ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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Inhibitors of the Epidermal Growth Factor Receptor (EGFR) May Provide Effective Treatment for Lung Adenocarcinoma

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Title:	2,6-Substituted Purine Derivatives and Their Use in the Treatment of Proliferative Disorders		
Patent Application Number:	WO 2015/075598 Al	**Publication date:**	28 May 2015
Priority Application:	US 61/907,322	**Priority date:**	21 November 2013
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Assignee Company:	Pfizer Inc., 235 East 42nd Street, New York, New York 10017, USA		
Disease Area:	Lung cancer	**Biological Target:**	Epidermal growth factor receptor (EGFR)

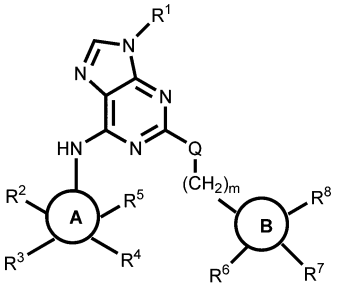
Summary:

The invention in this patent application relates to purine derivatives represented generally by formula (I). These compounds show activities as EGFR inhibitors and may potentially be useful for the treatment of abnormal cell growth, such as cancer, particularly certain forms of lung cancer.

Lung cancer is the leading cause of cancer-related deaths worldwide, with an estimated 1.2 million new cases diagnosed each year. The most common form of lung cancer is lung adenocarcinoma, which accounts for about 40% of all lung cancer cases. The epidermal growth factor receptor (EGFR) is a member of the ErbB family of receptor tyrosine kinases (RTK). Binding of EGFR to different ligands including the epidermal growth factor (EGF) induces its dimerization and subsequent phosphorylation. Overexpression of EGFR has been observed in several forms of lung cancers, and studies have led to the discovery of an association of some forms of lung cancers with mutations in EGFR. Patients with mutated EGFR constitute between 10 and 30% of the overall population and may benefit from treatment with the known EGFR inhibitors erlotinib or gefitinib. Some of the cases, particularly those associated with common EGFR mutations such as deletions within exon 19 (e.g., E7 40-A750) and point mutations in the activation loop (exon 21, in particular, L858R), show good response to treatments with EGFR inhibitors. However, the majority of patients who initially respond to erlotinib or gefitinib treatments tend to develop resistance. The primary cause of resistance, observed in approximately 50% of patients, is attributed to another EGFR mutation named T790M, which occurs at the gatekeeper threonine residue as a result of the substitution of threonine (T) at position 790 in EGFR with a methionine (M).

Thus, there is a need to discover and develop specific inhibitors of EGFR with T790M mutation that may provide more effective treatment for lung adenocarcinoma.

Important Compound Classes:



Formula (I)

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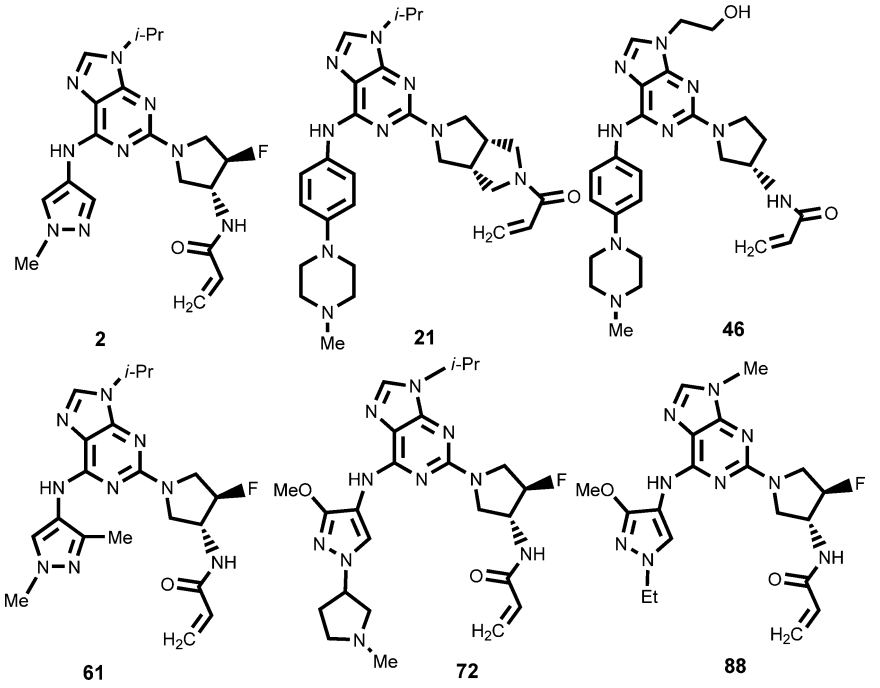
Key Structures: The inventors described the synthesis and structures of 90 compounds of formula (I) including the following representative examples:



Biological Assay: ***p*EGFR Y1068 ELISA Assay:** The effect of EGFR T790M inhibitors in cells with different EGFR mutation status was determined by measuring the inhibition of phosphorylation of EGFR at Tyr1068 (Y1068) in cells with wild-type EGFR or various EGFR mutations; either EGFR single mutant (L858R, E746-A750 deletion) or EGFR double mutant (L858R + T790M, deletion + T790M).

Biological Data: The results of the pEGFR Y1068 ELISA assay obtained from the above representative examples are listed in the following table:

Compound	H1975 IC_{50} (nM)	PC9 IC_{50} (nM)	H3255 IC_{50} (nM)	PC9-DRH IC_{50} (nM)	A549 IC_{50} (nM)
2	7	9	2	2	178
21	14	8	8	18	181
46	387	31	7	N/D	4192
61	6138	6651	N/D	2127	10000
72	6	2	5	3	142
88	6	6	2	1	194

Recent Review Articles:

1. D'Arcangelo, M.; Cappuzzo, F. *Biol. Targets Ther.* **2013**, *7*, 61−68.
2. Jamal-Hanjani, M.; Spicer, J. *Clin. Cancer Res.* **2012**, *18* (4), 938−944.
3. Okamoto, I.; Mitsudomi, T.; Nakagawa, K.; Fukuoka, M. *Ther. Adv. Med. Oncol.* **2010**, *2* (5), 301−307.

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Notes

The authors declare no competing financial interest.