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Synthesis and Antimicrobial Evaluation of Arylated 1,3,5-triphenyl Pyrazoline Derivatives using Suzuki-Miyaura Reactions

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Abstract

The first palladium –catalyzed coupling reactions of 1,3,5-triphenyl pyrazoline are reported. The Suzuki-Miyaura reaction of 3-(4-bromophenyl)-1,5-diphenyl pyrazoline with one equivalent of arylboronic acids afforded 3-(biphenyl)-1,5-diphenyl pyrazoline in 53-78 % yield. While the Suzuki-Miyaura reactions of 3,5-bis(4-bromophenyl)-1-phenyl pyrazoline with two equivalent of arylboronic acids gave 3,5-bis(biphenyl)-1-phenyl pyrazoline in 55-80% yield. The characterization of the synthesized derivatives (**5$_{a-h}$**) and (**6$_{a-h}$**) were accomplished on the basis of NMR, FT-IR, and mass techniques. The newly pyrazoline derivatives have been investigated for their in vitro antibacterial activity against gram- negative and gram-positive bacteria. The di-coupling compounds (**6$_{a-h}$**) exhibited promising antibacterial against all four bacterial strains compared to the mono-coupling compounds (**5$_{a-h}$**) which displayed a slight activity. The compound **6d** showed a potent activity significantly more active than Trimethoprim (100µg/ml).

Key words: Catalysis, Suzuki-Miyaura reaction, Pyrazoline, Synthesis.

1. Introduction

Among a broad variety of nitrogen heterocyclic compounds which have been investigated for reinforcing pharmaceutically significant molecules, Pyrazoline scaffold are one of synthetic attention because they comprise of an important class of natural products and they exhibited a remarkable role in medicine chemistry [1]. Interestingly, 2-pyrazoline a significantly derivative of this nitrogen five member heterocyclic compound, has been acquired a considerable attention and numerous studies have been directed toward this class of compounds, because of its high stability and the concurrent monoimin character. Plentiful chemotherapeutic agents contains 2-pyrazoline moiety and broad spectrum of their biological activities, have been studied such as antimicrobial [2], anti-inflammatory-analgesic [3], anticancer - antimalarial [4] , antidepressant [5], antiproliferative [6,7], and insecticidal activities [8,9]. Among the all of above activities, its essential to mention that 2-pyrazolines are not only valuable in treatment of different kinds of cancer, but also some of pyrazoline derivtives act as cancer chemo preventive agents [10-15]. In several studies, these derivatives were reported as inhibitors for factor receptor tyrosine kinase of epidermal

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growth [EGFR-TK] [16], aurora kinase inhibitors [17], inhibitors of COX-2/B-Raf [18], tubulin assembling inhibitors [19].

Several methods were carried out in the synthesis of various derivatives of 2-pyrazoline, including the cyclization reaction of chalcones with hydrazine hydrate, phenyl hydrazine [20,24] in ethanol either under acidic or basic conditions [25]. The pyrazoline ring resulting from this method contains three aryl groups, the additional arylation of this core structure has, to the best of our knowledge, not been previously described, so, in view of this target and also in continuation of our search for various biologically active molecules [26]. We report here a simple and convenient approach to aryl-substituted 1,3,5-triphenyl pyrazoline by Suzuki-Miyaura reactions of 3,5-bis(4-bromophenyl)-1-phenyl pyrazoline in addition to evaluation of their preliminary antibacterial activity.

2. Experimental

2.1 Materials and methods

The chemicals and solvents were purchased from (Sigma-Aldrich and Alfa-Aesar) companies. The determination of Melting points was accomplished by using Micro heating table HMK 67/1825 Kuestner (Büchi Apparatus). Bruker AVANCE 300 II (built 2007) spectrometry, was utilized to record ^{1}H-NMR spectra using $CDCl_3$ as solvent and internal standard of TMS. Shimadzu model FTIR-8400S was used to acquire the FT-IR spectra. Mass spectra were recorded by using an Advion expression S electrospray ionization mass spectrometer (ESI–MS) (Shimadzu Corporation, Kyoto, Japan) with TLC interface.

2.2 Synthesis of chalcone 1 : This compound was prepared according to the modified literature procedure [27]. To a solution of an equimolar of benzaldehyde or P-bromobenzaldehyde with P-bromoacetophenone in ethanol, a solution of 40%NaOH was added. The reaction mixture was stirred at 50 ^{o}C for a period of 8 hrs. The progress of reaction was monitored by TLC. After the completion of reaction the solution was poured into water of pH~2 (pH adjusted by HCl). The produced precipitate was filtered, washed, dried and recrystallized from ethanol.

2.3 Synthesis of Pyrazoline derivatives (2,3): These compounds were prepared according to the modified reported procedure [28]. An equimolar mixture of chalcone compound **1** (0.02 mole), phenylhydrazine (0.02 mole) in ethanol and a catalytic amount of glacial acetic acid, the mixture was refluxed at 80 ^{o}C for 12 hrs. The completion of the reaction was checked out by TLC (n-hexane:ethylacetate), then the mixture was cooled and poured into crushed ice. The produced precipitate was filtered, washed and recrystallized using absolute ethanol.

2.4 General procedure for the synthesis of Suzuki-mono-cross coupling compounds (5_{a-h}).: To a mixture of **2** (0.1gm, 0.266 mmole), arylboronic acid (0.293 mmole), $Pd(PPh_3)_4$ (12mg, 3mol%) inside a pressure tube were added 4ml of 1,4-dioxane and K_3PO_4 (0.11gm, 0.532 mmole) under Nitrogen atmosphere. The reaction mixture was stirred at 70 ^{o}C for 10h. The reaction was monitored by TLC. After the reaction was completed (TLC showed only one spot) it was subsequently allowed to cool to 20 ^{o}C. The solution was poured into H_2O and dichloromethane (25 ml each), the organic and the aqueous layers were separated. The latter was extracted with dichloromethane (3x 25ml), the combined organic layers was dried by (Na_2SO_4), filtered and concentrated in vacuo. The produced solid (residue) was purified by recrystallization for

some reactions and by small column chromatography (n-hexane/ethyl acetate) for another.

3-(4'-methoxy-[1,1'-biphenyl]-4-yl)-1,5-diphenyl-4,5-dihydro-1H-pyrazole **5a**.

5a was isolated as yellow solid. Yield: 71%; M.p. 220-222 ºC. IR (KBr) [υ, cm^{-1}]: 1635 (C=N), 2960 $(CH)_{alp}$, 3044, $(CH)_{arom}$. ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.13 (dd, 1H, *J*=6.5, 16.8 Hz, $CH_{pyraz.}$>CHH_a), 3.51 (s, 3H, OCH_3), 3.72 (dd, 1H, *J*=12.1, 17.8 Hz, $CH_{pyraz.}$>CHH_b), 5.24 (dd, 1H, *J*=6.3, 12.5 Hz, $CH_{pyraz.}$>CHH_c), 6.67-6.82 (m, 4H, ArH), 7.15-7.21 (m, 4H, ArH), 7.34-7.36 (m, 1H, ArH), 7.37 (d, 1H, *J*= 8.1 Hz, ArH), 7.54 (d, 1H, *J*=7.8, ArH), 7.81 (d, 2H, *J*= 8.4, ArH), 8.12-8.25 (m, 3H, ArH), 8.31 (d, 2H, *J*=8.0 Hz, ArH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 40.9 $(CH_2)_{pyraz}$, 52.9 (OCH_3), 62.9 $(CH)_{pyraz}$, 126.8, 126.9, 128.4, 128.5 (CH), 128.7, 128.9 (C), 129.7, 131.0, 131.3 (CH), 133.1, 133.4 (C), 134.1, 134.2, 134.5 (CH), 134.6, 135.5, 168.8 (C) ppm, HRMS (ESI): *m/z* found 405.1941, calcd for $C_{28}H_{25}N_2O$ ($[M + H]^+$) 405.1938.

3-(3',4'-dimethoxy-[1,1'-biphenyl]-4-yl)-1,5-diphenyl-4,5-dihydro-1H-pyrazole **5b**.

5b was isolated as brown solid. Yield: 73%; M.p. 215-217 ºC. IR (KBr) [υ, cm^{-1}]: 1235 (C-O), 1640 (C=N), 2965 $(CH)_{alp}$, 3033, $(CH)_{arom}$. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.23 (dd, 1H, *J*=6.3, 17.0 Hz, $CH_{pyraz.}$>CHH_a), 3.56, 3.65 (s, 6H, $2OCH_3$), 3.92 (dd, 1H, *J*=12.1, 17.6 Hz, $CH_{pyraz.}$>CHH_b), 5.26 (dd, 1H, *J*=6.2, 12.5 Hz, $CH_{pyraz.}$>CHH_c), 7.05-7.17 (m, 5H, ArH), 7.22-7.29 (m, 3H, ArH), 7.35 (d, 2H, *J*= 8.2 Hz, ArH), 7.47-7.56 (m, 3H, ArH), 7.92 (d, 2H, *J*=8.0 Hz, ArH), 8.26 (d, 2H, *J*= 7.9 Hz, ArH) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 40.5 $(CH_2)_{pyraz}$, 52.0, 52.9 ($2OCH_3$), 62.8 $(CH)_{pyraz}$, 125.0, 126.5, 127.9, 128.2 (CH), 129.2, 129.3, 129.5 (C), 129.8, 129.9, 130.3 (CH), 130.4, 130.8 (C), 134.4, 135.1, 135.5, 136.5 (CH), 137.7, 137.9, 162.0 (C) ppm, HRMS (ESI): *m/z* found 435.2038, calcd for $C_{29}H_{27}N_2O_2$ ($[M + H]^+$) 435.2042.

3-(4'-(methylthio)-[1,1'-biphenyl]-4-yl)-1,5-diphenyl-4,5-dihydro-1H-pyrazole **5c.**

5c was isolated as yellowish white solid Yield: 69%; M.p. 205-207 ºC. IR (KBr) [υ, cm^{-1}]: 1632 (C=N), 2635 (S-CH_3), 2963 $(CH)_{alp}$, 3041, $(CH)_{arom}$. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.45 (s, 3H, SCH_3), 3.24 (dd, 1H, *J*=6.1, 17.0 Hz, $CH_{pyraz.}$>CHH_a), 3.98 (dd, 1H, *J*=12.0, 17.1 Hz, $CH_{pyraz.}$>CHH_b), 5.76 (dd, 1H, *J*=6.3, 12.6 Hz, $CH_{pyraz.}$>CHH_c), 7.09-7.22 (m, 5H, ArH), 7.35 (d, 1H, *J*= 8.1 Hz, ArH), 7.42 (d, 2H, *J*=8.0, ArH), 7.45-7.50 (m, 3H, ArH), 7.71-7.80 (m, 3H, ArH), 8.17 (d, 2H, *J*= 7.9 Hz, ArH), 8.28 (d, 2H, *J*= 8.2 Hz, ArH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.5 (SCH3), 41.5 $(CH_2)_{pyraz}$, 63.3 $(CH)_{pyraz}$, 126.5, 127.2, 127.4, 127.8 (CH), 128.4, 128.5 (C), 128.9, 129.8, 130.9 (CH), 133.9, 134.3 (C), 134.5, 135.2, 136.7 (CH), 136.8, 137.6, 165.1 (C) ppm, HRMS (ESI): *m/z* found 421.1746, calcd for $C_{28}H_{25}N_2S$ ($[M + H]^+$) 421.1748.

1,5-diphenyl-3-(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-pyrazole **5d**

5d was isolated as brown solid. Yield: 60%; M.p. 195-197 ºC. IR (KBr) [υ, cm^{-1}]: 1644 (C=N), 2963 $(CH)_{alp}$, 3041, $(CH)_{arom}$. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.25 (dd, 1H, *J*=6.3, 17.2 Hz, $CH_{pyraz.}$>CHH_a), 3.92 (dd, 1H, *J*=12.2, 17.0 Hz, $CH_{pyraz.}$>CHH_b), 5.15 (dd, 1H, *J*=6.3, 12.3 Hz, $CH_{pyraz.}$>CHH_c), 7.11-7.21 (m, 5H, ArH), 7.38 (d, 1H, *J*= 8.1 Hz, ArH), 7.39-7.45 (m, 2H, ArH), 7.46-7.54 (m, 3H, ArH), 7.81-7.93 (m, 3H, ArH), 8.18 (d, 2H, *J*= 8.0, ArH), 8.28 (d, 2H, *J*= 8.3, ArH). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 41.5 $(CH_2)_{pyraz}$, 61.5 $(CH)_{pyraz}$, 110.9, 113.1, 122.1 (CH), 122.4 (q, $J_{F,C}$= 3.8 Hz, CH), 124.6 (q, $J_{C,F}$= 272 Hz, CF_3), 125.0 (q, $J_{F,C}$= 8.2 Hz, CH), 127.2 (CH), 128.2, 128.5, 128.9 (C), 129.4 (CH), 130.9 (q, $J_{F,C}$=

32.5 Hz, C-CF_3), 133.9, 134.3, 135.5 (CH), 136.8, 140.3, 165.0 (C) ppm, HRMS (ESI): *m/z* found 442.1785, calcd for $C_{28}H_{22}F_3N_2$ ([M + H]$^+$) 442.1788.

3-(4'-chloro-[1,1'-biphenyl]-4-yl)-1,5-diphenyl-4,5-dihydro-1H-pyrazole **5e.**

5e was isolated as yellow solid. Yield: 53%; M.p. 210-212 ^{o}C. IR (KBr) [υ, cm^{-1}]: 1636 (C=N), 2967 $(CH)_{alp}$, 3039, $(CH)_{arom}$. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.18 (dd, 1H, *J*=6.2, 17.5 Hz, $CH_{pyraz.}$>CHH_a), 3.94 (dd, 1H, *J*=12.2, 17.6 Hz, $CH_{pyraz.}$>CHH_b), 5.53 (dd, 1H, *J*=6.1, 12.5 Hz, $CH_{pyraz.}$>CHH_c), 7.08 (d, 2H, *J*= 8.0 Hz, ArH), 7.09-7.22 (m, 5H, ArH), 7.35-7.41 (m, 3H, ArH), 7.52 (d, 2H, *J*=8.1 Hz, ArH), 7.65 (d, 2H, *J*= 8.3, ArH), 8.15 (d, 2H, *J*= 8.4, ArH), 8.41 (d, 2H, *J*= 8.2, ArH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 40.4 $(CH_2)_{pyraz}$, 60.5 $(CH)_{pyraz}$, 125.5, 126.2, 126.4, 127.2 (CH), 127.4, 128.1, 128.3 (C), 128.7, 131.7, 132.8 (CH), 133.3, 133.5 (C), 134.1, 135.6, 135.7 (CH), 136.5, 164.8 (C) ppm, HRMS (ESI): *m/z* found 409.1489, calcd for $C_{27}H_{22}ClN_2$ ([M + H]$^+$) 421.1790.

3-(4'-methyl-[1,1'-biphenyl]-4-yl)-1,5-diphenyl-4,5-dihydro-1H-pyrazole **5f.**

5f was isolated as yellowish white solid. Yield: 70%; M.p. 198-200 ^{o}C. IR (KBr) [υ, cm^{-1}]: 1648 (C=N), 2970 $(CH)_{alp}$, 3042, $(CH)_{arom}$. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.21 (s, 3H, CH_3), 3.25 (dd, 1H, *J*=6.1, 17.0 Hz, $CH_{pyraz.}$>CHH_a), 3.96 (dd, 1H, *J*=12.1, 17.4 Hz, $CH_{pyraz.}$>CHH_b), 5.66 (dd, 1H, *J*=6.2, 12.6 Hz, $CH_{pyraz.}$>CHH_c), , 7.14 (d, 1H, *J*= 8.0 Hz, ArH), 7.15-7.19 (m, 2H, ArH), 7.21 (d, 2H, *J*=8.2 Hz, ArH), 7.33-7.39 (m, 3H, ArH), 7.50-7.55 (m, 3H, ArH), 7.77-7.84 (m, 3H, ArH), 8.17 (d, 2H, *J*= 7.6 Hz, ArH), 8.31 (d, 2H, *J*= 8.0, Hz, ArH). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 21.6 (CH_3), 42.8 $(CH_2)_{pyraz}$, 60.6 $(CH)_{pyraz}$, 123.8, 125.6, 126.7, 126.8 (CH), 127.2, 128.2, 128.4 (C), 128.5, 128.9 (CH), 129.2 (C), 130.1, 130.4, 133.9, 134.3 (CH), 135.3, 136.7, 165.1 (C) ppm, HRMS (ESI): *m/z* found 389.1993, calcd for $C_{28}H_{25}N_2$ ([M + H]$^+$) 389.1990.

3-(4'-ethyl-[1,1'-biphenyl]-4-yl)-1,5-diphenyl-4,5-dihydro-1H-pyrazole **5g.**

5g was isolated as brown solid. Yield: 72%; M.p. 204-206 ^{o}C. IR (KBr) [υ, cm^{-1}]: 1651 (C=N), 2972 $(CH)_{alp}$, 3044, $(CH)_{arom}$. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.29 (t, 3H, *J*= 7.6 Hz, CH_3), 2.23 (q, 2H, *J*= 7.7 Hz, CH_2), 3.24 (dd, 1H, *J*=6.1, 17.2 Hz, $CH_{pyraz.}$>CHH_a), 4.25 (dd, 1H, *J*=12.3, 17.5 Hz, $CH_{pyraz.}$>CHH_b), 5.27 (dd, 1H, *J*=6.3, 12.3 Hz, $CH_{pyraz.}$>CHH_c), 6.99 (d, 2H, *J*= 8.0 Hz, ArH), 7.00-7.09 (m, 2H, ArH), 7.12 (d, 2H, *J*=7.8 Hz, ArH), 7.17 (d, 1H, *J*= 7.5, ArH), 7.23-7.30 (m, 4H, ArH), 7.37 (d, 1H, *J*= 7.7, ArH), 7.39-7.43 (m, 1H, ArH), 7.65 (d, 1H, *J*= 8.1 Hz, ArH), 8.31 (d, 2H, *J*= 8.1 Hz, ArH), 8.56 (d, 2H, *J*= 8.2, Hz, ArH). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 31.5 (CH_3), 33.4 (CH_2), 41.8 $(CH_2)_{pyraz}$, 62.6 $(CH)_{pyraz}$, 125.5, 126.9, 127.3, 128.1 (CH), 128.4, 128.5, 128.6 (C), 128.8, 128.9 , 129.1 (CH), 129.6, 130.7 (C), 131.5, 133.6, 134.8 (CH), 136.2, 162.1 (C) ppm, HRMS (ESI): *m/z* found 403.2109, calcd for $C_{29}H_{27}N_2$ ([M + H]$^+$) 403.2103.

3-(4'-(tert-butyl)-[1,1'-biphenyl]-4-yl)-1,5-diphenyl-4,5-dihydro-1H-pyrazole **5h.**

5h was isolated as brown solid. Yield: 78%; M.p. 211-213 ^{o}C. IR (KBr) [υ, cm^{-1}]: 1649 (C=N), 2969 $(CH)_{alp}$, 3039, $(CH)_{arom}$. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 9H, $3CH_3$), 3.25 (dd, 1H, *J*=6.1, 17.0 Hz, $CH_{pyraz.}$>CHH_a), 4.24 (dd, 1H, *J*=12.1, 17.2 Hz, $CH_{pyraz.}$>CHH_b), 5.24 (dd, 1H, *J*=6.3, 12.4 Hz, $CH_{pyraz.}$>CHH_c), 7.09 (d, 2H, *J*= 8.1 Hz, ArH), 7.10-7.14 (m, 2H, ArH), 7.18-7.21 (m, 1H, ArH), 7.28-

7.35 (m, 3H, ArH), 7.44 (d, 1H, *J*=7.8 Hz, ArH), 7.50-7.56 (m, 4H, ArH), 7.72 (d, 1H, *J*= 7.8, ArH), 8.27 (d, 2H, *J*= 8.1 Hz, ArH), 8.53 (d, 2H, *J*= 8.2, Hz, ArH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 31.5 ($3CH_3$), 33.4 (C), 41.8 $(CH_2)_{pyraz}$, 62.8 $(CH)_{pyraz}$, 127.4, 128.2, 128.3, 128.5 (CH), 128.7, 129.1 (C), 129.2, 130.0 (CH), 130.2, 130.5 (C), 131.5, 131.9, 132.8, 133.3 (CH), 133.7, 134.3, 163.2 (C) ppm, HRMS (ESI): *m/z* found 431.2489, calcd for $C_{31}H_{31}N_2$ ($[M + H]^+$) 431.2496.

2.5 General procedure for the synthesis of Suzuki-di-cross coupling compounds (6_{a-h}): In a pressure tube the reaction was carried out. To a suspension of compound **3** (0.1gm, 0.22mmole), $Pd(PPh_3)_4$ (13mg, 5mol%), and arylboronic acid (0.5 mmole) in 5ml 1,4-dioxane, was added an aqueous solution of K_2CO_3 (2M, 1ml). The reaction mixture was heated at the 100 ^{o}C for 12 h under nitrogen atmosphere. The completion of the reaction was checked out by TLC. After finishing of the reaction (TLC showed only one spot), the reaction mixture was diluted with water and extracted with dichloromethane (3x 25ml). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The produced solid was purified for some reactions by recrystallization and for another by column chromatography (n-hexane/ethyl acetate).

3,5-bis(4'-methoxy-[1,1'-biphenyl]-4-yl)-1-phenyl-4,5-dihydro-1H-pyrazole **6a**.

6a was isolated as yellowish white solid. Yield: 74%; M.p. 228-230 ^{o}C. IR (KBr) [υ, cm^{-1}]: 1637 (C=N), 2963 $(CH)_{alp}$, 3054, $(CH)_{arom}$. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.12 (dd, 1H, *J*=6.4, 17.6 Hz, $CH_{pyraz.}$>CHH_a), 3.66 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.95 (dd, 1H, *J*=12.3, 17.7 Hz, $CH_{pyraz.}$>CHH_b), 5.36 (dd, 1H, *J*=6.4, 12.5 Hz, $CH_{pyraz.}$>CHH_c), 6.70-6.75 (d, 3H, ArH), 7.12 (d, 3H, *J*= 8.5 Hz, ArH), 7.35-7.39 (m, 3H, ArH), 7.45 (dd, 2H, *J*=1.7, 8.7 Hz, ArH), 7.51-7.55 (m, 3H, ArH), 7.81-8.12 (m, 3H, ArH), 8.13 (d, 2H, *J*= 8.4, ArH), 8.32 (d, 2H, *J*=7.8 Hz, ArH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 40.8 $(CH_2)_{pyraz}$, 54.8, 55.8 ($2OCH_3$), 62.6 $(CH)_{pyraz}$, 114.9, 115.2 (CH), 115.7, 116.0 (C), 125.8, 126.0, 128.1, 128.4 (CH), 129.5, 130.5, 130.7 (C), 131.6, 131.7, 132.2, 134.5, 134.8 (CH), 134.9, 136.1, 136.2, 137.0, 160.0 (C) ppm, HRMS (ESI): *m/z* found 511.2350, calcd for $C_{35}H_{31}N_2O_2$ ($[M + H]^+$) 511.2343.

3,5-bis(3',4'-dimethoxy-[1,1'-biphenyl]-4-yl)-1-phenyl-4,5-dihydro-1H-pyrazole **6b**.

6b was isolated as yellow solid. Yield: 75%; M.p. 219-221 ^{o}C. IR (KBr) [υ, cm^{-1}]: 1245 (C-O), 1648 (C=N), 2970 $(CH)_{alp}$, 3038, $(CH)_{arom}$. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.24 (dd, 1H, *J*=6.3, 17.6 Hz, $CH_{pyraz.}$>CHH_a), 3.54 (s, 3H, $2OCH_3$), 3.73, 3.76 (s, 6H, $2OCH_3$), 4.14 (dd, 1H, *J*=12.5, 17.9 Hz, $CH_{pyraz.}$>CHH_b), 5.40 (dd, 1H, *J*=6.2, 12.2 Hz, $CH_{pyraz.}$>CHH_c), 6.68 (d, 3H, *J*= 8.6 Hz, ArH), 7.11 (d, 3H, *J*= 8.6 Hz, ArH), 7.20 (d, 2H, *J*= 2.7 Hz, ArH), 7.25 (dd, 2H, *J*= 2.7, 9.3 Hz, ArH), 7.32-7.38 (m, 2H, ArH), 7.51 (d, 3H, *J*=3.7 Hz, ArH), 8.01 (d, 2H, *J*= 9.1 Hz, ArH), 8.27 (d, 2H, *J*= 7.4 Hz, ArH). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 42.7 $(CH_2)_{pyraz}$, 52.9, 53.0 ($2OCH_3$), 55.9, 56.0 ($2OCH_3$), 62.7 $(CH)_{pyraz}$, 110.9, 113.1, 122.1, 123.8 (CH), 126.6, 127.2, 128.3 (C), 128.4, 128.6, 128.8, 129.0 (CH), 129.6, 129.7, 134.0, 134.3 (C), 134.4, 134.8, 135.5, 136.7 (CH), 136.9, 140.4, 144.4 (C), 145.0 (CH), 164.1 (C) ppm, HRMS (ESI): *m/z* found 571.2551, calcd for $C_{37}H_{35}N_2O_4$ ($[M + H]^+$) 571.2548.

3,5-bis(4'-(methylthio)-[1,1'-biphenyl]-4-yl)-1-phenyl-4,5-dihydro-1H-pyrazole **6c.**

6c was isolated as yellowish white solid. Yield: 73%; M.p. 211-213 ^{o}C. IR (KBr) [υ, cm^{-1}]: 1637

(C=N), 2640 (S-CH_3), 2966 $(CH)_{alp}$, 3046, $(CH)_{arom}$. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3H, SCH_3), 2.64 (s, 3H, SCH_3), 3.26 (dd, 1H, *J*=6.2, 17.5 Hz, $CH_{pyraz.}$>CHH_a), 3.94 (dd, 1H, *J*=12.0, 17.1 Hz, $CH_{pyraz.}$>CHH_b), 5.56 (dd, 1H, *J*=6.2, 12.4 Hz, $CH_{pyraz.}$>CHH_c), 6.67-6.70 (m, 3H, ArH), 7.06-7.11 (m, 3H, ArH), 7.30-7.33 (m, 3H, ArH), 7.35-7.39 (m, 3H, ArH), 7.50-7.52 (m, 3H, ArH), 7.64 (d, 2H, *J*= 8.1 Hz, ArH), 8.08 (d, 2H, *J*=7.8 Hz, ArH), 8.36 (d, 2H, *J*= 7.5 Hz, ArH). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 21.8, 21.9 (2SCH3), 40.9 $(CH_2)_{pyraz}$, 62.9 $(CH)_{pyraz}$, 122.1, 123.8, 126.6 (CH), 126.7, 126.8 (C), 127.2, 128.2 (CH), 128.4, 128.5 (C), 129.0, 129.2, 130.3 (CH), 133.9, 134.3 (C), 135.3, 136.7, 137.6 (CH), 139.1, 140.4, 144.3, 162.1 (C) ppm, HRMS (ESI): *m/z* found 543.1939, calcd for $C_{35}H_{31}N_2S_2$ ([M + H]$^+$) 543.1943.

1-phenyl-3,5-bis(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-pyrazole **6d**. Product was isolated as yellowish white solid. Yield: 65%; M.p. 198-200 ^{o}C. IR (KBr) [υ, cm^{-1}]: 1649 (C=N), 2968 $(CH)_{alp}$, 3049, $(CH)_{arom}$. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.24 (dd, 1H, *J*=6.4, 17.5 Hz, $CH_{pyraz.}$>CHH_a), 3.95 (dd, 1H, *J*=12.5, 17.6 Hz, $CH_{pyraz.}$>CHH_b), 5.40 (dd, 1H, *J*=6.3, 12.4 Hz, $CH_{pyraz.}$>CHH_c), 7.00-7.23 (m, 5H, ArH), 7.26-7.34 (m, 4H, ArH), 7.39 (d, 2H, *J*= 8.5 Hz, ArH), 7.50 (d, 2H, *J*= 8.1 Hz, ArH), 7.52-7.65 (m, 4H, ArH), 8.03 (d, 2H, *J*= 7.6 Hz, ArH), 8.31 (d, 2H, *J*= 7.8, ArH). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 43.5 $(CH_2)_{pyraz}$, 63.5 $(CH)_{pyraz}$, 110.9, 113.2, 122.2 (CH), 122.4 (q, $J_{F,C}$= 3.9 Hz, CH), 124.7 (q, $J_{C,F}$= 272 Hz, CF_3), 124.9 (q, $J_{F,C}$= 8.3 Hz, CH), 127.2 (CH), 128.3, 128.5, 128.6 (C), 128.6, 129.3 (CH), 130.3 (q, $J_{F,C}$= 32.4 Hz, C-CF_3), 133.9, 134.3 (CH), 135.5, 136.7 (C), 136.9 (CH), 140.3, 144.4, 148.7, 148.8, 165.8, 166.8 (C) ppm, HRMS (ESI): *m/z* found 587.1884, calcd for $C_{35}H_{25}F_6N_2$ ([M + H]$^+$) 587.1888.

3,5-bis(4'-chloro-[1,1'-biphenyl]-4-yl)-1-phenyl-4,5-dihydro-1H-pyrazole **6e**.

6e was isolated as yellow soild. Yield: 55%; M.p. 213-215 ^{o}C. IR (KBr) [υ, cm^{-1}]: 1643 (C=N), 2977 $(CH)_{alp}$, 3045, $(CH)_{arom}$. ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.23 (dd, 1H, *J*=6.6, 17.8 Hz, $CH_{pyraz.}$>CHH_a), 3.92 (dd, 1H, *J*=12.4, 17.6 Hz, $CH_{pyraz.}$>CHH_b), 5.41 (dd, 1H, *J*=6.1, 12.4 Hz, $CH_{pyraz.}$>CHH_c), 7.13-7.17 (m, 3H, ArH), 7.21 (d, 2H, *J*= 7.3 Hz, ArH), 7.23-7.29 (m, 5H, ArH), 7.30-7.37 (m, 3H, ArH), 7.39-7.41 (m, 3H, ArH), 7.42-7.52 (m, 3H, ArH), 8.22 (d, 2H, *J*=7.6 Hz, ArH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 42.7 $(CH_2)_{pyraz}$, 60.4 $(CH)_{pyraz}$, 126.5, 127.2, 127.3 (CH), 127.4, 128.2, 128.5 (C), 129.1, 129.6 (CH), 133.9, 134.3, 134.5 (C), 135.1, 135.8, 136.7 (CH), 136.8, 137.4, 137.6 (C), 138.9, 140.9, 170.9 (CH), 171.9, 174.5 (C) ppm, HRMS (ESI): *m/z* found 519.1889, calcd for $C_{33}H_{25}Cl_2N_2$ ([M + H]$^+$) 519.1896.

3,5-bis(4'-methyl-[1,1'-biphenyl]-4-yl)-1-phenyl-4,5-dihydro-1H-pyrazole **6f**.

6f was isolated as brown solid. Yield: 72%; M.p. 199-201 ^{o}C. IR (KBr) [υ, cm^{-1}]: 1646 (C=N), 2973 $(CH)_{alp}$, 3046, $(CH)_{arom}$. ^{1}H- NMR (300 MHz, $CDCl_3$): δ = 2.31 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.13 (dd, 1H, *J*=6.2, 17.0 Hz, $CH_{pyraz.}$>CHH_a), 3.96 (dd, 1H, *J*=12.1, 17.6 Hz, $CH_{pyraz.}$>CHH_b), 5.62 (dd, 1H, *J*=6.2, 12.8 Hz, $CH_{pyraz.}$>CHH_c), 6.45 (d, 2H, *J*= 7.8 Hz, ArH), 7.21-7.27 (m, 3H, ArH), 7.34 (d, 1H, *J*=8.1 Hz, ArH), 7.48-7.53 (m, 3H, ArH), 7.63-7.76 (m, 4H, ArH), 7.80-7.88 (m, 3H, ArH), 7.95 (d, 1H, *J*= 8.1 Hz, ArH), 8.05 (d, 2H, *J*= 8.4, Hz, ArH), 8.48 (d, 2H, *J*= 8.2, Hz, ArH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 21.6, 21.7 (2CH_3), 43.7 $(CH_2)_{pyraz}$, 63.4

$(CH)_{pyraz}$, 125.6, 126.6, 126.7, (CH), 127.0, 127.1 (C), 128.0, 128.3, 128.6 (CH), 128.7, 129.0, 129.1 (C), 129.2, 130.1, 130.2 (CH), 130.4, 133.7, 134.3, 134.4 (C), 135.2, 135.8 (CH), 136.7, 162.1 (C) ppm, HRMS (ESI): *m/z* found 479.2493, calcd for $C_{35}H_{31}N_2$ ($[M + H]^+$) 479.2490.

3,5-bis(4'-ethyl-[1,1'-biphenyl]-4-yl)-1-phenyl-4,5-dihydro-1H-pyrazole **6g.**

6g was isolated as yellowish white solid. Yield: 78%; M.p. 205-208 °C. IR (KBr) [υ, cm^{-1}]: 1653 (C=N), 2976 $(CH)_{alp}$, 3041, $(CH)_{arom}$. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, 3H, *J*= 7.6 Hz, CH_3), 1.28 (t, 3H, *J*= 7.6 Hz, CH_3), 2.56-2.74 (m, 4H, $2CH_2$), 3.65 (dd, 1H, *J*=6.3, 17.1 Hz, $CH_{pyraz.}$>CHH_a), 4.46 (dd, 1H, *J*=12.2, 17.2 Hz, $CH_{pyraz.}$>CHH_b), 5.23 (dd, 1H, *J*=6.2, 12.4 Hz, $CH_{pyraz.}$>CHH_c), 7.31-7.39 (m, 4H, ArH), 7.42-7.48 (m, 4H, ArH), 7.50-7.57 (m, 5H, ArH), 7.58-7.67 (m, 4H, ArH), 7.69 (d, 1H, *J*=8.2 Hz, ArH), 7.72 (d, 1H, *J*= 8.0 Hz, ArH), 8.51 (d, 2H, *J*= 9.2, Hz, ArH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 15.4, 15.5 ($2CH_3$), 28.7, 29.4 ($2CH_2$), 40.8 $(CH_2)_{pyraz}$, 62.7 $(CH)_{pyraz}$, 116.6, 120.8, 122.0, 124.4 (CH), 125.0, 127.7, 127.9 (C), 129.3, 129.4, 129.5 (CH), 129.8, 130.4 (C), 130.8, 131.5 (CH), 135.1, 135.6 (C), 136.6, 137.7 (CH), 140.4, 141.9, 163.7 (C) ppm, HRMS (ESI): *m/z* found 507.2747, calcd for $C_{37}H_{35}N_2$ ($[M + H]^+$) 507.1749.

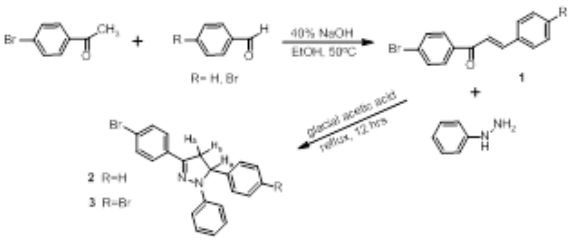
3,5-bis(4'-(tert-butyl)-[1,1'-biphenyl]-4-yl)-1-phenyl-4,5-dihydro-1H-pyrazole **6h**.

6h was isolated as yellow solid. Yield: 80%; M.p. 217-219 °C. IR (KBr) [υ, cm^{-1}]: 1640 (C=N), 2963 $(CH)_{alp}$, 3043, $(CH)_{arom}$. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 18H, $6CH_3$), 3.25 (dd, 1H, *J*=6.1, 17.2 Hz, $CH_{pyraz.}$>CHH_a), 4.25 (dd, 1H, *J*=12.2, 17.1 Hz, $CH_{pyraz.}$>CHH_b), 5.25 (dd, 1H, *J*=6.2, 12.3 Hz, $CH_{pyraz.}$>CHH_c), 7.09-7.14 (m, 4H, ArH), 7.19-7.23 (m, 4H, ArH), 7.25 (d, 2H, *J*=8.1 Hz, ArH), 7.34 (d, 2H, *J*= 7.9 Hz, ArH), 7.41 (d, 2H, *J*= 8.2 Hz, ArH), 7.43-7.47 (m, 3H, ArH), 7.56 (d, 2H, *J*= 7.8 Hz, ArH), 8.51 (d, 2H, *J*= 8.2, Hz, ArH). ^{13}C-NMR (62-9 MHz, $CDCl_3$): δ = 31.5 ($3CH_3$), 31.6 ($3CH_3$), 34.7, 34.8 (C), 41.9 $(CH_2)_{pyraz}$, 62.6 $(CH)_{pyraz}$, 123.8, 124.9, 126.2, 126.5 (CH), 127.2, 128.3, 128.4 (C), 129.1, 129.3 (CH), 129.4, 132.7, 133.8 (C), 134.3, 134.6, 135.5 (CH), 136.7, 136.9 (C), 140.0, 144.5 (CH), 150.6, 166.7 (C) ppm, HRMS (ESI): *m/z* found 563.3351, calcd for $C_{41}H_{43}N_2$ ($[M + H]^+$) 563.3348.

1. Results and discussion

3.1 Chemistry: As a results of a pharmaceutical importance of 2-pyrazoline, the development of synthetic approach of its aryl-substituted derivatives is of considerable current interest. The synthesis of the starting material (**2,3**) was accomplished according to the representation in **scheme 1**. The condensation of P-bromoacetophenone with benzaldehyde or P-bromobenzaldehyde in ethanoic alkali afforded substituted chalcone **1**. The characteristic band at 1645 cm^{-1} in IR spectrum of compound 1 indicates the presence of a -C═O group, and the ^{1}H-NMR spectrum exhibited two doublets at 7.35ppm (J═15 Hz) and 8.10ppm (J═15.2 Hz), which refer to the carbon-carbon double bond in the enone linkage of the chalcone is in a trans-conformation [27]. Pyrazoline derivatives (**2,3**) were prepared by cyclization reaction of chalcone compound (**1**) with phenyl hydrazine in the presence of glacial acetic

Scheme 1. Synthesis of Pyrazoline derivatives (**2,3**) from substituted chalcones (**1**).



acid. The geminal (H_a and H_b) and vicinal (H_x) protons of pyrazoline ring closure can be characterized from ^{1}H-NMR spectra as doublet of doublet peaks. The upfield doublet of doublet at 3.01-3.25 ppm (H_a) and 3.81-4.21 ppm (H_b) were identified for pyrazoline"s geminal protons. Furthermore, the vicinal proton (H_x) appeared as a characteristic peak at 5.64 -5.82 ppm [28].

The development of palladium-catalyzed cross-coupling reaction of halogenated heterocycles is of considerable current important [29,30]. The Suzuki-Miyaura reaction of 3-(4-bromophenyl)-1,5-diphenyl pyrazoline **2** with arylboronic acids **4$_{a-h}$** (1.2 equiv.) afforded the 3-(biphenyl)-1,5-diphenyl pyrazoline (**5$_{a-h}$**) in 53-78% yield (**Table 1, Scheme 2**). Reaction optimization proved that the best yields were obtained when $Pd(PPh_3)_4$ was utilized as a catalyst (3 mol%), and when K_3PO_4 (2 equiv.) was used as a base. Using the catalyst of $PdCl_2(PPh_3)_2$ is less efficient in terms of yield. It is important to add (1.2 equiv.) of the boronic acid otherwise there is still traces of starting material not reacted, this is may be due to dimerization of boronic acid. 1,4-dioxane was used as a solvent in the reaction, while the employment of toluene was less effective as the boronic acid has low solubility in this solvent. The use of THF give low yield. The temperature (70 ^{o}C) and the reaction time (10 h) also played an essential role. The conversion was not complete when the reaction was carried out at low than 70 ^{o}C, and the yield of reaction decreased when the mixture stirred for shorter than 10 h.

Inspection the TLC of reaction showed some bi-aryl formation (by dimerization of the boronic acid) was detected this led to decreasing in reaction yield. The cross-coupling and structure of the products was unambiguously confirmed by ^{1}H-NMR and ^{13}C-NMR.

Scheme 2. Synthesis of (**5$_{a-h}$**). (i) **2** (1.0 equiv.), **4$_{a-h}$** (1.2 equiv.), $Pd(PPh_3)_4$ (3mol.%), K_3PO_4 (2 equiv.), 1,4-dioxane, 70 ^{o}C, 10 h.

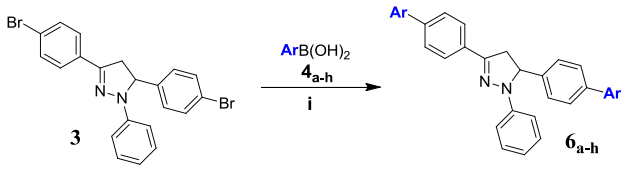


Table 1. Synthesis of 3-(biphenyl)-1,5-diphenyl pyrazoline (**5$_{a-h}$**) .

4	**5**	**Ar**	**Yield of 5 [%]^a**
a	a	4-(MeO)C_6H_4	71
b	b	3,4-(MeO)$_2C_6H_3$	73
c	c	4-(MeS)C_6H_4	69
d	d	4-(CF_3) C_6H_4	60
e	e	4-ClC_6H_4	53
f	f	4-MeC_6H_4	70
g	g	4-EtC_6H_4	72
h	h	4-*t*BuC_6H_4	78

[a] Isolated product.

The Suzuki-Miyaura reaction of 3,5-bis(4-bromophenyl)-1-phenyl pyrazoline (**3**) with arylboronic acid **4$_{a-h}$** (2.2 equiv.) afforded 3,5-bis(biphenyl)-1-phenyl pyrazoline (**6$_{a-h}$**) in 55-80% (**Table 2, Scheme 3**). It is important to be use (5 mol%) of the catalyst $Pd(PPh_3)_4$, less or more than this quantity resulted in diminishing in the yield, using of $PdCl_2(PPh_3)_2$ as a catalyst was inefficient because of producing two products mono-coupling and di-coupling detected by the TLC. For obtaining the best results the reaction temperature should be fixed at 100 ^{o}C for 12 h, carried out the reaction

lower than this temperature also led to uncompleted conversion (mixture of mono- and di- coupling). Significant amount of side-products derived from only mono-coupling, were formed when using K_3PO_4 as a base, so best results obtained (one spot in TLC for di-coupling product) when using K_2CO_3 (2M aqueous solution) as a base. The yields slightly decreased for products (**6e**), derived from boronic acids with electron poor substituent (**4e**). The reactions were proceed successfully for aryl boronic scids with both electron-poor and electron-rich substituents.

Scheme 3. Synthesis of (**6$_{a-h}$**). Reagents and conditions: (i) **3** (1.0 equiv.), **4$_{a-h}$** (2.2 equiv.), $Pd(PPh_3)_4$ (5mol.%), K_2CO_3 (2M, 1ml.), 1,4-dioxane, 100 °C, 12 h.

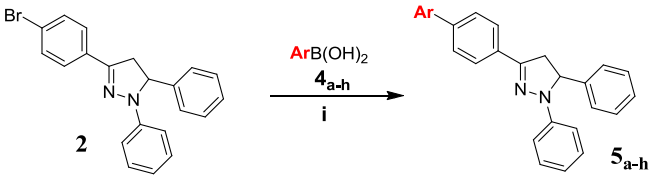


Table 2. Synthesis of 3,5-bis(biphenyl)-1-phenyl pyrazoline (**6$_{a-h}$**).

4,6	Ar	Yield of 6 [%][a]
a	4-(MeO)C_6H_4	74
b	3,4-$(MeO)_2C_6H_3$	75
c	4-(MeS)C_6H_4	73
d	4-(CF_3) C_6H_4	65
e	4-ClC_6H_4	55
f	4-MeC_6H_4	72
g	4-EtC_6H_4	78
h	4-*t*BuC_6H_4	80

[a] Isolated product.

3.1 Antimicrobial activity [31-34]:-

The newly synthesized compounds (**5$_{a-h}$**) and (**6$_{a-h}$**) have been screened in vitro for their antimicrobial activity against four bacterial strains including *Staphylococcus aureus* and *Bacillus substilis* as a Gram-positive bacteria and *Escherichia coli* and *Psendomonas aeruginosa* as a Gram-negative bacteria which obtained from biology department, college of science, Mustansiriyah university. The concentration was carried out using cup-plate agar diffusion (100µg/cm^3), using DMSO as a solvent and Trimethoprim as a positive control. After 24h and 48h of incubation at 37 °C, the antimicrobial activity was determined by measuring the zone of inhibition in mm. The results are summarized in Table (3).

Table 3. In vitro antibacterial activity of the synthesized compounds at a concentration of 100µg/ml (zone of inhibition in mm).

	Zone of inhibition (mm)			
Compounds	**Gram positive bacteria**		**Gram negative bacteria**	
	S. aureus	**B. subtilis**	**E-coli**	**P-aeruginosa**
5a	8	10	18	10
5b	9	11	20	11
5c	11	13	21	13
5d	14	16	24	12
5e	15	15	22	10
5f	9	10	17	9
5g	8	12	15	8
5h	11	11	19	10
6a	22	24	30	17
6b	24	25	32	18
6c	21	23	29	16
6d	26	28	37	21
6e	24	26	31	18
6f	20	24	28	16
6g	21	23	30	15
6h	20	24	29	15
Trimethoprim	**25**	**28**	**35**	**20**

When we examine the data of inhibition zone in (Table 3) we observed that the mono-coupling compounds (**5$_{a-h}$**) exhibited slight activity against both Gram-positive bacteria and Gram-negative bacteria, while the di-coupling compounds (**6$_{a-h}$**) showed significant bioactivity against four bacterial strains in comparison with positive control of Trimethoprim. Most of the di-coupling compounds (**6$_{a-h}$**) found have very good activity against Gram-positive bacteria with inhibition zone ranged from (20-26 mm) compared to positive control (25 and 28 mm), the compound **6d** showed a potent activity against (*S. aureus* and *B. subtilis*) with inhibition zone of (26-28 mm) higher than positive control. The mono-coupling compounds (**5$_{a-h}$**) in other hand showed moderate activity against *P-aeruginosa* bacteria compared to slight activity against *E-coli*. While di-coupling compounds (**6$_{a-h}$**) found to have excellent activity against both E.coli and P-aeruginosa bacteria, the compound **6d** exhibited activity (21-37 mm) even higher than positive control (20-35 mm). The type of substituents in the molecule play an important role in improving the activity of the synthesized compounds. Compounds **6d** and **6e** containing trifluoromethyl and chloro moieties on para-position exhibited better antibacterial inhibition compared to other derivatives, these results could be attributed to size of halogen or on the basis of polarity/electronics factor [35].

4. Conclusion:

In conclusion, we have reported the first palladium-catalyzed Suzuki-Miyaura cross-coupling reactions of 1,3,5-triphenyl pyrazoline. The pyrazoline molecule was functionalized with various aryl-substituted containing electron donating and electron withdrawing groups, via mono- and di-cross coupling Suzuki-Miyaura reaction. The in vitro antibacterial activity of the synthesized pyrazoline derivatives were investigated. The mono-aryl coupling products showed a moderate inhibitory activity while di-aryl coupling products exhibited a very good activity against gram-positive and gram-negative bacteria compared to Trimethoprim (positive control).

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