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PATENT HIGHLIGHT

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Tankyrase Inhibitors: Potential Treatment of Hyperproliferative Diseases

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Title:	Quinazolinediones as Tankyrase Inhibitors		
Patent Application Number:	WO2013/177349 A2	**Publication date:**	28 November 2013
Priority Application:	US 61/651,687	**Priority date:**	25 May 2012
	US 61/773,300		6 March 2013
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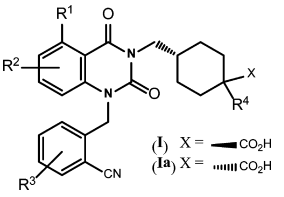
Assignee Company:	Glaxo SmithKline LLC; 2711 Centerville Road, Suite 400, Wilmington, New Castle, DE, 19808, USA		
Disease Area:	Cancers, fibrosis, and other hyperproliferative diseases	**Biological Target:**	Tankyrases (TNKS1 and TNKS2)

Summary: The invention in this patent application relates to quinazolinedione carboxylic acid derivatives represented generally by formula **I** or **Ia**, which are inhibitors of tankyrases (TNKS1 and TNKS2) and may potentially be useful for the treatment of cancer, fibrosis, and other hyperproliferative diseases.

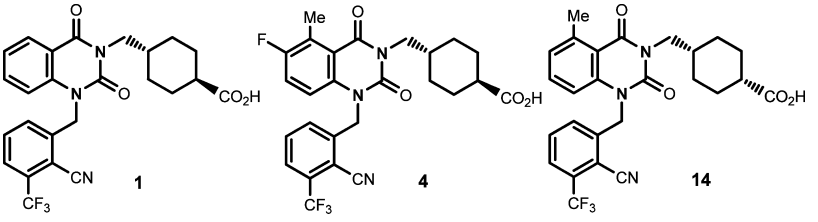
The tankyrases (TNKS1 and TNKS2) are members of the poly ADP-ribose polymerase (PARP) family of enzymes that act via mono- or poly-ADP-ribosylation (parsylation) of substrate proteins. These enzymes play important roles in cellular processes such as DNA repair and Wnt signaling. Tankyrases are also implicated in other processes, such as the positive regulation of telomere length and lung fibrogenesis. The deregulation of the Wnt/beta-catenin pathway has been linked to cancer, and studies have shown a possible link between increased activation of the canonical Wnt signaling and fibrogenesis. Additionally, pathologically activated canonical Wnt has been implicated in the pathogenesis of pulmonary-, renal-, dermal-, and liver-fibrosis. It has also been implicated in scarring after myocardial fibrosis following muscular dystrophy.

Thus, the inhibition of tankyrase activity could potentially have broad clinical utility and the use of tankyrase inhibitors such as the molecules described in this invention may potentially be a useful therapy for the treatment of hyperproliferative disorders, including cancer and fibrosis.

Important Compound Classes:



Key Structures: The application describes the synthesis of 14 specific examples of formula **I**/**Ia**, including the following three examples



Biological Assay:

- Inhibition of human TNKS1 [or TNKS 2] Fluorescence Polarization (FP) activity in vitro
- Inhibition of human TNKS 1 or TNKS 2 HTRF activity in vitro

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Biological Data: The 14 examples of the compounds of formula **I**/**Ia** were found to be inhibitors of Tankyrase with $pIC_{50} > 6$ in one or both TNKS assays. The data from the three represented examples **1**, **4**, and **14** (structures above) are listed in the following table:

Example	TNKS1 FP pIC_{50}	TNKS2 FP pIC_{50}	TNKS1 HTRF pIC_{50}	TNKS2 HTRF pIC_{50}
1	8.1	7.1	7.5	7.7
4	8.2	7.1	7.3	7.7
14			6.5	7

Claims: Claims 1−9: composition of matter; variations of formulas **I** and **Ia**

Claim 10: composition of matter; 13 examples of formula **I**

Claim 11: composition of matter; 1 example of formula Ia

Claim 12: pharmaceutical composition

Claim 13: method of treating cancer

Recent Review Articles:

1. Lehtioe, L.; Chi, N.-W.; Krauss, S. *FEBS J.* **2013**, *280* (15), 3576−3593.

2. Riffell, J. L.; Lord, C. J.; Ashworth, A. *Nat. Rev. Drug Discovery* **2012**, *11* (12), 923−936.

3. Jones, P. *Annu. Rep. Med. Chem.* **2010**, *45*, 229−243.

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Notes

The authors declare no competing financial interest.