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Synthesis and Antimycotic Activity of some 3-(1-Imidazolylmethyl)indoles

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The title compounds were synthesized and tested for their *in vitro* antimycotic activity. 1-Ethyl-3-{[2,4-dichloro-α-(1-imidazolyl)]phenethyl}indole **(5)** exhibited appreciable activity against Cr. neoformans (MIC = 12,5 μg/ml).

Synthese und antimykotische Wirkung einiger 3-(1-Imidazolylmethyl)indole

Die Titelverbindungen wurden hergestellt und auf ihre antimykotische *in vitro*-Aktivität untersucht. 1-Ethyl-3-{[2,4-dichlor-α-(1-imidazolyl)]phenethyl}indol **(5)** zeigte eine signifikante Wirksamkeit gegen Cr. neoformans (MIC = 12,5 μg/ml).

In a previous paper[1], we reported some 1-benzyl-3-(1-imidazolylmethyl)indoles **1**, carrying a 2,4-dichloro- or 3,4-dichlorobenzyl moiety at the 1-position, to be significantly active *in vitro* against *Cr. neoformans*.

In an attempt to further characterize the structural requirements of this class of imidazole derivatives as antifungal agents, it was of interest to investigate the effect of selected

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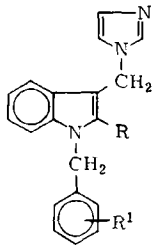
structural modifications. Thus, the results by *Strehlke* and *Kessler*[2] and the role of the lypophilicity in the antimycotic activity[3,4], led us to synthesize as analogues of **1** with a n-propyl substituent at the methylene bridge the compounds **2** and **3**. Moreower, as an exploratory investigation on the importance of the relative location of the chlorobenzyl and imidazolyl moieties, compounds **4** and **5** were also prepared. Synthesis and the *in vitro* antimycotic activity of these new imidazole derivatives are described in the present paper.



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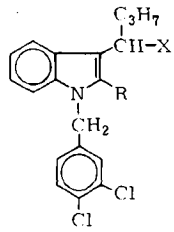
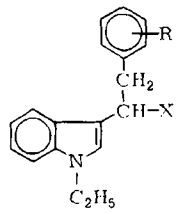


2,3



4,5

R = H, Cl, CH_3 **2** R = H **3** R = Cl **4** R = 4-Cl **5** R = 2,4-Cl_2
R^1 = Cl **2a** R = H **3a** R = Cl **4a** R = 4-Cl **5a** R = 2,4-Cl_2

2, 3, 4, 5: X =  **2a, 3a, 4a, 5a**: X = OH

Chemistry

The synthesis of 1-(3,4-dichlorobenzyl)-3-[1-(1-imidazolyl)butyl]indoles **2** and **3** was carried out from the appropriate indol-3-carboxaldehyde by reaction with n-propylmagnesium iodide followed by melting of the resulting secondary alcohols **2a** and **3a** in the presence of imidazole and p-toluensulphonic acid. Similarly, 2-ethyl-3-indolcarboxaldehyde on treatment with 4-chlorobenzyl- and 2,4-dichlorobenzylmagnesium chloride afforded the alcohols **4a** and **5a**, resp., which were then converted in the corresponding 1-ethyl-3-[α-(1-imidazolyl)phenethyl]-indoles **4** and **5**, under the described conditions.

Antimycotic Activity

The new imidazole derivatives **2–5** were tested for their antifungal activity *in vitro* against the following microorganisms: Candida albicans, Candida tropicalis, Candida pseudotropicalis, Candida guillermondi, Cryptococcus neoformans, Geotrichum candidum and Aspergillus fumigatus. The *in vitro* activity was evaluated according a previously described method[1] and was expressed as the minimal inhibitory concentration (MIC, μg/ml). Only Cr. neoformans, C. pseudotropicalis and G. candidum proved to be sensitive to **2–5**; the MIC values are reported in Table 1.

As it can be seen, the new imidazole derivatives are only moderately active, with an activity spectrum comparable to that of their analogues **1**. The most active compound **5** retains a preferential activity against *Cr. neoformans*.

Table 1: *Antimycotic activity in vitro of* **2–5**

Microorganism	MIC (μg/ml) 2	3	4	5
Cr. neoformans	100	50	100	12,5
C. pseudotropicalis	100	100	> 100	25
G. candidum	100	50	100	100

Experimental Part

M.p.: open capillaries (uncorr.); *IR spectra*: Perkin-Elmer 177 in nujol. *Elementary analyses*: Laboratory for microanalysis of the Faculty of Farmacy of the University of Pisa, Italy. The purety of **2–5** was checked by TLC on silica gel (Baker-Flex FB2-F) using ethylacetate/ethanol 9 : 1 as eluent and UV (254 nm) or iodine vapours for the detection.

1-Ethyl-3-indolcarboxaldehyde

To a solution of 1 g (about 7 mmol) indole-3-carboxaldehyde in 15 ml dry DMF, 0,5 g sodium hydride (55 % dispersion in mineral oil) was added portionwise with stirring at room temp. When the evolution of hydrogen ceased, 0,6 ml (8 mmol) ethylbromide was added. The reaction mixture was stirred for 0,5 h at room temp. and then the resulting precipitate was collected (1,11 g; yield 93 %) and purified by cristallization from ethanol-water. M.p. 99–101 °C. IR (nujol): 1655 (CO), 1240, 1175, 1125, 1075, 1035, 850, 775, 745 cm^{-1}. $C_{11}H_{11}NO$ (173,22) Calcd. C 76,3 H 6,40 N 8,1; Found C 76,4 H 6,60 N 7,9.

Preparation of the secondary alcohols **2a, 3a, 4a** *and* **5a**

General procedure: The Grignard reagents, chlorobenzylmagnesium chlorides and propylmagnesium iodide, were prepared following a standard method[5]. To the ethereal Grignard reagent (2.0 mmol) solution, the appropriate indol-3-carboxaldehyde (1.0 mmol) dissolved in THF (minimal necessary vol.) was added dropwise under gentle reflux. The mixture was refluxed until the reaction was complete (monitoring by TLC on silica gel using ethylacetate/n-hexane 1 : 1 or chloroform as eluent, and UV 254 nm and then the 2,4-dinitrophenylhydrazine reagent, for the detection). The reaction mixture was poured into 100 ml of saturated aqueous ammonium chloride solution and extracted with ether. The combined ethereal extracts were evaporated and the residue was purified by crystallization.

1-(3,4-Dichlorobenzyl)-3-(1-hydroxybutyl)indole **(2a)**

Yield: 96 %. M.p. 88–90 °C (n-hexane/ethylacetate); IR (nujol): 3280, 3200, 1175, 1060, 1025, 1010, 945, 735 cm^{-1}. $C_{19}H_{19}Cl_2NO$ (348,27) Calcd. C 65,5 H 5,50 N 4,0; Found C 65,6 H 5,36 N 3,7.

2-Chloro-1-(3,4-dichlorobenzyl)-3-(1-hydroxybutyl)indole **(3a)**

Yield 92 %. M.p. 83–85 °C (n-hexane). IR (nujol): 3340, 1130 (d), 1100, 1060, 1025, 735 cm^{-1}. $C_{19}H_{18}Cl_3NO$ (382,73) Calcd. C 59,6 H 4,74 N 3,7; Found C 59,9 H 4,76 N 3,6.

1-Ethyl-3-[(4-chloro-α-hydroxy)phenethyl]indole **(4a)**

Yield 95 %. M.p. 75–78 °C (n-hexane). IR (nujol): 3300, 3230, 1090, 1050, 1010, 795, 730 cm^{-1}. $C_{18}H_{18}ClNO$ (299,81) Calcd. C 72,1 H 6,05 N 4,7; Found C 72,4 H 6,01 N 4,7.

1-Ethyl-3-[(2,4-dichloro-α-hydroxy)phenethyl]indole **(5a)**

Yield 55 % M.p. 92–94 (n-hexane); IR (nujol): 3320, 3240, 1045, 985, 880, 825, 815, 735, 725 cm^{-1}. $C_{18}H_{17}Cl_2NO$ (334,25) Calcd. C 64,7 H 5,12 N 4,8; Found C 64,6 H 5,02 N 4,40.

Synthesis of the imidazole derivatives **2–5**

The previously described procedure[1] was followed. A mixture of appropriate secondary alcohol, imidazole and p-toluensulphonic acid (molar ratios 1 : 3 : 0,7) was heated at 100–120 °C for about 1 h. After cooling, the reaction mixture was chromatographed on silica gel column eluting with ethylacetate/ethanol 95 : 5 and the isolated product was crystallized as hydrochloride salt (**2** and **4**) or as free base (**3** and **5**).

1-(3,4-Dichlorobenzyl)-3-[1-(1-imidazolyl)butyl]indole **(2)**

Yield 30 %. M.p. 124–126 °C (methylene chloride/ether saturated with hydrogen chloride). IR (nujol; free base): 1070, 1020, 915, 825, 815, 730 cm^{-1}. $C_{22}H_{21}Cl_2N_3 \cdot HCl$ (434,77) Calcd. 60,8 H 5,1 N 9,7; Found C 60,8 H 5,02 N 9,4.

2-Chloro-1-(3,4-dichlorobenzyl)-3-[1-(1-imidazolyl)butyl]indole **(3)**

Yield 48 %. M.p. 99–101 °C (ethanol/water). IR (nujol; free base): 1125, 1070, 1025, 900, 810, 790, 730 cm^{-1}. $C_{22}H_{20}Cl_3N_3$ (432,79) Calcd. C 61,1 H 4,66 N 9,7; Found C 61,5 H 4,73 N 9,6.

1-Ethyl-3-{[4-chloro-α-(1-imidazolyl)]phenethyl}indole **(4)**

Yield 35 %. M.p. 181–184 °C (methylene chloride/ether saturated with hydrogen chloride). IR (nujol; hydrochloride): 1090, 1015, 835, 820, 795, 740 cm^{-1}. $C_{21}H_{20}ClN_3 \cdot HCl$ (386,34) Calcd. C 65,3 H 5,48 N 10,9; Found C 66,0 H 5,65 N 11,0.

1-Ethyl-3-{[2,4-dichloro-α-(1-imidazolyl)]phenethyl}indole **(5)**

Yield: 30 %. M.p. 145–147 °C (ethanol/water). IR (nujol; free base): 1210, 1070, 855, 825, 810, 740 cm^{-1}. $C_{21}H_{19}Cl_2N_3$ (384,32) Calcd. C 65,6 H 4,98 N 10,9; Found C 66,0 H 4,86 N 10,9.

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