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Research Article

SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL ACTIVITY OF SOME BENZOHYDRAZIDE DERIVATIVES OF EGONOL INTERMEDIATE

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Abstract

Egonol, Benzofuran and Aroyl Hydrazone derivatives attracted the attention of research scientists for their pharmacological activities *viz.,* antibacterial, antifungal, antiprotozoal, antitubercular activity and anti-infective agents. The present work is focused on synthesis and characterization of a series of some novel carbohydrazide derivatives of egonol intermediate for screening and assessing their bioactivitive characteristics for consideration in medicine and its related fields.

Keywords: Egonol, Benzofuran, Carbohydrazides, Anti-bacterial activity.

Introduction

Benzo[b]furan class of fused heterocycles has been of great interest as they are abundant in nature and for their wide pharmacological activities (Aslam et al., 2009). In the field of anti-infective agents, benzo[b]furans have been reported to show antifungal (Ryu et al., 2010. Abdel-Wahab et al., 2009. Jiang et al., 2011. Kirilmis et al., 2008.), antiprotozoal (Ryu et al., 2010) and antitubercular activity (Manna et al., 2010. Brandvang et al., 2009. Bakunova et al., 2007). According to the literature, several studies were carried out on benzo[b]furan nucleus as 2-substituted (Brandvang et al., 2009) or 2, 3-disubstituted benzofurans derivatives (Manna et al., 2010).

Another significant class of compounds which have a varied pharmacological profile is the aroyl hydrazone class of compounds. It has been demonstrated that aroyl hydrazones are an important and promising class of anti-infective agents (Kucukguzel et al., 1999. Kucukguzel et al., 2002. Kaymakcıoglu et al., 2006).

Egonol, a natural 2-aryl benzofuran, which is considered to be an effective pyrethrum synergist (Takanashi et al., 1988). Egonol and its derivatives attracted the attention of synthetic chemists for their antibacterial and antifungal (Pauletti et al., 2000) and anti-complement (Min et al., 2004) activities, cytotoxic activities against human leukaemic HL-60 cells (Hirano et al., 1994). Literature survey also reported about the significant activities for egonol against C6 (rat glioma) and Hep-2 (larynx epidermoid carcinoma) cell lines (Teles et al., 2005).

Infectious diseases caused by microorganisms are one of the main reasons of death in the world. The search for new antibacterial and antifungal drugs has become a continuous process because of the increasing resistance of microbial pathogens.

As a part of our present research study and in continuation to our early studies on benzo[b]furan carbohydrazide (Krishna Prasad et al., 2014), it is proposed to synthesize a new group benzo[b]furan carbohydrazide derivatives of egonol intermediate to

evaluate *in vitro* antimicrobial activity against some detected bacterial species *viz., E.coli, P.aeruginosa* (*Gram Negative bacteria*) and *S.aureus, S.pyogenes* (Gram Positive) with Ampicillin as control drug.

Materials and Methods

The solvents and the chemicals available commercially are employed for the chemical process. Silica gel 60 F24 of Merck pre-coated plates are employed for thin layer chromatography (TLC) and the spots are visualized by uv-light. Merck silica gel 60 (230-400) mesh employed for flash column chromatography and the eluting solvents are recorded in the procedures.

Melting point (mp) determined by Mel-temp apparatus. ^{1}H NMR spectra recorded in Varian MR-400 MHz devise. Chemical shifts are reported in δ parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal standard and the signals are reported as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet) and coupling constants in Hz. The data related are mass spectra recorded on Agilent ion trap MS. Infrared (IR) spectra are recorded on a Perkin Elmer FT-IR spectrometer.

5-iodobenzo[d][1,3]dioxole (2)

1,3,Benzodioxole (10 g, 73.78 mmol) solution in acetonitrile (180 ml), N-Iodosuccinamide (16.5 g, 73.34 mmol) in portions added over a period of 10 min followed by the addition of trifluoroacetic acid (2 ml). The reaction mixture is stirred at room temperature for 12 h and the reaction mixture is diluted with ethylacetate (200 ml) followed by water (200 ml) and stirred for 15 min. The organic layer is washed with 10% (2 x 25 ml) hypo solution, (2 x 100 ml) water followed by brine solution. The organic layer is separated, dried over Na_2SO_4, filtered and evaporated under reduced pressure for isolation of the crude dark yellow syrupy liquid. The crude product is passed through a short silica gel (60-120 mesh, elluant: pet-ether) column to afford the iodo compound **2**. Pale yellow oily liquid; the related IR, 1H NMR and ESI-MS spectral characteristic data is presented below.

Yield: 15g (82%);

IR (KBr): υ_{max} 2970, 2776, 1597, 1499, 1470, 1415, 1368, 1227, 1155, 1105, 1034, 933, 863, 797, 718, 662 cm^{-1};
^{1}H NMR (CDCl3, 400 MHz): δ 7.14 (d, *J* = 1.8 Hz, 1H), 7.12 (d, *J* = 1.8 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 5.94 (s, 2H);
ESI-MS: m/z, 248.1 $(M+H)^+$.

2-(benzo[d][1,3]dioxol-5-yl)ethynyl)trimethylsilane (3)

Solution of compound **2** (5g, 20.15 mmol) in triethylamine (35 ml) is sequentially added trimethylsillylacetylene (3.5 ml, 24.20 mmol), dichlorobis(triphenylphosphine) palladium (II) (1.5 g, 2.0 mmol), copper iodide (450 mg, 2.0 mmol) is added under nitrogen atmosphere. The reaction mixture is heated to 80°C for 1 h in a sealed tube. The reaction mass is distilled under vacuum and the obtained brown residue is purified by column chromatography (silica gel: 60-120 mesh, eluant: 5% EtoAc/pet-ether) to afford yellow oily liquid.

Yield 3.52 g, (82%)

IR (KBr): υ_{max} 3463, 3014, 2969, 2154, 1481, 1439, 1368, 1244, 1202, 1126, 1098, 1039, 929, 839, 810, 759, 721, 699, 654, 617 cm^{-1};
^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.92 (dd, *J* = 1.6, 8.0 Hz, 1H), 6.82 (d, *J* = 1.6 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.88 (s, 2H).

5-ethynylbenzo[d][1,3]dioxole (4)

Compound **3** (8.0 g, 36.70 mmol) in methanol (60 ml) is added Potassium Carbonate (0.5 g, 3.62 mmol). The reaction mixture is stirred at room temperature for 2.5h and poured into dichloromethane and washed with brine solution. The organic layer is dried over anhydrous Sodium sulfate, and evaporated under reduced pressure to afford crude compound **4**. Brown oily liquid;

Yield: 4.40 g, (82%)

IR (KBr): υ_{max} 3291, 3014, 2970, 1740, 1502, 1483, 1437, 1368, 1231, 1216, 1122, 1093, 1039, 938, 922, 862, 813, 661 cm^{-1};
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.04 (dd, *J* = 1.6, 8.0 Hz, 1H), 6.93 (d, *J* = 1.6 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 5.98 (s, 2H). ESI-MS: m/z, 146.1 $(M+H)^+$.

5-Iodo vanillin

Mixture of Vanillin (10 g, 65.80 mmol), $NaHCO_3$ (38 g, 452.40 mmol) in water (100 ml) heated to 100°C is added iodine (16.8 g, 65.80 mmol) in small portions for 1h and refluxed for 10 h. The reaction mixture is cooled to room temperature, acidified with 1N HCl and the precipitated solids are filtered and dried under vacuum to obtain 5-iodovanillin.
Yellow solid;

Yield; 17 g, 92 %; M.p. 183-184 ^{o}C.

IR (KBr): υ_{max} 3006, 2971, 1740, 1663, 1572, 1490, 1458, 1415, 1354, 1294, 1231, 1216, 1143, 1038, 968, 853, 783 cm^{-1};
^1H NMR ($CDCl_3$, 400 MHz): δ 7.40 (s, 1H), 7.90 (s, 1H), 9.75 (s, 1H), 10.70 (br.s, 1H); ESI-MS: m/z 278.2 $(M+H)^+$.

2-(benzo[d][1,3]dioxol-5-yl)-7-methoxybenzofuran-5-carbaldehyde (5)

Solution of DMF (9 ml) containing compound **4** (78 0mg, 5.35 mmol) and 5-iodovanillin (1.3 g, 4.45 mmol) are added dichlorobis(triphenylphosphine) palladium (II) (95 mg, 0.27 mmol), copper iodide (25 mg, 0.13 mmol) and triethylamine (1.25 ml, 8.90 mmol) are injected through the septum in a sealed tube. The reaction mixture is heated for 2 h at 80 ^oC. and is cooled to room temperature and diluted with ethylacetate (15 ml), the organic layer is separated and washed with water (2 x 15ml) followed by brine solution. The organic layer is dried over anhydrous Sodium Sulphate, filtered and evaporated under reduced pressure to obtain crude compound **5**. Purification is performed by flash chromatography (elluant: 7 % EtOAc: n-Hexane), to obtain compound **5** as an amorphous brown solid.

Yield: 1.3 g, (67%) M.p: 98-99 ^oC;

IR (KBr): υ_{max} 3463, 3015, 2970, 2851, 1740, 1498, 1475, 1449, 1368, 1287, 1230, 1217, 1132, 1108, 1036, 996, 970, 927, 897, 837, 815, 784, 744, 717 cm^{-1};
^1H NMR ($CDCl_3$, 400 MHz): δ 10.0 (s, 1H), 7.88 (s, 1H) ,7.54-7.52 (m, 3H), 7.38 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.12 (s, 2H), 4.05 (s, 3H). ESI-MS: m/z 494 $(M+H)^+$.

Synthesis of Benzohydrazide derivatives (a – e)

Solution of benzoic acids (6.42 mmol) in ethanol (3 ml) is added catalytic qty. of conc. H_2SO_4 and heated to reflux for 6 – 10 h. The reaction mixture is diluted with ethylacetate followed by water. The organic layer is washed with saturated $NaHCO_3$ followed by water and brine solution. The organic layer is dried over Sodium sulphate, filtered and evaporated to obtain respective ethyl benzoates derivatives.

To a solution of ethyl benzoates (3 mmol) derivatives in ethanol, add hydrazine-hydrate (5.44 mmol) and refluxed for 6 – 12 h. The reaction mixture is cooled to room temperature and filtered the precipitated solids and washed with hexane, to obtain the pure compounds **a-e**. The yield of the product varied from 75 – 90%. The hydrazide derivatives of benzoic acids have been synthesized and the quantified data along with the spectral data is presented.

4-methoxybenzohydrazide (a):

White solid; Yield: 88%; M.p.: 118-119 ^oC;
^1H NMR (DMSO-d6, 400 MHz): δ 9.60 (s, 1H), 7.66 (d, *J* = 6.4 Hz, 2H), 6.96 (d, *J* = 6.4 Hz, 2H), 4.40 (s, 2H), 3.80 (s, 3H).
ESI-MS: m/z, 167.2 $(M+H)^+$.

4-(methylsulfonyl)benzohydrazide (b):

Off white solid; Yield: 82%; M.p.: 101-102°C;
^1H NMR (DMSO-d6, 400 MHz): δ 10.03 (s, 1H), 8.04-7.99 (m, 4H), 4.60 (s, 2H), 3.30 (s, 3H), 3.25 (s, 3H).

benzohydrazide (c):

Pale yellow solid; Yield: 80%; M.p.: 125-126 ^oC;
^1H NMR (DMSO-d6, 400 MHz): δ 9.74 (br.s, 1H), 7.82 (d, *J* = 6.0 Hz, 2H), 7.52-7.44 (m, 3H), 2.28 (br.s, 2H).
ESI-MS: m/z 137.0 $(M+H)^+$.

4-Fluorobenzohydrazide (d):

White solid; Yield: 85 %; M.p.: 161 ^oC;
^1H NMR (DMSO-d6, 400 MHz): δ 9.75 (br.s, 1H), 7.90-7.85 (m, 2H), 7.30-7.25 (m, 2H), 4.46 (brs, 2H).

3-Nitrobenzohydrazide (e):

Pale yellow solid; Yield: 88 %; M.p.: 128-129 ^oC;
^1H NMR (DMSO-d6, 400 MHz): δ 10.13 (brs, 1H), 8.64 (t, J = 2.0Hz, 1H), 8.35 (dt, J = 1.2, 6.8 Hz, 1H), 8.26 (dt, J = 1.2, 6.8 Hz, 1H), 7.76 (t, J = 8.0 Hz, 1H), 4.61 (br.s, 2H).

Synthesis of Hydrazone derivatives (6a-6e)

Solution of compound **5** (100 mg, 0.34 mmol) in ethanol is added corresponding benzohydrazides (0.34 mmol) and refluxed for 2 h. The reaction mixture is cooled to room temperature and filtered the precipitated solids and washed with pet-ether, to obtain the pure compounds **6a-6e**. The Yield of the products varied between 85 - 97%.

(E)-N'-((2-(benzo[d][1,3]dioxol-5-yl)-7-methoxybenzofuran-5-yl)methylene)-4-methoxybenzohydrazide (6a):

Pale yellow solid; Yield: 78%; ^1H NMR ($CDCl_3$, 400 MHz): δ 11.76 (br.s, 1H), 9.08 (s, 1H), 7.98 (d, *J* = 10.8 Hz, 2H), 7.54-7.42 (m, 3H), 7.33 (d, *J* = 10.2 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 10.4 Hz, 2H), 6.10 (s, 2 H), 4.02 (s, 6H); ESI-MS: m/z, 444.39 $(M+H)^+$.

(E)-N'-((2-(benzo[d][1,3]dioxol-5-yl)-7-methoxybenzofuran-5-yl)methylene)-4-(methylsulfonyl)benzohydrazide (6b)

Pale yellow solid; Yield: 85%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.06 (br.s, 1H), 8.53 (s, 1H), 8.15 (d, *J* = 6.4 Hz, 2H), 8.09 (d, *J* = 6.4 Hz, 2H), 7.53 (s, 1H), 7.49-7.44 (m, 2H), 7.36 (s, 2H), 7.06 (d, *J* = 4.4 Hz, 1H), 6.15 (s, 2H), 4.05 (s, 3H), 3.30 (s, 3H); ESI-MS: m/z, 492.8 $(M+H)^+$.

(E)-N'-((2-(benzo[d][1,3]dioxol-5-yl)-7-methoxybenzofuran-5-yl)methylene)benzohydrazide (6c):

Pale yellow solid; Yield: 80%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.84 (s, 1H), 8.52 (s, 1H), 7.94 (d, *J* = 7.2 Hz, 2H), 7.60-7.44 (m, 7H), 7.35 (s, 2H), 7.05 (d, *J* = 7.2 Hz, 1H), 6.15 (s, 2H), 4.04 (s, 3H); ESI-MS: m/z, 414.41 $(M+H)^+$.

(E)-N'-((2-(benzo[d][1,3]dioxol-5-yl)-7-methoxybenzofuran-5-yl)methylene)-4-fluorobenzohydrazide (6d):

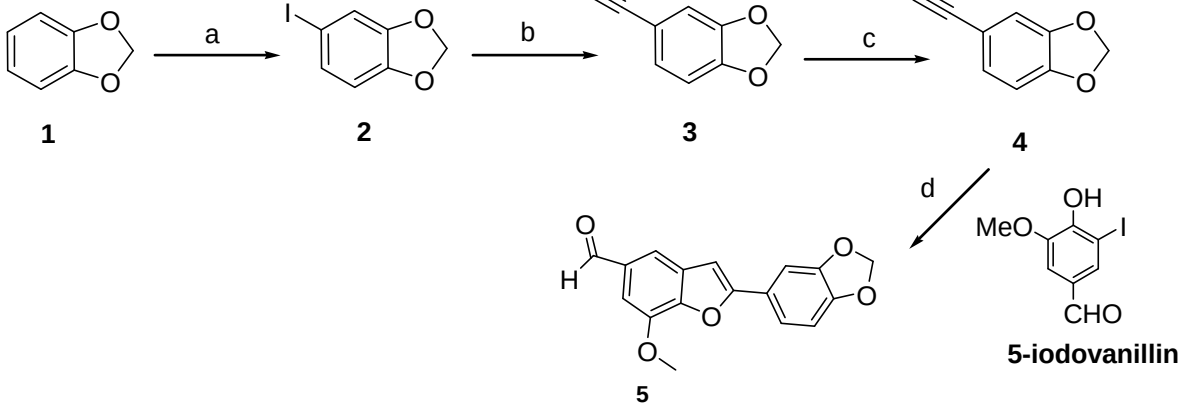
Pale yellow solid; Yield: 80%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.84 (br.s, 1H), 8.50 (s, 1H), 8.0 (q, *J* = 6.0 Hz, 2H), 7.50-7.34 (m, 7H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.10 (s, 2H), 4.04 (s, 3H); ESI-MS: m/z, 433.45 $(M+H)^+$.

E)-N'-((2-(benzo[d][1,3]dioxol-5-yl)-7-methoxybenzofuran-5-yl)methylene)-3-nitrobenzohydrazide (6e):

Pale yellow solid; Yield: 86%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.16 (* 12.05, s, 1H), 8.77 (* 8.81, s, 1H), 8.55 (s, 1H), 8.44(d, *J* = 6.8 Hz, 1H), 8.38(d, *J* = 6.8 Hz, 1H), 7.86 (t, *J* = 6.4 Hz, 1H), 7.54 (s, 1H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.37 (s, 2H), 7.05 (d, *J* = 6.4 Hz, 1H), 6.10 (s, 2H), 4.04 (s, 3H); ESI-MS: m/z, 460.8 $(M+H)^+$.

The synthetic scheme for the newly synthesized benzo[b]furan carbohydrazides **6a – 6e** described in this paper is depicted in **Scheme 1**. Iodination of 1,3,Benzodioxol **1** has been carried out using N-Iodosuccinamide in presence of trifluoroacetic acid in acetonitrile at room temperature (cost effective and less hazardous reagents) to produce iodinated compound **2** in considerable quantitative yields. The acetylene derivative **4** depicted in **Scheme 1** is prepared utilizing 1, 3-benzodioxol, (Sonogashira protocol). Sillylation of iodide compound **2** is carried out by coupling with trimethylsillyl acetylene in presence of Pd $(PPh_3)_2Cl_2$, CuI in triethylamine at 80°C afforded sillylated compound **3**. De-sillylation of compound **3** is by using K_2CO_3 in methanol to produce phenyl acetylene derivative **4**. Compound **4** is reacted with 5-iodovanillin (Krishna Prasad et al., 2014) in presence of Pd $(PPh_3)_2Cl_2$/CuI/Et_3N in DMF to furnish benzo[b]furan aldehyde **5**. Benzo[b]furan aldehyde **5** is reacted with corresponding benzohydrazide derivatives **a–e** in ethanol to afford benzo[b]furan derivatives **6a – 6e**.

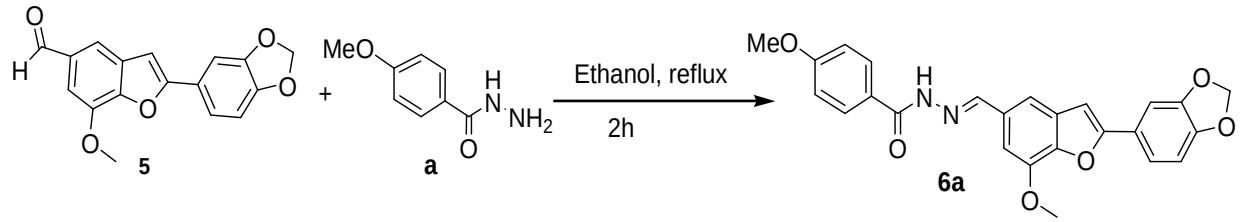
Scheme-1



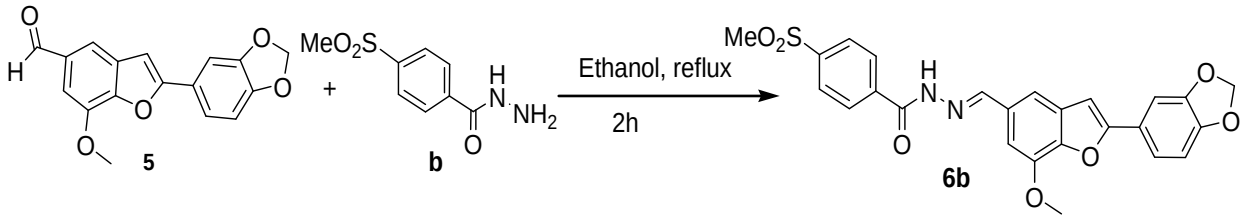
Experimental Conditions:

a) N-Iodosuccinamide, Trifluoroacetic acid, acetonitrile, r.t., 12 h;
b) Trimethylsillyl acetylene, $Pd(PPh_3)_2Cl_2$, CuI, triethylamine, 80 ^oC, 1 h;
c) K_2CO_3, MeOH, r.t, 2.5 h;
d) **5-iodovanillin**, Pd $(PPh_3)_2Cl_2$, CuI, triethyl amine, DMF, 80 ^oC, 2.0 h;

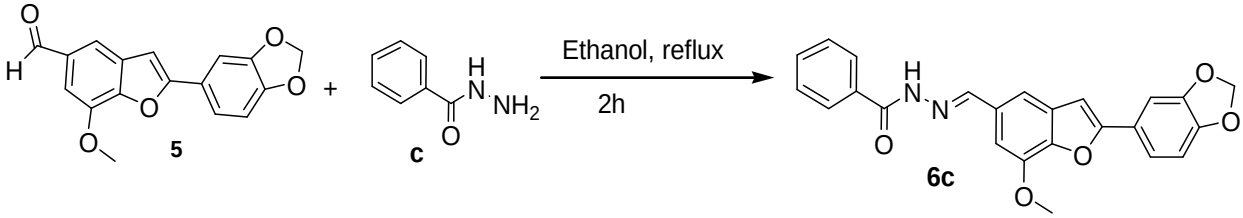
Synthetic route for 6a:



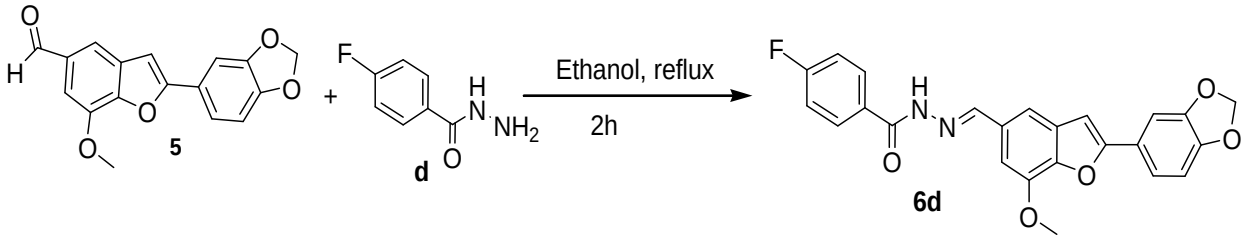
Synthetic route for 6b:



Synthetic route for 6c:



Synthetic route for 6d:



Synthetic route for 6e :

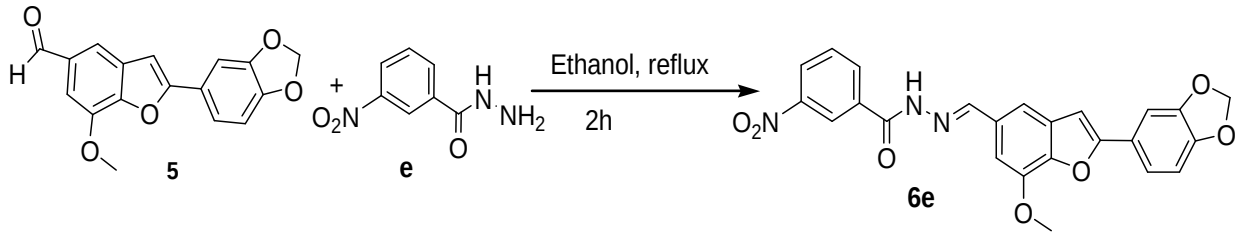
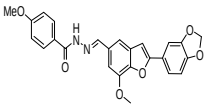
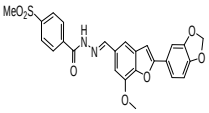
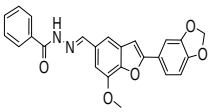
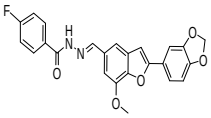
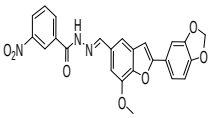


Table-1: The derivatives synthesized (6a-6e) are processed for Bioevaluation and the data is presented in table-1.

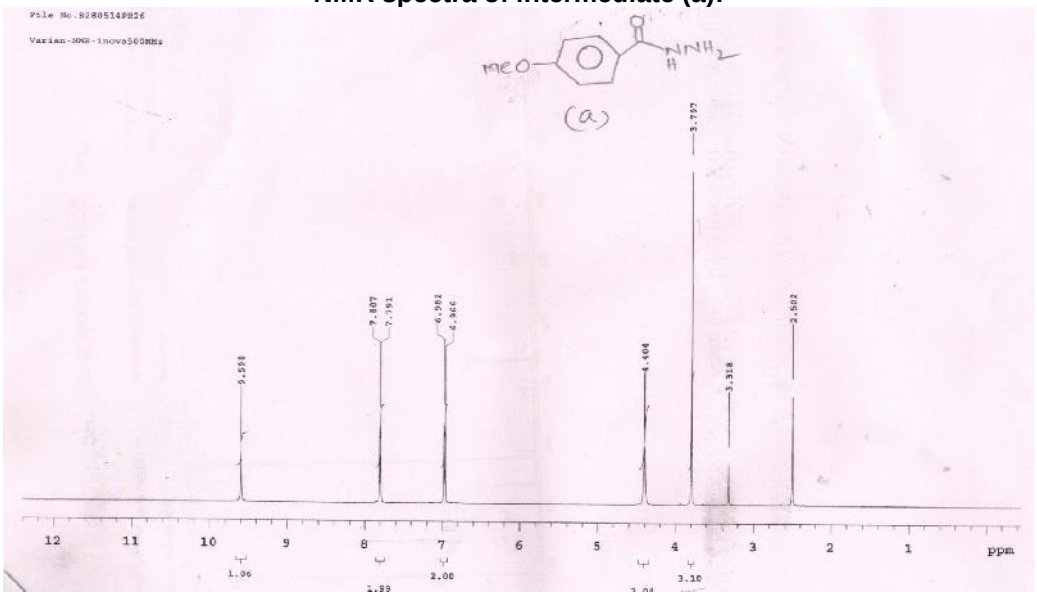
Compound No.	Product No; as in scheme	*Gram negative*		*Gram positive*	
		E.coli ***MTCC 443***	*P.aeruginosa* ***MTCC 424***	*S.aureus* ***MTCC 96***	*S.pyogenes* ***MTCC 442***
		Zones of Inhibition (ZI) of compounds 6a –6e in mm			
1	**6a** 	8 	9	5	6
2	**6b** 	15 	12 	9	8
3	**6c** 	-- 	-- 	-- 	-- 
4	**6d** 	9 	12	6	7
5	**6e** 	11 	8 	8	8
***Standard Drug**		14	14	10	11

* Ampicillin (5µg/mL of DMSO)

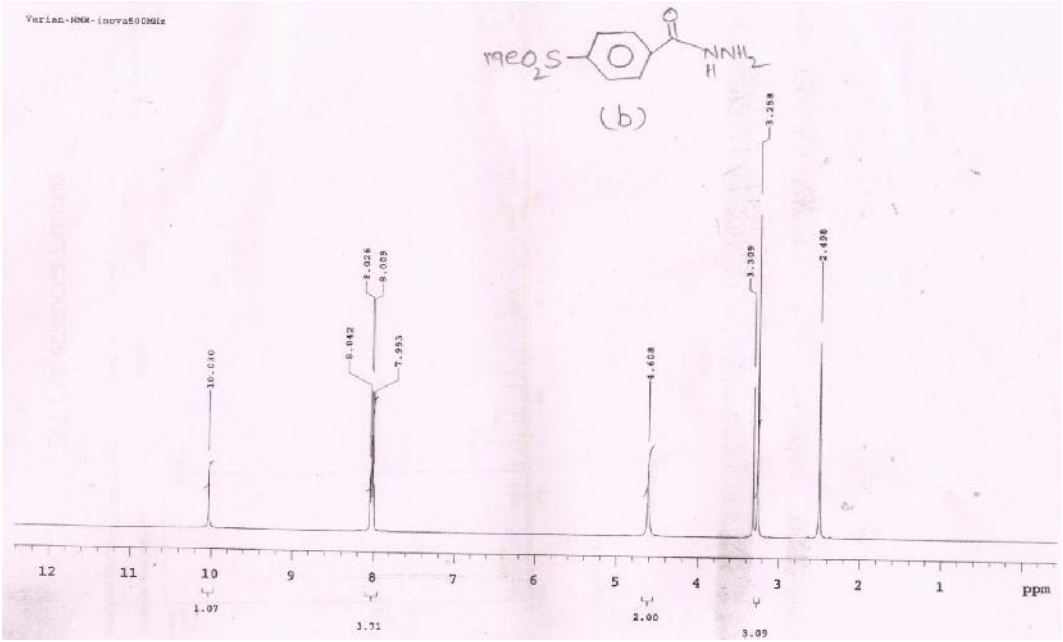
Results and Discussion

The structures of the synthesized compounds are confirmed by ^{1}H NMR, Mass and IR data. As a representative example, the ^{1} H NMR spectra of the compound **6d**, the broad singlets at 12.06 and 8.53 ppm corresponds to the protons representing to -N=C*H*- and -N*H*-N=C- groups respectively. The singlets appearing at 6.15 and 4.05 ppm represents to –$\underline{CH_2}$ (benzodioxole ring) and methoxy group in the structure. All the other aliphatic and aromatic protons were observed at expected regions. The ^{1}H-NMR data for the remaining derivatives **6b – 6e** are in agreement with the assigned structures. The mass spectra of compounds showed (M+1) peaks, in agreement with their molecular formula.

NMR spectra of intermediate (a):



NMR spectra of intermediate (b):



Biological Activity

Compounds (**6a-e)** were evaluated against four *pathogenic bacterial* studies which include two Gram negative strains *Pseudomonas aeruginosa and Escherichia coli* and two Gram positive strains *Staphylococcus aureus and Streptococcus pyogenes,* following agar well diffusion procedure as per the reference (Atta-ur-Rahman et al., 2001). The antibacterial activity of the synthesized benzo[b]furan carbohydrazide **6a-e** was compared with the zone of inhibition (ZI) of ampicillin as a reference drug. The MIC of the derived compounds (**6a-6e**) against all *bacterial* strains is determined by liquid dilution method [18-20]. Stock solutions of tested compounds with 2.5, 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 µg mL^{-1} concentrations are prepared with appropriate solvent. The solutions of control drugs, Ampicillin is prepared in the same concentrations. Inoculums of the *bacterial* culture are also prepared. The MIC at which no growth is observed is taken as the MIC values and the details are summarized in table 1.

Compound **6b** exhibited excellent activity (ZI: 15 mm) while compound **6e** displayed good activity (ZI: 11 mm) against *E.coli* and the compounds **6a**, **6d** showed moderate activity.

In case of *P.aeruginosa*, compound **6b**, **6d** (ZI: 12 mm) showed good activity while compounds **6a** and **6e** showed moderate activity. In case of *S.aureus,* compounds **6b** and **6e** (ZI: 8-9 mm) exhibited excellent activity while **6a**, **6d** (ZI: 5-6 mm) displayed moderate activity. In case of *S.pyogenes*, compounds **6a**, **6b**, **6c** and **6d** displayed moderate activity. It is observed from Table-1 that compound **6c** did not exhibit any activity towards all the tested *bacterial* strains. It is noteworthy to infer that the scaffold, benzo[b]furan carbohydrazide with R = SO_2Me, 4-F and 4-Nitro emerged as a potential antibacterial agent when tested against all the above *bacterial* strains. Hence it is suggested that a further lead optimization is essential to establish a broad spectrum of antibacterial activity.

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Conflict of Interest

The authors have reported no conflict of interest.

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