Available online at www.joac.info

ISSN: 2278-1862

Journal of Applicable Chemistry

2014, 3 (4): 1460-1467

(International Peer Reviewed Journal)

Synthesis, Characterization and Antibacterial activity of Novel Benzo[b]furan Carbohydrazide Derivative of Intermediate Egonol

Ch. Krishna Prasad*[1] and P. V. S Machi Raju[2]

1. Department of Chemistry, Jawaharlal Nehru Technological University, Kakinada-533003, A.P. (Escientia Bio Pharma, Hyderabad) **INDIA**
2. Department of Chemistry, Pragati Engeneering College, Surampalem-533437, A.P. **INDIA**

Email: kp.prasad07@gmail.com

Accepted on 18th June 2014

ABSTRACT

Egonol, a natural 2-aryl benzofuran an effective pyrethrum synergist. Egonol and its derivatives attracted the attention of synthetic chemists for their antibacterial, antifungal, anti-complement and cytotoxic activities against human leukaemic HL-60 cells. As a part of our present research study, a series of new benzo[b]furan carbohydrazide derivatives derived from egonol intermediate have been synthesized and evaluated for their in vitro antimicrobial activity against E.coli, K.pneumonae (Gram Negative bacteria) and S.aureus, B.subtilis (Gram Positive) bacterial strains with Ampicillin as a control drug.

Keywords: Antibacterial Activity, Benzo[b]furan, Benzohydrazides, Egonol, *Gram positive bacteria, Gram negative bacteria.*

INTRODUCTION

Hydrazones attracted considerable attention in medicinal chemistry for their distinctive structural features along with a wide range of pharmacological activities [1,2]. It is exemplified by the synthesis and pharmacological evaluation of a large number of hydrazone derivatives against various pharmacological targets [3-5]. *Benzofuran neolignans and norneolignans, which are constituent of most plants, such as Styrax officinalis, Styrax japonicum, Styrax formosanus, Styrax obassia, Styrax macranthus* and exhibit a variety of biological activities including antiproliferative, antisweet, insecticidal, fungicidal, antimicrobial, cytotoxic and antioxidant characteristics [6]. The phytochemical investigative studies on this genus were enhanced in 1915, when Okada isolated egonol for the first time, as an unsaponifiable constituent of the seed oil of *S. Japonica* [7]. Egonol, a natural 2-aryl benzofuran is considered to be an effective pyrethrum synergist [8]. Egonol and its derivatives attracted the attention of synthetic chemists for their antibacterial and antifungal [9] and anti-complement [10] activities, cytotoxic activities against human leukaemic HL-60 cells [11]. Literature survey also reported that significant activities were observed for egonol against C6 (rat glioma) and Hep-2 (larynx epidermoid carcinoma) cell lines [12]. Keeping in view the significance of the potential medicinal characterstics of egonol, it is proposed to synthesize a series of new benzo[b]furan carbohydrazide derivatives from egonol intermediate and to evaluate their *in vitro* antimicrobial activity

against *E.coli, K.pneumonae* (*Gram Negative bacteria*) and *S.aureus, B.subtilis* (Gram Positive) bacterial strains, with Ampicillin as control drug.

MATERIALS AND METHODS

The dry solvents and the chemicals available commercially are employed for the chemical process. Silica gel 60 F24 of Merck pre-coated plates are employed for their thin layer chromatography (TLC) analysis and the spots formed are visualized by UV-light. Merck silica gel 60 (230-400) mesh employed for flash column chromatography and the eluting solvents are mentioned 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 reported as s (singlet), d (doublet), dd (Doublet of doublet), t (triplet), q (quartet), m (multiple) 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. The details of chemicals employed and the procedures adapted for the synthesis of various derivatives of egonol are presented hereunder.

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 ^{o}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}; ^{1}H 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 (rel.abund. %) 278.2 (M+, 100).

5-Iodobenzo[d][1,3]dioxole: 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 **ii**. 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 (rel.abund. %) 248.1 (M+, 100).

2-(benzo[d][1, 3]dioxol-5-yl)ethynyl)trimethylsilane: Solution of compound **ii** (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 ^{o}C for 1 h in a seal tube. The reaction mixture 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: Compound **iii** (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 2.5 h. 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 **iv**. 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}; ^1H 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 (rel.abund. %) 146.1 (M+, 100).

2-(benzo[d][1,3]dioxol-5-yl)-7-methoxybenzofuran-5-carbaldehyde: Solution of DMF (9 mL) containing compound **iv** (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 amorphous brown solid. Yield: 1.3 g, (67%) M.p: 98-99 ^oC; IR (KBr): $\upsilon_{max\ 3463}$, 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 (rel.abund.%) 494 (M+, 100).

Synthesis of Benzohydrazide derivatives (a – e): Solution of various substituted benzoic acid (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 and is dried over Sodium Sulphate, filtered and evaporated to obtain respective ethyl benzoates derivatives. To the solution of ethyl benzoate (3 mmol) derivatives in ethanol, hydrazine-hydrate (5.44 mmol) is added and refluxed for 6 – 12 h. The reaction mixture is cooled to room temperature and filtered the precipitated solids and washed with pet-ether, to obtain the pure compounds (**a-e**) and product yield varied from 75 – 90%. The hydrazide derivatives have been synthesized and the quantified data, and the spectral data is presented.

4-hydroxybenzohydrazide (a): White solid; Yield: 78%; m.p.: 131-132 ^oC; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.92 (s, 1H), 9.48 (s, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 4.35 (s, 2H).
4-Chlorobenzohydrazide (b): White solid; Yield: 82%; m.p.: 160-162 ^oC; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.86 (s, 1H), 7.85 (d, *J* = 6.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 4.52 (s, 2H).

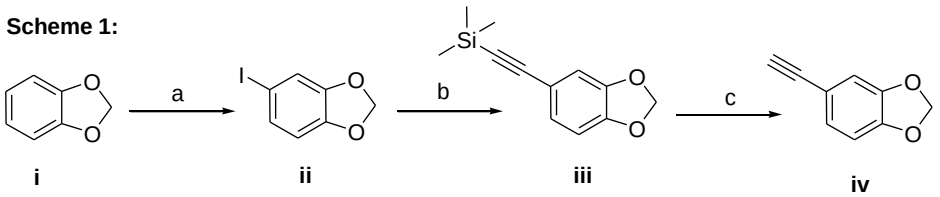
2-Bromobenzohydrazide(c): Pale yellow solid; Yield: 80%; m.p.: 112-113 ^oC; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.54 (s, 1H), 7.64 (d, *J* = 6.8 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.40-7.35 (m, 2 H), 4.48 (br.s, 2H).

2-Iodobenzohydrazide (d): White solid; Yield: 85 %; m.p.: 121-122 ^oC; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.50 (s, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.41 (dd, *J* = 7.2 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 4.45 (br.s, 2H).

3, 4, 5-Trimethoxybenzohydrazide (e): White solid; Yield: 85 %; m.p.: 158-160 ^oC; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.50 (s, 1H), 6.42 (s, 1H), 4.45 (br.s, 2H), 3.84 (s, 3H), 3.80 (s, 6H).

The present research is focused on the synthesis of Hydrazone derivatives from 6a-6e and the procedure of the scheme for the synthesis is presented herewith. Compound **5** solution (100 mg, 0.34 mmol) in ethanol is added to the corresponding benzohydrazides (0.34 mmol) and refluxed for 2 h. The reaction mixture is cooled to room temperature and filtered and the precipitated solids are washed with pet-ether, to obtain the pure compounds from **6a-6e** and the Yield of the products varied from 85 - 97%.

Scheme 1:



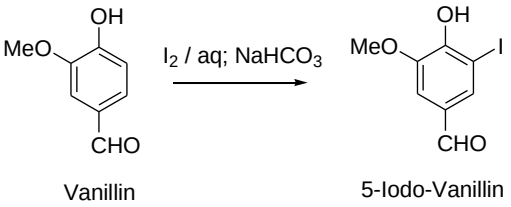
i) Benzodioxole

ii) 5-iodobenzo[*d*][1,3]dioxole

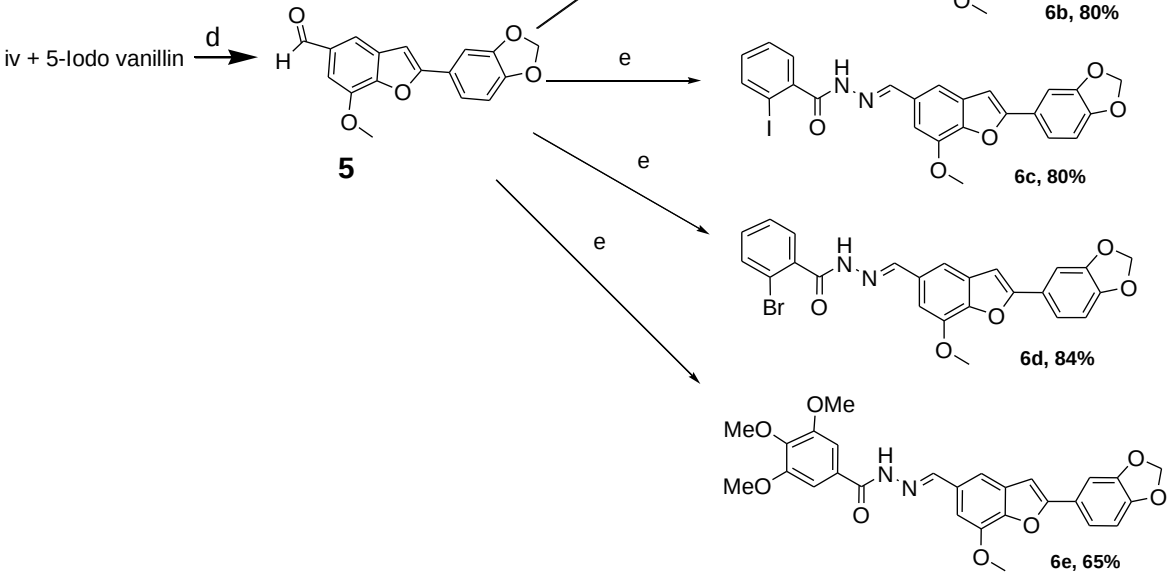
iii) (benzo[*d*][1,3]dioxol-5-ylethynyl)trimethylsilane

iv) 5-ethynylbenzo[*d*][1,3]dioxole

Scheme 2:



Scheme 3:



Scheme- 3: Synthesis of novel Benzo[b]furan carbohydrazides **6a –6e**

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) $Pd(PPh_3)_2Cl_2$, CuI, triethyl amine, DMF, 80 ^oC, 2.0 h;
e) Benzohydrazides **a-e**, EtOH, reflux, 2 h.

(E)-N'-((2-(benzo[d][1,3]dioxol-6-yl)-7-methoxybenzofuran-5-yl)methylene)-4-hydroxybenzo hydrazide (6a): Pale yellow solid; Yield: 82%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.60 (br.s, 1H), 10.09 (10.0*, s, 1H), 8.48 (7.85*, s, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.50-7.42 (m, 3H, *ap*: *sp* rotamer ratio 2:1), 7.38-7.31 (m, 2H, *ap*: *sp* rotamer ratio 2:1), 7.06-7.03 (m, 2H), 6.84 (d, *J* = 8.8 Hz, 1H), 6.09 (s, 2 H), 4.02 (s, 3H). ESI-MS: m/z (rel.abund. %) 431.3 (M+, 100).

(E)-N'-((2-(benzo[d][1,3]dioxol-6-yl)-7-methoxybenzofuran-5-yl)methylene)-4-chlorobenzohydrazide (6b): White solid; Yield: 80%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.89 (br.s, 1H), 8.50 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.46-7.42 (m, 3H), 7.34 (d, *J* = 4.6 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.10 (s, 2 H), 4.0 (s, 3H). ESI-MS: m/z (rel.abund. %) 449.3 (M+, 100).

(E)-N'-((2-(benzo[d][1,3]dioxol-6-yl)-7-methoxybenzofuran-5-yl)methylene)-2-iodobenzohydrazide (6c): Pale yellow solid; Yield: 80%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.98 (11.85*, br.s, 1H), 8.33 (8.10*, s, 1H), 7.94 (m, 1H), 7.52-7.40 (m, 4 H, , *ap*: *sp* rotamer ratio 2:1), 7.36 (7.38*, m, 2 H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.11 (s, 2 H), 4.05 (3.83 *, s, 2H). ESI-MS: m/z (rel.abund. %) 541.03 (M+, 100).

(E)-N'-((2-(benzo[d][1,3]dioxol-6-yl)-7-methoxybenzofuran-5-yl)methylene)-2-bromobenzohydrazide (6d): Pale yellow solid; Yield: 84%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.0 (11.95*, br.s, 1H), 8.32 (8.09*, s, 1H), 7.72 (br.t, *J* = 8.0 Hz, 1H), 7.56-7.40 (m, 6 H, , *ap*: *sp* rotamer ratio 2:1), 7.40 (7.38*, m, 2 H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.11 (6.09*, s, 2 H), 4.04 (3.81*, s, 3H). ESI-MS: m/z (rel.abund. %) 493.04 (M+, 100).

(E)-N'-((2-(benzo[d][1,3]dioxol-6-yl)-7-methoxybenzofuran-5-yl)methylene)-3,4,5-trimethoxy benzohydrazide (6e): Yellow syrupy liquid; Yield: 65%; IR (KBr): υ_{max} 3396, 2923, 2856, 1678, 1585, 1507, 1384, 1223, 1197, 1070, 979, 812,750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.62 (s, 1H), 8.54 (s, 1H), 7.50-7.43 (m, 3H), 7.39 (s, 2H), 7.25 (s, 2H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.11 (s, 2H), 4.04 (s, 3H), 3.84 (s, 6H), 3.74 (s, 3H). ESI-MS: m/z (rel.abund. %) 505.16 (M+, 100).

RESULTS AND DISCUSSION

The scheme for the synthesis of the newly synthesized benzo[b]furan carbohydrazides **6a – 6e** described in this paper is depicted in **Scheme 3**. Kazuhiko Orito et al [13] reported the synthesis of iodide derivative **1** using Mercury (II) Oxide-Iodine. Iodination of methoxy and methyl aromatic derivatives with NIS and CF_3COOH under suitable conditions was reported to be a new and an efficient method for electrophilic Iodination of activated aromatic compounds [14]. Colvin et al., [15] reported the synthesis of **iv** using piperonal as starting material. Da Hye Choi et al reported the synthesis of 5-iodovanillin using I_2 /$AgSO_4$ [16]. The acetylene derivative **iv** depicted in **Scheme 1** is prepared from 1, 3-benzodioxole by Sonogashira protocol which is of its first type in the literature [16]. The present research results confirm the synthesis of 5-iodovanillin using I_2 in aq.$NaHCO_3$ solution by a modified pathway compared to the existing synthesis reported [16, 17] in the literature.

The present research is also focused on Iodination of 1,3,Benzodioxole (**i)** using N-Iodosuccinamide in presence of trifluoroacetic acid in acetonitrile at room temperature to produce iodinated compound(**ii)** and the yield is quite **c**onsiderable. Sillylation of iodide compound (**ii)** has been carried out by coupling with Trimethylsillyl acetylene in presence of Pd $(PPh_3)_2Cl_2$, CuI in triethylamine at 80^{o}C afforded sillylated compound (**iii)**. De-Sillylation of compound **(iii)** has also been carried out by K_2CO_3 in methanol to produce phenyl acetylene derivative (**iv**).

In addition to the above the synthesis of 5-iodovanillin has been carried out from Vanillin using I_2 in aq.$NaHCO_3$ solution in a proposed modified pathway and the merits of the present iodination involve the usage of water as green solvent besides non-hazardous reagents employed in the synthetic scheme.

Compound (**iv**) with 5-iodovanillin in presence of $Pd(PPh_3)_2Cl_2/CuI/Et_3N$ in DMF to forms benzo[b]furan aldehyde **5**. Benzo[b]furan aldehyde **5** which reacts with corresponding benzohydrazide derivatives from experimental conditions **a–e** in ethanol to result in benzo[b]furan derivatives from **6a – 6e**. The structure of the respective compounds synthesized is confirmed by ^1H NMR, Mass and IR data.

Antimicrobial activity and Minimum inhibitory concentration (MIC) determination: The newly synthesized benzo[b]furan carbohydrazide derivatives are evaluated for their *in vitro* antimicrobial activity against E.coli, *K.pneumonae* (Gram Negative bacteria) and *S.aureus, B.subtilis* (Gram Negative) bacterial strains with Ampicillin as standard 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 presented in table 1. Compounds **6a-6e** is observed to have highest activity against all *bacterial* strains with MIC value (5-15 µg mL^{-1}). Among the series of newly synthesized benzo[b]furan carbohydrazides **6a** and **6e** exhibited significant inhibitory activity (MIC range 5 µg mL^{-1}) against all the bacterial strains even than control drug Ampicillin (5 µg mL^{-1}), while the compound **6b, 6c** and **6d** exhibited good (MIC range 10 µg mL^{-1}) to moderate (MIC range 15 µg mL^{-1}) inhibitory.

Table-1: Results of Minimum inhibitory concentration (µg/mL) of compounds **6a – 6e**

Compound[a]	*Gram negative*		*Gram positive*	
	E.coli	*K.pneumonae*	*S.aureus*	*B.subtilis*
	Minimum inhibitory concentration (MIC) (µg/mL)			
6a	5	5	5	5
6b	10	15	15	15
6c	15	15	15	15
6d	10	15	15	10
6e	5	5	5	5
Control Drug Ampicillin	15	10	10	20

APPLICATIONS

The present study describes the synthesis, characterization and antibacterial activity of novel benzo[b]furan derivatives which are quite promising as active pharmacophore. Extensive studies proposed are underway to explore the further scope of various biological activities.

CONCLUSIONS

The products generated [(ii), (iii) and (iv)] are found to be rich in yields, cost effective and the reagents and the catalyst employed are less hazardous compared to the methodologies available in the literature and hence the synthesis of the product derivatives in the present research work are novel and of its first kind. Among the series of newly synthesized benzo[b]furan carbohydrazides, compounds **6a** and **6e** exhibited prominent inhibitory activity (MIC range 5 µg mL^{-1}) against all the bacterial strains even than the control drug Ampicillin (5 µg mL^{-1}) while the compound **6b, 6c** and **6d** exhibited good (MIC range 10 µg mL^{-1}) to moderate (MIC range 15 µg mL^{-1}) inhibitory. These derivatives are further evaluated for *in vitro*

antimicrobial activity against *E.coli*, *K.pneumonae* (*Gram Negative bacteria*) and *S.aureus*, *B.subtilis* (*Gram Positive*) bacterial strains with Ampicillin as control drug.

ACKNOWLEDGEMENT

The authors sincerely thank Dr. P. Yadagiri Reddy, CEO, Escientia Bio Pharma, Hyderabad, Dr. B. Ram, Director Green Evolution Laboratories, Hyderabad and Dr. P. Krishna Rao, Chairman, Shri. M.V. Haranadh Babu, Director, Management and Dr. S. Sambhu Prasad, Principal of Pragati Engineering College, Surampalem, A.P. India for their valuable cooperation in completing the research work.

REFERENCES

[1] B.L. Alexandra, M. Eduardo, K. Arthur Eugen, R. Victor Marcos, M. Carlos Alberto, J. Eliezer Barreiro, *Molecules.*, **2013**, 18, 11683-11704.
[2] R.S Sevim, S.G. Küçükgüzel, *Molecules.*, **2007,** 12, 1910-1939.
[3] A. Nayyar, R. Jain, *Curr. Med. Chem.*, **2005**, 12, 1873-1886.
[4] T. Scior, S. J. Garcés-Eisele, *Curr. Med. Chem*., **2006,** 13, 2205-2219.
[5] Y. L. Janin, *Bioorg. Med. Chem.*, **2007,** 15, 2479-2513.
[6] D. H. Choi, J. W. Hwang, H.S. Lee, D.M. Yang, J.G. Jun, *Bull. Korean Chem. Soc.*, **2008**, 29, 1594.
[7] P.M. Pauletti, H.L. Teles, D.H.S. Silva, A.R. Araujo, V.S. Bolzani, *Braz .J. Pharmacogenetics.*, **2006**, 16, 576.
[8] M. Takanashi, Y. Takizawa, *Phytochemistry.*, **1988**, 27, 1224.
[9] P.M. Pauletti, A.R. Araujo, M.C.M. Young, A.M. Giesbrecht, V. Bolzani, *Phytochemistry.*, **2000**, 55, 597.
[10] B.S. Min, S.R. Oh, K.S. Ahn, J.H. Kim, J. Lee, D.Y. Kim, E.H. Kim, H.K. Lee, *Planta Med.*, **2004**, 70, 1210.
[11] T. Hirano, M. Gotoh, K. Oka, *Life Sci.*, **1994**, 55, 106.
[12] H.L. Teles, J.P. Hemerly, P.M. Pauletti, J.R.C. Pandolfi, A.R. Araujo, S.R. Valentini, M.C. M. Young, V.S. Bolzani, D.H.S. Silva, *Nat. Prod. Res.*, **2005**, 19, 319.
[13] O.Kazuhiko, H.Takahiro, T.Mitsuhiro, S.Hiroshi, *Synthesis.*, **1995**, 1273-1277.
[14] S.Anne, Catannet, C.Francoise, B.Pierre-Emmanuel, *Tett.Lett.*, **2002**, 43, 5047-5048.
[15] E.W. Colvin, B.J. Hamill, J.Chem.Soc. Perkin Trans., **1977**, 1, 869.
[16] Da Hye Choi, Jung Woon Hwang, Hyun Suck Lee, Deaok Mo Yang, Jong-Gab Jun, *Bull.Korean.Chem. Soc.*, **2008**, 29, 1594-1596.
[17] B.Ram, B.Balram, P.K. SaiPrakash, *Tetrahedron.*, **1999**, 51, 10163-10172.
[18] P.M. Reddy, Y.P. Ho, K. Shanker, R. Rohini, V. Ravinder, *Eur. J. Med. Chem.*, **2009**, 44, 2621.
[19] R. Rohini, K. Shanker, P.M. Reddy, Y.P. Ho, V. Ravinder, *Eur. J. Med. Chem.*, **2009**, 44, 3330.
[20] R. Rohini, K. Shanker, P.M. Reddy, V. Ravinder, *J. Braz.Chem. Soc.*, **2010**, 21, 49.
[21] V. Laxmi Prasanna, R. Narender. Synthesis and Antimicrobial Activity of Novel Benzohydrazide Derivatives of 2,4-Dichlorobenzoic acid, *Journal of Applicable Chemistry.*, **2014**, 3 (3): 1277-1288.
[22] Rajasekhar Narisetty, K.B. Chandrasekhar, Sandeep Mohanty, M. Rameswara Rao, B. Balram. Synthesis and Antimicrobial Evaluation of Some Novel Hydrazone Derivatives of 2, 5-Difluro benzoic acid, *Journal of Applicable Chemistry.*, **2013**, 2 (6): 1489-1498.
[23] T. Ravi Sankar, P. Venkata Ramana. Synthesis, Characterization and Applications of Polymer-metal chelates derived from Poly(4-acryloxybenzaldehyde)-divinylbenzene salicyloyl hydrazone resins, *Journal of Applicable Chemistry.*, **2013**, 2 (6): 1459-1467.
[24] Battula Sreenivasa Rao, Gurrala Srinivasa Rao, B.V.Kiran, K.Siva Nagaraju. Effect of Nonionic Surfactant (Triton X–114) on the Spectrophotometric Determination of Selenium (IV) With Isonitriso p-Isopropyl Acetophenone Phenyl Hydrazone, *Journal of Applicable Chemistry.*, **2012**,

(2):232-238.
[25] K. Siddappa, Mallikarjun Kote. Synthesis, Characterization and Antimicrobial studies of N-1-(1-(2-Hydroxy-5-Methylphenyl) Ethylidene)-2-Oxo-2H-Chromene-3-Carbohydrazide and its Metal Complexes, *Journal of Applicable Chemistry.*, **2013**, 2 (3): 405-414.