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Original Article

Development of novel antimicrobial agents: investigating the efficacy of 1,3,5-Triphenyl-2-pyrazoline derivatives

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Abstract

***Background & Aims*:** In this research, a novel series of heterocyclic compounds containing pyrazoline nuclei was synthesized in two steps.

***Materials & Methods*:** In the first step, chalcones were prepared using the Claisen-Schmidt reaction between substituted benzaldehydes and acetophenone derivatives. In the second step, the chalcones were cyclized under acidic conditions with hydrazine derivatives to produce pyrazolines. All compounds were characterized through physical, chromatographic, spectroscopic, and elemental analyses, and their antibacterial properties were tested using seven microorganisms. The minimum inhibitory concentrations of all compounds were determined using the broth dilution method.

***Results*:** Among them, compound 2f (4-(1, 5-diphenyl-4, 5-dihydro-1*H*-pyrazol-3-yl) phenol) exhibited the highest antibacterial and antifungal activity, making it the most potent compound in the series.

***Conclusion*:** These results indicate that increasing the polarity of the compounds enhanced their efficacy against Gram-positive strains, whereas derivatives containing at least one methoxy group in their structure suppressed Gram-negative growth.

***Keywords*:** Antibiotic resistance, Antimicrobial activity, Phenylhydrazine, Pyrazolines, Synthesis

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Introduction

Infectious diseases, such as bacterial and fungal contaminations, are on the rise globally due to immune suppression (1, 2). Malignancy, immunosuppressive medications, HIV infection, surgeries, and old age are all factors that put individuals at increased risk. The problem is exacerbated by the increasing incidence of resistance to the vast majority of antimicrobials currently available. Antimicrobial resistance is a serious public health concern, necessitating the development of innovative and effective antibiotics to address this issue (3, 4).

Heterocyclic compounds are widely recognized for their broad range of biological applications (5, 6). Pyrazolines, nitrogen-containing five-membered heterocyclic compounds have been extensively

employed in industry, medicine, and pesticide chemistry due to their ability to exhibit a wide range of bioactivities (6, 7). Pyrazolines play a crucial role in the development of heterocyclic chemistry and are widely utilized as agents in organic synthesis (8, 9).

They are used in textiles, paper, and fabrics as optical brightening agents, carrier compounds, and emitting materials. 2-pyrazoline has higher hole-transport efficiency and possesses certain photoelectronic properties. These compounds exhibit significant molecular hyperpolarizabilities and are typical heterocyclic transition molecular crystals. This means their nanoparticles may be used to enhance the photofractivity of a two-dimensional array in an applied light field (10, 11). 1, 3, 5-Triaryl-2-pyrazolines have also been used as scintillation solutes. Pyrazoline derivatives with a phenyl group at the 5-position have been found to possess good film-forming qualities, as well as excellent blue photoluminescence, fluorescence, and electroluminescence properties (12).

Pyrazoline compounds exhibit various biological activities, including anti-microbial (13), anti-fungal (10), anti-depressant (14), anti-convulsant (15), anti-tubercular (16), anti-amoebic (17), analgesic (18), tranquilizing (19), muscle relaxant (20), psychoanalytic (15), anti-epileptic (21), anti-inflammatory (22), insecticidal (23), antihypertensive (24), MAO-inhibitory (25), and amine oxidase inhibitory activities (26). These compounds have also been found to possess cytotoxic action, platelet aggregation inhibitory activity (27), herbicidal activity, and a cannabinoid CB1-receptor modulator effect (7). Their derivatives were also discovered to exhibit cytotoxic activity, platelet aggregation inhibitory activity (27), herbicidal activity, and cannabinoid CB1-receptor modulator effects (7).

This paper describes the synthesis, characterization, and biological activity of 1, 3, 5-Triaryl-2-pyrazoline derivatives (namely 2a-2g). The molecules were characterized by IR, ^{1}H NMR and elemental analysis. The in vitro antibacterial and antifungal activities of compounds 2a and 2g were investigated against a panel of gram-positive and gram-negative bacteria, as well as specific fungal species.

Materials & Methods

1. Chemistry

1.1. General Procedure for the Synthesis of 1, 3-Diaryl-2-Propen-1-Ones (1a-g)

The Claisen-Schmidt reaction was used to synthesize various substituted chalcones. A mixture of the appropriate derivatives of both ketone (1 mmol) and aldehyde (1 mmol) was utilized in a 100 mL round-bottomed flask in 95% ethanol (25mL). The solution was stirred magnetically at room temperature. Slow addition of 40% NaOH solution (10 mL) was added slowly (5). In most instances, a yellow precipitate formed immediately. The solid was filtered off, washed with cold water, dried and recrystallized from ethanol. Reactions were monitored by thin layer chromatography (TLC), and the structures of the isolated products were deduced based on infrared radiation (IR), Nuclear Magnetic Resonance (^{1}H NMR), and elemental analyses. The IR spectrum of compounds 1a-g, used as representative compounds of this series, showed an absorption band at 1650–1700 cm^{-1}, associated with the stretching vibration of the carbonyl group from the α,β-unsaturated derivatives. In the ^{1}H NMR spectra chalcones showed peaks in the region of δ 7.14–7.26 (CO–CH) and 7.53–7.58 (Ar-CH). The presence of CH = CH protons in the ^{1}H NMR spectra, of each molecule, as well as two doublets at 7.53 and 7.83 ppm with a coupling constant J > 15 Hz, ascribed to Hβ and Hα, respectively, indicates that the compounds were made with an (*E*)-configuration carbon-carbon double bond.

1.2. General Procedure for the Synthesis of Pyrazolines (2a-g)

General Procedure for Synthesis of 1, 3-Diaryl-2-Propen-1-Ones

Equal quantity of appropriate derivatives of 1, 3-diaryl-2-propen-1-ones (1 mmol) and phenylhydrazine (2 mmol) was taken in a 100 mL round-bottomed flask and acetic acid was added to it. The reaction mixture was refluxed for 8 hours, then cooled to room temperature, resulting in precipitation. The precipitate was filtered, washed step by step with water, and vacuum dried. In some cases where no precipitate formed after cooling to room temperature, precipitation was induced by adding

water (5, 7). Reactions were monitored by TLC, and the structures of the isolated products were deduced based on IR, ^{1}H NMR and elemental analyses. The IR spectrum of compounds 2a-g, used as representative compounds of this series, showed an absorption band at 1590-1620 cm^{-1} associated with the C = N stretch of the pyrazoline ring, 1495-1520 cm^{-1} (C = C stretch of the aromatic ring), and 1120-1220 cm^{-1} (C-N stretch of the pyrazoline ring).

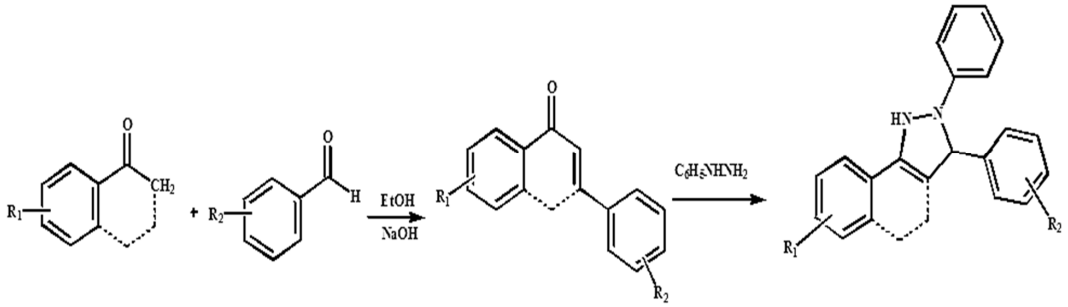

Fig. 1. Synthesis of chalcone and pyrozoline derivatives

2. Antimicrobial and Antifungal Activity Evaluation

Antimicrobial tests were performed by measuring the minimum inhibitory concentrations (MICs) and minimum bactericidal concentrations (MBCs) using the broth dilution method against *Staphylococcus aureus* ATCC 25923, *Bacillus subtilis* ATCC 12711, *Escherichia coli* ATCC 25922, *Burkholderia cepacia* ATCC 10673, *Pseudomonas aeruginosa* ATCC 27853, *Mycobacterium smegmatis* ATCC 607 and *Candida albicans* ATCC 170. The activity of the synthesized compounds was compared with standard antibiotics including Ciprofloxacin, Gentamicin, Tetracycline, Levofloxacin, Azithromycin, Amikacin, Fluconazole and Rifampicin. Dimethyl sulfoxide (DMSO), used as the solvent for the synthesized compounds, served as the negative control (Table 1).

Two-fold dilutions of each compound, ranging from 1 mg/mL to 0.001 mg/mL (1 g/mL) were prepared in DMSO. Ten microliters of microbial broth culture, adjusted to a turbidity equivalent to 0.5 McFarland standard (approximately 1.5×10^8 CFU/mL) of the tested microbial strain, was added to each tube and incubated at 37 °C for 24-48 hours (28). The minimum inhibitory concentration (MIC) was defined as the lowest concentration of the synthesized drug that prevents visible growth of the tested microbiological strain. The minimum bactericidal concentration (MBC) refers to the lowest concentration of the agent that completely inhibits the growth of the test organism after subculturing onto a medium without any antimicrobial agents. To determine the MBC, 10 µl from each tube was inoculated onto the surface of a Muller-Hinton agar (MHA) plate and incubated overnight at 37°C.

Results

According to Table 1, compounds 2a, 2b, 2f, and 2g were efficacious against *Candida albicans* ATCC 170. Compound 2g exhibited antibacterial activity against both gram-positive and gram-negative strains, including *Staphylococcus aureus* ATCC 25923, *Bacillus subtilis* ATCC 12711, and *Pseudomonas aeruginosa* ATCC 27853. Compound 2f demonstrated higher activity against *Mycobacterium smegmatis* ATCC 607, *Staphylococcus aureus* ATCC 25923, and *Bacillus subtilis* ATCC 12711 at concentrations of 16, 8, and 4 µg/ml, respectively. Interestingly, *Escherichia coli* ATCC 25922 showed resistance to all newly synthesized compounds.

Table 1. Minimum inhibitory concentration (MIC; µg/µl) of novel compounds in comparison with antibiotics

Compound number	Minimum inhibitory concentration of the synthesized derivatives (µg/µl)						
	E.coli	***M.smegmatis***	***S.aureus***	***P.aeroginosa***	***B.cepacia***	***B.subtilis***	***C.albicans***
2a	-	-	-	-	-	-	1
2b	-	-	-	-	-	-	1
2c	-	-	-	-	-	-	-
2d	-	-	-	-	-	-	1
2e	-	-	-	-	-	-	-
2f	-	0.016	0.008	0.25	1	0.004	0.25
2g	-	-	0.5	0.25	-	0.125	0.5
Tetracycline	0.008	-	0.008	-	-	-	-
Ciprofloxacin	0.002	-	0.002	0.002	-	0.00005	-
Levofloxacin	-	-	-	0.004	0.004	-	-
Amikacin	0.032	-	-	0.032	-	-	-
Fluconazole	-	-	-	-	-	-	0.016-0.032
Rifampicin	-	-	-	-	-	-	-
Gentamicin	0.008	0.5	0.008	0.008	-	0.00025	-
Azithromycin	-	-	0.004	-	-	-	-

Discussion

Seven novel compounds containing the phenyl pyrazoline moiety (2a-g) were synthesized in this work without the use of column chromatography or TLC plates to purify the target. These phenyl pyrazoline derivatives were synthesized and characterized with the help of spectral data (IR, 1H NMR) and elemental analysis studies. The antibacterial and antifungal properties of the target compounds were also evaluated against a variety of microorganisms. Standard procedures were used to determine the MIC of all newly synthesized phenyl pyrazoline derivatives. The antibacterial activity of phenyl pyrazoline derivatives (2f and 2g) was found to be superior to that of the other produced compounds. As a result, we may infer that these phenylpyrazoline compounds exhibit significant antibacterial activity.

Experimental

1. Chemistry—General Aspects

Chemicals and all solvents used in this study were purchased from Merck and Aldrich Chemical. Melting points were determined using a Thermo Fisher Scientific 9300 capillary apparatus and are uncorrected. The IR spectra were obtained using a Perkin Elmer Spectrum Shimadzu 470 spectrophotometer (potassium bromide disks). ^{1}H NMR spectra were recorded using a Bruker 500 spectrometer, and chemical shifts are expressed as δ (ppm) with tetramethylsilane (TMS) as the internal standard. The newly synthesized compounds' ^{1}H NMR spectra in chloroform solutions were measured using a Bruker DRX-500 AVANCE (at 500.1 and 125.8 MHz), and chemical shifts were reported as δ (ppm) relative to TMS as the internal standard. Mass spectra were recorded on an Agilent

Technologies (HP) 5973 mass spectrometer operating at an ionization potential of 20 eV. Elemental analyses were performed using a Perkin–Elmer 2400 CHN elemental analyzer for all synthesized compounds and were within ± 0.4% of theoretical values. TLC on F254 silica-gel precoated sheets (Merck, Darmstadt, Germany) was used to monitor the reactions, and each of the purified compounds revealed a single spot.

1.1. General Procedure for the Synthesis of Chalcones 1a-g

1.1.1. 1, 3-Diphenylpropenone (1a)

From acetophenone and benzaldehyde; White powder, yield (82%), mp 54-56 °C; IR (KBr) νmax/cm^{-1}: 3030 (C-H aromatic), 1705 (C = O), 1600 (ring C = C); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.02 (d, 2H, J = 7.5 Hz), 7.81 (d, 1H*β*, J = 15.5 Hz), 7.48–7.64 (m, 6H, Ar-H), 7.41–7.42 (m, 3H, Ar-H).

1.1.2. 1-(4-Chlorophenyl)-3-(4-(dimethylamino) phenyl) prop-2-en-1-one (1b)

From 4-chloroacetophenone and 4-dimethylaminobenzaldehyde; Light yellow powder, yield (75%), mp 66-68 °C; IR (KBr) ν_{max}/cm^{-1}: 1700 (C = O), 1710 (C = C), 2980 (Ar C-H), 3400 (R-NH_2); 1HNMR (CDCl3) δ (ppm): 7.92 (d, 2H, J = 3.6 Hz), 7.78 (d, 1Hβ, J = 15.5 Hz), 7.53 (d, 2H, J = 3.6 Hz), 7.45 (d, 1H, J = 3.6 Hz), 7.27 (d, 2Hα, J = 15.5 Hz), 3.05 (s, 6H, $N(CH_3)_2$).

1.1.3. 3-(4-(dimethylamino) phenyl)-1-(4-nitrophenyl) prop-2-en-1-one (1c)

From 4-nitroacetophenone and 4-dimethylaminobenzaldehyde; Red powder, yield (88%), mp: 70-72°C; IR (KBr) ν_{max}/cm-1: 1690 (C = O), 1620 (C = C) , 1550 (R-NO2), 1HNMR ($CDCl_3$) δ (ppm): 8.34 (d, 2H, J = 8.5 Hz), 8.12 (d, 2H, J = 8.5 Hz),7.84 (d, 1Hβ, J = 15.5 Hz), 7.57(d, 2H, J = 8 Hz), 7.26 (d, 1Hα, J = 15.5 Hz), 6.72 (d, 1H, J = 8.5 Hz).

1.1.4. 3-(4-(dimethylamino) pheny l)-1-(4-methoxyphenyl) prop-2-en-1-one (1d)

From 4-methoxyacetophenone and 4-dimethylaminobenzaldehyde; Yellow powder, yield (95%), mp: 47-49°C; IR (KBr) ν_{max}/cm^{-1}: 3020 (Ar C-H), 1705 (C = O), 1550 (C = C), 1250 (C-O), ^{1}HNMR ($CDCl_3$) δ (ppm): 8.02 (d, 2H, J= 8 Hz), 7.77 (d, 1Hβ, J = 15.5 Hz), 7.54 (d, 2H, J = 8 Hz), 7.34 (d, 1Hα, J = 15.5 Hz), 6.96 (d, 2H, J = 8 Hz), 6.69 (d, 2H, J = 8 Hz), 3.88 (s, 3H, -OCH_3), 3.04 (s, 6H, $N(CH_3)_2$).

1.1.5. 3-(4-(dimethylamino) phenyl)-1-phenylprop-2-en-1-one (1e)

From acetophenone and 4-dimethylaminobenzaldehyde; Yellow powder, yield (90%),

mp:112-114°C; IR (KBr) ν_{max}/cm^{-1}: 3010 (C-H aromatic), 1705 (C = O), 1600 (ring C = C), ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.03 (d, 2H, J = 7.5 Hz), 7.77 (d, 1Hβ, J = 15.5 Hz), 7.34–7.60 (m, 6H, Ar-H), 6.69 (d, 2H, J = 7.5 Hz), 3.04 (s, 6H, -$N(CH_3)_2$).

1.1.6. 1-(4-hydroxyphenyl)-3-phenylprop-2-en-1-one (1f)

From 4-hydroxyacetophenone and benzaldehyde; Light yellow powder, yield (80%), mp:176-178°C; IR (KBr) ν_{max}/cm^{-1}: 3305 (OH), 3073 (C-H aromatic), 1705 (C = O), 1495 (ring C = C), 1223 (C-O), ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.01 (d, 2H, J = 8 Hz), 7.81 (d, 1Hβ, J = 15.5 Hz), 7.63 (d, 2H, J = 5.5 Hz), 7.54 (d, 1Hα, J = 15.5 Hz), 7.41(m, 3H, Ar-H), 6.97 (d, 2H, J = 8 Hz), 6.73 (s, 1H, -OH).

1.1.7. 2-(4-(dimethylamino) benzylidene)-3, 4-dihydronaphthalen-1(2H)-one (1g)

From 3,4-dihydronaphthalen-1-(2H)-one and 4-dimethylaminobenzaldehyde; Orange powder, yield (60%), mp:110-114°C; IR (KBr)) ν_{max}/cm^{-1}: 2922 (C-H), 1650 (C = O), 1598 (C = C), 1448 (C_6H_6), 1191 (C-N), ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.10 (d, 1H, J = 7.9 Hz), 7.86 (s, 1H), 7.44 (t, 2H, J = 8.6, 15.7 Hz), 7.34 (t, 1H, J = 7.25, 15.15 Hz), 7.23 (d, 2H, J = 7.55 Hz), 6.73 (d, 2H, J = 8.85 Hz), 3.18 (t, 2H, J = 6.95, 13.25 Hz), 3.03 (s, 6H), 2.94 (t, 2H, J = 6.8, 13.15 Hz).

1.2. General Procedure for Preparation of Phenyl Pyrazoline Derivatives (2a-g)

Equal quantities of the proper derivatives of 1,3-diaryl-2-propene-1-ones (1 mmol) and phenylhydrazine (2 mmol) were taken in a 100 mL round-bottomed flask using acetic acid. The reaction mixture was refluxed for 8 hours to obtain a precipitate, then allowed to cool to room temperature. The precipitate was separated and washed using water, and the residue was dried under

vacuum. In some cases, when there was no precipitate observed upon cooling to room temperature, water was added to induce precipitation.

1.2.1. 1, 3, 5-Triphenyl-4, 5-dihydro-1H-pyrazole (2a)

Green powder, yield (80%), mp:133-135°C; IR(KBr) ν_{max}/cm^{-1}: 3031 (Ar-H), 1455 (CH_2), 1597 (C = N pyrazoline), 1492 (C = C), 1268 (C-N); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.73 (d, 2H, J = 7.75 Hz), 7.39 (d, 2H, J = 7.25, 14.75 Hz), 7.29 (m, 6H), 7.18 (t, 2H, J = 7.75, 15.45 Hz), 7.07 (d, 2H, J = 8.2 Hz), 6.78 (t, 1H, J = 7.35, 14.7 Hz), 5.28 (dd, 1H, J = 7.25, 12.45 Hz), 3.85 (dd, 1H, J = 12.35, 17.15 Hz), 3.15 (dd, 1H, J = 7.25, 17.1 Hz).

1.2.2. 4-(3-(4-Chlorophenyl)-1-phenyl-4, 5-dihydro-1H-pyrazol-5-yl)-N, N-dimethylaniline (2b)

Cream powder, yield (70%), mp:145-147°C; IR (KBr) ν_{max}/cm^{-1}: 2918 (C-H), 1522 (C-C), 1597 (C = N pyrazoline), 1496 (C = C), 1385 (CH_3), 1239 (C-N), 822 (C-Cl); 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.62 (d, 2H, J = 8.8 Hz), 7.33 (d, 2H, J = 8.8 Hz), 7.17 (m, 4H), 7.08 (d, 2H, 8 Hz), 6.77 (t, 1H, J = 7.2, 14.4 Hz), 6.69 (t, 1H, J = 4, 7.2 Hz), 5.20 (dd, 1H, 7.2, 12 Hz), 3.73 (dd, 1H, J = 12, 16.8 Hz), 3.07 (dd, 1H, J = 7.2, 16.8 Hz), 2.91 (s, 6H).

1.2.3. N, N-Nimethyl-4-(3-(4-nitrophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl) aniline (2c)

Red powder, yield (80%), mp: 208-210°C; IR (KBr) ν_{max}/cm^{-1}: 2929 (C-H), 1593 (C = N), 1549 (C = C), 1500 (N-O), 1326 (Ar-NO_2), 1395 (CH_3), 1248 (C-N); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.24 (d, 2H, J = 8.4 Hz), 7.82 (d, 2H, J = 8.45 Hz), 7.76 (d, 2H, J = 7.85 Hz), 7.45 (d, 2H, J = 7.8 Hz), 7.22 (d, 2H, j = 7.85 Hz), 7.04 (d, 2H, J = 8.1 Hz), 6.89 (t, 1H, j = 7.2, 14.6 Hz), 5.49 (t, 1H, J = 9.25, 15.4 Hz), 3.91 (dd, 1H, j = 12.6, 16.85 Hz), 3.14 (s, 8H).

1.2.4. 4-(3-(4-Methoxyphenyl)-1-phenyl-4, 5-dihydro-1H-pyrazol-5-yl)-N, N-dimethylaniline (2d)

Cream powder, yield (75%), mp: 158-160°C; IR (KBr) ν_{max}/cm^{-1}: 2929 (C-H),1596 (C = N), 1522 (C-C), 1497 (C = C), 1388 (CH_3), 1249 (C-N), 1036 (Ar-O-CH_3); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.65 (d, 2H, J = 8.8 Hz), 7.16 (dd, 4H, J = 8.8, 14.4 Hz), 7.07 (d, 2H, j = 7.6 Hz), 6.89 (d, 2H, J = 8.8 Hz), 6.72 (m, 3H), 5.13 (dd, 1H, J = 7.6, 12.4 Hz), 3.81 (s, 3H), 3.73 (dd, 1H, J = 12.4, 17.2 Hz), 3.07 (dd, 1H, J = 7.6, 17.2Hz), 2.93(m, 6H).

1.2.5. 4-(1, 3-Diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-N, N-dimethylaniline (2e)

Cream powder, yield (76%), mp: 196-198°C; IR (KBr) ν_{max}/cm^{-1}: 3028 (Ar-H), 1596 (C = N), 1497 (C = C), 1394 (CH_3), 1150 (C-N); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.72 (dd, 4H, J = 8.1, 15.45 Hz), 7.47 (d, 2H, J = 8.15 Hz), 7.39 (t, 2H, J = 7.55, 15.1 Hz), 7.35 (d, 1H, J = 7.2 Hz), 7.20 (t, 2H, J = 7.85, 15.6 Hz), 7.00 (d, 1H, J = 8.1 Hz), 6.81 (t, 1H, J = 7.4, 14.8 Hz), 5.34 (dd, 1H, J = 6.85, 12.5 Hz), 3.88 (dd, 1H, J = 12.5, 17.2 Hz), 3.13(m, 8H).

1.2.6. 4-(1, 5-Diphenyl-4, 5-dihydro-1H-pyrazol-3-yl) phenol (2f)

Orange powder, yield (40%), mp: 140-145°C; IR (KBr) ν_{max}/cm^{-1}: 3435 (O-H), 3249 (Ar-H), 2926 (C-H), 1596 (C = N), 1499 (C = C), 1458 (CH_2), 1248 (C-N), 1111 (C-O); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.61 (d, 2H, J = 8.25 Hz), 7.35 (s, 1H), 7.33 (d, 6H, J = 4.7 Hz), 7.27(t, 1H, J = 2.45, 4.65 Hz), 7.16 (t, 2H, J = 7.8, 15.5 Hz), 6.83 (d, 2H, J = 8.75 Hz), 5.23 (s, 1H), 3.80 (s, 1H), 3.10 (d, 1H, J = 13.7 Hz).

1.2.7. N, N-Dimethyl-4-(2-phenyl-3, 3a, 4, 5-tetrahydro-2H-benzo(g)indazol-3-yl) benzamine (2g)

Nut brown powder, yield (45%), mp: 124-125°C; IR (KBr) ν_{max}/cm^{-1}: 3031 (Ar-H), 1598 (C = N), 1496 (C = C), 1373 (CH_3), 1242 (C-N); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.60 (d, 1H, J = 8.8 Hz), 7.2 (m, 3H), 7.04 (d, 2H, j = 8 Hz), 6.94 (d, 2H, J = 7.2 Hz), 6.56 (m, 3H), 6.43 (dd, 2H, J = 7.6 Hz), 3.90 (d, 1H, J = 7.2 Hz), 2.85 (s, 6H), 2.55 (m, 2H), 2.1 (d, 1H, J = 8.8), 1.6 (m, 2H).

Conclusion

This study indicates that increasing the polarity of the compounds enhanced their efficacy against Gram-positive strains, whereas derivatives containing at least one methoxy group in their structure suppressed Gram-negative growth.

An optimal combination of hydrophilic and lipophilic character in these molecules may enhance membrane penetration, thus increasing their potential for cell integrity disruption.By increasing the lipophilicity of the compounds, we expected to observe anti-Bacillus activity. Accordingly, compound 2f exhibited good activity against Bacillus subtilis ATCC 1271, and compound 2g showed antifungal activity against Candida albicans ATCC 170. Therefore, determining the polarity of 1,3,5-triphenyl-2-pyrazoline derivatives is critical in the identification of new antibacterial compounds.

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Authors' Contributions

Maryam Allahyari-Devin was responsible for the management and coordination of the research project. She created the figures and tables, conducted the research, and contributed to the review and editing of the manuscript. Yaeghob Sharifi provided oversight and guidance for the research, managed data curation, and participated in the review and editing of the paper. Sevda Afzal Ahangaran developed the research idea and study design, collected data and conducted experiments, performed data analysis, and prepared the initial draft of the manuscript.

Data Availability

The data that support the findings of this study are available on request from the corresponding author.

Conflict of Interest

There are no conflicts of interest between the authors regarding the contents of this paper.

Ethical Statement

The code of ethics for this article is (IR.UMSU.REC.1395).

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References

1. Olczak-kowalczyk D, Daszkiewicz M, Krasuska-Sławińska E, Dembowska-Bagińska B, Gozdowski D, Daszkiewicz P, et al. Bacteria and Candida yeasts in inflammations of the oral mucosa in children with secondary immunodeficiency. Journal of oral pathology & medicine: official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology 2012; 41:568-76. doi: 10.1111/j.1600-0714.2012.01146.x.
2. Baker RE, Mahmud AS, Miller IF, Rajeev M, Rasambainarivo F, Rice BL, et al. Infectious disease in an era of global change. Nature Reviews Microbiology 2021; doi: 10.1038/s41579-021-00639-z.
3. Tuite N, Lacey K. Overview of Invasive Fungal Infections. Methods in molecular biology (Clifton, NJ) 2013; 968:1-23. doi: 10.1007/978-1-62703-257-5_1.
4. Dhingra S, Rahman NAA, Peile E, Rahman M, Sartelli M, Hassali MA, et al. Microbial Resistance Movements: An Overview of Global Public Health Threats Posed by Antimicrobial Resistance, and How Best to Counter. Frontiers in Public Health 2020; 8 doi: 10.3389/fpubh.2020.535668.
5. Agrawal M, Sonar PK, Saraf SK. Synthesis of 1,3,5-trisubstituted pyrazoline nucleus containing compounds and screening for antimicrobial activity. Med Chem Res 2012; 21(11):3376-81. doi: 10.1007/s00044-011-9871-2.
6. Kerru N, Gummidi L, Maddila S, Gangu KK, Jonnalagadda SB. A Review on Recent Advances in Nitrogen-Containing Molecules and Their Biological Applications. Molecules 2020; 25(8):1909.
7. Sapnakumari M, Narayana B, Gurubasavarajswamy P, Sarojini B. Design, synthesis, and pharmacological evaluation of new pyrazoline derivatives. Monatshefte für Chemie - Chemical Monthly 2015; 146:1015-24. doi: 10.1007/s00706-014-1371-x.
8. Praceka MS, Megantara S, Maharani R, Muchtaridi M. Comparison of various synthesis methods and synthesis parameters of pyrazoline derivates. Journal of advanced

pharmaceutical technology & research 2021; 12(4):321-6. doi: 10.4103/japtr.JAPTR_252_21.

9. Hamid Reza S, Yadollah Y, Ali E, Mehdi A. Extraction and determination of 2-pyrazoline derivatives using liquid phase microextraction based on solidification of floating organic drop. Journal of Pharmaceutical and Biomedical Analysis 2008; 48(4):1059-63. doi: https://doi.org/10.1016/j.jpba.2008.07.029.
10. Munawar M, Muhammad A, Makshoof A, Paul G. Synthesis and antimicrobial activity of quinoline-based 2-pyrazolines. Chemical Papers 2008; 62(3):288--93. doi: doi:10.2478/s11696-008-0025-z.
11. Yin J, Wang Z. Ordered Self-Assembling of Tetrahedral Oxide Nanocrystals. Physical Review Letters 1997; 79 doi: 10.1103/PhysRevLett.79.2570.
12. Sarojini B, Vidyagayatri M, Raj D, B.R B, Hanumanthappa M. DPPH Scavenging Assay of Novel 1,3-disubstituted-1H-pyrazol-5-ols and their in silico Studies on Some Proteins Involved in Alzheimer's Disease Signaling Cascade. Letters in Drug Design & Discovery 2010; 7:214-24. doi: 10.2174/157018010790596588.
13. Sano T, Fujii T, Nishio Y, Hamada Y, Shibata K, Kuroki K. Pyrazoline Dimers for Hole Transport Materials in Organic Electroluminescent Devices. Japanese Journal of Applied Physics 1995; 34(Part 1, No. 6A):3124-7. doi: 10.1143/jjap.34.3124.
14. Rajendra Prasad Y, Lakshmana Rao A, Prasoona L, Murali K, Ravi Kumar P. Synthesis and antidepressant activity of some 1,3,5-triphenyl-2-pyrazolines and 3-(2″-hydroxy naphthalen-1″-yl)-1,5-diphenyl-2-pyrazolines. Bioorganic & Medicinal Chemistry Letters 2005; 15(22):5030-4. doi: 10.1016/j.bmcl.2005.08.040.
15. Parmar SS, Pandey BR, Dwivedi C, Harbison RD. Anticonvulsant Activity and Monoamine Oxidase Inhibitory Properties of 1,3,5-Trisubstituted Pyrazolines. Journal of Pharmaceutical Sciences 1974; 63(7):1152-5. doi: 10.1002/jps.2600630730.
16. Vamaraju HB, Manna S, Srinivasan K, Giliyaru V. Synthesis and biological evaluation of 1,3,5-trisubstituted pyrazolines bearing benzofuran. Indian Journal of Heterocyclic Chemistry 2004; 13:253-6.
17. Abid M, Azam A. Synthesis and antiamoebic activities of 1-N-substituted cyclised pyrazoline analogues of thiosemicarbazones. Bioorganic & medicinal chemistry 2005; 13:2213-20. doi: 10.1016/j.bmc.2004.12.050.
18. Sahu S, Banerjee M, Samantray A, Behera C, Azam A. Synthesis, Analgesic, Anti-inflammatory and Antimicrobial Activities of Some Novel Pyrazoline Derivatives. Tropical Journal of Pharmaceutical Research (ISSN: 1596-5996) Vol 7 Num 2 2008; 7 doi: 10.4314/tjpr.v7i2.14664.
19. Patel V, Desai K. Eco-friendly synthesis of fluorine-containing pyrazoline derivatives over potassium carbonate. Arkivoc 2004; 2004.
20. Chen Y, Lam Y, Lai Y-H. Solid-Phase Synthesis of Pyrazolines and Isoxazolines with Sodium Benzenesulfinate as a Traceless Linker. Organic Letters 2003; 5(7):1067-9. doi: 10.1021/ol0340888.
21. Soni N, Pande K, Kalsi R, Gupta TK, Parmar SS, Barthwal JP. Inhibition of rat brain monoamine oxidase and succinic dehydrogenase by anticonvulsant pyrazolines. Res Commun Chem Pathol Pharmacol 1987; 56(1):129-32.
22. Smith SR, Denhardt G, Terminelli C. The anti-inflammatory activities of cannabinoid receptor ligands in mouse peritonitis models. European Journal of Pharmacology 2001; 432(1):107-19. doi: 10.1016/S0014-2999(01)01477-7.
23. Sakthinathan SP, Vanangamudi G, Thirunarayanan G. Synthesis, spectral studies and antimicrobial activities of some 2-naphthyl pyrazoline derivatives. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 2012; 95:693-700. doi: 10.1016/j.saa.2012.04.082.
24. Turan-Zitouni G, Chevallet P, Kiliç FS, Erol K. Synthesis of some thiazolyl-pyrazoline derivatives and preliminary investigation of their hypotensive activity. European Journal of Medicinal Chemistry 2000; 35(6):635-41. doi: 10.1016/S0223-5234(00)00152-5.
25. Chimenti F, Fioravanti R, Bolasco A, Manna F, Chimenti P, Secci D, et al. Synthesis, molecular modeling studies and selective inhibitory activity against MAO of N1-propanoyl-3,5-diphenyl-4,5-dihydro-(1H)-pyrazole derivatives. European journal of medicinal chemistry

2008; 43(10):2262-7. doi: 10.1016/j.ejmech.2007.12.026.

26. Reddy MVR, Billa VK, Pallela VR, Mallireddigari MR, Boominathan R, Gabriel JL, et al. Design, synthesis, and biological evaluation of 1-(4-sulfamylphenyl)-3-trifluoromethyl-5-indolyl pyrazolines as cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) inhibitors. Bioorganic & Medicinal Chemistry 2008; 16(7):3907-16. doi: 10.1016/j.bmc.2008.01.047.
27. Hasan A, Abbas A, Akhtar M. Synthesis, Characterization and Fluorescent Property Evaluation of 1,3,5-Triaryl-2-pyrazolines. Molecules (Basel, Switzerland) 2011; 16:7789-802. doi: 10.3390/molecules16097789.
28. Andrews JM. Determination of minimum inhibitory concentrations. Journal of antimicrobial Chemotherapy 2001; 48(suppl_1):5-16.