274 3,5-DIARYLAZAINDOLES AS DYRK1A PROTEIN INHIBITORS

Asset Overview

Product Type	Small molecule
Indication	CNS Diseases
Current Stage	Hit to Lead
Target(MoA)	Inhibition of DYRK1A (Dual specificity tyrosine-phosphorylation-regulated kinase 1A)
Brief Description	The present invention discloses compositions of novel DYRK1A protein inhibitors based on a 3,5-diarylazaindole motif and their preparation and use as medications in the treatment of cognitive disorders associated with dysfunction of DYRK1A protein, with Down's syndrome and with Alzheimer's disease
Organization	French National Centre for Scientific Research (CNRS)

Differentiation

□ **Importance of DYRK1A**

- DYRK1A (a member of DYRK family) has shown a significant role in a signaling pathway regulating cell proliferation in brain development
- Its defects associated with neurological disorders including Down syndrome, and Autism spectrum disorder, and Alzheimer's disease

□ **3,5-diaryl 7-azaindoles can inhibit DYRK1A with low toxicity**

- They discovered that the 3,5-diaryl 7-azaindoles are able to inhibit DYRK1A protein with low ICs values, are selective for this kinase and have little or no cytotoxicity
- Numerous compounds were prepared and the ability to inhibit DYRK1A tyrosine kinase was evaluated
- Among the compounds synthesized, the most effective is able to inhibit tyrosine kinase A with an IC50 of about 1-3 nM
- Others: synthetic derivatives based on a 2-aminoimidazolin-4-one motif (40 nM), 7-azaindoles substituted at the 3-position by amino-pyrimidines (about several tens of nM), Harmine; 7-Methoxy-1-methyl-9H-pyrido[3,4-b]indole (80 nM)

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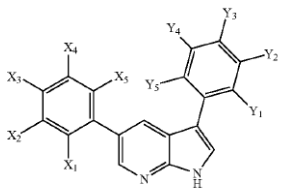
Key Data

Compositions of novel DYRK1A protein inhibitors based on a 3,5-diarylazaindole motif and their preparation



Example	X_1	X_2	X_3	X_4	X_5	Y_1	Y_2	Y_3	Y_4	Y_5	IC_{50}[1]
A	OH	H	H	H	H	H	H	H	H	H	3592
B	H	H	H	H	H	H	H	H	H	H	7490
C	H	H	OH	H	H	H	H	H	H	H	326
E	H	OH	OH	H	H	H	H	H	H	H	160
F	OH	H	OH	H	H	H	H	H	H	H	154
Ia	H	OH	H	H	H	H	OH	H	H	H	105
Ib	H	H	OH	H	H	H	H	OH	H	H	23.1
Ic	H	H	OH	H	H	H	F	OMe	H	H	41.5
I'a	OH	H	OH	H	H	H	H	OH	H	H	11.7
I'b	H	OH	OH	H	H	H	H	OH	H	H	3.0
I'c	H	OH	OH	H	H	H	OH	OH	H	H	12.4
I'd	OH	H	OH	H	H	H	OH	OH	H	H	14.3
I'e	OH	H	H	OH	H	H	OH	OH	H	H	39.1
I'f	H	OH	OH	H	H	H	H	F	H	H	20.7
I'g	H	OH	OH	H	H	H	F	F	H	H	56.6
I'h	H	H	OH	H	H	H	F	OH	H	H	9.3

[1]IC_{50} is expressed in nanomoles (nmol).

The ICs values for DYRK1A protein of the various compounds were then evaluated.

Ex.	X_1	X_2	X_3	X_4	X_5	Y_1	Y_2	Y_3	Y_4	Y_5	10^{-5} M[1]	10^{-6} M[1]
B	H	H	H	H	H	H	H	H	H	H	85	15
C	H	H	OH	H	H	H	H	H	H	H	94	5
E	H	OH	OH	H	H	H	H	H	H	H	63	12
F	OH	H	OH	H	H	H	H	H	H	H	75	9
Ia	H	OH	H	H	H	H	OH	H	H	H	77	4
Ib	H	H	OH	H	H	H	H	OH	H	H	95	51
Ic	H	H	OH	H	H	H	F	OMe	H	H	—[2]	23
I'a	OH	H	OH	H	H	H	H	OH	H	H	83	21
I'c	H	OH	OH	H	H	H	OH	OH	H	H	11	2
I'f	H	OH	OH	H	H	H	H	F	H	H	—	15
I'g	H	OH	OH	H	H	H	F	F	H	H	—	22
I'h	H	H	OH	H	H	H	F	OH	H	H	—	13

[1]Expressed as a percentage of inhibition of KB cell growth.
[2]"—" indicates that the value was not determined.

Cytotoxicity of the compounds was evaluated on cells of the KB line at various concentrations.

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Intellectual Property

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