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(54) Title: NEW SALT OF (2R,3R,4R)–3,4–DIHYDROXY–2–HYDROXYMETHYLPYRROLIDINE

(57) Abstract

This invention relates to (2R,3R,4R)–3,4–dihydroxy–2–hydroxymethylpyrrolidine D–tartrate, preparation thereof and use as therapeutic agent.

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TITLE

New salt of (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine

FIELD OF THE INVENTION

This invention relates to (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine D-tartrate, its preparation and use as therapeutic agent.

BACKGROUND OF THE INVENTION

Diabetes

Diabetes is characterised by an impaired glucose metabolism manifesting itself among other things by an elevated blood glucose level in the diabetic patients. Underlying defects lead to a classification of diabetes into two major groups: type 1 diabetes, or insulin demanding diabetes mellitus (IDDM), which arises when patients lack ß-cells producing insulin in their pancreatic glands, and type 2 diabetes, or non-insulin dependent diabetes mellitus (NIDDM), which occurs in patients with an impaired ß-cell function besides a range of other abnormalities.

Type 1 diabetic patients are currently treated with insulin, while the majority of type 2 diabetic patients are treated either with sulfonylureas that stimulate ß-cell function or with agents that enhance the tissue sensitivity of the patients towards insulin or with insulin. Among the agents applied to enhance tissue sensitivity towards insulin metformin is a representative example.

In normal as well as in diabetics, the liver produces glucose in order to avoid hypoglycaemia. This glucose production is derived either from the release of glucose from glycogen stores or from gluconeogenesis, which is a de novo intracellular synthesis of glucose. In type 2 diabetes, however, the regulation of hepatic glucose output is poorly controlled and is increased, and may be doubled after an overnight fast. Moreover, in these patients there exists a strong correlation between the increased fasting plasma glucose levels and the rate of hepatic glucose production (reviewed in R.A. De Fronzo: Diabetes 37 (1988), 667 - 687; A. Consoli:

Diabetes Care 15 (1992), 430 - 441; and J.E. Gerich: Horm.Metab.Res. 26 (1992), 18 - 21). Similarly, hepatic glucose production will be increased in type 1 diabetes, if the disease is not properly controlled by insulin treatment.

Since the liver in diabetes is known to have an increased glucose production, compounds inhibiting this activity are highly desirable. Recently, patent applications on inhibitors of the liver specific enzyme, glucose-6-phosphatase, which is necessary for the release of glucose from the liver, have been filed, for example German Offenlegungsschrift Nos. 4,202,183 and 4,202,184 and Japanese patent application No. 4-58565. All these known compounds are benzene derivatives.

Glycogen phosphorylase is another enzyme, which is necessary for the release of glucose from the liver. Substituted N-(indole-2-carbonyl)-glycinamides acting as glycogen phosphorylase inhibitors are disclosed in PCT-publications No. WO96/39384 and WO96/39385 and in EP-A-0 846 464. Piperidine and pyrrolidine compounds acting as glycogen phosphorylase inhibitor are disclosed in PCT-publication No. WO95/24391, WO 97/09040, WO 98/40353 and WO 98/50359.

A compound which effectively can be used for treatment or preventing of diabetes is (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine.

Obesity or appetite regulation

Another field for the invention is obesity or appetite regulation.

Obesity is a well-known risk factor for the development of many very common diseases such as atherosclerosis, hypertension and diabetes. The incidence of obese people and thereby also these diseases is increasing throughout the entire industrialised world.

Due to its indirect but important effect as a risk factor in mortal and common diseases it will be important to find treatment for obesity or appetite regulation.

Exercise, diet modification and food restriction will reduce body weight but for most patients, this is not feasible. Pharmacological treatment available up to date only consists of Sibutramine (acting via serotonergic mechanisms, Knoll Pharm) and Orlistat (reducing fat uptake from the gut, Roche Pharm) neither reducing body weight effectively nor acceptably.

The term obesity implies an excess of adipose tissue. In this context obesity is best viewed as any degree of excess adiposity that imparts a health risk. The cut off between normal and

obese individuals can only be approximated, but the health risk imparted by the obesity is probably a continuum with increasing adiposity. The Framingham study demonstrated that a 20% excess over desirable weight clearly imparted a health risk. (Mann GV N.Engl.J.Med 291:226, 1974). In the United States a National Institutes of Health consensus panel on obesity agreed that a 20% increase in relative weight or a body mass index (BMI = body weight in kilograms divided by the square of the height in meters) above the 85th percentile for young adults constitutes a health risk. By the use of these criteria 20 to 30 percent of adult men and 30 to 40 percent of adult women in the United States are obese. (NIH, Ann Intern Med 103:147, 1985).

Indeed, the prevalence of obesity has increased with 100% in most western countries the last 20 years, and this is very serious because even mild obesity increases the risk for premature death, type 2 diabetes, coronary heart disease, hypertension, atherosclerosis, sleep apnea and respiratory problems, osteoarthritis, gallbladder disease and certain types of cancer (endometrial, breast, prostate and colon). Because of the high prevalence of obesity and its health consequences, its prevention and treatment should be a high public health priority.

When energy intake exceeds expenditure, the excess calories are stored in adipose tissue, and if this net positive balance is prolonged, obesity results, i.e. there are two components to weight balance, and an abnormality on either side (intake or expenditure) can lead to obesity.

The regulation of feeding behaviour is incompletely understood. Certain is that brain neurochemicals located in specific hypothalamic nuclei regulate onset and termination of feeding. Several regulatory processes may influence these hypothalamic centres: *Metabolic signals* such as postprandial increases in plasma glucose and insulin; meal-induced *gastric distension* is another possible inhibitory factor. *Local control* by brain neurochemicals and catecholamines/beta3-adrenoceptors (inhibits feeding and stimulates energy expenditure). Psychological, social, and genetic factors also influence food intake.

At present a variety of techniques are available to effect initial weight loss. Unfortunately, initial weight loss is not an optimal therapeutic goal. Rather, the problem is that most obese patient eventually regain their weight. An effective means to establish and/or sustain weight loss is the major challenge in the treatment of obesity today.

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