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Synthesis, Characterization and Biological Evaluation of Some Novel Theino Pyridine Derivatives

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ABSTRACT

Pyridine and its derivatives have been observed intensively active biodynamically. Which is presented in this work. Pyridine derivatives have also been synthesized with the help of nucleophilic substitution reactions. The constitutions of the synthesized derivatives have been characterized with the help of Elemental analysis, IR, 1H NMR, 13C and MS. All the newly synthesized compounds were screened for antibacterial and antifungal activities (MIC) in vitro by both dilution method with two Gram positive bacteria (S. Aureus MTCC 96 and S. pyogenes MTCC 442), two Gram negative bacteria (E. Coli MTCC 443 and P. aeruginosa MTCC 1688) and fungi A. Niger MTCC 282.

Keywords : Synthesis, Characterization, Biological Evaluation, Pyridine Derivatives

I. INTRODUCTION

Keeping in view of wide spectrum biodynamic activities[1-45] of pyridine and with a view to have therapeutic agents, the synthesis of 5 - (4 - Substituted thiophenoxy - 3- Nitrobenzene - 1 - Sulfonyl) - 4, 5, 6, 7 -Tetrahydrothieno[3, 2 - C] Pyridine (2a-d) have been synthesized by the nucleophilicsubstitution of the chloro atom of 5 - (4 - Choro - 3- Nitrobenzene - 1 - Sulfonyl) - 4, 5, 6, 7 – Tetrahydrothieno [3, 2 - C] Pyridine with different substituted thiophenols.

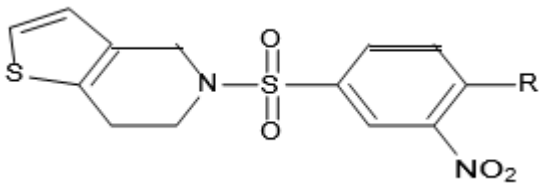

Fig 1 - Substituted thiophenoxy

The constitution of the synthesized products (Fig-1) have been characterized by using elemental analysis, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all compounds has been checked by thin layer chromatography.

Two gram positive bacteria (Staphalococcus Aureus, MTCC 96 and Staphalococcus pyogenus MTCC 442), two gram negative bacteria (E. Coli MTCC 443and P. aeruginosa MTCC 1688) and fungi A. niger MTCC 282 were used in broth dilution method [64] of all the newly prepared compounds 1a-d tested for antimicrobial and antifungal (MIC) in vitro.

Reaction Scheme

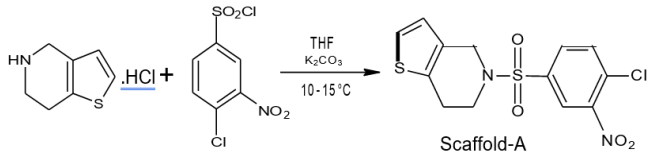

Fig 2

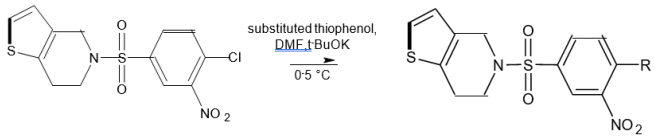

Fig 3

II. EXPERIMENTAL

[A] Synthesis of scaffold-A

A mixture of 4, 5, 6, 7 –Tetra hydro thieno [3, 2 – c] pyridine hydrochloride (1.0 mole) in THF and K2CO3 (3.0 mole) in RBF was added at 25 – 30 ^{0}C for 10 – 15 min on magnetic stirrer. Then 4 – chloro 3 – nitro benzene sulfonyl chloride (1.1 mole) slowly added in reaction mixture with constant stirring for 15 mins at 10-15 ^{0}C and then allowed to warm at room temperature. Reaction mixture was stirred at room temperature for 2 h. After completion of reaction, the reaction mixture was distilled out. Water was added to the obtained residue and then again it stirred for 1 h 30 min. Solid was filtered out, triturated with ethanol and filtered to get pure product. The solid was dried under reduced pressure. Yield; 55.50 %, m.p. 230- 232 ^{0}C.

[B] Synthesis of 5-{ 4- [(3 - methoxyphenyl) sulfanyl] - 3 – nitrobenzene – 1 - sulfonyl}-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine

To the stirred solution of scaffold-A (1 mole) in DMF was added t-BuOK and 3- methoxythiophenol (2.5 mole) at 0 - 5 ^{0}C for 40 mins in ice bath. The reaction mixture was stirred at reflux temperature for 3 hours at room temperature and the solvent was evaporated under reduced pressure. The pH of the mixture was more than 7.0, So dil. HCl was added to reduced pH upto 6.5 and stirred reaction mixture again for 2 hrs. at room temperature. Water was added to the obtained residue and stirred again for 1 hour at room temperature. Solid was filtered out, triturated with ethanol and filtered to get product. The solid was dried under reduced pressure. Yield; 65 % ,m.p.215 ^{0}C .

Elemental analysis of compound 3b.

Calculated amount of ; C (51.93%), H (3.92%), N (6.06%), O (17.29%), S(20.80%). And similarly results found ; C (51.90%), H(3.90%), N (6.04%), O (17.25%), S(20.75%).

Similarly, other compounds (3a-d) were synthesized by above mentioned process (B) from Scaffold - A using different substituted thiophenols. The physical data are recorded in Table- 1.

Physical Properties

Table 1: Physical constants of 5 - (4 - Substituted thiophenoxy - 3- Nitrobenzene - 1 - Sulfonyl) - 4, 5, 6, 7 –Tetrahydrothieno [3, 2 - C] Pyridine.

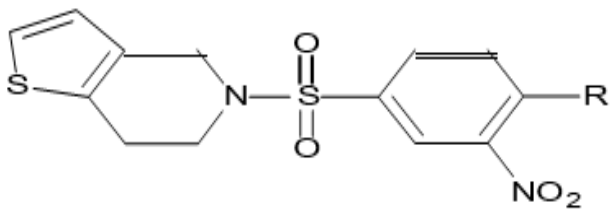

Table. 1 Physical properties of compound 3a-d.

Comp.	Substitution R	Molecular Formula/Weight	M.P.^{0}C	Yeild %	% Composition Calculated/Found		
					C	H	N
3a	2-methoxy thiophenol	C20H18N2S3 O5 462	235	66	51.93 51.90	3.92 3.90	6.06 6.04
3b	3-methoxy thiophenol	C20H18N2S3 O5 462	215	65	51.93 51.90	3.92 3.90	6.06 6.04
3c	4-nitro benzenethiol	C19H15N3S3 O6 450.	225	68	47.79 47.75	3.17 3.15	8.80 8.75
3d	4-methoxy thiophenol	C20H18N2S3O5 462	245	68	51.93 51.90	3.92 3.90	6.06 6.04

Spectral studies

Spectral studies like IR, 1H NMR, 13C NMR, Mass Spectra (MS) and HRMS have been car- ried out for all the Pyridine derivatives.

III. RESULTS AND DISCUSSION

IR Spectral study of 5 - { 4 - [(3 – methoxyphenyl) sulfanyl] – 3 – nitrobenzene – 1 – sulfonyl } - 4, 5 , 6, 7 – tetrahydrothieno [3, 2 - *c*]pyridine (3-b).

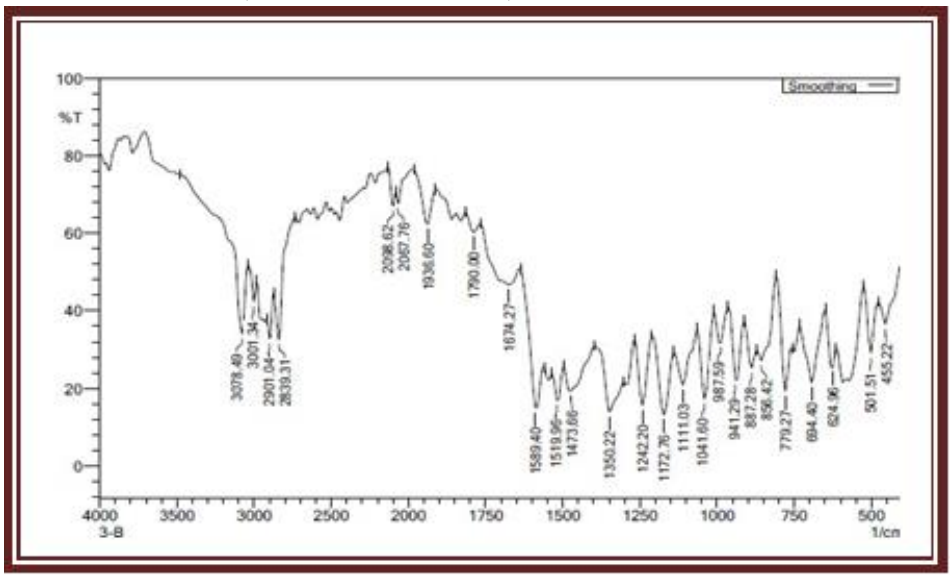

Fig. 4

Table. 2 IR data of compound 3b.

Vibration Mode	**Frequency in cm^{-1}**
C-H Str.	2918 2860
C=C ring skeleton	3080
C=N str. C-N str. NO2 str. NO2 str.	1635 1280 1581 1300
C-O-C Str. C-O-C str.	1230 1051
S=O str. S=O str. N-H str.	1199 1350 3294

^{1}H NMR Spectral study of 5 - { 4 - [(3 – methoxyphenyl) sulfanyl] – 3 – nitrobenzene – 1 – sulfonyl } - 4, 5, 6, 7 – tetrahydrothieno [3, 2 - *c*]pyridine (3-b).

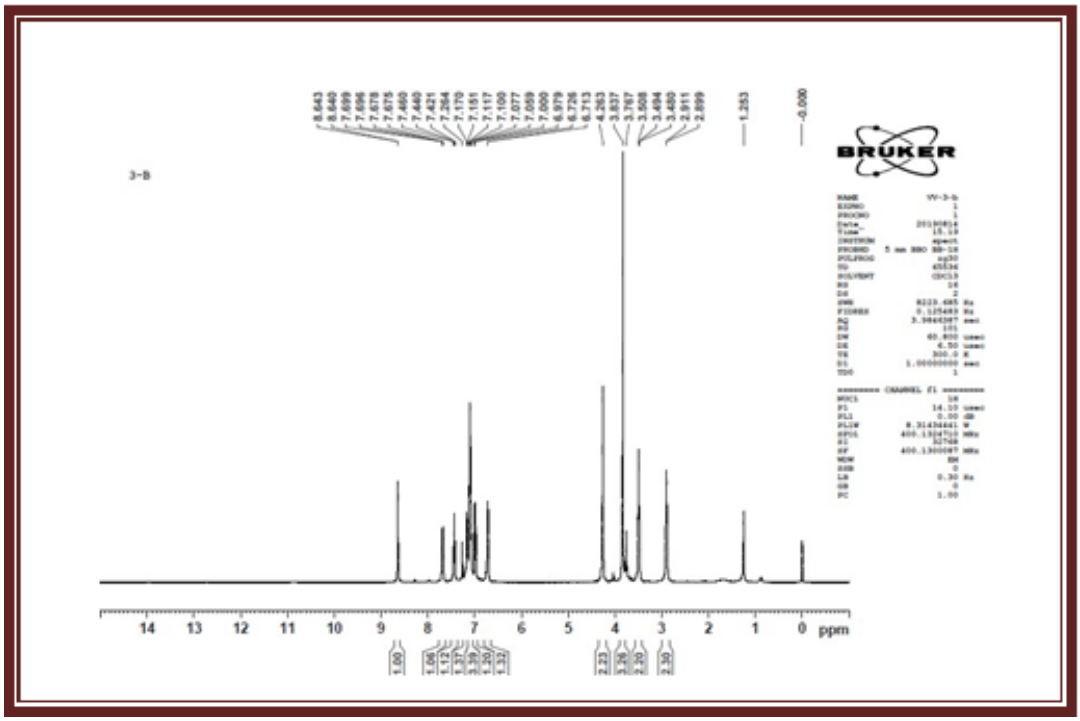

Fig 5

Table. 3 1H NMR interpretation of compound 3b

Sr. No.	Chemical Shift (δ ppm)	No. Of Protons	Multiplicity
1	3.8-3.9	3H	Singlet
2	4.2-4.4	2H	Singlet
3	3.4-3.6	2H	Triplet
4	2.8-3.0	2H	Triplet
5	8.6-8.7	1H	Singlet
6	7.6-7.8	1H	Doublet
7	7.4-7.5	1H	Triplet
8	7.2	1H	Doublet
9	6.7-6.8	1H	Doublet
10	7.0	1H	Doublet
11	7.1	3H	Multiplet

^{13}C NMR Spectral study of 5 - { 4 - [(3 – methoxyphenyl) sulfanyl] – 3 – nitrobenzene – 1 – sulfonyl } - 4, 5, 6, 7 – tetrahydrothieno [3, 2 - *c*]pyridine (3-b).

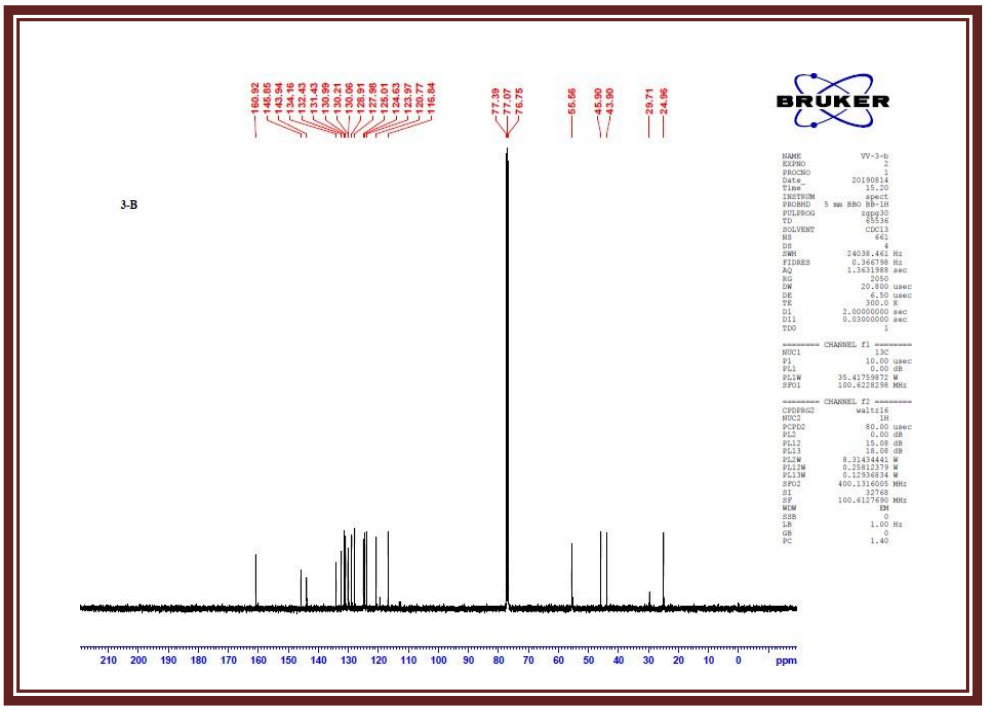

Table. 4 ^{13}C NMR interpretation of compound 3b.

Chemical Shift (δ ppm)	No. Of carbons	Chemical Shift (δ ppm)	No. Of carbons
24.96	1C	127.98	1C
43.90	1C	128.81	1C
45.90	1C	130.21	1C
55.56	1C	130.93	1C
116.84	2C	131.43	1C
120.77	1C	132.43	1C
123.97	1C	134.16	1C
124.16	1C	145.85	1C
124.43	1C	160.82	1C
125.01	1C		

Mass Spectral study of 5 - { 4 - [(3 – methoxy phenyl) sulfanyl]–3– nitrobenzene – 1 – sulfonyl } - 4, 5, 6, 7 – tetrahydrothieno [3, 2 - *c*]pyridine (3-b).

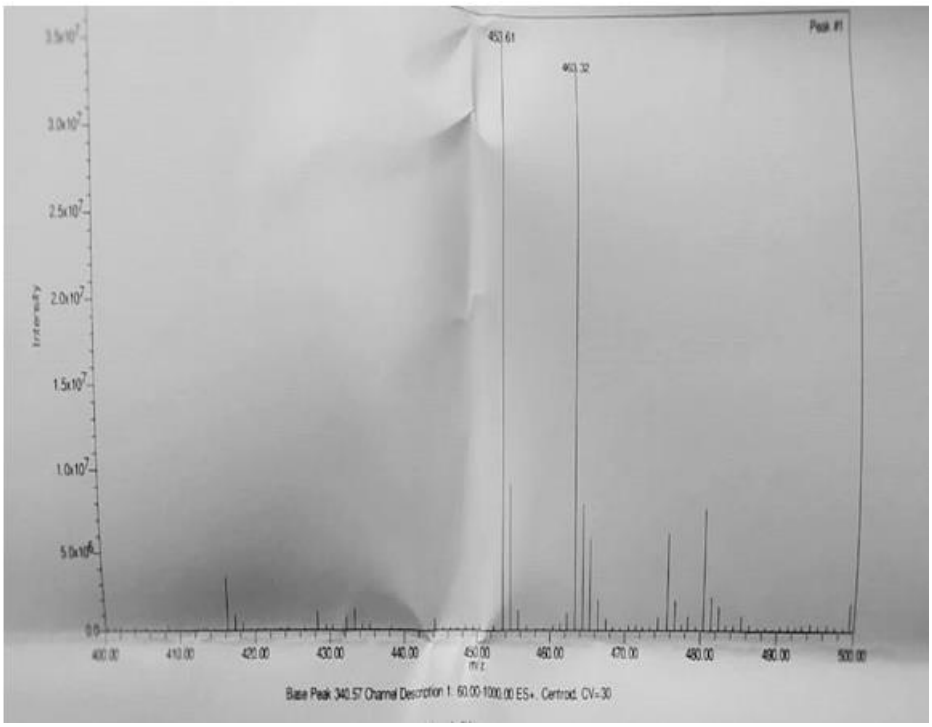

Fig 7

Mass m/z

Molecular ion peak observed at 463.32 [m+1]

Antimicrobial activity

Protocol for Antimicrobial activity

Two gram positive bacteria (Staphalococcus Aureus, MTCC 96 and Staphalococcus pyogenus MTCC 442), two gram negative bacteria (E. Coli MTCC 443and P. aeruginosa MTCC 1688) and fungi A. niger MTCC 282 were used in broth dilution method [64] of all the newly prepared compounds 3a-d tested for antimicrobial and antifungal (MIC) in vitro, taking ampicillin, chloramphenicol, nystatin and griseofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture Collection (MTCC) and Gene Bank, Institute of Microbial Technology, Chandigarh, India. The observed data of synthesized compounds are given in Table 5.

All the glass apparatus used were sterilized before use. The MICs of all the synthesized compounds was carried out by broth dilution method. Mueller Hinton broth was used as nutrient medium to grow and dilute the compound suspension for the test bacteria and Sabouraud Dextrose broth was used for fungal nutrition. Inoculum size for test strain was adjusted to 10^8 CFU [Colony Forming Unit] per milliliter by comparing the turbidity. Dimethyl sulfoxide (DMSO) was used as diluent to get desired concentration of drugs to test on standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic was immediately subcultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 ^oC overnight. The tubes were then incubated overnight. The MIC of the control organism was read to check the accuracy of the drug concentrations. The lowest concentration inhibiting growth of the organism was recorded as the MIC. All the tubes not showing visible growth (in the same manner as control tube described above) was subcultured and incubated overnight at 37 ^oC. The amount of growth from the control tube before incubation (which represents the original inoculum) was compared. Subcultures might show similar number of colonies indicating bacteriostatic; a reduced number of colonies indicating a partial or slow bactericidal activity and no growth if the whole inoculum has been killed. The test must include a second set of the same dilutions inoculated with an organism of known sensitivity. Each synthesized drug was diluted to 2000 µg/ml concentration, as a stock solution. In primary screening 1000, 500 and 250 µg/ml concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. The drugs found active in primary screening were similarly diluted to obtain 200, 125, 100, 62.5, 50 and 25 µg/ml concentrations. The highest dilution showing at least 99% inhibition is taken as MIC. The activities of all the synthesized compounds are recorded in Table 5.

Table 5 : Antimicrobial activity of 5 –[4-(Substituted thiophenoxy - 3- Nitrobenzene - 1 - Sulfonyl) - 4, 5, 6, 7 – Tetrahydrothieno [3, 2 - C] Pyridine.

Comp. No.	Minimal bactericidal concentration (µg/ml)				Minimal fungicidal concentration (µg/ml)
	Gram-negative		Gram-positive		
	E. coli	P. aeruginosa	S. aureus	S. pyogenes	A. niger
3a	75	150	200	125	500
3b	150	100	150	150	1000

3c	200	200	125	250	1000
3d	125	150	100	100	500
Ampicillin	100	--	250	100	--
Chloramphenicol	50	50	50	50	--
Nystatin	--	--	--	--	100
Griseofulvin	--	--	--	--	100

IV. ANTIMICROBIAL EVALUATION

In the series, 3a -d compound 3a having electron donating methoxy group at ortho position of the phenyl ring found almost two fold more potent against E. coli. with respect to ampicillin. Compound 3c found to possess comparative inhibition activity against E.coli. with respect to chloramphenicol. Replacement of methoxy group from ortho position to para position, resulting compound 3d found inhibition activity decrease, however , compound 3d still found equipotent inhibition activity against E. coli. with respect to ampicillin. Replacement of electron donating methoxy group from ortho position to meta position of the phenyl group, compound 3b found less inhibition activity against E. coli. with respect to ampicillin. After introducing electron withdrawing nitro group in the para position of the phenyl ring in compound 3c found possess less inhibition activity against E. coli. with respect to ampicillin.

For P. aeruginosa, compound 3a, 3b and 3d having electron donating methoxy group on the phenyl ring at ortho, meta and para position respectively found to possess equipotent inhibition activity against p. aeruginosa, however, found two fold less potent compare to chloramphenicol. Replacement of electron donating methoxy group from meta position to ortho position or para position of the phenyl ring, found decrease the activity against p. aeruginosa with respect to chloramphenicol. After introducing electron withdrawing nitro group in the para position of the phenyl ring in compound 3c, found to possess two fold less potent than compound 3b against p. aeruginosa with respect to chloramphenicol.

For S. aureus, compound 3a found more potent than ampicillin, still four fold less potent compare to chloramphenicol. After replacing the position of electron donating methoxy group from ortho position to meta position and para position in the phenyl ring, the inhibition activity increase against s. aureus with respect to ampicillin, however, still found two fold less potent compare to chloramphenicol. Electron donating methoxy group at the para position in the phenyl is much potent than position of the methoxy group at meta position or ortho position in the phenyl ring against p. aureus with respect to ampicillin, however, found still two fold less active against s. aureus with respect to chloramphenicol.

For S. pyogenes, electron donating methoxy group congaing compound 3a, 3b and 3c have inhibition activity but less potent against s. pyogenes with respect to ampicillin. Electron donating methoxy group at ortho or para position in the phenyl ring, compound 3a and 3d found equipotent but still less potent against s. pyogenes with respect to ampicillin. After replacement of electron donating methoxy group at the meta position, resulting compound 3b found less potent compare to compound 3a and 3d against s. pyogenes with respect to ampicillin. After replacement of electron donating methoxy group by electron withdrawing nitro group at the para position in the phenyl ring, resulting compound 3c found two fold less inhibition activity against s. pyogenes with respect to ampicillin. Electron donating methoxy group at the para position in the phenyl ring, resulting compound 3d found two fold more potent

than electron withdrawing nitro group at the para position in the phenyl ring, resulting compound 3c, however, found still less potent against s. pyogenes with respect to ampicillin. These finding suggested that thiophenol having electron donating substituent in chloro nitro pyridine were better substituent.

For fungi, compound 3a and 3d found to possess fivefold less potent against A. niger with respect to Nystatin and griseofulvin. Electron donating methoxy group in the ortho position or para position in the phenyl ring, resulting compound 3a and 3d found equipotent, however, found still five fold less potent against A. niger with respect to nystatin and griseofulvin. Replacement of electron donating methoxy group by electron withdrawing nitro group, resulting compound 3c diminished the inhibitory activity compare to 3a and 3d against A. niger with respect to nystatin and griseofulvin. The observed data on the microbial activity of the synthesized drugs are given in Table 5.

V. ACKNOWLEDGEMENTS

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