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Analogs of GHB Lacking GABAergic Activity

Key Investigator
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Field
Narcolepsy
Hypersomnia
Sleep Disorders

Technology
Therapeutic
New Chemical Entity

Advantages
Benefits of GHB in treating sleep disorders without potential for abuse.

Status
Available for licensing

Patent Status
U.S. Patent 7,838,556

UMB Docket Reference
AC-2006-050

External Reference
Bioorganic & Medicinal Chemistry Letters 15 (2005) 3201-3202

J. Pharmacol. Exp. Ther., 313, 1314 (2005) [11]

Summary
The present invention relates to esthers of 3-hydroxyphenyacetic acid and their use to treat narcolepsy and other sleep disorders. Gamma-hydroxybutyric acid (GHB) is a known agonist for the GHB receptor. Unfortunately it also acts at GABA receptors directly and through its metabolization into alpha aminobutyric acid (GABA). As a result, GHB is abused for its euporigenic effects. The investigators have designed several analogs of GHB that lack any GABAergic activity. These new chemcial entities (NCE) represent GHB active therapeutics which act exclusively with GHB receptors and therefore lack the euporigenic activity of GHB.

Market
Narcolepsy is a profoundly disabling, life-long sleep disorder characterized by excessive daytime sleepiness (hypersomnia), often in association with cataplexy. Narcolepsy has an estimated prevalence in the United States of between one in two thousand. It is estimated that only 25% of narcolepsy patients have been diagnosed to date.

Therapeutics to treat narcolepsy are either designed to reduce excessive sleepiness or are REM-suppressing. REM-supressing drugs are used to reduce the systems of cataplexy, hallucinations and sleep paraylysis.

It is expected that the global market for narcolespy therapeutics will reach $2.0 billion dolars by 2020. The market for narcolepsy therapeutics is growing at 2.8% CAGR.

Technology
The inventors have created a series of compounds having the general structure shown. The functional group R can be either an aromatic group or aryl alkyl substituent. The 3-esthers of 3-hydroxyphenylacetic acid claimed in U.S. Patent 7,838,556 were shown to have a high affinity at GHB sites, no significant affinity at GABA receptors and were not rapidly metabolized to GABAergic ligands. The lack of GABA affinity makes these compounds excellent candidates for treating sleep disorders through GHB receptor binding.

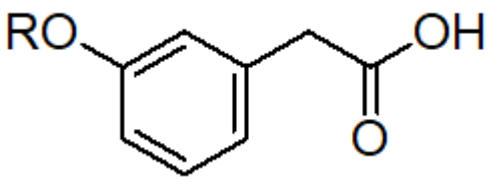

TABLE 1

Compound	[^{3}H]NCS382 IC_{50} (μM)	Percent displacement of [^{3}H]GABA at 1 mM	
	GHB sites	$GABA_A$	$GABA_B$
1 (GHB)[a] Comparative	25.0 ± 1.8	35.5 ± 3.7	41.1 ± 3.1
7[a] Comparative	12.0 ± 5.5	44.2 ± 2.0	14.0 ± 4.0
8 Comparative	210 ± 62	6.3 ± 1.7	6.5 ± 1.0
9 (UMB109) Inventive	4.5 ± 1.9	17.4 ± 13.2	6.0 ± 2.6
10 (UMB108) Inventive	8.3 ± 1.6	15.1 ± 7.5	-1.2 ± 7.3
11 **Inventive**	46.0 ± 10	11.0 ± 6.2	-4.7 ± 4.7
12 (UMB119) Inventive	16.3 ± 0.8	2.7 ± 0.5	-5.5 ± 1.2

[a]Data from **Carter et al., Novel γ-Hydroxybuyric Acid (GHB) Analogs Share Some, but Not All, of the Behavioral Effects of GHB and $GABA_B$ Receptor Agonists**, *J. Pharmacol. Exp. Ther.*, 313, 1314 (2005) [11].

Technology Status
Two lead compounds have been identified having the general structure shown above. Additional new chemical entities are being developed and behavioral assay studies planned.

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