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Short communication

Synthesis and antifungal activity of some 3-benzylidenechroman-4-ones, 3-benzylidenethiochroman-4-ones and 2-benzylidene-1-tetralones

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Summary — A series of 3-benzylidenechroman-4-ones, 3-benzylidenethiochroman-4-ones and 2-benzylidene-1-tetralones have been synthesised and tested for their *in vitro* antifungal activity. Some of them were inactive; others displayed good activity against *Cryptococcus neoformans, Torulopsis glabrata* and *Trichosporon cutaneum.*

Résumé — Synthèse et activité fongicide de quelques 3-benzylidène-chroman-4-ones, 3-benzylidène-thiochroman-4-ones, et 2-benzylidène-1-tétralones. *Une série de 3-benzylidène-chromanones-4, 3-benzylidène-thiochroman-4-ones et 2-benzylidène-1-tétralones diversement substituées a été synthétisée et essayée* in vitro *comme fongicides. Certains de ces produits ont montré une activité intéressante vis-à-vis de* Cryptococcus neoformans, Torulopsis glabrata *et* Trichosporon cutaneum *et semblent mériter une étude plus approfondie.*

3-benzylidenechroman-4-ones / 3-benzylidenethiochroman-4-ones / 2-benzylidene-1-tetralones / antifungal activity

Introduction

The most important antifungal agents currently available include flucytosine, griseofulvin, the polyene macrocycles nystatin and amphotericin B and the azole based antifungal agents of which micoanazole [1] ketoconazole [2] and fluconazole [3] are examples [4, 5].

We wish to describe herein the preparation and antifungal activity of some 3-benzylidenechroman-4-ones, 3-benzylidenethiochroman-4-ones and 2-benzylidene-1-tetralones against 3 *Candida* species (*C albicans, C parapsilosis* and *C tropicalis*), 3 *Cryptococcus* strains (*Farwaria*, 25 and 93/V), *Torulopsis glabrata* and *Trichosporon cutaneum.* These yeast-like fungi are important pathogens to man and cause a variety of chronic superficial and systemic diseases [6]. 3-Benzylidenechroman-4-ones (homo-isoflavones) have been isolated from members of the Liliaceae family [7, 8]. Révisé and Kirkiacharian have analysed the effect of a series of natural and synthetic 3-benzylidenechroman-4-ones on *Phytophthora parasitica* and on the activity of some of its enzymes. They have found inhibition of *in vitro* growth and sporogenesis of the micro-organism [9]. The enzyme β-glucosidase and 5 pectinolytic enzymes (*endo* PET/PATE and *endo* PMG/PG) which are directly involved in the infection mechanism are inhibited to a varying extent [8, 9].

Analgesic, antiinflammatory and platlet anti-aggregating activities have been reported for some 3-benzylidenechroman-4-one derivatives [10].

Chemistry

The chroman-4-ones **1a–d** and thiochroman-4-ones **(1e–g)** required for the present study were prepared using the available literature methods [11, 12].

The 3-benzylidenechroman-4-ones **(2–20)** were synthesised by acid catalysed condensation of the chroman-4-ones **1a–1d** with the appropriately substituted aryl aldehyde (scheme 1) [13, 14]. The yields and melting point data are displayed in table II. In the ^{1}H NMR spectrum of the 3-benzylidenechroman-4-ones **(2–20)** the vinyl proton H-α appears as a triplet in the range δ 7.81–8.12 which is coupled with the C–2 aliphatic protons which occur as a doublet in the

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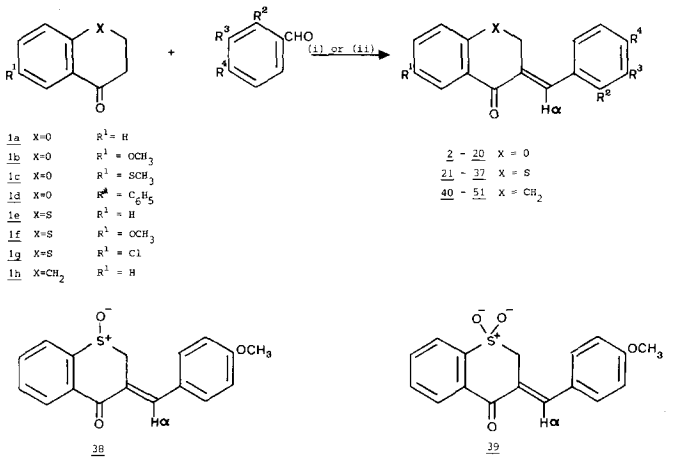

Scheme 1. Synthesis of 3-benzylidenechroman-4-ones, 3-benzylidenethiochroman-4-ones and 2-benzylidene-1-tetralones. Reagents (i): HCl, EtOH for compounds **2–37**, (ii): NaOH, EtOH for compounds **40–51**.

range δ 5.18–5.48 (J' = 1.5–2.0 Hz) [15, 18]. In the IR spectrum the α, β-unsaturated ketone is observed at 1635–1668 cm^{-1}, typical of the *E* configuration [19].

The 3-benzylidenethiochroman-4-ones **(21–37)** were prepared by acid catalysed condensation of the thiochroman-4-ones **(1e–1g)** with the appropriately substituted aryl aldehyde [20]. The yield and melting point data for the 3-benzylidenethiochroman-4-ones prepared are displayed in table I. In the IR spectrum conjugated carbonyl absorption occurs at 1665–1675 typical of the *E* configuration [21]. The ^{1}H NMR spectrum shows that only one isomer was obtained in each case and supports the proposed *E* configuration of the products. H-α appears downfield as a triplet at δ 7.71–7.93. The C-2 methylene protons occur as a doublet (δ 4.12–4.26 (S–CH_2), J = 1.2–2.0 Hz).

The sulfoxide **38** was prepared by treatment of **22** with hydrogen peroxide (1.1 mol) at 0°C in glacial acetic acid. The IR spectrum of **38** showed strong sulfoxide bands at 996 and 1030 cm^{-1}, and α, β-unsaturated carbonyl at 1670 cm^{-1}. The ^{1}H NMR spectrum displayed H-α as a double doublet (δ 7.80, 7.83 J = 5.0, 1.2 Hz). The C-2 protons appeared as 2 doublets at δ 4.40 (H–2a, $J_{a,b}$ = 1.9 Hz, $J_{a,\alpha}$ = 1.2 Hz) δ 4.69 (H-2b, $J_{b,a}$ = 1.9 Hz, $J_{b,\alpha}$ = 5.0 Hz) [22]. Oxidation of 3-(4'-methoxybenzylidene)thiochroman-4-one **22** with excess hydrogen peroxide in glacial acetic acid at 25°C afforded the sulfone **39** [23]. The IR spectrum showed asymmetric sulfone stretch at 1385, symmetric sulfone stretch at 1195 cm^{-1} and α, β-unsaturated carbonyl absorption at 1670 cm^{-1}. In the ^{1}H NMR spectrum the H-2 protons were observed as a doublet at δ 5.39, while H–α appeared as a triplet at δ 7.86 (J = 4.8 Hz).

The 2-benzylidene-1-tetralones **40–51** were prepared by base catalysed condensation of 1-tetralone 1h with the appropriately substituted aryl aldehydes (scheme 1) [24]. In the case of compounds **41, 44** and **50** the condensation reaction was carried out under acidic conditions to obtain reasonably good yields (table I). The IR spectra of the 2-benzylidene-1-tetralones **42–53** showed α, β-unsaturated carbonyl absorption at 1665–1675 cm^{-1} [19]. In the ^{1}H NMR spectrum H-α appears as a multiplet at δ 7.83–7.95 with long range coupling to the C-3 methylene protons. The H-8 signal appears as a multiplet at δ 8.10–8.25 due to the de-shielding influence of the carbonyl group. The C-3 and C-4 methylene protons appear as a complex multiplet centered at δ 2.85–3.14.

Results and Discussion

The MIC values (μg/ml) obtained for the 3-benzylidenechroman-4-ones **2–20**, 3-benzylidenethiochroman-4-ones **21–39** and 3-benzylidene-1-tetralones **40–51** are displayed in tables II, III and IV, respectively. Of the 3-benzylidenechroman-4-ones examined, compounds **3, 8, 10, 11** and **12** showed good activity against *Cryptococcus neoformans* MIC $\leq$ 25 μg/ml and indicated that the presence of a methoxy substituent at C-6 and methoxy, hydroxy or chloro substituents at C-4' were required for effective antifungal activity of these compounds. Compound **10** was also active against *Candida albicans* (MIC = 6 μg/ml), while compounds **5, 12** and **14** showed good activity against *Torulopsis glabrata* (MIC = 3 μg/ml) (table II).

Of the 3-benzylidenethiochroman-4-ones tested, only compounds **22** and **25** displayed significant activity against *Candida albicans* (MIC = 6 μg/ml). Many of the compounds displayed useful activity against *Cryptococcus neoformans*, particularly compounds **32, 33, 34** and **35** all of which contain a chloro substituent at C-6. The sulfoxide **38** together with compounds **22, 24** and **25** were active against *Toru-lopsis glabrata* (MIC = 6 μg/ml) while compounds **24, 33** and **38** showed useful activity against *Tri-chosporon cutaneum* (table III).

The 2-benzylidene-1-tetralones **40–51** were generally effective against *Torulopsis glabrata*; however only compounds **46, 48** and **51** showed good performance against *Cryptococcus neoformans* with MIC values of $\leq$ 12.5 μg/ml (table IV). The MIC values (μg/ml) obtained for the antifungal agents miconazole nitrate, tolnaftate, nystatin and amphotericin B against the organisms used in the study are also shown in table IV. These organisms were shown to be resistant to miconazole nitrate and tolnaftate (MIC = 100 μg/ml) but were susceptible to nystatin and amphotericin B.

Table I. 3-Benzylidenechroman-4-ones, 3-benzylidenethiochroman-4-ones and 2-benzylidene-1-tetralones.

Compound	X	R^1	R^2	R^3	R^4	Yield (%)	mp(°C)	Formula
2	O	H	OH	H	H	8.5	168-169	$C_{16}H_{12}O_3$
3	O	H	H	H	OH	55.7	230-231 [25]	$C_{16}H_{12}O_3$
4	O	H	OCH_3	H	H	61.1	106-107 [26]	$C_{17}H_{14}O_3$
5	O	H	H	H	OCH_3	71.8	133-134 [14]	$C_{17}H_{16}O_4$
6	O	H	H	OCH_3	OH	53.8	124-125	$C_{17}H_{14}O_4$
7	O	H	H	OCH_3	OCH_3	59.6	128-129 [27]	$C_{18}H_{16}O_4$
8	O	H	H	H	Cl	81.3	167-169 [10]	$C_{16}H_{11}ClO_2$
9	O	H	H	H	CH_3	88.0	117-118 [10]	$C_{17}H_{14}O_2$
10	O	OCH_3	OCH_3	H	H	52.9	145-146	$C_{18}H_{16}O_4$
11	O	OCH_3	H	H	OCH_3	79.3	132-133 [28]	$C_{18}H_{16}O_4$
12	O	OCH_3	H	OCH_3	OCH_3	64.5	157-159 [28]	$C_{19}H_{18}O_5$
13	O	OCH_3	H	OCH_2O		65.7	150-151	$C_{18}H_{14}O_5$
14	O	OCH_3	3-(2-naphthylidene)			65.8	130-131	$C_{21}H_{16}O_3$
15	O	OCH_3	3=CH-CH=CH-C_6H_5			61.3	149-150	$C_{19}H_{16}O_3$
16	O	SCH_3	H	H	OCH_3	32.6	108-109	$C_{18}H_{16}O_3S$
17	O	C_6H_5	OCH_3	H	H	70.2	159-160	$C_{23}H_{18}O_3$
18	O	C_6H_5	H	H	OCH_3	74.3	178-179	$C_{23}H_{18}O_3$
19	O	C_6H_5	H	OCH_3	OCH_3	60.1	171-172	$C_{24}H_{20}O_4$
20	O	C_6H_5	H	OCH_2O		61.7	181-182	$C_{23}H_{16}O_4$
21	S	H	OCH_3	H	H	63.6	101-102	$C_{17}H_{14}O_2S$
22	S	H	H	H	OCH_3	62.4	136-138	$C_{17}H_{14}O_2S$
23	S	H	H	OCH_3	OCH_3	50.7	126-128 [29]	$C_{18}H_{16}O_3S$
24	S	H	H	OCH_3	OH	67.8	146-147	$C_{17}H_{12}O_3S$
25	S	H	H	OCH_2O		32.3	152-154	$C_{17}H_{14}O_3S$

Table I. *(Continued)*

Compound	X	R^1	R^2	R^3	R^4	Yield (%)	mp(°C)	Formula
26	S	H	H	H	CH_3	64.1	118-119 [29]	$C_{17}H_{14}OS$
27	S	H	H	H	C_6H_5	52.1	143-145	$C_{22}H_{16}OS$
28	S	H	3-(2-naphthylidene)			67.8	146-147	$C_{20}H_{14}OS$
29	S	H	H	H	Cl	66.3	138-139 [29]	$C_{16}H_{11}Cl\ OS$
30	S	OCH_3	H	H	OCH_3	41.3	169-170	$C_{18}H_{16}O_3S$
31	S	OCH_3	H	OCH_2O		21.7	152-153	$C_{18}H_{14}O_4S$
32	S	Cl	H	H	H	25.6	112-113	$C_{16}H_{11}Cl\ OS$
33	S	Cl	OCH_3	H	H	41.6	145-147	$C_{17}H_{13}ClO_2S$
34	S	Cl	H	H	OCH_3	36.7	151-152	$C_{17}H_{13}ClO_2S$
35	S	Cl	H	OCH_3	OCH_3	30.9	125-126	$C_{18}H_{15}ClO_3S$
36	S	Cl	H	OCH_2O		31.8	168-169	$C_{17}H_{11}ClO_3S$
37	S	Cl	3-(2-naphthylidene)			46.9	165-167	$C_{20}H_{13}Cl\ OS$
38	SO	H	H	H	OCH_3	49.2	199-201	$C_{17}H_{14}O_3S$
39	SO_2	H	H	H	OCH_3	48.0	158-159 [23]	$C_{17}H_{14}O_4S$
40	CH_2	H	H	H	H	90.3	120-121 [19]	$C_{17}H_{14}O$
41	CH_2	H	H	H	OH	9.3	196-197	$C_{17}H_{14}O_2$
42	CH_2	H	H	H	OCH_3	78.3	87-88 [30]	$C_{18}H_{16}O_2$
43	CH_2	H	H	OCH_3	OCH_3	77.2	99-101 [31]	$C_{19}H_{18}O_3$
44	CH_2	H	H	OH	OH	20.5	225-127	$C_{17}H_{14}O_3$
45	CH_2	H	H	OCH_2O		78.5	107-109	$C_{18}H_{16}O_3$
46	CH_2	H	H	H	OC_2H_5	52.1	128-129	$C_{19}H_{18}O_2$
47	CH_2	H	H	H	CH_3	98.1	121-122 [32]	$C_{18}H_{16}O$
48	CH_2	H	H	H	C_2H_5	61.0	75-76	$C_{19}H_{18}O$
49	CH_2	H	NO_2	H	H	1.7	120-122 [19]	$C_{17}H_{13}NO_3$
50	CH_2	H	H	H	F	87.3	110-112 [32]	$C_{17}H_{13}F\ O$
51	CH_2	H	H	H	Cl	96.8	132-133 [34]	$C_{17}H_{13}Cl\ O$

Table II. MIC values (μg/ml) of 3-benzylidenechroman-4-ones **2–20** against *Cryptococcus neoformans* (3 strains), *Candida albicans, Candida parapsilosis, Candida tropicalis, Torulopsis glabrata* and *Trichosporon cutaneum.*

Compound	Cryptococcus neoformans			Candida	Candida	Candida	Torulopsis	Trichosporon
	Farwania	25	93/v	albicans	parapsilosis	tropicalis	glabrata	cutaneum
2	12.5	12.5	25.0	12.5	50.0	25.0	6.0	25.0
3	6.0	6.0	6.0	12.5	25.0	25.0	12.5	12.5
4	25.0	25.0	50.0	50.0	50.0	25.0	12.5	50.0
5	100.0	50.0	50.0	50.0	50.0	50.0	3.0	25.0
6	25.0	12.5	25.0	50.0	50.0	50.0	6.0	50.0
7	25.0	25.0	50.0	50.0	50.0	50.0	6.0	50.0
8	6.0	6.0	12.5	25.0	100.0	50.0	25.0	50.0
9	12.5	12.5	25.0	12.5	50.0	50.0	12.5	50.0
10	3.0	3.0	6.0	6.0	50.0	50.0	50.0	50.0
11	6.0	6.0	25.0	25.0	50.0	50.0	12.5	25.0
12	1.5	1.5	1.5	25.0	25.0	25.0	3.0	50.0
13	12.5	25.0	25.0	25.0	50.0	50.0	50.0	50.0
14	12.5	12.5	12.5	12.5	25.0	25.0	3.0	25.0
15	12.5	25.0	25.0	25.0	50.0	50.0	25.0	50.0
16	12.5	25.0	50.0	25.0	50.0	50.0	25.0	50.0
17	50.0	25.0	50.0	50.0	50.0	50.0	50.0	25.0
18	25.0	25.0	50.0	25.0	50.0	25.0	12.5	25.0
19	100.0	50.0	50.0	50.0	100.0	25.0	6.0	50.0
20	50.0	100.0	50.0	50.0	50.0	50.0	25.0	50.0

Table III. MIC values (μg/ml) of 3-benzylidenechroman-4-ones **21–39** against *Cryptococcus neoformans* (3 strains), *Candida albicans, Candida parapsilosis, Candida tropicalis, Torulopsis glabrata* and *Trichosporon cutaneum.*

Compound	Cryptococcus neoformans			Candida	Candida	Candida	Torulopsis	Trichosporon
	Farwania	25	93/v	albicans	parapsilosis	tropicalis	glabrata	cutaneum
21	25.0	25.0	25.0	25.0	50.0	50.0	12.5	12.5
22	25.0	3.0	6.0	6.0	25.0	25.0	6.0	12.5
23	100.0	50.0	100.0	100.0	100.0	50.0	25.0	12.5
24	50.0	25.0	6.0	50.0	25.0	25.0	6.0	1.5
25	12.5	1.5	6.0	6.0	50.0	50.0	6.0	25.0
26	100.0	50.0	50.0	50.0	100.0	50.0	12.5	25.0
27	25.0	12.5	6.0	25.0	50.0	50.0	12.5	25.0
28	12.5	12 5	25.0	25.0	100.0	50.0	25.0	25.0
29	12.5	3.0	12.5	50.0	50.0	50.0	25.0	25.0
30	12.5	12.5	25.0	25.0	100.0	50.0	12.5	12.5
31	25.0	12.5	25.0	50.0	50.0	50.0	25.0	12.5
32	6.0	6.0	50.0	50.0	50.0	50.0	25.0	50.0
33	12.5	1.5	12.5	12.5	25.0	12.5	12.5	3.0
34	6.0	6.0	12.5	25.0	50.0	50.0	25.0	25.0
35	6.0	6.0	12.5	50.0	50.0	50.0	25.0	50.0
36	12.5	12.5	12.5	25.0	50.0	50.0	25.0	25.0
37	12.5	50.0	50.0	50.0	50.0	50.0	50.0	25.0
38	50.0	50.0	25.0	25.0	25.0	50.0	6.0	6.0
39	25.0	25.0	25.0	12.5	50.0	50.0	12.5	25.0

Table IV. MIC values (μg/ml) of 2-benzylidene-1-tetralones **40–51** against *Cryptococcus neoformans* (3 strains), *Candida albicans, Candida parapsilosis, Candida tropicalis, Torulopsis glabrata* and *Trichosporon cutaneum.*

Compound	Cryptococcus neoformans			Candida albicans	Candida parapsilosis	Candida tropicalis	Torulopsis glabrata	Trichosporon cutaneum
	Farwania	25	93/V					
40	25.0	25.0	25.0	50.0	50.0	50.0	12.5	25.0
41	100.0	100.0	100.0	100.0	100.0	50.0	12.5	25.0
42	100.0	100.0	100.0	50.0	100.0	50.0	25.0	25.0
43	25.0	25.0	6.0	25.0	50.0	50.0	6.0	25.0
44	100.0	100.0	100.0	50.0	100.0	50.0	25.0	50.0
45	100.0	50.0	50.0	50.0	100.0	50.0	6.0	50.0
46	12.5	12.5	25.0	50.0	50.0	12.5	12.5	25.0
47	100.0	50.0	25.0	50.0	100.0	50.0	3.0	25.0
48	12.5	12.5	12.5	25.0	50.0	50.0	12.5	50.0
49	100.0	100.0	100.0	100.0	100.0	100.0	12.5	50.0
50	25.0	25.0	50.0	50.0	100.0	50.0	12.5	50.0
51	6.0	6.0	6.0	12.5	50.0	50.0	12.5	25.0
Tolnaftate	100	100	100	100	100	100	100	100
Miconazole nitrate	100	100	100	100	100	100	100	100
Nystatin	50.0	3.0	25.0	12.5	1.5	3.0	6.0	6.0
Amphotericin B	6.0	1.5	3.0	3.0	50.0	25.0	3.0	25.0

In conclusion, many of the 3-benzylidenechroman-4-ones, 3-benzylidenethiochroman-4-ones and 2-benzylidene-1-tetralones synthesised were found to be active *in vitro* against the pathogenic fungi *Cryptococcus neoformans, Torulopsis glabrata* and *Trichosporon cutaneum.* Further modification of these compounds are in progress.

Experimental protocols

Chemistry

Melting points were determined on a Gallenkamp melting point apparatus and were not corrected. The infra-red spectra were recorded on a Perkin–Elmer SP3-300 spectrometer. The ultraviolet spectra were recorded on a Pye-Unicam SP8-100 spectrometer. The ^{1}H NMR spectra were obtained on a Perkin–Elmer R12B spectrometer operating at 60 MHz with tetramethylsilane (TMS) as internal standard. Separations by column chromatography were carried out using Merck Kieselgel 60 silica gel while thin layer chromatography was carried out on pre-coated Merck HF silica-gel plates. Analyses of all new compounds in the text were within ±0.4% of the theoretical values for C, H and N.

The chroman-4-ones **1a** [35], **1b** [36], **1c** [37], **1d** [38] and the thiochroman-4-ones **1e** [39], **1f** [40] and **1g** [40] were prepared according to the literature procedures [9–12].

The experimental procedures are exemplified as follows:

3-(4'-Hydroxy-3'-methoxybenzylidene)chroman-4-one ***6***

Dry hydrogen chloride gas was passed through a solution of 4-hydroxy-3-methoxybenzaldehyde (15.2 g, 0.1 mol) and chroman-4-one (11.84 g, 0.08 mol) in ethanol (20 mol) for 15 min. The reaction mixture was allowed to stand at room temperature for 24 h. The precipitated product was then filtered, dried and recrystallized from ethanol (12.13 g, 43.8%) mp = 125°C. ^{1}H NMR ($CDCl_3$) δ : 8.10 (1H, m, H-5), 7.93 (1H, m, H-α), 6.78–7.39 (6H, m, aromatic H), 5.40 (2H, d, J = 1.8 Hz, H-2), 3.87 (3H, s, $-OCH_3$). IR (KBr) cm^{-1}: 3280 (OH), 1665 (C=O), 1595. Anal $C_{17}H_{14}O_4$ = 282.28.

6-Chloro-3-(2'-methoxybenzylidene)thiochroman-4-one ***33***

Dry hydrogen chloride gas was passed through a solution of 2-methoxybenzaldehyde (0.68 g, 0.005 mol) and 6-chlorothiochroman-4-one (0.99 g, 0.005 mol) in ethanol (20 ml) for 5 min. The solution was cooled, and the precipitated product was then filtered off, dried and recrystallised from ethanol (0.65 g, 41.6%) mp = 145–147°C. ^{1}H NMR ($CDCl_3$) δ : 8.41 (1H, d, J = 1.8 Hz, H-5), 7.86 (1H, m, H-α), 6.86–7.65 (6H, m, aromatic H), 4.17 (2H, d, J = 2 Hz, H-2), 3.86 (3H, s, OCH_3). IR (KBr) cm^{-1}: 1665 (C=O), 1585. Anal $C_{17}H_{13}ClO_2S$ = 316.78.

2-(3',4'-Methylenedioxybenzylidene)-1-tetralone ***45***

A mixture of 3,4-methylenedioxybenzaldehyde (3.8 g, 0.02 mol) and α-tetralone (2.92 g, 0.02 mol) was treated with ethanolic potassium hydroxide solution (20 ml, 4%) and stirred at 25°C for 16 h. The mixture was neutralised with acetic acid (20 ml) and water (10 ml) was added. The precipitated product was filtered off and recrystallised from ethanol. (4.4 g, 78.5%) mp = 107–108°C. ^{1}H NMR ($CDCl_3$) δ : 8.2 (1H, m, H-8), 7.95 (1H, m, H-α), 6.8–7.5 (6H, m, aromatic H), 6.15 (2H, s, $-OCH_2O-$), 2.9–3.1 (4H, m, $-CH_2CH_2-$). IR (KBr) cm^{-1}: 1670, 1608. Anal $C_{18}H_{16}O_3$ = 280.30.

3-(4'-Methoxybenzylidene)thiochroman-4-one-1-oxide ***38***

3-(4'-Methoxybenzylidene)thiochroman-4-one (0.71 g, 0.0025 mol) was dissolved in glacial acetic acid (5 ml) and the solution

cooled to 0°C. Hydrogen peroxide (0.2 ml, 35%, 0.0025 mol) was added dropwise over 30 min with stirring at 0–5°C. The mixture was stirred for 2 h at 0°C and then for 12 h at room temperature. The precipitated product was filtered off, and crystallised from benzene as needles, (0.37 g, 49.2%) mp = 199–201°C. ^{1}H NMR ($CDCl_3$) δ: 8.21 (1H, m, H-5), 7.81 (1H, dd, J = 5 Hz, 1.2 Hz, H-α), 7.38 (5H, m, aromatic H), 6.90 (2H, d, J = 7 Hz, H-3', H-5'), 4.69 (1H, dd, J = 1.2 Hz, 1.9 Hz, H-2 eq), 4.40 (1H, dd, J = 5 Hz, 1.9 Hz, H-2 ax), 3.94 (3H, s, 4'-OCH_3). IR (KBr) cm^{-1}: 1670 (C=O), 1601, 1030, 996. Anal $C_{17}H_{14}O_3S$ = 298.34.

3-(4'-Methoxybenzylidene)thiochroman-4-one-1,1-dioxide ***39***
This compound was prepared from 3-(4'-methoxybenzylidene)-thiochroman-4-one according to the literature procedure [23] mp = 158–159°C (lit [23] 161°C). ^{1}H NMR ($CDCl_3$) δ: 8.26 (1H, m, H-5), 7.86 (1H, d, J = 4.8 Hz, H-α), 7.41 (5H, m, aromatic H), 6.94 (2H, d, J = 7.3 Hz, H-3', H-5'), 5.39 (2H, d, J = 4.8 Hz, H-2), 3.95 (3H, s, –OCH_3). IR (KBr) cm^{-1}: 1670 (C=O), 1601, 1385, 1195 (SO_2). Anal $C_{17}H_{14}O_4S$ = 314.34.

Antimycotic activity
The *in vitro* antimycotic activity of tested compounds was determined against a series of yeasts and fungi and has been evaluated through the minimum inhibitory concentration (MIC) according to the method of progressive double dilutions in liquid Casitone medium [41].

The yeasts were originally clinical isolates obtained from Kuwait, and were typed by conventional methods [42, 43]. The cells were maintained by a periodic subculture on malt agar (Oxoid) slants. MIC determinations were performed by a microtitre technique on freshly subcultured 2-day-old cells from slants. One (1 mm) loopful of the freshly cultured cells was suspended in sterile distilled water (10 ml). The seeding rate was adjusted by successive dilution of this stock solution with sterile distilled water until the optical density reading of the solution is 0.05 (530 nm) [44, 45]. 25 μl of this diluted cell suspension is then added to the wells in the autotray-microtitre plate already containing liquid casitone medium (Difco; 20%, 0.1 mol). The compounds were then added to the wells in the concentration range of 0.1–100 μg/ml diluted with sterile distilled water from a 1 mg/ml stock solution of the pure compounds in DMSO (0.1 ml), with the highest content of DMSO in any well at 2.5%. The cells were incubated at 30°C for 24 h (for *Candida* spp and *Trichosporon cutaneum*) and 48 h (for *Cryptococcus neoformans* strains and *Tolulopsis glabrata*) and the MIC reading recorded at 24 h and 48 h respectively using a colony reader compared to control cultures incubated on the same plate at the same conditions above, and in duplicate sets.

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References

1 D'Arcy PF, Scott EM (1978) *In: Progress in Drug Research* (Jucker E, ed) Birkhäuser Verlag, Basel 22, 93–147
2 Thienpont D, Van Cutsem J, Van Gerven F, Heeres J, Janssen PAJ (1979) *Experientia* 35, 606–607
3 Richardson K, Bremmer KW, Marriot MS, Troke PF (1985) *Antimicrob Agents Chemother* 27, 832–835
4 Ellames GJ (1982) *In: Topics in Antibiotic Chemistry* (Sammes PG, ed) Ellis Horwood Limited, Chichester 6, 9–97
5 Ryley JF, Wilson RG, Gravestock MB, Poyser JP (1981) *In: Advances in Pharmacology and Chemotherapy* (Garatlini S, Goldin A, Hawking F, Kopin IJ, eds) Academic Press, New York, 18, 49–176
6 Speller DCE (1980) *In: Antifungal Chemotherapy* (Speller DCE, ed) John Wiley, Chichester 213–244
7 Heller W, Tamm C (1981) *Fortschr Chem Org Naturst* 40, 105–152
8 Geiger H (1988) *In: The Flavonoids* (Harborne JB, ed) Chapman & Hall Ltd, London 389–397
9 Ravisé A, Kirkiacharian BS (1978) *Phytopathol Z* 92, 36–50
10 Darmanaden R, Dhanutirto H, Castel J, Loubatiere J, Flandre O (1984) *Farmaco Ed Sci* 39, 876–889
11 Lockhart IM (1977) *In: Chromones Chromanones and Chromenes* (Ellis GP, ed) John Wiley & Sons, New York 207–428
12 Schneller SW (1975) *In: Advances in Heterocyclic Chemistry* (Katritzky AR, Boulton AJ, ed) Academic Press, New York 18, 58–97
13 Al Nakib T, Tyndall DV, Meegan MJ (1987) *J Chem Res* (S) 322–323, (M) 2743–2772
14 Dann O, Hofmann H (1962) *Chem Ber* 95, 1446–1450
15 Farkas L, Gottsegen A, Nogradi M, Strelisky J (1971) *Tetrahedron* 27, 5049–5054
16 Böhler P, Tamm C (1967) *Tetrahedron Lett* 3479–3483
17 Farkas L, Gottsegen A, Nogradi M (1970) *Tetrahedron* 26, 2787–2790
18 Sidwell MTL, Tamm C (1970) *Tetrahedron Lett* 475–478
19 Hassner A, Cromwell NH (1958) *J Am Chem Soc* 80, 893–900
20 Hofmann H, Westernacher H (1969) *Chem Ber* 102, 205–222
21 Beirne JJ, O'Sullivan WI (1977) *Proc R Ir Acad* 77, 331–325
22 McCormick J, McElhinney RS (1976) *J Chem Soc Perkin* 1, 2533–2540
23 Orlov VD, Midhed'kina EI, Shandula OV (1983) *Vestn Khar'k Un - ta* 61–66; (from *Ref Zh Khim* 1984 Abstr No 3Zh186); (*Chem Abstr* (1984) 101, 54864g)
24 Hassner A, Cromwell NH, Davis SJ (1957) *J Am Chem Soc* 79, 230–234
25 Levai A, Schag JB (1979) *Pharmazie* 34, 749
26 Mulvagh D, Meegan MJ, Donnelly DMX (1979) *J Chem Res* (S) 137, (M) 1713–1731
27 Morsingh F, Ong SH (1969) *Tetrahedron* 25, 361–367
28 Chatterjea JN, Shaw SC, Singh JN (1974) *J Indian Chem Soc* 51, 281–288
29 Chatterjea JN, Shaw SC, Singh RP (1978) *Natl Acad Sci Lett (India)* 1, 391–392; (*Chem Abstr* (1979) 90, 168484t)
30 Marvanyos E, Antus S, Nogradi M (1982) *Acta Chim Acad Sci Hung* 110, 93–96
31 Rosentreter U, Puls N, Bischoff H (1983) *Ger Offen* 3134945; *Chem Abstr* (1983) 98, 198047k

32 Azzolina O, Desimoni G, Di Toro V, Ghislandi V, Tacconi G (1975) *Gazz Chim Ital* 105, 971–983
33 Rehse K, Lang T, Rietbrock W (1977) *Arch Pharm (Weinheim)* 310, 979–987
34 Cromwell NH, Bambury RE, Barkley RP (1959) *J Am Chem Soc* 81, 4294–4298
35 Arndt F, Källner G (1924) *Chem Ber* 57, 202–206
36 Pfeiffer P, Oberlin H, Konermann E (1925) *Chem Ber* 58, 1947–1958
37 Canilini G, Degani I, Fochi R, Spunta G (1967) *Ann Chim (Rome)* 57, 1045–1072
38 Sarges R, Belletire JL (1980) (Pfizer Inc) US Patent 4181729 (*Chem Abstr* (1980) 92, P 163972g)
39 Arndt F, Flemming W, Scholz E, Lowensohn V (1923) *Chem Ber* 56, 1269–1279
40 Krollpfeiffer F, Schultze H, Schlumbohm E, Sommermeyer E (1925) *Chem Ber* 58, 1654–1676
41 Lodder J (1974) *In: The Yeasts–A Taxonomic Study* (Lodder J, ed) North Holland, Amsterdam, 3rd edn
42 Shadomy S, Espinel A (1980) *In: Manual of Clinical Microbiology, Am Soc Microbiol*, Washington, 3rd edn, 647
43 Koneman EW (1983) *In: Practical Laboratory Mycology* (Koneman EW, ed) Williams and Wilkins, Baltimore, 2nd edn 1–19, 103–106
44 Drouhet E, Barale T, Bastide J, Jouvet S, Maillie M, Biava MF, Kures L, Percebois G, Blanc C, Borderon JC, Camerlynck P, Cezaux M, Seguela J, Dupont B, Koening H, Kremer M, Billiault X, Goullier A, Grillot R, Ambroise-Thomas P, Regli P, Ferrari H, Viviani MA, Tortorano AM (1981) *Bull Soc Fr Mycol Med* 10, 131–134
45 Drouhet E, Dupont B (1978) *Bull Soc Fr Mycol Med* 7, 165–170