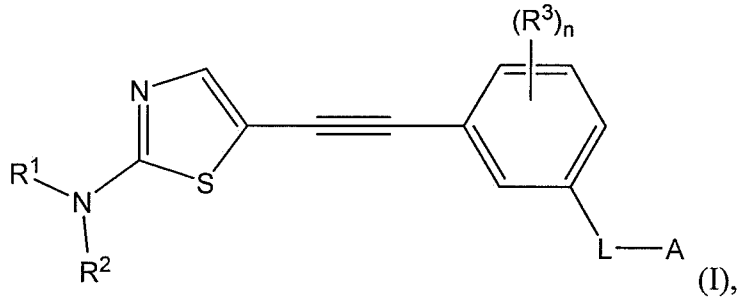
data suggest a limited spectrum of sensitive KIT mutants (George, S., *et al.*, *J. Clin. Oncol.* 2012, 30: 2401-7; and Serrano-Garcia, C., *et al.*, *ASCO Meeting Abstracts* 2013; 31(15_suppl): 10510). Thus, additional agents are needed to overcome resistance mutations in KIT, in particular those in the A-loop.

[0005] The KIT inhibitors imatinib, sunitinib and regorafenib are effective GIST therapies, though most patients develop resistance to these drugs due to somatic acquisition of polyclonal secondary KIT mutants. The lack of efficacy of any single agent against the complete set of potential ATP-binding pocket and A-loop secondary mutants makes achievement of prolonged complete disease control in late stage patients challenging. To address this unmet medical need, presented herein are compounds that target a broad range of primary and secondary KIT mutants, including those within the A-loop.

Summary

[0006] The present disclosure provides novel aminothiazole compounds and pharmaceutically acceptable salts as effective c-Kit inhibitors.

[0007] A first example of the disclosure relates to compounds of Formula (I):



(I),

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof,

wherein:

L is $-C(O)NR^5-$ or $-NR^5C(O)-$;

A is (C_3-C_8) cycloalkyl, (C_6-C_{10}) aryl, or 5- to 10-membered heteroaryl wherein the cycloalkyl, aryl, or heteroaryl is optionally substituted with one or more R^4;

R^1 is H, (C_1-C_6) alkyl, $-(CH_2)_qC(O)OH$, or $-C(O)N(R^7)_2$;

R^2 is (C_1-C_6) alkyl, $-C(O)R_8$, or $-C(O)NR^9R^{10}$;

each R^3 is independently at each occurrence (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, halogen, or OH;

each R^4 is independently at each occurrence (C_1-C_6) alkyl, (C_1-C_6) alkoxy,

(C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, halogen, -OH, CN, -$(C(R^6)_2)_p$-heterocycloalkyl wherein the heterocycloalkyl comprises a 4- to 7-membered ring and 1 to 3 heteroatoms selected from N, O, and S , or -$(C(R^6)_2)_p$-heteroaryl wherein the heteroaryl comprises a 5- or 6-membered ring and 1 to 3 heteroatoms selected from N, O, and S, and wherein the heterocycloalkyl or heteroaryl is optionally substituted with one or more substituents each independently selected from

(C_1-C_6) alkyl, -NH_2, (C_1-C_6) alkylamino, and (C_1-C_6) dialkylamino;

R^5 is H, (C_1-C_6) alkyl, or (C_1-C_6) haloalkyl;

each R^6 is independently H or (C_1-C_6) alkyl;

each R^7 is independently H or (C_1-C_6) alkyl;

R^8 is (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (C_2-C_6) alkenyl, (C_1-C_3) alkoxy, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, or 4 to 7-membered heterocycloalkyl comprising 1 to 3 heteroatoms selected from N, O, and S;

R^9 is H, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_3-C_7) cycloalkyl, or 4 to 7-membered heterocycloalkyl comprising 1 to 3 heteroatoms selected from N, O, or S;

R^{10} is H, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_3-C_7) cycloalkyl, or 4 to 7-membered heterocycloalkyl comprising 1 to 3 heteroatoms selected from N, O, or S, wherein the cycloalkyl or heterocycloalkyl is optionally substituted with one or more substituents each independently selected from (C_1-C_6) alkyl, -NH_2, (C_1-C_6) alkylamino, (C_1-C_6) dialkylamino, and -OH, and wherein the (C_1-C_6) alkyl is optionally substituted with one or more R^{11};

or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocycloalkyl ring comprising 1 to 3 heteroatom selected from N, O, and S, optionally substituted with one or more substituent each independently selected from

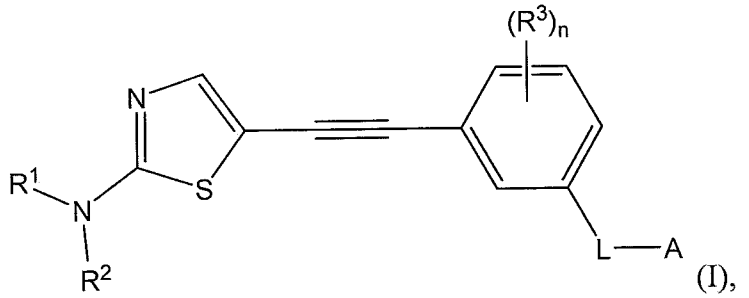
(C_1-C_6) alkyl, (C_1-C_6) hydroxyalkyl, -$(CH_2)_q$-NH_2, -$(CH_2)_q$-(C_1-C_6) alkylamino, -$(CH_2)_q$-(C_1-C_6) dialkylamino, -C(O)(C_1-C_6) alkyl, -OH, and 4- to 7-membered heterocycloalkyl comprising 1 to 3 heteroatom selected from N, O, and S, and optionally substituted with one or more (C_1-C_6) alkyl;

R^{11} is (C_1-C_6) alkoxy, -OH, -NH_2, (C_1-C_6) alkylamino, (C_1-C_6) dialkylamino, 5- or 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, or S, or 4- to 7-membered heterocycloalkyl comprising 1 to 3 heteroatoms selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with one or more substituents each independently selected from (C_1-C_6) alkyl and OH; and

each n, p, and q is independently 0, 1 or 2; and

provided that when A is phenyl and R_1 is H, then R_2 is not –C(O)CH_3.

[0007a] In one aspect, the present disclosure refers to a compound of Formula (I):



(I),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof,

wherein:

L is $-C(O)NR^5-$ or $-NR^5C(O)-$;

A is (C_3-C_8) cycloalkyl, (C_6-C_{10}) aryl, or 5- to 10-membered heteroaryl wherein the cycloalkyl, aryl, or heteroaryl is optionally substituted with one or more R^4;

R^1 is H, (C_1-C_6) alkyl, $-(CH_2)_qC(O)OH$, or $-C(O)N(R^7)_2$;

R^2 is (C_1-C_6) alkyl, $-C(O)R_8$, or $-C(O)NR^9R^{10}$;

each R^3 is independently at each occurrence (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, halogen, or OH;

each R^4 is independently at each occurrence (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, halogen, -OH, CN, $-(C(R^6)_2)_p$-heterocycloalkyl wherein the heterocycloalkyl comprises a 4- to 7-membered ring and 1 to 3 heteroatoms selected from N, O, and S , or $-(C(R^6)_2)_p$-heteroaryl wherein the heteroaryl comprises a 5- or 6-membered ring and 1 to 3 heteroatoms selected from N, O, and S, and wherein the heterocycloalkyl or heteroaryl is optionally substituted with one or more substituents each independently selected from

(C_1-C_6) alkyl, $-NH_2$, (C_1-C_6) alkylamino, and (C_1-C_6) dialkylamino;

R^5 is H, (C_1-C_6) alkyl, or (C_1-C_6) haloalkyl;

each R^6 is independently H or (C_1-C_6) alkyl;

each R^7 is independently H or (C_1-C_6) alkyl;

R^8 is (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (C_2-C_6) alkenyl, (C_1-C_3) alkoxy, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, or 4 to 7-membered heterocycloalkyl comprising 1 to 3 heteroatoms selected from N, O, and S;

R^9 is H, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_3-C_7) cycloalkyl, or 4 to 7-membered heterocycloalkyl comprising 1 to 3 heteroatoms selected from N, O, or S;

R^{10} is H, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_3-C_7) cycloalkyl, or 4 to 7-membered heterocycloalkyl comprising 1 to 3 heteroatoms selected from N, O, or S, wherein the cycloalkyl or heterocycloalkyl is optionally substituted with one or more substituents each independently selected from (C_1-C_6) alkyl, -NH_2, (C_1-C_6) alkylamino, (C_1-C_6) dialkylamino, and -OH, and wherein the (C_1-C_6) alkyl is optionally substituted with one or more R^{11};

or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocycloalkyl ring comprising 1 to 3 heteroatom selected from N, O, and S, optionally substituted with one or more substituent each independently selected from (C_1-C_6) alkyl, (C_1-C_6) hydroxyalkyl, -$(CH_2)_q$-NH_2, -$(CH_2)_q$-(C_1-C_6) alkylamino, -$(CH_2)_q$-(C_1-C_6) dialkylamino, -C(O)(C_1-C_6) alkyl, -OH, and 4- to 7-membered heterocycloalkyl comprising 1 to 3 heteroatom selected from N, O, and S, and optionally substituted with one or more (C_1-C_6) alkyl;

R^{11} is (C_1-C_6) alkoxy, -OH, -NH_2, (C_1-C_6) alkylamino, (C_1-C_6) dialkylamino, 5- or 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, or S, or 4- to 7-membered heterocycloalkyl comprising 1 to 3 heteroatoms selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with one or more substituents each independently selected from (C_1-C_6) alkyl and OH; and

each n, p, and q is independently 0, 1 or 2; and

provided that when A is phenyl and R^1 is H, then R^2 is not –C(O)CH_3.

[0007b] In another aspect, the present disclosure refers to a pharmaceutical composition comprising a compound of Formula (I) as disclosed herein, or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient or carrier.

[0008] A second example of the disclosure relates to a method of treating a c-Kit-mediated disease or disorder. The method comprises administering to a patient in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0008a] In yet another aspect, the present disclosure refers to a method of treating a c-Kit-mediated disease or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I) as disclosed herein, or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof.

[0009] Another example of the disclosure relates to a method of preventing a c-Kit-mediated disease or disorder. The method comprises administering to a patient in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0009a] In yet another aspect, the present disclosure refers to a method of modulating c-Kit comprising administering to a subject a compound of Formula (I) as disclosed herein.

[0010] Another example of the disclosure relates to a method of inhibiting c-Kit. The method comprises administering to a patient in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0010a] In yet another aspect, the present disclosure refers to a method of inhibiting c-Kit comprising administering to a subject a compound of Formula (I) as disclosed herein.

[0010b] In yet another aspect, the present disclosure refers to a method of treating or preventing a disease in which c-Kit plays a role, comprising administering to a subject in need thereof an effective amount of a compound of Formula (I) as disclosed herein.

[0011] Another example of the disclosure relates to a method of treating a disease or disorder associated with inhibiting c-Kit. The method comprises administering to a patient in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0012] Another example of the disclosure relates to a method of preventing a disease or disorder associated with inhibiting c-Kit. The method comprises administering to a patient in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0013] Another example of the disclosure relates to a method of treating cancer. The method comprises administering to a patient in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0014] Another example of the disclosure is directed to pharmaceutical compositions comprising a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof and a pharmaceutically acceptable carrier. The pharmaceutical acceptable carrier may further include an excipient, diluent, or surfactant.

[0015] Another example of the present disclosure relates to a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer

thereof, for use in the manufacture of a medicament for treating a disease associated with inhibiting c-Kit.

[0016] Another example of the present disclosure relates to a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the manufacture of a medicament for preventing a disease associated with inhibiting c-Kit.

[0017] Another example of the present disclosure relates to the use of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the treatment of a disease associated with inhibiting c-Kit.

[0018] Another example of the present disclosure relates to the use of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the prevention of a disease associated with inhibiting c-Kit.

[0019] The present disclosure further provides methods of treating or preventing a disease or disorder associated with modulation of c-Kit including, cancer, metastasis, inflammation and auto-immune pathogenesis, comprising administering to a patient suffering from at least one of said diseases or disorder a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0020] The present disclosure provides inhibitors of c-Kit that are therapeutic agents in the treatment of diseases such as cancer, metastasis, inflammation and auto-immune pathogenesis.

[0021] The present disclosure provides agents with novel mechanisms of action toward c-Kit enzymes in the treatment of various types of diseases including cancer and cell proliferative disorders, multiple sclerosis, asthma, mastocytosis, inflammatory disorders, allergic reactions, fibrotic disorders, auto-immune pathogenesis and metabolic disorders. Ultimately the present disclosure provides the medical community with a novel pharmacological strategy for the treatment of diseases and disorders associated with c-Kit.