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A REVIEW ON PYRIDAZINE AS A PHARAMACOLOGICALLY ACTIVE NUCLEUS

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Abstract :

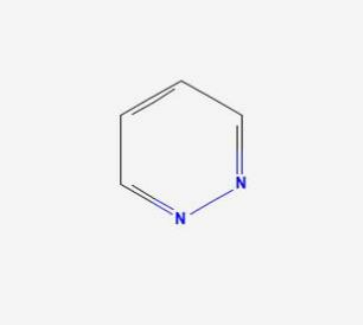
Pyridazines are the important heterocyclic compounds containing nitrogen atom in their cyclic rings . These pyridazines belongs to the heterocyclic class of diazines. The pyridazine is an important structure for various biological activities[1]. This fused heterocyclic systems represents a common structural features for many bioactive compounds showing a variety of pharmacological activities. These activities of pyridazine is important for the design and development of new drugs. Pyridazine shows a wide range of pharmacological activities such as antihypertensive, anti-depressant, hepatoprotective, antiviral, anti-cancer, antimicrobial, cardiotonic, vasodilation, analgesic, anti-inflammatory etc[2]. Synthetic pyridazine compounds acts as effective antiprostaglandins (PGs), S-lipoxygenase (S-LOX) and antiplatelet agents, that is, inhibitors of prostaglandin or cycloxygenase (COX-I & COX-II) enzyme, platelet cAMP , phosphodiesterase and thrombaxane A2 (TXA2) synthase. These pyridazines also acts as selective and non-selective COX inhibitors. This review summerizes about the most relevant pharmacological properties of pyridazine derivatives[3][12].

Key words : Pyridazine, heterocyclic compounds, biological activities, cyclooxygenase-2

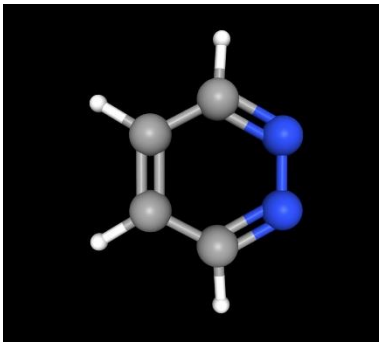
Introduction :

Pyridazine is an aromatic, heterocyclic, organic compounds with the molecular formula C4H4N2 . It contains a six membered ring with two adjacent nitrogen atoms. It is a colorless liquid with a boiling point of 208°c [4].

Structures of pyridazine :



. Chemical Structure



3D structure.

Crystal structure

Properties :

Chemical formula : C4H4N2

Molar mass : 80.090 g/mol

Colour : colourless liquid

Melting point. : -8°c (18°F ; 265K)

Boiling point. : 208°c (406°F ; 481K)

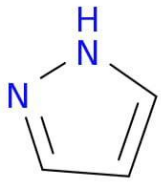
Refractive index : 1.52311(235°c)

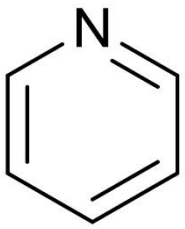
Solubility. : soluble in benzene , di ethyl ether . Miscible dioxane, ethanol and Water .

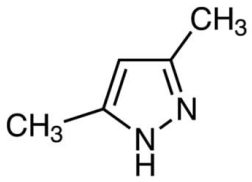
Source : Pyridazines are naturally occurring hydrazines which are found in herbicides such as Credazine, Pyridafol and Pyridate. It is also found In the structure of several drugs such as Cefozopran, Cadralazine, Minaprine , Pipofezine and Hydralazine[5].

Pyridazine derivatives :[6]

Pyrazole.	**Pyridine.**	**3,5-dimethylpyrazole**
Name : Pyrazole.	Name : pyridine.	Name : 3,5-dimethylpyrazole
Molecular formula : C3H4N2.	Molecular formula : C5H5N.	Molecular formula : C5H8N2
Molecular weight : 68.08 g/ mol.	Molecular weight : 79.01g/mol.	Molecular weight : 96.13g/mol.





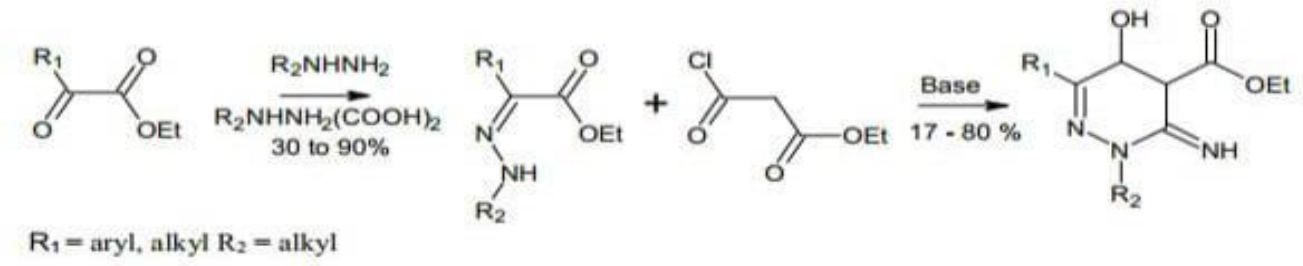


Synthetic methods of Pyridazine :

Synthetic methods involves synthetic reactions of pyridazine. The pyridazine synthesis is based on hydrazine addition to an 1,4-disubstituted carbon chain. There are various methods for the synthesis of pyridazine[20].

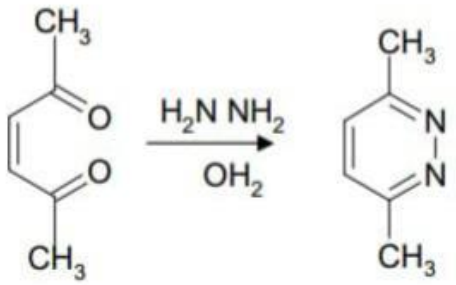
From diketones :

The DMF is added to the solution of diketones at i0 ° c . This mixture was heated at 100° c. Then the solution was concentrated under vaccum. By using column chromatography using suitable eluents or by recrystallization the residue is purified[22]



From 1,4-dicarbonyl compounds

This method involves direct one step cyclization process. The cyclization between 1,4-dicarbonyl compounds and hydrazine yields pyridazine compounds. This is the most common method used for the preparation of alkyl or aryl substituted pyridazine compounds[21].



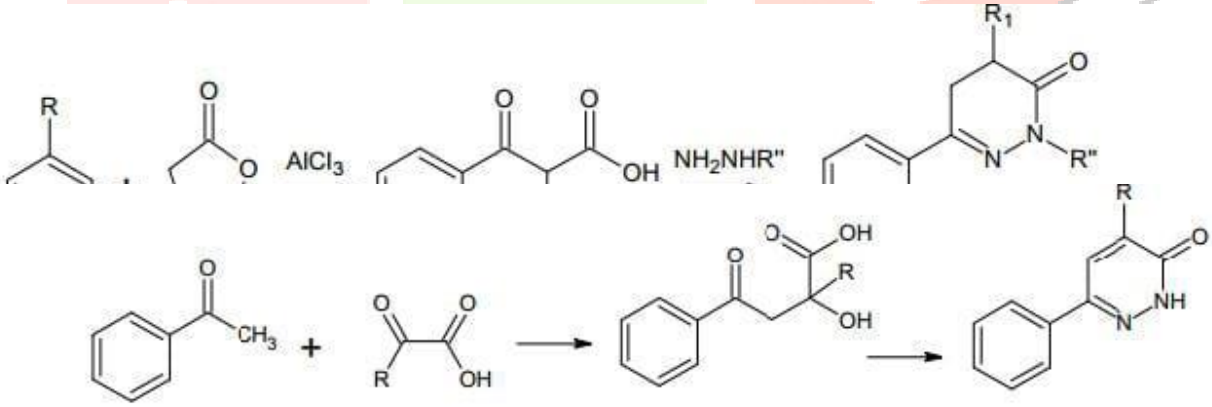
From succinic anhydride :

A mixture of succinic anhydride and hydrocarbons or phenyl groups are added to the solution of aluminum chloride in purified carbon disulphide. The mixture is filtered. The filtrate is acidified with HCL to produce a precipitate. Then hydrazine was added.Then the crystals are washed with cold ethanol, dried and recrystallized from ethanol[22].

From 1,4 ketoesters or ketoacids :

In this method , the hydrazine is added to the anhydrides or 1,4 ketoesters or ketoacids to produce pyridazines[21].

From 1,2 diketone compounds :



In this method , ketones reacts with hydrazine in the presence of an ester containing methyl group and produces pyridazine[22].

From maleic Anhydride :

In this method, the hydrazine derivatives undergoes condensation with maleic anhydride to yield pyridazine rings[22].

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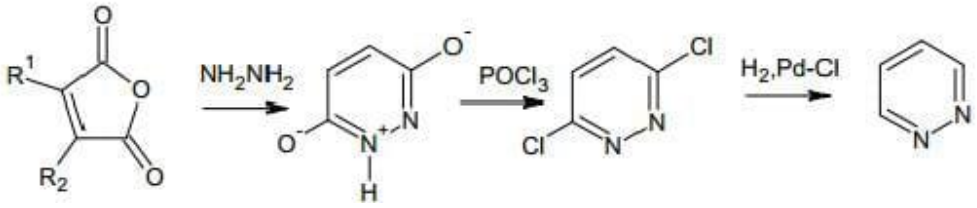


Biological Activities :

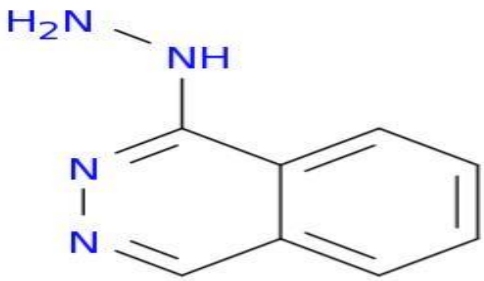
Drugs such as Hydralazine, Minaprine , Cefozopran and Pipofezine contains pridazine ring. The pyridazine and their derivatives show various biological activities like anti tubercular , anti asthma, anti platelet, anti feedant, anti convulsant, anti cancer , anti hypertensive, phosphodiesterase(PDE) inhibitors, antimicrobial , analgesic ,cyclo oxygenase(COX) inhibitors, insecticidal , anti anxiety , anti pyretic , anti depressant etc..[2][3].

Anti-Hypertension :

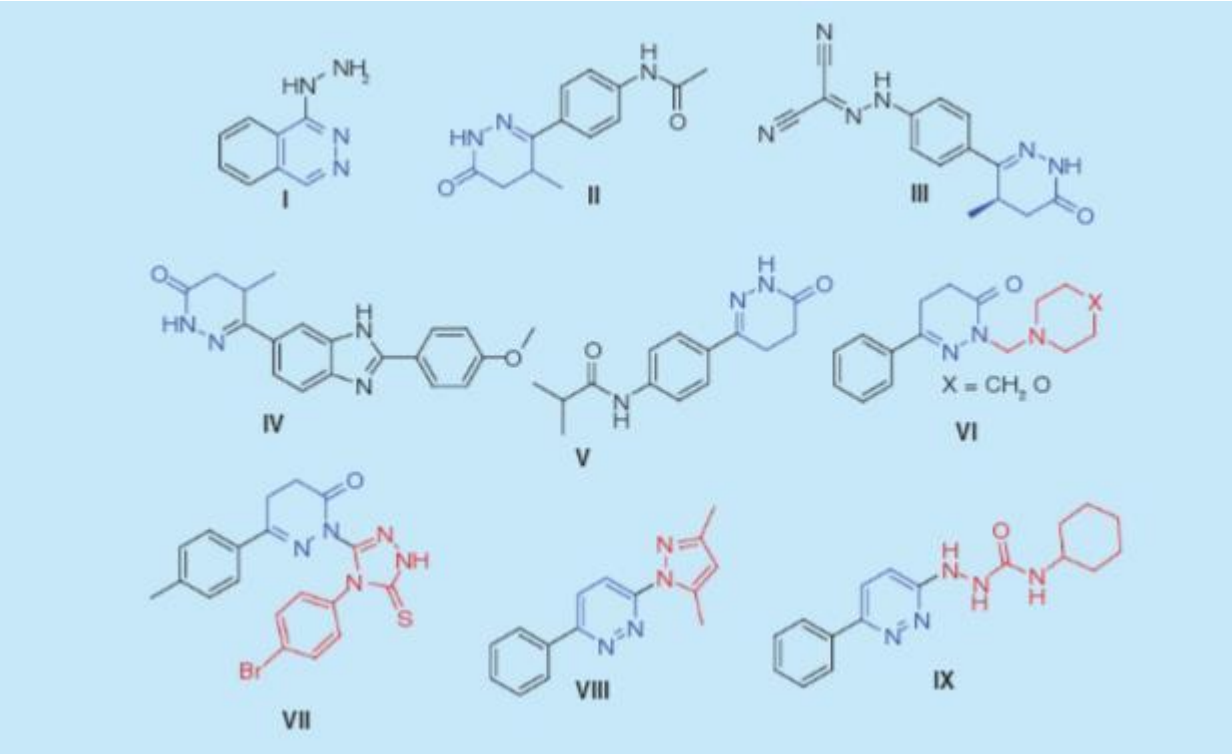
Hypertension is also known as high blood pressure. This hypertension is defined as a systolic blood pressure greater than 130 mmHg or a diastolic blood pressure greater than 80 mmHg. Hypertension is a major health problem in world wide .This hypertension can leads to the development of cardiovascular diseases like coronary diseases, myocardial infarction or stroke and congestive cardiac failure. The Anti hypertensive agents are used to control the blood pressure to maintain normal blood pressure that is 120/80[7].

The first line treatment used for hypertension can be achieved by using thiazides, diuretics , calcium channel blockers, ACE(Angiotensin converting enzyme) inhibitors and beta blockers. Hydralazine is the first drug containing pyridazine ring used for the treatment of hypertension. This hydralazine is a direct acting smooth muscle relaxant and acts as vasodilator. These hydralazine acts by dilating the blood vessels , relaxes vascular smooth muscles , decrease the peripheral resistance there by decreases blood pressure[7].

Hydralazine



The other drugs used for the treatment of hypertension containing pyridazine ring includes scaffold, 4,5-dihydro-6-phenyl pyridazin-3(2H)-ones, levosimendan, pimobendan, doxazosin mesylate, endralazine. A set of 5-methyl-6-p-cyanophenyl-4,5-dihydro-3(2H)-pyridazinone derivatives exhibits antihypertensive activity[7].



Pyridazine containing compounds with anti-hypertensive activity.

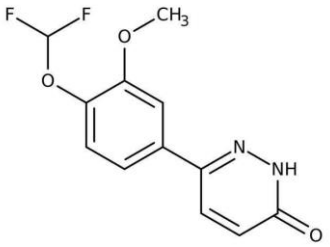
Anti-diabetic activity :

Diabetes is also known as Diabetes mellitus. It is a group of metabolic disorder characterised by a high blood glucose level (hyperglycemia) over a prolonged period of time. This diabetes is either due to insulin deficiency (Type-I) or insulin resistance (Type-II)[8]. The enzyme aldol reductase is responsible for the increased levels of glucose in the blood through sorbitol pathway[9]. So aldol reductase inhibitors are introduced to control blood glucose levels by inhibiting the enzyme aldol reductase. The dugs containing pyridazine ring and their derivatives like Pyrido([2,3-d] pyidazin-5-yl)acetic acid have the ability to block the enzyme aldol reductases[17].

Pyridazine containing drugs with anti-diabetic activity

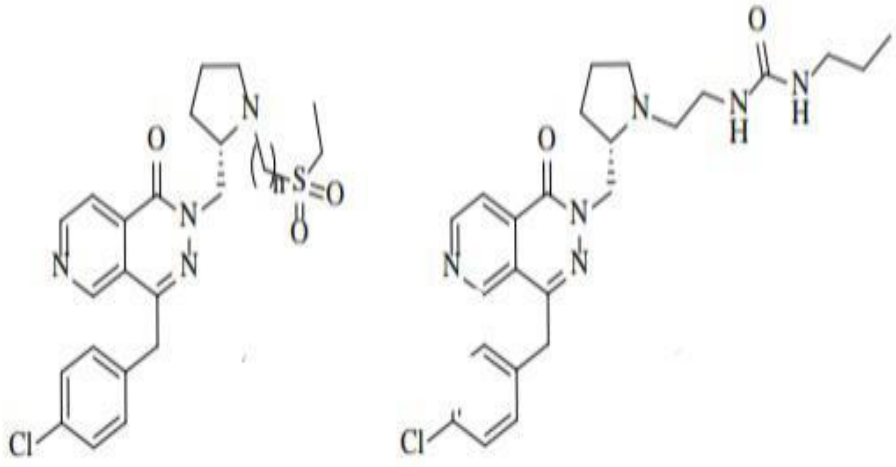
Anti-asthmatic activity :

Asthma is a chronic condition in which a person's airway becomes inflamed, narrow and swell and produce extra mucus , which makes it difficult to breathe. It is also known as bronchial asthma. In asthma the inflammation can be reduced by inhibiting or blocking the enzyme phosphodiesterase enzyme using phosphodiesterase inhibitors. This PDE is responsible for degradation of cAMP to 5-AMP. The blockade of PDE increases the cAMP. The increased level of cAMP leads to inhibition of inflammatory mediator and macrophages and cause bronchial smooth muscle relaxation. PDE-IV inhibitors are powerful anti-inflammatory drugs. The heterocyclic fused pyridazine inhibits PDE-IV enzymes[10]. The [1,2,4] triazolo [3,4-b][1,3,4] pyridazine act as PDE-IV inhibitor. The drug rolipram is a PDE-IV inhibitor prototype with inflammatory potential. Pyridazine derivative zardaverine is acts as a potent bronchodilator and used in the treatment of asthma. A series of substituted 7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine acts as PDE-IV inhibitors. The (R)-3-(2,5-dimethoxy phenyl)-6-(4-methoxy-3-(tetrahydrofuran-3-yloxy)phenyl)-[1,2,4]triazolo[4,3-b]pyridazine are identified as highly potent PDE-IV inhibitors. A series of 6-aryl-4,5-heterocyclic pyridazines are used as PDE-4 inhibitors[10].



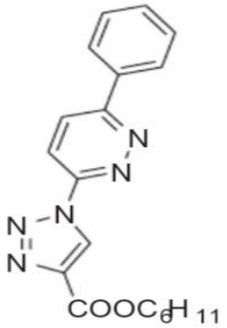
Zardaverine for asthma

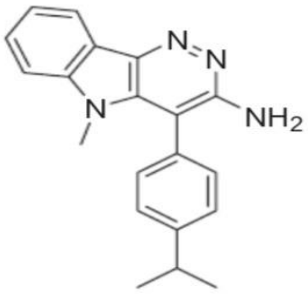
Pyridazine derivatives with anti-asthmatic activity



Anti-tubercular activity :

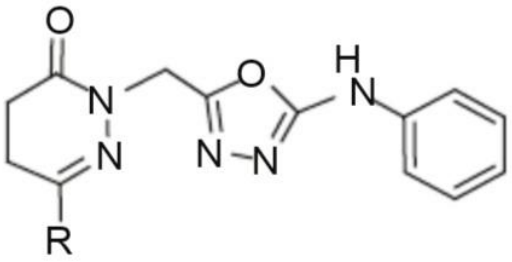
Tuberculosis is an infectious disease caused by bacteria known as Mycobacterium Tuberculosis. This tuberculosis mainly affects the lungs . A series of 6-substituted-3(2H)-pyridazine-2-acetyl-2-(substituted/non substituted acetophenone) hydrazone derivatives were tested for in vitro anti TB activity. A series of 6-substituted phenyl-2-(3isosubstitute phenyl pyridazin 6i-yl)-2,3,4,5-tetrahydro pyridazine-3-ones are tested for their anti-tubercular activity[11]. A Series of 5-(substituted Benzyl)-3-aryl-1,6-dihydro-6-pyridazinoes are tested for their anti-tubercular activity. Benzenesulfonohydrazine bearing 3(2H)-pyridazinone or 1(2H)-phthalzinone rings are tested for their Anti tubercular activity. The derivatives of pyrido[2,3-d]pyridazines were tested for its anti-tubercular activity. The derivatives of pyrido[3,4-d]pyridazine were tested for its antimycobacterial activity. A series of 6-substituted phenyl-2-(3'-substituted phenyl pyridazine-6'-yl)-tetrahydropyridazin-3-ones show anti-tubercular activity. The

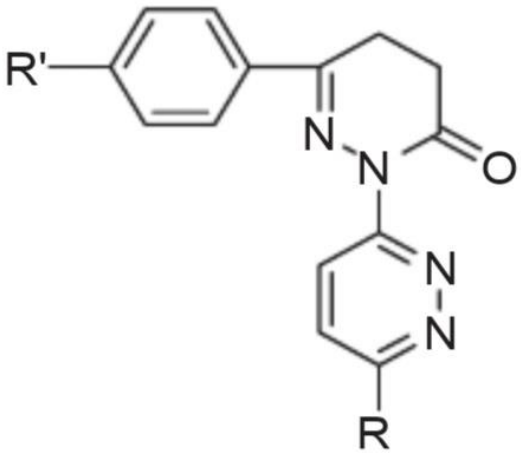


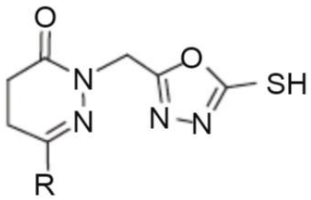


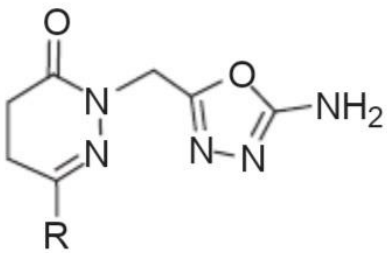
derivatives of 1,3,4-oxadiazole bearing 3(2H)-pyridazinone were tested for anti-tubercular activity[11].

Pyridazine derivatives with anti tubercular activity







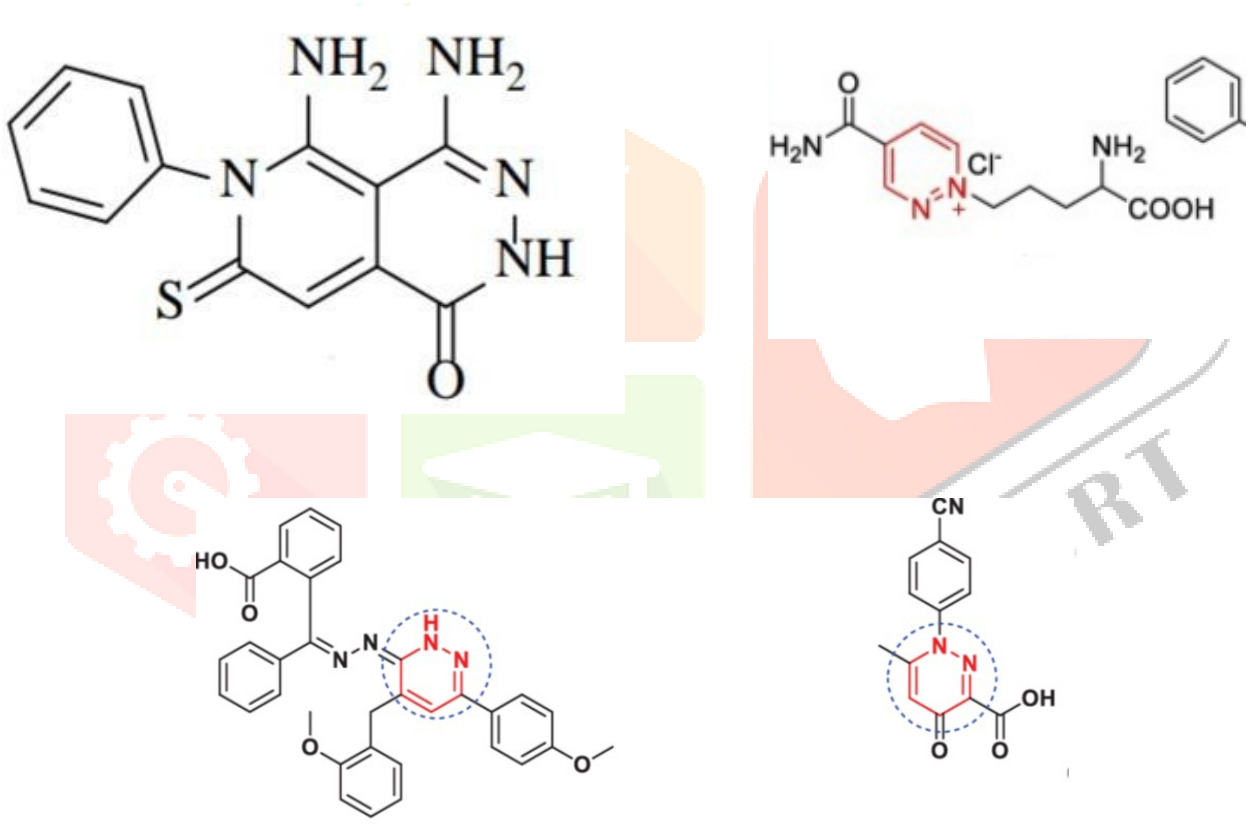


Antimicrobial activity :

Antimicrobial agents are used to treat microbial infections caused by microorganisms like bacteria, fungi and viruses. The drugs containing pyridazine derivatives can also be used for treating microbial infections. 4-cyano-3-oxido-1-beta-D-ribofuranosylpyri dazinium is prepared from 4-cyano 3(2H)-pyridazinone under low temperature. It is a mesoionic analogue of a pyrimidine nucleoside. It posses gram-negative antibacterial activity in vivo against Escherichia coli infections[18].

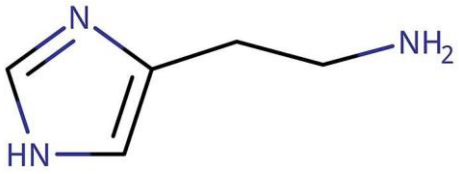
A series of 4-substituted 3-oxidopyridazinium ribonucleosides is 8 as analogue of 4-cyano-3-oxido-1-beta-D-ribofuranosyl pyridazinium. 4-chloro-3-oxido-1-beta-D-ribofuranosyl pyridazinium is more active against Escherichia coli . Pyridazomycin is a pyridazine containing drug used for the treatment of microbial infections[19].

Pyridazine derivatives with antimicrobial activity



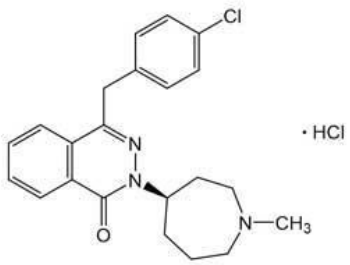
Anti-histaminic activity :

Histamine is a biologically active substance present in mast cells. It is produced from histidine. It acts as a chemical messenger that mediates a wide range of cellular responses, including allergic and inflammatory reactions. Antihistamine are the agents that blocks the action of histamine at the H1 receptor sites. Azelastine is a drug which contains a pyridazine ring. It acts as a selective histamine antagonist for H1 receptors, with a less affinity for H2 receptor and used for treatment of allergies. Azelastine is a mast cell stabilizer, this prevents the release of interleukin-1, tryptase , histamine and TNF-alpha from mast cells and reduces the inflammation[13].



Histamine.

Azelastine hydrochloride as Anti-histaminic agent



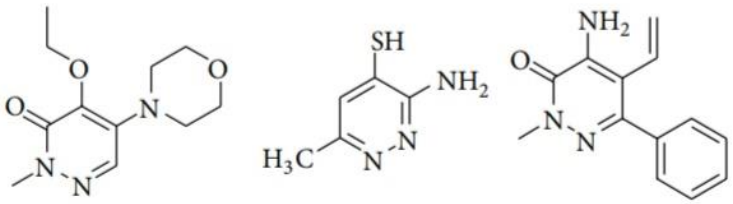
Anti-inflammatory and analgesic activity :

Inflammation is a part of the body's complex biological response to harmful stimuli, such as irritants , pathogens and damaged cells .Analgesics are a class of medications designed specially to relieve pain. Protein kinases are the enzymes which triggers the phosphorylation of protein substances. Among these enzymes, P38 kinase is mediated in the regulation of interleukin-1 and tumor necrotic factor alpha (TNF alpha) as pro inflammatory cytokine secreted by macrophages and monocytes in response of inflammatory stimuli as lipopoly saccharides. A set of pyrido-[2,3-d]pyridazine-2(1H)-one derivatives are used in the treatment of inflammation mediated by protein kinase and related diseases .Example : Pain, pulmonary diseases, Rhemutoid arthritis P38 alpha selective pyridopyridazin-6-1 is effective against autoimmune disorders[18].

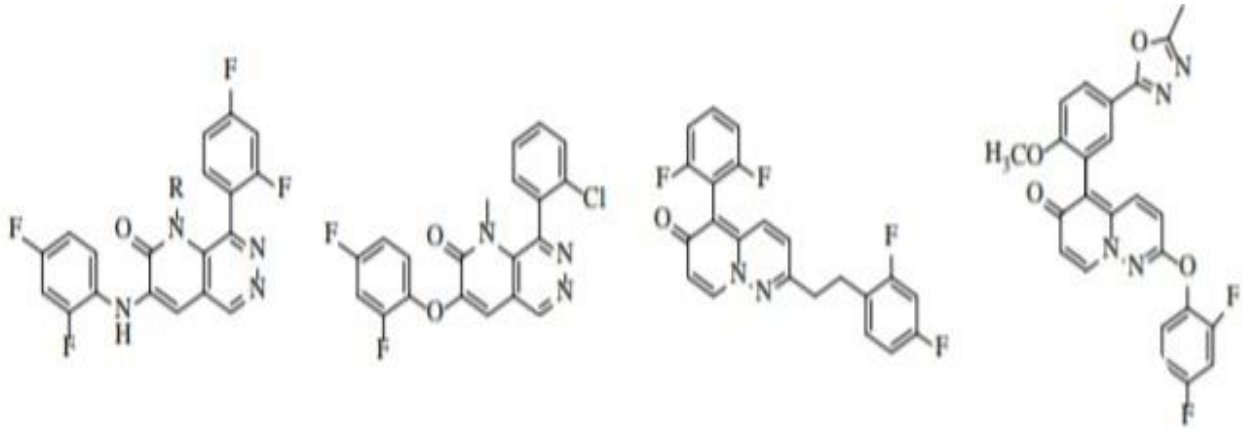
4-ethoxy-2-methyl-5-morpholino-3(2H)-pyridazinone and 3-amino-6-methyl-pyridazine-4-thiol acts as anti-inflammatory agent. A set of 2-(4-substituted-piperazin-1-yl methyl)-6-(thien-2-yl)-2H-pyridazin-3-ones, 2-(4-substituted-piperazin-1-yl carbonyl-methyl)-6-(thien-2-yl)-2H-pyridazin-3-ones, 2-[2-(4-substituted piperazine-1-yl-carbonyl ethyl)-6-(thien-2-yl)-2H-pyridazin-3-ones, 3-(4-substituted piperazin-1-yl-carbonyl-methyl-thio)-6-(thien-2-yl)pyridazines, 3-[2,4-substituted-piperazine-1-yl-carbonyl ethyl thio]-6-(thien-2yl)pyridazines and 5-(4-substituted piperazin-1-yl methyl)-6-(thien-2-yl)-2H-Pyridazin-3ones exhibits anti inflammatory activity[14].

Pain is a highly unpleasant physical sensation caused by illness and injury. Pain is regarded as a symptom for underlying condition. This pain can be relieved by using analgesics. A set of 4-aminosubstituted-2,6,7-trimethyl-1,5-dioxo-1,2,5,6-tetrahydropyrido[3,4-d]pyridazines shows analgesic properties. These compounds were assayed by using hot plate, tail flick and writhing tests for their analgesic activity. A set of 4-amino-2-methyl-6-phenyl-5-vinyl-3(2H)pyridazinones are more potent analgesics. A series of 3-oxo-5-benzylidene-6-methyl-(4H)-2substituted pyridazines possess analgesic activity. Some 2-(6-oxo-3,5-diphenyl-6H-pyridazin-1-yl)-acetamides and 3-(6-oxo-3,5-diphenyl-6H-pyridazin-1-yl)-propanamides exhibits analgesic activity. Some compounds like 2-substituted 4,5-dihalo-3(2H)-pyridazinones have high analgesic activity. The derivatives of 6-substituted-3(2H)cpyridazinone-2-acetyl-2-p-(substituted benzal)hydrazone are more potent than aspirin. A set of amide derivatives of 3-[1-(3-pyridazinyl)-5-phenyl-1H-pyrazole-3-yl]propanoic acid possess analgesic activity equipotent to aspirin. A set of 6-(4-methoxy phenyl)-3(2H)-pyridazone derivatives contains acetamide ring and it states that 1-[3[6-(4-methoxy phenyl)-3(2H)-pyridazinon-2yl]propanoyl]-4(4-fluoro phenyl)piperazine exhibits analgesic activity. Emorfazone is analgesic agent containing pyridazine ring used to relieve pain during dental surgery[15].

Pyridazine derivatives with anti-inflammatory and analgesic activity



Emorfazone (1) ES-1007 (2) (3)



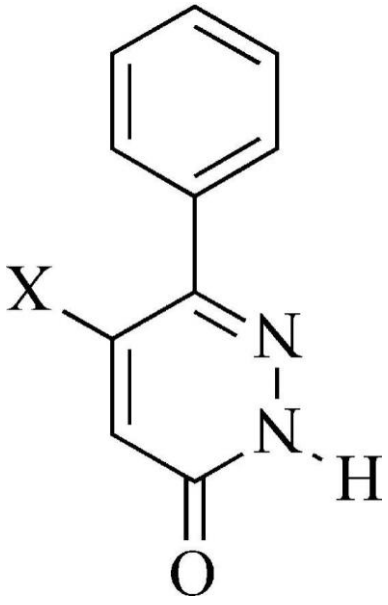
Anti-platelet agent :

Anti-platelet the agents, which are used to prevent platelet aggregation or coagulation or clotting of blood. Platelets are one type of blood cells and plays a major role in blood coagulation .when blood vessels are injured or damaged, platelets are aggregated to form a clot and prevents bleeding. Anti platelets prevents sticking of platelets together and decrease body's ability to form clots. These medications may also help in prevention of heart attack and stroke[16].

A sequence of 6-(4-(substituted-amino phenyl)-4,5-dihydro-pyridazin-3(2H)-ones show anti-platelet action. Pyridazine derivatives prevents platelets aggregation substantially when compared with the normal drug aspirin[16].

A series of 4,7-dimethyl-1,2,5-oxadiazolo[3,4-d] pyridazine 1,5,6-trioxide is effective against anti-platelet activity. In a set of 6-phenyl-3(2H)-pyridazinones, presence of different substituents on position 5 of pyrIdazine ring exhibits anti-platelet activity[16].

Pyridazine derivatives with anti-platelet activity



Anti-cancer activity :

Cancer is defined as a group of diseases involving abnormal growth or uncontrolled proliferation of cells. A cancer agents are used to control the proliferation and to treat cancer[1].

A series of pyrido[2,3 C]pyridazine derivatives were tested for antineoplastic activity. These compounds exhibit promising cytotoxicity and food safety index[3].

A series of pyrazolo [1,5-b] pyridazine derivatives are cyclin dependent kinase inhibitors , Used in the treatment of solid tumors. Modifications on pyrazolo-pyridazine core shows effective against VEGFR-2 and GSK-3 beta. In a high throughput test, the pyrazolo , pyridazine acts as potent inhibitor of CDK1/ cyclin B[3].

The pyrrole [2,3-d] pyridazine-4-one derivatives has cytotoxic action in vitro and effective against to human tumor cells lines which are derived from nine cancer cell types[3].

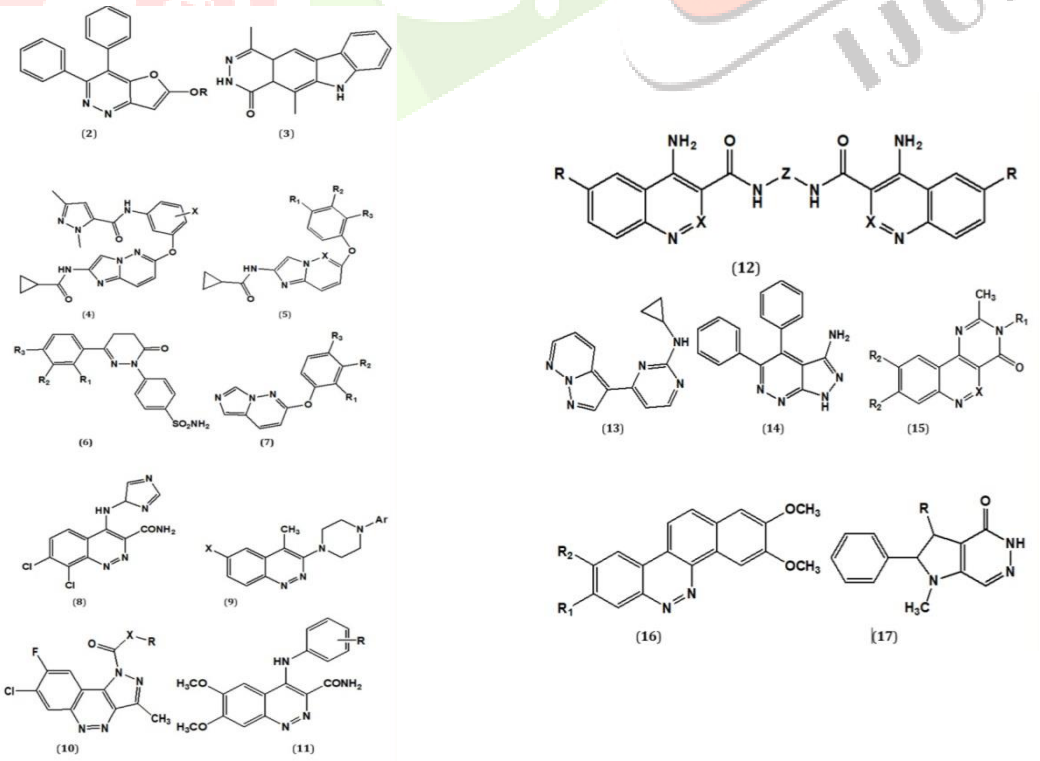
A series of 2-acylamino-6-phenoxy-imidaz[1,2-b] pyridazine derivatives were tested as anti-cancer agents . Among these, 4-[5 (2-[(cyclopropylcarbonyl) amino] imdezo [1,2-b] pyridazine-6yl) oxy-2-methyl phenyl]-1,3-dimethyl] – 1H – pyrazole -s - carboxamide is highly potent VEGFR 2 kinase inhibitor[3].

Two series of imidazo [1,2- pyridazine] and [1,2-a] pyridine derivatives acts as VEGFR 2 kinase inhibitors[3].

A series of 6-aryl-2 (p-sulfamylphenyl) – pyridazin -3(2H) – one derivatives are tested for their anti-cancer activity.

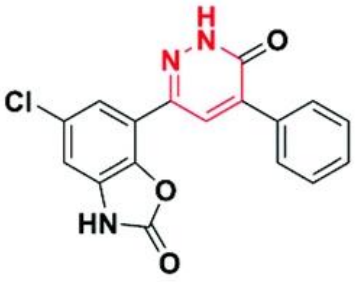
The imidazo [1,2-b] pyridazine derivatives have a benzamide ring are tested for its VEGFR 2 kinase inhibitor activity.

Other activities :

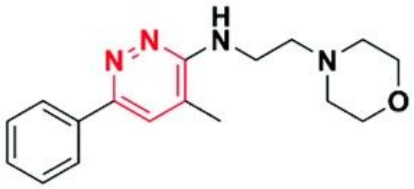


Pyridazine also possess other activities such as cardiotonic, anti ulcer, anti cholinergic, anti depressant, anti secretory etc.. This pyridazine containing drugs may also used in the treatment of congestive heart failure, Psychotic disorders, neurological disorders, epilepsy, cardio vascular diseases, depression etc.. The drugs containing pyridazines and possess biological activities includes levosimendan (congestive heart failure), milrinone (cardotoinc) minaprine (anti depressant) , imazodan (PDE-3 inhibitor) , etc..[12].

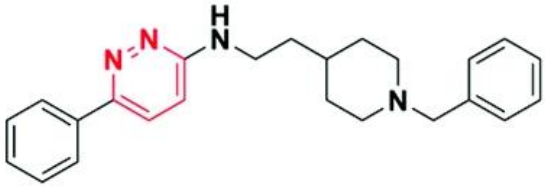
Other activities of pyridazine derivatives



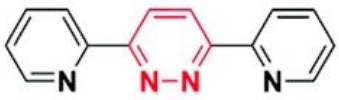
anti-inflammatory



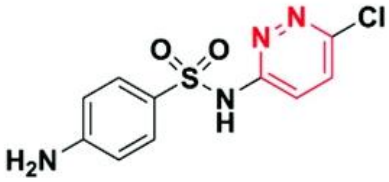
Minaprine (AChE inhibitor)



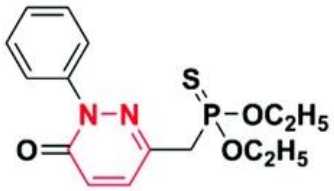
AChE inhibitor



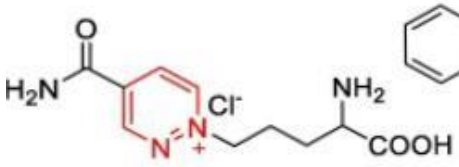
Ditopic pyridazine ligand



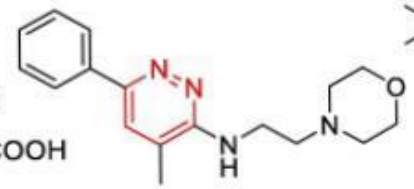
Sulfachloropyridazine (antibiotic)



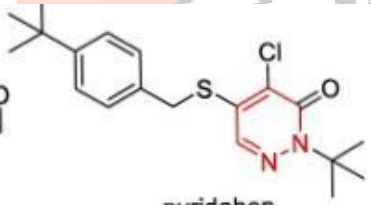
Pyridaphenthion (Insecticide)



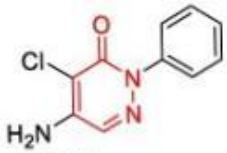
pyridazomycin



minaprine



pyridaben



chloridazone

Conclusion :

We can conclude that pyridazine is one of the compound in pharmaceutical chemistry. The study of this pyridazine may helps to researchers to discover new drugs. Various pyridazine derivatives were exhibited many biological activities. A small variation in substitution pattern on the pyridazine ring causes a large difference in their therapeutic activity. The novel pyridazine compounds have more biological characteristics than prior generation.

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