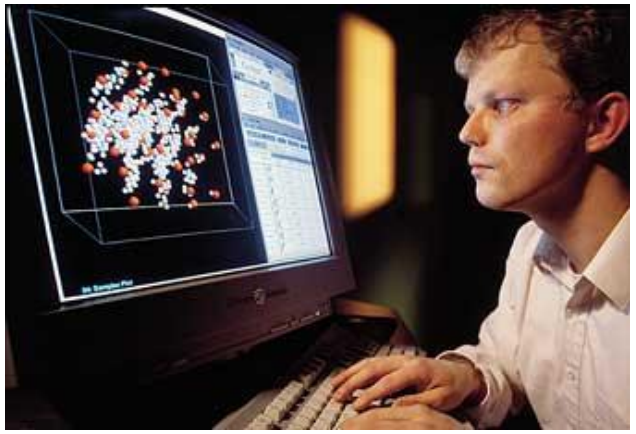
ORAL ANTIDIABETIC DRUGS



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2019

- Glucose is one of the most important nutrients in living organisms.
- The level of glucose in blood is regulated by insulin.
- Diabetes is a metabolic disease in which the concentration of glucose in blood is high.
- This condition results from either by abnormal functioning of beta cells that secret insulin in pancreas or by the development of resistance against insulin by cells.

As it brings complications through time, it is an important disease.

- When an insulin molecule shows its effects by binding on its receptor, it might be left back to the extracelluar media or it might be broken down by the cell.

- Most of the insulin molecule is broken up by liver cells.

DIABETES MELLITUS

Diabetes is a chronic metabolism disease that appears due to ineffective or lack of insulin in human body and then goes through metabolism disorders of carbohydrates, lipids and proteins.

Since it brings complications through time, it is an important disease.

Classification of Diabetes Mellitus

- **Type 1 Diabetes Mellitus**
  (%10-15, ß cell damage, No insulin secretion)
- **Type 2 Diabetes Mellitus**
  (%85-90, generally obese)
- **Other Specific Types**
  (Surgery, drug, infection, pancreas diseases)
- **Gestational Diabetes Mellitus**
  (it appears in pregnancy)

Type 1 Diabetes
(Diabetes depending on insulin)
(Young diabetes)

- **It constitutes % 5-10 of all the diabetes.**
- **Specially it appears on young people below 30 years.**
- **It is a chronic autoimmune disease.**
- **The immune system begins to distroy beta cells that produce insulin in the pancreas.**

Type 1 Diabetes

- Due to impaired immune system, organism destroys all the beta cells in its pancreas and there won't be insulin in the organism.

- In this condition if insulin isn't given, patient can't survive more than a few weeks or months. Thus, the survival of the patinet is dependent on the insulin given from outside.

Type 2 Diabetes

(Diabetes that doen't depend on insulin)

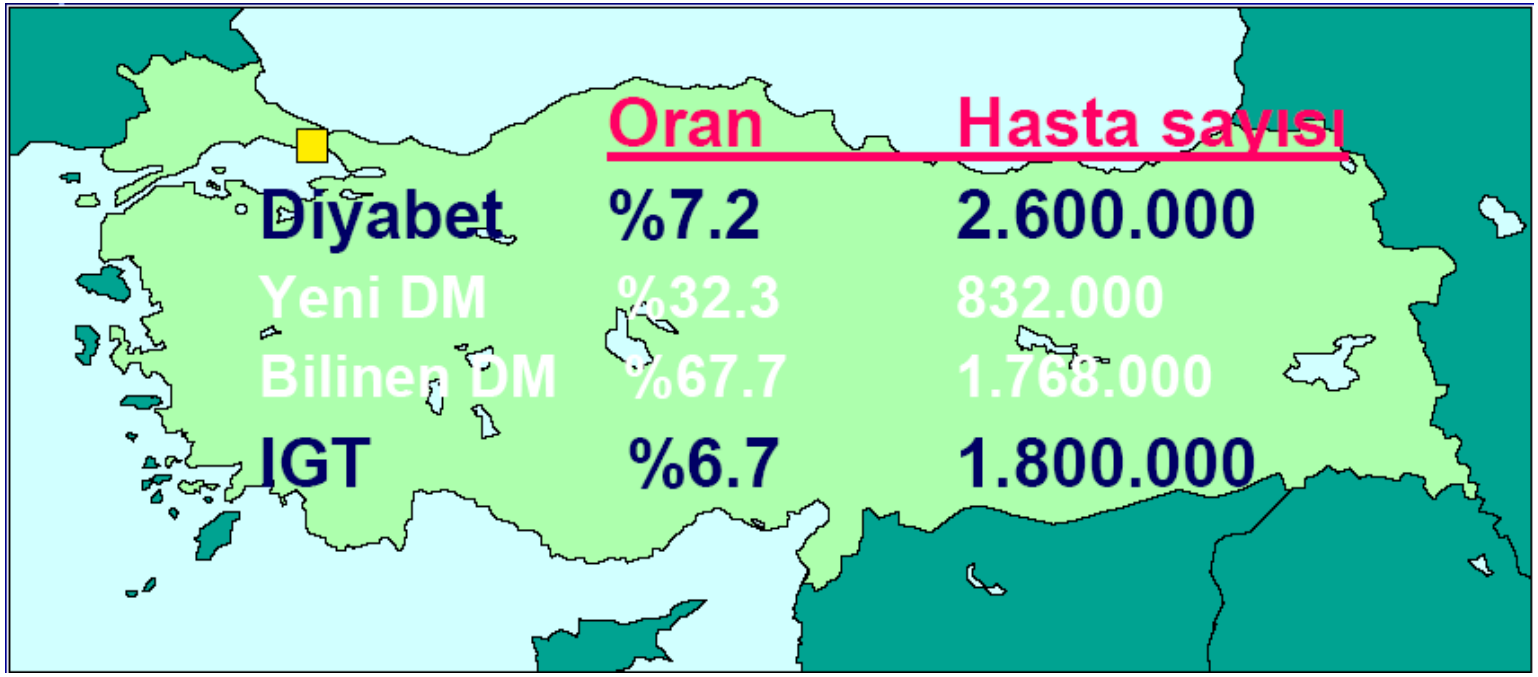
(Adult diabetes)

- It constitutes%90-95 of all the diabetes.
- These patients are generally above 40 years and fat.
- In peripheric tissues insulin sensitivity decreases or insulin resistance develops.
- In type 2 diabetes pancreas produces an amount of insulin, but it isn't enough to bring glucose into the cell.
- The number of pancreas beta cells doesn't decrease in number;however,the capability of the cells to produce and secret insulin decreases.
- Hepatic glucose production increases.
- In most patient tissues, there is unsteady and the enabilty of tissues to be affected by insulin decreases.

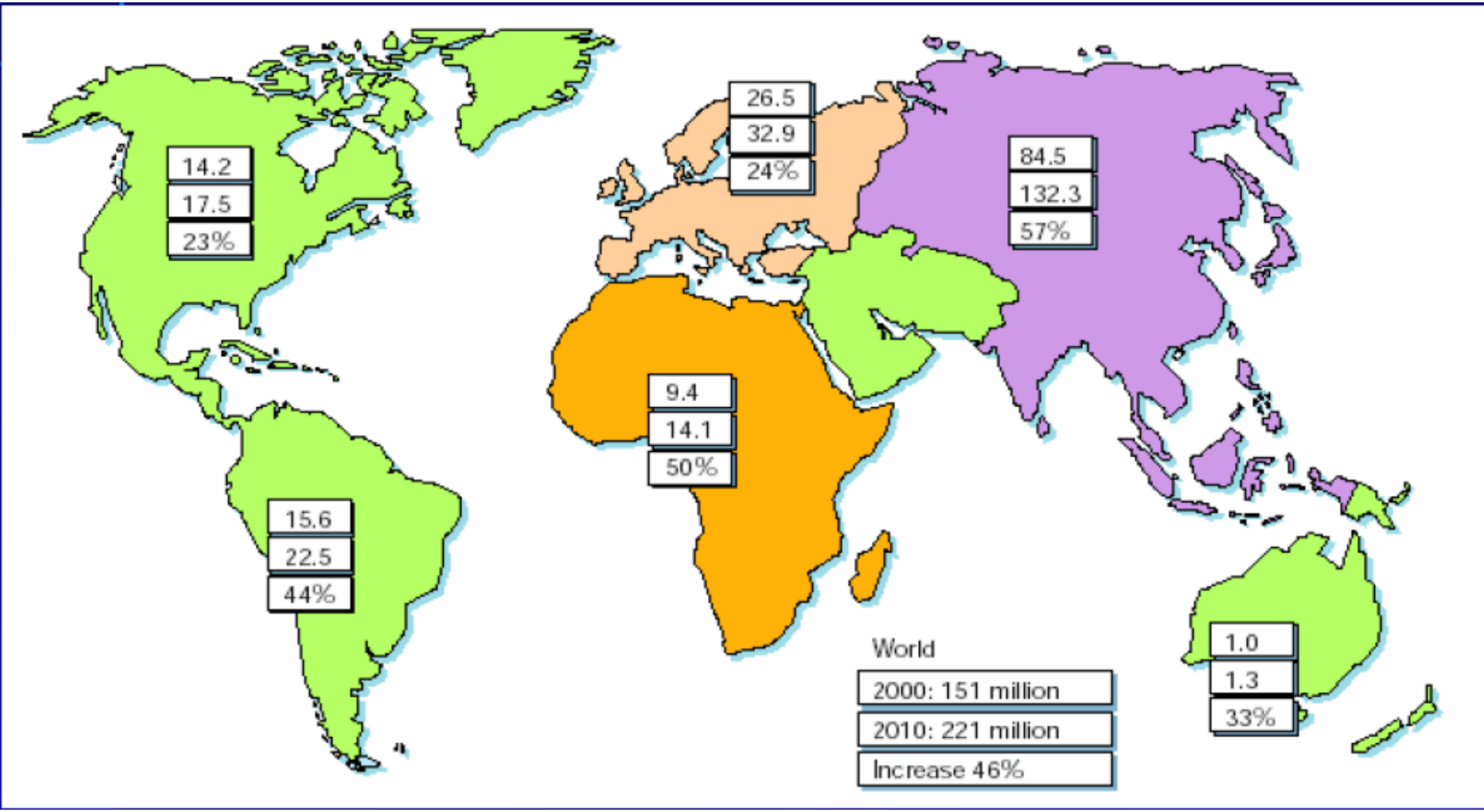
Type 2 Diabetes

- These individuals, even if they aren't healthy, they can live without any special treatment and without getting insulin from outside.
- Firstly the diabetes can be controlled by strict diet and exercise.
- Medical therapy and insulin injection may also be needed.

Diabetes Mellitus in Turkey

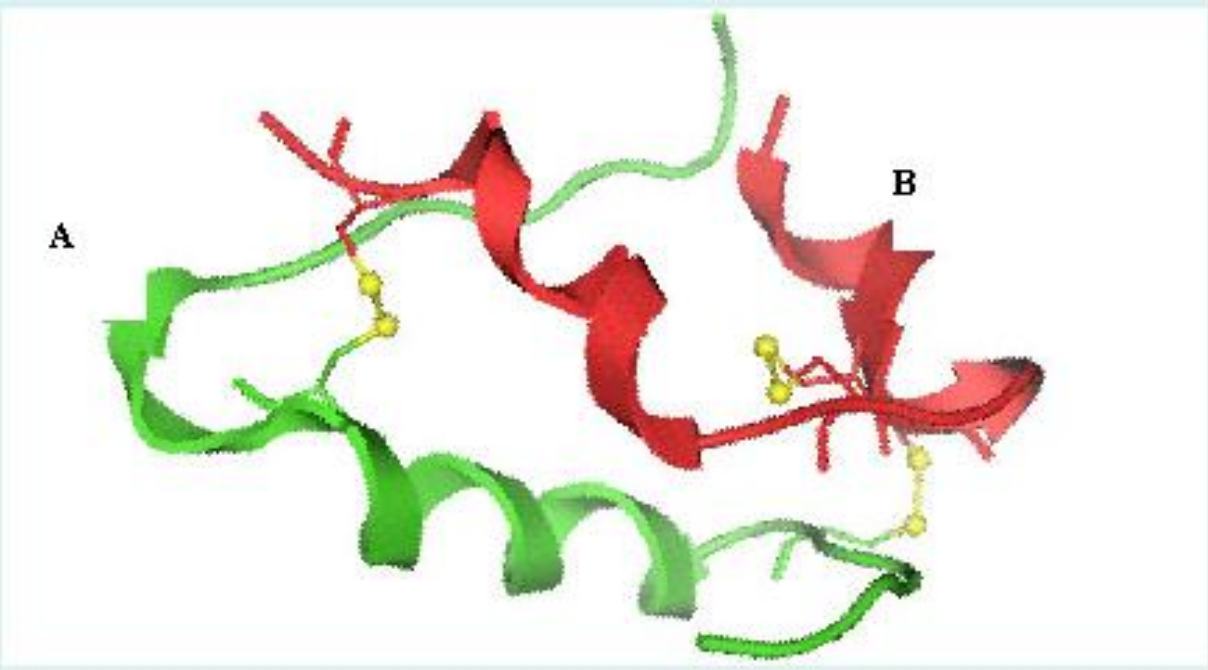


In our country around 2.6 million population with diabetes exists. In the next 15-20 years, this number is expected to increase and among 1.8 million individuals who have impaired glucose tolerance (IGT) atleast one out of three is expected to join the diabetics group.



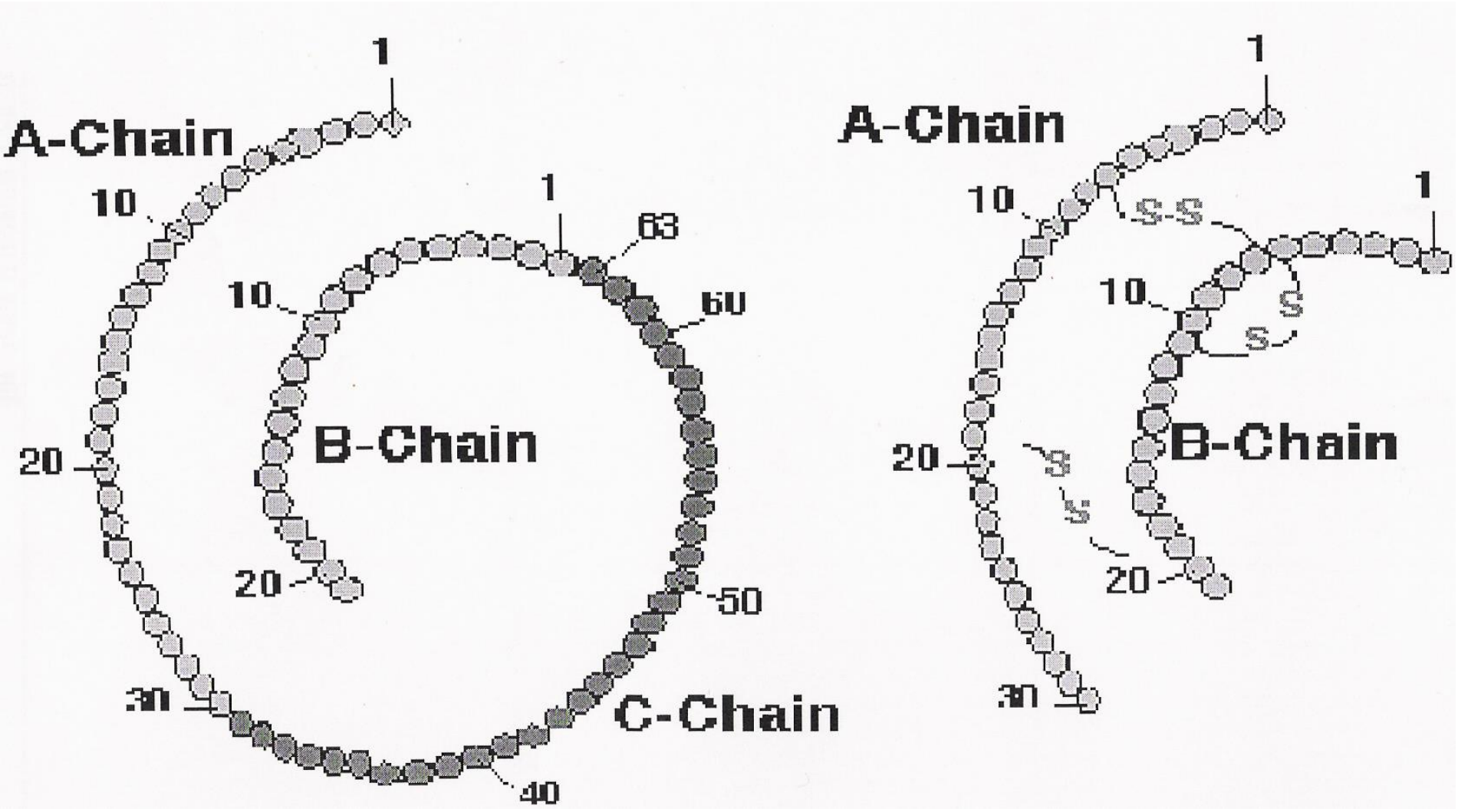
There are 230 million diabetics in the world and this number is estimated to reach 300 million by 2025.

INSULIN



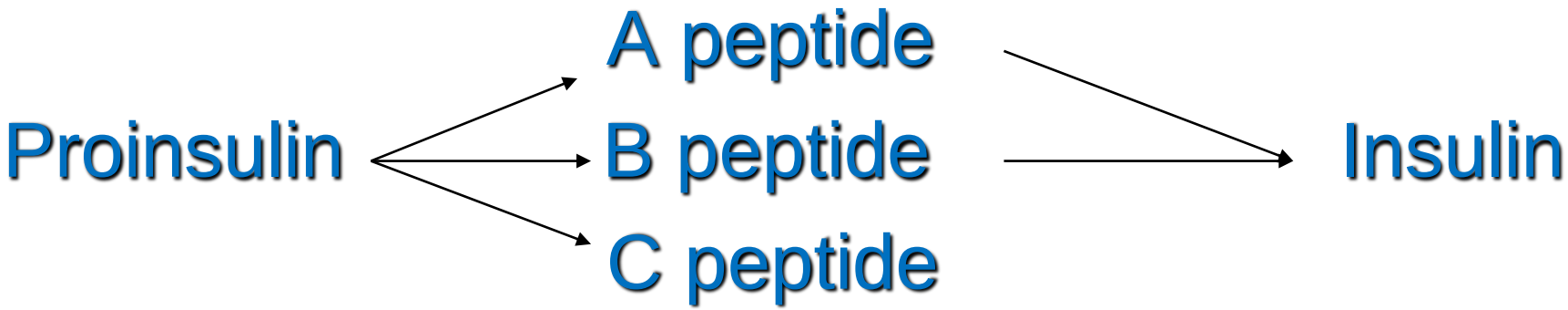
- Insulin regulates glucose level in the blood.
- It is secreted by beta cells in Langerhans islands of the pancreas, is deposited in vesiculles there.
- It is composed of 51 amino acids.
- Short chain consists 21, long chain consists 30 amino acids.
- The chains are bound with disulfide bridges between cysteine molecules.
- It is a hormone with 6000 Da molecular mass.
- Glucose triggers the production and secretion of insulin.

Structure of Insulin



INSULIN PRODUCTION AND SECRETION

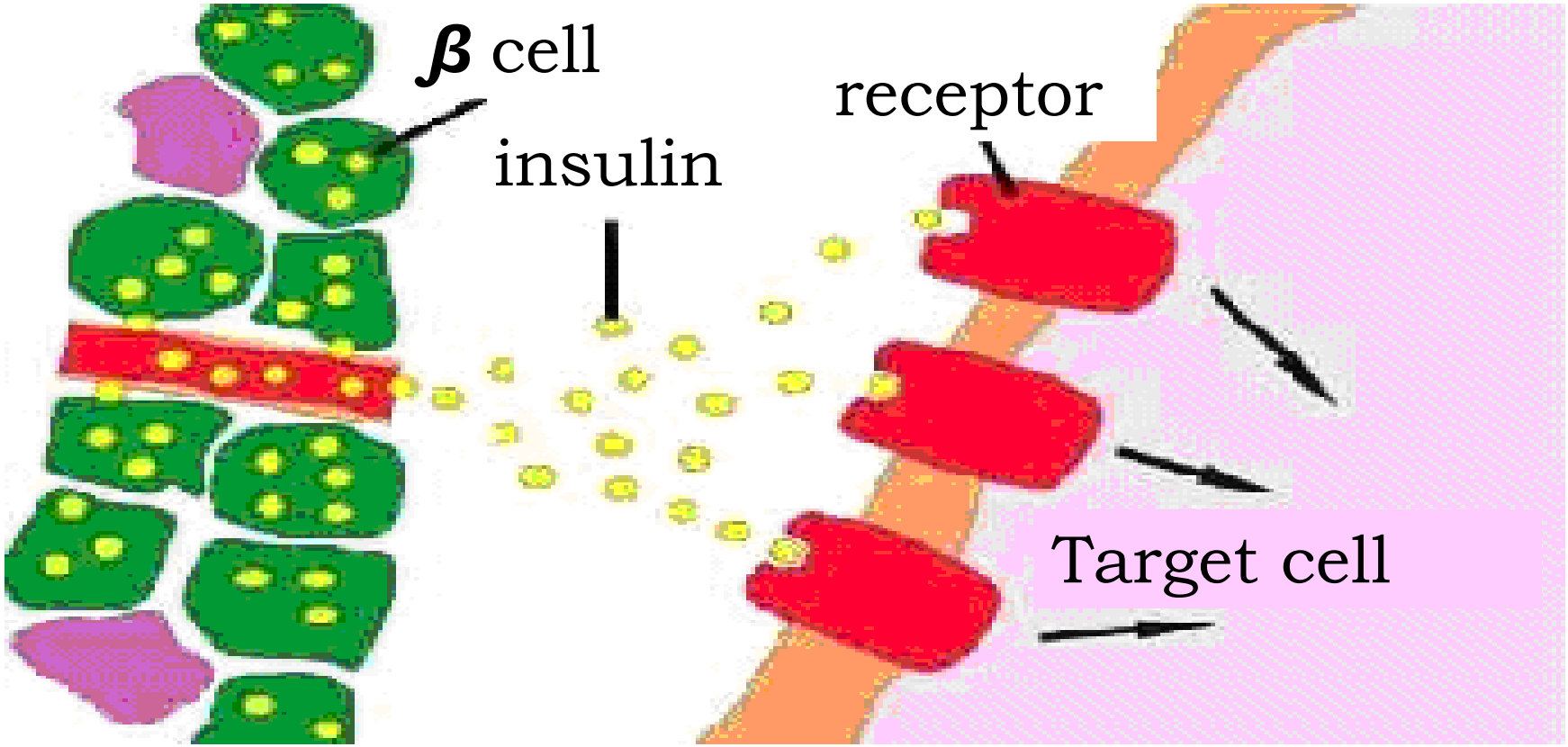
- With the entry of glucose into beta cells, proinsulin and then insulin production starts.



Proteolitic enzymes from proinsulin takes place. → **Production of insulin**

INSULIN RECEPTORS

- In order a cell to be affected by insulin, there should exist insulin receptor in its cell membrane.



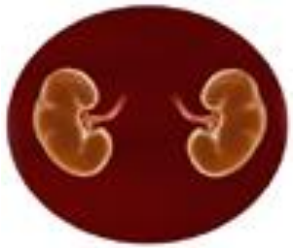
ORGANS AFFECTED BY DIABETES MELLITUS

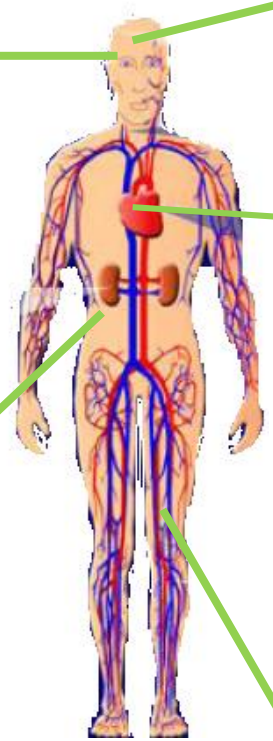
Diabetic retinopathy

Seizure

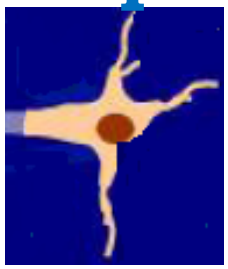
Cardio-vascular diseases

Diabetic nephropathy





Diabetic neuropathy



One of the most important non-traumatic exremity reasons ➡ amputation

Diabetes causes serious diseases like coronary heart disease, chronic kidney failure, blindness resulting from retinopathy.

According to the report by World Health Organization (WHO), type 2 diabetes:
*** Coronary heart disease is the prominent cause of death .**
**** Diabetes cause %34 deaths around the world.**

Effects of Insulin in the Organism

1.Its effect on Carbohydrate Metabolism

- **Increases glucose utilization.**
- **In the absence of insulin, since glucose utilization decreases, hyperglycaemia appears.**

2. Its effect on Lipid Metabolism

- **In the absence of insulin, in the cells of fat tissue lipolysis increases and the level of fatty acid in plasma increases.**

3. Its Effect on Protein Metabolism

- **In the absence of insulin protein synthesis decreases, protein destruction increases.**
- **In diabetics urea and ammonia excretion increases.**
- **The delay in wound scarring is related with the slow down of protein synthesis.**

4. Antiketogenic Effects (Ketonemia)

- **In the absence of insulin, the level of ketone bodies (acetone, acetic acid and ß-hydroxy butyric acid) increases.**

5. Other Effects

- **Insulin increases entry of K^+ ion into cell.**
- **Insulin increases entry of Mg^{++} ion into cell.**
- **İnsulin decreases the level of phosphate.**

- **It plays an important role in liver, stripped muscles, myocardial and fat tissue intermediate metabolisms.**

Important Complications of Diabete

- Hyperglycemia and in relation with this increase of glycocylated hemoglobin
- Large vascular disease (Macroangiopathy)
- Microvascular disease (Microangiopathy)
- Neuropathy

Side Effects of Insulin

- **Hypoglycemia**
- **Allergic reaction**
- **Lipodystrophy (In the application region fat tissue atrophy and hollowness in skin)**
- **Defect of vision: Osmotic balance defect, related with this defect in lens, decrease in its ability of refraction, in a few weeks it passes spontaneously)**
- **Edema on face**

Insulin Resistance

In long term therapy antibody formation

1 Unit Insulin:

is the amount of insulin that decreases glycemia from 120 mg/dl to 45 mg/dl in starved rabbit with 2 kg weight.

DIABETES THERAPY PLAN

EDUCATION

DIET

EXERCISE

DRUG

DIET

- Food with low glycemic index and complex carbohydrates should be preferred.
- Protein uptake in nephropathy should be 0.6 gr/kg/day.
- In hypertension and nephropathy sodium uptake should be decreased.
- Alcohol uptake should be restricted.
- A diet with balanced minerals and vitamins should be provided.

EXERCISE

- Increases the sensitivity to insulin.
- Helps to bring blood fats to the normal level.
- Helps to regulate blood pressure.
- Provides loss of body weight.
- Prevents osteoporosis.

Before Exercise;

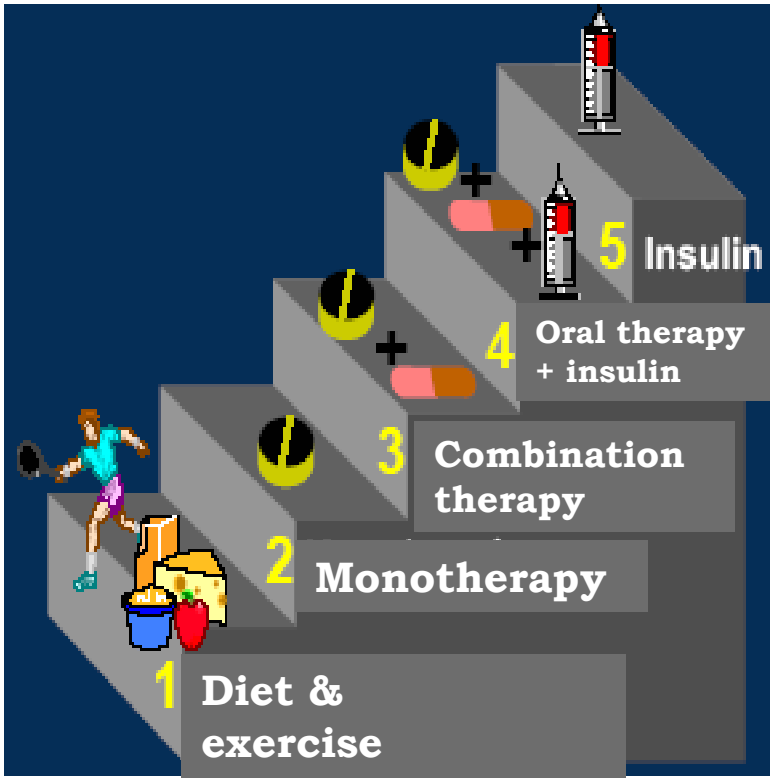
Health control.

Eye examination.

If the patient is above 35 and more than 10 years diabetic, exercise testing should be done.

THERAPY ALTERNATIVES

- **Life style change**
  - *Diet*
  - *Exercise*
- **Oral Antidiabetics(OAD)**
- **Combined therapy**
- **OAD – Insulin Therapy**
- **Insulin**



ORAL ANTIDIABETIC DRUGS

Prof. Dr. Esin AKI

According to their mechanism of action oral antidiabetic drugs are divided into four:

I- Drugs that promote insulin secretion (secretagogues)

- **Sulphonylureas**
- **Meglitinides**

II- Drugs that increase sensitivity to insulin

- **Biguanides**
- **Thiazolidinedione derivatives**

III- Drugs that slow down glucose absorption

- **Alpha glycosidase inhibitors**

IV- İncretins

I- Drugs that promote insulin secretion (Secretagogues)

1. SULPHONYLUREA DERIVATIVES

Historical background

I. 1920= A plant alkaloid

Synthalin A

Hepatotoxic

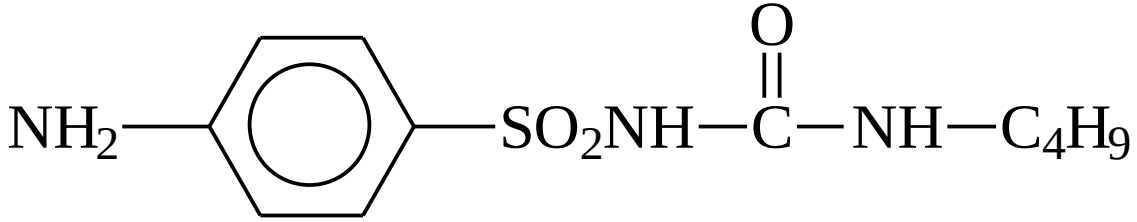
II.

Hypoglycin A (Alkaloid)

Hepatotoxic

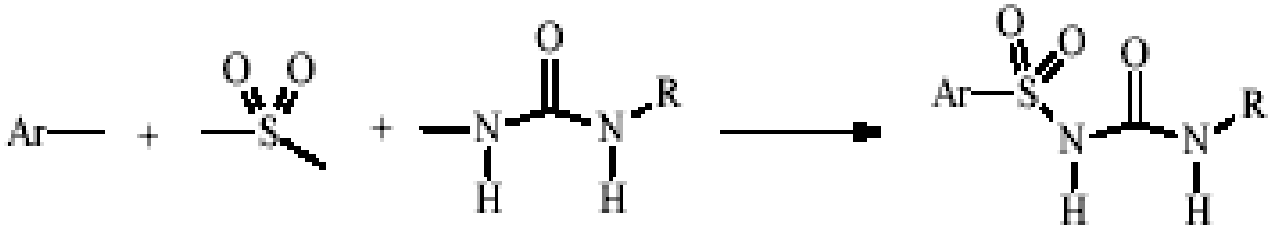
III. 1940= As sulphonamide derivatives were tested for Tuberculosis therapy >Hypoglycemia was observed.

1955 ⟶ **Carbutamide**



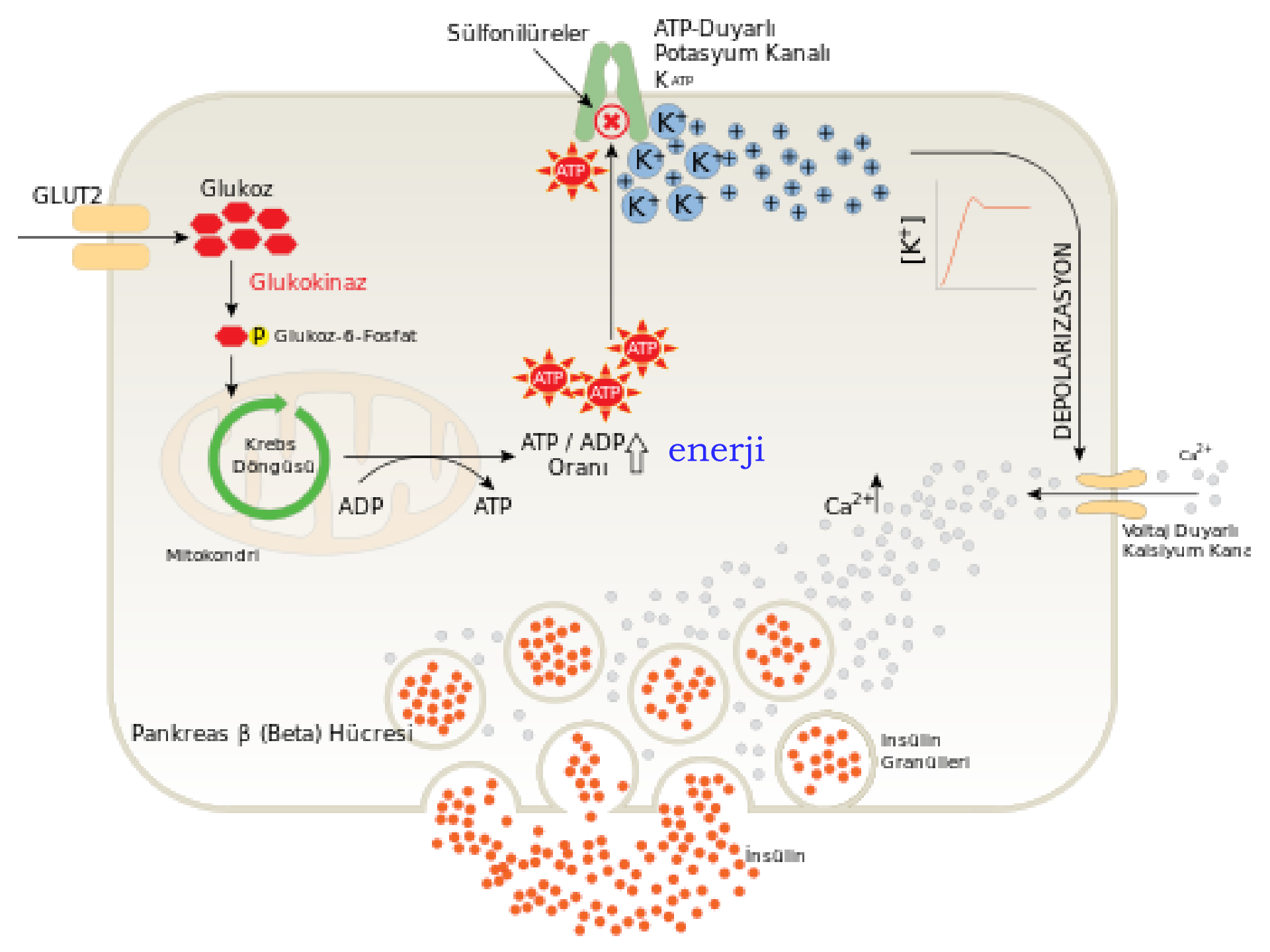
1-(4-aminophenyl sulphonyl)-3-butylurea

Sulphonylurea Structure-Activity Relationships



Aril Sülfonil üre

- Aryl and alkyl (R) groups add lipophilic charactor to the general structure.
  $–SO_2$-NH-CO-NH- part makes the structure hydrophilic.
- In the benzene ring 1 substituent, at para position:
  -CH_3, -NH_2, -$COCH_3$, -Cl, -Br, -I, -SCH_3, -CF_3
- Alkyl group 3-6 C maximum activity, after 12 C activity decreases, it can be alicyclic or heterocyclic ring.
- Aryl and R groups with lipophilic property plays an important role in binding to receptor, metabolism, appearance of continuity and ellimination differencess of sulphonylurea.
- Arylsulphonylurea are weak organic acids and are ionized at physiologic pH. The ionization of the drug increases its affinity to sulphonylurea receptors (SUR) and contributes to binding to plasma proteins.
- Alkylization of urea increases drug ionization and elimination. This brings short half life.


Sülfonilüreler
ATP-Duyarlı
Potasyum Kanalı
K ATP
GLUT2
Glukoz
Glukokinaz
Glukoz-6-Fosfat
Krebs
Döngüsü
ADP
ATP
ATP / ADP
Oranı
enerji
Mitokondri
[K+]
DEPOLARIZASYON
Ca2+
Ca2+
Voltaj Duyarlı
Kalsiyum Kanalı
Pankreas β (Beta) Hücresi
İnsülin
Granülleri
İnsülin

Mechanism of Action:

- Sulphonylureas bind to ATP-dependent channels found on the surface of pancreas beta cells. Binding of sulphonylurea to this channels prevents the hyperpolarizing potasium (K^+) current from inside to outside of the cell.

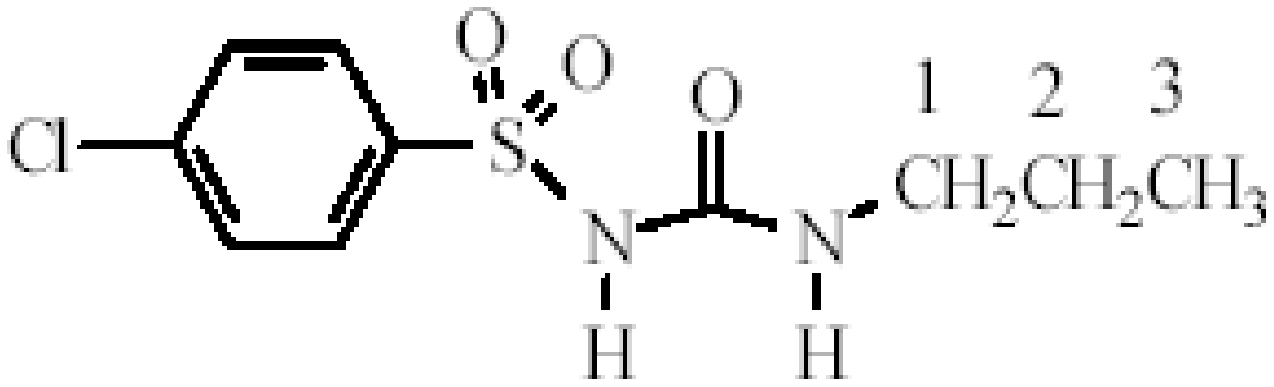
- The inability of potasium to move out of the cell makes the inside of the cell more positive than the outside and the cell becomes depolarized. The depolarization makes voltage-sensitive Ca^{2+} channels open and calcium (Ca^{2+}) molecules that entered into the cell cause the insulin deposited in granulated form to move outside of the cell by exocytosis.

Action Mechanism of Sulphonylureas

- ✓ **Show insulin like activity.**
- ✓ **Don’t have effect on insulin synthesis.**
- ✓ **Increase the secretion of insulin synthesized and deposited in vesicles.**
- ✓ **Depolarizes beta cells like glucose.**
- ✓ **Increase the entry of Ca^{++} into the cell and its mobilization.**
- ✓ **Raise the level of cyclic AMP.**
- ✓ **The increase in insulin secretion is related with their effect on Ca^{++} balance.**

First Generation Sulphonlyureas

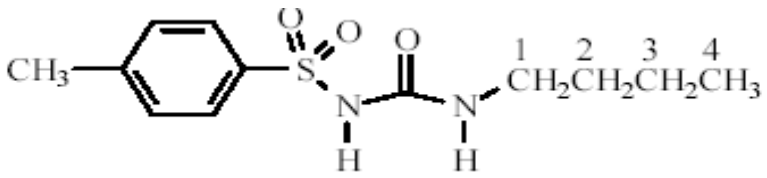
Chlorpropamide (*Diabenese*)



1-(4-chlorophenylsulphonyl)-3-propylurea

- Elimination <u>half life is too long</u> (33 hours) effective drug.
- -Cl at p-position protects against metabolic oxidation at the p-position and slows down metabolism.
- % 20 of the drug dose is eliminated from the body without any change. The rest %80 is metabolized with ω and ω-1 type oxidation.
- Especially in old patients with impaired renal function drug might accumulate.
- Symptoms like nausea feeling, hypotension and inability to breath might appear.

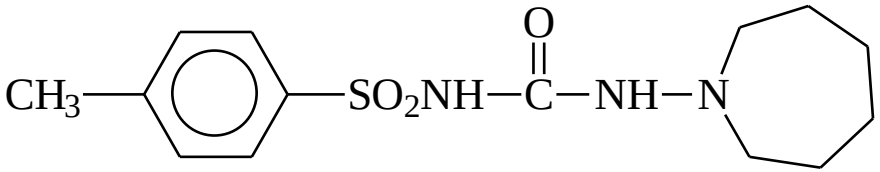
Tolbutamide - ORINASE



1-Butyl-3-(p-tolyl sulphonyl)urea

- Due to its low affinity to SUR, it has the lowest hypoglycemic effect ,
- Has short effective time.
- Has acute side effects.
- It is the safest sulphonylurea that can be used for patients with impaired kidney and old age.

Tolazamide TOLINASE

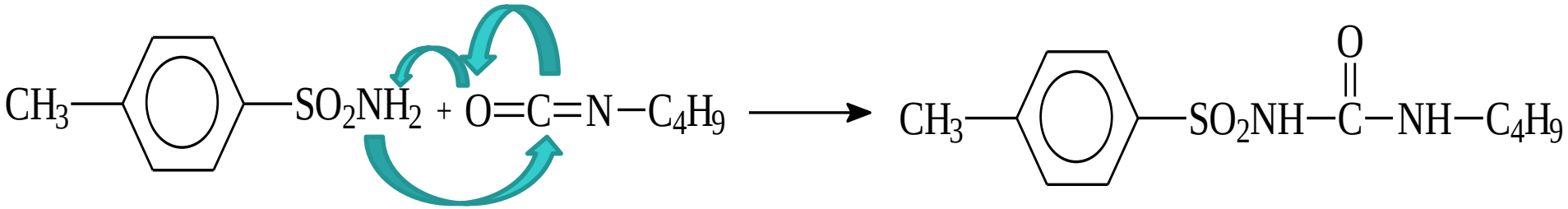


1-(Hexahydro-1H-azepine-1-yl)-3-(p-tolylsulphonyl)urea

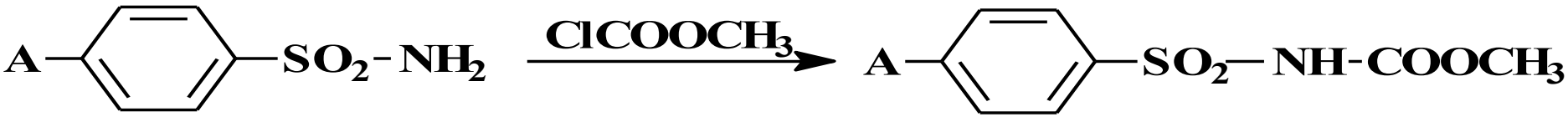
- It has hypoglycemic effect stronger than tolbutamide and almost the same as Chlorpropamide.
- It is metabolized by being exposed to benzyl oxidation like Tolbutamide.
- The slow absorption from gastro intestinal channel brings a long effective time together. This delayed effect causes hypoglycemia.
- It is inconvenient to use in patients with kidney damage.
- Its metabolite hydroxytolazamide is more active than tolbutamide

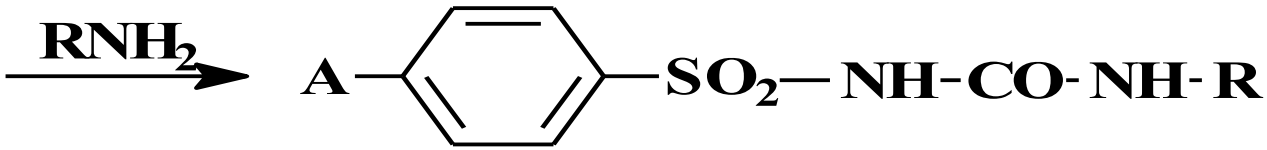
Tolbutamide Synthesis

Method 1

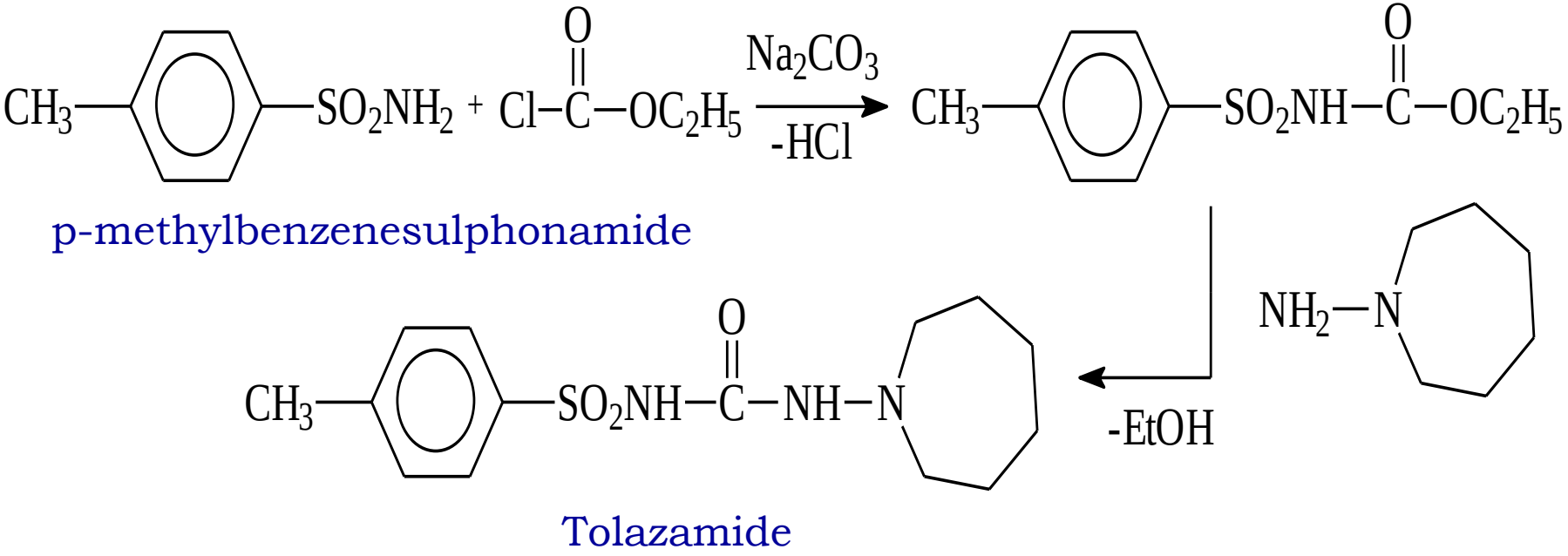


Method 2





Tolazamide Synthesis

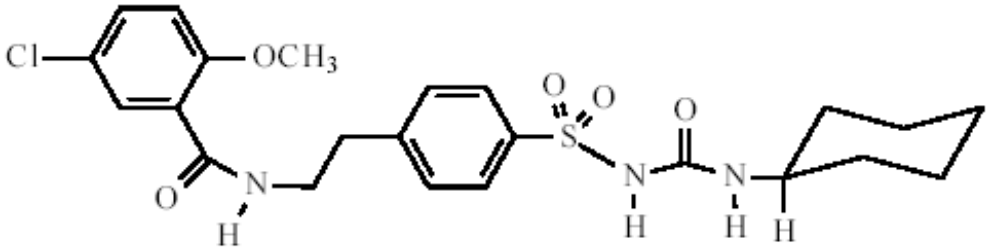


Second Generation Sulphonylureas

Second generation suphonylureas have been used for therapy since 1966.

In relative to first generation, they have stronger hypoglycemic activity.

Glybenclamide (Glyburide) - DIANORM*, DIABEN*, GLIBEN*, MİCRONASE, DIABETA, GLYNASE



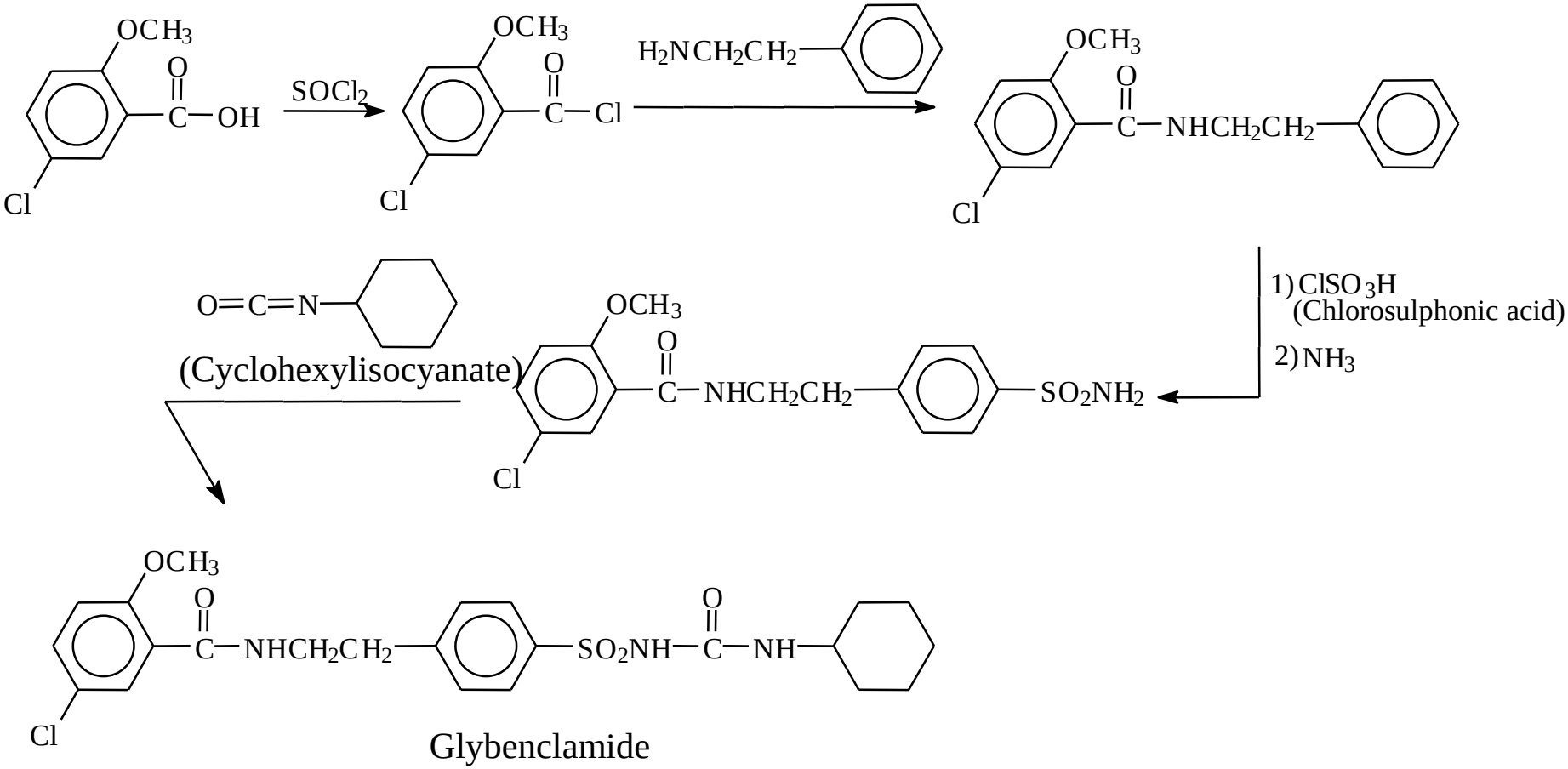
1-{4 - [2 - (5 -chloro-2-methoxy-benzamido) ethyl] phenylsulphonyl} – 3-cyclohexylurea

- **It is a hypoglycemic agent with strong effect.**
- **It is easily reabsorbed from liver.**
- **It is metabolized in liver.**

- **Even if it has short plasma half life (2-10 hours), because of the effective metabolites resulting from its metabolism, it has long biologic activity.**

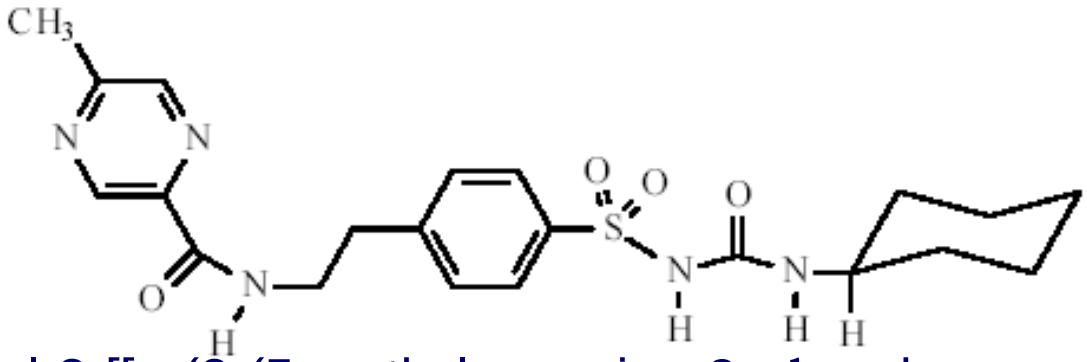
- **Firstly it is meatbolized at the cyclohexyl ring (ω and ω -1 type oxidation).**
-
- **As a result of long activity hypoglycemia might develop. However, in relative to first generation sulphonylureas, it has little side effects.**

Glybenclamide Synthesis



Glybenclamide

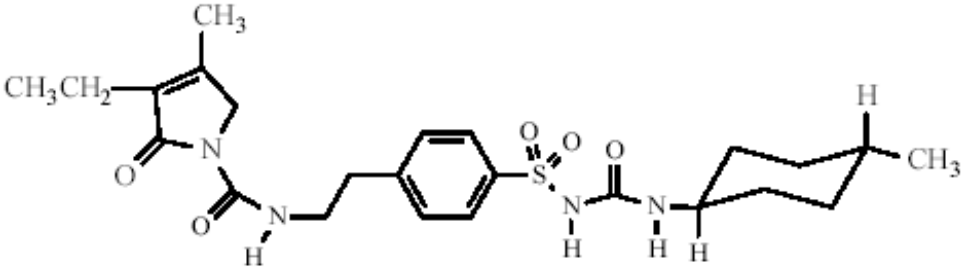
Glipizide - MINIDIAB*, GLUCOTROL XL*, GLUCOTROL



1-cyclohexyl-3-[[p-(2-(5-methyl-pyrazine-2-yl-carboxoamido)ethyl]phenyl] sulphonyl]urea

- **Because of its high binding capacity to plasma proteins, glipizides like glyburide depending on aryl group are strong and long effective second generation sulphonylureas.**
- **When it is taken with food, its absorption decreases. Thus, it should be taken with empty stomach.**
- **The controlled release form elongates its effective time.**
- **It is metabolized mainly in liver (%90). %10 is eliminated from kidney without any change (ω and ω -1 type oxidation).**

Glimepiride – AMARYL*, GLIMAX*, DIAMEPRID*

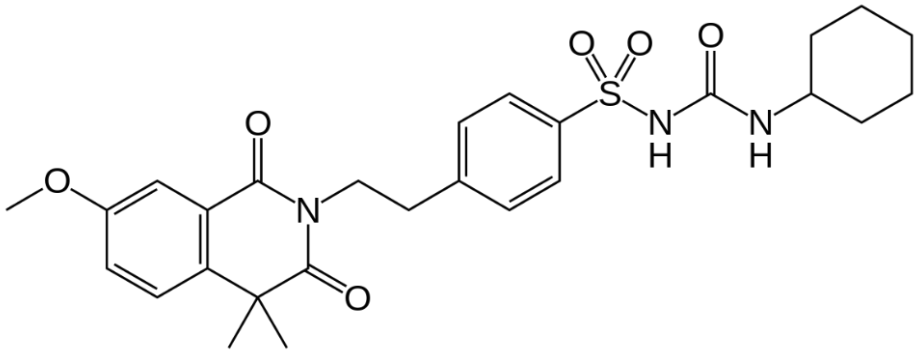


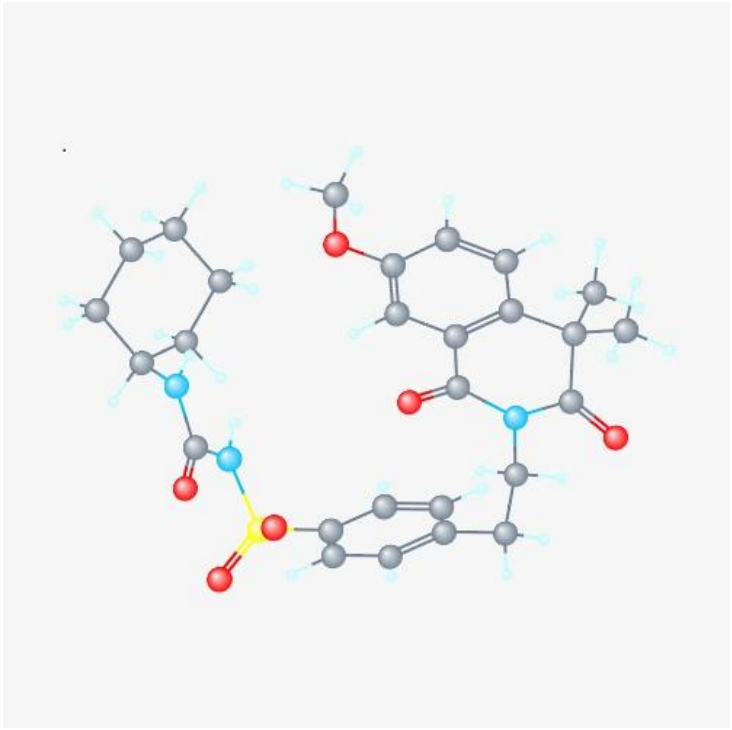
1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyroline-1-carboxamido) ethyl] phenyl] sulphonyl]-3-(trans-4-methyl cyclohexyl)urea

- **It has faster and longer activity than glyburide.**
- **Different from the other second generation sulphonylureas, the ureido group in its structure provides the binding at a different place on receptors of the beta cells and thus has longer activity time.**
- **From the sulphonylureas, at low dose, it is the most potent drug.**
- **By decreasing glucagon secretion and glucose transport and by activating non-oxidative glucose metabolism, it reduces blood sugar level even in the absence of insulin.**
- **The hypoglycemia risk is low.**
- **Taking the drug with empty or full stomach doesn't have an important impact on drug absorption.**
- **It doesn't accumulate on the body. Its hydroxy metabolite has negligible little effect on blood glucose and it is eliminated from the body with the equal effect of liver and kidney.**
- **It is safe for patients with impaired kidney and old age.**
- **It doesn't have known drug interaction.**
- **As a result of its weak bond to pancreatic, myocardial and ATP-dependent K^+ vascular system channels, in relative to sulphonylureas its vasoconstriction and cardiovascular side effects are reduced.**

Gliquidone – GLURENORM

New compound





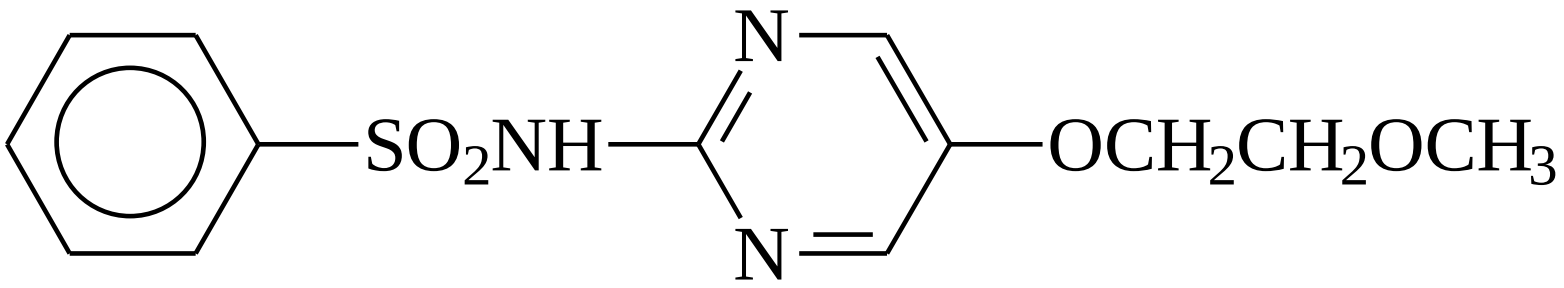
N-(Cyclohexylcarbomoyl))-4-[2-(7-methoxy-4,4-dimethyl-1,3-dioxo-3,4-dihydroisokinolin-2(1*H*)-il)ethyl]benzenesulfonamide

Half life 8 hours

Side effects of Sulphonylureas

- **Irritation in GIC; Nausea, vomiting, stomach burn, stomachache, diarrhea**
- **Allergic rush on skin**
- **Bone marrow depression; Leukopenia, thrombocytopenia, agranulocytosis**
- **Hypoglycemia —> Coma**

Sodium Glymidine (Glycodiazine)- REDUL-LYCANOL-GLYCONORMAL-GONDAFON



N-[5-(2-methoxyethoxy) prymidine-2-yl] benzene sulphonamide

- **No allergy like sulphonylureas. As a result of this it is used for patients who are allergic to sulphonylurea group.**

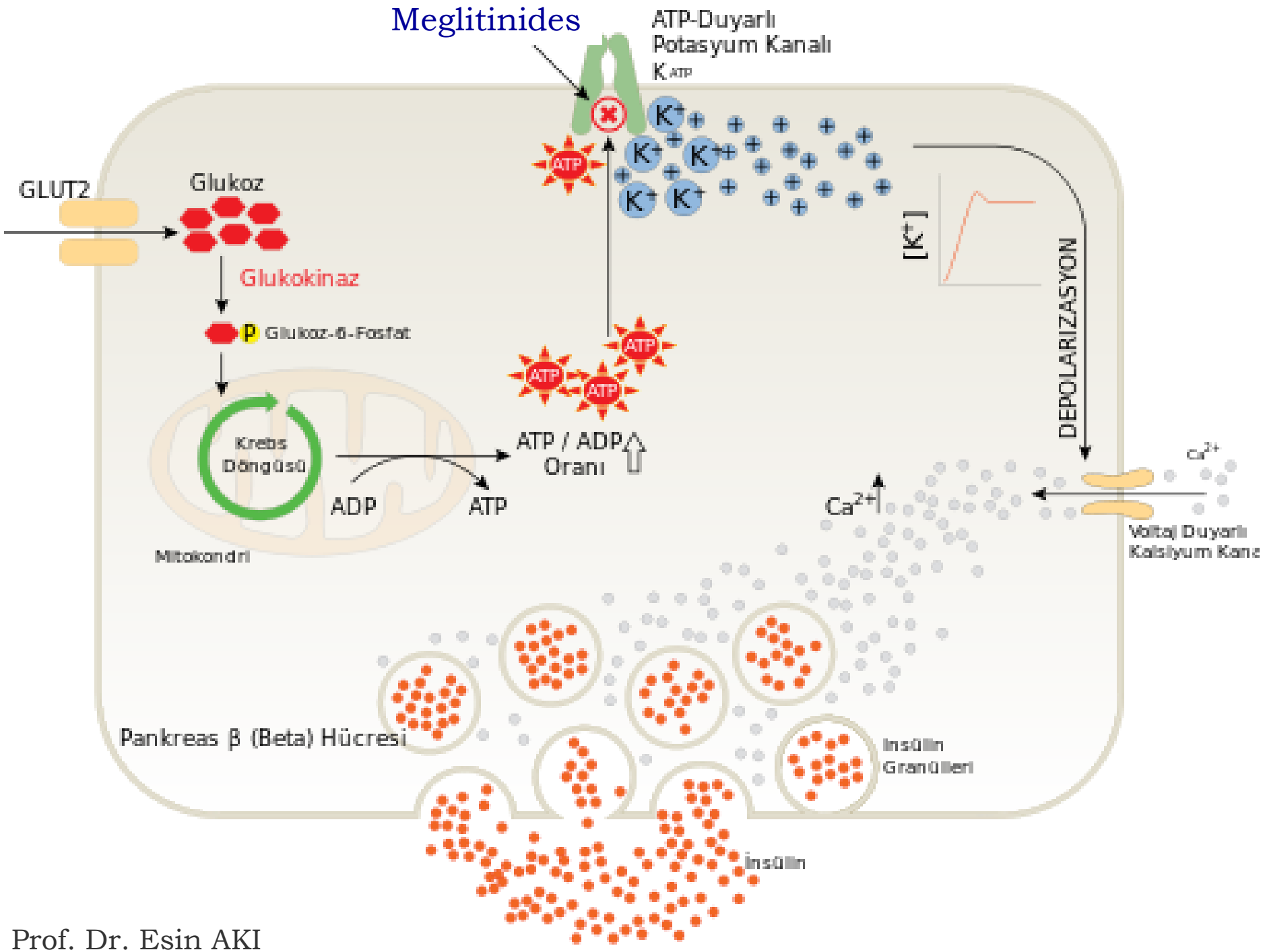
2- MEGLITINIDES

•Like the sulphonylurea compounds, Meglitinides, stimulates insulin secretion by inhibiting ATP-sensitive K_{ATP} channels on pancreatic beta cell membranes.

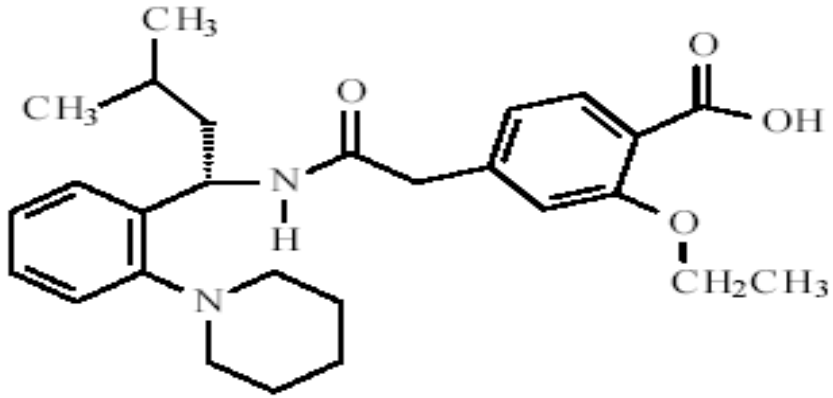
•Different from sulphonylurea group compounds it binds to sulphonylurea receptors at different places. With this binding, beta cell is depolarized. As a result calcium channels (Ca^{2+}) are opened and due to the increase in the flowing calcium ions into the cell insulin secretion is stimulated.

•Meglitinides are drugs that are taken before meal to prevent hyperglycemia that result from meal and has a rapid effect with short effective time.

•In Meglitinides, there is high tissue selectivity. They show little affinity to heart and skeletal muscles.


Meglitinides
ATP-Duyarlı
Potasyum Kanalı
K ATP
GLUT2
Glukoz
Glukokinaz
Glukoz-6-Fosfat
Krebs
Döngüsü
ADP
ATP
ATP / ADP
Oranı
Mitokondri
[K+]
DEPOLARIZASYON
Ca2+
Voltaj Duyarlı
Kalsiyum Kanalı
Pankreas β (Beta) Hücresi
İnsülin
Granülleri
İnsülin

Repaglinide - PRANDIN, NOVODORM*



[S(+)2-ethoxy-4(2-((3-methyl-1-(2-(1-piperidinyl) phenyl)-butyl)amino)-2-oxoethyl) benzoic acid

They are known as high glucose plasma level lowering agents.

In lowering high glucose concentration after meal, they are better than Glybenclamide.

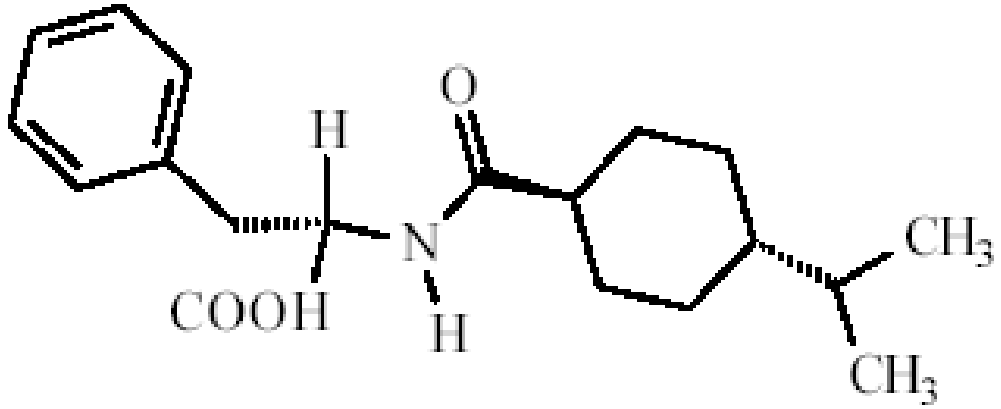
In maintaining glycemic control, they are better than Glipizide.

Flexible meal dependent dose adjustment, low hypoglycemia risk and its short effect on insulin secretion can increase patients quality of life.

Nateglinide - *STARLIX*

N-(trans-4-isopropylcyclohexancarbonyl)-D-phenylalanine]

(*R*)-2-(4-isopropylcyclohexyl-carboxamido)-3-phenyl-l-propanoic acid

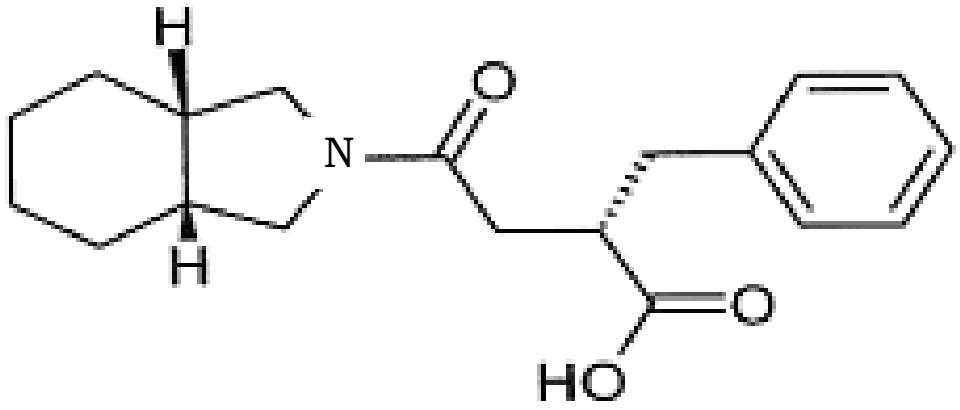


•Nateglinide is a phenylalanine derivative that increases especially primary secretion insulin, which is developed in Japan recently.

•When it is compared to other insulin secretagogues like Glybenclamide and Repaglinide, the drug effect appears more rapidly and the effective time is shorter.

•Nateglinide is metabolized in liver rapidly and is eliminated in urine. Thus, it can be used for patients with kidney failure.

Mitiglinide - GLUFAST



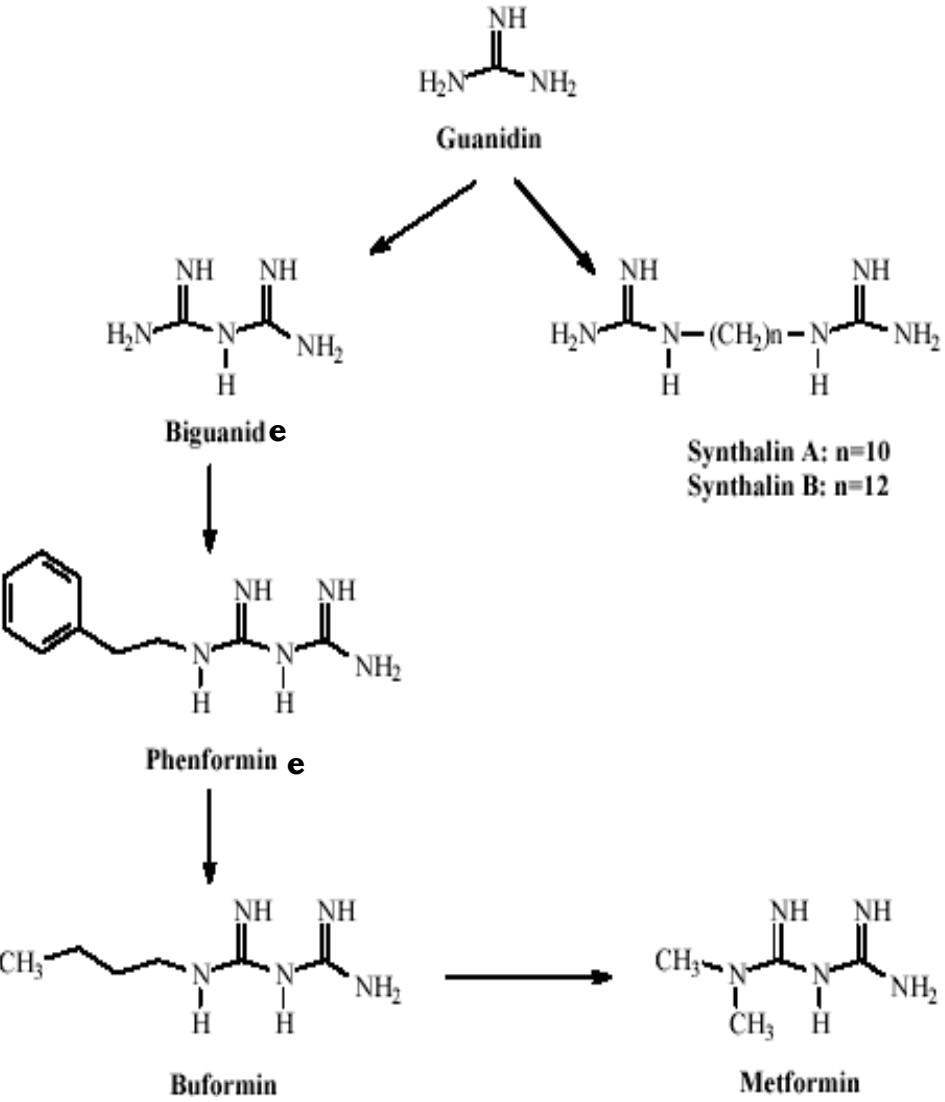
(S) 2-Benzyl-4-(3aR,7aS)-octahydro-isoindol-2-yl-4-oxo-butyric acid

(2*S*)-2-benzyl-4-[(3a*R*,7a*S*)-octahydro-2*H*-izoindol- 2-yl]-4-oxobutanoic acid

- *New compound*

II- DRUGS THAT INCREASE THE SENSITIVITY TO INSULIN

1- Biguanides



- Biguanides are guanide derivatives. Guanidine's ability to reduce blood glucose level in animals was discovered in 1918.
- However, in use of Sintalin A and B that are developed for Diabetes for a long time damage of kidney and liver occurs. Thus, their use has been stopped.
- In 1950s for the treatment of type 2 diabetes patients in addition to sulphonylurea 3 biguanide derivatives (Phenformin, Buformin and Metformin) were introduced as antidiabetics agents.
- Buformin and Phenformin cause lactic acidosis frequently.

Buformin is used in few countries (Romania).

Phenformin is out of use.

Metformin has been used in Europe and also Turkey for many years. In USA, it was approved by FDA for diabetes therapy in 1995.

1.Biguanides:

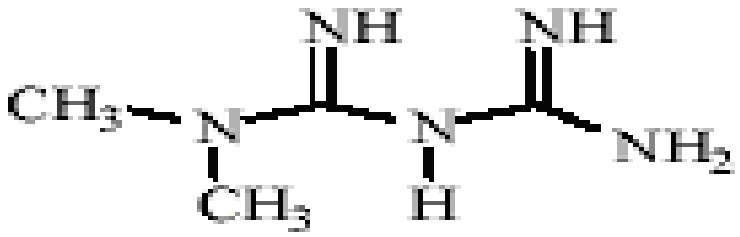
Three mechanisms are put forward:

1. They increase insulin activity at the peripheral tissues.

2. They decrease glucose absorption from small intestine.

3. They decrease gluconeogenesis (glucose is produced from glycogen-carbohydrates).

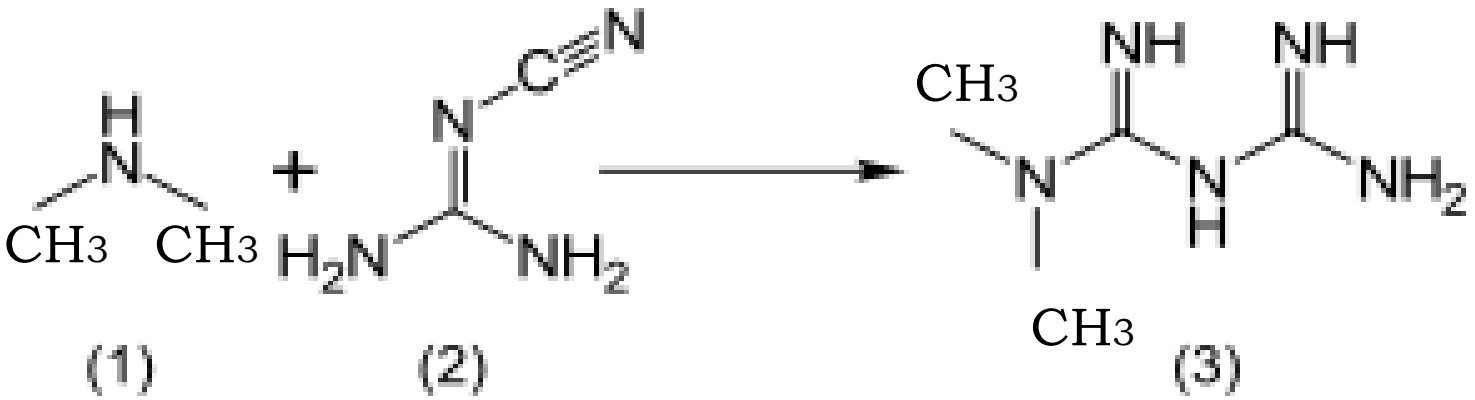
Metformin – GLUCOPHAGE*, *GLUKOFEN**, *GLUFORMIN**



Metformin

- Different from sulphonylureas, they don't make hypoglycemia when they are used solely at their maximum doses.
- Metformin doesn't affect insulin secretion. Even if it has been used for diabetes therapy for many years, its mechanism of action isn't clear.
- The major acceptable mechanism is the inhibition of gluconeogenesis.
- It affects glucose metabolism even in the absence of insulin.

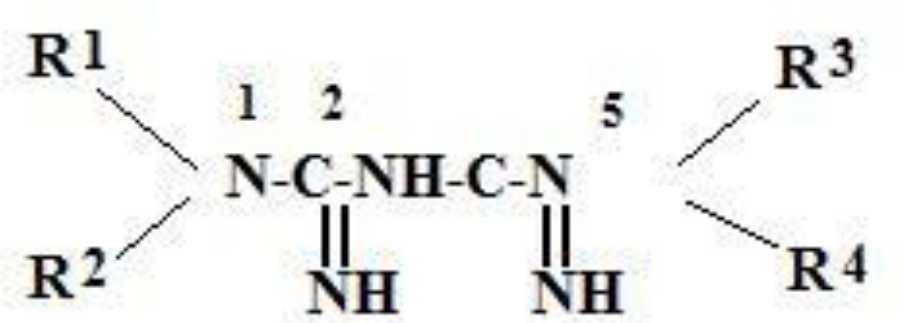
Metformin Synthesis



Metformin Side Effects

- Rarely Lactic Acidosis
- Gastrointestinal effects (like gas, diarrha)

Biguanide Structure-Activity Relationships



- **In conditions where there are one or more substituents at one of the nitrogens activity increases.**
- **When there are substituents at both of the nitrogens, activity decreases toxicity increases.**
- **It is known that the existence of methyl, propyl, penthyl and allyl groups at N1 increases the activity.**

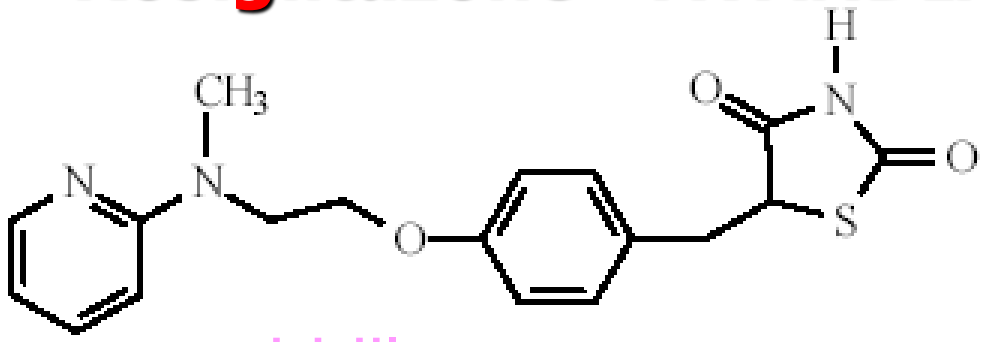
2- Thiazolidinedione Derivatives

- The first prototype Troglitazone was approved in 1997, then Rosiglitazone and Pioglitazone were introduced.

- In 2000 Troglitazone, as a result of its hepatotoxic effect, it was caused 61 deaths in America. Thus, it was removed from the market.

- Thiazolidinediones are also not drugs that stimulate insulin secretion.
- Like Biguanides, Thiazolidinediones don't make hypoglycemia when they are used solely.
- At first they play a role in increasing insulin sensitivity at peripheral tissues. They show their effect by activating PPAR (Peroxisome Proliferator-Activated Receptor) groups. There are three types of defined PPARs ; PPARα, PPARβ, PPARγ.
- Increase the insulin activity and decrease glucose and free fatty acid levels that are harmful to beta cells and insulin secretion.

Rosiglitazone - AVANDIA *)



-piridil-

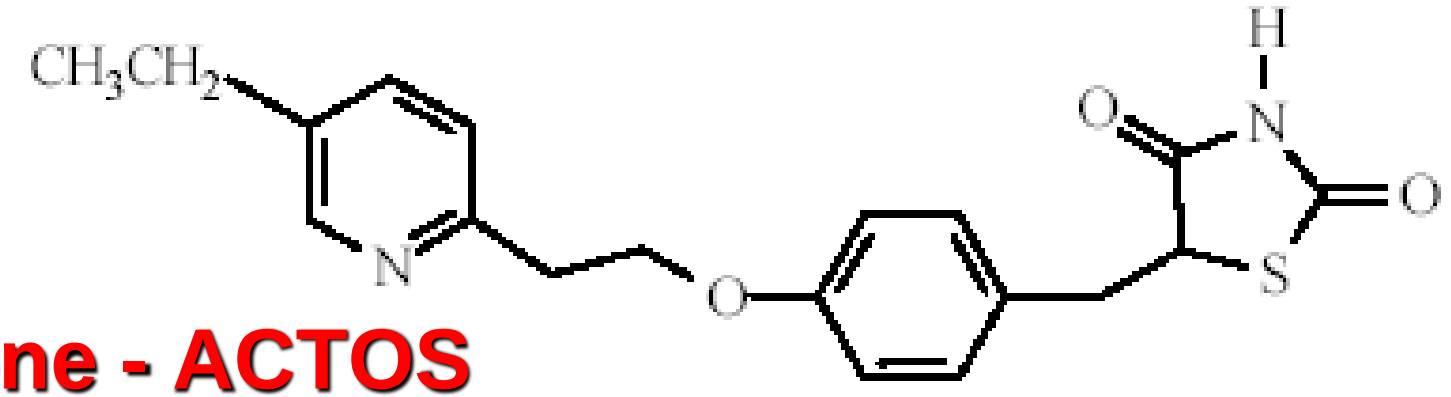
[(±)-5-[[4-[2-(-2-pyridinyl-N-methylamino) ethoxy] phenyl]- methyl]- 2,4 thiazolidinedione]

•It can be used solely or in combination with sulphonylureas and metformin.

•It is a thiazolidinedione derivative highly selective to PPARγ. As a result it is more potent than other drugs like Pioglitazone. The potency of Rosiglitazone in relative to other oral antidiabetic drugs makes it available in the market at suitable doses.

•Rosiglitazone reaches its peak plasma concentration in an hour after oral intake and has %99 bioavailability.

•The main metabolisms of Rosiglitazone are N-demethylation and hydroxylation followed by sulphate and glucuronic acid conjugation.

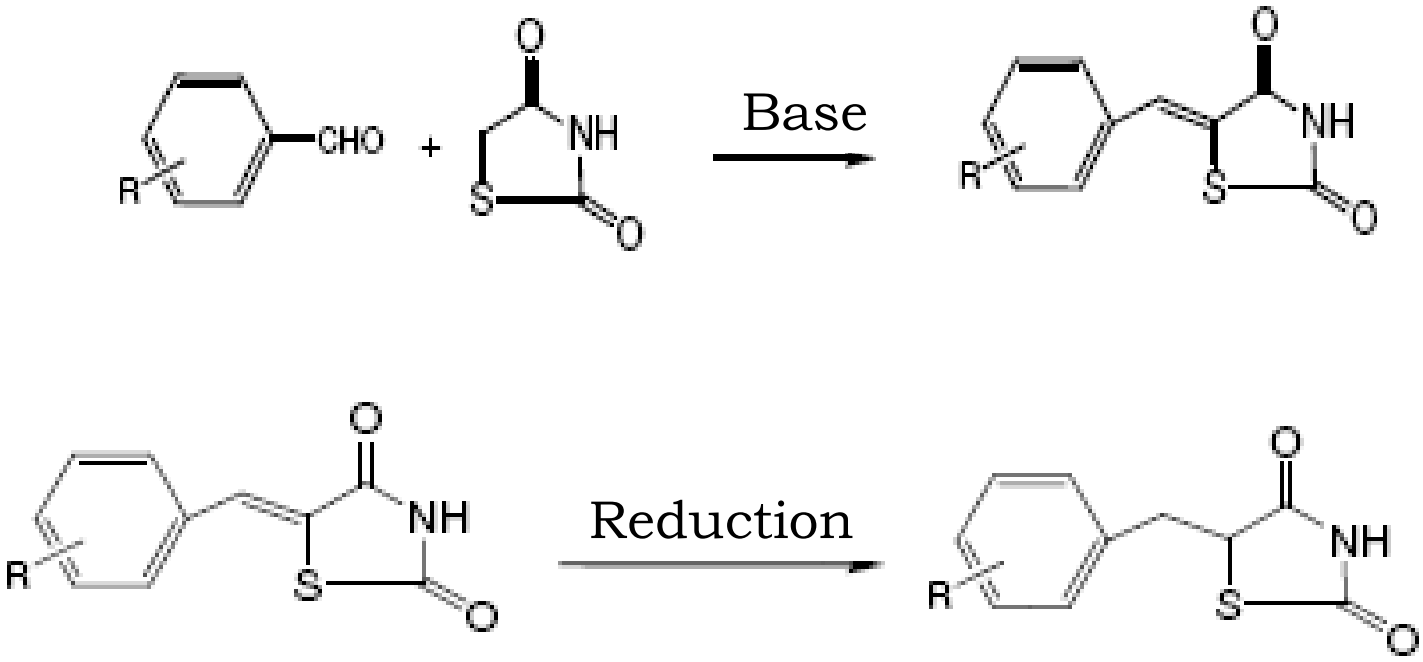


Pioglitazone - ACTOS

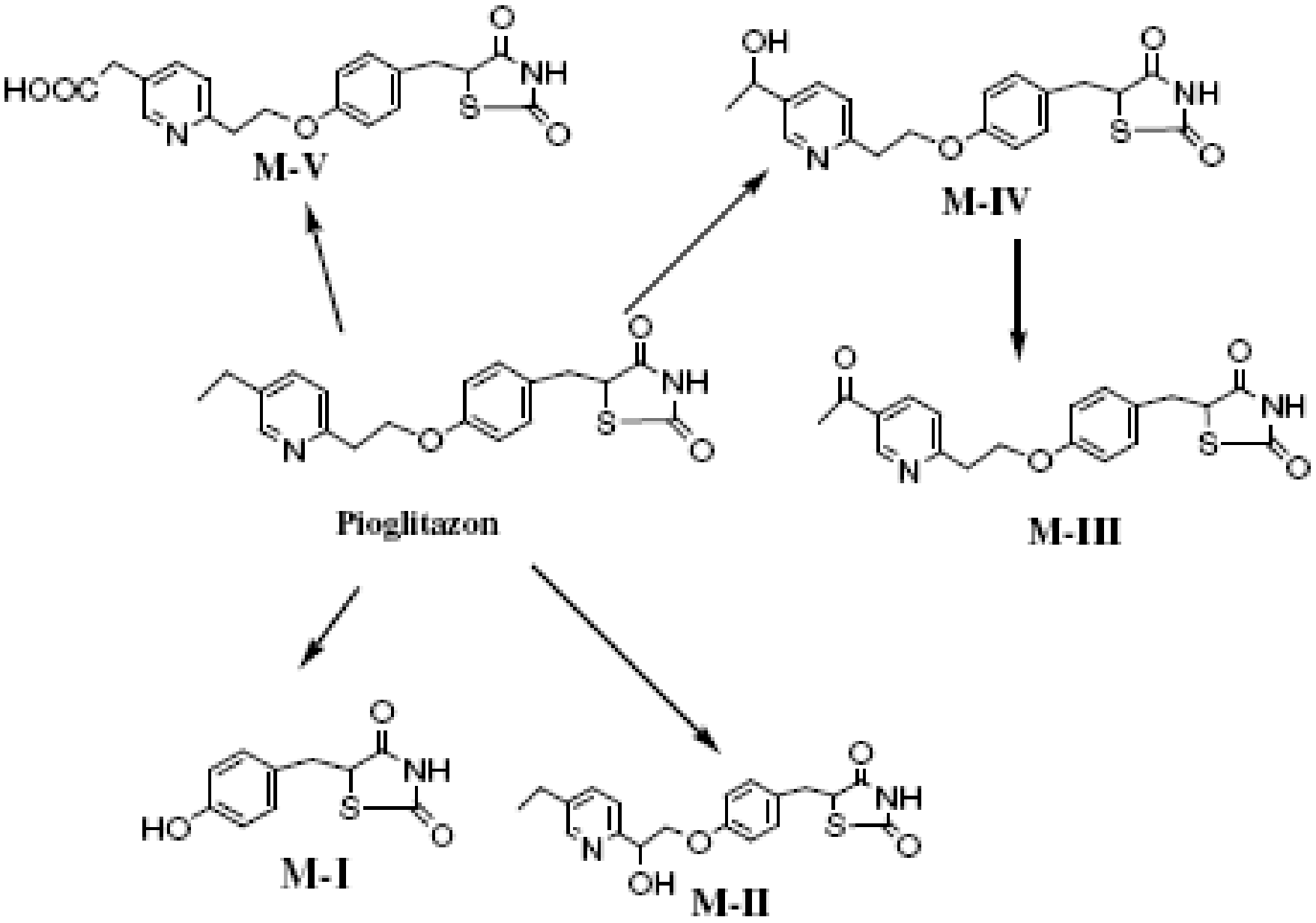
5-[[4-[2-(5-etil-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione

- It is the third thiazolidinedione derivative that was introduced to the market in 1999 for type 2 diabetes patients.
- It is more potent than Troglitazone but less potent than Rosiglitazone.
- It can be used solely or in combination with insulin, sulphonylureas and metformin.
- Side effects: respiratory system infection, edema, headache, weight gain and hypotension.

Synthesis of 2,4-TZD compounds substituted at 5. position



Metabolism:



In the past, only Biguanide derivative Metformin was used as glucose lowering drug.

However, approximately %15-20 of the patients don't have tolerance against Metformin.

As a result, now a days the biguanide alternative thiazolidines are also used as alternatives.

Combined Therapy

Sulphonylurea +Biguanide(Thiazolidinedione)

Side Effects of Thiazolidine Derivatives

- Both in single and combined form, they cause weight gain.
- Cause peripheric edema.
- Congestive heart failure. It couldn’t be determined yet whether the congestive heart failure and peripheric edema appeared on the use of the drug is related to the drug. However, heart failure was observed %4.5 in TZD users and %2.6 in non-users.
- They are contraindicated in patients with active liver disease.

III- DRUGS THAT SLOW DOWN GLUCOSE ABSORPTION

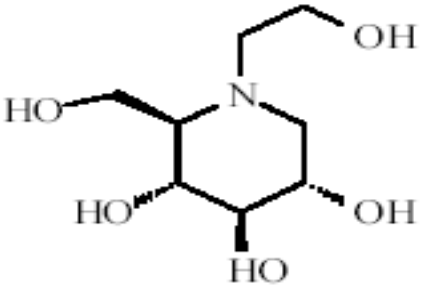
1. Alpha glucosidase inhibitors

•They help to prevent hyperglycemia indirectly by slowing down glucose absorption.

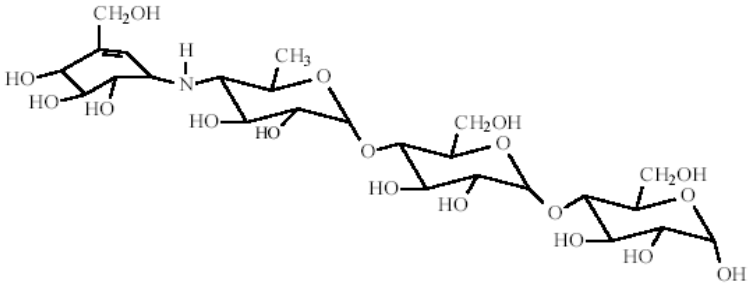
•Alpha-glucosidase enzymes are found on the brushed like surface of small intestine and are responsible for breaking of complex carbohydrates. These enzymes break down oligo and disaccharides. Monosaccharides are easily absorbed to the blood from the intestine wall.

•Alpha-glucosidase enzyme inhibitors inhibit this enzyme competatively. Glucoamylase, sucrase, maltase, isomaltase, lactase are the known alpha glucosidase enzymes.

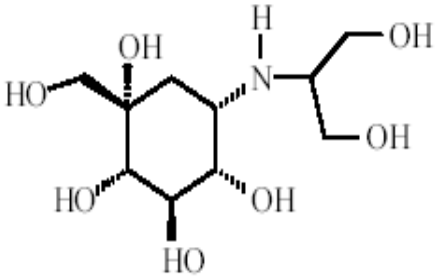
Miglitol (Glyset)



Acarbose (*Precose, Glucobay**)



Voglibose



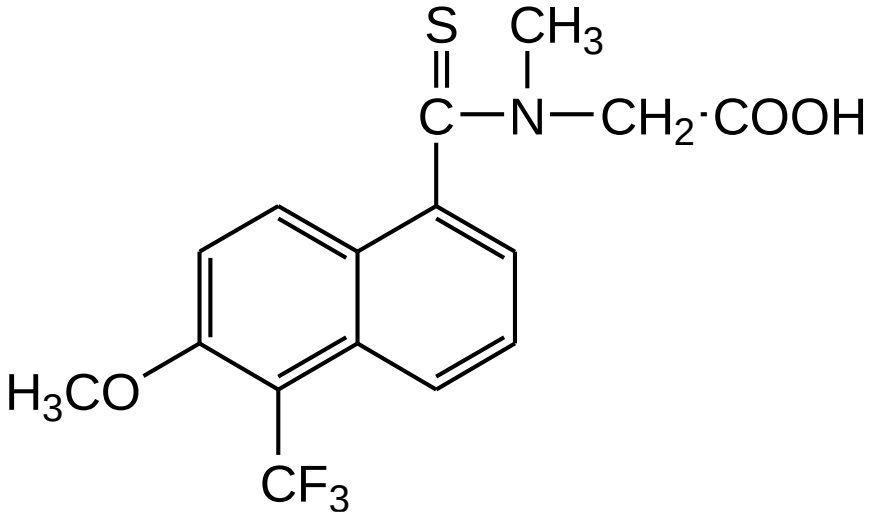
Miglitol: (2*R*,3*R*,4*R*,5*S*)-1-(2-hydroxyethyl)-2-(hydroxymethyl)piperidine-3,4,5-triol
Voglibose: 1*S*,2*S*,3*R*,4*S*,5*S*)-5-(1,3-dihydroxypropane-2-ylamino)-1-(hydroxymethyl) cyclohexane-1,2,3,4-tetraol

- Acarbose and Voglimose are microbial originated. Miglitol is synthetic.
- From this group the one which is mostly used and found in our country is acarbose. Acarbose is an inhibitor to both glucoamylase and sucrase. It delays the absorption of starch, sucrose and maltose.
- Its plasma half life is upto two hours. It doesn't accumulate on the body.
- Maximum effect of Acarbose can be obtained by applying 3 times 100 mg dose.
- It shouldn't be taken with full stomach. Due to its serious gastrointestinal side effects, it must be begun with low dose and be increased slowly.
- Miglitol, which is the second alpha glucosidase enzyme inhibitor and introduced in July 1996, primarily inhibits isomaltase. It interacts with intestinal sodium bind glucose transporters. Miglitol is absorbed from jejunum by a mechanism like glucose and excreted from kidney without any change.
- Voglibose is a potent inhibitor of many alpha glucosidase enzymes. Its effect on sucrose is less than acarbose. It has little effect on pancreatic amylase.

2. Aldose Reductase Enzyme Inhibitors

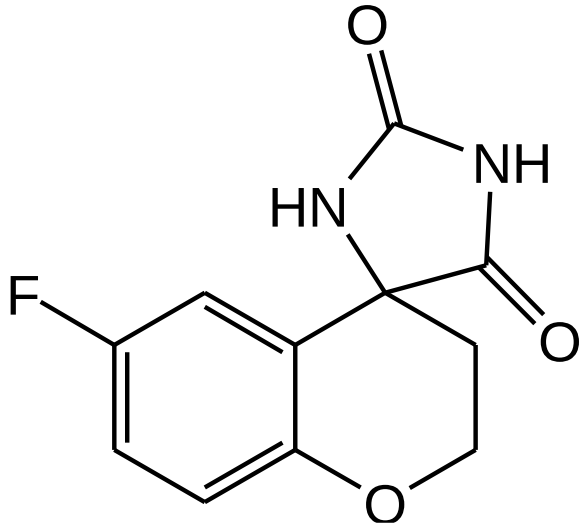
These group of drugs are used in nephropathy and retinopathy. With the mediation of glucose aldose reductase enzymes sorbitol comes about. Accumulation of sorbitol causes retinopathy in the eyes.
Aldose reductase enzyme inhibitors (sorbinil, tolrestat, ponalrestat, epalrestat, flavanoid) can be effective in the treatment of diabetic glomerulosclerosis (hardening of kidney capillaries)**. The effect of sorbitol in diabetic nephropathy is still controversial further more it has toxic effect. The side effects of tolrestat and ponalrestat are less and there are researches that show the prossible use in the control of early stage and short proteinurea.**

Tolrestat



N-((6-Methoxy-5-triflouromethyl-1-naphthalenyl) thioxomethyl)-N-methylglycine

Sorbinil



Glucagon

- It is a single chain relatively small polypeptide that consists of 29 amino acids.
- It is synthesized from alpha cells on Langerhans islets (islands) of the pancreas.
- Its secretion increases under hungry and hypoglycemia conditions.
- It has inverse effect to insulin.
- It is only applied parenterally.

IV. INCRETINS

INCRETINS

They are insulin secretion stimulating hormones that are secreted in response to food uptake.

- GLUCAGON LIKE PEPTIDE–1 (GLP-1)
- GLUCOSE DEPENDENT INSULINOTROPHIC POLYPEPTİDE (GIP)

GLUCAGON LIKE PEPTIDE–1 (GLP-1)

- GLP-1 (Glucagon Like Peptide-1) is the most potent incretin type and is responsible for the increase of insulin secretion from pancreas beta cells.
- GLP-1's amino acid sequence has %50 similarity to glucagon.

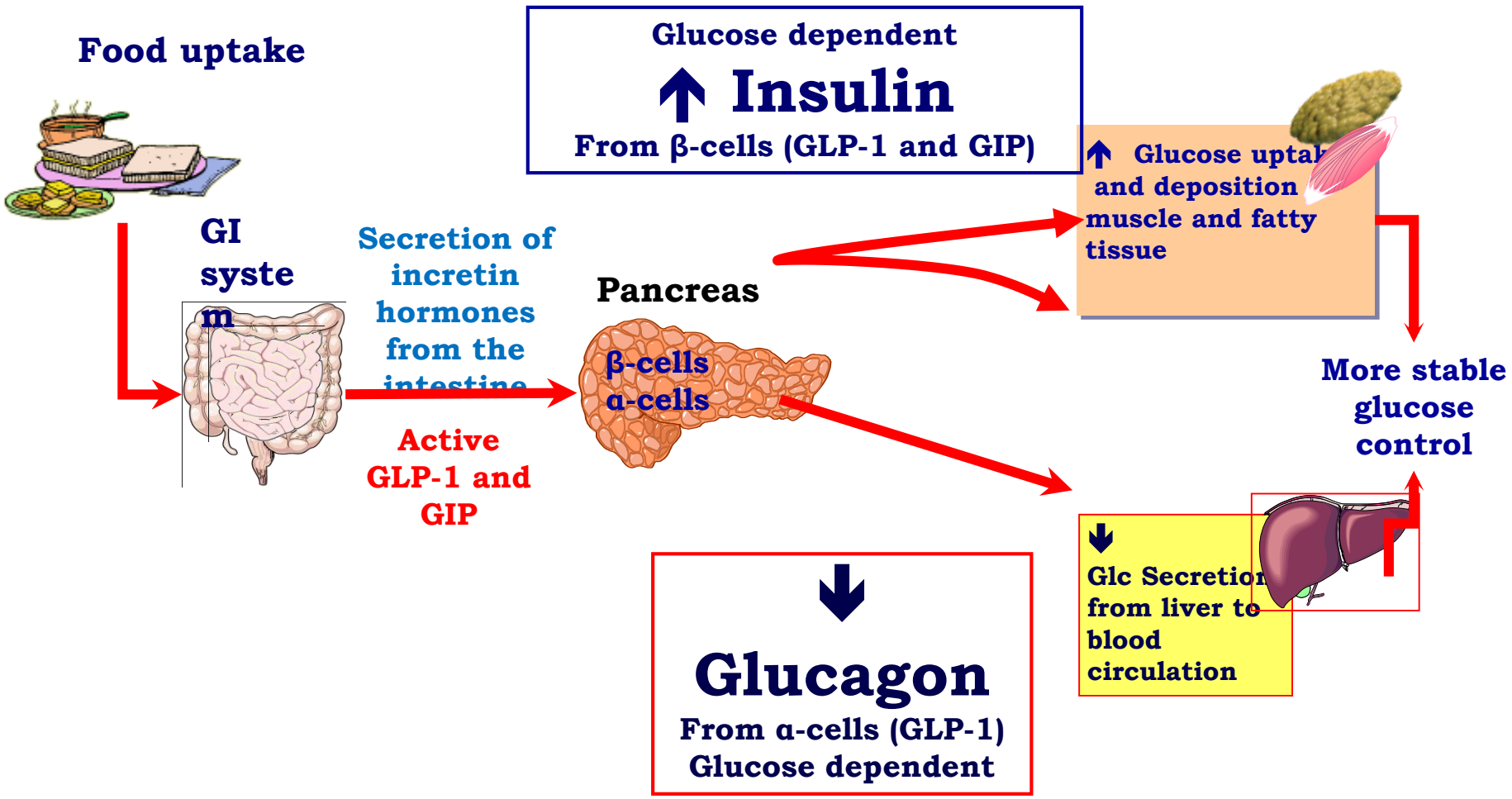
GLUCOSE DEPENDENT INSULINOTROPHIC POLYPEPTIDE (GIP)

- GIP is a plypeptide composed of 42 amino acids.
- The most important stimulant of GIP is food intake.

GLP-1's Physiologic Activities

- It increases glucose dependent insulin secretion from pancreas..
- It decreases glucagon secretion from pancreas.
- It increases beta cell mass and insulin gene expression.
- In stomach it inhibits acid secretion and gastric discharge.
- It decreases food uptake by suppressing appetite.
- It increases the sensitivity of cells to insulin.

The effect of incretins (GLP-1 and GIP) on glucose homeostasis islet cell functions



GI = gastrointestinal; GLP-1 = glucagon-like peptid-1; GIP = glucose-dependent insulinotrophic polypeptide

DIPEPTIDYLPEPTIDASE-IV (DPP-4)

- DPP-4 is an enzyme with complex structure that inhibits GLP-1, GLP-2 and GIP.
- It is a peptidase enzyme related with membrane that consists of 766 amino acids.

EKZENATİT (BYETTA®)

H–His–Gly–Glu–Gly–Thr–Phe–Thr–
Ser–Asp–Leu–Ser–Lys–Gln–Met–
Glu–Glu–Glu–Ala–Val–Arg–Leu–
Phe–Ile–Glu–Trp–Leu–Lys–Asn–
Gly–Gly–Pro–Ser–Ser–Gly–Ala–
Pro–Pro–Pro–Ser–NH_2

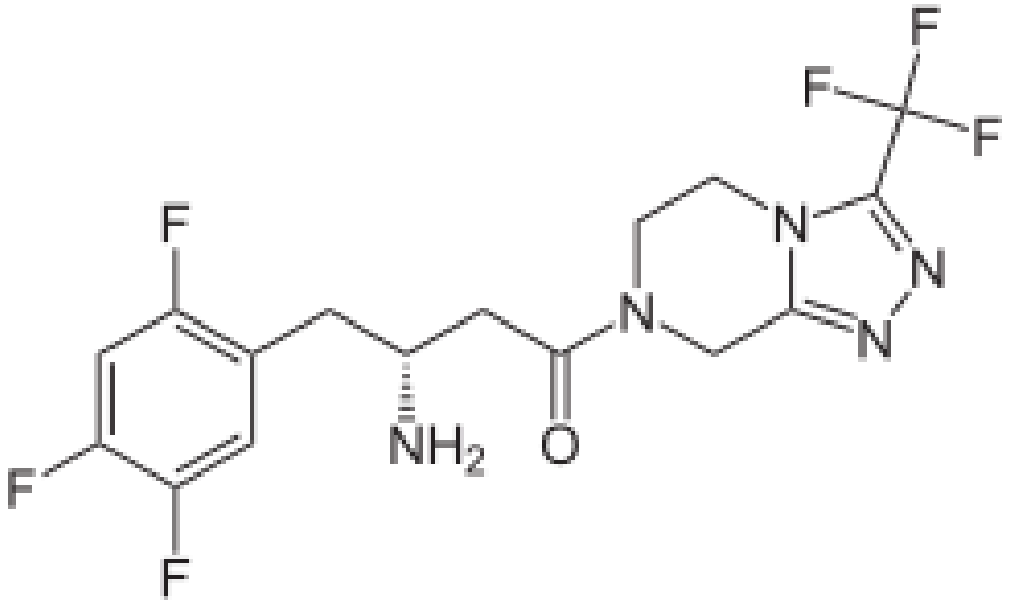
Its activity is as DPP-IV inhibitor..
With the inhibition of DPP-IV activity for 4-52 weeks, there is decrease in the level of HbA1c, weight loss, increase in the function of beta cells and in type 2 diabetic a decrease in plasma glucagon level occurs.

EKZENATİT (BYETTA®)

- It has properties like human GLP-1.
- It is the only compound (except insulin) that is used in injectable form for type II diabetes therapy but not applied orally.
- It increases insulin secretion, suppresses inappropriately high glucagon and slows down stomach discharge.
- Ekzenatit has %50 amino acid similarity to GLP-1 and has longer in vivo half life.

Sitagliptin (JANUVİA®)

R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine



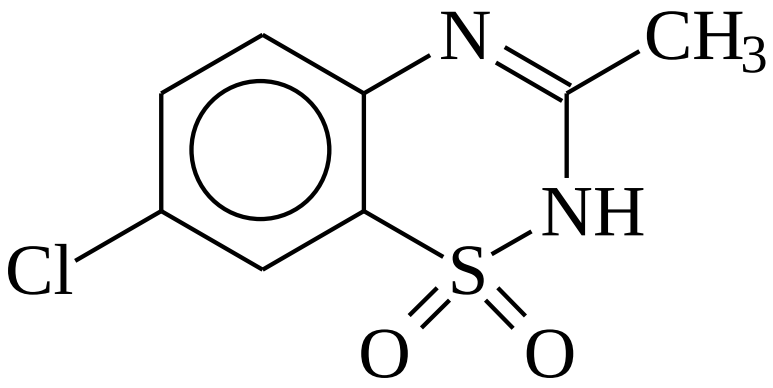
SITAGLIPTIN (JANUVIA®)

- It is active orally, taken once per day.
- It shows its activity by inhibiting dipeptidyl peptidase-4 (DPP-4) enzymes in competitional way. This enzyme breaks down GLP-1 secreted after meal and GIP gastrointestinal hormones.
- By preventing GLP-1 and GIP inactivation, it potentiates GLP-1 and GIP insulin secretion and suppresses glucagon secretion from pancreas.
- These effects bring the blood sugar level to normal.
- Its effect on body weight is neutral and doesn't have any GI side effects.

HYPERGLYCEMIC DRUGS

Prof. Dr. Esin AKI

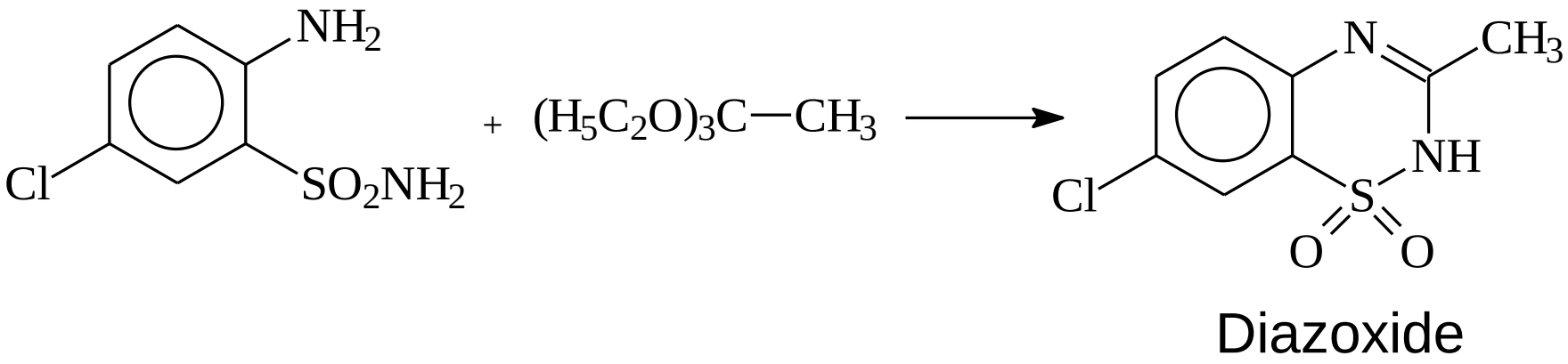
Diazoxide- HYPERSTAT



7-Chloro-3-methyl-2H-benzothiyadiazine-1,1-dioxide

- **By increasing the break down of glycogen in liver, it causes hyperglycemia.**
- **It is used oral.**

Diazoxide Synthesis



Diazoxide