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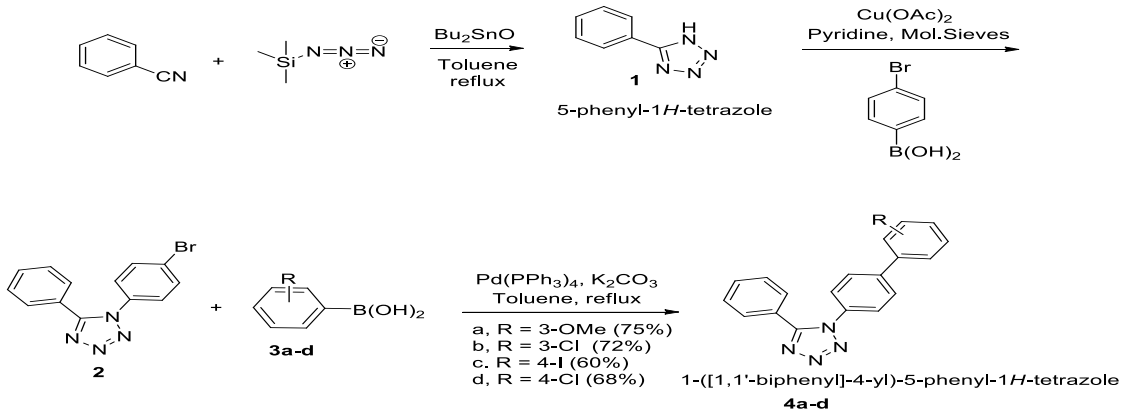
Synthesis and Biological Activity of Tetrazole – 5(4H) –one Derivatives

Veeranna Guguloth[1], Ravinder Vadde[2] CH. Venkata Ramana Reddy [3]
1.Department of Chemistry, SR &BGNR Government Arts and Science College (A) Khammam TG-507002
2. Department of Chemistry, Kakatiya University Warangal TG-506009
3i). Department of Chemistry, Jawaharlal Nehru Technological University Kukatpalli Hyderabad TG-500085
3ii.) Vignana Bharathi Institute of Technology Ghatkesar, Hyderabad TG-501301
Email:-gvchem3@gmail.com

Abstract
The Noval 1.5 di aryl tetrazole derivatives were synthesised by copper mediated N-arylation of 1 –(4 –Bromophenyl) 5- phenyl-1 H- tetrazole with aryl boronic acids these compounds were found to be stable to strong Lewis acid conditions. The novel compounds were synthesised with good yields and characterized by the analytical and I.R, 1HNMR,13C NMR & mass spectral data. All these compounds yellow in colour & was found to inhibit L1210 leukemia cell Proliferation and SK-BR-3 breast cancer cell growth over several days in culture in vitro. Hence the tetrazole ring is an important structural component in many biologically and medicinally relevant compounds.

Keywords: Tetrazole derivatives, Boronic acids, spectral characterization, culture, Pd Catalyzed, Heterogeneous catalytic transfer reductions, Suzuki coupling, TLC, Rf



1.1. Introduction:

Tetrazoles and their derivatives have drawn much attention due to their practical applications in agriculture, medicine and industry,[1-5] agriculture,[6-8] and photo imaging technology[9] etc. The tetrazole ring systems are present in drugs patented for the treatment of central nervous system disorders,[1] HIV,[10] sexual dysfunction,[11] asthma,[2] obesity[3] and diabetes,[5] antihypertensive,[12] antiallergic,[13] antibiotics[14] and anticonvulsants.[15] Tetrazole derivatives also find applications in agriculture as plant growth regulators, herbicides[6] and fungicides.[8] In addition, these are used as stabilizers in photography and photoimaging.[9] A tetrazole molecule loses dinitrogen upon decomposition and releases a high amount of energy because of their high enthalpy of formation and

therefore, these scaffolds have been explored as explosives, propellants for missiles and gas generators in air bags.[16]

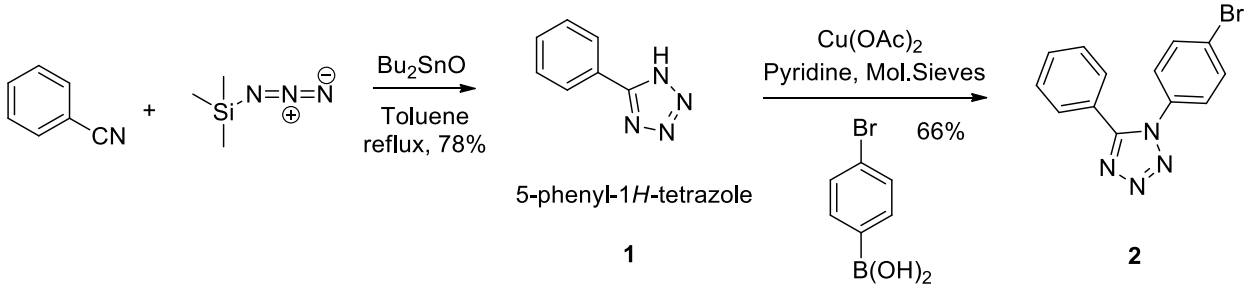
Supramolecular chemists have been interested in utilizing the coordination ability of the electron donating nitrogen atoms present on the tetrazole ring to build supramolecular assemblies.[17] Studies have shown that tetrazole ligand can bind to seven different coordination modes with a variety of metal ions such as nickel, ruthenium, palladium etc, leading to the construction of novel metal-organic frameworks such as bis (carbodiimido) complexes,[18] which is a novel tetrazole based ligand for heck reaction.[18-20] Recently, novel benzoisothiazole-tetrazole derivatives have also been developed that can coordinate with manganese to form benzoisothiazole-tetrazole manganese complexes, these are under investigation for their potential catalytic applications.[17]

The electron-withdrawing properties of tetrazolyl halide derivatives have been efficiently utilized for heterogeneous catalytic transfer reductions of benzylic and allylic alcohols.[21-23] The tetrazole derivatives these alcohols to form allyloxy[22] or benzyloxy tetrazole, that undergo chemical modification by hydrogenolysis,[23, 24] reduction[22, 25] etc to form alkanes or alkenes.

Our interest in these heterocycles stems from their aforementioned bioactivities. In particular, we are interested in the search of new anticancer compounds based on 1, 5-diaryl tetrazole derivatives scaffold. Herein, we report the facile synthesis of a series of 1,5-diarylated derivatives of these ring systems **4a–d** (Scheme 2) and evaluation of their antimicrobial activity in rapidly-growing suspension cultures of L1210 leukaemia cells and slow-growing monolayer cultures of SK-BR-3 mammary tumour cells, using tests of metabolic activity and DNA synthesis in vitro.[21,22] Since the fraction of Ki-67-positive tumour cells is often correlated with the clinical course of cancer, it was also of interest to determine whether treatments with synthesized tetrazole derivatives would inhibit the expression of human Ki-67 nuclear protein, which is an excellent marker of tumour cell proliferation.[23]

Although, there are several reports in the literature that discuss the preparation of 1,5-phenyl alkyl substituted tetrazole, the synthesis of the corresponding1,5-diaryl derivatives has not been directly carried out. There are no previous reports on the synthesis of 1, 5-diaryl tetrazole. Our approach to synthesize the title compounds is described below. In recent years, copper mediated C(aryl)–N bond formation through the cross coupling of aryl boronic acids with nitrogen nucleophiles has emerged as a powerful strategy for the synthesis of a variety of compounds.[26] This reaction has been successfully used for the N-arylation of a wide range of functional groups such as amines, amides, imides and sulfonamides.[27] Lam et al. have also reported the C(aryl)–N bond formation during the reaction of aryl boronic acids with 5-phenyl-2H-tetrazole in the presence of copper acetate.[28] We successfully synthesized 1,5-diaryl tetrazole derivatives **4a-d** by the Suzuki coupling of a series of ortho substituted boronic acids **3a–d** (R = OMe, Cl, I) with 1-(4-bromophenyl)-5-phenyl-1H-tetrazole **2**[29] in the presence of pyridine and molecular sieves (Scheme 2).

1.3.2. Synthesis of 1-(4-Bromophenyl)-5-phenyl-1H-tetrazole 2:

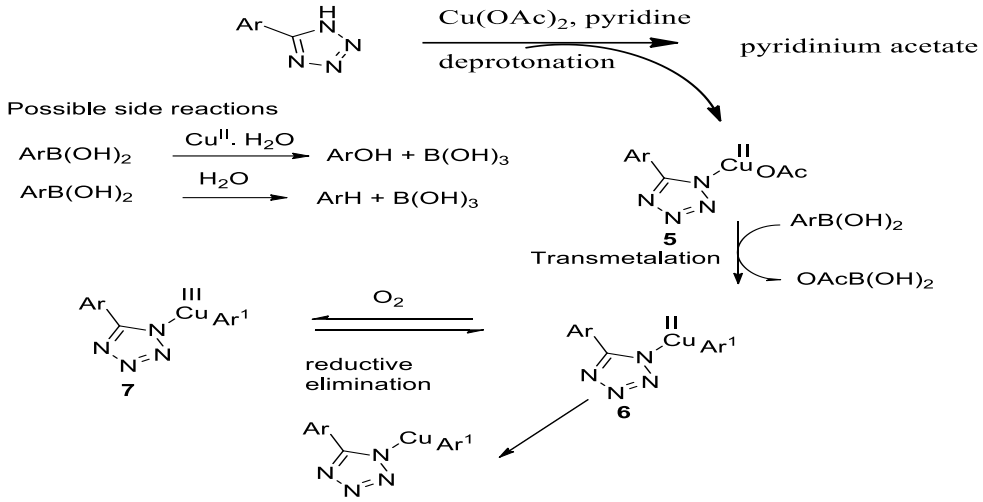


Scheme1. Synthesis of 1-(4-bromophenyl)-5-phenyl-1*H*-tetrazole

The synthesis of 1-(4-bromophenyl)-5-phenyl-1H-tetrazole **2** was started from Cyano benzene and trimethylsilyl azide in the presence of catalytic amount of *t*-butyl tinoxide in toluene to obtain 5-Phenyl-1*H*-Tetrazole **1** in 78% yield. The N-arylation of the tetrazole **1** was treated with 4-bromophenyl boronic acid and Copper (II) acetate in the presence of molecular sieves to furnish 1-(4-bromophenyl)-5-phenyl-1*H*-tetrazole **2** in 66% yield. Pyridine was used as a base in the reaction and 3A^{o} molecular sieves were added to absorb the excess water generated during the course of the reaction (Scheme 1). [37]

1.3.3. Mechanism of Copper catalyzed N-arylation with aryl boronic acid:

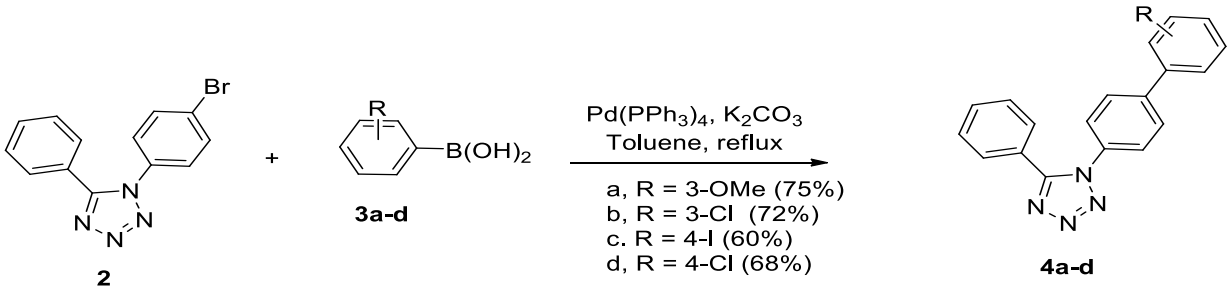
The plausible mechanism for the *N*-arylation reaction is shown[37] in Scheme 2. Pyridine assists in the formation of the copper complex **5**. The latter undergoes transmetallation with



Scheme2. Mechanism of N-arylation with phenyl boronic acid.

Aryl boronic acid to yield Cu (II)complex **6**. The reaction is carried out in the presence of air that oxidizes copper (II) complex **6** to Cu (III) complex **7** which undergoes reductive elimination faster. The excess water formed during the course of the reaction may result in possible side reactions with the aryl boronic acids. For this reason, the aryl boronic acid is added in excess to the reaction mixture. Molecular sieves are also added to the reaction mixture to absorb the water (Scheme 2).[37]

1.3.4. Synthesis of 1-([1,1'-Biphenyl]-4-yl)-5-phenyl-1*H*-tetrazole derivatives 4a-d:



Scheme3. Synthesis of 1-([1,1'-biphenyl]-4-yl)-5-phenyl-1*H*-tetrazole.

Additionally, we propose a facile synthesis of novel 1-([1,1'-biphenyl]-4-yl)-5-phenyl-1*H*-tetrazole **4a-d** derivatives in one step. Suzuki coupling of bromo substituted tetrazole **2** with boronic acid (**3a-d**) to afford the desired product (**4a-d)** in moderate to good yields (Scheme 3).

1.4. Conclusion:

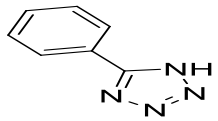
A facile synthesis of the target molecules 1-([1,1'-biphenyl]-4-yl)-5-phenyl-1*H*-tetrazole **4a-d** was carried out in moderate to good yields. In addition, we revised general method for the synthesis of 1,5-diaryl tetrazoles and their derivatives. The compound 1-([1,1'-biphenyl]-4-yl)-5-phenyl-1*H*-tetrazole **4a** has obtained is an excellent precursor to introduce other type of substituents on tetrazole through metalation followed by electrophilic quenching, or *via* palladium catalyzed Suzuki coupling reactions. The above reactions also demonstrate the stability of the tetrazole ring to diverse reaction conditions.

1.5. Experimental Section

1.5.1. General Remarks:

Thin layer chromatography was carried out on 250 µm silica gel plates and UV-light was used as a visualizing agent. Standard column chromatography was performed using 63–200 µm silica gel. Methylene chloride was dried by distillation over calcium hydride. Dry THF was obtained by distillation over sodium and benzophenone. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz and 200 MHz spectrometers as indicated. The carrier frequencies were 199.98 MHz (^{1}H) and 50.29 MHz (^{13}C) for the 200 MHz and 399.75 MHz (^{1}H) and 100.53 MHz (^{13}C) for 400 MHz spectrometers, respectively. Number of scans used was 64 for ^{1}H NMR spectra and for ^{13}C, it ranged from 3–5K depending on the sample concentration. Both the ^{1}H and ^{13}C spectra were recorded with longer relaxation time (10 s). Chemical shifts and the coupling constants are reported in parts per million and Hertz, respectively. The infrared frequencies are reported in cm^{-1}. High resolution mass spectra were acquired on an MDS SCIEX/Applied Bio systems QStar Elite hybrid quadrupole/time-of-flight mass spectrometer (Applied Biosystems, Foster City, CA). The samples were prepared in acetonitrile containing 0.1% formic acid and were introduced by continuous infusion into the electrospray ionization (ESI) source at a rate of 30µL/min. TOF scans were carried out in positive ionization mode. The ion spray voltage was set at 5 kV, the source temperature was 150 ºC, the curtain gas was at 25 (arbitrary units), and the ion source gases were set at 20 and 30 (arbitrary units). The declustering potential was set to 80 V, the declustering potential 2 at 15 V, and the focusing potential at 300 V. The collision gas, nitrogen, was set at 3 (arbitrary units). Data were collected over the range of *m/z* 100-500, 300 cumulative scans over 5 minutes. Data were collected and smoothed using the Analyst QS 2.0 software. In most cases, both $[M + H]^+$ and $[M + Na]^+$ ions were detectable for each species.

1.5.2. Synthesis of 5-Phenyl-1*H*-tetrazole (1):



To a stirred solution of Cyano benzene (0.8 g, 7.76 mmol) in toluene (50 mL) under a nitrogen atmosphere, were added azide (TMSA) (1.1 g, 9.32 mmol) and catalytic amount of *t*-butyl tinoxide (30 mg) and the resulting mixture was heated under reflux. at 100 ºC for 12 h. After completion of the reaction (monitored by TLC), excess TMSA was removed under reduced pressure to afford the crude product which on purification by silica gel column chromatography (EtOAc /hexane = 2:3) furnished the desired product **1** (0.9 g, 79%) as white solid. $[\alpha]_D^{20} = -14.9$ (*c* = 3.6, $CHCl_3$); IR (neat): *v* = 3248, 2854, 2743, 2725, 1742, 1539, 1035 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$ δ = 9.83 (S, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.56 (dd, *J* = 12.6, 5.3 Hz, 2H), 7.24 (s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.6, 135.6, 132.1, 132.0, 129.7, 128.9, 128.4, 127.9, 120.2, 119.0, 118.9 ppm. MS (ESI): *m/z* 147 $[M + H]^+$.

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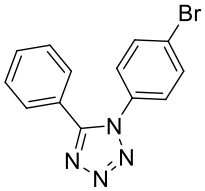
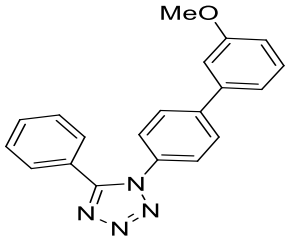
1.5.3. Synthesis of 1-(4-Bromophenyl)-5-phenyl-1*H*-tetrazole (2):



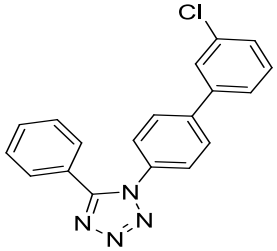
To a stirred suspension of dry copper acetate (0.43 g, 2.4 mmol), 5-Phenyl-1*H*-tetrazole **1** (0.6 g, 1.2 mmol), phenyl boronic acid (0.52 g, 2.6 mmol) and activated molecular sieves 3A^{o} (0.2 g) in dry methylene chloride (30 mL), was added pyridine (0.23 mL, 2.6 mmol). The reaction mixture was stirred over night at room temperature in air. Upon completion of the reaction, the mixture was diluted with methylene chloride, filtered through celite and washed with aqueous EDTA solution (1.7 mmol). The colorless organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes = 1:1) to give 1-(4-Bromophenyl)-5-phenyl-1*H*-tetrazole **2** (0.8 g, 65%) as a colorless liquid oil. IR (neat): ν = 3439, 2985, 2930, 2854, 1724, 1646, 1027 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.29 (d, J = 7.3 Hz, 2H), 8.12 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 8.5 Hz, 2H), 7.42-7.56 (m, 2H), 7.25-7.35 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.2, 132.1, 132.0, 130.6, 130.2, 128.9, 128.5, 128.4, 128.2, 127.2, 127.0, 120.2, 119.2 ppm: HRMS (ESI): *m/z* calcd. for $C_{13}H_{10}BrN_4$ $[M + H]^+$: 302.3116, found: 302.3146.

1.5.4. 1-(3'-Methoxy-[1,1'-biphenyl]-4-yl)-5-phenyl-1*H*-tetrazole (4a):



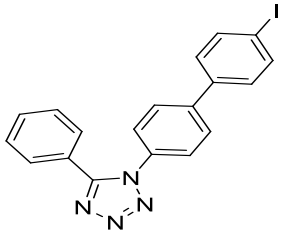
To a stirred solution of **2** (100 mg, 0.0003 mmol), $Pd(PPh_3)_4$ (0.006 g, 0.009 mmol), K_2CO_3 (0.003 g, 0.01 mmol) in distilled toluene (5 mL) under argon at 40 ^{o}C, was added (3-methoxyphenyl)boronic acid (0.05 g, 0.06 mmol) dropwise over a period of 10 min. The reaction mixture was heated at 85 ^{o}C until the starting material was completely consumed. The solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, yellow solid (75 mg, 75%), mp 119-120 ^{o}C. Rf (hexane:ethyl acetate 3:1) 0.3; FTIR (neat): 3860, 3733, 3619, 3002, 2360, 2252, 1440, 1038; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.31 (d, J = 8.3 Hz, 2H), 7.92 (d, J = 8.7 Hz, 2H), 7.80 (d, J = 8.1 Hz, 2H), 7.42-7.56 (m, 4H), 7.22-7.31 (m, 3H), 3.64 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.6, 164.2, 137.6, 132.9, 132.8, 132.2, 130.3, 127.6, 121.3, 120.5, 56.9 ppm: HRMS (ESI): *m/z* calcd. for $C_{20}H_{17}N_4O$ $[M + H]^+$: 329.3116, found: 329.3146.

1.5.5. 1-(3'-Chloro-[1,1'-biphenyl]-4-yl)-5-phenyl-1*H*-tetrazole (4b):



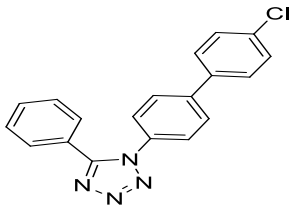
To a stirred solution of **2** (100 mg, 0.0003 mmol), $Pd(PPh_3)_4$ (0.006 g, 0.009 mmol), K_2CO_3 (0.003 g, 0.01 mmol) in distilled toluene (5 mL) under argon at 40 °C, was added (3-chlorophenyl)boronic acid (0.05 g, 0.06 mmol) dropwise over a period of 10 min. The reaction mixture was heated at 85 °C until the starting material was completely consumed. The solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, solid (80 mg, 72%), FTIR (neat): 3860, 3740, 3304, 2906, 2850, 2366, 1043, 984, 753; ^{1}H NMR (500 MHz, $CDCl_3$): δ = ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.41 (d, J = 7.5 Hz, 2H), 8.16 (d, J = 8.6 Hz, 2H), 7.71 (d, J = 8.6 Hz, 2H), 7.41-7.56 (m, 4H), 7.15-7.36 (m, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.2, 132.1, 132.0, 130.6, 130.2, 128.9, 128.5, 128.4, 128.2, 127.2, 127.0, 125.2, 120.2 ppm: HRMS (ESI): *m/z* calcd. for $C_{19}H_{14}ClN_4$ $[M + H]^+$: 333.3016, found: 333.3036.

1.5.6. 1-(4'-Iodo-[1,1'-biphenyl]-4-yl)-5-phenyl-1*H*-tetrazole (4c):



To a stirred solution of **2** (100 mg, 0.0003 mmol), $Pd(PPh_3)_4$ (0.006 g, 0.009 mmol), K_2CO_3 (0.003 g, 0.01 mmol) in distilled toluene (5 mL) under argon at 40 °C, was added (4-iodophenyl)boronic acid (0.05 g, 0.06 mmol) dropwise over a period of 10 min. The reaction mixture was heated at 85 °C until the starting material was completely consumed. The solution was concentrated in vacuo and reaction mixture was purified by silica gel column chromatography. Pale yellow solid (85 mg, 60%), mp 119-120 °C. Rf (hexane:ethyl acetate 4:1) 0.3; FTIR (neat): 3164, 3003, 2944, 2292, 2252, 1439, 1375, 1303, 984, 753; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.29 (d, J = 7.3 Hz, 2H), 8.14 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 8.6 Hz, 2H), 7.41-7.56 (m, 4H), 7.15-7.35 (m, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.6, 132.7, 132.1, 131.9, 131.1, 130.2, 129.3, 129.1, 128.6, 128.4, 128.1, 126.4, 117.4, 77.2 ppm: HRMS (ESI): *m/z* calcd.for $C_{19}H_{14}IN_4$ $[M + H]^+$: 425.3216, found: 425.3126.

1.5.7. 1-(4'-Chloro-[1, 1'-biphenyl]-4-yl)-5-phenyl-1*H*-tetrazole (4d):



To a stirred solution of **2** (100 mg, 0.3 mmol), $Pd(PPh_3)_4$ (0.006 g, 0.009 mmol), K_2CO_3 (0.003 g, 0.01 mmol) in distilled toluene (5 mL) under argon at 40 °C, was added (4-chlorophenyl)boronic acid (0.05 g, 0.6 mmol) dropwise over a period of 10 min. The reaction mixture was heated at 85 °C until the starting material was completely consumed. The solution was concentrated in vacuo and reaction mixture was purified by silica gel column chromatography, yellow solid (75 mg, 68%), mp 119-120 °C. Rf (hexane:ethyl acetate 2:1) 0.3; FTIR (neat): 3741, 2360, 1439, 1366, 1320, 1039, 1071, 1043, 984, 753; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.29 (d, J = 7.3 Hz, 2H), 8.14 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 8.6 Hz, 2H), 7.41-7.56 (m, 4H), 7.15-7.35 (m, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.6, 164.2, 137.6, 132.9, 132.8, 132.2, 130.3, 127.6, 121.3, 120.5 ppm: HRMS (ESI): *m/z* calcd. for $C_{19}H_{14}ClN_4$ $[M + H]^+$: 333.2016, found: 333.2146.

1.3. **Biological activity of tetrazole derivatives:**

Among various heterocycles, tetrazoles and their derivatives have attracted attention of researchers because of their wide spread applications particularly in biology and medicine[1-5]. Tetrazoles possess abnormally high acidity and very weak basicity compared to other chemically and thermally stable azoles.[6-9] this property has been efficiently utilized in the design of an antihypertensive drug Losartan[10]. The negatively charged acidic tetrazole ring present in the drug molecule interacts with the positively charged site in the receptor. Recently, a novel tetrazole containing angiotension receptor agonist for the treatment of hypertension has also been developed which is found to be about 8 times more potent than Losartan.[11]

The tetrazole fragment, CN_4H, has similar acidity to that of carboxylic acid, CO_2H and is almost isosteric with it, but it is metabolically more stable at physiological pH[12]. The replacement of carboxylic group with the tetrazole ring increased the efficiency of many drugs[12]. For instance, Abell and coworkers[14] developed a novel HIV protease-I inhibitor by replacing the carboxylic group in the drug with the tetrazole ring and this is found to increase the inhibition of the enzyme

In addition, tetrazole molecules are interesting because exhibit rich photochemistry. The focus of this project was to provide a new class of compounds based on 1-([1,1'-biphenyl]-4-yl)-5-phenyl-1*H*-tetrazole **4a-d** derivatives and utlilize their photochemistry for the cleavage of the DNA in the cell. During our efforts to optimize the synthesis of these compounds, we also obtained a series of 1,5-diarylated substituted tetrazole derivatives. Our interest in these heterocyclic molecules stems from the aforementioned applications. We are in particular interested in exploring the antimicrobial activity of diaryl tetrazole scaffolds. A facile synthesis of 1,5-diaryl tetrazole derivatives using copper (II) acetate for *N*-arylation has been carried out.

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