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Behavior of Adrenal Ectomized Rats in Chloro-Hydroxy Derivatives of Phenothiazine

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Abstract – Several new Chloro-hydroxy derivatives of phenothiazine such as N[10] -[e - (Benzlidene hydrazino)acetyl] 8-chloro 3-hydroxy phenothiazine 2-carboxyalic acid and 2-Substituted aryl, 3- N[10] [(acetyl amino)1,3-thiazolidin 4-ones] 8-chloro 3-hydroxy phenothiazine 2-carboxyalic acid have been synthesized and tested for their antimicrobial and anti-inflammatory activities. Structure of the synthesized compounds have been elucidated on the basis of their elemental analysis and spectral data. 8-chloro 3-hydroxy phenothiazine 2-carboxyalic acid produced a significant inhibition of granuloma growth in Carrageenan filter paper granuloma assay in adrenal ectomized rats.

Keywords – Antimicrobial and Anti-Inflammatory Activities, Elemental Analysis, Spectral Data, Carrageenan Filter Paper.

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INTRODUCTION

Phenothiazines are mild cholinesterase inhibitors and may therefore enhance the action of depolarizing neuromuscular blocking drugs[1] and ester- linked local anesthetics[2]. Derivatives of Phenothiazine are highly bioactive and have widespread use and rich history.

Phenothiazine derivatives are associated with potent biological activities such as anti-inflammatory[3], analgesic[4], insecticidal[5], fungicidal[6], bactericidal[7] and trypanocidal[8], anticonvulsant[9], diutatic[10], antiallergic[11] and neuroleptic[12].

Chloro- hydroxy derivatives of phenothiazine is 8-chloro, 3-hydroxy, 10-H phenothiazine 2-carboxyalic acid on treated with chloroacetyl chloride afforded N^{10}-chloroacetyl, 8- chloro, 3-hydroxy phenoyhiazine 2 - carboxyalic acid **I.** Which on reaction with hydrazine hydrate resulted in the formation of N^{10} – Hydrazinoacetyl, 8-chloro, 3-hydroxy phenothizine 2-carboxyalic acid **II.** The compound II which on condensation with various substituted aromatic carbonyls yielded substituted N^{10} -[α-(Benzylidene hydrazino) acetyl] 8-chloro,3- hydroxy phenothiazine 2-carboxyalic acid **III.** The compound III on reaction with thioglycolic acid underwent dehydrative annulations afforded 2- substituted aryl 3-N^{10} [(acetylamine) 1- 3 thiazolidin 4- ones] 8- chloro 3-hydroxy phenothiazine 2- carboxyalic acid **IV.**

ANTI- INFLAMMATORY ACTIVITY

Carrageenan is a natural polysaccharide obtained from edible red seaweeds. Carrageenan induced inflammation test[13] is widely used to investigate anti inflammatory activity of any compound and constitutes a simple and routine animal model for evaluation of pain at the site of inflammation, without any injury or damage to the inflamed tissue.

Carrageenan induced rat paw oedema male wister rats (g) divided into 6 animals in each groups used for study induced by subcutaneous injection of a 0.1 ml of 1% freshly prepared carrageenan in saline in the right hind paw of rats and sub- plantar- injection of histamine at dose of 0.1ml of 1%. Carrageenan solution (0.1ml/paw) was injected subcutaneously into planter surface of the right hind paw of rats. The paw volume of rats in control, standard and test groups was measured with the help of the Plethysmometer during the interval of 30, 60, 120, 180, 240 min.

EXPERIMENTAL SECTION

Synthesis of N^{10} - chloroacetyl, 8- chloro – hydroxy – phenothiazine - 2- carboxyalic acid (I) → A mixture of 8-chloro, 2-hydroxy, 10-H phenothiazine 2-carboxyalic acid (3.0ml) on electrophilic substitution by chloroacetyl chloride (0.5ml) was refluxed on a steam bath for about 10 hr. The solid thus obtained was dried , purified and crystalized from ethanol (yield 60%), M.P. 140- 144^{0}C and Calcd for $C_{15}H_9NSCI_2O_4$: C,61.32; H,5.46; N,4.25%; Found : C,1.38; H,5.40; N,4.23%; IR 1738(>C=0), 2175 and 2236 (>N-C=0), 3035, 1575, 1550, 1475, 870 (Phenothiazine nucleus), 764(C-CI) and 690 (C-S-

C). ^{1}H-NMR: 4.38 (S, 2H-CH_2), and 6.80-799 (m,8H,Ar-H).

Synthesis of N^{10}-Hydrazinoacetyl, 8- chloro, 3-hydroxy phenothiazine 2- Carboxyalic acid (II) → A mixture of (0.5ml) 1 and hydrazine hydrate (0.8ml) on methanol (40ml) was refluxed on a stream bath for about 10 hr. Methanol was then removed under reduced pressure and the solid thus obtained was dried, purified and crystallized from ethanol (yield 78%) , M.P. 160-163^{0}C ; And Caled for $C_{15}H_{12}N_3SC10_4$: C,62.47; H,4.47 ; N, 9.83%; Found: C,62.87; H,4.62; N,9.54% . IR: 3033, 1558,860 (phenothiazine nuclear), 3336 and 2885 (-CH_2NH), 3349(NH-NH_2), 2237 and 1782 (>N-C=0) and 712(C-S-C). ^{1}H-NMR : 4.36 (S,2H-CH_2), 4.44(S,2H,-NH_2), 7.72 (S,1H,-NH).

Synthesis of N^{10} - [α-(Benzylidenohydrazino) acetyl 8-chloro, 3- hydroxy phenothiazine 2-carboxyalic acid (III). → A mixture of compound 2(2.0ml) and substituted aromatic (0.5ml) with 4.5 drops of glacial acetic acid was refluxed on a water bath for about 12 hrs. Cooled, evaporated to obtain a residue and was purified. The product was recrystallised from methanol (yield 80%), M.P. 142-146^{0}C. Anal. Calcd. For $C_{22}H_{15}N_3SO_4^{-R1}$: C,68.74; H,4.37; N,9.65% Found: C,69.58; H,4.33; N,9.67, IR: 3032, 1545, 870, 735 (Phenothiazine and benzene nuclei) , 3340 and 2887 (-CH_2NH) , 2272 and 2235 (>N-C=0) and 1546 (N=CH). ^{1}H-NMR : 4.38 (S,2H-CH_2), 4.93 (S,1H, N=CH), 7.05-8.08 (m, 13H, Ar-H).

Synthesis of 2- Substituted aryl –3-N^{10} [(acetylamino) 1,3- Thiazolidin, 4- ones] 8- chloro, 3-hydroxy phenothiazine 2- carboxyalic acid (IV). → A mixture of compound 3 (2gm) in methanol and thioglycolic acid (1.15gm) with a pinch of anhydrous $ZnCl_2$ was refluxed for about 10 hours on a water bath. The separated solid was filtered purified and Crystallised form methanol (yield 80%), M.P. 143-145^{0}C, Anal Caled for $C_{24}H_{17}N_3S_2O_5^{-R1}$: C,62.39; H,4018; N,8.67% Found: C,63.37; H,4.15; N,8.64%; IR : 3037, 1569, 870, 707 (Phenothiazine and benzene nuclei), 3420, 3340 and 2887 (-CH_2NH), 2240 and 1785 (>N-C=0) and 1710 (C=0 cyclic) ^{1}H-NMR : 3.15 (S,1H,-N-CH), 3.52 (S,2H,-CH_2-S), 4.38(S,2H,-CH_2), 7.12 – 8.10 (m, 13H Ar-H).

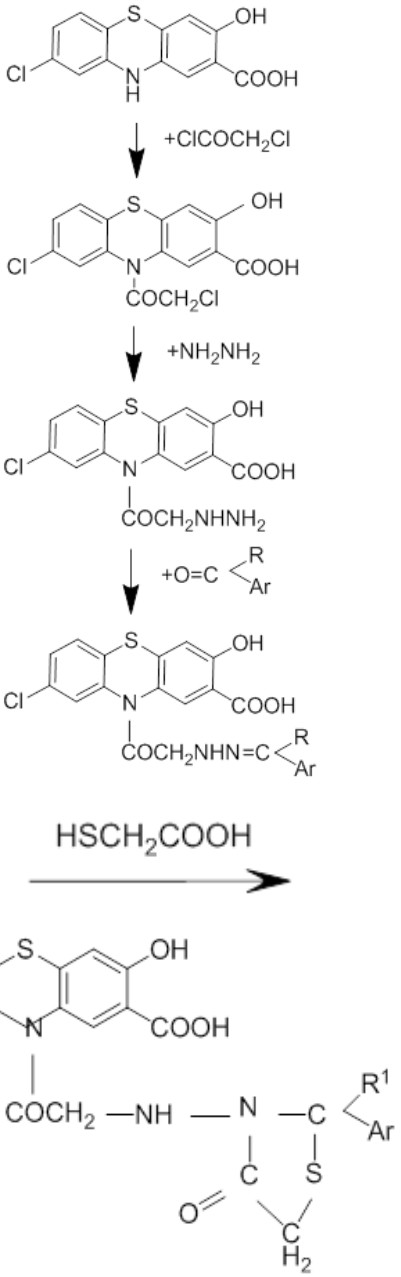
RESULT AND DISCUSSION

This section includes the result and discussion of anti-inflammatory activity of the synthesized products derived from phenothiazine. Some of the products exhibited pronounced biological activity. Structure of the synthesized compounds has been elucidated on the basis of their elemental analyses and spectral data.

Anti-inflammatory activity data of the Synthesized compounds VI-1-7

Comp. code no.	Before carrageenan administration	After drug administration (mean±SE) Volume of Paw (ml) 1 Hour	2Hours	3Hours	4Hours	5Hours	Total increase in paw volume after 5 hours	Percent inhibition
VI-1	0.66 ± 0.04	0.71±0.02	0.77±0.03	0.83±0.02	0.88±0.02	0.94±0.03	0.28 ± 0.02	6.66
VI-2	0.62 ± 0.02	0.68±0.01	0.72±0.02	0.79±0.02	0.34±0.02	0.89±0.02	0.27 ± 0.02	10. 00
VI-3	0.64 ± 0.03	0.69±0.02	0.73±0.02	0.80±0.02	0.87±0.02	0.91±0.02	0.27 ± 0.02	10. 00
VI-4	0.60 ± 0.02	0.72±0.02	0.78±0.02	0.83±0.02	0.89±0.02	0.93±0.03	0.25 ± 0.03	16.66
VI-5	0.74 ± 0.03	0.78±0.02	0.84±0.02	0.88±0.02	0.89±0.02	0.95±0.02	0.21 ± 0.02	30. 00
VI-6	0.71 ± 0.02	0.77±0.02	0.85±0.02	0.89±0.02	0.92±0.03	0.97±0.02	0.26 ± 0.02	13.33
VI-7	0.73 ± 0.02	0.76±0.02	0.82±0.01	0.87±0.02	0.89±0.02	0.94±0.02	0.21 ± 0.02	30. 00
Control	0.66 ± 0.03	0.74±0.02	0.78±0.02	0.83±0.02	0.92±0.01	0.96±0.02	0.30 ± 0.01	-
Standard	0.69 ± 0.02	0.73±0.02	0.76±0.02	0.79±0.02	0.82±0.02	0.85±0.02	0.16 ± 0.02	46.65

Standard: phenylbutazone.



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