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SYNTHESIS AND ANTI INFLAMMATORY ACTIVITY OF 1-(2-BENZYL-10H-PHENOTHIAZIN-10YL)-3-CHLOROPROPAN-1-ONE

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ABSTRACT

Phenothiazines are important class of heterocyclic compounds possessing interesting biological and Pharmacological properties as antipsychotic, anti-cancer, anti-bacterial, anti-viral, antipyretic, antiarrhythmic, tranquilizing, muscle relaxing, anticonvulsant, anti-diabetic, and anti-fungal agents. Phenothiazine is related to the thiazine class of heterocyclic compounds. It is a prototypical pharmaceutical lead structure in modern medicinal chemistry.

KEYWORDS: Phenothiazine, benzaldehyde, spectral analysis, anti inflammatory.

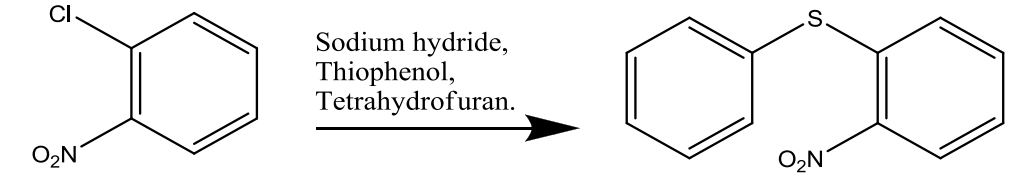
INTRODUCTION

Phenothiazine is the chemical species of fused heterocyclic ring compound with one nitrogen and one sulphur are replacing carbon -hydrogen units in the 9,10-dihydro anthracene ring structure. It is used in chemical manufacturing as a stabilizer or inhibitor.

MATERIALS AND METHODS

Scheme of the work

Step:1 Synthesis of (2-Nitro Phenyl) (Phenyl) Sulfone.



1-chloro-2-nitrobenzene

(2-nitrophenyl)(phenyl)sulfane

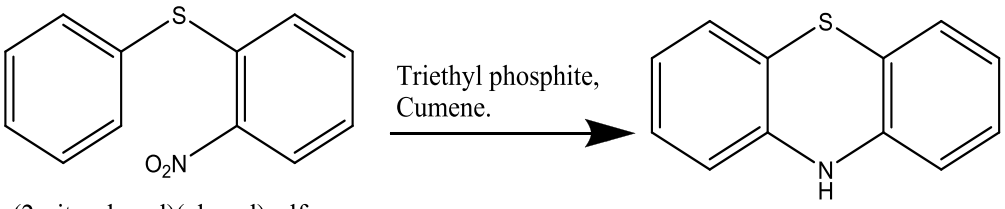
A mixture of O-Chloro-7-nitro benzene (0.1 mole), tetrahydrofuran (0.1 mole), sodium hydride (0.1 mole) & ethanol (70 ml) reflux for 4 hrs.

After completion of reaction, excess of solvent is removing under reduced pressure.

The solution is washed with 0.1N NaOH.

The reaction mixture is poured into crushed ice, the product is wash with water repeatedly, dried & recrystalline from ethanol.

Step: 2 Synthesis of Phenothiazine



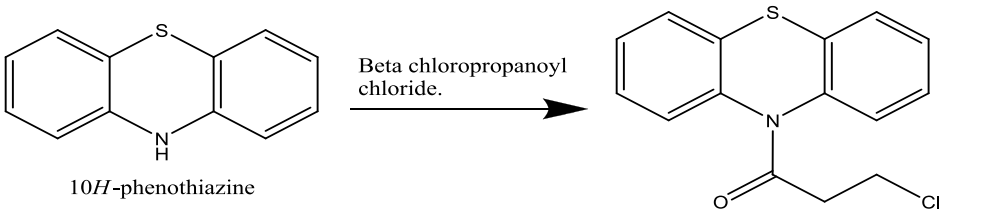
(2-nitrophenyl)(phenyl)sulfane

10*H*-phenothiazine

Equimolar quantities of compound-1 and tri ethylamine were reflux in ethanol using pyridine as catalyst for 8 hr.

The solution mixture is concentrated and poured into crushed ice .The product is washed with water repeatedly, dried and recrystallized from ethanol.

STEP: 3 Synthesis Of 3-Chloro-1-(10h-Phenothiazine-10-Yl) Propane-1-One.



10*H*-phenothiazine

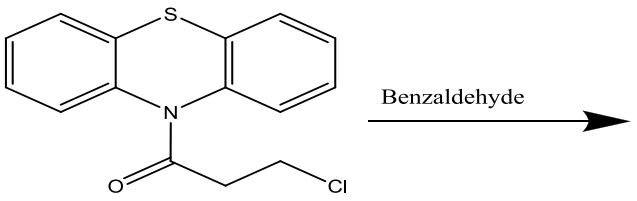
3-chloro-1-(10*H*-phenothiazin-10-yl)propan-1-one

Compound-2 (0.1 ml) in ethanol (30ml), 2 ml of hydrazine hydride is added to the mixture is added 50ml of 1,2-dicloroethane.

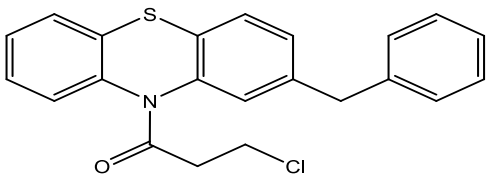
The mixture is maintained under reflux for 8 hrs.

After cooling, the mixture is poured in ice and solid formed is collected by filtration, washed with cold water and recrystallized with ethanol.

Step: 4 Synthesis Of 1-(2-Benzyl-10h-Phenothiazin-10yl)-3-Chloropropan-1-One.



3-chloro-1-(10*H*-phenothiazin-10-yl)propan-1-one



1-(2-benzyl-10*H*-phenothiazin-10-yl)-3-chloropropan-1-one

Compound-3 (0.1mole) in 20 ml of ethanol .it is added on equimolar amount of benzaldehyde in presence of acetic acid.

The mixture is maintained and reflux of 4hr then the reaction mixture is poured in cold water and precipitate is formed and washes with ethanol recrystallize in ethanol and DMF.

Physical characterization

- ✓ Molecular formula : $C_{22}H_{18}ClNOS$
- ✓ Molecular weight (gm) : 379.90g/mol
- ✓ Soluble in Methanol, Ethanol and DMF.
- ✓ Melting point : 110ºC
- ✓ Melting points were determined using Veego Digital melting point apparatus.
- ✓ The purity of synthesis compound was monitored on TLC.
- ✓ Absorbent used : Precoated Silica gel- G plate
- ✓ Mobile Phase : Chloroform : Methnol (3:7)
- ✓ R_f value: 0.83

Biological screening

***IN-VITRO* ANTI-INFLAMMATORY ACTIVITY**

Inflammation is normal protective response to tissue injury caused by physical trauma, noxious chemicals or microbiological agents and local response of living mammalian tissue to injurious agents, which may be due to physical agents like heat, cold, radiation, trauma;

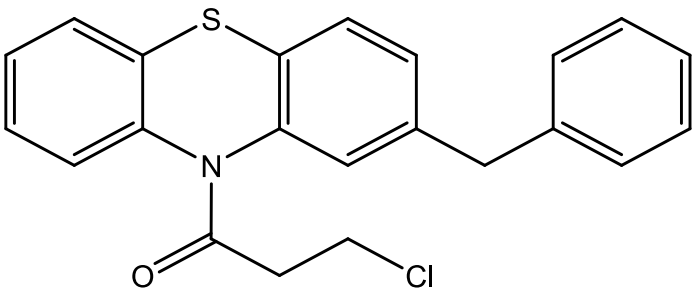
Chemical agents like organic and inorganic; Infective agents like bacteria, virus, parasites; Immunological agents like antigen-antibody reactions, cell mediated reaction. In the present study invitro anti-inflammatory activity was checked for the synthesized compounds.

Reagents

- HRBC suspension : 10%
- Alsiever solution
- Isotonic saline : 0.85%
- Phosphate buffer : 0.15M, pH-7.2
- Hypotonic saline : 0.36%

Standard: Diclofenac sodium.

Spectral analysis



IUPAC Name

1-(2-benzyl-10*H*-phenothiazin-10-yl)-3-chloropropan-1-one

^{1}HNMR Interpretation

^{1}HNMR Spectral data Absorption position (in PPM)	
7.02 - 7.49	m, 4H, CH
6.76 – 6.86	d, 6H, CH
5.35	s, 2H, CH_2
4.0	d, 2H, NH

RESULTS AND DISCUSSION

Synthesis

The present study report the synthesis of phenothiazine derivatives nucleophillic substitution of 1-chloro nitro benezene with sodium hydride and thiophenol was carried out stepwise at different temperature by various amines and aldehydes. The first step involves substitution of thiophenol and the next by cumene. The final phenothiazine derivative in the synthesized

compound 3 was replaced by benzaldehyde. Since the report regarding this compound suggest a phenothiazine posses a good bioactive moiety.

Physical Characterization

Melting points of the synthesized compound was taken in open capillary tubes and was uncorrected and were found to be in the range 105-125˚C.

TLC was performed using precoated silica gel plates of 0.25mm thickness. Eluents used were chloroform; methanol (3:7) spots were visualized in U.V. light.

At room temperature solubility of newly synthesized compounds were determined by various organic solvents and it was found that all compounds were freely soluble in Methanol, Ethanol and DMF.

***IN-VITRO* ANTI-INFLAMMATORY ACTIVITY**

The synthesized compounds are to be used for this study. They are to be made into doses of 1000 µg/ml with DMSO (5.0%) solution. Diclofenac sodium is taken as standard. The reaction mixture (4.5 ml) consist of 2 ml of hypotonic saline (0.36% sodium chloride), 1 ml of 0.15 M phosphate buffer (Ph 7.4), 1 ml of the test solution (1000 µg/ml) in normal saline and 0.5 ml of HRBC suspension in normal saline. For control test, 1 ml isotonic saline is to be used instead of test solution while product control lacked RBC. The mixture is then incubated at 56˚C for 30 minutes, then to be cooled under running tap water and centrifuged at 3000 rpm for 20 minutes. The absorbances of the supernatants are read at 560 nm. Percent membrane stabilization activity is calculated as follows:

$$\% \text{ stabilization} = \frac{\text{100-OD of test control-OD of test sample}}{\text{OD of test control}} \times 100$$

S.No	Compound code	Percentage Stabilization
1	S	80
2	STD	76.4

CONCLUSION

The compound was subjected to *in-vitro* anti-inflammatory activity using diclofenac sodium as a standard by HRBC Membrane Stabilization Method. Anti inflammatory activity revealed that the synthesized compound has shown significant anti-inflammatory activity when compared with that of standard drug.

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