Chapter – V

Synthesis of thiazoles containing pyrazolone moiety
The chemistry of thiazoles dates back to 1879 when benzothiazole came into light. The interest in the preparation of compounds containing the thiazole moiety has been increasing steadily in view of their utility in the field of medicine, dyes, fungicides, insecticides, wetting agents, photosensitizers and rubber vulcanization\textsuperscript{1-3}. The main applications of thiazoles are in the field of agriculture, pharmacy and polymers.

The unique physiological properties of the thiazoles owe their properties to the following facts.

1. Thiazoles are stable aromatic compounds with relatively small size.
2. Thioamide (R–CS-NH-) component structure is well known to display typical physiological activity due to substituents on –S-\_C=N- system.
3. The susceptibility of reactive sites at 2-, 3- and 5- positions of the thiazole nucleus to biochemical attack during the metabolism of a thiazole derivative involving reduction, hydrolysis, amination, decarboxylation of CO\textsubscript{2}H groups etc.
4. Non-carcinogenic nature of most of the thiazoles.

The thiazole chemistry has been developed extensively and is still developing. Presently, there are a number of drugs used clinically, which comprise of thiazole moiety substituted at various positions and in association with various other
heterocyclic rings. They are mainly used as chemotherapeutic agents, diuretics and antihistamines.

One of the first commercial synthetic drugs containing thiazole ring was sulphathiazole 1, a simple sulphonamide antibacterial derived from 2-amino thiazole.

Similarly, large numbers of natural products contain thiazole ring system. For example, Penicillin G 2 and Vitamin B₁ (thiamine) 3.

The thiamine pyrophosphate is the essential coenzyme in the enzymatic decarboxylation of pyruvate to acetaldehyde.

A series of nitrofuryl thiazolyl hydrazones 4 \([R = H, Me; R₁ = Me, Et, 2\text{-furyl}, Me (CH₂)₂, Me (CH₂)₂, Pr, PhNH₂, Ac]\) were reported in British Patent⁴. All the compounds were reported to possess antibacterial and antifungal activity.

Nitridazole 5 a schistosomicide⁵ is clinically used drug containing the thiazole moiety.
Brown et al. reported that, the potent anti-inflammatory agent in a series of 2,4-diaryl-5-thiazole acetic acid was 6 which has five times the potency of phenylbutazone in the carrageenan induced rat paw oedema test. It was also claimed that gastrointestinal disturbances were less in these compounds with equally effective doses of aspirin, phenylbutazone or indomethacin.

\[
\text{Cl} \quad \text{HO} \quad \text{N} \quad \text{C} \quad \text{S} \\
\text{N} \quad \text{C} \quad \text{S} \quad \text{N} \quad \text{C} \\
\text{S} \quad \text{N} \quad \text{C} \quad \text{S} \quad \text{N} \\
\text{S} \quad \text{N} \quad \text{C} \quad \text{S} \quad \text{N} \\
\text{N} \quad \text{H} \quad \text{R} \\
\text{Cl} 
\]

\text{6}

Sawhney et al. have prepared nonsteroidal anti-inflammatory agent 7 \([R = \text{alkyl or aryl}]\) which does not show any undesirable side effects in glucocorticoid therapy for the inhibition of inflammation. The activity of 7 was comparable with that of phenylbutazone.

\[
\text{N} \quad \text{C} \quad \text{S} \quad \text{N} \quad \text{C} \\
\text{S} \quad \text{N} \quad \text{C} \quad \text{S} \quad \text{N} \\
\text{S} \quad \text{N} \quad \text{C} \quad \text{S} \quad \text{N} \\
\text{S} \quad \text{N} \quad \text{C} \quad \text{S} \quad \text{N} \\
\text{H} \quad \text{N} \quad \text{R} \\
\text{7}
\]

Fenclozic acid 8 which is 2-(\(\rho\)-chlorophenyl)-4-thiazole acetic acid is an anti-inflammatory drug\(^8\). In the single dose carrageenan induced rat paw test, Fenclozic acid has potency equal to phenylbutazone.

\[
\text{O} \quad \text{C} \quad \text{N} \quad \text{S} \quad \text{N} \quad \text{C} \\
\text{H} \quad \text{O} \quad \text{H} \quad \text{S} \quad \text{N} \\
\text{S} \quad \text{N} \quad \text{C} \quad \text{S} \quad \text{N} \\
\text{S} \quad \text{N} \quad \text{C} \quad \text{S} \quad \text{N} \\
\text{Cl} \\
\text{8}
\]

Mndzhoyan and Afrikyan\(^9\) prepared a number of 4-methyl-2-acylaminothiazoles \(9 \ [R = \text{H, CH}_3, \text{C}_2\text{H}_5, \text{C}_6\text{H}_5-\text{CH}_2-, \text{Ph-CH}_2-\text{CH-CH}_3, \text{Ph-CH}_2-\text{CH-Ph}]\) and their activities against Mycobacterium \(B_5\) and Mycobacterium tuberculosis \(K_6\) was determined. Compound \(9\) with \(R = \text{Ph-CH}_2-\text{CH-Ph}\) was the most active bacteriostat.
2-arylvinyl -5-phenylthiazoles 10 were synthesized by Pappalardo et al.\textsuperscript{10} and tested them for antibacterial activity. [Ar = Phenyl, substituted phenyl, 2-furyl, 2-thienyl etc.]

\begin{center}
\begin{tikzpicture}
  \node [text width=2cm] (A) at (0,0) {9};
  \node [text width=2cm] (B) at (2,0) {10};
\end{tikzpicture}
\end{center}

Ahluwalia \textit{et al.},\textsuperscript{11} reported that 2-amino-4-aryl-5-arylazothiazoles 11 have bactericidal and fungicidal activities. [R = H, Cl, Br, OCH\textsubscript{3}; R\textsubscript{i} = 2-Cl-C\textsubscript{6}H\textsubscript{4}O, 4-Cl-C\textsubscript{6}H\textsubscript{4}O, 4-CH\textsubscript{3}-C\textsubscript{6}H\textsubscript{4}O, morpholino, piperidino].

\begin{center}
\begin{tikzpicture}
  \node [text width=2cm] (A) at (0,0) {11};
  \node [text width=2cm] (B) at (2,0) {12};
\end{tikzpicture}
\end{center}

Forester \textit{et al.},\textsuperscript{12} reported a series of 4-cyano-5-chloro-2-thiazolyloxyacetanides 12. These compounds were found to be effective herbicides.

\begin{center}
\begin{tikzpicture}
  \node [text width=2cm] (A) at (0,0) {13};
  \node [text width=2cm] (B) at (2,0) {14};
\end{tikzpicture}
\end{center}

Bhagwat \textit{et al.}\textsuperscript{13} reported the synthesis of compounds 13 and 14. The new compounds were evaluated for their antibacterial activities.

\begin{center}
\begin{tikzpicture}
  \node [text width=2cm] (A) at (0,0) {13};
  \node [text width=2cm] (B) at (2,0) {14};
\end{tikzpicture}
\end{center}

Sawhney and co-workers\textsuperscript{14} prepared thiazole derivatives of the type 15, 16 and 17 [R\textsubscript{1} = C\textsubscript{6}H\textsubscript{5}, 4-CH\textsubscript{3}O-C\textsubscript{6}H\textsubscript{4}, 4-Cl-C\textsubscript{6}H\textsubscript{4}; R\textsubscript{2} = CH\textsubscript{3}, C\textsubscript{2}H\textsubscript{5}, C\textsubscript{6}H\textsubscript{5}, 4-CH\textsubscript{3}O-C\textsubscript{6}H\textsubscript{4}, 4-
Few of them showed significant antifungal activity in vitro against *P. aphanidratum*, *A. solani* and *F. udum*.

Ebeid and co-workers synthesized certain new nitro thiazoles and studied their effect on the content of nucleic acids in white mice liver.

Mohan and Verma synthesized 2,5-disubstituted thiazolo [3,2-b]-s-triazoles starting from the appropriate 5-mercapto-s-triazoles. The diuretic, antibacterial and antifungal activities of these compounds have also been evaluated. Few of them showed moderate antibacterial activity against *P. aeruginosa*, *S. aureus* and antifungal activity against *C. albicans*.

2-sulfinyl or sulphonylthiazoles were prepared as possible agrochemical fungicides.

Bird et al reported the synthesis of aryl substituted thiazole compounds which were found to be useful in treating inflammatory and allergic diseases.

Synthesis of a series of thiazole derivatives [where R1, R2 = C1-6 alkyl; R3 = H, C1-6 alkyl; R2, R3 = (CH2)4; R4 = R5 = H, C1-20 alkyl, Ph, PhS, C1-6 alkylthio, halo,
NO₂, carbazoyl, COOH; A = NH, O, S, SO, SO₂, C₁₋₆ alkyl, excluding R₃ = H, R₄ = C₁₋₆ alkyl or Ph, R₅ = H and A = NH] were reported by Kanai and co-workers¹⁹.

Shah and co-workers²⁰ reported the synthesis of 2-(substituted amino acetamido)-4-(p-chlorophenyl)-thiazoles 24 [R = C₆H₅, 4-CH₃-C₆H₄, 2-Cl-C₆H₄, 2-NO₂-C₆H₄, 5-Br-(4-OH)-(3-OCH₃)-C₆H₂, 5-NO₂-(4-OH)-(3-OCH₃)-C₆H₂, 3-NO₂-C₆H₄, 4-NO₂-C₆H₄] starting from 2-amino-4-(p-chlorophenyl)-thiazoles 23. Compounds thus prepared exhibit moderate to good antibacterial, tuberculostatic and local anesthetic activities.

Thiazolyl pyridines 26 and 27 [R = H, CH₃, CH₂=CHCH₃; R₁ = 2-thienyl, p-Cl-C₆H₄, p-CH₂-C₆H₄, p-OCH₃-C₆H₄], were prepared by treating 2,6-di-(o-bromoacetyl)pyridine 25 with various thioureas and thiomides²¹. These compounds were tested for antifungal activity and photo toxicity against mosquito larvae.

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Several 2-amino-4H-(1)-benzothiopyrano-[4,3-d]thiazoles 28 \([R = H, \text{CH}_3, \text{Cl}]\) were prepared by the interaction of 3-bromothiochroman-4-ones with thiourea\(^{22}\). Few selected compounds from this series have been tested for their antimicrobial, analgesic and anti-inflammatory activities.

Sharma and co-workers\(^{23}\) synthesized some 3-(2-thiazolyl)-1,2-benzisothiazoles 29 and studied their anti-inflammatory activity.

Some thiazoles of the type 30, 31 and 32 were reported by Patel et al.\(^{24}\). These compounds display moderate to good antimicrobial and tuberculostatic activities.

Saifulla et al.\(^{25}\) reported the synthesis of substituted steroidal steroidal thiazoles 33 \([R = \text{OH, OAc, Dl}; R_1 = \text{NH}_2, \text{CH}_3]\) by the reaction of 5a-hydroxy-6-ketosteroids with NBS, thiourea/ thioacetamide employing benzoyl peroxide as catalyst.
Series of thiazoles of type 34 [R = H, Br], 35 [Ar = Ph, p-Cl-C₆H₄, p-Me-C₆H₄, o-Me-C₆H₄, o-Cl-C₆H₄, p-OMe-C₆H₄] and 36 [R = H, Br; R₁ = NO₂, p-Cl-C₆H₄, p-NO₂-C₆H₄, 2,4-Cl₂-C₆H₃, o-Cl-C₆H₄, p-Me-C₆H₄] were reported from kalluraya et al. These new compounds were screened for their antimicrobial activities. Most of them showed promising results.

Prompted by these biological and pharmacological applications of thiazoles, it would be interesting to prepare thiazole derivatives in combination with pyrazolone nucleus. Thus, Chapter V describes our work on the synthesis, characterization, antibacterial and antifungal activity studies of some diazole derivatives of pyrazolone system containing thiazole moiety.
Present work

Fused aryl hydrazono pyrazoline-5-one and their N-bridged thiazoles are found to be associated with diverse pharmacological activities on the other hand, it is well known that a number of heterocyclic compounds containing pyrazoline-5-one and thiazole moieties exhibit a wide variety of biological activities. In the last few years attempts have been made to develop simple and efficient methods for the synthesis of nitrogen bridged heterocyclic compounds utilizing inexpensive starting materials and reagents. Aryl hydrazono pyrazoline-5-one containing thiazole system have received considerable attention in pharmacological activity. In view of these, we report here the synthesis of aryl hydrazone pyrazoline-5-one containing different substituted thiazole moieties.

In this chapter, we present the synthesis and characterization of

I. phenyl aryl bromides 38a – g
II. 3-(4'-substituted phenyl)-4-bromo acetyl sydnone 45a – c
III. [3-methyl-5-oxo-4-(4'-substituted aryl hydrazono)-4,5-dihydro-pyrazol-1-yl]- acetic acid N-(4'-substituted thiazol-2-yl)-hydrazide 48a – h

I. Phenyl aryl bromides 38a – g

Phenyl aryl bromides 38a – g employed in the preparation of aryl hydrazono pyrazoline-5-one containing substituted thiazole moiety 48a – i are prepared by the reaction of various acetophenones 37a – g with bromine in diethyl ether in presence of anhydrous luminan chloride at 0°C [Scheme – V.1]
For example in a typical experiment acetophenone in pure anhydrous diethyl ether was cooled to 0°C in a three necked flask. The solution was cooled to 0°C and anhydrous aluminium chloride was added to it. The bromine was added to it gradually from dropping funnel with continuous stirring. The bromine colour disappears rapidly, and finally the solution turned to pink. After usual work up a compound was obtained in 68 – 82% yield.

Similar procedure is applied for other substituted acetophenones 37b – g. The substituted aryl bromides are characterized by their characteristic melting points reported in the literature.29–32.

II. 3-(4'-substituted phenyl)-4-bromo acetyl sydnone 45a – c

All the substituted anilines employed in preparation of N-substituted glycines were obtained commercially and are used after purification either by distillation or by recrystallization. The substituted anilinoacetic acids 40 required for the preparation of 3-aryl sydnones 43a – c were obtained by the hydrolysis of corresponding esters 39. The esters 39 were obtained by refluxing various anilines with ethyl chloroacetate, phenylamino acetic acid 40a, p-tolylaminoacetic acid 41b, and p-anisylaminoacetic acid 41c were used for the preparation of 3-aryl sydnones 43a – c.

4-acetyl-3-aryl sydnones 44a – c were obtained by the acylation of 3-aryl sydnones 43a – c with acetic acid and phosphorous pentoxide in dry benzene medium following the method of Greco et al.29. The 3-arylsydnones 43a – c were prepared by the cyclization of N-Nitroso-N-arylglycines 42a – c with acetic anhydride. The N-nitroso-N-arylglycines 42a – c were obtained by the nitrosation of phenylamino acetic acid 41c.
acids 41a, p-tolylaminoacetic acid 40b and p-anisyl-aminoacetic acid 41c respectively.

Further, 4-acetyl-3-aryl sydnones 44a–c was brominated to the corresponding bromoacetyl sydnone 45a–c in chloroform medium through a reaction\(^3\) described in Scheme -V.2.

\[
R - \text{NH}_2 + \text{Cl} \xrightarrow{\text{EtOH, AcO}Na} \xrightarrow{\Delta} \text{COOEt} \quad 39a-c
\]

\[
R = \text{H, CH}_3, \text{-OCH}_3
\]

\[
\xrightarrow{i)\text{OH}/H_2O \quad ii)\text{H}^+
\]

\[
R - \text{NH} \xrightarrow{\text{NaNO}_2/HCl} \xrightarrow{0^\circ C} \text{COOH}
\]

\[
R = \text{H, Me, OMe}
\]

\[
\xrightarrow{\text{Ac}_2\text{O}} \xrightarrow{\Delta}
\]

\[
\text{R} - \text{NH} \xrightarrow{\text{AcOH, P}_2\text{O}_5 \text{benzene, reflux}} \xrightarrow{\text{O}}
\]

\[
\text{R} \xrightarrow{\text{Br}/\text{CHCl}_3} \xrightarrow{h}
\]

\[
\text{Scheme -V.2}
\]
III. [3-methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-aceto thiosemicarbazone 47.

The reaction sequence leading to the formation of these compounds is outlined in scheme V.3 and V.4. [3-methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid hydrazide 46 employed in the present investigation was prepared as per procedure described in chapter 2 of this thesis. 3-methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro pyrazol-1-yl acetothiosemicarbazone 47 was obtained in very good yields by the condensation of 46 with potassiumthiocyanate.

\[
\begin{align*}
\text{NH} & \quad \text{N} \quad \text{CH}_3 \\
& \quad \text{N} \quad \text{N} \\
& \quad \text{O} \\
& \quad \text{CH}_2\text{CONHNH}_2 \\
\text{KSCN} \\
\text{H}_2\text{O, EtOH, Conc.HCl} \\
\text{NH} & \quad \text{N} \quad \text{CH}_3 \\
& \quad \text{N} \quad \text{N} \\
& \quad \text{O} \\
& \quad \text{CH}_2\text{CONHNHCSNH}_2 \\
\end{align*}
\]

Scheme - V.3

In a typical experiment a mixture of 46, potassium thiocyanate, con HCl, ethylalcohol, and water were refluxed for 3-hours. The solid obtained after cooling was identified as 47. It is recrystallized from ethanol, DMF mixture, with m.p 214°C, yield 76%. The structure of 47 was conformed by IR, $^1$HNMR and MS data.
IR spectra

The IR (KBr) spectra of 47 shows absorption bands around 3260, 1622, 1685, 1176, 2959 and 3180 cm⁻¹ due Ar-NH, C = N, C = O, C = S, C – H and NH functional groups respectively.

¹HNMR

The ¹HNMR (200MHz) spectra of 47 was recorded in CDCl₃+DMSO-d₆. The signals are noticed at δ2.29 (s,3H, CH₃), δ δ3.3 (s, 2H, NH₂) δ4.80 (s, 2H, N-CH₂), δ 9.36 and δ 10.27 due to NH-NH group appeared as a two broad singlets, δ7.8 (s, 1H, Ar-NH), δ 7.4-7.6 (m, 5H, Ar-H).

Mass Spectrum

The mass spectra of 3-methyl-5-oxo-4-(4'-phenylhydrazono)-4,5-dihydro pyrazol-l-yl aceto thiosemicarbazone 47 exhibit the molecular ion peak (M⁺) at m/z 347.

The fragmentation pattern noticed in mass spectrum of 47. is presented in chart I. The molecular ion (M⁺) was observed at m/z 347 (A,23.7%)disentigration of molecular ion (M⁺) A yielded the cation peak at m/z 331 (B,15.7%) by the loss of NH₂ radical. Eliminationof CH₃CN molecule from molecular on gave the fragment C at m/z 306 (C, 31.5%). Expulsion of CSNH₂ radical from molecular ion A produced the fragment D at m/z 287 (D,15.1%). Elimination of CSN₃H₄ radical afforded the cation E at m/z 257 appeared as base peak (100%). Finally disintegration of molecular ion A by the loss of C₆H₄ radical to give the cation F at m/z 132 (F, 51.3%). The fragmentation pattern clearly supported the structure of 47.

b) 3-methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid N'-(4-substituted thiazol-2-yl)-hydrazide 48

Condensation of 3-methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro pyrazol-1-yl acetothiosemicarbazone 47 with different bromo acetyl derivatives in ethanol afforded the corresponding 3-methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid N'-(4-substituted thiazol-2-yl)-hydrazide 48 in very good yields.
In a typical example a mixture of 47 and bromo acetophenone in ethanol was stirred at room temperature for 1 to 2 hours. After usual work-up 48 was obtained (R = C₆H₅) 66% yield, m.p. 258°C.

The above reaction of 47 with bromo acetophenone has been extended to p-tolyl, p-anisyl, p-hydroxy phenyl, p-nitrophenyl, p-chlorophenyl, p-bromo phenyl, N-phenyl hydronyl, N-p-tolyl hydronyl, N-p-ansyl hydronyl. The compounds synthesized 48a – j have been characterized by means of IR spectra, ¹HNMR, and MS data. The characterization is shown Table V. The reaction sequence leading to the formation of these compounds is outlined in Scheme V.4.

\[ R = \text{Phenyl(48a), p-Tolyl(48b), p-anisyl(48c), p-Hydroxyphenyl(48d)} \]
\[ \text{p-Nitrophenyl(48e), p-Chlorophenyl(48f), p-Bromophenyl(48g)} \]
\[ \text{p-Phenylsydnol(48h), N-p-tolysydnonyl(48i), N-p-ansylsydnonyl(48j)} \]

Scheme-V.4
IR spectra

The IR (KBr) spectra of 3-methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid N'-(4-phenyl thiazol-2-yl)-hydrazide 48a exhibited absorption band around 3230 cm⁻¹ (C = Ostr), 1546 cm⁻¹ (C = Nstr). The data recorded in Table I.

Table I: IR Spectral data of 3-methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid N’-(4-substituted thiazol-2-yl)-hydrazide 48.

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R</th>
<th>vₘₐₓ in cm⁻¹</th>
<th>NH</th>
<th>CH</th>
<th>C = O</th>
<th>C = N</th>
<th>sydnone C = O str</th>
</tr>
</thead>
<tbody>
<tr>
<td>48a</td>
<td>phenyl</td>
<td>3230</td>
<td>2962</td>
<td>1692</td>
<td>1546</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48c</td>
<td>p-anisyl</td>
<td>3240</td>
<td>2868</td>
<td>1687</td>
<td>1546</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48d</td>
<td>p-hydroxy phenyl</td>
<td>3250</td>
<td>2972</td>
<td>1710</td>
<td>1552</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48e</td>
<td>p-nitro phenyl</td>
<td>3260</td>
<td>2980</td>
<td>1720</td>
<td>1560</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48f</td>
<td>p-chloro phenyl</td>
<td>3222</td>
<td>2960</td>
<td>1687</td>
<td>1548</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48h</td>
<td>N-phenyl sydnonyl</td>
<td>3276</td>
<td>2930</td>
<td>1690</td>
<td>1560</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48i</td>
<td>p-tolyl sydnonyl</td>
<td>3276</td>
<td>2941</td>
<td>1689</td>
<td>1559</td>
<td>1739</td>
<td></td>
</tr>
<tr>
<td>48k</td>
<td>coumarinyl</td>
<td>3269</td>
<td>2910</td>
<td>1681</td>
<td>1541</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The $^1$HNMR (200MHz) spectra of [3-methyl-5-oxo-1(phenyl-hydrazono)-4,5-dihydro-pyrazol-1-yl] acetic acid N'-4-(substituted thiazol-2-yl)-hydrazide 48 in CDCl₃ + DMSO-d₆ showed the following signals δ2.23(S, 3H, CH₃), δ4.90 (s, 2H, NCH₂CO)δ7.35(s,H, thiazole, 4H),δ7.2 (s, H, Ar-NH), δ9.54 (s, H, NH), δ10.65(s,H, CONH),δ7.2-7.4 (m, 10H, Ar-H). The spectral data are recorded in Table II.

Table II – $^1$HNMR spectral data of [3-methyl-5-oxo-1(phenyl-hydrazono)-4,5-dihydro-pyrazol-1-yl] acetic acid N’-(4-substituted thiazol-2-yl)-hydrazide 48.

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R</th>
<th>$^1$HNMR (200 MHz, CDCl₃) (DMSO) (δ, ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>48a</td>
<td>phenyl</td>
<td>2.23 (s, 3H, CH₃), 4.90 (s, 2H, NCH₂CO), 7.35 (s, H, thiazole-4H), 7.2 (s, H, Ar-NH), 9.54 (s, H, NH), 10.65 (s, H, CONH), 7.2 – 7.4 (m, 10H, Ar-H)</td>
</tr>
<tr>
<td>48d</td>
<td>p-hydroxy</td>
<td>2.27 (s, 3H, CH₃), 4.90 (s, 2H, NCH₂CO), 7.46 (d,2H,o-protans of p-hydroxy phenyl), 7.60 (d,2H, m-protans of p-hydroxy phenyl), 7.36 (s, H, thiazole-4H), 7.4 (s, H, Ar-NH), 9.56 (s, H, NH), 10.67 (s, H, Co NH), 7.2-7.4 (m, 5H, Ar-H)</td>
</tr>
<tr>
<td>48f</td>
<td>phenyl</td>
<td>2.33 (s, 3H, CH₃), 4.95 (s, 2H, NCH₂CO), 7.59 (d,2H,o-protans of p-hydroxy phenyl), 7.77 (d,2H, m-protans of p-chloro phenyl), 7.37 (s, H, thiazole-4H), 7.8 (s, H, Ar-NH), 9.69 (s, H, NH), 10.71 (s, H, Co NH), 7.4-7.6 (m, 5H, Ar-H)</td>
</tr>
<tr>
<td>48h</td>
<td>N-phenyl</td>
<td>2.27 (s, 3H, CH₃), 4.66 (s, 2H, NCH₂CO), 7.26 (s,H, thiazole 4H), 7.98 (s,H, Ar NH), 9.85 (s,H, NH), 10.48 (s, H, Co NH), 7.6-7.77 (m,5H,Ar-H), 7.2 (d,2H, Ar-H), 7.4 (d, 2H, Ar-H)</td>
</tr>
<tr>
<td>48j</td>
<td>N-p-anisyl</td>
<td>2.26 (s, 3H, CH₃), 3.85 (s, 3H, OCH₃), 4.85 (s,2H, N-CH₂-Co), 7.13 (d,2H, o-protans of p-methoxy phenyl), 7.36 (d,2H, m protans of p-methoxy phenyl), 7.38 (s, H, thiazole-4H), 7.8 (s, H, Ar-NH), 9.52 (s, H, NH)</td>
</tr>
<tr>
<td>48k</td>
<td>coumaphenyl</td>
<td>2.48 (s, 3H, CH₃), 4.85 (s, 2H, NC H₂ Co), 7.53-8.11 (m,5H, aromatic and definie protans of coumanir), 7.37 (s, H, thiazole 4H), 7.9 (s, H, Ar-NH), 10.13 (s, H, NH), 10.72 (s, H, CoNH), 7.4 – 7.6 (m, 5H, Ar-H)</td>
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Mass spectrum

The mass spectrum of [3-methyl-5-oxo-1(phenyl-hydrazono)-4,5-dihydro-pyrazol-1-yl] acetic acid N’-(4-phenyl thiazol-2-yl)-hydrazide 48a exhibited the
molecular ion (M+) peaks at m/z 447 indicating in the presence of odd number of nitrogens. The fragmentation pattern noticed in the mass spectrum of 48a is presented in chart II. The molecular ion (M+) was observed at m/z 447 (22.4%). Disintegration of molecular ion A forms cation B at m/z 406 (24.3%) by loss of CH₃CN molecule. Loss of C₆H₅ radical from molecular ion afforded cation C at m/z 370 (31.2%). Expulsion of C₅H₇N₂S radical from molecular ion A produced the fragment D at m/z 272 (11.4%). Loss of nitrogen radical from D produces cation E at M/Z 258 (9.8%). The molecular ion on decomposition produces cation F at m/z 246 (2.8%). Finally the loss of C₁₀H₁₀N₃S radical for molecular ion A gave cation at m/z 243 (16.4%). The fragmentation pattern clearly supported the structure of 48a.

Characterization data of [3-methyl-5-oxo-4(phenyl(hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid N-(4-substituted-thiazol-2-yl)-hydrazide. 48a-k in Table III.
<table>
<thead>
<tr>
<th>Compd.</th>
<th>R</th>
<th>m.p. °C</th>
<th>Yield %</th>
<th>Mol. formula</th>
<th>Found (%)</th>
<th>(calcd)</th>
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<td></td>
<td></td>
<td></td>
<td>C</td>
<td>H</td>
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<tr>
<td>48a</td>
<td>phenyl</td>
<td>180</td>
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<td>C_{21}H_{28}N_{8}O_{3}S</td>
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<td>(4.42)</td>
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<td>48b</td>
<td>p-tolyl</td>
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<td>C_{26}H_{28}N_{8}O_{3}S</td>
<td>59.15</td>
<td>4.58</td>
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<td>(4.47)</td>
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<tr>
<td>48c</td>
<td>p-anisyl</td>
<td>189</td>
<td>80</td>
<td>C_{26}H_{28}N_{8}O_{3}S</td>
<td>57.10</td>
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<tr>
<td>48d</td>
<td>p-hydroxy</td>
<td>185</td>
<td>75</td>
<td>C_{26}H_{28}N_{8}O_{3}S</td>
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<td>4.35</td>
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<td>(3.54)</td>
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<td>3.75</td>
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<td>(3.67)</td>
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<td>N-p-tolyl</td>
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<td>(3.95)</td>
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<td>(52.65)</td>
<td>(3.83)</td>
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Experimental Section

I. phenyl aryl bromides 38

II. 3-(4'-substituted phenyl)-4-bromo acetyl sydnone 45

III. [3-methyl-5-oxo-4-(4'-substituted aryl hydrazono)-4,5-dihydro-pyrazol-1-yl]- acetic acid N-(4'-substituted thiazol-2-yl)-hydrazide 48

I. Preparation of phenacyl bromides 38a - g

A solution of aromatic ketone 37a - g (0.05mol) in pure anhydrous diethyl ether (10mL) was placed in a three necked flask fitted with mechanical stirrer and a thermometer. The solution was cooled to 0°C, and anhydrous aluminium chloride (50mg) was added to it. When the temperature falls to 0°C, bromine (0.05mol) was added to it gradually from a dropping funnel with continuous stirring. The bromine colour disappeared rapidly, although a very small amount of hydrogen bromide was evolved. Towards the end of the reaction, the solution turned pink.

After the addition was complete, ether and the dissolved hydrogen bromide were removed by applying suction with a slight current of air. The solid that formed was collected by filtration and shaken with 1 mL of petroleum ether. The crystals were washed with fresh portions of solvent and recrystallized from minimum quantity of ethanol. Compounds prepared by this procedure are:

Phenacyl bromide 38a: (Lit\textsuperscript{35} .m.p.50\textdegree C), yield 82%.
4-Methyl phenacyl bromide 38b: m.p. 61\textdegree C, (Lit\textsuperscript{36} m.p. 61\textdegree C), yield 71%.
4-Methoxy phenacyl bromide 38e: m.p. 75\textdegree C, (Lit\textsuperscript{36} m.p. 75-76\textdegree C), yield 68%.
4-Hydroxy phenacyl bromide 38d: m.p. 125\textdegree C, (Lit\textsuperscript{37} m.p. 125-26\textdegree C), yield 62%.
4-Nitro phenacyl bromide 38e: m.p. 98\textdegree C, (Lit\textsuperscript{38} m.p. 98-99\textdegree C), yield 72%.
4-Chloro phenacyl bromide 38f: m.p. 96\textdegree C, (Lit\textsuperscript{35} m.p. 96-96\textdegree C), yield 84%.
4-Bromo phenacyl bromide 38g: m.p. 108\textdegree C, (Lit\textsuperscript{39} m.p. 108-109\textdegree C), yield 61%.

II. 3-(4'-substituted phenyl)4-bromoacetyl sydnone 39a – c

i) General procedure for the synthesis of N-substituted glycines (aniline acetic acid) 45a – c.

A mixture of substituted aniline (0.5mol), ethylchloroacetate (73.0g, 0.6mol) and anhydrous sodium acetate (49.2g, 0.6mol) in 120mL of ethyl alcohol was
refluxed on an oil bath (120-120°C) for 6 hours. The reaction mixture was left overnight at room temperature and poured into crushed ice. The precipitate formed was collected by filtration and dried. The dried product, ethyl ester of N-substituted glycine without further purification was used for the next step.

The ethyl ester of N-substituted glycine (0.4 mol), sodium hydroxide (18 g, 0.45 mol) in 200 mL of water was added and refluxed for 0.5 hour. After cooling, the reaction mixture was acidified to pH = 2 using hydrochloric acid. The precipitated N-substituted glycine was filtered and washed thoroughly with cold water. Further purification was done by recrystallization from ethyl alcohol. The compounds prepared by this procedure are:

Anilino acetic acid 40a: m.p. 127-8°C, (Lit39 m.p. 128-9°C), yield 70%.
$p$-methylanilino acetic acid 40b: m.p. 163-64°C, (Lit39 m.p. 163-64°C), yield 75%.
$p$-methoxyanilino acetic acid 40c: m.p. 142°C, (Lit40 m.p. 144-45°C), yield 75%.

ii) Preparation of N-nitroso-N-substituted glycines 42a - c.

To a stirred suspension of N-substituted glycine 40a - c (0.1 mol) in water 120 mL at 0°C, a solution of sodium nitrite (6.9 g, 0.1 mol) in water 24 mL was added drop wise during 30 minutes. The reaction mixture was practically clear after 2 hours; it was filtered and acidified with concentrated hydrochloric acid. The precipitated product as filtered, washed with cold water and dried in air. The nitrosoglycines prepared by the above method were recrystallized from aqueous alcohol. Compounds prepared according to this procedure are:

N-nitroso-N-phenylglycine 42a: m.p. 101-2°C, (Lit41 m.p. 102-3°C), yield 80%.
N-nitroso-N-(p-tolyl)glycine 42b: m.p. 98-99°C, (Lit41 m.p. 102-3°C), yield 83%.
N-nitroso-N-(p-anisyl)glycine 42c: m.p. 120-21°C, (Lit40 m.p. 121°C), yield 84%.

iii) Preparation of 3-arylsydnone 43a - c.

N-nitroso-N-substituted glycine 42a - c (0.1 mol) was heated with acetic anhydride (51 g, 0.5 mol) on a water bath for 2-4 hours. The reaction mixture was kept aside at room temperature for overnight. Then it was poured into iced cold water, filtered and washed with water, 5% sodium bicarbonate solution and again with water.
The solid was dried and crystallized from benzene. Compounds prepared according to this procedure are:

3-phenylsydnone 43a: m.p. 134-35°C, (Lit41 m.p. 134-35°C), yield 73%.
3-(p-tolyl)sydnone 43b: m.p. 143-44°C, (Lit42 m.p. 144-45°C), yield 78%.
3-(p-anisyl)sydnone 43c: m.p. 125-26°C, (Lit40 m.p. 125-26°C), yield 75%.

iv) Preparation of 4-acetyl-3-arylsydnone 44a – c

To a suspension of phosphorus pentoxide (21.3g, 0.15mol) in sodium dried thionene free from benzene (125mL) taken in a three necked 500mL round bottom flask fitted with reflux condenser equipped with a calcium chloride drying tube, 3-arylsydnone 43a – c (0.05mol) was added. The magnetically stirred mixture was heated to reflux on a water bath. Glacial acetic acid 2.86mL (0.05mol) was added drop wise through dropping funnel over a period of 10 minutes. The stirred reaction mixture was then heated for 5 hours, during which the resultant clear solution turned black. After cooling to room temperature, the benzene was decanted and the remaining black residue was washed twice with 20mL of benzene. Combined washings and the decantate were evaporated to dryness to yield a pale yellow solid. The resulting solid was recrystallized from ethyl alcohol. Compounds prepared according to this procedure are:

4-Acetyl-3-phenylsydnone 44a: m.p. 140-41°C, (Lit43 m.p. 141-42°C), yield 65%.
4-acetyl-3-(p-tolyl)sydnone 44b: m.p. 111-12°C, (Lit44 m.p. 112°C), yield 78%.
4-acetyl-3-(p-anisyl)sydnone 44c: m.p. 71°C, (Lit44 m.p. 71°C), yield 70%.

v) General procedure for the synthesis of 4-bromoacetyl-3-arylsydones 45a – c.

To a solution of 4-acetyl-3-arylsydnone 44a – c (0.01 mol) in 30 mL of chloroform, 1.6g (0.01 mol) of bromine was added under irradiation of visible light (40 watt candle). After 15 minutes, colour of bromine was bleached, solvent was removed under vacuum. The residue was crystallized from ethyl alcohol. Compounds prepared as per this procedure are:

4-bromoacetyl-3-phenylsydnone 45a: m.p. 109-10°C, (Lit45 m.p. 110°C), yield 68%.
4-bromoacetyl-3-(p-tolyl)sydnone 45b: m.p. 110°C, (Lit46 m.p. 110°C), yield 75%.

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4-bromoacetyl-3-(p-anisyl)sydnone 45c: m.p. 64-65°C, (Lit m.p. 65°C), yield 60%.

III. 3-methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid N'-(4-substituted thiazol-2-yl)-hydrazide 48

a) Procedure for the synthesis of thiosemicarbazone 47

A mixture of [3-methyl-5-oxo -4-(phenyl hydrazono)-4,5-dihydro-pyrazol-1yl]-acetic acid hydrazide 46 (0.01 mol), potassium thiocyanate (0.02mol), concentrated hydrochloric acid (1mL), ethyl alcohol (10mL) and water (20mL) were refluxed for 3 hours. The solid obtained after cooling was collected by filtration, washed with water, dried and recrystallized from ethanol-DMF mixture to yield 3-methyl-5-oxo-4(4'-phenylhydrazono)4,5-dihydropyrazol-1-ylacetothiosemicarbazone 47 m.p. 213°C, yield 78%.

b) Synthesis of [3-methyl-5-oxo-4-(phenyl hydrazono) 4,5-hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid N-(4-substituted-thiazole-2-yl)-hydrazide 48.

A mixture of 3-methyl-5-oxo-4(4'-phenyl hydrazono)-4,5-dihydro pyrazol-1-yl acetothiosemicarbazone 47 (0.01 mol) in DMF (10mL) and various bromoacetyl derivatives (0.01 mol) in ethanol (10mL) was stirred at room temperature for 1-2 hours. The solid separated was filtered, dried and recrystallized from ethanol-DMF mixture. The yield, melting point and other characterization data of compounds prepared by this procedure are given in Table III.
Fig. 5.1a 1H NMR Spectrum of thiosemicarbazone 47
Fig. 5.1b $^1$HNMR Spectrum of thiosemicarbazone 47 [Solvent DMSO – d$_6$]
Fig. 5.2 IR Spectrum of thiozole 48h
Fig. 5.3 IR Spectrum of thiozole 48c
Fig. 5.4 IR Spectrum of thiozole 48f
Fig. 5.5 IR Spectrum of thiozole 48k
Fig. 5.6a $^1$HNMR Spectrum of thiozole 48f [Solvent: DMSO – d$_6$]

Fig. 5.6b $^1$HNMR Spectrum of thiozole 48g [Solvent: DMSO – d$_6$]
Fig. 5.7 $^1$HNMR Spectrum of thiozole 48k [Solvent: DMSO – d$_6$]

Fig. 5.8 $^1$HNMR Spectrum of thiozole 48h [Solvent: DMSO – d$_6$]
Mass spectral fragmentation of 3-methyl-5-oxo-4-(phenylhydrazono)-4,5-dihydro-pyrazol-1-yl-aceto thiosemicarbazone 47

Chart -
Mass spectral fragmentation of
3-methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid N'-(4-phenyl thiazol-2-yl)-
hydrazide 48a
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