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ORIGINAL ARTICLE

# PEG-mediated synthesis, antibacterial, antifungal and antioxidant studies of some new 1,3,5-trisubstituted 2-pyrazolines

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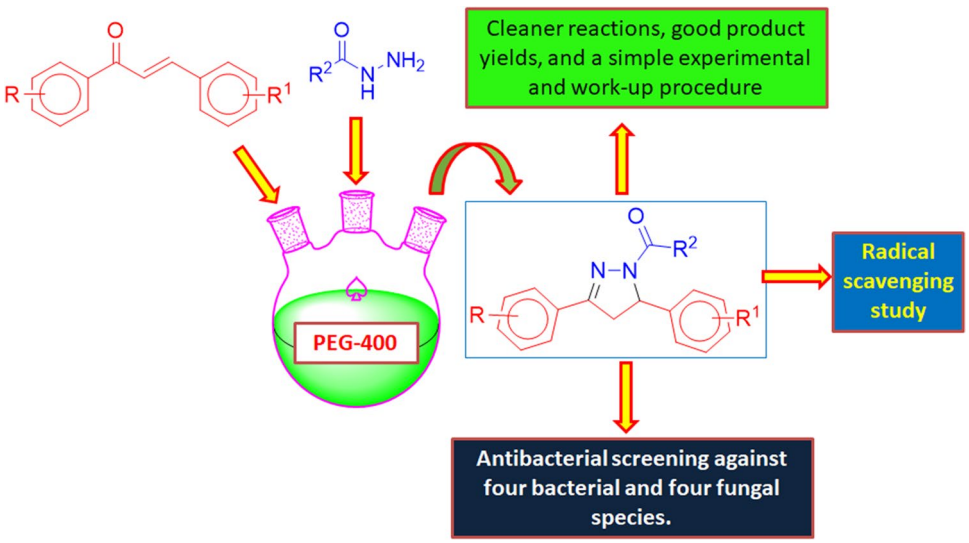
## Abstract

A new series of 1,3,5-trisubstituted 2-pyrazoline derivatives (3a–l) are synthesized in good to excellent yields from the corresponding chalcones (1a–h) and acid hydrazides (2a–e) in polyethylene glycol-400 (PEG-400) as a green reaction medium. The newly synthesized 2-pyrazoline derivatives are screened for their antibacterial and antifungal activity. The synthesized trisubstituted pyrazolines displayed moderate to good antibacterial and antifungal properties as compared with the standard reference penicillin and fluconazole drugs. Additionally, the antioxidant potential of the 1,3,5-trisubstituted 2-pyrazolines is evaluated by OH and DPPH assay. The 1,3,5-trisubstituted 2-pyrazolines showed good radical scavenger activity and were found as good antioxidant agents.

### Graphical abstract




**Keywords** Pyrazolines · Antimicrobial · Antioxidant · PEG solvent · Azoles

## Introduction

Several well-known antimicrobial drugs are no longer effective against microorganisms due to a rise in microbial resistance built on by the misuse of antimicrobial treatments [1–3]. Antimicrobial resistance is a severe global threat to the human, animal, and environmental health that is becoming increasingly concerning. Similarly, the imbalances in

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the formation and scavenging of reactive oxygen species may develop owing to a lack of antioxidant capabilities, as a result, biomolecules suffer severe oxidative damage, and diseases associated with oxidative stress, such as cancer and aging, are developed [4, 5].To avoid illnesses induced by oxidative damage to tissues and cells, a proper balance between reactive oxygen species production and components of the bio-immune system is required. In order to avoid microbial infection as well as to stop, lessen, and repair radical-induced damage to target biomolecules, newer organic compounds are desperately needed.

The α,β-unsaturated ketone moiety is a prominent structural motif in a wide range of biologically active compounds, including synthetic and natural products [6–8]. Chalcones and their analogs are particularly important starting materials or intermediates in the synthesis of naturally occurring flavonoids and several nitrogen-containing heterocyclic compounds such as pyrazolines [9], 1,5-benzodiazepine [10, 11], 1,5-benzothiazepines [12], thiazines [13], pyrimidines [14–18], indazole [19], 2-quinoline carboxylic acid [20, 21] and so on. Chalcones and their analogues shows a wide range of pharmacological properties, such as antibacterial [22], antifungal [23], antitumor [24], antioxidant [25], anti-inflammatory [26], antimalarial [27], and antiproliferative [28] activity.

The five membered ring heterocyclic compounds, serve as core components of a large number of substances that possess a wide range of interesting biological activities [29–34]. Azoles are five-membered heterocyclic compounds with two or more heteroatoms in their rings, with one of the heteroatoms being nitrogen [35–39]. Azoles are an essential class of heterocyclic compounds that has intrigued the interest of many researchers in the fields of pharmaceutical chemistry, medicinal chemistry, and pesticide chemistry [30, 40, 41]. Since azole derivatives, such as triazole, pyrazole, pyrazoline, imidazole, tetrazole, exhibit a wide range of biological activities, their synthesis and transformation have attracted the attention of researchers [42–47].

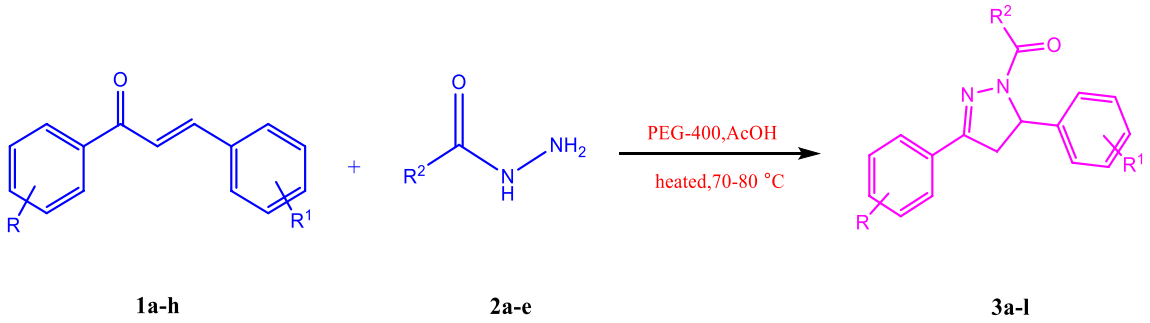
Amongst the azole family, pyrazolines have gained much attention due to their numerous applications [48–51]. Pyrazolines are a valuable synthon that is typically employed in organic synthesis, and they have contributed significantly to the theories and concepts generation of heterocycle chemistry [52]. Several pyrazoline derivatives are useful materials in drug development because they have key biological properties. Pyrazolines are classified into three types: 1-pyrazoline, 2-pyrazoline, and 3-pyrazoline. Amongst these, 2-pyrazoline appears to be the most commonly investigated since it has monoamine characteristics and stability. The 2-pyrazoline derivatives' lipophilic nature causes them to be insoluble in water but soluble in propylene glycol [53]. A wide range of biological activities have been documented for 2-pyrazolines including anticancer [54, 55], anticonvulsant [56], anti-inflammatory [57], analgesic [58–60], antimicrobial [61–64], antidepressant [65, 66], anti-HIV [67], antioxidant [68], antileishmanial [69], antitubercular [69], antihyperlipidemic [70] and anti-diabetic [71]. According to previous literature, the 1,3,5-trisubstituted 2-pyrazolines show significant antioxidant potential [72–77]. The N–N bond linkage in the pyrazoline ring is thought to be the most important component in their biological activity. As a result, there is ongoing interest in developing simple and efficient methods for preparing 1,3,5-trisubstituted 2-pyrazolines. A literature survey reveals that several methods were reported for the synthesis of 1,3,5-trisubstituted 2-pyrazolines from chalcones and acid hydrazide derivatives under various reaction conditions [78–84]. Many of these procedures, however, have one or more downsides, such as a time-consuming experimental protocol, drastic reaction conditions, inadequate yield, longer reaction time, and the usage of hazardous and toxic solvents. Due to strict environmental regulations and safety concerns, industries require environment friendly alternative ways for the synthesis of the heterocyclic compound. Polyethylene glycol (PEG) solvents have grown popular in recent years due to the numerous benefits they provide. It is well known that PEG solvents are inexpensive, widely available, non-toxic, recyclable, non-flammable, biologically friendly, and possess thermal stability [85, 86]. It is applied in chemical synthesis not only as a reaction medium but also as a phase transfer catalyst, usually substituting costly and ecologically hazardous catalysts [87]. PEG solvents are employed as solvents and catalysts in a variety of organic transformations owing to its superior properties [88–92].

In the present work, we report the synthesis of a new library of 1,3,5-trisubstituted 2-pyrazolines in polyethylene glycol-400 (PEG-400) as a green reaction medium. To discover the effective antibacterial and antioxidant agents, synthesized compounds are tested for antibacterial, antifungal, and radical scavenger activity.

## Experimental

### Material and physical measurements

All chemicals of AR grade with purity > 99% were used in the present research. The melting points of the synthesized compounds were taken in open capillaries. All reactions were monitored using thin layer chromatography method. The FT-IR study was performed on Shimadzu spectrometer using KBr method. The $^{1}$H NMR spectral study was performed on a Brucker Advance II 500 MHz instrument using TMS as an internal standard. The high-resolution mass spectral study was carried out using the ESI mode on the Bruker Impact II instrument.




**Scheme 1** Synthesis of pyrazolines via chalcone pathway in PEG-400 medium

## General method for the synthesis of 1,3,5-trisubstituted 2-pyrazoline derivatives

A mixture of previously synthesized chalcones (**1a–h**) (10 mmol) and benzohydrazide derivatives (**2a–e**) (12 mmol) were taken in a round bottom flask containing 10 mL PEG-400. To this reaction mass, 1 mL of glacial acetic acid was added. The reaction mass was then heated at 70–80 °C while being continuously stirred on a magnetic stirrer until the reaction was complete. The progress of the reaction was checked by TLC. After completion of the reaction, the reaction mass was cooled and then poured into a beaker with crushed ice. The precipitate was formed which was then filtered off and recrystallized using isopropanol to give the pure products (**3a–l**). The synthesis of pyrazolines via chalcone pathway in PEG-400 medium is depicted in scheme 1.

### (5-(2,6-Dichlorophenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)(phenyl) methanone (3a)

FT-IR (KBr, in $cm^{-1}$): 3057.50,3020.07,2923.55,2839.28,1627.92, 1593.20, 1433.11, 1327.03, 1247.94, 1172.72, 1099.43, 1026.13, 947.05, 833.25,752.24, 702.09, 597.93, 547.78, 507.28, 422.41; $^1$H NMR (500 MHz, DMSO) δ 7.74 (d, $J$ = 1.8 Hz, 1H), 7.56–7.50 (m, 4H), 7.39–7.37 (m, 2H), 7.35–7.29 (m, 3H), 6.98–6.95 (m, 2H), 5.72 (dd, $J$ = 11.7, 4.8 Hz, 1H), 3.94 (dd, $J$ = 18.1, 11.7 Hz, 1H), 3.77 (s, 3H), 3.21 (dd, $J$ = 18.1, 4.8 Hz, 1H); $^{13}$C NMR (126 MHz, DMSO) δ 163.38, 161.65, 156.48, 142.23, 135.69, 134.82, 131.67, 130.78, 129.29, 129.23, 128.95,127.92,127.79, 126.17, 123.54, 114.73, 60.46, 55.82, 42.94; HR-MS calculated 425.0824 [M + H], found 425.0821 [M + H].

### (3-(4-Fluorophenyl)-5-(4-isopropylphenyl)-4,5-dihydro-1H-pyrazol-1-yl)(phenyl)methanone (3b)

FT-IR (KBr, in $cm^{-1}$): 3055.24, 2962.66, 2872.01, 1635.64, 1602.85, 1506.41, 1423.47, 1328.95, 1222.87, 1145.72, 1103.28, 1058.92, 1020.34, 948.98, 831.32, 783.10, 707.88, 667.37, 563.21, 536.21; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, $J$ = 7.6 Hz, 2H), 7.72–7.66 (m, 2H), 7.50–7.47 (m, 1H), 7.44 (d, $J$ = 7.6 Hz, 2H), 7.26–7.17 (m, 4H), 7.12–7.05 (m, 2H), 5.81 (dd, $J$ = 11.7, 4.8 Hz, 1H), 3.75 (dd, $J$ = 17.5, 11.7 Hz, 1H), 3.20 (dd, $J$ = 17.5, 4.8 Hz, 1H), 2.87 (sept, $J$ = 6.9 Hz, 1H), 1.22 (d, $J$ = 6.9 Hz, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 166.45, 165.06, 163.08, 153.64, 148.34, 139.05, 134.41, 130.93, 130.10, 128.78, 128.71, 127.77, 127.74, 127.64, 127.04, 125.65, 115.97,115.80 61.06, 41.65, 33.80, 23.95, 23.93; HRMS calculated 387.1873; [M + H], found 387.1876 [M + H].

### (3-(4-Chlorophenyl)-5-(2,6-dichlorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(phenyl) methanone (3c)

FT-IR (KBr, in $cm^{-1}$): 3066.82, 1633.71, 1585.49, 1492.90, 1433.11, 1330.88, 1257.59, 1182.36, 1085.92, 1020.34, 954.76, 835.18, 792.74, 702.09, 530.42, 433.98; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, $J$ = 7.3 Hz, 2H), 7.64 (d, $J$ = 8.5 Hz, 2H), 7.51–7.37 (m, 6H), 7.31–7.26 (m, 1H), 7.16 (t, $J$ = 8.0 Hz, 1H), 6.48 (dd, $J$ = 12.9, 8.8 Hz, 1H), 3.71 (dd, $J$ = 17.6, 12.9 Hz, 1H), 3.37 (dd, $J$ = 17.6, 8.8 Hz, 1H);$^{13}$C NMR (126 MHz, $CDCl_3$) δ 166.63, 153.15, 136.28, 136.26, 134.60, 133.85, 133.82, 131.13, 130.22, 129.98, 129.76, 129.21,129.00, 128.61, 127.93, 127.63, 57.87, 38.03; HRMS calculated 429.0328 [M + H]; found 429.0331 [M + H].

### (4-Chlorophenyl)(5-(2,6-dichlorophenyl)-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (3d)

FT-IR (KBr, in $cm^{-1}$): 3074.53, 1618.28, 1504.48, 1427.32, 1325.10, 1230.58, 1170.79, 1091.71, 1016.49, 952.84, 835.18, 675.09, 590.22; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, $J$ = 8.4 Hz, 2H), 7.69 (dd, $J$ = 8.8, 5.3 Hz, 2H), 7.41–7.35 (m, 3H), 7.30–7.26 (m, 1H), 7.15 (t, $J$ = 8.0 Hz, 1H), 7.14–7.05 (m, 2H), 6.45 (dd, $J$ = 12.8, 8.7 Hz, 1H), 3.70 (dd, $J$ = 17.7, 12.8 Hz, 1H), 3.36 (dd, $J$ = 17.7, 8.7 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 165.44, 165.06, 163.06, 153.64, 137.21, 136.24, 134.50, 133.79, 132.30, 131.66, 130.00,129.27, 128.74, 128.68, 128.64, 128.33, 127.90,

127.36, 116.05, 115.88, 57.87, 38.24; HRMS calculated 447.0234 [M + H], found 447.0229 [M + H].

#### (4-Chlorophenyl)(5-(2,6-dichlorophenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl) methanone (3e)

FT-IR (KBr, in $cm^{-1}$): 3076.46, 2947.23, 2837.29, 1608.63, 1516.05, 1429.25, 1325.10,1247.94,1174.65, 1126.43, 1093.64, 1026.13, 956.69, 837.11, 790.81, 748.38, 675.09, 594.08, 526.57; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, $J$ = 8.7 Hz, 2H), 7.65 (d, $J$ = 8.9 Hz, 2H), 7.42–7.35 (m, 3H), 7.30–7.26 (m, 1H), 7.15 (t, $J$ = 8.1 Hz, 1H), 6.94 (d, $J$ = 8.9 Hz, 2H), 6.43 (dd, $J$ = 12.7, 8.6 Hz, 1H), 3.85 (s, 3H), 3.71 (dd, $J$ = 17.6, 12.7 Hz, 1H), 3.37 (dd, $J$ = 17.6, 8.6 Hz, 1H);$^{13}$C NMR (126 MHz, $CDCl_3$) δ 165.22, 161.44, 154.44, 137.05, 136.21, 134.69, 133.82, 132.42, 131.75, 129.98, 129.15, 128.58, 128.33,127.84, 123.66, 114.18, 57.68, 55.42, 38.27; HRMS calculated 459.0434 [M + H], found 459.0428 [M + H].

#### (5-(2,6-Dichlorophenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)(4-fluorophenyl) methanone (3f)

FT-IR (KBr, in $cm^{-1}$): 3080.32,2873.94,1610.56,1506.41,1429.25, 1323.17, 1242.16,1159.22, 1141.86, 1122.57, 1029.99, 952.84, 839.03, 788.89, 765.74,746.45, 678.94, 597.93, 542.00; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.05 (dd, $J$ = 8.9, 5.6 Hz, 2H), 7.66 (d, $J$ = 8.9 Hz, 2H), 7.42–7.36 (m, 1H), 7.29–7.26 (m, 1H), 7.15 (t, $J$ = 8.1 Hz, 1H), 7.12–7.05 (m, 2H), 6.94 (d, $J$ = 8.9 Hz, 2H), 6.44 (dd, $J$ = 12.8, 8.7 Hz, 1H), 3.85 (s, 3H), 3.71 (dd, $J$ = 17.5,12.8 Hz, 1H), 3.37 (dd, $J$ = 17.5, 8.7 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 165.19, 163.30, 161.41, 154.29, 136.21, 134.78, 133.83, 132.78, 132.71, 130.09, 130.07, 129.97, 129.11,128.56, 128.31, 123.72, 114.68, 114.51, 114.17, 70.56,57.68, 55.42, 38.23; HRMS calculated 443.0729 [M + H], found 443.0726 [M + H].

#### (2,4-Dichlorophenyl)(3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone (3g)

FT-IR (KBr, in $cm^{-1}$): 3057.17,1635.64,1587.42, 1487.12,1435.04, 1334.74,1246.02,1145.72, 1099.43,1064.71, 1022.27,952.84,848.68, 756.10,688.59, 549.71,466.77,422.41;$^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.63–7.58 (m, 2H), 7.45 (d, $J$ = 2.1 Hz, 1H), 7.42–7.35 (m, 8H), 7.31 (dd, $J$ = 8.2, 2.2 Hz, 2H), 5.76 (dd, $J$ = 11.7, 4.7 Hz, 1H), 3.84 (dd, $J$ = 17.8, 11.7 Hz, 1H), 3.26 (dd, $J$ = 17.8, 4.7 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 164.36, 155.54, 141.10, 139.99, 135.60, 134.56, 132.54, 130.97, 130.63, 130.08, 129.35, 129.00, 128.71,127.97, 126.83, 125.88, 60.66, 42.49; HRMS calculated 395.0718 [M + H], found 395.0720 [M + H].

#### (2,4-Dichlorophenyl)(3-(4-methoxyphenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl) methanone (3h)

FT-IR (KBr, in $cm^{-1}$): 3053.32,3013.22,2926.01, 2833.58,1625.99, 1593.20, 1433.11, 1327.03, 1249.87, 1172.72, 1095.57, 1024.20, 952.84, 833.25, 744.52, 704.02, 599.86, 530.42, 426.27; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, $J$ = 8.9 Hz, 2H), 7.43 (d, $J$ = 2.0 Hz, 1H), 7.40–7.34 (m, 5H), 7.29 (dd, $J$ = 8.3, 1.8 Hz, 2H), 6.87 (d, $J$ = 8.9 Hz, 2H), 5.72 (dd, $J$ = 11.7, 4.7 Hz, 1H), 3.84–3.76 (m, 4H), 3.21 (dd, $J$ = 17.6, 4.7 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 164.10, 161.56, 155.31, 141.21, 135.46, 134.71, 132.52, 130.07, 129.29, 128.95, 128.47,127.88, 126.78, 125.87, 123.59, 114.11, 60.53, 55.37, 42.54; HRMS calculated 425.0824 [M + H], found 425.0816 [M + H].

#### (2,4-Dichlorophenyl)(3-(4-fluorophenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone (3i)

FT-IR (KBr, in $cm^{-1}$): 3059.10, 1639.49, 1593.20, 1442.75, 1330.88, 1232.51, 1151.50, 1101.35, 842.89, 705.95, 601.79, 547.78, 507.28; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.63–7.56 (m, 2H), 7.45 (d, $J$ = 2.0 Hz, 1H), 7.40–7.34 (m, 5H), 7.33–7.28 (m, 2H), 7.10–7.03 (m, 2H), 5.76 (dd, $J$ = 11.7, 4.8 Hz, 1H), 3.83 (dd, $J$ = 17.6, 11.7 Hz, 1H), 3.23 (dd, $J$ = 17.6, 4.8 Hz, 1H);$^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.83, 164.33, 163.16, 154.48, 140.98, 135.66, 134.50, 132.50, 130.05, 129.36, 129.03, 128.89, 128.82, 128.03, 127.28,127.26, 126.86, 125.84, 116.00, 115.82, 60.76, 42.55; HRMS calculated 413.0624 [M + H], found 413.0617 [M + H].

#### (3,5-Bis(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-1-yl) (2,4-dichlorophenyl)methanone (3j)

FT-IR (KBr, in $cm^{-1}$): 3070.68,1639.49,1591.27,1483.26, 1431.18, 1332.81, 1139.93, 1093.64, 1014.56, 950.91, 835.18, 785.03, 667.37, 532.35, 489.92, 383.83;$^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, $J$ = 8.7 Hz, 2H), 7.46 (d, $J$ = 2.0 Hz, 1H), 7.37–7.29 (m, 8H), 5.72 (dd, $J$ = 11.8, 5.0 Hz, 1H), 3.83 (dd, $J$ = 17.8, 11.8 Hz, 1H), 3.19 (dd, $J$ = 17.8, 5.0 Hz, 1H); $^{13}$C NMR (126 MHz, DMSO) δ 163.73, 155.90, 140.89,135.78, 135.26, 135.06, 132.57, 131.66, 130.80, 129.88, 129.42, 129.36, 129.21, 129.01, 128.41,127.86, 60.22, 42.51; HRMS calculated 462.9938 [M + H], found 462.9933 [M + H].

#### (2,4-Dichlorophenyl)(5-(2,6-dichlorophenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (3k)

FT-IR (KBr, in $cm^{-1}$): 3055.24,2835.36, 1641.42, 1591.27, 1521.84, 1431.18, 1325.10, 1249.87, 1176.58,1047.35, 846.75, 785.03, 597.93, 551.64, 435.91; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, $J$ = 8.5 Hz, 2H), 7.43 (d, $J$ = 2.0 Hz, 1H), 7.42–7.39 (m, 2H), 7.31 (dd, $J$ = 8.1, 1.4 Hz, 1H), 7.28 (dd, $J$ = 8.1, 2.0 Hz, 1H), 7.19 (t, $J$ = 8.1 Hz, 1H), 6.89 (d, $J$ = 8.5 Hz, 2H), 6.42 (dd, $J$ = 12.7, 8.2 Hz, 1H), 3.83 (s, 3H), 3.75 (dd, $J$ = 17.6, 12.7 Hz, 1H), 3.38 (dd, $J$ = 17.6, 8.2 Hz, 1H);$^{13}$C NMR (126 MHz, $CDCl_3$) δ 164.15, 161.51, 154.81, 136.23, 135.46, 134.38, 134.33, 133.77, 132.53, 130.44, 129.95,129.40, 129.29, 128.67, 128.39,126.56, 123.53, 114.12, 57.09, 55.40, 39.16; HRMS calculated 493.0044 [M + H], found 493.0039 [M + H].

#### (5-(2,6-Dichlorophenyl)-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(p-tolyl)methanone (3l)

FT-IR (KBr, in $cm^{-1}$): 3072.60,2931.80,1618.28,1564.27,1510.26, 1429.25, 1363.67, 1325.10, 234.44,1176.58,1141.86,1026.13,954.76,839.03, 773.46,742.59,682.80,542.00, 476.42; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, $J$ = 8.2 Hz, 2H), 7.71 (dd, $J$ = 8.9, 5.3 Hz, 2H), 7.42–7.26 (m, 2H), 7.22 (d, $J$ = 8.2 Hz, 2H), 7.15 (t, $J$ = 8.0 Hz, 1H), 7.12–7.08 (m, 2H), 6.47 (dd, $J$ = 13.0, 8.9 Hz, 1H), 3.70 (dd, $J$ = 17.5, 13.0 Hz, 1H), 3.36 (dd, $J$ = 17.5, 8.9 Hz, 1H), 2.40 (s, 3H);$^{13}$C NMR (126 MHz, $CDCl_3$) δ 166.55, 164.92, 162.92, 152.95, 141.49, 136.23, 134.78, 133.87, 130.95, 130.34, 129.96, 129.11, 128.68, 128.61, 128.57, 128.31,127.63, 127.61, 115.95, 115.78, 57.84, 38.09, 21.57; HRMS calculated 427.0780 [M + H], found 427.0788 [M + H].

## Antimicrobial assay

### Disk diffusion assay

The antibacterial and antifungal potential of the synthesized pyrazolines was assessed using the previously described methods [93, 94].Briefly stated, each sterile, ready paper disc (Sterile Susceptibility test disc SD067 Himedia Labs Pvt Ltd.) contains 50 µL of the synthesized compounds (1 mg/mL). The Mueller–Hinton agar/potato dextrose agar medium, which had been speedily inoculated with 24 h old bacterial and fungal cultures, was then applied to the surface of each disc. Penicillin and Fluconazole, were chosen as standards (at concentrations of 1 mg/mL each) for their respective antibacterial and antifungal activities. The plates were placed in the incubator at 37 °C and 30 °C, respectively, for 24 h after being maintained in the refrigerator for 3 h to allow for diffusion. Following incubation, the zone scale was used to measure the zones surrounding the discs (Himedia Pvt. Ltd. Mumbai).

### Resazurin microtiter assay (REMA) for MIC evaluation

The REMA plate assay was performed as previous report [93, 94]. In brief, successive twofold dilutions of each synthesized pyrazolines and reference compound were taken in the plate, and 100 µL of Mueller–Hinton/Potato Dextrose broth medium was dispersed in each well of a sterile flat-bottom 96-well plate. Each well received 100 µL of inoculums (0.5 McFarland standards is about equivalent to 1.5 × 108 CFU/mL). All perimeter wells underwent sterile cold water addition to prevent evaporation throughout the incubation. The plate was placed in an incubator at 37 °C with a sterile lid on top. Alamer blue solution (0.01% in sterile D/W) (Himedia Labs. Pvt. Ltd.) was added to each well after 24 h of incubation, and the plate was then re-incubated for 8 h. The MIC was defined as the lowest medication concentration that inhibited the color change from blue to pink, which was an indication of the growth of bacteria or fungi.

## Antioxidant assay

The antioxidant studies were performed using previously published literature [93–95].

### Hydroxyl radical assay (OH)

The Fenton reaction was performed to investigate the OH radical scavenging activity. $FeCl_2$ (1 mM), 1–10 phenanthroline (1 mM), phosphate buffer (0.2 M, pH 7.8), $H_2O_2$ (0.17 M), and the synthesized pyrazolines (1 mg/mL) were all incorporated in the typical reaction vessel. The addition of $H_2O_2$ kicked off the reaction. The absorbance was measured at 560 nm following a 5-min incubation period at room temperature. As a reference, ascorbic acid (1 mM) was employed.

$$\% \text{ radical scavenging activity } = 1 - T/C \times 100$$

### 2-Diphenyl-1-picrylhydrazyl radical scavenging assay (DPPH)

The ability of the synthesized compounds to donate electrons was assessed through the bleaching of a 2,2-diphenyl-1-picrylhydrazyl solution, which was purple in color. In a brief, the assay was carried out by combining an equivalent amount of the synthesized pyrazolines with DPPH solution, bringing the total volume to 3 mL, incubating the samples for 20 min, and reading the absorbance at 517 nm. An ascorbic acid (1 mM) as a standard was employed. The following formula was used to get the percent inhibition:

$$\% \text{ radical scavenging activity } = 1 - T/C \times 100$$

## Result and discussion

### Chemistry

The 1,3,5-trisubstituted 2-pyrazoline derivatives (**3a–l**) were synthesized from chalcones and acid hydrazides in polyethylene glycol-400/acetic acid as an efficient reaction solvent system. Desirable 1,3,5-trisubstituted 2-pyrazolines (**3a–l**) were synthesized by heating chalcones (**1a–h**) and various acid hydrazides (**2a–e**) in PEG-400 with acetic acid. The physical parameters of the pyrazoline derivatives are shown in Table 1. The structures of the synthesized pyrazolines were investigated using FT-IR, $^{1}$H NMR, $^{13}$C NMR and HRMS techniques. In the $^{1}$H NMR spectra of pyrazolines (**3a–l**), the $CH_2$ protons of the pyrazoline ring appear as a pair of doublet of doublet at 3.19–3.38 ppm (Ha) and 3.70–3.85 ppm ($H_m$). The –CH ($H_x$) proton appeared as a doublet of doublet at 5.72–6.48 ppm due to vicinal coupling with the two magnetically non-equivalent protons of the methylene group at position 4 of the pyrazoline ring. The carbon atoms' nature was described and validated using $^{13}$C NMR. Because the $^{19}$F nucleus splits the fluorine substituted phenyl ring carbon signals, they appear as doublets in compounds 3b, 3d, 3i and 3l [96–98]. The exact molecular formula and molecular mass of the compounds were evaluated using HR-MS spectra. The probable mechanism for the formation of pyrazolines, by the cyclocondensation reaction of chalcones, and acid hydrazide derivative, is summarized in Scheme 2. The intermolecular nucleophilic attack of the primary nitrogen atom of acid hydrazide on the electron-deficient carbonyl carbon of the chalcone to form an intermediate, which loses water molecule to form an Imine bond (1,2 addition). Later, Intramolecular attacks of the secondary nitrogen atom of acid hydrazide on the olefinic carbon of the chalcone give trisubstituted 2-pyrazolines. The mechanism that occurs in an acidic media via 1, 2 addition and not by 1,4 addition is validated by prior research [99–101]. The result indicates that PEG-400/acetic acid mediated synthesis of pyrazoline derivative was efficient, environmentally benign, and simple. This approach also offers key advantages, like it is a non-toxic solvent, and it is far less harmful than other organic solvents.

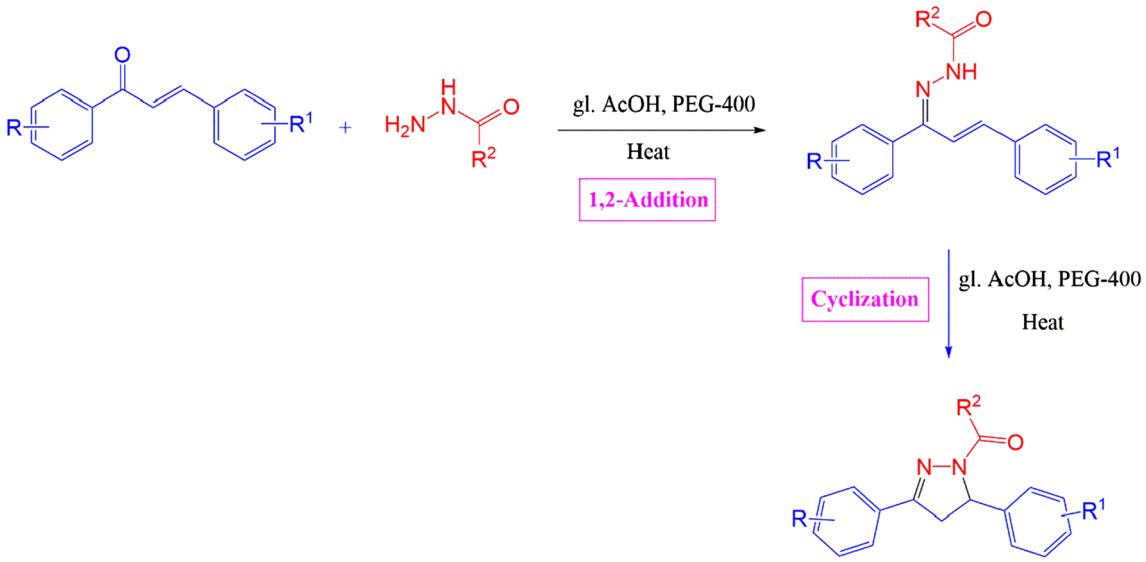
### Antimicrobial activity

The aromatic framework containing diverse substitution patterns of electrons withdrawing and electron releasing substituents such as $OCH_3$, Cl, $CH(CH_3)_2$, F were chosen for the synthesized 1,3,5-trisubstituted 2-pyrazolines to evaluate the antimicrobial activity (Fig. 1).Antibacterial activity of the synthesized pyrazolines were tested using the disc diffusion method against four bacterial agents namely *Escherichia coli* (MTCC 118), *Bacillus subtilis* (MTCC 2274), *Staphylococcus aureus* (MTCC 737), and *Streptococcus species* (MTCC 389*)*. Whereas the antifungal activities were also taken against four fungal species namely *R. oryzae* (MTCC 262), *P. chrysogenum* (MTCC 974*), A. niger* (MTCC 282), and *C. albicans* (MTCC 183). In Tables 2 and 3, respectively, the zone of inhibition information from the antibacterial and antifungal experiments is tabulated. In the antimicrobial experiments, the REMA assay was adopted to evaluate the MIC values, and the outcomes are shown in Tables 4 and 5. Synthesized pyrazolines have been proven to have robust antibacterial and antifungal properties.

The pyrazolines **3a**, **3f**, **3h**, and **3l** were found to show broad-spectrum antibacterial activities against all tested bacterial agents. Similarly, pyrazolines **3a**, **3c**, **3f**, and **3h** were also shown broad-spectrum antifungal action against all four fungal species. However, it has been observed from the present study that the synthesized pyrazolines are more potent antibacterial agents than antifungal agents. The present antimicrobial study indicates that the

**Table 1** Physical parameters of the pyrazoline derivatives

| Entry | R | $R^1$ | $R^2$ | Melting point (°C) | % Yield | Time (Min.) |
|---|---|---|---|---|---|---|
| 3a | 4-OMe | 2,6-Dichloro | $C_6H_5$ | 162–164 | 94 | 120 |
| 3b | 4-F | 4-Isopropyl | $C_6H_5$ | 170 | 78 | 160 |
| 3c | 4-Cl | 2,6-Dichloro | $C_6H_5$ | 174 | 92 | 110 |
| 3d | 4-F | 2,6-Dichoro | 4-Cl $C_6H_4$ | 220 | 87 | 145 |
| 3e | 4-OMe | 2,6-Dichoro | 4-Cl $C_6H_4$ | 220 | 93 | 150 |
| 3f | 4-OMe | 2,6-Dichoro | 4-F $C_6H_4$ | 186 | 90 | 140 |
| 3g | H | H | 2,4-Cl $C_6H_3$ | 154–156 | 89 | 120 |
| 3h | 4-OMe | H | 2,4-Cl $C_6H_3$ | 202–204 | 82 | 135 |
| 3i | 4-F | H | 2,4-Cl $C_6H_3$ | 178 | 90 | 140 |
| 3j | 4-Cl | 4-Cl | 2,4-Cl $C_6H_3$ | 164–166 | 90 | 95 |
| 3k | 4-OMe | 2,6-Dichloro | 2,4-Cl $C_6H_3$ | 166 | 91 | 89 |
| 3l | 4-F | 2,6-Dichloro | 4-$CH_3$ $C_6H_4$ | 212–214 | 89 | 85 |




**Scheme 2** The mechanistic pathway for the formation of pyrazoline compounds by hydrazone formation

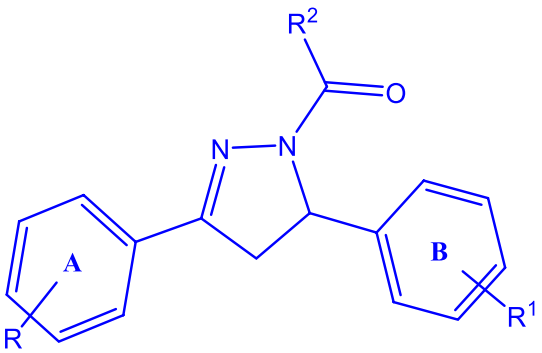



**Fig. 1** General structure of synthesized 1,3,5-trisubstituted 2-pyrazoline

synthesized compounds are as good antimicrobial agents as tested standard compounds. The zone of inhibition and MIC study shows that the pyrazoline **3f** has brilliant antibacterial action which is good as standard. The pyrazoline **3f** was also found to be a good antifungal agent. Similarly, the pyrazoline **3a**, **3h**, **3j** and **3l** have shown low MIC values for antibacterial study. Pyrazolines **3d** have been found to exert very poor antibacterial action along with pyrazolines **3c**, **3i**, **3j**, and **3k** in which the former were shown activities against one bacterial agent and the latter against two bacterial agents. The pyrazolines **3b**, **3e** and **3g** were observed to be active against three bacterial agents. The pyrazolines **3d**, **3k**, and **3l** were shown no antifungal activity. Similarly, pyrazolines **3b**, **3e** and **3g** were also investigated to be poor antifungal agents where they were active against only one fungal species. Compound **3i** was active against two fungal species and inactive against two fungal species. The antimicrobial investigation suggested that the pyrazolines **3d** are showing negligible or no antibacterial and antifungal activities. The whole study concluded that the presence of chloro, methoxy and fluoro substituents on aryl rings A,B and C of synthesized pyrazolines has shown good antibacterial activity.

**Table 2** Zone of inhibition of synthesized pyrazolines against some bacterial strains

| Entry | Bacterial strains | | | |
|---|---|---|---|---|
| | *E. coli* | *B. subtilis* | *S. aureus* | *S. species* |
| 3a | ++ | ++ | +++ | +++ |
| 3b | + | +++ | – | ++ |
| 3c | ++ | – | +++ | – |
| 3d | – | – | – | ++ |
| 3e | +++ | +++ | – | ++ |
| 3f | +++ | +++ | +++ | ++ |
| 3g | +++ | +++ | – | ++ |
| 3h | ++ | +++ | +++ | ++ |
| 3i | + | – | ++ | – |
| 3j | +++ | – | +++ | – |
| 3k | ++ | +++ | – | – |
| 3l | ++ | ++ | +++ | ++ |
| Penicillin | +++ | +++ | +++ | +++ |

Results are the average mean of three parallel experiments. + = < 5 mm, ++ = > 5 and < 10 mm, +++ = > 10 and < 18 mm, – = No zone

*NA* not applicable

**Table 3** Zone of inhibition of synthesized pyrazolines against some fungal strains

| Entry | Fungal strains | | | |
|---|---|---|---|---|
| | *R. oryzae* | *P. chrysogenum* | *A. niger* | *C. albicans* |
| 3a | ++ | ++ | ++ | ++ |
| 3b | – | ++ | – | – |
| 3c | ++ | ++ | ++ | ++ |
| 3d | – | – | – | – |
| 3e | – | – | – | ++ |
| 3f | ++ | ++ | ++ | ++ |
| 3g | ++ | – | – | – |
| 3h | ++ | ++ | ++ | ++ |
| 3i | ++ | ++ | – | – |
| 3j | – | ++ | – | – |
| 3k | – | – | – | – |
| 3l | – | – | – | – |
| Fluconazole | +++ | +++ | +++ | +++ |

Results are the average mean of three parallel experiments. + = < 5 mm, ++ = > 5 and < 10 mm, +++ = > 10 and < 18 mm, – = No zone

*NA* not applicable

**Table 4** Minimum inhibitory concentration of synthesized pyrazolines against some bacterial strains

| Entry | Bacterial strains | | | |
|---|---|---|---|---|
| | *E. coli* | *B. subtilis* | *S. aureus* | *S. species* |
| 3a | 125 | 125 | 31.2 | 31.2 |
| 3b | 250 | 62.5 | > 250 | 62.5 |
| 3c | 125 | > 250 | 250 | > 250 |
| 3d | > 250 | > 250 | > 250 | 62.5 |
| 3e | 7.8 | 7.8 | > 250 | 125 |
| 3f | 3.9 | 7.8 | 15.6 | 125 |
| 3g | 31.2 | 62.5 | > 250 | 15.6 |
| 3h | 125 | 62.5 | 15.6 | 62.5 |
| 3i | > 250 | > 250 | 62.5 | > 250 |
| 3j | 3.9 | > 250 | 31.2 | > 250 |
| 3k | 125 | 31.2 | > 250 | > 250 |
| 3l | 125 | 125 | 15.6 | 125 |
| Penicillin | 1.95 | 3.9 | 3.9 | 1.95 |

## Antioxidant activity

### % Radical scavenging studies

The 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) and hydroxyl radical (OH) scavenging assays were used to assess the antioxidant activity of the synthesized pyrazoline derivatives. Table 6 provides a summary of the characteristics of the investigations that used percent radical scavenging. All

**Table 5** Minimum inhibitory concentration of synthesized pyrazolines against some fungal strains

| Entry | Fungal strains | | | |
|---|---|---|---|---|
| | *R. oryzae* | *P. chrysogenum* | *A. niger* | *C. albicans* |
| 3a | 250 | 250 | 250 | 250 |
| 3b | > 250 | 250 | > 250 | > 250 |
| 3c | 125 | 250 | 250 | > 250 |
| 3d | > 250 | > 250 | > 250 | > 250 |
| 3e | > 250 | > 250 | > 250 | 125 |
| 3f | 250 | 250 | 125 | 250 |
| 3g | 250 | > 250 | > 250 | > 250 |
| 3h | 250 | 125 | 125 | 250 |
| 3i | 250 | 250 | > 250 | > 250 |
| 3j | > 250 | 250 | > 250 | > 250 |
| 3k | > 250 | > 250 | > 250 | > 250 |
| 3l | > 250 | > 250 | > 250 | > 250 |
| Fluconazole | 1.95 | 1.95 | 1.95 | 3.9 |

**Table 6** Antioxidant properties of synthesized pyrazolines

| Entry | % Free radical scavenging activity | |
|---|---|---|
| | DPPH | OH |
| 3a | 66.2 | 73.9 |
| 3b | 62.8 | 68.9 |
| 3c | 68.4 | 68.7 |
| 3d | 67.5 | 54.6 |
| 3e | 72.4 | 69.4 |
| 3f | 66.4 | 62.4 |
| 3g | 71.4 | 69.7 |
| 3h | 64.5 | 69.4 |
| 3i | 78.9 | 74.5 |
| 3j | 73.4 | 70.4 |
| 3k | 67.5 | 64.7 |
| 3l | 68.5 | 65.8 |
| Ascorbic acid | 87.6 | 84.2 |

Results are the mean values of three independent experiments ± SD

of the synthetic compounds (1 mg/mL) were proven to be effective DPPH reducers. When compared to ascorbic acid, the DPPH radical scavenging activity was found to have a moderate to high scavenging potential. The % DPPH scavenger activity increases in the order of **3i > 3j > 3e > 3g > 3l > 3c > 3d = 3k > 3f > 3a > 3h > 3b**. Comparing the synthesized pyrazoline derivatives to the standard ascorbic acid, it was discovered that they were effective OH radical scavengers with reducing ability up to **74.5%**. The radical reducing capability of the compounds (**3a-l**) was found to be between **54.6%** and **74.5%**. In a series of synthesized pyrazolines,

compound **3i** had the highest scavenger potential of **74.5%**, whereas compound **3d** had the lowest reducing ability of **54.6%**.

## Conclusion

The series of 1,3,5-trisubstituted 2-pyrazoline derivatives are synthesized by treatment of acid hydrazide derivatives with chalcones in PEG-400/AcOH as a green reaction medium. PEG-400 is a reaction media that offers a convenient, non-toxic, thermally stable, and low-cost reaction medium for the synthesis of pyrazolines. This method has various advantages, including cleaner reactions, good product yields, and a simple experimental and work-up procedure, making it a viable and appealing process for pyrazolines' synthesis. The synthesized 1,3,5-trisubstituted 2-pyrazolines were screened for their in vitro antimicrobial activity. Disk diffusion assay was used to explore the zone of inhibition. Resazurin microtiter assay (REMA) was used for MIC evaluation. The findings of the antibacterial and antifungal evaluation suggest that most of the screened compounds exhibit significant activities towards the tested microbial strains. Additionally, the OH and DPPH assay is used to test the 1,3,5-trisubstituted 2-pyrazoline for their capacity to scavenge free radicals. The screened 1,3,5-trisubstituted 2-pyrazolines showed good radical scavenger activity and found good antioxidant agents.

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## Declarations

**Conflict of interest** The authors declare that they do not have any conflict of interest.

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