

**SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY ON NITROGEN BASED
HETEROCYCLIC COMPOUNDS.**

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ABSTRACT

A novel compound namely N¹ - (Isonicotinoyl), 3, 5- dimethyl- 4-(N¹-4-sulphamoylazo)-1, 2-diazoles has been synthesized by two step processes. Synthesis of N¹-4-sulphamoylphenylhydrazono-3, 5-dimethyl propane-1, 3-dione and sulphonamide, which interacting with Isonicotinic acid hydrazide to form final compound. The newly synthesized compounds were screened for their anti-inflammatory activity.

KEYWORDS: Sulphonamide 1, 3- diketone, isonicotinic acid hydrazide, Anti-Inflammatory activity.

INTRODUCTION

A heterocyclic compound is a cyclic structure with atleast one heteroatom in the cyclic 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 exists 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.e.g vitamin B₆ (Pyridoxine), which is a derivative of Pyridine essential in amino acid metabolism.

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]

Various biologically active synthetic compounds have five membered nitrogen containing heterocyclic ring in their structures.^[2-5] Structural frame works have been described as privileged structures and in particular, N containing polycyclic structures have been reported to be associated with a wide range of biological activity. In the field of five membered heterocyclic structures imidazole (1, 3-Diazole) nucleus shows various properties. The high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Imidazole drugs have broadened scope in remedying various dispositions in clinical medicines. Medicinal properties of imidazole and benzimidazole include anticancer, beta-lactamase inhibitors, 20-HETE (20-

Hydroxy-5, 8, 11, 14-eicosatetraenoic acid) synthaseinhibitors, carboxy peptidase inhibitors, hemeoxygenase inhibitors, antiaging agents, anticoagulants, anti-inflammatory, antibacterial, antifungal, antiviral, antitubercular, antidiabetic and antimalarial^[6-19] 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.^[20-24]

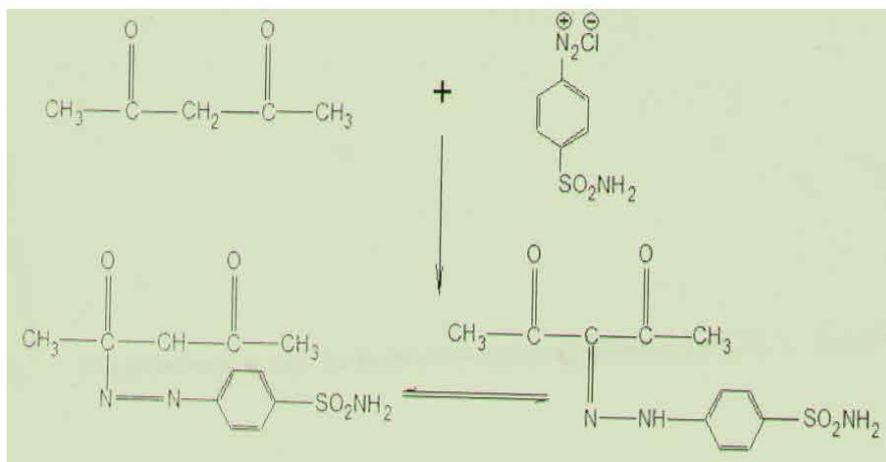
Supha /substituted 1,2 diazoles may serve as the alternative source for the development of new anti-inflammatory agents due to their biological activity. Supha /substituted 1,2 diazoles used for the treatment of anti-inflammatory in different systems of medicine have shown diuretic activity when tested 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 Supha /substituted 1,2 diazoles. The main aim of the present investigation was to evaluate the claimed anti-inflammatory activity of Supha /substituted 1,2 diazoles.

MATERIAL AND METHOD

1,3 diketones, sulphanilamide, isonicotinic 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).

General: Melting points of N¹-isonicotinoyl 3,5 dimethyl-4 (N1-4-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

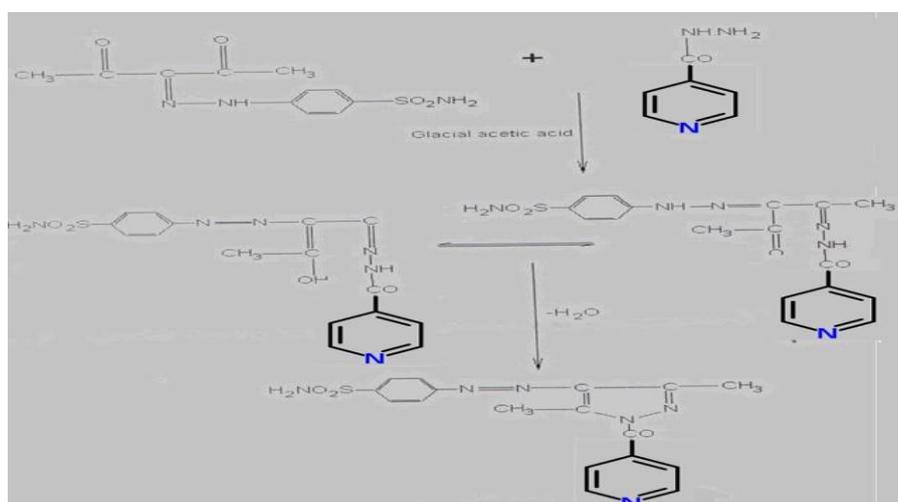
recorded on a Perkin- Elmer 1605 series FT-IR in a KBr Disc, HNMR spectra was recorded at 300MHZ on a Burker FT-NMRspectrophotometer using TMS as internal standard.



Scheme –I: Synthesis of N¹-sulphamoylphenyl hydrazono-3,5-dimethyl propane-1,3-dione

Step- I: Synthesis of N¹-4-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 (6grams) 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 hydrazono 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 N¹-4-sulphamoylphenyl hydrazono-3'5- dimethyl propane-1, 3-dione [Fig.1].

N¹-4-sulphamoyl phenyl hydrazono-3,5- dimethyl propane-1, 3-dione: A yellow crystalline powder. Mp 198-200⁰C, Yield 82.34%, molecular formula C₁₆H₁₅O₄N₃S (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⁻¹ 1440 (C-C), 1560 (C=C of aromatic ring), 1260 (C-N), 1680 (C=O), 3087 (NH), 3275 (SO₂NH₂).¹HNMR (CDCl₃) in ppm, 2.81 (s, 3H CH₃), 6.75-7.68 (m, 9H, Ar-H), 6.92(2H NH₂), 10.43 (s, 1H NH).



Scheme-II: Synthesis of N¹- (Isonicotinoyl)-3,5 –dimetyl-4(N1-4-sulphamoylphenylazo)-1,2-diazole

Step- II: Synthesis of N¹-(Isonicotinoyl, 3' 5-dimethyl-4-(N-4-sulphamoyl phenylazo)-1-2-diazole: A solution of N¹-4-sulphamoylphenyl hydrazono-3'5- dimethyl propane-1,3-dione (0.02 mole) in glacial acetic acid was added to isonicotinic acid hydrazide (0.05 mole) refluxed on water bath for 6 hours and left over night. 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 N¹-(Isonicotinoyl, 3'5- dimethyl-4-(N-4-sulphamoyl phenylazo)-1-2-diazole [Fig 2]

N¹-(Isonicotinoyl, 3'5-dimethyl-4-(N-4-sulphamoyl phenylazo)-1-2-diazole: A yellow crystalline powder. Mp 226-228^oC, Yield 72.13%, molecular formula C₂₃H₂₀O₃N₆S (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⁻¹ 740 (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 (NH₂). ¹HNMR (CDCl₃) in ppm, 2.79 (s, 3H CH₃), 6.75-7.58 (m, 13, Ar-H), 7.10 (m, 4H NH₂).

Anti-inflammatory activity: The activity of the newly synthesized compound 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 compound [24], as depicted in table 2. All the tested 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 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) | 4h oedema (cm) (% increase) | | | |
| Control | 1ml saline | 0.23±0.006 | 0.46±0.01 | 109.1±6.3 | ---- | ---- |
| a C ₁₄ H ₁₀ NCl | 70 | 0.20±0.002 | 0.37±0.01 | 81.3±4.8 | -25.48 | 0.9 |
| b C ₁₄ H ₁₀ NF | 70 | 0.22±0.002 | 0.38±0.03 | 78.3±4.1 | -28 | 0.9 |
| c C ₁₄ H ₁₀ N ₂ O ₂ | 70 | 0.21±0.003 | 0.41±0.2 | 94.8±5.3 | -13.1 | 0.4 |
| d C ₂₀ H ₁₆ N ₂ O ₂ S | 70 | 0.22±0.002 | 0.37±0.02 | 73.4±4.4 | -32.7 | 1.1 |
| e C ₂₄ H ₁₆ N ₄ O ₂ S | 70 | 0.20±0.00 | 0.32±0.001 | 60.7±4.9 | -44.4 | 1.5 |
| f C ₂₄ H ₁₈ N ₄ O ₂ S | 70 | 0.20±0.00 | 0.32±0.004 | 60.7±4.9 | -44.4 | 1.5 |
| indomethacin | 35 | 0.21±0.003 | 0.39±0.003 | 76.5±3.6 | -29.9 | 1s |

CONCLUSION

The present study that synthesized compound N¹-(Isonicotinoyl,3'5-dimethyl-4-(N-4-sulphamoyl phenylazo)-1-2-diazole possess significant at 100 and 200 mg/kg but the effect declined at higher dose.

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