Carbamoyl Phenylalaninol Analogs and Uses Thereof

Statement Of Priority

[0001] The present invention claims the benefit, under 35 U.S.C. § 119(e), of U.S. Provisional Application No. 62/539,088, filed July 31, 2017, the entire contents of which are incorporated by reference herein.

Field of the Invention

[0002] The present invention relates to carbamoyl phenylalaninol analogs and methods of using the same to treat disorders.

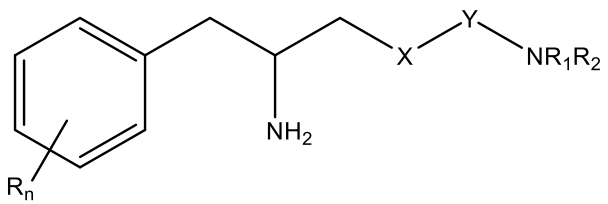
Background of the Invention

[0003] (*R*)-2-amino-3-phenylpropyl carbamate (APC) is a phenylalanine analog that has been demonstrated to be useful in the treatment of a variety of disorders, including excessive daytime sleepiness, cataplexy, narcolepsy, fatigue, depression, bipolar disorder, fibromyalgia, and others. See, for example, US Patent Nos. 8,232,315; 8,440,715; 8,552,060; 8,623,913; 8,729,120; 8,741,950; 8,895,609; 8,927,602; 9,226,910; and 9,359,290; and U.S. Publication Nos. 2012/0004300 and 2015/0018414. Methods for producing APC (which also has other names) and related compounds can be found in US Patent Nos. 5,955,499; 5,705,640; 6,140,532 and 5,756,817. All of the above patents and applications are hereby incorporated by reference in their entireties for all purposes.

[0004] The present invention overcomes shortcomings in the art by providing analogs of APC and a method of using the same to treat disorders.

Summary ~~of the Invention~~

[0005] The present ~~invention~~ disclosure relates to the development of analogs of APC with similar pharmacological activities. Accordingly, the present ~~invention~~disclosure relates to a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

X is CH_2, O, NH, or S;

Y is C=O, C=S, or SO_2;

R is optionally substituted C_{1-8} alkyl, halogen, optionally substituted C_{1-4} alkoxy, cyano, hydroxy, optionally substituted trifluoromethyl, or C_{1-4} thioalkoxy;

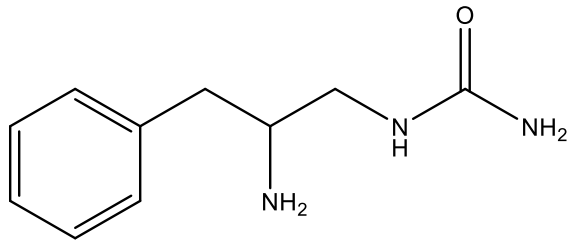
n is 0, 1, 2, or 3, with the proviso that R may be the same or different when x is 2 or 3; and

R_1 and R_2 can be the same or different and are independently selected from the group consisting of hydrogen, optionally substituted C_{1-8} alkyl, optionally substituted amide, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, and optionally substituted C_{3-7} cycloalkyl;

or R_1 and R_2 can be joined to form a 5 to 7-membered heterocycle optionally substituted with alkyl or aryl groups, wherein the cyclic compound can comprise 1 to 2 nitrogen atoms and 0 to 1 oxygen atom, wherein the nitrogen atoms are not directly connected with each other or with the oxygen atom;

wherein when Y is C=O, X is not O.

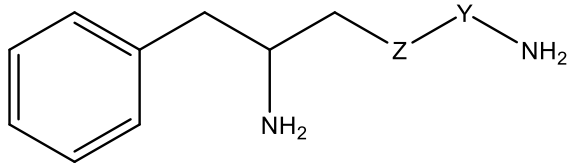
[0005a] In an aspect, there is provided a compound, which is compound 1:



1

or a pharmaceutically acceptable salt thereof.

[0005b] In another aspect, there is provided a compound, having Formula Va:



Va

or a pharmaceutically acceptable salt thereof; wherein

Z is S;

Y is C=S, or SO_2.

[0006] Another ~~aspect~~ example of the ~~invention~~ disclosure relates to a composition (*e.g.*, a pharmaceutical composition) and kit comprising the compound of the ~~invention~~disclosure.

[0006a] In another aspect, there is provided a composition comprising the composition as defined above.

[0006b] In another aspect, there is provided a pharmaceutical composition comprising the compound as defined above and a pharmaceutically acceptable carrier.

[0006c] In another aspect, there is provide a kit comprising the compound as defined above.

[0007] A further ~~aspect~~example of the ~~invention~~disclosure relates to a method of treating a disorder or condition selected from narcolepsy, cataplexy, excessive daytime sleepiness, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, atypical depression, freezing of gait, mild cognitive impairment, neurogenic orthostatic hypertension, binge eating disorder, or obesity in a subject in need thereof, or promoting smoking cessation in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the disclosure~~invention~~, thereby treating the disorder or condition or promoting smoking cessation.

[0007a] In another aspect, there is provided the use of the compound as defined above in the manufacture of a medicament for treating a disorder or condition selected from narcolepsy, cataplexy, excessive daytime sleepiness, idiopathic hypersomnia, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, atypical depression, binge eating disorder, or obesity in a subject in need thereof, or promoting smoking cessation in a subject in need thereof.

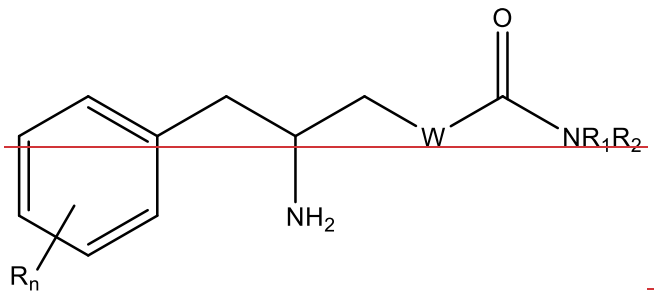
[0008] The present ~~invention~~ disclosure is explained in greater detail in the drawings herein and the specification set forth below.

Detailed Description of the Invention

[0009] The present invention can be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided to exemplify aspects of the invention as representatives of the full scope of the

What is claimed is:

1. A compound of Formula III:



III

or a pharmaceutically acceptable salt thereof, wherein:

W is CH_2 or NH;

R is optionally substituted C_{1-8} alkyl, halogen, optionally substituted C_{1-4} alkoxy, cyano, hydroxy, optionally substituted trifluoromethyl, or C_{1-4} thioalkoxy;

n is 0, 1, 2, or 3, with the proviso that R may be the same or different when n is 2 or 3; and

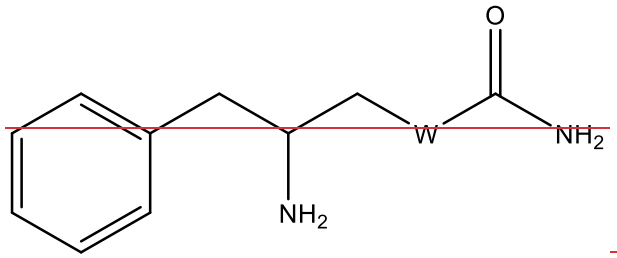
R_1 and R_2 can be the same or different and are independently selected from the group consisting of hydrogen, optionally substituted C_{1-8} alkyl, optionally substituted amide, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, and optionally substituted C_{3-7} cycloalkyl;

or R_1 and R_2 can be joined to form a 5 to 7-membered heterocycle optionally substituted with alkyl or aryl groups, wherein the cyclic compound can comprise 1 to 2 nitrogen atoms and 0 to 1 oxygen atom, wherein the nitrogen atoms are not directly connected with each other or with the oxygen atom.

2. The compound of claim 1, wherein R_1 and R_2 are hydrogen.

3. The compound of claim 1, wherein n is 0.

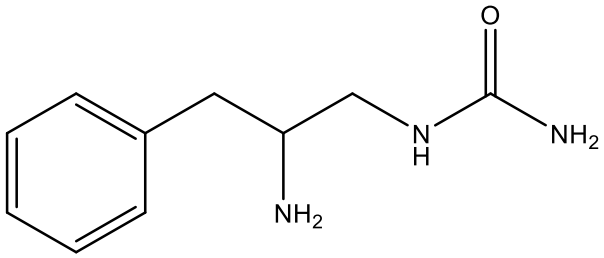
~~4. The compound of claim 1, having Formula IIIa:~~



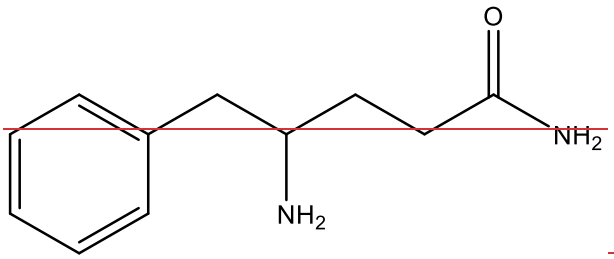
~~IIIa~~

~~or a pharmaceutically acceptable salt thereof.~~

1~~5~~. ~~The~~A compound ~~of claim 4~~, which is compound 1 ~~or 2~~:



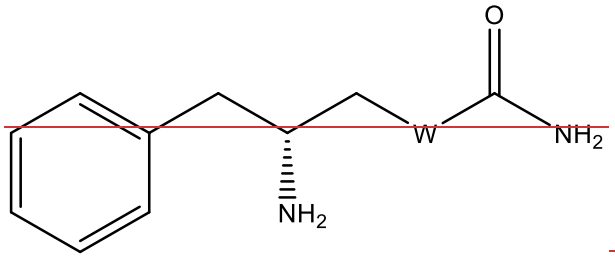
1



~~2~~

or a pharmaceutically acceptable salt thereof.

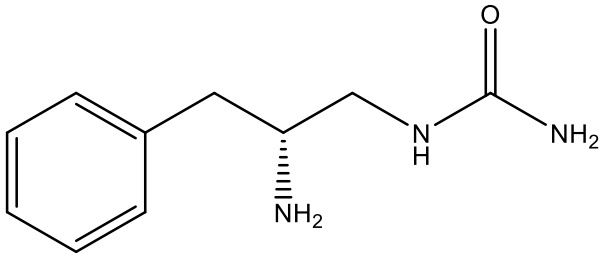
~~6. The compound of claim 1, having Formula IVa:~~



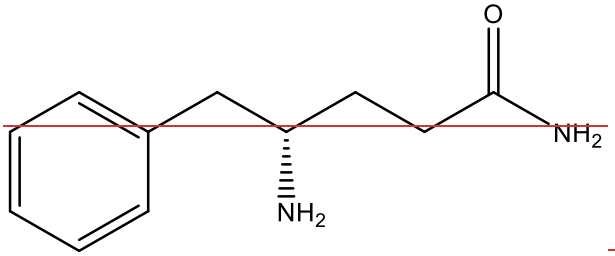
IVa

or a pharmaceutically acceptable salt thereof.

72. The compound of claim 16, which is compound 3 or 4:



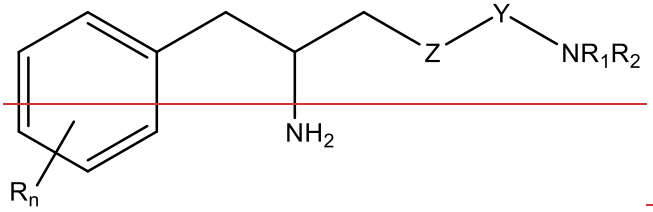
3



4

or a pharmaceutically acceptable salt thereof

8. A compound of Formula V:



V

~~or a pharmaceutically acceptable salt thereof, wherein:~~

~~Z is O or S;~~

~~Y is C=O, C=S, or SO_2;~~

~~R is optionally substituted C_{1-8} alkyl, halogen, optionally substituted C_{1-4} alkoxy, cyano, hydroxy, optionally substituted trifluoromethyl, or C_{1-4} thioalkoxy;~~

~~n is 0, 1, 2, or 3, with the proviso that R may be the same or different when n is 2 or 3; and~~

~~R_1 and R_2 can be the same or different and are independently selected from the group consisting of hydrogen, optionally substituted C_{1-8} alkyl, optionally substituted amide, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, and optionally substituted C_{3-7} cycloalkyl;~~

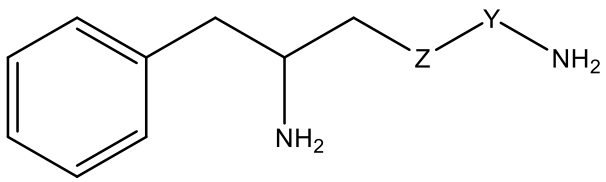
~~or R_1 and R_2 can be joined to form a 5 to 7-membered heterocycle optionally substituted with alkyl or aryl groups, wherein the cyclic compound can comprise 1 to 2 nitrogen atoms and 0 to 1 oxygen atom, wherein the nitrogen atoms are not directly connected with each other or with the oxygen atom;~~

~~wherein when Y is C=O, Z is not O.~~

~~9. The compound of claim 8, wherein R_1 and R_2 are hydrogen.~~

~~10. The compound of claim 8, wherein n is 0.~~

~~11~~3. ~~The~~A compound ~~of claim 8~~, having Formula Va:



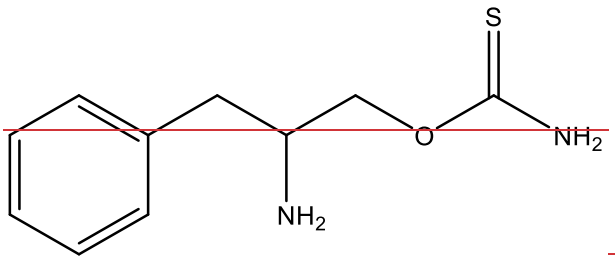
Va

or a pharmaceutically acceptable salt thereof; wherein

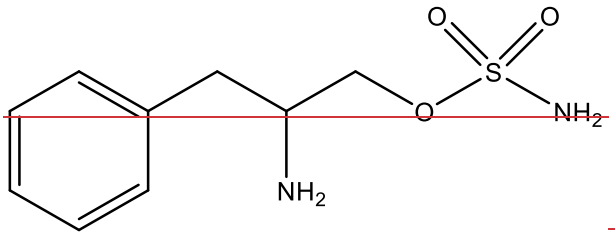
Z is S;

Y is C=S, or SO_2.

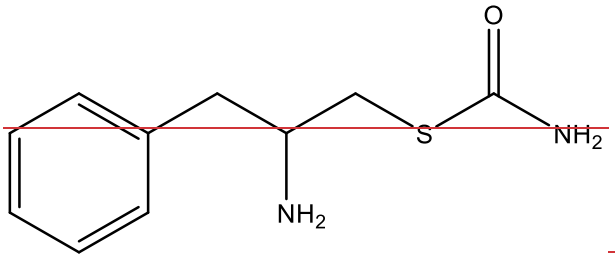
~~12. The compound of claim 11, which is compound 5, 6, or 7:~~



~~5~~



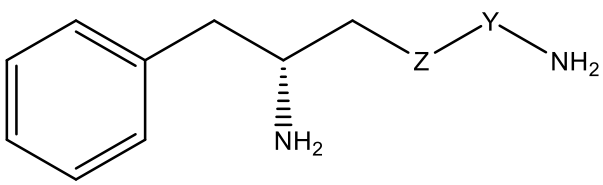
~~6~~



~~7~~

~~or a pharmaceutically acceptable salt thereof~~

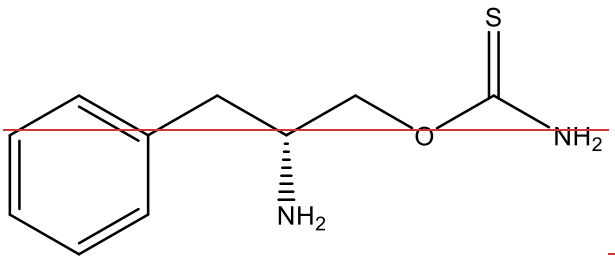
~~13~~4. The compound of claim ~~3~~8, having Formula VIa:



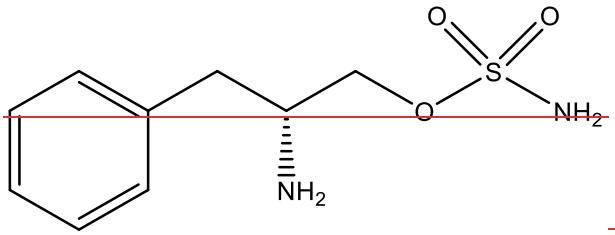
VIa

or a pharmaceutically acceptable salt thereof.

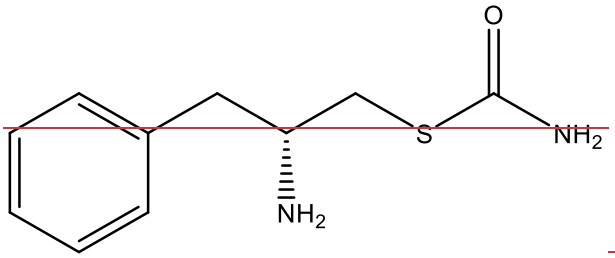
~~14. The compound of claim 13, which is compound 8, 9, or 10:~~



~~8~~



~~9~~



~~10~~

~~or a pharmaceutically acceptable salt thereof.~~

~~1~~5. The compound of any one of claims 1-~~1~~4, which is the hydrochloride salt.

~~1~~6. A composition comprising the compound of any one of claims 1-~~1~~5.

~~1~~7. A pharmaceutical composition comprising the compound of any one of claims 1-~~1~~5 and a pharmaceutically acceptable carrier.

~~1~~8. The composition of claim ~~1~~6 or ~~1~~7, wherein the composition is a dosage form, optionally an immediate release oral dosage form, optionally a tablet or a capsule.

~~1~~9. A kit comprising the compound of any one of claims 1-~~1~~5.

~~20~~10. Use of the compound of any one of claims 1 -~~1~~5 in the manufacture of a medicament for treating a disorder or condition selected from narcolepsy, cataplexy, excessive daytime sleepiness, ~~obstructive sleep apnea,~~ idiopathic hypersomnia, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, atypical depression, binge eating disorder, or obesity in a subject in need thereof, or promoting smoking cessation in a subject in need thereof.

~~21~~11. The use of claim 1~~2~~0, wherein the disorder or condition is selected from narcolepsy, cataplexy, excessive daytime sleepiness, ~~obstructive sleep apnea,~~ and idiopathic hypersomnia.

~~22~~12. The use of claim ~~21~~11, wherein the excessive daytime sleepiness is associated with idiopathic hypersomnia, obstructive sleep apnea, multiple sclerosis, atypical depression, or drug-associated excessive sleepiness.

~~23~~13. The use of any one of claims 1~~2~~0-1~~2~~2, comprising a composition comprising the compound, optionally a pharmaceutical composition comprising the compound and a pharmaceutically acceptable carrier, to be administered.

~~24~~14. The use of claim ~~23~~13, wherein the composition is a dosage form, optionally an immediate release oral dosage form, optionally a tablet or a capsule.

~~25~~15. The use of any one of claims ~~2~~10-~~2~~14, further comprising an additional therapeutic agent to be administered.