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Review Article

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A CONCISE REVIEW ON PYRAZOLINE DERIVATIVE FOR DIABETES MELLITUS

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ABSTRACT

The N-phenyl Pyrazoline ring with aryl substitution at third and fifth position exhibits better biological activities. The most common procedure for the synthesis of 2-pyrazolines is the reaction of an aliphatic or aromatic hydrazine with α,β-unsaturated carbonyl compounds. 2-Pyrazolines synthesized by the cycloaddition of diazomethane with substituted chalcones. 2-Pyrazolines can also be prepared by the condensation of chalcone dibromide with hydrazine. A number of diarylidene cycloalkanones on reaction with hydrazine hydrate produce pyrazolines. Dipolar cyclo addition of nitrilimines to dimethyl fumarate, fumaro nitrile and the N-aryl maleimides yields the corresponding pyrazolines. Reaction of Et 2-(phenylazo)-3-oxobutanoates with nicotinic acid hydrazide using glacial acetic acid gives pyrazoline derivatives. Diabetes mellitus is a common and very prevalent disease affecting the citizens of both developed and developing countries. It is estimated that 25% of the world population is affected by this disease. Most patients can be classified clinically as having either Type 1 diabetes mellitus. Historically, different substituted pyrazoles were known for their hypoglycemic activity, but in a search for novel structural classes of drugs inhibiting the activity of the ATP-K + channel of the beta cell pancreatic membrane, inducing the production of insulin we turned our attention to substituted pyrazoline derivatives.

KEYWORDS: Pyrazoline, Phenyl hydrazine, Acetophenone, Aldehyde, Diabetes mellitus.

INTRODUCTION

Among nitrogen containing five membered heterocycles, pyrazolines have proved to be the most useful framework for biological activities. The pharmaceutical importance of these compounds lies in the fact that they can be effectively utilized as antibacterial, antifungal, antiviral, antiparasitic, antitubercular and insecticidal agents. In 1967 Jarboe, reviewed the chemistry of pyrazolines, which have been studied extensively for their biodynamic behavior and industrial applications. Pyrazole belongs to the family of azoles i.e. five-membered ring containing nitrogen and carbon atom. Considerable attention has been focused on pyrazolines and substituted pyrazolines due to their interesting biological activities. The dihydro pyrazoles are called pyrazolines. Some substituted pyrazolines and their derivatives have been reported to possess some interesting biological activities such as anticancer, insecticidal, antibacterial etc. They have found to possess antifungal, antidepressant, anticonvulsant, anti-inflammatory, antibacterial and anti- tumor, anti diabetic properties.

Diabetes Mellitus

Diabetes mellitus is a disorder of carbohydrate, fat, protein metabolism. A defective or deficient insulin secretory response, which translates into impaired glucose use is a characteristic feature of Diabetes mellitus.

Classification and incidence

Diabetes Mellitus represents a group of disorder that have hyperglycemia as a common feature. it may arise secondarily from any disease causing extensive destruction of pancreatic islets, such as pancreatitis, tumors, certain drugs, iron overload (Hemochromatosis).

The most common and important forms of diabetes mellitus arise from primary disorders of the islet cell insulin system.

Types of Diabetes Mellitus

Primary (idiopathic)
Type-I (Insulin dependent Diabetes mellitus)
Type-II(Non-insulin dependent Diabetes Mellitus)

Secondary

Chronic Pancreatitis
Hormonal Tumors (eg. Pheochromocytoma).
Type-I DM is also called as Juvenile Diabetes.
Type-II DM is also called as Adult-onset diabetes.

Pathogenesis of Type I DM

This form of Diabetes results from a severe, absolute lack of insulin caused by a reduction in the beta cell mass. Type-I diabetes usually developed in childhood, becoming manifest and severe at puberty. Without insulin they develope serious metabolic complications such as acetic keto acidosis and coma.

The interlocking mechanism are resposible for the islet cell destruction.

1. Genetic susceptiblity
2. Autoimmunity
3. Environmental insult

Pathogenesis of type II DM

This type of DM is commonly seen in more than 30 years old. The metabolic defects that characterize type-II Diabetes are rearrangements in Beta cell secretion of insulin and an inability of peripheral tissues to respond to insulin.

MATERIAL AND METHODS

Preparation pyrazoline derivative

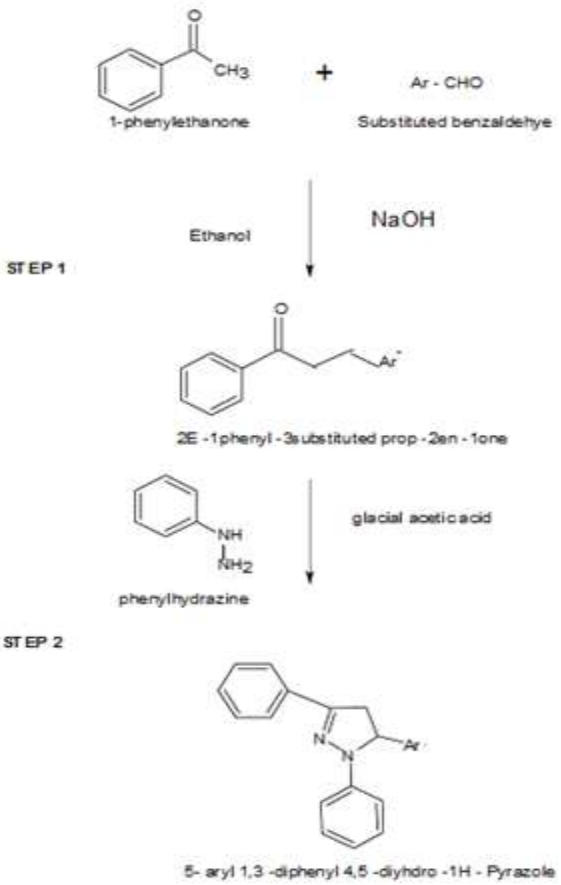
Step: 1

The solution of acetophenone (0.01M) and 4-chloro benzaldehyde (0.01M) in ethanol(20ml) at room temperature was add sodium hydroxide (0.01M) with constant stirring. The reaction mixture was stirred further until a precipitate was formed. The reaction mixture was diluted with ice water and neutralized by using (0.01M) diliuted hydrochloric acid. The product was filtered and recrystallized from ethanol.

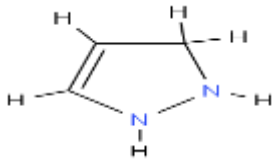
Step: 2

To (2E)-3-(4-chlorophenyl)-1-phenyl prop-2-en-1- one (0.0084) 20ml of 1,4-Dioxane and Phenyl hydrazine (0.024Mol) was added. To these mixture 2-3 drops of Sulphuric acid was added and the contents was allowed to get reflux for 4hrs. 5ml of glacial acetic acid was added; again reflux was done for next 2hrs. On cooling to room temperature the contents was poured on crushed ice. As a result the solid product was obtained which was recrystallized by using ethanol.

SCHEME OF REACTION-I



Pyrazoline Profile



Chemical Names:	2-Pyrazoline; 109-98-8; 4,5-Dihydro-1H-pyrazole; 1H-Pyrazole, 4,5-dihydro-; UNII-W1YN47L98V; EINECS 252-878-1 More...
Molecular Formula:	$C_3H_6N_2$
Molecular Weight:	**70.095 g/mol**

Evaluation of Antidiabetic Activit

(i) Evaluation of anti-diabetic activity by Non enzymatic glycosylation of haemoglobin assay

Procedure

The anti-diabetic activity of the compounds was evaluated by the non-enzymatic glycosylation of haemoglobin method. The assay is based on the inhibition of haemoglobin glycosylation by the compounds and subsequent formation of glucose haemoglobin complex.1Ml of compounds (100µg/ml, 200µg/ml, 300µg/ml) was combined with 1ml of 2% glucose solution then add 1ml of 0.06% haemoglobin and 0.02% Gentamycin(The solutions were prepared in 0.01M phosphate buffer(pH7.4) In case blank 1ml of phosphate buffer used in place of compounds. Mixture was incubated in dark place at room temperature for 72 hrs. The degree of glycosylation of haemoglobin was a measured at 520nm. Alpha- Tocopherol was used as standard drug for assay.

The percentage glycosylation of Haemoglobin was calculated by using following formula = **Test – Control / Test x 100.**

(ii) Evaluation of Anti-diabetic activity by Alpha amylase enzyme inhibition Assay

Procedure

The Anti-Diabetic activity of the compounds was evaluated by the α-amylase inhibition assay. The assay is based on the inhibition of α-amylase enzyme (α-amylase hydrolyses alpha-bonds of large alpha linked polysaccharide such as glycogen and starch to yield glucose and maltose. 1ml of compounds (100µg/ml, 200µg/ml, 300µg/ml) was combined with 1ml of potato starch(1%w/v) soution, 1ml of α-amylase enzyme(1%w/v) and 2ml of acetate buffer 0.1mM (Note:Potato starch solution, α-amylase enzyme solution and drug solution was prepared in acetate buffer). In case blank 1ml of Acetate buffer was used in the place of compounds. The above mixture was incubate for 1hr. Then 0.1ml iodine-iodide indicator was added in the mixture (635mg iodine and 1gm potassium iodide in 250ml distilled water). Absorbance was measured at 565nm in UV-Visible spectrosocopy. The anti-diabetic activity of each synthesized compounds was compared with the % inhibition of standard. The % Inhibition was calculated by using following formula,

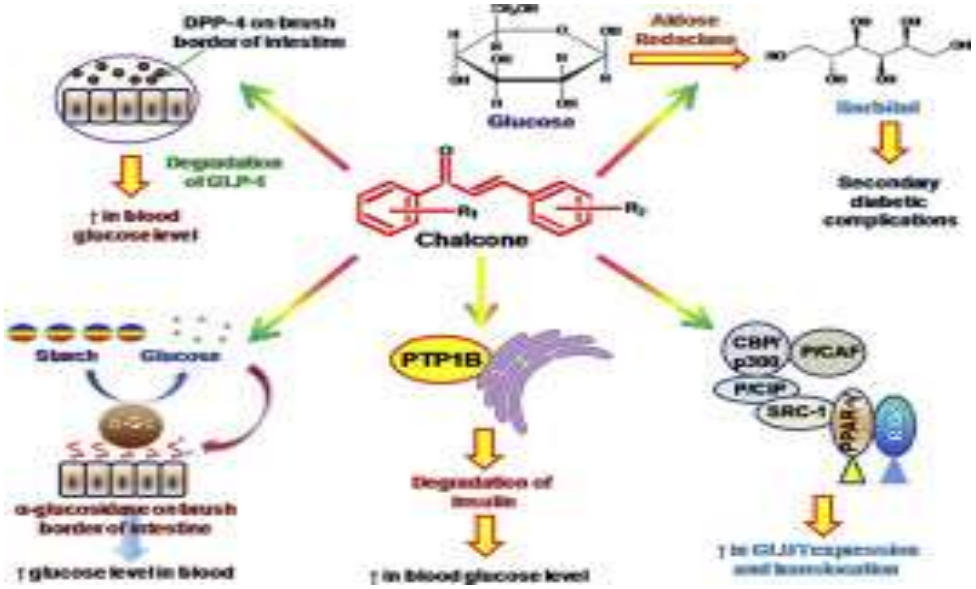
% Inhibition= Test - Control / Test x 100

(iii) Evaluation of Anti-diabetic activity by α-Glucosidase enzyme inhibition assay

Procedure

The anti-diabetic activity of the compound was evaluated by the α-glucosidase inhibition assay. The assay is based on the inhibition of α-Glucosidase enzyme and inhibits the formation of glucose level in blood. 1ml of compounds (100µg/ml, 200µg/ml, 300µg/ml) was combined with 1ml of 2%w/v of sucrose solution then add 1ml of 0.2M Tris Buffer PH8. The reaction was initiated by adding 1ml of α-Glucosidase enzyme (1U/ml) to it followed by incubation for 40 minutes at 35°C. Then the reaction was terminated by the addition of 2ml of 6N Hcl. Then the intensity of the colour was measured at 540nm. The % inhibition was calculated by using following formula.

% inhibition = Control - Test / Control x100



CONCLUSION

Pyrazolines have attracted particular interest due to the use of such ring system as the core structure in many drug molecules covering wide range of pharmaceutical and medicinal applications. The prevelance of pyrazole deravitives in pharmacologically effective drug molecules has increased the necess a site for needful ways to make them as an important lead moiety in heterocyclic chemistry. Several pyrazoline analogues are known to have biological properties which necessitated and inititated the research work in this field. Pyrazoline, afive-membered nitrogen bearing heterocyclic system can be denoted as pharmaceutically important molecules. The synthesis technique and exploration of pharmacological activities of pyrazolines have become a trending topic. Review result highlighted that there were several pyrazoline derivatives displayed significant anti diabetic activity and have higher activities compared to standard commercial drugs.

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