**Researches on Antibacterial and Antifungal Agents, XIV[1]:**

# Thiophene Analogues of Bifonazole

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Some thiophene analogues of bifonazole have been synthesized by standard procedures and their antifungal activity has been tested against *Candida albicans*. Among test derivatives biphenyl-4-yl-5-chloro-thien-2-ylimidazol-1-ylmethane and its 5-deschlorothien-2-yl analogue resulted to be the most active. Their antifungal potency was almost comparable to that of control substances, such as miconazole, ketoconazole, and bifonazole. Replacement of benzene by the pyrrole ring in the biphenyl portion retained almost quantitatively the antifungal activity, whereas substitution with other azoles and with nitrogen alicyclic rings led always to less potent derivatives.

**Antibakterielle und antimykotische Verbindungen, 14. Mitt.: Thiophen-Analoge des Bifonazols**

Einige Thiophen-Analoge von Bifonazol wurden mit Standardmethoden hergestellt und auf antimykotische Wirkung gegen *Candida albicans* geprüft. Von den Testverbindungen erwiesen sich Biphenyl-4-yl-5-chlor-thien-2-yl-imidazol-1-ylmethan und sein 5-Deschlor-thien-2-yl-Derivat als die aktivsten: ihre antimykotische Wirksamkeit erreichte fast die der Kontrollverbindungen Miconazol, Ketoconazol und Bifonazol. Ersatz des Phenylrestes durch einen Pyrrolring im Biphenylteil beeinträchtigte die antimykotische Aktivität fast nicht, während der Ersatz durch andere Azole und N-haltige Alicyclen immer zu schwächer wirkenden Verbindungen führte.

Sulfur bioisosteres play a fundamental role in the design of chemotherapeutic agents belonging to the modern antifungal azoles field. Replacing of benzene by thiophene and introduction of a phenylthio-moiety led to high potent derivatives as observed in the case of tioconazole and fenticonazole, two antifungal agents introduced rapidly into clinical practice. Other interesting sulfur-containing antifungal agents are sulconazole and butoconazole[2,3].

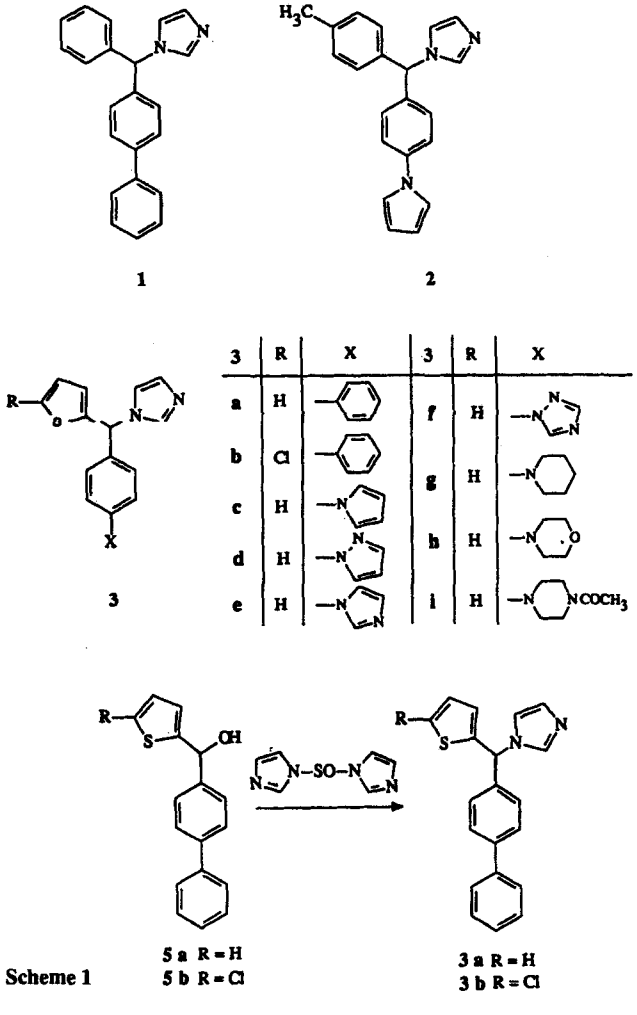
We recently were engaged in a search devoted to the synthesis and the microbiological assays of compounds strictly related to bifonazole **1**, a biphenylyl derivative of 1-benzylimidazole. Substitution of the biphenyl portion with the 4-(1*H*-pyrrol-1-yl)phenyl moiety led us to obtain derivatives with a very good antimicrobial profile, some of them, *e.g.* compound **2**, having antifungal activity comparable to that of the parent bifonazole[1,4,5].

In pursuing this search with the aim to prepare new potent antifungal agents we synthesized bifonazole-like derivatives containing a thiophene ring. The rationale of our approach was supported by previous noticeable results which showed the thiophene ring to exert excellent antifungal activity when replacing a 2,4-dichlorobenzene moiety, as in the case of the miconazole-tioconazole pair.

The planned derivatives **3** contain a fixed moiety formed by 2-thienyl-1-imidazolyl-methane and a changeable portion, modelled according to the biphenylyl group of the parent bifonazole (Scheme 1).

## *Chemistry*

Reaction of the known carbinols **5a** and **5b**[6] with 1,1'-sulfinyl diimidazole[7] afforded directly the azoles **3a** and **3b** (Scheme 1). Similarly carbinols **5d-i** (Scheme 2) and **5c** (Scheme 3) gave derivatives **3d-i** and **3c**, respectively, when reacted with 1,1'-sulfinyl diimidazole.

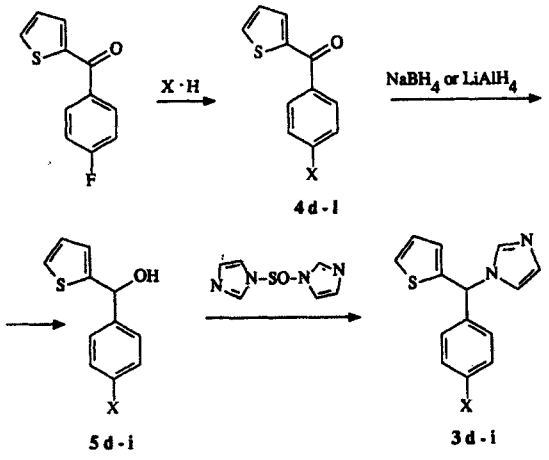



| 3 | R | X | 3 | R | X |
|---|---|---|---|---|---|
| a | H | | f | H | |
| b | Cl | | g | H | |
| c | H | | h | H | |
| d | H | | i | H | |
| e | H | | | | |

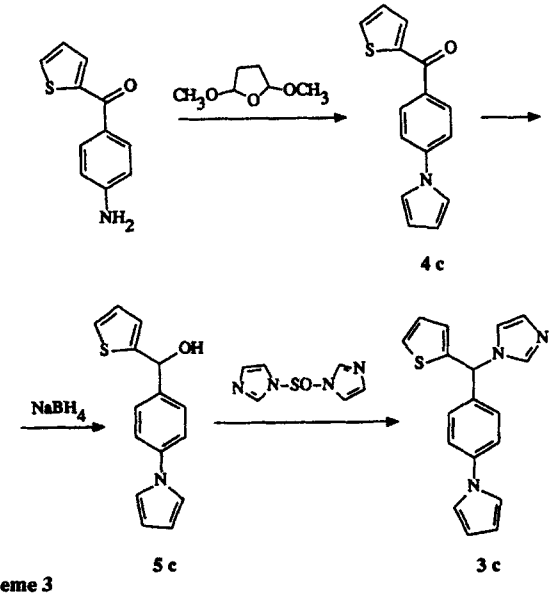
Scheme 1

  0365-6233/92/0404-0199 $ 3.50 + .25/0

The required carbinols were obtained by $NaBH_4$ reduction of ketones **4d-f**, **4i**, and **4c** or by $LiAlH_4$ reduction of ketones **4g** and **4h**.




**Scheme 2:** X = pyrazole (**d**), imidazole (**e**), 1,2,4-triazole (**f**), piperidine (**g**), morpholine (**h**), 1-acetylpiperazine (**i**) for derivatives **3d-i**, **4d-i**, and **5d-i**; 1,3,4-triazole for derivative **4l**.




**Scheme 3**

Reaction of 2-(4-fluorobenzoyl)thiophene[8] with azoles (pyrazole, imidazole, and 1,2,4-triazole) in DMSO in the presence of NaH furnished ketones **4d-f** and the isomeric 1,3,4-triazole **4l**. The same reaction with piperidine, morpholine, and 1-acetylpiperazine in DMF in the presence of $K_2CO_3$ gave ketones **4g-i** (Scheme 2).

Preparation of **4c** from 2-(4-aminobenzoyl)thiophene[9] was achieved by 2,5-dimethoxytetrahydrofuran in glacial acetic acid according to Clauson-Kaas[10] (Scheme 3).

## *Microbiological Part*

### *Materials and Methods*

The antimycotic activity against *Candida albicans* was calculated by means of the minimal inhibitory concentration (MIC) using the serial dilution test in a liquid nutrient medium[11]. For the preparation of the dilution series 5 mg of active ingredient were dissolved in DMSO (1 ml) and the solution was treated on shaking with distilled water (9 ml). Further progressive double dilutions with test medium furnished the required concentrations in the range from 0.25 to 256 µg/ml. Blanks were prepared in the test medium with the above reported quantities of water and DMSO.

MIC was defined as the lowest concentration of test substance at which there was no visible colonial growth in comparison with a blank experiment after the preset incubation time.

Bifonazole, ketoconazole and miconazole were used as controls. Strains with MIC > 256 µ/ml were regarded as resistant (R) and excluded from MICs calculation. $MIC_{50}$, $MIC_{90}$ and mean MIC values $n\bar{X}$ (Cmax at least 256 µg/ml) have been calculated as reported[4,5].

All the tested microorganisms were preliminarily incubated at 37°C on *Sabouraud* (BBL) dextrose broth. The incubation time was 18 h. Antimicrobial tests were performed on *Mueller-Hinton* (BBL) agar using inocula of $10^3$/ml cells. Readings of MICs were recorded after 36 h incubation at 37°C.

In the experiments were used 31 strains of *Candida albicans* freshly isolated from hospitalized patients.

## *Results and Discussion*

In Table 1 are reported the results of the antifungal screening of derivatives **3a-i** against *Candida albicans* at pH 7.2 and 5.8, respectively. Data reported refer to $n\bar{X}$, R%, $MIC_{50}$ and $MIC_{90}$ values using miconazole, ketoconazole, and bifonazole as controls.

As shown by the data of test at pH 7.2 the most potent derivatives against *C. albicans* are in the order compounds **3a**, **3c**, and **3b**. They show good antifungal activity like the control substances as noticeable by comparison of $n\bar{X}$, $MIC_{50}$ and $MIC_{90}$ values.

Introduction of a chlorine atom in the thiophene ring did not affect significantly the antifungal activity, **3b** being slightly inferior to **3a**. The same derivative **3b**, however, is superior to **3a** and **3c** when the test was performed at pH 5.8.

When an azole group replaced the outer benzene ring in the biphenylyl portion the $n\bar{X}$ values of antifungal activity decreased markedly from pyrazole to triazole in descending progressive order: pyrrole (5.28), pyrazole (55.6), imidazole (189.2), and triazole (205.1).

Replacing of azoles with nitrogen alicyclic rings gave only inactive derivatives as evidenced by R% (100) and $n\bar{X}$ (> 256) values displayed by derivatives **3g**, **3h**, and **3i**.

Data of experiments at pH 5.8 confirmed the above good results, with only slight differences. An increase of activity (see $MIC_{90}$ and $n\bar{X}$ values) was observed for derivatives **3a** and in particular for compound **3b**, which is superior to bifonazole and ketoconazole.

In comparison with the parent bifonazole we can observe that all test derivatives are inferior, with the exception of derivatives **3a**, **3b**, and **3c**. More in particular derivative **3a** showed activity similar to that of bifonazole at pH 7.2 and resulted to be more potent ($n\bar{X}$ = 3.41) than the parent compound ($n\bar{X}$ = 4.37) at pH 5.8. When compared to ketoconazole, **3a** was equipotent at pH 7.2, but superior at pH 5.8.

With the only exception of derivatives containing alicyclic nitrogen rings all test derivatives showed good activity

Table 1: Antimycotic activities of derivatives 3a-i at pH 7.2 and 5.8 against 31 strains of *Candida albicans*

| Tested substance | pH 7.2 R% | $n\bar{X}$ | $MIC_{50}$ | $MIC_{90}$ | Range (µg/ml) | pH 5.8 R% | $n\bar{X}$ | $MIC_{50}$ | $MIC_{90}$ | Range (µg/ml) |
|---|---|---|---|---|---|---|---|---|---|---|
| Bifonazole | 0 | 4.12 | 2 | 4 | 2-16 | 0 | 4.37 | 2 | 4 | 2-16 |
| Ketoconazole | 0 | 4.92 | 2 | 8 | 0.25-32 | 0 | 7.35 | 1 | 32 | 0.25-32 |
| Miconazole | 0 | 4.97 | 2 | 8 | 0.25-16 | 0 | 2.25 | 1 | 4 | 0.5-4 |
| 3a | 0 | 4.53 | 4 | 16 | 0.5-16 | 0 | 3.41 | 4 | 4 | 1-8 |
| 3b* | 0 | 10.46 | 8 | 32 | 1-32 | 0 | 3.30 | 2 | 8 | 0.5-8 |
| 3c | 0 | 5.28 | 2 | 16 | 0.5-16 | 0 | 6.29 | 8 | 8 | 1-8 |
| 3d* | 0 | 55.6 | 32 | 64 | 4-64 | 0 | 73.29 | 64 | 128 | 16-128 |
| 3e** | 0 | 189.2 | 128 | 256 | 64-256 | 0 | 202.32 | 256 | 256 | 32-256 |
| 3f | 0 | 205.1 | 128 | 256 | 128-256 | 25 | 297 | 256 | >256 | 64- >256 |
| 3g*** | 100 | >256 | | | >256 | 100 | >256 | | | >256 |
| 3h*** | 100 | >256 | | | >256 | 100 | >256 | | | >256 |
| 3i*** | 100 | >256 | | | >256 | 100 | >256 | | | >256 |

* mononitrate; ** dinitrate; *** monomaleate

Table 2: Preparative and analytical data

| Nr. | Yield (%)(a) | Formula (mol. weigth) | M.p. (°C) Solvent | Analysis (%): Found / Calcd. C | H | N | S |
|---|---|---|---|---|---|---|---|
| 3a | 52 | $C_{20}H_{16}N_2S$ (316.41) | 120-122 Cyclohexane | 76.03 / 75.91 | 5.13 / 5.09 | 8.66 / 8.85 | 10.02 / 10.13 |
| 3b(b) | 42 | $C_{20}H_{16}N_3O_3ClS$ (c) (413.87) | 172-174 Isopropanol | 57.75 / 58.03 | 3.99 / 3.89 | 9.99 / 10.15 | 7.59 / 7.74 |
| 3c | 65 | $C_{18}H_{15}N_3S$ (305.39) | 90-91 Cyclohexane | 70.68 / 70.78 | 4.90 / 4.95 | 13.61 / 13.76 | 10.62 / 10.52 |
| 3d(b) | 64 | $C_{17}H_{15}N_5O_3S$ (369.39) | 130-131 Isopropanol | 55.20 / 55.27 | 4.09 / 4.09 | 19.17 / 18.96 | 8.74 / 8.68 |
| 3e(d) | 42 | $C_{17}H_{16}N_6O_6S$ (432.41) | 160-161 Isopropanol | 47.27 / 47.21 | 3.88 / 3.73 | 19.25 / 19.43 | 7.46 / 7.41 |
| 3f | 52 | $C_{16}H_{13}N_5S$ (307.96) | 111-112 Benzene | 62.55 / 62.39 | 4.26 / 4.25 | 22.72 / 22.74 | 10.39 / 10.41 |
| 3g(e) | 75 | $C_{23}H_{25}N_5O_4S$ (439.52) | 136-138 Absolute ethanol | 62.55 / 62.84 | 5.62 / 5.73 | 9.55 / 9.56 | 7.31 / 7.29 |
| 3h(e) | 85 | $C_{22}H_{23}N_5O_5S$ (441.49) | 131-133 Absolute ethanol | 59.55 / 59.84 | 5.02 / 5.25 | 9.75 / 9.51 | 7.30 / 7.26 |
| 3i(e) | 43 | $C_{24}H_{26}N_6O_5S$ (482.54) | 113-115 Abs. ethanol/$(C_2H_5)_2O$ | 59.78 / 59.73 | 5.40 / 5.43 | 11.32 / 11.61 | 6.75 / 6.64 |
| 4c | 86 | $C_{15}H_{11}NOS$ (253.90) | 133-135 Toluene/cyclohexane | 71.25 / 70.95 | 4.39 / 4.36 | 5.61 / 5.51 | 12.74 / 12.62 |
| 4d | 87 | $C_{14}H_{10}N_2OS$ (254.30) | 93-97 Toluene/ligroin | 66.07 / 66.11 | 3.87 / 3.96 | 10.89 / 11.01 | 12.37 / 12.60 |
| 4e | 81 | $C_{14}H_{10}N_2OS$ (254.30) | 134-137 Toluene/ligroin | 65.97 / 66.11 | 3.96 / 3.96 | 11.14 / 11.01 | 12.87 / 12.60 |
| 4f | 63 | $C_{13}H_9N_3OS$ (255.29) | 137-140 Toluene/ligroin | 60.86 / 61.15 | 3.40 / 3.55 | 16.59 / 16.46 | 12.42 / 12.56 |
| 4g | 76 | $C_{16}H_{17}NOS$ (271.37) | 128-130 Toluene/ligroin | 70.68 / 70.81 | 6.20 / 6.31 | 5.18 / 5.16 | 11.90 / 11.87 |
| 4h | 81 | $C_{15}H_{15}NO_2S$ (273.34) | 1113-115 Toluene/ligroin | 65.94 / 65.90 | 5.74 / 5.53 | 5.11 / 5.12 | 11.91 / 11.73 |
| 4i | 65 | $C_{17}H_{18}N_2O_2S$ (314.39) | 159-161 Toluene | 65.04 / 64.94 | 5.60 / 5.57 | 8.98 / 8.91 | 10.37 / 10.20 |
| 4l | 5 | $C_{13}H_9N_3OS$ (255.29) | 189-190 Ethanol | 61.33 / 61.15 | 3.72 / 3.55 | 16.55 / 16.46 | 12.50 / 12.56 |
| 5c | 99 | $C_{15}H_{13}NOS$ (255.32) | 94-97 Toluene/ligroin | 70.77 / 70.55 | 5.21 / 5.13 | 5.47 / 5.48 | 12.51 / 12.55 |
| 5d | 98 | $C_{14}H_{12}N_2OS$ (256.31) | 118-120 Toluene/ligroin | 65.73 / 65.59 | 4.92 / 4.71 | 10.96 / 10.93 | 12.48 / 12.51 |
| 5e | 72 | $C_{14}H_{12}N_2OS$ (256.31) | 105-107 Toluene/ligroin | 65.64 / 65.59 | 4.63 / 4.71 | 11.10 / 10.93 | 12.67 / 12.51 |
| 5f | 92 | $C_{13}H_{11}N_3OS$ (257.30) | 109-110 Toluene | 60.60 / 60.67 | 4.36 / 4.30 | 16.40 / 16.33 | 12.55 / 12.46 |
| 5g | 90 | $C_{16}H_{19}NOS$ (273.36) | 112-112 Toluene | 70.31 / 70.28 | 6.97 / 7.00 | 5.37 / 5.12 | 11.63 / 11.72 |
| 5h | 93 | $C_{15}H_{17}NO_2S$ (275.36) | 124-126 Toluene | 65.16 / 65,42 | 6.36 / 6.22 | 4.94 / 5.08 | 11.46 / 11.64 |
| 5i | 95 | $C_{17}H_{20}N_2O_2S$ (316.41) | 151-153 Toluene | 64.68 / 64.52 | 6.52 / 6.37 | 8.62 / 8.85 | 9.91 / 10.13 |

(a) free base: (b) mononitrate: (c) analysis for chlorine: Found 8.36, Calcd. 8.56; (d) dinitrate; (e) monomaleate

Table 3: $^1$H-NMR Data of Derivatives 4-5[a]

| Nr. | Solvent | δ |
|---|---|---|
| 4c | $CDCl_3$ | 6.36 (m, 2H, pyrrole β -protons), 7.33 (m, 1H, H-$C_4$ thiophene), 7.56 (m, 2H, pyrrole α-protons), 7.71-8.26 (m, 6H, other aromatic protons). |
| 4d | $DMSOd_6$ | 6.65 (m, 1H, H-$C_4$ pyrazole), 7.36 (m, 1H, H-$C_4$ thiophene), 7.80-8.33 (m, 7H, H-$C_3$ pyrazole, benzene and other thiophene protons), 8.71 (m, 1H, H-$C_5$ pyrazole). |
| 4e | $CDCl_3$ | 7.08-7.90 (m, 7H, H-$C_4$ and H-$C_5$ imidazole, thiophene and two benzene protons), 7.90-8.18 (m, 3H, H-$C_2$ imidazole and other benzene protons). |
| 4f | $DMSOd_6$ | 7.38 (m, 1H, H-$C_4$ thiophene), 7.83 (m, 1H, H-$C_5$ thiophene), 8.08-8.31 (m, 5H, H-$C_3$ thiophene and benzene protons), 8.34 (s, 1H, H-$C_3$ triazole), 9.56 (s,1H, H-$C_5$ triazole) |
| 4g | $CDCl_3$ | 1.63 (s, broad, 6H, H-$C_3$, H-$C_4$ and H-$C_5$ piperidine protons), 3.36 (m, broad, 4H, H-$C_2$ and H-$C_6$ piperidine protons), 6.90 (d, J = 9 Hz, 2H, benzene protons), 7.16 (m, 1H, H-$C_4$ thiophene), 7.66 (m, 2H, H-$C_3$ and H-$C_5$ thiophene), 7.95 (d, J = 9 Hz, 2H, benzene protons). |
| 4h | $CDCl_3$ | 3.26 (m, 4H, H-$C_2$ and H-$C_6$ morpholine protons), 3.90 (m, 4H, H-$C_3$ and H-$C_5$ morpholine protons), 6.90 (d, J = 9 Hz, 2H, benzene protons), 7.16 (m, 1H, H-$C_4$ thiophene), 7.66 (m, 2H, H-$C_3$ and H-$C_5$ thiophene), 7.91 (d, J = 9 Hz, 2H, benzene protons). |
| 4i [d] | $CDCl_3$ | 2.10 (s, 3H, $COCH_3$), 3.36 and 3.73 (2m, 8H, piperazine protons), 6.93 (d, J = 9 Hz, 2H, benzene protons), 7.16 (m, 1H, H-$C_4$ thiophene), 7.70 (m, 2H, H-$C_3$ and H-$C_5$ thiophene), 7.91 (d, J = 9 Hz, 2H, benzene protons). |
| 4j | $DMSOd_6$ | 7.3 (m,1H, H-$C_4$ thiophene), 7.85 (m, 1H, H-$C_5$ thiophene), 8.05 (m, 4H, benzene), 8.25 (m, 1H, H-$C_3$ thiophene), 9.38 (s, 2H, H-$C_2$ and H-$C_5$ triazole) |
| 5c | $CDCl_3$ | 2.56 (m, 1H, OH), 6.00 (m, 1H, CH), 6.30 (m, 2H, pyrrole β-protons), 6.80-7.61 (m, 9H, other aromatic protons). |
| 5d | $DMSOd_6$ | 6.01 (d, J = 4.5 Hz, 1H, CH), 6.30 (d, J = 4.5 Hz, 1H, OH), 6.53 (m, 1H, H-$C_4$ pyrazole), 6.93 (m, 2H, thiophene protons), 7.33-8.00 (m, 6H, thiophene, H-$C_3$ pyrazole and benzene protons), 8.50 (m, 1H, H-$C_5$ pyrazole). |
| 5e | $CDCl_3$ | 5.21 (s,broad, 1H, OH), 6.06 (s, 1H, CH), 6.88-7.38 (m,7H, H-$C_4$ and H-$C_5$ imidazole, thiophene and two benzene protons), 7.48-7.73 (m,3H, H-$C_2$ imidazole and other benzene protons). |
| 5f | $DMSOd_6$ | 6.05 (d, J = 4.5 Hz, 1H, CH), 6.33 (d, J = 4.5 Hz, 1H, OH) 6.96 (m, 2H, thiophene protons), 7.46 (m, 1H, thiophene), 7.66 (d, J = 9 Hz, 2H, benzene protons), 7.91 (d, J = 9 Hz, 2H, benzene protons), 8.28 (s,1H, H-$C_3$ triazole), 9.36 (s, 1H, H-$C_5$ triazole). |
| 5g | $CDCl_3$ | 1.60 (m, broad, 6H, H-$C_3$, H-$C_4$ and H-$C_5$ piperidine protons), 2.61 (s, broad, 1H, OH), 3.13 (m, broad, 4H, H-$C_2$ and H-$C_6$ piperidine protons), 5.88 (s,1H,CH), 6.76-7.06 (m, 4H, two thiophene and two benzene protons), 7.16-7.43 (m, 3H, other thiophene and benzene protons) |
| 5h | $DMSOd_6$ | 3.10 (m, 4H, H-$C_2$ and H-$C_6$ morpholine), 3.70 (m, 4H, H-$C_3$ and H-$C_5$ morpholine), 5.86 (d, J = 4.5 Hz, 1H, CH), 6.03 (d, J = 4.5 Hz, 1H,OH), 6.86-7.06 (m, 4H, two thiophene and two benzene protons), 7.26-7.50 (m, 3H, other thiophene and aromatic protons) |
| 5i[e] | $CDCl_3$ | 2.05 (s, 3H, $COCH_3$), 2.98 (m, broad, 5H, OH and piperazine protons), 3.64 (m, 4H, piperazine protons), 5.95 (s, 1H, CH), 6.78-7.05 (m, 4H, two thiophene and two benzene protons), 7.21-7.34 (m, 3H, other thiophene and benzene protons) |

(a) Attribution of proton signals has been made accounting of references for arylazoles[12] and for acylthiophenes[13].
(b) All IR spectra of ketones **4** showed a peak in the range 1610-1620 $cm^{-1}$ ($^V$ CO).
(c) All IR spectra of alcohols **5** showed a broad band in the range 3140-3440 $cm^{-1}$ ($^V$ OH).
(d) $^V$ CO amide absorption at 1635 $cm^{-1}$.
(e) $^V$ CO amide absorption at 1600 $cm^{-1}$.

against tested strains (R% = 0) at pH 7.2. The same results were also obtained at pH 5.8, except for the triazole derivative **3f** (R% = 25).

We can, therefore, conclude that the introduction of the thiophene moiety in the bifonazole structure leads to very active compounds. Furthermore, we confirmed our remarks[4,5] that substitution of benzene with pyrrole did not affect substantially the antifungal power, whereas the antimicrobial activity is dramatically abated with introduction of azoles containing more than one N-atom.

An aromatic like-biphenylyl moiety is certainly crucial for antifungal activity as evinced by the comparison between the highly active derivatives **3a-c** and the totally inactive compounds **3g-i**. The lipophilic character of the above like-biphenylyl aromatic portion was also shown to affect the antimicrobial power in the test compounds, derivatives **3a-c** being more potent than the less lipophilic derivatives **3d-f**.

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## Experimental Part

M.p.: Electrothermal IA6304 (uncorr.).- IR-spectra (nujol mulls): Perkin Elmer 1310.- $^1$H-NMR-spectra: Varian EM-390 (90 MHz, TMS).- Column chromatography: silica gel Merck (70-230 mesh) and alumina Merck (70-230 mesh).- TLC: Stratocrom SIF Carlo Erba (silica gel precoated plates with fluorescent indicator) and Stratocrom ALF Carlo Erba (aluminium oxide precoated plates with fluorescent indicator). Microanalyses: Laboratories of Prof. A. Pietrogrande, University of Padova (Italy).- Organic extracts were dried over $Na_2SO_4$.- Evaporation of the solvents under reduced pressure.

Table 4: $^1$H-NMR Data of Derivatives 3

| Nr. | Solvent | δ |
|---|---|---|
| **3a** | $CDCl_3$ | 6.73 (s, 1H, alphatic CH), 6.85-7.65 (m, 15H, aromatic protons). |
| **3b** | $CDCl_3$ | 6.60-7.73 (m, 2H, aliphatic CH and chlorotiophene protons), 6.85 (m, 1H, chlorotiophene), 7.00 (m, 1H, imidazole), 7.15-7.70 (m, 11H, other aromatic protons). |
| **3c** | $CDCl_3$ | 6.35 (m, 2H, pyrrole β-protons), 6.71 (s, 1H, aliphatic CH), 6.86-7.65 (m, 12H, other aromatic protons). |
| **3d** | $CDCl_3$ | 6.46 (m, 1H, pyrazole), 6.73 (s,1H, aliphatic CH), 6.85-7.45 (m, 7H, two imidazole, two benzene and tiophene protons), 7.55 (s, 1H, imidazole), 7.65-7.91 (m, 3H, pirazole and two benzene protons), 7.95 (m, 1H, pyrazole). |
| **3e** | $CDCl_3$ | 6.78 (s, 1H, aliphatic CH), 6.90-7.61 (m, 12H, aromatic protons), 7.91 (m, 1H, imidazole) |
| **3f** | $CDCl_3$ | 6.80 (s, 1H, aliphatic CH), 6.90-7.86 (m, 10H, aromatic protons), 8.13 and 8.65 (2s, 2H, triazole) |
| **3g** | $CDCl_3$ | 1.61 (m, broad, 6H, piperidine), 3.16 (m, broad, 4H, piperidine), 6.60 (s, 1H, aliphatic CH), 6.80-7.41 (m, 9H, aromatic protons), 7.51 (s, 1H, imidazole) |
| **3h** | $CDCl_3$ | 3.13 (m, 4H, morpholine), 3.83 (m, 4H, morpholine), 6.63 (s,1H, aliphatic CH), 6.80-7.41 (m, 9H, aromatic protons), 7.53 (s, 1H, imidazole) |
| **3i** | $CDCl_3$ | 2.10 (s, 3H, $COCH_3$), 3.03 (m, 4H, piperazine), 3.70 (m, 4H,piperazine), 6.66 (s, 1H, aliphatic CH), 6.81-7.43 (m, 9H, aromatic protons), 7.53 (s, 1H, imidazole). |

(a) $^V$ CO amide absorption at 1660 cm$^{-1}$.

*Preparation of derivatives* **3a-i** *from carbinols* **5a-i**

$SOCl_2$ (0.0125 mol) was dropped while stirring into an ice-cooled solution of imidazole (0.05 mol) in anhydrous acetonitrile (50 ml). After stirring for further 1 h the precipitate was removed by suction and the solution was dropped into a stirred solution of the proper carbinol **5a-i** (0.0125 mol) in anhydrous acetonitrile (50 ml). Stirring was continued for 24 h at room temp. then the solvent was removed. The residue was treated with brine and $CHCl_3$. After shaking, the org. layer was removed, dried and evaporated to give a crude residue which was chromatographed on silica gel column (ethyl acetate) (**3a**, **3c**, and **3d**) or on alumina column ($CHCl_3$ for **3b** and **3g**; ethyl acetate for **3e**, **3f**, **3h**, and **3i**).

*$NaBH_4$ reduction of ketones* **4c-f** *and* **4i**: *synthesis of carbinols* **5c-f** *and* **5i**

A mixture of ketone **4c-f,i** (0.05 mol) and $NaBH_4$ (0.05 mol) in THF (150 ml) containing 3.5 ml of water was heated at reflux for 1 h. After cooling water (40 ml) was added under stirring and the solution was evaporated to a small volume. Extraction with ethyl acetate and subsequent evaporation of the solvent from the dried solution furnished a residue which was recrystallized from suitable solvent (**5c** and **5d**) or chromatographed on silica gel column (ethyl acetate) (**9f**) or on alumina column (ethyl acetate) (**5e** and **5i**).

*$LiAlH_4$ reduction of ketones* **4g** *and* **4h**: *synthesis of carbinols* **5g** *and* **5h**

A solution of ketone **4g,h** (0.05 mol) in dry THF (140 ml) was dropped while stirring into an ice-cooled suspension of $LiAlH_4$ (0.05 mol) in dry THF (35 ml), then the mixture was stirred at room temp. for 1 h. Crushed ice was carefully added and the precipitate which formed was filtered. The solution was evaporated to a small volume. Extraction with $CHCl_3$ and subsequent evaporation of the solvent from the dried solution furnished a residue which was recrystallized from suitable solvent.

*Pyrrole derivative* **4c**

A solution of 2-(4-aminobenzoyl)thiophene[9] (0.05 mol) and 2,5-dimethoxytetrahydrofuran (0.05 mol) in glacial acetic acid (90 ml) was heated at reflux for 30 min. The solvent was removed and the residue treated with crushed ice and solid $NaHCO_3$. The mixture was extracted with $CHCl_3$, the org. solution was separated, dried and evaporated to give a residue which was chromatographed on silica gel column ($CHCl_3$). The first eluates were collected and after evaporation of the solvent furnished **4c**.

*Reaction between 2-(4-fluorobenzoyl)thiophene and azoles: synthesis of derivatives* **4d-f** *and* **4i**

A solution of 2-(4-fluorobenzoyl)thiophene[8] (0.10 mol) and the appropriate azole (pyrazole, imidazole or 1,2,4-triazole) (0.15 mol) in anhydrous DMSO (240 ml) was slowly dropped into a well stirred suspension of NaH (80% in white oil) (0.12 mol) in the same solvent (70 ml). The mixture was heated at 100°C for 17 h. After cooling water was added and the mixture was treated with ethyl acetate. In the case of the imidazole derivative N HCl was added until pH 2. The org. extracts were then discarded and the aqueous solution was made basic by solid $Na_2CO_3$ under stirring. The precipitate was collected, washed with water and recrystallized from the proper solvent to give **4e**. In the preparation of the pyrazole and triazole derivatives, the ethyl acetate extracts were washed with brine and, after evaporation of the solvent, the crude solid was recrystallized to give **4d** or chromatographed on silica gel column (ethyl acetate) to give firstly the derivative **4f** and then the isomeric azole **4i**.

*Condensation of 2-(4-fluorobenzoyl)thiophene with piperidine, morpholine, and 1-acetylpiperazine: synthesis of derivatives* **4g**, **4h**, *and* **4i**

A mixture of 2-(4-fluorobenzoyl)thiophene (0.05 mol), piperidine (morpholine or 1-acetylpiperazine) (0.062 mol), and $K_2CO_3$ (0.062 mol) in DMF (20 ml) was heated at 160°C under stirring for 4 h. After cooling water was added and the mixture extracted with ethyl acetate. The org. layer was washed with brine, dried and evaporated to give a solid, which was recrystallized from suitable solvent (**4g**) or chromatographed on alumina column ($CHCl_3$) (**4i**) or on silica gel column ($CHCl_3$) (**4h**).

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