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Synthesis of 1-(5-Substituted Benzofuran-2-yl)-3-Arylurea Derivatives as Antimicrobial Agents

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ABSTRACT

Background: Benzofurans are very interesting heterocycles, which are available in nature and show a wide range of pharmacological activities viz antifungal, antibacterial, antitumor, antimalarial, molluscicidal and antioxidant activity etc. **Methods:** A convenient method for the preparation of 1-(5-substituted benzofuran-2-yl)-3-arylurea derivatives **6a-6r** have been developed. The target compounds 1-(5-nitrobenzofuran-2-yl)-3arylurea **6a-6i** and 1-(5-bromobenzofuran-2-yl)-3arylurea **6j-6r** has been prepared by reacting 5-nitrobenzofuran-2-carbonyl azide **5a** or 5-bromobenzofuran-2-carbonyl azide **5b** with aromatic amines in reasonable overall yields. All the synthesized compounds were characterized using FT-IR, ^{1}H NMR and mass spectrometry and were subjected to antimicrobial screening against two Gram positive bacteria (*Staphylococcus aureus, Bacillus subtilis*) two Gram negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*) and two fungi (*Candida albicans*, *Aspergillus niger*) using two fold dilution method. **Results and discussion:** All the values of FTIR, ^{1}H NMR and mass spectra were found to be prominent. The results indicate that synthesized compound **6d** showed potent antimicrobial activity comparable to standard. **Conclusion:** The detailed synthesis, spectroscopic data and antimicrobial activities of synthesized compounds were reported.

KEYWORDS: Benzofuran, Antibactrial Activity, Antifungal Activity

1. INTRODUCTION

Benzofuran is one of the most important classes of fused ring heterocyclic compounds. The benzofuran derivatives are naturally occurring and possess many biological applications [1–3]. Angelicin, Psoralen and bergapten are the examples of naturally occurring benzofuran derivatives with biological applications [4–6]. The isolation of benzofuran derivatives from natural sources is laborious and time consuming. So the synthetic chemists are interested in synthesizing the benzofuran derivatives. Numerous synthesized benzofuran derivatives were found to be biologically active [7–9]. Now a days many synthetic benzofurans are used as good inhibitor [10,11], antimicrobial [12–14], anti-inflammatory [15,16], antiviral [17], antioxidant [18,19], anti-tumour [20], antiproliferative [21,22] and anti-alzheimer [23].

Fight against the microbes is never ending battle. The harmful microbe's poses biggest problem in the society as far as health and hygiene is concerned. Antimicrobial chemotherapy has been a leading cause for the dramatic rise of average life expectancy in the Twentieth Century. However, disease causing microbes that have become resistant to antibiotic drug therapy are an increasing public health problem. One part of the problem is that bacteria and other microbes that cause infections are remarkably resilient and have developed several ways to resist antibiotics and other antimicrobial drugs. Another part of the problem is due to increasing use, and misuse, of existing antibiotics in human and veterinary medicine and in agriculture. As the resistance to antimicrobial agents increasing day by day, it is very necessary to synthesize new compounds which will show less bacterial resistance and good inhibitory activity. [24]

Hence in this paper, we report the synthesis of benzfuran derivatives and antimicrobial evaluation. All the synthesized compounds were characterized using FT-IR, ^{1}H NMR and mass spectrometry and were subjected to Minimum Inhibitory Concentration (MIC) antimicrobial screening against two Gram positive bacteria (*Staphylococcus aureus, Bacillus subtilis*) two Gram negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*) and two fungi (*Candida albicans*, *Aspergillus niger*) using two fold dilution method.

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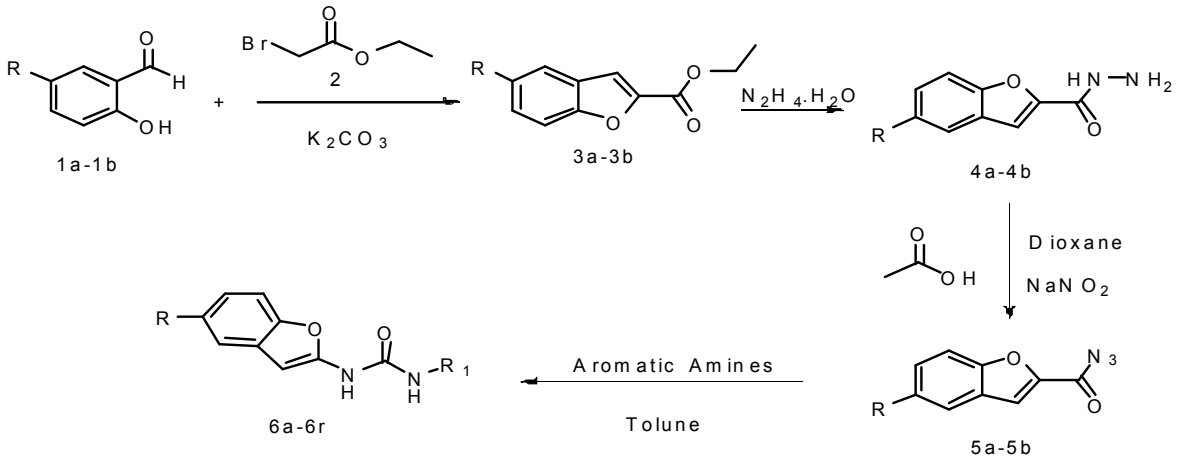
2. MATERIALS AND METHODS

All chemicals were purchased from Sigma Aldrich, SD Fine, Spectrochem, Merck, and Himedia. Yields refer to purified products and are not optimized. Melting points were determined on a VEEGO-VMP I melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO-FTIR 4100 spectrophotometer. ^{1}H NMR were recorded on a MERCURY VARIAN 400 MHz instrument and chemical shifts (δ) were reported in parts per million (ppm) with DMSO as the solvent. Trimethyl silane (TMS) was used as the internal standard for NMR. Mass Spectroscopy (MS) analyses were done on an Applied Biosystem API 2000. Thin layer chromatography (TLC) was performed on precoated aluminium plates with silica gel.

2.1. General method for Synthesis of 5-substituted benzofuran-2-carbonyl azide (5a-5b)

5-substituted benzofuran-2-carbohydrazide **4a-4b** (0.02 mole) was dissolved in a mixture of 30 ml of acetic acid and 30 ml of 1,4 dioxane and cooled to 0°C using ice salt bath. An ice cold solution of Sodium Nitrite (0.02 mole) in water (10 ml) was introduced in small portions with vigourous stirring while temperature of the mixture was maintained below 2°C. After addition was completed the reaction mixture was allowed to stay at room temperature for 30 min and then solid was collected, washed with cold water. Solid was dried in dessicator and used immediately in next reaction. [25]



Compound	R	R1
6a	NO2	
6b	NO2	
6c	NO2	
6d	NO2	
6e	NO2	
6f	NO2	
6g	NO2	
6h	NO2	
6i	NO2	

Compound	R	R1
6j	Br	
6k	Br	
6l	Br	
6m	Br	
6n	Br	
6o	Br	
6p	Br	
6q	Br	
6r	Br	

Scheme-1

***Synthesis of 5-nitro benzofuran-2-carbonyl azide* (5a)**

Yield: 55%, MP: 94-96 ^{0}C

***Synthesis of 5-bromo benzofuran-2-carbonyl azide* (5b)**

Yield: 48%, MP: 131-133 ^{0}C

2.2. General method for Synthesis of 1-(5-substituted benzofuran-2-yl)-3-arylurea (6a-6r)

A mixture of 5-substituted benzofuran-2-carbonyl azide **5a-5b** (0.0013 mole) and appropriate Amine (0.0013 mole) in anhydrous toluene (15 ml) was heated under reflux in an oil bath for 4 hour. Reaction was monitored by TLC. The crystaline product that seperated out from the reaction mixture was collected and washed with toluene and petroleum ether.

1-(5-nitrobenzofuran-2-yl)-3-phenylurea (6a)

Yield: 61 %, mp: 230-232 ^{o}C. IR cm^{-1}: 3360, 1715, 1525, 1430, 1335, 2910 ^{1}H NMR (DMSO-d6) W ppm: 7.38-7.82 (m, 9H, ArH), 10.50 (s, 1H, NH), 10.81 (s, 1H, NH) ESI-MS (m/z, [M+H]$^+$ %): 298.4

1-(5-nitrobenzofuran-2-yl)-3-(p-tolyl)urea (6b)

Yield: 75 %, mp: 282-285^{o}C. IR cm^{-1}: 3364, 1716, 1526, 1434, 1334, 2930 ^{1}H NMR (DMSO-d6) W ppm**:** 1.53 (s, 3H, CH3) 7.38-8.13 (m, 8H, ArH), 10.49 (s, 1H, NH), 10.82 (s, 1H, NH) ESI-MS (m/z, [M+H]$^+$ %): 312.3

1-(2-methoxyphenyl)-3-(5-nitrobenzofuran-2-yl)urea (6c)

Yield: 70 %, mp: 220-222^{o}C. IR cm^{-1}: 3344, 1726, 1516, 1424, 1335, 2920 ^{1}H NMR (DMSO-d6) W ppm: 3.69(s, 3H, OCH3) 6.96-8.57 (m, 8H, ArH), 9.56 (s, 1H, NH), 10.69 (s, 1H, NH) ESI-MS (m/z, [M+H]$^+$ %): 328.4

1-(4-methoxyphenyl)-3-(5-nitrobenzofuran-2-yl)urea (6d)

Yield: 63 %, mp: 249-251^{o}C. IR cm^{-1}: 3361, 1715, 1525, 1430, 1335, 2910 ^{1}H NMR (DMSO-d6) W ppm: 4.06(s, 3H, OCH3) 6.97-8.57 (m, 8H, ArH), 9.57 (s, 1H, NH), 10.69 (s, 1H, NH) ESI-MS (m/z, [M+H]$^+$ %):328.3

1-(4-ethoxyphenyl)-3-(5-nitrobenzofuran-2-yl)urea (6e)

Yield: 51 %, mp: 196-198^{o}C. IR cm^{-1}: 3364, 1717, 1526, 1434, 1334, 2930 ^{1}H NMR (DMSO-d6) W ppm: 1.28-1.32 (t, 3H, CH3) 3.46-3.50 (m, 2H, CH2) 6.96-8.57 (m, 8H, ArH), 9.92 (s, 1H, NH), 10.38 (s, 1H, NH) ESI-MS (m/z, [M+H]$^+$ %): 342.4

1-(3-chlorophenyl)-3-(5-nitrobenzofuran-2-yl)urea (6f)

Yield: 80%, mp: 222-224 ^{o}C. IR cm^{-1}: 3344, 1726, 1516, 1434, 1335, 2920 ^{1}H NMR (DMSO-d6) W ppm**:** 7.38-7.82 (m, 8H, ArH), 9.96 (s, 1H, NH), 10.29 (s, 1H, NH) ESI-MS (m/z, [M+H]$^+$ %): 332.7

1-(2-chlorophenyl)-3-(5-nitrobenzofuran-2-yl)urea (6g)

Yield: 65 %, mp: 190-192 ^{o}C. IR cm^{-1}: 3344, 1715, 1526, 1430, 1335, 2910 ^{1}H NMR (DMSO-d6) W ppm: 7.38-7.82 (m, 8H, ArH), 9.97(s, 1H, NH), 10.29 (s, 1H, NH) ESI-MS (m/z, [M+H]$^+$ %):332.6

1-cyclohexyl-3-(5-nitrobenzofuran-2-yl)urea (6h)

Yield: 63 %, mp: 105-107 ^{o}C. IR cm^{-1}: 3364, 1716, 1526, 1434, 1334, 2930 ^{1}H NMR (DMSO-d6) W ppm: 1.01-1.05 (m, 4H, CH2) 1.17-1.22 (m, 6H, CH2) 1.38-1.41 (m, 4H, CH2) 3.80-3.85 (m, 1H, CH) 6.52 (s, 1H, NH), 7.10-7.71 (m, 4H, ArH), 9.09 (s, 1H, NH) ESI-MS (m/z, [M+H]$^+$ %):304.2

1-(5-nitrobenzofuran-2-yl)-3-(thiazol-2-yl)urea (6i)

Yield: 48 %, mp: 94-96 ^{o}C. IR cm^{-1}: 3344, 1726, 1516, 1424, 1335, 2920 ^{1}H NMR (DMSO-d6) W ppm: 7.10-8.69 (m, 6H, ArH), 9.09 (s, 1H, NH), 9.40 (s, 1H, NH) ESI-MS (m/z, [M+H]$^+$ %):305.3

1-(5-bromobenzofuran-2-yl)-3-phenylurea (6j)

Yield: 59 %, mp: 221-223 ^{o}C. IR cm^{-1}: 3360, 1715, 1525, 1430, 2910, 620 ^{1}H NMR (DMSO-d6) W ppm: 7.39-7.80 (m, 9H, ArH), 10.50 (s, 1H, NH), 10.80 (s, 1H, NH) ESI-MS (m/z, [M+H]$^+$ %):332.2

1-(5-bromobenzofuran-2-yl)-3-(p-tolyl)urea (6k)

Yield: 57 %, mp: 228-230 ^{o}C. IR cm^{-1}: 3364, 1716, 1526, 1434, 2930, 610 ^{1}H NMR (DMSO-d6) W ppm: 1.59 (s, 3H, CH3) 7.37-7.89 (m, 8H, ArH), 10.50 (s, 1H, NH), 10.81 (s, 1H, NH) ESI-MS (m/z, [M+H]$^+$ %):346.2

1-(2-methoxyphenyl)-3-(5-bromobenzofuran-2-yl)urea (6l)

Yield: 76 %, mp: 220-223 ^{o}C. IR cm^{-1}: 3344, 1726, 1516, 1424, 2920, 605 ^{1}H NMR (DMSO-d6) W ppm: 3.69(s, 3H, OCH3) 6.96-7.57 (m, 8H, ArH), 9.57 (s, 1H, NH), 10.68 (s, 1H, NH) ESI-MS (m/z, [M+H]$^+$ %):362.2

1-(4-methoxyphenyl)-3-(5-bromobenzofuran-2-yl)urea (6m)

Yield: 63 %, mp: 149-151 ^{o}C. IR cm^{-1}: 3361, 1715, 1525, 1430, 2910, 620 ^{1}H NMR (DMSO-d6) W ppm: 4.06(s, 3H, OCH3) 6.97-7.56 (m, 8H, ArH), 9.56 (s, 1H, NH), 10.70 (s, 1H, NH) ESI-MS (m/z, [M+H]$^+$ %):362.2

1-(4-ethoxyphenyl)-3-(5-bromobenzofuran-2-yl)urea (6n)

Yield: 61 %, mp: 166-168 ^{o}C. IR cm^{-1}: 3364, 1717, 1526, 1434, 2930, 640 ^{1}H NMR (DMSO-d6) W ppm: 1.29-1.32 (t, 3H, CH3) 3.46-3.51 (m, 2H, CH2) 6.96-7.57 (m, 8H, ArH), 9.92 (s, 1H, NH), 10.38 (s, 1H, NH) ESI-MS (m/z, [M+H]$^+$ %):376.2

1-(3-chlorophenyl)-3-(5-bromobenzofuran-2-yl)urea (6o)

Yield: 75 %, mp: 202-204 ^{o}C. IR cm^{-1}: 3344, 1726, 1516, 1434, 2920, 640 ^{1}H NMR (DMSO-d6) W ppm: 7.38-7.82 (m, 8H, ArH), 9.95(s, 1H, NH), 10.30 (s, 1H, NH) ESI-MS (m/z, [M+H]$^+$ %):366.6

1-(2-chlorophenyl)-3-(5-bromobenzofuran-2-yl)urea (6p)

Yield: 75 %, mp: 194-196 °C. IR cm^{-1}: 3344, 1715, 1526, 1430, 2910, 670 ^{1}H NMR (DMSO-d6) W ppm: 7.38-7.82 (m, 8H, ArH), 9.97(s, 1H, NH), 10.29 (s, 1H, NH) ESI-MS (m/z, [M+H]$^+$ %):366.5

1-cyclohexyl-3-(5-bromobenzofuran-2-yl)urea (6q)

Yield: 73 %, mp: 85-87 °C. IR cm^{-1}: 3364, 1716, 1526, 1434, 2930, 610 ^{1}H NMR (DMSO-d6) W ppm: 1.01-1.051 (m, 4H, CH2) 1.17-1.23 (m, 6H, CH2) 1.39-1.41 (m, 4H, CH2) 3.80-3.85 (m, 1H, CH) 6.52 (s, 1H, NH), 7.10-7.75(m, 4H, ArH), 9.10(s, 1H, NH) ESI-MS (m/z, [M+H]$^+$ %):338.2

1-(5-bromobenzofuran-2-yl)-3-(thiazol-2-yl)urea (6r)

Yield: 48 %, mp: 96-98 °C. IR cm^{-1}: 3344, 1726, 1516, 1424, 2920, 610 ^{1}H NMR (DMSO-d6) W ppm: 7.11-7.69 (m, 6H, ArH), 9.10 (s, 1H, NH), 9.40 (s, 1H, NH) ESI-MS (m/z, [M+H]$^+$ %):339.2

2.3. Antimicrobial activity

Sterilized test tubes were numbered 1 through 9. All of the following steps were carried out using aseptic technique. A solution of 0.2 ml of 2000 µg/ml test stock solution in DMSO was transferred to a first sterile test tube containing 3.8 ml of double strength nutrient broth to arrive 100 µg/ml as starting dose and the remaining test tubes 2-9 were filled with 2 ml of double strength nutrient broth. DMSO as a control has no effect at 12.5% concentration against bacteria. These test tubes were serially diluted to give a concentration of 50, 25, 12.5, 6.25, 3.125, 1.56, 0.78 and 0.39 µg/ml. One test tube with no test compound but with equal volume of solvent DMSO (5%) served as the vehicle control. One test tube with no test compound and no vehicle but only with nutrient media served as the positive control to ensure the growth property of media. To all the test tubes 0.1 ml of suspension of bacteria (working inocula) was added and the test tubes were incubated at 35-37 ° C for 24 h in case of bacteria and the test tubes were incubated at 25- 27°C for 48 h in case of fungi. The highest dilution of the test compound that completely inhibited the growth of test organism was considered as the MIC value of the test compound and was expressed in µg/ml.[24]

3. RESULT AND DISCUSSIONS

3.1 Chemistry

We first synthesized 5-nitrobenzofuran-2-carbonyl azide **5a** and 5-bromobenzofuran-2-carbonyl azide **5b** from 5-nitro benzofuran-2-carbohydrazide **4a** and 5-bromo benzofuran-2-carbohydrazide **4b** by reported method and as per scheme 1. The target compounds **6a-6r** were synthesized from 5-nitrobenzofuran-2-carbonyl azide **5a** and 5-bromobenzofuran-2-carbonyl azide **5b** respectively by reacting with appropriate amine. The structures of synthesized compounds were characterized by IR, ^{1}H NMR and mass spectrometry.

3.2 Antimicrobial Activity

The benzfuran derivatives **6a-6r** were evaluated for antimicrobial activity against two Gram-positive bacteria *Staphylococcus aureus* (ATCC 6538P), *Bacillus subtilis* (ATCC 6633), two Gram-negative bacteria *Escherichia coli* (ATCC 8739), *Pseudomonas aeruginosa(ATCC 9027)* and two fungal strains *Candida albicans* (ATCC 10231), *Aspergillus niger* (ATCC 9029). Azithromycin and fluconazole were used as standard controls. The minimum inhibition concentration is given in Table 1 and 2.

Table 1. Minimum Inhibitory Concentration (MIC) of Test Compounds 6a to 6r against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa* .

Test Compound	MIC (µg/ml)			
	Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*
6a	>100	100	100	100
6b	50	25	25	50
6c	50	25	50	50
6d	25	6.25	6.25	6.25
6e	50	50	100	50
6f	25	12.5	25	25
6g	25	25	50	25
6h	50	25	25	50
6i	25	12.5	6.25	12.5
6j	100	50	50	100
6k	100	50	50	100
6l	100	50	100	100
6m	50	50	50	100
6n	50	50	50	50
6o	6.25	1.56	6.25	3.125
6p	12.5	1.56	6.25	12.5
6q	25	12.5	12.5	12.5
6r	25	12.5	12.5	6.25
Azithromycin	0.39	1.56	12.5	6.25

Table 2. Minimum Inhibitory Concentration (MIC) of Test Compounds 6a to 6r against *Candida albicans* and *Aspergillus niger*.

Test Compound	MIC (µg/ml)	
	C. albicans	*A.niger*
6a	50	50
6b	25	25
6c	25	25
6d	12.5	12.5
6e	25	25
6f	25	12.5
6g	50	25
6h	25	12.5
6i	12.5	12.5
6j	25	25
6k	12.5	12.5
6l	25	25
6m	25	50
6n	12.5	6.25
6o	12.5	25
6p	25	25
6q	25	25
6r	50	25
Fluconazole	12.5	12.5

4. CONCLUSION

We report herein the synthesis, structural elucidation and antimicrobial activities of eighteen new benzfurans **6a-6r**. The structures are fully supported by spectroscopic data. All the synthesized compounds were evaluated for their antimicrobial activities by the two fold dilution method. Compounds 6d, 6o, 6p, and 6r exhibited reasonably high degree of antibacterial activities against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Pseudomonas aeruginosa*. The other compounds exhibited varied degree of antibacterial activity. Compounds 6d, 6i, 6k, and 6n exhibited high degree of antifungal activities against both *Candida albicans* and *Aspergillus niger* while the other compounds showed moderate to weak antifungal activity.

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