Synthesis, Antifungal Activity, and Molecular Modeling Studies of New Inverted Oxime Ethers of Oxiconazole

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Some new oxime ethers of types **7** and **8**, in which the methyleneaminoxy group, C═N−O, of oxiconazole **6** is in an inverted atomic sequence, were synthesized and tested for their antifungal activities. Among them, the type **7** compounds, such as the *N*-ethoxy-morpholino-substituted derivatives **7l**−**o** (Table 1), showed good antifungal properties against the *Candida* strains tested, with minimum inhibitory concentration (MIC) values similar to those of the reference drug **6**. A remarkable result was obtained with these types of azoles, which had shown a cidal character against *Candida albicans*, while the reference drug oxiconazole was only fungistatic in the same tests. This fact may be seen from a comparison of the MIC values with those of the minimum fungicidal concentration (MFC) values for most of the type **7** compounds assayed that have shown differences between the MIC and the MFC, which are lower than three double diluitions. A simple molecular modeling of the P450 14-α-sterol demethylase from *C. albicans* (*Candida* P450DM) was built in order to understand how the structural differences between type **7** compounds and oxiconazole **6** can induce different antifungal profiles. The results of this work seem to confirm that it is possible to reverse the atomic sequence of the methyleneaminoxy group, C═N−O, of **6**, obtaining new imidazoles possessing good antifungal properties.

Introduction

During the past two decades, the incidence of infections caused by opportunistic fungal pathogens has increased substantially in immunocompromised patients. Amphotericin B, discovered in 1956, is still the drug of choice for the treatment of most severe systemic mycoses. However, more recently, there has been an expansion in the number of antifungal drugs available. Five major classes of antifungal compounds are currently in clinical use: polyenes, azole derivatives, allylamines, thiocarbamates, and fluoropyrimidines. Now, the new class of hexapeptide echinocandin antifungal compounds may be added to these drugs; the lead compound, capsofungin (MK-0991) by Merck, has been filed for approval by the Food and Drug Administration.[1] Despite this growing list of antifungal agents, in many cases, treatment of fungal diseases remains unsatisfactory. This situation has led to an ongoing search for fungicidal agents with a new mode of action and with fewer side effects, which can be administered both orally and parenterally.[2−6]

The imidazoles **1** (A = CH, Figure 1) represent one class of antifungal azole derivatives, which have been shown to have a broad spectrum of antifungal activities both in vitro and in vivo.[7,8] The development of compounds of type **1** has contributed significantly to the therapy of both superficial and systemic mycotic infections.

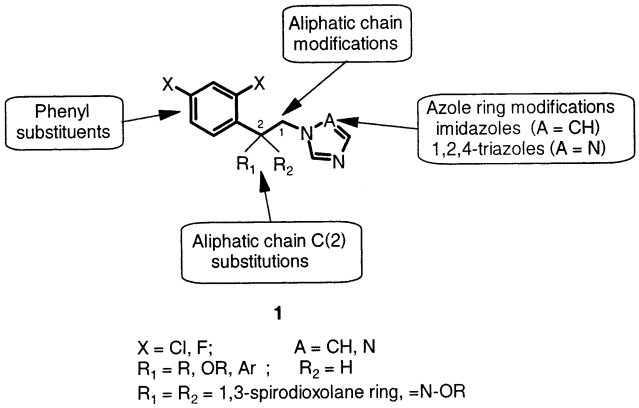

Figure 1. SAR studies in antifungal azoles.

Numerous studies on the SAR (structure−activity relationships) of antifungal azoles have been developed since the discovery of the first imidazoles, and these studies have led to new compounds endowed with better biological and/or pharmacological properties.

Figure 1 summarizes the principal structural modifications introduced by the SAR in this field of antifungal agents. These studies reveal the presence in all of these molecules of one common pharmacophoric portion, bolded in Figure 1, which is characterized by a 2,4-dihalophenyl ring linked by an ethane chain to a nitrogen of an azole ring (imidazole, A = CH, or triazole, A = N). The ethane chain is often substituted on its C(2) by ethereal groups, as in miconazole **2** or in econazole **3**, by the 1,3-spirodioxolane ring, as in ketoconazole **4** (A = CH) or in itraconazole **5** (A = N), or again,

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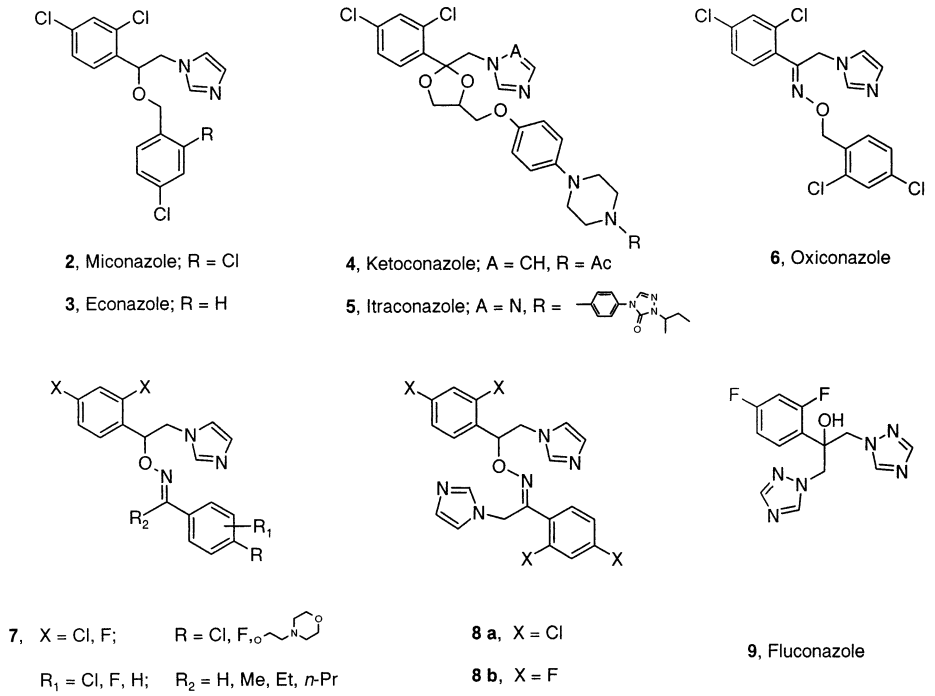


Figure 2.

oximethereal groups may be present in the same position as in oxiconazole **6** (Figure 2).

Starting from this observation, we decided to verify the effects on the antifungal properties of the formal inversion of the methyleneaminoxy group, C=N−O, of oxiconazole **6** to give compounds of type **7**. Type **7** compounds have the same oxime ethereal group as oxiconazole **6**, albeit with an inverted atomic sequence of the methyloxyimino group (O−N=C), so they may be considered as inverted oxime ethers of **6**. Thus, these latter compounds seem to be structurally more closely correlated with **6**, in view of the position of the oxygen atom, than the other C(2) ethers, which represent the largest class of derivatives of antifungal azoles, i.e., drugs **2**−**4**. So, type **7** derivatives may represent a further development of studies of the groups linked to the C(2) of the ethane chain of the pharmacophore of these antifungal agents. Finally, the same type of inversion of the atomic sequence of the C=N−O group had led to positive results in other classes of drugs, such as β-adrenergic antagonists,[9] β-lactam antibiotics,[10] and neuroleptics,[11] and the development of these studies, also through theoretical research, had made it possible to hypothesize the existence of a bioisosteric relationship of the methyleneaminoxy group, C=N−O, with the methyloxyimino group, O−N=C.[12]

As halogens, X substituents on the phenyl of the pharmacophoric portion, we chose chlorine or fluorine atoms, which are present as common substituents in almost all of the antifungal azoles. For the substitution on the iminic carbon of the oxime ethereal group, we decided to maintain a substituted phenyl ring like that which is present on the benzyl ethers of type **2**, miconazole, and **3**, econazole, considering that this group may be able to favor interaction with the structures of the target enzyme, the fungal lanosterol 14α-demethylase.[13] For this second phenyl ring, we chose either the halo substitution, with chlorine or fluorine atoms, compounds **7a**−**k** (Table 1), or the para *N*-ethoxy-morpholino substitution of compounds **7l**−**o**.

Halogens, like chlorine or fluorine, are very useful to modulate the electronic effects on phenyl rings of drugs. Chlorine has strong inductive electron-attracting effects, while those of fluorine are very weak. Moreover, these atoms may also influence the steric characteristics and the hydrophilic−hydrophobic balance of the molecules.[14]

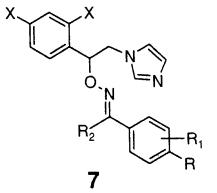
On the other hand, the introduction of both a hydrogen-bonding acceptor, such as fluorine, and a basic protonable moiety, such as the *N*-ethoxy-morpholino group of compounds **7l**−**o**, may be able to improve the inhibitory potency through an increase in the affinity toward the enzyme-recognizing sites.[15] Finally, these substituents may be able to improve the bioavailability of the new compounds and consequently their in vivo antifungal activity. Positive effects of the above-mentioned substituents had been already observed in the class of antifungal azoles.[16]

As the second substituent on the iminic carbon of the oxime ethereal group of type **7** derivatives, we decided to verify the effect on the antifungal activity of the introduction into R_2 of hydrogen atoms or aliphatic groups of increasing steric hindrance, as in compounds **7a**−**d**.

As an alternative to the increase of the steric hindrance of the R_2 group in the new type **7** ethers, we studied the diimidazoles **8a**, X = Cl, and **8b**, X = F, which may be viewed as compounds possessing at the same time two pharmacophoric portions (compare Figures 1 and 2) joined together through their respective C(2) atoms by an oxime ethereal bridge.

The new type **7** and **8** compounds were tested against the most important pathogenic fungi and yeasts. The activity of these new compounds was compared with that of oxiconazole **6**, to which types **7** and **8** may be considered structurally related. Oxiconazole **6** is an antifungal agent, which is characterized by a broad

Table 1. Antifungal Activities of Type **7** and **8** Imidazole Derivatives



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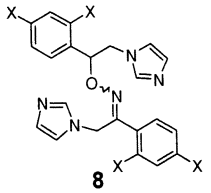


8

					C. albicans[a]		*C. glabrata*[b]		*C. parapsilosis*[c]		*A. fumigatus*[d]		*A. flavus*[e]		*T. mentagrophytes*[f]		*T. rubrum*[g]	
compd	X	R	R_1	R_2	MIC[h]	MFC[i]	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC
7a HCl	Cl	4′-Cl	2′-Cl	H	>128						64							
7b	Cl	4′-Cl	2′-Cl	Me	4	8	0.5	2	1	16	8	8	32	32	8	8	8	8
7c	Cl	4′-Cl	2′-Cl	Et	16						>128							
7d	Cl	4′-Cl	2′-Cl	*n*-Pr	>128						>128							
7e HCl	F	4′-F	2′-F	H	16						16							
7f	F	4′-F	2′-F	Me	32	32	0.03	2	2	32	8	16	16	16	1	4	8	16
7g HCl	F	6′-F	2′-F	H	32						32							
7h	F	5′-F	2′-F	Me	8	32	0.03	1	2	64	4	4	8	8	0.25	2	1	16
7i	F	6′-F	2′-F	Me	32	32	0.03	1	0.25	16	16	32	32	64	2	2	4	8
7j HCl	F	H	2′-F	Me	32						16							
7k	F	4′-F	H	Me	64						16							
7l	Cl	EM[j]	H	H	2	8	1	8	0.25	16	2	2	8	8	4	8	2	16
7m	Cl	EM	H	Me	1	8	0.06	8	0.004	8	32	32	32	32	4	8	2	16
7n	F	EM	H	H	64	64	2	8	0.25	4	64	64	64	64	>128	>128	8	16
7o	F	EM	H	Me	8	32	0.25	4	0.03	2	16	16	16	32	2	4	4	4
8a	Cl				32						128							
8b	F				2	>128	4	16	8	128	>128	>128	>128	>128	64	>128	64	64
6					0.03	64	0.01	0.25	0.008	4	2	2	2	2	2	4	2	2
9					0.12	>128	2	>128	0.5	>128	>128	>128	>128	>128	0.5	>128	0.5	>128

[a] *C. albicans* 4711E. [b] *C. glabrata* 2375E. [c] *C. parapsilosis* 2372E. [d] *A. fumigatus* 48238E. [e] *A. flavus* CM74. [f] *T. mentagrophytes* CM84. [g] *T. rubrum* CM1447. [h] MIC in μg/mL. [i] MFC in μg/mL. [j] *N*-Ethoxy-morpholino.

spectrum of activity in vitro and which shows fungicidal activity against fungi such as *Aspergillus fumigatus*, *Cryptococcus neoformans*, and *Trichophyton mentagrophytes*,[7] while it shows a lesser activity against yeasts such as *Candida albicans* and *Candida parapsilosis*.[17]

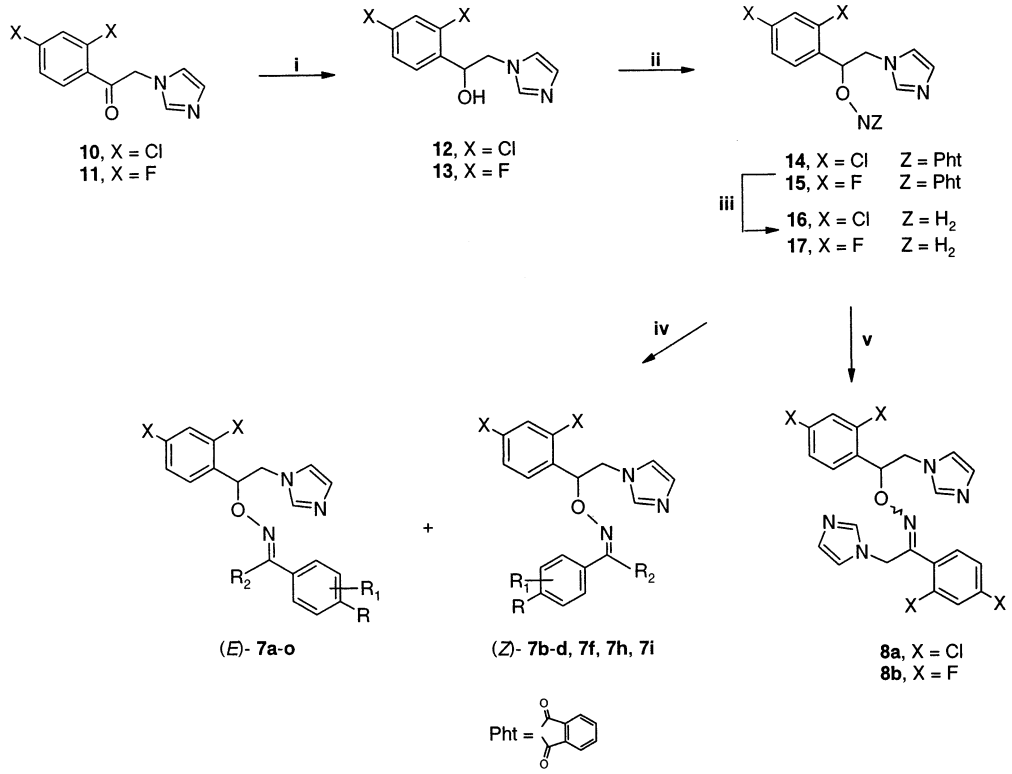
Chemistry

The synthetic pathways to the target compounds, oxime ethers **7a**−**o** and **8a**,**b**, are outlined in Schemes 1 and 2. Reduction with $NaBH_4$ in MeOH of the known ketones **10** (X = Cl)[18] or **11** (X = F)[19] gave the desired alcohols **12** (X = Cl)[20] or **13** (X = F), respectively, which were transformed into the Pht derivatives **14** (X = Cl) or **15** (X = F) by the Mitsunobu reaction, using *N*-hydroxyphthalimide, DEAD, and TPP in anhydrous benzene. Hydrazinolysis of the Pht derivatives **14** and **15** in refluxed EtOH gave the *O*-alkylhydroxylamines **16** (X = Cl) or **17** (X = F), respectively. The key intermediates **16** and **17** were condensed with the appropriate aldehydes or ketones to give the desired *O*-alkyloxime ethers (*E*)-**7a**−**o** and **8a**,**b**, which were purified by crystallization or flash chromatography. In the case of the preparation of compounds **7b**−**d**,**f**,**h**,**i**, also their *Z* isomers are contained in the crude reaction mixtures in small percentages ranging from 5 to 10% (^{1}H NMR spectroscopy); therefore, they were separated by flash chromatography from their *E* isomers and characterized by ^{1}H NMR.

Scheme 2 shows the synthetic route to known ketones **21** (R = Me)[21] and **22** (R = Et)[22] via Jones oxidation of benzyl alcohols **19** and **20**. 2,4-Dichlorobenzaldehyde **18** was reacted with the appropriate alkylmagnesium bromide in Et_2O[23] to give before crystallization compounds **19** (R = Me) and **20** (R= Et). Jones oxidation of alcohols **19** and **20** in acetone after workup gave the pure ketones **21** and **22**, which were used for the subsequent synthetic route without any purification. 4-[2′-Ethyloxy-*N*-morpholino]benzaldehyde **23** and 4-[2′-ethyloxy-*N*-morpholino]acetophenone **24**, used for the synthesis of *O*-alkyloxime ethers (*E*)-**7l**−**o**, were prepared as indicated in our preceding paper.[24]

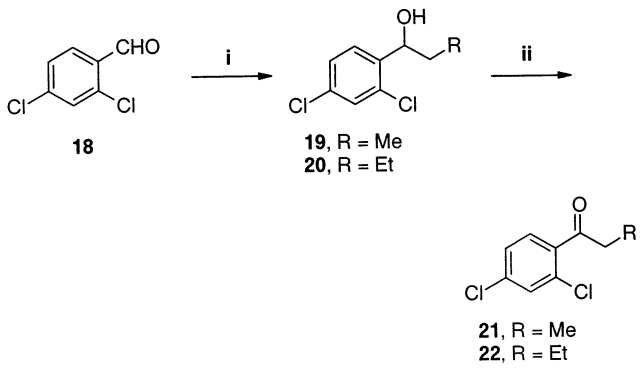
All described compounds **7** and **8**, which possess a chiral center on their ethane chain on C(2), are racemates.[25] The *E* configuration of the methyleneaminoxy molecular portion (O−N=C) of **7a**−**o** was assigned by ^{1}H NMR spectroscopy. In particular, the syn relationship between the oxime oxygen and the hydrogen or the α-methylene proton linked to the iminic carbon atom of the aldehyde and ketone derivatives of type **7** may be confirmed by the fact that the protons, in this type of spatial arrangement, resonate at a lower field with respect to the same types of protons of the corresponding *Z* isomers. This fact is due to the paramagnetic effect of the spatially proximal oxime ethereal oxygen. Therefore, the attribution of the *E*/*Z* isomerism for the newly synthesized compounds is directly confirmed for **7b**−**d**,**f**,**h**,**i**, for which the two forms were isolated and characterized. In the case of the other compounds, in which only one of the two possible isomers was isolated, compounds **7a**,**e**,**g**,**l**−**o**, the *E* configuration may be assumed on the basis of the comparison of the chemical shift values for the groups linked on their iminic carbon atom, hydrogen, or α-methylene protons, with those observed for their analogues with a certain *E* configuration described above. Moreover, for these last compounds, the results obtained for the chemical shift values of the groups linked directly to their iminic carbon are consistent with those reported in the literature for similar oxime ether derivatives with the *E* configuration.[9] On the contrary, for compounds of type

Scheme 1[a]



[a] All structures racemic. Reagents: (i) $NaBH_4$, MeOH, 5−10 °C, 1 h. (ii) *N*-Hydroxyphthalimide, TPP, anhydrous benzene. (iii) Hydrazine monohydrate, EtOH, reflux. (iv) Appropriate aldehyde or ketone, MeOH or CH_3CN, 5 days. (v) Compounds **9** or **10**, MeOH, 5 days.

Scheme 2[a]



[a] Reagents: (i) RCH_2MgBr, Et_2O, 0 °C−room temperature, 24 h. (ii) Jones, acetone, 0 °C, 30 min.

8, the spectroscopic data presently available do not allow us to indicate the exact configuration around their iminic double bond.

Results and Discussion

Table 1 shows the antifungal activity of the new C(2) oxime ether derivatives of types **7** and **8** and of oxiconazole, **6**, and fluconazole, **9**, taken as the reference drugs, on a panel of pathogenic strains belonging to the classes of yeasts and filamentous fungi, measured as minimum inhibitory concentration (MIC, μg/mL) and as minimum fungicidal concentration (MFC, μg/mL).[26]

The new compounds of types **7** and **8** were first evaluated against *C. albicans* and *A. fumigatus*, the most important human pathogens. Then, the most active compounds, selected in this first study, were further tested against a broader panel of fungi including *C.* non-*albicans* species, such as *Candida glabrata*, *C. parapsilosis*, *Aspergillus flavus*, and two dermatophytes such as *T. mentagrophytes* and *Tricophyton rubrum*.

Derivatives **7b**,**l**,**m**, and **8b** were the most active against *C. albicans*, showing MIC values ranging between 1 μg/mL of **7m** and 4 μg/mL of **7b**. For **7h**,**o**, the MIC values were 8 μg/mL, while for the other compounds tested, the activities were ≥16 μg/mL. Against *A. fumigatus*, the most active compounds were **7b**,**f**,**h**,**l**, which exhibited MIC values ranging between 2 μg/mL of **7l** and 8 μg/mL of **7b**,**f**.

In the following evaluation carried out on more strains, the compound **7m** was the most potent against the yeasts, with MIC values of 0.06 μg/mL for *C. glabrata* and 0.004 μg/mL for *C. parapsilosis* while derivatives **7l**,**h** were the most potent against filamentous fungi and dermatophytes. Compounds **7l**,**h** showed MIC values of 2 and 4 μg/mL, respectively, against *A. fumigatus* and of 8 μg/mL against *A. flavus*; their MIC values against dermatophytes were instead 4 and 0.25 μg/mL against *T. mentagrophytes* and 2 and 1 μg/mL, respectively, against *T. rubrum*. Finally, compound **7h** was also more potent than the reference drug, **6**, against the two species of dermatophytes tested (*T. mentagrophytes* and *T. rubrum*), with MIC values, against these last strains, of 0.25 and 1 μg/mL, respectively.

Most of the new imidazole derivatives of type **7** studied showed a cidal character against *C. albicans* while the reference drugs **6** and **9** were clearly fungistatic. As described in Table 1, the MFC values against *C. albicans* were no higher than 3-fold the MIC values for all of the compounds assayed. In addition, all of the derivatives, as well as the reference drug, oxiconazole **6**, were cidal against filamentous fungi and dermato-

phytes. Compound **8b**, instead, the only active one of type **8** derivatives, showed, like **6** and **9**, only a fungistatic activity.

On the basis of these results for the activity of the new C(2) oxime ethers **7** and **8**, shown in Table 1, it appears that the formal inversion of the methyleneaminoxy group, C═N−O, of oxiconazole **6** may be able to maintain a good antifungal activity. This type of structural modification of **6** acts in the new derivatives **7** by shifting the activity from fungistatic, as happens in the classic known imidazoles, to fungicidal.

In the case of compounds **7** and **8** derivatives, the fluorine substitutions on the phenyl ring of the pharmacophoric portion, substituents X, seem to be preferred instead of the chlorine ones, which are present in oxiconazole. The fluorine atom appears to be better than the chlorine atom also in the substitution on the phenyl ring linked to the iminic carbon atom (substituents R and R_1). Nevertheless, better results are obtained with the substitution in the para position (R) with the *N*-ethoxy-morpholino group (R = EM, Table 1). Compounds **7l**−**o** are, in fact, the most potent against all of the strains tested, both yeast fungi, such as *C. albicans*, and filamentous fungi and dermatophytes, such as *Aspergillus* and *Trichophyton*.

With regards to the second substituent on the iminic carbon atom of the compounds **7**, R_2, it seems that a hydrogen or a methyl group are allowed in this position. The introduction of an *N*-methylene-imidazole group, as in the case of ethers **8**, does not appear to be particularly favorable, causing a loss of activity with MIC values >128 μg/mL against filamentous fungi and dermatophytes such as *Aspergillus* and *Trichophyton*; it shifts the activity against *Candida* strains from fungicidal, typical of the new derivatives **7**, to fungistatic, like oxiconazole, as can be seen by comparing the MIC and MCF values.

Molecular Modeling Studies

With the aim of rationalizing the biological data obtained for the derivatives **7a**−**o**, a molecular modeling study was carried out in order to investigate the possible interaction of such compounds with cytochrome P450 14-α-sterol demethylase from *C. albicans* (*Candida* P450DM).

Because the target enzyme *Candida* P450DM is a membrane-bound enzyme, it is difficult to crystallize for X-ray analysis; therefore, no experimental data were available for the structure of this enzyme. On the contrary, the crystallographic structure of the complex between cytochrome P450 14-α-sterol demethylase from *Mycobacterium tuberculosis* (*Mycobacterium* P450DM) and fluconazole **9** was present in the Protein Data Bank with the ID 1EA1.[27]

The high homology existing between these two analogous enzymes[28] and the aim of this preliminary theoretical study suggested building only a simple model consisting of the crystallographic structure of the complex 1EA1 in which the residues that are arranged in a range of 7 Å from fluconazole, **9** (Figure 3), were substituted with those of *Candida* P450DM; only 12 substitutions listed in Table 2 were necessary, and only some of these were really important.

The complex between the chimeric enzyme thus obtained and **9** was then minimized through molecular mechanics calculations (fluconazole **9** maintained practically the same orientation as in the 1EA1). In this chimeric enzyme, fluconazole **9** was then replaced in turn with oxiconazole **6** and compounds **7l**,**m**; the replacement was made so that the imidazole ring interacts with the iron atom of the heme in the same manner as one of the two triazole rings of fluconazole **9** (see Figure 3).

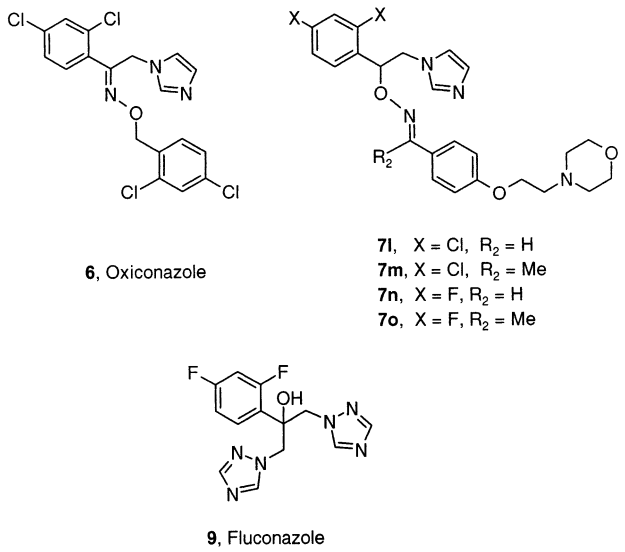


Figure 3.

Table 2. Residues Substituted in the Structure of P450 14-α-Sterol Demethylase from *Mycobacterium tubercolosis* for the Construction of the Chimeric Enzyme of P450 14-α-Sterol Demethylase of *C. albicans*

Mycobacterium P450DM	chimeric enzyme of *Candida* P450DM
Pro 77	Lys 77
Phe 78	His 78
Met 79	Leu 79
Arg 96	Leu 96
Met 99	Lys 99
Leu 100	Phe 100
Phe 255	Met 255
Ala 256	Gly 256
His 258	Gln 258
Ile 322	His 322
Ile 323	Ser 323
Leu 324	Ile 324

Figure 4 shows the complex between oxiconazole **6** and the chimeric enzyme. The 2,4-dichlorophenyl ring linked to the ethane chain was placed in an analogous manner as the 2,4-difluorinephenyl ring of **9**; therefore, it can interact with the lipophilic residues Leu96 and Phe100. The other phenyl ring of **6**, 2,4-dichlorobenzylic, was inserted into the pocket formed by residues Leu321, His322, Ser323, Ile324, and Met 433, which in the case of **9** is occupied by the other triazole ring.

The dimension of this pocket is not suitable to accept molecular moieties larger than the benzylic one of oxiconazole; therefore, it cannot accommodate the *N*-ethoxymorpholino substituent of the phenyl ring of compounds **7l**,**m**. This result seems to be different from that found for a recently published theoretical model of *Candida* P450DM[29] obtained on the basis of the crystallographic structures of four prokaryotic P450s, possessing, however, a lesser degree of homology with respect

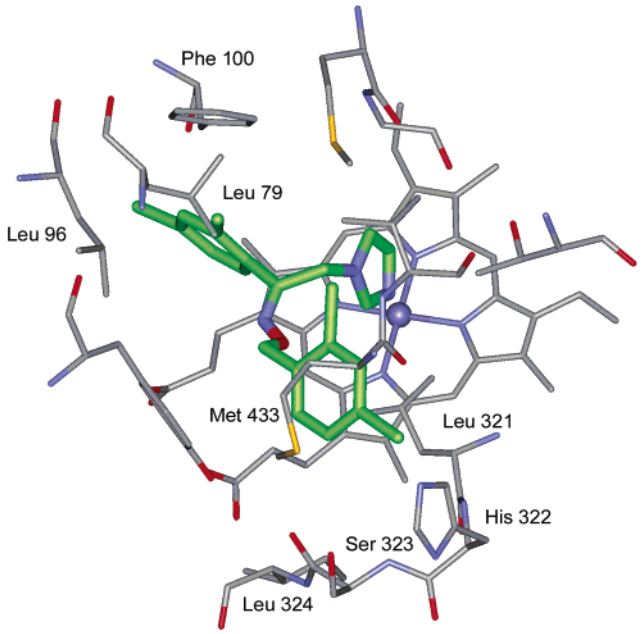


Figure 4. Structure of the interaction site of the chimeric enzyme complexed with oxiconazole, **6**. Heme and residues within a distance of 5 Å from oxiconazole are shown.

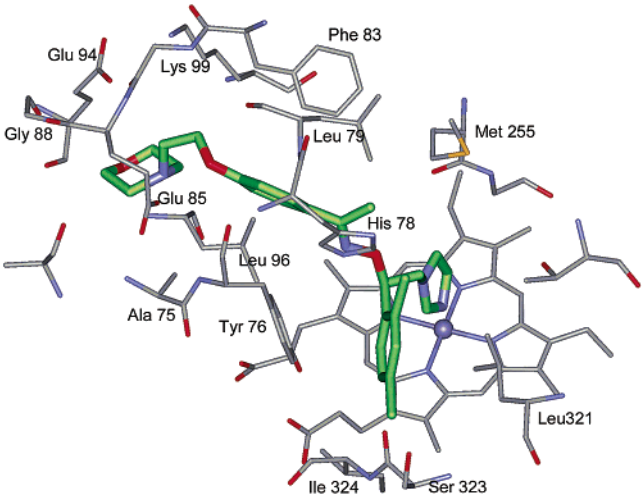


Figure 5. Structure of the interaction site of the chimeric enzyme complexed with **7m**; as in Figure 4.

to *Candida* P450DM than *Mycobacterium* P450DM. This large moiety of compounds **7l**,**m** was therefore placed (see Figure 4) in the position that is occupied by the 2,4-dichlorophenyl ring linked to the ethane chain of oxiconazole **6**. The complex between the chimeric enzyme and compound **7m** after minimization is shown in Figure 5, and it proved to be quite well-stabilized by several favorable interactions.

The 2,4-dichlorophenyl substituent is inserted into the pocket that in the case of fluconazole, **9**, accommodated the second triazole ring and, in the case of oxiconazole, the 2,4-dichlorobenzylic ring; it also interacts with Tyr76.

The phenyl ring is situated in a very lipophilic region and interacts with Ala75, Leu79, Phe83, and Leu96. The morpholine moiety is situated in a mainly polar region of the enzyme constituted by Ala75, Glu85, Gly88, Glu94, Leu96, and Lys99; residues Glu85 and Glu94 are found in a position suitable for an ionic interaction with the nitrogen of the morpholine ring, which should be charged at physiological conditions. Finally, the methyl substituent linked to the iminic carbon of **7m** is situated in a small pocket made up of Leu79 and Phe83 unable to accommodate larger groups.

Conclusions

This study was undertaken to evaluate the effects on the antifungal properties of the formal inversion of the C=N−O atomic sequence of oxiconazole **6**. The data shown in Table 1 indicate that compounds **7** and **8**, in which the oxime ethereal sequence (O−C=N) is inverted with respect to that of oxiconazole, **6**, have an antifungal activity similar to that of oxiconazole. This type of structural modification of **6** leads to positive results, especially because it seems to shift the fungistatic activity of this class of oxime ethers to fungicidal, especially on *C. albicans* strains.

Molecular modeling calculations on a chimeric structure of *Candida* P450DM show one different geometry of interaction of the new morpholino derivatives **7l**−**o** as compared with oxiconazole **6**. Despite their speculative nature, these results could be a starting point for the explanation of the fungicidal activities against *C. albicans* strains found in many of the type **7** compounds, with respect to the fungistatic activity of oxiconazole **6** against the same yeasts. They encourage us to consider the new molecular skeleton of type **7** compounds suitable to obtain, by means of appropriate substitutions, new therapeutically useful antifungal azoles.

Experimental Section

Materials and Methods. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared (IR) spectra for comparison of compounds were recorded on a Mattson 1000 FTIR spectrometer. ^{1}H NMR spectra were recorded on a Varian CFT-20 (80 MHz) or on a Varian Gemini 200 (200 MHz) in a ca. 2% solution of $CDCl_3$ or DMSO-d_6 for all compounds. The proton magnetic resonance assignments were established on the basis of the expected chemical shifts and the multiplicity of the signals. Mass spectra were recorded on a HP-5988 A spectrometer using a direct injection probe and an electron beam energy of 70 eV. Analytical thin-layer chromatography (TLC) was carried out on 0.25 mm layer silica gel plates containing a fluorescent indicator, and spots were detected under UV light (254 nm). Flash chromatography or preparative medium-pressure liquid chromatography (MPLC) was carried out through glass columns containing 40−63 μm silica gel (Macherey-Nagel Silica Gel 60) or reversed phase of octadecyl silica gel (C_{18} Polygosil 60−4063 Macherey-Nagel). The MPLCs were performed using a chromatographic apparatus consisting of a Buchi 681 pump, a Knauer differential refractometer detector, and a Philips PM 8220 pen recorder. Solvents and reagents were obtained from commercial vendors in the appropriate grade and were used without further purification unless otherwise indicated. Reactions were run under a nitrogen atmosphere. Elemental analyses were carried out by our analytical laboratory and were consistent with theoretical values to within ±0.4%.

1-(2,4-Dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethan-1-ol (12)[20] and 1-(2,4-Difluorophenyl)-2-(1*H*-imidazol-1-yl)-ethan-1-ol (13). Compound **10**·HNO_3 (7.85 g, 24. 7 mmol) was dissolved in MeOH (48 mL) and cooled to 5 °C. $NaBH_4$ (0.54 g, 14.3 mmol) was added portionwise. After 1 h, the reaction mixture was refluxed for another hour. At the end of this period, the solvent was taken away by evaporation at reduced pressure and the semisolid residue was taken up again with H_2O (38 mL). The resulting solution was acidified with aqueous 10% HCl (8 mL), refluxed for 15 min, and alkalinized with

aqueous 1 N NaOH (12 mL) obtaining the precipitation of the desired alcohol **12** as a pure solid; mp 134 °C (6.03 g, 95%). ^{1}H NMR ($CDCl_3$): δ 1.70 (brs, 1H, exchangeable D_2O), 3.90 (dd, J = 14.1, 8.0 Hz, 1 H), 4.25 (dd, J = 14.1, 3.2 Hz, 1 H), 5.28 (dd, J = 8, 3.2 Hz,1H), 6.8−7.7 (m, 6H). Anal. ($C_{11}H_{10}Cl_2N_2O$) C H N. Treatment of **11**·HNO_3 in the same conditions gave **13** as a pure solid; mp 106−107 °C (97%). ^{1}H NMR ($CDCl_3$): δ 3.92 (dd, J = 13.6, 7.2 Hz, 1 H), 4.16 (dd, J = 13.6, 3.2 Hz, 1 H), 5.17 (dd, J = 7.2, 3.2 Hz, 1H), 6.6−7.7 (m, 6H). Anal. ($C_{11}H_{10}F_2N_2O$) C H N.

1-(2,4-Dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethan-1-oxy-*N*-phthalimide (14) and 1-(2,4-Difluorophenyl)-2-(1*H*-imidazol-1-yl)ethan-1-oxy-*N*-phthalimide (15). A suspension of alcohol **12** (0.26 g, 1.0 mmol), triphenylphosphine (0.26 g, 1.0 mmol), and *N*-hydroxyphthalimide (0.16 g, 1.0 mmol) in anhydrous benzene (7 mL) was refluxed under Ar, and the azeotropic mixture (3.5 mL) was collected by means of a Dean−Stark apparatus. DEAD (0.19 g, 1.08 mmol) was added to the resulting mixture and cooled at room temperature, and the reaction was maintained in the same conditions for 24 h. Evaporation in vacuo of the solvent gave an oil, which was purified by flash chromatography on silica (75% EtOAc in hexane) giving **14** as a pure solid; mp 141 °C (0.24 g, 60%). ^{1}H NMR ($CDCl_3$): δ 4.46 (dd, J = 4.8, 4.0 Hz, 2 H), 5.98 (t, J = 4.0 Hz, 1 H), 6.97−8.00 (m, 10H). EIMS *m*/*z*: 367 (3, M^+-Cl), 320 (5), 241 (30), 205 (22) 163 (7). Anal. ($C_{19}H_{13}Cl_2N_3O_3$) C H N. Treatment of **13** in the same conditions gave **15** as a pure solid; mp 162−163 °C (34%). ^{1}H NMR ($CDCl_3$): δ 4.51 (d, J = 4.8 Hz, 2 H), 5.80 (t, J = 4.8 Hz, 1H), 6.80−7.80 (m, 10H). EIMS *m*/*z*: 369 (M^+), 207 (22), 163 (3). Anal. ($C_{19}H_{13}F_2N_3O_3$) C H N.

1-(2,4-Dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethan-1-*O*-hydroxylamine Hydrochloride (16)·HCl and 1-(2,4-Difluorophenyl)-2-(1*H*-imidazol-1-yl)ethan-1-*O*-hydroxylamine Hydrochloride (17)·HCl. A mixture of the phthalimido derivative **14** (0.37 g, 0.92 mmol) and hydrazine hydrate (0.029 mL, 0.92 mmol) in absolute EtOH (5 mL) was refluxed for 3 h. After this period, the reaction was cooled at room temperature obtaining a solid residue, which was eliminated by filtration. The resulting solution was evaporated at reduced pressure, yielding an oily residue, which was solubilized in EtOH (2 mL) and treated with Et_2O·HCl, obtaining the precipitation of hydroxylamine hydrochloride **16** as a pure solid; mp 199 °C (0.17 g, 61%). ^{1}H NMR (DMSO-d_6): δ 4.74 (d, J = 4.8 Hz, 2H), 5.87 (t, J = 4.8 Hz, 1H), 7.20−7.70 (m, 6H), 9.15 (s, 1H). EIMS *m*/*z*: 241 (63,M^+-NH_2OHCl), 205 (28), 174 (29). Anal. ($C_{11}H_{11}Cl_3N_3O$) C H N. Treatment of **15** in the same conditions gave **17**·HCl as a pure solid; mp 162 °C (47%). ^{1}H NMR (DMSO-d_6): δ 4.75 (d, J = 5.6 Hz, 2H), 5.75 (t, J = 5.6 Hz, 1H), 7.10−8.00 (m, 6H), 9.16 (s, 1H). EIMS *m*/*z*: 239 (4, M^+-HCl), 207 (100), 141 (43). Anal. ($C_{11}H_{11}ClF_2N_3O$) C H N.

General Procedure for Preparation of Imidazolyl Oxime Ethers 7 and 8. A solution of the hydroxylamine hydrochloride **16** or **17** (0.32 mmol) and the appropriate aldehyde or ketone (0.32 mmol) in CH_3CN (3.5 mL) (for compounds **7a**,**e**,**g**,**j**) or in MeOH (3.0 mL) (for compounds **7b**−**d**,**f**,**h**,**i**,**k**−**o** and **8a**,**b**) was stirred at room temperature for 5 days. After this period, the solvent was evaporated under a vacuum giving a semisolid residue. In the case of compounds **7a**,**e**,**g**,**j**, the residue was solubilized in MeOH (1.5 mL) and supplemented with Et_2O·HCl to pH 3, yielding their pure hydrochlorides. In the case of **7b**−**d**,**f**,**h**,**i**,**k**−**o** and **8a**,**b** compounds, a solution of the residue in EtOAc (12 mL) was sequentially alkalinized with aqueous $NaHCO_3$, washed with brine, dried on Na_2SO_4, filtered, and evaporated under a vacuum to give a pure oily residue consisting of **7k**,**m**−**o** and **8a**,**b** compounds. In the case of **7b**−**d**,**f**,**h**,**i**,**l**, their crude oily residues were purified by flash chromatography.

(*E*)-1-(2,4-Dichlorobenzylideneaminoxy)-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethan Hydrochloride (7a)·HCl. The compound was prepared from **16**·HCl and 2,4-dichlorobenzaldehyde by following the general procedure. Compound **7a**·HCl was a white solid (60%); mp 198 °C. ^{1}H NMR ($CDCl_3$): δ 4.77 (d, J = 4.8 Hz, 2H), 5.87 (t, J = 4.8 Hz, 1H), 7.05−7.63 (m, 9H), 8.55 (s, 1H). EIMS *m*/*z*: 427 (1, M-2(−HCl)), 348 (2), 241 (1). Anal. ($C_{18}H_{14}Cl_5N_3O$) C H N.

(*E*)-1-[1-(2,4-Dichorophenyl)ethylideneaminoxy)]-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethan (7b). The compound was prepared from **16**·HCl and 2,4-dichloroacetophenone by following the general procedure. Compound **7b** was purified by flash chromatography on silica using 67% EtOAc in hexane as the eluent and obtained as an oil (66%). ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H), 4.34 (dd, J = 10.4, 5.6 Hz, 1H), 4.57 (dd, J = 10.4, 3.2 Hz, 1H), 5.62 (dd, J = 5.6, 3.2 Hz, 1H), 6.80−7.54 (m, 9H). EIMS *m*/*z*: 407 (2, M^+-HCl), 241 (1), 203 (6). Anal. ($C_{19}H_{15}Cl_4N_3O$) C H N. [The previous fractions gave the *Z* isomer of **7b** as an oil (10%). ^{1}H NMR ($CDCl_3$): δ 1.95 (s, 3H), 4.20 (dd, J = 10.2, 5.6 Hz, 1H), 4.37 (dd, J = 10.2, 3.2 Hz, 1H), 5.59 (dd, J = 5.6, 3.2 Hz, 1H), 6.80−7.54 (m, 9H).]

(*E*)-1-[1-(2,4-Dichorophenyl)propylideneaminoxy)]-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethan (7c). The compound was prepared from **16**·HCl and 2,4-dichloropropiophenone **21** by following the general procedure. Compound **7c** was purified by flash chromatography on silica using 50% EtOAc in hexane as the eluent and was obtained as an oil (25%). ^{1}H NMR ($CDCl_3$): δ 1.05 (t, J = 7.6 Hz, 3H), 2.83 (q, J = 7.6, Hz, 2H), 4.29 (dd, J = 14.8, 5.6 Hz, 1H), 4.56 (dd, J = 14.8, 2.8 Hz, 1H), 5.76 (dd, J = 5.6, 2.8 Hz, 1H), 6.79−7.27 (m, 9H). EIMS *m*/*z*: 457 (1, M^+), 256 (1), 241 (2), 217 (1). Anal. ($C_{20}H_{17}Cl_4N_3O$) C H N. [The previous fractions gave the *Z* isomer of **7c** as an oil (∼ 5%). ^{1}H NMR ($CDCl_3$): δ 1.03 (t, J = 7.5 Hz, 3H), 2.42 (m, 2H), 4.10 (m, 1H), 4.65 (m, 1H), 5.30 (m, 1H).]

(*E*)-1-[1-(2,4-Dichorophenyl)butylideneaminoxy)]-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethan (7d). The compound was prepared from **16**·HCl and 2,4-dichlorobutyrophenone **22** by following the general procedure. Compound **7d** was purified by flash chromatography on silica using 50% EtOAc in hexane as the eluent and was obtained as an oil (63%). ^{1}H NMR ($CDCl_3$): δ 0.98 (t, J = 7.5 Hz, 3H), 1.44 (m, 2H), 2.81 (t, J = 7.5 Hz, 2H), 4.32 (dd, J = 14.9, 5.6 Hz, 1H), 5.06 (dd, J = 14.9, 2.9 Hz, 1H), 5.78 (dd, J = 5.6, 2.9 Hz, 1H), 6.81−7.44 (m, 9H). EIMS *m*/*z*: 471 (1, M^+), 257 (2), 241 (2), 217 (5). Anal. ($C_{21}H_{19}Cl_4N_3O$) C H N. [The previous fractions gave the *Z* isomer of **7d** as an oil (∼ 5%). ^{1}H NMR ($CDCl_3$): δ 2.40 (m, 2H), 4.10 (m, 1H), 4.65 (m, 1H), 5.63 (m, 1H)].

(*E*)-1-(2,4-Difluorobenzylideneaminoxy)-1-(2,4-difluorophenyl)-2-(1*H*-imidazol-1-yl)ethan Hydrochloride (7e)·HCl. The compound was prepared from **17**·HCl and 2,4-difluorobenzaldeyde by following the general procedure. Compound **7e**·HCl was a white solid (45%); mp 179 °C. ^{1}H NMR (DMSO-d_6): δ 4.82 (m, 2H), 5.86 (t, J = 4.8 Hz, 1H), 7.02−7.76 (m, 9H), 8.39 (s, 1H). EIMS *m*/*z*: 363 (4, M^+-HCl), 283 (2), 207 (5). Anal. ($C_{18}H_{14}ClF_4N_3O$) C H N.

(*E*)-1-[1-(2,4-Difluorophenyl)ethylideneaminoxy)]-1-(2,4-difluorophenyl)-2-(1*H*-imidazol-1-yl)ethan (7f). The compound was prepared from **17**·HCl and 2,4-difluoroacetophenone by following the general procedure. Compound **7f** was purified by flash chromatography on silica using 50% EtOAc in hexane as the eluent and was obtained as an oil (53%). ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H), 4.33 (dd, J = 14.6, 5.9 Hz, 1H), 4.52 (dd, J = 14.6, 3.6 Hz, 1H), 5.73 (dd, J = 5.9, 3.6 Hz, 1H), 6.82−7.37 (m, 9H). EIMS *m*/*z*: 377 (1, M^+), 296 (1), 207 (1), 154 (20). Anal. ($C_{19}H_{15}F_4N_3O$) C H N. [The previous fractions gave the *Z* isomer of **7f** as an oil (8%). ^{1}H NMR ($CDCl_3$): δ 2.15 (s, 3H), 4.18 (dd, J = 14.6, 5.6 Hz, 1H), 4.60 (dd, J = 14.6, 3.2 Hz, 1H), 5.61 (dd, J = 5.6, 3.2 Hz, 1H), 6.80−7.54 (m, 9H)].

(*E*)-1-(2,6-Difluorobenzylideneaminoxy)-1-(2,4-difluorophenyl)-2-(1*H*-imidazol-1-yl)ethan Hydrochloride (7g)·HCl. The compound was prepared from **17**·HCl and 2,6-difluorobenzaldeyde by following the general procedure. Compound **7g**·HCl was a white solid (45%); mp 156−157 °C. ^{1}H NMR (DMSO-d_6): δ 4.80 (m, 2H), 5.86 (t, J = 6.4 Hz, 1H), 7.04−7.76 (m, 9H), 8.36 (s, 1H). EIMS *m*/*z*: 363 (3, M^+-HCl), 283 (1), 207 (4). Anal. ($C_{18}H_{14}ClF_4N_3O$) C H N.

(*E*)-1-[1-(2,5-Difluorophenyl)ethylideneaminoxy)]-1-(2,4-difluorophenyl)-2-(1*H*-imidazol-1-yl)ethan (7h). The compound was prepared from **17**·HCl and 2,5-difluoroacetophenone by following the general procedure. Compound **7h** was purified by flash chromatography on silica using 63% EtOAc in hexane as the eluent and was obtained as an oil (51%). ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H), 4.33 (dd, J = 14.6, 6.1 H, 1 Hz), 4.46 (dd, J = 14.6, 3.5 Hz, 1H), 5.73 (dd, J = 6.1, 3.5 Hz, 1H), 6.82−7.37 (m, 9H). EIMS *m*/*z*: 377 (3, M^+), 296 (2), 207 (7), 154 (100). Anal. ($C_{19}H_{15}F_4N_3O$) C H N. [The previous fractions gave the *Z* isomer of **7h** as an oil (∼5%). ^{1}H NMR ($CDCl_3$): δ 2.16 (s, 1H), 4.13 (m, 1H), 4.62 (m, 1H), 5.65 (m, 1H).]

(*E*)-1-[1-(2,6-Difluorophenyl)ethylideneaminoxy)]-1-(2,4-difluorophenyl)-2-(1*H*-imidazol-1-yl)ethan (7i). The compound was prepared from **17**·HCl and 2,6-difluoroacetophenone by following the general procedure. Compound **7i** was purified by flash chromatography on silica using 50% EtOAc in hexane as the eluent and was obtained as an oil (55%). ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H), 4.33 (dd, J = 14.6, 4.2 Hz, 1H), 4.58 (dd, J = 14.6, 2.7 Hz, 1H), 5.73 (dd, J = 4.2, 2.7 Hz, 1H), 6.76−7.45 (m, 9H). EIMS *m*/*z*: 377 (3, M^+), 296 (7), 207 (6), 154 (100). Anal. ($C_{19}H_{15}F_4N_3O$) C H N. [The previous fractions gave the *Z* isomer of **7i** as an oil (∼5%). ^{1}H NMR ($CDCl_3$): δ 2.17 (s, 1H), 4.10 (m, 1H), 4.60 (m, 1H), 5.63 (m, 1H).]

(*E*)-1-[1-(2-Fluorophenyl)ethylideneaminoxy)-1-(2,4-difluorophenyl)-2-(1*H*-imidazol-1-yl)ethan Hydrochloride (7j)·HCl. The compound was prepared from **17**·HCl and 2-fluoroacetophenone by following the general procedure. Compound **7j**·HCl was a white solid (37%); mp 148 °C. ^{1}H NMR (DMSO-d_6): δ 2.30 (s, 3H), 4.79 (d, J = 5.6 Hz, 2H), 5.83 (t, J = 5.6 Hz, 1H), 7.07−7.73 (m, 10H). EIMS *m*/*z*: 359 (2, M^+), 278 (1), 207 (5). Anal. ($C_{18}H_{15}ClF_3N_3O$) C H N.

(*E*)-1-[1-(4-Fluorophenyl)ethylideneaminoxy)]-1-(2,4-difluorophenyl)-2-(1*H*-imidazol-1-yl)ethan (7k). The compound was prepared from **17**·HCl and 4-fluoroacetophenone by following the general procedure. Compound **7k** was obtained as a pure oil (34%). ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H), 4.40 (dd, J = 14.6, 4.0 Hz, 1H), 4.55 (dd, J = 14.6, 2.6 Hz, 1H), 5.70 (dd, J = 4.0, 2.6 Hz, 1H), 6.80−7.62 (m, 10H). EIMS *m*/*z*: 359 (3, M^+), 207 (7), 153 (7). Anal. ($C_{19}H_{16}F_3N_3O$) C H N.

(*E*)-1-[1-[4-[2-(4-Morpholinyl)ethoxy]phenyl]methyleneaminoxy]-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethan (7l). Treatment of **16**·HCl with 4-[2′-ethyloxy-*N*-morpholino]benzaldehyde **23**[22] by following the general procedure gave an oily residue, which was purified by flash chromatography on silica (4.7% MeOH in EtOAc). Compound **7l** was an oil (40%). ^{1}H NMR ($CDCl_3$): δ 2.58 (t, J = 4.8 Hz, 4H), 2.81 (t, J = 5.7 Hz, 2H), 3.74 (t, J = 4.8 Hz, 4H), 4.13 (t, J = 5.7 Hz, 2H), 4.28 (dd, J = 14.7, 6.2 Hz, 1H), 4.55 (dd, J = 14.7, 2.9 Hz, 1H), 5.80 (dd, J = 6.2, 2.9 Hz, 1H), 6.90−7.81 (m, 10H), 8.16 (s, 1H). EIMS *m*/*z*: 431 (1, M^+-58), 375 (10), 175 (3), 114 (6). Anal. ($C_{24}H_{26}Cl_2N_4O_3$) C H N.

(*E*)-1-[1-[4-[2-(4-Morpholinyl)ethoxy]phenyl]ethylideneaminoxy]-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)-ethan (7m). Treatment of **16**·HCl with 4-[2′-ethyloxy-*N*-morpholino]acetophenone **24**[24] by following the general procedure gave compound **7m** as a pure oil (70%). ^{1}H NMR ($CDCl_3$): δ 2.33 (s, 3H), 2.58 (t, J = 4.7 Hz, 4H), 2.80 (t, J = 5.5 Hz, 2H), 3.74 (t, J = 4.7 Hz, 4H), 4.12 (t, J = 5.5 Hz, 2H), 4.29 (dd, J = 14.6, 5.7 Hz, 1H), 4.56 (dd, J = 14.6, 3.0 Hz, 1H), 5.80 (dd, J = 5.7, 3.0 Hz, 1H), 6.79−7.55 (m, 10H). EIMS *m*/*z*: 389 (1, M^+-114), 241 (1), 176 (1), 114 (8). Anal. ($C_{25}H_{28}Cl_2N_4O_3$) C H N.

(*E*)-1-[1-[4-[2-(4-Morpholinyl)ethoxy]phenyl]methyleneaminoxy]-1-(2,4-difluorophenyl)-2-(1*H*-imidazol-1-yl)-ethan (7n). Treatment of **17**·HCl with **23**[24] by following the general procedure gave compound **7n** as a pure oil (52%). ^{1}H NMR ($CDCl_3$): δ 2.61 (m, 4H), 2.81 (m, 2H), 3.74 (m, 4H), 4.13 (m, 2H), 4.28 (m, 1H), 4.55 (m, 1H), 5.70 (m, 1H), 6.83−8.17 (m, 10H), 8.16 (s, 1H). EIMS *m*/*z*: 343 (15, M^+-114), 114 (7). Anal. ($C_{24}H_{26}F_2N_4O_3$) C H N.

(*E*)-1-[1-[4-[2-(4-Morpholinyl)ethoxy]phenyl]ethylideneaminoxy]-1-(2,4-difluorophenyl)-2-(1*H*-imidazol-1-yl)ethan (7o). Treatment of **17**·HCl with **24**[24] by following the general procedure gave compound **7o** as a pure oil (52%). ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H), 2.58 (t, J = 4.6 Hz, 4H), 2.82 (t, J = 5.6 Hz, 2H), 3.74 (t, J = 4.6 Hz, 4H), 4.13 (t, J = 5.6 Hz, 2H), 4.38 (dd, J = 14.6, 5.6 Hz, 1H), 4.54 (dd, J = 14.6, 3.6 Hz, 1H), 5.72 (dd, J = 5.6, 3.6 Hz, 1H), 6.79−7.55 (m, 10H). EIMS *m*/*z*: 357 (1, M+1 −114), 114 (12). Anal. ($C_{25}H_{28}F_2N_4O_3$) C H N.

1-[(1-(2,4-Dichorophenyl)ethylideneaminoxy)]-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)]-2-(1*H*-imidazol-1-yl)ethan (8a). Treatment of **16**·HCl with 1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethan-1-one **10** by following the general procedure gave compound **8a** as a pure oil (27%). ^{1}H NMR ($CDCl_3$): δ 4.36 (dd, J = 14.8, 6.4 Hz, 1H), 4.56 (dd, J = 14.8, 3.6 Hz, 1H), 5.23 (s, 2H), 5.65 (dd, J = 6.4, 3.6 Hz, 1H), 6.80−8.04 (m, 12H). EIMS *m*/*z*: 474 (1, M^+-Cl), 253 (11), 241 (2), 175 (100), 161 (3), 82 (55). Anal. ($C_{22}H_{17}Cl_4N_5O$) C H N.

1-[(1-(2,4-Difluorophenyl)ethylideneaminoxy)]-1-(2,4-difluorophenyl)-2-(1*H*-imidazol-1-yl)]-2-(1*H*-imidazol-1-yl)ethan (8b). Treatment of **17**·HCl with 1-(2,4-difluorophenyl)-2-(1H-imidazol-1-yl)ethan-1-one **11** by following the general procedure gave compound **8b** as a pure oil (40%). ^{1}H NMR ($CDCl_3$): δ 4.40−4.50 (m, 2H), 5.23 (s, 2H), 5.77 (m, 1H), 6.70−7.40 (m, 12H). EIMS *m*/*z*: 443 (1, M-1), 223 (2), 219 (1), 207 (2), 143 (1), 128 (2), 82 (5). Anal. ($C_{22}H_{17}F_4N_5O$) C H N.

1-(2,4-Dichlorophenyl)propan-1-ol (19) and 1-(2,4-Dichlorophenyl)butan-1-ol (20). 2,4-Dichlorobenzaldehyde **18** (5.0 g, 28.57 mmol) was dissolved in dry Et_2O (60 mL) and cooled to 0 °C under Ar. Ethylmagnesium bromide (40 mL, 3.0 M in Et_2O) was added dropwise at 0 °C. The resulting mixture was stirred for 24 h at room temperature, and then, NH_4Cl(aq) was added. After aqueous workup, crude **19** was obtained as an oil. Crystallization of **19** by hexane gave a pure solid; mp 48−50 °C (5.57 g, 95%). ^{1}H NMR ($CDCl_3$): δ 0.97 (t, J = 7.2 Hz, 3H), 1.73 (m, 2H), 4.99 (t, J = 6.4 Hz, 1H) 7.14−7.50 (m, 3H). EIMS *m*/*z*: 205 (1, M^+), 177 (69), 161 (1). Anal. ($C_9H_{10}Cl_2O$) C H N. Treatment of **18** with propylmagnesium bromide (2 M in Et_2O) in the conditions for **19** gave **20** as a pure solid; mp 38−40 °C (56%). ^{1}H NMR ($CDCl_3$): δ 0.96 (t, J = 7.4 Hz, 3H), 1.60 (m, 4H), 5.10 (t, J = 5.2 Hz, 1H), 7.25−7.53 (m, 3H). EIMS *m*/*z*: 219 (1, M^+), 177 (6), 160 (3). Anal. ($C_{10}H_{12}Cl_2O$) C H N.

1-(2,4-Dichlorophenyl)propan-1-one (21)[21] and 1-(2,4-Dichlorophenyl)butan-1-one (22). 1-(2,4-Dichlorophenyl)-propan-1-ol **19** (1.0 g, 4.88 mmol) was dissolved in acetone (25 mL) and cooled to 0 °C. Jones reagent (1.5 mL) was added dropwise, and the reaction mixture was stirred for 30 min in these conditions. The mixture was diluted with H_2O (15 mL) and extracted with EtOAc (25 mL), and after workup, 0.92 g (93%) of **21**[21] was obtained as a pure oil. Treatment of **20** in the above conditions gave **22**[22] as a pure oil (90%).

Antifungal Susceptibility Studies. Susceptibility testing was performed by the broth microdilution method. For yeasts, MIC values were determined by the broth microdilution technique in accordance with NCCLS reference document M27-A.[30] Microdilution panels were prepared containing 2-fold dilutions of the drugs in 0.1 mL of medium, ranging from 0.001 to 128 μg/mL. Starting inocula were adjusted by the spectrophotometric method to 10^6 CFU/mL. Then, the adjusted yeast suspensions were diluted 1:10 with medium and microtiter plates were inoculated with 10 μL of this dilution, to obtain a final inoculum of approximately 10^4 yeast cells per mL. The inoculated plates were incubated at 35 °C without agitation for 24 h in a humid atmosphere. Following incubation and after agitation with a microtiter plate shaker for 5 min, plates were read visually with the aid of a reading mirror and spectrophotometrically with an automatic plate reader (IEMS, Labsystems, Helsinki, Finland) set at 450 nm. MIC values were defined as the lowest concentration of the antifungal agent that prevents any discernible growth, approximately 90% reduction of growth as compared with drug-free control wells.

For filamentous fungi, susceptibility testing was performed as described[31] in RPMI-2% glucose medium. To induce conidia formation, filamentous fungi and dermatophytes were grown on Sabouraud dextrose agar slants at 27 °C until they were judged to have formed maximal numbers of conidia. Then, fungal cultures were covered with 1 mL of sterile saline containing 0.1% Tween 80 and spores were washed off by gently probing the colonies with the tip of a pipet. Finally, the suspension was vortexed for 10 s to break up clumps of cells and filtered through a 4-fold layer of sterile gauze. The number of conidia was counted by using a hemocytometer, adjusted to 10^6 conidia/mL and stored at −70 °C in small lots until required. MIC values were determined by performing microdilution tests as described above for yeasts but using double dilutions of drugs from 0.25 to 128 μg/mL. Stock conidia suspensions were diluted with medium to obtain the final desired inoculum size of approximately 10^4 conidia/mL. Inoculum quantitation was performed by plating dilutions of the conidia on SAB agar to determine the viable number of CFU/mL. Plates were incubated at 35 °C and read as soon as growth became visible in control wells, using a microplate mirror. MIC values were defined as the lowest concentration of the antifungal agent that inhibited development of visible growth.

Fungicidal Activity. MFC values were determined by subculturing 10 and 100 μL of broth from the drug-free control well, the first well containing growth and each clear well on agar Sabouraud plates. To ensure that there was no antifungal agent carry-over, broth samples were centrifuged and resuspended in antifungal agent-free medium. MFC values were defined as the lowest concentration of the drug expressed in μg/mL that killed ≥99.9% of the initial inoculum.

Computational Details. In all calculations, the Discover program and the CVFF force field were used;[32] the parameters for the iron atom of heme were defined in accordance with a described procedure.[33] An RMS derivative of 0.1 was selected as the convergence criterion, and a distance-dependent dielectric constant equal to four was selected. The sequences of P450 14-α-sterol demethylase from *M. tuberculosis* and that of the analogous enzyme from *C. albicans* (*Candida* P450DM) were aligned through the program Clustalw;[34] then, the residues that are within 7 Å around the fluconazole, **9**, in the crystallographic structure 1EA1 of enzyme from *M. tuberculosis* were substituted with those of enzyme from *C. albicans* (see Table 2). The chimeric enzyme thus obtained complexed with **9** was minimized starting with a tether force of 50 kcal/Å^2 on the backbone, followed by a complete relaxation of whole structure. The complexes with oxiconazole **6** and with compounds **7l**,**m** were minimized in the same manner, but the heme and the imidazole ring were fixed during the calculation, and a 20 ps molecular dynamics simulation at 300 °K was performed before the minimization.

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