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Hydroxylated analogues of the orally active broad spectrum antifungal, Sch 51048 (1), and the discovery of posaconazole [Sch 56592; 2 or (*S*,*S*)-5]

Frank Bennett,* Anil K. Saksena, Raymond G. Lovey, Yi-Tsung Liu, Naginbhai M. Patel, Patrick Pinto, Russel Pike, Edwin Jao, Viyyoor M. Girijavallabhan, Ashit K. Ganguly, David Loebenberg, Haiyan Wang, Anthony Cacciapuoti, Eugene Moss, Fred Menzel, Roberta S. Hare and Amin Nomeir

Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA

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Abstract—As part of a detailed study, the syntheses, biological activities, and pharmacokinetic properties of hydroxylated analogues of the previously described broad spectrum antifungal agents, Sch 51048 (**1**), Sch 50001 (**3**), and Sch 50002 (**4**), are described. Based on an overall superior profile, one of the alcohols, Sch 56592 (**2**), was selected for clinical studies.

The incidence of life-threatening Candidiasis, Cryptococcus, and Aspergillosis have increased significantly over the last several decades due to the development of new intensive chemotherapy regimens, use of high-dose corticosteroids, and increased use of immunosuppressive regimens for autoimmune diseases.[1]

Currently, antifungal therapies can be limited because of toxicity, low efficacy rates, and drug resistance. Despite the introduction of new formulations of older drugs (i.e., cyclodextrin—itraconazole[2] and PEG—amphotericin B[3]), the search for relatively less toxic and more efficacious treatments continues. As a result the development of new azoles, such as voriconazole[4] and ravuconazole,[5] has come to the forefront. Concurrently, as part of an extensive, detailed campaign we previously reported the in vitro antifungal activities and efficacy studies in animal models of some of or lead compounds **1**, **3**, and **4** (Fig. 1).[6]

As a continuation of these studies we would now like to report on the syntheses and biological activities of all eight possible secondary alcohols represented by substructures **5**–**7** (Fig. 2).

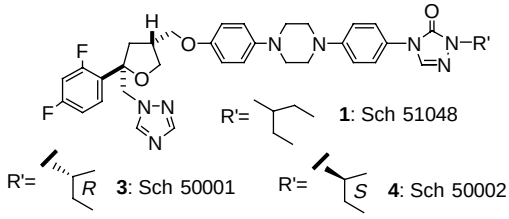

Figure 1. Structures of Sch 51048 (**1**), Sch 50001 (**3**), and Sch 50002 (**4**).

In addition to providing polar functionality to these hydrophobic molecules, the alcohols can be used as a

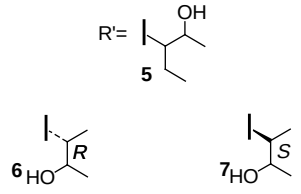

Figure 2. Structures of secondary alcohols Sch 51048 (**5**), Sch 50001 (**6**), and Sch 50002 (**7**).

Keywords: Antifungal; Posaconazole.
* Corresponding author. Tel.: +1 908 7403 103; fax: +1 908 7407 152; e-mail: frank.bennett@spcorp.com

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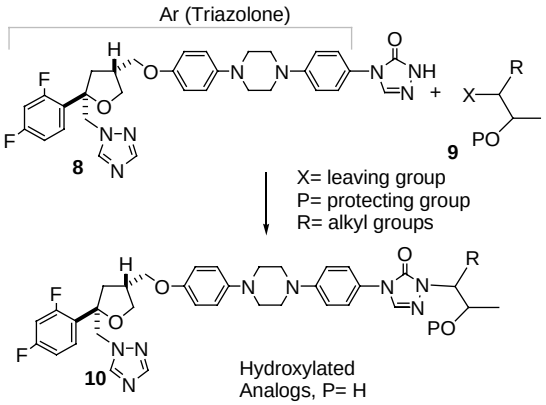
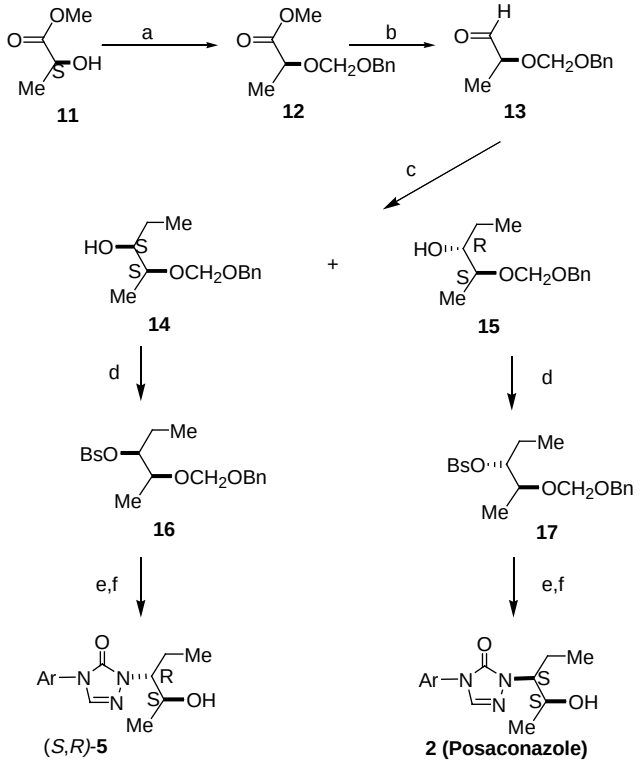


Figure 3. General synthetic approach to hydroxylated analogues (**5**–**7**).

handle to prepare water-soluble prodrugs for iv administration where the oral route is impractical (e.g., AIDS and cancer patients). Our general synthetic approach is shown in Figure 3 involving the anion generated from the known triazolone **8**,[6] requiring chiral syntheses of the electrophilic side chains **9**. Following alkylation, removal of the protecting group provides the desired alcohols **10.**

Beginning with methyl (*S*)-lactate, the syntheses of two of the possible four diastereomers represented by substructure **5** are shown in Scheme 1. The methyl ester **11** is converted directly into the corresponding benzyloxymethyl ether **12**.[7] DIBAL-H reduction provides the propanal **13** which, on exposure to ethyl magnesium bromide, generates the 'chelation controlled'–(*S*,*S*)–alcohol **14** identified by removal of benzyloxymethyl ether and compared with the known diols,[8] along with its relatively polar (*S*,*R*)-isomer **15** (**14**:**15**; at 6:1 in diethyl ether as the solvent, at 2:1 in THF), which were partially separated by careful column chromatography on silica gel. The alcohol **14** is transformed into the brosylate **16**, which is displaced in a SN_2 manner with the anion generated from the triazolone **8** and cesium carbonate in hot DMF. Finally, the benzyloxymethyl ether is removed by hydrolysis in acidic media to the desired target (*S*,*R*)-**5** (Sch 56588).[9]



Scheme 1. Reagents and conditions: (a) benzyl chloromethyl ether; (b) DIBAL-H; (c) EtMgBr, diethyl ether or THF, −78 °C to rt; (d) brosyl chloride, DMAP; (e) **8**, Cs_2CO_3, DMF, heat; (f) 6 N HCl (aq), MeOH.

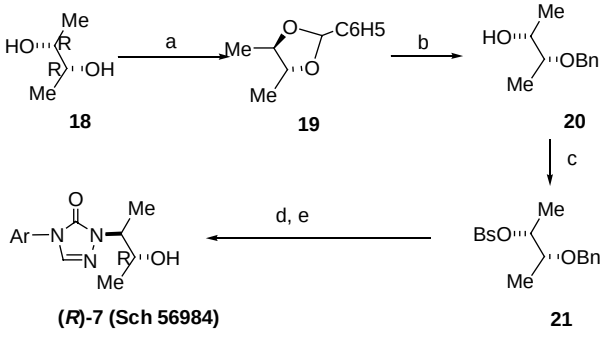
Using the same sequence of events, the (*S*,*R*) isomer alcohol **15** was transformed into (*S*,*S*)-**5** or posaconazole **2** (Sch 56592),[10] via the brosylate **17**. Similarly, using the chemistry described in Scheme 1 and (D)-lactate as starting material, (*R*,*R*)-**5** and (*R*,*S*)-**5** can be synthesized.

Preparation of the representatives of substructure **7** is shown in Schemes 2 and 3. The commercially available (*R*,*R*)-2,3-butane diol **18** was converted to the benzylidene acetal **19**, which was subsequently reduced to the benzyl ether **20** and then the brosylate **21**. Alkylation and removal of the benzyl protective group provides (*R*)-**7** as Sch 56984.[11]

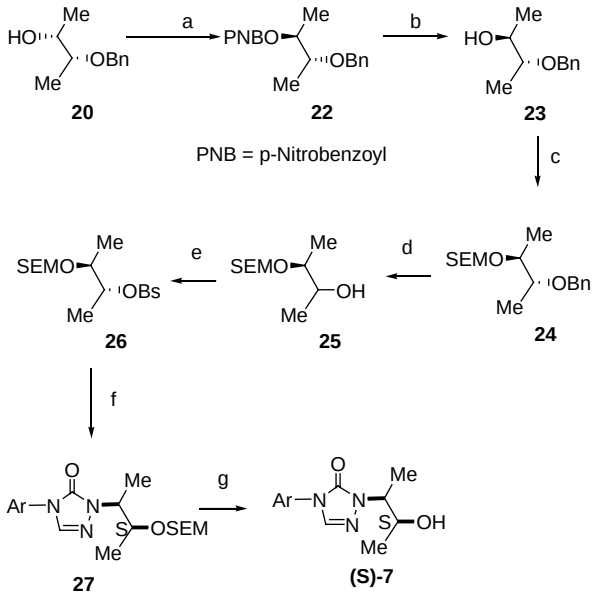
The corresponding (*S*)-isomer was also obtained from intermediate **20**. Martin's version of the Mitsonobu reaction[12] provided the benzoate **22**. Saponification and protection of the resulting alcohol **23** provided the acetal **24**. The benzyl ether was removed via catalytic hydrogenation and activation of the carbinol **25** to the corresponding *p*-bromotoluenesulfonate **26** prior to alkylation with the anion of the triazolone **8**. Finally, hydrolysis of the silyl alcohol **27** under acidic condition gave the (*S*)-**7** alcohol.

Using the same sequence of events compounds represented by substructure **6** can be prepared from (*S*,*S*)-2,3-butane diol.

All compounds proved to be very active in vitro against *Candida albicans* and *Aspergillus* species (Table 1).



Scheme 2. Reagents and conditions: (a) benzaldehyde, TsOH, heat; (b) DIBAL-H; (c) *p*-bromosulfonyl chloride, DMAP; (d) **8**, Cs_2CO_3, DMF, heat; (e) catalytic hydrogenation.



Scheme 3. Reagents and conditions: (a) 4-nitrobenzoic acid, PPh3, DEAD; (b) 1 N NaOH (aq); (c) SEM-Cl, *i*-Pr_2NEt; (d) H_2–10% Pd/C; (e) BsCl, Py; (f) **8**, Cs_2CO_3, DMF, 80 °C; (g) HCl (aq).

Table 1. Antifungal activities of alcohols **5**, **6**, and **7**

Compound	*Candida albicans* (geomean MIC, μg/ml)[a]	*Aspergillus* sp. (geomean MIC, μg/ml)[a]
(*R*,*R*)-**5**	0.014	<0.077
(*R*,*S*)-**5**	0.019	<0.086
(*S*,*R*)-**5** (Sch 56588)	0.022	<0.090
(*S*,*S*)-**5** (or **2**; posaconazole, Sch 56592)	0.018	<0.048
(*R*)-**6**	<0.006	0.090
(*S*)-**6**	0.030	0.080
(*R*)-**7** (Sch 56984)	<0.007	<0.050
(*S*)-**7**	0.020	0.060

[a] Geometric mean MIC values were determined against 26–30 strains of *C. albicans*, and 37 strains of *Aspergillus* species, including 17 *A. fumigatus*, 11 *A. flavus*, 5 *A. niger*, and 4 *A. terreus* as described previously.[13] The geomean MICs for Sch 51048 were 0.020–0.053 for *C. albicans*; 0.20–0.32 for *Aspergillus* sp.

A selection of these potent antifungal agents Sch 56588 and Sch 56592, both containing 5-carbon side chains, prepared from readily available L-lactate and one analogue containing a 4-carbon side chain, Sch 56984, were then examined in vivo. In mice (Chart 1), Sch 56592 and Sch 56984 had similar serum levels following oral administration to mice. These compounds exhibited considerably higher blood levels relative to Sch 56588 and Sch 51048 when administered from 20 to 150 mpk.[14]

In cynomolgus monkeys at 10 mpk (Chart 2) Sch 56592 clearly demonstrated higher serum levels relative to Sch 56588, Sch 56984 or Sch 51048.[15,16]

Subsequently, the compounds were examined in infection models. Sch 56592 (2.5 mg/kg) was the most effective antifungal against *C. albicans* C72 systemic infection in immunocompromised mice (Chart 3). Sch

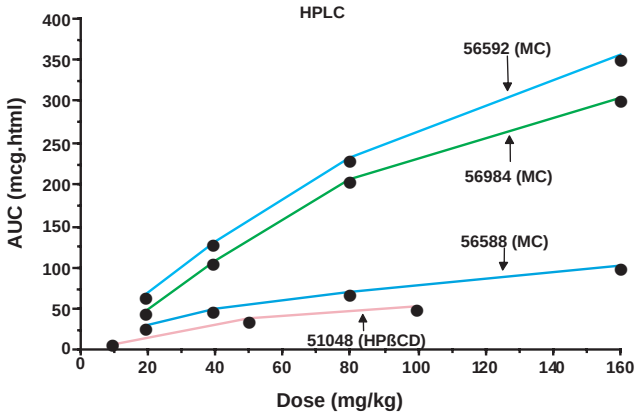


Chart 1. Mouse dose response (PO).

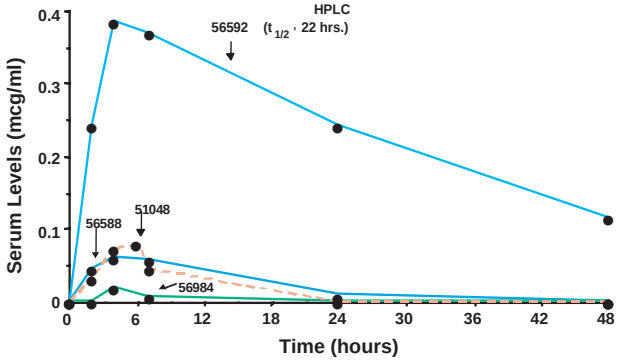


Chart 2. PO, 10 mpk, C. monkeys.

56592 prolonged the survival of mice longer than Sch 51048.[16,17] Sch 56588, Sch 56984, and fluconazole (FLZ) at the same dose.

Sch 56592 was similar to Sch 56588 and Sch51048 in prolonging the survival of immunocompromised mice infected (pulmonary) with *Aspergillus fumigatus* ND159. Sch 56984 was less effective and itraconazole (ITZ; 100 mg/kg) was ineffective (Chart 4).[16,17]

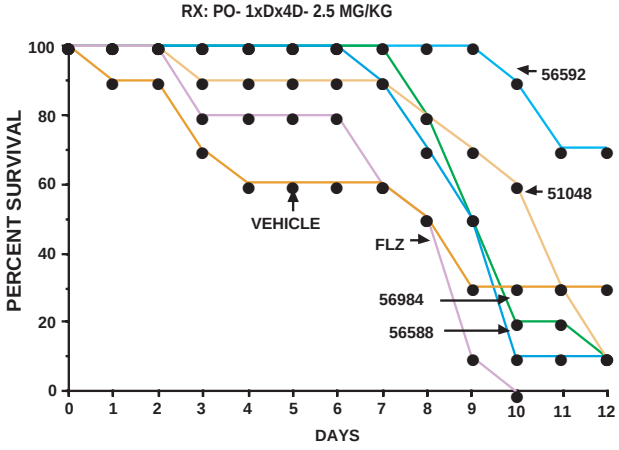


Chart 3. *Candida albicans*, C72 systemic infection in mice.

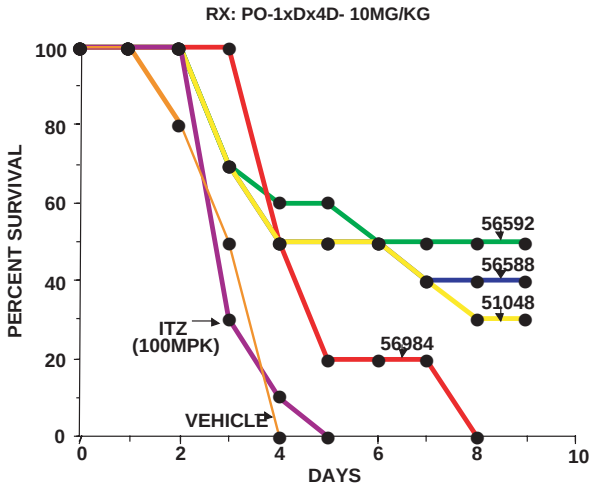


Chart 4. *Aspergillus fumigatus*, ND159 pulmonary infection in mice.

In summary, based on previous leads, a series of hydroxylated potential antifungal agents were synthesized. All alcohols proved to be extremely potent in vitro. A selected number of these analogues were evaluated in vivo and based on an overall superior profile, Sch 56592 was selected for clinical studies. Extension of this work including the evaluation of water-soluble prodrugs of posaconazole will be published elsewhere.

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9. Selected analytical data: Sch 56588: $[\alpha]_D^{25}$ −20.1 (*c* 1.02, $CHCl_3$); $[\alpha]_D^{25}$ −20.8 (*c* 0.35, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 Hz) δ 8.11 (s, 1H), δ 7.80 (s, 1H), δ 7.64 (s, 1H), δ 7.42 (m, 2H), δ 7.39 (m, 1H), δ 7.03 (m, 2H), δ 6.94 (m, 2H), δ 6.86 (m, 1H), δ 6.83 (m, 1H), δ 6.78 (m, 2H), δ 4.65–4.51 (d, J = 14.4 Hz, d, J = 14.4 Hz, 2H), δ 4.17 (m, 1H), δ 4.12–3.78 (dd, J = 8.7, 7.4 Hz, dd, J = 8.7, 3.8 Hz, 2H), δ 4.07 (dt, J = 10.9, 3.4, 3.4 Hz, 1H), δ 3.71–3.62 (dd, J = 8.9, 5.5 Hz, dd, J = 8.9, 7.1 Hz, 2H), δ 3.38 (m, 4H), δ 3.30 (d, J = 2.6 Hz, 1H), δ 3.23 (m, 4H), δ 2.61 (m, 1H), δ 2.56–2.08 (m, J = 12.3, 8.0, 2.5 Hz, dd, J = 12.3, 8.0 Hz, 2H), δ 2.02–1.87 (mm, 2H), δ 1.25 (d, J = 6.5 Hz, 3H), δ 0.91 (t, J = 7.4 Hz, 3H). HR-FABMS calcd for $C_{37}H_{43}N_8O_4F_2$: 701.3375. Found: 701.3385 $(M+H)^+$.
10. Selected analytical data: Sch 56592: mp 170–172 °C. $[\alpha]_D^{21}$ −23.3 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 Hz) δ 8.11 (s, 1H), δ 7.80 (s, 1H), δ 7.66 (s, 1H), δ 7.43 (m, 2H), δ 7.39 (m, 1H), δ 7.03 (m, 2H), δ 6.95 (m, 2H), δ 6.86 (m, 1H), δ 6.83 (m, 1H), δ 6.78 (m, 2H), δ 4.65–4.51 (d, J = 14.5 Hz, d, J = 14.5 Hz, 2H), δ 4.11–3.78 (dd, J = 8.7, 7.4 Hz, dd, J = 8.7, 6.8 Hz, 2 H), δ 4.06 (m, 1H), δ 4.02 (m, 1H), δ 3.70–3.62 (dd, J = 9.0, 5.6 Hz, dd, J = 9.0, 7.3 Hz, 2H), δ 3.38 (m, 4H), δ 3.24 (m, 4H), δ 3.08 (d, J = 9.0 Hz, 1H), δ 2.61 (m, 1H), δ 2.55–2.08 (m, J = 12.7, 7.9, 2.5 Hz, dd, J = 12.7, 8.3 Hz, 2H), δ 2.00–1.89 (mm, 2H), δ 1.22 (d, J = 6.3 Hz, 3H), δ 0.94 (t, J = 7.4 Hz, 3H). HR-FABMS calcd for $C_{37}H_{43}N_8O_4F_2$: 701.3375. Found: 701.3378 $(M+H)^+$.
11. Selected analytical data: Sch 56984: $[\alpha]_D$ −23.65 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 Hz) δ 8.11 (s, 1H), δ 7.80 (s, 1H), δ 7.63 (s, 1H), δ 7.40 (m, 2H), δ 7.39 (m, 1H), δ 7.03 (m, 2H), δ 6.94 (br, 2H), δ 6.84 (m, 1H), δ 6.84 (m, 1H), δ 6.78 (m, 2H), δ 4.65–4.51 (d, J = 14.4 Hz, d, J = 14.4 Hz, 2H), δ 4.28–4.19 (m, 1H), δ 4.28–4.19 (m, 1H), δ 4.11–3.77 (mm, 2H), δ 3.63 (mm, 2H), δ 3.36 (m, 4H), δ 3.23 (m, 4H), δ 2.61 (m, 1H), δ 2.54–2.07 (m, J = 12.5, 7.8, 2.3 Hz, dd, J = 12.5, 7.7 Hz, 2H), δ 1.42 (d, J = 6.9 Hz, 3H), δ 1.24 (d, J = 6.2 Hz, 3H). MS m/z: 687.5 $(M+H)^+$.
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14. *Methods*. Drugs were administered orally to mice (Charles River CF1 white males, ca. 20 g) which had been fasted for 18 h. Six mice were used per time point. The AUC was calculated from 0 to 24 h. The compounds were prepared in methyl cellulose (0.4%) containing polysorbate 80 (0.5%) and NaCl (0.9%), except for Sch 51048, which was prepared in 40% hydroxypropyl-β-cyclodextrin. HPLC was used to determine the drug concentrations in serum.
15. *Methods*. Drugs were administered orally to cynomolgus monkeys (weight range 5.9–7.3 kg). The compounds were prepared in methyl cellulose (0.4%) containing polysorbate 80 (0.5%) and NaCl (0.9%), except for Sch 51048, which was prepared in 40% hydroxypropyl-β-cyclodextrin. HPLC was used to determine the drug concentrations in serum.
16. *Methods*. Immunocompromised mice (γ-irradiated, 500 rads, 3 days prior to infection) were infected intravenously with 1×10^6 CFU/mouse of *C. albicans* C72.

Treatment (oral) began 4 h postinfection and continued once daily for 4 days. The compounds were prepared in methyl cellulose (0.4%) containing polysorbate 80 (0.5%) and NaCl (0.9%). The mice were Charles River CF1 white males.

17. *Methods*. The mice were immunocompromised with cortisone acetate (100 mg/kg, SC) on the day before, the day of, and the day after inhalation infection (30 s exposure) of *A. fumigatus* ND159 conidia in an inhalation flask. Treatment (oral) began 24 h postinfection and continued once daily for 4 days. The compounds were prepared in methyl cellulose (0.4%) containing polysorbate 80 (0.5%) and NaCl (0.9%). The mice were Charles River CF1 white males.