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Synthesis, Characterization, Antimicrobial Screening of 5-Bromobenzofuranyl Aryl Ureas and Carbamates

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ABSTRACT

Present work reports the biologically important benzofuran aryl ureas and carbamates. The benzofuran ring was formed by reacting bromo salicylaldehyde with diethyl bromomalonate in presence of dry acetone and anhydrous potassium carbonate to obtain 5-bromo-2-ethyl carboxylate **(1)**. The obtained ester **(1)** was converted into corresponding hydrazide **(2)** by treating with hydrazine hydrate in ethanol. Compound **2** was then converted into 5-bromobenzofuran-2-carbonyl azide **(3)** by treating it with sodium nitrite in dioxane and acetic acid. The compound **3** is converted into 5-bromobenzofuranyl aryl ureas **(4a-e)** after treating primary amines and anhydrous toluene. 5-Bromobenzofuranyl aryl carbamate **(5)** and ethyl carbamate **(6)** were also synthesized by treating compound **3** with substituted phenol in toluene and ethanol respectively. All the compounds were characterized by NMR, IR and screened for antimicrobial activities.

KEYWORDS

Benzofuran, Hydrazide, Carbonyl azide, Aryl ureas, Carbamates, Antimicrobial activity.

INTRODUCTION

The heterocyclic compounds containing furan nucleus were widely distributed in nature majorly in plants kingdom. In recent days, they are found to have an attractive wide spectrum of biological activities. Many compounds have been reported to posses interesting pharmacological and physiological properties [1-4]. However the number of synthetic benzofuran derivatives have been synthesized and found to posses biological activities such as antiviral, antimicrobial, analgesic and anti-inflammatory activities [5,6].

Alkaloids containing benzofuran moiety have acquired a most prominent place in medicinal chemistry, *e.g.*, morphine is a 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 [7-10]. 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 bezofuranyl substituted ureas. These compounds were observed

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to be potent development toxicants producing embryo-fetal lethality, fetal growth, retardation and malformations [11].

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, antitubercular, antidiabetic, antiobesity, antialzheimer drugs. Some of the recent molecules in which the extensive role of incorporation of carbamates have been studied are discodermolide, 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 [12,13]. In continuation of our research for pharmaceutically active benzofuran compounds [14], we now report the synthesis and screening of 5-bromobenzofuranyl ureas and carbamates.

EXPERIMENTAL

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

General procedure

5-Bromobenzofuran-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 acidified with dil. HCl. The product obtained was recrystallized from ethanol.

5-Bromobenzofuran-2-carboxylic acid hydrazide (2): To a solution of 5-bromobenzofuran-2-carboxylic acid ethylester (**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 colourless needles.

5-Bromobenzofuran-2-carbonyl azide (3): 5-Bromobenzofuran-2-carboxylic acid hydrazide (**2**) (10 g, 0.048 mol) was treated with a mixture of dioxan (60 mL) and acetic acid (60 mL) cooled to 0 °C in a freezing mixture. An ice cold solution of sodium nitrite (5.2 g 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-Bromobenzofuran-2-yl)-3-aryl-ureas 4(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 products **4**, thus separated from the reaction mixture was collected, washed with toluene and petroleum ether. The pure sample was obtained by crystallization from suitable solvent.

(5-Bromobenzofuran-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 (about 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.

(5-Bromobenzofuran-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.

Detection method: The structures of newly synthesized compounds (**3**, **4a-e**, **5** and **6**) were detected by IR and ^{1}H NMR spectra.

5-Bromobenzofuran-2-carboxylic acid ethyl ester (1): Yield: 75 %, m.p.: 68 °C, m.f.: $C_{11}H_9O_3Br$. IR (KBr, ν_{max}, cm^{-1}): 1728 (-CO), ^{1}H NMR (400 MHz, DMSO-d_6): 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): Yield: 90 %, m.p.: 210 °C, m.f.: $C_9H_6N_2O_2Br$. IR (KBr, ν_{max}, cm^{-1}): 3402 ($NHNH_2$), ^{1}H NMR (400 MHz, DMSO-d_6): 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): Yield: 92 %, m.p.: 120 °C, m.f.: $C_9H_4N_3O_2Br$. IR (KBr, ν_{max}, cm^{-1}): 2144 (-CON_3) ^{1}H NMR (400 MHz, DMSO-d_6): 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-phenylureas (4a): Yield: 80 %, m.p.: 180 °C, m.f.: $C_{15}H_{11}N_2O_2Br$. IR (KBr, ν_{max}, cm^{-1}): 3550 (-NH) ^{1}H NMR (400 MHz, DMSO-d_6): 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)-3-*o*-methylphenylureas (4b): Yield: 78 %, m.p.: 190 °C, m.f.: $C_{16}H_{13}N_2O_2Br$. IR (KBr, ν_{max}, cm^{-1}): 3400 (-NH); ^1H NMR (400 MHz, DMSO-d_6): 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).

1-(5-Bromobenzofuran-2-yl)-3-*m*-chlorophenylureas (4c): Yield: 75 %, m.p.: 165 °C, m.f.: $C_{15}H_{10}N_2O_2BrCl$. IR (KBr, ν_{max}, cm^{-1}): 3350 (-NH); ^1H NMR (400 MHz, DMSO-d_6): 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), 7.73 (s, 1H).

1-(5-Bromobenzofuran-2-yl)-3-*o*-chlorophenylureas (4d): Yield: 80 %, m.p.: 210 °C, m.f.: $C_{15}H_{10}N_2O_2BrCl$. IR (KBr, ν_{max}, cm^{-1}): 3360 (-NH); ^1H NMR (400 MHz, DMSO-d_6): 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-*o*-nitrophenylureas (4e): Yield: 90 %, m.p.: 200 °C, m.f.: $C_{15}H_{10}N_3O_4Br$. IR (KBr, ν_{max}, cm^{-1}): 3200 (-NH); ^1H NMR (400 MHz, DMSO-d_6): 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), 9.79(s, 1H) 11.191(s, 1H).

(5-Bromobenzofuran-2-yl)carbamic acid *p*-methylphenyl ester (5): Yield: 80 %, m.p.: 220 °C, m.f.: $C_{16}H_{12}NO_3Br$. IR (KBr, ν_{max}, cm^{-1}): 3224; (-NH), ^1H NMR (400 MHz, DMSO-d_6): 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): Yield: 76 %, m.p.: 212 °C, m.f.: $C_{11}H_{10}NO_3Br$. IR (KBr, ν_{max}, cm^{-1}): 3400 (-NH); ^1H NMR (400 MHz, DMSO-d_6): 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).

RESULTS AND DISCUSSION

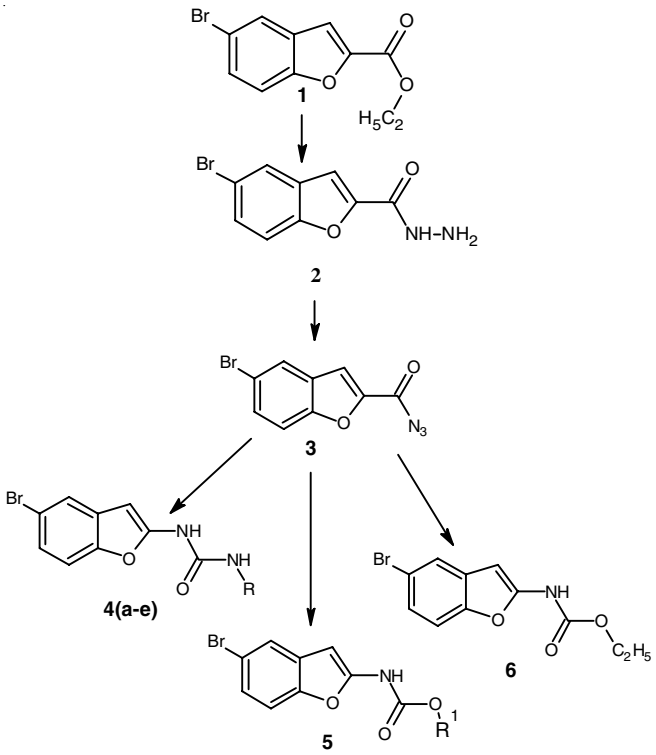
All the eight compounds of 5-bromobenzofuranyl aryl ureas and carbamates were synthesized and the entire reaction path is shown in **Scheme-I**. It is confirmed that in IR analysis that 5-bromobenzofuran-2-carbonyl azide **(3)** obtained from carbohydrazide **(2)** gave azide peak at 2144 cm^{-1}, further the formation aryl ureas **(4a-e)** are confirmed by IR peaks observed between 3550-3200 cm^{-1} region 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 and 3400 cm^{-1} indicates the presence NH in aryl carbamates **(5)**. ^1H NMR spectrum of compound **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-bromobenzofuran-2-yl)-carbamic acid ethyl ester **(6)**.

The newly synthesized compounds also screened for their *in vitro* antibacterial activity against the bacterias *S. aureus, E. coli, P. aureginosa* by cup plate method in 50 µg/mL (Table-1). 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 against *P. aureginosa.* The compounds **4b** and **6** are showing considerably good activity with reference to the standard drug pencillin and streptomycin in 50 µg/mL. Further all compounds are screened for antibacterial activity in 100 µg/mL (Table-1), the compound **6**, against *S. aureus,* **3** and **4a**, against *E. coli* and **4b, 6** against *P. aureginosa* are showing good activity compared to other compounds with respect to standard drug.

Antifungal activity of all the compounds were also screened against *Aspergillus niger* and *Candida albicans* by cup plate method in 50 µg/mL (Table-1). Among all the compound **4a**, against *Candida albicans,* compounds **4b, 4c** and **6** against *Aspergillus niger* shows better results comparatively. The

TABLE-1
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF THE COMPOUNDS **3**, **4a-e**, **5** AND **6** FOR THE CONCENTRATIONS (50 AND 100 µg/mL)

Compounds	Zone of inhibition (mm)									
	Antibacterial activity						Antifungal activity			
	S. aureus		*E. coli*		*P. aureginosa*		*Aspergillus niger*		*Candida albicans*	
	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL
1	12	15	13	16	14	17	09	14	10	15
2	14	17	14	18	13	18	12	15	10	14
3	13	18	14	19	12	19	10	15	12	17
4a	12	18	14	19	15	19	12	17	11	19
4b	11	18	13	18	16	20	13	18	14	17
4c	12	16	10	14	11	18	12	18	13	17
4d	12	18	11	16	13	19	13	17	12	18
4e	13	18	12	16	13	19	12	16	11	15
5	12	16	13	18	11	14	14	17	11	17
6	13	19	12	18	15	20	12	18	13	18
Penicillin	15	22	–	–	–	–	–	–	–	–
Streptomycin	–	–	21	28	22	27	–	–	–	–
Griseofulvin	–	–	–	–	–	–	23	27	23	28
DMF	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil



Scheme-I: Synthetic way for 5-bromobenzofuranyl aryl ureas and carbamates; **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); **R^1:** $C_6H_4CH_3$ (P)

compound **4a**, against *Candida albicans* and the compounds **4b, 4c, 6** against *Aspergillus niger* exhibited good activity in 100 µg/mL (Table-1) with respective to all compounds with reference to standard drug griseofulvin.

Conclusion

All newly synthesized compounds were confirmed by IR and ^{1}H NMR spectral data and they are showing considerably good antibacterial and antifungal activity with reference to the standard drugs.

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