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Viewpoint

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Inhibitors of LRRK2 as Treatment for Parkinson's Disease

Patent Highlight

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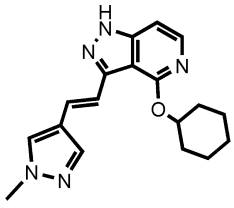
Title:	Pyrazolopyridines as Inhibitors of the Kinase LRRK2		
Patent Application Number:	WO 2012/038743 Al	**Publication Date:**	March 29, 2012
Priority Application:	US 61/385,522	**Priority Date:**	September 22, 2010
	GB 1015949.9		
Inventors:	Chan, B.; Chen, H.; Estrada, A.; Shore, D.; Sweeney, Z.; McIver, E.		
Assignee Company:	Medical Research Council Technology, London WC1H 9LT, GB		
	Genentech Inc., San Francisco, California 94080-4990, United States		
Disease Area:	Cancer and neurodegenerative diseases such as Parkinson's disease	**Biological Target:**	Kinases: preferably LRRK kinase; more preferably, LRRK2

Summary: The pyrazolopyridines represented by formula (I) are capable of inhibiting one or more kinases, more particularly, LRRK2, and may provide a treatment of a variety of disorders caused by this kinase, including cancer and neurodegenerative diseases such as Parkinson's disease (PD). The leucine-rich repeat kinase 2 (LRRK2) is a member of the leucine-rich repeat kinase family (LRRK). Mutations of this enzyme are associated with hereditary and nonhereditary forms of PD. In the patent application mentioned, there are almost 40 known single amino acid substitution mutations on LRRK2 linked to autosomal-dominant PD. Inhibition of the LRRK2 kinase with any of the molecules represented by formula (I) may potentially offer a treatment for any of the disorders caused by its abnormal activity such as PD and cancer.

Important Compound Classes:

Formula (**I**)

Key Structures: The following structures are representative examples of 239 total reported compounds using their listed numbers in the patent application; their K_i values are reported below:



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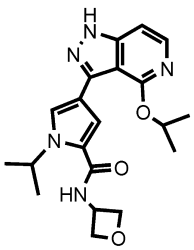

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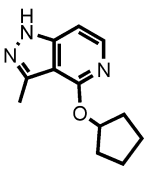

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Biological Assay: In Vitro LRRK2 Assay

This assay was used to determine a compound's potency in inhibiting activity of LRRK2 by determining $K_{i\ app}$, IC_{50}, or percent inhibition values.

Biological Data: The patent application reported the affinity values for LRRK2 (K_i, in μM) for 119 of the 239 listed compounds.

The K_i values ranged from 0.0003 and 0.0024 μM (for compounds **52** and **59**, respectively) to 0.858 μM (for compound **196**).

Claims: 1: This claim, the only composition of matter claim, lists 239 specific structural variations of formula (I).

2−10: Claim pharmaceutical composition and therapeutic use of compounds for treating cancer and neurodegenerative diseases resulting from abnormal LRRK2 activity.

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Notes

The authors declare no competing financial interest.