ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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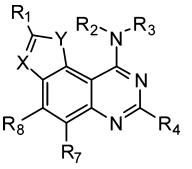
Tricyclic Pyrimidines As Inhibitors of DYRK1A/DYRK1B As Potential Treatment for Down's Syndrome or Alzheimer's Disease

Gerard Rosse*

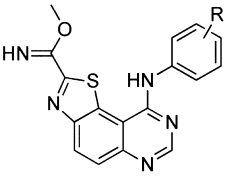
Structure Guided Chemistry, Dart Neuroscience LLC, 7473 Lusk Boulevard, San Diego, California 92121, United States, and Adjunct Associate Professor, Department of Pharmacology and Physiology, College of Medicine, Drexel University, New College Building, 245 North 15th Street, Philadelphia, Pennsylvania 19102, United States

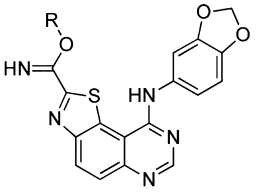
Title:	Tricyclic Pyrimidines As Inhibitors of DYRK1A/DYRK1B As Potential Treatment for Down's Syndrome or Alzheimer's Disease		
Patent/Patent Application Number:	WO 2013/026806A1	**Publication date:**	February 28, 2013
Priority Application:		**Priority date:**	August 17, 2012
Inventors:	Leblond, B.; Casagrande, A.-S.; Désiré, L.; Foucourt A.; Besson, T.		
Assignee Company:	Exonhit SA		
Disease Area:	Alzheimer's disease, Down's Syndrome	**Biological Target:**	DYRK1A/DYRK1B
Summary:	The patent application claims tricyclic pyrimidine derivatives as inhibitors of dual-specific tyrosine-regulated kinases (DYRKs) for the treatment of Alzheimer's disease or Down's Syndrome.		

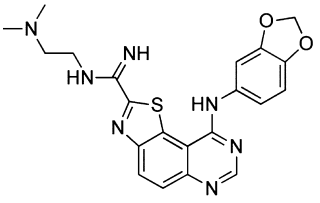
Important Compound Classes:



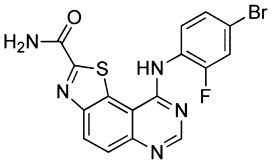
Key Structures:







Compound 33



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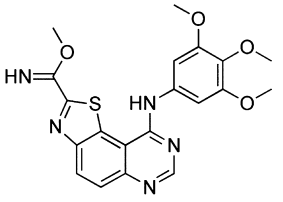

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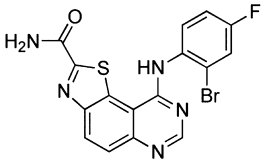
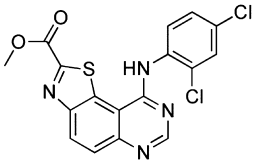


Compound 86



Compound 89

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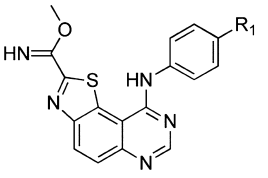
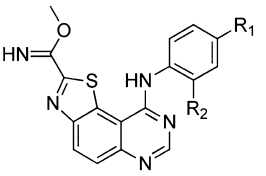
Biological Assays: Sixty-seven compounds described in this invention were evaluated for their ability to inhibit DYRK1A and DYRK1B using an in vitro kinase functional assay

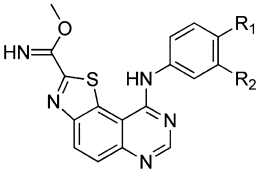
Pharmacological Data: Inhibition of DYRK1A and DYRK1B



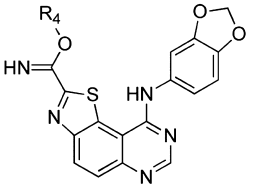
Compound	R_1	DYRK1A (IC_{50} nM)	DYRK1B (IC_{50} nM)
45	OMe	13.08	19.22
56	Cl	1.13	4.74
64	H	1.81	3.48
65	CH_3	0.98	2.83
66	F	6.06	9.64
70	CN	3.89	7.69
74	tBu	39.03	93.84
76	$N(CH_3)_2$	35.64	64.28
80	CF_3	18.26	25.21



Compound	R_1	R_2	DYRK1A (IC_{50} nM)	DYRK1B (IC_{50} nM)
44	F	Br	3.60	6.55
62	OMe	OMe	9.53	11.13
68	Br	F	0.16	0.24
69	F	OMe	0.36	0.59
71	F	Cl	0.99	1.63
72	Cl	Cl	0.22	0.28
78	F	F	0.94	1.07



Compound	R_1	R_2	DYRK1A (IC_{50} nM)	DYRK1B (IC_{50} nM)
60	OH	NO_2	4.91	5.68
67	H	CN	42.70	71.98
75	H	Cl	13.64	18.78
79	OH	F	8.63	11.00



Compound	R_4	DYRK1A (IC_{50} nM)	DYRK1B (IC_{50} nM)
48	Me	1.65	4.20
82	Et	6.02	7.72
83	Bzl	33.93	37.34

Compound	DYRK1A (IC_{50} nM)	DYRK1B (IC_{50} nM)
33	431.2	-
36	194.4	-
61	436.1	485.8
86	26.2	31.5
89	5.1	7.7

Synthesis: Synthesis of 89 examples is described

AUTHOR INFORMATION

Corresponding Author

*E-mail: grosse@dartneuroscience.com.

Notes

The authors declare no competing financial interest.

NOTE ADDED AFTER ASAP PUBLICATION

This paper was published on the Web on 4/26/2013 with an incomplete list of inventors. The revised version was reposted on May 3, 2013.