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Synthesis characterization and Preliminary Pharmacological Evaluation of new 2-pyrazoline derivatives derived from resorcinol

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ABSTRACT

Chalcones were used to create a number of 2-pyrazoline derivatives, which were then tested for their pharmacological effects.

Claisen-Schmidt prepared the chalcones (1–5). Acetophenone was used as the condensing agent in a reaction with several para-substituted benzaldehydes while KOH was present. The reaction was monitored by TLC, and the resultant intermediates were examined by melting point and FT-IR.

Various In a single pot, chalcones (1–5) and Hydrazine monohydrate were reacted with glacial acetic acid at a temperature of 50 °C for roughly 24 hours to produce 2-pyrazoline derivatives. The antioxidant chemical (guaiacol) was added after pyrazoline II (1–5) was produced, and the reaction was then watched by TLC to make sure it was finished. The mixture was chilled until crystal formation was complete in an ice-water bath. the 2-pyrazoline derivatives a1, b1, c1, d1, and e1 by adding them to crushed ice, storing them in the refrigerator for the next day, filtering, recrystallizing, and drying them. Based on their spectral data, the structures of the recently synthesized 2-pyrazoline derivatives have been established. The synthetic compounds were tested for their anti-inflammatory and antibacterial properties.

Keywords: *Pharmacological, derivatives, Synthesis, antioxidant*

INTRODUCTION

Heterocyclic compounds can be classified into two types: Aliphatic Heterocyclic Compounds. Aromatic Heterocyclic Compounds based on the electronic arrangement(1).

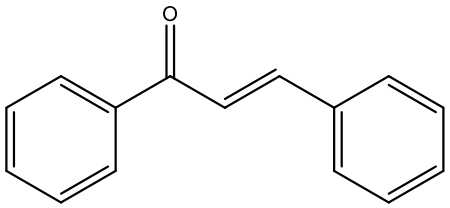
The size of the heterocyclic ring, as well as the kind and quantity of the heteroatoms, are typically used to categorize heterocyclic compounds.it represent the largest and most diversified family of organic molecules. Aromatic heterocyclic compounds are among them and form structural components used in a large variety of physiologically active natural and synthetic substances, agrochemicals, and pharmaceuticals(2)

Heterocyclic compounds are cyclic organic compounds that contain at least one hetero atom, the most common heteroatoms are nitrogen, oxygen, and sulfur but heterocyclic rings containing other hetero atoms are also widely known.

Pyrazoline is a heterocyclic chemical compound with the molecular formula $\mathbf{C_3H_6N_2}$, it has a broad diversity of biological activities and recognize as one of the most important

heterocyclic nuclei responsible for many researchers to use it as an open gate to synthesize new derivatives that possess biological activities such as; anticancer(3), antimicrobial(4)(5),antioxidant(6), antidiabetic(7), anti-inflammatory(8), antidepressant(9)….etc.

pyrazoline is the most important type of Chalcone derivatives Chalcones are a group of plant-derived polyphenolic compounds belonging to the flavonoid's family, they consist of open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α, β-unsaturated carbonyl system.



(*E*)-chalcone

FIGURE (1-1): Chalcone structure

The structural adaptation of the chalcone rings has led to a high range of diversity that has proven useful for the development of new medicinal agents

The chalcones are well documented for a wide spread of biological activities including antimicrobial(10), anticancer(11),antidiabetic(12), antioxidative(13), anti-inflammatory(14), and others.

Resorcinol is phenolic compound with molecular formula **($C_6H_6O_2$)**, it has potent antimicrobial activity(15), it also consider as antioxidant due to it is ability to free radical scavenger(16)

METHODS AND METERIALS

The Electronic Melting Point Apparatus (Stuart SMP30) was used to calculate melting points. The IR spectra of the substances were obtained from Schimadzu, Japan. Thin layer chromatography (TLC) was employed to monitor the reactions, and the mobile phase solvent system used was n-hexane: ethyl acetate: methanol (5:3:2)

I-General synthesis of chalcones (I-)

Acetophenone (0.01mole, 1.12 ml) was dissolved in absolute ethanol (12 ml) in 250 mL RB flask then different substituted benzaldehyde (0.01mole) (a-Br- 4.9gm, b-Cl- 3,3 ml, c-CH_3- 3.3 ml, d-OCH_3- 3.7gm, e-NO_2- 4.1 gm, f-NH_2- 3.3gm, g-OH-3.4 gm) were added to the solution and the mixture was stirred until formation of a clear solution. Then potassium hydroxide 40% (15ml) was added drop by drop. To obtain a homogenous mixture, the mixture was stirred for 15 minutes. Next, a drop by drop of potassium hydroxide 40% (15ml) was added. In an ice bath, the liquid was stirring until it solidified. The resulting mass was kept in the refrigerator overnight, Crushed ice was added, neutralized by 5% HCl, and then filtered before being recrystallized by 99% ethanol.

1-Synthesis of (E)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one

Bright yellow crystals, yield (95%), M.P (110–111 °C), R_f = 0.65, ATR-FTIR (ύ, cm^{-1}): 3059, 3035 Ar (CH) str, 2908, 2870 asymmetric and symmetric (CH_2) str. respectively, 1654 (C=O) str. of (α&β unsaturated ketone), 1604,1581,1562 Ar(C=C) str, 771 (C-Br).

2-Synthesis of (E)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one

Light yellow crystals. Yield: 85%. M.P.: 74-75 °C. R_f=0.55. FT-IR: 3016 Ar (CH)str, 2954, 2900 (asymmetric CH str. of CH_3), 2843 asymmetric (CH3) str, 1654 (C=O) str. of (α&β unsaturated ketone), 1593, 1573, 1508 Ar(C=C) str, 1261 (C-O-C) str.

3-Synthesis of (E)-3-(4-(dimethyl amino) phenyl)-1-phenylprop-2-en-1-one

Bright orange crystals, yield (90%), M.P (110-111 °C), R_f = 0.7, ATR-FTIR (ύ, cm^{-1}): 3151 - 3028 Ar (CH) str, 2904, 2858 asymmetric and Bright yellow crystals, yield (90%), m.p (74-75 °C), R*f* = 0.55, ATR-FTIR (ύ, cm^{-1}): 3016 Ar (CH) str, 2908, symmetric (CH_3) str. respectively, 1647 (C=O) str. of (α&β unsaturated ketone), 1597,1577, 1558 Ar (C=C) str, 1157 (C-N).

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4- Synthesis of (E)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one

Yellow to brown powder, yield (80%), M.P (155-156 °C), R_f = 0.59, ATR-FTIR (ύ, cm^{-1}): 3132, 3070 Ar (CH) str, 2908, 2870 asymmetric and symmetric (CH_2) str. respectively, 1658 (C=O) str. of (α&β unsaturated ketone), 1608, 1573Ar (C=C) str, 1527, 1350 (NO_2) str asymmetric and symmetric respectively.

5- Synthesis of (E)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one

Yellow crystals, yield (96%), M.P (113-115 °C), R_f = 0.6, ATR-FTIR (ύ, cm^{-1}): 3059, 3028 Ar (CH) str, 1658 (C=O) str. of (α&β unsaturated ketone), 1600,1573 Ar (C=C) str, 771 (C-Cl) str.

II-General synthesis of 2-pyrazoline derivatives using one – pot reaction.

Chalcones (0.01 mmole) dissolved in glacial acetic acid (30 ml), hydrazine monohydrate (0.02 mmole) was added to the mixture and reflex in hot water bath at 50 ^{0}C for 24 hr. until the pyrazoline formation check it by TLC using mobile phase n-hexene :ethyl acetate (4:1), then KI (0.01 mmole) dissolved in distilled water (10 ml) was added to the mixture and still reflux for 1\2 hr. finally resorcinol (0.01 mmole, 1.2 gm) was added and the mixture still reflux in hot water bath for 24-48 hr. then the temperature decrease and still stirring until the precipitate appear and the reaction is completed ensure that buy TLC using three mobile phase n-hexene : ethyl acetate : methanol (5:3:2) , the mixture then poured in ice crash, kept in refrigerator overnight, filtered, washed by cold distilled water recrystallized by n-hexene: ethanol (8:3).

1-Synthesis of 1-(5-(4-bromophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-(3-hydroxyphenoxy) ethan-1-one

($C_{23}H_{19}BrN_2O_3$): Description: Bright beige crystal. Yield: 45%. M.P.: 113°C. R_f=0.7. FT-IR: 3213 (stretching vibration of OH), 3070 (Stretching Vibration of CH aromatic), 3020, 2962 (Asymmetric CH stretching of CH_2), 2846 (symmetric CH stretching of CH_2), 1666 (C=O), 1593(C=N stretching vibration overlap with C=C aromatic), 1566, 1543(C=C aromatic), 759 (C-Br).

^{1}H NMR (δ ppm) 3.08-3.14 (1H, d of d, CH of CH_2 of pyrazoline ring), 3.70-3.77(1H, d of d, CH of CH_2 of pyrazoline ring), 4.37 (2H, S, CH_2 of group), 5.51-5.55 (1H, d of d, CH of pyrazoline), 6.81 (1H, s, aromatic proton ortho to OH group ring C), 6.88-7.11 (3H, m, aromatic protons ring C), 7.10 (2H, d, meta to Br), 7.39-7.43 (5H, m, aromatic protons ring a), 7.73 (2H, d, ortho to Br ring B), 9.21 (1H, s, phenolic group)

2-Ssynthesis of (3-hydroxyphenoxy)-1-(5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl) ethan-1-one

($C_{24}H_{22}N_2O_4$): Description: Brown crystal. Yield: 50%. M.P.: 127-129°C. R_f =0.67. FT-IR: 3387 (OH stretching vibration) 3062, (Stretching Vibration of CH aromatic), 3035 (stretching vibration of CH_2, CH_3), 1654 (C=O), 1597 (C=N stretching vibration overlap with C=C aromatic), 1570, 1543 (C=C aromatic), 1246 (C-O-C), 1157 (C-N).

^{1}H NMR (δ ppm) 3.12-3.18 (1H, d of d, CH of CH_2 of pyrazoline ring), 3.82-3.90 (1H, d of d, CH of CH_2 of pyrazoline ring), 3.95 (3H, OCH_3), 4.44 (2H, s, CH_2 group), 5.51-5.55 (1H, d of d, CH of pyrazoline ring),6.83 (1H, s, ortho to OH group ring C) 7.15-7.24 (3H, m, aromatic protons ring C), 7.34(2H, d, ortho to OCH_3 ring B), 7.52 (2H, d, meta to OCH_3 ring B), 7.77-7.84 (5H, m, aromatic protons ring A), 9.21(1H, s, phenolic group).

3- Synthesis of 1-(5-(4-(dimethyl amino) phenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-(3-hydroxyphenoxy) ethan-1-one

($C_{25}H_{25}N_3O_3$): Description: Bright beige crystals. Yield: 55%. M.P.: 133-135°C. R_f=0.65. FT-IR: 3221 (OH stretching vibration) 2978 (Stretching Vibration of CH aromatic), 2943 (Asymmetric CH stretching of CH3), 2835 (symmetric CH stretching of CH3), 1662 (C=O), 1620 (C=N overlap with C=C aromatic)1566, 1527 (C=C aromatic), 1157 (C-N).

^{1}H NMR (δ ppm) 2.84 (6H, s, 3ºamine), 3.07-3.13 (1H, d of d, CH of CH2 of pyrazoline ring), 3.74-3.81 (1H, d of d, CH of CH_2 of pyrazoline), 4.46 (2H, s, CH_2), 5.41-5.44(1H, d of d, CH of pyrazoline ring), 6.64 (1H, d, ortho to OH group ring C), 6.98-7.01 (3H, m, aromatic protons ring C), 7.27 (2H, d, ortho to $N(CH_3)_2$ group), 7.46

(2H, d, meta to $N(CH_3)_2$ group ring B), 7.77-7.80 (5H, m, aromatic protons ring A), 9.21(1H, s, phenolic group)

4- Synthesis of 2-(3-hydroxyphenoxy)-1-(5-(4-nitrophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl) ethan-1-one

($C_{23}H_{19}N_3O_5$): Description: Beige powder. Yield: 50%. M.P.: 120-123°C. R_f =0.55. FT-IR: 3371 (OH stretching vibration) 3291,3259 (Stretching Vibration of CH aromatic), 2912 (Asymmetric CH stretching of CH_2), 3032 (symmetric CH stretching of CH_2), 1666 (C=O), 1608 (C=N stretching vibration overlap with C=C aromatic), 1577 (C=C aromatic), 1500, 1361 (asymmetric and symmetric stretching of NO_2 respectively), 1157 (C-N).

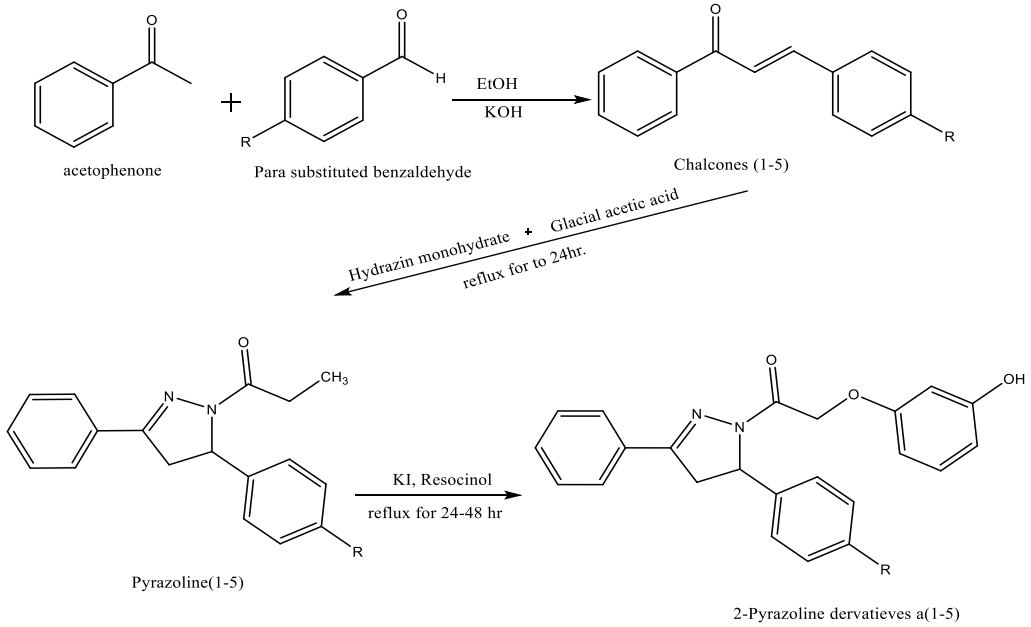
^{1}H NMR (δ ppm) 3.14-3.20 (1H, d of d, CH of CH_2 of pyrazoline ring), 3.81-3.89 (1H, d of d, CH of CH_2 of pyrazoline), 4.53 (2H, s, CH_2), 5.65-5.70 (1H, d of d, CH of pyrazoline ring), 6.26 (1H, d, ortho to OH group ring C), 7.05-7.09 (3H, m, aromatic protons ring C), 7.44-7.53 (3H, m, aromatic protons ring A), 7.59 (2H, d, aromatic protons ring A), 7.75 (2H, d, aromatic protons meta to NO_2 ring B),8.12 (2H, d, aromatic protons ortho to NO_2 ring B), 9.63 (1H, s, phenolic group

5- Synthesis of 1-(5-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-(3-hydroxyphenoxy) ethan-1-one

($C_{23}H_{19}ClN_2O_3$): Beige powder, Yield: 30%, M.P: 110-112 ^{0}C, R_f=0.45, FT-IR: 3390 (OH str. vib), 3059,3016 (CH Ar. Str. vib.), 2954, 2900 (asymmetric and symmetric CH_2 str. respectively), 1654 (C=N str. vib), 1593 (C=O str. vib overlap with C=C aromatic), 1573, 1505 (C=C str. vib), 779 (C-Cl) str.

^{1}H NMR (δ ppm) 3.10-3.15 (1H, d of d, CH of CH_2 of pyrazoline ring), 3.72-3.79 (1H, d of d, CH of CH_2 of pyrazoline ring), 4.88 (2H, s, CH_2 group), 5.54-5.58 (1H, d of d, CH of pyrazoline ring),6.58 (1H, s, ortho to OH group ring C) 7.16-7.21 (3H, m, aromatic protons ring C), 7.278 (2H, d, ortho to Cl ring B), 7.43 (2H, d, meta to Cl ring B),7.70-7.75 (5H, m, aromatic protons ring A), 9.21 (1H, s, phenolic group)

Scheme



R	1	2	3	4	5
	Br	OCH_3	$N(CH_3)_2$	NO_2	Cl

SCHEME (1-1): synthesis of 2-pyrazoline derivatives

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RESULT AND DISCUSSION

Antibacterial Activity

Using the well diffusion method to evaluate the antibacterial activity of the final synthesized compounds a1, b1, c1, d1, and e1 against gram-negative, gram-positive bacteria, and fungi. The antibacterial agents utilized were amoxicillin and ciprofloxacin, and the antifungal agent employed was fluconazole. Diclofenac and DMSO were selected as the control and solvent.

All of these synthetic compounds exhibit strong inhibition to moderate impact against Gram negative and Gram-positive microbes due to the powerful antibacterial action of resorcinol, as shown in the table:

TABLE 1: Antibacterial activity of final synthesized compounds.

Drugs	***E. coli***	***Psuedomonas aeruginosa***	***Staphylococcus aurous***	***Streptococcus pyogenes***	***Candida albicans***
	Gram -ve		***Gram +ve***		
a1	------	8 mm	38 mm	25 mm	------
b1	28 mm	20 mm	10 mm	------	20
c1	42 mm	35 mm	30 mm	5 mm	------
d1	------	4 mm	25 mm	35 mm	------
e1	8 mm	25 mm	45 mm	20 mm	25
Ciprofloxacin	28 mm	42 mm	50 mm	47 mm	------
Fluconazole	-----	------	------	------	20 mm
Amoxicillin	20 mm	25 mm	45 mm	32 mm	------
DMSO	------	------	------	------	------

Antifungal Activity

Using the well diffusion method, the antifungal activity of the final synthesized compounds (a1, b1, c1, d1, and e1) was assessed. Fluconazole was used as the reference antifungal agent, and DMSO was used as the solvent and control.

TABLE 2: antifungal activity of final synthesized compounds

compounds	Zone inhibition in (mm)
	Candida albicans
b1	20 mm
e1	25 mm
Fluconazole	20 mm

Evaluation of the Anti-Inflammatory activity

Acute inflammation was created in order to research the anti-inflammatory properties of the final compounds (a1, b1, c1, d1, and e1) by injecting undiluted egg white under the rat's skin on the intraplanter side of its left hind paw. Inflammation results from enhanced neutrophil extravasations, plasma extravasations, tissue water and plasma protein exudation, all of which are brought on by the metabolism of arachidonic acid, when egg white is subcutaneously injected into a rat paw.

This in vivo method is advantageous due to its quick evaluation by detecting inflammation at the start and throughout a short period of time, high paw sensitivity to inflammation, lack of anesthesia, cost-effectiveness, technique that is more in line with human nature, and other factors, this in vivo technique outperforms conventional methods.

Comparison of the effect of Diclofenac Sodium (Standard) versus Propylene Glycol(control)

When it came to the reduction of paw edema, there was no discernible difference between the control group and Standard in the beginning or after 30 minutes. When compared to propylene glycol, diclofenac sodium which used as standard(17) caused a considerable percent reduction (P 0.0001) in paw edema after 2, 3, 4, and 5 hours, as shown in the table.

TABLE 3: mean paw thickness in control and standard

Time (hours)	Thickness of Paw (mm)	
	Control	**Standard**
0	4.50 ± 0.02	4.45 ± 0.02
1/2	4.76 ± 0.03	4.61 ± 0.03
1	5.90 ± 0.03	5.88 ± 0.03
2	7.53 ± 0.04	6.94 ± 0.05
3	7.96 ± 0.05	6.40 ± 0.03
4	6.85 ± 0.02	6.15 ± 0.02
5	6.73 ± 0.09	5.68 ± 0.01

Anti-inflammatory Effect of Tested Compounds

Table (4) provides an indication of the investigated chemicals' anti-inflammatory effectiveness by displaying how they affected egg-white-induced edema. Egg white was injected intra-plantarly into the rat hind paw, causing a gradual edema that peaked (measured in millimeters) after one hour. The degree of the anti-inflammatory effect that the intra-peritoneal injection of the investigated substances produced varied in this investigation. Compounds a1, b1, c1, d, and e1 (3 mg/kg, i.p.) showed effects similar to those of diclofenac. Additionally, chemicals (a1- d1) significantly reduced paw edema.

Nevertheless, after 2 to 5 hours, compounds (a1, d1) demonstrated good activity and high significance to reduce paw thickness, greater than the standard, where compounds (c1 and e1) had the same effect in reducing paw thickness when compared to standard, compound (b1) has a minimal impact on paw thickness reduction. regarding the impact of the control group's 50% v/v propylene glycol. At 0 time, 0.5 hour, and 1 hour, there is no discernible difference between the tested synthesized compounds (a1-d1) and the standard.

TABLE 4: Anti-inflammatory activity of the final synthesized compounds

time(hr)	0 hr	0.5 hr	1 hr	2 hr	3 hr	4 hr	5 hr
control	4.5±0.02	4.76±0.03	5.9±0.03	7.53±0.04	7.96±0.05	6.85±0.02	6.73±0.09
standard	4.45±0.02	4.61±0.03	5.88±0.03	6.94±0.05*	6.4±0.03*	6.15±0.02*	5.68±0.01*
a1	4.44±0.02	4.63±0.01	5.98±0.03	6.12±0.02*[a]	5.14±0.02*[b]	5.03±0.01*[b]	4.6±0.03*
b1	4.43±0.03	4.68±0.02	6.02±0.02	6.9±0.02*	6.75±0.04*	6.8±0.02*	6.6±0.02*
c1	4.49±0.01	4.58±0.01	5.95±0.04	6.7±0.02*	6.5±0.02*	6.3±0.04*	6.01±0.02*
d1	4.5±0.02	4.7±0.02	5.85±0.02	6.35±0.01*	5.75±0.04*[a]	5.3±0.02*[b]	5.03±0.02*
e1	4.42±0.03	4.66±0.02	5.66±0.01	6.21±0.01*	6.08±0.02*	5.99±0.03*	5.83±0.02*

A substantial difference ($p < 0.05$) is considered to exist between non-identical superscripts (a, b) among the tested groups.

(*) significantly different compared to control ($p < 0.05$). Data are expressed in mm paw thickness as mean ± SD.

n= number of rats.

Time (0) is the time of i.p. injection of diclofenac sodium, tested compounds and propylene glycol.

Time (30) is the time of egg white injection to induce edema.

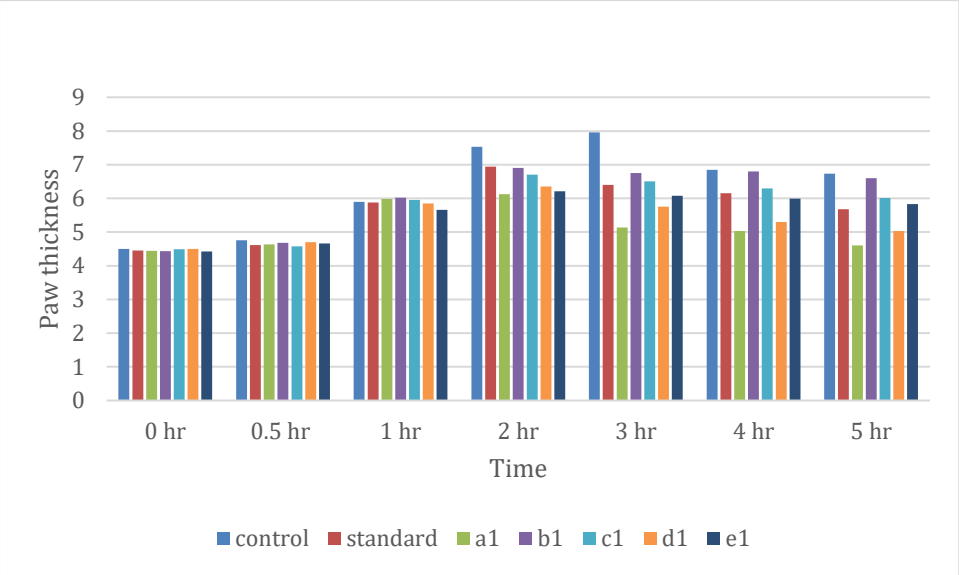

FIGURE 1: Anti-inflammatory activity of the final compounds

CONCLUSION

- The chemical synthesis of a new pyrazolines linked with resorcinol compounds (a1-d1) has been achieved successfully.
- The results of checking physical characteristics (melting point and description), FT-IR, and 1H-NMR spectra for the identification and characterization of the produced compounds confirm their chemical structure.
- All of the compounds tested and the reference drug significantly reduced paw thickness when compared to propylene glycol 50% v/v (control group), and compounds c1 and e1 had effects that were similar to those of diclofenac sodium (3 mg/kg). While compound a1 and compound d1 demonstrated superior anti-inflammatory efficacy in comparison to diclofenac sodium (reference medication).
- The final compounds that contain the electron withdrawing groups Br, NO_2 and Cl show more antimicrobial activity against gram (+ve) bacteria, whereas the compounds that incorporate the electron donating groups OCH_3 and $N(CH_3)_2$ show greater antimicrobial activity against gram (-ve) bacteria.
- •compound b1 show the same antifungal activity comparable with fluconazole, while compound e1 show more antifungal activity than fluconazole (reference)

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