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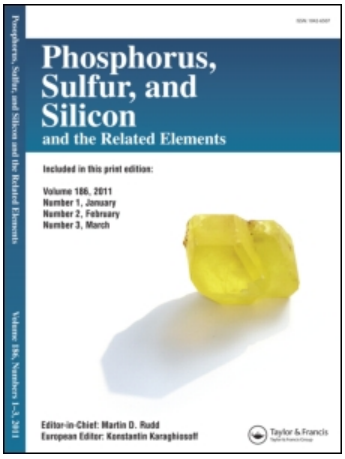

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Pyridazine Derivatives and Related Compounds, Part 22[1]: Synthesis, Reactions, and Insecticidal Activity of 3-Amino-5,6-diaryl-1*H*-pyrazolo[3,4-*c*]pyridazines

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PYRIDAZINE DERIVATIVES AND RELATED COMPOUNDS, PART 22: SYNTHESIS, REACTIONS, AND INSECTICIDAL ACTIVITY OF 3-AMINO-5,6-DIARYL-1*H*-PYRAZOLO[3,4-*c*] PYRIDAZINES

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Starting with 3-amino-5,6-diaryl-1*H*-pyrazolo[3,4-c]pyridazine, the syntheses of thiourea derivatives, dithiocarbamates, ethyl carbamate, phosphoranylidene amino, and substituted acetamido derivatives are described. The products were screened for their insecticidal activity against* Mucsa, domestica*, and* Aphid, Macrosiphum pisi*.

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Keywords Insecticidal activity; 3-substituted amino-5,6-diaryl-1*H*-pyrazolo[3,4-*c*]pyridazine

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INTRODUCTION

Pyridazines and heterocyclic annelated pyridazines have been investigated intensively for their applications in agriculture, and in particular for their biological activity for use as potential drugs.[1] The recent discovery of pyridazomycin,[2] a new antifungal antibiotic produced by *Streptomyces violaceoniger* and zazissine,[3] a new cytotoxic guanidine alkaloid isolated from the Mediterranean sponge *Anchinoe paupertas*, both containing this heteroarene system, most likely will stimulate an even broader interest in 1,2-diazine chemistry. On the other hand, one of the most important classes of five-membered heterocycles is represented by the pyrazole ring. Pyrazoles are found in a broad variety of pharmaceutical, agrochemical, and veterinary products.[4]

Guided by these observations and in continuation of our earlier work[5] on pyridazine derivatives and related compounds, in this article we report the synthesis and insecticidal activities and results of our toxicity studies of novel pyrazolo[3,4-*c*]pyridazines.

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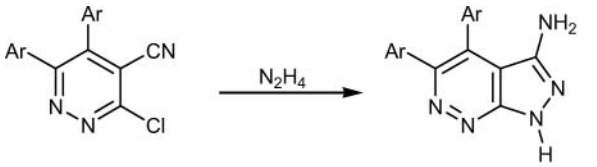
RESULTS AND DISCUSSION

As starting substance, we used 5,6-diaryl-3-chloropyridazine-4-carbonitrile, which reacted with hydrazine hydrate in ethanol to give 3-amino-4,5-diaryl-1*H*-pyrazolo[3,4-*c*]pyridazine (**1a,b**).[6]



1a, Ar = C_6H_5

1b, Ar = 4-ClC_6H_4

The structures of **1a**,**b** were supported by their infrared, ^{1}H NMR, and elemental analyses. The infrared spectrum showed the presence of NH_2 groups (3450 and 3100 cm^{-1}). The ^{1}H NMR spectrum of **1a** showed the presence of a broad singlet 1H, NH at δ 8.1, 10H multiplet at 7.55–7.22 due to the aromatic phenyl protons, and a broad singlet 2H at δ 4.3 due to NH_2 protons.

3-Amino-5,6-diphenyl-1*H*-pyrazolo[3,4-*c*]pyridazine **1a** reacted with an equimolar quantity of methyl or phenyl isothiocyanate to give (N-heteroaryl)thioureas (**2a**,**b**) (Scheme 1). Similarly the reaction of 3-amino-4,5-bis(4-chlorophenyl)-1*H*-pyrazolo[3,4-*c*]pyridazine **1b** with an equimolar amount of benzoyl isothiocyanate in situ prepared from ammonium thiocyanate and benzoyl chloride in acetone at reflux temperature led to the formation of N-[4,5-bis(4-chlorophenyl)-1*H*-pyrazolo[3,4-*c*]pyridazin-3-*yl*]-N‘-benzoylthiourea (**3**). In an analogous manner, the reaction of **1b** with ethoxycarbonyl isothiocyanate led to the formation of N-[4,5-bis(4-chloro-phenyl)-1*H*-pyrazolo[3,4-*c*]pyridazin-3-*yl*]-N′-ethoxycarbonylthiourea (**4**), in which the soft nucleophile amino group attacks the isothiocyanate group, not the carbonyl group of the ethoxycarbonyl isothiocyanate. The structural elucidations of **3** and **4** were accomplished from their analytical and spectroscopic data.

The reaction of **1a** with aqueous 20 mol potassium hydroxide and carbon disulfide in ethanol yielded potassium 3-N-dithiocarbamate (**5**), which was converted, without previous isolation, into ethyl N-[(4,5-diphenyl)-1*H*-pyrazolo[3,4-*c*]pyridazine]-3-dithiocarbamate (**6**) by reaction with diethylsulfate.

On other hand, the potassium 3-N-dithiocarbamate **5** was converted into the manganese(II), zinc(II), ferrous(II), cobalt(II), and nickel(II) bis-3-N-dithiocarbamate derivatives (**7a–e)** by reaction with manganese sulfate, zinc sulfate ferrous sulfate, cobalt sulfate, and nickel sulfate, respectively .

Heating **1b** with excess ethyl chloroformate at reflux temperature produced 3-ethoxycarbonylamino-4,5-bis(4-chlorophenyl)-1*H*-pyrazolo[3,4-*c*]pyridazine (**8**) as the only product. The structure of **8** is corroborated by microanalysis, and by the mass spectra, which show the expected molecular ion peaks at 428 and peaks for [M^+ –H], and [M^+ –$CO_2CH_2CH_3$].

3-Diazo-4,5-diphenylpyrazolo[3,4-*c*]pyridazine (**9**) and 3-azido-4,5-diphenyl-1*H*-pyrazolo[3,4-*c*]pyridazine (**10**) were prepared in excellent yields, following the conditions

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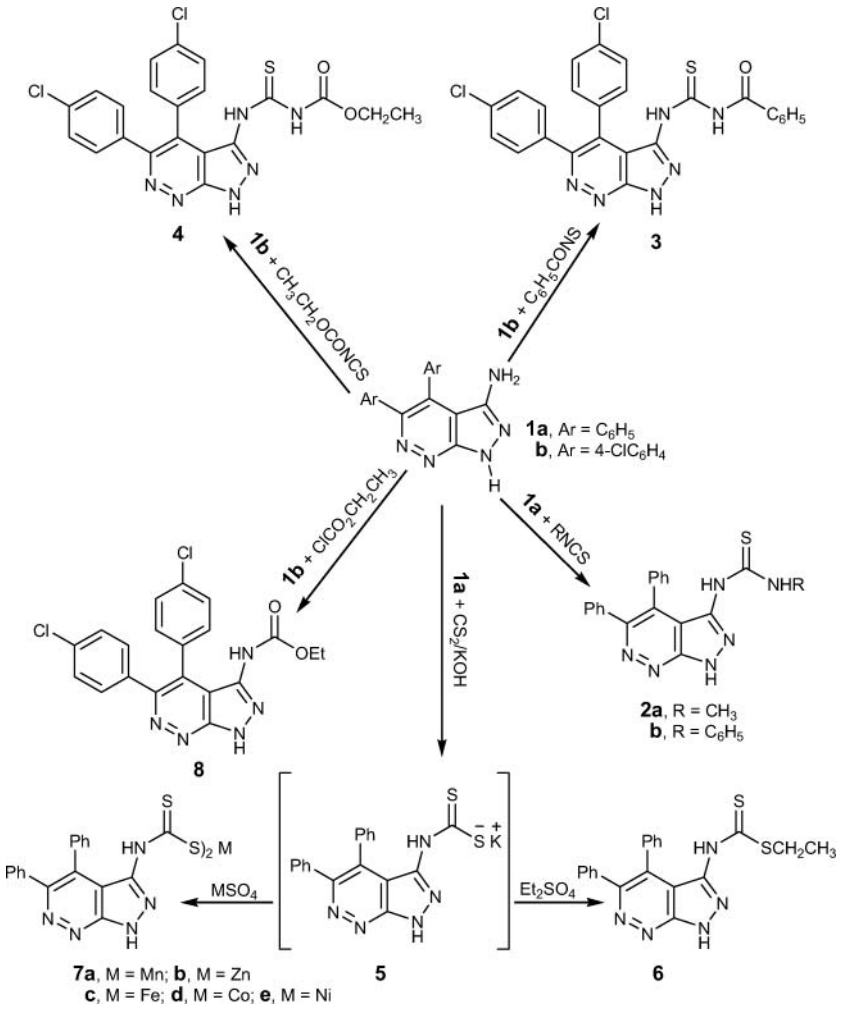

Scheme 1

previously reported in our laboratory.[7,8] Compound **9** was prepared in 96% yield as yellow crystals (mp 135 °C) by diazotization of **1a** with sodium nitrate in glacial acetic acid at room temperature. Compound **10** was prepared as light yellow crystals (mp 164°C) by addition sodium azide portionwise to 3-diazo derivative (**9**) in conc. HCl at room temperature.

Compound **10** reacts in ethanol at ambient temperature with triphenylphosphine (**11a**) with the evolution of nitrogen to yield 3-triphenylphosphoranylideneamino-4,5-diphenyl-1*H*-pyrazolo[3,4-*c*]pyridaz-ine (**12a**). Trimethyl phosphate (**11b**) and triethyl phosphate (**11c**) react in the same manner to furnish **12b** and **12c**, respectively (Scheme 2).

The reaction of **1b** with an excess of chloroacetyl chloride under reflux affords 3-chloroacetylamino-4,5-bis(4-chlorophenyl)-1*H*-pyrazolo[3,4-*c*]-pyridazine (**13**). The feasibility of the chlorine atom in **13** to undergo a nucleophilic displacement reaction was proven by its reaction with morpholine and piperidine to yield 3-morpholino and

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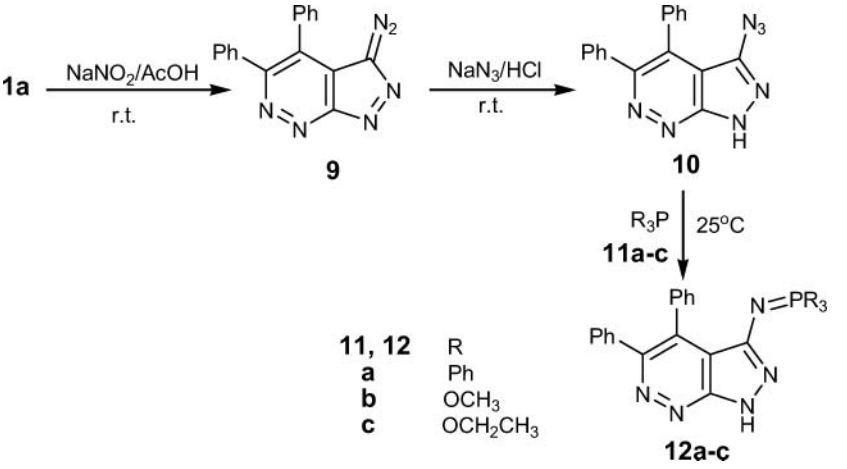

Scheme 2

3-piperidinoacetylamino-4,5-bis(4-chlorophenyl)-1*H*-pyr-azolo[3,4-*c*]pyridazine (**14a**) and (**14b**) in a good yield.

When the 3-chloroacetylamino derivative **13** was reacted with ethanolamine, it gave a single product. The isolated product was proven to be identical in every respect with the product 3-amino-4,5-bis(4-chlorophenyl)-1*H*-pyrazolo[3,4-*c*]pyridazine (**1b**), resulting from the basic hydrolysis of the chloroacetyl group rather than the 3-ethanolaminoacetylamino derivative (**14c**), as shown by the analytical and spectral data. The infrared spectrum of the product displays no absorption referred to the carbonyl group and showed an absorption band at 3442 and 3297 cm^{-1}, referred to the amino group and the mass spectrum gave a molecular ion at *m/z* 356 (71%) in accordance with the proposed structure.

The reaction of 3-chloroacetylamino (**13**) gave rise to 3-(2-imino-4-oxothiazol-3-yl)-4,5-bis(4-chlorophenyl)-1*H*-pyrazolo[3,4-*c*]pyridazine (**15**) when reacted with potassium thiocyanate in butanol. The indicated intermediate can not be isolated but can be rationalized as follows. The 3-thiocyanoacetylamino underwent smooth cyclization to the corresponding thiazolone derivative (**15**) (Scheme 3). The assignment of structure **15** was based on analytical and spectral data. The IR spectrum showed the presence of NH groups at 3448, 3137 cm^{-1} and a strong sharp carbonyl group at 1711 cm^{-1}. The mass spectrum gave a molecular in at *m/z* 455 in accord with the proposed structure. The ^{1}H NMR showed the presence of a 2H singlet at δ 3.97, a 8H multiplet at δ 7.42–7.65 due to aromatic phenyl protons, a 1H weak broad singlet at δ 11.74 due to NH, and a 1H weak broad singlet at δ 14.3 due to = NH group.

Insecticidal Activity

Out of the synthesized compounds, only compounds **1b, 2a, 2b, 3, 4, 6, 7a, 7b, 7c, 7d, 7e, 8, 12b, 12c, 13, 14,** and **15** were examined for their insecticidal activity against two insects viz. *Mucsa, domestica* and *Aphid, Macrosiphum pisi* by the dipping method[9] at 2.5×10^3, 5×10^3, 10×10^3, 15×10^3, and 20×10^3 ppm concentration, and the results are recorded in Table I (available in the Supplemental Materials online).

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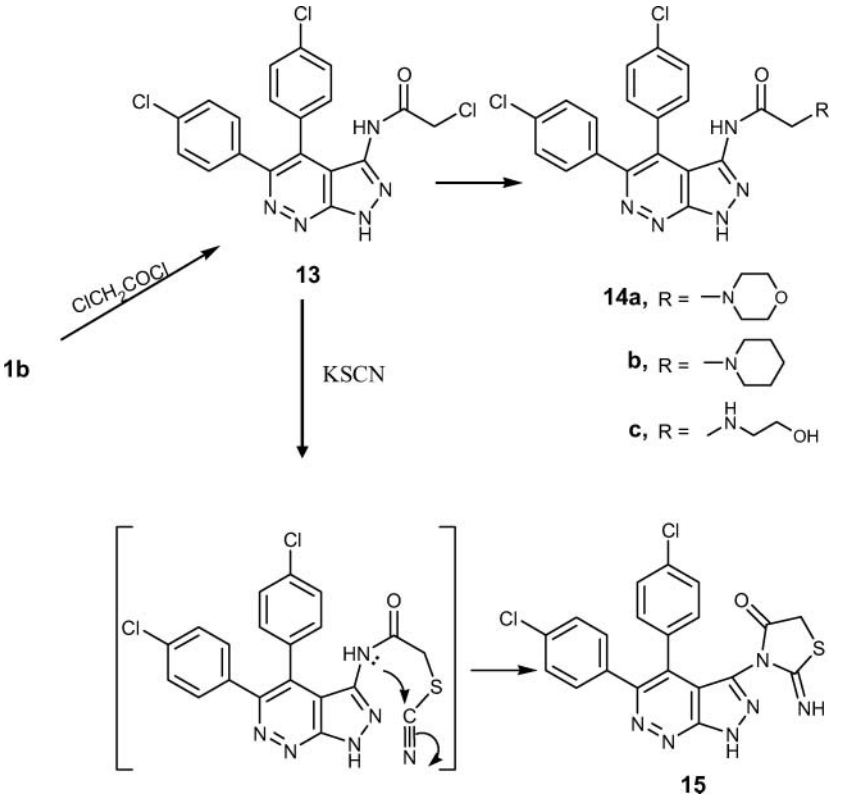

Scheme 3

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EXPERIMENTAL

Melting points were determined in open-glass capillaries using a Büchi 510 apparatus and were reported uncorrected. Infrared spectra were recorded as potassium bromide disks on a Bruker Vector 22 (Germany) spectrometer. ^{1}H NMR spectra were obtained on a Varian Gemini 200 MHz spectrometer, and chemical shifts are expressed in δ ppm using TMS as an internal standard. Electron impact mass spectra were obtained at 70 eV using a GCMS-1000 EX Shimadzu spectrometer. All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60 F-254 (Merck) plates using UV light (254 and 366 nm).

3-Amino-4,5-diaryl-1*H*-pyrazolo[3,4-*c*]pyridazine (**1a**,**b**), 3-diazo-4,5-diphenyl-pyrazolo[3,4-*c*]pyridazine (**9**), and 3-azido-4,5-diphenyl-1*H*-pyr-azolo[3,4-*c*]pyridazine (**10**) were prepared according to previously reported procedures.[6–8]

N-(4,5-Diphenyl-1H-pyrazolo[3,4-c]pyridazin-3-yl)-N′-methylthioures (2a)

A solution of 3-amino-4,5-diphenyl-1*H*-pyrazolo[3,4-*c*]pyridazine (**1a**) (0.57 g, 2.0 mmol) and methyl isocyanate (0.15 g, 2.0 mmol) in dry benzene (20 mL) was heated under reflux for 6 h. The reaction mixture was evaporated under reduced pressure, and the residue was collected and recrystallized from ethanol to give **2a**. Yield: 0.6 g (85.7%), mp

273–275°C, IR: 3260 (NH), 3062 ($CH_{arom.}$), 2828 ($CH_{aliph.}$), 1057 (C=S) cm^{-1}; ^1H NMR (DMSO-d_6): δ: 14.4 (s, 1H, NH), 8.80 (s, 1H, NH-C=S), 8.00 (s, 1H, $NHCH_3$), 7.60–7.20 (m, 10H, 2Ph), 2.60 (s, 3H, CH_3) ppm. Anal. Calcd for $C_{19}H_{16}N_6S$: C, 63.33; H, 4.48; N, 23.33. Found: C, 63.20; H, 4.40; N, 23.20.

N-(4,5-Diphenyl-1H-pyrazolo[3,4-c]pyridazin-3-yl)-N′-phenylthioures (2b)

A solution of 3-amino derivative (**1a**) (1.7 g, 6.0 mmol) and an equimolar amount of phenyl isothiocyanate (0.81 g, 6.0 mmol) in dry benzene (20 mL) was heated under reflux for 5 h. The reaction mixture was evaporated under reduced pressure, and the residue was collected and recrystallized from ethanol to give **2b**. Yield 2.3 g (92%), mp 216–218 °C, IR: 3376 (NH), 3062 ($CH_{arom.}$), 1459 (C=C), 1151 (C=S) cm^{-1}; MS: *m/z* (%): 422 (M^+, 3.2), 330 (M^+-NHPh, 13.1, ion A), 286 (ion A-CS, 99.9, ion B), 259 (ion B-HCN, 20), 245 (ion B-C(NH)=N, 17.8). Anal. Calcd for $C_{24}H_{18}N_6S$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.10; H, 4.10; N, 18.70.

N-[4,5-Bis(4-chlorophenyl)-1H-pyrazolo[3,4-c]pyridazin-3-yl]-N′-benzoylthiourea (3)

To a stirred solution of in situ prepared benzoyl isothiocyanate (1.46 g, 9.0 mmol) in anhydrous acetone (10 mL), a solution of 3-amino-4,5-bis(4-chlorophenyl)-1*H*-pyrazolo[3,4-*c*]pyridazine (**1b**) (3.20 g, 9.0 mmol) in anhydrous acetone (20 mL) was slowly added dropwise, and the mixture was gently refluxed for 24 h. The reaction mixture was cooled, and the solid product was collected, dried, and recrystallized from acetone to give **3**. Yield: 3.0 g (65%), mp 218–220°C, IR: 3051 ($CH_{arom.}$), 2340 (NCS), 760 (C-Cl) cm^{-1}; MS = *m/z* (%) : 521 ($M^+ + 2$, 1.4), 411 (M^+-PhCO/3H, 1.9, ion A), 353 (ion A-NCS, 4.9, ion B), 276 (ion B-$C_3H_3N_3$, 1.4). Anal. Calcd for $C_{25}H_{16}Cl_2N_6OS$: C, 57.81; H, 3.11; N, 16.18. Found: C, 57.70; H, 3.00; N, 16.10.

N-[4,5-Bis(4-chlorophenyl)-1H-pyrazolo[3,4-c]pyridazin-3-yl]-N′-ethoxy-carbonylthiourea (4)

A solution of ethoxycarbonyl isothiocyanate [prepared by mixing ethyl chloroformate (0.66 g, 6.0 mmol) in anhydrous acetone (10 mL) with ammonium thiocyanate (0.66 g, 8.7 mmol) and heating on a water bath for 20 min] was added to a stirred solution of compound **1b** (1.4 g, 4.0 mmol) in anhydrous acetone (20 mL). The whole mixture was heated under reflux for 5 h, and then evaporated under reduced pressure. The residue was recrystallized from ethanol to give **4**, yield 1.3 g (71%), mp 223–225 °C; IR: 3376, 3314 (NH), 1726 (C=O), 1128 (C=S) cm^{-1}; MS = *m/z* (%): 487 (M^+, 0.3), 486 (M^+-1, 10, ion A), 397 (ion A-$NHCO_2CH_2CH_3$, 17, ion B), 354 (ion B-C=S, 100). Anal. Calcd for $C_{21}H_{16}Cl_2N_6O_2S$: C, 51.75; H, 3.31; N, 17.25. Found: C, 51.60; H, 3.20; N, 17.00.

Ethyl N-[(4,5-diphenyl)-1H-pyrazolo[3,4-c]pyridazine]-3-dithiocarbamate (6)

To a vigorously stirred solution of 3-amino derivative (**1a**) (0.86 g, 3.0 mmol) in ethanol (25 mL) at room temperature, carbon disulfide (0.98 g, 13.0 mmol) and aq.

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KOH (0.9 g, 20 M) were added. After stirring for 10 min, the reaction mixture was cooled in an ice bath (5–10°C) and diethyl sulfate (0.6 g, 3.8 mmol) was added with stirring. The reaction mixture was refluxed for 3 h, and thereafter the cooled reaction mixture was poured into ice water (250 mL). The solid thus separated was filtered, dried, and recrystallized from ethanol to afford **6** as yellow crystalline solid, yield 1.0 g (91%), mp 183–184 °C; IR: 3392, 3320 (NH), 2928 ($CH_{aliph.}$), 1128 (C=S) cm^{-1}. Anal. Calcd for $C_{20}H_{17}N_5S_2$: C, 61.35; H, 4.38; N, 17.89. Found: C, 61.10; H, 4.20; N, 17.70.

Bis N-[(4,5-diphenyl)-1H-pyrazolo[3,4-c]pyridazine]-3-dithiocarbamate metal salt (7a–e)

General procedure. To a vigorously stirred of 3-amino derivative (**1a**) (0.86 g, 3.0 mmol) in ethanol (25 mL) at room temperature, carbon disulphide (0.98 g, 13.0 mmol) and aq. KOH (0.9 g, 20 M) were added. After stirring for 10 min, the reaction mixture was cooled in an ice bath (5–10°C), and metal sulfate (3.0 mmol) was added with stirring. The reaction mixture was refluxed for 2 h. The solvent was removed under reduced pressure, water (100 mL) was added to the residue, and the precipitate was filtered off and dried.

Manganese(II) Bis-N[-[(4,5-diphenyl)-1H-pyrazolo[3,4-c]pyridazine]-3-dithiocarbamate (7a). Yield: 2.2 g (95%), mp > 300 °C, IR: 3412 (NH), 3030 ($CH_{arom.}$), 1114 (C=S) cm^{-1}.

Zinc(II) Bis-N-[(4,5-diphenyl)-1H-pyrazolo[3,4-c]pyridazine]-3-dithio-carbamate (7b). Yield: 2.2 g (95%), mp > 300 °C, IR: 3396 (NH), 1616 (C=N), 1112 (C=S) cm^{-1}.

Ferous(II) Bis-N-[(4,5-diphenyl)-1H-pyrazolo[3,4-c]pyridazine]-3-dithiocarbamate (7c). Yield: 2.0 g (87%), mp > 300 °C, IR: 3354 (NH), 1610 (C=N), 1116 (C=S) cm^{-1}.

Cobalt(II) Bis-N-[(4,5-diphenyl)-1H-pyrazolo[3,4-c]pyridazine]-3-dithiocarbamate (7d). Yield: 2.1 g (91%), mp > 300 °C, IR: 3446 (NH), 1620 (C=N), 1116 (C=S) cm^{-1}.

Nickel(II) Bis-N-[(4,5-diphenyl)-1H-pyrazolo[3,4-c]pyridazine]-3-dithiocarbamate (7e). Yield: 2.2 g (96%), mp > 300 °C, IR: 3468 (NH), 1606 (C=N), 1096 (C=S) cm^{-1}.

3-Ethoxycarbonylamino-4,5-bis(4-chlorophenyl)-1H-pyrazolo [3,4-c]-pyridazine (8)

A mixture of 3-amino derivative (**6b**) (1.0 g, 2.8 mmol) and ethyl chloroformate (5 mL) was refluxed for 2 h. The cooled reaction mixture was poured onto water (100 mL) and left overnight. The separated solid product was filtered, dried, and recrystallized from ethanol to give **8**. Yield: 0.81 g (68%), mp 230–231 °C; IR: 3054 ($CH_{arom.}$), 2903 ($CH_{aliph.}$), 1738 (C=O, ester), 728 (C-Cl) cm^{-1}; MS = *m/z* (%): 428 (M^+, 3.9), 427 (M^+-H, 9.6), 357 (M^+-CO_2Et, 60), 355 (M^+-2H, CO_2Et, 100). Anal. Calcd for $C_{20}H_{15}Cl_2N_5O_2$: C, 56.09; H, 3.53; N, 16.35. Found: C, 55.80; H, 3.40; N, 16.10.

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3-Triphenylphoranylideneamino-4,5-diphenyl-1H-pyrazolo[3,4-c]pyrid-azine (12a)

To a solution of 3-azido-4,5-diphenyl-1*H*-pyrazolo[3,4-*c*]pyridazine (**10**) (0.3 g, 0.95 mmol) in ethanol (15 mL), triphenylphosphine (0.5 g, 1.9 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated, and the solid product was filtered, washed with cyclohexane, dried, and recrystallized from ethanol to give **12a**. Yield: 0.4 g (77%), mp 292–294 °C; IR: 3320 (NH), 3090 ($CH_{arom.}$), 1601 (C=N) cm^{-1}; MS = *m/z* (%): 547 (M^+, 87), 547 (M^+-1, 68), 285 (M^+-PPh_3, 5.7). Anal. Calcd for $C_{35}H_{26}N_5P$: C, 76.77; H, 4.79; N, 12.79. Found: C, 76.50; H, 4.60; N, 12.10.

3-Trialkoxyphosphoranylideneamino-4,5-diphenyl-1H-pyrazolo [3,4-c]-pyridazine (12b,c)

General procedure. A mixture of 3-azido derivative (**10**) (0.7 g, 2.85 mmol) and trimethylphosphite or triethylphophite (2.5 mL) was stirred at room temperature for 1 h. Nitrogen evolution started instantly, followed by precipitation of the product. The reaction product was filtered, dried, and recrystallized from ethanol.

3-Trimethoxyphosphoranylideneamino Derivative (12b). Yield: 1.1 g (94%), mp 143–144 °C; IR: 3445 (NH), 3059 ($CH_{arom.}$), 2910 ($CH_{aliph.}$), 1077 (P—O—C) cm^{-1}; MS = *m/z* (%): 409 (M^+, 10), 368 (M^+-CMe_2, 14, ion A), 339 (ion A—N_2H, 3, ion B), 257 (ion B—HPO_3H, 4.9). Anal. Calcd for $C_{20}H_{20}N_5O_3P$: C, 58.69; H, 4.93; N, 17.11. Found: C, 58.60; H, 4.80; N, 17.00.

3-Triethoxyphosphoranylideneamino Derivative (12c). Yield: 2.2 g (84.6%), mp 158–160 °C; IR: 3322 (NH), 3151 ($CH_{arom.}$), 2909 ($CH_{aliph.}$), 980 (P—O—C) cm^{-1}; MS = *m/z* (%): 451 (M^+, 13), 315 (M^+-$()_3$, 14, ion A), 286 (ion A—P, 100). Anal. Calcd for $C_{23}H_{26}N_5O_3P$: C, 61.19; H, 5.81; N, 15.52. Found: C, 61.00; H, 5.70; N, 15.40.

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3-Chloroacetylamino-4,5-bis(4-chlorophenyl)-1H-pyrazolo[3,4-c]pyrid-azine (13)

A mixture of 3-amino derivative (**1b**) (3.56 g, 10.0 mmol) and chloroacetylchloride (20 mL) was refluxed for 30 min. The cooled reaction mixture was poured into water (100 mL), then the precipitate was filtered off, dried, and recrystallized from ethanol to give **13**, 4.0 g (92.5%), mp 274–275 °C; IR: 3062 ($CH_{arom.}$), 2972 ($CH_{aliph.}$), 1665 (C=O, amide), 727 (C—Cl) cm^{-1}. Anal. Calcd for $C_{19}H_{12}Cl_3N_5O$: C, 52.74; H, 2.80; N, 16.19. Found: C, 52.60; H, 2.70; N, 16.00.

3-Morpholinoacetylamino-4,5-bis(4-chlorophenyl)-1H-pyrazolo [3,4-c]-pyridazine (14a)

A mixture of 3-chloroacetylamino derivative **(13)** (0.4 g, 0.92 mmol) and morpholine (6 mL) was refluxed for 2 h. The cooled reaction mixture was poured into water (100 mL). Upon acidification with hydrochloric acid, the precipitate that was obtained was filtered, washed several times with water, dried, and recrystallized from benzene to give **14a**,

4.0 g (83%), mp 238–240 °C; IR: 3315 (NH), 3029 ($CH_{arom.}$), 2820 ($CH_{aliph.}$), 1688 (C=O, amide) cm^{-1}. MS = *m/z* (%): 483 (M^+, 0.4), 397 (M^+-$N(CH_2CH_2)_2O$, 0.8, ion A), 354 (ion A−$COCH_2$, 2.5). Anal. Calcd for $C_{23}H_{20}Cl_2N_6O_2$: C, 57.15; H, 4.17; N, 17.39. Found: C, 57.00; H, 4.10; N, 17.30.

3-Piperidinoacetylamino-4,5-bis(4-chlorophenyl)-1H-pyrazolo [3,4-c]-pyridazine (14b)

To a solution of 3-chloroacetylamino derivative (**13**) (0.4 g, 0.92 mmol) in ethanol (20 mL), piperidine (0.26 g, 3.0 mmol) was added. The reaction mixture was refluxed for 16 h. The solvent was evaporated under reduced pressure. Water (100 mL) was added to the residue followed by a few drops of HCl. The precipitate was filtered, dried, and recrystallized from benzene to give **14b**, 0.4 g (85%), mp 263–264°C; IR: 3087 ($CH_{arom.}$), 2933 ($CH_{aliph.}$), 1690 (C=O, amide), 775 (C-Cl) cm^{-1}. Anal. Calcd for $C_{24}H_{22}Cl_2N_6O$: C, 59.88; H, 4.59; N, 17.46. Found: C, 59.70; H, 4.50; N, 17.30.

Reaction of 3-Chloroacetylamino derivative (13) with Ethanolamine

A mixture of 3-chloroacetylamino derivative (**13**) (0.4 g, 0.92 mmol) and ethanolamine (5 mL) was refluxed for 2 h. The cooled reaction mixture was poured onto water (100 mL). The solid product was filtered, washed several times with water, dried, and recrystallized from ethanol to give a product that was proven to be identical with 3-amino-4,5-bis(chlorophenyl)-1*H*-pyrazolo[3,4-*c*]pyridazine (**1b**) (0.4 g, 88%), mp 249–250°C.

3-(2-Imino-4-oxothiazol-3-yl)-4,5-bis(4-chlorophenyl)-1H-pyrazolo [3,4-c]-pyridazine (15)

A suspension of 3-chloroacetylamino derivative (**13**) (1.7 g, 3.93 mmol) and potassium thiocyanate (0.3 g, 4.0 mmol) in n-butanol (50 mL) was heated under reflux for 40 h. The reaction mixture was concentrated to its half volume. After cooling, the precipitate was separated, washed with water several times, dried, and recrystallized from ethanol to give **15**, 1.5 g (84%), mp > 300°C; IR: 3073 ($CH_{arom.}$), 2931 ($CH_{aliph.}$), 2366 (NCS), 1711 (C=O, amide), 767 (C−Cl) cm^{-1}; ^{1}HNMR (DMSO-d_6): δ 14.30 (s, 1H, NHCO), 11.74 (s, 1H, NH), 7.27-7.65 (m, 8H, 2Ar), 3.97 (s, 2H, CH_2); MS = *m/z* (%): 454 (M^+, 11), 343 (M^+-ClC_6H_4, 5, ion A), 246 (ion A−COCNCS, 18). Anal. Calcd for $C_{20}H_{12}Cl_2N_6OS$: C, 52.75; H, 2.66; N, 18.46. Found: C, 52.60; H, 2.60; N, 18.20.

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