5-{[Aryl or Aryloxy (or thio)]methyl}-3-(1*H*-imidazol-1-ylmethyl)-3-(2-thienyl)-2-methylisoxazolidine Derivatives as Novel Antifungal Agents

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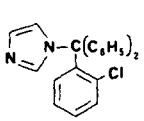
Abstract □ The in vitro antifungal activity of a novel series of *cis*- and *trans*-5-{[aryl or aryloxy (or thio)]methyl}-3-(1*H*-imidazol-1-ylmethyl)-3-(2-thienyl)-2-methylisoxazolidines (**13–24**) was evaluated and compared with ketoconazole. The title series of compounds was prepared via a 1,3-dipolar cycloaddition reaction of 1-(2-thienyl)-2-(1*H*-imidazol-1-yl)-*N*-methylethanimine *N*-oxides with appropriate styrenes, allyl phenyl ethers, or allyl phenyl thioether precursors. The resulting products were mixtures of the corresponding *cis*- and *trans*-diastereomers which were readily separated by flash chromatography on neutral silica gel. The majority of compounds **13–24**, when tested in solid agar cultures, exhibited moderate to potent activity against *Trichophyton rubrum*, *Aspergillus fumigatus*, and *Candida albicans* at concentrations ranging between ≤2.0 and 70.0 μg/mL.

Clotrimazole (**1**),[1] along with miconazole (**2**)[2,3] and econazole (**3**),[2,4] were the first azole derivatives to be successfully introduced for clinical use as antifungals. Since then, a number of other azole compounds were developed and mar keted as antimycotic agents. One of them, ketoconazole (**4**),[5–12] became the first orally active antifungal drug having activity against a broad spectrum of various superficial and systemic mycoses.[5] Recently, two new azoles, itraconazole (**5**)[13–16] and fluconazole (**6**),[17–20] were reported to have little of the major side effects of ketoconazole (mainly hepatotoxicity) and to display a better pharmacokinetic profile.[21] However, like **4**, **5** and **6** are fungistatic rather than fungicidal in their mechanism of action.

Recently,[22,23] we reported the synthesis and antifungal activity of a series of 3,5-substituted isoxazolidine derivatives (**7**) that were found to possess potent antifungal activity against a wide variety of dermatophytes and yeast and systemic mycoses. We explored the effects of substitution in both phenyl rings and the alkyl moiety of the C-5 substituent



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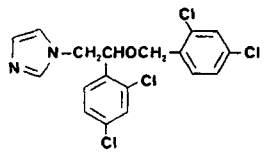

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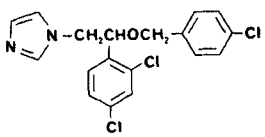

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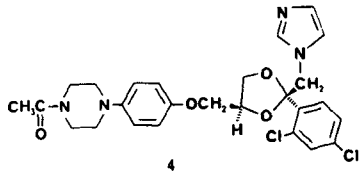

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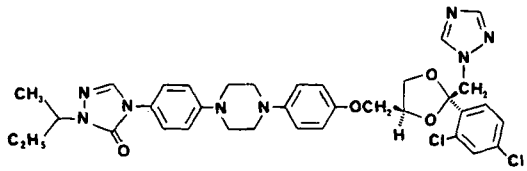

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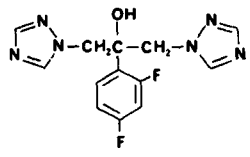

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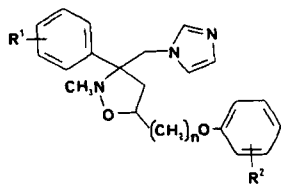

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on the in vitro antifungal activity of **7**. In the present communication, we report the extension of these studies, namely, the synthesis and antifungal activity of a novel series of 5-{[aryl or aryloxy (or thio)]methyl}-3-(1*H*-imidazol-1-ylmethyl)-3-(2-thienyl)-2-methylisoxazolidines, **13–24**.

Results and Discussion

As seen from Scheme I, the title thienyl compounds were prepared by an initial bromination of 2-acetylthiophene (**8**) to form the corresponding bromo derivative **9**. Reaction of **9** with imidazole provided 1-(2-thienyl)-2-(1*H*-imidazol-1-yl)ethanone (**10**), which in turn, was treated with *N*-methylhydroxylamine hydrochloride to yield the 1-(2-thienyl)-2-(1*H*-imidazol-1-yl)-*N*-methylethanimine N-oxide (**11**). Next, the α-substituted ketonitrone **11** underwent a 1,3-dipolar cycloaddition reaction[24,25] with an appropriate styrene **12** (or allyl phenyl ether or allyl phenyl thioether), leaving the desired 3,5-substituted isoxazolidine compound as a *cis*/*trans*-diastereomeric mixture (**13**, **14**).[26] The latter was conveniently separated by flash chromatography on neutral silica gel. The 1,3-dipolar cycloaddition of (*E*)-nitrones **11** with **12** proceeded in a regiospecific manner, affording exclusively the 5-substituted isoxazolidines **13** and **14**. The corresponding 4-substituted isoxazolidine derivatives (see Structure iv in Scheme II) are excluded on the basis of electronic factors.

The configuration of the asymmetric centers of *cis*-/*trans*-isoxazolidines **13** and **14** was determined by ^{1}H NMR spectroscopy using the difference (Δ) between the coupling constants (*J*) of H_{4A}, H_{4B}, and H_5 protons (Table I). The corresponding Δ values for *cis*-**13**-**19** (e.g., **14**) and *trans*-**20**-**24** (e.g., **20**) were 5.5 and 0 Hz, respectively. Similar correlations

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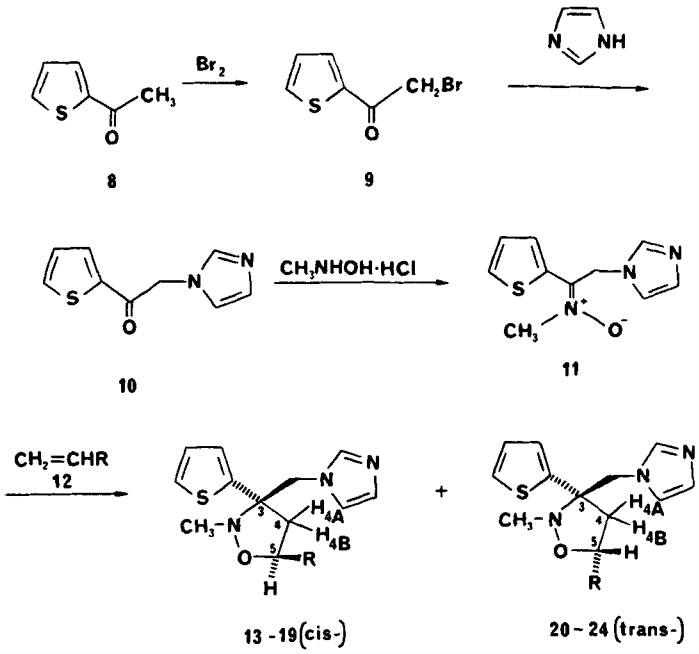


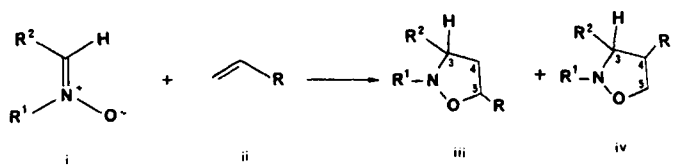
Scheme I

for Δ values had been observed previously[23] for the structurally related *cis*- and *trans*-3-aryl-5-[(aryloxy)methyl]-3-[(1*H*-imidazol-1-yl)methyl]-2-methylisoxazolidines **25** and **26**, respectively. As seen from Table I, the Δ value for *cis*-**25** is 4.1 Hz and significantly higher than the 1.4 Hz observed for *trans*-**26**. An X-ray crystal structure determination[27] of *cis*-**25** unambiguously confirmed its structure. The configuration of all remaining *cis*- and *trans*-isoxazolidines was determined using the same correlations of *J* values (see *Experimental Section* for details). All compounds that were prepared during the present study are listed in Table II.

The antifungal activity of the thienyl derivatives **13–24** was assayed in vitro in solid agar tests performed in 24-well tissue culture plates. The activity was measured by the minimum inhibitory concentration (MIC) values which are interpreted as the lowest dilution at which no visible growth of fungus is observed. The results from the in vitro screening of **13–24** are summarized in Table III. When tested against *Trichophyton rubrum*, *Aspergillus fumigatus*, and *Candida albicans*, all compounds exerted moderate to potent in vitro activity. In general, the antifungal potency against the dermatophyte *T. rubrum* was greater than that against *A. fumigatus* and *C. albicans*. Of the three *cis*-analogues **13–15**, the 5-(4-chlorophenyl) compound **14** was the most active one, having MIC values of <0.2–20.0 μg/mL; **14** was equipotent with ketoconazole against *A. fumigatus* and *C. albicans*, but more potent against *T. rubrum*. It is of interest to note that when compared with its *trans*-isomer **20**, the latter compound was significantly less active against *T. rubrum* and *A. fumigatus* (2.0 versus <0.2 and >70.0 versus 7.0 μg/mL, respectively), but considerably more effective against *C. albicans* (7.0 versus 20.0 μg/mL). In the two pairs of *cis*-/*trans*-5-(4-chlorophenoxy) diastereomers **16**/**21** and **17**/**22**, the configuration of the two asymmetric centers seems of less importance for activity against the yeast *C. albicans*; however, the ratio of activity against the dermatophyte *T. rubrum* remained similar to that of the 5-(4-chlorophenyl) analogues **14** and **20**. In general, compounds having a 4-chloro substituent (**14**, **17**, **20**, **22**) showed improved in vitro antifungal activity when compared with the corresponding unsubstituted phenyl analogues (**13**, **16**, **21**). The two 5-phenylthiomethyl derivatives **18** and **19** had activity comparable to that of the 5-phenoxymethyl compounds **16** and **17**.

The in vitro antifungal activity of the 3-(2-thienyl) compounds **13–24** was also compared with that of the corresponding 3-(2-furanyl) analogues **27–29**[28] (Table III). Three pairs of derivatives (**14**, **15**, and **20** versus **27–29**, respectively) were examined. While **14** and **27** displayed about the same activity, the thienyl analogue **15** was found to be inferior to its furanyl counterpart **28**. The *trans*-**20** compound was less potent than *trans*-**29** against *T. rubrum* and *A. fumigatus*, but more effective against *C. albicans*. Overall, the presence of a 3-(2-thienyl) ring in the molecule of the 3,5-substituted isoxazolidines led to a decreased in vitro potency against *A. fumigatus*.

Based on the results of in vitro screening, the title series of 5-{[aryl or aryloxy (or thio)]methyl}-3-(1*H*-imidazol-1-ylmethyl)-3-(2-thienyl)-2-methylisoxazolidines **13–24** represent a novel class of antifungal agents.[29]



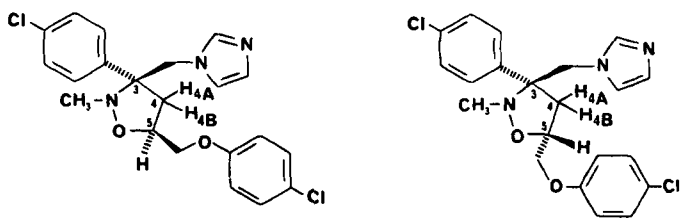
Scheme II

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The infrared (IR) spectra of the compounds as KBr discs were obtained on a Nicolet MX-1 FT spectrometer. The proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained on a Varian EM-360A (60 MHz) spectrometer using tetramethylsilane as an internal standard. The 200 MHz ^{1}H NMR spectra were obtained on a Bruker-IBM-200-SY Fourier-transform instrument using the same internal standard. All spectra were consistent with the assigned structures.

2-(1*H*-Imidazol-1-yl)-1-(2-thienyl)ethanone (10)—Bromine (19.0 mL, 0.371 mol) was added in a dropwise manner to an ice-cold solution of 40.75 g (0.323 mol) of 2-acetylthiophene in 200 mL of ether under a nitrogen atmosphere. After stirring for 90 min, the

Table I—^{1}H NMR Coupling Constants (*J*) for *cis*- and *trans*-Diastereomeric Isoxazolidines[a]



cis-25 trans-26

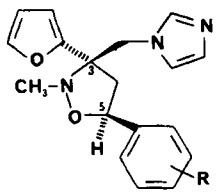
Compound	$J(H_5–H_{4A})$	$J(H_5–H_{4B})$	$\Delta[J(H_5–H_{4B}) - J(H_5–H_{4A})]$
cis-**25**	5.4	9.5	4.1
trans-**26**	7.7	9.1	1.4
cis-**14**	4.4	9.9	5.5
trans-**20**	9.4	9.4	0

[a] Expressed in Hz.

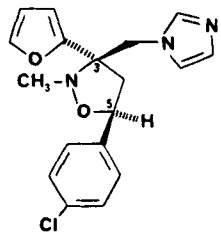
Table II—5-[[(Aryl or Aryloxy (or thio)]methyl]]-3-(1*H*-imidazol-1-ylmethyl]-3-(2-thienyl)-2-methylisoxazolidines

Compound	R	mp, °C	Recrystallization Solvent	Formula
13	C_6H_5	89–92	Ethanol	$C_{18}H_{19}N_3OS$
14	C_6H_4Cl-4	125–127	Ethyl acetate	$C_{18}H_{18}ClN_3OS$
15	$C_6H_4NO_2$-3	154.5–156	Ethanol	$C_{18}H_{18}N_4O_3S$
16	$CH_2OC_6H_5$	107–109	Ethyl acetate	$C_{19}H_{21}N_3O_2S$
17	$CH_2OC_6H_4Cl$-4	118–120	Ethyl acetate	$C_{19}H_{20}ClN_3O_2S$
18·HCl	$CH_2SC_6H_4CH_3$-4	205–210	Ethanol	$C_{20}H_{24}ClN_3OS_2$
19	$CH_2SC_6H_4Cl$-4	101–104	Ethyl acetate	$C_{19}H_{20}ClN_3OS_2$
20	C_6H_4Cl-4	149–152	Ethyl acetate	$C_{18}H_{18}ClN_3OS$
21	$CH_2OC_6H_5$	144–146	Ethyl acetate	$C_{19}H_{21}N_3O_2S$
22	$CH_2OC_6H_4Cl$-4	95–99	Ethyl acetate	$C_{19}H_{20}ClN_3O_2S$
23·HCl	$CH_2SC_6H_4CH_3$-4	149–161	Ethanol:Ether (1:1)	$C_{20}H_{24}ClN_3OS_2$
24·HCl	$CH_2SC_6H_4Cl$-4	168–173	2-Propanol	$C_{19}H_{21}Cl_2N_3OS_2$

Table III—In Vitro Antifungal Activity of 5-[[(Aryl or Aryloxy (or thio)]methyl]]-3-(1*H*-imidazol-1-ylmethyl)-3-(2-thienyl or 2-furanyl)-2-methylisoxazolidines[a]



27: R = 4-Cl (*cis*-)
28: R = 3-NO_2 (*cis*-)



trans-**29**

Compound	*Trichophyton rubrum* ATCC 18762	*Aspergillus fumigatus* ATCC 28212	*Candida albicans* ATCC 10259
13	7.0	>70.0	70.0
14	<0.2	7.0	20.0
15	<2.0	>70.0	>70.0
16	<2.0	70.0	20.0
17	<2.0	20.0	7.0
18	<0.2	20.0	20.0
19	<2.0	7.0	7.0
20	2.0	>70.0	7.0
21	20.0	>20.0	>20.0
22	7.0	>20.0	7.0
23	<2.0	20.0	7.0
27	0.7	2.0	20.0
28	2.0	20.0	>20.0
29	0.7	70.0	20.0
Ketoconazole	0.7	7.0	20.0

[a] Measured as the MIC in μg/mL.

reaction was quenched with 100 mL of saturated aqueous ammonium chloride. The two layers were separated and the organic extract was washed with 100 mL of water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give a yellow oil. The oil was dissolved in 100 mL of ether and added over a period of 60 min to an ice-cold solution of 89.75 g (1.32 mol) of imidazole in 150 mL of methanol under a nitrogen atmosphere. The reaction mixture was stirred at ambient temperature for 22 h, then diluted with 1 L of water and extracted with chloroform (4 × 300 mL). The combined organic extract was dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and flash-chromatographed on neutral silica gel, using a 99:1 mixture of chloroform and methanol as eluant, to give 36.10 g (58%) of ketone **10**, mp 87–89 °C (ethyl acetate); IR (KBr): 3107 (m), 1673 (s), 1505 (m), 1410 (s), 1237 (s), 1230 (s), 1081 (m), 1055 (m), 752 (s), and 732 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 5.31 (s, 2H, NCH_2), 6.96 (s, 1H), 7.11 (s, 1H), 7.20 (t, 1H, J = 4.4 Hz), 7.51 (s, 1H), and 7.76 ppm (d, 2H, J = 4.4 Hz).

Anal.—Calc. for $C_9H_8N_2OS$: C, 56.23; H, 4.19; N, 14.57; S, 16.68. Found: C, 56.03; H, 4.28; N, 14.48; S, 16.39.

2-(1*H*-Imidazol-1-yl)-*N*-methyl-1-(2-thienyl)ethanimine *N*-Oxide (11)—Under a nitrogen atmosphere, a mixture of 22.0 g (0.114 mol) of 2-(1*H*-imidazol-1-yl)-1-(2-thienyl)ethanone, 11.49 g (0.138 mol) of *N*-methylhydroxylamine hydrochloride, and 22.55 g (0.275 mol) of sodium acetate in 250 mL of ethanol was heated to 50 °C and stirred at that temperature for 4 d. The reaction mixture was filtered while hot and the filtrate was concentrated under reduced pressure. Crystallization from ethanol provided 22.62 g (89%) of nitrone **11**, mp 162–164 °C; IR (KBr): 3109 (m), 3100 (m), 3083 (m), 1507 (m), 1365 (s), 1226 (s), 1180 (s), 1090 (s), 826 (m), 712 (s), and 668 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 3.98 (s, 3H, NCH_3), 5.39 (s, 2H, NCH_2), 6.91 (s, 1H), 7.10 (s, 1H), 7.19 (t, 1H, J = 4.4 Hz), and 7.52–7.56 ppm (m, 3H).

Anal.—Calc. for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99. Found: C, 54.16; H, 5.06; N, 18.86.

3-(1*H*-Imidazol-1-ylmethyl)-2-methyl-5-phenyl-3-(2-thienyl)isoxazolidine (13)—A suspension of 4.04 g (0.018 mol) of 2-(1*H*-imidazol-1-yl)-*N*-methyl-1-(2-thienyl)ethanimine *N*-oxide and 3.1 mL (1.5 equiv) of styrene in 100 mL of toluene was refluxed for 72 h under a nitrogen atmosphere. The reaction mixture was cooled to ambient temperature and filtered; from the undissolved solid, 0.73 (18%) of nitrone **11** was recovered. The filtrate was concentrated and then flash chromatographed on neutral silica gel using a 98:2 mixture of chloroform and methanol as eluant, to furnish 2.68 g (45%) of *cis*-**13**, mp 89–92 °C (ethyl acetate); IR (KBr): 3100 (m), 2998 (m), 2970 (m), 2893 (m), 1503 (s), 1449 (s), 1347 (m), 1230 (s), 1079 (s), 1036 (m), 1002 (m), 930 (m), 841 (m), 820 (m), 746 (s), 741 (s), 720 (s), 704 (s), and 664 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 2.42 (dd, 1H, J = 5.0, 13.2 Hz, OHC*H*CH), 2.64 (s, 3H, NCH_3), 3.18 (dd, 1H, J = 9.4, 13.2 Hz, OHCHC*H*), 4.26 (d, 1H, J = 14.3 Hz, N*H*CH), 4.39 (d, 1H, J = 14.3 Hz, NHC*H*), 5.64 (dd, 1H, J = 5.0, 9.4 Hz, OCH), 6.19 (s, 1H), 6.70 (s, 1H), 6.80 (s, 1H), 6.83–6.85 (m, 1H), 6.98–7.03 (m, 1H), and 7.29–7.44 ppm (m, 6H).

Anal.—Calc. for $C_{18}H_{19}N_3OS$: C, 66.44; H, 5.88; N, 12.91. Found: C, 66.34; H, 5.91; N, 12.92.

Compounds 14–24—The remaining 3-(2-thienyl)isoxazolidines **14–24** were prepared by methods similar to that described for the synthesis of *cis*-**13**, and the yield, mp (°C), solvent of recrystallization, IR, ^1H NMR, and analysis data are given below.

5-(4-Chlorophenyl)-3-(1H-imidazol-1-ylmethyl)-2-methyl-3-(2-thienyl)isoxazolidine—cis-Diastereomer **14**—42%; mp 125–127 °C (ethyl acetate); IR (KBr): 3077 (m), 2971 (m), 1507 (s), 1491 (s), 1447 (m), 1235 (s), 1092 (m), 1077 (s), 1035 (m), 1009 (m), 928 (m), 836 (m), 825 (s), 744 (m), and 717 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 2.39 (dd, 1H, J = 4.4, 13.2 Hz, OHC*H*CH), 2.61 (s, 3H, NCH_3), 3.17 (dd, 1H, J = 9.9, 13.2 Hz, OHCHC*H*), 4.22 (d, 1H, J = 14.9 Hz, N*H*CH), 4.39 (d, 1H, J = 14.9 Hz, NHC*H*), 5.56 (dd, 1H, J = 4.4, 9.9 Hz, OCH), 6.27 (s, 1H), 6.79–6.85 (m, 3H), 7.00–7.05 (m, 1H), and 7.31–7.41 ppm (m, 5H).

Anal.—Calc. for $C_{18}H_{18}ClN_3OS$: C, 60.08; H, 5.04; Cl, 9.85; N, 11.68. Found: C, 60.12; H, 5.05; Cl, 10.10; N, 11.70.

trans-Diastereomer **20**—13%; mp 149–152 °C (ethyl acetate); IR (KBr): 3120 (m), 3064 (m), 2977 (m), 2952 (m), 2910 (m), 2880 (m), 1511 (s), 1505 (m), 1230 (s), 1093 (s), 1074 (m), 1069 (m), 1010 (m), 990 (m), 830 (m), 745 (s), and 735 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 2.50 (s, 3H, NCH_3), 2.67 (dd, 1H, J = 9.4, 13.2 Hz, OHC*H*CH), 2.84 (dd, 1H, J = 9.4, 13.2 Hz, OHCHC*H*), 4.45 (s, 2H, NCH_2), 5.09 (t, 1H, J = 9.4 Hz, OCH), 6.77 (s, 1H), 6.83 (d, 1H, J = 4.4 Hz), 6.98–7.02 (m, 2H), and 7.24–7.37 ppm (m, 6H).

Anal.—Calc. for $C_{18}H_{18}ClN_3OS$: C, 60.08; H, 5.04; Cl, 9.85; N, 11.68. Found: C, 60.17; H, 5.16; Cl, 10.13; N, 11.69.

3-(1H-Imidazol-1-ylmethyl)-2-methyl-5-(3-nitrophenyl)-3-(2-thienyl)isoxazolidine **(15)**—29%; mp 154.5–156 °C (ethanol); IR (KBr): 3112 (w), 3092 (m), 3073 (w), 2978 (w), 2893 (m), 1533 (s), 1505 (m), 1460 (m), 1356 (s), 1347 (s), 1234 (m), 1078 (m), 1040 (m), 895 (m), 822 (m), 732 (m), and 717 (m) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): 2.43 (dd, 1H, J = 6.5, 13.1 Hz, OHC*H*CH), 2.54 (s, 3H, NCH_3), 3.22 (dd, 1H, J = 8.6, 13.1 Hz, OHCHC*H*), 4.54 (d, 1H, J = 15.1 Hz, N*H*CH), 4.55 (d, 1H, J = 15.1 Hz, NHC*H*), 5.42 (dd, 1H, J = 6.5, 8.6 Hz, OCH), 6.76 (s, 1H), 7.08–7.13 (m, 2H), 7.42 (s, 1H), 7.57–7.76 (m, 3H), and 8.10–8.17 ppm (m, 2H).

Anal.—Calc. for $C_{18}H_{18}N_4O_3S$: C, 58.36; H, 4.90; N, 15.12. Found: C, 57.50; H, 4.87; N, 14.92.

3-(1H-Imidazol-1-ylmethyl)-2-methyl-5-(phenoxymethyl)-3-(2-thienyl)isoxazolidine—cis-Diastereomer **16**—35%; mp 107–109 °C (ethyl acetate); IR (KBr): 3198 (m), 2970 (m), 2931 (m), 2878 (m), 1593 (m), 1582 (m), 1501 (m), 1491 (s), 1453 (m), 1290 (m), 1247 (s), 1235 (s), 1078 (s), 1044 (m), 1016 (m), 818 (m), 766 (s), 754 (m), and 729 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 2.53 (s, 3H, NCH_3), 2.54 (dd, 1H, J = 5.5, 13.2 Hz, OHC*H*CH), 2.86 (dd, 1H, J = 8.8, 13.2 Hz, OHCHC*H*), 4.10 (dd, 1H, J = 3.9, 11.0 Hz, O*H*CH), 4.19 (dd, 1H, J = 5.0, 11.0 Hz, OHC*H*), 4.45 (d, 1H, J = 14.3 Hz, N*H*CH), 4.48 (d, 1H, J = 14.3 Hz, NHC*H*), 4.77–4.88 (m, 1H, OCH), 6.70 (s, 1H), 6.77–6.80 (m, 1H), 6.91–7.03 (m, 5H), and 7.26–7.35 ppm (m, 4H).

Anal.—Calc. for $C_{19}H_{21}N_3O_2S$: C, 64.20; H, 5.95; N, 11.82. Found: C, 64.30; H, 6.09; N, 11.84.

trans-Diastereomer **21**—11%; mp 144–146 °C (ethyl acetate); IR (KBr): 3115 (m), 2942 (m), 1598 (m), 1589 (m), 1491 (s), 1442 (m), 1292 (m), 1281 (m), 1250 (s), 1236 (s), 1071 (m), 1034 (s), 1018 (m), 841 (m), 768 (m), 759 (s), and 738 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 2.49 (dd, 1H, J = 7.2, 13.2 Hz, OHC*H*CH), 2.54 (s, 3H, NCH_3), 2.73 (dd, 1H, J = 8.8, 13.2 Hz, OHCHC*H*), 4.05–4.20 (m, 2H, OCH_2), 4.35 (d, 1H, J = 14.3 Hz, N*H*CH), 4.41 (d, 1H, J = 14.3 Hz, NHC*H*), 4.46–4.59 (m, 1H, OCH), 6.68 (s, 1H), 6.89–7.03 (m, 6H), and 7.25–7.38 ppm (m, 4H).

Anal.—Calc. for $C_{19}H_{21}N_3O_2S$: C, 64.20; H, 5.95; N, 11.82. Found: C, 64.31; H, 6.18; N, 11.79.

5-(4-Chlorophenoxymethyl)-3-(1H-imidazol-1-ylmethyl)-2-methyl-3-(2-thienyl)isoxazolidine—cis-Diastereomer **17**—35%; mp 118–120 °C (ethyl acetate); IR (KBr): 2977 (w), 2920 (m), 1595 (m), 1508 (m), 1492 (s), 1443 (m), 1281 (m), 1234 (s), 1073 (m), 992 (m), 820 (s), 721 (m), and 699 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 2.47 (dd, 1H, J = 5.5, 13.2 Hz, OHC*H*CH), 2.51 (s, 3H, NCH_3), 2.81 (dd, 1H, J = 9.4, 13.2 Hz, OHCHC*H*), 4.02 (dd, 1H, J = 3.9, 11.0 Hz, O*H*CH), 4.12 (dd, 1H, J = 5.0, 11.0 Hz, OHC*H*), 4.43 (s, 2H, NCH_2), 4.73–4.85 (m, 1H, OCH), 6.68 (s, 1H), 6.78–7.02 (m, 5H), and 7.22–7.35 ppm (m, 4H).

Anal.—Calc. for $C_{19}H_{20}ClN_3O_2S$: C, 58.53; H, 5.17; N, 10.78; S, 8.22. Found: C, 58.69; H, 5.23; N, 10.76; S, 8.50.

trans-Diastereomer **22**—11%; mp 95–99 °C (ethyl acetate); IR (KBr): 2947 (w), 2910 (m), 2877 (w), 1506 (m), 1486 (s), 1452 (m), 1301 (m), 1230 (s), 1221 (s), 1092 (m), 1041 (m), 1020 (m), 826 (m), and 737 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 2.48 (dd, 1H, J = 7.7, 13.2 Hz, OHC*H*CH), 2.52 (s, 3H, NCH_3), 2.69 (dd, 1H, J = 8.8, 13.2 Hz, OHCHC*H*), 4.01–4.16 (m, 2H, OCH_2), 4.35 (d, 1H, J = 13.8 Hz, N*H*CH), 4.41 (d, 1H, J = 13.8 Hz, NHC*H*), 4.42–4.56 (m, 1H, OCH), 6.68 (s, 1H), 6.80–7.03 (m, 5H), and 7.21–7.38 ppm (m, 4H).

Anal.—Calc. for $C_{19}H_{20}ClN_3O_2S$: C, 58.53; H, 5.17; Cl, 9.09; N, 10.78; S, 8.22. Found: C, 58.50; H, 5.23; Cl, 9.29; N, 10.68; S, 8.18.

3-(1H-Imidazol-1-ylmethyl)-2-methyl-5-[(4-methylphenyl)thiomethyl]-3-(2-thienyl)isoxazolidine—cis-Diastereomer **18**—43%; mp 205–210 °C (decomp) (ethanol) as its monohydrochloride salt; IR (KBr): 3049 (s), 3025 (s), 2988 (s), 2953 (s), 2942 (s), 2919 (s), 2904 (s), 2881 (s), 2791 (s), 2787 (s), 1568 (m), 1430 (m), 1285 (m), 1089 (m), 992 (m), 858 (m), and 721 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$-TFA): 2.35 (s, 3H, $ArCH_3$), 2.93 (s, 3H, NCH_3), 2.87–2.98 (m, 1H), 3.09 (dd, 1H, J = 8.3, 14.3 Hz, OHCHC*H*), 3.34–3.52 (m, 2H, SCH_2), 4.97–5.12 (m, 1H, OCH), 5.19 (d, 1H, J = 14.3 Hz, N*H*CH), 5.33 (d, 1H, J = 14.3 Hz, NHC*H*), 7.07–7.13 (m, 2H), 7.22–7.28 (m, 4H), 7.38–7.44 (m, 2H), 7.60–7.63 (m, 1H), and 8.61 ppm (s, 1H).

Anal.—Calc. for $C_{20}H_{24}ClN_3OS_2$: C, 56.92; H, 5.73; Cl, 8.40; N, 9.96; S, 15.20. Found: C, 56.88; H, 5.92; Cl, 8.66; N, 9.97; S, 15.30.

trans-Diastereomer **23**—8.5%; mp 149–161 °C (ethanol:ether, 1:1) as its monohydrochloride salt; ^1H NMR (200 MHz, $CDCl_3$): 2.34 (s, 3H, $ArCH_3$), 2.53 (s, 3H, NCH_3), 2.63–2.82 (m, 2H, SCH_2), 3.02 (dd, 1H, J = 8.3, 13.2 Hz, OHC*H*CH), 3.39 (dd, 1H, J = 5.5, 13.2 Hz, OHCHC*H*), 4.21–4.35 (m, 1H, OCH), 4.38 (d, 1H, J = 13.8 Hz, N*H*CH), 4.56 (d, 1H, J = 13.8 Hz, NHC*H*), 6.65 (d, 1H, J = 3.3 Hz), 6.94–7.06 (m, 3H), 7.16–7.32 (m, 5H), 8.77 (s, 1H), and 15.1 ppm (HCl salt).

Anal.—Calc. for $C_{20}H_{24}ClN_3OS_2$: C, 56.92; H, 5.73; N, 9.96. Found: C, 56.78; H, 5.82; N, 9.92.

5-[(4-Chlorophenyl)thiomethyl]-3-(1H-imidazol-1-ylmethyl)-2-methyl-3-(2-thienyl)isoxazolidine—cis-Diastereomer **19**—32%; mp 101–104 °C (ethyl acetate); IR (KBr): 3091 (m), 2993 (m), 2968 (m), 2929 (m), 1505 (s), 1478 (s), 1454 (s), 1249 (s), 1236 (s), 1091 (s), 1078 (s), 1009 (m), 935 (m), 820 (s), 725 (m), and 693 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 2.23 (dd, 1H, J = 5.5, 13.2 Hz, OHC*H*CH), 2.42 (s, 3H, NCH_3), 2.79 (dd, 1H, J = 8.8, 13.2 Hz, OHCHC*H*), 3.03 (dd, 1H, J = 6.6, 13.8 Hz, S*H*CH), 3.18 (dd, 1H, J = 5.5, 13.8 Hz, SHC*H*), 4.26 (d, 1H, J = 14.3 Hz, N*H*CH), 4.42 (d, 1H, J = 14.3 Hz, NHC*H*), 4.45–4.59 (m, 1H, OCH), 6.70 (s, 1H), 6.76–6.79 (m, 1H), 6.96–7.01 (m, 2H), and 7.23–7.33 ppm (m, 6H).

Anal.—Calc. for $C_{19}H_{20}ClN_3OS_2$: C, 56.21; H, 4.97; Cl, 8.73; N, 10.35; S, 15.79. Found: C, 56.30; H, 5.02; Cl, 8.98; N, 10.37; S, 15.47.

trans-Diastereomer—**24**—3%; mp 168–173 °C (2-propanol) as its monohydrochloride salt; IR (KBr): 3093 (s), 3016 (s), 2995 (s), 2988 (s), 2962 (s), 2919 (s), 2890 (s), 1566 (s), 1477 (m), 1455 (m), 1433 (m), 1289 (m), 1095 (s), 1074 (m), 1001 (m), 852 (m), and 717 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 2.54 (s, 3H, NCH_3), 2.65–2.87 (m, 2H, $OHCCH_2$), 2.98–3.15 (m, 1H, S*H*CH), 3.29–3.45 (m, 1H, SHC*H*), 4.25–4.66 (m, 3H, OCH + NCH_2), 6.71 (s, 1H), 6.95–7.05 (m, 2H), 7.19–7.42 (m, 7H), and 8.93–9.01 ppm (m, 1H).

Anal.—Calc. for $C_{19}H_{21}Cl_2N_3OS_2$: C, 51.58; H, 4.78; Cl, 16.03; N, 9.50; S, 14.49. Found: C, 51.67; H, 4.72; Cl, 15.92; N, 9.50; S, 14.28.

Antifungal Screening Assay—The antifungal activity of the title 3-(2-thienyl)isoxazolidine compounds was assayed in vitro in solid

agar tests performed in 24-well tissue culture plates. The test media was prepared by diluting the test compounds 10-fold into Antibiotic Medium 3 + 2% agar. The testing was performed using either a four-point (70, 20, 7, and 2 μg/mL) or a six-point (70, 20, 7, 2, 0.7, and 0.2 μg/mL) dilution scheme, with ketoconazole being used as a control in all assays. All test organisms were grown on potato flake agar at 26 °C. *Candida albicans* was grown overnight, *Aspergillus fumigatus* was grown for ~1 week, and *Trichophyton rubrum* was grown for ~2 weeks. Cells were either removed from the plates with a sterile cotton swab and suspended in sterile water (*C. albicans* and *A. fumigatus*) or washed from the surface of the plate with sterile water and diluted in sterile water (*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 °C until visible growth was evident in the compound-free control plates. The minimum inhibitory concentration (MIC) values were interpreted as the lowest dilution at which no visible growth occurred.

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