# Mi-181: A Potent Small Synthetic Microtubule-Targeting Anticancer Agent

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## SUMMARY

UCLA researchers in the Department of Chemistry & Biochemistry and Department of Molecular & Medical Pharmacology have discovered compound MI-181 and successfully synthesized its derivatives and analogs, which have the potential for use in cancer therapy by arresting cells during the process of cell division and promoting apoptosis.

## BACKGROUND

The cell cycle consists of four major phases: G1 growth phase, DNA synthesis phase, G2 growth phase, and mitotic phase. The cell cycle is a set of coordinated events, which function to integrate environment sensing signaling pathways with cell growth and proliferation. Cancer cells often deregulate cell cycle and undergo uncontrolled cell divisions. Therefore, inhibition of the cell cycle represents an opportunity for therapeutic intervention in treating proliferative diseases such as cancer.

Most anticancer drugs perturb the proliferation cycle of tumor cells by inhibiting cell cycle events. These drugs are broadly classified into two categories: DNA damaging drugs that target DNA replication, and antimitotic drugs that act in mitosis. Antimitotic drugs work by activating the spindle assembly checkpoint, arrest cells mitosis and eventually induce apoptosis after prolonged mitotic arrest. Current antimitotic drugs work through binding and inhibition of microtubules, kinases, or kinesins. Although microtubule-targeting agents are some of the most common chemotherapeutic agents used to treat a wide variety of cancers, they show important dose-limiting cytotoxicities, including neutropenia and neurotoxicity, largely a consequence of disturbing microtubule dynamics in neurons. In addition, many drugs are substrates for transport out of the cancer cells by multidrug resistance (MDR) efflux pumps, which are often overexpressed by cancer cells. Therefore, there is a critical need to identify novel tubulin-targeting drugs with improved properties that can be used as anticancer agents.

## INNOVATION

Researchers at UCLA have discovered a novel MI-181 class of compounds that can inhibit cell proliferation. The described MI-181 class of small molecules, including its derivatives and analogs, inhibits microtubule polymerization, arrests cells in mitosis, activates the spindle assembly checkpoint, and/or triggers apoptotic cell death. This class of small molecules shows good potency in treatment of a variety of cancers as a monotherapy or combined with other therapies to treat patients.

Alternatively, the MI-181 class of small molecules can be used to synthesize additional derivatives and analogs to improve the anticancer drug activity while minimizing side effects. These small molecules help improve drug stability, solubility, potency, specificity, bioavailability, efficacy, and delivery, as well as minimizing unwanted side effects and toxicity.

## APPLICATIONS

- Anticancer therapy
- Treatment of myelodysplastic syndrome
- Improve stability, solubility, potency, specificity, bioavailability, efficacy and delivery when is used to synthesize additional analogs and derivatives
- Minimize side effects, including but not limited to drug toxicity or unwanted metabolites when is used to synthesize additional analogs and derivatives
- Research tool or chemical probes for studying cell cycle

## ADVANTAGES

### CONTACT

UCLA Technology Development Group
ncd@tdg.ucla.edu
tel: 310.794.0558.



### INVENTORS

- Torres, Jorge

### OTHER INFORMATION

#### KEYWORDS

Anticancer therapy, antimitotic, small molecule, therapeutic, tumor, oncology, tubulin, cell cycle, myelodysplastic syndrome

#### CATEGORIZED AS

- **Medical**
  - Disease: Cancer
  - New Chemical Entities, Drug Leads
  - Therapeutics

#### RELATED CASES

2015-811-0

- Potential for fewer side effects compared to other antimitotic drugs
- Potential for the MI-181 class of small molecules to bypass MDR efflux pumps, and thus more effective against cancers that overexpress drug efflux pumps
- Potential for the MI-181 class of small molecules to be highly soluble in aqueous saline solutions, which could allow them to be delivered without any additional delivery vehicles
- Potential for the MI-181 class of small molecules to effectively pass the blood brain barrier when administrated

## STATE OF DEVELOPMENT

The MI-181 class of small molecules was successfully tested with in vitro assays. The mechanism of action has been characterized at the atomic level through X-ray crystallography studies.

## RELATED MATERIALS


- Senese, S., Lo, Y.C., Huang, D., Zangle, T.A., Gholkar, A.A., Robert, L., Homet, B., Ribas, A., Summers, M.K., Teitell, M.A., Damoiseaux, R., and Torres J.Z., 2014. Chemical dissection of the cell cycle: probes for cell biology and anti-cancer drug development. Cell Death & Disease, 5(10), p.e1462.
- McNamara, D.E., Senese, S., Yeates, T.O. and Torres, J.Z., 2015. Structures of potent anticancer compounds bound to tubulin. Protein Science, 24(7), pp.1164-1172.


## PATENT STATUS

| Country | Type | Number | Dated | Case |
|---|---|---|---|---|
| United States Of America | Issued Patent | 10,913,750 | 02/09/2021 | 2015-811 |
| Switzerland | Issued Patent | 3303346 | 09/16/2020 | 2015-811 |
| Germany | Issued Patent | 3303346 | 09/16/2020 | 2015-811 |
| France | Issued Patent | 3303346 | 09/16/2020 | 2015-811 |
| United Kingdom | Issued Patent | 3303346 | 09/16/2020 | 2015-811 |
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**UCLA Technology Development Group**

10889 Wilshire Blvd., Suite 920,Los Angeles,CA 90095

https://tdg.ucla.edu

Tel: 310.794.0558 | Fax: 310.794.0638 | ncd@tdg.ucla.edu