CERTAIN CHEMICAL ENTITIES, COMPOSITIONS, AND METHODS

[0001] This application claims the benefit of U.S. Patent Application No. 60/569,510, filed May 6, 2004, which is hereby incorporated by reference.

[0002] This invention relates to 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.

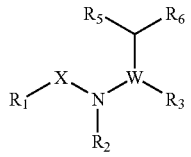
[0004] Improvements in the specificity of agents used to treat cancer is of considerable interest because of the therapeutic benefits which would be realized if the side effects associated with the administration of these agents could be reduced. Traditionally, dramatic improvements in the treatment 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 dysfumction of the mitotic spindle, frequently resulting in cell cycle arrest and cell death.

[0006] In one aspect, the invention relates to methods for treating cellular proliferative diseases, and for treating disorders by inhibiting the activity of one or more mitotic kinesins.

[0007] 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

[0008] R_1 is optionally substituted aryl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl;

[0009] X is —CO or —SO_2—;

[0010] R_2 is hydrogen or optionally substituted lower alkyl;

[0011] W is —CR_4—, —CH_2CR_4—, or N;

[0012] R_3 is —CO—R_7, hydrogen, optionally substituted alkyl, optionally substituted heterocyclyl, cyano, optionally substituted sulfonyl, or optionally substituted aryl;

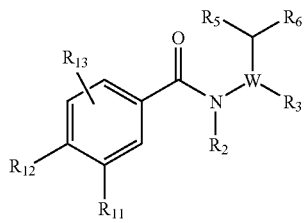
[0013] R_4 is hydrogen or optionally substituted alkyl;

[0014] R_5 is hydrogen, hydroxyl, optionally substituted amino, optionally substituted heterocyclyl; or optionally substituted lower alkyl;

[0015] R_6 is hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted heteraryloxy, optionally substituted alkoxycarbonyl-, optionally substituted aminocarbonyl-, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, or optionally substituted aralkyl; and

[0016] R_7 is optionally substituted lower alkyl, optionally substituted aryl, hydroxyl, optionally substituted amino, optionally substituted aralkoxy, or optionally substituted alkoxy.

[0017] In some embodiments, if W is N, then R_5 is not hydroxyl or optionally substituted amino, and R_6 is not optionally substituted alkoxy, optionally substituted aralkoxy, optionally substituted heteroaralkoxy, or optionally substituted amino.

[0018] Also provided is at least one chemical entity chosen from compounds of Formula II

(Formula II)