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(54) **Title:** ALPHA-KETOGLUTARATES AND THEIR USE AS THERAPEUTIC AGENTS

(57) **Abstract:** The present invention relates generally to the field of pharmaceuticals and medicine. More particularly, the present invention relates to certain compounds (e.g., α-ketoglutarate compounds; compounds that activate HIFα hydroxylase; compounds that increases the level of α ketoglutarate, etc.) and their use in medicine, for example, in the treatment of cancer (e.g., cancer in which the activity of one of the enzymes in the tricarboxylic acid (TCA) cycle is down regulated), in the treatment of angiogenesis (e.g., hypoxia-induced angiogenesis). One preferred class of compounds are α-ketoglutarate compounds having a hydrophobic moiety that is, or is part of, an ester group formed from one of the acid groups of α ketogluartic acid; and pharmaceutically acceptable salts, solvates, amides, esters, ethers, N oxides, chemically protected forms, and prodrugs thereof.

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ALPHA-KETOGLUTARATES AND THEIR USE AS THERAPEUTIC AGENTS

RELATED APPLICATIONS

This application is related to United Kingdom patent application GB 0417715.0 filed 09 August 2004 and United Kingdom patent application GB 0421921.8 filed 01 October 2004, the contents of each of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

The present invention relates generally to the field of pharmaceuticals and medicine. More particularly, the present invention relates to certain compounds (e.g., α-ketoglutarate compounds; compounds that activate HIFα hydroxylase; compounds that increases the level of α-ketoglutarate, etc.) and their use in medicine, for example, in the treatment of cancer (e.g., cancer in which the activity of one of the enzymes in the tricarboxylic acid (TCA) cycle is down regulated), in the treatment of angiogenesis (e.g., hypoxia-induced angiogenesis), etc.

BACKGROUND

A number of patents and publications are cited herein in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided herein. Each of these references is incorporated herein by reference in its entirety into the present disclosure.

Throughout this specification, including any claims which follow, unless the context requires otherwise, the word "comprise," and variations such as "comprises" and "comprising," will be understood to imply the inclusion of a stated integer or step or group of integers or steps, but not the exclusion of any other integer or step or group of integers or steps.

It must be noted that, as used in the specification and any appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical excipient" includes mixtures of two or more such excipients, and the like.

Ranges are often expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by the use of the antecedent "about," it will be understood that the particular value forms another embodiment.

Cancer is a serious disease and a major killer. Although there have been advances in the treatment of certain cancers in recent years, there is still a need for improvements in the treatment of the disease.

Cancer is characterised by the uncontrolled growth of cells due to cellular changes, which are mostly caused by inherited or somatic mutations of genes. The identification of such genes and the elucidation of the mechanism by which these genes affect the development of cancer is important in devising strategies of combating cancer.

Enzymes of the mitochondrial tricarboxylic acid (TCA) cycle have long been associated with cancer. Several mitochondrial proteins are tumour suppressors including succinate dehydrogenase (SDH) and fumarate hydratase (FH). Inherited or somatic mutations in subunits *B, C* or *D* of the *SDH* genes are associated with the development of phaeochromocytoma and paraganglioma (Baysal et al., 2000; Eng et al., 2003). Recently, other types of cancer have also been shown to carry or develop mutations in mitochondrial genes. For example, it has been shown that significant SDH down-regulation occurs in gastric and colorectal carcinoma, particularly during transition to the more aggressive Dukes' stage C, colorectal cancer, as compared to the confined Dukes' stage B tumours (Frederiksen et al., 2003; Habano et al., 2003).

Eng et al. (2003) discuss the link between mutations of gene encoding FH and SDH and cancer. The authors hypothesise that impaired mitochondrial function due to dysfunction of enzymes of the TCA cycle leads to severe energy deficiency and large amounts of oxygen free radicals. These radicals lead in turn to the induction of Hypoxia-inducible Factor - 1α (HIF-1α) promoting cell proliferation or preventing apoptosis and thereby leading to neoplasia. The authors also suggest that mutant forms of SDH, which do not insert in the mitochondrial membrane, might have anti-apoptotic activity. However, the authors are unable to explain the mechanism underlying the anti-apoptotic activity.

Baysal (2003) suggests that SDH and FH could be involved in the control of cell proliferation under normal physiological conditions in the affected tissue types. However, the author provides no further suggestion regarding the mechanism of control.

Furthermore, tumours similar to phaeochromocytoma and paraganglioma are observed in the apparently unrelated von Hippel-Lindau (VHL) syndrome with a common feature of these tumours being elevated levels of HIF-1α (Eng et al., 2003, Pollard et al., 2003). Importantly, *SDH* or *VHL* mutations in these tumours are mutually exclusive (Eng et al., 2003).

Hypoxia-inducible factor-1 (HIF-1) is a heterodimer composed of an alpha (α) subunit and a beta (β) subunit. (However, the terms "HIF-1" and "HIF-1α" are often used interchangeably to mean the complete protein, HIF-1). The beta subunit has been identified as the aryl hydrocarbon receptor nuclear translocator (ARNT/HIF-1β) and its protein level is unaffected by oxygen. Similar to HIF-1β, HIF-1α is constitutively expressed regardless of the oxygenation state. However, under normoxic conditions this subunit is rapidly targeted for proteasome-mediated degradation via a protein-ubiquitin ligase complex containing the product of the von Hippel Lindau tumour suppressor protein (pVHL). pVHL recognizes the oxygen degradation domain (ODDD) of HIF-1α only under normoxic conditions. Following exposure to a hypoxic environment, this degradation pathway is blocked, allowing HIF-1α accumulation and subsequent movement to the nucleus where it activates hypoxia-responsive genes. In other words, the physiological function of HIF is to promote adaptation of cells to low oxygen by inducing neovascularization and glycolysis (Semenza et al., 2002; Pugh et al., 2003).

HIF-1α stability is controlled by HIFα prolyl hydroxylase (PHD) which hydroxylases two specific prolyl residues. More specifically, PHD hydroxylases the prolyl residues in the ODDD which regulate the binding of the pVHL to HIFα (Ivan et al., 2001; Jaakkola et al., 2001; Yu et al., 2001). Hydroxylation at the 4-position of Pro-402 and Pro-564 of HIFα (numbers refers to human HIF-1α) enables formation of two hydrogen bonds to pVHL and increases the binding of pVHL to HIFα by several orders of magnitude (Bruick et al., 2001; Epstein et al., 2001). This post-translational modification is catalyzed by the HIFα-prolyl hydroxylases (HPH1-3 or PHD1-3) (Bruick et al., 2001; Epstein et al., 2001; Ivan et al., 2002). PHD activity is dependent on molecular oxygen and is considered to be an important oxygen sensing mechanism in animal cells (Safran et al., 2003). In addition to oxygen, the PHDs utilize α-ketoglutarate as a co-substrate and require ferrous iron (Fe^{2+})

and ascorbate as cofactors (Kaelin et al., 2002; Schofield et al., 1999). The PHD isozymes belong to the Fe^{2+}- and α-ketoglutarate-dependent family of oxygenases that split molecular oxygen in order to hydroxylate their substrates and, in parallel, oxidize and decarboxylate α-ketoglutarate to succinate (Schofield et al., 1999).

WO 03/028663 discloses methods and compositions for assaying hypoxia-inducible factor prolyl hydroxylation to identify compounds that modulate the hydroxylation; however, the document fails to disclose any such compounds.

Although the events around the carcinogenic pathway involving HIF-1α stabilisation have been investigated, there are still numerous questions that remain unanswered.

In particular, a simple and effective way to inhibit HIF-1α stabilisation – and thereby inhibit the carcinogenic pathway – is still very much needed.

Furthermore, until now, there has been no clear indication or suggestion about how mutations in genes coding for enzymes of the TCA cycle might result in elevated levels of HIF-1α. Therefore, the range of treatment available for these cancers is limited. The primary treatment of pheochromocytomas and paragangliomas is surgical resection after appropriate medical hormonal blockade. Unresectable tumours may be treated with palliative chemotherapy with compounds such as cyclophosphamide, decarbazine, and vincristine, or external beam radiotherapy for bony metastases or ^{131}I-labeled MIGB. However these therapies are either highly invasive or have large undesired side effects. Therefore, there remains a great need for treatments which are less invasive and which have little or no side effects. Preferably such a treatment would be tailor-made for the biochemical mechanism underlying these specific types of cancers.

Moreover, compounds that inhibit hypoxia-induced angiogenesis are still required as treatment for diseases that are characterised by this type of angiogenesis, including cancer.

The inventors have demonstrated how mutations and dysfunctions of genes and enzymes of the TCA cycle are linked to cancer. The inventors have developed strategies for treating cancer and have identified classes of compounds that are useful in these treatments.

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