



## **Preparation and Analysis of New 1,3,5-Trisubstituted-2-Pyrazolines Derivative for Their Analgesic Potential**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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### **ABSTRACT**

The goal of the study was to develop, synthesise, and characterise a novel 1,3,5-trisubstituted-2-pyrazolines derivative, as well as to assess its analgesic potential. The reaction of chalcone derivatives with 4-hydrazinylbenzene sulfonamide hydrochloride and phenyl hydrazine hydrochloride yielded 1,3,5-tri-substituted-2-pyrazolines derivatives. The IR, <sup>1</sup>HNMR, and mass spectrum analyses were used to characterise a total of sixteen substances. Analgesic activity of the proposed substances has been tested. The analgesic effect of the produced compounds was tested using two methods: the hot plate test technique and acetic acid induced writhing in mice. To compare the effectiveness, pentazocine and acetyl acetic acid were utilised as reference drugs. The hot plate test technique and acetic acid induced writhing in mice were used to assess the analgesic effect of the 16 produced chemical series A1-A8, and B1-B8. The evaluation's outcomes were viewed using Pentazocine and acetyl acetic acid as the standard drugs. In a 90-minute hot plate test, compounds A2 (10.30 s), A4 (9.45 s), A7 (11.65 s), and A8 (11.26 s) showed a delay in paw withdrawal latency time. Compounds B2 (9.10 s) and B7 (10.42 s) prolong the paw withdrawal latency time after 90 minutes in series B1-B8, reduce the pain feeling, and inhibit pain induced by heat methods. Compounds A2, A5, A6, A7, and A8 from Series A1-A8 showed 83.00, 76.01, 80.34, 86.99, 88.15 percent inhibition, substantially (p0.05 and p0.001, respectively), and decreased the number of wriths caused by 0.6 percent acetic acid at a dosage of 10 mg/kg. Acetylsalicylic acid

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(10 mg/kg) appears to be more successful in lowering the number of wriths, with a 99.0% reduction in the number of wriths (p0.001). B1, B3, and B4 have the least amount of active activity. These all finding suggest that these synthesized compounds have the potential as analgesic agent.

*Keywords: Analgesic; pyrazoline; pentazocine; hot plate method; writhing.*

## 1. INTRODUCTION

Any member of the category of medications used to induce analgesia (pain alleviation) is referred to as an analgesic. [1] Analgesic medications affect the peripheral and central nerve systems in a variety of ways. Paracetamol, non-steroidal anti-inflammatory medications like salicylates, and opioid pharmaceuticals like morphine and opium are examples of narcotics, which reversibly remove feeling. An analgesic is a medicine that reduces pain selectively by acting in the central nervous system (CNS) or on peripheral pain mechanisms without affecting consciousness.

Medicinal chemistry is virtually usually focused on drug development and discovery. Biochemistry, combinatorial chemistry, chemical biology, phytochemistry, pharmacology, Pharmacognosy, statistics, physical chemistry, and molecular biology have all been included into medicinal chemistry as a result of the focus on developing novel synthetic medicine molecules. [2] Medicinal chemists are also attempting to speed up the drug development process in order to uncover the lead molecule. Chalcone is a 1,3-diphenyl-2-propene-1-one compound with two aromatic rings connected by a three-carbon, -unsaturated carbonyl system. These are found in large quantities in edible plants and are thought to be precursors of flavonoids and isoflavonoids. Chalcones, which feature conjugated double bonds and a totally delocalized -electron system on both benzene rings, have a low melting point due to their low intermolecular force. Molecules with this structure have comparatively low redox potentials and are more likely to conduct electron transfer processes. [3] The study of chemical properties, particularly the peculiarities of the behaviour of pyrazole derivatives and the clarification of their physicochemical features, has recently gotten a lot of interest. This allowed for the collection of fresh data that was crucial. Pyrazole derivatives have a long history of use as herbicides and insecticides in agriculture, as well as in the pharmaceutical sector as antipyretics and anti-inflammatory drugs. One of the first synthetic drugs was antipyrine. [4-8]. Various chalcone derivatives with suitable

substitutions may be synthesised, which then undergo a cyclo-addition process with substituted hydrazine to provide desirable 1,3,5-tri substituted pyrazole derivatives. As a result, several chalcone derivatives were synthesised and employed as intermediates in the synthesis of 1,3,5 tri substituted pyrazole in the current work.

The objective of the paper was to design, synthesis and characterization of new 1,3,5-trisubstituted-2-pyrazolines derivative and evaluate for analgesic potential.

## 2. MATERIALS AND METHODS

Hi-media, New Delhi, provided the chemical 3'-methoxy-4'-hydroxy acetophenone. CDH (Chemical Drug House), New Delhi, India, provided benzaldehyde, 4-chlorobenzaldehyde, 4-bromobenzaldehyde, 4-nitrobenzaldehyde, 4-methylbenzaldehyde, 4-methoxybenzaldehyde, 4-ethylbenzaldehyde, and 4-(dimethyl amino)benzaldehyde. Sigma Aldrich, New Delhi, provided 4-hydrazinylbenzenesulfonamide hydrochloride and Phenyl hydrazine hydrochloride. Chemicals of synthetic grade were utilised in the experiments. In open glass capillaries, the melting points of the produced compounds were determined. ALPHA (Bruker) FTIR Spectrometer was used to record IR spectra. Elemental analysis was carried out, and the results were determined to be within 0.4 percent of the theoretical values. On a Bruker Avance 400 spectrophotometer with a 400 MHz, 5mm multi-nuclear inverse probe head, low and high-temperature facility, and HRMAS accessory, <sup>13</sup>C NMR spectra were acquired. ESI used mass spectrometers Jeol SX-102 (FAB) to record the spectra.

### 2.1 Chemistry

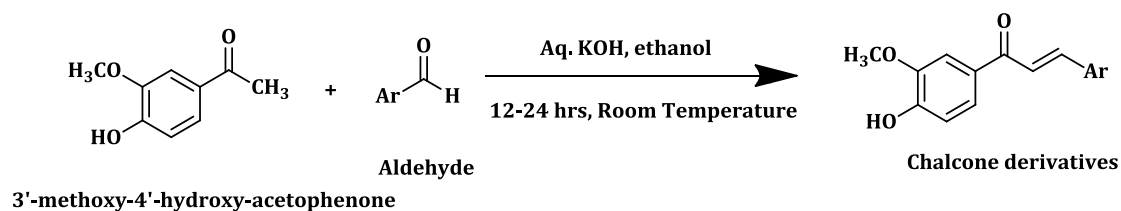
#### 2.1.1 Present synthesis comprises

- A. Synthesis scheme-I: Synthesis of chalcone of 3'-methoxy-4'-hydroxyacetophenone by Claisen Schmidt condensation
- B. Synthesis scheme-II: Synthesis of 1,3,5- tri-substituted-2-pyrazolines derivatives.

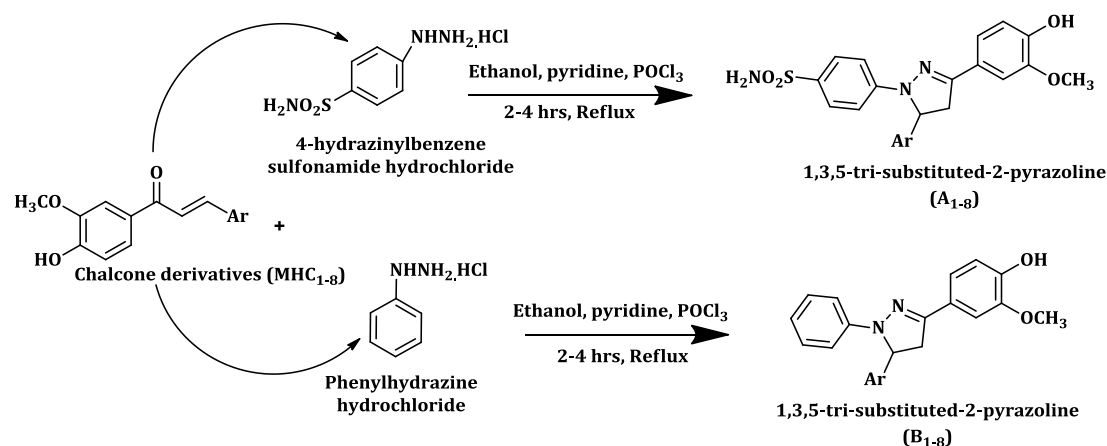
In the aforementioned procedure, an equimolar quantity (0.01 M) of 3-methoxy-4-hydroxyacetophenone (0.83g) was collected and combined with an equimolar quantity of benzaldehyde. In ethanol, the mixture was dissolved. The mixture was stirred for 5 minutes before adding a 50 percent aqueous potassium hydroxide solution slowly and stirring for 24 hours at room temperature. [9] The TLC was used to monitor the reaction's completion. The synthesis was then finished by pouring the liquid onto crushed ice and obtaining a solid result; however, if a solid product was not produced, it was acidified with dilute hydrochloric acid. The resulting solid was filtered, dried, and purified using a solvent system in column chromatography (hexane: ethyl acetate). In synthesis scheme-I, the reaction is shown. Infrared spectroscopy and proton NMR spectroscopy were used to analyse the produced compounds, and they were confirmed to be trustworthy with a likely structure. The obtained compounds were analysed using IR and <sup>1</sup>H NMR and found to have a structure that was compatible with what was predicted. 1500-1520 (C=C Quadrant of Ar), 1430-1470 (CH=CH), 1105 (C-F), 848 (C-Cl), 1015 (C-Br), and 1160 (O-H str) (OCH<sub>3</sub>). These compounds further

confirmed by proton NMR revealed the characteristic ethylenic protons of the chalcone system in between δ 6.94 and 8.19 confirm the compound. The reaction was monitored by the TLC using Hexane: ethyl acetate as mobile phase.

The synthesised chalcone derivatives were combined in absolute alcohol with equimolar amounts of 4-hydrazinylbenzene sulfonamide hydrochloride and phenylhydrazine hydrochloride (0.005M) and a tiny amount of pyridine (0.01M) (5-7 ml). The reaction mixture was refluxed for 2-6 hours at 65°C. TLC was used to monitor the reaction, which used ethyl acetate:hexane as the mobile phase. The solvent was entirely evaporated before being placed into ice cold water and constantly stirred to convert the liquid form into a solid product, which yielded the synthesised product. [10] Scheme-II depicted the synthesis. This substance was filtered and dried under vacuum. Purified by column chromatography, the synthesised chemical was produced as a pale yellow solid colour powder. For phenyl hydrazine hydrochloride, the similar technique was followed, in which chalcone derivatives interacted with the phenyl hydrazine hydrochloride.



### Synthesis scheme-I: Synthesis of the chalcone of 3'-methoxy-4'-hydroxyacetophenone



### Synthesis scheme-II: Synthesis of 1,3,5- tri-substituted-2-pyrazolines

## 2.2 Pharmacological Evaluation

### 2.2.1 Analgesic activity

#### 2.2.1.1 Determination of LD50 value and acute toxicity

In this study, healthy and mature male albino Swiss rats weighing 120-150 g were employed. The animals were fasted for 24 hours and then separated into five groups of five. The test chemicals were given intraperitoneally at dosages of 10 mg, 100 mg, 1000 mg, and 2000 mg per kg body weight, suspended in sodium carboxymethyl cellulose solution (1%) Only the vehicle was given to the animals in the control group (1 percent sodium CMC). To record the mortality, the animals were watched for 48 hours after the test chemicals were administered. Even at a high dose of 2000 mg/kg body weight [11], all of the synthesised compounds used in the pharmacological screening were determined to be devoid of toxicity and toxic symptoms, and hence were deemed safe. Rats in groups of 34 were given varied doses orally using the staircase approach, starting at 10 mg/kg and increasing dosage by a factor 1.5 if no death occurred [12], and lowering succeeding dose by a factor 0.7 if mortality occurred. [13] The hit and try approach was used to identify the least tolerated (100 percent mortality) and most tolerated (0% mortality). The following formulae were used to correct for 0% and 100% mortality: 100 (0.25/n); 100 (n0.025/n); 100 (n0.025/n); 100 (n0.025/n); 100 (n0.025/n); 100 (n0.025/n); 100 (n0.025/n); 100 (n0.025/n); 100 (n0.025/n); 100 (n0.025/n); 100 (n0.025/n); 100 (n0.025/n); 100 (n0.025/n) For a 100% chance of death: LD50 S.E. = Log Dose with Highest Mortality- Log Dose with Lowest Mortality/ n Between these two, doses were chosen, and any mortality was tracked for 24 hours, with the number of fatalities recorded. To calculate the dosage for probit value 5, which was assumed to represent LD50, a log dose versus probit value curve was drawn. For this investigation, a dose range significantly below LD50 was used. All the 2-pyrazolines employed in the pharmacological screening have been found to be free from toxicity as well as toxic symptoms even at a high dose of 1000 mg/kg body weight and hence they were considered safe.

#### 2.2.1.2 Dose planning and grouping of animals

The dosages employed were comparable to or less than 1/10th of the doses corresponding to LD50 values, with no major behavioural or CVS

abnormalities. When opposed to the standard, which exhibited some alterations at greater dosages, there were no CNS or CVS effects even at larger levels. [14-18].

### 2.2.2 Analgesic effect

The analgesic effect of the produced compounds was tested using two methods: the hot plate test technique and acetic acid induced writhing in mice. To compare the effectiveness, pentazocine and acetyl acetic acid were utilised as reference drugs.

#### 2.2.3 Hot plate test in mice

Female Swiss albino mice weighing 25–30 g were given the treatment reported by Eddy and Leimback in 1953. [19] Mice were screened by putting them on a hot plate set to 551°C and recording their reaction time in seconds. The time it took for a paw to lick the hot plate or jump on it was deemed a response time. The reactions were collected before and after the injection of synthetic compounds and pentazocine for 30, 60, 90, 120, 150, and 180 minutes. To protect the animals, a 15-second cut-off period was chosen. The mice were separated into thirty-four groups, each containing six animals.

Group 1: - Vehicle control (2% Tween 80).

Group 2: - Standard (Pentazocine 10 mg/kg, s.c.).

Group 3-18: Synthesized compounds (10 mg/kg, p.o.) respectively.

#### 2.2.4 Acetic acid induced writhing in mice

Female Swiss albino mice (25–30g) were treated according to Collier et al 1963 's procedure. [20] Mice were given synthetic compounds and acetylsalicylic acid orally 60 minutes before receiving acetic acid solution at a rate of 10 ml/kg (0.6 percent , i.p.). [21] Over the course of 15 minutes, the number of abdominal constrictions (complete extension of both hind paws) was tallied.

The mice were divided into eleven groups of six mice each:

Group 1: - Vehicle control (2% Tween 80).

Group 2: - Standard (Acetylsalicylic acid 10 mg/kg p.o.).

Group 3-18: Synthesized compounds (10 mg/kg, p.o.) respectively.

The percent inhibition of writhing was calculated as follows: % Inhibition =  $(VC-VT/VC) \times 100$

Where, VT, number of writhes in drug treated mice; VC, number of writhes in control group mice.

### 3. RESULTS AND DISCUSSION

#### 3.1 Spectral Analysis

The infrared spectra of the synthesized compounds showed characteristic absorption band between 3402(O-H str.); 1592 (C=N); 1489 [C=C (Quadrant of Ar)]; 1174 (-C<sub>6</sub>H<sub>5</sub>); 1430 (CH=CH str.); 3418 (SO<sub>2</sub>-NH str.); 1330, 1168 (S=O); 853 (C-Cl); 2938 (C-H aromatic), 853 (C-Cl), 1024 (C-Br); 1120 (C-F) and 1072 (OCH<sub>3</sub>). In 1H-NMR spectra of the synthesized compounds represents the 6.21 (m, 2H, C<sub>6</sub>H<sub>5</sub>-NH<sub>2</sub>), 6.84–7.34 (m, 3H, Ar-H); 8.52 (s, 1H, pyrazole-CH), 7.45–7.72 (d, 3H, Ar-H, J=8.6 Hz), 3.60 (1H, dd); 5.36 (1H, dd), 6.82–7.62 (m, 2H, Ar-H); 2.55 (m, 3H, C<sub>6</sub>H<sub>5</sub> N(CH<sub>3</sub>)<sub>2</sub>), 3.81 (m, 3H, C<sub>6</sub>H<sub>5</sub>-OCH<sub>3</sub>), 2.15 (m, 3H, C<sub>6</sub>H<sub>5</sub>-CH<sub>3</sub>), 7.15 (bs, 2H, SO<sub>2</sub>NH<sub>2</sub>), 3.81 (m, 3H, C<sub>6</sub>H<sub>5</sub>-OCH<sub>3</sub>) respectively. Methyl carbons were observed at 2.15 ppm.

All of the produced compounds' elemental analyses were within 0.4 percent of theoretical values. After nitration of the compounds, the existence of an aromatic ring was confirmed by the production of a strong sooty flame and the creation of an oily layer. Two significant peaks were identified in the FAB mass spectra. Using silica gel G and different solvent systems such as hexane, thin layer chromatography (TLC) has been used to evaluate reactivity and purity of produced chemicals. For visualisation, ethyl acetate and iodine chambers were employed, with UV chambers being used in some situations. All these characterization parameter showed that the structure of the synthesized compounds were near to expected.

#### 3.1.1 Compound A1: 4-(3-(4-hydroxy-3-methoxyphenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)phenylsulfite

Molecular formula: C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub>S; Molecular weight: 423.48; TLC (Rf value): 0.45; Element (Found/Calc.): Nitrogen (9.85/9.92); Sulphur (7.59/7.57); Oxygen (15.10/15.11); IR (cm<sup>-1</sup>): 3405 O-H str.; 1670 C=N; 1487 C=C; 1172 C<sub>6</sub>H<sub>5</sub>; 1428 CH=CH str.; 3415 SO<sub>2</sub>NH str.; 1328 S=O; 2936 C-H; 1HNMR (ppm): 7.15 (bs, 2H, SO<sub>2</sub>NH<sub>2</sub>), 5.53 (1H, s, Ar-OH), 3.81 (3H, s, -OCH<sub>3</sub>); 8.52 (s, 1H, pyrazole-CH), 3.60 (1H, dd); 5.36 (1H,

dd), 7.45 (d, 2H, Ar-H, J=8.6 Hz), 6.90–7.40 (m, 3H, Ar-H), 7.72–7.86 (m, 3H, Ar-H). FAB Mass (m/z): 423.13 (Quasi-molecular ion peak (M+H)).

#### 3.1.2 Compound A2: 4-(5-(4-chlorophenyl)-3-(4-hydroxy-3-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)phenylsulfite

Molecular formula: C<sub>22</sub>H<sub>20</sub>ClN<sub>3</sub>O<sub>4</sub>S; Molecular weight: 457.93; TLC (Rf value): 0.38; Element (Found/Calc.): Nitrogen (9.12/9.18); Sulphur (6.59/7.00); Oxygen (13.95/13.98); IR (cm<sup>-1</sup>): 3400 O-H str.; 1668 C=N; 1484 C=C; 1170 C<sub>6</sub>H<sub>5</sub>; 1420 CH=CH str.; 3416 SO<sub>2</sub>NH str.; 1325 S=O; 853 C-Cl; 2936 C-H; 1HNMR: 7.15 (bs, 2H, SO<sub>2</sub>NH<sub>2</sub>), 5.53 (1H, s, Ar-OH), 3.81 (3H, s, OCH<sub>3</sub>); 8.52 (s, 1H, pyrazole-CH), 7.45 (d, 2H, Ar-H, J=8.6 Hz), 3.60 (1H, dd); 5.36 (1H, dd) 6.90–7.40 (m, 3H, Ar-H), 7.45–7.88 (m, 3H, Ar-H); FAB Mass (m/z): 457.09 (Quasi-molecular ion peak (M+H)+).

#### 3.1.3 Compound A3: 4-(5-(4-bromophenyl)-3-(4-hydroxy-3-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)phenylsulfite

Molecular formula: C<sub>22</sub>H<sub>20</sub>BrN<sub>3</sub>O<sub>4</sub>S; Molecular weight: 502.38; TLC (Rf value): 0.40; Element (Found/Calc.): Nitrogen (8.38/8.36); Sulphur (6.35/6.38); Oxygen (12.72/12.74); IR (cm<sup>-1</sup>): 3409 O-H str.; 1672 C=N; 1491 C=C; 1176 C<sub>6</sub>H<sub>5</sub>; 1424 CH=CH str.; 3410 SO<sub>2</sub>NH str.; 1325 S=O; 1020 C-Br; 2930 C-H; 1HNMR: 7.15 (bs, 2H, SO<sub>2</sub>NH<sub>2</sub>), 5.53 (1H, s, Ar-OH), 3.81 (3H, s, OCH<sub>3</sub>); 8.52 (s, 1H, pyrazole-CH), 7.45 (d, 2H, Ar-H, J=8.6 Hz), 3.60 (1H, dd); 5.36 (1H, dd) 6.90–7.40 (m, 3H, Ar-H), 7.56–7.68 (m, 3H, Ar-H); FAB Mass (m/z): 503.03 (Quasi-molecular ion peak (M+H)+)

#### 3.1.4 Compound A4: 4-(5-(4-fluorophenyl)-3-(4-hydroxy-3-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)phenylsulfite

Molecular formula: C<sub>22</sub>H<sub>20</sub>FN<sub>3</sub>O<sub>4</sub>S; Molecular weight: 441.48; TLC (Rf value): 0.54; Element (Found/Calc.): Nitrogen (9.50/9.52); Sulphur (7.25/7.26); Oxygen (14.48/14.50); IR (cm<sup>-1</sup>): 3410 O-H str.; 1670 C=N; 1484 C=C; 1170 C<sub>6</sub>H<sub>5</sub>; 1436 CH=CH str.; 3415 SO<sub>2</sub>NH str.; 1326 S=O; 1118 C-F; 2929 C-H; 1HNMR: 7.15 (bs, 2H, SO<sub>2</sub>NH<sub>2</sub>), 5.53 (1H, s, Ar-OH), 3.81 (3H, s, OCH<sub>3</sub>); 8.52 (s, 1H, pyrazole-CH), 7.45 (d, 2H, Ar-H, J=8.6 Hz), 3.60 (1H, dd); 5.36 (1H, dd) 6.90–7.40 (m, 3H, Ar-H), 7.30–8.10 (m, 3H, Ar-H); FAB Mass (m/z): 441.12 (Quasi-molecular ion peak (M+H)+)

**3.1.5 Compound A5: 4-(3-(4-hydroxy-3-methoxyphenyl)-5-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl)phenylsulfite**

Molecular formula:  $C_{22}H_{20}N_4O_6S$ ; Molecular weight: 468.48; TLC (Rf value): 0.30; Element (Found/Calc.): Nitrogen (11.94/11.96); Sulphur (6.82/6.84); Oxygen (20.47/20.49); IR ( $cm^{-1}$ ): 3410 O-H str.; 1668 C=N; 1490 C=C; 1172  $C_6H_5$ ; 1428 CH=CH str.; 3418  $SO_2NH$  str.; 1328 S=O; 1569 N=O str.; 1365 N-O str.; 2932 C-H;  $^1H$ NMR: 7.15 (bs, 2H,  $SO_2NH_2$ ), 5.53 (1H, s, Ar-OH), 3.81 (3H, s, C-3'-OCH<sub>3</sub>); , 8.52 (s, 1H, pyrazole-CH), 7.45 (d, 2H, Ar-H, J=8.6 Hz), 3.60 (1H, dd); 5.36 (1H, dd) 6.90–7.40 (m, 3H, Ar-H), 8.00–8.25 (m, 3H, Ar-H). FAB Mass (m/z): 468.11 (Quassi-molecular ion peak (M+H)<sup>+</sup>)

**3.1.6 Compound A6: 4-(3-(4-hydroxy-3-methoxyphenyl)-5-(p-tolyl)-4,5-dihydro-1H-pyrazol-1-yl)phenylsulfite**

Molecular formula:  $C_{23}H_{23}N_3O_4S$ ; Molecular weight: 437.51; TLC (Rf value): 0.64; Element (Found/Calc.): Nitrogen (9.58/9.60), Sulphur (7.32/7.33), Oxygen (14.60/14.63); IR ( $cm^{-1}$ ): 3408 O-H str.; 1665 C=N; 1481 C=C; 1168  $C_6H_5$ ; 1426 CH=CH str.; 3424  $SO_2NH$  str.; 1324 S=O; 1069 OCH<sub>3</sub>; 2930 C-H;  $^1H$ NMR: 7.15 (bs, 2H,  $SO_2NH_2$ ), 5.53 (1H, s, Ar-OH), 3.81 (3H, s, OCH<sub>3</sub>); , 8.52 (s, 1H, pyrazole-CH), 6.95–7.45 (d, 2H, Ar-H, J=8.6 Hz), 3.60 (1H, dd); 5.36 (1H, dd) 7.20–7.40 (m, 3H, Ar-H), 7.19–7.77 (m, 2H, Ar-H), 2.15 (m, 3H,  $C_6H_5-CH_3$ ). FAB Mass (m/z): 437.14 (Quassi-molecular ion peak (M+H)<sup>+</sup>)

**3.1.7 Compound A7: 4-(3-(4-hydroxy-3-methoxyphenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)phenylsulfite**

Molecular formula:  $C_{23}H_{23}N_3O_5S$ ; Molecular weight: 453.51; TLC (Rf value): 0.23; Element (Found/Calc.): Nitrogen (9.25/9.27); Sulphur (7.02/7.07); Oxygen (17.62/17.64); IR ( $cm^{-1}$ ): 3412 O-H str.; 1673 C=N; 1491 C=C; 1172  $C_6H_5$ ; 1428 CH=CH str.; 3422  $SO_2NH$  str.; 1323 S=O; 1067 OCH<sub>3</sub>; 2928 C-H;  $^1H$ NMR (ppm): 7.15 (bs, 2H,  $SO_2NH_2$ ), 5.53 (1H, s, Ar-OH), 3.81 (6H, s, OCH<sub>3</sub>); , 8.52 (s, 1H, pyrazole-CH), 6.95–7.45 (d, 2H, Ar-H, J=8.6 Hz), 3.60 (1H, dd); 5.36 (1H, dd) 7.20–7.40 (m, 3H, Ar-H), 7.35–7.55 (m, 2H, Ar-H). FAB Mass (m/z): 453.14 (Quassi-molecular ion peak (M+H)<sup>+</sup>)

**3.1.8 Compound A8: 4-(5-(4-(dimethylamino)phenyl)-3-(4-hydroxy-3-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)phenyl sulphite**

Molecular formula:  $C_{24}H_{26}N_4O_4S$ ; Molecular weight: 453.51; TLC (Rf value): 0.42; Element (Found/Calc.): Nitrogen (11.58/12.01); Sulphur (6.86/6.87); Oxygen (13.70/13.72); IR ( $cm^{-1}$ ): 3407 O-H str.; 1665 C=N; 1493 C=C; 1170  $C_6H_5$ ; 1425 CH=CH str.; 3416  $SO_2NH$  str.; 1327 S=O; 2932 C-H;  $^1H$ NMR (ppm): 7.15 (bs, 2H,  $SO_2NH_2$ ), 5.53 (1H, s, Ar-OH), 3.81 (3H, s, OCH<sub>3</sub>); 8.52 (s, 1H, pyrazole-CH), 3.60 (1H, dd); 5.36 (1H, dd) 6.95–7.45 (d, 2H, Ar-H, J=8.6 Hz), 7.20–7.40 (m, 3H, Ar-H), 6.68–7.70 (m, 2H, Ar-H), 2.15 (m, 6H,  $C_6H_5-N(CH_3)_2$ ). FAB Mass (m/z): 466.17 (Quassi-molecular ion peak (M+H)<sup>+</sup>).  $^1H$ NMR spectra was shown in Fig. 2.

**3.1.9 Compound B1: 4-(1,5-diphenyl-4,5-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol**

Molecular formula:  $C_{22}H_{20}N_2O_2$ ; Molecular weight: 344.41; TLC (Rf value): 0.38; Element (Found/Calc.): Nitrogen (8.10/8.13); Oxygen (9.27/9.29); IR ( $cm^{-1}$ ): 3409 O-H str.; 1596 C=N; 1484 C=C; 1166  $C_6H_5$ ; 1432 CH=CH str.; 2934 C-H;  $^1H$ NMR (ppm): 5.53 (1H, s, Ar-OH), 3.81 (3H, s, C-3'-OCH<sub>3</sub>); 6.80–7.20 (m, 3H, Ar-H), 8.52 (s, 1H, pyrazole-CH), 7.10–7.51 (d, 3H, Ar-H, J=8.6 Hz), 3.60 (1H, dd); 5.36 (1H, dd) 7.45–7.62 (m, 3H, Ar-H). FAB Mass (m/z): 344.15 (Quassi-molecular ion peak (M+H)<sup>+</sup>)

**3.1.10 Compound B2: 4-(5-(4-chlorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol**

Molecular formula:  $C_{22}H_{19}ClN_2O_2$ ; Molecular weight: 378.85; TLC (Rf value): 0.42; Element (Found/Calc.): Nitrogen (7.38/7.39); Oxygen (8.42/8.45); IR ( $cm^{-1}$ ): 3406 O-H str.; 1596 C=N; 1488 C=C; 1170  $C_6H_5$ ; 1428 CH=CH str.; 850 C-Cl; 2936 C-H;  $^1H$ NMR (ppm): 5.53 (1H, s, Ar-OH), 3.81 (3H, s, OCH<sub>3</sub>); 6.80–7.20 (m, 3H, Ar-H), 8.52 (s, 1H, pyrazole-CH), 7.35–7.55 (d, 3H, Ar-H, J=8.6 Hz), 3.60 (1H, dd); 5.36 (1H, dd) 7.55–7.88 (m, 2H, Ar-H). FAB Mass (m/z): 378.11 (Quassi-molecular ion peak (M+H)<sup>+</sup>).  $^1H$ NMR spectra was shown in Fig. 1.

**3.1.11 Compound B3: 2-methoxy-4-(5-(4-nitrophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)phenol**

Molecular formula:  $C_{22}H_{19}N_3O_4$ ; Molecular weight: 389.40; TLC (Rf value): 0.40; Element

(Found /Calc.)%: Nitrogen (10.78/10.79); Oxygen (16.42/16.43); IR (cm<sup>-1</sup>): 3410 O-H str.; 1596 C=N; 1487 C=C; 1172 C<sub>6</sub>H<sub>5</sub>; 1428 CH=CH str.; 1025 C-Br; 2936 C-H; 1H NMR (ppm): 5.53 (1H, s, Ar-OH), 3.81 (3H, s, OCH<sub>3</sub>); 6.80–7.20 (m, 3H, Ar-H), 8.52 (s, 1H, pyrazole-CH), 3.60 (1H, dd); 5.36 (1H, dd) 7.35–7.55 (d, 3H, Ar-H, J=8.6 Hz), 7.66–7.78 (m, 2H, Ar-H). FAB Mass (m/z): 389.14 (Quasi-molecular ion peak (M+H)<sup>+</sup>)

**3.1.12 Compound B4: 4-(5-(4-fluorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-2-methoxy phenol**

Molecular formula: C<sub>22</sub>H<sub>19</sub>FN<sub>2</sub>O<sub>2</sub>; Molecular weight: 362.40; TLC (R<sub>f</sub> value): 0.45; Element (Found/Calc.)%: Nitrogen (7.70/7.73); Oxygen (8.82/8.83); IR (cm<sup>-1</sup>): 3402 O-H str.; 1593 C=N; 1485 C=C; 1168 C<sub>6</sub>H<sub>5</sub>; 1424 CH=CH str.; 1115 C-F; 2932 C-H; 1H NMR: 5.53 (1H, s, Ar-OH), 3.81 (3H, s, OCH<sub>3</sub>); 6.80–7.20 (m, 3H, Ar-

H), 8.52 (s, 1H, pyrazole-CH), 7.45–7.62 (d, 3H, Ar-H, J=8.6 Hz), 3.60 (1H, dd); 5.36 (1H, dd), 7.35–8.15 (m, 2H, Ar-H). FAB Mass (m/z): 362.14 (Quasi-molecular ion peak (M+H)<sup>+</sup>)

**3.1.13 Compound B5: 2-methoxy-4-(5-(4-nitrophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl) phenol**

Molecular formula: C<sub>22</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub>; Molecular weight: 389.40; TLC (R<sub>f</sub> value): 0.32; Element (Found/Calc.)%: Nitrogen (10.76/10.79); Oxygen (16.40/16.43); IR (cm<sup>-1</sup>): 3406 O-H str.; 1588 C=N; 1484 C=C; 1170 C<sub>6</sub>H<sub>5</sub>; 1428 CH=CH str.; 1576 N=O str.; 1366 N-O str.; 2935 C-H; 1H NMR: 5.53 (1H, s, Ar-OH), 3.81 (3H, s, OCH<sub>3</sub>); 6.80–7.20 (m, 3H, Ar-H), 8.52 (s, 1H, pyrazole-CH), 3.60 (1H, dd); 5.36 (1H, dd), 7.45–7.62 (d, 3H, Ar-H, J=8.6 Hz), 8.05–8.32 (m, 2H, Ar-H). FAB Mass (m/z): 389.14 (Quasi-molecular ion peak (M+H)<sup>+</sup>).

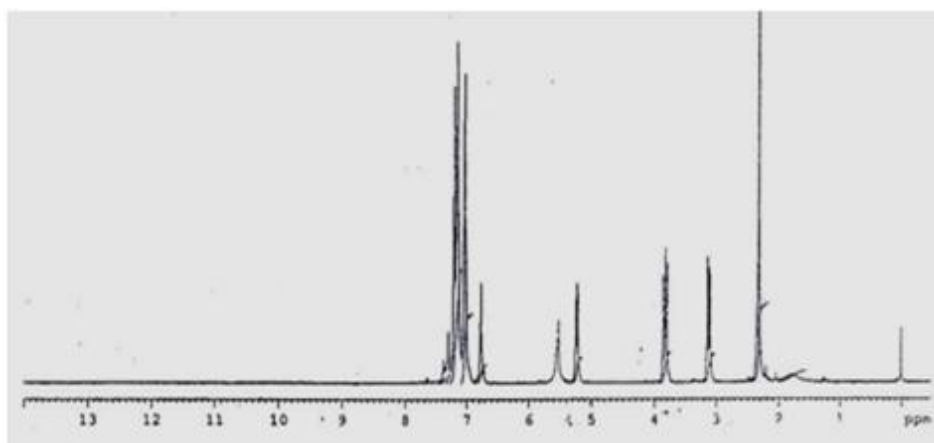


Fig. 1. 1NMR spectra of compound B2

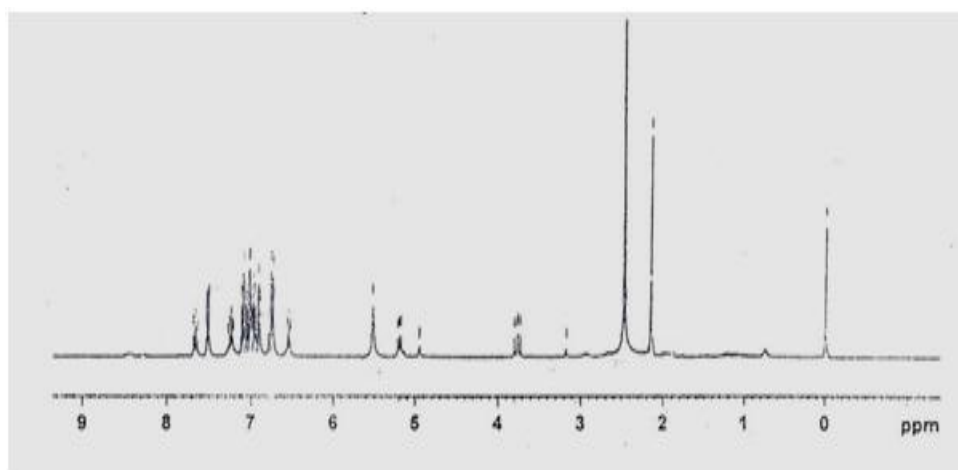


Fig. 2. 1NMR spectra of compound A8

### 3.1.14 Compound B6: 2-methoxy-4-(1-phenyl-5-(p-tolyl)-4,5-dihydro-1H-pyrazol-3-yl)phenol

Molecular formula:  $C_{23}H_{22}N_2O_2$ ; Molecular weight: 358.43; TLC (Rf value): 0.36; Element (Found/Calc.): Nitrogen (7.82/7.82); Oxygen (8.90/8.93); IR ( $cm^{-1}$ ): 3400 O-H str.; 1584C=N; 1491C=C; 1172  $C_6H_5$ ; 1425CH=CH str.; 2935 C-H; <sup>1</sup>HNMR: 5.53 (1H, s, Ar-OH), 3.81 (3H, s, OCH<sub>3</sub>); 6.80–7.20 (m, 3H, Ar-H), 8.52 (s, 1H, pyrazole-CH), 3.60 (1H, dd); 5.36 (1H, dd), 7.45-7.62 (d, 3H, Ar-H, J=8.6 Hz), 7.39-7.67 (m, 2H, Ar-H), 2.15 (m, 3H, C<sub>6</sub>H<sub>5</sub>-CH<sub>3</sub>). FAB Mass (m/z): 358.17 (Quasi-molecular ion peak (M+H)+).

### 3.1.15 Compound B7: 2-methoxy-4-(5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl) phenol

Molecular formula:  $C_{23}H_{22}N_2O_3$ ; Molecular weight: 374.43; TLC (Rf value): 0.30; Element (Found/Calc.): Nitrogen (7.45/7.48); Oxygen (12.78/12.82); IR ( $cm^{-1}$ ): 3412O-H str.; 1586C=N; 1485C=C; 1170C<sub>6</sub>H<sub>5</sub>; 1428CH=CH str.; 2930 C-H; <sup>1</sup>HNMR: 5.53 (1H, s, Ar-OH), 3.81 (6H, s, OCH<sub>3</sub>); 6.80–7.20 (m, 3H, Ar-H), 8.52 (s, 1H, pyrazole-CH), 3.60 (1H, dd); 5.36 (1H, dd), 7.45-7.62 (d, 3H, Ar-H, J=8.6 Hz), 7.05-7.50 (m, 2H, Ar-H). FAB Mass (m/z): 374.16 (Quasi-molecular ion peak (M+H)+).

### 3.1.16 Compound B8: 4-(5-(4-(dimethylamino)phenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol

Molecular formula:  $C_{24}H_{25}N_3O_2$ ; Molecular weight: 387.47; TLC (Rf value): 0.48; Element (Found/Calc.): Nitrogen (10.82/10.84); Oxygen (8.20/8.26); IR ( $cm^{-1}$ ): 3412O-H str.; 1594 C=N; 1491C=C; 1175  $C_6H_5$ ; 1428CH=CH str.; 2935C-H; <sup>1</sup>HNMR: 5.53 (1H, s, Ar-OH), 3.81 (6H, s, OCH<sub>3</sub>); 6.80–7.20 (m, 3H, Ar-H), 8.52 (s, 1H, pyrazole-CH), 3.60 (1H, dd); 5.36 (1H, dd), 7.45-7.62 (d, 3H, Ar-H, J=8.6 Hz), 6.82-7.61 (m, 2H, Ar-H), 2.15 (m, 6H, C<sub>6</sub>H<sub>5</sub>-N(CH<sub>3</sub>)<sub>2</sub>). FAB Mass (m/z): 387.19 (Quasi-molecular ion peak (M+H)+).

## 3.2 Pharmacological Assessment

### 3.2.1 Acute toxicity test

Administration of 2000 mg/kg, p.o. of synthesized compounds did not produce any behavioral

abnormalities and mortality. So the dose selected for further study was used is 10 mg/kg, p.o. for each compounds.

### 3.2.2 Analgesic activity

#### 3.2.2.1 Effect of oral administration of synthesized compounds on hot plate test in mice

In hot plate test, pentazocine (10 mg/kg, s.c.) significantly ( $p < 0.001$ ) increased the paw withdrawal latency at 60 and 90 minutes. Onset of action was observed at 60 minutes of administration of pentazocine. However, In series A1-A8, shown delay the paw withdrawal latency time for compound A2 (10.30 s), A4 (9.45 s), A7 (11.65 s) and A8 (11.26 s) after 90 minutes. In series B1-B8, shown delay the paw withdrawal latency time for compound B2 (9.10 s) and B7 (10.42 s) after 90 minutes. In series C1-C8, shown delay the paw withdrawal latency time for compound C2 (9.15), C5 (10.42 s), C7 (11.54 s) and C8 (10.45 s) after 90 minutes and series D1-D8, shown delay the paw withdrawal latency time for compound D2 (10.32 s), D5 (5.30 s), D7 (12.45 s) and D8 (11.30 s) after 90 minutes. inhibit the pain sensation and inhibit pain produced by thermal means (Table 1).

#### 3.2.2.2 Effect of oral administration of synthesized compounds on acetic acid induced writhing in mice

Compounds A2 (83.00 percent), A5 (76.01 percent), A6 (80.34 percent), A7 (86.99 percent), and A8 (88.15 percent) from the Series A1-A8 have shown that the percent inhibition significantly ( $p < 0.05$  and  $p < 0.001$ , respectively) reduced the number of wriths induced by 0.6 percent acetic acid at a dose of 10 mg/kg. When compared to the vehicle control group, chemicals B2 (72.25 percent), B7 (74.27 percent), and B8 (74.56 percent) showed the percent inhibition, significant ( $p < 0.05$ ) reduction in the number of wriths. B1, B3, and B4 have the least amount of active activity. Acetylsalicylic acid (10 mg/kg) appears to be better effective in reducing the number of wriths, it significantly ( $p < 0.001$ ) reduced the number of wriths by 99.0% (Fig. 3).

## 3.3 Analgesic Activity

### 3.3.1 Hot plate method

Using a carrageenan-induced rat paw edoema rat model, the analgesic effect of several newly synthesised chemical series A1-A8, B1-B8, C1-



**Table 1. Effect of oral administration of synthesized compounds on hot plate test in mice**

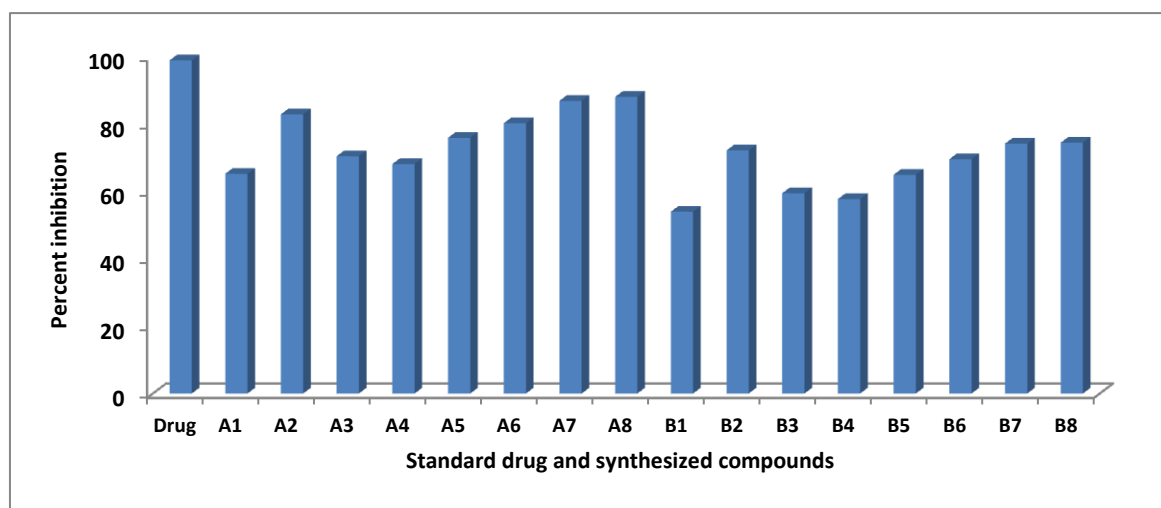
Treatment Groups	Paw withdrawal latency (Sec)						
	0 min	30 min	60 min	90 min	120 min	150 min	180 min
Vehicle Control	6.02 ± 0.45	5.45 ± 0.44	5.50 ± 0.62	4.83 ± 0.21	5.65 ± 0.55	5.83 ± 0.41	5.68 ± 0.58
Pentazocine (10 mg/kg)	5.65 ± 0.50	5.90 ± 0.38	9.15 ± 0.50***	11.33 ± 0.36***	7.98 ± 0.40**	6.08 ± 0.58	5.87 ± 0.40
A1 (10 mg/kg)	5.95 ± 0.58	5.03 ± 0.38	4.88 ± 0.67	6.10 ± 0.49*	4.35 ± 0.21	5.27 ± 0.58	5.10 ± 0.35
A2 (10 mg/kg)	4.73 ± 0.53**	5.58 ± 0.57**	8.55 ± 0.49***	10.30 ± 0.24***	6.77 ± 0.58***	4.82 ± 0.38***	5.78 ± 0.21**
A3 (10 mg/kg)	6.50 ± 0.40	4.98 ± 0.51	7.63 ± 0.46	9.15 ± 0.51**	5.92 ± 0.32	5.55 ± 0.37	5.22 ± 0.60
A4 (10 mg/kg)	4.90 ± 0.39**	5.43 ± 0.54**	5.86 ± 0.39**	09.45 ± 0.44**	9.38 ± 0.27**	7.80 ± 0.38**	5.97 ± 0.69**
A5 (10 mg/kg)	5.22 ± 0.38	5.35 ± 0.40	7.96 ± 0.49	8.20 ± 0.51**	6.20 ± 0.47	5.20 ± 0.30	5.27 ± 0.54
A6 (10 mg/kg)	5.38 ± 0.43	5.85 ± 0.45	8.65 ± 0.36	8.32 ± 0.57**	6.62 ± 0.57	5.17 ± 0.33	5.72 ± 0.47
A7 (10 mg/kg)	5.18 ± 0.58***	6.55 ± 0.53***	9.02 ± 0.34***	11.65 ± 0.37***	9.28 ± 0.60***	6.55 ± 0.26***	5.60 ± 0.36**
A8 (10 mg/kg)	5.30 ± 0.40**	5.55 ± 0.30**	8.55 ± 0.34***	11.26 ± 0.26***	7.02 ± 0.47***	6.17 ± 0.30***	5.33 ± 0.41***
B1 (10 mg/kg)	5.62 ± 0.44	5.32 ± 0.40	6.26 ± 0.25	7.15 ± 0.30**	5.68 ± 0.45	5.30 ± 0.23	5.55 ± 0.51
B2 (10 mg/kg)	5.95 ± 0.58**	5.03 ± 0.38**	6.63 ± 0.67**	9.10 ± 0.49**	5.35 ± 0.21**	5.27 ± 0.58**	5.10 ± 0.35**
B3 (10 mg/kg)	4.73 ± 0.53	5.58 ± 0.57	4.60 ± 0.49	5.30 ± 0.24	5.77 ± 0.58	5.82 ± 0.38	5.78 ± 0.21
B4 (10 mg/kg)	6.50 ± 0.40*	4.98 ± 0.51**	7.63 ± 0.46*	6.15 ± 0.51**	5.92 ± 0.32**	5.55 ± 0.37**	5.22 ± 0.60**
B5 (10 mg/kg)	4.90 ± 0.39	5.43 ± 0.54	5.86 ± 0.39	7.45 ± 0.44*	5.38 ± 0.27	5.80 ± 0.38	5.97 ± 0.69
B6 (10 mg/kg)	5.22 ± 0.38	5.35 ± 0.40	6.96 ± 0.49	8.43 ± 0.51**	6.40 ± 0.47	5.20 ± 0.30	5.27 ± 0.54
B7 (10 mg/kg)	5.38 ± 0.43***	5.85 ± 0.45**	10.42 ± 0.36***	7.45 ± 0.57**	6.62 ± 0.57***	5.17 ± 0.33***	5.72 ± 0.47**
B8 (10 mg/kg)	5.18 ± 0.58***	4.55 ± 0.53***	5.52 ± 0.34***	5.98 ± 0.37***	5.28 ± 0.60***	5.55 ± 0.26**	5.60 ± 0.36**

Values are expressed as mean ± S.E.M.; n=6 mice per group. Two way ANOVA followed by Bonferroni post hoc test when compared with vehicle control \*\*p<0.01, \*\*\*p<0.001

**Table 2. Effect of oral administration of synthesized compounds on acetic acid induced writhing in mice**

Group No.	Treatment groups	Number of writhing	Percentage inhibition
1.	Vehicle control	68 ± 1.5	-
2.	Acetyl salicylic acid (10 mg/kg)	18 ± 2.1***	99.00
3.	A1	23± 1.1	65.31
4.	A2	11± 1.2	83.00
5.	A3	20± 0.8	70.52
6.	A4	22± 0.6	68.20
7.	A5	16± 0.7	76.01
8.	A6	14± 1.9	80.34
9.	A7	10± 2.2	86.99
10.	A8	08± 1.5	88.15
11.	B1	31± 1.1	54.04
12.	B2	19± 1.2	72.25
13.	B3	28± 1.7	59.53
14.	B4	29± 1.3	57.80
15.	B5	23± 1.8	65.02
16.	B6	21± 1.2	69.65
17.	B7	17± 1.4	74.27
18.	B8	16± 1.7	74.56

Values are expressed as mean ± S.E.M.; n=6 mice per group. One way ANOVA followed by Dunnett's test when compared with vehicle control \*p<0.05, \*\*\*p<0.00

**Fig. 3. Percent inhibition of oral administration of synthesized compound on acetic acid induced writhing in mice**

C8, and D1-D8 was examined. The evaluation's outcomes were viewed using Pentazocine and acetyl acetic acid as the standard drugs. Pentazocine (10 mg/kg, s.c.) substantially (p0.001) enhanced paw withdrawal latency at 60 and 90 minutes in a hot plate test. The onset of activity was detected 60 minutes after the pentazocine was administered. However, after 90 minutes, compound A2 (10.30 s), A4 (9.45 s), A7 (11.65 s), and A8 (11.26 s) showed a delay in paw withdrawal latency time in series A1-A8. In

series B1-B8, shown delay the paw withdrawal latency time for compound B2 (9.10 s) and B7 (10.42 s) after 90 minutes inhibit the pain sensation and inhibit pain produced by thermal means.

### 3.3.2 Acetic acid induced writhing in mice model

Compounds A2, A5, A6, A7, and A8 from Series A1-A8 showed 83.00, 76.01, 80.34, 86.99, 88.15

percent inhibition, substantially (p0.05 and p0.001, respectively), and decreased the number of wriths caused by 0.6 percent acetic acid at a dosage of 10 mg/kg. When compared to the vehicle control group, compounds B2, B7, and B8 showed 72.25, 74.27, and 74.56 percent inhibition, respectively, and a substantial (p0.05) reduction in the number of wriths. Acetylsalicylic acid (10 mg/kg) appeared to be more successful in reducing the number of wriths; it decreases the amount of wriths by 99.0 percent (p0.001).

#### 4. CONCLUSION

The 1,3,5-pyrazoline derivatives were successfully synthesised and evaluated for analgesic activity in a mouse model, with compounds A2, A5, A6, A7, and A8 showing 83.00, 76.01, 80.34, 86.99, 88.15 percent inhibition, and compounds B2, B7, and B8 showing 72.25, 74.27, and 74.56 percent inhibition, respectively. Out of a total of 16 compounds, 8 are the most active. This evident that the presence of SO<sub>2</sub>NH<sub>2</sub> is essential for the anti-inflammatory and analgesic activity and methyl, Chloro, methoxy and N(CH<sub>3</sub>)<sub>2</sub> group attached at phenyl ring enhance the anti-inflammatory and analgesic activity. B1, B3, and B4 have the least amount of active activity. These all finding suggest that these synthesized compounds have the potential as analgesic agent.

#### DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

#### CONSENT

It is not applicable.

#### ETHICAL APPROVAL

It is not applicable.

#### ACKNOWLEDGEMENT

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mass spectroscopy for characterization of synthesized compounds.

#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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