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Laboratory note

Sulfonylamido derivatives of aminoglutethimide and their copper(II) complexes: a novel class of antifungal compounds

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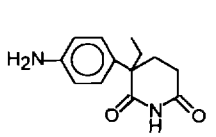
Summary — Reaction of aminoglutethimide (3-(*4*-aminophenyl)-3-ethyl-2,6-piperidinedione) with sulfonyl halides or sulfonic acid anhydrides affords a series of 3-[*4*-(alkyl/arylsulfonylamido)phenyl]-3-ethyl-2,6-piperidinediones. Some of these derivatives, containing free amino groups, have been further derivatized by reaction with 2,4,6-trimethylpyrylium perchlorate, 3,4-dichlorophenyl isocyanate or tosyl isocyanate. Cu(II) complexes containing as ligands the conjugate bases of some of these compounds have also been obtained. The new derivatives generally act as moderate antifungal agents against *Aspergillus* and *Candida spp*, but one of them shows activities comparable to ketoconazole.

aminoglutethimide / sulfonyl halides / Cu(II) complex / antifungal compound

Introduction

Aminoglutethimide (3-(*4*-aminophenyl)-3-ethyl-2,6-piperidinedione) **1** is a widely used pharmacological agent for the treatment of breast cancer [1–3], adrenocortical carcinomas [4, 5], Cushing's syndrome [6, 7] and prostate cancer [8], among others. Its mechanism of action involves inhibition of aromatase, as well as other cytochrome P-450 mediated steroid hydroxylating enzymes, required for the conversion of androgens to estrogens [9–13]. The inhibitor interacts with the heme moiety of cytochrome P-450, binding by means of a nitrogen atom (presumably the aniline NH_2) to the ferric (low-spin) ion of the enzyme, as the sixth ligand [14].



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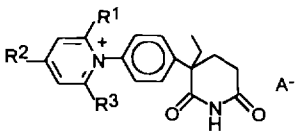

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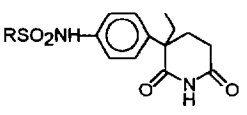

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Recently, the pyridinium derivatives of aminoglutethimide of type **2** have been prepared by reaction of **1** with substituted pyrylium salts [15]. These derivatives, as well as their Cu(II) complexes showed some activity as enzyme inhibitors [16], and this prompted us to continue research in this class of compounds.

In this paper we report the preparation of sulfonamido derivatives of aminoglutethimide of type **3**, obtained by reaction of **1** with sulfonyl halides or sulfonic acid anhydrides. Cu(II) complexes containing the conjugate bases of **3** as ligands have also been synthesized. The new compounds reported here have been characterized by elemental analysis and spectroscopic methods (IR and ^{1}H-NMR spectroscopy), and the complexes also by means of EPR spectroscopy, magnetic, thermogravimetric and conductometric measurements.

Since the mechanism of action of many fungistatic drugs consists in the inhibition of sterol 14-α-demethylase, also a microsomal cytochrome P-450 dependent enzyme system [17], we have assayed the aminoglutethimide derivatives and their complexes synthesized in the present work, for their antifungal activity against several widespread fungi or moulds, such as *Aspergillus* and *Candida spp*, evidencing interesting activity for some of them. Although the mechanism of action of these compounds is unknown for the moment, it is not improbable that they might inhibit lanosterol-14-α-demethylase, affecting cytochrome $P\text{-}450_{14\text{-}\alpha DM}$.

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Chemistry

The new compounds **3**, prepared by reaction of aminoglutethimide **1** with sulfonyl halides or sulfonic acid anhydrides, are shown in table I. Generally they were synthesized from **1** and the corresponding sulfonyl chloride/fluoride in acetonitrile and in the presence of triethylamine. The only exceptions are constituted by the trifluoromethyl derivative **3c**, obtained from **1** and triflic anhydride, in acetone as solvent at molar ratios of the two reactants of 2:1, and the 2-carboxyphenyl derivatives **3o,p**, respectively, prepared from **1** and sulfobenzoic acid cyclic anhydrides in refluxing acetonitrile.

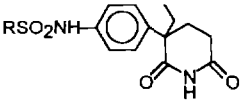
Further derivatization of compounds **3l** and **3m**, containing a free NH_2 group, with 2,4,6-trimethylpyrylium perchlorate, tosyl isocyanate and 3,4-dichlorophenyl isocyanate afforded the new compounds **4–9** (scheme 1).

The new derivatives were characterized by elemental analysis (±0.4% of the theoretical values, calculated for the proposed formulas, see the *Experimental protocols*), IR and ^{1}H-NMR spectroscopy.

The sodium salts of the synthesized derivatives, obtained in situ from compounds **3** and the stoichiometric amount of NaOH have been used for the preparation of Cu(II) complexes, working at a molar ratio **3** (as sodium salt)/Cu(II) of 2:1 (the two fluorosulfonylamido derivatives **3c** and **3n**, as well as the carboxyphenylsulfonamido compounds **3o** and **3p**, have not been included in these experiments – see table II).

Elemental analysis showed the complexes **10–21** to possess the general formula $[CuL_2(H_2O)_4]$, where L stands for the glutarimide deprotonated species of ligands **3**. Spectroscopic and magnetic data confirmed the presence of Cu(II) in octahedral surrounding in these derivatives, with the two glutarimide moieties coordinated *trans* with respect to each other, and four water molecules in equatorial positions as ligands.

Table I. Sulfonamido derivatives of aminoglutethimide **3a–p** and their pK_a values.



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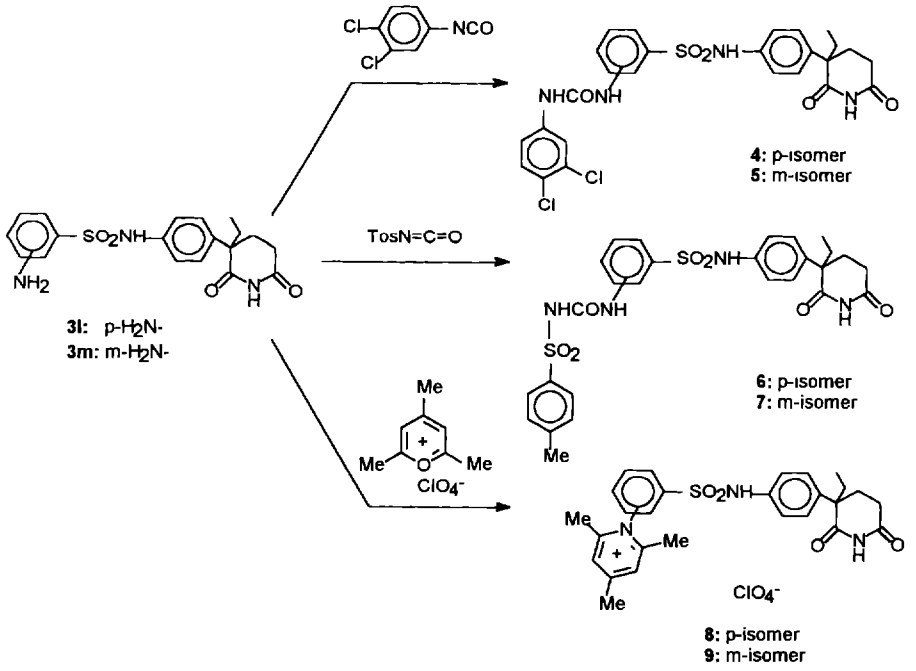
3	*R*	*Yield*	*Synthesis method*	pK_{a1}[a]
a	Me_2N	54	A	6.79 ± 0.07
b	$PhCH_2$	51	B	6.84 ± 0.11
c	CF_3	60	C	5.41 ± 0.10;[b] 6.76 ± 0.14
d	*p*-F–C_6H_4–	62	A	6.79 ± 0.10
e	*p*-Cl–C_6H_4–	76	A	6.81 ± 0.12
f	*p*-Br–C_6H_4–	73	A	6.82 ± 0.21
g	*p*-I–C_6H_4–	85	A	6.85 ± 0.08
h	*p*-CH_3–C_6H_4–	69	A	6.89 ± 0.15
i	*p*-O_2N–C_6H_4–	55	A	6.83 ± 0.06
j	*o*-O_2N–C_6H_4–	42	A	6.84 ± 0.13
k	*p*-AcNH–C_6H_4–	89	A	6.87 ± 0.12
l	*p*-H_2N–C_6H_4–	50	B	6.90 ± 0.09
m	*m*-H_2N–C_6H_4–	39	B	6.88 ± 0.17
n	C_6F_5–	82	A	6.56 ± 0.15;[b] 6.80 ± 0.07
o	*o*-HOOC–C_6H_4–	93	D	4.96 ± 0.12;[c] 6.87 ± 0.10
p	*o*-HOOC–C_6Br_4–	88	D	4.71 ± 0.09;[c] 6.85 ± 0.06

[a]Mean ± standard error (from two determinations), in water/ethanol (4:1, v/v), by potentiometric titration, corresponding to: ionization of the –CO*NH*CO– moiety (for aminoglutethimide **1**, the value is 6.89); [b]ionization of the $C_xF_ySO_2NH$– moiety; [c]ionization of the CO*OH* group. A: aminoglutethimide + RSO_2Cl; B: aminoglutethimide + RSO_2F; C: aminoglutethimide + triflic anhydride; D: aminoglutethimide + sulfobenzoic cyclic anhydride.



Scheme 1.

Pharmacology

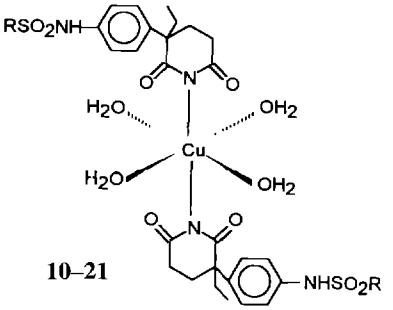
Antifungal activity of the new compounds reported here has been determined by a modification of the growth method, as reported earlier [18, 19]. The activity of the new compounds is shown in table III. Two *Aspergillus* species and one strain of *Candida albicans* were included in our assays, as these are widespread fungi/moulds, which easily develop resistance against many anti-fungal compounds [20]. Ketoconazole, a well-known imidazole possessing strong antifungal activity has been included as standard in these assays.

Discussion

Analytic and spectral data confirmed the proposed structure for the newly synthesized derivatives **3–9**. In the IR spectra of compounds **3**, the following bands were detected: (i) strong amide vibrations, at 1680–1700 cm^{-1} (amide I), 1520–1540 cm^{-1} (amide II) and 1290–1300 cm^{-1} (amide III), respectively; (ii) intense sulfonamido vibrations, at 1140–1175 cm^{-1} (SO_2^{sym}), and 1320–1345 cm^{-1} (SO_2^{as}), respectively; (iii) NH vibrations at around 3060 cm^{-1}; (iv) bands of the aromatic rings (C=C) around 1490–1500 cm^{-1}, as well as bands due to the other structural elements present in these molecules (such as NH_2 for derivatives **3l,m** or COOH for **3o**).

In the 200 MHz ^{1}H-NMR spectra of derivatives **3** (in DMSO–d_6), the following signals were detected: (i) the methyl group of the ethyl moiety appeared as a sharp triplet centered at 0.90 ppm; (ii) the six protons of the three methylenic moieties (one from ethyl and the CH_2CH_2 bridge of the glutarimide moiety) afforded a complicated multiplet in the region 1.80–2.60 ppm, as follows: the diastereotopic CH_2 protons from ethyl as two multiplets centered at 1.95 and 2.20 ppm, whereas the other four protons as two multiplets centered at 2.25 and 2.52 ppm, respectively; (iii) the NH proton of the glutarimide moiety appear as a singlet at 8.40 ppm (the same as in **1**) [15], whereas the SO_2NH protons as a broad singlet at 7.60–7.80 ppm; both of these signals are in fast exchange with the bulk solvent, as they disappear by addition of D_2O into the NMR tube after 3–10 min; (iv) the four aromatic protons of the phenylene moiety directly bound to the piperidinedione ring appeared as an AA'BB' multiplet generally centered at 6.95 ppm (similarly to the same signal of aminoglutethimide **1**) [15], while the signals of the protons of the R group appeared in their normal ranges (see *Experimental protocols* for details). For derivatives **4–9**, the spectral data also confirmed the proposed structures (see *Experimental protocols*).

Table II. Copper(II) complexes **10–21** containing the conjugate base of derivatives **3** as ligands, with the general formula $[CuL_2(H_2O)_4]$.



10–21

Complex	*Ligand (HL)*	*Formula*[a]	*Yield*	*Colour*
10	**3a**	$[Cu(C_{30}H_{40}N_6O_8S_2)(H_2O)_4]$	81	blue
11	**3b**	$[Cu(C_{30}H_{42}N_4O_8S_2)(H_2O)_4]$	76	blue
12	**3d**	$[Cu(C_{38}H_{38}F_2N_4O_8S_2)(H_2O)_4]$	71	blue
13	**3e**	$[Cu(C_{38}H_{38}Cl_2N_4O_8S_2)(H_2O)_4]$	85	blue
14	**3f**	$[Cu(C_{38}H_{38}Br_2N_4O_8S_2)(H_2O)_4]$	92	blue
15	**3g**	$[Cu(C_{38}H_{38}I_2N_4O_8S_2)(H_2O)_4]$	94	blueish–green
16	**3h**	$[Cu(C_{40}H_{42}N_4O_8S_2)(H_2O)_4]$	88	blue
17	**3i**	$[Cu(C_{38}H_{36}N_6O_{12}S_2)(H_2O)_4]$	68	green
18	**3j**	$[Cu(C_{38}H_{36}N_6O_{12}S_2)(H_2O)_4]$	74	green
19	**3k**	$[Cu(C_{42}H_{44}N_6O_8S_2)(H_2O)_4]$	90	blue
20	**3l**	$[Cu(C_{38}H_{40}N_6O_8S_2)(H_2O)_4]$	74	green
21	**3m**	$[Cu(C_{38}H_{40}N_6O_8S_2)(H_2O)_4]$	80	green

[a]±0.4% of the theoretical values, calculated for the above formulas, for Cu (by gravimetry) and C, H, N (by combustion).

Since derivatives **3** possess at least two acidic protons in their molecule, ie, the glutarimidic and the sulfonamidic NH moieties, and since the acido-basic properties of these compounds are essential not only for their biological activity, but also for their behaviour as ligands towards metal ions, the acidity constants have been determined by potentiometric titration in water–ethanol (table I). The glutarimidic NH proton has a pK_a value of 6.89 in aminoglutethimide **1**. Arylsulfonylation leads obviously to compounds with an increased acidic character, but since the distance between the two functional groups is relatively large, the acidifying effect is not very important. But derivatives **3**, in contrast to **1**, possess at least a second acidic proton, at the SO_2NH moiety. Except for the fluorosulfonyl derivatives **3c** and **3n**, in which these protons are very acidic (table I), in the other compounds **3**, the SO_2NH protons have pK_a values in the range 8.0–8.9 (data not shown), being less acidic than the CONHCO protons. Thus, in the presence of one equivalent of NaOH, the glutarimide sodium salt will be obtained, and this is the moiety interacting with Cu(II) ions in the newly prepared complexes **10–21**.

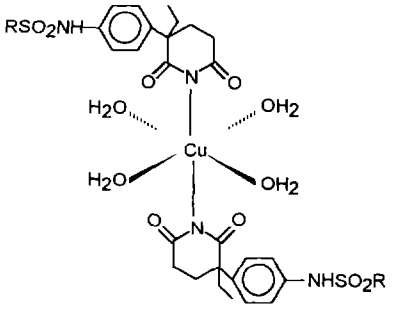
Cu(II) complexes of diverse organic ligands, such as 1,10-phenanthroline derivatives [21], bis-acylhydrazones [22], quinazolinones [23] as well as a variety of clinically used pharmacological agents [24–27] have been reported to inhibit bacterial, fungal, yeast, algal, mycoplasma and viral replication. It appeared thus of interest to prepare and assay for biological activity the corresponding coordination compounds of derivatives of type **3** reported in this paper. Mention should be made that except for the Cu(II) complexes of the aminoglutethimide derivatives **2**, previously reported by us (and which act as weak inhibitors of the zinc enzyme carbonic anhydrase (EC 4.2.1.1)), the coordination chemistry of ligands of type **1–3** as well as their biological activity, had not been investigated [16].

Table III. Antifungal activity of compounds **3–21** against several organisms.

Compound	*MIC (μg/mL)*		
	Aspergillus flavus *C1150*	Aspergillus niger *C418*	Candida albicans *C316*
3a	41	69	54
3b	120	> 125	120
3c	15	40	37
3d	22	81	63
3e	28	90	58
3f	21	97	90
3g	35	102	81
3h	115	> 125	106
3i	50	86	78
3j	62	110	90
3k	104	> 125	> 125
3l	90	> 125	> 125
3m	89	> 125	101
3n	8	14	7
3o	12	37	16
3p	15	28	12
4	4.5	18	6
5	1.5	6	1.1
6	3	10	6
7	5	17	6
8	> 125	> 125	> 125
9	> 125	> 125	> 125
10	11	24	32
11	32	48	56
12	6	9	8
13	8	15	12
14	7	12	11
15	7	10	10
16	24	28	19
17	8	15	14
18	12	17	13
19	64	89	55
20	29	33	30
21	31	40	35
1	> 1000	> 1000	> 1000
Ketoconazole	1.20	1.80	0.06

Generally the donor system of ligands derived from aminoglutethimide is simple, consisting of the ionized glutarimidic nitrogen atom [16]. The fact that the glutarimidic moiety also participates in the interaction with the Cu(II) ions in the case of complexes **10–21** reported in this paper, has been confirmed by studying the IR spectra of the prepared complexes. The major modifications in these spectra, as compared to the corresponding spectra of the ligands, involve just the amide bands, which are shifted 15–25 cm^{-1} towards lower wavenumbers for the complexes (data not shown), whereas the sulfonamido vibrations appear at the same wavenumber for the complex and the corresponding ligand. The NH vibrations on the other hand are badly resolved in the IR spectra of the complexes, and large OH bands appear in the region 3400–3600 cm^{-1}, due to the presence of the coordinated water molecules.

Thermogravimetric analysis showed the four water molecules to be lost in one step, between 160–190 °C, from complexes **10–21**, proving that this is coordinated water (data not shown). Magnetic moments of the Cu(II) complexes **10–21** were in the range 1.90–1.95 BM, which correlated with the presence of a large, structureless band in the range 16500–16850 cm^{-1} in the reflectance diffuse spectra and axial EPR spectra with parameters $g_{\perp}$ = 2.06–2.07 and $g_{||}$ = 2.35–2.37 (data not shown) suggest an octahedral surrounding of Cu(II) in these compounds [28, 29] as shown below. All these complexes are non-electrolytes (data not shown) at room temperature, in DMSO as solvent.



10 - 21

The new compounds **3–9** described here, as well as their Cu(II) complexes **10–21** represent a novel class of antifungal derivatives, with broad activity against fungi and moulds such as *Aspergillus* and *Candida spp.* In the derivative series **3**, best activity was correlated with the presence of halogeno atoms and nitro groups as substituents of the alkyl/arylsulfonamido moiety. Still, all these compounds have only modest antifungal action against all three species, as compared to ketoconazole (table III). The Cu(II) complexes **10–21**, although proving enhanced activity, are again not particularly potent. Totally inactive are the pyridinium salts **8** and **9** as well as aminoglutethimide **1** itself. The most potent action was detected for the urea-containing compounds **4–7**, with derivative **5** being equally potent to ketoconazole against *Aspergillus flavus* and only slightly less active against the other two strains. This may constitute in fact a good lead for developing more potent derivatives from this new class of antifungal agents. The susceptibility of these fungi was as follows: *A flavus* was the most easy to be inhibited, followed by *Candida*, and *A niger* being the most resistant to this class of inhibitors.

Experimental protocols

Chemistry

Elemental analysis was done by combustion with a Carlo Erba Instrument or gravimetrically (for the metal ion). Mps were obtained with a heating plate microscope and are uncorrected. Electronic spectra were recorded by the diffuse reflectance technique using MgO as a reference material, in the range 300–1100 nm. IR spectra were recorded in CsBr pellets with a Nicolet 2DXFT-IR apparatus. ^{1}H-NMR spectra were recorded with a Bruker CPX 200 instrument operating at 200 MHz. EPR spectra of a crystalline powder were recorded on a Varian E-9 spectrometer at room temperature. The field was calibrated using crystalline diphenylpicrylhydrazyl (g = 2.0036). Magnetic susceptibility measurements were carried out at room temperature with a fully automated AZTEC DSM8 pendulum-type susceptometer. Mercury(II) tetrakis-(thiocyanato)cobaltate(II) was used as a susceptibility standard. Corrections for the diamagnetism were estimated from Pascal's constants [28].

D,L-Aminoglutethimide and ketoconazole were from Sigma, whereas sulfonyl halides, sulfonic acid anhydrides, tosyl isocyanate, triethylamine and 3,4-dichorophenyl isocyanate were commercially available from Acros, Merck or Aldrich, and were used without further purification. 2,4,6-Trimethylpyrylium perchlorate was prepared by literature procedures [30]. Cu(II) chloride dihydrate and solvents were from Merck (analytical grade).

Synthesis of derivatives 3

Methods A and B

232 mg (10 mmol) of aminoglutethimide suspended in 10 mL of acetonitrile were treated with 10 mmol of sulfonyl chloride (method A) or fluoride (method B) dissolved in a small amount of anhydrous acetonitrile. A stoichiometric amount of triethylamine was added, and the mixture was stirred at 40 °C for 4 h (A) or at 60 °C for 6 h (B), then the solvent was evaporated in vacuo and the reaction mixture poured into 40 mL of water and ice. The precipitated sulfonylamido derivatives **3** were recrystallized from ethanol–water (1:1, v/v).

Method C
232 mg (10 mmol) of aminoglutethimide and 0.84 mL (5 mmol) of triflic anhydride were suspended in 10 mL of acetone and magnetically stirred at 4 °C for 15 h. The solvent was then evaporated in vacuo, and the tan residue treated with 10 mL of cold water. Aminoglutethimide triflate being water soluble has thus been separated from **3c** by filtration. The latter compound was recrystallized from iso-propanol.

Method D
232 mg (10 mmol) of aminoglutethinide and 10 mmol of sulfobenzoic cyclic anhydride or tetrabromo-*O*-sulfobenzoic cyclic anhydride were heated at reflux in 50 mL of anhydrous acetonitrile for 2 h, with a small amount of *p*-toluenesulfonic acid added as catalyst. After evaporation of the solvent, the products **3o,p** were recrystallized from ethanol.

*Synthesis of derivatives **4** and **5***

5 mmol of amino-derivative **3l** or **3m** dissolved in 30 mL of anhydrous acetonitrile were heated at reflux and 0.94 g (5 mmol) of 3,4-dichlorophenyl isocyanate dissolved in 5 mL of the same solvent were added dropwise. The mixture was heated at reflux for 3 h, then the solvent was evaporated and the residue recrystallized from absolute ethanol. Yields were around 90–95%.

*Synthesis of derivatives **6** and **7***

5 mmol of amino-derivative **3l** or **3m** dissolved in 40 mL of anhydrous acetonitrile were treated with 0.76 mL (5 mmol) tosyl isocyanate. The mixture was stirred at room temperature for 1 h, then the precipitated derivatives were filtered off and recrystallized from ethanol–water (1:2, v/v). Yields were over 95%.

*Synthesis of derivatives **8** and **9***

5 mmol of amino-derivative **3l** or **3m** dissolved in 30 mL of anhydrous acetonitrile were treated with 1.11 g (5 mmol) of 2,4,6-trimethylpyrylium perchlorate. The mixture was magnetically stirred at room temperature for 15 min, then 0.69 mL (5 mmol) of triethylamine were added and stirring was continued for another 2 h. After this time, 1.5 mL of acetic acid were added and the reaction mixture was heated at reflux for 3 h. After cooling, the pyridinium salt was precipitated by addition of 150 mL of diethyl ether. Filtration and recrystallization from iso-propanol afforded the title compounds with yields of 55–58%.

*Preparation of complexes **10–21** containing the conjugate bases of 3 as ligands*

2 mmol of ligand **3** were treated with a stoichiometric amount of 1 N NaOH solution in order to obtain the monosodium salt. This was treated with a solution obtained by dissolving 0.17 g (1 mmol) of $CuCl_2 \cdot 2H_2O$ in 5 mL water. The mixture was magnetically stirred at room temperature for 1 h, then the obtained precipitate was filtered off and abundantly washed with water. Air-drying afforded the title compounds in an almost quantitative yield.

*3-[4-(N,N-Dimethylsulfamoyl)phenyl]-3-ethyl-2,6-piperidinedione **3a***
Colorless crystals, mp 210–212 °C. IR (KBr), cm^{-1}: 1143 (SO_2^{sym}), 1290 (amide III), 1334 (SO_2^{as}), 1527 (amide II); 1680 (amide I); 3060 (NH); ^{1}H-NMR (DMSO–d_6), δ, ppm: 0.90 (t, 3H, Me from ethyl); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.52 (m, 4H, CH_2CH_2 from glutarimide); 4.80 (s, 6H, Me_2N); 6.95 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene); 7.66 (s, 1H, SO_2NH); 8.39 (s, 1H, CONHCO); Anal $C_{15}H_{21}N_3O_4S$ (C, H, N).

*3-Ethyl-3-[phenylmethylsulfamoyl)phenyl]-2,6-piperidinedione **3b***
Colorless crystals, mp 168–169 °C. IR (KBr), cm^{-1}: 1176 (SO_2^{sym}), 1290 (amide III), 1369 (SO_2^{as}), 1528 (amide II); 1680 (amide I); 3060 (NH); ^{1}H-NMR (DMSO–d_6), δ, ppm: 0.90 (t, 3H, Me from ethyl); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.52 (m, 4H, CH_2CH_2 from glutarimide); 3.17 (s, 2H, PhCH_2); 6.95 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene); 7.12–7.49 (m, 5H, ArH from Ph); 7.68 (s, 1H, SO_2NH); 8.38 (s, 1H, CONHCO); Anal $C_{20}H_{22}N_2O_4S$ (C, H, N).

*3-Ethyl-3-[(trifluorolmethylsulfamoyl)phenyl]-2,6-piperidinedione **3c***
Colorless crystals, mp 222–225 °C (dec). IR (KBr), cm^{-1}: 1169 (SO_2^{sym}), 1290 (amide III), 1345 (SO_2^{as}), 1528 (amide II); 1680 (amide I); 3060 (NH); ^{1}H-NMR (DMSO–d_6), δ, ppm: 0.90 (t, 3H, Me from ethyl); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.54 (m, 4H, CH_2CH_2 from glutarimide); 6.95 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene); 7.35 (s, 1H, SO_2NH); 8.38 (s, 1H, CONHCO); Anal $C_{14}H_{15}F_3N_2O_4S$ (C, H, N).

*3-Ethyl-3-[4-(fluorophenylsulfamoyl)phenyl]-2,6-piperidinedione **3d***
Colorless crystals, mp 203–205 °C. IR (KBr), cm^{-1}: 1171 (SO_2^{sym}), 1290 (amide III), 1364 (SO_2^{as}), 1527 (amide II); 1680 (amide I); 3060 (NH); ^{1}H-NMR (DMSO–d_6), δ, ppm: 0.90 (t, 3H, Me from ethyl); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.52 (m, 4H, CH_2CH_2 from glutarimide); 6.95 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene bound to glutarimide); 7.11 (m, AA'BB', J_{AB} = 7.4 Hz, 4H, ArH, *p*-F-phenylene); 7.60 (s, 1H, SO_2NH); 8.39 (s, 1H, CONHCO); Anal $C_{19}H_{19}FN_2O_4S$ (C, H, N).

*3-Ethyl-3-[4-(chlorophenylsulfamoyl)phenyl]-2,6-piperidinedione **3e***
Colorless crystals, mp 209–211 °C. IR (KBr), cm^{-1}: 1175 (SO_2^{sym}), 1290 (amide III), 1366 (SO_2^{as}), 1527 (amide II); 1680 (amide I); 3060 (NH); ^{1}H-NMR (DMSO–d_6), δ, ppm: 0.90 (t, 3H, Me from ethyl); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.52 (m, 4H, CH_2CH_2 from glutarimide); 6.95 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene bound to glutarimide); 7.10 (m, AA'BB', J_{AB} = 7.4 Hz, 4H, ArH, *p*-Cl-phenylene); 7.60 (s, 1H, SO_2NH); 8.39 (s, 1H, CONHCO); Anal $C_{19}H_{19}ClN_2O_4S$ (C, H, N).

*3-Ethyl-3-[4-(bromophenylsulfamoyl)phenyl]-2,6-piperidinedione **3f***
Colorless crystals, mp 215–217 °C. IR (KBr), cm^{-1}: 1179 (SO_2^{sym}), 1290 (amide III), 1370 (SO_2^{as}), 1527 (amide II); 1680 (amide I); 3060 (NH); ^{1}H-NMR (DMSO–d_6), δ, ppm: 0.90 (t, 3H, Me from ethyl); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.52 (m, 4H, CH_2CH_2 from glutarimide); 6.95 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene bound to glutarimide); 7.15 (m, AA'BB', J_{AB} = 7.4 Hz, 4H, ArH, *p*-Br-phenylene); 7.55 (s, 1H, SO_2NH); 8.42 (s, 1H, CONHCO); Anal $C_{19}H_{19}BrN_2O_4S$ (C, H, N).

3-Ethyl-3-[4-(iodophenylsulfamoyl)phenyl]-2,6-piperidinedione ***3g***
Colorless crystals, mp 221–222 °C. IR (KBr), cm^{-1}: 1185 (SO_2^{sym}), 1290 (amide III), 1377 (SO_2^{as}), 1527 (amide II); 1680 (amide I); 3060 (NH); ^{1}H-NMR (DMSO-d_6), δ, ppm: 0.90 (t, 3H, Me from ethyl); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.52 (m, 4H, CH_2CH_2 from glutarimide); 6.95 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene bound to glutarimide); 7.17 (m, AA'BB', J_{AB} = 7.4 Hz, 4H, ArH, *p*-I-phenylene), 7.59 (s, 1H, SO_2NH); 8.41 (s, 1H, CONHCO); Anal $C_{19}H_{19}IN_2O_4S$ (C, H, N)

3-Ethyl-3-[p-(tosylamido)phenyl]-2,6-piperidinedione ***3h***
Colorless crystals, mp 201–204 °C. IR (KBr), cm^{-1}: 1165 (SO_2^{sym}), 1290 (amide III), 1351 (SO_2^{as}), 1526 (amide II); 1680 (amide I); 3060 (NH); ^{1}H-NMR (DMSO-d_6), δ, ppm: 0.90 (t, 3H, Me from ethyl); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.52 (m, 4H, CH_2CH_2 from glutarimide); 2.50 (s, 3H, Me from tosyl); 6.95 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene bound to glutarimide); 7.05 (m, AA'BB', J_{AB} = 7.4 Hz, 4H, ArH, *p*-Me-phenylene); 7.51 (s, 1H, SO_2NH); 8.42 (s, 1H, CONHCO); Anal $C_{20}H_{22}N_2O_4S$ (C, H, N).

3-Ethyl-3-[4-(nitrophenylsulfamoyl)phenyl]-2,6-piperidinedione ***3i***
Yellow crystals, mp 218–221 °C. IR (KBr), cm^{-1}: 1152 (SO_2^{sym}), 1290 (amide III), 1368 (SO_2^{as}), 1527 (amide II); 1680 (amide I); 3060 (NH); ^{1}H-NMR (DMSO-d_6), δ, ppm: 0.90 (t, 3H, Me from ethyl); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.52 (m, 4H, CH_2CH_2 from glutarimide); 6.95 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene bound to glutarimide); 7.08 (m, AA'BB', J_{AB} = 7.4 Hz, 4H, ArH, *p*-O_2N-phenylene); 7.71 (s, 1H, SO_2NH); 8.39 (s, 1H, CONHCO); Anal $C_{19}H_{19}N_3O_6S$ (C, H, N).

3-Ethyl-3-[2-(nitrophenylsulfamoyl)phenyl]-2,6-piperidinedione ***3j***
Yellow crystals, mp 220–222 °C. IR (KBr), cm^{-1}: 1178 (SO_2^{sym}), 1290 (amide III), 1381 (SO_2^{as}), 1527 (amide II); 1680 (amide I); 3060 (NH); ^{1}H-NMR (DMSO-d_6), δ, ppm: 0.90 (t, 3H, Me from ethyl); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.52 (m, 4H, CH_2CH_2 from glutarimide); 6.95 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene bound to glutarimide); 7.12–7.50 (m, 4H, ArH, *o*-O_2N-phenylene); 7.74 (s, 1H, SO_2NH); 8.38 (s, 1H, CONHCO); Anal $C_{19}H_{19}N_3O_6S$ (C, H, N).

3-[4-(Acetylaminophenylsulfamoyl)phenyl]-3-ethyl-2,6-piperidinedione ***3k***
Colorless crystals, mp 247–249 °C. IR (KBr), cm^{-1}: 1152 (SO_2^{sym}), 1290 and 1296 (amide III), 1351 (SO_2^{as}), 1527 and 1533 (amide II); 1670 and 1680 (amide I); 3060 (NH); ^{1}H-NMR (DMSO-d_6), δ, ppm: 0.90 (t, 3H, Me from ethyl); 1.80 (s, 3H, Me from Ac); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.52 (m, 4H, CH_2CH_2 from glutarimide); 6.18 (s, 1H, Ac*NH*); 6.95 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene bound to glutarimide); 7.07 (m, AA'BB', J_{AB} = 7.4 Hz, 4H, ArH, *p*-AcNH-phenylene); 7.68 (s, 1H, SO_2NH); 8.39 (s, 1H, CONHCO); Anal $C_{21}H_{23}N_3O_4S$ (C, H, N).

3-[4-(Aminophenylsulfamoyl)phenyl]-3-ethyl-2,6-piperidinedione ***3l***
Colorless crystals, mp 234–235 °C. IR (KBr), cm^{-1}: 1155 (SO_2^{sym}), 1290 (amide III), 1348 (SO_2^{as}), 1527 (amide II); 1680 (amide I); 3060 (NH); ^{1}H-NMR (DMSO-d_6), δ, ppm: 0.90 (t, 3H, Me from ethyl); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.52 (m, 4H, CH_2CH_2 from glutarimide); 5.46 (s, 2H, H_2N-phenylene) 6.95 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene bound to glutarimide); 7.05 (m, AA'BB', J_{AB} = 7.4 Hz, 4H, ArH, *p*-H_2N-phenylene); 7.69 (s, 1H, SO_2NH); 8.39 (s, 1H, CONHCO); Anal $C_{19}H_{21}N_3O_4S$ (C, H, N).

3-[3-(Aminophenylsulfamoyl)phenyl]-3-ethyl-2,6-piperidinedione ***3m***
Tan crystals, mp 223–226 °C. IR (KBr), cm^{-1}: 1172 (SO_2^{sym}), 1290 (amide III), 1360 (SO_2^{as}), 1527 (amide II); 1680 (amide I); 3060 (NH); ^{1}H-NMR (DMSO-d_6), δ, ppm: 0.90 (s, 3H, Me from ethyl); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.52 (m, 4H, CH_2CH_2 from glutarimide); 5.18 (s, 2H, H_2N-phenylene) 6.95 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene bound to glutarimide); 7.21–7.45 (m, 4H, ArH, *m*-H_2N-phenylene); 7.65 (s, 1H, SO_2NH); 8.38 (s, 1H, CONHCO); Anal $C_{19}H_{21}N_3O_4S$ (C, H, N).

3-Ethyl-3-[(pentafluorolphenylsulfamoyl)phenyl]-2,6-piperidinedione ***3n***
Colorless crystals, mp 165–168 °C (dec). IR (KBr), cm^{-1}: 1148 (SO_2^{sym}), 1290 (amide III), 1332 (SO_2^{as}), 1525 (amide II); 1680 (amide I); 3060 (NH); ^{1}H-NMR (DMSO-d_6), δ, ppm: 0.90 (t, 3H, Me from ethyl); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.54 (m, 4H, CH_2CH_2 from glutarimide); 6.94 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene); 7.78 (s, 1H, SO_2NH); 8.44 (s, 1H, CONHCO); Anal $C_{19}H_{15}F_5N_2O_4S$ (C, H, N).

3-[2-(Carboxyphenylsulfamoyl)phenyl]-3-ethyl-2,6-piperidinedione ***3o***
Colorless crystals, mp 251–253 °C (dec). IR (KBr), cm^{-1}: 1153 (SO_2^{sym}), 1290 (amide III), 1358 (SO_2^{as}), 1526 (amide II); 1680 (amide I); 1720 (COOH); 3060 (NH); ^{1}H-NMR (DMSO-d_6), δ, ppm: 0.90 (t, 3H, Me from ethyl); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.52 (m, 4H, CH_2CH_2 from glutarimide); 6.95 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene bound to glutarimide); 7.15–7.43 (m, 4H, ArH, *o*-HOOC-phenylene); 7.54 (s, 1H, SO_2NH); 8.42 (s, 1H, CONHCO); 10.15 (br s, 1H, COOH); Anal $C_{20}H_{20}N_2O_6S$ (C, H, N).

3-[2-(Carboxytetrabromophenylsulfamoyl)phenyl]-3-ethyl-2,6-piperidinedione ***3p***
Colorless crystals, mp 211–212 °C (dec). IR (KBr), cm^{-1}: 1158 (SO_2^{sym}), 1290 (amide III), 1377 (SO_2^{as}), 1525 (amide II); 1680 (amide I); 1720 (COOH); 3060 (NH); ^{1}H-NMR (DMSO-d_6), δ, ppm: 0.90 (t, 3H, Me from ethyl); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.52 (m, 4H, CH_2CH_2 from glutarimide); 6.95 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene bound to glutarimide), 7.69 (s, 1H, SO_2NH); 8.45 (s, 1H, CONHCO); 10.42 (br s, 1H, COOH); Anal $C_{20}H_{16}Br_4N_2O_6S$ (C, H, N).

3-[4-[(3,4-Dichlorophenylureido)phenylsulfamoyl]phenyl]-3-ethyl-2,6-piperidinedione ***4***
Colorless crystals, mp 148–151 °C. IR (KBr), cm^{-1}: 1165 (SO_2^{sym}), 1290 (amide III), 1362 (SO_2^{as}), 1527 and 1560 (amide II); 1675 and 1680 (amide I); 1730; 3060 (NH); ^{1}H-NMR (DMSO-d_6), δ, ppm. 0.90 (t, 3H, Me from ethyl); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.52 (m, 4H, CH_2CH_2 from glutarimide); 5.23 (s, 2H, HN–CO–NH); 6.95 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene bound to glutarimide); 7.12 (m, AA'BB', J_{AB} =

7.4 Hz, 4H, ArH, *p*-HNCONH-phenylene), 7.25–7.39 (m, 3H, ArH, dichlorophenyl); 7.68 (s, 1H, SO_2NH); 8.39 (s, 1H, CONHCO); Anal $C_{26}H_{24}Cl_2N_4O_5S$ (C, H, Cl, N).

3-{3-[(3,4-Dichlorophenylureido)phenylsulfamoyl]phenyl}-3-ethyl-2,6-piperidinedione ***5***
Tan crystals, mp 123–124 °C. IR (KBr), cm^{-1}: 1170 (SO_2^{sym}), 1290 (amide III), 1367 (SO_2^{as}), 1527 (amide II); 1675 and 1680 (amide I); 1730; 3060 (NH); ^{1}H-NMR (DMSO–d_6), δ, ppm: 0.90 (t, 3H, Me from ethyl); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.52 (m, 4H, CH_2CH_2 from glutarimide), 5.10 (s, 2H, HN–CO–NH); 6.95 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene bound to glutarimide); 7.23–7.55 (m, 7H, ArH, *m*-HNCONH-phenylene + dichlorophenyl), 7.67 (s, 1H, SO_2NH); 8.39 (s, 1H, CONHCO); Anal $C_{26}H_{24}Cl_2N_4O_5S$ (C, H, Cl, N).

3-Ethyl-3-{4-[4-(tosylsulfonylureido)phenylsulfamoyl]phenyl}-2,6-piperidinedione ***6***
Colorless crystals, mp 188–191 °C. IR (KBr), cm^{-1}: 1150 and 1165 (SO_2^{sym}), 1290 (amide III), 1360 and 1375 (SO_2^{as}), 1528 and 1566 (amide II); 1670 and 1680 (amide I); 1730; 3060 and 3190 (NH); ^{1}H-NMR (DMSO–d_6), δ, ppm: 0.90 (t, 3H, Me from ethyl); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.52 (m, 4H, CH_2CH_2 from glutarimide); 2.50 (s, 3H, Me from tosyl); 5.20 (s, 2H, HN–CO–NH); 6.95 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene bound to glutarimide); 7.05 (m, AA'BB', J_{AB} = 7.1 Hz, 4H, ArH, phenylene from tosyl); 7.12 (m, AA'BB', J_{AB} = 7.4 Hz, 4H, ArH, *p*-HNCONH–phenylene–SO_2–); 7.61 (s, 1H, SO_2NH); 8.56 (s, 1H, CONHCO); Anal $C_{27}H_{28}N_4O_7S$ (C, H, N).

3-Ethyl-3-{3-[4-(tosylsulfonylureido)phenylsulfamoyl]phenyl}-2,6-piperidinedione ***7***
Colorless crystals, mp 163–164 °C. IR (KBr), cm^{-1}: 1159 and 1171 (SO_2^{sym}), 1290 (amide III), 1356 and 1374 (SO_2^{as}), 1528 and 1569 (amide II); 1670 and 1680 (amide I); 1730; 3060 and 3180 (NH); ^{1}H-NMR (DMSO–d_6), δ, ppm: 0.90 (t, 3H, Me from ethyl); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.52 (m, 4H, CH_2CH_2 from glutarimide); 2.50 (s, 3H, Me from tosyl); 5.24 (s, 2H, HN–CO–NH); 6.95 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene bound to glutarimide); 7.08 (m, AA'BB', J_{AB} = 7.1 Hz, 4H, ArH, phenylene from tosyl); 7.24–7.49 (m, 4H, ArH, *m*-HNCONH–phenylene–SO_2–); 7.65 (s, 1H, SO_2NH); 8.67 (s, 1H, CONHCO); Anal $C_{27}H_{28}N_4O_7S$ (C, H, N).

1-{[4-(2-Ethyl-2-glutarimido)phenylaminosulfonyl]phenyl}-2,4,6-trimethylpyridinium perchlorate ***8***
Colorless crystals. Yield of 55%, mp 169–170 °C. IR (KBr), cm^{-1}: 1100 (perchlorate); 1157 (SO_2^{sym}), 1290 (amide III), 1375 (SO_2^{as}), 1528 (amide II); 1670 (amide I); 3060 (NH); ^{1}H-NMR (DMSO–d_6), δ, ppm: 0.90 (t, 3H, Me from ethyl); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.52 (m, 4H, CH_2CH_2 from glutarimide), 2.45 (s, 6H, 2,6-Me_2); 2.69 (s, 3H, 4-Me); 6.95 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene bound to glutarimide); 7.09 (m, AA'BB', J_{AB} = 7.1 Hz, 4H, ArH, phenylene bound to pyridinium); 7.58 (s, 2H, ArH, 3,5-H from pyridinium); 7.68 (s, 1H, SO_2NH); 8.67 (s, 1H, CONHCO); Anal $C_{27}H_{30}N_3O_4S^+ClO_4^-$ (C, H, N).

1-{[3-(2-Ethyl-2-glutarimido)phenylaminosulfonyl]phenyl}-2,4,6-trimethyl pyridinium perchlorate ***9***
Colorless crystals, yield of 58%, mp 150–153 °C. IR (KBr), cm^{-1}: 1100 (perchlorate); 1162 (SO_2^{sym}), 1290 (amide III), 1378 (SO_2^{as}), 1526 (amide II); 1670 (amide I); 3060 (NH); ^{1}H-NMR (DMSO–d_6), δ, ppm: 0.90 (t, 3H, Me from ethyl); 1.95–2.20 (m, 2H, the diastereotopic CH_2 protons from ethyl); 2.25–2.52 (m, 4H, CH_2CH_2 from glutarimide); 2.43 (s, 6H, 2,6-Me_2); 2.70 (s, 3H, 4-Me); 6.95 (m, AA'BB', J_{AB} = 7.2 Hz, 4H, ArH, phenylene bound to glutarimide); 7.13–7.38 (m, 4H, ArH, phenylene bound to pyridinium); 7.59 (s, 2H, ArH, 3,5-H from pyridinium); 7.68 (s, 1H, SO_2NH); 8.65 (s, 1H, CONHCO); Anal $C_{27}H_{30}N_3O_4S^+ClO_4^-$ (C, H, N).

Assay of fungistatic activity of compounds ***3–21***

Fungistatic activity was determined by a modification of the growth method recently reported by us [18, 19], utilizing two *Aspergillus* and one *Candida spp.* Minimum inhibitory concentrations (MICs) have been determined by the agar dilution method with Iso-Sensitest agar as described by Kinsman et al [31]. The fungi/moulds were cultivated in agar plates at 37 °C for 5 days, in the nutrient broth (NB, Diagnostic Pasteur), in the absence and in the presence of 100–0.1 μg/mL of compounds **3–21**. The minimum concentration at which no growth was observed was taken as MIC value (μg/mL), and represents the mean of at least two determinations.

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