Asian Journal of Chemistry Vol. 21, No. 6 (2009), 4357-4365

Synthesis and *in vitro* Calcium Channel Blocking Activity of Symmetrical and Unsymmetrical Substituted 1,4-Dihydropyridine Derivatives

D.R. HARISH KUMAR, NAYEEM NAIRA, T.S. DHARMARAJAN and MANJUNATH GHATE*
Department of Pharmaceutical Chemistry,
Krupanidhi College of Pharmacy, Bangalore-560 035, India
E-mail: ghate72@gmail.com

Symmetrical substituted 1,4-dihydropyridines (**3a-e**) was synthesized by Hantzsch synthesis method. In the first step benzaldehydes (**1a-e**) was treated with methyl acetoacetate (**2**) in the presence of ammonia and methanol to afford diester compound **3a-e**. Further these diester **3a-e** was reacted with ammonia solution (25 %) to give the compound **4a-b** and with hydrazine hydrate to form hydrazides **5a-b**. The unsymmetrical substituted 1,4-dihydropyridine was prepared by modified Hantzsch method. Here the α,β-unsaturated ketone reacted with β- amino crotonate in the methyl alcohol at room temperature to afford unsymmetrical 1,4-dihydropyridine (**8a-b**). The required α,β-unsaturated ketone was prepared by the reaction of substituted benzaldehyde with ethylaceto acetate in the presence of acetic acid and piperidine at room temperature. Whereas β-amino crotonate was prepared by the reaction of methylaceto acetate in the presence of ammonia and methanol at ice bath temperature for 2 h. Six compounds were screened for calcium channel blocking activity using guinea pig ileum. The **3a**, **3b**, **8b** were shown promising activity compared with standard felodipine.

Key Words: Substituted 1,4-dihydropyridine derivatives, Calcium channel blocking activity.

INTRODUCTION

Hypertension is common disorder in human life, which is linked with age, life style and diet. Antihypertensive are the drugs which are used to treat hypertension. There is large number of drugs available in the market act by different mechanisms. Calcium channel blocking is one of the mechanisms used to treat hypertension. Calcium channel blockers act by blocking calcium in the smooth muscles in different parts of body. Blocking the calcium in the smooth muscle reduce contraction there by lowering blood pressure. Nefidipine, felodipine, amlodipine are very important commercial drugs having 1,4-dihydropyridine moiety acts by blocking the calcium channel[1]. There is an extensive research in the 1,4-dihydropyridine as calcium channel blockers[2-6]. Some of the 1,4-dihydropyridines found to possess various other pharmacological activities like antimicrobial[7], as modulators of P-glycoprotein-mediated

multi drug resistance[8], radio protective[9] calcium channel antagonists labelled with carbon-11 for *in vivo* cardiac PET imaging[10]. Due to the importance of 1,4-dihydropyridines, it is planned to synthesize various symmetrical and unsymmetrical 1,4-dihydropyridines and screened for calcium channel blocking activity.

EXPERIMENTAL

Melting point is recorded in open capillary tubes and is uncorrected. The TLC is taken in silica gel G precoated TLC plates. The solvents and the reagents were used of laboratory grade for synthesis. The IR is recorded Perkin-Elmer FT IR spectrophotometer using KBr press pellet technique. The NMR is recorded in Bruker 300 MHz FT NMR spectrophotometer using $CDCl_3$ as solvent and TMS as internal standard.

Synthesis of 1,4-dihydro-2,6-dimethyl-4-(3',4',5'-trimethoxy phenyl)-3,5-pyridine dicarboxylic acid ethyl ester (3a): To the solution of trimethoxy benzaldehyde (4 g, 0.01mol), ethyl acetoacetate (8.28 g, 0.03 mol) in methanol (20 mL) was treated with 4 mL ammonia solution (25 %, 0.02 mol) and refluxed for 5 h. After the completion of the reaction the mixture was cooled to obtain crude crystals. The solid separated was filtered and washed with aqueous methanol and dried. Recrystallization was done in methanol to afford symmetrical 1,4-dihydropyridine (Yield: 76 %).

Synthesis of 1,4-dihydro-2,6-dimethyl-4-(3'4',5'-trimethoxy phenyl)-3,5-pyridine diamide (4a): To the solution of **3a** (1 g, 0.001 mol), in dioxane (10 mL) was treated with 20 mL ammonia solution (25 %, 0.02 mol) was stirred at room temperature for 24 h. 50 mL ethyl acetate was added and extracted and separated the ethyl acetate layer and dried over sodium sulphate. The solution was concentrated and the solid separated was dried. It was recrystallized from diethyl ether to afford diamide compound **4a** (Yield: 76 %).

Synthesis of 1,4-dihydro-2,6-dimethyl-4-(3',4',5'-trimethoxy phenyl)-3,5-pyridine dihydrazide (5b): To the solution of analogue **3a** (2.0 g) in methanol, 5.0 mL of hydrazine hydrate was added and refluxed for 5 h. Then methanol was removed, crystals of hydrazide derivative was formed immediately. The crystals were washed with water and recrystallized from methanol (Yield 90 %).

Synthesis of 1,4-dihydro-2,6-dimethyl-4-(3'-methoxy 4'-hydroxy phenyl)-3,5-pyridine dicarboxylic ethyl methyl ester (8b): Step-1: About 5.2 g (0.04 mol) ethyl acetoacetate and 6 g (0.04 mol) of vanillin were taken in a beaker and stirred for 15 min at room temperature. 0.06 g (0.001 mol) of acetic acid was added drop wise which was followed by 0.08 g of piperidine. This mixture was heated to 38-40 ºC and maintained for 15 min. Cooled to room temperature and stirred for 12 h. Finally cooled to 5 ºC, filtered and dried. It was recrystallized from methanol (Yield 75 %).

Step-2: Methyl acetoacetate (23.23 mL), ammonia (25 %) (27.5 mL) and methanol (25 mL) are mixed in a beaker, kept in an ice bath, temperature maintained

between 5 to 10 ºC white shining crystals are formed within 2 h in pure form (Yield 80 %).

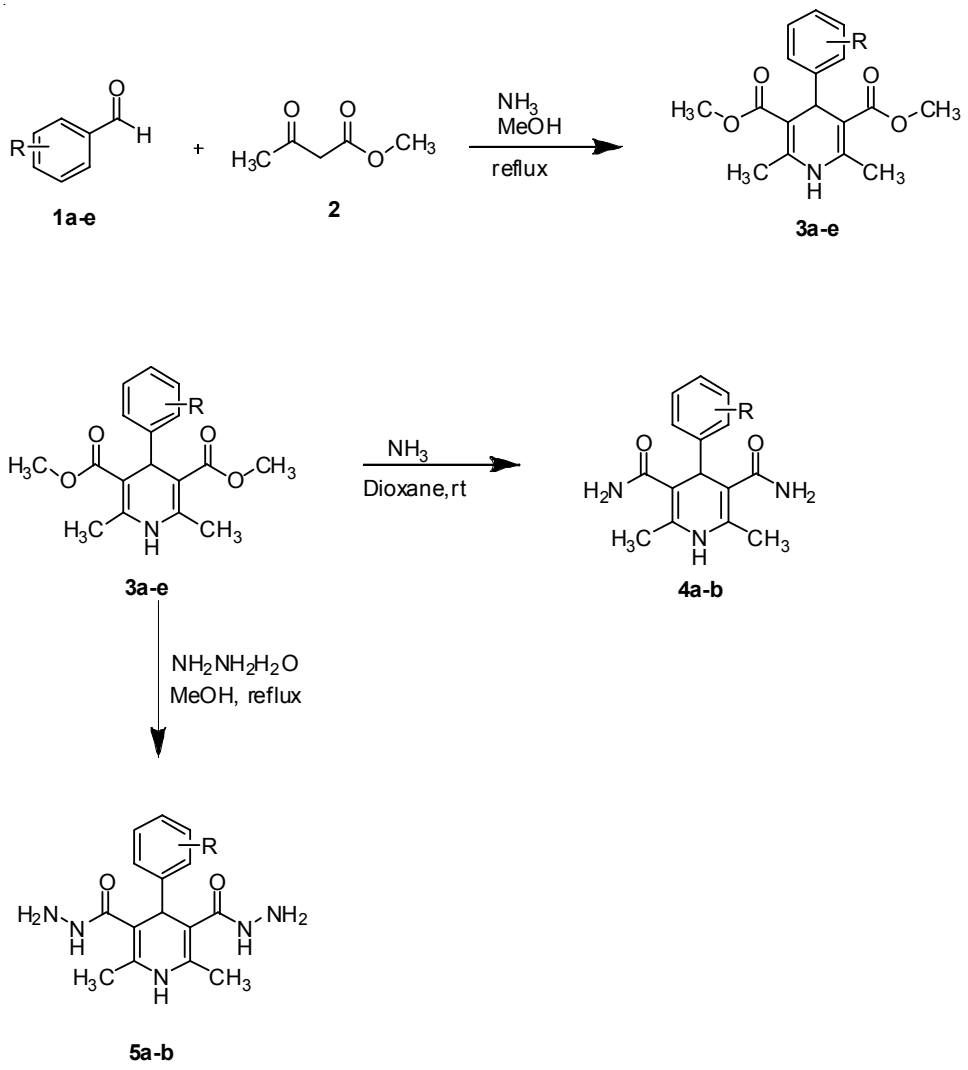
Step-3: Condensation of ethyl α-acetyl 3-methoxy 4-hydroxy cinnamate with methyl α-amino crotonate. About 2.67 g (0.01 mol) of ethyl α-acetyl 3-methoxy 4-hydroxy cinnamate and 1.15 g (0.01 mol) of methyl α-amino crotonate in methanol were condensed by refluxing for 10 h. The solid thus obtained was recrystallized from methanol (Yeild 76 %).

RESULTS AND DISCUSSION

The scheme for the synthesis of titled compounds was depicted in the (**Scheme-I**). In order to prepare the symmetrical 1,4-dihydropyridine, methyl acetoacetate (**2**) was treated with different substituted aldehyde (**1a-e**) in the presence of ammonia and methanol at refluxing temperature to afford symmetrical 1,4-dihydropyridine (**3a-e**) (**Scheme-I**). The reaction undergone smoothly at refluxing temperatures and methanol was found to be best for the synthesis as compared with other solvents. The physical data of the synthesized compounds were given in the Table-1. These compounds were characterized by IR and NMR data. The IR spectral data **3d** showed peaks at 3338, 2980 cm^{-1} corresponding to NH and CH stretching, respectively. The peak due to carbonyl stretching of ester was found at 1740 cm^{-1} where as the C=C was found at 1490 cm^{-1}. The PMR spectral data showed presence of methyl group of 1,4-dihydropyridine δ 2.4 ppm as singlet resonating for six hydrogens. Whereas the peak at δ 3.6 ppm as a singlet integrating for 6 protons is due to methyl ester. A singlet found at δ 3.8 resonating for three protons is assigned as methoxy group of benzene ring. The methine proton was found as singlet at δ 5.0 ppm was assigned as 4th position of 1,4-dihydropyridine ring. The aromatic protons found as multiplet in the δ 7.2-7.8 ppm. The NH proton found as broad peak at 5.7 δ ppm.

TABLE-1
PHYSICAL DATA OF SYNTHESIZED COMPOUNDS **3a-8b**

Compd.	R	m.f.	m.p. (ºC)	R_f value	Solvent for recrystallization
3a	3,4,5-Trimethoxy	$C_{22}H_{29}NO_7$	139	0.76	Methanol
3b	3-Methoxy-4-benzyloxy phenyl	$C_{25}H_{28}NO_6$	180	0.85	Methanol
3c	3-Methoxy-4-benzyloxy phenyl	$C_{27}H_{32}NO_6$	158	0.87	Ethanol
3d	4-Methoxy	$C_{18}H_{21}NO_5$	176	0.61	Methanol
3e	3,4,5-Trimethoxy	$C_{20}H_{25}NO_5$	154	0.65	Methanol
4a	3,4,5-Trimethoxy	$C_{18}H_{23}N_3O_5$	152	0.54	Diethylether
5a	3,4,5-Trimethoxy	$C_{18}H_{25}N_5O_5$	150	0.58	Methanol
4b	Cl	$C_{15}H_{16}N_3O_2Cl$	130	0.48	Diethylether
4c	2,3-Dichloro	$C_{15}H_{16}N_3O_2Cl_2$	110	0.69	Diethylether
5b	2,3-Dichloro	$C_{15}H_{18}N_5O_2Cl_2$	131	0.71	Methanol
8a	3,4,5-Trimethoxy	$C_{21}H_{27}NO_7$	176	0.72	Methanol
8b	3-Methoxy 4-hydroxy	$C_{19}H_{23}NO_6$	190	0.82	Methanol

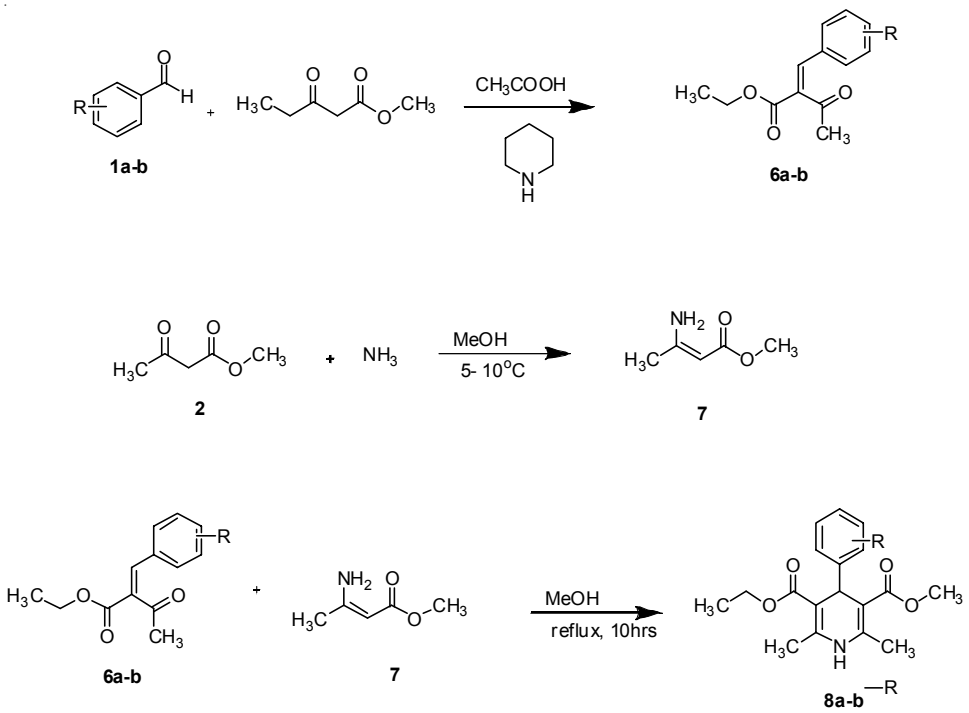


R= 3,4,5-trimethoxy; 3-OCH_3,4-OH;p-benzyloxyvanillin; Cl; 2,3-dichloro; 4-OCH_3

Scheme-I: Synthesis of symmetrical 1,4-dihydropyridines

Further the symmetrical methyl ester was converted to amide **4a-c** and hydridazide **5a-b** by treating with ammonia and hydrazine hydrate. The formation of amide and hydrazide was easily known by absence of ester carbonyl at 1742 and formation amide carbonyl at 1650 cm^{-1}. The NMR spectral data also showed the absence methyl ester group at 3.6 ppm.

In order to prepare unsymmetrical 1,4-dihydropyridine we followed the modified Hantzsch method[11]. Here we have first prepared two intermediate compounds, α,β-unsaturated ketone **6** and β-amino crotonate **7**. The α,β-unsaturated ketone **6**



Scheme-II: Synthesis of unsymmetrical 1,4-dihydropyridines **8a-b**

inturn prepared by the reaction of substituted aldehyde **1a-b** with ethyl acetoacetate in the presence of acetic acid and piperidine. The β-amino crotonate **7** was prepared by the reaction of methyl acetoacetate, ammonia and methanol at 5-10 ºC. In the last step both intermediate compound **6a-b** and **7** were refluxed for 10 h in methanol to afford unsymmetrical substituted 1,4-dihydropyridine **8a-b**. The completion of the reaction was checked by TLC and solid separates out which was recrystallized by methanol (Table-1). These compound were characterized by IR and NMR spectral data. The IR spectral data of **8a** showed the presence of peaks at 3340, 2980 cm^{-1} corresponding to NH and CH stretching, respectively.The peaks due to carbonyl stretching of ester was found in 1745 cm^{-1} whereas the C=C was found at1490 cm^{-1}. The PMR spectral data showed presence of methyl group of 1,4- dihydropyridine δ 2.4 ppm as singlet resonating for six hydrogens at C-2 and C-6 of 1,4-dihydro-pyridine. Whereas the peak at δ 3.6 ppm as a singlet integrating for three protons is due to methyl ester of C-3 of 1,4-dihydropyridine ring. A singlet found at δ 3.8 resonating for nine protons is assigned as trimethoxy group of benzene ring. A

triplet observed at δ 2.2 ppm resonating for three protons is due to methyl group of ethyl ester. The methylene group of ethyl ester was observed as quartet at δ 3.4 ppm.The methine proton was found as singlet at δ 5.0 ppm was assigned as 4th position of 1,4-dihydropyridine ring. The aromatic protons found as singlet at δ 7.8ppm integrating for two protons. However, the NH proton found as broad peak at 5.8 δ ppm. The spectral data of the synthesized compounds are as follows:

1,4-Dihydro-2,6-dimethyl-4-(3,4,5-trimethoxy phenyl)-3,5-pyridine dicarboxylic acid ethyl ester (3a): IR (KBr, ν_{max}, cm^{-1}) 3338 N-H, 2980 CH, 1696 C=O, 1490 C-C, 778 (Ar bend). ^1H NMR (300 MHz, $CDCl_3$ δ ppm) 2.4 (s, 6H, CH_3 at C-2 & C-6), 3.8 (s, 9H, OCH_3), 4.2 (q, 4H, CH_2), 5.0 (s, CH, at C-4 in dihdropyridine ring), 5.7 (s, NH in dihydropyridine ring), 6.7 (s, 2CH in aromatic ring).

1,4-Dihydro-2,6-dimethyl-4-(3-methoxy,4-benzyloxy phenyl)-3,5-pyridine dicarboxylic acid methyl ester (3b): IR (KBr, ν_{max}, cm^{-1}) 3340 N-H, 2960 C-H, 1730 C=O ester; 1125 C-O aryl alkyl ether, 750 phenyl (bend). ^1H NMR (300 MHz, $CDCl_3$ δ ppm) 2.4 (s, 6H, CH_3 at C-2 & C-6), 3.7 (s, 3H, OCH_3 ester), 3.8 (s, OCH_3 in aryl), 5.1 (s, OCH_2 at 4-phenyl), 5.7 (s, NH in dihydropyridine ring), 6.8 (d, 3 (CH) in aromatic ring at C-4),6.9 (m, 5 (CH) of phenyl).

1,4-Dihydro-2,6-dimethyl-4-(3-methoxy-4-benzyloxy phenyl)-3,5-pyridine dicarboxylic acid ethyl ester (3c): IR (KBr, ν_{max}, cm^{-1}) 3351 N-H, 2976 C-H, 1735 C=O ester, 1213 C-O aryl alkyl ether, 746 phenyl (bend). ^1H NMR (300 MHz, $CDCl_3$ δ ppm): 2.4 (s, 6H, CH_3 at C-2 & C-6), 3.8 (s, 3H, OCH_3 of aryl), 5.1 (s, OCH_2 at 4-phenyl), 5.6 (s, NH in dihydropyridine ring), 6.8 (d, 3 (CH) in aromatic ring at C-4),7.2 (m, 5 (CH) of phenyl).

1,4-Dihydro-2,6-dimethyl-4-(*p*-methoxy phenyl)-3,5-pyridine dicarboxylic acid methyl ester (3d): IR (KBr, ν_{max}, cm^{-1}) 3343 N-H, 2948 C-H, 1735 C=O ester, 1215 C-O aryl alkyl ether, 753 phenyl (bend), 1507 C=C. ^1H NMR (300 MHz, $CDCl_3$ δ ppm): 2.4 (s, 6H, CH_3 at C-2 & C-6), 3.8 (s, 3H, OCH_3 of aryl), 5.7 (s, NH in dihydropyridine ring), 3.6 (s, OCH_3 in ester), 7.2 (m, 4 (CH) in aromatic ring).

1,4-Dihydro-2,6-dimethyl-4-(3,4,5-trimethoxy phenyl)-3,5-diacetyl pyridine (3e): IR (KBr, ν_{max}, cm^{-1}) 3320 N-H, 2950 C-H, 1705 C=O at C-3,700 phenyl (bend), 1125 C-O aryl alkyl ether. ^1H NMR (300 MHz, $CDCl_3$ δ ppm): 2.4 (s, 6H, CH_3 at C-2 & C-6), 3.8 (s, 9H, OCH_3 at 3, 4, 5 on aryl), 5.3 (s, NH in dihydropyridine ring), 6.6 (s, 2 (CH) in aromatic ring).

1,4-Dihydro-2,6-dimethyl-4-(3,4,5-trimethoxy phenyl)-3,5-pyridine diamide (4a): IR (KBr, ν_{max}, cm^{-1}) 3340 N-H, 2950 C-H, 1700 C=O at C-3, 750 phenyl (bend), 1495 C=C. ^1H NMR (300 MHz, $CDCl_3$ δ ppm): 2.4 (s, 6H, CH_3 at C-2 & C-6), 3.8 (s, 9H, OCH_3 at 3, 4, 5 on aryl group), 5.7 (s, NH in dihydropyridine ring), 6.5 (s, 2 (CH) in aromatic ring), 5.0 (s, CH, at C-4 in dihdropyridine ring).

1,4-Dihydro-2,6-dimethyl-4-(3,4,5-trimethoxy phenyl)-3,5-pyridine dihydrazide (5a): IR (KBr, ν_{max}, cm^{-1}) 3340 N-H, 3098 C-H, 2979 C-H (alkyl),

1696 C=O at C-3, 777 phenyl (bend). ^{1}H NMR (300 MHz, $CDCl_3$ δ ppm): 2.4 (s, 6H, CH_3 at C-2 & C-6), 3.8 (s, 9H, OCH_3 at 3, 4, 5, on aryl group), 5.0 (s, CH in dihydropyridine ring), 5.7 (s, NH in dihydropyridine ring), 6.6 (s, 2(CH) in aromatic ring).

1,4-Dihydro-2,6-dimethyl-4-(pchlorophenyl)-3,5-pyridine diamide (4b): IR (KBr, ν_{max}, cm^{-1}) 3340 N-H, 3030 C-H (aromatic), 2950 C-H (alkyl), 750 phenyl (bend), 550 C-Cl. ^{1}H NMR (300 MHz, $CDCl_3$ δ ppm): 2.4 (s, 6H, CH_3 at C-2 & C-6), 5.0 (s, CH in dihydropyridine ring), 5.7 (s, NH in dihydropyridine ring), 7.3 (m, 4 (CH) in aromatic ring).

1,4-Dihydro-2,6-dimethyl-4-(2,3-dichlorophenyl)- 3,5-pyridine diamide (4c): IR (KBr, ν_{max}, cm^{-1}) 3340 N-H, 3101 C-H (aromatic), 2982 C-H (alkyl), 1696 C=O at C-3, 734 phenyl (bend). ^{1}H NMR (300 MHz, $CDCl_3$ δ ppm): 2.4 (s, 6H, CH_3 at C-2 & C-6), 5.4 (s, CH in dihydropyridine ring), 5.7 (s, NH in dihydropyridine ring), 7.2 (m, 3 (CH) in aromatic ring).

1,4-Dihydro-2,6-dimethyl-4-(2,3-dichlorophenyl)-3,5-pyridine dihydrazide (5b): IR (KBr, ν_{max}, cm^{-1}) 3340 N-H, 2950 C-H, 1700 C=O, 700 phenyl (bend), 450 C-Cl. ^{1}H NMR (300 MHz, $CDCl_3$ δ ppm): 2.4 (s, 6H, CH_3 at C-2 & C-6), 5.5 (s, CH in dihydropyridine ring), 5.8 (s, NH in dihydropyridine ring), 7.3 (m, 3 (CH) in aromatic ring).

1,4-Dihydro-2,6-dimethyl-4-(3,4,5-trimethoxy phenyl)-3,5-pyridine dicarboxylic acid ethyl methyl ester (8a): IR (KBr, ν_{max}, cm^{-1}) 3340 N-H, 2980 CH, 1735 C=O ester, 1490 C=C, 1125 C-O. Aryl alkyl ether, 750 phenyl (bend). ^{1}H NMR (300 MHz, $CDCl_3$ δ ppm): 2.4 (s, 6H, CH_3 at C-2 & C-6), 3.6 (s, 3H, CH_3 at C-3), 3.8 (s, 9H, OCH_3 at 3, 4, 5, on aryl group), 3.9 (s, 2H, CH_2 at C-5), 4.1 (d; 3H CH_3 at C-5), 5.0 (s, CH at C-4 in dihydropyridine ring), 5.8 (s, NH in dihydropyridine ring), 6.7 (s, 2 (CH) in aromatic ring).

1,4-Dihydro-2,6-dimethyl-4-(3-methoxy-4-hydroxy phenyl)-3,5-pyridine dicarboxylic ethyl methyl ester (8b): IR (KBr, ν_{max}, cm^{-1}) 3600 O-H, 3354 N-H, 2948 C-H, 1740 C=O ester, 1219 C-O. Of aryl alkyl ether, 784 phenyl (bend). ^{1}H NMR (300 MHz, $CDCl_3$ δ ppm): 2.4 (s, 6H, CH_3 at C-2 & C-6), 3.7 (s, OCH_3, methyl ester at C-3), 3.8 (s, OCH_3 in aryl ring), 4.1 (q, 5H, ethyl ester at C-5), 5.4 (s, CH in dihydropyridine ring), 5.7 (s, NH in dihydropyridine ring), 6.7 (s, 3 (H) in aromatic ring).

***In vitro* calcium channel blocking activity[12]:** Guinea pig of either sex weighing between 250-300 g was selected and fasted overnight, being allowed water *ad libitum*. The animal was sacrificed by head blow and the lower portion of the ileum was isolated. Three centimeter long muscle strip was suspended in an organ bath of 30-40 mL capacity, filled with calcium free tyrode solution maintained at 37 ºC. Tissue was fixed to the bottom of aerator tube with a thread and the other end was attached to a writing point. The preparation was aerated with oxygen and allowed to stabilize for 1.5 h. The muscle response were recorded on a slow moving kymograph using a frontal writing point with 8 fold magnification and a tension of 0.5 g.

After the stabilization period the control maximum response for calcium was recorded followed by washing at regular intervals after each response. The antagonist was then injected, allowed to act for 5 min and then the contractions were elicited using selected dose of calcium chloride. The results are given in the Table-2. The PA_2 value was obtained by plotting percentage response against negative log molar concentration.

TABLE-2
CALCIUM CHANNEL BLOCKING ACTIVITY

Compd.	R	A	B	C	D	E	F	PA_2 value
3a	3,4,5-Trimethoxy	200	28	20	28.57	71.43	7.6234	7.32
		400	28	14	50.00	50.00	7.3224	
		600	28	8	71.42	28.58	7.1463	
		800	28	4	85.71	14.29	7.0214	
4a	3,4,5-Trimethoxy	200	20	16	20.00	80.00	7.5576	7.08
		400	20	13	35.00	65.00	7.2565	
		600	20	10	50.00	50.00	7.0804	
7b	3-Methoxy-4-hydroxy	200	34	18	47.05	52.95	7.5575	7.48
		400	34	14	58.82	41.18	7.2565	
		600	34	12	64.70	35.30	7.0804	
		800	34	6	82.35	17.65	6.9556	
3b	3-Methoxy-4-benzyloxy phenyl	200	36	20	44.44	55.56	7.6415	7.53
		400	36	15	58.33	41.67	7.3411	
		600	36	10	72.22	27.78	7.1650	
		800	36	5	86.11	13.89	7.0401	
4d	2,3-Dichloro	200	26	20	23.07	76.93	7.5315	6.99
		400	26	18	30.76	69.24	7.2305	
		600	26	16	38.46	61.54	7.0544	
		800	26	11	57.69	42.31	6.9294	
3d	4-Methoxy	200	21	18	14.28	85.72	7.5200	6.95
		400	21	17	19.04	80.96	7.2190	
		600	21	16	23.80	76.20	7.0429	
		800	21	8	61.90	38.10	6.9180	

A = Concentration calcium antagonist nanogms; B = Contraction height of calcium chloride mm; C = Contraction height of calcium antagonist mm; D = Percentage inhibition; E = Percentage response; F = Negative log molar concentration.

ACKNOWLEDGEMENTS

The authors are thankful to Chairman, Secretary and The Principal of Krupanidhi College of Pharmacy Bangalore for encouragement and providing facilities

REFERENCES

1. D.A. Williams and T.L. Lamthe, Foye's Principles of Medicinal Chemistry, edn. 5, p. 552 (2002).
2. R. Miri, K. Javidnia, H. Sarkarzadeh and B. Hemmateenejad, *Bio. Med. Chem.*, **14**, 4842 (2006).
3. J.S. Mojarrad, D. Vo, C. Velázquez and E.E. Knaus, *Bio. Med. Chem.*, **13**, 4085 (2005).

4. R. Budriesi, A. Bisi, P. Ioan, A. Rampa, S. Gobbi, F. Belluti, L. Piazzi, P. Valenti and A. Chiarini, *Bio. Med. Chem.*, **13**, 3423 (2005).
5. C. Velázquez and E.E. Knaus, *Bio. Med. Chem.*, **12**, 3831 (2004).
6. J.C. Liang, J.L. Yeh, C.S. Wang, S.F. Liou, C.H. Tsai and I.J. Chen, *Bio. Med. Chem.*, **10**, 719 (2002).
7. A.K. Chhillar, P. Arya, C. Mukherjee and P. Kumar, *Bio. Med. Chem.*, **14**, 973 (2006)
8. H. Tanabe, S. Tasaka, H. Ohmori, N. Gomi, Y. Sasaki, T. Machida, M. Iino, A. Kiue, S. Naito and M. Kuwano, *Bio. Med. Chem.*, **6**, 2219 (1998).
9. I.O. Donkor, X. Zhou, J. Schmidt, K.C. Agrawal and V. Kishore, *Bio. Med. Chem.*, **6**, 563 (1998).
10. F. Dollé, F. Hinnen, H. Valette, C. Fuseau, R. Duval, J.L. Péglion and C. Crouzel, *Bio. Med. Chem.*, **5**, 749 (1997).
11. S. Yoshinari, I. Masaharu and O. Kazuo, *Chem. Pharm. Bull.*, **39**, 3189 (1991).
12. L. Hurwitz, L.J. McGuffee, S.A. Little and H. Blumberg, *J. Pharmcol. Exp. Ther.*, **214**, 574 (1980).

(*Received*: 30 April 2008; *Accepted*: 12 March 2009) AJC-7338