

Abstract #244

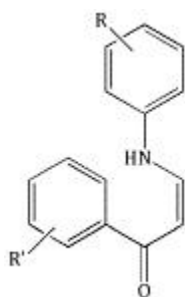
(Z)-1-Aryl-3-(arylamino)prop-2-en-1-ones: A novel class of antitubulin agents

Baliah Akula, PhD, Stephen C. Cosenza, PhD, Venkat R. Pallela, PhD, Vinaykumar Billa, MSc, Revathi Patti, MSc, E. Premkumar Reddy, PhD, M. V. Ramana Reddy, PhD

Fels Institute for Cancer Research, Temple University School of Medicine, Philadelphia, PA United States, Medicinal Chemistry, Onconova Therapeutics, Inc., Newtown, PA United States

Among the cellular structures necessary to maintain the growth and function of normal and malignant cells, the microtubules play a pivotal role. Microtubules are of particular importance for the formation of the mitotic spindle, which provides the structural framework for the physical segregation of chromosomes during cell division (mitosis). Many drugs that interfere with dynamics of microtubule formation generate abnormal mitotic spindles there by inducing cell cycle arrest in mitosis and finally apoptotic cell death. A variety of natural products, such as Paclitaxel, Epothilone A, Vinblastine, Colichine, Combretastatin A4 interferes with microtubule formation by changing the dynamics of polymerization and depolymerization of tubulins. One of the most important antimitotic agents is Combretastatin A4 selectively target the formation of new vasculature at tumor site. This process irreversibly shutdown the blood flow to neoplastic cells while leaving the blood supply to healthy cells intact.

Here, we describe a new class of small molecule antitubulin agents, which appear to satisfy many of the criteria for successful development of new anticancer agents. These compounds belong to the enaminone family and could readily inhibit the polymerization of tubulins. They exhibit potent cytotoxicity against wide spectrum of cancer cell lines. In this presentation we focus on the stereo-specific synthesis, structure-activity relationships and biological activity of these compounds.



Sunday, March 21, 2010 07:00 PM

General Poster Session (07:00 PM - 09:00 PM)

Abstract #75

Stereospecific synthesis and biological evaluation of (E) and (Z)-styryl benzylsulfides, sulfoxides, and sulfones

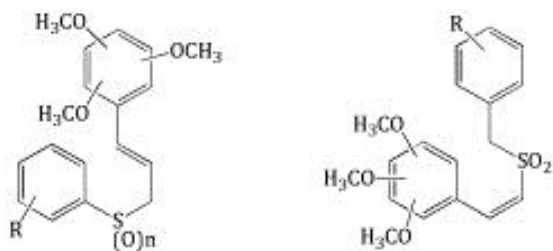
***Muralidhar R Mallireddigari, PhD, Stephen C. Cosenza, PhD, Venkat R. Pallela, PhD
E. Premkumar Reddy, PhD, M. V. Ramana Reddy, PhD***

Fels Institute for Cancer Research Temple University School of Medicine Philadelphia PA United States, Medicinal Chemistry Division Onconova Therapeutics Inc Newtown PA United States

Many antimetabolic agents that interfere with polymerization / depolymerization of α and β -tubulins have been successfully used for cancer treatment. These agents cause dynamic instability of microtubules resulting in cell cycle arrest in the M-phase, forming abnormal mitotic spindles. Agents such as vincristine and paclitaxel have gained wide clinical use for the treatment of various cancers, they suffer from undesired side effects, particularly neurotoxicity and are substrates various efflux mechanism leading to drug resistance. More recently, alternative components of the mitotic machinery have been targeted in an attempt to develop novel anti cancer agents.

These include critical signaling kinases such as the Plk, Aurora, wee1 and the Cdk-2 kinases.

In an attempt to identify potent inhibitors of tumor cell progression, a series of novel cell cycle inhibitors, styryl benzyl sulfides, sulfoxides and sulfones were synthesized and evaluated their activity in tumor cell cytotoxicity assay. This led to the identification of ON 01370, as a potent cytotoxic agent that kills tumor cells and sparing normal cells at much higher concentration. Further modification of ON 01370 led to analogs with enhanced potency and bioavailability. The stereospecific synthesis, structure-activity relationships and biological activity of this series of compounds will be discussed.



Sunday, March 21, 2010 07:00 PM

General Poster Session (07:00 PM - 09:00 PM)

Abstract 255**(E)-Styryl-N-aryl carboxamides: Novel antimetabolic agents**

Venkat R. Pallela, PhD, Stephen C. Cosenza, PhD, Srinivas R. Natala, PhD, Baliah Akula, PhD, Muralidhar R. Mallireddigari, PhD, Vinay Billa, MSc, Revathi Patti, MSc, E. Premkumar Reddy, PhD, M.V. Ramana Reddy, PhD

Fels Institute for Cancer Research, Temple University School of Medicine, Philadelphia, PA United States, Medicinal Chemistry, Onconova Therapeutics, Inc., Newtown, PA United States

Treatment of cancer cells with agents that interfere with microtubule assembly causes mitotic arrest and eventually cell death. Many antimetabolic agents that interfere with polymerization/depolymerization of α and β -tubulins have been successfully used for cancer treatment, especially for ovarian cancer. Ovarian cancer is the eighth most common cancer among women and accounts for about 3% of all cancers in women. It ranks fifth in cancer deaths among women, accounting for more deaths than any other cancer of the female reproductive system. The mitotic agents cause dynamic instability of microtubules resulting in cell cycle arrest in the M-phase, forming abnormal mitotic spindles. Agents such as vincristine and paclitaxel have gained wide clinical use for the treatment of various cancers, but suffer from undesired side effects, particularly neurotoxicity, and are substrates of various efflux mechanism leading to drug resistance. It is therefore desirable to discover novel antitubulin agents with fewer side effects, and better efficacy against MDR+ cancer cells.

Here, we describe the synthesis, structure activity relationship, cytotoxicity and microtubule depolymerization studies of a new class of propenamides, small molecule antitubulin agents. They exhibit potent (IC_{50} of 25-500 nM) activity against a wide spectrum of cancer cell-lines including ovarian cancer cell lines and drug resistant cell-lines.

Sunday, March 21, 2010 07:00 PM

General Poster Session (07:00 PM - 09:00 PM)

Abstract #372

N-Aryl-N-(arylsulfonyl)benzamides: Potent mitotic cell cycle inhibitors

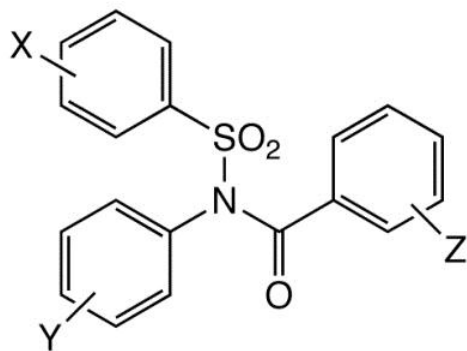
Sushmita Sen, PhD, Venkata S. Dandu R C, PhD, Muralidhar R. Mallireddigari, PhD, Baliah Akula, PhD, E. Premkumar Reddy, PhD, M. V. Ramana Reddy, PhD

Fels Institute for Cancer Research, Temple University School of Medicine, Philadelphia, PA United States,

Medicinal Chemistry, Onconova Therapeutics, Inc., Newtown, PA United States

Microtubules are linear polymers of α - and β - tubulin dimers. The tubulin dimers polymerize end to end in protofilaments. Microtubules are a part of the cell's cytoskeleton and are involved in the formation of mitotic spindles in eukaryotic cells to segregate their chromosomes correctly during cell division. They connect the chromosomes, help them with their first split and then move to each new daughter cell. There are some toxins and drugs like taxol, colchicines, vinblastine and Nocodazole that can bind to tubulin to either polymerize or depolymerize it. For example, Taxol blocks dynamic instability of GDP bound β - tubulin by stabilizing it and thus inhibiting the shrinkage. Development of microtubule inhibitors, which interfere with microtubule assembly and disassembly specific in M phase is useful for the investigation of the biological function of microtubules-associated proteins (MAPs) as well as for cancer therapy.

Here, we describe the synthesis of a new class of small molecules containing keto-sulfonamides, which we suspect to be a tubulin inhibitor thus effecting the mitotic cell cycle. We also report the structure-activity relationships and biological activity of these compounds tested against two cancer cell lines.



Wednesday, March 24, 2010 07:00 PM

General Poster Session (07:00 PM - 09:00 PM)