

## Synthesis And Anti-Inflammatory Activity On Sulpha/Substituted Pyrazoles(1,2-Diazole)

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**ABSTRACT:** A Novel compound namely *N*<sup>1</sup>-(Nicotinoyl) 3,5 dimethyl-4-(*N*<sup>1</sup>-4-sulfamoylazo)-1,2-diazole has been synthesised by two step processes. Synthesis of *N*<sup>1</sup>-4-sulphamoylphenylhydrazono-3,5-dimethyl propane-1,3-dione and sulphonamide, which interacting with Nicotinic acid hydrazide to form final compound. The newly synthesised compound *N*<sup>1</sup>-(nicotinoyl)-3,5-dimethyl 4-(*N*-4-sulfamoyl phenyl azo) 1,2-diazoles was screened for anti-inflammatory activity.

**KEYWORDS:** synthesis, anti-inflammatory activity, sulphonamide 1,3-diketone, Nicotinic acid hydrazide.

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### I. INTRODUCTION

A heterocyclic compound is one which possess a cyclic structures with atleast one hetero atom in the ring. Nitrogen oxygen and sulphur are the most common hetero atoms. Heterocyclic compounds are very widely distributed in nature and essential to the life in various ways. Vitamin C exist in the form of five membered (furan) or six membered (Pyran) rings containing one oxygen atom. Most member of Vitamin B group possess heterocyclic ring containing nitrogen. One example is vitamin B<sub>6</sub> (Pyridoxine), which derivative of pyridine essential in amino acid metabolism. 1,2-diazole is a heterocyclic compound having varied biological activity and still of great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry with application in drug discovery. Nitrogen based heterocyclic compounds are very important in the field of medicinal chemistry. The present diazoles were prepared because of its good biological activity. Compounds including a 1,2-diazole nucleus and N-substituted derivatives are known to possess various biological activity[1]. Among these types of molecules have been shown to have various important biological activity such as antibacterial, antifungal, antiviral, diuretic, antituberculostatic, anti-HIV, antihistaminic anticancer, anticonvulsant, anti-inflammatory and analgesic properties[3-7].

Sulpha/substituted 1,2-diazoles may serve as the alternative sources for the development of new antiinflammatory agents due to their biological activity. Sulpha/substituted 1,2-diazoles used for the treatment of anti-inflammatory in different systems of medicine have shown diuretic activity when tested on animal models. On the basis of the use of diuretics, but no previous pharmacological study was carried out to test anti-inflammatory the activity of sulpha/substituted 1,2-diazoles. The main aim of the present investigation was to evaluate the claimed anti-inflammatory activity of sulpha/substituted 1,2-diazoles.

### II. MATERIAL AND METHOD

The 1,3-diketones, sulphanilamide, nicotinic acid hydrazide and all reference compound were purchased from Aldrich Chemicals, Ethanol, sodium acetate, glacial acetic acid and all other reagents were purchased from S.D. Chem. TLC was performed on pre-coated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany).

#### 2.1.General

Melting points of the (*N*<sup>1</sup>-nicotinoyl) 3,5 dimethyl-4(*N*<sup>1</sup>-4-sulfamoylphenylazo)-1,2-diazole was determined using an open-ended capillary tube method and are uncorrected. The purity of the synthesized compound was checked by TLC. A FT-IR spectrum was recorded on a Perkin-Elmer 1605 series FT-IR in a KBr Disc, <sup>1</sup>H NMR spectra was recorded at 300 MHz on a Burker FT-NMR spectrophotometer using TMS as internal standard.

#### Step-1

##### *Synthesis of N*<sup>1</sup>-4-sulphamoylphenyl hydrazono-3,5-dimethyl propane-1,3-dione

An ice cooled solution of 3,5-dimethyl propane-1,3-dione (0.03 mole) in ethanol containing sodium acetate (6 grams) a diazotized solution of sulphonamide (0.05 mole) were gradually added with stirring and

cooling. The reaction mixture was further stirring for 20 minutes, the coloured hydrazone compounds precipitated by addition of ice cold water. It was filtered off, washed with water, dried and recrystallised from ethanol/acetic acid [Fig. 1]. On analysis, it was found to be N<sup>1</sup>-4-sulphamoylphenyl hydrazone-3,5-dimethyl propane-1,3-dione [Fig. 1].

#### **N<sup>1</sup>-4-sulphamoylphenyl hydrazone 3,5-dimethyl propane-1,3-dione**

A yellow crystalline powder. mp 198-200<sup>0</sup>C, Yield 82.34%, molecular formula C<sub>16</sub>H<sub>15</sub>O<sub>4</sub>N<sub>3</sub>S (348.76): C, 55.10; H, 4.34; O, 18.35; N, 12.04; S, 10.17. Found: 54.92; 4.56; O, 18.17; N, 12.48; S, 9.87, IR (KBr) in cm<sup>-1</sup> 1440 (C-C), 1560 (C=C of aromatic ring), 1260 (C-N), 1680 (C=O), 3087 (NH), 3275 (SO<sub>2</sub>NH<sub>2</sub>). <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ in ppm, 2.81 (s, 3H CH<sub>3</sub>), 6.75-7.68 (m, 9H, Ar-H), 6.92 (s, 2H NH<sub>2</sub>), 10.43 (s, 1H NH).

#### **Step-II**

#### **Synthesis of N<sup>1</sup>-(nicotinoyl, 3,5-dimethyl-4(N-4-sulfamoyl phenylazo)-1,2-diazole**

A solution of N<sup>1</sup>-4-sulphamoylphenyl-hydrazone 3,5-dimethyl propane-1,3-dione (0.02 mole) in glacial acetic acid was added to Nicotinic acid hydrazide (0.05 mole) refluxed on water bath for 6 hours and left overnight. On cooling, shining recrystallised crystals, separated out which was collected by filtration, washed well with water, dried and recrystallised from glacial acetic acid to give N<sup>1</sup>-(nicotinoyl)3,5 dimethyl-4(N-4-sulfamoylphenylazo)-1,2-diazole [Fig. 2].

#### **N<sup>1</sup>(Nicotinoyl)-3,5-dimethyl-4(N-sulfamoylphenylazo)-1,2-diazole**

A yellow crystalline powder, mp 226-228 <sup>0</sup>C, Yield 72.13%. molecular formula C<sub>23</sub>H<sub>20</sub>O<sub>3</sub>N<sub>6</sub>S, anal. Calcd for C<sub>23</sub>H<sub>20</sub>O<sub>3</sub>N<sub>6</sub>S (463.90: C, 59.55; H, 4.34; O, 10.35; N, 18.12; S, 18.12; S, 7.64. Found: C, 58.97; H, 4.64; O, 10.29; N, 18.37; S, 7.73. IR (KBr) in cm<sup>-1</sup> 740 (C-C), 1240 (C-N), 1535 (C=C of aromatic ring), 1585 (C=N), 1460 (N=N), 3055 (aromatic C-H), 3135 (NH), 1707 (C=O), 3082 (NH<sub>2</sub>). <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ in ppm, 2.79 (s, 3H CH<sub>3</sub>), 6.65-7.58 (m, 13, Ar-H), 7.10 (m, 4H NH<sub>2</sub>).

#### **Animals**

Adult's male Wistar albino rats, each in the weight range of 180-200 gm were used for this experiment. They were procured from National Veterinary Research centre, Bareilly, India. The animals were randomly allocated to six treatment groups of six animals each and kept in polypropylene cages and housed under standard conditions of temperature, humidity, dark light cycle (12h-12h) and diet.

#### **Anti-inflammatory activity<sup>8,9</sup>**

The activity of the newly synthesized compounds compared to indomethacin as a reference compound was measured before and 4h after carrageenan injection. Percent of the oedema inhibition was calculated as regards saline control group and potency was calculated as regards the percentage of the change of indomethacin and tested compounds [24], as depicted in Table 2. All the tested compounds showed a reasonable inhibition of oedema size ranging between a 13.5%, for compound 25.4% for compound (b) 28% for compound, 32.7% for compound sulphonamide 1,2-diazole (c), 44.4% for compound sulphapyrimidine 1,2-diazole (d) and 29.9% for indomethacin. In activity relationship point of view, the anti-inflammatory activity of the pyrimidine was found to be the promising one. But sulphonamide also showed good anti-inflammatory activity (32.7%).

**Table 1. Anti-inflammatory effect of sulpha/substituted-1,2-diazoles**

Compound	Dose (mg/kg)	Oedema		Oedema (%) (X±SE)	Oedema inhibition (%)	Potency
		Zero min (basal)	4 h oedema (cm) (%) increase)			
Control	1 mL saline	0.23±0.006	0.46±0.01	109.1±6.3	--	--
a C <sub>14</sub> H <sub>10</sub> NCl	70	0.20±0.002	0.37±0.01	81.3±4.8	-25.48	0.9
b C <sub>14</sub> H <sub>10</sub> NF	70	0.22±0.002	0.38±0.03	78.3±4.1	-28	0.9
c C <sub>14</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub>	70	0.21±0.003	0.41±0.2	94.8±5.3	-13.1	0.4
d C <sub>20</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub> S	70	0.22±0.002	0.37±0.02	73.4±4.4	-32.7	1.1
e C <sub>24</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub> S	70	0.20±0.00	0.32±0.001	60.7±4.9	-44.4	1.5
f C <sub>24</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub> S	70	0.20±0.00	0.32±0.004	60.7±4.9	-44.4	1.5
Indomethacin	35	0.26±0.003	0.39±0.03	76.5±3.6	-29.9	1

### **III. CONCLUSION**

The present study that, synthesised compound N<sup>1</sup>(Nicotinoyl)-3,5-dimethyl 4-sulfamoylphenylazo)-1,2-diazole possess significant at 100 and 200 mg/kg but the effect declined at higher dose.

#### IV. ACKNOWLEDGMENT

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#### REFERENCES

- [1] Achson a, An introduction to the chemistry of heterocyclic compounds 3<sup>rd</sup> edition, Wiley interscience, India 2000.
- [2] G. capan, N. Ulusoy, N. Ergenc, M. Krtaz, New 6-phenylimidazo[2,1-b]thiazole derivatives: Synthesis and antifungal activity. *Monatsh. Chem.* 1999, 130, 1399
- [3] R.U. Roy, a. R. Desai, K.R. Desai, "synthesis and Antimicrobial Activity of 1,2,4-Thiazoles, *E-Journal of Chemistry*, 2005, 2(6),1.
- [4] M.G. Vigorita, R. Ottana, F. Monforte, R. maccari, A. Trovato, M. T. Monforte, M.F. Taviano, Synthesis and anti-inflammatory, analgesic activity of 3,3-(1,2-ethandiyl)-bis[2-aryl-4-thiazolidinone] chiral compounds. Part 10. *Bioorg. Med. Chem.* 2001, 11, 2791.
- [5] C.V. Kavitha, S. Basappa, S. Nanjunda, K. Mantelingu, S. Doreswamy, M. A. Sridhar, J.S. Prasad, K.S. Rangappa, Synthesis of new bioactive venlafaxine analogs: Novel thiazolidin-4-ones as antimicrobilas. *Bioorg. Med. Chem.* 2006, 14, 2290.
- [6] R. Ottana, R. Maccari, M.L. Barreca, G.Bruno, A. Rotondo, A. Rossi, G. Chiricosta, R. Di Paola, L. Sautebin, S. Cuzzocrea, M.G. Vigorita, 5-Arylidene-2-imino-4-thiazolidinones: Design and synthesis of novel anti-inflammatory agents. *Bioorg. Med. Chem.* 2005, 13, 4243.
- [7] G. kukuguzel, A. Kocatepe, E. De Clercq, F. Sahin, M. Gulluce, Synthesis and biological activity of 4-thiazolidinones, thiosemicarbazides derived from diflunisal hydrazide. *Eur. J. med. Chem.* 2006, 41, 353.
- [8] Radwan, M.A.A., Rageb E.A. Saby, N.M. El-Shenaway, S.M., Potential anti-inflammatory and analgesic agents, *Bioorganic and medicinal chemistry* 2007, 15, pp 3832-3841.
- [9] Singh N, Bhatia, S.K., Kumar A, Thiazolyl/formazanyl-1,2-diazoles as potent anti-inflammatory agent, *European Jour. Of medicinal Chem.*, 2008, 43, 2597-2609.

#### Synthesis of novel $N^1$ -(Nicotinoyl)-3,5-dimethyl-4(N-4-sulfamoylphenylazo)-1,2-diazole

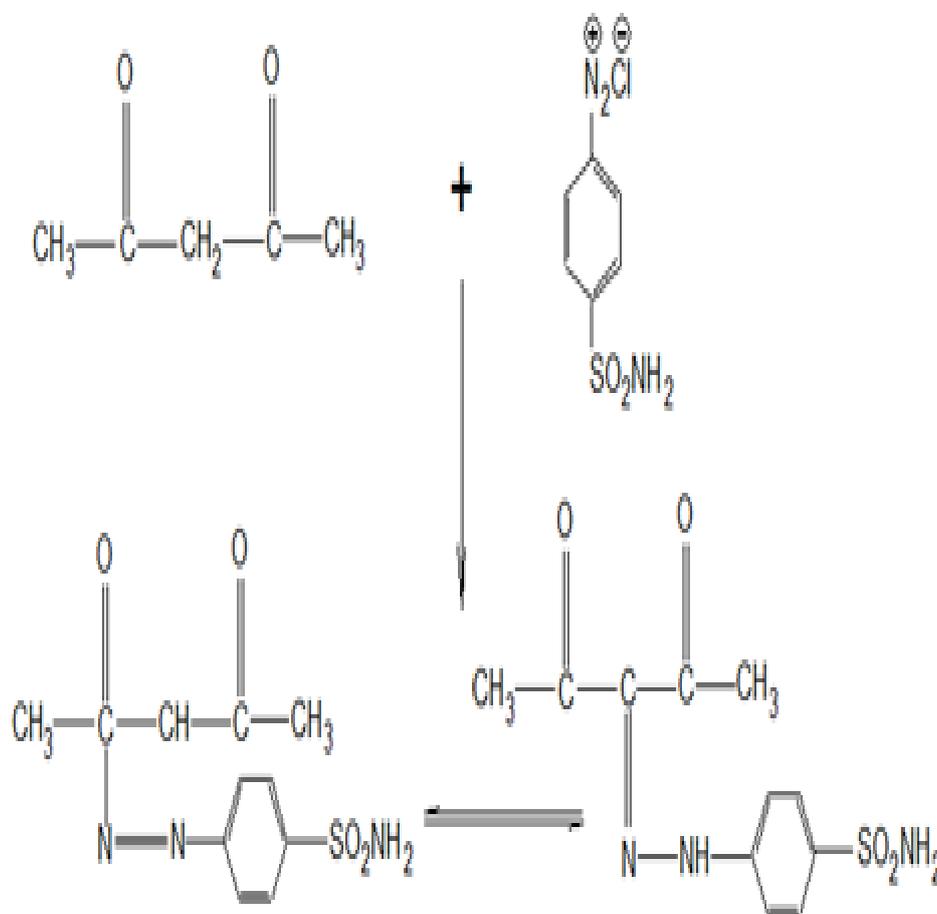


Fig.1 Synthesis of  $N^1$ -(4-sulfamoylphenyl)hydrazono-3,5-dimethylpropane-1,3-dione

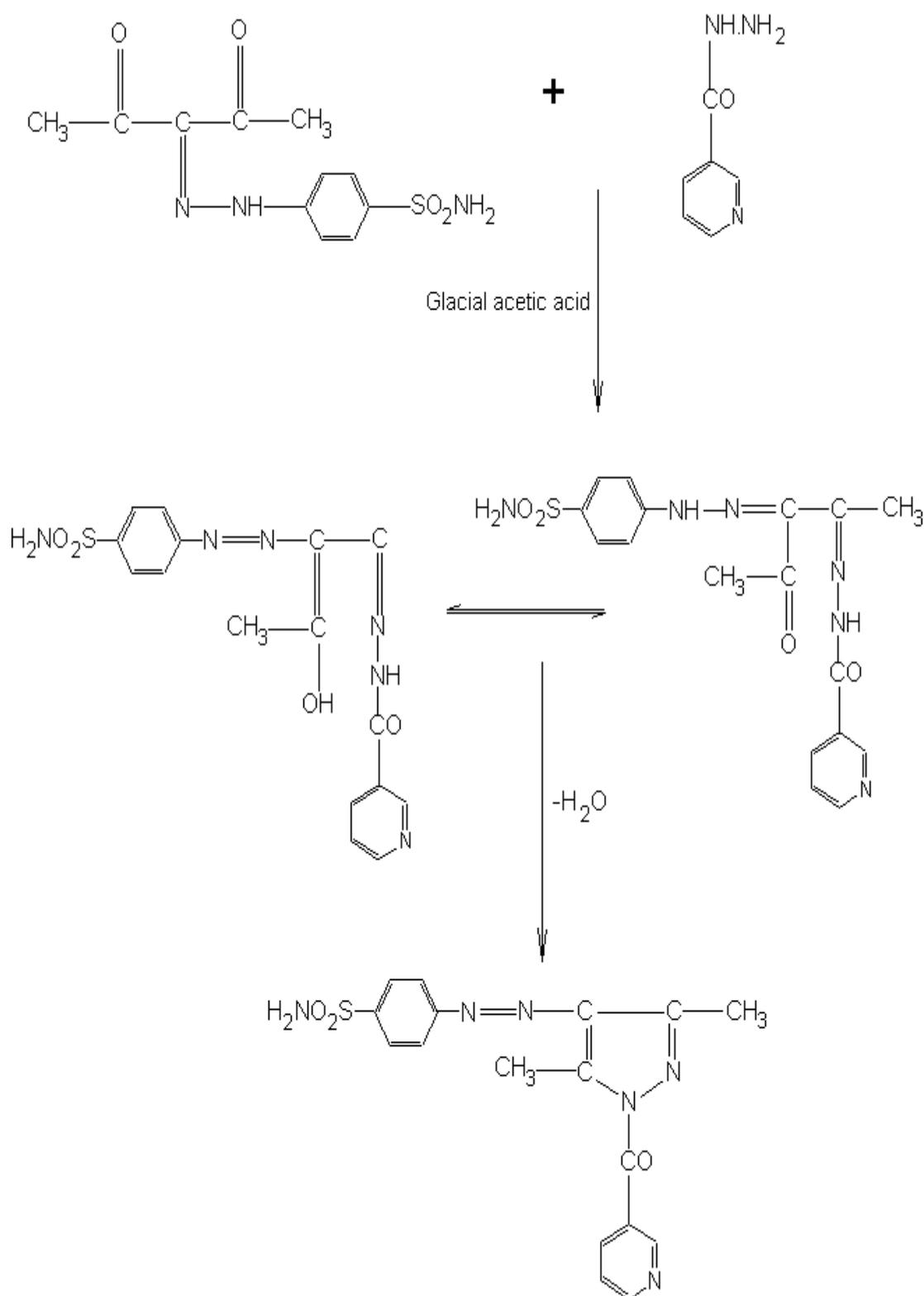


Fig.2 Synthesis of  $N^1$ -3,5-dimethyl-4-(N-4-sulphamoylphenylazo)-1,2-diazole