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First inhibitors of the human mitotic Kinesin MKLP-2 synthesis, biological evaluation and structure-activity relationships

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Kinesins constitute a superfamily of microtubule-based motor proteins with important cellular functions ranging from intracellular transport to cell division. Some kinesin family members function during the mitotic phase of the eukaryotic cell cycle and are crucial for the successful progression of cell division. MKLP-2 (also known as Kif20A, RabK6, RB6K, Rab6KIFL, Rabkinesin6) a member of the kinesin-6 family plays an essential role during cytokinesis and is overexpressed in various cancers such as pancreatic cancer, bladder cancer, breast cancer, small-cell lung cancer, hepatocarcinogenesis, melanoma and gastric cancer. Furthermore, MKLP-2 is weakly detectable or absent in the normal spleen, lymph nodes, pancreas, lung, brain, liver, kidney and skeletal muscle. MKLP2 is involved in the relocation of chromosome passenger complex CPC (which consists of Aurora B, INCENP, surviving and borealin) to the spindle midzone. Down regulation of MKLP2 inhibits the growth of gastric and pancreatic cancer cells. We recently identified one compound (named paprotrain) as the first known inhibitor of MKLP-2. Paprotrain does not inhibit others members of the kinesin superfamily involved in mitosis. The synthesis, the structure-activity relationships and the biological activities will be discussed.

Biography

Research activities developed within Catherine Guillou's group are centred on the development of new methodologies, their application to the total synthesis of biologically active natural products and the design of enzyme inhibitors involved in cancer and Alzheimer's disease. She is co-authors of 52 publications and 8 patents.

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