



A Review on Synthetic Protocols of Pyridazine and Pyridazone Analogues

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ABSTRACT: Several methods for syntheses are available in literatures which involve conventional synthesis methods. Most synthesis of pyridazine is based on the addition of hydrazine or its derivative to an appropriately 1,4-disubstituted carbon chain. As part of our program aimed at utilizing β -aroylpropionic acid derivatives containing the different aromatic moiety as starting materials react with different hydrazine derivatives for the synthesis of pyridazine and pyridazinone derivatives, these reports of interesting biological activities prompted us to synthesize a new series of pyridazinones containing different other moieties to give the corresponding pyridazinone. © 2015 iGlobal Research and Publishing Foundation. All rights reserved.

INTRODUCTION

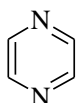
The diazines are six membered ring containing two nitrogen atoms. Three isomeric diazines are theoretically possible and all of them are known.



1,2-Diazine
(Pyridazine)



1,3-Diazine
(Pyrimidine)

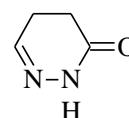


1,4-Diazine
(Pyrazine)

Knorr Coined the term pyridazine for 1,2 diazine ring system¹, however Fischer first prepared substituted pyridazines in 1886 & later on by Tauber² in 1895.

Pyridazines have not been investigated as thoroughly as the other isomeric diazines especially pyrimidine because they are not known to occur in nature and are not easily produced by nitrogen biochemical transformation. Since, some pyridazines have been found useful as growth inhibitors or medicinal compounds; the literature has been expanding day by day.

Pyridazine has been assumed to be a planar molecule for which two Kekule structures are given as mentioned. Pyridazine is a resonance hybrid in which the greater contribution is made by the structure containing =N-N=configuration³. The 1,2 diazine systems that contain a carbonyl group in the ring are called pyridazinone.



4,5-Dihydropyridazin-3(2H)-one

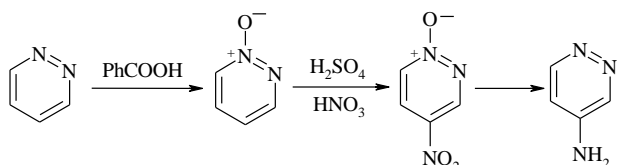
During last two decade numbers of pyridazines have been synthesized due to variety of biological activities specially related to cardiovascular system.

Properties of Pyridazine

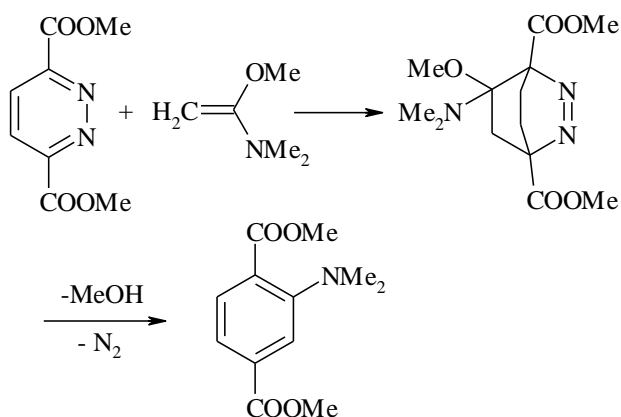
Pyridazine being a pie electron deficient heteroaromatic compound is a colorless liquid at room temperature with pyridine like odour & melting point of -8°C.

Pyridazine is a weak base with boiling point 208°C. This unusually high boiling point compared to benzene (80°C) indicates the involvement of some type of intermolecular association and is attributed to the polarisability of N-N unit, which results in extensive dipolar association in the liquid⁴.

Pyridazine forms pyridazinium mono-cation with acids. It undergoes nucleophilic substitution with great difficulty; but conversion into 1-oxide gives a means of preparing various pyridazine substitution products⁵.



Facile elimination of nitrogen can be used in conjugation with Diels-Alder addition to construct aromatic rings. Pyridazine-3,6-dicarboxylate ester reacts with electron rich alkene to give adducts that undergo subsequent elimination of nitrogen⁶.



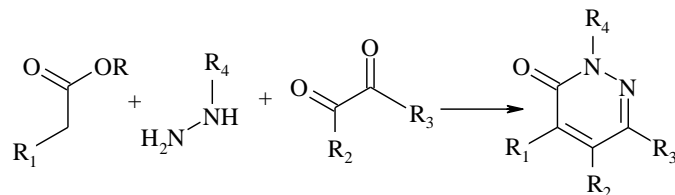
Methods of Preparation of Pyridazines/Pyridazinones

The methods for the preparing pyridazine and pyridazinones can be grouped into three main categories:

- Ring closure of acyclic compounds,
- Alteration and or Fusion with Other Heterocyclic Ring System, and
- Substitution and Displacement on Pyridazinone System

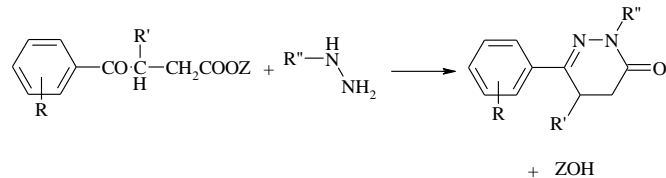
(A) Ring Closure of Acyclic Compounds

i) 1,2-Dicarbonyl compounds: Compounds containing carboxylic group and an active methylene group on condensation with 1,2-dicarbonyl group containing compounds in presence of hydrazine give substituted pyridazinones⁷.



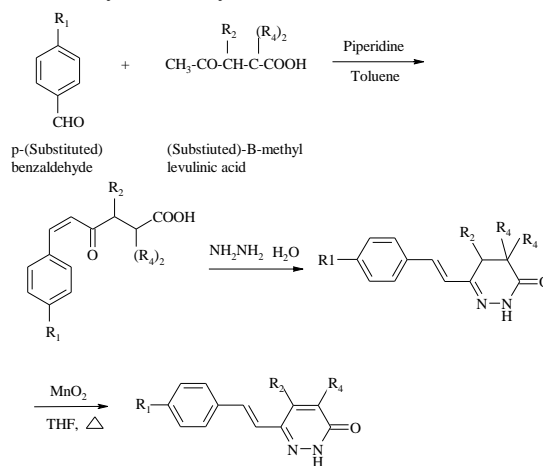
Method 1

ii) Most of the compounds having 6-(alkylaminophenyl)-6-dimethylaminophenyl, and 6-(o-substituted phenyl) constituents are prepared by treatment of appropriate γ -keto acid or γ -keto ester with hydrazine⁸ (Method 2).



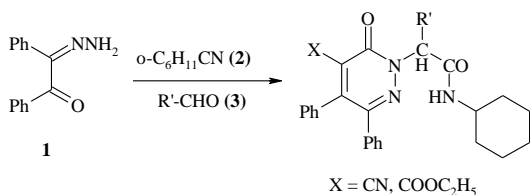
Method 2

iii) Pyridazinone derivatives are also synthesized from Claisen condensation of levulinic acid with benzaldehyde followed by reaction with hydrazine hydrate⁹ (Method 3).



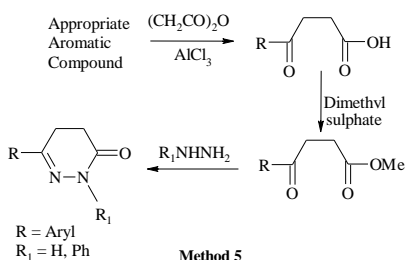
Method 3

iv) The reaction between diarylglyoxal monohydrazone (1), isocyanides (2), aldehydes (3), affords a series of 3(2H)-pyridazinones¹⁰ in very simple manner (Method 4). The intermediate Ugi-four component condensation products are never observed due to their tendency to cyclize when the less reactive cyclopentanone is used instead of aldehyde. Satisfactory yield is obtained for 3(2H)-pyridazinone with the preformed azine.



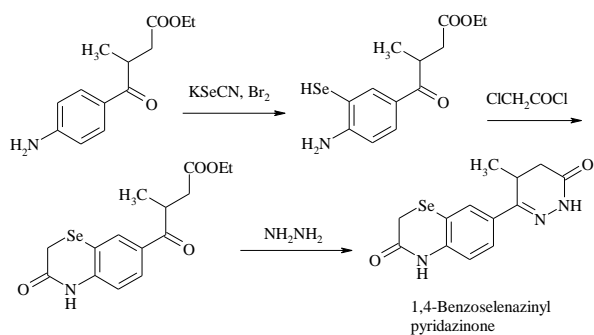
Method 4

v) 6-Aryl-2,3,4,5-tetrahydro-3-pyridazinones can also be obtained by dehydrocyclisation of various hydrazides formed by the reaction of appropriate methyl β -aroyl propionate and hydrazine hydrate in presence of sodium acetate¹¹ (Method 5).



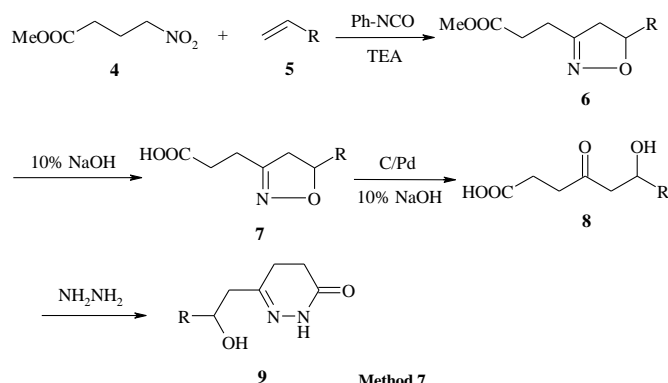
Method 5

vi) Pyridazinone ring system fused with benzoselenazine moiety is synthesized from aminophenyl-3-methyl oxybutyrate¹². It is treated with potassium selenocyanate in acetic acid and bromine. The resultant cyanate is hydrolyzed with sodium sulfide to give aminoselenol; which is then cyclised to the selenazine with chloroacetyl chloride. Reaction with alcoholic hydrazine gives the desired compound (Method 6).



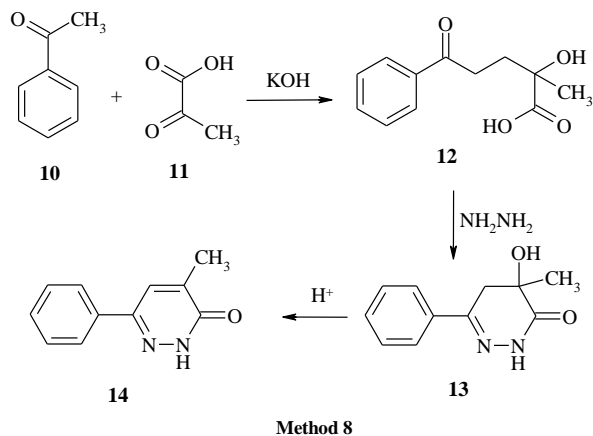
Method 6

vii) Synthesis of new series of 4,5-dihydro-3(2H)-pyridazinones has been carried out according to Method 7. Ring closure of the requisite β -keto acid is readily accomplished in high yield with hydrazine in refluxing ethanol¹³.

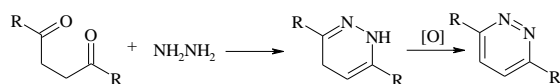


Intermediate (8) is obtained through a two step sequence involving a 1,3-dipolar cycloaddition reaction between the nitric oxide generated from 4-nitrobutyric acid methyl ester (4) and the appropriate alkene (5) followed by reductive ring opening of the formed cycloproduct.

viii) A number of 4,6-disubstituted pyridazinone analogues¹⁴ have been synthesized since the original synthesis of Minaprine (psychotropic drug with pyridazine nucleus) is applicable to a great number of such types of analogues, which starts with the use of acetophenone (Method 8). The first step of the synthesis involves a ketolization reaction between acetophenone (10) and pyruvic acid (11) to give α -methyl- β -benzollactic acid (12). The cyclocondensation of the γ -ketoacids with hydrazine gives the hydroxydihydropyridazinones (13). Tertiary alcoholic group is then easily dehydrated in an acidic medium giving pyridazinone (14).

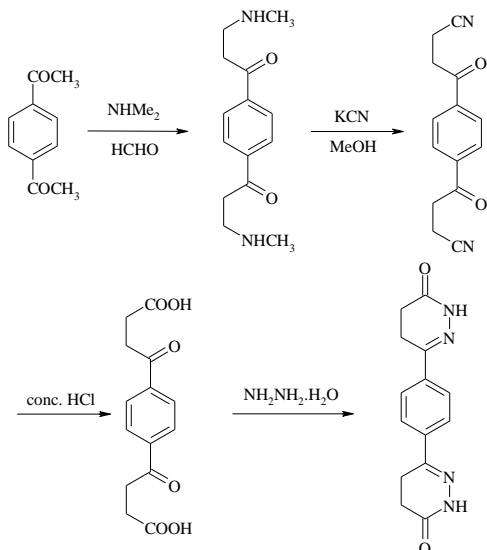


ix) Saturated 1,4-diketones have also been used for the pyridazine synthesis. The intermediate dihydro compound may be oxidized by chromium trioxide in acetic acid¹⁵ (Method 9).



Method 9

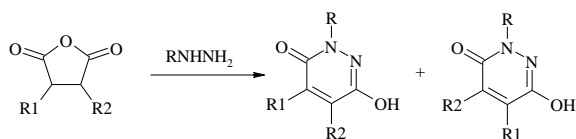
x) Bis-pyridazinone derivatives can be synthesized through the formation of Mannich bases¹⁶. 1,4-diacetyl benzene on treatment with formaldehyde and dimethylamine gets converted to Mannich bases. These undergo elimination-addition with cyanide to give the dinitrile derivative; which on hydrolysis gives corresponding diacid. Cyclocondensation of diacid with hydrazine hydrate gives bis-pyridazinone compound.



Method 10

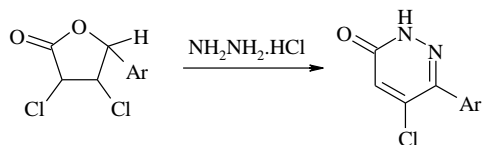
(B) Alteration and/ or Fusion with Other Heterocyclic Ring System

i) A common versatile method for the preparation of pyridazine diones consists of condensation of maleic acid derivatives and their mono- and disubstituted analogues with hydrazines¹⁷.



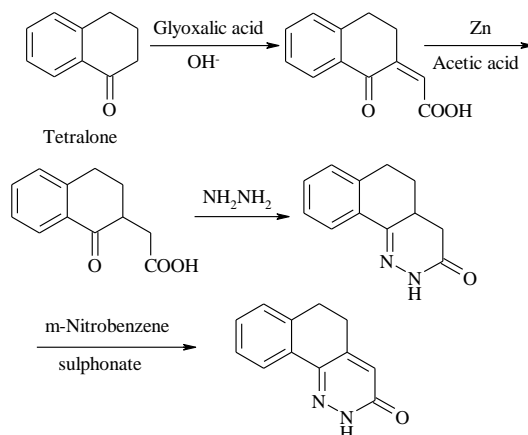
Method 11

ii) Treatment of aromatic γ -lactones of α,β -dihalocinnamic acids with hydrazine also yield substituted pyridazinone.



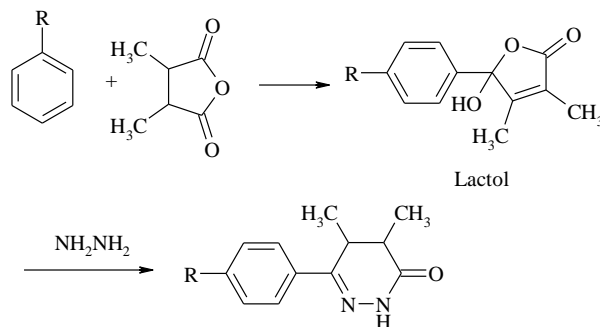
Method 12

iii) Pyridazinone can be synthesized in an unusual way from the reaction of glyoxalic acid and tetralone¹⁸ as illustrated in Method 13.



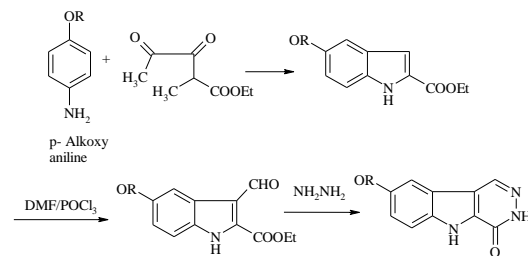
Method 13

iv) Pyridazinone derivatives can also be synthesized by Friedel Crafts acylation of substituted benzene with dimethyl maleic anhydride which gives lactol¹⁹. Reduction of olefinic center in lactol is accomplished with zinc and acetic acid. The crude reduction product is then treated with hydrazine, to get dihydropyridazinone.



Method 14

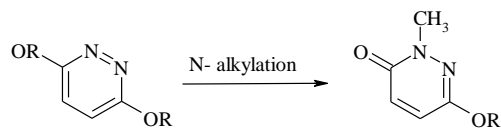
v) Pyridazino-indole derivatives are synthesized from the reaction of p-alkoxy anilines and ethyl- α -methyl acetoacetate²⁰ (Method 15). These alkoxy indoles formed in first step are then formylated using DMF/ POCl_3 through Vilsmeier-Haack reaction. Formyl indol carboxylates on boiling with hydrazine for 2-3 h gives respective pyridazino-indole derivatives.



Method 15

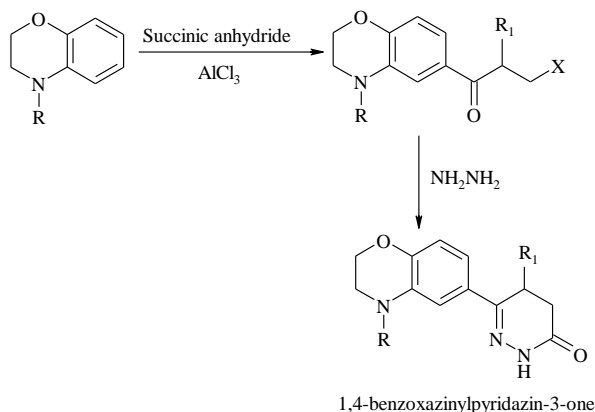
(C) Substitution and Displacement on Pyridazinone System

i) Most commonly used method for synthesis of 3-(2-substituted)-pyridazinones involves N-alkylation of 3,6-dialkoxy pyridazinones²¹.



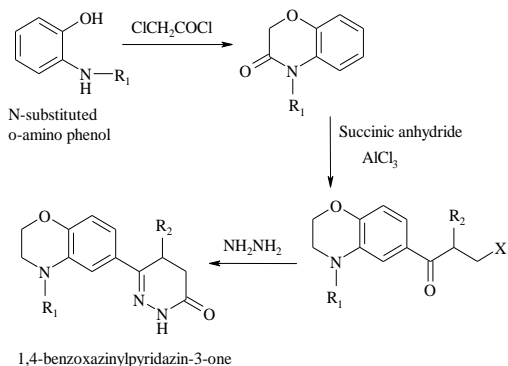
Method 16

ii) Pyridazinone derivatives having benzoxazine substitution on it can be synthesized by using Thyes method²². In this method, keto acids are prepared by Friedel-Crafts acylation of 3,4-dihydro-1,4-(2H)-benzoxazine with succinic anhydride and aluminum chloride. The resultant keto acid is heated with hydrazine hydrate to form 1,4-benzoxazinyl pyridazin-3-one.



Method 17

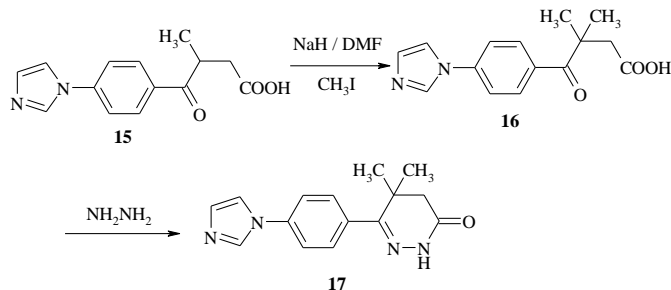
In another method, chloroacetyl chloride is used with appropriate o-aminophenol to give desired benzoxazine. These compounds are then acylated by using succinic anhydride to give oxobutyric acid. Cyclization with hydrazine gives pyridazinones.



Method 18

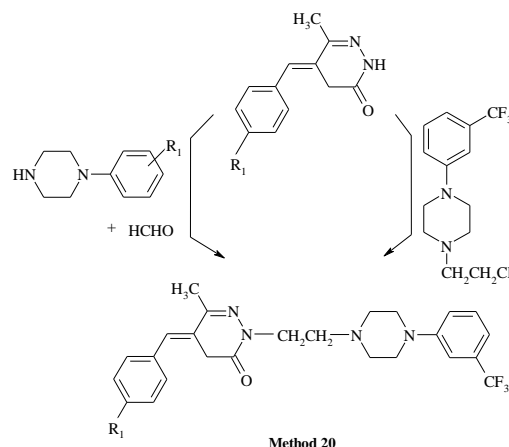
iii) Synthesis of pyridazinones substituted with imidazolyl moiety²³ is accomplished with the formation of 4-(1H-imidazol-1-yl)-β-methyl-γ-oxobenzene butanoic acid (15) or

(16), which on cyclisation with hydrazine gives pyridazinone (17) (Method 19).



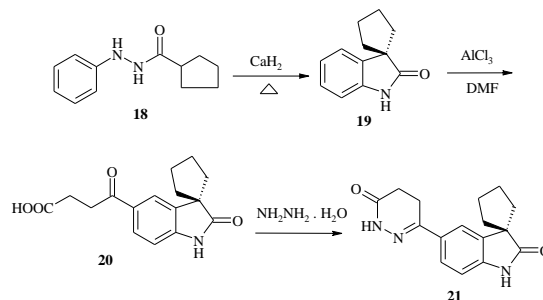
Method 19

iv) A series of 5-aryliendene pyridazinone substituted in 2-position by Mannich bases have also been synthesized²⁴. Introduction of aryl or heteroaryl piperazino group on different pharmacophores has been of considerable interest for medicinal compounds. Synthetic procedure involves refluxing a solution of formaldehyde, pyridazinone and arylpiperazine in ethanol for 12 h and evaporating the mixture under reduced pressure.



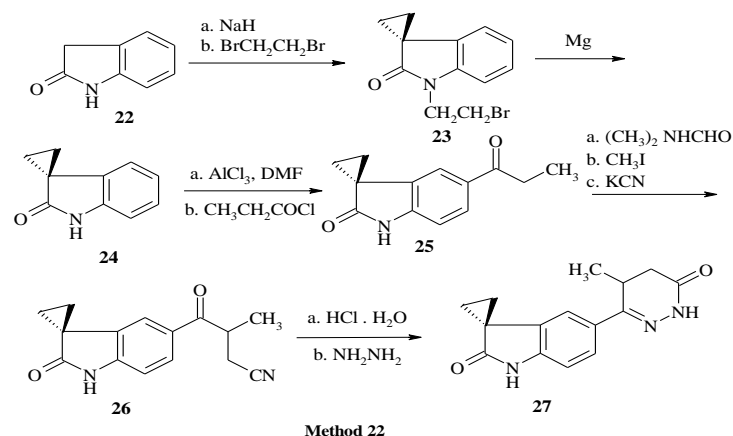
Method 20

v) Spirocyclopentaneindolepyridazinone is synthesized from cyclopentane carboxylic acid-2-phenylhydrazide (18). Base induced rearrangement of this product results in formation of spirocyclopentaneindol-2-one (19). The dihydropyridazinone ring is then synthesized by using succinic anhydride in AlCl₃/DMF according to Thyes method. Finally cyclization with hydrazine hydrate results into pyridazinone derivative (21) with spirocyclic substitution in it.



Method 21

Another method can be used to synthesize similar compounds as given below in the Method 22.



CONCLUSION

Therefore, the synthesis of new compounds devoid of such side effects has become an important goal for medicinal chemists in recent years. For this purpose, various compounds incorporating a 3(2H)-pyridazinone ring have been synthesized and their pharmacological activities have been reported. Recently, it has been reported that a considerable number of 3(2H)-pyridazinone derivatives bear different biological activities. Among these compounds, emorfazone (4-ethoxy-2-methyl-5-morpholino-3(2H)-pyridazinone) is an analgesic and antiinflammatory compound marketed as pentoil and nandron. Rohet et al. reported that most 4,6-diphenyl-2-[3-(4-aryl-piperazin-1-yl)propyl]-3(2H)-pyridazinone derivatives, which were synthesized by inspiration from Trazodone (an antidepressant compound), were more potent than acetaminophen and noramidopyrine in a p-benzoquinone-induced writhing test. In addition, Santagati et al. claimed that 2-substituted 4,5-dihalo-3(2H)-pyridazinone derivatives had high analgesic activity. Vetmedin (pimobendan) 4,5-dihydro-6-[2-(4-methoxyphenyl)-1H-benzimidazole-5-yl]-5-methyl-3(2H)-pyridazinone, is a benzimidazole-pyridazinone derivative, is a nonsympathomimetic, non-glycoside inotropic drug with vasodilative properties. Pyridazine derivatives show various biological activities such as antimicrobial activity, enzyme inhibition, herbicides, etc. Research on the biological action of pyridazines intensified four decades, with many papers and patents on this subject are available.

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