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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY STUDIES OF SOME BENZODIAZEPINE AND ISOXAZOLINE DERIVATIVES VIA COMMON INTERMEDIATE CHALCONE

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ABSTRACT

Reaction of 2- acetyl thiophene (I) in ethanol with substituted benzaldehyde (II) in presence of NaOH yielded corresponding intermediate 3-(substituted phenyl)-1-(thiophen-2-yl)prop-2-en-1-one(chalcones:-(III) which on treatment with o phenylenediamine in presence of catalytic amount of NaOH yielded 4-(substituted phenyl)-2-(thiophen-2yl)-2,3-dihydro-1H-benzo[b][1,4] diazepine (IV). Further (III) on treatment with hydrazine hydrate yielded 3-(substituted phenyl)-5-(thiophen-2-yl)-2,3-dihydroisoxazole (V). Structures of the compounds (III ,IV &V) were established on the basis of spectral data. These compounds were screened for antibacterial and antifungal activities at 1000μg/ml levels and are described.

Keywords: chalcones, benzodiazepine, isoxazoline, antibacterial, antifungal, analgesic and anti-inflammatory.

INTRODUCTION

The synthesis of benzodiazepine and isoxazoline containing compounds and their derivatives attracted considerable attention from organic and medicinal chemist due to their considerable bioactivity. In recent year, a significant portion of research in heterocyclic chemistry has been devoted to isoxazoline and benzodiazepine containing different groups as substituents. Chalcones show impressive physiological properties, these are used as intermediates in the synthesis of several bioactive heterocycles viz benzodiazepines and isoxazolines. Literature survey reveals that benzodiazepine derivatives posses antileukemic, antineoplastic[1], anticonvulsant, anxiety, analgesic, anti-inflammatory agents, sedative, antidepressive, hypnotic[2], tranquilizing, muscle relaxant effects[3] anti antipsychotic[4] activities.

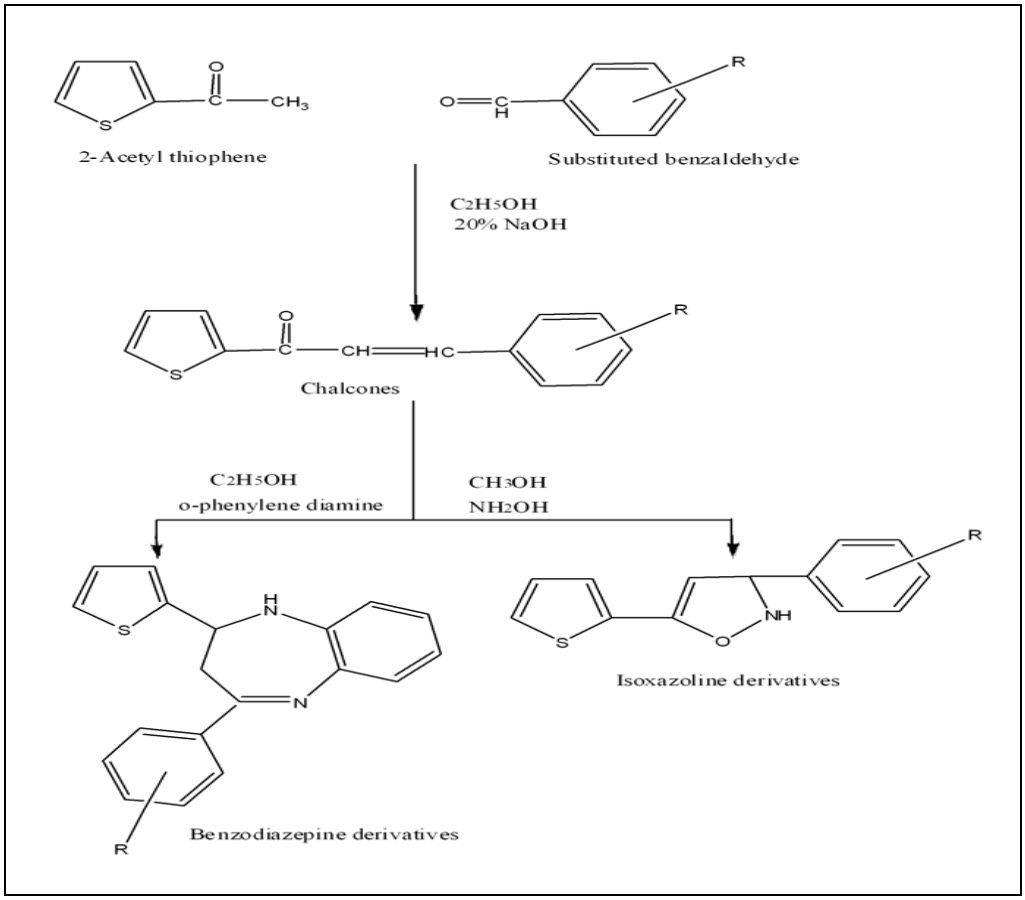
The survey of literature shows that isoxazoline derivatives posses a widw spectrum of anti-microbial, analgesic, anti-inflammatory[5], antifungal[6], herbicidal[7], antibacterial[8], anti-convulsant[9], anti HIV and anti tubercular[10] properties.

It has been observed that substituted chalcones are the best starting compound for the synthesis of substituted benzodiazepines and isoxazolines.Thus the present communication describes the synthesis of yielded 4-(substituted phenyl)-2-(thiophen-2yl)-2,3-dihydro-1H-benzo[b][1,4] diazepine and 3-(substituted phenyl)-5-(thiophen-2-yl)-2,3-dihydroisoxazole.

MATERIALS AND METHODS

Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. All the melting points were determined by open capillary method and are uncorrected .Silica gel G plates were used for TLC and spots were located by UV or in iodine chamber. The IR spectra is recorded by using shimadzu perkin ekmer 8201 PC IR spectrometer using a thin film on potassium bromide pellets techniques and frequencies are expressed in cm^{-1}. The PMR spectra were recorded on bruker avance II 400 NMR spectrometer in $CDCl_3$ and DMSO with TMS as an internal standard. And values are expressed in δ ppm.

Scheme:



Synthesis of 3-(substituted phenyl)-1-(thiophen-2-yl)prop-2-en-1-one (IIIa-IIIh)

A mixture of 2-acetyl thiophene (0.01mol) and substituted benzaldehyde (0.01 mole) in absolute ethanol (20 ml) were stirred together for 24 hr in presence of 20% NaOH (3-4ml). The mixture was poured into crushed ice and acidified with HCl. The product (substituted chalcones) obtained was filtered, washed with water and recrystallized from suitable solvent. **Table 1** summarizes physical data of these compounds.

Synthesis of 4-(substituted phenyl)-2-(thiophen-2yl)-2,3-dihydro-1H-benzo[b][1,4] diazepine (IVa-IVh)

Chalcones (0.01 mole) and ortho phenylenediamine (0.01 mol) were dissolved in absolute ethanol (30 ml) and the reaction mixture is refluxed for about 6 hrs. After the completion of the reaction, the reaction mixture is poured into crushed ice. The products (substituted benzodiazepine) was filtered, washed with water and recrystallized from suitable solvents. **Table 2** summarizes physical data of these compounds.

Synthesis of 3-(substituted phenyl)-5-(thiophen-2-yl)-2,3-dihydroisoxazole (Va-Vh)

Chalcones (0.01 mole) and hydroxyl amine (0.01 mol) were dissolved in methanol (30 ml) in the presence of 3-4 ml 2% NaOH and the reaction mixture is refluxed for about 10 hrs. After the completion of the reaction, the reaction mixture is poured into crushed ice. The products (substituted isoxazolines) was filtered, washed with water and recrystallized from suitable solvents.**Table 2** summarizes physical data of these compounds.

IIIa: IR (KBr) cm^{-1} : Absorption at 1224 cm^{-1} indicates the presence of C-F group, Absorption at 1644 cm^{-1} indicates the presence of C=O group, Absorption at 3088 cm^{-1} indicates the presence of C-H group.
^{1}H NMR(δ ppm) : 7.16 to 7.67 (m, 7H of aromatic ring),7.53 (d, 2H, CH=CH)
MASS in m/z : The molecular ion peak was observed at 232.

IVa : IR (KBr) cm^{-1} : Absorption at 3357 cm^{-1} indicates the presence of N-H group, Absorption at 1584 cm^{-1} indicates the presence of C=N group, Absorption at 1643 cm^{-1} indicates the presence of C=C group, Absorption at 1587cm^{-1} indicates the presence of C=C group, Absorption at 1223 cm^{-1} indicates the presence of C-F group, Absorption at 3357 cm^{-1} indicates the presence of C-H group.
^{1}H NMR (δ ppm) : 7.22 to 7.66 (12H, m, Ar-H), 3.22 to 3.44 (d, 3H of benzodiazepine), 5.16 to 5.20 (dd, 1H, Hx), 6.87 to 7.27 (m, 8H, Ar-H+ NH).
MASS in m/z : The molecular ion peak was observed at 322.
Va : IR (KBr) cm^{-1} : Absorption at 3391 cm^{-1} indicates the presence of N-H group, Absorption at 1654 cm^{-1} indicates the presence of C=C group, Absorption at 1222 cm^{-1} indicates the presence of C-F group.
^{1}H NMR (δ ppm) : 7.16 to 7.25 (10H, m, Ar-H) and NH proton merged with aromatic proton.
MASS in m/z : The molecular ion peak was observed at 247.
IIIf : IR (KBr) cm^{-1} : Absorption at 1643 cm^{-1} indicates the presence of C=O group, Absorption at 1585 cm^{-1} indicates the presence of C=C group, Absorption at 2924 cm^{-1} indicates the presence of C-H group in CH_3.
^{1}H NMR (δ ppm) : 7.18 to 7.68 (12H, m, Ar-H), 7.537 (s, 1H, CH=CH), 1.57 (s, 3H, CH_3)
MASS in m/z : The molecular ion peak was observed at 233.
IVf : IR (KBr) cm^{-1} : Absorption at 3347 cm^{-1} indicates the presence of N-H group, Absorption at 1644 cm^{-1} indicates the presence of C=N group, Absorption at 3111 cm^{-1} indicates the presence of C-H group, Absorption at 2920 cm^{-1} indicates the presence of C-H group in CH_3.
^{1}H NMR (δ ppm) : 7.14 to 7.66 (12H, m, Ar-H), 1.58 (s, 3H, CH_3)
MASS in m/z : The molecular ion peak was observed at 317.
Vf : IR (KBr) cm^{-1} : Absorption at 3344 cm^{-1} indicates the presence of N-H group, Absorption at 1636 cm^{-1} indicates the presence of C=C group, Absorption at 2964 cm^{-1} indicates the presence of C-H stretching in CH_3,

Absorption at 1636 cm^{-1} indicates the presence of C-H stretching, Absorption at 1506 cm^{-1} indicates the presence of aromatic methyl C-H stretching.

^{1}H NMR (δ ppm) : 7.16 to 7.25 (10H, m, Ar-H) and NH proton merged with aromatic proton.

MASS in m/z : The molecular ion peak was observed at 247.

RESULTS AND DISCUSSION

The aim of this work was to synthesize various **4-(substituted phenyl)-2-(thiophen-2yl)-2,3-dihydro-1H-benzo[b][1,4] diazepine** and **3-(substituted phenyl)-5-(thiophen-2-yl)-2,3-dihydroisoxazole (scheme).** Initially **of 3-(substituted phenyl)-1-(thiophen-2-yl)prop-2-en-1-one)** were synthesized from the reaction of 2-acetyl thiophene and corresponding substituted benzaldehyde in ethanol in presence of NaOH. The titled compounds (IVa-IVh) and (Va-Vh) were obtained by refluxing the chalcones with o-phenylenediamine hydrazine hydrate in presence of catalytic amount of NaOH respectively. They were confirmed by IR(KBr) spectral data as sharp bands were obtained at 3422.8-3325.9cm^{-1}(N-H from pyrazoline),1619-1593.5cm^{-1}(C=N), 3109-2854.3(C-H),1599-1559.5(C=C).Their structure ,as in case of **IVa, IVg, IVh** was supported by ^{1}H NMR spectral data as a sharp multiplet is observed at 6.65 to8.24 assigned for 8H,Ar-H,NH.Subsequent purification yielded final compounds in moderate yields. The physical data of the titled compounds (IVa-IVh) and(Va-Vh) is described in **Table 2** and **Table 3.** Some of these compounds have shown good antibacterial, antifungal, analgesic and anti-inflammatory activity as compared to respective standard drugs

Table 1:Physical data of compounds(IIIa-IIIh)

Code No	Compound ($R\text{-}COCH_3$)	Physical State	Molecular Formula	Molecular Weight	MP (°C)	% Yield
IIIa	p-F	Orange crystals	$C_{13}H_8FOS$	232.27	92 -94	81
IIIb	p-OH	Yellow crystals	$C_{13}H_9O_2S$	230.28	68-70	46
IIIc	m-OH	Yellow crystals	$C_{13}H_9O_2S$	230.28	90 -92	65
IIId	o-OH	Yellow crystals	$C_{13}H_9O_2S$	230.28	84 -86	54
IIIe	m-No_2	Brown crystals	$C_{13}H_8NO_3S$	259.27	104- 106	66
IIIf	m-CH_3	Green Yellow crystals	$C_{13}H_8ClOS$	228.31	64 -66	78
IIIg	p-Cl	Red crystals	$C_{15}H_8ClOS$	248.73	67 -69	69
IIIh	p-$N(CH)_2$	White crystals	$C_{15}H_{14}NOS$	257.35	122 -124	76

Table 2: Physical data of compounds (IVa-IVh)

Code No:	Compound [R-$COCH_3$]	Physical State	Molecular Formula	Molecular Weight	MP (°C)	% Yield
IVa	p-F	Brown crystals	$C_{19}H_{14}FN_2S$	322.40	202 -205	84
IVb	p-OH	Brownish Yellow crystals	$C_{19}H_{15}N_2OS$	320.42	178 -180	53
IVc	m-OH	Yellow crystals	$C_{19}H_{15}N_2OS$	320.42	210 -212	51
IVd	o-OH	Brown crystals	$C_{19}H_{15}N_2OS$	320.42	213 -205	46
IVe	p-NO_2	Dark brown crystals	$C_{19}H_{14}N_3O_2S$	349.41	239 -241	62
IVf	m-CH_3	Yellow crystals	$C_{20}H_{17}N_2S$	318.44	170 -174	77
IVg	p-Cl	Dark red crystals	$C_{19}H_{14}ClN_2S$	338.68	182-187	82
IVh	p-$N(CH)_2$	White crystals	$C_{21}H_{20}N_3S$	347.49	164 -167	79

Table 3: Physical data of compounds (Va-Vh)

Code No:	Compound [R-$COCH_3$]	Physical State	Molecular Formula	Molecular Weight	MP (°C)	% Yield
IVa	p-F	Brown crystals	$C_{13}H_9FNOS$	247.29	60 -64	68
IVb	p-OH	Brownish yellow crystals	$C_{13}H_{10}NOS$	245.05	200 -202	50
IVc	m-OH	Yellow crystals	$C_{13}H_{10}NO_2S$	245.05	178 -180	63
IVd	p-OH	Brown crystals	$C_{13}H_{10}NO_2S$	245.05	210 -212	45
IVe	m-NO_2	Dark brown crystals	$C_{13}H_9N_3O_3S$	274.30	203 -205	51
IVf	m-CH_3	Yellow crystals	$C_{14}H_{12}NOS$	243.33	239 -241	49
IVg	p-Cl	Dark red crystals	$C_{13}H_9ClNOS$	263.73	70-72	60
IVh	p-NH_2	White crystals	$C_{15}H_{15}N_2OS$	272.38	82 -84	62

BIOLOGICAL EVALUATION

Antibacterial and antifungal activity

Antibacterial activity was done by cup plate method in Muller Hinton agar medium. This medium was inoculated with one bacterial culture by spreading the suspension of the organism with a sterile glass rod with a bended tip. In each plate cups of 6 mm diameter were made at equal distances using sterile cork borer. The test solution was prepared by dissolving 10mg of the synthesized compound in 10ml of DMF to obtain a concentration of 1000µg/ml. Ampicillin was used as standard. The cups filled with only DMF were used as control. The Petri dishes were incubated at 37°C for 24 hrs .Diameter of the zone of inhibition was measured and the average diameter for each sample was calculated. The diameters obtained for the test sample were compared with that produced by standard. All the synthesized compounds were screened for their antibacterial activity against *B.subtilis, S.aureus, E.coli & P.aeruginosa.*

Antifungal activity was done in the similar manner using Sabouraud's agar medium. Griseofulvin was used as the standard. The petri dishes were incubated at 37°C for 48hrs.All the synthesized compound were screened for their antifungal activity against *C.albicans and A.niger.*

Table 4 Data of antimicrobial activity of substituted benzodiazepine derivatives.

Sl. no.	Comp Code	Diameter of zone of inhibition (mm)					
		B.subtilis	***S.aureus***	***E.coli***	***P.aeruginosa***	***C.albicans***	***A.niger***
1	IV a	13	19	20	12	10	13
2	IVb	15	18	17	14	11	09
3	IVc	12	17	18	10	08	10
4	IVd	12	14	18	11	10	12
5	IVe	13	18	19	13	09	11
6	IVf	14	13	15	12	10	11
7	IVg	11	15	16	10	12	09
8	IVh	13	16	18	12	08	10
09	Ampicillin	28	20	21	15	-	-
10	Griseofulvin	-	-	-	-	13	16
11	Control(DMF)	-	-	-	-	-	-

Table 5 Data of antimicrobial activity of substituted isoxazoline derivatives.

Sl. no.	Comp Code	Diameter of zone of inhibition (mm)					
		B.subtilis	***B.aureus***	***E.coli***	***P.aeruginosa***	***C.albicans***	***A.niger***
1	IVa	13	19	17	12	10	13
2	IVb	10	18	16	13	11	11
3	IVc	12	13	16	10	08	15
4	IVd	12	17	18	11	10	10
5	IVe	11	14	19	13	09	13
6	IVf	14	18	17	12	10	12
7	IVg	11	15	16	10	12	14
8	IVh	13	16	18	12	08	14
09	Ampicillin	28	20	21	15	-	-
10	Grieseofulvin	-	-	-	-	13	19
11	Control(DMF)	-	-	-	-	-	-

CONCLUSION

All the 2-substituted pyrazoline derivatives presented herein showed moderate activity against the bacteria but less activity against the fungi organisms. In the antibacterial activity the compounds showed good activity against *B.subtilis* and *E.coli* when compared to the *P.aeruginosa* and *S.aureus*. Derivatives **IVa, IVc, IVf** exhibited maximum activity against the *Gram negative P.aeruginosa* and *E.coli.* The rest of the compounds showed good activity against the other two organisms. But most of the synthesized compounds are highly active only against the *Gram negative E.coli.* Among the antifungal activity, all the synthesized compounds exhibited moderate antifungal activity against both the fungal organisms. Only the compounds with substituents like **IVg** and **IVh** showed high activity against both the organisms.

Table 6:Analgesic effect of substituted Benzodiazepines by Tail Immersion Method in rats

Treatment	Dose mg/kg	Reaction time in sec at time (min)				
		0min	30 min	60 min	90 min	120 min
Control	_	2.18±0.06	2.13±0.04	2.50±0.05	2.73±0.06	2.62±0.02
Pentazocine	46.8	2.88±0.06	4.91±0.02* (130.5)	7.74±0.04* (209.6)	8.80±0.9* (222.34)	5.46±0.08* (108.39)
MI_1	50	2.53±0.05	3.35±0.07* (57.27)	5.20±0.05* (108)	7.31±0.07* (167.76)	4.16±0.04* (58.77)
MI_2	50	2.41±0.03	4.11±0.03* (93.28)	6.10±0.03 (144)	8.30±0.07* (204.63)	3.36±0.18* (28.24)
MI_3	50	2.78±0.06	4.68±0.06* (199.27)	5.31±0.05* (112)	8.06±0.03* (193.04)	3.48±0.10* (32.82)
MI_4	50	2.68±0.03	3.67±0.04* (72.15)	5.48±0.09* (119)	6.18±0.14* (126.37)	5.0±0.12 (94.84)
MI_5	50	2.26±0.04	3.38±0.04* (58.82)	5.75±0.04* (130)	7.56±0.17* (176.92)	3.66±0.33* (39.69)
MI_6	50	2.06±0.03	4.41±0.05* (107.04)	6.19±0.05* (147.60)	7.18±0.04* (163)	5.38±0.09* (105.34)
MI_7	50	2.48±0.06	3.1±0.03* (45.50)	6.25±0.07* (150)	7.90±0.09* (189.37)	4.41±0.07* (56.87)
MI_8	50	2.24±0.07	4.68±0.07* (119.71)	4.70±0.03* (88)	5.73±0.14* (109.89)	3.33±0.03* (19.46)

Table 7: Analgesic effect of substituted Isoxazolines by Tail Immersion Method in rats.

Treatment	Dose mg/kg	Reaction time in sec at time (min)				
		0min	30 min	60 min	90 min	120 min
Control	_	2.41±0.04	2.36±0.07	2.45±0.00	2.40±0.06	2.31±0.04
Pentazocine	46.8	2.56±0.07	4.48±0.04* (89.83)	7.41±0.06* (202.44)	8.6±0.10* (258.33)	5.38±0.09* (132.90)
MI_1	50	2.53±0.06	3.31±0.04* (40.25)	5.23±0.02* (113.46)	7.33±0.05* (205.41)	4.26±0.03* (84.41)
MI_2	50	2.50±0.05	3.63±0.04* (53.81)	6.46±0.056 (163.67)	7.88±0.03* (228.33)	4.83±0.05* (109.09)
MI_3	50	2.60±0.05	4.25±0.04* (80.08)	7.25±0.03* (195.91)	8.26±0.04* (244.16)	5.43±0.06* (135.06)
MI_4	50	2.61±0.07	3.71±0.03* (57.20)	6.75±0.04* (175.51)	7.75±0.04* (222.91)	4.78±0.04 (106.92)
MI_5	50	2.58±0.05	3.80±0.02* (61.01)	7.0±0.04* (185.71)	7.91±0.03* (229.58)	5.08±0.04* (119.91)
MI_6	50	2.55±0.06	3.53±0.04* (49.57)	6.30±0.03* (157.14)	7.33±0.03* (205.41)	4.75±0.03* (105.62)
MI_7	50	2.63±0.08	4.5±0.03* (90.67)	7.81±0.03* (218.77)	8.81±0.04* (267.08)	5.40±0.03* (133.76)
MI_8	50	2.53±0.11	3.85±0.02* (63.13)	6.68±0.03* (172.65)	7.58±0.03* (215.83)	4.80±0.03* (107.79)

All values are expressed as mean ± SEM (n = 6)

***P < 0.05 significant compared to control.**

Table 8: Anti-inflammatory effect of substituted Benzodiazepines on Carrageenin induced paw edema in rats.

Treatment	Dose mg/kg	Increase in paw volume (in ml)			
		1h	2h	3h	4h
Control	_	0.46±0.01	0.73±0.01	0.81±0.01	0.94±0.03
Diclofenac Sodium	13.5	0.18±0.01* (58.1)	0.32±0.02* (56.16)	0.40±0.01* (50.61)	0.50±0.05* (46.80)
MB_1	50	0.23±0.01* (50)	0.39±0.01* (46.5)	0.48±0.02* (40.74)	0.55±0.03* (41.48)
MB_2	50	0.27±0.02* (41.3)	0.42±0.01* (42.4)	0.45±0.01* (44.44)	0.53±0.04* (43.61)
MB_3	50	0.27±0.02* (41.3)	0.45±0.01* (38.35)	0.51±0.02* (37.03)	0.54±0.01* (42.55)
MB_4	50	0.21±0.02* (54.34)	0.46±0.01* (36.98)	0.49±0.01* (39.50)	0.58±0.01* (38.29)
MB_5	50	0.26±0.01 (39.5)	0.38±0.01* (47.94)	0.55±0.01 (32.09)	0.59±0.02* (37.23)
MB_6	50	0.23±0.01* (50)	0.41±0.03* (43.8)	0.45±0.03* (44.44)	0.60±0.03* (36.17)
MB_7	50	0.32±0.01 (30.4)	0.35±0.03* (52.05)	0.52±0.01* (35.80)	0.63±0.01 (32.9)
MB_8	50	0.28±0.01* (39.13)	0.47±0.03 (35.61)	0.47±0.02* (41.97)	0.62±0.02* (34.04)

Table 9: Anti-inflammatory effect of substituted Isoxazoline on Carrageenin induced paw edema in rats.

Treatment	Dose mg/kg	Increase in paw volume (in ml)			
		1h	2h	3h	4h
Control	_	0.36±0.06	0.68±0.05	0.77±0.03	0.81±0.03
Diclofenac Sodium	13.5	0.18±0.03* (50)	0.35±0.05* (48.52)	0.41±0.04* (46.75)	0.45±0.05* (44.44)
MI_1	50	0.26±0.04 (27.77)	0.43±0.04 (36.76)	0.50±0.04 (35.06)	0.56±0.03 (30.86)
MI_2	50	0.23±0.04 (36.11)	0.41±0.04 (39.70)	0.47±0.04 (38.96)	0.52±0.04 (35.80)
MI_3	50	0.24±0.03 (33.33)	0.42±0.02 (38.23)	0.46±0.03 (40.25)	0.52±0.03 (35.80)
MI_4	50	0.19±0.04* (47.22)	0.37±0.03* (45.58)	0.42±0.03* (45.45)	0.46±0.04* (43.20)
MI_5	50	0.21±0.02 (41.66)	0.38±0.03* (44.11)	0.43±0.04* (44.15)	0.48±0.02* (40.74)
MI_6	50	0.20±0.03* (44.44)	0.37±0.03* (45.58)	0.42±0.03* (45.45)	0.46±0.03* (43.20)
MI_7	50	0.19±0.04* (47.22)	0.36±0.03* (47.05)	0.41±0.03* (46.75)	0.48±0.03* (40.74)
MI_8	50	0.21±0.04* (41.66)	0.38±0.03 (44.11)	0.43±0.03* (44.15)	0.48±0.03* (40.74)

All values are expressed as mean ± SEM (n = 6).

***P<0.05 significant compared to control.**

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