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Research Article

Synthesis, Characterization and Antihypertensive Activity of 4,5 Dihydropyridazin-3(*2H*)-One Derivatives

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Abstract

Some new 6-(substitutedphenyl)-2-(substitutedmethyl)-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, VJ22) were evaluated for antihypertensive activities by non-invasive method using Tail Cuff method. Most of the compounds showed good antihypertensive activity.

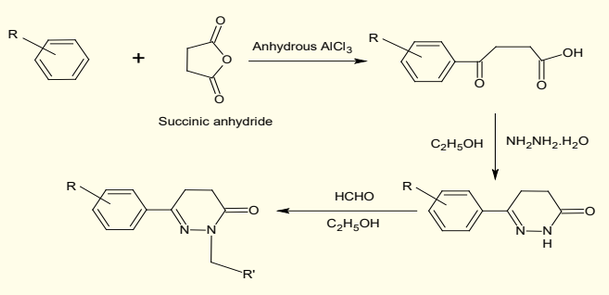
Keywords: *β*-Aroyl Propionic Acid; Pyridazinone; Antihypertensive Activity; Non-Invasive Method

Introduction

Pyridazinone 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], pimobendan [13], levosimendan [14] (antihypertensive), minaprine [15] (antidepressant), emorfazone [16] (anti-inflammatory), and azanrinone [17] (cardiotonic), already appeared in the clinical market. In continuation to the work on pyridazine/pyridazinone ring system in our lab, we have synthesized some pyridazinone derivatives and evaluated them for antihypertensive activity by non-invasive method.

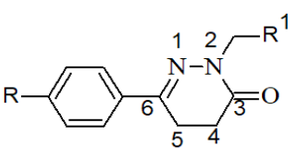
Chemistry

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



Scheme 1: Synthesis of 6-(substituted-phenyl)-2-(substituted methyl)-4,5-dihydropyridazin-3(2H)-one derivatives.

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-VJ22) as shown in table 1.



Compound (20 mg/kg)	MAP (Mean ± SEM)	% Reduction in MAP	R	R^1
Control	101.33 ± 4.64			
Toxic control	162.33 ± 4.02**			
Hydralazine [a]	96.16 ± 4.70**	40.76		
VJ1	111.66 ± 10.28**	31.21	H	N-Morpholine
VJ2	94.16 ± 6.36**	41.99	H	N-Piperazine
VJ3	108 ± 12.76**	33.46	H	N-Piperidine
VJ4	97.5 ± 6.18**	39.93	H	N-(4-N-Methylpiperazine)
VJ5	93.5 ± 3.09**	42.40	H	N-Phenothiazine
VJ6	136.66 ± 1.76*	15.81	H	N-Indole

VJ7	131.3 ± 2.06**	19.11	H	N-Pyrrolidine
VJ8	99.5 ± 5.54**	38.70	H	N-(1,2,4-triazole)
VJ9	139.4 ± 6.83ns	14.12	CH_3	N-Morpholine
VJ10	95.8 ± 2.15**	40.98	CH_3	N-Piperazine
VJ11	104.6 ± 2.78**	35.56	CH_3	N-Piperidine
VJ12	98.8 ± 2.41**	39.13	CH_3	N-(4-N-Methylpiperazine)
VJ13	105.6 ± 3.86**	34.94	CH_3	N-Phenothiazine
VJ14	123.6 ± 3.18**	23.85	CH_3	N-Indole
VJ15	110.8 ± 2.65**	31.74	CH_3	N-Pyrrolidine
VJ16	95.5 ± 1.93**	41.16	CH_3	N-(1,2,4-triazole)
VJ17	114 ± 6.60**	29.77	OCH_3	N-Morpholine
VJ18	104.8 ± 3.92**	35.44	OCH_3	N-Piperazine
VJ19	118 ± 7.56**	27.16	OCH_3	N-Piperidine
VJ20	103.8 ± 4.59**	36.05	OCH_3	N-(4-N-Methylpiperazine)
VJ21	107.4 ± 5.54**	33.83	OCH_3	N-Phenothiazine
VJ22	109.2 ± 7.32**	32.72	OCH_3	N-Indole

Table 1: Mean arterial pressure (mmHg) and substituents of compounds (VJ1-VJ22).

a Dose of hydralazine was taken as 2.6 mg/kg [18].

All values were expressed as Mean ± SEM (*∞p ≤ 0.05), each group comprised of 5 animals (i.e. n=5).

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 and ns non-significant.

Methodology

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; υmax 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 tungsten (VI) oxide as a combusting agent and analyses for C, H, N were within ±0.4% of the theoretical values.

General Procedure for the synthesis of substituted β-aroyl propionic acids (1-7)

The substituted β-aroyl propionic acids (1-7) were synthesized from respective aromatic hydrocarbon and characterized on the basis of spectral data as per reported procedure [18].

General procedure for the synthesis of 6-Substituted-4,5-Dihydropyridazin-3-one (8-14)

The appropriate substituted β-aroyl propionic acids were reacted with hydrazine hydrate to get corresponding pyridazinone and characterized on the basis of spectral data as per earlier reported procedure [19].

General procedure for the preparation of 6-(substituted phenyl)-2-(substituted methyl)-4,5-dihydropyridazin-3(2H)-one (VJ1-VJ22)

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-Phenyl-2-(morpholin-4-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (VJ1)

Morpholine was used as cyclic secondary amine for Mannich reaction. Yield: 72%; m.p. 103 - 104°C; IR (KBr) υ_{max} (cm^{-1}): 2964 (CH), 1665 (C=O), 1446(C=C); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.60 (t, 2H, CH_2), 2.73 (t, 2H, CH_2), 2.95 (m, 4H, 2xCH_2), 3.69 (m, 4H, CH_2-O-CH_2), 4.78 (s, 2H, -N-CH_2-N-), 7.43(m, 3H, Ar-H), 7.73 (m, 2H, Ar-H); Ms (m/z): 273 (M^++1), 187, 100, 96. Anal. Calc. for $C_{15}H_{19}N_3O_2$: C: 65.91, H: 7.01, N: 15.37. Found: C: 65.88, H: 7.10, N: 15.32.

6-Phenyl-2-(piperazin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (VJ2)

Piperazine was used as cyclic secondary amine for Mannich reaction. Yield: 52%; m.p. 117 - 118°C; IR (KBr) υ_{max} (cm^{-1}): 3325 (NH), 2964 (CH), 1661 (C=O), 1424 (C=C); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.604 (t, 2H, CH_2), 2.79 (m, 8H, 4xCH_2), 2.97 (t, 2H, CH_2), 5.2 (s, 2H, -N-CH_2-N-), 7.31 (t, 3H, Ar-H), 7.74 (m, 2H, Ar-H), 9.7 (s, 1H, NH); Ms (m/z): 272 (M^++1), 187, 99. Anal. Calc. for $C_{16}H_{21}N_3O$: C: 66.15, H: 7.40, N: 20.57. Fond: C: 66.08, H: 7.36, N: 20.49.

6-Phenyl-2-(piperidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (VJ3)

Piperidine was used as cyclic secondary amine for Mannich reaction. Yield: 48%; m.p. 104 - 106°C; IR (KBr) υ_{max} (cm^{-1}): 2933 (CH), 1677 (C=O), 1425 (C=C); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.61 (t, 2H, CH_2), 2.65 (m, 6H, 3xCH_2), 2.89 (t, 2H, CH_2), 2.98 (m, 4H, 2xCH_2), 5.2 (s, 2H, -N-CH_2-N-), 7.40 (m, 3H, Ar-H), 7.74 (m, 2H, Ar-H); Ms (m/z): 272/273 (M^+/M^++1), 187, 98, 96. Anal. Calc. for $C_{16}H_{21}N_3O$: C: 70.82, H: 7.80, N: 15.49. Found: C: 70.80, H: 7.75, N: 15.46.

6-Phenyl-2-[(4-methylpiperazin-1-yl)methyl]-4,5-dihydropyridazin-3(2H)-one (VJ4)

1-methylpiperazine was used as cyclic secondary amine for Mannich reaction. Yield: 56%; m.p. 109 - 110°C; IR (KBr) υ_{max} (cm^{-1}): 3002 (CH), 1675 (C=O), 1500 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.2 (s, 1H, N-CH_3), 2.55 (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 (m, 3H, Ar-H), 7.7 (m, 2H, Ar-H); Ms (m/z): 287 (M^++1), 187, 99. Anal. Calc. for $C_{16}H_{22}N_4O$: C: 67.11, H: 7.74, N: 19.56. Found: C: 67.10, H: 7.63, N: 19.46.

6-Phenyl-2-(1,2-dihydro-10H-phenothiazin-10-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (VJ5)

Phenothiazine was used as cyclic secondary amine for Mannich reaction. Yield: 64%; m.p. 88 - 90°C; IR (KBr) υ_{max} (cm^{-1}): 2965 (CH), 1661 (C=O), 1631 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.62 (t, 2H, CH_2), 2.99 (t, 2H, CH_2), 5.39 (s, 2H, -N-CH_2-N-), 6.99-7.80 (m, 13H, Ar-H); Ms (m/z): 386 (M^++1). Anal. Calc. for $C_{23}H_{19}N_3OS$: C: 71.66, H: 4.97, N: 10.90. Found: C: 71.56, H: 4.88, N: 10.78.

6-Phenyl-2-(1H-indol-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (VJ6)

Indole was used as cyclic secondary amine for Mannich reaction. Yield: 40%; m.p. 98 - 100°C; IR (KBr) υ_{max} (cm^{-1}): 2998 (CH), 1680 (C=O), 1590 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.63 (t, 2H, CH_2), 2.97 (t, 2H, CH_2), 5.3 (s, 2H, -N-CH_2-N-), 7.42-7.78 (m, 11H, Ar-H); Ms (m/z): 304 (M^++1). Anal. Calc. for $C_{19}H_{17}N_3O$: C: 75.23, H: 5.65, N: 13.85. Found: C: 75.18, H: 5.54, N: 13.72.

6-Phenyl-2-(pyrrolidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (VJ7)

Pyrrolidine was used as cyclic secondary amine for Mannich reaction. Yield: 43%; m.p. 118 - 120°C; IR (KBr) υ_{max} (cm^{-1}): 3006 (CH), 1682 (C=O), 1580 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.61 (t, 2H, CH_2), 2.95 (t, 2H, CH_2), 3.01 (m, 8H, 4xCH_2), 5.36 (s, 2H, -N-CH_2-N-), 7.39 (m, 3H, Ar-H), 7.74 (m, 2H, Ar-H); Ms (m/z): 258 (M^++1). Anal. Calc. for $C_{15}H_{19}N_3O$: C: 70.01, H: 7.44, N: 16.33. Found: C: 69.88, H: 7.34, N: 16.22.

6-Phenyl-2-(1,2,4-triazolin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (VJ8)

1,2,4-triazole was used as cyclic secondary amine for Mannich reaction. Yield: 50%; m.p. 120 - 122°C; IR (KBr) υ_{max} (cm^{-1}): 3010 (CH), 1680 (C=O), 1590 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.66 (t, 2H, CH_2), 3.0 (t, 2H, CH_2), 5.3 (s, 2H, -N-CH_2-N-), 7.38-7.83 (m, 7H, Ar-H); Ms (m/z): 256 (M^++1). Anal. Calc. for $C_{13}H_{13}N_5O$: C: 61.17, H: 5.13, N: 27.43. Found: C: 61.12, H: 4.98, N: 27.22.

6-Tolyl-2-(morpholin-4-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (VJ9)

Morpholine was used as cyclic secondary amine for Mannich reaction. Yield: 68%; m.p. 113 - 114°C; IR (KBr) υ_{max} (cm^{-1}): 3010 (CH), 1685 (C=O), 1600 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.29 (s, 3H, CH_3), 2.62 (t, 2H, CH_2), 2.76 (t, 2H, CH_2), 2.95 (m, 4H, 2xCH_2), 3.69 (m, 4H, CH_2-O-CH_2), 4.78 (s, 2H, -N-CH_2-N-), 7.43 (dd, J=8.2, 2H, H-3', H-5'), 7.73 (dd, J=8.2, 2H, 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: 66.72, H: 7.32, N: 14.56.

6-Tolyl-2-(piperazin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (VJ10)

Piperazine was used as cyclic secondary amine for Mannich reaction. Yield: 52%; m.p. 122 - 124°C; IR (KBr) υ_{max} (cm^{-1}): 2970 (CH), 1664 (C=O), 1528 (C=C); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 2.60 (t, 2H, CH_2), 2.90 (t, 2H, CH_2), 3.0 (m, 8H, 4xCH_2), 4.78 (s, 2H, -N-CH_2-N-), 7.22 (dd, J=8.4, 2H, H-3', H-5'), 7.74 (dd, J=8.4, 2H, H-2', H-6'), 9.3 (brs, 1H, NH) ; Ms (m/z): 287 (M^++1). Anal. Calc. for $C_{16}H_{22}N_4O$: C: 67.11, H: 7.74, N: 19.56. Fond: C: 66.96, H: 7.64, N: 19.50.

6-Tolyl-2-(piperidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (VJ11)

Piperidine was used as cyclic secondary amine for Mannich reaction. Yield: 41%; m.p. 123 - 125°C; IR (KBr) υ_{max} (cm^{-1}): 2936 (CH), 1660 (C=O), 1420 (C=C); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.26 (s, 3H, CH_3), 2.63 (t, 2H, CH_2), 2.68 (m, 6H, 3xCH_2), 2.90 (t, 2H, CH_2), 3.01 (m, 4H, 2xCH_2), 5.18 (s, 2H, -N- CH_2-N-), 7.38 (dd, J=8.4, 2H, H-3', H-5'), 7.72 (dd, J=8.4, 2H, H-2', H-6'); Ms (m/z): 286 (M^++1). Anal. Calc. for $C_{17}H_{23}N_3O$: C: 71.56, H: 8.12, N: 14.72. Found: C: 71.38, H: 7.96, N: 14.52.

6-Tolyl-2-[(4-methylpiperazin-1-yl)methyl]-4,5-dihydropyridazin-3(2H)-one (VJ12)

1-Methylpiperazine was used as cyclic secondary amine for Mannich reaction. Yield: 52%; m.p. 119 - 120 °C; IR (KBr) υ_{max} (cm^{-1}): 3002 (CH), 1675 (C=O), 1500 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.25 (s, 1H, N-CH_3), 2.34 (s, 3H, CH_3), 2.52 (t, 2H, CH_2), 2.90 (t, 2H, CH_2), 3.12 (m, 4H, 2xCH_2), 3.32 (m, 4H, 2xCH_2), 5.18 (s, 2H, -N-CH_2-N-), 7.42 (dd, 2H, H-3', H-5'), 7.76 (dd, 2H, H-2', H-6'); Ms (m/z): 301 (M^++1). Anal. Calc. for $C_{17}H_{24}N_4O$: C: 67.97, H: 8.05, N: 18.65. Found: C: 67.84, H: 7.88, N: 18.54.

6-Tolyl-2-(1,2-dihydro-10H-phenothiazin-10-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (VJ13)

Phenothiazine was used as cyclic secondary amine for Mannich reaction. Yield: 62%; m.p. 100 - 102°C; IR (KBr) υ_{max} (cm^{-1}): 3000 (CH), 1672 (C=O), 1510 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.35 (s, 3H, CH_3), 2.60 (t, 2H, CH_2), 2.98 (t, 2H, CH_2), 5.40 (s, 2H, -N-CH_2-N-), 6.92-7.78 (m, 12H, Ar-H); Ms (m/z): 400 (M^++1). Anal. Calc. for $C_{24}H_{21}N_3OS$: C: 72.15, H: 5.30, N: 10.52. Found: C: 71.98, H: 5.28, N: 10.36.

6-Tolyl-2-(1H-indol-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (VJ14)

Indole was used as cyclic secondary amine for Mannich reaction. Yield: 44%; m.p. 105 - 107°C; IR (KBr) υ_{max} (cm^{-1}): 2995 (CH), 1680 (C=O), 1570 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.36 (s, 3H, CH_3), 2.64 (t, 2H, CH_2), 2.98 (t, 2H, CH_2), 5.36 (s, 2H, -N-CH_2-N-), 7.46-7.78 (m, 10H, Ar-H); Ms (m/z): 318 (M^++1). Anal. Calc. for $C_{20}H_{19}N_3O$: C: 75.69, H: 6.03, N: 13.24. Found: C: 75.46, H: 5.88, N: 13.12.

6-Tolyl-2-(pyrrolidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (VJ15)

Pyrrolidine was used as cyclic secondary amine for Mannich reaction. Yield: 39%; m.p. 118 - 120 °C; IR (KBr) υ_{max} (cm^{-1}): 3006 (CH), 1682 (C=O), 1580 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 2.62 (t, 2H, CH_2), 2.96 (t, 2H, CH_2), 3.08-3.28 (m, 8H, 4xCH_2), 5.24 (s, 2H, -N- CH_2-N-), 7.42 (dd, J=8.0, 2H, H-3', H-5'), 7.78 (dd, J=8.0, H-2', H-6'); Ms (m/z): 272 (M^++1). Anal. Calc. for $C_{16}H_{21}N_3O$: C: 70.82, H: 7.80, N: 15.49. Found: C: 70.68, H: 7.74, N: 15.36.

6-Tolyl-2-(2,3-dihydro-1H-1,2,4-triazol-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (VJ16)

1,2,4-triazole was used as cyclic secondary amine for Mannich reaction. Yield: 56%; m.p. 126 - 127°C; IR (KBr) υ_{max} (cm^{-1}): 3020 (CH), 1675 (C=O), 1600 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.36 (s, 3H, CH_3), 2.68 (t, 2H, CH_2), 3.02 (t, 2H, CH_2), 5.32 (s, 2H, -N- CH_2-N-), 7.40-7.84 (m, 6H, Ar-H); Ms (m/z): 270 (M^++1). Anal. Calc. for $C_{14}H_{15}N_5O$: C: 62.44, H: 5.61, N: 26.01. Found: C: 62.22, H: 5.48, N: 25.92.

6-Anisyl-2-(morpholin-4-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (VJ17)

Morpholine was used as cyclic secondary amine for Mannich reaction. Yield: 53%; m.p.135 - 136°C; IR (KBr) υ_{max} (cm^{-1}): 2970 (CH), 1672 (C=O), 1452 (C=C); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.48 (t, 2H, CH_2), 2.73 (t, 2H, CH_2), 2.9 (m, 4H, 2xCH_2), 3.6 (m, 4H, 2xCH_2), 3.85 (s, 3H, CH_3O), 4.76 (s, 2H, -N-CH_2-N-), 6.91(dd, 2H, J= 8.7, H-3', H-5'), 7.68 (dd, 2H, J=8.7, H-2', H-6'); Ms (m/z): 304 (M^++1). Anal. Calc. for $C_{16}H_{21}N_3O_3$: C: 63.35, H: 6.98, N: 13.85. Found: C: 63.10, H: 6.88, N: 13.66.

6-Anisyl-2-(piperazin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (VJ18)

Piperazine was used as cyclic secondary amine for Mannich reaction. Yield: 46%; m.p. 127 - 128 °C; IR (KBr) υ_{max} (cm^{-1}): 2972 (CH), 1678 (C=O), 1530 (C=C); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.60 (t, 2H, CH_2), 2.9 (t, 2H, CH_2), 3.0 (m, 8H, 4xCH_2), 3.8 (s, 3H, CH_3O), 4.74 (s, 2H, -N-CH_2-N-), 7.32 (dd, J=8.4, 2H, H-3', H-5'), 7.74 (dd, J=8.4, 2H, H-2', H-6'), 9.3 (brs, 1H, NH); Ms (m/z): 303 (M^++1). Anal. Calc. for $C_{16}H_{22}N_4O_2$: C: 63.55, H: 7.33, N: 18.53. Fond: C: 63.38, H: 7.12, N: 18.44.

6-Anisyl-2-(piperidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (Vj19)

Piperidine was used as cyclic secondary amine for Mannich reaction. Yield: 50%; m.p. 132 - 134 °C; IR (KBr) υ_{max} (cm^{-1}): 2998 (CH), 1688 (C=O), 1455 (C=C); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.61 (t, 2H, CH_2), 2.65 (m, 6H, 3xCH_2), 2.82 (t, 2H, CH_2), 2.98 (m, 4H, 2xCH_2), 3.86 (s, 3H, CH_3O), 5.2 (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: 67.55, H: 7.48, N: 13.76.

6-Anisyl-2-[(4-methylpiperazin-1-yl)methyl]-4,5-dihydropyridazin-3(2H)-one (VJ20)

1-Methylpiperazine was used as cyclic secondary amine for Mannich reaction. Yield: 56%; m.p. 135-137 °C; IR (KBr) υ_{max} (cm^{-1}): 2980 (CH), 1685 (C=O), 1590 (C=N); ^{1}H-NMR ($CDCl_3$-d_6) δ (ppm): 2.2 (s, 1H, N-CH_3), 2.55 (t, 2H, CH_2), 2.91 (t, 2H, CH_2), 3.01 (m, 4H, 2xCH_2), 3.3 (m, 4H, 2xCH_2), 3.86 (s, 3H, CH_3O), 5.24 (s, 2H, -N-CH_2-N-), 7.35 (dd, J=8.4, 2H, H-3', H-5'), 7.76 (dd, J=8.4, 2H, H-2', H-6'); Ms (m/z): 317 (M^++1). 287 (M^++1), 187, 99. Anal. Calc. for $C_{17}H_{24}N_4O_2$: C: 64.53, H: 7.65, N: 17.71. Found: C: 64.42, H: 7.53, N: 17.54.

6-Anisyl-2-(1,2-dihydro-10H-phenothiazin-0-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (VJ21)

Phenothiazine was used as cyclic secondary amine for Mannich reaction. Yield: 60%; m.p. 108 - 110°C; 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 (VJ22)

Indole was used as cyclic secondary amine for Mannich reaction. Yield: 46%; m.p. 116 - 118°C; 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.

Pharmacology

Procurement, Identification, and Housing of Animals

Albino rats (body weight 200-250 g) were 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* [20].

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 -250g) 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 20 mg/kg body weight was injected intraperitoneally then mean arterial blood pressure was recorded after one hour.

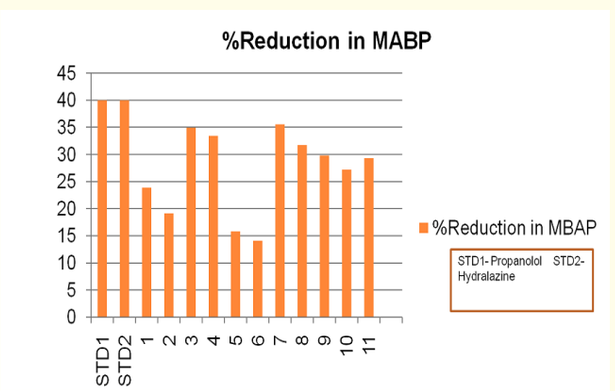


Figure 1: Percent reduction in Mean arterial blood pressure (MABP) at a dose of 20 mg/kg after 1 hour (VJ1-VJ11).

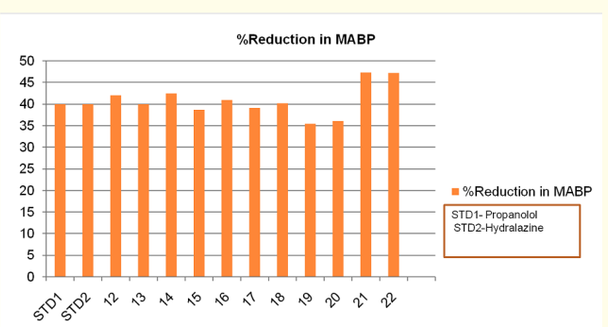


Figure 2: Percent reduction in Mean arterial blood pressure (MABP) at a dose of 20 mg/kg after 1 hour (VJ12-VJ22).

Result and Discussion

Antihypertensive activities of the compounds were tested by using Tail Cuff method. The results were shown in table and compared with standard drug hydralazine [20]. Some compounds were found to show highly significant reduction in mean arterial blood pressure as shown in graph 1 and 2 but at higher dose in comparison with standard.

Conclusions

On this basis, it can be concluded that small electron releasing groups like p-CH3, p-ethyl in phenyl ring at 6-position increases the activity.

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