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Design, synthesis, molecular docking and biological evaluation of some pyridinone bearing scaffold benzofuran as antimicrobial and antioxidant activity

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A series of benzofuran derivatives compounds have been designed and synthesized. Here, Benzofuran linked with pyridinone compounds is reported. The desired compounds were prepared by using 2-nitrosalisaldehydnitrile **(1).** After, this is treated with chloroacetone, which results in the formation of 1-(3-amino-5-nitro-1-benzofuran-2-yl) ethanone (**2**). Later the **3a-b** is produced by a reaction of acetylation and benzylation on compound **2** respectively. The alkylation of compounds **4a-b** react with sodium hydroxide, we get new pyridinone compounds**.** All the synthesized compounds were characterized by IR, ^{1}H NMR, and GCM. Further, these have been screened for their antimicrobial, and antioxidant activity. Along with this activity reference we design drug discovery of Molecular docking study by using different computational software.

1. Introduction

Since long time, we are working on the synthesis of various benzofuran derivatives of biological interest, which have been reported in a wide spectrum of biological and pharmacological activities.[1-2] The benzofuro pyridinone ring is the essential feature of many biologically active compounds, namely *penicillins, cephalosporins, carumonam, aztreonam, thienamycine*, and *the nocardicins*. In recent references to antibacterial activity, antifungal, antitubercular, and antitumor, we have reported cholesterol absorption inhibition and enzyme inhibition activity in compounds containing 2-azetidinone ring systems.[3-4.] Because of their relevance in both clinical and economic fields, various substituted 2-azetidinones represent a very attractive target for contemporary organic synthesis [5-10]. The various benzo [2, 1-*b*] furan derivatives synthesized in this laboratory have been shown to possess a wide spectrum of biological and pharmacological activities[11-16]. There are several pieces of evidence that the nitro group enhances the biological activities of the compounds many folds.[17-18] Thus 5-nitrobenzofuran, 5-nitro-3-aminobenzo [2, 1-*b*] furan and 5-nitro-3-aminobenzo [2, 1-*b*] furan have been synthesized and evaluated for possible antimalarial and mutagenic activities and they also find application in veterinary medicine. Hence, with a view to further assess the pharmacological profile of this class of compounds, it was thought worthwhile to synthesize some new congeners of heterocycles by incorporating the benzo [2, 1-b] furan nucleus bearing nitro group and pyridinone moieties in a single molecular framework[19-20]. The present work deals with the synthesis of the title compounds starting from 2-methyl-8-nitrobenzofuro [3, 2-*b*] pyridin-4 (3*H*)-one, followed by their antifungal and antimicrobial screening[21].

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2. Results and discussion

2.1 Chemistry

The synthesis of the titled compounds is depicted in the Scheme **(Fig 1).** All the intermediate and targeted molecules were confirmed by TLC, IR, NMR and Mass spectral data. 2-Acetyl-3-amino-5-bromo-1- benzofuran **(2)** was synthesized by treating 5-nitro-2-hydroxybenzonitrile **(1)** and chloroacetone in presence of anhydrous potassium carbonate as per the established procedure in this laboratory. 3-Acylaminobenzo [2, 1-b] furan-2-corboxylate **(3a-b)** was prepared by stirring acetyl chloride **(3a)** and benzylchloride **(3b)** respectively in presence of NaOH in 15 ^{0}C cold condition. Compounds 2-methyl-4-oxo-benzo [2, 1-b]furo-[3,2-d]pyridinone **4(a-b)** were obtained by refluxing in presence of sodium hydroxide. All the synthesized compounds physical characterization of melting point, solvents and percentage of yield depicted in **Table 1.**

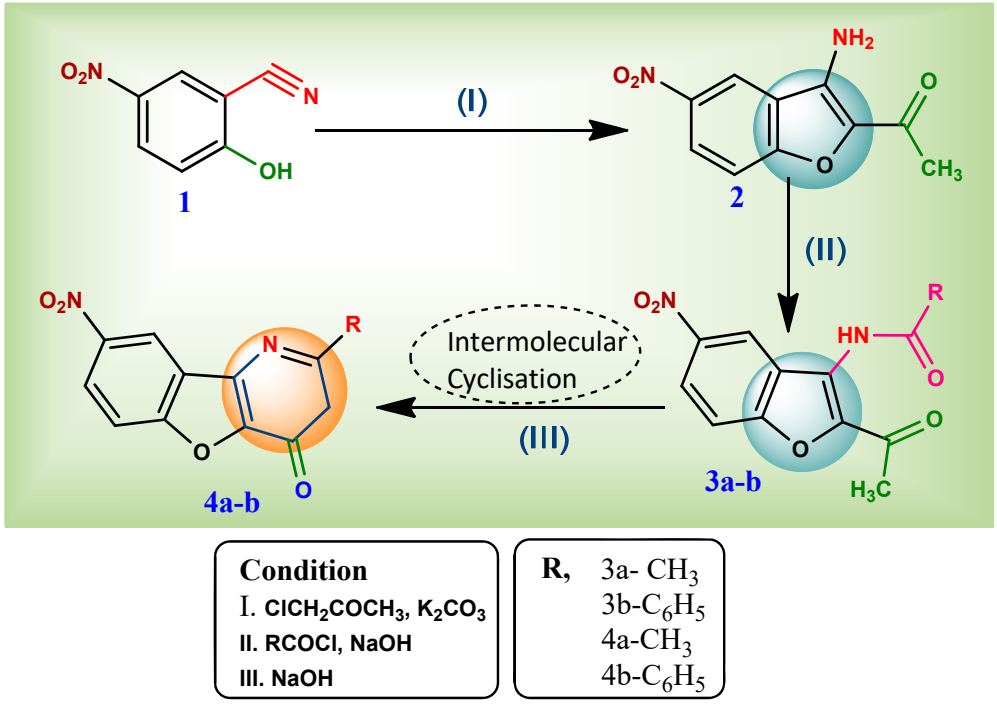

Fig. 1. Synthesis of benzofuran-pyridinone

The targeted molecule **4b**. The IR spectra revealed the peak at 1645 cm-1 showing the Presence of C=O stretching vibration of cyclic amide. The C-H stretching frequency was at 2921 cm-1 indicated their presence in pyridinone ring in compound **3a-b**. From ^{1}H NMR spectra the signal at δ ppm 2.8 was assigned to methylene (-CH_2-) protons and the multiplet signal δ ppm 7.15 to 7.69 were due to aromatic protons. The structure of the compound (**4b**) was further supported by its ESI MS Spectra indicating molecular ion peak was at 305 *m/z* and fragmented ion peak at 285 *m/z.*

Table 1. Physical characterization data of synthesized compounds

Compound	R	Molecular Formula	M.P ^{0}C	Yield (%)	Solvents
1	-	$C_7H_4N_2O_3$	94	62.5%	Ethanol
2	-	$C_{10}H_8N_2O_4$	114	68.2%	Ethanol
3a	CH_3	$C_{12}H_{10}N_2O_5$	113	59.5%	Ethanol
3b	C_6H_5	$C_{17}H_{12}N_2O_5$	162	56.8%	DMF
4a	CH_3	$C_{12}H_8N_2O_4$	120	61.3%	Ethanol
4b	C_6H_5	$C_{17}H_{10}N_2O_4$	112	63.8%	DMF

2.2. Physical and Spectral data

The synthesized compounds spectral studies (FT-IR, ^{1}H NMR, Mass) of data is enclosed as supplementary data file with this manuscript

Compound **1**:
IR in cm^{-1}(KBr) 3303 (OH Aromatic stretching), 2238(C≡N), 1535 (NO_2);
^{1}H NMR in δ ppm (DMSO) 8.19-8.21 (s, 1H, aromatic OH), 7.05-8.19 (m, 3H, Ar-H);
Mass M^+ peak (m/z) 165 (164) $(M+1)^+$

Compound **2**:
IR in cm^{-1}(KBr) 3452 (NH_2 stretching), 1658 (C=O), 1525 (NO_2);
^{1}H NMR in δ ppm (DMSO) 6.17-6.14 (s, 2H, -NH_2), 2.33-2.52(s, 3H, CH_3), 8.46(s, 1H Ar-H), 7.78-8.09 (m, 2H, Ar-H);
Mass M^+ peak (m/z) 219-220 (220)

Compound **3b**:
IR in cm^{-1}(KBr) 3330(-NH-CO-C_6H_5), 1721(-C=O), 1665(-CO-NH-),1523(-NO_2);
^{1}H NMR in δ ppm (DMSO) 2.32-2.55(s, 3H, -CH_3), 7.12-7.52(s, 1H, -NH-), 7.44-7.51(t, 2H, Ar-H), 7.41-8.11(m, 6H, Ar-H);
Mass M^+ peak (m/z) 324.99 (324 may be due to M+1)

Compound **4b**:
IR in cm^{-1}(KBr) 2921(CH_2 Ar-), 1645(-C=O), 1618 (C=N-), 1526(-NO_2);
^{1}H NMR in δ ppm (DMSO) 2.5-2.8 (s, 2H, -CH_2), 7.12-7.3(m, 3H, Ar-H), 7.6-8.1(d, 4H, Ar-H), 8.4-8.56 (s, 1H, Ar H);
Mass M^+ peak (m/z) 305-306(305 may be M-1 peak)

2.3. Antimicrobial activity

The antimicrobial activity of newly synthesized compounds was determined by well diffusion method.[22-23] The amoxicillin and Fluconazole were used as standard drugs for comparison of antibacterial and antifungal activities respectively. The zone of inhibition was compared with the standard drug after 24 h and incubation at 30^0C for antibacterial activity and 72 hrs at 25 ^{0}C for antifungal activity. All the compounds were screened for their antibacterial activity against Gram-positive bacterial strains *Staphylococcus aureus,* and Gram-negative strains *Klebsiella pneumonia and* Escherichia *coli using* well diffusion method. Results of the study are depicted in **Table 2**. However, these compounds were good active when compared to the standard drug Amoxicillin. Further, the antifungal activities of the synthesized compounds were performed against standard fungal strains *Candida, Aspergillum Niger,* in DMF. To ensure that the solvent had no effect on the fungal growth, a control was performed with the test medium supplemented with DMF at the same method as used in the experiments. The results are incorporated in **Table 3.** The compound **4b** showed promising activity against *Pseudomonas aureginosa, Escherichia coli* and *Staphylococcus aureus.* The compounds **3a** and **3b** exhibited moderate activity against E. *coli.* For antifungal activity, there was a good zone of inhibition.

Table 2. Antibacterial activities of compounds 3a-b and 4a-b

Synthetic Compounds	Diameter of Zone of inhibition (mm)					
	Staphylococcus aureus		*Pseudomonas aeruginosa*		*Escherichia coli*	
	20 µg/ml	50 µg/ml	20 µg/ml	50 µg/ml	20 µg/ml	50 µg/ml
3a	7	8	8	9	9	9
3b	9	10	10	10	8	7
4a	-	7	-	7	10	11
4b	8	8	13	13	11	10
Amoxicillin	15	18	19	22	18	21

[2]Explaines diameter of the inhibition zone for antibacterial activity.

Table 3. Antifungal activities of compounds 3a-b and 4a-b

Synthetic Compounds	Comp. zone of inhibition (mm)			
	Candida albiacans		*Aspergillus niger*	
	20 µg/ml	50 µg/ml	20 µg/ml	50 µg/ml
3a	9	12	10	10
3b	9	9	9	8
4a	11	13	7	8
4b	10	12	10	9
Fluconazole	13	16	12	14

[3]Explaines diameter of the inhibition zone for antifungal activity.

The synthesized compounds were screened for *in vitro* antibacterial and antifungal activity to the concentrations 20 µg/ml and 50 µg/ml. The compound shows excellent antibacterial activity against the three organisms *Staphylococcus aureus, E.coli,* and *P. aureginosa* which are compared with the standard drugs Amoxicillin and Fluconazole. The antibacterial activity of the compounds was prominent in comparison through flow charts to the concentrations 20 µg/ml and 50 µg/ml against all the organisms (See **Fig 2 and Fig. 3)**

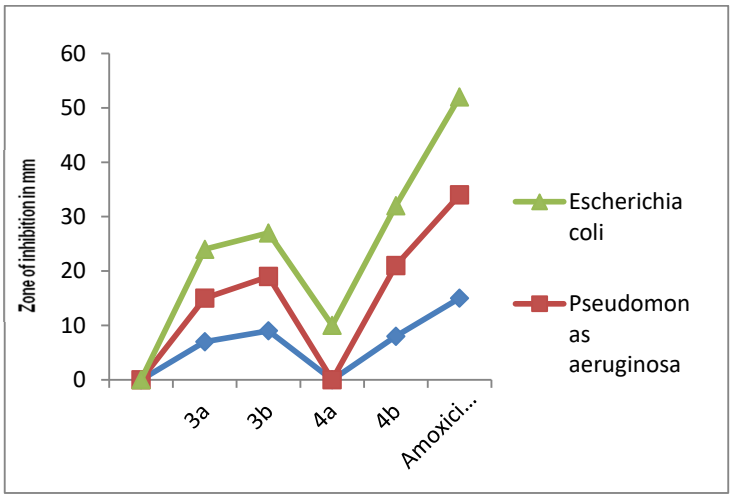

Fig. 2. Antibacterial activity of the Concentration **(20 µg/ml)** Compounds 3a-b and 4a-b *Comparison* With the Standard Drug (Amoxicillin).

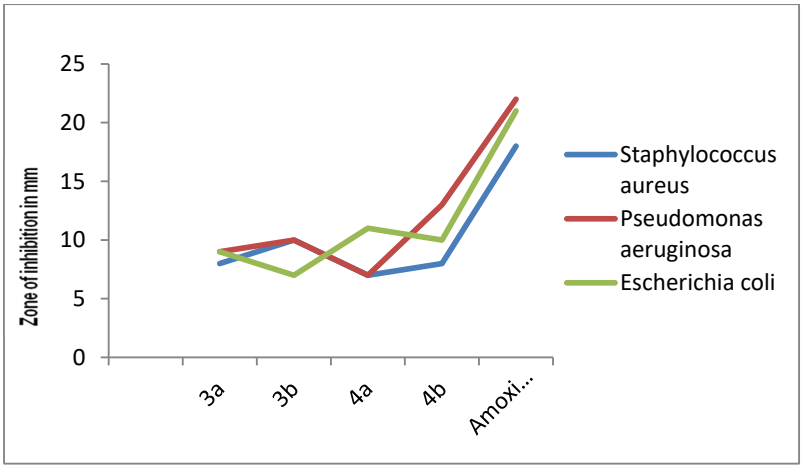

Fig. 3. Antibacterial activity of the Concentration **(50 µg/ml)** Compounds 3a-b and 4a-b *Comparison* With the Standard Drug (Amoxicillin).

The antifungal activity of the all the synthetic compounds exhibits predominant activity against the organisms, *Candida and Aspergillums Niger* to the concentrations 20 µg/ml and 50 µg/ml, these synthesized compounds were compared with standard drug *Fluconazole* which is depicted in **Fig 4 and Fig. 5**. In this fig blue lines indicate Candida inhabitation and brown indicates Aspergillus Niger.

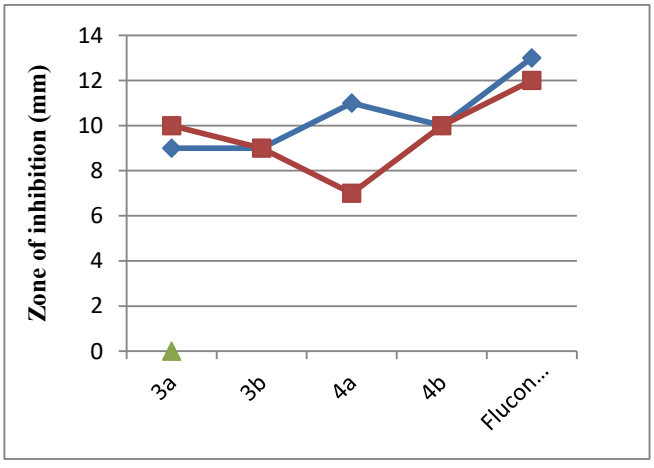

Fig. 4. Antifungal activity of the Compounds (20 µg/ml) 3a-b and 4a-b are compared with standard drug Fluconazole.

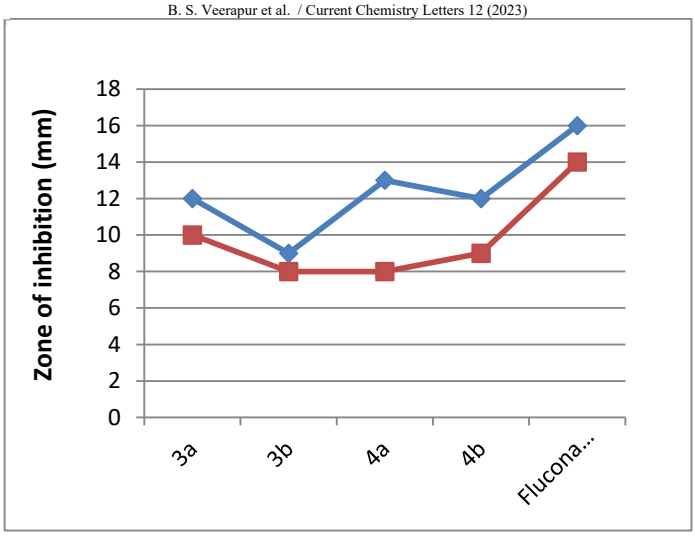

Fig. 5. Antifungal activity of the Compounds (50 µg/ml) 3a-b and 4a-b are compared with standard drug Fluconazole.

2.4. Antioxidant activity

The free radical scavenging activity of titled compounds was measured *In-vitro* by 2, 2-Diphenyl-1-picrylhydrazyl (DPPH) assay. The stock solution was prepared by dissolving 24 mg DPPH with 100 ml methanol and stored at 20°C until required. The working solution was obtained by diluting the DPPH solution with methanol to attain an absorbance of about 0.98±0.02 at 517 nm using the spectrophotometer. All the tested samples in various concentrations (50, 75 and 100 μg/ml) were prepared in methanol and the homogeneous solutions were achieved by stirring. A liquid of test sample (1 ml) was added to 4 ml of 0.004% (w/v) methanol solution of DPPH and then reaction mixture was vortexed for 1 min and kept at room temperature for 30 min in the dark to complete the reaction. The absorbance was read against blank at 517 nm. This absorbance result was depicted in **Table 4**.

The synthetic antioxidant butyrate hydroxytoluene (BHT) was used as positive control. The ability of the tested samples at tested concentration to scavenge DPPH radicals was calculated using the following equation,

$$Scavenging\ ratio\ (\%) = [(A_i - A_0) / (A_c - A_0)] \times 100\%$$

where A_i is the absorbance in the presence of the test compound; A_0 is absorbance of the blank in the absence of the test compound; A_c is the absorbance in the absence of the test compound.

Table 4. antioxidant activities of synthesized compounds 4a-b

Compounds	DPPH radical scavenging activity (%) of different concentrations (μg/ml) of compounds		
	50 (μg/ml)	100(μg/ml)	200 (μg/ml)
3a	69.22	73.05	78.71
3b	93.91	96.11	89.22
4a	64.96	67.14	68.14
4b	92.06	93.56	93.54

[4]Explaines percentage of radical scavenging antioxidant activity.

2.5. Molecular docking studies

To identify potential antimicrobial lead among the compounds 3a-b and 4a-b docking calculations were performed using Patch dock. The docking of molecules with the *colicin e7 immunity* protein (imme7) inhibits its bactericidal activity and the pore-forming domain at 2.4 angstroms resolution. Our synthesized molecules which are having inhibitory capability are exhibiting the interactions with one or the other amino acids in the active pockets. The docking results for inhibitor compounds are documented in **Table 5**. All the molecules showed good dock score, ACE, Bond distance and Bond interaction energy respectively. Among the molecules, docking with Antibacterial organisms containing protein (PDB Id: 1CEI and 1COL) using Patch dock is an algorithm for molecular docking.

In vitro studies also compounds have emerged as a active molecule against all the screen microorganisms, so it can be predicted as the activity may be due to inhibition of enzyme the *colicin e7 immunity* protein (imme7) that binds its bactericidal activity and the pore-forming domain. Hence, this Interaction study of patch dock score results as predicted from the PLIP (the protein-ligand interaction Profiler) This interaction studies 3d images in **Fig 6.**

Table 5. Molecular docking results and their interaction results of the compounds 4a-b (PDB Id)

Sample Code	Protein Receptor (PDB Id)	Patch dock Score	ACE	No. of H interaction	Bond Distance	Bonded Residue	Bond Protein
4a	1CEI	3772	-108.33	1	3.56	N-----O	LYS-139
4b		4792	-116.24	4	3.26	N-----O	PRO-101
					2.89	N-----O	SER-122
					4.04	N-----N	LYS-120
					2.77	N-----O	GLU-137
4a	1COL	4500	-101.80	2	3.08	N-----O	ILE-150
					2.65	O-----O	TYR-124
4b		5610	-156.14	6	2.44	O-----O	THR-103
					2.61	N-----O	MET-159
					2.32	N-----O	ILE-125
					2.47	Ng----O	ARG-148
					3.33	O-----Ng	ARG-150
					4.05	O-----O	GLY-144

[5]provides interaction results of molecular docking.

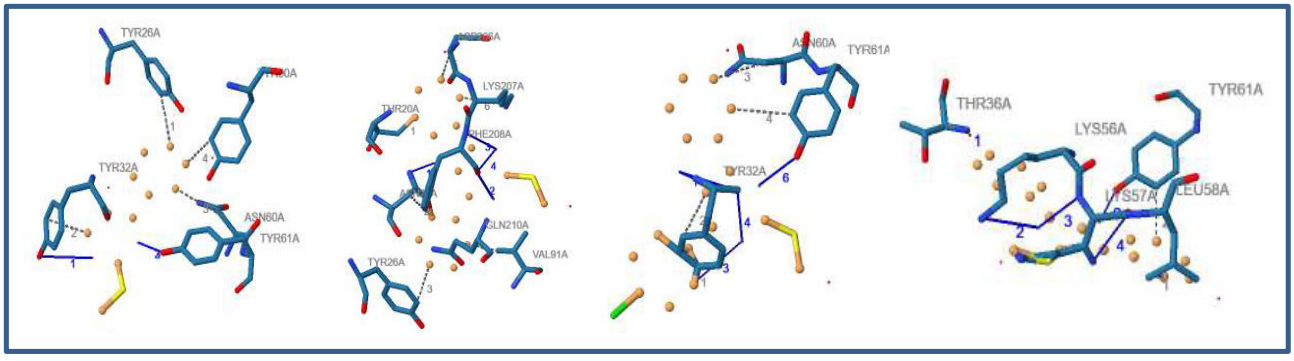

Fig. 6. Docking and their interaction study 3d images of compounds 4a-b at different PDB Id

3. Conclusion

A series of novel 5-nitro-benzofuropiridinone derivatives have been synthesized with good yield and screened for their antibacterial, antifungal, and antioxidant activities. In the series, the compounds bearing nitro and the carboxyl group exhibited potent activities compared to the remaining. However, these *in vitro* evaluations in different experimental models and detailed studies are necessary to further support Molecular docking and their interaction results.

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This work is considered as evidence for the importance of organic compounds in different fields as reported before.

Conflict of interest

The authors declare no conflict of interest, financial and otherwise.

4. Experimental

4.1 Materials and methods

All the chemicals, reagents and solvents used obtained from commercial sources and analytical grade. All the reactions were monitored by thin layer chromatography (TLC) using silica gel as stationary phase, different solvent systems as mobile phase and uv chamber as detecting agent. Melting point was determined on an electronic apparatus and is uncorrected. IR spectra were recorded on the Shimadzu model IR-435 spectrophotometer using KBr discs for solids and thin films for liquids. 1H NMR spectra were recorded on JOEL AC (400 MHz) in DMSO-d_6 and $CDCl_3$ using tetramethylsilane (TMS) as an internal slandered peak in δ ppm. TOF ES+ Mass spectra (m/z) were recorded on micro mass Auto spec LCTKC455. Substituted benzofuran pyridinone were prepared by starting from the corresponding salicylaldehyde oxime and the other reactants. 2-methyl-8-nitrobenzofuropyridinone was prepared following in five steps.

4.2. General procedure

Preparation of 5-nitro-2-hydroxybenzonitrile (1)

The dried 5-nitrosalicyldehyde oxime **(1)** (0.01 mol) obtained above was transferred to a round bottomed flask and added with anhydrous acetic anhydride (20 ml) was refluxed for 30 min.; excess of acetic anhydride was removed by distillation under reduced pressure. The dark dense liquid of benzo [1, 2-d] isoxazole was treated with freshly prepared sodium ethoxide [prepared by adding freshly cut dry sodium (20 g) into absolute ethanol (100 ml) at 0^0 C. The mixture was stirred for 30 min. at room temperature and poured into ice-cold water. On acidification with Hal, it gave 5-nitro-2-hydroxybenzonitrile **(2)** as light brown solid, which was collected and recrystalisation from ethanol (Melting point-94^o C, yield: 62.5%)

Preparation of 2-actyl-3-amino-5-bromo-1-benzofuran (2)

5-Nitro-2-hydroxybenzonitrile (**2)** (1.64 g, 0.01mol) was dissolved in dry acetone (50ml). To this solution, finely grounded anhydrous potassium carbonate (3g) and chloroacetone (1.10ml, 0.01mol) was refluxed for 12 hours. The potassium carbonate was filtered off and from the filtrate acetone was removed under reduced pressure. The resulting light brown solid was collected and recrystalisation from ethanol. (Melting point: 1140C, yield: 68.2%)

Preparation of 3-acyalaminobenzofuro [2, 1-b]-2-corboxylate (3a-b)

The compound **3** (2.28 g 0.01 mol) was heated on hot water-bath(60-70^{0}C) for 20 min with acetyl chloride (4 ml) in the presence of aqueous sodium hydroxide (2 N, 2 ml). The product **4a** thus separated as solid was collected and recrystallized from ethanol. Similarly compound **4b** was obtained by treating compound **3** with benzyl chloride**.** Yields, melting points and solvent used are given in table 01.

Preparation of 2-methyl-4-oxo-benzo [2, 1-b] furo-(3, 2-d) pyridinone (4a-b)

Acetyl compound **4a** (2.62 g 0.02 mol) was suspended in aqueous sodium hydroxide (1N 500ml) and warmed on a water-bath (60-70^{0}C) for 30 min. The resulting solution when carefully acidified with dilute HCl gave compound **5a**, which was then purified by recrystalisation aqueous ethanol. The same procedure was followed to obtain compound **5b** from compound **4b.** Yields, melting points and solvent used are given in **Table 1**.

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