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Note

Synthesis and evaluation of some 1, 4-dihydropyridine and their derivatives as antihypertensive agents

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A series of 1, 4-dihydro-2, 6-dimethyl-4-{4-[3-(2-aminopyrazine/1-amino-4-methyl piperazine)-2-hydroxy propoxy]-phenyl}-pyridine-3, 5-carbamoyl have been synthesized and the structure of the compounds have been confirmed by IR, ^{1}H NMR , MS & elemental analysis. The title compounds have been evaluated for antihypertensive activity by tail-cuff method. Some of these compounds have been found to exhibit excellent antihypertensive activity.

Keywords: Antihypertensive, vasodilators, antidiabetic, anti-tumour, antimicrobial

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1,4-Dihydropyridines[1,2] are well known as calcium channel blockers and have emerged as one of the important classes of drugs for the treatment of hypertension[3]. 1,4-Dihydropyridine plays a significant role in the world of medicine because of their effectiveness as calcium channel blockers. Among 1,4-dihydropyridines, 4-aryl-1,4-dihydropyridine dicarboxylic diester of nifedipine have been used in the cardiovascular disease. Due to their vasodilator[4] properties in the angina and hypertension. The dihydropyridine heterocyclic ring is the common feature of various bioactive compounds such as vasodilator[5], antitumour and antidiabetic[1].

Recently reported studies have shown that compounds possessing 1,4-dihydropyridine nucleus possess variety of biological activities including antimicrobial agents[6], myocardial infarction, peripheral vascular disorders[4], antitubercular, antiinflammatory agents. The studies have revealed that 1,4-DHP's exhibit several other medicinal applications, which include neuroprotectant and platelet antiaggregatory activity, in addition to acting as a cerebral anti-ischemic agent in the treatment of Alzheimer's disease and a chemosensitiser[7] in the therapy. The examples clearly demonstrate the potential of novel DHP derivatives as a source of valuable drug candidates.

Dihydropyridine appears to be a privileged structure in medicinal chemistry and pharmacology. They display the affinity for many diverse binding sites. This adaptability has been utilized to optimise the affinity in binding to many receptors. Thus by careful structural modification, regioselectivity has been possible at sites other than Ca^{2++} channels[8].

A recent computational analysis of compressive medicinal chemistry database found the DHP framework to be among the most prolific chemo-types found. Thus the synthesis of this heterocyclic nucleus is of continuing interest. The success of these calcium antagonists has led to the development of novel synthetic strategies to improve their classical methods of preparation. In view of the above facts, five new derivatives of 1,4-dihydropyridine have been synthesized, characterised (**Table I**) and evaluated for their antihypertensive activity.

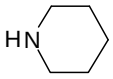
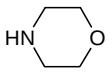
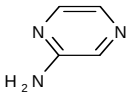
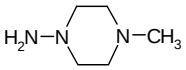
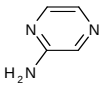
Experimental Section

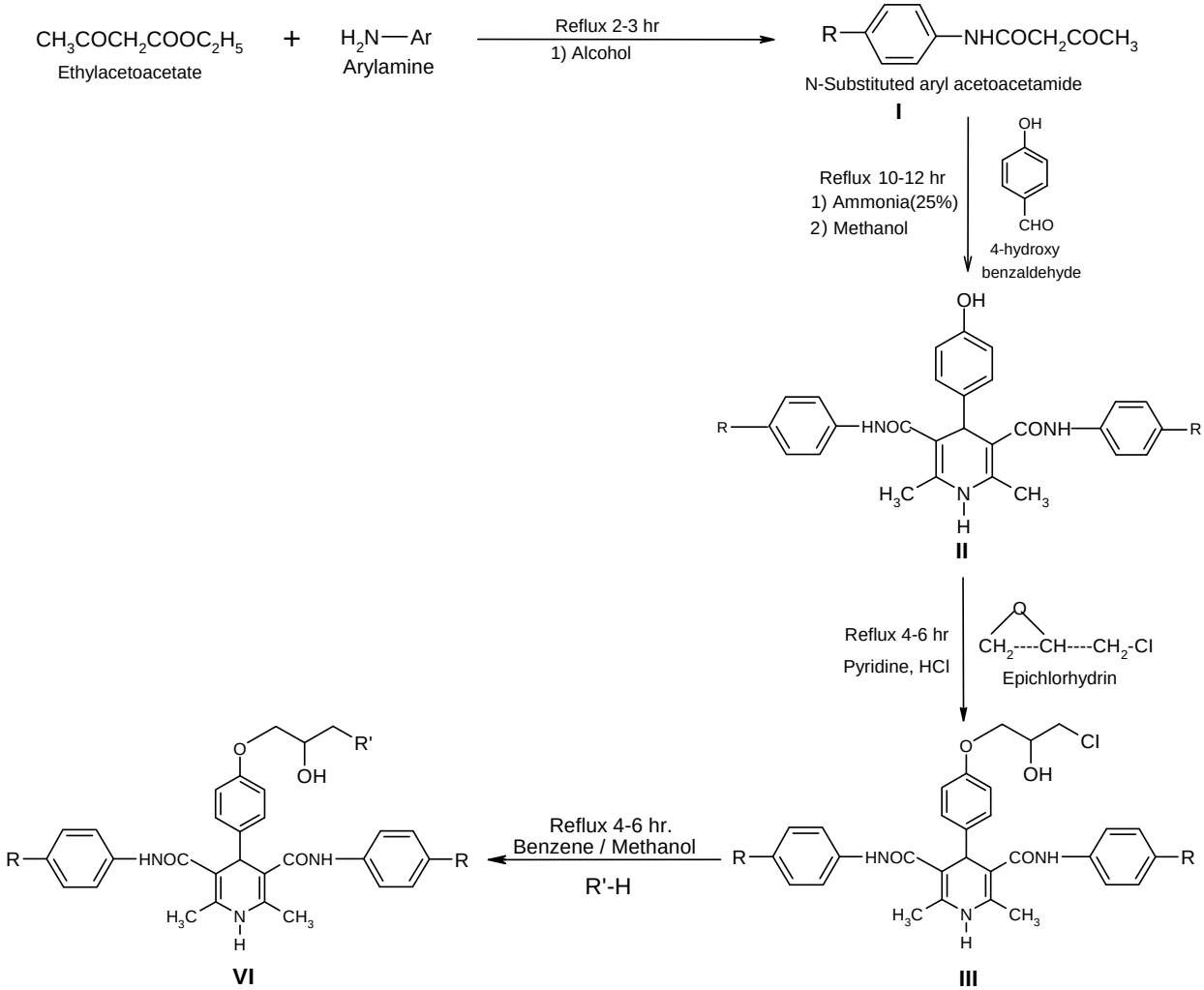
All the melting points reported are uncorrected. The IR spectra was recorded on a NICOLET FTIR spectrometer and ^{1}H NMR spectra (DMSO-d_6) was recorded on *VXRO*-300 MHz using TMS as internal standard (chemical shift in δ, ppm). Mass spectra were obtained on a VG micro mass 7070H.

Preparation of N-substituted aryl acetoacetamide I

An equimolar amount of ethyl acetate and different aryl amine were taken in the round bottom flask and dissolved in alcohol and refluxed for about 2-3 hr. The reaction mixture was cooled. The solid that separated out was filtered, washed with cold water and dried. The crude solid of anilide **I** was purified by recrystallization twice from appropriate solvent to give colourless crystal (**Scheme I)**.

Table I — Characterization data of compounds (C_1-C_5)

Compd	R	R'	Molecular formula	Mol. Wt.	m.p. ^{0}C	Yield %	Rf value	Elemental analyses Found (Calcd) C	H	N
C_1	OCH_3		$C_{37}H_{50}O_6N_4$	646	267	25	0.61	68.73 (68.53	7.73 7.47	8.66 8.86)
C_2	OCH_3		$C_{36}H_{48}O_7N_4$	648	254	22	0.49	66.66 (66.30	7.40 7.56	8.64 8.90)
C_3	OCH_3		$C_{36}H_{44}O_6N_6$	656	232	18	0.52	65.85 (65.95	6.70 6.56	12.80 12.48)
C_4	OCH_3		$C_{37}H_{42}O_6N_6$	666	262	23	0.54	66.66 (66.96	6.30 6.01	12.61 12.35)
C_5	p-Cl		$C_{34}H_{38}O_4N_6Cl_2$	594	147	10	0.49	68.68 (69.00	6.39 6.09	14.14 14.40)



Scheme I

IR (KBr): 3449 (-NH str.), 3270 (-CH-CH str.), 1701 (-CONH), 1672 (C=O str.), 1457 (-C-N str.), 836, 748 (CH=CH str.) cm^{-1}.

Preparation of 1,4-dihydropyridine II

N-aryl (substituted) acetoacetamide **I** (0.01 mole) was dissolved in methanol and an appropriate aldehyde (0.05 mole) was added followed by the addition of excess of ammonia (25%). The reaction mixture was mechanically stirred for 10 min. and then heated on water bath under reflux for 10-12 hr. Methanol was removed under reduced pressure and cooled. The product thus separated **II** was filtered and washed with methanol (**Scheme I**). It was purified by recrystallization from alcohol to give yellowish crystalline compound.

IR (KBr): 3546 (-OH str.), 3243 (-CH-CH aromatic str.), 1646 (-C=O str.), 1559 (-C=N str.), 832, 746 cm^{-1} (-CH-CH def.)

Preparation of 1,4-dihydro-2,6-dimethyl- 4-{4-[3-(piperidine / morpholine / 2-aminopyrazine / 1-amino-4-methylpiperazine)-2-hydroxypropoxy]-phenyl}-pyridine-3,5-carbamoyl C_1 - C_5

A mixture of 1, 4-dihydropyridine (0.01 mole) and 1-chloro-2,3-epoxypropane (25mL) was refluxed on a water bath in presence of basic catalyst, pyridine, for about 4-6 hr. The crude epoxide separated was added into an equal volume of chloroform and excess of conc. HCl (10 mL) and a mixture was stirred for 30 min. the chloroform layer that separated was washed with small amount of ice cold water to remove the excess of HCl. The organic layer was dried (Na_2SO_4) and the resulting chlorhydrine **III** compound was refluxed with 2-aminopyrazine/1-amino-4-methyl-piperazine in benzene about 6 hr. The resulting solution was concentrated under reduced pressure, the mixture was then poured into ice-cold water, when solid separated out it was filtered and recrystallized from ethanol to afford brownish crystals (**Scheme I**).

C_1: IR (KBr): 3423 (-N-H str.) amide, 1630 (-C=O str.), 1111, 1182 (-C-O str.), 757, 699 (-C-H def.), 2963 cm^{-1} (ar. -CH str.): ^{1}H NMR: δ 9.7 (1H, NH), 8.4 (2 H, 2 CONH), 6.7 - 7.91 (2 H, ar- CH), 4.1 (1 H, O-H), 3.4-3.6 (10 H, piperidine), 2.6 (6H, 2 CH_3), 7.9 (1H, -CH, dihydropyridine). m/z: 609.0, (M = 100 %)

C_2: IR (KBr): 3436 (-N-H str.), 2926 (-CH-CH ar str), 3446 (-OH str.), 1631 (-C=O str.), 1590 (C=N str.), 878,757,728 cm^{-1} (CH def.) ^{1}H NMR: δ 6.5-7.5 (12 H, ar CH), 5.3 (1H, NH), 4.1-4.4 (10H, morpholine), 3.4 (4 H, 2 CH_2), 2.6 (6H, 2 CH_3), 3.8 (8H, 2 CH_2 piperazine), 2.19-3.78 (4 H, 2 CH_2), 3.60 (3 H, CH_3 piperazine), 2.55 (6 H, 2 CH_3), 7.9 (1H, -CH, dihydropyridine). m/z: 610.5, (M = 100 %)

C_3: IR (KBr): 3429 (-O-H str.), 1631 (-C=O str), 1591 (-C=N str.), 1421 (-C-N str.), 832, 753 cm^{-1} (CH def.). ^{1}H NMR: δ 7-8 (12 H, ar-CH), 5.4 (1 H, OH), 5.2 (1H, NH), 3.1-3.6 (12 H, 4 CH_3), 1.3-1.5 (2H, 2 CONH), 7.9 (1H, -CH, dihydropyridine). m/z: 624.00, (M = 100 %)

C_4: IR (KBr): 3448 (-NH, -OH str.), 2959 (-CH-CH str), 1631 (-C=O str.), 1590 (-C=N str.), 603, 637 (C-Cl str.), 766, 874 cm^{-1} (-CH def.). ^{1}H NMR: δ 7-8 (12 H, ar-CH), 5.4 (1 H, OH), 5.2 (1H, NH), 2.6 (6 H, 2 CH_3), 1.3-1.5 (2H, 2 CONH), 5.6 (2H, NH_2), 5.6 (12 H -1, amino-4,methyl piperazine). m/z: 623, (M = 100 %)

Table II — Antihypertensive activity

Sl No.	Compd	MEAN ± SE	
		Before	After
1	Control	186.8 ± 6.64	184.7 ± 6.63**
2	Nifedipine	179.1 ± 3.24	73.09 ± 7.71**
3	C_1	166.6 ± 6.55	115.5 ± 5.15**
4	C_2	191.2 ± 7.83	101.8 ± 8.69**
5	C_3	181.5 ± 9.40	103.6 ± 1.92**
6	C_4	160.0 ± 9.29	113.5 ± 10.0**
7	C_5	176.3 ± 6.67	104.1 ± 9.08**

*P < 0.05 Moderate activity

** P < 0.01 significant activity

The mean ± S.E. of the blood glucose level was calculated for each group and the results were analyzed by ANOVA and student t-test by comparing the results at interval of 1,3,6 hrs. with 0 hr. This test is applied to access the statistical significance of difference between two independently drawn sample means. The P-value indicates whether the observed difference in the mean is statistically significant.

C_5: IR (KBr): 3436 (-NH str.), 2926 (-CH-CH aromatic str.), 3446 (-OH str.), 1631 (-C=O str.), 1590 (-C=N str.), 878, 757, 728 cm^{-1} (-CH def.) ^1H NMR: δ 7-8 (12 H, ar-CH), 5.4 (1 H, OH), 5.2 (1H, NH), 3.1-3.6 (6 H, 2 CH_3), 1.3-1.5 (2H, 2 CONH), 7.9 (1H, -CH, dihydropyridine). m/z: 644.5, (M = 100 %).

Antihypertensive activity[9]

Male Sprague-Dawley rats weighing 80-100 mg were anaesthetized by intra-peritoneal injection of 4% chloralhydrate solution 0.8 mL. Both kidneys were exposed retro-peritoneally. To include renal hypertension, a silver clip (0.2 mm diameter, 4 mm length) was placed on to both renal arteries, the kidney was reposed and the wound was closed by suture. Within 5-6 weeks, operated animals attained a renal hypertension with a systolic blood pressure of 170-200 mm of Hg (mean normal physiology BPs for rats is mm of Hg). Only animals with a blood pressure of 180 mm of hg were used for the test.

Groups of 6 animals were used per dose. The test substance was administered intra peritoneally once a day. The control group received saline only. The screening dose of compound was 100 mg/kg blood pressure and the heart rate measurements were taken at pre dose and one hr postdrug. The standard drug used was Nifedipine (3 mg/kg). (**Table II)**.

Result and Discussion

The title compounds were screened for their antihypertensive activity by tail-cuff method using selected male Sprague-Dawley rats weighing 80-100 gms of either sex. The hypertension was induced by renal clip method. The rats having hypertension more than 180 mm of Hg were taken for the experiment. Each group contains six animals.

All the five compounds synthesized **(C_1-C_5)**, showed good antihypertensive activity. Compounds **C_2**, **C_3** and **C_5** have shown the maximum antihypertensive activity when compared with the standard drug. Compounds **C_1** and **C_4** have also shown the better antihypertensive activity. The results were calculated by measuring the mean SE ± and finding the 'p' value. 1,4-dihydropyridine and their derivatives were found to be significant antihypertensive agent when compared to the standard drug Nifedipine.

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