drug without eliciting adverse effects, and where frequent dosing schedules are required, the cost of therapy may increase. In addition, as the required dosing frequency increases, patient compliance tends to decrease. It would therefore be desirable to provide additional compounds that modulate CNS activity and have improved properties, such as, e.g., an increased half-life, increased activity (i.e., improved efficacy), and/or increased metabolic stability (e.g., fewer toxic metabolites) when compared to those of currently available therapies. Furthermore, improved and simpler/simplified synthetic and chemical manufacturing processes can be developed which can help to make the useful compounds of the invention more widely available to a larger portion of the patient population.

[0004] Related art may be found in U.S. Patent 5,463,125 (Sandoval *et al.*, "Phenyl alcohol amides having anticonvulsant activity"), WO9941229 [Carvajal Sandoval *et al.*, "Halogenated phenyl alcohol amides (ligands of GABAB receptor) having an anticonvulsant activity"], WO03091201 (Carvajal Sandoval *et al.*, "DL-Hydroxy-alkyl-phenylamides having anticonvulsive activity"), WO2005085182 (Meza Toledo, "DL-Hydroxybenzamides having anticonvulsive activity"), and U.S. Patent Application 20060287397 (Meza Toledo, "Dl-Hydroxy-alkyl-phenylamides having anticonvulsive activity"). An important distinction between the art cited above and that of the present invention is that the cited art contains and refers to compounds which are structurally related to *gamma*-hydroxybutyric acid (*gamma*-hydroxybutyrate, or GHB), whereas the compounds of the present invention are structurally related to 3-methylbutyramide.

BRIEF SUMMARY

[0005] A series of novel amides with anticonvulsant activity are herein disclosed, many of which have a phenyl group attached to the amide moiety via a short and variously branched/substituted aliphatic linker. Other compounds of the ~~invention~~disclosure (as shown below) are amides which are derivatives of optically active amino acids (e.g., D or L), such as alanine (Z = CH_3, below), valine [Z = $CH(CH_3)_2$], leucine [Z = $CH_2CH(CH_3)_2$], isoleucine [Z = $CH(CH_3)CH_2CH_3$], or phenylalanine (Z = $CH_2C_6H_5$), or the optically inactive amino acids, glycine (Z = H) or taurine [R_2 = $(CH_2)_2SO_3H$, below]. Such compounds are exemplified by the following formulas:

[0006] A CNS-active compound having the Formula I:

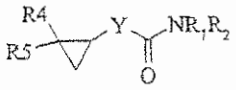
[0010] In Formula I, R_3 is either hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, or together with R_4 cycloalkyl. Optionally, if R_3 is OH, then R_4 is not an ethyl.

[0011] In Formula I, R_4 is one of a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, or together with R_3 cycloalkyl.

In Formula I, X is one of nothing, substituted or unsubstituted alkylene, methylene, ketone, CHOH, oxygen, NR_1, sulfur, sulfone, or sulfoxide.

[0012] A CNS-active compound having Formula II:

FORMULA II



[0013] In Formula II, R_1 and R_2 are each independently at least one of H, long or short chain substituted or unsubstituted alkyl, substituted or unsubstituted, cycloalkyl, CW_2phenyl, or combinations thereof. W is independently selected from the group consisting of H, methyl and ethyl, except that both Ws cannot be ethyl. Up to 5 substituents may be present in the phenyl group or cylcoalkyl group, and each substituent is independently selected from the group consisting of halogen, alkoxy, thioalkyl, sulfoxyalkyl, sulfonylalkyl, haloalkyl, haloalkoxy, $CONH_2$, CN, acetoxy, N(alkyl)$_2$, NO_2, and acetyl. Optionally, R_1 is H and R_2 is $(CH_2)_2SO_3H$, or CHZCOOH, wherein Z is one of the group consisting of H, CH_3, $CH(CH_3)_2$, $CH_2C_6H_5$, $CH_2CH(CH_3)_2$, and $CH(CH_3)CH_2CH_3$. In another option, or R_1 and R_2 together are cycloalkyl.

[0014] R_4 and R_5 are each independently either optionally substituted phenyl or optionally substituted heterocyclic aryl, wherein up to 5 substituents may be present and each substituent is independently selected from the group consisting of halogen, alkoxy, thioalkyl, sulfoxyalkyl, sulfonylalkyl, haloalkyl, haloalkoxy, CH_2OH, $CONH_2$, CN, acetoxy, N(alkyl)$_2$, NO_2, acetyl, and OCH_2COOH.

[0015] Y is either nothing, substituted or unsubstituted methylene, or other substituted or unsubstituted alkylene.

[0016] In one embodiment, the present ~~invention~~disclosure includes a CNS-active compound having one of the following formulas:

$N(alkyl)_2$, NO_2, and acetyl. Optionally, R_1 is H and R_2 is $(CH_2)_2SO_3H$, or CHZCOOH, wherein Z is one of the group consisting of: H, CH_3, $CH(CH_3)_2$, $CH_2C_6H_5$, $CH_2CH(CH_3)_2$, and $CH(CH_3)CH_2CH_3$. In another option, R_1 and R_2 together are cycloalkyl.

[0018] In one embodiment, R_1 is H and R_2 is $(CH_2)_2SO_3H$, or CHZCOOH, wherein Z is one of the group consisting of: H, CH_3, $CH(CH_3)_2$, $CH_2C_6H_5$, $CH_2CH(CH_3)_2$, and $CH(CH_3)CH_2CH_3$. Optionally, R_1 and R_2 together are cycloalkyl.

[0019] In one embodiment, R_3 is either hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, or together with R_4 cycloalkyl. Optionally, if R_3 is OH, then R_4 is not an ethyl.

[0020] In one embodiment, R_4 is one of a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, or together with R_3 cycloalkyl.

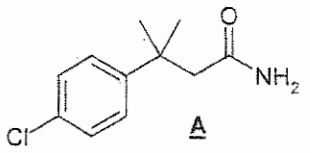
[0021] In one embodiment, R_5 is one of H, Cl, F, CF_3, CN, C1-C5 alkyl, C1-C5 alkoxy, OCF_3, $CONR_1R_2$, halogen-substituted alkyl, halogen-substituted alkoxy,

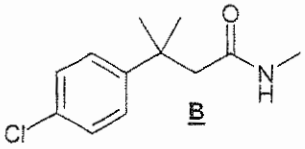
[0022] In one embodiment, X is one of nothing, substituted or unsubstituted alkylene, methylene, ketone, CHOH, oxygen, NR_1, sulfur, sulfone, or sulfoxide.

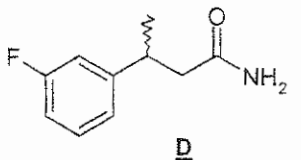
[0023] In one embodiment, n can be from 0-5, more preferably from 1-3, and most preferably from 1 to 2.

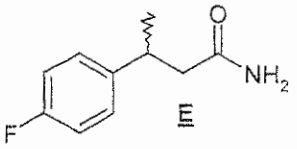
[0024] In one embodiment, any of Formulas 1-8 can be characterized as follows: R_1 is one of H, CH_3, $(CH_2)_2SO_3H$, or CHZCOOH, wherein Z is one of the group consisting of: H, CH_3, $CH(CH_3)_2$, $CH_2C_6H_5$, $CH_2CH(CH_3)_2$, and $CH(CH_3)CH_2CH_3$, combination thereof, or derivative thereof; R_2, R_3, and R_4 are independently one of H, CH_3, substituted or unsubstituted alkyl, OH, OCH_3, substituted or unsubstituted alkoxy, combination thereof, or derivative thereof; R_5 is one of H, Cl, F, CF_3, CN, C1-C5 substituted or unsubstituted alkyl, C1-C5 substituted or unsubstituted alkoxy, OCF_3 $CONR_1R_2$, combination thereof, and derivative thereof; n = 1 - 5, preferably 1-3; and X = O, NR_1, nothing, C=O, S, SO_2, combination thereof, and derivative thereof.

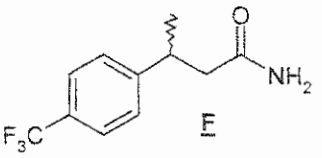
[0024a] In a first aspect, there is provided a CNS-active compound having one of Formulas A, B, D-O, R, S, T, or AW:

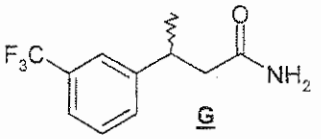

A

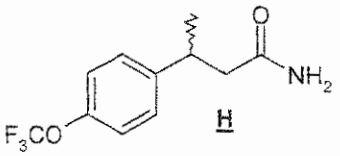

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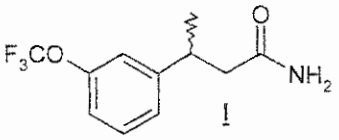

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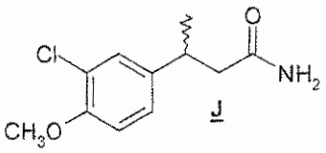

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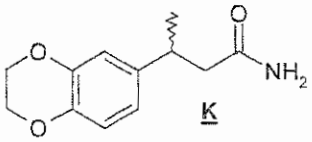

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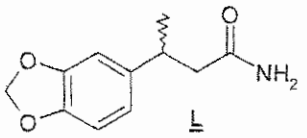

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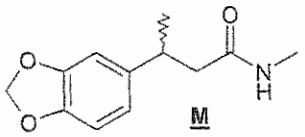

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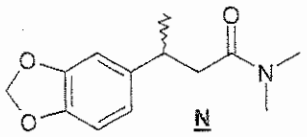

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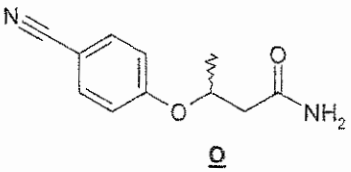

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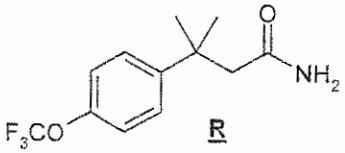

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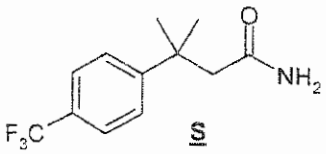

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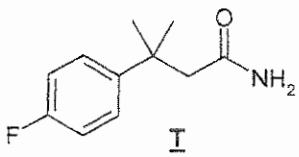

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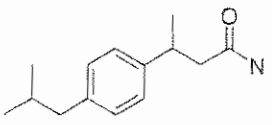

N


O


R


S


T


Formula AW

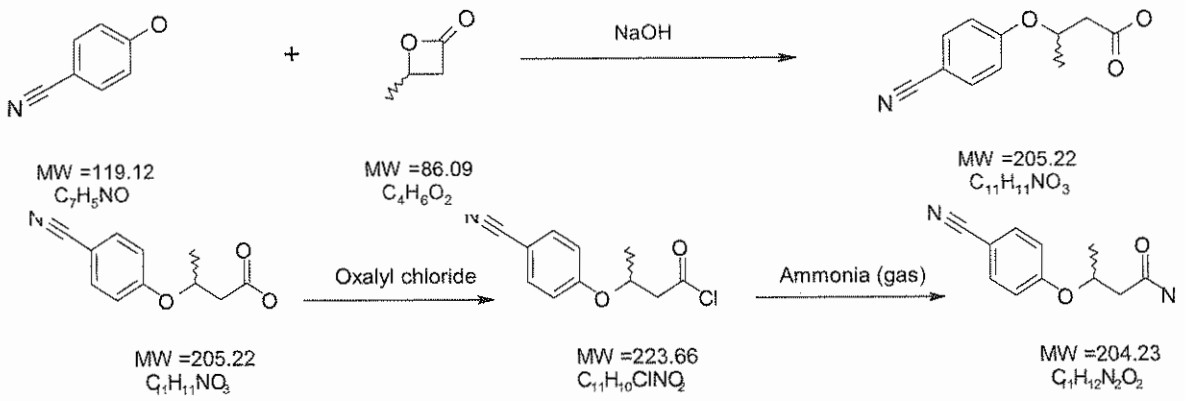
[0024b] In a second aspect, there is provided a pharmaceutical composition, the composition comprising:

a pharmaceutically-acceptable carrier; and

a CNS-active compound as defined above combined with the carrier.

[0024c] In a third aspect, there is provided the use of a CNS-active compound as defined above in the manufacture of a medicament for the treatment of central nervous system diseases and disorders.

[0024d] In a fourth aspect, there is provided a method of manufacturing a CNS-active compound [3-(4-cyanophenoxy)butyramide], the method comprising:



[0025] These and other embodiments and features of the present ~~invention~~disclosure will become more fully apparent from the following description and appended claims, or may be learned by the practice of the ~~invention~~disclosure as set forth hereinafter.