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Synthesis of Novel 2,4-Thiazolidinedione Derivatives and Study of their Various Activities

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Abstract: *The synthesis and antimicrobial activity of 2,4-thiazolidinedione derivatives were investigated. Thiazolidinediones are synthetic agonists for various transcription factors, such as peroxisome proliferator-activated receptor gamma (PPAR-γ). This suggests that the synthesized derivatives may exert their antimicrobial activity through interactions with PPAR-γ or other related pathways. Further studies are warranted to elucidate the exact mechanisms underlying the antimicrobial properties of these derivatives and their potential interaction with transcription factors like PPAR-γ. The 2,4-thiazolidinedione derivative exhibits a variety of biological activities, including antibacterial, anti-inflammatory, antitumor, anticonvulsant, and cardiotonic activities. Additionally, it shows promising anti-diabetic activity, which is particularly noteworthy given the growing prevalence of diabetes worldwide. These diverse pharmacological properties highlight the potential of 2,4-thiazolidinedione derivatives as versatile therapeutic agents for addressing a range of medical conditions. Further research into the mechanisms underlying these activities can help in optimizing the development of these derivatives for clinical use. The 2,4-thiazolidinedione was synthesized by thiourea and chloroacetic acid in presence of conc. Hydrochloric acid.*

Keywords: 2, 4-thiazolidinedione, antimicrobial activity

I. INTRODUCTION

Thiazolidinediones (TZDs), often referred to as "glitazones," were indeed introduced in the late 1990s as adjunctive therapy for type II diabetes mellitus and related conditions. They work by increasing insulin sensitivity in peripheral tissues, helping to improve glucose control. Actually, thiazolidinediones (TZDs) are not typically known for their bactericidal activity against Gram-positive and Gram-negative bacteria. TZDs are primarily used as antidiabetic drugs and are not commonly prescribed for their antibacterial properties. Their main mechanism of action is related to insulin sensitization and glucose control in patients with type II diabetes mellitus.Indeed, the bactericidal activity of thiazolidinedione derivatives is often influenced by substitutions on the heterocyclic thiazolidine ring rather than the aromatic moiety. This class of compounds, including 2,4-thiazolidinedione derivatives, is known for its diverse biological properties, including antibacterial and antifungal activities. These structural modifications play a crucial role in determining the pharmacological properties of thiazolidinedione derivatives.

2,4-Thiazolidinedione (TZD) derivatives, commonly referred to as glitazones, are indeed a class of drugs approved for their anti-hyperglycemic effects in clinical use. They work by improving insulin sensitivity in peripheral tissues, thereby helping to lower blood sugar levels in patients with type II diabetes mellitus. thiazolidinediones (TZDs) bind to the gamma isoform of the peroxisome proliferator-activated receptor (PPARγ). This interaction helps to modulate gene expression involved in glucose and lipid metabolism, ultimately leading to improved insulin sensitivity and glucose control in patients with type II diabetes mellitus. When thiazolidinediones (TZDs) bind to the gamma isoform of the peroxisome proliferator-activated receptor (PPARγ), it stimulates peripheral adipocytes (fat cells) to increase their uptake of free fatty acids. This leads to a reduction in fat stored in muscles, liver, and visceral fat deposits. By redistributing fat and improving lipid metabolism, TZDs contribute to improved insulin sensitivity and glucose control in patients with type II diabetes mellitus. Analogues of 2,4-thiazolidinediones have been extensively explored for various pharmacological properties, including their roles as insulin sensitizers, aldose reductase inhibitors, and agonists of peroxisome proliferator-activated receptors (PPARs). These compounds have shown promise in the treatment of

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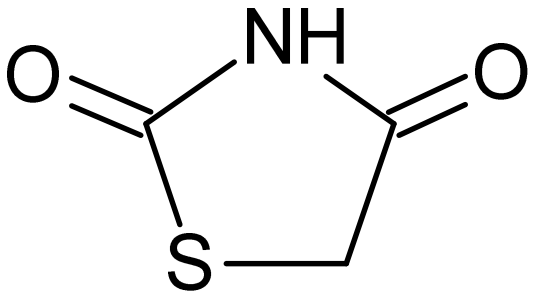
conditions such as type II diabetes mellitus and related metabolic disorders.many substituted TZD derivatives have indeed been reported as aldose reductase inhibitors, which hold potential for treating type II diabetes and related secondary complications.

Additionally, TZDs have been shown to increase the secretion of adiponectin, a hormone involved in regulating glucose levels and fatty acid breakdown, while simultaneously decreasing the production of resistin and tumor necrosis factor. This modulation of adipokine secretion contributes to the overall metabolic effects of TZDs, including improved insulin sensitivity and reduced inflammation.

Chemistry:



2,4 Thaizolidinedione

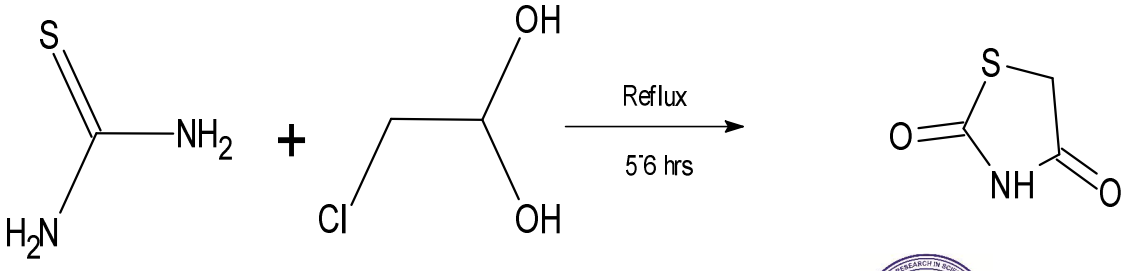
Thiazolidinediones are five-membered heterocyclic compounds containing sulfur, nitrogen, and oxygen atoms in their ring structure. They exhibit potent and wide-ranging pharmacological activities, including but not limited to their use as insulin sensitizers in the treatment of type II diabetes mellitus. Thiazolidinediones have been studied for their effects on lipid metabolism, inflammation, and various other biological processes, making them an important class of compounds in medicinal chemistry.

II. MATERIALS AND METHODS

It's common practice in scientific research to use materials obtained from commercial suppliers without further purification unless explicitly stated otherwise. This approach helps streamline experimental procedures and ensures consistency in results across different laboratories. Using a Veego microprocessor-based programmable melting point apparatus for determining melting points in open capillary tubes is a standard method in laboratory practice. The melting points obtained are typically reported as uncorrected values, meaning they are not adjusted or calibrated for any potential systematic errors in the apparatus. This information provides transparency regarding the experimental procedure and allows others to replicate the results under similar conditions. Using thin layer chromatography (TLC) on glass plates with silica gel G as the adsorbent and chloroform: methanol as the solvent system is a common method for monitoring the progress of reactions in organic synthesis. TLC allows for the visualization of different compounds present in the reaction mixture and helps determine when the reaction has reached completion. This technique is widely used in organic chemistry laboratories due to its simplicity, speed, and effectiveness in assessing reaction progress.

Scheme of Synthesis:

Step 1-Synthesis of 2,4-thaizolidinedione



Thiourea Chloroacetic acid

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Procedure:

It seems like you're describing a reaction setup in which chloroacetic acid and thiourea are being dissolved in water in a 250 ml three-necked flask. The amounts you've provided correspond to approximately 0.6 moles of each compound, and they are being dissolved in 60 ml of water each.

The occurrence of white precipitates after stirring the mixture for 15 minutes indicates that a reaction has occurred between chloroacetic acid and thiourea.Adding concentrated hydrochloric acid slowly to the reaction mixture containing the white precipitates serves to dissolve the precipitates, likely forming soluble chloride salts. Refluxing the reaction mixture for 5-6 hours after the dissolution of the precipitates suggests that further chemical transformations or reactions are taking place under elevated temperature conditions.

This procedure indicates that the reaction is likely more complex and involves multiple steps. Refluxing the reaction mixture allows for thorough mixing and heating under controlled conditions, which can promote the completion of the desired reactions and the formation of the intended product. The solidification of the reaction mixture to a mass of clusters of white needles upon cooling suggests that the reaction product has crystallized out of solution. The formation of needle-like crystals often indicates the presence of a pure compound or a compound with a well-defined crystal structure.Filtering the product and washing it with water serves to remove any traces of hydrochloric acid and other soluble impurities that may be present in the solid. This step is important for obtaining a pure product with the desired properties. After washing, the product is typically dried to remove any remaining moisture and to ensure its stability during storage and further characterization. Recrystallizing the product from ethanol is a common purification technique in organic chemistry. A yield of 80% suggests that a significant amount of the desired product was obtained relative to the starting materials.

The melting point range of 123-125°C indicates that the recrystallized product has a relatively narrow melting point range, suggesting high purity.

Additionally, the TLC (thin layer chromatography) solvent system of chloroform:methanol (9:1) indicates that this system was used to monitor the purity and progress of the reaction. The specific ratio of 9:1 chloroform to methanol may have been chosen to optimize separation and visualization of the compounds on TLC plate.

Antihyperglycemic study:

Using alloxan-induced diabetic albino mice of the Laca strain for in vivo studies is a common experimental model in diabetes research. Alloxan is a chemical compound known to induce diabetes by damaging the insulin-producing beta cells in the pancreas. By using this model, researchers can study the effects of various interventions, such as drugs or treatments, on diabetes and its complications.The Laca strain of albino mice is often chosen for its susceptibility to alloxan-induced diabetes and its ease of handling in laboratory settings. Both male and female mice are typically used to account for potential gender differences in response to treatments or disease progression.Keeping the mice under standard laboratory conditions, as described, ensures consistency and minimizes external variables that could affect the experimental results. These conditions, including temperature, humidity, lighting, and cage density, are carefully controlled to provide a stable and comfortable environment for the animals while also complying with ethical guidelines.Approval from the Institutional Animal Ethics Committee (IAEC) is essential to ensure that the research involving animals is conducted ethically and in accordance with established guidelines and regulations. The letter reference provided (PU/IAEC/ S/14/105) indicates that the research protocol has undergone review and approval by the committee at Punjab University, Chandigarh.

It sounds like you're describing an experiment involving mice and the induction of hyperglycemia using alloxan following CPCSEA guidelines. It seems like you're describing an experiment where mice were given a 5% glucose solution for the first 12 hours to prevent hypoglycemic shock. After 72 hours, their blood sugar levels were measured, and those with levels ≥250 mg/dL were considered hyperglycemic.

Acute Anti hyperglycemic study:

Thank you for providing more details. It seems like you have three groups for comparison: a negative control group treated with only the standard vehicle, a positive control group treated with the standard drug pioglitazone, and a test group treated with the synthesized compound. This setup allows for comparing the effects of the synthesized compound

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against both the negative control (no treatment) and the positive control (standard drug). So, the fasting blood sugar levels of the animals were established at 0 hours, after an overnight fast. Then, a fixed dose of 30 mg/kg body weight was orally administered in the form of a homogenized suspension (0.5% CMC + Tween 80) to both the pioglitazone treatment group and the final compound treatment group. This ensures that both groups received the same dosage method. So, the negative control group (vehicle-treated mice) received the same volume and quantity of 0.5% CMC with Tween 80 as the treatment groups, ensuring that any observed effects are due to the administered compounds rather than the vehicle. The control group, on the other hand, did not receive any drug or vehicle. Blood obtained through tail prick technique was used for monitoring blood sugar levels at various time points (2nd, 4th, 6th, and 24th hour) after administering the test compounds. This allows for the assessment of how the blood sugar levels change over time in response to the administered compounds.The percentage decrease in blood sugar was determined by comparing the blood sugar levels of the treatment groups to those of the control group animals. A decrease of at least 10% in blood sugar level was considered a positive screening outcome. This threshold helps identify compounds that exhibit a significant effect on lowering blood sugar levels compared to the control group.

Groups		2 hr	4 hr	6 hr	24 hr	7th day
Negative control (vehicle)		1.16±0.70	1.35±0.47	2.31±0.42	6.76±1.52	8.02±0.70
Positive control (pioglitazone)		-36.02±0.87	-44.78±1.66	-40.67±1.4	-34.9±0.79	-37.4±2.15
Test group (10-17)	10	-29.62±0.64	-42.90±0.15	-33.8±0.01	-26.5±0.41	-39.1±2.30
	11	-21.99±0.10	-29.75±0.32	-25.9±0.72	-16.1±0.14	-30.7±1.59
	12	-27.91±2.37	-39.94±0.54	-31.4±0.43	-20.1±2.05	-36.5±1.29
	13	-18.97±0.80	-23.72±0.76	-21.5±1.38	-14.3±1.62	-22.4±0.28
	14	-25.15±1.50	-36.15±2.39	-29.6±0.37	-17.1±0.16	-34.0±2.12
	15	-22.18±0.24	-31.47±0.58	-28.5±0.84	-16.8±0.09	-39.7±1.12
	16	-17.61±1.99	-20.79±1.22	-18.5±2.16	-11.3±0.42	-14.1±1.17
	17	-23.45±1.35	-28.43±1.29	-25.0±0.94	-17.7±0.80	-27.3±1.34

Antibacterial and antifungal activity:

It sounds like you're describing the process of obtaining cultures from bacterial strains using Mueller-Hinton broth and from fungi using Sabouraud dextrose broth after specific periods of incubation at controlled temperatures. Testing was then conducted using Mueller-Hinton broth and Sabouraud dextrose broth at pH 7.4, and the twofold serial dilution technique was applied. This technique involves diluting a substance by a factor of two with each successive step, allowing for a range of concentrations to be tested.It seems like you're describing the experimental setup for antibacterial and antifungal assays. The final inoculum size for the antibacterial assay was 10^5 CFU/ml, while for the antifungal assay, it was 10^4 CFU/ml. Additionally, a set of tubes with only inoculated broth was used as a control. So, for the antibacterial assay, after incubating for 24 hours at 37 ± 1°C, and for the antifungal assay, after incubating for 48 hours at 25 ± 1°C, the tube that showed no growth of the microorganism was recorded. This tube represents the Minimum Inhibitory Concentration (MIC) expressed in grams per milliliter (g/ml).Each experiment in both the antibacterial and antifungal assays was replicated twice for consistency and to ensure the reliability of the results.

III. RESULTS AND DISCUSSION

It sounds like a synthesis method for thiazolidinedione derivatives. The process involves reacting 5-(4-chlorosulfonylbenzylidene)-2,4-thiazolidinedione (0.01 mole) with aromatic amines R (0.01 mole) to synthesize the thiazolidinedione derivatives. The structures of the synthesized compounds were determined using various analytical techniques, including Infrared Spectroscopy (IR), Nuclear Magnetic Resonance (NMR) spectroscopy, and elemental analysis. These methods helped in characterizing the chemical bonds, functional groups, and overall composition of the compounds. A series of Mannich base derivatives of 2,4-thiazolidinedione were synthesized using the Mannich reaction, where different secondary amines and formaldehyde were employed as reactants. The synthesis of Mannich base derivatives of 2,4-thiazolidinedione likely produced compounds with diverse substituents on the thiazolidinedione

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scaffold. To assess their antioxidant activity, the DPPH assay method was employed to measure their capability to scavenge free radicals. This method helps in understanding the potential antioxidant properties of the synthesized compounds.The degree of discoloration observed in the DPPH assay indicates the scavenging activity of the synthesized compounds, with greater discoloration suggesting higher scavenging activity against free radicals. Additionally, the title compounds were screened for their anti-diabetic activity using the alloxan-induced tail tipping method. This method assesses the potential of the compounds to counteract the effects of alloxan-induced diabetes in experimental animals, providing insights into their anti-diabetic properties.The experimental setup involved selecting albino rats of either sex weighing between 150-200 grams. Alloxan was used to induce elevated blood glucose levels in these rats, simulating diabetic conditions. The study was then conducted using six different groups of rats, likely comprising various treatment groups and controls, to evaluate the effects of the synthesized compounds on blood glucose levels and their potential anti-diabetic activity.

IV. CONCLUSION

The synthesis of novel 5-substituted 2,4-thiazolidinedione derivatives has led to the discovery of a new series of compounds with potential antimicrobial properties. The results of antimicrobial screening indicate that these compounds exhibit antibacterial and antifungal activity, highlighting their potential as agents for combating bacterial and fungal infections. This discovery opens up avenues for further research and development of these compounds as pharmaceutical agents. The mode of action of these synthesized compounds, particularly the 2,4-thiazolidinedione derivatives, is currently unknown. However, given their ability to improve insulin sensitivity, they hold potential for use in the treatment of type II diabetes. These compounds were synthesized using standard chemicals and procedures, and their efficacy in enhancing insulin sensitivity suggests promise for further investigation and potential therapeutic applications in diabetes management. Characterization of the synthesized compounds through various analytical techniques such as IR (Infrared Spectroscopy), NMR (Nuclear Magnetic Resonance), UV (Ultraviolet-Visible Spectroscopy), and TLC (Thin Layer Chromatography) is crucial for understanding their structure and properties. These findings provide valuable insights that can aid in the design and synthesis of more potent thiazolidinedione derivatives as antihyperglycemic agents. By refining the chemical structure based on the observed characteristics and activity profiles, researchers can optimize the compounds for enhanced efficacy in managing hyperglycemia associated with type II diabetes.Comparing the chemical structures of thiazolidinediones to rosiglitazone, an oral hypoglycemic agent, provides valuable insights into the potential pharmacological activity of the synthesized compounds. Rosiglitazone belongs to the class of thiazolidinediones and is known for its insulin-sensitizing properties, making it effective in treating type II diabetes. By comparing the chemical structures of the synthesized thiazolidinedione derivatives to rosiglitazone, researchers can gain a better understanding of the structural features responsible for their antihyperglycemic activity, facilitating the design of novel compounds with improved efficacy and reduced side effects.

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