REVIEW ON THE SIGNIFICANCE OF QUINAZOLINONE DERIVATIVES AS POTENT ANTIHYPERGLYCEMIC AGENTS

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ABSTRACT

Diabetes mellitus is a chronic metabolic disease which is characterized by high blood sugar levels over a prolonged period of time. Uncontrolled hyperglycemia can lead to serious damage to many vital organs in the body, including kidney damage, heart disease, and nerve damage. The goal of treatment of diabetes mellitus is reduction of blood glucose levels and controlling subsequent complications. Different mechanisms are involved in diabetes mellitus treatment.

Quinazolinone and its derivatives have been found as effective and versatile pharmacophoric units in medicinal chemistry to design and develop a wide range of bioactive compounds.

The present review summarizes the advances in lead compounds of quinazolinone hybrids and their related heterocycles

in treatment of diabetes mellitus. Moreover, the review also helps to intensify the drug development process by providing an understanding of the potential role of these hybridized pharmacophoric features in exhibiting the hypoglycemic effect. Keywords: Quinazolinone, Diabetes mellitus, Drug design, Antidiabetic

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Objectives

The aim of this study is to highlight the role of quinazolinone containing compounds in management of diabetes mellitus as well as to suggest some new aspects of treatment of hypoglycemia using quinazolinone scaffold in the near future.

Introduction

Diabetes mellitus is a chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar) (Lopez-Candales 2001). This elevation may lead to serious damage to the heart, blood vessels, eyes, kidneys and nerves over the time. Three main types of diabetes are well defined, type 1, type 2 and gestational (Deshpande, Harris-Hayes et al. 2008). According to WHO, about 422 million people worldwide have diabetes, the majority living in low-and middle-income countries. Besides, 1.6 million deaths are directly attributed to diabetes each year (Organization 2021).

Type 2 diabetes is the most common type specially in adults (Passos, Barreto et al. 2005). It occurs when the body becomes resistant to insulin or doesn't make enough insulin (Taha, Ismail et al. 2016). In the past three decades the prevalence of type 2 diabetes has risen dramatically in countries of all income levels. For people living with diabetes, access to affordable treatment, including insulin, is critical to their survival. There is a globally agreed target to halt the rise in diabetes and obesity by 2025 (Roth, Nguyen et al. 2015).

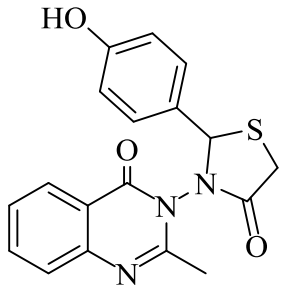
Currently, a wide range of oral antidiabetic drugs are being utilized due to the absence of efficient and affordable interventions. In most cases, the prescribed antidiabetic drugs are responsible for various side effects such as liver problems, diarrhea, lactic acidosis, and high rate of secondary failure. So that, the discovery of novel small molecules with potential usefulness as potent hypoglycemic agents is still a major challenge to medicinal chemistry researchers (Barmak, Niknam et al. 2019).

Quinazolinone and its derivatives have been found as effective and versatile pharmacophoric units in medicinal chemistry to design and develop a wide range of bioactive compounds. Some medicinal properties such as anticancer (Faraji, Motahari et al. 2021), antimicrobial (Khodarahmi, Jafari et al. 2012), anti-cholinesterase (Sarfraz, Sultana et al. 2018), anti-inflammatory (Zayed and Hassan 2014), and dihydrofolate reductase inhibitory (Al-Rashood, Aboldahab et al. 2006) activities have been successfully documented in the literature. Furthermore, recent studies confirmed the oral hypoglycemic activity of quinazolinones.

1- Quinazolinones as peroxisome proliferator-activated receptor γ (PPAR γ) agonist:

In 2019, a series of new 3-(2-substituted-4-oxothiazolidin-3-yl)-2-methylquinazolin-4(3*H*)-ones was synthesized and evaluated for its peroxisome proliferator-activated receptor γ (PPAR γ) agonist effect. Significant lowering of glycated hemoglobin level was induced by the compounds after 21 days of treatment.

Among the tested compounds, members **1**, **2**, **3** and **4** exhibited the highest hypoglycemic effects (Jangam and Wankhede 2019).



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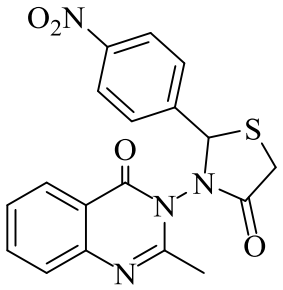

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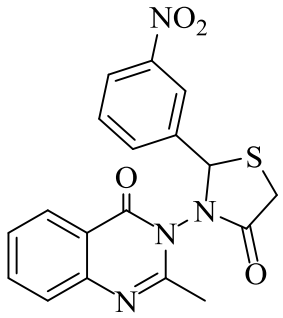

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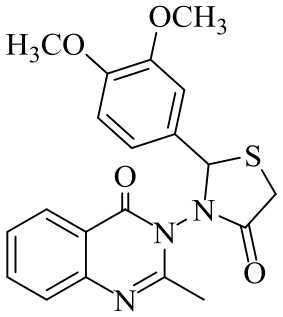

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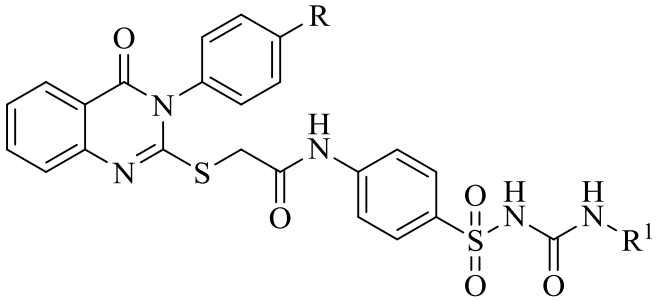
Additionally, a series of quinazoline-4(3*H*)-one sulfonylurea hybrids were designed and synthesized as dual PPAR **γ** and SUR agonists. The synthesized compounds were evaluated for their *in vivo* anti-hyperglycemic activities against STZ-induced hyperglycemic rats. Compounds **5_{a-c}** demonstrated potent activities with reduction in blood glucose levels of 40.43, 46.42 and 41.23 %, respectively (Ibrahim, Eissa et al. 2017).



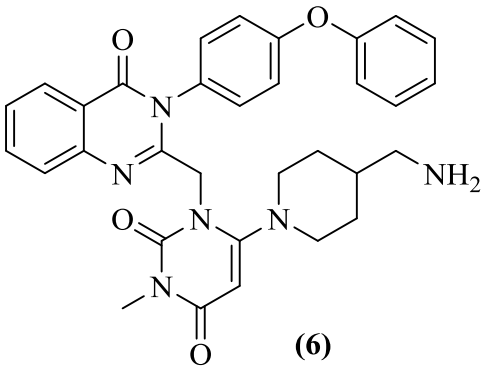
(5_{a-c})

	R	R^1
5_a	CH_3	cyclohexyl
5_b	OCH_3	cyclohexyl
5_c	OCH_3	butyl

2- Quinazolinones as dipeptidyl peptidase-4 (DPP-4) inhibitors

The dipeptidyl peptidase-4 inhibition potencies of new quinazolinone-pyrimidine and benzyl-pyrimidine hybrids were assessed by L. Emami *et. al* (Emami,

Faghih *et al*. 2020). Compound **6** was found to be the most potent agent with an IC_{50} value of 34.3 ± 3.3 μM.



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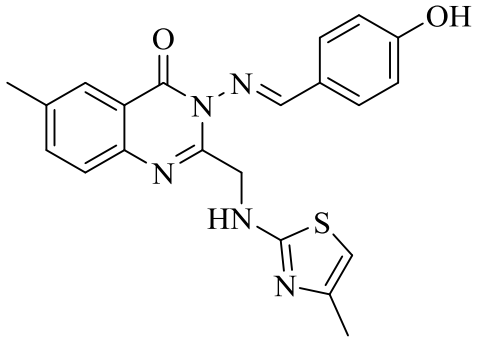
A series of quinazoline clubbed thiazoline derivatives was rationally designed and synthesized in 2017. The newly synthesized compounds were evaluated for in vitro dipeptidyl peptidase IV (DPP-4) inhibitory activity. Compounds that showed good to moderate activity were compared using linagliptin as standard. Compound **7** exhibited the most promising results with IC_{50} of 1.12 nM (Ali, Akhtar *et al*. 2017).



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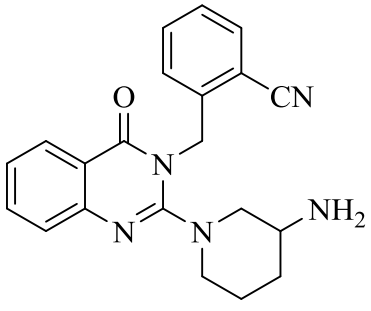
Compound **8** was designed, prepared and identified as a potent and selective DPP-4 inhibitor with IC_{50} = 0.013 μM. However, due to the short metabolic half-life of **8** in rat, caused by the metabolism via oxidation at C-5 or C-6 of the fused benzene ring, fluorinated derivative **9** was synthesized (Havale and Pal 2009).



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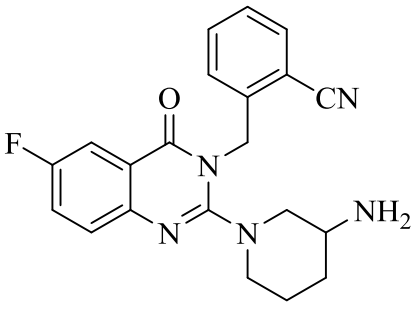

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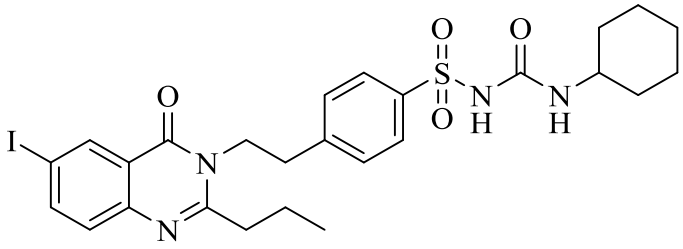
3- Quinazolinones as sulfonylurea agonist

A series of quinazolinone bearing sulfonylurea were synthesized in 2009. The target compounds were evaluated for their oral hypoglycemic effect. Member **10** was

the best regarding the hypoglycemic effect compared to the reference drug, glibenclamide (Ibrahim, El-Helby *et al*.).



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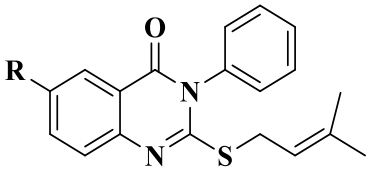
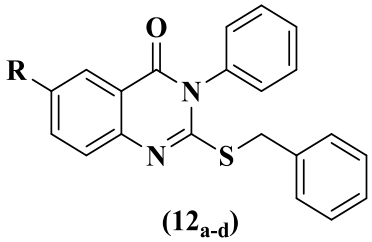
4- Quinazolinones as protein tyrosine phosphatase 1B inhibitors

In 2012, a series of 2-mercapto-4 (3*H*)-quinazolinone derivatives was designed and synthesized. The target derivatives **11_{a-d}**, **12_{a-d}**, **13_{a-c}** and **14_{a-c}** were biologically evaluated and proved to have protein tyrosine phosphatase 1B inhibitory effects (Li, Wang et al. 2012).



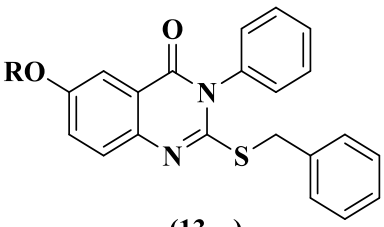
(11_{a-d})



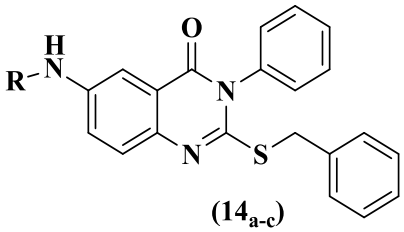
(12_{a-d})

Comp.	11_a	11_b	11_c	11_d
R	I	Br	Cl	H

Comp.	12_a	12_b	12_c	12_d
R	Br	Cl	OCH_3	H



(13_{a-c})



(14_{a-c})

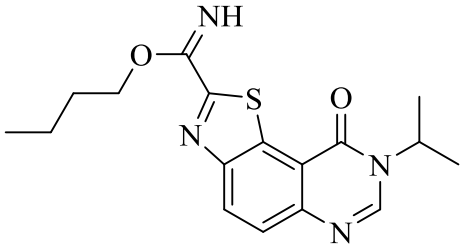
Comp.	13_a	13_b	13_c
R	$COCH_3$	SO_2CH_3	$SO_2C_6H_5CH_3$

Comp.	14_a	14_b	14_c
R	H	$COCH_3$	$SO_2C_6H_5CH_3$

5- Quinazolinones as glycogen synthase kinase-3 (GSK-3) inhibitors

A rapid and efficient synthesis of series of 9-oxo-thiazolo[5,4-f]quinazoline-2-carbonitrile derivatives was performed and optimized under microwave irradiation.

Most of the quinazolinone derivatives exhibited potent GSK-3 inhibitory effect. Among these molecules, compound **15** exhibits an efficient capacity to inhibit GSK-3 (IC_{50} values of 0.13 μM) (Logé, Testard *et al*. 2008).



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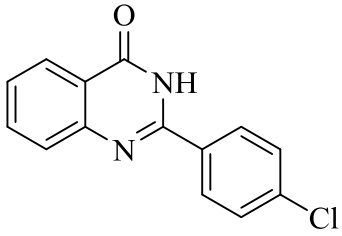
6- Quinazolinones as α-glucosidase inhibitors

In 2017 eight quinazolinone derivatives were designed and synthesized. Their inhibitory activities on α-glucosidase were assessed *in vitro*. Two compounds: 2-(4-chlorophenyl)-quinazolin-4(3*H*)-one **16** and 2-(4-bromophenyl)-quinazolin-4(3*H*)-one **17** were found to be potent inhibitors of a-glucosidase with IC_{50} values of 12.5 ± 0.1 μM and 15.6 ± 0.2 μM, respectively (Wei, Chai *et al*. 2017).



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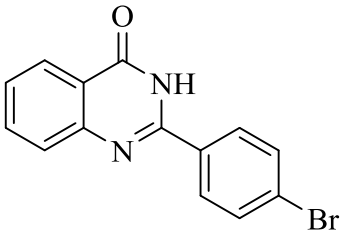

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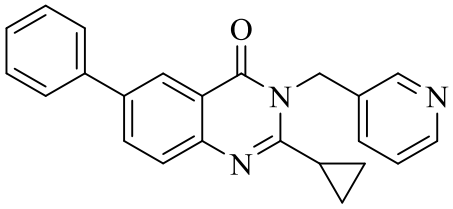
R. Garlapati *et al*. developed a series of quinazolinone based α-glucosidase inhibitors. Virtual screening model has been generated and validated utilizing acarbose as a standard α-glucosidase inhibitor. Among the tested compounds, compounds **18**, **19** and **20** possessed the highest α-glucosidase inhibitory effects IC_{50} values <20 μM (Garlapati, Pottabathini *et al.* 2013).



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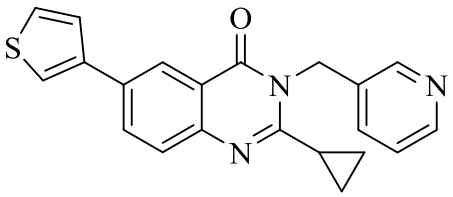

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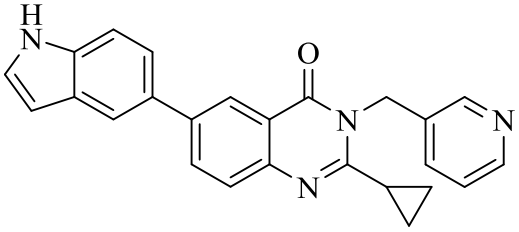
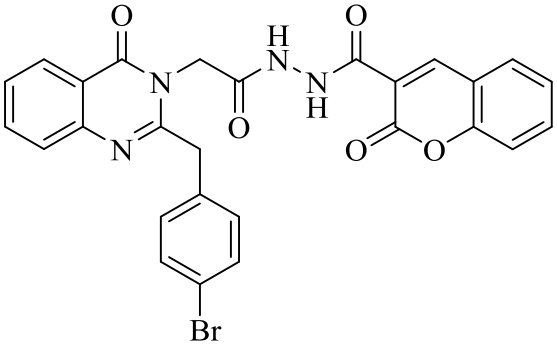


(20)

A series of 2-substituted quinazolin-4(3*H*)-one derivatives including coumarin nucleus has been synthesized and screened for their α-glucosidase inhibition properties. Among the synthesized compounds, *N*'-(2-(2-(3,4-dichlorobenzyl)-4-oxoquinazolin-3(4*H*)-yl)acetyl)-2-oxo-2*H*-chromene-3-carbohydrazide **21** and *N*'-(2-(2-(4-bromobenzyl)-4-oxoquinazolin-3(4*H*)-yl)acetyl)-2-oxo-2*H*-chromene-3-carbo-hydrazide **22** showed the best inhibitory effect against α-glucosidase with IC_{50} values of 6.11 ± 0.40 and 7.34 ± 0.37 µM, respectively (Menteşe, Karaali *et al.* 2016).



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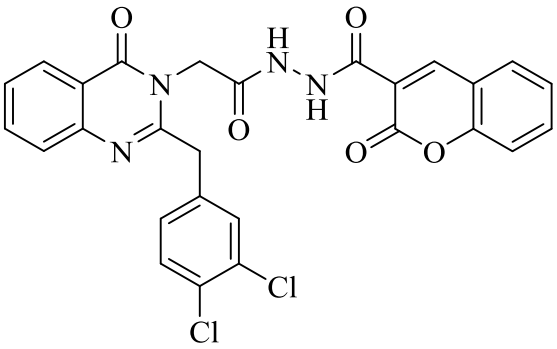
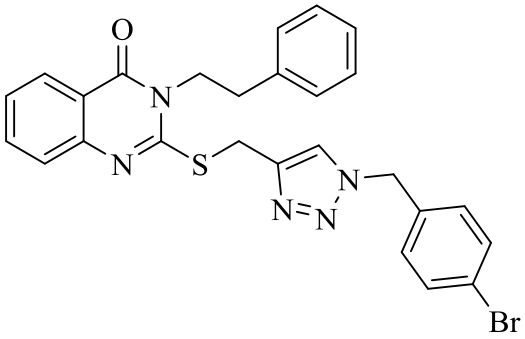


(22)

A series of quinazolinone-1,2,3-triazole hybrids were designed, synthesized and evaluated for their *in vitro* α-glucosidase inhibitory activity leading to efficient anti-diabetic agents. All synthesized compounds exhibited good inhibitory activity against yeast α-glucosidase (IC_{50} values in the range of 181.0 - 474.5 µM) even much more potent than standard drug acarbose (IC_{50} = 750.0 µM). Among them, quinazolinone-1,2,3-triazoles possessing 4-bromobenzyl moiety connected to 1,2,3-triazole ring (**23** and **24**) demonstrated the most potent inhibitory activity towards α-glucosidase (Saeedi, Mohammadi-Khanaposhtani *et al*. 2019).



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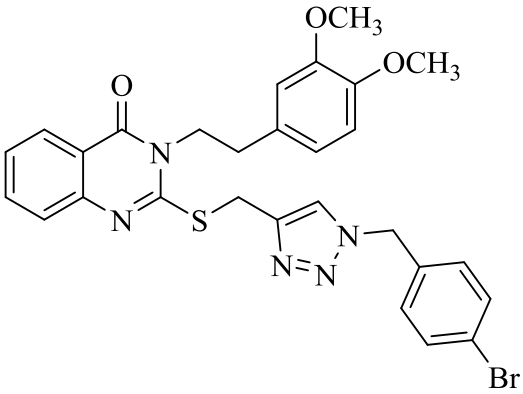
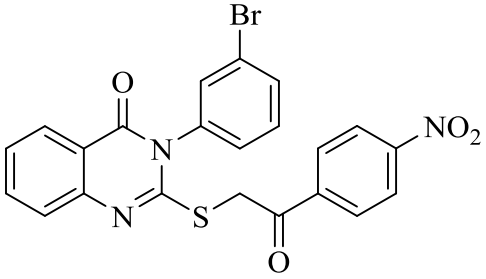


(24)

In 2021, different quinazolinone analogs were designed and tested for their α-glucosidase inhibitory effects. Results showed that most of the tested members were found potent and showed many folds increased *α*-glucosidase enzyme inhibition as compared to standard acarbose (IC_{50} = 750.0 ± 10.0 µM). Compound 25 (IC_{50} = 85.0 ± 0.5 µM) was recognized as the most potent analog of the whole series, with nine-fold enhanced inhibitory potential than the standard acarbose (Wali, Anwar *et al*. 2021).



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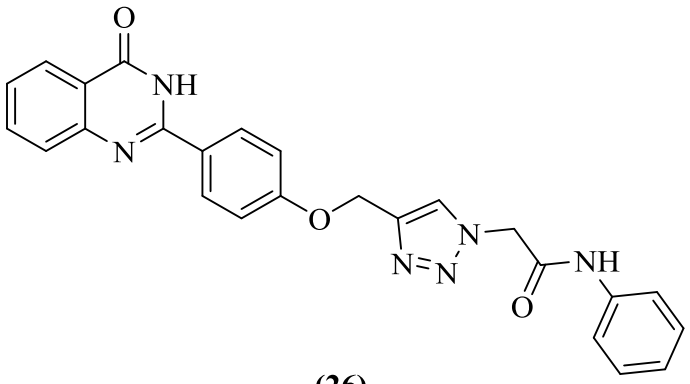
A series of quinazolinone-1,2,3-triazole-acetamide hybrids synthesized *via* molecular hybridization of the potent α-glucosidase inhibitor pharmacophores was designed and evaluated against carbohydrate-hydrolyzing enzyme, α-glucosidase. All the synthesized compounds with IC_{50} values in the range of 45.3 ± 1.4 µM to 195.5 ± 4.7 µM were significantly more potent than standard α-glucosidase inhibitor, acarbose. Representatively, compound **26** with IC_{50} = 45.3 ± 1.4 µM was around 17 times more potent than standard inhibitor acarbose (IC_{50} = 750.0 ± 12.5 µM) (Yavari, Mohammadi-Khanaposhtani *et al.* 2021).



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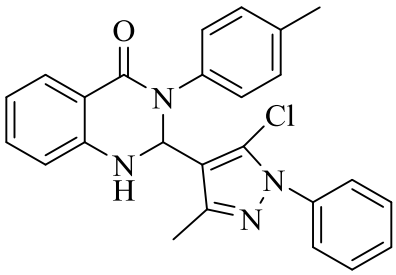
A series of 2,3-dihydroquinazolin-4(1*H*)-ones derived from pyrazol-4-carbaldehyde and anilines was designed and synthesized in 2019. The ability of synthesized compounds in the inhibition of α-glucosidase was investigated. The entire synthesized compounds showed the potent α-glucosidase inhibitory activity compared with acarbose as a standard material. Amongst, compounds **27** and **28** showed the strongest enzyme inhibitory potentials than the standard drug acarbose (Barmak, Niknam *et al.* 2019).



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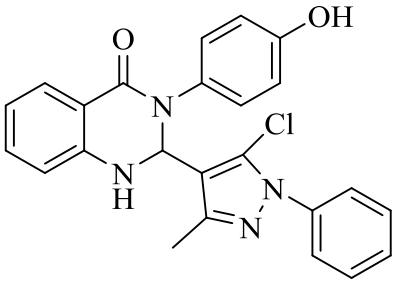

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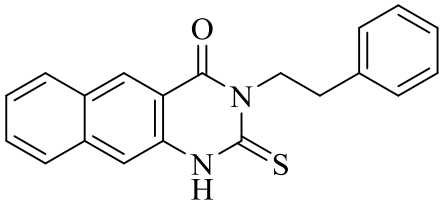
In vitro α-glucosidase inhibitory activity was evaluated for a newly synthesized 3-benzyl(phenethyl)-2-thioxobenzo[g]quinazolin-4(3*H*)-one series using Baker's yeast α-glucosidase enzyme. Compounds **29**, **30**, **31**, **32** and **33** exhibited the highest activity (IC_{50} = 69.20, 59.60, 49.40, 50.20 and 83.20 μM, respectively) compared with the standard acarbose (IC_{50} = 143.54 μM) (Al-Salahi, Ahmad *et al*. 2018).



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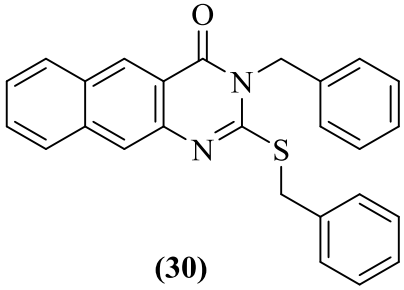

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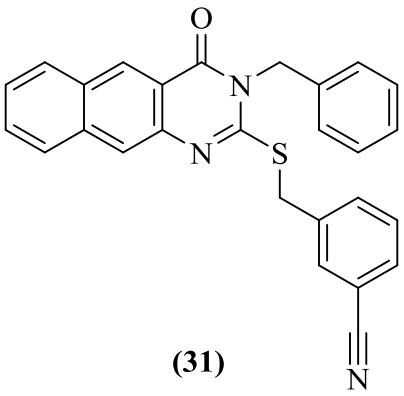

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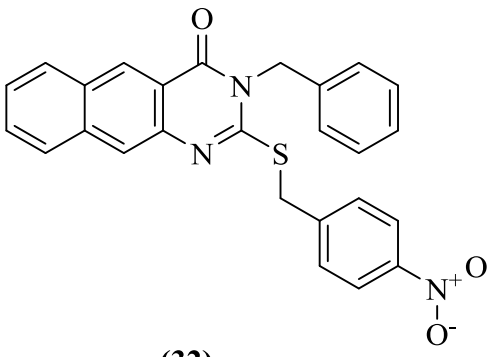

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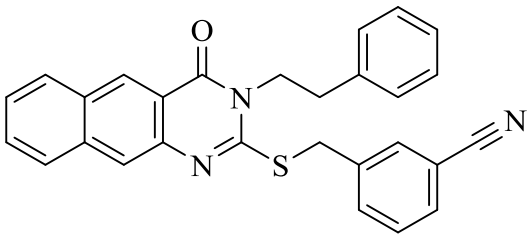
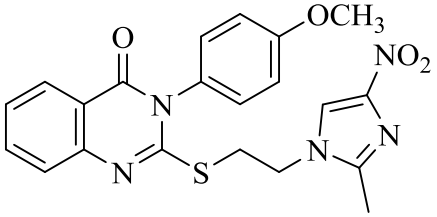


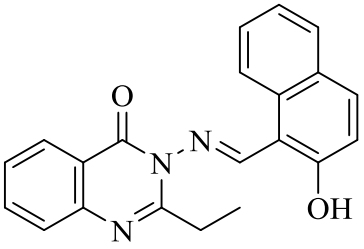
(33)

In 2021, moreover, a series of quinazolinone-2-thio-metronidazole derivatives was designed, synthesized and assayed for their activity against α-glucosidase enzyme. The results indicated that all the synthesized compounds exhibited excellent inhibitory activities against mentioned enzyme as compared with standard inhibitor. Biological testing proved that the most active α-glucosidase inhibitor was compound **34** with 4-methoxyphenyl moiety. It was 5-times more active that acarbose as standard inhibitor (Ansari, Mohammadi-Khanaposhtani *et al*. 2021).

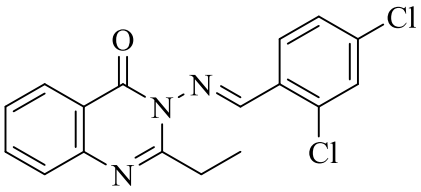


(34)

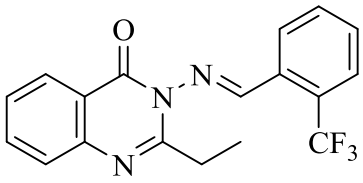
In addition, some quinazolinone derivatives were synthesized from different aldehydes and 2-ethyl-3-aminoquinazolin-4(3*H*)-one in 2021. The compounds were tested against some metabolic enzymes particularly α-glucosidase. Compounds **35**, **36** and **37** were the most active inhibitor among the tested members with IC_{50} values of 215 ± 29, 278 ± 28 and 250 ± 26 μM, respectively (Tokalı, Taslimi *et al*. 2021).



(35)

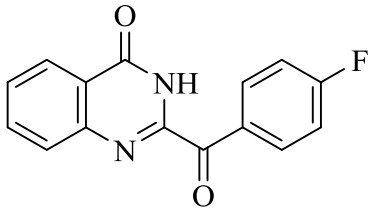


(36)

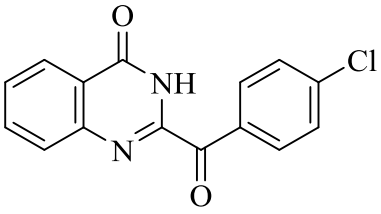


(37)

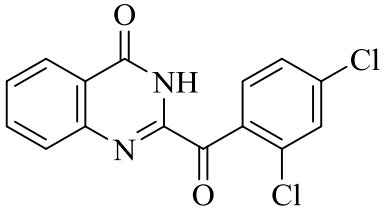
Several benzoylquinazolinone derivatives were synthesized and evaluated for *in vitro* α-glucosidase inhibitory activity. Compounds **38**, **39**, **40**, **41**, **42** and **43** showed more inhibitory activity than standard drug acarbose (IC_{50} = 750.0 ± 1.5 μM), and among them, compound **38** displayed the highest α-glucosidase inhibitory activity (IC_{50} = 261.6 ± 0.1 μM).



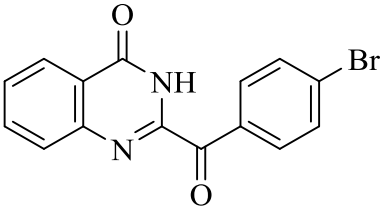
(38)



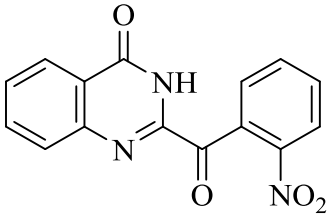
(39)



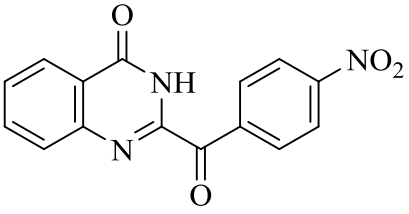
(40)



(41)



(42)



(43)

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مقال عن أهمية مشتقات كينازولينون كعوامل قوية لخفض السكر في الدم

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يعتبر مرض السكري من أهم الأمراض وأخطرها على مستوى العالم مما دفع الى تطوير العديد من العقاقير والانظمه الدوائية المتخصصة فى علاجه. وبالبحث والرجوع الى المراجع العلمية المتعددة التى تتناول تشيد مركبات جديده ذات فاعلية مضاده لداء السكري وجد لبعض المشتقات الجديدة لنواه الكينازولينون فعالية عالية فى تقليل نسبة السكر بالدم. وقد تناولنا فى هذا البحث بعض المشتقات لنواه الكينازولينون ذات الفعالية العالية فى علاج السكري وتم تصنيفها على اساس طريقة عملها.

الكلمات المفتاحية: الكينازولينون، مرض السكري، تصميم الادوية، مضاد للسكر