Available online at www.sciencedirect.com
SCIENCE DIRECT®
Il Farmaco 58 (2003) 315–322
IL FARMACO
www.elsevier.com/locate/farmac

Synthesis and antifungal activity of (±)-1-(5-aryl-3-pyridin-2-yl-4,5-dihydro-pyrazol-1-yl)-2-imidazol-1-yl-ethanone derivatives☆

Maria Grazia Mamolo [a,*], Daniele Zampieri [a], Valeria Falagiani [a], Luciano Vio [a], Elena Banfi [b]

[a] *Dipartimento di Scienze Farmaceutiche, Università di Trieste, Piazzale Europa 1, I-34127 Trieste, Italy*
[b] *Dipartimento di Scienze Biomediche (Sez. Microbiologia), Università di Trieste, Via Fleming 22, I-34127 Trieste, Italy*

Received 16 July 2002; accepted 26 September 2002

Abstract

(±)-1-(5-Aryl-3-pyridin-2-yl-4,5-dihydro-pyrazol-1-yl)-2-imidazol-1-yl-ethanone derivatives were synthesized and tested for their in vitro antifungal activity. The compounds showed a moderate activity against strains of *Candida parapsilosis*, *Candida pseudotropicalis* and *Candida glabrata*.

Keywords: (±)-1-(5-Aryl-3-pyridin-2-yl-4,5-dihydro-pyrazol-1-yl)-2-imidazol-1-yl-ethanone derivatives; Antifungal activity; *Candida spp.*

1. Introduction

In our search for new antimycobacterial compounds we reported [1] on the synthesis and microbiological evaluation of some (±)-(5-aryl-3-pyridin-2-yl-4,5-dihydro-pyrazol-1-yl)-pyridin-4-yl-methanones (**1**) in which the nitrogen atom at 1 position of the pyrazoline cycle was linked to the isonicotinoyl residue. Because all the synthesized compounds exhibited an interesting in vitro antimycobacterial activity toward a strain of *M. tuberculosis* H_4, and other 4,5-dihydro-1*H*-pyrazole derivatives had been described for their antibacterial [2–6] and antifungal [2,5,7] activities, we made a modification of the active structure **1** by replacing the isonicotinoyl group with the 1*H*-imidazol-1-yl-acetyl one, in order to verify if the presence of the azole residue might confer antifungal activity to the compounds **4 a**–**m** (Table 1). The structure of compounds **4 a**–**m**, even if different from those of the classic antimycotic drugs, is characterized by the presence of the 1*H*-imidazol-1-yl-acetyl moiety connected to the pyrazoline ring by an amide linkage, in consideration of the antifungal activity of a number of 2-imidazol-1-yl-acetamide derivatives [8–10]. All the synthesized compounds were tested in vitro for their antifungal activity toward *Candida albicans* and *Candida* spp. in comparison with antimycotic drugs.

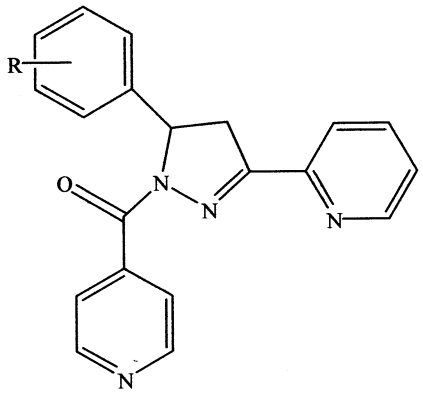
2. Chemistry

The synthesis of (±)-2-bromo-1-(5-aryl-3-pyridin-2-yl-4,5-dihydro-pyrazol-1-yl)-ethanones (**3 a**–**m**) (Table 1) was carried out (Scheme 1) by reacting bromoacetyl chloride with the corresponding (±)-5-aryl-3-(pyridin-2-yl)-4,5-dihydro-1*H*-pyrazoles (**2 a**–**m**) which in turn were prepared, as previously described, from the corresponding 3-aryl-1-(pyridin-2-yl)-propenones (**1 a**–**m**) by treatment with hydrazine hydrate [1]. However, when the α,β-unsaturated ketones were allowed to react with hydrazine hydrate, very unstable products were obtained, from which the corresponding 4,5-dihydro-1*H*-pyrazoles (**2**) should be isolated [1,11]. The crude products were directly used for the preparation of the corresponding 4,5-dihydro-1*H*-pyrazole derivatives (**3c**, **3f**, **3h**, **3i** and **3k**–**m**). The (±)-1-(5-aryl-3-pyridin-2-yl-4,5-dihydro-pyrazol-1-yl)-2-imidazol-1-yl-ethanones

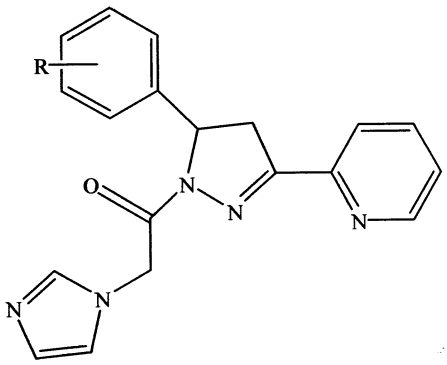
☆ A preliminary account of this work was presented at XVIth International Symposium on Medicinal Chemistry, 18–22 September 2000, Bologna, Italy.

* Corresponding author.
E-mail address: mamolo@univ.trieste.it (M.G. Mamolo).

0014-827X/03/$ - see front matter
doi:10.1016/S0014-827X(02)00006-X



1



4 a-m

(**4a**–**m**) (Table 2) were obtained by treatment of the (±)-2-bromo-1-(5-aryl-3-pyridin-2-yl-4,5-dihydro-pyrazol-1-yl)-ethanone derivatives (**3a**–**m**) with imidazole in acetonitrile.

The ^{1}H NMR spectra of compounds **3a**–**m**, and **4a**–**m** reveal the presence of three doublets of doublet signals due to pyrazoline magnetically non equivalent protons H_A (upfield H of CH_2) and H_B (downfield H of CH_2), and to the vicinal methine proton H_X. The values of the coupling constants between the protons are consistent with the expected structures. Moreover, the methylene protons in the bromoacetyl side-chain of compounds **3a**–**m** resonate as two doublets characterized by coupling constants typical of two geminal magnetically non equivalent protons. However, the signals of corresponding methylene protons of the compounds **4a**–**m** undergo a fusion to a single signal.

The general synthetic procedure is described in Section 3 for the preparation of the new compounds **3a**–**m** and **4a**–**m**.

3. Experimental

3.1. Chemistry

Melting points (m.p.) were determined with a Büchi 510 capillary apparatus, and are uncorrected. Infrared spectra in Nujol mulls were recorded on a Jasco FT 200 spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were determined on a Varian Gemini 200 spectrometer; chemical shifts are reported as δ (ppm) relative to tetramethylsilane as internal standard, deuterochloroform as solvent. Reaction courses and product mixtures were routinely monitored by thin-layer chromatography (TLC) on silica gel precoated F_{254} Merck plates. EI-MS spectra (70 eV) were taken on a VG 7070 spectrometer. Elemental analyses (C, H, N) were performed on a Carlo Erba analyzer and were within ±0.3 of the theoretical value.

3.1.1. (±)-2-Bromo-1-(5-phenyl-3-pyridin-2-yl-4,5-dihydro-pyrazol-1-yl)-ethanone (**3a**)

To a stirred solution of 5.29 g (23.7 mmol) of (±)-5-phenyl-3-(pyridin-2-yl)-4,5-dihydro-1*H*-pyrazole (**2a**) [1] and 2.39 g (23.7 mmol) of triethylamine in 40 ml of benzene, 3.73 g (23.7 mmol) of bromoacetyl chloride was added dropwise at room temperature (r.t.). The reaction mixture was further stirred for 4 h and concentrated under reduced pressure. The residue was filtered, washed several times with water, dried in a vacuum dessicator and recrystallized from absolute ethanol to obtain 4.11 g (50%) of **3a**; m.p. 100–102 °C.

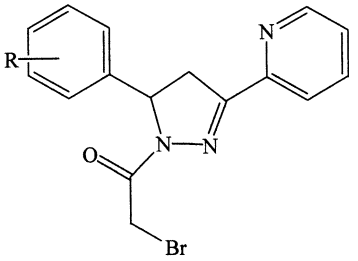
IR (Nujol, per cm): 1665. ^{1}H NMR ($CDCl_3$-TMS): δ 3.37 (dd, 1H, H_A, upfield H of pyrazoline CH_2; J_{AB} = 19.04, J_{AX} = 4.88 Hz), 3.87 (dd, 1H, H_B, downfield H of pyrazoline CH_2; J_{BA} = 19.04, J_{BX} = 11.72 Hz), 4.26 (d, 1H, $H_{A'}$, exocyclic CH_2; $J_{A'B'}$ = 10.74 Hz), 4.35 (d, 1H, $H_{B'}$, exocyclic CH_2; $J_{B'A'}$ = 10.74 Hz), 5.53 (dd, 1H, H_X; J_{XA} = 4.88, J_{BX} = 11.72 Hz), 7.30–8.60 (m, 9H, arom. and pyr.) MS: *m/z* 343 [M^+], 345.

Compounds **3b**–**m** were prepared similarly. Yields, m.p. and spectral data of compounds **3a**–**m** are reported in Table 1. Yields of compounds **3c**, **3f**, **3h**, **3i**, **3k**–**3m**, prepared starting, as previously described [1], from the corresponding crude products of the reaction between the α,β-unsatured ketones and hydrazine hydrate, were calculated on the basis of the amount of ketone employed.

3.1.2. (±)-1-(5-Phenyl-3-pyridin-2-yl-4,5-dihydro-pyrazol-1-yl)-2-imidazol-1-yl-ethanone (**4a**)

To a stirred solution of 1.1 g (3.2 mmol) of (±)-2-bromo-1-(5-phenyl-3-pyridin-2-yl-4,5-dihydro-pyrazol-1-yl)-ethanone (**3a**) in 20 ml of acetonitrile 0.45 g (6.6

Table 1
Spectral data of compounds **3a**–**m**

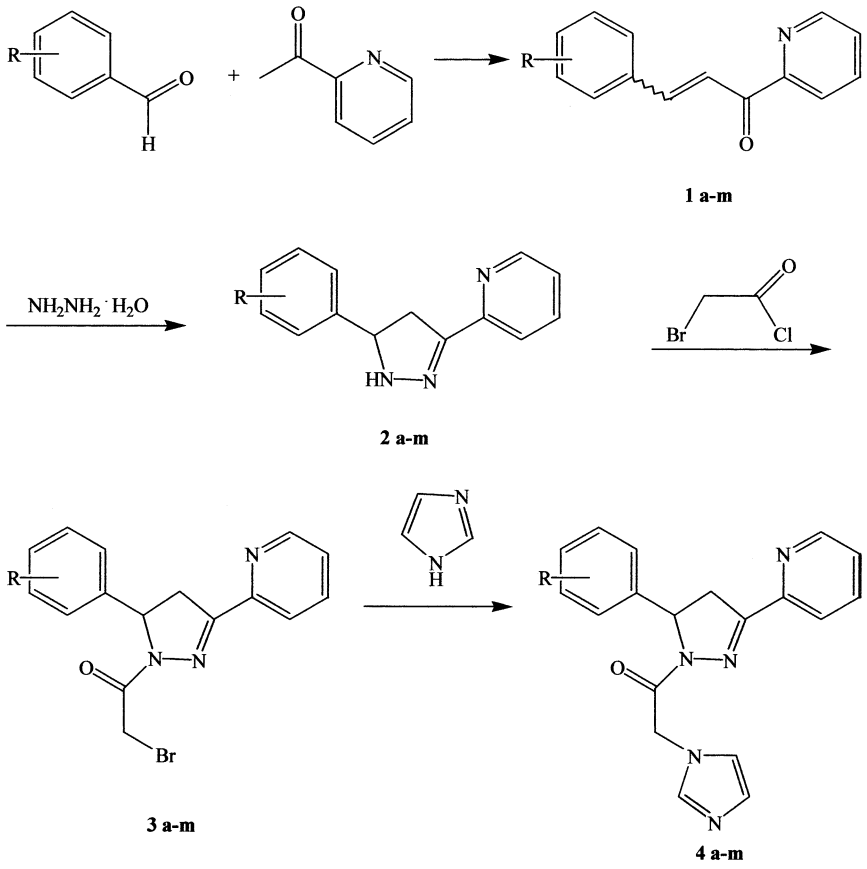


3 a-m

Comp.	R	Yield (%)	m.p. (°C)	IR (Nujol, per cm)	^{1}H NMR ($CDCl_3$) (δ)	Mass m/z [M^+]	Formula (C,H,N)
3a	H	50	102	1665	3.37 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 19.04$, $J_{AX} = 4.88$ Hz), 3.87 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 19.04$, $J_{BX} = 11.72$ Hz), 4.26 (d, 1H, $H_{A'}$, exocyclic CH_2; $J_{A'B'} = 10.74$ Hz), 4.35 (d, 1H, $H_{B'}$, exocyclic CH_2; $J_{B'A'} = 10.74$ Hz), 5.53 (dd, 1H, H_X; $J_{XA} = 4.88$, $J_{BX} = 11.72$ Hz), 7.30–8.60 (m, 9H, arom. and pyr.)	343–345	$C_{16}H_{14}N_3OBr$
3b	2-Cl	46	155	1680	3.38 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 19.04$, $J_{AX} = 5.37$ HZ), 4.07 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 19.04$, $J_{BX} = 11.72$ Hz), 4.29 (d, 1H, $H_{A'}$, exocyclic CH_2; $J_{A'B'} = 10.74$ Hz), 4.46 (d, 1H, $H_{B'}$, exocyclic CH_2; $J_{B'A'} = 10.74$ Hz), 5.94 (dd, 1H, H_X; $J_{XA} = 5.37$, $J_{XB} = 11.72$ Hz), 7.06–8.68 (m, 8H, arom. e pyr.)	377–379	$C_{16}H_{13}N_3OBrCl$
3c	3-Cl	49	159	1667	3.37 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 19.04$, $J_{AX} = 4.88$ Hz), 3.87 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 19.04$, $J_{BX} = 11.72$ Hz), 4.27 (d, 1H, $H_{A'}$, exocyclic CH_2; $J_{A'B'} = 10.74$ Hz), 4.34 (d, 1H, $H_{B'}$ exocyclic CH_2; $J_{B'A'} = 10.74$ Hz), 5.53 (dd, 1H, H_X; $J_{XA} = 4.88$, $J_{XB} = 11.72$ Hz), 7.12–8.58 (m, 8H, arom. e pyr.)	377–379	$C_{16}H_{13}N_3OBrCl$
3d	4-Cl	41	130	1661	3.40 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 18.92$, $J_{AX} = 4.88$ Hz), 3.89 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 18.92$, $J_{BX} = 11.60$ Hz), 4.25 (d, 1H, $H_{A'}$, exocyclic CH_2; $J_{A'B'} = 10.38$ Hz), 4.35 (d, 1H, $H_{B'}$, exocyclic CH_2; $J_{B'A'} = 10.38$ Hz), 5.55 (dd, 1H, H_X; $J_{XA} = 4.88$, $J_{XB} = 11.60$ Hz), 7.14–8.61 (m, 8H, arom. e pyr.)	377–379	$C_{16}H_{13}N_3OBrCl$
3e	2-Br	53	137	1667	3.29 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 19.04$, $J_{AX} = 4.88$ Hz), 4.00 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 19.04$, $J_{BX} = 11.72$ Hz), 4.28 (d, 1H, $H_{A'}$, exocyclic CH_2; $J_{A'B'} = 10.74$ Hz), 4.46 (d, 1H, $H_{B'}$, exocyclic CH_2; $J_{B'A'} = 10.74$ Hz), 5.90 (dd, 1H, H_X; $J_{XA} = 4.88$, $J_{XB} = 11.72$ Hz), 7.06–8.59 (m, 8H, arom. e pyr.)	421–423	$C_{16}H_{13}N_3OBr_2$
3f	3-Br	58	160	1667	3.37 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 19.04$, $J_{AX} = 4.39$ Hz), 3.87 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 19.04$, $J_{BX} = 11.72$ Hz), 4.27 (d, 1H, $H_{A'}$, exocyclic CH_2; $J_{A'B'} = 10.98$ Hz), 4.35 (d, 1H, $H_{B'}$, exocyclic CH_2; $J_{B'A'} = 10.98$ Hz), 5.52 (dd, 1H, H_X; $J_{XA} = 4.39$, $J_{XB} = 11.72$ Hz), 7.15–8.59 (m, 8H, arom. e pyr.)	421–423	$C_{16}H_{13}N_3OBr_2$

Table 1 (*Continued*)

Comp.	R	Yield (%)	m.p. (°C)	IR (Nujol, per cm)	^{1}H NMR ($CDCl_3$) (δ)	Mass m/z [M^+]	Formula (C,H,N)
3g	4-Br	48	148	1662	3.38 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 19.04$, $J_{AX} = 4.88$ Hz), 3.88 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 19.04$, $J_{BX} = 11.72$ Hz), 4.25 (d, 1H, $H_{A'}$, exocyclic CH_2; $J_{A'B'} = 10.74$ Hz), 4.34 (d, 1H, $H_{B'}$, exocyclic CH_2; $J_{B'A'} = 10.74$ Hz), 5.53 (dd, 1H, H_X; $J_{XA} = 4.88$, $J_{BX} = 11.72$ Hz), 7.09–8.60 (m, 8H, arom. e pyr.)	421–423	$C_{16}H_{13}N_3OBr_2$
3h	2-F	42	98	1660	3.39 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 19.04$, $J_{AX} = 5.37$ Hz), 3.90 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 19.04$, $J_{BX} = 11.72$ Hz), 4.28 (d, 1H, $H_{A'}$, exocyclic CH_2; $J_{A'B'} = 10.74$ Hz), 4.38 (d, 1H, $H_{B'}$, exocyclic CH_2; $J_{B'A'} = 10.74$ Hz), 5.78 (dd, 1H, H_X; $J_{XA} = 5.37$, $J_{XB} = 11.72$ Hz), 6.98–8.59 (m, 8H, arom. e pyr.)	361–363	$C_{16}H_{13}N_3OBrF$
3i	3-F	47	100	1668	3.37 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 18.68$, $J_{AX} = 4.94$ Hz), 3.87 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 18.68$, $J_{BX} = 12.08$ Hz), 4.26 (d, 1H, $H_{A'}$, exocyclic CH_2; $J_{A'B'} = 10.44$ Hz), 4.36 (d, 1H, $H_{B'}$, exocyclic CH_2; $J_{B'A'} = 10.44$ Hz), 5.56 (dd, 1H, H_X; $J_{XA} = 4.94$, $J_{XB} = 12.08$ Hz), 6.89–8.58 (m, 8H, arom. e pyr.)	361–363	$C_{16}H_{13}N_3OBrF$
3j	4-F	48	117	1660	3.40 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 18.68$, $J_{AX} = 4.94$ Hz), 3.87 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 18.68$, $J_{BX} = 12.08$ Hz), 4.26 (d, 1H, $H_{A'}$, exocyclic CH_2; $J_{A'B'} = 10.99$ Hz), 4.35 (d, 1H, $H_{B'}$, exocyclic CH_2; $J_{B'A'} = 10.99$ Hz), 5.56 (dd, 1H,H_X; $J_{XA} = 4.94$, $J_{XB} = 12.08$ Hz), 6.93-8.60 (m, 8H, arom. E pyr.)	361–363	$C_{16}H_{13}N_3OBrF$
3k	2-CH_3	53	133	1656	2.42 (s, 3H, –CH_3), 3.25 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 18.31$, $J_{AX} = 4.88$ Hz), 3.91 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 18.31$, $J_{BX} = 11.60$ Hz), 4.31 (d, 1H, $H_{A'}$, exocyclic CH_2; $J_{A'B'} = 10.38$ Hz), 4.40 (d, 1H, $H_{B'}$, exocyclic CH_2; $J_{B'A'} = 10.38$ Hz), 5.75 (dd, 1H, H_X; $J_{XA} = 4.88$, $J_{XB} = 11.60$ Hz), 6.98–8.58 (m, 8H, arom. e pyr.)	357–359	$C_{17}H_{16}N_3OBr$
3l	3-CH_3	59	oil	1659	2.32 (s, 3H, -CH_3), 3.35 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 18.91$, $J_{AX} = 4.88$ Hz), 3.81 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 18.91$, $J_{BX} = 11.60$ Hz), 4.30 (d, 1H, $H_{A'}$, exocyclic CH_2; $J_{A'B'} = 10.58$ Hz), 4.41 (d, 1H, $H_{B'}$, exocyclic CH_2; $J_{B'A'} = 10.58$ Hz), 5.65 (dd, 1H, H_X; $J_{XA} = 4.88$, $J_{XB} = 11.60$ Hz), 6.70–8.50 (m, 8H, arom. e pyr.)	357–359	$C_{17}H_{16}N_3OBr$
3m	4-CH_3	57	138	1663	2.28 (s, 3H, –CH_3), 3.40 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 19.04$, $J_{AX} = 5.13$ Hz), 3.86 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 19.04$, $J_{BX} = 11.72$ Hz), 4.28 (d, 1H, $H_{A'}$, exocyclic CH_2; $J_{A'B'} = 10.99$ Hz), 4.35 (d, 1H, $H_{B'}$, exocyclic CH_2; $J_{B'A'} = 10.99$ Hz), 5.56 (dd, 1H, H_X; $J_{XA} = 5.13$, $J_{XB} = 11.72$ Hz), 7.07–8.59 (m, 8H, arom. e pyr.)	357–359	$C_{17}H_{16}N_3OBr$



Scheme 1.

mmol) of imidazole was added and the reaction mixture was then stirred under reflux for 2 h. The solvent was evaporated to dryness under reduced pressure to leave a residue which was dissolved in chloroform. The obtained solution was washed with several portions of cold water, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (60 mesh, eluent acetonitrile/ethanol 95:5). Evaporation of solvents gave 0.56 g (53%) of the pure compound **4a**; m.p. 186–88 °C.

IR (Nujol, per cm): 1681. ^{1}H NMR ($CDCl_3$-TMS): δ 3.43 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 19.04$, $J_{AX} = 4.88$ Hz), 3.89 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 19.04$, $J_{BX} = 11.72$ Hz), 5.18 (s, 2H, exocyclic CH_2), 5.54 (dd, 1H, H_X; $J_{XA} = 4.88$, $J_{XB} = 11.72$ Hz), 7.61 (s, 1H, H-2 imid.), 6.98–8.61 (m, 11H, arom., pyr. and imid.).

In the same manner, compounds **4b**–**m** were prepared. Yields, m.p. and spectral data of compounds **4a**–**m** are reported in Table 2.

3.2. Microbiology

3.2.1. Antifungal susceptibility testing

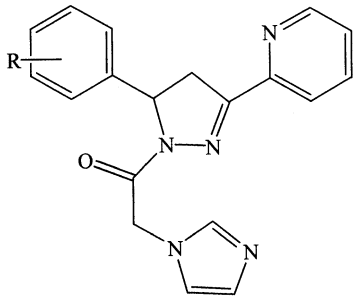
Test organisms. Five clinical isolates of Candida species were selected for testing the new compounds, including *Candida glabrata* 80, *C. glabrata* 67, *C. albicans* 135, *Candida parapsilosis* 208 and *Candida pseudotropicalis* 801.

The susceptibility of the *Candida* spp isolates to the newly synthesized compounds was determined by means of the agar dilution technique, according to the recommendations of the National Committee for Clinical Laboratory Standards (NCCLS, 1995). Stock solutions of chemicals were prepared in DMSO at a concentration of 4 mg/ml; MICs were determined in Sabouraud quadrant agar plates containing serial twofold dilutions of the tested compounds; 20 μl inoculum of each fungal strain, containing $1–5 \times 10^2$ cells per ml was added onto agar surface; controls were performed without chemicals and with reference antifungal drugs (miconazole (Mic), 5-fluorouracil (5-FC), amphotericin B (AMB)). All the plates were then placed at 35 °C and read after 24 and 48 h incubation.

4. Results and discussion

A series of (±)-1-(5-aryl-3-pyridin-2-yl-4,5-dihydropyrazol-1-yl)-2-imidazol-1-yl-ethanone derivatives (**4a**–**m**) have been synthesized with the aim of evaluating their in vitro antimycotic activity. Some of the synthe-

Table 2
Spectral data of compounds **4a**–**m**



4 a-m

Comp.	R	Yield (%)	m.p. (°C)	IR (Nujol, per cm)	^{1}H NMR ($CDCl_3$) (δ)	Mass m/z [M^+]	Formula (C,H,N)
4a	H	53	186	1681	3.43 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 19.04$, $J_{AX} = 4.88$ Hz), 3.89 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 19.04$, $J_{BX} = 11.72$ Hz), 5.18 (s, 2H, exocyclic CH_2), 5.54 (dd, 1H, H_X; $J_{XA} = 4.88$, $J_{XB} =$ 11.72 Hz), 7.61 (s, 1H, H-2 imid.), 6.98–8.61 (m, 11H, arom., pyr. and imid.)	331	$C_{19}H_{17}N_5O$
4b	2-Cl	45	195	1684	3.31 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 19.04$, $J_{AX} = 6.83$ Hz), 3.96 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 19.04$, $J_{BX} = 11.72$ Hz), 5.22 (s, 2H, exocyclic CH_2), 5.88 (dd, 1H, H_X; $J_{XA} = 6.83$, $J_{XB} =$ 11.72 Hz), 7.58 (s, 1H, H-2 imid.), 6.94–8.60 (m, 10H, arom., pyr. and imid.)	365-367	$C_{19}H_{16}N_5OCl$
4c	3-Cl	50	178	1683	3.40 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 18.92$, $J_{AX} = 4.88$ Hz), 3.89 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 18.92$, $J_{BX} = 12.20$ Hz), 5.21 (s, 2H, exocyclic CH_2), 5.49 (dd, 1H, H_X; $J_{XA} = 4.88$, $J_{XB} =$ 12.20 Hz), 7.54 (s, 1H, H-2 imid.), 6.98–8.61 (m, 10H, arom., pyr. and imid.)	365- 367	$C_{19}H_{16}N_5OCl$
4d	4-Cl	51	222	1679	3.40 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 19.53$, $J_{AX} = 5.37$ Hz), 3.89 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 19.53$, $J_{BX} = 12.21$ Hz), 5.15 (s, 2H, exocyclic CH_2), 5.51 (dd, 1H, H_X; $J_{XA} = 5.37$, $J_{XB} =$ 12.21 Hz), 7.53 (s, 1H, H-2 imid.), 6.96–8.62 (m, 10H, arom., pyr. and imid.)	365-367	$C_{19}H_{16}N_5OCl$
4e	2-Br	55	193	1684	3.27 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 19.04$, $J_{AX} = 5.37$ Hz), 3.97 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 19.04$, $J_{BX} = 11.71$ Hz), 5.22 (s, 2H, exocyclic CH_2), 5.86 (dd, 1H, H_X; $J_{XA} = 5.37$, $J_{XB} =$ 11.71 Hz), 7.59 (s, 1H, H-2 imid.), 6.88–8.58 (m, 10H, arom., pyr. and imid.)	409-411	$C_{19}H_{16}N_5OBr$

Table 2 (*Continued*)

Comp.	R	Yield (%)	m.p. (°C)	IR (Nujol, per cm)	^{1}H NMR ($CDCl_3$) (δ)	Mass m/z [M^+]	Formula (C,H,N)
4f	3-Br	56	188	1684	3.38 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 19.04$, $J_{AX} = 5.12$ Hz), 3.88 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 19.04$, $J_{BX} = 11.72$ Hz), 5.16 (s, 2H, exocyclic CH_2), 5.47 (dd, 1H, H_X; $J_{XA} = 5.12$, $J_{XB} =$ 11.72 Hz), 7.53 (s, 1H, H-2 imid.), 6.96–8.61 (m, 10H, arom., pyr. and imid.)	409-411	$C_{19}H_{16}N_5Obr$
4g	4-Br	51	227	1679	3.39 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 18.67$, $J_{AX} = 4.94$ Hz), 3.88 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 18.67$, $J_{BX} = 12.08$ Hz), 5.15 (s, 2H, exocyclic CH_2), 5.48 (dd, 1H, H_X; $J_{XA} = 4.94$, $J_{XB} =$ 12.08 Hz), 7.53 (s, 1H, H-2 imid.), 6.96–8.61 (m, 10H, arom., pyr. and imid.)	409-411	$C_{19}H_{16}N_5OBr$
4h	2-F	48	170	1671	3.41 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 18.67$, $J_{AX} = 5.49$ Hz), 3.89 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 18.67$, $J_{BX} = 12.08$ Hz), 5.18 (s, 2H, exocyclic CH_2), 5.77 (dd, 1H, H_X; $J_{XA} = 5.49$, $J_{XB} =$ 12.08 Hz), 7.54 (s, 1H, H-2 imid.), 6.98–8.61 (m, 10H, arom., pyr. and imid.)	350	$C_{19}H_{16}N_5OF$
4i	3-F	46	179	1684	3.40 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 19.22$, $J_{AX} = 4.94$ Hz), 3.89 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 19.22$, $J_{BX} = 12.08$ Hz), 5.17 (s, 2H, exocyclic CH_2), 5.52 (dd, 1H, H_X; $J_{XA} = 4.94$, $J_{XB} =$ 12.08 Hz), 7.54 (s, 1H, H-2 imid.), 6.84–8.61 (m, 10H arom., pyr. and imid.)	350	$C_{19}H_{16}N_5OF$
4j	4-F	49	179	1682	3.41 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 19.04$, $J_{AX} = 4.88$ Hz), 3.87 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 19.04$, $J_{BX} = 11.71$ Hz), 5.15 (s, 2H, exocyclic CH_2), 5.57 (dd, 1H, H_X; $J_{XA} = 4.88$, $J_{XB} =$ 11.71 Hz), 7.53 (s, 1H, H-2 imid.), 6.91–8.62 (m, 10H, arom., pyr. and imid.)	350	$C_{19}H_{16}N_5OF$
4k	2-CH_3	55	178	1676	2.28 (s, 3H, -CH_3), 3.25 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 19.05$, $J_{AX} = 5.13$ Hz), 3.97 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 19.05$, $J_{BX} = 11.72$ Hz), 5.20 (s, 2H, exocyclic CH_2), 5.72 (dd, 1H, H_X; $J_{XA} = 5.13$, $J_{XB} = 11.72$ Hz), 7.55 (s, 1H, H-2 imid.), 6.85–8.58 (m, 10H, arom., pyr. and imid.)	346	$C_{20}H_{19}N_5O$
4l	3-CH_3	62	169	1686	2.27 (s, 3H, –CH_3), 3.41 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 19.05$, $J_{AX} = 4.88$ Hz), 3.87 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 19.05$, $J_{BX} = 11.59$ Hz), 5.17 (s, 2H, exocyclic CH_2), 5.51 (dd, 1H, H_X; $J_{XA} = 4.88$, $J_{XB} = 11.59$ Hz), 7.55 (s, 1H, H-2 imid.), 6.95–8.52 (m, 10H, arom., pyr. and imid.)	346	$C_{20}H_{19}N_5O$
4m	4-CH_3	61	181	1671	2.27 (s, 3H, –CH_3), 3.42 (dd, 1H, H_A, upfield H of pyrazoline CH_2; $J_{AB} = 18.92$, $J_{AX} = 4.88$ Hz), 3.86 (dd, 1H, H_B, downfield H of pyrazoline CH_2; $J_{BA} = 18.92$, $J_{BX} = 11.59$ Hz), 5.15 (s, 2H, exocyclic CH_2), 5.51 (dd, 1H, H_X; $J_{XA} = 4.88$, $J_{XB} = 11.59$ Hz), 7.53 (s, 1H, H-2 imid.), 6.97–8.62 (m, 10H, arom., pyr. and imid.)	346	$C_{20}H_{19}N_5O$

Table 3
Activity of the (±)-1-(5-aryl-3-pyridin-2-yl-4,5-dihydro-pyrazol-1-yl)-2-imidazol-1-yl-ethanone derivatives **4** against three clinical isolates of *Candida* species

Comp.	Range (μg/ml)	CP 208		CPs 801		CG 80	
		24 h	48 h	24 h	48 h	24 h	48 h
AMB	0.5–8	1	2	2	< 0.5	2	2
Mic	5–80	< 5	< 5	< 5	< 5	< 5	< 5
5FC	2–32	< 2	4	< 2	8	< 2	< 2
4a	1000–16			62.5	62.5	62.5	62.5
4b	1000–16			62.5	62.5	62.5	62.5
4e	1000–16			62.5	62.5	62.5	62.5
4f	1000–16			62.5	62.5	62.5	62.5
4h	1000–62.5	62.5	62.5				
4i	1000–16	62.5	62.5				
4j	1000–16			62.5	62.5	62.5	62.5
4k	1000–16	62.5	62.5				

sized compounds exhibited a feeble in vitro antifungal activity against the tested strains of *Candida* species (Table 3). Compounds **4a**, **4b**, **4e**, **4f**, **4j** were characterized by the same degree of activity against the strains of *C. pseudotropicalis* 801 (CPs 801) and *C. glabrata* 80 (CG 80), with MIC values of 62.5 μg/ml after 24 and 48 h but their MIC values toward the strain of *C. glabrata* 67 increase from 62.5–125 μg/ml after 24 h to 500 μg/ml after 48 h. Only compounds **4h**, **4i** and **4k** exhibited MIC values of 62.5 μg/ml toward the tested strain of *C. parapsilosis* 208 (CP 208). None of the synthesized compounds showed activity against the tested strain of *C. albicans* 135. The moderately active compounds are generally characterized by the presence of halogen atoms at the *ortho* or *meta* position on the phenyl ring linked to the 5-position of the pyrazoline cycle, with the exception of the unsubstituted compound **4a** and the 4-fluoro derivative **4j**. None of the other *para*-substituted compounds were active. Since the substituents on the phenyl residue of the compounds **4a**, **4b**, **4e**, **4f** and **4j**, which explicated some activity against *C. pseudotropicalis* 801 and *C. glabrata* 80, do not exert any modulatory effect on their activity, the synthesis and the antifungal activity evaluation of new (±)-1-(4,5-dihydro-pyrazol-1-yl)-2-imidazol-1-yl-ethanone derivatives, with different substituents in the 3 and 5 positions, are now in progress.

Acknowledgements

The Authors would like to thank dott. M. Cebulec for the microanalyses. This research was carried out with the financial support of the Italian MURST (60%).

References

[1] M.G. Mamolo, D. Zampieri, V. Falagiani, L. Vio, E. Banfi, Synthesis and antimycobacterial activity of 5-aryl-1-isonicotinoyl-3-(pyridin-2-yl)-4,5-dihydro-1*H*-pyrazole derivatives, Farmaco 56 (2001) 593–599.
[2] A. Attia, M. Michael, Azachalcones. Part 2: reaction of 3,3-diazachalcones, Pharmazie 37 (1982) 551–553.
[3] P. Descacq, A. Nuhrich, M. Varache-Beranger, M. Capdepuy, G. Devaux, Arylpyrazolines nitrofuraniques: synthèse et propriétés antibactériennes, Eur. J. Med. Chem. 25 (1990) 285–290.
[4] P. Patel, S. Koregaokar, M. Shah, H. Parekh, Synthesis of some novel pyrazoline and cyanopyridine derivatives as antimicrobial agents, Farmaco 51 (1996) 59–63.
[5] N. Grant, N. Mishriky, F.M. Asaad, N.G. Fawzi, Pyridines and pyrazolines from salicylic acid derivatives with propenone residue and their antimicrobial properties, Pharmazie 53 (1998) 543–547.
[6] A.M. Kamal El-Dean, S.M. Radwan, Synthesis and antimycobacterial activity of pyrazolo [3′,4′:4,3] pyrido [6,5-c] pyridazine and thieno [2,3-e] pyridazine derivatives, Pharmazie 53 (1998) 839–843.
[7] (a) S.P. Sachchar, A.K. Singh, Synthesis of some new fluorinated heteroarylpyrazolines and isoxazolines as potential biocidal agents, J. Indian Chem. Soc. 62 (1985) 142;
(b) S.P. Sachchar, A.K. Singh, Synthesis of some new fluorinated heteroarylpyrazolines and isoxazolines as potential biocidal agents, Chem. Abstr. 105 (1986) 42707c.
[8] K.H. Buechel, W. Meiser, C. Metzger, M. Plempel, Antimycotic imidazolyldiphenylacetic acid derivatives. Ger. Offen 1,925,994 (C1. C 07*d*, A 61*k*), 26 November, 1970, Application, 21 May 1969 [Chem. Abstr. 74, 53800v (1971)].
[9] K.H. Buechel, W. Meiser, M. Plempel, C. Metzger, Phenyl-imidazolyl-fatty acid derivatives for treating mycotic infections, US 3,826,836 (C1. 424-273; A 61*k*), 30 July 1974, Application, 18 May 1970 [Chem. Abstr. 83, 58819d (1975)].
[10] F. Özkanli, S. Dalkara, U. Çalis, A. Willke, Synthesis of some N-arylazole acetamide derivatives and their anticonvulsant and antimicrobial activities, Arzneim-Forsch. Drug Res. 44 (1994) 920–924.
[11] N. Mishriky, F.M. Asaad, Y.A. Ibrahim, A.S. Girgis, New 2-pyrazoline of anticipated molluscicidal activity, Pharmazie 51 (1996) 544–548.