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Synthesis of new benzofuran analogues from 5-bromosalicylaldehyde and their biological activities

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ABSTRACT

The reaction of 5-bromosalicyladehyde **(2)** with hydroxylamine hydrochloride in dimethylfromamide gave 5-Bromosalicylonitrile **(3)** required in the present work has been obtained by a single step method by the reaction of 5-bromosalicylaldehyde **(2)** with hydroxylamine hydrochloride in dimethyl formamide. Condensation of 5-bromosalicylonitrile **(3)** with ethylchloro acetate/chloroacetamide gave ethyl-4-bromo 2-cyanophenoxyacetate and 4-bromo-2-cyanophenoxyacetamide **(4-5)** which underwent cyclisation in presence of base in dimethyl formamide to offer ethyl 5-bromo-3-amino-2-benzofurancarboxylate and 5-bromo-3-amino-2-benzofurancarboxamide **(6-7)**. However the reaction of 5-bromosalicylonitrile with chloroacetone/ phenacylbromide furnished the formation of 5-bromo-3-aminobenzofuran-2-acetate **(8)** and 5-bromo-3-aminobenzofuran-2-benzoate **(9)** in single step. The structures of all benzofuran analogues were assigned on the basis of spectral data. All the synthesized compounds were screened for antimicrobial and pharmacological activities.

KEYWORDS

Synthesis of 5-bromosalicylonitrile;
2-Substitutedbenzofurans;
Antimicrobial;
Anti-inflammatory activity.

INTRODUCTION

Benzofuran nucleus is widely distributed in natural products[1-2], particularly among plant kingdom. Many such compounds have been reported[3-4] to possess very interesting pharmacological and physiological properties. During the last several years, constant efforts are being made to isolate and identify such compounds[5-7]. As a result of such an investigations several furan derivatives brought to light were found to exhibit wide biological activity. They include a variety of compounds ranging from benzofuran derivatives to highly complicated alkaloids like morphine. In a search to find more potent compounds than the nature has provided, numerous synthetic analogous are prepared[8-10].

Synthetic benzofuran derivatives have received considerable attention owing to their antifungal N-myristoyl transferase inhibitor activity[11] and their activity as potent non-steroidal reversible inhibitors of P450 aromatase[12]. The benzofuran ring itself is a common structural element that appears in a large number of medicinally important compounds[13]. Some natural benzofuran analogues have attracted much attention in medicinal chemistry for their wide range of biological activities including insecticidal, fungicidal, antimicrobial and antioxidant properties[14].

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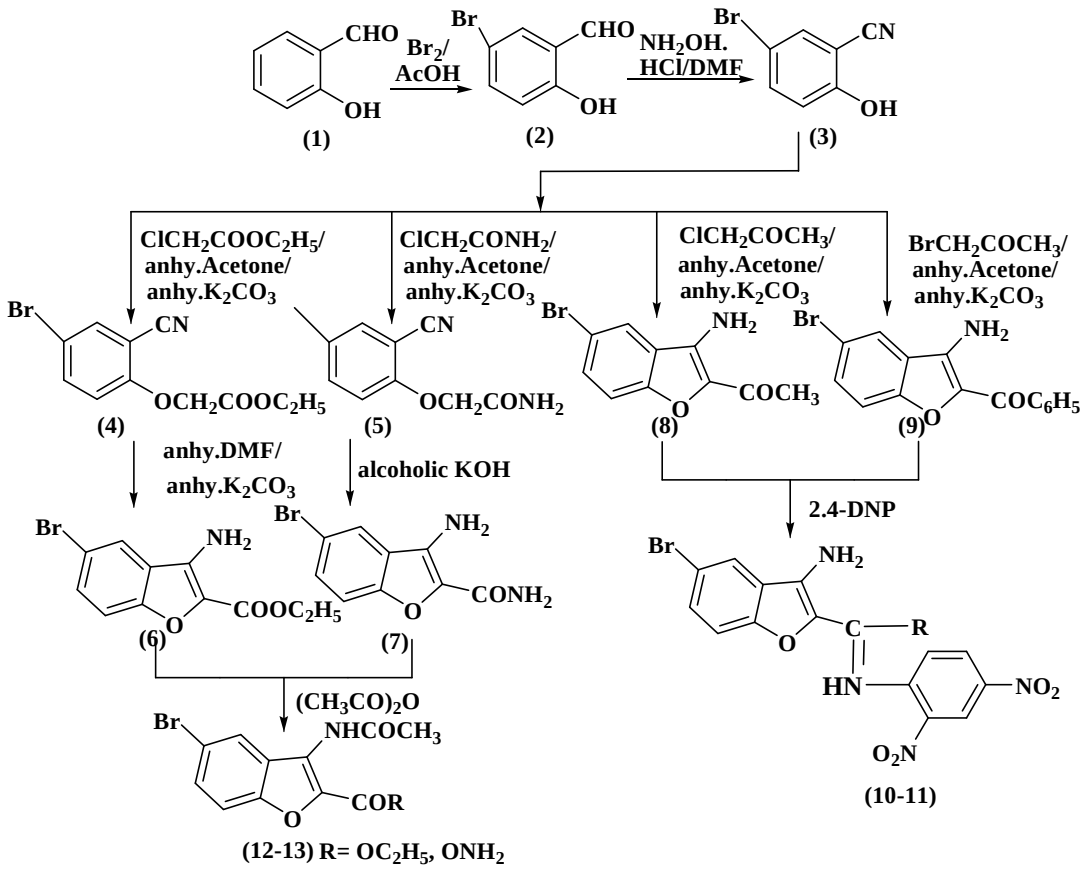

In view these observations and our continued interest in the synthesis of biologically active heterocycles of benzofuran analogues[5-7], it is considered worthwhile to synthesize some benzofuran analogues from 5-bromosalicylaldehyde and to carryout their biological activities.

EXPERIMENTAL

General procedure

All the reagents were obtained commercially and used with further purification. The melting points were determined on an open capillary method and are uncorrected; IR spectra were recorded with a Perkin-Elmer Spectrum ONE FTIR spectrophotometer. ^{1}H NMR spectra were recorded with a AMX-400 AV III Solids NMR. The chemical shifts were expressed in the ppm (δ scale) downfield from TMS. Mass spectra were recorded with an LCMS-2010A Data Report-Shimadzu and elemental analysis with a Flash EA 1112 Series CHNS Report Thermo Finnigan. Silica gel Merck (60-120 mesh) and DC-Alufoline 60 F254 were normally used for column and TLC Chromatography respectively.

1. 5-Bromosalicylaldehyde 2

The treatment of Salicylaldehydes **(1)** upon treated with bromine in acetic acid at room temperature gave 5-bromosalicylaldehyde **(2)**.

2. 5-Bromosalicylonitrile 3

5-Bromosalicylaldehyde (0.05 mol) was treated with hydroxylamine hydrochloride (0.055 mol) in anhydrous dimethyl formamide and at gentle reflux temperature for 20 min. The contents were poured into cold water to give solid 5-bromosalicylonitrile **(3)**.

3. Ethyl 4-bromo-2-cyanophenoxyacetate 4 and 5-bromo-2-anophenoxyacetamide (5):(General method)

To a solution of 5-bromosalicylonitrile **(3)** (0.01 mol) in anhydrous acetone was added ethylchloroacetate/ chloroacetamide (0.01 mol) and anhydrous potassium carbonate. The reaction mixture was refluxed for 8-10 h. potassium salts filtered off; removal of acetone under

TABLE 1: Characterisation data of synthesized compounds

Comp no.	Yield (%)	M.P. (^{0}C)	Mol. formula	IR (cm^{-1})	^{1}H NMR (δ ppm)	CHN analysis (%); found/(Calculated)		
						C	H	N
3	78.681	57-58	C_7H_4ONBr	2236 (-C≡N), 3249 (-OH)	s, 6.4 (-OH); m, 7-8(Ar-H)	42.42 (42.42)	2.05 2.02	7.24 (7.07)
4	68.31	58-60	$C_{11}H_{10}O_3NBr$	1747 (-CO), 2224 (-C≡N)	-	46.42 (46.48)	3.55 (3.52)	4.88 (4.93)
5	62.75	240-242	$C_9H_7O_2N_2Br$	2224 (-C≡N), 3463 (-NH_2)	-	42.14 (42.35)	2.69 (2.75)	10.96 (10.98)
6	76.66	144-145	$C_{11}H_{10}O_3NBr$	1667 (-CO), 3330, 3496 (-NH_2)	q, 4.5 and t, 1.4 (-CH_2, CH_3); s, 7.5 (-NH_2); m, 7-8 (Ar-H)	46.28 (46.48)	3.45 (3.52)	4.90 (4.93)
7	81.50	220-222	$C_9H_7O_2N_2Br$	1679 (-CO), 3457, 3476 (-NH_2)	s, 6.0 (-$CONH_2$); s, 8.1 (NH_2); m, 7.2-7.9 (Ar-H)	42.11 (42.35)	2.69 (2.75)	10.94 (10.98)
8	86.27	215-216	$C_9H_8O_2NBr$	1638 (-CO), 3456, 3327 (-NH_2)	s, 2.7 (-CH_3); s, 7.5 (NH_2); m, 6.5-7.5 (Ar-H)	47.31 (47.24)	3.18 (3.15)	5.77 (5.79)
9	78.95	180-182	$C_{15}H_{10}O_2NBr$	1618 (-CO), 3422 (-NH_2)	s, 7.3 (NH_2); m, 7.5-8.4 (Ar-H)	56.85 (56.96)	3.12 (3.16)	4.40 (4.43)
10	68.82	275 (d)	$C_{16}H_{12}O_5N_5Br$	3430 (-NH_2)	-	44.22 (44.24)	2.67 (2.76)	16.18 (16.13)
11	62.91	>300	$C_{21}H_{14}O_5N_5Br$	-	-	50.73 (50.81)	2.77 (2.82)	14.16 (14.11)
12	79.46	221	$C_{13}H_{12}O_4NBr$	1680 (-CO), 3430, 3321 (-NH_2)	s, 1.3 (CH_3); q, 4.5 and t, 2.2 (-CH_2, CH_3); s, 7.8 (-NH_2); m, 7.1-8.2(Ar-H)	47.78 (47.85)	3.56 (3.68)	4.34 (4.29)
13	82.19	268	$C_{11}H_9O_3N_2Br$	-	-	44.37 (44.44)	2.98 (3.03)	9.36 (9.43)

reduced pressure gave ethyl 4-bromo-2-cyanophenoxy acetate **(4)** and 4-bromo-2-cyanophenoxyacetamide **(5)** respectively.

4. 4-bromo-3-amino-2-benzofurancarboxylate (6)

Cyclisation of 5-bromo-2-cyanophenoxyacetate **(4)** was carried out with anhydrous dimethyl formamide in the presence of anhydrous potassium carbonate gave ethyl 5-bromo-3-amino-2-benzofurancarboxylate **(6)**.

5. 5-bromo-3-amino-2-benzofurancarboxamide (7)

5-bromo-2-cyanophenoxyacetamide **(5)** underwent cyclisation with potassium hydroxide in alcohol to give 5-bromo-3-amino-2-benzofurancarboxamide **(7)**.

6. 5-bromo-3-amino-2-acetylbenzofuran (8) and 5-bromo-3-amino-2-benzoylbenzofuran (9) (General procedure)

A mixture of 5-bromosalicylonitrile (0.01 mol) anhydrous acetone and chlororacetone/phenacylbromide and anhydrous potassium carbonate. The reaction mixture was heated at reflux temperature for 8-10 hours. The product was isolated and identified as 5-bromo-3-amino-2-acetylbenzofuran **(8)** and 5-bromo-3-amino-2-benzoylbenzofuran **(9)**.

7. Ethyl 3-acetamido-5-bromobenzofuran-2-carboxylate (12)

A mixture of ethyl -3-amino-5-bromo-2-benzofuran carboxylate (0.004 mole) and acetic anhydride (4 ml) was warmed on a water bath for 30 min. The reaction product on decomposition with ice cold water furnished a colourless solid **(12)**.

8. 3-acetamido-5-bromobenzofuran-2-carboxamide (13)

A mixture of 3-amino-5-bromo-2-benzofuran carboxamide (0.029 mole) was warmed with acetic anhydride on a water bath for 15 min and then poured into ice cold water. The colourless solid **(13)** was collected.

Physical constant, percentage yield, elemental analysis and spectral data are presented in TABLE 1.

RESULT AND DISCUSSION

The structures of the synthesized compounds **(1-13)** were confirmed by their IR, ^{1}H NMR, and Mass spectral data. The IR spectrum of 3 displayed an absorption band at 2236 cm^{-1} for CN and 3249 cm^{-1} for OH functional groups of 5-bromosalicylonitrile which confirms aldehydes (-CHO) function is transformed nitrile (-CN) function. The characteristic signals of a hydroxyl (-OH) proton in salicylonitrile confirm the presence of singlet at 6.4 δ and multiplet at δ 7-8 ppm for three aromatic protons. Also, its mass spectrum revealed a molecular ion peak at m/Z 198 (M^+) corresponding to the molecular formula C_7H_4ONBr. The elemental

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TABLE 2: Antibacterial activity results of synthesized compounds

Compd. no.	Dose concentration (μg/ml)	Antibacterial activity Zone of inhibition in mm		
		E-coli	*P.aeruginosa*	*S.aureus*
3	1000	17	18	16
4	1000	14	20	18
5	1000	14	19	15
6	1000	17	18	16
7	1000	15	16	19
8	1000	16	21	18
9	1000	16	21	17
10	1000	17	17	17
11	1000	15	18	15
12	1000	19	22	19
13	1000	18	23	20
Ciprofloxacin	1000	20	24	22
Control(DMF)	-	Nil	Nil	Nil

Control : DMF; Size of borer = 6 mm; Standard : Ciprofloxacin

TABLE 3: Antifungal activity results of synthesized compounds

Compd. no.	Dose concentration (μg/ml)	Antifungal activity Zone of inhibition in mm		
		A.niger	*A.flavus*	*A.terrus*
3	1000	18	25	15
4	1000	21	26	17
5	1000	20	31	18
6	1000	19	24	12
7	1000	18	19	15
8	1000	16	26	13
9	1000	19	22	16
10	1000	17	18	17
11	1000	17	27	14
12	1000	21	20	16
13	1000	19	28	15
Fluconazole	1000	22	30	18
Control(DMF)	-	Nil	Nil	Nil

Control : DMF; Size of borer = 6 mm; Standard : Fluconazole

analysis of **(3)** shows C- 42.42% (found), (calculated 42.42%), H-2.05% (found), (calculated 2.02%) and N-7.24% (found), (calculated 7.07%) and these values confirm to the molecular formula C_7H_4ONBr, 5-bromosalicylonitrile **(3)**. The condensation of 5-bromo salicylonitrile **(3)** with ethyl chloroacetate/chloroaceta mide in anhydrous potassium carbonate and dry acetone furnished ethyl-4-bromo-2-cyanophenoxy acetate/4-bromo-2-cyanophenaoxy acetamide in good yields **(4-5)**. The structure of **(4)** was confirmed by IR, NMR and mass spectral analysis. The IR spectrum of compound **(4)** exhibit a sharp absorption peak at 2236 and 1710 cm^{-1} for –CN function and phenoxyacetate carbonyl function respectively. The disappearance of absorption of 3249 cm^{-1} for OH confirms the conversion of **(3)** into **(4)**. The structure of compound **5** was also confirmed by IR, NMR and mass spectral analysis. The IR spectrum of compound **(6)** exhibited a strong absorption band at 1710 and 3330 cm^{-1} due to presence of the ester carbonyl and amine function respectively. The ^1H NMR characteristic signals of an ester moiety confirm the presence of ester group in the structure by resonating as quartet and triplet for CH_2 and CH_3 at δ 4.5 and δ1.4 ppm respectively and one singlet at δ 7.5 ppm for $–NH_2$ group present in the structure. The aromatic protons resonate as multiplet at δ 7-8 ppm. Also its mass spectra revealed a molecular ion peak at 285 (M^+) corresponding to the molecular formula $C_{11}H_{10}O_3NBr$ **(6)**. The IR spectrum of compound **(7)** showed a 1667, 3330 and 3496 cm^{-1} for amide carbonyl and amine peaks respectively and absence of 2236 cm^{-1} in IR spectra confirmed that **(5)** is cyclised and formed 5-bromo-3-amino-2-benzofurancar boxamide **(7)**. The ^1H NMR and mass spectral data are in conformation with assigned structure of compound **(7)**. The compound **(8)** and **(9)** were confirmed by spectral data. The IR spectrum of compound **(8)** showed 1638 cm^{-1}, 3456 and 3327 cm^{-1} due to presence of one acetyl carbonyl and amine functions present in the structure. The ^1H NMR spectra of compound **(8)** showed a singlet at δ 2.7 ppm corresponds to the presence three protons of acetyl group and one singlet at δ 7.5 ppm for $-NH_2$ group present in the structure and a multiplet at δ 7-8 ppm.

Evaluation of antimicrobial activity

Antibacterial and antifungal activity

The *in vitro* antimicrobial activity was carried out against 24 hr old cultures of three bacteria and three fungi by cup-plate method[15]. Compounds **(3-13)** has been tested for their antimicrobial activity against *E.coli, P.aeruginosa* and *S.aureus* and antifungal activity against *A.niger, A.flavus* and *A.terrus* at a concentration of 1000 μg/ml in distilled DMF using cup plate diffusion method. Nutrient agar and potato dextrose agars were used to culture the bacteria and fungus respectively. The solution of Gentamycin 1000 μg/ml and Fluconazole 1000 μg/ml were prepared in sterilized water and used as standards for comparison of antibacterial and antifungal activities respectively the results were discussed in TABLES 2 and 3.

The compounds **(12)** and **(13)** exhibiting good activity against *E.coli* and compounds **(4, 8, 9, 12** and **13)** showing good activity against *P.aeruginosa*, and

TABLE 4: Results of anti-inflammatory activities of synthesized compounds

Compound	No. of animals	Dose (mg/kg)	Paw oedema percent protection (h)± S.E.			
			1/2hr	1 hr	2 hr	4 hr
Control	06	1 ml (1 %,)	0.185(±0.08)	0.301(±0.01)	0.452(±0.02)	0.465(±0.40)
Standard (Dichlofenac sodium)	06	25	44.5**(±0.08)	47.43**(±0.09)	74.71**(±0.04)	63.51**(±0.01)
3	06	25	7.75(±0.07)	7.42(±0.02)	24.14*(±0.01)	15.06(±0.08)
4	06	25	8.24(±0.01)	8.58(±0.07)	42.67**(±0.07)	32.42*(±0.09)
5	06	25	14.81(±0.08)	33.22**(±0.05)	63.19**(±0.05)	51.31**(±0.01)
6	06	25	14.22(±0.05)	17.79(±0.05)	24.30*(±0.02)	27.11*(±0.05)
7	06	25	17.93(*±0.01)	34.23**(±0.03)	66.11**(±0.07)	50.63**(±0.01)
8	06	25	35.12*(±0.02)	38.23**(±0.01)	71.13**(±0.04)	51.13**(±0.19)
9	06	25	5.41(±0.07)	15.11(±0.05)	22.13*(±0.20)	6.21(±0.08)
10	06	25	10.11(±0.06)	20.34*(±0.01)	24.00*(±0.02)	12.44(±0.01)
11	06	25	23.04*(±0.01)	41.41**(±0.02)	63.03**(±0.04)	44.33**(±0.02)
12	06	25	8.48(±0.05)	25.21*(±0.05)	34.70*(±0.01)	13.32(±0.04)
13	06	25	16.4(±0.04)	34.41**(±0.06)	55.47**(±0.07)	41.08**(±0.01)

compounds **(7, 12** and **13)** showing good activity against *S.aureus*. All remaining compounds exhibited moderate activity against all the organisms used for screening.

In anti-fungal activity the compounds **(4, 5** and **12** exhibited excellent activity against *A.niger* and compounds **(3, 4, 8, 11** and **13)** exhibiting good activity against *A.flavus* and compounds **(4, 5** and **10)** showed a good activity against *A.terrus* and all remaining compounds exhibiting moderate activity against all the three organisms used for screening.

Anti-inflammatory activity

Anti-inflammatory activity was evaluated by carrageenan paw oedema test in rats[16]. Acute inflammation was produced by sub plantar injection of 0.1 ml of 1% suspension of carrageenan in 1% Tween-80, in the right hind of the rats. Diclofenac sodium 25 mg/kg, b.w. suspended in 1% Tween-80 was used as the standard drug for comparison and test compounds having dose level of 25 mg/kg, b.w. suspended in 1% Tween-80 were administered orally. The paw volume was measured using the mercury displacement technique with the help of plethysmograph (Ugo Basile, Italy) immediately before and 0.5, 1.0, 2.0 and 4.0 hr after the carrageenan injection. The are summarized in TABLE 4.

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