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ARTICLE

Synthesis and Biological Evaluation of Biphenyl Derivatives of Hydrazine *via* Palladium Catalyzed Suzuki-Miyaura Coupling Reaction

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ABSTRACT

Generally, several methods for the construction of biphenyls, including Stille coupling, Gomberg-Bachmann reaction, Ullmann reaction and Suzuki-Miyaura cross-coupling are reported. In present research, considering the particularities of these methods and the characteristics of the target compounds by Suzuki-Miyaura cross-coupling reaction. To investigate the optimal conditions, a model reaction was performed using 1-bromo-4-iodobenzene and phenyl boronic acid under different conditions. The products were characterized by FT-IR, mass, ¹H NMR and ¹³C NMR spectroscopy.

KEYWORDS

Suzuki-Miyaura reactions, 1-Bromo-4-iodobenzene, Boronic acid, 2-Phenylacetic acid, Biological evaluation.

INTRODUCTION

Metal catalyzed cross-coupling reactions have developed various electron rich aryl or hetero aryl halides with various components like aryl/hetero aryl boronates (B) [1], aryl/alkyl silyl [2], aryl/hetero aryl stannous [3] and aryl/hetero aryl zinc [4] in synthetic chemist's toolbox. These metal-catalyzed cross-coupling reactions date back to the work of Ullmann & Goldberg in early 1900s on copper-promoted carbon-carbon and carbon heteroatom like carbon-nitrogen and carbon-oxygen bond formations.

Chan-Lam reaction and Buchwald reaction used copper which remains the catalyst of choice for these reactions until Suzuki [1], Hiyama [2], Stille [3], Negishi [4], Sonogashira [5] and Heck [6] coupling reactions were discovered by employing palladium as catalyst. These palladium-catalyzed reactions are generally carried out under milder conditions at ambient to higher temperature with a wider range of substrates than reactions catalyzed by copper or other metals at higher temperature, have become standard methods for formation of carbon-carbon and carbon-heteroatom like carbon-nitrogen and carbon-oxygen bonds [7-12]. Key steps in these cross-coupling reactions include oxidative addition of organic halide, transmetalation of nucleophilic carbon (negatively charged) and reductive elimination to form the product. The Heck coupling of aryl halides and alkenes also falls into this class of reactions, although

it involves a migratory insertion and elimination sequence in the key bond-forming step rather than reductive elimination.

All cross-coupling reactions are differentiated by the metal catalyzed coupling of organic electrophiles, typically sp -, sp^2 - or sp^3 - hybridized carbon in an organic halide (**1**) as a leaving group. The majority of research centralized on sp^2 carbon-halogen bonds (electrophiles) with halogen or pseudo halogen as releasing groups. Varieties of name reactions have been discovered employing organometallic carbon nucleophiles. The substrate with sp^2 carbon-halogen bonds (electrophiles) with halogen or pseudo-halogen as releasing groups reacts with different organic nucleophiles (Fig. 1).

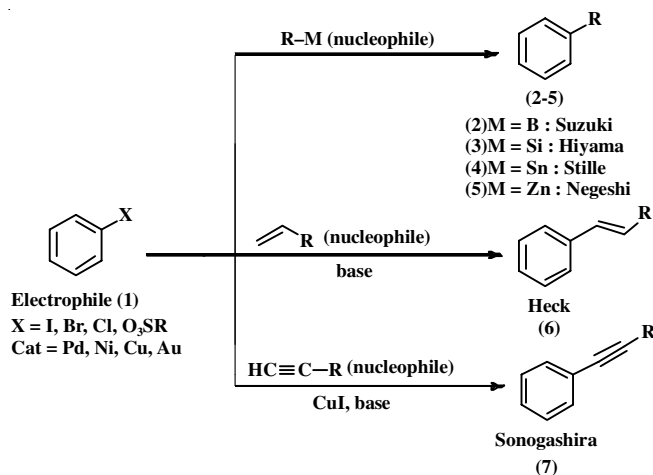


Fig. 1. Major classes of metal-catalyzed reactions

EXPERIMENTAL

Melting points were determined in open capillary tubes. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by UV and iodine. IR spectra were recorded Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. ^1H NMR and ^{13}C NMR were determined in DMSO- d_6 solution on a Bruker Ac 400 MHz spectrometer.

Synthesis of 4-bromo-1,1'-biphenyl (3): A mixture of 1-bromo-4-iodobenzene (**1**) (1 mmol) and boronic acid (**2**) (1 mmol) were dissolved in solvent 1,4-dioxane (10 mL) and stirred for 5 min at room temperature under nitrogen atmosphere.

To this mixture, Cs_2CO_3 (2 mmol) was added followed by *tetrakis*(triphenyl phosphine)palladium (0.2 mmol). The reaction mixture was heated at 100-130 °C for 16 h, the progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was allowed to cool, filtered over a plug of celite bed and diluted with water to yield solid product, which was isolated by filtration and washed with distilled water.

Synthesis of 2-phenylacetyl chloride (5): 2-Phenylacetic acid (**4**) (1 mmol) dissolved in methylene dichloride (MDC) was treated dropwise with SOCl_2 (1.5 mmol) at 0 °C and stirred the reaction mixture at room temperature for 6-7 h in the presence of triethylamine (TEA, 3 mmol) as base catalyst and methylene dichloride (20 mL) as solvent. After completion of reaction, the reaction mixture was poured into ice-water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulphate and evaporated *in vacuo*. The crude product was purified by distillation using ethanol to afford compound **5**.

Synthesis of 1-(4'-bromo-[1,1'-biphenyl]-4-yl)-2-phenyl ethanone (6): A Friedel-Crafts acylation of 4-bromo-1,1'-biphenyl (1 mmol, **3**) dissolved in methylene dichloride (20 mL) and mixed with 2-phenylacetyl chloride (1 mmol, **5**) with portion wise addition of anhydrous AlCl_3 (1.2 mmol) at 0 °C temperature. The content was refluxed at 80 °C for 16 h. After completion of the reaction, the content was pour into ice-cold water, filtered to give the solid product **6** and then crystallized.

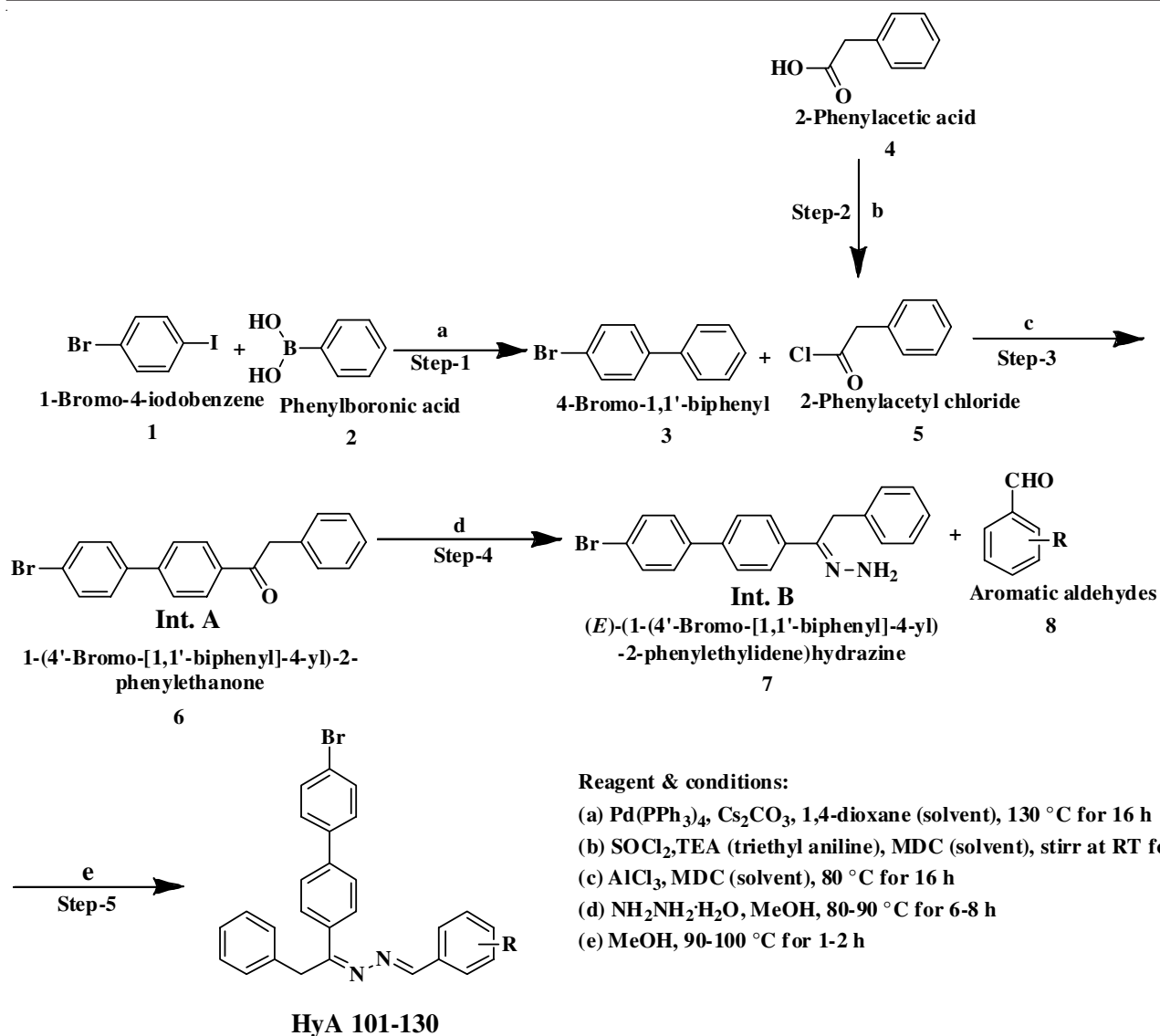
Synthesis of (1-(4'-bromo-[1,1'-biphenyl]-4-yl)-2-phenylethylidene)hydrazine (7): A reaction mixture of 1-(4'-bromo-[1,1'-biphenyl]-4-yl)-2-phenylethanone (1 mmol, **6**) and hydrazine hydrate (2 mmol) was refluxed at 80 °C in methanol (20 mL) in the presence of a catalytic amount of 1-2 drops of conc. HCl for about 6-8 h. After completion of the reaction, the reaction mixture was filtered to give the solid product **7**.

General synthesis of 1-benzylidene-2-(1-(4'-bromo-[1,1'-biphenyl]-4-yl)-2-phenylethylidene)hydrazine (HyA 101-130): A reaction of (1-(4'-bromo-[1,1'-biphenyl]-4-yl)-2-phenylethylidene)hydrazine (**7**, 1 mmol) and various aromatic aldehydes (1 mmol) was refluxed at 90-100 °C in methanol (20 mL) in the presence of a catalytic amount of 1-2 drops of conc. HCl for about 1-2 h. After completion of the reaction, the reaction mixture was filtered to give the solid products (**HyA 101-110**), which were recrystallized from ethanol (**Scheme-I**). The physico-chemical parameters of the synthesized compounds are given in Table-1.

TABLE-1
PHYSICAL PARAMETERS OF (HyA 101-110)

Code	R	m.f.	m.w.	m.p. (°C)	Yield (%)	R _f
HyA-101	H	C ₂₇ H ₂₁ N ₂ Br	452	113-115	71	0.79
HyA-102	4-CH ₃	C ₂₈ H ₂₃ N ₂ Br	466	109-111	69	0.83
HyA-103	3-Br	C ₂₇ H ₂₀ N ₂ Br ₂	530	140-142	73	0.86
HyA-104	4-Cl	C ₂₇ H ₂₀ N ₂ BrCl	486	151-153	78	0.87
HyA-105	4-NO ₂	C ₂₇ H ₂₀ N ₃ O ₂ Br	497	193-195	84	0.93
HyA-106	3-OC ₆ H ₅	C ₃₃ H ₂₃ N ₂ OBr	544	189-191	85	0.91
HyA-107	Pyridine	C ₂₆ H ₂₀ N ₃ Br	453	180-182	86	0.89
HyA-108	2,5-CH ₃	C ₂₉ H ₂₅ N ₂ O ₂ Br	512	106-108	68	0.81
HyA-109	3-OCH ₃	C ₂₈ H ₂₃ N ₂ OBr	482	165-167	73	0.84
HyA-110	3,4,5-OCH ₃	C ₃₀ H ₂₇ N ₂ O ₃ Br	542	177-179	78	0.82

TLC solvent system R_f: ethyl acetate:hexane - 2:8



Scheme-I: Synthetic route for the final compounds

Spectral data

1-Benzylidene-2-(1-(4'-bromo-[1,1'-biphenyl]-4-yl)-2-phenylethylidene)hydrazine (HyA 101): IR (KBr, ν_{max} , cm⁻¹): 3024, 2990, 2939 (=C-H *str.* of aromatic ring), 2330 (C=N *str.*), 1612, 1573 (C=C *str.* of aromatic ring), 1481 (N-N *str.*), 1442 (C-H bend. of alkane), 1211 (C-C *str.* of alkane), 856 (C-C bend. of *p*-disubstituted aromatic ring), 810 (C-H bend. of mono-substituted aromatic ring), 516 (C-Br *str.* of halogen); ¹H NMR (CDCl₃, 400 MHz) δ ppm: 4.569 (s, 2H, H_a), 7.15-7.17 (m, 1H, H_b), 7.21-7.26 (m, 4H, H_c), 7.42-7.46 (m, 5H, H_d), 7.54-7.56 (d, 4H, H_e, $J = 8.4$ Hz), 7.83-7.86 (dd, 2H, H_f), 7.99-8.01 (d, 2H, H_g, $J = 8.4$ Hz), 8.60 (s, 1H, H_h); ¹³C NMR (CDCl₃, 100 MHz) δ ppm: 34.74, 122.03, 126.29, 126.92, 128.19, 128.61, 128.66, 128.70, 128.77, 131.06, 131.98, 134.61, 136.43, 137.47, 139.27, 141.52, 159.93, 165.82; MS: m/z 452; Anal. calcd. (found) % for C₂₇H₂₁N₂Br: C, 71.53 (71.56); H, 4.67 (4.64); N, 6.18 (6.14).

1-(1-(4'-Bromo-[1,1'-biphenyl]-4-yl)-2-phenylethylidene)-2-(4-chlorobenzylidene) hydrazine (HyA 104): IR (KBr, ν_{max} , cm⁻¹): 3024, 2924 (=C-H *str.* of aromatic ring), 2330 (C=N *str.*), 1612, 1449 (C=C *str.* of aromatic ring), 1489 (N-N

str.), 1427 (C-H bend. of alkane), 1211 (C-C *str.* of alkane), 856 (C-C bend. of *p*-disubstituted aromatic ring), 817 (C-H bending of monosubstituted aromatic ring), 709 (C-Cl *str.* of halogen), 509 (C-Br *str.* of halogen); ¹H NMR (CDCl₃, 400 MHz) δ ppm: 4.55 (s, 2H, H_a), 7.16-7.18 (m, 1H, H_b), 7.23-7.25 (m, 4H, H_c), 7.39-7.41 (d, 2H, H_d), 7.44-7.46 (d, 2H, H_e), 7.54-7.57 (d, 4H, H_f), 7.76-7.78 (d, 2H, H_g, $J = 8.4$ Hz), 7.98-8.01 (d, 2H, H_h, $J = 8.4$ Hz), 8.55 (s, 1H, H_i); ¹³C NMR (CDCl₃, 100 MHz) δ ppm: 34.76, 122.06, 126.34, 126.94, 128.20, 128.55, 128.72, 129.08, 129.70, 131.98, 133.07, 136.29, 136.99, 137.35, 139.21, 141.65, 158.61, 166.14; MS: m/z 486; Anal. calcd. (found) % for C₂₇H₂₀N₂BrCl: C, 66.48 (66.56); H, 4.13 (4.09); N, 5.74 (5.71).

1-(1-(4'-Bromo-[1,1'-biphenyl]-4-yl)-2-phenylethylidene)-2-(3-phenoxybenzylidene)hydrazine (HyA 106): IR (KBr, ν_{max} , cm⁻¹): 3063, 3032 (=C-H *str.* of aromatic ring), 2330 (C=N *str.*), 1612, 1581 (C=C *str.* of aromatic ring), 1489 (N-N *str.*), 1435 (C-H bend. of alkane), 1211 (C-C *str.* of alkane), 1003, 1072 (C-O *str.* of ether), 856 (C-C bend. of *p*-disubstituted aromatic ring), 794 (C-H bend. of monosubstituted aromatic ring), 694 (C-C bend. of *m*-disubstituted aromatic

ring), 516 (C-Br *str.* of halogen); ^1H NMR (DMSO- d_6 , 400 MHz) δ ppm: 4.49 (s, 2H, H_a), 7.074-7.093 (d, 2H, H_b , $J = 8$ Hz), 7.113-7.239 (m, 7H, H_c), 7.405-7.444 (m, 2H, H_d), 7.493-7.550 (m, 2H, H_e), 7.666 (m, 5H, H_f), 7.728-7.749 (d, 2H, H_g , $J = 8.4$ Hz), 8.052-8.073 (d, 2H, H_h , $J = 8.4$ Hz), 8.665 (s, 2H, H_i); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ ppm: 33.32, 117.31, 118.92, 121.15, 121.46, 123.61, 123.85, 126.16, 126.62, 128.15, 128.35, 128.58, 128.77, 130.14, 130.64, 131.86, 135.56, 136.18, 137.29, 138.29, 140.54, 156.13, 157.19, 158.83, 165.20; MS: m/z 544; Anal. calcd. (found) % for $\text{C}_{33}\text{H}_{25}\text{N}_2\text{OBr}$: C, 72.66 (72.71); H, 4.62 (4.56); N, 5.14 (5.20).

1-(1-(4'-Bromo-[1,1'-biphenyl]-4-yl)-2-phenylethylidene)hydrazono)methylpyridine (HyA 107): IR (KBr, ν_{max} , cm^{-1}): 3055, 3032 (=C-H *str.* of aromatic ring), 2330 (C=N *str.*), 1597, 1566 (C=C *str.* of aromatic ring), 1489 (N-N *str.*), 1435 (C-H bend. of alkane), 1235 (C-C *str.* of alkane), 856 (C-C bend. of *p*-disubstituted aromatic ring), 810 (C-H bend. of monosubstituted aromatic ring), 516 (C-Br *str.* of halogen); ^1H NMR (DMSO- d_6 , 400 MHz) δ ppm: 4.545 (s, 2H, H_a), 7.144-7.153 (m, 1H, H_b), 7.233 (m, 4H, H_c), 7.669 (m, 4H, H_d), 7.742-7.762 (d, 2H, H_e , $J = 8$ Hz), 7.814-7.826 (d, 2H, H_f), 8.075-8.095 (d, 2H, H_g , $J = 8.4$ Hz), 8.662 (s, 1H, H_h), 8.718-8.730 (d, 2H, H_i); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ ppm: 33.49, 121.53, 121.89, 126.26, 126.67, 128.29, 128.36, 128.65, 128.79, 131.87, 135.26, 137.07, 138.23, 140.77, 141.02, 150.44, 157.27, 165.56; MS: m/z 453; Anal. calcd. (found) % for $\text{C}_{26}\text{H}_{20}\text{N}_3\text{Br}$: C, 68.73 (68.56); H, 4.44 (4.39); N, 9.25 (9.32).

1-(1-(4'-Bromo-[1,1'-biphenyl]-4-yl)-2-phenylethylidene)-2-(3-methoxybenzylidene)hydrazine (HyA 109): IR (KBr, ν_{max} , cm^{-1}): 3024, 2931 (=C-H *str.* of aromatic ring), 2330 (C=N *str.*), 1612, 1581 (C=C *str.* of aromatic ring), 1489 (N-N *str.*), 1435 (C-H bend. of alkane), 1273 (C-C *str.* of alkane), 1003, 1049, 1072 (C-O *str.* of ether), 864 (C-C bend. of *p*-disubstituted aromatic ring), 810 (C-H bend. of monosubstituted aromatic ring), 694 (C-C bend. of *m*-disubstituted aromatic ring), 516 (C-Br *str.* of halogen); ^1H NMR (DMSO- d_6 , 400 MHz) δ ppm: 3.809 (s, 3H, H_a), 4.564, 4.503 (s, 2H, H_b), 7.087-7.107 (m, 2H, H_c), 7.199-7.245 (m, 4H, H_d), 7.399-7.498 (m, 2H, H_e), 7.663 (m, 5H, H_f), 7.726-7.745 (d, 2H, H_g , $J = 8$ Hz), 8.064-8.082 (d, 2H, H_h , $J = 8$ Hz), 8.661 (s, 1H, H_i); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ ppm: 33.54, 55.17, 112.96, 117.08,

120.94, 121.45, 126.16, 126.61, 126.70, 128.05, 128.13, 128.37, 128.42, 128.60, 128.76, 130.04, 131.85, 135.59, 135.61, 135.95, 137.27, 137.41, 138.31, 140.36, 140.48, 159.43, 159.49, 162.48, 165.03; MS: m/z 483; Anal. calcd. (found) % for $\text{C}_{28}\text{H}_{23}\text{N}_2\text{OBr}$: C, 69.57 (69.64); H, 4.80 (4.70); N, 5.80 (5.70).

Antimicrobial activity: All the synthesized compounds biphenyl derivatives (**HyA 101-110**) were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method with two Gram-positive bacteria *Staphylococcus aureus* MTCC-96, *Streptococcus pyogenes* MTCC-443, two Gram-negative bacteria *Escherichia coli* MTCC-442, *Pseudomonas aeruginosa* MTCC-441 and three fungal strains *Candida albicans* MTCC-227, *Aspergillus niger* MTCC-282, *Aspergillus clavatus* MTCC-1323 using ampicillin, chloramphenicol and griseofulvin as standard drugs [13-16]. The standard strains were procured from the microbial type culture collection (MTCC) and Microcare Laboratory & Tuberculosis Research centre, Surat, India.

The minimal inhibitory concentration (MIC) values for all the compounds are given in Table-2. Serial dilutions of the test compounds and reference drugs were prepared in Mueller-Hinton agar. Drugs (10 mg) were dissolved in DMSO (1 mL). Further progressive dilutions with melted Mueller-Hinton agar were performed to obtain the required concentrations. In primary screening 1000, 500 and 250 $\mu\text{g mL}^{-1}$ concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution at 125, 100, 50, 25, 12.5 and 6.25 $\mu\text{g mL}^{-1}$ against all microorganisms. The tubes were inoculated with 10^8 cfu mL^{-1} and incubated at 37 °C for 24 h. To ensure that the solvent had no effect on the bacterial growth, a control was performed with the test medium supplemented with DMSO at the same dilutions.

RESULTS AND DISCUSSION

Recognizing these facts, here in we report syntheses of biphenyl derivatives (**HyA 101-110**) have been reaction of aromatic aldehydes with hydrazine derivatives using acid as a catalyst in methanol. The newly synthesized compounds were characterized by FT-IR, ^1H NMR, ^{13}C NMR and mass spectral analyses. All the synthesized compounds are subjected to

TABLE-2
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF SYNTHESIZED COMPOUNDS HyA 101-110

Code	Minimum inhibition concentration ($\mu\text{g mL}^{-1}$)						
	Gram-positive		Gram-negative		Fungal species		
	<i>S. aureus</i>	<i>S. pyogenes</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>C. albicans</i>	<i>A. niger</i>	<i>A. clavatus</i>
HyA-101	500	500	500	250	500	250	250
HyA-102	500	1000	500	100	1000	>1000	1000
HyA-103	100	100	250	250	500	500	250
HyA-104	100	250	250	125	100	100	125
HyA-105	62.5	100	125	100	250	250	250
HyA-106	500	500	250	250	1000	500	500
HyA-107	500	500	250	250	1000	500	500
HyA-108	500	250	500	250	500	250	250
HyA-109	250	250	250	500	500	500	250
HyA-110	500	250	250	500	500	250	250
Ampicillin	250	100	100	100	–	–	–
Chloramphenicol	50	50	50	50	–	–	–
Griseofulvin	–	–	–	–	500	100	100

various biological activities *viz.*, antibacterial, antitubercular and antifungal activity.

Conclusion

Biphenyl derivatives (**HyA 101-110**) were synthesized *via* Suzuki-Miyaura coupling reaction followed by the reaction of aromatic aldehydes with hydrazine derivatives using acid as a catalyst in methanol. The newly synthesized compounds were characterized by FT-IR, ¹H NMR, ¹³C NMR, mass spectra analyses and subjected to various biological activities *viz.*, antibacterial and antifungal activity.

Among the synthesized compounds, compound **HyA 105** showed the highest activity against the both Gram-positive and Gram-negative bacteria, whereas compound **HyA 104** the highest activity against the three studied fungal strains (Table-2).

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