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Synthesis and Antimicrobial Activity of Phthalimido(2-Aryl-3-Isonicotinamido-4-Oxo-1,3-Thiazolidine-5-yl) Ethanoates

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2-Aryl-3-isonicotinamido-4-oxo-1,3-thiazolidine-5-yl ethanoic acid (2a-h) have been synthesized via cycloaddition of 4-arylidenehydrazido pyridine (1a-h) with mercaptosuccinic acid in THF containing a pinch of $ZnCl_2$, which on treatment with thionyl chloride give corresponding ethanoyl chloride derivatives (3a-h). These on treatment with N-hydroxyphthalimide afford titled compounds (4a-h). IR, ^1H NMR, Mass and ^{13}C NMR determined their structures. All the synthesized compounds were screened for antibacterial (*Bacillus subtilis, Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris, Pseudomonas aeruginosa* and *Salmonella typhi*) and antifungal (*Candida albicans* and *Aspergillus fumigatus*) activities. All the compounds exhibited significant activity against the bacteria and fungi tested.

In the present investigation an attempt has been made to synthesize phthalimido (2-aryl-3-isonicotinamido-1,3-thiazolidine-5-yl) ethanoates and to evaluate their antimicrobial activity. Inroduction of phthalimidoxy group into heterocyclic ring system generates compounds of biological interest[1-3]. Several compounds such as methyl N-phthalimidoxy-2-methacrylate, ethyl N-phthalimidoxy acetate and 3-N-(4-cyanobenzyl)phthalimidoxide containing phathalimidoxy group have been demonstrated to possess anticonvulsant[4], anticancer[5], antimalarial[6], hypotensive[7], antifungal[8], antiamoebic[9] and human leukocyte inhibitory[10] properties. Isoniazid (INH) on their own exhibit moderate antimicrobial activity[11] but their derivatives are known to possess pharmaceutical values[12,13]. Equipotent antimicrobial activity of some isoniazide derivatives such as 2-ketoindol-3-isonicotinoyl hydrazone and 2-aryl sulphonamido/α-carbamylaryl methylamino-5-(4'-pyridyl)-1,3,4-oxadiazole[14,15] has been reported. Review of literature shows that thiazolidinones are endowed a variety of biological activities[16-19]. Therefore, it was planned to introduce phthalimidoxy group to thiazolidino derivatives of isoniazide at appropriate position under reaction conditions with the object of studying their biological effects.

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MATERIALS AND METHODS

Melting points of synthesized compounds were determined in open capillary tubes are therefore uncorrected. The structures of compounds were established on the basis of elemental analysis and spectral data. The IR spectra were recorded in the range of 4000-450 cm^{-1} using KBr disc on a FTIR RXI Perkin-Elmer spectrophotometer. ^1H NMR and ^{13}C NMR were recorded on a Bruker DRX 300 MHz spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent with TMS as an internal standard. The FAB mass spectra were recorded on a Jeol SX-102/DA-6000 spectrophotometer data system using argon/xenon (6 KV, 10 mA) as FAB gas. Purity of synthesized compounds was checked by silica gel-G plate of 2 mm thickness using benzene and ethyl acetate as developer. N-Hydroxyphthalimide was prepared by the reported[20] method.

4-Arylidenehydrazido pyridine (1a-h):

A mixture of isoniazid (13.7 g, 0.1 mol), corresponding aldehydes (0.1 mol) and glacial acetic acid (4-5 drops) in ethanol (30 ml) was heated under reflux for 4 h. The solid thus separated on cooling was filtered, washed with water, dried and recrystallized from ethanol.

2-Aryl-3-isonicotinamido-4-oxo-1,3-thiazolidine-5-yl

ethanoic acid (2a-h):

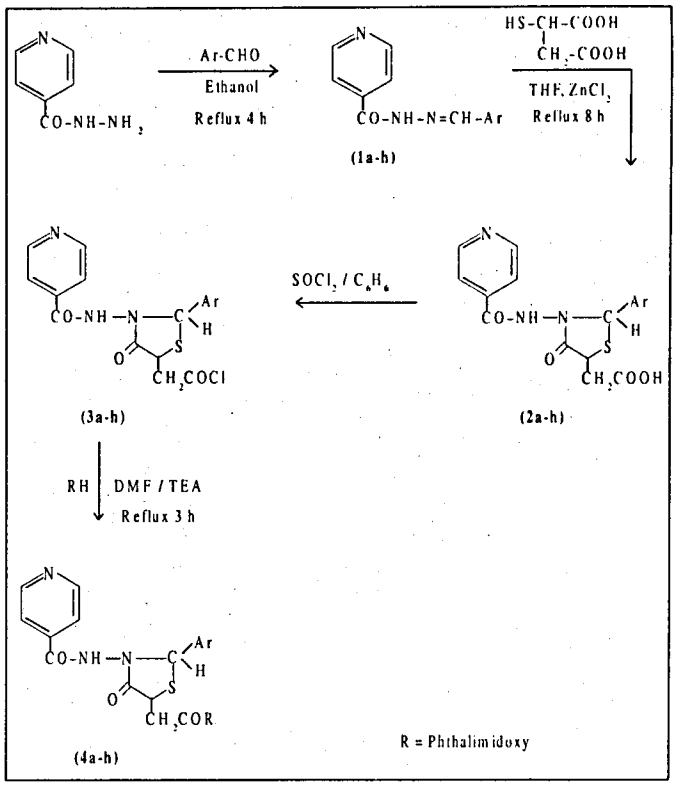
A mixture of (1a, 0.1 mol) and mercaptosuccinic acid in THF containing a pinch of anhydrous $ZnCl_2$ was refluxed on water bath for 8 h. The separated solid was filtered, dried and recrystallized from ethanol. Compounds (2a-h) have been synthesized by similar method using reagents in proper mole ratio.

2-Aryl-3-isonicotinamido-4-oxo-1,3-thiazolidine-5-yl ethanoyl chloride (3a-h):

A solution of (2a, 0.01 mol) in benzene (25 ml) and thionyl chloride (0.02 mol) was refluxed for 60 min on water bath. Excess of thionyl chloride was removed under reduced pressure. On cooling, solid obtained, was filtered, dried and recrystallized from ethanol. Likewise ethanoyl chloride derivatives (3b-h) were also prepared.

Phthalimido(2-aryl-3-isonicotinamido-4-oxo-1,3-thiazolidine-5-yl)ethanoates (4a-h) (Scheme 1):

To a solution of compound (3a, 0.01 mol) in dry DMF (25 ml) N-hydroxyphthalimide (1.63 g, 0.01 mol) and TEA (0.01 mol) was added. The reaction mixture was stirred at room temperature for an hour. It was refluxed for 3 h. It was filtered and solvent was removed under reduced pressure. Thus, solid was obtained, dried and recrystallized from ethanol. Compounds (4b-h) were prepared by the similar process with minor modification in mole ratio of reagents by changing in refluxing time.



Scheme 1: Synthetic scheme for phthalimido (2-aryl-3-isonicotinamido-4-oxo-1,3-thiazolidine-5-yl) ethanoates.

4a: IR (KBr, ν_{max} in cm^{-1}): 3360 (N-H str.), 1705 (C=O, CONH), 1669 (CO-N-CO), 1507 (C=N), 1170 (C-O), 697 (C-S); PMR (DMSO-d_6, δ in ppm): 8.7 (s, 1H, CONH), 8.4 (d, 2H, Ar-H of pyridine ring, near N), 7.6 (m, 4H, Ar-H), 7.0 (d, 2H, Ar-H), 6.9 (d, 2H, Ar-H of pyridine ring), 6.8 (d, 2H, Ar-H, near OCH_3), 3.7 (s, 3H, OCH_3), 3.3 (s, 1H, N-CH), 3.0 (t, 1H, CH-CH_2CO), 2.9 (d, 2H, CH-CH_2CO) ; m/z : 532 $[M]^{+\bullet}$, 504, 425, 204, 190, 162, 146, 132, 121, 106, 104, 78, 76.

4b: IR (KBr, ν_{max} in cm^{-1}): 3355 (N-H str.), 1710 (C=O, CONH), 1670 (CO-N-CO), 1570 (C=N), 1250 (C-O), 754 (C-Cl), 670 (C-S); PMR (DMSO-d_6, δ in ppm): 8.6 (s, 1H, CONH), 8.55 (d, 2H, Ar-H of pyridine ring), 7.5 (m, 4H, Ar-H), 7.49 (d, 2H, Ar-H, near Cl), 6.84 (d, 2H, Ar-H of pyridine ring), 6.8 (d, 2H, Ar-H), 3.5 (s, 1H, N-CH), 3.3 (t, 1H, CH-CH_2CO), 2.85 (d, 2H, CH-CH_2CO); m/z: 536 $[M+2]^{+\bullet}$, 534 $[M]^{+\bullet}$, 425, 204, 190.

4c: IR (KBr, ν_{max} in cm^{-1}): 1717 (C=O, CONH), 1660 (CO-N-CO), 679 (C-S); PMR (DMSO-d_6, δ in ppm): 8.5 (s, 1H, CONH), 8.33 (d, 2H, Ar-H of pyridine ring), 7.2 (m, 4H, Ar-H), 6.8 (d, 2H, Ar-H of pyridine ring), 3.62 (s, 9H, OCH_3), 3.55 (s, 1H, N-CH) 3.43 (t, 1H, CH-CH_2CO); m/z: 592 $[M]^{+\bullet}$, 425, 204, 190, 162.

4d: IR (KBr, ν_{max} in cm^{-1}): 3333 (N-H str.), 1525, 1317 (NO_2), 675 (C-S) ; PMR (DMSO-d_6, δ in ppm): 8.72 (s, 1H, CONH), 8.4 (d, 2H, Ar-H of pyridine ring), 8.2 (d, 2H, Ar-H, near NO_2), 8.1 (m, 4H, Ar-H), 7.6 (d, 2H, Ar-H), 6.95 (d, 2H, Ar-H of pyridine ring), 3.41 (s, 1H, N-CH), 3.5 (t, 1H, CH-CH_2CO), 3.1 (d, 2H, CH-CH_2CO); m/z: 547 $[M]^{+\bullet}$, 425, 204, 190,162.

4f: IR (KBr, ν_{max} in cm^{-1}): 3354 (N-H str.), 1253 (C-N), 670 (C-S); PMR (DMSO-d_6, δ in ppm): 8.6 (s, 1H, CONH), 8.49 (d, 2H, Ar-H of pyridine ring), 7.3 (m, 4H, Ar-H), 6.8 (d, 2H, Ar-H, near $N(CH_3)_2$), 6.7 (d, 2H, Ar-H of pyridine ring), 6.69 (d, 2H, Ar-H), 3.6 (s, 1H, N-CH), 3.0 (d, 2H, CH_2CO); m/z: 545 $[M]^{+\bullet}$, 517, 425, 204, 190, 162.

4g: IR (KBr, n_{max} in cm^{-1}): 3332 (N-H str.), 1675 (CO-N-CO), 1620 (C=N), 1250 (C-N), 682 (C-S); PMR (DMSO-d_6, δ in ppm): 8.62 (s, 1H, CONH), 8.46 (d, 2H, Ar-H of pyridine

ring), 7.6 (m, 9H, Ar-H), 6.92 (d, 2H, Ar-H of pyridine ring), 3.5 (s, 1H, N-CH), 3.39 (d, 2H, CH-CH_2CO); m/z: 502 $[M]^{+1}$, 474, 425, 204, 190, 162, 146, 132, 121.

4h: IR (KBr, ν_{max} in cm^{-1}): 3350 (N-H str.), 3022 (Ar-H), 1712 (C=O, CONH), 1672 (CO-N-CO), 685 (C-S); PMR (DMSO-d_6, δ in ppm): 8.9 (s, 1H, CONH), 8.32 (d, 2H, Ar-H of pyridine ring), 7.8 (d, 1H, Ar-H furyl ring), 7.5 (m, 4H, Ar-H), 7.2 (d, 1H, Ar-H furyl ring), 6.93 (d, 2H, Ar-H of pyridine ring) 6.5 (quarted, 1H, Ar-H of furyl ring), 3.31 (t, 1H, CH-CH_2CO); m/z : 492 $[M]^{+\bullet}$, 425, 204, 190, 162.

Antimicrobial activity:

Antimicrobial activity was assayed by well or cup method[21] in Nutrient agar and Sabouraud dextrose agar. Media was inoculated with 0.2 ml suspension of organisms by spread plate method[19]. With the help of sterile borer, a well was made in the center of the medium and filled with 100 μg/ml concentration of synthesized compounds. The incubation time was 24 h at 37° for bacteria and 74 h at 37° for fungal strains. Antimicrobial activity was measured as a function of diameter of zone inhibition (mm). The experiment was repeated 3 times. The results were compared to ciprofloxacin and gentamicin for antibacterial activity and griseofulvin and fluconazole for antifungal activity by measuring zone of inhibition in mm at 100 μg/ml concentration using disc diffusion method[22].

RESULTS AND DISCUSSION

Isoniazid on reaction with various aldehydes in ethanol produces 4-arylidenehydrazido pyridine (1a-h) in good yield. The structures of compounds (1a-h) have been proved by IR, ^1H NMR and Mass spectral data. The IR absorption due to ν (C=O) str. and n (C=N) str. appeared at 1710-1678 cm^{-1} and 1590-1492 cm^{-1}, respectively. The ^1H NMR spectra of these compounds in DMSO-d_6 exhibited the following signals: (δ in ppm) 9.0-8.7 (s, 1H, CONH) 8.6-8.4 (d, 2H, Ar-H, protons of pyridine ring near N) and 7.13-7.0 (s, 1H, N=CH). The mass spectrum of compound (1a) showed a fairly intense molecular ion peak at m/z 255 $[M]^{+\bullet}$ confirming the molecular formula, $C_{14}H_{13}N_3O_2$ assigned structure for this compound. These arylidene derivatives (1a-h) on cycloaddition with mercaptosuccinic acid furnish 2-aryl-3-isonicotinamido-4-oxo-1,3-thiazolidine-5-yl ethanoic acid (2a-h). The reaction conditions, however were depended upon aromatic substituents in (1a-h). Reflux time for completion of reaction varied between 8-10 h. When DMF was used as solvent, the reaction was very slow. Tetrahydrofuran and benzene gave suitable product formation. The structures of products were elucidated on the basis of physical, chemical and spectral studies. In IR spectrum, the -OH and C=O stretching bands were visible at 3100- 2870 br. and 1750-1710cm^{-1}, respectively, which showed the presence of -COOH group whereas 1675-1670cm^{-1} and 750-710cm^{-1} indicated the presence of cyclic C=O and C-S-C bonds respectively. The structures of (2a-h) also based on ^1H NMR spectrum, which reveals the presence of signals of thiazolidinone -CH proton at δ 3.5-3.3 (t) ppm and -CH_2 protons at δ 3.0-2.8 (d) ppm indicating the formation of compounds (2a-h). When compounds (2a-h) have been refluxed with thionyl chloride in benzene on a water bath for 60 min to give corresponding ethanoyl chloride derivatives (3a-h). Formations of the products were again confirmed by disappearance of the IR band at 3100-2870 br. and appearance of new IR band at 775-760 cm^{-1} due to formation of C-Cl bond. Here the chlorine atoms of -CH_2-CO-Cl are replaced by N-hydroxyphthalimide to furnish final products (4a-h). Spectral evidence such as IR, ^1H NMR, ^{13}C NMR and MS spectra confirmed the structure of products (4a-h). The ^1H NMR signals at δ 8.7-8.5 (singlet), at 7.8-7.3 (multiplet) and 3.3-3.1 (doublet) confirm the presence of -CONH, Ar-H and -CH_2COO groups, respectively. Furthermore stretching of CO-N- CO around at 1680-1620 cm^{-1} confirming the presence of imidoxy moiety in the structures of (4a-h). The absorption bands associated with other functional groups appeared in expected regions. The ^{13}C NMR spectra of compound (4a) also showed the following characteristic signals: (δ in ppm) 161.4, 161.2, 150.1, 149.3 (C=O), 141.4 (2Carbon, near C=O of phthalimido ring), 129.1 (C-CO), 128 (CH, near OCH_3), 126 (2CH of pyridine ring, near N), 124 (2CH of pyridine ring), 122 (2CH of aryl ring), 114 (2CH of aryl ring), 55.4 (CH-Ar), 40.3 (CH_2CO) and 39.8 (CH-CH_2). The structures of (4a-h) were also established from the mass spectra, which gave correct molecular ion peaks. Melting points, yields and elemental analysis of those compounds are given in Table 1.

Using 100 μg/ml concentration in DMF, the synthesized compounds (4a-h) were tested *in vitro* for antibacterial and antifungal activities against *Bacillus subtilis, Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella typhi, Candida albicans* and *Aspegillus fumigatus* (Tables 2 and 3). The results showed that activity depends upon type and position of the substituents. For example compounds (4e) (NO_2 groups at para position) was more active than the compound (4b) (Cl-group at para position). Among phthalimido(2-aryl-3-isonicotinamido-4-oxo-1,3-thiazolidine-5-yl)ethanoates

TABLE 1: PHYSICAL AND ANALYTICAL DATA OF COMPOUNDS SYNTHESIZED COMPOUNDS

Compd.	Ar	Mol. for. / Mol. wt.	mp (°)	Yield (%)	Elem. Analysis Cal./found (%)		
					C	H	N
1a	4-OCH_3. C_6H_4	$C_{14}H_{13}N_3O_2$ / 255	140	85	65.88/65.83	5.09/5.01	16.47/16.43
1b	4-Cl.C_6H_4	$C_{13}H_{10}N_3OCl$ / 259.5	175	82	60.11/60.99	3.85/3.82	16.18/16.15
1c	3,4,5-OCH_3.C_6H_2	$C_{16}H_{17}N_3O_4$ / 315	189	81	60.95/60.93	5.39/5.34	13.33/13.30
1d	3-NO_2.C_6H_4	$C_{13}H_{10}N_4O_3$ / 270	195	77	55.77/57.73	3.70/3.66	20.74/20.71
1e	4-NO_2.C_6H_4	$C_{13}H_{10}N_4O_3$ / 270	177	72	57.77/57.72	3.70/3.66	20.74/20.70
1f	4-$N(CH_3)_2$ C_6H_4	$C_{15}H_{16}N_4O$ / 268	163	63	67.16/67.13	5.97/5.94	20.89/20.83
1g	-C_6H_5	$C_{13}H_{11}N_3O$ / 225	110	70	69.33/69.28	4.88/4.83	18.66/18.61
1h	-C_4H_3O (2-furyl)	$C_{11}H_9N_3O_2$ / 215	157	78	61.39/61.31	4.18/4.13	14.88/14.84
2a	4-OCH_3. C_6H_4	$C_{18}H_{17}N_3O_5S$ / 387	172	78	55.81/55.77	4.39/4.34	10.85/10.75
2b	4-Cl.C_6H_4	C_{17}-H_{14}-N_3O_4SCl / 391.5	193	71	52.10/52.06	3.57/3.50	10.72/10.65
2c	3,4,5-OCH_3.C_6H_2	$C_{20}H_{21}N_3O_7S$ / 447	198	70	53.69/53.63	4.69/4.66	09.39/09.30
2d	3-NO_2.C_6H_4	$C_{14}H_{14}N_4O_6S$ / 402	212	73	50.74/50.70	3.48/3.41	13.93/13.81
2e	4-NO_2.C_6H_4	$C_{14}H_{14}N_4O_6S$ / 402	167	76	50.74/50.70	3.48/3.41	13.93/13.81
2f	4-$N(CH_3)_2$ C_6H_4	$C_{19}H_{20}N_4O_4S$ / 400	133	74	57.00/56.96	5.00/4.99	14.00/13.89
2g	-C_6H_5	$C_{17}H_{15}N_3O_4S$ / 357	187	69	57.14/57.12	4.20/4.17	11.76/11.66
2h	-C_4H_3O (2-furyl)	$C_{15}H_{13}N_3O_5S$ / 347	164	65	51.87/51.81	3.74/3.71	12.10/12.00
3a	4-OCH_3. C_6H_4	C_{18}-H_{16}-N_3O_4SCl / 405.5	159	62	53.26/53.23	3.94/3.91	10.35/10.31
3b	4-Cl.C_6H_4	$C_{17}H_{13}N_3$ O_3SCl_2 / 410	162	60	49.75/49.70	3.17/3.13	10.24/10.21
3c	3,4,5-OCH_3.C_6H_2	$C_{20}H_{20}N_3$ O_6SCl / 465.5	180	66	51.55/51.49	4.29/4.23	09.02/09.00
3d	3-NO_2.C_6H_4	$C_{17}H_{13}N_3$ O_5SCl / 406.5	191	58	50.08/50.16	3.19/3.16	10.33/10.30
3e	4-NO_2.C_6H_4	$C_{17}H_{13}N_3$ O_5SCl / 406.5	158	55	50.18/50.16	3.19/3.16	10.33/10.30
3f	4-$N(CH_3)_2$ C_6H_4	$C_{19}H_{19}N_4$ O_3SCl / 418.5	123	67	54.48/54.43	4.54/4.51	13.38/13.33
3g	-C_6H_5	$C_{17}H_{14}N_3$ O_3SCl / 375.5	177	53	54.32/54.30	3.72/3.69	11.18/11.16
3h	-C_4H_3O (2-furyl)	$C_{15}H_{12}N_3$ O_4SCl / 365.5	155	59	49.24/49.21	3.28/3.21	11.49/11.43
4a	4-OCH_3. C_6H_4	$C_{26}H_{20}N_4O_7S$ / 532	190	73	58.60/58.12	3.75/3.69	10.52/10.48
4b	4-Cl.C_6H_4	$C_{25}H_{17}N_4O_6SCl$ / 536.5	185	68	55.91/55.88	3.16/3.10	10.43/10.35
4c	3,4,5-OCH_3.C_6H_2	$C_{28}H_{24}N_4O_9$ / 592	210	70	56.75/56.66	4.05/4.02	09.45/09.39
4d	3-NO_2.C_6H_4	$C_{25}H_{17}N_5O_8S$ / 547	222	63	54.84/54.80	3.10/3.06	12.79/12.62
4e	4-NO_2.C_6H_4	$C_{25}H_{17}N_5O_8S$ / 547	197	60	54.84/54.80	3.10/3.06	12.79/12.62
4f	4-$N(CH_3)_2$ C_6H_4	$C_{27}H_{23}N_5O_6S$ / 545	176	59	59.44/59.41	4.22/4.20	12.84/12.71
4g	-C_6H_5	$C_{25}H_{18}N_4O_6S$ / 502	243	65	59.76/59.70	3.58/3.53	11.15/11.08
4h	-C_4H_3O (2-furyl)	$C_{23}H_{16}N_4O_7S$ / 492	231	74	56.09/56.00	3.25/3.23	11.38/11.30

(4a-h), compound (4e) was found to be the most active of the compounds studied, with 20 mm zone of inhibition. All the compounds show moderate activity against *B. subtilis*, *E. coli* and *S. typhi* compared to standards, but none showed better or comparable activity to ciprofloxacin and gentamicin. In antifungal activity all the compounds exhibited good activity against *Aspergillus fumigatus* but showed moderate activity against *Candida albicans* as compared to griseofulvin and fluconazole.

It can be concluded from antimicrobial activity that when the thiazolidino derivatives of isoniazide are substituted with phthalimidoxy group the antimicrobial activity is altered to appreciable extent. It is also observed that for antimicrobial activity, the aryl ring in compounds should be substituted with NO_2 group at para position.

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TABLE 2: ANTIBACTERIAL ACTIVITY OF THE SYNTHESIZED COMPOUNDS

Compounds	Dose (µg/ml)	Zone of Inhibition (mm)					
		B. subtilis	*E. coli*	*K. pneumoniae*	*P. vulgaris*	*P. aeruginosa*	*S. typhi*
4a	100	10	13	12.75	9.31	9	13.4
4b	"	12.2	14	13.25	10	9.5	14.31
4c	"	9.3	10	11	8.8	8	11
4d	"	13.1	14.5	16.5	11	9.1	15.25
4e	"	13.5	16	18.5	12	10.5	20
4f	"	9.4	11	16.7	10.5	10.1	16
4g	"	8.1	9.5	14	9.1	8.6	12.5
4h	"	11.0	12.5	10.3	8.3	9.3	11.2
Ciprofloxacin*	"	30	28	20	32	21	39
Gentamicin*	"	28	22	23	25	21	24

*Diameter of disc is 5mm.

TABLE 3: ANTIFUNGAL ACTIVITY OF THE SYNTHESIZED COMPOUNDS

Compounds	Dose (µg/ml)	Zone of Inhibition (mm)	
		C. albicans	*A. fumigatus*
4a	100	16.8	12
4b	"	18	15
4c	"	14.5	11.5
4d	"	18.5	14
4e	"	20	15
4f	"	15.8	11.5
4g	"	14.5	13.7
4h	"	16	13.5
Griseofulvin*	"	24	15
Fluconazole*	"	25	18

*Diameter of disc is 5 mm.

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