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# SYNTHESIS AND BIOLOGICAL EVALUATION OF 5-((3-(ARYL)-1-PHENYL-1H- PYRAZOL-4-YL) METHYLENE)-2-(P-ARYLIMINO) THIAZOLIDIN-4-ONES AS A-AMYLASE INHIBITORS

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## ABSTRACT

An essential responsibility of organic and medicinal chemists is the design and synthesis of organic molecules to increase the inventory of medicinal medicines. Chemical libraries based on favored structures containing heterocyclic moieties have been made available in the previous decades using 1-3 combinatorial chemistry. It is clear that synthetic and medicinal chemists are quite interested in the synthesis of heterocyclic molecules containing nitrogen and sulfur, as there are many research articles on the topic. Rings with five members and two heteroatoms are common in physiologically active compounds. Research into pyrazole and thiazolidin-4-one is particularly intriguing to medicinal chemists.

**KEYWORDS:** Biological Evaluation, Thiazolidin-4-Ones, Amylase Inhibitors, glycogenolytic pathways, antidiabetic drugs

## INTRODUCTION

One milligram per milliliter of acarbose was utilized as the reference standard. One milliliter of enzyme solution and one milliliter of various concentrations of produced compounds 2.59a-2.59u (25, 50, 100 µg/mL) in DMSO were mixed to conduct the experiment. The mixture was then incubated at 37ºC for 30 minutes. Before being incubated for another 15 minutes at 37ºC, 1 mL of starch solution was added to the mixture. Following that, 1 milliliter of DNSA coloring reagent, which has a concentration of 96 millimolar, was added to the aforementioned solution. After the reaction mixture was shaken, the sealed test tubes were submerged in a water bath set at 85 degrees Celsius for duration of 15 minutes. The next step was to take the reaction mixture out of the water bath, let it cool, and then measures its absorbance at 650 nm. Separate blanks were made to

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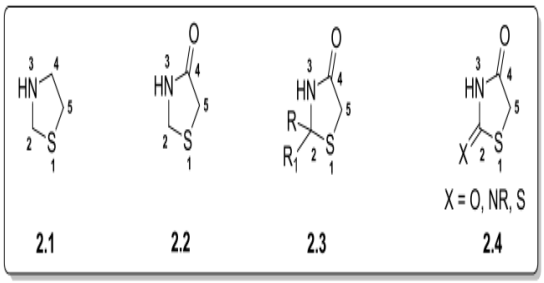
rectify the absorbance of the backdrop. Access to chemical libraries based on favored structures, containing heterocyclic moieties, has been made possible in the recent decades through 1-3 combinatorial chemistry. It is clear that synthetic and medicinal chemists are quite interested in the synthesis of heterocyclic molecules containing nitrogen and sulfur, as there are many research articles on the topic.

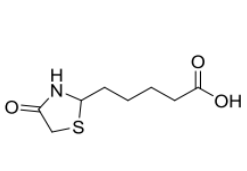
Rings with five members and two heteroatoms are common in physiologically active compounds. Research into pyrazole and thiazolidin-4-one is particularly intriguing to medicinal chemists.

**Thiazolidin-4-one**

The oxo derivatives of thiazolidine (2.1), a saturated thiazole form with a carbonyl group at the 4th position, are known as 4-thiazolidinones (2.2). Modifications at specific places can convert thiazolidine (2.1) into 2.2, 2.3, or 2.4.9, 10




The clinical importance and broad range of pharmacological properties of thiazolidin-4-one have made it a compelling scaffold for use in various applications, including antibacterial, antimycobacterial, anti-inflammatory, anticancer, antioxidant, antihyperglycemic, antiviral, antihyperglycemic, antihyperglycemic, antihyperglycemic, antihyperglycemic, antiviral, antihyperglycemic, antihyperglycemic, antihyperglycemic,17,18—and antiviral, among many others. The favored pharmacophore thiazolidine-4-one is an antihyperglycemic agent and is found in various antidiabetic medications.A naturally occurring acid with antimycobacterial effects, actithiazic acid22 (2.5), was discovered from an actinomycete. It contains a thiazolidin-4-one ring. Latrunculin A 3-25(2.6), an ichthyotoxic molecule with anticancer properties, was isolated from the red sea sponge Negombata magnifica. It is the first marine macrolide to contain 2-thiazolidinone.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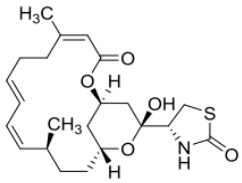
2.6

The thiazolidin-4-one pharmacophore is found in a wide variety of popular drugs. For example, ralitoline26(2.7) has

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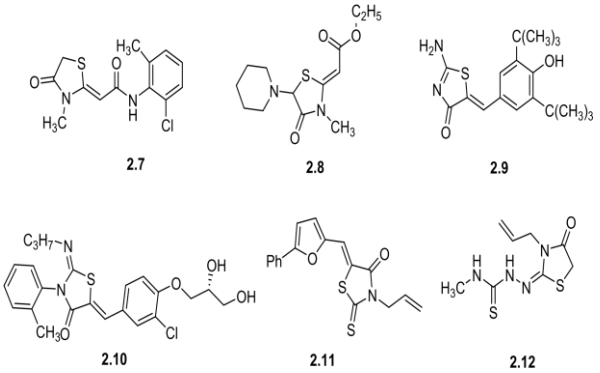
impressive anticonvulsant effects, etozolin27,28(2.8) shows antihypertensive effects, darbufelone29,30(2.9) acts as a dual COX/LOX inhibitor, ponesimod31(2.10) treats MS, LJ-00132(2.11) is an effective broad-spectrum antiviral, and CGP5260833(2.12) relieves arthritis.



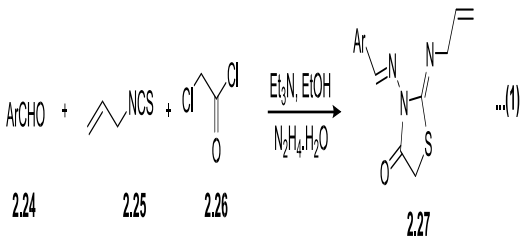

Antifungal, anti-inflammatory, antioxidant, anti-tumor, anti-bacterial, anti-cancer, antidiabetic, analgesic, anticonvulsant, and so on are some of its attributes.

Some naturally occurring compounds contain the pyrazole ring system, which is particularly important. For example, 1-pyrazolyl-alanine, an isomer of histidine that was extracted from the seeds of Citrullus vulgaris, has antidiabetic activity (L-α-amino-β-(pyrazolyl-N)propanoic acid, 45(2.13).

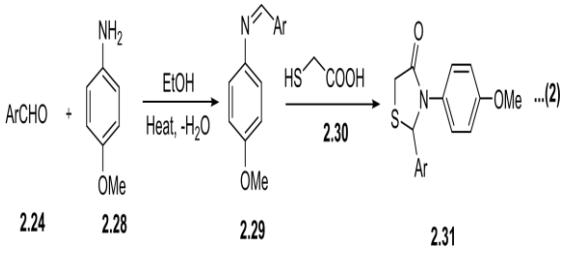
**3Method of synthesis**

Several different approaches have een used to produce thiazolidin-4-one, some of which are more generic and others of which are more targeted. Many medicinal and synthetic chemists have done extensive work on the thiazolidine-4-one moiety because of the large range of substitutions it can undergo.

A one-pot four-component synthesis involving substituted aldehydes (2.24), allyl isothiocyanate (2.25), α-chloroacetyl chloride (2.26), hydrazine in ethanol using Et3N as a catalyst has been used to create thiazolidine-4-one derivatives (2.27) (eq.1).




The two-step synthesis of 3-(methoxyphenyl)-2-aryl thiazolidin-4-one (2.31) derivatives was described by Jubie et al.60. The reaction consisted of combining aldehyde (2.24) and p-methoxy aniline (2.28) to form Schiff bases (2.29). The Schiff bases were then further reacted with mercaptoacetic acid (2.30) to yield the desired product (eq.2).



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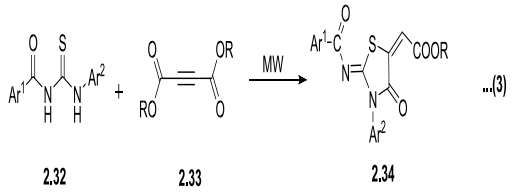
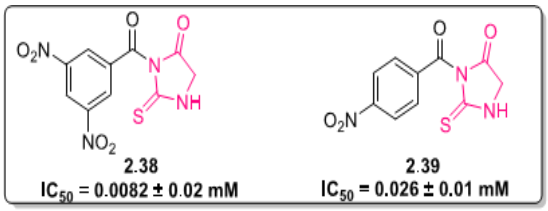
In a study conducted by Mahmoodi et al.15, (eq.3), it was found that 1,3-thiazolidine-4-ones (2.34) can be synthesized by reacting N-aryl-N′-acyl thiourea (2.32) with acetylenic esters (dimethyl acetylenedicarboxylate, or diethyl acetylenedicarboxylate, or DEAD) (2.33) under solvent-free conditions using microwave irradiation.




By reacting 2-(2,4-dimethoxy-phenylamino)thiazol-4-one (2.35), substituted 1,3-diphenyl-1H-pyrazole-4-carbaldehydes (2.36), and refluxing the resulting mixture in acetic acid for two to four hours while adding sodium acetate (eq.4), Gawande et al.61 were able to synthesize 2-(2,4-dimethoxy-phenylamino)-5methylene-thiazol-4-one (2.37).

**Thiazolidin-4-one and pyrazole as α-amylase inhibitors**

The 3-(3,5-dinitrobenzoyl)-2thioxoimidazolidin-4-one (2.38) and 3-(4-nitrobenzoyl)-2-thioxoimidazolidin-4-one (2.39) were effectively synthesized by Qamar et al.62 from 3-(substituted benzoyl)-2-thioimidazolidin-4-ones, and they showed remarkable α-amylase inhibitory activity. We found an IC50 value of 0.0082 mM for 2.38 and 0.026 mM for 2.39.




Sharma et al.63 reported the biological potential of 3-(2-(4-(4-substituted benzylideneamino)5-phenyl-4H-1,2,4-triazol-3-ylthio)acetyl)-2-(arylimino)thiazolidin-4-one derivatives via in vitro α-amylase inhibition study and found that highest α-amylase inhibition activity of 92.17% was shown by (Z)-3-(2-((4-(((E)-4-methoxybenzylidene)amino)-5-phenyl-4H-1,2,4triazol-3-yl)thio)acetyl)-2-((4-methoxyphenyl)imino)thiazolidin-4-one (2.40) at 1 mg/mL concentration. the chemical formula for (E)-3-Ethyl-5-(3-ethylbenzo[d]Another component of the root extract of Khaya senegalensis that has demonstrated promising inhibitory effects against α-amylase is thiazol-2(3H)-ylidene)-2-(p-tolyl(vinyl)amino) thiazolidin-4-one (2.41).64

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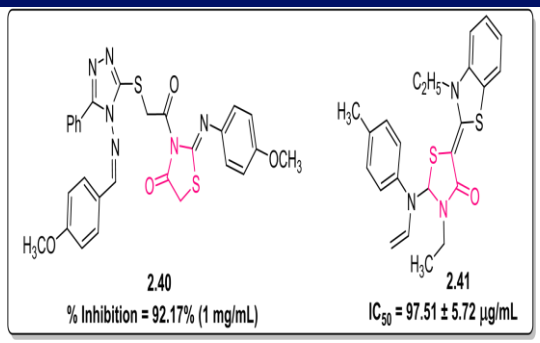
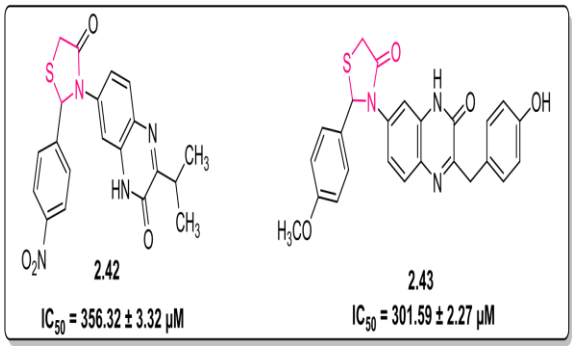
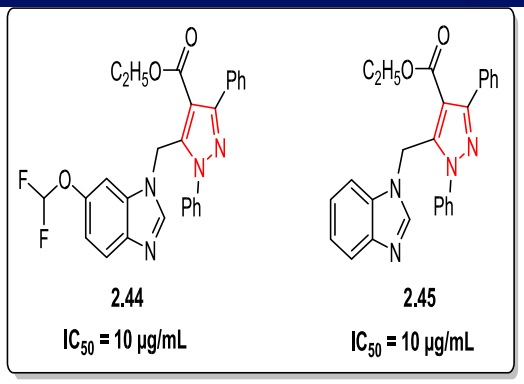



In particular, 3-(2-isopropyl-3oxo-3,4-dihydroquinoxalin-6-yl) and other new thiazolidine-containing quinoxaline rings2.42 and 3-(2-(4hydroxybenzyl)-2-(4-nitrophenyl)thiazolidin-4-one"-3-oxo-3,4-dihydroquinoxalin-6-yl (The compound 2.43 had a substantial inhibitory effect on α-amylase with an IC50 value of 356.32 ± 3.32 µM and 301.59 ± 2.27 µM, respectively.65



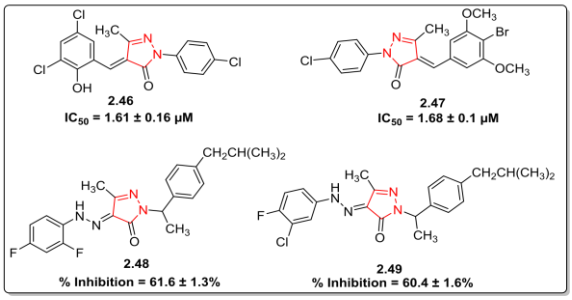

The hybrid molecule ethyl 5-((6-(difluoromethoxy)1H-benzo[d]imidazol-1-yl)methyl)-1,3-diphenyl-1H-pyrazole-4-carboxylate (2.44) and ethyl 5-((1H-benzo[d]imidazol-1-yl)methyl)-1,3-diphenyl-1H-pyrazole-4-carboxylate (2.45) have demonstrated significant in vitro α-amylase inhibition (2024).66




The pyrazolone compounds, for example, 2-(4-chlorophenyl)-5-methyl-4'-(3",5"-dichloro-2"hydroxybenzylidene) chemical formula (E)The compound in question is known as (E)-4′-(4″-bromo-3″,5″-di methoxybenzylidene, and its molecular formula is 2.46.2-[1-(4-isobutylphenyl)ethyl] and 2-[-2′-(4-chlorophenyl)-5′-methyl-2,4′dihydro-3H-pyrazol-3′-one (2.47).

Hydrazinylidene, 5-methyl-4-[2-(2,4-difluorophenyl)](2.48), 2,4-dihydro-3-hydroxypyrazol-3-one together with 2-[1-(4-isobutylphenyl)ethyl]Hydrazinylidene, 5-methyl-4-[2-(3chloro-4-fluorophenyl)]The compound 2.49, which is -2,4-dihydro-3H-pyrazol-3-one,

exhibited maximum α-amylase inhibition.[67,68]



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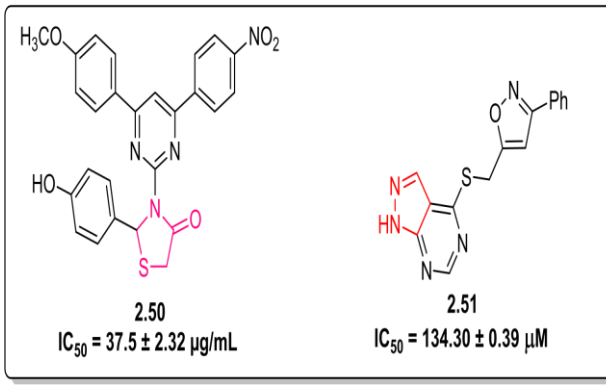
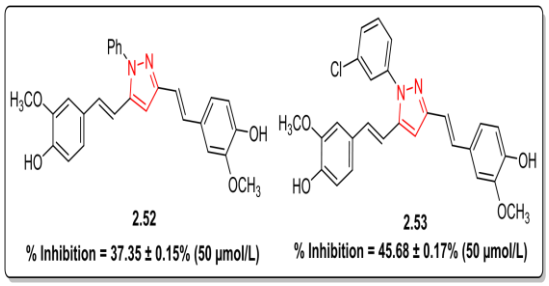
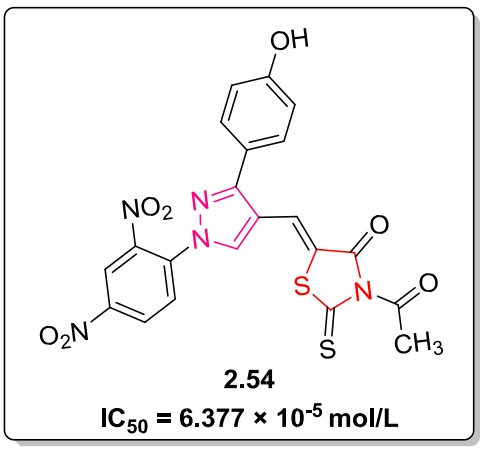
The novel scaffolds produced by Andhale et al. 69 are 2-(4-hydroxyphenyl)-3-(4-(4methoxyphenyl)The compound 2.50, which contains the rings of pyrimidine and thiazolidinone, has demonstrated encouraging activity as an inhibitor of α-amylase. The in vitro α-amylase inhibition investigation of new derivatives of fused pyrazolo[3,4-d]pyrimidine has been assessed by El Fal et al.70. Out of all the compounds that were produced, the one with the highest inhibitory potential against α-amylase was 5-(((1Hpyrazolo[3,4-d]pyrimidin-4-yl)thio)methyl)-3-phenylisoxazole (2.51).




When compared to curcumin,the compounds 4,4'-((1E,1'E)-(1-phenyl-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) (2.52) and 4,4'-((1E,1'E)-(1-(3-chlorophenyl)-1H-pyrazole-3,5diyl)bis (ethene-2,1-diyl))bis(2-methoxyphenol) (2.53) demonstrated significant inhibitory activity against α-amylase. 71 At doses of 50, 100, and 200 µmol/L, respectively, compound 2.52 showed an inhibition of 37.35 ± 0.15, 53.87 ± 0.57, and 71.98 ± 0.41%. At doses of 50, 100, and 200 µmol/L, respectively, compound 2.53 exhibited a notable inhibitory effect with an inhibition of 45.68 ± 0.17, 55.74 ± 0.34, and 80.02 ± 0.23%. At 50, 100, and 200 µmol/L, curcumin inhibited α-amylase with a relative efficiency of 43.96 ± 0.97, 57.47 ± 0.52, and 84.33 ± 0.74%, respectively.




A class of molecular hybrids known as rhodanine-pyrazole (Z)-3-acetyl-5-((1-(2,4dinitrophenyl)-3-(4-hydroxyphenyl)(-1H-pyrazol-4-yl) (methyl)2.54-thioxothiazolidin-4one showed substantial inhibition of α-amylase.



Research on the inhibitory potential of the thiazolidin-4-one and pyrazole moiety towards α-amylase could be a promising field, as shown in the previous study. But the hybrid compounds that include both of these moieties have received surprisingly little research focus. This article details the design and synthesis of a hybrid scaffold including thiazolidin-4-one and pyrazole in a single matrix 2.59a-2.59u (Figure 1), continuing our interest in the design and development of physiologically active heterocyclic compounds73-75 and new inhibitors of α-amylase.

## CONCLUSION

Diabetes mellitus is one of the most common non-communicable metabolic disorders characterized by chronic hyperglycemia or increased blood glucose levels with disturbances in carbohydrate, fat and protein metabolism resulting from the absolute or relative lack of insulin secretion. Therefore, enzymes that regulate glycogenolytic pathways are key biological targets for therapeutic interventions. Out of several enzymes known, α-amylase is an important key enzyme responsible for carbohydrate digestion. So, inhibitors of α-amylase can effectively retard the digestion and assimilation at the early steps of starch digestion, and thus succeed in the significant delay of postprandial hyperglycemia and have a beneficial effect on insulin resistance. α-amylase is considered to be one of the best targets for the development of type 2 diabetes therapeutic agents due to its ability to catalyze the hydrolysis of α-(1,4)-glycosidic linkages in starch.Acarbose and voglibose are two known inhibitors of α-amylase which are in clinical use nowadays. However, they often cause severe gastrointestinal side effects such as abdominal pain, flatulence, and diarrhea. In recent years, α-amylase has been a point of interest for the development of novel antiobesity and antidiabetic drugs. In search of new inhibitors of αamylase that induce no deleterious side effects, various studies have been carried out.

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