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PATENT HIGHLIGHT

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Dual Leucine Zipper Kinase Inhibitors: Potential Treatments for Neurodegenerative Diseases

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Title:	3-Substituted Pyrazoles and Use as DLK Inhibitors		
Patent Application Number:	WO 2014/111496 A1	**Publication Date:**	24 July 2014
Priority Application:	US 61/754,501	**Priority Date:**	18 January 2013
Inventors:	Estrada, A.; Liu, W.; Patel, S.; Siu, M.		
Assignee Company:	(For all designated States except US): F. Hoffmann-La Roche AG, Grenzacherstrasse 124, CH-4070 Basel (CH) (For US only): Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080 (USA)		
Disease Area:	Neurodegenerative diseases and disorders	**Biological Target:**	Dual leucine zipper-bearing kinase (DLK); a.k.a. MAP3K12

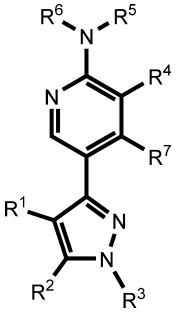
Summary:

The invention in this patent application relates to 3-substituted pyrazole derivatives represented generally by formula (I). These compounds are inhibitors of DLK and may be useful for the treatment of neurodegenerative diseases and disorders.

Neurons or axons are the unit cells of the nervous system. Unlike other cells in the human body, they do not reproduce or replace themselves. Therefore, when they start to function abnormally, deteriorate, or even die, they cannot be replaced. The progression of deterioration of neurons results in neurodegeneration and neurodegenerative diseases. Examples of neurodegenerative diseases include amyotrophic lateral sclerosis (ALS), glaucoma, Alzheimer's disease, and Parkinson's disease, as well as traumatic injury to the brain and spinal cord. These diseases are mostly age related and can be devastating to patients and caregivers, both physically and financially. There are currently no adequate treatments for neurodegenerative diseases, and there is a great need for the development of new effective treatments.

Dual leucine zipper kinase (DLK) [also known as mitogen-activated protein kinase kinase kinase 12 (MAP3K12)] is a member of the serine/threonine protein kinase family that contains a leucine zipper domain and is expressed predominately in neuronal cells. DLK and its downstream enzyme, c-Jun N-terminal kinase (JNK), play major roles in neuron apoptosis and degeneration. Therefore, DLK inhibitors may potentially be effective in the inhibition of the DLK/JNK pathway to provide greatly needed treatments for many neurological diseases and disorders resulting from neurodegeneration.

Important Compound Classes:



Formula (I)

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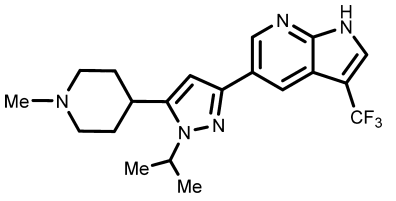
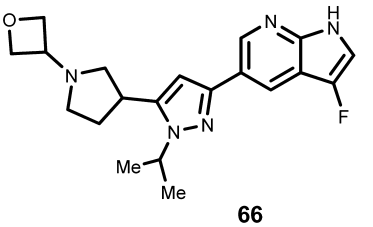
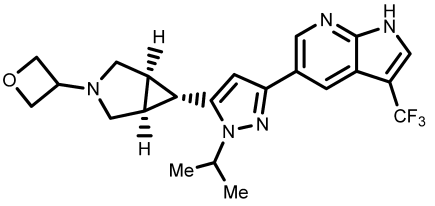
Key Structures: The inventors described the structures and methods of preparation of 182 examples of the compounds of formula (I) including the following four representative compounds:



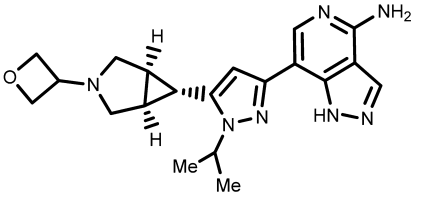
40



66



133



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Biological Assay: •DLK TR-FRET inhibition assay

Biological Data: The inventors reported the activities of the compounds of formula (I) as inhibitors of DLK kinase as K_i values in μM, according to the above assay. The results from examples **40**, **66**, **133**, and **172** (structures above) are listed in the following table:

DLK TR-FRET inhibition assay	
Example	DLK (Ki) μM
40	0.00017
66	0.11
133	0.0004
172	0.27

Recent Review Articles:

1. Ferraris, D.; Yang, Z.; Welsbie, D. *Future Med. Chem.* **2013**, *5* (16), 1923−1934.
2. Tedeschi, A.; Bradke, F. *EMBO Rep.* **2013**, *14* (7), 605−614.
3. Nix, P.; Bastiani, M. *Neuron* **2012**, *74* (6), 961−963.

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Notes

The authors declare no competing financial interest.