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Synthesis and antibacterial screening of novel 1,3,5-triaryl-4,5-dihydro-1*H*-pyrazole derivatives

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Abstract

Novel 1,3,5-triaryl-4,5-dihydro-1*H*-pyrazole derivatives like 5-(2,4-Dichloro-phenyl)-3-(3-fluoro-4-methoxy-phenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (**3a-p**) were synthesized from 3-fluoro-4-methoxy acetophenone and screened for their antibacterial activity. Chalcones (**2a-f**) prepared by the condensation of 3-fluoro-4-methoxy acetophenone with different aromatic aldehydes were reacted with phenyl hydrazine hydrate or substituted phenyl hydrazine to obtain 1,3,5-triaryl-4,5-dihydro-1*H*-pyrazole (**3a-p**). Structures of the synthesized 1,3,5-triaryl-4,5-dihydro-1*H*-pyrazole compounds (**3a-p**) were characterized using IR, ^{1}H NMR, ^{13}C NMR, MS spectral data. All synthesized compounds screened for their antibacterial activity against *E. coli, P. aeruginosa, S. aureus, B. Subtilis* with standard drugs ampicillin and ciprofloxacin. Some of the 1,3,5-triaryl-4,5-dihydro-1H-prazole derivatives, specially **3f, 3m, 3n** and **3p** showed excellent antibacterial activity and have the potential to convert into antibacterial agent.

Keywords: *Azole, Chalcone, Pyrazole, Antibacterial.*

1. Introduction

Azoles are found in naturally occurring substances and there are so many drug molecules containing azole ring available in market. Being a key player in many drug molecules, azoles are well known for their biological activities including antimicrobial, anticonvulsive, anti-inflammatory, diuretic, analgesic and many other uses. Azole having resistant strains led to develop a new antimicrobial compound. Being a part of azole, pyrazole derivatives are interestingly studied by the young researchers as antimicrobial agents [1-14]. Pyrazole are potential bioactive agent due to their biological activities like anti-inflammatory, anti-HCV, antitumor [15-17], anti-proliferative [18], antiviral [19], anticancer [20], anti-tubercular [21, 22], anticonvulsant [23], antimalarial [24], antidepressant [25], antibacterial [26]. Pyrazole derivatives also act as a cyclooxygenase (COX-1 and COX-2) inhibitor [27] and DNA gyrase inhibitors [28]. In considering the biological importance of these and our efforts to synthesize potentially active new agents, we have synthesized some new triaryl pyrazole derivatives. Synthesized triaryl pyrazole derivatives (3a-p) were confirmed with the help of analytical results and further tested for their antibacterial activities.

2. Experiment

Melting points of the synthesized compounds were determined using Buchi M-565 melting point analyzer and are uncorrected. Purity of compounds was monitored by TLC on silica gel 60 F_{254} coated aluminium plates (Merck) as adsorbent and visualized under U.V. light and Iodine chamber. IR spectra (KBr in cm^{-1}) were recorded using Perkin Elmer Spectrum-100 analyzer. NMR spectra were recorded on a Bruker operating at 200 MHz (^{1}H NMR) and 50 MHz (^{13}C NMR) using $CDCl_3$ as a solvent and TMS as an internal standard (Chemical shift in ppm). All chemicals and solvents used are laboratory reagent grade.

2.1General procedure for the synthesis of 1-(3-fluoro-4-methoxy-phenyl)-3-(substituted phenyl)-propenone (2a-f)

A mixture of 4-methoxy-3-fluoroacetophenone (0.01mol), substituted aromatic aldehydes (0.01mol) and potassium hydroxide (0.02mol) in ethanol (20ml) was stirred at room temperature for 10-12 hrs. TLC technique was used to check the reaction progress. After reaction completion observed on TLC, reaction mass was then poured in ice cold water and neutralized with hydrochloric acid. The obtained solid was filtered under vacuum, washed with water, suck dried and recrystallized using ethanol to get *(2a-f).*

(E)-1-(4-chlorophenyl)-3-(3-fluoro-4-methoxyphenyl)prop-2-en-1-one (2a)

Yield 78%; off white solid; mp 179-182°C; IR (KBr, cm^{-1}): 3017 (C=C-H str.), 1671 (C=O str.), 1498 (C=C str.), 1256 (C-F str.); ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 3.98 (s, 3H, -OCH_3), 7.04-7.10 (m, 1H, Ar-H), 7.42 (d, J=15.00 Hz, 1H, -CO-CH=), 7.68-7.77 (m, 6H, Ar-H), 7.81 (d, J=15.7 Hz, 1H, Ar-CH=); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 56.93, 113.05, 116.65, 117.04, 122.19, 126.39, 129.86, 130.19, 131.83, 133.94, 137.05, 143.75, 150.24, 152.39, 155.17, 188.03; MS: *m/z* 291.0 (M^+).

*(E)-3-(3-fluoro-4-methoxyphenyl)-1-(4-fluorophenyl)prop-2-en-1-one (2b***)**

Yield 81%; off white solid; mp 203-206°C; IR (KBr, cm^{-1}): 2953 (C=C-H str.), 1686 (C=O str.), 1508 (C=C str.), 1264 (C-F str.) ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 3.98 (s, 3H, -OCH_3), 7.05-7.16 (m, 3H, Ar-H), 7.35 (d, J=16.00 Hz, 1H, -CO-CH=), 7.61-7.65 (m, 4H, Ar-H), 7.75 (d, J=15.15 Hz, 1H, Ar-CH=); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 56.92, 113.02, 116.53, 116.97, 121.47, 126.29, 126.34, 130.87, 131.04, 131.92, 143.95, 150.24, 152.39, 155.17, 162.18, 188.03; MS: *m/z* 275.2 (M^+).

(E)-1-(2,4-difluorophenyl)-3-(3-fluoro-4-methoxyphenyl)prop-2-en-1-one (2c)

Yield 83%; off white solid; mp 191-193°C; IR (KBr, cm^{-1}): 2981 (C=C-H str.), 1684 (C=O str.), 1489 (C=C str.), 1269 (C-F str.); ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 3.99 (s, 3H, $-OCH_3$), 6.86-7.05 (m, 3H, Ar-H), 7.42 (d, J=15.00 Hz, 1H, -CO-CH=), 7.77-7.82 (m, 3H, Ar-H), 7.83 (d, J=16.10 Hz, 1H, Ar-CH=); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 56.95, 112.40, 116.75, 117.12, 124.84, 126.55, 128.17, 129.11, 130.77, 143.95, 150.24, 152.39, 155.17, 162.83,164.60 187.39; MS: *m/z* 293.1 (M^+).

(E)-1-(2,3-dimethoxyphenyl)-3-(3-fluoro-4-methoxyphenyl)prop-2-en-1-one (2d)

Yield 75%; off white solid; mp 183-186°C; IR (KBr, cm^{-1}): 3015 (C=C-H str.), 1680 (C=O str.), 1492 (C=C str.), 1260 (C-F str.); ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 3.97-3.99 (m, 9H, $-OCH_3$), 7.05-7.10 (m, 3H, Ar-H), 7.32(d, J=16.10 Hz, 1H, -CO-CH=), 7.61-7.77 (m, 3H, Ar-H), 8.07-8.11 (d, J= 15.15 Hz, 1H, Ar-CH=); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 56.30, 87.70, 104.27, 111.93, 112.38, 116.05, 116.43, 123.36, 125.83, 126.55, 128.23, 131.08, 143.95, 149.63, 150.24, 152.02, 154.55, 188.03; MS: *m/z* 317.1 (M^+).

(E)-1-(2,4-dichlorophenyl)-3-(3-fluoro-4-methoxyphenyl)prop-2-en-1-one (2e)

Yield 79%; off white solid; mp 135-137°C; IR (KBr, cm^{-1}): 2990 (C=C-H str.), 1682 (C=O str.), 1489 (C=C str.), 1279 (C-F str.); ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 3.98 (s, 3H, $-OCH_3$), 7.04-7.09 (m, 1H, Ar-H), 7.38 (d, J=16.20 Hz, 1H, -CO-CH=), 7.73-7.77 (m, 5H, Ar-H), 7.81 (d, J= 15.00Hz, 1H, Ar-CH=); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 55.69, 115.49, 115.86, 123.57, 125.28, 126.90, 127.85, 129.51, 131.16, 135.42, 138.52, 143.95, 150.24, 152.39, 155.17, 188.03; MS: *m/z* 326.4 (M^+).

(E)-3-(3-fluoro-4-methoxyphenyl)-1-(3-methoxyphenyl)prop-2-en-1-one (2f)

Yield 71%; off white solid; mp 140-143°C; IR (KBr, cm^{-1}): 2959 (C=C-H str.), 1679 (C=O str.), 1484 (C=C str.), 1262 (C-F str.); ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 3.76-3.78 (m, 6H, $-OCH_3$), 6.84-7.00 (m, 2H, Ar-H), 7.12-7.19 (m, 3H, Ar-H), 7.44 (d, J=15.10 Hz, 1H, -CO-CH=), 7.70-7.76 (m, 2H, Ar-H), 7.90-7.94 (d, J=16.00 Hz, 1H, Ar-CH=); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 55.65, 111.74, 113.02, 115.38, 116.53, 116.97, 120.20, 125.07, 126.34, 129.59, 130.65, 135.42, 142.68, 150.24, 155.17, 165.91, 186.83; MS: *m/z* 287.1 (M^+).

2.2General procedure for the synthesis of 3-(3-fluoro-4-methoxy-phenyl)-1-(substituted phenyl)-5-(substituted phenyl)-4,5-dihydro-1H-pyrazole (3a-p)

To a solution of chalcones (2a-h) (0.01mol) in ethanol (20ml), phenyl hydrazine or substituted phenyl hydrazine hydrochloride (0.02mol) was added at room temperature and reaction mass was refluxed for 8-10 hours. TLC technique was used to check the reaction progress. After reaction completion observed on TLC, reaction mass was then cooled, poured on crushed ice. The obtained solid was filtered under vacuum, washed with water, suck dried and purified by silica -flash chromatography (hexane/ethyl acetate = 8:2).

5-(2,4-dichlorophenyl)-3-(3-fluoro-4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (3a)

Yield 83%; light yellow solid; mp 176-178°C; IR (KBr, cm^{-1}): 2932 (-C=C-H str.), 1567 (C=N str.), 1494 (C=C str.), 1260 (C-F str.), 1138 (C-N str.); ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 3.02-3.14 (m, 1H, $-CH_2$), 3.76-3.80 (m, 1H, $-CH_2$), 4.00 (s, 3H, $-OCH_3$), 5.55-5.65 (m, 1H, -CH), 6.85-6.98 (m, 6H, Ar-H), 7.11-7.41 (m, 4H, Ar-H), 7.64-7.75 (m, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 55.84, 56.28, 60.41, 106.09, 111.58, 113.27, 113.82, 121.60, 122.98,

123.97, 124.37, 125.09, 126.34, 127.03, 128.74, 128.91, 139.52, 140.61, 146.87, 150.09, 152.90, 154.96; MS: *m/z* 416.2 (M^+).

3-(3-fluoro-4-methoxyphenyl)-5-(4-fluorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (3b)

Yield 89%; yellow solid; mp 130-133°C; IR (KBr, cm^{-1}): 2964 (-C=C-H str.), 1573 (C=N str.), 1484 (C=C str.), 1279 (C-F str.), 1123 (C-N str.); ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 3.03-3.15 (m, 1H, $-CH_2$), 3.78-3.90 (m, 1H, $-CH_2$), 3.98 (s, 3H, $-OCH_3$), 5.23-5.33 (m, 1H, -CH), 6.76-7.10 (m, 5H, Ar-H), 7.23-7.33 (m, 6H, Ar-H), 7.39-7.73 (m, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 55.62, 56.30, 60.24, 113.41, 113.89, 115.45, 115.82, 121.60, 123.53, 123.79, 124.35, 125.09, 126.46, 127.63, 128.74, 128.91, 139.52, 140.61, 146.87, 150.09, 152.90, 155.04; MS: *m/z* 365.4 (M^+).

1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-3-(3-fluoro-4-methoxyphenyl)-4,5-dihydro-1H-pyrazole (3c)

Yield 82%; light yellow solid; mp 156-158°C; IR (KBr, cm^{-1}): 2936 (-C=C-H str.), 1612 (C=N str.), 1492 (C=C str.), 1254 (C-F str.), 1132 (C-N str.); ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 3.00-3.12 (m, 1H, $-CH_2$), 3.78-3.90 (m, 1H, $-CH_2$), 3.95 (s, 3H, $-OCH_3$), 5.49-5.59 (m, 1H, -CH), 6.76-7.01 (m, 6H, Ar-H), 7.10-7.14 (m, 2H, Ar-H), 7.27-7.28 (m, 1H, Ar-H), 7.53-7.83 (m, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 55.81, 56.26, 60.46, 113.41, 113.89, 115.45, 115.82, 116.42, 119.61, 121.59, 123.53, 123.99, 124.18, 125.29, 127.63, 129.01, 139.51, 140.70, 146.72, 150.09, 152.94, 154.72; MS: *m/z* 450.4 (M^+).

1-(4-chlorophenyl)-3-(3-fluoro-4-methoxyphenyl)-5-(4-fluorophenyl)-4,5-dihydro-1H-pyrazole (3d)

Yield 87%; orange solid; mp 126-128°C; IR (KBr, cm^{-1}): 2967 (-C=C-H str.), 1618 (C=N str.), 1495 (C=C str.), 1258 (C-F str.), 1136 (C-N str.); ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 3.02-3.14 (m, 1H, $-CH_2$), 3.75-3.90 (m, 1H, $-CH_2$), 3.99 (s, 3H, $-OCH_3$), 5.19-5.30 (m, 1H, -CH), 6.96-7.17 (m, 5H, Ar-H), 7.27-7.46 (m, 2H, Ar-H), 7.61-7.64 (m, 2H, Ar-H), 7.75-7.83 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 55.90, 56.34, 60.32, 113.41, 113.89, 115.96, 116.39, 119.61, 121.61, 123.53, 123.79, 124.03, 125.77, 127.63, 129.18, 130.68, 139.51, 140.47, 146.72, 150.13, 152.26, 155.58; MS: *m/z* 399.3 (M^+).

5-(2,4-dichlorophenyl)-3-(3-fluoro-4-methoxyphenyl)-1-(3-fluorophenyl)-4,5-dihydro-1H-pyrazole (3e)

Yield 81%; yellow solid; mp 145-147°C; IR (KBr, cm^{-1}): 2954 (-C=C-H str.), 1600 (C=N str.), 1509 (C=C str.), 1263 (C-F str.), 1141 (C-N str.); ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 3.02-3.15 (m, 1H, $-CH_2$), 3.76-3.90 (m, 1H, $-CH_2$), 3.95 (s, 3H, $-OCH_3$), 5.48-5.58 (m, 1H, -CH), 6.40-6.45 (m, 1H, Ar-H), 6.72-7.07 (m, 7H, Ar-H), 7.27-7.52 (m, 1H, Ar-H), 7.58-7.78 (m, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 55.75, 56.29, 60.82, 113.18, 113.79, 115.06, 116.08, 119.13, 121.71, 123.63, 123.87, 124.80, 125.18, 127.63, 129.97, 130.68, 139.55, 141.67, 147.48, 150.85, 152.61, 154.96; MS: *m/z* 434.0 (M^+).

3-(3-fluoro-4-methoxyphenyl)-1-(3-fluorophenyl)-5-(4-fluorophenyl)-4,5-dihydro-1H-pyrazole (3f)

Yield 88%; yellow solid; mp 111-114°C; IR (KBr, cm^{-1}): 2953 (-C=C-H str.), 1598 (C=N str.), 1502 (C=C str.), 1273 (C-F str.), 1129 (C-N str.); ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 3.03-3.17 (m, 1H, $-CH_2$), 3.74-3.92 (m, 1H, $-CH_2$), 3.98 (s, 3H, $-OCH_3$), 5.26-5.32 (m, 1H, -CH), 6.45-6.57 (m, 1H, Ar-H), 6.65-7.20 (m, 6H, Ar-H), 7.25-7.49 (m, 2H, Ar-H), 7.51-7.90 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 55.47, 56.23, 60.22, 113.41, 114.67, 115.58, 116.32, 119.58, 121.68, 123.53, 123.89, 124.03, 125.77, 127.27, 129.18, 130.45, 139.51, 140.90, 147.81, 150.06, 151.93, 154.94; MS: *m/z* 383.4 (M^+).

5-(2,3-dimethoxyphenyl)-3-(3-fluoro-4-methoxyphenyl)-1-(3-fluorophenyl)-4,5-dihydro-1H-pyrazole (3g)

Yield 80%; yellow solid; mp 139-141°C; IR (KBr, cm^{-1}): 3007 (-C=C-H str.), 1594 (C=N str.), 1485 (C=C str.), 1264 (C-F str.), 1142 (C-N str.); ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 2.92-3.04 (m, 1H, $-CH_2$), 3.69-3.80 (m, 1H, $-CH_2$), 3.92 (s, 9H, $-OCH_3$), 5.50-5.59 (m, 1H, -CH), 6.54-6.55 (m, 2H,Ar-H), 6.95-6.99 (m, 1H, Ar-H), 7.10-7.12 (m, 1H, Ar-H), 7.14-7.27 (m, 3H, Ar-H), 7.48-7.52 (m, 1H Ar-H), 7.58-7.62 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 55.81, 56.26, 60.64, 65.29, 69.60, 113.29, 113.85, 115.96, 116.47, 119.11, 121.68, 123.50, 123.79, 124.06, 125.83, 127.87, 129.47, 130.03, 139.23, 141.12, 147.86, 150.13, 151.26, 154.92; MS: *m/z* 425.1 (M^+).

3-(3-fluoro-4-methoxyphenyl)-5-(4-fluorophenyl)-1-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole (3h)

Yield 90%; reddish solid; mp 134-136°C; IR (KBr, cm^{-1}): 2931 (-C=C-H str.), 1599 (C=N str.), 1508 (C=C str.), 1290 (C-F str.), 1137 (C-N str.); ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 3.02-3.14 (m, 1H, $-CH_2$), 3.74-3.90 (m, 1H, $-CH_2$), 3.99 (s, 6H, $-OCH_3$), 5.26-5.32 (m, 1H, -CH), 6.87-7.17 (m, 6H, Ar-H), 7.47-7.64 (m, 2H, Ar-H), 7.76-7.86 (m, 3H, Ar-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 55.82, 56.24, 60.42, 65.70, 113.36, 113.50, 116.09, 116.47, 119.11, 121.68, 123.50, 123.79, 124.06, 125.83, 127.87, 129.47, 130.03, 139.23, 141.12, 147.86, 150.13, 151.04, 154.92; MS: *m/z* 395.3 (M^+).

5-(2,3-dimethoxyphenyl)-3-(3-fluoro-4-methoxyphenyl)-1-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole (3i)

Yield 89%; light brown solid; mp 165-167°C; IR (KBr, cm^{-1}): 2949 (-C=C-H str.), 1609 (C=N str.), 1494 (C=C str.), 1271 (C-F str.), 1126 (C-N str.); ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 2.96-3.10 (m, 1H, $-CH_2$), 3.76-3.86 (m, 1H, $-CH_2$), 3.99 (s, 12H, $-OCH_3$), 5.46-5.56 (m, 1H, -CH), 6.73-7.14 (m, 2H, Ar-H), 7.27-7.49 (m, 5H, Ar-H), 7.67-8.15 (m, 3H, Ar-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 55.81, 56.26, 60.46, 65.92, 66.37, 82.10, 113.40, 113.91, 116.09, 116.47, 119.11, 121.68, 123.79, 124.06, 125.64, 127.10, 127.87, 129.47, 130.03, 139.23, 141.12, 147.86, 150.13, 151.04, 154.92; MS: *m/z* 437.5 (M^+).

5-(2,4-difluorophenyl)-3-(3-fluoro-4-methoxyphenyl)-1-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole (3j)

Yield 85%; light brown solid; mp 144-146°C; IR (KBr, cm^{-1}): 3005 (-C=C-H str.), 1610 (C=N str.), 1508 (C=C str.), 1274 (C-F str.), 1140 (C-N str.); ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 3.02-3.14 (m, 1H, $-CH_2$), 3.69-3.80 (m, 1H, $-CH_2$), 3.99 (s, 6H, $-OCH_3$), 5.46-5.56 (m, 1H, -CH), 6.88-7.27 (m, 5H, Ar-H), 7.59-7.77 (m, 2H, Ar-H), 7.81-7.88 (m, 3H, Ar-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 55.90, 56.26, 60.42, 65.70, 113.40, 113.91, 116.09, 116.47, 119.11, 121.68, 122.50, 124.40, 125.83, 127.10, 127.87, 129.47, 130.03, 139.23, 141.12, 147.86, 150.56, 152.60, 154.92; MS: *m/z* 413.4 (M^+).

1-(4-bromophenyl)-3-(3-fluoro-4-methoxyphenyl)-5-(3-methoxyphenyl)-4,5-dihydro-1H-pyrazole (3k)

Yield 76%; yellow solid; mp 155-157°C; IR (KBr, cm^{-1}): 2984 (-C=C-H str.), 1578 (C=N str.), 1487 (C=C str.), 1288 (C-F str.), 1132 (C-N str.); ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 3.30-3.45 (m, 1H, $-CH_2$), 3.96-4.00 (m, 1H, $-CH_2$), 4.08 (s, 6H, $-OCH_3$), 5.44-5.56 (m, 1H, -CH), 7.14-7.27 (m, 5H, Ar-H), 7.56-7.60 (m, 3H, Ar-H), 7.64-8.15 (m, 3H, Ar-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 55.20, 56.26, 60.46, 61.80, 113.30, 114.27, 116.09, 116.47, 119.11, 121.68, 123.84, 125.64, 126.62, 127.10, 127.87, 129.47, 130.03, 139.86, 141.12, 147.56, 150.13, 151.00, 155.73; MS: *m/z* 456.1 (M^+).

1-(4-bromophenyl)-5-(2,4-difluorophenyl)-3-(3-fluoro-4-methoxyphenyl)-4,5-dihydro-1H-pyrazole (3l)

Yield 84%; yellow solid; mp 145-147°C; IR (KBr, cm^{-1}): 2937 (-C=C-H str.), 1589 (C=N str.), 1492 (C=C str.), 1279 (C-F str.), 1131 (C-N str.); ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 3.10-3.27 (m, 1H, -CH_2), 3.86-4.00 (m, 1H, -CH_2), 4.07 (s, 3H, -OCH_3), 5.55-5.68 (m, 1H, -CH), 6.88-7.09 (m, 5H, Ar-H), 7.14-7.45 (m, 3H, Ar-H), 7.73-7.85 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 55.90, 56.26, 60.42, 105.37, 111.72, 113.31, 113.89, 115.82, 116.09, 119.61, 121.28, 121.59, 123.53, 124.57, 125.80, 127.63, 129.01, 137.34, 147.86, 150.09, 151.27, 154.63; MS: *m/z* 462.2 (M^+).

1-(4-bromophenyl)-3-(3-fluoro-4-methoxyphenyl)-5-(4-fluorophenyl)-4,5-dihydro-1H-pyrazole (3m)

Yield 82%; orange solid; mp 168-170°C; IR (KBr, cm^{-1}): 2949 (-C=C-H str.), 1581 (C=N str.), 1502 (C=C str.), 1284 (C-F str.), 1128 (C-N str.); ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 3.52-3.69 (m, 1H, -CH_2), 4.28-4.42 (m, 1H, -CH_2), 4.48 (s, 3H, -OCH_3), 5.72-5.84 (m, 1H, -CH), 7.27-7.63 (m, 5H, Ar-H), 7.77-7.84 (m, 4H, Ar-H), 8.07-8.23 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 55.87, 56.24, 60.46, 113.41, 113.89, 115.62, 116.14, 119.61, 121.09, 121.59, 123.87, 124.18, 125.29, 126.53, 127.63, 129.18, 130.59, 138.76, 141.12, 147.86, 151.47, 155.07; MS: *m/z* 444.3 (M^+).

5-(2,4-dichlorophenyl)-3-(3-fluoro-4-methoxyphenyl)-1-(4-fluorophenyl)-4,5-dihydro-1H-pyrazole (3n)

Yield 87%; orange solid; mp 115-117°C; IR (KBr, cm^{-1}): 2956 (-C=C-H str.), 1602 (C=N str.), 1489 (C=C str.), 1289 (C-F str.), 1139 (C-N str.); ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 2.96-3.13 (m, 1H, -CH_2), 3.74-3.86 (m, 1H, -CH_2), 3.93 (s, 3H, -OCH_3), 5.40-5.57 (m, 1H, -CH), 6.72-7.10 (m, 6H, Ar-H), 7.26-7.37 (m, 1H, Ar-H), 7.48-7.90 (m, 2H, Ar-H), 8.05-8.17 (m, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 55.78, 56.29, 60.82, 113.18, 113.79, 115.06, 116.10, 119.53, 121.67, 123.13, 123.87, 124.70, 125.56, 127.63, 129.97, 130.68, 139.45, 141.67, 147.48, 150.85, 152.81, 154.96; MS: *m/z* 434.1 (M^+).

5-(2,4-difluorophenyl)-3-(3-fluoro-4-methoxyphenyl)-1-(4-fluorophenyl)-4,5-dihydro-1H-pyrazole (3o)

Yield 79%; light yellow solid; mp 126-128°C; IR (KBr, cm^{-1}): 2939 (-C=C-H str.), 1586 (C=N str.), 1486 (C=C str.), 1286 (C-F str.), 1137 (C-N str.); ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 2.99-3.14 (m, 1H, -CH_2), 3.74-3.90 (m, 1H, -CH_2), 3.92 (s, 3H, -OCH_3), 5.34-5.52 (m, 1H, -CH), 6.76-7.05 (m, 6H, Ar-H), 7.10-7.39 (m, 2H, Ar-H), 7.52-7.60 (m, 1H, Ar-H), 7.81-7.93 (m, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 55.90, 56.34, 60.32, 113.43, 113.89, 115.67, 116.19, 119.50, 121.61, 123.53, 123.79, 124.73, 125.31, 128.75, 129.18, 130.03, 137.46, 139.51, 140.47, 146.72, 151.00, 154.92; MS: *m/z* 401.4 (M^+).

3-(3-fluoro-4-methoxyphenyl)-1,5-bis(4-fluorophenyl)-4,5-dihydro-1H-pyrazole (3p)

Yield 83%; yellow solid; mp 127-129°C; IR (KBr, cm^{-1}): 2967 (-C=C-H str.), 1594 (C=N str.), 1494 (C=C str.), 1269 (C-F str.), 1123 (C-N str.); ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 3.98-3.11 (m, 1H, -CH_2), 3.70-3.84 (m, 1H, -CH_2), 3.93 (s, 3H, -OCH_3), 5.11-5.21 (m, 1H, -CH), 6.70-7.07 (m, 6H, Ar-H), 7.26-7.31 (m, 3H, Ar-H), 7.58-7.82 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm: 55.68, 56.29, 60.21, 113.41, 113.89, 115.55, 115.92, 116.39, 120.88, 121.60, 123.79, 124.00, 125.77, 128.74, 129.18, 130.48, 131.08, 139.52, 146.87, 150.81, 152.64, 155.21; MS: *m/z* 383.2 (M^+).

2.3Antibacterial screening

The antibacterial activity of 1,3,5-triaryl-4,5-dihydro-1H-pyrazole derivatives **3(a-p)** was evaluated against two Gram-negative bacteria namely, *Escherichia coli* (NCIM-2256) and *Pseudomonas aeruginosa* (NCIM-2036) and two Gram-

positive bacteria namely, *Staphylococcus aureus* (NCIM-2901) and *Bacillus subtilis* (NCIM-2063) using ampicillin and ciprofloxacin as standard drugs. Minimum inhibitory concentration (MIC) values for antibacterial were determined using standard agar method [29-31]. Dimethyl sulfoxide was used as solvent control. MIC values of the screened compounds are presented in **Table-1**. Majority of the synthesized compounds (MIC range= 50-250 µg/mL) had shown less activity than standard ciprofloxacin (MIC range= 25.00-50.00 µg/mL) against all the tested bacterial strains. When compared with ampicillin all the compounds except **3g** and **3i** shows better activity against *B. subtilis.* Compound **3a** shows less activity against all tested compound except against *B. subtilis.* Compound **3b** and **3f** shows better activity compared with ampicillin against all tested organisms except *E.Coli.* Compound **3h, 3k and 3l** have shown good activity compared to ampicillin against *S. aurius* and *B. Subtilis.* Compounds **3f, 3m, 3n and 3p** can be said to have broad spectrum activity against both Gram-positive and Gram-negative bacteria when compared with standard ampicillin. The comparative result of the antibacterial activity of the pyrazole derivatives indicated that compounds with fluoro substituent are showed excellent activity than other derivatives.

Table-1: Minimum bacterial inhibitory concentrations (MIC) of the compounds **3a-p**

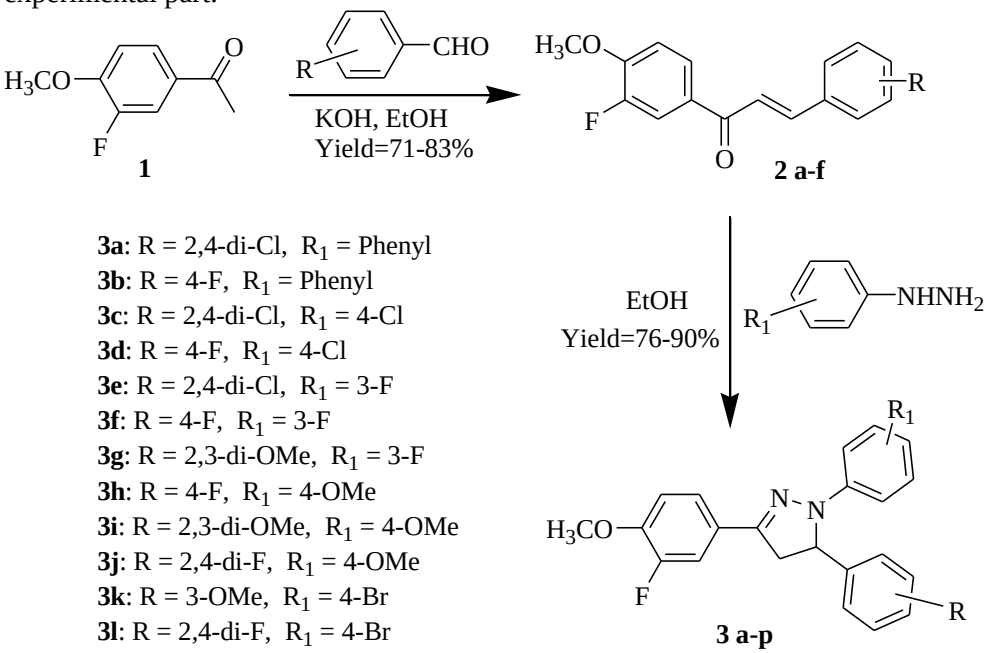
Entry	*E.coli*	*P.aeruginosa*	*S.aureus*	*B.subtilis*
3a	125±0.28	150±0.30	**137.5±0.45**	**162.5±0.19**
3b	150±0.24	**100±0.70**	**125±0.20**	250±0.20
3c	150±0.22	187.5±0.37	**137.5±0.05**	**87.5±0.27**
3d	175±0.69	112.5±0.79	**100.5±1.09**	**162.5±0.71**
3e	167.5±0.31	167.5±1.5	**87.5±0.29**	**75±0.88**
3f	112±0.14	**87.5±0.24**	**67.5±0.35**	**125±0.29**
3g	267.5±1.5	--	--	225±0.08
3h	225±0.17	187.5±0.11	**175±0.10**	**75±0.49**
3i	--	--	225±0.70	--
3j	175±0.55	--	--	**50±0.17**
3k	--	125±0.39	**100±0.58**	**167.5±0.21**
3l	112.5±0.01	200±0.87	**75±0.48**	**112.5±0.06**
3m	**100±0.24**	**87.5±0.11**	**150±0.31**	--
3n	**75±0.45**	125±0.10	**137.5±0.31**	**150±0.11**
3o	150±0.31	175±0.41	--	**112.5±0.39**
3p	**100±0.19**	137.5±0.99	**187.5±0.27**	**175±0.04**
Ampicillin	100±1.24	100±2.14	250±2.99	250±0.88
Ciprofloxacin	25±1.00	25±1.15	50±1.44	50±0.96

--No activity upto 400ug/ml

Result and Discussion

Initially, 4-methoxy-3-fluoro acetophenone **1** treated with substituted benzaldehyde in presence of potassium hydroxide in ethanol to obtain chalcone **2a-f**. Formed chalcones **2a-f** was refluxed with substituted phenyl hydrazine in ethanol to obtain substituted pyrazole **3a-p** as depicted in **Scheme-1** with good yield. Purity of all the synthesized compounds was checked by TLC, with the help of spectral data structures of the proposed compounds were proved. IR spectra of the chalcone compounds **2a-f** showed a characteristic band in the region of 1690-1670 cm^{-1} which indicate

the presence of –C=O group. The compounds **2a-f** also showed the absorption band corresponding to –C=C group at 1510-1480cm^{-1}. The structures of chalcones **2a-f** were confirmed ^{1}H NMR spectra. The chemical shifts at δ 7.04 and 7.80 ppm indicate the presence of vinylic protons H-α and H-β respectively. ^{13}C NMR spectra showed a peak at δ 180-190 which is indicates presence of –C=O group. 1,3,5- triaryl pyrazole compounds **3a-p** were characterised by IR, ^{1}H NMR, ^{13}C NMR and MS. IR spectra of compounds **3a-p** showed characteristic band in the region of 1620-1550 cm^{-1} due to –C=N group. The IR spectra of compounds **3a-p** do not showed any absorption band in the region of 1690-1670 cm^{-1} which indicates the absence of –C=O group. The ^{1}H NMR spectra of the compounds **3a-p** showed multiplate of -CH_2 protons at δ 3.0 and 3.78 ppm confirmed the cyclization in pyrazoline moiety. Similarly, the structures of all other synthesized compounds were proved by analytical data, the results are presented in the experimental part.



3a: R = 2,4-di-Cl, R_1 = Phenyl
3b: R = 4-F, R_1 = Phenyl
3c: R = 2,4-di-Cl, R_1 = 4-Cl
3d: R = 4-F, R_1 = 4-Cl
3e: R = 2,4-di-Cl, R_1 = 3-F
3f: R = 4-F, R_1 = 3-F
3g: R = 2,3-di-OMe, R_1 = 3-F
3h: R = 4-F, R_1 = 4-OMe
3i: R = 2,3-di-OMe, R_1 = 4-OMe
3j: R = 2,4-di-F, R_1 = 4-OMe
3k: R = 3-OMe, R_1 = 4-Br
3l: R = 2,4-di-F, R_1 = 4-Br
3m: R = 4-F, R1 = 4-Br
3n: R = 2,4-di-Cl, R_1 = 4-F
3o: R = 2,4-di-F, R_1 = 4-F
3p: R, R_1 = 4-F

Scheme-1: Synthesis of triaryl Pyrazole **3a-p.**

Conclusion

In conclusion, we have synthesized 1,3,5-triaryl-4,5-dihydro-1H-pyrazole derivatives (**3a-p**) and all the synthesized compounds were evaluated for their antibacterial activity. Almost all the compounds except **3g** and **3i** showed good activity. Compounds **3f**, **3m**, **3n** and **3p** showed excellent antibacterial activity compare to ampicillin. The comparative results of antibacterial activity indicated compounds bearing fluoro group are more effective than other substituents to inhibit the bacterial strains so there are the new opportunités for the possible modification in future as per the therapeutical requirements.

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References

[1] M. Ladani, S. Tala, J. Akbari, M. Dhaduk, H. Joshi, *J. Indian Chem. Soc.*, 86 (2009) 104-108.

[2] A. Noranyan, A. Organisyan, G. Grigoryan, S. Vartanyan, *Chem. Abstr*., 126 (1997) 70176f.

[3] H. Hafez, A. E1-Gazzar, S. Al-Hussain, *Bioorg. Med. Chem. Lett*., 26 (2016) 2428-2433.

[4] M. Mamaghani, N. Hossein, F. Shirini, K. Tabatabaeian, M. Rassa, *Med. Chem. Res*., 24 (2015) 1916-1926.

[5] A. Gadakha, S. Rindheb, B. Karale, *Indian J Het. Chem*., 24 (2014) 213-222.

[6] A. Vijesh, A. Isloor, P. Shetty, S. Sundershan, H. Fun, *Eur. J Med. Chem*., 62 (2013) 410-415.

[7] S. Levent, B. Caliskan, M. Ciftci, Y. Ozkan, I. Yenicesu, H. Unver, E. Banoglu, *Eur. J Med. Chem*., 64 (2013) 42-53.

[8] N. Gaikwad, S. Patil, V. Bobade, *J Het Chem*., 50 (2013) 519-527.

[9] P. Horrocks, M. Pickard, H. Parekh, S. Patel, R. Pathak, *Org. Biomol. Chem*., 11 (2013) 4891-4898.

[10] S. Tala, P. Vekariya, R. Ghetiya, B. Dodiya, H. Joshi, *Indian J. Chem*., 52B (2013) 807-809.

[11] S. Malladi, A. Isloor, S. Peethambar, H. Fun, *Med. Chem. Res*., 22 (2013) 2954-2963.

[12] R. Aggarwal, V. Kumar, P. Tyagi, S. Singh, *Bioorg. Med. Chem*., 14 (2006) 1785-1791.

[13] D. Wang, H. Liu, Y. Kang, Y. Hu, X. Wei, *J. Chilean Chem. Soc*., 60 (2015) 2857-2860.

[14] P. Nayak, B. Narayana, B. Sarojini, J. Fernades, B. Bharath, L. Madhu, *Med. Chem. Res*., 24 (2015) 4191-4206.

[15] M. Sayed, A. Thoraya, A. Magda, M. Mohamed, R. Mohamed, *Eur. J. Med. Chem*., 45 (2010) 1042-1050.

[16] Y. Li, C. Li, J. Liu, M. Guo, T. Zhang, L. Sun, C. Zheng, H. Piao, *Bioorg. Med. Chem. Lett*., 25 (2015) 5052-5057.

[17] P. Harathi, P. Rajendra, D. Satyavati, S. Subramanian, V. Boya, P. Gali, *Asian J. Pharm. Clinical Res*., 8 (2015) 82-86.

[18] T. Reddy, H. Kulhari, V. Reddy, V. Bansal, A. Kamal, R. Shukla, *Eur. J. Med. Chem*., 101 (2015) 790-805.

[19] A. Rashad, M. Hegab, R. Abdel-Megeid, J. Micky, F. Abdel-Megeid, *Bioorg. Med. Chem*., 16 (2008) 7102-7106.

[20] A. Balbi, M. Anzaldi, C. Maccio, C. Aiello, M. Mazzei, R. Gangemi, P. Castagnola, M. Miele, C. Rosano, M. Viale, *Eur. J. Med. Chem*., 46 (2011) 5293-5309.

[21] J. Mao, H. Yuan, Y. Wang, B. Wan, D. Pak, R. He, S. Franzblau, *Bioorg. Med. Chem. Lett*., 20 (2010) 1263-1268.

[22] P. Gunasekaran, S. Perumal, P. Yogeswari, D. Sriram, *Eur. J. Med. Chem*., 46 (2011) 4530-4536.

[23] Z. Ozdemir, H. Kandilci, B. Gumusel, U. Calis, A. Bilgin, *Eur. J. Med. Chem*., 42 (2007) 373-379.

[24] B. Acharya, D. Saraswat, M. Tiwari, A. Shrivastava, R. Ghorpade, S. Bapna, M. Kaushik, *Eur. J. Med. Chem.*, 45 (2010) 430-438.

[25] O. Can, U. Ozkay, Z. Kaplancikli, Y. Ozturk, *Arch Pharm. Res*., 32 (2009) 1293-1299.

[26] S. Shinde, W. Jadhav, R. Pawar, S. Bhusare, *J. Chinese Chem. Soc*., 51 (2004) 775-778.

[27] S. Alegaon, M. Hirpara, K. Alagawadi, K. Hullatti, K. Kashniyal, *Bioorg. Med. Chem. Lett*., 24 (2014) 5324-5329.

[28] J. Liu, J. Sun, Y. Fang, Y. Yang, R. Jiao, H. Zhu, *Org. Biomol. Chem*., 12 (2014) 998-1008.

[29] A. Collins, *Microbiological Methods*, 2nd ed. (Butterworth, London, 1976).

[30] Z. Khan, *In Vitro and In Vivo Screening Techniques for Bioactivity Screening and Evaluation*, Proc. Int. Workshop UNIDO-CDRI (1997) 210.

B. Duraiswamy, S. Mishra, V. Subhashini, S. Dhanraj, B. Suresh, *Indian J. Pharm. Sci*., 68 (2006) 389-3