Asaumi, et al.). Recently, it was demonstrated that a pan-Trk inhibitor inhibits the tyrosine signaling activated by neurotrophins binding to all three of the Trk receptors in human hFOB osteoblasts (J. Pinski, et al., (2002) 62, 986-989). These data support the rationale for the use of Trk inhibitors for the treatment of bone remodeling diseases, such as bone metastases in cancer patients.

[0011] Several classes of small molecule inhibitors of Trk kinases said to be useful for treating pain or cancer are known (*Expert Opin. Ther. Patents* (2009) 19(3)).

[0012] International Patent Application Publications WO 2006/115452 and WO 2006/087538 describe several classes of small molecules said to be inhibitors or Trk kinases which could be useful for treating pain or cancer.

[0013] Pyrazolo[1,5-a]pyrimidine compounds are known. For example, International Patent Application Publication WO 2008/037477 discloses pyrazolo[1,5-a]pyrimidine compounds bearing an alkyl, aryl or heterocyclic group at the 3-position. These compounds are asserted to be PI3K and/or mTOR Lipid Kinase inhibitors.

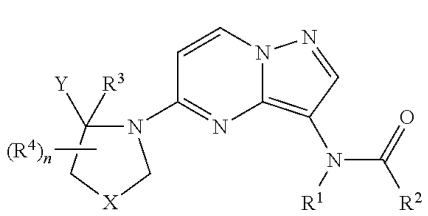
[0014] International Patent Application Publication WO 2008/058126 discloses pyrazolo[1,5-a]pyrimidine compounds bearing a phenyl group at the 3-position. These compounds are asserted to be Pim-kinase inhibitors.

[0015] U.S. Publication US 2006/0094699 discloses pyrazolo[1,5-a]pyrimidine compounds bearing a –C(=O)NH-phenyl, –C(=O)(4-methylpiperidinyl) or –C(=O)NMe(CH_2-trimethylpyrazolyl) group at the 3-position for use in combination therapy with a glucocorticoid receptor agonist.

SUMMARY

[0016] It has now been found that certain pyrazolo[1,5-a]pyrimidine compounds bearing an aryl or heteroaryl-substituted heterocyclic group at the 5-position and a group having the formula $NR^1C(=O)R^2$ at the 3-position, wherein R^1 and R^2 are as defined herein, are inhibitors of Trk kinases, in particular inhibitors of TrkA and/or TrkB, which are useful for treating disorders and diseases which can be treated by inhibiting TrkA and/or TrkB kinases, such as pain, including chronic and acute pain, or cancer. Certain compounds which are dual inhibitors of TrkA and TrkB may be useful in the treatment of multiple types of pain including inflammatory pain, neuropathic pain, surgical pain, and pain associated with cancer, surgery and bone fracture. Selectivity for TrkA and/or TrkB is particularly desirable in compounds for use in treating pain. In addition, compounds of the disclosure may be useful for treating cancer, inflammation, neurodegenerative diseases and certain infectious diseases.

[0016a] In one aspect, the disclosure provides a compound of Formula (I):



I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H or (1-6C)alkyl;

R^2 is NR^bR^c;

NR^bR^c forms a 5-6 membered heterocyclic ring having a ring heteroatom which is nitrogen and optionally having a second ring heteroatom or group selected from N, O and SO_2, wherein the heterocyclic ring formed by NR^bR^c is optionally substituted with one or two substituents independently selected from OH, F, NH_2, CO_2H, CO_2Et, $NHCO_2C(CH_3)_3$, CF_3, methyl, ethyl, isopropyl, $CO_2C(CH_3)_3$ and oxo;

Y is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, CF_3 and CHF_2;

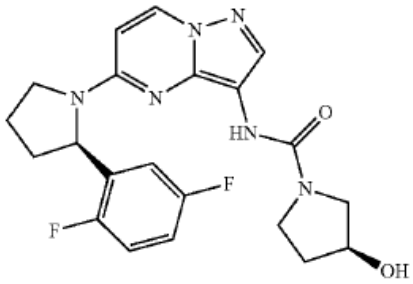
X is —CH_2—;

R^3 is H or (1-4C)alkyl;

each R^4 is independently selected from halogen, (1-4C)alkyl, OH, (1-4C)alkoxy, NH_2, NH(1-4C)alkyl and CH_2OH; and

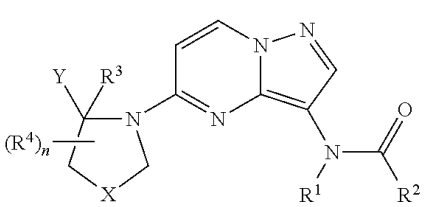
n is 0, 1, or 2.

[0016b] In one aspect, the disclosure provides a compound:



(S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

[0016c] In one aspect, the disclosure provides a pharmaceutical composition comprising a compound of Formula (I):



I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H or (1-6C)alkyl;

R^2 is NR^bR^c;

NR^bR^c forms a 5-6 membered heterocyclic ring having a ring heteroatom which is nitrogen and optionally having a second ring heteroatom or group selected from N, O and SO_2, wherein the heterocyclic ring formed by NR^bR^c is optionally substituted with one or two substituents independently selected from OH, F, NH_2, CO_2H, CO_2Et, $NHCO_2C(CH_3)_3$, CF_3, methyl, ethyl, isopropyl, $CO_2C(CH_3)_3$ and oxo;

Y is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, CF_3 and CHF_2;

X is —CH_2—;

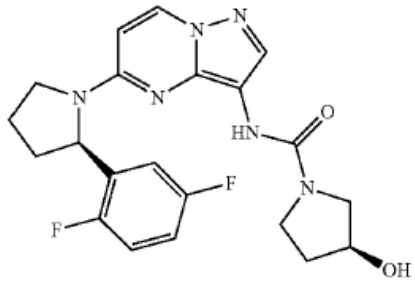
R^3 is H or (1-4C)alkyl;

each R^4 is independently selected from halogen, (1-4C)alkyl, OH, (1-4C)alkoxy, NH_2, NH(1-4C)alkyl and CH_2OH; and

n is 0, 1, or 2; and

a pharmaceutically acceptable diluent or carrier.

[0016d] In one aspect, the disclosure provides a pharmaceutical composition comprising a compound:



(S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

DETAILED DESCRIPTION