

**NOVEL COMPOUNDS ADVANTAGEOUS IN THE TREATMENT OF
CENTRAL NERVOUS SYSTEM DISEASES AND DISORDERS**

RELATED APPLICATIONS

[0001] This application claims the benefit of United States Provisional Patent Application Serial No. 61/037,987 filed 19 March 2008 and entitled "NOVEL COMPOUNDS ADVANTAGEOUS IN THE TREATMENT OF CENTRAL NERVOUS SYSTEM DISEASES AND DISORDERS," the entirety of which is incorporated herein by specific reference.

BACKGROUND OF THE INVENTION

1. The Field of the Invention

[0002] The present invention relates to novel compounds showing activity in the central nervous systems (CNS) of experimental animals. More specifically, the present invention relates to novel compounds with anticonvulsant activity that exhibit increased/improved toxicological safety (i.e., decreased toxicity), increased/improved metabolic stability, longer half-life, and/or a superior side effect profile, while producing similar or increased biological activity (i.e., efficacy), when compared to currently available CNS therapeutic agents.

2. The Related Technology

[0003] A number of pathological conditions (e.g., epilepsy, stroke, bipolar affective disorder, migraine headaches, anxiety, depression, insomnia, schizophrenia, chronic or neuropathic pain, spasticity, spinal cord injury, and chronic neurodegenerative disorders), and diseases (e.g., Parkinson's disease, Huntington's disease, and Alzheimer's disease) are characterized by abnormalities in the normal function of the central nervous system (CNS). These conditions and diseases typically respond to pharmacologic intervention with compounds or substances that modulate CNS activity. Compounds with this activity include the compounds of the present invention, which are herein disclosed to treat abnormalities of the CNS, such as epilepsy. While currently available therapeutants often have good CNS activity, they frequently exhibit other undesirable properties, such as chronic toxicity, severe and/or unpleasant side effects, and inadequate pharmacokinetic properties, such as a short pharmacologic half-life. For example, a short half-life in a CNS therapeutant may require its frequent administration in order to sustain therapeutic concentrations of the

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.

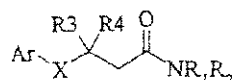
[0004] Related art may be found in U.S. Patent 5,463,125 (Sandoval *et al.*, "Phenyl alcohol amides having anticonvulsant activity"), WO9941229 [Carvajal Sandoval *et al.*, "Halogenated phenyl alcohol amides (ligands of GABAB receptor) having an anticonvulsant activity"], WO03091201 (Carvajal Sandoval *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 disclosure (as shown below) are amides which are derivatives of optically active amino acids (e.g., D or L), such as alanine ($Z = \text{CH}_3$, below), valine [$Z = \text{CH}(\text{CH}_3)_2$], leucine [$Z = \text{CH}_2\text{CH}(\text{CH}_3)_2$], isoleucine [$Z = \text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$], or phenylalanine ($Z = \text{CH}_2\text{C}_6\text{H}_5$), or the optically inactive amino acids, glycine ($Z = \text{H}$) or taurine [$R_2 = (\text{CH}_2)_2\text{SO}_3\text{H}$, below]. Such compounds are exemplified by the following formulas:

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

FORMULA I



[0007] In Formula I, Ar can be an optionally substituted phenyl, optionally substituted naphthyl, optionally substituted tetrahydronaphthyl, optionally substituted indane, or an optionally substituted heterocyclic aryl, wherein up to 5 substituents may be present. Each substituent on Ar can be independently selected from the group consisting of alkyl, cycloalkyl, halogen, alkoxy, thioalkyl, sulfoxyalkyl, sulfonylalkyl, alkylene dioxy, haloalkyl, haloalkoxy, OH, CH₂OH, CONH₂, CN, acetoxy, N(alkyl)₂, benzyl, benzyloxy, α,α -dimethylbenzyl, NO₂, CHO, CH₃CH(OH), acetyl, OCH₂COOH, and combinations thereof. Also, the Ar can include an optionally substituted aromatic ring system attached to one or two atoms of the Ar, such aromatic rings being selected from the group consisting of phenyl, phenoxy, heterocyclic aryl, and combinations thereof. The Ar and/or substituent thereon can have up to 5 substituents, and each substituent can be independently selected from the group consisting of alkyl, cycloalkyl, halogen, alkoxy, thioalkyl, sulfoxyalkyl, sulfonylalkyl, alkylene dioxy, haloalkyl, haloalkoxy, OH, CH₂OH, CONH₂, CN, acetoxy, N(alkyl)₂, NO₂, CHO, CH₃CH(OH), acetyl, and OCH₂COOH. Optionally, the Ar and/or aromatic rings can include bifunctional substituents that form a ring with the Ar and/or aromatic rings, wherein the bifunctional substituents are an optionally substituted alkyl, cycloalkyl, methylenedioxy, ethylenedioxy, or other alkylendioxy, and combinations thereof.

[0008] In Formula I, R₁ and R₂ can each be independently at least one of, H, long or short chain substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, CW₂phenyl. Each 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, and each substituent is independently selected from the group consisting of halogen, alkoxy, thioalkyl, sulfoxyalkyl, sulfonylalkyl, haloalkyl, haloalkoxy, CONH₂, CN, acetoxy, N(alkyl)₂, NO₂, and acetyl.

[0009] In another embodiment, R₁ is H and R₂ is (CH₂)₂SO₃H, or CHZCOOH, wherein Z is one of the group consisting of H, CH₃, CH(CH₃)₂, CH₂C₆H₅, CH₂CH(CH₃)₂, and CH(CH₃)CH₂CH₃. Optionally, R₁ and R₂ together are cycloalkyl.

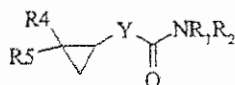
[0010] In Formula I, R_3 is either hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, or together with R_4 cycloalkyl. Optionally, if R_3 is OH, then R_4 is not an ethyl.

[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

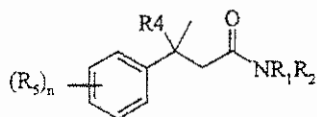


[0013] In Formula II, R_1 and R_2 are each independently at least one of H, long or short chain substituted or unsubstituted alkyl, substituted or unsubstituted, cycloalkyl, CW_2 phenyl, or combinations thereof. W is independently selected from the group consisting of H, methyl and ethyl, except that both Ws cannot be ethyl. Up to 5 substituents may be present in the phenyl group or cycloalkyl 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, R_1 and R_2 together are cycloalkyl.

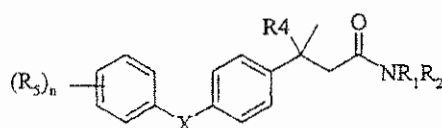
[0014] R_4 and R_5 are each independently either optionally substituted phenyl or optionally substituted heterocyclic aryl, wherein up to 5 substituents may be present and each substituent is independently selected from the group consisting of halogen, alkoxy, thioalkyl, sulfoxyalkyl, sulfonylalkyl, 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.

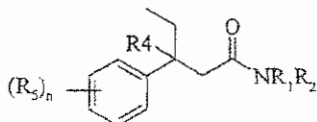
[0016] In one embodiment, the present disclosure includes a CNS-active compound having one of the following formulas:



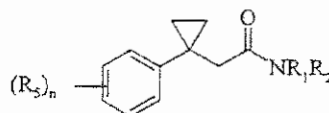
Formula 1



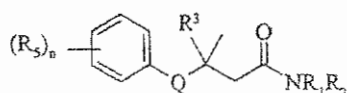
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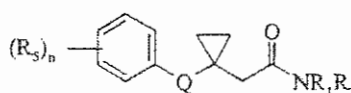
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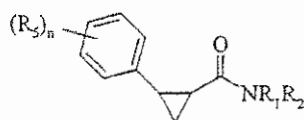
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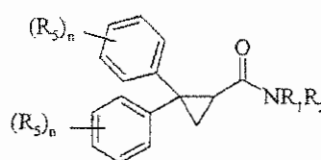
Formula 5



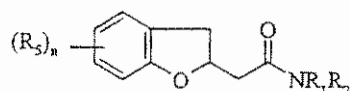
Formula 6



Formula 7



Formula 8



Formula 9

$R_1 = \text{H, CH}_3, \text{C}_2\text{H}_5, (\text{CH}_2)_2\text{SO}_3\text{H, or CH}_2\text{COOH,}$

$Z = \text{H, CH}_3, \text{CH}(\text{CH}_3)_2, \text{CH}_2\text{C}_6\text{H}_5, \text{CH}_2\text{CH}(\text{CH}_3)_2, \text{or CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$

$R_2 \text{ and } R_3 = \text{H or CH}_3$

$R_4 = \text{H, CH}_3, \text{OH, or OCH}_3$

$R_5 = \text{H, Cl, F, CF}_3, \text{CN, C}_1\text{-C}_5 \text{ alkyl, C}_1\text{-C}_5 \text{ alkoxy, OCF}_3 \text{ or CONR}_1\text{R}_2$

$n = 1 - 5$

$Q = \text{O, NR}_2, \text{C=O, S, SO, or SO}_2$

$X = \text{O, NR}_2, \text{nothing, C=O, S, SO, or SO}_2$

[0017] In one embodiment, 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, C_6H_5 phenyl, 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 cycloalkyl group, and each substituent is independently selected from the group consisting of halogen, alkoxy, thioalkyl, sulfoxyalkyl, sulfonylalkyl, haloalkyl, haloalkoxy, CONH_2 , CN, acetoxy,

$N(\text{alkyl})_2$, NO_2 , and acetyl. Optionally, R_1 is H and R_2 is $(\text{CH}_2)_2\text{SO}_3\text{H}$, or CHZCOOH , wherein Z is one of the group consisting of: H, CH_3 , $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{C}_6\text{H}_5$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, and $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$. In another option, R_1 and R_2 together are cycloalkyl.

[0018] In one embodiment, R_1 is H and R_2 is $(\text{CH}_2)_2\text{SO}_3\text{H}$, or CHZCOOH , wherein Z is one of the group consisting of: H, CH_3 , $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{C}_6\text{H}_5$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, and $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$. 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.

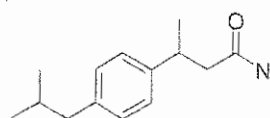
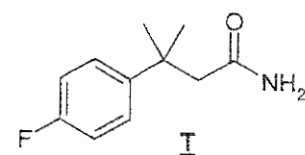
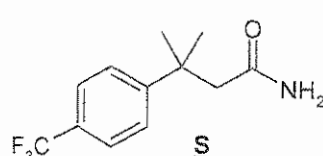
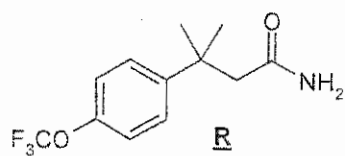
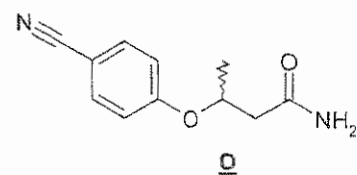
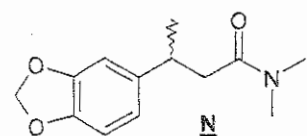
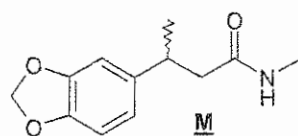
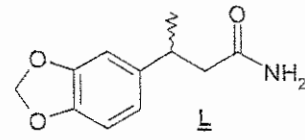
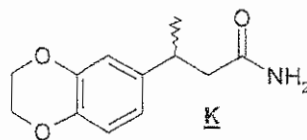
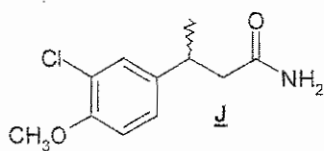
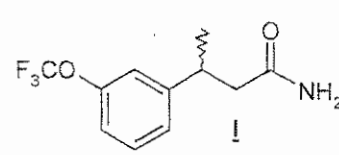
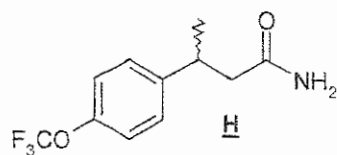
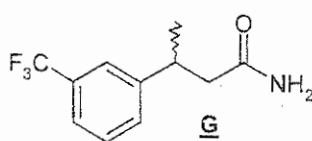
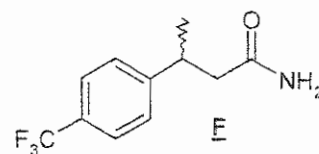
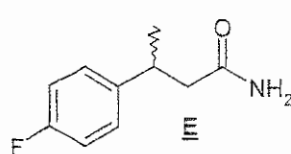
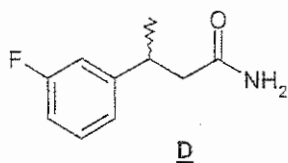
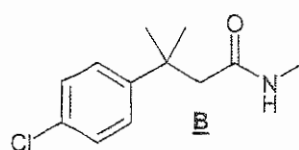
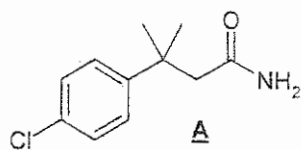
[0021] In one embodiment, R_5 is one of H, Cl, F, CF_3 , CN, C1-C5 alkyl, C1-C5 alkoxy, OCF_3 , CONR_1R_2 , halogen-substituted alkyl, halogen-substituted alkoxy,

[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 , $(\text{CH}_2)_2\text{SO}_3\text{H}$, or CHZCOOH , wherein Z is one of the group consisting of: H, CH_3 , $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{C}_6\text{H}_5$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, and $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, 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 $X = \text{O}$, NR_1 , nothing, $\text{C}=\text{O}$, 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:



Formula AW

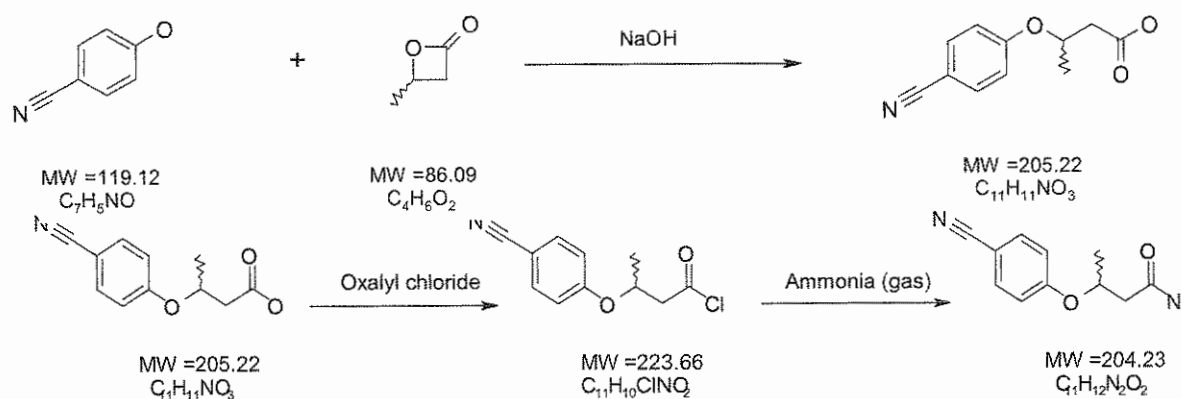
[0024b] In a second aspect, there is provided a pharmaceutical composition, the composition comprising:

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 disclosure will become more fully apparent from the following description and appended claims, or may be learned by the practice of the disclosure as set forth hereinafter.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] FIGURE 1 shows the chemical structures of the novel compounds of the invention that are pharmacologically active in the central nervous systems (CNS) of (for example) mammals, and which exemplify embodiments of the present invention.

[0027] FIGURE 2 shows the relative biological activity of the compounds of the invention, specifically showing those compounds which are preferred (second category, $ED_{50} < 300$ mg/kg) and most preferred (first category, $ED_{50} < 100$ mg/kg).

[0028] FIGURE 3A shows the structures of further compounds of the invention which are also in the category of most preferred compounds.

[0029] FIGURE 3B shows the structures of further compounds of the invention which are also in the category of most preferred compounds.

[0030] FIGURES 4A-4O illustrate examples of the syntheses of various compounds and key intermediates.

DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

1. OVERVIEW

[0031] The inventors have discovered that the compounds of the invention and certain of their pharmacologically active analogs and congeners can be administered *in vivo* to effect a modulation of CNS activity. That is, these agents modulate CNS activity, by enhancing inhibitory, or decreasing excitatory, neurotransmission centrally, without complete suppression of all activity. Pursuant to the present invention, therefore, a subject who receives such an agent is not overtly sedated, anesthetized, or paralyzed in the context of, for example, decreasing seizures (no anesthesia), decreasing muscle tone (no paralysis), eliciting a calmatative effect (no sedation), or ameliorating an ambulatory syndrome such as spasticity (no weakness or flaccidity).

[0032] A number of pathologies, exemplified by convulsions (seizures), spasticity, affective mood disorders, such as bipolar mood disorder, headaches (chronic, cluster, migraine), restlessness syndromes, neuropathic pain, and movement disorders, have at least one symptom that is alleviated by a modulation of CNS activity. Accordingly, an individual who suffers from such a pathology is a candidate for therapy that entails, pursuant to the present invention, the individuals receiving a pharmaceutical formulation or composition containing the compounds of the invention or one of their structurally related analogs or congeners as one of the principal active ingredients.

2. EXEMPLARY PATHOLOGIES AMELIORATED BY A MODULATION OF CENTRAL NERVOUS SYSTEM (CNS) ACTIVITY

[0033] CONVULSIONS: Epilepsy is a common disorder which has many causes, and it can be very difficult to control clinically, often requiring treatment for many years to keep seizures under control. Researchers have stated that "[a]t this time, there is no satisfactory treatment for epilepsy in a substantial proportion of patients. Clinical trials have shown that certain patients have a better response to one drug than another, even when the patients have similar types of seizures and the drugs have similar mechanisms of action. The frequency and severity of side effects also varies substantially. Thus, multiple medications with different mechanisms of action and attendant side effects will be needed for treatment of epilepsy until either epilepsy can be cured or a potent, safe new drug with broad activity is discovered" and developed. Dichter *et al.*, *Drug Therapy* 334:1583 (1996).

[0034] Due to the widespread availability of reasonably predictive and experimentally accessible animal models of convulsant states, a number of clinically useful anticonvulsants have been prepared and developed. For example, see Cereghino *et al.*, "Introduction," in *ANTIPILEPTIC DRUGS*, 4th ed., pages 1-11 (Rave Press 1995), which states: "In many patients, seizures can be controlled with currently available antiepileptic drugs, but 25 to 30 percent of patients continue to have seizures despite optimal therapy, while many others experience unacceptable side effects." Dichter *et al.* (1996) *supra*.

[0035] Thus, many anticonvulsants in clinical use are plagued by the occurrence of significant side effects, including troublesome daytime sedation, muscular weakness, tolerance, gingival hyperplasia, and potentially fatal blood dyscrasias and hepatotoxicity. Many of these side effects are especially of concern in the clinical management (treatment) of epilepsy in children.

[0036] The present invention can be used to treat convulsive disorders such as epilepsy. That is, the compositions and pharmaceutical formulations and compositions of the invention display "anticonvulsant activity," which is evidenced by a reduction of the severity, number, or duration of convulsions in animal models of epilepsy. To alleviate convulsions includes reducing the severity, number of duration of convulsions in a patient. Accordingly, the novel compositions and pharmaceutical formulations and compositions should be useful in treating conditions such as, but not limited to, generalized tonic-clonic seizures, absence seizures, myoclonic seizures,

simple partial seizures, complex partial seizures, secondarily generalized partial seizures, *status epilepticus*, and trauma-induced seizures, as occur following head injury or surgery.

[0037] SPASTICITY: Spasticity is a disorder characterized by an increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks resulting from hyperexcitability of the stretch reflex. Lance, *Symposia synopsis*, in SPASTICITY--DISORDERED MOTOR CONTROL, Feldman *et al.* (Eds.) (1980). Major disease states and conditions associated with spasticity include multiple sclerosis, cerebral palsy, stroke, trauma or injury to the spinal cord, and head trauma. Symptoms that occur with spasticity include painful flexor and extensor spasms, increased or exaggerated deep-tendon reflexes, clonus, muscular weakness, fatigue, lack of dexterity, various degrees of loss of general motor function, paralysis, and impairment of sleep.

[0038] The pathological states observed in spasticity are fundamentally different at the physiological level from the commonly experienced acute muscular aches, strains, and sprains that occur from a localized external insult to a particular muscle, i.e., outside of or peripheral to the CNS. These pathological states also are different from the relatively common involuntary spasms or smooth muscle, such as vascular spasms, bladder spasms, and bronchial spasms. Such non-spastic (non-CNS), peripheral or localized symptoms are commonly treated with so-called "antispasmodic" or "spasmolytic" agents, but these generally are not useful in treating spasticity. Cedarbaum & Schleifer, "Drugs for Parkinson's Disease, Spasticity and Acute Muscle Spasms," in GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 8th ed. [hereafter GOODMAN AND GILMAN'S], pages 463-484 (Pergamon Press 1990).

[0039] The compositions of matter and pharmaceutical formulations and compositions employed in accordance with the present invention can effect a centrally mediated decrease in muscle tone and, hence, are useful for the acute or chronic alleviation of one or more symptoms or side effects of spasticity. In this context, "spasticity" refers to a heightened tone of skeletal muscle which is manifested by symptoms such as, but not limited to, painful flexor or extensor spasms, increased or exaggerated deep-tendon reflexes, hyperreflexia, loss of dexterity, muscular weakness, exaggerated tendon jerks, and clonus. The phrase "antispasticity agent" refers here to a composition that is useful for the symptomatic treatment of spasticity,

as demonstrated by the alleviation of at least one of the following manifestations or side effects of spasticity: painful flexor or extensor spasms, increased or exaggerated deep-tendon reflexes, hyperreflexia, loss of dexterity, muscular weakness, exaggerated tendon jerks, and clonus, or the reduction of the frequency of these manifestations or side effects.

[0040] Accordingly, the "alleviation" of spasticity refers here to the lessening of one or more symptoms of spasticity, including, but not limited to, painful flexor or extensor spasms, increased or exaggerated deep-tendon reflexes, hyperreflexia, loss of dexterity, muscle weakness, exaggerated tendon jerks, and clonus, or the reduction of the frequency of these manifestations or side effects.

[0041] AFFECTIVE MOOD DISORDERS: These include conditions ranging from depression to dysphoric mania, for example, mania, schizoaffective disorder, traumatic brain injury-induced aggression, post-traumatic stress disorder, bipolar mood disorder, panic states, and behavioral dyscontrol syndromes. See Emrich *et al.*, *J. Affective Disorders* 8:243-250 (1985) and Bernasconi *et al.*, in ANTICONVULSANTS IN AFFECTIVE DISORDERS, pages 14-32 (*Excerpta Medica* 1984). The novel compositions and pharmaceutical formulations and compositions according to the present invention are effective in the treatment of these diseases, disorders, and conditions, and should exhibit improved side effect profiles when compared to currently existing therapeutic agents in this therapeutic category.

[0042] NEUROPATHIC PAIN SYNDROMES: Conditions in this category, involving "neuropathic pain," affect a significant number of patients suffering from disorders of the brain or spinal cord, such as stroke, trauma, multiple sclerosis, and diabetes. Casey, in PAIN AND CENTRAL NERVOUS SYSTEM DISEASE (Raven 1991). The use of anticonvulsants to treat various pain states has been documented extensively. Swendlow, *J. Clin. Neuropharmacol.* 7: 51-82 (1984). Thus, a novel composition or pharmaceutical formulation or composition of the present invention can be applied in similar fashion to ameliorate neuropathic pain.

[0043] HEADACHES: Headaches of the migraine type [Hering and Kuritzky, *Cephalgia* 12: 81-84 (1992)], the cluster type [Hering and Kuritzky, *loc. cit.* 9:195-198 (1989)], and the chronic type [Mathew and Sabiha, *Headache* 31: 71-74 (1991)] have been treated with anticonvulsants. The compositions and formulations of the present invention can therefore be used to alleviate the symptoms associated with

each of these three headache types, without the adverse side effects of current existing therapies.

[0044] RESTLESSNESS SYNDROME: The phrase "restlessness syndrome" denotes a somatic (non-mental) restlessness characterized by involuntary movement of the limbs, as well as by a sense of physical (rather than mental) agitation, which is independent of mood and, hence, is distinguished from restlessness per se. [See Sachev *et al.*, *Austral. New Zealand J. Psychiatry* 30:38-53 (1996)].

[0045] Restlessness syndromes, inclusive of numerous indications, can be observed in association with many organic and non-organic psychiatric illnesses. For example, drug-induced restlessness (tardive, chronic, and withdrawal akathisias), such as drug-induced extrapyramidal symptoms, is one of the most common side effects of neuroleptic drug therapy. Also within the restlessness-syndrome rubric are the so-called "restless leg syndrome" and "sleep-related periodic leg movements," pathologies that can be associated with head and/or spinal cord trauma and with lesions of the spinal cord. Idiopathic restless leg syndrome follows an autosomal dominant inheritance, with a variable clinical expression of symptoms. See O'Keefe, *Arch. Intern. Med.* 156: 243-248 (1996); Danek *et al.*, in *NEUROLOGICAL DISORDERS: COURSE AND TREATMENT*, pages 819-823 (Academic Press 1996); Mellick and Mellick, *Neurology* 45(suppl.): 285-286 (1995). The present invention provides an effective therapy for restlessness syndromes with minimal side effects.

[0046] MOVEMENT DISORDERS: Various agents are known to decrease the dyskinetic movement characterizing movement disorders such as Parkinson's disease, Huntington's chorea, Alzheimer's disease, tardive dyskinesia, and stiff-man syndrome. Lloyd and Morselli, in *PSYCHOPHARMACOLOGY: THE THIRD GENERATION OF PROGRESS* (Raven Press 1987). A therapy within the present invention alleviates one or more symptoms of a movement disorder.

[0047] The compounds of the invention may also be useful as anxiety-reducing (anxiolytic) agents.

[0048] By "neurological disorder or disease" is meant a disorder or disease of the nervous system including, but not limited to, epilepsy, anxiety, multiple sclerosis, strokes, head trauma, spinal cord injuries, and chronic neurodegenerative diseases such as Parkinson's and Huntington's diseases, Alzheimer's disease, and amyotrophic lateral sclerosis. Also meant by "neurological disorder or disease" are those disease

states and conditions in which an antispastic or anticonvulsant may be indicated, useful, recommended and/or prescribed.

[0049] By "neurodegenerative disease" is meant diseases such as, but not limited to, Huntington's Disease, Parkinson's Disease, Alzheimer's Disease, and amyotrophic lateral sclerosis (ALS).

[0050] By "anticonvulsant" is meant a compound capable of reducing the severity, number, or duration of convulsions produced, observed, or found in conditions such as generalized tonic-clonic seizures, absence seizures, myoclonic seizures, simple partial seizures, complex partial seizures, secondarily generalized partial seizures, status epilepticus, and trauma-induced seizures as occur following head injury or surgery.

[0051] By "anticonvulsant activity" is meant efficacy in reducing the severity, number, or duration of convulsions produced, observed, or found in conditions such as generalized tonic-clonic seizures, absence seizures, myoclonic seizures, simple partial seizures, complex partial seizures, secondarily generalized partial seizures, *status epilepticus*, and trauma-induced seizures, as occur following head injury or surgery.

[0052] By "therapeutic dose" is meant an amount of a compound that relieves to some extent one or more symptoms of the disease or condition of the patient. Additionally, by "therapeutic dose" is meant an amount that returns to normal, either partially or completely, physiological or biochemical parameters associated with or causative of the disease or condition. Generally, it is an amount between about 0.1-15-20-30 mg/kg body weight, depending on the age, size, and disease associated with the patient. The dosing can be one to four times a day.

[0053] By "pharmaceutical composition" is meant a therapeutically effective amount of a compound of the present invention in a pharmaceutically acceptable carrier, i.e., a formulation to which the compound can be added to dissolve or otherwise facilitate administration of the compound. Examples of pharmaceutically acceptable carriers include water, saline, and physiologically buffered saline. Such a pharmaceutical composition is provided in a suitable dose. Such compositions are generally those which are approved for use in treatment of a specific disorder by the FDA or its equivalent in non-U.S. countries.

[0054] It is understood that certain of the compounds of the present invention have one or more chiral stereocenter(s). Such compounds may demonstrate preferred

biological activity as a racemic (or diastereomeric) mixture, as a mixture of *R* and *S* enantiomers (or diastereomers), or as pure enantiomers (*R* or *S*) (or diastereomers). When one pure enantiomer shows preferred biological activity, it is this preferred enantiomer is referred to as the eutomer, whereas the less preferred, less biologically active enantiomer is referred to as the distomer.

[0055] METHODS FOR PREPARING PHARMACEUTICAL FORMULATIONS AND COMPOSITIONS, AND METHODS FOR ADMINISTRATION: As demonstrated herein, useful pharmaceutical formulations and compositions of this invention may be used to treat neurological disorders or diseases. While these preparations will typically be used in therapy for human patients, they may also be used to treat similar or identical diseases in other vertebrates such as other primates, domestic animals, farm animals such as swine, cattle, and poultry, and sports animals and pets such as horses, dogs, and cats.

[0056] The present invention also is directed to pharmaceutical formulations and compositions containing combinations of two or more of the active compounds described above. The compounds of the present invention can be prepared (formulated) according to known methods for preparing pharmaceutically useful compositions, whereby active agents are combined in a mixture with a pharmaceutically acceptable carrier(s). For instance, see Gennaro (Ed.), REMINGTON'S PHARMACEUTICAL SCIENCES, 18th ed. (Mack Publishing Co., Easton, PA, 1990) and GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS. A compound and/or a composition is said to be in a "pharmaceutically acceptable carrier" if its administration can be tolerated by a recipient patient. Sterile phosphate-buffered saline is one example of a pharmaceutically acceptable carrier. Other suitable carriers (e.g., saline and Ringer's solutions) are well known to those skilled in the art (see below).

[0057] The pharmaceutically acceptable carrier includes a suitable excipient and/or auxiliary whose administration is tolerated by the patient. Pharmaceutically acceptable carriers which are known in the art include, but are not limited to, calcium carbonate, calcium phosphate, calcium sulfate, sucrose, dextrose, lactose, fructose, xylitol, sorbitol, starch, starch paste, cellulose derivatives, gelatin, polyvinylpyrrolidone, sodium chloride, dextrans, stearic acid, magnesium stearate, calcium stearate, vegetable oils, polyethylene glycol, sterile phosphate-buffered

saline, saline, and Ringer's solutions, and mixtures thereof. See, for example, REMINGTON'S PHARMACEUTICAL SCIENCES, *supra*.

[0058] Pharmaceutically acceptable salts of organic acids (such as amino acids) which have been approved by the U.S. Food and Drug Administration for commercial marketing include sodium, potassium, lithium, zinc, aluminum, calcium, and magnesium salts. See REMINGTON'S PHARMACEUTICAL SCIENCES, 18th ed., page 1445 (Mack Publishing Co. 1990).

[0059] The compounds of the present invention and pharmaceutical compositions thereof are formulated as known in the art. For instance, the compound(s) of the present invention may be combined with a pharmaceutically acceptable carrier(s) and processed into a desired dosage form. The pharmaceutical compositions of the present invention may be produced or manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes which involve both the pharmaceutical composition of interest and its pharmaceutically acceptable carrier.

[0060] In general, the dosages of the compounds, formulations, and compositions described herein will vary depending upon such factors as the patient's age, weight, height, sex, general medical condition, and previous medical history. For purposes of therapy, a composition of the present invention and a pharmaceutically acceptable carrier are administered to a subject in need of such treatment in a therapeutically effective amount. The combination of active agents and carrier (formulation or composition) is said to be administered in a "therapeutically effective amount" if the amount administered is physiologically significant. A pharmaceutical composition is physiologically significant if its presence results in a detectable change in the physiology of a recipient patient. In the present context, for example, an anticonvulsant composition is physiologically significant if the presence of the composition results in the alleviation of one or more symptoms of epilepsy, such as seizures and/or convulsions. Further, the dose and perhaps dose frequency, will also vary according to the age, body weight, and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

[0061] The compounds of the present invention can be administered orally using solid oral dosage forms such as, for example, enteric-coated tablets, caplets, gelcaps, sprinkles, or capsules, or via liquid oral dosage forms such as syrups or elixirs. Unit

solid oral dosage forms preferably contain appropriate amounts of active compounds per tablet or capsule such that they can be taken 1-2 at a time for a maximum of two times per day. Liquid formulations can also be employed with active compounds so as to provide 1-2 teaspoonfuls per dose. Furthermore, corresponding reduced dosage pediatric chewable and liquid oral dosage forms can also be prepared and administered. These compounds can also be added to foods and beverages in the form of drops (with a dropper from a "concentrate" preparation) for oral administration. In addition, the compounds of the present invention may also be formulated into chewing gum to facilitate oral delivery and absorption. Appropriate dosages for each of the compounds used in the formulations and compositions of the present invention can be discerned from the foregoing descriptions by those skilled in the art.

[0062] Alternatively, the compounds of the present invention can be administered by injection or other systemic routes, such as transdermal or transmucosal administration, for example, nasally, sublingually, buccally, vaginally, or rectally, via suppositories. Other routes of administration (e.g., useful in veterinary applications) include intestinal and parenteral delivery, including intramuscular, subcutaneous, and/or intramedullary injections, as well as intrathecal, direct intracerebroventricular, intravenous, intraperitoneal, intranasal, or intraocular injections. Oral administration is much more convenient, however, and therefore is preferred.

[0063] The present invention thus contemplates a variety of compounds that are suitable for oral, parenteral, transdermal, transmucosal, intranasal, sublingual, buccal, or rectal administration. It is further understood that the compounds of the present invention can be used in combination with other pharmaceutically active ingredients to prepare still other novel pharmaceutical compositions.

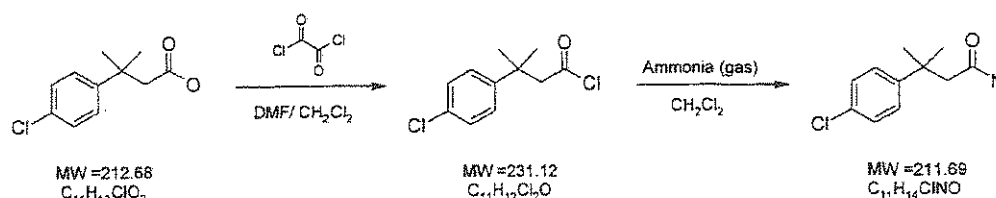
[0064] DEMONSTRATING THERAPY-IMPLICATING AND THERAPEUTICALLY RELEVANT ACTIVITY: The suitability and therapeutic effectiveness of a given pharmaceutical formulation or composition for the alleviation of symptoms, as discussed above, can be demonstrated by using the animal models, testing, and screening methods which are described in, e.g., U.S. Patents 6,589,994, 6,617,358, and 7,265,155, which are hereby incorporated herein in their entirety.

[0065] The therapeutic effects of the compounds of the invention described above, combined with a general lack of toxicity, make the compounds of the present invention ideal agents for the treatment of the conditions described above. With this

background, the present invention will be understood more readily by those skilled in the art by reference to the examples below, which are provided for purposes of illustration and are not intended to be limiting of the invention.

EXAMPLES

Example 1. Preparation of Compound A [3-(4-Chlorophenyl)-3-methylbutyramide].

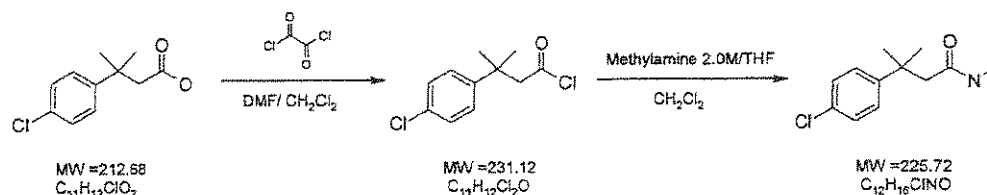


[0066] A solution of 3-(4-chlorophenyl)-3-methylbutyric acid (6.1 g, 41.9 mmol) in CH₂Cl₂ (100 mL) and DMF (0.2 mL) was treated with oxalyl chloride (5.2 mL, 7.45 mmol) at 0°C under static nitrogen. The reaction solution was stirred at room temperature overnight under nitrogen. The excess dichloromethane was removed under reduced pressure. The resulting residue was azeotroped by toluene (50 mL).

[0067] Ammonia (gas) was bubbled through the solution of the acid chloride [3-(4-chlorophenyl)-3-methylbutyryl chloride] in anhydrous THF (100 mL) at 5 degrees Celsius for 15 minutes. The reaction mixture was stirred overnight at room temperature under static nitrogen.

[0068] The white precipitate (ammonium chloride) was filtered and washed with THF (100 mL). The filtrate and wash-solution were combined and evaporated under reduced pressure. The resulting white solid was re-dissolved in ethyl acetate (300 mL). The ethyl acetate layer was washed with H₂O, 1.0 M HCl, a saturated solution of sodium bicarbonate, and brine solution. The ethyl acetate solution was then dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The resulting white solid was triturated with a chilled solution of diethyl ether and hexane (50:50). This afforded 4.22 g of white flakes [3-(4-chlorophenyl)-3-methylbutyramide] (69% yield). This material was determined to be 100% pure by GC/MS analysis. ¹H NMR spectroscopy gave signals consistent with the product's structure and indicated greater than 98% purity.

Example 2. Preparation of Compound B [3-(4-Chlorophenyl)-3,*N*-dimethylbutyramide].

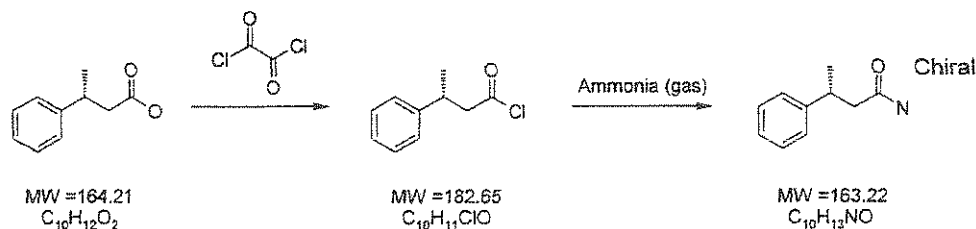


[0069] A solution of 3-(4-chlorophenyl)-3-methylbutyric acid (5.95 g, 28 mmol) in CH_2Cl_2 (100 mL) and DMF (0.2 mL) was treated with oxalyl chloride (5.2 mL, 7.45 mmol) at 0 °C under static nitrogen. The reaction solution was stirred at room temperature overnight under nitrogen. The excess dichloromethane was removed under reduced pressure. The resulting residue was azeotroped by toluene (50 mL).

[0070] The residue was dissolved in 150 mL of dry THF and treated with methylamine solution (2.0 M in THF, 45 mL, 84 mmol) at 5 degrees Celsius. The reaction mixture was stirred overnight at room temperature under static nitrogen.

[0071] The white precipitate was filtered and washed with THF (100 mL). The filtrate and wash-solution were combined and evaporated under reduced pressure. The resulting white solid was re-dissolved in diethyl ether (300 mL). The ether layer was washed with H_2O , 1.0 M HCl, a saturated solution of sodium bicarbonate, and brine solution. The ether solution was then dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The resulting white solid was triturated with a chilled solution of diethyl ether and hexane (50:50). This afforded 5.46 g of white flakes [3-(4-chlorophenyl)-3,*N*-dimethylbutyramide] (86% yield). This material was determined to be 100% pure by GC/MS analysis. ^1H NMR spectroscopy gave signals consistent with the product's structure and indicated greater than 98% purity.

Example 3. Preparation of Compound C [(*R*)-3-Phenylbutyramide].

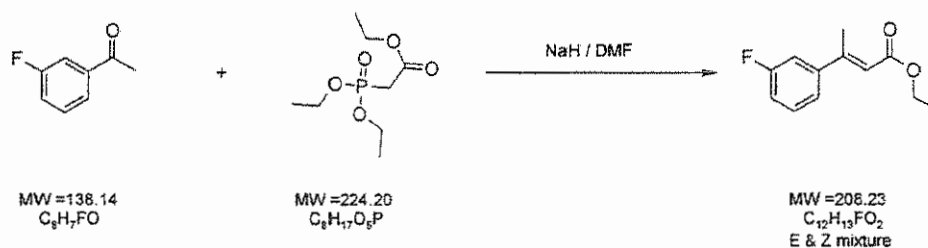


[0072] A solution of (*R*)-3-phenylbutyric acid (4 g, 24.36 mmol) in CH₂Cl₂ (75 mL) and DMF (0.1 mL) was treated with oxalyl chloride (3.0 mL, 34.0 mmol) at 0°C under static nitrogen. The reaction solution was stirred at room temperature overnight under nitrogen. The excess dichloromethane was removed under reduced pressure. The resulting residue was azeotroped by toluene (50 mL).

[0073] Ammonia (gas) was bubbled through the solution of the acid chloride [(*R*)-3-phenylbutyryl chloride] in anhydrous THF (100 mL) at 5 degrees Celsius for 15 minutes. The reaction mixture was stirred overnight at room temperature under static nitrogen.

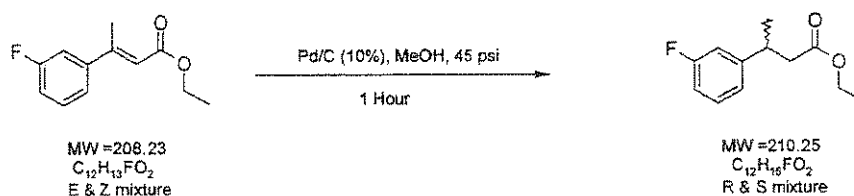
[0074] The white precipitate (ammonium chloride) was filtered and washed with THF (100 mL). The filtrate and wash-solution were combined and evaporated under reduced pressure. The resulting white solid was re-dissolved in ethyl acetate (300 mL). The ethyl acetate layer was washed with H₂O, 1.0 M HCl, a saturated solution of sodium bicarbonate, and brine solution. The ethyl acetate solution was then dried over magnesium sulfate, filtered, and evaporated under reduced pressure. Crude material was purified using a Biotage SP4 System (Column Si 40+M 0344-1, 95:5, CH₂Cl₂: MeOH). The resulting off-white solid was triturated with a chilled solution of diethyl ether and hexane (50:50). This afforded 2.9 g of white solid [(*R*)-3-phenylbutyramide] (73% yield). This material was determined to be 100% pure by GC/MS analysis. ¹H NMR spectroscopy gave signals consistent with the product's structure and indicated greater than 98% purity.

Example 4. Preparation of Compound D [3-(3-Fluorophenyl)butyramide].

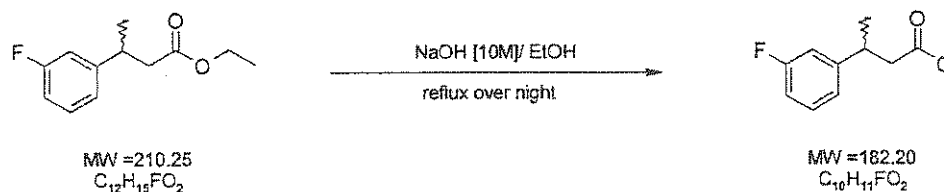


[0075] In a 3-necked, 500-mL round-bottomed flask, a suspension of sodium hydride (60% in oil, 1.1 eq. 80 mmol, 3.20 g) in *N,N*-dimethylformamide (DMF, 100 mL) under nitrogen was treated drop-wise with a solution of triethyl phosphonoacetate (1.2 eq. 87 mmol, 19.50 g) in DMF (50 mL). After the addition, the reaction mixture was heated in a water bath (100°C) until all visible signs of the sodium hydride were gone (30 minutes). The mixture was cooled to ambient temperature and then treated with a

solution of 3'-fluoroacetophenone (1.0 eq, 10 g, 72.4 mmol) in DMF (50 mL). The reaction mixture was stirred for 2 hours at ambient temperature and a 1-mL aliquot was removed and quenched in water (~ 2 mL). Diethyl ether (~2 mL) was added to this and the mixture was equilibrated. Analysis of the organic layer by GC/MS showed complete consumption of the starting benzophenone. As a result, the reaction mixture was quenched by the addition of water. The mixture was transferred to a large round-bottomed flask and the majority of the solvents were removed using a rotary evaporator. The mixture was cooled and transferred to a separatory funnel using [a] diethyl ether (500 mL) and water (250 mL). The mixture was equilibrated and the aqueous layer was removed. The organic layer was washed an additional 3 times with water (3 x 250 mL). GC/MS analysis of this solution showed only product (with no remaining phosphonoacetate). The organic solution was dried over anhydrous MgSO_4 , filtered, and concentrated to afford 18.09 g of crude material (containing oil from the sodium hydride).

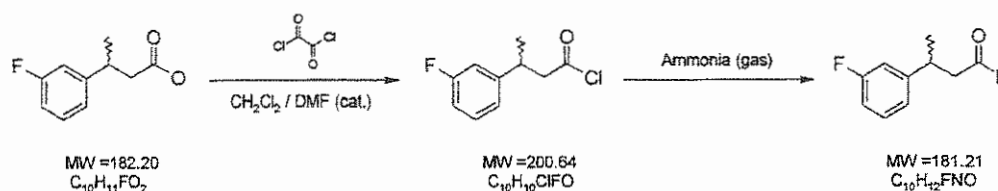


[0076] A solution of crude of [3-(3-fluorophenyl)-but-2-enoic acid ethyl ester] (9 g, 0.015 mmol) in methanol (75 mL) was treated with Pd/C (10%, 450 mg). The reaction mixture was subjected to hydrogenation at 45 psi for 1 hour. The reaction mixture was passed through a Celite plug to remove palladium on carbon. The filtrate was concentrated under reduced pressure. This afforded 10.1 g of a colorless oil [3-(3-fluorophenyl)butyric acid ethyl ester]. The material was determined to be 94% pure by GC/MS analysis. This product was used without purification (to remove mineral oil).



[0077] A crude solution of 3-(3-fluorophenyl)butyric acid ethyl ester, 10.1 g, 48 mmol] in ethanol (50 mL) was treated with 10 M NaOH solution (50 mL, 857 mmol).

The reaction mixture was refluxed overnight. The reaction mixture was dried under reduced pressure in order to get rid of the ethyl alcohol. The resulting residue was re-dissolved in 150 mL of water. The mixture was transferred to a separatory funnel using water (50 mL) and diethyl ether (200 mL). The mixture was equilibrated and the ether layer was removed. The aqueous layer was acidified by HCl solution ($pH \sim 2$) and extracted with diethyl ether (300 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. This afforded 8.1 g of an orange viscous oil, 3-(3-fluorophenyl)butyric acid (92.6% yield). This material was determined to be 100% pure by GC/MS analysis.



[0078] A solution of 3-(3-fluorophenyl)butyric acid (8.1 g, 44.46 mmol) in CH_2Cl_2 (100 mL) and DMF (0.7 mL) was treated with oxalyl chloride (5.43 mL, 7.9 mmol) at $0^\circ C$ under static nitrogen. The reaction solution was stirred at room temperature overnight under nitrogen. The excess dichloromethane was removed under reduced pressure. The resulting residue was azeotroped by toluene (70 mL).

[0079] Ammonia (gas) was bubbled through the solution of the acid chloride [3-(3-fluoro-phenyl)butyryl chloride] in anhydrous THF (100 mL) at 5 degrees Celsius for 15 minutes. The reaction mixture was stirred overnight at room temperature under static nitrogen.

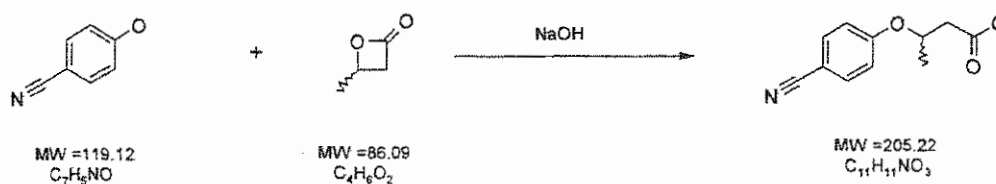
[0080] The white precipitate (ammonium chloride) was filtered and washed with THF (200 mL). The filtrate and wash-solution were combined and evaporated under reduced pressure. The resulting white solid was re-dissolved in ethyl acetate (350 mL). The ethyl acetate layer was washed with H_2O , 1.0 M HCl, a saturated solution of sodium bicarbonate, and brine solution. The ethyl acetate solution was then dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The resulting white solid was triturated with a chilled solution of diethyl ether and hexane (50:50). This afforded 6.8 g of off-white powder of 3-(3-fluorophenyl)butyramide (84% yield). This material was determined to be 100% pure by GC/MS analysis (a mixture of *R* and *S* enantiomers). 1H -NMR spectroscopy gave signals consistent with the product's structure and indicated greater than 98% purity.

Examples 5-14. Preparation of Compounds E-N.

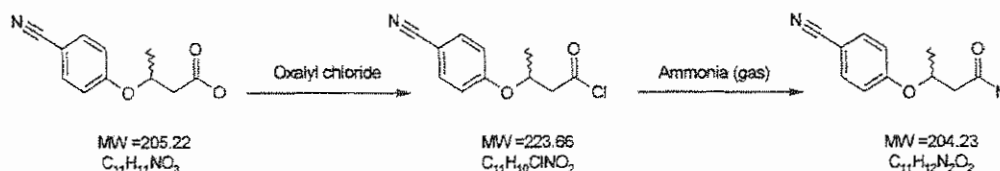
[0081] Compounds E-N were prepared using the corresponding acetophenones (shown in Table 1 below) with the method used for the preparation of Compound D in Example 4, above. In addition, Compound M (Example 13) and Compound N (Example 14) were prepared using the corresponding amines, i.e., methylamine and dimethylamine, respectively. All of the final products were determined to be 100% pure by GC/MS analysis. ¹H-NMR spectroscopy of each final product gave signals consistent with its structure and indicated greater than 98% purity.

Example No.	Formula	Weight (g)	% Yield	Product Chemical Name	Corresponding Acetophenone
5	E	3.2	91	3-(4-fluorophenyl)-butyramide	4'-fluoroacetophenone
6	F	5.7	79	3-[4-(trifluoromethyl)-phenyl]butyramide	4'-(trifluoromethyl)acetophenone
7	G	6.8	84	3-[3-(trifluoromethyl)-phenyl]butyramide	3'-(trifluoromethyl)acetophenone
8	H	3.8	81	3-[4-(trifluoromethoxy)-phenyl]butyramide	4'-(trifluoromethoxy)acetophenone
9	I	1.9	86	3-[3-(trifluoromethoxy)-phenyl]butyramide	3'-(trifluoromethoxy)acetophenone
10	J	2.3	84	3-(3-chloro-4-methoxy-phenyl)butyramide	3'-chloro-4'-methoxyacetophenone
11	K	3.6	70	3-(3,4-ethylenedioxyphenyl)-butyramide	3',4'-ethylenedioxyacetophenone
12	M	2.5	91	3-(3,4-methylenedioxyphenyl)-butyramide	3',4'-methylenedioxyacetophenone
13	M	2.7	90	<i>N</i> -methyl-3-(3,4-methylenedioxy-phenyl)butyramide	3',4'-methylenedioxyacetophenone
14	N	2.3	73	<i>N,N</i> -dimethyl-3-(3,4-methylene-dioxyphenyl)butyramide	3',4'-methylenedioxyacetophenone

Table 1

Example 15. Preparation of Compound Q [3-(4-Cyanophenoxy)butyramide].

[0082] A solution of 4 g (0.1 mol) of sodium hydroxide in 100 mL of H₂O and 11.9 g (0.1 mol) of 4-cyanophenol was heated at reflux for 15 minutes. β-Butyrolactone (8.6 g, 0.1 mol) was added to the refluxing solution over 15 hours. The reaction was then cooled to room temperature. The reaction solution was transferred to a separatory funnel using water (200 mL) and diethyl ether (200 mL). The mixture was equilibrated and the ether layer was removed. The aqueous layer was acidified by HCl solution (pH~2) and extracted with ethyl acetate (300 mL). The ethyl acetate layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 10.78 g of crude product. This crude material was purified using a Biotage SP4 System (Column Si 65i, 9:1 CH₂Cl₂:MeOH), which afforded 9.87 g of a pale-yellow viscous oil [3-(4-cyanophenoxy)butyric acid], which solidified upon standing at room temperature. This material was determined to be 96% pure by GC/MS analysis. This material was used without further purification.

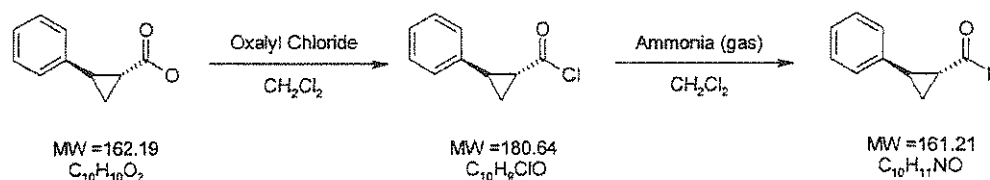


[0083] A crude solution of [3-(4-cyanophenoxy)butyric acid] (10.8 g, 52.6 mmol) in CH₂Cl₂ (100 mL) and DMF (0.21 mL) was treated with oxalyl chloride (6 mL, 68.4 mmol) at 0 °C under static nitrogen. The reaction solution was stirred at room temperature overnight under nitrogen. The excess dichloromethane was removed under reduced pressure.

[0084] Ammonia (gas) was bubbled through the solution of the acid chloride [3-(4-cyanophenoxy)butyryl chloride] in anhydrous CH₂Cl₂ (150 mL) at 5 degrees Celsius for 15 minutes. The reaction mixture was stirred overnight at room temperature under static nitrogen.

[0085] The white precipitate (ammonium chloride) was filtered and washed with CH_2Cl_2 (100 mL). The filtrate and wash-solution were combined and evaporated under reduced pressure. The resulting white solid was re-dissolved in ether (250 mL). The ether layer washed with H_2O , 1.0 M HCl, a saturated solution of sodium bicarbonate, and brine solution. The ether solution was then dried over magnesium sulfate, filtered, and evaporated under reduced pressure. Crude material was purified using a Biotage SP4 System (Column Si 40+M 0344-1, 95:5, CH_2Cl_2 :MeOH). This afforded 2.987 g of an off-white solid [3-(4-cyanophenoxy)butyramide] (29% yield). This material was determined to be 97% pure by GC/MS analysis. ^1H NMR spectroscopy gave signals consistent with the product's structure and indicated greater than 98% purity.

Example 16. Preparation of Compound P [(1*R*,2*R*)-*trans*-2-phenylcyclopropane-1-carboxamide].



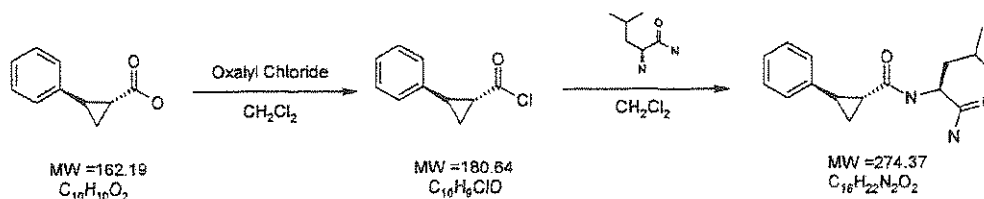
[0086] A solution (1*R*,2*R*)-*trans*-2-phenylcyclopropane-1-carboxylic acid (2.1 g., 12.8 mmol) in CH_2Cl_2 (50 mL) and DMF (0.20 mL) was treated with oxalyl chloride (1.5 mL, 16.7 mmol) at 0°C under static nitrogen. The reaction solution was stirred at room temperature overnight under nitrogen. The excess dichloromethane was removed under reduced pressure.

[0087] Ammonia (gas) was bubbled through the solution of the acid chloride [(1*R*,2*R*)-*trans*-2-phenylcyclopropane-1-carboxyl chloride] in anhydrous CH_2Cl_2 (100 mL) at 5 degrees Celsius for 15 minutes. The reaction mixture was stirred overnight at room temperature under nitrogen.

[0088] The reaction mixture was evaporated under reduced pressure and the resulting residue re-dissolved in an ethyl acetate/water mixture. The mixture was transferred to a separatory funnel using H_2O (60 mL) and ethyl acetate (100 mL). The mixture was equilibrated and the aqueous phase was removed. The organic layer was washed with 1.0 M HCl (10 mL), H_2O (70 mL), and brine (75 mL), consecutively. The organic layer was dried over anhydrous magnesium sulfate, filtered, and [the] excess solvent was removed under reduced pressure. The resulting light-brown solid was purified

using a Biotage SP4 System (Column Si 40+S 90:10 CH₂Cl₂:MeOH), which afforded 1.127 g of white powder [(1*R*,2*R*)-*trans*-2-phenylcyclopropane-1-carboxamide] (54% yield). This material was determined to be 100% pure by GC/MS analysis. ¹H-NMR spectroscopy gave signals consistent with the product's structure and indicated greater than 98% purity.

Example 17. Preparation of Compound Q [(1*R*,2*R*)-2-Phenylcyclopropane-carboxylic acid-((*S*)-1-carbamoyl-3-methylbutyl)amide].



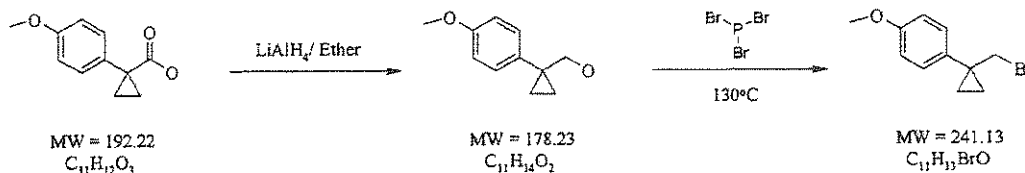
[0089] A solution of (1*R*,2*R*)-*trans*-2-phenylcyclopropane-1-carboxylic acid (0.905 g, 5.6 mmol) in CH₂Cl₂ (30 mL) and DMF (0.05 mL) was treated with oxalyl chloride (0.65 mL, 7.23 mmol) at 0°C under static nitrogen. The reaction solution was stirred at room temperature overnight under nitrogen. The excess dichloromethane was removed under reduced pressure.

[0090] The solution of the acid chloride [(1*R*,2*R*)-*trans*-2-phenylcyclopropane-1-carboxyl chloride] in CH₂Cl₂ (50 mL) was added drop-wise in to a solution of H-Leu-NH₂ [L-leucine amide, (*S*)-2-amino-4-methyl-*n*-valeramide] (0.761 g, 5.8 mmol) and triethylamine (1.13 g, 11.1 mmol) in CH₂Cl₂ (60 mL) at zero degrees Celsius. The reaction mixture was stirred at room temperature under nitrogen overnight.

[0091] The reaction mixture was evaporated under reduced pressure and the resulting residue was re-dissolved in an ethyl acetate/water mixture. The mixture was transferred to a separatory funnel using H₂O (50 mL) and ethyl acetate (80 mL). The mixture was equilibrated and the aqueous phase was removed. The organic layer was washed with 1.0 M HCl (20 mL), H₂O (90 mL), and brine (120 mL), consecutively. The organic layer was dried over anhydrous magnesium sulfate, filtered, and the excess solvent was removed under reduced pressure. The resulting orange-brown solid was purified using a Biotage SP4 System (Column Si 40+M 90:10, CH₂Cl₂:MeOH), which afforded 0.365 g of white powder [(1*R*,2*R*)-2-phenylcyclopropanecarboxylic acid-((*S*)-1-carbamoyl-3-methylbutyl)-amide] (24% yield). This material was determined to be 100% pure by GC/MS analysis. ¹H-NMR

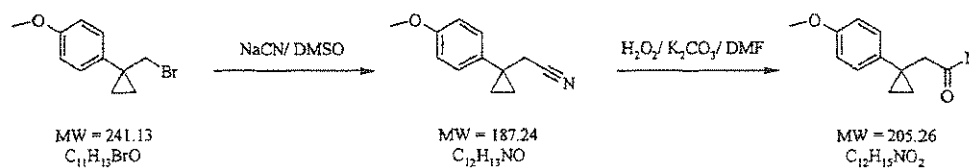
spectroscopy gave signals consistent with the product's structure and indicated greater than 98% purity.

Example 18. Preparation of Compound U [2-[1-(4-Methoxyphenyl)cyclopropyl]-acetamide].



[0092] A stirred suspension of lithium aluminum hydride (0.211 mol) in anhydrous ether (200 mL) is treated with 1-(4-methoxyphenyl)-1-cyclopropanecarboxylic acid (0.1406 mol) in 100 mL of ether at 0°C. The reaction mixture is then stirred at room temperature under nitrogen overnight. The reaction mixture is quenched by the drop-wise addition of 100 mL of deionized H₂O. The mixture is filtered and the cake solid is washed with diethyl ether (1 L). The filtrate mixture (ether and water) is transferred into a separatory funnel. The organic layer is separated from the aqueous layer and washed with brine solution. The ether layer is dried over magnesium sulfate, filtered, and concentrated under reduced pressure at room temperature. This affords [1-(4-methoxy-phenyl)-cyclopropyl]-methanol.

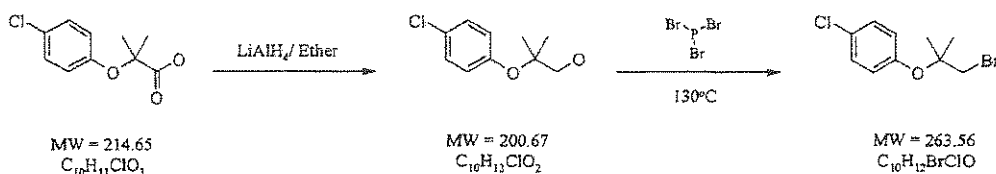
[0093] A neat solution of [1-(4-methoxyphenyl)cyclopropyl]methanol (0.074 mol) is treated with phosphorous tribromide (0.081 mol) drop-wise at 0 °C under static nitrogen. The reaction solution is heated to 130 °C and the temperature is maintained for 6 hours. The reaction mixture is cooled down to room temperature and the orange precipitate is filtered off. The orange precipitate is washed with 200 mL of diethyl ether. The filtrate is transferred into a separatory funnel using 150 mL of water and 200 mL of diethyl ether. The mixture is equilibrated and the aqueous layer is extracted one more time with 200 mL of diethyl ether. The ether extracts and ether-wash are combined and washed with saturated sodium bicarbonate solution and brine. Then the ether extracts are dried over magnesium sulfate and the excess diethyl ether is removed under reduced pressure at 30°C. This affords 1-(1-bromomethyl-cyclopropyl)-4-methoxybenzene. The crude material is converted into the corresponding nitrile without further purification.



[0094] A crude solution of 1-(1-bromomethyl-cyclopropyl)-4-methoxybenzene (60.3 mmol) in dimethyl sulfoxide (60 mL) is treated with sodium cyanide (180.7 mmol). The reaction mixture is heated to 95 degrees Celsius overnight under nitrogen. The reaction mixture is transferred to a separatory funnel using brine (150 mL) and chloroform (300 mL). The reaction mixture is equilibrated and the aqueous layer is removed. The aqueous layer is extracted an additional two times with chloroform (2 x 300 mL). The combined organic extract is dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to afford [1-(4-methoxyphenyl)cyclopropyl]acetonitrile. This crude material is used in the next step (hydrolysis of the nitrile to the corresponding amide) without further purification. [Alternatively, the corresponding carboxylic acid can be obtained from this material by acid hydrolysis (e.g., using sulfuric acid).]

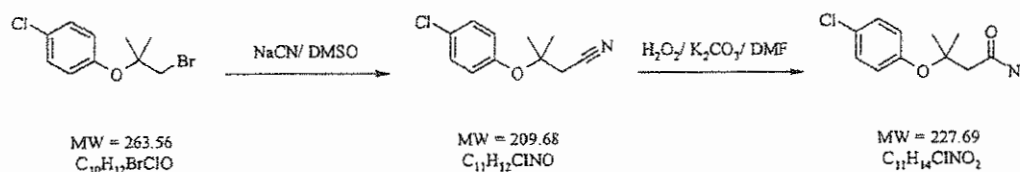
[0095] A solution of [1-(4-methoxyphenyl)cyclopropyl]acetonitrile (60.4 mmol) in DMSO (75 mL) is treated with H₂O₂ (50% w/w) (434 mmol) and potassium carbonate (121 mmol) at zero degrees Celsius. The reaction mixture is stirred at room temperature over the weekend. The reaction mixture is transferred into a separatory funnel using water (100 mL) and CH₂Cl₂ (200 mL). The mixture is equilibrated and the CH₂Cl₂ layer is removed. The aqueous layer is extracted two additional times with CH₂Cl₂ (2 x 300 mL). The combined CH₂Cl₂ extracts are washed 5 consecutive times with water (5 x 200 mL) followed by a brine (500 mL) wash, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure, which affords 2-[1-(4-methoxyphenyl)-cyclopropyl]-acetamide.

Example 19. Preparation of Compound V [3-(4-Chlorophenoxy)-3-methylbutyr-amide].



[0096] A stirred suspension of lithium aluminum hydride (0.211 mol) in anhydrous ether (200 mL) is treated with 2-(4-chlorophenoxy)-2-methylpropanoic acid (0.1406 mol) in 100 mL of ether at 0 °C. The reaction mixture is stirred at room temperature under nitrogen overnight. The reaction mixture is quenched by the drop-wise addition of 100 mL of deionized H₂O. The mixture is filtered and the cake solid is washed with diethyl ether (1 L). The filtrate mixture (ether and water) is transferred into a separatory funnel. The organic layer is separated from the aqueous layer and washed with brine solution. The ether layer is dried over magnesium sulfate, filtered, and concentrated under reduced pressure at room temperature. This affords 2-(4-chlorophenoxy)-2-methylpropan-1-ol.

[0097] A neat solution of 2-(4-chlorophenoxy)-2-methylpropan-1-ol (0.074 mol) is treated with phosphorous tribromide (0.081 mol) drop-wise at 0 °C under static nitrogen. The reaction solution is heated to 130°C and the temperature is maintained for 6 hours. The reaction mixture is cooled down to room temperature and the orange precipitate is filtered off. The orange precipitate is washed with 200 mL of diethyl ether. The filtrate is transferred into a separatory funnel using 150 mL of water and 200 mL of diethyl ether. The mixture is equilibrated and the aqueous layer is extracted one more time with 200 mL of diethyl ether. The ether extracts and ether-wash are combined and washed with saturated sodium bicarbonate solution and brine. Then the ether extract is dried over magnesium sulfate and the excess diethyl ether is removed under reduced pressure at 30 °C. This affords 1-(2-bromo-1,1-dimethylethoxy)-4-chlorobenzene. The crude 1-(2-bromo-1,1-dimethylethoxy)-4-chlorobenzene is converted into the corresponding nitrile without further purification.

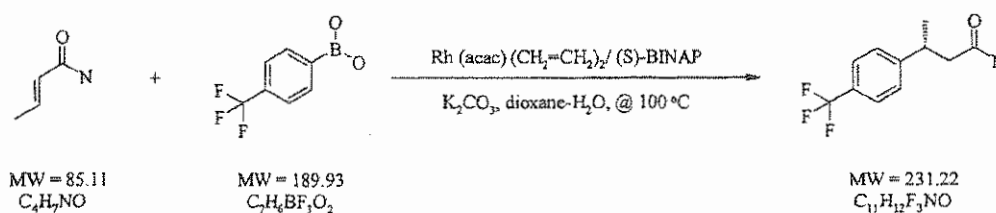


[0098] A crude solution of 1-(2-bromo-1,1-dimethylethoxy)-4-chlorobenzene (60.3 mmol) in dimethyl sulfoxide (60 mL) is treated with sodium cyanide (180.7mmol). The reaction mixture is heated to 95 degrees Celsius overnight under nitrogen. The reaction mixture is transferred into a separatory funnel using brine (150 mL) and chloroform (300 mL). The reaction mixture is equilibrated and the aqueous layer is removed. The aqueous layer is extracted an additional two times with chloroform (2

x 300 mL). The combined organic extracts are dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure to afford 3-(4-chlorophenoxy)-3-methylbutyronitrile. This crude material is used in the next step (hydrolysis of the nitrile into the corresponding amide) without further purification. [Alternatively, the corresponding carboxylic acid can be obtained from this material by acid hydrolysis (e.g., using sulfuric acid).]

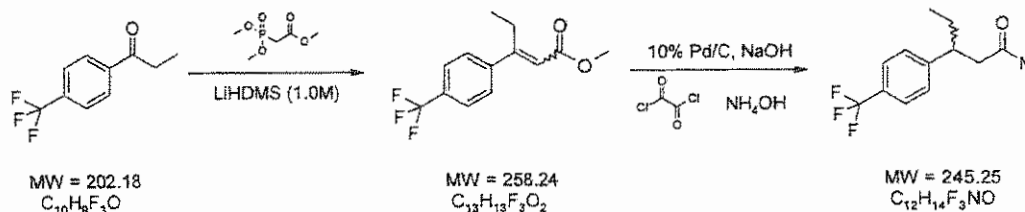
[0099] A solution of 3-(4-chlorophenoxy)-3-methylbutyronitrile (60.4 mmol) in DMSO (75 mL) is treated with H_2O_2 (50% w/w) (434 mmol) and potassium carbonate (121 mmol) at zero degrees Celsius. The reaction mixture is stirred at room temperature over the weekend. The reaction mixture is transferred into a separatory funnel using water (100 mL) and CH_2Cl_2 (200 mL). The mixture is equilibrated and the CH_2Cl_2 layer is removed. The aqueous layer is extracted two additional times with CH_2Cl_2 (2 x 300 mL). The combined CH_2Cl_2 extracts are washed 5 consecutive times with water (5 x 200 mL) followed by a brine (500 mL) wash, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure, which affords 3-(4-chlorophenoxy)-3-methylbutyramide.

Example 20. Preparation of Compound AG [(R)-3-(4-Trifluoromethylphenyl)-butyramide].



[00100] Acetylacetonatobis(ethylene)rhodium(I) (0.3 mmol), (S)-(-)-2,2'-Bis(diphenyl-phosphino)-1,1'-binaphthalene (0.045 mmol), 4-(trifluoromethyl)phenylboronic acid (2 mmol), K_2CO_3 (0.5 mmol), and but-2-enoic acid amide (1 mmol) are added into a 25-mL round-bottomed flask containing a magnetic stirrer bar, a septum inlet, and a reflux condenser. The flask is flashed with argon and then charged with 1,4-dioxane (3 mL) and de-ionized H_2O (0.5 mL). The reaction mixture is stirred for 16 hours at 100°C . The (R)-3-(4-trifluoromethylphenyl)butyramide is extracted with ethyl acetate, washed with brine, and dried over anhydrous magnesium sulfate. Chromatography over silica gel gives the desired product.

Example 21. Preparation of Compound AA [3-(4-Trifluoromethylphenyl)-pentanamide].

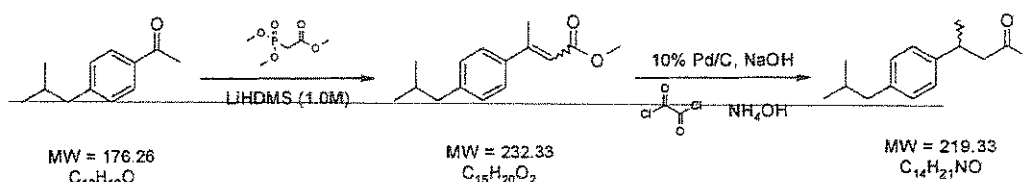


[00101] To a chilled (0 °C) solution of lithium bis(trimethylsilyl)amide (1.0 M, 50 mL) was dropwise added a solution of trimethylphosphonoacetate, keeping the temperature below 10 °C. The solution was then allowed to warm to room temperature and stirred for an additional five minutes, after which a solution of 4'-(trifluoromethyl)propiophenone in THF (25 mL) was added in one portion. The solution was slowly heated to 50 °C for eight hours. The solution was cooled to room temperature, then diluted with a 10% NH_4Cl solution (100 mL), and extracted with ethyl acetate (2 x 100 mL). The organic layers were combined and dried over MgSO_4 , filtered, and the filtrate concentrated to a white solid which was recrystallized from hexane/ethyl acetate to give 5.42 grams of 3-(4-trifluoromethylphenyl)pent-2-enoic acid methyl ester intermediate (85% yield).

[00102] To a solution of 3-(4-trifluoromethylphenyl)pent-2-enoic acid methyl ester in THF/MeOH was added a solution of sodium hydroxide in H_2O (15 mL). The resulting solution was stirred at room temperature for 12 hours, and acetic acid (3 grams) was added. The solution was then concentrated to an oil. The oil was dissolved in ethyl acetate (100 mL) and washed with H_2O (3 x 100 mL). The ethyl acetate extracts were combined and dried over MgSO_4 , filtered, and concentrated to a semi-solid which was then dissolved in MeOH/THF (2:1, 50 mL) and shaken with 10% Pd/C under 50 psi of hydrogen pressure for 24 hours. TLC showed that the reaction was incomplete. Additional 10% Pd/C was added (500 mg) and the suspension was shaken for an additional 24 hours. The suspension was then filtered and the filtrate concentrated to a semi-solid (4.97 g). The solid was dissolved in CH_2Cl_2 (30 mL) and the resulting solution cooled to 0 °C. To this solution was added oxalyl chloride followed by one drop of DMF from a 9-inch disposable pipette. The solution was stirred for 8 hours and then concentrated to a solid which was dissolved in additional CH_2Cl_2 (30 mL). The solution was again concentrated to a semi-solid

which was dissolved in additional CH_2Cl_2 (50 mL), and the resulting solution added dropwise to a chilled (5°C) and mechanically stirred solution of NH_4OH (10 mL) over approximately five minutes. The suspension was then concentrated to a gummy/aqueous mixture which was extracted with ethyl acetate (2 x 100 mL). The ethyl acetate extracts were combined and dried over MgSO_4 , filtered, and the filtrate concentrated to a crude amber-solid which was adsorbed onto silica gel (50 g) using $\text{CH}_2\text{Cl}_2/\text{THF}$. The solid was then chromatographed on silica gel ($\text{EtOAc}/\text{hexane}$) to give 2.25 grams of off-white solid (37% yield). This material was determined to be 100% pure by LC/MS. H-NMR gave signals consistent with the product's structure and indicated greater than 98% purity.

Example 22. Preparation of Compound AW [3-(4-Isopropylphenyl)butyramide].

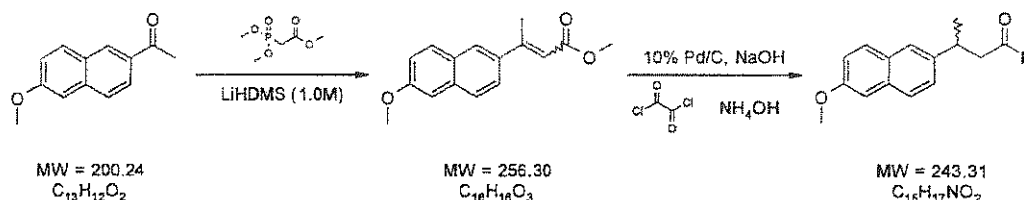


[00103] To a chilled (0°C) solution of lithium bis(trimethylsilyl)amide (1.0 M, 56 mL) was dropwise added a solution of trimethylphosphonoacetate, keeping the temperature below 10°C . The solution was then allowed to warm to room temperature and stirred for an additional five minutes after which a solution of p-isobutyrylacetophenone in THF (25 mL) was added in one portion. The solution was slowly heated to 65°C and allowed to reflux for thirty hours. The solution was cooled to room temperature then diluted with a 10% NH_4Cl solution (100 mL), and extracted with ethyl acetate (2 x 100 mL). The organic layers were combined and dried over MgSO_4 , filtered, and filtrate concentrated to a white solid which was recrystallized from hexane/ethyl acetate to give 5.93 grams of 3-(4-isobutylphenyl)but-2-enoic acid methyl ester intermediate (89.9% yield).

[00104] To a solution of 3-(4-isobutylphenyl)but-2-enoic acid methyl ester in THF/MeOH was added a solution of sodium hydroxide in H_2O (15 mL). The resulting solution was stirred at room temperature for 12 hours and acetic acid (3 grams) was added. The solution was then concentrated to an oil. The oil was dissolved in ethyl acetate (150 mL) and washed with H_2O (3 x 100 mL). The ethyl acetate extracts were combined and dried over MgSO_4 , filtered, and concentrated to a solid (4.98 g) which was then dissolved in MeOH/THF (2:1, 50 mL) and shaken with

10% Pd/C under 50 psi of hydrogen pressure for 24 hours. TLC showed that the reaction was incomplete. Additional 10% Pd/C was added (500 mg) and the suspension was shaken for an additional 24 hours. The suspension was then filtered and the filtrate concentrated to a solid (4.75 g). The solid was dissolved in CH₂Cl₂ (30 mL) and the resulting solution cooled to 0 °C. To this solution was added oxalyl chloride followed by one drop of DMF from a 9-inch disposable pipette. The solution was stirred for six hours and then concentrated to a solid which was dissolved in additional CH₂Cl₂ (30 mL). The solution was again concentrated to a semi-solid which was dissolved in additional CH₂Cl₂ (50 mL), and the resulting solution added dropwise to a chilled (5 °C) and mechanically stirred solution of NH₄OH (10 mL) over approximately five minutes. The suspension was then concentrated to a solid/aqueous mixture which was extracted with ethyl acetate (2 x 100 mL). The ethyl acetate extracts were combined and dried over MgSO₄, filtered, and the filtrate concentrated to a crude solid which was adsorbed onto silica gel (50 g) using CH₂Cl₂/THF. The solid was then chromatographed on silica gel (EtOAc/Hexane) to give 2.5 grams of off-white solid (40% yield). This material was determined to be 100% pure by LC/MS. H-NMR gave signals consistent with the product's structure and indicated greater than 98% purity.

Example 23. Preparation of Compound AE [3-(6-Methoxynaphthalen-2-yl)-butyramide].

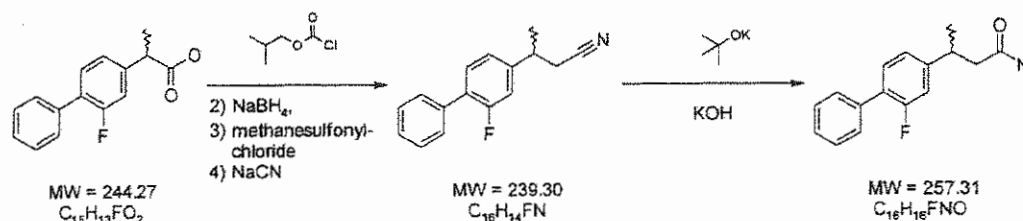


[00105] To a chilled (0°C) solution of lithium bis(trimethylsilyl)amide (1.0 M, 50 mL) was dropwise added a solution of trimethylphosphonoacetate, keeping the temperature below 10 °C. The solution was then allowed to warm to room temperature and stirred for an additional ten minutes after which a solution of 2-acetyl-6-methoxynaphthalene in THF (20 mL) was added in one portion. The solution was slowly heated to 50 °C for fourteen hours. The solution was cooled to room temperature then diluted with a 10% NH₄Cl solution (100 mL), and extracted with ethyl acetate (2 x 100 mL). The organic layers were combined and dried over

MgSO₄, filtered, and filtrate concentrated to a white solid which was recrystallized from hexane/ethyl acetate to give 5.88 grams of 3-(6-methoxynaphthalen-2-yl)but-2-enoic acid methyl ester intermediate (92% yield).

[00106] To a solution of 3-(6-methoxynaphthalen-2-yl)but-2-enoic acid methyl ester in THF/MeOH was added a solution of sodium hydroxide in H₂O (15 mL). The resulting solution was stirred at room temperature for 12 hours and acetic acid (3 grams) was added. The solution was then concentrated to a solid residue. The solid was dissolved in ethyl acetate (150 mL) and washed with H₂O (3 x 100 mL). The ethyl acetate extracts were combined and dried over MgSO₄, filtered, and concentrated to a solid which was then dissolved in MeOH/THF (2:1, 50 mL) and shaken with 10% Pd/C under 50 psi of hydrogen pressure for 24 hours. TLC showed that the reaction was incomplete. Additional 10% Pd/C was added (500 mg) and the suspension was shaken for an additional 24 hours. The suspension was then filtered and the filtrate concentrated to a semi-solid (4.97 g). The solid was dissolved in CH₂Cl₂ (30 mL) and the resulting solution cooled to 0 °C. To this solution was added oxalyl chloride followed by one drop of DMF from a 9-inch disposable pipette. The solution was stirred for six hours and then concentrated to a solid which was dissolved in additional CH₂Cl₂ (30 mL). The solution was again concentrated to a semi-solid which was dissolved in additional CH₂Cl₂ (50 mL), and the resulting solution added dropwise to a chilled (5 °C) and mechanically stirred solution of NH₄OH (10 mL) over approximately fifteen minutes. The suspension was then concentrated to a gummy/aqueous mixture which was extracted with ethyl acetate (2 x 100 mL). The ethyl acetate extracts were combined and dried over MgSO₄, filtered, and the filtrate concentrated to a crude solid which was adsorbed onto silica gel (50 g) using CH₂Cl₂/THF. The solid was then chromatographed on silica gel (EtOAc/hexane) to give 1.87 grams of off-white solid (32% yield). This material was determined to be 100% pure by LC/MS. H-NMR gave signals consistent with the product's structure and indicated greater than 98% purity.

Example 24. Preparation of Compound AX [3-(2-Fluoro-biphenyl-4-yl)butyramide].



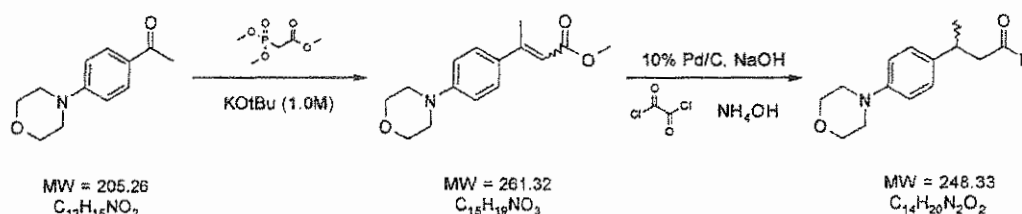
[00107] To a chilled (0 °C) solution of 2-(2-fluoro-biphenyl-4-yl)propionic acid in THF was added isobutyl chloroformate followed by dropwise addition of TEA. The resulting white slurry was allowed to stir for 1 hour and then diluted with THF (50 mL) and filtered. The filter cake was washed with additional THF (50 mL) and the filtrate was concentrated to approximately 50 mL using a rotary evaporator. The concentrated filtrate was then stirred at -20 °C and a solution of $NaBH_4$ in H_2O (20 mL) was dropwise added over a period of 15 minutes. The resulting suspension was stirred for 2 hours at 0 °C, diluted with water (200 mL), and extracted with ethyl acetate (2 x 100 mL). The ethyl acetate layers were combined and washed with 1.0 N HCl solution (100 mL) followed by a 5% bicarbonate solution wash (100 mL). The ethyl acetate solution was then concentrated to an oily residue of 2-(2-fluoro-biphenyl-4-yl)propanol (4.47 g, 95% yield).

[00108] To a chilled (0 °C) solution of 2-(2-fluoro-biphenyl-4-yl)propanol in CH_2Cl_2 was added methanesulfonyl chloride followed by dropwise addition of TEA. The resulting white slurry was allowed to stir for 1 hour and then diluted with H_2O (200 mL). The suspension was extracted with CH_2Cl_2 (2 x 100 mL). The CH_2Cl_2 layers were combined and with water (2 x 100 mL) and a 5% NH_4OH solution (100 mL). The CH_2Cl_2 layer was then washed with additional H_2O (200 mL) and dried over $MgSO_4$. The CH_2Cl_2 layer was concentrated to an oily residue which was dissolved in anhydrous DMF (50 mL). This solution was treated with NaCN and stirred at 60 °C for 14 hours. The TLC indicated one major less polar eluting product (relative to mesylate) and several minor less polar eluting products relative to both the major and mesylate products. The reaction was cooled to room temperature and diluted with H_2O (100 mL). The solution was extracted with ethyl acetate (2 x 100 mL), dried over $MgSO_4$, and concentrated to an oily residue which was chromatographed on

silica gel (90% Hex, 10% EtOAc) to give 3-(2-fluoro-biphenyl-4-yl)butyronitrile as an oil which slowly solidified on standing at room temperature (2.05 g, 49% yield).

[00109] To a solution of 3-(2-fluoro-biphenyl-4-yl)butyronitrile in *tert*-butyl alcohol was added 1.87 g of finely powdered potassium hydroxide. The resulting suspension was stirred and heated to 70 °C for 2.5 hours and cooled to room temperature. The reaction suspension was diluted with 1.0 N HCl solution (100 mL) and extracted with ethyl acetate (2 x 100 mL). The ethyl acetate extracts were combined and washed with 5% bicarbonate solution (100 mL) and then with H₂O (100 mL). The organics were then dried over MgSO₄, and concentrated to a white solid which was re-crystallized several times with EtOAc/Hex to give white flaky prisms (1.62 g, 75% yield).

Example 25. Preparation of Compound AY [3-(4-Morpholin-4-yl-phenyl)-butyramide].

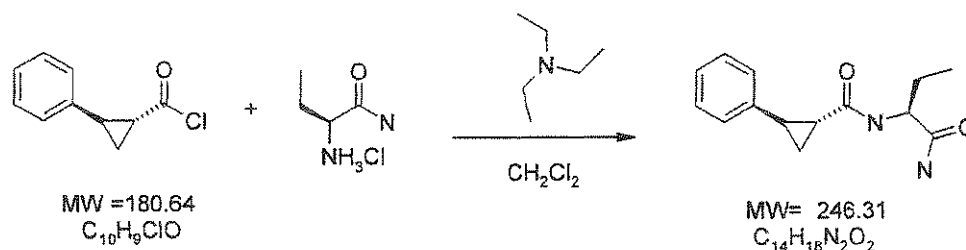


[00110] To a chilled (0 °C) solution of potassium *tert*-butoxide (1.0 M, 37.1 mL) was dropwise added a solution of trimethylphosphonoacetate, keeping the temperature below 25 °C. The solution was then allowed to warm to room temperature and stirred for an additional five minutes, after which a solution of 4-morpholinoacetophenone in THF (20 mL) was added in one portion. The solution was slowly heated to 60 °C for 36 hours. The solution was cooled to room temperature, then diluted with a 1.0N HCl solution (100 mL), and extracted with ethyl acetate (2 x 100 mL). The organic layers were combined and dried over MgSO₄, filtered, and the filtrate concentrated to a white solid which was recrystallized from hexane/ethyl acetate to give 3.33 grams of 3-(4-morpholinophenyl)but-2-enoic acid methyl ester intermediate (69.9% yield).

[00111] To a solution of 3-(4-morpholinophenyl)but-2-enoic acid methyl ester in THF/MeOH (1:1) was added a solution of sodium hydroxide in H₂O (15 mL). The resulting solution was stirred at room temperature for 15 hours and acetic acid (3 grams) was added. The pH of the solution was measured at 6.5. The solution was

then concentrated to an oil. The oil was dissolved in ethyl acetate (150 mL) and washed with H₂O (3 x 100 mL). The ethyl acetate extracts were combined and dried over MgSO₄, filtered, and concentrated to an amorphous solid which was then dissolved in MeOH (50 mL) and shaken with 10% Pd/C under 50 psi of hydrogen pressure for 8 hours. TLC showed that the reaction was complete. The suspension was then filtered and the filtrate concentrated to a semi-solid (2.77 g). The semi-solid was dissolved in CH₂Cl₂ (30 mL) and the resulting solution cooled to 0 °C. To this solution was added oxalyl chloride followed by one drop of DMF from a 9-inch disposable pipette. The solution was stirred for four hours and then concentrated to a solid which was dissolved in additional CH₂Cl₂ (30 mL). The solution was again concentrated to a semi-solid which was dissolved in additional CH₂Cl₂ (50 mL), and the resulting solution added dropwise to a chilled (5 °C) and mechanically stirred solution of NH₄OH (15 mL) over approximately five minutes. The solution was then concentrated to a solid/aqueous mixture which was extracted with ethyl acetate (2 x 100 mL). The ethyl acetate extracts were combined and dried over MgSO₄, filtered, and the filtrate concentrated to a crude solid which was adsorbed onto silica gel (50 g) using CH₂Cl₂/THF. The solid was then chromatographed on silica gel (EtOAc/hexane) to give 2.1 grams of beige plates (46% yield). This material was determined to be 100% pure by LC/MS. H-NMR gave signals consistent with the product's structure and indicated greater than 98% purity.

Example 26. Preparation of Compound Q-1 [(1*R*,2*R*)-2-Phenylcyclopropanecarboxylic acid-((*S*)-1-carbamoyl-propyl)amide].



[00112] A solution of *trans*-2-phenyl-cyclopropanecarbonylchloride in CH₂Cl₂ (20 mL) was added dropwise into a solution of L-2-aminobutanamide hydrochloride (1.61 g, 11.6 mmol) and triethylamine (3.36 g, 33.2mmol) in CH₂Cl₂ (60 ml) at zero

degree Celsius. The reaction mixture stirred at room temperature under nitrogen overnight.

[00113] The reaction mixture was evaporated under reduced pressure and resulting residue re-dissolved in ethyl acetate/water mixture. The mixture was transferred into a separatory funnel using H₂O (50 mL) and ethyl acetate (80 mL). The mixture was equilibrated and the aqueous phase was removed. The organic layer was washed with 1.0M HCl (20 mL), H₂O (90 mL) and brine (120 mL) consecutively. The organic layer was dried over anhydrous magnesium sulfate, filtered, and excess solvent was removed under reduced pressure. The resulting orange-brown solid was purified using a Biotage SP4 System (Column Si 40+M 90:10, CH₂Cl₂/MeOH), which afforded 0.365g of white powder (24% yield). This material was determined to be 100% pure by GC/MS. ¹H-NMR gave signals consistent with the product's structure and indicated greater than 98% purity.

[00114] Figures 4A-4O illustrate additional examples of the syntheses of various compounds and key intermediates (Schemes 1-15), drawn from the literature of synthetic organic chemistry, from which skilled artisans will be able to envision the preparation of various additional compounds of the present invention.

Example 27. Demonstration of Biological Activity in Rodent Anticvulsant Models of Epilepsy.

[00115] The anticonvulsant activities of various compounds of the invention were demonstrated *in vivo* in various rodent (mouse and rat) models of epilepsy. The animal testing was performed as described in White *et al.*, "Discovery and preclinical development of antiepileptic drugs," in *Antiepileptic Drugs*, 5th ed., Levy *et al.* (Eds.), Lippincott Williams and Wilkins, Philadelphia, PA, 2002 (968 pp.), pp. 36-48, and references contained therein, which are hereby incorporated herein in their entirety. The results for compounds A, G, H, I, and F are summarized below in Tables 2 and 3.

TABLE 2. ANTICONVULSANT PROFILES OF COMPOUNDS OF THE PRESENT INVENTION, FOLLOWING I.P. ADMINISTRATION TO MICE

MID ₅₀ or ED ₅₀ (mg/kg) and (PI)*					
Compound	MID ₅₀	MES ^a (PI)	s.c. MET ^b (PI)	AGS ^c (PI)	6 Hz (PI)
A	<100	<100	≤100	-----	>30 (<3.3)
G	<100	<100	≤100	-----	-----
I	<100	<100	≤100	-----	-----
H	158.98	76.11 (2.1)	91.36 (1.74)	22.5 (7.1)	54.98 (2.9)
F	208.37	85.32 (2.4)	85.47 (2.4)	41.30 (5)	80.8 (2.6)

MID₅₀ = median minimal motor impairment dose; ED₅₀ = median effective dose;

- a) Maximal Electroshock Seizure test.
 b) Subcutaneous Metrazol Seizure threshold.
 c) Audiogenic Seizure susceptible.

(PI)* = Protective Index = MID₅₀/ED₅₀.

TABLE 3. MINIMAL MOTOR IMPAIRMENT AND PROFILES OF ANTICONVULSANT ACTIVITY OF COMPOUNDS OF THE PRESENT INVENTION IN RATS

Compound	MID ₅₀ (mg/ kg)	MES (mg/ kg) (PI)	s.c. MET (mg/ kg) (PI)
A	244.90	28.80 (8.5)	45.00 (5.4)
H	>500	56.73 (>9)	88.09 (>5.7)
F	>500 (none observed)	26.39 (>19)	>250

Example 28. Demonstration of Biological Activity in Rat Anticonvulsant Models of Status Epilepticus.

[00116] The anticonvulsant activities of various compounds of the present invention were also demonstrated *in vivo* in two rat models of *status epilepticus*. The animal testing was performed using the protocols developed in the Anticonvulsant Screening Program (ASP) at the National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH). The results are summarized below in Table 4.

Table 4. Compound Activities in *Status Epilepticus* Models (ASP/ NINDS/ NIH data)
(Pilocarpine-induced *Status Epilepticus* in Rats)

Counter-Measures Screening: Test 71 = "Prevention of Pilocarpine-induced Status Epilepticus, in Rats" Test 72 = "Pilocarpine-induced Status Epilepticus - Acute Intervention, in Rats"		
	(Prevention)	(Acute Intervention)
Test Compound	Test 71 (time 0)	Test 72 (30 min.)
A ^a	65 mg/kg	120 mg/kg
B	300 mg/kg	----
D	200 mg/kg	400 mg/kg
O	450 mg/kg	Inactive
L	450 mg/kg	----
M	600 mg/kg	Inactive
K	300 mg/kg	600 mg/kg
I ^a	65 mg/kg	130 mg/kg
H ^a	200 mg/kg	176 mg/kg
G ^a	200 mg/kg	200 mg/kg
F ^a	65 mg/kg	----
J	600 mg/kg	----
AW ^a	<450 mg/kg	----

^aWeight gain or weight maintenance in rats.

Example 29. Demonstration of Lack of Toxicity in *In Vitro* (LDH and Cell Proliferation) Assays.

[00117] Compounds A, I, H, and F were tested by Stem Cell Innovations, Inc. (Houston, TX) in their ACTIVTox[®] Human Liver Cell-based assays (using C3A hepatocyte cells). Specifically, the compounds were tested in the LDH release assay, which determines the release of Lactate DeHydrogenase (an indicator of cell death) at various concentrations of test compound.

[00118] A concentration of 100 μ M of test compound is a much higher level of exposure to liver cells than would ever be expected under physiological conditions. Therefore, using 100 μ M as a standard test concentration (for comparative purposes), the ratio of the absorbance (which measures the level of LDH release) resulting from the presence of the test compound *versus* the negative control is a value known as the "average (or mean) fold control" (Average Fold Control = Average of Absorbance/Average of Negative Control). An average fold control value below 1.75 indicates that the test compound has no cyto- or hepatotoxic activity in the LDH release assay.

[00119] The ACTIVTox data (see Table 5, below) show that the compounds A, I, H and F are not cyto- or hepatotoxic at physiologically relevant concentrations (*i.e.*, < 100 μ M).

Table 5. Cytotoxic and hepatotoxic data (mean fold control at 100 μ M) from the ACTIVTox LDH release assay.

	LDH release, mean
Test Compound	fold control (at 100 μ M)
A	1.05
I	1.03
H	1.32
F	1.47

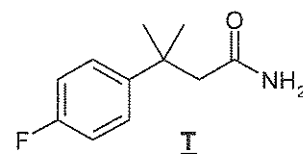
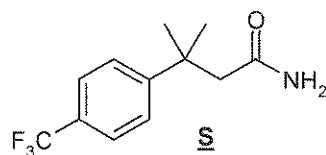
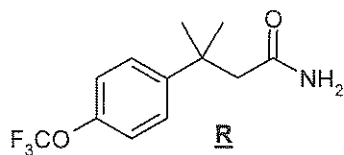
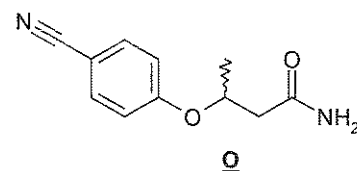
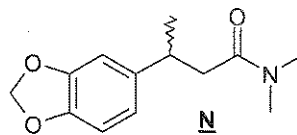
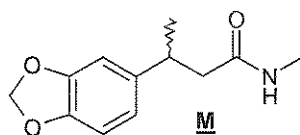
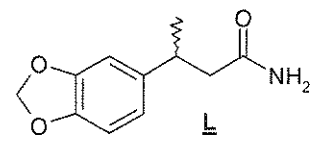
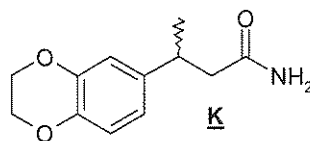
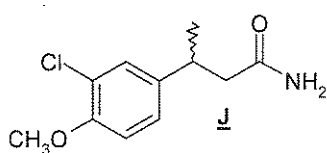
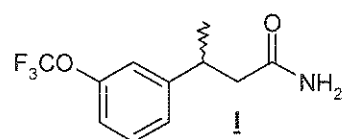
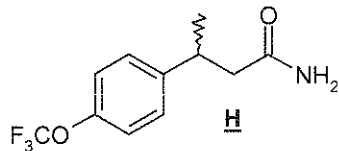
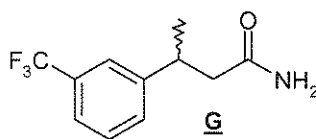
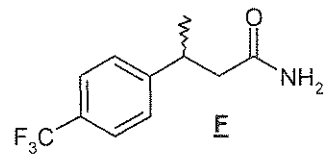
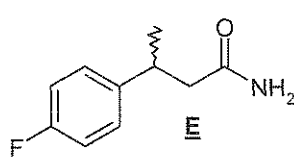
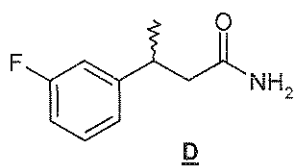
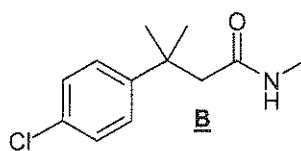
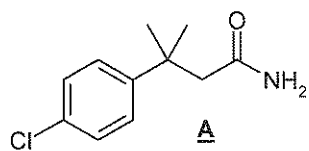
Compounds A and I were also tested in the ACTIVTox Cell Proliferation Assay and were found to be non-toxic to proliferating cells at a concentration of 100 μ M, with mean fold control values of 1.15 and 1.25, respectively.

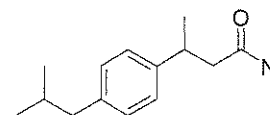
[00120] The present invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope. All references recited herein are incorporated herein in their entirety by specific reference.

What is claimed is:

CLAIMS

1. A CNS-active compound having one of Formulas A, B, D-O, R, S, T, or AW:





Formula AW

2. A pharmaceutical composition, the composition comprising:
a pharmaceutically-acceptable carrier; and
a CNS-active compound of claim 1 combined with the carrier.
3. A pharmaceutical composition as in claim 2, further comprising an excipient.
4. A pharmaceutical composition as in claim 2, wherein the CNS-active compound is present in a therapeutically effective amount.
5. A pharmaceutical composition as in claim 4, wherein the therapeutically effective amount is sufficient for at least one of the following:
 - to provide anticonvulsant activity to a subject;
 - to treat and/or prevent convulsions in a subject;
 - to treat and/or prevent seizures in a subject;
 - to treat and/or prevent spasticity in a subject;
 - to treat and/or prevent affective mood disorders in a subject;
 - to treat and/or prevent bipolar mood disorder in a subject;
 - to treat and/or prevent chronic headaches in a subject;
 - to treat and/or prevent cluster headaches in a subject;
 - to treat and/or prevent migraine headaches in a subject;
 - to treat and/or prevent restlessness syndromes in a subject;

to treat and/or prevent neuropathic pain in a subject; or
to treat and/or prevent movement disorders in a subject.

6. The use of a CNS-active compound of claim 1 in the manufacture of a medicament for the treatment of central nervous system diseases and disorders.

7. The use as in claim 6, wherein the CNS-active compound is combined with a pharmaceutically-acceptable carrier.

8. The use as in claim 6, wherein the CNS-active compound is to be administered to the subject in a therapeutically effective amount.

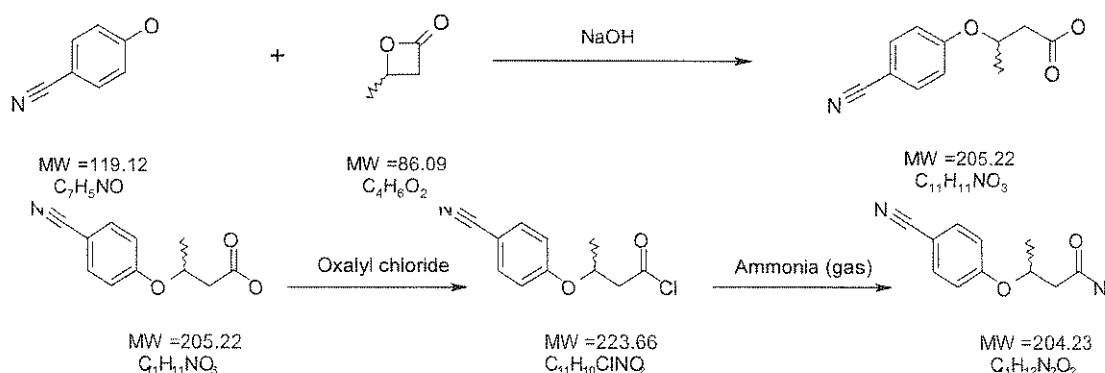
9. The use as in claim 8, wherein the therapeutically effective amount is sufficient for at least one of the following:

to provide anticonvulsant activity to a subject;
to treat and/or prevent convulsions in a subject;
to treat and/or prevent seizures in a subject;
to treat and/or prevent spasticity in a subject;
to treat and/or prevent affective mood disorders in a subject;
to treat and/or prevent bipolar mood disorder in a subject;
to treat and/or prevent chronic headaches in a subject;
to treat and/or prevent cluster headaches in a subject;
to treat and/or prevent migraine headaches in a subject;
to treat and/or prevent restlessness syndromes in a subject;
to treat and/or prevent neuropathic pain in a subject: or
to treat and/or prevent movement disorders in a subject.

10. The use as in claim 8, wherein the therapeutically effective amount is sufficient to treat and/or prevent the symptoms of at least one of anxiety, depression, insomnia, migraine headaches, schizophrenia, Parkinson's disease, spasticity, Alzheimer's disease, bipolar disorder, chronic or neuropathic pain, stroke, chronic neurodegenerative diseases, Huntington's disease, traumatic brain injury, spinal cord injury, or *status epilepticus*.

11. The use as in claim 8, wherein the therapeutically effective amount is sufficient for a chemical countermeasure.

12. A method of manufacturing a CNS-active compound [3-(4-cyanophenoxy)butyramide], the method comprising:



13. A method as in claim 12, further comprising:
 heating 4-cyanophenol in a basic solution at reflux;
 adding β -butyrolactone to the refluxing solution;
 cooling the solution to room temperature;
 preparing a biphasic mixture of the solution by adding water and diethyl ether;
 removing a diethyl ether layer after formation;
 acidifying the aqueous layer after formation by adding a HCl solution at about pH ~2;
 extracting the acidified aqueous layer with ethyl acetate;
 drying the ethyl acetate layer to yield 3-(4-cyanophenoxy)butyric acid];
 preparing a solution of 3-(4-cyanophenoxy)butyric acid in an organic solvent;

treating the solution with oxalyl chloride to obtain [3-(4-cyanophenoxy)butyryl chloride];

bubbling ammonia gas through the solution of 3-(4-cyanophenoxy)butyryl chloride; and

obtaining [3-(4-cyanophenoxy)butyramide] from the solution.

**NOVEL COMPOUNDS ADVANTAGEOUS IN THE TREATMENT OF
CENTRAL NERVOUS SYSTEM DISEASES AND DISORDERS**

ABSTRACT

A series of novel compounds showing anticonvulsant activity is described. Such pharmaceutically active compounds may also show utility in the treatment of other central nervous system ("CNS") diseases and disorders, such as anxiety, depression, insomnia, migraine headaches, schizophrenia, Parkinson's disease, spasticity, Alzheimer's disease, and bipolar disorder. Furthermore, such compounds may additionally find utility as analgesics (e.g., for the treatment of chronic or neuropathic pain) and as neuroprotective agents useful in the treatment of stroke(s), chronic neurodegenerative diseases (such as Alzheimer's disease and Huntington's disease), and/or traumatic brain and/or spinal cord injuries. Moreover, these/such compounds may also be useful in the treatment of status epilepticus and/or as chemical countermeasures.

FIG. 1