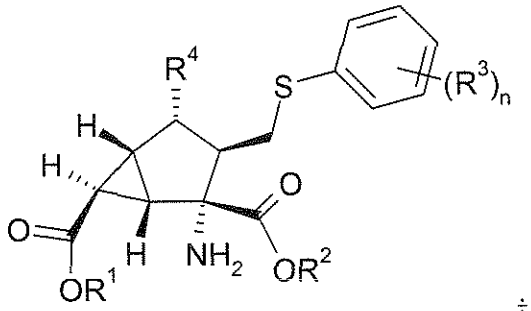
may be useful for the treatment of depressive disorders (which may include major depressive disorder (MDD), unipolar depression, dysthymia, and/or cyclothymia) and disorders of excessive sleepiness (which may include excessive daytime sleepiness (EDS), hypersomnia associated with obstructive sleep apnea or narcolepsy, circadian rhythm sleep disorders (including, but not limited to shift work sleep disorder, jet lag disorder, delayed sleep phase disorder, advanced phase sleep disorder, and non-24 hour sleep-wake syndrome), idiopathic hypersomnolance and/or excessive sleepiness associated with non-restorative sleep (NRS)). The antidepressant-like and wake-promoting effects of this mechanism also predict impact on symptoms of depressive disorders such as fatigue that are otherwise difficult to treat with existing antidepressants.

In one aspect, there is~~The present invention~~ provideds a compounds of the f~~F~~ormula ~~I:~~



~~I~~

where R^1 and R^2 are each independently hydrogen, C_1-C_3 alkoxycarbonyloxymethyl, C_1-C_5 alkylcarbonyloxymethyl, or C_{3-6} cycloalkylcarbonyloxymethyl;

R^3 is independently at each occurance methyl, fluoro, or chloro;

R^4 is hydroxyl, amino, methylcarbonylamino, or 1,2,4-triazolylthio; and

n is 1 or 2;

or a pharmaceutically acceptable salt thereof. The above compound may be referred to as Formula (I).

It is a feature of the present disclosure~~invention~~ that compounds of Formula I wherein R^1 and R^2 are both hydrogen (the di-acid compounds) are the therapeutically active compounds in vivo, whereas compounds where R^1 or R^2 or both are other than hydrogen are prodrugs of their therapeutically active di-acid analogs. The compounds where R^1 or R^2 or both are other than hydrogen are hydrolyzed in vivo to provide the therapeutically active di-acid analog. The prodrug compounds when administered orally, particularly di-ester prodrugs, provide improved bioavailability of the di-acid metabolite compared to

oral administration of the di-acid compounds (R^1 and R^2 both hydrogen), but the di-acid compounds provide better activities when administered intravenously, intramuscularly or subcutaneously.

In another aspect ~~of the invention~~, there is provided a pharmaceutical composition comprising a compound as defined above, ~~of Formula I~~ or a pharmaceutically acceptable salt thereof, in combination with at least one pharmaceutically acceptable carrier, diluent, or excipient. Furthermore, this disclosure ~~aspect of the invention~~ provides a pharmaceutical composition adapted for the treatment of depressive disorders, as for example major depressive disorder, unipolar depression, dysthymia, and/or cyclothymia, comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents thereof. In another aspect, there is provided the use of a compound as defined above, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of depressive disorders.

A further embodiment ~~of this aspect of the invention~~ provides a pharmaceutical composition comprising a compound according to Formula I, or pharmaceutically acceptable salt thereof, in combination with at least one pharmaceutically acceptable carrier, exciepient or diluents, and optionally other therapeutic ingredients. In a yet further embodiment ~~of this aspect of the invention~~, the pharmaceutical composition further comprises a second therapeutic agent which is a drug useful in the treatment of depressive disorders, as for example a serotonin reuptake inhibitor, as for example fluoxetine and/or citalopram. In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above, or a pharmaceutically acceptable salt thereof and a serotonin reuptake inhibitor in combination with at least one pharmaceutically acceptable carrier, excipient or diluent.

In yet another embodiment ~~of this aspect of the invention~~, there is provided a pharmaceutical composition adapted for the treatment of disorders of excessive sleepiness, as for example, excessive daytime sleepiness (EDS), hypersomnia associated with obstructive sleep apnea or narcolepsy, circadian rhythm sleep disorders (including, but not limited to shift work sleep disorder, jet lag disorder, delayed sleep phase disorder, advanced phase sleep disorder, and non-24 hour sleep-wake syndrome), idiopathic

hypersomnolance and/or excessive sleepiness associated with non-restorative sleep (NRS), comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents thereof. In another aspect, there is provided the use of a compound as defined above, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of disorders of excessive sleepiness.

The present disclosure~~invention~~ also provides a method of treating depressive disorders, as for example major depressive disorder (MDD), unipolar depression, dysthymia, and/or

cyclothymia, in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof. In another embodiment ~~of this aspect of the invention~~, the method further comprises administering in simultaneous, separate or sequential combination, a second therapeutic agent which is a drug useful in the treatment of depressive disorders, as for example a serotonin reuptake inhibitor, as for example fluoxetine and/or citalopram.

Other embodiments of the disclosure~~invention~~ provide methods of treating disorders of excessive sleepiness comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof. In other embodiments ~~of this aspect of the invention~~, the excessive sleepiness is due to any one or more of the following: excessive daytime sleepiness (EDS), hypersomnia associated with obstructive sleep apnea or narcolepsy, circadian rhythm sleep disorders (including, but not limited to shift work sleep disorder, jet lag disorder, delayed sleep phase disorder, advanced phase sleep disorder, and non-24 hour sleep-wake syndrome), idiopathic hypersomnolance or excessive sleepiness associated with non-restorative sleep (NRS).

In one particular embodiment of these methods of treatment, the mammal is a human.

This disclosure~~invention~~ also provides a compound of Formula I or a pharmaceutically acceptable salt thereof for use in therapy. Within this ~~aspect~~, the disclosure~~invention~~ provides a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in the treatment of depressive disorders. In further embodiments, the depressive disorder is any one of major depressive disorder (MDD), unipolar depression, dysthymia, and/or cyclothymia. In another embodiment ~~of this aspect of the invention~~, the disclosure~~invention~~ provides a compound according to Formula I, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate or sequential combination with a serotonin reuptake inhibitor, as for example fluoxetine and/or citalopram, in the treatment of depressive disorders.

Further, this disclosure~~aspect of the invention~~ includes a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in the treatment of disorders of excessive sleepiness. In particular embodiments ~~of this aspect of the invention~~, the excessive

sleepiness is due to any one or more of the following: ~~excessive~~ daytime sleepiness (EDS), hypersomnia associated with obstructive sleep apnea or narcolepsy, circadian rhythm sleep disorders (including, but not limited to shift work sleep disorder, jet lag disorder, delayed sleep phase disorder, advanced phase sleep disorder, and non-24 hour sleep-wake syndrome), idiopathic hypersomnolance or excessive sleepiness associated with non-restorative sleep (NRS).

In o~~O~~ne particular embodiment ~~of this aspect of the inventions~~, the uses are in mammals, particular humans.

Another embodiment~~aspect~~ of this disclosure~~invention~~ provides the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of depressive disorders, as for example major depressive disorder (MDD), unipolar depression, dysthymia, and/or cyclothymia. Another embodiment ~~of this aspect of the invention~~ provides the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a second therapeutic agent useful in the treatment of depressive disorders, as for example a serotonin reuptake inhibitor, as for example fluoxetine and/or citalopram, in the manufacture of a medicament for the treatment of depressive disorders. Another embodiment ~~of the invention~~ provides the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of disorders of excessive sleepiness. In particular embodiments ~~of this aspect of the invention~~, the medicament is for the treatment of any one or more of the following: excessive daytime sleepiness (EDS), hypersomnia associated with obstructive sleep apnea or narcolepsy, circadian rhythm sleep disorders (including, but not limited to shift work sleep disorder, jet lag disorder, delayed sleep phase disorder, advanced phase sleep disorder, and non-24 hour sleep-wake syndrome), idiopathic hypersomnolance or excessive sleepiness associated with non-restorative sleep (NRS).

Compounds of this invention have basic and acidic moieties, and accordingly react with a number of organic and inorganic acids and bases to form pharmaceutically acceptable salts. Pharmaceutically acceptable salts of each of the compounds of the present invention are contemplated within the scope of the present application. The term "pharmaceutically acceptable salt" as used herein, refers to any salt of a compound of the