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Synthesis of novel naphtho[2,1-*b*]furo[3,2-*b*]pyridine derivatives as potential antimicrobial agents

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The starting materials 2-acyl-3-aminonaphtho[2,1-*b*]furans **4a-b** have been directly synthesized from 2-hydroxy-1-naphthaldehyde oxime by treating with α-haloketone through Thrope-Ziegler reaction. The compounds **4a-b** undergo Friedlander cyclization on treatment with active methylene compounds, and produce title compounds **5a-b, 6a-b** and **7a-b**. Some other routes for the synthesis of various derivatives of this new heterocycle have been investigated. All the newly synthesized compounds are characterized by elemental analysis, spectral studies, and have been evaluated for antimicrobial activity.

Keywords: Naphthofuran, naphthofuropyridine, Thrope-Zielger reaction, Friedlander reaction, antimicrobial activity

The condensed derivatives of pyridines play significant role in bioactive molecules[1,2], especially in the form of furo[2,3-*b*]pyridines which are structurally analogous to indoles and quinolines[3]. The furo[2,3-*b*]pyridine ring system has been claimed as potent herbicide, as integral components of cephalosporine and backbone of alkaloids isolated from plants belonging to Rutaceae family[4-7]. The furopyridine-derivative, cicletanine, is an antihypertensive drug with a vasorelaxant effect and diutetic property[8,9]. In addition, the furopyridine moiety has emerged as a useful pharmacophore in several therapeutic areas including treatment of skin disease and relief of intraoccular pressure[10,11].

Pyridyl compounds have received interest of organic chemists in recent years owing to their wide spectrum of physiological activity[12-17]. It is reported in the literature that when pyridine ring is coupled with coumarines, the biological activity gets enhanced many fold[18,19]. Recently, derivatives of naphtho[2,1-*b*]furan synthesized in this laboratory have been found to exhibit a wide range of pharmacological and biological activity[20-26]. Encouraged by these interesting biological properties associated pyridine ring and naphthofuran nucleus, condensed heterocycles comprising naphthofuran and pyridine ring systems were synthesized and investigated for antimicrobial activity.

The synthesis of 2-acyl-3-aminonaphtho[2,1-*b*]furan **4a-b** from 2-hydroxy-1-naphthonitrile **3** has already been reported from this laboratory[20]. It involved two steps *viz*., conversion of 2-hydroxy-1-naphthaldehyde **1** into its oxime **2** followed by dehydration using acetic anhydride, to obtain 2-hydroxy-1-naphthonitrile **3**. The compound **3** on reaction with haloketone in presence of K_2CO_3 produced **4a-b**. Herein is reported a one-step conversion of oxime **2** directly into 2-acyl-3-amino[2,3-*b*]furan **4a-b** without isolation of intermediate nitrile **3**. Dehydration, condensation and Thrope-Ziegler cyclization occurred in a single step and the compounds were obtained in good yield. The compounds **4a-c** synthesized by this method were identical with the authentic samples, produced by an alternate method[20,27] as indicated by superimposable IR, and ^{1}H NMR spectra and determination of mixed melting point.

The synthesis of naphtho[2,1-*b*]furo[3,2-*b*]pyridine derivatives was accomplished by Friedlander reaction, which involves reaction of *ortho* amino ketones/aldehydes with active methylene compounds. Generally, such types of reactions are carried out in presence of a base or acid catalyst. However, in the present study, more satisfactory results were obtained by carrying out the reaction without using any catalyst.

The compounds **4a,b**, having *ortho*-amino ketonic functionality, were treated with active methylene compounds. Thus, compound **4a** on treatment with diethyl malonate at elevated temperature furnished 3-

carbethoxy-4-methyl-2-oxo-1,2-dihydronaphtho[2,1-*b*] furo[3,2-*b*]pyridine **5a**. The structure of **5a** was confirmed by studying spectral data and comparing the same with that of compound **4a**.

In the IR spectrum of **5a**, absorption band at 1728 cm^{-1} was observed due to ester group, which was obviously absent in **4a** and ring carbonyl group resonated at 1627 cm^{-1}. A broad absorption band at 3095 cm^{-1} indicated the existence of **5a** in enolic form. Similarly ^1H NMR spectrum of **5a** exhibited triplet at δ 1.5 due to $–CH_3$ protons of ester group and singlet at δ 2.9 due to protons of $–CH_3$ group attached to pyridine nucleus and quartet at δ 4.45 due to of $–CH_2$ protons of ester group. Aromatic protons showed multiplet at δ 7.5–8.1 whereas –NH and -OH protons appeared as singlet at δ 9.21 and 9.29, which were exchangeable with D_2O.

To provide further evidence for the proposed structure, ^{13}C NMR was recorded, which showed peaks at δ 13.21 and 61.74 due to ester carbon atoms, which were not present in its starting material. Ester carbonyl carbon and ring carbonyl carbon gave signals at δ 169.67 and 163.21 respectively, whereas methyl carbon attached to pyridine ring showed a signal at δ 29.71. The proposed structure was substantiated by its mass spectra, which exhibited molecular ion peak at *m/z* 321 corresponding to its molecular weight and other peaks appearing at *m/z* 276, 247, 220, 181, and 154 were inconsistent with its structure. The compound **5a** on alkali hydrolysis produced carboxylic acid **8a**, which on decarboxylation gave **9a**. The structure of **8a** was evident by the absence of triplet and quartet due to ester group and loss of CO_2 molecule, as indicates in its mass spectra of **9a**, supported decarboxylation.

Similarly reaction of **4b** with diethyl malonate yielded 3-carbethoxy-4-phenyl-2-oxo-1, 2-dihydronaphtho[2,1-*b*]furo[3,2-*b*]pyridine **5b**, evidences for the proposed structure were obtained by its spectral data. The compound **5b** underwent hydrolysis to produce carboxylic acid **8b** subsequent decarboxylation of which gave **9b** (**Scheme I**).

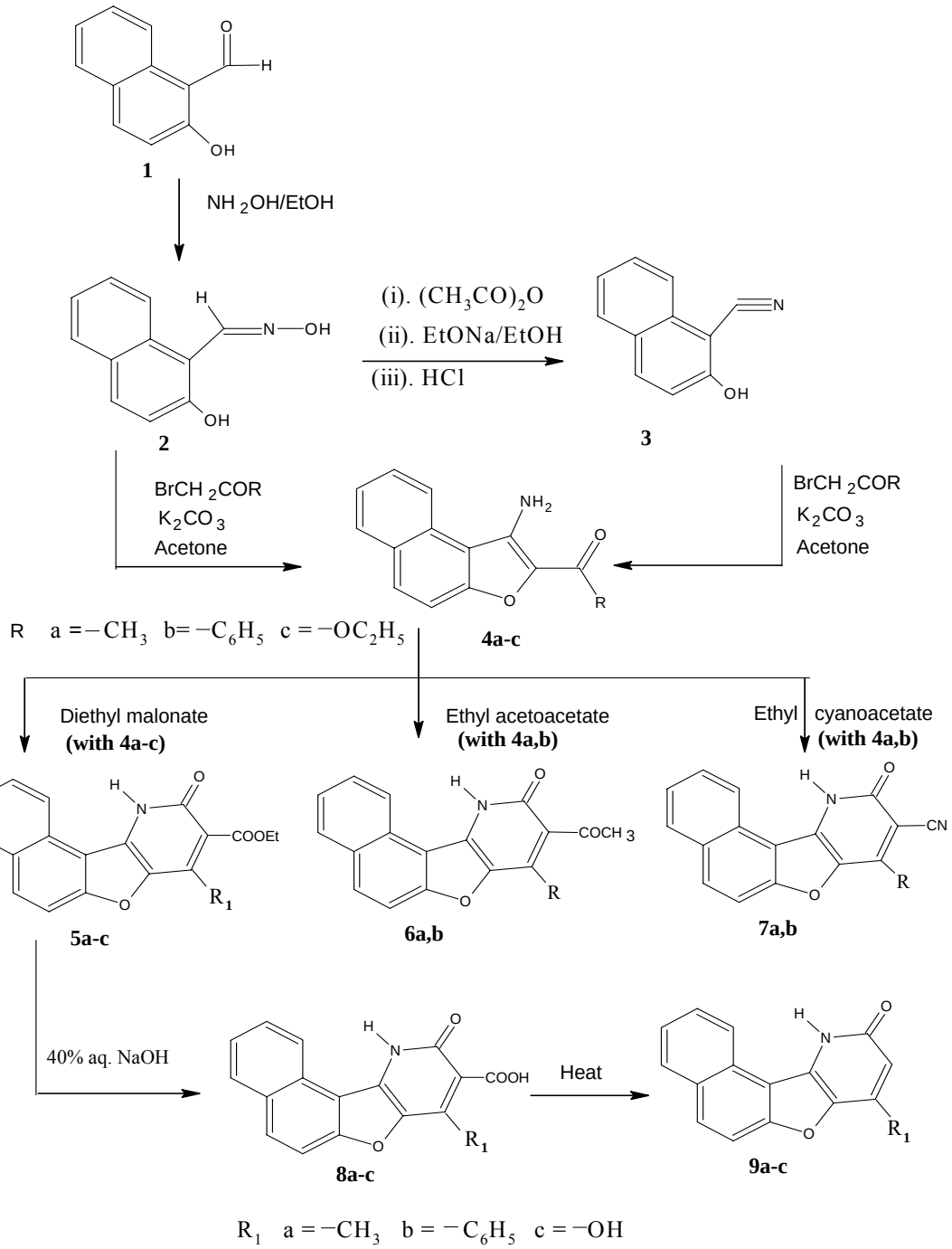
The compounds **4a**,**b** underwent similar Friedlanders reaction on reaction with ethyl acetoacetate to furnish 3-acetyl-4-methyl -2-oxo-1,2-dihydronaphtho[2,1-*b*]furo [3,2-*b*]pyridine **6a** and 3-acetyl-4-phenyl-2-oxo-1,2-dihydronaphtho[2,1-*b*]furo-[3,2-*b*] pyridine **6b** respectively. Evidence for formation of pyridine ring was obtained by IR, ^1H and ^{13}C NMR, and mass spectra of **6a** and **6b**. The ^{13}C NMR spectrum of **6a** showed two signals at δ 25.80 and 29.60 due to methyl carbon of acetyl group and methyl carbon atom attached to pyridine ring. The reaction of **4a**,**b** with ethyl cyanoacetate gave 3-cyano-4-methyl-2-oxo-1,2-dihydronaphtho[2,1-*b*]furo[3,2-*b*]pyridine **7a** and 3-cyano-4-phenyl-2-oxo-1,2-dihydronaphtho[2,1-*b*]furo[3,2-*b*]pyridine **7b**. Appearance of absorption band around 2214 cm^{-1} in their IR spectra proved the structure. In addition other spectral data supported the assigned structure.

Another route for the construction of pyridine nucleus on naphthofuran moiety involved ethyl-3-aminonaphtho[2,1-*b*]furan-2-carboxylate **4c**, synthesis of which has been reported from this laboratory, as starting material. The desired condensation was accomplished by reacting **4c** with diethyl malonate in the presence of sodium ethoxide, the product isolated was identified as 3-carbethoxy-2,4-dioxo-1,2,3,4-tetrahydronaphtho[2,1-*b*]furo[3,2-*b*]pyridine **5c** on the basis of spectral data. The compound **5c** on treatment with alkali followed by acidification underwent simultaneous hydrolysis and decarboxylation to yield **9c** in moderate yield. The physical data of all the newly synthesized compounds is presented in **Table I**.

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. IR spectra (in cm^{-1}) were recorded in KBr on a Perkin-Elmer 157 infrared spectrometer, ^1H NMR on AMX 400 using $CDCl_3$/DMSO-d_6 solvent, TMS as internal standard, and mass spectra on a MF- linear mass spectrometer operating at 70 eV. Compounds were checked for their homogeneity by TLC on silica gel G plates using chloroform and methanol (v/v) of varying polarities and spots were visualized by iodine vapour.

2-Acetyl-3-aminonaphtho[2,1-*b*]furan, **4a**: To a solution of 2-hydroxy-1-naphthaldehyde oxime **2** (1.87 g, 0.01 mole) in dry acetone (50 mL), bromoacetone (1.4 g, 0.01 mole) and anhydrous potassium carbonate (13.8 g, 0.1 mole) were added and reaction mixture was refluxed on a water bath for 8 hr. The potassium salt was filtered off and washed thoroughly with acetone. Removal of the solvent from the filtrate and subsequent trituration with ethanol gave 2-acetyl-3-aminonaphtho[2,1-*b*]furan as a light brown coloured solid, which was purified by column chromatography over 60-120 mesh silica gel and 5% methanol in chloroform as eluting solvent. Mixed melting point with the sample synthesized by an alternative method[20] was not depressed.



Scheme I

3-Amino-2-benzoylnaphtho[2,1-*b*]furan, **4b**: The reaction was carried out as under **4a** using phenacyl bromide in place of bromoacetone. The reaction mixture was refluxed on a water-bath for 12 hr. Working up the reaction-mixture and purification as described above gave the product **4b**. Mixed melting point with the known sample was not depressed.

Ethyl 3-aminonaphtho[2,1-*b*]furan-2-carboxylate, **4c**: To a solution of 2-hydroxy-1-naphthaldehyde oxime **2** (1.87 g**,** 0.01 mole) in dry DMF (25 mL), ethyl bromoacetate (1.67 g, 0.01 mole) and anhydrous potassium carbonate (13.8 g, 0.1 mole) were added and reaction-mixture was refluxed on a water-bath for 24 hr. The reaction mixture was poured into crushed ice, and kept overnight. The pasty product on

Table I — Physical characterization data of newly synthesized compounds

Compd	R/R_1	Mol. formula	Yield (%)	m.p.°C	Found (Calcd) %		
					C	H	N
4a	CH_3	$C_{14}H_{11}NO_2$	77	170	74.62 (74.66	4.65 4.88	6.15 6.22)
4b	C_6H_5	$C_{19}H_{13}NO_2$	60	155	79.02 (79.44	4.35 4.52	4.75 4.87)
4c	OC_2H_5	$C_{15}H_{13}NO_3$	70	118	70.45 (70.58	5.00 5.09	5.38 5.49)
5a	CH_3	$C_{19}H_{15}NO_4$	70	270	71.00 (71.02	4.58 4.67	4.25 4.36)
5b	C_6H_5	$C_{24}H_{17}NO_4$	76	180	75.03 (75.19	4.22 4.43	3.45 3.65)
5c	OH	$C_{18}H_{13}NO_5$	20	175	66.75 (66.87	4.00 4.02	4.25 4.33)
6a	CH_3	$C_{18}H_{13}NO_3$	85	>250	75.00 (75.19	4.24 4.43	3.25 3.65)
6b	C_6H_5	$C_{23}H_{15}NO_3$	43	>250	78.03 (78.18	4.10 4.24	3.85 3.96)
7a	CH_3	$C_{17}H_{10}N_2O_2$	25	>250	74.21 (74.45	3.55 3.64	10.00 10.21)
7b	C_6H_5	$C_{22}H_{12}N_2O_2$	15	>250	78.25 (78.57	3.25 3.57	8.22 8.33)
8a	CH_3	$C_{17}H_{11}NO_4$	17	>250	69.01 (69.62	3.36 3.75	4.56 4.77)
8b	C_6H_5	$C_{22}H_{13}NO_4$	21	>250	74.21 (74.36	3.45 3.66	3.88 3.94)
8c	OH	$C_{16}H_9NO_5$	15	>250	65.00 (65.08	3.00 3.05	4.68 4.74)
9a	CH_3	$C_{16}H_{11}NO_2$	78	210	77.06 (77.10)	4.28 4.41	5.50 5.62)
9b	C_6H_5	$C_{21}H_{13}NO_2$	73	200	81.00 (81.02	4.08 4.18	4.38 4.50)
9c	OH	$C_{15}H_9NO_3$	20	240	71.50 (71.71	3.50 3.58	5.54 5.57)

trituration with cold and dilute sodium hydroxide gave ethyl 3-aminonaphtho[2,1-*b*]furan-2-carboxylate **4c** as a light brown coloured solid, which was purified by column chromatography over 60-120 mesh silica gel and 10% ethyl acetate in hexane as eluting solvent. Mixed melting point of the compound with the sample obtained by an alternative method[27] was not depressed.

4c: IR (KBr): 1752 (ester carbonyl), 3457 cm^{-1} (NH_2); ^1H NMR ($CDCl_3$): δ 1.6 (t, 3H, $-CH_3$), 4.3 (q, 2H, $-CH_2$), 5.8 (b, 2H, $-NH_2$), 7.2-8.1(m, 6H, Ar-H); MS: *m/z* 255 (M^+).

3-Carbethoxy-4-methyl/phenyl-2-oxo-1,2-dihydronaphtho[2,1-*b*]furo[3,2-*b*]pyridines:

5a,**b**: A mixture of **4a** (2.25 g, 0.01 mole) and diethyl malonate (1.6 g, 0.01mole) was heated at 160-170ºC in an oil-bath for 12 hr, when the product was obtained as a brown sticky solid. The reaction mixture was poured into ice-cold water, solid separated was washed with ethanol and then with water. The product was purified by column chromatography over 60-120 mesh silica gel and methanol as eluting solvent. Similarly the compound **5b** was prepared from **4b**.

5b: IR (KBr): 1625 (C=O of pyridine ring), 1728 (C=O of ester group), 3410 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ 0.70 (t, 3H, $-CH_3$), 4.1. (q, 2H, $-CH_2$), 7.4-8.1 (m, 11H, Ar-H), 9.29 and 9.31 (s, 1H, NH/OH tautomeric).

3-Carbethoxy-2,4-dioxo-1,2,3,4-tetrahydronaphtho[2,1-*b*]furo[3,2-*b*]pyridine, **5c**:

Freshly distilled diethyl malonate (6.4 g, 0.04 mol) was treated with sodium ethoxide solution prepared from sodium (1.3 g) and abs. ethanol (45 mL). Compound **4c** (5.1 g, 0.02 mole) was then added in portions while stirring and the reaction-mixture

heated under reflux for 6 hr, when colourless bulky precipitate of the salt separated out. It was filtered, dissolved in minimum volume of water and the solution acidified with dil. HCl to precipitate the product. **5c**: IR (KBr): 1631 (ester carbonyl), 3370 cm^{-1} (broad, hydrogen bonded).

3-Acetyl-4-methyl/phenyl-2-oxo-1,2-dihydronaphtho[2,1-*b*]furo[3,2-*b*]pyridines, **6a**,**b**: A mixture of **4b** (2.87 g, 0.01 mole) and ethyl acetoacetate (3.1 g, 0.01 mole) was heated at 160-170ºC in an oil-bath for 12 hr, when the product was obtained as a brown sticky solid. The reaction-mixture was poured into ice-cold water, solid separated was washed with ethanol and then with water. The product **6b** was purified by column chromatography over 60-120 mesh silica gel and methanol as eluting solvent. Similarly the compound **6a** was prepared from **4a**.

6a: IR (KBr): 1685 (acetyl group ketone), 1620 cm^{-1} (ring ketone). **6b**: IR (KBr): 1693, 1623 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.5 (s, 3H, -CH_3), 7.5-8.2 (m, 11H, Ar-H), 9.15 and 9.20 (s, 1H, NH/OH tautomeric); MS: *m/z* 354 (M^+).

3-Cyano-4-methyl/phenyl-2-oxo-1,2-dihydronaphtho[2,1-*b*]furo[3,2-b]pyridines, **7a,b**:

A mixture of **4a** (2.25 g, 0.01 mole) and ethyl cyanoacetate (1.13 g, 0.01 mole) was heated at 160-170ºC in an oil-bath for 12 hr, the reaction-mixture was poured into ice-cold water; solid separated was filtered, and washed with rectified spirit. Similarly, the compound **7b** was prepared from **4b**.

7a: IR (KBr): 1641 (C=O), 2214 (C≡N), 3098 cm^{-1} (NH/OH); ^1H NMR ($CDCl_3$): δ 2.5 (s, 3H, -CH_3), 7.4-8.4 (m, 6H, Ar-H), 9.0 and 9.65 (s, 1H NH/OH tautomeric); ^{13}C NMR: δ 163.21 (ring –C=O), 29.71 (-CH_3); MS: *m/z* 274(M^+), 246,181(base peak), 166.**7b**: IR (KBr): 1627 (C=O), 2214 cm^{-1} (C≡N).

4-Methyl/phenyl-2-oxo-1,2-dihydronaphtho[2,1-*b*]furo[3,2-*b*]pyridine-3-carboxylic acids, **8a**,**b**: Compound **5a**,**b** (0.01 mole) was heated under reflux in 40% aq. sodium hydroxide (15 mL) and ethanol (5 mL) for 8 hr. The reaction-mixture on cooling and acidification gave the product. Compound obtained was purified by recrystallization from ethanol.

8a: IR (KBr): 1654, 1635 cm^{-1}. **8b**: IR (KBr): 1664, 1633 cm^{-1}; MS: *m/z* 293 (M^+).

4-Hydroxy-2-oxo-1,2-dihydronaphtho[2,1-*b*]furo-[3,2-*b*]pyridine-3-carboxylic acid, **8c**: Compound **5c** (3.23 g, 0.01 mole) was heated under reflux in 40% aq. sodium hydroxide (15 mL) and ethanol (5 mL) for 8 hr. The reaction-mixture on cooling and acidification gave the product. Compound obtained was purified by recrystallization from absolute ethanol. **8c**: IR (KBr): 1635 cm^{-1}.

4-Methyl/phenyl-2-oxo-1,2-dihydronaphtho[2,1-*b*]furo[3,2-*b*]pyridines, **9a**,**b**: Compounds **8a**,**b** (0.01 mole) were heated just above its melting point till the decomposition subsided. The solid product was washed with sodium bicarbonate and purified by column chromatography using suitable eluting solvent mixtures. **9a**: IR (KBr): 1631 cm^{-1} (C=O). **9b**: IR (KBr): 1630 cm^{-1} (C=O).

2,4-Dioxo-1,2,3,4-tetrahydronaphtho[2,1-*b*]furo-[3,2- *b*]pyridine, **9c**: The compound **8c** (2.95 g, 0.01 mole) was heated under reflux in 40% aq. sodium hydroxide (15 mL) for 8 hr. The resulting solution was cooled and acidified. The product thus obtained **9c** was purified by column chromatography. **9c**: IR (KBr): 1630 cm^{-1}.

Antimicrobial activity

All the newly synthesized compounds were screened for antibacterial activity against both gram-positive, *Staphylococcus aureus*, and gram-negative, *Streptococcus pyrogens*, and antifungal activity against *Candida albicans* and *Aspergillus flavus* according to cup plate method[25] at a concentration of 0.005 mol/mL. Chloramphenicol and Flucanazole were used as standards for antibacterial and antifungal activity respectively. The results are recorded in **Table II**.

Table II — Results of antimicrobial activity of the compounds **4a-c, 5a-c, 6a,b, 7a,b** and **8a-c, 9a-c**

Compd	Zone of Inhibition in mm			
	Antibacterial activity		Antifungal activity	
	S. aureus	*S. pyrogens*	*A. flavus*	*C. albicans*
4a	17	15	17	19
4b	12	17	16	14
4c	14	18	15	13
5a	13	14	11	14
5b	12	11	12	19
5c	13	11	13	12
6a	8	12	9	19
6b	-	-	11	14
7a	14	14	14	14
7b	7	13	10	9
8a	14	9	18	15
8b	8	10	9	-
8c	15	-	16	15
9a	9	6	8	12
9b	14	14	18	11
9c	12	10	15	13
Standard	18	16	20	19
DMSO	+ve	+ ve	+ve	+ve

+ve indicates growth of microbes. DMSO used as control.

The results of antimicrobial activity revealed that compounds **4b**,**c** were found to be more active and **4a** is moderately active against *S. pyrogens.* The compounds **4a, 5b, 6a** were found to be active against *C. albicans.*

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