ISSN 0976 – 3333

Available Online at www.ijpba.info.
International Journal of Pharmaceutical & Biological Archives 2010; 1(3):300 - 304

ORIGINAL RESEARCH ARTICLE

Synthesis and Biological Evaluation of Some Novel Pyrimidine Derivatives

P.Muthumani[*1], Manojith[1], R. Meera[1] S.Venkataraman[1], N.Chidambaranathan[2], P.Devi[3], A, C.A.Sureshkumar[1]

[1]*Department of Pharmaceutical Chemistry, K.M. College of Pharmacy, Madurai , TamilNadu, India*
[2]*Department of Pharmacology, K.M. College of Pharmacy, Madurai , TamilNadu, India*
[3]*Department of Pharmacognosy, K.M. College of Pharmacy, Madurai , TamilNadu, India*

Received 8 June 2010; Accepted 21 July 2010

ABSTRACT

Synthesis of some novel pyrimidine derivatives has been done. The entire synthesized compounds were characterized by UV, IR and ^{1}HNMR spectroscopy. The antimicrobial activity was evaluated. The present investigation deals with the synthesized compounds possessing good antimicrobial activity. Analgesic activity of the compounds by Eddy's hot plate method was evaluated against Diclofenac Sodium as the standard the tail flick response was considered as the end point to remove the animals from the source of the pain stimulus. The basal reaction time (latency between the application of the stimulus and the response) of the control animals ranged between (2.2 ± 0.33 - 3.3 ±0.33) after treatment of the animals the basal reaction time was prolonged (statistically significant increase) by the compounds (P1, P2, P6, P7 and P8) which reached maximum levels at the 2ndhr. However all the compounds showed analgesic activity less than the reference standard. The result of anti-inflammatory activity showed significant reaction in paw volume by the compounds P_1 P_2, P_6, P_7 and P_8 when compared to control at ($p < 0.01$).

KEYWORDS: Some novel pyrimidine derivatives, analgesic and anti inflammatory activity.

INTRODUCTION

Unlike purines, pyrimidines are assembled before being attached to 5-phosphoribosyl-1-pyrophosphate (PRPP). The first step begins with formation of Carbamoyl phosphate by carbamoyl phosphate synthetase II. This is the regular step in the pyrimidine biosynthesis. This second major step in the creation of carbonyl aspartic acid formed by aspartic transcarbamoylyase (aspartate carbonyl transferase).The next reaction involves dehydration of the acid catalyzed by the enzyme dihydraorotase to form hydro orate. Pyrimidines are ultimately catabolized (degraded) to CO_2, H_2O and urea. Cytosine can be broken down to uracil, which can be further broken down to N-carbamoyl-β-alanine. Thymine is broken down into β-aminioisobutytrate, which can be further broken down into intermediates eventually leading into the citric acid cycle. Pyrimidines can also be prepared in the laboratory by organic synthesis. Many methods rely on condensation of carbonyls with amines, for instance the synthesis of 2-thio-6-methyluracil from thiourea and ethyl acetoacetate or the synthesis of 4-methyl pyrimidine with 4,4-dimethoxy-2-butanone and formamide .A novel method is by reaction of certain amides with carbonitriles under electrophilic activation of the amide with 2-chloro-pyridine and trifluromethane sulfonic anhydride . Literature survey reveals that some novel pyrimidines derivatives possess broad spectrum biological activities, which include Anti microbial [1,2] ,antibacterial and fungal [3,4], anti helmentic [5], anti-inflammatory[6], anti ulcer[7], antioxidant[8], anticancer[9,10], anti allergic[11], Termiticidal [12], Anti histamine [13], Anti viral [14], HIV induced cytopathic activity[15]. On the basis of our observation the present research work was carried out to synthesize novel pyrimidines derivatives and to further evaluate analgesic and anti inflammatory activity.

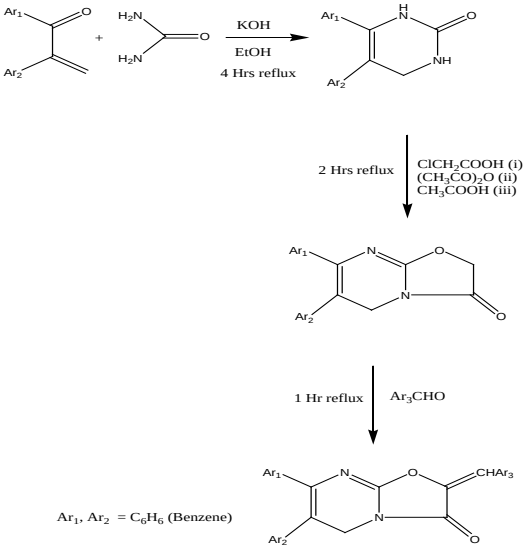
MATERIALS AND METHODS:

All the chemicals are analytical grade and were purified by the established methods. Melting points and were determined by open capillary tubes method purity and homogeneity of the

***Corresponding Author:** Mr. P.Muthumani, **Email:** Sabareesanmuthu@gmail.com, **Contact No:**

compounds was routinely determined by thin layer chromatography on glass plates using silica gel G as absorbent and solvent system. Benzene: Ethylacetate: Methanol (8.5:1.4:0.1). Spots were visualized by iodine vapor by irradiation with UV light.[1]HNMRspectra was recorded on Bruker Ultra shield (300MHZ) spectrometer using DMSO (TMS as internal standard). The anti microbial activities of the synthesized compounds were evaluated on *S.aureus* and *E. coli.*

SCHEME



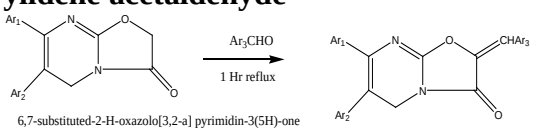
EXPERIMENTAL WORK

Step 1:1,2-substituted-prop-2-en-1-one react with urea in presence of ethanolic potassium hydroxide or sodium ethoxide to give 3,4-dihydro-5,6-substituted-pyrimidine-2(1*H*)-one

Step 2 : 3,4-dihydro-5,6-substituted-pyrimidine-2(1*H*)-one on treatment with chloro acetic acid in acetic acid in presence of fused sodium acetate to give 6,7-substituted-2*H*-oxazolo[3,2-a] pyrimidin-3(5*H*)-one

Step 3 : 6,7-substituted-2*H*-oxazolo[3,2-a] pyrimidin-3(5*H*)-one were condensed with aromatic aldehyde in refluxing acetic anhydride to give 2,3-oxo-6,7-subsitututed-3*H*-oxazolo[3,2-a] pyrimidin-2(5*H*)-ylidene acetaldehyde.

Synthesis of various substituted 2,3-oxo-6,7-subsitututed-3*H*-oxazolo[3,2-a]pyrimidin-(5*H*)-ylidene acetaldehyde

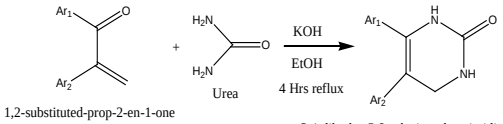


6,7-substituted-2-H-oxazolo[3,2-a] pyrimidin-3(5H)-one

2,3-oxo-6,7-subsitututed-3-H-oxazolo[3,2-a] pyrimidin-2(5H)-ylidene acetaldehyde

Synthesis of substituted 3,4-dihydro-5,6-substituted-pyrimidine-2(1*H*)-one

A mixture of 0.02 mole of 1,2-substituted-prop-2-en-1-one, urea (1.5 g) and KOH (2g) in ethanol (100 ml) was heated on a water bath for 4 Hrs. ethanol was evaporated to its half and the mixture was left overnight. The precipitate was filtered and then washed the product with water until free from alkali.

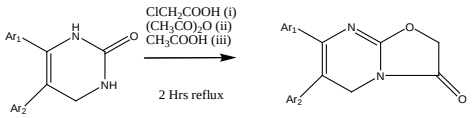


1,2-substituted-prop-2-en-1-one

3,4-dihydro-5,6-substituted-pyrimidine-2(1H)-one

Synthesis of substituted 6,7-substituted-2-H-oxazolo[3,2-a] pyrimidin-3(5*H*)-one

To a substituted 3,4-dihydro-5,6-substituted-pyrimidine-2(1H)-one (0.01 mole) chloroacetic acid (0.01 mole) fused sodium acetate (2 g) in acetic acid (10 ml) and acetic anhydride (7 ml) was refluxed for 2 Hrs, allowed to cool and then poured gradually while stirring into cold water. The solid obtained was filtered off and recrystallized from proper solvent (ethanol).



3,4-dihydro-5,6-substituted-pyrimidine-2(1H)-one

6,7-substituted-2-H-oxazolo[3,2-a] pyrimidin-3(5H)-one

Synthesis of various substituted 2,3-oxo-6,7-subsitututed-3-H-oxazolo[3,2-a] pyrimidin-2(5*H*)-ylidene acetaldehyde

Take a mixture of substituted 6,7-substituted-2-H-oxazolo[3,2-a] pyrimidin-3(5H)-one (0.01 mole), aromatic aldehyde (0.01 mole) and sodium acetate (1 g) in acetic anhydride (6 ml) was refluxed for 1 Hr poured into cold water and the precipitate was filtered and recrystallized from the proper solvent (ethanol).

Table 1: Solubility of the synthesized compounds

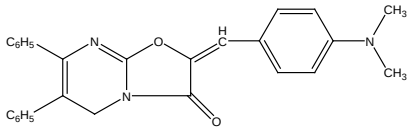
S.No.	Compound code	Solubility
1	P_1	Soluble in ethanol, methanol benzene
2	P_2	Soluble in ethanol, methanol benzene
3	P_3	Soluble in ethanol, methanol benzene
4	P_4	Soluble in ethanol, methanol benzene
5	P_5	Soluble in ethanol, methanol benzene
6	P_6	Soluble in ethanol, methanol benzene
7	P_7	Soluble in benzene, methanol, ethanol
8	P_8	Soluble in benzene, methanol, ethanol
9	P_9	Soluble in benzene, methanol, ethanol

Table 2: Physical characteristics of the synthesized compounds

S. No	Comp Code	Nature	Colour	Mol. Formula	Mol. Wt	Melting point	Percentage yield (%)	R_f Value
1	P_1	Powder	Yellow	$C_{27}H_{22}N_2O_4$	438.77	138° C	68 %	0.6
2	P_2	Powder	Pale yellow	$C_{25}H_{18}N_2O_3$	394.42	196° C	72 %	0.72
3	P_3	Powder	Straw colored	$C_{25}H_{17}N_3O_4$	423.42	153° C	58 %	0.8
4	P_4	Powder	Pale yellow	$C_{25}H_{18}N_2O_3$	394.42	106° C	56 %	0.55
5	P_5	Powder	Light blue	$C_{27}H_{23}N_3O_2$	421.49	147° C	71 %	0.66
6	P_6	Powder	Yellow	$C_{25}H_{18}N_2O_2$	378.42	138° C	62 %	0.55
7	P_7	Powder	Yellow	$C_{25}H_{17}FN_2O_2$	396.41	141° C	76 %	0.72
8	P_8	Powder	Pale yellow	$C_{25}H_{17}ClN_2O_4$	498.41	167° C	55 %	0.82
9	P_9	Powder	Pale yellow	$C_{25}H_{17}ClN_2O_2$	498.41	169° C	63 %	0.76

Spectral analysis [16,17]

P1) (2E)-2-(4-(dimethylamino)benzylidene)-6,7-diphenyl-2*H*-oxazolo[3,2-a]pyrimidin-3(5*H*)-one

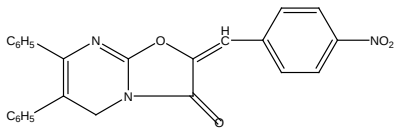


IR Spectral data

3438.84 N-H Stretching, 2918.10 C-H Stretching,1552.59 / 1515.94 C=C Stretching,1361.65 C-N Stretching,1677.95 C=O Stretching.

NMR Spectral data

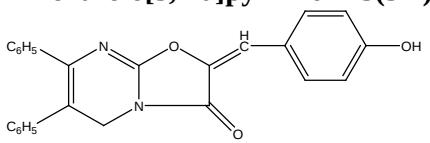
2.645 Aromatic proton, 7.639 Ar-CH_3, 7.495 Ar-$COCH_3$, 6.682 C-NH_2. **P3) (2E)-2-(4-nitrobenzylidene)-6,7-diphenyl-2*H*-oxazolo[3,2-a]pyrimidin-3(5*H*)-one**



NMR Spectral data

2.659 Aromatic proton, 5.523 C-NO_2, 7.715 Ar-H, 8.109 C-CH_3, 10.177 OH.

P4) (2E)-2-(4-hydroxybenzylidene)-6,7-diphenyl-2*H*-oxazolo[3,2-a]pyrimidin-3(5*H*)-one



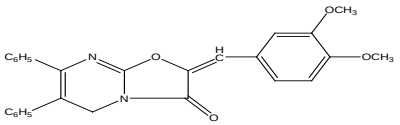
IR Spectral data

3342.41 N-H Stretching,2999.10 / 2916.17 C-H Stretching,3438.84 OH Bonding,1677.95 C=O Stretching,3031.89 C-O Stretching,1598.88 / 1558.38 C=C Stretching.

NMR Spectral data

3.664 C=O, 2.648 Aromatic proton, 7.967 Ar-H, 8.019 C-CH_3, 7.255 Ar-OH.

P5) (2E)-2-(3,4-dimethoxybenzylidene)-6,7-diphenyl-2*H*-oxazolo[3,2-a]pyrimidin-3(5*H*)-one



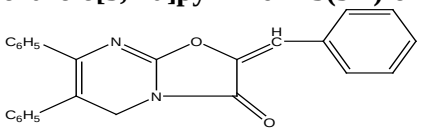
IR Spectral data

3429.20 N-H Stretching,2999.10 C-H Stretching,1677.95 C=O Stretching,1598.88 C=C Stretching,1317.29 / 1263.29 C-O Stretching.

NMR Spectral data

2.625 Aromatic proton,7.615 Aromatic C-H,7.686 C-CH_3,8.023 Ar-CH_3.

P6) (2E)-2-benzylidene-6,7-diphenyl-2*H*-oxazolo[3,2-a]pyrimidin-3(5*H*)-one



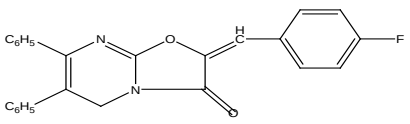
IR Spectral data

3440.77 N-H Stretching,2999.10 C-H Stretching,1677.95 C=O Stretching,3033.82 C-O Stretching,1558 C=C Stretching.

NMR Spectral data

2.652 Aromatic proton,7.626 Ar-H,8.038 C-CH_3,7.5 C-H.

P7) (2E)-2-(4-fluorobenzylidene)-3,5-dihydro-6,7-diphenyl-2*H*-oxazolo[3,2-a]pyrimidine



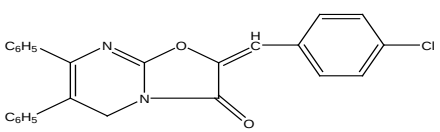
IR Spectral data

3340.48 N-H Stretching,2997.17 / 2962.46 C-H Stretching,1400.22 C-F Stretching,1552.59 C=C Stretching,1600.81 / 1677.95 C=O Stretching.

NMR Spectral data

2.638 Aromatic proton,8.018 C-CH_3,7.613 C-H,5.577 C-F.

P8) (2E)-2-(4-chlorobenzylidene)-6,7-diphenyl-2*H*-oxazolo[3,2-a]pyrimidin-3(5*H*)-one



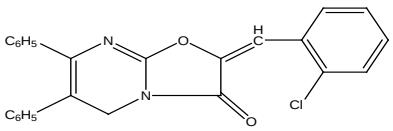
IR Spectral data

3340.48 N-H Stretching,2999.10 / 2960.53 C-H Stretching,1552.59 C=C Stretching,1677.95 C=O Stretching.

NMR Spectral data

2.636 Aromatic proton,7.638 Ar-H protons,7.693 Ar-CH_3 protons,8.023 C-CH_3 protons,2.625 Aromatic protons.

P9) (2E)-2-(2-chlorobenzylidene)-6,7-diphenyl-2*H*-oxazolo[3,2-a]pyrimidin-3(5*H*)-one



3340.48 N-H Stretching,2999.10 / 2992.6 C-H Stretching,837.05 / 719.40 C-Cl Stretching,1598.88 C=C Stretching,1677.95 C=O Stretching.

Analgesic activity[18,19]

The analgesic activities of various synthesized compounds were screened by employing tail flick method. Rats of either sex weighing between 150 – 200 gm were taken in 7 groups of each 6 animals. Diclofenac sodium 10mg/kg were used as a standard drug for comparison of analgesic activity. Tail flick response was evoked by placing rat tail over a wire heated electrically. The intensity of heat was adjusted so that the baseline flick latency averaged 3-4 seconds in all the animals. Cut off period of 15 seconds was observed to prevent the damage to the tail.

Table 3: Effect of analgesic activities of synthesized compounds in rats

Treatment Group	Dose	Times in minutes					
		0 min	30 min	60 min	90 min	120 min	180 min
Control	10ml/kg normal saline	2.3±0.21	2.2±0.24	2±0.16	2.2±0.16	2.0±0.27	2.4±0.19
Standard	Diclofenac sodium 10mg/kg	2.4±0.21	4.3±0.17	6.3±0.32	6.3±0.31	6.4±0.3	6.0±0.20
P1	10mg/kg	2.2±0.19	3.4±0.26	4.2±0.32	4.8±0.39	4.6±0.36	5.0±0.42
P2	10mg/kg	2.0±0.21	3.8±0.24	4.3±0.33	4.9±0.32	5.1±0.41	5.2±0.42
P6	10mg/kg	1.9±0.21	3.7±0.24	4.0±0.31	4.8±0.30	5.1±0.32	5.1±0.40
P7	10mg/kg	2.3±0.26	3.3±0.25	4.1±0.28	4.5±0.32	5.3±0.42	5.3±0.42
P8	10mg/kg	2.4±0.30	3.1±0.23	4.1±0.32	4.8±0.32	5.4±0.40	5.4±0.40

Values are expressed as mean ± SEM

Anti inflammatory activity[20,21,22]

Anti inflammatory activity was measured using the Carrageenan induced paw edema in the rats. Test compounds were administered intra peritonially at dose of 10 mg/kg as a solution of DMSO (0.05 ml), while the control group was fed with the same volume (0.05 ml) of DMSO solution. Thirty minutes later, the rats were challenged by a subcutaneous injection of 0.05 ml of 1% w/v solution of Carrageenan into the plantar side of the left hint paw. The paw volume was measured using the mercury displacement techniques with the help of a Plethysmometer. Paw volume of the test compounds, standard and control groups were measured at 30, 60, 120 and 240 minutes after Carrageenan challenge. The difference between the mean paw volume of control and standard is considered as 100% and the difference between the mean paw volume of control and test compounds treated groups were expressed with reference to standard and percentage of inhibition was also calculated.

RESULTS AND DISCUSSION

Analgesic activity

Analgesic activity of the compounds by Eddy's hot plate method was evaluated against Diclofenac Sodium as the standard the tail flick response was considered as the end point to remove the animals from the source of the pain stimulus. The basal reaction time (latency between the application of the stimulus and the response) of the control animals ranged between (2.2 ± 0.33 - 3.3 ±0.33) after treatment of the animals the basal reaction time was prolonged (statistically significant increase) by the compounds (P1, P2, P6, P7 and P8) which reached maximum levels at the 2ndhr. However all the compounds showed analgesic activity less than the reference standard.

Anti inflammatory activity

The result of anti-inflammatory activity showed significant reaction in paw volume by the compounds P_1 P_2, P_6, P_7 and P_8 when compared to control at ($p < 0.01$).

Table 4: Effect of anti-inflammatory activities of synthesized compounds in rats

Group	Treatment	Dose mg/kg	Before treatment	Paw volume (mean ± SEM)			
				0 min	60 mins	120 mins	240 mins
Group I	Control	0.5 ml DMSO	4.26±0.32	6.12±0.30	6.92±0.26	7.30±0.52	8.42±0.28
Group II	Standard	Diclofenac Sodium 10mg/kg	4.10±0.11	6.90±0.42	6.18±0.15	5.90±0.18	5.12±0.09
Group III	P1	compound 1 10mg/kg 0.5ml DMSO	4.26±0.22	7.10±0.58	6.22±0.26	5.82±0.36	5.26±0.16
Group IV	P2	compound 2 10mg/kg 0.5ml DMSO	4.16±0.26	7.05±0.66	6.30±0.32	5.75±0.30	5.38±0.22

Group V	P6	compound 3 10mg/kg 0.5ml DMSO	4.11±0.18	7.01±0.18	6.38±0.42	5.70±0.28	5.20±0.36
Group VI	P7	compound 4 10mg/kg 0.5ml DMSO	3.90±0.20	6.92±0.26	6.40±0.36	5.68±0.32	5.18±0.20
Group VII	P8	compound 5 10mg/kg 0.5ml DMSO	4.01±0.22	6.82±0.36	6.32±0.30	5.60±0.28	5.15±0.20

Table 5: Effect of anti-inflammatory activities of synthesized compounds in rats

Treatment	Dose mg/kg	Increase in paw volume in mm (Mean ± SEM)	Inhibition of paw edema
Group I Normal saline	10ml/kg Normal saline	4.16± 0.22	----------
Group II	positive control 10mg/kg diclofenac sodium	1.02± 0.11	75.48%
Group III P1	compound 1 10mg/kg 0.5ml DMSO	1.00±0.09	75.96%
Group IV P2	compound 2 10mg/kg 0.5ml DMSO	1.22±0.21	70.67%
Group V P6	compound 3 10mg/kg 0.5ml DMSO	1.09±0.21	73.79%
Group VI P7	compound 4 10mg/kg 0.5ml DMSO	1.28±0.16	69.23%
Group VII P8	compound 5 10mg/kg 0.5ml DMSO	1.14±0.26	72.59%

Values are expressed as mean ± SEM when compared to control at ($p < 0.01$).

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REFERENCES

1. Pandeya SN, Yogeswari P, Sriram D, and Nath G, Ind. J. Pharm. Sci., 64, May – June, 2002: 209 – 212.
2. Padhy AK, Bardhan M, Panda CS, Ind. J. Chem., Vol.42B, 2003: 910.
3. Salama MA, and El-Essa SA, Ind. J. Chem., Vol.42B, January 2003: 173 – 179.
4. Basavaraja KM, Patil VM and Agasimundin YS, Ind. J. Hetero. Chem. Mahadevan KM, Vaidya VP, and Vagdevi HM, Ind. J. Chem., Vol.42B, August 2003: 1931 – 1936.
5. Shishoo CJ, Ravikumar T, Jain KS, Rathod IS, Gandhi TP, and Satia MC., Ind. J. Chem., Vol.38B, September 1999: 1075 – 1085.
6. Veerachamy alagarsamy, Durairaj Shankar and Viswas raja saloman, Department of Pharmacy (ARISM), Sastra University, Tirumalaisamudram, Thanjavur, India.
7. Gordon BL, Donald AE, Lees, Banitt, Kenneth BL, Stephan, MA, Palmer JR, Tustin JM, J. Med. Chem., 1995; 38: 4161
8. Abdou O abdelhamid, Hussain F ZOhdi and Mohamoud Mziada, Ind. J. Chem., Vol.40B, April 2001: 284, 289.
9. Baheti KG, Jadhav JS, Suryavanshi AT, and Kuberkar SV, Ind. J. Chem.,Vol.44B, April 2005:834 – 837.
10. Naresh kumar, Sangeta Tiwari and Ashok, K. yadav, Ind. J, Chem., Vol.46B, April 2007: 702 – 706.
11. Singh Y, Nayal SS, Rawat BS, and Mahesh pal, Ind. J. Chem., Vol.41B, May 2002: 1056 – 1060.
12. Karale BK, and Gill CH, Ind. J. Chem., Vol.41B, September 2002: 1957 – 1959.
13. Pasha MA, Ramachandra swamy N, and Jayashankara VP, Ind. J. Chem.,Vol.44B, April 2005: 823 – 826.
14. Sheriff A, Rostom H, Hesham T, Fahmy Y, Manal N, Saudi S, Scientia Pharmaceutica, 2003; 71: 57.
15. John R. Dyer, Application of absorption spectroscopy of organic compounds, Prentice-Hall of India (P), New Delhi,1969, 1st edition, 33
16. Robert M. Silverstein, Francis X. Webster, Spectrometric identification of organic compounds, John Wiley and sons, Inc.1998, 6th edition.
17. Eddy NB, Studies of morphine and codine and their derivaties. J. Pharmacol.1932;45:339.
18. Kamant JV and Rana AC. Indian Drugs. 2003;40:292.
19. Winter CA, Risley EA, Nuss GW. Carrageenan-induced oedema in hind paw of the rat as an assay for anti-inflammatory drugs. Proc Soc Exp Biol Med 1962; 111: 544-547.
20. Chattopadhyay RN. Chattopadhyay R,Roys, Moitra SK. A Simple method for plethysmometric measurement of paw volume of small laboratory animals in evaluation of anti-inflammatory effects. Bull calcutta school Trop Med, 1986, 34: 5-8
21. Vinegar R, Schreiber W, Higo R, Biphasic development of Carrageenan oedema in rats. J.Pharmacol Exp Ther 1969; 166: 96-103.

