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Organotin(IV) Complexes of 4-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic Acid: Synthesis, Spectral Characterization and Biological Applications

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4-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic acid and its complexes with methyl-, n-butyl-, phenyl-, benzyl- and octyl-tin have been synthesized and characterized by elemental analysis and spectral studies. The geometry around the tin atom has been deduced from both solid and solution studies. These complexes were also tested against different bacteria and fungi to determine their toxicity. LD_{50} data was also calculated using the Brine Shrimp method.

Keywords: Organotin(IV) carboxylates, Spectroscopic characterization, Biological applications

INTRODUCTION

Organotin(IV) carboxylates comprise an important class of compounds [1-4]. Certain derivatives have industrial applications, for example, as homogeneous catalysts. Other uses relate to agricultural applications, where organotin carboxylates have been used as biocides and the like. More recently, the pharmaceutical properties of organotin carboxylates have been investigated with particular reference to their antitumor activity [5,6]. In this paper, we report the synthesis, spectral characterization and biological activity of the organotin derivatives of 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic acid (Fig.1) .

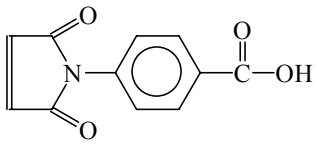

Fig. 1. Structure of the of 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic acid.

EXPERIMENTAL

Di- and triorganotin(IV) salts were purchased from Aldrich. Tribenzyltin chloride was prepared as previously described [7]. All other reagents were of the purest grade available. Solvents were purified by as previously published [8]. Melting points were determined in capillary tubes on an electrothermal melting point apparatus, model MP-D Mitamura Rikero Kogyo (Japan) and are uncorrected. C, H and N analyses were carried out at Midwest Microlab, Indianapolis (USA). Infrared spectra were recorded in the range of 4000-400 cm^{-1} as KBr pellets or thin film (Nujol) on a Bio-Rad Elmer 16FPc FT-IR spectrophotometer. ^{1}H, ^{13}C and ^{119}Sn NMR spectra were recorded on a Brucker AM-250

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spectrometer (Germany) using $CDCl_3$ as an internal reference [δ ^{1}H ($CDCl_3$) = 7.25: δ ^{13}C ($CDCl_3$) = 77.0]. ^{119}Sn NMR spectra were obtained with Me_4Sn [Ξ(Sn) = 37.296665] as an external reference. Mass spectra were recorded on a MAT 8500 Finnigan (Germany) at 70 eV.

Synthesis of 4-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl) benzoic Acid

The ligand acid was synthesized by the reaction of maleic anhydride and 4-aminobenzoic acid, according to the reported method [9].

Synthesis of Organotin(IV) Complexes of 4-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic Acid

a) 4-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic acid (2.17 g, 10 mmol) was suspended in dry toluene (100 ml) and treated with Et_3N (2.78 ml, 20 mmol). The mixture was refluxed for 3-4 h. To a reaction flask containing a solution of triethylammonium maleoyl benzoate in dry toluene, diorganotin dichloride (5 mmol) or triorganotin chloride (10 mmol) was added with constant stirring. The reaction mixture was refluxed for 8-10 h. The reaction mixture containing Et_3NHCl was filtered off, such that the organotin derivative remained in the filtrate. The solvent was removed by a rotary apparatus. The mass left behind was crystallized from CH_2Cl_2 and n-hexane (1:1).

b) The ligand 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) benzoic acid (2.17 g, 10 mmol) was suspended in dry toluene, (100 ml). To this solution, solid Oct_2SnO (5 mmol) was added with constant stirring and refluxed for 8-10 h. Water formed during the reaction was removed *via* a Dean and Stark trap. The solvent was evaporated by rotary apparatus and the product obtained was recrystallized in CH_2Cl_2 and n-hexane (1:1).

The general chemical reactions for both di- and triorganotin compounds are given below:

$$R_2SnCl_2 + 2LHNEt_3 \longrightarrow R_2SnL_2 + 2Et_3NHCl$$

$$R_3SnCl + LHNEt_3 \longrightarrow R_3SnL + Et_3NHCl$$

$$Oct_2SnO + 2LH \longrightarrow Oct_2SnL_2 + 2H_2O$$

HL = 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic acid

RESULTS AND DISCUSSION

The physical and analytical data for the investigated compounds are given in Tables 1 and 2, respectively. All complexes are non-hygroscopic and are stable in air and light.

Infrared Spectra

Table 3 records the IR data for the ligand and its tin(IV) complexes. The IR spectra of the ligand show strong absorption in the region 3412 cm^{-1}, which is attributable to ν (OH) stretching vibrations. The band in the 1705 cm^{-1} region is assigned to ν (C=O) vibration. It shows a bathochromic shift after the ligand complexes with tin. In addition, the bands in the regions 1514 and 1310 cm^{-1} are attributed to COO (asym)

Table 1. Physical and Analytical Data for Organotin(IV) Complexes of 4-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic Acid

Comp. No.	General formula	Molecular formula	M.W.	M.P. (°C)	Yield (%)
(1)Me_2	Me_2SnL_2	$C_{24}H_{20}N_2O_8Sn$	583	70	85
(2)Bu_2	Bu_2SnL_2	$C_{30}H_{30}N_2O_8Sn$	665	190	80
(3)Ph_2	Ph_2SnL_2	$C_{34}H_{24}N_2O_8Sn$	707	111	65
(4)Oct_2	OCt_2SnL_2	$C_{38}H_{48}N_2O_8Sn$	779	120	68
(5)Me_3	Me_3SnL	$C_{14}H_{15}NO_4Sn$	380	–	70
(6)Bu_3	Bu_3SnL	$C_{23}H_{33}NO_4Sn$	506	–	72
(7)Ph_3	Ph_3SnL	$C_{29}H_{22}NO_4Sn$	566	98	82
(8)Bz_3	Bz_3SnL	$C_{32}H_{27}NO_4Sn$	608	–	75

Table 2. Analytical Data for Organotin(IV) Complexes of 4-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic Acid

Comp. No.	Calcd. (Found)		
	%C	%H	%N
(1)Me_2	49.60 (49.39)	3.12 (3.29)	4.82 (4.69)
(2)Bu_2	54.16 (53.92)	4.55 (4.41)	4.12 (4.31)
(3)Ph_2	57.90 (58.11)	3.14 (3.23)	3.97 (4.14)
(4)Oct_2	58.70 (58.93)	5.96 (6.11)	3.60 (3.42)
(5)Me_3	44.25 (44.11)	3.98 (3.88)	3.69 (3.58)
(6)Bu_3	54.57 (54.70)	6.57 (6.70)	2.77 (2.40)
(7)Ph_3	61.52 (61.32)	3.74 (3.65)	2.47 (2.58)
(8)Bz_3	63.19 (62.98)	4.47 (4.39)	2.30 (2.36)

and COO (sym) vibrations, respectively. The spectra of the complexes show bands in the region 590-528 cm^{-1} and 496-420 cm^{-1}, which are due to Sn-C and Sn-O stretching vibrations. It is known that denticity of a -COO group can be determined with a high level of probability based on the of values ν_{asym} (COO) and ν_{sym} (COO) and/or their difference: $\Delta\nu$ (COO) = ν_{asym} (COO)-ν_{zym} (COO). The $\Delta\nu$ (COO) from 189-135 cm^{-1} in the investigated compounds aids in the evaluation of the denticity of the -COO group both in $CHCl_3$ solution and in the solid state [10,11].

Mass Spectra

The mass spectral data for tri- and diorganotin(IV) derivatives of 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) benzoic acid are given in Table 4. A molecular ion peak of very low intensity is observed in compounds **(2)**, **(5)**, **(6)** and **(8)**, while it is absent in the other compounds. The base peaks in compounds **(1)**, **(3)** and **(5)** are due to a $[C_{11}H_6NO_4]^+$ fragment at m/z 217. While in compound **(2)**, a $[C_{26}H_{22}N_2O_8Sn]^+$ fragment is responsible for the base peak. In compounds **(4)** and **(7)**, the base peak is due to a $[C_4H_9]^+$ fragment at m/z 57. The base peaks in compounds **(6)** and **(8)** are observed due to $[C_{19}H_{24}NO_4Sn]^+$ and $[C_7H_7]^+$ fragments at m/z 450 and 91, respectively. Primary fragmentation is due to the loss of an R group. However, secondary and tertiary fragmentation occurs by the loss of an R group in the triorganotin(IV) derivatives, while the diorganotin(IV) derivatives exhibit slightly different patterns. Secondary fragmentation is achieved due to a loss of either an R group or CO_2 molecule.

The general fragmentation pattern for di- and triorganotin(IV) carboxylates is given in Schemes 1 and 2 .

NMR Spectra

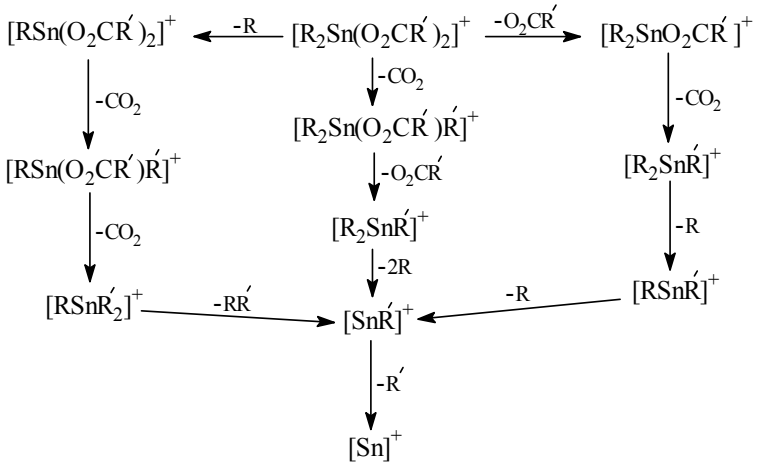
^{1}H NMR Spectra. The ^{1}H NMR studies for these compounds have been carried out in the deuterated solvent, $CDCl_3$, at room temperature. Different proton resonances were assigned on the basis of their multiplicity and intensity patterns. The integration spectra were in accordance with the number of protons proposed for each molecular fragment. Compounds **(1)** and **(5)** give singlet at 1.22 and 0.59 ppm, respectively, for the CH_3 group. Compounds **(3)** and **(7)** show

Table 3. IR Spectral Data (cm^{-1}) for Organotin(IV) Complexes of 4-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl) benzoic Acid

Comp. No.	ν (NH)	ν (COO_{sym})	ν (COO_{asym})	Δν	ν (CO)	ν (Sn–C)	ν (Sn–O)
HL	3310	1310	1614	304	1705	–	–
(1)Me_2	3351	1398	1535	137	1716	584	440
(2)Bu_2	3320	1365	1512	143	1720	590	485
(3)Ph_2	3398	1369	1556	187	1712	550	420
(4)Oct_2	3396	1361	1513	144	1713	556	460
(5)Me_3	3303	1363	1509	146	1716	530	475
(6)Bu_3	3384	1325	1510	185	1717	529	460
(7)Ph_3	3352	1379	1514	135	1716	541	496
(8)Bz_3	3314	1361	1550	189	1712	528	449

Table 4. Mass Spectral Data for Organotin(IV) Complexes of 4-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic Acid

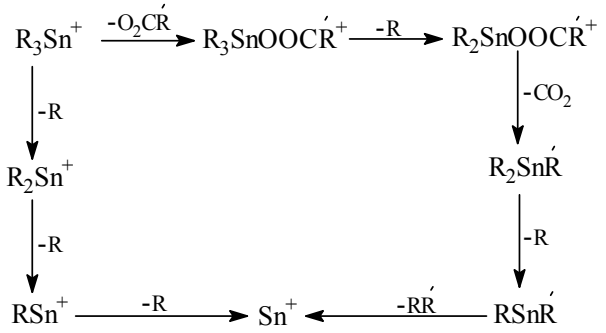
Fragment ion	**(1)**Me_2	**(2)**Bu_2	**(3)**Ph_2	**(4)**Oct_2	**(5)**Me_3	**(6)**Bu_3	**(7)**Ph_3	**(8)**Bz_3
$R_3SnOOCR'$	–	–	–	–	380 (3)	567 (4)	567 (n.o)	608 (3)
$R_2Sn(OOCR')_2$	583 (n.o)	665 (8)	707 (n.o)	779 (n.o)	–	–	–	–
$R_2SnOOCR'$	–	–	–	–	366 (52)	450 (100)	490 (n.o)	518 (4)
$RSnOOCR'$	350 (n.o)	392 (1)	411 (4)	448 (72)	350 (n.o)	392 (2)	414 (n.o)	427 (6)
$SnOCOR'$	335 (3)	335 (32)	335 (10)	335 (6)	335 (4)	335 (16)	335 (n.o)	335 (3)
R_3Sn^+	–	–	–	–	164 (10)	290 (6)	347 (n.o)	392 (6)
R_2Sn^+	149 (9)	233 (n.o)	271 (22)	345 (4)	149 (9)	233 (5)	271 (3)	301 (11)
Sn^+	120 (72)	120 (4)	120 (5)	120 (6)	120 (68)	120 (4)	120 (6)	120 (2)
	76 (3)	76 (n.o)	76 (5)	76 (4)	76 (2)	76 (n.o)	76 (8)	76 (4)
$[C_{11}O_4H_6N]^+$	217 (100)	217 (n.o)	217 (100)	217 (80)	217(100)	217 (n.o)	217 (n.o)	217 (n.o)
$[C_{26}H_{22}O_8N_2Sn]^+$	609 (n.o)	609 (100)	609 (n.o)	609 (5)	609 (n.o)	609 (n.o)	609 (n.o)	609 (n.o)
$[C_4H_9]^+$	–	57 (24)	57 (38)	57 (100)	–	57 (9)	57 (100)	57 (19)
$[C_7H_7]^+$	–	–	–	–	–	–	–	91(100)



Scheme 1. Fragmentation Pattern for Diorganotin Dicarboxylates

multiplet for the phenyl group at 7.59 and 7.40-7.48 ppm, respectively. The phenyl group gives multiplet due to a complex pattern. Compound **(8)** gives singlet at 1.23 ppm for the CH_2 group and multiplet at 7.23-7.39 ppm for C_6H_5. ^1H NMR data for the reported compounds is given in Table 5.

^{13}C NMR Spectra. The parameters of the ^{13}C NMR spectra are given in Table 6. The complete assignment of signals confirms the identity of the compounds. The downfield shift of the ^{13}C (COO) group in the range of 177.3-174.3 ppm reflects the structure and the way the bonds of the COO group



Scheme 2. Fragmentation Pattern for Triorganotin Carboxylates

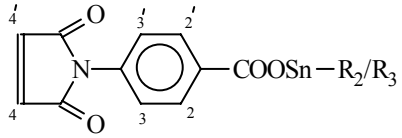
groups in all investigated compounds are within the expected range.

^{119}Sn NMR Spectra. In Table 6 are also included the δ (^{119}Sn) values of the studied compounds in solution with $CDCl_3$ as the non-coordinating solvent. The central tin atoms in this solvent have a distorted tetrahedral geometry according to their δ (^{119}Sn) values from 149.9 to -149.2 ppm [11,12].

BIOLOGICAL ACTIVITY

All the reported compounds were tested for their toxicity by using the Brine Shrimp method [13]. Etoposide (LD_{50} = 7.4625 μg ml^{-1}) was used as a standard drug. The results are given in Table 7. Compounds **(1)** and **(2)** both had an LD_{50} of 17.1238 μg ml^{-1}, while the compounds **(5)**, **(7)** and **(8)** did not exhibit any toxicity at all. Previous reports [14,15] have shown that the toxicity of organotin compounds depends upon the

Table 5. ^{1}H NMR Data for Organotin(IV) Complexes of 4-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic Acid



where R = Me, Bu, Ph, Bz, Oct

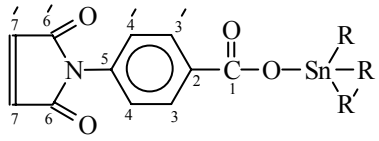
Comp. No.	Proton Number			R
	2,2′	3,3′	4,4′	
HL	7.90d (8.1)	8.03d (8.2)	8.12 s	–
(1)Me_2	7.86d (8.1)	8.12d (8.2)	8.23 s	1.22s
(2)Bu_2	7.43d (8.1)	8.06d (8.2)	8.15 s	1.12-1.17t, 1.28-1.30m, 0.85t, 1.55-1.60m
(3)Ph_2	7.66d (8.1)	8.10d (8.2)	8.33 s	7.59m
(4)Oct_2	7.44d (8.1)	8.09d (8.2)	8.12 s	0.73-2.1m
(5)Me_3	7.49d (8.1)	8.15d (8.2)	8.25 s	0.59s
(6)Bu_3	7.84d (8.1)	8.06d (8.2)	8.20 s	0.82t, 1.12-1.17t, 1.23-1.31m, 1.55-1.58m
(7)Ph_3	7.64d (8.1)	8.09d (8.2)	8.11 s	7.40-7.48m
(8)Bz_3	7.45d (8.1)	8.13d (8.2)	8.14 s	1.23s, 7.23-7.39m

are connected to the central tin atom. The chemical shift values δ (^{13}C) (CO) of all compounds are in the region of 169.5-166.9 ppm. The remaining carbons do not show much shift in their values. Compound **(2),** Bu_2SnL_2, gives signal at 13.4, 26.5 (63.2), 27.4 (213) and 16.1 (363) ppm for carbons 8 to 11, respectively. The values of the chemical shifts of the R

Table 6. ^{13}C and ^{119}Sn NMR Data for Organotin(IV) Complexes of 4-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic Acid

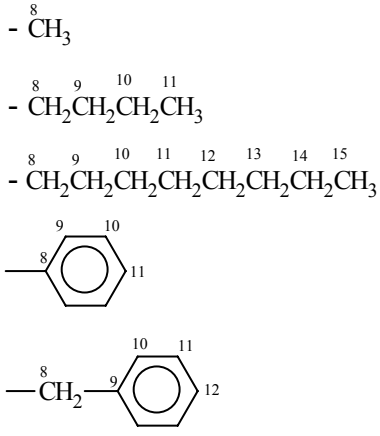
Carbon No.	**HL**	**(1)**Me_2	**(2)**Bu_2	**(3)**Ph_2	**(4)**Oct_2	**(5)**Me_3	**(6)**Bu_3	**(7)**Ph_3	**(8)**Bz_3
1	169.9	174.9	177.3	177.3	174.3	174.8	175.1	176.5	175.1
2	129.8	130.0	129.0	129.5	129.6	129.6	129.5	130.1	130.9
3,3′	134.8	134.8	134.3	134.8	134.8	134.3	134.3	134.8	134.3
4,4′	126.1	125.7	125.1	125.7	125.7	125.1	125.1	125.7	125.0
5	135.2	135.8	135.4	136.8	136.1	138.2	135.4	136.4	136.5
6,6′	166.9	169.5	168.9	169.3	169.4	169.2	168.9	169.3	169.5
7,7′	133.2	133.2	133.2	133.2	133.2	133.2	133.2	133.4	133.2
8	–	4.82	13.4	131.5	24.9	8.4	13.4	135.4	29.6
9	–	–	26.5 (63.2)[a]	129.5	22.9	–	25.2	137.7	134.8
10	–	–	27.4 (213)[a]	128.6	32.1	–	26.5	129.5	128.9
11	–	–	16.1 (363)[a]	125.7	29.7	–	26.2	128.6	126.5
12	–	–	–	–	29.5	–	–	–	125.5
13	–	–	–	–	32.3	–	–	–	–
14	–	–	–	–	22.9	–	–	–	–
15	–	–	–	–	14.2	–	–	–	–
^{119}Sn	–	–	146.9	-125.78	-146.3	145.79	-149.2	–	142.45

[a] Values in parentheses are ^{119}Sn-^{13}C couplings.



R′ = R for triorganotin

R′ = L for diorganotin



nature of their organic groups.

The antibacterial activity of the synthesized compounds was tested against six different bacteria. The agar well diffusion method [16] was used for screening their antibacterial effects. The results given in Table 8 show that methyl, butyl and phenyltin carboxylates are the most potent candidates against the tested bacteria. All of these compounds were active against *Bacillus subtilis*.

Earlier reports show that higher antifungal activity is associated with tributyl and triphenyltin compounds [13]. In the present series, the highest antifungal activity was exhibited by the tributyltin carboxylates. Miconazole and ketoconazole

Table 7. Brine Shrimp (*Artemia Salina*) Bioassay for the Toxicity of Organotin(IV) Complexes of 4-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic Acid

Comp. No.	Dose (μg ml^{-1})	No. of Shrimps	No. of Survivors	LD_{50} (μg ml^{-1}) for Brine Shrimp	LD_{50} (μg ml^{-1}) for Etoposide as a Standard Drug
HL	100	30	0	< 1	7.4625
	10	30	0		
	1	30	0		
(1)Me_2	100	30	0	17.1238	7.4623
	10	30	23		
	1	30	30		
(2)Bu_2	100	30	0	17.1238	7.4625
	10	30	8		
	1	30	10		
(3)Ph_2	100	30	0	13.0923	7.4625
	10	30	7		
	1	30	10		
(4)Oct_2	100	30	0	< 1	7.4625
	10	30	0		
	1	30	0		
(5)Me_3	100	30	10	–	7.4625
	10	30	10		
	1	30	10		
(6)Bu_3	100	30	0	5.8399	7.4625
	10	30	2		
	1	30	10		
(7)Ph_3	100	30	10	–	7.4625
	10	30	10		
	1	30	10		
(8)Bz_3	100	30	10	–	7.4625
	10	30	10		
	1	30	10		

were also used as standard drugs and the corresponding results are summarized in Table 9.

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Table 8. Antibacterial Activity for Organotin(IV) Complexes of 4-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl) benzoic Acid Using Ampicilline $(H_2O)_3$ and Cephalexin Na as Standard Drugs

Bacteria	Comp. No.								
	HL	**(1)**Me_2	**(2)**Bu_2	**(3)**Ph_2	**(4)**Oct_2	**(5)**Me_3	**(6)**Bu_3	**(7)**Ph_3	**(8)**Bz_3
Escherichia coli	–	9	12	–	–	6	–	–	–
Bacillus subtilis	12	17	17	15	15	17	17	14	15
Shigella flexnari	10	9	13	10	–	8	19	11	–
Staphylococcus aureus	10	12	14	15	12	16	18	12	13
Pseudomonas aeruginosa	11	11	11	10	14	11	12	–	12
Salmonella typhi	–	9	13	10	–	10	10	14	10

Table 9. Antifungal Activity for Organotin(IV) Complexes of 4-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic Acid

Name of fungi	Comp. No.									Standard drug
	HL	**(1)**Me_2	**(2)**Bu_2	**(3)**Ph_2	**(4)**Oct_2	**(5)**Me_3	**(6)**Bu_3	**(7)**Ph_3	**(8)**Bz_3	
Trichophyton long fusum	42.1	60	0	0	67.2	72.6	94.7	36.84	68.4	Miconazole Ketoconazole
Candida albicans	31.5	0	0	0	0	0	100	0	0	Miconazole Ketoconazole
Aspergillus flavus	0	0	44.4	10	0	44.4	100	0	0	Amphotericin-B Flucytosine
Microsporum canis	65	0	20	0	0	36.84	100	36.84	72.2	Miconazole Ketoconazole
Fusarium solani	0	0	45	0	0	0	100	0	0	Miconazole
Candida glabrata	0	0	0	0	0	0	100	0	0	Miconazole

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