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Antimitotic Epothilone Analogues as Antileukemia Agents

The clinically used anticancer drug paclitaxel (taxol) exerts its cytotoxic activity by a mechanism invoking the stabilization of microtubules. However, the susceptibility of taxol to multiple drug resistance has stimulated an extensive research for molecules with a paclitaxel-like mechanism of action. The most extensively investigated of the new molecular entities discovered are the epothilones, a class of macrolide natural products initially isolated from a soil bacterium. Some epothilones exhibit more potent anticancer activity than paclitaxel and have favorable attributes that may improve their pharmacological profile. The design of new epothilone analogues may be conveniently approached by dividing the structure into three distinct sectors. The extensive data-base on structure-activity relationship for epothilone has led to the discovery of potent epothilones, with several analogues currently in different stages of clinical development. However, most of the current potent epothilone analogues bear close structural resemblance to the parent compounds, and compounds with more stringent structural modifications of the epothilone scaffold may produce new lead structures with altered pharmacological profiles for drug discovery. Therefore, a new class of conformationally restrained analogues of epothilones has been developed.

The University of Toledo is seeking a company interested in utilizing this class of conformationally restrained analogues of epothilones which has been developed by restricting the mobility of the aromatic side chain. One of the conformationally constrained analogues synthesized showed very high and selective activity against leukemia cell lines.

Applications:

1. Strong growth inhibitory activity on CCRF-CEM and SR leukemia cell lines
2. Strategy should be applicable to the synthesis of other important analogues of the series

Advantages:

1. Retention of biological activity
2. Designed to rigidify the side chain
3. Permits sufficient mobility of the pyridine ring
4. Allows for the preferred orientation for interaction with the receptor

This invention is patent pending

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