DESIGN &SYNTHESIS OF 4-PYRAZOLYL-1, 4-DIHYDROPYRIDINES AND THEIR ANTIHYPERTENSIVE ACTIVITY

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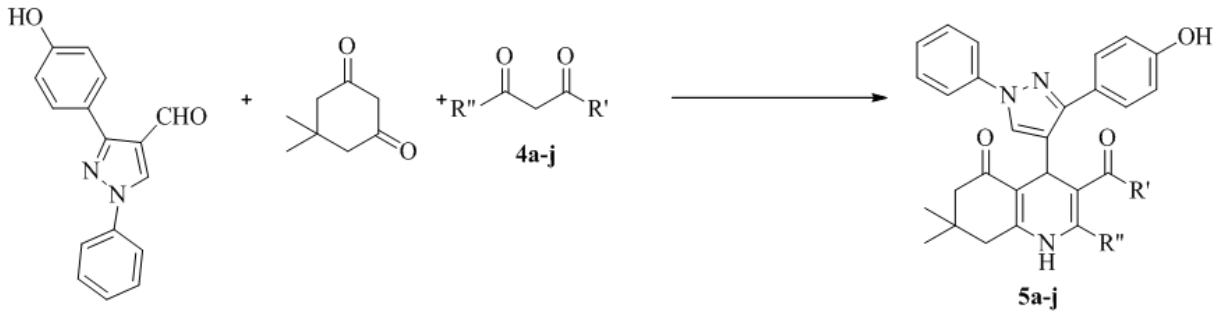
GRAPHICAL ABSTRACT



ABSTRACT

In light of the pharmacological and therapeutic importance of 1,4-dihydropyridine (1,4-DHP) class we have synthesizednovel 4-pyrazolyl-1,4-dihydropyridines. The reaction 3-(4'-hydroxyphenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (3), dimedone, β-keto esters& amides (4a-j) and ammonium acetate in the presence of barium nitrate as catalyst yields alkyl 4-(3'-(4"-hydroxyphenyl)-1'-phenyl-1'H-pyrazol-4'-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5a-g), N-phenyl 4-(3'-(4"-hydroxyphenyl)-1-phenyl-1H-pyrazol-4'-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8 hexahydroquinoline-3-carboxamide (5h-i) and alkyl 4-(3'-(4"-hydroxyphenyl)-1'-phenyl-1'H-pyrazol-4'-yl)-2-triflouro-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5j). The structure of these compounds has been investigated by FTIR, [1]H-NMR, [13]C-NMR and mass spectroscopy. These 4-

pyrazolyl-1,4-dihydropyridine derivatives were screened for antihypertensive activity in vivo by measuring mean arterial pressure (MAP) and heart rate (HR) on12 weeks old male spontaneously hypertensive rats.

Keywords: 1, 4-Dihydropyridines; Pyrazoles; Hantzsch synthesis; Antihypertensive activity; Hypertensive rats.

I INTRODUCTION

The 1,4-dihydropyridine (1,4-DHP) scaffold is a common component of pharmacologically active molecules which possess a variety of biological activity. [1]They areparticularly well known as L-type calcium channel blockers, used in the treatment of hypertension. The presence of heterocyclic ring at 4-position is required for various pharmacological activities such as antihypertensive, antianginal, [2-4] antitumor, [5]antiinflammatory, [6-7]antitubercular, [8]analgesic, [9] antithrombotic, [10-11] vasodilation, [12] anticonvulsant activity, [13] stress protective effect, [14] cardio depressant activity [15] etc.

The first synthesis of 1,4-dihydropyridines (1,4-DHPs) *via* a three component cyclocondensation reaction of acetoacetic ester, aldehyde and ammonia was reported by Arthur Hantzsch in 1881. [16] Since then a lot of new variants of original method have been developed, allowing synthesis of different substituted 1,4-DHPs. [17]

Over the past few decades, 4-aryl-1,4-dihydropyridines have generated considerable interest in the management of heart-related disorders and have been the focus of activity for many medicinal chemists and pharmacologists in exploring this phramacophore. This is a result of their high potency, selectivity of action, and excellent therapeutic profile. Although the DHP nucleus offers a wide scope of structural diversity at various positions, the improved cardiovascular efficacy has been achieved mainly by variations in phenyl substitutions and ester functionalities.

The 1,4-dihydropyridines are valued not only for their pharmacological effect, but also as a tool for the investigation of the calcium channel, particularly since the discovery that this class also include compounds that have exactly the opposite action profile and are known as calcium agonists. There are even instances in which this reversal of activity is found between enantiomers. [18]

In view of the pharmacological properties of 1,4-DHP class, it appearedof interest to design and synthesize new derivatives of 1,4-DHP.Herein, we report the synthesis of 4-pyrazolyl-1,4-dihydropyridines **5a-j** and results of their antihypertensive activity *in vivo* by measuring mean arterial pressure (MAP) and heart rate (HR) on12 weeks old male spontaneously hypertensive rats.

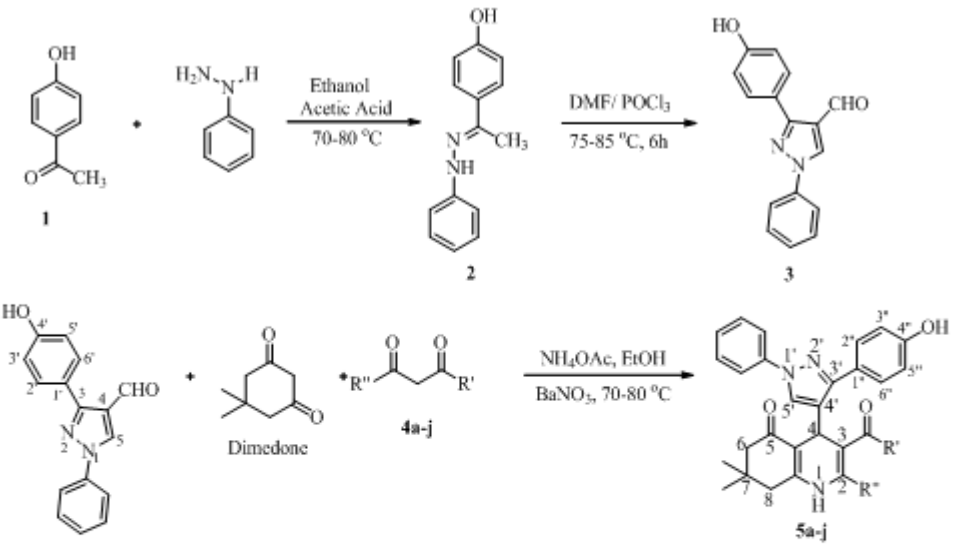
II RESULTS AND DISCUSSION

2.1 Chemistry

In the present work, the synthesis of 4-pyrazolyl-1,4-dihydropyridines (**5a-j**) was accomplished by the reaction of 3-(4-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**3**), dimedone, β-ketoesters& amides (**4a-j**) and ammonium acetate in ethanol by using barium nitrate as catalyst. The compound 3-(4'-hydroxyphenyl)-1-phenyl-

1*H*-pyrazole-4-carbaldehyde (**3**) in turn was prepared by the Vilsmeir-Haack reaction of compound **2**at 75-85 ^{o}C for 6h. [19] The compound **2** was prepared by the reaction of 4-hydroxyacetophenone (**1**) and phenyl hydrazine in ethanol at 70-80^{o}C in acidic medium for 2h. [20] (**Scheme 1**)

All the compounds synthesized were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. Spectroscopic data was in complete agreement with those expected. The IR spectrum of **5a** showed band at 1599 and 1689 cm^{-1} for C=O ester and C=O carbonyl, respectively. The frequency band for -NH and -OH groups appeared at 3205 and 3268 cm^{-1}, respectively. In ^{1}H NMR spectra of **5a**, chemical shift values of all the compounds were in accordance with the expected values. A quartet for -OC$\underline{H_2}$CH$_3$ group of ester and triplet for -OCH$_2$C$\underline{H_3}$ appeared at δ 3.47 and 0.41, respectively. Pyrazole hydrogen at 5'-position appeared at δ 8.16 as singlet. Three methyl groups, two at H-7 and one at H-2 appeared at δ 0.59, 0.66 and 2.16, respectively.The characteristic proton at 4-position appeared at δ 4.75 as singlet. The –CH$_2$ protons at H-6 and H-8 appeared at δ 1.89 and 1.76, respectively. The OH and NH protons resonated at δ 8.96 and 9.34, respectively. All other aromatic protons appeared in the range of δ 6.46-7.41. Spectral signals of dihydropyridine derivatives in ^{13}C NMR were in good agreement with proposed structures. Details of ^{1}H NMR and ^{13}C NMR spectra of **5a-j** are given in experimental section.



Compounds 4 &5	R'	R''	Compounds 4 &5	R'	R''
a	OCH_2CH_3	CH_3	f	$C(CH_3)_3$	CH_3
b	OCH_3	CH_3	g	$CH(CH_3)_2$	CH_3
c	CH_3	CH_3	h	NHC_6H_4Cl	CH_3
d	$CH_2CH{=}CH_2$	CH_3	i	NHC_6H_5	CH_3
e	$CH_2C_6H_5$	CH_3	j	CH_2CH_3	CF_3

Scheme 1.Synthesis of compounds **5a-j**.

2.2 Antihypertensive Activity

The effect of the compounds on MAP and HR was studied for 20 min. None of the compound was found to affect MAP significantly. But compound **5b** was found to be effective in reducing the mean arterial pressure of rats in 1 mg/kg as well as 5mg/kg concentration. Similarly, there was no significant change in heart rates following the administration of the compounds. Out of all the compounds **5e, 5f, 5g** was found to be effective in reducing heart rate effectively at concentration. The results are summarized in **Table1** and **2**, respectively.

Table 1.Mean arterial pressure (MAP) in mmHg

Compound	Dose	Time				
		0 min	5 min	10 min	15 min	20 min
5a	1 mg/kg	115	116	115	117	116
	5 mg/kg	124	121	119	118	119
5b	1 mg/kg	83	87	78	69	69
	5 mg/kg	93	103	105	107	111
5c	1 mg/kg	114	114	116	117	116
	5 mg/kg	117	117	115	116	117
5d	1 mg/kg	89	87	86	87	85
	5 mg/kg	82	89	82	84	81
5e	1 mg/kg	69	81	93	91	96
	5 mg/kg	97	106	98	96	94
5f	1 mg/kg	93	96	98	94	96
	5 mg/kg	96	105	95	93	88
5g	1 mg/kg	81	86	90	94	96
	5 mg/kg	92	94	99	95	92
5h	1 mg/kg	96	96	100	103	109
	5 mg/kg	108	104	107	109	110
5i	1 mg/kg	113	113	112	114	112
	5 mg/kg	107	110	111	109	110
5j	1 mg/kg	103	106	106	108	109
	5 mg/kg	109	110	112	111	111

Table 2. Heart rate (HR) in BPM

Compound	Dose	Time				
		0 min	5 min	10 min	15 min	20 min
5a	1 mg/kg	395	405	402	411	426
	5 mg/kg	426	429	428	428	429
5b	1 mg/kg	240	172	161	239	262
	5 mg/kg	161	230	138	133	280
5c	1 mg/kg	329	330	308	203	210
	5 mg/kg	295	277	309	333	330

5d	1 mg/kg	335	316	320	334	330
	5 mg/kg	297	339	333	330	333
5e	1 mg/kg	357	206	205	192	128
	5 mg/kg	136	114	141	115	104
5f	1 mg/kg	156	225	281	191	147
	5 mg/kg	106	201	173	150	182
5g	1 mg/kg	451	439	435	415	375
	5 mg/kg	363	362	334	327	329
5h	1 mg/kg	334	343	332	321	320
	5 mg/kg	349	348	330	327	333
5i	1 mg/kg	427	400	402	404	410
	5 mg/kg	416	402	399	405	406
5j	1 mg/kg	431	425	422	416	423
	5 mg/kg	429	423	424	424	425

III EXPERIMENTAL PROTOCOL

3.1 Materials and Methods

All reagents were of commercial grade and used as received. Solvents were dried and purified using standard techniques. ^{1}H-NMR (400MHz) and ^{13}C-NMR (100.5 MHz) were recordedon JNM ECX- 400P (Jeol, USA) spectrometer using TMS as an internal standard. Chemical shifts are reported in parts per million (ppm). Mass spectra were recorded on API-2000 mass spectrometer in negative mode. IR absorption spectra were recorded in the 400-4000 cm^{-1} range on a Perkin-Elmer FT-IR spectrometer using KBr pallets. Melting points were determined using Buchi M-560 and are uncorrected. The reactions were monitored by thin layer chromatography (TLC), on aluminium plates coated with silica gel 60 F_{254} (Merck). UV radiation and iodine were used as the visualizing agents. Column chromatography was performed on silica gel (100-200 mesh).

3.2 General Procedure for the synthesis of 4-pyrazolyl-1,4-dihydropyridine derivatives, 5a-j

3-(4'-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**3**) (1 mmol), dimedone(1mmol), β-keto esters and amides (**4a-j**) (1mmol) and ammonium acetate (1.5mmol) were dissolved in ethanol in round bottom flask. To this reaction mixture pinch of barium nitrate was added and it was refluxed for 6h at 70-80 ^{o}C. After completion of reaction as monitored by TLC, reaction mixture was put on ice cold water and precipitated solid was filtered and washed with cold water and dried. The crude product was purified by column chromatography (70% Ethyl acetate:pet ether).

3.2.1. Ethyl 4-(3'-(4″-hydroxyphenyl)-1'-phenyl-1'*H*-pyrazol-4'-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8 hexahydroquinoline-3-carboxylate, 5a:Yield, 92.2%, Light yellow solid, mp239-242 ^{o}C.IR (KBr, cm^{-1})ν_{max}: 1599 (C=O ester)1689 (C=O), 2953 (Ar C-H), 3205 (NH), 3268 (OH) ; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm)0.41(3H, t, -OCH_2CH_3),0.59 (3H, s, -CH_3), 0.66 (3H, s, CH_3), 1.76 (2H, s, -CH_2), 1.89 (2H, s, -CH_2), 2.16

(3H, s, CH_3), 3.47 (2H, q, OCH_2CH_3), 4.75 (1H, s, -C*H*), 6.46 (2H, d, J = 8.8 Hz, ArH), 6.78 (1H, t, ArH), 6.97 (2H, t, ArH), 7.20 (1H, d, J = 8.4 Hz, ArH), 7.33-7.41 (3H, m, ArH), 8.16 (1H, s, -C*H*), 8.96 (1H, s, N*H*), 9.34 (1H, s, O*H*);^{13}C NMR (100MHz, $CDCl_3$): δ(ppm)13.02, 17.54, 25.77, 26.60, 28.13, 31.53, 49.83, 58.16, 104.96, 110.03, 113.97, 117.38, 124.74, 126.00, 128.27, 129.13, 138. 90, 142.73, 148.94, 155.98, 166.52, 194.56; ESI-MS *m/z*: $[M+Na]^+$=520.1840.

3.2.2. Methyl 4-(3'-(4″-hydroxyphenyl)-1'-phenyl-1'*H*-pyrazol-4'-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8 hexahydroquinoline-3-carboxylate, 5bYield, 92.0%, Light yellow solid, mp 195-197 ^{o}C.IR (KBr, cm^{-1})ν_{max}: 1601 (C=O ester) 1699 (C=O), 2956 (Ar C-H), 3339 (NH), 3420 (OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm)0.93 (3H, s, -CH_3), 0.98 (3H, s, CH_3), 2.13 (3H, s, CH_3), 2.35 (2H, s, -CH_2), 2.46 (2H, s, -CH_2), 2.89 (3H, s, OCH_3), 4.98 (1H, s, -C*H*), 6.81 (2H, d, J = 8.79 Hz, ArH), 7.19 (1H, t, ArH), 7.40 (2H, t, ArH), 7.68 (2H, d, J = 7.32 Hz, ArH), 7.77 (2H, d, J = 8.79 Hz, ArH), 7.90 (1H, s, -C*H*), 9.01 (1H, s, N*H*), 9.46 (1H, s, O*H*); ^{13}C NMR (100MHz, DMSO-d_6): δ(ppm)14.02, 20.97, 26.21, 27.20, 28.87, 32.35, 49.98, 50.43, 59.84, 104.66, 110.29, 114.75, 117.92, 125.55, 125.79, 127.20, 129.53, 129.76, 139.64, 143.91, 149.75, 150.60, 156.90, 167.30, 170.53, 195.01; ESI-MS *m/z*: $[M+Na]^+$ = 506.1840.

3.2.3. 3-Acetyl-4-(3'-(4″-hydroxyphenyl)-1'-phenyl-1'*H*-pyrazol-4'-yl)-2,7,7-trimethyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one, 5cYield, 84.7%, Yellow solid, m.p. 191-193 ^{o}C.IR (KBr, cm^{-1})ν_{max}: 1601 (C=O), 2957 (Ar C-H), 3289 (NH, OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm)0.90 (3H, s, -CH_3), 0.97 (3H, s, CH_3), 1.64 (3H, s, CH_3), 1.89-2.02 (5H, m, -$COCH_3$, -CH_2), 2.45-2.46 (2H, m, -CH_2), 4.95 (1H, s, -C*H*), 6.79 (2H, d, J = 8.79 Hz, ArH), 7.21 (1H, t, ArH), 7.40 (2H, t, ArH), 7.68 (2H, d, J = 7.32 Hz, ArH), 7.76 (2H, d, J = 8.05 Hz, ArH), 7.94 (1H, s, -C*H*), 8.96 (1H, s, N*H*), 9.54 (1H, s, O*H*);^{13}C NMR (100MHz, DMSO-d_6): δ(ppm)18.71, 27.08, 28.95, 29.13, 32.35, 50.63, 59.93, 110.38, 114.34, 115.10, 117.94, 124.74, 126.23, 127.40, 129.06, 129.60, 130.14, 139.52, 141.68, 149.66, 150.18, 157.25, 195.02, 198.29; ESI-MS*m/z*: $[M+Na]^+$ = 490.2494.

3.2.4. Allyl 4-(3'-(4″-hydroxyphenyl)-1'-phenyl-1'*H*-pyrazol-4'-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 5dYield, 85.0%, Yellow solid, mp 158-160 ^{o}C.IR (KBr, cm^{-1})ν_{max}: 1527 (C=O ester), 1602 (C=O), 2957 (Ar C-H), 3394 (NH, OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm)0.94 (3H, s, -CH_3), 1.01 (3H, s, CH_3), 2.17 (3H, s, CH_3), 2.36 (2H, d, J = 4.4 Hz,-CH_2), 2.48-2.49 (2H, m, -CH_2), 3.71-3.76 (1H, dd, J = 5.86 Hz, J = 13.18 Hz, =CH), 4.20-4.25 (1H, dd, J = 5.84 Hz, J = 13.16 Hz, =CH), 4.95-4.97 (2H, m, -CH_2), 5.05 (1H, s, -CH), 5.36-5.45 (1H, m, CH=C), 6.81 (2H, d, J = 8.79 Hz, ArH), 7.23 (1H, t, ArH), 7.43 (2H, t, ArH), 7.72 (2H, d, J = 8.05 Hz, ArH), 7.79 (2H, d, J = 8.05 Hz, ArH), 7.95 (1H, s, -C*H*), 9.03 (1H, s, N*H*), 9.42 (1H, s, O*H*);^{13}C NMR (100MHz, DMSO-d_6): $\delta\nu_{max}$ 18.16, 26.19, 27.02, 28.73, 32.22, 50.36, 63.45, 104.39, 110.29, 114.63, 117.20, 117.80, 125.35, 125.64, 127.16, 129.69, 133.13, 139.49, 144.18, 149.50, 150.37, 156.89, 166.37, 194.72; ESI-MS *m/z*: $[M+Na]^+$ = 532.0840.

3.2.5. Benzyl 4-(3'-(4″-hydroxyphenyl)-1'-phenyl-1'*H*-pyrazol-4'-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 5eYield, 88.9%, White solid, mp 177-179 ^{o}C.IR (KBr, cm^{-1})ν_{max}: 1701 (C=O ester), 1736 (C=O), 2957 (Ar C-H), 3381 (NH, OH); ^{1}H NMR (400 MHz, DMSO-d$_6$): δ(ppm)0.89 (3H, s, -CH$_3$), 0.95 (3H, s, CH$_3$), 2.11 (3H, s, CH$_3$), 2.29-2.30 (2H, m,-CH$_2$), 2.45-2.46 (2H, m, -CH$_2$), 4.12 (1H, d, J = 12.45 Hz, Benzylic H), 4.86 (1H, d, J = 12.45 Hz, Benzylic H), 5.03 (1H, s, -CH), 6.77 (2H, d, J = 8.79 Hz, ArH), 6.95 (1H, t, ArH), 7.17-7.20 (4H, m, ArH), 7.40 (2H, t, ArH), 7.67 (2H, d, J = 7.32 Hz, ArH), 7.73 (2H, d, J = 8.79 Hz, ArH), 7.91 (1H, s, -C*H*), 8.99 (1H, s, N*H*), 9.42 (1H, s, O*H*) ;^{13}C NMR (100MHz, DMSO-d$_6$): δ(ppm) 14.14, 18.32, 20.83, 26.39, 27.21, 28.73, 32.25, 50.42, 59.84, 64.08, 104.17, 110.28, 114.70, 117.87, 127.73, 128.22, 129.49, 129.84, 137.06, 139.56, 144.71, 149.55, 150.64, 156.95, 166.53, 194.86; ESI-MS *m/z*: [M+Na]$^{+}$ = 582.0587.

3.2.6.*Tert*-Butyl 4-(3'-(4″-hydroxyphenyl)-1'-phenyl-1'*H*-pyrazol-4'-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 5fYield, 92.7%, Light yellow solid, mp 226-228 ^{o}C.IR(KBr, cm^{-1})ν_{max}: 1696 (C=O ester), 1734 (C=O), 2965 (Ar C-H), 3347 (NH, OH); ^{1}H NMR (400 MHz, DMSO-d$_6$): δ(ppm)0.91 (3H, s, -CH$_3$), 0.99 (3H, s, CH$_3$), 1.04 (9H, s, CH$_3$) 1.96 (3H, s, CH$_3$), 2.31-2.33 (2H, m,-CH$_2$), 2.48-2.49 (2H, m, -CH$_2$), 5.00 (1H, s, -CH), 6.79 (2H, d, J = 8.05 Hz, ArH), 7.22 (1H, t, ArH), 7.43 (2H, t, ArH), 7.72 (2H, d, J = 7.32 Hz, ArH), 7.80 (2H, d, J = 8.79 Hz, ArH), 7.94 (1H, s, -C*H*), 8.84 (1H, s, N*H*), 9.39 (1H, s, O*H*) ;^{13}C NMR (100MHz, DMSO-d$_6$): δ(ppm)14.07, 18.02, 20.75, 26.56, 26.95, 27.48, 28.71, 32.14, 50.56, 59.74, 78.62, 106.87, 109.80, 114.68, 117.73, 125.06, 125.65, 127.20, 129.00, 129.44, 129.94, 139.47, 141.39, 149.70, 150.25, 156.99, 166.78, 170.21, 194.55; ESI-MS *m/z*: [M+Na]$^{+}$ = 548.2994.

3.2.7.*Iso*-Propyl 4-(3'-(4″-hydroxyphenyl)-1'-phenyl-1'*H*-pyrazol-4'-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 5gYield, 90.7%, Yellow solid, mp 228-230 ^{o}C.IR (KBr, cm^{-1})ν_{max}: 1601 (C=O ester), 1686 (C=O), 2954 (Ar C-H), 3274 (NH), 3403 (OH) ; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ (ppm) 0.65 (3H, d, J = 5.88 Hz, CHC*H*$_3$), 0.77 (3H, d, J = 6.6 Hz, CHC*H*$_3$), 0.90 (3H, s, -CH$_3$), 0.99 (3H, s, CH$_3$), 2.19 (3H, s, CH$_3$), 2.36-2.37 (2H, m,-CH$_2$), 2.48-2.49 (2H, m, -CH$_2$), 4.60-4.63 (1H, m, C*H*CH$_3$), 5.05 (1H, s, -CH), 6.82 (2H, d, J = 8.79 Hz, ArH), 7.22 (1H, t, ArH), 7.43 (2H, t, ArH), 7.72 (2H, d, J = 8.05 Hz, ArH), 7.90 (2H, d, J = 8.79 Hz, ArH), 7.95 (1H, s, -C*H*), 9.18 (1H, s, N*H*), 9.51 (1H, s, O*H*);^{13}C NMR (100MHz, DMSO-d$_6$): δ (ppm) 18.28, 20.82, 21.12, 26.16, 26.99, 28.77, 32.20, 50.44, 65.73, 105.17, 110.44, 114.68, 117.68, 125.31, 125.55, 127.34, 129.39, 129.79, 139.53, 143.74, 149.71, 150.02, 157.02, 166.47, 194.73; ESI-MS*m/z*: [M+Na]$^{+}$ = 534.6496.

3.2.8. N-(4-chlorophenyl)-4-(3'-(4″-hydroxyphenyl)-1'-phenyl-1'*H*-pyrazol-4'-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide, 5hYield, 86%, Light yellow solid, mp 183-184 ^{o}C.IR (KBr, cm^{-1})ν_{max}: 1600 (C=O), 2956 (Ar C-H), 3282 (NH, OH); ^{1}H NMR (400 MHz, DMSO-d$_6$): δ(ppm) 0.96 (3H, s, -CH$_3$), 1.02 (3H, s, CH$_3$), 1.91 (3H, s, CH$_3$), 2.32-2.33 (2H, m,-CH$_2$), 2.48-2.49 (2H, m, -CH$_2$), 5.08 (1H, s, -CH), 6.62 (2H, d, J = 8.05 Hz, ArH), 7.16 (2H, t, ArH), 7.22-7.27 (3H, m, ArH),7.43 (2H, t, ArH), 7.56 (2H, d, J = 8.05 Hz, ArH), 7.71 (2H, d, J = 7.32 Hz, ArH), 7.94 (1H, s, -C*H*), 8.64 (1H, s, N*H*), 9.30 (1H, s, CON*H*), 9.40 (1H, s,

O*H*),^{13}C NMR (100MHz, DMSO-d_6): δ(ppm) 16.66, 27.48, 28.58, 32.10, 48.44, 50.30, 108.13, 111.77, 114.62, 117.61, 120.87, 124.56, 124.97, 125.56, 126.17, 127.89, 128.88, 129.43, 129.58, 133.30, 138.03, 139.50, 150.27, 156.86, 167.17, 193.85; ESI-MS *m/z*: $[M+Na]^+$ = 601.2088.

3.2.9. 4-(3'-(4″-hydroxyphenyl)-1'-phenyl-1'*H*-pyrazol-4'-yl)-2,7,7-trimethyl-5-oxo-N-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide, 5iYield, 96.4%, Light yellow solid, mp 185-187 ^{o}C.IR (KBr, cm^{-1})ν_{max}: 1599 (C=O), 2956 (Ar C-H), 3266 (NH, OH) ; ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 0.93 (3H, s, -CH_3), 1.00 (3H, s, CH_3), 1.93 (3H, s, CH_3), 2.30-2.33 (2H, m,-CH_2), 2.48-2.49 (2H, m, -CH_2), 5.06 (1H, s, -CH), 6.64 (2H, d, J = 8.05 Hz, ArH), 6.94 (1H, t, ArH), 7.13 (2H, t, ArH), 7.20-7.28 (3H, m, ArH),7.42 (2H, t, ArH), 7.58 (2H, d, J = 8.05 Hz, ArH), 7.70 (2H, d, J = 8.05 Hz, ArH), 7.94 (1H, s, -C*H*), 8.61 (1H, s, N*H*), 9.28 (1H, s, CON*H*), 9.32 (1H, s, O*H*),^{13}C NMR (100MHz, DMSO-d_6): δ (ppm) 17.00, 27.41, 28.72, 31.95, 48.76, 50.27, 79.03, 108.15, 112.00, 114.61, 117.61, 119.56, 122.78, 124.65, 125.54, 127.05, 128.11, 128.77, 129.42, 129.64, 132.95, 138.93, 139.52, 150.05, 150.52, 156.85, 167.12, 193.85; ESI-MS *m/z*: $[M+Na]^+$ = 567.2487.

3.2.10. Ethyl 4-(3'-(4″-hydroxyphenyl)-1'-phenyl-1'*H*-pyrazol-4'-yl)-7,7-dimethyl-5-oxo-2-(trifluoromethyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 5jYield, 74.8%, Light brown solid, mp 230-231 ^{o}C.IR (KBr, cm^{-1})ν_{max}: 1612 (C=O), 2958 (Ar C-H), 3185 (NH, OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm)0.87 (3H, s, -CH_3), 1.00 (3H, s, CH_3), 1.16 (3H, t, -CH_2CH_3), 1.93-1.97 (2H, m,-CH_2), 2.06-2.10 (2H, m, -CH_2), 3.99-4.04 (2H, m, -CH_2CH_3) 4.93 (1H, s, -CH), 6.78 (2H, d, J = 8.05 Hz, ArH), 7.21 (1H, t, ArH), 7.42 (2H, t, ArH), 7.70 (2H, d, J = 8.05 Hz, ArH), 7.79 (2H, d, J = 8.05 Hz, ArH), 7.97 (1H, s, -C*H*), 9.19 (1H, s, N*H*), 9.37 (1H, s, O*H*);^{13}C NMR (100MHz, DMSO-d_6): δ (ppm) 23.68, 27.11, 28.56, 32.06, 50.32, 79.24, 111.97, 114.23, 117.62, 125.47, 125.58, 126.87, 128.81, 129.42, 129.83, 139.73, 148.42, 151.10, 156.93, 194.56; ESI-MS *m/z*: $[M+Na]^+$ = 574.2023.

3.3 Study of antihypertensive activity in rat

To study the antihypertensive potential of the compound, 12 weeks old male spontaneously hypertensive rats (SHRs, 200–250 g) were procured from Laboratory Animal Division, CSIR-CDRI and 3 rats were housed per cage. Food and water were provided *ad libitum*. They were habituated to the animal room at 22–25 ^{o}C for a week on a 12 hour/12 hour light/dark cycle before the experiments. The animals were handled according to the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India, and Institutional Animal Ethics Committee of CSIR-CDRI.

The animals were weighed and anaesthetized with urethane (1.25 g kg^{-1}, i.p.; Sigma, USA) for surgery. The trachea was cannulated with polyethylene tube for respiration. To measure bloodpressure (BP) and heart rate (HR), the left carotid artery was cannulatedby polyethylene tube which was connected with a pressure transducer which, in turn, was connected to a Data acquisition system (AD Instruments, Australia). The right external jugular vein was

cannulated for the administration of drugs/compounds. Candesartan, an AT1 receptor blocker, was used as a standard drug intravenously (i.v.) at the doses of 0.5, 1 and 2 mg/kg.

3.5 Preparation and administration of compounds

Compounds **5a, 5d, 5e, 5f, 5g, 5i, 5j**were dissolved in 40% DMSO while, **5b, 5c, 5h**were dissolved in 20%, 10% and 50% DMSO respectively. In few compounds milky suspension was obtained. Compounds were administered at the doses of 1 and 5 mg/kg byi.v. route in a constant volume of 0.5 ml over a period of 10–15 s and the venous catheter was flushed with an additional 0.2 ml of saline.

IV CONCLUSION

A series of ten new pyrazolo-1,4-dihydropyridines were synthesized and tested for their antihypertensive activity *in vivo*. It was concluded that these compounds did not affect mean arterial blood pressure and heart rate significantly.

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