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Conventional as well as Eco-Friendly Microwave Irridiated Synthesis and Antimicrobial Evaluation of Some New Benzotriazole Derivatives.

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Abstract
A Series of 5- [(2'-N-sub.arylidene hydrazinothioacetyl)-1-(methylene)-1,'3'4'-thiadiazoles]-1,2,3-benzotriazoles **3a-k** and 5-[(2'"sub. Aryl-1'",3'"-thiazolidine-4'"-ones)-1"-(iminothioacetyl)-1-(methylene)-1,'3'4'-thiadiazoles]-1,2,3-benzotriazoles **4a-k,** were synthesized by using 5-[2'-Marcapto-1-(methylene)- 1,'3'4'-thiadiazoles]-1,2,3-benzotriazoles as the starting material. The Structure of the synthesized products were assigned on the basis of elemental analysis, IR and ^{1}HNMR spectral data. All the products were screened against different strains of bacteria and fungi.

Key Words
4- Thiazolidinones, antibacterial and antifungal activities.

Introduction
1,2,3-benzotriazoles and 4- thiazolidinones are structural subunits of several biologically active compounds. The pharmacological properties of the 4-thiazolidinones encouraged our interest in synthesizing several new compounds featuring various heterocyclic rings, attached to 4-thiazolidinones moieties. 4- thiazolidinones are well know heterocyclic compounds for their spectrum of biological activities such as antibacterial[1-3], antifungal[4-5], anticonvulsant[6,] local analgesic[7], antitubercular[8,9], etc. The recent finding indicated that 1,2,3-triazole nucleus is associated with diverse pharmacological properties such as analgesic[10], diuretic[11], pesticidal [12]. The microwave irradiation is used for carrying out chemical transformations which are pollution free and eco-friendly[13]. Microwave heating has emerged as a powerful technique to promote a variety of chemical reaction due to the short reaction time and the operational simplicity[14].

Materials and Methods
The melting points were taken in an open capillary tube. IR spectra (KBr) were recorded on Shimadzu 8201 PC spectrophotometer (ν_{max} in cm^{-1}) and ^{1}HNMR spectra in $CDCl_3$ at 300 MHz on Bruker DRX 300 spectrometer using TMS as an internal standard (Chemical shifts inδ, ppm).

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All the compounds gave satisfactory C, H and N percentage within the experimental limit. Microwave assisted reaction were carried out in a Q Pro-M-modified microwave oven.

Synthesis of 5- [(2'-Ethylthioacetate) –1- (methylene) -(1',3',4'- thiadiazoles)] -1,2,3-benzotriazoles:
Ethyl chloro acetate (3.44 mL, 0.028 M), was added to a solution of 5-[(2'-marcapto)-1-(methylene)-(1',3',4'-thiadiazoles)]-1,2,3-benzotriazole in MeOH (50 mL) about 4 hr. The solvent was removed in *Vacuo* and the residue was purified over the column of silica gel using $CHCl_3$ as an eluent. The product was crystallized from chloroform to give **1**, yield 80% m.p. 145-48ºC, [Found C, 46.54; H, 3.86; N, 20.87; $C_{13}H_{13}N_5S_2O_2$ requires C, 46.56; H, 3.88; N, 20.89; IR (KBr) : 3254, 3072, 2951, 2802, 1593, 1468, 1362, 996, 934, 865 and 742 (1,2,3-benzotriazole nucleus), 2829, 1476 and 1212 (>N-CH_2), 1604, 1442, 1310, 1177 and 692 (thiadiazole nucleus) 2826, 2245 and 1790 (C-CH_2), 1675, 918 (C=O) 1446, 1420 (S-CH_2); ^{1}HNMR ($CDCl_3$) : 3.62 (s, 2H, >N-CH_2), 7.28-7.81 (m, 4H Ar-H), 3.2 (s, 2H,-S-CH_2), 1.21 (t,3H,J=7Hz, $COOCH_2$-CH_3), 4.10 (q, 2H, J=7Hz, $COOCH_2CH_3$).

Microwave Method
The mixture prepare as given above was taken in a round bottomed flask and irradiated in microwave oven for 6 min. The completion of the reaction was monitored by TLC. The solvent was removed in

Vacuo and the product was recrystallized from chloroform to give **1** yield 85% spectral data and analytical data were found to be similar as far the conventional method.

Synthesis of 5-[(2'hydrazino thioacetyl)-1 (methylene)-(1', 3', and 4'-thiadiazoles)]-1, 2, 3 Benzotriazole:

Equimolar solution of compound, 1 (6g, 0.18 M) and hydrazine hydrate, (0.870 mL, 0.18 M) in methanol (30 mL) was refluxed for about 8 hr on a water bath. After cooling the solution was filtered, dried and recrystallized from chloroform to give compound **2**, yield 85%, m.p. 157-59ºC, [found c,41.10; H, 3.40; N, 30.50; $C_{11}H_{11}N_7S_2O$ requires C, 41.12; H, 3.42; N, 30.52); IR (KBr) : 3250, 3073, 2950, 2808, 1592, 1472, 1363, 996, 936, 866 and 740 (1,2,3-benzotriazole nucleus) 2826, 1473 and 1211 (>N-CH_2), 1602, 1443, 1314, 1174 and 688 (thiadiazole nucleus) 2824, 2243 and 1792 (C-CH_2), 1673, 916 (C=O) 1438 and 1418 (S-CH_2); 3348 ($NHNH_2$); ^{1}HNMR ($CDCl_3$) : 3.63 (s, 2H, >N-CH_2), 2.99 (s, 2H,-S-CH_2), 8.17 (s, 1H-CONH), 4.44 (s, 2H, -NH_2) and 7.32-7.82 (m, 4H Ar-H).

Microwave Method

The mixture prepare as given above was taken in a round bottomed flask and irradiated in microwave oven for 8 min. The completion of the reaction was monitored by TLC. The solvent was removed in *Vacuo* and the product was recrystallized from chloroform to give **2** yield 88% spectral data and analytical data were found to be similar as far the conventional method.

Synthesis of 5-[(2'-N-sub.Arylidene hydrazinothioacetyl)-1-(methylene)-(1', 3', 4'-thiadiazoles)]-1, 2, 3-benzotriazole (3a):

A mixture of compound 2 (5 g, 0.015 M) and benzaldehyde (1.574 mL, 0.015 M) and 2-3 drops of glacial acetic acid in methanol (50 mL) was refluxed on a water bath for about 6 hr. The solvent was removed under reduced pressure and the residue was purified over the column of silica gel using $CHCl_3$ as an eluent. The product was crystallized from chloroform to give a product **3a**, yield 76%, m.p. 174-77ºC. [found C,52.79; H, 3.64; N, 23.94; $C_{18}H_{15}N_7S_2O$ requires C, 52.81; H, 3.66; N, 23.96); IR (KBr) : 3255, 3070, 2954, 2809, 1190, 1474, 1368, 995, 930, 864 and 744 (1,2,3-benzotriazole nucleus) 2825, 1470 and 1216 (>N-CH_2), 1600, 1438, 1316, 1178 and 694 (thiadiazole nucleus) 2828, 2245 and 1795 (C-CH_2), 1666, 915 (C=O), 1592 and 1546 (CH=N), 1441 and 1415 (S-CH_2); ^{1}HNMR ($CDCl_3$) : 3.60 (s, 2H, >N-CH_2), 8.19 (s, 1H, NHN), 4.92 (s, 1H, N=CH), 3.0 (s, 2H,-S-CH_2), 7.14-7.93 (m, 9H, Ar-H).

Microwave Method

The mixture prepare as given above was taken in a round bottomed flask and irradiated in microwave oven for 7 min. The completion of the reaction was monitored by TLC. The solvent was removed in *Vacuo* and the product was recrystallized from chloroform to give **3a** yield 80% spectral data and analytical data were found to be similar as far the conventional method. Other compound **3b-k** were prepared by the similar way using compound 2 and different sub. aryl. Characterization data are presented Table 1.

Synthesis of 5-[(2'''-Aryl-1''',3'''-thiazolidine-4'''-ones)-1''-(iminothioacetyl)-1-(methylene)-1',3',4'-thiadiazoles]-1, 2,3-benzotriazoles (4a):

To a stirred solution of the compound **3a** (3.5 g, 0.007 M) in methanol (30 mL), containing a pinch of anhyd. ZnCl2 thioglycolic acid (0.64 g, 0.007M) was added and the mixture was refluxed on a water-bath for about 10 hr. The separated solid was purified over the column of silica gel, eluted with CHCl3 and recrystallized from chloroform to give compound **4a**, yield 70%,m.p. 180ºC -182ºC, [found C,49.68; H,3.52; N, 20.29; $C_{20}H_{17}N_7S_3O_2$ requires C, 49.66; H, 3.50; N, 20.27); IR (KBr) : 3253, 3077, 2955, 2805, 1588, 1473, 1375, 996,940 and 746 (1,2,3-benzotriazole nucleus with aromatic ring) 2828, 1471 and 1208 (>N-CH_2), 1605, 1448, 1316, 1178 and 694 (thiadiazole nucleus) 1670(>C=0 amide), 1714(>C=0 cyclic), 2980 (N-CH-S), 2962 (CH2-S, cyclic), 1443 and 1413 (S-CH_2); ^{1}HNMR ($CDCl_3$) : 4.40 (s, 2H, >N-CH_2), 8.15 (s, 1H, CONH), 8.25 (s,1H, NH-N), 3.56 (s, 2H, S-CH_2), 3.22(s, 1H, N-CH-Ar), 7.25-7.52 (m, 9H, Ar-H).

Microwave Method:

The mixture prepare as given above was taken in a round bottomed flask and irradiated in microwave oven for 9 min. The completion of the reaction was monitored by TLC. The solvent was removed in *Vacuo* and the product was recrystallized from chloroform to give **4a** yield 78% spectral data and analytical data were found to be similar as far the conventional method. Other compound **4b-k** were prepared by the similar way using compound **3b-k** and thioglycolic acid. Characterization data are presented Table 1.

Results and Discussion

5-[(2'-Marcapto)- 1- (methylene)- (1',3',4' thiadiazole)] -1,2,3-benzotriazole on reaction with ethyl chloroacetate gave 5-[(2'-ethylthioacetate)-1-(methylene)-1',3',4'-thiadiazole)]-1,2,3-benzotriazole **1**. Which on amination with hydrazine hydrate yielded 5-[(2'-Hydrazinothioacetyl)-1-(methylene)-(1', 3', 4' thiadiazole)]-1, 2, 3-benzotriazole **2**. The compound **2** on condensation with various aromatic aldehydes afforded 5-[(2'-N-sub. arylidene hydrazinothioacetyl)-1-(methylene)-(1',3',4'-thiadiazole)]-1,2,3 benzotriazole **3**. The compound **3** on reaction with thioglycolic acid in presence of anhys.ZnCl2 underwent dehydrative annulation to afford 5-[(2'''-sub.aryl-1''',3'''-thiazolidine-4'''-ones)-1''-(iminothioacetyl)-1 (methylene) - (1',3',4'-thiadiazole)]-1, 2, 3-benzotriazole 4a. **(Scheme1)**.

Antimicrobial Activity

The synthesized compounds were screened for their antibacterial activity against *Escherichia coli*, *Staphylococcus aureus Klebsiella pneumoniae* and *Bacillus substilis* by filter paper disc technique at two concentrations (50 and 100 ppm) and antifungal activity against *Aspergillus niger, Aspergillus flavus, Fusarium oxisporum* and *Trichoderma viride* by disc diffusion technique at two concentrations (100 and 500 ppm). Standard antibacterial streptomycin and antifungal griseofulvin were also screened under the similar condition for comparison. The analytical data are presented in **Table 2** and **Table 3** respectively.

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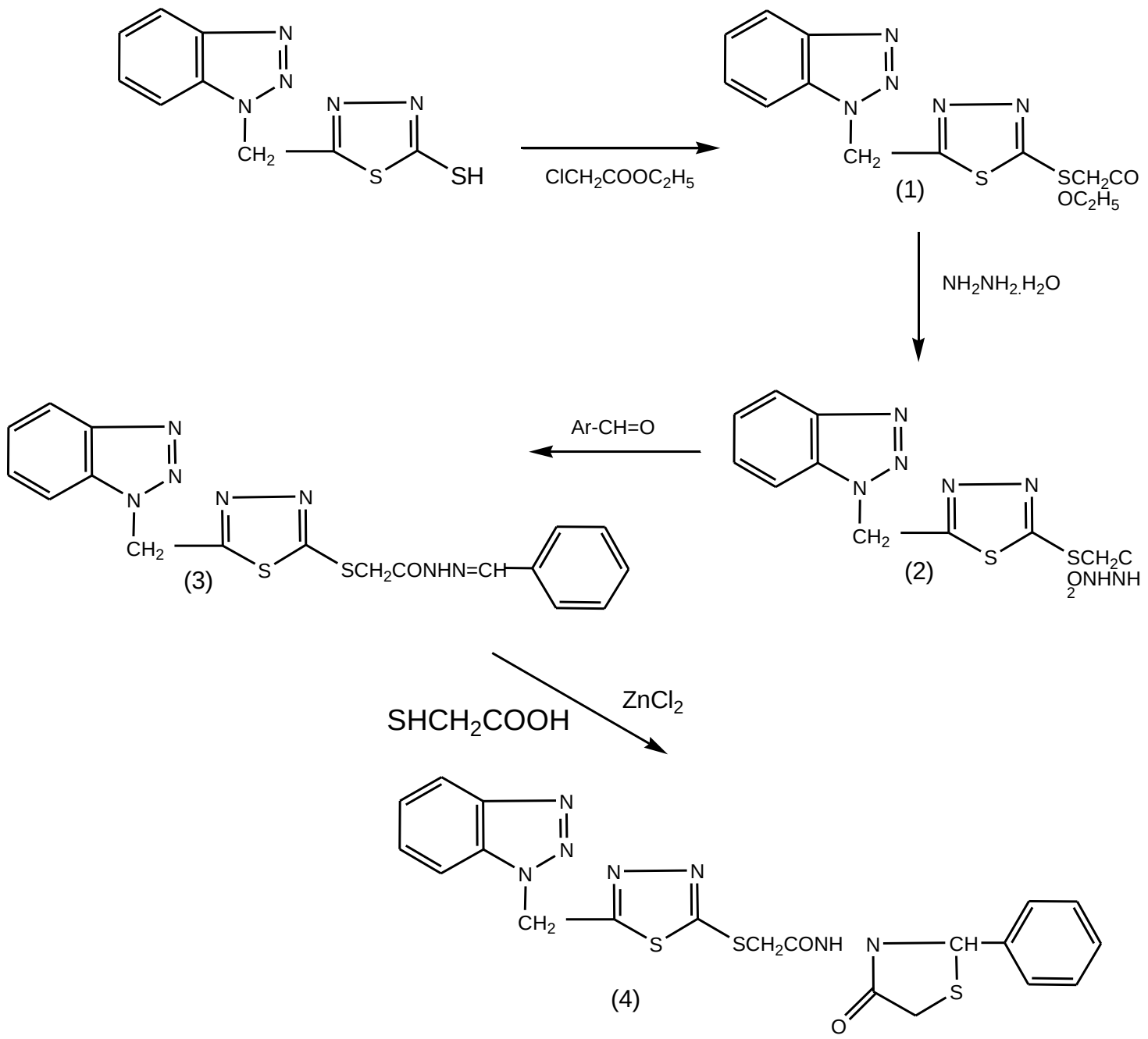

Where Ar = - C_6H_5/2,3,4-BrC_6H_4/2,3,4, - ClC_6H_4/2,3,4-$NO_2C_6H_4$/-N$(CH_3)_2C_6H_4$

Scheme - 1

Table 1 : Characterization data of the compounds (3b-k) and (4b-k)

Table 1: Characterization data of the compounds (3b-k) and (4b-k).

Compd.	Ar	Yield (%)	m.p. (°C)	M. Formula	Calc. (Found) %		
					C	H	N
3b	2-BrC_6H_4	70	117-119	$C_{18}H_{14}ON_7S_2Br$	44.27 (44.25)	2.86 (2.83)	20.08 (20.07)
3c	3-BrC_6H_4	72	127-128	$C_{18}H_{14}ON_7S_2Br$	44.27 (44.26)	2.86 (2.84)	20.08 (20.06)
3d	4-BrC_6H_4	71	136-138	$C_{18}H_{14}ON_7S_2Br$	44.27 (44.24)	2.86 (2.85)	20.08 (20.05)
3e	2-ClC_6H_4	70	160-162	$C_{18}H_{14}ON_7S_2Cl$	48.70 (48.68)	3.15 (3.13)	22.09 (22.06)
3f	3-ClC_6H_4	73	165-168	$C_{18}H_{14}ON_7S_2Cl$	48.70 (48.69)	3.15 (3.12)	22.09 (22.07)
3g	4-ClC_6H_4	72	172-175	$C_{18}H_{14}ON_7S_2Cl$	48.70 (48.66)	3.15 (3.14)	22.09 (22.08)
3h	2-$NO_2C_6H_4$	69	168-170	$C_{18}H_{14}O_3N_8S_2$	47.57 (47.55)	3.08 (3.06)	24.66 (24.64)
3i	3-$NO_2C_6H_4$	70	169-171	$C_{18}H_{14}O_3N_8S_2$	47.57 (47.54)	3.08 (3.07)	24.66 (24.63)
3j	4-$NO_2C_6H_4$	71	176-179	$C_{18}H_{14}O_3N_8S_2$	47.57 (47.54)	3.08 (3.04)	24.66 (24.62)
3k	4,4'-$N(CH_3)_2C_6H_4$	68	150-155	$C_{20}H_{15}O_2N_7S_2ClBr$	53.09 (53.07)	4.42 (4.40)	24.77 (24.75)
4b	2-BrC_6H_4	69	197-199	$C_{20}H_{16}O_2N_7S_3Br$	42.71 (42.70)	2.84 (2.82)	17.44 (17.42]
4c	3-BrC_6H_4	72	192-196	$C_{20}H_{16}O_2N_7S_3Br$	42.71 (42.68)	2.84 (2.81)	17.44 (17.41]
4d	4-BrC_6H_4	70	198-200	$C_{20}H_{16}O_2N_7S_3Br$	42.71 (42.69)	2.84 (2.83)	17.44 (17.43]
4e	2-ClC_6H_4	71	181-183	$C_{20}H_{16}O_2N_7S_3Cl$	46.37 (46.35)	3.09 (2.07]	18.93 (18.91)
4f	3-ClC_6H_4	73	186-188	$C_{20}H_{16}O_2N_7S_3Cl$	46.37 (46.36)	3.09 (2.08]	18.93 (18.92)
4g	4-ClC_6H_4	69	190-191	$C_{20}H_{16}O_2N_7S_3Cl$	46.37 (46.37)	3.09 (2.06]	18.93 (18.90)
4h	2-$NO_2C_6H_4$	75	203-205	$C_{20}H_{16}O_4N_8S_3$	45.45 (45.42)	3.03 (3.01)	21.21 (21.18)
4i	3-$NO_2C_6H_4$	73	208-210	$C_{20}H_{16}O_4N_8S_3$	45.45 (45.43)	3.03 (3.02)	21.21 (21.19)
4j	4-$NO_2C_6H_4$	70	214-216	$C_{20}H_{16}O_4N_8S_3$	45.45 (45.44]	3.03 (3.00)	21.11 (21.20)
4k	4,4'-$N(CH_3)_2C_6H_4$	76	220-222	$C_{22}H_{22}O_2N_8S_3$	50.19 (50.17)	4.18 (4.16)	21.29 (21.27)

Table 2: Antibacterial data of the compounds (3a-k) and (4a-k).

Comp	*E. coli*		*S. aureus*		*K. pneumoniae*		*B. substilis*	
	50 ppm	100 ppm	50 ppm	100 ppm	50 ppm	100 ppm	50 ppm	100 ppm
3a	+	++	+	++	+	++	+	+
3b	++	+++	+++	++++	+++	++++	+	++
3c	+++	++++	++	+++	+	++	+++	++++
3d	++	++	+++	+++	++	+++	+++	++++
3e	+	+	+	++	-	+	+	++
3f	-	+	++	++	+	+	-	+
3g	-	-	+	+	-	+	+	++
3h	+	++	-	+	+	++	-	-
3i	++	++	+	-	-	+	-	+
3j	-	++	-	+	+	+	-	-
3k	+	+	+	++	-	+	+	+
4a	+	++	-	+	-	+	+	++
4b	++	+++	+++	+++	++	+++	+++	++++
4c	+++	++++	+++	++++	+++	+++	+++	+++
4d	++	++	++	+++	++	+++	+++	++++
4e	+	+	-	+	+	+	-	+
4f	+	++	-	+	-	+	-	-
4g	-	+	+	++	-	-	-	+
4h	+	+	-	++	-	++	-	+
4i	+	++	+	++	-	+	-	-
4j	++	++	-	+	-	-	+	++
4k	+	+	-	+	-	+	-	+
SM	+++	++++	+++	++++	+++	++++	+++	++++

Table 3: Antifungal data of the compounds (3a-k) and (4a-k).

Comp	*A. niger*		*A. flavus*		*F. oxisporum*		*T. viride*	
	100 ppm	500 ppm	100 ppm	500 ppm	100 ppm	500 ppm	100 ppm	500 ppm
3a	+	++	++	+++	++	+++	+	++
3b	++	+++	+++	++++	++	+++	+++	++++
3c	+++	++++	++	+++	++	+++	++	+++
3d	++	+++	+++	++++	+++	++++	+++	++++
3e	+	++	-	+	+	++	-	+
3f	-	+	+	++	-	++	+	++
3g	+	++	-	+	-	+	-	+
3h	-	+	+	++	+	++	-	-
3i	+	++	-	-	+	++	+	+
3j	-	-	++	+	-	+	-	-
3k	-	+	+	++	-	-	-	+
4a	+	++	-	+	-	+	+	++
4b	++	+++	+++	++++	+	++	++	+++
4c	++	+++	++	+++	++	+++	+++	++++
4d	+++	++++	++	++	+++	++++	+++	+++
4e	+	+	-	+	-	+	+	++
4f	-	-	-	+	+	++	+	+
4g	+	++	++	+	-	+	-	-
4h	+	+	-	-	+	+	-	+
4i	-	+	+	++	-	+	-	-
4j	-	-	+	-	+	++	+	++
4k	+	+	+	++	-	+	+	+
GF	+++	++++	+++	++++	+++	++++	+++	++++

GF = Griseofulvin, inhibition diameter in mm; (-) 5; (+) 5-11, (++) 11-15; (+++) 15-19 and (++++) 19-24.