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Synthesis, Characterization, Biological Screening of 5-Bromo-Benzofuranyl Aryl Ureas and Carbamates

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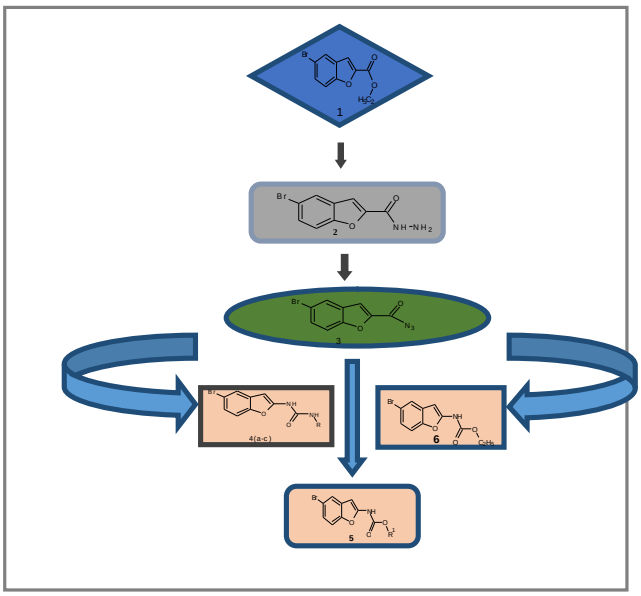
ABSTRACT

The present work is carried to construct biologically important 5-Bromo- benzofuran aryl ureas. The benzofuran ring was constructed by reacting bromosalicylaldehyde with diethyl bromomalonate in the presence of dry acetone and anhydrous potassium carbonate to obtain 5-Bromo-benzofuran-2-ethyl carboxylate ***(1)****. The obtained ester* ***(1)*** *was converted into corresponding hydrazide* ***(2)*** *by treating with hydrazine hydrate. The compound (2) which was then converted into 5-Bromo- benzofuran-2-carbonyl azide* ***(3)*** *by treating it with sodium nitrite in dioxan and acetic acid, the compound* ***(3)*** *was converted into5-bromobenzofuranyl aryl ureas* ***(4a-e)*** *after treating it with primary amines and anhydrous toluene. 5-Bromobenzofuranyl aryl carbamate* ***(5)*** *and ethyl carbamate* ***(6)*** *were also synthesized by treating compound* ***(3)*** *with phenol in toluene and ethanol respectively. All the compounds synthesized were in agreement with the assigned structure which was supported by spectral and analytical data. All the compounds synthesized were screened for their antibacterial, antifungal and calf thymus DNA cleavage activities. Some of the compounds have exhibited moderate to appreciable biological activity.*

Graphical Abstract



Keywords: Benzofuran,hydrazide, Carbonyl azide, Aaryl ureas, Carbamate, Antibacterial activity.

INTRODUCTION

The heterocyclic compounds containing furan nucleus were widely distributed in nature majorly in plants kingdom. In the recent days they are found to have an attractive wide spectrum of biological activity. Many compounds have been reported to possess very interesting pharmacological and physiological properties [**1-5**]. However, the number of synthetic benzofuran derivatives have been synthesized and found to possess biological activities such as antiviral, antimicrobial, analgesic and anti-inflammatory.

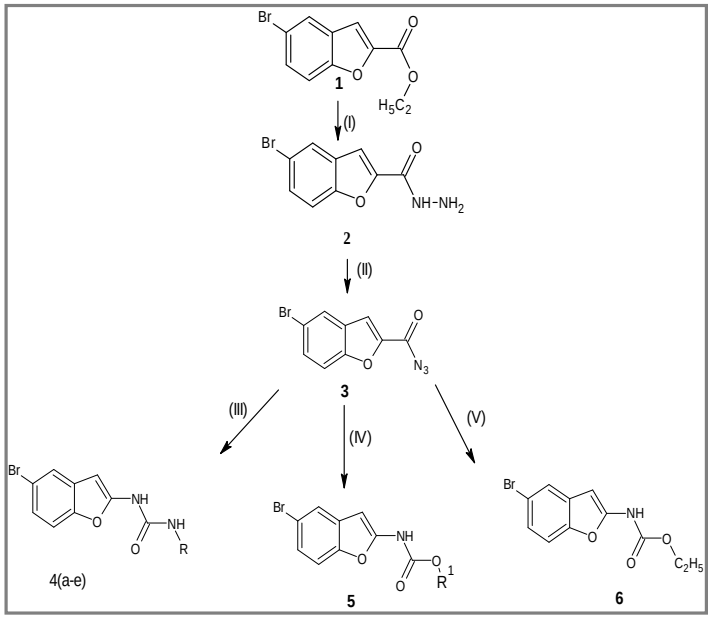
Alkaloids containing benzofuran moiety have acquired a most prominent place in medicinal chemistry, Morphine is an good example which was used as an analgesic, contains dihydrobenzofuran nucleus condensed with nitrogen heterocycles. The presence of furan ring has been proved to be an essential part of the molecule for its pharmacological properties [**6-7**]. Benzofuranyl ureas have been found to have inhibition of 5-lipoxygenase, blocking the metabolism of arachidonic acid to leukotrienes and hydroxyeicasatetrenoic acids. Standard development toxicity studies were conducted in rats with some benzofuranyl substituted ureas, these compounds were observed to be potent development toxicants producing embryo-fetal lethality, fetal growth, retardation and malformations [**8-10**].

The carbamate group is a key structural motif in many approved drugs and prodrugs. There is an increasing use of carbamates in medicinal chemistry and many derivatives are specifically designed to make drug target interactions. Organic carbamates are a stable class of compounds which are derived from unstable carbamic acid(NH_2-COOH) by substitution of the amino and carboxyl moieties with various kinds of structurally diverse alkyl/aryl groups and are identified by the presence of the linkage -O-CO-NH-. In recent years, several reports have indicated that the carbamate linkage present in the active pharmacophores of various structurally diverse molecules increases the biological activities of semi-synthetic/synthetic/natural molecules against various diseases, such as anticancer, antibacterial, antifungal, antimalarial, anti-HIV, anti-tubercular, anti-diabetic,anti-obesity, anti-Alzheimerdrugs [**11-13**]. Some of the recent molecules in which the extensive role of incorporation of carbamates have been studied are discodermia, cholesterol etc. Several kinds of other structurally divers natural/ synthetic molecules have also been reported in the recent years where in carbamates play crucial role in improving the biological activity than the parent molecules [**14-15**]. In continuation of our search for pharmaceutically active benzofuran compounds [**16**], we now report the synthesis and screening of 5-Bromo benzofuranyl carbamides and carbamates.

MATERIALS AND METHODS

All reagents and solvents used were of analytical grade.^{1}H NMR (400MHZ) were obtained by Bruker spectrometer in the appropriate ($CDCl_3$) solvent. IR spectra were recorded on Perkin Elmer spectrum two spectrometer (4000-400 cm^{-1}) instruments. Melting points were determined in open capillary tubes and are uncorrected.

5-Bromo benzofuran-2-carboxylic acid ethyl ester (1): A solution of 5-Bromo-salicylaldehyde (0.01 mol) and diethyl bromomalonate (0.013 mol) in acetone (40 mL) was treated with anhydrous potassium carbonate (10 g). The reaction mixture was refluxed for 10 h on steam bath, solvent was distilled off under reduced pressure and the residual salts were dissolved in about 200 mL of ice water and carefully acidified with dil.HCl. The obtained product recrystallized from ethanol (melting point and % yields are given in table 1).



Conditions; (i)$N_2H_4.H_2O/C_2H_5OH$; (ii)$NaNO_2$/Dioxan/Acetic acid;(iii)RNH_2/Anhy. Toluene;(iv)Ar-OH/Anhy.Toluene;(V)Absolute C_2H_5OH;
R: a=C_6H_5**b**=$C_6H_4CH_3$(o),**c**=C_6H_4Cl(m),**d**=C_6H_4Cl(o),**e**=$C_6H_4NO_2$(o);$\mathbf{R^1}$=$C_6H_4CH_3$(P).

Scheme 1. Synthesis of benzofuranyl carbamides and carbamates.

5-Bromo benzofuran-2-carboxylic acid hydrazide (2): To a solution of 5-Bromo benzofuran-2-carboxylic acid ethyl ester**1** (0.01 mol) in ethanol (30 mL), hydrazine hydrate (99%, 5 mL) was added and the mixture was heated under reflux for 4 h on the water bath. The excess of ethanol was removed under the reduced pressure and then diluted with water. The separated carbohydrazide was collected and recrystallized from ethanol as colorless needles (melting point and % yields are given in table 1).

5-Bromo benzofuran-2-carbonyl azide (3): 5-Bromo benzofuran-2-carboxylic acid hydrazide **2** (10g, 0.048 mol) was treated with a mixture of dioxin (60 mL) and acetic acid (60 mL) cooled to 0°C in a freezing mixture. An ice-cold solution of sodium nitrite (5.2g in 20 mL) was introduced in small portion with vigorous stirring. The temperature of the reaction mixture was maintained below 2°C after the complete addition, the reaction mixture was allowed to stand at room temperature for 30 min and the pale-yellow solid that separated was collected, washed with cold water. The product was dried over phosphorous pentoxide in vacuum (not crystallized due to the decomposition of azides).

1-(5-Bromo benzofuran-2-yl)-3-aryl-ureas4 (a-e): A mixture of azide **3** (0.001 mol) and appropriate amine (0.001 mol) in anhydrous toluene (15 mL) was heated under reflux (120°C) in an oil bath for 5 h. The crystalline products **4**, thus separated out from the reaction mixture were collected washed with toluene and petroleum ether. The analytical sample was obtained by crystallization from suitable solvent (melting point and % yields are given in table 1).

(5-Bromo benzofuran-2-yl)-carbamic acid aryl ester (5): An azide **3** (0.001 mol) was suspended in anhydrous toluene (30 mL) and heated in an oil bath at 70-80°C till the evolution of nitrogen gas stopped (~1 h). The appropriate phenol (0.01 mol) in toluene (10 mL) was added and the reaction mixture was heated at 110-120°C for 3 h. After the removal of toluene under reduced pressure, the residue was dissolved in ether; the ethereal solution was washed with 10% aqueous solution of sodium hydroxide to remove any unreacted phenol and with water. The organic layer was dried over anhydrous calcium chloride. The removal of solvent furnished a resinous mass which was solidified on cooling. Further purification was achieved by crystallization from suitable solvent (melting point and % yields are given in table 1).

(5-Bromo benzofuran-2-yl)-carbamic acid ethyl ester (6): A suspension of azide 3(0.01) in absolute ethanol (10 mL) was refluxed on steam bath for 3 h. The reaction mixture was concentrated under reduced pressure and then diluted with water. The product that separated was collected and crystallized from mixture of benzene and petroleum ether (melting point and % yields are given in table 1).

.**Table 1.** Physical data of compounds

Compounds	Yield %	MP°C	MF
1	75	68	$C_{11}H_9BrO_3$
2	90	210	$C_9H_6BrN_2O_2$
3	92	120	$C_9H_4BrN_3O_2$
4a	80	180	$C_{15}H_{11}BrN_2O_2$
4b	78	190	$C_{16}H_{13}BrN_2O_2$
4c	75	165	$C_{15}H_{10}BrClN_2O_2$
4d	80	210	$C_{15}H_{10}BrClN_2O_2$
4e	90	200	$C_{15}H_{10}BrN_3O_4$
5	80	220	$C_{16}H_{12}BrNO3$
6	76	212	$C_{11}H_{10}BrNO_3$

RESULTS AND DISCUSSION

5-Bromobenzofuran-2-carboxylic acid ethyl ester (1): IR(KBr);vcm^{-}1;1728 (-CO),1H-NMR(400 MHz, DMSO-d6): δ 1.34 (s, 3H), 4.37 (q, J = 6.80 Hz, 2H), 7.66-7.68 (m, 3H), 8.03 (s,1H), .MS m/z;270.

5-Bromobenzofuran-2-carboxylic acid hydrazide (2):IR(KBr);vcm^{-}1; 3402($NHNH_2$),1H-NMR (400 MHz, DMSO-d6): δ 4.60 (s, 2H), 7.49 (s, 1H), 7.57 (d, J = 2.00 Hz, 2H), 7.59 (d, J = 1.60 Hz, 1H), 7.63 (s, 1H), 7.65 (s, 1H), 8.00 (d, J = 1.60 Hz, 1H), 10.11 (s, 1H), .MS m/z;256.

5-Bromobenzofuran-2-carbonyl azide (3): IR(KBr);vcm^{-1};2144 (-CON_3) 1H-NMR(400 MHz, DMSO-d6): δ 7.26 (s, 3H), 7.47 (d, J = Hz, 3H), 7.49 (d, J = Hz, 3H), 7.53 (d, J = Hz, 3H), 7.53 (d, J = Hz, 3H), 7.58 (q, J = Hz, 2H), 7.58 (q, J = Hz, 2H), 7.59 (q, J = Hz, 2H), 7.60 (q, J = Hz, 2H), 7.85 (d, J = Hz, 1H), 7.85 (d, J = Hz, 1H).

1-(5-Bromobenzofuran-2-yl)-3-Phenyl-urea 4(a): IR(KBr);vcm^{-1};3550(-NH) 1H-NMR(400 MHz, DMSO-d6): δ 6.95 (s, 1H), 6.96 (s, 1H), 6.98 (s, 1H), 7.47 (s, 2H), 7.28 (s, 2H), 7.30 (s, 2H), 7.44 (s, 2H), 7.45 (s, 2H), 8.64 (s, 1H).

1-(5-Bromobenzofuran-2-yl)-2-methyl phenyl urea 4(b): IR(KBr);vcm^{-1};3400(-NH); 1H-NMR(400 MHz, DMSO-d6): δ 2.19 (s, 3H), 6.15 (s, 1H), 7.12 (s, 1H), 7.13 (s, 1H), 7.15 (s, 1H), 7.21 (s, 2H), 7.23 (s, 2H), 7.25 (s, 2H), 7.26 (s, 2H), 7.61 (s, 1H), 7.62 (s, 1H), 9.55 (s, 1H), 10.25 (s, 1H).

1-(5-Bromobenzofuran-2-yl)- 3-chloro phenyl urea 4(c): IR(KBr);vcm^{-1};3350(-NH); 1H-NMR(400 MHz, DMSO-d6): δ 2.19 (s, 3H), 6.15 (s, 1H), 7.33 (s, 1H), 7.34 (s, 1H), 7.44 (s, 1H), 7.44 (s, 2H), 7.53 (s, 2H), 7.25 (s, 2H), 7.26 (s, 2H), 7.61 (s, 1H), 7.62 (s, 1H), 8.72 (s, 1H).

1-(5-Bromobenzofuran-2-yl)-3-2-chloro phenyl urea 4(d): IR(KBr);vcm^{-1};3360(-NH);1H-NMR(400 MHz, DMSO-d6): δ 7.02 (s, 1H), 7.04 (s, 1H), 7.06 (s, 1H), 7.08 (s, 1H), 7.28 (s, 1H), 7.30 (s, 1H), 7.32 (s, 1H), 7.46 (s, 1H), 7.48 (s, 1H), 8.06 (s, 1H), 8.08 (s, 1H), 9.03 (s, 1H).

1-(5-Bromobenzofuran-2-yl)-3-2-nitro phenyl urea 4(e): IR(KBr);vcm^{-1};3200(-NH); 1H-NMR(400 MHz, DMSO-d6): δ 6.51 (s, 1H), 7.26 (t, J = 7.60 Hz, 2H), 7.43 (d, J = 0.40 Hz, 1H), 7.68 (d, J = 1.20 Hz, 2H), 7.72 (s, H), 7.73 (s, 1H), 7.75 (s, 2H), 8.11 (s, 1H), 8.13 (s, 1H), 8.29 (s, 1H), 8.32 (s, 1H).

(5-Bromobenzofuran-2-yl)-carbamic acid 4-methyl phenyl urea ester (5): IR(KBr);vcm-1;3224; (-NH),1H-NMR (400 MHz, DMSO-d6): δ 2.56 (s, 3H), 5.24 (s, 1H), 7.25 (s, 2H), 7.34 (s, 4H), 7.36 (s, 4H), 7.38 (d, J = Hz, 1H), 7.39 (d, J = Hz, 1H).

(5-Bromobenzofuran-2-yl)-carbamic acid ethyl ester (6): IR(KBr);vcm^{-1};3400; 1H-NMR(400 MHz, DMSO-d6): δ 2.56 (s, 3H), 5.24 (s, 1H), 1.24 (t, J = Hz, 3H), 1.26 (t, J = Hz, 3H), 1.27 (t, J = Hz, 3H), 4.16 (q, J = Hz, 2H), 4.18 (q, J = Hz, 2H), 4.20 (q, J = Hz, 2H), 4.22 (q, J = Hz, 2H), 6.41 (s, 1H), 6.76 (d, J = Hz, 1H), 6.78 (d, J = Hz, 1H), 7.25 (d, J = Hz, 2H), 7.25 (d, J = Hz, 2H), 7.27 (d, J = Hz, 2H), 7.27 (d, J = Hz, 2H), 7.39 (d, J = Hz, 1H), 7.41 (d, J = Hz, 1H), 7.67 (d, J = Hz, 1H), 7.68 (d, J = Hz, 1H).

DNA cleavage analysis: Further the compounds 3b, 3c and 3d are screened for calf thymus DNA cleavage test, the compounds were added separately to the DNA sample. The sample mixtures were incubated at 37°C for 2 h the report has been showing all three samples have cleaved DNA (50 µg $test^{-1}$) completely at two different concentrations that are 100 µg $test^{-1}$ and 200 µg $test^{-1}$ with reference to the M- DNA ladder as shown in figure 1.

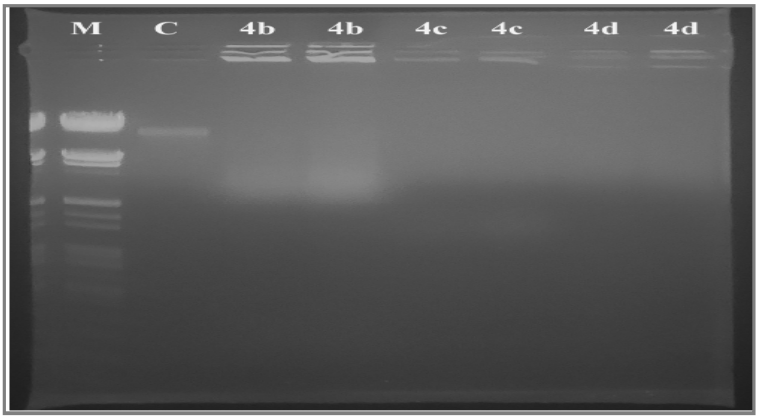


Figure 1. Gel picture showing the DNA cleavage analysis of samples.

APPLICATION

The physical data of 8 new compounds were interpreted in table 1 and their structures were supported by the spectral data, the entire reactions path is given in scheme 1, firstly 5-Bromobenzofuran-2-carbonyl azide **(3)** obtained from carbohydrazide (2) gave azide peak at $2144cm^{-1}$, further the formation aryl ureas **(4a-e)** are confirmed by the IR peaks observed between 3200-3550 cm^{-1} due to NH group and disappearance of azide peak at 2144 cm^{-1}, ^1H NMR of these compound exhibited the NH peak at 7.62-9.79 ppm. Appearance of absorption peak at 3224 cm^{-1} and 3400 cm^{-1} indicates the presence NH in aryl carbamates **(5)**. ^1H NMR spectrum of **(6)** was observed at 11.2 due to NH proton and two peaks at 1.23 and 4.19 ppm indicates the presence of ethyl protons in compound (5-Bromo-benzofuran-2-yl)-carbamic acid ethyl ester **(6)**.

The newly synthesized compounds also screened for their *in vitro* antibacterial activity against the bacteria *S. aureus, E. coli, P. aeuroginosa by* cup plate method in 50 µg mL^{-1} (Table 2). The compound **6,** showing good antibacterial activity among all the compounds against *S. aureus* and the compounds **3** and **4a** are showing better antibacterial activity against *E. coli* in DMF. Against *P. aeruginosa*, compounds **4b** and **6** are showing considerably good activity with reference to the standard drug Penicillin and Streptomycin in 50 µg mL^{-1}. Further all compounds are screened for antibacterial activity in 100 µg mL^{-1} (Table-2) the compound **6**, against *S. aureus* **3** and **4a**, against *E.*

coli, and **4b, 6** against *P. aeruginosa are* showing good activity compared to other compounds with respect to standard drug.

Antifungal activities of all the compounds were also screened against *Aspergillus niger and candida albicans* by cup plate method in 50 µg mL^{-1} (Table-3). Among all **4a,** against *candida albicansans*, compounds **4b, 4c** and **6** against *Aspergillus niger* shows better results comparatively. The compounds **4a**, against *candida albicansans* and the compounds **4b, 4c, 6** against *Aspergillus niger* exhibited good activity in 100 µg mL^{-1} (Table 3) with respective to all compounds with reference to standard drug Griseofulvin.

Table 2. Antibacterial activity (50 and 100µgmL^{-1})

Compound No.	Zone of Inhibition(in mm)					
	S. aureus		*E. coli*		*P. aureginosa*	
	50 µg mL^{-1}	100 µg mL^{-1}	50 µg mL^{-1}	100 µg mL^{-1}	50 µg mL^{-1}	100 µg mL^{-1}
1	12	15	13	16	14	17
2	14	17	14	18	13	18
3	13	18	14	19	12	19
4a	12	18	14	19	15	19
4b	11	18	13	18	16	20
4c	12	16	10	14	11	18
4d	12	18	11	16	13	19
4e	13	18	12	16	13	19
5	12	16	13	18	11	14
6	13	19	12	18	15	20
Standard Pencillin	15	22	--	--	--	--
Streptomycin	--	--	21	28	22	27
Control D.M.F.	Nil	Nil	Nil	Nil	Nil	Nil

Table 3. Antifungal activity (50 and 100µgmL^{-1})

Compound No.	Zone of inhibition (in mm)			
	Aspergillus niger		*candida albicans*	
	50 µg mL^{-1}	100 µg mL^{-1}	50 µg mL^{-1}	100 µg mL^{-1}
1	09	14	10	15
2	12	15	10	14
3	10	15	12	17
4a	12	17	11	19
4b	13	18	14	17
4c	12	18	13	17
4d	13	17	12	18
4e	12	16	11	15
5	14	17	11	17
6	12	18	13	18
Standard Griseofulvin	23	27	23	28
Control D.M.F.	Nil	Nil	Nil	Nil

CONCLUSION

All newly synthesized compounds were confirmed by IR and ^{1}HNMR spectral data and they are showing considerably good antibacterial and antifungal activity with reference to the standard drugs. Further the compounds 4a, 4b and 4d cleaved DNA of calf thymus at two different concentrations.

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