ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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RET Kinase Inhibitors May Treat Cancer and Gastrointestinal Disorders

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Title:	Pyridine derivatives as rearranged during transfection (RET) kinase inhibitors		
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Priority Application:	PCT/CN2013/072683	**Priority Date:**	15 March 2013
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Disease Area:	Pain associated with irritable bowel syndrome (IBS) and proliferative diseases associated with increased RET kinase activity	**Biological Target:**	Rearranged during transfection (RET) tyrosine kinase

Summary:

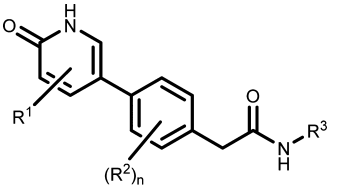
The invention in this patent application relates to pyridine derivatives represented generally by Formula (I), which are inhibitors of the rearranged during transfection (RET) kinase. These compounds may potentially provide treatments for irritable bowel syndrome (IBS), proliferative diseases, and any other disorders related to increased RET kinase activity.

Rearranged during transfection (RET) is a receptor tyrosine kinase that is involved in numerous cellular activities including cell proliferation, neuronal navigation, cell migration, and cell differentiation. RET is activated upon binding with glial cell derived neurotrophic factor family ligands. RET plays an important role in the development and survival of afferent nociceptors in the skin and gut. Studies suggest that a functional RET kinase protein product is required during development of enteric nervous system (ENS) and renal organogenesis during embryonic life. The ENS is responsible for the functions of the gastrointestinal system.

Mutations in the RET gene are associated with several diseases and disorders. Mutations resulting in the loss of RET function are implicated in the development of Hirschsprung's disease (HD), which is characterized by colonic obstruction due to lack of normal colonic enervation. Studies revealed that HD patients have a higher proportion of both familial and sporadic loss of RET function mutations. Mutations resulting in increased RET function are associated with the development of various types of human cancers, including multiple endocrine neoplasia (MEN 2A and 2B), familial medullary thyroid carcinoma (FMTC), and papillary thyroid carcinoma (PTC).

Thus, the inhibition of RET may be a viable therapeutic target for the treatment of pain associated with gastrointestinal disorders including irritable bowel syndrome (IBS) and for the treatment of cancers with constitutive RET kinase activity. RET inhibitors such as the compounds described in this patent application may potentially provide a treatment for these diseases.

Important Compound Classes:



Formula (I)

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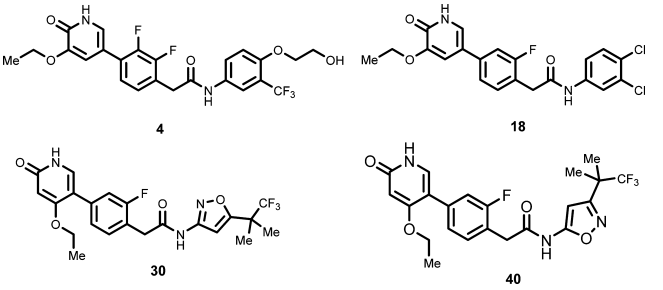
Key Structures: The inventors described the synthesis and structures of 46 examples of the compounds of Formula (I). The following four compounds are representative examples:



Biological Assay:

- RET Kinase Enzymatic Assay
- RET Kinase Cell-Based Mechanistic Assay
- RET Kinase Cell-Based Proliferation Assay

Biological Data: The biological data for the above representative examples are listed in the following table:

Compound	human RET kinase enzymatic assays IC_{50}	human RET kinase cell-based mechanistic assay IC_{50}	human RET kinase cell-based proliferation assay IC_{50}
4	+++	++	++
18	++	+	+
30	+++	+++	+++
40	+++	+++	+++

+: 10 μM > IC_{50} > 500 nM
++: 500 nM ≥ IC_{50} > 100 nM
+++: IC_{50} ≤ 100 nM

Claims: Claims 1−13: Composition of matter, variations of Formula (I)
Claims 14−16: Composition of matter, specific compounds listed by chemical names
Claim 17: Pharmaceutical composition
Claim 18−19: Methods of treating diseases
Claims 20−22: Claiming compounds and use of compounds

Recent Review Articles:
1. Degrauwe, N.; Sosa, J. A.; Roman, S.; Deshpande, H. A. *Clin. Med. Insights Oncol.* **2012**, *6*, 243−252.
2. Harris, P. J.; Bible, K. C. *Expert Opin. Investig. Drugs* **2011**, *20* (10), 1357−1375.

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Notes

The authors declare no competing financial interest.