PROLYL HYDROXYLASE INHIBITORS

PRIORITY

This application claims the benefit of Provisional Application Serial number 61/258,914 and Provisional Application Serial number 61/258,918 that were both filed on November 6, 2009, the entirety of which applications are incorporated herein by reference.

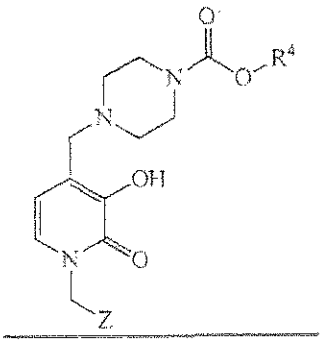
FIELD OF THE DISCLOSURE

Disclosed herein are prolyl hydroxylase inhibitors that can stabilize hypoxia inducible factor-1 alpha (HIF-1α), as well as hypoxia inducible factor-2 alpha (HIF-2α). Also disclosed herein are pharmaceutical compositions comprising one or more of the disclosed compounds. Yet further disclosed are methods for stimulating the cellular immune response in a mammal such as increasing phagocytosis, for example, prolonging the life of phagocytes, *inter alia*, keratinocytes, neutrophils. As such the disclosed compounds provide methods for treating diseases that relate to the body's immune response.

SUMMARY

The disclosed compounds stabilize HIF-1α and HIF-2α, as well as other factors that are present in a compromised immune system or which are depleted or over taxed by the presence of a disease state and the manifestations of the disease state, *inter alia*, sepsis. The disclosed compounds can be used to treat cancer and can be co-administered with other cancer therapy drugs. In addition, the disclosed compounds can be used to boost the immune response by a mammal when co-administered with a vaccine, for example, flu vaccines, malarial vaccines, yellow fever vaccines, cancer vaccines, and the like.

In one aspect, there is provided a compound having the formula:



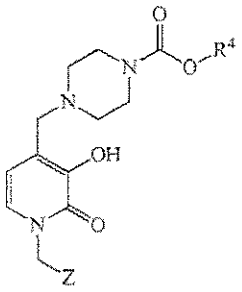
wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;

R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl;

or a pharmaceutically acceptable salt thereof.

In one aspect, there is provided a composition comprising:

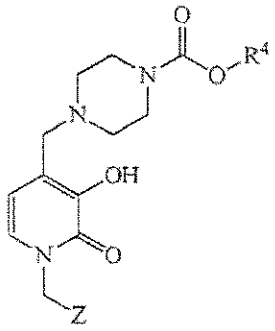
a) one or more compounds having the formula:



wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine; wherein R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl; or a pharmaceutically acceptable salt thereof; and

b) one or more pharmaceutically acceptable excipients.

In one aspect, there is provided the use of a compound for treating a wound, the compound having the formula:

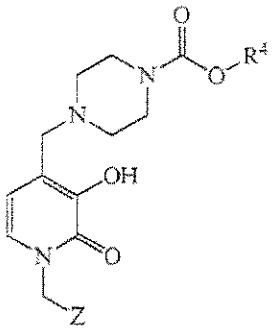


wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;

R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl;

or a pharmaceutically acceptable salt thereof.

In one aspect, there is provided the use of a compound for making a medicament for treating a wound, the compound having the formula:



wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;

R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl;

or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 depicts the normal metabolic pathway of HIF-1α during normoxia.

Figure 2 depicts the enhancement of neutrophil killing of *S. aureus* (Newman strain) with 50 μM and 200 μM of a compound disclosed in Table VIII versus control (DMSO) at 60 and 90 minutes.

Figure 3 depicts the enhancement of human monocyte cell line (U937) against *S. aureus* (Newman strain) by 10 μM a compound disclosed in Table VIII versus untreated samples.

Figure 4 depicts the average percent surviving bacteria in treated vs. untreated U937 cells after infection with *S. aureus* (Newman strain) after 1 hour pre-treatment (black) or 2 hour (hatched) pre-treatment with 10 μM of a compound disclosed in Table VIII.