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A FACILE SYNTHESIS OF 2-CHLORO-1,8-NAPHTHYRIDINE-3-CARBALDEHYDE; THEIR TRANSFORMATION INTO DIFFERENT FUNCTIONALITIES AND ANTIMICROBIAL ACTIVITY

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ABSTRACT

2-Chloro-1,8-naphthyridines-3-carbaldehyde **(10-18)** has been synthesized by treating various substituted N-(pyridin-2-yl) acetamides **(1-9)** with $POCl_3$ in dimethyl formamide. It proceeds through Vilsmeier-Haack cyclization. The cyclization was facilitated by N-(pyridin-2-yl)acetamides bearing electron donating groups at meta position. The condensation of compound **(10-18)** with hydrazine hydrate and sodium acetate in methanol led to the formation of compound **(19-27)**. The 2-chloro-1,8-naphthyridine-3-carbaldehyde was treated with sodium azide in ethanol underwent cyclization to afford tetrazolo (1,5-a)(1,8) naphthyridine-4-carbaldehyde **(28-36)** via unstable 2-azido compound. The reaction of compound **(10-18)** with sodium sulphide in DMF yielded 2-mercapto-1,8-naphthyridines-3-carbaldehyde **(37-45)**. The synthesized new compounds have been screened for their antimicrobial activity.

Key words: 2-Chloro-1,8-naphthyridines-3-carbaldehyde**,** 1-((2-Chloro-1,8-naphthyridin-3-yl) methylene) hydrazines, Tetrazolo-1,8-naphthyridines-4-carbaldehyde, 2-Mercapto-yl)1,8-naphthyridines-3-carbaldehyde, Antifungal activity.

INTRODUCTION

Several 1,8-naphthyridine derivatives have attracted considerable attention because the 1,8-naphthyridine skeleton is present in many compounds that have been isolated from natural substances, with various biological activities. Nalidixic acid, for example, possesses

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strong antibacterial activity and used mainly for the treatment of urinary tract infections by gram negative pathogens[1]. Gemifloxacin is antimicrobial and antibacterial[2], which have naphthyridine skeleton. It is known that (*E*)- and (*Z*)-*O*-(diethylamino)ethyl oximes of 1,8-naphthyridine series are potential drugs for local anesthesia[3] and 1-(2-fluorobenzyl)-3-(2-tolyl)-1,8-naphthyridin-2(1*H*)-one is used for the treatment of memory disorders, particularly in Alzheimer disease[4].

2-Amino-*N*-hydroxy-1,8-naphthyridine-3-carboxamidine possesses herbicidal properties and used for the selective control of weeds in barley, wheat, maize, sorghum and rice crops[5]. 1,8-Naphthyridine derivatives also react with adenosine receptors of subtypes A1 and A2A[6]. The important biological properties just described stimulated studies on the synthesis of various functionalized (particularly, at positions 2, 4 and 7) 1,8-naphthyridines, with the goal of designing new drugs for oral administration. Indeed, some 3-phenyl-1,8-naphthyridines containing piperidyl, piperazinyl or morpholinyl groups or an *N*-diethanolamine side-chain in the 2,7- positions have been reported to show significant activity as inhibitors of human platelets aggregation induced by arachidonate and collagen[7]. In addition, 4-(*N*-methylenecycloalkylamino)-1,8-naphthyridine derivatives substitution in positions 2 and 7 are effective as antihypertensive agents[8]. 7-Amino-2-(4-carbethoxypiperazin-1-yl)-4-phenyl-1,8-naphthyridine has recently been synthesized and reported to have marked activity against *mycobacterium tuberculosis*[9].

A few derivatives of 1,8-naphthyridine were synthesized earlier in this laboratory were found effective as antibacterial agents[10-12]. A survey of the literature shows that the major synthetic approaches that are used to prepare various types of 1,8-naphthyridine system involve condensation of 2-aminopyridine derivatives with carbonyl compounds containing an activated methylene group[13-19] or with β-ketoesters[20]. Another general procedure for the preparation of 1,8-naphthyridine is condensation of ethanolic 2-amino-3-formylpyridines, in the presence of piperidine base, with active methylene compounds, aldehydes, acyclic and cyclic ketones or diketones[21-27]. The Vilsmeier-Haack reagent has been proved to be a versatile reagent capable of executing a large variety of synthetic transformations[28]. It finds application in formylation[29], cyclohaloaddition[30], cyclisation[31] and ring annulation[32]. Recently, its potentiality was explored in the synthesis of 4-(N,N-dimethylaminomethylene)-2-alkyl/aryl-2-oxazolin-5-ones[33] from N-acy1 derivatives of α-amino acid esters and α-aminoacetanilides. To develop novel quinolines based fused heterocyclic systems as potential anticancer agents[34], a quinoline nucleus with different substituents at 2-and 3-positions was required, which afforded a versatile synthon for further heteroannulations[35]. In this communication, we report the synthesis of 2-chloro-3-formyl-

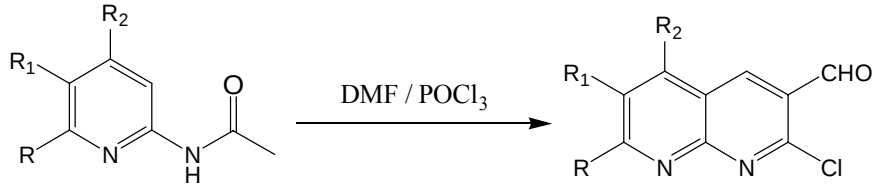
1,8-naphthyridines from N-(pyridin-2-yl)acetamides and their transformation into different functionalities.

EXPERIMENTAL

Chemicals and solvents were reagent grade and used without further purification. Melting points were determined on a capillary melting point apparatus and are uncorrected. The ^{1}H NMR were recorded in the indicated solvent on a Varian 500 MHz and 200 MHz spectrometer with TMS as internal standard. All chemical shifts (δ) are reported in ppm from internal TMS. Mass spectra were measured on a Jeol JMS D-300 spectrometer. Infrared spectra were recorded in KBr on Brucher-IFS-66 FTIR spectrophotometer. The homogeneity of the compounds was checked using precoated TLC plates (E. Merck Kieselger 60 F_{254}).

General procedure for the preparation of 2-chloro-1,8-naphthyridines-3-carbaldehyde (10-18)

To a solution of 5 µ moles of N-(pyridin-2-yl) acetamides **(1-9)** in 15 µL dry DMF, 60 µ moles of $POCl_3$ was added drop wise at 0-5^{0}C. The reaction mixture was refluxed for about 4-15 hrs with stirring. The reaction mixture was poured into crushed ice and the precipitated solid was filtered and washed with excess of water and recrystallised from ethyl alcohol (**10-18) (Scheme 1).** The chemical and spectral data of the compounds **(10-18)** are given in Tables 1, 2 and 3.



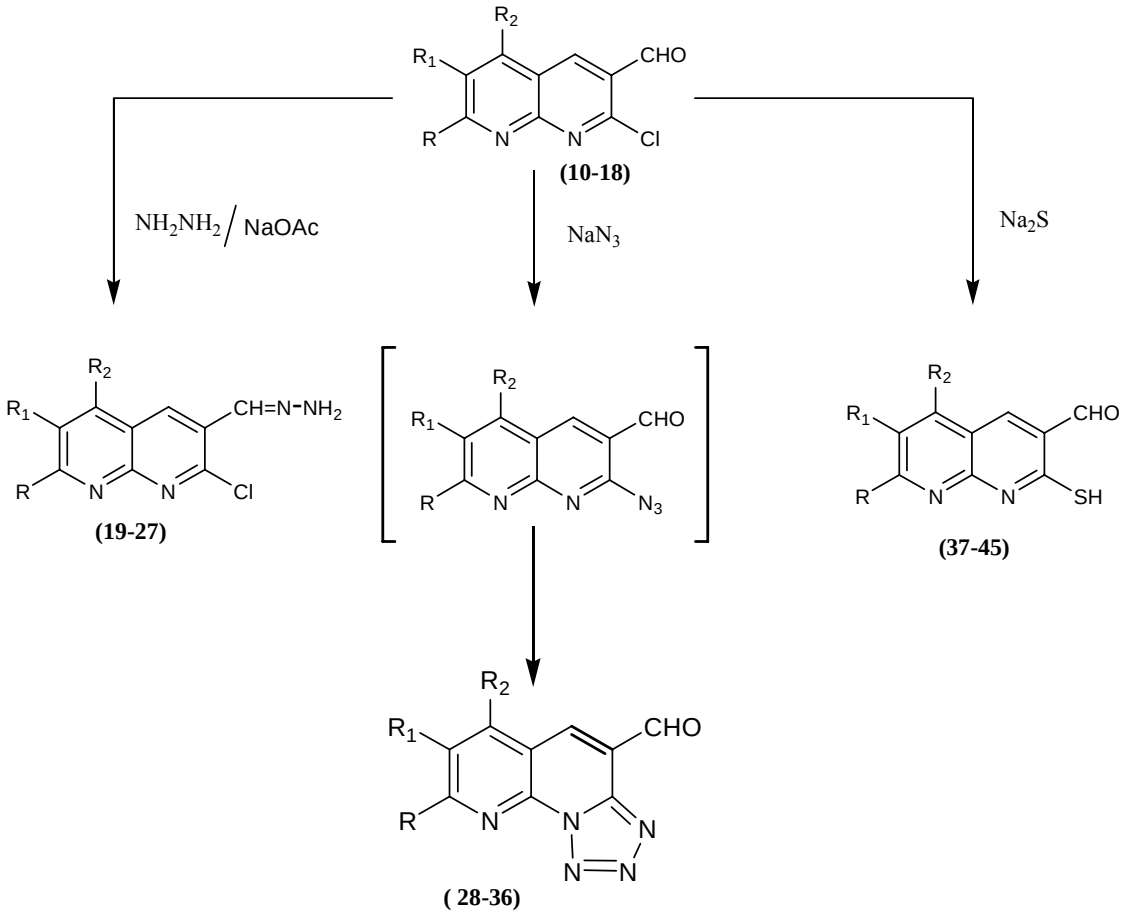
(1-9) **(10-18)**

(1) R = R_1 = R_2 = H
(2) R = NH_2, R_1 = R_2 = H
(3) R = Cl, R_1 = R_2 = H
(4) R = CH_3, R_1 = R_2 = H
(5) R = H, R_1 = CH_3, R_2 = H
(6) R = H, R_1 = Cl, R_2 = H
(7) R = H, R_1 = Br, R_2 = H
(8) R = R_1 = H, R_2 = CH_3
(9) R = Br, R_1 = R_2 = H

Scheme 1: Synthesis of 2-chloro-(1,8) naphthyridine-3-carbaldehyde and their derivatives (10-18)

General procedure for the preparation of 1-((2-chloro-1,8-naphthyridin-3-yl)-methylene) hydrazines (19-27)

A mixture of 1 μ moles of 2-chloro-1,8-naphthyridine-3-carbaldehyde in 10 μL methanol, 1.2 μ moles of hydrazine hydrate and 1.2 μ moles sodium acetate was stirred at room temperature for 30 min. The reaction mixture was diluted with ice cold water.The solid thus obtained was filtered and recrystallised from ethyl alcohol (**19-27) (Scheme 2**).The chemical and spectral data of the compounds **(19-27)** are given in Tables 1,2 and 3.



Scheme 2: Synthesis from 2-chloro-(1,8) naphthyridine-3-carbaldehyde and their various transformations into different functionalities (19-45)

Table 1: Chemical data of compounds (19-45)

Comp.	R	R_1	R_2	M. Formula	m.p. (^oC)	Yield (%)
19	H	H	H	$C_9H_7ClN_4$	220	66
20	NH_2	H	H	$C_9H_8ClN_5$	224	64
21	Cl	H	H	$C_9H_6Cl_2N_4$	220	70
22	CH_3	H	H	$C_{10}H_9ClN_4$	216	72
23	H	CH_3	H	$C_{10}H_9ClN_4$	222	69
24	H	Cl	H	$C_9H_6Cl_2N_4$	226	68
25	H	Br	H	$C_9H_6ClBrN_4$	221	72
26	H	H	CH_3	$C_{10}H_9ClN_4$	220	70
27	Br	H	H	$C_9H_6ClBrN_4$	222	75
28	H	H	H	$C_9H_5N_5O$	223	69
29	NH_2	H	H	$C_9H_6N_6O$	217	65
30	Cl	H	H	$C_9H_4ClN_5O$	221	82
31	CH_3	H	H	$C_{10}H_7N_5O$	226	78
32	H	CH_3	H	$C_{10}H_7N_5O$	223	70
33	H	Cl	H	$C_9H_4ClN_5O$	224	68
34	H	Br	H	$C_9H_4BrN_5O$	221	65
35	H	H	CH_3	$C_{10}H_7N_5O$	220	76
36	Br	H	H	C_9H_4 Br N_5O	224	65
37	H	H	H	$C_9H_6N_2OS$	221	66
38	NH_2	H	H	$C_9H_7N_3OS$	227	62
39	Cl	H	H	C_9H_5Cl N_2OS	226	66
40	CH_3	H	H	$C_{10}H_8N_2OS$	228	63
41	H	CH_3	H	$C_{10}H_8N_2OS$	221	65

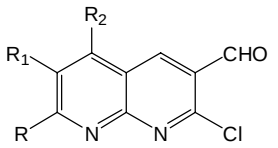
Cont...

Comp.	R	R_1	R_2	M. Formula	m.p. (^oC)	Yield (%)
42	H	Cl	H	$C_9H_5ClN_2OS$	227	68
43	H	Br	H	$C_9H_5BrN_2OS$	218	62
44	H	H	CH_3	$C_{10}H_8N_2OS$	216	69
45	Br	H	H	$C_9H_5BrN_2OS$	219	62

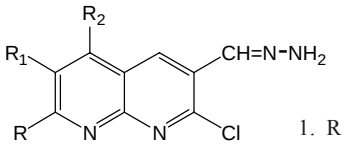
Elemental analyses for C, H, N are within ± 0.4% of the theoretical values.

*Solvent for crystallization: Ethyl alcohol for **19-45**

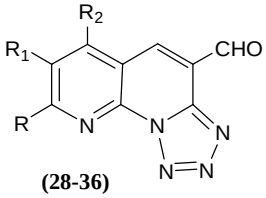
Table 2: ^{1}H NMR spectral data of the compounds (10-45)



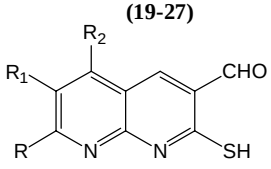
(10-18)



(19-27)



(28-36)



(37-45)

1. R = R_1 = R_2 = H
2. R = NH_2, R_1 = R_2 = H
3. R = Cl, R_1 = R_2 = H
4. R = CH_3, R_1 = R_2 = H
5. R = H, R_1 = CH_3, R_2 = H
6. R = H, R_1 = Cl, R_2 = H
7. R = H, R_1 = Br, R_2 = H
8. R = R_1 = H, R_2 = CH_3
9. R = Br, R_1 = R_2 = H

Compd.	^{1}H NMR (DMSO-d_6, ppm)
10	7.23 (1H,d,C-6-H), 7.41 (1H, t, C-5-H), 7.82 (1H ,d, C-4-H), 8.41 (1H, m,C-7-H), 9.13 (1H,s,-CHO)
11	6.0 (2H, brs,-NH_2), 7.12 (1H, d, C-6-H), 7.82 (1H, d, C-5-H), 8.32 (1H, s, C-4-H), 9.12 (1H, s,-CHO)
12	6.0 (2H, d,C-6-H), 8.21 (1H, d, C-5-H), 8.41 (1H, d, C-4-H), 9.15 (1H, s,-CHO)
13	2.47 (3H ,s,-CH_3), 7.23 (1H, d, C-6-H), 8.20 (1H, d, C-5-H), 8.45 (1H ,s, C-4-H) 9.10 (1H,s,-CHO)
14	2.35 (3H, s,-CH_3), 8.20 (1H, d,C-5-H), 8.44 (1H ,s,C-4-H), 8.89 (1H ,s,C-7-H) 9.11 (1H, s,-CHO)

Cont...

Compd.	^{1}H NMR (DMSO-d_6, ppm)
15	8.21 (1H, d, C-5-H), 8.42 (1H, d, C-4-H), 8.87 (1H, d, C-7-H), 9.20 (1H, s,-CHO)
16	8.27 (1H ,d, C-5-H), 8.51 (1H ,s, C-4-H), 8.93 (1H, d, C-7-H), 9.18 (1H, s,-CHO)
17	2.34 (3H ,s,-CH_3), 8.19 (1H, d, C-6-H)), 8.45 (1H, s, C-4-H)), 8.90 (1H, d, C-7-H), 9.12 (1H,s,-CHO)
18	8.20 (1H ,d, C-6-H), 8.31(1H ,d, C-5-H), 8.63 (1H ,s, C-4-H), 9.19 (1H ,s,-CHO)
19	3.25(2H ,brs,-NH_2) 7.41(1H, t,C-6-H), 7.81(1H, d, C-5-H), 8.12(1H, s,-CH), 8.63(1H, d, C-4-H), 8.91 (1H, m, C-7-H)
20	5.63(4H,brs,-2 NH_2), 7.13(1H,d, C-6-H), 7.83(1H,s,-CH), 8.52(1H,d,C-5-H), 8.89(1H,s, C-4-H)
21	3.42(2H,brs,-NH_2), 7.61 (1H,d, C-6-H), 8.12(1H,s,-CH), 8.44 (1H, d, C-5-H), 8.87(1H, d, C-4-H)
22	2.46 (3H,s,-CH_3), 3.18 (2H,brs,-NH_2), 7.47 (1H,d, C-6-H), 7.92 (1H, s,-CH), 8.23 (1H,d, C-5-H), 8.63 (1H,s, C-4-H)
23	2.35 (3H,s,-CH_3), 3.31(2H,brs,-NH_2), 7.98(1H,s,-CH), 8.21(1H,d, C-5-H), 8.44 (1H,s, C-4-H), 8.91 (1H,d, C-7-H)
24	3.21 (2H,brs,-NH_2), 8.04 (1H,s,-CH), 8.29 (1H,d, C-5-H), 8.42 (1H,d, C-4-H), 8.72 (1H,d, C-7-H)
25	3.52(2H,brs,-NH_2), 8.01(1H,s,-CH), 8.25(1H,d, C-5-H), 8.45 (1H,s, C-4-H), 8.92 (1H,d, C-7-H)
26	2.38 (3H,s,-CH_3), 3.25 (2H,brs,-NH_2), 8.01 (1H,s,-CH), 8.22 (1H,d, C-6-H), 8.45 (1H,s, C-4-H), 8.89 (1H,d, C-7-H)
27	3.26 (2H,brs, -NH_2), 8.02 (1H,s,-CH), 8.28 (1H,d, C-6-H), 8.56 (1H,d, C-5-H), 8.94 (1H ,s, C-4-H)
28	7.32 (1H,t, C-6-H), 7.61 (1H,d, C-5-H), 7.88 (1H,d, C-4-H), 8.26 (1H,d, C-7-H), 9.04 (1H,s,-CHO)
29	5.56 (2H,brs,-NH_2), 7.21 (1H,d, C-6-H), 7.83 (1H,d, C-5-H), 8.28 (1H,s, C-4-H), 9.04 (1H,s,-CHO)
30	7.65 (1H,d, C-6-H), 8.22 (1H,d, C-5-H), 8.44 (1H,d, C-4-H), 9.08 (1H,s,-CHO)

Cont...

Compd.	^{1}H NMR (DMSO-d_6, ppm)
31	2.45 (3H,s,-CH_3), 7.27 (1H,d, C-6-H), 8.19 (1H,d, C-5-H), 8.40 (1H,s, C-4-H), 9.02 (1H,s,-CHO)
32	2.35 (3H,s,-CH_3), 8.18 (1H,d, C-5-H), 8.42 (1H,s, C-4-H), 8.80 (1H,d, C-7-H), 9.10 (1H,s,-CHO)
33	8.26(1H,d,C-5-H), 8.50(1H,d,C-4-H), 8.82(1H,d, C-7-H), 9.05(1H,s,-CHO)
34	8.19(1H,d,C-5-H), 8.44(1H,s, C-4-H), 8.89(1H,d, C-7-H), 9.10 (1H,s,-CHO)
35	2.37 (3H,s,-CH_3), 8.20 (1H,d, C-6-H), 8.41 (1H,s, C-4-H), 8.82 (1H,d, C-7-H), 9.08 (1H,s,-CHO)
36	8.20(1H,d,C-6-H), 8.32(1H,d, C-5-H), 8.58 (1H,s, C-4-H), 9.02 (1H,s,-CHO)
37	7.41 (1H,t, C-6-H), 7.80 (1H,d, C-5-H), 8.21 (1H,d, C-4-H), 8.65 (1H,d, C-7-H), 9.01 (1H,s,-CHO), 9.82 (1H,brs,-SH)
38	5.10 (2H,brs,-NH_2), 7.13 (1H,d, C-6-H), 7.82 (1H,d, C-5-H), 8.30 (1H,s, C-4-H), 9.03 (1H,s,-CHO), 9.90 (1H,brs,-SH)
39	7.67 (1H,d, C-6-H),8.20 (1H,d, C-5-H), 8.44 (1H,d, C-4-H), 9.05 (1H,s,-CHO), 9.82 (1H,brs,-SH)
40	2.44 (3H,s,-CH_3), 7.29 (1H,d, C-6-H), 8.20 (1H,d, C-5-H), 8.46 (1H,s, C-4-H), 9.08 (1H,s,-CHO), 9.80 (1H,brs,-SH)
41	2.35 (3H,s, -CH_3), 8.20 (1H,d, C-5-H), 8.45 (1H,s, C-4-H), 8.90 (1H,d, C-7-H), 9.10 (1H,s,-CHO), 9.82 (1H,brs,-SH)
42	8.20 (1H,d, C-5-H), 8.49 (1H,d, C-4-H), 8.87 (1H,d, C-7-H), 9.08 (1H,s, -CHO), 9.78 (1H,brs,-SH)
43	8.21 (1H,d, C-5-H), 8.44 (1H,s, C-4-H), 8.86 (1H,d, C-7-H), 9.01 (1H,s,-CHO), 9.72 (1H,brs,-SH)
44	2.36 (3H,s,-CH_3), 8.19 (1H,d, C-6-H), 8.45 (1H,s, C-4-H), 8.90 (1H,d, C-7-H), 9.10 (1H,s,-CHO), 9.80 (1H,brs,-SH)
45	8.05 (1H,d, C-6-H), 8.28 (1H,d, C-5-H), 8.64 (1H,s, C-4-H), 9.05 (1H,s,-CHO), 9.81 (1H,brs,-SH)

S, singlet; d, doublet ; dd, doublet of doublets; m, multiplet

Table 3: IR spectral data of the compounds (10-45)

Compd.	IR (KBr, cm^{-1})
10-18	3068 (C-H aromatic); 1721 (C=O); 1590 (C = N)
19-27	3392 (N-H); 3061 (C-H aromatic); 1625 (C = N)
28-36	3099 (C-H aromatic); 1676 (C=O); 1610 (C = N)
37-45	2615 (-SH); 1592 (C=N); 700 (C-S)

General procedure for the preparation of tetrazolo(1,5-a) (1,8)naphthyridine-4-carbaldehydes (28-36)

To a solution of 1 μ moles of 2-chloro-1,8-naphthyridine-3-carbaldehyde in 10 μL ethanol, 1.5 μ moles of sodium azide was added under stirring and then the reaction mixture was refluxed for 30 min. The reaction mixture was diluted with 10 μL of ice cold water and the solid thus obtained was filtered and recrystallised from ethyl alcohol **(28-36) (Scheme 2).** The chemical and spectral data of the compounds **(28-36)** are given in Tables 1, 2 and 3.

General procedure for the preparation 2-mercapto-1,8-naphthyridine-3-carbaldehydes (37-45)

To a solution of 1 μ moles of 2-chloro-3-formyl-1,8-naphthyridine in 5 1 μL dry DMF, 1.51 μ moles of sodium sulphide was added and then the reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was poured into 20 μL of crushed ice and acidified with acetic acid. The solid thus obtained was filtered and recrystallised from ethyl alcohol (**37-45) (Scheme 2)**. The chemical and spectral data of the compounds **(37-45)** are given in Tables 1, 2 and 3.

RESULTS AND DISCUSSION

The compounds synthesized were evaluated for their antifungal activity against *Alternaria alternate, Fusarium oxysporum and Curvularia lunata* employing the glass slide humid chamber technique[36]. Compounds were screened *in vitro* for their antifungal activity using griseofulvin as standard for comparison. Compounds **(12)**, **(24)**, **(30)** and **(42)** showed promising activity against all the three types organisms used. Compounds **(10)**, **(28)** and **(37)**

were active against *Alternaria alternate*. Compounds **(16)**, **(27)**, **(36)** and **(45)** were active against *Fusarium oxysporum*. Compounds **(13)**, **(23)**, **(31)**, **(35)** and **(44)** were active against *Curvularia lunata*. Compounds **(11)**, **(20)** and **(38)** exhibited feeble activity. None of the compounds were found to exhibit significant antibacterial activity against *Bacillus subtilis*, *Streptococcus fecalis* and *Psuedomonas aeruginosa*.

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