CERTAIN CHEMICAL ENTITIES, COMPOSITIONS AND METHODS

[0001] This application is a continuation-in-part of application Ser. Nos. 11/121,709, filed May 3, 2005 and 11/124,608, filed May 6, 2005, and claims the benefit of U.S. Patent Application No. 60/569,510, filed May 6, 2004. Each of those applications is hereby incorporated by reference.

[0002] Provided are certain chemical entities which are inhibitors of one or more mitotic kinesins and are useful in the treatment of cellular proliferative diseases, for example cancer, hyperplasias, restenosis, cardiac hypertrophy, immune disorders, fungal disorders, and inflammation.

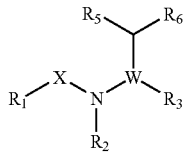
[0003] Among the therapeutic agents used to treat cancer are the taxanes and vinca alkaloids, which act on microtubules. Microtubules are the primary structural element of the mitotic spindle. The mitotic spindle is responsible for distribution of replicate copies of the genome to each of the two daughter cells that result from cell division. It is presumed that disruption of the mitotic spindle by these drugs results in inhibition of cancer cell division, and induction of cancer cell death. However, microtubules form other types of cellular structures, including tracks for intracellular transport in nerve processes. Because these agents do not specifically target mitotic spindles, they have side effects that limit their usefulness.

[0004] Improvements in the specificity of agents used to treat cancer is of considerable interest because of the therapeutic benefits which would be realized if the side effects associated with the administration of these agents could be reduced. Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. Examples of this include not only the taxanes, but also the camptothecin class of topoisomerase I inhibitors. From both of these perspectives, mitotic kinesins are attractive targets for new anti-cancer agents.

[0005] Mitotic kinesins are enzymes essential for assembly and function of the mitotic spindle, but are not generally part of other microtubule structures, such as in nerve processes. Mitotic kinesins play essential roles during all phases of mitosis. These enzymes are "molecular motors" that transform energy released by hydrolysis of ATP into mechanical force which drives the directional movement of cellular cargoes along microtubules. The catalytic domain sufficient for this task is a compact structure of approximately 340 amino acids. During mitosis, kinesins organize microtubules into the bipolar structure that is the mitotic spindle. Kinesins mediate movement of chromosomes along spindle microtubules, as well as structural changes in the mitotic spindle associated with specific phases of mitosis. Experimental perturbation of mitotic kinesin function causes malformation or dysfunction of the mitotic spindle, frequently resulting in cell cycle arrest and cell death.

[0006] Provided is at least one chemical entity chosen from compounds of Formula I

Formula I



and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, prodrugs, and mixtures thereof, wherein

[0007] R_1 is chosen from optionally substituted aryl, optionally substituted heterocycloalkyl, and optionally substituted heteroaryl;

[0008] X is chosen from —CO and —SO_2—;

[0009] R_2 is chosen from hydrogen and optionally substituted lower alkyl;

[0010] W is chosen from —CR_4—, —CH_2CR_4—, and N;

[0011] R_3 is chosen from —CO—R_7, hydrogen, optionally substituted alkyl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, cyano, sulfonyl, and optionally substituted aryl;

[0012] R_4 is chosen from hydrogen and optionally substituted alkyl;

[0013] R_5 is chosen from hydrogen, hydroxy, optionally substituted amino, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl; optionally substituted heteroaryl, and optionally substituted lower alkyl;

[0014] R_6 is chosen from hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted heteraryloxy, optionally substituted alkoxycarbonyl-, aminocarbonyl-, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl; and

[0015] R_7 is chosen from optionally substituted lower alkyl, optionally substituted aryl, hydroxy, optionally substituted amino, optionally substituted aralkoxy, and optionally substituted alkoxy;

[0016] provided that if W is N, then R_5 is not hydroxy or optionally substituted amino, and R_6 is not optionally substituted alkoxy, optionally substituted aralkoxy, optionally substituted heteroaralkoxy, or optionally substituted amino.

[0017] Also provided is a composition comprising a pharmaceutical excipient and at least one chemical entity described herein.

[0018] Also provided is a method of modulating CENP-E kinesin activity which comprises contacting said kinesin with an effective amount of at least one chemical entity described herein.

[0019] Also provided is a method of inhibiting CENP-E which comprises contacting said kinesin with an effective amount of at least one chemical entity described herein.

[0020] Also provided is a method for the treatment of a cellular proliferative disease comprising administering to a subject in need thereof at least one chemical entity described herein.

[0021] Also provided is a method for the treatment of a cellular proliferative disease comprising administering to a subject in need thereof a composition comprising a pharmaceutical excipient and at least one chemical entity described herein.

[0022] Also provided is the use, in the manufacture of a medicament for treating cellular proliferative disease, of at least one chemical entity of described herein.

[0023] Also provided is the use of at least one chemical entity described herein for the manufacture of a medicament for treating a disorder associated with CENP-E kinesin activity.

[0024] As used in the present specification, the following words and phrases are generally intended to have the mean-