SULFONYLUREAS

1. Tolbutamide (Orinase)
2. Chlorpropamide (Diabinase)
3. Tolazamide (Tolinase)
4. Acetohexamide (Dymelor)
5. Glipizide (Glucotrol, Glucotrol-XL)
6. Glyburide (Micronase, Diabeta)
7. Glimepiride (Amaryl)
8. Gliclazide (Diamicron)

General Formula: 

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>R₁</th>
<th>R₂</th>
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</thead>
<tbody>
<tr>
<td>Tolbutamide</td>
<td>H₃C—</td>
<td>C₄H₉</td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>Cl—</td>
<td>C₃H₇</td>
</tr>
<tr>
<td>Tolazamide</td>
<td>H₃C—</td>
<td>N</td>
</tr>
<tr>
<td>Acetohexamide</td>
<td>H₃CC—</td>
<td></td>
</tr>
<tr>
<td>Glipizide</td>
<td>H₃C—CONH(CH₂)₂—</td>
<td></td>
</tr>
<tr>
<td>Glyburide (Gibenclamide, Micronase, Diabeta, Glynase)</td>
<td>Cl—CONH(CH₂)₂—</td>
<td></td>
</tr>
<tr>
<td>Gliclazide</td>
<td>H₃C—</td>
<td>N</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>C₂H₅—CONH(CH₂)₂—</td>
<td>CH₃—CH₂—</td>
</tr>
</tbody>
</table>
**Structure Activity Relationships:**

R1 (see figure on p. 2) should be a p-substituted benzene. A wide variety of substituents are possible. But methyl groups on aromatic rings are usually susceptible to metabolic enzymes. They can be oxidized to carboxylic acids, which can be quickly eliminated from the body. These susceptible groups can sometimes be replaced with groups that are more stable to oxidation in order to prolong the lifetime of the drug. For, example, the methyl group of tolbutamide was replaced with a chlorine atom to give chlorpropamide, which is much longer lasting.

R2 should be lipophilic with 3 – 6 carbons optimal (in case of aliphatic chain such as in tolbutamide and chlorpropamide). A single CH₃ shows no activity and C12 shows a loss of activity relative to intermediate length chains. If an alicyclic ring is used, the number of carbons can be increased.

**SAR of Glyburide (glibenclamide)**
MEGLITINIDES (METAGLINIDES)

1. Repaglinide (Prandin)
2. Nateglinide (Starlix)
Dose response relationships for inhibition of beta cell and cardiac type $\mathrm{K}_{\text{ATP}}$ currents by sulfonylureas and metaglinides. Kir6.2/SUR1 and Kir6.2/SUR2 currents are inhibited by increasing concentrations of sulfonylureas and metaglinides.
relatively selective for SUR1-type channels

inhibit channels containing either SUR1 or SUR2.
The reversibility of different sulfonylureas and metaglinides was measured on Kir6.2/SUR1 and Kir6.2/SUR2A currents expressed in Xenopus oocytes. Currents are shown in response to repeated voltage ramps from $-110$ to $+110$ mV.

Most drugs that have only one active group (either a sulfonylurea or a non-sulfonylurea) are rapidly reversible over a recording period of less than 30s. This group includes tolbutamide, chlorpropamide, gliclizide, and meglitinide. By contrast, drugs that posses both sulfonylurea and non-sulfonylureas moieties (glibenclamide and glimepiride) are effective irreversible in patch clamp experiments (measured over several minutes). An exception to the rule, repaglinide, which does not posses a sulfonylurea group, yet is very difficult to wash off $K_{ATP}$ channels in membrane patches.
BIGUANIDES

1. Phenformin (withdrawn) caused lactic acidosis.
2. Metformin (Glucophage, Glucophage XR)
3. Metformin + Glyburide (Glucovance)

Resonance stabilizes positive charge. With a pKa of 12.4, metformin has nearly a permanent positive charge.

Phenformin is much more lipophilic than metformin. Potency: phenformin > metformin. However, lipophilicity may correlate to its toxicity (lactic acidosis). It may bind more strongly to mitochondrial membranes and inhibits mitochondrial oxidative phosphorylation (inhibits oxygen consumption) causing a shift to anaerobic glycolysis.
THIAZOLIDINEDIONES (GLITAZONES)

1. Pioglitazone (Actos)
2. Rosiglitazone (Avandia)
3. Troglitazone (Rezulin) - withdrawn
AMINOCYCLITOLS (α-glucosidase inhibitors)

Acarbose (Precose)
Voglibose (Basen)
Miglitol (Glyset)

Acarbose is produced by the soil bacterium Actinoplanes sp. Its strong inhibitory activity against α-glucosidases is widely attributed to the enhanced binding of the core aminocyclitol valienamine, whose half-chair conformation mimics the substrate distortion expected in the oxocarbonium ion transition state. In addition, the adjacent N-linked glycosidic bond prevents enzymatic hydrolysis. This amino linkage forms salt link to the acidic group of the glucosidases, which probably contributes significantly to the unusually tight binding of the inhibitor with the enzymes.

Miglitol is a second-generation alpha-glucosidase inhibitor derived from 1-desoxynojirimycin. In contrast to acarbose, miglitol is almost completely absorbed in the small intestine.