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Some Conventional and Convenient Process for Functionalization of 6-Phenyl-4,5-Dihydropyridazinone Compounds

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Abstract

The pyridazinone derivatives, particularly those bearing substituted different group or atom at a different position, have attracted considerable attention due to their characteristic pharmacological and other anticipated activities. These activities promoted the synthesis of a large number of substituted pyridazinone derivatives in order to explore the usefulness of this heterocyclic system. In the present review, various synthetic methods have been studied for the synthesis of substituted pyridazinone derivatives. The behaviour of the pyridazinone toward formaldehyde/piperidine, ethyl chloroacetate, chloroacetic acid, benzene sulfonyl chloride, bromine/acetic acid and aromatic aldehydes has also been studied. However, the reactions of the chloro derivative resulting from the reaction of pyridazinone with phosphorus oxychloride ($POCl_3$). The behavior of chloropyridazine toward hydrazines, thiourea, sodium azide, anthranilic acid, aromatic amines and sulfa compounds have also been taken into consideration. Thethiopyridazinone derivativeswere prepared from the reaction of pyridazinone with phosphorus pentasulphide (P_2S_5). All the structures of were established on the based of spectroscopic data.

Keywords: Biologically Active, Pyridazinone, Substitution Reaction, Synthetic Methods

1. Introduction

Nitrogen-containing heterocyclic plays an important role, not only for health science, but also in many other industrial fields related to special and fine chemistry. The interesting pharmacological activity displayed by pyridazine derivatives has been demonstrated in recent years not only by the growing number of papers and patents describing them, but also by the development of several pyridazine-based drugs and other pharmacological tools[1–3]. Pyridazines are important biologically active scaffolds, possessing antihypertensive and antiplatelets[4,5], cardiotonic[6–8], analgesic, antipyretics, anti-inflammatory[9–12], central nervous system disorders[13], antibacterial antifeedant, and herbicidal[14–16], anticancer and anti-HIV[17–19],and other anticipated activities, in particular, intermediates for drugs and agrochemicals[20]. Pyridazines further drew our attention because of their easy functionalization at various ring positions of pyridazine ring, which makes them attractive synthetic building blocks for designing and development of novel pyridazine based pharmacotherapeutic agents. The discovery of biological activity in a series of pyridazine derivatives stimulated the vigorous growth of investigations in this area.

2. Chemistry of Pyridazine

Pyridazine is heterocyclic 1,2-diazine, formally derived from benzene by the replacement of two of the ring carbon atoms by nitrogen atoms. In pyridazine (Fig.1a and 1b), two nitrogen atoms are presented adjacent to each other (Fig. 1). Pyridazine is assumed to be a planar six member ring structure and is represented as a resonance hybrid of two structures (Fig. 1a) and (Fig. 1b) with a greater contribution from the canonical structure (Fig. 1a). The 3-oxy derivatives of pyridazine are called pyridazinone. Pyridazinone compounds showed tautomeric structures (Fig. 2a) and (Fig. 2b)[21].

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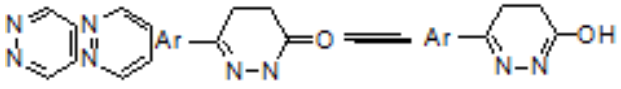


(1a) (1b) (2a) (2b)

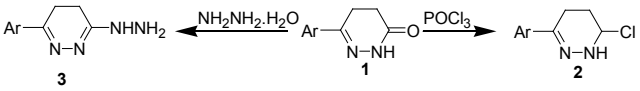
Figure 1. Resonance structure of pyrdaizine (1a and 1b) and tautomeric structure of aryl pyridazinone (2a and 2b).

3. Synthesis of Various 6-Arylsubstituted Pyridazinone Derivatives

Recently, a series of pyridazines have been studied, in the ongoing research program, these compounds will be subjected to further synthesis of newer pyridazinone compounds for pharmacological investigations. This study aimed at utilizing pyridazinone for the synthesis of substituted-arylpyridazinone derivatives for interesting biological activities by prompting us to synthesize a new substituted aryl pyridazinones. The compounds were characterized on the basis of spectral data (IR, 1H-NMR, mass and elemental analysis). Spectral data of the synthesized compoundswere in full agreement with the proposed structure[22–24].

4. Synthesis of Various 6-Aryl-Pyridazinone Derivatives

4.1 Synthesis of 4,5-Dihydro-6-Phenyl-3(2H)-Pyridazinone(1)



To a solution of phenyl-4-oxobutanoic acid (0.01mol) in 20 ml ethanol, 1 ml of (80%) hydrazine hydrate was added. The reaction mixture was heated under reflux for 3 h. The solid product obtained after cooling was filtered off and crystallized from ethanol to give a compound 1 as a white crystals[25].

4.2 Synthesis of 3-Chloro-6-Aryl-4,5-Dihydropyridazine (2)

A mixture of 6-aryl-4,5-tetrahydropyridazin-3(2H)-one (0.01 mol) and phosphorous oxychloride ($POCl_3$) (20 mL) or PCl_5, was heated on a steam bath for 6 h. After heating, the mixture was carefully poured on crushed ice and rendered alkaline by the addition of sodium bicarbonate (Na_2CO_3). Crude compound 2 was collected by filtration and re-crystallized with appropriate solvent[26].

4.3 Synthesis of 3-Hydrazino-6-Arylpyridazine or 6-Phenyl-Pyridazin-3-yl-Hydrazine(3)

The ethanolic solution of compound **2** (0.01 mol), hydrazine hydrate (99%,10 mL), was added and the resulting reaction mixture was refluxed on a steam bath for 16 h. The mixture was concentrated, cooled and poured into crushed ice. The resulting solid compound **3**was separated out and filtered, washed with water, dried and re-crystallized from ethanol[26].

4.4 Synthesis of 6-Aryl-4,5-Dihydropyridazin-3(2H)Thione(4)

Compound 1 (0.1 mol) dissolved in xylene was refluxing with phosphorus pentasulphide(P_2S_5) (0.1 mol) for 4 h at a temperature of 150°C. The contents were concentrated to a smaller volume, then crystals were obtained and collected, crystallized from ethanol and dried[27] or a solution of compound 1(0.01 mol), P_2S_5 (0.03 mol) in dry xylene (50 mL) was boiled under reflux for 6 h. The reaction mixture was filtered while hot and the filtrate concentrated. The product 4 which separated on cooling was filtered off and recrystallized[26].

4.5 Synthesis of 3-Imino-6-Arylpyridazine (5)

A mixture of compound 1 (0.04 mol) and ammonium acetate (12.3 g, 0.20 mol) was heated in an oil bath at 180°C for 4 h. Then the reaction mixture was poured into water and the solid separated was filtered and crystallized from ethanol[26].

4.6 Synthesis of 2-Hydroxy-Methyl-6-Aryl-4,5-Dihydropyridazin-3(2*H*)-one (6)

To a solution of compound 1 (0.001 mol) in methanol (30 mL) was added formaldehyde (37–41% aqueous solution) (2.5 mL) and the mixture was refluxed for 6 h. After completion of the reaction, methanol was distilled off and the residue was poured into the crushed ice to separate out compound 6. The solid which separated was

filtered and crystallized from methanol[28], or a solution of compound 1(0.01 mol) in methanol (20 ml) was treated with formaldehyde (0.1 mol), and the reaction mixture was refluxed for 6 h. The colourless solid which precipitated after cooling, filtered off, dried and crystallized from a suitable solvent to afford compound 6, oramixture of compound**1**(0.01 mol), aqueous formaldehyde (10 ml, 35%) and 20 ml waterwere refluxed for 4h. The solid product obtained after cooling was filtered off and crystallized from ethanol to give 6 as white crystals.

4.7 Synthesis of 6-Aryl-2-Methyl Pyridazin-3(2*H*)-one (7)

The compound 1(1.2 g, 5 mmol) under solvent free condition was added potassium carbonate (0.692 g, 5 mmol), TBAB (0.3 g, 1 mmol) and methyl iodide (0.73 g, 5 mmol). The mixture was introduced into a microwave monomode reactor, fitted with a rotational system. At the end of the irradiation time (10 min, 90 W irradiation power), the mixture was cooled to ambient temperature. The precipitate formed was filtered and washed with water to give compound **7**[29].

4.8 Synthesis of 6-Phenyl-Pyridazin-3-yl-Methylamine (8)

The aliphatic or aromatic amine (1 mmol) was added to a mixture of 1 (1 mmol) in dry benzene (5 mL) and the reaction mixture was heated in an oil bath for 6 h. The solid that separated on cooling was recrystallized from benzene to give compounds 8**,** or Methylamine (1 mmol) was added to a mixture of compound 1(1 mmol) and the reaction mixture was heated for 4 h on an oil-bath at 140 ˚C then cooled and triturated with methanol. The solid that separated was recrystallized from methanol to give 8 as white crystals[22].

4.9 Synthesis of 4-Arylidene-6-Aryl-4,5-Dihydro-Pyridazin-3(*2H*)-one (9)

Appropriate aliphatic or aromatic aldehyde(1 mmol) was added to a mixture of compound 1 (1 mmol), NaOH (10%) in ethanol (5 mL) and the reaction mixture was refluxed for 6 h. The solid that separated on cooling was re-crystallized from benzene to give a compound 9, orcondensation of compound 1 with appropriate aldehydeby a solution of sodium ethoxide (prepared from 0.23 g sodium and 30 ml absolute ethanol), compound 1 (0.01 mol) was added. The appropriate aldehyde (0.01 mol), was added with stirring. The reaction mixture was kept overnight the solid product obtained was filtered off and crystallized from the proper solvent, orcondensation of compound 1(0.01 mol)with appropriate aldehyde (0.01 mol) in glacial acetic acid (20 ml) and add sodium acetate (2 g.) was refluxed for 6-8 h (monitored by TLC) and cooled and poured onto ice. The solid compound was obtained and then recrystallized with ethanol, a mixture of the compound 1 (0.75 g, 0.0018 mol) and aromatic aldehydes (0.0019 mol) in ethanol (20 ml) was treated with 4% ethanolic sodium hydroxide solution (20 ml) and the whole mixture was refluxed for 3 h. The solid product which formed after cooling and acidification was filtered off and crystallized from a suitable solvent to furnish[13,30].

4.10 Synthesis of 4-Benzylamino-2-Cyanoethyl-4,5-Dihydropyridazin-3-one (10)

A mixture of compound 1(0.58 g, 0.0014 mol) and acrylonitrile (0.08 g, 0.0015 mol) in ethanol (25 ml) was treated with a few drops of 10% NaOH solution and the mixture was heated under reflux for 4 h. The colourless solid which formed after concentration and cooling were crystallized from a proper solvent to furnish 10[22].

4.11 Synthesis of 2-(Amino-1-yl-Methyl)-6-Aryl-4,5-Dihydropyridazin-3(2*H*)-one (11)

A mixture of compound 1(0.001 mol), formaldehyde (0.02 mol) and secondary amines (0.002 mol) in ethanol (30 ml) was left overnight at room temperature and then heated under reflux for 3 h. The solid which formed after evaporation of most of the solvent was crystallized from a suitable solvent to obtain the compound 11, or The aliphatic or aromatic amine (1 mmol) was added to a mixture of compound 2(1 mmol) in dry benzene (5 mL) and the reaction mixture was heated in oil bath for 6 h. The solid that separated on cooling was recrystallized from benzene to give compound11, or a mixture of compound 1 (0.01mol), amine (0.02 mol), formaldehyde (2.5 ml) and methanol (50 ml) was refluxed for 5 h, then kept overnight at room temperature, then treated with H_2O and the precipitated solid filtered and crystallized from ethanol to give compound 11 by Mannich reaction, oramixture of compound **6**(0.5 g, 0.001 mol) and secondary amines

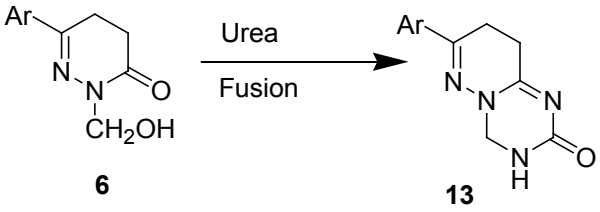
(0.1 g, 0.0012 mol) in ethanol (25 ml) was heated under reflux for 3 h. The solid that separated after concentration and cooling was crystallized from a proper solvent to yield a compound 11**,** or a mixture of compound **1**(0.75 g, 0.0018 mol), formaldehyde (0.81 g, 0.027 mol) and secondary amines (0.17 g, 0.002 mol) in ethanol (30 ml) was left overnight at room temperature and then heated under reflux for 3 h. The solid which formed after removal of most of the solvent was crystallized from a suitable solvent to afford compound 11 as colourless crystal[22,31].

4.12 Synthesis of 5-Bromo-6-Phenyl-3(2H)-Pyridazinone (12)

A stirred solution of compound 1(0.01 mol) in glacial acetic acid (20 mL) was treated dropwise with bromine (0.02 mol) at 60-70˚C. The solution was further stirred for 2 hand then cooled in ice. The precipitated product was filtered off, washed with petroleum ether (40-60˚C) and stirred with concentrated ammonium hydroxide for 50 min. The resulting solid product was filtered off and recrystallized to give 12**,** or a solution of compound 1 (0.01 mol) in glacial acetic acid (10ml) and bromine (0.01 mol) was stored at room temperature for 3 h. The solid product obtained was filtered off, washed with petroleum ether (40-60˚C) and recrystallized from ethanol give compound 12.

4.13 Pyridazino[1,6-a]-1,3,5-Triazin-2-one (13)

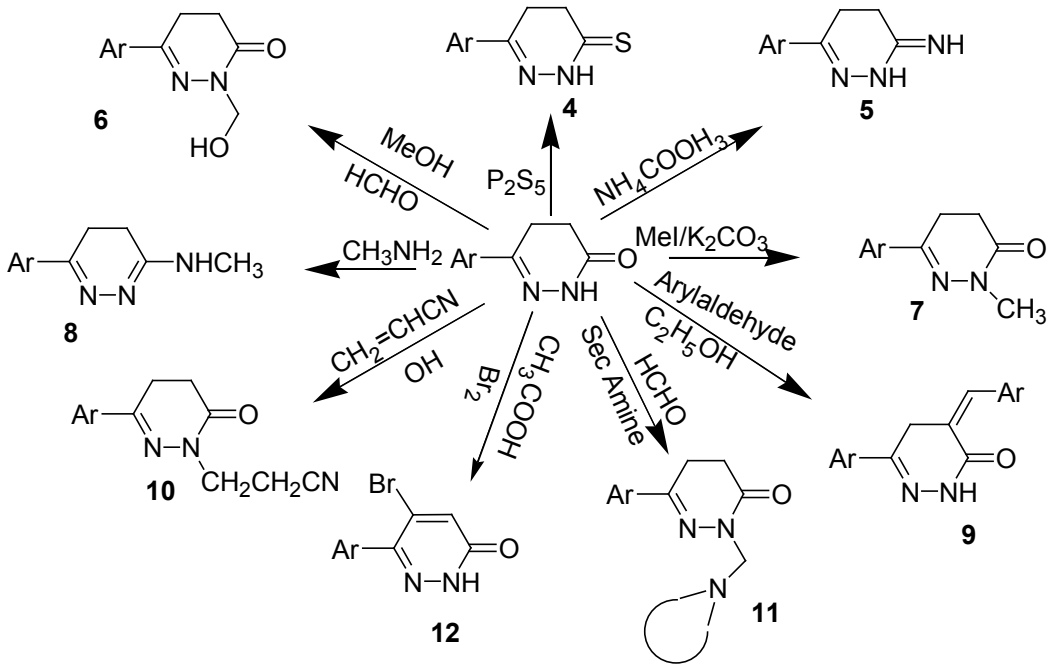
A mixture of compound 6(0.54 g, 0.0012 mol) and urea (0.09 g, 0.0015 mol) was heated in an oilbath at 180 ˚C for 3 h, cooled and triturated with ethanol. The solid obtained was crystallized from a suitable solvent to give compound 13.



6 13

4.14 Synthesis of 6-Phenyl-[1,2,3,4]-Tetrazolo [1,5-b] Pyridazine (14)

A mixture of compound **2** (1 g), sodium azide (2 g), water (5 mL) and dimethylformamide (20 mL) was refluxed for 2 h. The solid obtained upon dilution with water was filtered off and recrystallized to give a compound 14, or a mixture of compound **2**(0.52 g, 0.0012 mol) and sodium azide(NaN_3) (0.1 g, 0.0015 mol) in DMF (25 ml) was refluxed for 6 h. The reaction mixture was evaporated to dryness *in vacuo* and the residue was recrystallized from a proper solvent to give a compound 14.



4.15 Synthesis of 6-Phenyl-3-Hydrazinopyridazines (15)

To a solution of compound 2(0.01 mol) in absolute ethanol (50 mL), hydrazine derivatives (0.01 mol) was added and the reaction mixture was refluxed for 3 h. The solid that separated on cooling was recrystallized to give compound15[32].

4.16 6-Phenyl-4,5-Dihydropyridazin3(2H)-Thione (16)

To a solution of compound 2(0.01 mol) in absolute ethanol (50 ml) and an equimolar amount of thiourea was added and the reaction mixture was refluxed for 4-10 h. (determined by TLC). The crude material obtained after concentration and cooling were filtered off and recrystallized from the suitable solvent to give a compound 16**,** thiourea (0.01 mol) was added to a solution of compound 1 (0.01 mol) in butanol (50 mL), and the reaction mixture refluxed for 5 h. The solid that separated on cooling was washed with water and recrystallized to give 16[22,33].

4.17 Synthesis of 3-(4-Hydroxy-3-Iminnophenol)-6-Phenylpyridazinone Derivative (17)

To a solution of compound 2(0.01 mol) in absolute ethanol (50 ml) and equimolar amount of para-aminophenol was added and the reaction mixture was refluxed for 4-10 h. The crude material of compound 17 was obtained after concentration and cooling were filtered off and recrystallized from the suitable solvent to give compound 17.

4.18 Synthesis of 6-Phenyl-N-Pyridin-2-yl-Pyridazin-3-Amineor3-Iminnopyridine-6-Phenylpyridazinone Derivative (18)

To a solution of compound 2(0.01 mol) in absolute ethanol (50 ml) and equimolar amount of aminopyridine was added and the reaction mixture was refluxed for 4-10 h. The crude material 18 was obtained after concentration and cooling were filtered off and recrystallized from the suitable solvent to give compound 18.

4.19 Synthesis of 6-Phenyl-N-(Benzenesulfonyl-2-Amino-Pyrimidine)-Pyridazin-3-Amine (19)

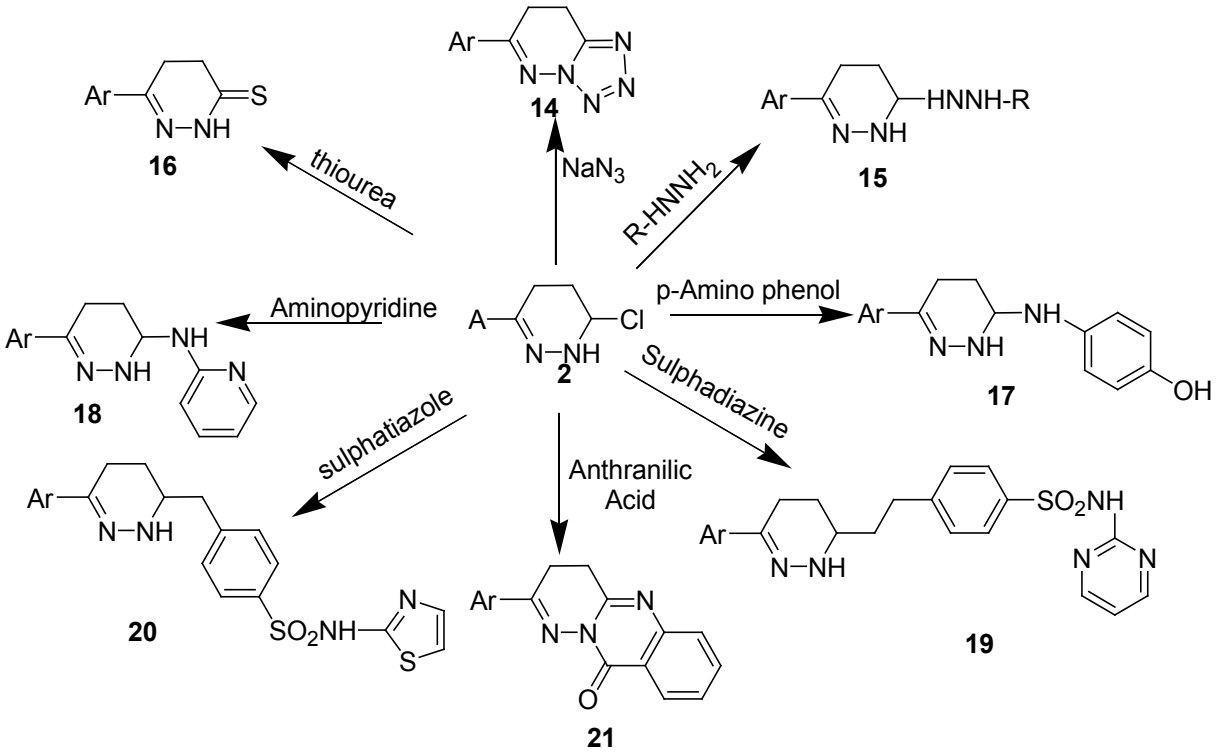
To a solution of compound 2(0.01 mol) in absolute ethanol (50 ml) and equimolar amount of sulphadiazine was added and the reaction mixture was refluxed for 4-10 h. The crude material 19 was obtained after concentration and cooling was filtered off and recrystallized from the suitable solvent to give compound 19.

4.20 Synthesis of 6-Phenyl-N-(Benzenesulfonyl-2-Aminothiazol)-Pyridazin-3-Amine (20)

To a solution of compound 2(0.01 mol) in absolute ethanol (50 ml) and equimolar amount of sulphathiazole was added and the reaction mixture was refluxed for 4-10 h. The crude material 20 was obtained after concentration and cooling was filtered off and recrystallized from the suitable solvent to give compound 20.

4.21 Synthesis of Pyridazino[3,2-b] quinazolinone or 2-Phenyl-10H-Pyridazino (6,1-b)quinazolin-10-one or 2-(4-Methoxy-3-Methylphenyl)-10-oxo-Pyridazino[3,2-b]quinazoline (21)

The compound 2 was reacted with an anthranilic acid, in DMF affording pyridazino[3,2-b]quinazolinone. A mixture of compound **2**(0.01 mol) and anthranilic acid (0.012 mol) was heated in an oil bath at 150˚C for 3 h, cooled and triturated with ethanol. The solid obtained was filtered off and recrystallized to give acompound 21 (60 % yield), or a mixture of the compound **2** (1 mmol) and anthranilic acid (2 mmol) was heated in an oil bath for 4 h, the solid product was collected and crystallized from ethanol to give a compound 21 as colourless crystal[22].



4.22 Synthesis of 2-[Dialkylaminomethyl]-4,5-Dihydro-6-Phenyl-3(2H)-Pyridazinone (22)

An aqueous solution of formaldehyde(3 ml, 35%) was added to a mixture of compound **1**(0.01 mol) and the appropriate secondary amine (0.02 mol) in ethanol, the reaction mixture was kept overnight at room temperature. The solid product obtained after dilution with water was filtered off and crystallized from the proper solvent to give compound 22.

4.23 Synthesis of 3-Benzylamino-6-Phenyl-Pyridazine (23)

A mixture of the compound 2 (1 mmol) and benzylamine (2 mmol) was heated inan oil bath for 6 h and the residue was triturated with diethyl ether, followed by crystallization from ethanol to give 23 as a buff powder.

4.24 Synthesis of 3-*o*-Carboethoxymethyl-4,5-Dihydropyridazine(24)

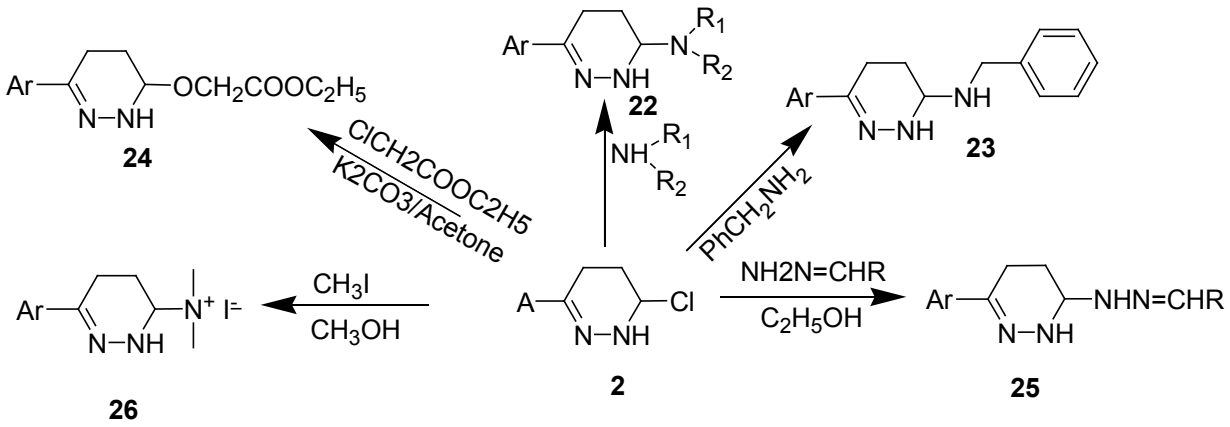
A mixture of compound 2 (1.8 g, 0.004 mol), anhydrous K_2CO_3 (2.20 g, 0.016 mol), ethyl chloroacetate (1.96 g, 0.016 mol) and dry acetone (50 ml) was refluxed for 35 h. The excess acetone was removed by distillation and the reaction mixture then poured into water and the content was extracted with ether. After evaporation of the dried ethereal solution, the solid that separated was crystallized from a suitable solvent to afford the corresponding ester 24.

4.25 Synthesis of5-[6-Phenyl-Pyridazin-3-yl]hydrazono-pentane-1,2,3,4,-tetraol (25a), 6-[6- Phenyl-pyridazin-3-yl]-hydrazono-hexane-1,2,3,4,5-pentaol (25b) and 6-[6-Phenyl-pyridazin-3-yl] hydrazono-hexane-1,2,3,4,5-pentaol (25c)

The appropriate carbohydrate hydrazone (1 mmol) was added to a mixture of compound 2 (1 mmol) in ethanol (5 mL) and the reaction mixture was refluxed for 6 h. The solid that separated on cooling was recrystallized from ethanol to give compounds **2**5a, 25b, and 25c respectively.

4.26 Synthesis of 6-Phenyl-Pyridazin-3-yl-Trimethylammonium Iodide(26)

Excess methyl iodide (5 mL) was added to a mixture



of compound **2** (1 mmol) in methanol (10 mL) and the reaction mixture was refluxed for 8 h. After evaporation of all the solvent, the solid residue was recrystallized from methanol to give 26 as white crystals.

4.27 Synthesis of 3-[1N-(3-Methylpyrazolin-5-one)]-4,5-Dihydropyridazine (27)

A mixture of compound 3(0.52 g, 0.0012 mol) and ethyl acetoacetate (0.2 g, 0.0015 mol) in ethanol (25 ml) was refluxed for 6 h. The solid that separated, after concentration and cooling, the compound was crystallized from a suitable solvent to give compound 27.

4.28 Synthesis of1,2,4-Triazolo[4,3-b]-7,8-Dihydropyridazine(28)

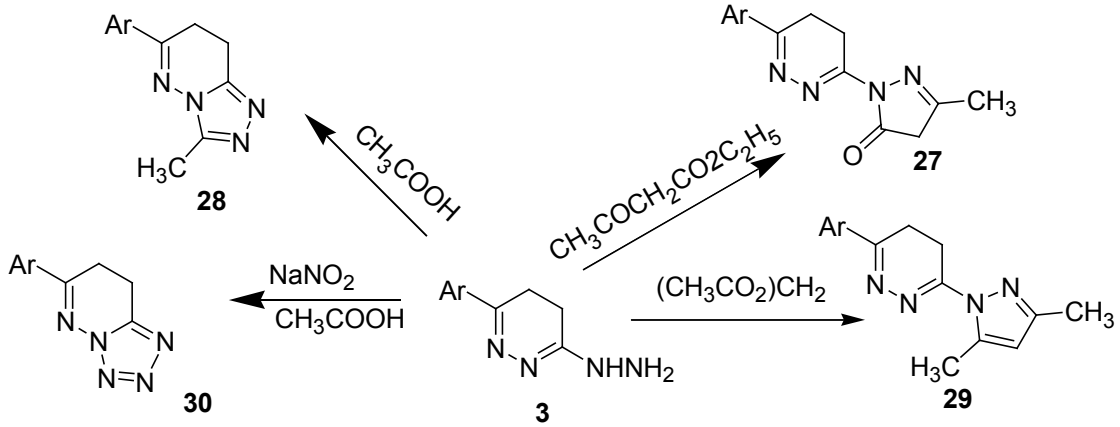
The compound **3**(0.52 g, 0.0012 mol) in acetic acid (25 ml) was heated under reflux for 8 h. The solid separated after concentration and cooling were crystallized from a proper solvent to give compound 28.

4.29 Synthesis of3-Phenyl-6-(3,5-Dimethylpyrazol-1-yl)Pyridazine(29)

Acetylacetone (1 mmol) was added to a mixture of compound 3 (1 mmol) in methanol (10 mL) and the reaction mixture was refluxed for 5 h. The solid that separated after cooling was recrystallized from methanol to give 29 as yellow crystals.

4.30 Synthesis of1,2,3,4-Tetrazolo[1,5-b]-7,8-Dihydropyridazine(30)

To a solution of compound **3**(0.52 g, 0.0012 mol) dissolved in 10% aq. HCl (10 ml) was added a solution of sodium nitrite (0.1 g, 0.0014 mol) dissolved in water (2 ml) dropwise under cooling and the mixture was allowed to stand for 45 min. The mixture was basified with solid $NaHCO_3$, extracted into $CHCl_3$ and the organic layer was dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was crystallized from a proper solvent to give 30.



4.31 Some Other Common Reaction of Pyridazinone Derivatives: Synthesis of 6-Phenyl-2-Methyl-4,5-Dihydro-3(2H)-Pyridazinone (31)

A mixture of compound 1 (0.01 mol), anhydrous potassium carbonate (0.03 mol), chloroacetic acid (0.03 mol) and dry acetone (50 ml) was refluxed for 24 h. After filtration while hot and removing the excess solvent, the product was recrystallized from ethanol to give compound 31.

4.32 Synthesis of 6-Phenyl-2-Benzenesulfonyl-4,5-Dihydro-2H-Pyridazin-3-one(32a) and 6-Phenyl-2-Phenyl-Sulfonyl-4,5-1H-(3H) Pyridine(32b)

Benzenesulfonyl chloride (1 mmol) was added to a mixture of compound 1 (1 mmol), anhydrous K_2CO_3 (1 mmol) in dry acetone (5 mL) and the reaction mixture was refluxed for 24 h. The solid that separated on cooling was recrystallized from benzene to give 32a as a white solid and a mixture of compound 1(0.01mol), anhydrous potassium carbonate (0.03 mol), benzenesulfonyl chloride (0.03 mol) and dry acetone (50 ml) was refluxed for 24 h. After filtration while hot and removing the excess solvent, the product was recrystallized from ethanol to give compound 32b.

4.33 Synthesis of Ethyl-2-(5,6-Dihydro-3-Phenyl-6-oxo-5-Pyridazin-1(4H-yl)-Acetate (33)

A mixture of compounds 1 (0.01 mol), anhydrous potassium carbonate (0.03 mol), ethyl chloroacetate (0.03 mol) and dry acetone (50 ml) was refluxed for 24 h. After filtration while hot and removing the excess solvent, the product was recrystallized from ethanol to give compound 33.

4.34 Synthesis of N-(6-Phenyl-4,5-Dihydro-3(2H)-Pyridazin-3-yl)-Hydroxy Amine (34)

To a solution of compound 2 (0.01 mol) in absolute ethanol (50 ml) and equimolar amount of hydroxylamines hydrochloridewas added and the reaction mixture was refluxed for 4-10 h. The crude material obtained after concentration and cooling were filtered off and recrystallized from the suitable solvent to give compounds 34[22].

4.35 Synthesis of 4,5-Dihydro-6-Phenyl-4-[3-oxo-1,3-Diphenylpropyl]-3(2H)-Pyridazinone (35)

To a solution of compound 1 (0.01) and potassium ethoxide (0.01 mol) in absolute ethanol (30 mL), 1,3-diphenyl propanone (0.01 mol) was added. The reaction mixture was heated under reflux for 4 h then left overnight at room temperature. The reaction mixture was acidified with dilute HCl. The solid product obtained was filtered off, washed with H_2O and crystallized from ethanol to give compound 35.

4.36 Synthesis of Acectic acid-N′-(6-Phenyl-3(2*H*)-4,5-Dihydropyridazin-3-yl)-Hydrazine (36)

A mixture of compound 2(0.52 g, 0.0012 mol) and acetyl-hydrazine (0.09 g, 0.0012 mol) in *n*-butanol (30 ml) was heated under reflux for 48 h. The solid product that separated after concentration and cooling was crystallized from a proper solvent to yield a compound 36.

4.37 Synthesis of 6-Phenyl-3-(Ethylsulfanyl) Pyridazine (37a) and 6-Phenyl-3-(Benzylsulfanyl) Pyridazine (37b)

A mixture of compound 1 (0.01 mol), anhydrous potassium carbonate (0.03 mol), diethyl sulfate or benzyl chloride (0.03 mol) and dry acetone (100 mL) was refluxed for 40 h. After filtration while hot and removing the excess solvent, the product was recrystallized to give 37a and 37b respectively.

4.38 Synthesis of 7-Phenyl-2,3-Dimethyl-4H-Thieno-[2',3':4,5] Pyrimido-[1,2-b]-Pyridazin-4-one (38a) and 2-Phenyl-7,8,9,10-Tetrahydro-11H-[1]-Benzothieno-[2',3':4,5]-Pyrimido-[1,2-b]-Pyridazin-11-one (38b)

To a solution of compound 2 (0.01 mol) in absolute ethanol (50 mL), 2-amino-3-carbethoxy-4,5-dimethylthiophene

or 2-amino-3-carbethoxytetrahydrobenzothiophene (0.01 mol) were added and the reaction mixture was refluxed for 5 h. The solids that separated on cooling were recrystallized to give compound 38a and 38b respectively.

4.39 Synthesis of 4-Benzylamino-3-o-(pht- or tos-amino acid)-4,5-Dihydropyridazine Derivatives(39a and 39b)

An *N*-phthalyl or *N*-tosylamino acids**,** namely, glycine and DL-alanine (0.001 mol) and compound**2** (0.5 g,0.001 mol) were dissolved in tetrahydrofuran (50 ml). The reaction mixture was cooled to 0 ˚C, then dicyclohexylcarbodiimide (0.021 g) was added and the mixture stirred for 2 h at 0 ˚C, left for 24 h at 0 ˚C and for another 24 h at room temperature. The dicyclohexylurea was filtered off, the filtrate evaporated *in vacuo* and the residue recrystallized from a suitable solvent to furnish compound 39a and 39b respectively.

The reaction of 6-aryl-4,5-dihydropyridazinone (1) with formaldehyde and secondary amines under goes Mannich reaction and/or ethylchloro acetate, benzenesulfonyl chloride in boiling ethanol in the presence of potassium carbonate (K_2CO_3) afforded the substituted pyridazinone derivatives, respectively. Interestingly, the reaction of compound 1 with monochloroacetic acid in dry acetone/K_2CO_3 yielded the 2-methyl pyridazinone derivativethrough nucleophilic substitution and decarboxylation. The 2-methyl pyridazinone(7)can be prepared through an alternative route, by reacting with compound 1 with methyl iodide in dry acetone/K_2CO_3 to give the compound 7. Treatment of compound 1 with bromine-acetic acid mixture afforded compound 12. The formation of this compound can be explained on the basis that the first step is dehydrogenation followed by addition of bromine on the formed double bond and the elimination of hydrogen bromide. The behaviour of pyridazinone derivative 1towards electrophilic reagents like $POCl_3$ gave 3-chloro pyridazine derivative 2, by substitution of the enolic hydroxyl group with chlorine together with dehydrogenation. The compound 2 has been used as starting material for the preparation of a series of new compounds. Thus, reaction of compound 2 with hydrazine hydrate and/or phenylhydrazine gave the hydrazine derivatives 3, respectively. The reaction of compound 2 with thiourea in absolute ethanol gave the pyridazine-thione 4, while the reaction of compound 2 with sodium azide in DMF gave tetrazolopyridazine derivative. The behaviour of compounds 1towards carbon electrophiles, namely, ethyl chloroacetate, acrylonitrile, formaldehyde and secondary amines (Mannich reaction), aromatic aldehydes and carbon nucleophiles, namely, $POCl_3/PCl_5$ and P_2S_5 has been investigated. The compound 2 reacts with hydrazine hydrate to give the 3-hydrazino derivative (3).On treatment with ethyl acetoacetate and/or acetylacetone with the compound 3undergoes cyclization to afford pyrazolone derivative and 3-(3,5-dimethylpyrazol-1-yl)-pyridazine derivative, respectively. On reaction with acetylhydrazine in boiling butanol and/or sodium azide in DMF the compounds 2 affords the triazolo[4,3-b]pyridazine and the tetrazolo[1,5-b]pyridazine, respectively.Reactivity of pyridazinone,whichbearsbulkyheterylmoietiesatposition 4 and 6 and the effects of steric hindrance of these groups has been studied with different carbon electrophiles and nitrogen nucleophiles. Thus, pyridazinone reacted with ethyl chloroacetate in boiling dry acetone and dry K_2CO_3 to afford 3-o-carboethoxymethyl-4,5-dihydropyridazine. Thus, on treatment of 2 with acrylonitrile in boiling ethanol containing catalytic amounts of aqueous sodium hydroxide solution, a Michael-type addition occurred at the activated double bond and afforded the 2-cyanoethyl-4,5-dihydropyridazin-3-one (Wasfy 2002)[24], On the other hand, 2-hydroxymethyl derivative 7 which on cyclocondensation with urea yielded 9-benzylamino-2,3,4,8,9-pentahydropyridazino[1,6-a]-1,3,5-triazin-2-one (8). In continuation, we considered to synthesize novel congeners bearing pyridazine and amino acid moieties in a single molecular framework. Thus, compound 2 reacted with phthalyl and/or tosyl derivatives of the amino acids glycine and/or DL-alanine to furnish 3-o-(pht- or tos-amino acid)-4,5-dihydropyridazine derivatives, respectively.

The reaction of compound 1 with $POCl_3$ for 30 min gave the chloropyridazine 2, which reacted with carbohydrate hydrazones of ribose, glucose, galactose and lactose in ethanol to give hydrazonopyradazine derivatives. Mixing chloropyridazine 2 with aliphatic or aromatic amines, methylamine, ethylamine, aniline, sulphanilinic acid, α-naphthylamine or diphenylamine in dry benzene gave corresponding pyridazine derivatives (Abubshait 2007)[23], The reaction of chloropyridazine 2 with hydrazine hydrate in boiling

benzene gave the hydrazinopyridazine derivative 3. The structure of 3 was further confirmed by its reaction with acetyl acetone in boiling methanol that gave 3-phenyl-(3,5-dimethylpyrazol-1-yl) pyridazine. On the other hand, when compound 1 was reacted with excess CH_3I in methanol the quaternary ammonium iodide derivative was formed (Abusait, 2007). The reaction of compound 1 with benzene/4-toluenesulfonyl chloride and anhydrous K_2CO_3 in dry acetone at reflux for 24 h gave 6-phenyl-2-(benzenesulfonyl or 4-toluenesulfonyl)-4,5-dihydro-2H-pyridazin-3-ones, respectively (Abusait, 2007). Thus, treatment of compound 1with phosphorus pentasulfide in dry xylene, gave 6-phenyl-4-(1,5-dimethyl-2-phenyl-3-thioxo-2,3-dihydro-1H-pyrazol-4-yl)-3(2H) pyridazine-thione 4. The hitherto unknown reaction of chloropyridazine 2with 2-amino-3-carbethoxy-4,5-dimethylthiophene affording the three fused ring compound 7-phenyl-2,3-dimethyl-4H-thieno-[2',3':4,5]-pyrimido-[1,2-b] pyridazin-4-one formed. Similarly, compound 2reacted with 2-amino-3-carbethoxy tetrahydrobenzothiophene to afford a compound containing four fused rings: 2-phenyl-7,8,9,10-tetrahydro-11H-[1]-benzothieno-[2',3':4,5] pyrimido-1,2-b]-pyridazin-11-one. The behaviour of the compound 2towards thiourea, in dry xylene gave the 6-phenyl-3(2H)-pyridazine-thione (4). The proposed structure of the compound 4 is supported by its reaction with dimethylsulfate and benzylchloride in dry acetone in the presence of anhydrous K_2CO_3 to give 6-phenyl-3-(ethylsulfanyl)-pyridazine and 6-phenyl-3-(benzylsulfanyl)-pyridazine, respectively. The pyridazine derivative has also been used as the key starting material for the preparation of some other new heterocyclic compounds. Thus, compound 2 reacts with sodium azide, anthranilic acid or hydrazine hydrate to give 6-phenyl[1,2,3,4] tetrazolo [1,5-b] pyridazine, 2-phenyl-10H-pyridazino-(6,1-b)-quinazolin-10-one and 6-phenyl-3-hydrazine pyridazine respectively. Thereaction of the compound 3 with acetylacetone in methanol gave 6-phenyl-3-(3,5-dimethyl-1H-pyrazol-1-yl)pyridazine, while the reaction of 3 with benzil in boiling methanol gave the condensation product 1,2-diphenyl-1,2-ethanedione-1-N-[6-phenyl-3-pyridazinyl]-hydrazone.

The pyridazinones have also been used as the key material for the synthesis of some new heterocyclic compounds. Thedifferent synthetic methods are used for the synthesis of 6-aryl-pyridazinone derivatives by using different reagents[34–39]. The reactions of pyridazinones with $PCl_5/POCl_3$, arylsulphonyl chloride derivatives, aliphatic/aromatic aldehydes and towards reaction with hydrazine hydrate, carbohydrate hydrazones, aliphatic/aromatic amines, etc. Sometimes the incorporation of amino acid residues in various sulfur- and nitrogen-containing heterocycles enhances the biological profile much folds over that of its parent nucleus[40–44].

5. Conclusion

Pyridazine belongs to an important group of heterocyclic compounds and lot of research work on has been done in the past. The pyridazine moiety possesses almost all types of pharmacological activities and also used as intermediates for drugs and agrochemicals agents. Recently, pyridazine derivatives have received considerable interest due to their wide range of applications. We encouraged by these reports, series of pyridazines containing a substitution of a different group at the different position hoping to improve the biological activities of these compounds in the future. Pyridazines further drew our attention because of their easy functionalization at various ring positions, which makes them attractive synthetic building blocks for designing and development of novel pyridazines[45–50]. The structures of all newly synthesized compounds were established from their spectral data and elemental analysis. By the present scenario, it can be concluded that pyridazinone have a great potential which remains to be disclosed till date.The discovery of biological activity in a series of pyridazine derivatives stimulated the vigorous growth of investigations in this area.

6. References

1. Dinesh K, Rosalia C,de la Carmen C, Dharam PJ, Ranju B. Synthesis and evaluation of 2-substituted-6-phenyl-4,5-dihydropyridazin-3(2H)-ones as potent inodilators. Acta Pharm. 2008; 58:393–405.
2. Smolyar NN, Yutilov YM, Gresko SV. Synthesis of 4-amino-6-(hetaryl)pyridazin-3-ones as analogs of pyridazine-based cardiotonic agents. Pharm Chem J. 2009: 43:87–8.
3. Youssef AS, Marzouk MI, Madkour HMF, El-Soll AMA, El-Hashash MA. Synthesis of some heterocyclic systems of anticipated biological activities via 6-aryl-4-pyrazol-1-yl-pyridazin-3-one. Can J Chem. 2005;83:251–9.
4. Monge A, Parrado P, Font M, Fernández-Alvarez E. Se-

lective thromboxane synthetase inhibitors and antihypertensive agents. New derivatives of 4-hydrazinopyridazino[4,5-a]indole and related compounds. J Med Chem. 1987;30:1029–35.
5. Bristol JA, Sircar I, Moss WH, Evans DB, Weishmaar E. Cardiotonic agents. 1. 4,5- Dihydro-6-[4-(1H-imidazol-1-yl)phenyl]-3(2H)-pyridazinones: novel positive inotropic agents for the treatment of congestive heart failure.J Med Chem. 1984;27:1099–101.
6. Demirayak S, Karaburun AC, Beis R. Some pyrrole substituted aryl pyridazinone and phthalazinone derivatives and their antihypertensive activities. Eur J Med Chem. 2004;39:1089–95.
7. Bansal R, Kumar D, Carron R, de la Calle C. Synthesis and vasodilatory activity of some amide derivatives of 6-(4-carboxymethyloxyphenyl)-4,5-dihydro-3(2H)-pyridazinone. Eur J Med Chem. 2009; 44(11):4441–7.
8. Sircar I, Duell BL, Cain MH, Bruke SE, Bristol JA. Cardiotonic agents. 4. Synthesis and biological evaluation of N-substituted 2,4,4a,5-tetrahydro-3H-indeno[1,2-c]pyridazin-3-ones: rigid structures derived from CI-930 and analogs.J Med Chem. 1986;29:2142–8.
9. Gokce M, Utku S, Kupeli E. Synthesis and analgesic and anti-inflammatory activities 6-substituted-3(2H)-pyridazinone-2-acetyl-2-(p-substituted/nonsubstituted benzal) hydraz-one derivatives. Eur J Med Chem. 2009; 44(9):3760–4.
10. Mirzoeva S, Sawkar A, Zasadzki M, Guo L, Velentza AV, Ramstrom H, Haiech J,van Eldik LJ, Watterson DM, Dunlap V, Bourguignon JJ. Discovery of a 3-Amino-6-phenyl-pyridazine derivative as a new synthetic antineuroinflammatory compound. J Med Chem. 2002;45:563–6.
11. Sondhi SM, Sharma VK, Singhal N, Verma RP, Shukla R, Raghubir R, Dubey MP. Synthesis and anti-inflammatory activity evaluation of some acridinyl amino antypyrine, acridinyl amino anthraquinone, acridino thiourea and thiazolino thiourea derivatives. Phosphorus, Sulfur, Silicon Relat Elem. 2000; 156:21–34.
12. Turan-Zitouni G, Sivaci M, Kilic FS, Erol K. Synthesis of some triazolyl-antypyrine derivatives and investigation of analgesic activity. Eur J Med Chem. 2001; 36:685–9.
13. Asif M, Singh A, Lakshmayya. Anticonvulsant activity of 4-(Substituted Benzylidene)-6-(3-nitrophenyl)-4,5-dihydro pyridazin-3(2H)-ones against maximal electro shock induced seizure. Middle-East J Sci Res. 2011; 9(4):481–5.
14. Cao S, Qian X, Song G, Chai B, Jiang Z. Synthesis and antifeedant activity of new oxadiazolyl 3(2H)-pyridazinones. J Agric Food Chem. 2003;51:152–5.
15. Chung KT, Chen SC, Wong TY, Wei CI. Effects of benzidine and benzidine analogues on growth of bacteria including *Azotobacter vinelandii*. Environ Toxicol Chem. 1998;17:271–5.
16. El-Hashash MA, Amine MS, Soliman FM, Morsi MA. Behavior of aroylacyclic acids toward hydrazine hydrate and some on the cyclized products. J Serb Chem Soc. 1992;57:563–9.
17. Sayed GH, Hamed AA, Meligi GA, Boraie WE, Shafik M. The use of 4-(3,4- dichlorophenyl)-4-oxo-2-(4-antipyrinyl)-butonoic acid in the preparation of some new heterocyclic compounds with expected biological activity. Molecules2003;8:322–32.
18. Sotelo E, Pita B, Ravina E. Pyridazines. Part 22:1 Highly efficient synthesis of pharmacologically useful 4-cyano-6-phenyl-5-substituted-3(2H)-pyridazinones. TetrahedronLett. 2000;41:2863–6.
19. Livermore DGH, Bethell RC, Cammack N, Hancock AP, Hann MM, Green DVS, Lamont RB, Noble SA, Orr DC, Payne JJ, Ramsay MVJ, Shingler AH, Smith C, Storer R, Williamson C, Willson T. Synthesis and anti-HIV-1 activity of a series of imidazo[1,5-b]pyridazines. J Med Chem. 1993;36:3784–94.
20. References and further reading may be available for this article. To view references and further reading you must purchase this article.Wang T, Dong Y, Wang LC, Chen Z. Synthesis and bioactivity of 6-phenyl-4,5-dihydro-3(2H)-pyridazinone derivatives. Arzneimittelforschung. 2007; 57(10):641–6.
21. Asif M, Singh A. Exploring potential, synthetic methods and general chemistry of pyridazine and pyridazinone: abrief introduction. Inter J Chem Tech Res. 2010:2(2):1112–28.
22. El-GhaffarANF, Mohamed MK, Kadah MS, Radwan AM, Said GH, Abdel-al SN. Synthesis and anti-tumor activities of some new pyridazinones containing the 2-phenyl-1H-indolyl moiety. J Chem Pharm Res. 2011; 3(3):248–59.
23. Abubshait SA. An efficient synthesis and reactions of novel indolylpyridazinone derivatives with expected biological activity. Molecules.2007;12:25–42.
24. Wasfy AAF, Arief MMH, Amine MS, Donia SG, Aly AA. γ-oxo carboxylic acids in heterocyclic synthesis, III. Synthesis of biologically active 4-Benzylamino-6-(5,5-dioxodibenzothiophen-2-yl)-2,3,4,5-tetrahydropyridazin-3-ones. Verlag der Zeitschrift fur Naturforschung. 2002;668–76.
25. Soliman MHA, El-Sakka SS. 4,5-Dihydro-6-(4-methoxy-3-methylphenyl)-3(2H)-pyridazinone. J Korean Chem Soc. 2011; 55(2):230–34.
26. Islam M, Siddiqui AA, Rajesh R. Synthesis, antitubercular, antifungal and antibacterial activities of 6-substituted phenyl-2-(3-substituted phenyl pyridazin-6-yl)-2,3,4,5-tetrahydropyridazin-3-one. Acta Pol Pharm. 2008; 65(4):441–7.
27. Banerjee PS, Sharma KP, Nema KR. Synthesis and anticonvulsant activity of pyridazinone derivatives. Intr J Chem Tech. 2009; 1(3):522–5.
28. Siddiqui AA, Mishra R, Shaharyar M, HusainA, Rashid M, Pal M, Yathirajan HS. Synthesis of 7-Phenyl-3,4,8,9-tetrahydro-2H-pyridazino[1,6-a][1,3,5]triazin-2-imine. Molbank.2011; M717.Doi: 10.3390/M717.
29. Benchat N, Benalla A, El Kalai F, Ramdani M, Daoui S. Synthesis of 5-benzyl-2,6-dimethylpyridazin-3(2H)-one. Molbank.2008; M580.
30. Asif M, Singh D, Singh A. Analgesic activity of some 6-phenyl-4-substituted benzylidene tetrahydro pyridazin-3(2H)-ones. Global J Pharmacol. 2011; 5(1):18–22.
31. Siddiqui AA, Mishra R, Shaharyar M. Synthesis, character-

ization and antihypertensive activity of pyridazinone derivatives. Eur J Med Chem.2010; 45(6):2283–90.
32. Sayed GH, Sayed MA, Shaaban SS, Mahmoud MR. Synthesis and reactions of 4-(p- bromophenyl)-4-oxo-2-(4-antipyrinyl)butanoic acid and some unexpected products. Egypt J Chem. 2000;43:17–29.
33. Islam M, Siddiqui AA, Rajesh R.Synthesis, antitubercular, antifungal and antibacterial activities of 6-substituted phenyl-2-(3i-substituted phenyl pyridazin-6i-yl)-2,3,4,5-tetrahydropyridazin-3-one. Acta Pol Pharm.2008;65(3):353–62.
34. Burdulene D, Palaima A, Stumbryavichyute Z, Talaikite Z. Synthesis and anti-inflammatory activity of 4-aminoantipyrine derivatives of succinamides. Pharm Chem J. 1999; 33:191–3.
35. Coates WJ, McKillop A. One pot preparation of 6-substituted 3(2H)-pyridazinones from ketones. Synthesis.1993;334–42.
36. Dogruer SD, Onkol T, Ozkan S, Ozgen S, Sahin MS. Synthesis and antimicrobial activity of some 3(2H)-pyridazinone and 1(2H)-phthalazinone derivatives. Turk J Chem. 2008; 32:469–79.
37. Foks H, Wisterowicz K, Miszke A, Brozewicz K, Wisnlewska K, Dabrowska-Szponar M. Synthesis, fungicidal and antibacterial activity of new pyridazine derivatives. Heterocycles 2009;78:961–75.
38. Halasz BD, Monsieurs K, Elias O, Karolyhazy L, Tapolcsanyi P, Maes BU, Riedl Z, Hajos G, Dommisse RA, Lemiere GL, Kosmrlj J, Matyus P. Synthesis of 5-H-pyridazino[4,5-b] indoles and their benzofurane analogues utilizing an intramolecular Heck-type reaction. Tetrahedron. 2004;60:2283–91.
39. Jaihne H, Sayed A, Zaher HA, Sherif O. Reaction of 3-chloro- and 3-hydrazino-6-(p-tolyl) pyridazines. Indian J Chem. 1977;250–1.
40. Tao J,Cao L-H, Wang C-F,Wang D-Z. Synthesis of 1,3,4-oxadiazoles and 1,3-thiazolidinones containing 1,4,5,6-tetrahydro-6-pyridazinone. J Chinese Chem Soc. 2006;53:1193–7.
41. Károlyházy L, Horváth G, Mátyus P. A novel pyridazino-fused ring system: synthesis of pyridazino[3,4-b]diazepam. Acta Pharm Hung. 2001; 71(2):168–70.
42. Kassab RR. Simple synthesis and reactions of some new pyridazinono derivatives and their antimicrobial activity. Egypt J Chem. 2002;45:1055–73.
43. Kassab RR, Sayed GH, Radwan AM,El-Azzez NA. Some reactions with (biphenyl)-4-(5-oxo-1,3-diphenyl-2-pyrazolin-4-yl)-4,5-dihydropyridazin-3-(2H)ones. Rev Roum Chim. 2001;46:649–55.
44. Okcelik B, Unlu S, Banoglu E, Kupeli E, Yesilada E, Sahin MF. Investigation of new pyridazinone derivatives for the synthesis of potent analgesic and anti-inflammatory compounds with cyclooxygenase inhibitory activity. Arch Pharm Pharm Med Chem. 2003;336:406–12.
45. Piaz VD, Ciciani G, Giovannoni MP. 5-Acetyl-2-Methyl-4-Nitro-6-Phenyl-3(2H)-Pyriazinone: versatile precursor to hetero-condensed pyridazinones. Synthesis.1994;669–71.
46. Sayed GH, El-Kady MY,Elhalim MSA. Synthesis and reactions of some α-aryl-β-(4-bromobenzoyl)-propionic acids. Indian J Chem. 1981; 20:845–8.
47. Sayed GH, Radwan A, Mohamed SM, Shiba SA, Khalil M. Synthesis and reactions of some 6-aryl and 2,6-diaryl-4(4`-antipyrinyl)-2,3,4,5-tetrahydropyridazin-3-ones and screening for their antibacterial activities. Chin J Chem. 1992; 10:475–80.
48. Sotelo E, Coelho A, Ravina E. Pyridazines. Part 34: Retro-ene-assisted palladium-catalyzed synthesis of 4,5-disubstituted-3(2H)-pyridazinones. Tetrahedron Lett. 2003;44:4459–62.
49. Toth G, Molnar S, Tamas T, Borbely I. An efficient synthesis of 4,5-dihydro-3(2H)-pyridazinone derivative. Synth Commun. 1997;27:3513–24.
50. Vassilev GN, Yonova PA, Bohland H, Vassilev NG, Yordanov B. Synthesis and grouth-regulating activity of some metal coordination compounds with thioureas and antipyrines. Dokl Bulg Akad Nauk 1997; 50:59–62.