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ISSN: 2278-1862

*Journal of Applicable Chemistry*

2020, 9 (2): 223-228

(International Peer Reviewed Journal)

# Synthesis, Characterization, Biological Activity of 5-Bromo-benzofuran-2-carboxylic acid (Substituted-benzylidene)-hydrazides and their Derivatives

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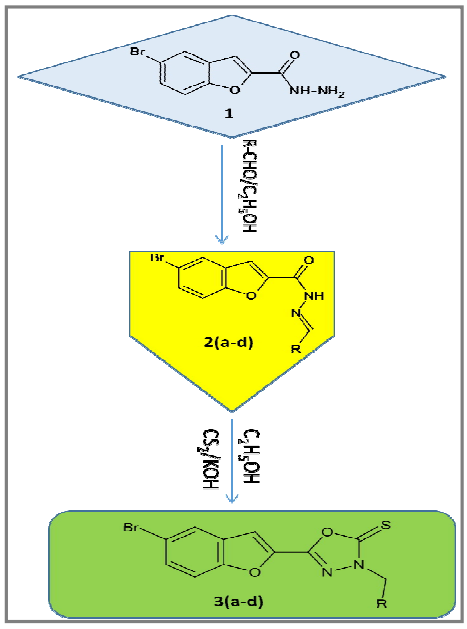
**Accepted on 1st February, 2020**

## ABSTRACT

*In continuation of our research work in the laboratory, we have synthesized new 5-Bromo benzofuranyl Schiff bases and their derivatives. The previously synthesized key compound 5-Bromo -benzofuran-2-carboxylic acid hydrazide **1** was treated with benzaldehyde/substituted benzaldehyde in ethanol to get 5-Bromo-benzofuran-2-carboxylic acid (substituted-benzylidene)-hydrazides **2(a-d)**, these newly formed Schiff bases were treated with potassium hydroxide and carbon disulphide in ethanol to form various respective 3-(Substituted-benzyl)-5-(5-Bromo-benzofuran-2-yl)-3H-[1,3,4]oxadiazole-2-thiones **3(a-d)**. The newly formed compounds were in agreement with the spectral and analytical data and screened for their biological activity.*

## Graphical Abstract




**Keywords:** Benzofuran,benzylidene, Oxadiazole, Thiones, Biological activity.

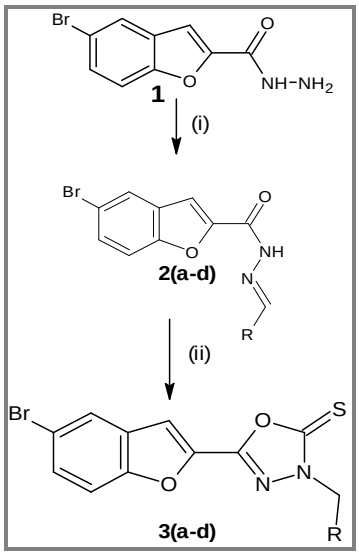
## INTRODUCTION

Benzofuran derivatives display potent biological properties including antihyperglycemic, analgesic, antiparasitic, antimicrobial, antitumor [**1-2**]. In addition, substituted benzofurans find application such as of fluorescent sensor, oxidant, antioxidants, brightening agents, a variety of drugs and in other field of chemistry and agriculture [**3**]. Several benzofuranyl imidazole derivatives were prepared and evaluated *invitro* against a panel of human tumor cell lines. The results showed that most of the compounds were selective toward an ovarian carcinoma cell line. Number of benzofuran derivatives was found to exhibit more excellent antitumor activity against human tumor xenografts than the clinical trial candidates carzelesin and cisplatin [**4**]. The HIV inhibitory activity of compounds were tested and indicated that the compounds were more active than atevirdine and compounds having imidazo pyrimidine as heterocyclic moiety has 20 times active than atevirdine with higher therapeutic index (TI). Testing of the HIVRT (reverse transcriptase) inhibitory activity of the compounds, showed lower TI than the standard (HIV) [**5**]. Several benzofuran compounds were synthesized and screened for their antimicrobial activity against fungal species and bacterial species against all test organisms. The highest antibacterial and antifungal activities were showed by benzofuran derivatives [**6-7**].

Among heterocyclic compounds, oxadiazoles have attracted significant interest in medicinal chemistry and displayed a wide range of pharmaceutical and biological activities [**8**]. Oxadiazole is a heterocyclic compound containing an oxygen atom and two nitrogen atoms in a five-membered ring. There are four structurally isomericoxadiazoles: 1,3,4-oxadiazole, 1,2,4-oxadiazole,1,2,3-oxadiazole and 1,2,5-oxadiazole. The 1,3,4-oxadiazole and 1,2,4-oxadiazoleare more extensively studied because of their many important chemical and biological properties [**9-10**]. In the continuation of our work [**11**], in this session we have focused to synthesize oxadiazoles by using various Schiff bases which have been synthesized by 2-hydrazide of 5-Bromobenzofuran.

## MATERIALS AND METHODS

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




**Conditions**: **(i).** R-CHO/$C_2H_5OH$, ii**),** $CS_2$/KOH/$C_2H_5OH$; **R:** **a**=$C_6H_5$ **b**=$C_6H_4OCH_3$(p), **c**=$C_6H_4Cl$(m), **d**=$C_6H_4Cl$(o).

**Scheme.** Synthetic route for 5-Bromobenzofuran-2-carboxylicacid (substituted-benzylidene)-hydrazides.

**5-Bromobenzofuran-2-carboxylicacidhydrazide (1):** To a solution of ethyl-5-Bromobenzo-furan-2-carboxylate (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 % yield are given in table 1.

**5-Bromobenzofuran-2-carboxylicacid (substituted benzylidene) hydrazides2(a-d):** 5-Bromo benzofuran-2-carboxylicacidhydrazide **1**(0.01 mol) and benzaldehyde/substituted benzaldehyde (0.01 mol) dissolved in ethanol (30 mL) were refluxed for 5 h. The excess of solvent was distilled off under reduced pressure. The product obtained was filtered and washed with sodium bisulphite solution to remove the unreached aldehydes and washed with dil.hydrochloric acid and water, the product obtained was dried and crystallized from suitable solvent. Melting point and % yield is given in table 1.

**5-Bromobenzofuran-2-yl -3'-(Substituted-benzyl)- 3'H-[1', 3', 4']oxadiazole-2-thiones 3(a-d):** The benzofuranyl Schiff base **2(a-d)** (0.01 mol) were taken in ethanol (20 mL). To this solution potassium hydroxide (0.05g, 0.008 mol) and carbon disulphide (1 mL, 0.013 mol) were added. The reaction mixture was refluxed on a steam bath for 12 h. The solution was allowed to cool overnight and then dissolved in 150 mL ice cold water. The resulting solution was acidified with dil. HCl and allowed to stand for 10 h. The solid thus obtained was filtered, dried and recrystallized from suitable solvent.

**Table 1.** Physical data of compounds

| Compounds | Yield % | MP°C | MF |
|---|---|---|---|
| 1 | 90 | 210 | $C_9H_6BrN_2O$ |
| 2a | 70 | 205 | $C_{16}H_{11}BrN_2O_2$ |
| 2b | 80 | 210 | $C_{17}H_{13}BrN_2O_3$ |
| 2c | 73 | 185 | $C_{16}H_{10}BrClN_2O_2$ |
| 2d | 84 | 190 | $C_{16}H_{10}BrClN_2O_2$ |
| 3a | 70 | 180 | $C_{17}H_{11}BrN_2O_2S$ |
| 3b | 81 | 175 | $C_{18}H_{13}BrN_2O_3S$ |
| 3c | 68 | 170 | $C_{17}H_{10}BrClN_2O_2S$ |
| 3d | 73 | 182 | $C_{17}H_{10}BrClN_2O_2S$ |

## RESULTS AND DISCUSSION

**5-Bromo-benzofuran-2-carboxylicacid(substituted-benzylidene)hydrazides-2(a-d):** A series of 5-Bromo-benzofuranyl Schiff bases **2(a-d)** were synthesized by treating the compound 5-Bromo-benzofuran-2-carboxylic acid hydrazide **1** with various aromatic substituted aldehydes dissolved in ethanol in the presence of catalytic amount of concentrated sulfuric acid.

In IR spectra of **2(a-d)** sharp bands observed in range between 3260-3450 $cm^{-1}$ due to NH group in the 5-Bromo benzofuranyl Schiff bases. The absorption band at 1590$cm^{-1}$ due to C=N and 1680 $cm^{-1}$ due to C=O group of amides which was absent in the compound **1**, IR spectra of compounds were mentioned below (Table 2).

The additional proof was provided to the offered structures, by $^1$HNMR and mass spectra. The $^1$HNMR spectrum in $CDCl_3$ exhibited a multiplet between 6.93-7.84δ ppm, the two singlets were observed at 8.27 δ ppm and 9.47 δ ppm due to the presence of methine (-CH) and NH protons respectively. The mass spectrum showed the molecular ion peak at *m/z*=372.9 which confirmed the formation of proposed structure to the compound **2b.**

**5-Bromobenzofuran-2-yl -3'-(Substituted-benzyl)- 3'H-[1', 3', 4']oxadiazole-2-thiones 3(a-d):** The treatment of 5-Bromo-benzofuranyl Schiff bases **2(a-d)** with carbon disulphide and potassium hydroxide in ethanol produced 5-Bromo-benzofuranyl oxadiazoles **3(a-d)**.

In IR spectrum of **3(a-d)** the disappearance of peak at 1680 $cm^{-1}$ indicated the absence of carbonyl group which was present in compound **2(a-d)** and also absorption band in the range of 1020-1060 $cm^{-1}$ due to C=S stretching frequency was appeared. In addition, the C=N and C-N frequencies at 1585 $cm^{-1}$ and 1317 $cm^{-1}$ respectively were also observed which were tabulated in (Table 3).

Further proof for the proposed structures were confirmed by $^1H$ NMR and mass spectral data of compound **3a**. $^1H$ NMR spectrum in DMSO was resulted in a singlet at 3.70 δ ppm due to N-$CH_2$ protons. The multiplet in the range of 6.94-7.73 δ ppm was due to the aromatic protons. The molecular ion peak was observed at *m/z* =387 in its mass spectrum confirmed the formation of **3a**.

**Table 2.** IR data of compounds 2(a-d)

| Compound No. | Substituent 'R' | IR data in ($cm^{-1}$) | | |
|---|---|---|---|---|
| | | NH | C=O | C=N |
| 2a | $C_6H_5$ | 3437 | 1661 | 1577 |
| 2b | $C_6H_4OCH_3$(p) | 3448 | 1680 | 1590 |
| 2c | $C_6H_4Cl$(m) | 3420 | 1670 | 1586 |
| 2d | $C_6H_4Cl$(o) | 3361 | 1665 | 1593 |

**Table 3.** IR data of compounds 3(a-d)

| Compound No. | Substituent 'R' | IR data in ($cm^{-1}$) | | |
|---|---|---|---|---|
| | | C=S | C-N | C=N |
| 3a | $C_6H_5$ | 1051 | 1317 | 1585 |
| 3b | $C_6H_4OCH_3$(p) | 1060 | 1300 | 1639 |
| 3c | $C_6H_4Cl$(m) | 1027 | 1328 | 1595 |
| 3d | $C_6H_4OH$(p) | 1054 | 1309 | 1603 |

## APPLICATION

**Antibacterial activity:** The newly synthesized compounds **2(a-d)** and **3(a-d)** were screened for their antibacterial activity against ***S. aureus* , *E. coli, P. aeuroginosa, Staphylococcus albus, Klebsiella pneumoniae,*** in **50** µg $mL^{-1}$ and **100** µg $mL^{-1}$ in comparison with standard drugs Penicillin, Streptomycin and Azithromycin by using cup plate method. The zones of inhibition of sample compounds against bacteria were measured in millimeter and were tabulated below in table 4.

The compound **3c** exhibited maximum inhibition compared to standard drug Penicillin in **50** µg $mL^{-1}$ and also in **100** µg $mL^{-1}$ against ***S. aureus***. Effective inhibition of ***E. coli*** and ***P. aeruginosa*** can be seen with **2c** at meta position in both the concentrations due to the chloro substitution in phenyl group. All other compounds exhibited good inhibition against the given bacteria. In the 4$^{th}$ series, the compound **3c** have shown very good activity compared to all other derivatives against ***E. coli,*** **3a** and **3c** exhibited good inhibition against ***P. aeuroginosa,*** also **2a** acted as good inhibitor against ***S.aureus***.

**Antifungal activity:** The novel compounds **2(a-d)** and **3(a-d),** were also screened for their antifungal activity against ***Candida albicans*** and ***Aspergillus niger*** in two concentrations **50** µg $mL^{-1}$ and 100 µg $mL^{-1}$ with standard drug Griseofulvin by broth micro-dilution method. The zone of inhibition of sample compounds against two fungi were recorded in millimeter and were displayed in table 5.

In 3$^{rd}$ series, the compounds **2a** and **2b** against ***Candida albicans,*** **2a** against ***Aspergillus niger*** displayed very potentize activity with respect to the standard drug may be due to the substituent

**Table 4.** Results of antibacterial activity of novel compounds in 50 and 100 μg $mL^{-1}$

| 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 $mL^{-1}$ |
| 2a | 12 | 16 | 11 | 16 | 12 | 18 |
| 2b | 14 | 18 | 12 | 18 | 13 | 17 |
| 2c | 16 | 20 | 10 | 16 | 11 | 15 |
| 2d | 12 | 18 | 11 | 16 | 13 | 19 |
| 3a | 13 | 18 | 12 | 16 | 13 | 19 |
| 3b | 11 | 18 | 13 | 18 | 12 | 18 |
| 3c | 12 | 17 | 14 | 19 | 13 | 20 |
| 3d | 13 | 16 | 13 | 17 | 10 | 13 |
| **Standard** | | | | | | |
| Penicillin | 15 | 22 | -- | -- | -- | -- |
| Streptomycin | -- | -- | 21 | 28 | 22 | 27 |
| **Control** | | | | | | |
| D.M.F. | Nil | Nil | Nil | Nil | Nil | Nil |

**Table 5.** Results of antifungal activity of novel compounds in 50 and100 μg $mL^{-1}$

| 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 $mL^{-1}$ |
| 2a | 14 | 18 | 14 | 19 |
| 2b | 14 | 20 | 11 | 18 |
| 2c | 12 | 17 | 11 | 16 |
| 2d | 13 | 17 | 12 | 18 |
| 3a | 12 | 16 | 11 | 15 |
| 3b | 13 | 18 | 10 | 15 |
| 3c | 10 | 15 | 11 | 17 |
| 3d | 12 | 18 | 10 | 16 |
| **Standard** | | | | |
| Griseofulvin | 23 | 27 | 23 | 28 |
| **Control** | | | | |
| D.M.F. | Nil | Nil | Nil | Nil |

effect. Compounds **2b, 2c** has shown moderate activity against ***Aspergillus niger*** in **50** μg $mL^{-1}$. Compounds **2b, 2c** and **2d** exhibited good and moderate zone of inhibition respectively, compared to standard Griseofulvin against ***Candida albicans*** in **100** μg $mL^{-1}$.

In $4^{th}$ series, the derivative **3a** have shown very good activity and **3c** exhibited weak activity against ***Candida albicans***, the compounds **3a** and **3d** displayed moderate and weak activity against ***Aspergillus niger*** respectively in **50** μg $mL^{-1}$. The compounds **3a** and **3c** displayed very good and average inhibition against ***Candida albicans*** respectively, compared to all $3^{rd}$series derivatives. The compound **3c** acted as efficient inhibitor of ***Aspergillus niger*** compared to all $3^{rd}$ series analogs with respect to standard one in **100** μg $mL^{-1}$.

## CONCLUSION

All newly synthesized compounds were confirmed by IR. The $^{1}$HNMR and mass spectra of representative compounds of **$2^{nd}$** and **$3^{rd}$** series adds additional proof and all compounds were shown encouragingly good antibacterial and antifungal activity with reference to the standard drugs.

## ACKNOWLEDGEMENT

It gives me an immense pleasure to acknowledge Dr. Shiva Kumar Hugar department of Pharmaceutical Chemistry, BLDE College of Pharmacy, Vijapura, Karnataka and the Department of Chemistry/Industrial Chemistry, VSKU Ballari for providing chemicals and laboratory facility during my work

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