ISSN 1070-3632, Russian Journal of General Chemistry, 2017, Vol. 87, No. 9, pp. 2021–2026. © Pleiades Publishing, Ltd., 2017.

Synthesis of Hydrazone Derivatives of Benzofuran and Their Antibacterial and Antifungal Activity[1]

N. J. P. Subhashini[a]*, P. Janaki[a], and B. Bhadraiah[a]

Department of Chemistry, University College of Science, Osmania University, Hyderabad, 500007 India
**e-mail: njsubhashini@yahoo.co.in*

Received December 31, 2016

Abstract—A series of benzofuran hydrazones **6a–6n** were synthesized from benzofuran aldehyde and substituted aromatic hydrazides **5a–5n**. Structures of all compounds were confimed by IR, ^{1}H and ^{13}C NMR, and Mass spectral data. These compounds were evaluated for their antibacterial activity against gram-negative bacteria (*Escherichia coli,* –ve), gram-positive bacteria (*Bacillus Subtillis,* +ve), and antifungal activity against *Candida albicans.* All compounds demonstrated considerable activity against bacteria and fungi.

Keywords: benzofuran, hydrazide, hydrozone, benzofuran aldehyde, antibacterial and antifungal activities

DOI: 10.1134/S1070363217090183

INTRODUCTION

Benzofuran derivatives such as Cicerfuran and Conocarpan [1, 2] display potent biological properties including antimicrobial [3], anti-inflammatory [4, 5], anticonvulsant [6–7], antitumor [8], anti-HIV [9], antidiabetic [10], antitubercular [11], antihyperglycemic [12], analgesic [13], antiparasitic [14], and antioxidant [15].

Similarly, aroyl hydrazone containing the azomethine –NHN=CH protons constitute the compounds important in new drugs development [16]. Some widely used antibacterial drugs such as furacilin and ftivazide contain this group (Scheme 1).

Herein, we report synthesis, characterization and biological evaluation of some hydrozone derivatives of benzofurans.

RESULTS AND DISCUSSION

Synthetic routs for the target compounds **6a–6n** are summarized in Scheme 2. The structures of products **6a–6n** were confirmed by their IR, ^{1}H, ^{13}C NMR, and mass spectral data.

All synthesized compounds **6a–6n** were evaluated for their antibacterial and antifungal activities. The antibacterial activity against gram-negative bacteria (*Escherichia coli,* –ve), gram-positive bacteria (*Bacillus Subtillis,* +ve) and antifungal activity against *Candida albicans* (see table) and demonstrated distinctive potential, particularly compounds **6a–6c**, **6g–6i**, and **6k**.

Antifungal activity of synthesized compounds **6a–6n** was tested against *Candida albicans* by the poison plate technique at a concentration of 100 μL (see the table). Amphoteracin-B (10 μL) was used as the standard control.

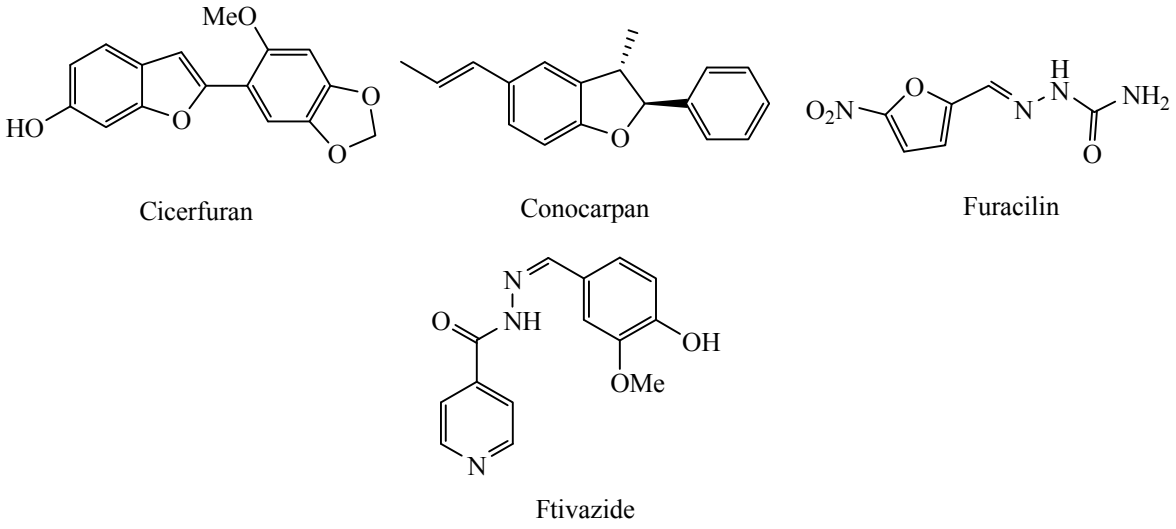
EXPERIMENTAL

All chemicals were of commercially pure grade. TLC was carried out on aluminium plates coated with silica gel (SiO_2; Merck 60 F254). Melting points were determined on a Stuart SMP3 melting point apparatus. IR spectra (KBr pellets) were recorded on a Shimadzu FTIR 8400 S spectrophotometer. NMR spectra were measured on a Bruker Avance-400 spectrometer in DMSO-d_6 using TMS as the internal standard. Mass spectra were measured on a Finnigan MAT 1020 mass spectrometer.

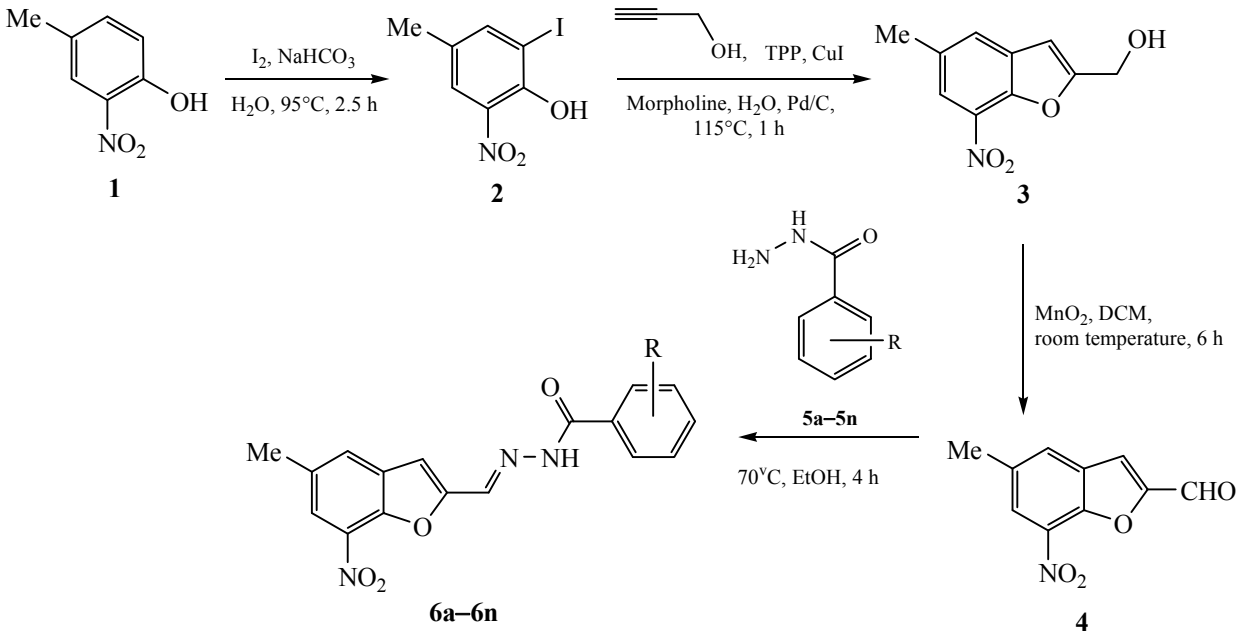
Synthesis of 2-iodo-4-methyl-6-nitrophenol (2). To the stirred solution of compound **1** (10 g, 65.40 mmol) in water (100 mL) was added sodium bicarbonate (523 mmol) followed by addition of iodine (16.6 g, 65.40 mmol) in small portions within 1 h and heating at 95°C for 2.5 h. The reaction mixture was cooled down to room temperature, acidified with 1 N

[1] The text was submitted by the authors in English.

Scheme 1.



Scheme 2. Synthetic route for the benzofuran-hydrazone derivatives **6a–6n**.



R = 4-chloro- (**a**), 4-methoxy- (**b**), 4-fluoro- (**c**), 4-bromo- (**d**), 6-bromo- (**e**), 5-nitro- (**f**), 4,6-dichloro- (**g**), 3,6-difluoro- (**h**), 3,4,5-trimethoxy- (**i**), 4-hydroxy- (**j**), 3,5-dichloro- (**k**), 4-methylsulphonyl- (**l**), H (**m**), 6-iodo- (**n**).

HCl and then extracted with diethyl ether (3×50 mL). The organic layer was separated and washed with water, brine solution, dried over sodium sulphate, filtered, and evaporated to obtain compound **2** as a yellow solid.

Synthesis of (5-methyl-7-nitrobenzofuran-2-yl)-methanol (3). A mixture of compound **2** (2 g, 7.16 mmol) with 10% Pd/C (0.3 g), triphenylphosphine (0.23 g, 0.86 mmol), CuI (80 mg, 0.43 mmol), and morpholine (23 mmol) in water (10 mL) was stirred at room temperature for 1 h under the atmosphere of N_2. Propargyl alcohol (23 mmol) was added to the above reaction mixture and refluxed for 1 h. The reaction mixture was cooled down to room temperature, diluted with ethyl acetate (100 mL) and filtered through cellite

In vitro antibacterial and antifungal activities of compounds **6a–6n**

Compound	Zone of inhibition, mm					
	antibacterial activity				antifungal activity	
	E. coli (–ve)		*B. Subtillis* (+ve)		*Candida albicans*	
	concentration *c*, μL					
	100	200	100	200	100	200
6a	9	12	17	28	12	19
6b	10	14	19	23	12	17
6c	11	15	9	19	12	22
6d	8	15	14	19	11	18
6e	9	13	8	9	10	15
6f	11	17	9	10	3	3
6g	10	13	15	22	4	10
6h	9	13	10	17	10	16
6i	13	19	9	14	5	10
6j	9	10	9	12	8	12
6k	10	18	8	9	10	14
6l	8	14	No activity	7	5	9
6m	11	16	9	8	16	21
6n	9	12	No activity	No activity	11	14
Gentamycin (c = 10 μL)	16	No activity	13	No activity	–	–
Amphoteracin-B (c = 10 μL)	–	–	–	–	10	No activity

bed. The filtrate was washed with water (2×50 mL), dried over sodium sulphate, filtered and concentrated to afford compound **3** as a yellow solid.

Synthesis of 5-methyl-7-nitrobenzofuran-2-carbaldehyde (4). A mixture of compound **3** (2 g, 9.66 mmol) with MnO_2 (67.7 mmol) in dichloromethane (40 mL) was stirred at room temperature for 6 h. The reaction mixture was filtered through celite pad and the organic layer was evaporated to obtain pale yellow solid compound **4**.

Synthesis of benzofuran hydrazide derivatives 6a–6n. To a solution of 5-methyl-7-nitrobenzofuran-2-carbaldehyde **5** (1 mmol) and hydrazides **5a–5n** (1.2 mmol) in ethanol (10 mL) was added the above reaction mixture and stirred at 70°C for 4 h. Upon completion of the reaction, the solvent was evaporated under vacuo and the residue was triturated with *n*-hexane, filtered and dried over vacuo to obtain the pure compounds **6a–6n**. Yields of the products varied from 80 to 90%.

2-Iodo-4-methyl-6-nitrophenol (2). Yield 88%, mp 97–99°C. IR spectrum, ν, cm^{-1}: 3079, 1537. ^1H NMR spectrum, δ, ppm: 2.30 s (3H, CH_3), 7.98 s (2H, Ar-H), 11.20 s (1H, OH). ^{13}C NMR spectrum, δ, ppm: 19.9, 86.6, 125.0, 131.6, 132.6, 148.0, 151.9. MS, *m/z*: 277.78 $[M - H]^-$.

(5-Methyl-7-nitrobenzofuran-2-yl)methanol (3). Yield 62%, mp 153–154°C. IR spectrum, ν, cm^{-1}: 3200, 1585. ^1H NMR spectrum, δ, ppm: 2.10 t (J = 6.6 Hz, 1H, OH), 2.58 s (3H, CH_3), 4.85 d (2H, J = 6.8 Hz, OCH_2), 6.68 s (1H, Ar-H), 7.62 s (1H, Ar-H), 7.98 s (1H, Ar-H). ^{13}C NMR spectrum, δ, ppm: 21.0, 57.8, 103.7, 121.4, 128.1, 132.2, 133.0, 133.1, 145.4, 159.5. MS, *m/z*: 207.96 $[M + H]^+$.

5-Methyl-7-nitrobenzofuran-2-carbaldehyde (4). Yield 78%, mp 179–180°C. IR spectrum, ν, cm^{-1}: 1740, 1524. ^1H NMR spectrum, δ, ppm: 2.51 s (3H, CH_3), 8.01 s (1H, Ar-H), 8.17 s (1H, Ar-H), 8.28 s (1H, Ar-H), 9.94 s (1H, CHO). MS, *m/z*: 206.07 $[M + H]^+$.

(*E*)-4-Chloro-*N*'-[(5-methyl-7-nitrobenzofuran-2-yl)methylene]benzohydrazide (6a). Yield 80%, mp 143–145°C. IR spectrum, ν, cm^{-1}: 3268, 1742, 1530. ^1H NMR spectrum, δ, ppm: 3.44 s (3H, CH_3), 7.56 s (1H, Ar-H), 7.62 d (2H, *J* = 8.54 Hz, Ar-H), 7.94 d (2H, *J* = 8.54 Hz, Ar-H), 7.97 s (1H, Ar-H), 8.06 s (1H, Ar-H), 8.56 s (1H, Ar-H), 12.2 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 20.3, 94.0, 109.6, 122.6, 127.6, 128.2, 128.5, 129.2, 131.8, 132.7, 133.7, 136.8, 139.2, 140.9, 145.1, 153.3, 165.2. MS, *m/z*: 358.18 $[M + H]^+$.

(*E*)-4-Methoxy-*N*'-[(5-methyl-7-nitrobenzofuran-2-yl)methylene]benzohydrazide (6b). Yield 82%, mp 148–150°C. IR spectrum, ν, cm^{-1}: 3282, 1654, 1513. ^1H NMR spectrum, δ, ppm: 3.41 s (3H, CH_3), 3.85 s (3H, OCH_3), 7.08 d (2H, *J* = 9.15Hz, Ar-H), 7.52 s (1H, Ar-H),7.93–7.96 m (3H, Ar-H), 8.06 s (1H, Ar-H), 8.58 s (1H, Ar-H), 12.04 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 18.6, 53.2, 108.5, 118.1, 121.9, 126.8, 128.9, 129.5, 130.6, 131.5, 134.6, 137.8, 143.3, 145.2, 153.8, 154.5, 162.5, 180.9. MS, *m/z*: 352.19 $[M - H]^-$.

(*E*)-4-Fluoro-*N*'-[(5-methyl-7-nitrobenzofuran-2-yl)methylene]benzohydrazide (6c). Yield 84%, mp 133–135°C. IR spectrum, ν, cm^{-1}: 3376, 1675, 1524. ^1H NMR spectrum, δ, ppm: 3.43 s (3H, CH_3), 7.36–7.43 m (3H, Ar-H), 7.56 s (1H, Ar-H), 7.98–8.18 m (3H, Ar-H), 8.57 s (1H, Ar-H), 12.17 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 21.2, 108.9, 113.4, 115.0, 115.3, 122.5, 123.6, 129.3, 130.9, 131.7, 132.9, 133.8, 136.5, 144.8, 154.3, 161.3, 161.5. MS, *m/z*: 342.21 $[M + H]^+$.

(*E*)-4-Bromo-*N*'-[(5-methyl-7-nitrobenzofuran-2-yl)methylene]benzohydrazide (6d). Yield 85%, mp 154–156°C. IR spectrum, ν, cm^{-1}: 3776, 1665, 1523. ^1H NMR spectrum, δ, ppm: 3.47 s (3H, CH_3), 7.58 s (1H, Ar-H), 7.78–7.80 m (2H, Ar-H), 7.88–7.91 m (2H, Ar-H), 7.99 s (1H, Ar-H), 8.08 s (1H, Ar-H), 8.57 s (1H, Ar-H), 12.21 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 20.3, 94.03, 109.6, 122.6, 127.6, 128.2, 128.5, 129.2, 131.8, 132.7, 133.7, 136.8, 139.2, 140.9, 145.1, 153.3, 165.2. MS, *m/z*: 402.21 $[M + H]^+$.

(*E*)-2-Bromo-*N*'-[(5-methyl-7-nitrobenzofuran-2-yl)methylene]benzohydrazide (6e). Yield 83%, mp 151–153°C. IR spectrum, ν, cm^{-1}: 3776, 1665, 1523. ^1H NMR spectrum, δ, ppm: 2.47 s (3H, CH_3), 6.94 s (1H, Ar-H), 7.59 s (2H, Ar-H), 7.71 s (1H, Ar-H), 7.82–7.86 m (3H, Ar-H), 7.90 s (1H, Ar-H), 12.4 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 18.67, 99.71, 118.3, 121.3, 123.9, 125.4, 125.8, 127.2, 128.9, 130.5, 130.8, 130.9, 142.4, 142.5, 142.7, 149.9, 154.5. MS, *m/z*: 402.21 $[M + H]^+$, 404.12 $[M + H]^{+2}$.

(*E*)-*N*'-[(5-Methyl-7-nitrobenzofuran-2-yl)-methylene]-3-nitrobenzohydrazide (6f). Yield 87%, mp 145-147°C. IR spectrum, ν, cm^{-1}: 3620, 1687, 1523. ^1H NMR spectrum, δ, ppm: 2.53 s (3H, CH_3), 7.62–7.66 m (1H, Ar-H), 7.85–7.90 m (1H), 8.00 s (1H, Ar-H), 8.10 s (1H, Ar-H), 8.18 s (1H, Ar-H), 8.38 d (1H, *J* =7.93 Hz, Ar-H), 8.47–8.49 m (1H, Ar-H), 8.78 s (1H, Ar-H), 12.3 s (1H, NH). MS, *m/z*: 369.27 $[M + H]^+$.

(*E*)-2,4-Dichloro-*N*'-[(5-methyl-7-nitrobenzofuran-2-yl)methylene]benzohydrazide (6g). Yield 86%, mp 159–161°C. IR spectrum, ν, cm^{-1}: 3323, 1663, 1525. ^1H NMR spectrum, δ, ppm: 2.46 s (3H, CH_3), 7.32 s (1H, Ar-H), 7.55–7.61 m (2H, Ar-H), 7.66 d (1H, *J* = 8.54 Hz, Ar-H), 7.75 s (1H, Ar-H), 7.82 d (1H, *J* = 1.83 Hz, Ar-H), 8.36 s (1H, Ar-H), 12.26 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 20.3, 109.2, 120.8, 121.6, 122.5, 127.7, 128.6, 129.1, 131.8, 132.1, 132.7, 133.0, 133.7, 136.8, 145.0, 153.6, 163.3. MS, *m/z*: 392.07 $[M + H]^+$.

(*E*)-2,5-Difluoro-*N*'-[(5-methyl-7-nitrobenzofuran-2-yl)methylene]benzohydrazide (6h). Yield 81%, mp 145–147°C. IR spectrum, ν, cm^{-1}: 3376, 1669, 1524. ^1H NMR spectrum, δ, ppm: 2.47 s (3H, CH_3), 7.36–7.59 m (2H, Ar-H), 7.61 s (1H, Ar-H), 7.91 s (1H, Ar-H), 7.99–8.01 m (1H, Ar-H), 8.09 s (1H, Ar-H), 8.42 s (1H, Ar-H), 12.22 s (1H, NH). MS, *m/z*: 360.20 $[M + H]^+$.

(*E*)-3,4,5-Trimethoxy-*N*'-[(5-methyl-7-nitrobenzofuran-2-yl)methylene]benzohydrazide (6i). Yield 85%, mp 161–163°C. IR spectrum, ν, cm^{-1}: 3151, 1654, 1510. ^1H NMR spectrum, δ, ppm: 2.47 s (3H, CH_3), 3.74 s (3H, OCH_3), 3.87 s (6H, $2OCH_3$), 7.26 s (2H, Ar-H), 7.56 s (1H, Ar-H), 7.98 s (1H, Ar-H), 8.07 s (1H, Ar-H), 8.62 s (1H, Ar-H), 12.00 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 20.3, 56.1, 60.1, 105.3, 109.2, 121.3, 122.5, 128.0, 129.1, 131.8, 132.7, 133.7, 136.8, 145.0, 152.7, 153.6, 162.7. MS, *m/z*: 414.22 $[M + H]^+$.

(*E*)-4-Hydroxy-*N*'-[(5-methyl-7-nitrobenzofuran-2-yl)methylene]benzohydrazide (6j). Yield 87%, mp 149–151°C. IR spectrum, ν, cm^{-1}: 3282, 1654, 1513. ^1H NMR spectrum, δ, ppm: 2.47 s (3H, CH_3), 7.60 s

(1H, Ar-H), 7.93–7.99 m (6H, Ar-H), 8.09 s (1H, Ar-H), 8.53 s (1H, Ar-H), 11.94 s (1H, OH). ^{13}C NMR spectrum, δ, ppm: 20.3, 108.5, 111.4, 115.0, 115.2, 122.3, 123.3, 129.0, 130.6, 131.9, 132.7, 133.6, 135.8, 144.9, 153.8, 160.9, 161.2. MS, *m/z*: 340.01 $[M + H]^+$.

(*E*)-3,5-Dichloro-*N*'-[(5-methyl-7-nitrobenzofuran-2-yl)methylene]benzohydrazide (6k). Yield 88%, mp 159–161°C. IR spectrum, ν, cm^{-1}: 3358, 1694, 1526. ^{1}H NMR spectrum, δ, ppm: 2.47 s (3H, CH_3), 7.50 s (1H, Ar-H), 7.83 d (2H, *J* = 7.9 Hz, Ar-H), 7.94–7.96 m (2H, Ar-H), 8.05–8.07 m (1H, Ar-H), 8.56 s (1H, Ar-H), 12.28 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 20.5, 96.3, 109.4, 123.5, 127.2, 128.5, 130.2, 131.3, 132.5, 132.9, 134.5, 138.2, 140.2, 141.5, 145.9, 153.8, 163.2, MS, *m/z*: 392.16 $[M + H]^+$.

(*E*)-*N*'-[(5-Methyl-7-nitrobenzofuran-2-yl)methylene]-4-(methylsulfonyl)benzohydrazide (6l). Yield 81%, mp 147–149°C. IR spectrum, ν, cm^{-1}: 3781, 1695, 1524, 1142 (SO_2Me), 1524. ^{1}H NMR spectrum, δ, ppm: 2.47 s (3H, CH_3), 3.30 s (3H, SO_2Me), 7.60 s (1H, Ar-H), 7.99 s (1H, Ar-H), 8.09–8.20 m (3H, Ar-H), 8.27 s (1H, Ar-H), 8.58 s (1H, Ar-H), 9.94 s (1H, Ar-H), 12.35 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 20.3, 43.2, 109.7, 118.1, 122.7, 125.8, 128.7, 129.2, 130.4, 131.3, 134.4, 137.6, 143.5, 145.1, 153.3, 154.0, 162.1,180.9. MS, *m/z*: 402.13 $[M + H]^+$.

(*E*)-*N*'-[(5-Methyl-7-nitrobenzofuran-2-yl)methylene]benzohydrazide (6m). Yield 83%, mp 149–151°C. IR spectrum, ν, cm^{-1}: 3618, 1645, 1524. ^{1}H NMR spectrum, δ, ppm: 3.43 s (3H, CH_3), 7.56–7.62 m (3H, Ar-H), 7.63–7.65 m (1H, Ar-H), 7.93–7.97 m (3H, Ar-H), 8.07 s (1H, Ar-H), 8.58 s (1H, Ar-H), 12.15 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 20.3, 109.2, 122.5, 127.7, 128.6, 129.1, 131.8, 132.1, 132.7, 133.0, 133.7, 136.8, 145.0, 153.6, 163.3. MS, *m/z*: 324.21 $[M + H]^+$.

(*E*)-2-Iodo-*N*'-[(5-methyl-7-nitrobenzofuran-2-yl)-methylene]benzohydrazide (6n). Yield 79%, mp 153–154°C. IR spectrum, ν, cm^{-1}: 3375, 1665, 1523. ^{1}H NMR spectrum, δ, ppm: 3.46 s (3H, CH_3), 7.23–7.29 m (2H, Ar-H), 7.48–7.56 m (2H, Ar-H), 7.90–7.99 m (2H, Ar-H), 8.08 s (1H, Ar-H), 8.36 s (1H, Ar-H), 12.15 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 20.3, 94.0, 109.6, 122.6, 127.6, 128.5, 129.2, 131.6, 131.8, 132.7, 133.7, 136.8, 139.2, 140.9, 145.1, 153.3, 165.2. MS, *m/z*: 450.02 $[M + H]^+$.

CONCLUSIONS

A new series of substituted benzofuran hydrazone derivatives **6a–6n** were synthesized, characterized by IR, ^{1}H and ^{13}C NMR, and Mass spectral data. Antibacterial activity against *Escherichia coli,* –ve, *Bacillus Subtillis,* +ve, and antifungal activity against *Candida albicans* were evaluated. All the above compounds demonstrated more potent antibacterial and antifungal activity than the standard controls.

ACKNOWLEDGMENTS

One of us (JP) is thankful to CSIR, New Delhi, for the award of research fellowship and also thankful to the Head, Department of Chemistry, Osmania University, Hyderabad for providing the laboratory facilities and also thankful to the CFRD, Osmania University for providing Analytical data. Another author (NJPS) is thankful to UGC/DST-purse A37/PURSE/coord/2011) for providing financial assistance.

REFERENCES

1. Aslam, S.N., Stevenson, P.C., and Phythian, S.J., *Tetrahedron,* 2006, vol. 62, p. 4214. doi org/10.1016/j.tet.2006.02.015
2. de Campos, M.P., Filho, V.C., and da Silva, R.Z., *Biol. Pharm. Bull.*, 2005, vol. 28, no. 8, p. 1527. doi org/10.1248/bpb.28.1527
3. Koca, M., Sevi, S., Kirilmis, C., Kazaz, C., Ozbek, B., and Otuk, G., *Eur. J. Med. Chem.,* 2005, vol. 40, p. 1351. doi org/10.1016/j.ejmech.2005.07.004
4. Dawood, K.M., Abdel-Gawad, H., Rageb, E.M., Ellithey, M., and Mohamed, H.A., *Bioorg. Med. Chem.*, 2006, vol. 14, p. 3672. doi org/10.1016/j.bmc.2006.01.033
5. Rajak, H., Behera, C.K., Pawar, R.S., Singour, P.K., and Kharya, M.D., *Chin. Chem. Lett.,* 2010, vol. 21, no. 10, p. 1149. doi org/10.1016/j.cclet.2010.04.012
6. Patel, H.J., Sarra, J., Caruso, F., Rossi, M., Doshi, U., and Stephani, R.A., *Bioorg. Med. Chem. Lett.,* 2006, vol. 16, p. 4644. doi org/10.1016/j.bmcl.2006.05.102
7. Jadhav, V.B., Kulkarni, M.V., Rasal, V.P., Biradar, S.S., and Vinay, M.D., *Eur. J .Med. Chem.*, 2008, vol. 43, p. 1721. doi org/10.1016/j.ejmech.2007.06.023
8. Hayakawa, I., Shioya, R., Agatsuma, T., Furukawa, H., and Sugano, Y., *Bioorg. Med. Chem. Lett.,* 2004, vol. 14, p. 3411. doi org/10.1016/j.bmcl.2004.04.079
9. Rida, S.M., El-Hawash, S.A.M., Fahmy, H.T.Y., Hazzaa, A.A., and El-Meligy, M.M.M., *Arch. Pharm. Res.*, 2006, vol. 29, no. 10, p. 826. doi 10.1007/BF02973901
10. Reddy, K.A., Lohray, B.B., Bhushan, V., Bajji, A.C., Reddy, K.V., Reddy, P.R., Krishna, T.H., Rao, I.N., Jajoo, H.K., Rao, N.V.S., Chakrabarti, R., Kumar, T.D., and Rajagopalan, R., *J. Med. Chem.*, 1999, vol. 42, p. 1927. doi 10.1021/jm980549x

11. Manna, K., Agarwal, Y.K., and Srinivasan, K.K., *Ind. J. Het. Chem.*, 2008, vol. 18, p. 87. doi 10.4236/ijoc.2012.24051
12. Cottineau, B., Toto, P., Marot, C., Pipaud, A., and Chenault, J., *Bioorg. Med. Chem. Lett.,* 2002, vol. 12, p. 2105. doi org/10.1016/S0960-894X(02)00380-3
13. Xie, Y.-S., Kumar, D., Bodduri, V.D.V., Tarani, P.S., Zhao, B.-X., Miao, J.-Y., Jang, K., Shin, D.-S., *Tetrahedron Lett.,* 2014, vol. 55, p. 2796. doi org/10.1016/j.tetlet.2014.02.116; Thévenin, M., Thoret, S., Grellier, P., and Dubois, J., *Bioorg. Med. Chem.,* 2013, vol. 21, p. 4885. doi org/10.1016/j.bmc.2013.07.002
14. Karatas, F., Koca, M., Kara, H., and Servi, S., *Eur. J. Med. Chem.*, 2006, vol. 41, p. 664. doi org/10.1016/j.ejmech.2006.01.003
15. Rollas, S. and Kucukguzel, S.G., *Molecule,* 2007, vol. 12, p. 1910. doi 10.3390/12081910
16. Narang, R., Narasimhan, B., and Sharma, S., *Curr. Med. Chem.*, 2012, vol. 19, p. 569. doi 10.2174/092986712798918789