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Triazolypyridazinones as a New Class of Antihypertensive Agents: Design, Synthesis and In vivo Screening

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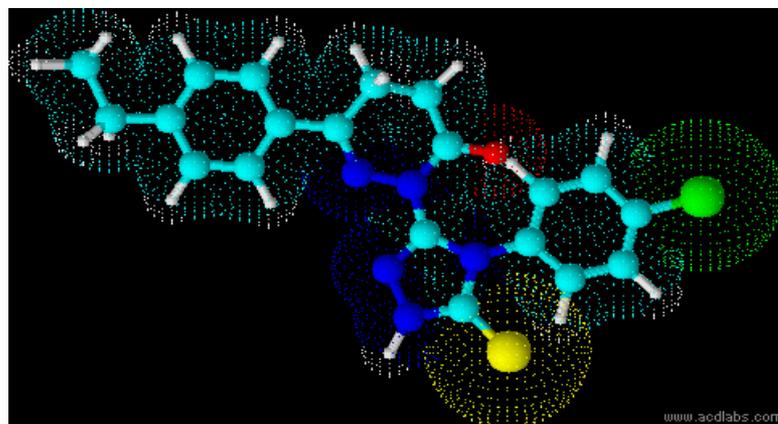
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Triazolylpyridazinones as a New Class of Antihypertensive Agents: Design, Synthesis and In vivo Screening

Graphical Abstract



The current work describes the design and synthesis of novel triazolylpyridazinones with encouraging *in vivo* antihypertensive activity by non-invasive method using Tail Cuff method.



Abstract:

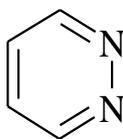
The synthesis of novel pyridazinone derivatives and investigation of their biological properties have gained more importance in recent decades. In particular, the pharmacological activity of 4,5-dihydro-6-phenyl-3(2*H*)-pyridazinones has been extensively studied and such substances are known for their cardiovascular effects. In this field, several compounds such as zardaverine or imazodan have been developed as PDE III inhibitors in the search for new antiplatelet or cardiotonic agents. A number of 6-aryl-2-(4-aryl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-4,5-dihydropyridazin-3(2*H*)-ones have been designed and synthesized by a sequence of reactions starting from the respective aryl hydrocarbons. The final products (**4a–4u**) were evaluated for their antihypertensive activity by a non-invasive protocol using the tail-cuff method. Compounds **4e**, **4i**, and **4k** showed appreciable properties comparable with that of hydralazine and propranolol.

Keywords: Pyridazinone; 1,2,4-Triazole; Antihypertensive activity; Non-invasive method

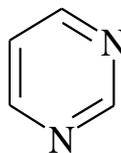


Introduction

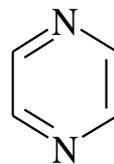
➤ Pyridazine and related compounds:



1,2-Diazine
(Pyridazine)



1,3-Diazine
(Pyrimidine)



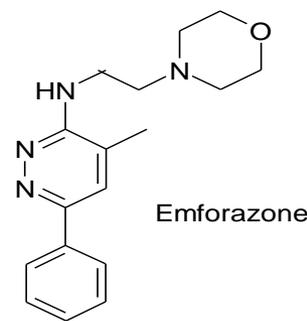
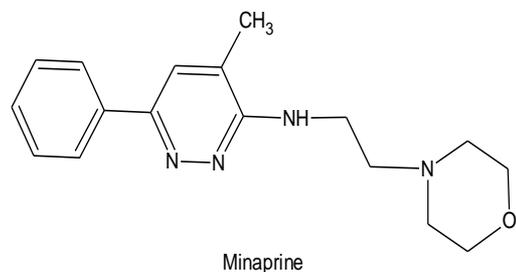
1,4-Diazine
(Pyrazine)

➤ Pyridazine nucleus (dinitrogen containing molecule) is noteworthy for the physiological and biological importance of its derivatives.

➤ Pyridazine and their related compounds are found to have diverse biological activities.



- Most of the compounds having pyridazine/pyridazinone nucleus possesses the higher biological activity related to the cardiovascular system¹⁻³.
- Minaprine and Emferazone emerged as antidepressant and antiinflammatory drugs in Japan⁴.



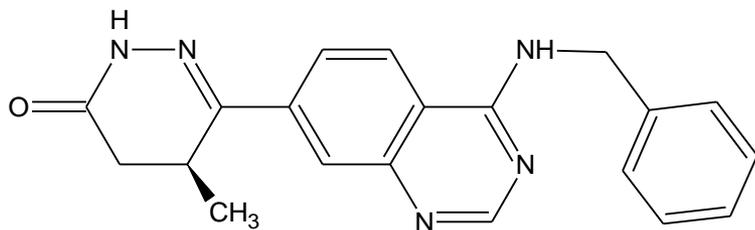
- In our lab several pyridazines/pyridazinones have been screened for antihypertensive and anti-inflammatory activity⁵⁻⁹.



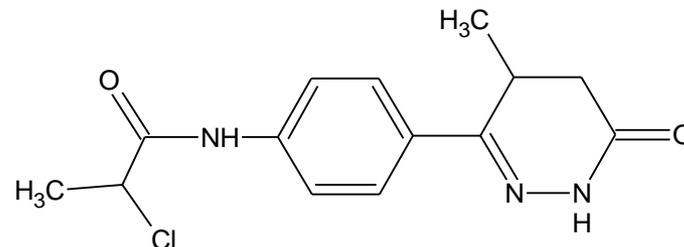
➤ In continuation to the work on pyridazine/pyridazinone ring system in our lab, we have synthesized various pyridazine derivatives and evaluated them for antihypertensive activity¹⁰ by non invasive method.



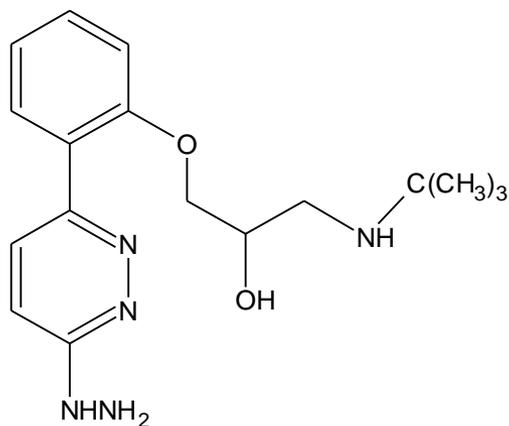
SOME PHARMACOLOGICALLY ACTIVE (CARDIOVASCULAR) PYRIDAZINE/PYRIDAZINONE DERIVATIVES



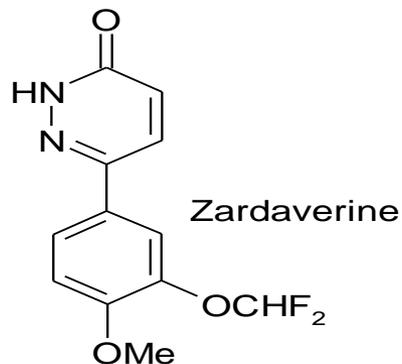
KF 15232 (In treatment of CHF)



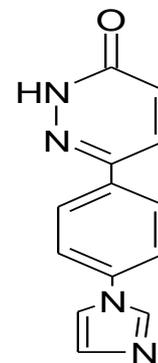
Amipizone (Antithrombotic)



Prizidilol (Antihypertensive)



Zardaverine

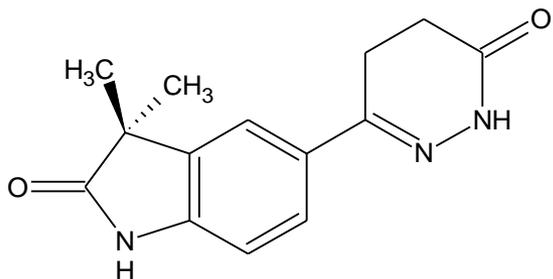


Imazodan

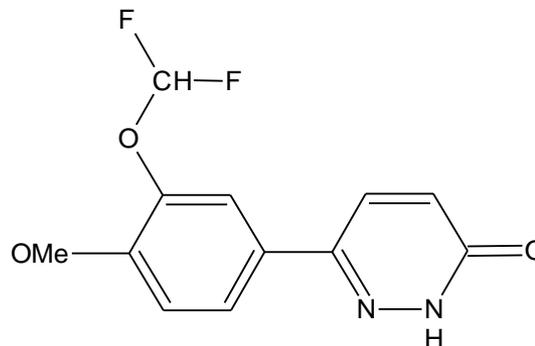
Antiplatelet (PDE III Inhibitors)



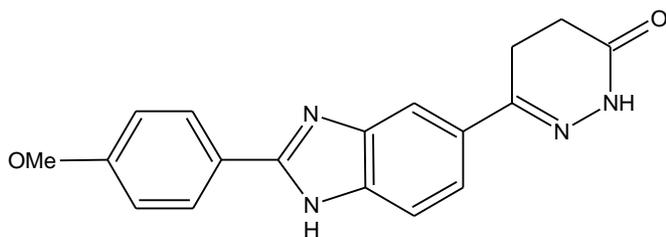
SOME PHARMACOLOGICALLY ACTIVE (CARDIOVASCULAR) PYRIDAZINE/PYRIDAZINONE DERIVATIVES



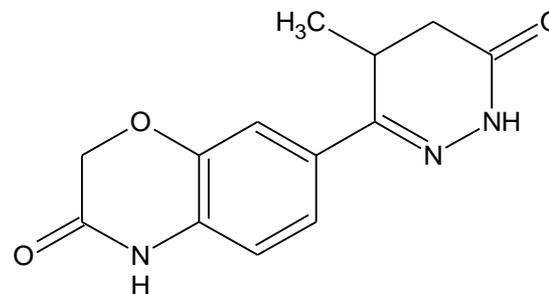
Indolidan (cardiotonic)



Zordaverine (vasodilator)



Pimobendan (cardiotonic)

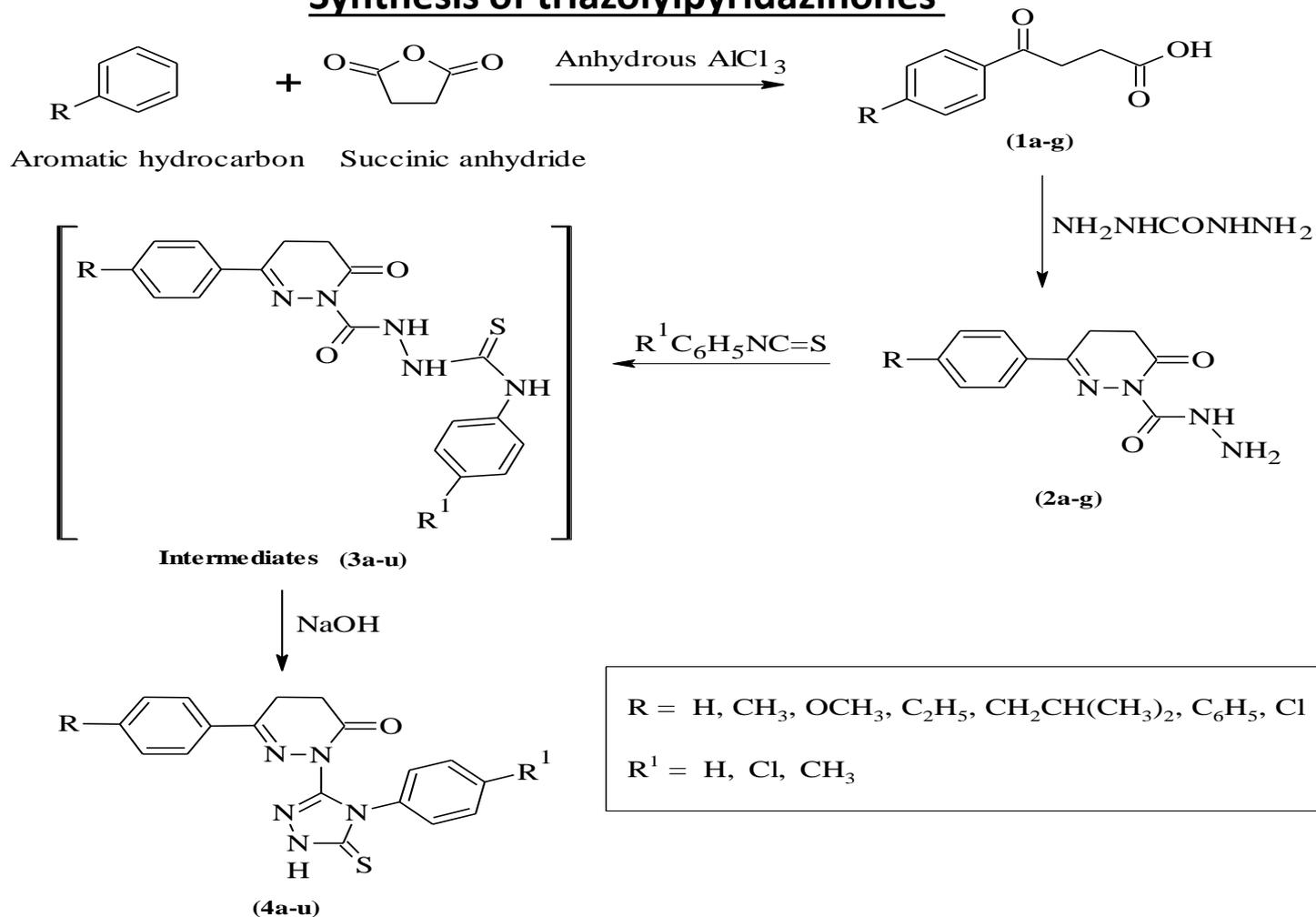


Bemorandan (vasodilator)



Results and discussion:

Synthesis of triazolylpyridazinones



Results and discussion:

- Heterocyclic derivatives constitute an integral part of the currently used drugs due to their diverse pharmacological actions.
- The chemical diversity and various mechanisms of action of antihypertensive agents make it difficult to identify a common pharmacophore. Therefore available antihypertensive drugs belong to different chemical classes.
- The most common structural elements of antihypertensive drugs derived from pyridazine must contain a nitrogen heteroatomic system bearing one or two phenyl rings and at least one carbonyl/-NH group.
- Many investigations indicated that the presence of at least one aryl unit, carbonyl/hydroxy function and NH group in a molecule seems to be necessary in the structure of antihypertensive drugs.



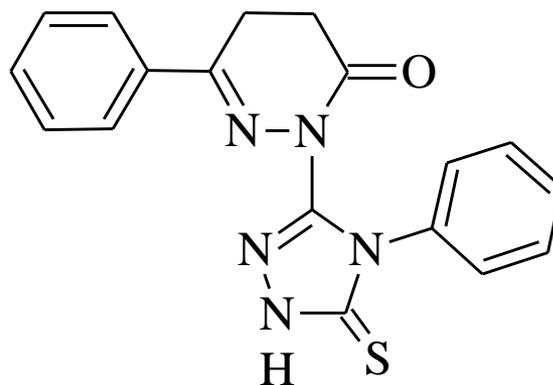
Results and discussion:

- Novel antihypertensive agents are discovered through conventional screening and/or structure modification rather than a mechanism driven design.
- Since several antihypertensive drugs have been associated with side effects and fail to control hypertension, there is a substantial need to develop new, more effective and less toxic Antihypertensive agents.
- Considering the 6-substituted aryl-3(2*H*)-pyridazinone and pyridazine residue as the pharmacophoric group for the activity, we have synthesized and characterized new pyridazine/pyridazinone derivatives as per proposed scheme; and evaluated them for antihypertensive activity in rats by non invasive Tail cuff method.



Results and discussion:

6-Phenyl-2-(4-phenyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydropyridazin-3(2H)-one:



IR: 3323 (NH), 2930 (CH), 2368 (C=S), 1685 (C=O), 1607 (C=N), 1030.

¹H-NMR: 1.40 (t, 2H, CH₂), 2.99 (t, 2H, CH₂), 7.13-7.93 (m, 10H, Ar-H), 10.9 (s, 1H, CSNH).

MS (*m/z*): 349/350 (M⁺/M⁺¹).



Pharmacology: Antihypertensive Activity (Non Invasive Method)

- Various synthesized compounds of proposed scheme were evaluated for antihypertensive activity in conscious rats using CODA Non Invasive Blood Pressure Recorder by Tail-Cuff method (Kent Scientific Corporation, USA).
- Hypertension was induced by Methylprednisolone acetate: 20mg/kg body wt/2 week.
- Dose of synthesized compounds: 20mg/kg body weight.
- Doses of standard drugs (Hydralazine HCl USP and Propranolol): 2.6mg/kg body wt; ip and 14 mg/kg body wt; ip.



Steps involved in measurement of Antihypertensive activity:

- Procurement, identification, and housing of animals: Albino rats (body wt 200-250 g); Kept under standard laboratory conditions in 12 h light/dark cycle at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$; Pellet diet, normal saline and water ad libitum.
- Conditioning/Training of animals: 15 minutes every day at least 10-15 days prior to the day of measurement of MABP.
- Induction of hypertension in rats.
- Animal preparation; placed in the restrainer 10-15 minutes prior.
- Measurement of mean arterial blood pressure (MABP): The MABP was recorded after 1, 3, 6, 12, 24, 48, 72, 96 and 120 h.
- Statistical analysis of data: GRAPHPAD INSTANT 3 software; ANOVA (one way); Effects in treatment groups compared with toxic control group by Dunnet's multiple comparison test.



Conclusions

The 4,5-dihydro-3(2H)-pyridazinone derivatives can be further modified to exhibit better potency than the standard drugs. Further studies to acquire more information about Quantitative Structure Activity Relationships (QSAR) are in progress in our laboratory. The triazolylpyridazinones discovered in this study may provide valuable therapeutic intervention for the treatment of hypertension.



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