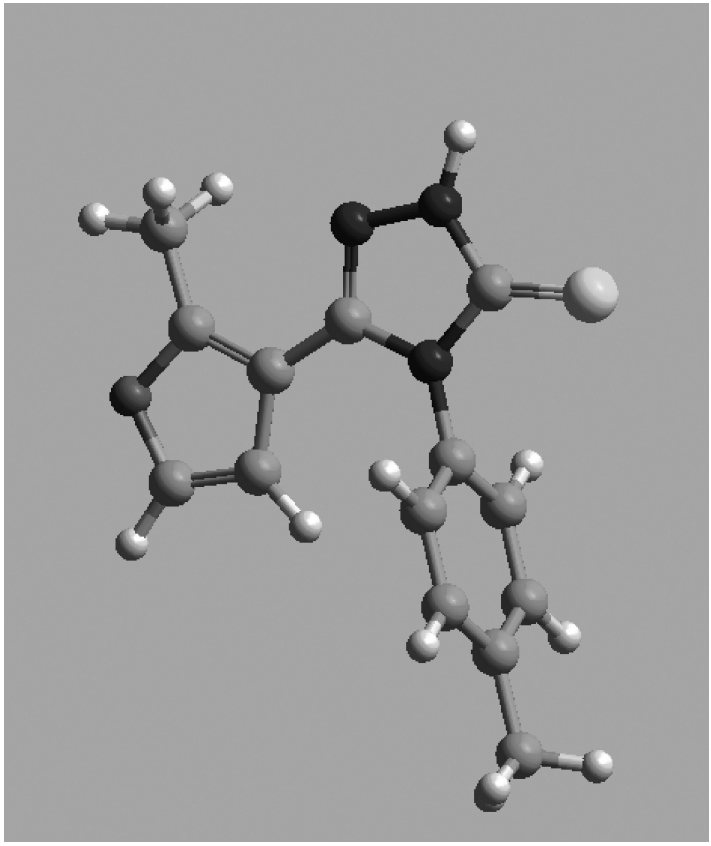


FIGURE 2 RM1 optimized structure of the compound **2a**.

level instead of DFT calculations. We have shown that for all triazoles studied, the thione tautomer is more stable by about 8–9 kcal/mol (see Table II). The optimal conformation of the triazole molecules is obtained for furan and triazole rings lying in the same plane and phenyl ring being perpendicular to this plane as illustrated in Figure 2 on the example of compound **2a**. Most of the QSAR properties are quite similar for all studied compounds, and their analysis does not provide any indication as to why they exhibit such different bioactivity.

In summary, four new 4-aryl-3-(2-methyl-furan-3-yl)-Δ^2-1,2,4-triazole-5-thiones have been investigated as antimicrobial agents. Among them only compound **2a** was found to have antimicrobial activity against Gram-positive bacteria, especially against *M. luteus* ATCC

9341. Minute structural differences between **2a** and **2b**, which result in significant difference of pharmacological activity, cannot be easily explained. It is probable that the structural characterizations are more important for this kind of activity. Studies with analogues of the title compounds aimed at understanding these differences are underway.

EXPERIMENTAL

Chemistry

Melting points were determined in a Fischer-Johns block and are uncorrected. IR spectra (ν, cm^{-1}) were recorded in KBr using a Specord IR-75 spectrophotometer. ^{1}H-NMR spectra (δ, ppm) were recorded on a Bruker Avance 300 in DMSO-d_6 with TMS as internal standard. All chemicals and reagents used were purchased from Lancaster.

4-Aryl-1-[(2-methyl-furan-3-yl)carbonyl]thiosemicarbazides **1a–1d** and their 1,2,4-triazole-thione analogs **2a–2d** were prepared according to the procedure reported previously.[3]

The characterization data of **1a–1d** and **2a**, **2c**, and **2d** are presented in Table IV. Compound **2b** is known (CAS:438231–54-0).

Microbiology

The assessment of the antimicrobial action of the synthesized compounds was performed using the disc-diffusion method and the MIC. MICs were defined as the lowest concentration of the compounds that inhibited visible growth of microorganisms after 18 h incubation at 35°C. Microorganisms used in this study were as follows: Gram-positive bacteria: four strains of *Staphylococcus aureus* (NCTC 4163, ATCC 25923, ATCC 6538, ATCC 2921), *Staphylococcus epidermidis* ATCC 12228, *Bacillus subtilis* ATCC 6633, *Bacillus cereus* ATCC 11778, *Enterococcus hirae* ATCC 10541, *Micrococcus luteus* ATCC 9341, *Micrococcus luteus* ATCC 10240 and Gram-negative rods: three strains of *Escherichia coli* (ATCC 10538, ATCC 25922, NCTC 8196), *Proteus vulgaris* NCTC 4635, three strains of *Pseudomonas aeruginosa* (ATCC 15442, NCTC 6749, ATCC 27863), and *Bordetella bronchiseptica* ATCC 4617. For testing antifungal activities of the compounds, the following reference strains were tested: *Candida albicans* ATCC 10231, *Candida albicans* ATCC 90028, and *Candida parapsilosis* ATCC 22019. Antimicrobial activity was tested under standard conditions using Mueller-Hinton II agar medium (Becton Dickinson) for bacteria and RPMI

TABLE IV The Characterization Data of the Compounds 1a–1d and 2a, 2c, and 2d

Compound No.	R	Yield [g,%]	Mp °C	% Carbon		% Hydrogen		% Nitrogen	
				Calcd	Found	Calcd	Found	Calcd	Found
1a	4-$CH_3C_6H_4$	2.8, 97	163–165	58.11	57.93	5.23	5.54	14.52	14.37
1b	2-$CH_3C_6H_4$	2.5, 89	143–145	58.11	58.40	5.23	5.24	14.52	14.36
1c	4-$OCH_3C_6H_4$	2.9, 95	170–172	55.07	54.96	4.95	5.05	13.76	14.07
1d	4-IC_6H_4	3.4, 89	187–189	38.92	39.23	3.01	3.36	10.47	10.35
2a	4-$CH_3C_6H_4$	2.4, 91	232–234	61.97	61.56	4.83	4.67	15.49	15.70
2c	4-$OCH_3C_6H_4$	2.7, 94	179–181	58.52	58.61	4.56	4.84	14.62	14.51
2d	4-IC_6H_4	3.1, 85	254–256	40.75	40.30	2.63	2.44	10.97	10.89

agar medium with 2% glucose (Sigma) for yeasts, according to CLSI guidelines.

The compounds were dissolved in DMSO. Then, for the disc diffusion assay, sterile filter paper discs (9 mm diameter, Whatman No. 3 chromatography paper) were soaked with solutions of tested compound to load 400 μg per disc. Dry discs were placed on the surface of appropriate agar medium. Diameter of the growth inhibition zone was read after 18 h of incubation at 35°C. For determination of MICs, concentrations of tested compounds were in the range from 6.25 to 400 μg/mL in a solid medium. The final inoculum of all microorganisms was 10^4 cfu/ml (colony forming units per mL), except the inoculum for *E. hirae* ATCC 10541, which was 10^5 cfu/mL. The results (MICs) were read after 18 h of incubation at 35°C. Ciprofloxacin and Fluconazole were used as standard antimicrobial powder.

Computational Methods

All calculations were carried out using new semiempirical parameterization RM1 as implemented in HyperChem.[7] Molecular geometries were fully optimized in the gas phase. Vibrational analysis has been carried out to confirm identity of the stationary points (3n-6 real vibrations). The QSAR module of the HyperChem and Molinspiration[8] programs were used to the calculate parameters collected in Table II.

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