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PATENT HIGHLIGHT

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Inhibition of CK2: An Attractive Therapeutic Target for Cancer Treatment

Ahmed F. Abdel-Magid*

Therachem Research Medilab (India) Pvt. Ltd., Jaipur, India

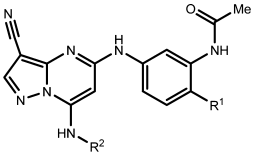
Title:	3-Cyano-5-arylamino-7-cycloalkylaminopyrrolo[1,5-A]pyrimidine Derivatives and Their Use as Antitumor Agents		
Patent Application Number:	WO 2013/144532 A1	**Publication date:**	3 October 2013
Priority Application:	PCT/GB2012/050732	**Priority date:**	30 March 2012
Inventors:	Chuaqui, C. E.; Dowling, J. E.; Lyne, P.; Pontz, T.; Ye, Q.		
Assignee Company:	Astrazeneca AB; SE-151 85 Södertälje (SE)		
	AstraZeneca UK Limited; 2 Kingdom Street, London Greater London W2 6BD, GB (MG only)		
Disease Area:	Cancer	**Biological Target:**	Casein Kinase 2 (CK2)

Summary: The invention in this patent application relates to pyrrolo[1,5-A]pyrimidine derivatives represented generally by formula (I). These compounds are inhibitors of CK2 and may potentially be used in the prevention and treatment of CK2-related conditions and diseases including cancer.

The casein kinase 2 (CK2) is a serine/threonine-selective protein kinase that exists as a tetramer of two catalytic (α and/or α') subunits and two regulatory (β) subunits. The level of CK2 in normal cells is tightly regulated to perform a variety of essential roles such as cell cycle control, cellular differentiation and proliferation, and promoting cell survival via modulation of apoptotic pathways. Studies have shown that elevated levels of CK2 are associated with cancer, while targeted overexpression of CK2 in transgenic animal models results in neoplastic growth. CK2 phosphorylates and regulates the activity and stability of multiple tumor suppressor proteins such as PML, p53, and PTEN, as well as oncogenes and transcriptional activators such as c-Myc, c-Myb, c-Jun, NFκB, and β-catenin. Recent studies provided evidence that CK2 can act as suppressor of apoptosis via phosphorylation of pro-apoptotic proteins, which protect them from caspase mediated cleavage. Studies also showed that inhibition of CK2 sensitizes cells to TNF-related apoptosis-inducing ligand (TRAIL) receptor-mediated apoptosis, ionizing radiation and chemotherapeutic agents.

Thus, inhibition of CK2 may be an effective therapeutic target for treatment of cancer. The inventors stated that the currently available small molecule inhibitors of CK2 lack the necessary balance of potency, selectivity, and drug-like properties for consideration as therapeutic agents. The CK2 inhibitors described in this patent application may possess improved properties that would provide a potentially useful treatment for cancer.

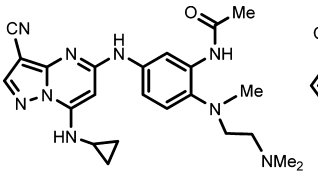
Important Compound Classes:



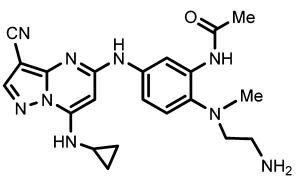
Formula (I)

Definitions: R^1 is selected from -$N(CH_3)(CH_2)_2NH_2$, and - $N(CH_3)(CH_2)_2N(CH_3)_2$; and R^2 is C_{3-5} cycloalkyl

Key Structures: The inventors described the synthesis of examples 1 and 2 and the trifluoroacetate salt of example 2.



Example 1



Example 2

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Biological Assay:

- CK2 in vitro mobility shift assay
- HCT-116 72hr alamarblue cell proliferation assay
- cell-based assay to determine antiproliferative effects on cancer cells in combination with EGFR inhibitors

Biological Data: Data for examples 1 and 2 from the first two assays above:

Compound	CK2 IC_{50} (mM)*	HCT116 GI_{50} (μM)**
Example 1	<0.004	0.030
Example 2	<0.003	0.009

* Data points are geometric means encompassing multiple test runs
** GI_{50} is the concentration that causes 50% reduction in proliferation of cancer cells

Claims: Claims 1−5: composition of matter, variations of formula (I)
Claims 6−9: use of compounds as medicaments
Claims 10−14: methods of treatment of cancer
Claim 15: method of inhibiting CK2
Claim 16: method of preparation of a compound of formula (I)
Claim 17: use of a compound of formula (I) in combination with antitumor agents

Recent Review Articles:
1. Cozza, G.; Pinna, L. A.; Moro, S. *Curr. Med. Chem.* **2013**, *20* (5), 671−693.
2. Kim, J.; Kim, S. H. *Arch. Pharmacal Res.* **2012**, *35* (8), 1293−1296.
3. Cozza, G.; Pinna, L. A.; Moro, S. *Expert Opin. Ther. Pat.* **2012**, *22* (9), 1081−1097.

AUTHOR INFORMATION

Corresponding Author

*Address: 1383 Jasper Drive, Ambler, Pennsylvania 19002, United States. Tel: 215-913-7202. E-mail: afmagid@comcast.net.

Notes

The authors declare no competing financial interest.