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SYNTHESIS, CHARACTERIZATION AND ANTIHYPERTENSIVE ACTIVITY OF PYRIDAZINONE DERIVATIVES

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ABSTRACT

The main objective present research work to synthesis, characterization and biological evaluation of pyridazine analogues. To study the different synthesized derivative 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 pyridazinone derivatives with a wide activity spectrum on cardiovascular system. Pyridazinone 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 6-(substituted phenyl)-2-(substituted methyl)-4,5-dihydropyridazin-3(2H)-one derivatives were synthesized by reacting 6-Phenyl substituted 2,3,4,5-Tetrahydro pyridazin-3-one with cyclic secondary amine under Mannich reaction conditions. The final compounds (vj1-vj15) were evaluated for antihypertensive activities by non invasive method using Tail Cuff method. The current work describes the synthesis of pyridazinone derivatives with encouraging *in vivo* antihypertensive activity by non-invasive method using Tail Cuff method. Compound number vj8, and vj12 were found to show highly significant reduction in mean arterial blood pressure. The current work describes the synthesis of pyridazinone derivatives with encouraging *in vivo* antihypertensive activity by non-invasive method using Tail Cuff method.

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INTRODUCTION

In the present scenario, a large number of medications acting through different mechanisms for the treatment of hypertension are available. Even the one has to admit that blood pressure of 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. The studies on the hydralazine group drugs led to the synthesis of many pyridazinone derivatives with a wide activity spectrum on cardiovascular system[1-3]. Pyridazinone derivatives, a class of compounds containing the N-N bond, exhibit a wide range of pharmacological activities such as antidepressant[4], antihypertensive[5-8], antithrombotic[9], anticonvulsant[10], cardiotonic[11], antibacterial[12], diuretics[13], antiHIV[14] and anticancer[15]. Some pyridazinone derivatives like indolidan[16], bemoradan[17], primobendan[18], levosimendan[19] (antihypertensive), already approved in the clinical market. The current work describes the synthesis of some new substituted pyridazine derivatives with encouraging antihypertensive activity by non-invasive method using Tail Cuff method.

The main objective present research work to synthesis, characterization and biological 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 derivative by using different analytical parameters. And also to find out the good pharmacologically active synthesized compounds.

EXPERIMENTAL PROTOCOLS:

CHEMISTRY:

Melting points were determined by open tube capillary method and are uncorrected. 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; υ_{max} values are given in cm^{-1}. ^{1}H-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 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 6-(substituted phenyl)-2-(substituted methyl)-4,5-dihydropyridazin-3(2H)-one (vj1-vj15).

To a solution of 6-substitued phenyl 2,3,4,5-tetrahydropyridazine-3-one (0.001 mole) in absolute ethanol (30 ml), formaldehyde (37-41%) (1.5 ml) and cyclic secondary amine (0.001 mole) were added and the contents refluxed for 24 hours. After completion of the reaction, ethanol was distilled off and the residue poured into crushed ice and kept in refrigerator for overnight to separate out the compound. The solid which separated out, was filtered and recrystallized from ethanol.

6-Anisyl-2-(1,2-dihydro-10H-phenothiazin-10-ylmethyl)-4,5-dihydropyridazin-3(2H)-one(vj1).

Phenothiazine was used as cyclic secondary amine for Mannich reaction.Yield: 60%; m.p. 108-110 ^oC; IR (KBr) υ_{max} (cm^{-1}): 2986 (CH), 1664 (C=O), 1600 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.62 (t, 2H, CH_2), 2.99 (t, 2H, CH_2), 3.82 (s, 3H, CH_3O), 5.40 (s, 2H, -N-CH_2-N-), 6.90-7.78 (m, 12H, Ar-H); Ms (m/z): 416 (M^++1). Anal. Calc. for $C_{24}H_{21}N_3O_2S$: C: 69.37, H: 5.09, N: 10.11. Found: C: 69.18, H: 4.88, N: 9.92.

6-Anisyl-2-(1H-indol-1-ylmethyl)- 4,5-dihydropyridazin-3(2H)-one(vj2).

Indole was used as cyclic secondary amine for Mannich reaction.Yield: 46%; m.p. 116-118 ^oC; IR (KBr) υ_{max} (cm^{-1}): 3005 (CH), 1680 (C=O), 1600 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.63 (t, 2H, CH_2), 2.97 (t, 2H, CH_2), 3.8 (s, 3H, CH_3O), 5.28 (s, 2H, -N-CH_2-N-), 7.32-7.67 (m, 10H, Ar-H); Ms (m/z): 323 (M^++1). Anal. Calc. for $C_{20}H_{19}N_3O_2$: C: 72.05, H: 5.74, N: 12.60. Found: C: 71.92, H: 5.54, N: 12.46.

6-Anisyl-2-(pyrrolidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (vj3).

Pyrrolidine was used as cyclic secondary amine for Mannich reaction. Yield: 41%; m.p. 128-130 ^oC; IR (KBr) υ_{max} (cm^{-1}): 3001 (CH), 1685 (C=O), 1600 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.61 (t, 2H, CH_2), 2.92 (t, 2H, CH_2), 3.04 (m, 8H, 4xCH_2), 3.9 (s, 3H, CH_3O), 5.26 (s, 2H, -N-CH_2-N-), 7.41 (dd, J=8.4, H-3', H-5'), 7.79 (dd, J=8.4, H-2', H-6'); Ms (m/z): 288 (M^++1). Anal. Calc. for $C_{16}H_{21}N_3O_2$: C: 66.88, H: 7.37, N: 14.62. Found: C: 66.64, H: 7.14, N: 14.56.

6-Anisyl-2-(1,2,4-triazolin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (vj4).

1,2,4-triazole was used as cyclic secondary amine for Mannich reaction.Yield: 58%; m.p. 130-132 ^oC; IR (KBr) υ_{max} (cm^{-1}): 3005 (CH), 1680 (C=O), 1580 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.62 (t, 2H, CH_2), 3.02 (t, 2H, CH_2), 3.76 (s, 3H, CH_3O), 5.34 (s, 2H, -N-CH_2-N-), 7.36-7.86 (m, 6H, Ar-H); Ms (m/z): 286 (M^++1). Anal. Calc. for $C_{14}H_{15}N_5O_2$: C: 58.94, H: 5.30, N: 24.55. Found: C: 58.72, H: 5.16, N: 24.36.

6-(p-Ethylphenyl)-2-(morpholin-4-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (vj5).

Morpholine was used as cyclic secondary amine for Mannich reaction. Yield: 62%; m.p. 133-135 ^{o}C; IR (KBr) υ_{max} (cm^{-1}): 2954 (CH), 1658 (C=O), 1448 (C=C); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 0.92 (t, 2H, CH_3), 2.54 (q, 2H, CH_2), 2.60 (t, 2H, CH_2), 2.74 (t, 2H, CH_2), 2.96 (m, 4H, 2xCH_2), 3.68 (m, 4H, CH_2-O-CH_2), 5.16 (s, 2H, -N-CH_2-N-), 7.42 (dd, J=8.2, 2H, H-3', H-5'), 7.78 (dd, J=8.2, 2H, H-2', H-6'); Ms (m/z): 302 (M^++1). Anal. Calc. for $C_{17}H_{23}N_3O_2$: C: 67.75, H: 7.69, N: 13.94. Found: C: 67.54, H: 7.46, N: 13.82.

6-(p-Ethylphenyl)-2-(piperazin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (vj6).

Piperazine was used as cyclic secondary amine for Mannich reaction.Yield: 50%; m.p. 137-138 ^{o}C; IR (KBr) υ_{max} (cm^{-1}): 3338 (NH), 2968 (CH), 1668 (C=O); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 0.92 (t, 2H, CH_3), 2.54 (q, 2H, CH_2), 2.60 (t, 2H, CH_2), 2.80-2.86 (m, 8H, 4xCH_2), 2.96 (t, 2H, CH_2), 5.24 (s, 2H, -N-CH_2-N-), 7.32 (dd, J=8.5, 2H, H-3', H-5'), 7.78 (dd, J=8.5, 2H, H-2', H-6'), 9.6 (s, 1H, NH) ; Ms (m/z): 301 (M^++1). Anal. Calc. for $C_{17}H_{24}N_4O$: C: 67.97, H: 8.05, N: 18.65. Fond: C: 67.84, H: 7.88, N: 18.43.

6-(p-Ethylphenyl)-2-(piperidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (vj7).

Piperidine was used as cyclic secondary amine for Mannich reaction.Yield: 48%; m.p. 147-148 ^{o}C; IR (KBr) υ_{max} (cm^{-1}): 2968 (CH), 1678(C=O), 1465 (C=C); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 0.90 (t, 3H, CH_3), 2.54 (q, 2H, CH_2), 2.60 (t, 2H, CH_2), 2.66 (m, 6H, 3xCH_2), 2.82 (t, 2H, CH_2), 3.0 (m, 4H, 2xCH_2), 5.32 (s, 2H, -N-CH_2-N-), 7.38 (dd, J=8.7, 2H, H-3', H-5'), 7.78 (dd, J=8.7, 2H, H-2', H-6'); Ms (m/z): 300 (M^++1). Anal. Calc. for $C_{18}H_{25}N_3O$: C: 72.16, H: 8.42, N: 14.03. Found: C: 71.96, H: 8.24, N: 13.97.

6-(p-Ethylphenyl)-2-[(4-methylpiperazin-1-yl)methyl]-4,5-dihydropyridazin-3(2H)-one(vj8).

1-Methylpiperazine was used as cyclic secondary amine for Mannich reaction.Yield: 52%; m.p. 139-140 ^{o}C; IR (KBr) υ_{max} (cm^{-1}): 2970 (CH), 1680 (C=O), 1595 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 0.96 (t, 2H, CH_3), 1.18 (q, 2H, CH_3), 2.2 (s, 1H, N-CH_3), 2.50 (q, 2H, CH_2), 2.62 (t, 2H, CH_2), 2.91 (t, 2H, CH_2), 3.01 (m, 4H, 2xCH_2), 3.3 (m, 4H, 2xCH_2), 5.2 (s, 2H, -N-CH_2-N-), 7.39 (dd, J=8.2, 2H, H-3', H-5'), 7.7 (dd, 2H, H-2', H-6'); Ms (m/z): 315 (M^++1). Anal. Calc. for $C_{18}H_{26}N_4O$: C: 68.76, H: 8.33, N: 17.82. Found: C: 68.66, H: 8.14, N: 17.76.

6-(p-Ethylphenyl)-2-(1,2-dihydro-10H-phenothiazin-10-ylmethyl)-4,5-dihydropyridazin-3(2H)-one(vj9).

Phenothiazine was used as cyclic secondary amine for Mannich reaction.Yield: 60%; m.p. 126-128 ^{o}C; IR (KBr) υ_{max} (cm^{-1}): 2968 (CH), 1664 (C=O), 1600 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 1.02 (t, 2H, CH_2), 2.54 (q, 2H, CH_2), 2.60 (t, 2H, CH_2), 2.96 (t, 2H, CH_2), 5.32 (s, 2H, -N-CH_2-N-), 6.96-7.82 (m, 12H, Ar-H); Ms (m/z): 414 (M^++1). Anal. Calc. for $C_{25}H_{23}N_3OS$: C: 72.16, H: 5.61, N: 10.16. Found: C: 71.92, H: 5.48, N: 9.98.

6-(p-Ethylphenyl)-2-(1H-indol-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one(vj10).

Indole was used as cyclic secondary amine for Mannich reaction.Yield: 42%; m.p. 125-127 ^{o}C; IR (KBr) υ_{max} (cm^{-1}): 3001 (CH), 1680 (C=O), 1600 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 0.88 (t, 2H, CH_3), 2.52 (q, 2H, CH_2), 2.602 (t, 2H, CH_2), 2.96 (t, 2H, CH_2), 5.28 (s, 2H, -N-CH_2-N-), 7.38-7.78 (m, 10H, Ar-H); Ms (m/z): 332 (M^++1). Anal. Calc. for $C_{21}H_{21}N_3O$: C: 67.11, H: 6.39, N: 12.68. Found: C: 66.92, H: 6.12, N: 12.51.

6-(p-Ethylphenyl)-2-(pyrrolidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (vj11).

Pyrrolidine was used as cyclic secondary amine for Mannich reaction. Yield: 42%; m.p. 140-142 ^{o}C; IR (KBr) υ_{max} (cm^{-1}): 3000 (CH), 1680 (C=O), 1600 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 1.01 (t, 2H, CH_3), 2.50 (t, 2H, CH_2), 2.60 (t, 2H, CH_2), 2.94 (t, 2H, CH_2), 3.0 (m, 8H, 4xCH_2), 5.16 (s, 2H, -N-CH_2-N-), 7.40 (m, 2H, Ar-H), 7.82 (m, 2H, Ar-H); Ms (m/z): 286 (M^++1). Anal. Calc. for $C_{17}H_{23}N_3O$: C: 76.11, H: 6.39, N: 12.68. Found: C: 75.88, H: 6.28, N: 12.56.

6-(p-Ethylphenyl)-2-(1,2,4-triazolin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one(vj12).

1,2,4-triazole was used as cyclic secondary amine for Mannich reaction.Yield: 51%; m.p. 141-143 ^{o}C; IR (KBr) υ_{max} (cm^{-1}): 3002 (CH), 1680 (C=O), 1600 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 1.18 (t, 2H, CH_3), 2.59 (t, 2H, CH_2), 2.66 (t, 2H, CH_2), 3.01 (t, 2H, CH_2), 5.32 (s, 2H, -N-CH_2-N-), 7.36-7.86 (m, 6H, Ar-H); Ms (m/z): 284 (M^++1). Anal. Calc. for $C_{15}H_{17}N_5O$: C: 63.59, H: 6.05, N: 24.72. Found: C: 63.52, H: 5.82, N: 24.58.

6-(p-Isobutylphenyl)-2-(morpholin-4-ylmethyl)-4,5-dihydropyridazin-3(2H)-one(vj13).

Morpholine was used as cyclic secondary amine for Mannich reaction. Yield: 38%; m.p. 152-154 ^{o}C; IR (KBr) υ_{max} (cm^{-1}): 2998 (CH), 1675 (C=O), 1600 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 0.9 (d, 6H, 2xCH_3), 1.8 (m, H, -CH), 2.69 (m, 4H, 2xCH_2), 2.92 (t, 2H, CH_2), 3.0 (m, 4H, 2xCH_2), 3.2 (m, 4H, 2xCH_2), 4.78 (s, 2H, -N-CH_2-N-), 7.34 (dd, J=8.2, 2H, H-3', H-5'), 7.42 (dd, J=8.2, 2H, H-2', H-6'); Ms (m/z): 330 (M^++1). Anal. Calc. for $C_{19}H_{27}N_3O_2$: C: 69.27, H: 8.26, N: 12.76. Found: C: 69.12, H: 8.12, N: 12.58.

6-(p-Isobutylphenyl)-2-(piperazin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one(vj14).

Piperazine was used as cyclic secondary amine for Mannich reaction.Yield: 52%; m.p. 147-148 ^{o}C; IR (KBr) υ_{max} (cm^{-1}): 3000 (CH), 1680 (C=O), 1590 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 0.89 (d, 6H, 2xCH_3), 1.8 (m, H, -CH), 2.62 (m, 4H, 2xCH_2), 2.79 (m, 8H, 4xCH_2), 2.92 (t, 2H, CH_2), 4.79 (s, 2H, -N-CH_2-N-), 7.42 (dd, J=8.3, 2H, H-3', H-5'), 7.80 (dd, J=8.2, 2H, H-2', H-6'), 8.1 (s, 1H, NH); Ms (m/z): 329 (M^++1). Anal. Calc. for $C_{19}H_{28}N_4O$: C: 69.48, H: 8.59, N: 17.06. Fond: C: 69.24, H: 8.36, N: 16.86.

6-(p-Isobutylphenyl)-2-(piperidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one(vj15).

Piperidine was used as cyclic secondary amine for Mannich reaction.Yield: 48%; m.p. 137-138 ^{o}C; IR (KBr) υ_{max} (cm^{-1}): 3010 (CH), 1685 (C=O), 1600 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 0.8 (d, 6H, 2xCH_3), 1.85 (m, H, -CH), 2.65 (m, 4H, 2xCH_2), 2.9 (t, 2H, CH_2), 3.0-3.4 (m, 10H, 5xCH_2), 5.02 (s, 2H, -N-CH_2-N-), 7.42 (dd, J=8.4, 2H, H-3', H-5'), 7.8 (dd, J=8.4, 2H, H-2', H-6'); Ms (m/z): 328 (M^++1). Anal. Calc. for $C_{20}H_{29}N_3O$: C: 73.36, H: 8.93, N: 12.83. Found: C: 73.23, H: 8.86, N: 12.76.

PHARMACOLOGY:

Procurement, Identification, and Housing of Animals:

Albino rats (body weight 200-250 g) were supplied by Central Animal House facility of Hamdard University and kept under standard laboratory conditions in 12-hour light/dark cycle at 25°C ± 2°C. Animals were provided with 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 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 methyl prednisolone acetate (20 mg/kg/wk) for 2 weeks as per method reported by Krakoff et al. [21].

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). 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 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 (body weight 200-250 g) were used in present study. Rats were assigned to groups of five animals in each. Each compound was suspended in 1% carboxymethyl cellulose (CMC) solution at the dose level of 20mg/kg body weight was injected intraperitoneally then mean arterial blood pressure was recorded after one hour.

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.

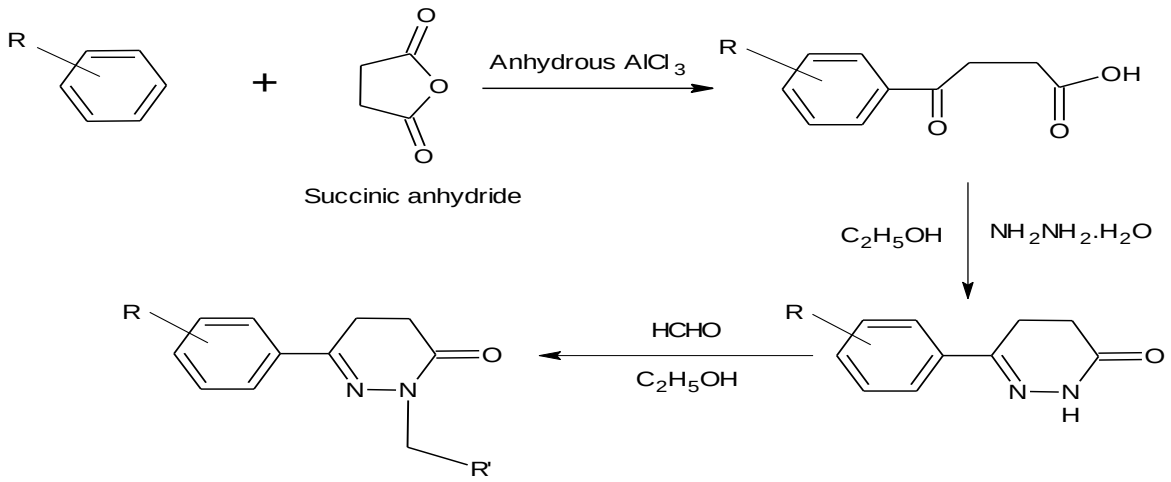
RESULT AND DISCUSSION:

Antihypertensive activities of the compounds were tested by using Tail Cuff method. The results were shown in Table 2 and compared with standard drug hydralazine [18]. Compound number vj8, and vj12 were found to show highly significant reduction in mean arterial blood pressure but at higher dose in comparison to hydralazine. On this basis, it can be concluded that small electron releasing groups like p-CH_3, p-ethyl in phenyl ring at 6- position increases the activity.

CHEMISTRY:

Some 6-(substituted phenyl)-2-(substituted methyl)-4,5-dihydropyridazin-3(2H)-one 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 pyridazinones . The pyridazinones were subjected to Mannich reaction with cyclic secondary amine and formaldehyde to get the final compounds. (vj1-vj15).

Fig: 1. Some 6-(substituted phenyl)-2-(substituted methyl)-4,5-dihydropyridazin-3(2*H*)-one derivatives were synthesized according to scheme.

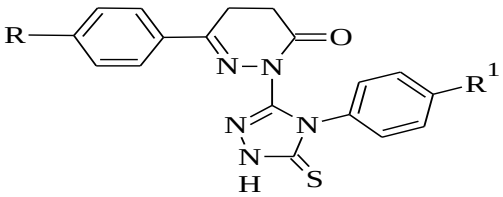


Synthesis of 6-(substituted-phenyl)-2-(substitutedmethyl)-4,5-dihydropyridazin-3(2*H*)-one derivatives.

Antihypertensive activity:

The final compounds (vj1-vj15) were evaluated for antihypertensive activity by non-invasive method using Tail Cuff method. The results were shown in Table 1 and compared with standard drug, hydralazine[20] and propanolol. Compound vj8 and vj12 were found to show highly significant reduction in mean arterial blood pressure but at higher dose in comparison to standard drugs.

Table: 1- Mean arterial blood pressure (mm Hg) and substituents of compounds (vj1-vj15).



Compound (20mg/kg)	MABP (Mean ± SEM)	% Reduction in MABP	R	R^1
Control	101.33±4.64			
Toxic control	162.33±4.02**			
Propranolol[a]	95.12±4.68**	41.40		
Hydralazine[b]	96.16±4.70**	41.76		
Vj1	114.4±7.38**	29.52	C_6H_5	*N*-Morpholine
Vj2	113.4±4.79**	30.14	C_6H_5	*N*-Piperazine
Vj3	114.4±4.85**	29.52	C_6H_5	*N*-Piperidine
Vj4	120.8±1.56**	25.58	C_6H_5	*N*-(4-*N*-Methylpiperazine)
Vj5	120.27±2.57**	25.91	C_6H_5	*N*-Phenothiazine
Vj6	108±1.88**	33.46	C_6H_5	*N*-Indole
Vj7	113.4±7.78**	30.14	C_6H_5	*N*-Pyrrolidine
Vj8	98.2±5.96**	39.50	C_6H_5	*N*-(1,2,4-triazole)
Vj9	120.4±4.02**	25.83	Cl	*N*-Morpholine
Vj10	115.6±6.17**	28.78	Cl	*N*-Piperazine
Vj11	122±2.90*	24.84	Cl	*N*-Piperidine
Vj12	98.2±6.62**	39.50	Cl	*N*-(4-*N*- Methylpiperazine)
Vj13	99.21±4.07**	38.88	Cl	*N*-Phenothiazine
Vj14	103.4±5.25**	36.30	Cl	*N*-Indole
Vj15	103.6±5.00**	30.01	Cl	*N*-Pyrrolidine

[a] Dose of Propanolol was taken as 14 mg/kg.
[b] Dose of hydralazine was taken as 2.6 mg/kg.
All values were expressed as Mean ±SEM (*$p \leq 0.05$), each group comprised of four animals (i.e. n=4).
Toxic control group was compared with control group. All the treatment groups were compared with toxic control group and $p < 0.05$ was considered to be significant.
**$P < 0.01$, *$P < 0.05$.

CONCLUSIONS

From above research study concluded that different pyridazine analogues compounds were synthesized by using different analytical parameters. And also to find out the good pharmacologically active synthesized compounds. 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. The final compounds **(vj1-vj15)** were evaluated for antihypertensive activity by non-invasive method using Tail Cuff method. Compound **vj8 and vj12** were found to show highly significant reduction in mean arterial blood pressure but at higher dose in comparison to standard drugs. Dihydropyridazinone analogues can be further modified to exhibit better potency than the standard drugs. The substituted pyridazine derivatives discovered in this study may provide valuable therapeutic intervention for the treatment of hypertension.

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REFERENCES

1. A. Coelho, E. Sotelo, E. Ravina, Tetrahedron. 59 (2003) 2477-2484.
2. S. Demirayak, A.C. Karaburun, R. Beis, Eur. J. Med. Chem. 39 (2004) 1089-1095.
3. A.A. Siddiqui, S.M. Wani, Indian J. Chem. 43B (2004) 1574-1579.
4. A. Monge, P. Parrado, M. Font, E.F. Alvarez, J. Med. Chem. 30 (6) (1987) 1029–1035.
5. C.Rubat, P.Coudert, B.Refouvelet, P.Tronche, P.Bastide, Chem. Pharm. Bull. 38(11) (1990) 3009-3013.
6. I. Sircar, R.E. Weishaar, D.Kobylarz,W.H.Moos, J.A.Bristol, J. Med. Chem. 30 (1987) 1955-1962.
7. J.G. Longo, I. Verde, M.E. Castro, J. Pharm. Sci. 82 (1993) 286-290.
8. A. Akahane, H. Katayama, T. Mitsunaga, J. Med. Chem. 42 (1999) 779-783.
9. D.G.H. Livermone, R.C. Bethell, N. Cammack, J. Med. Chem. 36 (1993) 3784-3794.
10. W. Malinka, A. Redzicka, O. Lozach, IL Farmaco. 59 (2004) 457–462.
11. K.Abouzid, M.A.Hakeem, O.Khalil,Y.Maklad, Biorg.Med.Chem.16 (2008) 382-389.
12. D.W. Combs, M.S. Rampulla, S.C. Bell, D.H. Klaubert, A.J. Tobia, R. Falotico, B. Haertlein, C.L. Weiss, J.B. Moore, J. Med. Chem. 22 (1990) 380-386.
13. D.W. Robertson, N.D. Jones, J.H. Krushinski, G.D. Pollock, J.K. Swartzendruber, J. Scott Hayes, J. Med. Chem. 30 (1987) 623-627.
14. S. Archan, W. Toller, Curr. Opin. Anesthesiol. 21 (1) (2008) 78-84.
15. E Sotelo, A. Coelho, E. Ravina, Tetrahedron Letters. 44 (2003) 4459-4462.
16. A.A. Siddiqui, S.R. Ahmad, S.A. Hussain, Acta Pol. Pharm. 64 (2) (2008) 223-228.
17. A.A. Siddiqui, Ashok, S.M. Wani, Indian J. Het. Chem. 13 (2004) 257-260.
18. R.E. Borchard, C.D. Barnes, L.G. Eltherington, Drug Dosage in Laboratory Animals: A Handbook, The Telford Press Inc, New Jersey, 1991 3rd ed.
19. M.S.Y. Khan, A.A. Siddiqui, Indian J. Chem. 39B (2000) 614-620.
20. A.A. Siddiqui, M. Islam, M. Asif, C. Asthana, Journal of Ultra Chem. 3 (2) (2007) 176-178.
21. L.R. Krakoff, R. Selvadurai, E. Sytter, Effect of methylprednisolone upon arterial pressure and the renin angiotensin system in the rat. Am J Physiol. 1975;228:613Y617.

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