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ORIGINAL ARTICLE

Preparation of some pyrazoline derivatives and evaluation of their antifungal activities

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Abstract

The synthesis of a new series of 1-[(benzazole-2-yl)thioacetyl]-3,5-diaryl-2-pyrazoline derivatives was obtained by reacting 1-(chloroacetyl)-3,5-diaryl-pyrazolines with 2-mercaptobenzimidazole/benzoxazole/benzothiazole. The chemical structures of the compounds were elucidated by ^{1}H-NMR, ^{13}C-NMR, and FAB^{+}-MS spectral data. Their antifungal activities against *Candida albicans*, *Candida glabrata*, *Candida utilis*, *Candida tropicalis*, *Candida krusei*, and *Candida parapsilosis* were investigated. A significant level of activity was observed.

Keywords: *Pyrazoline; antifungal activity;* Candida spp.

Introduction

Over the last three decades there has been a dramatic increase in the incidence of fungal infections. The discovery of new drugs for the treatment of systemic mycoses is a major challenge in infectious disease research. There is an urgent need for new antifungal remedies with novel modes of action, due to a decreased antifungal susceptibility of newly emerging fungi in the growing setting of the immunocompromised patient (e.g. human immunodeficiency virus (HIV)-positive and neutropenic patients). As is known, not only is the biochemical similarity of the human cell and fungi forms a handicap for selective activity, but also, easily gained resistance is the main problem encountered in developing safe and efficient antifungals[1–3].

In order to overcome this handicap, new agents should preferably have chemical characteristics that clearly differ from those of existing agents. In drug design programs, an essential component of the search for new leads is the synthesis of molecules that are novel yet resemble known biologically active molecules by virtue of the presence of critical structural features. Certain small heterocyclic molecules act as highly functionalized scaffolds and are known pharmacophores of a number of biologically active and medicinally useful molecules[4,5].

The benzimidazoles and their bioisosters the benzoxazoles have been proved to be the most important group of fungicides with systemic activity, and are well known for their pronounced ability to control a large number of fungal diseases[6,7]. Thiabendazole, benomyl, carbendazim, chlorfenazole, cypendazole, debacarb, fuberidazole, mecarbinzid, and rabenzazole, which include the benzimidazole moiety, are the main examples of this fungicide class[8,9]. In this group, the well-known fungicide thiabendazole inhibits fungal microtubular function, resulting in nondisjunction of chromosomes at cell division[10,11].

On the other hand, a literature survey showed that there have been many studies on the pyrazoline moiety and its antifungal activity[12–16].

In the interest of the above, we planned to synthesize a system that combines these two biolabile components, i.e. benzimidazoles/benzoxazoles/benzothiazoles and pyrazolines, to give compact-structure title compounds.

Experimental

Chemistry

All melting points (m.p.) were determined in open capillaries on a Gallenkamp apparatus (Weiss-Gallenkamp,

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Loughborough, UK) and are uncorrected. The purity of the compounds was routinely checked by thin layer chromatography (TLC) using silica gel 60G (Merck, Darmstadt, Germany). Spectroscopic data were recorded with the following instruments: ^{1}H-nuclear magnetic resonance (NMR), Bruker 400 MHz spectrometer and ^{13}C-NMR, Bruker 100 MHz spectrometer (Bruker, Billerica, MA, USA) in dimethylsulfoxide (DMSO)-d_6 using tetramethylsilane (TMS) as internal standard; and fast atom bombardment-mass spectrometry (FAB-MS), VG Quattro spectrometer (Agilent, Minnesota, USA).

General procedure for synthesis of the compounds

1-(2-Furanyl)-3-aryl-2-propen-1-ones A mixture of 2-acetylfuran (0.06 mol), aromatic aldehyde (0.06 mol), and 10% aqueous sodium hydroxide (10 mL) in ethanol (30 mL) was stirred at room temperature for about 3 h. The resulting solid was washed, dried, and crystallized from ethanol.

5-Aryl-3-(2-furanyl)-2-pyrazolines A solution of the appropriate furanyl chalcone (0.03 mol) and hydrazine hydrate (80%) (0.06 mol) in ethanol (30 mL) was refluxed for 3 h. The reaction mixture was cooled and kept at 0°C overnight. The resulting solid was recrystallized from ethanol.

1-(Chloroacetyl)-3-(2-furanyl)-5-aryl-2-pyrazolines The 5-aryl-3-(2-furanyl)-2-pyrazolines (0.02 mol) and triethylamine (0.02 mol) were dissolved in dry toluene (30 mL) with constant stirring. Later, the mixture was cooled in an ice bath, and chloroacetyl chloride (0.02 mol) was added dropwise with stirring. The reaction mixture thus obtained was further agitated for 1 h at room temperature. The precipitate was filtered, the solvent was evaporated to dryness under reduced pressure, and the products were recrystallized from ethanol.

*1-[(Benzazole-2-yl)thioacetyl]-3-(2-furanyl)-5-aryl-2-pyrazoline derivatives (**A1–23**)* A mixture of 1-(chloroacetyl)-3-(2-furanyl)-5-aryl-2-pyrazoline (0.01 mol), benzazol-2-thiole (0.01 mol), and K_2CO_3 (0.01 mol) in acetone (50 mL) was refluxed for 8 h. After cooling, the solution was evaporated until dryness. The residue was washed with water and recrystallized from ethanol[17].

Some characteristics of the synthesized compounds are shown in Table 1. Analytical and spectral data (^{1}H-NMR, ^{13}C-NMR, FAB^{+}-MS) confirmed the structures of the new compounds.

*1-[(Benzimidazole-2-yl)thioacetyl]-3-(2-furanyl)-5-(4-chlorophenyl)-2-pyrazoline (**A1**)* ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 3.07 (1H, dd, J = 18.0, 4.6 Hz), 3.84 (1H, dd, J = 18.0, 11.8 Hz), 4.57 (1H, d, J = 16.0 Hz), 4.82 (1H, d, J = 16.0 Hz), 5.59 (1H, dd, J = 11.7, 4.6 Hz), 6.67 (1H, dd, J = 3.4, 1.8 Hz), 7.02 (1H, d, J = 3.4 Hz), 7.10–7.17 (2H, m), 7.25–7.35 (4H, m), 7.47 (2H, m), 7.92 (1H, d, J = 1.2 Hz), 12.63 (1H, b). ^{13}C-NMR (100 MHz, δ, DMSO-d_6): 34.86 (CH_2), 41.83 (CH_2), 58.86 (CH), 109.45 (CH), 112.27 (CH), 114.77 (CH), 121.37 (CH), 122.26 (CH), 127.45 (2CH), 128.54 (2CH), 131.86 (C), 132.26 (CH), 140.37 (C), 145.84 (C), 145.88 (CH), 146.40 (C), 146.42 (C), 149.63 (C), 164.68 (C), 164.67 (C). FAB^{+}-MS: *m/z*: 436 (M^{+}), 437 (M^{+} + 1).

*1-[(5-Chlorobenzimidazole-2-yl)thioacetyl]-3-(2-furanyl)-5-(4-chlorophenyl)-2-pyrazoline (**A2**)* ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 3.09 (1H, dd, J = 18.0, 4.6 Hz), 3.82 (1H, dd, J = 18.0, 11.8 Hz), 4.56 (1H, d, J = 16.0 Hz), 4.80 (1H, d, J = 16.0 Hz), 5.58 (1H, dd, J = 11.7, 4.7 Hz), 6.67 (1H, dd, J = 3.5, 1.8 Hz), 7.01 (1H, d, J = 3.5 Hz), 7.11 (1H, d, J = 8.5), 7.25–7.35 (4H, m), 7.45 (1H, d, J = 8.5 Hz), 7.51 (1H, d, J = 2.0 Hz), 7.91 (1H, dd, J = 3.5, 2.3 Hz), 12.64 (1H, b). ^{13}C-NMR

Table 1. Some characteristics of the compounds.

Compound	R_1	R_2	R_3	X	Yield (%)	Molecular formula	Mol. weight	m.p. (°C)
A1	Cl	H	H	NH	78	$C_{22}H_{17}ClN_4O_2S$	436	232
A2	Cl	H	Cl	NH	75	$C_{22}H_{16}Cl_2N_4O_2S$	470	167
A3	Cl	H	CH_3	NH	72	$C_{23}H_{19}ClN_4O_2S$	450	132
A4	Cl	H	NO_2	NH	76	$C_{22}H_{16}ClN_5O_4S$	483	165
A5	O-CH_2-O		H	NH	69	$C_{23}H_{18}N_4O_4S$	446	189
A6	O-CH_2-O		Cl	NH	79	$C_{23}H_{17}ClN_4O_4S$	480	160
A7	O-CH_2-O		CH_3	NH	71	$C_{24}H_{20}N_4O_4S$	460	186
A8	O-CH_2-O		NO_2	NH	70	$C_{23}H_{17}N_5O_6S$	491	161
A9	H	H	H	NH	74	$C_{22}H_{18}N_4O_2S$	402	163
A10	H	H	Cl	NH	70	$C_{22}H_{17}ClN_4O_2S$	436	247
A11	H	H	CH_3	NH	62	$C_{23}H_{20}N_4O_2S$	416	180
A12	H	H	NO_2	NH	75	$C_{22}H_{19}N_5O_4S$	449	181
A13	H	H	H	O	77	$C_{22}H_{17}N_3O_3S$	403	177
A14	H	H	Cl	O	71	$C_{22}H_{16}ClN_3O_3S$	437	182
A15	H	H	CH_3	O	63	$C_{23}H_{19}N_3O_3S$	417	178
A16	Cl	H	Cl	O	80	$C_{22}H_{15}Cl_2N_3O_3S$	471	162
A17	Cl	H	CH_3	O	66	$C_{23}H_{18}ClN_3O_3S$	451	149
A18	O-CH_2-O		H	O	81	$C_{23}H_{17}N_3O_5S$	447	165
A19	O-CH_2-O		Cl	O	73	$C_{23}H_{16}ClN_3O_5S$	481	196
A20	O-CH_2-O		CH_3	O	70	$C_{24}H_{19}N_3O_5S$	461	156
A21	H	H	H	S	68	$C_{22}H_{17}N_3O_2S_2$	419	125
A22	Cl	H	H	S	76	$C_{22}H_{16}ClN_3O_2S_2$	453	138
A23	O-CH_2-O		H	S	81	$C_{23}H_{17}N_3O_4S_2$	463	144

(100 MHz, δ, DMSO-d_6): 34.86 (CH_2), 41.83 (CH_2), 58.85 (CH), 112.27 (CH), 113.72 (CH), 114.67 (CH), 114.78 (CH), 121.05 (CH), 125.42 (C), 127.46 (2CH), 128.54 (2CH), 131.87 (C), 138.56 (C), 140.38 (C), 141.24 (C), 145.84 (C), 145.82 (C), 145.86 (CH), 146.41 (C), 152.12 (C), 164.55 (C). FAB$^+$-MS: *m/z*: 470 (M^+), 471 ($M^+ + 1$), 472 ($M^+ + 2$).

1-[(5-Methylbenzimidazole-2-yl)thioacetyl]-3-(2-furanyl)-5-(4-chlorophenyl)-2-pyrazoline (***A3***) ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 2.39 (3H, s), 3.06 (1H, dd, *J* = 18.0, 4.6 Hz), 3.83 (1H, dd, *J* = 18.0, 11.8 Hz), 4.57 (1H, d, *J* = 15.9 Hz), 4.80 (1H, d, *J* = 15.9 Hz), 5.58 (1H, dd, *J* = 11.7, 4.6 Hz), 6.67 (1H, dd, *J* = 3.5, 1.8 Hz), 6.95 (1H, d, *J* = 8.2 Hz), 7.01 (1H, d, *J* = 3.4 Hz), 7.29 (6H, m), 7.91 (1H, d, *J* = 1.2 Hz), 12.46 (1H, s). ^{13}C-NMR (100 MHz, δ, DMSO-d_6): 30.62 (CH_3), 34.88 (CH_2), 41.82 (CH_2), 58.85 (CH), 112.25 (CH), 114.71 (CH), 122.65 (CH), 123.15 (CH), 127.44 (2CH), 128.54 (2CH), 130.46 (C), 131.85 (CH), 131.87 (C), 140.37 (C), 143.43 (C), 145.85 (CH), 145.81 (C), 146.35 (C), 148.95 (C), 149.63 (C), 164.73 (C), 164.77 (C). FAB$^+$-MS: *m/z*: 450 (M^+), 451 ($M^+ + 1$).

1-[(5-Nitrobenzimidazole-2-yl)thioacetyl]-3-(2-furanyl)-5--(4-chlorophenyl)-2-pyrazoline (***A4***) ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 3.08 (1H, dd, *J* = 18.0, 4.7 Hz), 3.85 (1H, dd, *J* = 18.0, 11.8 Hz), 4.61 (1H, d, *J* = 16.0 Hz), 4.84 (1H, d, *J* = 16.0 Hz), 5.59 (1H, dd, *J* = 11.8, 4.7 Hz), 6.67 (1H, dd, *J* = 3.5, 1.8 Hz), 7.03 (1H, dd, *J* = 3.5, 0.7 Hz), 7.31 (6H, m), 7.57 (1H, d, *J* = 8.8 Hz), 7.91 (1H, d, *J* = 1.8 Hz), 8.01 (1H, dd, *J* = 8.8, 2.3 Hz), 8.31 (1H, d, *J* = 2.0 Hz), 12.52 (1H, b). ^{13}C-NMR (100 MHz, δ, DMSO-d_6): 34.92 (CH_2), 41.83 (CH_2), 58.88 (CH), 110.22 (CH), 112.27 (CH), 113.28 (CH), 114.82 (CH), 116.89 (CH), 127.50 (2CH), 128.53 (2CH), 131.88 (C), 140.38 (C), 141.51 (C), 145.15 (C), 145.82 (C), 145.89 (CH), 146.48 (C), 150.26 (C), 157.21 (C), 164.50 (C). FAB$^+$-MS: *m/z*: 483 (M^+), 484 ($M^+ + 1$).

1-[(Benzimidazole-2-yl)thioacetyl]-3-(2-furanyl)-5-(3,4-methylenedioxyphenyl)-2-pyrazoline (***A5***) ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 3.08 (1H, dd, *J* = 17.9, 4.5 Hz), 3.79 (1H, dd, *J* = 17.9, 11.6 Hz), 4.60 (1H, d, *J* = 15.9 Hz), 4.79 (1H, d, *J* = 15.9 Hz), 5.50 (1H, dd, *J* = 11.6, 4.5 Hz), 5.97 (2H, s), 6.67 (1H, dd, *J* = 3.5, 1.8 Hz), 6.73 (1H, dd, *J* = 8.1, 1.7 Hz), 6.78–6.82 (2H, m), 7.02 (1H, d, *J* = 3.5 Hz), 7.13 (2H, m), 7.38 (1H, m), 7.55 (1H,m), 7.91 (1H, d, *J* = 1.8 Hz), 12.59 (1H, s). ^{13}C-NMR (100 MHz, δ, DMSO-d_6): 34.99 (CH_2), 42.03 (CH_2), 59.21 (CH), 100.97 (CH_2), 106.01 (CH), 108.19 (CH), 110.27 (CH), 112.24 (CH), 114.65 (CH), 117.34 (CH), 118.69 (CH), 121.07 (CH), 121.56 (CH), 135.39 (C), 135.51 (C), 143.58 (C), 145.80 (CH), 145.95 (C), 146.42 (C), 146.47 (C), 147.50 (C), 149.69 (C), 164.55 (C). FAB$^+$-MS: *m/z*: 446 (M^+).

1-[(5-Chlorobenzimidazole-2-yl)thioacetyl]-3-(2-furanyl)-5-(3,4-methylenedioxyphenyl)-2-pyrazoline (***A6***) ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 3.07 (1H, dd, *J* = 18.0, 4.5 Hz), 3.80 (1H, dd, *J* = 18.0, 11.8 Hz), 4.64 (1H, d, *J* = 16.0 Hz), 4.81 (1H, d, *J* = 16.0 Hz), 5.52 (1H, dd, *J* = 11.8, 4.5 Hz), 5.97 (2H, s), 6.68 (1H, dd, *J* = 3.5, 1.8 Hz), 6.73 (1H, dd, *J* = 8.1, 1.8 Hz), 6.79–6.82 (2H, m), 7.04 (1H, d, *J* = 3.5 Hz), 7.14 (2H, m), 7.36 (1H, m), 7.56 (1H, m), 7.92 (1H, d, *J* = 1.8 Hz), 12.60 (1H, s). FAB$^+$-MS: *m/z*: 480 (M^+), 481 ($M^+ + 1$), 482 ($M^+ + 2$).

1-[(5-Methylbenzimidazole-2-yl)thioacetyl]-3-(2-furanyl)-5-(3,4-methylenedioxyphenyl)-2-pyrazoline (***A7***) ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 2.38 (3H, s), 3.06 (1H, dd, *J* = 17.9, 4.5 Hz), 3.79 (1H, dd, *J* = 17.9, 11.6 Hz), 4.56 (1H, d, *J* = 15.8 Hz), 4.74 (1H, d, *J* = 15.8 Hz), 5.50 (1H, dd, *J* = 11.6, 4.5 Hz), 5.97 (2H, s), 6.67 (1H, dd, *J* = 3.5, 1.8 Hz), 6.73 (1H, dd, *J* = 8.2, 1.7 Hz), 6.77–6.82 (2H, m), 6.94 (1H, dd, *J* = 8.2, 1.2 Hz), 7.01 (1H, d, *J* = 3.5 Hz), 7.10–7.43 (2H, m), 7.91 (1H, d, *J* = 1.8 Hz), 12.44 (1H, s). ^{13}C-NMR (100 MHz, δ, DMSO-d_6): 21.16 (CH_3), 34.97 (CH_2), 42.02 (CH_2), 59.18 (CH), 100.96 (CH_2), 106.01 (CH), 108.20 (CH), 110.18 (CH), 112.24 (CH), 114.65 (CH), 117.32 (CH), 118.69 (CH), 122.42 (CH), 135.40 (C), 141.73 (C), 143.98 (C), 145.80 (CH), 145.95 (C), 146.40 (C), 146.43 (C), 147.49 (C), 148.83 (C), 149.25 (C), 164.59 (C). FAB$^+$-MS: *m/z*: 461 ($M^+ + 1$).

1-[(5-Nitrobenzimidazole-2-yl)thioacetyl]-3-(2-furanyl)-5-(3,4-methylenedioxyphenyl)-2-pyrazoline (***A8***) ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 3.06 (1H, dd, *J* = 17.9, 4.4 Hz), 3.80 (1H, dd, *J* = 17.9, 11.6 Hz), 4.57 (1H, d, *J* = 15.9 Hz), 4.78 (1H, d, *J* = 15.9 Hz), 5.51 (1H, dd, *J* = 11.6, 4.4 Hz), 5.97 (2H, s), 6.66–7.02 (6H, m), 7.46 (1H, d, *J* = 8.8 Hz), 7.88–7.95 (3H, m), 8.25 (1H, d, *J* = 2.3 Hz), 12.42 (1H, s). ^{13}C-NMR (100 MHz, δ, DMSO-d_6): 34.81 (CH_2), 42.03 (CH_2), 59.14 (CH), 100.95 (CH_2), 105.97 (CH), 108.19 (CH), 110.18 (CH), 112.23 (CH), 113.03 (CH), 114.60 (CH), 115.86 (CH), 118.71 (CH), 135.48 (C), 140.32 (C), 142.36 (C), 145.78 (CH), 145.99 (C), 146.33 (C), 146.37 (C), 147.46 (C), 150.71 (C), 159.74 (C), 164.82 (C). FAB$^+$-MS: *m/z*: 493 (M^+), 494 ($M^+ + 1$).

1-[(Benzimidazole-2-yl)thioacetyl]-3-(2-furanyl)-5-phenyl-2-pyrazoline (***A9***) ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 3.10 (1H, dd, *J* = 18.0, 4.5 Hz), 3.82 (1H, dd, *J* = 18.0, 11.8 Hz), 4.61 (1H, d, *J* = 15.8 Hz), 4.82 (1H, d, *J* = 15.8 Hz), 5.55 (1H, dd, *J* = 11.8, 4.5 Hz), 6.68 (1H, dd, *J* = 3.3, 1.6 Hz), 7.01 (1H, dd, *J* = 3.3, 0.7 Hz), 7.29 (6H, m), 7.56 (1H, d, *J* = 8.7 Hz), 7.89 (1H, d, *J* = 1.6 Hz), 8.01 (1H, dd, *J* = 8.7, 2.3 Hz), 8.32 (1H, d, *J* = 2.1 Hz), 12.54 (1H, s) FAB$^+$-MS: *m/z*: 403 ($M^+ + 1$).

1-[(5-Chlorobenzimidazole-2-yl)thioacetyl]-3-(2-furanyl)-5-phenyl-2-pyrazoline (***A10***) ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 3.08 (1H, dd, *J* = 18.0, 4.6 Hz), 3.83 (1H, dd, *J* = 18.0, 11.8 Hz), 4.56 (1H, d, *J* = 16.0 Hz), 4.81 (1H, d, *J* = 16.0 Hz), 5.58 (1H, dd, *J* = 11.7, 4.6 Hz), 6.67 (1H, dd, *J* = 3.4, 1.8 Hz), 7.03 (1H, d, *J* = 3.4 Hz), 7.10–7.18 (2H, m), 7.25–7.35 (4H, m), 7.48 (2H, m), 7.93 (1H, d, *J* = 1.2 Hz), 12.62 (1H, b). FAB$^+$-MS: *m/z*: 436 (M^+), 437 ($M^+ + 1$).

1-[(5-Methylbenzimidazole-2-yl)thioacetyl]-3-(2-furanyl)-5-phenyl-2-pyrazoline (***A11***) ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 2.38 (3H, s), 3.07 (1H, dd, *J* = 18.0, 4.6 Hz), 3.85 (1H, dd, *J* = 18.0, 11.8 Hz), 4.56 (1H, d, *J* = 15.9 Hz), 4.79 (1H, d, *J* = 15.9 Hz), 5.57 (1H, dd, *J* = 11.7, 4.6 Hz), 6.68 (1H, dd, *J* = 3.5, 1.8 Hz), 6.92 (1H, d, *J* = 8.2 Hz), 7.02 (1H, d, *J* = 3.4 Hz), 7.26 (7H, m), 7.89 (1H, d, *J* = 1.2 Hz), 12.48 (1H, s). FAB$^+$-MS: *m/z*: 416 (M^+), 417 ($M^+ + 1$).

1-[(5-Nitrobenzimidazole-2-yl)thioacetyl]-3-(2-furanyl)-5-phenyl-2-pyrazoline (***A12***) ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 3.06 (1H, dd, *J* = 17.9, 4.7 Hz), 3.80 (1H, dd, *J* = 17.9, 11.8 Hz), 4.63 (1H, d, *J* = 15.9 Hz), 4.87 (1H, d, *J* = 15.9 Hz), 5.56 (1H, dd, *J* = 11.8, 4.7 Hz), 6.69 (1H, dd, *J* =

3.5, 1.8 Hz), 7.01 (1H, dd, *J* = 3.5, 0.7 Hz), 7.28 (7H, m), 7.54 (1H, d, *J* = 8.8 Hz), 7.89 (1H, d, *J* = 1.8 Hz), 8.00 (1H, dd, *J* = 8.8, 2.3 Hz), 8.29 (1H, d, *J* = 2.0 Hz), 12.50 (1H, b). FAB$^+$-MS: *m/z*: 450 ($M^+ + 1$).

*1-[(Benzoxazole-2-yl)thioacetyl]-3-(2-furanyl)-5-phenyl-2--pyrazoline (**A13**)* ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 3.08 (1H, dd, *J* = 17.9, 4.5 Hz), 3.81 (1H, dd, *J* = 17.9, 11.8 Hz), 4.62 (1H, d, *J* = 16.0 Hz), 4.83 (1H, d, *J* = 15.9 Hz), 5.53 (1H, dd, *J* = 11.7, 4.6 Hz), 6.64 (1H, dd, *J* = 3.6, 1.7 Hz), 7.02 (1H, dd, *J* = 3.5, 0.6 Hz), 7.28–7.36 (6H, m), 7.58 (1H, m), 7.69 (1H, m), 7.89 (1H, dd, *J* = 8.6, 2.2 Hz), 8.27 (1H, d, *J* = 2.1 Hz). FAB$^+$-MS: *m/z*: 404 ($M^+ + 1$).

*1-[(5-Chlorobenzoxazole-2-yl)thioacetyl]-3-(2-furanyl)-5-phenyl-2-pyrazoline (**A14**)* ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 3.10 (1H, dd, *J* = 18.0, 4.7 Hz), 3.86 (1H, dd, *J* = 18.0, 11.8 Hz), 4.65 (1H, d, *J* = 16.3 Hz), 4.89 (1H, d, *J* = 16.3 Hz), 5.61 (1H, dd, *J* = 11.7, 4.7 Hz), 6.67 (1H, dd, *J* = 3.5, 1.8 Hz), 7.03 (1H, d, *J* = 3.5, 0.7 Hz), 7.27–7.36 (6H, m), 7.61 (1H, m), 7.66 (1H, m), 7.92 (1H, dd, *J* = 1.8, 0.7 Hz). ^{13}C-NMR (100 MHz, δ, DMSO-d_6): 35.73 (CH_2), 41.88 (CH_2), 59.00 (CH), 110.12 (CH), 112.29 (CH), 114.96 (CH), 118.20 (CH), 124.19 (CH), 124.56 (CH), 127.47 (2CH), 128.57 (2CH), 131.99 (C), 140.21 (C), 141.26 (C), 145.75 (C), 145.96 (CH), 146.79 (C), 151.31 (C), 163.70 (C), 163.82 (C). FAB$^+$-MS: *m/z*: 437 (M^+), 438 ($M^+ + 1$), 439 ($M^+ + 2$).

*1-[(5-Methylbenzoxazole-2-yl)thioacetyl]-3-(2-furanyl)-5-phenyl-2-pyrazoline (**A15**)* ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 2.38 (3H, s), 3.07 (1H, dd, *J* = 18.0, 4.5 Hz), 3.84 (1H, dd, *J* = 18.0, 11.6 Hz), 4.56 (1H, d, *J* = 15.9 Hz), 4.82 (1H, d, *J* = 15.9 Hz), 5.55 (1H, dd, *J* = 11.7, 4.5 Hz), 6.66 (1H, dd, *J* = 3.5, 1.7 Hz), 6.94 (1H, d, *J* = 8.3 Hz), 7.03 (1H, d, *J* = 3.5 Hz), 7.27 (7H, m), 7.90 (1H, d, *J* = 1.3 Hz). FAB$^+$-MS: *m/z*: 418 ($M^+ + 1$).

*1-[(5-Chlorobenzoxazole-2-yl)thioacetyl]-3-(2-furanyl)-5-(4-chlorophenyl)-2-pyrazoline (**A16**)* ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 3.11 (1H, dd, *J* = 18.0, 4.6 Hz), 3.87 (1H, dd, *J* = 18.0, 11.7 Hz), 4.66 (1H, d, *J* = 16.3 Hz), 4.87 (1H, d, *J* = 16.3 Hz), 5.60 (1H, dd, *J* = 11.7, 4.6 Hz), 6.68 (1H, dd, *J* = 3.4, 1.7 Hz), 7.05 (1H, d, *J* = 3.4 Hz), 7.25–7.38 (5H, m), 7.65 (1H, d, *J* = 8.7 Hz), 7.77 (1H, d, *J* = 2.0 Hz), 7.92 (1H, s). ^{13}C-NMR (100 MHz, δ, DMSO-d_6): 35.90 (CH_2), 41.86 (CH_2), 58.99 (CH), 111.39 (CH), 112.31 (CH), 115.08 (CH), 118.03 (CH), 124.14 (CH), 127.52 (2CH), 128.59 (2CH), 128.92 (C), 131.98 (C), 140.20 (C), 142.50 (C), 145.71 (C), 146.01 (C), 146.88 (CH), 150.06 (C), 163.50 (C), 165.87 (C). FAB$^+$-MS: *m/z*: 471 (M^+), 472 ($M^+ + 1$), 473 ($M^+ + 2$).

*1-[(5-Methylbenzoxazole-2-yl)thioacetyl]-3-(2-furanyl)-5-(4-chlorophenyl)-2-pyrazoline (**A17**)* ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 2.4 (3H, s), 3.10 (1H, dd, *J* = 18.0, 4.7 Hz), 3.86 (1H, dd, *J* = 18.0, 11.8 Hz), 4.63 (1H, d, *J* = 16.3 Hz), 4.85 (1H, d, *J* = 16.3 Hz), 5.60 (1H, dd, *J* = 11.8, 4.7 Hz), 6.68 (1H, dd, *J* = 3.5, 1.8 Hz), 7.04 (1H, d, *J* = 3.0 Hz), 7.10 (1H, dd, *J* = 8.4, 1.1 Hz), 7.25–7.38 (4H, m), 7.44 (1H, m), 7.48 (1H, d, *J* = 8.3 Hz), 7.92 (1H, d, *J* = 1.2 Hz). ^{13}C-NMR (100 MHz, δ, DMSO-d_6): 20.89 (CH_3), 35.66 (CH_2), 41.85 (CH_2), 58.97 (CH), 109.49 (CH), 112.29 (CH), 114.96 (CH), 118.17 (CH), 125.00 (CH), 127.49 (2CH), 128.58 (2CH), 131.97 (C), 133.95 (C), 140.23 (C), 141.46 (C), 145.76 (C), 145.97 (CH), 146.76 (C), 149.56 (C), 163.66 (C), 163.71 (C). FAB$^+$-MS: *m/z*: 451 (M^+), 452 ($M^+ + 1$).

*1-[(Benzoxazole-2-yl)thioacetyl]-3-(2-furanyl)-5-(3,4-methylenedioxyphenyl)-2-pyrazoline (**A18**)* ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 3.09 (1H, dd, *J* = 17.9, 4.5 Hz), 3.82 (1H, dd, *J* = 17.9, 11.6 Hz), 4.64 (1H, d, *J* = 16.3 Hz), 4.86 (1H, d, *J* = 16.3 Hz), 5.52 (1H, dd, *J* = 11.6, 4.5 Hz), 5.97 (2H, s), 6.68 (1H, dd, *J* = 3.5, 1.8 Hz), 6.74 (1H, dd, *J* = 8.0, 1.8 Hz), 6.77–6.84 (2H, m), 7.05 (1H, d, *J* = 3.5 Hz), 7.32 (2H, m), 7.64 (2H, m), 7.92 (1H, d, *J* = 1.8 Hz). ^{13}C-NMR (100 MHz, δ, DMSO-d_6): 35.81 (CH_2), 42.08 (CH_2), 59.31 (CH), 100.98 (CH_2), 105.99 (CH), 108.21 (CH), 110.11 (CH), 112.27 (CH), 114.89 (CH), 118.23 (CH), 118.74 (CH), 124.19 (CH), 124.56 (CH), 135.24 (C), 141.25 (C), 145.85 (C), 145.92 (CH), 146.45 (C), 146.82 (C), 147.49 (C), 151.28 (C), 163.55 (C), 163.84 (C). FAB$^+$-MS: *m/z*: 447 (M^+), 448 ($M^+ + 1$).

*1-[(5-Chlorobenzoxazole-2-yl)thioacetyl]-3-(2-furanyl)-5--(3,4-methylenedioxyphenyl)-2-pyrazoline (**A19**)* ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 3.08 (1H, dd, *J* = 18.0, 4.5 Hz), 3.82 (1H, dd, *J* = 18.0, 11.8 Hz), 4.68 (1H, d, *J* = 16.3 Hz), 4.87 (1H, d, *J* = 16.3 Hz), 5.52 (1H, dd, *J* = 11.6, 4.5 Hz), 5.97 (2H, dd, *J* = 7.8, 0.9 Hz), 6.69 (1H, dd, *J* = 3.5, 1.8 Hz), 6.73 (1H, dd, *J* = 8.1, 1.8 Hz), 6.80 (1H, d, *J* = 1.7 Hz), 6.83 (1H, d, *J* = 8.0 Hz), 7.05 (1H, d, *J* = 3.5 Hz), 7.35 (1H, dd, *J* = 8.7, 2.2 Hz), 7.67 (1H, d, *J* = 8.7 Hz), 7.76 (1H, d, *J* = 2.0 Hz), 7.92 (1H, d, *J* = 1.8 Hz). ^{13}C-NMR (100 MHz, δ, DMSO-d_6): 35.96 (CH_2), 42.10 (CH_2), 59.33 (CH), 100.98 (CH_2), 105.94 (CH), 108.23 (CH), 111.38 (CH), 112.29 (CH), 114.97 (CH), 118.04 (CH), 118.83 (CH), 124.12 (CH), 128.85 (C), 135.23 (C), 142.50 (C), 145.82 (C), 145.94 (CH), 146.43 (C), 146.88 (C), 147.46 (C), 150.07 (C), 163.37 (C), 165.94 (C). FAB$^+$-MS: *m/z*: 481 (M^+), 482 ($M^+ + 1$).

*1-[(5-Methylbenzoxazole-2-yl)thioacetyl]-3-(2-furanyl)-5--(3,4-methylenedioxyphenyl)-2-pyrazoline (**A20**)* ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 2.37 (3H, s), 3.09 (1H, dd, *J* = 18.0, 4.5 Hz), 3.83 (1H, dd, *J* = 18.0, 11.6 Hz), 4.57 (1H, d, *J* = 15.7 Hz), 4.76 (1H, d, *J* = 15.7 Hz), 5.54 (1H, dd, *J* = 11.6, 4.5 Hz), 5.99 (2H, s), 6.66 (1H, dd, *J* = 3.5, 1.8 Hz), 6.75 (1H, dd, *J* = 8.1, 1.8 Hz), 6.76–6.83 (2H, m), 6.95 (1H, dd, *J* = 8.1, 1.3 Hz), 7.03 (1H, d, *J* = 3.5 Hz), 7.12–7.42 (2H, m), 7.89 (1H, d, *J* = 1.8 Hz). FAB$^+$-MS: *m/z*: 462 ($M^+ + 1$).

*1-[(Benzothiazole-2-yl)thioacetyl]-3-(2-furanyl)-5-phenyl-2-pyrazoline (**A21**)* ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 3.07 (1H, dd, *J* = 18.0, 4.5 Hz), 3.84 (1H, dd, *J* = 18.0, 11.7 Hz), 4.68 (1H, d, *J* = 15.8 Hz), 4.83 (1H, d, *J* = 15.8 Hz), 5.58 (1H, dd, *J* = 11.6, 4.5 Hz), 6.67 (1H, dd, *J* = 3.3, 1.6 Hz), 7.05 (1H, dd, *J* = 3.2, 0.6 Hz), 7.22–7.34 (5H, m), 7.43 (2H, m), 7.81 (1H, m), 7.88 (1H, dd, *J* = 1.7, 0.7 Hz), 7.99 (1H, d, *J* = 8.0 Hz). FAB$^+$-MS: *m/z*: 420 ($M^+ + 1$).

*1-[(Benzothiazole-2-yl)thioacetyl]-3-(2-furanyl)-5-(4-chlorophenyl)-2-pyrazoline (**A22**)* ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 3.10 (1H, dd, *J* = 18.0, 4.7 Hz), 3.87 (1H, dd, *J* = 18.0, 11.8 Hz), 4.65 (1H, d, *J* = 16.0 Hz), 4.88 (1H, d, *J* = 16.0 Hz), 5.60 (1H, dd, *J* = 11.7, 4.7 Hz), 6.69 (1H, dd, *J* = 3.5, 1.8 Hz), 7.05 (1H, dd, *J* = 3.5, 0.6 Hz), 7.26–7.39 (5H, m), 7.47 (1H, dd, *J* = 12.3, 6.2 Hz), 7.87 (1H, m), 7.93 (1H, dd, *J* = 1.8, 0.6

Hz), 8.00 (1H, d, *J* = 8.1 Hz). ^{13}C-NMR (100 MHz, δ, DMSO-d_6): 36.21 (CH_2), 41.85 (CH_2), 58.92 (CH), 112.31 (CH), 114.97 (CH), 121.10 (CH), 121.79 (CH), 124.47 (CH), 126.32 (CH), 127.50 (2CH), 128.57 (2CH), 131.93 (C), 134.77 (C), 140.33 (C), 145.79 (C), 145.98 (CH), 146.66 (C), 152.51 (C), 163.87 (C), 165.93 (C). FAB$^+$-MS: *m/z*: 453 (M^+), 454 (M^+ + 1), 455 (M^+ + 2).

*1-[(Benzothiazole-2-yl)thioacetyl]-3-(2-furanyl)-5-(3,4-methylenedioxyphenyl)-2-pyrazoline (**A23**)* ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 3.08 (1H, dd, *J* = 17.9, 4.5 Hz), 3.81 (1H, dd, *J* = 17.9, 11.6 Hz), 4.65 (1H, d, *J* = 15.9 Hz), 4.86 (1H, d, *J* = 15.9 Hz), 5.51 (1H, dd, *J* = 11.6, 4.5 Hz), 5.96 (2H, s), 6.68 (1H, dd, *J* = 3.5, 1.8 Hz), 6.73 (1H, dd, *J* = 8.2, 1.7 Hz), 6.77–6.82 (2H, m), 7.04 (1H, dd, *J* = 3.5, 0.7 Hz), 7.46 (1H, dd, *J* = 8.2, 7.3 Hz), 7.86 (1H, d, *J* = 7.6 Hz), 7.92 (1H, d, *J* = 1.8 Hz), 7.99 (1H, d, *J* = 8.0 Hz). ^{13}C-NMR (100 MHz, δ, DMSO-d_6): 36.34 (CH_2), 42.05 (CH_2), 59.27 (CH), 100.98 (CH_2), 106.01 (CH), 108.20 (CH), 112.27 (CH), 114.83 (CH), 118.72 (CH), 121.11 (CH), 121.72 (CH), 124.43 (CH), 126.27 (CH), 134.74 (C), 135.32 (C), 145.89 (CH), 145.80 (C), 146.44 (C), 146.67 (C), 147.49 (C), 152.54 (C), 163.75 (C), 165.97 (C). FAB$^+$-MS: *m/z*: 463 (M^+), 464 (M^+ + 1).

Microbiology

Antifungal activity

The antifungal properties of compounds **A1–23** were evaluated by the broth microdilution method according to the National Committee on Clinical Laboratory Standards (NCCLS) reference document M27-A2[18] against *Candida albicans* (isolate, obtained from the Department of Microbiology, Faculty of Medicine, Osmangazi University, Eskişehir, Turkey), *Candida albicans* (ATCC 90028), *Candida glabrata* (isolate, obtained from the Department of Microbiology, Faculty of Medicine, Osmangazi University, Eskişehir, Turkey), *Candida utilis* (NRRL Y-900), *Candida tropicalis* (NRRL Y-12968), *Candida krusei* (NRRL Y-7179), *Candida parapsilosis* (NRRL Y-12696), and *Candida albicans* s(NRRL Y-12983). Ketoconazole was used as positive control.

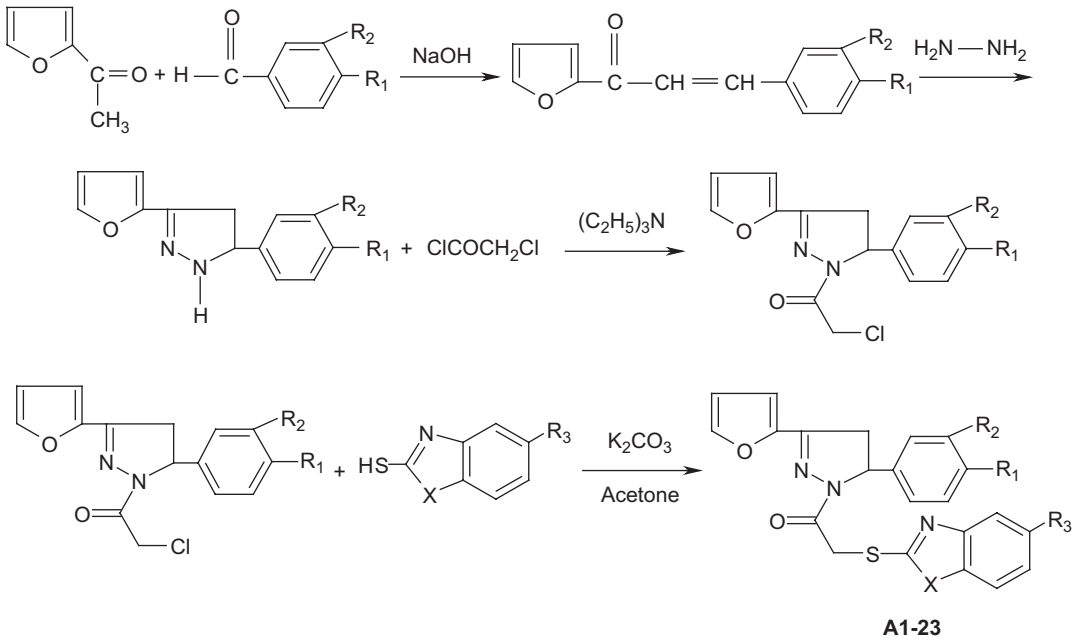
Broth microdilution assay

The test compounds and the antimicrobial standards were first dissolved in DMSO, which was used to prepare the stock solutions at an initial concentration of 2 mg/mL. Serial dilution series were prepared in 100 µL Müller–Hinton broth (MHB) with equal amounts of the test samples. The last row was filled only with water as a growth control for the microorganism. Overnight-grown microorganism suspensions were first diluted in double strength MHB and standardized to 10^8 CFU/mL (using McFarland No: 0.5) under sterile conditions. Then each microorganism suspension was pipetted into each well and incubated at 37°C for 24 h. Ketoconazole was used as a standard antifungal agent against *Candida* spp. Sterile distilled water and medium served as a positive growth control. The first well without turbidity was assigned as the minimum inhibitory concentration (MIC, in mg/mL). Average results of three separately performed experiments are given in Table 2.

Results and discussion

In the present work, 23 new compounds were synthesized. The reaction of 1-(chloroacetyl)-3-(2-furanyl)-5-aryl-2-pyrazolines with appropriate benzazol-2-thiole gave 1-[(benzazole-2-yl)thioacetyl]-3,5-diaryl-2-pyrazoline derivatives (Scheme 1, Table 1).

The structure of the compounds was elucidated by ^{1}H-NMR, ^{13}C-NMR, and FAB$^+$-MS spectra. In the 400 MHz



Scheme 1. General synthesis reaction (see Table 1 for **A1–23**, R_1, R_2, R_3, X details).

^{1}H-NMR spectra of the compounds, the CH_2 protons of the pyrazoline ring resonated as a pair of doublets at δ 3.06–3.11 ppm (Ha), 3.79–3.87 ppm (Hb). The CH proton appeared as a doublet of doublets at δ 5.50–5.61 ppm (H_X) due to vicinal coupling with the two magnetically non-equivalent protons of the methylene group at position 4 of the pyrazoline ring (J_{AB} = 17.9–18.0 Hz, J_{AX} = 4.4–4.7 Hz, J_{BX} = 11.6–11.8 Hz). The CH_2 protons of the acetyl at position 1 of the pyrazoline derivatives **A1–23** was observed at 4.56–4.87 ppm as a doublet (J = 15.7–16.3 Hz). The benzimidazole derivatives showed a specific NH proton at 12.42–12.64 ppm as a broad singlet. All the other aromatic and aliphatic protons were observed at the expected regions. ^{13}C-NMR chemical shift values of the carbon atoms at 41.82–42.85 ppm (C-4), 58.85–59.33 ppm (C-5), and about 149.25–152.54 ppm (C-3) corroborate the 2-pyrazoline character deduced from the ^{1}H-NMR data. Mass spectra (FAB) of compounds showed M + 1 peaks, in agreement with their molecular formulae.

The antifungal activity of the compounds was studied using eight pathogenic fungi. Ketoconazole was used as the reference agent for inhibitory activity against the tested fungi. Minimal inhibitory concentration (MIC) was recorded as the minimum concentration of a compound that inhibited the growth of a tested microorganism. All of the compounds tested illustrated medium to very good anticandidal inhibitory activity when compared with the reference agent. The MIC values were found to be within the range 0.003–2 mg/mL against all evaluated strains. The results are summarized in Table 2.

In comparing their MIC values with ketoconazole, all of the compounds were effective against *Candida parapsilosis*; **A1**, **A2**, **A5**, **A6**, **A7**, **A8**, **A10**, **A11**, **A13**, **A14**, **A18**, **A19**, **A20**, **A21**, **A22**, and **A23** especially showed strong activity; **A4**, **A9**, **A12**, and **A15** showed a similar level of activity to ketoconazole.

Compounds **A5**, **A6**, **A7**, **A18**, **A19**, **A20**, **A21**, **A22**, and **A23** were also effective against *C. krusei*. Compounds **A5**, **A6**, **A7**, **A19**, **A20**, **A22**, and **A23** especially showed strong inhibitory activity against the tested microorganisms. Compounds **A18** and **A21** showed a similar level of activity to the reference agent, whereas **A1** and **A8** showed moderate activity.

All of the compounds were effective against *Candida glabrata* (clinical isolate). The compounds **A1**, **A5**, **A6**, **A18**, **A20**, and **A23** especially showed strong activity. **A19** showed the same level of activity when compared with the reference agent.

On the other hand, the compounds exhibited comparable activities against *Candida albicans* (ATCC 90028). Strong inhibitory activity with a MIC value of 0.003 mg/mL was observed for compound **A18**. The compounds **A10**, **A21**, **A22**, and **A23** showed equal activity to, and the other compounds were found to be less active than, the reference agent.

Table 2. Anticandidal evaluation of 1-[(benzazole-2-yl)thioacetyl]-3,5-diaryl-2-pyrazoline derivatives (MIC values in mg/mL).

	Test substance							
Compound	A[a]	B	C[a]	D	E	F	G	H
A1	1	0.25	0.015	0.125	0.0625	0.25	0.015	0.125
A2	0.25	0.5	0.25	0.5	0.5	0.5	0.25	0.5
A3	2	0.5	2	2	2	2	2	2
A4	1	0.25	0.25	0.5	0.5	0.5	0.5	0.5
A5	1	0.125	0.015	0.125	0.0625	0.015	0.125	0.125
A6	0.5	0.125	0.007	0.031	0.031	0.015	0.031	0.125
A7	0.5	0.5	0.0625	0.125	0.015	0.031	0.125	0.25
A8	0.0625	1	0.25	0.5	0.5	0.25	0.25	0.5
A9	0.5	0.5	0.5	0.5	0.5	1	0.5	0.5
A10	1	0.0625	0.5	0.5	0.5	0.5	0.0625	0.5
A11	1	1	0.25	0.5	0.5	1	0.25	0.5
A12	2	1	1	0.5	1	0.5	0.5	0.25
A13	0.5	2	0.5	0.5	1	0.5	0.125	0.5
A14	1	0.5	0.5	1	1	0.5	0.25	1
A15	2	0.5	0.5	1	1	1	0.5	0.5
A16	2	0.125	2	2	2	2	2	2
A17	2	0.5	2	2	1	1	2	1
A18	1	0.003	0.015	0.125	0.0625	0.125	0.125	0.25
A19	0.5	0.125	0.031	0.125	0.015	0.015	0.015	0.125
A20	2	0.5	0.015	0.125	0.125	0.0625	0.031	0.25
A21	1	0.0625	0.25	0.25	0.125	0.125	0.25	0.125
A22	0.5	0.0625	0.125	0.125	0.015	0.0625	0.0625	0.125
A23	1	0.0625	0.007	0.0625	0.0625	0.015	0.0625	0.125
Ketoconazole	0.0625	0.0625	0.031	0.007	0.003	0.125	0.5	0.032

Note. A, *Candida albicans* (clinical isolate); B, *Candida albicans* (ATCC 90028); C, *Candida glabrata* (clinical isolate); D, *Candida utilis* (NRRL Y-900); E, *Candida tropicalis* (NRRL Y-12968); F, *Candida krusei* (NRRL Y-7179); G, *Candida parapsilosis* (NRRL Y-12696); H, *Candida albicans* (NRRL Y-12983).
[a]Clinical isolates were obtained from the Department of Microbiology, Faculty of Medicine, Osmangazi University, Eskisehir, Turkey.

When compared with ketoconazole, compound **A8** showed similar activity against *Candida albicans* (clinical isolate), whereas all other compounds showed less activity.

Compounds **A1–23** were found to be inactive against *Candida utilis*, *Candida tropicalis*, and *Candida albicans* (NRRL Y-12983) when compared with ketoconazole.

Considering all the results obtained from the antifungal screen, in comparison with the reference agent, it can be concluded that compounds **A5**, **A6**, **A18**, **A20**, and **A23** were more active than the others in the screen, including the reference agent.

Based on the 23 compounds evaluated, it appears that 3,4-methylenedioxyl substitution on the phenyl ring made a good contribution to the antifungal activity in this series of benzazolyl–pyrazoline combinations. Additionally, substitutional changes in benzimidazole/benzoxazole rings on the basic structure did not affect the activity.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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