Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 5, No. 2, pp. 127-132, 1995

0960-894X/95 $9.50+0.00

0960-894X(94)00471-4

SCH 51048, A NOVEL BROAD-SPECTRUM ORALLY ACTIVE ANTIFUNGAL AGENT: SYNTHESIS AND PRELIMINARY STRUCTURE-ACTIVITY PROFILE

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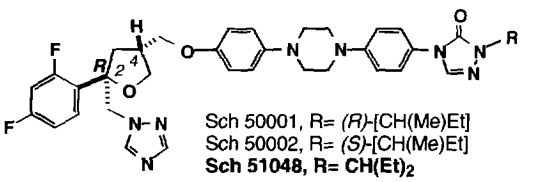
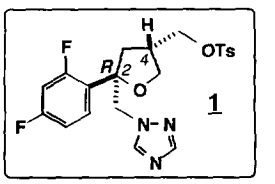
Abstract: Synthesis of Sch 51048, a novel orally active azole antifungal, is described. Based on its superior oral efficacy over other available agents against a variety of fungal pathogens in normal and immunocompromised animal infection models, Sch 51048 is a subject for possible clinical evaluation.

The management of life threatening invasive mycoses in severely immunocompromised patient populations remains a major challenge. In fact the response of systemic *Candida*, *Aspergillus* and meningeal *Cryptococcus* infections in the neutropenic patient to any form of antifungal therapy is anything but satisfactory. Use of parenteral amphotericin B (AMB), the only broad-spectrum drug for such infections is often limited by its high toxicity and lack of oral bioavailability.[1] Most recently introduction of itraconazole (ITZ) and fluconazole (FLZ) into clinical practice has provided some alternatives to available treatments for systemic infections. Both compounds offer certain advantages over AMB and ketoconazole in terms of oral efficacy and relative lack of toxicity; ITZ is the most effective of the azoles for the treatment of *Aspergillosis*.[2] As part of an extensive search for orally effective agents, we reported on a series of novel tetrahydrofuran based azole antifungals having broad-spectrum activity. Close attention to stereo and regiochemical requirements for optimal oral activity led to discovery of *2,2,4-cis*-substituted tetrahydrofurans with specific placement of the ring oxygen.[3a] *This interesting finding could not have been predicted at the outset.*



Sch 50001, R= *(R)*-[CH(Me)Et]
Sch 50002, R= *(S)*-[CH(Me)Et]
Sch 51048, R= $CH(Et)_2$



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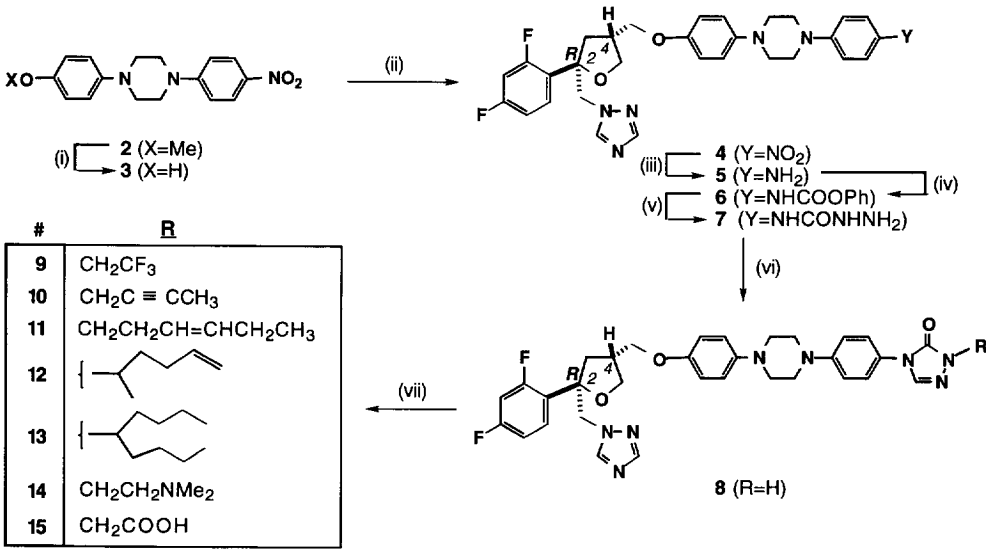
In a follow-up on the above observations we recently described a convergent enantioselective synthesis of the four stereoisomers of Sch 45012 providing Sch 50001 and Sch 50002 as the two "eutomers." The importance of relative and absolute stereochemistry was highlighted by the fact that the only isomers having antifungal activity had *2R* absolute configuration at the benzylic carbon. Derived from the key (-)-*2R-cis*-tosylate **1**,[4] these novel leads displayed greatly improved activity over ITZ and saperconazole (SPZ). Further, Sch 50002 having a *2S*-isobutyryl side chain was shown to be the most active stereoisomer in *Candida* as well as *Aspergillus* infection models.[4] It was therefore of interest to seek further improvement of *in vivo* antifungal activity in this series by variation of N-terminal side chains. We now describe systematic chemical modifications on the above structural leads culminating in disclosure of Sch 51048, having superior therapeutic potential over existing agents in various systemic infection models.

In order to prepare a variety of analogs with some expediency, the triazolone **8** was needed as a common intermediate for N-alkylations. Following a linear sequence starting from O-alkylation of the nitrophenol **3**[5] with the *2R-cis*-tosylate **1**, the phenol ether **4**, m.p. 167-168°C, $[\alpha]_D^{25}$ -30.6° (c = 1.01, $CHCl_3$) was obtained. Catalytic reduction of



#	R
9	CH_2CF_3
10	$CH_2C \equiv CCH_3$
11	$CH_2CH_2CH{=}CHCH_2CH_3$
12	
13	
14	$CH_2CH_2NMe_2$
15	CH_2COOH

Reagents: (i) Aq. 48% HBr; (ii) **3** Na-salt, DMSO, **1**, 60°C; (iii) H_2 , 5% Pd-C, EtOH (1 atmos.); (iv)PhOCOCl, pyridine, 0-5°C; (v) $NH_2NH_2.H_2O$, 1,2-dimethoxyethane, 80°C; (vi) formamidine acetate, 2-methoxyethanol, 80°C; (vii) **8** Na or Cs-salt, RBr or ROTs, DMSO or DMF, 60-65°C.

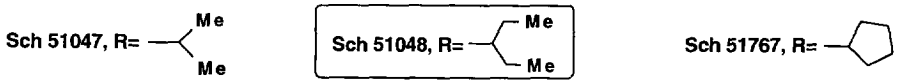
SCHEME

the nitro group in **4** gave the anilino compound **5** (as hydrochloride), m.p. 175-177°C, $[\alpha]_D^{25}$ -17.7° (c = 1.03, $CHCl_3$) in virtually quantitative yield. Construction of the triazolone ring from **5** was carried out *via* the known 3-step sequence[5] as follows. Treatment of **5** with phenyl chloroformate in the presence of pyridine afforded the carbamate **6**, m.p. 182-184°C, $[\alpha]_D^{25}$ -30.4° (c = 1.00, $CHCl_3$). Reaction of **6** with hydrazine hydrate in 1,2-dimethoxyethane at 80°C provided the semicarbazide **7**, m.p. 212-214°C, $[\alpha]_D^{25}$ -18.7° (c = 1.08, CH_3COOH). Final cyclization of **7** was carried out with formamidine acetate in DMF in the presence of triethylamine to give the desired triazolone **8**, m.p. 247-250°C (dec.), $[\alpha]_D^{25}$ -19.8° (c = 0.2, CH_3COOH) in an efficient sequence.[6, 7] Each step proceeded in consistently high yields (~ 90%) and no chromatography was necessary.

With ample quantities of **8** in hand, initial N-alkylations with the requisite alkyl halides or tosylates were carried out in the presence of sodium hydride or hydroxide in dimethyl sulfoxide. Although a number of saturated, unsaturated and polar side chains were introduced in this manner, formation of certain by-products required elaborate chromatography as an essential step. Use of cesium carbonate[8] as base and DMF as solvent significantly improved N-alkylation yields in reactions virtually free of side products.

A number of N-alkyl analogs (e.g. **9 - 15**) prepared in this manner had excellent broad-spectrum activity *in vitro*, but they were somewhat less active than Sch 50002 in animal infection models. In general, branched alkyl chains appeared to have a desirable effect on *in vivo* activity. However, the lack of activity of **13**, a 9-carbon branched analog,

highlighted the importance of optimal carbon chain length. The presence of either relatively basic or acidic side chains exemplified in **14** and **15** also resulted in profound loss in activity.[9]



In a most productive study aimed at elimination of the chirality of the N-alkyl side chain of Sch 50002, the isopropyl analog Sch 51047,[10] and the 3-pentyl analog Sch 51048[11] were synthesized according to the methodology described above. The efficacy of these three compounds was compared in *Candida albicans* and *Aspergillus* infection models.[3b] As shown in Table 1, Sch 51048 was the most active compound in a pulmonary *Aspergillus fumigatus* infection in mice induced via an inhalation route. At a dose of 100 mpk, Sch 51048 protected 100% of mice and insured good protection at 50 mpk. In contrast, Sch 50002 provided minimal protection at the higher dose and essentially no protection at 50 mpk. Both Sch 51047 and ITZ were virtually inactive at the 100 mpk dose. In a relatively less severe *Aspergillus flavus* infection as shown in the same Table, both Sch 51048 and Sch 50002 had comparable activity. Sch 51767, a conformationally rigid cyclopentyl analog of Sch 51048, was also tested in the same set and shown to have reduced albeit significant percent survival compared to ITZ.

TABLE 1. Oral Activity of Sch 51048 and Related Compounds in Immunocompromised CF-1 Mice Infected by Inhalation with *Aspergillus*.

		A. fumigatus[a]		*A . flavus*[b]	
Compound	**Dose (mpk)[c]**	**% Survival[d]**	**MICs[e]**	**% Survival[d]**	**MICs[e]**
51048	**100**	**100**	0.0625	**90**	0.0625
	50	**70**		**60**	
50002	**100**	30	0.0313	**90**	0.0625
	50	10		**80**	
51047	100	10	0.1250	ND	ND
	50	10		ND	
51767	100	ND[g]	ND	50	0.0156
	50	ND		40	
ITZ	100	10	0.5000	20	0.1250
Vehicle[f]	-	0	-	0	-

[a]Strain ND 142; animals infected with *Aspergillus* conidia (log 6.0-6.4 conidia/mouse) *via* inhalation chamber with prior and post-infection treatment with 100 mpk cortisone acetate subcutaneous.
[b]Strain ND 134 (log 6.0-6.4 conidia/mouse) administered as above.
[c]Mg/kg, once a day for 4 days; treatment commenced 24 hours after infection.
[d]11 Days post-infection.
[e] SDB: Sabouraud dextrose broth, pH 5.7, 72 h.
[f]Vehicle: Polyethylene glycol 200 (PEG-200).
[g]ND: Not done.

The oral activity of Sch 51048 was then compared with ITZ, SPZ and FLZ alongside Sch 50002 and Sch 51767 in normal and immunocompromised mice infected with *C. albicans*. As shown in Table 2, Sch 51048 provided maximal protection in normal mice with Sch 50002 and FLZ comparable in efficacy. Even Sch 51767 the cyclopentyl analog had better efficacy in this infection model than ITZ and SPZ. In general, immunocompromised mice treated with the same

compounds displayed greatly reduced percent survival. Based on survival alone, Sch 51048, Sch 50002 and FLZ had comparable activity. However, in terms of (higher) kidney counts, FLZ was the least active of these three compounds.[13]

TABLE 2. Oral Activity of Sch 51048 and Other Triazoles in Normal and Immunocompromised CF-1 Mice Infected with *C. Albicans*.[a]

Compound	Dose (mpk)[b]	Normal Mice % Survival[c]	Normal Mice CFUs[d]	Immunocomp. Mice[e] % Survival[f]	Immunocomp. Mice[e] CFUs[d]	MICs[g]
51048	**50**	**100**	4.70	**50**	6.54	0.0078
	25	**100**	4.61	**30**	7.54	
	10	**100**	4.66	**20**	7.82	
	1	**80**	6.38	ND[i]	ND	
50002	**50**	**100**	5.10	**40**	6.69	0.0078
	25	**90**	5.72	**40**	7.51	
	10	**80**	5.97	**30**	8.08	
51767	50	70	6.92	ND	ND	0.0078
	25	50	7.11	ND	ND	
ITZ	50	40	7.57	20	8.23	0.0156
	25	0	9.00	0	9.00	
SPZ	50	30	8.28	0	9.00	0.0039
	25	20	8.36	0	9.00	
FLZ	**25**	**100**	4.99	**40**	8.21	0.2508
	10	**90**	5.55	**30**	8.37	
	1	**0**	9.00	ND	ND	
Vehicle[h]	---	0	9.00	0	9.00	----------

[a]Strain C-65 (5 million CFU)
[b]mg/kg (P.O.). Treatment: once a day x 4 days.
[c]7 days post infection.
[d]Colony forming units (geometric mean; log 10; limit of detection: 2.00).
[e]Gamma irradiation, 600 rads[3b].
[f]4 days post infection (infection day is day 0).
[g]Eagles essential medium, pH 7.0, 48h.
[h]PEG-200;
[i]ND: Not done.

TABLE 3. Solubilities of SCH 51048 and Itraconazole in Selected Vehicles.

Compound	Solubility (mg/mL)			
	0.1 N HCl	Corn oil	Ethanol	PEG 400
51048	0.04	0.20	3.9	13.3
Itraconazole	≤0.01	0.03	0.4	0.9

Additional studies have shown impressive *in vitro* and *in vivo* activity of Sch 51048 against a large variety of fungal pathogens including *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Candida krusei*, *Aspergillus fumigatus*, *Coccidioides immitis* and *Trichosporon beigelii*.[14a-i] Against two strains of FLZ resistant *C. krusei*, Sch 51048 was more effective than AMB.[14f] In a murine model of systemic coccidioidomycosis Sch 51048 was 5 to 50-fold more efficacious than FLZ or ITZ.[14g] Disseminated trichosporonosis is often refractory to AMB and emerging as a significant infection in immunocompromised patients. Sch 51048 was as effective as FLZ and more effective than AMB in this experimental infection in mice.[14h] In a comparative pharmacokinetic study, in various animal

species, Sch 51048 (20 mg/kg, P.O.) was highly bioavailable in mice and monkeys.[14i] Table 3 shows a comparison of the solubility of SCH 51048 with ITZ in several possible vehicles.

In conclusion, based on its broad-spectrum activity and exceptional efficacy profile in various infection models, Sch 51048 may offer improved clinical utility over existing agents. We shall report on our further studies with this promising azole antifungal in forthcoming communications.

Acknowledgements: We would like to cordially thank Drs. Doris Schumacher and Ingrid Mergelsberg (Chemical Development) for providing bulk intermediates critical to our need. We also wish to thank Drs. Birendra Pramanik and Mohinder S. Puar (Analytical Department) for high resolution mass spectral and nmr support, and Dr. Kenneth DeFillipo for solubility determinations.

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   (b) For a detailed description of these infection models, see: Loebenberg, D.; Cacciapuoti, A..; Parmegiani, R.; Moss, E. L.; Menzel, F.; Antonacci, B.; Norris, C.; Yarosh-Tomaine, T.; Hare, R. S. and Miller, G. H. *Antimicrobial Agents and Chemotherapy,* **1992**, *36*, 64.
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5. Heeres, J.; Backx, L. J. J.; Van Cutsem, J. *J. Med Chem.*, **1984**, *27*, 894.
6. All new compounds were characterized by ^{1}HNMR (300 MHz) and high resolution mass spectra. Elemental analyses were obtained for crystalline compounds only. Yields refer to isolated products and have not been optimized. Selected spectral data are given here.
7. **4:** ^{1}HNMR [$CDCl_3$] δ 8.24 (d, 2H), 8.21 (s, 1H), 7.89 (s, 1H), 7.49 (m, 1H), m 7.03-6.92 (m, 6H), 6.86 (d, 2H), 4.74 (d, 1H), 4.59 (d, 1H), 4.20 (dd, 1H), 3.86 (dd, 1H), 3.78-3.68 (m, 2H), 3.77-3.65 (m, 4H), 3.32-3.29 (m, 4H), 2.66 (m, 2H), 2.17 (m, 1H).
   8: ^{1}HNMR [DMSO-d_6] δ 11.9 (broad s, 1H), 8.37 (s, 1H), 8.26 (s, 1H), 8.26 (s, 1H), 7.80 (s, 1H), 7.50 (d, 2H), 7.32 (m, 2H), 7.12 (d, 2H), 6.97 (m, 3H), 6.81 (d, 2H), 4.59 (m, 2H), 4.03 (t,1H), 3.8-3.6 (m, 3H), 3.31 (m, 4H), 3.27 (m, 4H), 2.6-2.4 (m, 2H), 2.14 (m, 1H).
8. DeVries, J. G. and Kellog, R. M. *J. Am. Chem. Soc.*, **1979**, *101*, 2759.
9. A full account of structure-activity relationships between these and a host of other analogs will be reported in forthcoming publications from our group.
   Typical Procedure: A stirred solution of **8** (0.2 g, 0.325 mmol), in anhydrous DMF (5ml), was treated with Cs_2CO_3 (0.106 g, 0.325 mmol), followed by addition of 3-bromopentane (0.078 g, 0.650 mmol). The reaction mixture was heated at 65-70°C for ~15 h, allowed to cool to room temperature and diluted with ethyl acetate (~50 ml). The resulting solution was washed with water (~50 ml), brine (~50 ml) and dried over anhydrous $MgSO_4$.

Evaporation of ethyl acetate on a rotary evaporator and chromatography of the crude product (0.214 g) on silica gel (eluent: ethyl acetate) gave pure **Sch 51048** (0.142 g; 68% yield).

9: m.p. 187-188°C. $[\alpha]_D^{25}$ -26.00° (c = 0.95, $CHCl_3$); ^{1}HNMR [$CDCl_3$] δ 8.23 (s, 1H), 7.82 (s, 1H), 7.70 (s, 1H), 7.41 (m, 3H), 7.06 (m, 3H), 6.82 (m, 5H), 4.59 (ABq, 2H), 4.46 (ABq,, 2H), 4.11 (t, 1H), 3.83-3.56 (m, 3H), 3.50-3.10 (m, 8H), 2.58 (m, 2H), 2.08 (m, 1H).

10: m.p. 158-159°C. $[\alpha]_D^{25}$ -25.30° (c = 0.33, $CHCl_3$); ^{1}HNMR [DMSO-d_6] δ 8.37 (s, 1H), 8.36 (s, 1H), 7.80 (s, 1H), 7.49 (d, 21H), 7.30 (m, 2H), 7.10 (d, 2H), 6.96 (m, 3H), 6.81 (d, 2H), 4.59 (ABq, 2H), 4.54 (q, 2H), 4.02 (t, 1H), 3.8-3.6 (d, 6H), 3.31(m, 4H), 3.27 (m, 4H), 2.6-2.35 (m, 2H), 2.14 (m, 1H), 1.81 (t, 3H).

11: m.p. 151-152°C. $[\alpha]_D^{25}$ -25.20° (c = 0.32, $CHCl_3$).

12: m.p. 147-150°C. $[\alpha]_D^{25}$ -25.50° (c = 0.34, $CHCl_3$); ^{1}HNMR [DMSO-d_6] δ 8.35 (s, 1H), 8.34 (s, 1H), 7.80 (s, 1H), 7.50 (d, 11H), 7.3 (m, 2H), 7.11 (d, 2H), 6.97 (m, 3H), 6.81 (d, 2H), 5.9-5.7 (m, 1H), 5.1-4.9 (m, 2H), 4.59 (ABq, 2H), 4.22 (m 1H), 4.02 (t, 1H), 3.80-3.60 (m, 3H), 3.31 (m, 4H), 3.27 (m, 4H), 2.6-2.35 (m, 1H), 2.14 (m, 2H), 2.00-1.65 (m, 3H), 1.30 (d, 3H).

13: m.p. 148-150°C. $[\alpha]_D^{25}$ -31.40° (c = 0.36, $CHCl_3$).

14: m.p. 184-186°C. $[\alpha]_D^{25}$ -26.30° (c = 0.41, $CHCl_3$).

15: m.p. 116-145°C dec. $[\alpha]_D^{25}$ -18.20° (c = 0.27, HOAc); ^{1}HNMR [DMSO-d_6] δ 13.20 (broad s, 1H), 8.42 (s, 1H), 8.37 (s, 1H), 7.79 (s, 11H), 7.50 (d, 2H), 7.29 (m, 2H), 7.14 (d, 2H), 6.97 (m, 3H), 6.81 (d, 2H), 4.59 (ABq, 2H), 4.52 (s, 2H), 4.02 (t, 1H), 3.8-3.6 (m, 3H), 3.31 (m, 4H), 3.27 (m, 4H), 2.6-2.4 (m, 2H), 2.14 (m, 1H).

10. **Sch 51047:** m.p. 184-186°C. $[\alpha]_D^{25}$ -26.47° (c = 0.98, $CHCl_3$); ^{1}HNMR [$CDCl_3$] δ 8.13 (s, 1H), 7.81 (s, 1H), 7.61 (s, 1H), 7.50-6.70 (m, 11H), 4.6 (d, 2H), 4.55 (d, 2H), 4.1 (t, 1H), 3.82-3.58 (m, 3H), 3.50-3.25 (broad m, 8H), 2.55 (m, 2H), 2.09 (m, 1H), 1.42 (d, 6H).
11. **Sch 51048:** m.p. 167-169°C, $[\alpha]_D^{25}$ -26.26° (c = 1.00, $CHCl_3$); ^{1}HNMR [$CDCl_3$] δ 8.19 (s, 1H), 7.88 (s, 1H), 7.72 (s, 1H), 7.80-7.60 (m, 11H), 4.60 (ABq, 2H), 4.20-4.05 (m, 2H), 3.85-3.10 (m, 11H), 2.75-2.65 (m, 2H), 2.20-2.10 (m, 1H), 2.00-1.70 (m, 4H), 0.95 (t, 6H).
12. **Sch 51767:** m.p. 191-193°C, - 23.94 (c = 1.00, $CHCl_3$); ^{1}HNMR [$CDCl_3$] δ 8.13 (s, 1H), 7.81 (s, 1H), 7.60 (s, 1H), 7.55-7.35 (m, 3H), 7.20-6.75 (m, 8H), 4.80-4.45 (m, 4H), 4.12 (t, 1H), 3.85-3.55 (m, 3H), 3.55-3.10 (m, 8H), 2.65-2.50 (m, 2H), 2.20-1.55 (m, 10H).
13. Fluconazole (FLZ) has been used successfully in the treatment of *Candida* and meningeal *Cryptococcus* infections in AIDS patients,[2] suggesting an improved potential for Sch 51048 in such indications.
14. *34th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Orlando,* 4-7 October 1994:
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    (i) Nomeir, A. A.; Kim, H. K.; Loebenberg D.; Hare, R. S.; Miller, G. H.; Lin, C. C. *Abstract No. F197.*

(*Received in USA* 26 *October* 1994; *accepted* 12 *December* 1994)