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# Sydnone derivatives. Part VII: Synthesis of some novel thiazoles and their pharmacological properties

The synthesis of some 4-(arylsydnonyl)-2-(4-arylhydrazono-3-methyl-5-oxo-2-pyrazolin-1-yl)-thiazoles by reacting 1-thiocarboxamido-3-methyl-4-(arylhydrazono)-2-pyrazolin-5-ones with different 4-bromoacetyl-3-arylsydnones is described. A few compounds from this series were screened for their anti-inflammatory, analgesic, and CNS depressant activities. Among the tested compounds **6s**, **6d**, **6n**, and **6u** showed significant anti-inflammatory activity comparable with that of standard drug Ibuprofen. Compounds containing chlorine and carboxylic substituents are more active. **6f**, **6r**, and **6u** showed marked analgesic activity and most of the compounds tested showed promising CNS depressant activity comparable with that of standard drug pentobarbitone.

**Key Words**: Thiazole; Arylsydnone; Pyrazoline; Anti-inflammatory; Analgesic; CNS depressant activity

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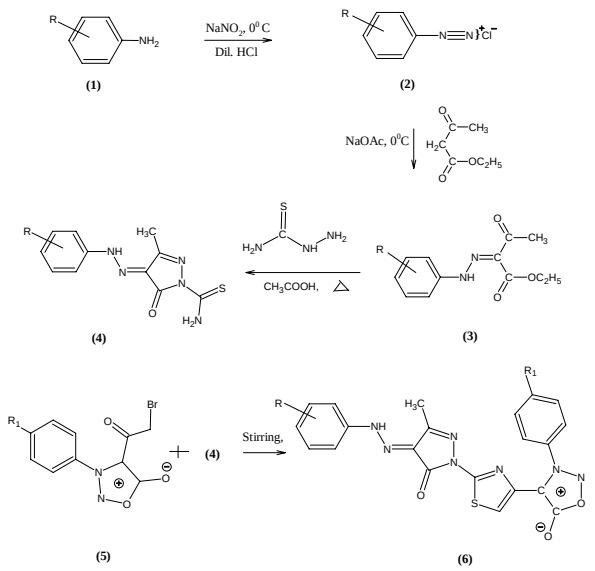
## Introduction

Sydnones constitute a well-defined class of mesoionic compounds obtained by the action of acetic anhydride on *N*-nitrosoderivative[1]. These compounds are of interest because of the varied types of biological activity displayed by some of them, particularly sydnone 4-heterocycles[2–4]. Of the many sydnone-4-heterocycles synthesized in this laboratory, sydnone-4-thiazoles have shown promising biological activities[5,6] viz, anti-inflammatory, analgesic, anthelmintic, and anticonvulsant activities. Prompted by these observations and in continuation of our research on biologically active sydnone-4-heterocycles[7,8], we synthesized some novel triheterocyclic thiazole derivatives carrying sydnone and pyrazole moieties with a view to evaluate their anti-inflammatory, analgesic, and CNS depressant activities.

## Synthesis

The synthetic route followed for obtaining compounds **6** is outlined in Scheme 1. Thus diazotization of substituted anilines **1** to give the diazonium salts **2** followed by coupling with ethyl acetoacetate in the presence of sodium acetate gave ethyl-2-arylhydrazono-3-oxobutyrates **3**. Reaction of **3** with thiosemicarbazide in acetic acid[9] gave the required thioamides **4**. The 3-arylsydnones were prepared following the literature method[10]. Acylation was carried out with phosphorus pentoxide and acetic acid in dry benzene following the method of Greco et al[11]. The resulting ketones were then brominated photochemically in chloroform[12] to yield 4-bromoacetyl-3-arylsydnones **5**. The classical Hantzch reaction between various thioamides **4** and 4-(bromoacetyl)-3-arylsydnones **5** gave the title compounds **6** (Scheme 1 and Table 1).




**Scheme 1**

## Results and Discussion

The structural elucidation of the new compounds was performed by elemental analysis, IR, $^1$H-NMR, and mass spectral studies.

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**Table 1.** Characterization data of 4-(arylsydnonyl)-2-(4-arylhydrozono-3-methyl-5-oxo-2-pyrazolin-1-yl)-thiazole **6**.

| Comp. No. | R | $R_1$ | Yield (%) Mp(°C) | Mol. Formula[a] | Colour and crystal *nature | IR($cm^{-1}$) $\nu_{C=O}$(pyrazole) $\nu_{C=O}$(sydnone) | $M^+$/ isotopic peak |
|---|---|---|---|---|---|---|---|
| **6a** | 4-Cl | H | 85<br>282–284 | $C_{21}H_{14}ClN_7O_3S$ | Orange yellow flakes | 1673<br>1750 | 479/481 |
| **6b** | 4-$CH_3$ | H | 80<br>266–268 | $C_{22}H_{17}N_7O_3S$ | Orange yellow flakes | 1664<br>1747 | 459 |
| **6c** | 4-$NO_2$ | H | 78<br>270–272 | $C_{21}H_{14}N_8O_3S$ | Orange yellow flakes | 1675<br>1752 | – |
| **6d** | 2-COOH | H | 78<br>280–282 | $C_{22}H_{15}N_7O_5S$ | Yellow flakes | – | 489 |
| **6e** | 4-COOH | H | 58<br>286–288 | $C_{22}H_{15}N_7O_5S$ | Brownish yellow flakes | –<br>– | |
| **6f** | 4-$OCH_3$ | H | 69<br>248–250 | $C_{22}H_{17}N_7O_4S$ | Orange red flakes | 1680<br>1745 | – |
| **6g** | H | H | 72<br>256–258 | $C_{21}H_{15}N_7O_3S$ | Orange yellow flakes | 1678<br>1752 | 445 |
| **6h** | 2-$CH_3$, 4-Cl | H | 73<br>250–252 | $C_{22}H_{16}ClN_7O_3S$ | Orange yellow flakes | 1682<br>1742 | |
| **6i** | 2-Cl, 5-Cl | H | 76<br>238–240 | $C_{21}H_{13}Cl_2N_7O_3S$ | Orange yellow flakes | – | – |
| **6j** | 4-$NO_2$ | $CH_3$ | 75<br>304–306 | $C_{22}H_{16}N_8O_5S$ | Orange yellow flakes | 1639<br>1755 | – |
| **6k** | 2-COOH | $CH_3$ | 71<br>290–292 | $C_{23}H_{17}N_7O_5S$ | Orange yellow flakes | – | 503 |
| **6l** | 4-$OCH_3$ | $CH_3$ | 74<br>238–240 | $C_{23}H_{19}N_7O_4S$ | Orange red flakes | 1638<br>1743 | – |
| **6m** | H | $CH_3$ | 70<br>265–267 | $C_{22}H_{17}N_7O_3S$ | Orange yellow flakes | – | – |
| **6n** | 2-$CH_3$, 4-Cl | $CH_3$ | 71<br>256–258 | $C_{23}H_{18}ClN_7O_3S$ | Orange red flakes | 1645<br>1748 | 507/509 |
| **6o** | 2-Cl, 5-Cl | $CH_3$ | 72<br>270–272 | $C_{22}H_{15}Cl_2N_7O_3S$ | Orange red flakes | 1668<br>1756 | – |
| **6p** | 4-Cl | $OCH_3$ | 76<br>268–270 | $C_{22}H_{16}ClN_7O_4S$ | Orange yellow flakes | 1638<br>1756 | 509/511 |
| **6q** | 4-$CH_3$ | $OCH_3$ | 71<br>258–260 | $C_{23}H_{19}N_7O_4S$ | Orange red flakes | 1646<br>1760 | – |
| **6r** | 4-$NO_2$ | $OCH_3$ | 72<br>302–304 | $C_{22}H_{16}N_8O_6S$ | Orange yellow flakes | 1652<br>1755 | 520 |
| **6s** | 2-COOH | $OCH_3$ | 75<br>306–308 | $C_{23}H_{17}N_7O_6S$ | Orange yellow flakes | – | – |
| **6t** | 4-COOH | $OCH_3$ | 59<br>295–97 | $C_{23}H_{17}N_7O_6S$ | Brownish yellow flakes | – | 519 |
| **6u** | 4-$OCH_3$ | $OCH_3$ | 70<br>252–54 | $C_{23}H_{19}N_7O_5S$ | Orange red flakes | 1650<br>1760 | 505 |
| **6v** | H | $OCH_3$ | 63<br>248–250 | $C_{22}H_{17}N_7O_4S$ | Brownish yellow flakes | – | – |
| **6w** | 2-$CH_3$, 4-Cl | $OCH_3$ | 65<br>252–54 | $C_{23}H_{18}ClN_7O_4S$ | Orange red flakes | 1638<br>1740 | 523/525 |
| **6x** | 2-Cl, 5-Cl | $OCH_3$ | 67<br>236–38 | $C_{22}H_{15}Cl_2N_7O_4S$ | Orange yellow flakes | 1648<br>1756 | – |

*Solvent for recrystallization: Ethanol-Dimethyl formamide. [a]Elemental analysis of the compounds was within ±0.4% of calculated values.

The characterization data of thiazoles **6a–x** are given in Table 1. The results of elemental analysis agree with the theoretical values within the limits of experimental error. The formation of **6** was supported by the disappearance of IR bands corresponding to $NH_2$ and C=S groups of **4**. In a typical example the IR spectrum of **6j** shows the absence of peak at 3454 $cm^{-1}$ ($NH_2$) and 1554 $cm^{-1}$ and 1231 $cm^{-1}$ (C=S attached to N atom). A peak at 1756 $cm^{-1}$ typical o f a carbonyl group clearly indicates the presence of a sydnone moiety in compound **6j**. The $^1$H-NMR spectrum of **6l** shows three singlets at δ = 2.31, 2.50, and 3.91, each integrating for three protons corresponding to a methyl group on phenyl, a methyl group of a pyrazole moiety, and a methoxy group, respectively. The signal due to thiazole proton appeared at δ = 7.68 as singlet[16]. The NH proton appeared as a broad singlet at δ = 13.6. The aromatic protons of *p*-anisyl group appeared as two doublets centered at δ = 6.97 and δ = 7.51 integrating for two protons each. The *p*-tolyl protons appeared as multiplets at δ = 7.3–7.4, integrating for four protons. Similarly the $^1$H-NMR spectra of few more compounds were recorded and the signals are assigned as follows:

**6c:** $^1$H-NMR, $CDCl_3$+DMSO-$d_6$; δ = 2.5 (s, 3H, $CH_3$), 7.79 (d, 2H,*ortho* protons of *p*-nitrophenyl), 8.28 (d, 2H, *meta* protons of *p*-nitrophenyl), 7.6–7.7 (m, 5H, phenyl protons), 7.79 (s, 1H, thiazole 5H),and δ = 13.4 (s, 1H, NH).

**6s:** $^1$H-NMR, $CDCl_3$+DMSO-$d_6$: δ = 2.56 (s, 3H, $CH_3$), 3.91 (s, 3H, $OCH_3$), 7.1 (d, 2H, anisyl *ortho* protons), 7.61 (d, 2H, anisyl *meta* protons), 7.87 (s, 1H, thiazole 5H), 14.7 (br, 1H, NH), and δ = 7.9–8.1 (m, 4H, Ar-H).

**6j:** $^1$H-NMR, $CDCl_3$+DMSO-$d_6$: δ = 2.38 (s, 3H, $CH_3$), 2.46 (s, 3H, $CH_3$), 7.76 (d, 2H, *ortho* protons of *p*-nitrophenyl), 8.18 (d, 2H, *meta* protons of *p*-nitrophenyl), 7.28 (d, 2H, *ortho* protons of *p*-tolyl), 7.46 (d, 2H, *meta* protons of *p*-tolyl), 7.78 (s, 1H, thiazole 5H) and δ = 13.3 (br, 1H, NH).

**6g:** $^1$H-NMR, $CDCl_3$: δ = 2.4 (s, 3H, $CH_3$), 7.4–7.8 (m, 10H, Ar-H), 7.81 (s, 1H, thiazole 5H) and δ = 13.1 (br. 1H, NH).

**6f:** $^1$H-NMR, DMSO-$d_6$: δ = 2.31 (s, 3H, $CH_3$), 3.86 (s, 3H, $OCH_3$), 6.91 (d, 2H, *ortho* protons of *p*-anisyl), 7.4 (d, 2H, *meta* protons of *p*-anisyl), 7.6–7.8 (m, 5H, phenyl protons), 7.78 (s, 1H, thiazole 5H) and δ = 13.5 (br, 1H, NH)

The mass spectrum of **6p** showed the molecular ion peak at *m/z*, 509/511 consistent with the molecular formula $C_{22}H_{16}ClN_7O_4S$. The peak at 451/453 is due to the loss of (NO-CO) fragment which is typical of sydnone containing molecules. Similarly the mass spectra of few more compounds were recorded and are in conformity with the assigned structure (Table 1).

Some selected compounds from this series were subjected to anti-inflammatory[13], analgesic[14], and CNS depressant activity[15] studies as per the procedures reported in the literature. The screening studies indicated that compounds **6s**, **6d**, **6n**, and **6u** showed significant anti-inflammatory activity in the 1$^{st}$ hour. However, at the end of the 3$^{rd}$ and 5$^{th}$ hours, compounds **6a**, **6d**, **6s**, and **6u** showed significant activity. From observation it can be concluded that compounds with chlorine and carboxylic substituents are more active (Table 2). Similarly, among the compounds tested for analgesic activity **6f**, **6r**, and **6u** showed a marked activity (Table 3). Most of the compounds tested showed promising CNS depressant activity comparable with that of standard drug pentobarbitone (Table 4).

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## Experimental section

All melting points were determined by the open capillary method and are uncorrected. IR spectra (KBr disc) were recorded on a JASCO FT IR 430 spectrophotometer. $^1$H-NMR spectra were recorded on Bruker AC 300F (300 MHz) NMR spectrometer using $CDCl_3$/DMSO-$d_6$ as solvent and tetramethylsilane as internal standard. The chemical shifts are expressed in δ scale downfield from TMS and proton signals are indicated s = singlet, d = doublet, t = triplet, m = multiplet. Mass spectra were recorded on a Jeol-JMS-D 300 mass spectrometer operating at 70 eV. UV spectra were recorded on UV-visible Anthelie spectrophotometer in quartz cell at room temperature. The purity of the compounds was confirmed by TLC.

*General procedure for the preparation of ethyl-2-arylhydrazono-3-oxobutyrate* **3**

Appropriate amine **1** (0.01 mol) was dissolved in dilute hydrochloric acid (10 ml) and cooled to 0 °C in an ice bath. To this, a cold solution of sodium nitrite (0.02 mol) was added. The diazonium salt **2** solution was filtered into a cold solution of ethyl acetoacetate (0.05 mol) and sodium acetate in ethanol. The separated yellow solid was filtered, washed with water and recrystallized from ethanol. The compounds prepared according to this procedure are:

*Ethyl-2-(4-chlorophenyl)hydrazono-3-oxobutyrate* **3a**

Mp 94 °C (lit [9], 94 °C), yield 80%.

*Ethyl-2-(4-tolyl)-hydrazono-3-oxobutyrate* **3b**

Mp 62 °C (lit [9], 63 °C ), yield 69%.

*Ethyl-2-(4-nitrophenyl)hydrazono-3-oxobutyrate* **3c**

Mp 123 °C, yield 78%. UV: $\lambda_{max}$ = 242 nm

IR: 3413$cm^{-1}$(NH); 1686$cm^{-1}$(C=O) & 1598$cm^{-1}$(NH-N=C)

*Ethyl-2-(2-carboxyphenyl)hydrazono-3-oxobutyrate* **3d**

Mp 142 °C, yield 70%.

*Ethyl-2-(4-carboxyphenyl)hydrazono-3-oxobutyrate* **3e**

Mp 195 °C, (lit.[9], 196 °C). yield 70%.

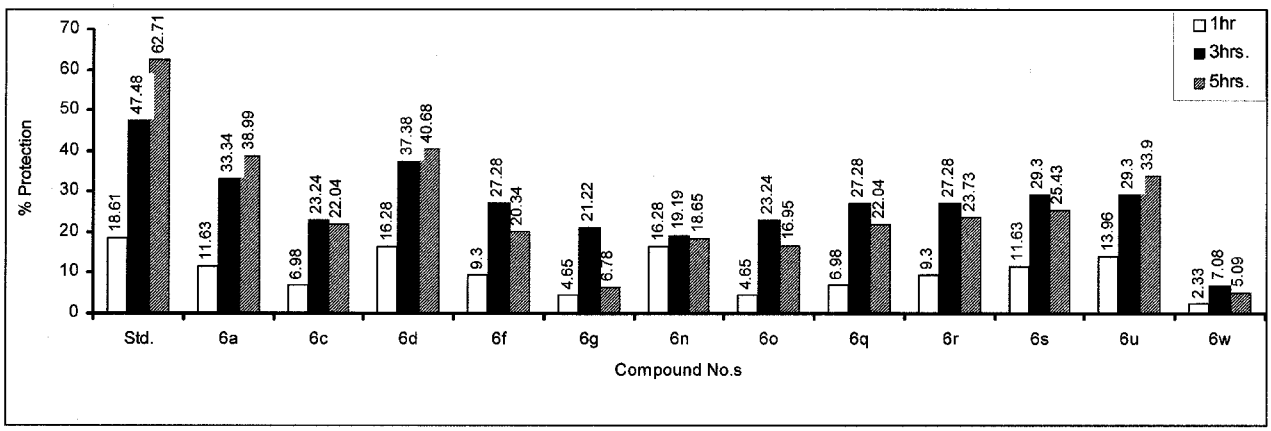
*Ethyl-2-(4-anisyl)hydrazono-3-oxobutyrate* **3f**

Mp 55 °C, (lit.[9], 56 °C). yield 72%.

*Ethyl-2-phenylhydrazono-3-oxobutyrate* **3g**

Mp 68 °C, yield 65%.

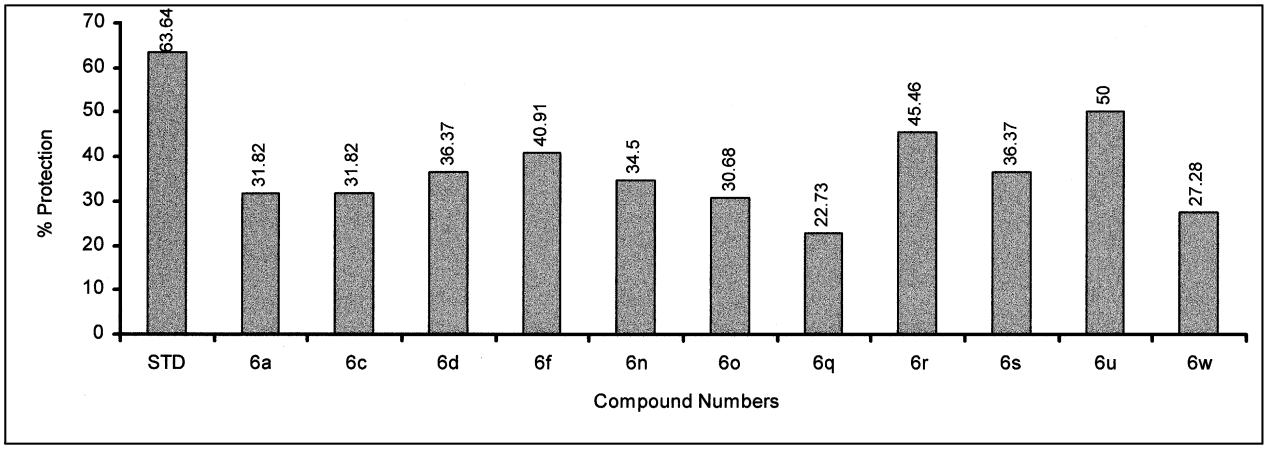
**Table 2.** Anti-inflammatory activity data of thiazoles **6**.




Index for anti-inflammatory activity:

| | |
|---|---|
| Model: | Acute anti-inflammatory |
| Method: | Formalin induced oedema test |
| Animals: | Albino rats (100–200 g) |
| No. of animals per group: | 05 |
| Route of administration: | Intra-peritoneally |
| Standard drug: | Ibuprofen |
| Dose: | 20mg/kg body weight |
| Average body weight of animals: | 150 g |
| Control: | 2% acacia mucilage |

**Table 3.** Analgesic activity data of thiazoles **6**.




Index for analgesic activity data:

| | |
|---|---|
| Method: | Acetic acid induced writhing, (acetic acid-0.6% concentration) |
| Animals: | Albino mice (20–25 g) |
| No. of animals per group: | 05 |
| Route of administration: | Intra-peritoneally |
| Standard drug: | Ibuprofen |
| Dose: | 100 mg/kg body weight. |

*Ethyl-2-(4-chloro-2-methylphenyl)hydrazono-3-oxobutyrate* **3h**

Mp 126 °C, yield 65%. UV: $\lambda_{max}$ = 248 nm

IR: 3415cm$^{-1}$(NH); 1701cm$^{-1}$(C=O) & 1515cm$^{-1}$(NH-N=C)

*Ethyl-2-(2,5-dichlorophenyl)hydrazono-3-oxobutyrate* **3i**

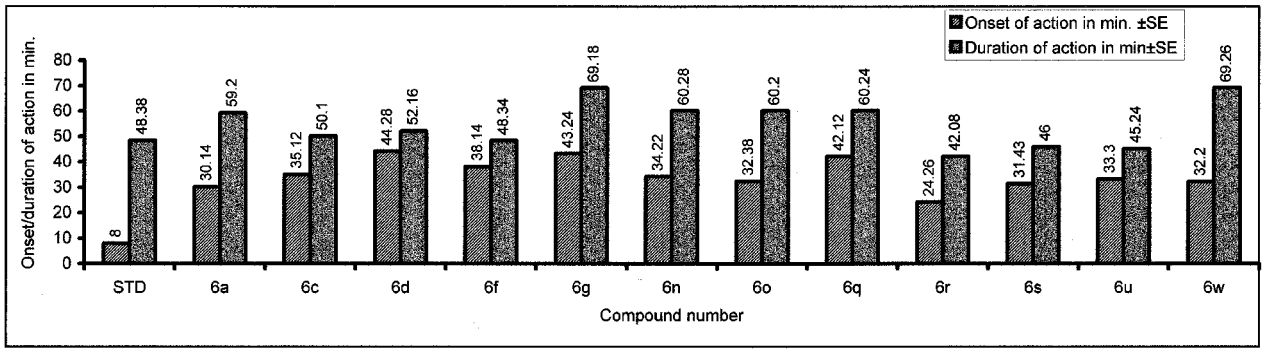
Mp 117 °C, yield 85%.

IR: 3412cm$^{-1}$(NH); 1689 cm$^{-1}$(C=O); & 1520 cm$^{-1}$(NH-N=C).

*General procedure for the preparation of 1-thiocarboxamido-3-methyl-4-(arylhydrazono)-2-pyrazolin-5-one* **4**

Ethyl-2-arylhydrazono-3-oxobutyrate **3** (0.01 mol) was dissolved in glacial acetic acid (20 ml), a solution of thiosemicarbazide (0.02 mol) in glacial acetic acid (25 ml) was added and the mixture was refluxed for 4 hours. It was cooled, and allowed to stand overnight. The separated solid was filtered, dried, and recrystallized from ethanol-dimethyl formamide mixture. The compounds prepared according to this procedure are:

**Table 4.** CNS depressant activity data of thiazoles **6**.




Index for CNS depressant activity:

| | |
|---|---|
| Model: | Effect of the drug on pentobarbitone induced sleep |
| Animals: | Albino rats (100–200g) |
| No. of animals per group: | 05 |
| Route of administration : | Intraperitoneally |
| Standard drug: | Pentobarbitone (35 mg/kg) intraperitoneally |
| Test compounds: | 35 mg/kg intraperitoneally |
| S.E.: | Standard Error |

*1-Thiocarboxamido-3-methyl-4-(4-chlorophenylhydrazono)-2-pyrazolin-5-one* **4a**

Mp 221 °C (lit.[9], 222 °C), yield 78%.

*1-Thiocarboxamido-3-methyl-4-(4-tolylhydrazono)-2-pyrazolin-5-one* **4b**

Mp 219 °C (lit.[9], 220 °C), yield 80%.

*1-Thiocarboxamido-3-methyl-4-(4-nitrophenylhydrazono)-2-pyrazolin-5-one* **4c**

Mp 245 °C, yield 72%.

IR: 3454 $cm^{-1}$ (NH); 1636 $cm^{-1}$(C=O); & 1554 $cm^{-1}$(NH-N=C).

*1-Thiocarboxamido-3-methyl-4-(2-carboxyphenylhydrazono)-2-pyrazolin-5-one* ***4d***

Mp 280 °C, yield 75%.

*1-Thiocarboxamido-3-methyl-4-(4-carboxyphenylhydrazono)-2-pyrazolin-5-one* **4e**

Mp 275 °C, (lit.[9], 280 °C), yield 68%.

*1-Thiocarboxamido-3-methyl-4-(4-anisylhydrazono)-2-pyrazolin-5-one* ***4f***

Mp 192 °C, (lit.[9], 195 °C), yield 74%.

*1-Thiocarboxamido-3-methyl-4-(4-phenylhydrazono)-2-pyrazolin-5-one* **4g**

Mp 224 °C, yield 68%.

*1-Thiocarboxamido-3-methyl-4-(4-chloro-2-methylphenylhydrazono)-2-pyrazolin-5-one* **4h**

Mp 243 °C, yield 60%. UV: $\lambda_{max}$ = 264 nm.

IR: 3409 $cm^{-1}$ (NH); 3280 $cm^{-1}$ ($NH_2$); 1670 $cm^{-1}$(C=O); & 1544 $cm^{-1}$(NH-N=C).

*1-Thiocarboxamido-3-methyl-4-(2,5-dichlorophenylhydrazono)-2-pyrazolin-5-one.* **4i.**

Mp 239 °C, yield 78%. UV: $\lambda_{max}$ = 264 nm.

IR: 3471 $cm^{-1}$ (NH); 3415 $cm^{-1}$ ($NH_2$); 1722 $cm^{-1}$(C=O); & 1546 $cm^{-1}$(NH-N=C).

*General procedure for the preparation of 4-(arylsydnonyl)-2-(4-arylhydrazono-3-methyl-5-oxo-2-pyrazolin-1-yl)-thiazole* ***6***

A mixture of 1-thiocarboxomido-3-methyl-4-(arylhydrazono)-2-pyrazolin-5-one **4 (**0.01 mol) in DMF (20 ml) and 4-(bromoacetyl)-3-arylsydnone **5** (0.01 mol) in ethanol (20 ml) was stirred at room temperature for 1–2 h. The separated solid was filtered, dried, and recrystallized from ethanol-DMF mixture.

## *Pharmacology*

### *Anti-inflammatory activity*

Twelve compounds were selected and tested for anti-inflammatory activity according to the method of Winter et al[13]. Groups of five albino rats of either sex weighing about 100–200 g were used. Formalin (6% 0.1 ml) was injected into the plantar surface of the rat's hind paw 30 minutes after administration of the test compounds (20 mg/kg). Paw volume was measured after 1,3, and 5 hours. Results are shown in Table 2.

### *Analgesic activity*[14]

Albino mice weighing 20–25 g were used for this test. One day prior to drug testing, these mice were given an injection of 0.6% acetic acid (1 ml/100g) intraperitoneally, only those which gave positive writhings episodes were selected. The number of writhing movement exhibited by each mouse over a period of 20 minutes was recorded. The selected mice were then divided into 6 groups containing 5 animals. The following day vehicles/drug was administered intraperitoneally to the mice. After half an hour an intraperitoneal injection of 0.6% acetic acid was given and the number of writhings in the treated and control groups was recorded. The % protection was calculated (see Table 3)

*CNS depressant activity*[15]

Thirty healthy albino rats of body weight 100–200 g were selected and kept for 8 hours fasting. These fasted animals were divided into 6 groups randomly, each of 5 animals. Group 1 animals received standard drug pentobarbitone 35 mg/kg body weight intraperitoneally. All other groups of animals received test compounds 35 mg/kg intraperitoneally along with pentabarbitone sodium. The time of onset of action was noted as the animal looses its righting reflux, i.e. falls sleep. The time of recovery from sleep is noted as it turns to recover its normal posture. The onset and duration of action is calculated (see Table 4).

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