Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 1739–1742

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis and Antifungal Activity of the 2,2,5-Tetrahydrofuran Regioisomers of SCH 51048

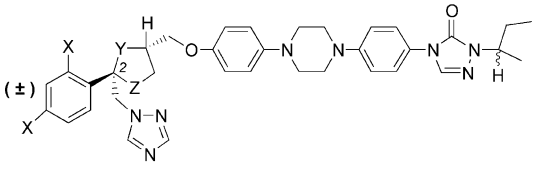
Raymond G. Lovey,[a,*] Anil K. Saksena,[a] Viyyoor M. Girijavallabhan,[a] Paul Blundell,[a] Henry Guzik,[a] David Loebenberg,[b] Raulo M. Parmegiani[b] and Anthony Cacciapuoti[b]

[a]*Department of Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*
[b]*Department of Infectious Diseases and Oncology, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*

Received 1 February 2002; accepted 16 April 2002

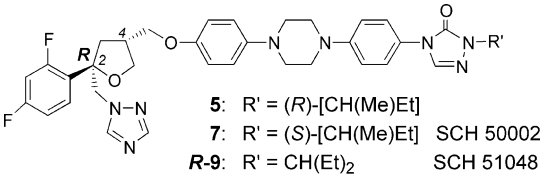
Abstract—The four 2,2,5-regioisomer counterparts of SCH 51048 were synthesized and evaluated. As with the parent series, only the two *cis* isomers possessed any in vitro activity, and only the activity of the isomer with the *R*-configuration at the tetrahydrofuran 2-carbon was significant. The activity data suggests that oxygen at only one of the two possible ring positions benzylic to the difluorobenzene participates usefully in active site binding.

We previously described the preparation and preliminary antifungal activity of **1** (a 2,2,4-substituted tetrahydrofuran) and **2** (a 2,2,5-substituted tetrahydrofuran) as mixtures of four *cis* diastereomers each.[1] Subsequently, we described the synthesis and activity of the four individual stereoisomers of **2** (**5**–**8**) to demonstrate that the antifungal activity was associated with the two (2*R-cis*)-isomers (**5** and **7**).[2] These isomers displayed improved activity over both itraconazole (**3**) and saperconazole (**4**) in *Candida* as well as *Aspergillus* models.

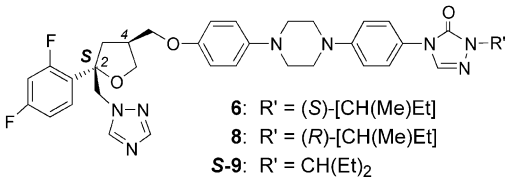


1: SCH 45009 (X = F, Y = O, Z = CH; 2,4-substitution)
2: SCH 45012 (X = F, Y = CH_2, Z =O; 2,5-substitution)
3: ITZ (X = Cl, Y = Z = O)
4: SPZ (X = F, Y = Z = O)

Based on these findings, the N-3-pentyl analogues ***R*-9** and ***S*-9**, which removed the stereochemical center from the triazolone substituent, were synthesized.[3] Compound ***R*-9** proved to be even more effective in vitro than either **5** or **7**.



5: R' = (*R*)-[CH(Me)Et]
7: R' = (*S*)-[CH(Me)Et] SCH 50002
***R*-9**: R' = $CH(Et)_2$ SCH 51048



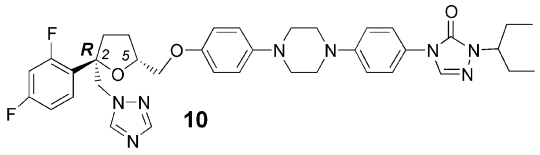
6: R' = (*S*)-[CH(Me)Et]
8: R' = (*R*)-[CH(Me)Et]
***S*-9**: R' = $CH(Et)_2$

Continuing our studies of orally effective broad-spectrum antifungal agents through systematic structure–activity evaluation, we examined regioisomers of **9**. We now describe the synthesis and preliminary biological activity of the two (*cis*)-regioisomers of **9**, **10**, and **11**, and the corresponding *trans*-isomers.

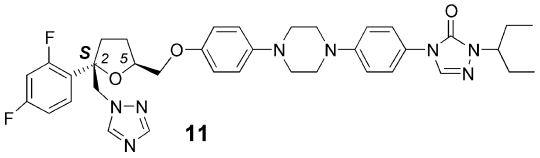
The synthesis of **10** was accomplished by starting with the chiral epoxide **12**[2] (Scheme 1). The yields of the copper-catalyzed Grignard alkylation of the (*R*)-epoxide **12** with allyl magnesium chloride to produce the olefin **13**[4–6] were better than for the Grignard reagent alone, but were consistently mediocre despite many attempts at variations of the reaction conditions.

*Corresponding author. Tel.: +1-908-740-3114; fax: +1-908-740-7152; e-mail: raymond.lovey@spcorp.com

0960-894X/02/$ - see front matter
PII: S0960-894X(02)00282-2



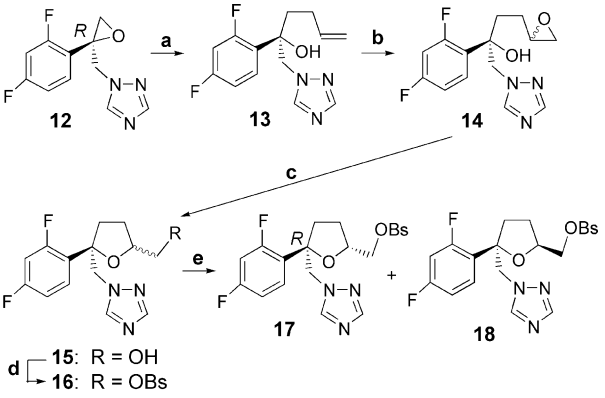
10



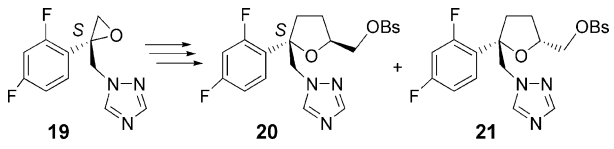
11

Epoxidation of the olefin **13**, followed by acid-catalyzed cyclization of **14** to the hydroxymethyltetrahydrofuran proceeded efficiently to give a *cis*/*trans* mixture of alcohol **15**.[7] The chromatographic separation of the two compounds was not practical, so the mixture was converted to 4-bromophenyl sulfonates (vide infra). The brosylate mixture **16** was easily separable chromatographically to give both (*R*-*cis*)-**17** and (*R*-*trans*)-**18**. Compound **11** was similarly obtained after the same sequence was executed with the (*S*)-epoxide **19**,[2] to afford the corresponding (*S*-*cis*)-**20** and (*S*-*trans*)-**21** isomers (Scheme 2).

With the tetrahydrofuranyl part of the target compounds in hand, the piperazinyl chain portion was available via **22a**.[8] Unfortunately, alkylation of deprotected **22b** with **17** went predominately on to the nitrogen. Thus, the synthesis of *N*-protected intermediates represented by **24** became important to the expedient synthesis of a range of analogues of **25** with varied substituents at both O- and N-termini of the compound by stepwise alkylations. However, alkylation of **22b** with typical alkylating protecting groups at a 1:1 ratio occurred competitively on oxygen. This pointed to



Scheme 1. (a) Allyl-MgCl (2 equiv), CuCN (cat.), THF (30–46%); (b) *m*-CPBA, CH_2Cl_2 (95%); (c) *p*-TSA, CH_2Cl_2 (96%); (d) 4-Br-$PhSO_2Cl$, Et_3N, CH_2Cl_2, (77%); (e) chrom'y (45% + 45%).



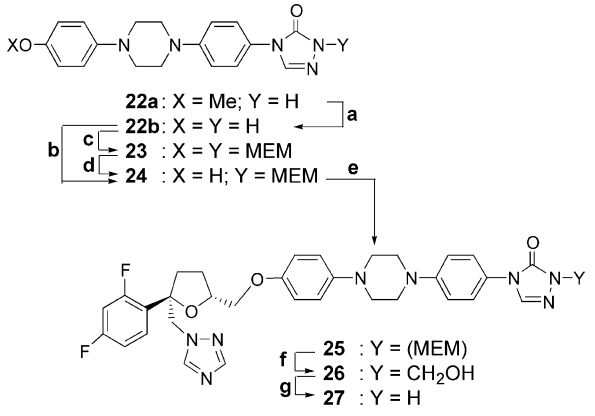
Scheme 2.

selective deprotection of an *O*,*N*-di-protected compound, and we chose the $-CH_2OCH_2CH_2OMe$ (MEM) protecting group. A mixture of *O*,*N*-di-MEM protected **23** and monoprotected **24** (Scheme 3) was prepared using two equivalents of MEM/chloride. When the mixture was hydrolyzed, the *O*-MEM was removed selectively to give the desired **24**[9] with reasonable overall efficiency.

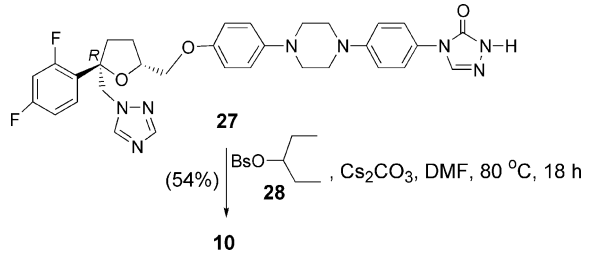
Pure brosylate diastereomers **17**, **18**, **20**, and **21**, were then used to alkylate the phenol **24** shown in Scheme 3, using **17** as an example to produce **25**.[10] Decomposition was minimized by use of cesium carbonate as the base instead of NaH or NaOH. Deprotection of **25** was accomplished by acid hydrolysis to give variable mixtures of the desired **27** along with **26**. The mixture was treated with base to convert **26** to **27**[6] in situ.

The intermediate **27** and corresponding diastereomers were then reacted with various alkylating agents, among them **28** (Scheme 4). The brosylates proved to be more effective than tosylates, and even more so than halides or mesylates, with respect to less elimination side reactions and less triazolone-*O*-alkylation of **27**. Thus, compound **10** was synthesized, and with these methods and the corresponding reactants, **11** was synthesized from **20**.[6]

The compounds prepared were tested in standard serial dilution minimum inhibitory concentration (MIC) screens to assess their inherent antifungal potency using



Scheme 3. (a) 48% HBr (5 mL/g), reflux, 6–10 h (61%); (b) NaH, DMSO, MEM-Cl (28%); (c) MEM-Cl (2.1 equiv), DMF, $(i\text{-Pr})_2NEt$, 10 days; (d) 3 N HCl/MeOH–H_2O (62% from **22b**); (e) **17**, Cs_2CO_3, DMF, 80 °C, 18 h (62%); (f) HCl, H_2O–dioxane; (g) 2 N NaOH (59% from **25**).



Scheme 4.

Table 1. Antifungal geometric mean minimum inhibitory concentrations (GMMICs)[a] of selected isomers (μg/mL)

Compd	SDB[a] Dermatophytes[b]	SDB[a] *Aspergillus*[c]	EMEM[a] *C.a., C.t.*[d]
***R*-9**	≥0.06	0.04	≤0.04
***S*-9**	≥128	≥128	0.27
10	≥0.35	0.25	0.02
11	≥128	≥128	≤0.10
ITZ	≥0.89	0.30	0.04

[a]Compounds were tested in serial dilutions from 64 to 0.0313 μg/mL. Abbreviations: SDB: Sabouraud dextrose broth, pH 5.7, 72 h. EMEM: Eagles minimum essential medium, pH 7.0, 48 h.
[b]Dermatophytes: *Trichophyton mentagrophytes* D24 and D30; *T. rubrum* D54 and D61; *T. tonsurans* D73; and *Microsporum canis* D18.
[c]*Aspergillus fumigatus* ND82 and ND152; and *A. flavus* ND83 and ND134.
[d]*C.a.*: *Candida albicans* C40, C41, C42, C43, C60, C79, C284 and C288; *C.t.*: *Candida tropicalis* C44 and C90.

methods previously described.[11] The results are shown in Table 1; compounds derived from *trans*-intermediates **18** and **21** were completely inactive.

Like other members of the broad class of azole antifungals, these compounds are inhibitors of the P-450 14-α-demethylase enzyme (unpublished experiments by the authors), and presumably act by the same mechanism: the azole portion of the inhibitor binding near the catalytic site, and the aryl/heteroaryl remainder binding in a specificity pocket of the active site. A structure–activity assessment for GMMICs was made concerning the relative importance of both oxygen and substituent position, shown pictorially in Figure 1.

The ***R*-9→10** (A representation) side-chain position change by itself leads to only a modest loss of activity, indicating some flexibility for this ring substituent to adapt to the active site. Since the modestly active **10** can physically position all atoms but the ring oxygen (B representation) identically with the inactive ***S*-9**, it suggests that oxygen at only one of the two possible benzylic ring positions contributes to active site binding of ***R*-9**. The substantial loss of activity for the ***R*-9→11** oxygen position change alone confirms the activity contribution of oxygen at only one of the two possible tetrahydrofuran ring positions.

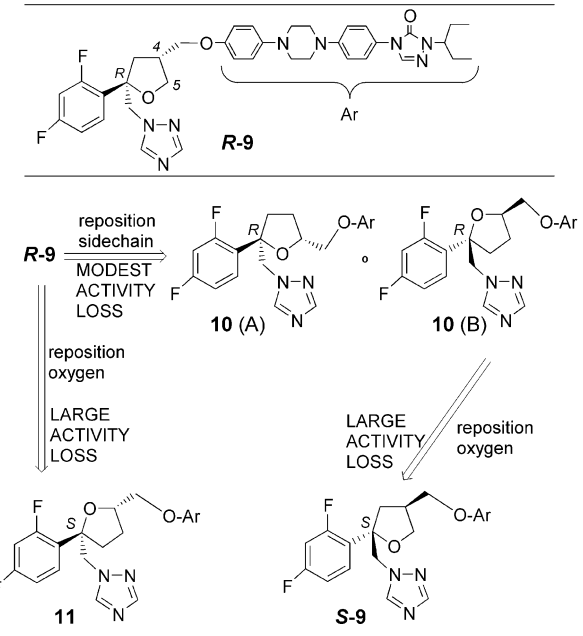


Figure 1.

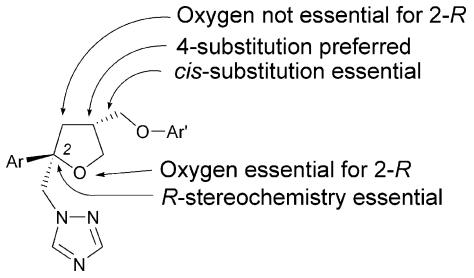


Figure 2.

The tetrahydrofuran compound **10** shows an in vitro spectrum and potency comparable to itraconazole, but is not as potent overall as its regioisomer ***R*-9**. For this broad series of tetrahydofuranyl antifungal compounds, this report further clarifies the one absolute spatial orientation of only three binding elements of a fluorobenzene–triazole–oxygen triad as the important determinant for active site binding near the catalytic site, and optimum antifungal activity (Fig. 2).

Acknowledgements

The authors thank Mr. Barry Antonacci and Ms. Taisa Yarosh-Tomaine for obtaining the biological data.

References and Notes

1. Saksena, A. K.; Girijavallabhan, V. M.; Rane, D. R.; Pike, R. E.; Desai, J. A.; Cooper, A. B.; Jao, E.; Ganguly, A. K.; Loebenberg, D.; Hare, R. S.; Paremegiani, R. M. In *9th International Symposium on Future Trends in Chemotherapy*, Geneva, Switzerland, 26–28 March 1990; Abstr. 128. *cis* and *trans* throughout refers to the relative stereochemistry of the triazole and C-4/5 substituents of the tetrahydrofuran ring.
2. Saksena, A. K.; Girijavallabhan, V. M.; Lovey, R. G.; Pike, R. E.; Desai, J. A.; Ganguly, A. K.; Loebenberg, D.; Paremegiani, R. M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2023.
3. (a) Saksena, A. K.; Girijavallabhan, V. M.; Lovey, R. G.; Desai, J. A.; Pike, R. E.; Jao, E.; Wang, H.; Ganguly, A. K.; Loebenberg, D.; Hare, R. S.; Cacciapuoti, A.; Parmegiani, R. M. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 127 and ref 14 therein. (b) Morgan, B.; Dodds, D. R.; Zaks, A.; Andrews, D. R.; Klesse, R. *J. Org. Chem.* **1997**, *62*, 7736.
4. Procedure: A solution of 15 g (63 mmol) of **12** and 0.3 g (3.5 mmol) of CuCN in 250 mL of dry THF was cooled to −70 °C and 47 mL of a 2 M solution of ethylmagnesium chloride/THF was added slowly. The reaction was allowed to warm slowly to room temperature and stirred for 18 h. The mixture was concentrated to 1/4 volume, the remainder was stirred vigorously for 10 min, and was then extracted with CH_2Cl_2. The extract was dried and evaporated, and the residue was chromatographed (silica gel, 3:7 acetone–hexane) to

afford 6.0 g (34%) of **13**.[5] Use of CuI gave similar results and by-product distributions.

5. This and subsequent compounds were examined for chemical homogeneity >97% by reverse-phase HPLC and TLC, and chiral composition where applicable by HPLC on a chiralcel® OD column with an appropriate EtOH–hexane eluant. They were characterized by consistent mass spectra and PMR spectra, and comparison to authentic samples[1] where available. Selective analytical data are given in ref 6.

6. Data for selected compounds. **10**: mp 162–163 °C; $[\alpha]_D^{21}$ +4.40° (*c* 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.19 (s, 1H), 7.82 (s, 1H), 7.64 (s, 1H), 7.45 (m, 3H), 7.1–6.8 (m, 8H), 4.63 (half AB q, Δν = 14 Hz, 1H), 4.40 (half AB q, Δν = 14 Hz, 1H), 4.39 (m, 1H), 4.08 (m, 1H), 3.90 (m, 2H), 3.38 (m, 4H), 3.22 (m, 4H), 2.54 (m, 1H), 2.38 (m, 1H), 2.0–1.5 (m, 6H), 0.89 (t, *J* = 7.2 Hz, 9H). **11**: mp 146–148 °C; $[\alpha]_D^{21}$ −8.59 (*c* 1, $CHCl_3$). **13**: mp 80–81 °C; $[\alpha]_D^{21}$ −83.9° (*c* 1.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.90 (s, 1H), 7.83 (s, 1H), 7.47 (m, 1H), 6.78 (m, 2H), 5.75 (m, 1H), 4.95 (m, 2H), 4.79 (half AB q, Δν = 14 Hz, 1H), 4.46 (half AB q, Δν = 14 Hz, 1H), 2.14 (m, 2H), 1.82 (m, 2H). **14**: mp 86–92 °C; $[\alpha]_D^{21}$ −62.7° (*c* 1.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.94, (d, *J* = 3.0 Hz, 1H), 7.83 (s, 1H), 7.47 (m, 1H), 6.77 (m, 2H), 4.74 (half AB q, Δν = 14 Hz, 1H), 4.47 (half AB q, Δν = 14 Hz, 1H), 2.88 (m, 1H), 2.71 (m, 1H), 2.42 (m, 1H), 2.20 (m, 1H), 2.0–1.6 (m, 2H), 1.49 (q, *J* = 5.6 Hz, 1H). **18**: mp 150–151 °C; $[\alpha]_D^{21}$ −11.8° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (s, 1H), 7.82 (s, 1H), 7.73 (m, 4H), 7.32 (m, 1H), 6.80 (m, 2H), 4.59 (half AB q, Δν = 14 Hz, 1H), 4.39 (half AB q, Δν = 14 Hz, 1H), 4.3–3.95 (m, 3H), 2.6 (m, 1H), 2.3 (m, 1H), 1.65 (m, 2H). **17**: mp 113 °C; $[\alpha]_D^{21}$ −9.1° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11, 7.78 (m, 5H), 7.28 (m, 2H), 6.80 (m, 2H), 4.53 (half AB q, Δν = 15 Hz, 1H), 4.41 (half AB q, Δν = 15 Hz, 1H), 4.24 (m, 1H), 4.00 (m, 2H), 2.48 (m, 1H), 2.26 (m, 1H), 1.82 (m, 1H), 1.31 (m, 1H). **24**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.64 (s, 1H), 7.38 (half AB q, Δν = 9 Hz, 2H), 7.01 (half AB q, Δν = 9 Hz, 2H), 6.89 (half AB q, Δν = 8 Hz 2H), 6.74 (half AB q, Δν = 8 Hz, 2H), 5.31 (s, 2H), 3.72 (m, 2H), 3.58 (m, 2H), 3.4 (s + m, 7H), 3.20 (m, 4H). **25**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.39 (s, 1H), 8.30 (s, 1H), 7.82 (s, 1H), 7.48 (d, *J* = 9 Hz, 2H), 7.45–7.2 (m, 2H), 7.10 (d, *J* = 9 Hz, 2H), 7.1–6.85 (m + half AB q, Δν = 8 Hz, 3H total), 6.90 (half AB q, Δν = 8 Hz, 2H), 5.13 (s, 2H), 4.52 (s, 2H), 4.30 (m, 1H), 3.92 (m, 2H), 3.64 (m, 2H), 3.44 (m, 2H), 3.2 (m, 4H), 3.22 (s, 3H), 3.18 (m, 4H), 2.13 (m, 1H), 1.83 (m, 1H), 1.46 (m, 1H). **27**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.32 (s, 1H), 8.25 (s, 1H), 7.83 (s, 1H), 7.49 (d, 2H, *J* = 9 Hz), 7.45–7.2 (m, 2H), 7.10 (d, 2H, *J* = 9 Hz), 7.02 (m + half AB q, Δν = 8 Hz, 3H total), 6.92 (half AB q, Δν = 8 Hz, 2H), 4.52 (s, 2H), 4.31 (m, 1H), 3.91 (m, 2H), 3.32 (m, 4H), 3.19 (m, 4H), 2.12 (m, 1H), 1.86 (m, 1H), 1.48 (m, 1H).

7. Base-catalyzed cyclization produced the same products, but also more oligomeric by-product and lower yields.

8. (a) Heeres, J.; Hendrickx, R.; Van Cutsem, J. *J. Med. Chem.* **1983**, *26*, 611. (b) Heeres, J.; Hendrickx, R.; Van Cutsem, J. *J. Med. Chem.* **1984**, *27*, 894.

9. Procedure: A mixture of 10 g (30 mmol) of **22b**, 13.5 mL (77 mmol) of diisopropylethylamine, and 200 mL of dry DMF was treated with 11 mL (63 mmol) of MEM–chloride, and the mixture was stirred for 24 h. The mixture was filtered, the filtrate was evaporated, the residue was treated with 300 mL of cold MeOH and 300 mL of cold 6 N HCl, the solution was stirred for 3 h, and then evaporated. The residue was chromatographed (silica gel, 3:7 acetone–CH_2Cl_2) to afford 7.5 g (67%) of **24**.[6] SEM-chloride could be substituted for MEM–chloride with equal results.

10. Procedure: A mixture of 1.5 g (3.5 mmol) of **17**, and 1.25 g (3.8 mmol) of Cs_2CO_3 in 50 mL of dry DMF was stirred for 0.75 h. To the mixture was added 1.5 g (2.9 mmol) of **24**, it was stirred at 80 °C for 18 h, then quenched in aqueous 5% KH_2PO_4, extracted with EtOAc, evaporated, and the residue was chromatographed (silica gel, 3:7 acetone–CH_2Cl_2) to afford 1.44 g (58%) of **25**.[6]

11. Minimum inhibitory concentrations were determined in Sabouraud dextrose broth at pH 5.7 for *Candida* species and dermatophytes, and in Eagle's minimum essential medium at pH 7.0 for *Candida* species. The MIC was defined as the lowest concentration of test compound at which fungal growth was completely inhibited when cultures were examined visually in 96-well microtiter plates. Test compounds were dissolved in DMSO or ethanol, serially diluted in growth medium, inoculated with microorganism ($\sim 10^4$/cc for SDB, and 5×10^2/cc for EMEM), and incubated at 37 °C in a CO_2 environment for EMEM, and at 27 °C for SDB. Growth MIC was determined at 48 h for Candida species and at 72 h for dermatophytes. All microorganisms used were from in-house collections derived from clinical isolates. Confer: Lovey, R. G.; Elliott, A. J.; Kaminski, J. J.; Loebenberg, D.; Parmegiani, R. M.; Rane, D. F.; Girijavallabhan, V. M.; Pike, R. E.; Guzik, H.; Antonacci, B.; Tomaine, T. Y. *J. Med. Chem.* **1992**, *35*, 4221.