International Journal of ChemTech Research
CODEN (USA): IJCRGG ISSN: 0974-4290
Vol.7, No.5, pp 2506-2513, 2014-2015

Synthesis of Some Novel Pyridazine Derivatives of Expected Antitumor Activity

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Abstract: 5,6-Diphenyl-3-thioxo-2,3-dihydropyridazine-4-carbonitrile (**1**) reacted with Wittig-Horner reagents **2a-g** in presence of sodium alkoxide to afford new pyridazine derivatives with antitumor activity.
Keywords: Furo[3,2-c]pyradazines, Wittig-Horner reagents, Cinnolin-5-amine, Antitumor activity.

Introduction

Several functionalized pyridazines exhibit antibacterial, antibiotic, antitumor, antiviral and antidiabetic activities[1]. These compounds also find application as ligands in supramolecular chemistry and in metallic complexes which exhibit catalytic properties[2-4]. On the basis of these reports and in continuation of our work in organophosphorus chemistry[5-8]; we have now synthesized some novel pyridazine derivatives of expected biological activities. The existing strategy for obtaining the target compounds relied on applying a variety of Wittig-Horner reagents **2a-g** to 5,6-diphenyl-3-thioxo-2,3-dihydropyridazine-4-carbonitrile (**1**) in presence of sodium alkoxide solution (Fig 1).

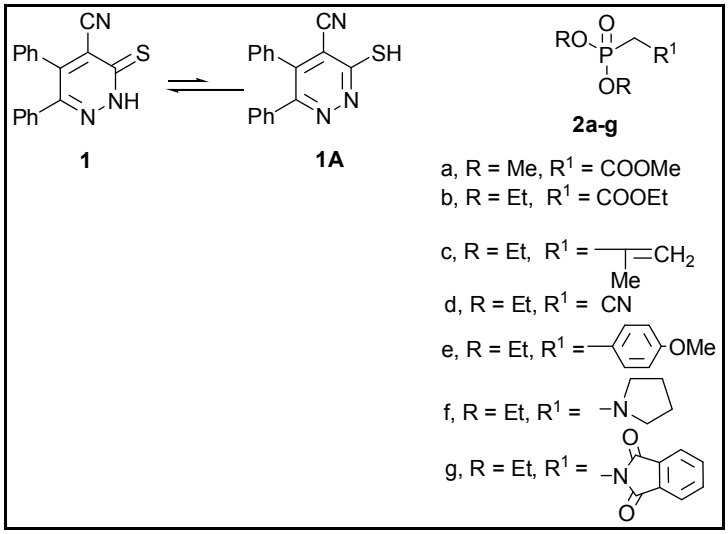


Fig 1: Starting materials (1, 2a-g)

Experimental Section

General:

Melting points were determined in open glass capillaries using Electrothermal IA 9000 series digital melting point apparatus (Electrothermal, Essex, UK) and are uncorrected. 5,6-Diphenyl-3-thioxo-2,3-dihydropyridazine-4-carbonitrile **1** was prepared in an 85% yield according to the literature [9]. The IR spectra were measured in KBr pellets with a Perkin-Elmer Infracord Spectrophotometer model 157(Grating). NMR spectra were obtained on JOEL-500 MHz Spectrometer (^{1}H NMR at 500 MHz, ^{13}C NMR at 125 Hz) in $CDCl_3$/ or DMSO-d_6 using TMS as internal standard. Chemical shifts (δ) were given in ppm and coupling constants (J) in Hz. The ^{31}P NMR spectra were taken with a Varian CFT-20 (vs. external 85% H_3PO_4 standard). The mass spectra were performed at 70eV on a Shimada GCS-OP 1000 Ex Spectrometer provided with a data system. Elemental analyses were performed using Elmenter Varu EL Germany Instrument. The reported yields are based upon pure materials isolated by column chromatography. Solvents were dried/purified according to conventional procedures.

General Procedure for the Reaction of 5,6-diphenyl-3-thioxo-2,3-dihydropyridazine-4-carbonitrile 1 with Wittig-Horner Reagents 2a-g in presence of sodium alkoxide

A solution of sodium alkoxide (1 mmol) in absolute alcohol (30 mL) was treated with an equimolar amount of the Wittig-Horner reagent **2a-g** (1 mmol) then 1 mmol of 5,6-diphenyl-3-thioxo-2,3-dihydropyridazine-4-carbonitrile (**1**) was added and the resulting reaction mixture was refluxed for 6 h (TLC), evaporated then poured onto a small amount of water (1-2 mL), extracted with ethyl acetate (3× 20 mL), dried over anhydrous sodium sulfate, filtered and the extracts were evaporated under reduced pressure. The residue was subjected to silica gel column chromatography to give the final products **3-8**. Product **5a** is separated from column chromatography in reactions of **1** with **2a** in 15% yield. Product **5b** is separated from column chromatography in reactions of **1** with **2b-g** in 25% yield.

6-Methoxy-3,4-diphenylfuro[3,2-*c*]pyridazine (3a)

Eluent: petroleum ether (60-80^{o}C)/acetone (95/5, *v/v*). Product **3a** was isolated as colorless crystals, yield 0.16g (35 %); mp 232-233 ^{o}C; IR: 3279 (NH), 2230 (CN), 1585 (C=N) cm^{-1} ; ^{1}H NMR ($CDCl_3$): δ = 3.98 (s, 3H, CH_3), 4.08 (s, 1H, CH), 7.09-7.34 (m, 10 H, $H_{arom.}$) ppm; ^{13}C NMR ($CDCl_3$): δ = 41.2 (CH_3), 77.9 (ring CH), 113.4 (C=N)128.3-151.2 (aromatic, C-H), 157.0 (cyclic =C-O-) ppm; MS (EI 70 eV): *m/z* (%) = 302 (5) $[M]^+$; Anal. Calcd. for $C_{19}H_{14}N_2O_2$ C, 75.48; H, 4.67; N, 9.27; found: C, 75.84; H, 3.98; N, 8.96 %.

6-Ethoxy-3,4-diphenylfuro[3,2-*c*]pyridazine (3b)

Eluent: petroleum ether (60-80^{o}C)/acetone (95/5, *v/v*). Product **3b** was isolated as orange crystals, yield 0.19g (35 %); mp 184-185 ^{o}C; IR: 1658 (C=N), 1610 (C=C) cm^{-1} ; ^{1}H NMR ($CDCl_3$): δ = 1.48 (t, 3H, CH_3), 4.35 (q, 2H, CH_2), 4.80 (s, 1H, ring CH), 7.10-7.35 (m, 10 H, $H_{arom.}$) ppm; ^{13}C NMR ($CDCl_3$): δ 14.4 (CH_3), 65.3 (CH_2), 81.3 (ring CH), 112.9 (cyclic C=N), 128.3-151.2 (aromatic, C-H), 157.0 (cyclic =C-O-) ppm; MS (EI 70 eV): *m/z* (%) = 302 (5) $[M]^+$; Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86; found: C, 75.33; H, 4.89; N, 8.44%.

Methyl 2-(4-cyano-5,6-diphenylpyridazin-3(2*H*)-ylidene)acetate (4a)

Eluent: petroleum ether (60-80^{o}C)/acetone (60/40, *v/v*). Product **4a** was isolated as yellow crystals, 0.11g (35 %); mp 171-172 ^{o}C; IR: 3375 (NH), 2361 (CN), 1690 (ester, C=O), 1641 (C-O, stretching), 1585 (C=N) cm^{-1} ; ^{1}H NMR ($CDCl_3$): δ = 3.98 (s, 3H, CH_3), 3.02 (s, 1H, NH, exchangeable with D_2O), 5.80 (s, 1H, cyclic CH), 7.05-7.25 (m, 10 H, $H_{arom.}$) ppm; ^{13}C NMR ($CDCl_3$): δ = 40.9 (CH_3), 99.7 (cyclic CH), 112.9 (C=N), 128.3-128.6 (aromatic, C-H), 154.0 (C=N), 164.6 (ester C=O) ppm; MS (EI 70 eV): *m/z* (%) = 329 (5) $[M]^+$, 315 (65) $[M-15]^+$; Anal. Calcd. for $C_{20}H_{15}N_3O_2$: C, 72.94; H, 4.59; N, 12.76; found: C, 73.03; H, 3.99; N, 12.67%.

Ethyl 2-(4-cyano-5,6-diphenylpyridazin-3(2*H*)-ylidene)acetate (4b)

Eluent: petroleum ether (60-80^{o}C)/acetone (60/40, *v/v*). Product **4b** was isolated as yellow crystals, 0.13g (35 %); mp 149-150 ^{o}C; IR: 3393 (NH), 2232 (CN), 1669 (ester, C=O), 1641 (C-O, stretching), 1553 (C=N) cm^{-1} ; ^{1}H NMR ($CDCl_3$): δ = 1.33 (t, 3H, CH_3), 4.20 (q, 2H, CH_2), 4.75 (s, 1H, cyclic CH), 7.09-7.37 (m,

10 H, $H_{arom.}$), 11.9 (s, 1H, NH, exchangeable with D_2O) ppm; ^{13}C NMR ($CDCl_3$): δ = 13.2 (CH_3), 60.2 (CH_2), 95.4 (cyclic CH), 113.9 (CN), 126.2-164.9 (aromatic, C-H), 166.3 (ester C=O) ppm; MS (EI 70 eV): *m/z* (%) = 343 (5) $[M]^+$, 298 (65) $[M-45]^+$; Anal. Calcd. for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24; found: C, 73.03; H, 5.09; N, 12.67%.

3-(Methylsulfanyl)-5,6-diphenylpyridazine-4-carbonitrile (5a)

Eluent: petroleum ether (60-80°C)/acetone (20/80, *v/v*). Product **5a** was isolated as colorless crystals, 0.08g (15 %); mp 215-217 °C; IR: 2230 (CN), 1658 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 3.95 (s, 3H, CH_3), 7.09-7.34 (m, 10 H, $H_{arom.}$) ppm; ^{13}C NMR ($CDCl_3$): δ = 41.2 (SCH_3), 113.4 (CN), 128.3-151.2 (aromatic, C-H) ppm; MS (EI 70 eV): *m/z* (%) = 303 (15) $[M]^+$; Calcd. for $C_{18}H_{13}N_3S$: C, 71.26; H, 4.32; N, 13.85; S, 10.57 found: C, 70.96; H, 4.23; N, 14.05; S, 10.50 %.

3-(Ethylsulfanyl)-5,6-diphenylpyridazine-4-carbonitrile (5b)

Eluent: petroleum ether (60-80°C)/acetone (20/80, *v/v*). Product **5b** was isolated as colorless crystals, 0.09 g (15 %); mp 168-170 °C; IR: 2230 (CN), 1658 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.32 (t, 3H, CH_3), 4.13 (q, 2H, CH_2), 7.12-7.61 (m, 10 H, $H_{arom.}$) ppm; ^{13}C NMR ($CDCl_3$): δ = 14.2 (CH_3), 31.1 (CH_2), 113.1 (CN), 128.2-152.3 (aromatic, C-H) ppm; MS (EI 70 eV): *m/z* (%) = 317 (25) $[M]^+$; Calcd. for $C_{19}H_{15}N_3S$: C, 71.90; H, 4.76; N, 13.24; S, 10.10; found: C, 71.96; H, 4.36; N, 14.05; S, 10.25 %.

6-Methyl-3,4-diphenyl-1*H*-cyclopenta[*c*]pyridazine (6)

Eluent: petroleum ether (60-80°C)/acetone (80/20, *v/v*). Product **6** was isolated as colorless crystals, 0.07g (15 %); mp 217-219 °C; IR: 3335 (NH), 1544 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.19 (s, 3H, CH_3), 3.46 (s, 1H, CH), 7.08-7.74 (m, 11 H, $H_{arom.}$, cyclic CH) ppm; ^{13}C NMR ($CDCl_3$): δ = 22.5 (CH_3), 106.4 (CH), 122.9 (CH), 126.4-150.9 (aromatic, C-H); MS (EI 70 eV): *m/z* (%) = 284 (35) $[M]^+$; Calcd. for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85; found: C, 84.65; H, 5.48; N, 10.03%.

2,3-Dihydro-3-(2-methylallylidene)-5,6-diphenylpyridazine-4-carbonitrile (7)

Eluent: petroleum ether (60-80°C)/acetone (65/35, *v/v*). Product **8** was isolated as yellow crystals, 0.12g (25 %); mp 190-192°C; IR: 3392 (NH), 2230 (CN), 1610 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.48 (t, 3H, CH_3), 3.50 (s, 1H, NH, exchangeable with D_2O), 4.36, 4.38 (d, 2H, CH_2), 5.77 (s, 1H, =CH), 7.06-7.25 (m, 10 H, $H_{arom.}$) ppm; ^{13}C NMR ($CDCl_3$): δ = 23.0 (CH_3), 103.3 (=CH), 111.2 (=CH_2), 115.6 (CN), 126.3-150.8 (aromatic, C-H) ppm; MS (EI 70 eV): *m/z* (%) = 311 (45) $[M]^+$; Calcd. for $C_{21}H_{17}N_3$: C, 81.00; H, 5.50; N, 13.49; found: C, 80.90; H, 5.25; N, 13.55 %.

3-(Cyanomethylene)-2,3-dihydro-5,6-diphenylpyridazine-4-carbonitrile (8a)

Eluent: petroleum ether (60-80°C)/acetone (75/25, *v/v*). Product **8a** was isolated as colorless crystals, 0.13g (30 %); mp 238-240 °C; IR: 3338 (NH), 2230 (CN), 1611 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 3.93 (s, 1H, CH), 4.07 (s, 1H, NH, exchangeable with D_2O), 7.08-7.41 (m, 10 H, $H_{arom.}$) ppm; ^{13}C NMR ($CDCl_3$): δ = 41.1 (=CH), 113.4 (CN), 128.3-157.0 (aromatic, C-H) ppm; MS (EI 70 eV): *m/z* (%) = 296 (20) $[M]^+$; Calcd. for $C_{19}H_{12}N_4$: C, 77.01; H, 4.08; N, 18.91; found: C, 76.96; H, 4.41; N, 18.56%.

3-(4-methoxybenzylidene)-2,3-dihydro-5,6-diphenylpyridazine-4-carbonitrile (8b)

Eluent: petroleum ether (60-80°C)/acetone (70/30, *v/v*). Product **8b** was isolated as yellow crystals, 0.19g (35 %); mp 166-168 °C; IR: 3334 (NH), 2230 (CN), 1611 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 3.33 (s, 3H, OCH_3), 5.10 (s, 1H, =CH), 7.01-7.74 (m, 10 H, $H_{arom.}$), 13.47 (s, 1H, NH, exchangeable with D_2O) ppm; ^{13}C NMR ($CDCl_3$): δ = 53.9 (CH_3), 107.2 (=CH), 113.4 (CN), 128.3-157.0 (aromatic, C-H) ppm; MS (EI 70 eV): *m/z* (%) = 377 (75) $[M]^+$; Calcd. for $C_{25}H_{19}N_3O$: C, 79.55; H, 5.07; N, 11.13; found: C, 80.05; H, 5.34; N, 11.23%.

2,3-Dihydro-5,6-diphenyl-3-((pyrrolidin-1-yl)methylene)pyridazine-4-carbonitrile (8c)

Eluent: petroleum ether (60-80°C)/acetone (50/50, *v/v*). Product **8c** was isolated as colorless crystals, 0.15g (30 %); mp 155-157 °C; IR: 3334 (NH), 2230 (CN), 1611 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.87, 1.95, 2.46 (M, 8H, pyrrolidine CH_2), 3.98 (s, 1H, =CH), 7.06-8.13 (m, 10 H, $H_{arom.}$), 13.46 (s, 1H, NH, exchangeable with D_2O) ppm; ^{13}C NMR ($CDCl_3$): δ = 22.6, 51.4 (CH_2), 112.3 (=CH), 113.4 (CN), 125.9-149.4 (aromatic, C-

H) ppm; MS (EI 70 eV): *m/z* (%) = 340 (25) $[M]^+$; Calcd. for $C_{22}H_{20}N_4$: C, 77.62; H, 5.92; N, 16.46; found: C, 77.26; H, 6.02; N, 16.33%.

2,3-Dihydro-3-((1,3-dioxoisoindolin-2-yl)methylene)-5,6-diphenylpyridazine-4-carbonitrile (8d)

Eluent: petroleum ether (60-80°C)/acetone (95/5, *v/v*). Product **8d** was isolated as colorless crystals, 0.2g (35 %); mp 250-252 °C; IR: 3421 (NH), 2229 (CN), 1659 (amide C=O), 1566 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 5.00 (s, 1H, =CH), 7.14-9.38 (m, 14 H, $H_{arom.}$), 13.59 (s, 1H, NH, exchangeable with D_2O) ppm; ^{13}C NMR ($CDCl_3$): δ = 96.3 (=CH), 113.4 (CN), 125.9-149.4 (aromatic, C-H), 165.2 amide C=O) ppm; MS (EI 70 eV): *m/z* (%) = 416 (55) $[M]^+$; Calcd. for $C_{26}H_{16}N_4O_2$: C, 74.99; H, 3.87; N, 13.45; found: C, 75.09; H, 3.73; N, 13.32; %.

Experimental of Cytotoxic and Biological Activity

Measurement of potential cytotoxicity by SRB assay:

The antitumor activities were carried out in Therapeutic Chemistry Department, National Research Centre. Potential cytotoxicity of the selected pyrrole derivatives was tested using the method of Skehan *et al*. [10] as follows:

Cells were plated in 96-multiwell plate (10^4cells/well) for 24h before treatment with the compound(s) to allow attachment of cells to the wall of the plate. Different concentrations of the compound under test (0, 1, 2.5, 5, 10 µg/ml) were added to the cell monolayer. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compound(s) for 48 h at 37°C and in an atmosphere of 5% CO_2. Cultures were then fixed with trichloroacetic acid and stained for 30 minutes with 0.4% (wt/vol) sulforhodamine B (SRB) dissolved in 1% acetic acid. Unbound dye was removed by four washes with 1% acetic acid, and protein-bound dye was extracted with 10 mM unbuffered Tris base [tris(hydroxymethyl) aminomethane] for determination of optical density in a computer-interfaced, 96-well microtiter plate reader. The SRB assay results were linear with the number of cells and with values for cellular protein measured by both the Lowry and Bradford assays at densities ranging from sparse subconfluence to multilayered supraconfluence. The signal-to-noise ratio at 564 nm was approximately 1.5 with 1,000 cells per well. The relation between surviving fraction and drug concentration is plotted to get the survival curve of both cancer cell lines after the specified compound.

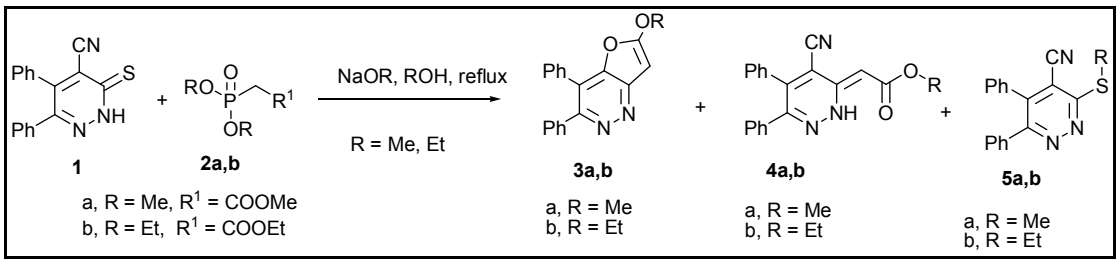
Results and Discussion

Chemistry

All of the synthesized compounds described below are new and they were characterized by their IR, MS, ^1H, ^{13}C NMR spectral data and their elemental analyses. Thus, 5,6-diphenyl-3-thioxo-2,3-dihydropyridazine-4-carbonitrile (1) reacted with two mole equivalents of methyl dimethylphosphonoacetate (2a) in presence of ethanolic sodium ethoxide solution at the reflux temperature to give a mixture of three products which were separated by column chromatography (Scheme 1). The first product (35%) was formulated as 6-methoxy-3,4-diphenylfuro[3,2-c]pyridazine (3a). Corrected elementary analyses and molecular weight determination (MS) corresponded to the molecular formula $C_{19}H_{14}N_2O_2$; MS: *m/z* 302, 5%. Its IR spectrum (KBr, cm^{-1}) revealed absence of absorption band around 3200 (NH), 2300 (CN) and 1275 (C=S) which were recorded in the IR spectrum of compound 1 at 3210 and 2213, respectively. The main characteristic feature in the ^1H NMR spectrum of 3a ($CDCl_3$, δ ppm) was the appearance of a sharp singlet (3H) for the OCH_3 group protons at δ_H = 3.98 ppm. The second product (30%) was formulated as methyl 2-(4-cyano-5,6-diphenylpyridazin-3(2H)-ylidene)acetate (4a) which recorded correct elementary analyses and molecular weight determination corresponding to $C_{20}H_{15}N_3O_2$; MS: *m/z* 329, 5%. Its IR spectrum (KBr, cm^{-1}) showed strong absorption bands at 3375 (NH), 2361 (CN), 1690 (ester, C=O), 1641 (C-O, stretching) and 1585 (C=N). Its ^1H NMR spectrum ($CDCl_3$, δ ppm) showed the NH proton as D_2O exchangeable singlet at 3.02 and the OCH_3 group protons also as singlet at 3.98 ppm. The main characteristic features of the ^{13}C NMR spectrum of 4a were presence of signals at 40.9 (OCH_3), 99.7 (cyclic CH), 112.9 (C=N) and 164.6 (C=O, ester). The third product (15%) was formulated as 3-(methylsulfanyl)-5,6-diphenylpyridazine-4-carbonitrile (5a) which recorded correct elementary analyses and molecular formula of $C_{18}H_{13}N_3S$; MS = *m/z* 303, $[M]^+$ 15%. Its IR spectrum (KBr, cm^{-1}) revealed the absence of absorption bands due to the NH and C=S groups while showing strong bands at 2230

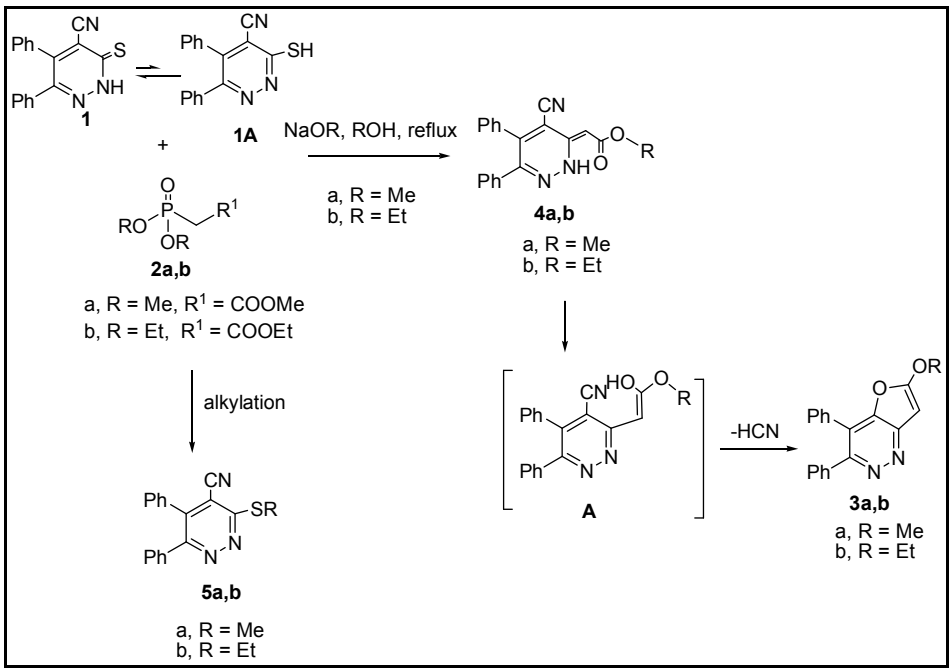
(CN) and 1658 (C=N). Its ^{1}H NMR spectrum ($CDCl_3$, δ ppm) showed a signal at 3.95 (3H, SCH_3) while the characteristic features of its ^{13}C NMR spectrum were presence of 41.2 (SCH_3), 113.4 (CN) (Scheme 1).

In the same sense, the reaction of compound 1 with ethyl diethyl phosphonoacetate (2b) in a 1:2 molar ratio yielded a mixture of compounds 3b, 4b, and 5b, respectively whose elementary and spectroscopic analyses were compatible with the assigned structures (*cf*. Experimental).



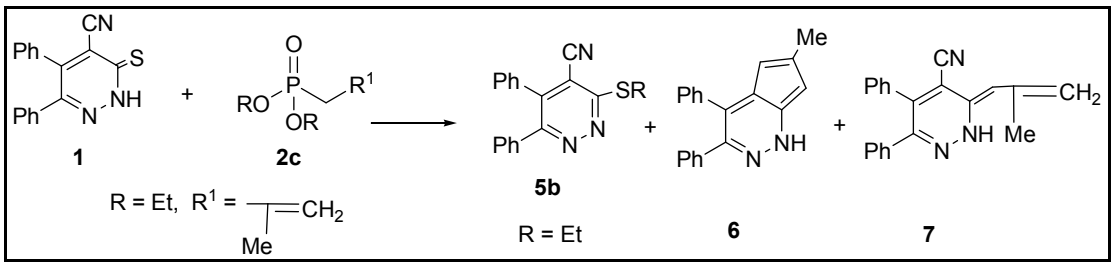
Scheme 1. Synthesis of the compounds 3a,b-5a,b

A possible explanation for the course of the reaction of 1 with 2a,b is shown in Scheme 2. 5,6-Diphenyl-3-thioxo-2,3-dihydropyridazine-4-carbonitrile (1) reacts with one mole of each of the anions of alkyl phosphonates 2a,b according to Wittig-Horner mechanism [11] to give the respective ethylene products 4a,b. Formation of 3a,b can takes place through intramolecular rearrangement of 4a,b followed by ejection of hydrogen cyanide molecule from the resulting transient intermediate A [12] (Scheme 2). The thionopyradizine 1 can also exist in the tautomeric thiol 1A which is readily alkylated by reagents 2 yielding form 5a,b. this supplements to the well known behavior of dialkyl phosphonates as alkylating agents [13].



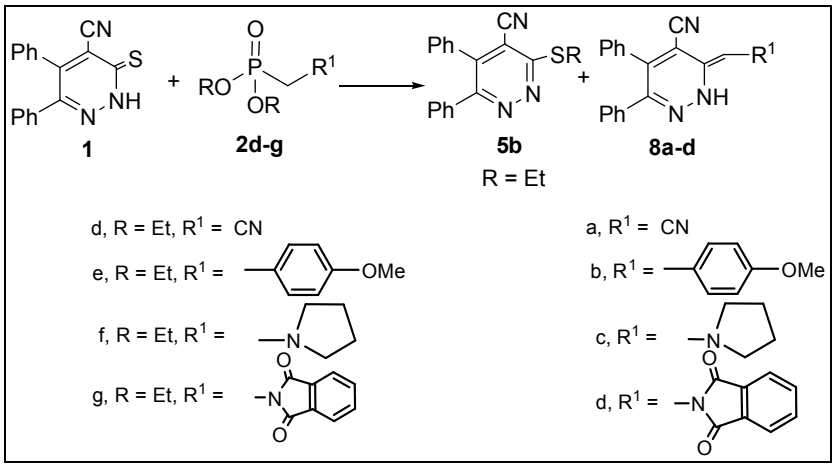
Scheme 2. Mechanism of formation of 3a,b - 5a,b

Next, the behavior of 1 towards phosphonyl carbanion, diethyl (2-methylprop-2-en-1-yl)phosphonate (2c) was studied. Thus, the reaction of 1 with 2c was carried out in ethanolic sodium ethoxide and the reaction mixture was refluxed for about 8h (TLC) to furnish 6-3-(ethylsulfanyl)-5,6-diphenylpyridazine-4-carbonitrile (5b) in a 25% yield and also, methyl-3,4-diphenyl-1*H*-cyclopenta[c]pyridazine (6), and 2,3-dihydro-3-(2-methylallylidene)-5,6-diphenylpyridazine-4-carbonitrile (7). The structure elucidation of compounds 5b, 6, 7 was confirmed on the basis of elemental analyses, IR, ^{1}H, ^{13}C NMR and mass spectral data (Scheme 3).



Scheme 3. Synthesis of the compounds 5b-7

In the same manner, 3-(cyanomethylene)-2,3-dihydro-5,6-diphenylpyridazine-4-carbonitrile (8a) was isolated together with 5b from the reaction of 1 with (diethylphospho)acetonitrile (2d) in 30% yield using the same reaction conditions (Scheme 4). The structure of compound 8a was confirmed on the basis of elemental analyses, IR, ^{1}H, ^{13}C NMR and mass spectral data (*cf.* Experimental). Also, diethyl (4-methylbenzyl) phosphonate (2e), diethyl(pyrrolidinomethyl)phosphonate (2f), and diethyl (1,3-dioxoisoindolin-2-yl)methyl phosphonate (2g) were reacted with 5,6-diphenyl-3-thioxo-2,3-dihydropyridazine-4-carbonitrile (1) in molar ratio in alcoholic sodium ethoxide solution at reflux temperature to afford 3-(4-methoxybenzylidene)-2,3-dihydro-5,6-diphenylpyridazine-4-carbonitrile (8b), 2,3-dihydro-5,6-diphenyl-3-((pyrrolidin-1-yl)methylene) pyridazine-4-carbonitrile (8c), 2,3-dihydro-3-((1,3-dioxoisoindolin-2-yl)methylene) -5,6-diphenylpyridazine-4-carbonitrile (8d) respectively, together with 3-(ethylsulfanyl)-5,6-diphenyl pyridazine-4-carbonitrile (5b) (Scheme 4). The structures of the new products 8b-d was elucidated according to the elemental analyses, IR, ^{1}H, ^{13}C NMR and mass spectral data (*cf.* Experimental).



Scheme 4. Synthesis of the compounds 5b and 8a-d

Cytotoxic and Biological Activity

Cytotoxic drugs remain the main stay of cancer chemotherapy and are being administered with novel ways of therapy such as inhibitors of signals [14]. It is therefore important to discover novel cytotoxic agents possessing a broader spectrum of antitumor activity and fewer toxic side effects than current agents. Moreover, chemotherapy is a major approach for both localized and metastasized cancers [15], and pyridazine derivatives have proved to have significant therapeutic potentials [1-4]. Based on these considerations, seven of the newly synthesized compounds 3a,b, 4b, 5b, 6, 7, and 8b were subjected to a screening system for evaluation of their *in vitro* antitumor activity against liver HEPG2 cancer cell lines in comparison to the known anticancer drugs: 5-Flurouracil (5-FU) and Doxorubicin (DOX) using SRB assay. The substances used are supposed to target mainly the cancer cells and doses are calculated to minimize the collateral damage to surrounding tissues, which nevertheless occurs [16]. This kind of treatment increases the entropy of the organism, suppresses the immune system, and forms a toxic cell environment which may destroy surrounding healthy cells [17]. So it is important to minimize curing doses to the least amount possible as well as trying to minimize the side effects of these drugs. Preliminary screening of the selected pyridazine derivatives showed that all selected compounds exhibited a moderate to strong growth inhibition activity on the tested cell line between 1-10 µg/ml concentrations in comparison to the known anticancer drugs: 5-Flurouracil and Doxorubicin. As shown in Table (1), compounds 3a and 4b were the most active and induced a reasonable growth inhibition, in a dose-dependent

manner against HEPG2 when compared to 5-FU and DOX (IC_{50} equals 3.92 and 5.23 µg/ml, while 5-FU and DOX were 5 and 3.56 µg/ml).

Table 1. Effect of some selected newly synthesized compounds on liver carcinoma cell line (HEPG2).

Compound	IC_{50} µg/ml
5-Flurouracil	5
Doxorubicin	3.56
3a	3.92
3b	7.11
4b	5.23
5b	9.38
6	6.53
7	9.33
8b	6.59

IC_{50}: dose of the compounds which reduces survival to 50%.

Conclusion

The results of the present investigation show that the reaction course of 5,6-diphenyl-3-thioxo-2,3-dihydropyridazine-4-carbonitrile (1) with Wittig-Horner reagents 2a-g differ from markedly from that of the respective phosphonium ylides [12]. Many of the new compounds revealed pronounced *in-vitro* antitumor activities when tested against liver carcinoma cell line (HEPG2). The most promising result against liver carcinoma cell line (HEPG2) was recorded by the 6-methoxy-3,4-diphenylfuro[3,2-*c*]pyridazine (3a). It showed IC_{50} value of (3.92 μg/mL) which is the closest in value to that recorded by the reference drug Doxorubicin (IC_{50}: 3.56μg/mL). Similarly, the cytotoxic and growth inhibitory activity of the same compound 3a (IC_{50}: 3.92 μg/mL) was very close to that of the 5-Flurouracil reference drug (IC_{50}: 5 μg/mL) against liver carcinoma cell line (HEPG2). Also, the cytotoxic and growth inhibitory activity effect of ethyl 2-(4-cyano-5,6-diphenylpyridazin-3(2*H*)-ylidene)acetate (4b) showed IC_{50} value of (5.23μg/mL) on liver carcinoma cell line (HEPG2).

Acknowledgment

The authors are grateful to Professor Abdel-Mohsen M. Soliman**,** Therapeutic Chemistry Department, National Research Centre, El-Buhouth St., P.O. 12622, Dokki, Giza, Egypt for antitumor evaluation.

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