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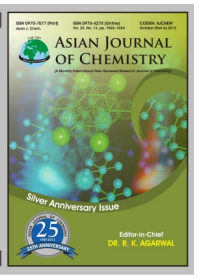

Synthesis, Antibacterial and Antioxidant Properties of Pyrazolylpyridazines

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A number of 6-chloro-3-(pyrazol-1'-yl) pyridazines were prepared from 3,6-dichloropyridazine *via* either reaction with hydrazine followed by reaction with appropriate reagents to develop the pyrazole or through a nucleophilic reaction with a pyrazole. Some electrophilic reactions gave the corresponding 4'-substituted pyrazolylpyridazines. All the compounds were tested for their *in vitro* antibacterial as well as their antioxidant properties.

Key Words: Nucleophilic substitutions, Nitration, Chlorination and bromination.

INTRODUCTION

Chemistry of pyridazines has been well documented[1]. Some pyridazine derivatives are reported to posses diverse biological activities[2]. A number of pyrazolylpyridazines have been described as effective antihypertensives while some as excellent herbicides[3] or chelating agents[4].

During our continuous work on the synthesis of various heterocyclic systems[5], we have now prepared a number of pyridazine derivatives, which were tested for their antibacterial and antioxidative properties.

EXPERIMENTAL

All the starting and other compounds and reagents were obtained from Merck or Fluka Chemicals. These were of reagent grades and were used without purification, however when required twere purified by standard methods. Melting points (m.p.) were determined on a Gallenkamp apparatus and are uncorrected. FTIR spectra were recorded on a Hitachi FTIR 4300 or Thermo Nicolet FTIR-200 spectrometer. NMR spectra (^{1}H and ^{13}C) were taken on a Bruker AVANCE 300-600 MHz and in solvents DMSO-d_6, $CDCl_3$ or CD_3OD. Chemical shifts are reported in ppm relative to tetramethylsilane an internal standard (abbreviations; d, doublet; t; triplet; m, multiplet). Mass spectra were taken either on Jeol JMS-HX110H or on Agilent GC-MS spectrophotometer 5890. Elemental analysis (C, H, N) was carried out on Elementar VarioMACRO CHNS Analyser. The X-ray crystallography of selected synthesized compounds was carried out on APEX2 (Bruker, 2007); cell refinement; APEX2; data reduction; SAINT (Bruker 2007); programe(s) used to solve structure; SHELLEX97 (Sheldrick, 2008); progame used to refine structure; SHELLEX97 (Sheldrick, 2008); molecular graphics; ORTEP-III for window (Farrugia, 1997) and PLATON (Spek, 2003); software used to prepare material for publication; WinGX (Farrugia, 1999) and PLATON.

Progress of all the reactions was monitored by thin layer chromatography (TLC), which was performed on aluminium sheets, precoated with silica gel (Merck, Kiselgel 60 F-254) (0.2 mm). Column chromatography, when required was carried out using E. Merck silica gel type 60 (70-230 mesh) and aluminium oxide basic (Panreac). Spots were checked under UVGL-25 Mineral light multi-band UV-254/366 nm lamp. Some plates were observed in iodine vapours.

The antibacterial screening was conducted by following the disk protocol[6] while antioxidant properties were determined by DPPN method[7].

Pyrazolylpyridazines

Synthesis

(i) Route (a) from 3-chloro-6-pyridylhydrazine

3-Chloro-6-hydrazinylpyridazine (2): A mixture of 15 g (0.1 mol) of 3,6-dichloropyridazine (**1**) and 7.3 mL of hydrazine hydrate (80 %) was heated under reflux for 1 h and concentrated under reduced pressure. The residue was dissolved in hot water which on cooling yielded the pure (**2**). Yield, 11 g (76 %) m.p. 130-135 ºC (lit.[6] 130-135), IR: 3255 cm^{-1} (-NH str), 3044 cm^{-1} (CH str, pyridazine ring), 1587, 1500, 1453 and 1280 cm^{-1} pyridazine ring str), ESIMS *m/z* %: 144 [M^+, 100], 146 [M^+ 33], elemental analysis for $C_4H_5ClN_4$: calculated C, 33.23; H, 3.49; N, 38.76 % found C, 33. 53. H, 3.75; N, 38.46 %.

3-Chloro-6-(1*H*-pyrazol-1-yl)pyridazine (3): A mixture of 3-chloro-6-hydrazinylpyridazine (**2**) (1 g, 6.9 mmol), ethanol 10 mL and acetic acid 3 mL was heated to a clear solution and an equimolar quantity (1.52 g, 6.9 mmol) of 1,1,3,3-tetraethoxypropane which was already diluted with 10 mL ethanol was added drop-wise during reflux. After addition the reaction mixture was heated under reflux for 3 h, concentrated under reduced pressure, cooled and diluted with 25 mL of water, ppts formed were filtered and crystallized from ethanol. Yield: 1.08 g (86 %) m.p. 138-140 ºC; IR (KBr, ν_{max}, cm^{-1}): 3064, 2925, 450 and 1283, pyridazine ring and pyridazine CH str, EIMS *m/z* % :180 [M^+ 100]. 182 [M^+, 33] elemental analysis: for $C_7H_5N_4Cl$: calculated, C, 46.55; H, 2.79; N, 31.02 % found, C, 45.83; H, 2.29; N, 30.46 %, ^{1}H NMR ($CDCl_3$): δ 6.54 (dd, *J* = 1.2, 2.0 Hz, 1H, H-4. pyrazole), 7.61 (d, *J* = 9.2 Hz, 1H, H-4, pyridazine), 7.80 (d, *J* = 1.2 Hz. 1H, H-3 pyrazole), 8.19 (d, *J* = 9.2 Hz, 1H, H-5 pyridazine), 8.72 (d, *J* = 2.0 Hz, 1H, H-5 pyrazole), ^{13}C NMR ($CDCl_3$) : (125 MHz); δ 109.35, 120.06, 127.62, 130.54, 143.48, 154.42, 155.60. Fig. 1 shows the ortep 3 diagram of the compound (**3**) with the atom numbering scheme. The thermal ellipsoids are drawn at the 50 % probability level. H-atoms are shown as small spheres of arbitrary radii.

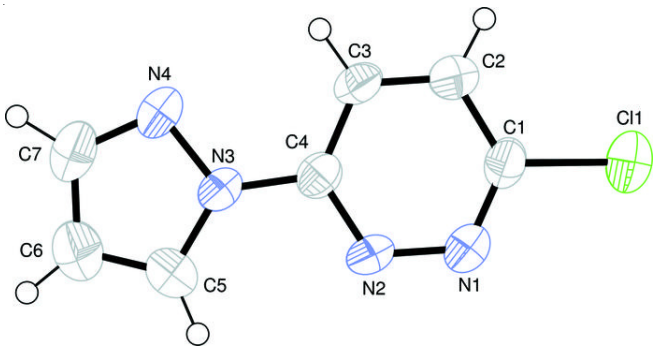


Fig. 1. Single crystal XRD ortep III diagram of compound **3**

3-Chloro-6-(3, 5-dimethyl-1*H*-pyrazol-1-yl)pyridazine (4): A mixture of an equimolar (6.9 mmol) quantities of 3-chloro-6-hydrazinylpyridazine (2) 1 g, acetylacetone 0.69 g and 0.5 mL acetic acid was stirred and heated at 80-90 ºC for 0.5 h, cooled and diluted with 25 mL of water, precipitates formed were filtered, washed with water and recrystallized from ethanol.

Another reaction carried out in ethanol and a few drops of hydrochloric acid also gave **4** in 75 % yield.Yield:1.27 g (88 %) m.p. 110-113 ºC, IR (KBr, ν_{max}, cm^{-1}): 3064, 2925, 1450 and 1283, pyridazine ring and pyridazine CH str EIMS *m/z* % 208 [M^+ 100], 210 [M^+, 33], elemental analysis for $C_9H_9N_4Cl$: calculated C, 51.80; H, 4.34; N, 26.85 % found C, 51.76; H, 4.31; N, 26.84 %. ^{1}H NMR ($CDCl_3$): δ 2.71 (s, 3H, 3-CH_3 pyrazole), 2.73 (s, 3H, 5-CH_3 pyrazole), 6.05 (s, 1H, H-4, pyrazole), 7.53 (d, *J* = 9.2 Hz, 1H, H-4 pyridazine), 8.13 (d, *J* = 9.2 Hz, 1H, H-5 pyridazine) ^{13}C NMR ($CDCl_3$): (75 MHz) δ: 13.62, 14.74, 109.98, 122.45, 130.02, 142.26, 151.18, 153.56, 154.90. Fig. 2 shows the title compound (**4**) with displacement ellipsoids drawn at the 50 % probability level. H-atoms are shown as small spheres of arbitrary radius.

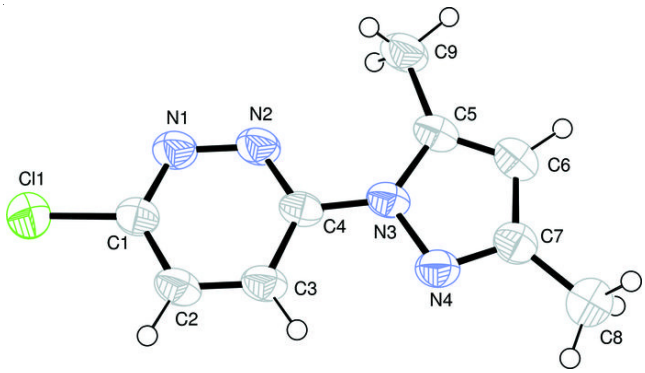


Fig. 2. Single crystal XRD Ortep III diagram of compund **4**

3-Chloro-6-(3, 5-diphenyl-1*H*-pyrazol-1-yl)pyridazine (5): A mixture of an equimolar (6.9 mmol) quantities of 3-chloro-6-hydrazinylpyridazine (**2**) 1 g, dibenzoylmethane (1,3-diphenyl-propan-1,3-dione) 2 g and 2 mL ethanol with a few drops of hydrochloric acid was stirred and heated at 80-90 ºC for 1 h, cooled and diluted with 25 mL of water, precipitates formed were filtered, washed with water and recrystallized from acetic acid. Yield, 2.20 g (67 %), m.p. 179-180 ºC; IR (KBr, ν_{max}, cm^{-1}): 3060, 3040, 1560,1535, 1475, 1455, 1440, 1425, 1390, 1365, 1140, 1110, 1040, 1020, 970, 955, 860, 775, 760, 755 and 700. EIMS *m/z* %, 332 [M^+ 100], 334 [M^+, 44]; ^{1}H NMR ($CDCl_3$): 6.82 (s, 1H, H-4, pyrazole), 7.00 (m, phenyl and pyridazine).

1-(3-Chloropyridazin-6-yl)-methyl-1*H*-pyrazol-5-ol (6): A mixture of an equimolar (6.9 mmol) quantities of 3-chloro-6-hydrazinylpyridazine (**2**) (1 g) ethyl acetoacetate (0.90 g) and ethanol 10 mL was heated under reflux for 1 h, cooled and diluted with 10 mL of water, ppts formed were filtered, washed with water and were recrystallized from ethanol identified as the intermediate hydrazone. Yield, 1.43 g (98 %), m.p. 115-117 ºC, IR (KBr, ν_{max}, cm^{-1}): 3544, 3433, 3285, (OH str) 3037, 2988, 1444 and 1283, pyridazine ring and pyridazine CH str, ^{1}H NMR (DMSO-d_6) δ: 2.48 (s, 3H, CH_3), 7.38 (d, *J* = 9.4 Hz, 1H, H-4 pyridazine), 7.59 (d, *J* = 9.4 Hz, 1H, H-5 pyridazine), 10.37 (s, 1H, NH). However a small amount obtained from the filtrate was identified as the pyrazolone (**6**) on the basis of its mass spectra (MS 210 [M^+, 16 %], 212 [M^+, 5 %]).

1-(3-Chloropyridazin-6-yl) 3,4-dimethylpyrano [2,3-c]pyrazol-6(1*H*)-one (8): A mixture of 3-chloro-6-hydrazinylpyridazine (**2**) (1 g, 6.9 mmol), ethyl acetoacetate (1.8 g,

13.8 mmol) and ethanol 10 mL was heated under reflux for 2 h, cooled and diluted with 10 mL of water, ppt formed were filtered, washed with water and recrystallized from ethanol. Yield, 1.42 g (97 %), m.p. 115-117 ºC; IR (KBr, ν_{max}, cm^{-1}): 1680 (lactone C=O) 2917, 1586 and 1265, pyridazine ring and pyridazine CH str. EIMS *m/z* %, 276 [M^+ 100 %], 278 [M^+ 33 %]; ^{1}H NMR (DMSO-d_6) δ: 1.37 (s, 3H, CH_3- 4), 2.74 (s, 3H, CH_3-3), 6.81 (d, *J* = 9.2 Hz, 1H, H-5), 7.70 (d, *J* = 9.4 Hz, 1H, H-4 pyridazine), 8.80 (d, *J* = 9.4 Hz, 1H, H-5 pyridazine).

Ethyl 5-amino-1-(3-chloropyridazin-6-yl)-1*H*-pyrazole-4-carboxylate (7): An equimolar quantity (6.9 mmol; 1 g) of 3-chloro-6-hydrazinylpyridazine and 1.17 g of ethyl ethoxymethylenecyanoacetate and 10 mL of acetic acid was heated under reflux for 4 h and diluted with 50 mL of water, ppts. formed were filtered, washed with water and recrystallized from ethanol. Yield, 1.53 g (81 %); m.p. 130-135 ºC; IR (KBr, ν_{max}, cm^{-1}): 3312 (NH_2), 2975, 1570, 1448 and 1275, (pyridazine ring and pyridazine CH str), 1681 (C=O str); EIMS *m/z* %, 267 [M^+ 100], 269 [M^+, 33], elemental analysis for $C_{10}H_{10}ClN_5O_2$; calculated, C, 44.82; H, 3.73; N, 26.15 %, Found C, 44.27; H, 3.12; N, 26. 50 %; ^{1}H NMR (DMSO-d_6) δ : 1.23 (t, *J* = 7.06 Hz, 3H, O-CH_2CH_3), 4.16 (q, *J* = 7.05 Hz, 2H, O-CH_2CH_3), 7.61 (d, *J* = 9.2 Hz, 1H, H-4 pyridazine), 7.74 (s, 1H, H-3 pyrazole), 8.17 (d, *J* = 9.2 Hz, 1H, H-5 pyridazine), 12.95 (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): (100 MHz) δ : 14.51, 59.82, 95.78, 121.30, 130.86, 143.09, 152.13, 153.44, 156.89,164.03. View of Fig. 3 with displacement ellipsoids drawn at the 50 % probability level. H-atoms are shown as small spheres of arbitrary radius. The dotted lines indicate the intramolecular H bonds.

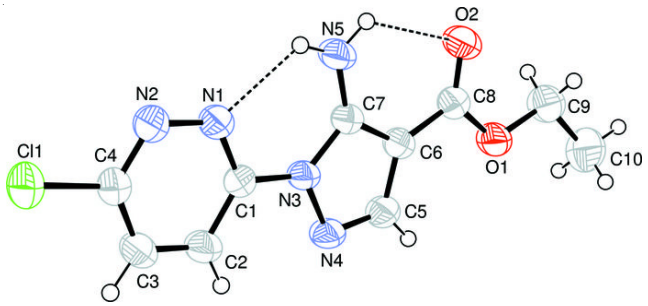


Fig. 3. Single crystal XRD Ortep III diagram of compound **7**

(ii) Route (b) *N*-Arylation

General method A: (In toluene): Sodium hydride emulsion in mineral oil (6.7 mmol), after washing with hexane was added to a stirring mixture of an azole (5.7 mmol) and 3,6-dichloropyridazine (6.7 mmol) in 10 mL of toluene and heated under reflux for 1 h. The solvent was removed under reduced pressure and the residue was poured over crushed ice, filtered and was recrystallized from ethanol to give the arylated products **3**, **4** and **12**.

General method B: In dioxane or DMSO: A mixture of 13 mmol of an azole and 13 mmol of 3,6-dichloropyridazine in 10 mL of dioxane was left with stirring at room temperature for 24 h. The reaction mixture was added to crushed ice, precipitates were filtered, dried and recrystallized from ethanol to give the arylated product.

3-Chloro-6-(1*H*-pyrazol-1-yl)pyridazine (3): An equimolar quantities (6.7 mmol) 1 g of 3,6-dichloro-pyridazine (**1**), 0.46 g of pyrazole and 0.16 g of hexane-washed sodium hydride was heated under reflux in 10 mL toluene for 1 h (**method A**). Solvent (toluene) was removed under reduced pressure and poured over crushed ice, ppts. formed were filtered, washed with water and recrystallized from ethanol. Yield, 1 g (83 %); m.p. 138-140 ºC; IR cm^{-1}, 3064, 2925, 1450 and 1283 pyridazine ring and pyridazine CH str; EIMS *m/z* %, 180 [M^+ 100], 182 [M^+, 33]. Elemental analysis for $C_7H_5N_4Cl$: calculated C, 46.55; H, 2.79; N, 31.02 % found C, 45.83; H, 2.29; N, 30.46 %; ^{1}H NMR ($CDCl_3$): δ 6.54 (dd, *J* = 1.2, 2.0 Hz, 1H, H-4 pyrazole), 7.61 (d, *J* = 9.2 Hz, 1H, H-4 pyridazine), 7.80 (d, *J* = 1.0 Hz. 1H, H-3 pyrazole), 8.19 (d, *J* = 9.2 Hz, 1H, H-5 pyridazine), 8.72 (d, *J* = 0.36 Hz,1H, H-5 pyrazole); ^{13}C NMR ($CDCl_3$): (125 MHz); δ 109.35, 120.06, 127.62, 130.54, 143.48, 154.42, 155.60.

3-Chloro-6-(1*H*-imidazol-1-yl)pyridazine (12): An equimolar quantities (6.7 mmol) 1 g of 3, 6-dichloro-pyridazine (**1**), 0.46 g of imidazole and 0.16 g of hexane-washed sodium hydride was heated under reflux in 10 mL toluene for 1 h (**method A**). Solvent (toluene) was removed under reduced pressure and the mixture was poured over crushed ice, precipitates formed were filtered, washed with water and was purified with column chromatography on aluminium oxide basic, benzene was used as an eluent. Yield, 1.2 g (96 %); m.p. 180 ºC; IR (KBr, ν_{max}, cm^{-1}): 3042, 2925, 1431 and 1260 pyridazine ring and pyridazine CH str; EIMS m/z %, 180 [M^+ 100], 182 [M^+ 33]. Another possible diarylated product (**11**) was not formed in this reaction.

3-Chloro-6-(3, 5-dimethyl-1*H*-pyrazol-1-yl)pyridazine (4): A mixture of an equimolar (6.7 mmol) 1 g of 3, 6-dichloro-pyridazine (**1**), 0.65 g 3,5-dimethylpyrazole and 0.16 g of hexane-washed sodium hydride was stirred in 10 mL of hexane at room temperature for 1 h. The solvent hexane was removed under reduced pressure, poured on crushed ice. The ppt. formed were filtered, washed with water and purified with column chromatography on aluminium oxide basic. Benzene was used as an eluent. Yield, 0.72 (88 %); m.p. 97-100 ºC; IR (KBr, ν_{max}, cm^{-1}): 3064, 2925, 1450 and 1283 pyridazine ring and pyridazine CH str; EIMS *m/z* %, 208 [M^+ 100], 210 [M^+ 33]; ^{1}H NMR ($CDCl_3$) δ: 2.71 (s, 3H, CH_3-3 pyrazole), 2.73 (s, 3H, CH_3-5 pyrazole), 6.05 (s, 1H, H-4 pyrazole), 7.53 (d, *J* = 9.2 Hz, 1H, H-4 pyridazine), 8.13 (d, *J* = 9.2 Hz, 1H, H-5 pyridazine); ^{13}C NMR ($CDCl_3$): (75 MHz) δ : 13.62, 14.74, 109.98, 122.45, 130.02, 142.26, 151.18, 153.56, 154.90. Identical in all respects (m.p., mixed m.p., TLC and FTIR and NMR spectra) with the one prepared from 3-chlopyridazinyl-hydrazine and pentan-2,4-dione condensation.

By using the two molar ratios of 3,5-dimethylpyrazole, the expected diarylated product (**10**) could not be isolated.

3-Chloro-6-(1*H*-pyrazol-1-yl)pyridazine (3): By using **method A**, **3** was obtained in 83 % yield. It was identical in all respects (mp, mixed mp and spectra to the one obtained from the chloropyridylhydrazine condensation above.

3,6-(Di-1*H*-pyrazol-1'-1''-yl)pyridazine (9): Following **method B**, this diarylated product was formed when 2 mol equivalents of pyrazole and one mole equivalent of 3,6-dichloropyridazine was used in the arylation reaction. Yield, almost quantitative; m.p. 197-198 ºC, EIMS *m/z* % 212 [M^+ 100] ; Elemental analysis for $C_{10}H_8N_6$: calculated C, 56.60; H,

3.80; N, 39.60 %, found C, 56.71 H, 3.42; N, 41.82 %; ^{1}H NMR CF_3CO_2H): δ: 7.10 (t, 2H, *J* = 2.0 Hz, H-4 pyrazole), 8.45 (d, *J* = 2.0 Hz, 2H, H-3, pyrazole), 9.00 (d, 2H. *J* = 2.0 Hz, H-5, pyrazole), 8.75 (s, 2H, pyridazine).

3,6-(Di-1*H*-1,2,4-triazol-1'-1''-yl)pyridazine (13): This arylated product was obtained by using **method B**. A twofold excess of 1, 2, 4-triazole was employed in this reaction. For the arylation dioxane did not provide the desired product. However DMSO proved to be another useful solvent for the arylation and yielded a disubstituted pyridazine. Yield, almost quantitative; m.p. >300 ºC; EIMS *m/z* %, 214 [M^+ 100] elemental analysis for $C_8H_6N_8$: calculated C, 44.85; H, 2.80; N, 52.33 % Found C, 44.96; H, 2.66; N, 54.29 %.

Electrophilic substitutions

Chlorination

3-Chloro-6-(4-chloro-1*H*-pyrazol-1-yl) pyridazine (14): A mixture of 3-chloro-6-(1*H*-pyrazol-1-yl) pyridazine (3) 1 g (6.9 mmol), ethanol 10 mL and 3 mL acetic acid was stirred and heated to a clear solution. A 20 mL 4 % sodium hypochlorite (commercial liquid bleach) was added drop-wise and stirred at 40 ºC for another half 1 h. Cooled and diluted with 20 mL of water. The precipitate formed were filtered, washed with water and recrystallized from ethanol. Yield, 1.33 g (74 %); m.p. 192-194 ºC; IR (KBr, ν_{max}, cm^{-1}): 3072, 2924, 1578 and 1444 (pyridazine ring and pyridazine CH str.) EIMS *m/z* %, 214 [100 %], 216 [64 %] and 215 [16 %], ^{1}H NMR ($CDCl_3$) δ: 7.58 (d, *J* = 9.2 Hz, 1H, H-4 pyridazine), 7.70 (s, 1H, H-3 pyrazole), 8.13 (d, *J* = 9.2 Hz, 1H, H-5 pyridazine), 8.67 (s, 1H, H-5 pyrazole) elemental analysis for $C_7H_4N_4Cl_2$: calculated C, 39.10; H, 1.87; N, 26.05 %, found C, 40.42; H,2.16; N, 27.18 %.

Bromination

3-Chloro-6-(4-bromo-1*H*-pyrazol-1-yl)pyridazine (15): A mixture of 1 g (5.5 mmol) of 3-chloro-6-(1*H*-pyrazol-1-yl)pyridazine (**3**), 10 mL acetic acid and 0.44 g bromine was stirred at 40 ºC for 1 h. The reaction mixture was treated with aqueous sodium sulphite. The ppts formed were filtered, washed with water, dried at room temperature and recrystallized from ethanol. Yield, 1 g (70 %); m.p. 210-215 ºC, IR (KBr, ν_{max}, cm^{-1}): 3069, 2926 and 1578 (pyridazine ring and pyridazine CH str); EIMS *m/z* %, 260 [M^+ 21], 261 [M^+ 5], 262 [M^+ 16]; ^{1}H NMR ($CDCl_3$) δ: 7.60 (d, *J* = 9.2 1H, H-4 pyridazine), 7.73 (s, 1H, H-3 pyrazole), 8.13 (d, *J* = 9.2 Hz, 1H, H-5 pyridazine), 8.72 (s, 1H, H-5 pyrazole).

3-Chloro-6-(4-bromo-3,5-dimethyl-1*H*-pyrazol-1-yl)-pyridazine (16): In this bromination, the above procedure was followed 0.40 g of 3-chloro-6-(3, 5-dimethyl-1*H*-pyrazol-1-yl)-pyridazine (**4**) was used for the purpose. The reaction product was recrystallized from ethanol; Yield, 0.41 g (74 %) m.p. 145-146 ºC (lit.[8], 143-145); EIMS *m/z* %, 286 [M^+ 38], 288 [M^+ 50]. ^{1}H NMR ($CDCl_3$): δ: 2.25 (s, 3H, CH_3-3 pyrazole), 2.75 (s, 3H, CH_3-5 pyrazole), 7.56 (d, *J* = 10 Hz, 1H, H-4 pyridazine), 8.17 (d, *J* = 10 Hz, 1H, H-5 pyridazine).

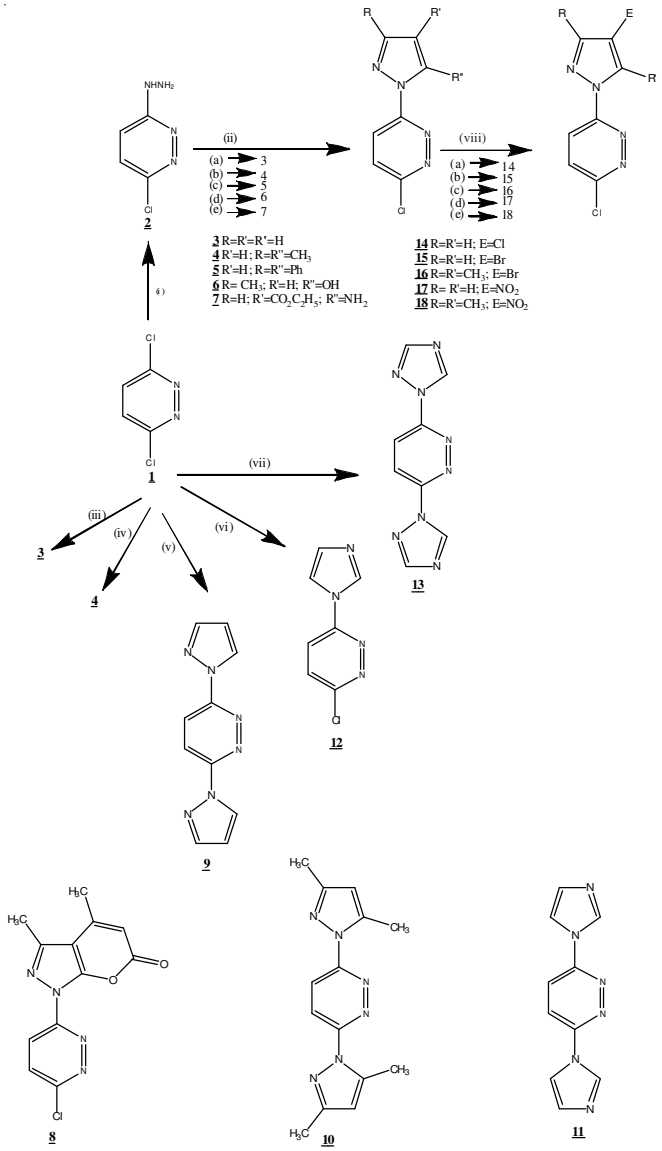
Nitrations

3-Chloro-6-(4-nitro-1*H*-pyrazol-1-yl)pyridazine (17): 1 g (5.5 mmol) of 3-chloro-6-(1H-pyrazol-1-yl)pyridazine (**3**) was slowly added with stirring to a nitrating mixture (conc. HNO_3: H_2SO_4; 2:3 mL) at 0-5 ºC. After the addition was complete, the temperature of the reaction was raized gradually to 40 ºC and stirred for further 2 h, cooled, poured on crushed ice. The precipitates formed were filtered, washed with water and recrystallized from ethanol; Yield: 1.2 g (80 %); m.p. 230-235 ºC (lit.[8], 169-172); IR (KBr, ν_{max}, cm^{-1}): 3064, 2925, 1450 and 1283 nitro, pyridazine ring and pyridazine CH str; EIMS *m/z* %, 225 [M^+ 100], 226 [M^+ 10], 227 [M^+ 33]; Elemental analysis for $C_7H_4N_5O_2Cl$: calculated C, 37.25 ; H, 1.77; N, 31.02 %, found, C, 37.70; H, 1.82; N, 31.76 % ^{1}H NMR (CF_3CO_2H) δ : 8.22 (d, *J* = 10.0, 1H, H-4 pyridazine), 8.51 (s, 1H, H-3 pyrazole), 8.74 (d, *J* = 10.0 Hz, 1H, H-5 pyridazine), 9.48 (s, 1H, H-5 pyrazole).

3-Chloro-6-(3,5-dimethyl-4-nitro-1*H*-pyrazol-1-yl)-pyridazine (18): In this nitration, the above procedure was followed and 1 g (4.8 mmol) of 3-chloro-6-(3, 5-dimethyl-1*H*-pyrazol-1-yl)pyridazine (**4**) was nitrated. The reaction product was recrystallized from ethanol; Yield, 0.98 g (80 %); m.p. 164 ºC (lit.[8], 164-167); IR: 3072, 3009, 2942, 1545, 1474 and 1424 cm^{-1} (nitro, pyridazine ring and pyridazine CH str.); EIMS *m/z* %, 253 [M^+ 100], 254 [M^+ 12], 255 [M^+ 33]; Elemental analysis for $C_7H_8N_5O_2Cl$: calculated C, 42.62 ; H, 3.18; N, 27.61 %, found C, 42.70; H, 3.50; N, 27.66 %; ^{1}H NMR (DMSO-d_6) δ: 2.19 (s, 3H, CH_3-3 pyrazole), 2.41 (s, 3H, CH_3-5 pyrazole), 7.53 (d, *J* = 9.0 Hz, 1H, H-4 pyridazine), 8.13 (d, *J* = 9.0 Hz, 1H, H- 5 pyridazine).

RESULTS AND DISCUSSION

Synthesis of various pyrazolyl pyridazines is formulated in the **Scheme-I**. 3-Pyrazol-1-ylpyridazines were prepared *via* two alternate routes. For route (a) a 3-chloro-6-hydrazinyl-pyridazine intermediate (**2**) was prepared from 3,6-dichloro-pyridazine (**1**) which was later used for various acid-catalyzed cyclizations using 1,3-dicarbonyl reagents[9] to give the desired 3-chloro-6-(pyrazol-1-yl)pyridazines (**3-5**). When the hydrazine (**2**) was heated under reflux for 1 h with ethyl acetoacetate 3-chloro-6-(3-methyl-5-hydroxy-pyrazol-1-yl)pyridazine (**6**) was obtained. However when an excess (> 2 mol eq) of ethyl acetoacetate was employed over a 2 h reflux period, it gave the pyridazinylpyrano[2,3-c]pyrazolone (**8**) in excellent yield. The pyranopyrazolone (**8**) was identified, besides other analytical data, through its FTIR spectra which showed a strong lactonic carbonyl peak at 1680 cm^{-1}. A reaction of **2** with ethyl α-cyano-β-ethoxyacrylate afforded 3-chloro-6-(ethyl 5-aminopyrazol-1-yl)pyridazine-4-carboxylate (**7**) which exhibited typical absorption bands in the FTIR spectra for the amino and the ester functions at 3312, 2975 and 1681 cm^{-1} respectively. The ^{1}H NMR showed a signal for two NH_2 protons at δ 12.95. All these synthesized 3-chloro-6-(pyrazol-1-yl)pyridazines exhibited typical signals for the H-4 and H-5 of the pyridazine ring around δ 7 and δ 8 ppm with coupling constants of *J* 4, 5 = 10 Hz. The route (b) for the preparation of pyrazolylpyridazines involves the *N*-arylation of an azole with a free NH by the use of sodium hydride[10]. It is an efficient method for *N*-arylations and is complimentary to the *N*-arylation procedure employing copper oxide[11]. The method is mild and very efficient and in the present work this was successfully achieved with the aid



Reagents and conditions: (i) $NH_2NH_2.H_2O/\Delta$; [(ii) (a) Tetraethoxy propane, AcOH/Δ, (b) Acetyl acetone, AcOH/Δ, (c) Dibenzoylmethane, HCl/Δ, (d) 1 mol $CH_3CO_2C_2H_5/\Delta$, (e) Ethyl ethoxymethylene cyanoacetate/AcOH/Δ]; (iii) Pyrazole, NaH, toluene; (iv) 3,5-dimethylpyrazole, NaH, toluene; (v) 2 mol pyrazole, NaH, dioxane/RT; (vi) Imidazole, NaH, toluene; (vii) 1,2-triazole, NaH, dioxane/RT; [(viii) (a) NaOCl-AcOH/RT; (b and c) Br_2-AcOH/ RT; (d and e) HNO_3-H_2SO_4/RT]

Scheme-I

of sodium hydride in refluxing hexane, dioxane or DMSO. Compounds thus obtained were identical with **3** and **4** prepared by the condensations of the hydrazine (**2**). When these reactions were performed in dioxane at room temperature both mono- (**3** and **4**) and 3, 6-dipyrazolyl pyridazines (**9** and **10**) were isolated. Arylation reaction of **1** with imidazole in refluxing hexane provided **11** in 96 % yield while the room temperature arylation of **1** with 1, 2, 4-triazole in DMSO afforded the 3, 6-disubstituted pyridazine **12** in small yield. It was tentatively characterized through its elemental analysis and mass spectral data and analogy from the earlier copper oxide arylations[11]. The pyrazolylpyridazines prepared during this work contain a highly π-electrons deficient pyridazine ring while the pyrazole ring might show affinity towards elctrophiles[9].

In view of this some electrophilic substitutions such as chlorination, bromination, nitration and formylation were carried out to obtain derivatives of pyrazolylpyridazine capable of further transformations. Except for a preliminary attempt at formylation (Vilsimier-Haack reaction) the other reactions went well to afford the 4'-substituted compounds **14-18**. These electrophilic substitutions are in tune with our earlier observation that 4-formylation of the 1-aryl (hetaryl) pyrazole is very sensitive and depends on their substituents thus with 2-(pyrazol-1'-yl)pyridines where pyridine, with just one nitrogen, deactivates enough the pyrazole ring[12]. Finar and Lord had also reported their inability to formylate 1-nitrophenylpyrazole[13]. However electron rich 1-methoxyphenylpyrazole gave excellent yield of the 4-formylated product[14]. On nitration with mixed acids at 0º nitrated products **17** and **18** were isolated while chlorination with hypochlorite and bromination with molecular bromine gave the respective chloro and bromo derivatives **14-16**. All the substituted products **14-18** lacked the H-4 signals (around δ 6.0 ppm) for the pyrazole nucleus while the H-3 and H-5 protons appeared as singlets at around δ 7.7 and δ 8.6 ppm respectively. The pyridazine H-4 and H-5 appeared as doublets at around δ 7 and δ 8 ppm with coupling constants of $J_{4,5}$ = 10 Hz. Although some of these compounds have been reported but our methods for these substitutions have the advantage of providing alternatives using cheaper reagents. For example the patent makes use of $SOCl_2$ for chlorinations and N-bromosuccinimide for bromination reactions[12].

Biological activities: All the synthesized compounds were screened for their antibacterial and antioxidant activity. The results are presented in Tables 1 and 2. On the basis of these results it seems that while a majority of the pyrazolylpyridazines screened for antibacterial properties are not active (< 50 % activity). However **4**, **8** and **15** are about 70 % active towards both the gram positive and gram negative bacteria and have the potential of, on further derivitization, producing better or equally active products as compared to the control, ciprofloxacin. As can be seen from the Table-2, only compound **6**, the 5-pyrazolone, seems to have some antioxidant property as compared to the control quercetin.

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REFERENCES

1. R.N. Castle, Pyridazines, Wiley New York, vols. 1 and 2 (1973); M. Tisler and B. Stanovnik, *Adv. Heterocycl, Chem.*, **49**, 385 (1990).
2. (a) J.R. Boissier, R. Ratouis and C. Dumont, *J. Med. Chem.*, **6**, 541 (1963); (b) Y. Dundar, M. Gokee, E. Kupeli and M.F. Sahin, *Arzeneim Forsch.*, **57**, 777 (2007); (c) M. Gokee, M.F. Sahin, E. Kupeli and Yesllada, *Arzeneim. Forsch.*, **54**, 396 (2004); (d) M. Gokee, S. Utku and E. Kupeli, *Eur. J. Med. Chem.*, **44**, 3760 (2009); P.S. Banerjee, *Asian J. Chem.*, **23**, 1905 (2011).
3. X.-M. Zou, Y.-Q. Zhu and H.-Z. Yang, *J. Heterocycl. Chem.*, **46**, 584 (2009).
4. (a) A.W. Addison and P.J. Burke, *J. Heterocycl. Chem.*, **18**, 803 (1981); (b) A.J. Blake, P. Hubberstey, W.-S. Li, C.E. Russell, B.J. Smith and L.D. Wraith, *J. Chem. Soc., Dalton Trans.*, 647 (1998).

TABLE-1
ANTIBACTERIAL PROPERTIES OF PYRAZOLYL PYRIDAZINES

% Inhibition (MIC_{50}) ; -, MIC not determined

Compd. No.	*S. aur.* g+	*E. coli*	*S. typhi*	*P. aur.*	*B. subtilus*	*S. soneris* g+
3	46.49	38.38	68.73	57.29	67.43	70.89
	(-)		(13.01 ± 0.11)	(-)	(13.39 ± 0.11)	(12.32 ± 0.02)
4	59.33	65.28	67.57	61.30	60.60	64.07
	(-)	(12.96 ± 0.16)	(12.33 ± 0.19)	(13.45 + 0.18)	(13.28 ± 0.11)	(13.05 ± 0.16)
6	46.04	40.46	23.53	25.68	40.10	45.17
	(-)	(-)	(-)	(-)	(-)	(-)
8	59.70	75.38	60.56	27.33	63.97	69.03
	(-)	(12.31 ± 0.13)	(13.99 ± 0.16)	(-)	(13.25 ± 0.25)	(12.88 ± 0.14)
14	36.62	46.82	24.25	25.19	51.33	45.47
	(-)	(-)	(-)	(-)	(-)	(-)
15	65.07	68.27	58.26	65.40	50.27	71.40
	(13.11± 0.10)	(13.00 ± 0.25)	(-)	(13.00 ± 0.33)	(-)	(12.87 ± 0.18)
17	44.55	61.58	47.36	70.80	68.77	48.81
	(-)	(13.96 ± 0.12)	(-)	(12.89 ± 0.28)	(13.04 ± 0.16)	(-)
18	-	40.25	51.28	-14.68	23.13	-1.31
	(-)	(-)	(-)	(-)	(-)	(-)
Ciprofloxacin	96.13	94.14	97.13	91.16	96.48	98.01
	(8.36 ± 0.22)	(9.17 ± 0.14)	(8.69 ± 0.16)	(10.64 ± 0.18)	(8.13 ± 0.01)	(8.11 ± 0.16)

TABLE-2
ANTIOXIDANT PROPERTIES OF PYRAZOLYL PYRIDINES- DPPH ACTIVITY

Compd. No.	Conc./well (mM)	Inhibition (%)	IC_{50} (µmol)
3	0.5	16.67±0.39	Nil
4	0.5	15.64±0.87	Nil
5	0.5	8.95±0.55	Nil
6	0.5	63.80±0.60	377.70 ± 0.31
7	0.5	12.17±0.71	Nil
8	0.5	28.02±0.08	Nil
14	0.5	12.49±0.35	Nil
15	0.5	17.79±0.61	Nil
17	0.5	15.18±0.05	Nil
18	0.5	10.33±0.63	Nil
Quercetin (control)			16.96 ± 0.14

All samples are soluble in methanol

5. (a) A. Karamat, M.A. Khan and A. Sharif, *J. Chin. Chem. Soc.*, **57**, 1099 (2010); (b) M.N. Khan, M.A. Khan and M.A. Munawar, *Lat. Am. J. Pharm.*, **30**, 980 (2011); (c) M.S. doSantos, A.O. Gomes, A.M.R. Bernardino, M.C. deSousa, M.A. Khan, M.A deBrito, H.C. Castro, P.A. Abreu, C.R. Rodrigues, R.M.M. deLeo, L.L. Leon and M.M. Canto-Cavalheiro, *J. Braz. Chem. Soc.*, **22**, 352 (2011); (d) F. Ijaz, S. Noreen, M.N. Khan, S. Naureen, M.A. Khan, M.A. Munawar and A.M.R. Bernardino, *Asian J. Chem.*, **24**, 5114 (2012).
6. C. Limban, M.-C.B. Chifiriuc, A.-V. Missir, H.C. Chirita and C. Boleotu, *Molecules*, **13**, 567 (2008).
7. H.D. Revanasiddapa, K.S. Parsad, L.S. Kumar and B. Jayalakshmi, *Int. J. Chem. Tech. Res.*, **2**, 1344 (2010).
8. G. Szilagyi, E. Kasztreiner, L. Tardos, E. Kosa, L. Jaszlits, G. Cseli, H. Kovacs, P. Tolnay, S. Elek, I. Elekes and I. Polgari, US Patent, 4,224,325 (1980).
9. L.C. Behr, R. Fusco and C.R. Jarboe, The Chemistry of Heterocyclic Compounds, Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings, New York: Wiley, vol. 22 (1967).
10. M.A. Khan and A.C.C. Freitas, *Monatsh. Chem.*, **112**, 675 (1981).
11. M.A. Khan and J.B. Polya, *J. Chem. Soc.* (c), 85 (1970); M.A. Khan and A.A.A. Pinto, *Monatsh Chem.*, **111**, 883 (1980).
12. M.A. Khan and A.A.A. Pinto, *J. Heterocycl. Chem.*, **18**, 9 (1981).
13. I.L. Finar and G.H. Lord, *J. Chem. Soc.*, 1819 (1959).
14. M.A. Khan and J. Ribeiro, *Polish J. Chem.*, **61**, 569 (1987).