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Gano

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(54) **SUBSTITUTED**
3-ISOBUTYL-9,10-DIMETHOXY-1,3,4,6,7,11B-
HEXAHYDRO-2H-PYRIDO[2,1-
A]ISOQUINOLIN-2-OL COMPOUNDS AND
METHODS RELATING THERETO

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(51) **Int. Cl.**
C07D 455/06 (2006.01)
A01N 43/42 (2006.01)

(52) **U.S. Cl.** **546/95**; 514/294

(58) **Field of Classification Search** 546/95;
514/294

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,843,591 A 7/1958 Brossi et al.
2,852,518 A 9/1958 Morgan
3,209,005 A 9/1965 Brossi et al.
2003/0087803 A1 5/2003 Latvin et al.

FOREIGN PATENT DOCUMENTS

WO WO91/16920 A1 11/1991
WO WO99/30561 A1 6/1999
WO WO2005/077946 A1 8/2005
WO WO2006/053067 A2 5/2006
WO WO2007/005283 A2 1/2007
WO WO2007/007105 A1 1/2007
WO WO2007/017643 A1 2/2007
WO WO2007/017654 A1 2/2007

OTHER PUBLICATIONS

Aranda et al. European Journal of Medicinal Chemistry, 25, 369-374, 1990.*

Kilbourn et al. Chirality, 9, 59062, 1997.*

Vig et al. Pharmaceutical Research, 20 (9), 1381-1388, 2003.*

Cho et al., Annual Reports in Medicinal chemistry, 41, 395-407, 2006.*

Communication pursuant to Article 94(3) (Form 2906) in EP App. No. 07864160.2 mailed Aug. 13, 2009.

Stock, A. M. et al. Structure and Tautomerism of the Esters of Several beta-Substituted Pyruvic Acids, Journal of Organic Chemistry, 1958, 1840-1848, 23.

Pletscher, A. et al, Benzoquinolizine Derivatives: A New Class of Monoamine Decreasing Drugs with Psychotropic Action, International Review of Neurobiology, 1962, 275-306.

Schwarz, D. E. et al, Metabolice Studies of Tetrabenazine, A Psychotropic Drug in Animals and Man, Biochemical Pharmacology, 1966, 645-655, 15.

Pritsch, L. E. et al, On the Pharmacology of a Benzoquinolizine Derivative: Ro-1284, Pharmacology 1969, 113-123, 2.

Mehvar, R. et al, Direct Injection High-Performance Liquid Chromatography of Tetrabenazine and Its Metabolite in Plasma of Humans and Rats, Journal of Pharmaceutical Sciences, 1986, 1006-1009, 75(10).

Mehvar, R. et al, Pharmacokinetics of Tetrabenazine and Is Major Metabolite in Man and Rat, Drug Metabolism and Disposition, 1987, 250-255, 15(2).

Aranda, G. et al, Synthesis and biological activity of iodinated and photosensitive derivatives of tetrabenazine, European Journal of Medicinal Chemistry, 1990, 369-374, 25.

Kilborn, M. et al, Binding of alpha-dihydro-tetrabenazine to the vesicular monoamine transporter is stereospecific, European Journal of Pharmacology, 1995, 249-252, 278.

Lee, L. C., In Vitro and In Vivo Studies of Benzisoquinoline Ligands for the Brain Synaptic Vesicle Monoamine Transporter, Journal of Medicinal Chemistry, 1996, 191-196, 39.

Kilborn, M.R. et al, Absolute Configuration of (+)-alpha-Dihydro-tetrabenazine, an Active Metabolite of Tetrabenazine. Chirality, 1997, 59-62, 9.

Vig, B. S. et al, Amino Acid Ester Prodrugs of Floxuridine: Synthesis and Effects of Structure, Stereochemistry, and Site of Esterification on the Rate of Hydrolysis, 2003, 1381-1388, 20(9). Kim, I. et al, A Novel Nucleoside Prodrug-Activating Enzyme: Substrate Specificity of Biphenyl Hydrolase-like Protein, Molecular Pharmaceutics, 2004, 117-127, 1(2).

Song, X., et al, Amino Acid Ester Prodrugs of the Anticancer Agent Gemcitabine: Synthesis, Bioconversion, Metabolic Bioevasion, and hPEPT1-Mediated Transport, Molecular Pharmaceutics, 2005, 157-167, 2(2).

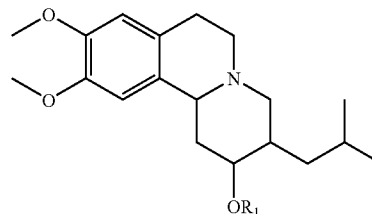
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(57) **ABSTRACT**

Substituted 3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol compounds are disclosed that are inhibitors of the vesicular monoamine transporter 2 (VMAT2). The compounds of this invention have the structure:



wherein R₁ is as defined herein, including stereoisomers and pharmaceutically acceptable salts and solvates thereof. Also disclosed are compositions containing a compound of this invention in combination with a pharmaceutically acceptable carrier, as well as methods relating to the use in a subject in need thereof.

OTHER PUBLICATIONS

Lorenz!, P. L. et al, Amino Acid Ester Prodrugs of 2-Bromo-5,6-dichloro-1-(beta-D-ribofuranosyl)benzimidazole Enhance Metabolic Stability in Vitro and in Vivo, The Journal of Pharmacology and Experimental Therapeutics, 2005, 883-890, 314(2).

Zheng, G. et al, Vesicular Monoamine Transporter 2: Role as a Novel Target for Drug Development, The AAPS Journal, 2006, 682-692, 8(4).

Cho, A., Recent Advances in Oral Prodrug Discovery, Annual Reports in Medicinal Chemistry, 2006, 395-407, 41.

Zheng, F. et al, Computational neural network analysis of the affinity of lobeline and tetrabenazine analogs for the vesicular monoamine transporter-2, Bioorganic and Medicinal Chemistry, 2007, 2975-2992, 15.

* cited by examiner

Figure 1a

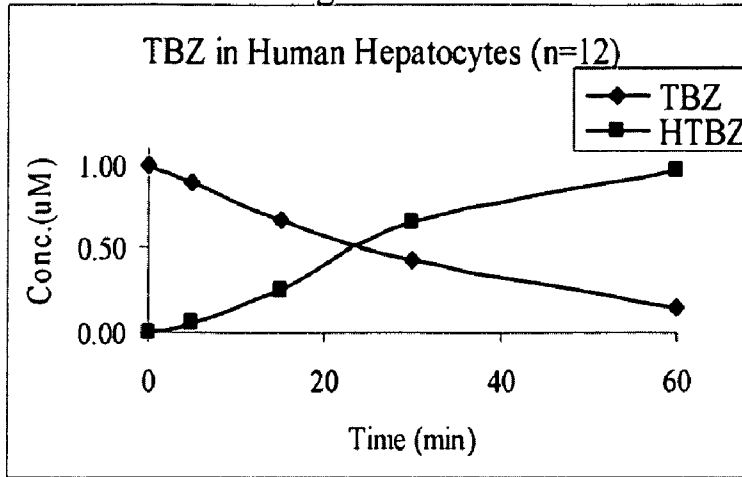


Figure 1b

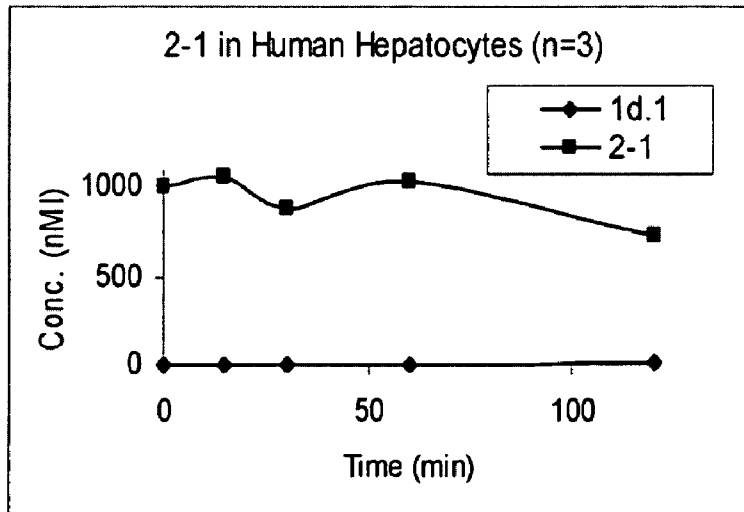


Figure 1c

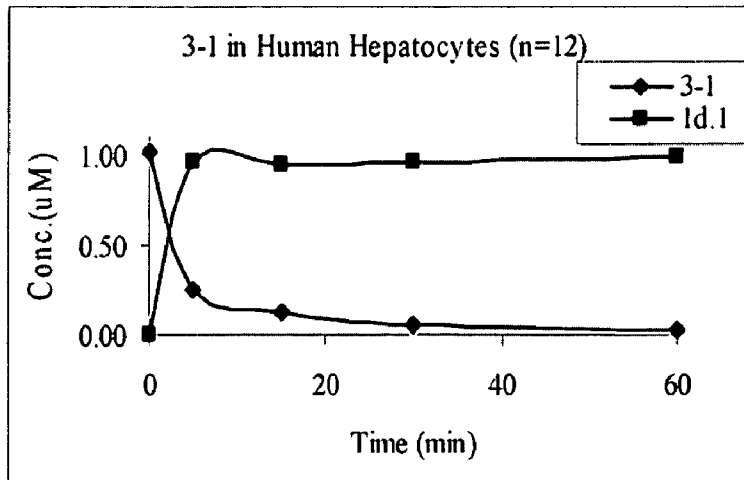


Figure 2a (rat)

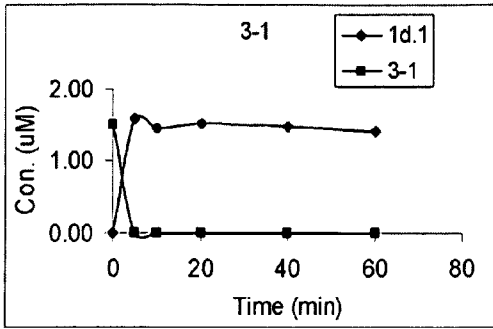


Figure 2b (rat)

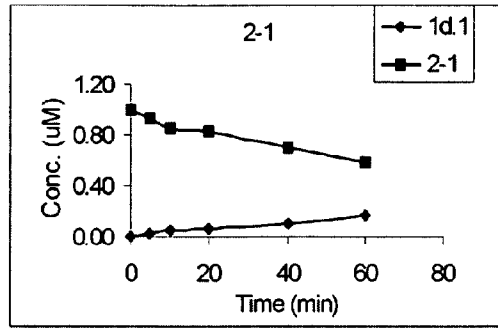


Figure 2c (dog)

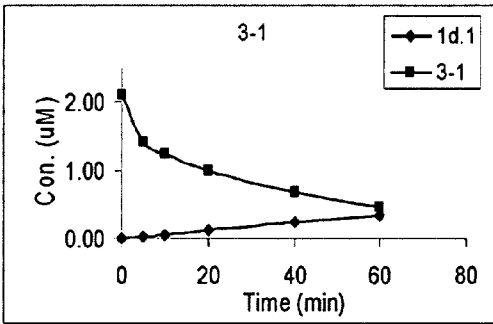


Figure 2d (dog)

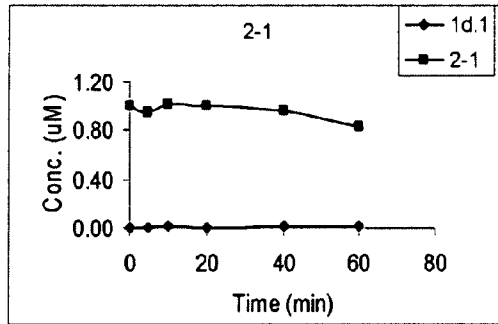


Figure 2e (human)

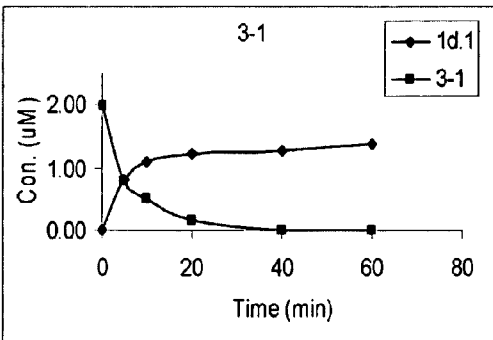


Figure 2f (human)

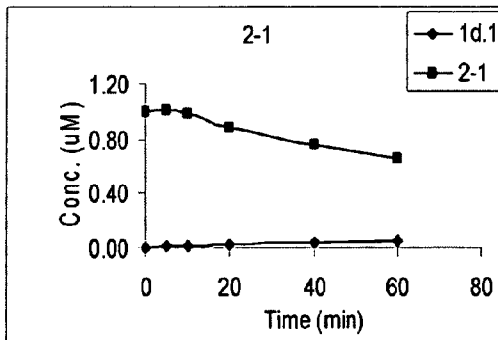


Figure 3a
Plasma Concentration-Time Profile of 10 mg/kg PO of 3-1 and 10 mg/kg PO of 1d.1 to male rats (N=3)

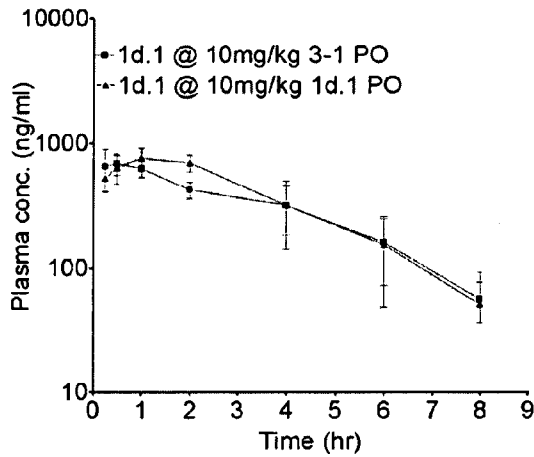


Figure 3b
Plasma Concentration-Time Profile of 10 mg/kg PO of 2-1 to Male Rats (N=3)

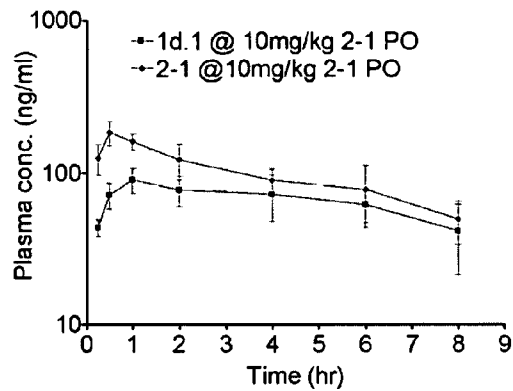


Figure 3c
Plasma Concentration-Time Profile of 6.1 mg/kg PO of 3-1 to Male Dogs (N=3)

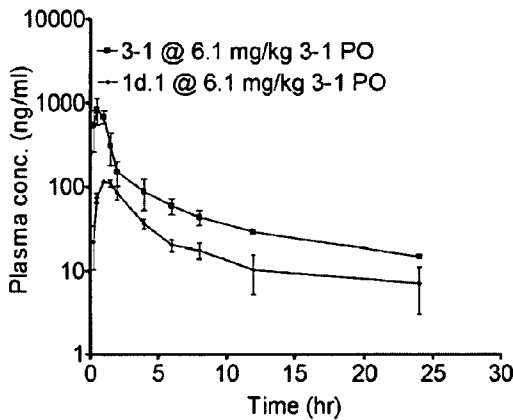
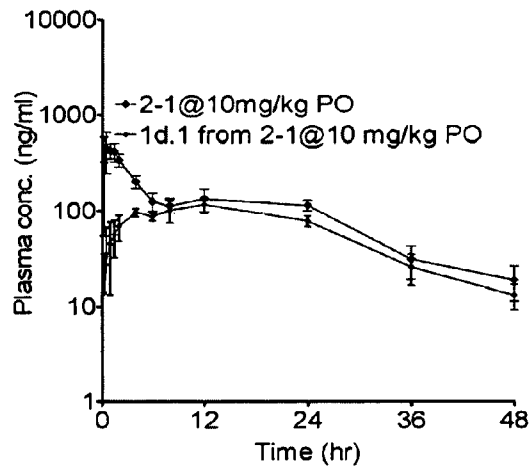


Figure 3d
Plasma Concentration-Time Profile of 10 mg/kg PO of 2-1 to Male Dogs (N=3)



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