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SYNTHESIS AND *IN-VIVO* ACTIVITY OF SOME ANTIHYPERTENSIVE AGENT BASED ON PYRIDAZINE SCAFFOLD DESIGN

Vikash Jakhmola

Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun - 248007, Uttarakhand, India.

Keywords:

β-Aroyl propionic acid; Pyridazine; Antihypertensive activity; Non-invasive method; *In-vivo.*

Correspondence to Author:
Dr. Vikash Jakhmola

Dean,
Department of Pharmacy, Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun - 248007, Uttarakhand, India.

E-mail: jakhmola.1979@gmail.com

ABSTRACT: The main objective presents research work to synthesize, characterization, and *in-vivo* evaluation of Pyridazine derivatives. To study the different synthesized derivatives by using different analytical parameters like IR, Mass, and NMR analysis. And also find out the antihypertensive activity. The studies on the hydralazine group drugs led to the synthesis of many Pyridazine derivatives with a wide activity spectrum on the cardiovascular system. Pyridazine derivatives, a class of compounds containing the N-N bond, exhibit a wide range of pharmacological activities such as antidepressant, antihypertensive and cardiotonic etc. Some 7-phenyl-3, 4, 8, 9-tetrahydro-2H-pyridazino [1, 6-a] [1, 3, 5] triazin-2-imine were synthesized by reacting 6-Phenyl substituted 2, 3, 4, 5-Tetrahydro pyridazin-3-one with cyclic secondary amine under Mannich reaction conditions. The total seven compounds (vj1-vj7) were synthesized under Mannich reaction conditions. All the synthesized derivatives were selected for evaluation of antihypertensive activities by a non-invasive method using Tail Cuff method. Most of the compounds showed good antihypertensive activity. Few compounds like vj4, vj5, and vj6 were found to show a highly significant reduction in mean arterial blood pressure but at a higher dose in comparison to standard drugs like proponolol and hydralazine. The substituted pyridazine derivatives discovered in this study may provide valuable therapeutic intervention for the treatment of hypertension.

INTRODUCTION: In the present scenario, a large number of medications acting through different mechanisms for the treatment of hypertension are available.

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Even one has to admit that the blood pressure of the majority of hypertensive patients is inadequately controlled, partly because the treatment is not conducted intensively enough, but partly also because the medication (s) are not taken as prescribed.

Lowering blood pressure in hypertensive patients requires, therefore, not only a broad choice of effective and well-tolerated medications but also skills to motivate them to comply lifelong with the treatment.

Hypertension is the most common cardiovascular disease. The definition of hypertension, therefore using any specific cut-off point, is arbitrary. Pyridazine derivatives were reported to exhibit diverse pharmacological activities such as antidepressant [1], antihypertensive [2, 3], antithrombotic [4], anticonvulsant [5], cardiotonic [6], antibacterial [7], diuretics [8] anti-HIV [9,] and anticancer [10]. Some pyridazinone derivatives like indolidan [11], bemoradan[12], primobendan [13], levosimendan[14] (antihypertensive), minaprine [15] (antidepressant), emorfazone [16] (anti-inflammatory) and azanrinone [17] (cardiotonic), already appeared in the clinical market. In continuation to work on the pyridazine/ pyridazinone ring system in our lab, we have synthesized some pyridazinone derivatives and evaluated them for antihypertensive activity by the non invasive method.

The main objective of present research study to synthesis, characterization and *in-vivo* evaluation of Pyridazine derivatives. All the synthesized compounds were obtained in good yield by optimizing various synthetic procedures. The structures of the compounds were established by elemental analysis, IR, ^{1}H-NMR, and Mass spectral data analysis. To study the different synthesized derivatives by using different analytical parameters. And also to find out the antihypertensive activity of active synthesized compounds.

MATERIALS AND METHODS:

Chemistry for Basic Compound: Some Synthesis of 7-phenyl-3, 4, 8, 9-tetrahydro-2H-pyridazino[1, 6-a] [1, 3, 5] triazin-2-imine derivatives were synthesized according to scheme. The Friedel Craft acylation of aromatic hydrocarbon with succinic anhydride afforded the β-substituted benzoyl propionic acid in presence of lewis acid, aluminium chloride. The resulting β-benzoyl propionic acids were on hydrazinolysis gave the Pyridazine. The Pyridazine were subjected to Mannich reaction with cyclic secondary amine and formaldehyde to get the final compounds. (vj1-vj7). General procedure for the synthesis of substituted β-aroyl propionic acids were synthesized from respective aromatic hydrocarbon and characterized on the basis of spectral data as per the reported procedure. The appropriate substituted β-aroyl propionic acid was reacted with hydrazine hydrate to get the corresponding pyradazinone and characterized on the basis of spectral basis as per earlier reported procedure [18, 21]. On the basis of the literature report, nitrogen-containing heterocyclic compounds showed diverse pharmacological activities. In this series, pyridazinone derivatives were reported to exhibit diverse pharmacological activities. In recent years substituted pyridazinones have been a subject of demanding research due to their wide range of pharmacological actions [22, 24]. Differently substituted pyridazinone derivatives were exhibited diverse potential pharmacological activities like an antidepressant, antihypertensive, anti-thrombotic, anticonvulsant, cardiotonic, analgesic, anti-inflammatory, diuretics, antibacterial, anti-fungal, antiviral, anticancer, hypotensive, antiulcer and another biological activities [25, 29].

General Procedure for the Preparation of 7-Phenyl-3, 4, 8, 9-Tetrahydro-2H-Pyridazino[1, 6-A] [1, 3, 5] Triazin-2-Imine (Vj1-Vj7): To a solution of 6-phenyl-4, 5-dihydropyridazine-3 (2H)- one (0.001 mol) in methanol (30 mL) was added formaldehyde (37-41%) (2.5 mL) and the contents were refluxed for 6 h. After completion of the reaction methanol was distilled off and the residue was poured into crushed ice to separate out the compound. The solid which separated out, was filtered and crystallized from methanol. The total around seven different derivatives were synthesized by using below scheme and characterized by IR, NMR and Mass spectroscopy.

Pharmacology of Experimental Pharmacology Protocol for Synthesized Derivatives:

Procurement, Identification and Housing of Animals: Albino rats were selected (bodyweight 200-250 g) were supplied by Central Animal House facility of Registration number 173/CPCSEA.

Conditioning/Training of Animals: For conducting the BP measurement studies, the animals were kept in a restrainer for 10 min every day for one week. This exercise was done to avoid the fluctuation in blood pressure due to aggressive behavior of the animal while keeping into the restrainer for measuring the activity.

Induction of Hypertension in Normotensive Rats: After recording the initial BP of rats, the animals were divided into groups of 5 animals each. One group was taken as control.

Measurement of Mean Blood Pressure of Rats: Mean arterial blood pressure was measured in conscious rats using CODA Non-Invasive Blood Pressure Recorder by Tail-Cuff method (Kent Scientific Corporation, USA).

Scheme:

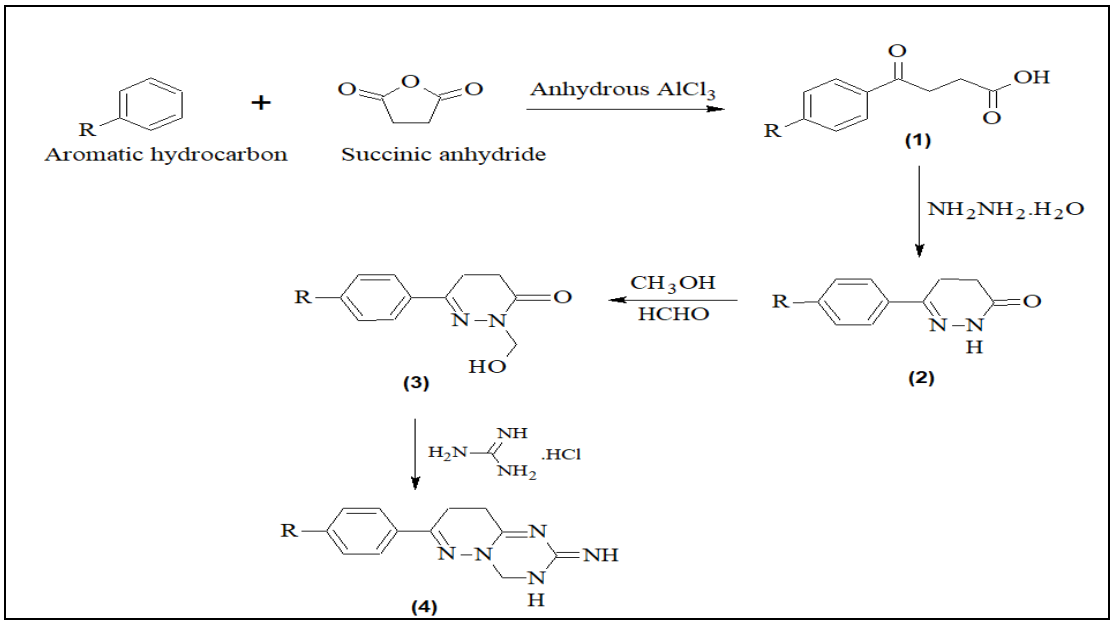


FIG. 1: SYNTHESIS PROTOCOL FOR VARIOUS 7-SUBSTITUTED-PHENYL-3,4,8,9-TETRAHYDRO-2H-PYRIDAZINO [1,6-A] [1,3,5]TRIAZIN-2-IMINE DERIVATIVES.

RESULT AND DISCUSSION: Antihypertensive activities of the compounds were tested by using Tail Cuff method. The results were compared with the standard drug hydralazine [30]. Compound number vj4, vj5, and vj6 were found to show a highly significant reduction in mean arterial blood pressure but at higher dose in comparison to hydralazine. On this basis, it can be concluded that groups like p-C_2H_5, p-CH_2CH $(CH_3)^2$ and p-C_6H_5 in phenyl ring at 6-position increase the activity as shown by the compound vj4, vj5, and vj6 with a percent reduction in MABP 40.88, 40.98, and 42.04% respectively.

Experimental Protocols:

Chemistry: Melting points were determined by the open tube capillary method and are uncorrected. The purity of the compounds was checked by thin-layer chromatography (TLC) plates (silica gel G) which were visualized by exposing to iodine vapors and UV light. The FT-IR spectra were recorded on Bio-rad FTS-135 spectrophotometer using KBr pellets; υmax values are given in cm-1. 1H-NMR spectra were recorded on Bruker Spectrospin DPX 300 MHz using $CDCl_3$ as a solvent and trimethylsilane (TMS) as an internal standard. Chemical shifts are given in δ (ppm) scale, and coupling constants (J values) are expressed in Hz. The FAB Mass spectra were obtained on JEOL-JMS-DX 303 system, equipped with a direct inlet probe system. Elemental analysis was carried out on CHNS Elementar (Vario EL III) using sulphanilic acid as a standard and tugsten (VI) oxide as a combusting agent and analyses for C, H, N were within ±0.4% of the theoretical values.

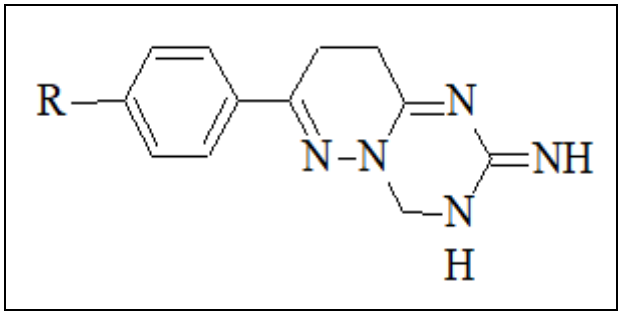
General Procedure for the Preparation of 7-Phenyl-3, 4, 8, 9-Tetrahydro-2H-Pyridazino[1,6-A] [1, 3, 5] Triazin-2-Imine (Vj1-Vj7): To a solution of 6-phenyl-4,5-dihydropyridazine-3(2H)-one (0.001 mol) in methanol (30 mL) was added formaldehyde (37-41%) (2.5 mL) and the contents were refluxed for 6 h. After completion of the reaction, methanol was distilled off, and the residue was poured into crushed ice to separate out the compound. The solid, which separated out, was filtered and crystallized from methanol. A total of around seven different derivatives was synthesized by using above mentioned scheme and characterized by IR, NMR and Mass spectroscopy were mentioned below. Different Synthesized Derivatives Are:

Synthesis of 7-Phenyl-3, 4, 8, 9-Tetrahydro-2H-Pyridazino[1, 6-A] [1,3,5] Triazin-2-Imine (Vj1):
Synthesis of 7-(4-Methylphenyl)-3, 4, 8, 9-Tetrahydro- 2H-Pyridazino [1, 6-A] [1, 3, 5] Triazin-2-Imine (Vj2):
Synthesis of 7-(4-Methoxyphenyl)-3, 4, 8, 9-Tetrahydro-2H-Pyridazino [1, 6-A] [1, 3, 5] Triazin-2-Imine (Vj3):
Synthesis of 7-(4-Ethylphenyl)-3, 4, 8, 9-Tetrahydro -2H-Pyridazino [1, 6-A] [1, 3, 5] Triazin-2-Imine (Vj4):
Synthesis of 7-[4-(2-Methylpropyl) Phenyl]-3, 4, 8, 9-Tetrahydro- 2H-Pyridazino [1, 6-A] [1, 3,5] Triazin-2-Imine (Vj5):
Synthesis of 7-(Biphenyl-4-Yl)-3, 4, 8, 9-Tetrahydro- 2H-Pyridazino [1,6-A] [1, 3, 5] Triazin-2-Imine (Vj6):
Synthesis of 7-(4-Chlorophenyl)-3, 4, 8, 9-Tetrahydro- 2H-Pyridazino [1, 6-A] [1, 3, 5] Triazin-2-Imine (Vj7): Total seven compounds (Vj1-Vj7) were synthesized and analyzed for IR, NMR, and mass analysis.

The three derivatives were selected As best compounds (Vj4, Vj5 and Vj6) were evaluated for antihypertensive activities by non-invasive method using tail cuff method.

TABLE 1: CHARACTERIZATION DATA OF 7-(SUBSTITUTED PHENYL)-3, 4, 8, 9-TETRAHYDRO-2H-PYRIDAZINO [1,6-A] [1,3,5] TRIAZIN-2-IMINE DERIVATIVES

Compound	R	m.p; R_f; IR υ_{max} (cm^{-1}); ^{1}H-NMR (δ ppm); MS (*m/z*)
Vj1	H	240-242 °C; 0.45; 3218 (N-H), 3014 (C-H^{str}), 1425 (C=N), 770; 2.17 (s, 1H, NH), 2.63 (t, 2H, CH_2), 2.96 (t, 2H, CH_2), 5.90 (s, 2H, CH_2), 7.38 (m, 3H, Ar-H), 7.73 (m, 2H, Ar-H), 8.50 (s, 1H, =NH); 227/228 (M^+/M^++1).
Vj2	CH_3	232-234 °C; 0.58; 3324 (N-H), 2922 (C-H^{str}), 1517 (C=N), 1037, 818; 2.18 (s, 1H, NH), 2.38 (s, 3H, CH_3), 2.60 (t, 2H, CH_2), 2.98 (t, 2H, CH_2), 3.90 (m, 2H, CH_2), 7.23 (d, 2H, *J*=8.1, H-3', H-5'), 7.26 (d, 2H, *J*=8.1, H-2', H-6'), 8.45 (s, 1H, =NH); 241/242 (M^+/M^++1).
Vj3	OCH_3	252-254 °C; 0.55; 3350 (N-H), 1608 (C=N), 1071; 2.20 (s, 1H, NH), 2.61 (t, 2H, CH_2), 2.91 (t, 2H, CH_2), 3.80 (s, 3H, CH_3O), 3.94 (m, 2H, CH_2), 7.32 (dd, 2H, *J*=8.8, H-3', H-5'), 7.74 (dd, 2H, *J*=8.8, H-2', H-6'), 8.45 (s, 1H, =NH); 257/258 (M^+/M^++1).
Vj4	C_2H_5	124-126 °C; 0.72; 3398 (OH), 2926 (C-H^{str}), 1604 (C=O), 1504 (C=N), 1052, 794; 2.46 (q, 2H, CH_2), 2.52 (t, 2H, CH_2), 2.60 (t, 2H, C-CH_2), 2.94 (t, 2H, CH_2), 3.32 (m, 1H, OH, exchangeable with D_2O), 5.29-5.32 (m, 2H, CH_2-N-O), 7.38 (dd, 2H, *J*=8.8, H-3', H-5'), 7.78 (dd, 2H, *J*=8.8, H-2', H-6'); 232/233 (M^+/M^++1).
Vj5	- $CH_2CH(CH_3)_2$	140-142 °C; 0.58; 3358 (OH), 2988 (C-H^{str}), 1612 (C=O^{str}), 1526 (C=N), 1012, 798; 0.92 (d, 6H, 2xCH_3), 1.70 (m, H, C-CH_2), 2.52(t,2H, CH_2),2.94(t, 2H, CH_2),3.32(m,1H,OH, exchangeable with D_2O),5.29-5.32,(m, 2H, CH_2-N-O),7.3 (dd, 2H,*J*=8.2,H-3,H-5'),7.68(dd,2H,*J*=8.8,H-2',H-6');226/261 (M^+/M^++1).



Pharmacology:

Procurement, Identification and Housing of Animals: Albino rats (bodyweight 200-250 g) were supplied by Central Animal House facility ragistration number 173/CPCSEA and kept under standard laboratory conditions in 12 h light/dark cycle at 25 °C ± 2 °C. Animals were provided with a pellet diet (Lipton, Calcutta, India) and water ad libitum. They were marked for easy identification.

Conditioning/Training of Animals: For conducting the BP measurement studies, the animals were kept in a restrainer for 10 minutes every day for one week. This exercise was done to avoid the fluctuation in blood pressure due to aggressive behavior of the animal while keeping into the restrainer for measuring the activity.

Induction of Hypertension in Normotensive Rats: After recording the initial BP of rats, the animals were divided into groups of 5 animals each.

One group was taken as control. Hypertension was induced in the remaining groups by subcutaneous injection of methylprednisolone acetate (20 mg/kg/wk) for 2 weeks as per the method reported by Krakoff *et al.* [31, 33].

Measurement of Mean Blood Pressure of Rats [31, 35]: Mean arterial blood pressure was measured in conscious rats using CODA Non-Invasive Blood Pressure Recorder by Tail-Cuff method (Kent Scientific Corporation, USA). The restrainer carrying the rat was placed in the BP instrument with tail protruding out. The tail was gently placed in contact with a transducer membrane, which was connected to the digital BP display panel. The instrument was then turned on and allowed to stabilize until a steady pulse rate was observed. Once the "pulse level ready" signal appeared, the BP recording button was pressed, and the mean arterial BP was recorded. Albino rats (bodyweight 200-250 g) were used in the present study. Rats were assigned to groups of five animals in each. Each compound was suspended in 1% carboxymethylcellulose (CMC) solution at the dose level of 20 mg/kg; body weight was injected intraperitoneally, then mean arterial blood pressure was recorded after one h. The percent reduction in mean arterial blood pressure (MABP) of compounds at a dose of 20 mg/kg after 1 h is depicted in the below shown **Fig. 2.**

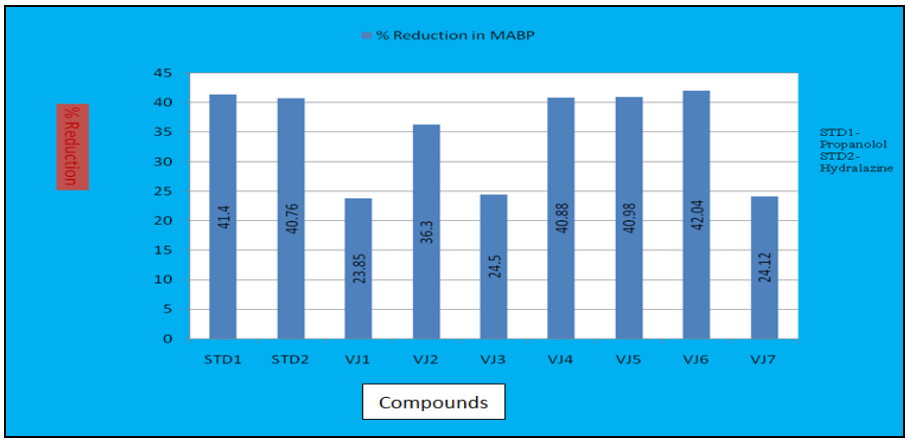


FIG. 2: PERCENT REDUCTION IN MEAN ARTERIAL BLOOD PRESSURE (MABP) BY THE COMPOUNDS VJ1-VJ7 AT A DOSE OF 20 MG/KG AFTER 1 H

Statistical Analysis of Data: The statistical analysis was performed using GRAPHPAD INSTAT 3 software (Graph Pad Software Inc, San Diego, CA). Data obtained from animal experiments were expressed as arithmetic mean ± SEM. The comparison between various groups was performed by one-way analysis of variance (ANOVA), and the effect in treatment groups were compared with toxic control group by Dunnet multiple comparison test. $p < 0.05$ was considered to be significant [*$p < 0.05$; ** $p < 0.01$]. The percentage reduction in BP for all the treatment groups was also calculated and compared.

CONCLUSIONS: From above research study concluded that different Pyridazinone derivatives compounds were synthesized by using different analytical parameters. And also to find out the antihypertensive activity of synthesized derivative compounds. All the synthesized derivatives were obtained in good yield by optimizing various synthetic procedures. The structures of the compounds were established by elemental analysis, IR, ^{1}H-NMR, and Mass spectral data analysis.

The final all the seven compounds (vj1-vj7) were evaluated for antihypertensive activity by a non-invasive method using Tail Cuff method. Few compounds like vj4, vj5 and vj6 were found to show a highly significant reduction in mean arterial blood pressure but at a higher dose in comparisons to standard drugs like proponolol and hydralazine. The substituted pyridazine derivatives discovered in this study may provide valuable therapeutic intervention for the treatment of hypertension.

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CONFLICTS OF INTEREST: Nil

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