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# Synthesis and pharmacological studies on some novel imidazo thiazoles

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## ABSTRACT

*A new series of 2-(-2-methyl-5-nitro-imidazo-1-acethydrazinyl)-4- substituted thiazoles **5a-l** were synthesized and are characterized by spectral and analytical data. The newly synthesized thiazoles were screened for their antibacterial, antifungal and anti-inflammatory activity. Most of the tested compounds showed promising activity.*

**Key Words**: Imidazole derivatives, thiazoles, antibacterial, antifungal and anti-inflammatory activity.

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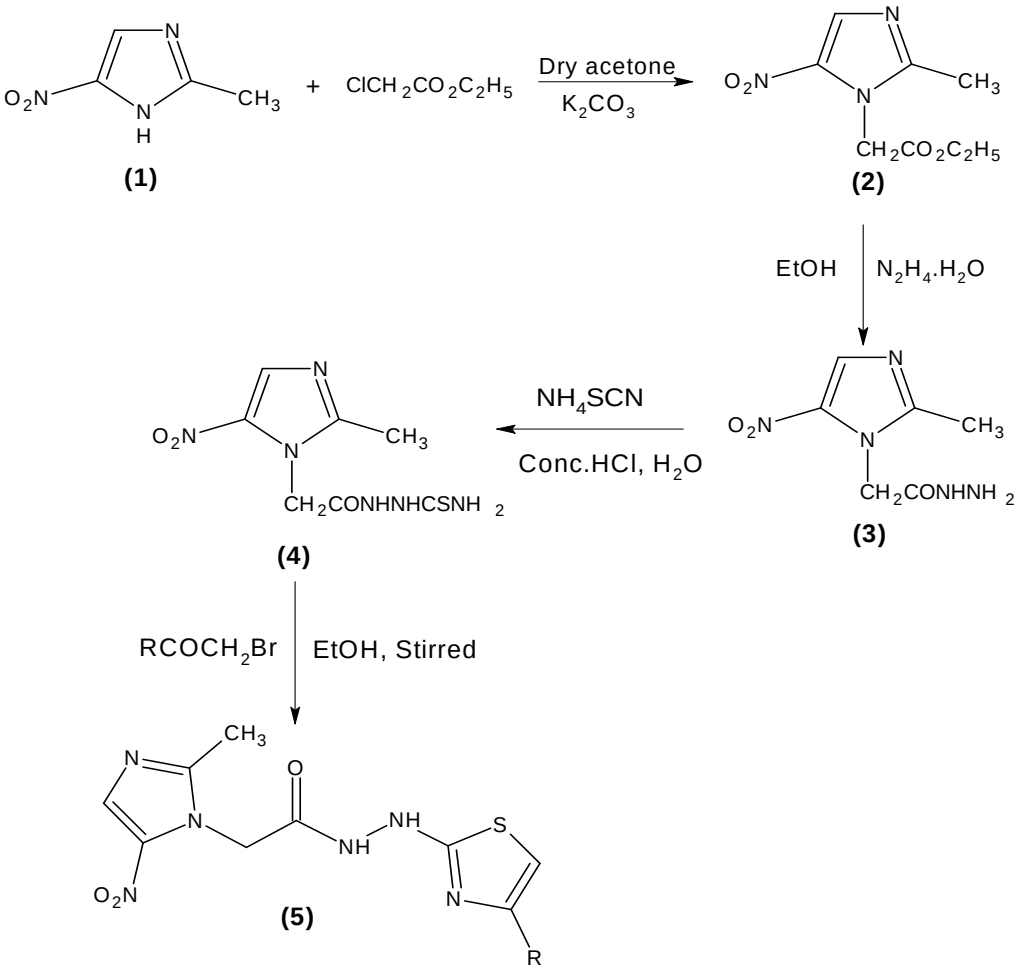
## INTRODUCTION

Thiazole [1] and imidazole [2-4] derivatives have been endowed with diverse pharmacological activities such as antibiotic, anti-inflammatory, antibacterial, antifungal properties. Prompted by these observations and in continuation of our work on biologically active nitrogen heterocycles [5-8], we present in this paper the synthesis and biological activity of a series of 2-(-2-methyl-5-nitro-imidazo-1-acethydrazinyl)-4-substituted thiazoles.

The title compounds were prepared by the reaction of imidazo-thiosemicarbazide with appropriate α-bromoketones **Scheme-1**. The structures of the newly synthesized compounds were confirmed on the basis of analytical, $^1$H NMR and mass spectral data. The characterization data of the compounds **5a-l** are given in Table-1.

## MATERIALS AND METHODS

Melting points were determined in open capillary tubes and are uncorrected. Elemental analysis was carried out in Vario EL-III Elementa model. IR spectra (KBr disc) were recorded on a Jasco FT IR 430 spectrophotometer; $^1$H NMR spectra on a Brucker AC 300 (300 MHz) NMR spectrometer using $CDCl_3$ or DMSO-$d_6$ as solvent and TMS as internal standard; and mass spectra on a Jeol-JMS-D-300 mass spectrometer operating at 70eV.




**Scheme-1**

**Synthesis of 2-methyl-5-nitro-1-imidazo-ethyl acetate (2)**

A mixture of 2-methyl-5-nitro-imidazole (12.7g, 0.1 mole), ethyl chloroacetate (0.1mole) and potassium carbonate (0.15mole) in dry acetone (200mL) was refluxed for 50 hr. The reaction mixture was filtered hot and the solvent was distilled off from the filtrate. The crude ester **2** thus obtained was purified by recrystallisation from ethanol, yield 84%, m.p. 97 $^{o}$C (Lit [9] 95$^{o}$C)

**Synthesis of 2-methyl-5-nitro-1-imidazo-acethydrazide (3)**

A mixture of ester (**2**) (0.1mole) and 99% hydrazine hydrate (0.1mole) in ethanol (50mL) was refluxed for 8 hr. The solution on cooling gave a solid mass of hydrazide **3**, which was collected by filtration, and recrystallised from ethanol, yield 66%, m.p. 189 $^{o}$C

Mol. Formula: $C_6H_9N_5O_3$; Analysis (Found): C, 36.37; H, 4.29; N, 35.46%; (Calculated for $C_6H_9N_5O_3$): C, 36.18; H, 4.52; N, 35.18%); MS: m/z 199 (M+, 70), 183 (02), 168 (48), 153 (20), 141 (100), 111 (05).

**Table1: Characterization data of 2-(-2-methyl-5-nitro-imidazo-1-acethydrazinyl)-4- substituted thiazoles, 5a-l**

| Compd no. | R | Mol. formula | m.p°C yield % | Elemental analysis Found (Calcd %) | | |
|---|---|---|---|---|---|---|
| | | | | C | H | N |
| **5a** | Phenyl | $C_{15}H_{14}N_6O_3S$ | 235<br>66 | 50.42<br>(50.28) | 3.74<br>(3.91) | 23.52<br>(23.46) |
| **5b** | *p*-Tolyl | $C_{16}H_{16}N_6O_3S$ | 225<br>51 | 51.70<br>(51.61) | 4.41<br>(4.30) | 22.45<br>(22.58) |
| **5c** | *p*-Anisyl | $C_{16}H_{16}N_6O_4S$ | 229<br>53 | 49.39<br>(49.48) | 4.23<br>(4.12) | 21.78<br>(21.65) |
| **5d** | *p*-Hydroxyphenyl | $C_{15}H_{14}N_6O_4S$ | 252<br>72 | 48.21<br>(48.13) | 3.69<br>(3.74) | 22.39<br>(22.46) |
| **5e** | *p*-Nitrophenyl | $C_{15}H_{13}N_7O_5S$ | 256<br>55 | 44.77<br>(44.67) | 3.31<br>(3.23) | 24.28<br>(24.32) |
| **5f** | *p*-Chlorophenyl | $C_{15}H_{13}N_6O_3ClS$ | 245<br>88 | 45.78<br>(45.87) | 3.25<br>(3.31) | 21.47<br>(21.40) |
| **5g** | *p*-Bromophenyl | $C_{15}H_{13}N_6O_3BrS$ | 268<br>52 | 41.32<br>(41.20) | 2.91<br>(2.98) | 19.35<br>(19.23) |
| **5h** | Coumarinyl | $C_{18}H_{14}N_6O_5S$ | 278-79<br>87 | 50.78<br>(50.70) | 3.32<br>(3.29) | 19.60<br>(19.72) |
| **5i** | 6-Bromo-coumarinyl | $C_{18}H_{13}N_6O_5BrS$ | 260<br>51 | 42.54<br>(42.78) | 2.62<br>(2.58) | 16.57<br>(16.64) |
| **5j** | N-phenyl sydnonyl | $C_{17}H_{16}N_8O_5S$ | 224-26<br>98 | 36.27<br>(36.18) | 3.41<br>(3.52) | 28.26<br>(28.14) |
| **5k** | N-*p*-tolyl sydnonyl | $C_{18}H_{18}N_8O_5S$ | 242-43<br>84 | 45.84<br>(45.95) | 3.55<br>(3.60) | 25.37<br>(25.23) |
| **5l** | N-*p*-anisyl sydnonyl | $C_{18}H_{18}N_8O_6S$ | 248<br>96 | 47.23<br>(47.16) | 3.96<br>(3.93) | 24.39<br>(24.45) |

*Solvent of crystallization: EtOH + DMF*

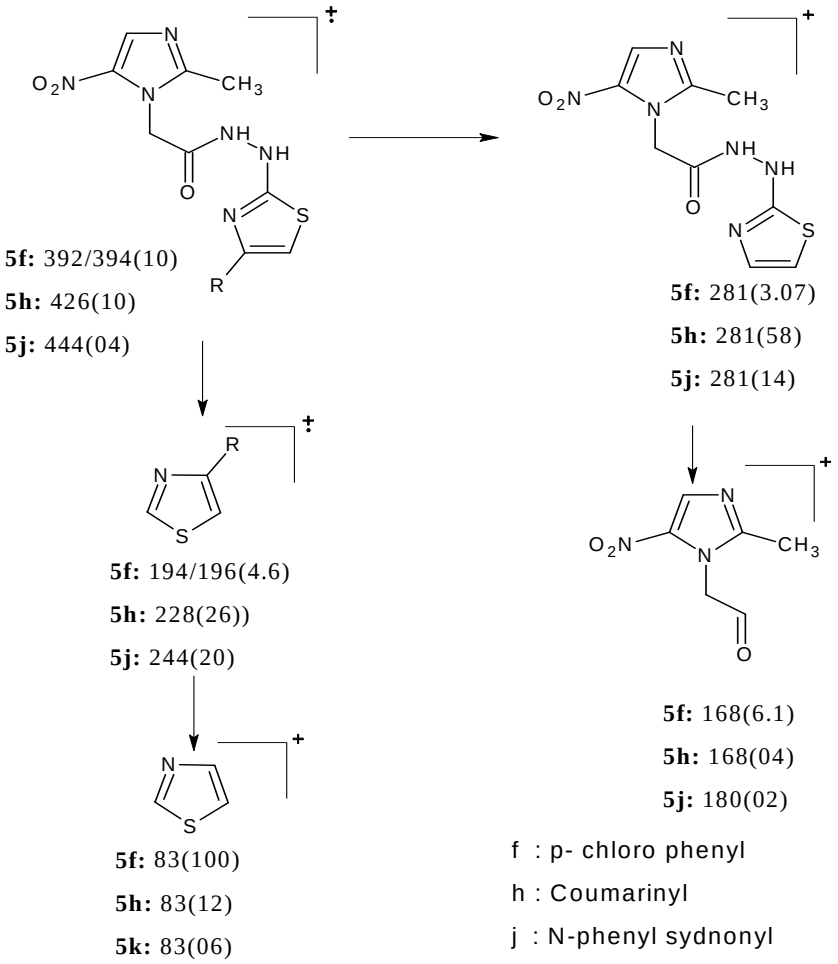
**Synthesis of 2-methyl-5-nitro-1-imidazo-thiosemicarbazide (4)**

A mixture of hydrazide (**3**) (0.05mole) and ammonium thiocyanide (0.1mol) in ethanol (20ml) was refluxed in the presence of 1ml of conc. HCl for 8 hours. The solution on cooling gave a solid mass of thiosemicarbazide **4**, which was collected by filtration, and recrystallized from ethanol DMF mixture, yield 78%, m.p. 213 $^oC$

Mol. Formula: $C_7H_{10}N_6O_3S$; Analysis (Found): C, 32.31; H, 3.72; N, 32.24. (Calculated for $C_7H_{10}N_6O_3S$): C, 32.56; H, 3.88; N, 32.56%); MS: m/z 258 (M+, 65), 242 (16), 198 (40), 168 (48), 141 (100), 111 (05).

**Synthesis of 2-(-2-methyl-5-nitro-imidazo-1-acethydrazinyl)-4-substituted thiazoles, 5a-l**

A mixture of thiosemicarbazide (**4**) (0.05mole) and appropriate bromoacetyl derivatives (0.05 mole) was dissolved in ethanol-DMF mixture and stirred overnight. The resultant solid was collected by filtration, and recrystallized from appropriate solvent. The characterization data of the newly synthesized compounds are given in **Table-1**.




**Mass fragmentation pattern**

## RESULTS AND DISCUSSION

### 3.1 Spectral data

The newly synthesized compounds were characterized by spectral data and elemental analysis. In the $^1$H NMR spectrum of compound **5j**, the signal due to methyl protons appeared as a singlet at $\delta$ 2.2, the $CH_2$ protons came into resonance at $\delta$2.5 as a singlet. The signal due to $OCH_3$ protons appeared at $\delta$3.3, the NH protons came into resonance at $\delta$3.8 and the CONH protons came into resonance at $\delta$ 4.9. The imidazole proton appeared as a singlet at $\delta$8.2, and the thiazole proton appeared as a singlet at $\delta$10.6. The mass spectrum of **5h** showed the molecular ion peak at m/z 426 consistent with the molecular formula $C_{18}H_{14}N_6O_5S$. The other compounds were also characterized by $^1$HNMR and mass spectral data.

### 3.2 Antibacterial activity

The newly synthesized compounds **5a-l** was screened for their antibacterial activity by the serial dilution method [10]. Antibacterial activity was carried out against *P. aeruginosa, E.coli, Klebsiella and S. coccus* by the disk diffusion technique. Among the tested compounds **5b** and **5d** showed significant antibacterial activity **Table-2**.

**Table-2: Antibacterial screening for compounds 5a-l**

| Compd No. | (Diameter of zone of inhibition in mm) | | | |
|---|---|---|---|---|
| | *E.coli* | *P.aeruginosa* | *Klebsiella* | *S.coccus* |
| **5b** | 24 | 26 | 26 | 26 |
| **5d** | 15 | 18 | 20 | 18 |
| **5e** | - | - | - | - |
| **5f** | - | 12 | - | - |
| **5h** | - | - | - | - |
| **5j** | - | 14 | - | - |
| **5k** | 14 | 09 | 11 | 12 |
| **Ciprofloxacin (Std)** | 20 | 22 | 22 | 20 |
| **Solvent control (DMF)** | --- | --- | --- | --- |

*Index for antibacterial activity:*
*Diameter of the cup : 5mm*
*Amount of the sample used : 25µg/cup*
*Control : Dimethyl formamide*
*Standard drug used : Ciprofloxacin*

## 3.3 Antifungal activity

The antifungal activity of these compounds was also determined against *C. albicans, A. flavus, A. fumigatus, Penicillium and Trichophyton*. Among them compound **5b** showed significant activity against all the fungi (**Table-3**).

**Table-3: Antifungal screening for compounds 5a-l**

| Compd No. | (diameter of zone of inhibition in mm) | | | | |
|---|---|---|---|---|---|
| | *C. albicans* | *A. Flavus* | *A. Fumigatus* | *Penicillium* | *Trichophyton* |
| **5b** | 22 | 26 | 24 | 21 | 22 |
| **5d** | 15 | 16 | 20 | 18 | 18 |
| **5e** | 10 | - | - | - | - |
| **5f** | - | 12 | - | - | 09 |
| **5h** | - | - | - | - | - |
| **5j** | - | 14 | - | - | - |
| **5k** | 13 | 08 | 11 | 13 | 11 |
| **Ciclopiroxolamine (std)** | 20 | 22 | 22 | 20 | 20 |
| **Solvent control (DMF)** | --- | --- | --- | --- | --- |

*Index for antifungal activity:*
*Diameter of the cup : 5mm*
*Amount of the sample used : 25µg/cup*
*Control : Dimethyl formamide*
*Standard drug used : Ciclopirox olamine*

## 3.4 Anti-inflammatory activity

The anti-inflammatory activity of these compounds was also determined by employing the formalin induced edema test [11]. The rat paw volume was measured by using modified method [12]. The tested compounds were found to have significant anti-inflammatory activity. Percentage of edema inhibition caused by standard (Ibuprofen) and test compounds at different time intervals are given in **Table-4**.

**Table-4: Anti-inflammatory screening for compounds 5a-l**

| Compd no. | No of animals used | Paw volume (ml) after | | | % inhibition of edema after | | |
|---|---|---|---|---|---|---|---|
| | | 1hr | 2hr | 3hr | 1hr | 2hr | 3hr |
| **5b** | 5 | 0.75 | 0.73 | 0.70 | 6.25 | 23.95 | 43.00 |
| **5c** | 5 | 0.73 | 0.71 | 0.70 | 8.75 | 26.04 | 43.09 |
| **5d** | 5 | 0.74 | 0.70 | 0.69 | 7.9 | 27.08 | 43.90 |
| **5h** | 5 | 0.75 | 0.72 | 0.68 | 6.25 | 25.00 | 44.71 |
| **Control** | 5 | 0.80 | 0.96 | 1.23 | - | - | - |
| **Ibuprofen** | 5 | 0.63 | 0.53 | 0.50 | 21.25 | 44.79 | 59.34 |

*Index for anti-inflammatory activity:*
*Animals : Albino rats (100-200g)*
*Route of administration : Intra-peritoneal*
*Dose : 20mg/kg body weight*

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