RESEARCH PAPER

Recent Advances in Coumarin-Based Hybrids as Potent α-Glucosidase Inhibitors for Type 2 Diabetes Mellitus

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ABSTRACT
Diabetes mellitus (DM) is a chronic metabolic disorder characterized by elevated blood glucose levels resulting from either insufficient insulin production or poor insulin sensitivity. One of the most effective strategies to control DM is the inhibition of α-glucosidase, an enzyme responsible for breaking down complex carbohydrates into monosaccharides. α-Glucosidase inhibitors, such as acarbose, are commonly used to delay the absorption of glucose and reduce post-meal blood sugar spikes. However, the adverse side effects and limited effectiveness of current α-glucosidase inhibitors have led researchers to explore novel compounds with improved pharmacological properties. Coumarins are a class of naturally occurring compounds found in various plants and are well-known for their beneficial effects on human health. Among the promising candidates, coumarin-based hybrids have emerged as potential therapeutic agents due to their diverse biological activities, including antioxidants, anti-inflammatory, and antidiabetic effects. The structural versatility of coumarins allows for the design of hybrid molecules by combining them with other bioactive scaffolds to enhance their pharmacological properties. Recent studies have indicated that coumarin derivatives exhibit significant α-glucosidase inhibitory activity, making them attractive candidates for the development of new antidiabetic drugs. By combining the coumarin scaffold with other bioactive groups such as flavonoids, peptides, or heterocycles, researchers aim to enhance both the efficacy and selectivity of these hybrids for α-glucosidase inhibition. In conclusion, coumarin-based hybrids represent a promising class of compounds for the management of diabetes mellitus, particularly in the context of α-glucosidase inhibition. With their potential to regulate blood glucose levels, coupled with their antioxidant and anti-inflammatory properties, these hybrids hold great promise as safer and more effective alternatives to existing α-glucosidase inhibitors. Future research and development in this area are likely to contribute significantly to the discovery of novel therapeutic agents for diabetes management, with the potential for improved patient outcomes and reduced side effects.

Keywords: *Diabetes mellitus, α-Glucosidase, natural products, medicinal chemistry, SAR, biological activity.*
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1. INTRODUCTION

Diabetes increases the risk factor for several serious health conditions, such as cardiovascular disease, kidney failure, stroke, limb amputation, vision impairment, and mental health issues like depression [1]. On 7th April 2016, the first World Health Organisation (WHO) report on Diabetes mellitus was published on World Health Day. A global report aims to raise awareness of diabetes and its growing impact because diabetes is a severe illness and the physician or healers do not commonly see it [2]. India is known as the "world capital of diabetic patients" since it is the nation with the greatest number of diabetic patients worldwide [3]. The number of diabetic patients is expected to rise to a concerning 80 million by 2030 [4]. In a 2017 report by the International Diabetes Federation (IDF), it stated that 425 million people globally have diabetes mellitus or simple diabetes, of which over 90% are adults, while 352 million were identified with impaired glucose tolerance (IGT) [5]. According to the data between 2002 to 2012, 1.8% of cases of type 1 diabetes increased per year, and 4.8% of cases of type 2 diabetes increased per year [6]. The World Atlas of Diabetes presents several important insights, reporting that approximately 463 million adults aged 20 to 79, representing 9.3% of the global population in this age range bracket have diabetes. This figure is expected to rise to 578 million (10.2%) by 2030 and 700 million (10.9%) by 2045, as per the IDF's 2019 data [7, 8].

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The pancreas is an organ that secretes insulin. Insulin helps our body cells get glucose, if the glucose (sugar) level is high, then it produces symptoms like frequent urination, increased thirst, increased hunger, and other symptoms. Insulin acts as both the anabolic and catabolic pathways, which is the metabolic process and an independent pathway. It generates macromolecules with the required energy in the anabolic pathway and produces energy to break down molecules in the catabolic pathway. Diabetes mellitus is also known as a chronic metabolic disease that is characterized by the deficiency of insulin refers to a condition where an individual`s glucose levels are higher than normal but not yet high enough for diabetes diagnosis. It's an early stage of diabetes, and there is an increased risk of developing chronic complications that are typically associated with diabetes [9]. Prediabetes results from impaired beta cell function and increased insulin resistance, with insulin resistance often developing many years earlier. The study conducted by Cerasi et. al. shows that glucose-induced insulin release diminishes in pre-diabetes and reduces insulin release in response to glucose. Initially, beta cell function may increase a few years before diabetes onset, but then sharply decline, contributing to the transition from pre-diabetes to diabetes [10]. The exact cause of type 1 diabetes is not definitively understood. It's believed to arise from genetic predisposition and environmental influences [11]. Excessive weight and obesity are the primary risk factors for acquiring type 2 diabetes in adults and other contributing risk factors include aging, a family history of diabetes, a history of gestational diabetes, as well as certain diet and lifestyle habits [12].

Diabetes is categorized into three types: type 1 (insulin-dependent), type 2 (insulin-independent), and gestational diabetes [13, 14]. In type 1 diabetes (insulin-dependent diabetes or juvenile diabetes), beta cells of the pancreas stop producing insulin, or the body`s failure to produce enough insulin causes a deficiency of insulin in the body, which increases the blood glucose in the blood. Type 1 diabetes can strike at any age, but it is most common between the ages of one and fourteen years.[15] Type 2 diabetes is also known as "noninsulin-dependent diabetes" or "adult-onset diabetes" [16]. Type 2 diabetes occurs when the pancreatic beta cells are impaired, which disrupts the body's ability to effectively utilize insulin [17].

Gestational diabetes occurs in pregnant women which increases blood glucose levels without any previous history of the patient. The lack of insulin does not cause gestational diabetes. It occurs in the second and third trimesters of the pregnancy due to tolerance of glucose causing variable severity of hyperglycemia [18, 19]. It's a general medical complication in pregnancy if it's not treated properly then it causes some serious problems for both the child and the mother [20]. The precise cause of diabetes remains unclear, in most cases, there is evidence of an immune response mechanism where auto-antibodies attack the beta cells in the islets [21].

2. PATHOPHYSIOLOGY OF DIABETES

2.1. Type 1 Diabetes

Beta cells are destructed by the cellular mediated autoimmune for the production of insulin in the endocrine pancreas worldwide only 8-10% of cases of type 1 diabetes but the incidence is increasing with time [22](**Figure 1**). Type 1 diabetes can manifest at any age but typically occurs in children and young adults [23]. It is a complex condition characterized by various features but mostly identifies two major pathways the Insulin autoantibodies pathway, and the Glutamic acid decarboxylase autoantibodies pathway [24]. The autoimmune process is indicated by the process of initiation of the first autoantibody [25] (**Figure 1**). Type 1 diabetic patients need to take insulin injections daily and it's known as insulin dependent. The blood glucose level in the blood is managed by insulin therapy and the blood glucose level in the blood is high or low (*i.e.* hyperglycemia or hypoglycemia). Insulin is administered in the body through the injection of insulin to regulate the blood glucose level in the body [26] (**Figure 2**). This condition involves the immune system targeting and destroying the insulin-producing beta cells in the pancreas, resulting in a deficiency of beta cells and a complete lack of insulin. it is classified as an autoimmune disorder, characterized by the presence of anti-insulin or anti-islet cell antibodies in the blood. These antibodies lead to lymphocytic infiltration and the destruction of the pancreatic islets [27]. Type 1 diabetes mellitus is primarily an autoimmune disorder where the immune system mistakenly attacks and destroys the insulin-producing beta cells in the pancreas [28]. Type 1 diabetes does not manifest clinically until 80-90% of the beta cells have been destroyed. Insulin plays a key role in promoting glucose uptake by tissues, storing glucose as glycogen, and inhibiting glucagon production by the liver. Therefore, the destruction of insulin-producing beta cells leads to elevated blood glucose levels or hyperglycaemia [29]. Latent autoimmune diabetes mellitus (LADA) that progresses gradually in older individuals and is considered a subtype of type 1 diabetes mellitus [30] (**Figure 2**).

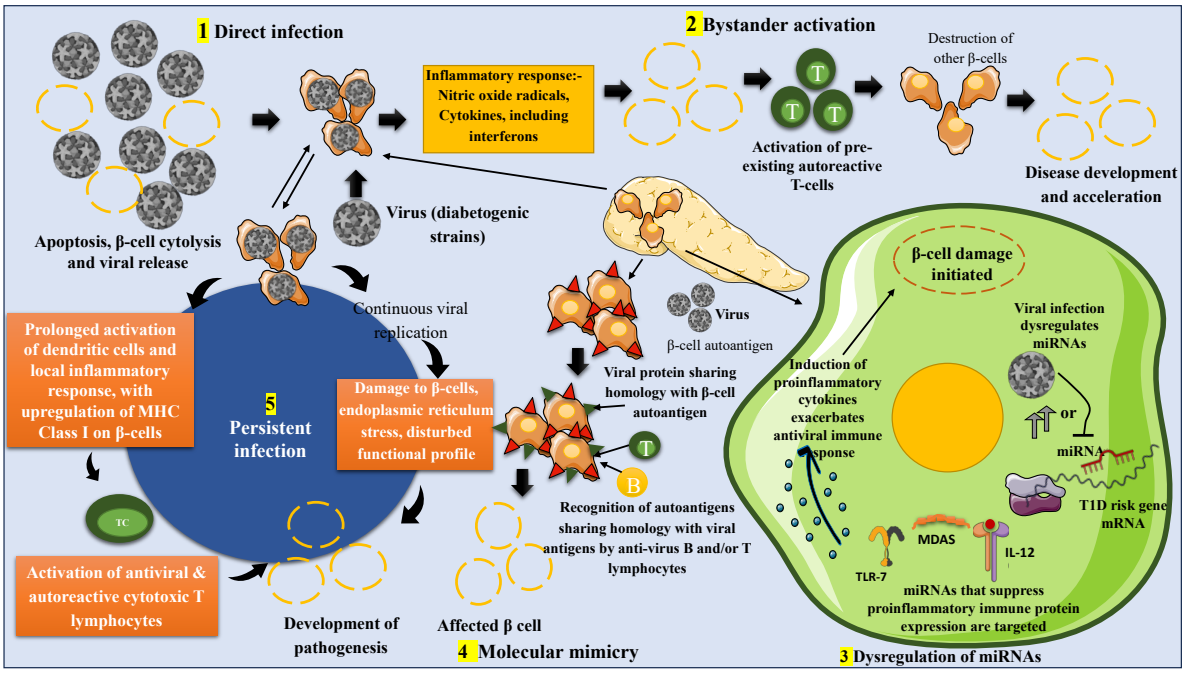


Figure 1. Pathophysiology of diabetes mellites (DM)

2.2. Type 2 Diabetes Mellitus

Type 2 Diabetes Mellitus (T2DM) is a widespread metabolic disorder that primarily develops due to two main factors: (i) Abnormal insulin secretion by the pancreatic β-cells. (ii)The inability of tissues sensitive to insulin to respond to its action properly [31]. In healthy individuals, beta cells are situated centrally and peripherally and are the most abundant cell type (~70%). Non-beta-cells are found in the periphery of islets and constitute ~30% of the cell population (20% alpha-cells and 10% other cell types) [32] (**Figure 2**). The pathophysiology of type 2 diabetes primarily involves peripheral insulin resistance, impaired regulation of hepatic glucose production, and decline in beta cell dysfunction, which can ultimately lead to beta cell failure. Initially, patients experience a deficit in insulin secretion, often accompanied by relative insulin deficiency, which is a critical factor in the development of the disease [33]. Deficiency of insulin secretion in the first phase, along with increased insulin resistance in the liver, leads to impaired fasting glucose. Meanwhile, reduced second-phase insulin secretion and heightened insulin resistance in skeletal muscles contribute to impaired glucose tolerance [34]. Type 2 diabetes mellitus is primarily characterized by two interrelated mechanisms insulin resistance and impaired insulin secretion. Insulin resistance occurs when the body's cells, particularly in muscles and fat tissues, do not respond effectively to insulin. This resistance leads to decreased glucose uptake, resulting in elevated blood sugar levels. Pancreatic beta cells, which produce insulin, become dysfunctional and are unable to secrete sufficient insulin to compensate for the resistance, further contributing to hyperglycemia [35, 36] (**Figure 2**). The development of type 2 diabetes mellitus is influenced by a combination of genetic and environmental factors. A family history of diabetes can increase an individual's susceptibility to the disease. Environmental factors, particularly obesity and a sedentary lifestyle, play a significant role in the onset of type 2 diabetes. Excess body fat, especially visceral fat, is associated with increased insulin resistance. This is due to the release of free fatty acids and inflammatory cytokines from adipose tissue, which can disrupt insulin signaling pathways, creating a cycle of metabolic dysfunction [37] (**Figure 2**). Hormonal changes associated with obesity also contribute to the pathophysiology of type 2 diabetes. Adipose tissue secretes various that can interfere with insulin action, making it more challenging for the body to maintain normal blood sugar levels. Additionally, the condition can be exacerbated by other factors, such as physical inactivity and poor dietary habits, which further impair glucose metabolism [38] (**Figure 2**).

The pathophysiology of type 2 diabetes highlights the critical importance of insulin regulation and glucose metabolism in maintaining normal physiology function. Disruptions in these processes can lead to various complications, including cardiovascular disease, neuropathy, and kidney damage. Understanding, these mechanisms is essential for developing effective management and prevention strategies for type 2 diabetes mellitus, emphasizing the need for lifestyle modifications and medical interventions to improve sensitivity and overall metabolic health [39] (**Figure 2**). Reduced function of β-cells has been identified as a key factor in the pathophysiology of T2DM [40].

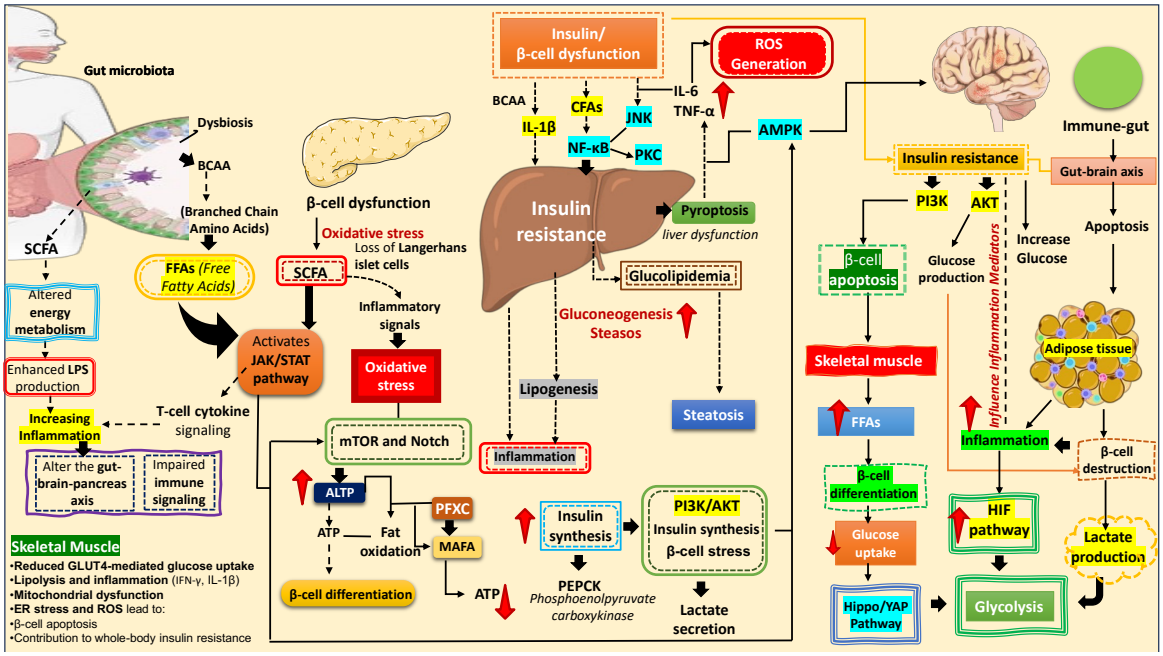
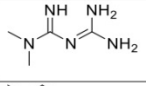
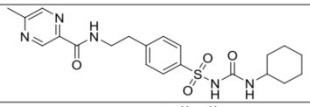
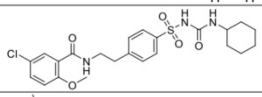
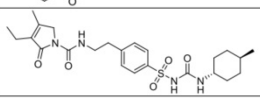
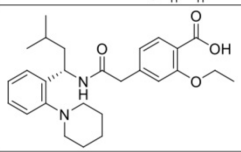
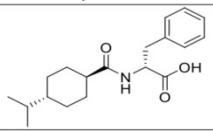


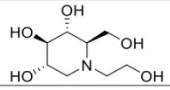
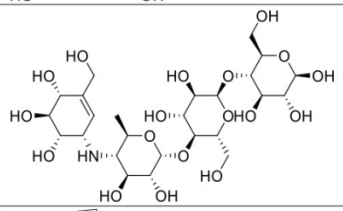
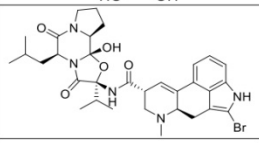
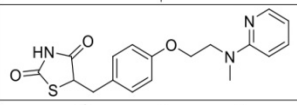
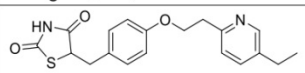
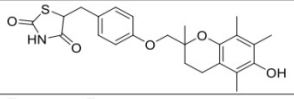
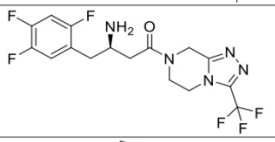
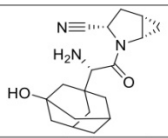
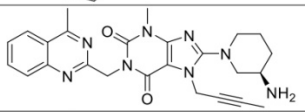
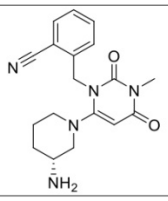
Figure 2. Pathways associated with diabetes mellites (DM).

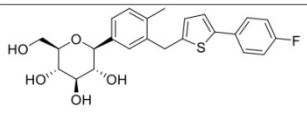
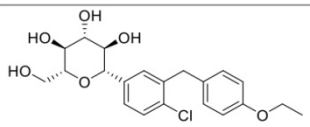
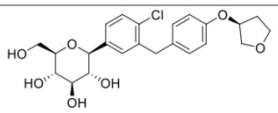
2. CURRENT TREATMENTS FOR DIABETES MELLITUS (DM)

Modern treatments for diabetes mellitus (DM) revolve around different classes of drugs tailored to manage and control blood glucose levels. The primary class of drugs includes Biguanides, such as Metformin, which activate protein kinase AMP-activated non-catalytic subunit beta 1 (PRKAB1) (**Table 1**). These medications help improve insulin sensitivity and decrease hepatic glucose production. Other classes include Sulfonylureas that stimulate insulin secretion from pancreatic β-cells, and DPP-4 inhibitors that prevent the degradation of incretin hormones, thus enhancing insulin release (**Table 1**). Additionally, SGLT2 inhibitors reduce glucose reabsorption in the kidneys, promoting glucose excretion. Each of these drugs targets specific pathways to mitigate the effects of diabetes and improve patients' metabolic health (**Table 1**).

Table 1. Currently available treatment option for diabetes mellitus (DM).

S. No.	Class	Drug Name	Structure	Target	Mode of Action
1.	Biguanides	Metformin (**1**)		Protein kinase AMP-activated non-catalytic subunit beta 1 activator (PRKAB1).	Metformin primarily lowers blood glucose levels by inhibiting glucogenesis in the liver.[41] [42]
2.	Sulfonylureas	Glipizide (**2**)		β-cells of the pancreas.	It stimulates insulin secretion from pancreatic beta cells, thereby lowering blood glucose levels.[43] [44]
		Glyburide (**3**)		β-cells of the pancreas.	It stimulates the pancreas to release more insulin.). [45]
		Glimepiride (**4**)		β-cells of the pancreas.	Glimepiride stimulates β-cells in the pancreas. [46]
3.	Meglitinides	Repaglinide (**5**)		Potassium channel blocker Voltage-gated potassium channel blockers (VGKCs).	Repaglinide works by stimulating the pancreas to release insulin.[47]
		Nateglinide (**6**)		Targets the pancreatic beta cells.	It works by stimulating insulin secretion from the pancreatic β-cells.[48]

4.	α-Glucosidase Inhibitors	Miglitol (**7**)		α-glucosidase	It works by slowing carbohydrate digestion and reducing postprandial blood glucose levels.[49]
		Acarbose (**8**)		α-glucosidase inhibitor	It inhibits α-glucosidase enzymes in the small intestine, which delays the digestion and absorption of carbohydrates. [50] [51]
5.	Dopamine-2 agonist	Bromocriptine (**9**)		D_2 receptors	It stimulates dopamine D_2 receptors (D_2R) in the brain. [52]
6.	Thiazolidinediones	Rosiglitazone (**10**)		PPARγ	Targets peroxisome proliferator-activated receptor. [53]
		Pioglitazone (**11**)		PPARγ	Pioglitazone regulated are genes involved in glucose metabolism, thereby improving glucose uptake and utilization in type 2 diabetes patients. [54]
		Troglitazone (**12**)		PPARγ	It targets PPARγ, which enhances insulin sensitivity and promotes glucose uptake in peripheral tissues. [55]
7.	Dipeptylpeptidase-4(DPP-4) inhibitors	Sitagliptin (**13**)		Target the dipeptidyl peptidase- 4 enzyme	Sitagliptin increases the levels of incretin hormones like glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). [56]
		Saxagliptin (**14**)		DPP4; SG LT2	It increases the levels of incretin hormones and enhances insulin secretion. [57]
		Linagliptin (**15**)		DPP4; SGLT2	It blocks the enzyme DPP-4. This enzyme breaks down incretin hormones, which help regulate blood sugar levels. [58]
		Alogliptin (**16**)		DPP4; PPARγ	Alogliptin increases the levels of active incretin hormones, leading to improved glucose-dependent insulin secretion. [59]

8.	Sodium-glucose cotransporter-2 (SGLT2) inhibitors	Canagliflozin (**17**)		Targets the sodium-glucose co-transporter 2in the kidneys	Canagliflozin primarily lowers blood glucose levels by promoting the excretion of glucose through urine, which helps manage diabetes and enhances fatty acid oxidation and energy while suppressing lipid synthesis and inflammation, contributing to its cardiovascular benefits. [60] [61]
		Dapagliflozin (**18**)		DPP4; SGLT2	Dapagliflozin SGLT2 in the kidneys leads to increased glucose excretion in urine and improved glycaemic control in type 2 diabetes patients. It minimizes the risk of hypoglycaemia and gastrointestinal side effects. [62]
		Empagliflozin (**19**)		SGLT2	Empagliflozin blocks the reabsorption of glucose in the kidneys, leading to increased glucose excretion in urine. This helps lower blood glucose levels in patients with type 2 diabetes mellitus (T2DM). [63] [64]

4. A-GLUCOSIDASE ENZYME

Alpha-glucosidase enzyme is a group of enzymes which is derived from the pancreas that are involved in the breakdown of 80-90% of the carbohydrates consumed, converting them into glucose. α-Glucosidase is an enzyme that facilitates glucose absorption from digested polysaccharides into the small intestine. Inhibiting the α-Glucosidase enzyme can help manage postprandial hyperglycemia (common in people with diabetes) [65]. α-Glucosidase is found in the small intestine and helps break down complex sugars into simple sugars, which can raise blood sugar levels [66]. Glucosidase enzyme plays an important role in metabolic pathways. Cleavage of glycosidic bonds releasing glucose from non-reducing sugar of a polysaccharide and oligosaccharide chain involved in the biosynthesis of glycoprotein [67]. The enzyme alpha-glucosidase is in the intestine. As glucose molecules are released and absorbed into the bloodstream, they can contribute to hyperglycemia. Therefore, inhibiting alpha-glucosidase activity slows down the breakdown of starch, preventing a rapid rise in glucose levels and ultimately helping to reduce postprandial hyperglycemia [68].

5. SEMISYNTHETIC, AND SYNTHETIC A-GLUCOSIDASE INHIBITORS

5.1. Coumarin-hydrazone hybrids

In the year 2016, Wang G. et. al, designed and synthesized a series of coumarin-hydrazone hybrids as a potential α-Glucosidase inhibitor for the treatment of DM. They systematically developed **20a**-**20g** compounds, among all, **20e** was the most potent inhibitor of α-Glucosidase with an IC_{50} value of 6.24±0.07 (**Figure 3**). The SAR studies revealed that the substitution of electron-withdrawing groups like fluorine, bromine, trifluoromethyl, and chlorine at the phenyl ring increases the α-Glucosidase inhibitory property of the candidate. The most potent compound having 3, 5-Chloro, 2-Hydroxy on the phenyl ring is the best lead of this study, the methoxy group at the phenyl decreases the biological activity of the compound. Enzyme kinetic studies showed that compound **20e** is a non-competitive inhibitor of α-Glucosidase. Furthermore, a molecular docking study revealed that the 3,5-dichloro-2-hydroxyphenyl group of **20e** formed arene-cation interactions with residues Arg439 and Arg312, respectively. Moreover, a Cl-π interaction was seen between the 9th residue Phe300 and the 5th position of the chlorine atom at the phenyl ring of **20e**. The overall study confirmed that **20e** could be a potent candidate for the treatment of DM [69] (**Figure 3**).

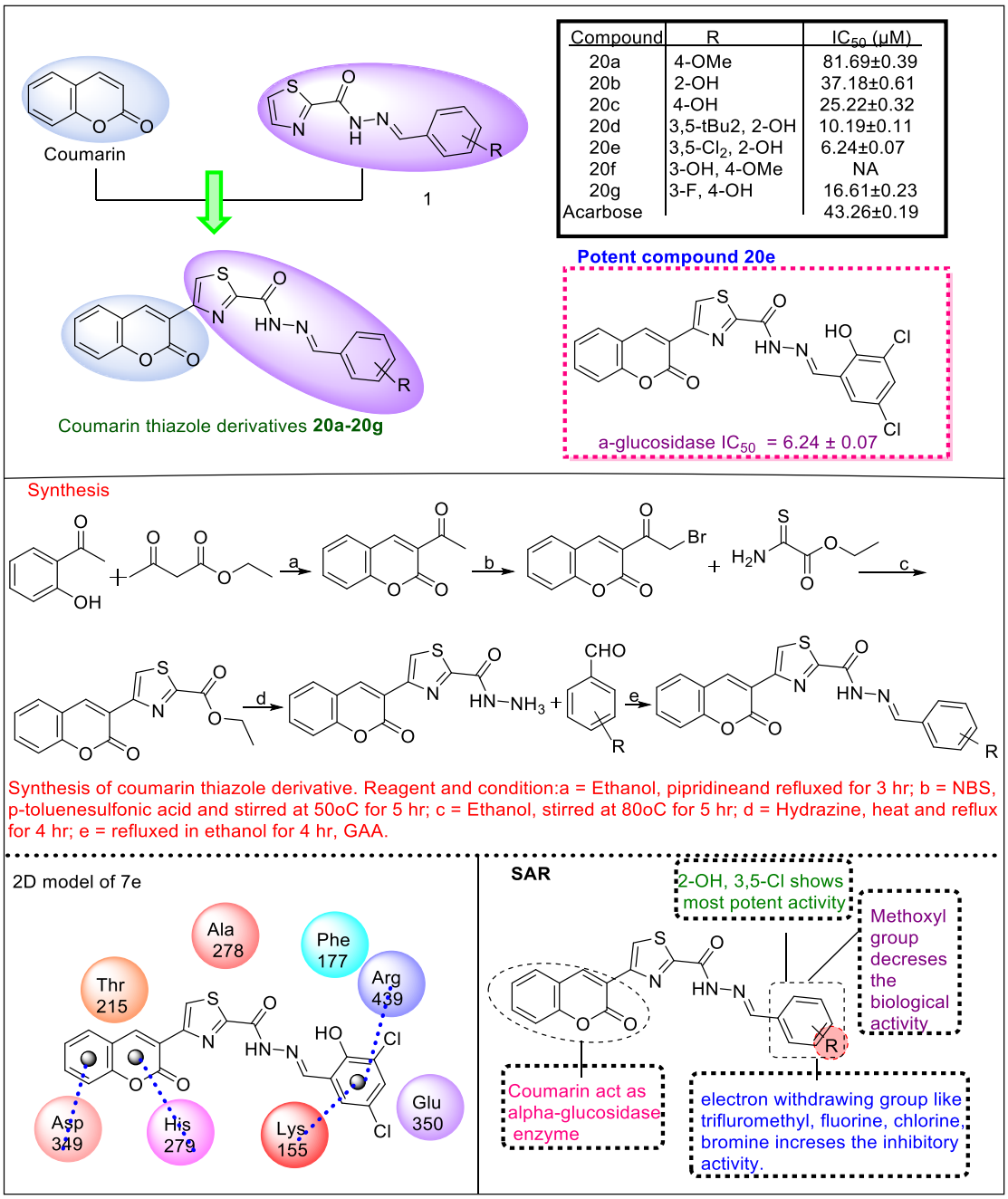
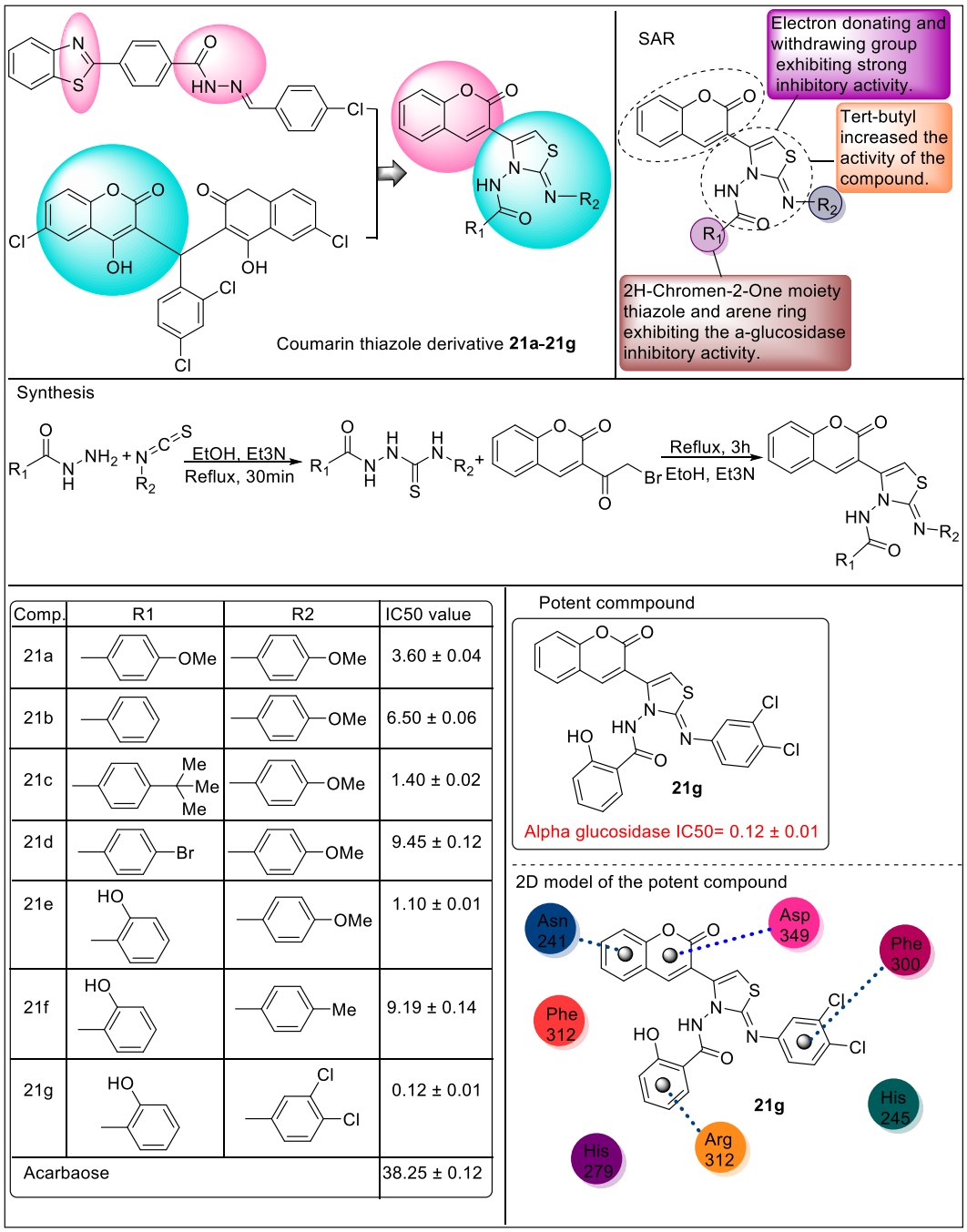


Figure 3. Design, synthetic scheme, and SAR analysis of Coumarin-hydrazone hybrids (**20a-20g**).

5.2. Coumarin-thiazole hybrids

In 2016, Salar U. et. al, designed and synthesized a series of coumarin-thiazole hybrids that showed the activity of an invitro α-glucosidase inhibitor for the treatment of DM. They developed **21a-21g** compounds (**Figure 4**); all compounds have inhibitory activity, but the most potent compound is **21g** for the α-glucosidase inhibitor with an IC_{50} value is 0.12 ± 0.01. The SAR study demonstrated the inhibitory activity of the molecules α-glucosidase by revealing the presence of electron-rich moiety at one end and an electron-withdrawing group at the other end. If substitution of the tert-butyl group at the R_1 it increased the activity of the compound. Ketone oxygen of 2H-chromen-2-one moiety substitute at R_1, exhibiting the alpha-glucosidase inhibitory activity. The molecular docking analysis revealed that compound **21g** exhibited interactions with three active sites (Asn241, Arg312, and Phe300), and the biological activity of compound **21g** was increased due to the interaction with the active site. A molecular docking study analyses the superior activity of compound **21g**, which is used as a lead compound to obtain the potent activity of α-glucosidase inhibitors for their effectiveness in managing DM. The conclusion of the overall study is that compound **21g** is effective in managing diabetes mellitus [70] (**Figure 4**).



Comp.	R1	R2	IC50 value
21a	OMe	OMe	3.60 ± 0.04
21b		OMe	6.50 ± 0.06
21c	Me, Me, Me	OMe	1.40 ± 0.02
21d	Br	OMe	9.45 ± 0.12
21e	HO	OMe	1.10 ± 0.01
21f	HO	Me	9.19 ± 0.14
21g	HO	Cl, Cl	0.12 ± 0.01
Acarbaose			38.25 ± 0.12

Figure 4. Design, synthetic scheme, and SAR analysis of Coumarin-thiazole hybrids (**21a-21g**).

5.3. coumarin iminothiazolidinone hybrids

In 2017, Ibrar A. et.al synthesized a series of coumarin iminothoiazolidinone hybrids used as an α-glucosidase inhibitor in the management of DM (**Figure 5**). Designed and synthesized **22a-22i** compounds which all have α-glucosidase inhibitor activity but the most effective compound is **22c** with IC_{50} value in the range of 0.09 ± 0.001 µM and in-vitro analysis compound **22c** is identified as several promising leads for the enhancement of potent α glucosidase inhibitors (**Figure 5**). In the SAR study of compound **22c,** when the methoxy group shifts from ortho to meta and para position, then it reduces the inhibition property of the α-glucosidase inhibitors. If the chloro group is substituted with an ortho position of the phenyl ring, then it shows strong inhibitory activity of the compound. Para-methyl substitution can enhance the activity of the compound. 2,4 and 3,4-dimethyl substitution shows strong inhibitory activity, but 2,3 and 3,6-dimethyl substituent lowers the inhibitory activity of the compound. in the kinetic study, the Lineweaver-Burk plots indicate that compound **22c** demonstrates inhibition competitively. Through molecular docking studies. Analysis of the binding interactions in the active site of the glucosidase enzyme [71].

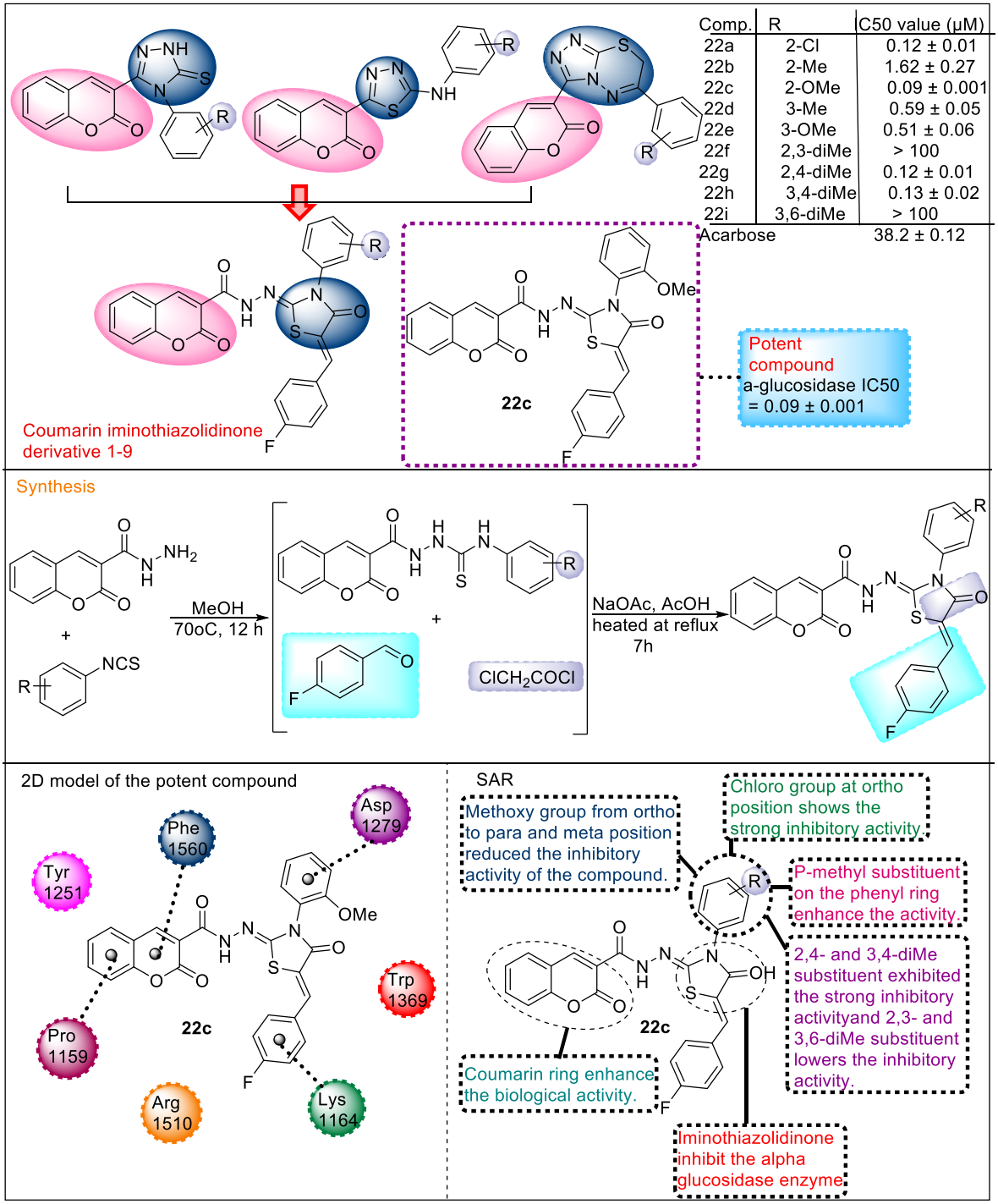


Figure 5. Design, synthetic scheme, and SAR analysis of coumarin-iminothiazolidinone hybrids (**22a-22i**).

5.4. Coumarin-pyrazole hybrids

In 2017, Chaudhry F. et.al, a series of hetarylcoumarin hybrids was synthesized and designed a **10** compound in the series of compounds (**Figure 6**). A halogenated compound **6** was identified to be the most effective, with an IC_{50} value of 2.53 ± 0.002 μM. The structure-activity relationship of compound **6** if, the substitution of bromine in place of chlorine then it reduces the inhibition activity of the compound. Methyl substitution in the R2 decreases the inhibition activity of the compound and alkyl-substituted have less inhibition potency. Halogen group like Bromo and choro substituents increases inhibition activity. In the molecular docking studies, 6th compound was effective, a hydrogen bond between the amino acid Gly280 (2.37 Å) and coumarin ring carbonyl oxygen was observed and several non-covalent bond interactions were also observed with Glu304, His279, Gln322, Ala326, Ser308, Pro309, Val305, Thr308, and Thr309. The overall study confirmed that the **6th** compound is more effective in the series of 10 compounds for managing diabetes mellitus [72](**Figure 6**).

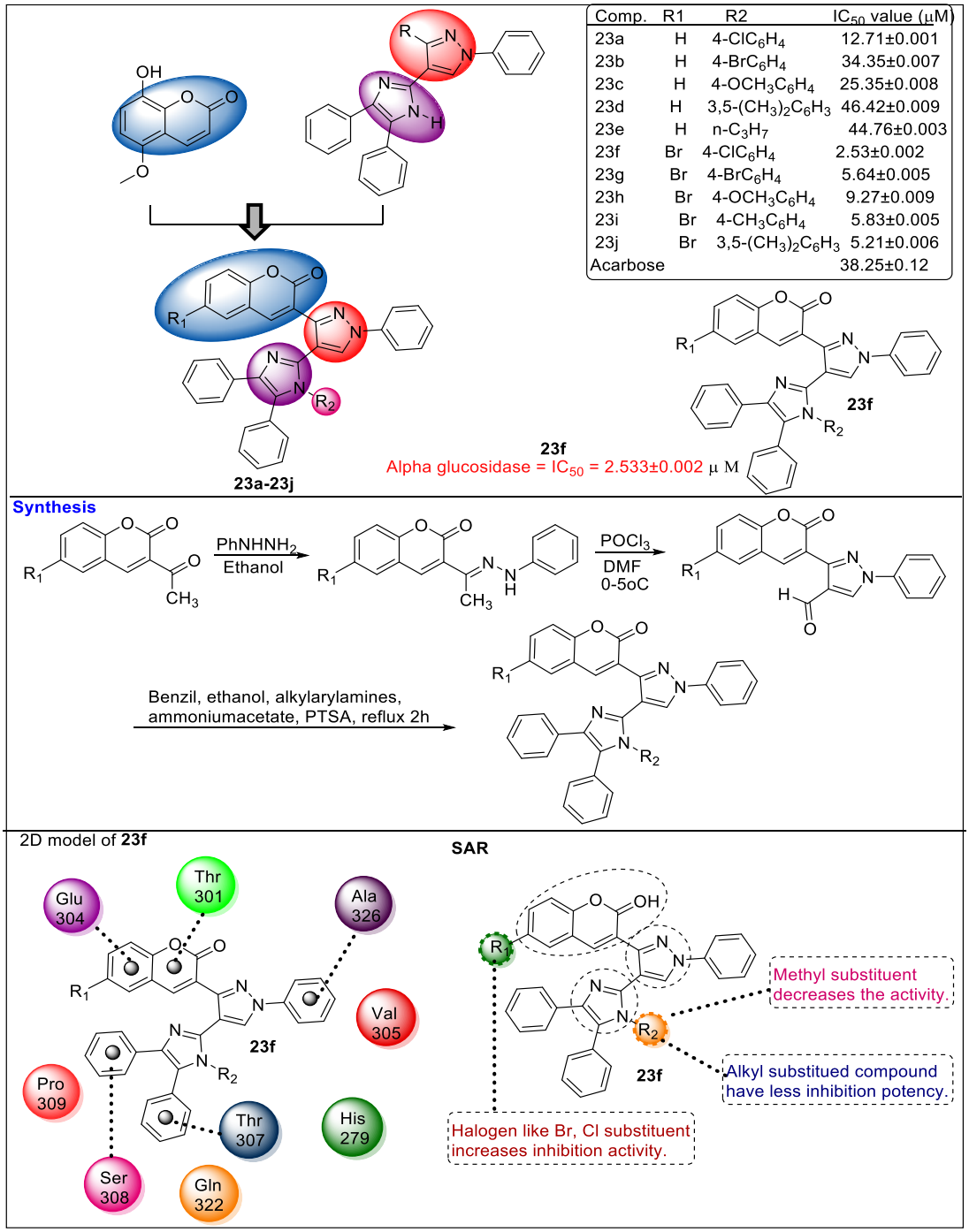


Figure 6. Design, synthetic scheme, and SAR analysis of coumarin-pyrazole hybrids (**23a-23j**).

5.5. Coumarin-flavonoid hybrids

In 2018, Sun H. et. al synthesized a series of flavonoid coumarin hybrids as a potential α-Glucosidase inhibitor for treating DM (**Figure 7**). They systematically developed 8 compounds, among all the eight of compounds, **24e** compound was the most potent inhibitor of α-Glucosidase with an IC_{50} value of 1.47 ± 0.07 μM. The SAR study of the compound is that the presence of a hydroxyl group is beneficial to the flavone moiety to α-Glucosidase inhibition. The flavone fragment hydroxylation/or coumarin unit *O*-methylation shows improvement of inhibitory activity. Enzyme kinetic study of the compound shows that the inhibitor activity of α-Glucosidase enzyme is irreversible mode, and inhibitory kinetics were measured by using the Lineweaver- Burk plot of the velocity and substrate concentration. The 4th series of Flavonoid- coumarin hybrids contain **24e** compounds and all over the 5th compound is potent for the activity of antidiabetic drug [73] (**Figure 7**).

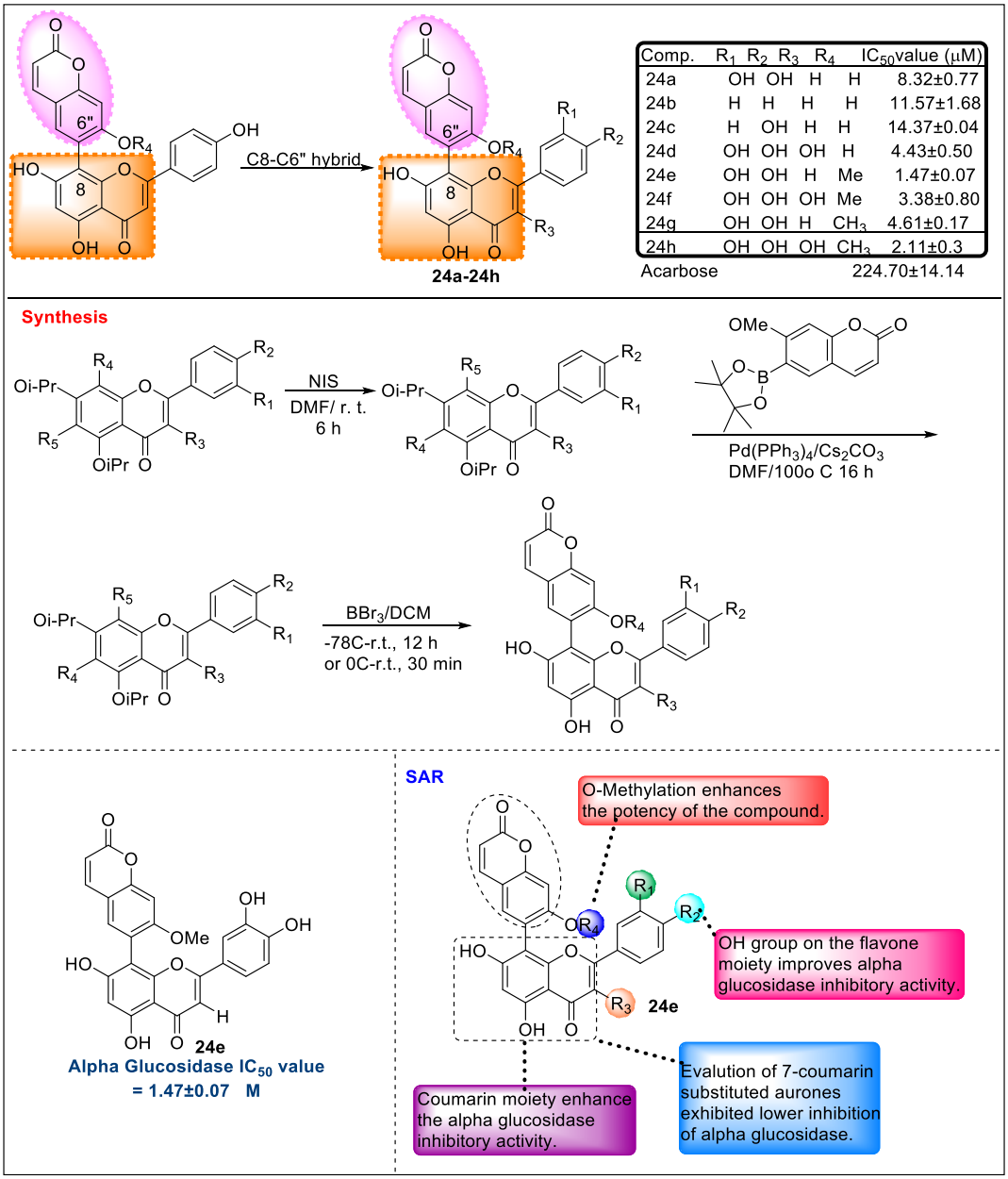
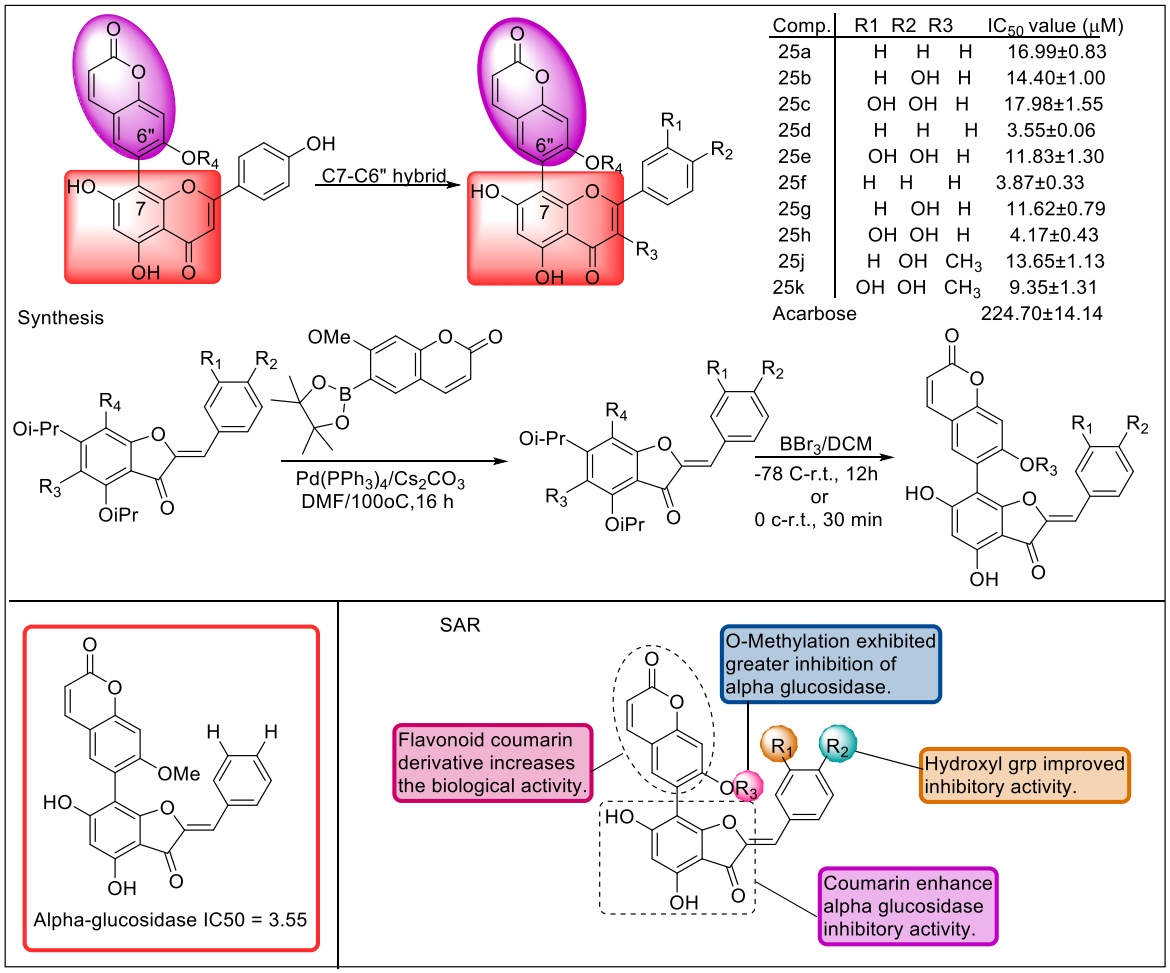


Figure 7. Design, synthetic scheme, and SAR analysis of coumarin-flavonoid hybrids (**24a-24h**).

5.6. Coumarin-flavonoid hybrids

In the year 2018, Sun H. et. al developed another series of flavonoid coumarin hybrids and tested them all against the α-Glucosidase enzyme. In compounds, they developed 10 compounds. **25d** compound is more potent in all the 10 synthesized compounds with an IC_{50} value of 3.55 ± 0.06 μM which is used to treat diabetes mellitus (**Figure 8**). The SAR of the **25d** compound showed higher inhibition activity of α-glucosidase and the coumarin and flavonoid hybrids showed beneficial activity, O-methylated product **25d** exhibited higher inhibition of α-glucosidase compared with their non-O-methylated counterparts and substitution of hydroxyl group improved inhibitory activity of the compound. Compound **25d** shows the most potent inhibition of the α-Glucosidase enzyme in this series. The enzyme kinetic inhibition activity of α-glucosidase was analysed by using the Lineweaver–Burk plot in the presence of different concentrations of enzyme and substrate. The compound **25d** shows glucose consumption promotion activity in insulin and hepG2 cells noninsulin resistant. **25d** compound is an effective drug candidate used as an antidiabetic drug [73] (**Figure 8**).



Comp.	R1	R2	R3	IC_{50} value (μM)
25a	H	H	H	16.99±0.83
25b	H	OH	H	14.40±1.00
25c	OH	OH	H	17.98±1.55
25d	H	H	H	3.55±0.06
25e	OH	OH	H	11.83±1.30
25f	H	H	H	3.87±0.33
25g	H	OH	H	11.62±0.79
25h	OH	OH	H	4.17±0.43
25j	H	OH	CH_3	13.65±1.13
25k	OH	OH	CH_3	9.35±1.31
Acarbose				224.70±14.14

Figure 8. Design, synthetic scheme, and SAR analysis of coumarin-flavonoid hybrids (**25a-25j**).

5.7. Coumarin benzothiazole hybrids

In the year 2018, T. Gabr M. et. al, designed and synthesized coumarin benzothiazole hybrids that showed the activity of the α-glucosidase inhibitor. Only **26a-26c** compounds are systematically developed and the most effective of these three is the **26c** compound with an IC_{50} value of 6.32 ± 0.51 μM (**Figure 9**). Structure-activity relationship study shows that coumarin moiety is linked to a benzothiazole group and it enhance the alpha glucosidase inhibitory activity of the compound. Methoxy group shows superior inhibitory activity and increases hydrophobic interaction, substitution of bromine and hydroxy group enhance the activity of the compound. The presence of a polar, ionizable amino group on the coumarin is essential for the activity. If lacking the amino group showed weaker activity. this amino group allows for crucial hydrogen bonding interactions with the target enzyme, enhancing binding activity. Substitution of the coumarin moiety greatly affects the biological activity of the compound. In the study of molecular docking, with an estimated binding energy of −21.59 kcal mol−1, the **26c** compound showed the binding affinity to the target enzyme (Phe178, Phe303, Glu277, Tyr158, and Gln353), which shows better activity in the invitro α-glucosidase inhibitor [74].

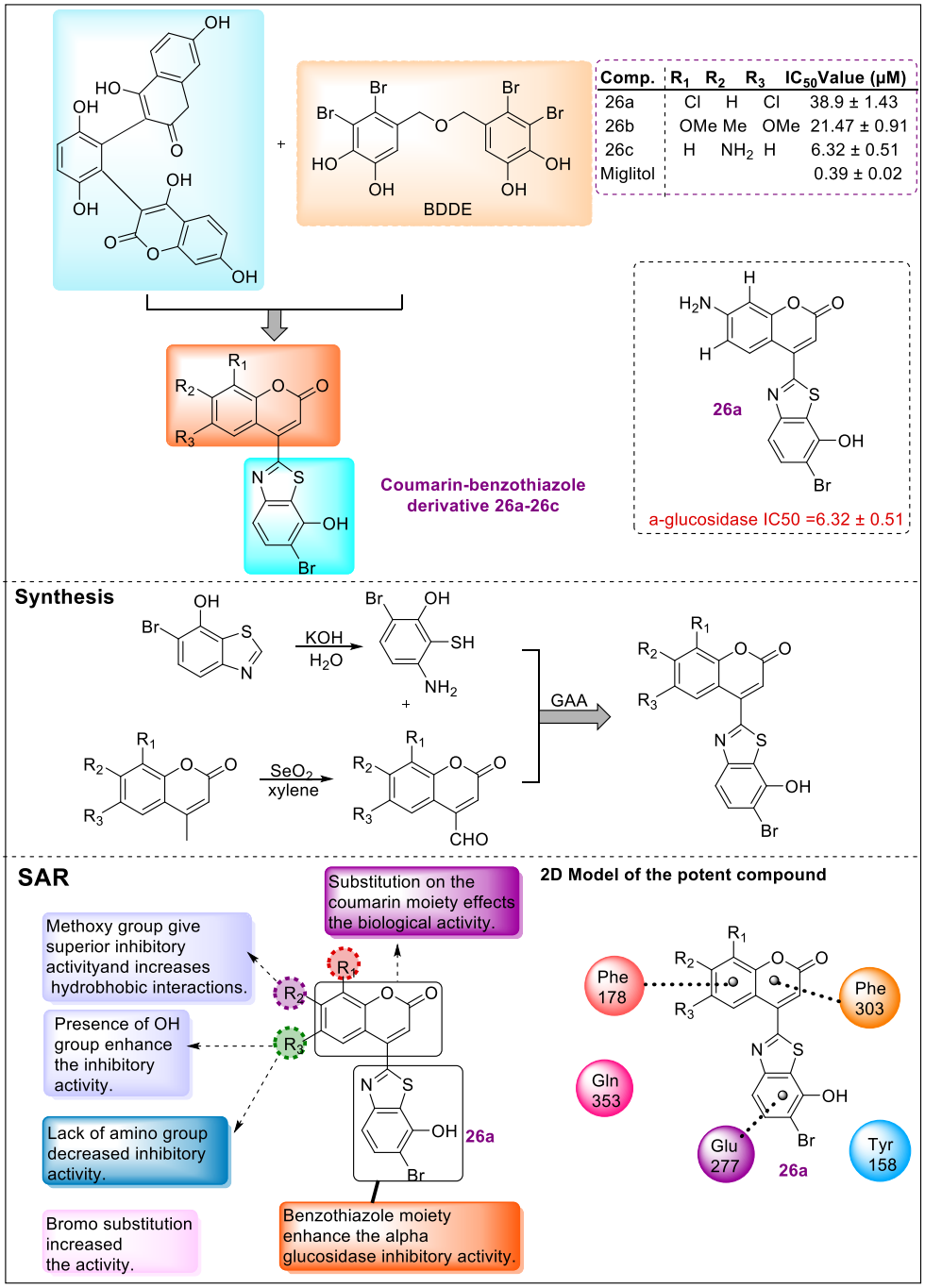
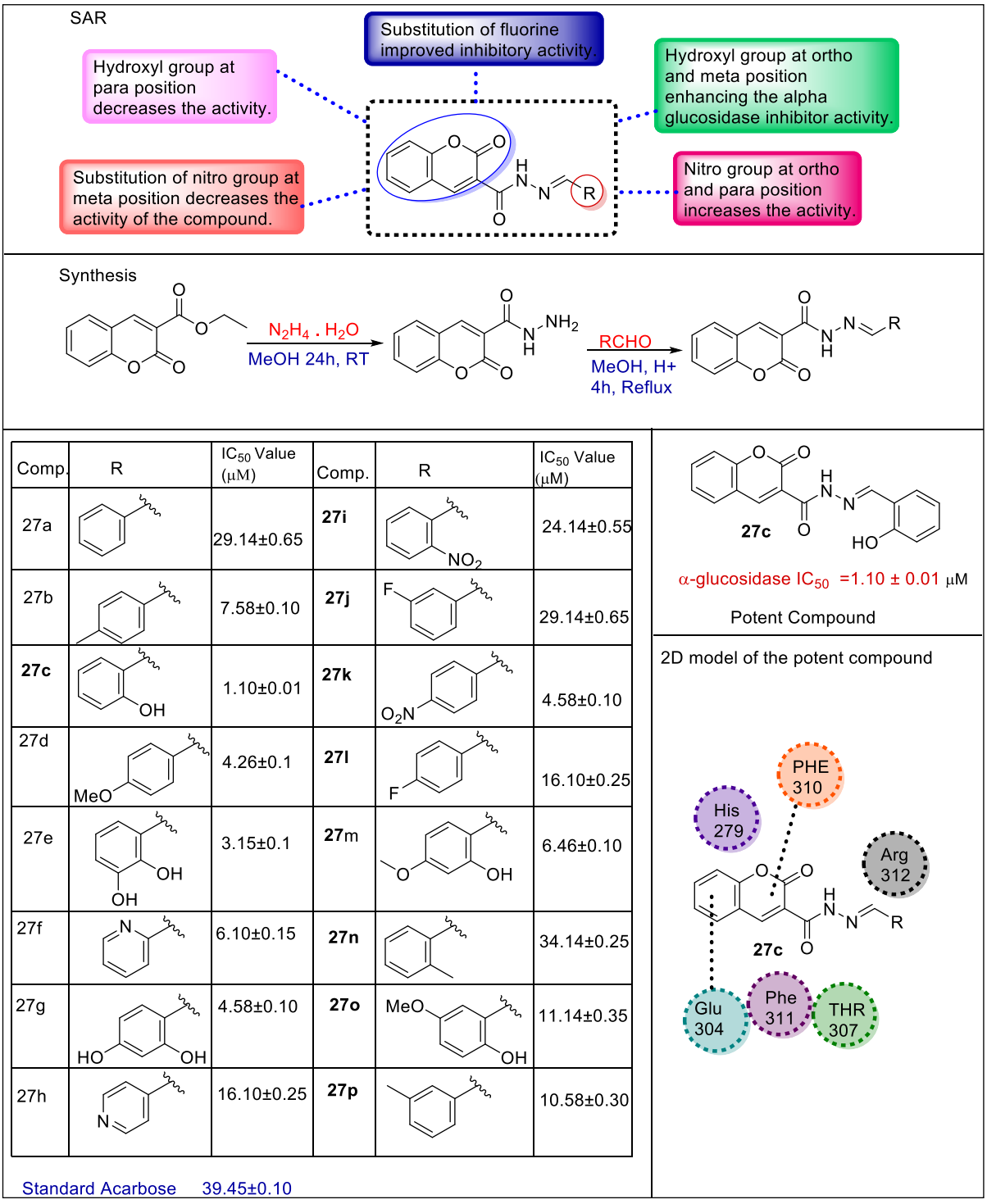


Figure 9. Design, synthetic scheme, and SAR analysis of coumarin-benzothiazole hybrids (**26a-26c**).

5.8. Coumarin hydrazone hybrids

In the year 2018, Taha M. et. al synthesized a series of coumarin-hydrazone hybrids evaluated as a potential α-glucosidase inhibitor for the treatment of DM. The designed a series of 16 compounds and all have the α-glucosidase inhibitor activity, but the most effective compound is **27c** with IC_{50} value 1.10 ± 0.01 μM (**Figure 10**). The SAR of the compound is dependent upon the various substitutions of the phenyl ring. In compound **27c** substitution on the phenyl ring, two hydroxy groups are attached at the meta and ortho position, if we substitute 2-hydroxy groups in the ortho and para position then slight variation in the compound's activity can occur. When substitution can occur in different positions of different groups in the phenyl ring, it affects the compound's inhibitory activity. substitution of fluorine improved the inhibitory activity. In the study of molecular docking, interaction between amino acid and coumarin moiety is observed, carbonyl oxygen is placed in the pyrone ring to make a hydrogen bond with His239, at a distance of 1.86 Å. Overall study of the **27c** compound confirmed the α-glucosidase inhibitor potential for the treatment of DM [75].



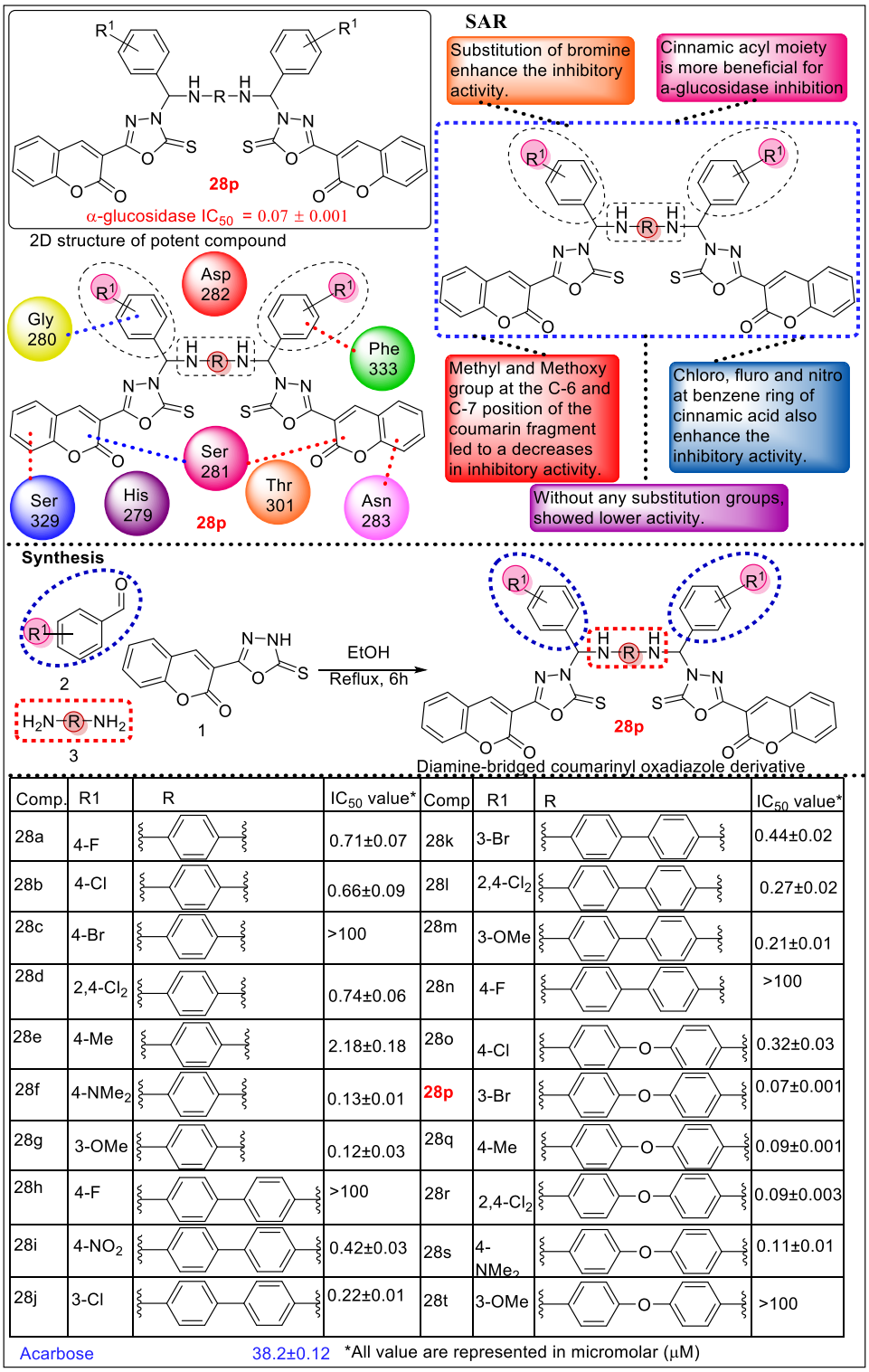
Comp.	R	IC_{50} Value (µM)	Comp.	R	IC_{50} Value (µM)
27a		29.14±0.65	**27i**	NO_2	24.14±0.55
27b		7.58±0.10	**27j**	F	29.14±0.65
27c	OH	1.10±0.01	**27k**	O_2N	4.58±0.10
27d	MeO	4.26±0.1	**27l**	F	16.10±0.25
27e	OH, OH	3.15±0.1	**27m**	O, OH	6.46±0.10
27f	N	6.10±0.15	**27n**		34.14±0.25
27g	HO, OH	4.58±0.10	**27o**	MeO, OH	11.14±0.35
27h	N	16.10±0.25	**27p**		10.58±0.30

Figure 10. Design, synthetic scheme, and SAR analysis of coumarin-hydrazone hybrids (**27a-27p**).

5.9. Coumarin-oxadiazole hybrids

In 2018, Kazmi M. et. al, designed and synthesized a series of coumarin hybrids that work against the α-Glucosidase enzyme in the management of diabetes mellitus. A series of 20 compounds (**28a-28t**) was synthesized and the **28p** compound is the most potent compound with the IC_{50} value in between 0.07 ± 0.001 µM (**Figure 11**). **28p** compound containing 4,40 -oxydianiline linker was identified as the lead compound and a selective α-Glucosidase inhibitor potential, the structure-activity relationship (SAR) of the compound containing 4, 40-oxydianiline linker with a meta-bromo substituent on the aryl ring, 4, 40-oxydianiline linker shows the superior activity as compared to compounds containing phenyl and biphenyl analogous with meta and bromo substitution activity in the α-Glucosidase enzyme. Substituent nature and position variation at the aryl ring influence the biological activity of the **28p** compound. In the enzyme kinetic study, both the enzymes exhibited a competitive mode of inhibition when analysing the Lineweaver-Burk

plots of the **28p** compound, and the Michaelis–Menten experiments were conducted to investigate the inhibition mechanism. In a molecular docking study, the synthesized compound of α -Glucosidase inhibitor was conducted to elucidate ligand-protein interactions at the molecular level. Furthermore, the strong binding interaction between the compounds and the amino acid residues was efficient for identifying the inhibitors against the α-Glucosidase enzyme which were effective in the treatment of DM [76].



Comp.	R1	R	IC50 value*	Comp	R1	R	IC50 value*
28a	4-F		0.71±0.07	28k	3-Br		0.44±0.02
28b	4-Cl		0.66±0.09	28l	2,4-Cl_2		0.27±0.02
28c	4-Br		>100	28m	3-OMe		0.21±0.01
28d	2,4-Cl_2		0.74±0.06	28n	4-F		>100
28e	4-Me		2.18±0.18	28o	4-Cl		0.32±0.03
28f	4-NMe_2		0.13±0.01	**28p**	3-Br		0.07±0.001
28g	3-OMe		0.12±0.03	28q	4-Me		0.09±0.001
28h	4-F		>100	28r	2,4-Cl_2		0.09±0.003
28i	4-NO_2		0.42±0.03	28s	4-NMe_2		0.11±0.01
28j	3-Cl		0.22±0.01	28t	3-OMe		>100

Acarbose 38.2±0.12 *All value are represented in micromolar (μM)

Figure 11. Synthetic scheme, and SAR analysis of coumarin-oxadiazole hybrids (**28a-27t**).

5.10. Biscoumarin hybrids

In 2018, Khanaposhtani M.M. et al. designed and synthesized a series of bis coumarin hybrids that work as an α-Glucosidase inhibitor in the management of diabetes mellitus. They developed a systematic 09 compounds series, and the most potent compound in this series is the **29c** compound with the IC_{50} value between 20.0 ± 0.70 µM, and the synthesized compound yield is found to be (81- 91%) (**Figure 12**). The most potent compound **29c** having 4-methyl phenyl moiety, if strong electron withdrawing and electron donating groups like hydroxyl and nitro group add on the 4th position of the phenyl group which reduced the activity of the α-Glucosidase inhibitor. Substitution of the bromo group exhibited moderate activity but when it modiefied by adding some additional substituent which influences the inhibitory activity of the compound. In the kinetic study, Lineweaver–Burk plots confirmed the inhibition type and Ki value (Ki = 22.4 µM) and it shows the competitive activity of the α-Glucosidase inhibitor. In the docking study, the α-Glucosidase active site reveals the interaction mode of compound **29c,** coumarin moieties of the compound exhibit specific hydrogen bonds with various functional groups, and the carbonyl groups form hydrogen bonds with Asn241and His279 while the amino group forms hydrogen bonds with Glu304 and Asp408. Coumarin ring causes many hydrophobic interactions, which play a major role in the activity of α-Glucosidase inhibitor [77].

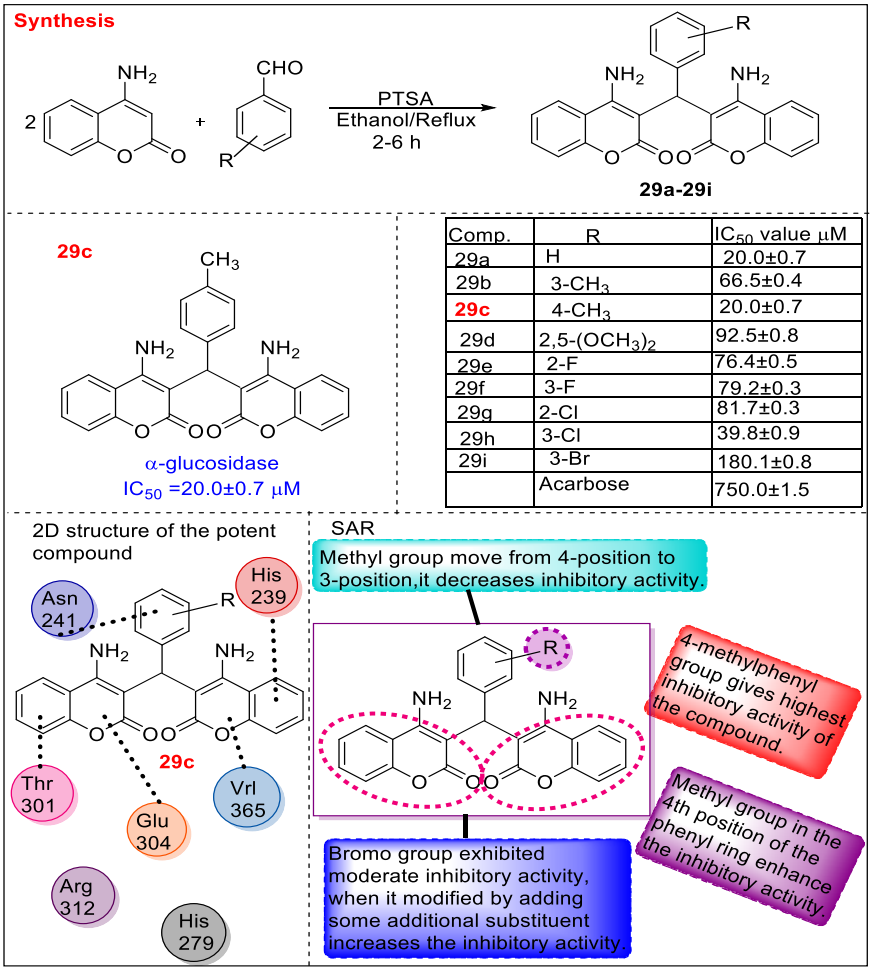


Figure 12. Synthetic scheme, and SAR analysis of biscoumarin hybrids (**29a-29i**).

5.11. Di-coumarin hybrids

In 2021, Ansari S. et. al synthesized a series of 13 compounds with high-yield products for their inhibitory activity against the α-Glucosidase enzyme in the treatment of diabetes mellitus (**Figure 13**). In 13 compound series, the **30f** compound is the most active compound with IC_{50} value between 750.0 ± 10.0 µM. The **30f** compound having the substitution on the phenyl ring is the bromo group, if the bromo group is replaced by the chloro and methoxy group then it decreases the activity of the α-Glucosidase inhibitor. If any substitution on the phenyl ring, then it decreases the activity of the compound, this is all about the structure-activity relationship (SAR) of the compound. The kinetic study of this compound is determined by the Lineweaver–Burk plots, if Km is increased with constant Vmax, then it shows the compound is a competitive inhibitor of α-Glucosidase enzyme and the value of Ki is 44 µM. The docking study of the 11th compound was found at the distal position region of the active site, demonstrating strong stability

through interaction with Phe311, Asp408, and Arg312 in the form of T-shaped π–π hydrophobic, hydrogen bonds, and π-cation interactions. This interaction caused it to be sandwiched between the two loops at the large hydrophobic entrance of the active site. Overall, the study confirmed that the most potent compound in the series is 6th which is most effective in the treatment of diabetes mellitus [78].

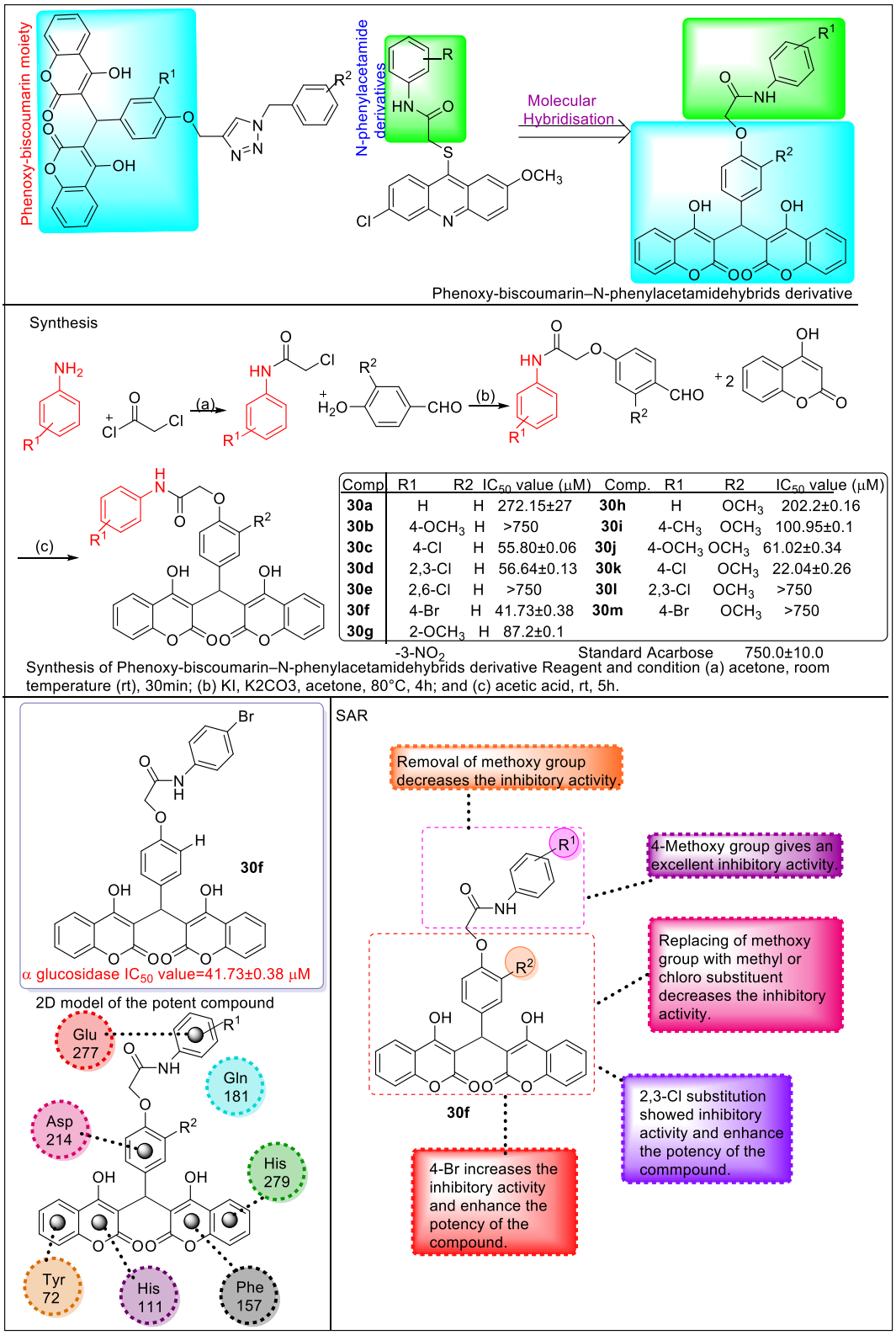


Figure 13. Design, synthetic scheme, and SAR analysis of di-coumarin hybrids (**30a-30m**).

5.12 Coumarin dithiocarbamate hybrids

In 2021, Elahabaadi E. et. al synthesized and designed a coumarin dithiocarbamate hybrids series of 11 compounds, which are used in the treatment of diabetes mellitus by showing its inhibitory activity against the α-Glucosidase enzyme (**Figure 14**). Among all the 11-compound series, the **31g** compound has more potent activity against the α-Glucosidase enzyme with IC_{50} value 85.00 ± 4.00. structure-activity relationship of the compound, the substitution of methyl reduced the inhibitory activity, and the nitro group increased the compound's activity. If the substitute fluoro (F) group at the para position reduced the activity but at the ortho position improved the biological activity. Substituting halogen can also improve the activity of the compound, but only at a specific position. The kinetic study of the **31g** compound is determined by the Lineweaver-Burk plots and the value of Vmax (lM/min) and Km (mM) were computed by using the Michaelis-Menten formula to fit the slope of linear regression and the **31g** compound displayed inhibition in a manner that competes with the substrate for binding to the enzyme [79] (**Figure 14**).

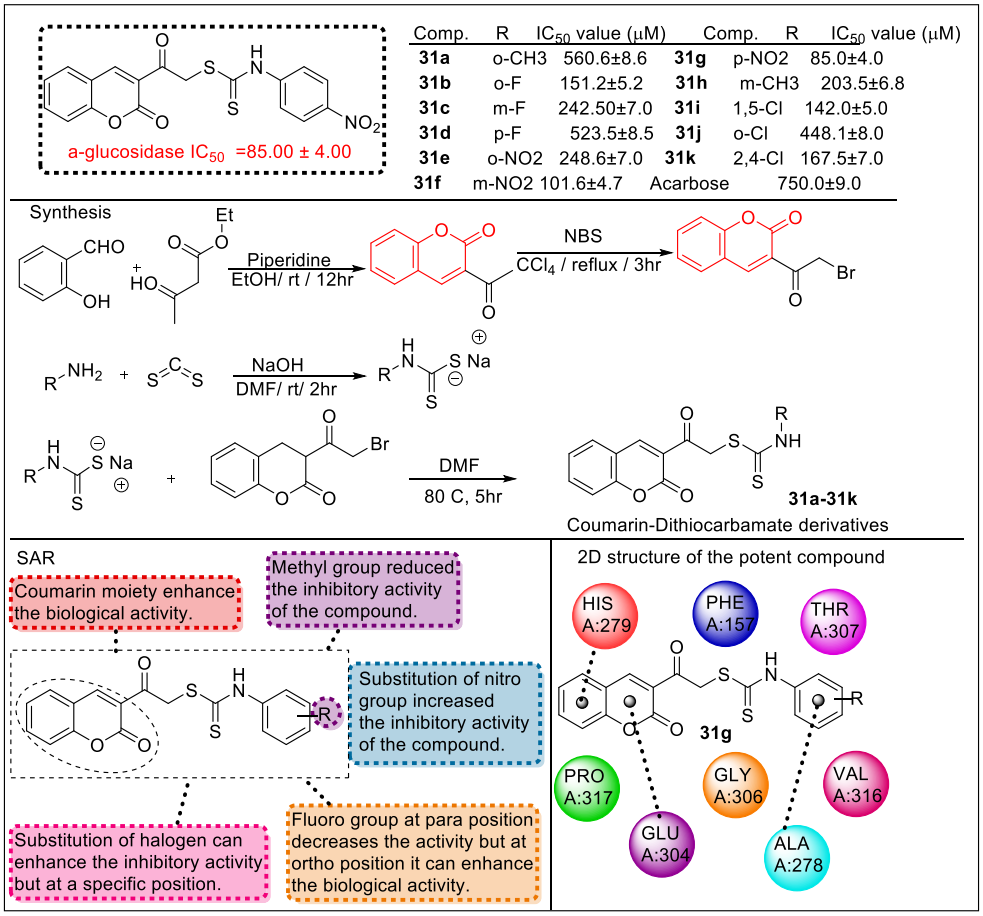


Figure 13. Synthesis, SAR, Molecular docking analysis of coumarin dithiocarbamate hybrids

5.13. Coumarin-cinnamic acid hybrids

In 2019, Xu. X. et. al, A two series of compounds were designed and synthesized of coumarin hybrid and two series containing 8 compounds, which shows the inhibitory activity against the α-Glucosidase enzyme to treat diabetes mellitus. In the 8 compounds series, the most active compound is **32b** with IC_{50} values of 12.98 μM (**Figure 14**). The structure-activity relationship of compound **32b** is the substitution of 4-hydroxycoumarin is a good choice than 7-hydroxycoumarin, if a methyl group, then it increases the inhibitory activity of the compound, and substitution of OCH_3, F, or Br group decreases an inhibitory activity of the compound, Cl or CF_3 group also decreases the inhibitory activity of the compound and methyl group at 4^{th} position of the phenyl ring increases the activity of the compound against the α-Glucosidase enzyme. The enzyme kinetic study of the compound shows reversible inhibition. Molecular Docking study analyses the synthesized derivative successfully incorporated into the a-glucosidase active pocket and hydrogen bond is formed with Lys293 to improve the binding affinity of the compound. The overall study confirmed that the **32b** compound could be a potent candidate for the treatment of DM [80] (**Figure 14**).

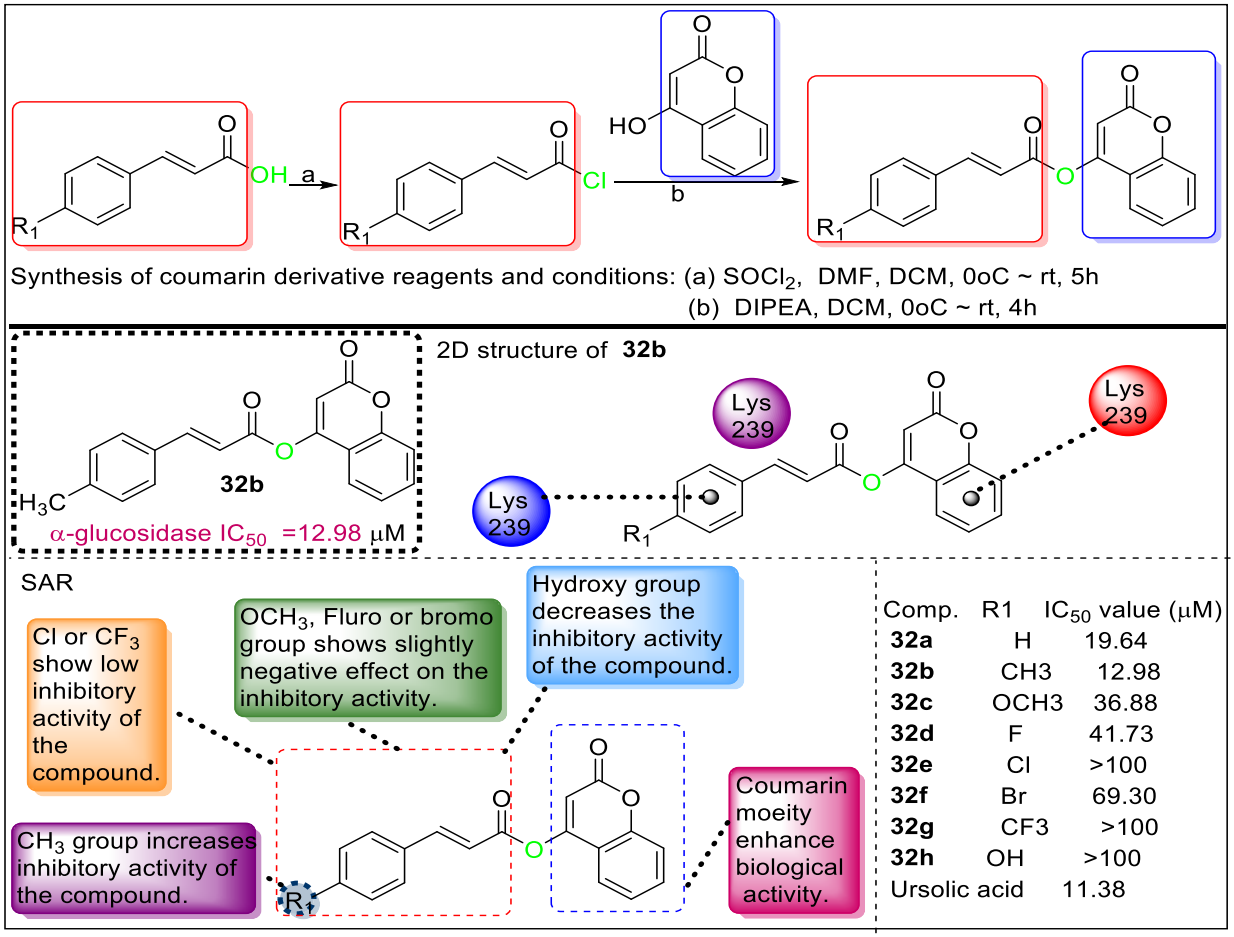
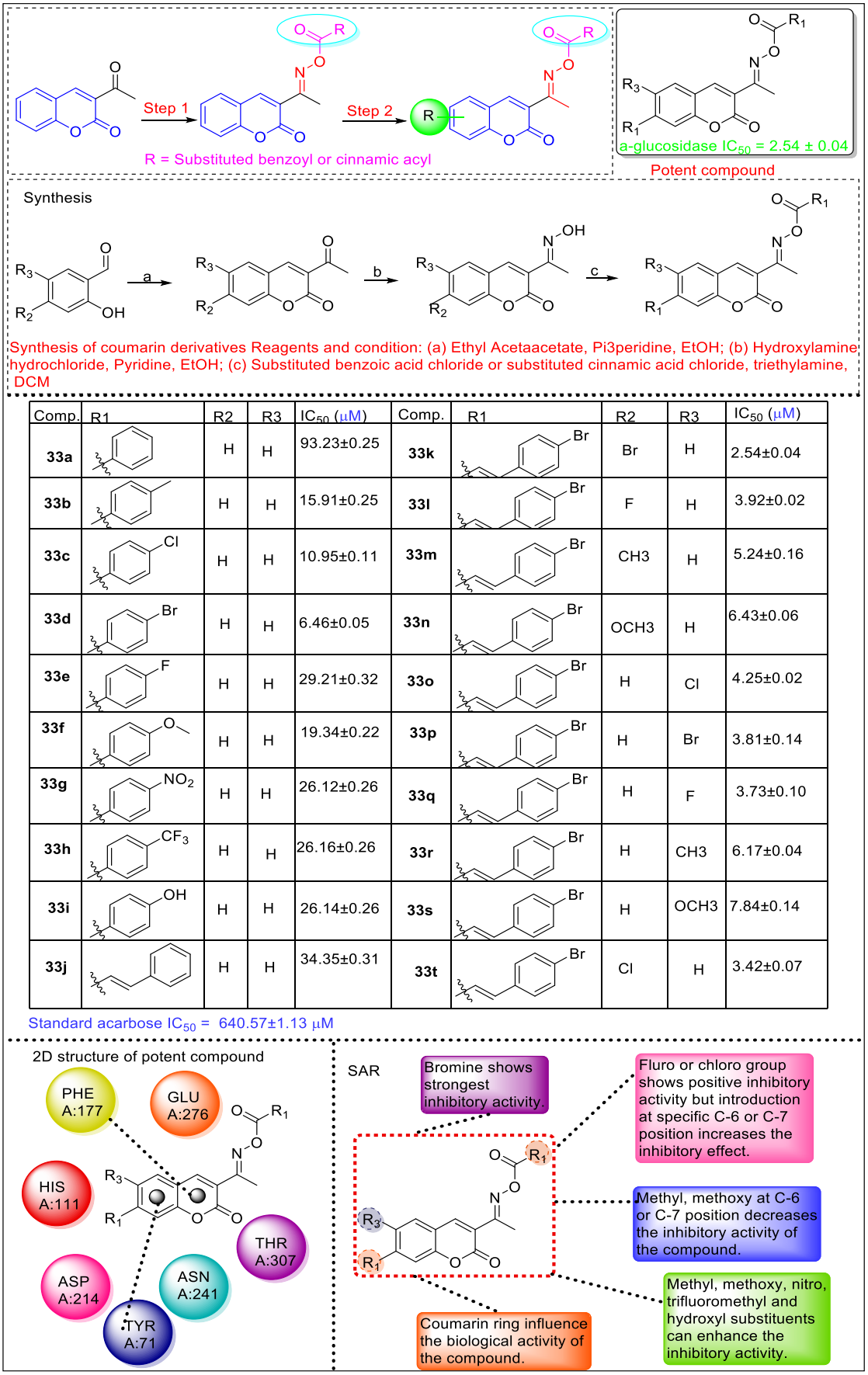


Figure 14. Design, SAR and molecular docking analysis of Coumarin-cinnamic acid hybrids

5.14. Miscellaneous hybrids

In 2022, Zhang. X. et. al, designed and synthesized a series of coumarin hybrids as a potential α-Glucosidase inhibitor for the treatment of DM. They systematically developed 20 compounds, among all the 20 compounds **33k** shows the excellent inhibitor property of α-Glucosidase with an IC_{50} value of 2.54 ± 0.04 µM. SAR of the compound **33k** is a coumarin fragment containing bromine at the 7th position of carbon exhibited the highest α-Glucosidase inhibitory action. Methyl (-CH_3), methoxy (-OCH_3), nitro (NO_2), trifluoromethyl (3-CF_3), and hydroxyl (-OH) substituents can enhance the inhibitory activity, and the bromine group shows the strongest inhibitory activity. The enzyme kinetic study of the compound performed by using Lineweaver-Burk plots of residual enzyme activity against substrate concentration was also used to determine the α-glucosidase inhibition activity and it shows the non-competitive inhibition, compound **33k** shows the calculated inhibition constant K is 1.5µM. Molecular docking was achieved to study the binding mode of the **33k** compound to α-Glucosidase and it shows a U-shaped conformation that allows it to fit well into the active site of alpha-glucosidase. The conclusion of the overall study is that compound **33k** is effective in the management of diabetes mellitus [81].



Comp.	R1	R2	R3	IC_{50} (μM)	Comp.	R1	R2	R3	IC_{50} (μM)
33a		H	H	93.23±0.25	**33k**	Br	Br	H	2.54±0.04
33b		H	H	15.91±0.25	**33l**	Br	F	H	3.92±0.02
33c	Cl	H	H	10.95±0.11	**33m**	Br	CH3	H	5.24±0.16
33d	Br	H	H	6.46±0.05	**33n**	Br	OCH3	H	6.43±0.06
33e	F	H	H	29.21±0.32	**33o**	Br	H	Cl	4.25±0.02
33f	O	H	H	19.34±0.22	**33p**	Br	H	Br	3.81±0.14
33g	NO_2	H	H	26.12±0.26	**33q**	Br	H	F	3.73±0.10
33h	CF_3	H	H	26.16±0.26	**33r**	Br	H	CH3	6.17±0.04
33i	OH	H	H	26.14±0.26	**33s**	Br	H	OCH3	7.84±0.14
33j		H	H	34.35±0.31	**33t**	Br	Cl	H	3.42±0.07

Standard acarbose IC_{50} = 640.57±1.13 μM

Figure 15. Design synthesis of miscellaneous class of hybrids (**33a-33t**).

In 2020, Sherafati. M. et. al, synthesized and designed a series of coumarin hybrids as a potential inhibitor against the α-Glucosidase enzyme for the treatment of diabetes mellitus. They systematically developed 4 compounds, compound **34a** is a more potent compound and shows the best inhibitory activity of the α-glucosidase with an IC_{50} value is 85.20 ± 1.70 µM (**Figure 16**). the structure-activity relationship studies indicate that the coumarin moiety, particularly the carbonyl unit, plays a crucial role in binding to the enzyme through hydrogen bonding interactions. Hydrophobic interactions involving the phthalimide and coumarins moiety also contribute to the compound's activity. specifically, the study highlights interactions with active site residues such as Val305, Arg312, Tyr313, and Pro309. 34a compound shows a lower free binding energy (-10.77 kcal/mol) compared to acarbose (-4.04 kcal/mol), suggesting stronger binding to α-glucosidase [82] (**Figure 16**).

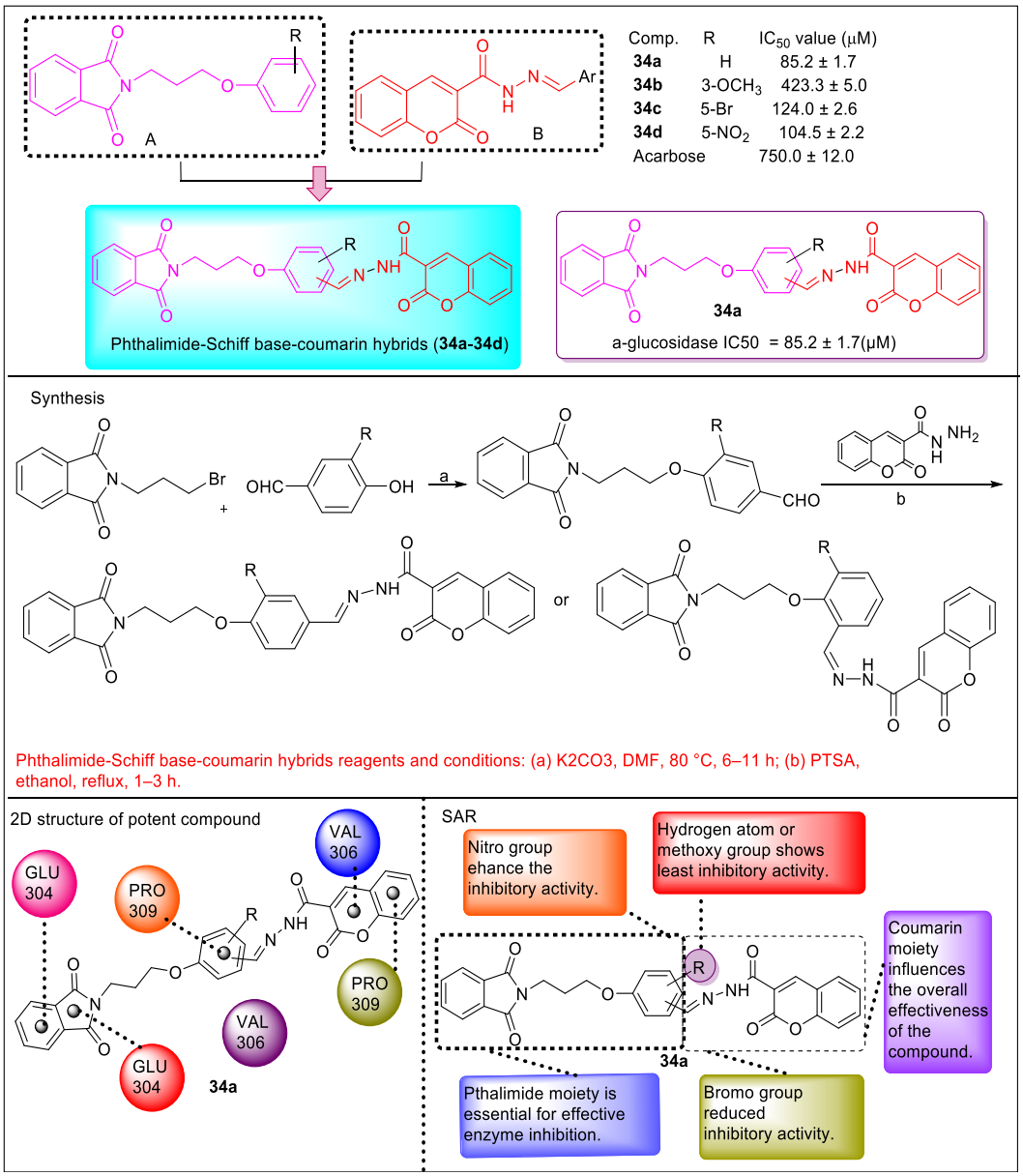


Figure 16. Design synthesis of miscellaneous class of hybrids (**34a-33d**).

6. CONCLUSION AND PROSPECTS

In recent years, the search for effective and safe α-glucosidase inhibitors has gained significant momentum in the field of diabetes mellitus (DM) management. Among the plethora of potential inhibitors, coumarin-based hybrids have emerged as a promising class of compounds due to their potent inhibitory activities and structural versatility. The research and development of these hybrids have shown a considerable impact on controlling postprandial hyperglycemia, a key factor in the management of DM. The inhibitory action against α-glucosidase, an enzyme responsible for carbohydrate digestion, helps to slow down glucose absorption and

subsequently maintain lower blood glucose levels after meals.

In conclusion, the ongoing research and development of coumarin-based hybrids have shown promising results in the search for effective α-glucosidase inhibitors. The structural diversity and the ability to fine-tune the inhibitory activity through various substitutions make these hybrids potent candidates for the management of DM. The promising results from SAR studies, enzyme kinetic studies, and molecular docking analyses provide a strong foundation for further investigation and development of coumarin-based hybrids as therapeutic agents in diabetes management. Continued research in this area holds the potential to uncover more potent and selective inhibitors that could significantly improve the quality of life for individuals living with diabetes mellitus.

Consent for publication
Not applicable

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Authors' contribution
Deepanshu Rajput: Writing manuscript's first draft. Shefali: Writing manuscript's final draft.

Conflict of interest
The authors declare no conflict of interest.

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