

NOVEL HETEROCYCLIC HYBRIDS OF PYRAZOLE: SYNTHESIS AND ANTIFUNGAL ACTIVITY

Antoniya Todorova¹, Yordanka Ivanova¹, Trayana Nedeva², Ognyan Petrov³

¹ Department of Plant Pathology and Chemistry
Faculty of Ecology and Landscape Architecture
University of Forestry, 1756 Sofia, Bulgaria
E-mail: yordanka_b_ivanova@abv.bg

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² Department of General and Industrial Microbiology, Faculty of Biology
Sofia University St. Kl. Ohridski, 1164 Sofia, Bulgaria

³ Department of Pharmaceutical and Applied Organic Chemistry
Faculty of Chemistry and Pharmacy
Sofia University St. Kl. Ohridski, 1164 Sofia, Bulgaria

ABSTRACT

A series of new pyrazole derivatives containing 2(3H)-benzoxazolone or 2(3H)-benzothiazolone ring were synthesized by condensation of different 6-(3-aryl-2-propenoyl)-2(3H)-benzoxa(thia)zolones and hydrazine hydrate in acetic acid with good yield. All compounds were tested *in vitro* against *Fusarium graminearum*, *Fusarium oxysporum*, and *Aspergillus niger*; and their antifungal potential was evaluated. The best results were observed for the main structure chalcone (3) and compound 3a demonstrated the most promising inhibition potential (27.8 - 38.1 %), especially against *Fusarium* representatives. Thus, the antifungal potential of chalcone and its synthetic hybrids contributes to widen the multiple biological activities of this class of compounds.

Keywords: chalcone, pyrazole, antifungal activity, radial growth rate.

INTRODUCTION

Fungi, a large and wide spread community of eukaryotes are recognized as playing a key role in maintaining the balance of ecosystems. Besides the mycorrhizal fungi that form a mutualistic symbiosis with vascular plants and exhibit beneficial effects on their growth and development, a significant part of the representatives of kingdom *Fungi* constitutes a diverse group of plant pathogens accounting for 70 - 80 % of plant diseases. Over 19,000 fungi are known to cause diseases in crop plants worldwide. They may remain dormant but alive on both living and dead plant tissues until conditions are favourable to their reproduction. Certain fungi may develop inside host plant tissues. Fungal spores are readily dispersed by wind, water, soil, insects, and other invertebrates. In this way, they may infest an entire crop [1]. The plant mycoses encompass diseases such as anthracnose, leaf spot, rust, wilt, blight, coils, scab, gall,

canker, damping-off, root rot, mildew, and dieback. They lead to commercial crops' yield losses and diminished crop quality [2, 3].

The traditional management practices that help to control and prevent fungal diseases, their spread and progress include application of fungicides. However, their excessive use causes health problems, environmental issues related to disruption of the ecological balance, and increased resistance of the fungal pathogens to the pesticides [4]. The study presents the synthesis of novel heterocyclic hybrids of pyrazole and assessment of their antifungal potential.

EXPERIMENTAL

All chemicals were purchased from Acros Organics. Reactions and purity of the final compound were monitored by thin-layer chromatography (TLC) on silica gel plates (Kieselgel 60 F₂₅₄) using ethylacetate/cyclohexane (3:2 v/v) as an eluent.

The melting points were determined on a melting point meter KS1D, Kruss. IR spectrum (nujol) was recorded on a Specord 71 spectrometer. NMR spectra were recorded in DMSO- d_6 on a Bruker Avance III HD 500, operating at 500 MHz for ^1H and at 125.8 MHz for ^{13}C . Chemical shifts are given in parts per million (δ) relative to the solvent peak. Coupling constants (J) were measured in hertz (Hz). Mass spectra were recorded on an Agilent 6890 system with MSD 5973 (single quadrupole and EI at 70 eV ionization), using a capillary column HP-5/MS (30 m \times 0.250 mm \times 0.25 μm). Carrier gas He was used at 0.8 mL/min. The temperature programmed mode was used (from 60°C for 2 min, then with 10°C/min to 300°C for 10 min). The sample was introduced in splitless injection mode. The elemental analysis was carried on a "VARI0 EL III Elemental analyzer" and the results for C, H, and N were within $\pm 0.4\%$ of the theoretical values.

General procedure for synthesis of compounds (3a-h)

To a suspension of 6-(3-aryl-2-propenoyl)-2(3H)-benzoxa(thia)zalone (1 mmol) in acetic acid (10 mL), hydrazine hydrate (200 mg, 4 mmol) was added. The reaction mixture was refluxed for 1 h, until the reaction went to completion as monitored by TLC. The resulting yellow solution was poured on crushed ice. The crystalline product was filtered, washed with water and dried.

6-[1-Acetyl-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-3-yl]-2(3H)-benzothiazalone (3a)

Yield: 90 % (331 mg), m.p.: 256 - 258°C (acetic acid). $^1\text{H-NMR}$ (500 MHz, DMSO- d_6): δ (ppm) 2.28 (s, 3H, CH_3), 3.09 (dd, 1H, pyrazoline, $J = 17.9$ Hz, $J = 4.2$ Hz), 3.71 (s, 3H, CH_3), 3.79 (dd, 1H, pyrazoline, $J = 17.8$ Hz, $J = 11.8$ Hz), 5.48 (dd, 1H, pyrazoline, $J = 11.7$ Hz, $J = 4.1$ Hz), 6.87 (d, 2H, arom. H, $J = 8.5$ Hz), 7.09 (d, 2H, arom. H, $J = 8.5$ Hz), 7.17 (d, 1H, arom. H, $J = 8.4$ Hz), 7.73 (dd, 1H, arom. H, $J = 8.3$ Hz, $J = 1.2$ Hz), 7.99 (d, 1H, arom. H, $J = 1.0$ Hz), 12.1 (brs, 1H, NH).

6-(1-Acetyl-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-3-yl)-2(3H)-benzoxazalone (3b)[5]

Yield: 84 % (294 mg), m.p.: 275 - 277°C (acetic acid). IR (nujol): 1610, 1780 (C=O) cm^{-1} . $^1\text{H-NMR}$ (500 MHz, DMSO- d_6): δ (ppm) 2.28 (s, 3H, CH_3), 3.12 (m, 1H, CH_2), 3.71 (s, 3H, CH_3), 3.80 (m, 1H, CH_2), 5.48 (m, 1H, CH), 6.87 (d, 2H, arom. H, $J = 8.7$ Hz), 7.10

(d, 2H, arom. H, $J = 8.7$ Hz), 7.15 (d, 1H, arom. H, $J = 8.1$ Hz), 7.58 (dd, 1H, arom. H, $J = 8.1$ Hz, $J = 1.5$ Hz), 7.68 (d, 1H, arom. H, $J = 1.3$ Hz), 11.9 (brs, 1H, NH). $^{13}\text{C-NMR}$ (125.8 MHz, DMSO- d_6): δ (ppm) 21.8, 42.2, 55.1, 59.0, 107.4, 109.8, 114.0, 123.0, 125.3, 126.8, 132.3, 134.5, 143.6, 153.9, 154.4, 158.4, 167.2. Anal. calcd. for $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_4$ (351.36): C, 64.95; H, 4.88; N 11.96. Found: C, 64.91; H, 4.79; N, 11.72. MS (EI): $[\text{M}]^+$ $m/z = 351(56)$, $[\text{M}+2]^+$ $m/z = 353(3)$, 308(100), 294(8), 278(9), 264(6), 202(17), 191(12), 176(25), 161(4), 149(9), 134(15), 121(8).

6-[1-Acetyl-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-3-yl]-2(3H)-benzoxazalone (3c)

Yield: 69 % (248 mg), m.p.: 264 - 266°C (acetic acid). $^1\text{H-NMR}$ (500 MHz, DMSO- d_6): δ (ppm) 2.29 (s, 3H, CH_3), 3.15 (dd, 1H, pyrazoline, $J = 18.0$ Hz, $J = 4.7$ Hz), 3.82 (dd, 1H, pyrazoline, $J = 18.0$ Hz, $J = 11.8$ Hz), 5.54 (dd, 1H, pyrazoline, $J = 11.8$ Hz, $J = 4.6$ Hz), 7.15 (d, 1H, arom. H, $J = 8.1$ Hz), 7.21 (d, 2H, arom. H, $J = 8.4$ Hz), 7.38 (d, 2H, arom. H, $J = 8.4$ Hz), 7.58 (d, 1H, arom. H, $J = 8.1$ Hz, $J = 1.5$ Hz), 7.68 (d, 1H, arom. H, $J = 1.3$ Hz), 11.9 (brs, 1H, NH).

6-[1-Acetyl-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-3-yl]-2(3H)-benzothiazalone (3d)

Yield: 89 % (329 mg), m.p.: 267 - 269°C (acetic acid). $^1\text{H-NMR}$ (500 MHz, DMSO- d_6): δ (ppm) 2.28 (s, 3H, CH_3), 3.12 (dd, 1H, pyrazoline, $J = 18.0$ Hz, $J = 4.4$ Hz), 3.71 (s, 3H, CH_3), 3.80 (dd, 1H, pyrazoline, $J = 18.0$ Hz, $J = 12.0$ Hz), 5.48 (dd, 1H, pyrazoline, $J = 12.0$ Hz, $J = 4.3$ Hz), 6.87 (d, 2H, arom. H, $J = 8.7$ Hz), 7.10 (d, 2H, arom. H, $J = 8.7$ Hz), 7.15 (d, 1H, arom. H, $J = 8.1$ Hz), 7.58 (dd, 1H, arom. H, $J = 8.1$ Hz, $J = 1.5$ Hz), 7.68 (d, 1H, arom. H, $J = 1.3$ Hz), 11.9 (brs, 1H, NH).

6-[1-Acetyl-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazole-3-yl]-2(3H)-benzoxazalone (3e)

Yield: 93 % (383 mg), m.p.: 267 - 270°C (acetic acid). $^1\text{H-NMR}$ (500 MHz, DMSO- d_6): δ (ppm) 2.32 (s, 3H, CH_3), 3.15 (dd, 1H, pyrazoline, $J = 18.0$ Hz, $J = 4.8$ Hz), 3.61 (s, 3H, CH_3), 3.71 (s, 6H, CH_3), 3.79 (dd, 1H, pyrazoline, $J = 18.0$ Hz, $J = 11.8$ Hz), 5.46 (dd, 1H, pyrazoline, $J = 11.7$ Hz, $J = 4.7$ Hz), 6.44 (s, 2H, arom. H), 7.15 (d, 1H, arom. H, $J = 8.1$ Hz), 7.57 (dd, 1H, arom. H, $J = 8.1$ Hz, $J = 1.1$ Hz), 7.67 (d, 1H, arom. H, $J = 1.3$ Hz), 11.8 (brs, 1H, NH).

6-[1-Acetyl-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazole-3-yl]-2(3H)-benzothiazolone (3f)

Yield: 83 % (355 mg), m.p.: 263 - 265°C (acetic acid). ¹H-NMR (500 MHz, DMSO-d₆): δ (ppm) 2.32 (s, 1H, CH₃), 3.14 (dd, 1H, pyrazoline, *J* = 17.9 Hz, *J* = 4.8 Hz), 3.61 (s, 3H, CH₃), 3.72 (s, 6H, CH₃), 3.79 (dd, 1H, pyrazoline, *J* = 17.9 Hz, *J* = 11.8 Hz), 5.47 (dd, 1H, pyrazoline, *J* = 11.7 Hz, *J* = 4.8 Hz), 6.45 (s, 2H, arom. H), 7.17 (d, 1H, arom. H, *J* = 8.3 Hz), 7.72 (dd, 1H, arom. H, *J* = 8.3 Hz, *J* = 1.6 Hz), 7.99 (d, 1H, arom. H, *J* = 1.4 Hz), 12.05 (brs, 1H, NH).

6-[1-Acetyl-5-(3,4-dimethoxyphenyl)-4,5-dihydro-1H-pyrazole-3-yl]-2(3H)-benzoxazolone (3g)

Yield: 67 % (127 mg), m.p.: 138°C (decomp.) (acetic acid). ¹H-NMR (500 MHz, DMSO-d₆): δ (ppm) 2.29 (s, 3H, CH₃), 3.12 (dd, 1H, pyrazoline, *J* = 17.9 Hz, *J* = 4.4 Hz), 3.71 (s, 3H, CH₃), 3.69 (s, 3H, CH₃), 3.71 (s, 3H, CH₃), 3.82 (m, 1H, pyrazoline), 5.46 (dd, 1H, pyrazoline, *J* = 11.6 Hz, *J* = 4.4 Hz), 6.63 (dd, 1H, arom. H, *J* = 8.2 Hz, *J* = 1.9 Hz), 6.78 (d, 1H, arom. H, *J* = 1.9 Hz), 6.86 (d, 1H, arom. H, *J* = 8.3 Hz), 7.15 (d, 1H, arom. H, *J* = 8.1 Hz), 7.57 (dd, 1H, arom. H, *J* = 8.1 Hz, *J* = 1.1 Hz), 7.66 (d, 1H, arom. H, *J* = 1.1 Hz), 11.9 (brs, 1H, NH).

6-[1-Acetyl-5-(3,4-dimethoxyphenyl)-4,5-dihydro-1H-pyrazole-3-yl]-2(3H)-benzothiazolone (3h)

Yield: 66 % (131 mg), m.p.: 140°C (decomp.) (acetic acid). ¹H-NMR (500 MHz, DMSO-d₆): δ (ppm) 2.28 (s, 3H, CH₃), 3.11 (dd, 1H, pyrazoline, *J* = 17.9 Hz, *J* = 4.4 Hz), 3.69 (s, 3H, CH₃), 3.71 (s, 3H, CH₃), 3.80 (m, 1H, pyrazoline), 5.46 (dd, 1H, pyrazoline, *J* = 11.6 Hz, *J* = 4.3 Hz), 6.63 (dd, 1H, arom. H, *J* = 8.2 Hz, *J* = 1.9 Hz), 6.78 (d, 1H, arom. H, *J* = 1.9 Hz), 6.86 (d, 1H, arom. H, *J* = 8.3 Hz), 7.15 (d, 1H, arom. H, *J* = 8.3 Hz), 7.71 (dd, 1H, arom. H, *J* = 8.3 Hz, *J* = 1.6 Hz), 7.66 (d, 1H, arom. H, *J* = 1.5 Hz), 12.1 (brs, 1H, NH).

Test microorganisms, media and cultivation conditions

Three representatives of filamentous fungi, *Fusarium graminearum* (NBIMCC 2294), *Fusarium oxysporum*, and *Aspergillus niger*, were used as model fungal strains. They were maintained on Potato Dextrose Agar (PDA). For radial growth rate measurements, the strains were cultured on the same medium at 28°C for 5 days until sporulation.

Measurement of radial growth rate of filamentous fungi

The inhibitory effect of compounds **1a-m**, **2a-h** and **3a-h** on fungal growth was evaluated through measurement of the radial growth rate of the model strains. Spores of the fungal cultures, prepared as described above were harvested and filtered through sterile cotton filter to avoid the presence of mycelia. Spores' suspensions in sterile saline solution were adjusted to a final concentration of 10⁵ spores/mL. Three μl of each suspension were used to inoculated PDA, over which 100 μl of 1.2 % solution in DMSO of the tested compound was spread. As controls, untreated cultures on PDA plates were used and the commercially available fungicide Topsin at 0.3 % concentration was applied as a reference for growth inhibition. In addition, as a negative control DMSO was used.

The growth of the fungal colonies was measured at daily basis for 7 days and the radial growth rate (Kr) was calculated according to the following formula [6]:

$$Kr = \frac{D_2 - D_1}{t_2 - t_1}, \text{ where}$$

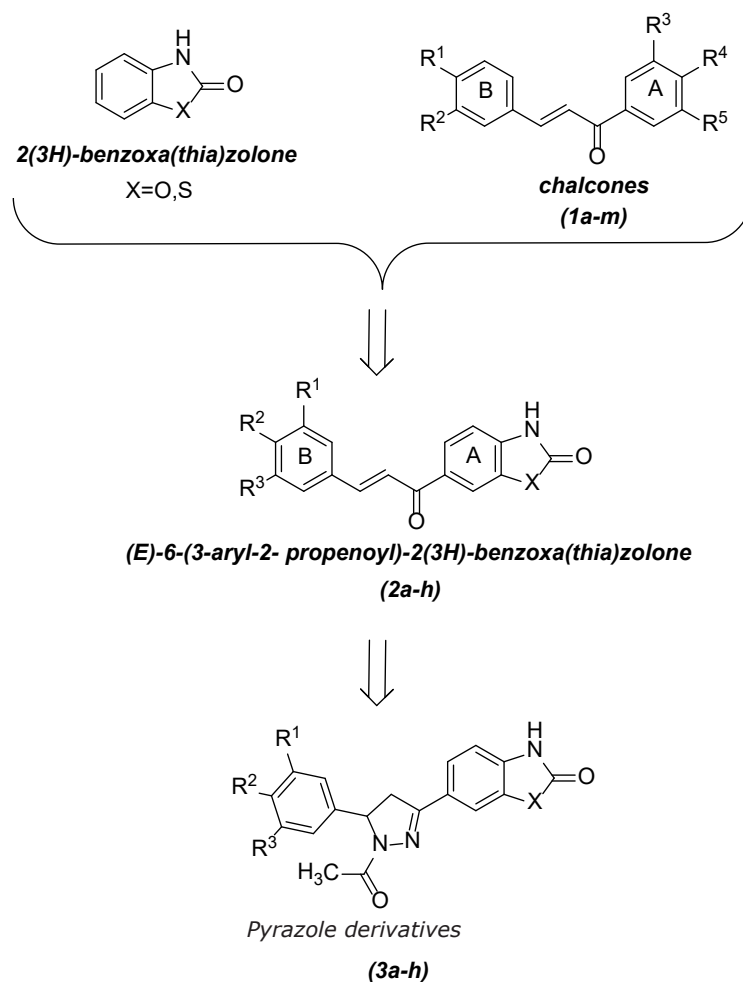
*D*₂ and *D*₁ are the colony diameters measured at the time points *t*₂ and *t*₁.

The inhibition effect (in %) was evaluated as a Kr decrease of a treated culture compared to an untreated control one. The values are averaged of three independent experiments.

RESULTS AND DISCUSSION**Chemistry**

A series of compounds (**1-3**) were synthesized in order to evaluate their antifungal activity and the relationship between structure and activity. The target compounds are presented in Scheme 1 and Table 1 and 2. 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone are commercially available. Chalcone derivatives **1a-m** were synthesized by acid-catalysed aldol condensation using SOCl₂/EtOH as a catalyst [7]. Heterocyclic chalcones **2a-h** were previously reported [8 - 11]. Eight new hybrid compounds combining a pyrazole fragment with a benzazole ring were synthesized (**3a-h**).

The synthesis of the pyrazole derivatives (**3a-h**) was achieved in one step, as presented in Scheme 2. Preparation was performed by reaction of different 6-(3-aryl-2-propenoyl)-2(3*H*)-benzoxa(thia)zolones



Scheme 1. Systematic representation of the tested compound (1a-m, 2a-h, 3a-h).

Table 1. Chemical structure of compounds 1a-m.

Compound	R¹	R²	R³	R⁴	R⁵
1a	H	H	H	H	H
1b	OH	H	H	H	H
1c	OCH ₃	H	H	H	H
1d	Cl	H	H	H	H
1e	H	H	H	OCH ₃	H
1f	H	H	H	Cl	H
1g	OCH ₃	H	H	OCH ₃	H
1h	OCH ₃	H	H	Cl	H
1i	Cl	H	H	OCH ₃	H
1j	OH	H	H	Cl	H
1k	Cl	H	H	Cl	H
1l	OH	OCH ₃	H	Cl	H
1m	OCH ₃	OH	OCH ₃	OCH ₃	OCH ₃

Table 2. Chemical structure of compounds **2a-h** and **3a-h**.

Compound	X	R ¹	R ²	R ³
2a	O	H	OCH ₃	H
2b	S	H	OCH ₃	H
2c	O	H	Cl	H
2d	S	H	Cl	H
2e	O	OCH ₃	OCH ₃	OCH ₃
2f	S	OCH ₃	OCH ₃	OCH ₃
2g	O	OCH ₃	OCH ₃	H
2h	S	OCH ₃	OCH ₃	H
3a	S	H	OCH ₃	H
3b	O	H	OCH ₃	H
3c	O	H	Cl	H
3d	S	H	Cl	H
3e	O	OCH ₃	OCH ₃	OCH ₃
3f	S	OCH ₃	OCH ₃	OCH ₃
3g	O	OCH ₃	OCH ₃	H
3h	S	OCH ₃	OCH ₃	H

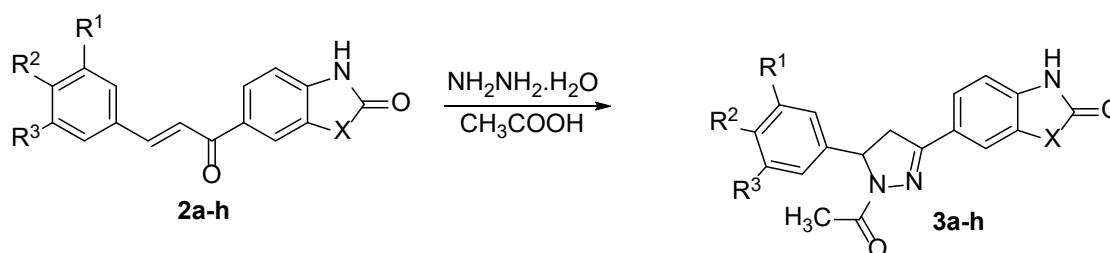
(**2a-h**) with hydrazine hydrate. The reaction was carried out in acetic acid at 115°C for 1 hour and led to only one product. Compounds **3a-h** were isolated in good yields and purified by recrystallization.

The structure of compounds **3a-h** was confirmed by ¹H-NMR and all data are in accordance with the assumed structure. In the ¹H-NMR spectrum the vinyl proton signals characteristic of the starting chalcones (**2a-h**) are replaced by three signals corresponding to pyrazole protons in the range $\delta = 3.09 - 5.54$ ppm. Aromatic protons are observed as doublets at $\delta = 6.87 - 7.99$ ppm. Two singlet signals corresponding to the acetyl group and azole NH are observed at about 2.28, and 12.0 ppm, respectively. The ¹³C-NMR spectrum displays 17 signals corresponding to the number the carbon atoms in compound **3b**.

Antifungal activity

To explore the antifungal potential of the novel heterocyclic hybrids of pyrazole, their inhibitory activity against filamentous fungi belonging to genera *Fusarium* and *Aspergillus* was investigated.

The model fungal strains were chosen due to the fact that they are considered among the most devastating plant pathogens. *Fusarium* and *Aspergillus* species are known to synthesize phytotoxins that, together with their ability to produce large amounts of ROS and plant cells degrading enzymes elucidate harmful effects to plant tissues and organs. Due to their broad host specificity and high genetic variability, the development and application of efficient management procedures to control their phytotoxic activity as a part of the Good Agriculture Practice is a real challenge [12 - 15].



Scheme 2. Synthesis of 6-(1-Acetyl-5-aryl-4,5-dihydro-1H-pyrazole-3-yl)-2(3H)-benzoxa(thia)zolones (**3a-h**).

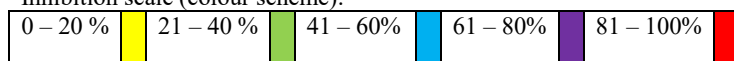
The ability of the novel heterocyclic hybrids of pyrazole to influence fungal growth was evaluated through measurement of the radial growth rate (Kr) of the model strains as described in the experimental section. The data about the antifungal activity of the tested com-

pounds are presented in Table 3. The results presented show a diverse inhibitory effect on the fungal growth that is dependent on both the chemical composition of the substance tested and the model strain. Although the inhibitory range varies between 1.2 and 88.8 %, the

Table 3. Inhibition of the radial growth rate (Kr) [mm/h] of filamentous fungi in the presence of compounds 1-33. Legend: K(+): untreated culture; T - commercially available fungicide Topsin (0.3 %); K(-): DMSO.

Compound	<i>F. graminearum</i>		<i>F. oxysporum</i>		<i>A. niger</i>	
	Kr (mm/h)	Growth inhibition (%)	Kr (mm/h)	Growth inhibition (%)	Kr (mm/h)	Growth inhibition (%)
1a	0.09	88.8	0.05	86.1	0.18	56.0
1b	0.53	33.8	0.42	12.5	0.38	32.1
1c	0.32	60.0	0.43	10.4	0.52	7.1
1d	0.59	26.2	0.44	8.3	0.49	12.5
1e	0.52	20.0	0.36	0	0.36	35.7
1f	0.41	36.9	0.41	0	0.48	14.3
1g	0.64	1.5	0.38	0	0.46	17.9
1h	0.7	16.7	0.35	2.8	0.31	26.2
1i	0.67	20.2	0.36	0.0	0.40	4.8
1j	0.7	16.7	0.31	13.9	0.34	19.0
1k	0.73	13.1	0.36	0.0	0.45	0
1l	0.78	7.1	0.35	2.8	0.37	11.9
1m	0.57	32.1	0.43	0	0.38	9.5
2a	0.8	4.8	0.35	2.8	0.42	0.0
2b	0.83	1.2	0.4	0	0.48	0
2c	0.78	7.1	0.36	0.0	0.40	4.8
2d	0.78	7.1	0.29	19.4	0.39	7.1
2e	0.78	7.1	0.41	0	0.33	21.4
2f	0.78	7.1	0.33	8.3	0.43	0
2g	0.83	1.2	0.32	11.1	0.50	0
2h	0.7	16.7	0.34	5.6	0.43	0
3a	0.52	38.1	0.26	27.8	0.46	0
3b	0.79	6.0	0.35	2.8	0.50	0
3c	0.78	7.1	0.36	0.0	0.47	0
3d	0.78	7.1	0.34	5.6	0.40	0
3e	0.79	6.0	0.39	0	0.50	0
3f	0.8	4.8	0.38	0	0.47	0
3g	0.76	9.5	0.38	0	0.49	0
3h	0.66	21.4	0.35	2.8	0.38	9.5
K(+)	0.76	0	0.41	0	0.49	0
T	0.40	49.7	0.39	4.9	0.20	51.4
K(-)	0.72	0	0.44	0	0.49	0

Inhibition scale (colour scheme):



following tendencies are observed.

The chalcone derivatives (**1a-m**) were the most effective among all tested substances against the tested fungal genera. Their inhibition potential was within the frames of 2.8 - 88.8 %. Best values were detected against *F. graminearum*. The substances **1a** and **1c** inhibited the fungal growth with 60.0 to almost 90 %, value that indicates better efficiency as compared with the commercial fungicide Topsin (49.7 %). As regards the other representative of g. *Fusarium* – *F. oxysporum*, about 60 % of the tested chalcone derivatives exhibited a moderate inhibitory effect (2.8 - 13.9 %) excluding substance **1a** with 86.1 %. The model strain *A. niger* was also sensitive to these compounds (except compound **1k**), and the inhibition efficiency varies between 4.8 % and 56.0 %. All these data indicate that chalcone derivatives exhibit antifungal potential that is substance- and fungal species dependent. Substances **1a-d**, **1h** and **1j** are of particular interest because they cover the whole spectrum of the fungal representatives with average inhibition potential of about 30 %. In fact, the substances **1j** (and **1k**) were proven to be effective against another fungal representative - *Penicillium claviforme*, showing 22.2 % and 38.7 % inhibition, respectively (data not shown).

The heterocyclic chalcones **2a-h** exhibit inhibitory effect (1.2 % - 19.4%) mainly against representatives of g. *Fusarium*. Substance **2e** was effective as well against *A. niger*.

The eight new hybrids, combining a pyrazole fragment with a benzazole (**3a-h**), showed the already observed with **1a-m** compounds inhibition pattern regarding *F. graminearum* – 4.8 % - 38.1 %. Less was the inhibition activity against *F. oxysporum*, with the exception of compound **3a** (27.8 %). The inhibitory effect against *A. niger* was insignificant.

CONCLUSIONS

The objective of the present study was to design and synthesize novel heterocyclic hybrids, and to screen these new structural entities for antifungal activity. In the three series of compounds synthesized, chalcone and 2(3*H*)-benzoxa(thia)zolone scaffolds were used as a core unit. The *in vitro* test of the new hybrids' antifungal activity against *Fusarium graminearum*, *Fusarium oxysporum*, and *Aspergillus niger* indicated that the best results were observed for the main structure chalcone

(**3**). Although chalcones have been extensively studied, the molecular mechanisms of action for their diverse biological activities are still not well understood [16]. According to the results obtained, structure - activity relationship can be speculated, since there are data that the presence of hydroxyl, allyl and prenyl groups in the chalcone structures commonly potentiates their activities [17]. The potent antifungal activity of the novel hybrids most probably is due to the presence of chloro and methoxy substituent in the phenyl ring of the chalcone unit. The compound **3a** demonstrated the most promising inhibition potential, especially against *Fusarium* representatives (27.8 - 38.1 %). The introduction of fused oxazolone or thiazolone cycle displayed weak antifungal activity, as compared to the standard compound. However, the pyrazole derivatives **3a** and **3h** combination with 2(3*H*)-benzothiazolone ring enhance the antifungal potential.

Thus, the antifungal potential of chalcone and its synthetic hybrids contributes to widen the multiple biological activities of this class of compounds.

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