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Synthesis, Biological Activities, and ADME Investigation of Acetyl Pyrazoline Derivatives from Different Chalcones

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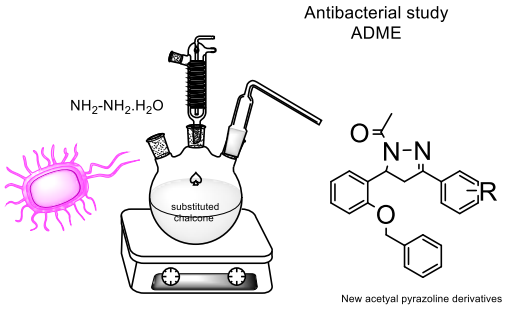
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ABSTRACT

This study focused on the synthesis of a new series of compounds, which are synthesised from chalcone derivatives by using different methods. Acetyl pyrazoline derivatives synthesised in a two-step reaction using 2-benzyloxybenzaldehyde react with a series of different ketones by Claisen-Schmidt condensation in the presence of a base to give chalcone. This series of chalcone intermediates underwent condensation by refluxing with hydrazine hydrate in the presence of glacial acetic acid to give acetyl pyrazoline derivatives (CHP-01 to CHP-11). The targeted compound was established and confirmed using melting point analysis alongside FTIR, ^{1}H-NMR, ^{13}C-NMR, and mass spectroscopy. This compound shows biological and pharmacological significance against tetracycline as a standard drug. In the presence of methoxy and halogen compounds, potent antimicrobial activities against *Bacillus* bacterial zones (CHP-01 and CHP-09). ADME prediction was carried out using SwissADME, and the results indicate highly favourable pharmacokinetic properties. Most of the compounds show high gastrointestinal absorption (CHP-01 to CHP-11) with favourable oral bioavailability and drug-likeness parameters.

Keywords: Chalcone, Hydrazine hydrate, Acetyl pyrazoline, Antimicrobial activity, SwissADME.

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Graphical Abstract

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1. INTRODUCTION

Chalcone derivatives are a class of chemical molecules that provide the backbone of several biological functions [1]. They are distinguished by their 1,3-diphenyl-2-propen-1-one structure [2] Chalcones and their derivatives are found in different plants and fruits in nature. [3] The field of medicine heavily relies on chalcones having an N-heterocyclic moiety, including pyrrole [4], pyrazole [5], imidazole [6], thiazole [7], oxazole [8], isoxazole [9], pyridine [10], pyrazoline [11], indole [12], benzothiazole [13], benzimidazole [14], and quinoline [15] scaffolds. When heterocyclic and chalcone structures are combined, molecules with increased medicinal potential may result. [16] Many chalcone-heterocycle hybrids have shown promise as potential next-generation medications, especially for leishmaniasis, cancer, and malaria. [17] A common method for creating chalcones is the Claisen-Schmidt condensation, in which an aromatic aldehyde and acetophenone (or a related ketone) combine when a base is present. [18] By reacting with substances such as urea, thiourea, hydroxylamine, hydrazine hydrate, phenyl hydrazine, etc., chalcone heterocyclic ring synthesis transforms a chalcone structure into a molecule with a ring [19].

In this, all pyrazoline derivatives draw attention due to their biological and therapeutic action against various diseases like cancer, malaria, and leishmaniasis [20]. Pyrazolines, which have the general formula $C_3H_6N_2$, are five-membered heterocycles with two neighboring nitrogen atoms. They are usually produced by cyclisation processes from chalcones and hydrazine derivatives. [21] Pyrazoline derivatives are synthesised from chalcones via different methods like Claisen-Schmidt condensation, microwave-assisted synthesis, ultrasound-assisted synthesis, solvent-free synthesis, and one-pot multicomponent synthesis. [22] Derivatives of pyrazolines have a variety of biological activities, such as antibacterial [23], anticancer [24], anti-inflammatory [25], and antidiabetic [26] effects. Additionally, they have antiviral, antileishmanial, and antioxidant properties [27]. In this work, we try to synthesize some new derivatives of chalcone by the condensation method. We prepared a series of compounds by reacting different ketones with 2-(benzyloxy) benzaldehyde in the presence of a base in methanol to give chalcones. Chalcones react with hydrazine hydrate in glacial acetic acid to give acetyl pyrazoline. There are some drugs in which pyrazoline derivatives are used. Biological activities of this series of compounds were evaluated against Gram-positive and Gram-negative bacteria in DMSO using tetracycline as a standard drug. In this series, we also predicted ADME properties of different acetyl pyrazoline derivatives using SwissADME, and the results show good pharmacokinetic properties.

2. RESULTS AND DISCUSSION

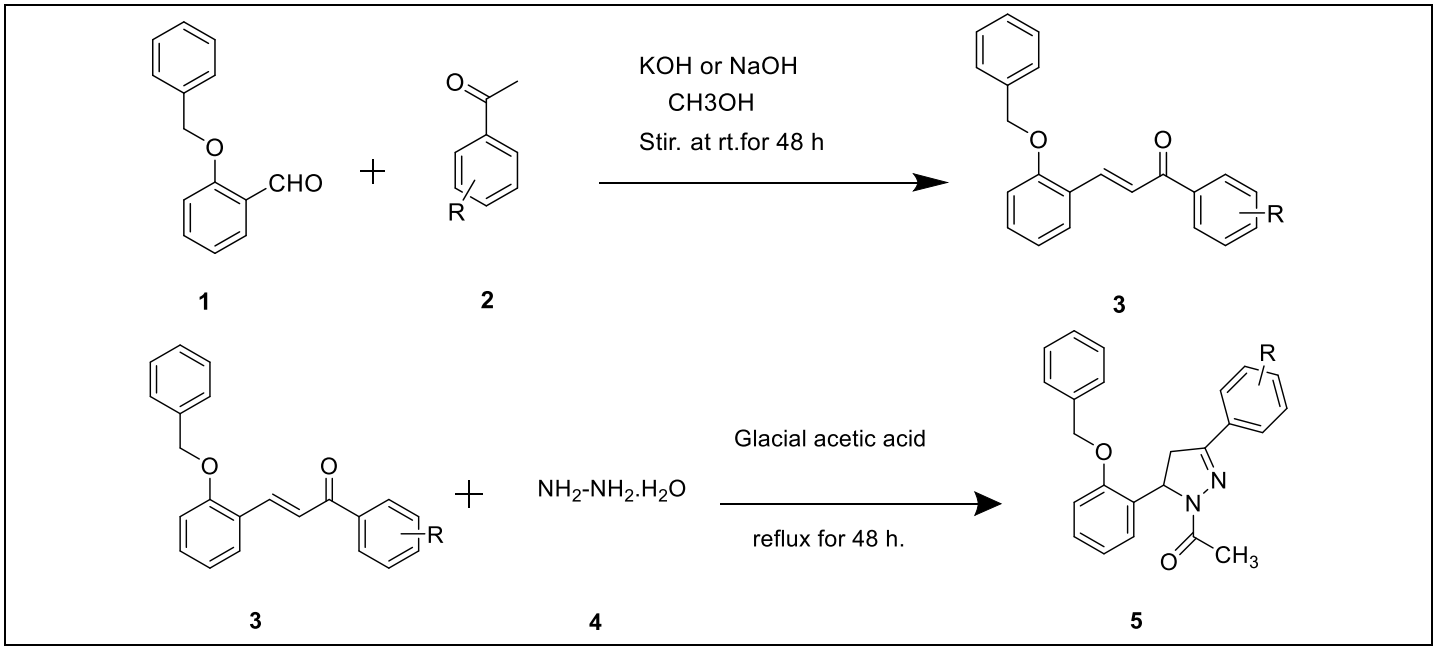
2.1. Chemistry and Spectroscopic Discussion

First, prepare chalcone by using 2- (benzyloxy) benzaldehyde **(1)** with a series of different ketones **(2)** in the presence of methanol and base (NaOH/KOH) under stirring. After completion of the reaction, the chalcone product (**3**) was poured into crushed ice water, neutralized with dilute HCl, the residue was filtered, and washed with water. Then recrystallized from methanol. The resulting chalcone was then reacted with hydrazine hydrate (**4**) to undergo cyclisation in the presence of glacial acetic acid, forming the pyrazoline derivative (**5**). (Scheme-1)

The Structure of compound (CHP-01) was confirmed by spectral data (MS, IR, NMR). The analytical data of the compound are $C_{25}H_{24}N_2O_3$ (M/Z =401). ^{1}H NMR data reveal that the two hydrogens of the pyrazoline ring show a doublet of doublets at (2.92, 3.59 and 5.64) due to the chiral centre present in the 5-membered ring and one singlet at (-OCH3 2.44); the aromatic region gives signals between 6.79 and 7.65.

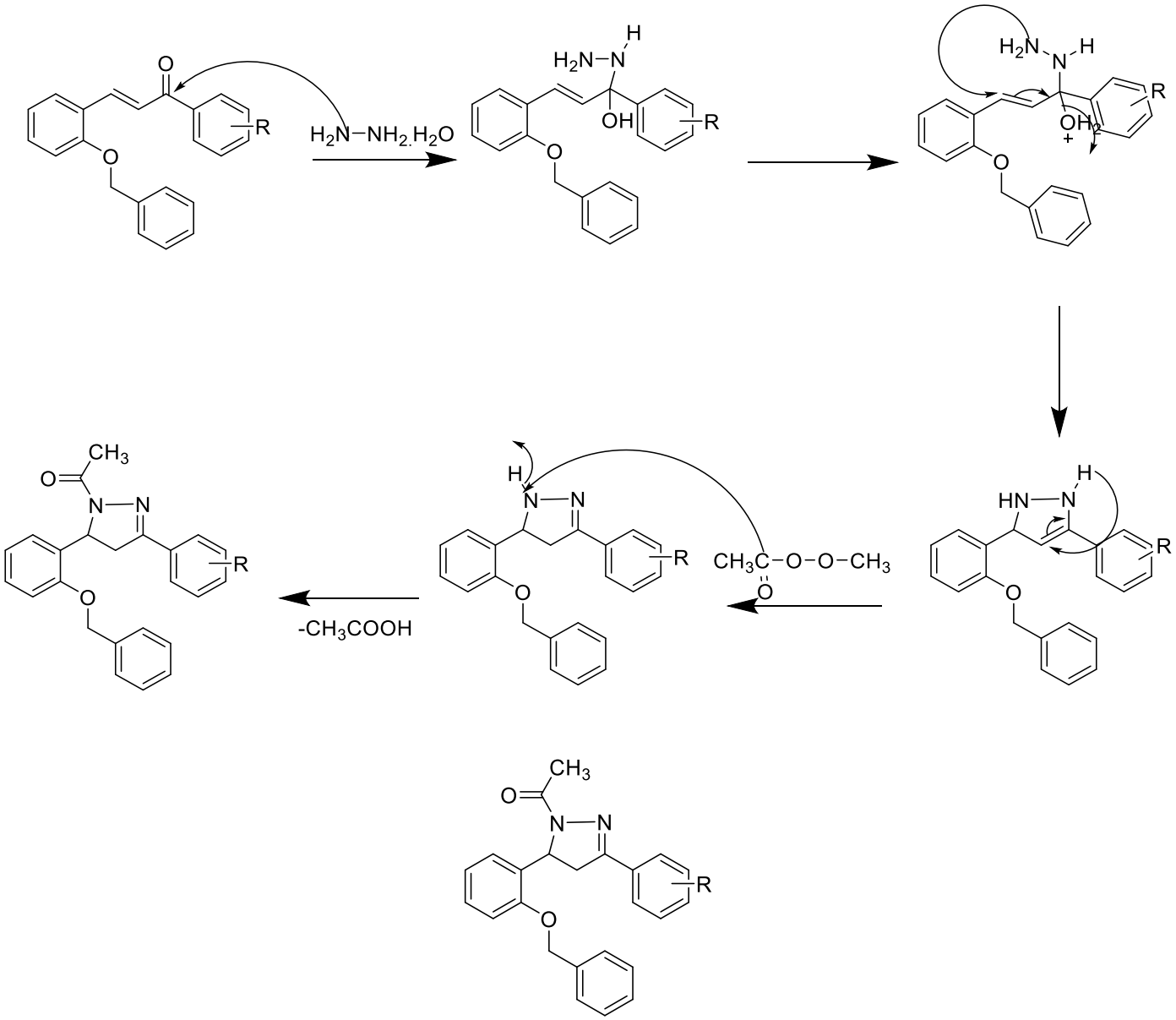
The structure of compound (CHP-02) was established on the basis of spectral data (MS, IR, NMR). In this structure, analytical data for compound (2) revealed its molecular formula $C_{22}H_{20}N_2O_2S$ (m/z=377). The ^{1}H NMR spectrum reveal one singlet at δ= 2.20 ppm assigned to the one -CH3, two doublet of doublet at δ= 2.95 to 3.00 and 3.72 to 3.79 revealed one magnetically inequivalent -CH2 proton, one doublet of doublet at δ= 5.64 to 5.68 ppm revealed one chiral -CH proton, one qt at δ= 5.03 to 5.14 ppm, two doublet of doublet at δ= 6.86 and 7.66 ppm assigned to the para disubstituted aromatic ring (4H), organic region show peak in the range between 6.8 to 7.7 ppm.

The structure (CHP-03) was established on the basis of spectral data (MS, IR, NMR). In this structure, analytical data for compound (3) revealed its molecular formula $C_{25}H_{24}N_2O_2$ (m/z= 385). The 1H NMR spectrum reveal two singlet at δ= 2.22 and 2.24 ppm assigned to the two -CH3, two doublet of doublet at δ= 2.88 to 2.94 and 3.61 to 3.70 revealed one magnetically inequivalent -CH2 proton, one doublet of doublet at δ= 5.60 to 5.64 ppm revealed one chiral -CH proton, two doublet of doublet at δ= 7.10 and 7.40 ppm assigned to the para disubstituted aromatic ring (4), organic region show peak in the range between 6.79 to 7.7 ppm.



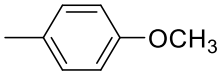
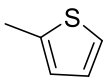
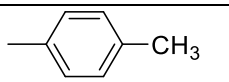
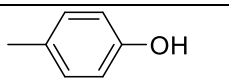
Scheme 1. Synthesis of Substituted Chalcone (1a-K) and Their Subsequent Cyclisation to Acetyl Pyrazoline Derivative (CHP-01 to 11).

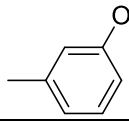
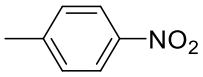
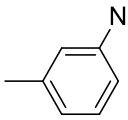
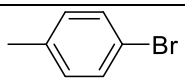
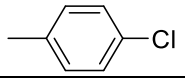
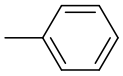
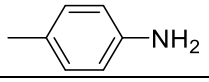
The plausible mechanism of formation of the acetyl pyrazoline derivative involves the reaction of chalcone with hydrazine hydrate in the presence of acetic acid, giving a cyclisation reaction that gives a pyrazoline intermediate. Later, in the presence of acetic acid, it gives acetyl pyrazoline derivatives.



CHP-01 to CHP-11

Table 1. Physical Properties of Acetyl Pyrazoline Derivatives (CHP-01 to 11).

Code	-R	Mole. weight	Mole. Formula	Melting point
CHP-01		400.48	$C_{25}H_{24}N_2O_3$	140
CHP-02		376.47	$C_{22}H_{20}N_2O_2S$	180
CHP-03		384.48	$C_{25}H_{24}N_2O_2$	162
CHP-04		386.45	$C_{24}H_{22}N_2O_3$	146

CHP-05		386.45	$C_{24}H_{22}N_2O_3$	180
CHP-06		415.45	$C_{24}H_{21}N_3O_4$	210
CHP-07		415.45	$C_{24}H_{21}N_3O_4$	200
CHP-08		449.35	$C_{24}H_{21}BrN_2O_2$	172
CHP-09		404.89	$C_{24}H_{21}ClN_2O_2$	164
CHP-10		370.45	$C_{24}H_{22}N_2O_2$	138
CHP-11		385.47	$C_{24}H_{22}N_3O_2$	168

2.2. Biological Activity

The newly synthesised acetyl pyrazoline derivatives (CHP- 01 to 11) were used to get the antibacterial activity [28,29,30], and they were tested against Gram-positive bacteria, in which we use *Staphylococcus aureus* and *Bacillus cereus*, as well as Gram-negative bacteria, including *Salmonella spp.* and *Escherichia coli*, using the agar well method [31,32,33,34]. The compound showed low to moderate activity at a concentration of 10mg/mL when compared against the standard drug tetracycline. In the agar well method, the solution was prepared in DMSO. The diameter of the zone of inhibition surrounding each well was used to calculate the antibacterial activity after the plates were incubated for 24 hours at 37°C. All experiments were performed. (Table 2)

Table 2. Antibacterial Activity of (CHP-01 to 11), Using Tetracycline as the Standard Drug in the Agar Well Diffusion Method. (Diameter of Zone of Inhibition, Mm).

Compound code	**Antibacterial activity (zone of inhibition in mm)**			
	Salmonella spp.	***E. coli***	***Staphylococcus aureus***	***Bacillus cereus***
CHP-1	0	2	2	9
CHP-2	0	0	0	6
CHP-3	0	0	0	8
CHP-4	0	0	3	6
CHP-5	1	1	1	7
CHP-6	0	0	0	8
CHP-7	0	0	2	6
CHP-8	0	0	0	5

CHP-9	0	0	3	12
CHP-10	0	0	4	8
CHP-11	0	0	1	6
Tetracycline	17	19	16	21

2.3. ADME Study

The ADME study of the synthesized acetyl pyrazoline derivatives (CHP-01 to 11) was performed using the SwissADME server to get drug-likeness, GI absorption, and pharmacokinetics behaviour [35, 36, 37, 38]. The predicted results are shown in Table 3. All synthesized compounds demonstrated good molecular descriptors with molecular weights ranging from 376.47 to 449.35 g/mol, which satisfy Lipinski's Rule of Five criteria [39, 40, 41], indicating favourable drug-like qualities. The number of hydrogen bond acceptors ranged from 4 -5, while hydrogen bond donors varied between 0 - 1, showing adequate hydrogen bonding capability for receptor contact and membrane permeability.

The compounds' topological polar surface area (TPSA) values varied from 41.09 to 87.22, and TPSA < 140 Å² is widely used alongside it to confirm good intestinal permeability. Even though CHP-06 and CHP-07 stickily pass Lipinski's rules, they fail to cross the BBB. This is driven by their higher TPSA values (87.22 Å²), as central nervous system (CNS) active drugs typically require a tighter TPSA threshold of <60 to 70 Å². The presence of strongly electron-withdrawing nitro ($–NO_2$) substituents, which increase molecular polarity and hydrogen bonding interactions with the aqueous environment, thereby reducing lipophilicity and membrane permeability, is primarily responsible for the elevated TPSA values of CHP-06 and CHP-07.

Every molecule sits well below the thresholds for H-bond donors, acceptors, and TPSA. This directly aligns with the "High" Gastrointestinal (GI) absorption noted across the entire set. The P-glycoprotein (P-gp) substrate prediction found that just one substance (CHP-11) behaved as a P-gp substrate, indicating the likelihood of active efflux transport that may alter intracellular drug accumulation and bioavailability.

The whole library of acetyl pyrazoline derivatives shows good drug-like properties and meets the main criteria of Lipinski's Rule of Five, which means it has great potential with regard to oral bioavailability. Yet, when active transport mechanisms and tissue barriers are taken into account, the library naturally divides itself into three different therapeutic groups: CNS-Targeted Agents, Peripherally Restricted Compounds, and a High-Risk Candidate (Table 3)

Table 3. ADME Properties Profile of the Synthesized Compounds (CHP-01 to 11) by SwissADME Software.

Molecule	H-bond acceptors	H-bond donors	MR	TPSA	GI absorption	BBB permeant	Pgp substrate
CHP-01	4	0	124.5	51.13	High	YES	NO
CHP-02	3	0	115.89	70.14	High	YES	NO
CHP-03	3	0	122.98	41.9	High	YES	NO
CHP-04	4	1	120.03	62.13	High	YES	NO
CHP-05	4	1	120.03	62.13	High	YES	NO

CHP-06	5	0	126.83	87.22	High	NO	NO
CHP-07	5	0	126.83	87.22	High	NO	NO
CHP-08	3	0	125.71	41.09	High	YES	NO
CHP-09	3	0	123.02	41.09	High	YES	NO
CHP-10	3	0	118.01	41.09	High	YES	NO
CHP-11	3	1	122.41	67.92	High	YES	YES

3. EXPERIMENTAL

3.1. Materials and Methods

Thin-layer chromatography was performed on 0.2-mm precoated plates of silica gel. Visualisation was made with UV light (250 and 365 nm). IR spectra were recorded on an FTIR-8400 spectrophotometer (Shimadzu) using a DRS prob. A Bruker AVANCE II spectrometer was used to record 1H (400 MHz) and 13C (100 MHz) NMR spectra in methanol and DMSO. As an internal standard, chemical shifts are represented as δ ppm downfield from TMS. A direct intake probe on an LC-MS mass spectrometer was used to calculate mass spectra. Mass spectra were determined using a direct inlet probe on an LC-MS mass spectrometer. Solvents were evaporated with a BUCHI rotary evaporator. Melting points were measured in open capillaries and are uncorrected.

3.2. General Synthesis Procedure

3.2.1. General Synthesis of Chalcone (1a-k)

A 100mL conical flask putting with a magnetic stirrer and conical flask was charged with a solution of 2- (Benzyloxy) benzaldehyde (0.01 M) and acetophenone (0.01 M) in 20 mL of methanol with a 60% base (NaOH/KOH) solution, and the mixture was stirred at room temperature for 24 h. The progress of the reaction was monitored by thin-layer chromatography. After completion of the reaction, it was poured into crushed ice. The precipitated crude product was purified by filtration followed by crystallization from EtOH. [18] (Table 1) (Scheme 1).

3.2.2. Synthesis of Substituted Acetyl Pyrazoline Derivatives (CHP-01 to CHP-11)

A mixture of chalcone (0.01 M) and hydrazine hydrate (0.01 M) in 20 mL of glacial acetic acid was heated to reflux for 24 to 48 h. The process of reaction mixture was monitored by thin-layer chromatography. After completion of the reaction, the mixture was cooled at room temperature and then poured into crushed ice water to separate the precipitate from the solution. After that, the solution was filtered and washed with water to remove salt. After that, it was recrystallized with ethanol to get a crystalline product. (Table-1) (Scheme-1).

3.3. Physical and Spectral Data

3.3.1. 1-(5-(2-(benzyloxy)phenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (CHP-01)

$C_{25}H_{24}N_2O_3$; molecular weight:400; M.P: 146^{0}c; Creamish solid; elemental analysis C, 74.98; H, 6.04; N, 7.00; O, 11.98 MS (*m/z*): 401 (M+H); IR (KBr):3035 (aromatic CH stretching), 2835 (asymmetric alkane CH stretching), 1608 (C=O stretching), 1517 (C=N stretching), 1178 (Ar-o-R assy. Streching). ^{1}H NMR (400 MHz, METHANOL-D_4) δ 7.66 – 7.58 (m, 2H), 7.51 – 7.32 (m, 2H), 7.32 – 7.26 (m, 1H), 7.29 – 7.23 (m, 1H), 7.21 (s, 1H), 7.26 – 7.15 (m, 1H), 7.04 (d, *J* = 8.1 Hz, 1H), 7.05 – 6.94 (m, 1H), 6.97 – 6.82 (m, 3H), 5.74 (dd, *J* = 11.7, 4.8 Hz, 1H), 5.15 – 5.02 (qt, 2H), 3.80 (d, *J* = 1.9 Hz, 3H), 3.76 – 3.64 (dd, 1H), 2.97- 2.97 (dd, *J* = 17.7, 4.9 Hz, 1H), 2.35 (d, *J* = 1.6 Hz, 3H) ^{13}C NMR(400 MHz, DMSO): δ ppm 161.69, 156.23, 155.37, 137.06, 129.31, 128.46, 128.15, 127.58, 127.41, 123.89, 122.47, 113.89, 113.75, 112.26, 69.94, 56.71, 54.51, 41.28, 20.49.

3.3.2. 1-(5-(2-(benzyloxy) phenyl)-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl) ethan-1-one (CHP-02)

$C_{22}H_{20}N_2O_2S$; molecular weight:376; M.P: 156^{0}c; Brown solid; elemental analysis C, 70.19; H, 5.35; N, 7.44; O, 8.50; S, 8.52, MS (*m/z*): 377 (M+H); IR (KBr): 3028 (aromatic CH stretching), 2927 (asymmetric alkane CH stretching), 1668 (C=O stretching), 1521 (C=N stretching), 1184 (Ar-o-R assy. Streching), 837 (C-S Streching). ^{1}H NMR (400 MHz, DMSO-D_6) δ 7.67 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.39 – 7.29 (m, 3H), 7.32 – 7.24 (m, 1H), 7.20 (ddd, *J* = 8.2, 7.2, 1.9 Hz, 1H), 7.12 – 7.04 (m, 2H), 6.91 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.85 (td, *J* = 7.3, 1.1 Hz, 1H), 5.70 (dd, *J* = 11.8, 4.6 Hz, 1H), 5.20 – 5.08 (m, 2H), 3.79 (dd, *J* = 17.7, 11.8 Hz, 1H), 3.01 (dd, *J* = 17.6, 4.6 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (400 MHz, DMSO-D_6) δ 167.61, 155.34, 151.08, 137.57, 134.92, 130.66, 130.00, 129.86, 128.99, 128.97, 128.49, 128.27, 127.90, 126.27, 121.14, 113.14, 69.94, 56.15, 42.35, 39.47, 22.17.

3.3.3. 1-(5-(2-(benzyloxy) phenyl)-3-(p-tolyl)-4,5-dihydro-1H-pyrazol-1-yl) ethan-1-one (CHP-03)

$C_{25}H_{24}N_2O_2$; molecular weight:384; M.P: 188^{0}c; Cremise solid; elemental analysis C, 78.10; H, 6.29; N, 7.29; O, 8.32; MS (*m/z*): 385 (M+H); IR (KBr): 3035 (aromatic CH stretching), 2922 (asymmetric alkane CH stretching), 1654 (C=O stretching), 1600 (C=N stretching), 1188 (Ar-o-R assy. Streching). ^{1}H NMR (400 MHz, DMSO-D_6) δ 7.62 – 7.55 (m, 2H), 7.54 – 7.42 (m, 2H), 7.46 – 7.14 (m, 6H), 7.11 – 6.95 (m, 1H), 6.94 – 6.80 (m, 2H), 5.68 (dd, *J* = 11.8, 4.6 Hz, 1H), 5.19 – 5.08 (m, 2H), 3.75 (dd, *J* = 17.8, 11.8 Hz, 1H), 2.97 (dd, *J* = 17.8, 4.7 Hz, 1H), 2.29 (d, *J* = 7.5 Hz, 6H). ^{13}C NMR (400 MHz, DMSO-D_6) δ 167.76, 155.35, 155.07, 140.51, 137.60, 130.29, 129.80, 129.05, 128.99, 128.95, 128.88, 128.25, 128.20, 127.92, 127.06, 126.23, 125.39, 121.09, 113.13, 69.92, 55.90, 41.68, 40.71, 22.23, 21.55.

3.3.4. 1-(5-(2-(benzyloxy) phenyl)-3-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl) ethan-1-one (CHP-04)

$C_{24}H_{22}N_2O_3$; molecular weight:386; M.P: 166^{0}c; Yellow solid; elemental analysis C, 74.59; H, 5.74; N, 7.25; O, 12.42. MS (*m/z*): 387 (M+H); IR (KBr): 3640 (Free -OH streching), 3030 (aromatic CH stretching), 2920 (asymmetric alkane CH stretching), 1640 (C=O stretching), 1548 (C=N stretching), 1184 (Ar-o-R assy. Streching); ^{1}H NMR (400 MHz, DMSO-D_6) δ 9.68 (s,1H,-OH), 7.62 – 7.55 (m, 2H), 7.54 – 7.42 (m, 2H), 7.46 – 7.14 (m, 6H), 7.11 – 6.95 (m, 1H), 6.94 – 6.80 (m, 2H), 5.68 (dd, *J* = 11.8, 4.6 Hz, 1H), 5.19 – 5.08 (m, 2H), 3.75 (dd, *J* = 17.8, 11.8 Hz, 1H), 2.97 (dd, *J* = 17.8, 4.7 Hz, 1H), 2.29 (d, *J* = 7.5 Hz, 3H), ^{13}C NMR (400 MHz, DMSO-d_6) δ 169.91, 159.69, 154.76, 152.88, 136.67, 128.81, 128.38, 128.30, 127.96, 127.67, 127.66, 127.05, 124.00, 122.13, 115.94, 113.77, 71.79, 57.99, 40.28, 20.81.

3.3.5. 1-(5-(2-(benzyloxy) phenyl)-3-(3-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl) ethan-1-one (CHP)-05)

$C_{24}H_{22}N_2O_3$; molecular weight:386; M.P: 160^0c; Yellow solid; elemental analysis C, 74.59; H, 5.74; N, 7.25; O, 12.42. MS (*m/z*): 387 (M+H); IR (KBr): 3640 (Free -OH streching), 3030 (aromatic CH stretching), 2920 (asymmetric alkane CH stretching), 1640 (C=O stretching), 1548 (C=N stretching), 1184 (Ar-o-R assy. Streching); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 7.62 – 7.55 (m, 2H), 7.54 – 7.42 (m, 2H), 7.46 – 7.14 (m, 6H), 7.11 – 6.95 (m, 1H), 6.94 – 6.80 (m, 2H), 5.68 (dd, *J* = 11.8, 4.6 Hz, 1H), 5.19 – 5.08 (m, 2H), 3.75 (dd, *J* = 17.8, 11.8 Hz, 1H), 2.97 (dd, *J* = 17.8, 4.7 Hz, 1H), 2.29 (d, *J* = 7.5 Hz, 3H), ^{13}C NMR (400 MHz, DMSO-d_6) δ 169.91, 156.27, 154.76, 153.12, 136.67, 133.50, 129.23, 128.38, 128.30, 127.96, 127.67, 127.66, 127.10, 122.13, 120.22, 118.45, 113.77, 113.44, 71.79, 57.98, 39.93, 20.81.

3.3.6. 1-(5-(2-(benzyloxy) phenyl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl) ethan-1-one (CHP-06)

$C_{24}H_{21}N_3O_4$; molecular weight:415; M.P: 200^0c; Mustard yellow solid; elemental analysis C, 69.39; H, 5.10; N, 10.11; O, 15.40; MS (*m/z*): 416(M+H); IR (KBr): 3032 (aromatic CH stretching), 2875 (asymmetric alkane CH stretching), 1648 (C=O stretching), 1558 (C=N stretching), 1188 (Ar-o-R assy. Streching); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 – 7.55 (m, 2H), 7.54 – 7.42 (m, 2H), 7.46 – 7.14 (m, 6H), 7.11 – 6.95 (m, 1H), 6.94 – 6.80 (m, 2H), 5.68 (dd, *J* = 11.8, 4.6 Hz, 1H), 5.19 – 5.08 (m, 2H), 3.75 (dd, *J* = 17.8, 11.8 Hz, 1H), 2.97 (dd, *J* = 17.8, 4.7 Hz, 1H), 2.29 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 169.91, 154.76, 151.90, 147.21, 138.11, 136.67, 128.38, 128.30, 127.96, 127.67, 127.66, 127.60, 127.05, 123.96, 122.13, 113.77, 71.79, 57.99, 40.31, 20.81.

3.3.7. 1-(5-(2-(benzyloxy) phenyl)-3-(3-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl) ethan-1-one (CHP-07)

$C_{24}H_{21}N_3O_4$**;** molecular weight:415; M.P: 182^0c; Brown solid; elemental analysis C, 69.39; H, 5.10; N, 10.11; O, 15.40; MS (*m/z*): 416 (M+H); IR (KBr): 3032 (aromatic CH stretching), 2875 (asymmetric alkane CH stretching), 1648 (C=O stretching), 1558 (C=N stretching), 1188 (Ar-o-R assy. Streching); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 – 8.19 (m, 2H), 7.99 (ddd, *J* = 7.4, 2.0, 1.1 Hz, 1H), 7.68 (dd, *J* = 8.8, 7.4 Hz, 1H), 7.50 – 7.15 (m, 7H), 7.13 – 6.82 (m, 2H), 5.52 (td, *J* = 6.6, 0.6 Hz, 1H), 5.11 (t, *J* = 0.8 Hz, 2H), 3.96 (dd, *J* = 14.5, 6.6 Hz, 1H), 3.52 – 3.32 (m, 1H), 2.29 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 169.91, 154.76, 151.40, 147.49, 136.67, 133.87, 132.40, 129.58, 128.38, 128.30, 127.96, 127.67, 127.66, 127.10, 123.32, 122.13, 121.09, 113.77, 71.79, 57.98, 39.73, 20.81.

3.3.8. 1-(5-(2-(benzyloxy) phenyl)-3-(4-bromophenyl)-4,5-dihydro-1H-pyrazol-1-yl) ethan-1-one (CHP-08)

$C_{24}H_{21}BrN_2O_2$; molecular weight:449; M.P: 220^0c; White solid; elemental analysis C, 64.15; H, 4.71; Br, 17.78; N, 6.23; O, 7.12; MS (*m/z*): 450 (M+H); IR (KBr): 3029 (aromatic CH stretching), 2830 (asymmetric alkane CH stretching), 1650 (C=O stretching), 1560 (C=N stretching), 1180 (Ar-o-R assy. Streching), 640 (C-Br streching); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 – 7.71 (m, 2H), 7.73 – 7.51 (m, 2H), 7.43 (dt, *J* = 7.3, 1.6, 0.8 Hz, 2H), 7.37 – 7.29 (m, 3H), 7.30 – 7.19 (m, 2H), 6.99 – 6.71 (m, 2H), 5.53 (td, *J* = 6.6, 0.6 Hz, 1H), 5.10 (t, *J* = 0.8 Hz, 2H), 3.88 (dd, *J* = 14.5, 6.6 Hz, 1H), 3.56 – 3.28 (m, 1H) 2.29 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 169.91, 154.76, 152.17, 136.67, 131.80, 131.55, 128.38, 128.30, 128.19, 127.96, 127.67, 127.66, 127.05, 126.22, 122.13, 113.77, 71.79, 57.88, 40.28, 20.81.

3.3.9. 1-(5-(2-(benzyloxy) phenyl)-3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-1-yl) ethan-1-one (CHP-09)

$C_{24}H_{21}ClN_2O_2$; molecular weight:403; M.P: 186^{0}c; White solid; elemental analysis C, 71.19; H, 5.23; Cl, 8.76; N, 6.92; O, 7.90; MS (*m/z*): 405 (M+H); IR (KBr): 3037 (aromatic CH stretching), 2818 (asymmetric alkane CH stretching), 1630 (C=O stretching), 1565 (C=N stretching), 1174 (Ar-o-R assy. Streching), 780 (C-Cl streching); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 – 7.60 (m, 2H), 7.56 – 7.38 (m, 3H), 7.41 – 7.32 (m, 2H), 7.35 – 7.20 (m, 4H), 7.08 – 6.71 (m, 2H), 5.53 (td, *J* = 6.6, 0.6 Hz, 1H), 5.10 (t, *J* = 0.8 Hz, 2H), 3.88 (dd, *J* = 14.5, 6.6 Hz, 1H), 3.50 – 3.35 (m, 1H), 2.32 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 169.91, 154.76, 151.96, 136.67, 135.88, 130.89, 129.01, 128.38, 128.30, 128.14, 127.96, 127.67, 127.66, 127.05, 122.13, 113.77, 71.79, 57.88, 40.28, 20.81.

3.3.10. 5-(2-(benzyloxy) phenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl) ethan-1-one (CHP-10)

$C_{24}H_{22}N_2O_2$; molecular weight:370; M.P: 180^{0}c; Creamish solid; elemental analysis C, 77.81; H, 5.99; N, 7.56; O, 8.64; MS (*m/z*): 371 (M+H);, IR (KBr): 3030 (aromatic CH stretching), 2928 (asymmetric alkane CH stretching), 1640 (C=O stretching), 1570 (C=N stretching), 1188 (Ar-o-R assy. Streching);^{1}H NMR (400 MHz, DMSO-D_6) δ 7.62 – 7.55 (m, 2H), 7.54 – 7.42 (m, 2H), 7.46 – 7.14 (m, 6H), 7.11 – 6.95 (m, 2H), 6.94 – 6.80 (m, 2H), 5.68 (dd, *J* = 11.8, 4.6 Hz, 1H), 5.19 – 5.08 (m, 2H), 3.75 (dd, *J* = 17.8, 11.8 Hz, 1H), 2.97 (dd, *J* = 17.8, 4.7 Hz, 1H), 2.29 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 169.91, 154.76, 153.07, 136.67, 132.53, 129.82, 128.43, 128.38, 128.30, 127.96, 127.67, 127.66, 127.05, 126.96, 122.13, 113.77, 71.79, 57.88, 40.19, 20.81.

3.3.11. 1-(3-(4-aminophenyl)-5-(2-(benzyloxy) phenyl)-4,5-dihydro-1H-pyrazol-1-yl) ethan-1-one (CHP-11)

$C_{24}H_{22}N_2O_2$; molecular weight:385; M.P: 194^{0}c; Creamish solid; elemental analysis C, 77.81; H, 5.99; N, 7.56; O, 8.64; MS (*m/z*): 386 (M+H); IR (KBr): 3450-3340 (Free NH_2 -Streching), 3030 (aromatic CH stretching), 2928 (asymmetric alkane CH stretching), 1640 (C=O stretching), 1570 (C=N stretching), 1188 (Ar-o-R assy. Streching). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 – 7.61 (m, 2H), 7.43 (dt, *J* = 7.3, 1.6, 0.8 Hz, 2H), 7.35 – 7.16 (m, 4H), 6.99 – 6.87 (m, 2H), 6.73 – 6.56 (m, 2H), 5.53 (td, *J* = 6.6, 0.6 Hz, 1H), 5.32 (s, 2H), 5.10 (t, *J* = 0.8 Hz, 2H), 3.88 (dd, *J* = 14.5, 6.6 Hz, 1H), 3.52 – 3.34 (m, 1H), 2.30 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 169.91, 154.76, 152.96, 149.77, 136.67, 128.70, 128.38, 128.30, 127.96, 127.67, 127.66, 127.05, 122.15, 122.13, 114.07, 113.77, 71.79, 57.88, 40.28, 20.81.

4. CONCLUSIONS

In this study, we synthesised a series of new acetyl pyrazoline compounds (CHP-01 to 11) using chalcone derivatives derived from 2-(benzyloxy) benzaldehyde and various ketone compounds. Biological investigation indicated selective antibacterial activity of the produced compounds, particularly against Gram-positive bacterial strains. Among the tested compounds, CHP-09 and CHP-01 show good activity against the *Bacillus* bacterial strain. Whereas CHP-10 shows activity against the *S. aureu*s bacterial strain. Other compounds show moderate to low activity against all bacterial strains. ADME profiling further confirmed the drug-like potential of the synthesized acetyl pyrazoline, as most derivatives demonstrated good lipophilicity, acceptable hydrogen-bonding properties, high anticipated gastrointestinal absorption, and absence of blood–brain barrier permeability. All the compounds show favourable TPSA values and high GI absorption, while compounds CHP-06 and CHP-07 do not show BBB penetration due to the presence of a nitro group.

The excellent antibacterial activity and favourable ADME properties of the synthesised acetyl pyrazoline derivatives imply that this scaffold may serve as a promising foundation for future antimicrobial research. Further research through molecular docking, target-oriented studies, molecular dynamics simulations, and structural optimisation may provide vital insights into the mechanistic features and help the creation of more potent and selective antibacterial medicines based on this pharmacophore.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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