Kurzmitteilung:

Synthesis and Antifungal Activity of Some 2-Aryl-3-substituted 4-Thiazolidinones

Synthese und antimykotische Aktivität einiger 2-Aryl-3-substituierter 4-Thiazolidinone

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In continuation of our studies on the synthesis and biological activity of 4-thiazolidinones^{1,2)}, we here report the synthesis of some hydrazones and 4-thiazolidinones carrying an imidazo[1,2-a]pyridine moiety at the N-atom, prepared with the objective of screening their antifungal activities.

2-Methylimidazo[1,2-a]pyridine-3-carbohydrazide $(1)^{2}$) was obtained by refluxing the corresponding ethyl ester with hydrazine hydrate. Condensation of 1 with appropriate aromatic aldehydes yielded the corresponding hydrazones **2a-h**, which on condensation with mercaptoacetic acid³) afforded the 4-thiazolidinones **3a-h** (Scheme).



The IR-spectra of **2a-h** and **3a-h** show CO bands at 1640-1580 cm⁻¹ (CONH-N). A new strong band at 1710 cm⁻¹ in the spectra of **3a-h** provides firm support for ring closure. After the reaction with mercaptoacetic acid the ¹H-NMR spectra of compounds **3a-h** display two doublets at about $\delta = 3.99-3.80$ ppm due to the non-equivalence of the methylene protons⁴). The singlet of N=CH at about 8.87-8.19 ppm in the spectra of **2a-h** is shifted upfield to 6.34-5.77 ppm by the loss of the sp² character of the involved C-atom. The thiazolidinones exhibit (MH)⁺ ions (except **3d** and **3g**) with different intensities (Table 1). Spectral data of respresentative derivatives are given in the Experimental Part.

Antifungal activity

The compounds were tested for antifungal activity against Candida albicans ATCC 10231 (A), Microsporum canis (B), Trichophyton mentagrophytes (C), NCPF-312 Trichopyton equinum (D), and NCPF-580 Microsporum gypseum (E) using the microdilution method^{5.6)}. Yeast Nitrogen Base (YNB, Difco) and Nutrient Broth media were used in the tests. Clotrimazole and miconazole were used as standards. The substances were dissolved in DMSO and solutions of 50-0.04 µg/ml (for A strain) and 25-0.2 µg/ml (for B, C, D, E strains) were prepared. The minimum concentration at which no growth was observed was taken as the MIC value (Table 2).

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Experimental Part

M.p.'s: Büchi 530 apparatus, uncorrected. - Elemental analysis: Perkin Elmer 240. - IR spectra: Perkin Elmer 577 (KBr): - ¹H-NMR: Bruker AC

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Compounds	R	Mo	Yield	Formula	Analysis (calcd./found)			HS (CI, CH ₄)
		[°C]	[8]	(Molecular mass)	C	н	N	(rel. int. %)
28	н	184-186	67	C16H14N40.H20	64.8	5.4	18.9	
				(296.3)	64.4	4,9	19.1	
21	CI (4)	262	82	C ₁₆ H ₁₃ CiN₄O	61.4	4.2	17.9	
				(312.8)	62.0	4.1	18.1	
2c	F (4)	250	95	C16H13 FN40	64.9	4.4	18.9	
				(296.3)	64.9	4.5	18.8	
24	NO ₂ (2)	245	91	C16H13 N503	59.4	4.1	21.7	
				(323.3)	59.4	3.8	21.1	
20	CH3 (4)	238-240	82	C17H16N40	69.8	5.5	19.2	
				(292.4)	70.9	5.6	19.4	



Table 1

2f	och ₂ 0 (3,4)	210	75	C17H14N4O3.H2O	60.0	4.7	16.5	
				(340.4)	59.9	5.3	15.7	
2g	0CH3.0H (3,4)	231	97	C _{I7} H _{I6} N₄O3	63.0	5.0	17.3	
	-			(324.4)	63.5	5.3	17.5	
2h	0C ₂ H ₅ ,0H (3,4)	224	91	C18HaNaO3	63.9	5.4	16.6	
	••			(338.4)	64.3	5.5	16.4	
3e	н	145	86	C18H16N402S.H20	58.4	4.9	15.1	353 (MH ⁺ , 23)
				(370.4)	57.9	5.2	14.8	
36	CI (4)	165	77	C18H15CIN402S.H20	53.4	4.2	13.8	389((11+ 2) ⁺ ,20),
				(404.9)	52.8	4.8	13.0	387 (MH ⁺ , 53)
3c	F (4)	147	73	C18H15FN402S.2H20	53.2	4.7	13.8	371 (MH+, 17)
				(406.5)	53.3	4.5	13.6	
34	NO ₂ (2)	223	48	C ₁₈ H ₁₅ N ₅ 0₄S.H ₂ 0	52.0	4.1	16.9	
	-			(415.4)	51.6	4.3	16.8	
3e	CH3 (4)	117-120	52	C ₁₉ H ₁₈ N₄0 ₂ 5.H ₂ 0	59.4	5.2	14.6	367 (MH ⁺ , 34)
	·			(384.5)	58.9	5.3	14.6	
3f	0CH ₂ 0 (3,4)	198	89	C19H16N404S.3H20	50.7	4.9	12.4	397 (MH ⁺ , 1)
	-			(450.5)	51.2	4.1	11.5	
39	0CH3,0H (3,4)	150	67	C19H18N404S.H20	54.8	4.8	13.5	
				(416.5)	54.9	5.1	13.1	
3h	0C ₂ H ₅ ,0H (3,4)	130-132	97	C ₂₀ H ₂₀ N ₄ 0 ₄ S.H ₂ 0	55.8	5.1	13.0	413 (MH ⁺ , 24)
				(430.5)	56.2	53	12.0	

Tab. 1: Continued

Table 2: MIC values (µg/ml) of 2a-h and 3a-h

Compound		Fungi			
	A	8	c	D	Ε
28	12.5	12.5	12.5	12.5	12.5
26	12.5	1.6	6	12.5	25
2c	12.5	12.5	12.5	25	12.5
24	12.5	12.5	12.5	25	6
20	25	6	6	25	12.5
2f	12.5	12.5	6	6	3
29	12.5	12.5	12.5	25	6
2h	12.5	12.5	12.5	25	6
3a	25	12.5	12.5	25	6
36	25	6	12.5	12.5	25
3c	12.5	12.5	12.5	3	25
34	12.5	12.5	12.5	25	12.5
3e	12.5	6	12.5	25	12.5
3f	12.5	12.5	12.5	12.5	12.5
39	25	12.5	12.5	25	12.5
36	12.5	12.5	12.5	6	12.5
Ciotrimazole	25	0.2	0.2	0.2	0.2
Miconazole	25	1.6	0.2	0.4	0.2

A: Candida albicans ATCC 10231, B: Microsporum canis, C: Trichophyton mentagrophytes, D: NCPF-312 Trichophyton equinum, E: NCPF-580 Microsporum gypseum

200 MHz, $[D_6]DMSO.$ - CI-MS (CH₄): Sittingbourne Research Centre, UK. - Water content: 665 Dosimat, Metrohm 682 Titroprocessor.

2-Methylimidazo[1,2-a]pyridine-3-carbohydrazide hydrazones 2a-h

0.01 Mol of 1 was refluxed with 0.01 mol of the appropriate aldehyde in 30 ml of EtOH (96%) for 0.5 h. The solid that separated was recrystallized from EtOH (96%). - 2a: IR: 1620 (CO) cm⁻¹. - ¹H-NMR: δ (ppm) = 11.51

(1H, s, NH), 8.87 (1H, s, N=CH), 8.31 (1H, d, J=7 Hz, 5-H), 7.75-7.40 (7H, m, 7-H, 8-H; phenyl), 7.04 (1H, t, J = 6.8 Hz, 6-H), 2.56 (3H, s, CH₃).

2-Aryl-3-[(2-methylimidazo[1,2-a]pyridine-3-yl)carbonyl]amino-4thiazolidinones **3a-h**

A mixture of the hydrazone **2a-h** (0.01 mol) and mercaptoacetic acid (0.01 mol) was refluxed in dry benzene (100 ml) using a Dean-Stark water separator. Excess benzene was evaporated *in vacuo*. The resulting residue was triturated with saturated NaHCO₃ solution until CO₂ evolution ceased and was allowed to stand overnight. The solid thus obtained was washed with water, dried, and recrystallized from EtOH-H₂O. - **3a**: IR: 1710 (CO, thiazolidinone), 1640 (NHCO) cm⁻¹. - ¹H-NMR: δ (ppm) = 10.14 (1H, s, NH), 8.77 (1H, d, J = 5.7 Hz, 5-H), 7.58-7.36 (7H, m, 7-H, 8-H; phenyl), 7.02 (1H, t, J = 6.8 Hz, 6-H), 5.97 (1H, s, N-CH-S), 3.96, 3.85 (1H each, 2d, J = 15.9 Hz, CH₂-S), 2.20 (3H, s, CH₃).

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