

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

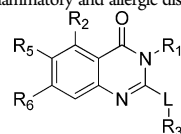
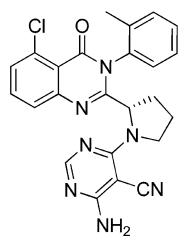
Adjunct Associate Professor, Department of Pharmacology and Physiology, College of Medicine, Drexel University, New College Building, 245 North 15th Street, Philadelphia, Pennsylvania 19102, United States

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:**

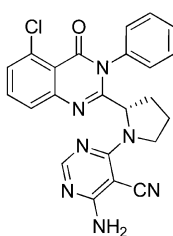
Autoimmune, inflammatory disorders, cancer therapy, and parasitic infections

Biological Target: Phosphoinositide-3 kinases (PI3K)**Summary:**

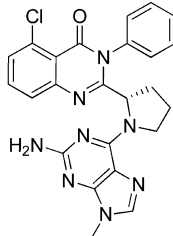
The present application discloses a series of quinalozinones as inhibitors of class I PI3K kinases. The compounds of the invention show a certain level of selectivity for PI3K δ , PI3K β , and PI3K γ over the PI3K α isoform. The compounds claimed here are potentially useful in the treatment of a wide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

Important Compound Classes:**Key Structures:**

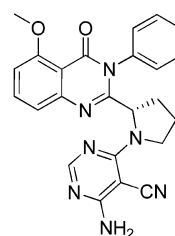
Compound A3



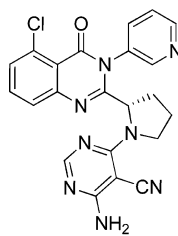
Compound A4



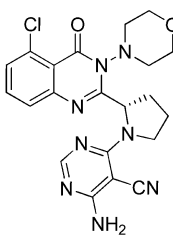
Compound A5



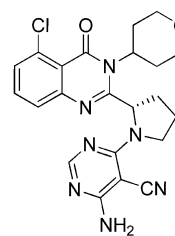
Compound A10



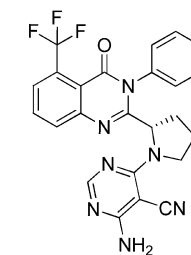
Compound A15



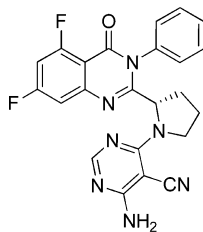
Compound A19



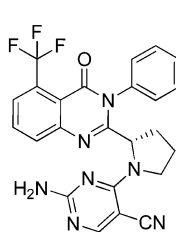
Compound A21



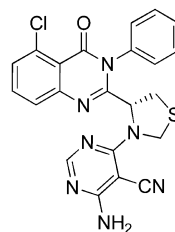
Compound A40



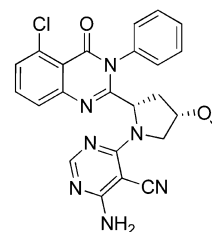
Compound A45



Compound A50



Compound B4



Compound C1

Special Issue: New Frontiers in Kinases**Received:** October 25, 2014**Published:** October 31, 2014

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	PI3K α IC ₅₀ (μ M)	PI3K δ IC ₅₀ (μ M)	PI3K γ IC ₅₀ (μ M)
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 PI3K α IC ₅₀ (μ M)	Cell PI3K δ IC ₅₀ (μ M)	Cell PI3K γ IC ₅₀ (μ M)
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.