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SYNTHESIS AND BIOLOGICAL ACTIVITY OF NOVAL IMIDAZOLINE DERIVATIVES

P.Shanmugasundaram*, B.Vijayakumar, G.Devadass, A.Appi Reddy and M.Vijey Aanandhi.

School of Pharmaceutical Sciences, Vels University, Chennai 600 117, Tamilnadu, India
E-mail:mvaanandhi@gmail.com

ABSTRACT

A new series of N substituted methyl 2 - phenyl imidazoline were synthesized from the reaction of phenyl imidazoline and methylene chloride. The structure of the compound was confirmed by IR, ^{1}H NMR. These compounds were evaluated for anticonvulsant activity and antibacterial activity. Among the compound 3b & 3d displayed significant anticonvulsant activity. Among the compound 3a & 3c displayed significant antibacterial activity.

Keywords: Phenyl imidazoline, anticonvulsant activity, antibacterial activity

INTRODUCTION

Compounds containing imidazoline moiety have shown a wide variety of activity and many of them have gained wide acceptance in clinical practice. [1-14] The β - adrenergic activity of biogenic amines epinephrine and nor epinephrine is highly specific and susceptible to structural changes. Compared to this α-adrenergic agonist and antagonists do not have such structural constraints. Some of the most active α-sympathomimetic agents contain imidazoline moiety as a pharmacophore which includes naphazoline[15], metazoline[16] and domazoline[17]. These compounds are mainly used in ophthalmic preparation and as nasal decongestants. Among the α-adrenergic blockers clonidine[18] has been used as an effective antihypertensive agent. Nowadays there is newer evidence that the centrally acting antihypertensive exhibit their activity through adrenergic receptors and imidazoline preferring receptors which are present in brain and peripheral nervous system. Another α-adrenergic blocker, tolazoline[19] has been used in the treatment of peripheral vascular disease as a vasodilator.

Analogs containing imidazoline are also found in antihistaminic. Substitution of imidazoline as one of the basic nitrogen has resulted in clinically effective anti-histaminic antazoline[20]. Structural modification of resulted in phentolamine[21] with complete change in biological activity and showing α-adrenergic blockade, which has been reported to be superior to tolazoline. Analogs like moxonidine[22] are also found in post myocardial infraction, which is also used to treat atherosclerosis. The structural modification of resulted in clibenzoline[23] is an antiarrhythmic agent. Another adrenergic antagonist tetrahydrozoline[24] has been used in treatment of nasal inflammation. Some of compounds are mainly used in treatment of chronic pelvic, behavioral disorder lofexidine[25] has been used an opiate dependence syndrome. Cirazoline[26] is used to inhibit the vasoconstrictor by calcium entry. Considering this, it is quite evident that imidazoline moiety offers immense possibility for preparation of therapeutically effective newer imidazoline analogs.

EXPERIMENTAL

The reagents/ chemical / solvents used during the course of these studies were obtained from Merck (India), SD fine and Sigma Aldrich, Laboratories and were of the laboratory grade. The solvents were purified by distillation before their use. Silica Gel G used for thin layer chromatography was of CDH brand Iodine chamber and UV lamps were used for visualization of TLC spots. Whatmann filter paper (No. 1 England) was used for filtration (Vacuum ordinary).

Solvent system TLC: Benzene: ethanol (4:1) used for TLC.
^{1}H NMR spectra were recorded on 300MHZ Bruker instruments. IR spectra were recorded on Shimadzu FT/IR instrument. Theoretical value and Physical properties are given in table – 1.

N substituted methyl 2 - phenyl imidazoline

1-(Chloromethyl)-2-phenyl-4, 5-dihydro-1H-imidazole (2)

A mixture of 2– Phenyl imidazoline(1) (0.01 mol) in dimethyl formamide (8 ml) was cooled to 0°C - 5°C and add sodium hydride (0.085gm) maintain the temperature below 5°C stirr and added methylene chloride with DME and maintain the temperature at 60°C upto completion of addition. The mixture was then allowed to cool for over night at room temperature. The obtained precipitate was filtered and finally recrystallized from acetone. IR (KBr): 790, 1031, 1271, 1344, 1569, 2961 CM^{-1}.^{1}HNMR ($CDCl_3$): δ 3.67(- N= C), 2.91 (- N – C), 4.64 (-Cl), 7.29 – 7.62 (-C).

1-(phenoxy methyl)-2-phenyl-4, 5-dihydro-1H-imidazole (3a)

A mixture of 1-(Chloromethyl)-2-phenyl-4, 5-dihydro-1H-imidazole (0.004mole) and phenol (0.05mol) in ethanol (10ml) containing 0.75gm of K_2CO_3. The mixture was refluxed for 3 hours. Finally the residue was evaporated and recrystallized with hexane. IR (KBr): 1031, 1050, 1271, 1344, 1569, 3487 CM^{-1}.^{1}HNMR ($CDCl_3$): δ 2.91 (- N – C), 3.67(- N= C), 5.20 (-N-C), 6.77 – 7.15 (-O-C-), 7.29 – 7.62 (-C).

N-((2-phenyl-4, 5-dihydroimidazol-1-yl) methyl) benzenamine (3b)

A mixture of 1-(Chloromethyl)-2-phenyl-4, 5-dihydro-1H-imidazole (0.004mole) and aniline (0.05mol) in ethanol (10ml) containing 0.75gm of K_2CO_3. The mixture was refluxed for 3 hours. Finally the residue was evaporated and recrystallized with hexane. IR (KBr): 779, 1342, 1690, 3251 CM^{-1}.^{1}HNMR ($CDCl_3$): δ 2.91 (- N – C), 3.67(- N= C), 4.0 (-N-CH_2), 6.43 (-N-C), 6.58(-N-C), 7.29 – 7.62 (-N-C).

1-(ortho phenoxymethyl)-2-phenyl-4, 5-dihydro-1H-imidazole (3c)

A mixture of 1-(Chloromethyl)-2-phenyl-4,5-dihydro-1H-imidazole (0.004mole) and ortho cresol (0.05mol) in ethanol (10ml) containing 0.75gm of K_2CO_3. The mixture was refluxed for 3 hours. Finally the residue was evaporated and recrystallized with hexane.
IR (KBr): 1031, 1050, 1271, 1344, 1569, 2339, 3251 CM^{-1}.^{1}HNMR ($CDCl_3$) ^{1}HNMR ($CDCl_3$): δ 2.91 (- N – C), 3.67(- N= C), 5.20 (-N-C), 6.77 – 7.15 (-O-C-), 7.29 – 7.62 (-C).

N Chloro-((2-phenyl-4, 5-dihydroimidazol-1-yl) methyl) benzenamine (3d)

A mixture of 1-(Chloromethyl)-2-phenyl-4,5-dihydro-1H-imidazole (0.004mole) and 3- Chloro aniline (0.05mol) in ethanol (10ml) containing 0.75gm of K_2CO_3. The mixture was refluxed for 3 hours. Finally the residue was evaporated and recrystallized with hexane. IR (KBr): 760, 780, 1342, 1650, 3251 CM^{-1}.^{1}HNMR ($CDCl_3$): δ 2.91 (- N – C), 3.67(- N= C), 4.0 (-N-CH_2), 6.43 (-N-C), 6.58(-N-C), 7.29 – 7.62 (-N-C), 7.27 (–Cl)

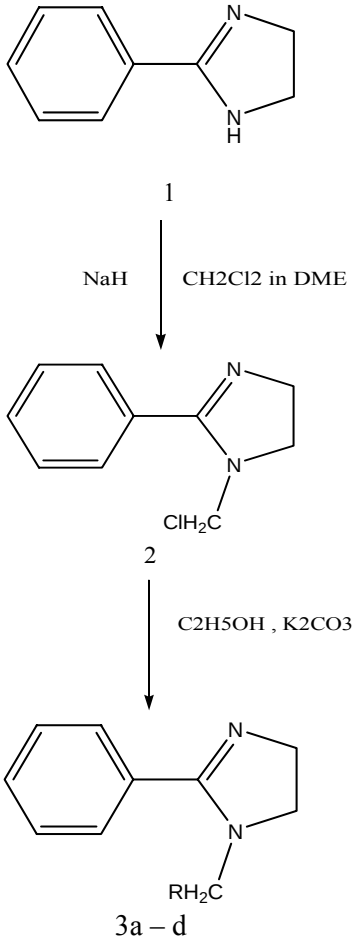
Anticonvulsant activity

In this present study the anticonvulsant activity of synthesized novel imidazoline derivatives were evaluated by Maximal Electroshock Seizure method. Male Swiss albino rat (150 – 200gm) was treated with 3a- 3d (100mg/kg) orally using oral feeding needle. CMC treated animal served as control and phenytoin (25mg/kg, orally) was administered as standard drug to a group of 6 animals. The anticonvulsant activity of test drug was determined by applying MES 150mA for 0.2 seconds using corneal electrodes. Six animals were used in each group. The pharmacological effects were noted for myoclonic flexion, extension, clonus, stupor and recovery/ mortality. Similarly for the standard drug, values were noted. The results are given in table (2)

Anti microbial activity

All the compound (3a-3d) was screened (doses 25, 50, 100 µg/ml for their antimicrobial activities against the gram –ve bacteria Escherichia coil & Salmonella typhi and gram +ve bacteria Bacillus Subtillis &

Staphylococcus Aureus using standard antibiotic drug as a control. The biological activities of these compounds have been evaluated by using disc diffusion method. Dimethyl formamide was used as a solvent. Activities were determined by using the cultivated Disc and the inhibition zones were measured in mm and results are shown in table (3).



Scheme-1

RESULTS AND DISCUSSION

Anticonvulsant activity

Synthesized compounds were evaluated for their anticonvulsant activity by Maximal Electroshock Seizure method. Phenytoin was used as standard. Among the compound 3b & 3d displayed significant anticonvulsant activity.

Anti microbial activity

The compound 3a & 3c in the concentration of 100µg/ml was found to posses good antibacterial activity against Escherichia coil & Salmonella typhi respectively. The compound 3c & 3a in the concentration of 100µg/ml was found to posses good antibacterial activity against Bacillus Subtillis & Staphylococcus Aureus respectively.

Table -1: Characterization data for compounds 3a – 3d

Compound	R	Mol. formula	Mol. wt	M.P(ºC)	R.F value	Yield (%)
3a	O C_6H_5	$C_{16}H_{16}N_2O$	252	208	0.74	73.45

3b	NH C_6H_5	$C_{16}H_{17}N_3$	251	237	0.49	68.72
3c	O C_6H_5	$C_{16}H_{16}N_2O$	252	204	0.64	64.48
3d	NH C_6H_{5Cl}	$C_{16}H_{17}N_3Cl$	285	179	0.45	69.24

Table 2: Anticonvulsant activity of the compounds 3a- 3d

Group	Compounds	Dose (mg/kg)	Flexion in sec	Extension in sec	Clonus in sec	Stupor in sec	Moratality
I	Control	2% CMC	4.1 ± 0.36	11.7 ± 0.55	2.9 ± 0.51	120.0 ± 0.95	0
II	Phenytoin	25	1.9 ± 0.31 $a^{@}$	7.0 ± 0.31 $a^{@}$	1.4 ± 0.22 $a^{@}$	90.0 ± 0.92 $a^{@}$	0
III	3a	100	2.1 ± 0.31 a^{*}	7.9 ± 0.28 $a^{\#}$	2.3 ± 0.20 $a^{\#}$	95.0 ± 0.62 $a^{\#}$	0
IV	3b	100	1.7 ± 0.25 $a^{\#}$	7.7 ± 0.30 $a^{*}b^{*}$	1.8 ± 0.22 b^{*}	89.0 ± 0.57 $a^{@}$	0
V	3c	100	2.0 ± 0.27 $a^{@}$	8.9 ± 0.31 $a^{*}b^{*}$	2.1 ± 0.22 $a^{*}b^{*}$	101.0 ± 0.59 $a^{\#}b^{*}$	0
VI	3d	100	1.8 ± 0.33 a^{*}	7.4 ± 0.31 $a^{@}b^{*}$	1.5 ± 0.21 b^{*}	92.0 ± 0.54 $a^{*}b^{\#}$	0

One way ANOVA followed by Dun nest's 'T' test (Multiple comparison test)
Values are expressed in mean ±SEM (n=4)

a. Group I Vs group II, III, IV, V and VI
b. Group II Vs group III, IV, V and VI

@ = P<0.001, # = P<0.01,* = P<0.05.

Table – 3: Antimicrobial activity of the compounds 3a – 3d

Organism	Conc. of compounds µg/ml	Antimicrobial activity (Zone of inhibition in mm)			
		Compd 3a	Compd 3b	Compd 3c	Compd 3d
E.coli	25	13	9	13	11
	50	16	11	15	15
	100	19	18	17	19
	Standard	25	24	25	25
Salmonella typhi	25	15	11	17	15
	50	19	11	19	18
	100	22	15	22	20
	Standard	24	24	26	25
Bacillus Subtillis	25	16	13	16	14
	50	18	16	17	18
	100	21	19	23	21
	Standard	25	24	25	24
Staphylococcus Aureus	25	16	14	12	13
	50	18	15	15	18
	100	23	18	22	22
	Standard	25	24	25	25

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