81. Studies on Antifungal Agents

Part 22

3-Aryl-5-[(aryloxy)alkyl]-3-[(1*H*-imidazol-1-yl)methyl]-2-methylisoxazolidines and Related Derivatives

by **George B. Mullen, Patricia A. Swift, David M. Marinyak, Stanley D. Allen, Jeffrey T. Mitchell, C. Richard Kinsolving,** and **Vassil St. Georgiev***

Department of Organic Chemistry, Pennwalt Corporation, Pharmaceutical Division, Rochester, New York 14623, and Laboratory Animal Research Center, Utah State University, Logan, Utah 84322, USA

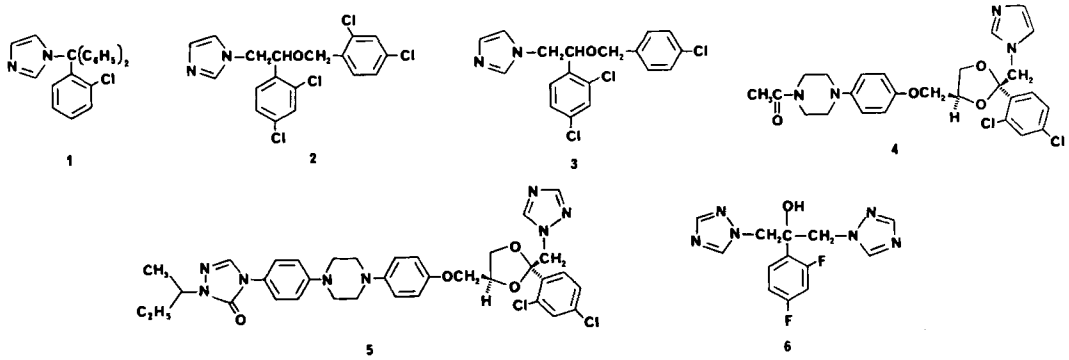
(1.III.88)

The synthesis and antifungal activity of a novel series of 3-aryl-5-[(aryloxy)alkyl]-3-[(1*H*-imidazol-1-yl)-methyl]-2-methylisoxazolidines and related compounds, are discussed. The synthesis of the title compounds was accomplished *via* a 1,3-dipolar cycloaddition of α-substituted ketonitrones with 1-alkenyl phenyl ethers (*Scheme 2* and *3*). The compounds were evaluated for *in vitro* antifungal activity in solid agar cultures against a broad variety of yeast and systemic mycoses and dermatophytes. While antifungal activity was evident throughout the series, in general, derivatives having halogen atom(s) in either or both aryl rings demonstrated the highest potency, especially against *Trichophyton rubrum* and *Candida albicans*. The dichloro analog **20** (PR 967-248) was found to possess the most useful activity. Its minimum inhibitory concentration (*MIC*) values ranged between 0.2 and 2.0 μg/ml, as compared to 0.2–20.0 μg/ml for the standard drug ketoconazole (**4**).

Over the past 25 years, the incidence of invasive fungal infections in man has risen dramatically. Severely immunocompromized patients [1–6], due to underlying diseases such as leukemia or, more recently, acquired immune deficiency syndrome [7], or those undergoing cancer chemotherapy or organ transplantation, are particularly susceptible to these opportunistic fungal infections. Although *Candida* species continue to be the major pathogenic fungi in these patients, cryptococcosis [8], aspergillosis [8], zygomycosis [8], coccidioidomycosis [9–11], paracoccidioidomycosis [12], and chromoblastomycosis [13], among others, have become a growing concern.

Two drugs are predominantly used in the treatment of systemic fungal infections: the polyene antibiotic amphotericin B [5] [14–17] and the azole derivative ketoconazole [5] [11] [12] [18–21]. Both of these drugs suffer from toxic side effects, including hepatotoxicity [21].

Since the introduction to the clinic of the first antifungal imidazoles, clotrimazole (**1**) [22], miconazole (**2**) and econazole (**3**) [23], several other azole derivatives, most notably ketoconazole (**4**) [21] [24], have been successfully developed and marketed as antifungal agents. The latter was the first orally active antifungal agent that was effective against a broad spectrum of systemic and superficial fungal infections [21]. Recently, two new azoles, itraconazole (**5**) [9] [13] [25] [26] and fluconazole (**6**) [27–30] have been introduced into clinical trials. These newer drugs are claimed to be free of the major side effects of ketoconazole (**4**) and to have a better pharmacokinetic profile [31]. However,



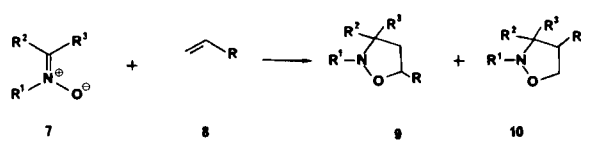
like **4**, they are fungistatic, rather than fungicidal agents. In spite of the introduction of these two new azole derivatives, the number of available drugs with sufficient efficacy to treat an increasing number of life-threatening systemic mycoses is rather limited. There still exists a great need for a more potent, broad-spectrum antimycotic agent with fungicidal properties and reduced side effects [10] [31].

We recognized an opportunity to apply our previous knowledge [32] [33] of 1,3-dipolar species to the synthesis of novel antifungal agents. Specifically, we envisioned that we could prepare a series of heterocyclic azole derivatives *via* the 1,3-dipolar cycloaddition reaction of nitrones (azomethine oxides) to monosubstituted olefins. The resulting isoxazolidine derivatives were expected to exhibit different chemical and biological properties from the known azole antimycotic agents, and would thus provide valuable information for the synthesis of a new generation of antifungal drugs.

The present communication represents part of our studies in this direction [34].

Chemistry. – The 1,3-dipolar cycloaddition of appropriately α-substituted nitrones **7** with monosubstituted olefins **8** results in the preparation of the corresponding isoxazolidines **9** and **10** *(Scheme 1)* [35].

Scheme 1



The 1,3-dipolar cycloaddition, like the *Diels-Alder* reaction, is generally considered to have a concerted mechanism and may be formally treated as an allowed [π^4s + π^2s] process *via* frontier MO theory. The regio- and stereospecificity of the reaction is highly dependent on the structures of the nitrone and the dienophile and involves both electronic and steric factors [35].

The compounds we were interested in preparing are derived from the α-substituted ketonitrones **12**. Nitrones **12**, which exist in the (*E*)-configuration, were prepared by condensation of the appropriate 2-azolylacetophenones **11** [36] with *N*-methylhydroxylamine hydrochloride *(Scheme 2)*. The 1,3-dipolar cycloaddition of nitrones **12** with 1-alkenyl phenyl ethers **13** proceeded in a regiospecific manner giving exclusively the 5-substituted isoxazolidines **14** and **15**. In this case, the corresponding 4-substituted

Scheme 2

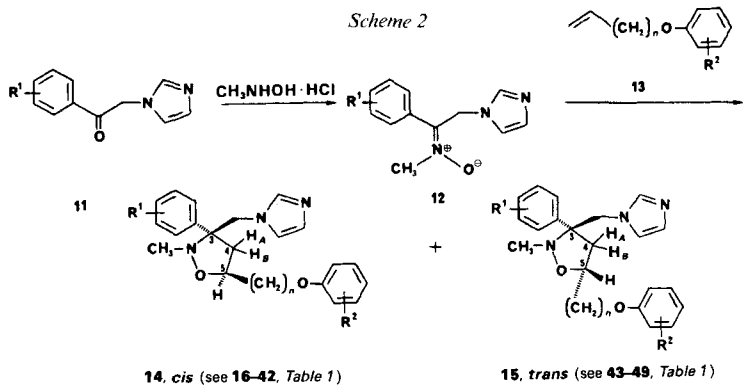


Table 1. *3-Aryl-5-[(aryloxy)alkyl]-3-[(1H-imidazol-1-yl)methyl]-2-methylisoxazolidines*

Compound	R^1	R^2	*n*	M.p. [°]	Recrystallization solvent	Yield [%]	*Method* [a]	Formula	Analyses
16	H	H	1	107–109	i-PrOH	38.4	*A*	$C_{21}H_{23}N_3O_2$	C, H, N
17	H	4-Cl	1	140–142	i-PrOH	35.8	*A*	$C_{21}H_{22}ClN_3O_2$	C, H, Cl, N
18	H	4-F	1	115–117	AcOEt	31.0	*A*	$C_{21}H_{22}FN_3O_2$	C, H, F, N
19	H	4-Cl, 3-CH_3	1	110–120	AcOEt	20.6	*A*	$C_{22}H_{24}ClN_3O_2$	C, H, Cl, N
20	4-Cl	4-Cl	1	126–132	AcOEt	49.4, 63.5	*A*, *B*	$C_{21}H_{21}Cl_2N_3O_2$	C, H, Cl, N
21	4-Cl	4-F	1	121–126	AcOEt	43.0	*A*	$C_{21}H_{21}ClFN_3O_2$	C, H, Cl, F, N
22	4-Cl	4-CH_3O	1	140–145	AcOEt	25.7	*A*	$C_{22}H_{24}ClN_3O_3$	C, H, Cl, N
23	4-Cl	4-CH_3	1	115–123	AcOEt	37.4	*A*	$C_{22}H_{24}ClN_3O_2$	C, H, Cl, N
24	4-Cl	4-AcNH	1	181–186	AcOEt	51.0	*A*	$C_{23}H_{25}ClN_4O_3$	C, H, Cl, N
25	4-Cl	4-CF_3	1	80–83	benzene	47.0	*A*	$C_{22}H_{21}ClF_3N_3O_2$	C, H, Cl, F, N
26	4-Cl	2-NO_2	1	135–138	AcOEt	24.0	*A*	$C_{21}H_{21}ClN_4O_4$	C, H, Cl, N
27	4-Cl	2,4-Cl_2	1	145–148	AcOEt	19.6	*A*	$C_{21}H_{20}Cl_3N_3O_2$	C, H, Cl, N
28	4-Cl	2,6-Cl_2	1	144–148	AcOEt	11.0	*A*	$C_{21}H_{20}Cl_3N_3O_2$	C, H, Cl, N
29	4-F	H	1	162–164	i-PrOH	13.0	*A*	$C_{21}H_{22}FN_3O_2$	C, H, F, N
30	4-F	4-Cl	1	125–127	AcOEt	17.0	*A*	$C_{21}H_{21}ClFN_3O_2$	C, H, Cl, F, N
31	4-F	4-F	1	141–143	AcOEt	6.0	*A*	$C_{21}H_{21}F_2N_3O_2$	C, H, F, N
32	4-CH_3O	4-Cl	1	130–132	AcOEt	37.0	*A*	$C_{22}H_{24}ClN_3O_3$	C, H, Cl, N
33	4-CH_3O	4-CH_3O	1	96–101	AcOEt	48.0	*A*	$C_{23}H_{27}N_3O_4$	C, H, N
34	4-CH_3	4-Cl	1	143–145	AcOEt	24.0	*A*	$C_{22}H_{24}ClN_3O_2$	C, H, Cl, N
35	3-CH_3O	4-Cl	1	92–95	Et_2O	30.0	*B*	$C_{22}H_{24}ClN_3O_3$	C, H, Cl, N
36	3-CH_3	4-Cl	1	122–124	AcOEt	18.0	*B*	$C_{22}H_{24}ClN_3O_2$	C, H, Cl, N
37	4-Cl, 3-CH_3	4-Cl	1	142–145	AcOEt	36.0	*B*	$C_{22}H_{23}Cl_2N_3O_2$	C, H, Cl, N
38	3,4-Cl_2	4-Cl	1	149–151	AcOEt	25.0	*A*	$C_{21}H_{20}Cl_3N_3O_2$	C, H, Cl, N
39	4-Cl	4-Cl	2	103–105	AcOEt	5.0	*A*	$C_{22}H_{23}Cl_2N_3O_2$	C, H, Cl, N
40	4-Cl	4-Cl	3	118–123	AcOEt	32.0	*B*	$C_{23}H_{25}Cl_2N_3O_2$	C, H, Cl, N
41	4-Cl	4-F	3	116–120	AcOEt	46.0	*B*	$C_{23}H_{25}ClFN_3O_2$	C, H, Cl, F, N
42	4-F	4-F	3	96–100	AcOEt/hexane 1:1	17.4	*B*	$C_{23}H_{25}F_2N_3O_2$	C, H, F, N
43	H	H	1	165–168	AcOEt	8.8	*A*	$C_{21}H_{23}N_3O_2$	C, H, N
44	H	4-Cl	1	141–143	AcOEt	7.2	*A*	$C_{21}H_{22}ClN_3O_2$	
45	H	4-F	1	111–115	AcOEt	7.1	*A*	$C_{21}H_{22}FN_3O_2$	C, H, F, N
46	4-Cl	4-Cl	1	134–137	i-PrOH	16.6, 12.2	*A*, *B*	$C_{21}H_{21}Cl_2N_3O_2$	C, H, Cl, N
47	4-F	4-Cl	1	61–65	i-PrOH	3.0	*A*	$C_{21}H_{21}ClFN_3O_2$	C, H, Cl, F, N
48	4-Cl	4-CH_3	1	111–134	AcOEt/hexane 1:1	2.6	*A*	$C_{22}H_{24}ClN_3O_2$	
49	4-CH_3O	4-Cl	1	36–38	benzene	4.0	*A*	$C_{22}H_{24}ClN_3O_3$	

[a] See *Exper. Part* for description of general methods.

isoxazolidine derivatives (see **10**) are excluded on the basis of electronic factors. The reaction products represent a *cis/trans* diastereoisomeric mixture **14/15**, in which the *cis*-isomer is the predominant component. The two diastereoisomers were conveniently separated by flash chromatography on silica gel (*cis*-isomers **16–42** and *trans*-isomers **43–49**, see *Table 1*).

The configuration of the two asymmetric centers in the isoxazolidine rings of **14** and **15** was determined initially by ^{1}H-NMR spectroscopy. Thus, for the *cis*-diastereoisomers **14** (*e.g.* **20**), the difference Δ between the coupling constants J of H–C(5) and H_A–C(4), and H_B–C(4) was much more significant (4.1 Hz) than the Δ observed for the *trans*-diastereoisomers **15** (*e.g.* **46**; Δ = 1.4 Hz; see *Table 2*). An X-ray crystal-structure determination of **20** was undertaken [37] to define unambiguously the structure of both *cis*- and *trans*-diastereoisomers *(Figure)*. The configuration of the asymmetric centers of all remaining isoxazolidines was defined by ^{1}H-NMR spectroscopy according to the J and Δ values of **20** and **46** (see *Exper. Part* for details).

Table 2. *^{1}H-NMR Coupling Constants* J [Hz] *for* **20** *and* **46**

Compound	$J(4A,5)$	$J(4B,5)$	$\Delta[J(4A,5)-J(4B,5)]$
20, *cis*	5.4	9.5	4.1
46, *trans*	7.7	9.1	1.4

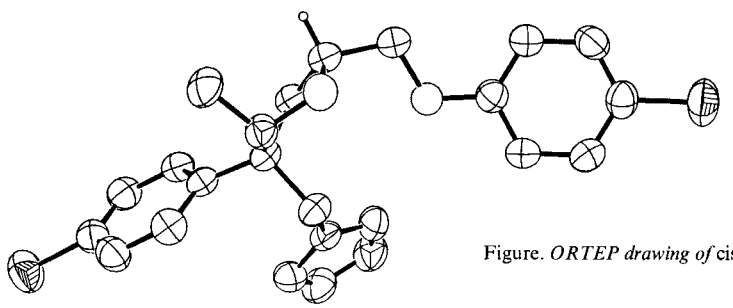


Figure. *ORTEP drawing of* cis-*configurated* **20**

The 5-[2-(4-chlorophenoxy)ethyl]-2-methylisoxazolidine **39** was prepared by 1,3-dipolar cycloaddition reaction of nitrone **12** (R^1 = 4-Cl) with the known [38] 1-[(3-butenyl)oxy]-4-chlorobenzene (**13**; R^2 = 4-Cl, n = 2). The 5-[3-(4-halogenophenoxy)propyl]-2-methylisoxazolidines **40–42** were synthesized from the corresponding nitrones **12** and 1-chloro- or 1-fluoro-4-[(4-pentenyl)oxy]benzene (**13**; R^2 = 4-Cl or -F, n = 3) [38].

The known [39] 1- or 2-[(2-propenyl)oxy]naphthalenes **50** were used in the synthesis of 5-(naphthalenyloxy)methyl derivatives **51** and **52**, whereas 6-[(2-propenyl)oxy]-1,3-benzoxathiol-2-one (**53**) was utilized in the 1,3-dipolar cycloaddition reaction with 1-(4-fluorophenyl)-2-(1*H*-imidazol-1-yl)ethanone to provide the 6-substituted 1,3-benzoxathiol-2-one **54** (*Scheme 3* and *Table 3*).

In addition to *N*-methyl analogs **16–49**, the two novel *N*-benzylated 5-[(aryloxy)-methyl]isoxazolidines **55** and **56** were also prepared using the corresponding *N*-benzyl-nitrones in a similar 1,3-dipolar cycloaddition reaction with 1-chloro-4-[(2-propenyl)oxy]benzene (**13**; R^2 = 4-Cl, n = 1; *Table* 3).

Scheme 3

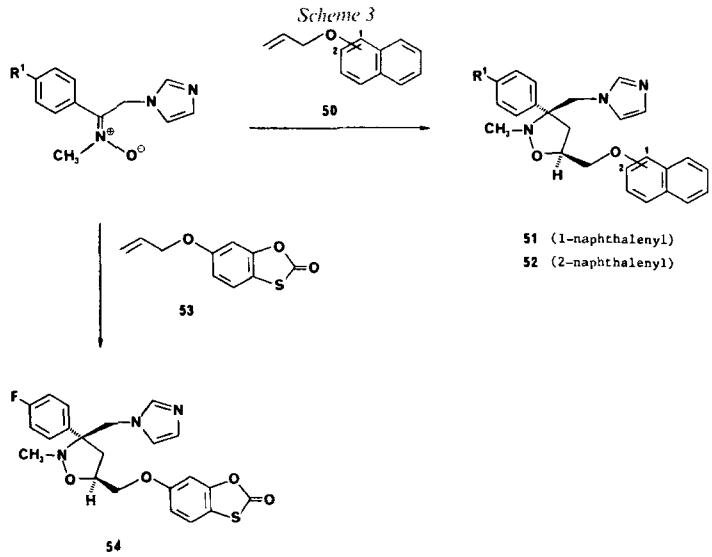
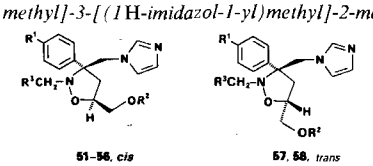


Table 3. *3-Aryl-5-[(aryloxy)methyl]-3-[(1H-imidazol-1-yl)methyl]-2-methyl(or benzyl)isoxazolidines*



Compound	R^1	R^2	R^3	M.p. [°]	Recrystallization solvent	Yield [%]	*Method* [a])	Formula	Analyses
51	H	naphthalen-1-yl	H	42–45	AcOEt	41.0	*B*	$C_{25}H_{26}N_4O_5$	C, H, N
52	4-F	naphthalen-2-yl	H	160–162	AcOEt	35.0	*B*	$C_{25}H_{24}FN_3O_2$	C, H, F, N
54	4-F	2-oxo-1,3-benzoxathiol-6-yl	H	140–142	AcOEt	36.0	*B*	$C_{22}H_{20}FN_3O_4S$	C, H, F, N, S
55	H	4-Cl-C_6H_4	C_6H_5	128–130	AcOEt/hexane 1:1	28.0	*A*	$C_{27}H_{26}ClN_3O_2$	C, H, Cl, N
56	H	4-Cl-C_6H_4	3-Cl-C_6H_4	103–107	AcOEt/hexane 1:1	25.0	*A*	$C_{27}H_{25}Cl_2N_3O_2$	C, H, Cl, N
57	4-F	naphthalen-2-yl	H	149–154[b])	EtOH[b])	3.5[b])	*B*	$C_{25}H_{25}FN_4O_5$[b])	C, H, F, N
58	H	4-Cl-C_6H_4	C_6H_5	110–113	AcOEt/hexane 1:1	4.3	*A*	$C_{27}H_{25}ClN_3O_2$	C, H, Cl, N

[a]) See *Exper. Part* for description of general methods.
[b]) As the nitrate salt.

Results and Discussion. – The antifungal activity of the 3-aryl-5-[(aryloxy)alkyl]-3-[(1*H*-imidazol-1-yl)methyl]-2-methylisoxazolidines **16**–**54** was evaluated *in vitro* in solid agar tests performed in 24-well tissue culture plates. The minimum inhibitory concentration (*MIC*) values (μg/ml) were interpreted as the lowest dilution at which no visible growth occurred. Ketoconazole (**4**) was used as control in all assays. The obtained results are summarized in *Table 4*.

Substitution was varied at the 3-aryl ring and the 5-(aryloxy)alkyl group. With the exception of *Aspergillus fumigatus*, all tested compounds were shown to possess moderate to very potent *in vitro* antifungal activity against both dermatophytes (*Trichophyton* and

Table 4. In vitro *Antifungal Activity of 3-Aryl-5-[(aryloxy)alkyl]-3-[(1H-imidazol-1-yl)methyl]-2-methylisoxazolidines and Related Derivatives.* Activity expressed as the minimum inhibitory concentration (*MIC*) in μg/ml.

Compd.	*T.m.*[a])	*T.r.*[b])	*T.t.*[c])	*T.s.*[d])	*E.f.*[e])	*M.a.*[f])	*M.c.*[g])	*A.f.*[h])	*C.a.*[i])	*C.s.*[j])
16	2.0	7.0	7.0	7.0	7.0	20.0	7.0	70.0	20.0	2.0
17	< 0.2	0.7	< 0.2	2.0	< 0.2	2.0	0.7	> 70.0	2.0	< 0.2
18	> 70.0	> 70.0	> 70.0	> 70.0	> 70.0	> 70.0	> 70.0	> 70.0	> 70.0	> 70.0
19	0.7	0.7	0.7	0.7	0.7	2.0	2.0	20.0	7.0	0.7
20	2.0	0.7	0.2	2.0	0.2	0.7	0.7	20.0	2.0	0.2
21	0.7	2.0	0.7	2.0	2.0	20.0	7.0	70.0	7.0	0.7
22	< 0.2	2.0	0.7	2.0	2.0	7.0	7.0	70.0	7.0	0.7
23	0.7	2.0	0.7	20.0	< 0.2	2.0	0.7	70.0	7.0	< 0.2
24	70.0	> 70.0	70.0	70.0	70.0	> 70.0	> 70.0	> 70.0	> 70.0	20.0
25	2.0	2.0	2.0	2.0	7.0	7.0	2.0	70.0	20.0	2.0
26	2.0	7.0	2.0	7.0	7.0	70.0	20.0	> 70.0	20.0	< 0.2
27	2.0	0.7	0.7	2.0	0.7	7.0	0.7	> 70.0	2.0	2.0
28	20.0	2.0	0.7	2.0	2.0	20.0	7.0	> 70.0	7.0	2.0
29	7.0	2.0	7.0	70.0	20.0	> 70.0	7.0	> 70.0	> 70.0	2.0
30	< 0.2	0.7	< 0.2	2.0	< 0.2	2.0	2.0	7.0	7.0	< 0.2
31	2.0	2.0	2.0	7.0	2.0	2.0	2.0	> 70.0	7.0	0.7
32	2.0	7.0	7.0	0.7	0.7	7.0	7.0	70.0	7.0	2.0
33	7.0	20.0	20.0	7.0	7.0	20.0	7.0	> 70.0	20.0	7.0
34	2.0	2.0	2.0	2.0	2.0	7.0	7.0	20.0	7.0	< 0.2
35	2.0	7.0	7.0	0.7	0.7	7.0	7.0	70.0	7.0	2.0
36	2.0	2.0	2.0	2.0	2.0	7.0	7.0	20.0	7.0	< 0.2
37		0.7						> 20.0	20.0	
38	0.7	2.0	2.0	7.0	0.7	7.0	7.0	> 70.0	7.0	0.2
39	< 0.2	0.7	< 0.2	0.7	< 0.2	2.0	0.7	> 70.0	2.0	< 0.2
40		< 0.2						> 70.0	20.0	
41		> 20.0						> 20.0	> 20.0	
42		0.7						20.0	7.0	
43	7.0	20.0	2.0	20.0	7.0	70.0	20.0	> 70.0	20.0	20.0
44	2.0	7.0	2.0	2.0	0.7	7.0	7.0	> 70.0	7.0	2.0
45	> 70.0	> 70.0	> 70.0	> 70.0	> 70.0	> 70.0	> 70.0	> 70.0	> 70.0	> 70.0
46	7.0	2.0	0.2	2.0	0.7	2.0	2.0	20.0	2.0	0.7
47	0.7	2.0	0.7	2.0	0.7	7.0	2.0	70.0	7.0	0.7
51		< 2.0						> 70.0	7.0	
52		< 2.0						20.0	7.0	
54		< 0.2						70.0	20.0	
55		7.0						> 70.0	> 70.0	
Ketoconazole (**4**)	2.0	0.7	< 0.2	0.7	< 0.2	7.0	2.0	7.0	20.0	20.0

[a]) *T.m.* = *Trichophyton mentagrophytes* ATCC 9533.
[b]) *T.r.* = *Trichophyton rubrum* ATCC 18762.
[c]) *T.t.* = *Trichophyton tonsurans* ATCC 9085.
[d]) *T.s.* = *Trichophyton schoenleinii* ATCC 22775.
[e]) *E.f.* = *Epidermophyton floccosum* ATCC E-18397.
[f]) *M.a.* = *Microsporum audouinii* ATCC 9079.
[g]) *M.c.* = *Microsporum canis* ATCC 44459.
[h]) *A.f.* = *Aspergillus fumigatus* ATCC 28212.
[i]) *C.a.* = *Candida albicans* ATCC 10259.
[j]) *C.s.* = *Candida stellatoidea* ATCC 36232.

Microsporum sp. and *Epidermophyton floccosum*) and yeast (*Candida* sp.) fungi. Of the four derivatives **16**–**19** having no substituent at the 3-aryl ring, only the 5-(4-fluorophenyl)methyl analog **18** was found inactive. Replacing the F- with the Cl-atom (**18**→**17**) led to a dramatic increase in activity against all (but *A.fumigatus*) fungi. However, introduction of a CH_3 group alongside with the Cl-atom (see **19**) significantly improved the activity against *A.fumigatus*. With the exception of **18**, *cis*-compounds **16**–**19** were

markedly superior to ketoconazole (**4**) in their inhibition of *Candida*. The *trans*-diastereoisomer **43** was considerably less active than its *cis*-counterpart **16**, especially against *Trichophyton* and *Microsporum* sp. and *C. stellatoidea*.

Next, we explored the effect of the substitution in the 3-aryl group on the *in vitro* potency of the *cis*-diastereoisomers while keeping the 5-(4-chlorophenoxy)methyl substituent constant (**17**, **20**, **30**, **32**, **34**–**38**). In this case, a halogen atom, CH_3O, CH_3, and H-atom in either the 4- or 3-position of the aryl group at C(3), had little effect on the potency against *T. rubrum* or *C. albicans*. Good activity, in comparison to **4**, was observed in all cases. A halogen atom, particularly 4-F (**30**), and CH_3 (**34**, **36**) were most beneficial for activity. A comparison of two pairs of halogen-substituted compounds (**20** *vs.* **30**, and **21** *vs.* **31**) led to an interesting observation. While the halogen atom (R^1) at the 3-aryl ring is either 4-chloro (**20**, **21**) or 4-fluoro (**30**, **31**), analogs **21** and **31** contain a 5-(4-fluorophenoxy)methyl moiety ($R^2 = F$) in place of the 5-(4-chlorophenoxy)methyl group ($R^1 = Cl$) of **20** and **30**. As seen from *Table 4*, when compared to its 3-(4-chlorophenyl) analog **20**, the 3-(4-fluorophenyl) derivative **30** showed superior activity; it was the reverse case for **21** *vs.* **31** – in general, the 3-(4-chlorophenyl) compound **21** was the more effective of the two.

The effect of aromatic substitution at the 5-(aryloxy)methyl group on the *in vitro* potency of the *cis*-diastereoisomers was also investigated. In compounds where the 3-(4-chlorophenyl) moiety was held constant, potent activity against *T. rubrum* and *C. albicans* was evident for most substitution patterns, the exception being the 5-[4-(acetamido)phenoxy]methyl group (**24**). Compounds with halogen (**20**, **21**, **27**, **28**) *or* electron-releasing substituents such as CH_3O (**22**) and CH_3 (**23**) were more potent than ketoconazole (**4**) against *C. albicans;* those with electron-withdrawing substituents (**25** and **26**) were equipotent with **4** against *C. albicans*. As generally observed, this series lacks potency against *A. fumigatus;* the 5-(4-chlorophenoxy)methyl derivative **20** was the only analog that showed moderate activity.

Thus far we have discussed structure-activity correlations for *cis*-diastereoisomers **16**–**38**, in which the 3-(1*H*-imidazol-1-yl)methyl substituent has a *cis*-relationship to the 5-(aryloxy)alkyl group. This same configurational relationship is also present in ketoconazole (**4**) about the 5-membered dioxolane ring. This relationship seemed to indicate that the minor diastereoisomers **43**–**49** from the 1,3-dipolar cycloaddition, in which the 3-(1*H*-imidazol-1-yl)methyl moiety has a *trans*-relationship to the C(5) substituent, would be less active *in vitro* when compared to their *cis*-counterparts **16**–**38**[1]). However, when tested *in vitro*, the *trans*-analogs **43**–**49** demonstrated moderate to potent activity against both dermatophytes and yeast fungi. Thus, the potency of the two halogen-substituted compounds **46** and **47** against *C. albicans* was equal to that of the corresponding *cis*-diastereoisomers **20** and **30**, and much better than that of **4**. However, when compared to the 3-phenyl *cis*-analogs **16**–**18**, the *trans*-diastereoisomers **43**–**45** showed less potent activity although **44** was still much more potent against *C. albicans* than **4**.

The effect of homologation of the alkyl moiety of the 5-(4-chlorophenoxy)methyl group to the corresponding ethyl and propyl analogs **39** and **40**–**42**, respectively, on the *in vitro* antifungal activity was also studied. When compared to **20**, the 5-(4-chloro-

[1]) So far, we have not been able to find any reference in the literature indicating that the *trans*-diastereoisomer of ketoconazole (**4**) has been isolated and/or tested for antifungal activity.

phenoxy)ethyl compound **39** exerted better activity against dermatophytes (*Trichophyton* sp. and *E. floccosum*) and *Candida*, but was less effective against *M. audouinii* and *A. fumigatus*. The propyl derivatives **40** and **42** were more potent against *T. rubrum* than the corresponding methyl analogs **20** and **31**, respectively; with the exception of **42**, the activity against *A. fumigatus* and *C. albicans* was less potent.

Overall, the 5-[(4-chlorophenoxy)methyl]-3-(4-chlorophenyl)-3-[(1*H*-imidazol-1-yl)-methyl]-2-methylisoxazolidine (PR 967-248; **20**) demonstrated the best *in vitro* antifungal activity. When compared to ketoconazole (**4**), **20** showed superior activity against *Candida* and *Microsporum* sp., coupled with very potent activity against *E. floccosum* and *Trichophyton* sp. and moderate activity against *A. fumigatus*. Its *MIC* values ranged between 0.2 and 2.0 μg/ml, as compared to 0.2–20.0 μg/ml for **4**.

In summary, the 3-aryl-5-[(aryloxy)alkyl]-3-[(1*H*-imidazol-1-yl)alkyl]-2-methylisoxazolidines **16–49** represent a novel class of potent antifungal agents, especially active against a wide variety of dermatophytes and yeast fungi. Their synthesis was accomplished *via* a 1,3-dipolar cycloaddition of α-substituted ketonitrones with 1-alkenyl phenyl ethers that resulted in the formation of both the *cis*- and *trans*-diastereoisomers in a regiospecific manner. While *in vitro* antifungal activity was evident throughout the series, in general, compounds having halogen atom(s) in either or both aryl rings demonstrated the highest potency, especially against *T. rubrum* and *C. albicans* [40].

Experimental Part

1. *General.* M.p.: *Thomas-Hoover* capillary melting point apparatus; uncorrected. IR spectra: *Nicolet-MX-1-FT* spectrometer; KBr discs. ^{1}H-NMR spectra: *Varian-EM-360A* (60 MHz) or *Bruker-IBM-200-SY Fourier*-transform (200 MHz) spectrometer using tetramethylsilane as an internal standard. All spectra were consistent with the assigned structures. Elemental analyses were within the acceptable limits of 0.4% of theory.

2. *1-Aryl-2-(1H-imidazol-1-yl)ethanones* **11** were prepared by the method of *Godefroi et al.* [36] from the corresponding 1-aryl-2-bromo- or 1-aryl-2-chloroethanones.

2-(1H-Imidazol-1-yl)-1-phenylethanone (**11**; R^1 = H). M.p. 117–119° (AcOEt; [36]: 117–118°).

1-(4-Chlorophenyl)-2-(1H-imidazol-1-yl)ethanone (**11**; R^1 = 4-Cl). M.p. 152–156° (AcOEt; [36]: 160–161°).

1-(4-Fluorophenyl)-2-(1H-imidazol-1-yl)ethanone (**11**; R^1 = 4-F). M.p. 150–155° (AcOEt; [36]: 154–156°).

2-(1H-Imidazol-1-yl)-1-(4-methoxyphenyl)ethanone (**11**; R^1 = 4-CH_3O). M.p. 134–137° (AcOEt). Registry No. 46720-41-6.

2-(1H-Imidazol-1-yl)-1-(4-methylphenyl)ethanone (**11**; R^1 = 4-CH_3). M.p. 133–137° (AcOEt; [36]: 136–138°).

2-(1H-Imidazol-1-yl)-1-(3-methoxyphenyl)ethanone (**11**; R^1 = 3-CH_3O). M.p. 111–113° (AcOEt). Anal. calc. for $C_{12}H_{12}N_2O_2$: C 66.65, H 5.59, N 12.95; found: C 66.48, H 5.67, N 12.77.

2-(1H-Imidazol-1-yl)-1-(3-methylphenyl)ethanone (**11**; R^1 = 3-CH_3). M.p. 102–104° (AcOEt). Anal. calc. for $C_{12}H_{12}N_2O$: C 71.98, H 6.04, N 13.99; found: C 71.84, H 6.17, N 13.89.

1-(4-Chloro-3-methylphenyl)-2-(1H-imidazol-1-yl)ethanone (**11**; R^1 = 4-Cl, 3-CH_3). M.p. 116–118° (AcOEt). Anal. calc. for $C_{12}H_{11}ClN_2O$: C 61.41, H 4.72, Cl 15.11, N 11.94; found: C 61.44, H 4.83, Cl 14.98, N 11.77.

1-(3,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)ethanone (**11**; R^1 = 3,4-Cl_2). M.p. 124–126° (AcOEt). Registry No. 37906-39-1.

3. *2-(1H-Imidazol-1-yl)-N-methyl-1-phenylethanimine N-Oxide* (**12**; R^1 = H). A suspension of 35.54 g (0.191 mol) of **11** (R^1 = H), 20.63 g (0.247 mol) of $CH_3NHOH \cdot HCl$, and 40.60 g (0.494 mol) of AcONa in 400 ml of EtOH was stirred for 48 h at r.t. under N_2. The mixture was poured into 500 ml of H_2O, then basified with $NaHCO_3$ and extracted with $CHCl_3$ (4 × 200 ml). The combined org. extract was dried ($MgSO_4$) and evaporated. Addition of Et_2O gave a yellow solid which was collected and recrystallized from AcOEt to furnish 29.82 g (72.6%) of **12** (R^1 = H) as white needles. M.p. 126–128°. IR (KBr): 1587*m*, 1507*m*, 1289*m*, 1246*s* (N–O), 1102*m*, 1078*m*, 962*m*, 831*m*, 771*s*, 699*m*, 677*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.59 (*s*, CH_3N); 5.25 (*s*, CH_2N); 6.80 (*s*, *1* H); 6.89 (*s*, *1* H);

6.97–7.02 (*m*, 2 H); 7.31–7.38 (*m*, 4 H). Anal. calc. for $C_{12}H_{13}N_3O$: C 66.96, H 6.09, N 19.52; found: C 66.74, H 6.18, N 19.38.

The following nitrones were prepared by the above procedure:

1-(4-Chlorophenyl)-2-(1H-imidazol-1-yl)-N-methylethanimine N-Oxide (**12**; R^1 = 4-Cl). Yield 54%. M.p. 98–102° (AcOEt).

1-(4-Fluorophenyl)-2-(1H-imidazol-1-yl)-N-methylethanimine N-Oxide (**12**; R^1 = 4-F). Yield 51%. M.p. 131–134° (AcOEt).

2-(1H-Imidazol-1-yl)-1-(4-methoxyphenyl)-N-methylethanimine N-Oxide (**12**; R^1 = 4-CH_3O). Yield 67%. M.p. 81–84° (AcOEt/Et_2O 1:1).

2-(1H-Imidazol-1-yl)-N-methyl-1-(4-methylphenyl)ethanimine N-Oxide (**12**; R^1 = 4-CH_3). Yield 23%. M.p. 73–76° (AcOEt/hexane 1:1).

2-(1H-Imidazol-1-yl)-1-(3-methoxyphenyl)-N-methylethanimine N-Oxide (**12**; R^1 = 3-CH_3O). Yield 48%. M.p. 87–90° (AcOEt/hexane 1:1).

2-(1H-Imidazol-1-yl)-N-methyl-1-(3-methylphenyl)ethanimine N-Oxide (**12**; R^1 = 3-CH_3). Yield 54%. M.p. 65–69° (AcOEt/Et_2O 1:1).

1-(4-Chloro-3-methylphenyl)-2-(1H-imidazol-1-yl)-N-methylethanimine N-Oxide (**12**; R^1 = 4-Cl,3-CH_3). Yield 56%. M.p. 85–88° (AcOEt).

1-(3,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)-N-methylethanimine N-Oxide (**12**; R^1 = 3,4-Cl_2). Yield 74%. M.p. 84–87° (AcOEt/hexane 3:1).

4. *1-(2-Propenyloxy)benzene* (**13**; R^2 = H, n = 1) is commercially available. Other ethers **13** were prepared by modified procedures of standard methods by reacting substituted phenols with allyl bromide.

1-Chloro-4-(2-propenyloxy)benzene (**13**; R^2 = 4-Cl, n = 1). B.p. 55–60°/0.05 Torr ([41]: B.p. 109–110°/15.0 Torr).

1-Fluoro-4-(2-propenyloxy)benzene (**13**; R^2 = 4-F, n = 1). B.p. 35–37°/0.2 Torr. Registry No. 13990-72-2.

1-Methoxy-4-(2-propenyloxy)benzene (**13**; R^2 = 4-CH_3O, n = 1). B.p. 65–68°/0.2 Torr ([41]: 116.5–117.5°/11.5 Torr).

1-Methyl-4-(2-propenyloxy)benzene (**13**; R^2 = 4-CH_3, n = 1). B.p. 45–47°/0.3 Torr ([41]: 97.5–98.5°/17.2 Torr).

N-[4-(2-Propenyloxy)phenyl]acetamide (**13**; R^2 = 4-AcNH, n = 1). M.p. 93.3–93.7° (benzene/cyclohexane 1:1; [41]: m.p. 93.3–93.7°).

1-(2-Propenyloxy)-3-(trifluoromethyl)benzene (**13**; R^2 = 3-CF_3, n = 1). B.p. 35–37°/0.2 Torr ([42]: 62–63°/4.0 Torr).

1-Nitro-2-(2-propenyloxy)benzene (**13**; R^2 = 2-NO_2, n = 1). B.p. 92–99°/0.15 Torr. Registry No. 55339-51-0.

2,4-Dichloro-1-(2-propenyloxy)benzene (**13**; R^2 = 2,4-Cl_2, n = 1). B.p. 62–65°/0.05 Torr. Registry No. 5441-16-7.

1,3-Dichloro-2-(2-propenyloxy)benzene (**13**; R^2 = 2,6-Cl_2, n = 1). B.p. 45–50°/0.05 Torr ([43]: 89–90°/2.0 Torr).

1-Chloro-2-methyl-4-(2-propenyloxy)benzene (**13**; R^2 = 4-Cl, 3-CH_3, n = 1). B.p. 75°/0.2 Torr.

The following ethers were prepared by the method of *Ruis-Alonso* and *Wain* [38].

1-(3-Butenyloxy)-4-chlorobenzene (**13**; R^2 = 4-Cl, n = 2). B.p. 70–75°/0.1 Torr. Registry No. 68537-05-3.

1-Chloro-4-(4-pentenyloxy)benzene (**13**; R^2 = 4-Cl, n = 3). B.p. 65–68°/0.1 Torr.

1-Fluoro-4-(4-pentenyloxy)benzene (**13**; R^2 = 4-F, n = 3). B.p. 50–51°/0.1 Torr.

The following ethers were prepared by the method of *Marcinkiewicz et al.* [39].

1-(2-Propenyloxy)naphthalene (**50a**). B.p. 75–80°/0.05 Torr ([39]: 55–60°/0.01 Torr).

2-(2-Propenyloxy)naphthalene (**50b**). B.p. 75–80°/0.05 Torr ([39]: 60°/0.01 Torr).

6-(2-Propenyloxy)-1,3-benzoxathiol-2-one (**53**). M.p. 78–80° (Et_2O).

5. cis-*5-[(4-Chlorophenoxy)methyl]-3-(4-chlorophenyl)-3-[(1H-imidazol-1-yl)methyl]-2-methylisoxazolidine* (**20**). *Method A.* Under N_2, a suspension of 19.90 g (90.2 mmol) of **11** (R^1 = 4-Cl), 10.26 g (0.123 mol) of $CH_3NHOH \cdot HCl$ and 10.37 g (0.123 mol) of $NaHCO_3$ in 200 ml of EtOH was refluxed for 27 h. After cooling to r.t., the suspension was filtered and the filtrate evaporated. The residual oily solid was taken up in $CHCl_3$, then filtered, and the filtrate evaporated. To the residual oil, containing **12** (R^1 = 4-Cl) in 200 ml of toluene under N_2, 22.8 g (1.5 equiv.) of **13** (R^2 = 4-Cl, n = 1) were added. The resulting soln. was refluxed for 42 h, then cooled to r.t. and the solvent evaporated. The residual dark-colored oil was flash chromatographed on neutral silica gel with $CHCl_3$/MeOH 98:2 (*v/v*), giving 18.64 g (49.4%) of **20** following crystallization from AcOEt. M.p. 126–132°. IR (KBr): 1595*m*, 1494*s*, 1453*m*, 1279*m* (C–N–C), 1241*s* (C–O–C), 1079*m*, 1005*m* (N–O), 827*m*, 822*m*, 751*m*, 665*m*.

^{1}H-NMR (200 MHz, $CDCl_3$): 2.52 (*s*, CH_3N); 2.59 (*dd*, *J* = 5.4, 13.0, H_A–C(4)); 2.83 (*dd*, *J* = 9.5, 13.0, H_B–C(4)); 4.18–4.31 (*m*, CH_2OAr); 4.26 (*d*, *J* = 14.0, 1 H, CH_2N); 4.44 (*d*, *J* = 14.0, 1 H, CH_2N); 4.82–4.89 (*m*, H–C(5)); 6.50 (*s*, 1 H); 6.75–7.47 (*m*, 10 H); decoupled CH_2OAr from H–C(5): 4.87 (*dd*, *J* = 5.4, 9.5, H–C(5)). Anal. calc. for $C_{21}H_{21}Cl_2N_3O_2$: C 60.30, H 5.06, Cl 16.95, N 10.04; found: C 60.36, H 5.15, Cl 17.14, N 9.97.

Further elution gave 6.28 g (16.6%) of the *trans*-isomer **46** which was crystallized from i-PrOH. M.p. 134–137°. IR (KBr): 1595*m*, 1492*s*, 1444*m*, 1283*m*, 1245*s* (C–O–C), 1095*m*, 1078*m*, 1039*m*, 1008*m* (N–O), 829*m*, 819*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.51 (*s*, CH_3N); 2.49 (*dd*, *J* = 7.7, 12.9, H_A–C(4)); 2.77 (*dd*, *J* = 9.1, 12.9, H_B–C(4)); 4.04–4.20 (*m*, CH_2OAr); 4.20 (*d*, *J* = 13.6, 1 H, CH_2N); 4.25 (*d*, *J* = 13.6, 1 H, CH_2N); 4.59–4.72 (*m*, H–C(5)); 4.46 (*s*, 1 H); 6.78–7.35 (*m*, 10 H); decoupled CH_2OAr from H–C(5): 4.65 (*dd*, *J* = 7.7, 9.0, H–C(5)). Anal. calc. for $C_{21}H_{21}Cl_2N_3O_2$: C 60.30, H 5.06, Cl 16.95, N 10.04; found: C 60.36, H 5.17, Cl 16.89, N 9.97.

Salt **20** *· 2 HCl.* M.p. 170–183° (MeOH/Et_2O 1:3). IR (KBr): 3063*s*, 2900–2000*m* (br. N · HCl), 1597*m*, 1580*m*, 1493*s*, 1445*m*, 1398*m*, 1305*m*, 1287*m*, 1242*s* (C–O–C), 1099*m*, 1029*m*, 1012*m* (N–O), 859*m*, 843*m*, 826*s*, 820*s*, 767*m*. ^{1}H-NMR (200 MHz, $CDCl_3$/CF_3COOH): 3.09 (br. *s*, $NCH_3 \cdot HCl$); 3.24–3.43 (*m*, 2 H–C(4)); 4.31–4.67 (*m*, CH_2OAr); 5.18–5.34 (*m*, H–C(5)); 5.41–5.66 (*m*, CH_2N); 6.55 (*s*, 1 H); 6.94–7.03 (*m*, 2 H); 7.24–7.38 (*m*, 3 arom. H, N · HCl); 7.54–7.58 (*m*, 4 H); 8.60 (*s*, 1 H). Anal. calc. for $C_{21}H_{23}Cl_4N_3O_2$: C 51.35, H 4.72, Cl 28.87, N 8.55; found: C 51.45, H 4.84, Cl 27.72, N 8.50.

Nitrate Salt of **20**. M.p. 165–167° (EtOH). IR (KBr): 2500–2000*w* (br., salt), 1597*m*, 1580*m*, 1493*s*, 1413*m*, 1398*s* (NO_2), 1300*s* (NO_2), 1284*m*, 1243*s* (C–O–C), 1172*m*, 1095*m*, 1013*m* (N–O), 880*m*, 832*m*, 820*m*. ^{1}H-NMR (200 MHz, (D_6)DMSO): 2.45 (*s*, CH_3N); 2.51 (*dd*, *J* = 5.5, 13.2, H_A–C(4)); 2.98 (*dd*, *J* = 9.9, 13.2, H_B–C(4)); 4.19 (*d*, *J* = 4.4, CH_2OAr); 4.39 (*d*, *J* = 14.9, 1 H, CH_2N); 4.79 (*d*, *J* = 14.9, 1 H, CH_2N); 4.70–4.84 (*m*, H–C(5)); 7.02 (*d*, *J* = 9.4, 2 H); 7.04 (*d*, *J* = 8.8, 2 H); 7.25 (*s*, 1 H); 7.35 (*d*, *J* = 9.4, 2 H); 7.40 (*d*, *J* = 8.8, 2 H); 7.58 (*s*, 1 H); 8.66 (*s*, 1 H). Anal. calc. for $C_{21}H_{22}Cl_2N_4O_5$: C 52.40, H 4.61, Cl 14.73, N 11.67; found: C 52.51, H 4.70, Cl 14.84, N 11.67.

Method B. A soln. of 9.95 g (39.8 mmol) of **12** (R^1 = 4-Cl) and 10.38 g (61.6 mmol) of **13** (R^2 = 4-Cl, *n* = 1) in 250 ml of toluene was heated to reflux under N_2 and stirred for 46 h. Then, the mixture was cooled to r.t. and the solvent evaporated. The dark residual oil in 300 ml of AcOEt was washed with H_2O (5 × 80 ml). The org. layer was dried ($MgSO_4$) and evaporated. Addition of 50 ml of Et_2O furnished 10.77 g of a yellow solid which was recrystallized from AcOEt to provide 8.84 g (53%) of pure **20** as white needles, identical to that obtained by *Method A*. The mother liquors were combined and flash chromatographed on neutral silica gel using AcOEt. An additional 1.75 g (10.5%) of **20** and 2.04 g (12.2%) of **46** were obtained, both compounds being identical to the ones prepared by *Method A*.

The following isoxazolidines were synthesized by procedures similar to those described for the preparation of **20** and **46** (*Method A* or *B*, yields, and m.p.'s in *Tables 1* and *3*).

cis-*3-[(1*H*-Imidazol-1-yl)methyl]-2-methyl-5-(phenoxymethyl)-3-phenylisoxazolidine* (**16**). IR (KBr): 1598*m*, 1494*s*, 1451*m*, 1238*s* (C–O–C), 1226*m*, 1079*m*, 1034*m*, 1005*m* (N–O), 905*m*, 861*m*, 762*m*, 749*m*, 700*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.55 (*s*, CH_3N); 2.66 (*dd*, *J* = 5.5, 13.2, H_A–C(4)); 2.85 (*dd*, *J* = 9.9, 13.2, H_B–C(4)); 4.22–4.36 (*m*, CH_2OAr); 4.43 (*s*, CH_2N); 4.83–4.94 (*m*, H–C(5)); 6.43 (*s*, 1 H); 6.82 (*s*, 1 H); 6.97–7.36 (*m*, 11 H). Anal. calc. for $C_{21}H_{23}N_3O_2$: C 72.18, H 6.63, N 12.03; found: C 72.04, H 6.65, N 12.01.

trans-*Isomer* **43**. IR (KBr): 1597*m*, 1581*m*, 1490*s*, 1445*m*, 1251*m*, 1235*s* (C–O–C), 1071*m*, 1035*s*, 1010*m* (N–O), 769*s*, 756*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.53 (*s*, CH_3N); 2.51 (*dd*, *J* = 7.7, 12.7, H_A–C(4)); 2.76 (*dd*, *J* = 9.9, 12.7, H_B–C(4)); 4.09–4.13 (*m*, CH_2OAr); 4.24 (*d*, *J* = 14.3, 1 H, CH_2N); 4.37 (*d*, *J* = 14.3, 1 H, CH_2N); 4.59–4.73 (*m*, H–C(5)); 6.38 (*s*, 1 H); 6.88–7.36 (*m*, 12 H). Anal. calc. for $C_{21}H_{23}N_3O_2$: C 72.18, H 6.63, N 12.03; found: C 71.94, H 6.71, N 11.83.

cis-*5-[(4-Chlorophenoxy)methyl]-3-[(1*H*-imidazol-1-yl)methyl]-2-methyl-3-phenylisoxazolidine* (**17**). IR (KBr): 1595*m*, 1493*s*, 1443*m*, 1282*m*, 1244*s* (C–O–C), 1073*m*, 1003*m* (N–O), 906*m*, 875*m*, 822*s*, 759*m*, 709*m*, 662*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.53 (*s*, CH_3N); 2.58 (*dd*, *J* = 5.5, 12.1, H_A–C(4)); 2.87 (*dd*, *J* = 10.5, 12.1, H_B–C(4)); 4.16–4.32 (*m*, CH_2OAr); 4.36 (*d*, *J* = 13.8, 1 H, CH_2N); 4.41 (*d*, *J* = 13.8, 1 H, CH_2N); 4.80–4.93 (*m*, H–C(5)); 6.39 (*s*, 1 H); 6.80–7.35 (*m*, 11 H). Anal. calc. for $C_{21}H_{22}ClN_3O_2$: C 65.71, H 5.78, Cl 9.24, N 10.95; found: C 65.69, H 5.84, Cl 9.57, N 10.85.

trans-*Isomer* **44**. IR (KBr): 1590*w*, 1576*w*, 1492*s*, 1443*m*, 1280*m*, 1247*s* (C–O–C), 1078*m*, 1025*m*, 841*m*, 747*m*, 704*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.52 (*s*, CH_3N); 2.52 (*dd*, *J* = 7.7, 12.7, H_A–C(4)); 2.73 (*dd*, *J* = 9.4, 12.7, H_B–C(4)); 4.06–4.20 (*m*, CH_2OAr); 4.25 (*d*, *J* = 14.9, 1 H, CH_2N); 4.37 (*d*, *J* = 14.9, 1 H, CH_2N); 4.58–4.72 (*m*, H–C(5)); 6.37 (*s*, 1 H); 6.80–7.36 (*m*, 11 H).

cis-*5-[(4-Fluorophenoxy)methyl]-3-[(1*H*-imidazol-1-yl)methyl]-2-methyl-3-phenylisoxazolidine* (**18**). IR (KBr): 1598*w*, 1508*s*, 1460*m*, 1451*m*, 1237*s*, 1203*m*, 1077*m*, 1060*m*, 1040*m*, 1005*m* (N–O), 827*s*, 752*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.55 (*s*, CH_3N); 2.60 (*dd*, *J* = 5.5, 12.7, H_A–C(4)); 2.86 (*dd*, *J* = 9.9, 12.7, H_B–C(4)); 4.17–4.32

(*m*, CH_2OAr); 4.40 (*s*, CH_2N); 4.81–4.93 (*m*, H–C(5)); 6.39 (*s*, 1 H); 6.81 (*s*, 1 H); 6.90–7.34 (*m*, 10 H). Anal. calc. for $C_{21}H_{22}FN_3O_2$: C 68.65, H 6.04, F 5.17, N 11.44; found: C 68.54, H 6.16, F 5.15, N 11.41.

trans-*Isomer* **45**. IR (KBr): 3115*m*, 1598*w*, 1508*s*, 1470*m*, 1448*m*, 1250*m*, 1238*m*, 1207*s*, 1078*m*, 1022*m*, 843*s*, 762*m*, 746*m*, 704*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.52 (*s*, CH_3N); 2.50 (*dd*, J = 7.7, 13.2, H_A–C(4)); 2.74 (*dd*, J = 9.4, 13.2, H_B–C(4)); 4.05–4.20 (*m*, CH_2OAr); 4.25 (*d*, J = 14.3, 1 H, CH_2N); 4.38 (*d*, J = 14.3, 1 H, CH_2N); 4.58–4.72 (*m*, H–C(5)); 6.38 (*s*, 1 H); 6.80–7.37 (*m*, 11 H). Anal. calc. for $C_{21}H_{22}FN_3O_2$: C 68.65, H 6.04, F 5.17, N 11.44; found: C 69.03, H 6.13, F 5.22, N 11.38.

cis-*5-[(4-Chloro-3-methylphenoxy)methyl]-3-[(1*H*-imidazol-1-yl)methyl]-2-methyl-3-phenylisoxazolidine* (**19**). IR (KBr): 1598*m*, 1572*m*, 1502*m*, 1480*s*, 1447*m*, 1294*m*, 1284*m*, 1244*s*, 1175*m*, 1074*m*, 1025*m*, 820*m*, 750*m*, 702*m*, 664*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.36 (*s*, CH_3Ar); 2.55 (*s*, CH_3N); 2.58 (*dd*, J = 5.5, 12.7, H_A–C(4)); 2.86 (*dd*, J = 9.9, 12.7, H_B–C(4)); 4.17–4.31 (*m*, CH_2OAr); 4.35 (*d*, J = 14.3, 1 H, CH_2N); 4.44 (*d*, J = 14.3, 1 H, CH_2N); 4.80–4.92 (*m*, H–C(5)); 6.40 (*s*, 1 H); 6.73–7.33 (*m*, 10 H). Anal. calc. for $C_{22}H_{24}ClN_3O_2$: C 66.41, H 6.08, Cl 8.91, N 10.56; found: C 66.34, H 6.19, Cl 8.87, N 10.46.

cis-*3-(4-Chlorophenyl)-5-[(4-fluorophenoxy)methyl]-3-[(1*H*-imidazol-1-yl)methyl]-2-methylisoxazolidine* (**21**). IR (KBr): 1595*w*, 1510*s*, 1490*m*, 1457*m*, 1383*w*, 1245*m*, 1225*s*, 1215*s*, 1078*m*, 1004*m* (N–O), 905*m*, 825*m*, 772*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.52 (*s*, CH_3N); 2.62 (*dd*, J = 5.5, 13.2, H_A–C(4)); 2.83 (*dd*, J = 9.9, 13.2, H_B–C(4)); 4.17–4.32 (*m*, CH_2OAr); 4.33 (*d*, J = 14.9, 1 H, CH_2N); 4.44 (*d*, J = 14.9, 1 H, CH_2N); 4.81–4.92 (*m*, H–C(5)); 6.47 (*s*, 1 H); 6.85–7.59 (*m*, 10 H). Anal. calc. for $C_{21}H_{21}ClFN_3O_2$: C 62.76, H 5.27, Cl 8.82, F 4.73, N 10.46; found: C 62.72, H 5.26, Cl 8.66, F 4.68, N 10.43.

cis-*3-(4-Chlorophenyl)-3-[(1*H*-imidazol-1-yl)methyl]-5-[(4-methoxyphenoxy)methyl]-2-methylisoxazolidine* (**22**). IR (KBr): 1633*w*, 1590*w*, 1510*s*, 1490*m*, 1455*m*, 1229*s*, 1071*m*, 1037*s*, 1006*m* (N–O), 862*m*, 820*m*, 759*m*, 742*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.52 (*s*, CH_3N); 2.62 (*dd*, J = 5.5, 13.2, H_A–C(4)); 2.78 (*dd*, J = 9.4, 13.2, H_B–C(4)); 3.78 (*s*, CH_3O); 4.15–4.31 (*m*, CH_2OAr); 4.35 (*d*, J = 12.7, 1 H, CH_2N); 4.41 (*d*, J = 12.7, 1 H, CH_2N); 4.78–4.91 (*m*, H–C(5)); 6.46 (*s*, 1 H); 6.83–7.31 (*m*, 10 H). Anal. calc. for $C_{22}H_{24}ClN_3O_3$: C 63.84, H 5.84, Cl 8.57, N 10.15; found: C 64.16, H 5.95, Cl 8.60, N 10.16.

cis-*3-(4-Chlorophenyl)-3-[(1*H*-imidazol-1-yl)methyl]-2-methyl-5-[(4-methylphenoxy)methyl]isoxazolidine* (**23**). IR (KBr): 1615*w*, 1512*s*, 1491*m*, 1457*m*, 1233*s*, 1078*m*, 1013*m* (N–O), 827*m*, 813*m*, 747*m*, 667*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.30 (*s*, CH_3Ar); 2.52 (*s*, CH_3N); 2.62 (*dd*, J = 5.5, 12.7, H_A–C(4)); 2.80 (*dd*, J = 9.9, 12.7, H_B–C(4)); 4.17–4.31 (*m*, CH_2OAr); 4.34 (*d*, J = 14.9, 1 H, CH_2N); 4.42 (*d*, J = 14.9, 1 H, CH_2N); 4.78–4.92 (*m*, H–C(5)); 6.48 (*s*, 1 H); 6.84–7.30 (*m*, 10 H). Anal. calc. for $C_{22}H_{24}ClN_3O_2$: C 66.41, H 6.08, Cl 8.91, N 10.56; found: C 66.35, H 6.20, Cl 9.20, N 10.49.

trans-*Isomer* **48**. IR (KBr): 1610*w*, 1510*s*, 1492*m*, 1454*m*, 1440*m*, 1285*m*, 1239*s*, 1093*m*, 1078*m*, 1040*m*, 1008*m* (N–O), 825*m*, 820*m*, 809*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.28 (*s*, CH_3Ar); 2.51 (*s*, CH_3N); 2.51 (*dd*, J = 7.7, 13.2, H_A–C(4)); 2.73 (*dd*, J = 9.9, 13.2, H_B–C(4)); 4.03–4.18 (*m*, CH_2OAr); 4.15 (*d*, J = 14.9, 1 H, CH_2N); 4.36 (*d*, J = 14.9, 1 H, CH_2N); 4.58–4.71 (*m*, H–C(5)); 6.45 (*s*, 1 H); 6.78 (*d*, J = 7.7, 2 H); 6.91 (*s*, 1 H); 7.02–7.10 (*m*, 5 H); 7.31 (*d*, J = 7.7, 2 H).

cis-*5-[(4-(Acetamido)phenoxy)methyl]-3-(4-chlorophenyl)-3-[(1*H*-imidazol-1-yl)methyl]-2-methylisoxazolidine* (**24**). IR (KBr): 1681*s* (C=O), 1616*m*, 1555*m*, 1506*s* (amide II), 1452*m*, 1232*m*, 1223*m*, 1093*m*, 1080*m*, 1015*m* (N–O), 845*m*, 826*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.16 (*s*, CH_3CO); 2.53 (*s*, CH_3N); 2.61 (*dd*, J = 5.5, 13.2, H_A–C(4)); 2.81 (*dd*, J = 9.9, 13.2, H_B–C(4)); 4.18–4.33 (*m*, CH_2OAr); 4.32 (*d*, J = 14.3, 1 H, CH_2N); 4.43 (*d*, J = 14.3, 1 H, CH_2N); 4.79–4.93 (*m*, H–C(5)); 6.47 (*s*, 1 H); 6.85–7.45 (*m*, 11 H). Anal. calc. for $C_{23}H_{25}ClN_4O_3$: C 62.65, H 5.72, Cl 8.04, N 12.71; found: C 62.52, H 5.76, Cl 8.09, N 12.58.

cis-*3-(4-Chlorophenyl)-3-[(1*H*-imidazol-1-yl)methyl]-2-methyl-5-[(3-(trifluoromethyl)phenoxy)methyl]-isoxazolidine* (**25**). IR (KBr): 1599*w*, 1493*m*, 1446*m*, 1335*s* (CF_3), 1321*s*, 1236*m*, 1173*m*, 1138*s*, 1095*m*, 1068*m*, 1006*m* (N–O), 889*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.50 (*s*, CH_3N); 2.58 (*dd*, J = 5.5, 13.2, H_A–C(4)); 2.86 (*dd*, J = 9.4, 13.2, H_B–C(4)); 4.19–4.36 (*m*, CH_2OAr); 4.24 (*d*, J = 14.8, 1 H, CH_2N); 4.47 (*d*, J = 14.8, 1 H, CH_2N); 4.81–4.92 (*m*, H–C(5)); 6.51 (*s*, 1 H); 6.87–7.48 (*m*, 10 H). Anal. calc. for $C_{22}H_{21}ClF_3N_3O_2$: C 58.48, H 4.68, Cl 7.85, F 12.61, N 9.30; found: C 58.78, H 4.60, Cl 7.84, F 12.42, N 9.01.

cis-*3-(4-Chlorophenyl)-3-[(1*H*-imidazol-1-yl)methyl]-2-methyl-5-[(2-nitrophenoxy)methyl]isoxazolidine* (**26**). IR (KBr): 1608*m*, 1530*s* (NO_2), 1517*s*, 1493*m*, 1354*s* (NO_2), 1282*s*, 1248*m*, 1093*m*, 1015*m* (N–O), 824*m*, 738*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.52 (*s*, CH_3N); 2.70 (*dd*, J = 5.5, 13.2, H_A–C(4)); 2.89 (*dd*, J = 9.9, 13.2, H_B–C(4)); 3.95 (*d*, J = 14.9, 1 H, CH_2N); 4.28–4.42 (*m*, CH_2OAr); 4.47 (*d*, J = 14.9, 1 H, CH_2N); 4.75–4.90 (*m*, H–C(5)); 6.56 (*s*, 1 H); 6.86–7.88 (*m*, 10 H). Anal. calc. for $C_{21}H_{21}ClN_4O_4$: C 58.81, H 4.94, Cl 8.27, N 13.06; found: C 58.88, H 4.98, Cl 8.38, N 13.12.

cis-*3-(4-Chlorophenyl)-5-[(2,4-dichlorophenoxy)methyl]-3-[(1*H*-imidazol-1-yl)methyl]-2-methylisoxazolidine* (**27**). IR (KBr): 1655*w*, 1507*m*, 1494*s*, 1484*s*, 1455*m*, 1395*m*, 1284*s*, 1096*m*, 1077*m*, 1003*m* (N–O), 863*m*, 807*m*,

765*m*, 742*m*, 661*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.53 (*s*, CH_3N); 2.68 (*dd*, *J* = 5.5, 13.2, H_A–C(4)); 2.86 (*dd*, *J* = 9.9, 13.2, H_B–C(4)); 4.14 (*d*, *J* = 14.9, 1 H, CH_2N); 4.21 (*dd*, *J* = 2.2, 11.0, 1 H, CH_2OAr); 4.38 (*dd*, *J* = 3.3, 11.0, 1 H, CH_2OAr); 4.58 (*d*, *J* = 14.9, 1 H, CH_2N); 4.78–4.92 (*m*, H–C(5)); 6.51 (*s*, 1 H); 6.82–7.38 (*m*, 9 H). Anal. calc. for $C_{21}H_{20}Cl_3N_3O_2$: C 55.71, H 4.45, Cl 23.49, N 9.28; found: C 55.55, H 4.51, Cl 23.32, N 9.18.

cis-*3-(4-Chlorophenyl)-5-[(2,6-dichlorophenoxy)methyl]-3-[(1*H*-imidazol-1-yl)methyl]-2-methylisoxazolidine* (**28**). IR (KBr): 1600*w*, 1570*m*, 1494*m*, 1451*m*, 1446*s*, 1383*m*, 1242*s*, 1231*m*, 1078*m*, 1015*m*, 905*m*, 868*m*, 818*m*, 782*m*, 776*m*, 756*m*, 665*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.53 (*s*, CH_3N); 2.82 (*dd*, *J* = 9.9, 12.7, H_B–C(4)); 2.93 (*dd*, *J* = 5.5, 12.7, H_A–C(4)); 4.27 (*dd*, *J* = 10.5, 1 H, CH_2OAr); 4.38 (*dd*, *J* = 2.7, 10.5, 1 H, CH_2OAr); 4.44 (*s*, CH_2N); 4.80–4.94 (*m*, H–C(5)); 6.41 (*s*, 1 H); 6.80 (*s*, 1 H); 7.01–7.36 (*m*, 8 H). Anal. calc. for $C_{21}H_{20}Cl_3N_3O_2$: C 55.71, H 4.45, Cl 23.49, N 9.28; found: C 55.72, H 4.58, Cl 23.14, N 9.22.

cis-*3-(4-Fluorophenyl)-3-[(1*H*-imidazol-1-yl)methyl]-2-methyl-5-(phenoxymethyl)isoxazolidine* (**29**). IR (KBr): 1598*m*, 1504*s*, 1455*m*, 1241*s*, 1222*s*, 1078*m*, 1030*m*, 1005*m* (N–O), 907*m*, 860*m*, 833*m*, 763*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.53 (*s*, CH_3N); 2.64 (*dd*, *J* = 5.5, 13.2, H_A–C(4)); 2.83 (*dd*, *J* = 9.9, 13.2, H_B–C(4)); 4.21–4.36 (*m*, CH_2OAr); 4.35 (*d*, *J* = 13.8, 1 H, CH_2N); 4.43 (*d*, *J* = 13.8, 1 H, CH_2N); 4.83–4.94 (*m*, H–C(5)); 6.47 (*s*, 1 H); 6.84 (*s*, 1 H); 6.96–7.36 (*m*, 10 H). Anal. calc. for $C_{21}H_{22}FN_3O_2$: C 68.65, H 6.04, F 5.17, N 11.44; found: C 68.62, H 5.96, F 5.12, N 11.37.

cis-*5-[(4-Chlorophenoxy)methyl]-3-(4-fluorophenyl)-3-[(1*H*-imidazol-1-yl)methyl]-2-methylisoxazolidine* (**30**). IR (KBr): 1597*m*, 1507*s*, 1493*s*, 1457*m*, 1238*s*, 1075*m*, 1028*m*, 825*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.52 (*s*, CH_3N); 2.60 (*dd*, *J* = 5.5, 12.7, H_A–C(4)); 2.84 (*dd*, *J* = 9.9, 12.7, H_B–C(4)); 4.18–4.34 (*m*, CH_2OAr); 4.29 (*d*, *J* = 13.2, 1 H, CH_2N); 4.43 (*d*, *J* = 13.2, 1 H, CH_2N); 4.81–4.92 (*m*, H–C(5)); 6.47 (*s*, 1 H); 6.86–7.30 (*m*, 10 H). Anal. calc. for $C_{21}H_{21}ClFN_3O_2$: C 62.76, H 5.27, Cl 8.82, F 4.73, N 10.46; found: C 62.92, H 5.33, Cl 8.86, F 4.55, N 10.35.

trans-*Isomer* **47**. IR (KBr): 1598*m*, 1506*m*, 1493*s*, 1446*m*, 1288*m*, 1247*s*, 1220*m*, 1077*m*, 1040*m*, 830*m*, 662*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.52 (*s*, CH_3N); 2.53 (*dd*, *J* = 7.7, 13.8, H_A–C(4)); 2.74 (*dd*, *J* = 9.4, 13.8, H_B–C(4)); 4.05–4.24 (*m*, CH_2OAr); 4.16 (*d*, *J* = 14.3, 1 H, CH_2N); 4.36 (*d*, *J* = 14.3, 1 H, CH_2N); 4.59–4.72 (*m*, H–C(5)); 6.43 (*s*, 1 H); 6.76–7.81 (*m*, 10 H). Anal. calc. for $C_{21}H_{21}ClFN_3O_2$: C 62.76, H 5.27, Cl 8.82, F 4.73, N 10.46; found: C 62.68, H 5.50, Cl 8.86, F 4.62, N 10.36.

cis-*5-[(4-Fluorophenoxy)methyl]-3-(4-fluorophenyl)-3-[(1*H*-imidazol-1-yl)methyl]-2-methylisoxazolidine* (**31**). IR (KBr): 1599*m*, 1511*s*, 1459*m*, 1246*m*, 1228*s*, 1216*s*, 1078*m*, 1007*m* (N–O), 830*m*, 773*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.53 (*s*, CH_3N); 2.62 (*dd*, *J* = 5.5, 13.2, H_A–C(4)); 2.83 (*dd*, *J* = 9.9, 13.2, H_B–C(4)); 4.17–4.33 (*m*, CH_2OAr); 4.33 (*d*, *J* = 14.9, 1 H, CH_2N); 4.42 (*d*, *J* = 14.9, 1 H, CH_2N); 4.81–4.93 (*m*, H–C(5)); 6.44 (*s*, 1 H); 6.84 (*s*, 1 H); 6.95–7.06 (*m*, 9 H). Anal. calc. for $C_{21}H_{21}F_2N_3O_2$: C 65.44, H 5.49, F 9.86, N 10.90; found: C 65.84, H 5.38, F 9.55, N 10.88.

cis-*5-[(4-Chlorophenoxy)methyl]-3-[(1*H*-imidazol-1-yl)methyl]-3-(4-methoxyphenyl)-2-methylisoxazolidine* (**32**). IR (KBr): 1618*m*, 1598*m*, 1562*m*, 1513*s*, 1493*s*, 1454*m*, 1238*s*, 1182*m*, 1027*m*, 1004*m* (N–O), 827*m*, 820*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.52 (*s*, CH_3N); 2.54 (*dd*, *J* = 5.5, 13.0, H_A–C(4)); 2.83 (*dd*, *J* = 9.4, 13.0, H_B–C(4)); 3.80 (*s*, CH_3O); 4.16–4.32 (*m*, CH_2OAr); 4.34 (*d*, *J* = 12.7, 1 H, CH_2N); 4.39 (*d*, *J* = 12.7, 1 H, CH_2N); 4.79–4.93 (*m*, H–C(5)); 6.45 (*s*, 1 H); 6.77–7.34 (*m*, 10 H). Anal. calc. for $C_{22}H_{24}ClN_3O_3$: C 63.84, H 5.84, Cl 8.57, N 10.15; found: C 63.91, H 5.94, Cl 8.59, N 10.21.

trans-*Isomer* **49**. IR (KBr): 1615*m*, 1513*s*, 1493*s*, 1450*m*, 1285*m*, 1236*s*, 1181*m*, 1041*m*, 1001*m* (N–O), 846*m*, 833*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.35 (*dd*, *J* = 7.7, 13.2, H_A–C(4)); 2.50 (*s*, CH_3N); 2.82 (*dd*, *J* = 9.4, 13.2, H_B–C(4)); 3.82 (*s*, CH_3O); 4.06–4.24 (*m*, CH_2OAr); 4.24 (*d*, *J* = 13.7, 1 H, CH_2N); 4.35 (*d*, *J* = 13.7, 1 H, CH_2N); 4.58–4.70 (*m*, H–C(5)); 6.42 (*s*, 1 H); 6.79–7.31 (*m*, 10 H).

cis-*3-[(1*H*-Imidazol-1-yl)methyl]-5-[(4-methoxyphenoxy)methyl]-3-(4-methoxyphenyl)-2-methylisoxazolidine* (**33**). IR (KBr): 1612*m*, 1508*s*, 1457*m*, 1444*m*, 1250*m*, 1230*s*, 1180*m*, 1076*m*, 1034*m*, 1005*m* (N–O), 905*m*, 827*m*, 764*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.52 (*s*, CH_3N); 2.59 (*dd*, *J* = 5.5, 13.2, H_A–C(4)); 2.80 (*dd*, *J* = 9.9, 13.2, H_B–C(4)); 3.77 (*s*, CH_3O); 3.81 (*s*, CH_3O); 4.15–4.30 (*m*, CH_2OAr); 4.36 (*d*, *J* = 14.3, 1 H, CH_2N); 4.41 (*d*, *J* = 14.3, 1 H, CH_2N); 4.78–4.90 (*m*, H–C(5)); 6.44 (*s*, 1 H); 6.81–7.02 (*m*, 10 H). Anal. calc. for $C_{23}H_{27}N_3O_4$: C 67.46, H 6.65, N 10.26; found: C 67.43, H 6.64, N 10.20.

cis-*5-[(4-Chlorophenoxy)methyl]-3-[(1*H*-imidazol-1-yl)methyl]-2-methyl-3-(4-methylphenyl)isoxazolidine* (**34**). IR (KBr): 1590*m*, 1505*m*, 1494*s*, 1456*m*, 1385*w*, 1235*s*, 1080*m*, 1002*m* (N–O), 825*m*, 817*m*, 750*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.34 (*s*, CH_3Ar); 2.53 (*s*, CH_3N); 2.54 (*dd*, *J* = 5.5, 12.7, H_A–C(4)); 2.85 (*dd*, *J* = 9.4, 12.7, H_B–C(4)); 4.17–4.31 (*m*, CH_2OAr); 4.34 (*d*, *J* = 14.3, 1 H, CH_2N); 4.40 (*d*, *J* = 14.3, 1 H, CH_2N); 4.80–4.90 (*m*, H–C(5)); 6.45 (*s*, 1 H); 6.79–7.32 (*m*, 10 H). Anal. calc. for $C_{22}H_{24}ClN_3O_2$: C 66.41, H 6.08, Cl 8.91, N 10.56; found: C 66.38, H 6.09, Cl 8.91, N 10.54.

cis-5-[(4-Chlorophenoxy)methyl]-3-[(1H-imidazol-1-yl)methyl]-3-(3-methoxyphenyl)-2-methylisoxazolidine (**35**). IR (KBr): 1610*m*, 1583*m*, 1495*s*, 1453*m*, 1435*m*, 1286*m*, 1233*s*, 1078*m*, 1045*m*, 1008*m* (N–O), 821*m*, 810*m*, 705*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.55 (*s*, CH_3N); 2.55 (*dd*, *J* = 5.5, 12.7, H_A–C(4)); 2.86 (*dd*, *J* = 9.9, 12.7, H_B–C(4)); 3.72 (*s*, CH_3O); 4.17–4.30 (*m*, CH_2OAr); 4.31 (*d*, *J* = 13.2, 1 H, CH_2N); 4.44 (*d*, *J* = 13.2, 1 H, CH_2N); 4.82–4.93 (*m*, H–C(5)); 6.47 (*s*, 1 H); 6.55–7.31 (*m*, 10 H). Anal. calc. for $C_{22}H_{24}ClN_3O_3$: C 63.84, H 5.84, Cl 8.57, N 10.15; found: C 63.61, H 5.90, Cl 8.55, N 10.14.

cis-5-[(4-Chlorophenoxy)methyl]-3-[(1H-imidazol-1-yl)methyl]-2-methyl-3-(3-methylphenyl)isoxazolidine (**36**). IR (KBr): 1494*s*, 1456*m*, 1243*s*, 1232*m*, 1079*m*, 1010*m* (N–O), 821*m*, 743*m*, 705*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.31 (*s*, CH_3Ar); 2.54 (*s*, CH_3N); 2.56 (*dd*, *J* = 5.5, 13.2, H_A–C(4)); 2.88 (*dd*, *J* = 9.9, 13.2, H_B–C(4)); 4.18–4.34 (*m*, CH_2OAr); 4.35 (*d*, *J* = 14.3, 1 H, CH_2N); 4.42 (*d*, *J* = 14.3, 1 H, CH_2N); 4.82–4.95 (*m*, H–C(5)); 6.41 (*s*, 1 H); 6.83–7.30 (*m*, 10 H). Anal. calc. for $C_{22}H_{24}ClN_3O_2$: C 66.41, H 6.08, Cl 8.91, N 10.56; found: C 66.45, H 6.14, Cl 9.09, N 10.63.

cis-3-(4-Chloro-3-methylphenyl)-5-[(4-chlorophenoxy)methyl]-3-[(1H-imidazol-1-yl)methyl]-2-methylisoxazolidine (**37**). IR (KBr): 1494*s*, 1451*m*, 1280*m*, 1242*s*, 1232*m*, 1080*m*, 1005*m* (N–O), 820*m*, 746*m*, 665*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.32 (*s*, CH_3Ar); 2.52 (*s*, CH_3N); 2.57 (*dd*, *J* = 5.5, 13.2, H_A–C(4)); 2.84 (*dd*, *J* = 9.9, 13.2, H_B–C(4)); 4.15–4.33 (*m*, CH_2OAr); 4.28 (*d*, *J* = 13.8, 1 H, CH_2N); 4.44 (*d*, *J* = 13.8, 1 H, CH_2N); 4.79–4.94 (*m*, H–C(5)); 6.47 (*s*, 1 H); 6.80–7.30 (*m*, 9 H). Anal. calc. for $C_{22}H_{23}Cl_2N_3O_2$: C 61.12, H 5.36, Cl 16.40, N 9.72; found: C 61.08, H 5.45, Cl 16.34, N 9.72.

cis-5-[(4-Chlorophenoxy)methyl]-3-(3,4-dichlorophenyl)-3-[(1H-imidazol-1-yl)methyl]-2-methylisoxazolidine (**38**). IR (KBr): 1592*w*, 1494*s*, 1473*m*, 1457*m*, 1242*s*, 1232*s*, 1076*m*, 1027*m*, 1007*m* (N–O), 831*m*, 752*m*, 666*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.53 (*s*, CH_3N); 2.60 (*dd*, *J* = 5.5, 13.2, H_A–C(4)); 2.83 (*dd*, *J* = 9.4, 13.2, H_B–C(4)); 4.15–4.30 (*m*, CH_2OAr); 4.23 (*d*, *J* = 13.7, 1 H, CH_2N); 4.48 (*d*, *J* = 13.7, 1 H, CH_2N); 4.78–4.90 (*m*, H–C(5)); 6.52 (*s*, 1 H); 6.76–7.41 (*m*, 9 H). Anal. calc. for $C_{21}H_{20}Cl_3N_3O_2$: C 55.71, H 4.45, Cl 23.49, N 9.28; found: C 55.65, H 4.50, Cl 23.61, N 9.21.

cis-5-[2-(4-Chlorophenoxy)ethyl]-3-(4-chlorophenyl)-3-[(1H-imidazol-1-yl)methyl]-2-methylisoxazolidine (**39**). IR (KBr): 1596*m*, 1496*s*, 1251*s*, 1098*m*, 1078*m*, 1045*m*, 1008*m* (N–O), 905*m*, 817*s*, 805*m*, 751*m*, 664*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.16–2.29 (*m*, H_A–C(4), CH_2CH_2OAr); 2.47 (*s*, CH_3N); 2.89 (*dd*, *J* = 9.4, 13.2, H_B–C(4)); 3.99 (*d*, *J* = 13.2, 1 H, CH_2N); 4.11 (*t*, *J* = 6.1, CH_2CH_2OAr); 4.39 (*d*, *J* = 13.2, 1 H, CH_2N); 4.65–4.80 (*m*, H–C(5)); 6.46 (*s*, 1 H); 6.82–7.30 (*m*, 10 H). Anal. calc. for $C_{22}H_{23}Cl_2N_3O_2$: C 61.12, H 5.36, Cl 16.40, N 9.72; found: C 61.08, H 5.44, Cl 16.50, N 9.64.

cis-5-[3-(4-Chlorophenoxy)propyl]-3-(4-chlorophenyl)-3-[(1H-imidazol-1-yl)methyl]-2-methylisoxazolidine (**40**). IR (KBr): 1650–1620*m*, 1485*s*, 1445–1380*m* (br.), 1232*s*, 1005*m* (N–O), 818*m*, 732*m*, 660*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.84–2.06 (*m*, $CH_2CH_2CH_2OAr$); 2.09 (*dd*, *J* = 5.5, 13.2, H_A–C(4)); 2.45 (*s*, CH_3N); 2.84 (*dd*, *J* = 9.9, 13.2, H_B–C(4)); 3.95–4.11 (*m*, CH_2OAr); 4.00 (*d*, *J* = 13.8, 1 H, CH_2N); 4.39 (*d*, *J* = 13.8, 1 H, CH_2N); 4.48–4.65 (*m*, H–C(5)); 6.44 (*s*, 1 H); 6.81–7.14 (*m*, 6 H); 7.20–7.29 (*m*, 4 H). Anal. calc. for $C_{23}H_{25}Cl_2N_3O_2$: C 61.89, H 5.65, Cl 15.88, N 9.41; found: C 61.99, H 5.71, Cl 15.47, N 9.42.

cis-3-(4-Chlorophenyl)-5-[3-(4-fluorophenoxy)propyl]-3-[(1H-imidazol-1-yl)methyl]-2-methylisoxazolidine (**41**). IR (KBr): 2958*m*, 1595*w*, 1506*s*, 1477*m*, 1450*m*, 1258*m*, 1246*m*, 1199*m*, 1097*m*, 1080*m*, 1020*m*, 1005*m* (N–O), 850*m*, 834*m*, 816*m*, 775*m*, 743*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.84–2.06 (*m*, $CH_2CH_2CH_2OAr$); 2.09 (*dd*, *J* = 5.5, 13.2, H_A–C(4)); 2.46 (*s*, CH_3N); 2.83 (*dd*, *J* = 9.9, 13.2, H_B–C(4)); 3.96–4.07 (*m*, CH_2OAr, 1 H of CH_2N); 4.38 (*d*, *J* = 14.9, 1 H, CH_2N); 4.50–4.64 (*m*, H–C(5)); 6.43 (*s*, 1 H); 6.81–7.02 (*m*, 8 H); 7.27 (*d*, *J* = 9.4, 2 H). Anal. calc. for $C_{23}H_{25}ClFN_3O_2$: C 64.26, H 5.86, Cl 8.25, F 4.42, N 9.77; found: C 64.07, H 5.76, Cl 8.53, F 4.49, N 9.67.

cis-5-[3-(4-Fluorophenoxy)propyl]-3-(4-fluorophenyl)-3-[(1H-imidazol-1-yl)methyl]-2-methylisoxazolidine (**42**). IR (KBr): 2956*m*, 1597*m*, 1508*s*, 1470*m*, 1450*m*, 1249*m*, 1223*m*, 1207*s*, 1076*m*, 1035*m*, 829*s*, 745*m*, 735*m*, 664*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.88–2.07 (*m*, $CH_2CH_2CH_2OAr$); 2.10 (*dd*, *J* = 5.5, 13.2, H_A–C(4)); 2.47 (*s*, CH_3N); 2.85 (*dd*, *J* = 9.9, 13.2, H_B–C(4)); 3.94–4.10 (*m*, CH_2OAr); 4.01 (*d*, *J* = 14.3, 1 H, CH_2N); 4.38 (*d*, *J* = 14.3, 1 H, CH_2N); 4.52–4.65 (*m*, H–C(5)); 6.41 (*s*, 1 H); 6.81–7.16 (*m*, 10 H). Anal. calc. for $C_{23}H_{25}F_2N_3O_2$: C 66.81, H 6.09, F 9.19, N 10.16; found: C 67.24, H 6.25, F 8.87, N 10.18.

cis-3-[(1H-Imidazol-1-yl)methyl]-2-methyl-5-[(1-naphthalenyloxy)methyl]-3-phenylisoxazolidine (**51**). M.p. of nitrate salt 160–163° (dec.; MeOH). IR (KBr): 2900–2700*w* (salt), 1578*m*, 1450*m*, 1405*s* (NO_3), 1325*s*, 1105*m*, 1017*m*, 797*m*, 781*m*, 770*m*, 725*m*, 705*m*. ^{1}H-NMR (200 MHz, $CDCl_3/CF_3COOH$): 2.80 (*s*, CH_3N); 2.92 (*dd*, *J* = 5.5, 13.2, H_A–C(4)); 3.18 (*dd*, *J* = 9.9, 13.2, H_B–C(4)); 4.43 (*d*, *J* = 13.2, 1 H, CH_2N); 4.53–4.67 (*m*, CH_2OAr); 5.00 (*d*, *J* = 13.2, 1 H, CH_2N); 5.14–5.30 (*m*, H–C(5)); 6.85–8.74 (*m*, 15 H). Anal. calc. for $C_{25}H_{26}N_4O_5$: C 64.92, H 5.67, N 12.11; found: C 64.85, H 5.73, N 12.15.

cis-3-(4-Fluorophenyl)-3-[(1H-imidazol-1-yl)methyl]-2-methyl-5-[(2-naphthalenyloxy)methyl]isoxazolidine (**52**). IR (KBr): 1629*m*, 1600*m*, 1508*s*, 1448*m*, 1263*m*, 1224*s*, 1187*m*, 1031*m*, 1019*m*, 858*m*, 839*m*, 822*m*, 748*m*.

^{1}H-NMR (200 MHz, $CDCl_3$): 2.55 (*s*, CH_3N); 2.67 (*dd*, *J* = 5.5, 13.2, H_A–C(4)); 2.88 (*dd*, *J* = 9.9, 13.2, H_B–C(4)); 4.33–4.48 (*m*, CH_2OAr); 4.36 (*d*, *J* = 13.8, 1 H, CH_2N); 4.49 (*d*, *J* = 13.8, 1 H, CH_2N); 4.89–5.00 (*m*, H–C(5)); 6.51 (*s*, 1 H); 6.86 (*s*, 1 H); 6.99–7.79 (*m*, 12 H). Anal. calc. for $C_{25}H_{24}FN_3O_2$ (adjusted for 0.59% H_2O): C 71.50, H 5.82, F 4.52, N 10.01; found: C 71.33, H 5.72, F 4.50, N 10.05.

trans-*Isomer* **57**. Nitrate salt: IR (KBr): 2600–2000*w* (salt), 1625*m*, 1598*m*, 1513*s*, 1411*s* (NO_3), 1392*s* (NO_3), 1322*m*, 1305*s*, 1260*m*, 1227*m*, 1010*m* (N–O), 845*m*, 755*m*, 746*m*. ^{1}H-NMR (200 MHz, (D_6)DMSO): 2.50 (*s*, CH_3N); 2.71–2.93 (*m*, 2 H–C(4)); 3.21–3.62 (*m*, NH^+); 4.14–4.35 (*m*, CH_2OAr); 4.55 (*d*, *J* = 14.9, 1 H, CH_2N); 4.67 (*d*, *J* = 14.9, 1 H, CH_2N); 4.67–4.80 (*m*, 1 H–C(5)); 7.12–7.86 (*m*, 13 H); 8.69 (*s*, 1 H). Anal. calc. for $C_{25}H_{25}FN_4O_5$: C 62.49, H 5.24, F 3.95, N 11.66; found: C 62.40, H 5.10, F 3.92, N 11.57.

cis-6-{*[3-(4-Fluorophenyl)-3-[(1*H*-imidazol-1-yl)methyl]-2-methylisoxazolidin-5-yl]methoxy}-1,3-benzoxathiol-2-one* (**54**). IR (KBr): 1757*s* (C=O), 1614*m*, 1516*m*, 1485*m*, 1458*m*, 1283*m*, 1241*m*, 1167*s*, 1079*m*, 1025*m*, 1008*m* (N–O), 837*m*, 818*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.53 (*s*, CH_3N); 2.59 (*dd*, *J* = 5.5, 13.2, H_A–C(4)); 2.88 (*dd*, *J* = 9.9, 13.2, H_B–C(4)); 4.22–4.36 (*m*, CH_2Ar); 4.27 (*d*, *J* = 13.8, 1 H, CH_2N); 4.44 (*d*, *J* = 13.8, 1 H, CH_2N); 4.81–4.96 (*m*, H–C(5)); 6.46 (*s*, 1 H); 6.87–7.34 (*m*, 9 H). Anal. calc. for $C_{22}H_{20}FN_3O_4S$: C 59.85, H 4.57, F 4.30, N 9.52, S 7.26; found: C 60.03, H 4.59, F 4.33, N 9.48, S 7.40.

cis-*5-[(4-Chlorophenoxy)methyl]-3-[(1*H*-imidazol-1-yl)methyl]-3-phenyl-2-benzylisoxazolidine* (**55**). IR (KBr): 1596*m*, 1495*s*, 1453*m*, 1448*m*, 1281*m*, 1247*s*, 1075*m*, 1004*m* (N–O), 903*m*, 822*m*, 731*m*, 697*m*, 662*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.59 (*dd*, *J* = 5.5, 13.2, H_A–C(4)); 2.96 (*dd*, *J* = 9.9, 13.2, H_B–C(4)); 3.55 (*d*, *J* = 14.3, 1 H, PhCH_2); 3.97 (*d*, *J* = 14.3, 1 H, PhCH_2); 4.14–4.32 (*m*, CH_2OAr); 4.44 (*d*, *J* = 13.2, 1 H, CH_2N); 4.59 (*d*, *J* = 13.2, 1 H, CH_2N); 4.84–5.01 (*m*, H–C(5)); 6.49 (*s*, 1 H); 6.84–7.40 (*m*, 16 H). Anal. calc. for $C_{27}H_{26}ClN_3O_2$: C 70.50, H 5.70, Cl 7.71, N 9.14; found: C 70.48, H 5.82, Cl 7.85, N 9.06.

trans-*Isomer* **58**. IR (KBr): 1492*s*, 1453*m*, 1283*m*, 1243*s*, 1079*m*, 1007*m* (N–O), 833*m*, 825*m*, 728*m*, 664*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.57 (*dd*, *J* = 7.7, 13.2, H_A–C(4)); 2.92 (*dd*, *J* = 9.4, 13.2, H_B–C(4)); 3.70 (*d*, *J* = 13.2, 1 H, PhCH_2); 3.87 (*d*, *J* = 13.2, 1 H, PhCH_2); 4.11–4.23 (*m*, CH_2OAr); 4.28 (*d*, *J* = 13.8, 1 H, CH_2N); 4.49 (*d*, *J* = 13.8, 1 H, CH_2N); 4.60–4.73 (*m*, H–C(5)); 6.47 (*s*, 1 H); 6.80–7.42 (*m*, 16 H). Anal. calc. for $C_{27}H_{26}ClN_3O_2$: C 70.50, H 5.70, Cl 7.71, N 9.14; found: C 70.16, H 5.65, Cl 7.88, N 9.12.

cis-*5-[(4-Chlorophenoxy)methyl]-2-(3-chlorobenzyl)-3-[(1*H*-imidazol-1-yl)methyl]-3-phenylisoxazolidine* (**56**). IR (KBr): 1599*m*, 1493*s*, 1452*m*, 1286*m*, 1249*s*, 1073*m*, 1006*m* (N–O), 905*m*, 824*m*, 778*m*, 704*s*, 663*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.73 (*dd*, *J* = 5.5, 13.2, H_A–C(4)); 2.93 (*dd*, *J* = 9.9, 13.2, H_B–C(4)); 3.50 (*d*, *J* = 14.9, 1 H, ArCH_2N); 3.92 (*d*, *J* = 14.9, 1 H, ArCH_2N); 4.14–4.31 (*m*, CH_2OAr); 4.44 (*d*, *J* = 14.3, 1 H, CH_2N); 4.57 (*d*, *J* = 14.3, 1 H, CH_2N); 4.80–4.94 (*m*, H–C(5)); 6.47 (*s*, 1 H); 6.85–7.36 (*m*, 15 H). Anal. calc. for $C_{27}H_{25}Cl_2N_3O_2$: C 65.59, H 5.10, Cl 14.34, N 8.50; found: C 65.47, H. 5.15, Cl 14.50, N 8.48.

Assay for Antifungal Activity in vitro. The antifungal activity was assayed *in vitro* in solid agar tests performed in 24-well tissue culture plates. The test media was prepared by diluting the test compound 10-fold into 'antibiotic medium 3' + 2% agar. The testing was performed using either a 4-point (70, 20, 2, and 2 μg/ml) or 6-point (70, 20, 7, 2, 0.7, and 0.2 μg/ml) dilution scheme with ketoconazole (**4**) being used as a control in all assays. All test organisms were grown in potato flake agar at 26°. *Candida albicans* was grown overnight, *Aspergillus fumigatus* for *ca.* 1 week, and *Trichophyton rubrum* for *ca.* 2 weeks. The cells were either removed from the plates with a sterile cotton swab and suspended in sterile H_2O (*C. albicans, A. fumigatus*) or washed from the surface of the plate with sterile H_2O and diluted in sterile H_2O (*T. rubrum*). The actual cell counts were performed using a hemacytometer and the suspensions were diluted to 1×10^4 cells/ml. The test and control plates were inoculated with 0.05 ml of the fungal suspension and were incubated at 26° until visible growth in the compound-free control plates was evident. The minimum inhibitory concentration (*MIC*) values were interpreted as the lowest dilution at which no visible growth occurred.

REFERENCES

[1] J. Klastersky, *Clin. Therapeutics* **1985,** *8,* 90.
[2] P. Periti, T. Mazzei, *Clin. Therapeutics* **1985,** *8,* 100.
[3] G. P. Bodey, Ed., 'Candidiasis: A Growing Concern', *Am. J. Med.* **1984,** *77* (4D), and ref. cit. therein.
[4] G. P. Bodey, *Am. J. Med.* **1986,** *80,* 112.
[5] E. Drouhet, B. Dupont, *Rev. Infect. Dis.* **1987,** *9* (Suppl. 1), S4.
[6] D. A. Stevens, *Drugs* **1983,** *26,* 334.
[7] F. W. Chandler, in 'Current Topics in Medical Mycology', Ed. M. R. McGinnis, Springer-Verlag, New York, 1985, Vol. 1, pp. 1–23.
[8] G. P. Bodey, in 'Antifungal Drugs', Ed. V. St. Georgiev, Annals of the New York Academy of Sciences, New York, 1988, in press.
[9] R. M. Tucker, P. L. Williams, E. G. Arathoon, D. A. Stevens, in [8].
[10] J. R. Graybill, in [8].
[11] J. R. Graybill, D. A. Stevens, J. N. Galgiani, A. M. Sugar, P. C. Craven, C. Gregg, M. Huppert, G. Cloud, W. E. Dismukes, in [8].
[12] R. Negroni, in [8].
[13] A. Restrepo, A. Gonzalez, I. Gomez, M. Arango, C. de Bedout, in [8].
[14] J. R. Graybill, P. C. Craven, *Med. Prog. (Hong Kong)* **1984,** *11,* 67.
[15] G. Medoff, J. Brajtburg, G. S. Kobayashi, J. Bolard, *Ann. Rev. Pharmacol. Toxicol.* **1983,** *23,* 303.
[16] D. J. Drutz, *Drugs* **1983,** *26,* 337.
[17] P. D. Hoeprich, N. M. Flynn, M. M. Kawachi, K. K. Lee, R. M. Lawrence, L. K. Heath, C. P. Schaffner, in [8].
[18] J. Symoens, G. Cauwenbergh, *Prog. Drug Res.* **1983,** *27,* 63.
[19] H. vanden Bossche, P. Marichal, J. Gorrens, H. Geerts, P. A. J. Janssen, in [8].
[20] C. H. Kirkpatrick, in [8].
[21] R. C. Heel, R. N. Brogden, A. Carmine, P. A. Morley, T. M. Speight, G. S. Avery, *Drugs* **1982,** *23,* 1.
[22] K. H. Buechel, M. Plempel, in 'Chronicles of Drug Discovery', Eds. J. S. Bindra and D. Lednicer, Wiley, New York, 1983, Vol. 2, pp. 235–269.
[23] G. Schar, F. H. Kayser, M. C. Dupont, *Chemotherapy* **1976,** *22,* 211.
[24] D. Thienpont, J. Van Cutsem, J. Van Gerven, J. Heeres, P. A. J. Janssen, *Experientia* **1979,** *35,* 606.
[25] M. Borgers, in 'The Scientific Basis of Antimicrobial Chemotherapy', Eds. D. Greenwood and F. O'Grady, Cambridge University Press, Cambridge, 1985, p. 133.
[26] Anon., *Drugs of the Future* **1986,** *11,* 335.
[27] K. Richardson, K. W. Brammer, M. S. Marriott, P. F. Troke, *Antimicrob. Agents Chemother.* **1985,** *27,* 832.
[28] K. Richardson, K. Cooper, M. S. Marriott, M. H. Tarbit, P. F. Troke, P. J. Whittle, in [8].
[29] P. F. Troke, M. S. Marriott, K. Richardson, M. H. Tarbit, in [8].
[30] K. W. Brammer, J. M. Feczko, in [8].
[31] K. Richardson, M. S. Marriott, *Annu. Rep. Med. Chem.* **1987,** *22,* 159.
[32] G. B. Mullen, V. St. Georgiev, *Heterocycles* **1986,** *24,* 3441.
[33] G. B. Mullen, P. A. Swift, V. St. Georgiev, *J. Pharm. Sci.* **1987,** *76,* 930.
[34] For preliminary communication see: G. B. Mullen, D. M. Maryniak, P. A. Swift, S. D. Allen, J. T. Mitchell, C. R. Kinsolving, V. St. Georgiev, in [8].
[35] J. J. Tufariello, in '1,3-Dipolar Cycloaddition Chemistry', Ed. A. Padwa, Wiley & Sons, New York, 1984, Vol. 2. pp. 83–168.
[36] E. F. Godefroi, J. Heeres, J. Van Cutsem, P. A. J. Janssen, *J. Med. Chem.* **1969,** *12,* 784.
[37] P. J. Carroll, G. B. Mullen, V. St. Georgiev, *Acta Crystallogr.*, in press.
[38] C. Ruis-Alonso, R. C. Wain, *Ann. Appl. Biol.* **1978,** *88,* 299.
[39] S. Marcinkiewicz, J. Green, P. Mamalis, *Tetrahedron* **1961,** *14,* 208.
[40] For Part 21 of the series 'Studies on Antifungal Agents', see [37].
[41] W. N. White, D. Gwynn, R. Schlitt, C. Girard, W. Fife, *J. Am. Chem. Soc.* **1958,** *80,* 3271.
[42] E. T. McBee, E. Rapkin, *J. Am. Chem. Soc.* **1951,** *73,* 2375.
[43] D. S. Tarbell, J. W. Wilson, *J. Am. Chem. Soc.* **1942,** *64,* 1066.