(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 May 2011 (19.05.2011)

PCT

(10) International Publication Number
WO 2011/058193 A1

(51) International Patent Classification:
C07D 245/06 (2006.01) *C07D 413/06* (2006.01)
C07D 245/04 (2006.01) *C07D 471/04* (2006.01)
C07D 403/06 (2006.01) *A61K 31/395* (2006.01)
C07D 403/14 (2006.01) *A61P 3/00* (2006.01)
C07D 407/06 (2006.01)

(21) International Application Number:
PCT/EP2010/067601

(22) International Filing Date:
16 November 2010 (16.11.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09176111.4 16 November 2009 (16.11.2009) EP
61/261,382 16 November 2009 (16.11.2009) US

(71) Applicant *(for all designated States except US)*: **MEL-LITECH** [FR/FR]; 2, rue des Gourmets, F-38100 Grenoble (FR).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **ROCHE, Didier** [FR/FR]; 53, chemin Grandvaux, F-69130 Ecully (FR). **CHIMIENTI, Fabrice** [FR/FR]; 43 bis, rue des eaux claires, F-38100 Grenoble (FR). **OHSTEN, Martin** [DK/FR]; 58, Vie des Mulets, F-38300 Ruy Montceau (FR).

(74) Agent: **TETAZ, Franck**; Cabinet Regimbeau, 139, rue Vendôme, F-69477 Lyon Cedex 06 (FR).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

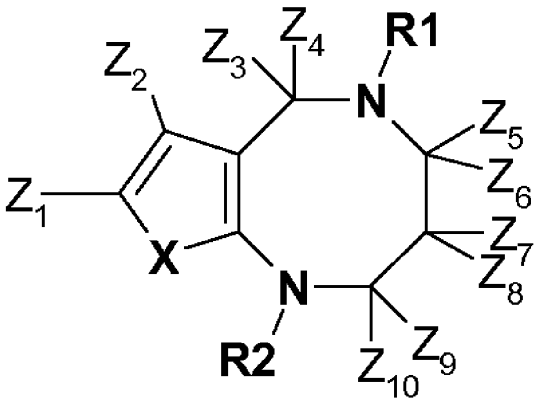
— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) **Title**: [1,5]-DIAZOCIN DERIVATIVES



(I)

(57) **Abstract**: The present invention relates to compounds of formula (I) compositions, in particular pharmaceutical compositions, and medicaments comprising at least one compound of formula (I). The invention also relates to the use of such a compound for manufacturing a medicament. In particular the medicament and the pharmaceutical composition are intended to treat diseases linked with insulin regulation problems, such as diabetes. This invention aims also to methods for treating or preventing such diseases.

WO 2011/058193 A1

[1,5]-DIAZOCIN DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to compounds having a [1,5]-diazocin, in particular a 4-oxo-[1,5]-diazocin, type of structure, to compositions and/or medicaments comprising at least one compound of this type, and their use as a constituent in a medicament, in particular for the treatment of diabetes, more particularly of non-insulin dependent diabetes mellitus (type II diabetes), insulin dependent diabetes mellitus (type I diabetes), and/or of hypertension, pre-diabetes, metabolic syndrome and obesity.

The chemical structure of formula I compounds may provide the substances with the capability of modulating, in particular enhancing or potentiating, the secretion of insulin. This may provide, for example, a self-regulatory treatment system for non-insulin dependent diabetes mellitus (type II diabetes), insulin dependent diabetes mellitus (type I diabetes), hypertension, pre-diabetes, the metabolic syndrome, obesity and/or related metabolic diseases.

BACKGROUND OF THE INVENTION

Diabetes classification, diagnosis and prevalence

Many diseases, conditions and disorders are linked with insulin regulation problems. Examples of such diseases, conditions and disorders are listed below.

Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin, or alternatively, when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar. Hyperglycaemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially nerves and/or blood vessels. People are diagnosed with diabetes if they show a fasting plasma glucose (FPG) level FPG ≥126 mg/dl (7.0 mmol/l) or a Random plasma glucose ≥ 200 mg/dl (11.1 mmol/l) plus symptoms (reference: American Diabetes Association: Standards of Medical Care in Diabetes Diabetes Care, Vol. 32, Supp 1, January 2009).

Type 1 diabetes (previously known as insulin-dependent or childhood-onset) is characterized by a lack of insulin production. Without daily administration of insulin, type 1 diabetes is rapidly fatal. Symptoms include excessive excretion of urine (polyuria), thirst (polydipsia), constant hunger, weight loss, vision changes and fatigue. These symptoms may occur suddenly.

Type 2 diabetes (formerly called non-insulin-dependent or adult-onset) results from the body's ineffective use of insulin. Type 2 diabetes comprises 90% of people with diabetes around the world, and is largely the result of excess body weight and physical inactivity. Symptoms may be similar to those of type 1 diabetes, but are often less marked. As a result,

the disease may be diagnosed several years after onset, once complications have already arisen. Until recently, this type of diabetes was seen only in adults but it is now also occurring in obese children.

Gestational diabetes is hyperglycaemia which is first recognized during pregnancy. Symptoms of gestational diabetes are similar to Type 2 diabetes. Gestational diabetes is most often diagnosed through prenatal screening, rather than reported symptoms.

Impaired Glucose Tolerance (IGT) and Impaired Fasting Glycaemia (IFG) are intermediate conditions in the transition between normality and diabetes. People with IGT or IFG are at high risk of progressing to Type 2 diabetes, although this is not inevitable.

Hyperglycemia not sufficient to meet the diagnostic criteria for diabetes is categorized as either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), depending on whether it is identified through the FPG (fasting plasma glucose) or the OGTT (oral glucose tolerance test):

- IFG = FPG 100 mg/dl (5.6 mmol/l) to 125 mg/dl (6.9 mmol/l)
- IGT = 2-h plasma glucose 140 mg/dl (7.8 mmol/l) to 199 mg/dl (11.0 mmol/l)

IFG and IGT have been officially termed “pre-diabetes.” Both categories of pre-diabetes are risk factors for future diabetes and for cardiovascular disease (CVD) (Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, Zinman B: Impaired fasting glucose and impaired glucose tolerance: implications for care. Diabetes Care 30:753–759, 2007).

Non-insulin dependent diabetes mellitus (type 2 diabetes) develops especially in subjects with insulin resistance and a cluster of cardiovascular risk factor's such as obesity, hypertension and dyslipidemia, a syndrome which first recently has been recognized and is named “the metabolic syndrome” or “syndrome X”. In accordance with the WHO (World Health Organization) definition, a patient has metabolic syndrome if he shows:

- Impaired fasting blood glucose (the American Diabetes Association considers the cutoff to be 100 mg/dL)
- Impaired glucose tolerance (blood glucose above 140 mg/dL two hours after a 75g glucose challenge)

AND any two or more of the following conditions:

- increased blood pressure (≥140/90 mmHg) or taking blood pressure medication
- increased plasma triglyceride (≥1.7 mmol/l)
- low HDL cholesterol (<0.9 mmol/l for men; <1.0 mmol/l for women)
- central adipositas (waist/hip ratio for men: >0.90 and for women >0.85) and/or Body Mass Index >30 kg/m^2)
- micro albuminuria (urine albumin excretion: ≥20 µg min^{-1} or albumin:creatinine ratio ≥ 30 mg/g).

In accordance with the IDF consensus worldwide definition of the metabolic syndrome (2006), a patient has metabolic syndrome if are present the following conditions:

- Central obesity (defined as waist circumference[#] with ethnicity specific values)

AND any two or more of the following conditions:

- Raised triglycerides : >150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality.
- Reduced HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in males, < 50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality
- Raised blood pressure: systolic BP >130 or diastolic BP >85 mm Hg, or treatment of previously diagnosed hypertension.
- Raised fasting plasma glucose: (FPG)>100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes. If FPG >5.6 mmol/L or 100 mg/dL, OGTT (oral glucose tolerance test) is strongly recommended but is not necessary to define presence of the syndrome.

[#] If BMI is >30kg/m², central obesity can be assumed and waist circumference does not need to be measured.

Hypertension is more prevalent in patients with type 2 diabetes than in the non-diabetic population. It is estimated that the prevalence of arterial hypertension (blood pressure greater than 160/95 mmHg) in patients with type 2 diabetes is in the range of 40-50%. In type 2 diabetes, hypertension is often present as part of the metabolic syndrome of insulin resistance also including central obesity and dyslipidemia. Management of hypertension includes lifestyle advice (dietary advice, reduce salt intake (<6g/day), increase aerobic exercise, the reduction of other risks of cardiovascular disease and other complications of diabetes (e.g. smoking cessation, weight reduction, improve glycaemic control, management of diabetic nephropathy (including microalbuminuria), management of hyperlipidaemia), and rigorous control of blood pressure.

Improving glycaemic control, via an improvement of insulin secretion, may be an efficient mean to delay or prevent all or part of the diseases, conditions and metabolic disorders described in this description.

The WHO estimates that more than 180 million people worldwide have diabetes. This number is likely to more than double by 2030. In 2005, an estimated 1.1 million people died from diabetes. Almost 80% of diabetes deaths occur in low and middle-income countries. Almost half of diabetes deaths occur in people under the age of 70 years; 55% of diabetes deaths are in women. WHO projects that diabetes-related deaths will increase by more than 50% in the next 10 years without urgent action. Most notably, diabetes deaths are projected to increase by over 80% in upper-middle income countries between 2006 and 2015. Diabetes and its complications impose significant economic consequences on individuals, families, health systems and countries. Without urgent action, diabetes-related deaths will increase by more than 50% in the next 10 years.

Diabetes has become one of the major causes of premature illness and death in most countries, mainly through the increased risk of cardiovascular disease (CVD). Cardiovascular disease is responsible for between 50% and 80% of deaths in people with diabetes.

Diabetes is a leading cause of blindness, amputation and kidney failure. These complications account for much of the social and financial burden of diabetes.

Although diabetes is sometimes considered a condition of developed nations, the loss of life from premature death among persons with diabetes is greatest in developing countries.

The burden of premature death from diabetes is similar to that of HIV/AIDS, yet the problem is largely unrecognized.

To help prevent type 2 diabetes and its complications, it is recommended:

- to achieve and maintain healthy body weight,
- to be physically active - at least 30 minutes of regular, moderate-intensity activity on most days. More activity is required for weight control,
- to accomplish early diagnosis through relatively inexpensive blood testing, and
- to follow treatment of diabetes involving lowering blood glucose and the levels of other known risk factors that damage to blood vessels.

Therapy for diabetes and related metabolic conditions

The ADA (American Diabetes Association) and the European Association for the Study of Diabetes published a consensus statement on the approach to management of hyperglycemia in individuals with type 2 diabetes (Nathan DM et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 29:1963–1972, 2006) and recently published an update (Nathan DM et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 32:193–203, 2009). Highlights of this approach are: intervention at the time of diagnosis with metformin in combination with lifestyle changes and continuing timely augmentation of therapy with additional agents (including early initiation of insulin therapy) as a means of achieving and maintaining recommended levels of glycemic control (i.e., A1C (glycated homoglobin) <7% for most patients). The overall objective is to achieve and maintain glycemic control and to change interventions when therapeutic goals are not being met. The algorithm took into account the evidence for A1C-lowering of the individual interventions, their additive effects, and their expense. The precise drugs used and their exact sequence may not be as important as achieving and maintaining glycemic targets

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.