WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 6, Issue 1, 1255-1266. Research Article ISSN 2277– 7105

SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF ACETOHYDRAZIDE-HYDRAZONE DERIVATIVES OF VANILLIN

A.L.V. Kumar Reddy*[,1, 2] and Niren E. Kathale [1]

[1]Department of Chemistry, Sardar Patel Mahavidyalaya, Chandrapur, Gondwana University, Gadchiroli, Maharashtra, India.

[2]Department of Uranium Oxide Plant, Nuclear Fuel Complex, ECIL Post, 500062, Hyderabad, Telangana State, India.

Article Received on
08 Nov. 2016,

Revised on 29 Nov. 2016,
Accepted on 21 Dec. 2016

DOI: 10.20959/wjpr20171-7626

***Corresponding Author**
Dr. A.L.V. Kumar Reddy
Department of Chemistry, Sardar Patel Mahavidyalaya, Chandrapur, Gondwana University, Gadchiroli, Maharashtra, India.

ABSTRACT

Synthesis of novel hydrazide-hydrazone derivatives *viz.*, substituted Phenyl-acetic acid [4-(4'-fluoro-bi phenyl-4-ylmethoxy)-3-methoxy-benzylidene]-hydrazide **(9a–e)** was achieved by condensation of the key intermediate aldehyde 4-[(4'-fluorobiphenyl-4-yl)methoxy]-3-methoxybenzaldehyde **8** with various acetohydrazides **3a-e**. The structural determination of the newly synthesized chalcone derivatives were established on the basis of the spectroscopic techniques *viz.*, ^{1}H NMR, mass and IR data. These compounds were evaluated for antibacterial screening against Gram positive (*Staphylococcus aureus, Streptococcus pyogenes*) and Gram negative pathogens (*Escherichia coli, Pseudomonas aeruginosa*) with reference to the standard drug Ampicillin (at 100µg/mL). It is observed that compounds **9a** (R = H, ZI = 7-9 mm) and **9b** (R = 3,5-dimethyl, ZI = 9-11 mm) displayed moderate antibacterial activity while the compounds **9c** (R = 2-Cl-4-F, ZI = 12-16 mm)**, 9d** (R = 4-NO_2, ZI = 14-16 mm) and **9e** (R = tetrahydrofuran, ZI = 15-18 mm) exhibited good antibacterial activity.

KEYWORDS: Antibacterial activity, Biphenyl ring, Hydrazones, Hydrazide, Vanillin.

1. INTRODUCTION

The development of new antimicrobial drugs is a very important objective not only from the rapidly developing drug resistance point of view, but also regarding the unsatisfactory status of present treatments of bacterial and fungal infections and drug side-effects. In recent years there has been a great deal of interest in exploiting multiple proximal functional groups in the

design of novel structures capable of performing a variety of functions. Synthesis of molecules that are novel but still resemble known biologically active molecules by virtue of the presence of some critical structural features is an essential component of the search for new leads in drug design.

Many synthetic compounds with antimicrobial activity have been discovered and are of considerable importance from the standpoint of research and practical applications: Aminoglycosides[1], Cephalosporins[2], Lipopeptides[3], Sulfonamides[4-7], Macrolides[8], Oxazolidinones[9], Quinolones[10], and Pyrimidines derivatives[11].

Biphenyl compounds are one of the valuable classes in the organic chemistry which constitutes structural moiety of various compounds with important medicinal properties. Some of the compounds having Biphenyl moiety possess valuable medicinal properties like antihypertensive and calcium channel blocker[12,13]. The molecules having Biphenyl moiety are also known to exhibit anti-inflammatory[14], diuretic[15], anti-diabetic[16] activity. Some of the Biphenyl containing compounds possesses antipsychotic and anxiolytic activity[17]. Some of the Biphenyl hydrazide-hydrazone are known to exhibit very good antimicrobial activity[18,19].

Hydrazones embedded with azometine –NH-N=CH- proton represent an important class of compounds for a therapeutic drug development program in the branch of medicinal chemistry. These compounds possess diverse biological and pharmacological properties such as cardio protective, antifungal, antiviral, antihelmintic, antimicrobial, anti‑inflammatory, analgesic, anticancer, antiplatelet, antimalarial, anticonvulsant, anti‑tubercular, antiprotozoal, anti‑trypanosomal, antischistosomiasis etc.[20-22]. Due to their biological and pharmacological properties, they are considered important for the synthesis of heterocyclic compounds[23,24]. In recent years, a number of hydrazone derivatives have been developed and evaluated for their antibacterial activity[25,26].

These reports prompted us to synthesize novel hydrazide-hydrazone derivatives (bearing vanillin and biphenyl moiety) *viz.*, substituted Phenyl-acetic acid [4-(4'-fluoro-bi phenyl-4-ylmethoxy)-3-methoxy-benzylidene]-hydrazide **(5a – e)** and evaluate for antibacterial activity.

2. MATERIALS AND METHODS

The solvents were purified according to standard procedures prior to use and all commercial chemicals were used as received. For thin-layer chromatography (TLC) analysis, Merck pre-coated Plates (silica gel 60 F254) were used and spots were visualized under UV light. Merck silica gel 60 (230-400 mesh) was used for flash column chromatography and the eluting solvents are indicated in the procedures. Melting point (mp) determinations were performed by using Mel-temp apparatus and are uncorrected. ^{1}H NMR spectra were recorded in Varian MR-400 MHz instrument. Chemical shifts are reported in δ parts per million (ppm) downfield from tetramethylsilane (TMS) as internal standard reference and the signals were reported as s (singlet), d (doublet), dd (doblet of doblet), t (triplet), q (quartet), m (multiplet) and coupling constants are measured in Hz. The mass spectra were recorded on Agilent ion trap MS and Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrometer.

2.1. EXPERIMENTAL

2.1.1 Preparation of 2-Aryylacetohydrazide derivatives (3a – e)

To a solution of various substituted arylacetic acid **1a-e** (7.35 mmol) in ethanol (20 mL) was added catalytic qty. of conc. H_2SO_4 and heated to reflux for 10 – 12 h. The reaction mixture was diluted with isopropylacetate (15 mL) followed by water (30 mL). The organic layer was washed with saturated $NaHCO_3$ solution followed by water and brine solution and was dried over sodium sulphate, filtered and evaporated to obtain respective ethyl 2-arylacetate derivatives **2a-e**. The crude compounds were utilized in the next step without any further purification.

To the solution of ethyl 2-arylacetates **2a-e** (3.04 mmol) derivatives in ethanol (7.5 mL, hydrazine-hydrate (21.30 mmol) is added and refluxed for 8 – 12 h. The reaction mixture was cooled to room temperature and filtered the precipitated solids and washed with pet-ether, to obtain the pure arylacetohydrazide compounds **3a-e.** The percentage yields of the products varied from 85 – 90%.

2-phenylacetohydrazide (3a)

Off-white solid; Yield; 85%; M.p: 116-117^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 6.8 Hz, 1H), 6.82 (d, *J* = 6.8 Hz, 2H), 6.70 (d, *J* = 6.6 Hz, 1H0, 5.80 (d, *J* = 6.6 Hz, 1H), 5.30 (br.s, 1H), 3.56 (s, 2H);

2-(3,5-dimethylphenyl)acetohydrazide (3b)

Pale brown solid; Yield: 88%; M.p.: 94-95^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90 (s, 1H), 6.82 (s, 2H), 6.70 (br.s, 1H), 3.90 (br.s, 2H), 3.50 (s, 2H), 2.40 (s, 6H);

2-(2-chloro-4-fluorophenyl)acetohydrazide (3c)

White solid; Yield: 82%; M.p.: 118-119^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.36 (m, 1H), 7.18-7.14 (m, 1H), 7.02-6.97 9m, 1H), 6.70 (br.s, 1H), 3.90 (br.s, 2H), 3.60 (s, 2H);

2-(4-nitrophenyl)acetohydrazide (3d)

Yellow solid; Yield: 88%; M.p.; 167^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 3.0 Hz, 2H), 7.42 (d, *J* = 2.6 Hz, 2H), 6.70 (br.s, 1H), 3.90 (br.s, 2H), 3.60 (s, 2H);

2-(2,3-dihydrobenzofuran-5-yl)acetohydrazide (3e)

White solid; Yield: 85%; M.p.: 112-113 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (s, 1H), 6.94 (d, *J* = 7.2 Hz, 1H), 6.78 (d, *J* = 7.2 Hz, 1H), 6.62 (br.s, 1H), 4.58 (t, *J* = 5.8 Hz, 2H), 3.84 (br.s, 2H), 3.42 (s, 2H), 3.18 (t, *J* = 5.8 Hz, 2H);

2.1.2. Preparation of 4-Fluoro-4'-Methylbiphenyl (6)

To a mixture of 1-iodo-4-methylbenzene **5** (1.0 g, 4.60 mmol), 2M sodium carbonate (5.52 mmol), Palladium tetrakis (0.01 mmol) in 50% Toluene: Water (10 mL) in sealed tube was added 4-fluorobenzene boronic acid **4** (0.71g, 5.06 mmol) and stirred at 110^{o}C temperature for 10 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and extracted with ethyl acetate and evaporated under reduced pressure to obtain the crude compound **6,** which was used as such for the next step.

2.1.3. Preparation of 4-(bromomethyl)-4'-fluorobiphenyl (7)

To a stirred solution of compound **6** (1.0 g, 5.40 mmol.) in carbon tetrachloride (8 mL) was added N-Bromosuccinamide (6.50 mmol.) followed by AIBN (catalytic qty.) and heated to reflux for 2h. The reaction mixture was filtered and the organic layer was washed with water (2 x 15 mL) followed by brine solution, dried over Na_2SO_4, filtered and evaporated under reduced pressure to obtain compound **7**. White solid; Yield: 82%; M.P: 97-98 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 9.6 Hz, 2H), 7.28 (t, *J* = 9.6 Hz, 2H), 4.78 (s, 2H).

2.1.4. Preparation of 4-[(4'-fluorobiphenyl-4-yl)methoxy]-3-methoxybenzaldehyde (8)

To a solution of Vanillin (1g, 6.6 mmol.) in DMF (7 mL) was added potassium carbonate (1g, 6.6 mmol.) followed by compound 7 (1.83g, 6.90 mmol.) at room temperature. The reaction mixture was heated to 90^{o}C for 2 h. The reaction mixture was cooled to room temperature and diluted with isopropyl acetate (25 mL), the organic layer was washed with water (3 X 25 mL) followed by brine solution (25 mL). The organic layer was separated, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure to obtain the crude compound. The crude compound was purified by column chromatography (6 % EtOAc in n-Hexane), yielding compound **8**. Yellow solid; Yield: 88%; M.P: 98-99 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.82 (s, 1H), 7.78-7.72 (m, 4H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.40 (s, 1H), 7.28 (t, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 1H), 5.22 (s, 2H), 3.82 (s, 3H); ESI-MS: m/z, 337.0 $(M-1)^{+}$;

2.1.5. General experimental procedure for the synthesis of acetohydrazide-hydrazone derivatives (9a-e)

To a stirred solution of compound **8** (0.30 mmol) in ethanol was added arylacetohydrazides **3a-e**, 0.30 mmol) and refluxed for 2-3h. The reaction mixture was cooled to room temperature and filtered the precipitated solids and washed with pet-ether, to obtain the pure compounds **9a-e.** Yields of the products varied between 90 and 98%.

Phenyl-acetic acid [4-(4'-fluoro-bi phenyl-4-ylmethoxy)-3-methoxy-benzylidene]-hydrazide (9a)

White solid; Yield: 84%; M.p.: 113-114^{o}C; ^{1}H NMR (500 MHz, DMSO-d6): 11.50 (* 11.22, s, 1H), 8.18 (* 7.90, s, 1H0, 7.74-7.70 (m, 4H), 7.50 (d, *J* = 7.6 Hz, 2H), 7.36-7.32 (m, 6H), 7.22-7.04 (m, 4H), 5.20 (s, 2H), 4.0 (* 3.58, s, 2H), 3.82 (* 3.80, s, 3H); ESI-MS: m/z, 469.1 $(M+1)^{+}$;

(3,5-Dimethyl-phenyl)-acetic acid [4-(4'-fluoro-biphenyl-4-ylmethoxy)-3-methoxy-benzylidene]-hydrazide (9b)

White solid; Yield: 80%; M.p.: 130-131^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): 11.42 (* 11.40, s, 1H), 8.18 (* 7.84, s, 1H), 7.78-7.64 (m, 4H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.38-7.26 (m, 3H), 7.18-7.06 (m, 2H), 6.90 (s, 1H), 6.80 (d, *J* = 8.0 Hz, 2H), 5.20 (s, 2H), 3.98 (* 3.42, s, 2H), 3.82 (* 3.80, s, 3H), 2.22 (s, 3H), 2.0 (s, 3H); ESI-MS: m/z, 497.1 $(M+1)^{+}$;

(2-Chloro-4-fluoro-phenyl)-acetic acid [4-(4'-fluoro-biphenyl-4-ylmethoxy)-3-methoxy-benzylidene]-hydrazide (9c)

Pale yellow solid; Yield: 88%; M.p.: 109-111^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): 11.50 (* 11.38, s, 1H), 8.18 (* 7.90, s, 1H), 7.76-7.72 (m, 4H), 7.58 (d, *J* = 7.8 Hz, 2H), 7.50-7.40 (m, 2H), 7.38-7.24 (m, 3H), 7.20-7.02 (m, 3H), 5.20 (s, 2H), 4.18 (* 3.70, s, 2H), 3.80 (s, 3H); ESI-MS: m/z, 521.1, $(M+1)^{+}$;

(4-Nitro-phenyl)-acetic acid [4-(4'-fluoro-biphenyl-4-ylmethoxy)-3-methoxy-benzylidene]-hydrazide (9d)

Yellow solid; Yield: 92%; M.p.: 109-111^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): 11.40 (* 11.20, s, 1H), 8.18 (* 7.98, s, 1H), 8.22 (d, *J* = 8.2 Hz, 4H), 7.86 (d, *J* = 8.2 Hz, 4H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 7.02 (d, *J* = 8.2 Hz, 1H), 5.20 (s, 2H), 4.10 (* 3.78, s, 2H), 3.84 (* 3.80, s, 3H);

(2,3-Dihydro-benzofuran-5-yl)-acetic acid [4-(4'-fluoro-biphenyl-4-ylmethoxy)-3-methoxy-benzylidene]-hydrazide (9e)

White solid; Yield: 88%; M.p.: 122-123^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): 11.40 (* 11.18, s, 1H), 8.18 (* 7.82, s, 1H), 7.76-7.66 (m, 4H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.30-7.26 (m, 3H), 7.18-7.08 (m, 3H), 7.0 (t, *J* = 8.2 Hz, 1H), 6.62 (dd, *J* = 6.8, 7.6 Hz, 1H), 5.20 (s, 2H), 4.50 (t, *J* = 8.2 Hz, 2H), 3.82 (* 3.80, s, 3H), 3.86 (* 3.40, s, 2H), 3.10 (t, *J* = 8.2 Hz, 2H); ESI-MS: m/z, 511.1 $(M+1)^{+}$;

2.2. ANTIBACTERIAL ASSAY

The newly prepared compounds **9a-e** were screened for their antibacterial activity against *Escherichia coli* (MTCC 443), *Staphylococcus aureus* (MTCC 96), *Pseudomonas aeruginosa* (MTCC 424) and *Streptococcus pyogenes* (MTCC 442) by disc diffusionmethod [27]. A standard inoculums (1-2 10^{7} c.f.u./ Ml 0.5 McFarland standards) was introduced on to the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculums. The discs measuring 6 mm in diameter were prepared from Whatman no. 1 filter paper and sterilized by dry heat at 130^{o}C for 1 h. The sterile discs previously soaked in a known concentration of the test compounds were placed in nutrient agar medium. Solvent and growth controls were kept. Ampicillin (100 µg / mL) was used as positive control. While the disk poured in DMSO was used as negative control. The plates were inverted and incubated for 24 h at 37 ^{o}C. The susceptibility was assessed on the basis of diameter of zone of inhibition against Gram-positive and Gram-negative strains of bacteria. Inhibition zones

were measured and compared with the controls. The bacterial zones of inhibition values are given in **Table 1**.

3. RESULTS AND DISCUSSION

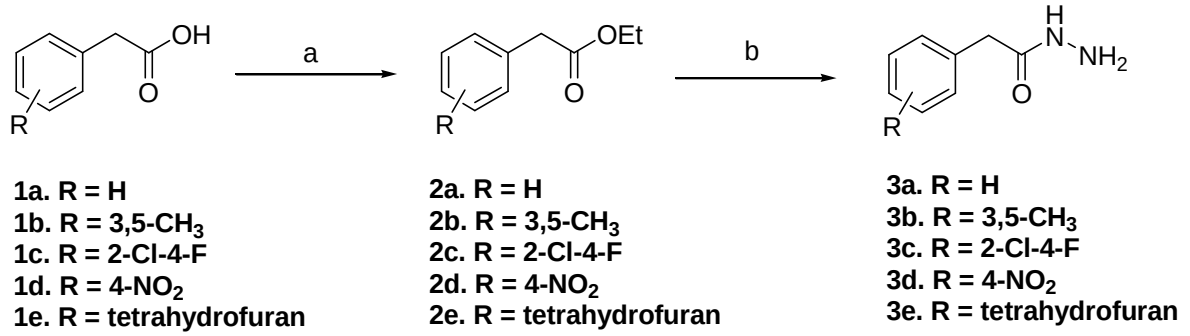
3.1. Chemistry

The synthetic sequence for the synthesis of final compounds hydrazide-hydrazone derivatives **9a-e** and and hydrazide compounds **3a-e** is given in the Scheme-**2** and Scheme-**1** respectively. Esterification of arylacetic acid **1a-e** was carried out in ethanol in presence of catalytic qty; of H_2SO_4 at reflux for 101-2h resulted in the corresponding 2-arylethylester derivatives **2a-e**. Hydrazinolysis of **2a-e** in presence of hydrazine-hydrate in ethanol at reflux 8-12 h gave arylacetohydrazide compounds **3a-e** in quantitative yields. Suzuki reaction of 1-iodo-4-methylbenzene and 4-fluorobenzene boronic acid in presence of $Pd(PPh_3)_4$, 2M Na_2CO_3 in 50% toluene:water in sealed tube at reflux resulted in the formation of 4-Fluoro-4'-Methylbiphenyl **6**. Allylic bromination of compound **6** in presence of N-Bromosuccinamide and catalytic qty; of AIBN in chloroform at reflux for 2h gave the desired product 4-(bromomethyl)-4'-fluorobiphenyl **7.** Coupling of **7** with Vanillin in presence of potassium carbonate in DMF at 90^oC for 2h resulted in the formation of the key intermediate 4-[(4'-fluorobiphenyl-4-yl)methoxy]-3-methoxybenzaldehyde **8** in 88% yield**.** Condensation of aldehyde **8** with various acetohydrazides **3a-e** in ethanol at reflux temperature resulted in the formation of hydrazide-hydrazone derivatives *viz.*, substituted Phenyl-acetic acid [4-(4'-fluoro-bi phenyl-4-ylmethoxy)-3-methoxy-benzylidene]-hydrazide **(9a – e)**

The structures of the newly synthesized derivatives **9a-e** were established by spectroscopic techniques like ^{1}H NMR, mass and IR spectral data. All the synthesized hydrazide-hydrazones derivatives **9a-e** compounds were found to exist as a mixture of two rotameric forms in solution [28] e.g. antiperiplanar (*ap*) and synperiplanar (*sp*) as indicated by their ^{1} H NMR spectra.

As a representative example, the ^{1}HNMR of compound **9b** is discussed here, the broad singlet at 11.42 (* 11.40 ppm) and 8.18 ppm (* 7.84 ppm) corresponds to the protons representing to –CO-**NH**- and -CO-NH-N=**CH**- groups respectively. The biphenyl and vallin ring protons appeared in the region 7.78 ppm – 7.06 (overlapped signals) while the 3,5-dimethyl phenyl ring appeared at 6.90 ppm (siglet, 1H) and 6.80 (doublet, 2H) respectively. The methylene protons flanked to biphenyl ring appeared at 5.20 ppm as singlet and the methylene proton attached to 3,5-dimethyl phenyl appeared at 3.98 ppm (* 3.42 ppm, singlet, 2H, rotameric

peaks). The methoxy protons appeared in the expected region at 3.82 ppm (* 3.42 ppm, singlet, 3H, rotameric peaks) and the methyl protons resonated at 2.22 ppm (3H) and 2.0 ppm (3H) as singlets. The mass spectrum of the compound 9b showed (M+1) peaks and is in agreement with the desired molecular ion (497.1, M+1). The mass spectra of the remaining compounds also showed desired (M+1) peaks, and are in agreement with their molecular formula.



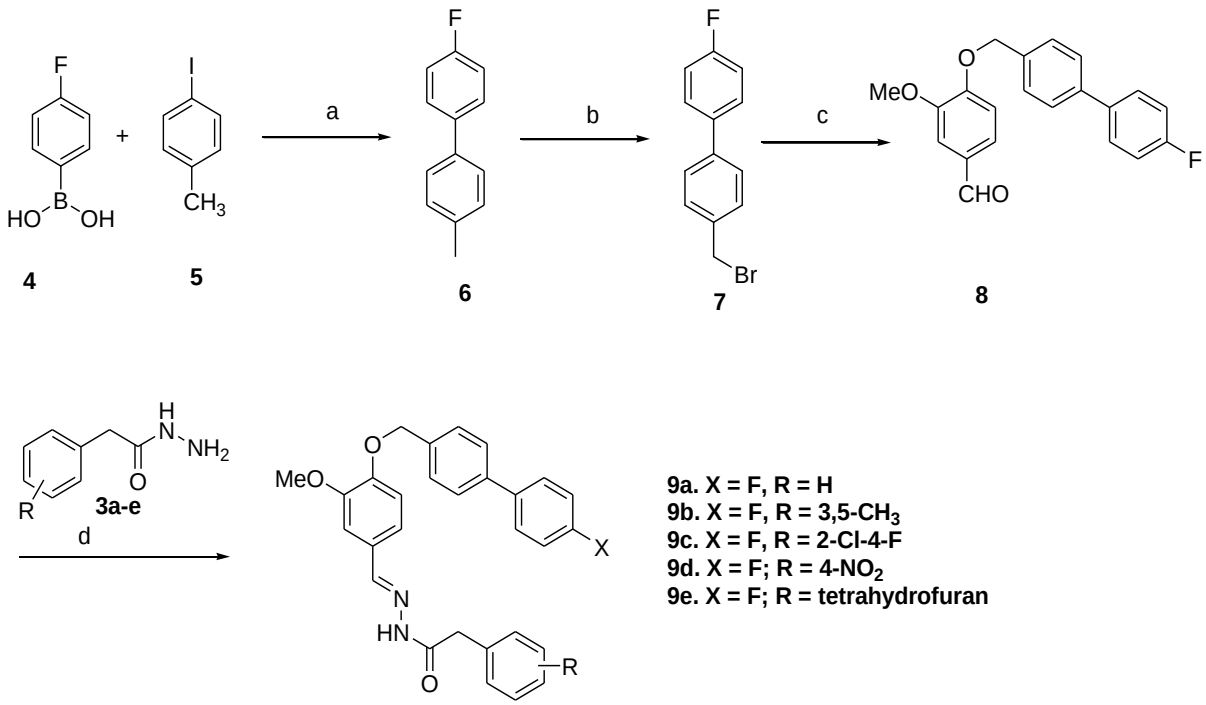
1a. R = H
1b. R = 3,5-CH_3
1c. R = 2-Cl-4-F
1d. R = 4-NO_2
1e. R = tetrahydrofuran

2a. R = H
2b. R = 3,5-CH_3
2c. R = 2-Cl-4-F
2d. R = 4-NO_2
2e. R = tetrahydrofuran

3a. R = H
3b. R = 3,5-CH_3
3c. R = 2-Cl-4-F
3d. R = 4-NO_2
3e. R = tetrahydrofuran

Scheme-1: Synthesis of arylacetohydrazide 3a-e

Reaction conditions: a) conc;H_2SO_4, ethanol, reflux, 10-12 h; b) **2a-e**, hydrazine-hydrate, ethanol, reflux, 8-12 h



9a. X = F, R = H
9b. X = F, R = 3,5-CH_3
9c. X = F, R = 2-Cl-4-F
9d. X = F; R = 4-NO_2
9e. X = F; R = tetrahydrofuran

Scheme-2: Synthesis of substituted Phenyl-acetic acid [4-(4'-fluoro-bi phenyl-4-ylmethoxy)-3-methoxy-benzylidene]-hydrazide (9a – e)

Reaction conditions: a) $Pd(PPh_3)_4$, 2M Na_2CO_3, Toluene:Water, 110°C, 10 h; b) NBS, AIBN, CCl_4, reflux, 2 h; c) Vanillin, K_2CO_3, DMF, 90°C, 2h; d) Acetohydrazides **3a-e**, Ethanol, reflux, 2-3h.

3.2 Antibacterial activity

The antibacterial results of the hydrazide-hydrazone derivatives **9a–e** is tabulated in **Table-1** and the results are evaluated on the basis of zone of inhibition (ZI). Compounds with the following ZI is assigned as follows, weak activity (0-6 mm), moderate activity (7-11 mm) and good activity (12-18 mm). Compounds **9a** (R = H, ZI = 7-9 mm) and **9b** (R = 3,5-dimethyl, ZI = 9-11 mm) displayed moderate antibacterial activity while the compounds **9c** (R = 2-Cl-4-F, ZI = 12-16 mm)**, 9d** (R = 4-NO_2, ZI = 14-16 mm) and **9e** (R = tetrahydrofuran, ZI = 15-18 mm) exhibited good antibacterial activity when compared to the ampicillin as the standard drug (at concentration 100 µg / mL). It is worth mentioning that compound **9c**, **9d** and **9e** with substitution R = 2-Cl-4F, 4-NO_2 and tetrahydrofuran showed good antibacterial activity while the compounds with substitution R = H and 3,5-dimethyl showed moderate antibacterial activity.

Table I: *In vivo* efficacy of Hydrazide-hydrazone derivatives 9a-e for demonstrating antibacterial activity against selected pathogens

Compound No	Gram negative bacteria		Gram positive bacteria	
	E.coli MTCC 443	*P.aeruginosa* MTCC 424	*S.aureus* MTCC 96	*S.pyogenes* MTCC 442
	Zone of inhibition[a]			
9a	8	9	7	7
9b	10	11	10	9
9c	12	14	15	16
9d	15	16	14	15
9e	17	18	15	17
Ampicillin ((100 µg /mL)	19	18	16	18
Control (DMSO)	-	-	-	-

[a]Diameter of well (bore size)- 6 mm;

4. CONCLUSION

In conclusion, we have prepared some novel hydrazide-hydrazone derivatives 5**a-e** bearing vanillin and biphenyl ring moiety and these were screened for antibacterial activity. Among the newly synthesized hydrazide-hydrazone derivatives, compounds **9a** (R = H, ZI = 7-9 mm) and **9b** (R = 3,5-dimethyl, ZI = 9-11 mm) displayed moderate antibacterial activity while the

compounds **9c** (R = 2-Cl-4-F, ZI = 12-16 mm)**, 9d** (R = 4-NO_2, ZI = 14-16 mm) and **9e** (R = tetrahydrofuran, ZI = 15-18 mm) exhibited good antibacterial activity when compared to the ampicillin as the standard drug (at concentration 100 µg / mL).

5. ACKNOWLEDGEMENT

One of the authors (ALV) is thankful to Dr. B. Ram, the Director, Green Evolution Laboratories for helpful suggestions and constant encouragement.

6. CONFLITCT OF INTEREST

"The author(s) declare(s) that there is no conflict of interest regarding publication of this article".

7. REFERENCES

1. Durante-Mangoni E, Grammatikos A, Utili R, Falagas M. Do we still need the aminoglycosides?. Int. J. Antimicrob. Agents, 2009; 33: 201-205.
2. Gonzalo-Garijo MA, Rodriguez-Nevado I, Argila D. Patch tests for diagnosis of delayed hypersensitivity to cephalosporins. Allergol. Immunopath, 2006; 34: 39-41.
3. Espuelas S, Roth A, Thuman C, Frisch B, Schuner F. Effect of synthetic lipopeptides formulated in liposomes on the maturation of human dendritic cells. Mol. Immunol, 2005; 42: 721-729.
4. Samide A, Tutunaru B, Negrila C, Trandafir I, Maxut A. Effect of sulfacetamide on the composition of corrosion products formed onto carbon steel surface in hydrochloride. Dig. J. Nanomater. Bios, 2011; 6: 663-673.
5. Samide A, Tutunaru B, Negrila C. CorrosionInhibition of Carbon Steel in Hydrochloric Acid Solution Using a Sulfa Drug. Chem. Biochem. Eng, 2011; Q. 25: 299-308.
6. Samide A, Tutunaru B, Negrila C, Prunaru I. Surface analysis of inhibitor film formed by 4-amino-N-(1,3-thiazol-2-yl) benzene sulfonamide on carbon steel surface in acidic media. Spectrosc. Lett, 2012; 45: 55-64.
7. Samide A, Tutunaru B, Negrila C, Dobritescu A. Study of the corrosion products formed on carbon steel surface in hydrochloric acid solution. J. Therm. Anal. Calorim, 2012; 110: 145.
8. Giamarellos-Bourboulis E. Immunomodulatory therapies for sepsis: unexpected effects with macrolides. Int. J. Antimicrob. Ag, 2008; 31: 12-20.
9. Bozdogan B, Appelbaum P. Oxazolidinones: activity, mode of action, and mechanism of resistance. Int. J. Antimicrob. Ag**,** 2004; 23: 113-119.

10. Bailey R. Quinolones in the treatment of uncomplicated urinary tract infections. Int. J. Antimicrob. Ag, 1992; 2: 19-28.
11. Samide A. A pharmaceutical product as corrosion inhibitor for carbon steel in acidic environments. J. Environ. Sci. Heal, 2013; A 48: 159-165.
12. Jain, ZJ, Gide PS, Kankate RS. Biphenyls and their derivatives as synthetically and pharmacologically important aromatic structural moieties. Arabian J. Chem, 2013 (*in press*).
13. Mojjarad JS, Zamani Z, Nazemiyeh H, Ghasemi S, Asgari D. Synthesis of Novel 1,4-Dihydropyridine Derivatives Bearing Biphenyl-2'- Tetrazole Substitution as Potential Dual Angiotensin II Receptors and Calcium Channel Blockers. Adv. Pharm. Bull, 2011; 9: 1-9.
14. Deep A, Jain S, Sharma PC. Synthesis and anti-inflammatory activity of some novel biphenyl-4-carboxylic acid 5-(arylidene)-2-(aryl)-4-oxothiazolidin-3-yl amides. Acta Pol. Pharm. Drug Res, 2010; 67: 63-67.
15. Yar MS, Ansari ZH. Synthesis and in vivo diuretic activity of biphenyl benzothiazole-2-carboxamide derivatives. Acta Pol. Pharm. Drug Res, 2009; 66: 387-392.
16. Sachan N, Thareja S, Agarwal R, Kadam SS, Kulkarni VM. Substituted biphenyl ethanones as antidiabetic agents: synthesis and *in-vivo* screening. Int. J. Chemtech. Res, 2009; 1: 1625-1631.
17. Ruggero G, Jones CK, Hemstapat K, Nong Y, Echemendia, NG, Williams LC, Paulis TD, Conn PJ. Biphenyl-indanone A, a positive allosteric modulator of the metabotropic glutamate receptor subtype 2, has antipsychotic- and anxiolytic-like effects in mice. J. Pharmacol. Exp. Ther, 2006; 318: 173-185.
18. Deep A, Jain S, Sharma PC, Verma P, Kumar M, Dora CP. Acta Pol. Pharm. Drug Res, 2010; 67: 225.
19. Madhkar A, Kannappan N, Deep A, Kumar P, Kumar M, Verma P. Synthesis and antimicrobial studies of biphenyl-4-carboxylic acid 2-(aryl)-4-oxo-thiazolidin-3-yl – amide. Int. J. Chemtech. Res, 2009; 1: 1376-1380.
20. Rollas S, Küçükgüzel SG. Biological activities of hydrazone derivatives. Molecule, 2007; 12: 1910-1939.
21. Narang R, Narasimhan B, Sharma S. A review on biological activities and chemical synthesis of hydrazide derivatives. Curr Med Chem, 2012; 19: 569-612.
22. Negi V J, Sharma A K, Negi J S, Ra V. A review exploring biological activities of hydrazones. Int J Pharm Chem, 2012; 4: 100-109.

23. Belskaya N P, Dehaen W, Bakulev V A. Synthesis and properties of hydrazones bearing amide, thioamide and amidine functions. Arch Org Chem. Arch Org Chem, 2010; 1: 275-335.
24. Xavier A J, Thakur M, Marie J M. Synthesis and spectral characterisation of hydrazone based 14-membered octaaza macrocyclic Ni (II) complexes. J Chem Pharm Res, 2012; 4: 986-990.
25. Rajasekhar Narisetty, Chandrasekhar KB, Sandeep Mohanty, Balram B. Synthesis of Novel Hydrazone Derivatives of 2, 5-difluorobenzoic Acid as Potential Antibacterial Agents. Letters in Drug Design & Discovery, 2013; 10**:** 620-627**.**
26. Srinivasa Rao Y, Aminul Islam, Nageswar D, Hari babu B. Synthesis, characterization and antibacterial activity of some new 3-{[4-(2-methoxyphenyl)piperazin-1-yl]sulfonyl}benzohydrazide-hydrazone derivatives. Asian J Chem, 2015; 27: 3729.
27. A.H. Collins, Microbiological Methods, second ed. Butterworth, London, 1976.
28. Nayyar, A.; Malde A.; Coutinho, E.; Jain, R. Synthesis, anti-tuberculosis activity, and 3D-QSAR study of ring-substituted-2/4-quinolinecarbaldehyde derivatives. Bioorg. Med. Chem, 2006; 14: 7302-7310.