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* Present address: Faculty of Pharmacy, University of Assiut, Assiut, Egypt, UAR.

x To whom inquiries should be directed.

Antidermatophytic Activity of 2-Thiotetrahydro-1,3,5-thiadiazines and Isothiocyanates

VIJAYA MANOHAR *, S. V. K. NARASIMHA MURTHY ‡§, M. SIRSI *, G. RAMANANDA RAO *x, and P. L. NARASIMHA RAO ‡

Abstract □ Benzyl, furfuryl, tetrahydronaphthyl, α-picolyl, and α-homopicolyl derivatives of 2-thiotetrahydro-1,3,5-thiadiazines were studied and found to be more active than β-picolyl and pyridyl analogs on dermatophytes, including the more resistant *Microsporum canis*.

Keyphrases □ 2-Thiotetrahydro-1,3,5-thiadiazines—antidermatophytic activity □ Isothiocyanates—antidermatophytic activity □ Antidermatophytic activity—2-thiotetrahydro-1,3,5-thiadiazines and isothiocyanates

It has been demonstrated that pterigospermin and its fission product benzyl isothiocyanate are potent antifungal agents (1–7). Phytopathogenic and saprophytic fungi, especially the yeasts, show sensitivity to isothiocyanates and their producers (8). However, inadequate dermal absorption, low solubility, and vesication are but a few of the factors that limit their topical application in the treatment of dermoid infections.

It was thought that substitution of the benzyl moiety by other isosteric groups, particularly those with basic residues, would make the compounds more water soluble to overcome the limitations in their use. This report presents the results of studies to test this hypothesis.

EXPERIMENTAL

Organisms—*Trichophyton mentagrophytes*[1] (HM115), *T. rubrum*[1] (HM186), *T. violaceum*[1] (HM164), *Epidermophyton floccosum*[1] (HM78), *Microsporum canis*[1] (I73), and *Candida albicans*[2] (Z248) were used. All dermatophytes and yeasts were maintained on Sabouraud's glucose agar slants.

Inocula—Spore suspensions from 15-day agar slant cultures in sterile saline were prepared, and 0.1 ml of the suspension or of an 18-hr broth culture of *C. albicans* was used as the inoculum in the serial dilution method.

Compounds—Solutions (1 mg/ml) were made in slightly acidified 50% ethanol (basic compounds), 20% dimethylformamide (griseofulvin), or acetone.

Antifungal Activity—Tubes in duplicate containing log concentrations, 0, 0.1, 1.0, 10.0, and 100 μg/ml, of the test compounds in 5.0 ml of Sabouraud's glucose broth were inoculated and incubated at 30° for 14 days (dermatophytes) or for 2 days (yeast). Tubes containing solvents at corresponding concentration levels were also included as blanks. The minimum inhibitory concentration (MIC) required for complete inhibition of growth was scored based on at least two independent experiments.

RESULTS AND DISCUSSION

The results of initial screening of antifungal activity of a few isothiocyanates and their producers, substituted 2-thiotetrahydro-1,3,5-thiadiazines, and other substances are reported in Table I. Benzyl isothiocyanate (XXI) inhibited the dermatophytes and *C. albicans* in the concentration range of 0.1–5.0 μg/ml, while the corresponding thiadiazine (X) did so at a level of 1.0–10.0 μg/ml. Similar levels of activity were displayed by furfuryl and tetrahydronaphthyl analogs (XIII and XIV, respectively). α-Picolyl and α-homopicolyl derivatives (III and VI, respectively) were distinctly more active then the β- and γ-isomers (IV and V, respectively) and far more potent than the pyridyl compounds (I and II, respectively).

[1] Isolated from clinical materials and characterized.

[2] Obtained from the School of Tropical Medicine and Hygiene, London, England.

Table I—Antifungal Activity of Thiadiazines and Isothiocyanates on Dermatophytes

	Compound	MIC, μg/ml					
		T. mentagrophytes	*T. rubrum*	*T. violaceum*	*E. floccosum*	*M. canis*	*C. albicans*
	3,5-Disubstituted 2-Thiotetrahydro-1,3,5-thiadiazines						
I	α-Pyridyl	100	100	100	100	100	50
II	β-Pyridyl	100	10	100	100	100	50
III	α-Picolyl	10	10	10	10	100	4
IV	β-Picolyl[a]	100	100	10	100	100	10
V	γ-Picolyl[a]	100	100	10	100	100	15
VI	α-Homopicolyl	10	1.0	10	0.1	0.1	10
VII	*o*-Methylphenyl	100	100	100	100	n.a.[a]	—[b]
VIII	*m*-Methylphenyl	100	100	100	100	n.a.	—
IX	*p*-Methylphenyl	100	100	100	100	n.a.	—
X	Benzyl	10	10	1.0	10	10	6
XI	*o*-Methylbenzyl	10	10	0.1	10	10	—
XII	*p*-Methylbenzyl	100	0.1	0.1	10	10	—
XIII	Furfuryl	1.0	0.1	0.1	10	10	—
XIV	Tetrahydronaphthyl	0.1	0.1	0.1	0.1	10	5
XV	Isobutyl	10	100	100	100	100	—
XVI	*o*-Chlorobenzyl[a]	n.a.	n.a.	n.a.	n.a.	n.a.	2
XVII	*o,p*-Dichlorobenzyl[c]	n.a.	n.a.	n.a.	n.a.	n.a.	5
XVIII	*m,p*-Dichlorobenzyl[c]	n.a.	n.a.	n.a.	n.a.	n.a.	5
XIX	*p*-Bromobenzyl[c]	n.a.	n.a.	n.a.	n.a.	n.a.	4
XX	*o,p*-Dibromobenzyl	n.a.	n.a.	n.a.	n.a.	n.a.	5
	Other Compounds						
XXI	Benzyl isothiocyanate	1.0	0.1	0.1	0.1	1.0	5
XXII	Allyl isothiocyanate	100	100	100	100	100	—
XXIII	*ac*-Tetrahydro-β-naphthyl isothiocyanate	1.0	1.0	0.1	0.1	10	5
XXIV	Griseofulvin	10	10	1.0	1.0	20	—

[a] Reference 11. [b] n.a. = not active up to 1000 μg/ml. — = not tested. [c] Reference 6.

While the homologous phenyl and other compounds were less active, halogenated derivatives (XVI–XX), which markedly inhibited yeasts and other phytopathogens (6), failed to show any antidermatophytic activity. Higher levels of thiadiazines, which expectedly produced active isothiocyanates *in vivo* (9, 10), may be needed to bring about complete inhibitory activity.

A few compounds seemed comparable to, or better than, griseofulvin in their antidermatophytic activity. *M. canis*, which was relatively more resistant to griseofulvin, was equally susceptible as the other dermatophytes to the action of furfuryl and tetrahydronaphthyl compounds (XIII and XIV, respectively) and even more susceptible to VI. These compounds are definitely more potent antidermatophytic agents than the benzyl analogs.

The solvents used, ethanol, dimethylformamide, and acetone, did not inhibit the growth of dermatophytes and yeasts.

In exploratory clinical trials, treatment with IV and X appears quite effective in superficial dermatomycoses.

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§ Present address: Department of Microbiology, School of Medicine, St. Louis University, St. Louis, MO 63104

ˣ To whom inquiries should be directed.