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

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

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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

Compound 36

Compound 61

Compound 86

Compound 89

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

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Notes
The authors declare no competing financial interest.

■ NOTE ADDED AFTER ASAP PUBLICATION

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