Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry 15 (2007) 1947–1958
Bioorganic & Medicinal Chemistry

# Synthesis, antimicrobial activity, and QSAR studies of furan-3-carboxamides

Nilo Zanatta,[a,*] Sydney H. Alves,[b,*] Helena S. Coelho,[a] Deise M. Borchhardt,[a] Pablo Machado,[a] Kelen M. Flores,[a] Fabio M. da Silva,[a] Tatiana B. Spader,[b] Jânio M. Santurio,[b] Helio G. Bonacorso[a] and Marcos A. P. Martins[a]

[a]*Núcleo de Química de Heterociclos (NUQUIMHE), Departamento de Química, Universidade Federal de Santa Maria, 97.015-900, Santa Maria, RS, Brazil*
[b]*Laboratório de Pesquisa Micológica (LAPEMI), Departamento de Microbiologia e Parasitologia, Universidade Federal de Santa Maria, 97.015-900, Santa Maria, RS, Brazil*

Received 17 October 2006; revised 22 December 2006; accepted 1 January 2007
Available online 4 January 2007

**Abstract**—The synthesis and characterization of a new series of furan-3-carboxamides, from the aromatization of 4-trichloroacetyl-2,3-dihydrofuran to 3-trichloroacetyl furan followed by nucleophilic displacement of the trichloromethyl group or the corresponding carboxylic acid chloride by nitrogen-containing compounds, is presented. Preliminary in vitro antimicrobial activity of the title compounds was assessed against a panel of microorganisms including yeast, filamentous fungi, bacteria, and alga. Some of the furan-3-carboxamides exhibited significant in vitro antimicrobial activity. QSAR investigation was applied to find a correlation between the different physicochemical parameters of the compounds studied and their biological activity.


## 1. Introduction

Fungal infections are associated with rates of attributable morbidity and mortality. Limited therapeutic options for treating these infections, as well as concerns over selection of non-*Candida* species with reduced susceptibilities to the triazole agents, have warranted surveillance for potential resistance development and demonstrated the need for expansion of available antifungal regimens.[1–4]

Furan derivatives, both obtained from synthetic and natural sources, have been attracting much interest due to the wide range of pharmaceutical applications they have demonstrated.[5–7] Many of the naturally occurring furans have shown interesting biological activities, such as cytotoxic and antitumor properties,[7,8] as well as antispasmodic,[9] antimicrobial,[10,11] and several other potentially useful activities.[12] A series of synthetic nitrofuranyl amides showed good in vitro inhibitory activity against *Mycobacterium tuberculosis*,[13,14] especially 5-nitro-furan-2-carboxylic acid *N*-[4-(4-benzylpiperazin-1-yl)-benzyl]-5-nitrofuran-2- carboxamide[13] and 2-methyl-*N*-phenylfuran-3-carboxamide, commercially known as Fenfuran,[15] which is used as fungicidal seed dressing for the control of bunts and smuts. In addition, furans are also present in commercially important products such as agrochemical bioregulators, dyes and photosensitizers, essential oils, cosmetics, and flavoring and fragrance compounds.[16–18]

Although a variety of furan syntheses are known, the development of new and convenient strategies to synthesize them is of considerable interest.[19] Furans can be, in principle, synthesized by either cyclization of acyclic precursors[20–22] or by derivatization of the furan ring.[23] Introduction of substituents at the 2- or 5-position of furan is relatively easy to carry out by aromatic electrophilic substitution,[18] whereas a special strategy is necessary to obtain 3- or 4-substituted furans.[24] Many methodologies to functionalize position 3 or 4 of furans

*Keywords*: Furan; Furan-3-carboxamides; Trichloroacetyl furan; Antimicrobial activity; Minimal inhibitory concentration; MIC; QSAR.
* Corresponding authors. Tel./fax: +55 55 3220 8756 (N.Z.); fax: +55 55 3220 8906 (S.H.A.); e-mail addresses: zanatta@base.ufsm.br; hartzsa@ccs.ufsm.br

0968-0896/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2007.01.003

have been reported, however, most of them involve multi-step synthesis,[25–27] modification of butyrolactone derivatives,[28] or the use of expensive reagents.[29] In addition, it is rare to find furan-containing carboxamide groups at the 3- or 4-positions in the literature.[30] For these reasons, there is a clear demand for the development of a modular and simple reaction to access strategically substituted furans.

Recently, we reported a simple and convenient procedure for preparing furan-3-carboxylic acid and derivatives from the aromatization of the readily available 4-trichloroacetyl-2,3-dihydrofuran[31] to 3-trichloroacetyl furan followed by nucleophilic displacement of the trichloromethyl group to give furan-3-carboxylic acids, esters, and amides.[32] These furan-3-carboxamides were assessed against a panel of microorganisms including yeast-like fungi, bacteria, and algae. Some of the furan-3-carboxamides[32] exhibited significant in vitro antimicrobial activity.[33] This encouraged us to synthesize a new series of furan-3-carboxamides by reacting 3-trichloroacetyl furan or the corresponding furan-3-carbonyl chloride with a series of nitrogen-containing compounds to access an array of compounds with promising antimicrobial activities. Thus, the aim of this study was the synthesis and characterization of an extended and planned series of new furan-3-carboxamides through the reaction of 3-trichloroacetyl furan or furan-3-carbonyl chloride derivatives with a series of amines and related nitrogenated compounds such as benzamidine, hydrazines, and imidazoles. The obtained furan-3-carboxamides were assessed against a panel of microorganisms including yeast, filamentous fungi, bacteria, and algae. Preliminary antimicrobial activity assays of some of the furan-3-carboxamides exhibited significant in vitro antimicrobial activity.

## 2. Chemistry

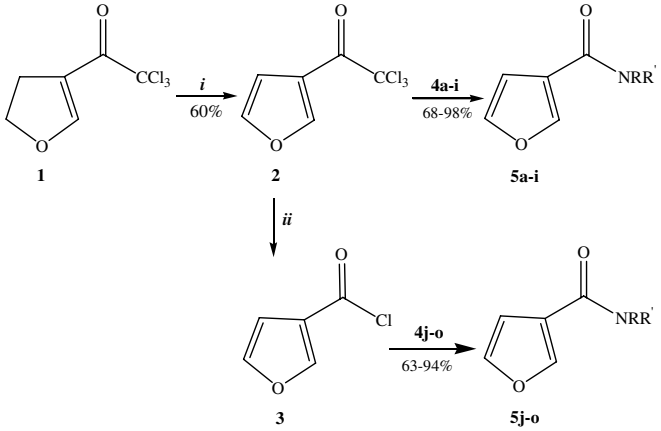
The synthesis of furan-3-carboxamides, outlined in Scheme 1, starts with the readily available 4-trichloroacetyl-2,3-dihydrofuran (**1**) whose synthetic versatility for the synthesis of 3-amino-methylene-dihydro-furan-2-ones,[34] isoxazoles,[35] pyrazoles,[36] pyrimidines,[37–39] and analogues of cyclophosphamide[40] has been reported. The aromatization of compound **1** was previously reported.[32]

Reaction of **2** with benzamidine, primary and secondary amines, furnished a series of furan-3-carboxamides, in good yields. The amines used in this study, the reaction conditions, and yields are reported in Table 1. It is interesting to note that, probably, due to the higher boiling point of the amines used in these reactions, the use of a sealed tube was not necessary.[32] For the reaction of **2** with benzamidine hydrochloride, the use of an equivalent amount of sodium hydroxide solution was necessary to obtain the amidine free base.

The reactions of **2** with the amines **4j**, **k**, hydrazines **4l**, **m**, and amino triazole derivatives **4n** and **4o** did not furnish the expected furan-3-carboxamides. In these reactions, probably due to the low nucleophilicity of the nitrogen atom, the reaction did not take place and the reagents were recovered. This problem was circumvented by converting the 3-trichloroacetyl furan (**2**) into the corresponding furan-3-carbonyl chloride (**3**). This conversion was done by reacting **2** with a solution of sodium hydroxide to obtain the furan-3-carboxylic acid[32] followed by the treatment of this acid with thionyl chloride in benzene in the presence of catalytic amount of *N*,*N*-dimethylformamide[40,41] to obtain the intermediate **3**, in good yields. The reactions of **3** with amines and amino triazole derivatives were carried out in toluene in the presence of an equivalent amount of triethylamine at 30 °C for the amines **4j**, **k** and at reflux for the hydrazines **4l**, **m** and for the amino triazoles **4n** and **4o** (Table 1).

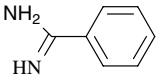
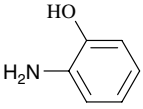
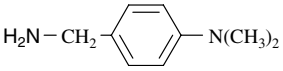
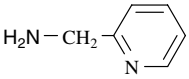
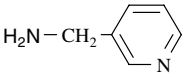
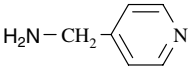
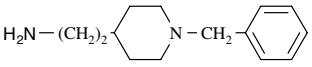
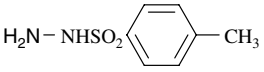
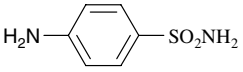
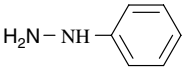
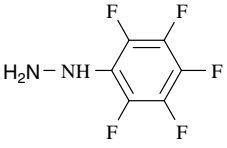
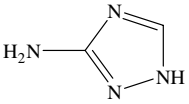
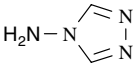
All compounds obtained in this study were analyzed by $^{1}H$ and $^{13}C$ NMR, GC–MS, and representative compounds by elemental analysis.

There was a concern about the correct structure of compound **5k** because the amine precursor could react with the furan-3-carbonyl chloride through the sulfonamide nitrogen or through the aniline nitrogen. To correctly define the structure of **5k**, an X-ray analysis was




**Scheme 1.** Reactions and conditions: (i) NBS, *m*-CPBA(cat), $CCl_4$, reflux, 2 h, Ref. 32; (ii) a—NaOH, benzene, reflux, 16 h; b—$SOCl_2$, toluene, *N*,*N*-DMF(cat), reflux, 2 h. For the structure of amines **4a–o** and reaction conditions to obtain compounds **5a–o**, see Table 1.

**Table 1.** Reaction conditions to obtain the furan-3-carboxamides **5a–o**

| Compound | Amine | Reaction conditions | Product | Yield[a] (%) | Mp (°C) |
|---|---|---|---|---|---|
| **4a** |  | $CH_2Cl_2$, NaOH 1 M, rt, 0.25 h | **5a** | 80 | 222–225 |
| **4b** | $H_2N(CH_2)_3OH$ | MeOH, rt, 2 h | **5b** | 70 | Oil |
| **4c** | $NH(CH_3)_2$ | MeOH, reflux, 15 h | **5c** | 68 | Oil |
| **4d** |  | MeOH, relux, 15 h | **5d** | 80 | 160–162 |
| **4e** |  | EtOH, reflux, 24 h | **5e** | 71 | 145–148 |
| **4f** |  | EtOH, reflux, 15h | **5f** | 97 | Oil |
| **4g** |  | EtOH, reflux, 15 h | **5g** | 92 | Oil |
| **4h** |  | EtOH, reflux, 15 h | **5h** | 98 | Oil |
| **4i** |  | Toluene, $Et_3N$, reflux, 15 h | **5i** | 97 | Oil |
| **4j** |  | Toluene, $Et_3N$, 30 °C, 0.25 h | **5j** | 94 | 195–198 |
| **4k** |  | Toluene, $Et_3N$, 30 °C, 0.25 h | **5k** | 91 | 275.3–275.8 |
| **4l** |  | Toluene, $Et_3N$, reflux, 4 h | **5l** | 93 | 230–232 |
| **4m** |  | Toluene, $Et_3N$ reflux, 4 h | **5m** | 94 | 183–184 |
| **4n** |  | Toluene, $Et_3N$ reflux, 15 h | **5n** | 85 | Decomposition |
| **4o** |  | Toluene, $Et_3N$ reflux, 15 h | **5o** | 63 | Decomposition |

[a] Yields after purification.

performed.[42] Figure 1 shows the ortep of **5k**, which demonstrates that the aniline nitrogen reacted with furan-3-carbonyl chloride (**3**).

## 3. Biological activity

Fifteen of the new synthesized compounds **5a–o** were evaluated for their in vitro antimicrobial activity against a panel of microorganisms including yeasts,

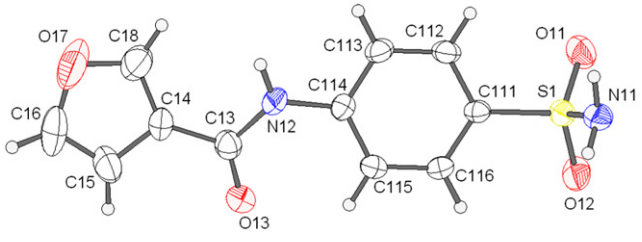



**Figure 1.** Ortep of compound **5k** showing atoms' labeling.

**Table 2.** In vitro antimicrobial activities of furan-3-carboxamides against yeast, alga, and pathogenic bacteria (MIC/MFC (MBC), μg/mL)

| Compound | MIC[a]/MFC[b] (MBC[c]) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Yeast | | | | | Alga | | | Bacteria | | |
| | *C.a.*[d] | *C.d.*[e] | *C.g.*[f] | *C.n.*[g] | *S.c.*[h] | *P.z.*[i] | *S.a.*[j] | *K.p.*[k] | *E.c.*[l] | *S.s.*[m] | *P.a.*[n] |
| **5a** | —[q] | —[q] | —[q] | 160/320 | —[q] | 160/320 | 320/ —[q] | 320/ —[q] | 320/ —[q] | 320/ —[q] | 320/ —[q] |
| **5b** | 80/160 | 160/160 | 160/160 | 40/80 | 320/ —[q] | 160/160 | 160/320 | 320/ —[q] | —[q] | —[q] | 160/160 |
| **5c** | —[q] | —[q] | —[q] | 320/ —[q] | —[q] | 320/ —[q] | 320/ —[q] | 320/ —[q] | 320/ —[q] | 320/ —[q] | 320/ —[q] |
| **5d** | 160/320 | 80/160 | 160/160 | 5/20 | 160/160 | 40/80 | 20/320 | 20/320 | 160/320 | 160/320 | 10/160 |
| **5e** | 80/160 | 80/160 | 80/160 | 160/320 | 160/ —[q] | 320/ —[q] | 80/80 | 160/160 | 160/ —[q] | 320/320 | 160/160 |
| **5f** | —[q] | —[q] | —[q] | 320/ —[q] | —[q] | 320/ —[q] | 320/ —[q] | 320/ —[q] | 320/ —[q] | 320/ —[q] | 320/ —[q] |
| **5g** | —[q] | 320/ —[q] | —[q] | 160/320 | 320/320 | 160/160 | 320/ —[q] | 320/ —[q] | 320/ —[q] | 320/ —[q] | 320/ —[q] |
| **5h** | —[q] | 320/320 | —[q] | 320/320 | —[q] | 160/160 | 80/320 | 320/ —[q] | 320/ —[q] | 320/ —[q] | 320/ —[q] |
| **5i** | 160/320 | 160/160 | 320/320 | 320/ —[q] | 80/160 | 320/320 | 40/160 | 160/320 | 160/320 | 320/ —[q] | 20/ —[q] |
| **5j** | —[q] | —[q] | —[q] | 320/320 | 160/320 | 320/ —[q] | 320/ —[q] | 320/ —[q] | 320/ —[q] | 320/ —[q] | 160/320 |
| **5k** | —[q] | —[q] | —[q] | —[q] | —[q] | —[q] | —[q] | —[q] | —[q] | 160/ —[q] | —[q] |
| **5l** | 320/320 | 320/320 | 320/ —[q] | 160/160 | 320/320 | 160/320 | 320/ —[q] | 320/ —[q] | 320/ —[q] | 320/ —[q] | 320/ —[q] |
| **5m** | 320/320 | 160/320 | 320/ —[q] | 320/320 | —[q] | 80/320 | 320/ —[q] | 320/ —[q] | 320/ —[q] | 320/ —[q] | 320/ —[q] |
| **5n** | 80/80 | 40/80 | 80/80 | 20/80 | 160/320 | 160/160 | 160/160 | 320/320 | 320/ —[q] | 320/ —[q] | 160/320 |
| **5o** | 40/40 | 40/40 | 40/80 | 10/40 | 80/160 | 80/320 | 320/320 | 320/ —[q] | 160/320 | 160/320 | 40/160 |
| F[o] | 4.0 | 2.0 | 8.0 | 2.0 | 1.0 | | | | | | |
| A[p] | | | | | | 0.5 | | | | | |
| I[r] | | | | | | | 0.06 | <4.0 | 0.06 | <4.0 | 2.0 |

Control: [o]Fluconazole; [p]Amphotericin; [r]Imipenen.
[a] Minimal inhibitory concentration.
[b] Minimal fungicidal concentration.
[c] Minimal bactericidal concentration.
[d] *Candida albicans* ATCC 44373.
[e] *Candida dubliniensis* CBS 7987.
[f] *Candida glabrata* ATCC 10231.
[g] *Cryptococcus neoformans* var. neoformans (sorotype D) ATCC 28952.
[h] *Saccharomyces cerevisiae* ATCC 2601.
[i] *Prototheca zopfii.*
[j] *Staphylococcus aureus* ATCC 25923.
[k] *Klebsiella pneumoniae* ATCC 1003.
[l] *Escherichia coli* ATCC 25922.
[m] *Salmonela setubal* ATCC 19196.
[n] *Pseudomonas aeruginosa* ATCC 27853.
[q] No activity.

filamentous fungi, bacteria, and alga by determining their minimal inhibitory concentration (MIC) and minimal fungicidal, bactericidal, and algacidal concentrations by broth microdilution methods according to NCCLS standards.[43–45] In order to classify the antimicrobial activity, we established comparisons with antibacterial agents and two antifungal agents currently employed in therapeutic treatment. For yeast-like fungi, the compounds were compared with fluconazol; thus, the range of MICs up to 10 μg/mL was considered to be significant activity; MIC-ranges between 20 and 40 μg/mL were interpreted as moderate activity, and concentrations above this range were not considered. For *Prototheca zopfii*, the MICs were compared with those of amphotericin B. For filamentous fungi, the compounds were compared with amphotericin B; so MICs up to 1.0 μg/mL were considered to represent strong activity; MIC-ranges from >1 to 4 μg/mL were considered as moderate activity and values above this range were not considered. For bacteria, compounds were compared with imipenen, an important carbapen agent. All MICs under 4.0 μg/mL were considered to be active and MICs above this value were not considered (Tables 2 and 3). The comparison between MICs and MCCs (minimal cidal concentrations) showed that they were similar in 59% of cases (76/128) and showed that in 41% (52/128) the MCCs were higher by one or more concentration. When the MICs were 320 μg/mL, comparisons were not established. Comparisons are important because they indicate differences between compounds that are only inhibitory and those able to inhibit and kill pathogenic microorganisms.

In this study, *Candida* spp. susceptibilities to furan-3-carboxamides did not show significant activity. The best activity was shown for **5n** and **5o**, which could be interpreted as moderate activity. On the other hand, in general, *Candida dubliniensis* was more susceptible than *Candida albicans* and *Candida glabrata* following the pattern observed with conventional antifungal agents such as polyene and azoles.[46] Compound **5a** was more active against *C. albicans* than against *C. dubliniensis* and this finding may establish new diagnostic tools in order to differentiate these species; the phenotypic identification of *C. dubliniensis* is a concern that is under intensive investigation (Table 2).

**Table 3.** In vitro antimicrobial activities of furan-3-carboxamides against filamentous pathogenic fungi (MIC/MFC, μg/mL)

| Compound | MIC[a]/MFC[b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Filamentous fungi | | | | | | | |
| | *R.*spp[c] | *S.s.*[d] | *F.s.*[e] | *A.fl.*[f] | *A.f.*[g] | *A.n.*[h] | *A.t.*[i] | *P.b.*[j] |
| **5a** | 320/320 | 320/320 | 320/—[k] | —[k] | 320/320 | 320/—[k] | 320/320 | 160/160 |
| **5b** | 320/320 | 320/320 | 320/320 | —[k] | 320/—[k] | 320/—[k] | 320/320 | 320/320 |
| **5c** | 320/320 | 160/320 | —[k] | —[k] | —[k] | 320/—[k] | —[k] | 160/320 |
| **5d** | 320/320 | 320/320 | 320/—[k] | 320/—[k] | 160/320 | 320/320 | 320/—[k] | 160/160 |
| **5e** | 320/—[k] | 320/—[k] | —[k] | 320/—[k] | 320/—[k] | 320/—[k] | —[k] | 40/320 |
| **5f** | 320/—[k] | 320/—[k] | 320/—[k] | 320/320 | —[k] | —[k] | 320/—[k] | 320/320 |
| **5g** | 320/320 | 320/320 | 320/—[k] | —[k] | 320/320 | 320/320 | 320/—[k] | 160/160 |
| **5h** | 320/320 | 320/320 | 320/—[k] | —[k] | 320/—[k] | 320/320 | 320/320 | 320/320 |
| **5i** | 320/—[k] | 20/—[k] | 320/—[k] | 320/—[k] | 320/—[k] | 320/—[k] | 320/—[k] | 40/80 |
| **5j** | 320/—[k] | 160/—[k] | 320/—[k] | 320/—[k] | 320/320 | —[k] | 320/—[k] | 160/160 |
| **5k** | —[k] | —[k] | —[k] | 320/320 | —[k] | 320/320 | —[k] | —[k] |
| **5l** | 320/320 | 10/320 | 2.5/2.5 | 10/20 | 20/20 | 20/40 | 40/40 | 10/320 |
| **5m** | 320/320 | 320/320 | 80/80 | —[k] | —[k] | 320/320 | 320/320 | —[k] |
| **5n** | 320/—[k] | 160/320 | 320/—[k] | —[k] | 320/—[k] | 320/—[k] | —[k] | 320/320 |
| **5o** | 320/—[k] | 320/—[k] | 320/—[k] | —[k] | 320/320 | 320/—[k] | 320/320 | —[k] |
| A[l] | 1.0 | 0.5 | 1.0 | 1.0 | 1.0 | 1.0 | 2.0 | 4.0 |

[a] Minimal inhibitory concentration.
[b] Minimal fungicidal concentration.
[c] *Rhizopus orizae* (clinical isolate).
[d] *Sporothrix schenckii* ATCC 1146.
[e] *Fusarium solani* (clinical isolate).
[f] *Aspergillus flavus* (clinical isolate).
[g] *Aspergillus fumigatus* (clinical isolate).
[h] *Aspergillus niger* (clinical isolate).
[i] *Aspergillus terreus* (isolado clínico).
[j] *Pseudallescheria boydii* (clinical isolate).
[k] No activity.
[l] Control: amphotericin B.

*Cryptococcus neoformans* is a yeast-like encapsulated fungi and an etiologic agent of meningoencephalitis affecting 5–30% of AIDS patients, from which 10–25% die.[47] Of the furan-3-carboxamides, compounds **5d** (MIC = 5 μg/mL) and **5o** (MIC = 10 μg/mL) showed excellent inhibitory activity. New and detailed studies deserve attention in order to evaluate the ability of these compounds to pass through the hematopoietic barrier as well as their activity against *C. neoformans* isolates that show resistance to amphotericin B and 5-flucytosine or azole agents. Compounds **5d** and **5o** did not show any significant or moderate activity against other yeast-like microorganisms studied.

The activity of the series of compounds against a clinically important panel of bacteria was poor. The best activity was observed with **5d** (MIC = 10 μg/mL) and **5i** (MIC = 20 μg/mL) against *Pseudomonas aeruginosa*, an opportunistic gram-negative rod. It is curious because, in general, the gram-positive cocci, here represented by *S. aureus*, are usually more sensitive than the gram-negative rods. On the other hand, *P. aeruginosa* is one of the species that show the most dramatic resistance problems related with nosocomial infections and multiresistant strains.[48]

As for the filamentous fungi, the activity of furan-3-carboxamides was tested against the most frequent agent of subcutaneous mycosis (*Sporothrix schenckii*), the four most frequent agents of aspergillosis (*Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus terreus*), an etiologic agent most frequently isolated from zygomycosis (*Rhizopus orizae*), and two agents of hyalohyphomycosis, *Fusarium solani* and *Pseudallescheria boydii*. It is important to comment that the antifungal therapy for all these microorganisms is difficult and therapeutic failures are frequent.[49]

With this panel of filamentous fungi, compound **5l** was the only one that showed a strong antifungal activity, although, restricted to *F. solani* (MIC = 2.5 μg/mL). Table 3 shows that **5l** was also able to kill the fungi at the same concentration, so we can affirm that **5l** is a compound with inhibitory and fungicidal activities. These characteristics are more important when considered in conjunction. Immunocompromised and neutropenic patients require fungicidal agents to treat their infections due to immunologic system failures.[49–52] Compound **5l** deserves more attention because the genus *Fusarium* frequently shows a refractory profile to conventional systemic antimycotics resulting in mortality rates around 80% among leukemic patients.[49]

As explained above, the breaking points for amphotericin B are not well defined, thus, we cannot reject activity with MIC = 10 μg/mL, as was observed against *S. schenckii*, *A. flavus*, and *P. boydii*. The activity against *P. boydii* is especially important because this mold shows intrinsic resistance in vivo to amphotericin B.

Another interesting point is absence of activity in **5m** against all the filamentous fungi studied, when compared with **5l**. The incorporation of fluorine at the aromatic ring resulted in the loss of antifungal activities. This shows that substituents on the phenyl ring can bring about significant differences in antimicrobial activities.

One hundred and fifty well-known microbial species cause human mycosis, but emergent species causing opportunistic mycosis are increasing rapidly. They represent a tremendous problem because the world of fungi encompasses 250.000 species, thus, new and more potent compounds are needed and the series, here presented, can be studied again with another panel including emergent fungus pathogens.

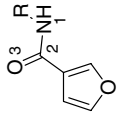
## 4. QSAR analysis

In an attempt to rationalize the molecular requirements for antimicrobial activity showed for furan-3-carboxamides **5a**–**o**, we have performed linear regression studies for the physicochemical, steric, electronic, and structural molecular descriptors with the antimicrobial activity shown for these compounds.

Biological activity data, reported as MIC values (Tables 2 and 3), are first transformed to *p*MIC (−log MIC) on a molar basis and used as dependent variables to obtain the linear relationship in these studies. The *p*MIC values were, therefore, correlated with different molecular descriptors such as the calculated log of octanol–water partition coefficient (*C* log *P*), surface area (SA), molecular volume (MV), molar refractivity (MR), polarizability (Polar), energy of highest occupied molecular orbital ($E_{HOMO}$) and lowest unoccupied molecular orbital ($E_{LUMO}$), hardness, dipole, net charge on the nitrogen of the amide, carbonyl carbon, and oxygen atom (NH1, C2, and O3 charge, respectively) (Table 4). The indicator variables, $I_{CH2}$, $I_{NH}$, and $I_{CH2/NH}$, denoted the presence or absence of $CH_2$, NH, and $CH_2$ or NH attached at the nitrogen of the amide, respectively (Table 4). Correlation coefficient values (*r*) of different molecular descriptors of furan-3-carboxamides with their antimicrobial activities (*p*MIC) for yeast, alga, and bacteria are presented in Table 5 and the correlation coefficient *r* for the antifungal activity of furan-3-carboxamides and their molecular descriptors is presented in Table 6. Table 7 shows significant Hansch 2D-QSAR models[53] obtained for the antimicrobial activity of furan-3-carboxamides **5a**–**o**.

Although, few significant 2D-QSAR models (Table 7) have been obtained from antimicrobial activity of furan-3-carboxamides, a regression coefficient analysis presented in Tables 5 and 6 showed some tendency with regard to molecular requirements for the activity of these compounds. The coefficients (in bold) were found to be significant at or above 90% confidence level (Tables 5 and 6). Therefore, the following conclusions can be obtained from the data presented in Tables 5 and 6: (i) Except for *S. cerevisiae*, which showed a better

**Table 4.** Molecular descriptors of furan-3-carboxamides **5a**–**o** used in regression analyses




| Compound | Clog *P* | SA (Å$^2$) | MV (Å$^3$) | MR (Å$^3$) | Polar (Å$^3$) | $E_{HOMO}$ (eV) | $E_{LUMO}$ (eV) | Hardness[a] | Dipole | $I_{R(CH2)}$ | $I_{R(NH)}$ | $I_{R(CH2/NH)}$ | NH1 charge | C2 charge | O3 charge |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **5a** | 0.38 | 232.12 | 194.52 | 60.15 | 23.29 | −9.34 | −0.30 | 9.04 | 3.93 | 0 | 0 | 0 | −0.333 | 0.393 | −0.349 |
| **5b** | −1.90 | 176.61 | 138.09 | 39.54 | 15.17 | −9.77 | 0.009 | 9.78 | 2.99 | 1 | 0 | 1 | −0.369 | 0.374 | −0.375 |
| **5c** | −1.21 | 162.62 | 131.00 | 38.15 | 14.54 | −9.51 | 0.21 | 9.72 | 3.53 | 1 | 0 | 1 | −0.336 | 0.378 | −0.369 |
| **5d** | −0.06 | 211.19 | 178.00 | 54.72 | 21.16 | −8.58 | −0.07 | 8.51 | 3.19 | 0 | 0 | 0 | −0.308 | 0.386 | −0.366 |
| **5e** | 0.58 | 279.22 | 234.13 | 72.29 | 27.38 | −8.29 | 0.14 | 8.43 | 4.25 | 1 | 0 | 1 | −0.353 | 0.367 | −0.377 |
| **5f** | −0.13 | 220.88 | 183.93 | 55.30 | 21.65 | −9.68 | −0.14 | 9.54 | 5.16 | 1 | 0 | 1 | −0.344 | 0.361 | −0.351 |
| **5g** | −0.07 | 220.37 | 183.71 | 54.64 | 21.65 | −9.78 | −0.21 | 9.57 | 4.46 | 1 | 0 | 1 | −0.356 | 0.364 | −0.354 |
| **5h** | −0.07 | 220.49 | 183.69 | 55.64 | 21.65 | −9.80 | −0.10 | 9.70 | 3.47 | 1 | 0 | 1 | −0.355 | 0.365 | −0.354 |
| **5i** | 1.04 | 349.75 | 307.58 | 92.81 | 35.78 | −9.11 | 0.23 | 9.34 | 3.08 | 1 | 0 | 1 | −0.373 | 0.372 | −0.373 |
| **5j** | 0.31 | 276.48 | 229.87 | 70.01 | 24.85 | −9.58 | −0.96 | 8.62 | 3.65 | 0 | 1 | 1 | −0.040 | 0.331 | −0.345 |
| **5k** | −0.89 | 259.38 | 212.90 | 66.37 | 23.01 | −9.47 | −0.75 | 8.72 | 6.22 | 0 | 0 | 0 | 0.041 | 0.331 | −0.358 |
| **5l** | 0.32 | 222.37 | 184.17 | 58.11 | 21.88 | −9.02 | −0.12 | 8.90 | 2.68 | 0 | 1 | 1 | −0.269 | 0.332 | −0.348 |
| **5m** | 1.02 | 240.93 | 197.06 | 59.19 | 21.42 | −9.74 | −1.22 | 8.52 | 3.53 | 0 | 1 | 1 | −0.278 | 0.340 | −0.344 |
| **5n** | −0.86 | 178.40 | 145.94 | 44.61 | 16.98 | −9.41 | 0.17 | 9.58 | 5.41 | 0 | 0 | 0 | −0.289 | 0.390 | −0.334 |
| **5o** | −1.50 | 180.94 | 147.53 | 45.16 | 16.98 | −10.10 | −0.64 | 9.46 | 2.79 | 0 | 0 | 0 | −0.232 | 0.361 | −0.308 |

SA, surface area; MV, molecular volume; MR, molar refractivity; Polar, polarizability.
[a] Hardness is energy difference between HOMO and LUMO (eV).

**Table 5.** Correlation coefficient values ($r$) of different molecular descriptors of furan-3-carboxamides with their antimicrobial activities ($p$MIC)[a]

| | Yeast | | | | | Alga | Gram-positive bacteria | | Gram-negative bacteria | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *C.a.* | *C.d* | *C.g.* | *C.n.* | *S.c.* | *P.z.* | *S.a.* | *K.p* | *E.c.* | *S.s.* | *P.a.* |
| *C*log *P* | −0.47 | −0.13 | −0.37 | **−0.39** | 0.42 | 0.19 | 0.24 | **0.41** | **0.47** | 0.20 | 0.16 |
| SA | −0.06 | −0.01 | −0.22 | −0.33 | **0.64** | −0.04 | **0.44** | **0.40** | **0.72** | **0.64** | **0.42** |
| MV | −0.05 | 0.00 | −0.21 | −0.31 | **0.66** | −0.04 | **0.47** | **0.42** | **0.73** | **0.65** | **0.45** |
| MR | −0.07 | 0.02 | −0.19 | −0.29 | **0.67** | −0.01 | **0.48** | **0.44** | **0.74** | **0.66** | **0.45** |
| Polar | −0.04 | −0.01 | −0.19 | −0.28 | **0.65** | −0.03 | **0.50** | **0.45** | **0.73** | **0.60** | **0.46** |
| $E_{HOMO}$ | −0.17 | 0.22 | −0.07 | 0.17 | 0.15 | 0.05 | **0.48** | **0.68** | **0.47** | 0.16 | 0.38 |
| $E_{LUMO}$ | 0.21 | −0.03 | 0.02 | 0.04 | −0.11 | **−0.47** | 0.22 | 0.08 | −0.04 | −0.28 | 0.06 |
| Hardness | 0.39 | −0.27 | 0.10 | −0.13 | −0.25 | **−0.46** | −0.29 | **−0.61** | **−0.52** | **−0.42** | −0.33 |
| Dipole | 0.25 | 0.26 | 0.38 | −0.14 | −0.10 | −0.33 | −0.30 | −0.18 | −0.36 | −0.04 | −0.35 |
| $I_{CH2}$ | 0.34 | −0.43 | −0.03 | **−0.48** | −0.08 | **−0.61** | 0.19 | −0.04 | 0.25 | −0.01 | −0.05 |
| $I_{NH}$ | **−0.80** | −0.28 | **−0.60** | −0.26 | −0.13 | 0.20 | −0.30 | −0.07 | −0.05 | −0.05 | −0.16 |
| $I_{CH2/NH}$ | −0.38 | **−0.71** | **−0.57** | **−0.77** | −0.20 | **−0.49** | −0.06 | −0.10 | 0.20 | −0.06 | −0.20 |
| NH1 charge | −0.10 | 0.41 | 0.26 | 0.08 | 0.21 | 0.11 | −0.16 | −0.03 | 0.00 | 0.39 | 0.08 |
| C2 charge | **0.53** | **0.45** | 0.38 | 0.37 | 0.06 | −0.03 | 0.26 | 0.18 | −0.03 | −0.23 | 0.18 |
| O3 charge | 0.20 | 0.32 | 0.44 | 0.30 | 0.14 | 0.32 | −0.22 | −0.35 | −0.23 | −0.09 | −0.07 |

[a] $r$ Coefficients with statistical significance at $\geqslant$90% level are indicated in bold.

**Table 6.** Correlation coefficient $r$[a] between the antifungal activity of furan-3-carboxamides and their molecular descriptors

| | Filamentous fungi | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *R.* spp. | *S.s.* | *F.s.* | *A.fl.* | *A.f.* | *A.n.* | *A.t.* | *P.b.* |
| *C*log *P* | **0.88** | **0.46** | 0.39 | 0.16 | 0.39 | 0.13 | **0.42** | **0.69** |
| SA | **0.90** | **0.54** | 0.12 | −0.23 | 0.14 | −0.12 | 0.23 | **0.62** |
| MV | **0.89** | **0.56** | 0.11 | −0.22 | 0.14 | −0.12 | 0.22 | **0.62** |
| MR | **0.89** | **0.57** | 0.15 | −0.18 | 0.19 | −0.09 | 0.28 | **0.66** |
| Polar | **0.85** | **0.56** | 0.11 | −0.17 | 0.17 | −0.13 | 0.24 | **0.64** |
| $E_{HOMO}$ | 0.26 | 0.30 | 0.32 | 0.05 | 0.40 | −0.20 | **0.43** | **0.61** |
| $E_{LUMO}$ | **−0.43** | 0.15 | −0.14 | 0.09 | 0.04 | **−0.46** | 0.02 | 0.05 |
| Hardness | **−0.63** | −0.17 | **−0.41** | 0.04 | −0.41 | −0.19 | −0.37 | **−0.56** |
| Dipole | −0.04 | −0.35 | −0.38 | −0.48 | **−0.42** | −0.10 | −0.35 | −0.44 |
| $I_{CH2}$ | −0.16 | −0.12 | −0.33 | −0.35 | −0.33 | **−0.50** | −0.34 | −0.07 |
| $I_{NH}$ | **0.46** | **0.45** | **0.72** | **0.67** | **0.69** | **0.68** | **0.66** | **0.51** |
| $I_{CH2/NH}$ | 0.23 | 0.28 | 0.32 | 0.29 | 0.22 | 0.08 | 0.28 | 0.33 |
| NH1 charge | 0.28 | 0.12 | 0.15 | −0.05 | 0.15 | 0.21 | 0.20 | 0.10 |
| C2 charge | **−0.42** | −0.39 | **−0.62** | −0.48 | **−0.55** | −0.40 | **−0.59** | **−0.48** |
| O3 charge | −0.06 | −0.11 | 0.04 | 0.39 | −0.05 | **0.73** | 0.03 | −0.18 |

[a] $r$ Coefficients with statistical significance $\geqslant$90% level are indicated in bold.

**Table 7.** Significant 2D-QSAR models obtained for antimicrobial activity of furan-3-carboxamides **5a**–**o**

| Model | Regression equation | Statistical parameters | | | | |
|---|---|---|---|---|---|---|
| | | $n$ | $r$ | $s$ | $F$ | $q^2$ |
| [a]1 | $p\text{MIC}_{C.n.}$ = −1.323(±0.315)$I_{CH2/NH}$ + 4.269(±0.273) | 12 | 0.946 | 0.215 | 85.3 | 0.819 |
| [a]2 | $p\text{MIC}_{C.n}$ = 0.190(±0.180) *C*log *P* − 1.514(±0.321) $I_{CH2/NH}$ + 4.423(±0.272) | 12 | 0.967 | 0.179 | 64.6 | 0.866 |
| [b]3 | $p\text{MIC}_{S.c.}$ = 0.014(±0.008) MR + 2.15123(±0.532) | 8 | 0.862 | 0.162 | 17.3 | 0.575 |
| [c]4 | $p\text{MIC}_{K.p.}$ = 0.010(±0.002) MR + 2.220(±0.128) | 12 | 0.961 | 0.049 | 119.4 | 0.850 |
| [b]5 | $p\text{MIC}_{E.c.}$ = 0.010(±0.004) MR + 0.156(±0.119) $E_{HOMO}$ + 3.763(±1.223) | 12 | 0.925 | 0.082 | 26.5 | 0.754 |
| [b]6 | $p\text{MIC}_{E.c.}$ = 0.003(±0.001) MV + 0.168(±0.111) $E_{HOMO}$ + 3.871(±1.124) | 12 | 0.934 | 0.077 | 30.6 | 0.780 |
| 7 | $p\text{MIC}_{R.spp.}$ = 0.006(±0.001) MR − 0.091(±0.032) $E_{LUMO}$ + 2.445(±0.059) | 14 | 0.976 | 0.024 | 109.2 | 0.898 |
| [d]8 | $p\text{MIC}_{A.n.}$ = 0.962(±0.356) $I_{NH}$ + 15.683(±7.331) O3 charge + 8.549(±2.630) | 12 | 0.947 | 0.200 | 39.2 | 0.537 |

[a] Obtained without compounds **5a** and **5b**.
[b] Obtained without compound **5o**.
[c] Obtained without compounds **5d** and **5e**.
[d] Obtained without compound **5n**.

correlation with the steric and polarity descriptors, the activity against yeasts showed a negative correlation with the indicator variables $I_{R(NH)}$ and $I_{R(CH2/NH)}$ suggesting that the absence of $CH_2$ and NH as the spacer groups between the furan-3-carboxiamide scaffold and the rest of the side chain is a correlated factor to

improve the activity of compounds **5a**–**o**. (ii) Similarly, the activity against alga *P. zopfii* is related with the absence of $CH_2$ and NH as the spacer group in the side chain of the tested compounds. (iii) On the other hand, the activity of compounds **5a**–**o** against gram-positive and gram-negative bacteria is related, generally speaking, to the increase of the steric volume and the polarizability of compounds since their activity was positively correlated with molecular descriptors such as MV, MR, and polarity, and negatively correlated with Hardness. Hardness, in a qualitative definition, is closely related to polarity since a decrease of the energy gap between HOMO and LUMO usually leads to easier polarization of the molecule.[54] In addition, the activity of gram-positive *S. aureus* and *K. pneumoniae* and gram-negative *Escherichia coli* bacteria showed an increase in activity as the *HOMO* energy increased, suggesting that the antibacterial activity of compounds **5a**–**o** involves an electron transfer with the substrate.[55] (iv) Although, for compounds **5a**–**o**, only one significant model of QSAR was obtained for filamentous fungi (*R. orizae*), one can suggest that the presence of a NH, as the spacer, is directly related to the activity presented by these compounds. The absence of the NH tends to decrease the activity of compounds **5** against this microorganism. (v) Table 7 shows the statistically significant Hansch 2D-QSAR models[53] obtained for the antimicrobial activity of furan-3-carboxamides **5a**–**o**. Some of the obtained models capture more than 80% of variance of antimicrobial activity. (vi) For *C. neoformans*, two models (1 and 2) endowed with good predictive capacity were obtained. These models indicate that the absence of a spacer ($CH_2$ or NH) is a determinant factor for improving the activity of compounds against this yeast. Nevertheless, the use of *C*log *P* in model 2 confers more predictive power than that of model 1 (Table 7). (vii) The models 3–5 and 7 showed that an increase of the molar refractivity (MR) increased the activity of compounds **5** against *S. cerevisiae*, *K. pneumoniae*, *E. coli*, and *R. orizae*. The molar refractivity reflects the effect of size and polarity of groups, therefore, MR places a positive contribution toward the expressed biological activity, possibly due to the steric interaction in the polar space. Our results clearly indicate that compounds with higher molar refractivity values exhibited increased inhibitory action on the growth of the tested bacteria and fungi. It has generally been assumed that a positive coefficient with an MR term in a correlation equation suggests a binding action *via* dispersion forces.[56] (viii) In models 5–7, the contribution of frontier orbital energies (HOMO and LUMO) suggests the existence of a charge transfer interaction via the consequent interaction of *HOMO* or *LUMO* of the compounds with the HOMO or LUMO of the possible active site that governs the antimicrobial activity.[55] Since the frontier molecular orbital plays a major role in governing many chemical reactions, these quantum-chemical descriptors have been extensively used in QSAR studies representing interactions in the complex drug-receptor.[54] (ix) Finally, model 8 (for *A. niger*) indicated that the presence of the spacer NH, from the hydrazine function, contributed positively to the increase of the activity of compounds **5a**–**o** against this microorganism. In addition, the increase of negative charges on the oxygen showed a tendency to increase the activity against this fungus. Such atomic charges are suitable for characterizing interactions according to the classical point-charge electrostatic model. The electrostatic model may involve matching parts of the electric fields of the two interacting species, which have opposite signs, rather than matching point charges.[55]

## 5. Conclusion

In conclusion, a series of fifteen new furan-3-carboxamides were synthesized from 3-trichloroacetylfuran (**2**) or furan-3-carbonyl chloride (**3**). The obtained compounds have a great interest because there have been few reports on the synthesis and antimicrobial studies of furan-3-carboxamides cited in the literature. In the present study, the in vitro antimicrobial activity of compound **5l** exhibited the best results, which were very significant against *F. solani*, a threatening agent of hyalohyphomycosis. Moreover, quantitative structure–activity relationship studies allowed to draw the following conclusion about the antimicrobial activities of the synthesized furan-3-carboxamides: (i) yeasts and *P. zopfii* showed a negative correlation with the indicator variables $I_{R(NH)}$ and $I_{R(CH2/NH)}$ suggesting that the absence of $CH_2$ and NH as the spacer groups between the furan-3-carboxamide scaffold and the rest of the side chain is a correlated factor to improve the activity, except for *S. cerevisiae*, which showed a better correlation with the steric and polarity descriptors; (ii) gram-positive and gram-negative bacteria correlate with the increase of the steric volume and the polarizability parameter and negatively correlated with Hardness; (iii) for filamentous fungi, it seems that the presence of a NH, as the spacer, is directly related to the activity exhibited by the tested compounds. In general, filamentous fungi such as *R. orizae*, *S. schenckii*, and *P.boydii* correlate with the increase of the steric volume and the polarity of groups. The QSAR study has provided key information regarding the structure of the furan-3-carboxamides which we believe will help to design more potent antimicrobial compounds.

## 6. Experimental

The solvents were purified and dried before being used and the 4-trichloroacetyl-2,3-dihydrofuran was prepared according to the literature procedures.[35] Melting points were determined on a Reichert Thermovar apparatus and are uncorrected. $^1H$ and $^{13}C$ NMR spectra were registered on a Bruker DPX 200 spectrometer or on a Bruker DPX 400 in $CDCl_3$ or DMSO-$d_6$ using TMS as the internal reference. Mass spectra were registered on a HP 5973 MSD connected to a HP 6890 GC and interfaced by a pentium PC. The GC was equipped with a split-splitless injector, autosampler, and cross-linked HP 5 capillary column (30 m of length, 0.32 mm of internal diameter, and 0.25 μm of film thickness), and helium was used as the carrier gas. Crystallographic measurements were performed

on a Bruker Kappa Apex II ccd diffractometer and graphite-monochromatized Mo Kα radiation ($\lambda$ = 0.71073 Å). The structure was solved by direct methods (SHELXS-97) and additional atoms were located in the difference Fourier map and refined on $F^2$ (SHELXL-97). The CHN elemental analyses were performed on EA 1110 Carlo Erba Instruments (University of São Paulo, São Carlos, SP, Brazil).

### 6.1. General procedure for the synthesis of compounds 5a–i

To a solution of 3-trichloroacetylfuran (0.43 g, 2.0 mmol) and the appropriate solvent (15.0 mL) (dichloromethane for **5a**, methanol for **5b–d**, ethanol for **5e–h**, and toluene for **5i**), amines **4** (2.0 mmol) were added under stirring at rt. For the synthesis of compound **5a**, a 1 M solution of NaOH (2.0 mL, 2.0 mmol) was added to liberate the benzamidine from its hydrochloric salt. The stirring was continued at room temperature or under reflux for the time indicated in Table 1. The solvent was removed by rotatory evaporator. Compounds **5a**, **5d**, and **5e** were obtained as solids and were recrystallized from a mixture of chloroform and methanol (1:1). For the other compounds, obtained as oils, ethyl acetate (15.0 mL) was added and the solution was washed with water (3× 15.0 mL) and the aqueous layer was extracted with ethyl acetate (3× 15.0 mL). The organic layers were combined, dried ($MgSO_4$), and the solvent removed by rotatory evaporator. Compounds **5b**, **5c**, and **5f–i** were obtained as oils and were purified by column chromatography in silica gel Aldrich 60A (230–400 Mesh) with a plug of $NaSO_4$ and active carbon, using chloroform (compounds **5b** and **5c**) or methanol (compounds **5f–i**) as the eluants. Yields and melting points of compounds **5a–i** are presented in Table 1. $^1$H and $^{13}$C NMR, mass spectrometry, and elemental analysis data are reported in the experimental section.

**6.1.1. *N*-[imino(phenyl)methyl]furan-3-carboxamide (5a).** $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 6.55 (d, $J_{H4–H5}$ = 1.2 Hz, 1H, H-4), 7.54 (d, $J_{H5–H4}$ = 1.2 Hz, 1H, H-5), 7.60 (t, 2H, $J$ = 8.0 Hz, Ph), 7.70 (t, 1H, $J$ = 8.0 Hz, Ph), 7.81 (s, 1H, H-2), 7.82 (d, 2H, $J$ = 7.2 Hz, Ph), 10,43 (br s, 2H, NH); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 111.0 (C-4), 126.8 (C-3), 127.5, 128.8, 129.3, and 133.1 (Ph), 142.6 (C-5), 144.9 (C-2), 166.3 (C=N), 168.5 (C6); Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.30; H, 4.22; N, 13.43.

**6.1.2. *N*-(3-hydroxypropyl)furan-3-carboxamide (5b).** MS-EI (70 ev): $m/z$ (%) = 169 ($M^+$, 5), 151 (4), 125 (9), 95 (100); $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 1.49–1.67 (m, 2H, –$CH_2$–), 2.65 (t, 1H, $J$ = 6.8 Hz, OH), 3.20–3.26 (m, 2H, –$NCH_2$–), 3.41–3.47 (m, 2H, –$CH_2$OH), 6.84 (d, 1H, $J_{H4–H5}$ = 1.5 Hz, H-4), 7.70 (d, 1H, $J_{H5–H4}$ = 1.5 Hz, H-5), 8.15 (s, 1H, H-2), 8.16 (br s, NH); $^{13}$C NMR (DMSO-$d_6$,100 MHz) $\delta$ 32.5 (–$CH_2$–), 35.9 (–$NCH_2$–), 58.5 (–$CH_2$OH), 108.9 (C-4), 122.9 (C-3), 143.9 (C-5), 145.0 (C-2), 161.7 (C-6); Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.40; H, 6.19; N, 8.04.

**6.1.3. *N*,*N*-dimethylfuran-3-carboxamide (5c).** MS-EI (70 ev): $m/z$ (%) = 139 ($M^+$, 16), 110 (42), 95 (100), 72 (6), 67 (8); $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 2.92–3.03 (s, 6H, 2 $NMe_2$), 6.64 (d, $J_{H4–H5}$ = 1.6 Hz, 1H, H-4), 7.66 (d, $J_{H5–H4}$ = 1.6 Hz, 1H, H-5), 8.00 (s, 1H, H-2); $^{13}$C NMR (DMSO-$d_6$,100 MHz) $\delta$ 34.0 and 37.0 (2 $NCH_3$), 110.7 (C-4), 121.2 (C-3), 143.1 (C-5), 143.9 (C-2), 163.5 (C-6).

**6.1.4. *N*-(2-hydroxyphenyl)furan-3-carboxamide (5d).** MS-EI (70 ev): $m/z$ (%) = 203 ($M^+$, 24), 185 (6), 95 (100); $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 6.85 (t, 1H, $J$ = 7.8 Hz, Ph), 6.89–7.03 (m, 2H, Ph), 7.56 (d, 1H, $J$ = 7.8 Hz, Ph), 6.95 (br s, 1H, H-4), 7.78 (br s, 1H, H-5), 8.40 (s, 1H, H-2), 9.31 (br s, 1H, OH), 9.68 (br s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$,100 MHz) $\delta$ 110.4 (C-4), 115.7, 117.4, 119.3, 121.8, 123.0, 149.2 (Ph), 126.4 (C-3), 145.1 (C-5), 152.0 (C-2), 176.5 (C-6); Anal. Calcd for $C_{11}H_9NO_3$: C:, 65.02; H, 4.46; N, 6.89. Found: C, 65.32; H, 4.85; N, 7.03.

**6.1.5. *N*-[4-(dimethylamino) benzyl]furan-3-carboxamide (5e).** MS-EI (70 ev): $m/z$ (%) = 244 ($M^+$, 73), 215 (7), 201 (3), 134 (100), 95 (60); $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 2.85 (s, 6H, $NMe_2$), 4.30 (d, 2H, $J$ = 6.0 Hz, $NCH_2$), 6.68 (d, 2H, $J$ = 8.7 Hz, Ph), 6.86 (d, 1H, $J_{H4–H5}$ = 1.4 Hz, H-4), 7.12 (d, 2H, $J$ = 8.7 Hz, Ph), 7.70 (d, 1H, $J_{H5–H4}$ = 1.4 Hz, H-5), 8.18 (s, 1H, H-2), 8.05 (br s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$,100 MHz) $\delta$ 40.5 ($N(CH_3)_2$) 41.5 ($NCH_2$), 108.9 (C-4), 112.3, 126.9, 128.2, 143.8 (Ph), 122.8 (C-3), 144.9 (C-5), 149.5 (C-2), 161.2 (C-6); Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 69.05; H, 6.20; N, 11.04.

**6.1.6. *N*-(pyridin-2-ylmethyl)furan-3-carboxamide (5f).** MS-EI (70 ev): $m/z$ (%) = 202 ($M^+$, 15), 107 (100), 95 (44); $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 4.52 (d, 2H, $J$ = 6.0 Hz, $NCH_2$), 6.91 (d, 1H, $J_{H4–H5}$ = 1.2 Hz, H-4), 7.24–7.33 (m, 3H, Py), 7.75 (d, 1H, $J_{H5–H4}$ = 1.2 Hz, H-5), 8.24 (s, 1H, H-2), 8.51 (d, 1H, $J$ = 4.2 Hz, Py), 8.85 (br s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$,100 MHz) $\delta$ 44.0 ($NCH_2$), 108.9 (C-4), 121.0, 122.0, 136.7, 143.9, 158.6 (Py), 122.5 (C-3), 145.2 (C-5), 148.6 (C-2), 161.7 (C-6); Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.76; H, 4.63; N, 13.50.

**6.1.7. *N*-(pyridin-3-ylmethyl)furan-3-carboxamide (5g).** MS-EI (70 ev): $m/z$ (%) = 202 ($M^+$, 25), 173 (50), 107 (12), 95 (100); $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 4.45 (d, 2H, $J$ = 5.8 Hz, $NCH_2$), 6.90 (br s, 1H, H-4), 7.36 (dd, 1H, $J$ = 8.0, 4.7 Hz, Py), 7.72 (d, 1H, $J$ = 8.0 Hz, Py), 7.74 (br s, 1H, H-5), 8.25 (s, 1H, H-2), 8.46 (d, 1H, $J$ = 4.7 Hz, Py), 8.54 (s, 1H, Py), 8.91 (br s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 40.2 ($NCH_2$) 108.9 (C-4), 122.5, 135.0, 135.2, 144.1, 148.1 (Py) 123.5 (C-3), 145.3 (C-5), 148.8 (C-2), 161.8 (C-6).

**6.1.8. *N*-(pyridin-4-ylmethyl)furan-3-carboxamide (5h).** MS-EI (70 ev): $m/z$ (%) = 202 ($M^+$, 20), 173 (41), 107 (8), 95 (100); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.55 (d, 2H, $J$ = 6.0 Hz, $NCH_2$), 6.69 (br s, 1H, H-4), 6.98 (br s, 1H, NH), 7.20 (d, 2H, $J$ = 6.0 Hz, Py), 7.43 (br s, 1H, H-5), 7.99 (s, 1H, H-2), 8.48 (d, 2H, $J$ = 6.0 Hz,

Py); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 42.2 (C-8), 108.3 (C-4), 122.4 (Py), 143.9 (C-5), 145.1 (C-2), 147.9 (Py), 149.6 (Py), 162.9 (C-6).

**6.1.9. *N*-[2-(1-benzylpiperidin-4-yl)ethyl]furan-3-carboxamide (5i).** MS-EI (70 ev): *m/z* (%) = 312 ($M^+$, 8), 221 (65), 95 (35), 91 (100); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.22–1.29 (m, 4H, 2 $CH_2$), 1.51–1.71 (m, 3H, CH, $CH_2$), 1.89–2.03 (m, 4H, 2 $CH_2$), 2.85–2.90, 3.40–3.50 (m, 2H, $CH_2$), 3.49 (s, 2H, $CH_2$), 5.85 (br s, 1H, NH), 6.59 (br s, 1H, H-4), 7.26–7.29 (m, 5H, Ph), 7.42 (br s, 1H, H-5), 7.91 (s, 1H, H-2); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 32.0 (2 $CH_2$), 33.5 ($CH_2$), 36.3 (CH), 37.26 ($CH_2$), 53.5 (2 $CH_2$), 63,2 ($CH_2$), 108.3 (C-4), 122.7 (C-3), 127.0, 128.1, 129.3, 138.0 (Ph), 143.6 (C-5), 144.5 (C-2), 162.6 (C-6).

### 6.2. General procedure for the preparation of compounds 5j–o

To a solution of furan-3-carbonyl chloride (0.26 g, 2.0 mmol), toluene (15.0 mL), and triethylamine (2.0 mmol), the amines **4j–o** (2.0 mmol) were added under stirring at rt. The stirring was continued at the temperatures and times indicated in Table 1. Compounds **5j–o** were obtained as solids and were recrystallized from a mixture of chloroform and methanol (1:4).

**6.2.1. *N*′-tosylfuran-3-carbohydrazide (5j).** MS-EI (70 ev): *m/z* (%) = 280 ($M^+$, 5), 202 (7), 95 (100); $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 2.36 (s, 3H, $CH_3$), 6.78 (br s, 1H, H-4), 7.33 (d, 2H, $J$ = 7.6 Hz, Ph), 7.70 (br s, 1H, H-5), 7.71 (d, 2H, $J$ = 7.6 Hz, Ph), 8.18 (s, 1H, H-2), 9.95 (br s, 1H, NH), 10.36 (br s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 20.9 (C-13), 108.7 (C-4), 119.8 (C-3), 127.5, 129.2, 136.3, 143.1 (Ph), 144.1 (C-5), 145.7 (C-2), 160.5 (C-6); Anal. Calcd for $C_{12}H_{12}N_2O_4S$: C, 51.42; H, 4.32; N, 9.99. Found: C, 51.27; H, 4.64; N, 10.24.

**6.2.2. *N*-(4-sulfamoylphenyl)furan-3-carboxamide (5k).** MS-EI (70 ev): *m/z* (%) = 266 ($M^+$, 14), 95 (100); $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 7.01 (d, $J_{H4-H5}$ = 1.2 Hz, 1H, H-4), 7.25 (br s, 2H, $NH_2$), 7.80 (d, 2H, $J$ = 8.8 Hz, H-9), 7.81 (d, $J_{H5-H4}$ = 1.2 Hz, 1H, H-5), 7.89 (d, 2H, $J$ = 8.8 Hz, Ph), 8.42 (s, 1H, H-2), 10.21 (br s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 109.1 (C-4), 119.5, 126.5, 138.5, 141.7 (Ph), 122.6 (C-3), 144.3 (C-5), 146.1 (C-2), 160.7 (C-6); Anal. Calcd for $C_{11}H_{10}N_2O_4S$: C, 49.62; H, 3.79; N, 10.52. Found: C, 49.30; H, 3.35; N, 10.61.

**6.2.3. *N*′-phenylfuran-3-carbohydrazide (5l).** MS-EI (70 ev): *m/z* (%) = 202 (27), 111 (7), 95 (100), 77 (3); $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 6.74 (m, 3H, Ph), 6.93 (d, 1H, $J_{H4-H5}$ = 1.3 Hz, H-4), 7.14 (d, 2H, $J$ = 7.8 Hz, Ph) 7.78 (t, 1H, $J_{H5-H4}$ = 1.3 Hz, H-5) 7.89 (br s, 1H, NH), 8.29 (s, 1H, H-2), 10.08 (br s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 108.7 (C-4), 112.1, 118.5, 128.6, 144.1 (Ph), 120.8 (C-3), 145.3 (C-5), 149.3 (C-2), 161.6 (C-6); Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.00; H, 4.58; N, 13.94.

**6.2.4. *N*′-(pentafluorophenyl)furan-3-carbohydrazide (5m).** MS-EI (70 ev): *m/z* (%) = 292 ($M^+$, 11), 197 (2), 95 (100); $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 6.88 (d, $J_{H4-H5}$ = 1.0 Hz, 1H, H-4), 7.77 (d, $J_{H5-H4}$ = 1.0 Hz, 1H, H-5) 8.20 (br s, 1H, NH) 8.25 (s, 1H, H-2), 10.49 (br s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 108.6 (C-4), 120.1 (C-3), 124.8 (m, 1C, Ph), 133.5 (d,m, 1C, $^1J_{C-F}$ = 244.5 Hz, Ph), 137.4 (d, m, 4C, $^1J_{C-F}$ = 239.4 Hz, Ph), 144.2 (C-5), 145.5 (C-2), 161.8 (C-6); Anal. Calcd for $C_{11}H_5F_5N_2O_2$: C, 45.22; H, 1.72; N, 9.59. Found: C, 45.77; H, 1.70; N, 9.72.

**6.2.5. *N*-(1*H*-1,2,4-triazol-3-yl)furan-3-carboxamide (5n).** $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 7.05 (br s, 1H, H-4), 7.80 (br s, 2H, H-5, N=CH), 8.51 (s, 1H, H-2), 11.71 (br s, 1H, NH), 13.52 (br s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 109.2 (C-4), 121.2 (C-3), 144.5 (C-5), 146.9 (C-2), 148.5 (2C, imidazole), 160.3 (C-6); Anal. Calcd for $C_7H_6N_4O_2$: C, 47.19; H, 3.39; N, 31.45. Found: C, 47.70; H, 3.33; N, 31.06.

**6.2.6. *N*-(4*H*-1,2,4-triazol-4-yl)furan-3-carboxamide (5o).** MS-EI (70 ev): *m/z* (%) = 178 ($M^+$, 4), 95 (100); $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 6.97 (d, 1H, $J_{H4-H5}$ = 1.2 Hz, H-4), 7.87 (d, 1H, $J_{H5-H4}$ = 1.2 Hz, H-5), 8.45 (s, 1H, H-2), 8.79 (s, 2H, imidazole), 12.07 (br s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 108.6 (C-4), 119.2 (C-3), 143.8 (2C, imidazole), 144.8 (C-5), 146.9 (C-2), 161.2 (C-6).

### 6.3. Biological assays

The in vitro antimicrobial activity of the furan-3-carboxamide compounds was assessed against a panel of microorganisms including yeast-like fungi, filamentous fungi, an alga, and bacteria, according to Tables 2 and 3.

The minimal inhibitory concentration (MIC) and minimal fungicidal, bactericidal, and algacidal concentrations were determined by broth microdilution methods according to NCCLS standards.[43–45] Compounds were dissolved in DMSO and the solutions were diluted with a culture medium. By further progressive dilutions with the test medium, the required concentrations (320, 160, 80, 40, 20, 10, 5, 2.5, and 1.25 μg/mL) were obtained. The antimicrobial activities were evaluated based on the minimal inhibitory concentration (MIC) according to the NCCLS M27-A2 procedures[43] for yeast-like fungi and algae. The filamentous fungi were tested based on the NCCLS M38-A[44] procedures and for the bacteria, the procedures described in NCCLS M7-A4[45] were employed. Bacteria were initially inoculated into Mueller–Hinton agar and, after overnight growth, four or five colonies were directly suspended in saline solution until the turbidity matched the turbidity of the McFarland standard (approximately $10^8$ cfu/mL). The suspensions were diluted to 1:100 in saline followed by a new dilution to 1:20 in Mueller–Hinton broth, resulting in a final inoculum concentration of $5 \times 10^4$ cfu/mL per well. Yeasts and *P. zopfii* were inoculated on potato dextrose agar and the procedures of inoculum standardization were similar; the test medium was RPMI 1640 broth. The filamentous fungi were initially inoculated on pota-

to dextrose agar; after the time required for each species to induce conidium and sporangiospore formation, the inoculum standardization followed that described in the M38-A[44] methodology. Briefly, each well of the microdilution tray was filled with 100 μL of compound diluted in 100 μL of the inoculum. The plates were incubated at 35 °C/24 h for the bacteria and *Candida* species; *S. cerevisiae*, *C. neoformans* and *P. zopfii* required up to 72 h of incubation. Growth or a lack of growth in the wells containing the antimicrobial agent was determined by comparison with the growth control, indicated by turbidity. The lowest concentration that completely inhibited visible growth of the organism was recorded as the MIC. All tests were carried out in duplicate and accepted when coincident. When the tests were not coincident they were repeated in duplicate, again.

The minimal fungicidal, bactericidal, and algacidal concentrations were determined by subculture of 20 μL of the content of each well that remained clear. The media employed were Sabouraud dextrose agar for fungi and *P. zopfii*, and Mueller–Hinton agar for bacteria. The plates were incubated at 35 °C during the same time periods for MIC determination and the lowest concentration required to demonstrate complete growth absence was named cidal.

The interpretation of the results was based on fluconazole and amphotericin B breakpoints for the fungi and based on imipenem for bacterial pathogens; all according to M27-A2[43], M38-A,[44], and M7-A4[45] techniques, respectively.

### 6.4. QSAR analysis

To calculate the quantum chemical descriptors, a geometry of all the compounds **5** has been completely optimized using the Polak–Ribiere algorithm, a conjugated gradient method, calculated with the semi-empirical AM1[57] and PM3[58] (for sulfurated compounds) method incorporated in the Hyperchem package (Hypercube Inc. version 7.52).[59] The *C*log*P*, SA, MV, MR, and Polar of optimized geometry were also computed by Hyperchem software. Hardness is defined as the energy difference between frontier orbitals (HOMO and LUMO).

The linear regression analyses were carried out using the SPSS and BuildQSAR[60] software. For the multivariate relations, predictor variables with lower intercorrelation ($r < 0.5$) were only considered. The *C*log*P*, SA, MV, MR, and Polar were obtained as collinear pairs (data not shown) and were not used in the same model. The overall quality of the obtained 2D-QSAR models was indicated by the correlation coefficient ($r$), the standard error of regression ($s$), Fischer ($F$-value), and Student's $t$-distribution (used to assess the significance of the individual regression terms). A correlation matrix was used to correlate the biological activity with the various molecular descriptors. Forward-stepping regression was used to build, when possible, each QSAR model. A data point was considered an outlier when its residual value exceeded 1.8×the standard error of estimate of the model. Self-consistency of the derived models was ensured using the leave-one-out (loo) process. The predictability of each model was assessed using cross-validated $r^2$, usually called $q^2$.

## Acknowledgments

The authors acknowledge the financial support from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (Universal Grant No. 477682/01-4) and fellowships from CNPq (D.M. Borchhardt, H.S. Coelho, and F.M. da Silva) and FAPERGS (K.M. Flores).

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2007.01.003.

## References and notes

1. Espinel-Ingroff, A.; White, T.; Pfaller, M. A. Antifungal agents and susceptibility tests. In *Manual of Clinical Microbiology*; Murray, P. R., Baron, E. J., Pfaller, M. A., Tenover, F. C., Eds., 7th ed.; ASM Press, 1999; pp 1640–1652.
2. Jorgensen, J. H.; Turnidge, J. D.; Washington, J. A. Antibacterial susceptibility tests: Dilution and disk diffusion methods. In *Manual of Clinical Microbiology*; Murray, P. R., Baron, E. J., Pfaller, M. A., Tenover, F. C., Yolken, R. H., Eds., 7th ed.; ASM Press, 1999; pp 1526–1543.
3. Leimann, B. C. Q.; Monteiro, P. C. F.; Lazéra, M.; Candanoza, E. R. U.; Wanke, B. *Protothecosis Med. Mycol.* **2004**, *42*, 95.
4. Messer, S. A.; Jones, R. N.; Fritsche, T. R. *J. Clin. Micobiol.* **2006**, *44*, 1782.
5. Shevchenko, N. E. *Chem. Heterocycl. Compd* **1999**, *35*, 164.
6. Bastian, G.; Royer, R.; Cavier, R. *Eur. J. Med. Chem.* **1983**, *21*, 365.
7. Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *111*, 1147.
8. Bandurraga, M. M.; Fenical, W.; Donovan, S. F.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6463.
9. Kobayashi, J.; Ohizumi, Y.; Nakamura, H. *Tetrahedron Lett.* **1986**, *27*, 2113.
10. Hofnung, M.; Quillardet, V. M.; Touati, E. *Res. Microbiol.* **2002**, *153*, 427.
11. Khan, M. W.; Alam, M. J.; Rashid, M. A.; Chowdhury, R. *Bioorg. Med. Chem.* **2005**, *13*, 4796.
12. Keay, B. A., Dibble, P. W. In Katritzky, A. R., Rees, C. W., Scriven, E. V. (Eds.), Comprehensive Heterocyclic Chemistry II, 1996; Vol. 9, p 395.
13. Tangallapally, R. P.; Lee, R. E. B.; Lenaerts, A. J. M.; Lee, R. E. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2584.
14. Tangallapally, R. P.; Yendapally, R.; Lee, R. E.; Lenaerts, A. J. M.; Lee, R. E. *J. Med. Chem.* **2005**, *48*, 8261.
15. Tomlin, C. *The Pesticide Manual*, 10th ed.; British Crop Protection Council and Royal Society of Chemistry: UK, 1994, p 295.
16. Wong, H. N. C.; Yang, Y. *Tetrahedron* **1994**, *50*, 9583.
17. Gabriele, B.; Salerno, G.; Lauria, E. *J. Org. Chem.* **1999**, *64*, 7688.

18. Koguro, K.; Sugimora, T.; Tai, A. *Tetrahedron Lett.* **1993**, *34*, 509.
19. Bellur, E.; Freifeld, I.; Langer, P. *Tetrahedron Lett.* **2005**, *46*, 2185.
20. Jiang, B.; Zang, F.; Xiong, W. *Tetrahedron Lett.* **2002**, *43*, 665.
21. Silva, G. V. J.; Pelisson, M. M. M.; Constantino, M. G. *Tetrahedron Lett.* **1994**, *35*, 7327.
22. Tius, M. A.; Savariar, S. *Tetrahedron Lett.* **1985**, *26*, 3638.
23. Bock, I.; Bornowski, H.; Ranft, A.; Theis, H. *Tetrahedron* **1990**, *46*, 1199.
24. Jeevanandam, A.; Narkunan, K.; Ling, Y-C. *J. Org. Chem.* **2001**, *66*, 6014.
25. Oda, K.; Mashida, M. *Tetrahedron Lett.* **1989**, *30*, 4421.
26. Inomata, K.; Sumita, M.; Kotake, H. *Chem. Lett.* **1979**, 709.
27. Zamojski, A.; Turner, S. *J. Chem. Soc. (C)* **1971**, 1632.
28. Grieco, P. A.; Pogonowski, C. S.; Burke, S. J. *J. Org. Chem.* **1975**, *40*, 542.
29. Bailey, T. R. *Synthesis* **1991**, 242.
30. Foot, J. S.; Kanno, H.; Giblin, G. M. P.; Taylor, R. J. K. *Synthesis* **2003**, 1055.
31. Colla, A.; Martins, M. A. P.; Clar, G.; Krimmer, S.; fischer, P. *Synthesis* **1991**, 483.
32. Zanatta, N.; Faoro, D.; Silva, S. C.; Bonacorso, H. G.; Martins, M. A. P. *Tetrahedron Lett.* **2004**, *45*, 5689.
33. Results not reported: benzylfuran-3-carboxamide exhibited activity against *Candida dubliniensis* (MIC = 8.0 μg/mL).
34. Zanatta, N.; Barichello, R.; Tramontina, R.; Bonacorso, H. G.; Martins, M. A. P. *Tetrahedron Lett.* **2003**, *44*, 961.
35. Colla, A.; Clar, G.; Martins, M. A. P.; Krimmer, S.; Fischer, P. *Synthesis* **1991**, 483.
36. Flores, A.F.C.; Zanatta, N, Rosa, A.; Brondani, S.; Martins, M. A. P. *Tetrahedron Lett.* **2002**, *43*, 5005.
37. Madruga, C. C.; Clerici, E.; Martins, M. A. P.; Zanatta, N. *J. Heterocycl. Chem.* **1995**, *32*, 735.
38. Zanatta, N.; Cortelini, M. F. M.; Carpe, M. J. S.; Martins, M. A. P. *J. Heterocycl. Chem.* **1997**, *34*, 509.
39. Zanatta, N.; Fagundes, M. B.; Ellenshon, R.; Marques, M.; Bonacorso, H. G.; Martins, M. A. P. *J. Heterocycl. Chem.* **1998**, *35*, 451.
40. Mainard-Faure, P.; Gonser, C.; Vaime, V.; Bouchu, D. *Tetrahedron Lett.* **1998**, *39*, 2315.
41. Qing, F-L.; Gao, W.-Z.; Ying, J. *J. Org. Chem.* **2000**, *63*, 2003.
42. Crystallographic data for structure **5k**, reported in this paper, have been deposited with the Cambridge Crystallographic Data Center (CCDC 624488). Copies of the data can be obtained, free of charge, on application to CCDC 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
43. National Committee for Clinical Laboratory Standards, 2002. Reference method for broth dilution antifungal susceptibility testing of yeast: approved standard. NCCLS document M27-A2. Wayne, P. A. National Committee for Clinical Laboratory Standards.
44. National Committee for Clinical Laboratory Standards, 2002. Reference methods for dilution antifungal susceptibility testing of conidium-forming filamentous fungi, Proposed standard M38-A, Wayne, P. A. National Committee for Clinical Laboratory Standards.
45. National Committee for Clinical Laboratory Standards, 2002. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard; 5th ed. NCCLS document M7-A5, Wayne, P. A. National Committee for Clinical Laboratory Standards.
46. Alves, S. H.; Milan, E. P.; Sant'Ana, P. L.; Oliveira, L. O.; Santurio, J. M.; Colombo, A. L. *Diag. Microbiol. Infec. Dis.* **2002**, *43*, 85.
47. Viviani, M. A.; Tortorano, A. M.; Ajello, L. Cryptococcus. In *Clinical Mycology*; Anaissie, E. J., McGinnis, M. R., Pfaller, M. A., Eds.; Churchil Livingstone: New York, 2003; pp 240–259.
48. Kiska, D. L.; Gilligan, P. H. Pseudomonas. In *Manual of Clinical Microbiology*; Murray, P. R., Baron, E. J., Pfaller, M. A., Tenover, F. C., Yolken, R. H., Eds., 7th ed.; ASM: Washington, 1999; pp 517–525.
49. Dignani, M. C.; Kiwan, E. N.; Anaissie, E. J. Hyalohyphomycoses. In *Clinical Mycology*; Anaissie, E. J., McGinnis, M. R., Pfaller, M. A., Eds.; Churchil Livingstone: New York, 2003; pp 309–324.
50. Nucchi, M.; Marr, K. A.; Queiroz-Telles, F.; Martins, C. A.; Trabasso, P.; Costa, S.; Voltarelli, J. C.; Colombo, A. L.; Imhof, A.; Pasquini, R.; Maiolino, A.; Souza, C. A.; Anaissie, E. *Clin. Infect.* **2004**, *38*, 1237–1242.
51. Walsh, T. J.; Groll, A.; Hiemenz, J.; Flemming, R.; Roilides, E.; Anaissie, E. *Clin. Microbiol. Infect.* **2004**, *10*(Suppl. 1), 48–66.
52. Pfaller, M. A.; Diekema, D. J. *J. Clin. Microbiol.* **2004**, *42*, 4419–4431.
53. Hansch, C.; Fujita, T. *J. Am. Chem. Soc.* **1964**, *86*, 1616.
54. Karelson, M.; Lobanov, V. S.; Katritzky, A. R. *Chem. Rev.* **1996**, *96*, 1027.
55. Campos, j.; Núñez, M. C.; Rodrígues, V.; Entrena, A.; Hermández-Alcoceba, R.; Fernándes, F.; Lacal, J. C.; Gallo, M. A.; Espinosa, A. *Eur. J. Med. Chem.* **2001**, *36*, 215.
56. (a) Tiwari, R. K.; Singh, D.; Singh, J.; Chhillar, A. K.; Chandra, R.; Verama, A. K. *Eur. J. Med. Chem.* **2006**, *41*, 40; (b) Sharma, P. et al. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4185.
57. Dewar, M. J. S.; Zoebisch, E. G.; Healey, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
58. (a) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209; (b) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 221.
59. HYPERCHEM(™) Professional 7.52, Hypercube, Inc., 1115 NW 4th Street, Gainesville, FL 32601, USA.
60. De Oliveira, D. B.; Gaudio, A. C. *Quant. Struct.-Act. Relat.* **2000**, *19*, 599.