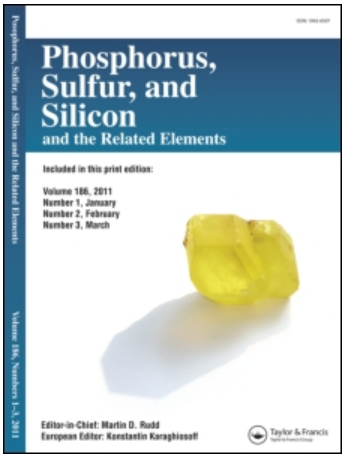


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# SYNTHETIC APPROACHES TO SOME NEW SULFUR-CONTAINING HETEROCYCLES OF ANTICIPATED IMMUNOSUPPRESSIVE ACTIVITY

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# SYNTHETIC APPROACHES TO SOME NEW SULFUR-CONTAINING HETEROCYCLES OF ANTICIPATED IMMUNOSUPPRESSIVE ACTIVITY†

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Several new isolated or fused heterocyclic ring systems that accommodate the isothiouredo functionality, often associated with immunosuppressive activity, were synthesized for possible use as immunosuppressive agents. Preparation of these anchored heterocycles was achieved via a multi-step synthesis starting with the key intermediate thiazolyl thiourea derivative (**I**). Structure of the newly synthesized products was confirmed using both of elemental and spectral analyses.

*Key words:* Sulfur-containing heterocycles, possible immunosuppressive agents.



## INTRODUCTION

Since recognition of the pharmacological role played by cyclophosphamide and/or azathioprine in treatment of some autoimmune diseases,[1] several reports have appeared in the literature describing the synthesis and pharmacological studies of some new immunosuppressive agents[2–4] that selectively suppress cell-mediated immunity without affecting humoral immunity. Pharmacologically important above all of these chemotherapeutic drugs are those embodying isothioureido functionality in their structure, such as nitridazole,[3] frentizole,[5] and levamisole.[6] Although the latter and other products have been widely used in organ transplantation, some of them[7] have side effects, such as hepatic and renal toxicities. Thus, in these aspects, less toxic and more potent immunosuppressive agents are needed.

Keeping this in mind together with the pharmacological importance of pyrazoline derivatives,[8,9] it seemed of interest to combine the analgesic potency of 2,3-dimethyl-1-phenyl-3-pyrazoline-5-one with immunosuppressive activity, often associated with isothioureido functionality. Thus the present investigation represents an attempt for anchored synthesis of a novel class of sulfur-containing chemotherapeutic agents embodying both the phenazonyl and isothioureido functionalities in one structure. A plan for the synthesis of some of the hitherto prepared chemotherapeutic agents was specifically designed to include products having two isothioureido functionality with a view to rationalize the effect of doubling of the latter functionality with pharmacological activity of these products as new possible immunosuppressive agents. Moreover, the antimicrobial activity of the newly syn-

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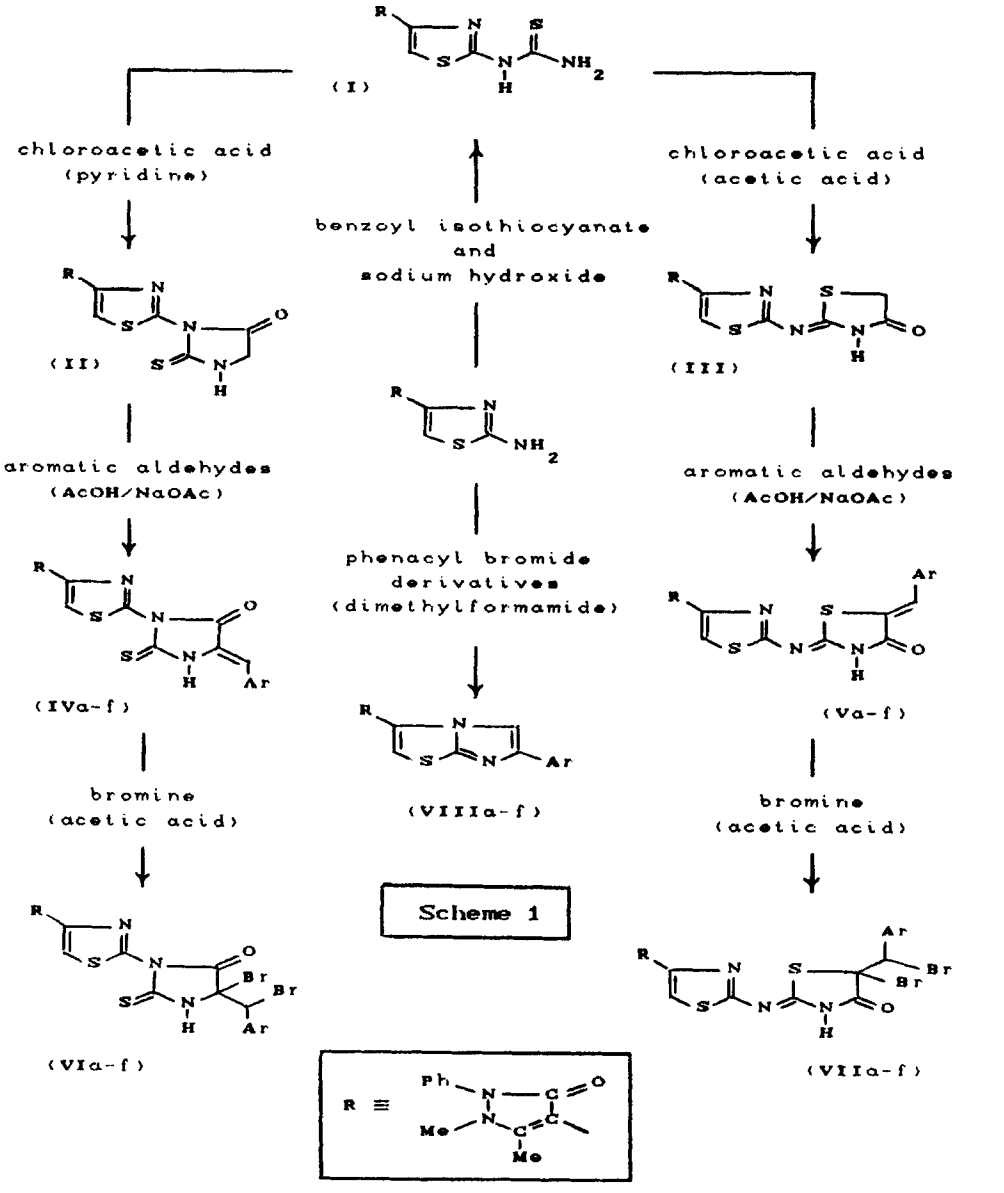
thesized products was also investigated. The assigned structure for the newly synthesized products was confirmed not only on the basis of the elemental and spectral data but also from the previously reported literature[10-12] on analogous synthetic pathways.




a) Ar = $C_6H_5$- b) Ar = P- F-$C_6H_4$- c) Ar = P- Cl-$C_6H_4$-

d) Ar = P- $(Me)_2N$-$C_6H_4$- e) Ar = P- OMe-$C_6H_4$- f) Ar = P- $O_2N$-$C_6H_4$-

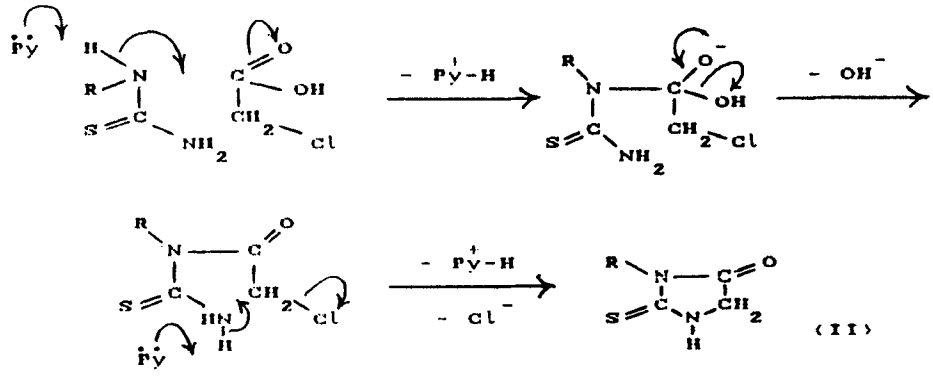
SCHEME I

## RESULTS AND DISCUSSION

As illustrated in Scheme I, $N^1$-[4-(2′,3′-dimethyl-1′-phenyl-5′-oxopyrazolin-4′-yl)thiazol-2-yl]thiourea (**I**) was prepared by the reaction of 2-amino-4-(2′,3′-dimethyl-1′-phenyl-5′-oxopyrazolin-4′-yl)-1,3-thiazole, that was previously prepared in our laboratories,[13] with benzoyl thiocyanate and subsequent hydrolysis of the product with dilute sodium hydroxide.

Insertion of the isothioureido functionality in the targeted products involved the interaction of thiourea derivative (**I**) with chloroacetic acid in pyridine medium to give the corresponding thiohydantoin derivative (**II**) in moderate yield.

The formation of the latter product might involve the action of pyridine, as a basic solvent, in abstracting a proton from the amidic nitrogen atom as follows:




R ≡ 4-(Substituted pyrazolin-4′-yl)-1,3-thiazol-2-yl radical

Py ≡ Pyridine molecule

The possibility of structural doubling of the isothioureido functionality in the targeted products was verified *via* prior preparation of the thiazolidone derivative (**III**). Thus when the thiazolyl-thiourea derivative (**I**) was allowed to react with chloroacetic acid in presence of glacial acetic acid and a catalytic amount of freshly fused sodium acetate, the thiazolylimino-thiazolidone derivative (**III**) was formed in good yield.

Structure of the key intermediates **II** and **III** was inferred from elemental and spectral data. Thus, while the IR spectrum of the latter product **III** exhibited a characteristic absorption band at 1645 $cm^{-1}$ corresponding to the exocyclic (—C=N—) function, the IR spectrum of the former one revealed the absence of this band and the presence of a new absorption band at 1215 $cm^{-1}$ that might be ascribed to stretching vibration of the thiocarbonyl function in this product. The $^1$H-NMR spectra of these two products showed their methylene proton signals at 4.32 and 4.15 ppm, respectively.

The reactivity of the keto-methylene group in the above mentioned structures **II** and **III** was utilized to explore the synthetic potentiality of these products as precursors for novel targeted immunosuppressants. Thus, refluxing any of these keto-methylene derivatives with aromatic aldehydes in the presence of a catalytic

amount of freshly fused sodium acetate readily yielded different isolable colored products of the corresponding arylidene derivatives (**IVa–f**) or (**Va–f**), respectively.

The formation of these products from their precursors was established not only from IR spectra which revealed the presence of new absorption bands at 1710 and 1680 $cm^{-1}$ assignable to $\alpha,\beta$-unsaturated carbonyl functions in these products but also from $^1$H-NMR spectra which revealed the absence of any proton signals corresponding to the methylene moiety and the presence of a new singlet signal near 6.28 ± 0.04 ppm corresponding to the ylidene proton in these arylidene derivatives.

Since bromine augments some biological activities,[14] it was considered worthwhile to brominate the arylidene derivatives (**IVa–f**) and (**Va–f**) to give the corresponding 5-bromo-5-(α-(bromo *p*-substituted benzyl)-3-[4′-(2″,3″-dimethyl-1″-phenyl-5″-oxopyrazolin-4″-yl)thiazol-2′-yl]-2-thiohydantoin and 5-bromo-5-(α-(bromo *p*-substituted benzyl)-3-[4′-(2″,3″-dimethyl-1″-phenyl-5″-oxopyrazolin-4″-yl)thiazol-2′-ylimino]-4-thiazolidone derivatives (**VIa–f**) and (**VIIa–f**), respectively.

The structure of these bromo derivatives was also confirmed by spectral studies. The IR spectrum of compound **VIIa** exhibited two strong absorption bands at 1705 and 1665 $cm^{-1}$ that might be assigned to stretching vibrations of the carbonyl group in secondary and tertiary amidic functions in this structure. The observed hypsochromic shift for carbonyl frequency of the secondary amidic function (amide I band), relative to the corresponding frequency of arylidene derivative **Va**, might be attributed to inhibition of conjugation arising from saturation.

A further synthetic approach for the preparation of such possible chemotherapeutic agents was realized by synthesis of new fused ring systems that accommodate the isothioureido functionality. Synthesis of these products was achieved *via* interaction of the 2-amino-4-(2′,3′-dimethyl-1′-phenyl-5′-oxopyrazolin-4′-yl)-1,3-thiazole with one equivalent of substituted phenacyl bromide derivatives in dimethyl-formamide (DMF) at the reflux temperature.

Supporting evidence for the imidazo [2,1-b]-thiazole derivatives **VIIIa–f** was gathered from IR spectral data which displayed characteristic absorption bands near 1662 ± 4 and 1625 ± 10 $cm^{-1}$ that might be assigned to stretching vibrations of tertiary amidic linkage and —C=N— functions, respectively, in these products.

Besides phenyl, N-methyl and C-methyl proton patterns, $^1$H-NMR spectra of these products exhibited two singlet signals near 7.70 ± 0.02 and 7.54 ± 0.03 ppm corresponding to the respective S—C<u>H</u>= and N—C<u>H</u>= protons in structure of these products.

The above mentioned IR and $^1$N-NMR spectral patterns could be intelligibly interpreted in terms of the assigned imidazo-[2,1-b]-1,3-thiazole ring system for these products.

Pharmacological properties for the prepared compounds are depicted in Table I. Although a consistent structure-activity relationship was not observed in the assay of DTH response (Table I), it seemed possible to deduce the effective role of electron withdrawing substituents, in the aromatic moiety, on the activity of these products as immunosuppressive agents. Moreover, it is clear that doubling of the isothioureido functionality, in the molecular structure, highly enhances this activity.

None of the hitherto prepared compounds, at the tested dose, revealed significant

TABLE I

Physical and pharmacological properties of the newly synthesized products (II–VIII)

| Sl. No. | M.p. °C | Molecular formula (M.Wt.) | Percentage inhibition in (DTH)[a,b] | Antimicrobial[c] activity MIC (μg/ml) | | | |
|---|---|---|---|---|---|---|---|
| | | | | A | B | C | D |
| II | 215–216 | $C_{17}H_{15}N_5O_2S_2$ (385.46) | 06.57 | 75 | 25 | 75 | b) |
| III | 235–236 | $C_{17}H_{15}N_5O_2S_2$ (385.46) | 18.72 | 25 | 75 | 50 | 25 |
| IVa | 239–240 | $C_{24}H_{19}N_5O_2S_2$ (473.57) | 11.40 | 75 | b) | 100 | 25 |
| IVb | 188–190 | $C_{24}H_{18}FN_5O_2S_2$ (491.56) | 46.30 | 50 | 75 | 100 | 50 |
| IVc | 223–224 | $C_{24}H_{18}ClN_5O_2S_2$ (508.01) | 33.80 | 75 | 50 | 25 | 75 |
| IVd | 140–141 | $C_{26}H_{24}N_6O_2S_2$ (516.64) | 04.50 | 75 | 75 | b) | b) |
| IVe | 218–220 | $C_{25}H_{21}N_5O_3S_2$ (503.60) | 01.30 | 50 | b) | 75 | 25 |
| IVf | 215–217 | $C_{24}H_{18}N_6O_4S_2$ (518.57) | 43.80 | 75 | b) | 75 | 50 |
| Va | 226–227 | $C_{24}H_{19}N_5O_2S_2$ (473.57) | −22.60 | b) | 100 | 50 | 50 |
| Vb | 172–174 | $C_{24}H_{18}FN_5O_2S_2$ (491.56) | 53.50 | 75 | b) | 100 | 50 |
| Vc | 204–206 | $C_{24}H_{18}ClN_5O_2S_2$ (508.01) | 16.40 | 50 | 50 | 50 | 75 |
| Vd | 157–159 | $C_{26}H_{24}N_6O_2S_2$ (516.64) | 12.30 | 25 | 75 | 25 | 75 |
| Ve | 147–148 | $C_{25}H_{21}N_5O_3S_2$ (503.60) | 14.60 | 100 | 75 | 50 | 75 |
| Vf | 131–133 | $C_{24}H_{18}N_6O_4S_2$ (518.57) | 64.30 | 25 | 100 | 50 | 50 |
| VIa | 261–262 | $C_{24}H_{19}Br_2N_5O_2S_2$ (633.38) | 10.50 | b) | 100 | b) | 25 |
| VIb | 207–209 | $C_{24}H_{18}Br_2FN_5O_2S_2$ (651.37) | 36.23 | 50 | b) | b) | 75 |
| VIc | 236–238 | $C_{24}H_{18}Br_2ClN_5O_2S_2$ (667.82) | 24.10 | 25 | 75 | 50 | 50 |
| VId | 166–168 | $C_{26}H_{24}Br_2N_6O_2S_2$ (676.44) | 25.10 | 100 | 25 | b) | 50 |

TABLE I (*Continued*)

| Sl. No. | M.p. °C | Molecular formula (M.Wt.) | Percentage inhibition in (DTH)[a,b] | Antimicrobial[c] activity MIC (μg/ml) | | | |
|---|---|---|---|---|---|---|---|
| | | | | A | B | C | D |
| VIe | 244-245 | $C_{25}H_{21}Br_2N_5O_3S_2$ (663.40) | 09.40 | 75 | 50 | b) | 75 |
| VIf | 254-255 | $C_{24}H_{18}Br_2N_6O_4S_2$ (678.37) | 40.40 | 75 | 50 | b) | 25 |
| VIIa | 235-237 | $C_{24}H_{19}Br_2N_5O_2S_2$ (633.38) | 33.70 | 100 | 50 | 50 | 75 |
| VIIb | 198-199 | $C_{24}H_{18}Br_2FN_5O_2S_2$ (651.37) | -11.30 | 50 | 25 | b) | 75 |
| VIIc | 186-188 | $C_{24}H_{18}Br_2ClN_5O_2S_2$ (667.82) | 35.70 | 50 | 25 | 50 | b) |
| VIId | 201-203 | $C_{26}H_{24}Br_2N_6O_2S_2$ (676.44) | 17.30 | 50 | 75 | 50 | 25 |
| VIIe | 192-194 | $C_{25}H_{21}Br_2N_5O_3S_2$ (663.40) | 20.20 | 75 | b) | 100 | 50 |
| VIIf | 155-157 | $C_{24}H_{18}Br_2N_6O_4S_2$ (678.37) | 65.90 | 25 | 25 | 75 | b) |
| VIIIa | 200-202 | $C_{22}H_{18}N_4OS$ (386.47) | 23.10 | b) | 50 | b) | 25 |
| VIIIb | 132-133 | $C_{22}H_{17}FN_4OS$ (404.46) | 56.30 | 75 | b) | 100 | 50 |
| VIIIc | 176-178 | $C_{22}H_{17}ClN_4OS$ (420.92) | 11.80 | 50 | 75 | 75 | 75 |
| VIIId | 127-128 | $C_{24}H_{23}N_5OS$ (429.54) | 15.80 | 75 | 50 | 100 | 50 |
| VIIIe | 218-220 | $C_{23}H_{20}N_4O_2S$ (416.50) | -03.20 | 50 | 25 | 75 | 25 |
| VIIIf | >300 | $C_{22}H_{17}N_5O_3S$ (431.47) | 38.70 | b) | 50 | 75 | b) |
| Frentizole | | | 40.40 | | | | |

a) Percentage inhibition in Delayed-Type Hyperaensitivity (DTH).

b) At a single dose of 50 mg/kg b.Wt.

c) Denotes MIC>100.

A ≡ Staphylococcus albus, B ≡ Staphylococcus aureus,
C ≡ Diplococcal N. catarrhalis D ≡ Escherichia coli

effect on antibody formation in comparison to cyclophosphamide which was reported to inhibit not only DTH response but also antibody formation in mice.[15]

The prepared compounds were also tested, in vitro, for their antimicrobial activities against Staphylococcus albus, Staphylococcus aureus, Diplococcal Neisseria catarrhalis, and Escherichia coli, the microorganisms and the minimum inhibitory concentrations (MIC) in $\mu$g/ml are also given in Table I unless they exceed 100 $\mu$g/ml.

## EXPERIMENTAL

The homogenicity and purity of the prepared compounds were checked by TLC. Melting points of the analytical samples were determined using a Fisher-Johns apparatus and are not corrected. IR spectra were recorded on a specord M-80 spectrophotometer using (KBr) pellets. $^1$H-NMR spectra ($CDCl_3$) were determined on a Varian EM 360 spectrometer 60 MHz relative to TMS as an internal standard. Nomenclature of the hitherto prepared compounds is given in accordance with (IUPAC) rules for nomenclature of organic compounds. Microanalyses of these products gave satisfactory results within ($\pm$0.40%) of the theoretical values.

### *A. Synthesis*

*Synthesis of N$^1$-[4-(2',3'-Dimethyl-1'-phenyl-5'-oxopyrazolin-4'-yl)-1,3-thiazol-2-yl]thiourea* (**I**): To a solution of ammonium thiocyanate (3.8 g) in dry acetone (20 ml) in a 250 ml three necked flask equipped with a reflux condenser, mechanical stirrer and a dropping funnel, benzoyl chloride (3 ml) was added dropwise with stirring. The mixture was refluxed for 30 min, then a solution of 2-amino-4-(2',3'-dimethyl-1'-phenyl-5-oxopyrazolin-4'-yl)-1,3-thiazole (0.05 mol) in dry acetone (20 ml) was added with stirring at such a rate that the solution refluxed gently. The mixture was poured carefully into cold water (500 ml) and the resulting deep orange precipitate was filtered, washed with acetone and hydrolysed by boiling in sodium hydroxide solution (20 ml, 10%) for 15 min and cooled. Acidification with hydrochloric acid yielded a yellowish white precipitate which was filtered off, washed with water, dried and recrystallized from methanol to give the pure product of m.p. 184°C in 71% yield. IR (cm$^{-1}$): 3325–3110 ($NH_2$ & NH), 1665 (ter. amidic CO), 1625 (C=N) and 1215 (C=S).

*Synthesis of 3-[4'-(2",3"-Dimethyl-1"-phenyl-5"-oxopyrazolin-4"-yl)-1',3'-thiazol-2'-yl]-2-thiohydantoin* (**II**): A mixture of N$^1$-[4-(2',3'-Dimethyl-1'-phenyl-5'-oxopyrazolin-4'-yl)-1,3-thiazol-2-yl]thiourea (**I**) (3.5 g, 0.01 mol) and mono chloro acetic acid (1.3 g, 0.018 mol) was put into anhydrous pyridine (10 ml) and the mixture was warmed for 5 min on a water bath where an exothermic reaction set in. On completion of the reaction and cooling to room temperature, a viscous material was separated. Absolute ethanol (30 ml) was added and the whole mixture was refluxed, under dry conditions for 5 h and left to cool. The crystalline material which formed was filtered off, dried and recrystallized from methanol in 58% yield. IR (cm$^{-1}$): 3355 (NH), 1760 (tert. amidic CO of imidazole moiety), 1665 (tert. amidic CO of pyrazole moiety), 1625 (C=N) and 1215 (N—C=S). $^1$H-NMR ($\delta$/ppm): 7.68 (s, 1H, =C<u>H</u>—S), 7.25–7.15 (m, 5H, Ar—H), 4.76 (br, 1H, exchanged with $D_2O$, N<u>H</u>), 4.32 (s, 2H, C<u>H</u>$_2$), 3.05 (s, 3H, N—C<u>H</u>$_3$) and 2.95 (s, 3H, C—C<u>H</u>$_3$).

*Synthesis of 2-[4'-(2",3"-Dimethyl-1"-phenyl-5"-oxopyrazolin-4"-yl)-1',3'-thiazol-2'-ylimino]-4-thiazolidone* (**III**): A mixture of N$^1$-[4-(2',3'-Dimethyl-1'-phenyl-5'-oxopyrazolin-4'-yl)-1,3-thiazol-2-yl]thiourea (**I**) (3.5 g, 0.01 mol) and mono chloro acetic acid (1.3 g, 0.018 mol), anhydrous sodium acetate (1.0 g) in glacial acetic acid (30 ml) was boiled under reflux for 6 h. The reaction mixture was concentrated under reduced pressure then poured, while stirring, onto cold water. The precipitated product was collected by filtration, dried and recrystallized from ethanol as yellow crystals in 68% yield. IR (cm$^{-1}$): 3335 (NH), 1720 (sec. amidic CO of thiazole moiety), 1665 (tert. amidic CO of pyrazole moiety), 1645 & 1625 (exo and endo C=N). $^1$H-NMR ($\delta$/ppm): 7.68 (s, 1H, =C<u>H</u>—S), 7.28–7.15 (m, 5H, Ar—H), 5.82 (br, 1H, exchanged with $D_2O$, N<u>H</u>), 4.15 (s, 2H, C<u>H</u>$_2$), 3.05 (s, 3H, N—C<u>H</u>$_3$), and 2.95 (s, 3H, C—C<u>H</u>$_3$).

*Synthesis of 5-Arylmethylene-3-[4'-(2",3"-dimethyl-1"-phenyl-5"-oxopyrazolin-4"-yl)-1',3'-thiazol-2'-yl]-2-thiohydantoin derivatives* (**IVa–f**) *and 5-Arylmethylene-2-[4'-(2",3"-dimethyl-1"-phenyl-5"-oxopyrazolin-4"-yl)-1',3'-thiazol-2'-ylimino]-4-thiazolidone derivatives* (**Va–f**): A mixture of keto-methylene derivative **II** or **III** (0.01 mol) and aromatic aldehyde (0.012 mol in each case) and anhydrous sodium

acetate (1.0 g) was refluxed in glacial acetic acid (20 ml) for 3–6 h (controlled by TLC) and left to cool. The yellowish-coloured product, obtained on pouring the reaction mixture on cold water, was filtered off, dried and recrystallized from ethanol to give the pure arylidene derivatives **IVa–f** and **Va–f** respectively, in 62–79% yield. Physical data for these products are listed in Table I. IR spectrum ($cm^{-1}$) of **IVc**: 3350 (NH), 1710 (tert. amidic CO of imidazole moiety), 1665 (tert. amidic CO of pyrazole moiety), 1625 (C=N) and 1215 (N—C=S). $^1$H-NMR ($\delta$/ppm) for the same compound: 7.73 (s, 1H, =CH—S), 7.32–7.18 (m, 9H, Ar—H), 6.29 (s, 1H, ylidene proton), 4.82 (br, 1H, exchangeable with $D_2O$, NH), 3.05 (s, 3H, N—$CH_3$) and 2.95 (s, 3H, C—$CH_3$).

IR spectrum ($cm^{-1}$) for compound **Vc**: 3335 (NH), 1680 (sec. amidic CO), 1660 (tert. amidic CO), 1640 & 1625 (exo and endo C=N).

*Synthesis of 5-Bromo-5-(α-(bromo p-substituted benzyl)-3-[4'-(2",3"-dimethyl-1"-phenyl-5"-oxopyrazolin-4"-yl)-1',3'-thiazol-2'-yl]-2-thiohydantoin derivatives* (**VIa–f**) and *5-Bromo-5-(α-(bromo p-substituted benzyl)-3-[4'-(2",3"-dimethyl-1"-phenyl-5"-oxopyrazolin-4"-yl)-1',3'-thiazol-2'-yl-imino]-4-thiazolidone derivatives* (**VIIa–f**): To a solution of arylidene derivatives **IVa–f** or **Va–f** (0.01 mol in each case), bromine (1.9 g, 0.012 mol) was added dropwise with stirring during 15 min. The reaction mixture was allowed to stand overnight at ambient temperature where an orange coloured product was separated. Filtration of the product followed by recrystallization from acetic acid afforded the corresponding dibromo derivatives **VIa–f** and **VIIa–f** in an average 47–64% yield. Pertinent data for these products are given in Table I. IR spectrum ($cm^{-1}$) of compound **VIa**: 3355 (NH), 1735 (tert. amidic CO of imidazole moiety), 1660 (tert. amidic CO of pyrazole moiety), 1620 (C=N), 1215 (N—C=S).

IR spectrum ($cm^{-1}$) of compound **VIIa**: 3325 (NH), 1705 (sec. amidic CO), 1665 (tert. amidic CO), 1645 and 1625 (exo and endo C=N). $^1$H-NMR spectrum ($\delta$/ppm) for the same product: 7.65 (s, 1H, =CH—S), 7.26–7.10 (m, 10H, Ar—H), 5.44 (br, 1H, exchangable with $D_2O$, NH), 3.32 (s, 1H, benzylic proton), 3.02 (s, 3H, N—$CH_3$) and 2.91 (s, 3H, C—$CH_3$).

*Synthesis of 6-Aryl-3-[4'-(2",3"-dimethyl-1"-phenyl-5"-oxo-pyrazolin-4"-yl)thiazol-2'-yl]imidazo[2,1-b]-1,3-thiazole derivatives* (**VIIIa–f**): A mixture of the phenacyl bromide derivative (0.01 mol) and 2-amino-4-(2',3'-dimethyl-1'-phenyl-5'-oxopyrazolin-4'-yl)-1,3-thiazole (0.012 mol) in (DMF) (25 ml) was refluxed for 5–8 h (followed by TLC) and left to cool. To the reaction mixture water (2 ml) was added and the whole mixture left overnight. The deposited product was collected by filtration, washed with methanol and recrystallized from methoxycellosolve to give the pure products in 57–69% yield. Physical data for the crystalline derivatives **VIIIa–f** are depicted in Table I. IR spectrum ($cm^{-1}$) of compound **VIIIe**: 1665 (tert. amidic CO) and 1632 (C=N). Its $^1$H-NMR spectrum ($\delta$/ppm): 7.28–7.05 (m, 9H, Ar—H), 7.69 (s, 1H, S—CH=), 7.52 (s, 1H, N—CH=), 4.10 (s, 3H, O—$CH_3$), 3.15 (s, 3H, N—$CH_3$) and 2.95 (s, 3H, C—$CH_3$).

### *B. Pharmacological Studies*

#### *1. Immunosuppressive Activity*

The newly synthesized products were screened out for their immunosuppressive activity adopting previously reported procedures.[16–18]

#### *2. Antimicrobial Activity*

The antimocrobial activity of the synthesized products were determined using the agar diffusion sensitivity test.[19] The micro-organisms were pure cultures grown on a bactonutrient broth and bactonutrient agar.

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