1-[(3-Aryloxy-3-aryl)propyl]-1*H*-imidazoles, New Imidazoles with Potent Activity against *Candida albicans* and Dermatophytes. Synthesis, Structure−Activity Relationship, and Molecular Modeling Studies

Giuseppe La Regina,[†] Felicia Diodata D'Auria,[§] Andrea Tafi,*[,‡] Francesco Piscitelli,[†] Stefania Olla,[‡] Fabiana Caporuscio,[‡] Lucia Nencioni,[§] Roberto Cirilli,[#] Francesco La Torre,[#] Nadja Rodrigues De Melo,[||] Steven L. Kelly,[||] David C. Lamb,[||] Marino Artico,[†] Maurizio Botta,[‡] Anna Teresa Palamara,[§] and Romano Silvestri*[,†]

Dipartimento di Studi Farmaceutici, Istituto Pasteur—Fondazione Cenci Bolognetti, Sapienza Università di Roma, Piazzale Aldo Moro 5, I-00185 Roma, Italy, Dipartimento di Scienze di Sanità Pubblica, Sezione di Microbiologia Farmaceutica, Sapienza Università di Roma, Piazzale Aldo Moro 5, I-00185 Roma, Italy, Dipartimento Farmaco Chimico Tecnologico, Università di Siena, Polo Scientifico Universitario San Miniato, Via Aldo Moro 2, I-53100 Siena, Italy, Dipartimento del Farmaco, Istituto Superiore di Sanità, Viale Regina Elena 299, I-00161 Roma, Italy, and Institute of Life Science, Swansea Medical School, Grove Building, Swansea University, Swansea SA2 8PP, Wales, U.K.

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New 1-[(3-aryloxy-3-aryl)propyl]-1*H*-imidazoles were synthesized and evaluated against *Candida albicans* and dermatophytes in order to develop structure−activity relationships (SARs). Against *C. albicans* the new imidazoles showed minimal inhibitory concentrations (MICs) comparable to those of ketoconazole, miconazole, and econazole, and were more potent than fluconazole. Several derivatives (**10**, **12**, **14**, **18**−**20**, **24**, **28**, **29**, **30**, and **34**) turned out to be potent inhibitors of *C. albicans* strains resistant to fluconazole, with MIC values less than 10 μg/mL. Against dermatophytes strains, compounds **20**, **25**, and **33** (MIC $\leq$ 5 μg/mL) were equipotent to ketoconazole, econazole, and miconazole. SARs of imidazoles **10**−**44** were rationalized with reasonable accuracy by a previously developed quantitative pharmacophore for antifungal agents.

Introduction

New chemotherapeutic agents useful for treating widespread fungal infections are urgently needed. Invasive mycoses have dramatically increased over the past 2 decades. Widespread reports of invasive infections are often associated with the growing use of anti-AIDS drugs to combat the HIV infection and also with the use of immunosuppressant agents in bone marrow and solid-organ transplantation, treatment of cancer, and other invasive procedures.[1–3] *Candida* and *Aspergillus* species (spp.) are primarily responsible for invasive fungal diseases, as well as for nosocomial infections. *Candida albicans* accounts for the majority of *Candida* infections.[2,4] Moreover, infections caused by other *Candida* spp., such as *C. glabrata* and *C. parapsilosis*, are spreading because they are inherently resistant to the current antifungal drugs.[5] Superficial mycosis are caused by the same *Candida* spp. and dermatophytes that may be responsible for life-threatening illness in debilitated people.[5]

Antifungal drugs fall into five major classes: azoles, polyenes, allylamines, thiocarbamates, and fluoropyrimidines.[6] The azole class is commonly used to treat *Candida* infections. The azoles inhibit the fungal cytochrome P450-dependent 14α-lanosterol demethylase ($P450_{14DM}$, CYP51),[a] which catalyzes the removal of the 14-methyl group (C-32) of lanosterol through three successive monooxygenation reactions in the fungal ergosterol biosynthesis pathway.[7] The N-3 atom of the azole ring binds to the ferric atom in the heme prosthetic group, thus preventing the binding of lanosterol. The efficacy of azoles depends on the strength of the binding to heme iron as well as the affinity of the N-1 substituent for the protein of the cytochrome.[8] The selective inhibition of $P450_{14DM}$ results in the reduction of the biosynthesis of ergosterol, thus causing lanosterol and 14-methylsterols accumulation and subsequent growth inhibition.[7]

Ketoconazole (**1**), itraconazole (**2**), econazole (**3**), miconazole (**4**), and fluconazole (**5**) are well established anti-*Candida* drugs (Chart 1). Voriconazole (**6**) is a new azole approved for the treatment of esophageal candidiasis; ravuconazole (**7**) is undergoing clinical trials; posaconazole (**8**) is already on the market. The therapeutic use of these drugs is often accompanied by problems of drug resistance, unwanted side effects, and limited biovailability.[9] For example, **5** shows limited spectrum of activity and selects for rapid drug resistance against *Candida* spp. The major drawback of **2** is its poor oral bioavailability. Continuing problems of antifungal therapy are still the high rate of mortality in the treatment of systemic candidemia[10] and the emergence of drug resistance in chronic patients.[11,12] The urgent need for new antifungal drugs has prompted intensive research worldwide.

* To whom correspondence should be addressed. For A.T. (on molecular modeling): phone, +39 0577 23 43 13; fax, +39 0577 23 43 33; e-mail, tafi@unisi.it.. For R.S.: phone, +39 06 4991 3800; fax, +39 06 491 491; e-mail, romano.silvestri@uniroma1.it.

[†] Istituto Pasteur—Fondazione Cenci Bolognetti, Sapienza Università di Roma.

[§] Sezione di Microbiologia Farmaceutica, Sapienza Università di Roma.

[‡] Università di Siena.

[#] Istituto Superiore di Sanità.

[||] Swansea University.

[a] Abbreviations: CYP450, fungal cytochrome P450; $P450_{14DM}$ and CYP51, fungal cytochrome P450 dependent 14α-lanosterol demethylase; NCCLS, National Committee for Clinical Laboratory Standards; ATCC, American Type Culture Collection; QC, quality control strain; MOD3, a computational model developed by us; UNA, enzyme heme moiety; HY1 and HY2, hydrophobics; RA, aromatic ring; EV1 and EV2, excluded volumes.

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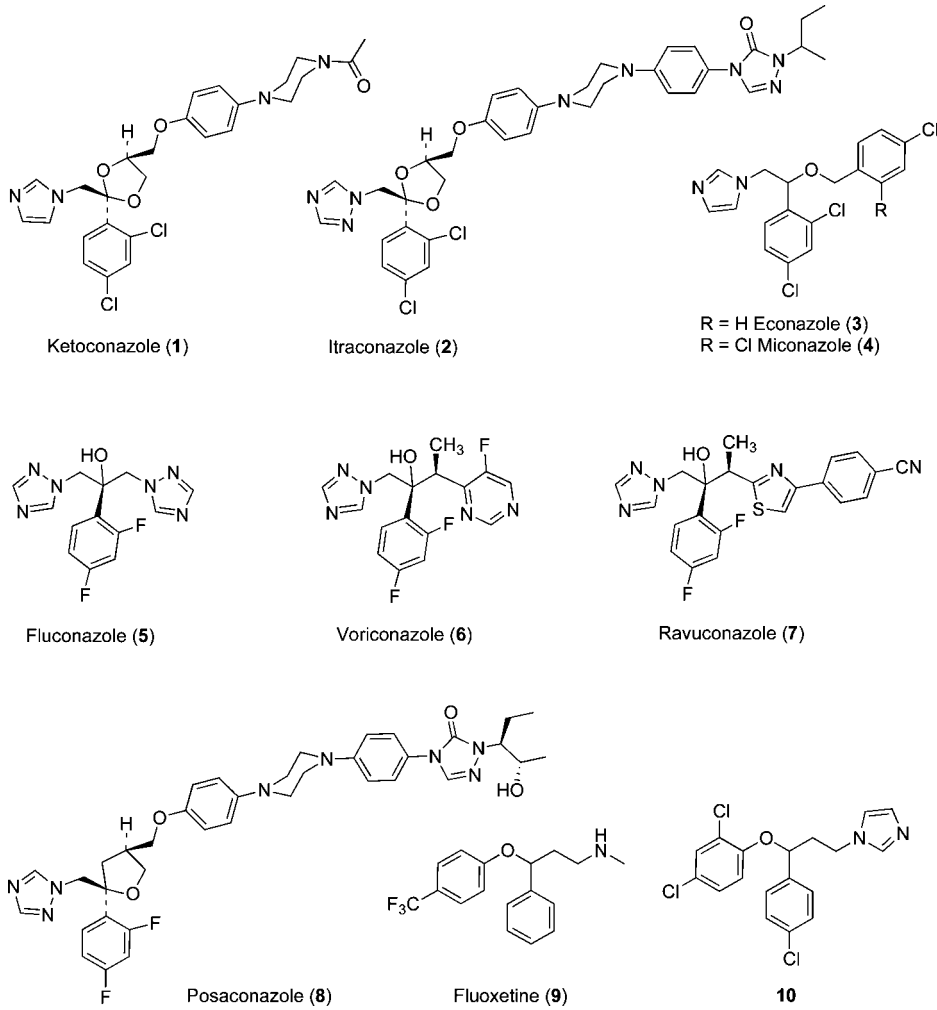
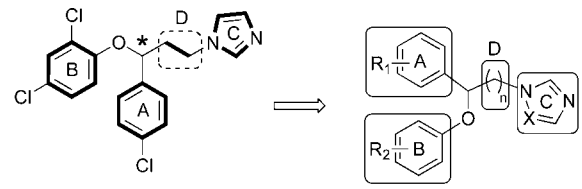
Chart 1. Known and New Azole Antifungal Agents



In our previous work we have described the discovery of new anti-*Candida* agents designed by replacing the methylamino terminus of fluoxetine (**9**) with the imidazole ring.[13] The new imidazoles showed potent anti-*Candida* activity superior to those of **4** and other antifungal agents of clinical interest. Several derivatives were less cytotoxic than the reference compounds, including **5**. As expected,[14] the anti-*Candida* activity was positively affected by the introduction of chlorine atoms, and 1-[3-(2,4-dichlorophenoxy)-3-(4-chlorophenyl)propyl]-1*H*-imidazole (**10**) was found to be the most potent tested derivative. Surprisingly, introducing unconventional substituents for the azole class, such as the methyl group, also furnished potent antifungal agents.[13]

To develop structure−activity relationships (SARs) studies, we dissected the lead structure **10** into four sections: (A) the phenyl ring, (B) the phenoxy group, (C) the imidazole ring, and (D) the alkyl chain (Chart 2). Using this model, we designed and synthesized new derivatives **11**, **15**−**28**, **30**−**37**, and **39**−**50** in order to (i) evaluate different substitutions/positions at phenyls (A) and (B); (ii) replace (C) with a triazole nucleus, and (iii) change the length of (D). We separated the enantiomers of the highly active racemates **13** and **14** to evaluate the role of the chiral carbon. Finally, molecular modeling studies were performed to correlate structure to activity in terms of superposition onto a quantitative pharmacophoric model previously developed for antifungal agents active against *C. albicans*.[15]

Chart 2. Structure of **10** Dissected in Four Sections for the SAR Study and General Structure of New Derivatives **11**, **15**−**28**, **30**−**37**, and **39**−**50**

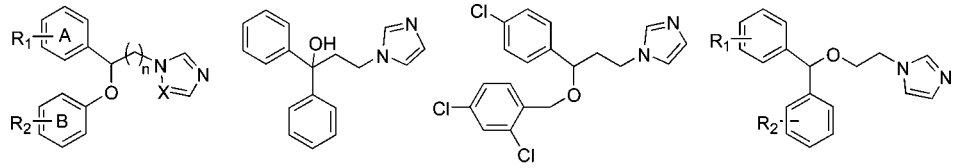


R_1 = H, 4-Cl, 4-F, 4-Me, 4-Me, 2,4-Cl_2; R_2 = H, 2-Cl, 4-Cl, 4-Me, 4-Et, 4-i-Pr, 4-t-Bu, 2,4-Cl_2, 2,6-Cl_2, 3.5-Cl_2, 2,4-Me_2; n = 1-4; X = CH, N.

Chemistry

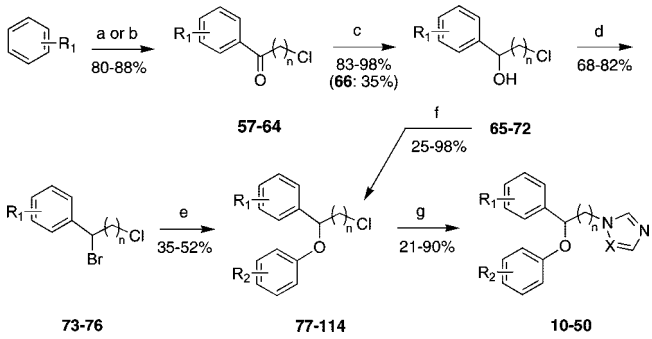
Compounds **10**−**47** were prepared from 1-aryl-3-chloropropanones **57**−**61** as starting material (Table 1), which were reduced to 1-aryl-3-chloropropanols **65**−**69** with sodium borohydride. Following our previous procedure,[13] we transformed **65**−**68** into the 1-aryl-1-bromo-3-chloropropanes **73**−**76** with phosphorus tribromide. The bromides **73**−**76** were then treated with appropriate phenols in the presence of sodium hydride to afford the corresponding 1-aryloxy-1-aryl-3-chloropropanes. Here, we adopted a more convenient procedure for the synthesis

Table 1. Structure of the Tested Derivatives **10**−**56**



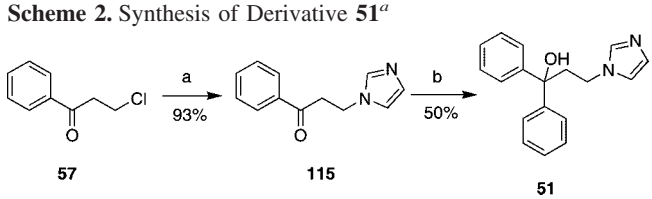
compd	R_1	R_2	X	*n*	compd	R_1	R_2	X	*n*
11	H	H	CH	2	34	4-Me	4-Me	CH	2
12	H	4-Cl	CH	2	35	4-Me	4-Et	CH	2
13	H	4-Me	CH	2	36	4-Me	4-*i*-Pr	CH	2
14	H	2,4-Cl_2	CH	2	37	4-Me	4-*t*-Bu	CH	2
15	H	2,6-Cl_2	CH	2	38	4-Me	2,4-Cl_2	CH	2
16	H	3,5-Cl_2	CH	2	39	4-Me	2,6-Cl_2	CH	2
17	4-Cl	H	CH	2	40	4-Me	3,5-Cl_2	CH	2
18	4-Cl	2-Cl	CH	2	41	4-Me	2-Cl,4-Me	CH	2
19	4-Cl	4-Cl	CH	2	42	4-Me	4-Cl,2-Me	CH	2
20	4-Cl	4-Me	CH	2	43	4-Me	2,4-Me_2	CH	2
21	4-Cl	4-Et	CH	2	44	2,4-Cl_2	2,4-Cl_2	CH	2
22	4-Cl	4-*i*-Pr	CH	2	45	H	2,4-Cl_2	N	2
23	4-Cl	4-*t*-Bu	CH	2	46	4-Cl	2,4-Cl_2	N	2
10	4-Cl	2,4-Cl_2	CH	2	47	4-Me	2,4-Cl_2	N	2
24	4-Cl	2,6-Cl_2	CH	2	48	4-Cl	4-Me	CH	1
25	4-Cl	3,5-Cl_2	CH	2	49	4-Cl	4-Me	CH	3
26	4-Cl	2,4-Me_2	CH	2	50	4-Cl	4-Me	CH	4
27	4-F	H	CH	2	51				
28	4-F	4-Me	CH	2	52				
29	4-F	2,4-Cl_2	CH	2	53	H	H		
30	4-F	2,6-Cl_2	CH	2	54	2,4-Cl_2	H		
31	4-F	3,5-Cl_2	CH	2	55	2,4-Cl_2	4-Cl		
32	4-Me	H	CH	2	56	2,4-Cl_2	2,4-Cl_2		
33	4-Me	4-Cl	CH	2					

Scheme 1. Synthesis of Derivatives **10**−**50**[a]



[a] Reagents and reaction conditions: (a) $ClCO(CH_2)_nCl$, (**57**−**60** *n* = 2, **62** *n* = 1, **63** *n* = 3, **64** *n* = 4), $AlCl_3$, room temp, 2 h; (b) (**61**) (i) (2,4-Cl_2-Ph)COMe, CH_2O, MW 250 W, 5 min, 25−175 °C, then 8 min, 175 °C, argon atmosphere; (ii) HCl, 1 h, 80 °C; (c) $NaBH_4$, THF−H_2O, room temp, 2 h; (d) PBr_3, Et_2O, room temp, 2 h; (e) (R_2-Ph)OH, NaH, DMF, room temp, 60 h; (f) (R_2-Ph)OH, PPh_3, DEAD, THF, room temp, overnight, argon atmosphere; (g) imidazole or 1,2,4-triazole, DMF, reflux, 24 h.

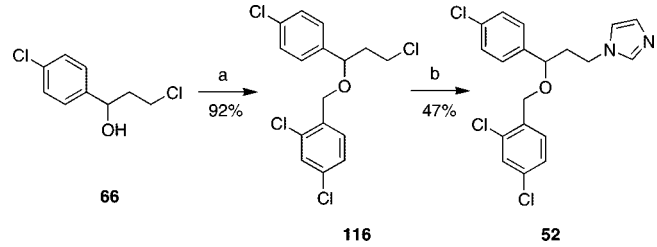
Scheme 2. Synthesis of Derivative **51**[a]



[a] Reagents and reaction conditions: (a) imidazole, DMF, reflux, 24 h; (b) phenylmagnesium bromide, THF, room temp, 72 h, argon atmosphere.

of 1-aryloxy-1-aryl-3-chloropropanes **77**−**111** by treating **65**−**69** with phenol in the presence of triethylposphine and diethyl azadicarboxylate. By the same method, compound **116** was obtained by reacting **66** with 2,4-dichlorobenzyl alcohol. Reaction of **77**−**111** with imidazole or triazole in DMF at reflux furnished derivatives **10**−**47**. Similarly we prepared compounds **48**−**50** starting from the corresponding 1-aryl-3-chloroalkanones **62**−**64**, **115** from **57**, and **52** from **116**. The ketone **115** was transformed into **51** by Grignard's reaction with phenylmagnesium bromide in THF at room temperature for 72 h.

Scheme 3. Synthesis of Derivative **52**[a]



[a] Reagents and reaction conditions: (a) 2,4-Cl_2-$PhCH_2OH$, PPh_3, DEAD, THF, room temp, overnight, argon atmosphere; (b) imidazole, DMF, reflux, 24 h.

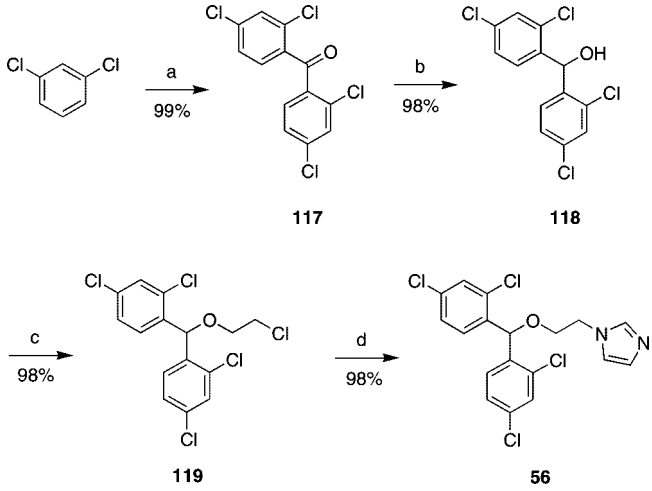
Treatment of **118** with chloroethanol in the presence of sulfuric acid gave the chloride **119**. The latter compound was transformed into the corresponding iodide by heating with sodium iodide, which was treated with imidazole in DMF to give **56** (Schemes 1–4).

The racemates **13** and **14** were separated to give the corresponding pure enantiomers **13a**, **13b** and **14a**, **14b**, respectively, by means of semipreparative HPLC equipped with Chiralcel column (ethanol/DEA, 100:0.1 (v/v), as eluent), according to the previously reported enantioselective HPLC method.[16]

Results and Discussion

Antifungal activity was determined in vitro against 20 strains of *C. albicans* and 10 strains of dermatophytes according to a

Scheme 4. Synthesis of Derivative **56**[a]



[a] Reagents and reaction conditions: (a) (i) $AlCl_3$, CCl_4, 4 h, 40 °C; (ii) $CH_3COOH-H_2SO_4$, 1 h, reflux; (b) $NaBH_4$, $THF-H_2O$, 2 h, reflux; (c) $ClCH_2CH_2OH$, H_2SO_4, 1.5 h, 110 °C; (d) (i) NaI, DMF, 30 min, 100 °C; (ii) imidazole, DMF, 4 h, 100 °C.

microdilution tray as described in the NCCLS document.[17] The compounds were tested at different concentrations ranging from 0.25 to 128 μg/mL. Compounds **1**−**6** were used as reference drugs. The cytotoxicity was evaluated in human histiocytic lymphoma (U937) and chronic myeloid leukemia (K562) cell lines obtained from the American Type Culture Collection (ATCC, Rockville, MD). The significance of differences in mean values was determined by using a paired *t* test (SigmaStat 2.03 statistical software for Windows). *p* values of <0.05 were considered statistically significant (Table 2).

Against *C. albicans* the 4-chloro- (**12**) and 4-methylphenoxy (**13**) derivatives showed minimal inhibitory concentrations (MICs) of 3.3 and 10.2 μg/mL while the corresponding 4-substituted phenyl derivatives **17** and **32** showed MICs of 8.8 μg/mL ($p < 0.001$) and 20.3 μg/mL ($p = 0.012$), respectively. Compound **12** was as active as the reference compounds **1** ($p = 0.28$) and **3** ($p = 0.16$). Given the high antifungal potency displayed by the trichloro derivative **10** (MIC = 2.85 μg/mL), we synthesized the tetrachloro counterpart **44** (which is an isomer of **4**). However, **44** (MIC = 51 μg/mL) was less active than **10** ($p < 0.001$). Surprisingly, this result reproduced that of the 2,4-dichlorophenoxy derivative **14**, which was less active than the corresponding 4-chlorophenoxy **12**.

The 4-chlorophenyl derivatives **17**−**26** were highly potent against *C. albicans*, with differences depending on the number and position of the chlorine atom(s) on the phenoxy group (compare **10** (MIC = 2.85 μg/mL) with **18** (MIC = 7.7 μg/mL, $p < 0.001$), **19** (MIC = 5.5 μg/mL, $p = 0.002$), **24** (MIC = 5.0 μg/mL, $p = 0.09$), and **25** (MIC = 7.7 μg/mL, $p = 0.002$)). The 4-fluorophenyl derivatives **29** and **31** and 4-methylphenyl derivatives **33**−**35**, **38**, and **41** also showed potent anti-*Candida* activity ($p < 0.001$). Replacing the 2,4-dichlorophenoxy group of **10** with the 2,4-dichlorophenylmethoxy (**52**) caused dramatic loss of activity. The potent antifungal activity displayed by the 4-methylphenoxy derivatives **20** (MIC = 3.2 μg/mL), **28** (MIC = 7.0 μg/mL), and **34** (MIC = 4.0 μg/mL) prompted the synthesis of some analogues. However, the antifungal activity seemed to decrease as bulkier alkyl substituents were introduced. Replacing the imidazole of **14**, **10**, and **38** with a triazole nucleus to give **45**, **46**, and **47**, respectively, led to an unexpected loss of activity (MIC > 128 μg/mL). Changing the ethyl chain of **20** ($n = 2$) to propyl (**49**, $n = 3$, MIC = 2.1 μg/mL) retained the antifungal activity of the parent compound. In contrast, the analogues **48** ($n = 1$) and **50** ($n = 4$) were dramatically less active.

The therapeutic indexes (TIs), calculated as the CC_{50}/MIC_{90} ratio, of the highly active compounds **20**, **33**, and **49** on U937 and K562 cells (**20**, 81.3, 56.8; **33**, 42, 42.8; **49**, 87.5, 64.8) were higher than those of the reference compounds **1** and **3**−**5** (**1**, 15.6, 12.8; **3**, 13.5, 8.8; **4**, 30, 20; **5**, 5.1, 6).

In order to establish chirality−activity relationships, the potent racemates **13** and **14** were separated through chiral HPLC to give the corresponding pure enantiomers **13a**, **13b** and **14a**, **14b**. Negligible differences of activity were found between the racemates and (+)-enantiomers (compare **13** with **13a** ($p = 0.36$), and compare **14** with **14a** ($p = 0.03$)) (Table 3). The (−)-enantiomers **13b** ($p = 0.13$) and **14b** ($p = 0.1$) were almost 2- to 3-fold less potent than the parent racemates. These results allowed the evaluation the other compounds as racemates.

The most potent derivatives were tested against a panel of five *C. albicans* strains resistant to **5**, which is a widely used antifungal agent. These compounds were potent inhibitors of the drug-resistant strains, with inhibitory potencies 4- to 18-fold greater than **5** ($p < 0.001$) (Table 4). The majority of these derivatives were also 2- to 4-fold more potent than **6** ($p = 0.02$, $p < 0.001$) against the same drug-resistant strains.

Addition of the azole antifungals **5**, **10**, and **33** to purified *C. albicans* CYP51 gave rise to type II difference spectra (Figure 3S, Supporting Information). Such spectra result from an interaction of the N4 of **5** and the N3 of **10** and **33** with the heme of CYP51, causing a shift toward the low-spin state.[18] Addition of all azole antifungals to purified *C. albicans* CYP51 reveal the spectra to exhibit a peak maximum at 433 nm and a spectral minimum at 412 nm. Determination of binding constant (K_s) values revealed no significant differences following comparison of all compounds, suggesting strong binding and inhibition of CYP51, as is the case for the control azole **5**.

Against a panel of 10 dermatophytes strains, 14 compounds were endowed with potent inhibitory activity with MIC values of <10 μg/mL (Table 5). Among them, the most powerful compounds **20**, **25**, **30**, **33**, and **40** showed MIC values of ≤5 μg/mL, which were close to those of **1**, **3**, and **4**.

Computational Investigations

We recently proposed a quantitative pharmacophore developed using the software Catalyst.[15,19,20] The pharmacophore was constituted by one feature simulating the coordination interaction with the enzyme heme moiety (UNA), two hydrophobics (HY1 and HY2), and one aromatic ring (RA), all possessing identical weights in explaining the antifungal activity of the inhibitors. Two excluded volumes (EV1 and EV2) completed the computational model, named MOD3.

MOD3 was able to estimate and predict with accuracy the antifungal activity of 66 imidazole derivatives (24-compounds training set plus a 42-compounds test set) in terms of their ability to match the pharmacophoric features. MIC values were estimated or predicted by the model within their measured order of magnitude, with the exception of three compounds of the test set, whose antifungal activity was underestimated by a factor of 10.[15] The overall regression of training and test sets compounds based on MOD3 is shown in Figure 1 (empty squares and diamonds, respectively).

The antifungal activity of the most active azoles was explained by MOD3 as a result of the complete matching of those molecules onto the pharmacophore. The weak inhibitory activity of the less potent derivatives was consistently explained

Table 2. Antifungal Activity of Derivatives **10**−**56** and Reference Compounds **1**−**6** against 20 *Candida albicans* Strains

compd	MIC ± SD[a]	MIC_{50}[b]	MIC_{90}[c]	MIC range	QC[d] MIC[e]	MFC ± SD[f]	MFC_{50}[g]	MFC_{90}[h]	MFC range	QC[d] MFC[i]	CC_{50} U937[j]	CC_{50} K562[k]
11	62.7 ± 46.1	32	128	4−128	16	83.2 ± 33.7	64	128	32−128	32	201.4	220.1
12	3.3 ± 1.9	2	4	1−8	4	10.3 ± 8.3	8	16	4−32	32	199.5	256.4
13	10.2 ± 5.04	8	16	4−16	2	15.8 ± 8.9	16	32	8−32	16	140.8	95.9
14	6.07 ± 2.9	8	8	1−16	2	12 ± 4.4	8	16	8−16	8	166.1	121.3
15	46.2 ± 22.7	64	64	2−64	2	64	64	64		32	nd[l]	nd[l]
16	13.8 ± 9.7	16	16	0.5−16	0.5	29.8 ± 20.5	32	64	4−64	4	nd[l]	nd[l]
17	8.8 ± 4.8	8	16	1−16	4	29.2 ± 22.9	16	64	2−64	16	248	186.1
18	7.7 ± 1	8	8	4−8	4	27 ± 7.6	32	32	16−32	32	209	205
19	5.5 ± 2.1	4	8	1−8	4	21.5 ± 10	16	32	8−32	8	327	265
20	3.2 ± 1.2	2	4	1−8	2	10 ± 5.2	8	16	4−16	4	325	227
21	6.5 ± 2	8	8	4−8	8	12.5 ± 6.5	8	16	8−32	16	265	185
22	18.5 ± 8.8	8	32	8−64	8	25.5 ± 8.8	32	32	8−32	32	208	138.2
23	57.1 ± 18.9	64	64	2−64	2	64 ± 0	64	64		64	nd[l]	nd[l]
10	2.85 ± 2.1	2	4	0.5−8	1	5.12 ± 3.5	4	8	1−16	8	172	68.8
24	5.0 ± 4.89	2	8	2−16	1	14.7 ± 20.3	8	16	2−64	4	271	135
25	7.7 ± 5	8	16	1−16	1	16.5−15.1	16	16	4−64	4	180.2	135
26	13.5 ± 6.3	16	16	8−32	8	28 ± 7.1	32	32	16−32	32	nd[l]	nd[l]
27	32.1 ± 19.6	32	64	2−64	8	57.6 ± 34.1	64	64	16−64	32	nd[l]	nd[l]
28	7.0 ± 4.1	4	8	4−16	4	23 ± 9.9	16	32	8−32	32	120	383
29	2.9 ± 1.2	4	4	1−4	0.5	6.9 ± 2.9	8	8	2−16	4	120	74.2
30	36.1 ± 44	8	64	1−128	4	78.9 ± 54.8	32	128	8−128	32	nd[l]	nd[l]
31	8.8 ± 5.8	8	16	1−16	1	11.7 ± 5.5	16	16	4−16	4	160.4	98.1
32	20.3 ± 16.1	16	32	2−32	4	38.4 ± 19.9	32	64	16−64	32	nd[l]	nd[l]
33	2.4 ± 1.4	2	4	1−4	4	12 ± 9.3	8	16	4−32	8	168	171
34	4.0 ± 1.85	4	4	2−8	2	20.5 ± 12.7	16	32	4−32	8	263	191
35	8.7 ± 6.2	4	16	4−16	4	28 ± 7.4	32	32	16−32	8	152.2	136.3
36	16.6 ± 8.75	16	32	8−32	2	32 ± 14.3	32	64	16−64	16	nd[l]	nd[l]
37	52.1 ± 21.9	64	64	2−64	8	58 ± 12.9	64	64	32−64	16	nd[l]	nd[l]
38	3.15 ± 1.3	4	4	2−8	1	8.4 ± 4.2	8	16	4−16	4	150	97
39	42 ± 54.4	8	128	1−128	1	62.9 ± 50.3	32	128	8−128	16	nd[l]	nd[l]
40	11.9 ± 6.3	16	16	1−16	1	34.6 ± 32.9	16	64	8−128	8	160.2	98
41	6.5 ± 2	8	8	4−8	4	24 ± 9.7	32	32	8−32	8	150.8	123.1
42	16 ± 14.5	16	16	4−64	4	58 ± 17	64	64	16−64	16	nd[l]	nd[l]
43	46.5 ± 18.9	32	64	8−64	8	62 ± 8	64	64	32−64	32	nd[l]	nd[l]
44	51 ± 21.04	64	64	8−64	8	64 ± 0	64	64		64	nd[l]	nd[l]
45	>128	>128	>128		32	>128	>128	>128		64	nd[l]	nd[l]
46	>128	>128	>128		32	>128	>128	>128		64	nd[l]	nd[l]
47	>128	>128	>128		32	>128	>128	>128		64	nd[l]	nd[l]
48	22.3 ± 12.6	16	32	4−32	4	32 ± 0					150	99
49	2.1 ± 1.4	2	4	0.5−4	0.03	5.6 ± 3.15	4	8	1−8	0.25	350	259
50	32 ± 0	32	32	32	8	32 ± 0	32	32	32	8	nd[l]	nd[l]
51	114 ± 38.3	128	128	2−128	32	128	128	128		64	nd[l]	nd[l]
52	60.2 ± 15	64	64	4−64	4	62 ± 8	64	64		32	nd[l]	nd[l]
53[m]	78.1 ± 56.5	64	128	32−128	32	229.6 ± 189	128	>256	64 to >256	64	nd[l]	nd[l]
54[m]	46.1 ± 17.8	32	64	16−64	16	158 ± 141	128	>256	64 to >256	32	nd[l]	nd[l]
55[m]	34.35 ± 29	32	64	8−64	16	145 ± 82	128	256	32−256	32	nd[l]	nd[l]
56	>128	>128	>128		32	>128	>128	>128		64	nd[l]	nd[l]
1	5.9 ± 3.1	4	8	2−16	0.06	16.3 ± 5.6	16	32	8−32	0.5	125	102
2	0.5 ± 0.4	0.5	1	0.03 to >1	0−06	>1	>1	>1		0.25	nd[l]	nd[l]
3	4.3 ± 1.7	4	8	2−8	2	15.04 ± 7.4	16	32	8−32	2	108	70
4	3.25 ± 1.6	4	4	1−8	1	12.2 ± 6.2	8	16	4−32	0.5	120	80
5	15.3 ± 23.2	2	64	0.125−64	0.5	>64			>64	8	328	385.2
6	0.89 ± 1	0.25	>1	0.008 to >1	0.015	26 ± 12.8	>16	>16	>16	0.125	nd[l]	nd[l]

[a] MIC ± SD: Arithmetic mean of minimal inhibitory concentration (μg/mL) values ± standard deviation. [b] MIC_{50}: MIC at which 50% of isolates are inhibited. [c] MIC_{90}: MIC at which 90% of isolates are inhibited. [d] QC: Quality control strain. [e] QC: *C. parapsilosis* ATCC22019 MIC values. [f] MFC ± SD: arithmetic mean of minimal fungicidal concentration (μg/mL) values ± standard deviation. When MIC/MFC ratio is lower than three double dilutions, the drug is regarded as fungicidal. [g] MFC_{50}: MFC required to cause 99% reduction of surviving cells in 50% of isolates. [h] MFC_{90}: MFC required to cause 99% reduction of surviving cells 90% of isolates. [i] QC: *C. parapsilosis* ATCC22019 MFC values. [j] CC_{50}: drug concentration (μM) required to reduce the human histiocytic lymphoma U937 cell viability by 50%. [k] CC_{50}: drug concentration (μM) required to reduce chronic myeloid leukemia K562 cell viability by 50%. [l] nd, no data. [m] Tested as nitrate.

Table 3. Antifungal Activity of Pure Enantiomers **13a**, **13b**, **14a**, and **14b** against 20 *Candida albicans* Strains[a]

compd	optical activity	MIC ± SD	MIC_{50}	MIC_{90}	MIC range	QC MIC	MFC ± SD	MFC_{50}	MFC_{90}	MFC range	QC MFC
13	±	9.4 ± 4.16	8	16	4−16	2	13.6 ± 3.7	16	16	8−16	8
13a	+	6.5 ± 5.3	8	8	0.5−16	1	14.9 ± 8.5	16	16	8−32	8
13b	−	28.3 ± 26.3	16	64	2−64	2	51.4 ± 22.5	64	64	8−64	8
14	±	5.3 ± 3.6	8	8	0.06−8	1	11.4 ± 4.3	8	16	8−16	8
14a	+	3.2 ± 2.7	4	4	0.125	0.5	7.4 ± 4.3	8	8	4−16	4
14b	−	11.8 ± 10.7	8	16	1−32	1	28.6 ± 18.4	32	32	8−64	8

[a] Antifungal activities of enantiomers and racemates were evaluated in parallel. Also, see footnotes for Table 2.

as being due to unmatching of one or more pharmacophoric features. Excluded volume spheres essentially contributed to the computational model by preventing overestimation of the less active compounds as a consequence of too advantageous

Table 4. Antifungal Activity of Compounds **10**, **12**, **14**, **17**−**20**, **24**, **28**, **29**, **31**, **33**, and **34** against 5 *C. albicans* Strains Resistant to **5**[a]

compd	MIC ± SD[b]	range	Fe40[c]	QC[d] MIC
10	6.4 ± 2.2	4−8	2	4
12	6.4 ± 1.9	4−8	2	1
14	7.2 ± 1.8	4−8	2	2
17	14.4 ± 3.2	8−16	8	8
18	8.0 ± 0	8	8	8
19	8.0 ± 0	8	4	4
20	5.6 ± 1.9	4−8	2	4
24	6.8 ± 2.7	2−8	2	4
28	9.6 ± 3.6	8−16	4	8
29	5.6 ± 1.9	4−8	2	1
31	12.8 ± 4.4	8−16	8	2
33	3.6 ± 0.9	2−4	2	4
34	4.8 ± 1.8	4−8	4	4
1	20 ± 13.8	8−32	4	0.031
2	16 ± 0	16	0.031	0.031
4	3 ± 1.15	2−4	4	0.125
5	128 ± 0	128	0.25	4
6	16 ± 0	16	0.016	0.031

[a] *C. albicans* strains: AIDS68, AIDS126, De64, 465, Co3. [b] MIC ± SD: arithmetic mean of minimal inhibitory concentration (μg/mL) values ± standard deviation. [c] MIC values of the *C. albicans* Fe40 strain sensitive to **5**. [d] Quality control strain (QC): *C. parapsilosis* ATCC22019.

matching onto the pharmacophore. The predictive ability of MOD3 was evaluated using a small external set of antifungal agents. Successful results of these predictions validated MOD3 as a useful tool for 3D-QSAR analysis of azole antifungal agents.

Initially, in this research MOD3 was applied to test its external predictivity on the large and structurally varied set of compounds **10**−**56**. To this end, the experimental MIC values of this external test set, which covered about 2 orders of magnitude (see Table 2) were converted to μM, normalized, and formulated as $MIC_{Compd}/MIC_{Bifonazole}$.[15] Triazole derivatives **45**−**47** were excluded from this computational analysis. In fact, Catalyst was unable to manage the weak antifungal activity attributed to the presence of the triazole ring.[19,20]

Because the chirality of asymmetric centers was not determined, alternative stereoisomers of all compounds were automatically generated by means of Catalyst 2D-3D sketcher.[20] Moreover, since no experimental data on the biologically relevant conformations of the selected compounds were available, we resorted to a molecular mechanics approach to build their multiconformational models.[21] Accordingly, a local minimum geometry of each compound was built and submitted to a conformational search protocol in Catalyst (see Experimental Section), with the aim of collecting a representative set of conformers.

MOD3 was used to estimate the activity of the new imidazoles. The conformational population of each compound was submitted to the automated Compare/Fit procedure in order to get its own set of ranked mappings. Catalyst then generated the corresponding predicted MIC values. Experimental and predicted MIC values of compounds **10**−**44** and **48**−**56** are reported in Table 6, together with the prediction errors calculated by Catalyst, and depicted in Figure 1 (empty triangles). The majority of MIC values was estimated within its measured order of magnitude, with the exception of compounds **43**, **44**, **52**, and

Table 5. Antifungal Activity of Compounds **10**−**17**, **23**, **25**−**31**, **33**, **34**, **37**, **38**, **40**, **45**−**47**, **52**, and **54** against 10 Dermatophytes Strains after 5 Days of Incubation at 28 °C[a]

compd	MIC ± SD[b]	MIC_{50}[c]	MIC_{90}[d]	MIC range	QC MIC[e]	MFC ± SD[f]	MFC_{50}[g]	MFC_{90}[h]	MFC range	QC MFC[i]
11	24.1 ± 19.03	16	32	0.5−64	16	56.5 ± 21.2	64	64	4−64	32
12	18.4 ± 10	16	32	8−32	4	25.6 ± 8.8	16	32	16−32	16
13	17.2 ± 8.8	16	32	4−32	2	28.8 ± 6.7	32	32	16−32	8
14	9.2 ± 4.3	8	8	4−16	2	28.8 ± 20.9	16	32	16−64	8
15	7.6 ± 1.3	8	8	4−8	2	28.8 ± 6.7	32	32	16−32	8
16	7.2 ± 1.7	8	8	4−8	1	15 ± 2.8	16	16	8−16	4
17	7.2 ± 1.7	8	8	4−8	4	30.4 ± 5	32	32	16−32	32
20	4.6 ± 1.9	4	8	2−8	2	28.8 ± 6.7	32	32	16−32	16
10	9.8 ± 5.2	8	16	2−16	2	11 ± 4	8	16	8−16	8
23	9.2 ± 4.6	8	16	2−16	1	26 ± 17	16	32	16−64	4
25	5 ± 2.2	4	8	4−8	1	10 ± 3.7	8	16	8−16	4
26	32.5 ± 16.1	32	32	4−64	8	58 ± 17	64	64	16−64	32
27	16.1 ± 8.4	16	16	0.5−32	4	28.5 ± 9.9	32	32	4−32	32
28	10 ± 4.3	8	16	4−16	1	16 ± 0	16	169	16	4
29	13.5 ± 4.75	16	16	4−16	4	41 ± 20.7	32	64	8−64	32
30	6.4 ± 2.1	8	8	4−8	1	15 ± 2.8	16	16	8−16	4
31	16.2 ± 8	16	16	2−32	4	28.5 ± 9.9	32	32	4−32	32
33	3.8 ± 1.7	4	4	2−8	4	25.6 ± 8.3	32	32	16−32	16
34	8 ± 3.3	8	8	4−16	2	30.4 ± 5	32	32	16−32	8
37	11.2 ± 4.1	8	16	8−16	1	14.4 ± 3.6	16	16	8−16	4
38	12 ± 4.3	8	16	8−16	1	24 ± 8.5	16	32	16−32	16
40	5.6 ± 3.1	4	8	4−8	1	14.4 ± 3.4	16	16	8−16	8
45	22.4 ± 8.3	16	32	16−32	16	44.8 ± 17.5	32	64	32−64	32
46	10.4 ± 3.8	8	16	8−16	16	137.6 ± 116.3	32	>128	16 to >128	64
47	17.6 ± 8.3	16	32	8−32	8	121.6 ± 122.7	32	>128	32 to >128	32
52	7 ± 5	8	8	2−16	16	17.3 ± 7.9	16	16	8−32	32
54	7 ± 2.4	8	8	2−8	16	7.5 ± 1.63	8	8	4−8	32
1	1.6 ± 1.1	1	2	0.5−4	0.06	6.6 ± 2.7	8	8	1−8	0.5
2	0.14 ± 0.07	0.125	0.25	0.03−0.25	0.06	1.4 ± 0.7	1	2	0.25−2	0.25
3	2.1 ± 1.6	1	4	0.25−4	2	6 ± 2.3	4	8	4−8	2
4	0.9 ± 0.2	1	1	0.5−1	0.06	3 ± 1.07	2	4	2,4	0.5
6	0.03 ± 0.02	0.016	0.06	0.016 ± 0.06	0.01	0.9 ± 0.2	1	1	0.5−1	0.12
9	45 ± 21	32	64	16−64	8	64 ± 0	64	64		64

[a] Strains tested: *Microsporum canis* (2), *Microsporum gypseum* (5), *Trychophyton mentagrophytes* (3). [b] Arithmetic mean of minimal inhibitory concentration (μg/mL) values ± standard deviation (SD). [c] MIC_{50}: MIC at which 50% of isolates are inhibited. [d] MIC_{90}: MIC at which 90% of isolates are inhibited. [e] Quality control strain (QC): *C. parapsilosis* ATCC22019. [i] Quality control strain (QC): *C. parapsilosis* ATCC22019. [f] MFC ± SD: arithmetic mean of minimal fungicidal concentration (μg/mL) values ± SD. When MIC/MFC ratio is lower than three double dilutions, the drug is regarded as fungicidal. [g] MFC_{50}: MFC required to cause 99% reduction of surviving cells in 50% of isolates. [h] MFC_{90}: MFC required to cause 99% reduction of surviving cells in 90% of isolates.

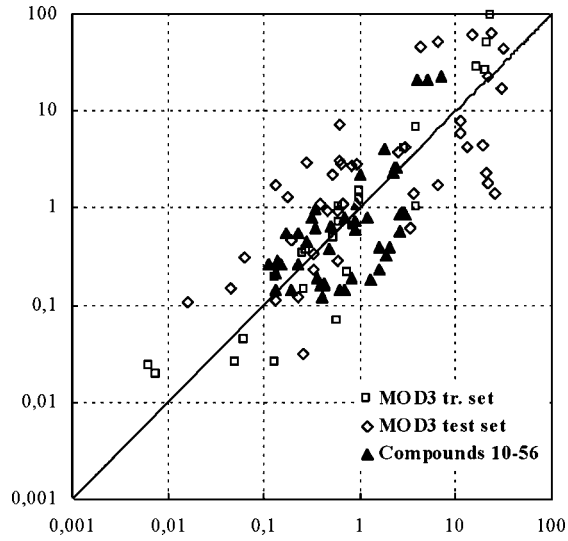


Figure 1. Regression of experimental versus estimated (training set, empty squares)[15] and predicted (test set, empty diamonds; derivatives **10**−**56**, filled triangles) anti-*Candida* activities (MIC values) based on MOD3 (logarithmic scale).

56 whose activity was automatically overestimated by a factor of 15, 15, 24, and >100, respectively. The superposition of **49** and **4** is shown in Figure 2A.

A SAR summary derived from the molecular modeling study and the biological results seemed to clarify the role of (i) the substituents on both phenyl ring and phenoxy group, (ii) the effect of the chain connecting the two aryl groups through the chiral carbon, and (iii) the chain connecting chiral carbon to the azole ring.

As a general rule, each compound matched UNA with the imidazole (ring C), while HY1 was matched alternatively by one of the two aromatic rings (mainly ring B, with the exception of compounds **12**−**16**, which matched HY1 with ring A) or, in the case of compounds **55** and **56**, by the para substituent of one of the two phenyl rings (Figure 2A). Finally, HY2 was matched by the para substituent on the second aromatic ring (mainly ring A, ring B in the case of compounds **12**−**16**). The weak activity of **11**, **51**, and **53**, the only exception to this rule, was explained as due matching only two pharmacophoric features (Figure 2B). The abnormal mapping shown in Figure 2B (compound **11**) was forced by the lack of any substituent on the phenyl rings, which left out the possibility of a regular matching of HY2 with a para substituent. The soundness of the mapping shown in Figure 2B cannot be excluded in principle.[22] Worse rated mappings (the 52nd one in the case of **11**, corresponding to an estimated MIC = 600 μM) showed the superposition of UNA with the imidazole ring.

SARs of compounds **10**−**44** were well explained by MOD3 (see Table 6). This result is shown, on the whole, in Figure 3A, where the mapping of the pharmacophore onto **10** is depicted. In principle, it came out that the presence of at least a hydrophobic para substituent on one of the two aromatic rings was necessary in order to guarantee good antifungal activity. Compound **15**, for instance, possessing a 2,6-dichloro substitution pattern only on ring B, was correctly recognized by MOD3 as a poorly active derivative. Indeed, MOD3 was not directly able to recognize the weak antifungal activity of **23** and **37** with respect to the analogues **19**−**22** and **33**−**36**. The model, actually, assigned pharmacophoric relevance to one hydrophobic para substituent but was not able to size up the probable steric hindrance of the 4-*tert*-Bu group present in both compounds.

Table 6. Experimental and Predicted MIC Values and Prediction Errors of Compounds **10**−**44** and **48**−**56**

	$MIC_{Compd}/MIC_{Bifonazole}$		
compd	experimental	predicted	pred error
10	0.13	0.14	1.1
11	4.0	21	5.2
12	0.19	0.14	−1.3
13	0.61	0.14	−4.3
14	0.31	0.78	2.5
15	2.4	2.6	1.1
16	0.70	0.81	1.2
17	0.50	0.66	1.3
18	0.39	0.16	2.5
19	0.28	0.45	1.6
20	0.17	0.56	3.3
21	0.34	0.98	2.9
22	0.92	1.1	1.2
23	2.9	0.88	−3.3
24	0.23	0.26	1.1
25	0.36	0.19	−1.9
26	0.70	0.14	−4.9
27	1.9	0.32	−6.0
28	0.40	0.12	−3.5
29	0.14	0.29	2.1
30	1.8	4.1	2.4
31	0.42	0.16	−2.7
32	1.2	0.81	−1.5
33	0.13	0.21	1.6
34	0.23	0.56	2.4
35	0.48	0.38	−1.3
36	0.88	0.72	−1.2
37	2.6	0.88	−3.0
38	0.15	0.26	1.7
39	2.0	0.40	−5.2
40	0.43	0.17	−3.3
41	0.34	0.63	1.8
42	0.83	0.19	−4.4
43	2.6	0.17 (0.58)[b]	−15 (−4.4)[b]
44	2.2	0.14 (2.3)[b]	−15 (1.0)[b]
48	1.3	0.18	−7.0
49	0.11	0.26	2.3
50	1.6	0.23	−6.8
51	7.2	23	3.2
52	2.7	0.11 (0.89)[b]	−24 (−3.0)[b]
53	5.0	21	4.2
54	2.3	2.6	1.1
55	1.6	0.4	−3.7
56	128	0.5	>100
BIF[a]	1.0	2.2	2.2
5	0.88	0.59	−1.5
4	0.14	0.27	1.9

[a] Bifonazole. [b] Data of the mapping consistent with the general alignment rule of the whole set of compounds onto MOD3, depicted in Figure 1.

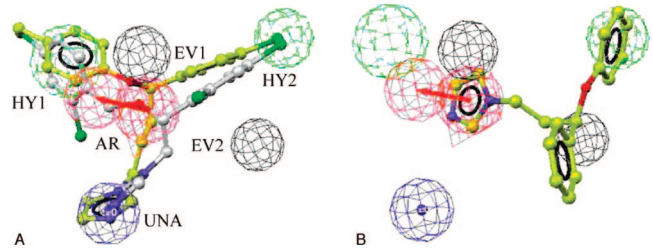


Figure 2. (A) Superposition of MOD3 with **49** (yellow) and **4** (white). Pharmacophore features are color coded: blue for unsubstituted aromatic nitrogen (UNA), red for aromatic ring (RA), green for hydrophobic (HY1 and HY2). In black are shown the excluded volumes (EV1 and EV2). (B) Superposition of MOD3 with **11** (yellow).

As already noticed, the activity of compounds **43** and **44** was overestimated by more than 1 order of magnitude by MOD3 (see Table 6). In both cases, the possible mappings proposed by the software were visually inspected. In fact, in the first mapping Catalyst found both the *p*-methyl groups of **43**

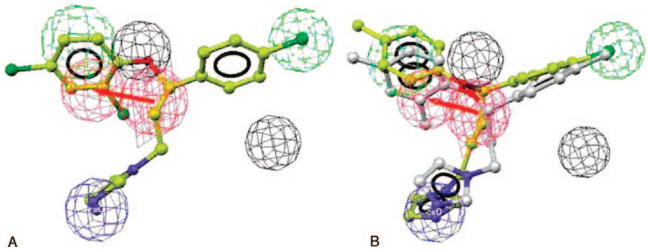


Figure 3. (A) Superposition of MOD3 with **10** (yellow). (B) Superposition of MOD3 with **49** (yellow) and **43** (white). The second mapping of **43** is shown.

superimposable to HY1 and HY2 (estimated MIC equal to 0.17). This alignment, however, forced the alkyl chains out of the general alignment, getting a divergent orientation of the imidazole nitrogen with respect to UNA (results not shown). Conversely, the second mapping (MIC = 0.58) gave pharmacophoric relevance to the methyl group on ring A, which was superimposed to HY2, while HY1 was mapped by the ring B (Figure 3B).

The visual inspection of the different mappings suggested a reasonable explanation for the weak activity of **44**. The first three mappings showed a conformation in which both the *o*-chloro atoms on ring A and the oxygen were very close each another (2.6 Å). In contrast, the fourth mapping gave an estimated MIC of 2.3, which was very close to the experimental value (2.2). The associated conformation (displayed in white in Figure 1SA, Supporting Information) showed these two electronegative atoms mutually distant in 3D space (3.7 Å). Therefore, the double substitution pattern of both phenyl rings, coupled with a not sufficiently long spacing chain between them (two atoms), seemed to act as a conformational restraint causing lower activity. Other details on molecular modeling studies are available in Supporting Information.

Conclusions

We synthesized new 1-[(3-aryloxy-3-aryl)propyl]-1*H*-imidazoles and some related azoles and evaluated the antibiotic activity against *C. albicans* and dermatophytes.[13] Computational analysis allowed the development of SARs for these new imidazoles.[13] Against *C. albicans* 19 derivatives showed MIC values comparable to those of **1**, **3**, and **4** and were more potent than **5**. Several derivatives (**10**, **12**, **14**, **18**−**20**, **24**, **28**−**30**, and **34**) were potent inhibitors of *C. albicans* strains resistant to **5**, with MIC values less than 10 μg/mL. Against dermatophyte strains, compounds **20**, **25**, and **33** (MIC ≤ 5 μg/mL) were equipotent to **1**, **3**, and **4**. Molecular modeling studies were performed applying the previously developed quantitative pharmacophore MOD3,[15] using imidazoles **10**−**44** as a new test to evaluate the predictive capability of that model. The antifungal activities of the imidazoles **10**−**44** were predicted by MOD3 with reasonable accuracy. The highly active compound **49** showed a nice superposition with **4**. MOD3 was also able to explain the weak activity displayed by some derivatives. The results obtained induce us to continue SAR studies on these new imidazoles. The validation of MOD3 suggests it can be used to evaluate virtual chemical libraries in order to discover novel potential azole antifungal leads.

Experimental Section

Chemistry. Microwave-assisted reactions were performed on Discover LabMate (CEM). Melting points (mp) were determined on a Büchi 510 apparatus and are uncorrected. Infrared spectra (IR) were run on a SpectrumOne FT spectrophotometer. Band position and absorption ranges are given in cm^{-1}. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Bruker 200 and 400 MHz FT spectrometers in the indicated solvent. Chemical shifts are expressed in δ units (ppm) from tetramethylsilane. Column chromatography was performed on columns packed with alumina from Merck (70−230 mesh) or silica gel from Merck (70−230 mesh). Aluminum oxide TLC cards from Fluka (aluminum oxide precoated aluminum cards with fluorescent indicator at 254 nm) and silica gel TLC cards from Fluka (silica gel precoated aluminum cards with fluorescent indicator at 254 nm) were used for thin layer chromatography (TLC). Developed plates were visualized by a Spectroline ENF 260C/F UV apparatus. Organic solutions were dried over anhydrous sodium sulfate. Evaporation of the solvents was carried out on Büchi Rotavapor R-210 equipped with Büchi V-850 vacuum controller and Büchi V-700 and V-710 vacuum pumps. Elemental analyses were found to be within ±0.4% of the theoretical values. Compounds **58**, **62**, and **63** were supplied by Aldrich. Compounds prepared as we previously reported: 3-chloropropanones **57**, **59**, and **60**;[13] 3-chloropropanols **65**-**68**;[13] 1-bromo-3-chloropropanes **73**-**76**;[13] 1-[(3-aryloxy-3-aryl)propyl]-1*H*-imidazoles **10**, **12**−**14**, **29**, and **38**;[13] 1-(2-diarylmethoxyethyl)-1*H*-imidazoles **53**−**55**.[23] Daicel Chiralcel column and Carlo Erba HPLC-grade solvents were used for HPLC enantioseparations with Perkin-Elmer 200 lc pump (Rheodyne injector, 1 mL sample loop), HPLC Perkin-Elmer oven, and Perkin-Elmer 290 detector. The signal was acquired and processed by DataApex Clarity software. Specific rotations were measured by Perkin-Elmer polarimeter model 241 equipped with a Na lamp.

General Procedure for the Synthesis of 1-(3-Aryloxy-3-arypropyl)-1*H*-imidazoles 11, 15−28, 30−37, and 39−50. Example. 1-(3-Phenoxy-3-phenylpropyl)-1*H*-imidazole (11). A mixture of **77** (0.54 g, 0.0022 mol) and imidazole (0.49 g, 0.0072 mol) in anhydrous DMF (3.49 mL) was refluxed for 24 h. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was separated, washed with brine, and dried. Removal of the solvent gave a crude product, which was purified on silica gel columm (ethyl acetate as eluent) to afford **11**. Yield 59%, as a yellow oil. ^1H NMR ($CDCl_3$): δ 2.24−2.29 (m, 1H), 2.37−2.45 (m, 1H), 4.08−4.15 (m, 1H), 4.21−4.28 (m, 1H), 4.97−5.00 (dd, J = 3.77 and 9.30 Hz, 1H), 6.79−6.82 (m, 2H), 6.87−6.91 (m, 2H), 7.07 (s, 1H), 7.16−7.20 (m, 2H), 7.26−7.35 (m, 5H), 7.44 ppm (s, 1H). Anal. ($C_{18}H_{18}N_2O$ (278.35)) C, H, N.

1-[3-(2,6-Dichlorophenoxy)-3-phenylpropyl]-1*H*-imidazole (15). **15** was prepared as **11** using **81**. Yield 68%, as a yellow oil. ^1H NMR ($CDCl_3$): δ 2.41−2.50 (m, 1H), 2.70−2.79 (m, 1H), 3.99−4.05 (m, 1H), 4.16−4.22 (m, 1H), 5.39−5.42 (m, 1H), 6.90−6.91 (m, 2H), 7.06 (s, 1H), 7.17 (s, 1H), 7.19 (s, 1H), 7.29−7.32 (m, 3H), 7.35−7.37 (m, 2H), 7.43 ppm (s, 1H). Anal. ($C_{18}H_{16}Cl_2N_2O$ (347.25)) C, H, Cl, N.

1-[3-(3,5-Dichlorophenoxy)-3-phenylpropyl]-1*H*-imidazole (16). **16** was prepared as **11** using **82**. Yield 50%, mp 90−93 °C (from toluene). ^1H NMR ($CDCl_3$): δ 2.24−2.29 (m, 1H), 2.38−2.42 (m, 1H), 4.05−4.12 (m, 1H), 4.15−4.23 (m, 1H), 4.90−4.93 (dd, J = 3.94 and 9.11 Hz, 1H), 6.68−6.69 (m, 2H), 6.88−6.90 (m, 2H), 7.08 (s, 1H), 7.24−7.37 (m, 5H), 7.43 ppm (s, 1H). Anal. ($C_{18}H_{16}Cl_2N_2O$ (347.25)) C, H, Cl, N.

1-[3-(4-Chlorophenyl)-3-phenoxypropyl]-1*H*-imidazole (17). **17** was prepared as **11** using **83**. Yield 78%, as a yellow oil. ^1H NMR ($CDCl_3$): δ 2.20−2.25 (m, 1H), 2.33−2.39 (m, 1H), 4.08−4.15 (m, 1H), 4.22−4.29 (m, 1H), 4.92−4.95 (dd, J = 3.54 and 9.50 Hz, 1H), 6.75−6.78 (m, 2H), 6.88−6.92 (m, 2H), 7.06 (s, 1H), 7.16−7.21 (m, 4H), 7.27−7.30 (m, 2H), 7.43 ppm (s, 1H). Anal. ($C_{18}H_{17}ClN_2O$ (312.80)) C, H, Cl, N.

1-[3-(2-Chlorophenoxy)-3-(4-chlorophenyl)propyl]-1*H*-imidazole (18). 18 was prepared as **11** using **84**. Yield 78%, as a yellow oil. ^1H NMR ($CDCl_3$): δ 2.24−2.30 (m, 1H), 2.44−2.49 (m, 1H), 4.23 (m, 1H), 4.38−4.45 (m, 1H), 4.93−4.96 (dd, J = 3.50 and 9.63 Hz, 1H), 6.55−6.57 (dd, J = 1.04 and 8.27 Hz, 1H), 6.86−6.90 (m, 1H), 6.91 (s, 1H), 7.00−7.05 (m, 1H), 7.09 (s, 1H), 7.25−7.27 (d, J = 8.57 Hz, 2H), 7.33−7.35 (d, J = 8.44 Hz, 2H), 7.38−7.40

(dd, J = 1.59 and 7.89 Hz, 1H), 7.51 ppm (s, 1H). Anal. ($C_{18}H_{16}Cl_2N_2O$ (347.24)) C, H, Cl, N

1-[3-(4-Chlorophenoxy)-3-(4-chlorophenyl)propyl]-1*H*-imidazole (19). 19 was prepared as **11** using **85**. Yield 72%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.20−2.29 (m, 1H), 2.35−2.44 (m, 1H), 4.11−4.19 (m, 1H), 4.22−4.30 (m, 1H), 4.89−4.92 (dd, J = 3.59 and 9.42 Hz, 1H), 6.70−6.72 (d, J = 9.02 Hz, 2H), 6.89 (s, 1H), 7.11 (s, 1H), 7.14−7.17 (d, J = 9.08 Hz, 2H), 7.20−7.22 (d, J = 8.32 Hz, 2H), 7.31−7.34 (d, J = 8.45 Hz, 2H), 7.55 ppm (s, 1H). Anal. ($C_{18}H_{16}Cl_2N_2O$ (347.24)) C, H, Cl, N

1-[3-(4-Chlorophenyl)-3-(4-methylphenoxy)propyl]-1*H*-imidazole (20). 20 was prepared as **11** using **86**. Yield 67%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.15−2.23 (m, 1H), 2.29 (s, 3H), 2.31−2.35 (m, 1H), 4.07−4.13 (m, 1H), 4.23−4.28 (m, 1H), 4.88−4.91 (dd, J = 3.63 and 9.50 Hz, 1H), 6.64−6.67 (m, 2H), 6.88 (s, 1H), 6.96−6.99 (m, 2H), 7.06 (s, 1H), 7.19−7.22 (m, 2H), 7.26−7.29 (m, 2H), 7.42 ppm (s, 1H). Anal. ($C_{19}H_{19}ClN_2O$ (326.83)) C, H, Cl, N.

1-[3-(4-Chlorophenyl)-3-(4-ethylphenoxy)propyl]-1*H*-imidazole (21). 21 was prepared as **11** using **87**. Yield 73%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.17−1.20 (t, J = 7.60 Hz, 3H), 2.19−2.25 (m, 1H), 2.33−2.38 (m, 1H), 2.53−2.38 (m, 1H), 2.53−2.58 (q, J = 7.57, 2H), 4.11−4.17 (m, 1H), 4.24−4.31 (m, 1H), 4.91−4.95 (dd, J = 3.51 and 9.51 Hz, 1H), 6.71 (d, J = 8.64 Hz, 2H), 6.91 (s, 1H), 7.03 (d, J = 8.73 Hz, 2H), 7.09 (s, 1H), 7.24 (d, J = 8.38 Hz, 2H), 7.31 (d, J = 6.69 Hz, 2H), 7.46 ppm (s, 1H). Anal. ($C_{20}H_{21}ClN_2O$ (340,85)) C, H, Cl, N.

1-[3-(4-Chlorophenyl)-3-(4-isopropylphenoxy)propyl]-1*H*-imidazole (22). 22 was prepared as **11** using **88**. Yield 69%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.19 (d, J = 6.82 Hz, 6H), 2.17−2.25 (m, 1H), 2.32−2.41 (m, 1H), 2.78−2.85 (m, 1H), 4.10−4.16 (m, 1H), 4.22−4.30 (m, 1H), 4.91−4.94 (dd, J = 3.03 and 9.35 Hz, 1H), 6.71 (d, J = 8.59 Hz, 2H), 6.90 (s, 1H), 7.04−7.08 (m, 3H), 7.23−7.32 (m, 4H), 7.45 ppm (s, 1H). Anal. ($C_{21}H_{23}ClN_2O$ (354.88)) C, H, Cl, N.

1-[3-(4-*tert*-Butylphenoxy)-3-(4-chlorophenyl)propyl]-1*H*-imidazole (23). 23 was prepared as **11** using **89**. Yield 62%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.27 (s, 9H), 2.19−2.25 (m, 1H), 2.33−2.40 (m, 1H), 4.12−4.19 (m, 1H), 4.23−4.31 (m, 1H), 4.96 (dd, J = 2.70 and 9.16 Hz, 1H), 6.72 (d, J = 8.84 Hz, 2H), 6.91 (s, 1H), 7.12 (s, 1H), 7.23−7.28 (m, 4H), 7.33 (d, J = 8.54 Hz, 2H), 7.59 ppm (s, 1H). Anal. ($C_{22}H_{25}ClN_2O$ (368.91)) C, H, Cl, N.

1-[3-(4-Chlorophenyl)-3-(2,6-dichlorophenoxy)propyl]-1*H*-imidazole (24). 24 was prepared as **11** using **91**. Yield 37%, as a white oil. ^{1}H NMR ($CDCl_3$): δ 2.36−2.44 (m, 1H), 2.68−2.77 (m, 1H), 4.00−4.07 (m, 1H), 4.19−4.24 (m, 1H), 5.36−5.39 (m, 1H), 6.90−6.92 (m, 2H), 7.07 (s, 1H), 7.18 (d, J = 8.07 Hz, 2H), 7.26−7.30 (m, 4H), 7.45 ppm (s, 1H). Anal. ($C_{18}H_{15}Cl_3N_2O$ (381.69)) C, H, Cl, N.

1-[3-(4-Chlorophenyl)-3-(3,5-dichlorophenoxy)propyl]-1*H*-imidazole (25). 25 was prepared as **11** using **92**. Yield 52%, as an oil. ^{1}H NMR ($CDCl_3$): δ 2.17−2.26 (m, 1H), 2.33−2.40 (m, 1H), 4.06−4.12 (m, 1H), 4.16−4.23 (m, 1H), 4.86−4.89 (dd, J = 3.19 and 9.30 Hz, 1H), 6.65−6.67 (m, 2H), 6.87 (s, 1H), 6.91−6.92 (t, J = 1.67 Hz, 1H), 7.08 (s, 1H), 7.17−7.20 (m, 2H), 7.31−7.34 (m, 2H), 7.43 ppm (s, 1H). Anal. ($C_{18}H_{15}Cl_3N_2O$ (381.69)) C, H, Cl, N.

1-[3-(4-Chlorophenyl)-3-(2,4-dimethylphenoxy)propyl]-1*H*-imidazole (26). 26 was prepared as **11** using **93**. Yield 80%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.22 (s, 3H), 2.22−2.28 (m, 1H), 2.29 (s, 3H), 2.30−2.33 (m, 1H), 4.12−4.19 (m, 1H), 4.24−4.31 (m, 1H), 4.99 (dd, J = 3.55 and 9.13 Hz, 1H), 6.37 (d, J = 8.28 Hz, 1H), 6.76 (d, J = 7.72 Hz, 1H), 6.89 (s, 1H), 6.98 (s, 1H), 7.09 (s, 1H), 7.24 (d, J = 8.33 Hz, 2H), 7.31 (d, J = 8.46 Hz, 2H), 7.51 ppm (s, 1H). Anal. ($C_{20}H_{21}ClN_2O$ (340.85)) C,H,Cl,N.

1-[3-(4-Fluorophenyl)-3-phenoxypropyl]-1*H*-imidazole (27). 27 was prepared as **11** using **94**. Yield 31%, as an oil. ^{1}H NMR ($CDCl_3$): δ 2.18−2.24 (m, 1H), 2.33−2.37 (m, 1H), 4.06−4.12 (m, 1H), 4.20−4.26 (m, 1H), 4.93−4.96 (dd, J = 3.68 and 9.44 Hz, 1H), 6.75−6.78 (m, 2H), 6.87−6.90 (m, 2H), 6.97−7.01 (m, 2H), 7.05 (s, 1H), 7.16−7.19 (m, 2H), 7.22−7.27 (m, 2H), 7.41 ppm (s, 1H). Anal. ($C_{18}H_{17}FN_2O$ (296.35)) C, H, F, N.

1-[3-(4-Fluorophenyl)-3-(4-methylphenoxy)propyl]-1*H*-imidazole (28). 28 was prepared as **11** using **95**. Yield 21%, as an oil. ^{1}H NMR ($CDCl_3$): δ 2.16−2.27 (m, 1H), 2.22 (s, 3H), 2.31−2.40 (m, 1H), 4.08−4.14 (m, 1H), 4.21−4.28 (m, 1H), 4.89−4.92 (dd, J = 3.61 and 9.49 Hz, 1H), 6.67 (d, J = 8.49 Hz, 2H), 6.88 (s, 1H), 6.97−7.02 (m, 4H), 7.06 (s, 1H), 7.23−7.26 (m, 2H), 7.43 ppm (s, 1H). Anal. ($C_{19}H_{19}FN_2O$ (310.37)) C, H, F, N.

1-[3-(2,6-Dichlorophenoxy)-3-(4-fluorophenyl)propyl]-1*H*-imidazole (30). 30 was prepared as **11** using **97**. Yield 41%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.37−2.46 (m, 1H), 2.71−2.80 (m, 1H), 4.03−4.10 (m, 1H), 4.17−4.24 (m, 1H), 5.37−5.40 (dd, J = 5.94 and 7.46 Hz, 1H), 6.88−7.01 (m, 3H), 7.07 (s, 1H), 7.17 (s, 1H), 7.19 (s, 1H), 7.26 (s, 1H), 7.32−7.35 (m, 2H), 7.45 ppm (s, 1H). Anal. ($C_{18}H_{15}Cl_2FN_2O$ (365.23)) C, H, Cl, F, N.

1-[3-(3,5-Dichlorophenoxy)-3-(4-fluorophenyl)propyl]-1*H*-imidazole (31). 31 was prepared as **11** using **98**. Yield 43%, mp 78−80 °C (from toluene). ^{1}H NMR ($CDCl_3$): δ 2.20−2.25 (m, 1H), 2.35−2.39 (m, 1H), 4.05−4.11 (m, 1H), 4.17−4.22 (m, 1H), 4.87−4.91 (dd, J = 3.83 and 9.26 Hz, 1H), 6.65−6.68 (m, 2H), 6.87−6.91 (m, 2H), 7.01−7.08 (m, 3H), 7.20−7.26 (m, 2H), 7.43 ppm (s, 1H). Anal. ($C_{18}H_{15}Cl_2FN_2O$ (365.23)) C, H, Cl, F, N.

1-[3-(4-Methylphenyl)-3-phenoxypropyl]-1*H*-imidazole (32). 32 was prepared as **11** using **99**. Yield 51%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.22−2.28 (m, 1H), 2.31 (s, 3H), 2.37−2.41 (m, 1H), 4.07−4.14 (m, 1H), 4.20−4.27 (m, 1H), 4.94−4.98 (dd, J = 3.80 and 9.16 Hz, 1H), 6.77−6.81 (m, 2H), 6.86−6.90 (m, 2H), 7.07 (s, 1H) 7.12−7.25 (m, 6H), 7.46 ppm (s, 1H). Anal. ($C_{19}H_{20}N_2O$ (292.38)) C, H, N.

1-[3-(4-Chlorophenoxy)-3-(4-methylphenyl)propyl]-1*H*-imidazole (33). 33 was prepared as **11** using **100**. Yield 66%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.20−2.28 (m, 1H), 2.32 (s, 3H), 2.37−2.40 (m, 1H), 4.10−4.12 (m, 1H), 4.19−4.21 (m, 1H), 4.88−4.90 (dd, J = 3.94 and 9.29 Hz, 1H), 6.70 (d, J = 2.22 Hz, 1H), 6.72 (d, J = 1.27 Hz, 1H), 6.89 (d, J = 1.07 Hz, 1H), 7.11 (d, J = 0.93 Hz, 1H), 7.13−7.14 (m, 6H), 7.44 ppm (s, 1H). Anal. ($C_{19}H_{19}ClN_2O$ (326.83)) C, H, Cl, N.

1-[-3-(4-Methylphenoxy)-3-(4-methylphenyl)propyl]-1*H*-imidazole (34). 34 was prepared as **11** using **101**. Yield 41%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.17−2.26 (m, 1H), 2.22 (s, 3H), 2.31 (s, 3H), 2.33−2.40 (m, 1H), 4.07−4.13 (m, 1H), 4.20−4.27 (m, 1H), 4.89−4.92 (dd, J = 3.86 and 9.23 Hz, 1H), 6.67−6.71 (m, 2H), 6.89 (s, 1H), 6.95−6.98 (m, 2H), 7.05 (s, 1H), 7.11−7.18 (m, 4H), 7.43 ppm (s, 1H). Anal. ($C_{20}H_{22}N_2O$ (306.41)) C, H, N.

1-[3-(4-Ethylphenoxy)-3-(4-methylphenyl)propyl]-1*H*-imidazole (35). 35 was prepared as **11** using **102**. Yield 67%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.14−1.18 (t, J = 7.58 Hz, 3H), 2.20−2.27 (m, 1H), 2.31 (s, 3H), 2.35−2.39 (m, 1H), 2.50−2.56 (q, J = 7.57 Hz, 2H), 4.07−4.14 (m, 1H), 4.19−4.27 (m, 1H), 4.91−4.94 (dd, J = 3.73 and 9.01 Hz, 1H), 6.72 (d, J = 8.56 Hz, 2H), 6.89 (s, 1H), 7.00 (d, J = 8.57 Hz, 2H), 7.07 (s, 1H), 7.13 (d, J = 7.90 Hz, 2H), 7.18 (d, J = 8.06 Hz, 2H), 7.48 ppm (s, 1H). Anal. ($C_{21}H_{24}N_2O$ (320.43)) C, H, N.

1-[3-(4-Methylphenyl)-3-(4-isopropylphenoxy)propyl]-1*H*-imidazole (36). 36 was prepared as **11** using **103**. Yield 55%, mp 73−76 °C. ^{1}H NMR ($CDCl_3$): δ 1.18 (d, J = 6.89 Hz, 6H), 2.20−2.24 (m, 1H), 2.32 (s, 3H), 2.35−2.39 (m, 1H), 2.77−2.83 (m, 1H), 4.07−4.14 (m, 1H), 4.19−4.27 (m, 1H), 4.92−4.95 (dd, J = 3.78 and 9.16 Hz, 1H), 6.73 (d, J = 8.65 Hz, 2H), 6.90 (s, 1H), 7.04 (d, J = 8.40 Hz, 2H), 7.07 (s, 1H), 7.14 (d, J = 7.99 Hz, 2H), 7.19 (d, J = 8.03 Hz, 2H), 7.46 ppm (s, 1H). Anal. ($C_{22}H_{26}N_2O$ (334.46)) C, H, N.

1-[3-(4-*tert*-Butylphenoxy)-3-(4-methylphenyl)propyl]-1*H*-imidazole (37). 37 was prepared as **11** using **104**. Yield 65%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.25 (s, 9H), 2.32 (s, 3H), 2.35−2.39 (m, 1H), 2.77−2.83 (m, 1H), 4.07−4.14 (m, 1H), 4.19−4.27 (m, 1H), 4.92−4.95 (dd, J = 3.78 and 9.16 Hz, 1H), 6.73 (d, J = 8.65 Hz, 2H), 6.90 (s, 1H), 7.04 (d, J = 8.40 Hz, 2H), 7.07 (s, 1H), 7.14 (d, J = 7.99 Hz, 2H), 7.19 (d, J = 8.03 Hz, 2H), 7.46 ppm (s, 1H). Anal. ($C_{23}H_{28}N_2O$ (348.49)) C, H, N.

1-[3-(2,6-Dichlorophenoxy)-3-(4-methylphenyl)propyl]-1*H*-imidazole (39). 39 was prepared as **11** using **106**. Yield 52%, a a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H), 2.38−2.47 (m, 1H), 2.68−2.88 (m, 1H), 3.99−4.05 (m, 1H), 4.12−4.21 (m, 1H), 5.36−5.39 (m, 1H), 6.85−6.91 (m, 2H), 7.06−7.10 (m, 3H), 7.16 (s, 1H), 7.18 (s, 1H), 7.20−7.24 (m, 2H), 7.47 ppm (s, 1H). Anal. ($C_{19}H_{18}Cl_2N_2O$ (361.27) C, H, Cl, N.

1-[3-(3,5-Dichlorophenoxy)-3-(4-methylphenyl)propyl]-1*H*-imidazole (40). 40 was prepared as **11** using **107**. Yield 48%, as a white oil. ^{1}H NMR ($CDCl_3$): δ 2.21−2.29 (m, 1H), 2.31 (s, 3H), 2.36−2.40 (m, 1H), 4.03−4.08 (m, 1H), 4.13−4.18 (m, 1H), 4.87−4.90 (dd, J = 4.07 and 9.01 Hz, 1H), 6.66−6.69 (m, 2H), 6.86−6.88 (m, 2H), 7.07 (s, 1H), 7.12−7.13 (m, 4H), 7.42 ppm (s, 1H). Anal. ($C_{19}H_{18}Cl_2N_2O$ (361.27)) C, H, Cl, N.

1-[3-(2-Chloro-4-methylphenoxy)-3-(4-methylphenyl)propyl]-1*H*-imidazole (41). 41 was prepared as **11** using **108**. Yield 57%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.20 (s, 3H), 2.22−2.26 (m, 1H), 2.32 (s, 3H), 2.41−2.45 (m, 1H), 4.12−4.18 (m, 1H), 4.34−4.39 (m, 1H), 4.86−4.89 (dd, J = 3.08 and 9.27 Hz, 1H), 6.46−6.48 (dd, J = 1.36 and 8.40 Hz, 1H), 6.77 (d, J = 8.33 Hz, 1H), 6.89 (d, J = 1.24 Hz, 1H), 7.06 (d, J = 0.93 Hz, 1H), 7.14 (d, J = 8.11 Hz, 2H), 7.17−7.19 (m, 3H), 7.43 ppm (s, 1H). Anal. ($C_{20}H_{21}ClN_2O$ (340.85)) C, H, Cl, N.

1-[3-(4-Chloro-2-methylphenoxy)-3-(4-methylphenyl)propyl]-1*H*-imidazole (42). 42 was prepared as **11** using **109**. Yield 54%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.18−2.23 (m, 1H), 2.32 (s, 6H), 2.41−2.46 (m, 1H), 4.09−4.14 (m, 1H), 4.19−4.24 (m, 1H), 4.93−4.95 (dd, J = 1.68 and 5.01 Hz, 1H), 6.41−6.44 (dd, J = 1.66 and 8.75 Hz, 1H), 6.87 (d, J = 1.30 Hz, 2H), 7.07 (d, J = 0.84 Hz, 1H), 7.10 (d, J = 1.03 Hz, 2H), 7.13−7.14 (m, 3H), 7.43 ppm (s, 1H). Anal. ($C_{20}H_{21}ClN_2O$ (340.85)) C, H, Cl, N.

1-[3-(2,4-Dimethylphenoxy)-3-(4-methylphenyl)propyl]-1*H*-imidazole (43). 43 was prepared as **11** using **110**. Yield 83%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.21 (s, 3H), 2.22−2.30 (m, 1H), 2.33 (s, 6H), 2.36−2.43 (m, 1H), 4.10−4.15 (m, 1H), 4.22−4.29 (m, 1H), 4.99 (dd, J = 3.81 and 8.91 Hz, 1H), 6.43 (d, J = 8.28 Hz, 1H), 6.75 (d, J = 8.26 Hz, 1H), 6.90 (s, 1H), 6.96 (s, 1H), 7.08 (s, 1H), 7.14 (d, J = 7.97 Hz, 2H), 7.18 (d, J = 7.99 Hz, 2H), 7.44 ppm (s, 1H). Anal. ($C_{21}H_{24}N_2O$ (320.43)) C, H, N.

1-[3-(2,4-Dichlorophenoxy)-3-(2,4-dichlorophenyl)propyl]-1*H*-imidazole (44). 44 was prepared as **11** using **111**. Yield 90%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.28−2.41 (m, 2H), 4.20−4.26 (m, 1H), 4.35−4.41 (m, 1H), 5.23−5.28 (dd, J = 3.56 and 9.19 Hz, 1H), 6.34 (d, J = 8.86 Hz, 1H), 6.90 (s, 1H), 6.98−7.01 (dd, J = 2.52 and 8.34 Hz, 1H), 7.07 (s, 1H), 7.22−7.24 (dd, J = 1.92 and 8.34 Hz, 1H), 7.35 (s, 1H), 7.38−7.39 (m, 2H), 7.43 ppm (s, 1H). Anal. ($C_{18}H_{14}Cl_4N_2O$ (416.13)) C, H, Cl, N.

1-[3-(2,4-Dichlorophenoxy)-3-phenylpropyl]-1*H*-1,2,4-triazole (45). 45 was prepared as **11** using **80** and triazole. Yield 64%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.51−2.56 (m, 2H), 4.34−4.40 (m, 1H), 4.53−4.60 (m, 1H), 4.95 (t, J = 6.70 Hz, 1H), 6.50 (d, J = 8.87 Hz, 1H), 6.94 (dd, J = 2.50 and 8.84 Hz, 1H), 7.25−7.36 (m, 6H), 7.96 (s, 1H), 7.98 ppm (s, 1H). Anal. ($C_{17}H_{15}Cl_2N_3O$ (348.23)) C, H, Cl, N.

1-[3-(4-Chlorophenoxy)-3-(2,4-dichlorophenoxy)propyl]-1*H*-1,2,4-triazole (46). 46 was prepared as **11** using **90** and triazole. Yield 51%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.48−2.53 (m, 2H), 4.33−4.40 (m, 1H), 4.52−4.60 (m, 1H), 4.95 (t, J = 6.63 Hz, 1H), 6.47 (d, J = 8.84 Hz, 1H), 6.96 (dd, J = 2.57 and 8.83 Hz, 1H), 7.22−7.26 (m, 2H), 7.30−7.36 (m, 3H), 7.96 (s, 1H), 7.99 ppm (s, 1H). Anal. ($C_{17}H_{14}Cl_3N_3O$ (382.68)) C, H, Cl, N.

1-[3-(2,4-Dichlorophenoxy)-3-(4-methylphenyl)propyl]-1*H*-1,2,4-triazole (47). 47 was prepared as **11** using **105** and triazole. Yield 44%, yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H), 2.48−2.54 (m, 2H), 4.33−4.39 (m, 1H), 4.51−4.59 (m, 1H), 4.90−4.94 (m, 1H), 6.51 (d, J = 8.84 Hz, 1H), 6.94 (dd, J = 2.59 and 8.85 Hz, 1H), 7.13−7.18 (m, 4H), 7.34 (d, J = 2.50 Hz, 1H), 7.96 (s, 1H), 7.98 ppm (s, 1H). Anal. ($C_{18}H_{17}Cl_2N_3O$ (362.26)) C, H, Cl, N.

1-[2-(4-Chlorophenyl)-2-(4-methylphenoxy)ethyl]-1*H*-imidazole (48). 48 was prepared as **11** using **112**. Yield 46%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.22 (s, 3H), 4.24−4.35 (m, 2H), 5.22−5.25 (m, 1H), 6.64 (d, J = 8.14 Hz, 2H), 6.92 (s, 1H), 6.96 (d, J = 8.17 Hz, 2H), 7.02 (s, 1H), 7.19 (d, J = 8.20 Hz, 2H), 7.31 (d, J = 8.12 Hz, 2H), 7.46 ppm (s, 1H). Anal. ($C_{18}H_{17}ClN_2O$ (312.80)) C, H, Cl, N.

1-[4-(4-Chlorophenyl)-4-(4-methylphenoxy)butyl]-1*H*-imidazole (49). 49 was prepared as **11** using **113**. Yield 60%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.18−2.10 (m, 4H), 2.24−2.25 (m, 3H), 3.95−4.04 (m, 2H), 5.01−5.04 (m, 1H), 6.68 (d, J = 8.56 Hz, 2H), 6.88−6.89 (m, 1H), 6.98−7.00 (m, 2H), 7.07−7.08 (m, 1H), 7.23 (d, J = 8.34 Hz, 2H), 7.28 (d, J = 5.37 Hz, 2H), 7.52 ppm (s, 1H). Anal. ($C_{20}H_{21}ClN_2O$ (340.85)) C, H, Cl, N.

1-[5-(4-Chlorophenyl)-5-(4-methylphenoxy)pentyl]-1*H*-imidazole (50). 50 was prepared as **11** using **114**. Yield 61%, yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.42−1.44 (m, 1H), 1.53−1.58 (m, 1H), 1.78−1.87 (m, 3H), 1.95−1.99 (m, 1H), 2.25 (s, 3H), 3.92−3.96 (t, J = 7.00 Hz, 2H), 5.00−5.03 (m, 1H), 6.69 (d, J = 8.45 Hz, 2H), 6.89 (s, 1H), 6.99 (d, J = 8.56 Hz, 2H), 7.07 (s, 1H), 7.25−7.32 (m, 4H), 7.47 ppm (s, 1H). Anal. ($C_{21}H_{23}ClN_2O$ (354.88)) C, H, Cl, N.

1-(3,3-Diphenyl-3-hydroxypropyl)-1*H*-imidazole (51). A solution of the Grignard reagent phenylmagnesium bromide (0.0054 mol, 1.54 mL of 1.0 M solution in THF) was added dropwise at 0 °C to a solution of **115** (0.98 g, 0.0049 mol) in anhydrous THF (35 mL) under argon stream. The reaction mixture was stirred for 72 h at room temperature under argon atmosphere. The solvent was evaporated, and the residue was diluted with water and extracted with ethyl acetate. The organic layer was separated, washed with brine, and dried. Removal of the solvent gave a crude product, which was purified by silica gel column chromatography (ethyl acetate:ethanol, 9:1, as eluent) to afford **51**. Yield 50% as white crystals, mp 165−168 °C (from ethanol). ^{1}H NMR ($CDCl_3$): δ 2.68−2.73 (m, 2H), 3.88−3.92 (m, 2H), 4.10−4.50 (broad s,1H, disappeared on treatment with D_2O), 6.77 (s, 1H), 6.83 (s, 1H), 7.13 (s, 1H), 7.22−7.24 (m, 2H), 7.30−7.34 (m, 4H), 7.40−7.43 ppm (m, 4H). Anal. ($C_{18}H_{18}N_2O$ (278.36)) C,H,N.

1-[3-(4-Chlorophenyl)-3-(2,4-dichlorobenzyloxy)propyl]-1*H*-imidazole (52). 52 was prepared as **11** using **116**. Yield 47%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.05−2.13 (m, 1H), 2.22−2.29 (m, 1H), 4.03−4.25 (m, 3H), 4.30−4.40 (m, 2H), 6.89 (s, 1H), 7.09 (s, 1H), 7.26−7.30 (m, 3H), 7.36−7.41 (m, 4H), 7.46 ppm (s, 1H). Anal. ($C_{19}H_{17}Cl_3N_2O$ (395.71)) C, H, Cl, N.

1-[2,2-[[Bis-(2,4-dichlorophenyl)]methoxy]ethyl]-1*H*-imidazole (56). A solution of **119** and sodium iodide (0.47 g, 0.0031 mol) in DMF (10 mL) was stirred for 30 min at 100 °C. Imidazole (0.53 g, 0.0078 mol) was added to the mixture, and the mixture was stirred for 4 h at 100 °C. After the mixture was cooled, water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried, and evaporated to give **56** (98%) as a red oil. ^{1}H NMR ($CDCl_3$): δ 3.76−3.79 (t, J = 5.14 Hz, 2H), 4.14−4.17 (t, J = 4.97 Hz, 2H), 5.99 (s, 1H), 6.90 (s, 1H), 6.95 (s, 1H), 6.97 (s, 1H), 7.06 (s, 1H), 7.17 (d, J = 2.09 Hz, 1H), 7.19 (d, J = 2.05 Hz, 1H), 7.38 (d, J = 2.13 Hz, 2H), 7.52 ppm (s, 1H). Anal. ($C_{18}H_{14}Cl_4N_2O$ (416.14)). C, H, Cl, N.

1-(2,4-Dichlorophenyl)-3-chloropropanone (61). A mixture of 1-(2,4-dichlorophenyl)-3-hydroxypropanone (0.1 g, 0.0005 mol) and 37% HCl (0.82 mL) was heated at 80 °C for 1 h. After cooling, the mixture was with diluted chloroform and brine while shaking. The organic layer was separated, washed with saturated solution of sodium hydrogen carbonate and then with brine, and dried. The solvent was evaporated to give **61** (80%) as a brown oil. ^{1}H NMR ($CDCl_3$): δ 3.46 (t, J = 6.47 Hz, 2H), 3.90 (t, J = 6.61 Hz, 2H),

7.37 (dd, J = 1.9 and 8.25 Hz, 2H), 7.47 (d, J = 1.7 Hz, 1H), 7.54 ppm (d, J = 8.33 Hz, 1H).

1-(2,4-Dichlorophenyl)-3-hydroxypropanone (66). In a 10 mL glass vessel was placed 2,4-dichloroacetophenone (1.0 g, 0.005 mol, 0.75 mL,) and 37% formaldehyde (0.30 g, 0.01 mol, 0.8 mL). The vessel was purged with argon, sealed, and placed into the microwave cavity. Microwave irradiation of 250 W was used, the temperature being ramped from 25 to 175 °C. Once this was reached, taking around 5 min, the reaction mixture was held at this temperature for 8 min while stirring. After cooling, reaction mixture was extracted with chloroform; the organic layer was washed with brine, dried, and filtered. Evaporation of the solvent gave a residue that was purified by silica gel column chromatography (dichloromethane as eluent) to furnish **66** (35%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.41 (t, J = 6.09 Hz, 1H), 3.24 (t, J = 5.4 Hz, 2H), 4.02−4.03 (m, 2H), 7.36 (dd, J = 2.3 and J = 8.91 Hz, 1H), 7.48 (d, J = 1.94 Hz, 1H), 7.56 ppm (d, J = 8.36 Hz, 1H).

5-Chloro-1-(4-chlorophenyl)pentan-1-one (64). 5-Chloropentanoyl chloride (8.37 g, 0.054 mol) was added dropwise to an ice-cooled solution of anhydrous aluminum chloride (8.67 g, 0.065 mol) in chlorobenzene (6.08 g, 0.054 mol). The reaction mixture was stirred for 2 h at room temperature. Then the mixture was poured into ice−water and extracted with dichloromethane. The organic layer was washed with brine, dried, and evaporated to give a crude product, which was purified by silica gel column chromatography (dichloromethane as eluent) to afford **64** (88%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.87−1.94 (m, 4H), 2.99−3.03 (t, J = 6.69 Hz, 2H), 3.59, 3.69 (t, J = 6.16 2H), 7.46 (d, J = 8.56 and 2H), 7.91 ppm (d, J = 8.56 Hz, 2H)

1-(2,4-Dichlorophenyl)-3-chloropropanonol (69). Sodium borohydride (0.91 g, 0.024 mol) was added to a solution of **61** (5.2 g, 0.022 mol) in THF (51.36 mL) containing 3.36 mL of water. Then, the mixture was stirred at room temperature for 2 h. Water (60 mL) was carefully added, and the mixture was concentrated to a small volume. After extraction with ethyl acetate, the organic solution was washed with brine, dried, and the solvent was evaporated to give **69** (83%) as an oil. This compound was used as a crude product without further characterization.

1-(4-Chlorophenyl)-2-chloroethanol (70). 70 was prepared as **69** using **62**. Yield 95%, yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.72 (s, 1H), 3.60−3.64 (m, 1H), 3.68−3.75 (m, 1H), 4.89 (d, J = 8.51 Hz, 1H), 7.33−7.38 ppm (m, 4H).

1-(4-Chlorophenyl)-4-chlorobutanol (71). 71 was prepared as **69** using **63**. Yield 98%, yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.62−1.94 (m, 5H), 3.57 (s, 2H), 4.72 (s, 1H), 7.29 (d, J = 8.52 Hz, 2H), 7.33 ppm (d, J = 8.45 Hz, 2H).

1-(4-Chlorophenyl)-5-chloropentanol (72). 72 was prepared as **69** using **64**. Yield 67% as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.41−1.48 (m, 1H), 1.55−1.64 (m, 1H), 1.67−1.74 (m, 1H), 1.76−1.85 (m, 3H), 1.94 (broad s, 1H disappeared on treatment with D_2O), 3.52−3.55 (t, J = 6.63 Hz, 2H), 4.67−4.70 (t, J = 5.20 Hz, 1H), 7.29 (d, J = 8.40 Hz, 2H), 7.34 ppm (d, J = 8.54 Hz, 2H).

General Procedure for the Synthesis of 1-Aryloxy-1-aryl-3-chloroalkanes 77−114. Example. 1-Phenyl-1-phenoxy-3-chloropropane (77). Triphenylphosphine (2.89 g, 0.011 mol) was added to a solution of 1-phenyl-3-chloropropanol (**65**, 1.88 g, 0.011 mol) and phenol (1.04 g, 0.011 mol) in anhydrous THF (64 mL) at room temperature under nitrogen stream. Diethyl azadicarboxylate (DEAD, 1.91 g, 0.011 mol, 40% solution in toluene) was added dropwise, and the reaction mixture was stirred at room temperature under nitrogen atmosphere overnight. The solvent was evaporated to dryness. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and dried. Evaporation of the solvent gave a crude product, which was purified by silica gel column chromatography (dichloromethane as eluent) to give **77** (35%) as a white oil. ^{1}H NMR ($CDCl_3$): δ 2.21−2.28 (m, 1H), 2.43−2.50 (m, 1H), 3.59−3.65 (m, 1H), 3.78−3.84 (m, 1H), 5.36−5.40 (dd, J = 4.43 and 8.58 Hz, 1H), 6.85−6.91 (m, 2H), 7.17−7.21 (m, 1H), 7.26−7.40 ppm (m, 7H).

1-Phenyl-1-(4-chlorophenoxy)-3-chloropropane (78). 78 was prepared as **77** using **65** and 4-chlorophenol. Yield 73%. This sample was identical to that obtained starting from **73**.[13]

1-Phenyl-1-(4-methylphenoxy)-3-chloropropane (79). 79 was prepared as **77** using **65** and 4-methylphenol. Yield 25%. This sample was identical to that obtained starting from **73**.[13]

1-Phenyl-1-(2,4-dichlorophenoxy)-3-chloropropane (80). 80 was prepared as **77** using **65** and 2,4-dichlorophenol. Yield 25%. This sample was identical to that obtained starting from **73**.[13]

1-Phenyl-1-(2,6-dichlorophenoxy)-3-chloropropane (81). 81 was prepared as **77** using **65** and 2,6-dichlorophenol. Yield 74%, as yellow oil. ^{1}H NMR: δ 2.38−2.48 (m, 1H), 2.69−2.78 (m, 1H), 3.42−3.48 (m, 1H), 3.70−3.76 (m, 1H), 5.63−5.67 (t, J = 6.76 Hz, 1H), 6.88−6.92 (t, J = 7.52 Hz, 1H), 7.20 (d, J = 8.01 Hz, 2H), 7.30−7.33 (m, 3H), 7.41−7.44 ppm (m, 2H).

1-(Phenyl)-1-(3,5-dichlorophenoxy)-3-chloropropane (82). 82 was prepared as **77** using **65** and 3,5-dichlorophenol. Yield 44%, as colorless oil. ^{1}H NMR: δ 2.19−2.26 (m, 1H), 2.42−2.49 (m, 1H), 3.56−3.61 (m, 1H), 3.74−3.80 (m, 1H), 5.35−5.39 (dd, J = 4.57 and 8.51 Hz, 1H), 6.79 (d, J = 1.70 Hz, 2H), 6.90−6.91 (t, J = 1.73 Hz, 1H), 7.26−7.40 ppm (m, 5H).

1-(4-Chlorophenyl)-1-phenoxy-3-chloropropane (83). 83 was prepared as **77** using **66** and phenol. Yield 74%, as a white oil. ^{1}H NMR ($CDCl_3$): δ 2.16−2.23 (m, 1H), 2.42−2.49 (m, 1H), 3.59−3.64 (m, 1H), 3.79−3.85 (m, 1H), 5.37−5.40 (dd, J = 4.39 and 8.63 Hz, 1H), 6.85−6.88 (m, 2H), 6.92−6.95 (m, 1H), 7.20−7.26 (m, 2H), 7.31−7.36 ppm (m, 4H).

1-(4-Chlorophenyl)-1-(2-chlorophenoxy)-3-chloropropane (84). 84 was prepared as **77** using **66** and 2-chlorophenol. Yield 67%, as a white oil. ^{1}H NMR ($CDCl_3$): δ 2.20−2.31 (m, 1H), 2.51−2.59 (m, 1H), 3.64−3.70 (m, 1H), 3.89−3.95 (m, 1H), 5.43−5.46 (dd, J = 4.23 and 8.75 Hz, 1H), 6.70−6.76 (m, 1H), 6.85−6.90 (m, 1H), 7.05−7.09 (m, 1H), 7.28−7.38 ppm (m, 5H).

1-(4-Chlorophenyl)-1-(4-chlorophenoxy)-3-chloropropane (85). 85 was prepared as **77** using **66** and 4-chlorophenol. Yield 50%, as a white oil. ^{1}H NMR ($CDCl_3$): δ 2.14−2.21 (m, 1H), 2.42−2.50 (m, 1H), 3.58−3.64 (m, 1H), 3.78−3.85 (m, 1H), 5.32−5.35 (dd, J = 4.56 and 8.62 Hz, 1H), 6.78 (d, J = 8.99 Hz, 2H), 7.17 (d, J = 10.29 Hz, 2H), 7.28−7.36 ppm (m, 4H).

1-(4-Chlorophenyl)-1-(4-methylphenoxy)-3-chloropropane (86). 86 was prepared as **77** using **66** and 4-methylphenol. Yield 62%, as a white oil. ^{1}H NMR: δ 2.17−2.21 (m, 1H), 2.25 (s, 3H), 2.41−2.47 (m, 1H), 3.59−3.64 (m, 1H), 3.79−3.85 (m, 1H), 5.32−5.35 (dd, J = 4.34 and 8.72 Hz, 1H), 6.75 (d, J = 8.56 Hz, 2H), 7.01 (d, J = 8.44 Hz, 2H), 7.32−7.33 ppm (m, 4H).

1-(4-Chlorophenyl)-1-(4-ethylphenoxy)-3-chloropropane (87). 87 was prepared as **77** using **66** and 4-ethylphenol. Yield 56%, as a white oil. ^{1}H NMR ($CDCl_3$): δ 1.18−1.21 (t, J = 7.60 Hz, 3H), 2.15−2.21 (m, 1H), 2.42−2.48 (m, 1H), 2.54−2.60 (q, J = 7.58 Hz, 2H), 3.60−3.66 (m, 1H), 3.80−3.86 (m, 1H), 5.33−5.36 (dd, J = 4.30 and 8.72 Hz, 1H), 6.78 (d, J = 8.57 Hz, 2H), 7.05 (d, J = 8.60 Hz, 2H), 7.33−7.36 ppm (m, 4H).

1-(4-Chlorophenyl)-1-(4-isopropylphenoxy)-3-chloropropane (88). 88 was prepared as **77** using **66** and 4-isopropylphenol. Yield 67%, as a white oil. ^{1}H NMR ($CDCl_3$): δ 1.20 (d, J = 6.93 Hz, 6H), 2.14−2.21 (m, 1H), 2.40−2.48 (m, 1H), 2.80−2.87 (m, 1H), 3.60−3.65 (m, 1H), 3.79−3.85 (m, 1H), 5.33−5.36 (dd, J = 4.27 and 8.76 Hz, 1H), 6.77 (d, J = 8.55 Hz, 2H), 7.07 (d, J = 8.78 Hz, 2H), 7.34−7.36 ppm (m, 4H).

1-(4-Chlorophenyl)-1-(4-*tert*-butylphenoxy)-3-chloropropane (89). 89 was prepared as **77** using **66** and 4-*tert*-butylphenol. Yield 72%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.25 (s, 9H), 2.10−2.19 (m, 1H), 2.37−2.45 (m, 1H), 3.54−3.62 (m, 1H), 3.74−3.81 (m, 1H), 5.27−5.31 (dd, J = 4.21 and 12.46 Hz, 1H), 6.75 (dd, J = 8.72, 2H), 7.20 (d, J = 8.81 Hz, 2H), 7.28−7.31 ppm (m, 4H).

1-(4-Chlorophenyl)-1-(2,4-dichlorophenoxy)-3-chloropropane (90). 90 was prepared as **77** using **66** and 2,4-dichlorophenol. Yield 60%. This sample was identical to that obtained starting from **74**.[13]

1-(4-Chlorophenyl)-1-(2,6-dichlorophenoxy)-3-chloropropane (91). 91 was prepared as **77** using **66** and 2,6-dichlorophenol. Yield 91%, as a white oil. ^{1}H NMR ($CDCl_3$): δ 2.28−2.41 (m, 1H), 2.68−2.76 (m, 1H), 3.40−3.46 (m, 1H), 3.71−3.77 (m, 1H), 5.61−5.65 (t, J = 6.75 Hz, 1H), 6.88−6.93 (m, 1H), 7.18−7.23 (m, 2H), 7.26−7.30 (m, 2H), 7.34−7.38 ppm (m, 2H).

1-(4-Chlorophenyl)-1-(3,5-dichlorophenoxy)-3-chloropropane (92). 92 was prepared as **77** using **66** and 3,5-dichlorophenol. Yield 78%, as a white oil. ^{1}H NMR ($CDCl_3$): δ 2.12−2.21 (m, 1H), 2.39−2.47 (m, 1H), 3.53−3.59 (m, 1H), 3.73−3.79 (m, 1H), 5.33−5.36 (dd, J = 4.51 and 8.60 Hz, 1H), 6.74−6.75 (m, 2H), 6.91−6.92 (m, 1H), 7.23−7.36 ppm (m, 4H).

1-(4-Chlorophenyl)-1-(2,4-dimethylphenoxy)-3-chloropropane (93). 93 was prepared as **77** using **66** and 2,4-dimethylphenol. Yield 45%, as a white oil. ^{1}H NMR ($CDCl_3$): δ 2.13−2.21 (m, 7H), 2.42−2.53 (m, 1H), 3.57−3.70 (m, 1H), 3.80−3.89 (m, 1H), 5.29−5.41 (m, 1H), 6.64−6.57 (m, 1H), 6.76−6.84 (m, 1H), 6.91−7.00 (m, 1H), 7.22−7.37 ppm (m, 4H).

1-(4-Fluorophenyl)-1-phenoxy-3-chloropropane (94). 94 was prepared as **77** using **67** and phenol. Yield 98%, as a white oil. ^{1}H NMR ($CDCl_3$): δ 2.16−2.23 (m, 1H), 2.42−2.50 (m, 1H), 3.58−3.63 (m, 1H), 3.78−3.84 (m, 1H), 5.37−5.40 (dd, J = 4.47 and 8.62 Hz, 1H), 6.84−6.87 (m, 2H), 6.89−6.93 (m, 1H), 7.02−7.06 (m, 2H), 7.19−7.23 (m, 2H), 7.32−7.38 ppm (m, 2H)

1-(4-Fluorophenyl)-1-(4-methylphenoxy)-3-chloropropane (95). 95 was prepared as **77** using **67** and 4-methylphenol. Yield 98%, as a yellow oil. ^{1}H NMR: δ 2.13−2.21 (m, 1H), 2.24 (s, 3H), 2.40−2.48 (m, 1H), 3.57−3.63 (m, 1H), 3.78−3.84 (m, 1H), 5.31−5.35 (dd, J = 4.42 and 8.67 Hz, 1H), 6.73−6.77 (m, 2H), 6.98−7.06 (m, 4H), 7.31−7.37 ppm (m, 2H).

1-(4-Fluorophenyl)-1-(2,4-dichlorophenoxy)-3-chloropropane (96). 96 was prepared as **77** using **67** and 2,4-dichlorophenol. Yield 54%. This sample was identical to that obtained starting from **75**.[13]

1-(4-Fluorophenyl)-1-(2,6-dichlorophenoxy)-3-chloropropane (97). 97 was prepared as **77** using **67** and 2,6-dichlorophenol. Yield 98%, as a white oil. ^{1}H NMR: δ 2.34−2.43 (m, 1H), 2.70−2.78 (m, 1H), 3.42−3.48 (m, 1H), 3.72−3.78 (m, 1H), 5.62−5.67 (t, J = 6.78 Hz, 1H), 6.89−6.93 (m, 1H), 6.97−7.03 (m, 1H), 7.19−7.22 (m, 2H), 7.31−7.35 (m, 1H), 7.37−7.41 ppm (m, 2H).

1-(4-Fluorophenyl)-1-(3,5-dichlorophenoxy)-3-chloropropane (98). 98 was prepared as **77** using **67** and 3,5-dichlorophenol. Yield 98%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.12−2.21 (m, 1H), 2.39−2.48 (m, 1H), 3.53−3.58 (m, 1H), 3.72−3.78 (m, 1H), 5.33−5.36 (dd, J = 4.62 and 8.54 Hz, 1H), 6.74 (d, J = 1.69 Hz, 2H), 6.90−6.91 (m, 1H), 7.03−7.09 (m, 2H), 7.30−7.34 ppm (m, 2H).

1-(4-Methylphenyl)-1-phenoxy-3-chloropropane (99). 99 was prepared as **77** using **68** and phenol. Yield 56%, as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.18−2.23 (m, 1H), 2.33 (s, 3H), 2.43−2.49 (m, 1H), 3.58−3.64 (m, 1H), 3.77−3.83 (m, 1H), 5.33−5.37 (dd, J = 4.51 and 8.50 Hz, 1H), 6.83−6.90 (m, 2H), 7.14−7.21 (m, 3H), 7.24−7.28 (m, 2H), 7.31−7.34 ppm (m, 2H).

1-(4-Methylphenyl)-1-(4-chlorophenoxy)-3-chloropropane (100). 100 was prepared as **77** using **68** and 4-chlorophenol. Yield 70%, as a white oil. ^{1}H NMR ($CDCl_3$): δ 2.16−2.23 (m, 1H), 2.33 (s, 3H), 2.40−2.48 (m, 1H), 3.56−3.61 (m, 1H), 3.75−3.81 (m, 1H), 5.28−5.31 (dd, J = 4.54 and 8.48 Hz, 1H), 6.78 (d, J = 8.98 Hz, 2H), 7.10−7.16 (m, 4H), 7.22−7.26 ppm (m, 2H).

1-(4-Methylphenyl)-1-(4-methylphenoxy)-3-chloropropane (101). 101 was prepared as **77** using **68** and 4-methylphenol. Yield 59%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.19−2.27 (m, 1H), 2.28 (s, 3H), 2.37 (s, 3H), 2.45−2.54 (m, 1H), 3.62−3.68 (m, 1H), 3.81−3.87 (m, 1H), 5.34−5.37 (dd, J = 4.46 and 8.55 Hz, 1H), 6.82 (d, J = 6.62 Hz, 2H), 7.03 (d, J = 8.44 Hz, 2H), 7.19 (d, J = 7.94 Hz, 2H), 7.31 ppm (d, J = 8.06 Hz, 2H).

1-(4-Methylphenyl)-1-(4-ethylphenoxy)-3-chloropropane (102). 102 was prepared as **77** using **68** and 4-ethylphenol. Yield 55%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.16−1.20 (t, J = 7.57 Hz, 3H), 2.17−2.24 (m, 1H), 2.34 (s, 3H), 2.41−2.46 (m, 1H), 2.52−2.58 (q, J = 7.57 Hz, 2H), 3.59−3.65 (m, 1H), 3.78−3.84 (m, 1H), 5.30−5.33 (dd, J = 4.34 and 8.28 Hz, 1H), 6.79 (d, J = 8.34 Hz, 2H), 7.02 (d, J = 8.13 Hz, 2H), 7.16 (d, J = 7.76 Hz, 2H), 7.34 ppm (d, J = 7.32 Hz, 2H).

1-(4-Methylphenyl)-1-(4-isopropylphenoxy)-3-chloropropane (103). 103 was prepared as **77** using **68** and 4-isopropylphenol. Yield 59%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.20 (d, J = 6.87 Hz, 6H), 2.18−2.25 (m, 1H), 2.36 (s, 3H), 2.42−2.49 (m, 1H), 2.79−2.85 (m, 1H), 3.61−3.66 (m, 1H), 3.79−3.85 (m, 1H), 5.31−5.34 (dd, J = 4.29 and 8.47 Hz, 1H), 6.81 (d, J = 8.55 Hz, 2H), 7.07 (d, J = 8.60 Hz, 2H), 7.18 (d, J = 7.64 Hz, 2H), 7.323 ppm (d, J = 4.43 Hz, 2H).

1-(4-Methylphenyl)-1-(4-*tert*-butylphenoxy)-3-chloropropane (104). 104 was prepared as **77** using **68** and 4-*tert*-buthylphenol. Yield 55%, as a white oil. ^{1}H NMR ($CDCl_3$): δ 1.26 (s, 9H), 2.12−2.24 (m, 1H), 2.34 (s, 3H), 2.41−2.49 (m, 1H), 3.59−3.64 (m, 1H), 3.77−3.83 (m, 1H), 5.30−5.33 (dd, J = 4.30 and 8.32 Hz, 1H), 6.80 (d, J = 7.82 Hz, 2H), 7.14 (d, J = 7.45 Hz, 2H), 7.18 (d, J = 11.14 Hz, 2H), 7.26 ppm (d, J = 8.50 Hz, 2H).

1-(4-Methylphenyl)-1-(2,4-dichlorophenoxy)-3-chloropropane (105). 105 was prepared as **77** using **68** and 2,4-dichlorophenol. Yield 50%. This sample was identical to that obtained starting from **76**.[13]

1-(4-Methylphenyl)-1-(2,6-dichlorophenoxy)-3-chloropropane (106). 106 was prepared as **77** using **68** and 2,6-dichlorophenol. Yield 98%, as a white oil. ^{1}H NMR ($CDCl_3$): δ 2.33 (s, 3H), 2.37−2.46 (m, 1H), 2.68−2.77 (m, 1H), 3.44−3.50 (m, 1H), 3.71−3.76 (m, 1H), 5.62−5.66 (t, J = 6.78 Hz, 1H), 6.87−6.91 (t, J = 8.05 Hz, 1H), 7.12 (d, J = 7.90 Hz, 2H), 7.20 (d, J = 8.05 Hz, 2H), 7.31 ppm (d, J = 8.06 Hz, 2H).

1-(4-Methylphenyl)-1-(3,5-dichlorophenoxy)-3-chloropropane (107). 107 was prepared as **77** using **68** and 3,5-dichlorophenol. Yield 82%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.15−2.23 (m, 1H), 2.35 (s, 3H), 2.41−2.49 (m, 1H), 3.54−3.60 (m, 1H), 3.73−3.79 (m, 1H), 5.31−5.35 (dd, J = 4.66 and 8.44 Hz, 1H), 6.77 (d, J = 1.64 Hz, 2H), 6.89−6.90 (t, J = 1.66 Hz, 1H), 7.18 (d, J = 7.98 Hz, 2H), 7.24 ppm (d, J = 8.08 Hz, 2H).

1-(4-Methylphenyl)-1-(2-chloro-4-methylphenoxy)-3-chloropropane (108). 108 was prepared as **77** using **68** and 2-chloro-4-methylphenol. Yield 62%, as a white oil. ^{1}H NMR ($CDCl_3$): δ 2.17−2.28 (m, 1H), 2.21 (s, 3H), 2.33 (s, 3H), 2.49−2.56 (m, 1H), 3.62−3.68 (m, 1H), 3.86−3.92 (m, 1H), 5.34−5.37 (dd, J = 4.31 and 8.60 Hz, 1H), 6.64 (d, J = 8.38 Hz, 1H), 6.81 (d, J = 7.68 Hz, 1H), 7.16 (d, J = 7.46 Hz, 2H), 7.27 (d, J = 7.93 Hz, 2H), 7.35 ppm (s, 1H).

1-(4-Methylphenyl)-1-(2-methyl-4-chlorophenoxy)-3-chloropropane (109). 109 was prepared as **77** using **68** and 2-methyl-4-chlorophenol. Yield 43%, as a white oil. ^{1}H NMR ($CDCl_3$): δ 2.18−2.24 (m, 1H), 2.27 (s, 3H), 2.33 (s, 3H), 2.45−2.50 (m, 1H), 3.57−3.63 (m, 1H), 3.75−3.80 (m, 1H), 5.30−5.33 (dd, J = 4.58 and 8.25 Hz, 1H), 6.55 (d, J = 8.72 Hz, 1H), 6.90−6.92 (dd, J = 2.10 and 8.66 Hz, 1H), 7.08 (d, J = 0.75 Hz, 1H), 7.14 (d, J = 7.88 Hz, 2H), 7.21 ppm (d, J = 7.88 Hz, 2H).

1-(4-Methylphenyl)-1-(2,4-dimethylphenoxy)-3-chloropropane (110). 110 was prepared as **77** using **68** and 2,4-dimethylphenol. Yield 30%, as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 3H), 2.24−2.30 (m, 1H), 2.30 (s, 3H), 2.35 (s, 3H), 2.47−2.51 (m, 1H), 3.62−3.68 (m, 1H), 3.79−3.86 (m, 1H), 5.33−5.36 (dd, J = 4.38 and 8.41 Hz, 1H), 6.57 (d, J = 8.24 Hz, 1H), 6.79 (d, J = 8.06 Hz, 1H), 6.96 (s, 1H), 7.17 (d, J = 7.87 Hz, 2H), 7.27 ppm (d, J = 7.93 Hz, 2H).

1-(2,4-Dichlorophenyl)-1-(2,4-dichlorophenoxy)-3-chloropropane (111). 111 was prepared as **77** using **69** and 2,4-dichlorophenol. Yield 54%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.26−2.41 (m, 2H), 3.72−3.78 (m, 1H), 3.87−3.93 (m, 1H), 5.76−5.79 (dd, J = 3.16 and 9.15 Hz, 1H), 6.54 (d, J = 8.79 Hz, 1H), 7.01−7.04 (dd, J = 0.65 and 8.83 Hz, 1H), 7.22−7.24 (dd, J = 1.48 and 8.41 Hz, 1H), 7.35−7.41 ppm (m, 3H).

1-(4-Chlorophenyl)-1-(4-methylphenoxy)-2-chloroethane (112). 112 was prepared as **77** using **70** and 4-methylphenol. Yield 34%, yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.26 (s, 3H), 3.71−3.76 (m, 1H),

3.84−3.89 (m, 1H), 5.23−5.26 (dd, J = 4.60 and 7.43 Hz, 1H), 6.77 (d, J = 8.57 Hz, 2H), 7.02 (d, J = 8.12 Hz, 2H), 7.36 ppm (s, 4H).

1-(4-Chlorophenyl)-1-(4-methylphenoxy)-4-chlorobutane (113). 113 was prepared as **77** using **71** and 4-methylphenol. Yield 63%, as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.92−2.09 (m, 4H), 2.25 (s, 3H), 3.57−3.66 (m, 2H), 5.07−5.11 (m, 1H), 6.71 (d, J = 8.59 Hz, 2H), 6.99−7.01 (dd, J = 0.61 and 8.71 Hz, 2H), 7.27−7.37 (m, 4H).

1-(4-Chlorophenyl)-1-(4-methylphenoxy)-5-chloropentane (114). 114 was prepared as **77** using **72** and 4-methylphenol. Yield 58%, as a white oil. ^{1}H NMR ($CDCl_3$): δ 1.54−1.58 (m, 1H), 1.67−1.71 (m, 1H), 1.80−1.88 (m, 3H), 1.96−2.01 (m, 1H), 2.25 (s, 3H), 3.54−3.57 (t, J = 6.60 Hz, 2H), 5.04−5.07 (dd, J = 4.81 and 7.65 Hz, 1H), 6.72 (d, J = 8.48 Hz, 2H), 7.00 (d, J = 8.18 Hz, 2H), 7.28−7.36 ppm (m, 4H).

1-(3-Phenyl-3-oxopropyl)-1*H*-imidazole (115). 115 was prepared as **11** using **57**. Yield 93%, white solid, mp 90−94 °C (from cyclohexane). ^{1}H NMR ($CDCl_3$): δ 3.44 (t, J = 6.54 Hz, 2H), 4.43 (t, J = 6.54 Hz, 2H), 6.96−6.97 (m, 1H), 7.02−7.03 (m, 1H), 7.44−7.48 (m, 2H), 7.55−7.60 (m, 2H), 7.89−7.82 ppm (m, 2H).

1-(4-Chlorophenyl)-1-(2,4-dichlorobenzyloxy)-3-chloropropane (116). 116 was prepared as **77** using **62** and 2,4-dichlorobenzylalcool. Yield 92%, as a yellow oil. This compound was used as a crude product without further purification.

Bis(2,4-dichlorophenyl)methanone (117). A solution of 1,3-dichlorobenzene (20.0 g, 0136 mol) in carbon tetrachloride (30 mL) was added dropwise to an ice-cooled solution of anhydrous aluminum chloride (20.0 g, 0.150 mol) in the same solvent (30 mL). The mixture was stirred for 4 h at 40 °C. The mixture was poured into ice−water (150 mL) and extracted with chloroform. The organic layer was washed with water, dried, and evaporated. A mixture of acetic acid (30 mL) and 96% sulfuric acid (10 mL) was added to the mixture and refluxed for 1 h. After cooling, the mixture was poured into ice−water and stirred for 30 min. The precipitate was filtered, washed with water, and then dissolved in chloroform and dried. Removal of the solvent gave **117** (99%) as yellow crystals, mp 75−77 °C (from ethanol). ^{1}H NMR ($CDCl_3$): δ 7.29 (dd, J = 1.98 and 8.31 Hz, 2H), 7.39 (d, J = 1.70 Hz, 2H), 7.41 (d, J = 8.31 Hz, 2H). Lit.[24]

Bis(2,4-dichlorophenyl)methanol (118). Sodium borohydride (1.2 g, 0.0034 mol) was added to a solution of **117** (11.0 g, 0.034 mol) in THF (70 mL) containing 1.7 mL of water. The mixture was stirred at 80 °C for 2 h. After the mixture was cooled, water was carefully added, and the mixture was concentrated to a small volume. After extraction with ethyl acetate, the organic solution was washed with brine and dried, and the solvent was evaporated to give **118** (98%), mp 92−94 °C (from ligroin). ^{1}H NMR ($CDCl_3$): δ 2.52 (d, J = 3.91 Hz, disappeared on treatment with D_2O, 1H), 6.40 (d, J = 3.77 Hz, 1H), 7.21−7.31 (m, 4H), 7.40 (d, J = 1.71 Hz, 2H).

1-[Bis(2,4-dichlorophenyl)]methoxy-2-chloroethane (119). A solution of **118** (1.0 g, 0.0031 mol) in benzene (8 mL) was added dropwise to a solution of 2-chloroethanol (0.37 g, 0.31 mL, 0.0046 mol) in benzene (2 mL) containing 0.05 mL of 96% sulfuric acid. The reaction mixture was stirred for 1.5 h at 110 °C. After cooling, the mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and dried. Removal of the solvent gave **119** (98%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 3.66 (t, J = 5.88 Hz, 2H), 3.81 (t, J = 5.69 Hz, 2H), 6.05 (s, 1H), 7.26 (dd, J = 1.94 and J = 8.41 Hz, 2H), 7.30 (d, J = 8.37 Hz, 2H), 7.40 ppm (d, J = 1.90 Hz, 2H).

Separation of Enantiomers 13a, 13b, 14a, and 14b. Semipreparative HPLC enantioseparations of racemates **13** and **14** to give the corresponding enantiomers **13a**, **13b** and **14a**, **14b** were performed on commercially available Chiralcel OD 250 mm × 10 mm i.d. column (ethanol/DEA, 100:0.1 (v/v), as eluent). The mobile phases were filtered and degassed by sonication immediately before use. The enantiomeric excesses (ee) of the collected enantiomers were >99%. Specific rotations of enantiomers **13a**, **13b**, **14a**, and **14b** were measured in ethanol at 589 nm. The volume of the cell was 1 mL, and the optical path was 10 cm. During the experiments the system was kept at 28 °C. Specific rotation values were in agreement with those previously found.[16]

Material and Methods. Stock drug solutions were prepared in 100% DMSO and further diluted in RPMI 1640 medium (Sigma-Aldrich) buffered at pH 7.0 with 0.165 M MOPS (4-morpholinepropanesulfonic acid) to yield twice the required final strength. Each microdilution well was filled with 0.1 mL of the 2-fold drug concentration. The concentrations assayed ranged from 0.25 to 128 μg/mL. The microdilution trays were sealed and stored at −70 °C.

The antifungal activity was evaluated against 20 *C. albicans* strains freshly isolated from patients suffering oropharyngeal or vaginal disease. Five *C. albicans* strains resistant to fluconazole were also used. Strain AIDS 68 and AIDS 126 were originally isolated from AIDS patients with oropharyngeal candidiasis; both strains were resistant to fluconazole at the time of isolation (MIC > 64 μg/mL). Strain De64 and strain 465 were isolated from recurrent vulvovaginal candidiasis and were resistant to fluconazole. Strain CO23 isolated from a vulvovaginal candidiasis was originally sensitive to fluconazole. It was made resistant by growth in stepwise increasing fluconazole concentrations.

C. albicans ATCC 10261, from the collection of the Institute of Microbiology, was included as internal control strain. All organisms were identified to the spp. level by microscan panels (Baxter). Prior to testing, each isolate was subcultured at least twice on Sabouraud dextrose agar (SDA, BBL Becton Dickinson and Co.) to ensure purity and optimal growth. *C. parapsilosis* ATCC22019 was included as quality control (QC) strain. The yeast inoculum was prepared according to NCCLS protocol[17a] and adjusted to 1000−5000 cells/mL in RPMI 1640 medium. The inoculum size was spectrophotometrically standardized, and also by quantitative plate counts.

Ten clinical isolates of dermatophytes were evaluated (two *Microsporum canis*, five *Microsporum gypseum,* three *Trichophyton mentagrophytes*). All isolates had been identified to the spp. level by standard procedure[25] and had been stored in sterile 0.85% saline at 4 °C. Prior to testing, the isolates were subcultured on potato dextrose agar (PDA, Oxoid), slant and incubated at 28 °C for 7 days or until a good conidiation was produced. The fungal colonies were covered with 3 mL of sterile 0.85% saline, and a suspension was prepared by gently probing the colonies with the tip of a transfer pipet generating a mixture of conidial and hyphal fragments. The mixture was withdrawn and transferred to a sterile tube. Heavy particles were allowed to settle for 3−5 min. The upper suspension density was adjusted with a spectrophotometer (OD_{530}) to a transmittance level of 65−70%. This suspension was diluted 1:50 in the RPMI 1640 medium. Inoculum quantitation was performed according to NCCLS protocol.[17b]

C. parapsilosis ATCC 22019 was included as quality control strain (QC) strain as recommended by the NCCLS procedure. Broth microdilution tests were performed according to NCCLS M27-A2 and NCCLS M38-A protocols for yeast and filamentous fungi, respectively.[17] Each microdilution well containing 0.1 mL of the 2-fold drug concentration was inoculated with 0.1 mL of the inoculum suspension. Drug free control and yeast or dermathopytes free control were included for each microdilution tray. The microdilution trays were incubated at 35 and 28 °C for yeast and dermathophytes, respectively. The MIC end points were read after 48 h of incubation for yeasts and until 7 days of incubation for dermatophytes. The MIC was defined as the lowest drug concentration showing 80% growth inhibition[26] when compared with the growth in the control well. The in vitro minimal fungicidal concentration (MFC) was evaluated as follows: for each *Candida* and dermatophyte isolate, 20 μL aliquots were removed from the MIC well and from wells having higher concentrations. Each aliquot was streaked onto SAB agar plates and incubated at 35 and 28 °C for 48−96 h for *Candida* and dermatophytes, respectively. The MFC was defined as the lowest drug concentration at which less than two colonies grew (99% killing).

Cytotoxicity of tested compounds was evaluated on human histiocytic lymphoma (U937) and chronic myeloid leukemia (K562) cell lines obtained from American Type Culture Collection (ATCC,

Rockville, MD). Cells were plated at 2×10^5/mL concentration in RPMI 1640 medium supplemented with 20% fetal bovine serum (FBS) and antibiotics (100 U/mL penicillin and 100 μg/mL streptomycin). After 2 h the compounds were added at concentrations ranging from 50 to 200 μg/mL. Cells were then incubated at 37 °C and counted at different time points after treatment using the vital dye Trypan Blue (0.02%). The cytotoxicity of the compounds was also performed on U937 and K562 cells by means of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. Briefly, cells were plated in a 96 well-plate at a concentration of 5×10^4/mL in RPMI-1640 without phenol red, supplemented with 20% FBS and antibiotics (100 U/mL penicillin and 100 μg/mLstreptomycin). Two hours after plating, compounds were added at different concentrations ranging from 25 to 100 μg/mL and cells were incubated at 37 °C for 24 h. Then the cells were incubated at 37 °C for 3 h with 1 mg/mL of MTT. After incubation, the remaining water insoluble formazan was solubilized in absolute isopropanol containing 0.1 N HCl. Absorbance of converted dye was measured in an ELISA plate reader at a wavelength of 570 nm. The cytotoxicity of the compounds was calculated as the percentage reduction of the viable cells compared with the drug free control culture. CC_{50} was defined as the drug concentration required for reducing the cell viability by 50%.

C. albicans CYP51 was expressed in HMS174 *Escherichia coli* strain (Novagen) and purified as described previously.[27] Reduced carbon monoxide difference spectra for quantification of cytochrome P450 content was measured and calculated according to the method described by Omura and Sato.[18] Protein quantification was performed by using the bicinchoninic acid assay (Sigma). Spectral studies of azole antifungal binding to purified *C. albicans* CYP51 were performed using a Hitatchi U3010 scanning spectrophotometer, according to the method of Wiggins and Baldwin.[28] Briefly, a baseline was recorded with isolated CYP51 (0.1 nmol of purified CYP51) in both sample and reference cuvettes. Azole antifungals dissolved in dimethyl sulfoxide (DMSO) were added directly to the sample cuvette; the contents were mixed, and after 1 min the spectrum between 500 and 350 nm was recorded. By addition of several increments of test substance, the change in absorbance between the type II peak (420−427 nm) and the corresponding trough (390−410 nm) was related to the concentration of added azole antifungal. The maximum concentration of DMSO used (1% (v/v)) caused no change in the spectrum over the region scanned.

Molecular Modeling. Calculations and graphic manipulations were performed on Silicon Graphic SGI Octane workstation by means of the Catalyst 4.8 software package. General Catalyst's methods have been described in detail elsewhere.[29] The compounds studied here were built using the 2-D and 3-D sketcher of the software. The conformational populations for the pharmacophore generation were built following Catalyst guidelines. Accordingly, the poling algorithm and Catalyst implementation of CHARMm force field were applied to submit each compound to both "fast" and "best" conformational searches. A representative set of conformers was collected by this procedure, within a range of 20 kcal/mol with respect to the global minimum. Alternative stereoisomers were automatically considered during the conformational search, since the chirality of the asymmetric center was not specified. The compounds were fitted to MOD3 pharmacophore using the Catalyst's Compare/Fit procedure. Fast fit method was chosen for each compound. Fast fit is a rigid fit protocol, which finds the optimum fit of a derivative to a hypothesis among all the conformers of the molecule, without performing further energy minimizations on the conformers. According to the Compare/Fit procedure each mapping represented a different 3D alignment between features of the pharmacophore and matching groups of the molecule, possibly shared by some energetically favorable conformations. The first mapping/first conformer output was selected by default as the one giving the predicted MIC value. Prediction errors were calculated by Catalyst as the ratio of predicted MIC values to measured MIC values.

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Supporting Information Available: Addional information on computational investigations. This material is available free of charge via the Internet at http://pubs.acs.org.

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