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Original Article

Synthesis of Novel Thiazolidinone and Its Application as Apha-Amylase Inhibitor

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Abstract:

In organic and medicinal chemistry, thiazolidinone and its derivatives are crucial because they have nearly all biological activities, including antimicrobial, anti-tubercular, anti-diarrheal, and anticonvulsant properties. We tried to synthesize thiazolidinone from a schiff base that garnered a lot more attention in order to achieve notable biological activities. Design and mild-condition synthesis of a new substituted thiazolidinone from 2-amino-thiazole and pyrazole-2-aldehyde using DCC. Derivatives substituted with thiazolidinone were discovered to be useful in inhibiting α-amylase.

Keywords: *Schiff base, DCC, α-amylase, and thiazolidinone*

Introduction:

One common therapeutic target used to treat and maintain postprandial blood glucose elevations is α-amylase. Diabetes mellitus is a metabolic disorder that develops when the body cannot properly use insulin, a crucial hormone that controls blood glucose levels, or when the pancreas is unable to produce enough of it. Type 1 diabetes and insulin-dependent diabetes, also known as juvenile diabetes, are the two main types of diabetes mellitus. On the other hand, type-2 diabetes typically affects adults and is frequently brought on by the body's inability to secrete enough insulin or its resistance to it. Type-2 diabetes now affects over 95% of the population. An astounding 422 million people worldwide suffer from diabetes, with low- to medium-income countries accounting for the majority of cases. Recently, α-amylase and α-glucosidase enzyme suppression has been used to treat diabetes. The calcium metalloenzyme α-amylase is essential for digestion because it encourages the breakdown of polysaccharide molecules into simpler forms like glucose and maltose. Among other things, the enzyme raises blood glucose levels and causes postprandial hyperglycemia. One common therapeutic target used to treat and maintain postprandial blood glucose elevations is α-amylase. By catalyzing the α-(1,4)-D-glycosidic bonds found in starch, it produces antioxidants. Both reactive oxygen species (ROS) and nitrogen species, which were derived from oxygen and nitrogen, respectively, make up the reactive molecule. The cellular membrane, mitochondria, nucleus, lysosome, peroxisome, endoplasmic reticulum, and cytoplasm are among the subcellular organelles that produce reactive particles. By donating electrons to free radicals or reactive oxygen species, antioxidants are molecular compounds that have strong scavenging properties that transform them into benign substances.

Experimental:

General procedure for the synthesis of substituted thiazolidin-4-one (3)

A mixture of substituted phenyl-2- aminothiazole 1 (0.61 mmol), pyrazole-4-carboxaldehyde 2 (0.56 mmol), and pyridine (2.13 mmol) in toluene (10 mL) was heated to 130C for 20 hours in a 25 mL round-bottom flask. Thin layer chromatography was used to monitor the reaction's progress. Following the completion of the reaction, the mixture was vacuum-evaporated before 1 mL of diethyl ether was added. Thioglycolic acid (68 mg, 0.737 mmol) was added to the separated yellow solid in 10 mL of THF, and it was stirred for 30 minutes at room temperature.

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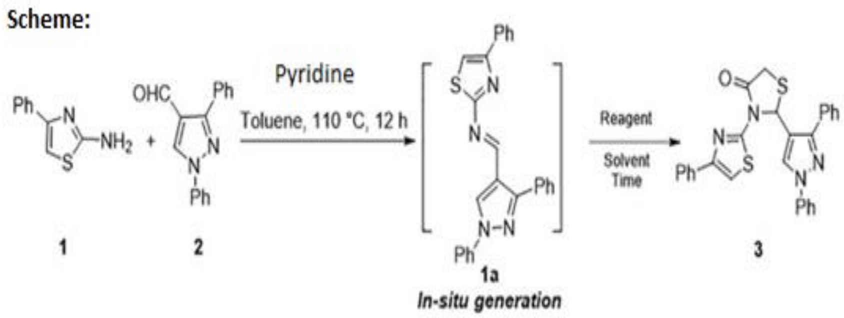
DCC (152 mg, 0.737 mmol) was added to the reaction mixture in portions after it had cooled. Thin layer chromatography was used to track the reaction's development. Once the reaction was finished, crushed ice was added. The solid product was taken out.

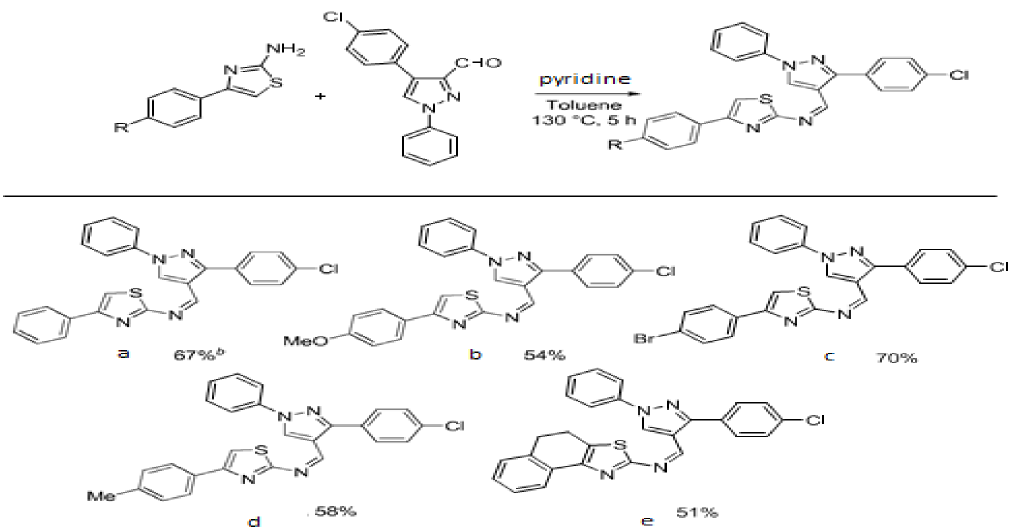
Results and discussion:

Our experiment began with the condensation of pyrazole-3-carbaldehyde and 2-amino-thiazole. We used substrates 1 and 2 as models to obtain substituted thiazolidin-4-one. Zinc chloride is typically used to treat schiff base and thioglycolic acid in order to produce substituted thiazolidin-4-one. We recently used pyridine as a base in toluene at 130 °C for 12 hours to create the schiff base hybrid from 2-amino-thiazole and pyrazole-3-carbaldehyde. A good yield of the corresponding Schiff base 1a was obtained.



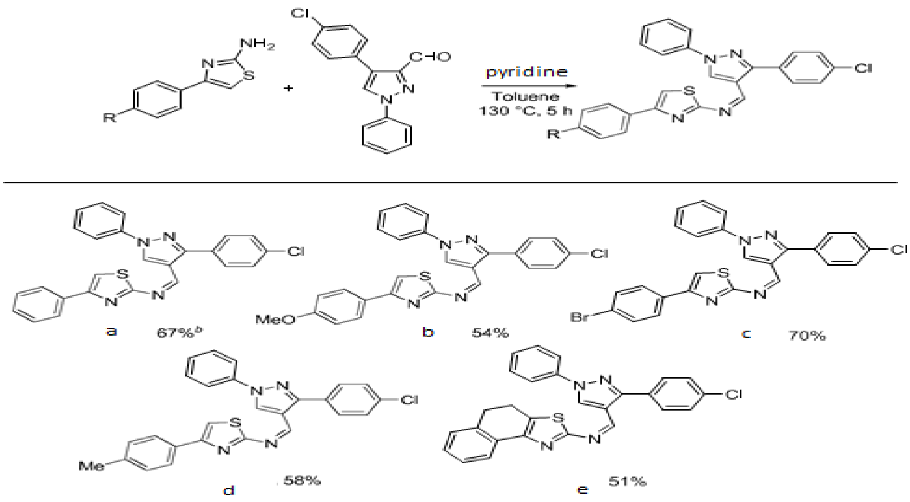
Entry	Reagent	Time (h)	Solvents	Yield[a] (%)
a	Anhydrous $ZnCl_2$	12	Toulene, THF, DMF,1,4-Dioxane	NR
b	$Cu(OAc)_2$	12	Toulene, THF, DMF, 1,4-Dioxane	NR
c	$MgCl_2$	12	Toulene, THF, DMF, 1,4-Dioxane	NR
d	I_2	12	Toulene, THF, DMF, 1,4-Dioxane	NR
e	DCC	6	THF[b]	87
f	HATU	6	THF	82
g	EDCL	12	THF	34
h	CDI	12	THF	21
i	HOBt	6	THF	NR
j	TPP	6	THF	NR

[a]Isolated yield; [b]Other solvents were also studied



Synthesis of pyrazole carbaldehyde and Schiff base derivatives:

The prepared derivatives, designated as a-e, underwent structural validation through the use of elemental analysis, FTIR, and NMR, among other analytical techniques. An examination of the product's infrared spectra revealed that a band in the 1718–1725 cm−1 range had disappeared, and a new band had appeared around 1609–1625 cm−1.The azomethine functional moiety is manifested in this up-and-coming band ensemble. 1H-NMR and 13C-NMR spectra were used to further validate the structures found in the product. The azomethine proton caused a singlet to appear at 9.40 ppm in the 1H-NMR spectra, while the aldehyde proton peak at 10.03 ppm vanished. The carbonyl carbon peak at about 186.8 ppm was absent from the 13C-NMR spectra, and the azomethine carbon atom caused the emergence of a new signal at about 156.1 ppm. In addition, other signals originating from the three carbons of the pyrazole nucleus were detected in the range of 114.24-116.01 ppm, 130.07-130.90 ppm, and 150.20-152.89 ppm.



Reaction condition: **1** (0.56 mmol), **2** (0.56 mmol), Pyridine (1.99 mmol) in Toluene (10 mL) at 130 ºC for 18 h; Isolated yield

Method for α- amylase inhibition activity:

Patil and his team's method was used to study amylase inhibition in vitro [15]. In short, 500 µL of 0.1 M phosphate buffer pH 6.9 containing 0.5% α-amylase enzyme fungal diastase (Research Lab) was allowed to react with 500 µL of the test compound 3a-n (1 mg/ml). 500 µL of 1% starch soluble, extra pure (Loba chemie) in 0.1 M phosphate buffer pH 6.8 (Research Lab) was added following a 10-minute incubation period at 25 ℃. once more incubated for 10 minutes at 25℃ C.. The controls underwent the same procedure, substituting buffer for 500 µL of the enzyme. Following incubation, 1000 µL of DNS (Loba Chemie) was added to the test and control samples. The standard medication is acarbose, which is an inhibitor of the α-amylase enzyme. After ten minutes in a boiling water bath, they were cooled. A spectrophotometer was used to measure the absorbance at 540 nm, and the formula Inhibition (%) = [Abs 540 (control) – Abs 540 (extract) × 100]/Abs 540 (control) was used to determine the percentage inhibition of the α-amylase enzyme.

Conclusion:

Using DCC as a ring closure reagent, we have created a mild and effective technique for the synthesis of thiazolidinone derivatives from the various 2-aminothiazole and pyrazole-aldehyde via schiff base formation. Regarding its MIC and IC50 values for α-amylase inhibition, glucose uptake, and antioxidant activity, the synthesized compound demonstrated encouraging outcomes. To find the ideal concentration of the synthesized compound for each of these uses and to detect any possible adverse effects, more investigation is required. Furthermore, new and improved compounds with improved properties could be developed using the synthesized compound as a starting point. All things considered, the findings of this study make a significant contribution to the field of natural product chemistry and demonstrate the potential of compounds derived from plants as sources of innovative medicines and food additives..

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Conflicts of interest
The authors declare that there are no conflicts of interest regarding the publication of this paper

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