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Synthesis and biological evaluation of imidazoline derivatives as potential CNS and CVS agents

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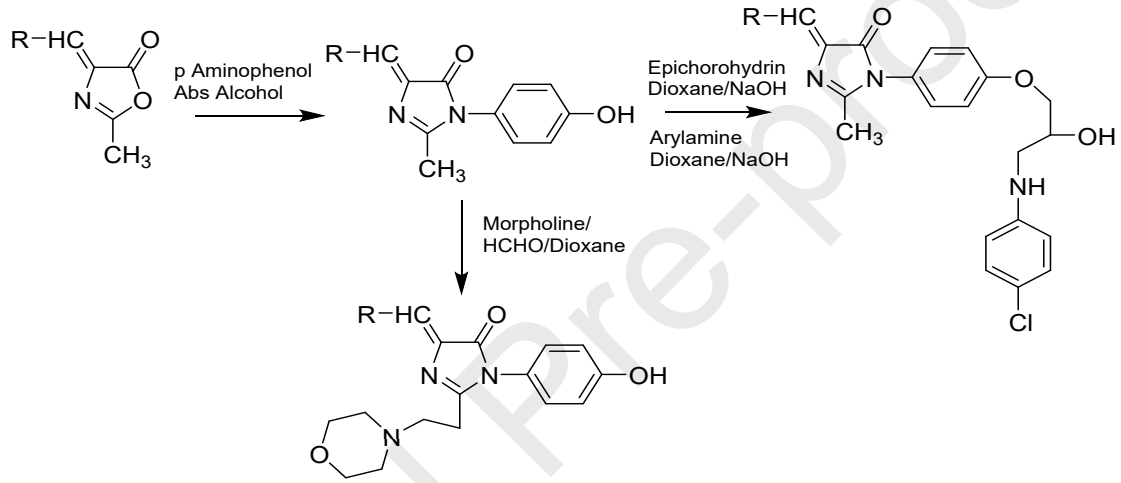

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ABSTRACT

A series of substituted imidazoline derivatives were synthesized and characterized. Compounds were tested in-vivo for their antihypertensive, analgesic, antiaggressive, depressant, antidepressant, and ALD_{50} activities. The compounds **3a**, **3c**, **4c**, **5a**, and **6c** showed cardiovascular as well as central nervous system activities and are potential candidate as drug among all fifteen compounds tested. All these compounds have shown better activity for antihypertensive, analgesic, antiaggressive, and depressant-antidepressant, properties than reference compounds clonidine, morphine, diazepam, and imipramine respectively. Most of the compounds have shown ALD_{50} > 500 mg/kg with maximum in **4a** and **5a** (>1000 mg/kg).

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Imi[illegible]edly medicinally privileged scaffolds.[1,2] 2-Imidazolines are widely recognized as pharmacophores having an affinity for a class of biological targets.[3] Derivatives of imidazoline have been recognized as an important class of drug which mediates their action by interacting with α 2–adrenoceptors and have shown a variety of physiological functions.[4,5] Additionally, imidazolines nucleus modulates adrenergic (a) receptors[6], and binds to them.[7-12] The toxicological effects of imidazoline receptor binding[13] along with a/I receptors are also reported.[14]

Imidazoline nucleus is constituent of a chemically useful antihypertensive agent, [2-(2, 6-dichlorophenylamine)]-imidazoline named as Clonidine **I** (Figure 1). Clonidine is an alpha-2 adrenergic agonist and is used for centrally acting hypotensive agent and have central nervous system activities,[15-17] viz. psychiatric disorders,[18] obsessive-compulsive disorders, schizophrenia, and panic states.[19-26] In addition, there are large number of compounds having an imidazoline nucleus possessing antidepressant activities.[27,28] The derivatives of imidazole (BFI **II**, BU224 **III**, TRIM **IV** (4-(2-ethylamino)-1H-imidazole) **V**, Figure 1) exhibit *in vivo* neuronal nitric-oxide synthase (NOS) inhibition activity and prevent glufosinate induced convulsions[29,30], leading to antiaggresive, and analgesic properties[30,31].

Earlier reports from our lab have elucidated that incorporation of various pharmacophores like morpholine, [32] substituted aryl group,[33] and arylamine [34] at different positions of heterocyclic nucleus viz. modulate antihypertensive activity and toxicity profiles. These reports gave us an impetus to design and synthesize some novel substituted imidazoline derivatives having different pharmacophoric moieties at 1, 3, and 5 positions, and evaluate them for their CVS, CNS and ALD_{50} activities.

In the present study, we have incorporated bulky pharmacophoric groups at position-1 of imidazoline nucleus with a view to studying the effect of these substitutions on CVS, CNS, and ALD_{50} activities.

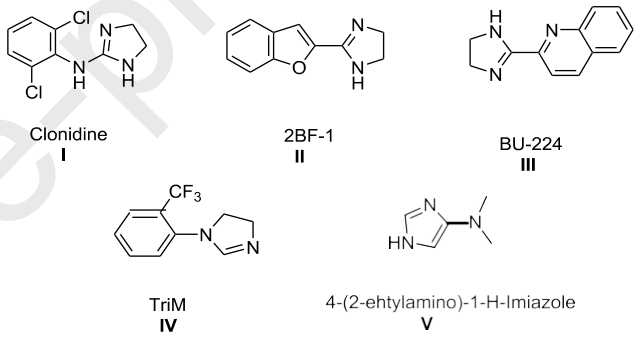
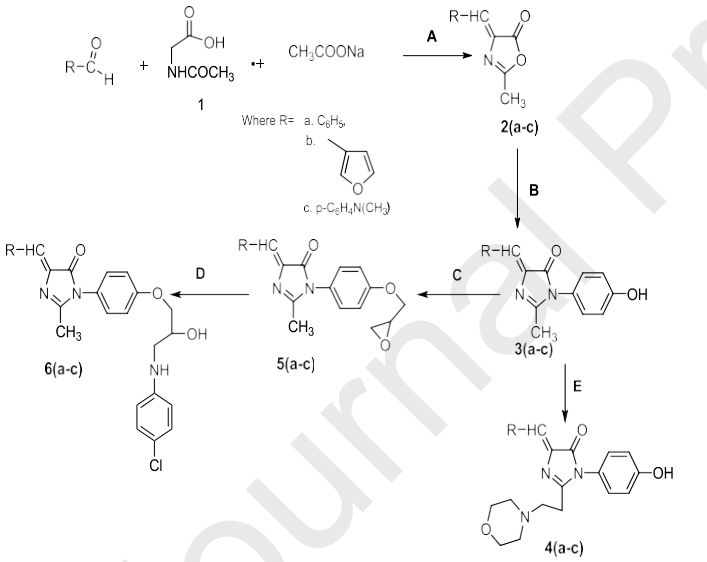


Figure 1

The synthetic procedure to obtain the final compounds is depicted in **Scheme 1**. Substitutions were made at 4 position of oxazolone nucleus by treating acetyl glycine with substituted aldehyde[35] and acetic anhydride leading to 4-arylidene-2-methyl-5-(4H) oxazoline-5-one **2(a-c)**. The compounds **2(a-c),** on refluxing with para aminophenol in ethanol resulted in 4-arylidene-1-(p-hydroxy-phenyl)-2-methylimidazoline-5-ones **3(a-c).** Compounds **3(a-c)** were undergone Manich reaction with secondary amines and formaldehyde in the presence of DMSO afforded 4-arylidene-1-(p–hydroxy-phenyl)-2-[2-morpholino ethyl]-3-imidazoline-5-one

with epichlorohydrine in presence of dioxane/NaOH resulted with 4-arylidene-1-[p-(epoxy propoxy) phenyl]-2-methyl-3-imidazoline-5-ones to yield **5(a-c).** Compounds **5(a-c)** were again condensed with aryl amines in basic condition in presence of DMF yielded 4-arylidene-1-[p-(2"-hydroxy-3'-arylamino propoxy) phenyl]-2-methyl-3-imidazoline-5-ones **6(a-c).** All the synthesized compounds were well characterized by several spectroscopic methods such as mass, ^{1}H NMR, ^{13}C NMR and elemental analysis (SI). These compounds were tested for their hypotensive, analgesic, antiaggressive, antidepressant and ALD_{50} activities as shown in **Table-1, 2, 3, 4, Graph 1, 2, 3**(SI).



Scheme-1 Reagents and Conditions: A. Acetic anhydride, reflux,10 hr. **B.** p-amino phenol, abs.alcohol, reflux,10-12 hr. **C.** Epichlorohydrin, dioxane, NaOH, reflux, 6-8 hr. **D.** Aryl amine(equimolar), NaOH(equimolar), dioxane, reflux, 8-10 hr. **E.** Morpholine, HCHO, dioxane, reflux,10 hr.

Screening of all fifteen compounds for hypotensive activity in a dose of 2.5 mg/kg & reference drug clonidine in a dose of 10 mg/kg was performed. Morphine in a dose of 5 mg/kg, Diazepam in a dose of mg/kg & Imipramine in a dose of 15 mg/kg wereused as reference drugs for activities respectively.

Substitutions were made at position 4 of the oxazolone nucleus with different aryl groups resulting in compound **2(a-c).** Compound **2a** produced moderated hypotension of a long duration. Compound **2c** has shown only delayed fall. Compound **2a** and **2c** also inhibited carotid occlusion (CO) and potentiated norepinephrine (NE) induced pressor response. In general, the oxazolone moiety having no substitution in the phenyl ring of the arylidene group exhibited an increase in hypotensive activity. Compound **2b** could not produce any change in mean arterial pressure (MAP). Furthermore, **2b** exhibited significant analgesic activity whereas the other two compounds in this series did not show any Central Nervous System (CNS) activity.

Substitution of oxygen of the oxazolone nucleus with para aminophenol resulted in compounds **3(a-c)**. Compound **3a** & **3c** exhibited moderate hypotension and **3a** inhibited both CO & NE pressor response. While **3c** inhibited CO response and potentiated NE pressor response. Compound **3b** exhibited only mild hypotensive activity. It can be concluded that after inserting the para aminophenol group at oxazolone nucleus the extent and duration of hypotension become more apparent for CVS activity. The compound **3a** exhibited mild analgesic as well as depressant activity and **3c** produced significant antiaggressive and antidepressant activity while **3b** only produced antiaggressive activity.

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N-morpholine group resulted in compounds **4(a-c)**. All the compounds **4(a-c)** of this series exhibited moderate hypotension and inhibited CO induced pressor response. It was observed that when H of the CH_3 group was replaced by CH_2-N-morpholine, the compounds **4(a-c)** lost their CVS activity. In addition, **4a** have shown mild analgesic and antidepressant activity while **4c** exhibited antiaggressive and antidepressant activity. However compound **4b** did not show any significant CNS activity.

Replacement of phenolic hydrogen of **4(a-c)** compounds by epichlorohydrin moiety resulted in compounds **5(a-c)**. Compounds **5a** exhibited moderate hypotension of longer duration, potentiated NE induced pressor response, and inhibited CO induced pressor response. Compound **5b** and **5c** produced mild hypotension of short duration. However, compound **5b** potentiated NE induced pressor response. In addition, compounds **5a** and **5b** exhibited significant analgesic as well as antiaggressive activity while **5c** did not possess any CNS activity.

In the last series, epoxy ring was opened and further substituted by the arylamino group resulting in compounds **6 (a-c)**. All the compounds of this series **6a**, **6b**, and **6c** induced severe initial fall in blood pressure. The compound **6a** also exhibited prolonged fall in BP. Compounds **6a** and **6c** potentiated NE induced pressor response, whereas compound **6b** did not modify CO and NE responses. In addition, **6c** has shown significant antiaggressive and antidepressant activity. Compound not shown any CNS activity.

The results suggest that compounds **2a** and **2c** showed better hypotension, CO inhibition, NE pressor response than **2b**. Compound **3a** showed NE inhibition while **3c** potentiated it. Compounds **4(a-c)** showed moderate hypotension and inhibited CO response. Compound **4c** also exhibited mild antiaggressive and antidepressant activity. Compound **5a** exhibited moderate hypotension of longer duration, potentiated NE induced pressor response, and inhibited CO induced pressor response. Compounds **5b** and **5c** produced mild hypotension of short duration. Compound **5b** potentiated NE induced pressor response. In addition, compound **5a** and **5b** exhibited significant analgesic as well as antigressive activity while **5c** did not possess any CNS activity. The compounds **6b** and **6c** induced severe initial fall in blood pressure while **6a** exhibited a prolonged fall as well. Compounds **6a** and **6c** potentiated NE induced pressor response, whereas, compound **6b** was not able to modify CO and NE response. In addition, **6c** have shown significant antiaggresive and antidepressant activity. Compound **6b** exhibited significant analgesic activity while **6a** has not shown any CNS activity. Form the above observation it is clear that substituting 1-position of oxazolone ring with para aminophenyl group increases cardiovascular and central nervous system activities of the compounds. Further substitution in the imidazoline ring has shown variable grades of hypotensive and CNS activity. All the compounds which displayed significant hypotensive activity (25-50 mm Hg) also showed bradycardia of varying grade (-6

to compounds having cardiovascular as well as central nervous system activities are **3a**, **3c**, **4c**, **5a**, and **6c**. The present study suggested that the newly synthesized imidazoline derivatives are good candidates for blood pressure-lowering along with analgesic, antiaggressive, depressant, antiantidepressant activities. These molecules can be very useful for further optimization work in antihypertensive and CNS activities. ALD_{50} values are much higher for most of the compounds which indicate that they are safe to be used as a drug.

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Table 1. Cardiovascular effects and ALD_{50} activities of compounds 2(a-c) to 6(a-c) (Dose-2.5 mg/kg)

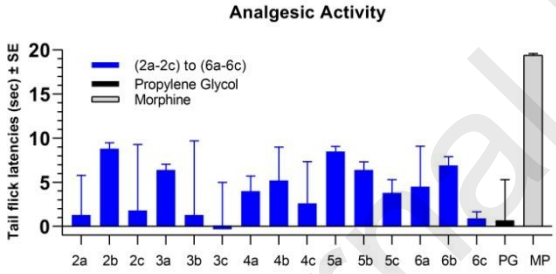
Compd	Effect on B.P (mmHg)		Effect on HR, Beats /min.	NE Response	CO Response	ALD_{50} mg/kg
	Immediate	Delayed				
2a	-25	-40	-36	↑	↓	>500
2b	--	--	--	--	--	>500
2c	--	-15	--	↑	↓	>500
3a	-15	-70	-12	↓	↓	>200
3b	-20	-20	-18	--	--	>500
3c	-25	-50	-27	↑	↓	>500
4a	-35	-15	-15	--	↓	>500
4b	-35	-20	-18	↑	↓	>1000
4c	-15	-37	-30	↑	↓	>500
5a	-25	-45	-21	↑	↓	>500
5b	-30	-20	-6	↑↑	↓	>1000
5c	-60	-28 to -35	-24	↓	↓	>500
6a	-50	-17	-6	↑↑	↓	>200
6b	-25	-20	-27	--	--	>500
6c	-15	-30	-21	↑↑	↓	>500
CL	-18	-28	-18	↓	↓	

Note: Compd: Compound numbers, CL: Clonidine (10 mg /kg);
+ indicates rise & - indicates fall in blood pressure and heart rate, respectively; ↑ indicates potentiation and ↓ indicates Inhibition of pressor response, - indicates no effect on CO & NE response; more than 20-25 mm Hg of decrease or 10 mm Hg increase as decrease or increase in B. P. and 6-12 beats per minute of decrease or increase was taken as decrease/increase in heart rate (HR);

Tab **a-c) maximum change in Tail flick latencies for analgesic activity of compounds 2(a-c) to 6(a-c) (Dose-10 mg/kg)**

Compd	Mean Maximum Change in Tail Flick Latency (in second)	Specific Time (Duration) of max change in latencies (in minutes)
2a	+1.3 ± 4.5	At 60’
2b	+8.8 ± 0.68**	At 15’
2c	+1.8 ± 7.5	At 60’
3a	+6.4 ± 0.65*	At 60’
3b	+1.3 ± 8.4	At 60’
3c	+0.1 ± 4.9	At 30’
4a	+4 ± 1.73	At 60’
4b	+5.2 ± 3.8	At 30’
4c	+2.6 ± 4.75	At 60’
5a	+8.5 ± 0.57**	At 60’
5b	+6.4 ± 0.92*	At 60’
5c	+3.8 ± 1.5	At 30’
6a	+4.5 ±.4.6	At 60’
6b	+6.9 ± 1.02*	At 30’
6c	+0.9 ± 0.75	At 30’
PG (0.1 ml / rat)	+0.7 ± 4.6	At 60’
Morphine (5 mg/kg)	+19.4± 0.2**	At 60’

[b]***P*< 0.05, ** **P**< 0.01 using Chi square test

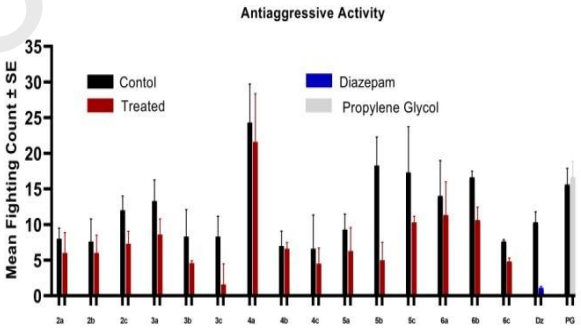


Graph 1. The analgesic activity of compounds 2(a-c) to 6(a-c) (10 mg/kg) along with control data of propylene glycol (PG) and standard drug Morphine (5 mg/kg) measured as tail flick latency time (in seconds).

to 6(a-c) (Dose-10 mg/kg, I.P.) on foot shock induced fighting behavior showing antiaggressive activity

Compd	Mean Fighting Count ± SE	
(Control)	(Treated)	
2a	8.0 ± 1.52	6.0 ± 2.88
	7.6 ± 3.18	6.0 ± 2.51
2c	12.0 ± 2.00	7.3 ± 1.76
3a	13.3 ± 2.96	8.6 ± 2.20
3b	8.3 ± 3.80	4.6 ± 0.33
3c	8.3 ± 2.88	1.6 ± 2.88**
4a	24.3 ± 5.45	21.6 ± 6.76
4b	7.0 ± 2.08	6.6 ± 0.88
4c	6.6 ± 4.75	4.5 ± 2.2
5a	9.3 ± 2.18	6.3 ± 3.28
5b	18.3 ± 3.99	5.0 ± 2.5**
5c	17.3 ± 6.43	10.3 ± 0.88*
6a	14.0 ± 4.98	11.3 ± 4.7
6b	16.6 ± 0.88	10.6 ± 1.85
6c	7.6 ± 0.3	4.8 ± 0.5
Diazepam (2.5 mg/kg, IP)	10.3 ± 1.5	1.1 ± 0.22**
PG (0.1 ml/rat, IP)	15.6 ± 2.3	16.6 ± 2.3

***P*< 0.05, ** **P**< 0.01 using Chi square test

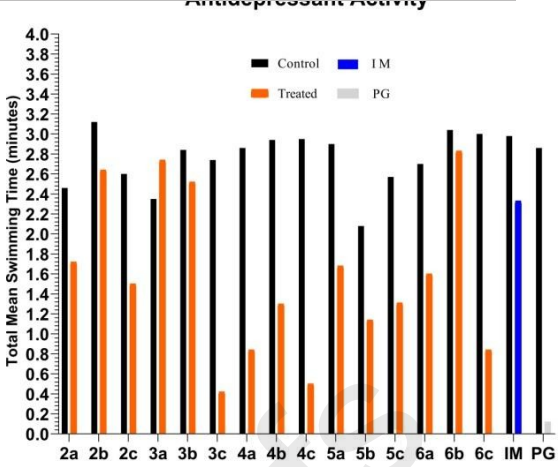


Graph 2. Antiaggresive effect of compounds 2(a-c) to 6(a-c) (10 mg/kg, I.P.) with control data of propylene glycol (PG) and standard drug Diazepam (2.5 mg/kg) on foot shock induced fighting behaviour

time (in min) of control and treated groups for antidepressant effect of compounds 2(a-c) to 6(a-c) (Dose- 5 mg/kg):

Compd	Dose	Total swimming time in minutes	mean
		Control	Treated
2a	5 mg/kg	2.46	1.72
2b	5 mg/kg	3.12	2.64
2c	5 mg/kg	2.60	1.50
3a	5 mg/kg	2.35	2.74*
3b	5 mg/kg	2.84	2.52
3c	5 mg/kg	2.74	0.42**
4a	5 mg/kg	2.86	0.84*
4b	5 mg/kg	2.94	1.30
4c	5 mg/kg	2.95	0.50**
5a	5 mg/kg	2.90	1.68
5b	5 mg/kg	2.08	1.14
5c	5 mg/kg	2.57	1.31
6a	5 mg/kg	2.70	1.60
6b	5 mg/kg	3.04	2.83
6c	5 mg/kg	3.00	0.84**
Imipramine	15 mg/kg	2.98	2.33
PG	0.1 ml/mice	2.86	0.12**

***P**< 0.05, ** **P**< 0.01 using Chi square test; compound **3a** showing increase in mean swimming time



Graph 3. Antidepressant effect of compounds 2(a-c) to 6(a-c) (5 mg/kg, I.P.) with control data of propylene glycol (PG) and standard drug imipramine(15mg/kg), *total mean immobility time (in minutes) of control and treated group*

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Supporting Information

1. Experimental

1.1. General Chemistry

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Synthesis and biological evaluation of imidazoline derivatives as potential CNS and CVS agents

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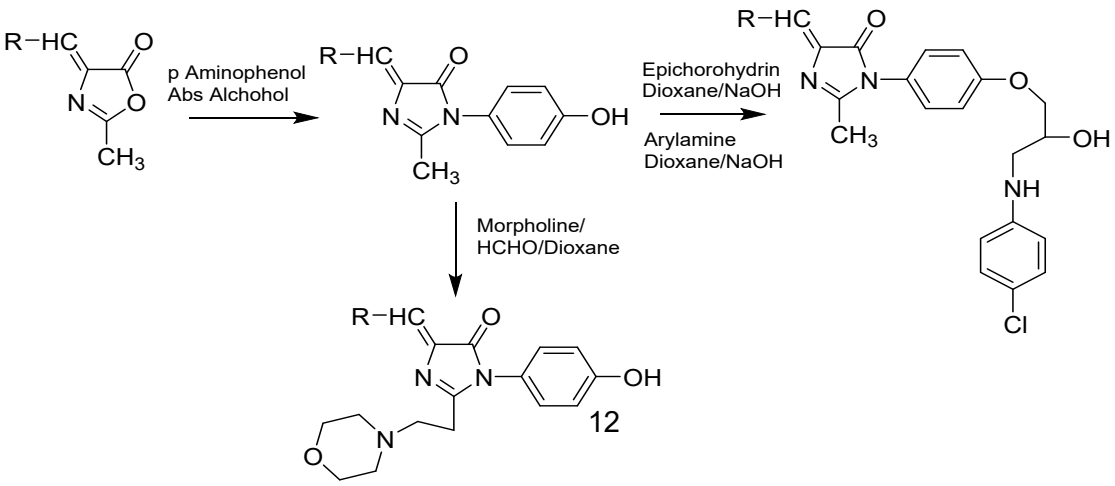


conditions as under at ambient temperature, and reagents were used without further purification.Melting points were taken in open capillary tubes and are uncorrected. Thin layer chromatography (TLC) was performed on silica gel G plates, Proton magnetic resonance (PMR) spectra in $CDCl_3$ were recorded on an JEOL AL 300 and AL500 FT-NMR spectrometer (300 and 500 MHz), using trimethylsilane (TMS) as internal standard (Chemical Shift in δ ppm) and mass spectra on a JMSD 300 instrument fitted with JMS 2000 data system 70 ev.

1.2. General Procedure for Preparation of Compounds

Acetyl Glycine (1)

Acetyl glycine was prepared by method of Vogel et al [34], M.P. 208^0C, yield 85%.

4-Arylidine -2-Methyl-5(4H)-Oxazoline-5- ones , 2 (a-c)

Actyl glycine **(1)** (0.1 mol) and aryl aldehyde (0.1 mol) were dissolved in acetic anhydride (100 ml), sodium acetate (anhydrous) was added to the reaction mixture. It was refluxed for 10 hrs. The excess of solvent was distilled off. The solid mass obtained on cooling was stirred with little methanol and poured over ice cold water. The compounds dried.

4- Arylidine -1-(4-hydroxyphenyl)-2-methyl-1H-imidazol-5(4H)-one, 3 (a-c)

A mixture of 4-arylidine-2-methyl-5(4H) oxazoline-5-one **2(a-c)** (0.1 mol) and paraminophenol (0.1 mol) was refluxed in absolute alcohol (100 ml) for 12 hrs. The excess of solvent was distilled off. The resulting solution was cooled and poured over crushed ice. The solid thus obtained was recrystallized from alcohol/water to give title compounds.

4-Arylidene-1(p–hydroxyl-phenyl)-2-[2-morpholino-ethyl]-3-imidazolines-5-ones, 4(a-c)

4-Arylidine-1-(p-hydroxy phenyl)-2-methyl imidazoline-5-ones **3(a-c)** (0.1 mol) and morpholine (a secondary amine) (0.1 mol) was refluxed in dioxane (50 ml) in the presence of formaldehyde (0.05 mol) for 10 hrs. The excess of solvent was distilled off. The residue was cooled and poured into ice cold water. The solid separated out, was filtered off and recrystallized from dioxane/water.

4-Arylidine -1-[p-(epoxy-propoxy)-phenyl]-2-methyl-3-imidazoline-5-ones, 5(a-c)

4-Arylidine-1-(p-hydroxy-phenyl)-2methyl-imidazoline-5-ones **3(a-c)** (0.1 mol) was dissolved

epichlorohydrine (0.01 mol) in dioxane was added drop wise. Simultaneously sodium hydroxide (0.1mol) was also added to this solution. The reaction mixture was refluxed for 6-8 hrs. The excess of solvent was distilled off. The residue was cooled and poured into ice cold water. The solid separated out was filtered and crystallized from dioxane/water to give desired compounds.

4-Arylidines-1-[p-(2"-hydroxy-3'-aryl-amino-propoxy)-phenyl]-2-methyl-3-imidazoline-5-ones, 6(a-c)

A mixture of 4-arylidine-1-[p-(epoxy-propoxy)-phenyl]-2-methyl-3-imidazoline-5-ones **5(a-c)** (0.1 mol), aryl amine (0.1 mol) and sodium hydroxide (0.1 mol) was refluxed in dioxane for 8-10 hrs. The solvent was distilled off and the residue was poured into ice cold water. The solid separated out was neutralized with dil HCl and was recrystallized from dioxane/water to give title compounds.

The characterization data of the synthesized compounds are given below.

3a: 5-Benzylidene-3-(4-hydroxy-phenyl)-2-methyl-3,5-dihydroimidazole-4-one, Yield: 70%; mp: 112; MS: MS: expected 277.0, obtained 278.0 (M+1); ^{1}H NMR ($CDCl_3$) δ: 7.1-7.5 (m,5H,Ar-H), 6.71 (d,2H,ArH), 7.47 (d,2H,ArH), 6.5 (s,1H,=CH), ($CDCl_3$) δ: 16.9, 160, 162, 137.6, 134.3, 131.9, 126.2, 128.4, 127.7, 150.9, 114.9, 121.5, 132, Anal for $C_{17}H_{13}N_2O_2$, calcd C: 73.64, H: 4.69, N: 10.10; found C: 73.23, H: 4.32, N: 10.42.

3b: 5-Furan-2-yl-methylene-3-(4-hydroxy-phenyl)-methyl-3,5-dihydroimidazole-4-one, Yield: 58%; mp: 122, MS: expected 268.0, obtained 269.0 (M+1); ^{1}HNMR ($CDCl_3$) δ: 6.65-7.8 (m,3H,oxazole),H), 6.71 (d,2H,ArH), 7.47 (d,2H,ArH), 6.5 (s,1H,=CH), 1.6 (s,3H,CCH_3), 5.0 (s,1H,OH); ^{13}C NMR ($CDCl_3$) δ: 16.9, 160, 162, 141.5, 133.3, 112.7, 111.8, 143.0, 155.3, 150.9, 114.9, 121.8, 130.6; Anal for $C_{15}H_{12}N_2O_3$; calcd: C: 67.16, H: 4.47, N, 10.4; found C: 67.23, H: 4.32, N: 10.32.

3c: 5-(4-Dimethylamino-benzylidene)-3-(4-hydroxy- phenyl)-2-methyl-3,5-dihydro-imidazol-4-one, Yield: 69%; mp: 158; MS: expected 321.0, obtained 322.0 (M+1); ^{1}H NMR ($CDCl_3$) 6.54 (d,2H,ArH), 7.12 (d,2H,ArH), 6.71 (d,2H,ArH), 7.47 (d,2H,ArH), 6.5 (s,1H,=CH), 1.6 (s,3H,C-CH_3), 2.85 (s,6H,N-CH_3) 5.0 (s,1H,-OH); ^{13}C NMR ($CDCl_3$) δ: 16.9, 160, 162, 137.6, 134.3, 125.5, 127, 115, 140.5, 130, 121.2, 115.5, 150.9, 42.6; Anal for $C_{19}H_{19}N_3O_2$; calcd C: 71.02, H: 5.91, N: 13.08; found C: 71.23, H: 5.32, N: 13.42.

4a: (4-morpholine-4-yl-ethyl)-3,5-dihydro-imidazole-4-one), Yield: 72%; mp: 180; MS: expected 377.0, obtained 378.0 (M+1); ^{1}H NMR ($CDCl_3$) δ: 7.1-7.5 (m,5H,ArH), 6.71(d,2H,ArH), 7.47 (d,2H,ArH), 6.5 (s,1H,=CH), 5.0 (s,1H,-OH), 2.9 (t,2H,CH-N of morpholine), 2.5 (t,2H,CH_2 attached to imidazoline nucleus), 2.37-3.67 (m,4xCH_2 ,8H); ^{13}C NMR ($CDCl_3$) δ: 160, 162, 137.6, 134.3, 131.9, 126.2, 128.4, 127.7, 150.9, 114.9, 121.5, 132, 32.0, 44.5, 56.2, 70.9; Anal for: $C_{22}H_{23}N_3O_3$; calcd C: 70.02, H: 6.10, N: 11.14; found C: 70.23, H: 6.32, N: 11.42.

4b: 5-Furan-2-yl-methylene-3-(4-hydroxy-phenyl)-2-(2-morpholin-4-yl-ethyl)-3,5-dihydro-imidazole-4-one, Yield: 60%; mp: 164; MS: expected 367.0, obtained 368.0 (M+1); ^{1}H NMR ($CDCl_3$) δ: 6.65-7.8 (m,3H,oxazole), 6.71 (d,2H,ArH), 7.47 (d,2H,ArH), 6.5 (s,1H,=CH), 5.0 (s,1H,-OH), 2.9 (t,2H,N-CH attached morpholine), 2.5 (t,2H,CH_2 attached to imidazoline nucleous), 2.37-3.67 (m,4xCH_2,8H) ,^{13}C NMR ($CDCl_3$) δ: 160, 162, 141.5, 133.3, 112.7, 111.8, 143.0, 155.3, 150.9, 114.9, 121.8,130, 32.0, 44.5, 56.2, 70.9; Anal for: $C_{20}H_{21}N_3O_4$; calcd C: 65.39, H: 5.72, N: 11.44; found C: 65.23, H, 5.32, N: 11.40.

4-hydroxy-phenyl)-2-(2-morpholin-4-yl-ethyl)-3,5-dihydro-imida-zol-4-one, Yield: 62%; mp: 192; MS: expected 417.0, obtained 416 (M+1) ; ^{1}H NMR ($CDCl_3$) δ: 6.54 (d,2H,ArH), 7.12 (d,2H,ArH), 6.71 (d,2H,ArH), 7.47 (d,2H,ArH), 6.5 (s,1H,=CH), 2.85 (s,6H,N-CH_3) 2.9 (t,2H,CH-N of morpholine), 2.5 (t,2H,CH_2 attached to imidazoline nucleus), 2.37-3.67 (m,4xCH_2,8H), 5.0 (s,1H,-OH); ^{13}C NMR ($CDCl_3$) δ: 160, 162, 137.6, 134.3, 125.5, 127.7, 115, 140.5, 42.6, 130, 121.2, 115, 150.9, 32.0, 44.5, 56.2, 70.9; Anal for: $C_{24}H_{28}N_4O_3$; calcd C: 69.39, H: 6.74, N:13.49: found C:69.23, H: 6.32, N:13.42.

5a:5-Benzylidene-2-methyl-3-(4-oxiranyl-methoxy-phenyl)-3,5-dihydro-imidazol-4-one, Yield: 68%; mp: 102; MS: expected 334.0, obtained 330.0 (M+1); ^{1}H NMR ($CDCl_3$) δ: 7.0-7.5 (m,5H,Ar-H), 6.71 (d,2H,ArH), 7.47 (d,2H,ArH), 6.5 (s,1H,=CH), 1.6 (s,3H,C-CH_3), 4.04 (d,2H,-CH_2), 3.04 (m,1H,CH), 2.5 (d,2H,-CH_2, cyclic); ^{13}C NMR ($CDCl_3$) δ: 16.5, 160, 162, 136.6, 134.3, 131.9, 126.2, 128.4, 127.7, 150.9, 114.9, 121.5, 132, 75.5, 50.5, 43.2; Anal for: $C_{20}H_{18}N_2O_3$; calcd: C: 72.94, H: 5.47, N: 8.51; found C: 72.23, H: 5.32, N: 8.42.

5b: %;

oxiranyl-methoxy-phenyl)-3,5-dihydro-imidazol-4-one, Yield: 54%; mp: 126; MS: expected 324.0, obtained 325.0 (M+1); ^{1}H NMR ($CDCl_3$) δ: 6.65-7.8 (m,3H,oxazole), 6.71 (d,2H,ArH), 7.47 (d,2H,ArH), 6.5 (s,1H,=CH), 1.6 (s,3H,C-CH_3), 4.04 (d,2H,-CH_2), 3.04 (m,1H,CH), 2.5 (d,2H,-CH_2, cyclic), ^{13}C NMR ($CDCl_3$) δ: 16.5, 160, 162, 141.5, 133.3, 112.7, 111.8, 143.0, 155.3, 150.9, 114.9, 121.8, 130, 75.5, 50.5, 43.2; Anal for: $C_{18}H_{16}N_2O_4$; calcd C: 66.66, H: 4.93, N: 8.64; found C: 66.23, H: 4.32, N: 8.42.

5c: 5-(4-Dimethylamino-benzylidene)-2-methyl-3-(4-oxiranyl-methoxy-phenyl)-3,5-dihydro imidazol-4-one, Yield: 59%; mp: 164; MS: expected 378.0, obtained 378.0 (M+1); ^{1}H NMR ($CDCl_3$) δ: 6.54 (d,2H,ArH), 7.12 (d,2H,ArH), 6.71 (d,2H,ArH), 7.47 (d,2H,ArH), 6.5 (s,1H,=CH), 2.85 (s,6H,N-CH_3), 5.0 (s,1H,-OH), 1.6 (s,3H,C-CH_3), 4.04 (d,2H,-CH_2), 3.04 (m,1H,CH), 2.5 (d,2H,-CH_2, cyclic), ^{13}C NMR ($CDCl_3$) δ: 6.5, 160, 162, 137.6, 134.3, 125.5, 127.7, 115, 140.5, 42.6, 130, 121.2, 115.5, 150.9, 75.5, 50.5, 43.2; Anal for: $C_{22}H_{23}N_3O_3$; calcd C: 70.02, H: 6.10, N: 11.14; found C: 70.23, H: 6.32, N: 11.42.

6a: 5-Benzylidene-3-{4-[3-(4-chloro-phenylamino)-3-hydroxy-propoxy]-phenyl}-2- mp: 238; expected 461.5, obtained 462.0 (M+1; ^{1}H NMR ($CDCl_3$) δ: 7.1-7.5 (m,5H,ArH), 6.71 (d,2H,ArH), 7.53 (d,2H,ArH), 7.05 (d,2H,ArH), 6.37 (d,2H,ArH), 6.5 (s,1H,=CH), 1.6 (s,3H,CCH_3), 3.94 (d,2H,OCH_2), 3.09 (m,2H,CCH_2), 4.35 (t,1H,CH-OH), 4.8 (brs,1H,C-NH), 5.1(s,1H,-OH); ^{13}C NMR ($CDCl_3$) δ: 16.5, 160, 162, 137.6, 134.3, 131.9, 126.2, 128.4, 127.7, 150.9, 114.9, 121.5, 132, 63.5, 39.7, 79.5, 113.7, 129.7, 122.2; Anal for: $C_{26}H_{24}N_3O_3Cl$; calcd C: 67.60; H: 5.20; N: 9.10; found C: 67.23, H: 5.32, N: 9.22.

6b: 3-{4-[3-(4-Chloro-phenylamino)-3-hydroxy-propoxyl]-phenyl}-5-furan-2-yl-methylene-2-methyl-3,5-dihydro-imidazol-4-one, Yield: 56%; mp: 180; expected 451.5, obtained 452.0 (M+1); ^{1}H NMR ($CDCl_3$) δ: 6.65-7.8 (m,3H,oxazole), 6.71 (d,2H,ArH), 7.47 (d,2H,ArH), 6.5 (s,1H,=CH), 1.6 (s,3H,C-CH_3), 7.05 (d,2H,Ar-H), 6.37 (d,2H,ArH), 3.94 (d,2H,OCH_2), 3.09 (m,2H,CCH_2), 4.35 (t,1H,CH-OH) 4.8 (brs,1H,C-NH) 5.1 (s,1H,-OH), ^{13}C NMR ($CDCl_3$) δ: 16.5 160, 162, 141.5, 133.3, 112.7, 111.8, 143.0, 155.3, 150.9, 114.9, 121.8, 130, 141.6, 113.7, 129.7, 122.2, Anal for: $C_{24}H_{22}N_3O_4Cl$, calcd C: 63.78, H: 4.87, N: 9.30; found C: 63.23, H: 4.32, N:9.42.

propoxyl]-phenyl}-5-(dimethylamino-benzylidene)-2-methyl-3,5-dihydro-imidazol-4-one, Yield: 62%; mp: 205; MS: expected 504.5, obtained 505.0 (M+1); ^{1}H NMR ($CDCl_3$) δ: 6.54 (d,2H,ArH), 7.12 (d,2H,ArH), 6.71 (d,2H,ArH), 7.47 (d,2H,ArH), 6.5 (s,1H,=CH), 2.85 (s,6H,N-CH_3), 1.6 (s,3H,C-CH_3), 7.05 (d,2H,Ar-H), 6.37 (d,2H,ArH), 3.94 (d,2H,OCH_2), 3.09 (m,2H,CCH_2), 4.35 (t,1H,CH-OH), 4.8 (brs,1H,C-NH), 5.1(s,1H,-OH); ^{13}CNMR ($CDCl_3$) δ: 16.5, 160,162, 137.6, 134.3, 125.5,127.7, 115, 140, 150.9, 114.9, 121.8, 130, 63.5, 39.6, 79.5, 141.6, 113.7, 129.7, 122.2; Anal for: $C_{28}H_{29}N_4O_3Cl$; calcd C: 66.60, H: 5.74, N: 11.10; found C: 66.23, H: 5.32, N: 11.22.

2.1. Biological Studies

All these new compounds **2(a-c)**, **3(a-c), 4(a-c), 5(a-c), 6(a-c)** were tested *in vivo* in order to evaluate their hypotensive, analgesic, antiaggressive, and antidepressant and ALD_{50} activities according to following standard methods.

2.1.1. Cardiovascular activities

The cardiovascular activities were carried out on cats of either sex weighing between 2.5-4.0 kg. The cats were anaesthetized by giving intravenous prepared in propylene glycol. A femoral artery was cannulated and the blood pressure was recorded by connecting through p23 db pressure transducer to two channel polygraphs. Test compounds (dose of 2.5 mg/kg body weight) and normal saline were administrated through cannulated femoral vein. The animals were kept on positive pressure artificial respiration throughout the experiment with the help of artificial respirator. The both side (left and right) carotid arteries were also traced for occlusion (10-15sec). Exogenously administered norepinephrine induced pressor and carotid occlusion responses were taken as control. Transient effects appearing just after administering test compound taken as immediate while the effect which persisted for longer period were termed as delayed. The cardiovascular profile of compounds is shown in **Table-1.**

2.1.2. Approxiamte leathel dose

Compounds of the series **2(a-c) to 6(a-c)** were investigated for Approximate Lethal Dose (ALD_{50}). For evaluating ALD_{50}, swiss albino mice (either sex, of weight from 20 to 25 gm) were used for the study. The test compounds were injected intra-peritoneally at various doses in group of ten mice. The percent mortality within 24 hrs of oral drug

[1]). The results are summarized in **Table 1**.

2.2.1. Central nervous system activities

2.2.1.1. Analgesic activity

Analgesic activity of compounds **2(a-c) to 6(a-c)** have been done by tail flick method (Columbus Instruments). Albino rats of 150-200 gm of either sex, which have been given food and water ad libitum and maintained the temperature at 24 ±2°C. A set of 6 rats were taken for each compound and measured tail flick latency time (in seconds) with the help of electronic timer fitted in machine. Student's t test was performed to find out significance of values of latencies (in seconds) of different compounds at specific time interval along with control data of propylene glycol (PG) and standard drug Morphine. The results are summarized in **Table-2 & Graph 1.**

2.2.2.2. Anti aggressive activity

Antiaggressive Activity of compounds **2(a-c) to 6(a-c)** have been conducted on only male albino rats weighing between 100-150 gm, according to reported method.[37] Fights were counted between the rat's group and mean fighting count was calculated for each group. The significance of mean values of the different groups was determined by chi square test. Control data of propylene glycol taken. The results are summarized in **Table 3 & Graph 2**.

2.2.2.3. Depressant & antidepressant activity

Compounds 2**(a-c) to 6(a-c)** were also evaluated for antidepressant effect with help of swimming despair test according to the reported method.[38] The adult albino mice weighing 20-25 gm (male or female) was taken and total mean swimming time of control as well as of drug treated group was calculated. The significance of the result was analyzed by Chi square test. The results for antidepressant effect are summarized in **Table 4 & Graph 3**.

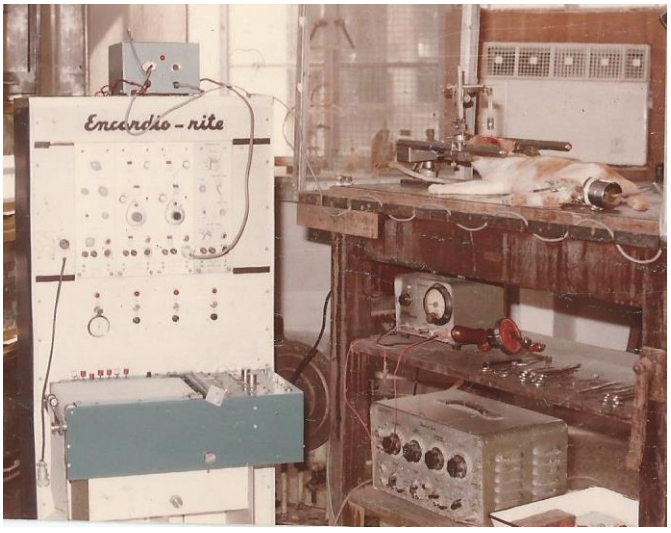
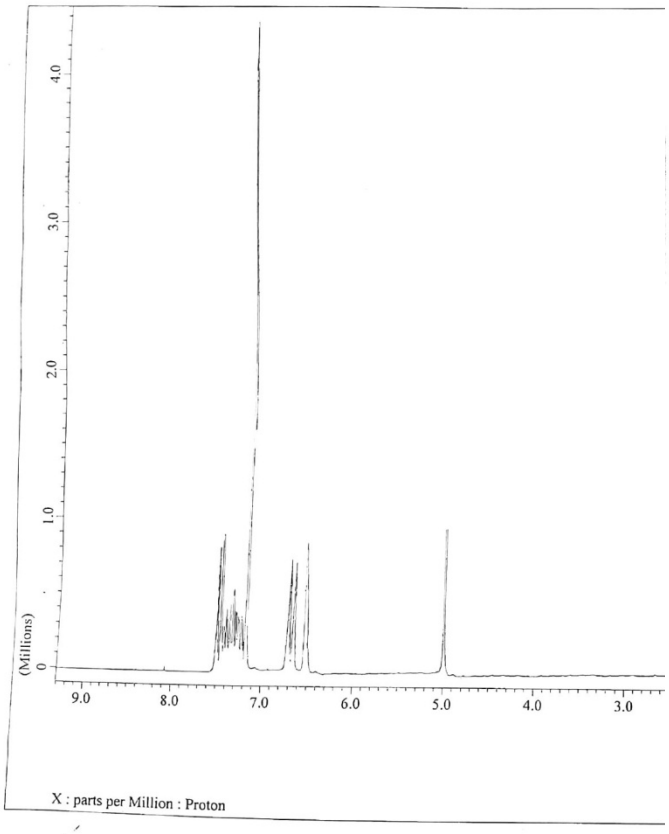
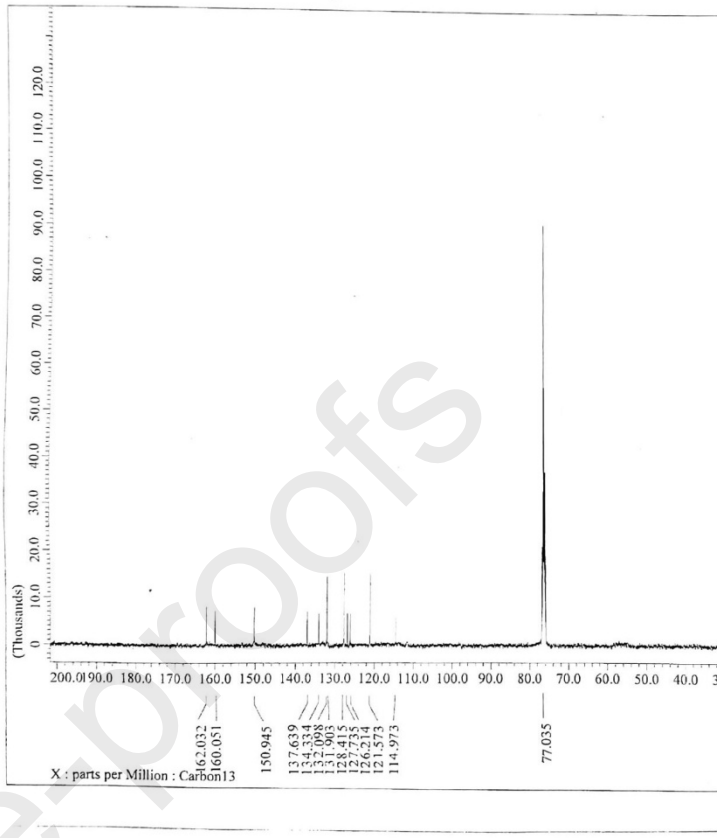


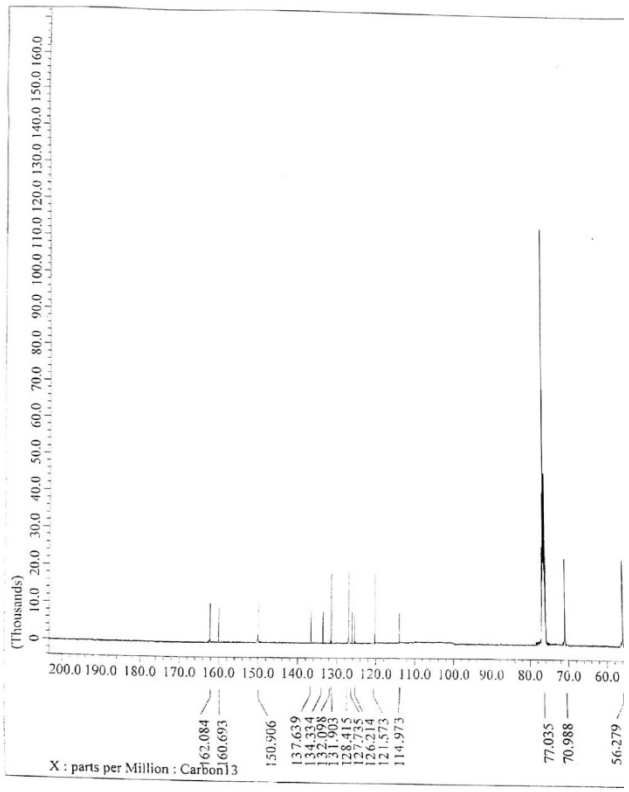
Image of *In-vivo* Cardiovascular Activity



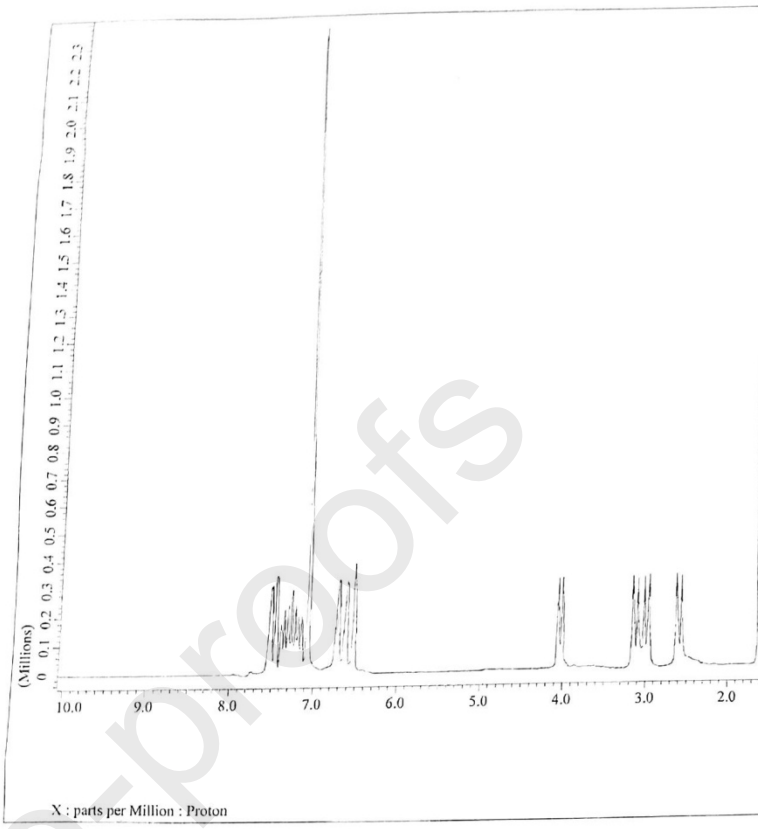
^{1} H Spectra of Compound **3a**



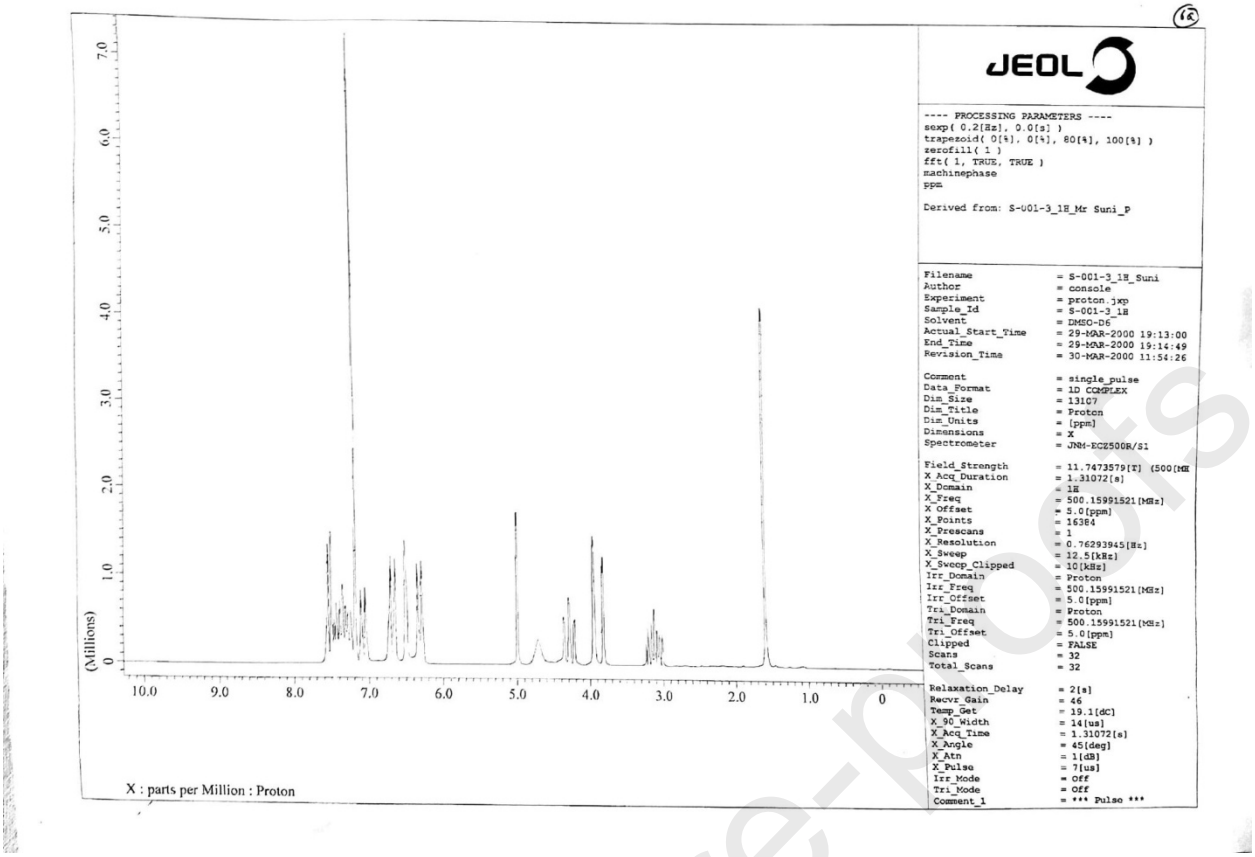
^{13} C spectra of Compound **3a**



^{13} C spectra of Compound **4a**



^{1}H Spectra of Compound **5a**



^{1}H Spectra

of Compound **6a**

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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