ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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Quinalozinones as Inhibitors of Class I PI3K Kinases

Gerard Rosse*

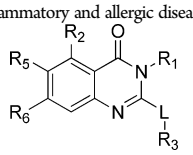
Structure Guided Chemistry, Dart Neuroscience LLC, 7473 Lusk Boulevard, San Diego, California 92121, United States

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

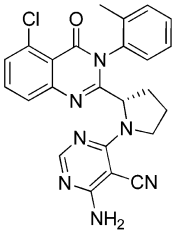
Title:	Quinalozinones as Inhibitors of Class I PI3K Kinases		
Patent/Patent Application Number:	WO 2014/128612 A1	**Publication date:**	August 8, 2014
Priority Application:	US 2013-61766920	**Priority date:**	February 20, 2013
Inventors:	Guibourdenche, C.; Hintermann, S.; Hurth, K.; Jacquier, S.; Kalis, C.; Moebitz, H.; Soldermann, N.		
Assignee Company:	Novartis, Inc.		
Disease Area:	Autoimmune, inflammatory disorders, cancer therapy, and parasitic infections	**Biological Target:**	Phosphoinositide-3 kinases (PI3K)

Summary: The present application discloses a series of quinalozinones as inhibitors of class I PI3K kinases. The compounds of the invention show a certain level of selectivity for PI3Kδ, PI3Kβ, and PI3Kγ over the PI3Kα isoform. The compounds claimed here are potentially useful in the treatment of a wide range of disorders such as autoimmune, inflammatory and allergic diseases, asthma, COPD, parasitic infections, and cancer.

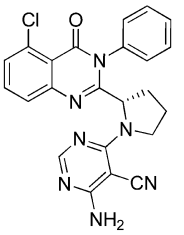
Important Compound Classes:



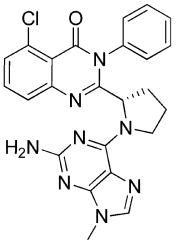
Key Structures:



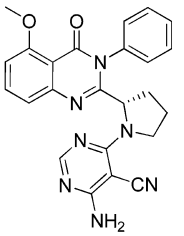
Compound A3



Compound A4



Compound A5



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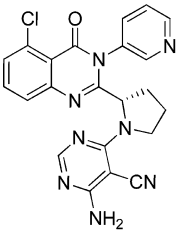

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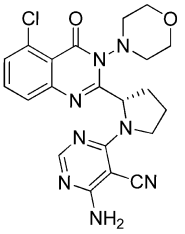

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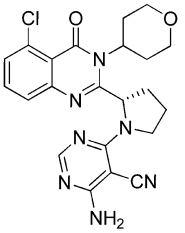

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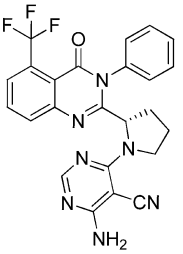

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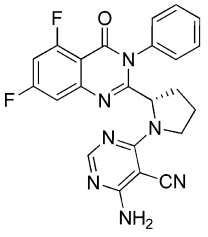

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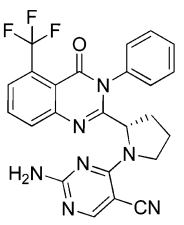

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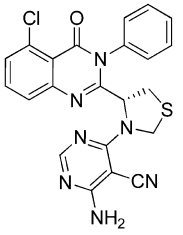
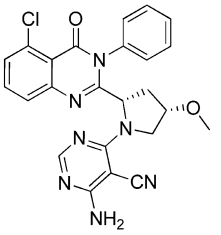


Compound B4



Compound C1

Special Issue: New Frontiers in Kinases

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Recent Review Articles: Zhou, H.; Huang, S. *Adv. Anticancer Agents Med. Chem.* **2013**, *1*, 72−106.

Biological Assay: The enzymatic activity of the compounds was evaluated using a TR-FRET inhibition assay. The cellular inhibition activity of the compounds was tested by monitoring PI3K-mediated Akt 1/2 (S473) phosphorylation in rate cells.

Pharmacological Data:

Enzymatic assay

Compound	PI3Kα IC_{50} (μM)	PI3Kδ IC_{50} (μM)	PI3Kγ IC_{50} (μM)
A3	5.208	< 0.003	0.070
A4	0.393	<0.003	0.024
A5	3.7	0.052	0.305
A10	>10	0.076	5.20
A15	7.7	0.014	0.150
A19	1.6	0.011	0.200
A21	4.7	0.008	0.280
A40	2.8	0.012	0.14
A45	>10	0.043	>10
A50	3.1	0.023	0.230
B4	2.34	0.005	0.129
C1	1.3	0.004	0.035

Cellular assay

Compound	Cell PI3Kα IC_{50} (μM)	Cell PI3Kδ IC_{50} (μM)	Cell PI3Kγ IC_{50} (μM)
A3	5.208	< 0.003	0.070
A4	0.393	<0.003	0.024
A5	3.7	0.052	0.305
A10	>10	0.076	5.20
A15	7.7	0.014	0.150
A19	1.6	0.011	0.200
A21	4.7	0.008	0.280
A40	2.8	0.012	0.14
A45	>10	0.043	>10
A50	3.1	0.023	0.230
B4	2.34	0.005	0.129
C1	1.3	0.004	0.035

Synthesis: The synthesis of 182 compounds is described.

AUTHOR INFORMATION

Corresponding Author

*E-mail: grosse@dartneuroscience.com.

Notes

The authors declare no competing financial interest.