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A Simple Synthesis and Biological Evaluation of Heteroannulated Some Novel Azocine Derivatives

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Abstract: *Azocine is the chemical species of unsaturated eight membered heterocyclic ring with nitrogen as hetero atom. The IUPAC name of Azocine is Azacyclooctatetraene. The saturated or partially saturated azocine rings form the core structure of a group of opioid compounds sometimes known as Azocines. Azocine rings are found in many Natural products. The starting compounds for the synthesis of azocine is Ethyl-3-oxobutanoate. The N structural assignments are supported by NMR, IR spectroscopy and chromatography Thin Layer Chromatography and Paper Chromatography. These include cyclazocine, pentazocine and phenazocine. The compounds possessing interesting biological and pharmacological properties as anti-inflammatory, anticancer, anti- bacterial, anti-fungal, anti-viral, antiIndia. arrhythmic, tranquilizing, muscle relaxing and anti-diabetic agents.*

Keywords: Azocine, synthesis of azocine derivatives, Physical property, structural conformation and Biological Screening

I. INTRODUCTION

Medicinal Chemistry is the applications of chemical research techniques to the synthesis of pharmaceuticals. During the early stages of medicinal chemistry development, scientists were primarily concerned with the isolation of medicinal agents found in the plants. Today, scientists in this field are also equally concerned with the creation of new synthetic compounds as drugs. Medicinal chemistry is almost always geared toward drug discovery and development. They also work on improving the process by which other pharmaceuticals are made. It concerns the discovery, the development, the dentification and the interpretation of the mode of action of biologically active compounds at the molecular level1.

1. AZOCINE

Medium-sized nitrogen heterocyclic is an extremely important class of compounds. The term "medium ring" is usually used to refer to alicyclic compounds with a ring size of from 8 to 11. The primary concern of this chapter is eight-membered azaheterocycles, azocines. Azocines are a diverse class of compounds, that frequently occur as biologically active compounds as well as being widely used in synthetic chemistry. Azocine is a heterocyclic organic compound with the molecular formula C7H7N. It consists of an unsaturated eightmembered ring having seven carbon atoms, one nitrogen atom and four double bonds. Saturated or partially saturated azocine rings form the core structure of a group of opioid compounds sometimes known as azocines. These include cyclazocine, pentazocine, and phenazocine. The fully saturated analog of azocine is azocane. Although foundations providing pioneering work on azocines had been started in the 1920s and 1930s, only limited systematic or comparative studies of azocines as a class have been done. Azocines have received more attention because of their increasing usefulness both as synthetic intermediates and as therapeutic agents.

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1.1 STRUCTURE AND NOMENCLATURE:

Eight-membered rings with one nitrogen atom can be classified broadly into five categories: unsaturated, partially saturated, fully saturated, bridge-head, and fused ring system. The most commonly used systematic nomenclature for eight- membered heterocyclic compounds is the Hantzsch-Widman system. According to this system, the compound with four noncumulative double bonds is named azocine, with the prefix "aza" indicating the nitrogen atom, followed by the stem "ocine" indicating the ring size and unsaturation. The nitrogen atom takes the atom number one. Partially saturated systems are expressed by the prefixes dihydro-, tetrahydro-, hexahydro-, and octa hydro- with azocine. For example, is named 1,8-dihydroazocine. The fully saturated system is named "azocane" or "perhydroazocine". The names azacyclooctane and heptamethyleneimine have also been used in the literature. The most prevalent term is 'azocine' with suitable prefix (es).

1.2 STRUCTURE:

Another name: Azacyclooctatetraene

1.3 PROPERTIES:

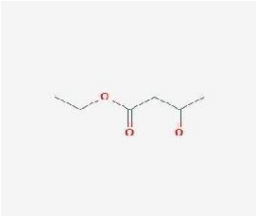
Molecular formula - C7H7N
Molecular weight - 105.140 g·mol−1
Melting point - −37 °C
Boiling point - 138 °C
Solubility - Acetone, chloroform
Monoisotopic Mass - 105.057849 g/mol

II. STARTING MATERIAL

ETHYL 3-OXO BUTANOATE

Ethyl3-oxobutanoate is also known as, ethyl acetoacetate (CH3COCH2COOC2H5), and also called acetoacetic ester, an ester widely used as an intermediate in the synthesis of many varieties of organic chemical compounds. Industrially it is employed in the manufacture of synthetic drugs and dyes. The organic compound ethyl acetoacetate (EAA) is the ethyl ester of acetoacetic acid. It is mainly used as a chemical intermediate in the production of a wide variety of compounds, such as amino acids, analgesics, antibiotics, antimalarial agents, antipyrine and aminopyrine, and vitamin B1; as well as the manufacture of dyes, inks, lacquers, perfumes, plastics, and yellow paint pigments.

STRUCTURE:



Other name: Ethyl acetoacetate, acetoacetic acid

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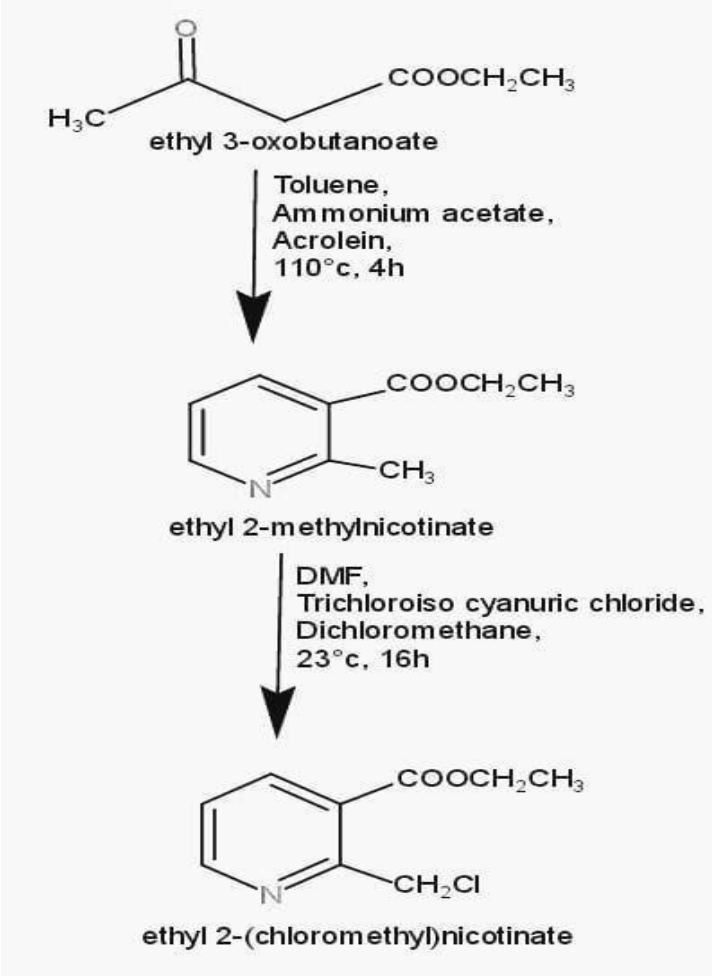
PROPERTIES:

Molecular formula - C6H10O3
Molecular weight - 130.142 g/mol
Melting point - -45°C
Boiling point - 180.8°C
Solubility - Benzene, Chloroform

III. SCHEME OF WORK



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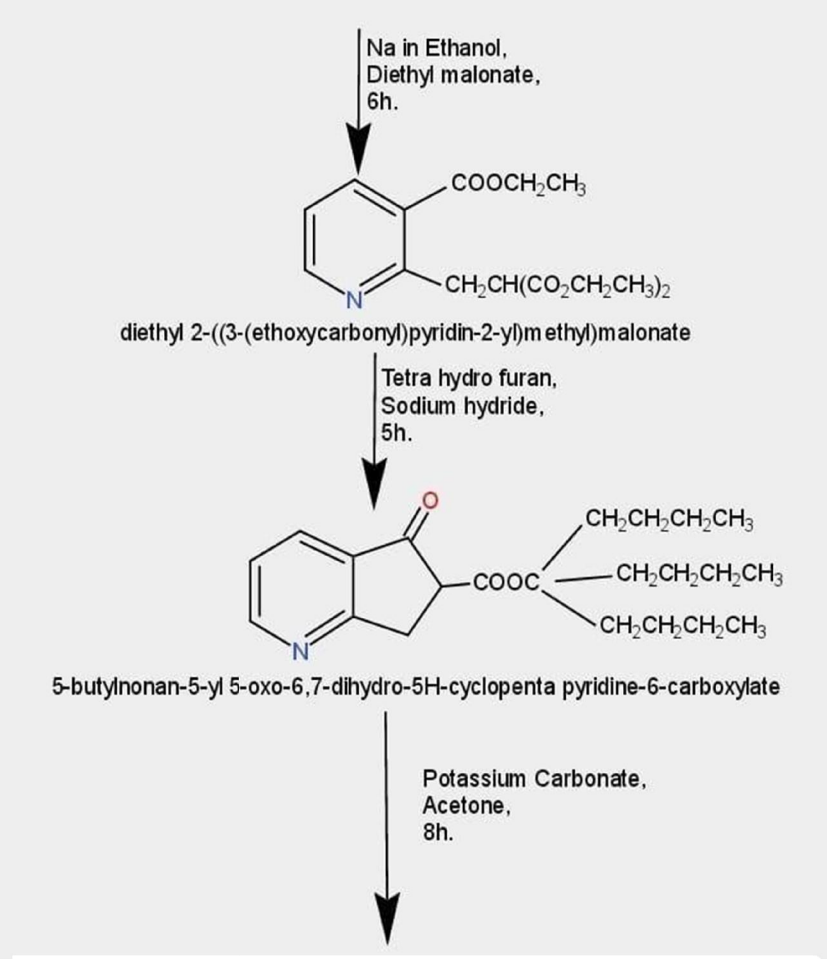

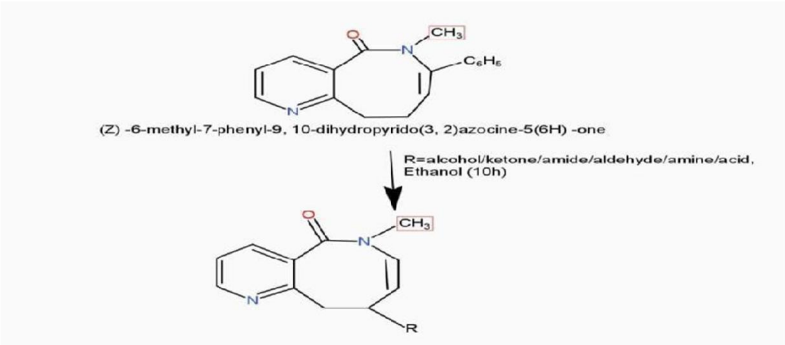

IV. PROCEDURE

STEP- 1: GENERAL PROCEDURE FOR AZOCINE SYNTHESIS

1. A mixture of ethyl 3-oxo butanoate (0.1mole), toluene (0. 1 mole), acrolein (0.1mole) and ethanol (70 ml) reflux for 4 hours.
2. Ammonium acetate (0.5M) solution add drop wise with vigorous stirring.
3. The solution is washed with 0.1 N NaOH.

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4. The reaction mixture is poured into crushed ice, the product is wash with water repeatedly, dried and recrystallize from ethanol.

STEP- 2:

5. Equimolar quantities of compound 1, dimethyl formamide and tri chloro cyanuric chloride were reflux in ethanol using dichloro methane as a catalyst for 16 hours. the solution mixture is concentrated and poured on crushed ice. The compound thus obtained is filter, dry and recrystallize from ethanol.

STEP- 3:

6. Compound 2 (0.1mole) is to be dissolve in diethyl malonate (0.1mole) is reflexed sodium in ethanol for 5 hours. The content is evaporated to dryness and the product so obtained is washed with water repeatedly and recrystallized from ethanol.

STEP- 4:

7. Compound 3 (0.1mole) is to be dissolve in tetra hydro furan (50ml) which is to be added to sodium hydride (0.1mole) in acetone (50ml) and the contents to be refluxed in ethanol for5 hours. The reaction mixture is reduced to half of its volume and poured onto crushed ice. The product so obtain is wash with water repeatedly, dried and recrystallized from ethanol.

STEP- 5:

8. Compound 4 (0.1mole) is to be dissolved in potassium carbonate (0.5M) is refluxed in acetone for 8 hours. The content is evaporated to dryness and the product so obtained is washed with water repeatedly and recrystallized from ethanol.

STEP- 6: SYNTHESIS OF VARIOUS ACIDS/ ACETATES/ KETONES/ AMINES/ ALCOHOLS/ AMIDES

Azocine (0.1M), various acids/ acetates/ ketones/ amines/ alcohols/ amides (0.1M) were refluxed in ethanol (30ml) for 10hrs.

On cooling solid appears which is recrystalize from the mixture with ethanol

V. EXPERIMENTAL WORK

LIST OF SYNTHESIZED COMPOUNDS

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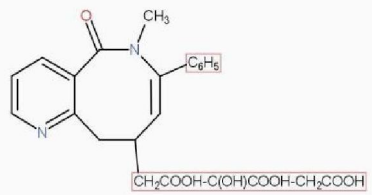
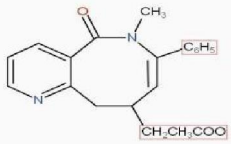
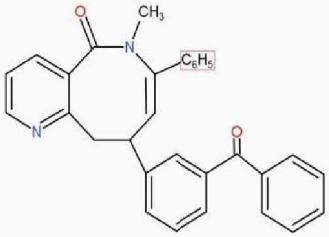
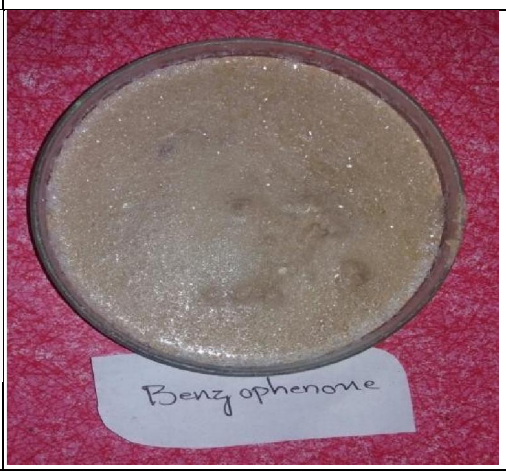
S4	 6-Methyl-7-phenyl-9,10 -dihydropyrido[3,2c]azocin-5(6H)9-citric acid	
S5	 6-Methyl-7-phenyl-9,10 -dihydropyrido[3,2c]azocin-5(6H)9-ethyl acetate	
S6	 6-Methyl-7-phenyl-9,10 -dihydropyrido[3,2c]azocin-5(6H)-9-benzophenone	

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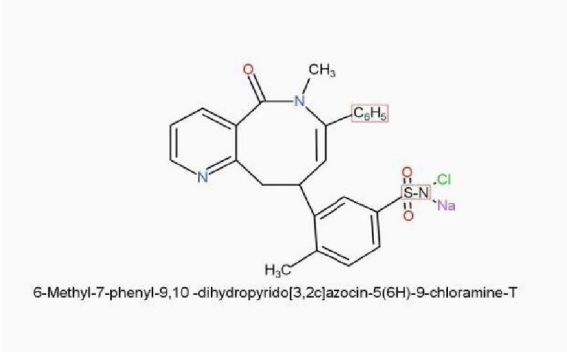
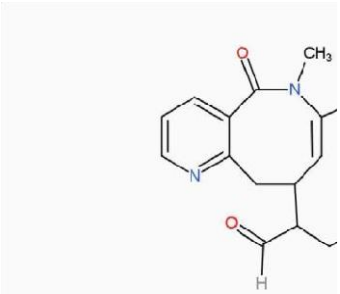
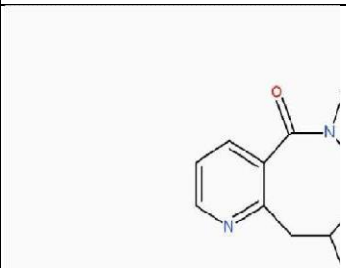
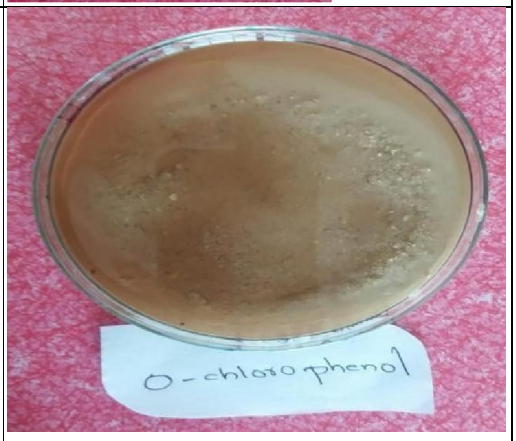
S7	 6-Methyl-7-phenyl-9,10 -dihydropyrido[3,2c]azocin-5(6H)-9-chloramine-T	
S8	 6-Methyl-7-phenyl-9,10 -dihydropyrido[3,2c]	
S9	 6-Methyl-7-phenyl-9,10-dihydropyrido[3,	

VI. PHYSICAL CHARACTERISATION

All the synthesized compounds are to be characterized by following methods:

• Melting point

Melting point will be measured in open-end capillary tube method by electrically heating melting point apparatus.

• Solubility

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At room temperature solubility of newly synthesized compound will be determined.

• Thin layer chromatography

The purity of new compound will be analyzed and reaction completion will be checked by thin layer chromatography by measuring Rf value of product.

• Analytical character

IR Sceptroscopy

6.1. Solubility

At the room temperature, solubility of all synthesized compounds was determined and shown in the table no.2

Table No.2

S.NO	DERIVATIVES											
1	PHENYL ACETIC ACID	_	_	+ +	-	-	+ +	+ +	+ +	+ +	+ +	+ +
2	4-AMINO BENZOIC ACID	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +
3	PICRIC ACID	-	-	+	-	+ +	+ +	+ + +	+ +	-	+ + +	+ + +
4	CITRIC ACID	-	+ +	+ +	+ +	+	+	+ +	+ +	+ +	+ +	+ +
5	ETHYL ACETATE	-	-	-	+ +	-	+	-	+	_	+ +	+ +
6	BENZO PHENONE	+ +	+ +	+ +	+ +	+ +	+ +	+	+ +	+ +	+ +	+
7	CHLORAMINE	+	-	-	+	+ +	+ +	+ +	+ +	+ +	+ +	+ +
8	GLUTAR ALDEHYDE	+ +	+ +	+ +	+	-	+ +	+	+ +	+ +	+ +	+ +
9	O-CHLORO PHENOL	-	+	-	+	+	+	+ +	+ +	+ +	+ +	+ +

6.2. Thin layer Chromatography

The purity of all synthesized compounds was monitored on TLC. Mobile phase : Butanol, Chloroform, water (4:7:5)
Detecting Technique : UV visible spectrophotometer

Rf = Distance travelled by solute / Distance travelled by solvent

Table No: 3

S. No	Compound Code	Rf value
1	S1	0.66
2	S2	0.71
3	S3	0.87
4	S4	0.54
5	S5	0.76
6	S6	0.82
7	S7	0.65
8	S8	0.79

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9	S9	0.84
10	S10	0.77

VII. BIOLOGICAL SCREENING

ANTI-INFLAMMATORY:

Non-steroidal anti-inflammatory drugs (NSAIDs) are the backbone for the management of pain which arises due to inflammatory diseases. These drugs suppress natural processes that are responsible for inflammation. A number of non-selective nonsteroidal anti-inflammatory drugs (NSNS-AIDs) such as indomethacin, ibuprofen, phenylbutazone, oxyphenbutazone, diclofenac, fenoprofen, caprofen, benoxaprofen, sulindac and aspirin etc. are available in the market. NSNSAIDs are nonselective inhibitors of the enzymes which are responsible for the conversion of arachidonic acid to prostaglandins. The use of these drugs is associated with adverse gastrointestinal effects, such as dyspepsia, gastroduodenal ulcers, gastritis and bleeding. NSAIDs are useful not only in the treatment of inflammatory diseases but can also prevent cancers, Alzheimer's disease, neurodegenerative and related dementias, immunodeficiency disorders, cataract formation, and even assist in the prevention of cardiovascular complications in diabetic patients. NSAIDs etodolac and nabumetone, which are mildly selective for COX-2 may lead to a somewhat lower risk for ulcers than traditional NSNSAIDs. Celecoxib, rofecoxib and meloxicam are known as COX-2 selective non-steroidal anti-inflammatory drugs. These drugs have improved gastrointestinal safety but may cause acute renal failure. Since serious side 1effects are associated with the use of various NSAIDs and COX-2 selective NSAIDs, they cannot be taken for long time continuously. Before describing different approaches about the development of safer anti-inflammatory drugs it will be worthwhile to review what is known as the mode of action of non-steroidal anti- inflammatory drugs.

MATERIALS AND METHOD

The chemicals used were purchased from Sri Devi chemicals, Bangalore, India, and the solvents were purified by distillation and residual water was removed. The test compounds azocine derivatives were synthesized.

HRBC Membrane Stabilization method:

The method involves the stabilization of human red blood cell membrane by hypotonicity induced membrane lysis.

Principle:

The lysosomal enzymes released during inflammatory condition produce a variety of disorders. The extra cellular activity of these enzymes is said to be related to acute or chronic inflammation. The antiinflammatory agents act by either inhibiting the lysosomal enzymes or by stabilizing the lysosomal membrane since the human red blood cell membrane are similar to lysosomal membrane components. The prevention of hypotonicity induced HRBC membrane lysis is taken as a measure of antiinflammatory activity of the drug.

Reagents:

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

Preparation of Alsievier's solution:

2g dextrose + 0.8g sodium citrate + 0.05g citric acid + 0.42g sodium chloride was made up with distilled water to 100ml.

Preparation of 0.5 ml of 10 % HRBC Suspension

To 3 ml of blood, add 3 ml of Alsievier's solution and centrifuge at 3000 rpm for 20 minutes then packed cells were washed with isotonic saline and later10% v/v suspension of the packed cells was made with isotonic saline.

Preparation of Hypotonic Saline: 0.36g of sodium chloride in 100 ml of distilled water.

Preparation of Isotonic Saline: 0.85g of sodium chloride in 100 ml of distilled water.

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Procedure:

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 (4.5ml) consist of 2ml hypotonic solution (0.36% sodium chloride). 1ml of 0.15 M of HRBC suspension in normal saline. For control test, 1ml isotonic solution 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 3000rpm for 20 minutes. The absorbances of the supernatants are read at 560 nm. Percent membrane stabilization activity as calculated as follows,

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

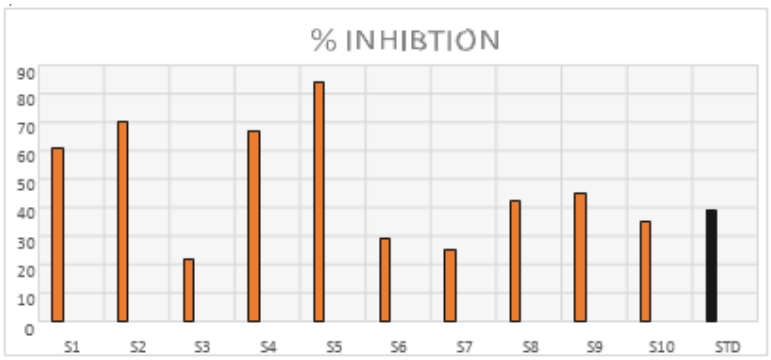
Anti-inflammatory activity of compounds S1-S10 in µg/ml

HRBC membrane Stabilization Method

Table No: 4

S. No	Compound code	Percentage Stabilization
1	S1	60.78
2	S2	70.14
3	S3	21.61
4	S4	67.03
5	S5	84.43
6	S6	29.30
7	S7	25.09
8	S8	42.12
9	S9	45.23
10	S10	34.79
11	STANDARD (Diclofenac)	39.08

HRBC membrane Stabilization method



VIII. RESULTS AND DISCUSSION

Synthesis

The present study reports the synthesis of azocine derivatives. Electrophilic addition of Ethyl 3-oxo butanoate in acrolein was carried out stepwise at different temperatures by various acids, ketone, amine, aldehyde, alcohol and

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amide groups. The final azocine derivative in the synthesized compound-5 was replaced by phenyl acetic acid, 4-amino benzoic acid, picric acid, citric acid, ethyl acetate, benzophenone, chloramine, glutaraldehyde, o-chlorophenol, formamide. Since the report regarding this compound suggest a azocine possesses a good biological activity.

Physical characterization

1. Melting point of the synthesized compound was taken in open capillary tubes and was uncorrected and were found to be in a range 94°C -130°C.
2. TLC was performed using precoated silica gel plates of 0.25mm thickness. Eluents used were chloroform, butanol and spots were visualized in U. V. light.
3. 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 Ethanol, DMSO, DMF, Acetone, chloroform, butanol.

In-vitro Anti-oxidant activity

All the compounds were subjected to in-vitro anti-oxidant activity using ascorbic acid as standard by two methods i.e., by Hydrogen peroxide scavenging method and nitric oxide radical scavenging method. Antioxidant activity revealed that all the synthesized compounds have shown significant anti-oxidant activity when compared with that of standard drug. The compound S7 and S10 showed more activity as compared to the other derivative.

In-vitro Anti-inflammatory activity

The synthesized compounds were subjected to in-vitro anti-inflammatory activity using HRBC membrane stabilizing method. The method involves the stabilization of human red blood cell membrane by hypotonicity induced membrane lysis. The prevention of hypotonicity induced HRBC membrane lysis is taken as a measure of antiinflammatory activity of the drug. The compound S10 showed better activity as compared to the standard diclofenac.

Rest of the compounds showed less activity.

IX. CONCLUSION

1. The synthesized compounds were subjected to various biological evaluations. The compounds were evaluated for antioxidant and anti-inflammatory studies revealed that the substitution of different acids, acetates, ketones, aldehydes, alcohols, amides, amines to parent azocine nucleus show the moderate activity.
2. Anti-oxidant activity revealed that all the synthesized compounds have showed significant antioxidant activity when compared with that of standard by hydrogen peroxide and nitric oxide scavenging method,
3. Anti-inflammatory activity revealed that all the synthesized compounds have showed significant activity when compared with that of standard by HRBC membrane stabilization method.

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