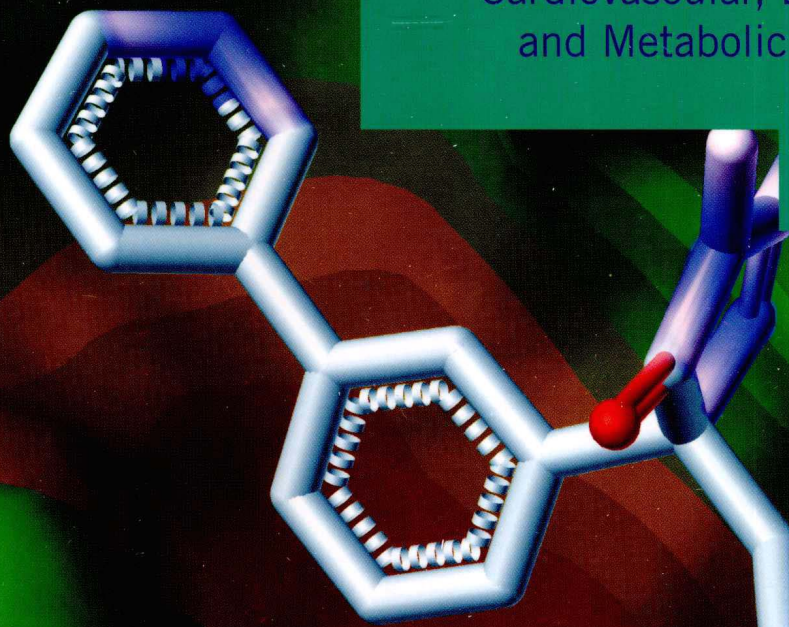
SEVENTH EDITION

Burger's Medicinal Chemistry, Drug Discovery, and Development

Cardiovascular, Endocrine, and Metabolic Disease

Volume 4



Edited by
Donald J. Abraham
David P. Rotella

BURGER'S MEDICINAL CHEMISTRY, DRUG DISCOVERY AND DEVELOPMENT

Seventh Edition

Volume 4: Cardiovascular, Endocrine and Metabolic Diseases

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PREFACE

The seventh edition of Burger's Medicinal Chemistry resulted from a collaboration established between John Wiley & Sons, the editorial board, authors, and coeditors over the last 3 years. The editorial board for the seventh edition provided important advice to the editors on topics and contributors. Wiley staff effectively handled the complex tasks of manuscript production and editing and effectively tracked the process from beginning to end. Authors provided well-written, comprehensive summaries of their topics and responded to editorial requests in a timely manner. This edition, with 8 volumes and 116 chapters, like the previous editions, is a reflection of the expanding complexity of medicinal chemistry and associated disciplines. Separate volumes have been added on anti-infectives, cancer, and the process of drug development. In addition, the coeditors elected to expand coverage of cardiovascular and metabolic disorders, aspects of CNS-related medicinal chemistry, and computational drug discovery. This provided the opportunity to delve into many subjects in greater detail and resulted in specific chapters on important subjects such as biologics and protein drug discovery, HIV, new diabetes drug targets, amyloid-based targets for treatment of Alzheimer's disease, high-throughput and other screening methods, and the key role played by metabolism and other pharmacokinetic properties in drug development.

The following individuals merit special thanks for their contributions to this complex endeavor: Surlan Alexander of John Wiley & Sons for her organizational skills and attention to detail, Sanchari Sil of Thomson Digital for processing the galley proofs, Jonathan Mason of Lundbeck, Andrea Mozzarelli of the University of Parma, Alex Tropsha of the University of North Carolina, John Block of Oregon State University, Paul Reider of Princeton University, William (Rick) Ewing of Bristol-Myers Squibb, William Hagmann of Merck, John Primeau and Rob Bradbury of AstraZeneca, Bryan Norman of Eli Lilly, Al Robichaud of Wyeth, and John Lowe for their input on topics and potential authors. The many reviewers for these chapters deserve special thanks for the constructive comments they provided to authors. Finally, we must express gratitude to our lovely, devoted wives, Nancy and Mary Beth, for their tolerance as we spent time with this task, rather than with them.

As coeditors, we sincerely hope that this edition meets the high expectations of the scientific community. We assembled this edition with the guiding vision of its namesake in mind and would like to dedicate it to Professor H.C. Brown and Professor Donald T. Witiak. Don collaborated with Dr. Witiak in the early days of his research in sickle cell drug discovery. Professor Witiak was Dave's doctoral advisor at Ohio State University and provided essential guidance to a young

scientist. Professor Brown, whose love for chemistry infected all organic graduate students at Purdue University, arranged for Don to become a medicinal chemist by securing a postdoctoral position for him with Professor Alfred Burger.

It has been a real pleasure to work with all concerned to assemble an outstanding and up-to-date edition in this series.

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March 2010

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CONTENTS

DIABETES DRUGS: PRESENT AND EMERGING

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1. INTRODUCTION TO DIABETES

Type 2 diabetes is a disorder of carbohydrate metabolism characterized by hyperglycemia due to defects in both insulin release and insulin action. It is the more prevalent form of diabetes mellitus representing ~90–95% of those with diabetes and is a leading cause of morbidity and mortality; globally the incidence is increasing at an alarming rate. By 2030, it is estimated that 366 million people will be afflicted with diabetes worldwide posing an enormous public health burden [1]. Although the specific etiologies are unknown, reduced physical activity combined with increased caloric intake result in an overweight and obese population many of whom are genetically predisposed to developing diabetes.

Excess calories in the form of triglycerides are stored in adipose tissue in healthy humans but in the obese state, energy intake exceeds the storage capacity of the adipose tissue leading to an inappropriate energy overflow to muscle and liver [2]. The accumulation of triglyceride in these ectopic tissues is associated with insulin resistance or attenuated insulin-stimulated glucose uptake. Insulin resistance in non-obese patients is also associated with increased accumulation of fat in the intra-abdominal cavity leading to a state referred to as visceral adiposity. These abnormalities in fat metabolism result in increased free fatty acid release causing lipotoxicity [3] and activation of inflammatory pathways [4]. Prior to the development of diabetes, euglycemia is maintained in the insulin resistant state by a compensatory increase in insulin release from the pancreatic β-cells. During this prediabetes period, which can last a decade [5], abnormal glycemic control is manifest either by moderately elevated fasting plasma glucose (100–125 mg/dL) or by impaired glucose tolerance (2 h plasma glucose 140–199 mg/dL following a glucose challenge) depending on whether or not it was identified by a fasting plasma glucose test or an oral glucose tolerance test (OGTT) [6]. Prediabetic patients have an annual risk of developing diabetes ranging from 5–10% per year compared to 0.7% per year for someone that has normal insulin sensitivity [7]. Even in the prediabetic patients, the insulin resistant state is associated with cardiovascular risk factors and increased incidence of cardiovascular disease [8].

Prediabetic patients generally progress to overt diabetes, which is defined as fasting plasma glucose $\geq$126 mg/dL or 2 h plasma glucose $\geq$200 mg/dL during an OGTT or symptoms of hyperglycemia and a random plasma glucose $\geq$200 mg/dL [6]. This occurs when the compensatory insulin response can no longer overcome insulin resistance due to a progressive decline in β-cell function [9–11] and reduced β-cell mass [12,13]. The decline in β-cell function is manifest by the loss of an early, first phase insulin response with a blunted and delayed second phase [14]. Strikingly, the sensitivity of the β-cell to secrete insulin in response to glucose is attenuated not only in frank diabetes but also across the various stages of the prediabetic state [15]. The relative insulin deficiency results in excessive rates of lipolysis and enhanced hepatic glucose production in the fasted and postprandial state [16] in addition to reduced glucose uptake in tissues, primarily in skeletal muscle.

The dynamics of hepatic glucose production and whole body glucose clearance rates has been studied using glucose clamp techniques. The major factor responsible for mild fasting hyperglycemia (<140 mg/dL) is reduced glucose uptake in tissues whereas among patients with fasting plasma glucose levels >140 mg/dL, basal hepatic glucose production is elevated and tightly correlated with increases with fasting plasma glucose levels [17]. In summary, the classical view for the pathogenesis of diabetes involves impaired insulin secretion, excessive hepatic glucose production and decreased glucose uptake in the insulin sensitive tissues [18]. However, this view is changing due to an increasing awareness of the role of the incretin effect from the gut,

increased lipolysis from adipose tissue, increased glucagon release from pancreatic α-cells and neurotransmitter dysfunction in the CNS, all of which appear to contribute to the hyperglycemic state. An ongoing challenge in the diabetes field is to determine which of these factors contribute to the etiology of the disease and which are the consequences.

The degree of long-term glycemic control in patients can be assessed by measuring percentage of glycosylated hemoglobin (HbA1c) in plasma. Glycosylated hemoglobulin results from a reaction between glucose metabolites and hemoglobulin and in healthy adults typically amounts to 4–6% of total hemoglobulin. In diabetic patients, HbA1c is higher, commonly 8–9% or more. The strategy for the management of diabetes and establishment of treatment goals was driven by the results of multicenter clinical trials which highlight the relationship between HbA1c and the development of diabetes complications. Trials comparing intensive versus standard glycemic control in patients with type 1 diabetes, the Diabetes Control and Complications Trial [19], and in patients with type 2 diabetes, the Kumamoto study [20] and the UKPDS [21,22], have shown reduced rates of microvascular (retinopathy and nephropathy) and neuropathic complications in the intensively controlled patients. Due to the uncertainty of the relationship between intensive glycemic control and cardiovascular disease from these studies, several large, long-term trials were initiated including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) [23], the ADVANCE [24], and the VADT [25]. Somewhat surprisingly, intensive glycemic control did not lead to a significant reduction in cardiovascular disease in these three trials. In fact, the intensive glycemic control group of the ACCORD trial (goal <6% HbA1c) was prematurely terminated after 3.5 years due to excess mortality. These results suggest that the risks of intensive glycemic control outweigh the benefits of reduced microvascular and neuropathic complications, also demonstrated in the ADVANCE trial, in some patients, such as those with very long durations of diabetes, known history of severe hypoglycemia, advanced atherosclerosis and advanced age/frailty [6].

The current target HbA1c goals are <7% based on the evidence that lowering HbA1c to below or around 7% has been shown to reduce microvascular and neuropathic complications of type 1 and type 2 diabetes [6]. This is a challenging goal as existing therapies achieve only a modest decrease. Diabetes management can be significantly improved with the development of new therapies capable of improving the percentage of patients that achieve target levels of glycemic control of <7% HbA1c and correcting some of the other associated conditions such as hyperlipidemia and inflammation [26].

2. CURRENT THERAPIES

The following sections describe classes of drugs currently in use for the treatment of diabetes that are not covered in other chapters in this volume.

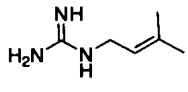
2.1. Biguanides: History and Introduction

The use of guanidine derivatives for the treatment of type 2 diabetes stems from medieval times when *Galega officinalis*, also know as Goat's rue, French lilac, or Italian fitch was useful for the treatment of the symptoms of diabetes [27]. The active principal in this plant was isolated in the early 1900s and was later assigned as the guanidine derivative Galegin [28]. In an experiment to investigate whether excess guanidine was responsible for the tetany associated with hypoparathyroidism, it was found that infusing rabbits with 200 mg/kg of guanidine hydrochloride itself caused a profound hypoglycemia [29]. This finding inspired further investigation and several derivatives were marketed for diabetes during the 1920s. However, guanidines have safety issues for use as therapeutics for diabetes and they were discontinued once insulin became widely available. Even though metformin and its ability to lower blood glucose in animals was first described in 1929, [30] the superior tolerability and utility of the biguanides for the treatment of diabetes was not recognized for a considerable period of time.

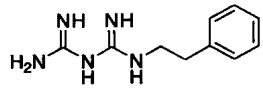
2.1.1. Biguanide Structure and SAR Structure–activity studies of the biguanides, including phenformin, buformin, and metformin in

normal guinea pigs were published in the late 1950s. Mono- and *N,N*-disubstituted biguanides with relatively small alkyl (<8 carbons) and aryl lower alkyl substituents were most effective in lowering glucose in normal guinea pigs [31–33] and phenformin, buformin, and metformin were marketed in the late 1950s. As a note of caution to modern medicinal chemists, in the early studies, compounds were administered at high doses, at one fifth or one-third the tolerated dose subcutaneously or orally, respectively in normal animals. There were no dose response data and, as is still the case, the pharmacological target(s) was not known. Thus it is difficult to draw more than qualitative inferences from this data.

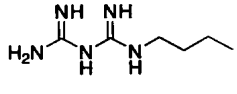
Phenformin was in clinical use in the United States during the 1960s, but was discontinued in 1977 due to its propensity to cause potentially fatal lactic acidosis [34–36]. Likewise, buformin which was available outside the United States, is also associated with lactic acidosis and is now only available in a few countries. Unlike metformin, the more lipophilic phenformin and buformin tend to associate with the mitochondrial membranes and inhibit electron coupling, causing a decrease in lactate oxidation. They also undergo extensive oxidative metabolism in the liver, thus making exposure hard to predict when patients are taking other drugs that may influence the activity or expression of the relevant cytochromes. Interestingly, cases of drug induced lactic acidosis attributed to use of these two agents continued to appear in the United States for many years among patients who acquired them from overseas markets where they were still available [37]. Metformin is as effective as other members of the class and has a significantly lower risk of causing lactic acidosis as long as use in renal compromised patients is avoided [38].



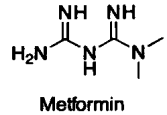
Galegine



Phenformin



Buformin



Metformin

2.1.2. Metformin Chemistry Metformin is sold as the hydrochloride salt which is a stable, white to off-white crystalline solid, mp 223–226°C, MW 165.63. Metformin is freely soluble in water, but virtually insoluble in polar organic solvents like acetone, ether or chloroform. It is a strong base, pK_a 12.4 and is fully protonated at all physiological pHs. Metformin is available as tablets, an oral solution or an extended release formulation.

2.1.3. Metformin Absorption, Distribution, Metabolism, and Excretion The results of several human pharmacokinetic studies of metformin have been summarized in a review [39]. After intravenous administration, the elimination data are consistent with a 2-compartment model with an alpha $t_{1/2}$ of approximately 2 h and a beta terminal elimination $t_{1/2}$ of 12–14 h. Virtually all of the drug is excreted unchanged in the urine after intravenous dosing. Renal and total clearance are similar, 20.1–36.9 and 26.5–36.9 L, respectively, and are higher than creatinine clearance, suggesting an active tubular clearance [40]. The compound is not protein bound and the volume of distribution is 62.7–256 L [39]. Over a period of time, the blood to plasma ratio increases indicating a partitioning of the drug into erythrocytes [41].

The absolute bioavailability after oral administration is 40–60%. The extent of absorption is dose dependent, decreasing moderately with increasing doses between 500 and 1500 mg indicating a limiting, saturable uptake from the small intestine. Absorption is complete within 6 h, with C_{max} occurring 2–3 h after oral dosing; in the presence of food, C_{max} is prolonged by about 40 min and there is an approximately 25% decrease of overall exposure. Metformin distributes into the intestinal wall resulting in a prolonged absorption phase that may compensate in part for its rapid renal clearance. The elimination $t_{1/2}$ after oral administration is 4–8.7 h. Metformin is normally administered with meals in two to three doses daily. Steady state is normally obtained within 24–48 h [42]. Although careful pharmacodynamic studies have not been reported, plasma levels of <2 μg/mL are generally associated with efficacy in patients.

No hepatic metabolites of metformin have been detected. As noted above, it undergoes

nearly exclusive renal clearance. Thus, clearance is reduced in patients with compromised renal function with an attendant increase in plasma concentration. Because of the lack of protein binding and active metabolism, drug–drug interactions with metformin are uncommon. Other drugs such as cimetidine, digoxin, amiloride, trimethoprim, and others that undergo renal clearance may impact clearance. For example, addition of 250 mg of cimetidine given once a day (qd) to 400 mg of metformin given twice a day (bid) led to a 50% increase in the metformin concentration versus time curve (AUC) [43].

Metformin is actively transported into the liver by the liver specific organic cation transporter OCT1. This transporter is highly polymorphic in humans and at least four of the isoforms, are deficient in their ability to mediate metformin transport. One of these, OCT1-420del, is present in approximately 20% of Caucasian Americans. An oral glucose challenge was carried out in normal human volunteers bearing either the wild-type or one of the four OCT1 polymorphisms deficient in metformin transport and showed that the expected decrease in the glucose versus time curve was significantly reduced in only those carrying the normal alleles. Diet induced obese mice in which the *Oct1* gene was knocked out had lower hepatic metformin concentrations and higher fasting glucose levels after metformin treatment relative to wild-type mice [44]. Thus variability in response to metformin treatment among patients may be in part due to the presence of hypomorphic polymorphisms in their gene coding for OCT1.

2.1.4. Metformin Mechanism of Action The molecular mechanism of the beneficial actions of metformin in diabetic patients is not fully understood. Treatment with metformin results in the phosphorylation and activation of adenosine monophosphate activated protein kinase (AMPK) through an indirect mechanism [45]. AMPK is a highly conserved heterotrimeric protein that is a key central regulator of whole body energy homeostasis [46,47]. AMPK is allosterically activated by AMP and by phosphorylation on Thr172. Thus, under conditions of energy stress, as the ratio of AMP to ATP increases, AMPK is activated to promote catabolic pathways leading to ATP production. In this setting, AMPK promotes glucose uptake into skeletal muscle, fatty acid oxidation in the liver and simultaneously inhibits hepatic gluconeogenesis and lipolysis in adipose tissue. One possibility is that metformin and other biguanides activate AMPK through inhibition of complex 1 of the respiratory chain, thus increasing the concentration of AMP [48].

However, it has also been demonstrated and confirmed in several laboratories that metformin activates the tumor suppressor kinase LKB1 which in turn phosphorylates AMPK on Thr172 in hepatocytes and *in vivo*. In the absence of functional liver LKB1, no metformin mediated phosphorylation of AMPK or glucose lowering occurs in mice [49]. Recent studies suggest further that isoforms of protein kinase C (PKC) may lie upstream of LKB1 and activate it by phosphorylation of Ser248 [50,51]. The mechanisms of these events are still under investigation and it is possible additionally that metformin has pharmacological actions independent of its effects on AMPK activation. Among them is a reduction in the plasma levels of plasminogen activator inhibitor-1 (PAI-1), an inhibitor of the conversion of plasminogen to plasmin, a protease involved in blood clot dissolution.

2.1.5. Metformin Clinical Pharmacology Despite extensive experience in Europe, metformin was not approved in the United States until 1995 at which time it was marketed as Glucophage® by Bristol-Myers Squibb. It is presently available as a generic drug and by 2006, was the 10th most widely prescribed generic drug in the United States [52]. It is considered the first line therapy for the treatment of type 2 diabetes mellitus by both the American Diabetes Association [6] and the International Diabetes Federation [53].

In order to minimize gastrointestinal side effects, metformin is generally taken with food and introduced at a dose of 500–850 mg in the morning, increasing gradually to a maximum of 2550 mg (3×850 mg) or 3000 mg in some countries. A common dosing schedule is 2×850 mg with breakfast and a second 850 mg dose with the evening meal. Taken together several clinical trials suggest that

long-term treatment with metformin leads to a reduction of fasting blood glucose of 60–70 mg/dL and of HbA1c by 1–2%, with the response dependent on the degree of hyperglycemia at the start of treatment. In contrast to drugs that promote insulin secretion, insulin levels remain constant or decrease as insulin sensitivity improves. As a consequence, there is little risk of hypoglycemia and no drug induced weight gain. Metformin enhances fatty acid oxidation in the liver resulting in an overall decrease in serum triglycerides and a modest lowering of LDL [40].

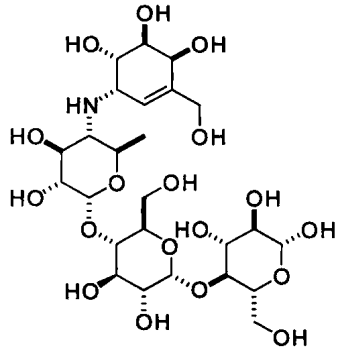
In the United Kingdom Prospective Diabetes Study (UKPDS 34), a group of obese, diabetic patients were treated with either metformin or diet and exercise for an average of 10.7 years. In this group of patients, there was a 32% decrease in any diabetes end point, a 42% reduction in death caused by diabetes, and 36% decrease from mortality of all causes for patients treated with in metformin relative to those on diet and exercise alone [22]. Metformin can be combined with other drugs used to treat type 2 diabetes, including insulin. Fixed combinations of metformin with most classes of oral antidiabetic agents are widely marketed.

2.1.6. Metformin Safety Gastrointestinal side effects are common, but rarely lead to discontinuation of therapy. Diarrhea occurs in approximately half and nausea and vomiting in a quarter of patients; other gastrointestinal side effects include abdominal bloating and flatulence. The risk of lactic acidosis in patients with normal renal function is extremely low, estimated to be less than 8 cases/100,000 patient years, not substantially different from the incidence among patients on alternative diabetes therapies [38]. Prescribing recommendations include determination that serum creatinine is $\leq$1.5 mg/dL in males and $\leq$1.4 mg/dL in females as a measure of renal function prior to initiating therapy, particularly in elderly patients. Furthermore, metformin should be discontinued prior to treatment with drugs such as iodine containing contrast agents known to impair renal function. Metformin should not be used in patients with cardiac or liver conditions likely to result increased lactate [42].

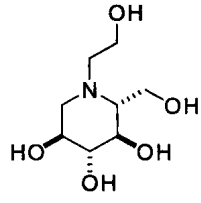
Symptoms of lactic acidosis can be vague and develop without warning. They include malaise, lethargy, abdominal discomfort, somnolence, and respiratory distress. Lactic acidosis is often fatal and should be treated immediately in a hospital setting. In many cases of lactic acidosis associated with metformin treatment, patients had other conditions leading to elevated lactate and metformin treatment probably did not materially contribute [54]. In any case, metformin can be removed by dialysis and treatment recommendations include placing patients on dialysis to decrease serum metformin and is often done even before determining metformin blood levels.

2.2. α-Glucosidase Inhibitors

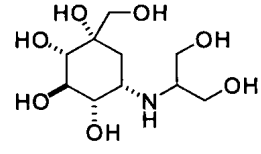
α-Glucosidase Inhibitors (AGIs) acarbose, miglitol, and voglibose act as reversible, competitive inhibitors of α-glucosidase and pancreatic α-amylase and are used to control postprandial hyperglycemia in patients with type 2 diabetes.



Acarbose



Miglitol



Voglibose

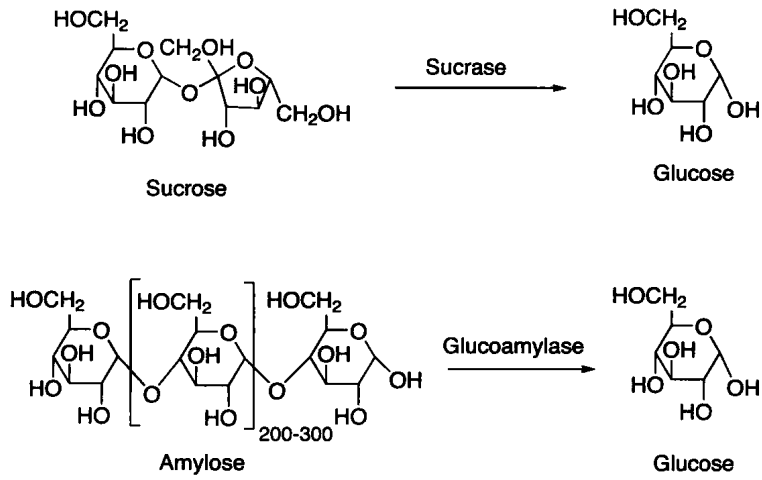


Figure 1. Reactions catalyzed by sucrase and glucoamylase.

α-Glucosidases are enzymes found on the brush border of the intestinal wall that act to break down disaccharides into readily absorbed monosaccharides such as glucose (Fig. 1) and fructose. Sucrase and isomaltase are two important α-glucosidases. α-Amylase is an enzyme found in the lumen of the small intestine that catalyzes the hydrolysis of complex starches to smaller starches and ultimately to maltose, a dimer of glucose.

Inhibition of these enzymes in the intestine delays the digestion of dietary carbohydrate; specifically, sucrose and starch, thereby delaying absorption of glucose into the bloodstream and thus reducing postprandial glucose and insulin secretion [55]. Due to their mechanism of action, the AGIs do not lower fasting blood glucose by enhancing insulin secretion nor do they require insulin to exert their effect. Because of their unique mechanism, the α-glycosidase inhibitors can be safely taken in combination with sulfonylureas and other drugs for type 2 diabetes. Because the drugs act to inhibit digestion, they are most efficacious when taken at the start of a meal. Lactose is a β-disaccharide; therefore, the drugs possess no lactase activity and do not induce lactose intolerance.

2.2.1. ADME of the AGIs Acarbose, Miglitol, and Voglibose are the three orally administered α-glucosidase inhibitors that have been developed as drugs. Acarbose, sold as Precose® in North America, was the first of this class of drugs to reach the market. It is a pseudotetrasaccharide containing a maltose unit linked by an NH to an acarviosine unit. Its oral bioavailability is only 1–2% and it pharmacodynamic effect is confined to the small intestine. After a ^{14}C-labeled dose of acarbose, approximately 50% of radioactivity was excreted in feces and 35% in urine where it appeared in at least 13 metabolites. Upon intravenous administration, 89% of the drug was excreted in the urine unchanged [56].

Miglitol is a structural analog of glucose and is readily absorbed in the intestine via the glucose transport mechanism. Miglitol has a half-life in man of approximately 2 h and is excreted unchanged by the kidneys [57]. There is no data, however, to clearly demonstrate that systemic exposure contributes to miglitol's efficacy. Thus, it shows effects very similar to those of acarbose and must be administered at the beginning of a meal to be efficacious. Voglibose, sold in Japan as Basen® and in India as Volix®, is poorly absorbed. It is excreted unchanged in the feces with less than 5% excreted in the urine [58]. Like miglitol and acarbose, it is taken at the beginning of each meal.

2.2.2. Mode of Action of AGIs α-Glucosidases are enzymes that inhibit cleavage of the α-glycosidic linkage between C-1 of glucose and C-4 or C-6 of the adjacent glucose in starch or the fructose C-2 linkage in sucrose. Glycolysis is believed to proceed through two distinct high-energy oxonium intermediates re-

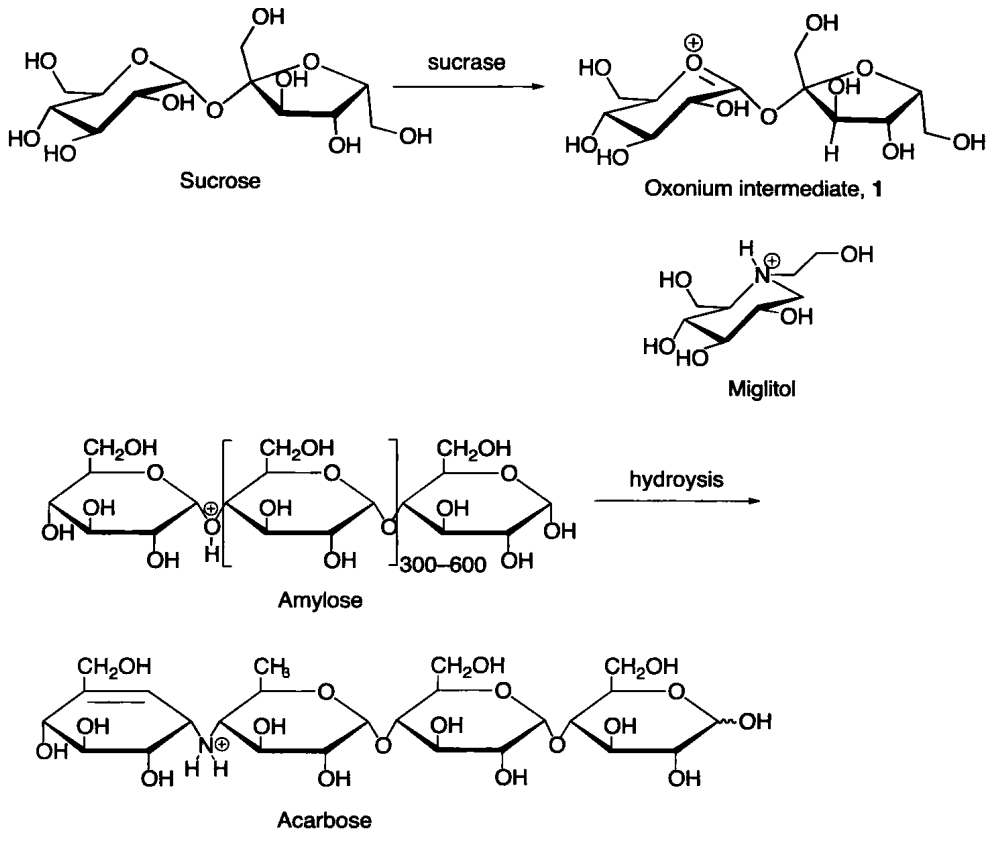


Figure 2. Mechanism of inhibition of glycosidase inhibitors.

presented in Fig. 2 by structure **1**. Glucosidases stabilize these intermediates, thus lowering their free energy and accelerating cleavage. The AGIs contain a basic amine that is protonated at physiological pH. This protonated amine mimics one of the high energy intermediates that the enzymes evolved to bind with high affinity.

In fact, α-amylase and sucrase bind AGIs with 10–100,000 higher affinity than their natural di- and polysaccharide substrate [59]. The primary α-glucosidases inhibited by acarbose and miglitol are sucrase, isomaltase and glucoamylase. Table 1 shows the affinity of the two drugs for these three enzymes [60,61].

Acarbose is a tetrasaccharide mimetic; therefore, it is not surprising that it has relatively potent glucoamylase activity. Miglitol, on the other hand, structurally similar to glucose is a much more potent sucrase inhibitor.

Table 1. α-Glucosidase Inhibition by Acarbose and Miglitol

	Acarbose K_i (μM)	Miglitol K_i (μM)
Sucrase	0.99	0.086
Isomaltase	46.3	0.36
Glucoamylase	0.009	0.21

2.2.3. Safety of AGIs The α-glucosidase inhibitors delay digestion of starch and saccharides. Consequently, a larger amount of undigested carbohydrate reaches the colon and the attendant gas-producing bacteria. The resulting flatulence, diarrhea, and abdominal pain are the most common side effects associated with these drugs. For example, the incidence of these three symptoms in a 1255-patient U.S. trial of acarbose was 74%, 34%, and 19%, respectively.

These side effects trended toward pretreatment levels over a year of treatment and can be minimized by the "start low, go slow" approach common to the prescription of most drugs with known side effects.

2.2.4. Physiology and Pharmacology Of the three α-glucosidase drugs, acarbose has been tested most extensively in clinical trials; miglitol to a lesser degree and vogliobose much less. A meta-analysis of 30 acarbose clinical trials found that drug treatment reduced fasting glucose by 1.09 mmol/L, postprandial glucose levels by 2.3 mmol/L and HbA1c by up to 0.77%. For acarbose, there was no evidence for dose-dependent effects on HbA1c for doses from 50–300 mg tid. In contrast, the data did support dose-dependent effects for miglitol at 25, 50, 100 and 200 mg tid. The smaller number of miglitol trials, however, make this data less convincing. Compared with placebo, acarbose had no effect on fasting insulin levels but had a modest lowering effect on 1 h postprandial insulin levels of 40.8 pmol/L. Miglitol showed similar effects [62]. Both acarbose and miglitol increase carbohydrate concentration in the intestine. Thus it is not surprising, but nevertheless intriguing, that both drugs have been shown to increase concentrations of GLP-1 and to decrease those of GIP [63].

Two studies have compared AGIs to metformin in patients with type 2 diabetes not controlled with diet alone. The comparison of acarbose, 100 mg, tid with meals had efficacy similar to metformin, 850 mg bid resulting in a mean reduction of HbA1c of 1.0% after 6 months of treatment. In a head-to-head comparison, miglitol, 100 mg tid, was less effective than metformin, 500 mg tid at reducing HbA1c, 0.4% versus 1.2% after one year of treatment. However, the combination of these doses of miglitol and metformin showed synergy with a combined reduction of HbA1c of 1.8% [64].

The α-glycosidase inhibitors acarbose, miglitol and voglibose are efficacious as monotherapy or, more commonly, in combination with metformin, sulfonylureas, or insulin. The efficacy of the AGIs is not dependent upon insulin and they have been shown to be effective in all patients exhibiting postprandial hyperglycemia. They are very safe and modestly effective drugs whose major side effects are gastrointestinal symptoms. [65–67].

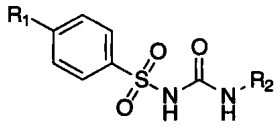
2.3. Insulin Secretagoges: Sulfonylureas

The first sulfonylurea hypoglycemic agent, VK 57, was discovered more then a half a century ago by Rhone-Poulenc chemists and tested at Montpellier Hospital. This finding represented the first effective oral treatment for diabetes [68]. Despite their age, the sulfonyl ureas remain popular due to their low cost, good efficacy and well understood side effects. They remain on formularies across the globe including the United States as single agents or in combination with newer oral antidiabetics. The most common side effects are hypoglycemia and weight gain. The hypoglycemia risk has been mitigated to some degree through the introduction of shorter acting compounds that are given with meals. However, the weight gain, a lack of a significant effect on lipids, cardiovascular safety issues, and competition from newer agents have decreased the attractiveness of these compounds in the United States [69,70].

2.3.1. Medicinal Chemistry All representatives of this class incorporate the core pharmacophore **2** (Table 2), differing in the identity of R_1 and R_2. The first-generation sulfonylureas include tolbutamide, chlorpropamide, acetohexamide, tolazamide, gliclazide, and glibornuride and are listed in Table 2. They appeared on the market in the late 1950s to early 1960s. They are lower molecular weight, structurally less complex, less potent and longer acting than analogs introduced later. They are characterized by possessing only a short side chain (R_1) in the *para*-position of the phenyl ring. The R_2 group became increasingly complex over time. Aside from impacting patentability, these initial modifications resulted in only a modest effect on metabolism, excretion and ultimately dose, with chlorpropamide being four-fold more potent than tolbutamide (equivalent therapeutic dose of 250 mg versus 1000 mg) [71].

Second and third-generation agents are shown in Table 3. These compounds are 20–50-fold more potent and have a two- to four-fold longer duration of action than the first-generation analogs. Second-generation agents appeared on the market in the 1970s and include glyburide, glipizide, and gliquidone. These derivatives all have acylamino ethyl moieties in the *para*-position of the phe-

Table 2. First Generation Sulfonyl Ureas



2

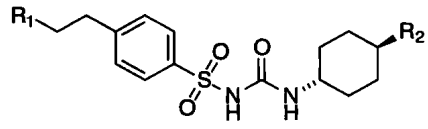
Generic Name	Trade Name	R_1	R_2	Launch
Tolbutamide	Orinase®	Methyl	*n*-Butyl	1956
Chlorpropamide	Diabinese®	Chloro	*n*-Propyl	1958
Acetohexamide	Dymelor®	Acetyl	c-Hexyl	1962
Tolazamide	Tolinase®	Methyl	Azepan-1-yl	1967
Gliclazide	Diamicron®	Methyl	3-Azabicyclo[3.3.0]-octane	1972[a]
Gibornuride	Glutril®	Methyl	2-Bornanol	1973[a]

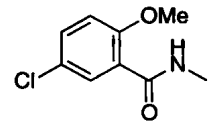
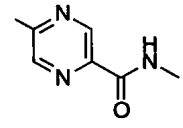
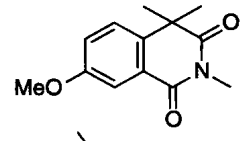
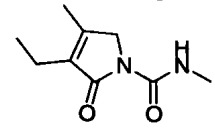
[a] Outside of the United States.

nyl ring (R_1). The R_2 group of this class is invariably a cyclohexyl, or a *trans*-4-methylcyclohexyl moiety [71].

The lone third-generation compound, glimepiride (Amaryl®) first appeared in 1995 and is also marketed in combination with pioglitazone and rosiglitazone under the trade names Duetact® and Avandaryl®, respectively. In addition to effecting release of insulin from functioning pancreatic beta-cells, glimepiride may also increase insulin sensitivity. Despite its longer duration of action,

Table 3. Second and Third Generation Sulfonylureas



Generic Name	Trade Name	R_1	R_2	Launch
Glibenclamide or Glyburide	Micronase® Diabeta®		H	1969
Glipizide	Glucotrol®		H	1971
Gliquidone	Glurenorm®		H	1975
Glimepiride	Amaryl®		Methyl	1995

glimepiride appears to have a relatively low risk of hypoglycemia when used according to guidelines. However, in combination with other highly protein bound drugs or compounds, including alcohol, it is capable of producing hypoglycemia that may result in loss of glycemic control. Glimepiride is the most potent sulfonylurea on the market, requiring oral dosing of 1 to a maximum of 8 mg once per day and is the only sulfonylurea approved for use in combination with insulin in the United States [72].

2.3.2. Mechanism of Action The target organ for the sulfonylureas is the pancreas, more specifically functioning beta-cells, where they act as insulin secretagogues [73]. They bind to the sulfonylurea receptor subunit of adenosine triphosphate (ATP)—sensitive potassium channels (K_{ATP}) located on the β-cell membrane causing them to close. This closure leads to a depolarization of the cell membrane followed by an opening of voltage-dependent calcium channels. Preformed insulin is released from storage granules after an influx of calcium. Since this release is independent of glucose concentration, these agents carry a risk of causing hypoglycemia. This mechanism is also completely dependent on the presence of functioning beta-cells still capable of synthesizing insulin; thus, they are little use for the treatment of type 1 diabetics or advanced type 2 diabetics since these patients have already lost their beta-cell function [74]. Elderly patients, patients with tightly controlled diabetes, and those with impaired organ functions are at higher risk of hypoglycemia, as are individuals that are fasting, physically active or seriously ill. With proper vigilance these agents can, however, be safely used [54,69].

2.3.3. Clinical Pharmacology Sulfonylureas have proven to be very efficacious in the appropriate patient population and can decrease fasting plasma glucose 60–70 mg/dL as well as achieve HbA1c reductions by 1.0–2.0%. They are generally dosed twice daily and are typically well absorbed and well tolerated. They have no effect on plasma lipids or blood pressure. The first, and early second generation sulfonyl ureas chlorpropamide and glyburide are associated with higher incidences of hypoglycemia most likely due to their longer durations of action [75]. In a large prospective study (UKPDS), sulfonylurea therapy was associated with a decrease in microvascular events, but not with a significant decrease in mortality or macrovascular events [76]. Despite having adequate glycemic control, type 2 diabetics on sulfonylurea therapy experience an estimated 5–7% loss of beta-cell function per year [77]. Fifty percent of patients initially treated with sulfonylureas required combination therapy after 3 years of treatment; by 9 years this number rose to 75% [78,79]. Weight gain, although not as significant as for other agents, is a common side effect of sulfonylurea therapy and is most likely due to improved glucose utilization and reduction of glycosuria [54].

2.3.4. Pharmacokinetics and ADME properties The pharmacokinetics of the sulfonylureas has been summarized in a comprehensive review [72]. Most sulfonylureas are rapidly and completely absorbed, with maximal effects and peak plasma levels seen in 1.5–5 h depending on the agent [80,81]. Duration of action of these compounds range from 6–24 h [80,82,83]. Compounds exhibit high protein binding (65–99%) with most analogs greater than 95% [84]. Metabolism of these compounds occurs primarily in the liver, producing several biologically active metabolites [80,82,85,86]. Table 4 provides a summary of pharmacokinetic and ADME properties of several representative sulfonylureas.

2.4. Glinides History and Introduction

A search for novel insulin secretagogues that might offer improved safety over the sulfonylureas resulted in the identification of the benzoic acid derivative meglitinide, which shares considerable structural homology with glimepiride and is proposed to act at the same site on pancreatic K_{ATP} channels [108]. This discovery provided incentive to search for related benzoic acids and led to the selection of repaglinide, the first member of the glinide class of insulin secretogogues. Repaglinide entered the market in the late 1990s [109–111].

The other two members of this class, nateglinide and mitiglinide, are structurally distinct from the benzoic acids meglitinide and repaglinide and were identified later.