Mustard like yellow powder. Yield: 76%. MP: 155-156°C. RF=0.61. FT-IR: 3105, -3708 (stretching vibration of CH aromatic), 1658 (C=O), 1600 1573 (C=C aromatic), 1512 (NO_2 asymmetric stretching), 1334 (NO_2 symmetric stretching).

3-(4-Hydroxyphenyl)-1-phenylprop-2-en-1-one (compound CH_3) ($C_{15}H_{12}O_2$)

Description: Bright yellow crystals. Yield: 68%. MP: 184-185°C. RF=0.93. FT-IR: 3205 (OH stretching vibration), 3167,3070 (stretching vibration of CH aromatic), 1647 (C=O), 1597,-1554,-1508 (C=C aromatic), 1346 (OH bending), 1215 (C-O).

3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (compound CH_4) ($C_{16}H_{14}O_2$)

Description: Light yellow crystals. Yield: 95%. MP: 74-75°C. RF=0.55. FT-IR: 3059, 3012 (stretching vibration of CH aromatic), 2943 (asymmetric CH stretching of CH_3), 2843 (symmetric CH stretching of CH_3), 1654 (C=O), 1593,1573,-1508 (C=C aromatic), 1261(C-OCH_3).

3-(4-Chlorophenyl)-1-phenylprop-2-en-1-one (compound CH_5) ($C_{15}H_{11}OCl$)

Description: Off white powder. Yield: 99%. MP: 113-115°C. RF=0.5. FT-IR: 3059,-3032 (stretching vibration of CH aromatic), 1654 (C=O), 1600, 1589, 2562 (C=C aromatic), 821 (C-Cl).

3-(4-(Dimethyl amino) phenyl)-1-phenylprop-2-en-1-one (compound CH_6) ($C_{17}H_{17}NO$)

Description: bright orange crystal. Yield: 87%. MP: 110-111°C. RF=0.7. FT-IR: 308693,-3051 (stretching vibration of CH aromatic), 2908 (asymmetric CH stretching of CH_3), 2858 (symmetric CH stretching of CH_3), 1647 (C=O), 1597, 1558 (C=C aromatic), 1157 (C-N).

Synthesis of 2-chloro-N-(4-sulfamoylphenyl) acetamide (intermediate)

Chloro acetyl chloride (2.16 ml, 0.278 mol) was added drop wise with continuous stirring to a solution of sulfanilamide (4 g, 0.232 mol) in DMF (25 ml) in ice bath. After the completion of dropping, the mixture was stirred for 4 h and left over night, then poured into the iced water (125 ml). Precipitated product was filtered, washed with water, dried and recrystallized from ETOH 99% [18].

2-chloro-N-(4-sulfamoylphenyl) acetamide (compound S) ($C_8H_9ClN_2O_3S$)

Description: pure white powder. Yield: 97%. MP: 1170C. RF=0.68. FT-IR: 3321(asymmetric stretching vibration of NH),-3299 (symmetric stretching vibration of NH), 3205 (Stretching vibration of NH amide), 3136, -3089 (stretching vibration of CH aromatic), 1685 (C=O amide), 1597, -1543, -1500 (C=C aromatic), 1338, -1315, -1149 (O=S=O stretching vibration), 833 (C-Cl). 1HNMR (500 MHz, DMSO-d6, ppm): 4.31 (2H, s, protons of methylene group to carbonyl), 7.29 (2H, s, protons of amino of sulfonamide), 7.74-7.76 (2H, d, aromatic protons ortho to amide), 7.78-7.8 (2H, d, aromatic protons ortho to sulfonamide), 10.63 (1H, s, NH proton of amide group).

Synthesis of 2-hydrazineyl-N-(4-sulfamoylphenyl) acetamide (intermediate)

Excess of hydrazine hydrate (5 ml) was added in portions into a solution of 2-chloro-N-(4-sulfamoylphenyl) acetamide (S) in ETOH 99%. The reaction mixture was stirred for 15 hours at 25°C. The precipitated product was filtered and washed with cold ETOH 99%. The product was dried and recrystallized from EtOH [19].

2-hydrazineyl-N-(4-sulfamoyl phenyl) acetamide (compound SH) ($C_8H_{12}N_4O_3S$) Description: bright white powder. Yield: 54%. MP: 208-210°C. RF=0.21. FT-IR: 3429 (asymmetric stretching vibration of NH_2 hydrazine), -3336 (asymmetric stretching vibration of NH_2 sulfonamide), 3305 (stretching vibration of N-H hydrazine), 3248 (stretching vibration of NH amide), -168951 (C=O amide), 1573 (C=C aromatic), 1311, -1153 (O=S=O stretching vibration), 825 (C-Cl). 1HNMR (500 MHz, DMSO-d6, ppm) : 3.4 (2H, s, protons of methylene group to carbonyl), 3.83 -3.86 (1H, dd, proton proton of secondary amine), 4.41–4.42 (2H, dd, protons of primary amine), 7.25 (2H, s, protons of amino of sulfonamide), 7.70–7.78 (2H, m, aromatic protons ortho to amide), 7.8–7.89 (2H, m, aromatic protons ortho to sulfonamide), 10.21 (1H, s, NH proton of amide group).

Synthesis of 2-(3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)-N-(4-sulfamoylphenyl) acetamide derivative (final compounds)

Hydrazine derivative (SH) (2.44 g), (0.01 mol) was dissolved in EtOH 99% (20 ml) then add the appropriate aromatic chalcone derivative (0.01 mol) $CH_{1\text{-}6}$ with catalytic amount of glacial acetic acid, the solution was refluxed for 6-8 hrs. After cool down the reaction mixture, the formed precipitate was filtered, washed, dried and crystallized from EtOH 99% to give the pyrazoline derivatives final compounds [20].

2-(3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)-N-(4-sulfamoylphenyl) acetamide (compound Z1) ($C_{23}H_{22}N_4O_3S$)

Description: Off white powder. Yield: 42%. MP: 200-2020C. RF=0.62. FT-IR: 3356, 3336 (stretching vibration of NH_2), -3267 (stretching vibration of NH amide), 3136 (stretching vibration of CH aromatic), 1693 (C=O amide), 1637 (C=N 2-pyrazoline), 1597 (C=C aromatic), 1307, 1153 (O=S=O stretching vibration). 1HNMR (500 MHz, DMSO-d6, ppm): 3.16–3.24 and 3.62–3.83 (2H, dd, protons of methylene pyrazoline), 3.83-4.19 (2H, dd, protons of methylene to carbonyl), 4.53-4.68 (1H, dd, proton of methine of pyrazoline), 7.29 (2H, s, protons of amino of sulfonamide), 7.08–7.79 (10H, m, aromatic protons ring A,B), 7.82–7.85 (2H, m, aromatic protons ortho to amide), 7.78-7.8 (2H, m, aromatic protons ortho to sulfonamide), 10.46 (1H, s, NH proton of amide group).

2 (5 (4 nitrophenyl) 3 phenyl 4,5 dihydro 1H pyrazol 1 yl) N (4 sulfamoylphenyl)acetamide (compound Z_2) ($C_{23}H_{21}N_5O_5S$)

Description: Light yellow powder. Yield: 48%. MP: 238-2390C. RF=0.5. FT-IR: 3325, 3290 (stretching vibration of NH_2), -3209 (stretching vibration of NsH amide), 3074 (stretching vibration of CH aromatic), 1685 (C=O amide), 1634 (C=N 2-pyrazoline), 1597_(C=C aromatic), 1519, 1315 (stretching vibration NO_2), 1307, 1153 (O=S=O stretching vibration). 1HNMR (500 MHz, DMSO-d6, ppm): 3.18–3.21 and 3.45–3.51 (2H, dd, protons of methylene of pyrazoline), 3.80–4.19 (2H, dd, protons of methylene to carbonyl), 5.14–5.22 (1H, dd, proton of methine of pyrazoline), 7.17–7.20 (2H, m aromatic protons meta to NO_2), 7.23 (2H, s, Protons of amino of sulfonamide), 7.28–7.75 (5H, m, aromatic protons ring A), 7.77–7.80 (2H, m, aromatic protons ortho to amide), 7.88–7.89 (2H, m, aromatic protons ortho to sulfonamide), 8.13–8.32 (2H, m aromatic protons ortho to NO_2, 10.46 (1H, s, NH proton of amide group)

2(5(4hydroxy phenyl)3phenyl4,5dihydro1Hpyrazol1 yl)N(4sulfamoylphenyl)acetamide (compound Z3) ($C_{23}H_{22}N_4O_4S$)

Description: Light yellow powder. Yield: 68%. MP: 245-2460C. RF=0.6. FT-IR: 3321, 3294 (stretching vibration of NH_2), -3205 (stretching vibration of NH amide), 3136 (stretching vibration of CH aromatic), 1685 (C=O amide), 1626 (C=N 2-pyrazoline), 1597_(C=C aromatic), 1519, 1315 (stretching vibration NO_2), 1327, 1153 (O=S=O stretching vibration). 1HNMR (500 MHz, DMSO-d6, ppm): 2.95–3.01 and 3.43–3.47 (2H, dd, protons of methylene of pyrazoline), 3.72–3.86 (2H, dd, protons of methylene to carbonyl), 4.66–4.71 (1H, dd, proton of methine of pyrazoline), 6.71–7.73 (2H, m aromatic protons ortho to OH), 7.17–7.19 (2H, m aromatic protons meta to OH), 7.20 (2H, s, protons of amino of sulfonamide), 7.37–7.48 (3H, m, aromatic protons meta and para to pyrazoline of ring A), 7.65–7.68 (aromatic protons ortho to pyrazoline ring A) and aromatic protons ortho to amide ring C), 7.70–7.73 (4H, m, aromatic protons ortho to sulfonamide), 9.74 (1H, s, phenolic protons), 10.23 (1H, s, NH proton of amide group).

2(5(4methoxy phenyl)3phenyl4,5dihydro1Hpyrazol1 yl)N(4sulfamoylphenyl) acetamide (compound Z_4) ($C_{24}H_{24}N_4O_4S$)

Description: bright white powder. Yield: 75%. MP: 225-2270C. RF=0.6. FT-IR: 3348, 3313 (stretching vibration of NH_2),-3248 (stretching vibration of NH amide), 3128, 3101 (stretching vibration of CH aromatic), 1678 (C=O amide), 1622 (C=N 2-pyrazoline), 1589 (C=C aromatic), 1323, 1149 (O=S=O stretching vibration). 1HNMR (500 MHz, DMSO-d6, ppm): 2.95-3.01 and 3.56–3.62 (2H, dd, protons of methylene of pyrazoline), 3.72–3.86 (2H, dd, protons of methylene to carbonyl), 3.73 (3H, s, protons of OCH_3), 4.66 –4.71 (1H, dd, proton of methine of pyrazoline), 6.91-6.94 (2H, m aromatic protons ortho to OCH_3), 7.34–7.43 (2H, m aromatic protons meta to OCH_3), 7.36 (2H, s, protons of amino of sulfonamide), 7.46–7.65 (5H, m, aromatic protons of ring A), 7.65–7.68 (aromatic protons ortho to pyrazoline ring A), 7.66–7.67 (2H, m, aromatic protons ortho to amide), 7.71–7.72 (4H, m, aromatic protons ortho to sulfonamide), 10.29 (1H, s, NH proton of amide group) (Figure 5).

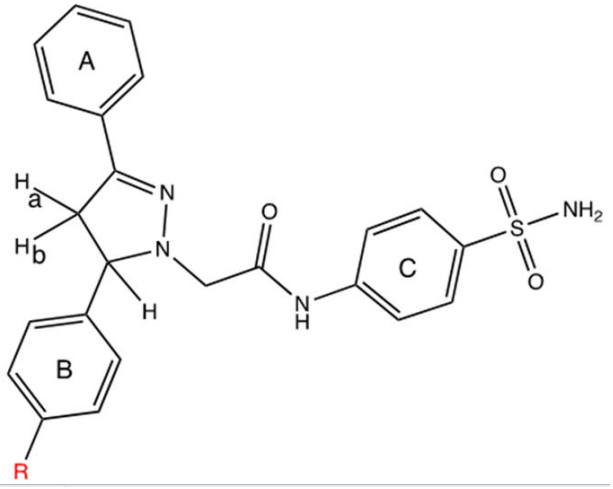

Figure 5: Chemical structure of the synthesized compounds.

2(5(4chlorophenyl)3phenyl4,5dihydro1Hpyrazol1yl)N(4sulfamoylphenyl)acetamide (compound Z_5) ($C_{23}H_{21}ClN_4O_3S$)

Description: Creamy white powder. Yield: 81%. MP: 230-2320C. RF=0.55. FT-IR: 3356, 3336 (stretching vibration of NH_2), 3267 (stretching vibration of NH amide), 3116 (stretching vibration of CH aromatic), 1687 (C=O amide), 1631 (C=N 2-pyrazoline), 1593 (C=C aromatic), 1307-1153 (O=S=O stretching vibration), 829 (C-Cl) 1HNMR (500 MHz, DMSO-d6, ppm): 3.12–3.19 and 3.43–3.47 (2H, dd, protons of methylene pyrazoline), 3.60–3.89 (2H, dd, protons of methylene to carbonyl), 4.67–4.72 (1H, dd, proton of methine of pyrazoline), 7.17–7.19 (2H, m aromatic protons meta to Cl), 7.24 (2H, s, protons of amino of sulfonamide), 7.34–7.38 (2H, m aromatic protons ortho to Cl), 7.36–7.61 (5H, m, Aromatic protons ring A), 7.65–7.67 (2H, m, aromatic protons ortho to amide), 7.70–7.72 (2H, m, aromatic protons ortho to sulfonamide), 10.46 (1H, s, NH proton of amide group).

2-(5-(4-dimethyaminophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-N-(4-sulfamoylphenyl)acetamide (compound Z_6) ($C_{25}H_{27}N_5O_3S$)

Description: Light red powder. Yield: 94%. MP: 214-2150C. RF=0.54. FT-IR: 3340 (stretching vibration of NH_2), 3267 (stretching vibration of NH amide), 3120 (CH stretching vibration diethylamino), 3082 (stretching vibration of CH aromatic), 1683 (C=O amide), 1625 (C=N 2-pyrazoline), 1593 (C=C aromatic), 1300-1149 (O=S=O stretching vibration). 1HNMR (500 MHz, DMSO-d6, ppm): 2.91 (6H, s, protons of dimethyl amino), 2.96–3.00 and 3.02 – 3.05 (2H, dd, protons of methylene of

pyrazoline), 3.92–4.19 (2H, dd, protons of methylene to carbonyl), 4.38 (1H, dd, proton of methine of pyrazoline), 6.67–6.69 (2H, m aromatic protons ortho to dimethyl amino), 6.76–6.78 (2H, m aromatic protons meta to OCH_3), 7.26 (2H, s, protons of amino of sulfonamide), 7.28–7.34 (3H, m, aromatic protons meta and para to pyrazoline of ring A), 7.64–7.77 (4H, m, aromatic protons ortho to pyrazoline ring A and aromatic protons ortho to amide ring C), 7.79–7.82 (2H, m, aromatic protons ortho to sulfonamide), 10.27 (1H, s, NH proton of amide group).

Pharmacological studies

Antimicrobial activity: The antimicrobial activity of the target compounds was done in college of biological science, University of Baghdad. A preliminary antibacterial activity has been performed according to well diffusion method. *In vitro* study used one fungus (*Candida albicans*) and four bacteria (*Staphylococcus aureus*, *Streptococcus pyogenes*), as a gram positive bacteria and (*Pseudomonas aeruginosa*, *Escherichia coli*), as gram negative bacteria). Ciprofloxacin, ceftriaxone and ampicillin, was used as references for antibacterial activity. Fluconazole was used as a reference for anti-fungal activity. The synthesized compounds were studied by maximum concentration of (1000 µg/mL) and (250 µg/mL) in Dimethyl Sulfoxide (DMSO). The zones of inhibitions were measured after 24 h incubation at 37°C.

Anti-inflammatory studies: *In vivo* acute anti-inflammatory effects of the new chemically synthesized compounds (Z_{1-6}) are evaluated by egg white induced paw edema, to study of sulfonamide pyrazoline derivatives with standard diclofenac sodium a well-known COX inhibitor. Eight groups of albino rats (both sex) weighing (160 ± 10 g) were supplied by the animal house of the university of Fallujah, college of veterinary medicine and were put in the same location under standardized conditions. Animals were fed commercial chaw and had free access to water. Animals divided into eight groups (each group consist of 6 rats).

All rats' groups were injected intra peritoneally after thirty minutes of Subcutaneous injection (SC) of 0.05 ml undiluted egg white into the planter side of the left hind paw of the rats. Vernier calliper was used to measure paw thickness at seven time intervals of (0, 30, 60, 120, 180, 240 and 300 min), zero time was the time were tested compounds, standard and control administered by intra peritoneal route. The doses of the newly synthesized compounds were calculated by applying the general formula.

$$\frac{\text{Dose of reference compound}}{\text{Molecular weight reference compound}} = \frac{\text{Dose of tested compound}}{\text{Molecular weight tested compound}}$$

All data collected were manifested as the mean ± SD (standard deviation) and results were analyzed for statistical significance using student T test (two sample assuming equal variances) for comparison between mean values. While comparisons between different groups were made using ANOVA: Two factors without replication. P value (probability) of less than 0.05 was regarded as a significant value.

RESULTS AND DISCUSSION

Chemistry

Chalcones (CH_{1-6}) were synthesized by claisen schmitt condensation through reacting aromatic aldehydes with acetophenone in ethanol with NaOH 30% solution. Chalcones were characterized FTIR that shows appearance of C=O stretching at (1658-1647).

First intermediate (S) where synthesized by the reaction of sulfanilamide and chloroacetyl chloride in DMF, amide formation were characterized by FTIR that shows appearance of C=O stretching at (1685), 1HNMR by appearance of 10.63 (1H, s, NH Proton of amide group).

Second intermediate (SH) where synthesized by the reaction of first intermediate (S) with hydrazine hydrate in ethanol, characterized by FTIR by appearance of all bands related hydrazinyl amino groups at (3429), (3305) and 1HNMR by the shielding of the protons of methylene group to carbonyl from (4.31) ppm to (3.41) ppm as a clue of hydrazinyl intermediate formation. The final compounds (Z_{1-6}) was synthesized by refluxing chalcones (CH_{1-6}) with Second intermediate (SH) in ethanol using catalytic amount glacial acetic (Figure 6 and Table 1).

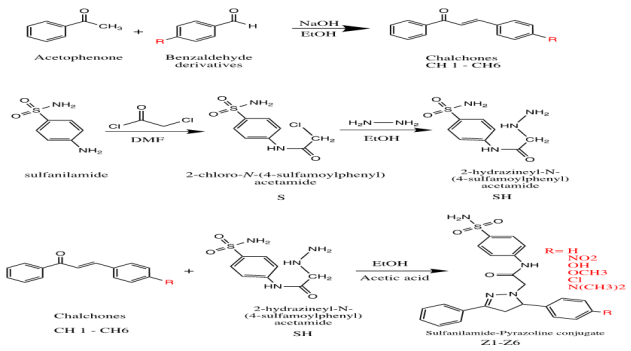

Figure 6: Chemical synthesis.

Table 1: Anti-bacterial activity of the synthesized compound.

Compound	Conc. µg/mL	Gram –ve		Gram +ve	
		E. Coli	*Pseudomonas aeruginosa*	*S. Aureus*	*Streptococcus pyogenes*
		Zone of inhibition			
Z1	1000	15	18	-----	20
	250	-----	4	-----	9
Z2	1000	37	35	35	30
	250	18	21	20	12
Z3	1000	15	10	-----	14
	250	----	2	-----	5
Z4	1000	22	24	16	15
	250	10	7	-----	------
Z5	1000	19	21	15	7
	250	-----	-----	-----	-----
Z6	1000	10	12	20	21
	250	5	7	12	8
Ciprofloxacin	1000	28	21	15	10
	250	15	10	10	7
Ceftriaxone	1000	35	20	32	27
	250	30	20	23	25
Ampicillin	1000	14	-----	12	7
	250	12	-----	10	-----
Tetracycline	1000	12	16	7	4
	250	5	9	2	-----

Anti-microbial evaluation

The antibacterial testing of the newly synthesized compounds (Z_{1-6}) were determined using Mueller Hinton agar medium. All synthesized compounds were evaluated against gram negative bacteria of *Escherichia coli* and *Pseudomonas aeruginosa*; *Staphylococcus aureus* and *Streptococcus pyogenes*, as a gram positive bacteria and ciprofloxacin, ceftriaxone and ampicillin was used as references for antibacterial activity, Dimethyl Sulfoxide (DMSO) was used as solvent. The zone of inhibition illustrated in table 1 was measured by millimeter. The tested compound is considered highly active when inhibition zone (more than 15 mm), moderately active when inhibition zone in between (10-15 mm), slightly active when inhibition zone in between (5-10 mm) and inactive when inhibition zone (less than 5 mm) (Figure 7 and 8) [22].

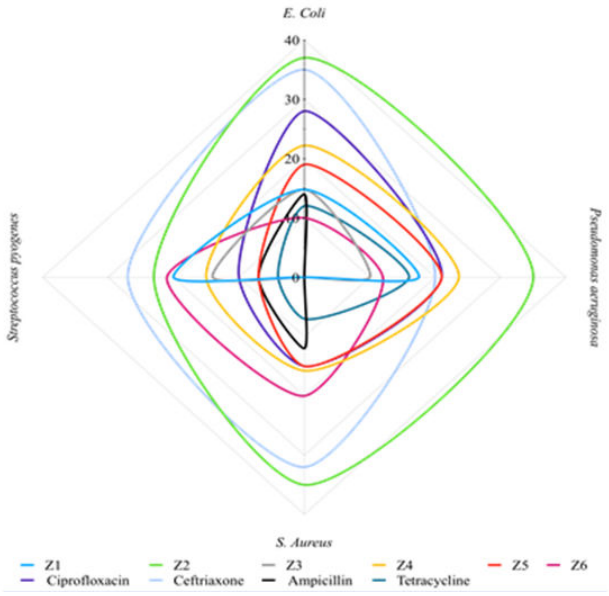

Figure 7: Anti-bacterial activity of synthesized compound 1000 µg/mL.

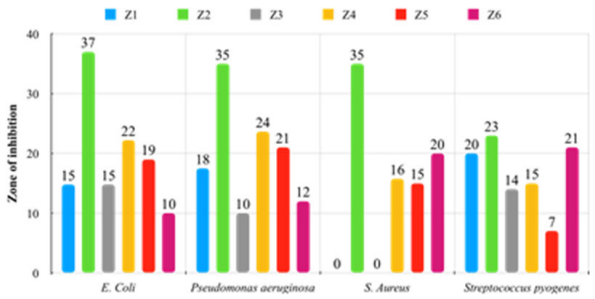

Figure 8: Anti-bacterial activity of the synthesized compound 1000 µg/ml.

In comparisons with standards, the newly synthesized compounds have mostly ranged between high to moderate antibacterial activity in concentration (1000 µg/mL), compound Z_2 and compound Z_4 have high activity against gram +ve and gram -ve bacteria, while compound Z_5 is more effective on gram -ve bacteria and compound Z_6 is more effective on gram +ve bacteria. In comparison with dose difference between (250 µg/mL) and (1000 µg/mL), compound Z_2 exert a high activity in both concentration. The anti-fungal testing of the newly synthesized compounds ($Z_{1\text{-}6}$) were evaluated against *Candida albicans* and using fluconazole as reference. The zone of inhibition illustrated in Figure 7 was measured by millimeter, compound Z_2 and compound Z_4 show a high anti-fungal activity against *Candida albicans* in dose 1000 µg/mL, compound Z_4 has greater inhibition of the fungal growth when compared with fluconazole (reference anti-fungal) (Figure 9).

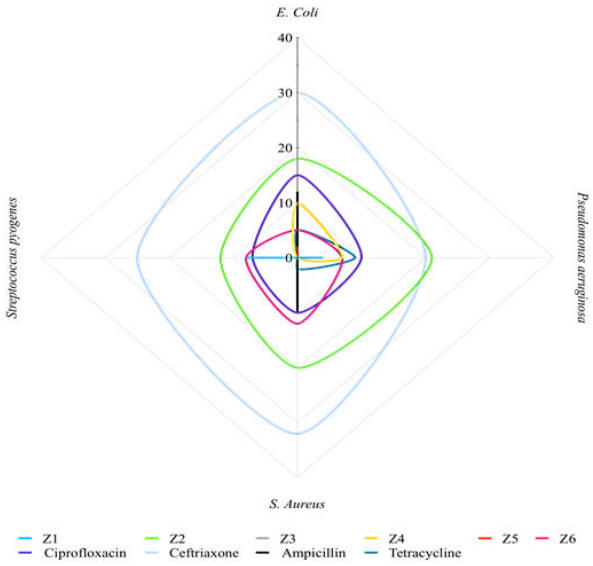

Figure 9: Anti-bacterial activity of the synthesized compound 1000 µg/ml.

Anti-inflammatory evaluation

The effect of newly synthesized compounds on egg white induced edema as an indicator for their anti-inflammatory activity showed in figure 10 and table 2.

Table 2: Inflammatory activity of the synthesized compound.

Time	Mean paw thickness (mm) ± SD							
	Control	Diclofenac sodium	Z_1	Z_2	Z_3	Z_4	Z_5	Z_6
0	4.51 ± 0.07	4.49 ± 0.02	4.52 ± 0.01	4.49 ± 0.03	4.50 ± 0.05	4.48 ± 0.01	4.46 ± 0.08	4.47 ± 0.12
30	4.78 ± 0.03	4.81 ± 0.13	4.81 ± 0.05	4.67 ± 0.05	4.69 ± 0.08	4.83 ± 0.05	4.75 ± 0.05	4.78 ± 0.05
60	5.83 ± 0.05	5.74 ± 0.04	5.78 ± 0.11	5.76 ± 0.09	5.79 ± 0.02	5.75 ± 0.03	5.72 ± 0.07	5.70 ± 0.02
120	6.81 ± 0.05	6.62 ± 0.03*	6.76 ± 0.08*	6.71 ± 0.18*	6.67 ± 0.06*	6.65 ± 0.09*	6.61 ± 0.10*	6.62 ± 0.06*
180	7.12 ± 0.03	6.45 ± 0.09*	6.67 ± 0.03*	6.42 ± 0.02*	6.51 ± 0.04*	6.42 ± 0.04*	6.32 ± 0.03*a	6.39 ± 0.02*
240	6.92 ± 0.02	6.27 ± 0.05*	6.49 ± 0.06*	6.18 ± 0.07*a	6.39 ± 0.03*	6.28 ± 0.03*	6.08 ± 0.09*b	6.25 ± 0.02*
300	6.74 ± 0.02	5.89 ± 0.08*	6.14 ± 0.02*	5.76 ±0.01*a	6.07 ± 0.01*	5.83 ± 0.04*	5.72 ± 0.03*b	5.85 ± 0.04*

Non-identical superscripts (a,b) among different tested group are regarded significantly different ($p<0.05$).(*) 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 injection of egg white to induce edema.

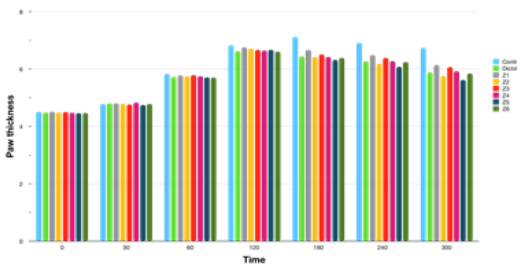

Figure 10: Anti-bacterial activity of the synthesized compounds 250 µg/ml.

All tested compounds and the reference drug produced significant reduction of paw edema in comparison with the effect of propylene glycol 50%v/v (control group), furthermore compound Z_6 and compound Z_4, exhibited comparable effect to that of diclofenac (3 mg/kg). While compound Z_2 and compound Z_5 exhibited superior anti-inflammatory effect when compared to diclofenac (Figure 11).

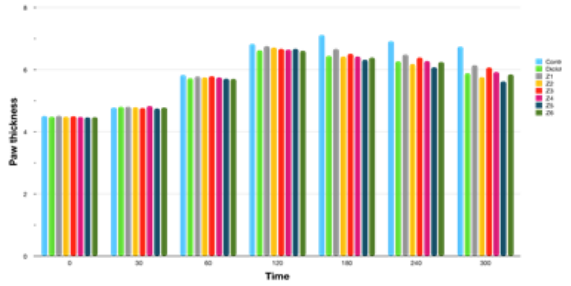

Figure 11: Anti-inflammatory activity of the synthesized compound.

CONCLUSION

- The chemical synthesis of a new pyrazolines linked with sulfonamide compounds Z1-6 has been achieved successfully.
- Physical properties (melting point and description), FT-IR, 1H-NMR spectra have been checked for the identification and characterization of the synthesized compounds and the results confirm their chemical structure.
- *In vivo* anti-inflammatory evaluation of all tested compounds and the reference drug produced significant reduction of paw thickness in comparison with the effect of propylene glycol 50% v/v (control group), furthermore compound Z6 and compound Z4, exhibited comparable effect to that of diclofenac sodium (3 mg/kg). While compound Z2 and compound Z5 exhibited superior anti-inflammatory effect when compared to diclofenac sodium (reference drug).
- The anti-microbial assessment of the final compounds with the incorporation of electron withdrawing groups OCH, $N(CH_3)_2$ display more activity to gram (+ve) bacteria while the compounds incorporate than the electron withdrawing groups Cl, NO_2 display more activity against gram (-ve) bacteria, compound Z2 exert the highest activity even in small concentration. Compound Z4 has greater inhibition of the fungal growth when compared with fluconazole.

REFERENCES

1. Arkawazi B, Mohammed MH. Synthesis and characterization of pyrazoline, dithiocarbamate derivatives with expected biological activity. Biochem Cell Arch 2021; 21:1507–1511.
2. Alkorta I, Rozas I, Elguero J. Interaction of anions with perfluoro aromatic compounds. J Am Chem Society 2002; 124:8593-8598.
3. Panchal AD, Patel PM. Synthesis, anti-bacterial and anti-fungal evaluation of pyrazoline derivatives. E J Chem 2012; 9:1801–1809.
4. Jasril J, Teruna HY, Aisyah A, et al. Micro wave assisted synthesis and evaluation of toxicity and antioxidant activity of pyrazoline derivatives. Indones J Chem 2019; 19:583–591
5. Ahn JH, Kim HM, Jung SH, et al. Synthesis and DP-IV inhibition of cyano pyrazoline derivatives as potent anti-diabetic agents. Bioorg Med Chem Lett 2004; 14:4461–4465.
6. Bhandari S, Tripathi AC, Saraf SK. Novel 2 pyrazoline derivatives as potential anti-convulsant agents. Med Chem Res 2013; 22:5290–5296.
7. Revanasiddappa B, Kumar MV, Kumar H. Synthesis and anti-depressant activity of pyrazoline derivatives. Dhaka Univ J Pharm Sci 2020; 19:179–184.
8. Fioravanti R, Bolasco A, Manna F, et al. Synthesis and biological evaluation of N-substituted-3,5-diphenyl-2-pyrazoline derivatives as Cyclooxygenase (COX-2) inhibitors. Eur J Med Chem 2010; 45:6135–6138.
9. Matiadis D, Sagnou M. Pyrazoline hybrids as promising anticancer agents: An up to date overview. Int J Mol Sci 2020; 21:1–41.
10. Nair AS, Oh JM, Koyiparambath VP, et al. Development of halogenated pyrazolines as selective monoamine oxidase-B inhibitors: Deciphering *via molecular dynamics approach*. Molecules 2021; 26:3264.
11. Salian VV, Narayana B, Sarojini BK, et al. A comprehensive review on recent developments in the field of biological applications of potent pyrazolines derived from chalcone precursors. Lett Drug Des Discov 2018; 15:516–574.
12. Ozdemir A, Turan Zitouni G, Kaplancikli ZA, et al. Synthesis and antimicrobial activity of 1-(4-aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives. Eur J Med Chem 2007; 42:403-409.
13. Skocovska M, Ferencik M, Svoboda M, et al. Residues of selected sulfonamides, non-steroidal anti-

inflammatory drugs and analgesics antipyretics in surface water of the Elbe river basin (czech republic). Vet Med 2021; 66:208–218.

14. Sridhar S, Rajendraprasad Y. Synthesis and analgesic studies of some new 2-pyrazolines. E J Chem 2012; 9:476989.
15. Gungor T, Ozleyen A, Yilmaz YB, et al. New nimesulide derivatives with amide/sulfonamide moieties: Selective cox-2 inhibition and antitumor effects. Eur J Med Chem 2021; 221:113566.
16. Al-Nakeeb MR, Omar TNA. Synthesis, characterization and preliminary study of the anti-inflammatory activity of new pyrazoline containing ibuprofen derivatives. Iraqi J Pharm Sci 2019; 28:133–139.
17. Zhou W, Zhang W, Peng Y, et al. Design, synthesis and anti-tumor activity of novel benzimidazole chalcone hybrids as non-intercalative topoisomerase II catalytic inhibitors. Molecules 2020; 25:3180.
18. Saglik BN, Cevik UA, Osmaniye D, et al. Synthesis, molecular docking analysis and carbonic anhydrase I-II inhibitory evaluation of new sulfonamide derivatives. Bioorg Chem 2019; 91:103153.
19. Mishra D, Singh R, Rout C. A facile amidation of chloroacetyl chloride using DBU. Int J ChemTech Res 2017; 10:365-372.
20. Farooq S, Ngaini Z. Chalcone derived pyrazole synthesis via one pot and two pot strategies. Curr Org Chem 2020; 24:1491–1506.
21. Karabacak M, Altintop MD, Ciftci HI, et al. Synthesis and evaluation of new pyrazoline derivatives as potential anticancer agents. Molecules 2015; 20:19066–19084.
22. El Kolli M. Mechanism of antimicrobial activity and antioxidant activities of the essential oil and the methanolic extract of carum montanum from algeria. Ann Agric Sci Moshtohor 2018; 56:253–262.