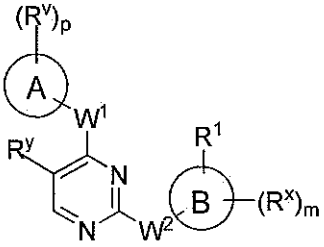
regulate the target protein biological function. These phosphorylation events are ultimately triggered in response to a variety of extracellular and other stimuli. Examples of such stimuli include environmental and chemical stress signals (e.g., osmotic shock, heat shock, ultraviolet radiation, bacterial endotoxin, and H_2O_2), cytokines (e.g., interleukin-1 (IL-1) and tumor necrosis factor α (TNF-α)), and growth factors (e.g., granulocyte macrophage-colony-stimulating factor (GM-CSF), and fibroblast growth factor (FGF)). An extracellular stimulus may affect one or more cellular responses related to cell growth, migration, differentiation, secretion of hormones, activation of transcription factors, muscle contraction, glucose metabolism, control of protein synthesis, and regulation of the cell cycle.

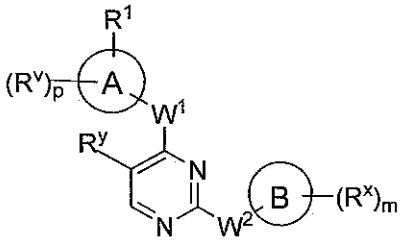
[0006] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events as described above. These diseases include, but are not limited to, autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies and asthma, Alzheimer's disease, and hormone-related diseases. Accordingly, there remains a need to find protein kinase inhibitors useful as therapeutic agents.

SUMMARY

[0007] It has now been found that compounds of this disclosure, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of one or more protein kinases. Such compounds have general formulae **I-a** and **I-b**:



I-a



I-b

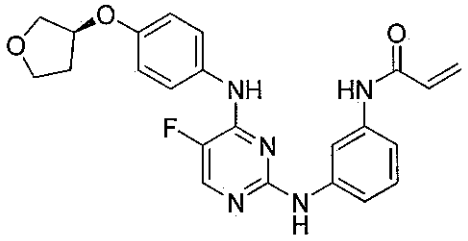
or a pharmaceutically acceptable salt thereof, wherein Ring A, Ring B, m, p, R^x, R^y, R^v,W^1, W^2, and R^1 are as defined herein.

[0008] Compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with

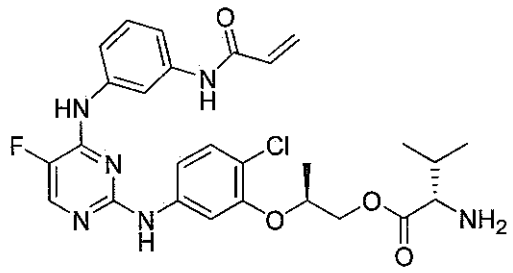
abnormal cellular responses triggered by protein kinase-mediated events. Such diseases, disorders, or conditions include those described herein.

[0009] Compounds provided by this disclosure are also useful for the study of kinases in biological and pathological phenomena; the study of intracellular signal transduction pathways mediated by such kinases; and the comparative evaluation of new kinase inhibitors.

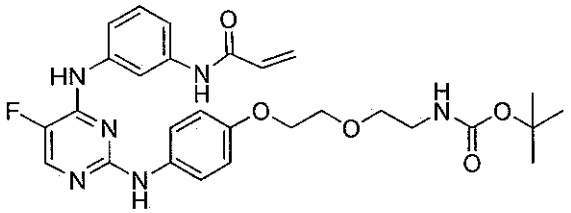
[0009a] In one aspect of the present disclosure, there is provided a compound selected from the group consisting of:



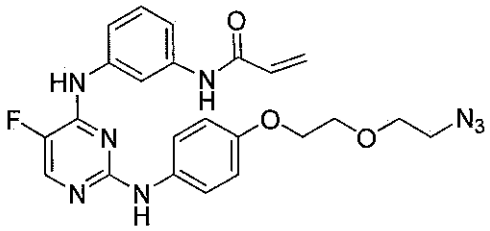
I-338



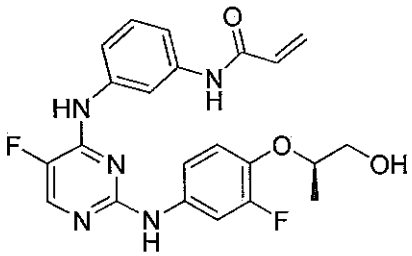
I-369



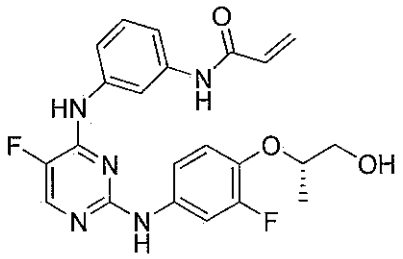
I-370



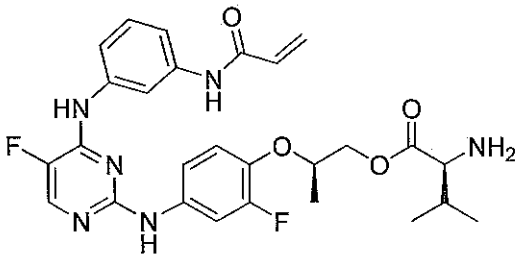
I-371



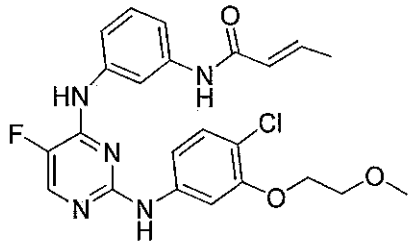
I-372



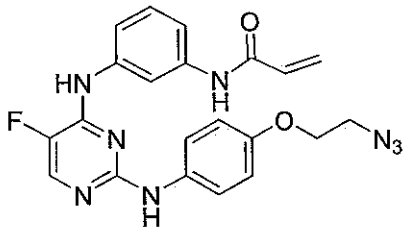
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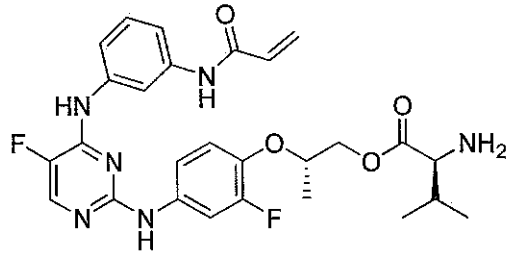
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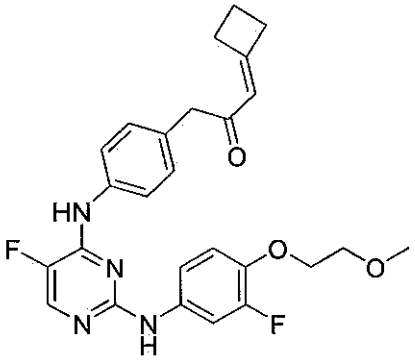
I-375



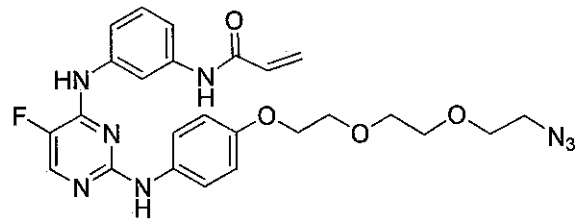
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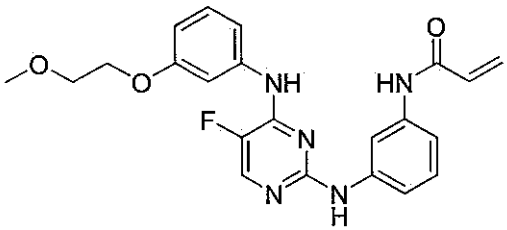
I-377



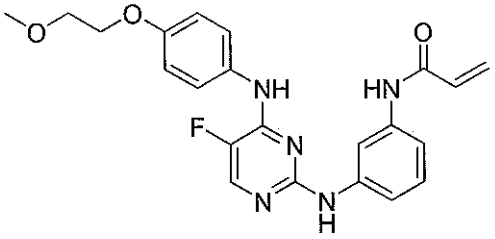
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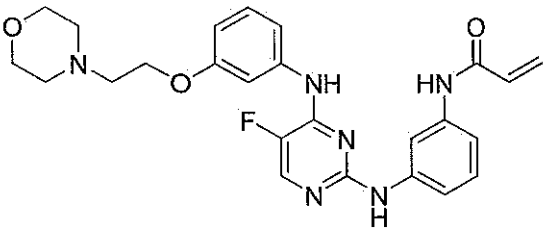
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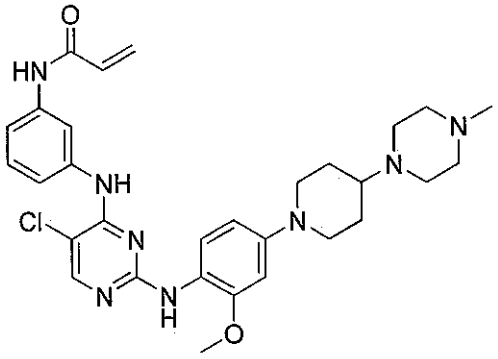
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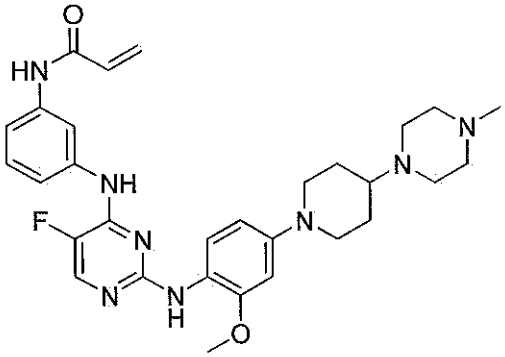
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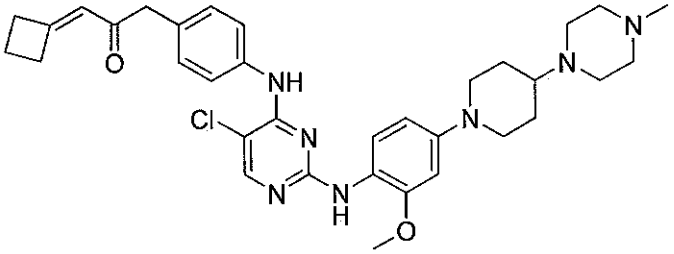
I-382



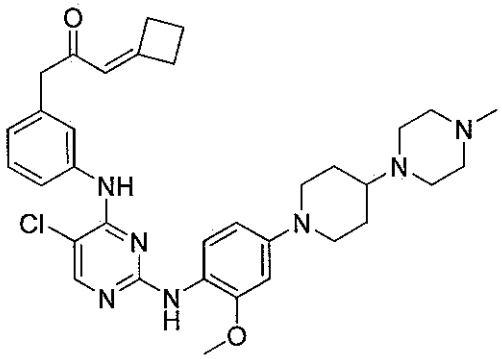
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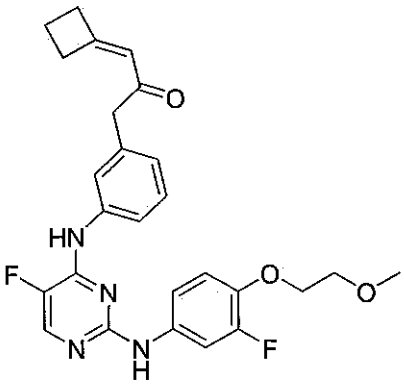
I-384



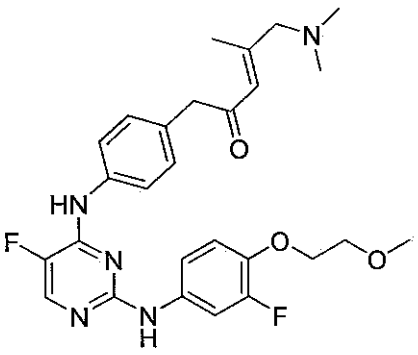
I-385



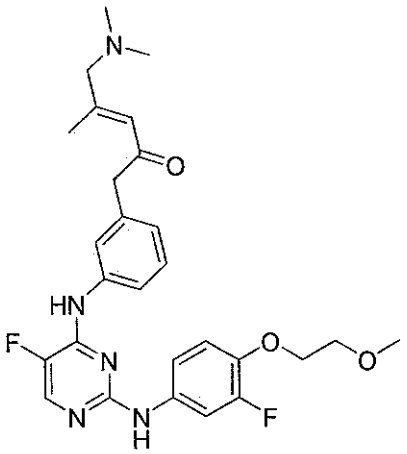
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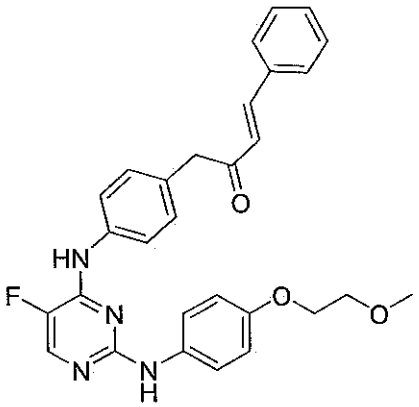
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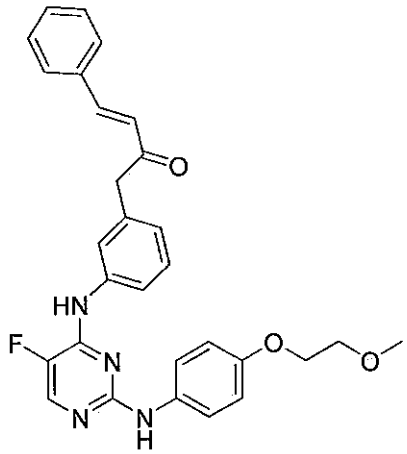
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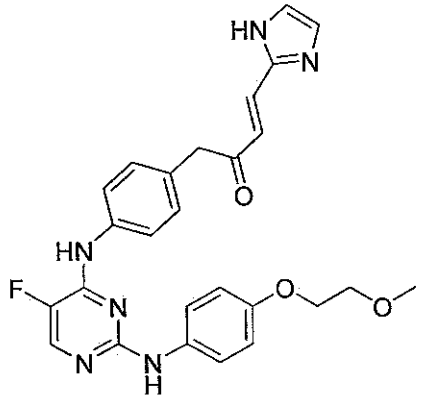
I-389



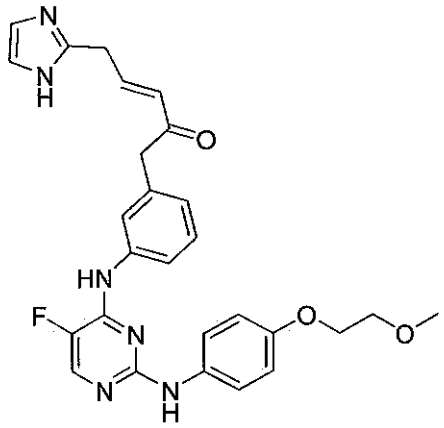
I-390



I-391



I-392



and **I-393**,

or a pharmaceutically acceptable salt thereof.

[0009b] In another aspect of the present disclosure, there is provided a composition comprising a compound as defined herein, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.

[0009c] In yet another aspect of the present disclosure, there is provided a use of a compound as defined herein in the manufacture of a medicament for treating a disorder, wherein the disorder is an autoimmune disease, a heteroimmune disease, an inflammatory disease, a cancer, a disease of the bone and joints, or a thromboembolic disorder.

[0009d] In a further aspect of the present disclosure, there is provided a use of a compound as defined herein in the manufacture of a medicament for treating a disorder selected from a proliferative disorder, a hyperproliferative disease, an immunological-mediated diseases, a disease of the respiratory tract, a skin disorder, a gastrointestinal disorder, a systeminc disease, or allograft rejection.

[0009e] In another aspect of the present disclosure, there is provided a use of a compound as defined herein in the manufacture of a medicament for treating a disorder, wherein the disorder is a carcinoma selected from breast cancer, glioblastoma, lung cancer, cancer of the head and neck, colorectal cancer, bladder cancer, non-small cell lung cancer, squamous cell carcinoma, salivary gland carcinoma, ovarian carcinoma, colorectal cancer, or pancreatic cancer.

[0009f] In yet another aspect of the present disclosure, there is provided a use of a compound as defined herein in the manufacture of a medicament for treating neurofibromatosis type I (NF1), neurofibromatosis type II (NF2) Schwann cell neoplasms (e.g. MPNST's), or a Schwannoma.

[0009g] In a further aspect of the present disclosure, there is provided a use of a compound as defined herein in the manufacture of a medicament for treating a disorder in a patient selected from a neurodegenerative disorder, or a solid or hematologic malignancy.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts dose-response inhibition of phospho-plc gamma2 (p-plc gamma 2) with compound **I-2** in Ramos Cells; and the results of compound **I-2** in a "washout" experiment.

Figure 2 depicts dose-response inhibition of p-plc gamma2 with compound **I-4** in Ramos Cells; and the results of compound **I-4** in a "washout" experiment.

Figure 3 depicts dose response inhibition of p-plc gamma2 with compound **I-7** in Ramos cells; and the results of compound **I-7** in a "washout" experiment.

Figure 4 depicts dose response inhibition of p-plc gamma2 with compound **I-35** in Ramos cells.

Figure 5 depicts dose response inhibition of p-plc gamma2 with compound **I-38** in Ramos cells.

Figure 6 depicts MS analysis confirming covalent modification of TEC kinase at Cys449 by compound **I-2**.

Figure 7 depicts MS analysis confirming covalent modification of TEC kinase at Cys449 by compound **I-4**.

Figure 8 depicts MS analysis confirming covalent modification of TEC kinase at Cys449 by compound **I-7**.

Figure 9 depicts the results of compound **I-2** in a "washout" experiment as compared to results of compound **I-4** and compound **I-7** in the same "washout" experiment in HCC827 cells containing EGFR deletion mutant.

Figure 10 depicts the results of compound **I-7** in a "washout" experiment as compared to results of an EGF control in A431 cells containing EGFR wild type.

Figure 11 depicts MS analysis confirming covalent modification of JAK-3 kinase at Cys909 by compound **I-7**.

Figure 12 depicts dose-response inhibition of P-Stat5 with compound **I-2** in IL-2 stimulated CTLL-2 cells; and dose-response inhibition of P-JAK-3 with compound **I-2** in IL-2 stimulated CTLL-2 cells.