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Pharmacological importance and some conventional methods for derivatization of pyridazine and pyridazinone derivatives

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Abstract
Pyridazine belong to an important group of heterocyclic compounds and lot of research work on has been done in the past. The substituted pyridazinone derivatives have attracted considerable attention due to their characteristic pharmacological activities. Various substitueted pyridazine derivatives have been used as clinically used drug molecules. These diverse pharmacological activities promoted us for the synthesis of various substituted pyridazinone derivatives in order to explore the usefulness. In the present review, various synthetic chemical methods have been studied for the synthesis of different types of substituted pyridazinone derivatives. The behaviour of the pyridazinone toward formaldehyde/piperidine, ethyl chloroacetate, chloroacetic acid, benzenesulfonyl chloride, bromine/acetic acid and aromatic aldehydes has also been studied. However, the chloro-derivatives are resulting from the reaction of pyridazinone with phosphorus oxychloride. The behavior of chloropyridazine toward hydrazines, thiourea, sodium azide, anthranilic acid, aromatic amines and sulfa compounds has also been considered. The thio pyridazinone derivatives were prepared from the reaction of pyridazinone with phosphorus pentasulfide.

Keywords: pyridazinone, substitution, synthetic, pharmacologically active

Introduction
Nitrogen-containing heterocyclic compounds are plays an important role, not only for pharmacologically active but also in chemical and agrochemical fields. Various interesting pharmacological activities were displayed by pyridazine derivatives and also the developed several pyridazine-based drugs and other pharmacological tools in recent years [1-5]. Pyridazine and pyridazinone derivatives are biologically active scaffolds, possessing divers pharmacological activities such as antihypertensive and antiplatelets, cardiovascular disorders, cardiotonic [6-10], analgesic, anti-inflammatory, antipyretics, central nervous system disorders, antibacterial, antifungal, antiviral, antifeedant, and herbicidal, anticancer and other anticipated activities [11-15]. Pyridazines further drew our attention because of their usefulness in intermediates for drugs and agrochemicals and easy substituted at various ring positions of pyridazine ring, which makes them attractive synthetic building blocks for development of novel biologically active pyridazine and pyridazinone derivatives [16-20]. The discovery of biological activities of pyridazine and pyridazinone derivatives will be the area of investigations.

Table 1: Pyridazine containing marketed drugs

S. No.	Drug Name	Uses
1	Hydralazine (Apresoline)	Antihypertensive
2	KF 15232	Congestive Heart Failure
3	Minaprine	Anti-depressant
4	Pipofezine (Azaphen)	Anti-depressant
5	Pyridate	Herbicide
6	Cadralazine	Antihypertensive
7	Credazine	Herbicide
8	Pyridafol	Herbicide

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.

Table 2: Pyridazinone containing marketed drugs

S. No.	Name of Drug	Use
1	Azelastine	Bronchodilator
2	Emorfazon	Analgesic
3	Ag 246	Analgesic
4	Imazodan	Cardiotonic
5	Amipizon	Antithrombotic
6	CI 930	Phosphodiesterase inhibitor
7	Indolidan	Cardiotonic
8	Zardaverine	Phosphodiesterase III/IV inhibitor
9	Pimobendan	Cardiotonic
10	Zopolrestat	Antidiabetic
11	KK 505	Antiasthmatic
12	Bemorandan	Cardiotonic
13	Chloridazon	Herbicide
14	Norflurazon	Herbicide
15	BAS 44521 OR SAN 9789	Herbicide
16	Pyridaben	Insecticide and acaricide
17	Phthalazin-1-one	Antifungal
18	Brompyrazon	Herbicide
19	Metflurazon	Herbicide
20	Flufenpyr	Herbicide
21	Oxapyrazon	Herbicide

Chemistry of Pyridazine
Pyridazine are heterocyclic 1, 2-diazine, derived from

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

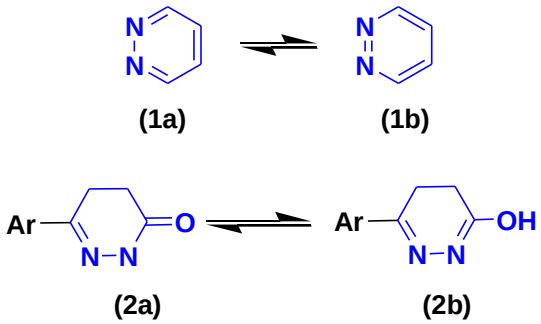
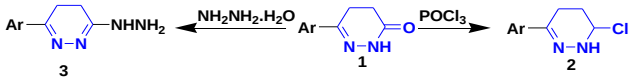


Fig 1: Resonance structure of pyrdaizine (1a and 1b) and tautomeric structure of aryl pyridazinone (2a and 2b).

Synthesis of various 6-arylsubstituted pyridazinone derivatives

A series of pyridazines will be subjected to further synthesis of newer substituted pyridazinone compounds. This study aimed at utilizing pyridazinone for the synthesis of substituted-arylpyridazinone derivatives for attractive biological activities by prompted us to synthesize a new substituted aryl pyridazinones. The compounds were characterized on the basis of spectral data [22-24].

Synthesis of various 6-aryl-pyridazinone derivatives



Scheme 1: Reactions of substituted pyridazinone derivatives

Synthesis of 6-phenyl-pyridazinone (1)

Phenyl-4-oxobutanoic acid dissolved in ethanol and added hydrazine hydrate was added. The reaction mixture was heated under reflux for 3 hrs. The solid product obtained after cooling, filtered off and crystallized from ethanol to give compound **1** as white crystals [25].

Synthesis of 3-chloro-6-aryl-4, 5-dihydropyridazine (2)

A mixture of 6-aryl-4,5-tetrahydropyridazinone and phosphorous oxychloride ($POCl_3$) or phosphorus pentachloride (PCl_5), was heated on a steam bath for 6 hrs. After heating, the mixture was carefully poured on crushed ice and make alkaline by addition of sodium bicarbonate (Na_2CO_3). Compound 2 was filter off and re-crystallized with aropriate solvent [26].

Synthesis of 3-hydrazino-6-arylpyridazine or 6-phenyl-pyridazin-3-yl-hydrazine (3)

The ethanolic solution of compound 2, hydrazine hydrate, was added and the resulting reaction mixture was refluxed on steam bath for 16 hrs. The mixture was concentrated, cooled and poured into crushed ice. The resulting solid compound 3 was filtered, washed with water, dried and re-crystallized from ethyl alcohol [26].

Synthesis of 6-aryl-4, 5-dihydropyridazinthione (4)

Compound 1 dissolved in xylene was refluxing with phosphorus pentasulphide (P_2S_5) for 4 hrs at a temperature of 150º C. The mixture was concentrated to a small volume then crystals were obtained and collected, recrystallized from ethanol [27] OR A solution of compound 1, P_2S_5 in dry xylene was boiled under reflux for 6 hrs. The reaction mixture was filtered while hot and then filtrate was concentrated. The compound 4 was separated on cooling, filtered off and recrystallized from aropriate solvents [26].

Synthesis of 3-Imino-6-arylpyridazine (5)

A mixture of compound 1 and ammonium acetate was heated in an oil bath at 180°C for 4 hrs. Then the reaction mixture was poured into cold water and the solid compound was separated, filtered off and recrystallized from ethanol [26].

Synthesis of 2-hydroxy- methy l-6-aryl-4, 5-dihydropyridazinone (6)

Compound 1 was dissolved in methanol and added formaldehyde (37–41% solution). The mixture was refluxed for 6 hrs. After completion of the reaction, methanol was distilled off and the residue was poured into crushed ice to separate out compound 6, filtered off and recrystallized from methanol [28]. OR Compound 1was dissolved in methanol and then treated with formaldehyde. The reaction mixture was refluxed for 6 hrs. The colorless solid compound was formed after cooling, filtered off, dried and recrystallized from a suitable solvent to obtained compound 6, OR A mixture of compound 1, aqueous formaldehyde (37–41% solution) and water was refluxed for 4 hrs. The solid product obtained after cooling, filtered off and recrystallized from ethanol to give compound **6** as white crystals.

Synthesis of 6-Aryl-2-methyl pyridazinone (7)

The compound 1 under solvent free condition were added potassium carbonate, TBAB and methyl iodide. 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 precipitated product was filtered and washed with water to give compound **7** [29].

Synthesis of 6-phenyl-pyridazin-3-yl-methylamine (8)

The aliphatic or aromatic amine was added to a mixture of compound 1 in dry benzene and the reaction mixture was heated in oil bath for 6 hrs. The solid compound was separated on cooling and recrystallized from benzene to give compounds 8. OR

Methylamine was added to a mixture of compound 1 and the reaction mixture was heated for 4 hrs on an oil-bath at 140 °C; then cooled and triturated the mixture with methanol. The solid product was separated and recrystallized from methanol to give compound 8 as white crystals [22].

Synthesis of 4-arylidene-6-aryl-4, 5-dihydro-pyridazinone (9)

Aropriate aliphatic or aromatic aldehyde was added to a mixture of compound 1, sodium hydroxide in ethanol and

the reaction mixture was refluxed for 6 hrs. The solid compound was separated on cooling and re-crystallized from benzene to give compound 9. OR Condensation of compound 1 with aropriate aldehyde by a solution of sodium ethoxide, compound 1 was added with stirring. The reaction mixture was kept overnight; the solid product 9 obtained was filtered off and crystallized from the proper solvent. OR Condensation of compound 1 with aropriate aldehyde in glacial acetic acid and add sodium acetate was refluxed for 6-8 hours and cooled and poured on to ice. The solid compound 9 was obtained and then recrystallized with ethanol. OR A mixture of the compound 1 and aromatic aldehydes in ethanol was treated with ethanolic sodium hydroxide solution and the whole mixture was refluxed for 3 hrs. The solid compound 9 was formed after cooling and acidification, filtered off and recrystallized from a suitable solvent.

Synthesis of 4-Benzylamino-2- cyanoethyl-4, 5-dihydropyridazinone (10)

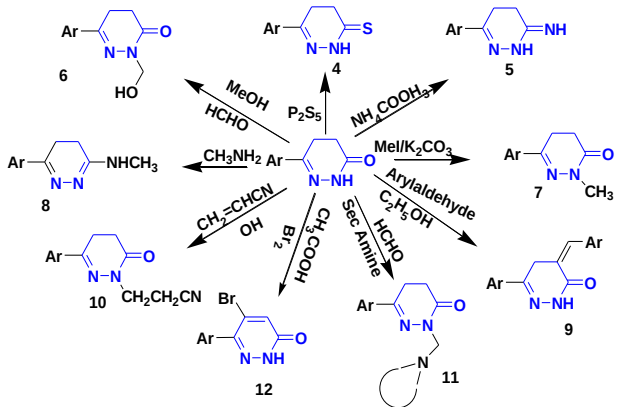
A mixture of compound 1 and acrylonitrile in ethanol was treated with a few drops of 10% NaOH solution and the mixture was heated under reflux for 4 hrs. The colorless solid compound 10 was formed after concentration and cooling and recrystallized from a proper solvent [22].

Synthesis of 2-(amino-1-ylmethyl)-6-aryl-4, 5-dihydropyridazinone (11)

A mixture of compound 1, formaldehyde and secondary amines in ethanol was left overnight at room temperature and then heated under reflux for 3 hrs. The solid compound 11 was formed after evaporation of the solvent and crystallized from a suitable solvent. OR The aliphatic or aromatic amine was added to a mixture of compound 2 in dry benzene and the reaction mixture was heated in oil bath for 6 hr. The solid compound 11 was separated on cooling and recrystallized from benzene. OR A mixture of compound 1, amine, formaldehyde and methanol was refluxed for 5 hrs, and then kept overnight at room temperature, then treated with H_2O and the precipitated solid compound 11 was formed by Mannich reaction, filtered and recrystallized from ethanol. OR A mixture of compound 6 and secondary amines in ethanol was heated under reflux for 3 hrs. The solid compound 11 was separated after concentrated and cooled than recrystallized from a proper solvent. OR A mixture of compound 1, formaldehyde and secondary amines in ethanol was left overnight at room temperature and then heated under reflux for 3 hrs. The solid compound 11 was formed after removal of most of the solvent and recrystallized from a suitable solvent to given colorless crystals [22, 31].

Synthesis of 5-bromo-6-phenylpyridazinone (12)

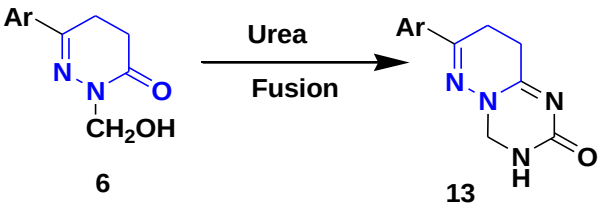
A compound 1 dissolved in glacial acetic acid and treated drop wise with bromine at 60-70^{0}C. The solution was stirred for 2 hrs and then cooled in ice. The precipitated product was filtered off, washed with petroleum ether (40-60^{0}C) and stirred with concentrated ammonium hydroxide for 50 minutes. The solid product 12 was filtered off and recrystallized. OR A compound 1 dissolved in glacial acetic acid and bromine was stored at room temperature for 3 hrs. The solid product 12 obtained was filtered off, washed with petroleum ether (40-60°C) and recrystallized from ethanol 12.



Scheme 2: Reactions of substituted pyridazinone derivatives

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

A mixture of compound **6** and urea was heated in an oil-bath at 180 °C for 3 h, cooled and triturated with ethanol. The solid compound 13 obtained was crystallized from a suitable solvent.



Scheme 3: Reactions of substituted pyridazinone derivatives

Synthesis of 6-phenyl-[1, 2, 3, 4]-tetrazolo [1, 5-b] pyridazine (14)

A compound 2, sodium azide, water and dimethylformamide was refluxed for 2 hrs. The solid compound were obtained upon dilution with water was filtered off and recrystallized with suitable solvent. OR

A compound 2 and sodium azide (NaN_3) in DMF was refluxed for 6 hrs. The reaction mixture was evaporated to dryness *in vacuo* and the residue was recrystallized from a proper solvent to give a compound 14.

Synthesis of 6-phenyl-3-hydrazinopyridazines (15)

The compound 2 in absolute ethanol, hydrazine derivatives were added and the reaction mixture was refluxed for 3 hrs. The solid compound was separated on cooling and recrystallized to give compound 15 [32].

6-phenyl-4, 5-dihydropyridazinthione (16)

The compound 2 dissolved in absolute ethanol and equmolar amount of thiourea was added and the reaction mixture was refluxed for 4-10 hrs. The crude compound was obtained after concentration and cooling was filtered off and recrystallized from the suitable solvent to give compound 16, Thiourea was added to a solution of compound 1 in butanol, and the reaction mixture refluxed for 5 hrs. The solid compound was separated and washed with water and recrystallized to give 16 [22, 33].

Synthesis of 3-(4-hydroxy-3-iminnophenol)-6-phenylpyridazinone derivative (17)

The compound 2 dissolved in absolute ethanol and equimolar amount of para aminophenol was added and the

reaction mixture was refluxed for 4-10 hrs. The crude compound 17 was obtained after concentration and cooling was filtered off and recrystallized from the suitable solvent**.**

Synthesis of 6-phenyl-N-pyridin-2-yl-pyridazin-3-amine or 3-iminnopyridine-6-phenyl pyridazinone derivative (18)

The compound 2 dissolved in absolute ethanol and equmolar amount of aminopyridine was added and the reaction mixture was refluxed for 4-10 hrs. The crude material 18 was obtained after concentration and cooling was filtered off and recrystallized from the suitable solvent.

Synthesis of 6-phenyl-N-(benzenesulfonyl-2-amino-pyrimidine)-pyridazin-3-amine (19)

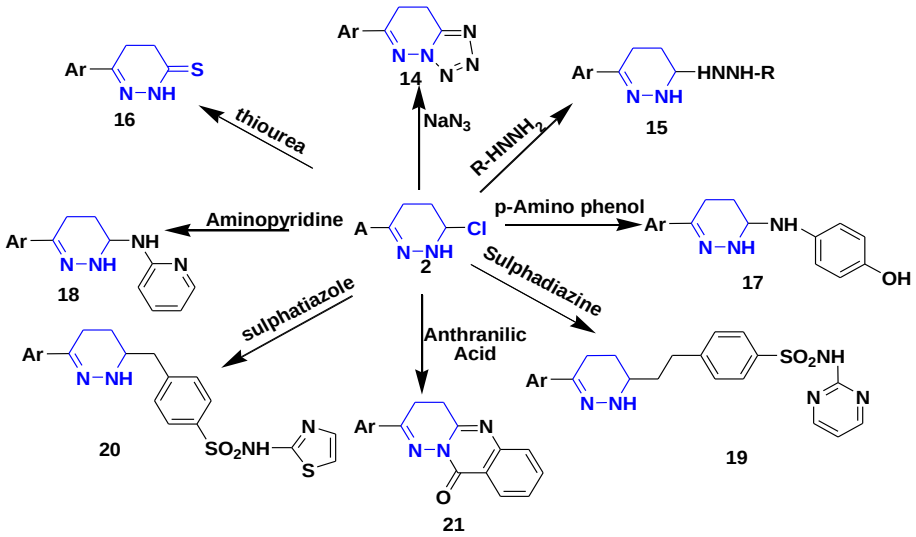
The compound 2 dissolved in absolute ethanol and equmolar amount of sulphadiazine was added and the reaction mixture was refluxed for 4-10 hrs. The crude material 19 was obtained after concentration and cooling was filtered off and recrystallized from the suitable solvent.

Synthesis of 6-phenyl- N- (benzenesulfony l-2-aminothiazol)-pyridazin-3-amine (20)

The compound 2 dissolved in absolute ethanol and equmolar amount of sulphathiazole was added and the reaction mixture was refluxed for 4-10 hrs. The crude material 20 was obtained after concentration and cooling was filtered off and recrystallized from the suitable solvent.

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 anthranilic acid, in dimethyl for mamide (DMF) affording pyridazino[3,2-b] quinazolinone. A mixture of compound 2 and anthranilic acid was heated in an oil bath at 150^0C for 3 hrs, cooled and triturated with ethanol. The solid compound 21 obtained was filtered off and recrystallized. OR A mixture of the compound 2 and anthranilic acid was heated in an oil bath for 4 hrs, the solid product was collected and crystallized from ethanol to give compound 21 as colorless crystal [22].



Scheme 4: Reactions of substituted pyridazinone derivatives

Synthesis of 2-[dialkylaminomethyl]-4,5-dihydro-6-phenyl-pyridazinone (22)

An aqueous solution of formaldehyde (35-37%) was added to a mixture of compound 1 and the aropriate secondary amine in ethanol, the reaction mixture was kept overnight at room temperature. The solid compound 22 obtained after dilution with water was filtered off and crystallized from the proper solvent.

Synthesis of 3-benzylamino-6-phenyl-pyridazine (23)

A mixture of the compound 2 and benzylamine was heated on oil bath for 6 hrs and the residue was triturated with diethyl ether, followed by crystallization from ethanol to give 23 as buff powder.

Synthesis of 3-*o*-carboethoxymethyl-4, 5-dihydropyridazine (24)

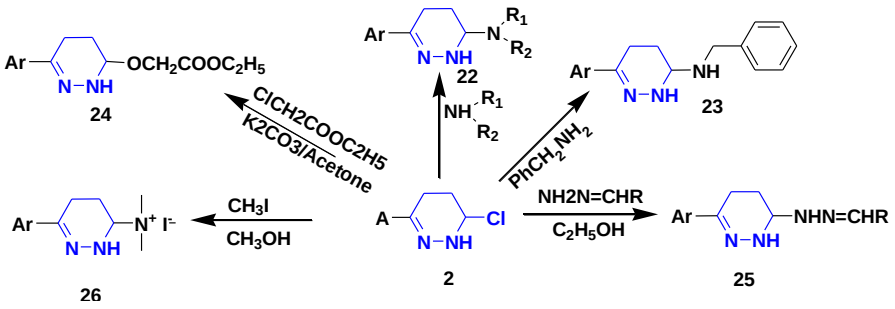
A mixture of compound 2, anhydrous K_2CO_3, ethyl chloroacetate and dry acetone was refluxed for 35 hrs. The excess acetone was removed by distillation and the reaction mixture then poured into water and the reaction mixture was extracted with ether. After evaporation of the dried ethereal solution, the solid that separated was crystallized from a suitable solvent to afford the corresponding ester 24.

Synthesis of 5-[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 was added to a mixture of compound 2 in ethanol and the reaction mixture was refluxed for 6 hrs. The solid compound was separated and recrystallized from ethanol to give compounds 25a, 25b and 25c respectively.

Synthesis of 6-phenyl-pyridazin-3-yl-trimethylammonium iodide (26)

Excess methyl iodide was added to a mixture of compound 2 in methanol and the reaction mixture was refluxed for 8 hrs. After evaporation of all the solvent, the solid compound residue was recrystallized from methanol to give 26 as white crystals.



Scheme 5: Reactions of substituted pyridazinone derivatives

Synthesis of 3-[1N-(3-methylpyrazolin-5-one)]-4, 5-dihydropyridazine (27)

A mixture of compound **3** and ethyl acetoacetate in ethanol was refluxed for 6 hrs. The solid that separated, after concentration and cooling, compound **27** was crystallized from a suitable solvent.

Synthesis of 1, 2, 4-triazolo [4, 3-b]-7, 8-dihydropyridazine (28)

The compound 3 in acetic acid was heated under reflux for 8 hrs. The solid compound was separated and recrystallized from a proper solvent to give compound 28.

Synthesis of 3-(3, 5-dimethylpyrazol-1-yl)-4, 5-dihydropyridazine (29)

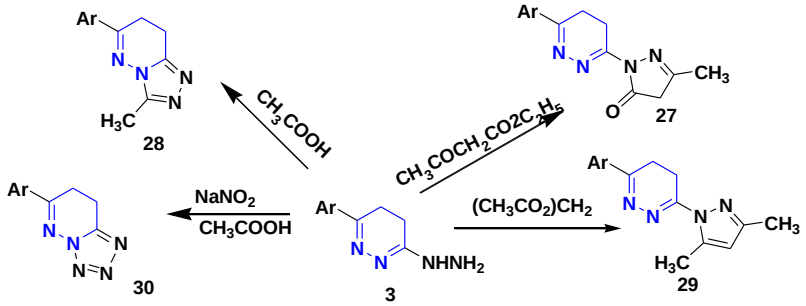
A mixture of compound **3** and 2,4-pentanedione in ethanol was heated at reflux for 4 hrs. The solid compound **29** was separated and filtered off and crystallized from a suitable solvent.

Synthesis of 3-phenyl-6-(3, 5-dimethylpyrazol-1-yl) pyridazine (29)

Acetylacetone was added to a mixture of compound 3 in methanol and the reaction mixture was refluxed for 5 hrs. The solid compound 29 was separated after cooling was recrystallized from methanol to give yellow crystals.

Synthesis of 1, 2, 3, 4-tetrazolo [1, 5-b]-7, 8-dihydropyridazine (30)

The compound **3** was dissolved in 10% aq. HCl was added a solution of sodium nitrite dissolved in water drop wise 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). Solvent was removed in vacuo and the residue was crystallized from a proper solvent to give 30.



Scheme 6: Reactions of substituted pyridazinone derivatives

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, anhydrous potassium carbonate, chloroacetic acid and dry acetone was refluxed for 24 hrs. After filtration while hot and removing the excess solvent, the compound 31 was recrystallized from ethanol.

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 was added to a mixture of compound 1, anhydrous K_2CO_3 in dry acetone and the reaction mixture was refluxed for 24 hrs. The compound solid 32a that separated on cooling was recystallized from benzene to give 32a as a white solid and a mixture of compound, anhydrous potassium carbonate, benzenesulfonyl chloride and dry acetone was refluxed for 24 hrs. After filteration while hot and removing the excess solvent, the compound 32b product was recrystallized from ethanol.

Synthesis of Ethyl-2-(5, 6-dihydro-3-phenyl-6-oxo-5-pyridazin-1(4H-yl)-acetate (33)

A mixture of compound 1, anhydrous potassium carbonate, ethyl chloroacetate and dry acetone was refluxed for 24 hrs. After filteration while hot and removing the excess solvent, the compound 33 was recrystallized from ethanol.

Synthesis of N-(6-phenyl-4, 5-dihydro-3(2H)-pyridazin-3-yl)-hydroxy amine (34)

To a solution of compound 2 in absolute ethanol and equmolar amount of hydroxylamines hydrochloride was added and the reaction mixture was refluxed for 4-10 hrs. The crude compound 34 obtained after concentration and cooling was filtered off and recrystallized from the suitable solvent [22].

Synthesis of 4, 5-dihydro-6-phenyl-4-[3-oxo-1, 3-diphenylpropyl]-3(2H)-pyridazinone (35)
To a solution of compound 1 and potassium ethoxide in absolute ethanol, 1, 3-diphenyl propanone was added. The reaction mixture was heated under reflux for 4 hrs then left overnight at room temperature. The reaction mixture was acidified with dil. HCl. The solid compound 35 obtained was filtered off, washed with H_2O and crystallized from ethanol.

Synthesis of acectic acid-N´-(6-phenyl-3(*2H*)-4, 5-dihydropyridazin-3-yl)-hydrazine (**36)**
A mixture of compound 2 and acetyl-hydrazine in *n*-butanol was heated under reflux for 48 h. The solid compound 36 was separated after concentration and cooling was crystallized from a proper solvent.

Synthesis of 6-phenyl-3-(ethylsulfanyl) pyridazine (**37a**) and **6-phenyl-3-(benzylsulfanyl) pyridazine** (**37b**)
A compound 1, anhydrous potassium carbonate, diethyl sulfate or benzyl chloride and dry acetone were refluxed for 40 hrs. After filtration while hot and removing excess solvent, the product was recrystallized to give 37a and 37b respectively.

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 in absolute ethanol, 2-amino-3-carbethoxy-4, 5-dimethylthiophene or 2-amino-3-carbethoxytetrahydrobenzothiophene were added and the reaction mixture was refluxed for 5 hrs. The solids compound was separated on cooling and recrystallized to give compound 38a and 38b respectively.

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 and compound 2 were dissolved in tetrahydrofuran. The reaction mixture was cooled to 0°C, then dicyclohexyl carbodiimide was added and the mixture stirred for 2 hrs at 0 °C, left for 24 hrs at 0 °C and for another 24 hrs at room temperature. The dicyclohexylurea was filtered off, the filterate evaporated *in vacuo* and the residue recrystallized from a suitable solvent to give compound 39a and 39b respectively.

Discussion
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 ethanol and of K_2CO_3 given substituted pyridazinone derivatives. The reaction of compound 1 with monochloroacetic acid in dry acetone/K_2CO_3 yielded the 2-methyl pyridazinone derivative by nucleophilic substitution and decarboxylation. The 2-methyl pyridazinone (7) can be prepared by 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 behavior of pyridazinone derivative 1 towards electrophilic reagents like $POCl_3$ gave 3-chloro pyridazine 2, by substitution of the enolic hydroxyl group with chlorine together with dehydrogenation. The reaction of compound 2 with hydrazine hydrate and/or phenylhydrazine gave the hydrazine derivatives 3. 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 compound 1 towards carbon electrophiles, namely, ethyl chloroacetate, acrylonitrile, formaldehyde and secondary amines (Mannich reaction), aromatic aldehydes and carbon nucleophiles, like $POCl_3/PCl_5$ and P_2S_5 has tested. 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 3 undergoes cyclization to afford pyrazolone derivative and 3-(3, 5-dimethylpyrazol-1-yl)-pyridazines. On reaction with acetylhydrazine in boiling butanol and/or sodium azide in DMF the compounds 2 affords the triazole [4, 3-b] pyridazine and the tetrazolo [1, 5-b] pyridazine. Reactivity of pyridazinones bears bulky moieties at position 4 and 6 and the effects of steric hinderance of these groups with carbon electrophiles and nitrogen nucleophiles. Thus, pyridazinone reacted with ethyl chloroacetate in acetone and K_2CO_3 to afford 3-*o*-carboethoxymethyl-4, 5-dihydropyridazine. Treatment of compound 2 with acrylonitrile in ethanol containing sodium hydroxide solution, a Michael-type addition occurred at the activated double bond and given the 2-cyanoethyl-4,5-dihydropyridazin-3-one. The 2-hydroxymethyl derivative 7 which on cyclo-condensation with urea given 9-benzylamino-2,3,4,8,9-pentahydro-pyridazino[1,6-a]-1,3,5-triazin-2-one (8). The 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-dihydro-pyridazines, respectively [34-40].
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 hydrazono-pyradazines. Mixing chloropyridazine 2 with amines, aniline, sulphanilinic acid, α-naphthylamine or diphenylamine in benzene gave different pyridazine derivatives. Reaction of chloropyridazine 2 with hydrazine hydrate in boiling benzene gave the hydrazine-pyridazine 3. The structure of 3 was confirmed by its reaction with acetyl acetone in hot methanol that gave 3-phenyl-(3,5-dimethyl pyrazol-1-yl) pyridazine. Compound 1 was reacted with excess CH_3I in methanol the quaternary ammonium iodide derivative was formed. The reaction of compound 1 with benzene/4-toluenesulfonyl chloride and K_2CO_3 in acetone under reflux gave 6-phenyl-2-(arylsulfonyl)-dihydro-pyridazinones, respectively. Treatment of compound 1 with P_2S_5 in xylene gave 6-phenyl-4-(1,5-dimethyl-2-phenyl-3-thioxo-2,3-dihydro-1H-pyrazol-4-yl)-pyridazine-thione 4. The hitherto reaction of chloropyridazine 2 with 2-amino-3-carbethoxy-4,5-dimethyl thiophene given the three fused ring 7-phenyl-2,3-dimethyl-4H-thieno-[2',3':4,5]-pyrimido-[1,2-b]pyridazin-4-one. Compound 2 reacted with 2-amino-3-carbethoxy tetra-hydro-benzothiophene to afford a compound having 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 compound 2 react with thiourea, in dry xylene gave the 6-phenyl-pyridazine-thione (4). The compound 4 is supported by its reaction with DMF and benzylchloride in acetone and K_2CO_3 to given 6-phenyl-3-(ethylsulfanyl)-pyridazine and 6-phenyl-3-(benzylsulfanyl)-

pyridazine. The 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. Reaction of the compound 3 with acetylacetone in methanol gave 6-phenyl-3-(3,5-dimethyl-1H-pyrazol-1-yl)pyridazine, while reaction of 3 with benzil in methanol gave the compound 1,2-diphenyl-1,2-ethanedione-1-N-[6-phenyl-3-pyridazinyl]-hydrazone [34-40]. The pyridazinones have been used as the key material for the synthesis of some novel compounds. The different synthetic methods were used for synthesis of substituted pyridazinone derivatives by using different chemical reagents [40-45]. The reactions of pyridazinones with PCl_5/$POCl_3$, arylsulphonyl chlorides, aliphatic and aromatic aldehydes, hydrazine hydrate, hydrazones, aliphatic and aromatic amines etc gives different type of pyridazinone derivatives. Sometimes the incorporation of amino acid residues in various sulfur- and nitrogen-containing heterocycles enhances the biological activities [46-50].

Conclusion

Pyridazine belong to a vital group of heterocyclic compounds and lot of research work on has been done in the past. The pyridazine moiety posses almost all types of biological activities and also used as intermediates for drugs and agrochemicals agents. Recently, pyridazine derivatives have received substantial interest due to their wide range of alications. Encouraged by these reported that pyridazine derivatives containing substitution of different group to improve the biological activities of these compounds in future. Pyridazines drew our attention because of their easy substitution at various ring positions, which makes them attractive synthetic building blocks for designing and development of novel pyridazines. By the present scenario it can be concluded that pyridazinone have a great potential which remain to be disclosed till date. The innovation of biological activities in a series of pyridazine derivatives stimulated the dynamic growth of investigation in this area.

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