AL Chemistry Group Project 6S
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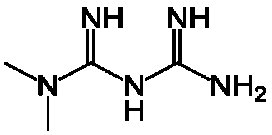
Topic: Metformin

Introduction:

Structural formula of metfomrin:



IUPAC name: *N*,*N*-dimethylimidodicarbonimidic diamide

Metformin is an oral diabetes medicine that helps control blood sugar levels. It helps to treat type 2 diabetes (insulin independent) in overweight and obese people and those with normal kidney function. Unlike the other most-commonly prescribed class of oral diabetes drugs, the sulfonylureas, metformin does not increase the concentration of insulin in the blood and, therefore, does not cause excessively low blood glucose levels (hypoglycemia) when used alone. It acts by increasing the sensitivity of liver, muscle, fat, and other tissues to the uptake and effects of insulin. These actions lower the level of sugar in the blood.

Lead compound discovery:

It mainly involves two steps: lead identification and lead optimization.

Lead Identification

Lead compound is believed to have potential to treat disease due to its desired biological activity. It serves as a prototype for further modified molecule (analog). The new compounds developed will then compare with known substance to determine their probability to success. Testing is then done on each of these molecules to confirm its effect on the drug target.

Lead Optimization

Lead optimization compares the properties of various lead compounds and provides information to select the compounds with the greatest potential to be developed into safe and effective medicines. The lead compound that helps to prevent and correct the abnormalities will be designed afterwards.

Metformin belongs to the class biguanide (a class of anti-diabetic drugs) originates from the French lilac (*Galega officinalis*), a plant used in folk medicine for several

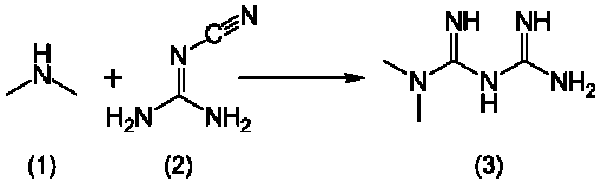
centuries, which serves as a prototype.

After the modification of the active ingredients of the plant, metformin was first described in the scientific literature in 1922, by Emil Werner and James Bell, as a product in the synthesis of *N*,*N*-dimethylguanidine. In 1929, Slotta and Tschesche discovered its sugar-lowering action was the most potent of the biguanide analogs they studied. However, the discovery of the action of metfomrin was soon overshadowed by insulin.

Later, French diabetologist Jean Sterne re-investigate the blood sugar lowering activity of metformin and several biguanide analogs. He successfully found out the efficacy of metformin in the treatment of diabetes on humans in 1957. Metformin reduced overall mortality by about 30% when compared with insulin as it is not associated with any measurable harm in people with heart failure.

Molecular modification:

The usual synthesis of metformin, originally described in 1922 and reproduced in multiple later patents and publications, involves the reaction of dimethylamine hydrochloride(1) and 2-cyanoguanidine(2) (dicyandiamide) under the condition of heating.



(1) (2) (3)

Equimolar amounts of dimethylamine and 2-cyanoguanidine are dissolved in toluene with cooling to make a concentrated solution, and equimolar amount of hydrogen chloride is slowly added. The mixture begins to boil on its own, and after cooling, metformin hydrochloride (3) precipitates with 96% yield.

Formulation development:

Metformin is sold under several trade names, including *Glucophage XR*, *Riomet*, *Fortamet*, *Glumetza*, *Obimet*, *Dianben*, *Diabex*, and *Diaformin*.

Metformin IR (immediate release) is available in 500 mg, 850 mg, and 1000 mg tablets, all now generic in the US.

Metformin SR (slow release) or XR (extended release) was introduced in 2004, in 500 mg and 750 mg strengths, mainly to counteract the most common gastrointestinal

side effects, as well as to increase patient compliance by reducing pill burden. No difference in effectiveness exists between the two preparations.

Combinations with other drugs

In 2002, metformin is prescribed to type 2 diabetes patients in combination with rosiglitazone. This drug actively reduces insulin resistance, complementing the action of the metformin.
In the United States, metformin is also available in combination with pioglitazone, sulfonylureas glipizid, glibenclamide, dipeptidyl peptidase-4 inhibitor sitagliptin, and meglitinide repaglinide.

Safety tests and human trials:
In 1929, scientists Slotta and Tschesche discovered the sugar-lowering action of metformin in rabbits, noting that it was the most potent of the biguanide (a class of anti-diabetic drugs) analogs they studied. However, this result is forgotten as scientists shifted their attention to insulin later.

In 1950, metformin, unlike some other similar compounds, was found not to decrease blood pressure and heart rate in animals. That same year, a prominent Philippine physician, Eusebio Y. Garcia, used metformin (he named it *Fluamine*) to treat influenza; he noted that the drug "lowered the blood sugar to minimum physiological limit" in treated patients and was non-toxic. Garcia also believed metformin to have bacteriostatic, antiviral, antimalarial, antipyretic and analgesic actions. In 1954, Polish pharmacologist Janusz Supniewski observed some antiviral effects in humans.

French diabetologist Jean Sternewas was the first to try metformin on humans for the treatment of diabetes; he coined the name "Glucophage" (glucose eater) for the drug and published his results in 1957. He confirmed the blood sugar lowering activity of metformin on humans.

Approval for marketing:
Metformin became available in the British National Formulary in 1958. It was sold in the UK by a small Aron subsidiary called Rona.
Metformin was approved in Canada in 1972, but did not receive approval by the U.S. Food and Drug Administration (FDA) for Type 2 diabetes until December 1994. Produced under license by Bristol-Myers Squibb, Glucophage was the first branded formulation of metformin to be marketed in the United States, beginning on March 3, 1995. Generic formulations are now available in several countries. Metformin is now

believed to be the most widely prescribed anti-diabetic drug in the world; in the United States alone, more than 40 million prescriptions were filled in 2008 for its generic formulations.

Reference:
http://www.medicinenet.com/metformin/article.htm
http://www.drugs.com/metformin.html
http://en.wikipedia.org/wiki/Metformin

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