3-CARBONYLAMINO-5-CYCLOPENTYL-1H-PYRAZOLE COMPOUNDS HAVING INHIBITORY ACTIVITY ON CDK2

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to compounds of Formula (I) and pharmaceutically acceptable salts thereof, to pharmaceutical compositions comprising such compounds and salts, and to the uses thereof. The compounds, salts and compositions of the present invention may be useful for the treatment of abnormal cell growth, such as cancer, in a subject.

Description of the Related Art

Cyclin-dependent kinases (CDKs) and related serine/threonine protein kinases are important cellular enzymes that perform essential functions in regulating cell division and proliferation. CDKs 1-4, 6, 10, 11 have been reported to play a direct role in cell cycle progression, while CDKs 3, 5 and 7-9 may play an indirect role (e.g., through activation of other CDKs, regulation of transcription or neuronal functions). The CDK catalytic units are activated by binding to regulatory subunits, known as cyclins, followed by phosphorylation. Cyclins can be divided into four general classes (G_1, G_1/S, S and M cyclins) whose expression levels vary at different points in the cell cycle. Cyclin B/CDK1, cyclin A/CDK2, cyclin E/CDK2, cyclin D/CDK4, cyclin D/CDK6, and likely other heterodynes are important regulators of cell cycle progression.

Overexpression of CDK2 is associated with abnormal regulation of the cell-cycle. The cyclin E/CDK2 complex plays and important role in regulation of the G1/S transition, histone biosynthesis and centrosome duplication. Progressive phosphorylation of retinoblastoma (Rb) by cyclin D/Cdk4/6 and cyclin E/Cdk2 releases the G1 transcription factor, E2F, and promotes S-phase entry. Activation of cyclin A/CDK2 during early S-phase promotes phosphorylation of endogenous substrates that permit DNA replication and inactivation of E2F, for S-phase completion. (Asghar et al. *The history and future of targeting cyclin-dependent kinases in cancer therapy*, Nat. Rev. Drug. Discov. 2015; 14(2): 130-146).

Cyclin E, the regulatory cyclin for CDK2, is frequently overexpressed in cancer. Cyclin E amplification or overexpression has long been associated with poor outcomes in breast cancer. (Keyomarsi et al., Cyclin E and survival in patients with breast cancer. *N Engl J Med.* (2002) 347:1566-75). Cyclin E2 (CCNE2) overexpression is associated