

## Schiff Bases of 5-bromo-1-Benzofuran-2-Carbohydrazide

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Received: February 19, 2018, Accepted: March 20, 2018, Published: March 20, 2018.

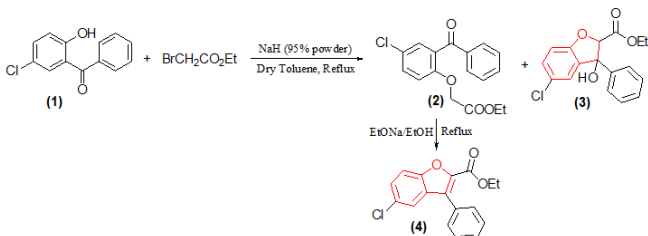
### ABSTRACT

The 5-bromo-1-benzofuran-2-carbohydrazide was synthesized from 5-bromosalicylaldehyde through propan-2-yl 5-bromo-benzofuran-2-carboxylate by series of reactions. The 5-bromo-1-benzofuran-2-carbohydrazide was treated with variety of substituted aldehydes forming corresponding hydrazones. All synthesized compounds were characterized by IR, NMR and mass spectra.

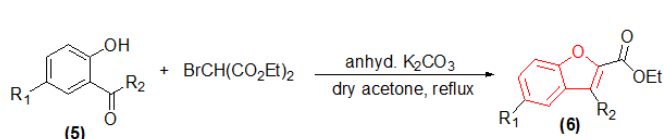
**Keywords:** Benzofuran, Salicylaldehyde, Hydrazide, Hydrazones, Schiff bases.

### 1. INTRODUCTION

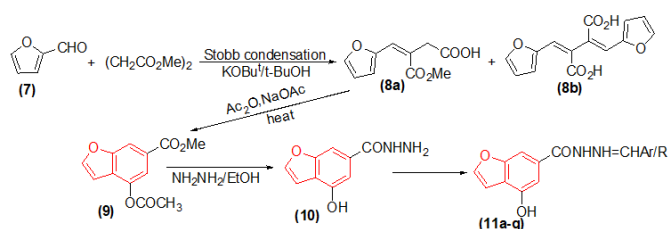
The synthesis of ester of 1-benzofuran-2-carboxylate derivatives was reported by number of scientists, some of them are reported here. They can be synthesized by direct condensation of 2-hydroxybenzophenones (1) with ethyl 2-bromoacetate in dry toluene in the presence of sodium hydride forming ethyl 2-benzoylphenoxy acetate derivatives (2) with very small amount of benzofuran ethyl ester (3) which was separated by column chromatography [1].



Searching in the literature for the alternative procedure allowing a direct and high yielding synthesis of benzofuran-2-ester (6); some of the furochromes are synthesized by the direct cyclisation with diethyl bromomalonate in the presence of anhydrous potassium carbonate in dry acetone [2]. The presence of in fact of an electron withdrawing group R<sub>1</sub> increased the reactivity of carbonyl function. By contrast, as expected the presence of R<sub>1</sub> as an electron donor group like methyl or lacking of the substitution decreases the electrophilic properties of ketone functionality affording the lower yield of the corresponding benzofuran (< 40%).

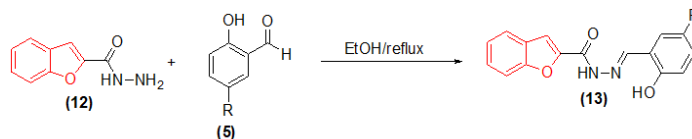


The Schiff bases of 4-hydroxy benzofuran-6-carboxhydrazide (10) and their hydrazone derivatives (11a-q) shows moderate to high degree of antibacterial activity when compared to standard drugs [3]. 4-Hydroxy benzofuran-6-carboxhydrazide has been synthesized from furfuraldehyde (7) and dimethyl succinate via series of reaction [4].



Hydrazides can be synthesized by hydrazinolysis of amine, ester and thioesters [5]. The reaction of hydrazines with acyl chlorides or anhydrides is also well known [6]. Novel Schiff bases [4] of 1-benzofuran-2-carbohydrazide were synthesized and studied their pharmacological activities.

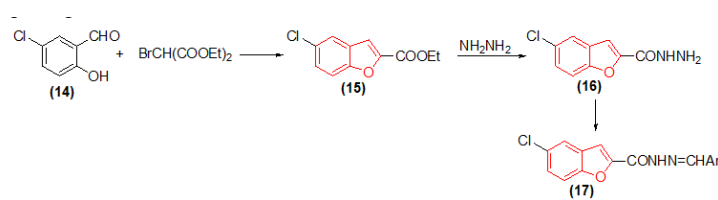
Most of the benzofuran compounds [7] frequently occur in natural products and are good chelating agents. The compound amiodarone hydrochloride used as an ideal antiarrhythmic drug [8] contains a 2, 3-substituted benzofuran moiety. The microbial activities of ligands are altered many fold on coordination with metal ions [9]. Hence, there is a need for information on coordination compounds of simple benzofuran Schiff's bases (13) and their metal complexes. In view of the biological importance of Schiff's bases and benzofuran it was thought worthwhile to synthesize the benzofuran Schiff's bases (13) derived from the condensation of benzofuran-2-carbohydrazide (12) [10] with 5-methyl-salicylaldehyde and 5-chlorosalicylaldehyde and to prepare their metal complexes with metal ions like Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Hg(II), UO<sub>2</sub>(II)



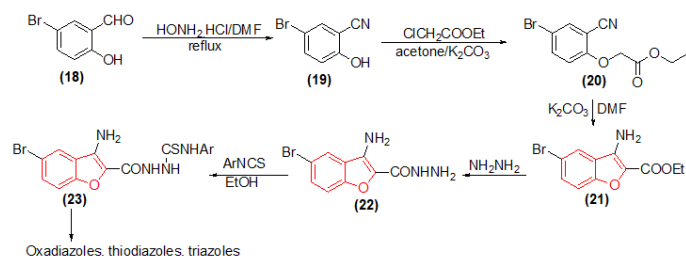
and Th(IV). All the complexes and ligands are screened for their antimicrobial activity.

5-Chlorobenzofuran-2-carbohydrazides (17) [11] were synthesized from ethyl 5-Chlorobenzofuran -2-carboxylate (15) and condensed with various substituted aromatic aldehyde to give Schiff base and obtained compound were cyclised with carbon disulphide and alcoholic potassium hydroxide to obtain various 5-Chlorobenzofuran derivatives. Some of them found to be shown good activity against gram positive and gram negative bacteria like

5-Bromosalicylaldehyde (**18**) was treated with hydroxylamine hydrochloride in N,N-dimethyl formamide under reflux conditions for about 20 minutes forming 5-bromo salicylonitrile (**19**) which is the important precursor for the synthesis of benzofuran skeleton. The 5-bromo salicylonitrile (**19**) was further treated with ethyl chloroacetate in anhydrous acetone in presence of anhydrous potassium carbonate forming its ethyl ester (**20**). The crude ester was treated with potassium carbonate in DMF under reflux condition forming ethyl 5-bromo-3-amino-1-benzofuran-2-carboxylate (**21**) [12]. This ester was converted into hydrazide (**22**) by treating it with hydrazine hydrate in ethanol. It undergoes cyclisation under different reaction conditions forming oxadiazoles, triazoles and thiadiazoles.



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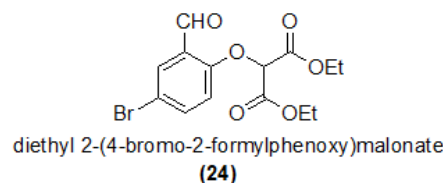


Many methodologies for the synthesis of benzofuran-2-carboxylic acid skeleton were developed and most of them are based on the reaction of salicylaldehydes with haloacetates followed by cyclization of formylphenoxyacetic acid derivatives intermediates [13-19]. The cyclizations were usually carried out in an alcoholic solution in the presence of a basic catalyst such as sodium ethanolate [13], 1,8-diazobicyclo-[5.4.0]-7-undecane, potassium carbonate [14-15] or phosphine [16]. Moreover, ethyl 5-nitrobenzofuran-2-carboxylate was prepared by cyclocondensation of 2-hydroxy-5-nitrobenzaldehyde with bromomalonic acid [20] as well as palladium catalysed carbonylative cyclization of *o*-alkynylphenols [21-23]. Hydrazines are the attractive targets compounds for new drug development due to their synthetic and

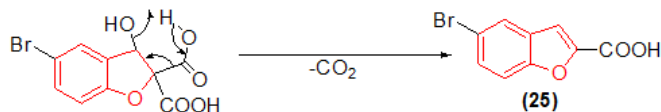
biological versatility including anti-TB activities [24-28].

## 2. EXPERIMENTAL WORK

5-Bromo-1-benzofuran-2-carbohydrazide was synthesized from 5-bromosalicylaldehyde (**18**) by known literature method [29]. The carbon atom of diethyl (4-bromo-2-formylphenoxy)propanedioate (**24**) is more acidic than the carbon atom of diethyl malonate containing chlorine due to more electro negativity of oxygen atom.



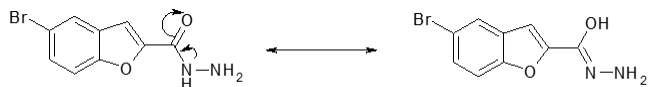
The  $-\text{CH}-$  group of (**24**) is more acidic than that of diethyl chloromalonate, therefore undergoes deprotonation forming carbanion which shows intramolecular nucleophilic attack on aldehyde group in presence of 10% alcoholic KOH forming solid dipotassium carboxylate salt. Both the ester groups undergo hydrolysis. The salt was dissolved in 3M sulphuric acid forming free dicarboxylic acid which undergoes decarboxylation on heating forming 5-bromo-1-benzofuran-2-carboxylic acid (**25**).



The isopropyl ester of 5-Bromo-1-benzofuran-2-carboxylic acid (**25**) was formed by the esterification of (**25**) in presence of excess 2-propanol and concentrated sulphuric acid (as a dehydrating agent). Pour the reaction mixture into ice and neutralized by ammonia; extract the product by using ether and dried by using anhydrous calcium chloride to remove the water from ether. Distilled out ether under reduced pressure forming propan-2-yl 5-bromo-1-benzofuran-2-carboxylate (**26**). The formation of product (**26**) was confirmed by TLC, m.p., and FT-IR spectra. The carbonyl group of ester shows stretching vibration at  $1727\text{ cm}^{-1}$  confirms the formation of product (**26**).

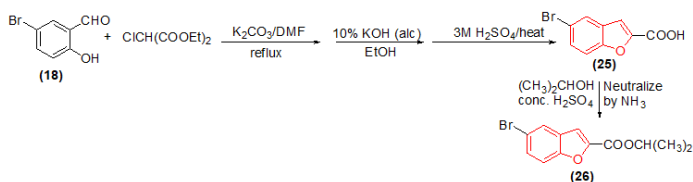
The propan-2-yl 5-bromo-1-benzofuran-2-carboxylate (**26**) was treated with hydrazine hydrate in 2-propanol in presence of acetic acid as catalyst. The solid 5-Bromo-1-benzofuran-2-carbohydrazide (**27**) obtained was filtered and recrystallized from ethanol. The melting points of all Schiff bases and their starting compounds are recorded by using Labtronics Digital Melting point apparatus. The formation of product (**27**) was confirmed by TLC, m.p., sodium fusion test, FT-IR, NMR spectroscopy. The compound (**27**) shows frequencies at  $3322$  and  $3183\text{ cm}^{-1}$  is due to  $-\text{NH}-$  and  $-\text{NH}_2$  stretching vibrations &  $1668\text{ cm}^{-1}$  is due to stretching vibrations of carbonyl group of hydrazide. It does not show any absorption band in the frequency region of carbonyl group of ester.

Hydrazides having two nitrogen atoms available for the donation of electron pair. The lone pair of electrons present over the nitrogen atom of  $-\text{NH}-$  group is in conjugation with double bond of carbonyl and not easily available for donation but in case of  $-\text{NH}_2$  group, lone pair is free for donation and easily donated towards electrophilic center like carbonyl group as shown below:



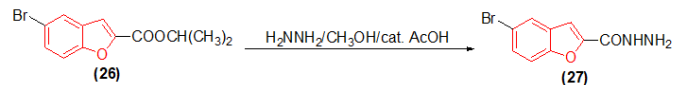
The 5-Bromo-1-benzofuran-2-carbohydrazide (**27**) has been condensed with series of aldehydes in ethanol in presence of acetic acid forming Schiff bases. The catalyst does not added for the aldehydes containing active phenolic and carboxylic acid groups. The formation of Schiff bases has been confirmed by TLC, m.p., FT-IR, NMR and mass spectroscopy. The -NH- and -NH<sub>2</sub> groups show absorption at 3322 and 3183 cm<sup>-1</sup> is due to -N-H stretching vibrations. During the reaction, -NH<sub>2</sub> group is converted to imine group (>C=N-) so that only one signal observed in the region 3100 – 3400 cm<sup>-1</sup> along with new signal in the region of 1650-1590 cm<sup>-1</sup>. But this signal get overlapped with the signal of amide carbonyl or C=C (aromatic) bond signals.

## 2.1 Synthesis of propan-2-yl 5-bromo-benzofuran-2-carboxylate (**26**) [29]:



Dissolve 200 mg of 5-bromosalicylaldehyde and 470 mg of diethyl chloromalonate (65% pure, freshly prepared from diethyl malonate and thionyl chloride) in 2 ml of 2-butanone. Add 270 mg of

anhydrous potassium carbonate slowly with constant stirring for the period of 15 minutes and reflux the given reaction mixture about 135 minutes. Check the completion of reaction by monitoring TLC time to time. Pour the reaction mixture into ice cold water and



extract the compounds by using 2 x 5 ml of ethyl acetate or MDC and wash it with water and brine. Distilled out the solvent and ethyl acetate or MDC under reduced pressure to obtain red colour viscous oil. Dissolve it in 1.25 ml 10% potassium hydroxide in ethanol and warm it. Cool the reaction mixture and filter the solid product. Dissolve the crude solid product in 3.5 ml 3M sulphuric acid and heat it to 80-85°C in water bath (till evolve of carbon dioxide by product of decarboxylation) till the effervescences of gas get stop. The solid separated was filtered and recrystallized by hot water.

Dissolve the crude product in 1 ml of isopropyl alcohol and add 0.5 ml conc. sulphuric acid slowly with constant stirring. Reflux the reaction for about 6 hrs on water bath. The completion of reaction was confirmed by taking TLC. Cool the reaction mixture and add into 1 gm crushed ice slowly with stirring and neutralized by aqueous ammonia solution. Extract the product by ether 2 x 2 ml and dry the organic layer anhydrous calcium chloride. Evaporate the ether in boiling water bath to obtain isopropyl 5-bromo-1-benzofuran-2-carboxylate (**26**) as white solid. Recrystallized it from ethanol. Yield is 72 %. m.p. = 85 – 87°C.

**FTIR (KBr):** 3095, 2977, 1727, 1563, 1311, 1182 cm<sup>-1</sup>. (3424 cm<sup>-1</sup> water proton).

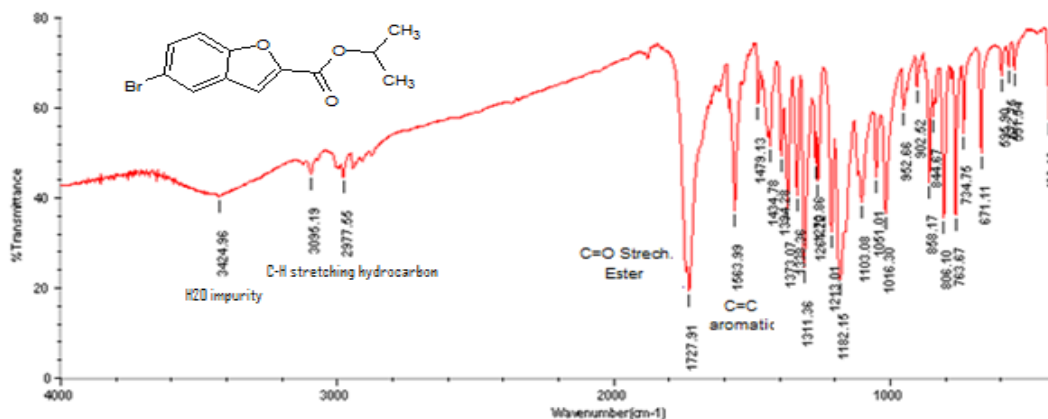


Fig. 1: FTIR of propan-2-yl 5-bromo-benzofuran-2-carboxylate (**26**)

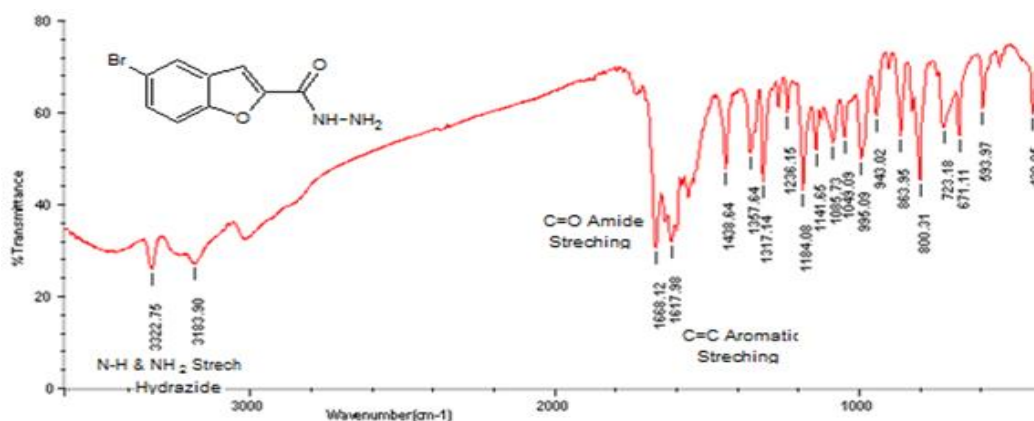


Fig. 2: FTIR of 5-Bromo-1-benzofuran-2-carbohydrazide (**27**)

## 2.2. Synthesis of 5-Bromo-1-benzofuran-2-carbohydrazide (27) [29]:

Dissolve 0.300 (6 mmol) gm of hydrazine hydrate in 20 ml of isopropyl alcohol; add 1.420 gm (5 mmol) of propan-2-yl 5-bromo-1-benzofuran-2-carboxylate and catalytic amount of acetic acid. Reflux the reaction mixture to 5 hrs and cool, the solid product separated was filtered. The purity of the product was checked by IR, NMR and mass spectra. M.p. 165°C and yield 83%.

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**FT-IR (KBr):** 3322, 3183, 1668, 1617, 1317, 1184, 800  $\text{cm}^{-1}$ .

**NMR (300MHz,  $\text{CDCl}_3$ ):** 12.224 and 8.436 (bs, 1H, -CO-NH); 8.091 (s, 1H, Ar-H); 7.706 (m, 2H, Ar-H); 7.659 (s, 1H, Furan-H); 7.040 (bs, 2H, -NH<sub>2</sub>).

**Mass spectra:** 91, 253, 254.8 (M-1), 256.9 (M+1, Br is <sup>81</sup>Br), 257.9 (M+2).

The strong absorption in FT-IR spectra of **27** at 3322 and 3183  $\text{cm}^{-1}$  is due to symmetric stretching vibrations of N-H bond of -NH-NH<sub>2</sub> group of hydrazide. The formation of hydrazide functionality is also confirmed by the carbonyl stretching frequency. The ester

carbonyl group of **26** shows absorption at 1727  $\text{cm}^{-1}$  which is absent in hydrazide and new absorption band observed at 1668  $\text{cm}^{-1}$  indicate the formation of amide -CO- group. The aromatic double bonds show strong absorption bands in 1617 and 1578  $\text{cm}^{-1}$ .

The NMR spectrum of 5-bromo-1-benzofuran-2-carbohydrazide (**27**) and its Schiff bases was recorded by using 300 MHz NMR instrument by using DMSO-D<sub>6</sub> solvent and TMS is reference compound. The amide proton of hydrazide linkage [-CO-NH-N<] shows two chemical shifts, one at  $\delta$  12.224 ppm (due to -C(OH)=N-N) and second at  $\delta$  8.436 ppm (is due to -CO-NH-N). The -NH<sub>2</sub> protons are highly deshielded and therefore shows chemical shift at  $\delta$  7.040 ppm. The aromatic proton present at C-4 position (C<sub>4</sub>-H) is highly deshielded and shows chemical shift at  $\delta$  8.091 ppm. The C<sub>6</sub>-H and C<sub>7</sub>-H are also deshielded and shows multiplet at  $\delta$  7.706 ppm. The furan proton (C<sub>3</sub>-H) is shielded proton as compared to other aromatic protons even though it is present 2-position with respect to electron-withdrawing -CONHNH<sub>2</sub> group because of high average electron density of five membered ring carbon and +R effect of furan oxygen atom.

The presence of one bromine atom in the **27** has been confirmed from its mass spectra. The compound shows two fragments 254.8 is M-1 (when Br is <sup>79</sup>Br) and 256.9 is M+1 (when Br is <sup>81</sup>Br) with equal intensity indicate the presence of one bromine atom.

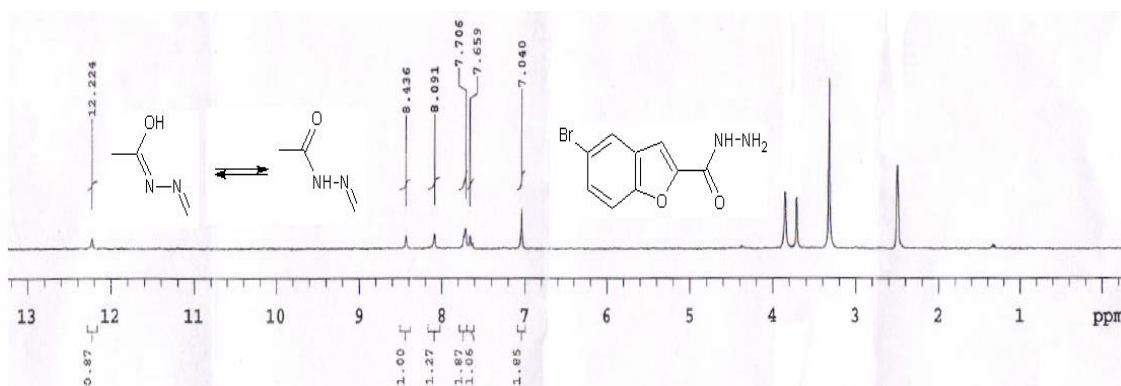


Fig. 3: NMR of 5-Bromo-1-benzofuran-2-carbohydrazide (27)

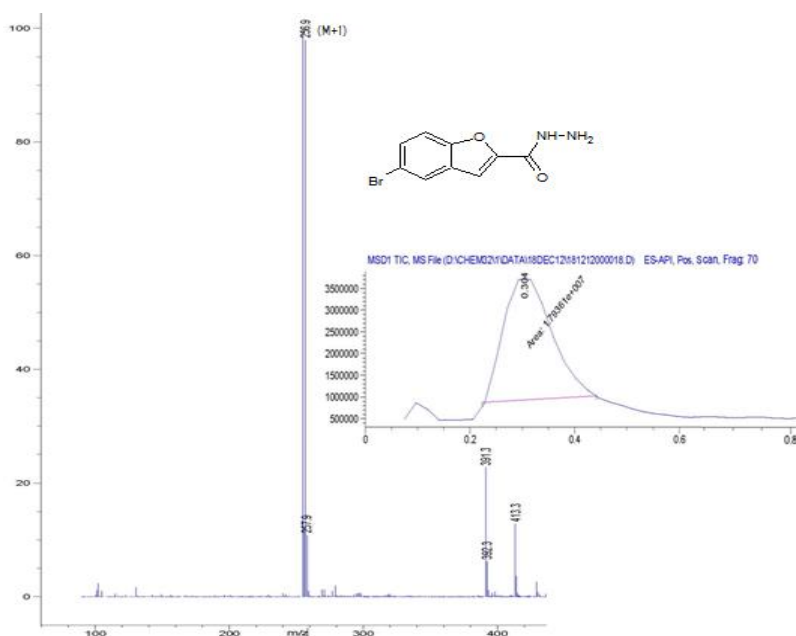


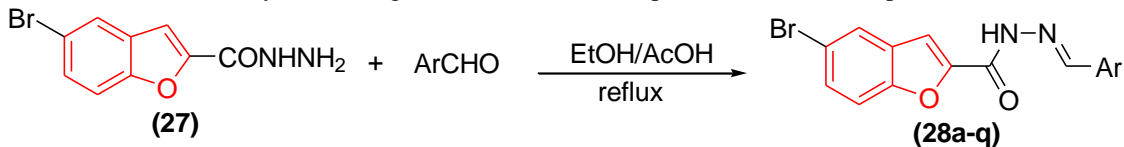
Fig. 4: GC-MS of 5-Bromo-1-benzofuran-2-carbohydrazide (27)

### 2.3. Synthesis of Schiff bases of 5-bromo-1-benzofuran-2-carbohydrazide (27):

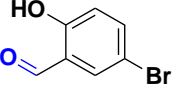
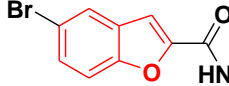
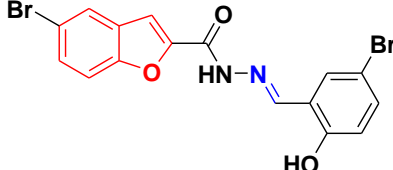
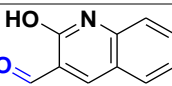
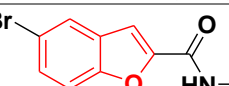
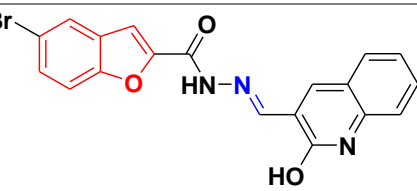
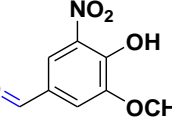
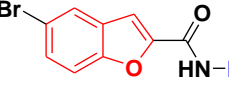
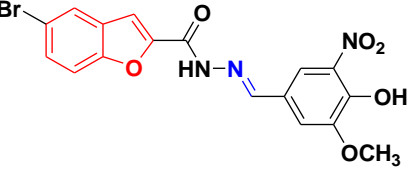
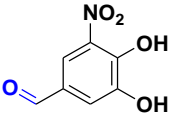
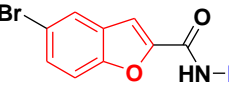
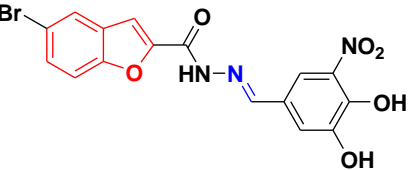
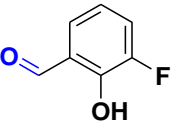
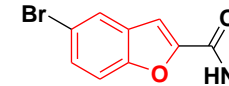
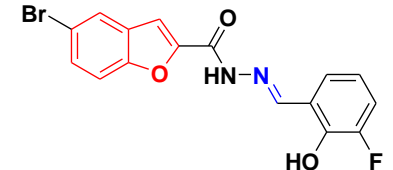
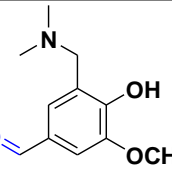
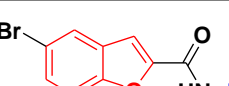
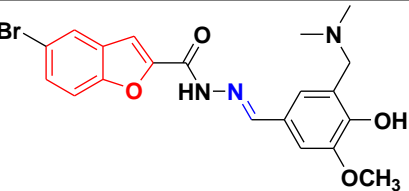
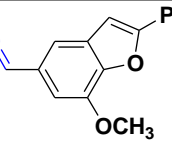
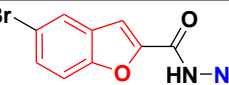
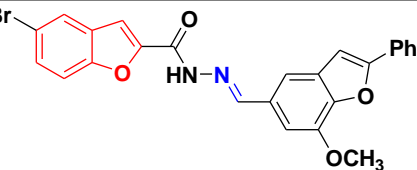
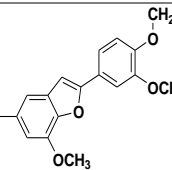
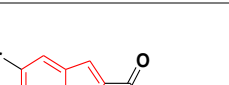
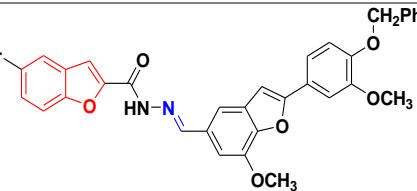
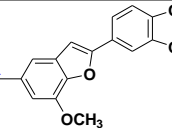
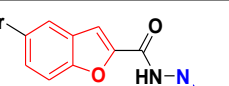
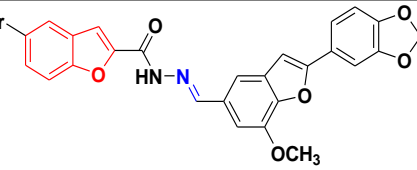
Dissolve 0.127 g (0.5 mmol) of 5-bromo-1-benzofuran-2-carbohydrazide (27) in 10 ml of ethyl alcohol. Add ethanolic solution of aldehydes (0.52 mmol in 5 ml ethyl alcohol) slowly with stirring and catalytic amount of glacial acetic acid (acetic acid was not added in case of aldehyde containing acidic phenolic or carboxylic group). Reflux the reaction mixture for about 3-6 hrs. Completion of the reaction was checked by monitoring TLC time to

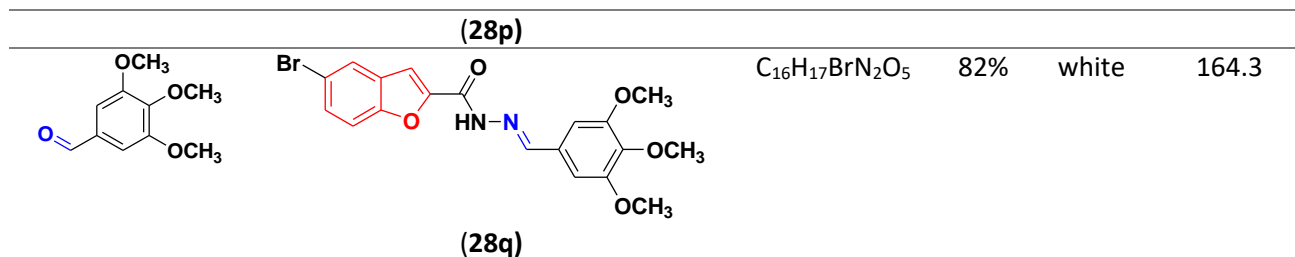
time. Cool the reaction mixture and the solid separated was filtered and washed by cold ethyl alcohol. Record the yield and m.p. of the product.

The reaction conditions required for the completion of the reaction depends on the nature of reactants. The aldehydes in which the aldehydic carbonyl carbon atom shows more electrophilic character reacts easily (required less time for completion of reaction). The electron withdrawing groups which show (-R) effect present at 2- and or 4-position are more reactive.

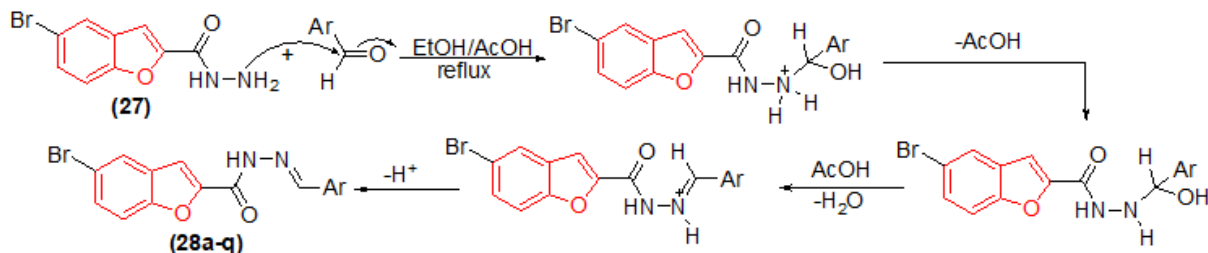


Aldehyde	Hydrazone	Formula	Yield	Colour	m.p. <sup>o</sup> C
		C <sub>16</sub> H <sub>10</sub> BrN <sub>2</sub> O <sub>2</sub> F	86%	white	235
		C <sub>17</sub> H <sub>9</sub> BrN <sub>3</sub> O <sub>2</sub> F	74%	white	250
		C <sub>17</sub> H <sub>10</sub> BrN <sub>2</sub> O <sub>3</sub> F <sub>3</sub>	80%	white	120
		C <sub>13</sub> H <sub>9</sub> BrN <sub>4</sub> O <sub>2</sub>	87%	buff white	280
		C <sub>15</sub> H <sub>11</sub> BrSN <sub>2</sub> O <sub>2</sub>	69%	gray	248
		C <sub>18</sub> H <sub>12</sub> BrN <sub>3</sub> O <sub>2</sub>	74%	pink	242
		C <sub>16</sub> H <sub>11</sub> BrN <sub>2</sub> O <sub>3</sub>	72%	yellow	198

			$C_{16}H_{10}Br_2N_2O_3$	80%	yellow	257
<b>(28h)</b>						
			$C_{19}H_{12}BrN_3O_3$	78%	spongy yellow	above 278 (decompose)
<b>(28i)</b>						
			$C_{17}H_{12}BrN_3O_6$	83%	reddish yellow	220
<b>(28j)</b>						
			$C_{16}H_{10}BrN_3O_6$	87%	dark reddish	270 (turns black and melt at 297)
<b>(28k)</b>						
			$C_{16}H_{10}BrFN_2O_3$	69%	faint yellow	259
<b>(28l)</b>						
			$C_{20}H_{20}BrN_3O_4$	58%	greenish yellow	150
<b>(28m)</b>						
			$C_{25}H_{17}BrN_2O_4$	73%	shiny white	262
<b>(28n)</b>						
			$C_{33}H_{25}BrN_2O_6$	78%	shiny faint yellow	246
<b>(28o)</b>						
			$C_{26}H_{17}BrN_2O_6$	79%	yellow	256
<b>(28p)</b>						



### Reaction Mechanism:



#### 5-bromo-N'-[(E)-(4-fluorophenyl)methylidene]-1-benzofuran-2-carbohydrazide (28a):

**FT-IR (KBr):** 3272, 1664, 1602, 1556, 1552, 1504, 1234, 1182, 962, 809  $cm^{-1}$ .

**NMR ( $\delta$  in ppm, 300MHz, DMSO):** 12.416 and 8.545 (bs, 1H, -CO-NH); 8.094 (s, 1H, Ar-H); 7.802-7.745 (m, 4H, Ar-H); 7.708-7.595 (m, 3H, Ar-H); 7.478 (s, 1H, Furan-H).

**Mass spectra:** 359, 361 (basic ion peak), 362.

Peak at 3272  $cm^{-1}$  is due to the stretching vibrations of amide -N-H bond which shifted to higher frequency because of electron-withdrawing effect of fluorine present at para-position. It is weak because of conjugation with C=O and N=C bonds. The amide C=O shows strong bond at 1664  $cm^{-1}$ . The aromatic conjugated C=C bond shows stretching vibration at 1602, 1556, 1552, 1504  $cm^{-1}$ .

#### 5-bromo-N'-[(E)-(3-cyano-4-fluorophenyl)methylidene]-1-benzofuran-2-carbohydrazide (28b):

**FT-IR (KBr):** 3274, 2242, 1691, 1616, 1562, 1500, 1270, 1189, 973, 798  $cm^{-1}$ .

**NMR ( $\delta$  in ppm, 300MHz, DMSO):** 12.467 and 8.519 (bs, 1H, -CO-NH); 8.270 (s, 1H, Ar-H); 8.192 (m, 2H, Ar-H); 8.091 (s, 1H, Ar-H); 7.742 - 7.615 (m, 4H, Ar-H, Furan-H).

**Mass spectra:** 385, (M + 1) 387.

The C=O group of amide stretching frequency (1691  $cm^{-1}$ ) has been shifted to higher value because of conjugated electron withdrawing group to amide nitrogen and therefore to carbonyl (in resonance hybrid) at para and meta position aromatic ring. The cyano-group shows strong band at 2242  $cm^{-1}$ .

#### 5-bromo-N'-[(E)-[3-(trifluoromethoxy)phenyl]methylidene]-1-benzofuran-2-carbohydrazide (28c):

**FT-IR (KBr):** 3212, 1702, 1648, 1594, 1542, 1272, 1164, 958, 806  $cm^{-1}$ .

**NMR ( $\delta$  in ppm, 300MHz, DMSO):** 12.260 and 8.512 (bs, 1H, -CO-NH); 8.086 (s, 1H, Ar-H); 7.815 (m, 2H, Ar-H); 7.717-7.701 (m, 2H, Ar-H); 7.660 (s, 1H, Furan-H); 7.350-7.291 (m, 2H, Ar-H).

**Mass spectra:** 420, (M + 1) 422, (M + 2) 423 (weak).

The C=O group of amide (1702  $cm^{-1}$ ) and N-H of amide (3212  $cm^{-1}$ ) stretching frequency has been shifted to higher value because of strong electron withdrawing group present at meta position at aromatic ring.

#### 5-bromo-N'-[(E)-1H-imidazol-4-ylmethylidene]-1-benzofuran-

#### 2-carbohydrazide (28d):

**FT-IR (KBr):** 3450, 3143, 1679, 1619, 1577, 1313, 1276, 1224, 1191, 977, 808  $cm^{-1}$ .

**NMR ( $\delta$  in ppm, 300MHz, DMSO):** 14.568 (bs, 1H, NH-diazole); 12.912 (bs, 1H, -CO-NH); 8.155 (s, 1H, Ar-H); 7.042 (s, 1H, Ar-H); 7.790 - 7.571 (m, 5H, Ar-H, Furan-H).

**Mass spectra:** 332.12, (M + 1) 334.

#### 5-bromo-N'-[(E)-(3-methylthiophene-2-yl)methylidene]-1-benzofuran-2-carbohydrazide (28e):

**FT-IR (KBr):** 3210, 1656, 1598, 1552, 1440, 1349, 1294, 1176, 966, 871, 806, 715  $cm^{-1}$ .

**NMR ( $\delta$  in ppm, 300MHz, DMSO):** 12.099 (bs, 1H, -CO-NH); 8.795 (s, 1H, Ar-H); 8.075 (s, 1H, Ar-H); 7.712-7.607 (m, 4H, Ar-H); 7.002 (s, 1H, Furan-H); 2.344 (s, 3H, Ar-CH<sub>3</sub>).

**Mass spectra:** 363, 365.

#### 5-bromo-N'-[(E)-1H-indol-5-ylmethylidene]-1-benzofuran-2-carbohydrazide (28f):

**FT-IR (KBr):** 3340, 3214, 1671, 1612, 1594, 1521, 1473, 1440, 1346, 1286, 1212, 1174, 902, 867, 802, 730  $cm^{-1}$ .

**NMR ( $\delta$  in ppm, 300MHz, DMSO):** 12.018 (bs, 1H, -CO-NH); 11.981 (s, 1H, Indol-H); 8.341 (d, 1H, Ar-H); 8.224 (s, 1H, Ar-H); 8.102 (d, 1H, Ar-H); 7.881 (d, 1H, Ar-H); 7.713 (m, 2H, Ar-H); 7.664 - 7.608 (m, 3H, Ar-H); 6.687 (s, 1H, Furan-H).

**Mass spectra:** (M + 1) = 383

#### 5-bromo-N'-[(E)-(2-hydroxyphenyl)methylidene]-1-benzofuran-2-carbohydrazide (28g):

**FT-IR (KBr):** 3355, 3135, 2998, 1670, 1623, 1608, 1579, 1513, 1488, 1440, 1359, 1267, 1174, 923, 788, 744  $cm^{-1}$ .

**NMR ( $\delta$  in ppm, 300MHz, DMSO):** 12.465 (bs, 1H, -CO-NH); 11.038 (bs, 1H, OH); 8.727 (s, 1H, Ar-H); 8.091 (s, 1H, Ar-H); 7.729 - 7.576 (m, 4H, Ar-H); 7.317 (s, 1H, Furan-H); 6.906 - 6.950 (m, 2H, Ar-H).

**Mass spectra:** 358, (M + 1) 360.

#### 5-bromo-N'-[(E)-(5-bromo-2-hydroxyphenyl)methylidene]-1-benzofuran-2-carbohydrazide (28h):

**FT-IR (KBr):** 3423, 3205, 3029, 1650, 1617, 1590, 1479, 1438, 1357, 1292, 1267, 1180, 971, 806, 730  $cm^{-1}$ .

**NMR ( $\delta$  in ppm, 300MHz, DMSO):** 12.533 (bs, 1H, -CO-NH); 11.074 (bs, 1H, Ar-OH); 8.688 (s, 1H, Ar-H); 8.090 (s, 1H, Ar-H); 7.816 (s, 1H, Ar-H); 7.737-7.664 (m, 2H, Ar-H); 7.428 (s, 1H,

Furan-H); 6.924 – 6.893 (m, 2H, Ar-H).

**Mass spectra:** 437, (M+1) 439, (M+3) 441.

**5-bromo-N'-[(E)-(2-hydroxyquinolin-3-yl)methylidene]-1-benzofuran-2-carbohydrazide (28i):**

**FT-IR (KBr):** 3438, 3185, 1660, 1644, 1598, 1563, 1498, 1420, 1348, 1357, 1220, 1180, 970, 865, 802, 759 cm<sup>-1</sup>.

**NMR ( $\delta$  in ppm, 300MHz, DMSO):** 12.402 and 8.506 (bs, 1H, -CO-NH); 12.065 (bs, 1H, Ar-OH); 10.240 (s, 1H, N=C-H); 8.769 (s, 1H, Ar-H); 8.098 (s, 1H, Ar-H); 7.937 (m, 1H, Ar-H); 7.758 – 7.532 (m, 4H, Ar-H); 7.361 (d, 1H, Furan-H); 7.254 (d, 1H, Ar-H).

**Mass spectra:** 410, 412.

**5-bromo-N'-[(E)-(4-hydroxy-3-methoxy-5-nitrophenyl)methylidene]-1-benzofuran-2-carbohydrazide (28j):**

**FT-IR (KBr):** 3320 (sharp peak indicate presence of intramolecular H-bonded –OH group), 3205, 1685, 1621, 1579, 1544, 1469, 1440, 1409, 1324, 1268, 1166, 948, 863, 804, 763 cm<sup>-1</sup> (1544 and 1324 is due to aromatic nitro group).

**NMR ( $\delta$  in ppm, 300MHz, DMSO):** 12.327 (bs, 1H, -CO-NH); 9.869 (bs, 1H, Ar-OH); 8.450 (s, 1H, Ar-H); 8.110 (d, 1H, N=C-H); 7.792 (s, 1H, Ar-H); 7.730-7.602 (m, 4H, Ar-H, Furan-H); 3.970 (s, 3H, OCH<sub>3</sub>).

**Mass spectra:** 433, 434.

**5-bromo-N'-[(E)-(3,4-dihydroxy-5-nitrophenyl)methylidene]-1-benzofuran-2-carbohydr-azide (28k):**

**FT-IR (KBr):** 3301 (sharp peak indicate presence of intramolecular H-bonded –OH group), 3210, 3029, 1650, 1621, 1594, 1542, 1442, 1396, 1321, 1247, 1180, 1133, 871, 811, 761 cm<sup>-1</sup> (1542 and 1321 are due to nitro group).

**NMR ( $\delta$  in ppm, 300MHz, DMSO):** 12.268 (bs, 1H, -CO-NH); 10.674 (bs, 2H, 2-OH); 8.385 (s, 1H, N=C-H); 8.080 (s, 1H, Ar-H); 7.711-7.639 (m, 4H, Ar-H); 7.587 (s, 1H, Furan-H).

**Mass spectra:** 418, 420.

**5-bromo-N'-[(E)-(3-fluoro-2-hydroxyphenyl)methylidene]-1-benzofuran-2-carbohydrazide (28l):**

**FT-IR (KBr):** 3457, 3357, 1691, 1610, 1586, 1527, 1469, 1440, 1361, 1247, 1170, 971, 869, 782, 725 cm<sup>-1</sup>.

**NMR ( $\delta$  in ppm, 300MHz, DMSO):** 12.626 (bs, 1H, -CO-NH); 11.356 (bs, 1H, OH); 8.745 (s, 1H, N=C-H); 8.103 (s, 1H, Ar-H); 7.753-7.651 (m, 3H, Ar-H); 7.448 (d, 1H, Ar-H); 7.334-7.275 (m, 1H, Ar-H); 6.930 (m, 1H, Ar-H).

**Mass spectra:** 375, 377.

**5-bromo-N'-[(E)-{3-[(dimethylamino)methyl]-4-hydroxy-5-methoxyphenyl)methylidene]-1-benzofuran-2-carbohydrazide (28m):** Sticky mass separated, extract with ethyl acetate, wash organic layer by saturated sodium bicarbonate and brine water, evaporate organic solvent, again wash with n-hexane to obtain greenish yellow solid.

**FT-IR (in KBr):** 3442, 3214, 1727, 1650, 1596, 1565, 1482, 1309, 1294, 1265, 1178, 970, 865, 765 cm<sup>-1</sup>.

**NMR ( $\delta$  in ppm, 300MHz, DMSO):** 12.291 (bs, 1H, -CO-NH); 9.100 (bs, 1H, OH); 8.103 (s, 1H, N=C-H); 7.802 (d, 1H, Ar-H); 7.632 (s, 1H, Ar-H); 7.442 – 7.342 (m, 4H, Ar-H, furan-H); 3.918 (s, 3H, OCH<sub>3</sub>); 2.721 (s, 2H, -NCH<sub>2</sub>-), 2.108 (s, 6H, 2 NCH<sub>3</sub>).

**Mass spectra:** 446, 448.

**5-bromo-N'-[(E)-(7-methoxy-2-phenyl-1-benzofuran-5-yl)methylidene]-1-benzofuran-2-carbohydrazide (28n):**

**FT-IR (KBr):** 3218, 3102, 1654, 1598, 1536, 1498, 1481, 1321, 1268, 1218, 1153, 910, 867, 804, 740 cm<sup>-1</sup>.

**NMR ( $\delta$  in ppm, 300MHz, DMSO):** 12.190 (bs, 1H, -CO-NH); 8.770 (s, 1H, N=C-H); 8.108 (s, 1H, Ar-H); 8.002 – 7.442 (m, 9H,

Ar-H); 7.332 (m, 1H, Furan-H); 7.112 (s, 1H, benzofuran-H); 4.098 (s, 3H, OCH<sub>3</sub>).

**Mass spectra:** 489, 491.

**5-bromo-N'-{(E)-[2-[4-(benzyloxy)-3-methoxyphenyl]-7-methoxy-1-benzofuran-5-yl)methylidene]-1-benzofuran-2-carbohydrazide (28o):**

**FT-IR (KBr):** 3205, 3035, 1644, 1598, 1540, 1508, 1465, 1349, 1245, 1226, 1157, 933, 833, 790, 744 cm<sup>-1</sup>.

**NMR ( $\delta$  in ppm, 300MHz, DMSO):** 12.115 (bs, 1H, -CO-NH); 8.476 (s, 1H, -N=CH); 7.875 (s, 1H, Ar-H); 7.730 (s, 1H, Ar-H); 7.618 – 7.356 (m, 10H, Ar-H); 7.043 – 6.916 (m, 3H, Ar-H); 5.211 (s, 2H, OCH<sub>2</sub>-Ar); 4.104 (s, 3H, OCH<sub>3</sub>); 4.006 (s, 3H, OCH<sub>3</sub>).

**Mass spectra:** 625, 627.

**5-bromo-N'-{(E)-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl)methylidene]-1-benzofuran-2-carbohydrazide (28p):**

**FT-IR (KBr):** 3174, 1650, 1592, 1550, 1354, 1336, 1230, 1178, 1031, 929, 808, 738 cm<sup>-1</sup>.

**NMR ( $\delta$  in ppm, 300MHz, DMSO):** 12.180 (bs, 1H, -CO-NH); 8.589 (s, 1H, N=C-H); 7.880 (s, 1H, Ar-H); 7.737 (s, 1H, Ar-H); 7.548 – 7.355 (m, 6H, Ar-H); 6.927 (m, 2H, Ar-H); 6.053 (s, 2H, O-CH<sub>2</sub>-O); 4.099 (s, 3H, OCH<sub>3</sub>).

**Mass spectra:** 533, 535.

**5-bromo-N'-[(E)-(3,4,5-trimethoxyphenyl)methylidene]-1-benzofuran-2-carbohydrazide (28q):**

**FT-IR (KBr):** 3197, 2994, 1650, 1577, 1548 1504, 1334, 1226, 1178, 1129, 958, 835, 721 cm<sup>-1</sup>.

**NMR ( $\delta$  in ppm, 300MHz, DMSO):** 12.168 (bs, 1H, -CO-NH); 8.502 (s, 1H, -N=CH); 7.902 (s, 1H, Ar-H); 7.612 (s, 1H, Ar-H); 7.444 – 7.328 (m, 4H, Ar-H); 4.112 (s, 3H, OCH<sub>3</sub>); 4.006 (s, 6H, 2OCH<sub>3</sub>).

**Mass spectra:** 102, 391, 433 (M-1), 435 (M+1), 436 (M+3).

### 3. RESULT AND DISCUSSION

1-Benzofuran-2-hydrazide derivatives are biologically important. The –CO-NH-NH<sub>2</sub> group has wide scope in the synthetic organic chemistry and converted into various products by treating with carbonyl compounds, halides, etc. 5-bromosalicylaldehyde was treated with diethyl chloromalonate in 2-butanol in presence of potassium carbonate as base followed treatment of sulphuric acid and heat. This reaction was carried out by using weak base such as potassium carbonate not by using strong bases such as alkali hydroxides or alkoxides, to avoid the cross condensation of diethyl (4-bromo-2-formylphenoxy)propanedioate (**24**) with its another molecule or unreacted salicylaldehyde. The 5-bromosalicylaldehyde on series of reactions forming 5-bromo-1-benzofuran-2-carboxylic acid (**25**). The isopropyl ester of 5-Bromo-1-benzofuran-2-carboxylic acid (**25**) was formed by conventional esterification [esterification of (**25**) in presence of excess 2-propanol and concentrated sulphuric acid (as a dehydrating agent)]. The formation of the product was confirmed by monitoring TLC and from the FT-IR spectra. The carbonyl group of ester shows stretching vibration at 1727 cm<sup>-1</sup> confirms the formation of product (**26**). The propan-2-yl 5-bromo-1-benzofuran-2-carboxylate (**26**) was treated with hydrazine hydrate in 2-propanol in presence of acetic acid as catalyst. The solid 5-Bromo-1-benzofuran-2-carbohydrazide (**27**) obtained was filtered and recrystallized from ethanol. The formation of product (**27**) was confirmed by TLC, m.p., sodium fusion test, FT-IR, NMR and mass spectroscopy. In FT-IR spectra of compound (**27**) shows absorption at the frequencies 3322 and 3183 cm<sup>-1</sup> is due to –NH- and –NH<sub>2</sub> stretching



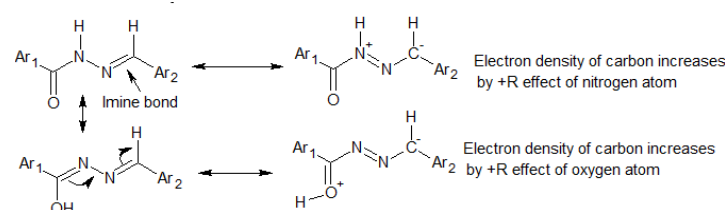
vibrations & 1668  $\text{cm}^{-1}$  is due to stretching vibrations of carbonyl group of hydrazide. Compound (**27**) not shows any absorption band in the frequency region of carbonyl group of ester. The formation of compound (**27**) was also confirmed from its NMR spectra. The amide proton of hydrazide linkage [-CO-NH-N<] shows two chemical shifts, one at  $\delta$  12.224 ppm (due to -C(OH)=N-N) and second at  $\delta$  8.436 ppm (is due to -CO-NH-N). The -NH<sub>2</sub> protons are highly deshielded and therefore shows chemical shift at  $\delta$  7.040 ppm. The aromatic proton present at C-4 position (C<sub>4</sub>-H) is highly deshielded and shows chemical shift at  $\delta$  8.091 ppm. The C<sub>6</sub>-H and C<sub>7</sub>-H are also deshielded and shows multiplet at  $\delta$  7.706 ppm. The furan proton (C<sub>3</sub>-H) is shielded proton as compared to other aromatic protons even though it is present 2-position with respect to electron-withdrawing -CONHNH<sub>2</sub> group because of high average electron density of five membered ring carbon and +R effect of furan oxygen atom. The formation and presence of bromine atom in the compound (**27**) was also confirmed from its mass spectra. The compound shows two fragments 254.8 is M-1 (when Br is <sup>79</sup>Br) and 256.9 is M+1 (when Br is <sup>81</sup>Br) with equal intensity indicate the presence of one bromine atom.

The 5-Bromo-1-benzofuran-2-carbohydrazide (**27**) was treated with series of aldehydes (**a-q**) in ethanol in presence of acetic acid as catalyst (acetic acid was not added in case of aldehyde containing acidic phenolic or carboxylic group) forming series of Schiff bases (**28a-q**) under reflux conditions. The formation of product was confirmed by monitoring TLC and recrystallize by using column chromatography. The structure of the product was determined from its FT-IR, NMR and mass spectra. The reaction conditions required for the completion of the reaction was depends on the nature of reactants. The aldehydes in which the aldehydic carbonyl carbon atom shows more electrophilic character are reacts easily (required less time for completion of reaction) such as **a-c**. The electron withdrawing groups which shows -R effect present at 2- and or 4-position are more reactive. The aldehydes containing phenolic -OH such as **g-l** are reacts at room temperature, but for the increasing yield and purity, reaction mixture was reflux for few hours.

The formation of product was confirmed by monitoring FT-IR, NMR and mass spectra. The FT-IR spectra shows moderate to strong band in the region 3300  $\text{cm}^{-1}$  to 3100  $\text{cm}^{-1}$  (depending on the nature of substituents of aldehyde) is due to stretching vibrations of -N-H group. The Schiff bases (**28a-q**) do not shows absorption frequency in aldehydic carbonyl, aldehydic C-H and hydrazide -NH<sub>2</sub> group region. The carbonyl group of hydrazide shows absorption in 1700 - 1610  $\text{cm}^{-1}$  region, depending on the nature of substituents attached to aldehydic aromatic ring. The carbonyl group shows absorption at higher frequency side if electron withdrawing groups are present on aldehydic aromatic ring [shows strong -I inductive effect or -R effect if group are in conjugation with carbonyl group] such as in **28b-d**, **28g**, **28j**, **28l** and **28m**. When the substituent attach to the group which is under consideration shows electron withdrawing inductive effect on N-H group absorption is shifted towards higher stretching frequency. But when substituent attached shows electro donating inductive effect is shifted the absorption frequency towards lower value. The aromatic N-H group in **28d** and **28f** are highly deshielded therefore shows absorption at higher frequency 3450 and 3340  $\text{cm}^{-1}$  respectively. The Schiff bases containing phenolic -OH group shows absorption in 3300 - 3460  $\text{cm}^{-1}$  region [**28g** - 3355  $\text{cm}^{-1}$ , **28h** - 3423  $\text{cm}^{-1}$ , **28i** - 3438  $\text{cm}^{-1}$ , **28j** - 3320  $\text{cm}^{-1}$ , **28k** - 3301  $\text{cm}^{-1}$  and **28l** - 3457  $\text{cm}^{-1}$ ]. The presence of nitrile or cyanide group in **28b** can be confirmed from its FT-IR spectra. It shows strong absorption at 2242  $\text{cm}^{-1}$  is due to -C $\equiv$ N stretching vibrations.

The NMR spectra of Schiff bases (**28a-q**) were recorded by using 300 MHz NMR instrument in DMSO-D<sub>6</sub> solvent and TMS is used as reference. The chemical shift value of amide proton indicate that, it is highly deshielded is due chemical anisotropic effect of C=N bond and electro negativity of nitrogen atom. The chemical shift value of N-NH=CO- proton was observed in the region 12.000 to 12.650 ppm [-C(OH)=N-N] and 8.000 to 9.000 ppm [-CO-NH-N] is due to tautomeric effect. Its chemical shift value can be shifted to upfield or downfield from  $\delta$  12.224 & 8.436 ppm value which is depends on nature of aromatic ring & its substituents. The N-NH=CO- proton is deshielded in Schiff bases except **28e**, **28f**, **28n**, **28o**, **28p** and **28q**. The two chemical shifts for N-NH=CO- and -C(OH)=N-N proton is not observed in all Schiff bases such as **28d-h**, **28j-q**. The -NH- proton of heterocyclic rings is highly deshielded in **28d** and **28f**. In **28d**, the chemical shift of proton (-NH-) is  $\delta$  14.568 ppm indicates that the proton attached to nitrogen (which is part of aromatic ring) is highly deshielded because of electro negativity of nitrogen, -R effect of another ring nitrogen, chemical anisotropy and aromaticity of ring. But in case of **28f**, the chemical shift of proton (-NH-) is  $\delta$  11.981 ppm. The phenolic -OH proton (**28g-l**) shows chemical shift in the range 9.0 to 11.5 ppm which is highly deshielded in **28g** and comparatively more shielded in **28j**. The imine proton of -CH=N-NH-CO- group is not as deshielded compared to proton of -CH=N- group. This can be explaining with the help of following electronic shifting. The electron density of imine carbon was increased by lone pair of electrons of nitrogen or oxygen as shown below.

#### In Schiff bases of carbohydrazides:



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**Citation:** Bapu R Thorat (2018). Schiff Bases of 5-bromo-1-Benzofuran-2-Carbohydrazide. *J. of Physical and Chemical Sciences*. V6I2-02. DOI: 10.5281/zenodo.1205726

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