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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL BENZOFURANPYRIDINE DERIVATIVES

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5-Bromo-3-amino-2-acetyl benzofuran **3** was prepared by the reaction of 5-bromosalicylonitrile **2** with chloroacetone in dry acetone in presence of anhydrous potassium carbonate to maintain basic condition. The Claisen-Schmidt condensation of compound **3** with various substituted aromatic aldehydes in presence of strong base in absolute ethanol gave 5-bromo-3-amino-2-arylidine acetyl benzofuran **4**a-f in good yields. The compounds **4**a-f upon treatment with orthophosphoric acid in acetic acid underwent cyclisation and resulted in the formation of above titled compounds **5**a-f. All synthesized compounds were characterized on the basis of its physical constant, analytical and spectral studies. Further these compounds were evaluated for their antibacterial and antifungal activities.

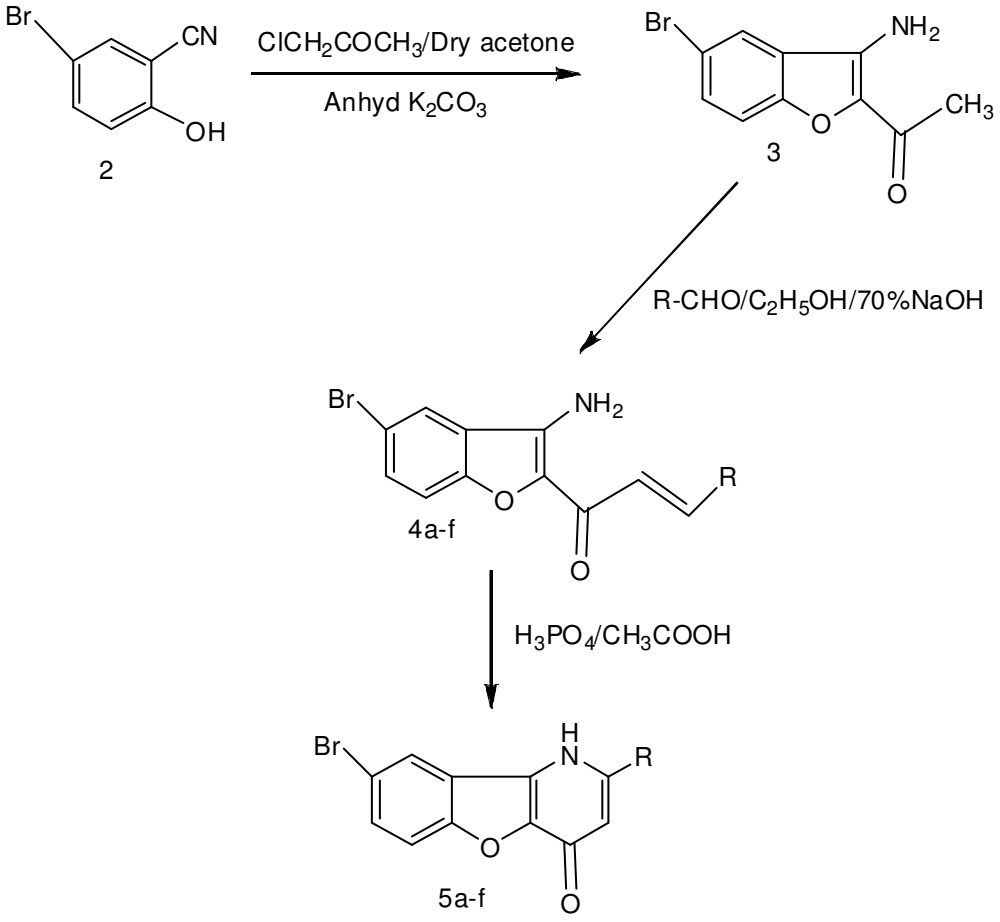
Compounds containing pyridine nucleus has led to the exploration of several polycyclic heterocycles such as benzofuro [2,3-*b*] pyridine, benzofuro [2,3-*c*] pyridine and benzofuro [3,2-*c*] pyridine, have received considerable attention and are reported to possess analgesic, analeptic, antiviral, antibacterial and antifungal activities[1-5]. The isomeric benzofuro [3,2-*b*] pyridine has been little investigated biologically. Now we are reporting a new series of benzofuropyridine derivatives. A convenient route has been developed for the synthesis of benzofuro [3,2-*b*] pyridines. The starting compound 5-bromo-3-amino-2-acetyl benzofuran **3** was obtained by reacting 5-bromosalicylonitrile with chloroacetone in the presence of anhyd potassium carbonate in dry acetone.

Compound **3** was characterized by using its physical, analytical and spectral data such as IR, ^{1}H NMR and mass spectra. The IR spectrum of compound **3** revealed its absorbance bands at 3456-3327, 1643, 1520 and 1413 cm^{-1} due to symmetric and asymmetric streatching of NH, C=O and C=C groups respectively and another absorbance band at 1208 due to C-N stretching frequency.

The ^{1}H NMR spectrum of compound **3** exhibited three signals in the spectrum. A singlet at 2.50 due to three proton of acetyl group and another singlet at 5.60 due to two protons of amino group. A multiplet observed in the region at 7.26-7.72 was due to three aromatic protons. The mass spectrum of compound **3** exhibited a molecular ion peak at m/z 253 which is in agreement with molecular weight of compound **3** and its isotopic peak at m/z 255 (M+2).

The Claisen-Schmidt condensation of compound **3** with different substituted aromatic aldehydes in presence of strong base in absolute ethanol gave 5-bromo-3-amino-2-arylidene acetyl benzofuran **4**a-f in good yield (65-90%).

The IR, ^{1}H NMR and mass spectra of compound **4**a-f were in agreement with the assigned structures. The IR spectrum of compound **4**a showed an absorbance bands at 3431-3360 due to NH_2 symmetric and asymmetric stretching frequency another absorbance band at 1615 due to C=O stretching, 1566 and 1511 due to C=C stretching. The ^{1}H NMR spectrum of representative compound **4**a exhibited a peak at 5.80 as a singlet due to two protons of amino group, a doublet at 6.80 due to one proton of –CO-CH- another doublet at 7.20 due to one proton of –COCH=CH-. A multiplet observed in the region at 7.41-7.87 was due to aromatic protons. The mass spectrum of **4**a showed a molecular ion peak at m/z 342 (M^+) corresponding with molecular weight of compound **4**a.



Where	R
a	C_6H_5
b	$C_6H_4NO_2(p)$
c	$C_6H_4CH_3(p)$
d	$C_6H_4F(p)$
e	$C_6H_4OCH_3(p)$
f	$C_6H_4N(CH_3)_2(p)$

SCHEME-1

Table-1
Physical characterization data of synthesised compounds **4**a-f and **5**a-f

Compd	R	S	M.P. (^{0}C)	Yield (%)
4a	C_6H_5	A	162	87
4b	$C_6H_4NO_2$(*p*)	A	181	90
4c	$C_6H_4CH_3$(*p*)	A	160	73
4d	C_6H_4F(*p*)	A	140	88
4e	$C_6H_4OCH_3$(*p*)	A	170	82
4f	$C_6H_4N(CH_3)_2$(*p*)	A	218	85
5a	C_6H_5	B	139	90
5b	$C_6H_4NO_2$(*p*)	B	165	88
5c	$C_6H_4CH_3$(*p*)	B	125	89
5d	C_6H_4F(*p*)	B	180	60
5e	$C_6H_4OCH_3$(*p*)	B	158	79
5f	$C_6H_4N(CH_3)_2$(*p*)	B	190	89

S=Solvent for crystallization, A=Ethanol, B=Benzene.

The benzofuran analogues of chalcones **4**a-f were treated with orthophosphoric acid in acetic acid and heated at reflux temp for 5 hr to give 8-bromo-2-phenyl benzofuran [3,2-*b*] pyridine-4(1*H*)-ones **5**a-f and the structure of these compounds were confirmed by analytical and spectral data.

The IR, ^{1}H NMR and mass spectra of **5**a were recorded to substantiate the structure assigned. The IR spectrum of **5**a exhibited absorbance band at 3200 due to NH frequency. Another absorbance band was at 3050 due to C-H stretching of aromatic ring. The band at 1716 was due to C=O stretching and other absorbance bands observed at 1461 due to C=C stretching. The ^{1}H NMR spectrum of **5**a displayed a multiplet at 7.20-7.70 due to aromatic protons, a peak observed at 8.60 as singlet due to one proton of NH of pyridine. The mass spectrum of compound **5**a showed a molecular ion peak at m/z 339 corresponding to the molecular weight of compound **5**a.

Antibacterial and antifungal activity

All newly synthesized compounds **4**a-f and **5**a-f were evaluated for *in-vitro* antimicrobial activity. The *in-vitro* antimicrobial activity was carried out using MIC method. The organism selected were *S. aureus* and *E. coli* for antibacterial activity where as *C. albicans* and *A. niger* for fungicidal activity. The standard drug and test compounds were used in the concentration of 2.5µg to 100 µg/ml. The Ciprofloxacin and fluconazole were used as standard drug for antibacterial and antifungal activity respectively.

Compounds **4**b, **4**c, **4**d and **4**f exhibited good antibacterial activity against *S. aureus* and *E. coli* and remaining compounds showed moderate activity against both organism, when compared with standard drug Ciprofloxacin.

Compounds **4**c, **4**d, **4**f, **5**e and **5**d displayed high activity against *A. niger* and *C. albicans* where as other test compounds of the series showed moderate to weak activity against both fungi when compared with standard drug fluconazole.

Experimental

The melting points were determined by open capillaries and are uncorrected. IR spectra were recorded with a FTIR-8400S (SHIMADZU) spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker 300 MHz spectrophotometer. The chemical shifts were expressed in δ ppm down field from TMS. The mass spectra were recorded with an LCMS-2010A data report Shimadzu and elemental analysis were done with a flash EA 1112 series CHN report thermo finnigan Silica gel Merck (60-120 mesh).

5-Bromosalicylonitrile 2

5-Bromosalicylaldehyde (0.05 mol) was treated with hydroxylamine hydrochloride (0.055 mol) in anhyd dimethylformamide at gentle reflux temp for 20 min. The contents were cooled and poured into cold water to give solid 5-bromosalicylonitrile **2** which was recrystallized from benzene, m.p. 156^0, yield 82%.

5-Bromo-3-amino-2-acetyl benzofuran 3

To a solution of 5-bromosalicylonitrile **2** (0.01 mol) in anhyd acetone (15 ml), chloroacetone (0.01 mol) was added followed by anhyd potassium carbonate to maintain basic condition. The reaction mixture was refluxed for 8 hr, the potassium salt was filtered off. The solvent was removed under reduced pressure and

Table-2
Antibacterial activity results of synthesized compounds **4**a-f and **5**a-f

Compd	100 µg/ml	50 µg/ml	25 µg/ml	12.5 µg/ml	6.25 µg/ml	3.125 µg/ml	1.6 µg/ml	0.8 µg/ml	0.4 µg/ml	0.2 µg/ml
S. aureus										
4a	S	S	R	R	R	R	R	R	R	R
4b	S	S	R	S	R	R	R	R	R	R
4c	S	S	S	R	R	R	R	R	R	R
4d	S	S	R	R	R	R	R	R	R	R
4e	S	S	S	R	R	R	R	R	R	R
4f	S	S	R	R	R	R	R	R	R	R
5a	R	R	R	R	R	R	R	R	R	R
5b	R	R	R	R	R	R	R	R	R	R
5c	S	S	R	R	R	R	R	R	R	R
5d	S	S	R	R	R	R	R	R	R	R
5e	R	S	S	R	R	R	R	R	R	R
5f	S	S	R	R	R	R	R	R	R	R
E. coli										
4a	S	S	R	R	R	R	R	R	R	R
4b	S	S	R	S	R	R	R	R	R	R
4c	S	S	S	S	R	R	R	R	R	R
4d	S	S	S	R	R	R	R	R	R	R
4e	S	S	R	S	R	R	R	R	R	R
4f	S	S	S	S	R	R	R	R	R	R
5a	R	S	S	R	R	R	R	R	R	R
5b	R	S	R	S	R	R	R	R	R	R
5c	R	R	R	R	R	R	R	R	R	R
5d	S	S	R	R	R	R	R	R	R	R
5e	S	S	R	R	R	R	R	R	R	R
5f	S	S	R	R	R	R	R	R	R	R
Standard drug										
Ciprofloxacin	S	S	S	S	S	S	S	S	S	S
S-Senstitive, R-Resistant										
C. albicans										
4a	S	R	R	R	R	R	R	R	R	R
4b	S	S	R	R	R	R	R	R	R	R
4c	S	S	S	R	R	R	R	R	R	R
4d	S	S	S	R	R	R	R	R	R	R
4e	S	R	R	R	R	R	R	R	R	R
4f	S	S	S	R	R	R	R	R	R	R
5a	S	S	R	R	R	R	R	R	R	R
5b	S	S	R	R	R	R	R	R	R	R
5c	S	S	S	S	R	R	R	R	R	R
5d	S	S	S	S	R	R	R	R	R	R
5e	S	S	R	S	R	R	R	R	R	R
5f	S	S	R	R	R	R	R	R	R	R

A. niger										
4a	S	S	R	R	R	R	R	R	R	R
4b	S	S	S	R	R	R	R	R	R	R
4c	S	S	S	R	R	R	R	R	R	R
4d	S	S	S	R	R	R	R	R	R	R
4e	S	S	R	R	R	R	R	R	R	R
4f	S	S	S	R	R	R	R	R	R	R
5a	R	S	S	R	R	R	R	R	R	R
5b	R	S	R	S	R	R	R	R	R	R
5c	R	R	R	R	R	R	R	R	R	R
5d	S	S	R	R	R	R	R	R	R	R
5e	R	S	R	R	R	R	R	R	R	R
5f	S	S	R	R	R	R	R	R	R	R
Standard drug										
Fluconazole	S	S	S	S	S	S	S	S	S	S

S-Senstitive, R-Resistant

gave 5-bromo-3-amino-2-acetyl benzofuran **3** as yellowish solid and it was crystallized from suitable solvent. M.p. 215^0 and yield 88%.

5-Bromo-3-amino-2-arylidene acetyl benzofurans 4a-f : General procedure

A mixture of 5-bromo-3-amino-2-acetyl benzofuran **3** (0.01 mol) and aromatic aldehyde (0.01 mol) in ethanol (30 ml) was treated with aq solution of sodium hydroxide (70%, 2.5 ml) in small portions. The reaction mixture was stirred for 3 hr and left overnight. The solid mass separated was collected and crystallized from suitable solvent.

4d: IR (KBr) cm^{-1}: 3420-3200 (NH_2), 1648 (C=O), 1521, 1418 (C=C), 1234 (C-N), 822 (C-Br). ^1H NMR (δ ppm): 5.79 (s, 2H, NH_2), 6.82 (d, 1H, -COCH-), 7.10 (d, 1H, -COCH=CH-), 7.32-7.80 (m, ArH).

4e : IR (KBr) : 3420-3300 (NH_2), 1650 (C=O), 1522, 1421 (C=C), 1170 (C-N), 809 (C-Br).

4f: IR (KBr): 3412-3314 (NH_2), 1645 (C=O), 1416, 1357 (C-O), 1208 (C-N), 805 (C-Br).

8-Bromo-2-phenyl benzofuran [3,2-*b*] pyridine-4 (1*H*)-ones 5a-f : General procedure

5-Bromo-3-amino benzofuran chalcones **4**a-f (0.001 mol) were treated with orthophosphoric acid (0.001 mol) in acetic acid (5 ml) and heated at reflux temp for 5 hr. The reaction mixture was cooled and poured into ice cold water. Thus solid separated was filtered and the products were recrystallized from a suitable solvent.

5c: IR (KBr) cm^{-1} : 3300 (NH), 1645 (C=O), 1521 (C=C). ^1H NMR (δ ppm): 1.25 (s, 3H, CH_3), 6.90-7.67 (m, ArH), 8.40 (s, 1H, NH). MS : 354 (M^+), 356 (M+2, 100%), 280 (30%), 264 (10%).

5d : IR (KBr): 3190 (NH), 1690 (C=O), 1509, 1461 (C=C). ^1H NMR : 7.26-7.6 (m, ArH), 8.50 (s, 1H, NH). MS 360 (M^+, 100%), 362 (M+2, 100%), 280 (30%), 264 (10%).

5e: IR (KBr): 3260 (NH), 3090 (-CH, Ar), 1745 (C=O), 1465 (C=C). MS : 369 (M^+), 371 (M+2).

5f : IR (KBr): 3270 (NH), 1715 (C=O), 1464 (C=C). ^1H NMR : 7.20-7.70 (m, ArH), 8.60 (s, 1H, NH), 2.16 (s, 6H, CH_3). MS 383 (M^+), 385 (M+2).

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