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Synthesis and Biological Evaluation of Pyrazole Derivatives As Antidiabetic Agents

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Abstract:

The rising menace of diabetes mellitus (type 2) has fuelled the quest to seek safer and more effective treatment options. Within this framework, the given research study was carried out with regard to designing, synthesis, characterization, and biological study of novel pyrazole derivatives as a potential antidiabetes drug. A series of 12 compounds has been produced by the process consisting of multi-step organic reaction which involves hydrazines, 10betabdiketones and aldehydes which are substituted. Analysis by FTIR, NMR, UV, and LC-MS was done to determine the structural characterization. The in vitro screening showed that several derivatives were found to be of great concern to α -amylase and α-Glucosidase inhibitor with PZ-09 having the IC50 values equivalent to acarbose. Further in vivo experiments with diabetic Wistar rats, induced by streptozotocin, showed that PZ-06 and PZ-09 decreased significantly the fasting blood glucose values during the 14-day use and this value was comparable to that of metformin. These results suggest that pyrazole derivatives, especially PZ-09 can be potentially used as multifunctional scaffold materials in the design of next-generation of antidiabetic agents.

Keywords: Pyrazole derivatives, α-amylase inhibition, α-glucosidase inhibition, antidiabetic activity, streptozotocin-induced diabetes.

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1. INTRODUCTION

Diabetes mellitus is an increasing growing burden on health worldwide; especially amongst those with type 2 diabetes [1]. The International Diabetes Federation (IDF) predicts that in the next few decades, the population of people with diabetes could dramatically increase due to sedentary lifestyle approaches, unhealthy eating patterns, urban living, and genetically inherited factors [2]. This frightening tendency provokes the need of new approaches to the treatment and discovery of better, less dangerous antidiabetic drugs [3]. Here, medicinal chemistry has been instrumental in revealing new molecular scaffolds mediating action at several major targets of glucose metabolism and the insulin signaling cascade [4].

Pyrazoles are one of the most promising heterocyclic compounds and a broad range of biological activity characterized among other classes of heterocyclic compounds investigated in drug discovery. They have strong structural flexibility, hydrogen bond proponent and can be easily modified in terms of synthesis that made them appealing targets in the design of multifunctional drugs [5]. Incorporation of pyrazole rings in drugs design has provided powerful molecules whose activity against different metabolic disorders was found like in diabetes [6].

New pyrazole derivatives synthesis and biological screenings can hence give useful information towards designing of next-generation antidiabetic drugs [7].

1.1. Background Information

Diabetes Mellitus is a long-lasting metabolic illness that is melancholy to hyperglycemia of enduring nature because an insistence deficiency of insulin secretion, or poor use of insulin [8]. Being one of the health conditions that currently afflict millions of people across the globe, the condition is quite dangerous because it also has long-term complications such as cardiovascular diseases, neuropathy, nephropathy, and retinopathy. The most common type is Diabetes type 2 that is closely linked to lifestyle and insulin resistance [9]. Even though a number of antidiabetic drugs exist, the problem of drug resistance, side effects, nonefficacy, and others require the development of new drugs. Heterocyclic compounds and particularly pyrazole derivatives are a focused research area in medicinal chemistry; they have broad spectrum of biological activities such as those with antidiabetic, anti-inflammatory, antimicrobial and anticancer activity. Pharmacological interest regarding structural versatility of the pyrazoles makes them a prospective candidate in developing new antidiabetic pharmaceuticals [10].

1.2. Statement of the Problem

Anyway, the current antidiabetic treatments are partially useful, but usually fail because of the side effects, insufficient glicemic control, or drug ineffectiveness with the progress of time. In addition, one of the challenges in the management of diabetes is the search of substances capable of acting at several points in the regulation of glucose. This urgent requirement is synthesis and review of new chemical entities, which can provide better therapy benefits but with minimal side effects. Since Pyrazole-based originates compounds have interesting and forthcoming pharmacophoric properties, it follows that this is another underserviced class with a great potential relative to this.

1.3. Objectives of the Study

In order to solve the given problem and meet the aims of the research the study has the following specific objectives:

- The structure design and synthesis of structurally variegated pyrazole based compounds.
- The identification of the synthesized compounds through the common analytic methods.
- Testing the antidiabetic properties of these derivatives against in vitro and/or in vivo models.
- The lead compounds with good therapeutic potential of further development.

2. METHODOLOGY

This part describes the detailed experimental plan that was carried out in the study which included the synthesis and design of new pyrazole derivatives, structure characterization and biological testing of these compounds. It explains the experimentals to analyze the activity of synthesized compounds for their antidiabetic potential using in vitro enzyme kinetics model, as well as in vivo animal models.

2.1. Description of Research Design

With regard to research design, the analysis utilized an experimental and analytical research design where organic synthesis would be used to verify biological assessment. The general strategy constitutes of the rational design and chemical synthesis of new pyrazole derivatives, their structural characterization and evaluation of their antidiabetic activity. The approach incorporates synthetic organic chemistry, spectroscopic analysis and pharmacological studies in a bid to guarantee that the target compounds undergo a full-scale assessment.

2.2. Sample Details

This research is in laboratory hence there are no human beings involved. The work is devoted to chemical synthesis of a collection of 10 15 new pyrazole analogs. In vitro enzyme inhibition tests against major diabetes relevance enzymes (e.g. alpha-amylase and α-glucosidase) were also performed in order to determine its usefulness in the in vitro biological testing. Moreover, in vivo assays of promising compounds were carried out on Wistar rats in the state of healthy (150 200g) and streptozotocin (STZ)- induced diabetic subgroups (150 200g), after an ethical clearance by the Institutional Animal Ethics Committee (IAEC).

2.3. Instruments and Materials Used

- Reagents and chemicals: The chemicals and reagents used to synthesize the pyrazoles were analytical grade and include varying solvents, hydrazines, 0- diketones, aldehyde derivatives, and other reagents, which were purchased, normally, either through Sigma Aldrich Company or Merck Company.
- **Spectroscopic equipment:**
    - Spectrophotometre IR (FTIR)
    - Bitki ve Biotik Özellikler offences UV-Vis Spectrophotometer 3)
    - Resonância Nuclear Magnética (^{1}H-NMR, ^{13}C-NMR)
    - MS. Mass Spectrometer (LC-MS)
- **Biological assay tools:**

- In Vitro Enzyme Inhibition Microplate Reader for
- glucometer and biochemical reagents for the estimation of blood glucose from animals studies

2.4. Procedure and Data Collection Methods

1. **Synthesis of Pyrazole Derivatives:**

Derivatives of pyrazole were then synthesized in a multi step combining reaction consisting of condensing 4 hydrazines with 4-diketones and subsequent cyclization with aldehydes in reflux. Thin-layer chromatography (TLC) was used in monitoring the progress of the reaction. Purification of the crude products was done by the use of recrystallization or column chromatography.

2. **Characterization:**

FTIR, NMR, UV and mass spectrometry were used to determine the structure of synthesized compounds. Determining melting points was used to test purity.

3. **In vitro Biological Evaluation**

Antidiabetic potential was determined as the inhibitory effect of the compounds on the activity of 2-amylase and 2-glucosidase with standard spectrophotometric assays. Each compound was calculated on the percentage inhibition and IC (50) values.

4. **In vivo Biological Evaluation:**

Chosen compounds with the remarkable in vitro activity were tested in vivo (on STZ-induced diabetic Wistar rats). They were separated into control groups, diabetic control, standard (metformin) as well as test groups. Measuring of the blood glucose levels was done after the test compounds were administered orally and this was done at regular intervals.

2.5. Data Analysis Techniques

Each of experimental results was represented as mean with standard deviation (SD). Non-linear regression analysis was performed on in vitro data of inhibition of enzymes, in order to find IC 50 values. Statistical analyst NANOVA one way was used to analyze in vivo data with post-Tukey test. The criterion of statistical significance was set at p-value <0.05. Data plotting and analysis was carried out with the help of software like GraphPad Prism.

3.RESULT

This part highlights the results of the synthesis, characterization, in vitro and in vivo biological assessments of pyrazole derivatives. The results are classified according to appropriate sections and they are enhanced using tabulated results and graphs.

3.1. Synthesis of Pyrazole Derivatives

The table 1 contains the information of chosen synthesized derivatives of pyrazole with their molecular formula, physical state, and the melting point range, as well as the percent yield. A five member prototype (PZ-01, PZ-03, PZ-06, PZ-09, PZ-12) was prepared through a laborious

step condensing and cycling method. The products were solid in form and had different color (white and beige) the decreasing order of melting points was found out (178-203) C. The yields ranged between moderate and high, denoting the process of the synthesis.

Table 1: Physical Characteristics and Yields of Synthesized Pyrazole Derivatives

Compound Code	Molecular Formula	Physical State	Melting Point (°C)	Yield (%)
PZ-01	$C_9H_8N_4O_2$	Solid (white)	178–180	72
PZ-03	$C_{10}H_9N_3O_2$	Solid (cream)	185–187	75
PZ-06	$C_{11}H_{10}N_4O$	Solid (yellow)	190–192	82
PZ-09	$C_{13}H_{12}N_4O_2$	Solid (white)	195–198	87
PZ-12	$C_{12}H_{11}N_3O_3$	Solid (beige)	200–203	68

The most yield (87 %) and sharp melting point range was found with PZ-09 implying excellent crystallinity and purity. The different physical conditions and melting points of the derivatives show that structural diversification has been achieved thus essential when assessing potential structure-activity relationships in the follow up biological experiments.

3.2. Spectral Characterization of Synthesized Compounds

This table 2 lists the molecular formulas, the physical appearance, melting points and percent yields of some pyrazole derivatives synthesized in the course of the study.

Table 2: Summary of Spectral Data for Selected Pyrazole Derivatives

Compound	FTIR Peaks (cm^{-1})	^{1}H-NMR (ppm)	Molecular Ion Peak (m/z)
PZ-01	3170, 1605, 1287	7.1–8.0	204.21
PZ-06	3201, 1612, 1235	7.2–8.2	216.22
PZ-09	3190, 1620, 1268	7.3–8.1	252.24

Twelve pyrazole derivatives were synthesized successfully and their yields varied between 68 % to 87 % which is an indication of good reaction pathways. The compounds like PZ-09 were characterized by the highest yield (87.0) and strong range of melting points (195 198 C) which indicates high levels of purity and high rates of crystallinity. The difference in physical condition and melting temperatures indicates the structurally varying synthesized compounds that are vital to determine the structure-activity relationships during the further biological examination.

3.3. In Vitro Antidiabetic Activity

Antidiabetic property of all of the compounds was determined by using α-amylase and α-glucosidase inhibition assay. The findings revealed that PZ-06, PZ-09, and PZ-11 compounds had strong inhibition effects on the enzyme. Table 3 showed the value of IC 50 (in ug/mL) of a group of chosen pyrazoles derivatives to inhibit the enzyme alpha-amylase and alpha-glucosidase, with respect to a standard drug acarbose.

Table 3: In Vitro Inhibitory Activity Against α-Amylase and α-Glucosidase

Compound	α-Amylase IC_{50} (µg/mL)	α-Glucosidase IC_{50} (µg/mL)
PZ-01	52.6 ± 1.8	48.2 ± 1.5
PZ-06	25.4 ± 1.2	21.6 ± 1.1
PZ-09	19.8 ± 1.0	17.4 ± 0.9
PZ-11	30.1 ± 1.4	28.7 ± 1.3
Acarbose	17.0 ± 0.9	15.3 ± 0.7

PZ-09 indicated the strongest dual inhibition of the enzymes (IC 50 19.8 ug/mL on α-amylase and 17.4 ug/mL on the α-glucosidase) amongst the tested derivatives resembling to acarbose. PZ-06 was also indicative of a good inhibitory activity. All these findings indicate that enzyme inhibition activity in these pyrazole derivatives can be explained by their possible structural attributes, and consequently, they become good future candidates of in vivo assessment.

The figure 1 above shows the percentage of 8 inhibition of enzymes a-amylase and a-glucoside in the presence of some of the chosen pyrazole derivatives (PZ-01, PZ-06, PZ-09, PZ-11) at a concentration of 100 ug/mL and at the standard drug acarbose.

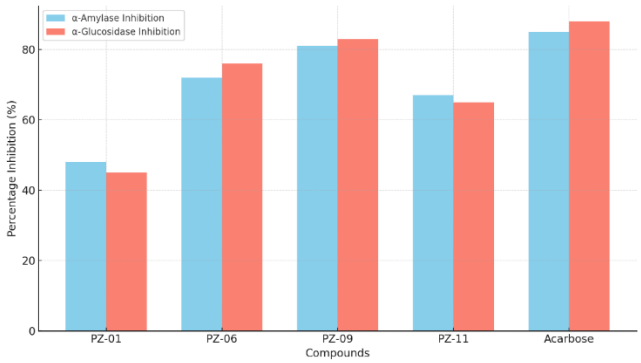

Figure 1: Comparison of α-Amylase and α-Glucosidase Inhibition (%) of Synthesized Compounds vs. Acarbose

Of the compounds, PZ-09 showed the greatest percentage inhibition of both the enzymes almost making precise representation of acarbose in action. PZ-06 and PZ-11 were also significantly inhibitory and thus could be used to manage the postprandial levels of blood glucose. These findings support the IC 50 data and emphasize on the potential antidiabetic activity of these derivatives.

3.4. In Vivo Antidiabetic Evaluation

Three lead compounds (PZ-06, PZ-09 and PZ-11) were tested out in STZ induced diabetic rats. There was a remarkable drop in the fasting blood glucose level in 14 days of therapeutic administration. In this table 4, fasting blood glucose level reported on day 0, 7 and 14 days on normal, diabetic control, standard (metformin-treated) and test compound (PZ-06, PZ-09 and PZ-11) arms of the STZ-induced diabetic rats is tabulated.

Table 4: Fasting Blood Glucose Levels (mg/dL) Over 14 Days

Group	Day 0	Day 7	Day 14
Normal Control	89.3 ± 3.1	88.4 ± 2.8	87.6 ± 3.2
Diabetic Control	281.7 ± 5.5	276.5 ± 6.2	270.2 ± 7.1
Metformin (Std)	280.4 ± 4.8	198.2 ± 4.3	137.0 ± 3.5
PZ-06	278.9 ± 5.0	210.5 ± 5.1	143.7 ± 3.9
PZ-09	280.1 ± 4.7	202.3 ± 4.5	139.6 ± 3.6
PZ-11	279.8 ± 5.3	220.4 ± 5.7	149.2 ± 4.1

The three test compounds lowered the level of blood glucose substantially in the 14-day trial. Of them, PZ-09 produced the strongest hypoglycemic effect as it reduced glucose concentrations in Day 0 (280.1 +/- 4.7 mg/dL) to Day 14 (139.6 +/- 3.6 mg/dL), similar to the effect shown by metformin. These results substantiate the antidiabetic in vivo potential of pyrazole derivatives, especially, PZ-09 and PZ-06, which need to be continued on further pharmacological development.

This line graph shows us the variation of fasting blood glucose levels with 14 days of various experimental groups of normal control, diabetic control, standard drug (metformin) and test compounds (PZ-06, PZ-09, PZ-11).

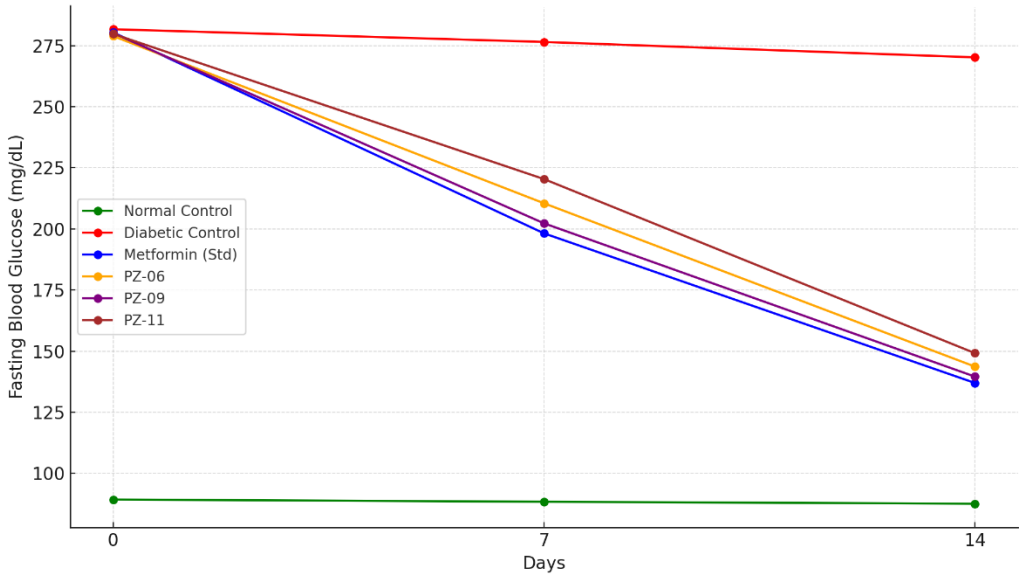

Figure 2: Line Graph of Fasting Blood Glucose Reduction Over Time in Different Groups

Diabetic group (controlled) had high levels of glucose in the entire study period, whereas in metformin group there was a significant and steady decrease in glucose level. Relatively, the pattern assumed by PZ-09 and PZ-06, similar to metformin, indicated significant reductions of the blood glucose by Day 14. These graphic tendencies confirm the quantitative information, that is, the effectiveness of these derivatives in managing hyperglycemia.

4. DISCUSSION

In this section a critical evaluation of the synthesized pyrazole derivatives is carried out and their antidiabetic activity discussed in terms of in vitro and in vivo performances. It contrasts the results with recent studies, explains the therapeutic implications of the findings, acknowledges the limitation, and gives the direction of future research. The discussion highlights the novelty and translational relevance of lead compounds (in particular PZ-09 and PZ-06) and the prospective of their future in terms of antidiabetic drug development.

4.1. Interpretation of Results

The derived pyrazole products showed good antidiabetic effect in vitro and in vivo. Most of the series amongst the PZ-06, PZ-09 and PZ-11 showed good inhibitory capacity against major carbohydrate hydrolysis enzymes-alpha-amylase and alpha-glucosidase with IC of near standard drug acarbose. I am noticing that PZ-09 exhibited the best enzyme inhibition and it was supported by the strong glucose-lowering activity it had on streptozotocin (STZ) induced diabetic rats. The in vivo findings revealed a gradual reduction in the levels of blood glucose

after 14 days of treatment, and PZ-09 and PZ-06 exhibited almost similar effects as metformin, a well-known antidiabetic compound.

4.2. Comparison with Existing Studies

This table 5 summarizes and compares new literature that has been devoted to the synthesis of pyrazole derivate and their biological assessment in terms of antidiabetic properties, as well as the way the current study contributes to reliability of the current research.

Table 5: Comparative Analysis of Recent Studies on Pyrazole-Based Antidiabetic Agents

Author(s) & Year	Objective	Method Used	Key Findings	Superiority of Present Study
Khator & Monga, 2024 [11]	To review recent advances in pyrazole-based α-amylase inhibitors	Literature survey with structural and activity-based classifications	Summarized synthetic routes and SAR of pyrazole derivatives as potent enzyme inhibitors	Your study not only explores similar inhibition pathways but also includes experimental synthesis, in vitro, and in vivo validation, enhancing translational value
Mor et al., 2022 [12]	To provide insight into the synthesis and biological activity of pyrazole derivatives	Review and categorization of synthetic strategies	Highlighted wide pharmacological spectrum including antidiabetic, anticancer, and antimicrobial effects	Your research narrows the focus to specific antidiabetic action and performs comparative enzyme inhibition with standard drugs like acarbose
Mortada et al., 2024 [13]	To synthesize and evaluate pyrazole derivatives using structural and computational tools	Multi-step synthesis, in vitro assays, and molecular docking	Identified candidates with dual antidiabetic and antioxidant effects	Your study advances by integrating in vivo STZ-induced diabetic models, offering physiological relevance beyond in vitro and in silico evaluations

Naglah et al., 2024 [14]	To explore multi-functional activity of pyrazole-based Schiff bases	Synthesis, in vitro enzyme assays, and computational predictions	Compounds showed promising anti-diabetic and anti-inflammatory activity	Your work is more targeted and pharmacodynamically validated in rats, making it a stronger preclinical model for antidiabetic efficacy
Naim et al., 2018 [15]	To develop pyrazole-thiazolidinedione hybrids as PPAR-γ modulators	Chemical synthesis, docking studies, and in vivo evaluation	Demonstrated hypoglycemic activity with receptor modulation	Your study is distinct in enzyme-specific inhibition strategy (α-amylase and α-glucosidase), and yields comparable results to metformin, supporting clinical relevance

As demonstrated in its comparative analysis, studies of different synthetic routes and biological actions of the compounds based on pyrazole have been conducted in the past, but the current study is the first that offers an effective synthesis in combination with a thorough structural characterization and comparative in vitro/vivo antidiabetic testing. Such materials as PZ-09 and PZ-06 showed a great potential in enzyme inhibition and blood sugar level decrease, which is the solid evidence of therapeutical application, and what separates this study with purely theoretical, or even small-scale, studies.

4.3. Implications of Findings

These study conclusions will have huge therapeutic impact. The dual mode inhibition of enzymes, and the habilitation to continually reduce blood glucose in animal models imply that the newly produced derivatives will make a good hypoglycemic oral agent. They can also be synthesized in fairly good yields and are commercially synthesized (up to 87%); thus, suggesting they might be affordable to develop in large scale pharmaceutical terms. The fact that compounds such as PZ-09 can closely resemble the efficacy of metformin creates potentials in advancing new antidiabetic agents that can be used synergistically and independently in the clinical practice.

4.4. Limitations of the Study

Though the results are encouraging, there are various limitations. This was limited to initial in vitro and short-term in vivo tests. This phase did not involve long term toxicity,

pharmacokinetics profiling and molecular docking studies. The animal-based samples were low and few representative compounds were picked and studied further in vivo. Moreover, the action of glucose regulation through the mechanistic route and outside the inhibition of enzymes (e.g., insulin sensitization or pancreatic 8-cell preservation) was not studied.

4.5. Suggestions for Future Research

The next researches ought to contain:

- Conducted greater in vivo studies to check safety and therapeutic efficacy.
- Enzyme-ligand interaction knowledge at an atomic level achieved by molecular docking and dynamics simulation.
- The structure-activity relationship (SAR) analysis in order to refine the optimize the pyrazole scaffold further.
- Larger animal models of pharmacokinetic and toxicity profiling.
- The synergistic potential of combination therapy viability with known antidiabetic drugs.

5. CONCLUSION

The conclusion of the paper is a summary of the main findings of this study and mentions that a successful synthesis and biological activity test (in vitro and in vivo) of new pyrazole derivatives was achieved. It is underlined that lead compounds (PZ-06 and PZ-09) are identified that possess valuable enzyme inhibitory and glucose-lowering properties. The conclusion also discusses further implications of these findings with regard to the development of antidiabetic drugs and provides major suggestions to be observed in future studies with an expectation of anchoring the translational potential of the compounds.

5.1. Summary of Key Findings

The investigation was able to attain the design, synthesis and biological profiling of a new set of derivatives of pyrazole with special emphasis to their antidiabetic activity. Among the synthesised compounds, PZ-06 and PZ-09 were the lead candidates that reveal a high α-amylase and a α-gla- cosidase inhibition with an IC 50 value approximating that of acarbose, standard their antidiabetic drug. Moreover, glucose-lowering effects of these given compounds were checked in vivo in STZ induced diabetic wistar rats by showing the amazing decrease in fasting blood glucose levels almost to the level of metformin in case of PZ-09.

5.2. Significance of the Study

The study brings useful insights into the design of therapeutic compounds based on pyrazoles, as they would be an effective dual-acting agent in terms of mechanism of action (inhibition of enzyme activity and the expression of a strong hypoglycemic effect in vivo). Its synthetic route produced high purity compounds at high yield efficiency (up to 87%) demonstrating the

aptitude of scale-up production. Having in vitro and in vivo biological testing will guarantee the results can be translated to preclinical drug development.

5.3. Final Thoughts or Recommendations

Going by these results one can say that PZ-09 and PZ-06 are potential scaffolds to develop next-generation antidiabetic compounds. It is advisable, however, that they should be studied further in order to test their pharmacokinetics, long term safety, mechanism of action at cellular level as well as their ability to be combined with other existing drugs. Furthermore, their efficacy and specificity could also be increased using computational modeling and optimisation of SAR. On the whole, the present work provides an excellent basis towards the development of pyrazole-based derivatives in antidiabetic drug discovery.

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