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Short communication

New imidazole anti-fungal agents derived from benzo[*b*]thiophene. Part II*

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Summary — 1-[(Aryl)(benzo[*b*]thienyl)methyl]-1*H*-imidazoles **22**, 1-[(benzo[*b*]thien-3-yl)(thienyl)methyl]-1*H*-imidazoles **25** and 1-[(diaryl)(benzo[*b*]thien-3-yl)methyl]-1*H*-imidazoles **28** have been synthesized and tested for anti-fungal activity. All compounds showed good activity against a broad spectrum of fungi (yeasts, dermatophytes).

Résumé — **Nouveaux agents anti-fongiques imidazoliques dérivés du benzo[*b*]thiophene. Partie II.** *Les [(aryl)(benzo*[b]*thiényl)méthyl]-1-1*H*-imidazoles **22**, les [(benzo*[b]*thién-3-yl)(thiényl)méthyl]-1-1*H*-imidazoles **25** et les [(diaryl)(benzo*[b]*thién-3-yl)méthyl]-1-1*H*-imidazoles **28** ont été synthétisés et essayés comme fongicides. Tous les composés ont montré une bonne activité vis-à-vis de nombreux champignons (levures, dermatophytes).*

imidazole anti-fungal agents / benzo[*b*]thienyl anti-fungal agents / anti-fungal activity / structure—activity relationships

Introduction

The introduction in 1969 of clotrimazole [1, 2] opened new avenues in the treatment of fungal diseases. Since then many related compounds have been successfully used, bearing an imidazole or 1,2,4-triazole ring substituted with a lipophilic moiety frequently containing one or more chlorine atoms [3—5].

However, contact allergies have been observed upon topical administration of imidazole anti-fungal agents [6—8]. Moreover, during the past few years an important increase in the number of mycoses has been observed. This is due to several different factors, such as the antibiotic-mediated selective destruction of microorganisms which are replaced by fungi, the generalized use of oral contraceptives, changes in behavioral habits both social and hygienic and some metabolic perturbations [9]. This justifies new research to broaden the therapeutic armamentarium with new improved azole anti-fungal agents.

Since the benzo[*b*]thiophene system has good lipophilicity and a low level of toxicity [10, 11], we considered the possibility of synthesizing and testing azole agents containing this heterocyclic moiety. Thus, we have developed 1-[2-[(7-chloro-3-benzo[*b*]thienyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole (sertaconazole) [12, 13] which is at present in the clinical trials phase.

As a result of our continuing effort in this field, we wish to report herein the synthesis and biological testing of new imidazole anti-fungal agents, namely 1-[(aryl)(benzo[*b*]thienyl)methyl]-1*H*-imidazoles **22**, 1-[(3-benzo[*b*]thienyl)-(thienyl)methyl]1*H*-imidazoles **25** and 1-[(diaryl)(3-benzo[*b*]thienyl)methyl]-1*H*-imidazoles **28**.

Synthesis

The required 2-lithiobenzo[*b*]thiophene **1** [14], 3-lithiobenzo[*b*]thiophene **2** [15, 16] and 5-chloro-3-lithiobenzo[*b*]thiophene **3** [17] were obtained, respectively, following described procedures, by direct lithiation of benzo[*b*]thiophene [14], by treatment of 3-bromobenzo[*b*]thiophene [15] with butyl-lithium [16] and by treatment of 3-bromo-5-chlorobenzo[*b*]thiophene [17] with butyl-lithium (Scheme 1). Only two required substituted benzaldehydes were not commercially acquired: 3-phenylbenzaldehyde **6** and 3-(*t*-butyl)benzaldehyde **7** (Scheme 2). The Grignard reagent from 3-iodotoluene **4** was coupled with bromobenzene under nickel(0) catalysis [18] to afford 3-methyl-

*For part I, see [12].
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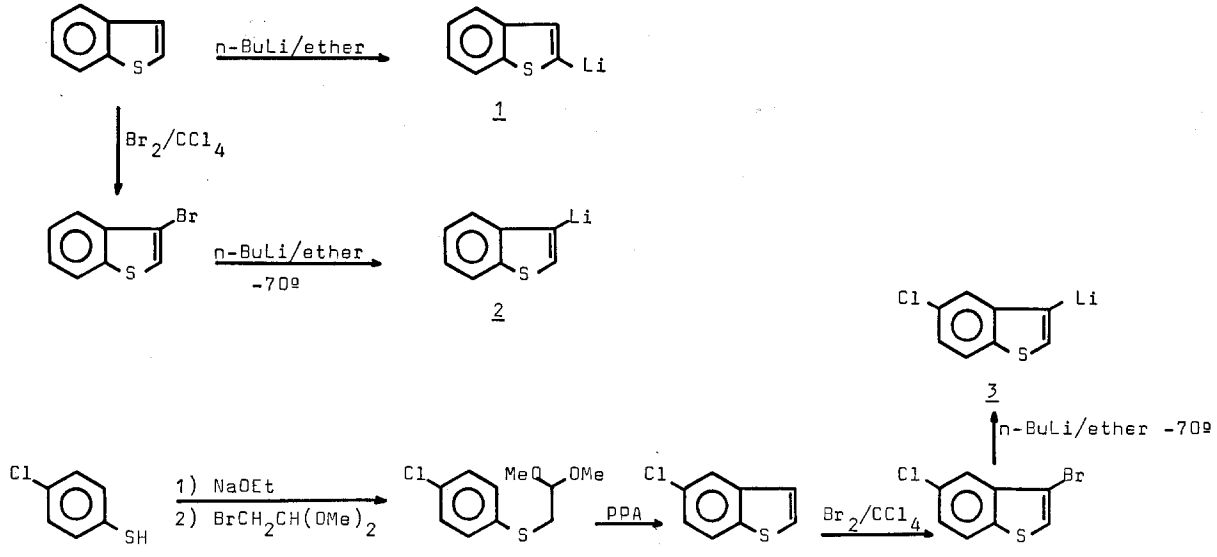
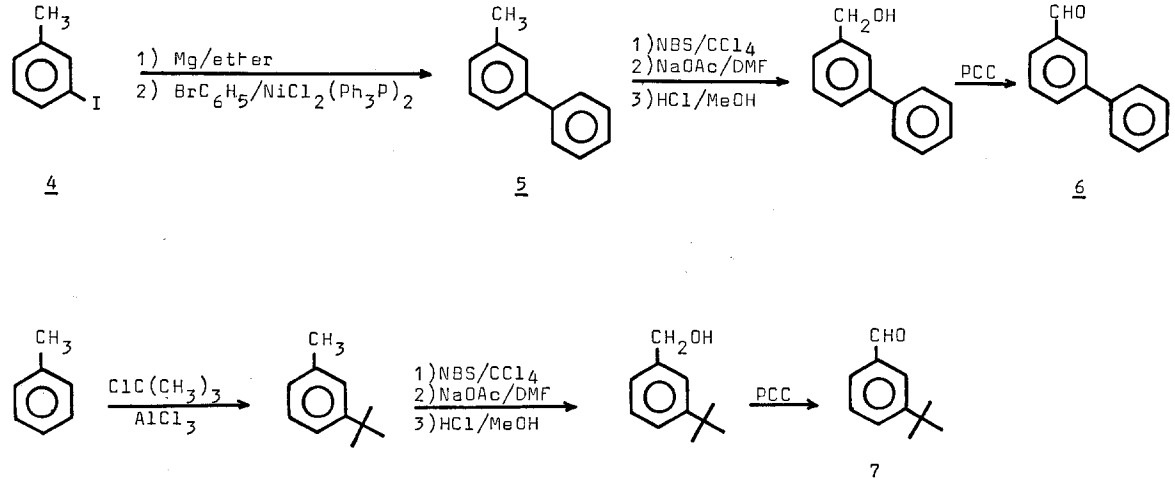
biphenyl **5** which was transformed into **6** by a described procedure [19]. The same method [19] was adopted to convert 3-(*t*-butyl)toluene [20] into **7**. The chlorinated thiophenealdehydes **8** [21], **9**, **10** [22, 23], **11**, **12** [24] and **13** [25] were prepared by known procedures or adaptations thereof (Scheme 3). The known aldehyde **14** [26] was prepared by an alternative procedure: chlorination of **13** in the presence of aluminium chloride. The required ketones were prepared as follows (Scheme 4): monochlorobenzophenones, **15**—**17**, by Friedel—Craft reactions as previously described [27]; 3,3′-dichlorobenzophenone, **18** by oxidation of the corresponding alcohol [28, 29] and 5-chlorothien-2-yl phenyl ketone **19** was obtained by Friedel—Craft reaction between benzene and 5-chloro-2-thienoyl chloride.

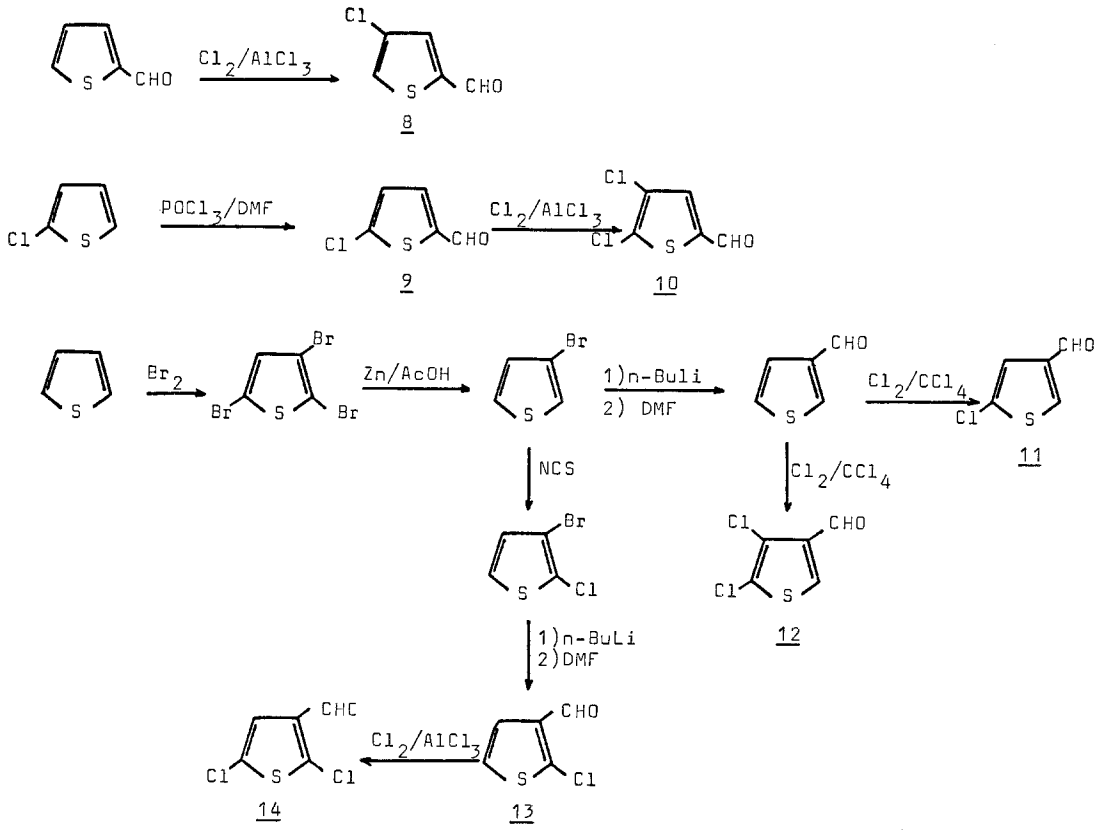
The reactions of **1** and **2** with several benzaldehydes afforded the (aryl)(benzo[*b*]thienyl)methanols **20** (Scheme 5). All of them presented broad infrared bands (KBr pellet or film) at 3400—2800 cm^{-1} and a singlet in the PMR spectrum at δ 5.8—6.5 corresponding to the methine proton. The alcohols **20** were converted into the unstable [(aryl)-(benzo[*b*]thienyl)]chloromethanes **21** by treatment with thionyl chloride in benzene. They presented singlets in the range δ 6.2—7.0 corresponding to the methine proton. Similarly, the reactions of the lithiobenzo[*b*]thiophenes **2** and **3** with the chlorothiophenealdehydes **8**—**14** afforded the alcohols **23** which were converted into the chlorides **24**. Also, the reactions of **2** with ketones **15**—**19** afforded the alcohols **26** which were converted into the corresponding chlorides **27**. Finally, treatment of the chlorides **21**, **24** and **27** without further purification with three equivalents of imidazole in dichloromethane afforded the final products **22**, **25** and **28**. Most of the compounds **22** and **25** were converted into their salts with naphthalene-1, 5-disulfonic acid (NDS) (2 mol of bases **22** and **25** with 1 mol of the disulfonic acid) for elemental analysis purposes (Tables I and II), but compounds **28** were very unstable and decompos-



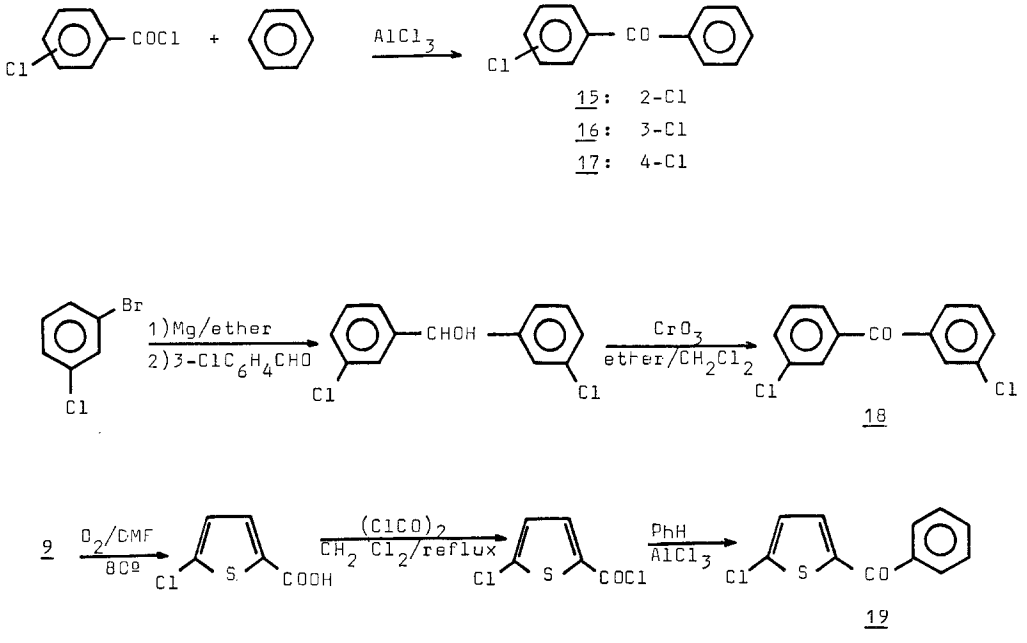
Scheme 1.



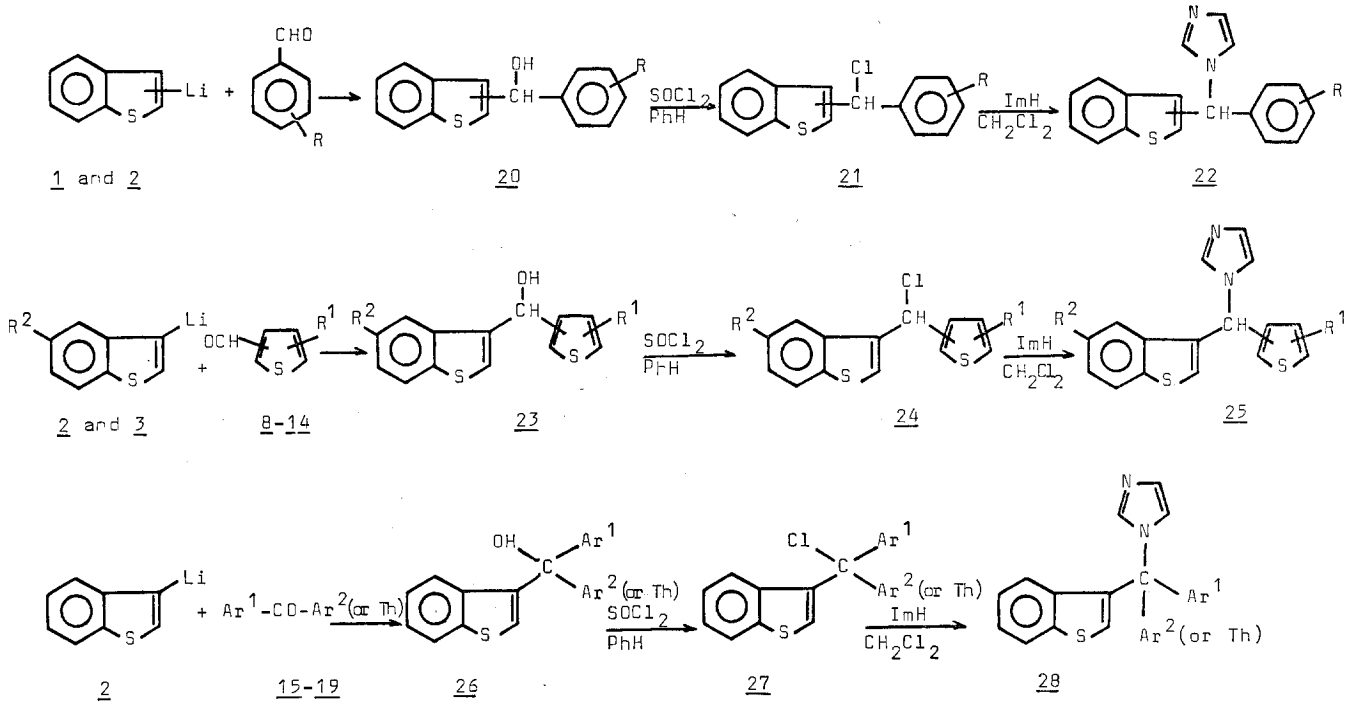
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5. Th: thienyl.

ed upon attempted salt formation in ethanol. Some salts were prepared but they did not give correct elemental analyses. PMR spectra of products **28** were uninformative, but the mass spectra given in Table III fully support the structures.

Table I. Compounds **22.**

Compd.	Benzothiophene linking atom	R	mp	Yield (%)	mp (NDS salt)
22a	C2	H	oil	53	186—8[a]
22b	C2	2-Cl	oil	76	214—6[a]
22c	C2	3-Cl	oil	81	202—3[a]
22d	C2	4-Cl	oil	80	160—2[a]
22e	C3	H	oil	28	215—7[b]
22f	C3	3-F	oil	84	223—4[a]
22g	C3	2-Cl	129—30[a]	74	
22h	C3	3-Cl	oil	70	203—6[a]
22i	C3	4-Cl	oil	71	258—60[a]
22j	C3	3-Br	oil	62	235—6[a]
22k	C3	3,5-Cl_2	56—9	47	266—9[a]
22l	C3	3-*t*-Bu	123—4[a]	78	
22m	C3	3-CF_3	oil	58	225—6[a]
22n	C3	3-C_6H_5	63—5[c]	65	231—2

[a]C and H elemental analyses within ±0.4.
[b]C and H elemental analyses within ±0.6 and ±0.5, respectively.
[c]Correct elemental analysis including 1 mol of water.

Table II. Compounds **25.**

Compd.	Thiophene linking atom	R^1	R^2	mp	Yield (%)	mp (NDS salt)
25a	C2	4-Cl	H	oil	73	217—9[a]
25b	C2	5-Cl	H	oil	44	188—90[a]
25c	C2	4,5-Cl_2	H	143—4[a]	54	
25d	C3	2-Cl	H	oil	68	158—60[a]
25e	C3	5-Cl	H	oil	71	209—10[a]
25f	C3	2,5-Cl_2	H	oil	72	201—2[a]
25g	C3	4,5-Cl_2	H	48—50	65	247—8[a]
25h	C2	5-Cl	Cl	oil	57	190—2[a]

[a]C and H elemental analyses within ±0.4.

Experimental protocols

Chemistry

Melting points were determined on a Köfler block (Reichert, Vienna) and are uncorrected. IR spectra were recorded on Perkin—Elmer 720 or 1300 spectrometers. 60 MHz PMR spectra were determined on a Perkin—Elmer R-12A spectrometer, using tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained under electron impact (70 eV) using a Hewlett—Packard 5985-B spectrometer.

3-Methylbiphenyl **5**

3-Iodotoluene (10 g, 46 mmol) was added dropwise under stirring and inert atmosphere to a suspension of Mg (1.2 g, 50 mmol) in anhydrous ether (30 ml). The reaction was exothermic and after the spontaneous heating was over the mixture was refluxed for 2 h. After cooling, the resulting solution was filtered through glass wool in a closed system and added dropwise to a mixture of bromobenzene (7.85 g, 50 mmol),

Table III. Compounds **28.**

Compd.	Ar^1	Ar^2 or HetAr	mp	Yield (%)	Mass spectra
28a	C_6H_5	2-ClC_6H_4	70—2	50	*m/e* 402(1.6), 400(M, 4.9), 335(39), 333(100), 221(72)
28b	C_6H_5	3-ClC_6H_4	68—70	61	*m/e* 402(0.3), 400(M, 0.7), 335(43), 333(100), 221(13)
28c	C_6H_5	4-ClC_6H_4	67—9	82	*m/e* 402(0.2), 400(M, 0.5), 335(34), 333(100), 221(51)
28d	3-ClC_6H_4	3-ClC_6H_4	55—7	67	*m/e* 438(0.1), 436(0.6), 434(M, 0.9), 371(17), 369(77), 367(100), 257(8), 255(28)
28e	C_6H_5	5-Cl-2-thienyl	58—9	64	*m/e* 408 and 406(undetected), 371(7), 341(40), 339(100), 299(62), 221(78), 134(35), 77(75)

nickel(II) chloride bistriphenylphosphine (250 mg, 0.38 mmol) and anhydrous ether (30 ml). The mixture was refluxed for 20 h, cooled and partitioned between ether and dilute hydrochloric acid. The organic layer was washed with water, dried and evaporated to afford 3.43 g of **5** (44% yield), bp: 133—140°C/15 mm Hg. PMR($CDCl_3$): δ 7.2—7.7 (m, 9H); 2.45 (s, 3H).

The experimental procedures for the series of products are exemplified as follows.

[(2-Benzo[b]*thienyl)(2-chlorophenyl)]methanol* ***20b***
Benzo[*b*]thiophene (2.0 g, 15 mmol) in dimethoxyethane (15 ml) was added under stirring to a cooled (—15°C) mixture containing 1.6 M butyl-lithium in hexane (9.4 ml, 15 mmol) and anhydrous dimethoxyethane (10 ml). The mixture was stirred for 1 h at 0°C. 2-Chlorobenzaldehyde (2.1 g, 15 mmol) in dimethoxyethane (5 ml) was then added. The mixture was kept under stirring at room temperature for 1.5 h and finally at 40°C for 30 min. The solvent was then evaporated and the residue was partitioned between ether and aqueous ammonium chloride. The organic layer was washed with water, dried and evaporated. The residue was purified through a silica gel column to give **20b** (3.23 g, 83%), mp: 77—78°C. IR(film): 3600—3100 (broad), 3050, 1590, 1565, 1430, 740 cm^{-1}. PMR($CDCl_3$): δ 7.95—7.65 (m, 3H); 7.45—7.25 (m, 5H); 7.15 (s, 1H); 6.5 (s, 1H); 3.23 (broad s, 1H, OH).

[(3-Benzo[b]*thienyl)(2-chlorophenyl)]methanol* ***20g***
3-Bromobenzo[*b*]thiophene (2.83 g, 13.3 mmol) in ether (15 ml) was added under stirring to a cooled (—70°C) mixture containing 1.6 M butyl-lithium in hexane (8.3 ml, 13.3 mmol) and anhydrous ether (15 ml). The mixture was stirred for 0.5 h at —70°C. 2-Chlorobenzaldehyde (2.16 g, 15.3 mmol) in ether (6 ml) was then added. The mixture was kept under stirring at —70°C for 4 h and finally at —5°C for 15 min. The solution was partitioned with aqueous ammonium chloride. The organic layer was washed with water, dried and evaporated. The residue was recrystallized from ether to afford **20g** (1.37 g, 38%), mp: 110—112°C. IR(film): 3550—3200 (broad), 3105, 3050, 1580, 1420, 750, 730 cm^{-1}. PMR($CDCl_3$): δ 7.90—7.65 (m, 3H); 7.55—7.05 (m, 6H); 6.45 (s, 1H); 2.75 (broad s, 1H, OH).

Other alcohols 20, 23 and 26
20a: mp: 84—85°C (Lit. [14], mp: 83°C). **20b**: mp: 77—78°C. **20d**: mp: 99—100°C (Lit. [14], mp: 102°C). **20g**: mp: 110—112°C. **20k**: mp: 101—103°C. **20l**: mp: 90—91°C. **23d**: mp: 67—9°C. **26a**: mp: 111—4°C. All other alcohols were oils.

[(3-Benzo[b]*thienyl)(3-fluorophenyl)]chloromethane* ***21f***
A solution of **20f** (2.71 g, 10.5 mmol) in benzene (20 ml) was added to a solution of thionyl chloride (1.37 g, 11.5 mmol) and pyridine (0.94 g, 12 mmol) in benzene (10 ml). The mixture was refluxed overnight and, after cooling, was filtered. The resulting solution was evaporated to afford **21f** (2.22 g, 77%) which was used in the next step without further purification. IR(film): 3060, 1610, 1590, 770, 730, 710 cm^{-1}. PMR($CDCl_3$): δ 7.95—7.65 (m, 3H); 7.45—7.10 (m, 6H); 6.35 (s, 1H).

Other chlorides 21, 24 and 27
They were unstable and were used without further purification. However, two of them crystallized: **21a**: mp: 88—89°C; **21d** mp: 99—101°C. All the other chlorides were oils.

1-[(2-Benzo[b]*thienyl)(3-chlorophenyl)methyl]-1H-imidazole* ***22c***
A solution of **21c** (0.73 g, 2.49 mmol) and imidazole (0.51 g, 7.5 mmol) in dichloromethane (23 ml) was refluxed overnight. The solution was washed with water, dried and evaporated. The residue was purified by passage through a silica gel column with dichloromethane—ethanol as the eluent to afford **22c** (0.65 g, 81%) as an oil. IR(film): 3050, 2920, 1585, 1565, 745, 720, 700, 655 cm^{-1}. PMR($CDCl_3$): δ 7.8—7.5 (m, 3H); 7.4—6.95 (m, 8H); 6.7 (s, 1H). MS: *m/e* 326(6), 324(M, 15), 259(34), 257(100), 221(71).

The *naphthalene-1,5-disulfonate* of **22c** was prepared from equimolar amounts of the free base and wet naphthalene disulfonic acid. It exhibited an mp: 202—3°C and its elemental analysis (C and H) was within ±0.13.

Anti-mycotic activity

The anti-mycotic activities of a series of yeasts and fungi have been evaluated as the minimal inhibitory concentration (*MIC*), according to the method of progressive double dilutions in solid media [30].

Drugs
The first solution of the tested products (oils or solids) was carried out by dissolving 10 mg into 1 ml of dimethylformamide (DMF) and adding water to a total volume of 10 ml (in some cases dissolution was completed by the addition of several drops of dilute hydrochloric acid).

Cultures
The 30 test organisms are shown in Table IV and comprise 20 strains of yeasts and 10 of dermatophytes. Isolates were grown on Sabouraud slants. Mature cultures were harvested with sterile saline and the resulting suspensions were adjusted by turbidity (dermatophytes) or colony plate counting (yeasts) to approximately 10^5 cfu/ml.

MIC *procedure*
The test medium was the base nitrogen yeast (Difco) complemented with L-asparagine (1.5 g/ml) and dextrose (10.0 g/l); the pH value of the medium thus prepared was about 5.4. Serial dilutions of each drug (640—0.32 μg/ml) were prepared from the initial ones, in sterile water. Molten agar (18 ml) was added to each of the 2 ml drug concentrations. Blanks were prepared with the same quantities of water and DMF but without test drugs. These mixtures were mixed and poured into sterile Petri dishes and allowed to harden. Two drug-free plates of the same medium (18 ml of agar plus 2 ml of water) were added to each set of drug concentrations. Each set of plates was inoculated with the Steer replicator. One of the drug-free plates was inoculated at the beginning and the other at the end of the series.

Table IV. Anti-mycotic activity (*MIC* range in μg/ml) of compounds **22, 25** and **28.**

Compound	Pathogenic yeasts				Dermatophytic fungi	
	Candida albicans (7 strains)	*Candida tropicalis* (1 strain)	*Candida pseudotrop.* (5 strains)	*Cryptococcus neoformans* (7 strains)	*Microsporum gypseum* (3 strains)	*Trichophyton mentagrophytes* (7 strains)
Bifonazole	10	32	2	3.3	2	2.3
22a	35	128	21.1	13	2.8	8
22b	16	32	4.6	21	2	2.9
22c	10	32	3	10	4	4
22d	12.7	32	8	14	8	5
22e	29	128	27.8	13	4	5.7
22f	23	128	16	47	2	2
22g	20	64	7	10	1	1
22h	8	16	4	11	2	2.5
22i	25	64	6	23	4	5.3
22j	6.6	32	6.1	21	3.1	2.5
22k	13.1	128	16	64	8	8
22l	17.6	64	16	26	2.7	6.7
22m	11.9	128	8	16	4	4
22n	19.5	128	16	1	16	128
25a	13	64	8	14	2.5	4
25b	4.4	32	1.7	10.7	2.5	0.79
25c	10.7	128	8	14.5	6.3	6.8
25d	8	32	4.6	20	1.6	2
25e	8	64	4.6	23	3.1	2.5
25f	2.9	32	2.6	26	6.3	2.9
25g	8.8	32	5.3	13	2.5	4
25h	14.5	128	13.9	13.1	2	2
28a	3.6	16	1.5	58	12.7	13.7
28b	8.8	128	2.28	3.6	4	2.3
28c	14.5	128	4.6	128	40.3	128

Yeasts cultures were incubated at 35°C for 5 days, and were read on days 2 and 5.

Dermatophytes were incubated at 30—32°C, and the plates were read on days 7 and 14.

We have taken as minimal inhibitory concentrations, those which completely inhibited or inhibited to an extent of greater than 95% the growth of the corresponding test organism when compared with a blank experiment after the described incubation time.

The *MIC* (geometric averages) thus obtained are presented in Table IV. All the tested products exhibit broad spectra of anti-mycotic activities which include pathogenic yeasts and dermatophytic fungi. Compounds **22h, 25b, 25f** and **28b** are noteworthy. The most active compounds *in vitro* were tested *in vivo* against dermatophytosis caused by *Trichophyton* in guinea pigs. The animals were treated with a 1% cream the third day after infection. Under these conditions, compound **28b** presented a clinical efficiency [31] of 48%.

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