HETEROCYCLIC COMPOUNDS AND METHODS OF USE

TECHNICAL FIELD

[0001] This present application relates to heterocyclic compounds that are useful for treating proliferative disorders such as cancer.

BACKGROUND

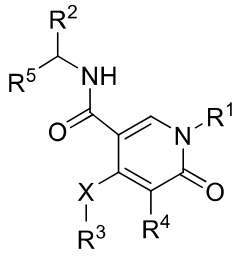
[0002] Cancer is characterized by aberrant cell growth and proliferation. Ras proteins are critical components of signaling networks responsible for controlling cellular proliferation, differentiation, and survival. *See, e.g.*, Fernandes-Medarde and Santos, Genes Cancer, Vol. 2, No. 3, pp. 344-358 (2011). Ras is a GTPase that acts as a molecular switch between an active GTP-bound state and an inactive GDP-bound state. GTP-bound Ras can activate several downstream signaling pathways involved in cell cycle progression, survival, and apoptosis.

[0003] Guanine nucleotide exchange factors (GEFs), such as SOS1, are required to activate Ras by facilitating the exchange of GDP (inactive Ras) for GTP (active Ras). SOS1 is itself activated by Ras via an allosteric interaction, which strongly activates the GEF function of SOS1, thus creating a positive feedback loop between SOS1 and Ras. *See, e.g.*, Bandaru, et al., Cold Spring Harb. Perspect Med., Vol. 9, No. 2, a031534 (2019). Mutations in Ras occur in many human cancers, but currently no drug targeting Ras proteins has been approved. *See* Hillig, et al., Proc. Nat. Acad. Sci., Vol. 117, No. 7, pp. 2551-2560 (2019). Thus, there remains a need for novel therapeutics to disrupt Ras signaling.

SUMMARY

[0004] It has now been found that certain heterocyclic compounds are inhibitors of SOS1 activity, and are useful for treating various diseases and disorders, such as cancers.

[0004a] In an aspect, there is provided a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is a C_1-C_6 alkyl, 4 to 10-membered heterocyclyl or C_3-C_{10} cycloalkyl, wherein each alkyl, heterocyclyl, and cycloalkyl is optionally substituted with one or more R^a;

R^a is each independently C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, halogen, -C(O)C_1-C_3 alkyl, or -C(O)-C_3-C_6 cycloalkyl, wherein each cycloalkyl is optionally substituted with one or more halogen;

R^2 is a C_6 aryl or 5 to 10-membered heteroaryl, wherein each aryl and heteroaryl is optionally substituted with one or more R^b;

R^b is each independently halogen, C_1-C_3 haloalkyl, C_1-C_3 alkyl, or C_3 cycloalkyl;

R^3 is -H, 4 to 10-membered heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkylene-O-NH-C(NH)(NH_2), C_3-C_{10} cycloalkyl, C_1-C_6 alkylene-5 to 10-membered heteroaryl, C_1-C_6 alkylene-4 to 10-membered heterocyclyl, C_1-C_6 alkylene-(C_3-C_{10} cycloalkyl), or C_3-C_{10} cycloalkyl, wherein each alkyl heterocyclyl, cycloalkyl, and heteroaryl is optionally substituted with one or more R^c;

R^c is each independently C_1-C_6 alkyl, -OH, -O-(C_1-C_6 alkyl), C_1-C_6 alkylene-O-CH_3, halogen, C_1-C_6 alkylene-5 to 10 -membered heterocyclyl, -N(CH_3)(CH_3), C_3-C_{10} cycloalkyl, C_1-C_6 haloalkyl, wherein each heterocyclyl, cycloalkyl, and alkyl is optionally substituted with one or more deuterium, C_1-C_6 alkyl, -OH, halogen, CN, or C_1-C_6 haloalkyl;

R^4 is H, -CH_3, -CN, -OMe, or halogen;

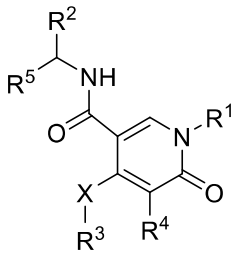
R^5 is C_1-C_3 alkyl or C_1-C_3 haloalkyl; and

X is NH or S.

[0004b] In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

[0004c] In another aspect, there is provided a method for treating cancer in a subject in need thereof, comprising administering to the subject an effective amount of a compound as defined above.

[0005] Accordingly, provided herein is a compound of the Formula (I):



(I)